

KV1.3 potassium channel antagonists

Technical field

5 The present invention relates to K_V1.3 potassium channel antagonists and their use in the treatment and management of inflammatory diseases, including neuroinflammatory diseases.

Background

10 The K_V1.3 potassium channel, a voltage-gated potassium channel, is widely expressed in the immune and nervous systems, playing crucial roles in the function of T-cells and microglia.

The activation, proliferation, and effector functions of T-cells are tightly regulated by the interplay of ion channels, including the K_V1.3 channel. In T-cells, K_V1.3 channels are
15 involved in the modulation of calcium signalling, which is critical for T-cell receptor (TCR) signalling and subsequent activation.

Upon TCR engagement, the membrane potential of T-cells becomes depolarized, leading to the opening of voltage-gated K_V1.3 channels. This results in the efflux of
20 potassium ions, which stabilizes the membrane potential and promotes the opening of calcium channels. The influx of calcium activates the calcium-dependent signalling pathways that drive T-cell activation, differentiation, and proliferation. Consequently, the inhibition of K_V1.3 channels can prevent the activation and proliferation of T-cells, modulating immune responses and potentially ameliorating autoimmune and
25 inflammatory conditions.

Microglia are the resident immune cells of the central nervous system (CNS), responsible for maintaining homeostasis and responding to injury or infection. In the context of neuroinflammation and neurodegenerative diseases, microglial activation
30 can contribute to the release of pro-inflammatory cytokines, chemokines, and reactive oxygen species (ROS), ultimately exacerbating neuronal damage.

The K_V1.3 potassium channel has been found to play a critical role in microglial activation and function. Under resting conditions, microglia express low levels of K_V1.3
35 channels, but upon stimulation by pro-inflammatory signals, the expression and activity

of these channels increase significantly. This upregulation of K_v1.3 channels enhances the production of ROS and pro-inflammatory cytokines, perpetuating the inflammatory response and amplifying neuronal injury.

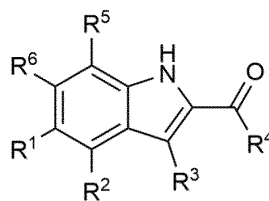
5 The functional involvement of K_v1.3 channels in T-cells and microglia suggests that their selective antagonism could be a promising therapeutic strategy for mitigating inflammation, particularly neuroinflammation associated with neurodegenerative diseases such as Multiple Sclerosis, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease. In preclinical studies, the use of K_v1.3 channel
10 antagonists has been shown to suppress T-cell activation and proliferation, reduce microglial activation, and decrease the production of pro-inflammatory mediators. These effects translate into reduced neuroinflammation and improved outcomes in animal models of neurodegenerative diseases, such as Alzheimer's and Parkinson's disease.

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Summary

The present invention relates to K_v1.3 potassium channel antagonists.

In one aspect, the present invention relates to a compound of Formula (I),



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Formula (I)

wherein

R¹ is halogen or H;

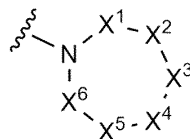
R² is halogen;

25 R³ is halogen;

R⁵ is H or halogen;

R⁶ is H or halogen;

R⁴ is of Formula (II):



Formula (II)

wherein

X^1 is $C(R^7)(R^8)$;

5 X^2 is $C(R^9)(R^{10})$ or a bond;

X^3 is $N(C(O)R^{11})$, $C(R^{12})(C(O)R^{13})$, $C(R^{14})(R^{15})$ or $N(R^{16})$;

X^4 is $C(R^{17})(R^{18})$, O or $C(O)$;

X^5 is $C(R^{19})(R^{20})$ or a bond;

X^6 is a bond or $C(R^{21})(R^{22})$;

10 wherein R^9 and R^{11} , R^9 and R^{13} , R^{10} and R^{11} , R^{10} and R^{13} , R^{13} and R^{17} , R^{13} and R^{18} , or R^{14} and R^{15} are optionally joined together to form a ring together with the intervening atom(s);

R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

15 R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

R^9 is H, C_{1-3} alkyl optionally substituted with 1 to 3 halogens, halogen, such as F, or - $C(O)N(R^{31})(R^{32})$, wherein R^{31} is H or C_{1-3} alkyl and R^{32} is H or C_{1-3} alkyl, or when R^9 is linked to R^{11} or R^{13} to form a ring, then R^9 is a bond, - $C(O)$ - or a C_{1-3} alkanediyl

20 optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 halogens, halogen, such as F, , or - $C(O)N(R^{31})(R^{32})$, wherein R^{31} is H or C_{1-3} alkyl and R^{32} is H or C_{1-3} alkyl, or when R^{10} is linked to R^{11} or R^{13} to form a ring, then R^{10} is a bond, - $C(O)$ - or a C_{1-3} alkanediyl

25 optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

R^{11} is - X^{13} - R^{33} ;

X^{13} is a bond, C_{1-3} alkanediyl optionally substituted with C_{1-3} alkyl, -O-, or C_{1-3} alkanediyl-O-;

30 R^{33} is selected from the group consisting of C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, pyridinyl, azetidiny, pyrrolidinyl, oxetanyl, tetrahydrofuranyl, and morpholinyl, each of which is optionally substituted with one or more substituents individually selected from

halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂;

or when R¹¹ is linked to R⁹ or R¹⁰ to form a ring, then R¹¹ is -O-, -N(R²⁸)-, or C₁₋₃

alkanediyl optionally substituted with 1 to 3 substituents individually selected from

5 halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein

- 10
- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
 - said azetidiny optionally substituted with NH₂;

15 or when R¹³ is linked to R⁹, R¹⁰, R¹⁷, or R¹⁸ to form a ring, then R¹³ is -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),

wherein

X⁷ is a bond or C₁₋₃ alkanediyl;

20 R²⁴ is C₁₋₃ alkyl; and

R²³ is H or C₁₋₃ alkyl, and R¹⁵ is H or C₁₋₃ alkyl,

or R²³ is a bond or C₁₋₃ alkanediyl, and R¹⁵ is a bond or C₁₋₃ alkanediyl

and R²³ is linked to R¹⁵ to form a ring;

or R¹⁴ is -X⁹C(O)X¹¹-, R¹⁵ is a bond or C₁₋₃ alkanediyl, and X¹¹ is linked to R¹⁵ to form a

25 ring,

wherein

X⁹ is a bond or -N(R²⁹)-;

R²⁹ is C₁₋₃ alkyl;

X¹¹ is -O-, C₁₋₃ alkanediyl, or -N(R³⁰)-; and

30 R³⁰ is C₁₋₃ alkyl;

R¹⁶ is H or C₁₋₃ alkyl;

R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or when

R¹⁷ is linked to R¹³ to form a ring, then R¹⁷ is a bond or a C₁₋₃ alkanediyl optionally

substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or when R¹⁸ is linked to R¹³ to form a ring, then R¹⁸ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl; R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

5 R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; R²¹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; R²² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; any two of R⁷, R⁸, R⁹, R¹⁰, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, and R²² are optionally linked together to form a ring;

10 with the proviso that when X⁴ is O, then X³ is C(R¹²)C(O)R¹³ and R¹³ is NH₂, N(H)(CH₃) or N(CH₃)₂;

with the proviso that when X³ is N(R¹⁶), then X⁴ is C(O),

with the proviso that when X⁴ is C(O), then X³ is N(R¹⁶), and

with the proviso that when X² is a bond, then X³ is C(R¹²)(C(O)R¹³) or C(R¹⁴)(R¹⁵),

15 or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention relates a compound of Formula (I) as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or medical condition where inhibition of Kv1.3 potassium channel is beneficial.

20 Definitions

As used herein, the singular forms “a,” “an” and “the” include plural referents unless the content clearly dictates otherwise.

25 The terms “approximately” and “about” as referred herein are synonymous. In some embodiments, “about” refer to the recited amount, value, or duration $\pm 20\%$, $\pm 10\%$, $\pm 5\%$, $\pm 4\%$, $\pm 3\%$, $\pm 2\%$, $\pm 1\%$, or $\pm 0.5\%$.

30 As used herein, the term “antagonist” refers to any compound which inhibits (e.g., antagonizes, reduces, decreases, blocks, reverses, or alters) the effect of a given agonist of a protein (including the protein itself). More particularly, an antagonist is capable of acting in a manner relative to the activity of the protein, such that the biological activity of the natural agonist, is decreased in a manner that is antagonistic (e.g., against, a reversal of, contrary to) to the natural action of the protein. The terms “antagonist”, “inhibitor” and “blocker” are used herein interchangeably to refer to an

agent that decreases or suppresses a biological activity, such as to repress an activity of an ion channel, such as K_v1.3.

5 The term, "compound," as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted, unless otherwise specified.

10 The terms "C₁₋₃ alkyl" and "C₁₋₆ alkyl" as used herein refer to a straight or branched hydrocarbon chains containing from 1 to 3 and 1 to 6 carbon atoms, respectively. Representative examples of C₁₋₃ alkyl and C₁₋₆ alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl and hexyl.

15 The term "C₃₋₆ cycloalkyl" as used herein refers to a saturated carbocyclic molecule wherein the cyclic framework has 3 to 6 carbon atoms. Representative examples of C₃₋₆ cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

20 The term "C₁₋₃ alkoxy" as used herein refer to -OR[#], wherein R[#] represents a C₁₋₃ alkyl as defined herein. Representative examples of C₁₋₃ alkoxy include methoxy, ethoxy, propoxy, and iso-propoxy.

25 The term "halogen" as used herein refers to -F, -Cl, -Br, or -I. In some embodiments, the halogen is F. In some embodiments, the halogen is Cl.

30 As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art.

35 The term "spiro compound" as used herein refers to a compound having one atom (usually a quaternary carbon) as the only common member of two rings. The term "C₅₋₈ spiroalkyl" as used herein refers to a bicyclic ring system comprising 5 to 8 carbon atoms, wherein the two rings are connected through a single common carbon atom.

Representative examples of C₅₋₈ spiroalkyl include, but are not limited to, spiro[2.2]pentanyl, spiro[3.2]hexanyl, spiro[3.3]heptanyl, spiro[3.4]octanyl, and spiro[2.5]octanyl.

5 As described herein, compounds of the present invention may contain “substituted” moieties. In general, the term “substituted” means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at one or more
10 substitutable position of the group, and when more than one position in any given structure is substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position, i.e. the substituent may be individually/independently selected from a group of substituents. Combinations of substituents envisioned by the present invention are preferably those that result in the formation of stable or chemically feasible compounds.

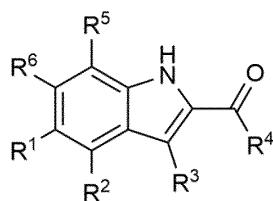
15 In some embodiments, a chemical group is “a bond”, which may also be referred to as said chemical group is absent. For example, when R^a in CH₃-R^a-OH is “a bond”, it refers to CH₃OH.

20 In some embodiments, two R groups are linked together to form a ring, i.e. a ring is formed by the two R groups and the intervening atom(s).

The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in
25 certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

Detailed description

30 In one aspect, the present invention relates to a compound of Formula (I),



Formula (I)

wherein

R¹ is halogen or H;

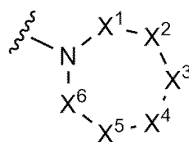
5 R² is halogen;

R³ is H or halogen;

R⁵ is H or halogen;

R⁶ is H or halogen;

R⁴ is of Formula (II):



Formula (II)

wherein

X¹ is C(R⁷)(R⁸);

X² is C(R⁹)(R¹⁰) or a bond;

15 X³ is N(C(O)R¹¹), C(R¹²)(C(O)R¹³), C(R¹⁴)(R¹⁵) or N(R¹⁶);

X⁴ is C(R¹⁷)(R¹⁸), O or C(O);

X⁵ is C(R¹⁹)(R²⁰) or a bond;

X⁶ is a bond or C(R²¹)(R²²);

20 wherein R⁹ and R¹¹, R⁹ and R¹³, R¹⁰ and R¹¹, R¹⁰ and R¹³, R¹³ and R¹⁷, R¹³ and R¹⁸, or R¹⁴ and R¹⁵ are optionally joined together to form a ring together with the intervening atom(s);

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen, such as F;

25 R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen, such as F;

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, halogen, such as F, or -C(O)N(R³¹)(R³²), wherein R³¹ is H or C₁₋₃ alkyl and R³² is H or C₁₋₃ alkyl, or when R⁹ is linked to R¹¹ or R¹³ to form a ring, then R⁹ is a bond, -C(O)- or a C₁₋₃ alkanediyl

- optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;
- R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, halogen, such as F, , or -C(O)N(R³¹)(R³²), wherein R³¹ is H or C₁₋₃ alkyl and R³² is H or C₁₋₃ alkyl, or when R¹⁰ is
- 5 linked to R¹¹ or R¹³ to form a ring, then R¹⁰ is a bond, -C(O)- or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;
- R¹¹ is -X¹³-R³³;
- X¹³ is a bond, C₁₋₃ alkanediyl optionally substituted with C₁₋₃ alkyl, -O-, or C₁₋₃ alkanediyl-
- 10 O-;
- R³³ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidiny, pyrrolidinyl, oxetanyl, tetrahydrofuranyl, and morpholinyl, each of which is optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally
- 15 substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂;
- or when R¹¹ is linked to R⁹ or R¹⁰ to form a ring, then R¹¹ is -O-, -N(R²⁸)-, or C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;
- 20 R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein
- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂,
 - 25 N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
 - said azetidiny optionally substituted with NH₂;
- or when R¹³ is linked to R⁹, R¹⁰, R¹⁷, or R¹⁸ to form a ring, then R¹³ is -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;
- 30 R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),
- wherein
- X⁷ is a bond or C₁₋₃ alkanediyl;
- R²⁴ is C₁₋₃ alkyl; and
- R²³ is H or C₁₋₃ alkyl, and R¹⁵ is H or C₁₋₃ alkyl,

or R^{23} is a bond or C_{1-3} alkanediyl, and R^{15} is a bond or C_{1-3} alkanediyl
and R^{23} is linked to R^{15} to form a ring;

or R^{14} is $-X^9C(O)X^{11}-$, R^{15} is a bond or C_{1-3} alkanediyl, and X^{11} is linked to R^{15} to form a ring,

5

wherein

X^9 is a bond or $-N(R^{29})-$;

R^{29} is C_{1-3} alkyl;

X^{11} is $-O-$, C_{1-3} alkanediyl, or $-N(R^{30})-$; and

R^{30} is C_{1-3} alkyl;

10

R^{16} is H or C_{1-3} alkyl;

R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or when R^{17} is linked to R^{13} to form a ring, then R^{17} is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or when

15

R^{18} is linked to R^{13} to form a ring, then R^{18} is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{21} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

20

R^{22} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F; any two of R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , and R^{22} are optionally linked together to form a ring;

with the proviso that when X^4 is O, then X^3 is $C(R^{12})C(O)R^{13}$ and R^{13} is NH_2 , $N(H)(CH_3)$ or $N(CH_3)_2$;

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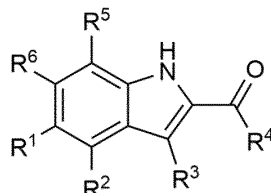
with the proviso that when X^3 is $N(R^{16})$, then X^4 is $C(O)$,

with the proviso that when X^4 is $C(O)$, then X^3 is $N(R^{16})$, and

with the proviso that when X^2 is a bond, then X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$,
or a pharmaceutically acceptable salt thereof.

30

In one aspect, the present invention relates to a compound of Formula (I),



Formula (I)

wherein

R¹ is halogen or H;

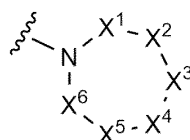
R² is halogen;

5 R³ is H or halogen;

R⁵ is H or halogen;

R⁶ is H or halogen;

R⁴ is of Formula (II):



10

Formula (II)

wherein

X¹ is C(R⁷)(R⁸);

X² is C(R⁹)(R¹⁰) or a bond;

X³ is N(C(O)R¹¹), C(R¹²)(C(O)R¹³), C(R¹⁴)(R¹⁵) or N(R¹⁶);

15 X⁴ is C(R¹⁷)(R¹⁸), O or C(O);

X⁵ is C(R¹⁹)(R²⁰) or a bond;

X⁶ is a bond or C(R²¹)(R²²);

wherein R⁹ and R¹¹, R⁹ and R¹³, R¹⁰ and R¹¹, R¹⁰ and R¹³, R¹³ and R¹⁷, R¹³ and R¹⁸, or R¹⁴ and R¹⁵ are optionally joined together to form a ring together with the intervening

20 atom(s);

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, or when R⁹ is linked to R¹¹ or R¹³ to form a ring, then R⁹ is a bond or a C₁₋₃ alkanediyl

25 optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, or when R¹⁰ is linked to R¹¹ or R¹³ to form a ring, then R¹⁰ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋

30 ₃ alkyl;

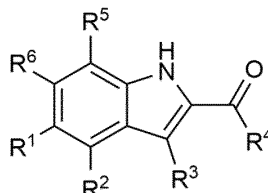
R¹¹ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidiny, pyrrolidinyl, oxetanyl, and morpholinyl, wherein

- 5
- said C₁₋₃ alkyl is optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, C₁₋₃ alkoxy, morpholinyl, azetidiny, -O-azetidiny, and -O-oxetany, and said azetidiny is optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl;
 - said C₃₋₅ cycloalkyl is optionally substituted with one or more substituents selected from halogen, and C₁₋₃ alkoxy;
 - said pyridiny is optionally substituted with one or more NH₂;
 - 10 • said pyrrolidiny is optionally substituted with one or more substituents individually selected from the group consisting of C₁₋₃ alkyl, halogen, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens;
 - 15 • said azetidiny optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkyl, and NH₂;
- and
- said morpholinyl is optionally substituted with C₁₋₃ alkyl;
- or when R¹¹ is linked to R⁹ or R¹⁰ to form a ring, then R¹¹ is -O-, -N(R²⁸)-, or C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from
- 20 halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;
- R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidiny, azetidiny, and piperaziny, wherein
- 25
- said pyrrolidiny is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
 - said azetidiny optionally substituted with NH₂;
- 30 or when R¹³ is linked to R⁹, R¹⁰, R¹⁷, or R¹⁸ to form a ring, then R¹³ is -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;
- R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),
- wherein
- X⁷ is a bond or C₁₋₃ alkanediyl;
- 35 R²⁴ is C₁₋₃ alkyl; and

R^{23} is H or C_{1-3} alkyl, and R^{15} is H or C_{1-3} alkyl,
 or R^{23} is a bond or C_{1-3} alkanediyl, and R^{15} is a bond or C_{1-3} alkanediyl
 and R^{23} is linked to R^{15} to form a ring;
 or R^{14} is $-X^9C(O)X^{11}-$, R^{15} is a bond or C_{1-3} alkanediyl, and X^{11} is linked to R^{15} to form a
 5 ring,

wherein
 X^9 is a bond or $-N(R^{29})-$;
 R^{29} is C_{1-3} alkyl;
 X^{11} is $-O-$, C_{1-3} alkanediyl, or $-N(R^{30})-$; and
 10 R^{30} is C_{1-3} alkyl;
 R^{16} is H or C_{1-3} alkyl;
 R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or when
 R^{17} is linked to R^{13} to form a ring, then R^{17} is a bond or a C_{1-3} alkanediyl optionally
 substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;
 15 R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or when
 R^{18} is linked to R^{13} to form a ring, then R^{18} is a bond or a C_{1-3} alkanediyl optionally
 substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;
 R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 20 R^{21} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{22} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 any two of R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , and R^{22} are optionally linked together
 to form a ring;
 with the proviso that when X^4 is O, then X^3 is $C(R^{12})C(O)R^{13}$ and R^{13} is NH_2 , $N(H)(CH_3)$
 25 or $N(CH_3)_2$;
 with the proviso that when X^3 is $N(R^{16})$, then X^4 is $C(O)$, and
 with the proviso that when X^4 is $C(O)$, then X^3 is $N(R^{16})$, or a pharmaceutically
 acceptable salt thereof.

30 In one aspect, the present invention relates to a compound of Formula (I),



Formula (I)

wherein

R¹ is halogen or H;

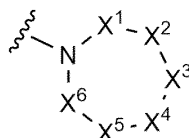
R² is halogen;

5 R³ is H or halogen;

R⁵ is H or halogen;

R⁶ is H or halogen;

R⁴ is of Formula (II):



10

Formula (II)

wherein

X¹ is C(R⁷)(R⁸);

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

15 X² is C(R⁹)(R¹⁰) or a bond;

X³ is N(C(O)R¹¹), C(R¹²)(C(O)R¹³), C(R¹⁴)(R¹⁵) or N(R¹⁶);

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

R¹¹ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy,

20 pyridinyl, azetidiny and pyrrolidinyl, wherein

- said C₁₋₃ alkyl is optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, C₁₋₃ alkoxy, and morpholinyl,
- said pyridinyl is optionally substituted with one or more NH₂;
- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of C₁₋₃ alkyl, halogen, C₁₋₃ alkoxy, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
- said azetidiny optionally substituted with NH₂;

25

30 or R¹¹ is linked to R⁹ to form a ring and

R⁹ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl,

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, and

R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

or R¹¹ is linked to R¹⁰ to form a ring and

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F,

R¹⁰ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, and R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein

- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
- said azetidiny optionally substituted with NH₂;

R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),

wherein

X⁷ is a bond or C₁₋₃ alkanediyl;

R²⁴ is C₁₋₃ alkyl; and

R²³ is H or C₁₋₃ alkyl, and R¹⁵ is H or C₁₋₃ alkyl,

or R²³ is a bond or C₁₋₃ alkanediyl, and R¹⁵ is a bond or C₁₋₃ alkanediyl

and R²³ is linked to R¹⁵ to form a ring;

or R¹⁴ is -X⁹C(O)X¹¹-, R¹⁵ is a bond or C₁₋₃ alkanediyl, and X¹¹ is linked to R¹⁵ to form a ring,

wherein

X⁹ is a bond or -N(R²⁹)-;

R²⁹ is C₁₋₃ alkyl;

X^{11} is -O-, C_{1-3} alkanediyl, or -N(R³⁰)-; and

R³⁰ is C_{1-3} alkyl;

R¹⁶ is H or C_{1-3} alkyl;

X^4 is C(R¹⁷)(R¹⁸), O or C(O);

5 R¹⁷ is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁸ is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

X^5 is C(R¹⁹)(R²⁰) or a bond;

R¹⁹ is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R²⁰ is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

10 X^6 is a bond or C(R²¹)(R²²);

R²¹ is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F; and

R²² is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

any two of R⁷, R⁸, R⁹, R¹⁰, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, and R²² are optionally linked together to form a ring,

15 with the proviso that when X^4 is O, then X^3 is C(R¹²)C(O)R¹³ and R¹³ is NH₂, N(H)(CH₃) or N(CH₃)₂;

with the proviso that when X^3 is N(R¹⁶), then X^4 is C(O), and

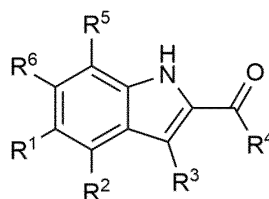
with the proviso that when X^4 is C(O), then X^3 is N(R¹⁶),

or a pharmaceutically acceptable salt thereof.

20

In some embodiments, when X^3 is N(C(O)R¹¹) or N(R¹⁶), then X^2 is not a bond. In some embodiments, when X^3 is N(C(O)R¹¹) or N(R¹⁶), then X^5 and X^6 are not both bonds.

In one aspect, the present invention relates to a compound of Formula (I),



25

Formula (I)

wherein

R¹ is halogen or H;

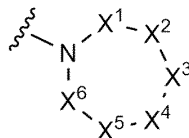
R² is halogen;

30 R³ is H or halogen;

R⁵ is H or halogen;

R⁶ is H or halogen;

R⁴ is of Formula (II):



Formula (II)

5 wherein

X¹ is C(R⁷)(R⁸);

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

X² is C(R⁹)(R¹⁰) or a bond;

10 X³ is N(C(O)R¹¹), C(R¹²)(C(O)R¹³), C(R¹⁴)(R¹⁵) or N(R¹⁶);

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

R¹¹ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidiny and pyrrolidinyl, wherein

- 15
- said C₁₋₃ alkyl is optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, C₁₋₃ alkoxy, and morpholinyl,
 - said pyridinyl is optionally substituted with one or more NH₂;
 - said pyrrolidinyl is optionally substituted with one or more substituents
- 20
- individually selected from the group consisting of C₁₋₃ alkyl, halogen, C₁₋₃ alkoxy, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
- said azetidiny optionally substituted with NH₂;

or R¹¹ is linked to R⁹ to form a ring and

- 25
- R⁹ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl,
- R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, and
- R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents
- 30
- individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

or R¹¹ is linked to R¹⁰ to form a ring and

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F,

R¹⁰ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3

5

substituents individually selected from halogen and C₁₋₃ alkyl, and

R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

10

R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein

- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
- said azetidiny optionally substituted with NH₂;

15

R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),

wherein

20

X⁷ is a bond or C₁₋₃ alkanediyl;

R²⁴ is C₁₋₃ alkyl; and

R²³ is H or C₁₋₃ alkyl, and R¹⁵ is H or C₁₋₃ alkyl,

or R²³ is a bond or C₁₋₃ alkanediyl, and R¹⁵ is a bond or C₁₋₃ alkanediyl

and R²³ is linked to R¹⁵ to form a ring;

25

or R¹⁴ is -X⁹C(O)X¹¹-, R¹⁵ is a bond or C₁₋₃ alkanediyl, and X¹¹ is linked to R¹⁵ to form a ring,

wherein

X⁹ is a bond or -N(R²⁹)-;

R²⁹ is C₁₋₃ alkyl;

30

X¹¹ is -O-, C₁₋₃ alkanediyl, or -N(R³⁰)-; and

R³⁰ is C₁₋₃ alkyl;

R¹⁶ is H or C₁₋₃ alkyl;

X⁴ is C(R¹⁷)(R¹⁸), O or C(O);

R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

35

R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

X^5 is $C(R^{19})(R^{20})$ or a bond;

R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

X^6 is a bond or $C(R^{21})(R^{22})$;

5 R^{21} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F; and

R^{22} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

any two of R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , and R^{22} are optionally linked together to form a ring;

with the proviso that when X^4 is O, then X^3 is $C(R^{12})(C(O)R^{13})$ and R^{13} is NH_2 ,

10 $N(H)(CH_3)$ or $N(CH_3)_2$;

with the proviso that when X^3 is $N(R^{16})$, then X^4 is $C(O)$,

with the proviso that when X^4 is $C(O)$, then X^3 is $N(R^{16})$,

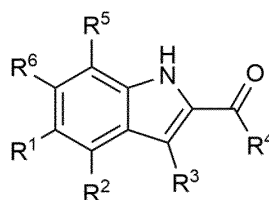
with the proviso that when X^3 is $N(C(O)R^{11})$ or $N(R^{16})$, then X^2 is not a bond, and

with the proviso that when X^3 is $N(C(O)R^{11})$ or $N(R^{16})$, then X^5 and X^6 are not both

15 bonds,

or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention relates to a compound of Formula (I),



Formula (I)

20

wherein

R^1 is halogen or H;

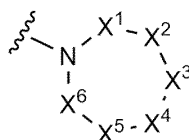
R^2 is halogen;

R^3 is H or halogen;

25 R^5 is H or halogen;

R^6 is H or halogen;

R^4 is of Formula (II):



Formula (II)

wherein

X^1 is $C(R^7)(R^8)$;

R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or F;

5 R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or F;

X^2 is $C(R^9)(R^{10})$ or a bond;

R^9 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or F;

R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or F;

X^3 is $N(C(O)R^{11})$, $C(R^{12})(C(O)R^{13})$, $C(R^{14})(R^{15})$ or $N(R^{16})$;

10 R^{11} is selected from the group consisting of C_{1-3} alkyl, C_{3-5} cycloalkyl, C_{1-3} alkoxy, pyridinyl, azetidiny and pyrrolidinyl,

a. said C_{1-3} alkyl is optionally substituted with one or more substituents individually selected from the group consisting of NH_2 , $N(H)(CH_3)$, $N(CH_3)_2$ and C_{1-3} alkoxy,

15 b. said pyridinyl is optionally substituted with one or more NH_2 ;

c. said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of NH_2 , $N(H)(CH_3)$, $N(CH_3)_2$ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and

20 d. said azetidiny optionally substituted with NH_2 ;

e. when R^{11} is C_{1-3} alkyl or C_{1-3} alkoxy, then R^{11} is optionally linked to R^9 or R^{10} to form a ring;

R^{12} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or F;

R^{13} is selected from the group consisting of NH_2 , $N(H)(CH_3)$, $N(CH_3)_2$, pyrrolidinyl,

25 azetidiny, and piperazinyl, wherein

a. said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of NH_2 , $N(H)(CH_3)$, $N(CH_3)_2$ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and

30 b. said azetidiny optionally substituted with NH_2 ;

R^{14} is $-X^7N(R^{23})(C(O)R^{24})$;

X^7 is a bond or CH_2 ;

R^{23} is H or C_{1-3} alkyl, or R^{23} is a bond and R^{15} is C_{1-3} alkanediyl and R^{23} is linked to R^{15} to form a 4 or 5 membered ring;

35 R^{24} is C_{1-3} alkyl;

R^{15} is H or C_{1-3} alkyl;

R^{16} is H or C_{1-3} alkyl;

X^4 is $C(R^{17})(R^{18})$, O or $C(O)$;

R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or F;

5 R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or F;

X^5 is $C(R^{19})(R^{20})$ or a bond;

R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or F;

R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or F;

X^6 is a bond or $C(R^{21})(R^{22})$;

10 R^{21} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or F; and

R^{22} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or F;

any two of R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , and R^{22} are optionally linked together to form a ring;

with the proviso that when X^4 is O, then X^3 is $C(R^{12})(C(O)R^{13})$ and R^{13} is NH_2 ,

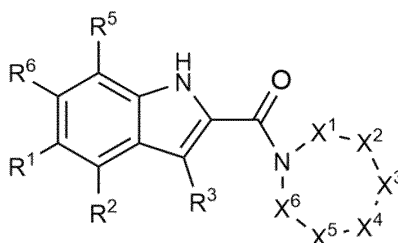
15 $N(H)(CH_3)$ or $N(CH_3)_2$;

with the proviso that when X^3 is $N(R^{16})$, then X^4 is $C(O)$, and

with the proviso that when X^4 is $C(O)$, then X^3 is $N(R^{16})$,

or a pharmaceutically acceptable salt thereof.

20 Thus, in said aspect, the current invention relates to a compound of Formula (XIII):



Formula (XIII)

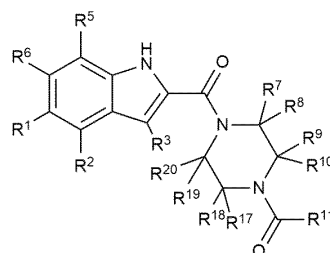
wherein R^1 , R^2 , R^3 , R^5 , R^6 , X^1 , X^2 , X^3 , X^4 , X^5 , and X^6 , are as defined herein, or a pharmaceutically acceptable salt thereof.

25

In one aspect, the present invention relates to a compound of Formula (I), wherein R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are as defined herein, or a pharmaceutically acceptable salt thereof.

30

In one aspect, the present invention relates to a compound of Formula (LVII),



Formula (LVII)

wherein

R¹ is halogen or H;

5 R² is halogen;

R³ is H or halogen;

R⁵ is H or halogen;

R⁶ is H or halogen;

wherein R⁹ and R¹¹ or R¹⁰ and R¹¹ are optionally joined together to form a ring together
10 with the intervening atoms;

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, or
15 when R⁹ is linked to R¹¹ to form a ring, then R⁹ is a bond or a C₁₋₃ alkanediyl optionally
substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

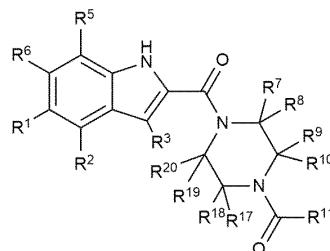
R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, or
when R¹⁰ is linked to R¹¹ to form a ring, then R¹⁰ is a bond or a C₁₋₃ alkanediyl
optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

20 R¹¹ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy,
pyridinyl, azetidiny, pyrrolidinyl, oxetanyl, and morpholinyl, wherein

- said C₁₋₃ alkyl is optionally substituted with one or more substituents
individually selected from the group consisting of NH₂, N(H)(CH₃),
N(CH₃)₂, C₁₋₃ alkoxy, morpholinyl, azetidiny, -O-azetidiny, and -O-
25 oxetanyl, and said azetidiny is optionally substituted with one or more
substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl;
- said C₃₋₅ cycloalkyl is optionally substituted with one or more
substituents selected from halogen, and C₁₋₃ alkoxy;
- said pyridinyl is optionally substituted with one or more NH₂;

- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of C₁₋₃ alkyl, halogen, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens;
 - said azetidiny optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkyl, and NH₂;
 - and
 - said morpholinyl is optionally substituted with C₁₋₃ alkyl;
- or when R¹¹ is linked to R⁹ or R¹⁰ to form a ring, then R¹¹ is -O-, -N(R²⁸)-, or C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;
- R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; and
- any two of R⁷, R⁸, R⁹, R¹⁰, R¹⁷, R¹⁸, R¹⁹, and R²⁰, are optionally linked together to form a ring; or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention relates to a compound of Formula (LVII),



Formula (LVII)

wherein

- R¹ is halogen or H;
- R² is halogen;
- R³ is halogen;
- R⁵, R⁶, R⁸, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H;
- wherein R⁹ and R¹¹ or R¹⁰ and R¹¹ are optionally joined together via R³³ to form a ring together with the intervening atoms;

R^7 is H or C_{1-3} alkyl optionally substituted with 1 to 3 F;

R^{10} is H, or when R^{10} is linked to R^{11} to form a ring, then R^{10} is a bond or a C_{1-3} alkanediyl;

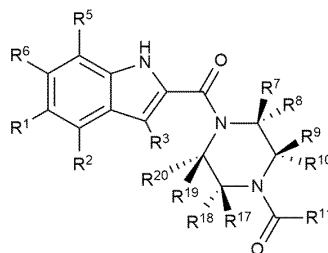
R^9 is H, or when R^9 is linked to R^{11} to form a ring, then R^9 is a bond or a C_{1-3} alkanediyl;

5 R^{11} is $-X^{13}-R^{33}$;

X^{13} is a bond, C_{1-3} alkanediyl optionally substituted with C_{1-3} alkyl, $-O-$, or C_{1-3} alkanediyl- $O-$; and

R^{33} is C_{1-3} alkyl, azetidiny, pyrrolidinyl, oxetanyl, and tetrahydrofuranyl, each of which is optionally substituted with one or more F; or when R^{11} is linked to R^9 or R^{10} via R^{33} to form a ring, then R^{33} is a bond or a C_{1-3} alkanediyl,
10 or a pharmaceutically acceptable salt thereof.

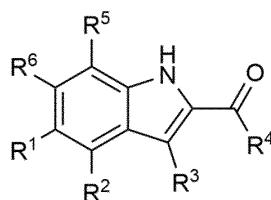
In some embodiments, the compound of Formula (LVII) is of Formula LVIIa):



15

Formula (LVIIa)

In one aspect, the present invention relates compound of Formula (I),



Formula (I)

20 wherein

R^1 is halogen or H;

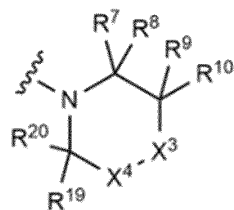
R^2 is halogen;

R^3 is H or halogen;

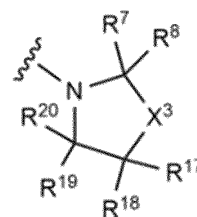
R^5 is H or halogen;

25 R^6 is H or halogen;

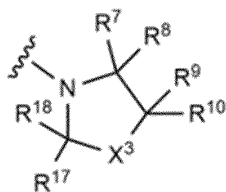
R^4 is of Formula (XXIV), Formula (XXV), Formula (XXVI) or Formula (XXVII):



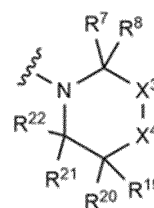
Formula (XXIV)



Formula (XXV)



Formula (XXVI)



Formula (XXVII)

wherein

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

5 X³ is N(C(O)R¹¹), C(R¹²)(C(O)R¹³), C(R¹⁴)(R¹⁵) or N(R¹⁶);

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

R¹¹ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidinyl and pyrrolidinyl, wherein

- 10
- said C₁₋₃ alkyl is optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, C₁₋₃ alkoxy, and morpholinyl,
 - said pyridinyl is optionally substituted with one or more NH₂;
 - said pyrrolidinyl is optionally substituted with one or more substituents
- 15
- individually selected from the group consisting of C₁₋₃ alkyl, halogen, C₁₋₃ alkoxy, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidinyl, and said azetidinyl is optionally substituted with one or more halogens, and
 - said azetidinyl optionally substituted with NH₂;

or R¹¹ is linked to R⁹ to form a ring and

- 20
- R⁹ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl,

- R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, and
- R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;
- 5 or R¹¹ is linked to R¹⁰ to form a ring and
- R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F,
- 10 R¹⁰ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, and
- R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;
- 15 R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein
- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
 - said azetidiny optionally substituted with NH₂;
- 20 R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),
- 25 wherein
- X⁷ is a bond or C₁₋₃ alkanediyl;
- R²⁴ is C₁₋₃ alkyl; and
- R²³ is H or C₁₋₃ alkyl, and R¹⁵ is H or C₁₋₃ alkyl,
- or R²³ is a bond or C₁₋₃ alkanediyl, and R¹⁵ is a bond or C₁₋₃ alkanediyl
- 30 and R²³ is linked to R¹⁵ to form a ring;
- or R¹⁴ is -X⁹C(O)X¹¹-, R¹⁵ is a bond or C₁₋₃ alkanediyl, and X¹¹ is linked to R¹⁵ to form a ring,
- wherein
- X⁹ is a bond or -N(R²⁹)-;
- 35 R²⁹ is C₁₋₃ alkyl;

X^{11} is -O-, C_{1-3} alkanediyl, or -N(R^{30})-; and

R^{30} is C_{1-3} alkyl;

R^{16} is H or C_{1-3} alkyl;

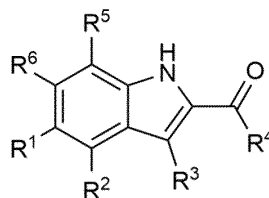
X^4 is $C(R^{17})(R^{18})$, O or $C(O)$;

- 5 R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{21} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 10 R^{22} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 and any two of R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , and R^{22} are optionally linked together to form a ring;
 or a pharmaceutically acceptable salt thereof.

- 15 In some embodiments, R^4 is of Formula (XXV), and X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$. In some embodiments, R^4 is of Formula (XXVI), and X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$. In some embodiments, R^4 is of Formula (XXVII), and X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$. In some embodiments, R^4 is of Formula (XXIV), and X^4 is $C(R^{17})(R^{18})$ or $C(O)$.

20

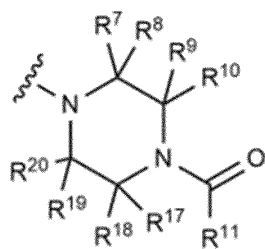
In one aspect, the present invention relates to a compound of Formula (I),



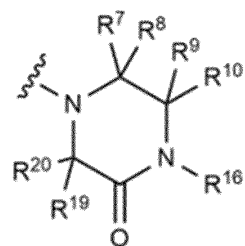
Formula (I)

wherein

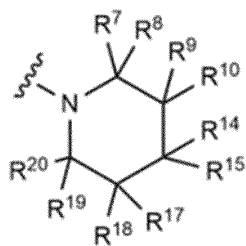
- 25 R^1 is halogen or H;
 R^2 is halogen;
 R^3 is H or halogen;
 R^5 is H or halogen;
 R^6 is H or halogen;
 30 R^4 is of Formula (III), Formula (XXXIV), Formula (XXXV), Formula (XXXVI), Formula (XXXVII), Formula (XXXVIII), Formula (XXXIX), or Formula (XL):



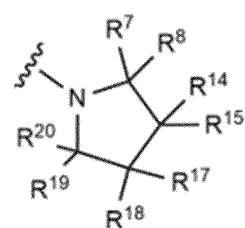
Formula (III)



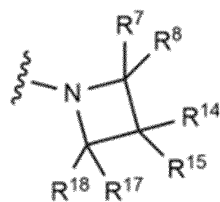
Formula (XXXIV)



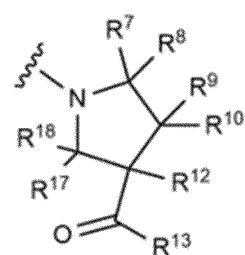
Formula (XXXV)



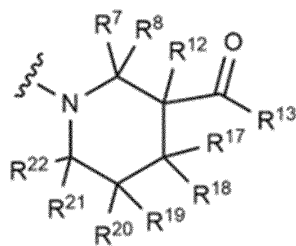
Formula (XXXVI)



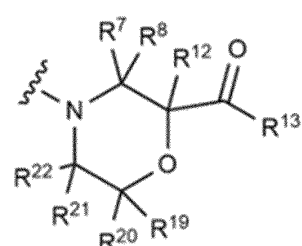
Formula (XXXVII)



Formula (XXXVIII)



Formula (XXXIX)



Formula (XL)

wherein

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

5 R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

R¹¹ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidiny and pyrrolidinyl, wherein

- 5 • said C₁₋₃ alkyl is optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, C₁₋₃ alkoxy, and morpholinyl,
- said pyridinyl is optionally substituted with one or more NH₂;
- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of C₁₋₃ alkyl, halogen, 10 C₁₋₃ alkoxy, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
- said azetidiny optionally substituted with NH₂;

or R¹¹ is linked to R⁹ to form a ring and

- 15 R⁹ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl,
- R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, and
- R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene 20 group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

or R¹¹ is linked to R¹⁰ to form a ring and

- R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F,
- 25 R¹⁰ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, and
- R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene 30 group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein

- 35 • said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂,

N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and

- said azetidiny optionally substituted with NH₂;

R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),

5

wherein

X⁷ is a bond or C₁₋₃ alkanediyl;

R²⁴ is C₁₋₃ alkyl; and

R²³ is H or C₁₋₃ alkyl, and R¹⁵ is H or C₁₋₃ alkyl,

or R²³ is a bond or C₁₋₃ alkanediyl, and R¹⁵ is a bond or C₁₋₃ alkanediyl

10

and R²³ is linked to R¹⁵ to form a ring;

or R¹⁴ is -X⁹C(O)X¹¹-, R¹⁵ is a bond or C₁₋₃ alkanediyl, and X¹¹ is linked to R¹⁵ to form a ring,

wherein

X⁹ is a bond or -N(R²⁹)-;

15

R²⁹ is C₁₋₃ alkyl;

X¹¹ is -O-, C₁₋₃ alkanediyl, or -N(R³⁰)-; and

R³⁰ is C₁₋₃ alkyl;

R¹⁶ is H or C₁₋₃ alkyl;

R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

20

R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R²¹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; and

R²² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

25

and any two of R⁷, R⁸, R⁹, R¹⁰, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, and R²² are optionally linked together to form a ring,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is a K_v1.3 potassium channel inhibitor.

30

In some embodiments, R¹ is halogen. In some embodiments, R¹ is Cl. In some embodiments, R¹ is F. In some embodiments, R¹ is H. In some embodiments, R² is Cl.

In some embodiments, R³ is halogen. In some embodiments, R³ is Cl. In some embodiments, R³ is F. In some embodiments, R³ is H. In some embodiments, R⁵ is H.

35

In some embodiments, R⁵ is halogen. In some embodiments, R⁵ is F. In some

embodiments, R^6 is H. In some embodiments, R^6 is halogen. In some embodiments, R^6 is F. In some embodiments, R^1 is F or Cl, R^2 is Cl, R^3 is Cl, R^5 is H, and R^6 is H. In some embodiments, R^5 is H and R^6 is H. In some embodiments, R^1 is halogen, and R^2 is halogen. In some embodiments, R^2 is halogen, and R^3 is halogen. In some

5 embodiments, R^1 is halogen, R^2 is halogen, and R^3 is halogen. In some embodiments, R^1 is halogen, R^2 is halogen, R^3 is halogen, R^5 is H, and R^6 is H. In some embodiments, R^1 is halogen, R^2 is halogen, R^3 is H, R^5 is H, and R^6 is H. In some embodiments, R^1 is halogen, R^2 is halogen, R^3 is H, R^5 is halogen, and R^6 is H. In some embodiments, R^1 is halogen, R^2 is halogen, R^3 is H, R^5 is H, and R^6 is halogen.

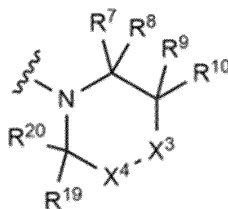
10 In some embodiments, R^1 is H, R^2 is halogen, R^3 is halogen, R^5 is H, and R^6 is H. In some embodiments, R^1 is F or Cl, R^2 is Cl or F, and R^3 is Cl or F. In some embodiments, R^1 is F, R^2 is Cl, and R^3 is Cl. In some embodiments, R^1 is F, R^2 is Cl, and R^3 is F. In some embodiments, R^1 is Cl, R^2 is Cl, and R^3 is Cl. In some embodiments, R^1 is Cl, R^2 is Cl, and R^3 is F. In some embodiments, R^1 is F or Cl, R^2 is Cl or F, and R^3 is Cl or F, R^5 is H, and R^6 is H. In some embodiments, R^1 is F, R^2 is Cl, R^3 is Cl, R^5 is H, and R^6 is H. In some embodiments, R^1 is F, R^2 is Cl, R^3 is F, R^5 is H, and R^6 is H. In some embodiments, R^1 is Cl, R^2 is Cl, R^3 is Cl, R^5 is H, and R^6 is H. In some embodiments, R^1 is Cl, R^2 is Cl, R^3 is F, R^5 is H, and R^6 is H. In some

15 embodiments, R^1 is Cl, R^2 is Cl, R^3 is H, R^5 is F, and R^6 is H. In some embodiments, R^1 is Cl, R^2 is Cl, R^3 is H, R^5 is H, and R^6 is F. In some embodiments, R^1 is Cl, R^2 is Cl, R^3 is H, R^5 is H, and R^6 is H. In some embodiments, R^1 is F, R^2 is Cl, R^3 is H, R^5 is H, and R^6 is H. In some embodiments, R^1 is H, R^2 is Cl, R^3 is Cl, R^5 is H, and R^6 is H.

In some embodiments, X^6 is a bond. In some embodiments, X^7 is a bond. In some

25 embodiments, X^7 is C_{1-3} alkanediyl. In some embodiments, X^7 is CH_2 .

In some embodiments, X^2 is $C(R^9)(R^{10})$; X^5 is $C(R^{19})(R^{20})$; and X^6 is a bond. In some embodiments, R^4 is of Formula (XXIV):

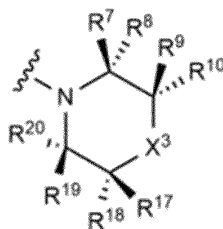


30

Formula (XXIV)

wherein R^7 , R^8 , R^9 , R^{10} , R^{19} , R^{20} , X^3 , and X^4 are as defined herein. In some embodiments, R^4 is of Formula (XXIV), wherein R^7 , R^8 , R^9 , R^{10} , R^{19} , R^{20} , and X^3 are as defined herein, and X^4 is $C(R^{17})(R^{18})$ or $C(O)$. In some embodiments, X^2 is $C(R^9)(R^{10})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; and X^6 is a bond. In some embodiments, R^4 is of

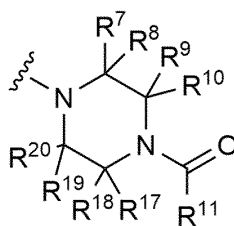
5 Formula (XXVIII):



Formula (XXVIII)

wherein R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , R^{20} , and X^3 are as defined herein.

10 In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; and X^6 is a bond. In some embodiments, R^4 is of Formula (III):

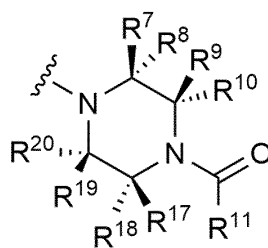


Formula (III)

wherein R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{17} , R^{18} , R^{19} , and R^{20} are as defined herein.

15

In some embodiments, R^4 is of Formula (IV):

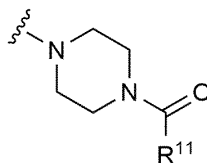


Formula (IV)

wherein R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{17} , R^{18} , R^{19} , and R^{20} are as defined herein.

20

In some embodiments, R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , and R^{20} are H. In some embodiments, R^4 is of Formula (V):

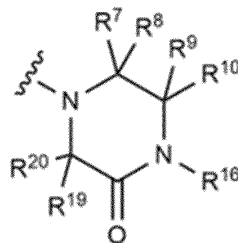


Formula (V)

5 wherein R^{11} is as defined herein.

In some embodiments, R^7 is C_{1-3} alkyl, such as CH_3 , and R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , and R^{20} are H. In some embodiments, R^8 is C_{1-3} alkyl, such as CH_3 , and R^7 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , and R^{20} are H. In some embodiments, R^7 and R^8 are C_{1-3} alkyl, such as CH_3 ,
 10 and R^9 , R^{10} , R^{17} , R^{18} , R^{19} , and R^{20} are H. In some embodiments, R^{17} is C_{1-3} alkyl, such as CH_3 , and R^7 , R^8 , R^9 , R^{10} , R^{18} , R^{19} , and R^{20} are H. In some embodiments, R^{18} is C_{1-3} alkyl, such as CH_3 , and R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{19} , and R^{20} are H. In some embodiments, R^{17} and R^{18} are C_{1-3} alkyl, such as CH_3 , and R^7 , R^8 , R^9 , R^{10} , R^{19} , and R^{20} are H. In some embodiments, R^8 and R^{17} are C_{1-3} alkyl, such as CH_3 , and R^7 , R^9 , R^{10} , R^{18} , R^{19} ,
 15 and R^{20} are H. In some embodiments, when R^{11} is linked to R^9 or R^{10} to form a ring, then R^9 or R^{10} is linked to R^{33} of R^{11} , i.e. R^9 or R^{10} and R^{11} are joined together via R^{33} to form a ring together with the intervening atoms. In some embodiments, R^9 is linked to R^{33} to form a ring. In some embodiments, R^{10} is linked to R^{33} to form a ring. In some embodiments, R^{11} is C_{1-3} alkyl or C_{1-3} alkoxy; R^9 is H; R^{10} is a bond; and R^{11} is linked to
 20 R^{10} to form a ring. In some embodiments, R^{11} is C_{1-3} alkyl or C_{1-3} alkoxy; R^{10} is H; R^9 is a bond; and R^{11} is linked to R^9 to form a ring.

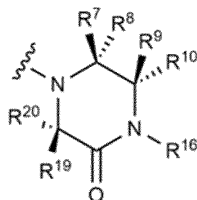
In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $N(R^{16})$; X^4 is $C(O)$; X^5 is $C(R^{19})(R^{20})$; and X^6 is a bond. In some embodiments, R^4 is of Formula (XXXIV):



Formula (XXXIV)

25

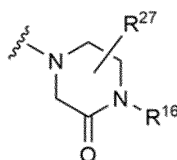
wherein R^7 , R^8 , R^9 , R^{10} , R^{16} , R^{19} , and R^{20} are as defined herein. In some embodiments, R^4 is of Formula (XLI):



Formula (XLI)

5 wherein R^7 , R^8 , R^9 , R^{10} , R^{16} , R^{19} , and R^{20} are as defined herein.

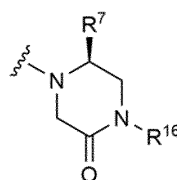
In some embodiments, R^4 is of Formula (VI):



Formula (VI)

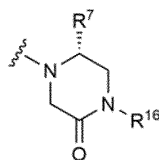
10 wherein R^{16} is H or C_{1-3} alkyl; and R^{27} is H or C_{1-3} alkyl.

In some embodiments, R^4 is of Formula (VIA-1):



Formula (VIA-1)

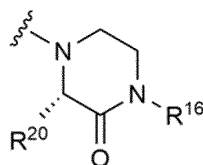
15 wherein R^{16} is H or C_{1-3} alkyl; and R^{27} is H or C_{1-3} alkyl. In some embodiments, R^4 is of Formula (VIA-2):



Formula (VIA-2)

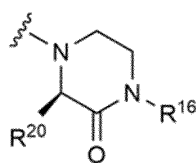
wherein R^{16} is H or C_{1-3} alkyl; and R^{27} is H or C_{1-3} alkyl.

In some embodiments, R⁴ is of Formula (VIB-1):



Formula (VIB-1)

wherein R¹⁶ is H or C₁₋₃ alkyl; and R²⁷ is H or C₁₋₃ alkyl. In some embodiments, R⁴ is of Formula (VIB-2):



Formula (VIB-2)

wherein R¹⁶ is H or C₁₋₃ alkyl; and R²⁷ is H or C₁₋₃ alkyl.

- 10 In some embodiments, R⁷ and R¹⁹ are linked together to form a bridged bicyclic ring. In some embodiments, R⁸ and R²⁰ are linked together to form a bridged bicyclic ring. In some embodiments, R⁹ and R¹⁷ are linked together to form a bridged bicyclic ring. In some embodiments, R¹⁰ and R¹⁸ are linked together to form a bridged bicyclic ring. In some embodiments, R⁹ and R¹⁹ are linked together to form a bridged bicyclic ring. In some embodiments, R¹⁰ and R²⁰ are linked together to form a bridged bicyclic ring. In some embodiments, R⁷ and R¹⁷ are linked together to form a bridged bicyclic ring. In some embodiments, R⁸ and R¹⁸ are linked together to form a bridged bicyclic ring.

- 20 In some embodiments, X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R⁷ and R¹⁹ are linked together to form a bridged bicyclic ring. In some embodiments, X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R⁸ and R²⁰ are linked together to form a bridged bicyclic ring or a pharmaceutically acceptable salt thereof.

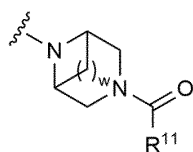
- 25 In some embodiments, X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R⁹ and R¹⁷ are linked together to form a bridged bicyclic ring or a pharmaceutically acceptable salt thereof. In some embodiments, X² is

$C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is a bond; and R^{10} and R^{18} are linked together to form a bridged bicyclic ring or a pharmaceutically acceptable salt thereof.

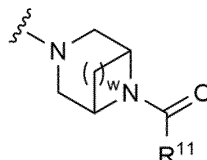
5 In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is a bond; and R^9 and R^{19} are linked together to form a bridged bicyclic ring or a pharmaceutically acceptable salt thereof. In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is a bond; and R^{10} and R^{20} are linked together to form a bridged bicyclic ring or a pharmaceutically acceptable salt thereof.

In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is a bond; and R^7 and R^{17} are linked together to form a bridged bicyclic ring or a pharmaceutically acceptable salt thereof. In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is a bond; and R^8 and R^{18} are linked together to form a bridged bicyclic ring or a pharmaceutically acceptable salt thereof.

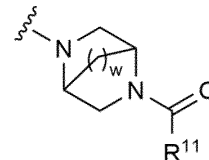
In some embodiments, R^4 is of Formula (VII), Formula (VIII) or Formula (IX):



Formula (VII)



Formula (VIII)



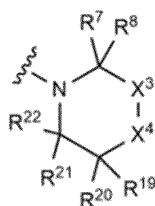
Formula (IX)

20 wherein R^{11} is as defined herein and w is 1 or 2.

In some embodiments, R^4 is of Formula (VII). In some embodiments, R^4 is of Formula (VII) and w is 1. In some embodiments, R^4 is of Formula (VII) and w is 2. In some embodiments, Formula (VIII). In some embodiments, R^4 is of Formula (VIII) and w is 1. In some embodiments, R^4 is of Formula (VIII) and w is 2. In some embodiments, R^4 is of Formula (IX). In some embodiments, R^4 is of Formula (IX) and w is 2.

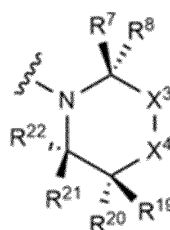
In some embodiments, X^2 is a bond; X^5 is $C(R^{19})(R^{20})$; and X^6 is $C(R^{21})(R^{22})$.

In some embodiments, R^4 is of Formula (XXVII):



Formula (XXVII)

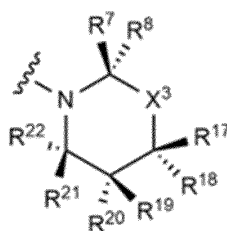
wherein R^7 , R^8 , R^{19} , R^{20} , R^{21} , R^{22} , X^3 and X^4 are as defined herein. In some
embodiments, R^4 is of Formula (XXVII), wherein R^7 , R^8 , R^{19} , R^{20} , R^{21} , R^{22} , X^4 are as
5 defined herein, and X^3 is $C(R^{12})(C(O)R^{13})$, or $C(R^{14})(R^{15})$. In some embodiments, R^4 is
of Formula (XXXI):



Formula (XXXI)

wherein R^7 , R^8 , R^{19} , R^{20} , R^{21} , R^{22} , X^3 and X^4 are as defined herein. In some
10 embodiments, R^4 is of Formula (XXXI), wherein R^7 , R^8 , R^{19} , R^{20} , R^{21} , R^{22} , X^4 are as
defined herein, and X^3 is $C(R^{12})(C(O)R^{13})$, or $C(R^{14})(R^{15})$.

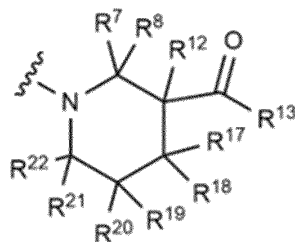
In some embodiments, X^2 is a bond; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; and X^6 is
 $C(R^{21})(R^{22})$. In some embodiments, R^4 is of Formula (XXXII):



Formula (XXXII)

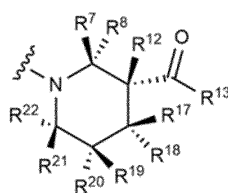
wherein R^7 , R^8 , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , and X^3 are as defined herein.

In some embodiments, X^2 is a bond; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^5 is
20 $C(R^{19})(R^{20})$; and X^6 is $C(R^{21})(R^{22})$. In some embodiments, R^4 is of Formula (XXXIX):



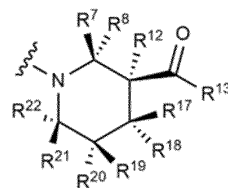
Formula (XXXIX)

wherein R^7 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{17} , and R^{18} are as defined herein. In some embodiments, R^4 is of Formula (XLVII):



Formula (XLVII)

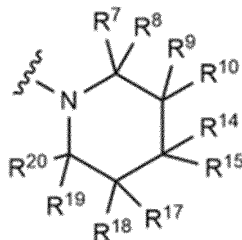
wherein R^7 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{17} , and R^{18} are as defined herein. In some embodiments, R^4 is of Formula (XLVIII):



Formula (XLVIII)

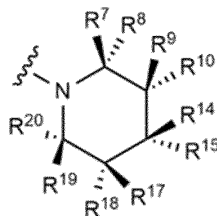
wherein R^7 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{17} , and R^{18} are as defined herein.

In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{14})(R^{15})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; and X^6 is a bond. In some embodiments, R^4 is of Formula (XXXV):



Formula (XXXV)

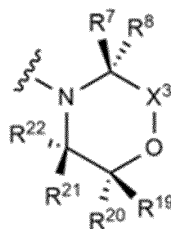
wherein R^7 , R^8 , R^9 , R^{10} , R^{14} , R^{15} , R^{17} , R^{18} , R^{19} , and R^{20} are as defined herein. In some embodiments, R^4 is of Formula (XLII):



Formula (XLII)

5 wherein R^7 , R^8 , R^9 , R^{10} , R^{14} , R^{15} , R^{17} , R^{18} , R^{19} , and R^{20} are as defined herein.

In some embodiments, X^2 is a bond; X^4 is O; X^5 is $C(R^{19})(R^{20})$; and X^6 is $C(R^{21})(R^{22})$. In some embodiments, R^4 is of Formula (XXXIII):



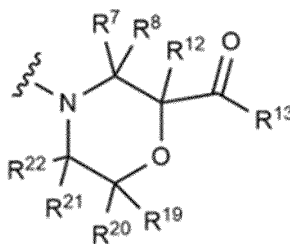
Formula (XXXIII)

10

wherein R^7 , R^8 , R^{19} , R^{20} , R^{21} , R^{22} , and X^3 are as defined herein. In some embodiments, R^4 is of Formula (XXXIII), wherein R^7 , R^8 , R^{19} , R^{20} , R^{21} , R^{22} are as defined herein, and X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$.

15

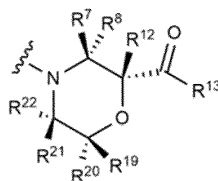
In some embodiments, X^2 is a bond; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is O; X^5 is $C(R^{19})(R^{20})$; and X^6 is $C(R^{21})(R^{22})$. In some embodiments, R^4 is of Formula (XL):



Formula (XL)

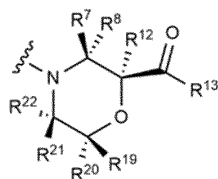
wherein R^7 , R^8 , R^{12} , R^{13} , R^{19} , R^{20} , R^{21} , and R^{22} are as defined herein. In some embodiments, R^4 is of Formula (XLIX):

20



Formula (XLIX)

wherein R^7 , R^8 , R^{12} , R^{13} , R^{19} , R^{20} , R^{21} , and R^{22} are as defined herein. In some embodiments, R^4 is of Formula (L):



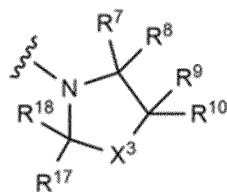
5

Formula (L)

wherein R^7 , R^8 , R^{12} , R^{13} , R^{19} , R^{20} , R^{21} , and R^{22} are as defined herein.

In some embodiments, X^2 is $C(R^9)(R^{10})$; X^4 is $C(R^{17})(R^{18})$; X^5 is a bond; and X^6 is bond.

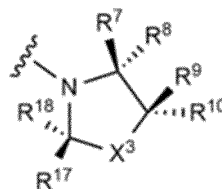
10 In some embodiments, R^4 is of Formula (XXVI):



Formula (XXVI)

wherein R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , and X^3 are as defined herein. In some embodiments, R^4 is of Formula (XXVI), wherein R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} are as defined herein, and X^3

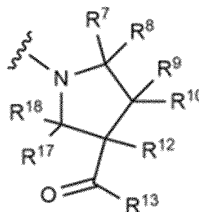
15 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$. In some embodiments, R^4 is of Formula (XXX):



Formula (XXX)

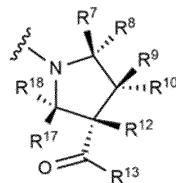
wherein R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , and X^3 are as defined herein. In some embodiments, R^4 is of Formula (XXX), wherein R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} are as defined herein, and X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$.

- 5 In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^5 is a bond; and X^6 is bond. In some embodiments, R^4 is of Formula (XXXVIII):



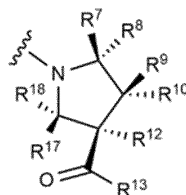
Formula (XXXVIII)

- 10 wherein R^7 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{17} , and R^{18} are as defined herein. In some embodiments, R^4 is of Formula (XLV):



Formula (XLV)

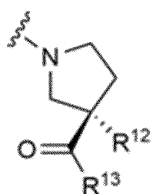
wherein R^7 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{17} , and R^{18} are as defined herein. In some embodiments, R^4 is of Formula (XLVI):



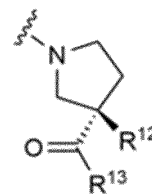
15

Formula (XLVI)

wherein R^7 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{17} , and R^{18} are as defined herein. In some embodiments, R^4 is of Formula (Xa) or Formula (Xb):



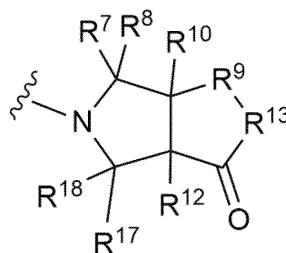
Formula (Xa)



Formula (Xb)

wherein R^{12} and R^{13} are as defined herein.

In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; and R^{13} is linked to R^9 to form a ring together with the intervening atoms. In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; and R^{13} is linked to R^9 to form a ring together with the intervening atoms. In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^6 is a bond; and R^{13} is linked to R^9 to form a ring together with the intervening atoms. In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^5 is a bond; X^6 is a bond; and R^{13} is linked to R^9 to form a ring together with the intervening atoms. In some embodiments, R^4 is of Formula (LIII):

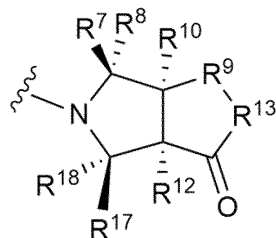


Formula (LIII)

wherein

- 15 R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^9 is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;
 R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 20 R^{12} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{13} is $-N(R^{28})-$, wherein R^{28} is H or C_{1-3} alkyl;
 R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F; and
 R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F.

In some embodiments, R⁴ is of Formula (LIIIa):

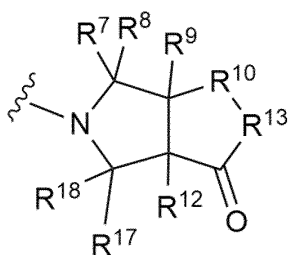


Formula (LIIIa)

- 5 wherein R⁷, R⁸, R⁹, R¹⁰, R¹², R¹³, R¹⁷, and R¹⁸ are as defined herein. In some embodiments, the moiety of Formula (LIII) is of Formula (LIIIa).

- In some embodiments, R⁴ is of Formula (LIII) or Formula (LIIIa) and R⁷, R⁸, R¹⁰, R¹², R¹⁷, and R¹⁸ are H. In some embodiments, R⁴ is of Formula (LIII) or Formula (LIIIa) and R¹³ is -N(CH₃)-. In some embodiments, R⁴ is of Formula (LIII) or Formula (LIIIa) and R⁹ is -CH₂-.

- In some embodiments, X² is C(R⁹)(R¹⁰); X³ is C(R¹²)(C(O)R¹³); and R¹³ is linked to R¹⁰ to form a ring together with the intervening atoms. In some embodiments, X² is C(R⁹)(R¹⁰); X³ is C(R¹²)(C(O)R¹³); X⁴ is C(R¹⁷)(R¹⁸); and R¹³ is linked to R¹⁰ to form a ring together with the intervening atoms. In some embodiments, X² is C(R⁹)(R¹⁰); X³ is C(R¹²)(C(O)R¹³); X⁴ is C(R¹⁷)(R¹⁸); X⁶ is a bond; and R¹³ is linked to R¹⁰ to form a ring together with the intervening atoms. In some embodiments, X² is C(R⁹)(R¹⁰); X³ is C(R¹²)(C(O)R¹³); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is a bond; X⁶ is a bond; and R¹³ is linked to R¹⁰ to form a ring together with the intervening atoms. In some embodiments, R⁴ is of Formula (LIV):



Formula (LIV)

wherein

- 25 R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^9 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{10} is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

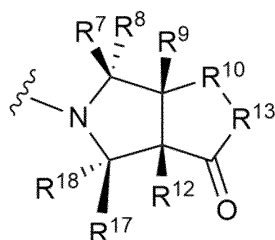
5 R^{12} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{13} is $-N(R^{28})-$, wherein R^{28} is H or C_{1-3} alkyl;

R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F; and

R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F.

10 In some embodiments, R^4 is of Formula (LIVa):



Formula (LIVa)

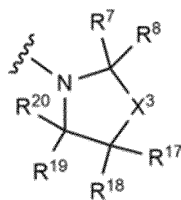
wherein R^7 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{17} , and R^{18} are as defined herein. In some embodiments, the moiety of Formula (LIV) is of Formula (LIVa).

15

In some embodiments, R^4 is of Formula (LIV) or Formula (LIVa) and R^7 , R^8 , R^9 , R^{12} , R^{17} , and R^{18} are H. In some embodiments, R^4 is of Formula (LIV) or Formula (LIVa) and R^{13} is $-N(CH_3)-$. In some embodiments, R^4 is of Formula (LIV) or Formula (LIVa) and R^{10} is $-CH_2-$.

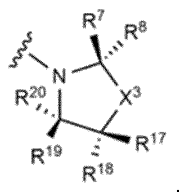
20

In some embodiments, X^2 is a bond; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; and X^6 is bond. In some embodiments, R^4 is of Formula (XXV):



Formula (XXV)

wherein R^7 , R^8 , R^{17} , R^{18} , R^{19} , R^{20} , and X^3 are as defined herein. In some embodiments, R^4 is of Formula (XXV), wherein R^7 , R^8 , R^{17} , R^{18} , R^{19} , R^{20} are as defined herein, and X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$. In some embodiments, R^4 is of Formula (XXIX):

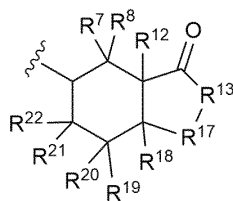


5

Formula (XXIX)

wherein R^7 , R^8 , R^{17} , R^{18} , R^{19} , R^{20} , and X^3 are as defined herein. In some embodiments, R^4 is of Formula (XXIX), wherein R^7 , R^8 , R^{17} , R^{18} , R^{19} , R^{20} are as defined herein, and X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$.

- 10 In some embodiments, X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; and R^{13} is linked to R^{17} to form a ring together with the intervening atoms. In some embodiments, X^2 is a bond; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; and R^{13} is linked to R^{17} to form a ring together with the intervening atoms. In some embodiments, X^2 is a bond; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is $C(R^{21})(R^{22})$; and R^{13} is linked to R^{17} to form a ring together with the intervening atoms. In some embodiments, R^4 is of Formula (LV):
- 15



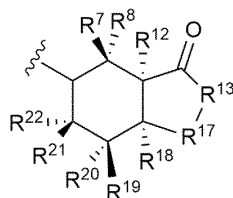
Formula (LV)

wherein

- R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- 20 R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R^{12} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R^{13} is $-N(R^{28})-$, wherein R^{28} is H or C_{1-3} alkyl;
- R^{17} is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;
- 25 R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R²¹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; and
 R²² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F.

In some embodiments, R⁴ is of Formula (LVa):



5

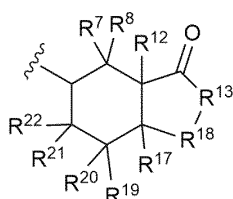
Formula (LVa)

wherein R⁷, R⁸, R¹², R¹³, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹ and R²² are as defined herein. In some embodiments, the moiety of formula (LV) is of Formula (LVa).

10 In some embodiments, R⁴ is of Formula (LV) or Formula (LVa) and R⁷, R⁸, R¹², R¹⁸, R¹⁹, R²⁰, R²¹, and R²² are H. In some embodiments, R⁴ is of Formula (LV) or Formula (LVa) and R¹³ is -N(CH₃)-. In some embodiments, R⁴ is of Formula (LV) or Formula (LVa) and R¹⁷ is -CH₂-.

15 In some embodiments, X³ is C(R¹²)(C(O)R¹³); X⁴ is C(R¹⁷)(R¹⁸); and R¹³ is linked to R¹⁸ to form a ring together with the intervening atoms. In some embodiments, X² is a bond; X³ is C(R¹²)(C(O)R¹³); X⁴ is C(R¹⁷)(R¹⁸); and R¹³ is linked to R¹⁸ to form a ring together with the intervening atoms. In some embodiments, X² is a bond; X³ is C(R¹²)(C(O)R¹³); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is C(R²¹)(R²²); and R¹³ is linked to R¹⁸ to form a ring together with the intervening atoms. In some embodiments, R⁴ is of Formula (LVI):

20



Formula (LVI)

wherein

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

25 R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹³ is -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

R¹⁷ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

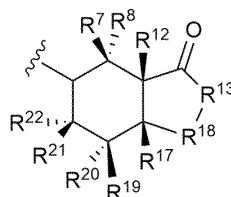
R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

5 R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R²¹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; and

R²² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F.

In some embodiments, R⁴ is of Formula (LVla):



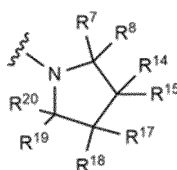
10

Formula (LVla)

wherein R⁷, R⁸, R¹², R¹³, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹ and R²² are as defined herein. In some embodiments, the moiety of formula (LV) is of Formula (LVb).

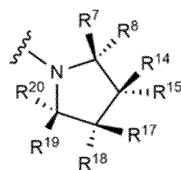
15 In some embodiments, R⁴ is of Formula (LVI) or Formula (LVla) and R⁷, R⁸, R¹², R¹⁸, R¹⁹, R²⁰, R²¹, and R²² are H. In some embodiments, R⁴ is of Formula (LVI) or Formula (LVla) and R¹³ is -N(CH₃)-. In some embodiments, R⁴ is of Formula (LVI) or Formula (LVla) and R¹⁷ is -CH₂-.

20 In some embodiments, X² is a bond; X³ is C(R¹⁴)(R¹⁵); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); and X⁶ is bond. In some embodiments, R⁴ is of Formula (XXXVI):



Formula (XXXVI)

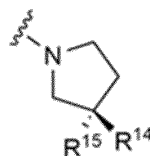
wherein R⁷, R⁸, R¹⁴, R¹⁵, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are as defined herein. In some
25 embodiments, R⁴ is of Formula (XLIII):



Formula (XLIII)

wherein R^7 , R^8 , R^{14} , R^{15} , R^{17} , R^{18} , R^{19} , and R^{20} are as defined herein.

In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{14})(R^{15})$; X^4 is $C(R^{17})(R^{18})$; X^5 is a bond; and X^6 is bond. In some embodiments, R^4 is of Formula (XI):



Formula (XI)

wherein

R^{14} is $-X^7N(R^{23})(C(O)R^{24})$;

10 X^7 is a bond or CH_2 ;

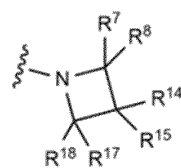
R^{23} is H or C_{1-3} alkyl, or R^{23} is a bond and R^{15} is C_{1-3} alkanediyl and R^{23} is linked to R^{15} to form a 4 or 5 membered ring;

R^{24} is C_{1-3} alkyl; and

R^{15} is H or C_{1-3} alkyl.

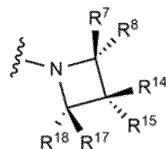
15

In some embodiments, X^2 is a bond; X^3 is $C(R^{14})(R^{15})$; X^4 is $C(R^{17})(R^{18})$; X^5 is a bond; and X^6 is bond. In some embodiments, R^4 is of Formula (XXXVII):



Formula (XXXVII)

20 wherein R^7 , R^8 , R^{14} , R^{15} , R^{17} , and R^{18} are as defined herein. In some embodiments, R^4 is of Formula (XLIV):



Formula (XLIV)

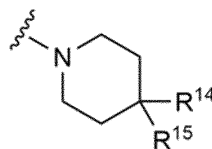
wherein R^7 , R^8 , R^{14} , R^{15} , R^{17} , and R^{18} are as defined herein.

- 5 In some embodiments, R^{14} and R^{15} are linked together to form a 5 membered ring. In some embodiments, R^{14} and R^{15} are linked together to form a 4 membered ring.

In some embodiments, R^{14} and R^{15} are linked together to form a ring, and wherein R^{14} is $-X^9C(O)X^{11}-$, wherein

- 10 X^9 is a bond or $-N(R^{29})-$;
 R^{29} is C_{1-3} alkyl;
 X^{11} is $-O-$, $-CH_2-$, or $-N(R^{30})-$; and
 R^{30} is C_{1-3} alkyl; and
 R^{15} is a bond or C_{1-3} alkanediyl.

- 15 In some embodiments, R^4 is of Formula (XVI):

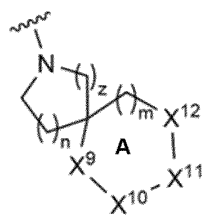


Formula (XVI)

wherein

- 20 R^{14} and R^{15} are linked together to form a ring;
 R^{14} is $-X^9C(O)X^{11}-$;
 X^9 is a bond or $-N(R^{29})-$;
 R^{29} is C_{1-3} alkyl;
 X^{11} is $-O-$, $-CH_2-$, or $-N(R^{30})-$;
25 R^{30} is C_{1-3} alkyl; and
 R^{15} is a bond or C_{1-3} alkanediyl.

In some embodiments, R^4 is of Formula (XIX):



Formula (XIX)

wherein

X⁹ is a bond or -N(R²⁹)-;

5 R²⁹ is C₁₋₃ alkyl;

X¹⁰ is -C(O)-, -CH₂-, or a bond;

X¹¹ is -O-, -CH₂-, or -N(R³⁰)-;

R³⁰ is C₁₋₃ alkyl;

X¹² is -N(C(O)R²⁴)- or a bond;

10 m is 1 or 2;

n is 0 or 1; and

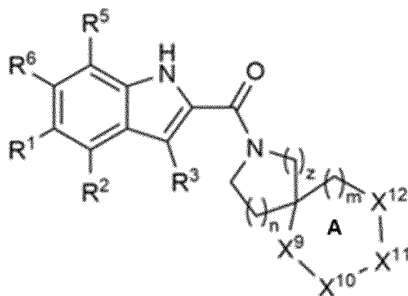
z is 1 or 2;

with the proviso that when X¹⁰ is -C(O)-, then X¹² is a bond;

with the proviso that when X¹⁰ is -CH₂- or a bond, then X¹² is -N(C(O)R²⁴)-; and with the

15 proviso that ring A is a 4 to 6 membered ring.

In one aspect, the present invention relates to a compound of Formula (XXII):

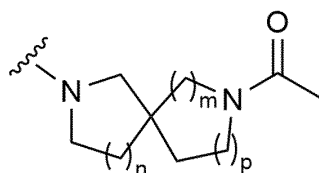


Formula (XXII)

20 wherein R¹, R², R³, R⁵, R⁶, X⁹, X¹⁰, X¹¹, X¹², m, n, and z are as defined herein.

In some embodiments, X² is C(R⁹)(R¹⁰); X³ is C(R¹⁴)(R¹⁵); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); and X⁶ is bond and R¹⁴ and R¹⁵ are linked together to form a ring.

In some embodiments, X^7 is a bond; R^{23} is H or C_{1-3} alkyl; R^{24} is C_{1-3} alkyl; and R^{15} is H or C_{1-3} alkyl. In some embodiments, X^2 is a bond; X^3 is $C(R^{14})(R^{15})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; and X^6 is bond. In some embodiments, R^{14} and R^{15} are linked together to form a ring. In some embodiments, R^{23} is a bond and R^{15} is C_{1-3} alkanediyl and R^{23} is linked to R^{15} to form a 4 or 5 membered ring. In some embodiments, R^4 is of Formula (XII):

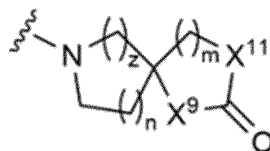


Formula (XII)

wherein

- 10 m is 0 or 1;
 n is 0 or 1; and
 p is 0, 1 or 2,
 or a pharmaceutically acceptable salt thereof.

- 15 In some embodiments, R^4 is of Formula (XVII):

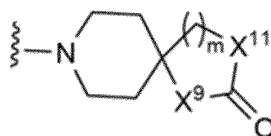


Formula (XVII)

wherein

- X^9 is a bond or $-N(R^{29})-$;
 20 R^{29} is C_{1-3} alkyl;
 X^{11} is $-O-$, $-CH_2-$, or $-N(R^{30})-$;
 R^{30} is C_{1-3} alkyl;
 m is 1 or 2;
 n is 0 or 1; and
 25 z is 1 or 2.

In some embodiments, R^4 is of Formula (XVIII):



Formula (XVIII)

wherein

X^9 is a bond or $-N(R^{29})-$;

5 R^{29} is C_{1-3} alkyl;

X^{11} is $-O-$, $-CH_2-$, or $-N(R^{30})-$;

R^{30} is C_{1-3} alkyl; and

m is 1 or 2.

10 In some embodiments, X^9 is a bond. In some embodiments, X^9 is $-N(R^{29})-$. In some embodiments, R^{29} is CH_3 .

In some embodiments, X^{11} is $-O-$. In some embodiments, X^{11} is C_{1-3} alkanediyl. In some embodiments, X^{11} is $-CH_2-$. In some embodiments, X^{11} is $-N(R^{30})-$. In some

15 embodiments, R^{30} is CH_3 .

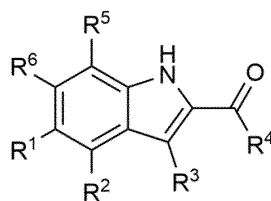
In some embodiments, R^4 is of Formula (XII) and with the proviso that when m is 0 then p is 1 or 2. In some embodiments, R^4 is of Formula (XII) and with the proviso that when p is 2, then m is 0. In some embodiments, R^4 is of Formula (XII), with the proviso that

20 when m is 0 then p is 1 or 2 and with the proviso that when p is 2, then m is 0. In some embodiments, R^4 is of Formula (XII), wherein m is 0 or 1; n is 0 or 1; and p is 0, 1 or 2, with the proviso that when m is 0 then p is 1 or 2, and with the proviso that when p is 2, then m is 0,.

25 In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, m is 0 and p is 1. In some embodiments, m is 1 and p is 1. In some embodiments, m is 1 and p is 0. In some embodiments, m is 0 and p is 2. In some embodiments, n is 0. In some embodiments, n is 1. In some

30 embodiments, z is 1. In some embodiments, z is 2. In some embodiments, n is 1 and z is 1. In some embodiments, n is 1 and z is 2. In some embodiments, n is 0 and z is 2.

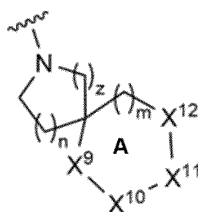
In one aspect, the present invention relates to a compound of Formula (I),



Formula (I)

wherein

- 5 R^1 is halogen or H;
 R^2 is halogen;
 R^3 is H or halogen;
 R^5 is H or halogen;
 R^6 is H or halogen;
 10 R^4 is of Formula (XIX):



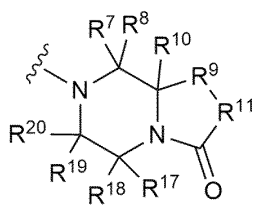
Formula (XIX)

wherein

- X^9 is a bond or $-N(R^{29})-$;
 15 R^{29} is C_{1-3} alkyl;
 X^{10} is $-C(O)-$, $-CH_2-$, or a bond;
 X^{11} is $-O-$, $-CH_2-$, or $-N(R^{30})-$;
 R^{30} is C_{1-3} alkyl;
 X^{12} is $-N(C(O)R^{24})-$ or a bond;
 20 m is 1 or 2;
 n is 0 or 1; and
 z is 1 or 2;
 with the proviso that when X^{10} is $-C(O)-$, then X^{12} is a bond;
 with the proviso that when X^{10} is $-CH_2-$ or a bond, then X^{12} is $-N(C(O)R^{24})-$; and with the
 25 proviso that ring A is a 4 to 6 membered ring, or a pharmaceutically acceptable salt
 thereof.

In some embodiments, ring A is a 4 membered ring. In some embodiments, ring A is a 5 membered ring.

In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; and R^{11} is linked to R^9 to form a ring together with the intervening atoms. In some embodiments, R^{11} is linked to R^9 to form a 6-membered ring. In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; and R^{11} is linked to R^9 to form a ring together with the intervening atoms. In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is a bond; and R^{11} is linked to R^9 to form a ring together with the intervening atoms. In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is a bond; and R^{11} is linked to R^9 to form a 6-membered ring. In some embodiments, R^4 is of Formula (LI):



Formula (LI)

wherein

R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

R^9 is a bond, $-C(O)-$, or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{11} is $-O-$, $-N(R^{28})-$, or C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl, wherein one methylene group of the C_{1-3} alkanediyl is optionally replaced by $-O-$ or $-N(R^{28})-$, wherein R^{28} is H or C_{1-3} alkyl;

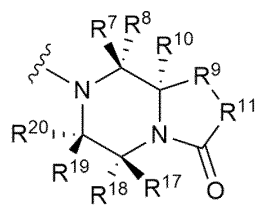
R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F; and

R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F.

In some embodiments, R^4 is of Formula (LIa):



Formula (Lia)

wherein R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{17} , R^{18} , R^{19} , and R^{20} are as defined herein. In some embodiments, the moiety of Formula (LI) is of Formula (Lia).

5

In some embodiments, R^4 is of Formula (LI) or Formula (Lia) and R^7 , R^8 , R^{10} , R^{17} , R^{18} , R^{19} , and R^{20} are H. In some embodiments, R^4 is of Formula (LI) or Formula (Lia) and R^{11} is -O-. In some embodiments, R^4 is of Formula (LI) or Formula (Lia) and R^{11} is -CH₂-. In some embodiments, R^4 is of Formula (LI) or Formula (Lia) and R^{11} is -CH₂CH₂-

10

In some embodiments, R^{11} is linked to R^9 to form a ring and

R^9 is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 F,

R^{10} is H, and

15

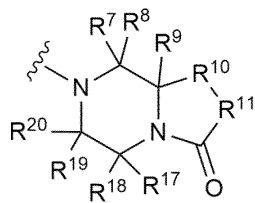
R^{11} is C₁₋₃ alkanediyl wherein one methylene group is optionally replaced by -O- or -N(R^{28})-, wherein R^{28} is H or C₁₋₃ alkyl.

In some embodiments, R^{11} is linked to R^9 to form a 5-membered ring.

20

In some embodiments, X^2 is C(R^9)(R^{10}); X^3 is N(C(O) R^{11}); and R^{11} is linked to R^{10} to form a ring together with the intervening atoms. In some embodiments, R^{11} is linked to R^{10} to form a 6-membered ring. In some embodiments, X^2 is C(R^9)(R^{10}); X^3 is N(C(O) R^{11}); X^4 is C(R^{17})(R^{18}); and R^{11} is linked to R^{10} to form a ring together with the intervening atoms. In some embodiments, X^2 is C(R^9)(R^{10}); X^3 is N(C(O) R^{11}); X^4 is C(R^{17})(R^{18}); X^5 is C(R^{19})(R^{20}); X^6 is a bond; and R^{11} is linked to R^{10} to form a ring together with the intervening atoms. In some embodiments, X^2 is C(R^9)(R^{10}); X^3 is N(C(O) R^{11}); X^4 is C(R^{17})(R^{18}); X^5 is C(R^{19})(R^{20}); X^6 is a bond; and R^{11} is linked to R^{10} to form a 6-membered ring. In some embodiments, R^4 is of Formula (LII):

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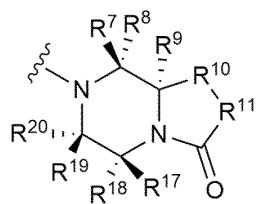


Formula (LII)

wherein

- 5 R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen, such as F;
- R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen, such as F;
- R¹⁰ is a bond, -C(O)-, or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;
- 10 R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R¹¹ is -O-, -N(R²⁸)-, or C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;
- 15 R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; and
- R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F.

In some embodiments, R⁴ is of Formula (LIIa):



Formula (LIIa)

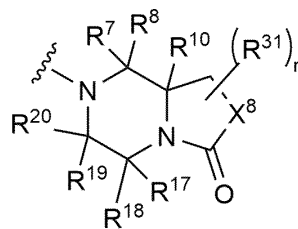
wherein R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are as defined herein. In some embodiments, the moiety of Formula (LII) is of Formula (LIIa).

- 25 In some embodiments, R⁴ is of Formula (LII) or Formula (LIIa) and R⁷, R⁸, R¹⁰, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H. In some embodiments, R⁴ is of Formula (LII) or Formula (LIIa) and

R¹¹ is -O-. In some embodiments, R⁴ is of Formula (LII) or Formula (LIIa) and R¹¹ is -CH₂-. In some embodiments, R⁴ is of Formula (LII) or Formula (LIIa) and R¹¹ is -CH₂CH₂-.

- 5 In some embodiments, R¹¹ is linked to R¹⁰ to form a ring and R⁹ is H, R¹⁰ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 F, and R¹¹ is C₁₋₃ alkanediyl wherein one methylene group is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl.
- 10 In some embodiments, R¹¹ is linked to R¹⁰ to form a 5-membered ring.
- In some embodiments, R¹¹ is linked to R⁹ or R¹⁰ to form a ring together with the intervening atoms, and R¹¹ is -O-. In some embodiments, R¹¹ is linked to R⁹ or R¹⁰ to form a ring together with the intervening atoms, and R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl. In some embodiments, R¹¹ is linked to R⁹ or R¹⁰ to form a ring together with the intervening atoms, and R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl.
- 15 In some embodiments, R¹¹ is linked to R⁹ or R¹⁰ to form a ring together with the intervening atoms, and R¹¹ is -CH₂-. In some embodiments, R¹¹ is linked to R⁹ or R¹⁰ to form a ring together with the intervening atoms, and R¹¹ is -CH₂CH₂-. In some embodiments, R¹¹ is linked to R⁹ or R¹⁰ to form a ring together with the intervening atoms, and R¹¹ is -CH₂O-. In some embodiments, R¹¹ is linked to R⁹ or R¹⁰ to form a ring together with the intervening atoms, and R¹¹ is -N(R²⁸)-. In some embodiments, R¹¹ is linked to R⁹ or R¹⁰ to form a ring together with the intervening atoms, and R¹¹ is -N(CH₃)-. In some embodiments, R¹¹ is linked to R⁹ or R¹⁰ to form a ring together with the intervening atoms, and R¹¹ is -O-. In some embodiments, R¹¹ is linked to R⁹ to form a ring together with the intervening atoms, and R¹¹-R⁹ is -(CH₂)₃-, -(CH₂)O-, -(CH₂)₂O-, -CH₂OCH₂-, -C(H)(CH₃)CH₂-, -C(O)N(H)-. In some embodiments, R¹¹ is linked to R¹⁰ to form a ring together with the intervening atoms, and R¹¹-R¹⁰ is -(CH₂)₃-, -(CH₂)O-, -(CH₂)₂O-, -CH₂OCH₂-, -C(H)(CH₃)CH₂-, -C(O)N(H)-.
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- 25
- 30

In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is a bond; and R^{11} is linked to R^9 to form a 5-membered ring. In some embodiments, R^4 is of Formula (XX):



Formula (XX)

wherein

R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

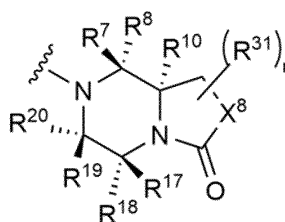
R^{31} is individually halogen or C_{1-3} alkyl;

r is 0, 1, 2, 3 or 4;

X^8 is $-CH_2-$, $-O-$, $-CH_2O-$, $-OCH_2-$, $-N(R^{28})-$, or $-CH_2N(R^{28})-$; and

R^{28} is H or C_{1-3} alkyl.

In some embodiments, the moiety of Formula (XX) is of Formula (XXa):



Formula (XXa)

In some embodiments, R^4 is of Formula (XXa) wherein:

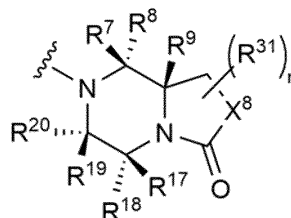
R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 5 R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{31} is individually halogen or C_{1-3} alkyl;
 r is 0, 1, 2, 3 or 4;
 X^8 is $-CH_2-$, $-O-$ or $-N(R^{28})-$; and
 R^{28} is H or C_{1-3} alkyl.

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In some embodiments, X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is a bond; and R^{11} is linked to R^{10} to form a 5 membered ring.
 In some embodiments, the moiety of Formula (XX) is of Formula (XXb):



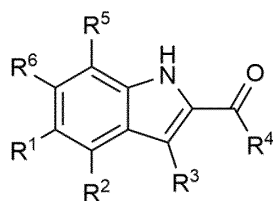
15

Formula (XXb)

In some embodiments, R^4 is of Formula (XXb) wherein:

R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^9 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 20 R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{31} is individually halogen or C_{1-3} alkyl;
 25 r is 0, 1, 2, 3 or 4;
 X^8 is $-CH_2-$, $-O-$ or $-N(R^{28})-$; and
 R^{28} is H or C_{1-3} alkyl.

In one aspect, the present invention relates to a compound of Formula (I),



Formula (I)

wherein

R¹ is halogen or H;

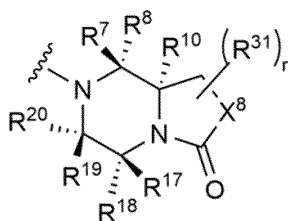
5 R² is halogen;

R³ is H or halogen;

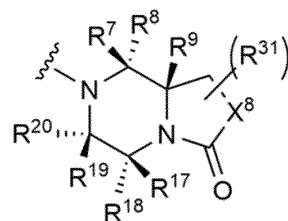
R⁵ is H or halogen;

R⁶ is H or halogen;

R⁴ is of Formula (XXa) or Formula (XXb):



Formula (XXa)



Formula (XXb)

10 wherein

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen, such as F;

15 R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

20 R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R³¹ is individually halogen or C₁₋₃ alkyl;

r is 0, 1, 2, 3 or 4;

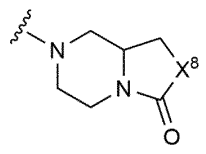
X⁸ is -CH₂-, -O- or -N(R²⁸)-; and

R²⁸ is H or C₁₋₃ alkyl,

or a pharmaceutically acceptable salt thereof.

In some embodiments, R^4 is of Formula (XXa) and R^7 , R^8 , R^{10} , R^{17} , R^{18} , R^{19} , and R^{20} are H. In some embodiments, R^4 is of Formula (XXb) and R^7 , R^8 , R^9 , R^{17} , R^{18} , R^{19} , and R^{20} are H.

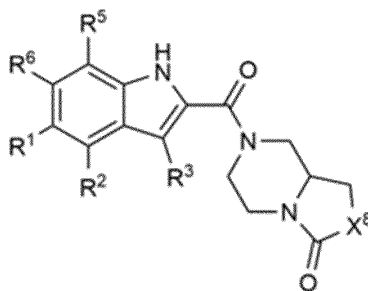
In some embodiments, R^4 is of Formula (XV):



Formula (XV)

wherein X^8 is $-CH_2-$, $-O-$ or $-N(R^{28})-$; and R^{28} is H or C_{1-3} alkyl.

In one aspect, the present invention relates to a compound of Formula (XXIII):



Formula (XXIII)

wherein

R^1 is halogen or H;

R^2 is halogen;

R^3 is H or halogen;

R^5 is H or halogen;

R^6 is H or halogen;

X^8 is $-CH_2-$, $-O-$ or $-N(R^{28})-$; and

R^{28} is H or C_{1-3} alkyl,

or a pharmaceutically acceptable salt thereof.

In some embodiments, X^8 is $-CH_2-$. In some embodiments, X^8 is $-O-$. In some embodiments, X^8 is $-N(R^{28})-$. In some embodiments, X^8 is $-CH_2O-$. In some

embodiments, X^8 is $-OCH_2-$. In some embodiments, X^8 is $-CH_2N(R^{28})-$. In some embodiments, R^{28} is C_{1-3} alkyl. In some embodiments, R^{28} is CH_3 . In some embodiments, X^8 is $-N(CH_3)-$.

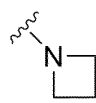
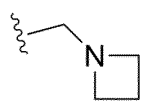
- 5 In some embodiments, R^7 is H. In some embodiments, R^7 is C_{1-3} alkyl. In some embodiments, R^7 is CH_3 . In some embodiments, R^7 is C_{1-3} alkyl substituted with 1 to 3 F. In some embodiments, R^7 is C_{1-3} alkyl substituted with C_{1-3} alkoxy. In some embodiments, R^7 is CH_2OCH_3 . In some embodiments, R^7 is halogen, such as F.
- 10 In some embodiments, R^8 is H. In some embodiments, R^8 is C_{1-3} alkyl. In some embodiments, R^8 is CH_3 . In some embodiments, R^8 is C_{1-3} alkyl substituted with C_{1-3} alkoxy. In some embodiments, R^8 is CH_2OCH_3 . In some embodiments, R^8 is C_{1-3} alkyl substituted with 1 to 3 F. In some embodiments, R^8 is halogen, such as F.
- 15 In some embodiments, R^9 is H. In some embodiments, R^9 is C_{1-3} alkyl. In some embodiments, R^9 is C_{1-3} alkyl substituted with 1 to 3 halogens. In some embodiments, R^9 is C_{1-3} alkyl substituted with 1 to 3 F. In some embodiments, R^9 is $-C(O)N(R^{31})(R^{32})$, wherein R^{31} is H or C_{1-3} alkyl and R^{32} is H or C_{1-3} alkyl. In some embodiments, R^9 is $-C(O)N(H)(CH_3)$. In some embodiments, R^9 is $-C(O)NH_2$. In some embodiments, R^9 is $-C(O)N(CH_3)_2$. In some embodiments, R^9 is halogen, such as F. In some embodiments, R^9 is linked to R^{11} to form a ring, and R^9 is a bond. In some embodiments, R^9 is linked to R^{11} to form a ring, and R^9 is $-C(O)-$. In some embodiments, R^9 is linked to R^{11} to form a ring, and R^9 is C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl. In some embodiments, R^9 is linked to R^{11} to form a ring, and R^9 is $-CH_2-$. In some embodiments, R^9 is linked to R^{11} to form a ring, and R^9 is $-(CH_2)_2-$. In some embodiments, R^9 is linked to R^{11} to form a ring, and R^9 is $-C(H)(CH_3)-$. In some embodiments, R^9 is linked to R^{11} or R^{13} to form a ring, and R^9 is a bond. In some embodiments, R^9 is linked to R^{11} or R^{13} to form a ring, and R^9 is C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl. In some embodiments, R^9 is linked to R^{11} or R^{13} to form a ring, and R^9 is $-CH_2-$. In some embodiments, R^9 is linked to R^{11} or R^{13} to form a ring, and R^9 is $-CH_2CH_2-$.
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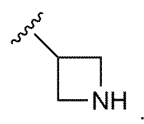
In some embodiments, R^{31} is H. In some embodiments, R^{31} is C_{1-3} alkyl. In some embodiments, R^{31} is CH_3 . In some embodiments, R^{32} is H. In some embodiments, R^{32} is C_{1-3} alkyl. In some embodiments, R^{32} is CH_3 .

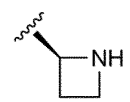
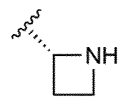
- 5 In some embodiments, R^{10} is H. In some embodiments, R^{10} is C_{1-3} alkyl. In some embodiments, R^{10} is C_{1-3} alkyl substituted with 1 to 3 halogens. In some embodiments, R^{10} is C_{1-3} alkyl substituted with 1 to 3 F. In some embodiments, R^{10} is - $C(O)N(R^{31})(R^{32})$, wherein R^{31} is H or C_{1-3} alkyl and R^{32} is H or C_{1-3} alkyl. In some embodiments, R^{10} is - $C(O)N(H)(CH_3)$. In some embodiments, R^{10} is - $C(O)NH_2$. In some
10 embodiments, R^{10} is - $C(O)N(CH_3)_2$. In some embodiments, R^{10} is halogen, such as F. In some embodiments, R^{10} is linked to R^{11} to form a ring, and R^9 is a bond. In some embodiments, R^{10} is linked to R^{11} to form a ring, and R^9 is - $C(O)-$. In some embodiments, R^{10} is linked to R^{11} to form a ring, and R^9 is C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl. In
15 some embodiments, R^{10} is linked to R^{11} to form a ring, and R^9 is - CH_2- . In some embodiments, R^{10} is linked to R^{11} to form a ring, and R^9 is - $(CH_2)_2-$. In some embodiments, R^{10} is linked to R^{11} to form a ring, and R^9 is - $C(H)(CH_3)-$. In some embodiments, R^{10} is linked to R^{11} or R^{13} to form a ring, and R^{10} is a bond. In some embodiments, R^{10} is linked to R^{11} or R^{13} to form a ring, and R^{10} is C_{1-3} alkanediyl
20 optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl. In some embodiments, R^{10} is linked to R^{11} or R^{13} to form a ring, and R^{10} is - CH_2- . In some embodiments, R^{10} is linked to R^{11} or R^{13} to form a ring, and R^{10} is - CH_2CH_2- .

- In some embodiments, X^{13} is a bond. Hence, in one embodiment, R^{11} is R^{33} . In some
25 embodiments, X^{13} is C_{1-3} alkanediyl. In some embodiments, X^{13} is - CH_2- . In some embodiments, X^{13} is C_{1-3} alkanediyl substituted with C_{1-3} alkyl. In some embodiments, X^{13} is - $C(H)(CH_3)-$. In some embodiments, X^{13} is -O-. In some embodiments, X^{13} is - C_{1-3} alkanediyl-O-. In some embodiments, X^{13} is - CH_2O- . In some embodiments, X^{13} is bond, - CH_2- , - $C(H)(CH_3)-$, -O-, or - CH_2O- . In some embodiments, when X^{13} is -O- or -
30 C_{1-3} alkanediyl-O-, then R^{33} is linked to X^{13} via a carbon atom of R^{33} .

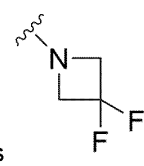
- In some embodiments, R^{33} is azetidiny optionally substituted with one or more substituents individually selected from halogen; C_{1-3} alkoxy optionally substituted with one or more F; C_{1-3} alkyl optionally substituted with one or more F; NH_2 ; $N(H)(CH_3)$; and $N(CH_3)_2$. In some embodiments, R^{33} is azetidiny. In some embodiments, R^{33} is
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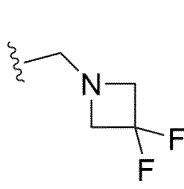
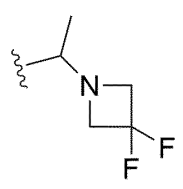
 . In some embodiments, R¹¹ is  . In some embodiments, R¹¹ is

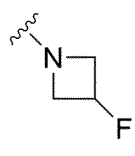
azetidiny. In some embodiments, R¹¹ is  . In some embodiments, R¹¹ is

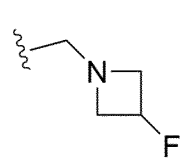
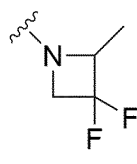
 . In some embodiments, R¹¹ is  . In some embodiments, R³³ is

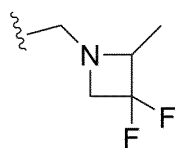
azetidiny optionally substituted with one or more substituents selected from halogen,
 5 C₁₋₃ alkoxy, and C₁₋₃ alkyl. In some embodiments, R¹¹ is azetidiny optionally substituted
 with one or more substituents selected from halogen, C₁₋₃ alkyl, and NH₂. In some
 embodiments, R¹¹ is azetidiny substituted with one or more substituents selected from
 halogen, and C₁₋₃ alkyl. In some embodiments, R¹¹ is azetidiny substituted with
 halogen, such as F. In some embodiments, R³³ is azetidiny substituted with one or
 10 more substituents halogen(s) and/or one or more C₁₋₃ alkyl. In some embodiments, R³³
 is azetidiny substituted with one or more halogens. In some embodiments, R³³ is
 azetidiny substituted with one or more F. In some embodiments, R³³ is azetidiny

substituted with one or two F. In some embodiments, R¹¹ is  . In some

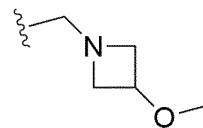
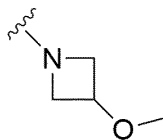
embodiments, R¹¹ is  . In some embodiments, R¹¹ is  .

In some embodiments, R³³ is  . In some embodiments, R¹¹ is

 . In some embodiments, R³³ is  . In some embodiments,

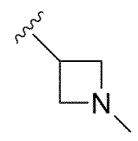


R^{11} is . In some embodiments, R^{33} is azetidiny substituted with C_{1-3} alkoxy. In some embodiments, R^{33} is azetidiny substituted with $-OCH_3$. In some

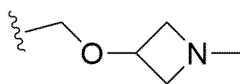


embodiments, R^{33} is . In some embodiments, R^{11} is

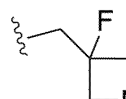
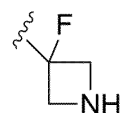
In some embodiments, R^{11} is C_{1-3} alkyl substituted with $-O$ -azetidiny, wherein the



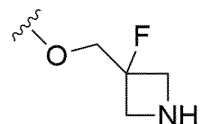
5 azetidiny is optionally substituted with CH_3 . In some embodiments, R^{33} is



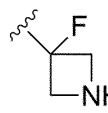
In some embodiments, R^{11} is . In some embodiments, R^{33} is



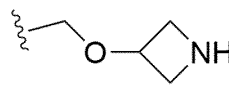
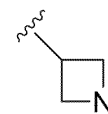
. In some embodiments, R^{11} is . In some embodiments, R^{11} is



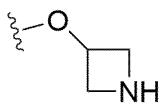
. In some embodiments, R^{11} is azetidiny substituted with C_{1-3} alkyl,



such as CH_3 . In some embodiments, R^{11} is . In some embodiments, R^{33} is

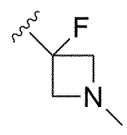


10 . In some embodiments, R^{11} is . In some

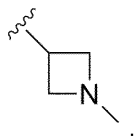


embodiments, R^{11} is . In some embodiments, R^{33} is azetidiny optionally

substituted with C_{1-3} alkyl. In some embodiments, R^{11} is

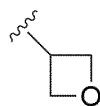


. In some



embodiments, R^{11} is

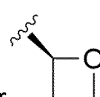
5 In some embodiments, R^{33} is oxetanyl optionally substituted with one or more substituents individually selected from halogen; C_{1-3} alkoxy optionally substituted with one or more F; C_{1-3} alkyl optionally substituted with one or more F; NH_2 ; $N(H)(CH_3)$; and $N(CH_3)_2$. In some embodiments, R^{33} is oxetanyl. In some embodiments, R^{33} is



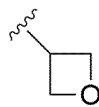
. In some embodiments, R^{33} is



or

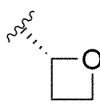


. In some embodiments,

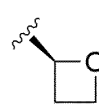


R^{11} is oxetanyl. In some embodiments, R^{11} is

. In some embodiments, R^{11} is

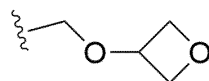


. In some embodiments, R^{11} is



. In some embodiments, R^{11} is

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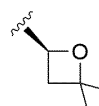
. In some embodiments, R^{33} is oxetanyl substituted with one or

more C_{1-3} alkyl. In some embodiments, R^{33} is oxetanyl substituted with one or more -

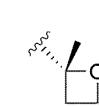
CH_3 . In some embodiments, R^{33} is



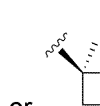
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,



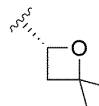
, or



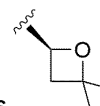
.

In

some embodiments, R^{11} is



. In some embodiments, R^{11} is



. In some

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embodiments, R^{11} is



. In some embodiments, R^{11} is

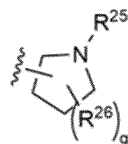


.

In some embodiments, R^{33} is pyrrolidinyl optionally substituted with one or more substituents individually selected from halogen; C_{1-3} alkoxy optionally substituted with

one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂. In some embodiments, R³³ is pyrrolidinyl optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F.

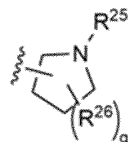
- 5 In some embodiments, R³³ is pyrrolidinyl substituted with one or more F. In some embodiments, R³³ is pyrrolidinyl substituted with one or more C₁₋₃ alkyl optionally substituted with one or more F. In some embodiments, R³³ is pyrrolidinyl substituted with one or more -CH₃. In some embodiments, R³³ is pyrrolidinyl substituted with one or more -CF₃. In some embodiments, R¹¹ is pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of C₁₋₃ alkyl, halogen, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens. In some embodiments, R³³ is of Formula (XIV):



15

Formula (XIV)

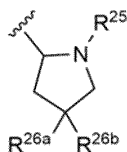
wherein R²⁵ is H or C₁₋₃ alkyl; R²⁶ is individually halogen, such as F, C₁₋₃ alkyl, or C₁₋₃ haloalkyl, such as CF₃; and q is 0, 1 or 2. In some embodiments, R¹¹ is of Formula (XIV):



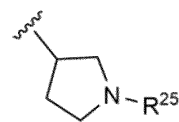
20

Formula (XIV)

- wherein R²⁵ is H or C₁₋₃ alkyl; R²⁶ is individually halogen, such as F, C₁₋₃ alkyl, or C₁₋₃ haloalkyl, such as CF₃; and q is 0, 1 or 2. In some embodiments, R¹¹ is pyrrolidinyl optionally substituted with one or more substituents individually selected from C₁₋₃ alkyl and halogen. In some embodiments, R¹¹ is of Formula (XIV) wherein R²⁵ is H or C₁₋₃ alkyl; R²⁶ is halogen, such as F, or C₁₋₃ alkyl; and q is 0, 1 or 2. In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, R³³ is of Formula (XIVa) or Formula (XIVb):
- 25



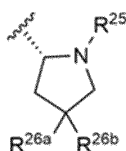
Formula (XIVa)



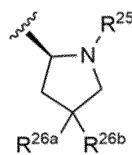
Formula (XIVb)

wherein R^{25} is H or C_{1-3} alkyl; R^{26a} is H or F; and R^{26b} is H or F.

- 5 In some embodiments, q is 2. In some embodiments, R^{11} is of Formula (XIVa) wherein R^{25} is H or C_{1-3} alkyl; R^{26a} is H or F; and R^{26b} is H or F. In some embodiments, the moiety of Formula (XIVa) is of Formula (XIVa-1) or Formula (XIVa-2):



Formula (XIVa-1)



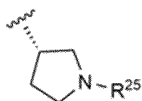
Formula (XIVa-2)

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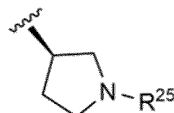
In some embodiments, R^{11} is of Formula (XIVa-1) wherein R^{25} is H or C_{1-3} alkyl; R^{26a} is H or F; and R^{26b} is H or F. In some embodiments, R^{11} is of Formula (XIVa-2) wherein R^{25} is H or C_{1-3} alkyl; R^{26a} is H or F; and R^{26b} is H or F.

- 15 In some embodiments, R^{26a} is F. In some embodiments, R^{26b} is F. In some embodiments, R^{26a} is F and R^{26b} is F. In some embodiments, R^{26a} is F and R^{26b} is H. In some embodiments, R^{26a} is H and R^{26b} is F.

- 20 In some embodiments, R^{11} is of Formula (XIVb) wherein R^{25} is H or C_{1-3} alkyl. In some embodiments, the moiety of Formula (XIVb) is of Formula (XIVb-1) or Formula (XIVb-2):



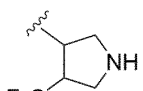
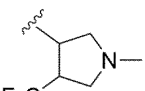
Formula (XIVb-1)

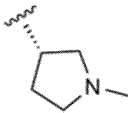
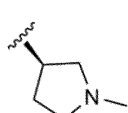
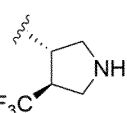
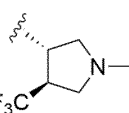
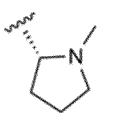
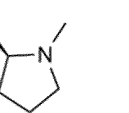
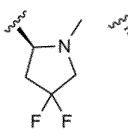
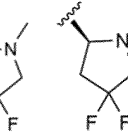
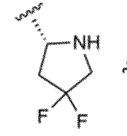
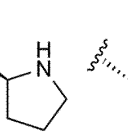
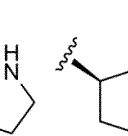
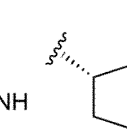
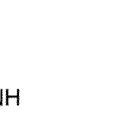
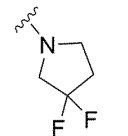
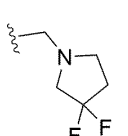


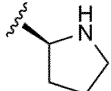
Formula (XIVb-2)

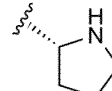
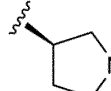
- 25 In some embodiments, R^{11} is of Formula (XIVb-1) wherein R^{25} is H or C_{1-3} alkyl. In some embodiments, R^{11} is of Formula (XIVb-2) wherein R^{25} is H or C_{1-3} alkyl.

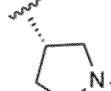
In some embodiments, R^{25} is H. In some embodiments, R^{25} is C_{1-3} alkyl. In some embodiments, R^{25} is CH_3 .

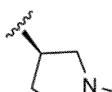
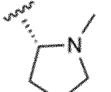
In some embodiments, R^{33} is  or . In some embodiments,

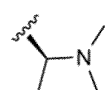
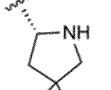
5 R^{33} is , , , , , ,
, , , , , , ,
or, , . In some embodiments, R^{11} is

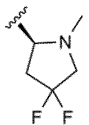
In some embodiments, R^{11} is pyrrolidinyl. In some embodiments, R^{11} is . In

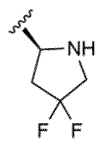
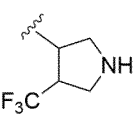
some embodiments, R^{11} is . In some embodiments, R^{11} is . In

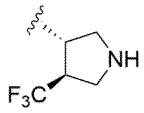
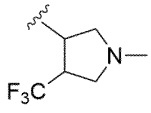
10 some embodiments, R^{11} is . In some embodiments, R^{11} is . In

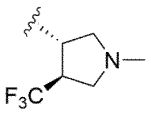
some embodiments, R^{11} is . In some embodiments, R^{11} is . In

some embodiments, R^{11} is . In some embodiments, R^{11} is . In some

embodiments, R¹¹ is . In some embodiments, R¹¹ is . In some

embodiments, R¹¹ is . In some embodiments, R¹¹ is . In some

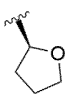
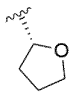
embodiments, R¹¹ is . In some embodiments, R¹¹ is . In

some embodiments, R¹¹ is .

5

In some embodiments, R³³ is tetrahydrofuranyl optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂. In some embodiments, R³³ is tetrahydrofuranyl. In some embodiments, R¹¹ is tetrahydrofuranyl. In some embodiments, R³³ is tetrahydrofuran-2-yl. In some

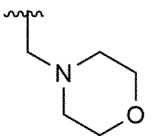
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embodiments, R³³ is  or . In some embodiments, R¹¹ is tetrahydrofuran-

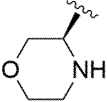
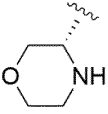
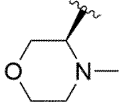
2-yl. In some embodiments, R¹¹ is . In some embodiments, R¹¹ is .

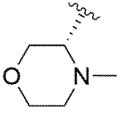
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In some embodiments, R³³ is morpholinyl optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂. In some embodiments, R³³ is morpholinyl. In some embodiments, R³³ is N-morpholinyl.

In some embodiments, R¹¹ is . In some embodiments, R¹¹ is morpholinyl optionally substituted with C₁₋₃ alkyl. In some embodiments, R¹¹ is morpholinyl. In some

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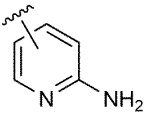
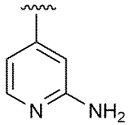
embodiments, R¹¹ is . In some embodiments, R¹¹ is . In some embodiments, R¹¹ is morpholinyl substituted with C₁₋₃ alkyl. In some embodiments, R¹¹ is morpholinyl substituted with CH₃. In some embodiments, R¹¹ is . In some

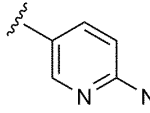
embodiments, R¹¹ is .

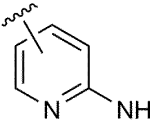
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In some embodiments, R³³ is pyridinyl optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂. In some embodiments, R³³ is pyridinyl optionally substituted with one or more NH₂. In some embodiments, R³³ is pyridinyl substituted with NH₂. In some

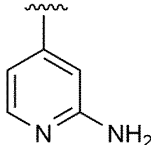
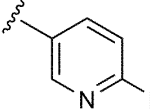
10

embodiments, R³³ is . In some embodiments, R³³ is . In some

embodiments, R³³ is . In some embodiments, R¹¹ is pyridinyl optionally substituted with one or more NH₂. In some embodiments, R¹¹ is pyridinyl substituted

with NH₂. In some embodiments, R¹¹ is . In some embodiments, R¹¹ is

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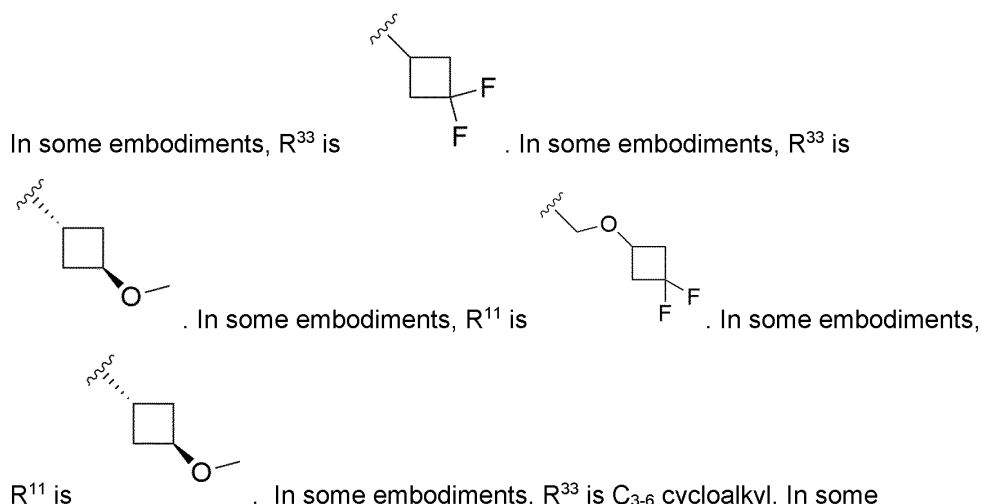
. In some embodiments, R¹¹ is .

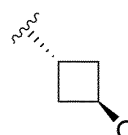
In some embodiments, R³³ is C₁₋₃ alkyl optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with

one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂. In some embodiments, R¹¹ is C₁₋₃ alkyl optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, C₁₋₃ alkoxy, morpholinyl, azetidiny, -O-azetidiny, and -O-oxetanyl, and said
5 azetidiny is optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl. In some embodiments, R¹¹ is C₁₋₃ alkyl optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(CH₃)₂, N(H)(CH₃), C₁₋₃ alkoxy, and morpholinyl. In some embodiments, R¹¹ is C₁₋₃ alkyl optionally substituted with one or more substituents individually selected from the
10 group consisting of NH₂, N(CH₃)₂, N(H)(CH₃) and C₁₋₃ alkoxy.

In some embodiments, R³³ is C₁₋₃ alkyl. In some embodiments, R³³ is CH₃. In some embodiments, R¹¹ is C₁₋₃ alkyl. In some embodiments, R¹¹ is CH₃. In some
15 embodiments, R³³ is NH₂. In some embodiments, R³³ is N(H)(CH₃). In some
embodiments, R³³ is N(CH₃)₂. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with one or more N(CH₃)₂. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with one or more NH₂. In some embodiments, R¹¹ is -CH₂NH₂. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with one or more N(CH₃)₂. In some embodiments, R¹¹ is -CH₂N(CH₃)₂.
In some embodiments, R¹¹ is -CH₂-N(H)(CH₃). In some embodiments, R³³ is C₁₋₃ alkoxy
20 optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂. In some embodiments, R³³ is C₁₋₃ alkoxy. In some embodiments, R³³ is -OCH₃. In some embodiments, R¹¹ is C₁₋₃ alkyl is substituted with one or more C₁₋₃ alkoxy. In some embodiments, R¹¹ is -CH₂OCH₃. In
25 some embodiments, R¹¹ is C₁₋₃ alkoxy. In some embodiments, R¹¹ is -OCH₃. In some
embodiments, R³³ is C₁₋₃ alkyl optionally substituted with one or more F. In some
embodiments, R³³ is CF₃. In some embodiments, R³³ is CHF₂. In some embodiments, R¹¹ is -CH₂-O-CF₃. In some embodiments, R¹¹ is -CH₂-O-CHF₂. In some embodiments, R¹¹ is CHF₂. In some embodiments, R³³ is C₃₋₆ cycloalkyl optionally substituted with one
30 or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂. In some embodiments, R³³ is C₃₋₆ cycloalkyl. In some
embodiments, R³³ is C₃₋₆ cycloalkyl substituted with one or more substituents
individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more
35 F; and C₁₋₃ alkyl optionally substituted with one or more F. In some embodiments, R³³

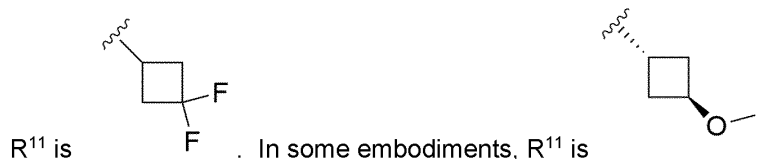
is C₃₋₆ cycloalkyl substituted with one or more substituents selected from halogen, and C₁₋₃ alkoxy. In some embodiments, R³³ is C₃₋₆ cycloalkyl substituted with one or more F. In some embodiments, R¹¹ is C₃₋₆ cycloalkyl substituted with C₁₋₃ alkoxy. In some embodiments, R¹¹ is C₃₋₆ cycloalkyl substituted with -OCH₃. In some embodiments, the C₃₋₆ cycloalkyl is C₃₋₅ cycloalkyl. In some embodiments, the C₃₋₅ cycloalkyl is cyclobutyl.



R¹¹ is . In some embodiments, R³³ is C₃₋₆ cycloalkyl. In some embodiments, R³³ is cyclopropyl. In some embodiments, R¹¹ is C₃₋₅ cycloalkyl. In some embodiments, R¹¹ is cyclopropyl. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with morpholinyl. In some embodiments, R¹¹ is C₁ alkyl substituted with morpholinyl. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with azetidiny, wherein the azetidiny is optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl. In some embodiments, R¹¹ is C₁ alkyl substituted with azetidiny, wherein the azetidiny is optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with azetidiny. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with azetidiny, wherein the azetidiny is substituted with one or more halogens. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with azetidiny, wherein the azetidiny is substituted with one or more F. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with azetidiny, wherein the azetidiny is substituted with one or two F. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with -O-azetidiny, wherein the azetidiny is optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with -O-azetidiny. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with -O-azetidiny, wherein the azetidiny is optionally substituted with C₁₋₃ alkyl. In some embodiments, R¹¹ is C₁₋₃ alkyl

substituted with -O-azetidynyl, wherein the azetidynyl is optionally substituted with CH₃. In some embodiments, R¹¹ is C₁₋₃ alkyl substituted with -O-oxetanyl.

In some embodiments, R¹¹ is C₃₋₅ cycloalkyl is optionally substituted with one or more substituents selected from halogen, and C₁₋₃ alkoxy. In some embodiments, R¹¹ is C₃₋₅ cycloalkyl is optionally substituted with one or more halogen, such as F. In some embodiments, R¹¹ is C₃₋₅ cycloalkyl is optionally substituted with C₁₋₃ alkoxy, such as -OCH₃. In some embodiments, the C₃₋₅ cycloalkyl is cyclobutyl. In some embodiments,

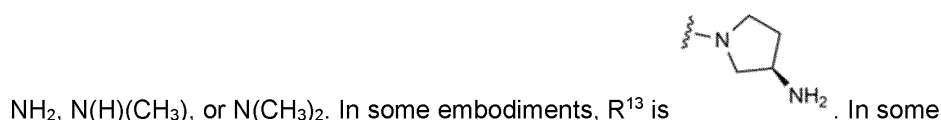


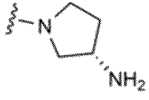
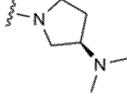
In some embodiments, R¹² is H. In some embodiments, R¹² is C₁₋₃ alkyl. In some embodiments, R¹² is CH₃.

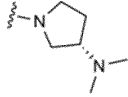
In some embodiments, R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidynyl, and piperazinyl, wherein

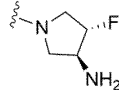
- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidynyl, and said azetidynyl is optionally substituted with one or more halogens, and
- said azetidynyl optionally substituted with NH₂.

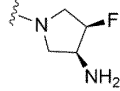
In some embodiments, R¹³ is N(H)(CH₃). In some embodiments, when R¹³ is pyrrolidinyl, azetidynyl, or piperazinyl, said pyrrolidinyl, azetidynyl, or piperazinyl is attached to the rest of the molecule via an N atom in said pyrrolidinyl, azetidynyl, or piperazinyl. In some embodiments, R¹³ is pyrrolidinyl optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidynyl, and said azetidynyl is optionally substituted with one or more halogens. In some embodiments, R¹³ is pyrrolidinyl optionally substituted with

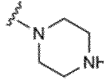


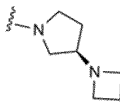
embodiments, R¹³ is . In some embodiments, R¹³ is . In some

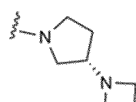
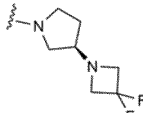
embodiments, R¹³ is . In some embodiments, R¹³ is pyrrolidinyl substituted with one or more substituents individually selected from the group consisting of

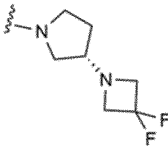
halogen, NH₂, N(H)(CH₃), and N(CH₃)₂. In some embodiments, R¹³ is . In

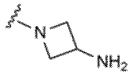
5 some embodiments, R¹³ is . In some embodiments, R¹³ is piperazinyl. In

some embodiments, R¹³ is . In some embodiments, R¹³ is pyrrolidinyl optionally substituted with azetidiny, and the azetidiny is optionally substituted with

one or more halogens. In some embodiments, R¹³ is . In some

embodiments, R¹³ is . In some embodiments, R¹³ is . In some

10 embodiments, R¹³ is . In some embodiments, R¹³ is azetidiny

optionally substituted with NH₂. In some embodiments, R¹³ is . In some embodiments, R¹³ is NH₂, N(H)(CH₃), or N(CH₃)₂. In some embodiments, R¹³ is linked to R⁹, R¹⁰, R¹⁷, or R¹⁸ to form a ring together with the intervening atoms, and R¹³ is -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl. In some embodiments, R¹³ is -N(CH₃)-.

15 In some embodiments, R¹⁴ is N(H)(C(O)CH₃).

In some embodiments, R¹⁵ is H.

In some embodiments, R¹⁶ is H. In some embodiments, R¹⁶ is C₁₋₃ alkyl. In some embodiments, R¹⁶ is CH₃.

5

In some embodiments, R¹⁷ is H. In some embodiments, R¹⁷ is C₁₋₃ alkyl. In some embodiments, R¹⁷ is CH₃. In some embodiments, R¹⁷ is C₁₋₃ alkyl substituted with 1 to 3 F. In some embodiments, R¹⁷ is halogen, such as F.

10 In some embodiments, R¹⁸ is H. In some embodiments, R¹⁸ is C₁₋₃ alkyl. In some embodiments, R¹⁸ is CH₃. In some embodiments, R¹⁸ is C₁₋₃ alkyl substituted with 1 to 3 F. In some embodiments, R¹⁸ is halogen, such as F.

15 In some embodiments, R¹⁹ is H. In some embodiments, R¹⁹ is C₁₋₃ alkyl. In some embodiments, R¹⁹ is C₁₋₃ alkyl substituted with 1 to 3 F. In some embodiments, R¹⁹ is halogen, such as F.

20 In some embodiments, R²⁰ is H. In some embodiments, R²⁰ is C₁₋₃ alkyl. In some embodiments, R²⁰ is CH₃. In some embodiments, R²⁰ is C₁₋₃ alkyl substituted with 1 to 3 F. In some embodiments, R²⁰ is halogen, such as F.

In some embodiments, R²¹ is H. In some embodiments, R²¹ is C₁₋₃ alkyl. In some embodiments, R²¹ is CH₃. In some embodiments, R²¹ is C₁₋₃ alkyl substituted with 1 to 3 F. In some embodiments, R²¹ is halogen, such as F.

25

In some embodiments, R²² is H. In some embodiments, R²² is C₁₋₃ alkyl. In some embodiments, R²² is CH₃. In some embodiments, R²² is C₁₋₃ alkyl substituted with 1 to 3 F. In some embodiments, R²² is halogen, such as F.

30 In some embodiments, R²³ is H. In some embodiments, R²³ is C₁₋₃ alkyl. In some embodiments, R²³ is a bond and R¹⁵ is C₁₋₃ alkanediyl and R²³ is linked to R¹⁵ to form a 4 or 5 membered ring.

In some embodiments, R²⁴ is CH₃.

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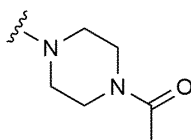
In some embodiments, no more than two of X^2 , X^5 and X^6 are bonds.

In some embodiments, the azetidiny is azetidin-1-yl. In some embodiments, the azetidiny is azetidin-2-yl. In some embodiments, the azetidiny is azetidin-3-yl. In some
5 embodiments, the morpholinyl is morpholin-4-yl.

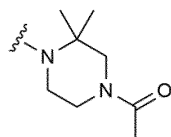
In some embodiments, the morpholinyl is morpholin-3-yl. In some embodiments, the pyrrolidinyl is pyrrolidin-1-yl.

10 In some embodiments, the pyrrolidinyl is pyrrolidin-2-yl. In some embodiments, the pyrrolidinyl is pyrrolidin-3-yl.

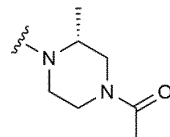
In some embodiments, the oxetanyl is oxetan-2-yl. In some embodiments, the oxetanyl is oxetan-3-yl.



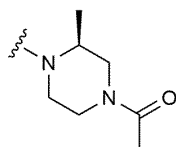
15 In some embodiments, R^4 is . In some embodiments, R^4 is



. In some embodiments, R^4 is

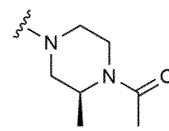


. In some embodiments,

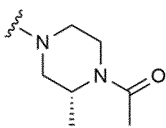


R^4 is

. In some embodiments, R^4 is

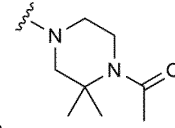


. In some

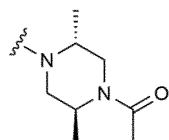


embodiments, R^4 is

. In some embodiments, R^4 is

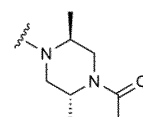


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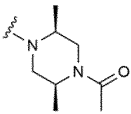
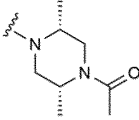


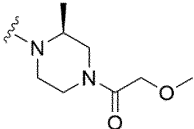
some embodiments, R^4 is

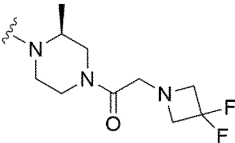
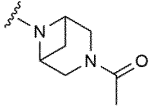
. In some embodiments, R^4 is

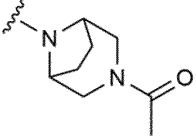
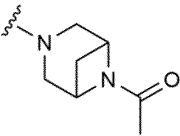


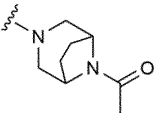
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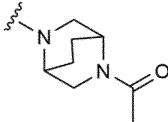
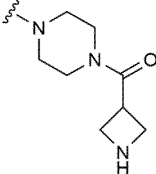
some embodiments, R⁴ is . In some embodiments, R⁴ is . In

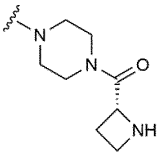
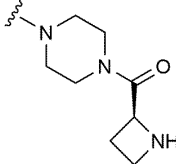
some embodiments, R⁴ is . In some embodiments, R⁴ is

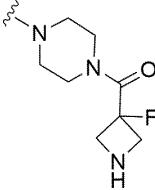
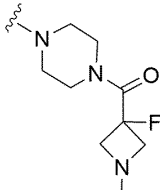
. In some embodiments, R⁴ is . In some

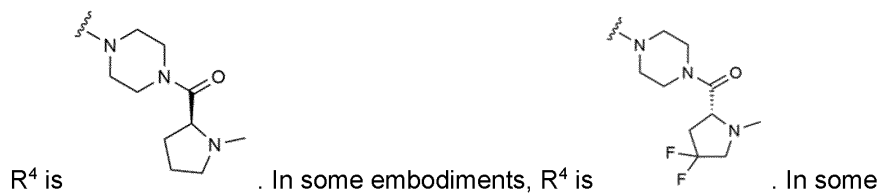
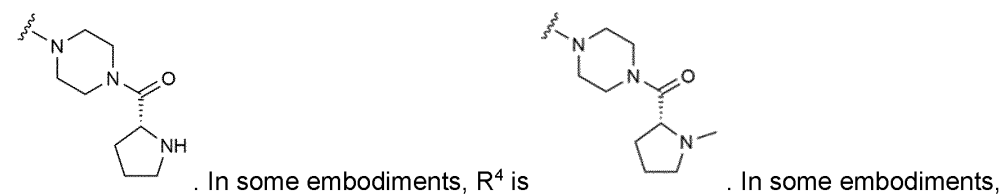
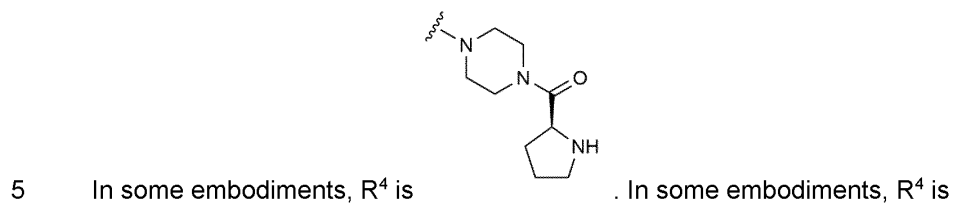
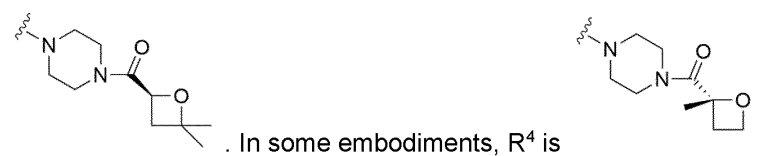
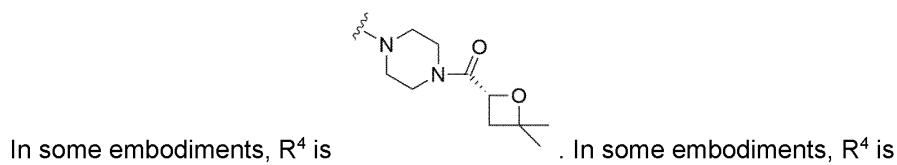
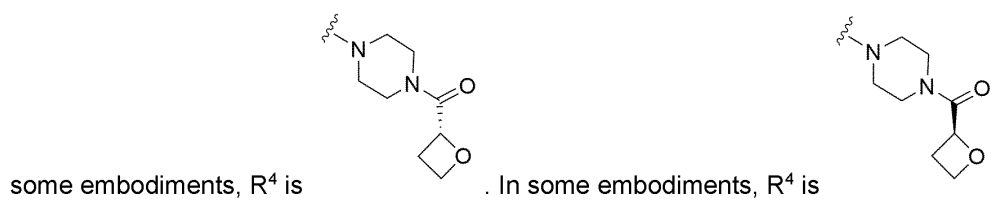
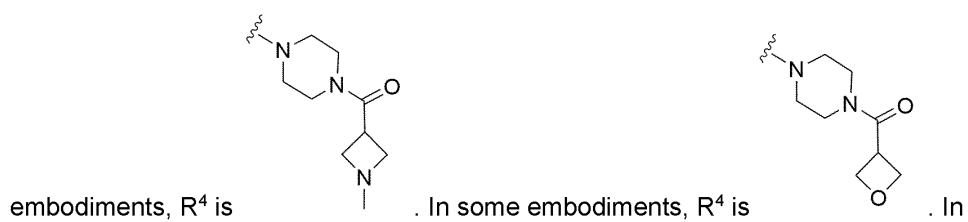
embodiments, R⁴ is . In some embodiments, R⁴ is .

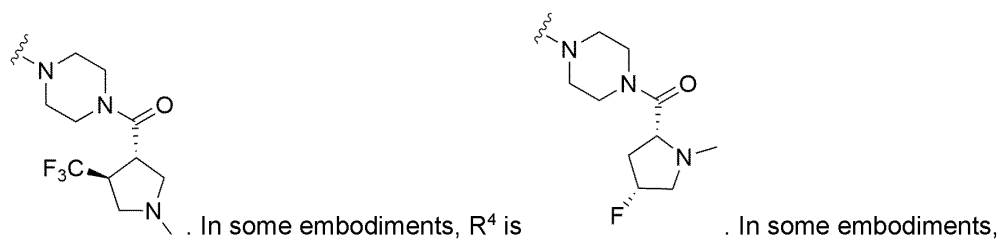
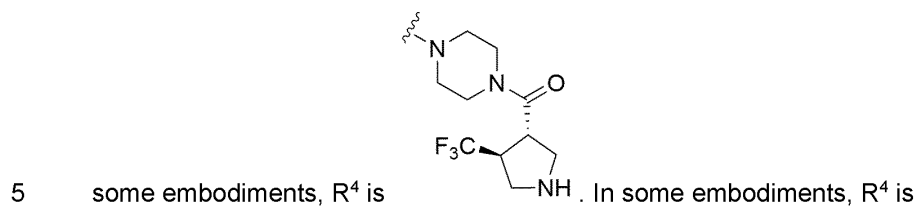
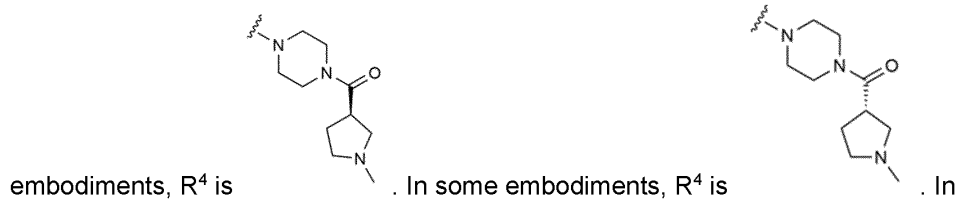
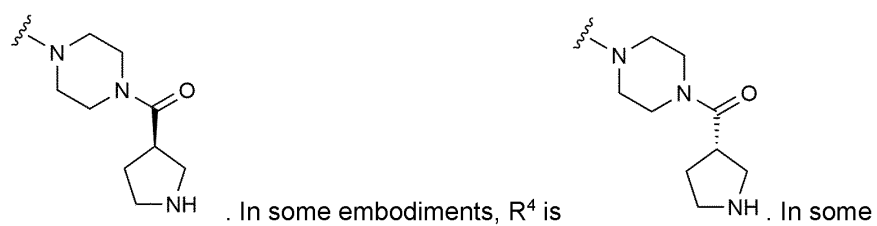
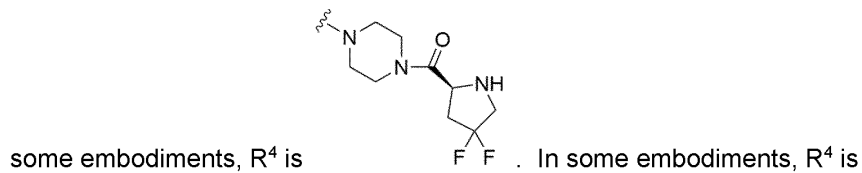
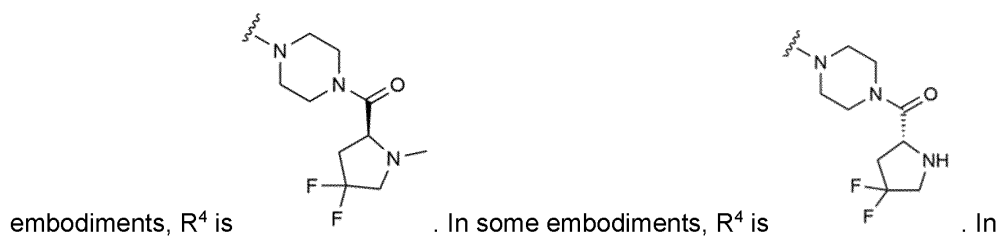
5 In some embodiments, R⁴ is . In some embodiments, R⁴ is

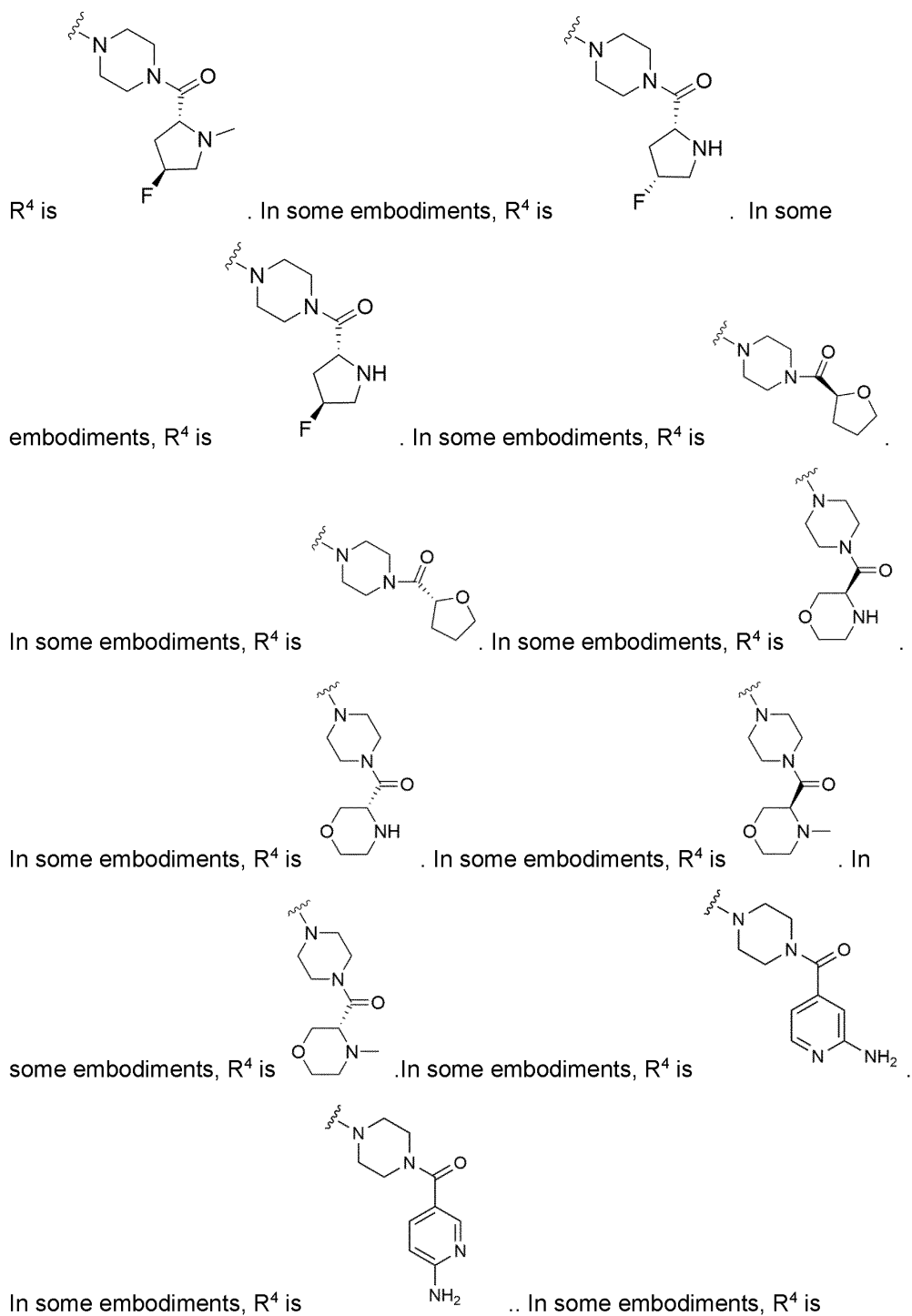
. In some embodiments, R⁴ is . In some embodiments, R⁴

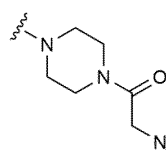
is . In some embodiments, R⁴ is . In some embodiments,

R⁴ is . In some embodiments, R⁴ is . In some

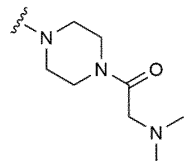




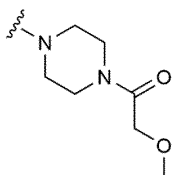




. In some embodiments, R⁴ is

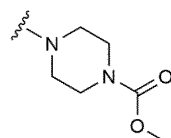


. In some

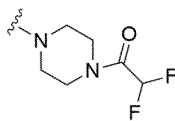


embodiments, R⁴ is

. In some embodiments, R⁴ is

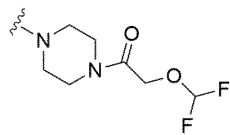


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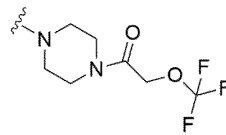


some embodiments, R⁴ is

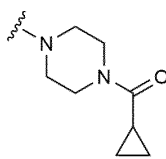
. In some embodiments, R⁴ is



. In some embodiments, R⁴ is

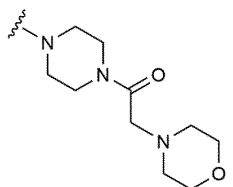


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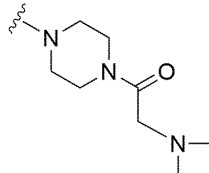


5 In some embodiments, R⁴ is

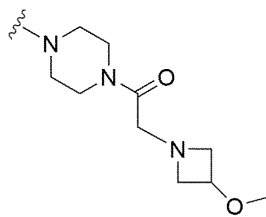
. In some embodiments, R⁴ is



. In some embodiments, R⁴ is

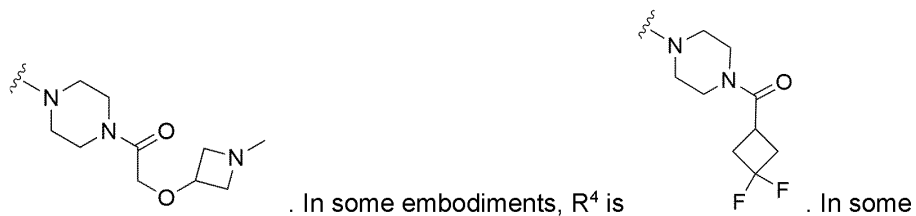
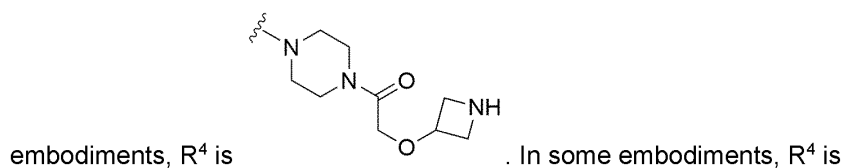
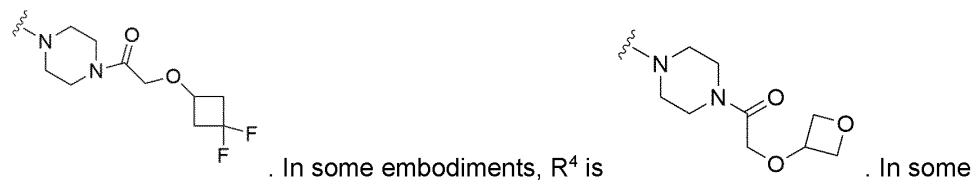
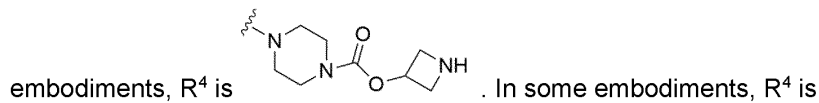
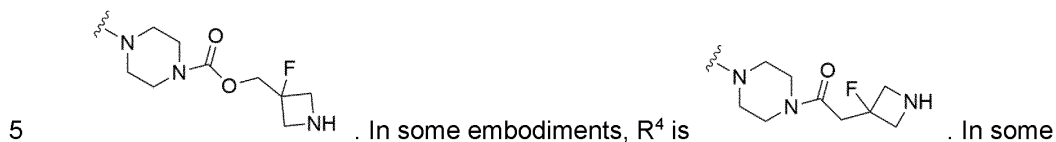
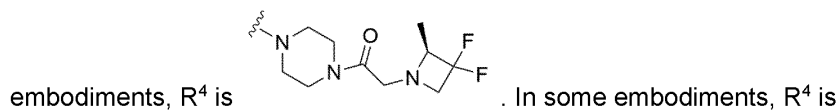
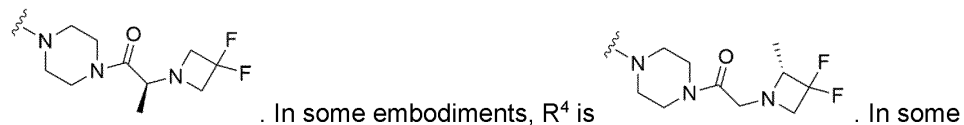
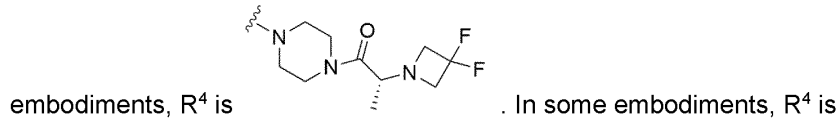
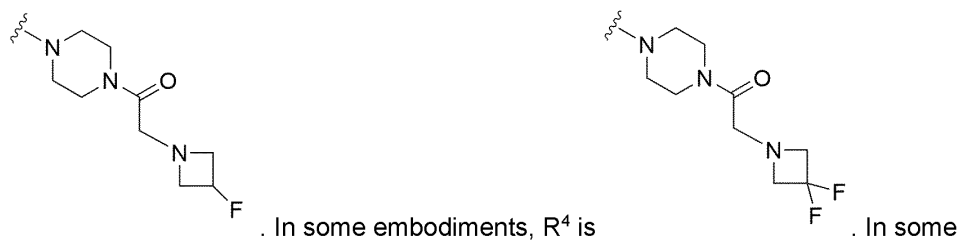


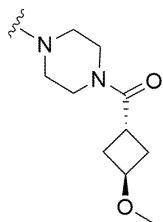
. In some



embodiments, R⁴ is

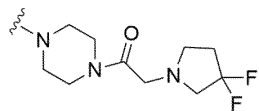
. In some embodiments, R⁴ is



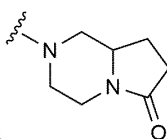


embodiments, R⁴ is

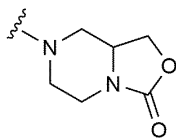
. In some embodiments, R⁴ is



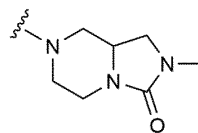
In some embodiments, R⁴ is



. In some embodiments, R⁴ is

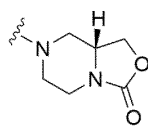


. In some embodiments, R⁴ is



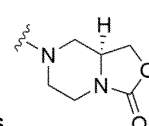
. In some

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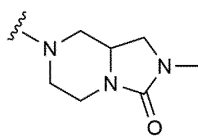


embodiments, R⁴ is

. In some embodiments, R⁴ is

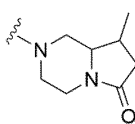


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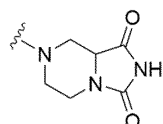


some embodiments, R⁴ is

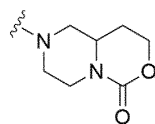
. In some embodiments, R⁴ is



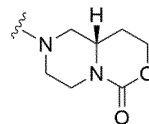
. In some embodiments, R⁴ is



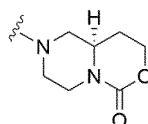
. In some embodiments, R⁴



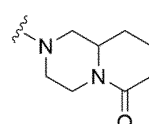
is . In some embodiments, R⁴ is



. In some embodiments,

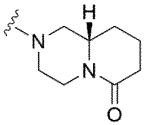
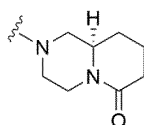


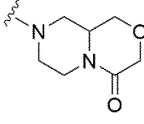
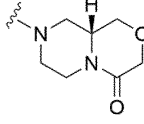
R⁴ is . In some embodiments, R⁴ is

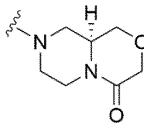
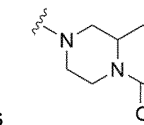


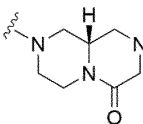
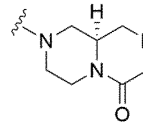
. In some

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embodiments, R⁴ is  . In some embodiments, R⁴ is  . In some

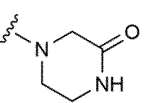
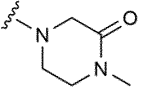
embodiments, R⁴ is  . In some embodiments, R⁴ is  . In some

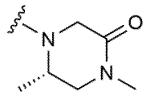
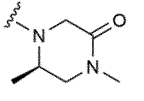
embodiments, R⁴ is  . In some embodiments, R⁴ is  . In

some embodiments, R⁴ is  . In some embodiments, R⁴ is  .

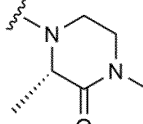
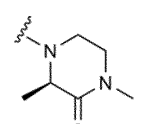
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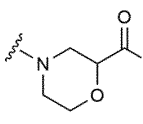
In some embodiments, R⁴ is

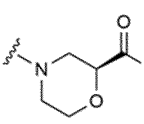
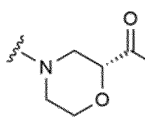
 . In some embodiments, wherein R⁴ is  . In some

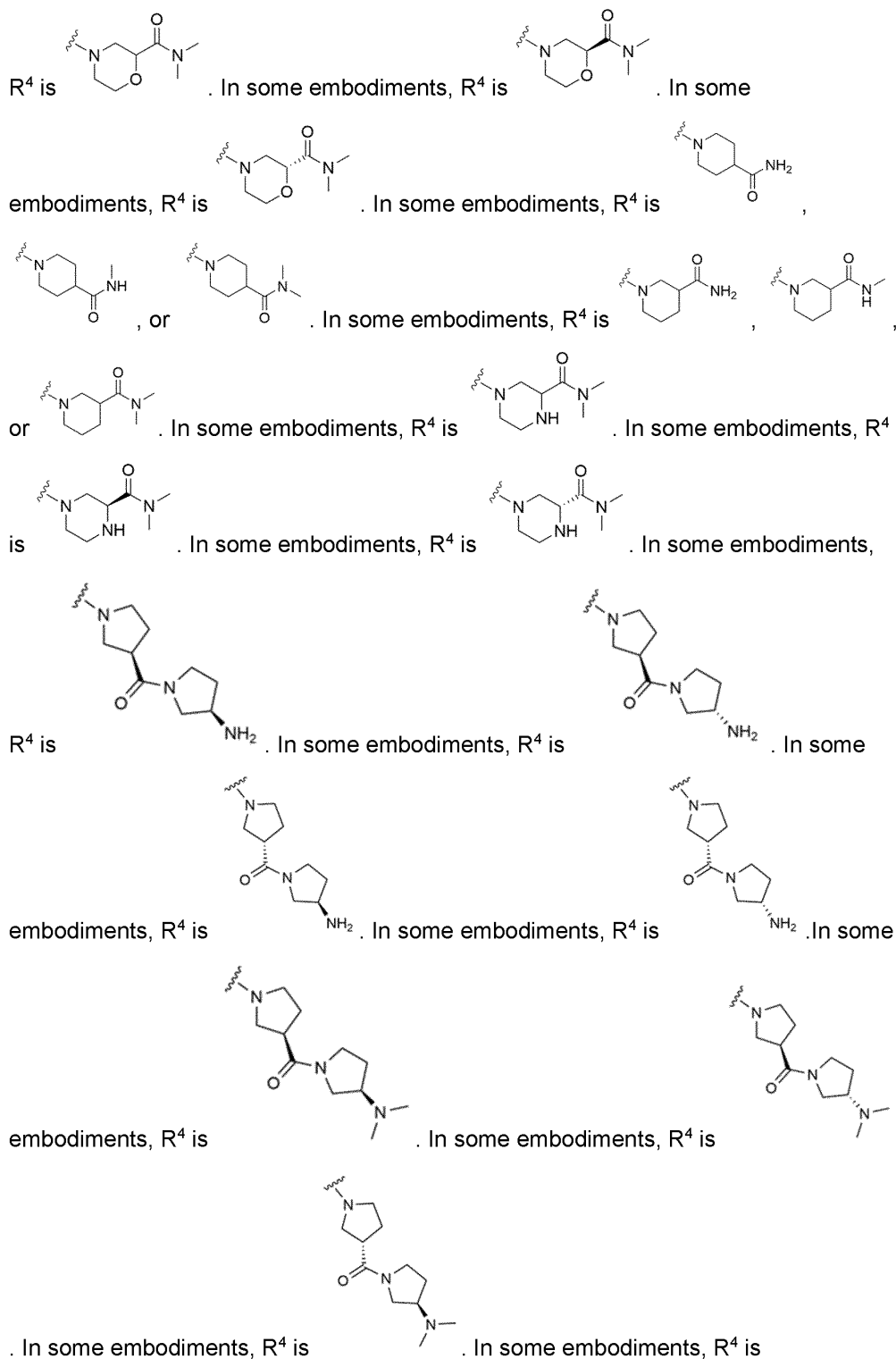
embodiments, R⁴ is  . In some embodiments, R⁴ is  .

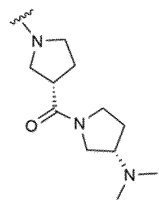
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In some embodiments, R⁴ is  . In some embodiments, R⁴ is  .

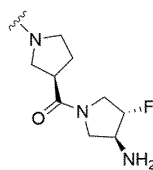
In some embodiments, R⁴ is  . In some embodiments, R⁴ is

 . In some embodiments, R⁴ is  . In some embodiments,

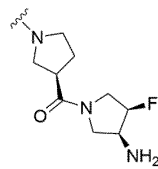




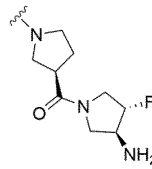
. In some embodiments, R⁴ is



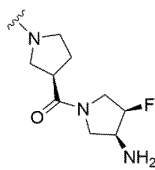
. In some embodiments, R⁴



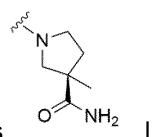
is . In some embodiments, R⁴ is



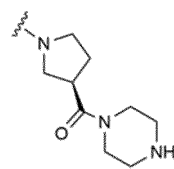
. In some embodiments,



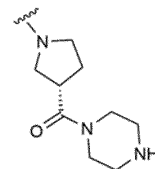
R⁴ is . In some embodiments, R⁴ is



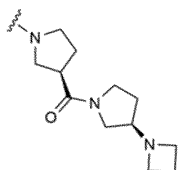
. In some embodiments,



R⁴ is . In some embodiments, R⁴ is

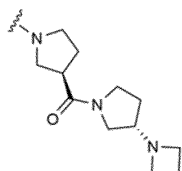


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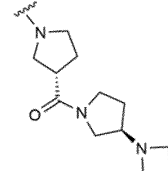


5 In some embodiments, R⁴ is

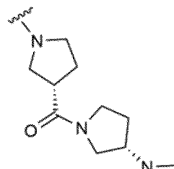
. In some embodiments, R⁴ is



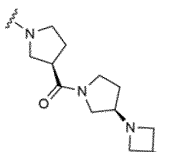
. In some embodiments, R⁴ is



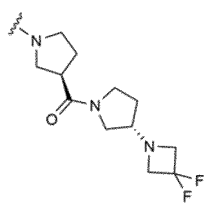
. In some embodiments,



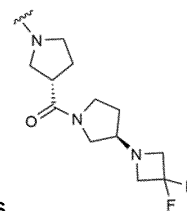
R⁴ is . In some embodiments, R⁴ is



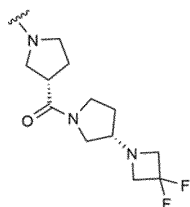
. In some



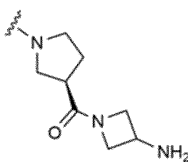
embodiments, R⁴ is



. In some embodiments, R⁴ is

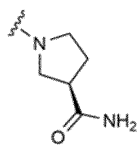


In some embodiments, R⁴ is

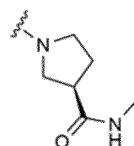


5 In some embodiments, R⁴ is

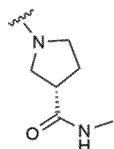
. In some embodiments, R⁴ is



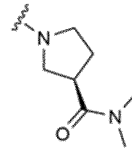
. In some embodiments, R⁴ is



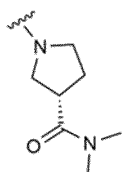
. In some embodiments, R⁴ is



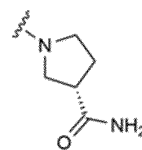
. In some embodiments, R⁴ is



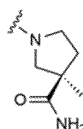
. In some embodiments, R⁴ is



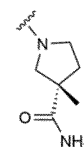
. In some embodiments, R⁴ is

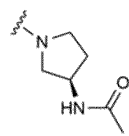


In some embodiments, R⁴ is



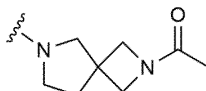
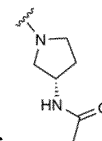
. In some embodiments, R⁴ is





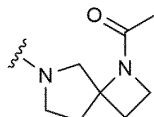
In some embodiments, R⁴ is

. In some embodiments, R⁴ is

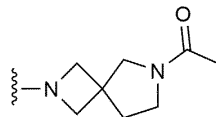


In some embodiments, R⁴ is

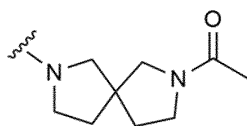
. In some embodiments, R⁴ is



. In some embodiments, R⁴ is

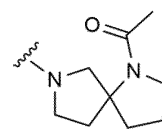


. In some embodiments,



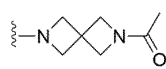
R⁴ is

. In some embodiments, R⁴ is

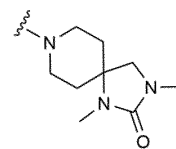


. In some

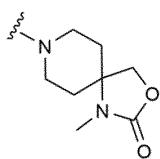
5 embodiments, R⁴ is



. In some embodiments, R⁴ is

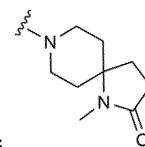


. In

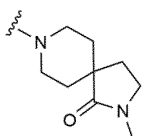


some embodiments, R⁴ is

. In some embodiments, R⁴ is

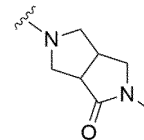


. In

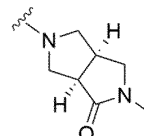


some embodiments, R⁴ is

. In some embodiments, R⁴ is

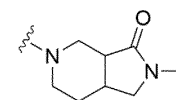


. In



some embodiments, R⁴ is

. In some embodiments, R⁴ is



.

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In some embodiments, the compound is not a compound selected from the group consisting of:

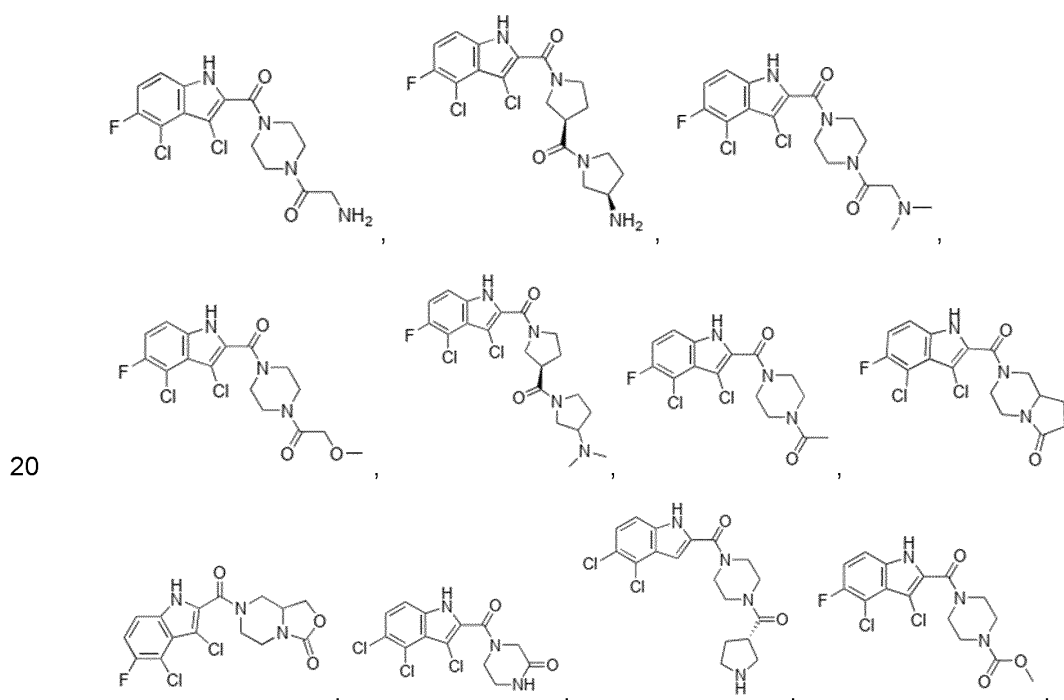
(3a*R*,7a*R*)-2-[(4-Fluoro-1*H*-indol-2-yl)carbonyl]hexahydropyrano[3,4-*c*]pyrrole-7a(1*H*)-carboxamide;

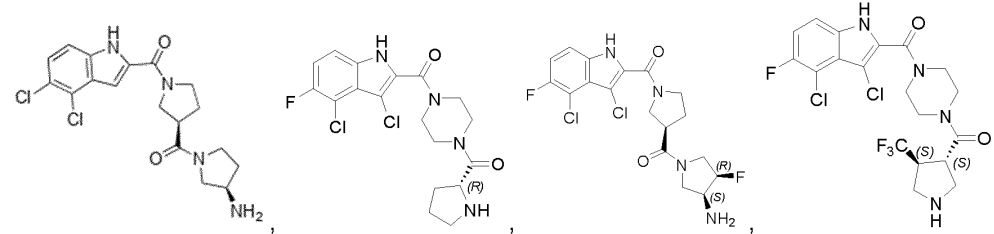
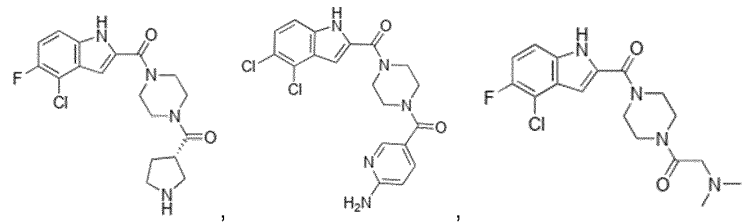
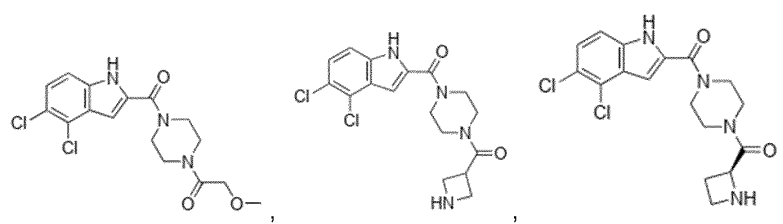
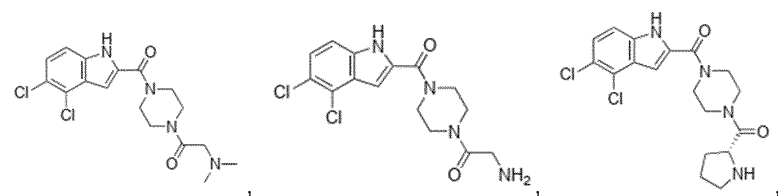
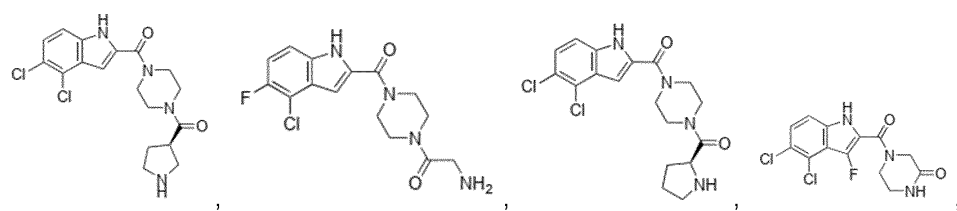
(4,5-dichloro-1*H*-indol-2-yl)(3-(pyrrolidine-1-carbonyl)piperidin-1-yl)methanone;

- (4a*R*,7a*S*)-1-[(4,5-Dichloro-1*H*-indol-2-yl)carbonyl]octahydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one;
- (4-chloro-1*H*-indol-2-yl)(4-(cyclobutanecarbonyl)piperazin-1-yl)methanone;
- (4-chloro-5-methyl-1*H*-indol-2-yl)(4-(cyclopropanecarbonyl)-2,2-dimethylpiperazin-1-yl)methanone;
- 5 (4-fluoro-1*H*-indol-2-yl)(3-(pyrrolidine-1-carbonyl)piperidin-1-yl)methanone;
- [2-(cyclopropylcarbonyl)-4-morpholinyl](4,5-dichloro-1*H*-indol-2-yl)-methanone;
- [2-(cyclopropylcarbonyl)-4-morpholinyl](4-fluoro-1*H*-indol-2-yl)-methanone;
- [4-[(6-bromo-4-fluoro-1*H*-indol-2-yl)carbonyl]-2-morpholinyl]cyclopropyl-methanone;
- 10 1-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-3-methyl-3-pyrrolidinecarboxamide;
- 1-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-3-piperidinecarboxamide;
- 1-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-3-pyrrolidinecarboxamide;
- 1-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-*N*-methyl-3-piperidinecarboxamide;
- 1-[(4-bromo-1*H*-indol-2-yl)carbonyl]-3-methyl-3-pyrrolidinecarboxamide;
- 15 1-[(4-bromo-1*H*-indol-2-yl)carbonyl]-3-piperidinecarboxamide;
- 1-[(4-bromo-1*H*-indol-2-yl)carbonyl]-*N*-methyl-3-piperidinecarboxamide;
- 1-[(4-fluoro-1*H*-indol-2-yl)carbonyl]-*N*-methyl-3-piperidinecarboxamide;
- 1-[(6-bromo-4-fluoro-1*H*-indol-2-yl)carbonyl]-3-methyl-3-pyrrolidinecarboxamide;
- 1-[(6-bromo-4-fluoro-1*H*-indol-2-yl)carbonyl]-3-piperidinecarboxamide;
- 20 1-[(6-bromo-4-fluoro-1*H*-indol-2-yl)carbonyl]-*N*-methyl-3-piperidinecarboxamide;
- 1-[4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1-piperazinyl]-2,2-dimethyl-1-propanone;
- 1-[4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1-piperazinyl]-2-methoxyethanone;
- 1-[4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1-piperazinyl]-2-methyl-1-propanone;
- 1-[4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1-piperazinyl]ethanone;
- 25 1-[4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-3,3-dimethyl-1-piperazinyl]ethanone;
- 1-[4-[(4-chloro-1*H*-indol-2-yl)carbonyl]-1-piperazinyl]ethanone;
- 2-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
- 2-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
- 2-[(4-bromo-1*H*-indol-2-yl)carbonyl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
- 30 2-[(4-chloro-1*H*-indol-2-yl)carbonyl]-7-(2-hydroxyethyl)-2,7-diazaspiro[4.5]decan-6-one;
- 2-[(4-fluoro-1*H*-indol-2-yl)carbonyl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
- 2-[(6-bromo-4-fluoro-1*H*-indol-2-yl)carbonyl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
- 2-amino-1-[4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1-piperazinyl]-ethanone;
- 4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1-(1-methylethyl)-2-piperazinone;
- 35 4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1,6-dimethyl-2-piperazinone;

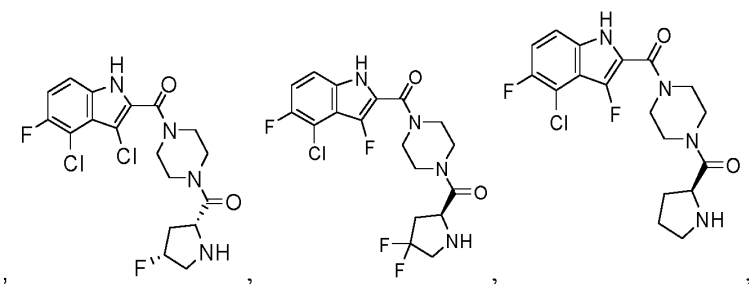
- 4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-2-piperazinone;
 4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-3,3-dimethyl-2-piperazinone;
 4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-3-propyl-2-piperazinone;
 4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-*N*-methyl-2-morpholinecarboxamide;
 5 4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]octahydro-2(1*H*)-quinoxalinone;
 7-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-2,7-diazaspiro[4.4]nonan-3-one;
 7-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]hexahydroimidazo[1,5-*a*]pyrazin-3(2*H*)-one;
 7-[(4-chloro-1*H*-indol-2-yl)carbonyl]hexahydro-3*H*-oxazolo[3,4-*a*]pyrazin-3-one;
 7-[(4-chloro-5-fluoro-1*H*-indol-2-yl)carbonyl]-2,7-diazaspiro[4.4]nonan-3-one;
 10 *rel*-(3*aR*,7*aR*)-2-[(4-Fluoro-1*H*-indol-2-yl)carbonyl]hexahydropyrano[3,4-*c*]pyrrole-
 7*a*(1*H*)-carboxamide;
rel-(3*R*,4*R*)-1-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-4-methyl-3-pyrrolidinecarboxamide;
rel-(3*R*,4*R*)-1-[(4-bromo-1*H*-indol-2-yl)carbonyl]-4-methyl-3-pyrrolidinecarboxamide;
 and
 15 *rel*-(3*R*,4*R*)-1-[(6-bromo-4-fluoro-1*H*-indol-2-yl)carbonyl]-4-methyl-3-
 pyrrolidinecarboxamide.

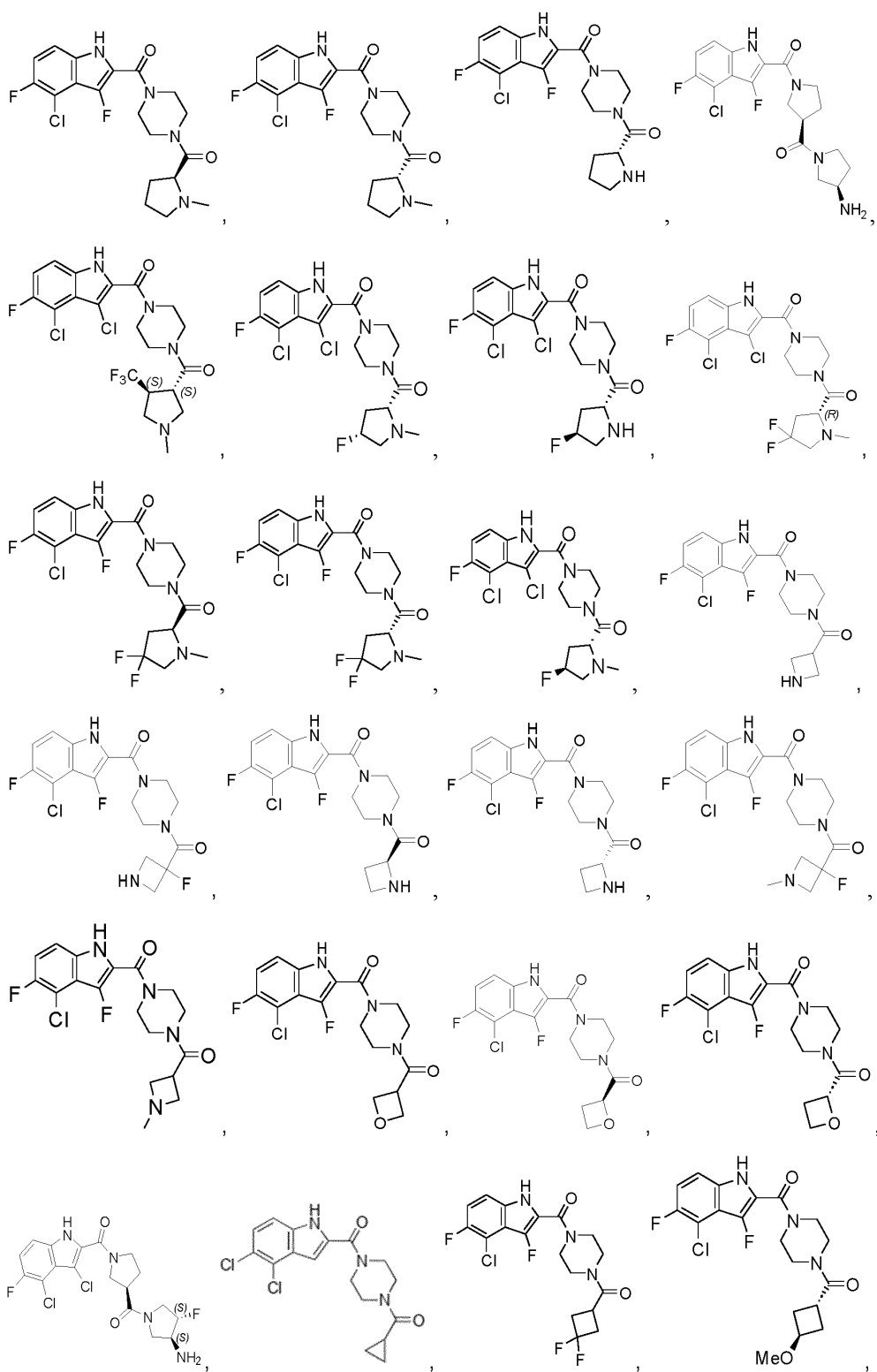
In some embodiments, the compound is selected from Group A consisting of:

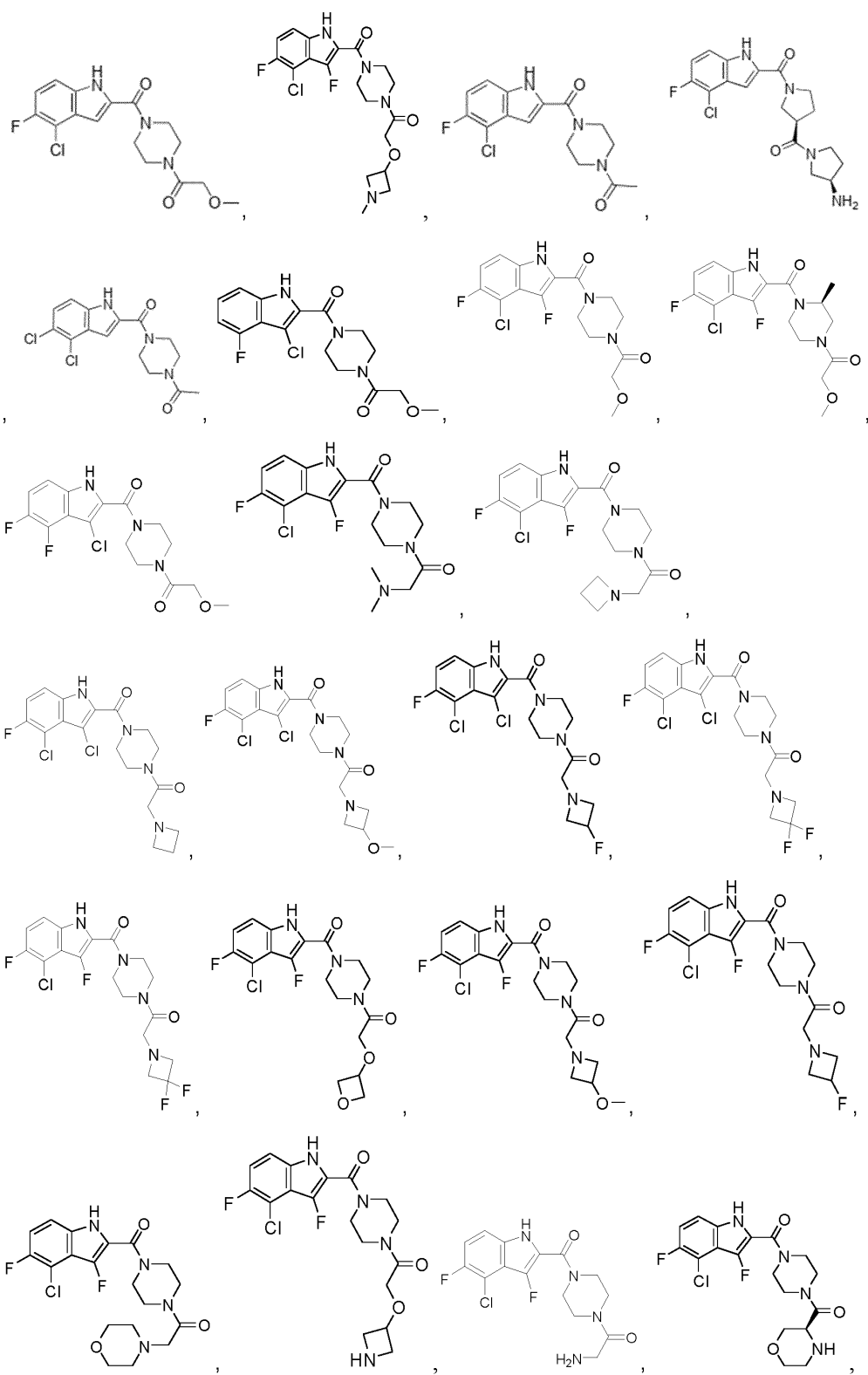


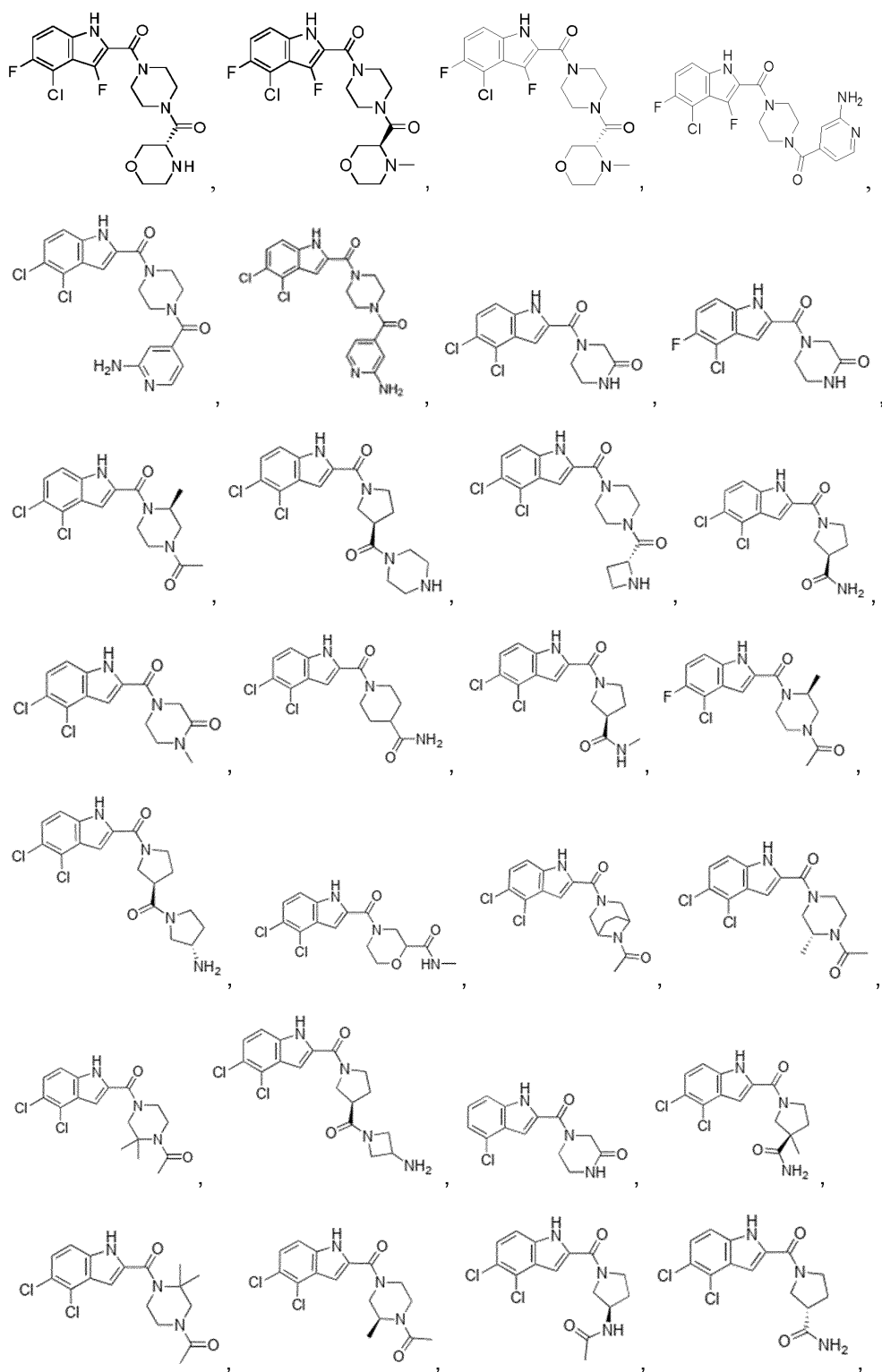


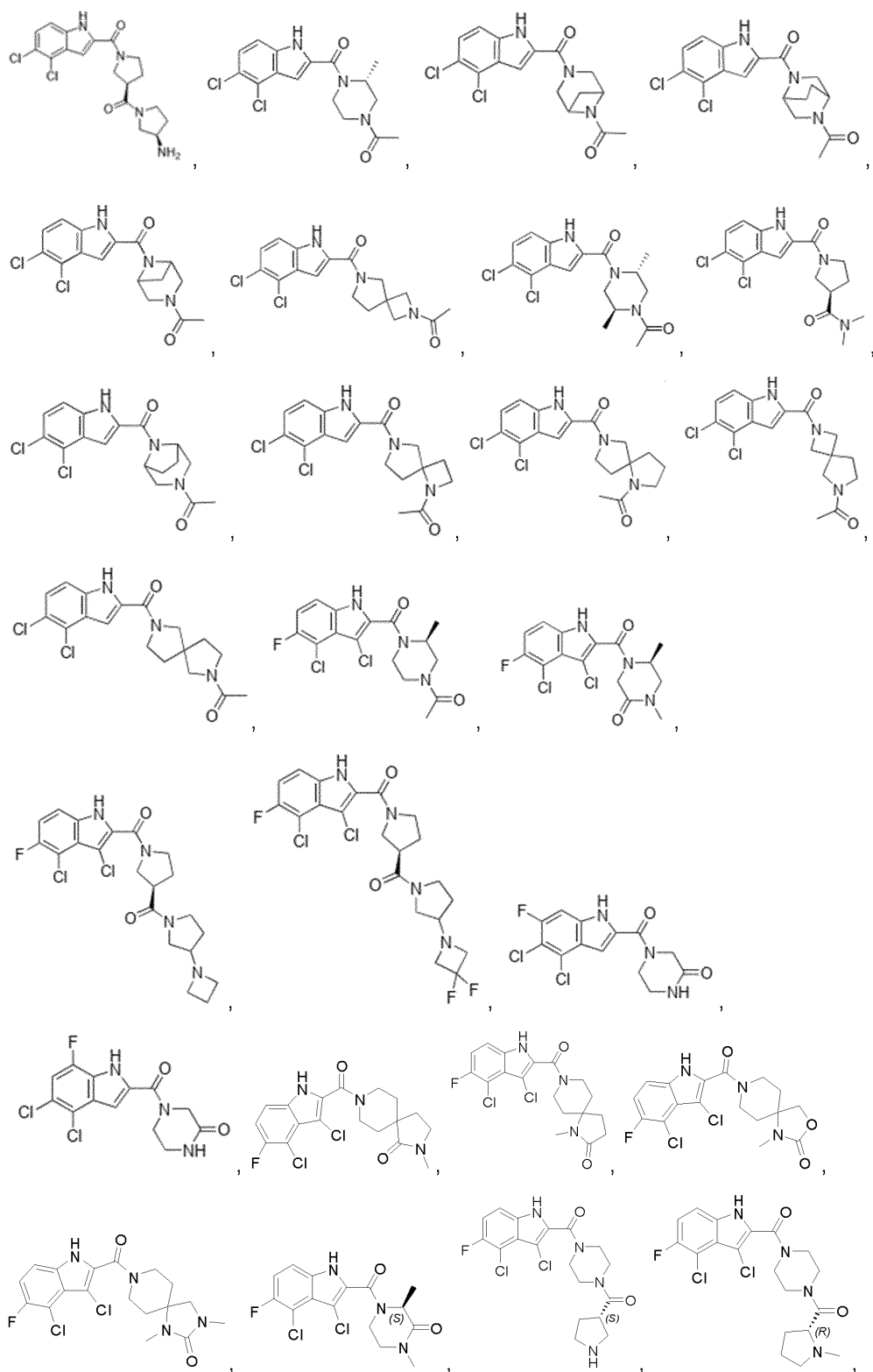
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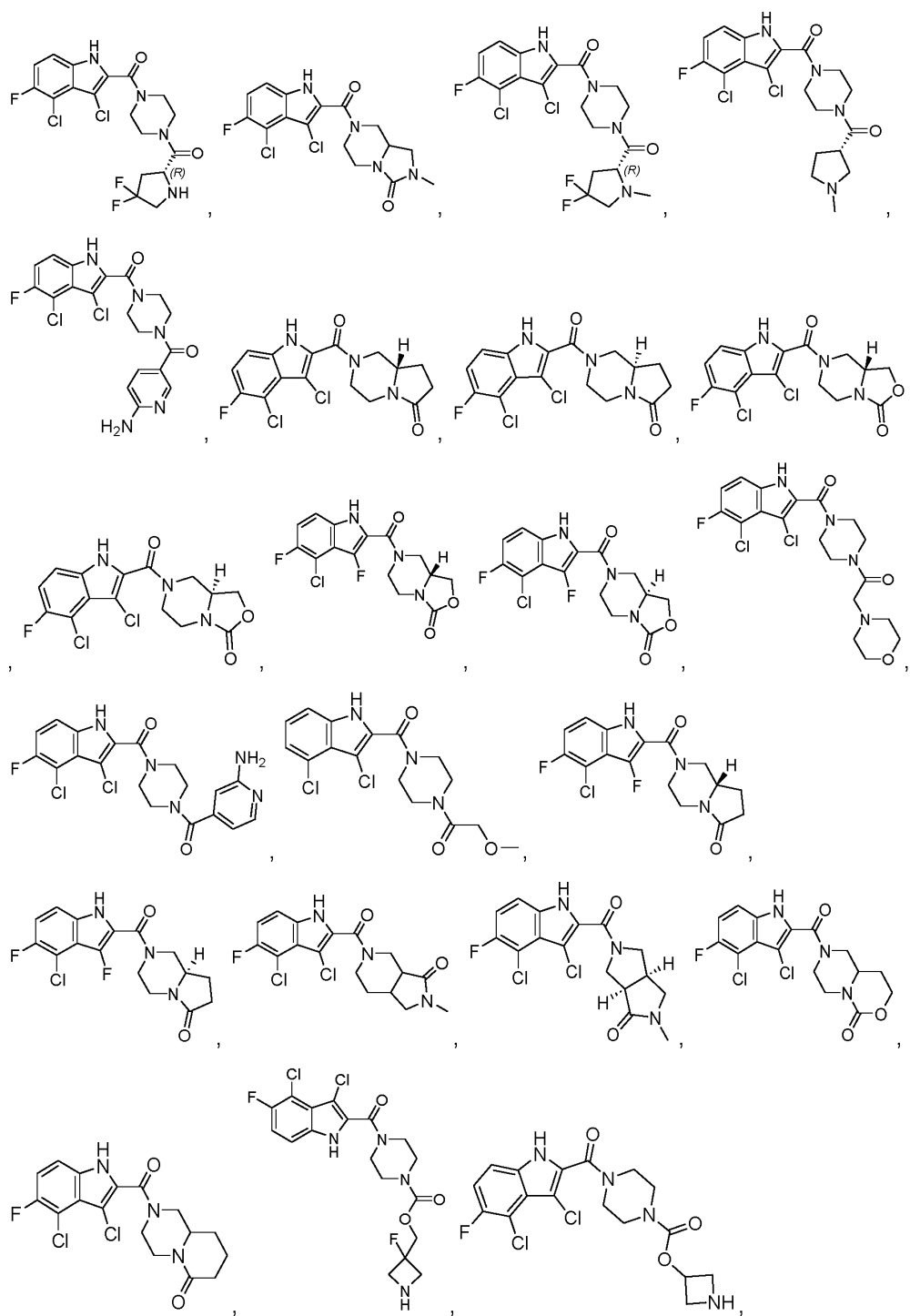


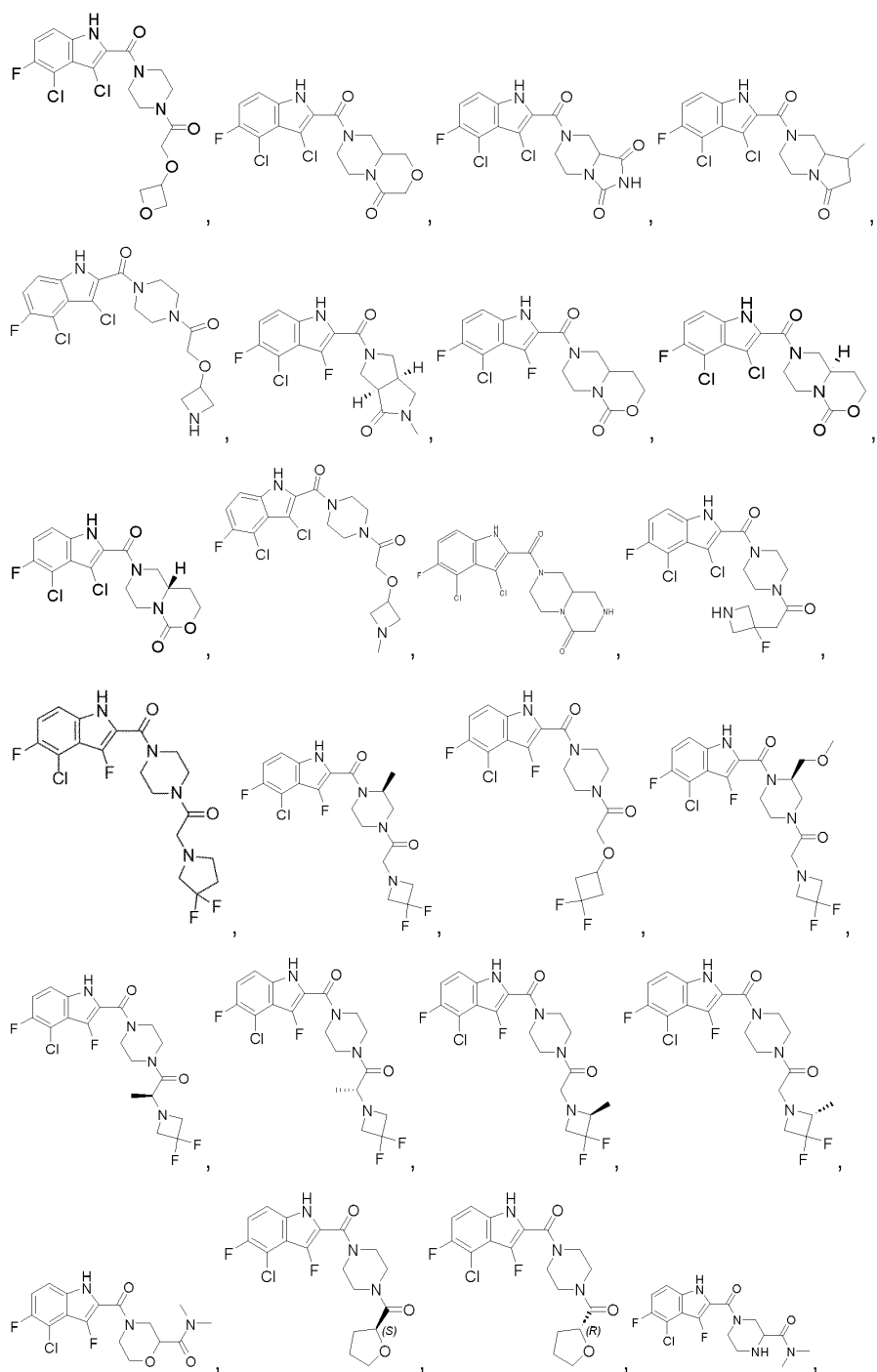


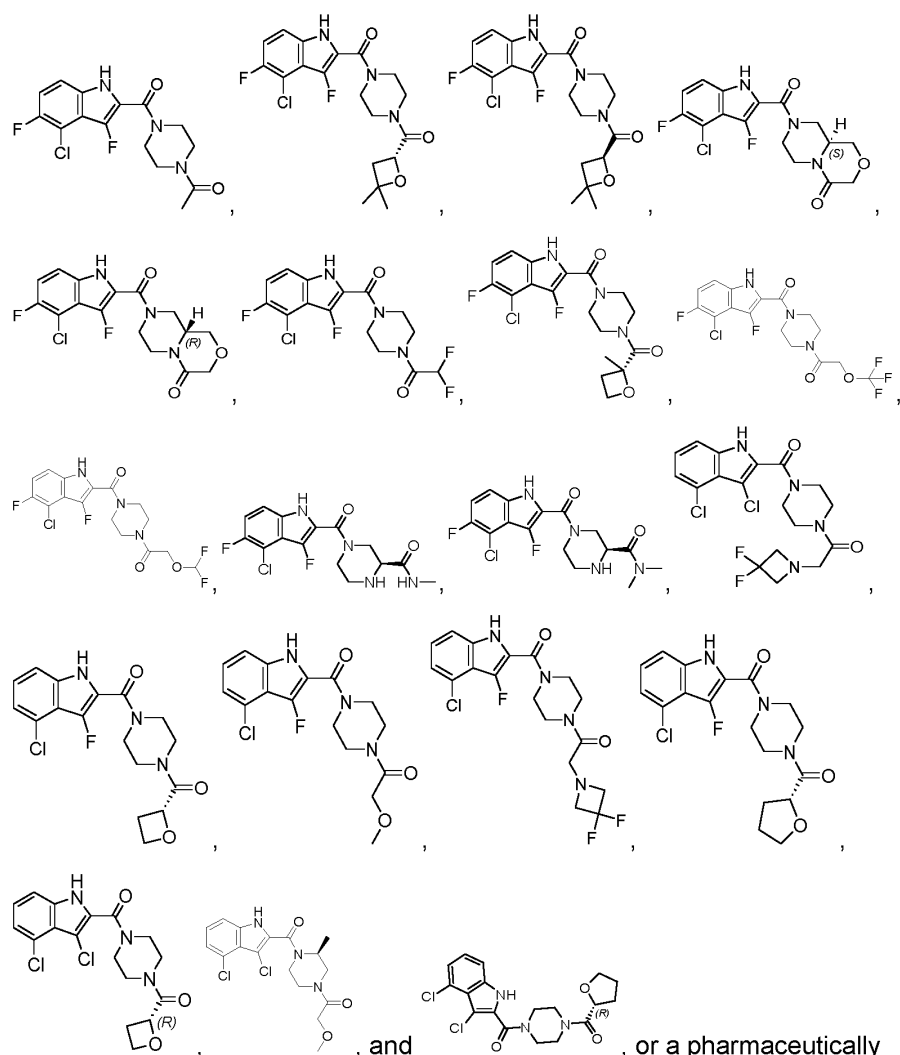












, and , or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention relates to a compound selected from Group A, or a pharmaceutically acceptable salt thereof.

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In some embodiments, the compound is 4-(3,4,5-trichloro-1H-indole-2-carbonyl)piperazin-2-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some

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embodiments, the compound is 1-[(2R)-4-(4,5-dichloro-1H-indole-2-carbonyl)-2-methylpiperazin-1-yl]ethanone, or a pharmaceutically acceptable salt thereof. 1-[(2S)-4-(4,5-

dichloro-1H-indole-2-carbonyl)-2-methyl-piperazin-1-yl]ethanone. In some
embodiments, the compound is 1-[4-(4,5-dichloro-1H-indole-2-carbonyl)-2,2-dimethyl-
piperazin-1-yl]ethanone, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 1-[(3S)-4-(4,5-dichloro-1H-indole-2-carbonyl)-3-methyl-
5 piperazin-1-yl]ethanone, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 1-[(3R)-4-(4,5-dichloro-1H-indole-2-carbonyl)-3-methyl-
piperazin-1-yl]ethanone, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 1-[3-(4,5-dichloro-1H-indole-2-carbonyl)-3,8-
diazabicyclo[3.2.1]octan-8-yl]ethanone, or a pharmaceutically acceptable salt thereof.
10 In some embodiments, the compound is (3R)-1-(4,5-dichloro-1H-indole-2-
carbonyl)pyrrolidine-3-carboxamide, or a pharmaceutically acceptable salt thereof. In
some embodiments, the compound is (3S)-1-(4,5-dichloro-1H-indole-2-
carbonyl)pyrrolidine-3-carboxamide, or a pharmaceutically acceptable salt thereof. In
some embodiments, the compound is 4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-2-
15 one, or a pharmaceutically acceptable salt thereof. In some embodiments, the
compound is 4-(4,5-dichloro-1H-indole-2-carbonyl)-1-methyl-piperazin-2-one, or a
pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-[4-
(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl]ethanone, or a pharmaceutically
acceptable salt thereof. In some embodiments, the compound is 4-(4,5-dichloro-6-
20 fluoro-1H-indole-2-carbonyl)piperazin-2-one, or a pharmaceutically acceptable salt
thereof. In some embodiments, the compound is 4-(4-chloro-5-fluoro-1H-indole-2-
carbonyl)piperazin-2-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is (3R)-1-[(4,5-dichloro-1H-indol-2-yl)carbonyl]-N-
methylpyrrolidine-3-carboxamide, or a pharmaceutically acceptable salt thereof. In
25 some embodiments, the compound is (3S)-1-[(4,5-dichloro-1H-indol-2-yl)carbonyl]-N-
methylpyrrolidine-3-carboxamide, or a pharmaceutically acceptable salt thereof. In
some embodiments, the compound is 4-(4-chloro-1H-indole-2-carbonyl)piperazin-2-
one, or a pharmaceutically acceptable salt thereof. In some embodiments, the
compound is 1-[4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl]-2-methoxy-
30 ethanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the
compound is 1-(4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one,
or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is
1-[4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl]-2-
(dimethylamino)ethanone, or a pharmaceutically acceptable salt thereof. In some
35 embodiments, the compound is 1-[4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-

1-yl]-2-methoxy-ethanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(4,5-dichloro-7-fluoro-1H-indole-2-carbonyl)piperazin-2-one, or a pharmaceutically acceptable salt thereof. In some

5 carbonyl)piperazin-2-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4,5-dichloro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(4,5-dichloro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In

10 some embodiments, the compound is 2-amino-1-[4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl]ethanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is [4-(azetidine-3-carbonyl)piperazin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4,5-dichloro-1H-indol-2-yl)-[4-[(3R)-pyrrolidine-3-carbonyl]piperazin-1-yl]methanone, or a pharmaceutically acceptable salt thereof. In

15 some embodiments, the compound is (4,5-dichloro-1H-indol-2-yl)-[4-[(3S)-pyrrolidine-3-carbonyl]piperazin-1-yl]methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is [4-[(2S)-azetidine-2-carbonyl]piperazin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is [4-[(2R)-azetidine-2-carbonyl]piperazin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4,5-dichloro-1H-indol-2-yl)-[4-[(2S)-pyrrolidine-2-carbonyl]piperazin-1-yl]methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4,5-dichloro-1H-indol-2-yl)-[4-[(2R)-pyrrolidine-2-carbonyl]piperazin-1-yl]methanone, or a pharmaceutically acceptable salt thereof. In

25 some embodiments, the compound is 2-amino-1-[4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl]ethanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-(cyclopropanecarbonyl)piperazin-1-yl)(4,5-dichloro-1H-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-(2-aminoisonicotinoyl)piperazin-1-yl)(4,5-dichloro-1H-indol-2-yl) methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((R)-3-aminopyrrolidin-1-yl)((R)-1-(4,5-dichloro-1H-indole-2-carbonyl) pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((S)-3-aminopyrrolidin-1-yl)((S)-1-(4,5-dichloro-1H-indole-2-carbonyl) pyrrolidin-3-yl)methanone, or a pharmaceutically

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acceptable salt thereof. In some embodiments, the compound is ((R)-3-aminopyrrolidin-1-yl)((S)-1-(4,5-dichloro-1H-indole-2-carbonyl) pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((S)-3-aminopyrrolidin-1-yl)((R)-1-(4,5-dichloro-1H-indole-2-carbonyl) pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some
5 embodiments, the compound is [(3R)-3-(3-aminoazetidine-1-carbonyl)pyrrolidin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is [(3S)-3-(3-aminoazetidine-1-carbonyl)pyrrolidin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is [(3R)-3-[(3S)-3-aminopyrrolidine-1-carbonyl]pyrrolidin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone, or a
10 pharmaceutically acceptable salt thereof. In some embodiments, the compound is [(3S)-3-[(3R)-3-aminopyrrolidine-1-carbonyl]pyrrolidin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is [(3R)-3-[(3R)-3-aminopyrrolidine-1-carbonyl]pyrrolidin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In
15 some embodiments, the compound is [(3S)-3-[(3S)-3-aminopyrrolidine-1-carbonyl]pyrrolidin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is N-[1-(4-acetamidophenyl)sulfonyl-4-piperidyl]-3,5-dimethyl-1H-pyrrole-2-carboxamide, or a
20 pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-N-(1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidin-3-yl)acetamide, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-N-(1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidin-3-yl)acetamide, or a
25 pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpyrrolidine-3-carboxamide, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-1-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpyrrolidine-3-carboxamide, or a
30 pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the
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compound is methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-1-(4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-1-(4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(4,5-dichloro-1H-indole-2-carbonyl)-N-methylmorpholine-2-carboxamide, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-3,3-dimethylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-2-methylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-2-methylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidine-3-carboxamide, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidine-3-carboxamide, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(3-(4,5-dichloro-1H-indole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(5-(4,5-dichloro-1H-indole-2-carbonyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(6-(4,5-dichloro-1H-indole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-((2S,5R)-4-(4,5-dichloro-1H-indole-2-carbonyl)-2,5-dimethylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-((2R,5S)-4-(4,5-dichloro-1H-indole-2-carbonyl)-2,5-dimethylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-((2S,5S)-4-(4,5-dichloro-1H-indole-2-carbonyl)-2,5-dimethylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-((2R,5R)-4-(4,5-dichloro-1H-indole-2-

carbonyl)-2,5-dimethylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-N,N-dimethylpyrrolidine-3-carboxamide, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-1-(4,5-dichloro-1H-indole-2-carbonyl)-N,N-dimethylpyrrolidine-3-carboxamide, or a pharmaceutically acceptable salt thereof. In some embodiment, the compound is 1-(8-(4,5-dichloro-1H-indole-2-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,5-dimethylpiperazin-2-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,5-dimethylpiperazin-2-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 2-amino-1-[4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl]ethanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 2-amino-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(4,5-dichloro-1H-indol-2-yl)(4-propylpiperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4,5-dichloro-1H-indol-2-yl)(4-propylpiperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4-chloro-5-fluoro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(4-chloro-5-fluoro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-azetidin-2-yl(4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-azetidin-2-yl(4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-

yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((R)-3-aminopyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((S)-3-aminopyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3,4-dichloro-5-fluoro-1H-indol-2-yl)((3R)-3-(3-(dimethylamino)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3,4-dichloro-5-fluoro-1H-indol-2-yl)((3S)-3-(3-(dimethylamino)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((R)-3-aminopyrrolidin-1-yl)((R)-1-(4-chloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((S)-3-aminopyrrolidin-1-yl)((S)-1-(4-chloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((R)-3-aminopyrrolidin-1-yl)((S)-1-(4-chloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((S)-3-aminopyrrolidin-1-yl)((R)-1-(4-chloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3-(azetidin-1-yl)pyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3-(azetidin-1-yl)pyrrolidin-1-yl)((S)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3,4-dichloro-5-fluoro-1H-indol-2-yl)((3R)-3-(3-(3,3-difluoroazetidin-1-yl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3,4-dichloro-5-fluoro-1H-indol-2-yl)((3S)-3-(3-(3,3-difluoroazetidin-1-yl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (2-amino-4-pyridyl)-[4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl]methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(6-(4,5-dichloro-1H-indole-2-carbonyl)-2,6-diazaspiro[3.4]octan-2-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(6-(4,5-dichloro-1H-indole-2-carbonyl)-1,6-diazaspiro[3.4]octan-1-yl)ethan-1-one, or a pharmaceutically

acceptable salt thereof. In some embodiments, the compound is 1-(7-(4,5-dichloro-1H-indole-2-carbonyl)-1,7-diazaspiro[4.4]nonan-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(2-(4,5-dichloro-1H-indole-2-carbonyl)-2,6-diazaspiro[3.4]octan-6-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(7-(4,5-dichloro-1H-indole-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methyl-2,8-diazaspiro[4.5]decan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1-methyl-1,8-diazaspiro[4.5]decan-2-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1-methyl-3-oxa-1,8-diazaspiro[4.5]decan-2-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,3-dimethyl-1,3,8-triazaspiro[4.5]decan-2-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,3-dimethylpiperazin-2-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,3-dimethylpiperazin-2-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(methyl-D-prolyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(4,4-difluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(4,4-difluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methylhexahydroimidazo[1,5-a]pyrazin-3(2H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is

(S)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(1-methylpyrrolidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (*R*)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(1-methylpyrrolidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-(6-aminonicotinoyl)piperazin-1-yl)(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-2-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (*R*)-2-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (*R*)-7-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydro-3*H*-oxazolo[3,4-*a*]pyrazin-3-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-7-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydro-3*H*-oxazolo[3,4-*a*]pyrazin-3-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)piperazin-1-yl)-2-morpholinoethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-(2-aminoisonicotinoyl)piperazin-1-yl)(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3,4-dichloro-1*H*-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-2-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (*R*)-2-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-(2-aminoisonicotinoyl)piperazin-1-yl)(4,5-dichloro-1*H*-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((*R*)-3-aminopyrrolidin-1-yl)((*R*)-1-(4,5-dichloro-1*H*-indole-2-carbonyl)pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 2-amino-1-(4-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl)piperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (*R*)-(3,4-dichloro-5-fluoro-1*H*-indol-2-

yl)(4-propylpiperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((3S,4R)-3-amino-4-fluoropyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((3S,4S)-4-(trifluoromethyl)pyrrolidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is azetidin-3-yl(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(3-fluoroazetidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((3S,4S)-3-amino-4-fluoropyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidine-3-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(morpholine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(morpholine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-azetidin-2-yl(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-azetidin-2-yl(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4R)-4-fluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-(2-aminoisonicotinoyl)piperazin-1-yl)(4-chloro-3,5-difluoro-1H-indol-2-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 2-(azetidin-3-yloxy)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-propylpiperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-

(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-prolylpiperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is ((R)-3-aminopyrrolidin-1-yl) ((R)-1-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl) pyrrolidin-3-yl) methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3-chloro-4-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-2-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-morpholinoethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(oxetane-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(3,3-difluorocyclobutane-1-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-((1R,3R)-3-methoxycyclobutane-1-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3-chloro-4,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 2-(azetidin-1-yl)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(1-methylazetidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3aR,6aR)-5-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methylhexahydropyrrolo[3,4-c]pyrrol-1(2H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one, or a pharmaceutically acceptable salt thereof. In

some embodiments, the compound is (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(methyl-L-prolyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(methyl-D-prolyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some

5 embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-methoxyethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 2-(

10 zetidine-1-yl)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl) piperazin-1-yl) ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl) (4-(4-methylmorpholine-3-carbonyl) piperazin-1-yl) methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl) (4-(4-

15 methylmorpholine-3-carbonyl) piperazin-1-yl) methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)octahydro-6H-pyrido[1,2-a]pyrazin-6-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-methoxyazetidin-1-

20 yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-

25 carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-methoxyazetidin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-1-

30 yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-

35 carbonyl)piperazin-1-yl)-2-(oxetan-3-yloxy)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-7-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one, or a

pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-7-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4S)-4-fluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 5-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methyloctahydro-3H-pyrrolo[3,4-c] yridine-3-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((3S,4S)-1-methyl-4-(trifluoromethyl)pyrrolidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4R)-4-fluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(3-fluoro-1-methylazetidine-3-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-((1-methylazetidin-3-yl)oxy)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4S)-4-fluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3-fluoroazetidin-3-yl)methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is azetidin-3-yl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl) piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(oxetan-3-yloxy)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one, or a pharmaceutically

acceptable salt thereof. In some embodiments, the compound is 7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)tetrahydroimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-8-methylhexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 2-(azetidin-3-yloxy)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3aR,6aR)-5-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-2-methylhexahydropyrrolo[3,4-c]pyrrol-1(2H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (3aS,6aS)-5-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-2-methylhexahydropyrrolo[3,4-c]pyrrol-1(2H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 2-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-((1-methylazetidin-3-yl)oxy)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)octahydro-4H-pyrazino[1,2-a]pyrazin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-3-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoropyrrolidin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluorocyclobutoxy)ethan-1-one, or a pharmaceutically acceptable salt thereof. In

some embodiments, the compound is (R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-(methoxymethyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)propan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)propan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoro-2-methylazetidin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoro-2-methylazetidin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylmorpholine-2-carboxamide, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylpiperazine-2-carboxamide, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-dimethyloxetane-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-dimethyloxetane-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-8-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-8-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2,2-difluoroethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(4-chloro-3,5-difluoro-1H-indol-2-

yl)(4-(2-methyloxetane-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(2-methyloxetane-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-
5 (4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(trifluoromethoxy)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(difluoromethoxy)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some
10 embodiments, the compound is (S)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N-methylpiperazine-2-carboxamide, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N-methylpiperazine-2-carboxamide, or a pharmaceutically acceptable salt thereof. In some
15 embodiments, the compound is (S)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylpiperazine-2-carboxamide, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylpiperazine-2-carboxamide, or a pharmaceutically acceptable salt thereof. In some
20 embodiments, the compound is 1-(4-(3,4-dichloro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(4-chloro-3-fluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some
25 embodiments, the compound is 1-(4-(4-chloro-3-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 1-(4-(4-chloro-3-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one, or a pharmaceutically acceptable salt thereof. In some
30 embodiments, the compound is (R)-(4-chloro-3-fluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(4-chloro-3-fluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some
35 embodiments, the compound is (R)-(3,4-dichloro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(3,4-dichloro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is (S)-1-(4-(3,4-dichloro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-methoxyethan-1-one, or a

pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-1-(4-(3,4-dichloro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-methoxyethan-1-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-(3,4-dichloro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-(3,4-dichloro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. Tautomeric forms can also include methyltropic tautomers, which result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a methyl group.

Compounds of the invention also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. In some embodiments, the compounds of the invention include one or more isotopes of atoms in an amount greater than the natural abundance of the isotope. For example, isotopes of hydrogen include tritium and deuterium. In some embodiments, a compound of the invention includes at least one deuterium atom in an amount that is greater than the natural abundance of deuterium (e.g., the compound is enriched in deuterium).

All compounds described herein, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g., in the form of hydrates and solvates).

In one aspect, the present invention is directed to an intermediate compound, or a pharmaceutically acceptable salt thereof, which can be used in the synthesis of the compounds of the present invention. For example, said intermediate compound is in some embodiments one of the intermediate compounds, or a pharmaceutically acceptable salt thereof, of any one of examples 1 to 194 disclosed herein. In some
5 embodiments the compound of the present invention is selected from any of the intermediate compounds, or a pharmaceutically acceptable salt thereof, disclosed in any one of examples 1 to 194 herein.

10 The compounds of the present invention may contain, for example, one or more asymmetric carbon atoms, and therefore may exist as stereoisomers, enantiomers and diastereomers. Accordingly, the scope of the instant invention is to be understood to encompass all possible stereoisomers of the illustrated compounds, including the stereoisomerically pure form and stereoisomeric mixtures of any chemical structures
15 disclosed herein, unless the stereochemistry is specifically identified. If the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it. If the stereochemistry of a structure or a portion of a structure is indicated with, for example, bold or dashed lines,
20 the structure or portion of the structure is to be interpreted as encompassing only the stereoisomer indicated.

The term "stereoisomer" or "stereoisomerically pure" compound as used herein refers to one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereoisomerically pure compound having one chiral
25 center will be substantially free of the mirror image enantiomer of the compound and a stereoisomerically pure compound having two chiral centers will be substantially free of the other enantiomer and diastereomers of the compound. A typical stereoisomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and equal or less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the
30 compound and equal or less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and equal or less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound
35

and equal or less than about 3% by weight of the other stereoisomers of the compound.

In some embodiments, the compound as defined herein is stereoisomerically pure.

5

Mixtures of stereoisomers may be resolved using standard techniques, such as chiral columns or chiral resolving agents, for example as outlined in the example section.

Pharmaceutical composition

10 The present invention also relates to a pharmaceutical composition comprising, for example as an active ingredient, a pharmaceutically effective amount of a compound as disclosed herein. In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically
15 acceptable carrier, excipient and/or diluent.

While a compound as disclosed herein for use in therapy may be administered in the form of the raw chemical compound, it is often preferred to introduce the active ingredient, optionally in the form of a pharmaceutically acceptable salt, in a
20 pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In some embodiments, the invention provides pharmaceutical compositions comprising a compound as disclosed herein or a pharmaceutically acceptable salt thereof,
25 together with one or more pharmaceutically acceptable carriers, and, optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

30 A therapeutic amount or therapeutically effective amount or dose refers to that amount of active ingredient, i.e. the compounds or compositions as disclosed herein, which treats, alleviates, abates, or reduces the severity of symptoms of a disease in a subject, such as ameliorates one or more symptoms of the condition or the condition itself. A therapeutic amount of a compound as described herein may improve patient survival,
35 increase survival time or rate, diminish symptoms, make an injury, disease, or condition

(e.g. a neurodegenerative disease) more tolerable, slow the rate of degeneration or decline, or improve a patient's physical or mental well-being.

Therapeutic efficacy and toxicity, e.g. ED₅₀, may be determined by standard
5 pharmacological procedures in cell cultures or experimental animals. The dose ratio
between therapeutic and toxic effects is the therapeutic index and may be expressed
by ratio between plasma levels resulting in therapeutic effects and plasma ratios
resulting in toxic effects. Pharmaceutical compositions exhibiting large therapeutic
indexes are preferred. In some embodiments, the therapeutically effective dose of a
10 compound as disclosed herein is in the range of about 0.01 mg/kg to about 100 mg/kg
bodyweight/day.

The dose administered must of course be carefully adjusted to the age, weight and
condition of the individual being treated, as well as the route of administration, dosage
15 form and regimen, and the result desired, and the exact dosage should of course be
determined by the practitioner.

To administer refers to a method of delivering agents, compounds, or compositions to
the desired site of biological action. These methods include, but are not limited to,
20 enteral delivery, oral delivery, topical delivery, parenteral delivery, intravenous delivery,
intradermal delivery, intramuscular delivery, intrathecal delivery, colonic delivery, rectal
delivery, or intraperitoneal delivery.

Biological activity

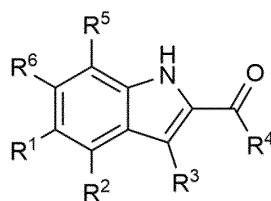
25 As demonstrated in Example 195, compounds of the present invention are K_v1.3
potassium channel antagonists.

Medical use

Being K_v1.3 potassium channel antagonists, the compounds of the present invention
30 are of use in the treatment of diseases and disorders of a living body, including human.
As used herein, the term "treatment" includes treatment, prevention, and/or alleviation
or amelioration of one or more diseases and disorders or one or more symptoms of a
disease or disorder. In one aspect, the compound as described herein is for use as a
medicament.

35

In one aspect, the present invention relates to a compound of Formula (I),



Formula (I)

wherein

R¹ is halogen or H;

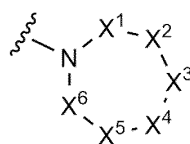
5 R² is halogen;

R³ is H or halogen;

R⁵ is H or halogen;

R⁶ is H or halogen;

R⁴ is of Formula (II):



Formula (II)

wherein

X¹ is C(R⁷)(R⁸);

X² is C(R⁹)(R¹⁰) or a bond;

15 X³ is N(C(O)R¹¹), C(R¹²)(C(O)R¹³), C(R¹⁴)(R¹⁵) or N(R¹⁶);

X⁴ is C(R¹⁷)(R¹⁸), O or C(O);

X⁵ is C(R¹⁹)(R²⁰) or a bond;

X⁶ is a bond or C(R²¹)(R²²);

20 wherein R⁹ and R¹¹, R⁹ and R¹³, R¹⁰ and R¹¹, R¹⁰ and R¹³, R¹³ and R¹⁷, R¹³ and R¹⁸, or R¹⁴ and R¹⁵ are optionally joined together to form a ring together with the intervening atom(s);

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen, such as F;

25 R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen, such as F;

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, halogen, such as F, or -C(O)N(R³¹)(R³²), wherein R³¹ is H or C₁₋₃ alkyl and R³² is H or C₁₋₃ alkyl, or when R⁹ is linked to R¹¹ or R¹³ to form a ring, then R⁹ is a bond, -C(O)- or a C₁₋₃ alkanediyl

- optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;
- R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, halogen, such as F, , or -C(O)N(R³¹)(R³²), wherein R³¹ is H or C₁₋₃ alkyl and R³² is H or C₁₋₃ alkyl, or when R¹⁰ is
- 5 linked to R¹¹ or R¹³ to form a ring, then R¹⁰ is a bond, -C(O)- or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;
- R¹¹ is -X¹³-R³³;
- X¹³ is a bond, C₁₋₃ alkanediyl optionally substituted with C₁₋₃ alkyl, -O-, or C₁₋₃ alkanediyl-
- 10 O-;
- R³³ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidiny, pyrrolidinyl, oxetanyl, tetrahydrofuranyl, and morpholinyl, each of which is optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally
- 15 substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂;
- or when R¹¹ is linked to R⁹ or R¹⁰ to form a ring, then R¹¹ is -O-, -N(R²⁸)-, or C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;
- 20 R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein
- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂,
 - 25 N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
 - said azetidiny optionally substituted with NH₂;
- or when R¹³ is linked to R⁹, R¹⁰, R¹⁷, or R¹⁸ to form a ring, then R¹³ is -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;
- 30 R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),
- wherein
- X⁷ is a bond or C₁₋₃ alkanediyl;
- R²⁴ is C₁₋₃ alkyl; and
- R²³ is H or C₁₋₃ alkyl, and R¹⁵ is H or C₁₋₃ alkyl,

or R²³ is a bond or C₁₋₃ alkanediyl, and R¹⁵ is a bond or C₁₋₃ alkanediyl
and R²³ is linked to R¹⁵ to form a ring;

or R¹⁴ is -X⁹C(O)X¹¹-, R¹⁵ is a bond or C₁₋₃ alkanediyl, and X¹¹ is linked to R¹⁵ to form a
ring,

5

wherein

X⁹ is a bond or -N(R²⁹)-

R²⁹ is C₁₋₃ alkyl;

X¹¹ is -O-, C₁₋₃ alkanediyl, or -N(R³⁰)-; and

R³⁰ is C₁₋₃ alkyl;

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R¹⁶ is H or C₁₋₃ alkyl;

R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or when
R¹⁷ is linked to R¹³ to form a ring, then R¹⁷ is a bond or a C₁₋₃ alkanediyl optionally
substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or when

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R¹⁸ is linked to R¹³ to form a ring, then R¹⁸ is a bond or a C₁₋₃ alkanediyl optionally
substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R²¹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

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R²² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; any two of
R⁷, R⁸, R⁹, R¹⁰, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, and R²² are optionally linked together to form a
ring;

with the proviso that when X⁴ is O, then X³ is C(R¹²)C(O)R¹³ and R¹³ is NH₂, N(H)(CH₃)
or N(CH₃)₂;

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with the proviso that when X³ is N(R¹⁶), then X⁴ is C(O),

with the proviso that when X⁴ is C(O), then X³ is N(R¹⁶), and

with the proviso that when X² is a bond, then X³ is C(R¹²)(C(O)R¹³) or C(R¹⁴)(R¹⁵),

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt
thereof, for use in the treatment of a disease or medical condition where inhibition of

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K_v1.3 potassium channel is beneficial.

In one aspect, the present invention relates to a compound as defined herein, or a
pharmaceutically acceptable salt thereof, or the pharmaceutical composition as defined
herein, for use in the treatment of a disease or medical condition where inhibition of

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K_v1.3 potassium channel is beneficial.

In one aspect, the present invention relates to a method for treatment of a disease or medical condition where inhibition of K_V1.3 potassium channel is beneficial comprising administering a compound, or a pharmaceutically acceptable salt thereof, as described
5 herein to a subject in need thereof.

In one aspect, the present invention relates to use of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the manufacture of a medicament for treatment of disease or medical condition where inhibition of K_V1.3
10 potassium channel is beneficial.

The compounds of the present invention may be utilized in any therapy where it is desired to treat, reduce or alleviate symptoms of K_V1.3 mediated diseases such as inflammatory and autoimmune diseases, diabetes, obesity or cancers.
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In one aspect, the present invention relates to the compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the prophylaxis and/or treatment of K_V1.3 mediated conditions.

20 In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of a neurodegenerative disease. A "neurodegenerative disease" refers to a central nervous system characterized by progressive, normally gradual, loss of functional neural tissue.

25 In some embodiments, the neurodegenerative disease is a tauopathy. Tauopathies depicts some neurodegenerative disorders characterized by tau deposits in the brain, with symptoms of dementia and parkinsonism. In some embodiments, the neurodegenerative disease is a tauopathy selected from the group consisting of Primary age related tauopathy (PART), globular glial tauopathy, Chronic traumatic
30 encephalopathy (CTE), Progressive supranuclear palsy, Corticobasal degeneration, diffuse neurofibrillary tangles with calcification (DNTC), Frontotemporal dementia (FTD), and FTD with parkinsonism-17 (FTD with parkinsonism linked to chromosome 17; FTDP-17).

In some embodiments, the neurodegenerative disease is a neurodegenerative disorders associated with TDP-43 (TDP-43 proteinopathies or TDP-43-opathies). Inclusions of pathogenic deposits containing TAR DNA-binding protein 43 (TDP-43) are evident in the brain and spinal cord of patients that present across a spectrum of neurodegenerative diseases.

In some embodiments, the neurodegenerative disease is a TDP-43 proteinopathy selected from the group consisting of amyotrophic lateral sclerosis (ALS), sporadic amyotrophic lateral sclerosis (sALS), familial amyotrophic lateral sclerosis (fALS), frontotemporal lobar degeneration/disease (FTLD), Primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), FTLD-tau, FTLD-FUS (bvFTLD), FTLD-TDP-43 or FTLD-U (types a, b and c), Facial onset sensory and motor neuronopathy (FOSMN), Limbic-predominant age-related TDP-43 encephalopathy (LATE), cerebral age-related TDP-43 with sclerosis (CARTS), Guam Parkinson-dementia complex (G-PDC) and ALS (G-ALS), Kii ALS/PDC, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam (ALS-PDC), Multisystem proteinopathy (MSP; also referred to as inclusion body myopathy (IBM) associated with early-onset Paget disease of the bone and FTLD dementia), Perry disease, and disorders with concomitant TDP-43 pathology, including Alzheimer's disease (AD) and Chronic traumatic encephalopathy (CTE).

In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of muscular dystrophy such as myotonic dystrophy (DM) including Type 1 DM (DM1) and Type 2 DM (DM2).

In some embodiments, the neurodegenerative disease is Multisystem proteinopathy (MSP). MSP is a dominantly inherited, pleiotropic, degenerative disorder of humans that can affect muscle, bone, and/or the central nervous system. MSP can manifest clinically as classical amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), inclusion body myopathy (IBM), Paget's disease of bone (PDB), or as a combination of these disorders (IBMPFD, IBMPFD/ALS).

In some embodiments, the neurodegenerative disease is a synucleinopathy.

Synucleinopathies (also called α -Synucleinopathies) are neurodegenerative diseases characterised by the abnormal accumulation of aggregates of alpha-synuclein protein in neurons, nerve fibres or glial cells.

- 5 In some embodiments, the neurodegenerative disease is a synucleinopathy selected from the group consisting of Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), neuroaxonal dystrophies, Alzheimer's Disease with Amygdalar Restricted Lewy Bodies (AD/ALB).
- 10 In some embodiments, the neurodegenerative disease is cognitive deficit and/or memory loss. In some embodiments, the neurodegenerative disease is dementia. In some embodiments, the neurodegenerative disease is dementia selected from the group consisting of Alzheimer's disease, Parkinson's disease dementia, Huntingtons disease dementia, vascular dementia, HIV dementia, frontotemporal dementia,
- 15 dementia with lewy bodies, prion disease dementia, argyrophilic grain dementia, dementia pugilistica, Guadeloupean parkinsonism with dementia, neurofibrillary tangle-predominant dementia, tangle only dementia, Down's syndrome, semantic dementia, familial British dementia, familial Danish dementia, and other dementias caused by another medical condition such as brain tumors, subdural hematoma, endocrine
- 20 disorders, nutritional deficiencies, infections, immune disorders, liver or kidney failure, metabolic disorders such as Kufs disease, some leukodystrophies, some neurological disorders such as epilepsy, and multiple sclerosis.
- 25 Disorders of peripheral nerves (peripheral neuropathy) are the most common neurological complications of systemic amyloidosis. In some embodiments, the neurodegenerative disease is peripheral amyloidosis (peripheral neuropathy in systemic amyloidosis).
- 30 In some embodiments, the neurodegenerative disease is a demyelinating disorder. In some embodiments, the neurodegenerative disease is a demyelinating disorder of the central nervous system, CNS. In some embodiments, the demyelinating disorder is a myelinoclastic or demyelinating disorder, such as selected from the group consisting of multiple sclerosis, neuromyelitis optica (Devic's disease) and idiopathic inflammatorydemyelinating diseases. In some embodiments, the demyelinating
- 35 disorder is a leukodystrophic or dysmyelinating disorder, such as selected from the

group consisting of CNS neuropathies such as vitamin B12 deficiency, central pontine myelinolysis, myelopathies such as tabes dorsalis (syphilitic myelopathy), leukoencephalopathies and leukodystrophies.

5 In some embodiments, the neurodegenerative disease is a demyelinating disorder of the peripheral nervous system, PNS. In some embodiments, the demyelinating disorder is selected from the group consisting of Guillain–Barré syndrome and its chronic counterpart, chronic inflammatory demyelinating polyneuropathy; Anti-MAG peripheral neuropathy; Charcot–Marie–Tooth disease and its counterpart Hereditary
10 neuropathy with liability to pressure palsy; Copper deficiency-associated conditions (peripheral neuropathy, myelopathy, and rarely optic neuropathy); and Progressive inflammatory neuropathy.

In some embodiments, the neurodegenerative disease is Alzheimer’s disease (AD). In
15 some embodiments, the neurodegenerative disease is Alzheimer’s disease (AD) with the R47H mutation. In some embodiments, the neurodegenerative disease is early Alzheimer’s disease. In some embodiments, the neurodegenerative disease is Frontotemporal lobar degeneration (FTLD). In some embodiments, the neurodegenerative disease is frontotemporal dementia. In some embodiments, the
20 neurodegenerative disease is Parkinson’s disease. In some embodiments, the neurodegenerative disease is Nasu-Hakola disease (NHD). In some embodiments, the neurodegenerative disease is FTLD-like syndrome. In some embodiments, the neurodegenerative disease is Huntington disease. In some embodiments, the neurodegenerative disease is Amyotrophic lateral sclerosis (ALS). In some
25 embodiments, the neurodegenerative disease is multiple sclerosis (MS). In some embodiments, the neurodegenerative disease is Guillain-Barre syndrome. In some embodiments, the neurodegenerative disease is chronic inflammatory demyelinating polyneuropathies. In some embodiments, the neurodegenerative disease is progressive subcortical gliosis. In some embodiments, the neurodegenerative disease
30 is Charcot-Marie-Tooth disease. In some embodiments, the neurodegenerative disease is prion disease, such as prion protein cerebral amyloid angiopathy. In some embodiments, the neurodegenerative disease is stroke. In some embodiments, the neurodegenerative disease is cerebral amyloid angiopathy (CAA). In some embodiments the neurodegenerative disease is fragile X-associated tremor ataxia
35 syndrome (FXTAS). In some embodiments the neurodegenerative disease is herpes

simplex virus (HSV) encephalitis. In some embodiments the neurodegenerative disease is HIV-associated neurocognitive disorders (HAND). In some embodiments the neurodegenerative disease is progressive supranuclear palsy (PSP). In some
5 embodiments the neurodegenerative disease is corticobasal degeneration. In some
embodiments the neurodegenerative disease is Hallevorden-Spatz disease. In some
embodiments the neurodegenerative disease is pallido-ponto-nigral degeneration. In
some embodiments the neurodegenerative disease is postencephalitic parkinsonism.
In some embodiments the neurodegenerative disease is subacute sclerosing
panencephalitis (SSPE). In some embodiments the neurodegenerative disease is
10 retinal degeneration (e.g., macular degeneration).

In some embodiments the neurodegenerative disease is a Leukoencephalopathy.
Leukoencephalopathy (leukodystrophy-like diseases) is a term that describes all of the
brain white matter diseases, whether their molecular cause is known or unknown. In
15 some embodiments the neurodegenerative disease is a Leukoencephalopathy selected
from the group consisting of Progressive multifocal leukoencephalopathy, Toxic
leukoencephalopathy, Leukoencephalopathy with vanishing white matter,
Leukoencephalopathy with neuroaxonal spheroids, Reversible posterior
leukoencephalopathy syndrome, Megalencephalic leukoencephalopathy with
20 subcortical cysts, and Hypertensive leukoencephalopathy. In some embodiments, the
neurodegenerative disease is ALSP (Adult-onset leukoencephalopathy with axonal
spheroids and pigmented glia).

In some embodiments the neurodegenerative disease is selected from the group
25 consisting of cerebral autosomal dominant arteriopathy with subcortical infarcts or
leukoencephalopathy; cerebral autosomal recessive arteriopathy with subcortical
infarcts and leukoencephalopathy; and retinal vasculopathy with cerebral
leukoencephalopathy (or cerebroretinal vasculopathy).

In some embodiments the neurodegenerative disease is a leukodystrophy. In some
embodiments the neurodegenerative disease is vanishing white matter disease (VWM).
Leukodystrophies are a group of rare, genetic disorders that affect the white matter of
the brain. In some embodiments the neurodegenerative disease is a leukodystrophy
selected from the group consisting of metachromatic leukodystrophy (MLD, also known
35 as globoid cell leukodystrophy), Krabbe disease, Canavan disease, X-linked

adrenoleukodystrophy, Alexander disease, hypomyelinating leukodystrophy type 7 (4H syndrome), Pelizaeus-Merzbacher disease, cerebrotendineous xanthomatosis and leukoencephalopathy with vanishing white matter. In some embodiments the neurodegenerative disease is adult-onset autosomal dominant leukodystrophy (ADLD).

5 In some embodiments the neurodegenerative disease is X-linked adrenoleukodystrophy (X-ALD). In some embodiments the neurodegenerative disease is Nasu-Hakola disease also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, PLOSL).

10 In some embodiments, the neurodegenerative disease is a transmissible spongiform encephalopathy (TSE), including Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease (GSS), kuru, and fatal familial insomnia.

15 In one aspect, the present invention relates to a method for treatment of a neurodegenerative disease comprising administering a compound, or a pharmaceutically acceptable salt thereof, as described herein to a subject in need thereof.

20 In one aspect, the present invention relates to a method for treatment of a neurodegenerative disease comprising one or more steps of administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, as defined herein to a subject in need thereof.

25 In one aspect, the present invention relates to use of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the manufacture of a medicament for treatment of a neurodegenerative disease.

30 In one aspect, the present invention concerns a compound as defined herein, or pharmaceutically acceptable salt thereof, for use in a method of inhibiting or reducing inflammation. In one aspect, the present invention concerns a compound as defined herein, or pharmaceutically acceptable salt thereof, for use in the treatment of an inflammatory condition or disorder.

35 In some embodiments, said $K_v1.3$ mediated condition is selected from the group consisting of inflammatory conditions, allergies and allergic conditions, hypersensitivity

reactions, autoimmune diseases, severe infections, and organ or tissue transplant rejection. Exemplary Kv1.3 mediated conditions include inflammatory conditions, immune and proliferative disorders, including but not limited to rheumatoid arthritis (RA), osteoarthritis, osteoporosis, uveitis, inflammatory fibrosis (e.g., scleroderma, lung
5 fibrosis, and cirrhosis), inflammatory bowel disorders (e.g., Crohn's disease, ulcerative colitis and inflammatory bowel disease), multiple sclerosis, psoriasis, contact-mediated dermatitis, systemic lupus erythematosus (SLE) and other forms of lupus, diabetes, type I diabetes, cancer, lupus, scleroderma, Sjogren syndrome, and vasculitis.

10 In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of a lysosomal storage disorder (LSD). Most lysosomal storage disorders cause progressive neurodegeneration leading to early death. In some embodiments the LSD is a
15 lipidoses, such as a lipidoses selected from the group consisting of cholesteryl ester storage disease, fucosidosis, Schindler disease and Wolman disease. In some embodiments the LSD is a sphingolipidoses, such as a sphingolipidoses selected from the group consisting of Fabry disease, Gaucher disease, Krabbe disease (globoid cell leukodystrophy), metachromatic leukodystrophy (MLD), Niemann-Pick disease (Types A, B and C), Sandhoff disease, Farmer disease, multiple sulfatase deficiency and Tay-
20 Sachs disease. In some embodiments the LSD is a mucopolysaccharidoses, such as a mucopolysaccharidoses selected from the group consisting of Hunter syndrome, Hurler syndrome, Hurler-Scheie syndrome, Scheie syndrome, Sanfilippo syndrome (A, B, C, D), Morquio syndrome, Maroteaux-Lamy syndrome, Sly syndrome and Natowicz syndrome. In some embodiments the LSD is selected from the group consisting of
25 Batten disease, cystinosis, Danon disease and Pompe disease.

In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of a disease or disorder of the bones and/or joints. In some embodiments, said disease or disorder is
30 selected from the group consisting of arthritis, rheumatoid arthritis, pyle disease, osteoporosis, osteopetrosis, osteosclerosis, skeletal dysplasia and dysosteoplasia.

In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of traumatic brain
35 injuries (TBI) and spinal cord injuries. Traumatic brain injuries (TBI), may also be

known as intracranial injuries. Traumatic brain injuries occur when an external force traumatically injures the brain. Spinal cord injuries (SCI) include any injury to the spinal cord that is caused by trauma instead of disease. In some embodiments the TBI is chronic traumatic encephalopathy (CTE).

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In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of inflammation. In some embodiments said inflammation is selected from the group consisting of inclusion-body myositis, systemic lupus erythematosus (SLE), RA, gout, and certain bowel conditions including Inflammatory bowel disease (IBD).

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In one aspect, the present invention relates to a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition selected from the group consisting of cancer, an immunological disorder, a central nervous system disorder, an inflammatory disorder, a gastroenterological disorder, a metabolic disorder, a cardiovascular disorder, and a kidney disease.

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K_v1.3 channel expression is associated with the control of proliferation in multiple cell types, apoptosis, and cell survival. These processes are crucial for cancer progression. Thus, inhibitors of K_v1.3 channels may be used as anticancer agents. In one aspect, the present invention relates to a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer. In some embodiments, the cancer is selected from the group consisting of biliary tract cancer, brain cancer, breast cancer, cervical cancer, choriocarcinoma, colon cancer, endometrial cancer, esophageal cancer, gastric (stomach) cancer, intraepithelial neoplasms, leukemias, lymphomas, liver cancer, lung cancer, melanoma, neuroblastomas, oral cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, renal (kidney) cancer, sarcomas, skin cancer, testicular cancer, and thyroid cancer.

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K_v1.3 channel blockers are potential therapeutic agents as immunosuppressants or immune system modulators. The K_v1.3 channel is also considered as a therapeutic target for the treatment of obesity and for enhancing peripheral insulin sensitivity in patients with type II diabetes mellitus. These compounds can also be utilized in the prevention of graft rejection and the treatment of immunological (e.g., autoimmune) and inflammatory disorders. The term "autoimmune diseases" generally refers to diseases

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in which "self" components undergo attack by the immune system. Such diseases may affect a single organ, as in, for example, multiple sclerosis and type I diabetes mellitus, or may involve multiple organs, as in, for example, rheumatoid arthritis and systemic lupus erythematosus. In one aspect, the present invention relates to a compound as
5 defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of an autoimmune disease. In some embodiments, the autoimmune disease is Graves' disease. In some embodiments, the autoimmune disease is Hashimoto's thyroiditis. In some embodiments, the autoimmune disease is myasthenia gravis.

10 Autoimmune encephalitis (AIE) is a type of encephalitis (inflammation of the brain) which can result from a number of autoimmune diseases including Rasmussen encephalitis, Systemic lupus erythematosus, Behçet's disease, Hashimoto's encephalopathy, Autoimmune limbic encephalitis, and Sydenham's chorea. In one aspect, the present invention relates to a compound as defined herein, or a
15 pharmaceutically acceptable salt thereof, for use in the treatment of autoimmune encephalitis. In some embodiment, the AIE is selected from the group consisting of Anti-NMDAR encephalitis; Anti-AMPA encephalitis; Anti-GABA encephalitis, such as Anti-GABA-AR encephalitis and Anti-GABA-BR encephalitis; Anti-LGI1 encephalitis; Anti-CASPR2 encephalitis; Anti-GAD encephalitis; Anti-GlyR encephalitis; Anti-DPPX
20 encephalitis; Encephalopathy associated with anti-IgLON5 antibodies; Anti-mGluR1 encephalitis; and anti-mGluR5 encephalitis.

In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of atopic dermatitis
25 (eczema).

In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of coeliac disease.

30 In one aspect, the present invention relates to a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of an inflammatory disorder. In some embodiments, the inflammatory disorder is an inflammatory skin condition, arthritis, psoriasis, spondylitis, parodontitis, or an inflammatory neuropathy.

Kv1.3 channels play a role in gastroenterological disorders including, but not limited to, inflammatory bowel diseases, such as, but not limited to, ulcerative colitis and Crohn's disease. Ulcerative colitis is a chronic inflammatory bowel disease characterized by excessive T cell infiltration and cytokine production. Kv1.3 channels are thought to serve as a marker of disease activity and pharmacological blockade might constitute an immunosuppressive strategy in ulcerative colitis. Crohn's disease is a type of inflammatory bowel disease which may affect any part of the gastrointestinal tract. Crohn's disease is thought to be the result of intestinal inflammation due to a T cell-driven process initiated by normally safe bacteria. Thus, Kv1.3 channel inhibition can be utilized in treating the Crohn's disease. In one aspect, the present invention relates to a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of a gastroenterological disorder. In some embodiments, the gastroenterological disorder is an inflammatory bowel disease such as Crohn's disease or ulcerative colitis.

In one aspect, the present invention relates to a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of an immunological disorder. In some embodiments, the immunological disorder is transplant rejection or an autoimmune disease (e.g., rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, or type I diabetes mellitus).

Expression of Kv1.3 channels is elevated in microglia of human Alzheimer's disease brains, suggesting that Kv1.3 channel is a pathologically relevant microglial target in Alzheimer's disease. Thus, the Kv1.3 channel may be a therapeutic target for Alzheimer's disease. In one aspect, the present invention relates to a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of Alzheimer's disease. In some embodiments, the central nervous system disorder is Alzheimer's disease. In some embodiments, the metabolic disorder is obesity or type II diabetes mellitus. In some embodiments, the kidney disease is chronic kidney disease, nephritis, or chronic renal failure.

Kv1.3 channel blockers can be useful for ameliorating pathology in cardiovascular disorders such as, but not limited to, ischemic stroke, where activated microglia significantly contributes to the secondary expansion of the infarct. In one aspect, the present invention relates to a compound as defined herein, or a pharmaceutically

acceptable salt thereof, for use in the treatment of a cardiovascular disorder. In some embodiments, the cardiovascular disorder is an ischemic stroke.

5 In some embodiments, the condition is selected from the group consisting of cancer, transplant rejection, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, type I diabetes mellitus, Alzheimer's disease, inflammatory skin condition, inflammatory neuropathy, psoriasis, spondylitis, parodontitis, inflammatory bowel disease, obesity, type II diabetes mellitus, ischemic stroke, chronic kidney disease, nephritis, chronic renal failure, and a combination thereof.

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In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of bipolar disorder.

15 In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of Major depressive disorder (MDD, also known as clinical depression). In some embodiments, said MDD is selected from the group consisting of melancholic depression; atypical depression; catatonic depression; depression with anxious distress; depression with peri-partum onset; and seasonal affective disorder.

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In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of schizophrenia.

25 In one aspect, the present invention relates to a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of pain, such as neuropathic pain or inflammatory pain.

30 In one aspect, the present invention relates to a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of CNS complications of COVID-19 infection and/or post-COVID-19 conditions (also known as post-COVID syndrome, long COVID-19, long-haul COVID-19, and post acute sequelae of SARS COV-2 infection (PASC)).

35 In one aspect, the present invention relates to a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of epilepsy, such as

genetic epilepsy or sporadic epilepsy. The term "compound" as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted, unless otherwise specified. Accordingly, the scope of the methods and uses herein is to be understood to encompass methods and uses employing all such forms.

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Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may be administered in combination with compounds and compositions of the present invention. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated." In some embodiments, a provided combination, or composition thereof, is administered in combination with another therapeutic agent. In some embodiments, the present invention provides a method of treating a disclosed disease or condition comprising administering to a patient in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and co-administering simultaneously or sequentially an effective amount of one or more additional therapeutic agents. In some embodiments, the method includes co-administering one or more additional therapeutic agent. Examples of therapeutic agents the combinations of the present invention may also be combined with include, without limitation: treatments for Parkinson's disease, rheumatoid arthritis, Alzheimer's disease, Nasu- Hakola disease, frontotemporal dementia, multiple sclerosis, prion disease, or stroke. In some embodiments, the therapeutic agents the combinations of the present invention may also be combined with include, without limitation: treatments for a disease selected from the group consisting of a tauopathy, a TDP-43 proteinopathy, a synucleinopathy, dementia, amyloidosis, a demyelinating disorder of the CNS, a demyelinating disorder of the PNS, a Leukoencephalopathy, a leukodystrophy, a transmissible spongiform encephalopathy (TSE) and a lysosomal storage disorder (LSD). As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with the present invention. For example, a combination of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form.

The compounds of the present invention may be used to treat an animal patient belonging to any classification. Examples of such animals include mammals such as

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humans, rodents, dogs, cats, zoo animals and farm animals. In some embodiments, the subject referred to herein is a mammal, such as a human.

5 In one aspect, the present invention concerns a method of blocking K_v1.3 potassium channel in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound as defined herein.

10 In one aspect, the present invention relates to a method of modulating the activity of K_v1.3 in a biological tissue, the method comprising contacting a biological tissue expressing K_v1.3 with a K_v1.3 modulating amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof.

15 In one aspect, the present invention concerns a method of suppressing T cell activation in a subject having a condition associated with undesired T cell activation. T cell activation can be measured by well-known methods, such as measuring reduction of IL-2 production by T cells. "Suppressing T cell activation" as used herein refers to the ability of the compound as defined herein, or a pharmaceutically acceptable salt thereof, to inhibit and reduce T cell activation by at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

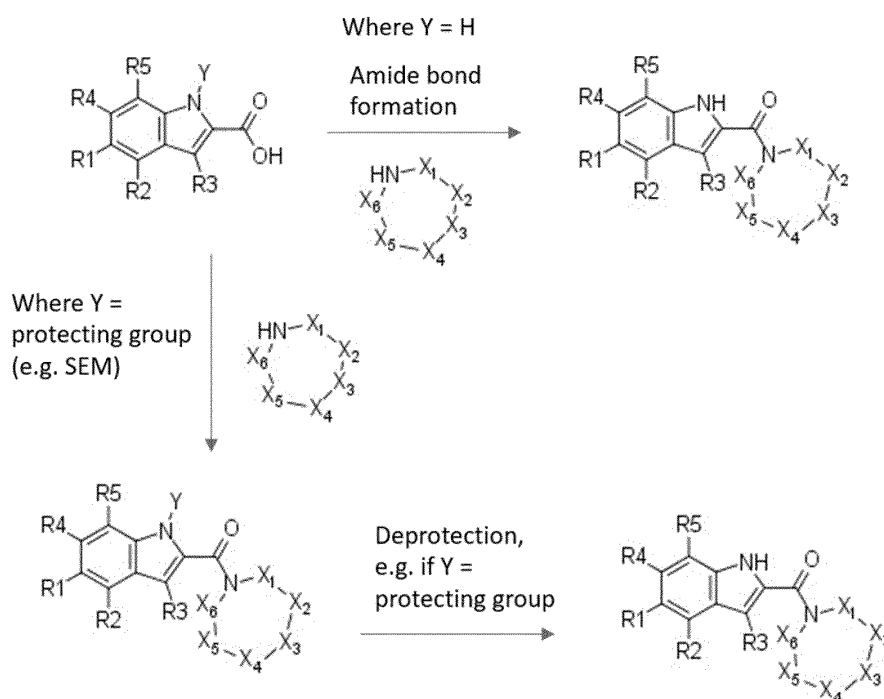
20 In some embodiments, the condition associated with undesired T cell activation is an inflammatory condition, an immune and proliferative disorder, including but not limited to rheumatoid arthritis (RA), osteoarthritis, osteoporosis, uveitis, inflammatory fibrosis (e.g., scleroderma, lung fibrosis, and cirrhosis), inflammatory bowel disorders (e.g., Crohn's disease, ulcerative colitis and inflammatory bowel disease), multiple sclerosis, psoriasis, contact-mediated dermatitis, systemic lupus erythematosus (SLE) and other
25 forms of lupus, diabetes, type I diabetes, cancer, lupus, scleroderma, Sjogren syndrome, and vasculitis.

Method of manufacturing

30 The compounds of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Substituted 2-indole carboxylic acids are made using known literature procedures and in some cases a R³ halogen group is introduced via a halogenation reaction using known procedures and reagents such as NCS for chlorination and Selectfluor™ for fluorination. In some cases an indole protecting group, such as SEM, may be introduced using known procedures, which is then removed later in the sequence using known procedures. In other cases no protecting group is used and the indole NH remains in place during subsequent steps.

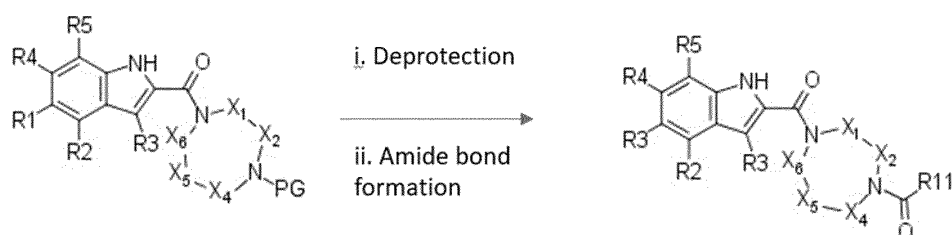
Scheme 1



The appropriately substituted indole-2-carboxylic acids are coupled with amines using standard procedures and reagents such as EDC & HOBt, HATU, TCFH & NMI and DIPEA & COMU (Scheme 1). In some cases a Y protecting group (e.g. SEM) is in place during amide bond formation, which is then removed using standard procedures to afford the desired product where Y = H. In some cases the amide bond formation is performed without protection, i.e. where Y = H.

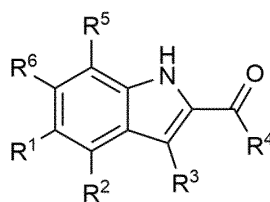
In some cases the indole amide substituent includes a protected amine (e.g. Boc protected) which is deprotected to afford final products or further modified using standard procedures such as amide formation with the appropriate coupling reagents (Scheme 2). In some cases the R11 group also contains a protecting group (e.g. Boc) which is subsequently deprotected to afford the final products.

Scheme 2



All starting materials are either commercially available or known in the art and may be synthesised by using known procedures. Starting materials may also be synthesised using the procedures disclosed herein. Reaction conditions such as reaction temperature, solvent and reagents for the Schemes in this section may be found in the experimental section herein.

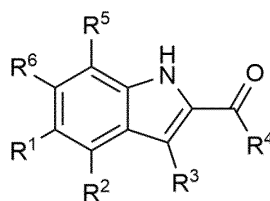
In one aspect, the present invention relates to a method for manufacturing a compound of Formula (I):



Formula (I)

wherein R¹, R², R³, R⁴, R⁵, and R⁶ are as defined herein.

In one aspect, the present invention relates to a method for manufacturing a compound of Formula (I):



Formula (I)

wherein

R¹ is halogen or H;

5 R² is halogen;

R³ is H or halogen;

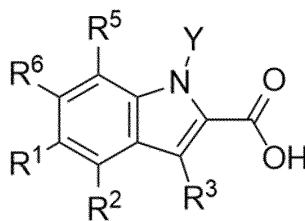
R⁴ is as defined herein;

R⁵ is H or halogen;

R⁶ is H or halogen,

10 said method comprising the steps of:

a. providing a compound of Formula (SI),



Formula (SI)

wherein

15 R¹ is halogen or H;

R² is halogen;

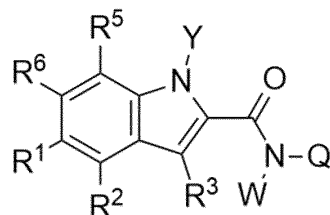
R³ is H or halogen;

R⁵ is H or halogen;

R⁶ is H or halogen; and

20 Y is H or a protecting group;

b. reacting the compound of step a) with $\text{H}-\text{N}^{\text{Q}}_{\text{W}}$, wherein $\text{N}^{\text{Q}}_{\text{W}}$ is R⁴ as defined herein or a precursor for R⁴ as defined herein, to generate the compound of Formula (SII):



Formula (SII)

wherein

R¹ is halogen or H;

5 R² is halogen;

R³ is H or halogen;

R⁵ is H or halogen;

R⁶ is H or halogen;

Y is a H or a protecting group; and

10  is R⁴ as defined herein or a precursor for R⁴ as defined herein.

In some embodiments, Y is a protecting group (e.g. SEM) and said method for manufacturing a compound of Formula (I) includes a step subsequent to step b) wherein the protecting group is removed. In some embodiments, Y is H.

15

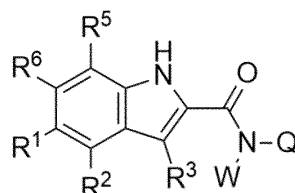
In some embodiments,  is R⁴ as defined herein. In some embodiments,

 is a precursor for R⁴ as defined herein. For example,  may be R⁴ including a protecting group, such as if R⁴ includes an amine, said amine may be protected (e.g. Boc protected), or if R⁴ includes an acid, said acid may be protected (e.g. by an alkyl ester). Further, a precursor for R⁴ also includes groups that are further modified to afford R⁴ as defined herein, for example using standard procedures such as

20

amide formation with the appropriate coupling reagents. When  is a precursor for R⁴ as defined herein, one or more steps are included subsequent to step b) to afford the compound of Formula (I).

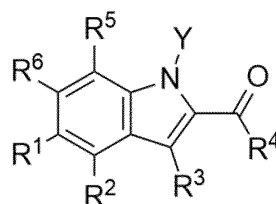
In some embodiments, Y is a protecting group and $\begin{array}{c} \text{Q} \\ | \\ \text{N} \\ | \\ \text{W} \end{array}$ is a precursor for R⁴ as defined herein, and step b) is followed by step c-1), wherein the protecting group in position Y is removed to generate the compound of Formula (SIII):



Formula (SIII)

Step c-1) is then followed by step c-2), wherein $\begin{array}{c} \text{Q} \\ | \\ \text{N} \\ | \\ \text{W} \end{array}$ is modified to R⁴ to generate the compound of Formula (I). In some embodiments, step c-1) and step c-2) occur simultaneously.

Alternatively, in some embodiments, Y is a protecting group and $\begin{array}{c} \text{Q} \\ | \\ \text{N} \\ | \\ \text{W} \end{array}$ is a precursor for R⁴ as defined herein, and step b) is followed by step d-1), wherein $\begin{array}{c} \text{Q} \\ | \\ \text{N} \\ | \\ \text{W} \end{array}$ is modified to R⁴ to generate the compound of Formula (SIV):



Formula (SIV)

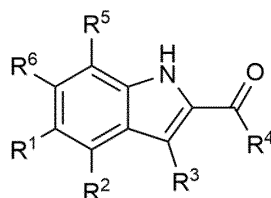
Step d-1) is then followed by step d-2), wherein the protecting group in position Y is removed, and the compound of Formula (I) is generated. In some embodiments, step d-1) and step d-2) occur simultaneously.

In some embodiments, R^3 in Formula (SI) is H. In some embodiments, R^3 in Formula (SI) is H and step a) includes introducing a halogen in position R^3 of the compound of Formula (SI) via a halogenation reaction. In some embodiments, said halogenation reaction includes using known procedures and reagents such as for example NCS for chlorination and SelectfluorTM for fluorination.

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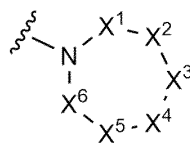
Items

1. A compound of Formula (I),



Formula (I)

- 5 wherein
 R^1 is halogen or H;
 R^2 is halogen;
 R^3 is H or halogen;
 R^5 is H or halogen;
 10 R^6 is H or halogen;
 R^4 is of Formula (II):



Formula (II)

- wherein
 15 X^1 is $C(R^7)(R^8)$;
 X^2 is $C(R^9)(R^{10})$ or a bond;
 X^3 is $N(C(O)R^{11})$, $C(R^{12})(C(O)R^{13})$, $C(R^{14})(R^{15})$ or $N(R^{16})$;
 X^4 is $C(R^{17})(R^{18})$, O or $C(O)$;
 X^5 is $C(R^{19})(R^{20})$ or a bond;
 20 X^6 is a bond or $C(R^{21})(R^{22})$;
 wherein R^9 and R^{11} , R^9 and R^{13} , R^{10} and R^{11} , R^{10} and R^{13} , R^{13} and R^{17} , R^{13} and R^{18} , or R^{14} and R^{15} are optionally joined together to form a ring together with the intervening atom(s);
 R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen,
 25 such as F;
 R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, halogen, such as F, or -C(O)N(R³¹)(R³²), wherein R³¹ is H or C₁₋₃ alkyl and R³² is H or C₁₋₃ alkyl, or when R⁹ is linked to R¹¹ or R¹³ to form a ring, then R⁹ is a bond, -C(O)- or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, halogen, such as F, , or -C(O)N(R³¹)(R³²), wherein R³¹ is H or C₁₋₃ alkyl and R³² is H or C₁₋₃ alkyl, or when R¹⁰ is linked to R¹¹ or R¹³ to form a ring, then R¹⁰ is a bond, -C(O)- or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R¹¹ is -X¹³-R³³;

X¹³ is a bond, C₁₋₃ alkanediyl optionally substituted with C₁₋₃ alkyl, -O-, or C₁₋₃ alkanediyl-O-;

R³³ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidiny, pyrrolidinyl, oxetanyl, tetrahydrofuranyl, and morpholinyl, each of which is optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂;

or when R¹¹ is linked to R⁹ or R¹⁰ to form a ring, then R¹¹ is -O-, -N(R²⁸)-, or C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein

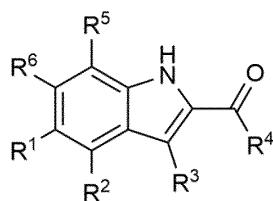
- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
- said azetidiny optionally substituted with NH₂;

or when R¹³ is linked to R⁹, R¹⁰, R¹⁷, or R¹⁸ to form a ring, then R¹³ is -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),

wherein

- X⁷ is a bond or C₁₋₃ alkanediyl;
R²⁴ is C₁₋₃ alkyl; and
R²³ is H or C₁₋₃ alkyl, and R¹⁵ is H or C₁₋₃ alkyl,
or R²³ is a bond or C₁₋₃ alkanediyl, and R¹⁵ is a bond or C₁₋₃ alkanediyl
5 and R²³ is linked to R¹⁵ to form a ring;
or R¹⁴ is -X⁹C(O)X¹¹-, R¹⁵ is a bond or C₁₋₃ alkanediyl, and X¹¹ is linked to R¹⁵ to form a ring,
wherein
X⁹ is a bond or -N(R²⁹)-;
10 R²⁹ is C₁₋₃ alkyl;
X¹¹ is -O-, C₁₋₃ alkanediyl, or -N(R³⁰)-; and
R³⁰ is C₁₋₃ alkyl;
R¹⁶ is H or C₁₋₃ alkyl;
R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or
15 when R¹⁷ is linked to R¹³ to form a ring, then R¹⁷ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;
R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or
when R¹⁸ is linked to R¹³ to form a ring, then R¹⁸ is a bond or a C₁₋₃ alkanediyl
20 optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;
R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
R²¹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
25 R²² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
any two of R⁷, R⁸, R⁹, R¹⁰, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, and R²² are optionally linked together to form a ring;
with the proviso that when X⁴ is O, then X³ is C(R¹²)C(O)R¹³ and R¹³ is NH₂, N(H)(CH₃) or N(CH₃)₂;
30 with the proviso that when X³ is N(R¹⁶), then X⁴ is C(O),
with the proviso that when X⁴ is C(O), then X³ is N(R¹⁶), and
with the proviso that when X² is a bond, then X³ is C(R¹²)(C(O)R¹³) or C(R¹⁴)(R¹⁵),
or a pharmaceutically acceptable salt thereof.
35 2. A compound of Formula (I),



Formula (I)

wherein

R¹ is halogen or H;

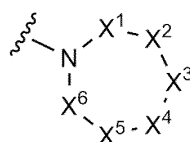
5 R² is halogen;

R³ is H or halogen;

R⁵ is H or halogen;

R⁶ is H or halogen;

R⁴ is of Formula (II):



10

Formula (II)

wherein

X¹ is C(R⁷)(R⁸);

X² is C(R⁹)(R¹⁰) or a bond;

15 X³ is N(C(O)R¹¹), C(R¹²)(C(O)R¹³), C(R¹⁴)(R¹⁵) or N(R¹⁶);

X⁴ is C(R¹⁷)(R¹⁸), O or C(O);

X⁵ is C(R¹⁹)(R²⁰) or a bond;

X⁶ is a bond or C(R²¹)(R²²);

20 wherein R⁹ and R¹¹, R⁹ and R¹³, R¹⁰ and R¹¹, R¹⁰ and R¹³, R¹³ and R¹⁷, R¹³ and R¹⁸, or R¹⁴ and R¹⁵ are optionally joined together to form a ring together with the intervening atom(s);

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

25 R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, or when R⁹ is linked to R¹¹ or R¹³ to form a ring, then R⁹ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, or when R¹⁰ is linked to R¹¹ or R¹³ to form a ring, then R¹⁰ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

- 5 R¹¹ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidiny, pyrrolidinyl, oxetanyl, and morpholinyl, wherein
- said C₁₋₃ alkyl is optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, C₁₋₃ alkoxy, morpholinyl, azetidiny, -O-azetidiny, and -O-oxetanyl, and said azetidiny is optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl;
 - said C₃₋₅ cycloalkyl is optionally substituted with one or more substituents selected from halogen, and C₁₋₃ alkoxy;
 - said pyridinyl is optionally substituted with one or more NH₂;
 - 15 • said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of C₁₋₃ alkyl, halogen, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens;
 - 20 • said azetidiny optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkyl, and NH₂;
- and
- said morpholinyl is optionally substituted with C₁₋₃ alkyl;
- or when R¹¹ is linked to R⁹ or R¹⁰ to form a ring, then R¹¹ is -O-, -N(R²⁸)-, or C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;
- R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂,
- 30 pyrrolidinyl, azetidiny, and piperazinyl, wherein
- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
 - 35 • said azetidiny optionally substituted with NH₂;

or when R^{13} is linked to R^9 , R^{10} , R^{17} , or R^{18} to form a ring, then R^{13} is $-N(R^{28})-$, wherein R^{28} is H or C_{1-3} alkyl;

R^{14} is $-X^7N(R^{23})(C(O)R^{24})$,

wherein

5 X^7 is a bond or C_{1-3} alkanediyl;

R^{24} is C_{1-3} alkyl; and

R^{23} is H or C_{1-3} alkyl, and R^{15} is H or C_{1-3} alkyl,

or R^{23} is a bond or C_{1-3} alkyl, and R^{15} is a bond or C_{1-3} alkanediyl and R^{23} is linked to R^{15} to form a ring;

10 or R^{14} is $-X^9C(O)X^{11}-$, R^{15} is a bond or C_{1-3} alkanediyl, and X^{11} is linked to R^{15} to form a ring,

wherein

X^9 is a bond or $-N(R^{29})-$;

R^{29} is C_{1-3} alkyl;

15 X^{11} is $-O-$, C_{1-3} alkanediyl, or $-N(R^{30})-$; and

R^{30} is C_{1-3} alkyl;

R^{16} is H or C_{1-3} alkyl;

R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or

20 when R^{17} is linked to R^{13} to form a ring, then R^{17} is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or

25 when R^{18} is linked to R^{13} to form a ring, then R^{18} is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{21} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{22} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

30 any two of R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , and R^{22} are optionally linked together to form a ring;

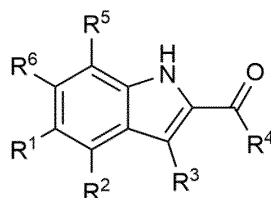
with the proviso that when X^4 is O, then X^3 is $C(R^{12})C(O)R^{13}$ and R^{13} is NH_2 , $N(H)(CH_3)$ or $N(CH_3)_2$;

with the proviso that when X^3 is $N(R^{16})$, then X^4 is $C(O)$, and

35 with the proviso that when X^4 is $C(O)$, then X^3 is $N(R^{16})$,

or a pharmaceutically acceptable salt thereof.

3. A compound of Formula (I),



Formula (I)

5 wherein

R¹ is halogen or H;

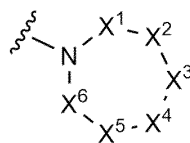
R² is halogen;

R³ is H or halogen;

R⁵ is H or halogen;

10 R⁶ is H or halogen;

R⁴ is of Formula (II):



Formula (II)

wherein

15 X¹ is C(R⁷)(R⁸);

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

X² is C(R⁹)(R¹⁰) or a bond;

X³ is N(C(O)R¹¹), C(R¹²)(C(O)R¹³), C(R¹⁴)(R¹⁵) or N(R¹⁶);

20 R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

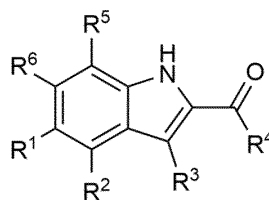
25 R¹¹ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidiny, and pyrrolidinyl, wherein

- said C₁₋₃ alkyl is optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, C₁₋₃ alkoxy, and morpholinyl,

- said pyridinyl is optionally substituted with one or more NH_2 ;
 - said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of C_{1-3} alkyl, halogen, C_{1-3} alkoxy, NH_2 , $\text{N}(\text{H})(\text{CH}_3)$, $\text{N}(\text{CH}_3)_2$ and azetidiny, and said
- 5 azetidiny is optionally substituted with one or more halogens, and
- said azetidiny optionally substituted with NH_2 ;
- or R^{11} is linked to R^9 to form a ring and
- R^9 is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl,
- 10 R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, and
- R^{11} is C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl, wherein one methylene group of the C_{1-3} alkanediyl is optionally replaced by $-\text{O}-$ or $-\text{N}(\text{R}^{28})-$,
- 15 wherein R^{28} is H or C_{1-3} alkyl;
- or R^{11} is linked to R^{10} to form a ring and
- R^9 is H, C_{1-3} alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F,
- R^{10} is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3
- 20 substituents individually selected from halogen and C_{1-3} alkyl, and
- R^{11} is C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl, wherein one methylene group of the C_{1-3} alkanediyl is optionally replaced by $-\text{O}-$ or $-\text{N}(\text{R}^{28})-$,
- wherein R^{28} is H or C_{1-3} alkyl;
- 25 R^{12} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R^{13} is selected from the group consisting of NH_2 , $\text{N}(\text{H})(\text{CH}_3)$, $\text{N}(\text{CH}_3)_2$, pyrrolidinyl, azetidiny, and piperazinyl, wherein
- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH_2 ,
- 30 $\text{N}(\text{H})(\text{CH}_3)$, $\text{N}(\text{CH}_3)_2$ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
- said azetidiny optionally substituted with NH_2 ;
- R^{14} is $-\text{X}^7\text{N}(\text{R}^{23})(\text{C}(\text{O})\text{R}^{24})$,
- wherein
- 35 X^7 is a bond or C_{1-3} alkanediyl;

- R^{24} is C_{1-3} alkyl; and
 R^{23} is H or C_{1-3} alkyl, and R^{15} is H or C_{1-3} alkyl,
 or R^{23} is a bond or C_{1-3} alkanediyl, and R^{15} is a bond or C_{1-3} alkanediyl
 and R^{23} is linked to R^{15} to form a ring;
 5 or R^{14} is $-X^9C(O)X^{11}-$, R^{15} is a bond or C_{1-3} alkanediyl, and X^{11} is linked to R^{15} to
 form a ring,
 wherein
 X^9 is a bond or $-N(R^{29})-$;
 R^{29} is C_{1-3} alkyl;
 10 X^{11} is $-O-$, C_{1-3} alkanediyl, or $-N(R^{30})-$; and
 R^{30} is C_{1-3} alkyl;
 R^{16} is H or C_{1-3} alkyl;
 X^4 is $C(R^{17})(R^{18})$, O or $C(O)$;
 R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 15 R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 X^5 is $C(R^{19})(R^{20})$ or a bond;
 R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 X^6 is a bond or $C(R^{21})(R^{22})$;
 20 R^{21} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{22} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 any two of R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , and R^{22} are optionally linked
 together to form a ring;
 with the proviso that when X^4 is O, then X^3 is $C(R^{12})C(O)R^{13}$ and R^{13} is NH_2 ,
 25 $N(H)(CH_3)$ or $N(CH_3)_2$;
 with the proviso that when X^3 is $N(R^{16})$, then X^4 is $C(O)$, and
 with the proviso that when X^4 is $C(O)$, then X^3 is $N(R^{16})$,
 or a pharmaceutically acceptable salt thereof.

4. A compound of Formula (I),



Formula (I)

wherein

R¹ is halogen or H;

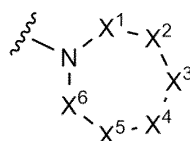
R² is halogen;

R³ is H or halogen;

5 R⁵ is H or halogen;

R⁶ is H or halogen;

R⁴ is of Formula (II):



Formula (II)

10 wherein

X¹ is C(R⁷)(R⁸);

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or F;

X² is C(R⁹)(R¹⁰) or a bond;

15 R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or F;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or F;

X³ is N(C(O)R¹¹), C(R¹²)(C(O)R¹³), C(R¹⁴)(R¹⁵) or N(R¹⁶);

R¹¹ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidinyl and pyrrolidinyl, wherein

- 20
- said C₁₋₃ alkyl is optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂ and C₁₋₃ alkoxy,
 - said pyridinyl is optionally substituted with one or more NH₂;
 - said pyrrolidinyl is optionally substituted with one or more substituents
- 25
- individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidinyl, and said azetidinyl is optionally substituted with one or more halogens, and
- said azetidinyl optionally substituted with NH₂;
 - when R¹¹ is C₁₋₃ alkyl or C₁₋₃ alkoxy, then R¹¹ is optionally linked to R⁹
- 30
- or R¹⁰ to form a ring;

R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or F;

R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein

- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
- said azetidiny optionally substituted with NH₂;

R¹⁴ is -X⁷N(R²³)(C(O)R²⁴);

X⁷ is a bond or CH₂;

R²³ is H or C₁₋₃ alkyl, or R²³ is a bond and R¹⁵ is C₁₋₃ alkanediyl and R²³ is linked to R¹⁵ to form a 4 or 5 membered ring;

R²⁴ is C₁₋₃ alkyl;

R¹⁵ is H or C₁₋₃ alkyl;

R¹⁶ is H or C₁₋₃ alkyl;

X⁴ is C(R¹⁷)(R¹⁸), O or C(O);

R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or F;

R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or F;

X⁵ is C(R¹⁹)(R²⁰) or a bond;

R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or F;

R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or F;

X⁶ is a bond or C(R²¹)(R²²);

R²¹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or F; and

R²² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or F;

any two of R⁷, R⁸, R⁹, R¹⁰, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, and R²² are optionally linked together to form a ring;

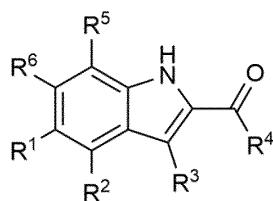
with the proviso that when X⁴ is O, then X³ is C(R¹²)(C(O)R¹³) and R¹³ is NH₂, N(H)(CH₃) or N(CH₃)₂;

with the proviso that when X³ is N(R¹⁶), then X⁴ is C(O), and

with the proviso that when X⁴ is C(O), then X³ is N(R¹⁶),

or a pharmaceutically acceptable salt thereof.

5. A compound of Formula (I),



Formula (I)

wherein

R¹ is halogen or H;

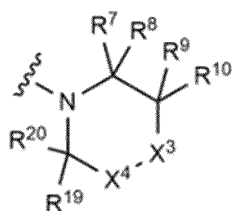
R² is halogen;

R³ is H or halogen;

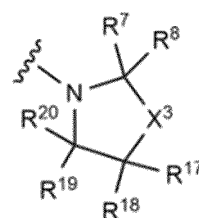
R⁵ is H or halogen;

R⁶ is H or halogen;

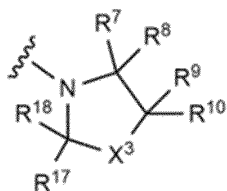
R⁴ is of Formula (XXIV), Formula (XXV), Formula (XXVI) or Formula (XXVII):



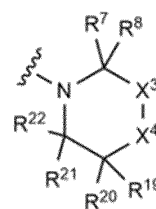
Formula (XXIV)



Formula (XXV)



Formula (XXVI)



Formula (XXVII)

wherein

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

X³ is N(C(O)R¹¹), C(R¹²)(C(O)R¹³), C(R¹⁴)(R¹⁵) or N(R¹⁶);

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

R¹¹ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidiny and pyrrolidinyl, wherein

- said C₁₋₃ alkyl is optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, C₁₋₃ alkoxy, and morpholinyl,
- said pyridinyl is optionally substituted with one or more NH₂;
- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of C₁₋₃ alkyl, halogen, C₁₋₃ alkoxy, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
- said azetidiny optionally substituted with NH₂;

or R¹¹ is linked to R⁹ to form a ring and

R⁹ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl,

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, and

R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

or R¹¹ is linked to R¹⁰ to form a ring and

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F,

R¹⁰ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, and

R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein

- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂,

N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and

- said azetidiny optionally substituted with NH₂;

R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),

5

wherein

X⁷ is a bond or C₁₋₃ alkanediyl;

R²⁴ is C₁₋₃ alkyl; and

R²³ is H or C₁₋₃ alkyl, and R¹⁵ is H or C₁₋₃ alkyl,

or R²³ is a bond or C₁₋₃ alkanediyl, and R¹⁵ is a bond or C₁₋₃ alkanediyl

10

and R²³ is linked to R¹⁵ to form a ring;

or R¹⁴ is -X⁹C(O)X¹¹-, R¹⁵ is a bond or C₁₋₃ alkanediyl, and X¹¹ is linked to R¹⁵ to form a ring,

wherein

X⁹ is a bond or -N(R²⁹)-;

15

R²⁹ is C₁₋₃ alkyl;

X¹¹ is -O-, C₁₋₃ alkanediyl, or -N(R³⁰)-; and

R³⁰ is C₁₋₃ alkyl;

R¹⁶ is H or C₁₋₃ alkyl;

X⁴ is C(R¹⁷)(R¹⁸), O or C(O);

20

R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R²¹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

25

and

R²² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

any two of R⁷, R⁸, R⁹, R¹⁰, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, and R²² are optionally linked together to form a ring;

with the proviso that when X⁴ is O, then X³ is C(R¹²)C(O)R¹³ and R¹³ is NH₂,

30

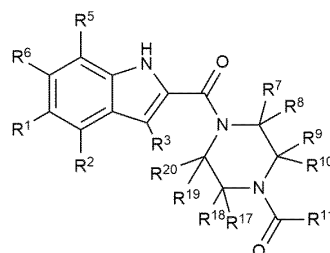
N(H)(CH₃) or N(CH₃)₂;

with the proviso that when X³ is N(R¹⁶), then X⁴ is C(O), and

with the proviso that when X⁴ is C(O), then X³ is N(R¹⁶),

or a pharmaceutically acceptable salt thereof.

6. A compound of Formula (LVII),



Formula (LVII)

wherein

R¹ is halogen or H;

5 R² is halogen;

R³ is H or halogen;

R⁵ is H or halogen;

R⁶ is H or halogen;

10 wherein R⁹ and R¹¹ or R¹⁰ and R¹¹ are optionally joined together to form a ring together with the intervening atoms;

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

15 R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, or when R⁹ is linked to R¹¹ to form a ring, then R⁹ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

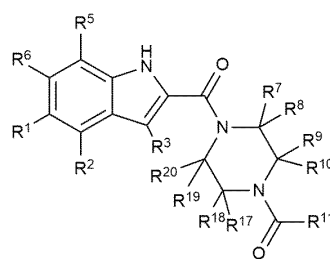
20 R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, or when R¹⁰ is linked to R¹¹ to form a ring, then R¹⁰ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R¹¹ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidynyl, pyrrolidinyl, oxetanyl, and morpholinyl, wherein

- said C₁₋₃ alkyl is optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, C₁₋₃ alkoxy, morpholinyl, azetidynyl, -O-azetidynyl, and -O-oxetanyl, and said azetidynyl is optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl;
 - said C₃₋₅ cycloalkyl is optionally substituted with one or more substituents selected from halogen, and C₁₋₃ alkoxy;
 - said pyridinyl is optionally substituted with one or more NH₂;
- 25
- 30

- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of C₁₋₃ alkyl, halogen, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens;
 - said azetidiny optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkyl, and NH₂;
 - and
 - said morpholinyl is optionally substituted with C₁₋₃ alkyl;
- or when R¹¹ is linked to R⁹ or R¹⁰ to form a ring, then R¹¹ is -O-, -N(R²⁸)-, or C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;
- R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- and
- any two of R⁷, R⁸, R⁹, R¹⁰, R¹⁷, R¹⁸, R¹⁹, and R²⁰, are optionally linked together to form a ring;
- or a pharmaceutically acceptable salt thereof.

7. A compound of Formula (LVII),



Formula (LVII)

- wherein
- R¹ is halogen or H;
- R² is halogen;
- R³ is halogen;
- R⁵, R⁶, R⁸, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H;

wherein R^9 and R^{11} or R^{10} and R^{11} are optionally joined together via R^{33} to form a ring together with the intervening atoms;

R^7 is H or C_{1-3} alkyl optionally substituted with 1 to 3 F;

R^{10} is H, or when R^{10} is linked to R^{11} to form a ring, then R^{10} is a bond or a C_{1-3} alkanediyl;

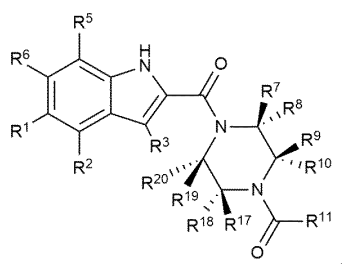
R^9 is H, or when R^9 is linked to R^{11} to form a ring, then R^9 is a bond or a C_{1-3} alkanediyl;

R^{11} is $-X^{13}-R^{33}$;

X^{13} is a bond, C_{1-3} alkanediyl optionally substituted with C_{1-3} alkyl, $-O-$, or C_{1-3} alkanediyl- $O-$; and

R^{33} is C_{1-3} alkyl, azetidiny, pyrrolidinyl, oxetanyl, and tetrahydrofuranyl, each of which is optionally substituted with one or more F; or when R^{11} is linked to R^9 or R^{10} via R^{33} to form a ring, then R^{33} is a bond or a C_{1-3} alkanediyl, or a pharmaceutically acceptable salt thereof.

8. The compound according to any one of the preceding items, wherein the compound of Formula (LVII) is of Formula LVIIa):



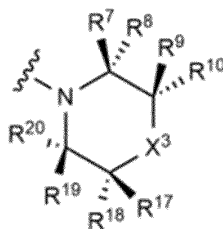
Formula (LVIIa)

or a pharmaceutically acceptable salt thereof.

9. The compound according to any one of the preceding items, with the proviso that when R^4 is of Formula (XXV), then X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$, or a pharmaceutically acceptable salt thereof.
10. The compound according to any one of the preceding items, with the proviso that when R^4 is of Formula (XXVI), then X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$, or a pharmaceutically acceptable salt thereof.
11. The compound according to any one of the preceding items, with the proviso that when R^4 is of Formula (XXVII), then X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$, or a pharmaceutically acceptable salt thereof.

12. The compound according to any one of the preceding items, with the proviso that when R^4 is of Formula (XXVII), then of Formula (XXIV), then X^4 is $C(R^{17})(R^{18})$ or $C(O)$, or a pharmaceutically acceptable salt thereof.

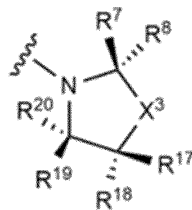
- 5 13. The compound according to item 4, wherein R^4 is of Formula (XXVIII):



Formula (XXVIII)

or a pharmaceutically acceptable salt thereof.

14. The compound according to item 4, wherein R^4 is of Formula (XXIX):

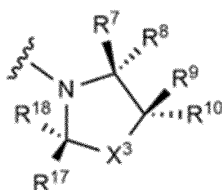


Formula (XXIX)

or a pharmaceutically acceptable salt thereof.

15. The compound according to any one of the preceding items, wherein R^4 is of Formula (XXIX), and X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$, or a pharmaceutically acceptable salt thereof.

16. The compound according to item 4, wherein R^4 is of Formula (XXX):

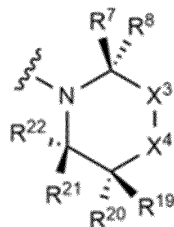


Formula (XXX)

or a pharmaceutically acceptable salt thereof.

17. The compound according to any one of the preceding items, wherein R^4 is of Formula (XXX), and X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$, or a pharmaceutically acceptable salt thereof.

18. The compound according to item 4, wherein R^4 is of Formula (XXXI):

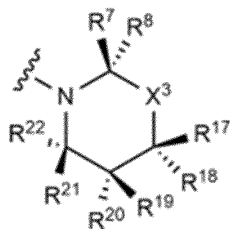


Formula (XXXI)

or a pharmaceutically acceptable salt thereof.

19. The compound according to any one of the preceding items, wherein R^4 is of Formula (XXXI), and X^3 is $C(R^{12})(C(O)R^{13})$ or $C(R^{14})(R^{15})$, or a pharmaceutically acceptable salt thereof.

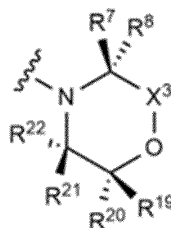
20. The compound according to item 4, wherein R^4 is of Formula (XXXII):



Formula (XXXII)

or a pharmaceutically acceptable salt thereof.

21. The compound according to item 4, wherein R^4 is of Formula (XXXIII):



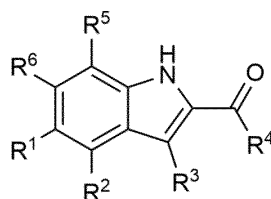
Formula (XXXIII)

or a pharmaceutically acceptable salt thereof.

22. The compound according to any one of the preceding items, with the proviso that when X^3 is $N(C(O)R^{11})$ or $N(R^{16})$, then X^2 is not a bond, or a pharmaceutically acceptable salt thereof.

23. The compound according to any one of the preceding items, with the proviso that when X^3 is $N(C(O)R^{11})$ or $N(R^{16})$, then X^5 and X^6 are not both bonds, or a pharmaceutically acceptable salt thereof.

24. A compound of Formula (I),



Formula (I)

wherein

R^1 is halogen or H;

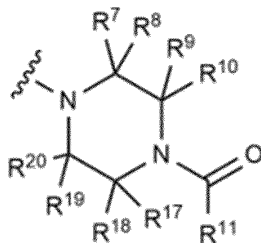
R^2 is halogen;

R^3 is H or halogen;

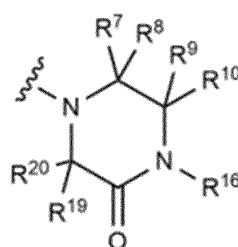
R^5 is H or halogen;

R^6 is H or halogen;

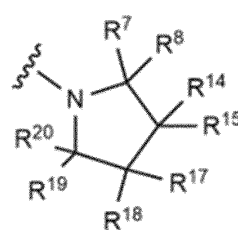
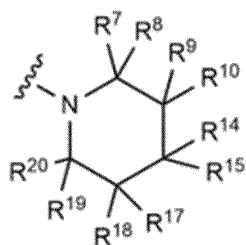
R^4 is of Formula (III), Formula (XXXIV), Formula (XXXV), Formula (XXXVI), Formula (XXXVII), Formula (XXXVIII), Formula (XXXIX), or Formula (XL):



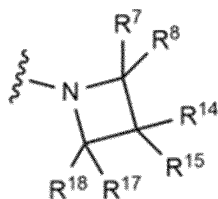
Formula (III)



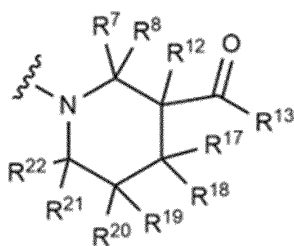
Formula (XXXIV)



Formula (XXXV)

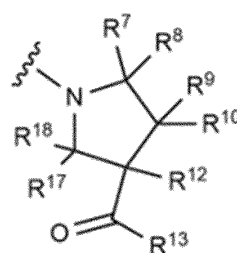


Formula (XXXVII)

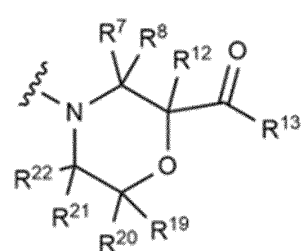


Formula (XXXIX)

Formula (XXXVI)



Formula (XXXVIII)



Formula (XL)

wherein

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

5 R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F;

10 R¹¹ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₅ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidinyl and pyrrolidinyl, wherein

- said C₁₋₃ alkyl is optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, C₁₋₃ alkoxy, and morpholinyl,
- said pyridinyl is optionally substituted with one or more NH₂;
- 15 • said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of C₁₋₃ alkyl, halogen, C₁₋₃ alkoxy, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidinyl, and said azetidinyl is optionally substituted with one or more halogens, and
- said azetidinyl optionally substituted with NH₂;

or R¹¹ is linked to R⁹ to form a ring and

R⁹ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl,

5 R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F, and

R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

10 or R¹¹ is linked to R¹⁰ to form a ring and

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, or halogen, such as F,

R¹⁰ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, and

15 R¹¹ is C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

20 R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein

- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
- 25 • said azetidiny optionally substituted with NH₂;

R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),

wherein

X⁷ is a bond or C₁₋₃ alkanediyl;

30 R²⁴ is C₁₋₃ alkyl; and

R²³ is H or C₁₋₃ alkyl, and R¹⁵ is H or C₁₋₃ alkyl,

or R²³ is a bond or C₁₋₃ alkanediyl, and R¹⁵ is a bond or C₁₋₃ alkanediyl and R²³ is linked to R¹⁵ to form a ring;

35 or R¹⁴ is -X⁹C(O)X¹¹-, R¹⁵ is a bond or C₁₋₃ alkanediyl, and X¹¹ is linked to R¹⁵ to form a ring,

wherein

X^9 is a bond or $-N(R^{29})-$;

R^{29} is C_{1-3} alkyl;

X^{11} is $-O-$, C_{1-3} alkanediyl, or $-N(R^{30})-$; and

5

R^{30} is C_{1-3} alkyl;

R^{16} is H or C_{1-3} alkyl;

R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

10

R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{21} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

and

R^{22} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

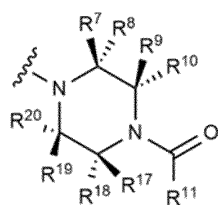
and any two of R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , and R^{22} are optionally

15

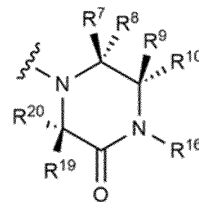
linked together to form a ring,

or a pharmaceutically acceptable salt thereof.

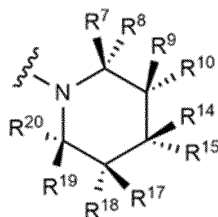
25. The compound according to item 22, wherein R^4 is of Formula (IV), Formula (XLI), Formula (XLII), Formula (XLIII), Formula (XLIV), Formula (XLV), Formula (XLVI), Formula (XLVII), Formula (XLVIII), Formula (XLIX) or Formula (L):



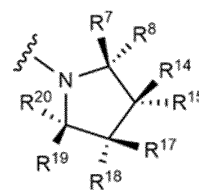
Formula (IV)



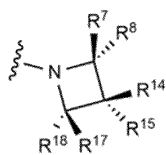
Formula (XLI)



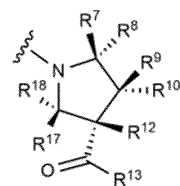
Formula (XLII)



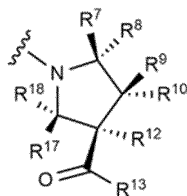
Formula (XLIII)



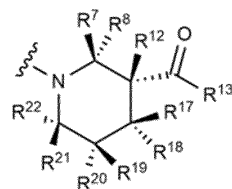
Formula (XLIV)



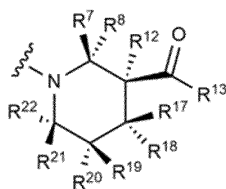
Formula (XLV)



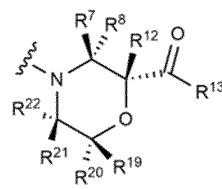
Formula (XLVI)



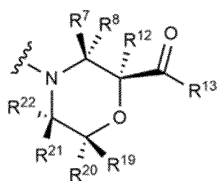
Formula (XLVII)



Formula (XLVIII)



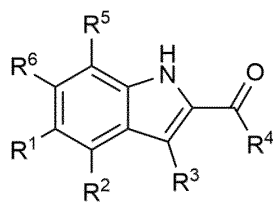
Formula (XLIX)



Formula (L)

or a pharmaceutically acceptable salt thereof.

26. A compound of Formula (I),



Formula (I)

5

wherein

R¹ is halogen or H;

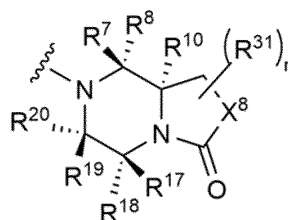
R² is halogen;

R³ is H or halogen;

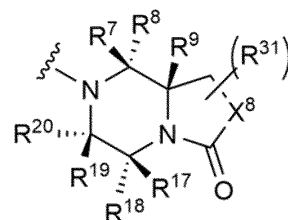
R⁵ is H or halogen;

R⁶ is H or halogen;

R⁴ is of Formula (XXa) or Formula (XXb):



Formula (XXa)



Formula (XXb)

5

wherein

R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen, such as F;

R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen, such as F;

10

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

15

R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R³¹ is individually halogen or C₁₋₃ alkyl;

r is 0, 1, 2, 3 or 4;

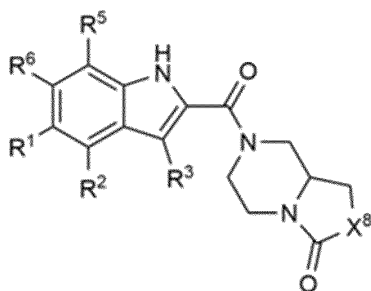
X⁸ is -CH₂-, -O-, -CH₂O-, -OCH₂-, -N(R²⁸)-, or -CH₂N(R²⁸)-; and

R²⁸ is H or C₁₋₃ alkyl,

20

or a pharmaceutically acceptable salt thereof.

27. A compound of Formula (XXIII):



Formula (XXIII)

wherein

R¹ is halogen or H;

5 R² is halogen;

R³ is H or halogen;

R⁵ is H or halogen;

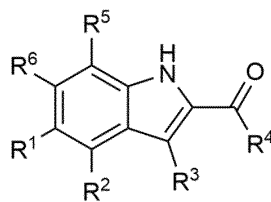
R⁶ is H or halogen;

X⁸ is -CH₂-, -O- or -N(R²⁸)-; and

10 R²⁸ is H or C₁₋₃ alkyl,

or a pharmaceutically acceptable salt thereof.

28. A compound of Formula (I),



Formula (I)

15 wherein

R¹ is halogen or H;

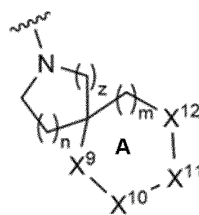
R² is halogen;

R³ is H or halogen;

R⁵ is H or halogen;

20 R⁶ is H or halogen;

R⁴ is of Formula (XIX):



Formula (XIX)

wherein

X^9 is a bond or $-N(R^{29})-$;

5 R^{29} is C_{1-3} alkyl;

X^{10} is $-C(O)-$, $-CH_2-$, or a bond;

X^{11} is $-O-$, $-CH_2-$, or $-N(R^{30})-$;

R^{30} is C_{1-3} alkyl;

X^{12} is $-N(C(O)R^{24})-$ or a bond;

10 m is 1 or 2;

n is 0 or 1; and

z is 1 or 2;

with the proviso that when X^{10} is $-C(O)-$, then X^{12} is a bond;

with the proviso that when X^{10} is $-CH_2-$ or a bond, then X^{12} is $-N(C(O)R^{24})-$; and

15 with the proviso that ring A is a 4 to 6 membered ring, or a pharmaceutically acceptable salt thereof.

29. The compound according to any one of the preceding items, wherein R^1 is halogen, or a pharmaceutically acceptable salt thereof.

20 30. The compound according to any one of the preceding items, wherein R^1 is Cl, or a pharmaceutically acceptable salt thereof.

31. The compound according to any one of the preceding items, wherein R^1 is F, or a pharmaceutically acceptable salt thereof.

32. The compound according to any one of the preceding items, wherein R^1 is H, or a pharmaceutically acceptable salt thereof.

25 33. The compound according to any one of the preceding items, wherein R^2 is Cl, or a pharmaceutically acceptable salt thereof.

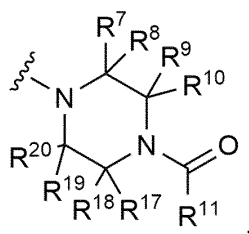
34. The compound according to any one of the preceding items, wherein R^3 is halogen, or a pharmaceutically acceptable salt thereof.

30 35. The compound according to any one of the preceding items, wherein R^3 is Cl, or a pharmaceutically acceptable salt thereof.

36. The compound according to any one of the preceding items, wherein R^3 is F, or a pharmaceutically acceptable salt thereof.
37. The compound according to any one of the preceding items, wherein R^3 is H, or a pharmaceutically acceptable salt thereof.
- 5 38. The compound according to any one of the preceding items, wherein R^5 is H, or a pharmaceutically acceptable salt thereof.
39. The compound according to any one of the preceding items, wherein R^5 is halogen, or a pharmaceutically acceptable salt thereof.
- 10 40. The compound according to any one of the preceding items, wherein R^5 is F, or a pharmaceutically acceptable salt thereof.
41. The compound according to any one of the preceding items, wherein R^6 is H, or a pharmaceutically acceptable salt thereof.
42. The compound according to any one of the preceding items, wherein R^6 is halogen, or a pharmaceutically acceptable salt thereof.
- 15 43. The compound according to any one of the preceding items, wherein R^6 is F, or a pharmaceutically acceptable salt thereof.
44. The compound according to any one of the preceding items, wherein R^5 is H and R^6 is H, or a pharmaceutically acceptable salt thereof.
- 20 45. The compound according to any one of the preceding items, wherein R^1 is halogen, and R^2 is halogen, or a pharmaceutically acceptable salt thereof.
46. The compound according to any one of the preceding items, wherein R^2 is halogen, and R^3 is halogen, or a pharmaceutically acceptable salt thereof.
- 25 47. The compound according to any one of the preceding items, wherein R^1 is halogen, R^2 is halogen, and R^3 is halogen, or a pharmaceutically acceptable salt thereof.
48. The compound according to any one of the preceding items, wherein R^1 is F or Cl, R^2 is Cl or F, and R^3 is F or Cl, or a pharmaceutically acceptable salt thereof.
- 30 49. The compound according to any one of the preceding items, wherein R^1 is halogen, R^2 is halogen, R^3 is halogen, R^5 is H, and R^6 is H, or a pharmaceutically acceptable salt thereof.
50. The compound according to any one of the preceding items, wherein R^1 is F or Cl, R^2 is Cl or F, and R^3 is F or Cl, R^5 is H, and R^6 is H, or a pharmaceutically acceptable salt thereof.

51. The compound according to any one of the preceding items, wherein R^1 is halogen, R^2 is halogen, R^3 is H, R^5 is H, and R^6 is H, or a pharmaceutically acceptable salt thereof.
52. The compound according to any one of the preceding items, wherein R^1 is halogen, R^2 is halogen, R^3 is H, R^5 is halogen, and R^6 is H, or a pharmaceutically acceptable salt thereof.
53. The compound according to any one of the preceding items, wherein R^1 is halogen, R^2 is halogen, R^3 is H, R^5 is H, and R^6 is halogen, or a pharmaceutically acceptable salt thereof.
54. The compound according to any one of the preceding items, wherein R^1 is H, R^2 is halogen, R^3 is halogen, R^5 is H, and R^6 is H, or a pharmaceutically acceptable salt thereof.
55. The compound according to any one of the preceding items, wherein R^1 is F, R^2 is Cl, and R^3 is Cl, or a pharmaceutically acceptable salt thereof.
56. The compound according to any one of the preceding items, wherein R^1 is F, R^2 is Cl, and R^3 is F, or a pharmaceutically acceptable salt thereof.
57. The compound according to any one of the preceding items, wherein R^1 is Cl, R^2 is Cl, and R^3 is Cl, or a pharmaceutically acceptable salt thereof.
58. The compound according to any one of the preceding items, wherein R^1 is Cl, R^2 is Cl, and R^3 is F, or a pharmaceutically acceptable salt thereof.
59. The compound according to any one of the preceding items, wherein R^1 is F or Cl, R^2 is Cl, R^3 is Cl, R^5 is H, and R^6 is H, or a pharmaceutically acceptable salt thereof.
60. The compound according to any one of the preceding items, wherein R^1 is F, R^2 is Cl, R^3 is Cl, R^5 is H, and R^6 is H, or a pharmaceutically acceptable salt thereof.
61. The compound according to any one of the preceding items, wherein R^1 is F, R^2 is Cl, R^3 is F, R^5 is H, and R^6 is H, or a pharmaceutically acceptable salt thereof.
62. The compound according to any one of the preceding items, wherein R^1 is Cl, R^2 is Cl, R^3 is Cl, R^5 is H, and R^6 is H, or a pharmaceutically acceptable salt thereof.
63. The compound according to any one of the preceding items, wherein R^1 is Cl, R^2 is Cl, R^3 is F, R^5 is H, and R^6 is H, or a pharmaceutically acceptable salt thereof.

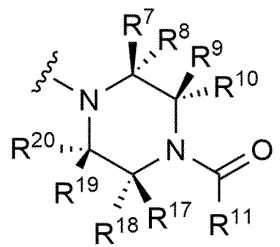
64. The compound according to any one of the preceding items, wherein R^1 is Cl, R^2 is Cl, R^3 is H, R^5 is F, and R^6 is H, or a pharmaceutically acceptable salt thereof.
- 5 65. The compound according to any one of the preceding items, wherein R^1 is Cl, R^2 is Cl, R^3 is H, R^5 is H, and R^6 is F, or a pharmaceutically acceptable salt thereof.
66. The compound according to any one of the preceding items, wherein R^1 is Cl, R^2 is Cl, R^3 is H, R^5 is H, and R^6 is H, or a pharmaceutically acceptable salt thereof.
- 10 67. The compound according to any one of the preceding items, wherein R^1 is F, R^2 is Cl, R^3 is H, R^5 is H, and R^6 is H, or a pharmaceutically acceptable salt thereof.
68. The compound according to any one of the preceding items, wherein R^1 is H, R^2 is Cl, R^3 is Cl, R^5 is H, and R^6 is H, or a pharmaceutically acceptable salt thereof.
- 15 69. The compound according to any one of the preceding items, wherein X^6 is a bond, or a pharmaceutically acceptable salt thereof.
70. The compound according to any one of the preceding items, wherein X^7 is a bond, or a pharmaceutically acceptable salt thereof.
- 20 71. The compound according to any one of the preceding items, wherein X^7 is C_{1-3} alkanediyl, or a pharmaceutically acceptable salt thereof.
72. The compound according to any one of the preceding items, wherein X^7 is CH_2 , or a pharmaceutically acceptable salt thereof.
- 25 73. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; and X^6 is a bond, or a pharmaceutically acceptable salt thereof.
74. The compound according to any one of the preceding items, wherein R^4 is of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt thereof.

75. The compound according to any one of the preceding items, wherein R^4 is of Formula (IV):

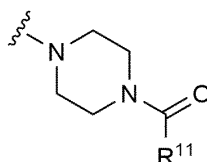


Formula (IV)

5 or a pharmaceutically acceptable salt thereof.

76. The compound according to any one of the preceding items, wherein R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , and R^{20} are H, or a pharmaceutically acceptable salt thereof.

77. The compound according to any one of the preceding items, wherein R^4 is of Formula (V):



Formula (V)

10

or a pharmaceutically acceptable salt thereof.

15

78. The compound according to any one of the preceding items, wherein R^7 is C_{1-3} alkyl, such as CH_3 , and R^8 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , and R^{20} are H, or a pharmaceutically acceptable salt thereof.

79. The compound according to any one of the preceding items, wherein R^8 is C_{1-3} alkyl, such as CH_3 , and R^7 , R^9 , R^{10} , R^{17} , R^{18} , R^{19} , and R^{20} are H, or a pharmaceutically acceptable salt thereof.

20

80. The compound according to any one of the preceding items, wherein R^7 and R^8 are C_{1-3} alkyl, such as CH_3 , and R^9 , R^{10} , R^{17} , R^{18} , R^{19} , and R^{20} are H, or a pharmaceutically acceptable salt thereof.

81. The compound according to any one of the preceding items, wherein R^{17} is C_{1-3} alkyl, such as CH_3 , and R^7 , R^8 , R^9 , R^{10} , R^{18} , R^{19} , and R^{20} are H, or a pharmaceutically acceptable salt thereof.

25

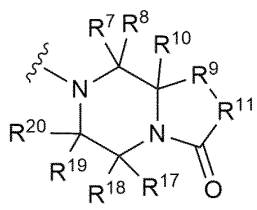
82. The compound according to any one of the preceding items, wherein R^{18} is C_{1-3} alkyl, such as CH_3 , and R^7 , R^8 , R^9 , R^{10} , R^{17} , R^{19} , and R^{20} are H, or a pharmaceutically acceptable salt thereof.

83. The compound according to any one of the preceding items, wherein R^{17} and R^{18} are C_{1-3} alkyl, such as CH_3 , and R^7 , R^8 , R^9 , R^{10} , R^{19} , and R^{20} are H, or a pharmaceutically acceptable salt thereof.
- 5 84. The compound according to any one of the preceding items, wherein R^8 and R^{17} are C_{1-3} alkyl, such as CH_3 , and R^7 , R^9 , R^{10} , R^{18} , R^{19} , and R^{20} are H, or a pharmaceutically acceptable salt thereof.
85. The compound according to any one of the preceding items, wherein when R^{11} is linked to R^9 or R^{10} to form a ring, then R^9 or R^{10} is linked to R^{33} of R^{11} , or a pharmaceutically acceptable salt thereof.
- 10 86. The compound according to any one of the preceding items, wherein R^9 is linked to R^{33} to form a ring, or a pharmaceutically acceptable salt thereof.
87. The compound according to any one of the preceding items, wherein R^{10} is linked to R^{33} to form a ring, or a pharmaceutically acceptable salt thereof.
- 15 88. The compound according to any one of the preceding items, wherein R^{11} is C_{1-3} alkyl or C_{1-3} alkoxy; R^9 is H; R^{10} is a bond; and R^{11} is linked to R^{10} to form a ring, or a pharmaceutically acceptable salt thereof.
89. The compound according to any one of the preceding items, wherein R^{11} is C_{1-3} alkyl or C_{1-3} alkoxy; R^{10} is H; R^9 is a bond; and R^{11} is linked to R^9 to form a ring, or a pharmaceutically acceptable salt thereof.
- 20 90. The compound according to any one of the preceding items, wherein R^{11} is linked to R^9 to form a ring and R^9 is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 F, R^{10} is H, and R^{11} is C_{1-3} alkanediyl wherein one methylene group is optionally replaced by -O- or -N(R^{28})-, wherein R^{28} is H or C_{1-3} alkyl,
- 25 or a pharmaceutically acceptable salt thereof.
91. The compound according to any one of the preceding items, wherein R^{11} is linked to R^{10} to form a ring and R^9 is H,
- 30 R^{10} is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 F, and R^{11} is C_{1-3} alkanediyl wherein one methylene group is optionally replaced by -O- or -N(R^{28})-, wherein R^{28} is H or C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.

92. The compound according to any one of the preceding items, wherein R¹¹ is linked to R⁹ to form a 5-membered ring, or a pharmaceutically acceptable salt thereof.
- 5 93. The compound according to any one of the preceding items, wherein R¹¹ is linked to R¹⁰ to form a 5-membered ring, or a pharmaceutically acceptable salt thereof.
94. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); and R¹¹ is linked to R⁹ to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.
- 10 95. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); and R¹¹ is linked to R⁹ to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.
- 15 96. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R¹¹ is linked to R⁹ to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.
- 20 97. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R¹¹ is linked to R⁹ to form a 5-membered ring, or a pharmaceutically acceptable salt thereof.
- 25 98. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); and R¹¹ is linked to R¹⁰ to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.
- 30 99. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); and R¹¹ is linked to R¹⁰ to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.
100. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R¹¹ is linked to R¹⁰ to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.
101. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰);

X^6 is a bond; and R^{11} is linked to R^{10} to form a 5-membered ring, or a pharmaceutically acceptable salt thereof.

102. The compound according to any one of the preceding items, wherein R^4 is of Formula (LI):



Formula (LI)

wherein

R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

R^9 is a bond, $-C(O)-$ or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{11} is $-O-$, $-N(R^{28})-$, or C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl, wherein one methylene group of the C_{1-3} alkanediyl is optionally replaced by $-O-$ or $-N(R^{28})-$, wherein R^{28} is H or C_{1-3} alkyl;

R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

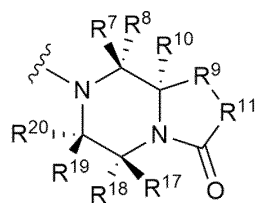
R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

and

R^{28} is H or C_{1-3} alkyl,

or a pharmaceutically acceptable salt thereof.

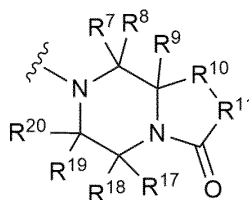
103. The compound according to any one of the preceding items, wherein the moiety of Formula (LI) is of Formula (LIa):



Formula (Lla)

or a pharmaceutically acceptable salt thereof.

104. The compound according to any one of the preceding items, wherein R⁴ is of Formula (LI) or Formula (Lla) and R⁷, R⁸, R¹⁰, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H, or a pharmaceutically acceptable salt thereof.
105. The compound according to any one of the preceding items, wherein R⁴ is of Formula (LI) or Formula (Lla) and R¹¹ is -O-, or a pharmaceutically acceptable salt thereof.
106. The compound according to any one of the preceding items, wherein R⁴ is of Formula (LI) or Formula (Lla) and R¹¹ is -CH₂-, or a pharmaceutically acceptable salt thereof.
107. The compound according to any one of the preceding items, wherein R⁴ is of Formula (LI) or Formula (Lla) and R¹¹ is -CH₂CH₂-, or a pharmaceutically acceptable salt thereof.
108. The compound according to any one of the preceding items, wherein R⁴ is of Formula (LII):



Formula (LII)

- wherein
- R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen, such as F;
- R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen, such as F;
- R¹⁰ is a bond, -C(O)-, or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R¹¹ is -O-, -N(R²⁸)-, or C₁₋₃ alkanediyl optionally substituted with 1 to 3
 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one
 methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-,
 wherein R²⁸ is H or C₁₋₃ alkyl;

R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

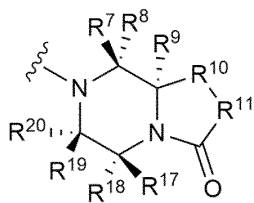
R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

and

R²⁸ is H or C₁₋₃ alkyl,

or a pharmaceutically acceptable salt thereof.

109. The compound according to any one of the preceding items, wherein the
 moiety of Formula (LII) is of Formula (LIIa):



Formula (LIIa)

or a pharmaceutically acceptable salt thereof.

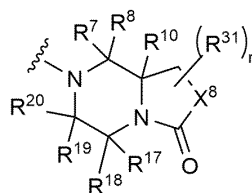
110. The compound according to any one of the preceding items, wherein R⁴
 is of Formula (LII) or Formula (LIIa) and R⁷, R⁸, R¹⁰, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H,
 or a pharmaceutically acceptable salt thereof.

111. The compound according to any one of the preceding items, wherein R⁴
 is of Formula (LII) or Formula (LIIa) and R¹¹ is -O-, or a pharmaceutically
 acceptable salt thereof.

112. The compound according to any one of the preceding items, wherein R⁴
 is of Formula (LII) or Formula (LIIa) and R¹¹ is -CH₂-, or a pharmaceutically
 acceptable salt thereof.

113. The compound according to any one of the preceding items, wherein R⁴
 is of Formula (LII) or Formula (LIIa) and R¹¹ is -CH₂CH₂-, or a pharmaceutically
 acceptable salt thereof.

114. The compound according to any one of the preceding items, wherein R⁴
 is of Formula (XX):

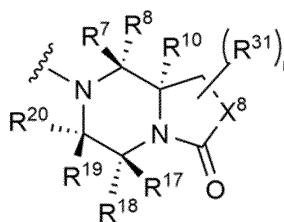


Formula (XX)

wherein

- 5 R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;
- R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;
- R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- 10 R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
- R^{31} is individually halogen or C_{1-3} alkyl;
- r is 0, 1, 2, 3 or 4;
- 15 X^8 is $-CH_2-$, $-O-$, $-CH_2O-$, $-OCH_2-$, $-N(R^{28})-$, or $-CH_2N(R^{28})-$; and
- R^{28} is H or C_{1-3} alkyl,
- or a pharmaceutically acceptable salt thereof.

115. The compound according to any one of the preceding items, wherein the moiety of Formula (XX) is of Formula (XXa):

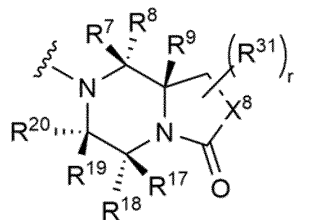


Formula (XXa)

or a pharmaceutically acceptable salt thereof.

- 20 116. The compound according to any one of the preceding items, wherein R^4 is of Formula (XXa) and R^7 , R^8 , R^{10} , R^{17} , R^{18} , R^{19} , and R^{20} are H, or a
- 25 pharmaceutically acceptable salt thereof.

117. The compound according to any one of the preceding items, wherein the moiety of Formula (XX) is of Formula (XXb):

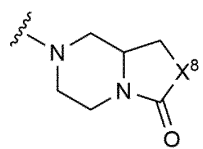


Formula (XXb)

- 5 wherein R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F or a pharmaceutically acceptable salt thereof.

118. The compound according to any one of the preceding items, wherein R⁴ is of Formula (XXb) and R⁷, R⁸, R⁹, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H, or a pharmaceutically acceptable salt thereof.

- 10 119. The compound according to any one of the preceding items, wherein R⁴ is of Formula (XV):



Formula (XV)

wherein

- 15 X⁸ is -CH₂-, -O- or -N(R²⁸)-, and

R²⁸ is H or C₁₋₃ alkyl,

or a pharmaceutically acceptable salt thereof.

120. The compound according to any one of the preceding items, wherein X⁸ is -CH₂-, or a pharmaceutically acceptable salt thereof.

- 20 121. The compound according to any one of the preceding items, wherein X⁸ is -O-, or a pharmaceutically acceptable salt thereof.

122. The compound according to any one of the preceding items, wherein X⁸ is -N(R²⁸)-, or a pharmaceutically acceptable salt thereof.

123. The compound according to any one of the preceding items, wherein X⁸ is -CH₂O-, or a pharmaceutically acceptable salt thereof.

- 25 124. The compound according to any one of the preceding items, wherein X⁸ is -OCH₂-, or a pharmaceutically acceptable salt thereof.

125. The compound according to any one of the preceding items, wherein X^8 is $-\text{CH}_2\text{N}(\text{R}^{28})-$, or a pharmaceutically acceptable salt thereof.
126. The compound according to any one of the preceding items, wherein R^{11} is linked to R^9 to form a 6-membered ring, or a pharmaceutically acceptable salt thereof.
127. The compound according to any one of the preceding items, wherein R^{11} is linked to R^{10} to form a 6-membered ring, or a pharmaceutically acceptable salt thereof.
128. The compound according to any one of the preceding items, wherein X^2 is $\text{C}(\text{R}^9)(\text{R}^{10})$; X^3 is $\text{N}(\text{C}(\text{O})\text{R}^{11})$; X^4 is $\text{C}(\text{R}^{17})(\text{R}^{18})$; X^5 is $\text{C}(\text{R}^{19})(\text{R}^{20})$; X^6 is a bond; and R^{11} is linked to R^9 to form a 6-membered ring, or a pharmaceutically acceptable salt thereof.
129. The compound according to any one of the preceding items, wherein X^2 is $\text{C}(\text{R}^9)(\text{R}^{10})$; X^3 is $\text{N}(\text{C}(\text{O})\text{R}^{11})$; X^4 is $\text{C}(\text{R}^{17})(\text{R}^{18})$; X^5 is $\text{C}(\text{R}^{19})(\text{R}^{20})$; X^6 is a bond; and R^{11} is linked to R^{10} to form a 6-membered ring, or a pharmaceutically acceptable salt thereof.
130. The compound according to any one of the preceding items, wherein R^{11} is linked to R^9 or R^{10} to form a ring together with the intervening atoms, and R^{11} is $-\text{O}-$, or a pharmaceutically acceptable salt thereof.
131. The compound according to any one of the preceding items, wherein R^{11} is linked to R^9 or R^{10} to form a ring together with the intervening atoms, and R^{11} is C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl, wherein one methylene group of the C_{1-3} alkanediyl is optionally replaced by $-\text{O}-$ or $-\text{N}(\text{R}^{28})-$, wherein R^{28} is H or C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
132. The compound according to any one of the preceding items, wherein R^{11} is linked to R^9 or R^{10} to form a ring together with the intervening atoms, and R^{11} is C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
133. The compound according to any one of the preceding items, wherein R^{11} is linked to R^9 or R^{10} to form a ring together with the intervening atoms, and R^{11} is $-\text{CH}_2-$, or a pharmaceutically acceptable salt thereof.

134. The compound according to any one of the preceding items, wherein R^{11} is linked to R^9 or R^{10} to form a ring together with the intervening atoms, and R^{11} is $-\text{CH}_2\text{CH}_2-$, or a pharmaceutically acceptable salt thereof.

5 135. The compound according to any one of the preceding items, wherein R^{11} is linked to R^9 or R^{10} to form a ring together with the intervening atoms, and R^{11} is $-\text{CH}_2\text{O}-$, or a pharmaceutically acceptable salt thereof.

136. The compound according to any one of the preceding items, wherein R^{11} is linked to R^9 or R^{10} to form a ring together with the intervening atoms, and R^{11} is $-\text{N}(\text{R}^{28})-$, or a pharmaceutically acceptable salt thereof.

10 137. The compound according to any one of the preceding items, wherein R^{28} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.

138. The compound according to any one of the preceding items, wherein R^{28} is CH_3 , or a pharmaceutically acceptable salt thereof.

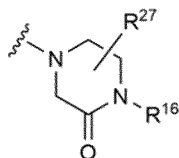
15 139. The compound according to any one of the preceding items, wherein R^{11} is linked to R^9 or R^{10} to form a ring together with the intervening atoms, and R^{11} is $-\text{O}-$, or a pharmaceutically acceptable salt thereof.

20 140. The compound according to any one of the preceding items, wherein R^{11} is linked to R^9 to form a ring together with the intervening atoms, and $R^{11}-R^9$ is $-(\text{CH}_2)_3-$, $-(\text{CH}_2)\text{O}-$, $-(\text{CH}_2)_2\text{O}-$, $-\text{CH}_2\text{OCH}_2-$, $-\text{C}(\text{H})(\text{CH}_3)\text{CH}_2-$, $-\text{C}(\text{O})\text{N}(\text{H})-$, or a pharmaceutically acceptable salt thereof.

141. The compound according to any one of the preceding items, wherein R^{11} is linked to R^{10} to form a ring together with the intervening atoms, and $R^{11}-R^{10}$ is $-(\text{CH}_2)_3-$, $-(\text{CH}_2)\text{O}-$, $-(\text{CH}_2)_2\text{O}-$, $-\text{CH}_2\text{OCH}_2-$, $-\text{C}(\text{H})(\text{CH}_3)\text{CH}_2-$, $-\text{C}(\text{O})\text{N}(\text{H})-$, or a pharmaceutically acceptable salt thereof.

25 142. The compound according to any one of the preceding items, wherein X^2 is $\text{C}(\text{R}^9)(\text{R}^{10})$; X^3 is $\text{N}(\text{R}^{16})$; X^4 is $\text{C}(\text{O})$; X^5 is $\text{C}(\text{R}^{19})(\text{R}^{20})$; and X^6 is a bond, or a pharmaceutically acceptable salt thereof.

143. The compound according to any one of the preceding items, wherein R^4 is of Formula (VI):



Formula (VI)

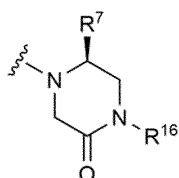
wherein

R^{16} is H or C_{1-3} alkyl; and

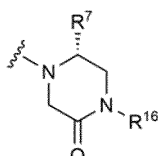
R^{27} is H or C_{1-3} alkyl,

or a pharmaceutically acceptable salt thereof.

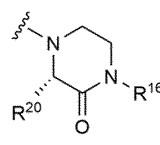
144. The compound according to any one of the preceding items, wherein R^4 is of Formula (VIA-1), Formula (VIA-2), Formula (VIB-1), or Formula (VIB-2):



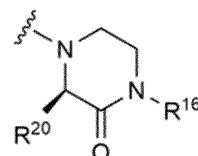
Formula (VIA-1)



Formula (VIA-2)



Formula (VIB-1)



Formula (VIB-2)

wherein

R^7 is H or C_{1-3} alkyl;

R^{16} is H or C_{1-3} alkyl; and

R^{20} is H or C_{1-3} alkyl,

or a pharmaceutically acceptable salt thereof.

145. The compound according to any one of the preceding items, wherein R^7 and R^{19} are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.

146. The compound according to any one of the preceding items, wherein R^8 and R^{20} are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.

147. The compound according to any one of the preceding items, wherein R^9 and R^{17} are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.

148. The compound according to any one of the preceding items, wherein R^{10} and R^{18} are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.

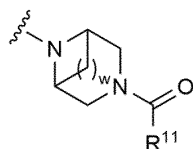
149. The compound according to any one of the preceding items, wherein R^9 and R^{19} are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.

150. The compound according to any one of the preceding items, wherein R^{10} and R^{20} are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.

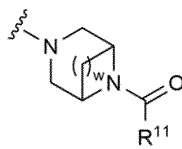
151. The compound according to any one of the preceding items, wherein R⁷ and R¹⁷ are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.
152. The compound according to any one of the preceding items, wherein R⁸ and R¹⁸ are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.
153. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R⁷ and R¹⁹ are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.
154. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R⁸ and R²⁰ are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.
155. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R⁹ and R¹⁷ are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.
156. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R¹⁰ and R¹⁸ are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.
157. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R⁹ and R¹⁹ are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.
158. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R¹⁰ and R²⁰ are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.
159. The compound according to any one of the preceding items, wherein X² is C(R⁹)(R¹⁰); X³ is N(C(O)R¹¹); X⁴ is C(R¹⁷)(R¹⁸); X⁵ is C(R¹⁹)(R²⁰); X⁶ is a bond; and R⁷ and R¹⁷ are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.

160. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $N(C(O)R^{11})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is a bond; and R^8 and R^{18} are linked together to form a bridged bicyclic ring, or a pharmaceutically acceptable salt thereof.

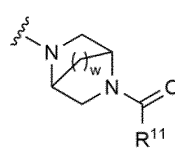
5 161. The compound according to any one of the preceding items, wherein R^4 is of Formula (VII), Formula (VIII), or Formula (IX):



Formula (VII)



Formula (VIII)



Formula (IX)

10 wherein w is 1 or 2, or a pharmaceutically acceptable salt thereof.

162. The compound according to any one of the preceding items, wherein R^4 is of Formula (VII) and w is 1, or a pharmaceutically acceptable salt thereof.

163. The compound according to any one of the preceding items, wherein R^4 is of Formula (VII) and w is 2, or a pharmaceutically acceptable salt thereof.

15 164. The compound according to any one of the preceding items, wherein R^4 is of Formula (VIII) and w is 1, or a pharmaceutically acceptable salt thereof.

165. The compound according to any one of the preceding items, wherein R^4 is of Formula (VIII) and w is 2, or a pharmaceutically acceptable salt thereof.

20 166. The compound according to any one of the preceding items, wherein R^4 is of Formula (IX) and w is 2, or a pharmaceutically acceptable salt thereof.

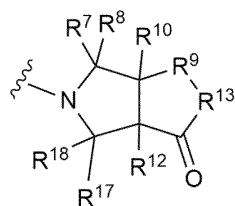
167. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; and R^{13} is linked to R^9 to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.

25 168. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; and R^{13} is linked to R^9 to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.

30 169. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^6 is a bond; and R^{13} is linked to R^9 to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.

170. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^5 is a bond; X^6 is a bond; and R^{13} is linked to R^9 to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.

5 171. The compound according to any one of the preceding items, wherein R^4 is of Formula (LIII):

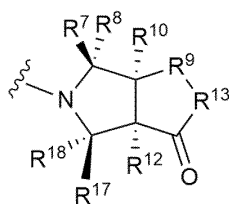


Formula (LIII)

wherein

10 R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^9 is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;
 R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 15 R^{12} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{13} is $-N(R^{28})-$, wherein R^{28} is H or C_{1-3} alkyl;
 R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 and
 R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F,
 20 or a pharmaceutically acceptable salt thereof.

172. The compound according to any one of the preceding items, wherein the moiety of Formula (LIII) is of Formula (LIIIa):



Formula (LIIIa)

25 or a pharmaceutically acceptable salt thereof.

173. The compound according to any one of the preceding items, wherein R^4 is of Formula (LIII) or Formula (LIIIA) and R^7 , R^8 , R^{10} , R^{12} , R^{17} , and R^{18} are H, or a pharmaceutically acceptable salt thereof.

174. The compound according to any one of the preceding items, wherein R^4 is of Formula (LIII) or Formula (LIIIA) and R^{13} is $-N(CH_3)-$, or a pharmaceutically acceptable salt thereof.

175. The compound according to any one of the preceding items, wherein R^4 is of Formula (LIII) or Formula (LIIIA) and R^9 is $-CH_2-$, or a pharmaceutically acceptable salt thereof.

10

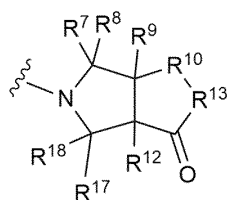
176. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; and R^{13} is linked to R^{10} to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.

177. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; and R^{13} is linked to R^{10} to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.

178. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^6 is a bond; and R^{13} is linked to R^{10} to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.

179. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^5 is a bond; X^6 is a bond; and R^{13} is linked to R^{10} to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.

180. The compound according to any one of the preceding items, wherein R^4 is of Formula (LIV):



Formula (LIV)

30

wherein

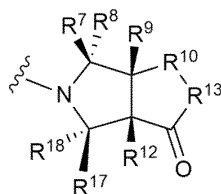
R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^9 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{10} is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

5 R^{12} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 R^{13} is $-N(R^{28})-$, wherein R^{28} is H or C_{1-3} alkyl;
 R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
 and

10 R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F,
 or a pharmaceutically acceptable salt thereof.

181. The compound according to any one of the preceding items, wherein the moiety of Formula (LIV) is of Formula (LIVa):



Formula (LIVa)

15 or a pharmaceutically acceptable salt thereof.

182. The compound according to any one of the preceding items, wherein R^4 is of Formula (LIV) or Formula (LIVa) and R^7 , R^8 , R^9 , R^{12} , R^{17} , and R^{18} are H, or a pharmaceutically acceptable salt thereof.

183. The compound according to any one of the preceding items, wherein R^4 is of Formula (LIV) or Formula (LIVa) and R^{13} is $-N(CH_3)-$, or a pharmaceutically acceptable salt thereof.

184. The compound according to any one of the preceding items, wherein R^4 is of Formula (LIV) or Formula (LIVa) and R^{10} is $-CH_2-$, or a pharmaceutically acceptable salt thereof.

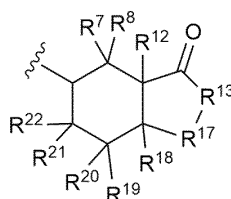
25 185. The compound according to any one of the preceding items, wherein X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; and R^{13} is linked to R^{17} to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.

30 186. The compound according to any one of the preceding items, wherein X^2 is a bond; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; and R^{13} is linked to R^{17} to form

a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.

187. The compound according to any one of the preceding items, wherein X^2 is a bond; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is $C(R^{21})(R^{22})$; and R^{13} is linked to R^{17} to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.

188. The compound according to any one of the preceding items, wherein R^4 is of Formula (LV):



Formula (LV)

wherein

R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{12} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{13} is $-N(R^{28})-$, wherein R^{28} is H or C_{1-3} alkyl;

R^{17} is a bond or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

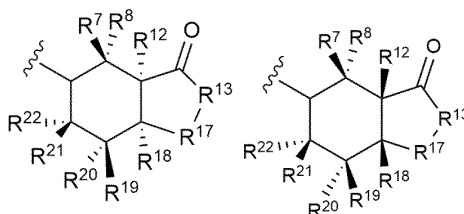
R^{21} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

and

R^{22} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F,

or a pharmaceutically acceptable salt thereof.

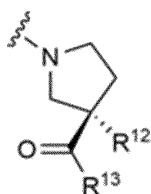
189. The compound according to any one of the preceding items, wherein the moiety of Formula (LV) is of Formula (LVa) or Formula (LVb):



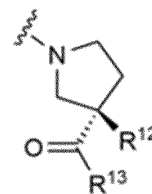
Formula (LVa) Formula (LVb)

or a pharmaceutically acceptable salt thereof.

190. The compound according to any one of the preceding items, wherein R^4 is of Formula (LV), Formula (LVa) or Formula (LVb) and R^7 , R^8 , R^{12} , R^{18} , R^{19} , R^{20} , R^{21} , and R^{22} are H, or a pharmaceutically acceptable salt thereof.
191. The compound according to any one of the preceding items, wherein R^4 is of Formula (LV), Formula (LVa) or Formula (LVb) and R^{13} is $-N(CH_3)-$, or a pharmaceutically acceptable salt thereof.
192. The compound according to any one of the preceding items, wherein R^4 is of Formula (LV), Formula (LVa) or Formula (LVb) and R^{17} is $-CH_2-$, or a pharmaceutically acceptable salt thereof.
193. The compound according to any one of the preceding items, wherein X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; and R^{13} is linked to R^{18} to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.
194. The compound according to any one of the preceding items, wherein X^2 is a bond; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; and R^{13} is linked to R^{18} to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.
195. The compound according to any one of the preceding items, wherein X^2 is a bond; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; X^6 is $C(R^{21})(R^{22})$; and R^{13} is linked to R^{18} to form a ring together with the intervening atoms, or a pharmaceutically acceptable salt thereof.
196. The compound according to any one of the preceding items, wherein X^2 is a bond; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is O; X^5 is $C(R^{19})(R^{20})$; and X^6 is $C(R^{21})(R^{22})$, or a pharmaceutically acceptable salt thereof.
197. The compound according to any one of the preceding items, wherein X^2 is a bond; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; and X^6 is $C(R^{21})(R^{22})$, or a pharmaceutically acceptable salt thereof.
198. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{12})(C(O)R^{13})$; X^4 is $C(R^{17})(R^{18})$; X^5 is a bond; and X^6 is bond, or a pharmaceutically acceptable salt thereof.
199. The compound according to any one of the preceding items, wherein R^4 is of Formula (Xa) or Formula (Xb):



Formula (Xa)

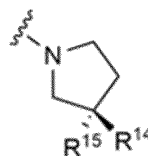


Formula (Xb)

or a pharmaceutically acceptable salt thereof.

200. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{14})(R^{15})$; X^4 is $C(R^{17})(R^{18})$; X^5 is a bond; and X^6 is bond, or a pharmaceutically acceptable salt thereof.

5 201. The compound according to any one of the preceding items, wherein R^4 is of Formula (XI):



Formula (XI)

wherein

10 R^{14} is $-X^7N(R^{23})(C(O)R^{24})$;

X^7 is a bond or CH_2 ;

R^{23} is H or C_{1-3} alkyl, or R^{23} is a bond and R^{15} is C_{1-3} alkanediyl and R^{23} is linked to R^{15} to form a 4 or 5 membered ring;

R^{24} is C_{1-3} alkyl; and

15 R^{15} is H or C_{1-3} alkyl;

or a pharmaceutically acceptable salt thereof.

202. The compound according to any one of the preceding items, wherein X^7 is a bond; R^{23} is H or C_{1-3} alkyl; R^{24} is C_{1-3} alkyl; and R^{15} is H or C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.

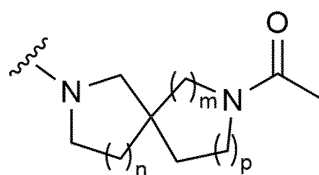
20 203. The compound according to any one of the preceding items, wherein X^2 is a bond; X^3 is $C(R^{14})(R^{15})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; and X^6 is bond, or a pharmaceutically acceptable salt thereof.

204. The compound according to any one of the preceding items, wherein X^2 is a bond; X^3 is $C(R^{14})(R^{15})$; X^4 is $C(R^{17})(R^{18})$; X^5 is a bond; and X^6 is bond, or a pharmaceutically acceptable salt thereof.

25

211. The compound according to any one of the preceding items, wherein R^{23} is a bond and R^{15} is C_{1-3} alkanediyl and R^{23} is linked to R^{15} to form a 4 or 5 membered ring, or a pharmaceutically acceptable salt thereof.

212. The compound according to any one of the preceding items, wherein R^4 is of Formula (XII):



Formula (XII)

wherein

m is 0 or 1;

n is 0 or 1; and

p is 0, 1 or 2,

or a pharmaceutically acceptable salt thereof.

213. The compound according to any one of the preceding items, wherein R^4 is of Formula (XII) and with the proviso that when m is 0 then p is 1 or 2, or a pharmaceutically acceptable salt thereof.

214. The compound according to any one of the preceding items, wherein R^4 is of Formula (XII) and with the proviso that when p is 2, then m is 0, or a pharmaceutically acceptable salt thereof.

215. The compound according to any one of the preceding items, wherein m is 0, or a pharmaceutically acceptable salt thereof.

216. The compound according to any one of the preceding items, wherein m is 1, or a pharmaceutically acceptable salt thereof.

217. The compound according to any one of the preceding items, wherein p is 0, or a pharmaceutically acceptable salt thereof.

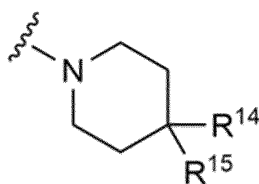
218. The compound according to any one of the preceding items, wherein p is 1, or a pharmaceutically acceptable salt thereof.

219. The compound according to any one of the preceding items, wherein p is 2, or a pharmaceutically acceptable salt thereof.

220. The compound according to any one of the preceding items, wherein m is 0 and p is 1, or a pharmaceutically acceptable salt thereof.

221. The compound according to any one of the preceding items, wherein m is 1 and p is 1, or a pharmaceutically acceptable salt thereof.

222. The compound according to any one of the preceding items, wherein m is 1 and p is 0, or a pharmaceutically acceptable salt thereof.
223. The compound according to any one of the preceding items, wherein m is 0 and p is 2, or a pharmaceutically acceptable salt thereof.
- 5 224. The compound according to any one of the preceding items, wherein n is 0, or a pharmaceutically acceptable salt thereof.
225. The compound according to any one of the preceding items, wherein n is 1, or a pharmaceutically acceptable salt thereof.
- 10 226. The compound according to any one of the preceding items, wherein X^2 is $C(R^9)(R^{10})$; X^3 is $C(R^{14})(R^{15})$; X^4 is $C(R^{17})(R^{18})$; X^5 is $C(R^{19})(R^{20})$; and X^6 is bond, or a pharmaceutically acceptable salt thereof.
227. The compound according to any one of the preceding items, wherein R^{14} and R^{15} are linked together to form a ring, or a pharmaceutically acceptable salt thereof.
- 15 228. The compound according to any one of the preceding items, wherein R^{14} and R^{15} are linked together to form a ring, and wherein R^{14} is $-X^9C(O)X^{11}-$, wherein
 X^9 is a bond or $-N(R^{29})-$;
 R^{29} is C_{1-3} alkyl;
 X^{11} is $-O-$, $-CH_2-$, or $-N(R^{30})-$; and
 R^{30} is C_{1-3} alkyl; and
 R^{15} is a bond or C_{1-3} alkanediyl,
or a pharmaceutically acceptable salt thereof.
- 20 229. The compound according to any one of the preceding items, wherein R^4 is of Formula (XVI):
- 25



Formula (XVI)

- wherein
- R^{14} and R^{15} are linked together to form a ring;
- 30 R^{14} is $-X^9C(O)X^{11}-$;
 X^9 is a bond or $-N(R^{29})-$;

R^{29} is C_{1-3} alkyl;

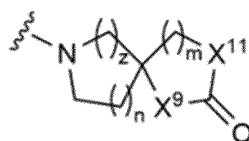
X^{11} is -O-, -CH₂-, or -N(R³⁰)-;

R^{30} is C_{1-3} alkyl; and

R^{15} is a bond or C_{1-3} alkanediyl,

5 or a pharmaceutically acceptable salt thereof.

230. The compound according to any one of the preceding items, wherein R^4 is of Formula (XVII):



Formula (XVII)

10 wherein

X^9 is a bond or -N(R²⁹)-;

R^{29} is C_{1-3} alkyl;

X^{11} is -O-, -CH₂-, or -N(R³⁰)-;

R^{30} is C_{1-3} alkyl;

15 m is 1 or 2;

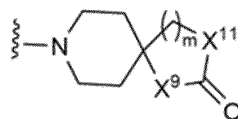
n is 0 or 1; and

z is 1 or 2,

or a pharmaceutically acceptable salt thereof.

231. The compound according to any one of the preceding items, wherein R^4 is of Formula (XVIII):

20



Formula (XVIII)

wherein

X^9 is a bond or -N(R²⁹)-;

25

R^{29} is C_{1-3} alkyl;

X^{11} is -O-, -CH₂-, or -N(R³⁰)-;

R^{30} is C_{1-3} alkyl; and

m is 1 or 2,

or a pharmaceutically acceptable salt thereof.

232. The compound according to any one of the preceding items, wherein X^9 is a bond, or a pharmaceutically acceptable salt thereof.
233. The compound according to any one of the preceding items, wherein X^9 is $-N(R^{29})-$, or a pharmaceutically acceptable salt thereof.
- 5 234. The compound according to any one of the preceding items, wherein R^{29} is CH_3 , or a pharmaceutically acceptable salt thereof.
235. The compound according to any one of the preceding items, wherein X^{11} is $-O-$, or a pharmaceutically acceptable salt thereof.
236. The compound according to any one of the preceding items, wherein X^{11} is C_{1-3} alkanediyl, or a pharmaceutically acceptable salt thereof.
- 10 237. The compound according to any one of the preceding items, wherein X^{11} is $-CH_2-$, or a pharmaceutically acceptable salt thereof.
238. The compound according to any one of the preceding items, wherein X^{11} is $-N(R^{30})-$, or a pharmaceutically acceptable salt thereof.
- 15 239. The compound according to any one of the preceding items, wherein R^{30} is CH_3 , or a pharmaceutically acceptable salt thereof.
240. The compound according to any one of the preceding items, wherein m is 1, or a pharmaceutically acceptable salt thereof.
241. The compound according to any one of the preceding items, wherein m is 2, or a pharmaceutically acceptable salt thereof.
- 20 242. The compound according to any one of the preceding items, wherein z is 1, or a pharmaceutically acceptable salt thereof.
243. The compound according to any one of the preceding items, wherein z is 2, or a pharmaceutically acceptable salt thereof.
- 25 244. The compound according to any one of the preceding items, wherein n is 1 and z is 1, or a pharmaceutically acceptable salt thereof.
245. The compound according to any one of the preceding items, wherein n is 1 and z is 2, or a pharmaceutically acceptable salt thereof.
246. The compound according to any one of the preceding items, wherein n is 0 and z is 2, or a pharmaceutically acceptable salt thereof.
- 30 247. The compound according to any one of the preceding items, wherein R^7 is H , or a pharmaceutically acceptable salt thereof.
248. The compound according to any one of the preceding items, wherein R^7 is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.

249. The compound according to any one of the preceding items, wherein R^7 is CH_3 , or a pharmaceutically acceptable salt thereof.
250. The compound according to any one of the preceding items, wherein R^7 is C_{1-3} alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
- 5 251. The compound according to any one of the preceding items, wherein R^7 is C_{1-3} alkyl substituted with C_{1-3} alkoxy, or a pharmaceutically acceptable salt thereof.
252. The compound according to any one of the preceding items, wherein R^7 is CH_2OCH_3 , or a pharmaceutically acceptable salt thereof.
- 10 253. The compound according to any one of the preceding items, wherein R^7 is halogen, such as F, or a pharmaceutically acceptable salt thereof.
254. The compound according to any one of the preceding items, wherein R^8 is H, or a pharmaceutically acceptable salt thereof.
- 15 255. The compound according to any one of the preceding items, wherein R^8 is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
256. The compound according to any one of the preceding items, wherein R^8 is CH_3 , or a pharmaceutically acceptable salt thereof.
257. The compound according to any one of the preceding items, wherein R^8 is C_{1-3} alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
- 20 258. The compound according to any one of the preceding items, wherein R^8 is halogen, such as F, or a pharmaceutically acceptable salt thereof.
259. The compound according to any one of the preceding items, wherein R^8 is C_{1-3} alkyl substituted with C_{1-3} alkoxy, or a pharmaceutically acceptable salt thereof.
- 25 260. The compound according to any one of the preceding items, wherein R^8 is CH_2OCH_3 , or a pharmaceutically acceptable salt thereof.
261. The compound according to any one of the preceding items, wherein R^9 is H, or a pharmaceutically acceptable salt thereof.
- 30 262. The compound according to any one of the preceding items, wherein R^9 is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
263. The compound according to any one of the preceding items, wherein R^9 is C_{1-3} alkyl substituted with 1 to 3 halogens, or a pharmaceutically acceptable salt thereof.
- 35

264. The compound according to any one of the preceding items, wherein R^9 is C_{1-3} alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
- 5 265. The compound according to any one of the preceding items, wherein R^9 is $-C(O)N(R^{31})(R^{32})$, wherein R^{31} is H or C_{1-3} alkyl and R^{32} is H or C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
266. The compound according to any one of the preceding items, wherein R^9 is $-C(O)N(H)(CH_3)$, or a pharmaceutically acceptable salt thereof.
- 10 267. The compound according to any one of the preceding items, wherein R^9 is $-C(O)NH_2$, or a pharmaceutically acceptable salt thereof.
268. The compound according to any one of the preceding items, wherein R^9 is $-C(O)N(CH_3)_2$, or a pharmaceutically acceptable salt thereof.
269. The compound according to any one of the preceding items, wherein R^9 is halogen, such as F, or a pharmaceutically acceptable salt thereof.
- 15 270. The compound according to any one of the preceding items, wherein R^9 is linked to R^{11} to form a ring, and R^9 is a bond, or a pharmaceutically acceptable salt thereof.
- 20 271. The compound according to any one of the preceding items, wherein R^9 is linked to R^{11} to form a ring, and R^9 is $-C(O)-$, or a pharmaceutically acceptable salt thereof.
272. The compound according to any one of the preceding items, wherein R^9 is linked to R^{11} to form a ring, and R^9 is C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
- 25 273. The compound according to any one of the preceding items, wherein R^9 is linked to R^{11} to form a ring, and R^9 is $-CH_2-$, or a pharmaceutically acceptable salt thereof.
- 30 274. The compound according to any one of the preceding items, wherein R^9 is linked to R^{11} to form a ring, and R^9 is $-(CH_2)_2-$, or a pharmaceutically acceptable salt thereof.
275. The compound according to any one of the preceding items, wherein R^9 is linked to R^{11} to form a ring, and R^9 is $-C(H)(CH_3)-$, or a pharmaceutically acceptable salt thereof.

276. The compound according to any one of the preceding items, wherein R^9 is linked to R^{11} or R^{13} to form a ring, and R^9 is a bond, or a pharmaceutically acceptable salt thereof.
- 5 277. The compound according to any one of the preceding items, wherein R^9 is linked to R^{11} or R^{13} to form a ring, and R^9 is C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
- 10 278. The compound according to any one of the preceding items, wherein R^9 is linked to R^{11} or R^{13} to form a ring, and R^9 is $-CH_2-$, or a pharmaceutically acceptable salt thereof.
279. The compound according to any one of the preceding items, wherein R^9 is linked to R^{11} or R^{13} to form a ring, and R^9 is $-CH_2CH_2-$, or a pharmaceutically acceptable salt thereof.
- 15 280. The compound according to any one of the preceding items, wherein R^{10} is H, or a pharmaceutically acceptable salt thereof.
281. The compound according to any one of the preceding items, wherein R^{10} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
- 20 282. The compound according to any one of the preceding items, wherein R^{10} is C_{1-3} alkyl substituted with 1 to 3 halogens, or a pharmaceutically acceptable salt thereof.
283. The compound according to any one of the preceding items, wherein R^{10} is C_{1-3} alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
- 25 284. The compound according to any one of the preceding items, wherein R^{10} is $-C(O)N(R^{31})(R^{32})$, wherein R^{31} is H or C_{1-3} alkyl and R^{32} is H or C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
285. The compound according to any one of the preceding items, wherein R^{10} is $-C(O)N(H)(CH_3)$, or a pharmaceutically acceptable salt thereof.
- 30 286. The compound according to any one of the preceding items, wherein R^{10} is $-C(O)NH_2$, or a pharmaceutically acceptable salt thereof.
287. The compound according to any one of the preceding items, wherein R^{10} is $-C(O)N(CH_3)_2$, or a pharmaceutically acceptable salt thereof.
288. The compound according to any one of the preceding items, wherein R^{31} is H, or a pharmaceutically acceptable salt thereof.

289. The compound according to any one of the preceding items, wherein R^{31} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
290. The compound according to any one of the preceding items, wherein R^{31} is CH_3 , or a pharmaceutically acceptable salt thereof.
- 5 291. The compound according to any one of the preceding items, wherein R^{32} is H, or a pharmaceutically acceptable salt thereof.
292. The compound according to any one of the preceding items, wherein R^{32} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
293. The compound according to any one of the preceding items, wherein R^{32} is CH_3 , or a pharmaceutically acceptable salt thereof.
- 10 294. The compound according to any one of the preceding items, wherein R^{10} is halogen, such as F, or a pharmaceutically acceptable salt thereof.
295. The compound according to any one of the preceding items, wherein R^{10} is linked to R^{11} to form a ring, and R^9 is a bond, or a pharmaceutically acceptable salt thereof.
- 15 296. The compound according to any one of the preceding items, wherein R^{10} is linked to R^{11} to form a ring, and R^9 is $-C(O)-$, or a pharmaceutically acceptable salt thereof.
297. The compound according to any one of the preceding items, wherein R^{10} is linked to R^{11} to form a ring, and R^9 is C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
- 20 298. The compound according to any one of the preceding items, wherein R^{10} is linked to R^{11} to form a ring, and R^9 is $-CH_2-$, or a pharmaceutically acceptable salt thereof.
- 25 299. The compound according to any one of the preceding items, wherein R^{10} is linked to R^{11} to form a ring, and R^9 is $-(CH_2)_2-$, or a pharmaceutically acceptable salt thereof.
- 30 300. The compound according to any one of the preceding items, wherein R^{10} is linked to R^{11} to form a ring, and R^9 is $-C(H)(CH_3)-$, or a pharmaceutically acceptable salt thereof.
301. The compound according to any one of the preceding items, wherein R^{10} is linked to R^{11} or R^{13} to form a ring, and R^{10} is a bond, or a pharmaceutically acceptable salt thereof.

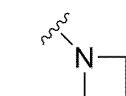
302. The compound according to any one of the preceding items, wherein R^{10} is linked to R^{11} or R^{13} to form a ring, and R^{10} is C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
- 5 303. The compound according to any one of the preceding items, wherein R^{10} is linked to R^{11} or R^{13} to form a ring, and R^{10} is $-CH_2-$, or a pharmaceutically acceptable salt thereof.
304. The compound according to any one of the preceding items, wherein R^{10} is linked to R^{11} or R^{13} to form a ring, and R^{10} is $-CH_2CH_2-$, or a pharmaceutically acceptable salt thereof.
- 10 305. The compound according to any one of the preceding items, wherein X^{13} is bond, $-CH_2-$, $-C(H)(CH_3)-$, $-O-$, or $-CH_2O-$, or a pharmaceutically acceptable salt thereof.
306. The compound according to any one of the preceding items, wherein X^{13} is a bond, or a pharmaceutically acceptable salt thereof.
- 15 307. The compound according to any one of the preceding items, wherein X^{13} is C_{1-3} alkanediyl, or a pharmaceutically acceptable salt thereof.
308. The compound according to any one of the preceding items, wherein X^{13} is $-CH_2-$, or a pharmaceutically acceptable salt thereof.
- 20 309. The compound according to any one of the preceding items, wherein X^{13} is C_{1-3} alkanediyl substituted with C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
310. The compound according to any one of the preceding items, wherein X^{13} is $-C(H)(CH_3)-$, or a pharmaceutically acceptable salt thereof.
- 25 311. The compound according to any one of the preceding items, wherein X^{13} is $-O-$, or a pharmaceutically acceptable salt thereof.
312. The compound according to any one of the preceding items, wherein X^{13} is $-C_{1-3}$ alkanediyl- $O-$, or a pharmaceutically acceptable salt thereof.
313. The compound according to any one of the preceding items, wherein X^{13} is $-CH_2O-$, or a pharmaceutically acceptable salt thereof.
- 30 314. The compound according to any one of the preceding items, wherein R^{33} is azetidiny optionally substituted with one or more substituents individually selected from halogen; C_{1-3} alkoxy optionally substituted with one or more F; C_{1-3} alkyl optionally substituted with one or more F; NH_2 ; $N(H)(CH_3)$; and $N(CH_3)_2$, or a pharmaceutically acceptable salt thereof.
- 35

315. The compound according to any one of the preceding items, wherein R³³ is azetidinyloptionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

5 316. The compound according to any one of the preceding items, wherein R¹¹ is azetidinyloptionally substituted with one or more substituents selected from halogen, C₁₋₃ alkyl, and NH₂, or a pharmaceutically acceptable salt thereof.

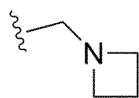
317. The compound according to any one of the preceding items, wherein R³³ is azetidinyloptionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

10 318. The compound according to any one of the preceding items, wherein R³³



is , or a pharmaceutically acceptable salt thereof.

319. The compound according to any one of the preceding items, wherein R¹¹



is , or a pharmaceutically acceptable salt thereof.

15 320. The compound according to any one of the preceding items, wherein R³³ is azetidinyloptionally substituted with one or more substituents halogen(s) and/or one or more C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

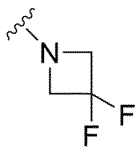
321. The compound according to any one of the preceding items, wherein R³³ is azetidinyloptionally substituted with one or more halogens, or a pharmaceutically acceptable salt thereof.

20 322. The compound according to any one of the preceding items, wherein R³³ is azetidinyloptionally substituted with one or more F, or a pharmaceutically acceptable salt thereof.

323. The compound according to any one of the preceding items, wherein R³³ is azetidinyloptionally substituted with one or two F, or a pharmaceutically acceptable salt thereof.

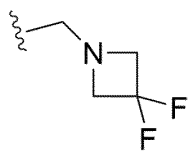
25

324. The compound according to any one of the preceding items, wherein R¹¹



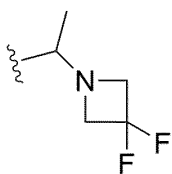
is , or a pharmaceutically acceptable salt thereof.

325. The compound according to any one of the preceding items, wherein R¹¹



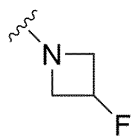
is , or a pharmaceutically acceptable salt thereof.

326. The compound according to any one of the preceding items, wherein R¹¹



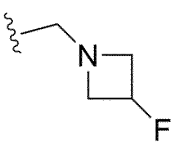
is , or a pharmaceutically acceptable salt thereof.

5 327. The compound according to any one of the preceding items, wherein R³³



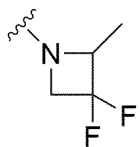
is , or a pharmaceutically acceptable salt thereof.

328. The compound according to any one of the preceding items, wherein R¹¹



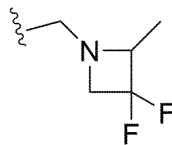
is , or a pharmaceutically acceptable salt thereof.

329. The compound according to any one of the preceding items, wherein R³³



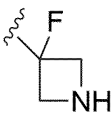
10 is or a pharmaceutically acceptable salt thereof.

330. The compound according to any one of the preceding items, wherein R¹¹



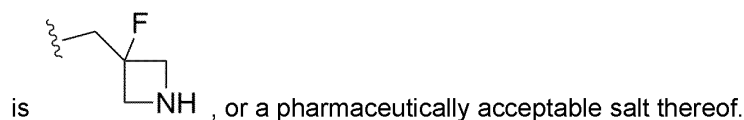
is , or a pharmaceutically acceptable salt thereof.

331. The compound according to any one of the preceding items, wherein R³³

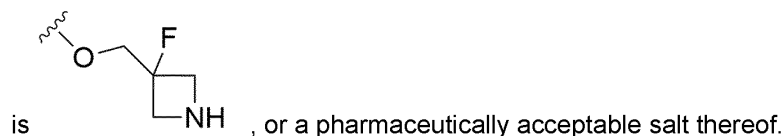


is , or a pharmaceutically acceptable salt thereof.

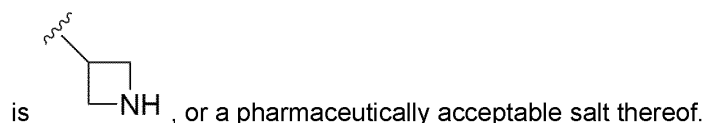
332. The compound according to any one of the preceding items, wherein R¹¹



333. The compound according to any one of the preceding items, wherein R¹¹



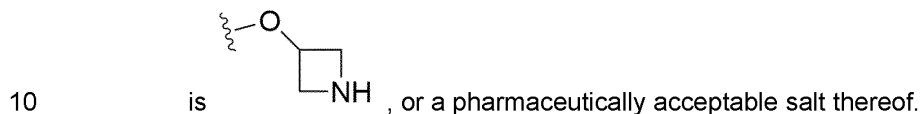
5 334. The compound according to any one of the preceding items, wherein R³³



335. The compound according to any one of the preceding items, wherein R¹¹



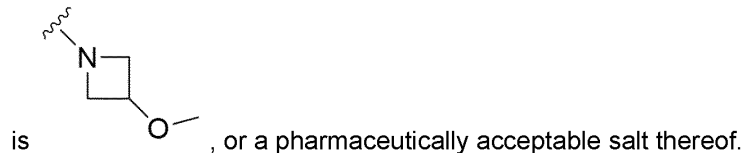
336. The compound according to any one of the preceding items, wherein R¹¹



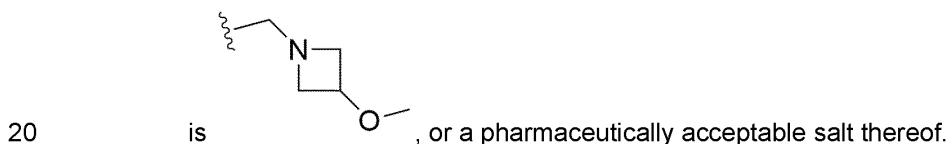
337. The compound according to any one of the preceding items, wherein R³³
is azetidynyl substituted with C₁₋₃ alkoxy, or a pharmaceutically acceptable salt thereof.

15 338. The compound according to any one of the preceding items, wherein R³³
is azetidynyl substituted with -OCH₃, or a pharmaceutically acceptable salt thereof.

339. The compound according to any one of the preceding items, wherein R³³



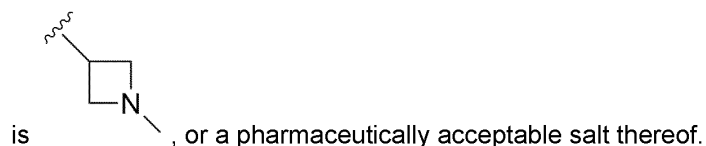
340. The compound according to any one of the preceding items, wherein R¹¹



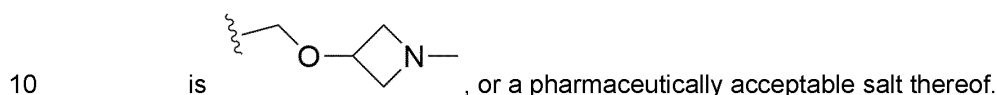
341. The compound according to any one of the preceding items, wherein R³³ is azetidinyloptionally substituted with C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

5 342. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl substituted with -O-azetidinyloptionally substituted with CH₃, or a pharmaceutically acceptable salt thereof.

343. The compound according to any one of the preceding items, wherein R³³

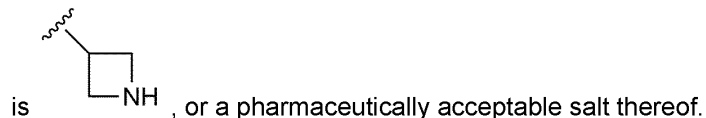


344. The compound according to any one of the preceding items, wherein R¹¹

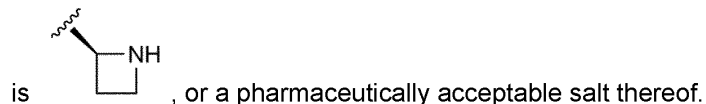


345. The compound according to any one of the preceding items, wherein R¹¹ is azetidinyloptionally substituted with C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

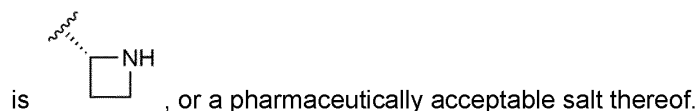
346. The compound according to any one of the preceding items, wherein R¹¹



15 347. The compound according to any one of the preceding items, wherein R¹¹



348. The compound according to any one of the preceding items, wherein R¹¹

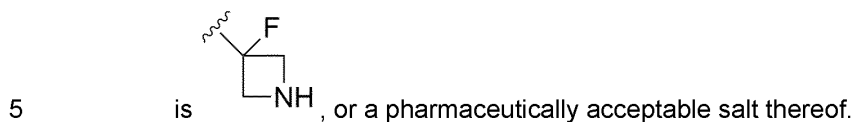


20 349. The compound according to any one of the preceding items, wherein R¹¹ is azetidinyloptionally substituted with one or more substituents selected from halogen, and C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

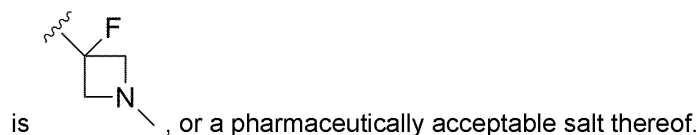
350. The compound according to any one of the preceding items, wherein R¹¹ is azetidinyloptionally substituted with halogen, such as F, or a pharmaceutically acceptable salt thereof.

351. The compound according to any one of the preceding items, wherein R¹¹ is azetidiny substituted with C₁₋₃ alkyl, such as CH₃, or a pharmaceutically acceptable salt thereof.

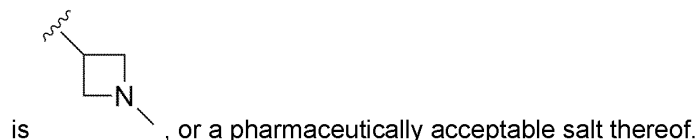
352. The compound according to any one of the preceding items, wherein R¹¹



353. The compound according to any one of the preceding items, wherein R¹¹



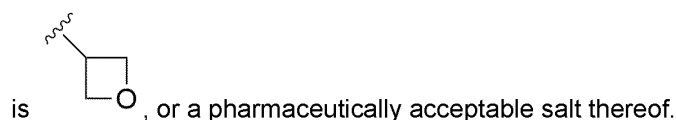
354. The compound according to any one of the preceding items, wherein R¹¹



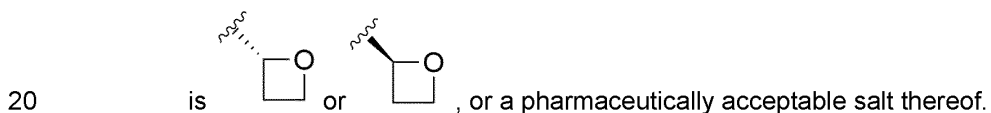
10 355. The compound according to any one of the preceding items, wherein R³³ is oxetanyl optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂, or a pharmaceutically acceptable salt thereof.

15 356. The compound according to any one of the preceding items, wherein R³³ is oxetanyl, or a pharmaceutically acceptable salt thereof.

357. The compound according to any one of the preceding items, wherein R³³

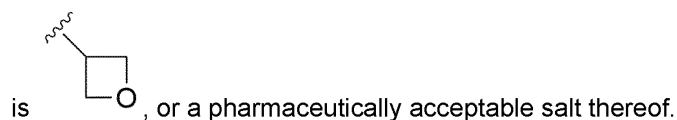


358. The compound according to any one of the preceding items, wherein R³³



359. The compound according to any one of the preceding items, wherein R¹¹ is oxetanyl, or a pharmaceutically acceptable salt thereof.

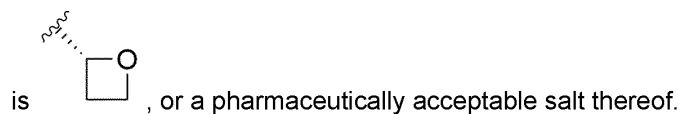
360. The compound according to any one of the preceding items, wherein R¹¹



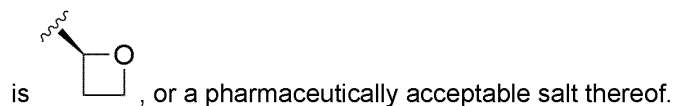
361. The compound according to any one of the preceding items, wherein R¹¹



5 362. The compound according to any one of the preceding items, wherein R¹¹



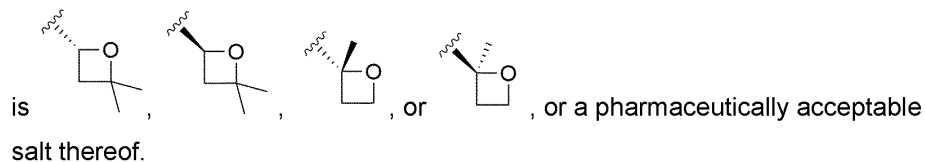
363. The compound according to any one of the preceding items, wherein R¹¹



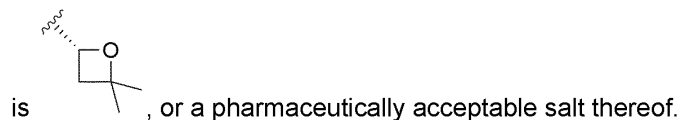
364. The compound according to any one of the preceding items, wherein R³³
10 is oxetanyl substituted with one or more C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

365. The compound according to any one of the preceding items, wherein R³³
is oxetanyl substituted with one or more -CH₃, or a pharmaceutically acceptable salt thereof.

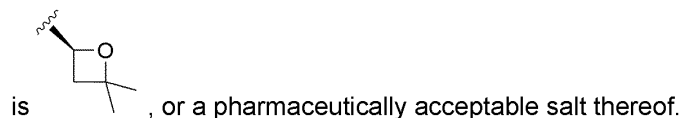
15 366. The compound according to any one of the preceding items, wherein R³³



367. The compound according to any one of the preceding items, wherein R¹¹



20 368. The compound according to any one of the preceding items, wherein R¹¹

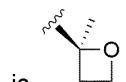


369. The compound according to any one of the preceding items, wherein R¹¹



is , or a pharmaceutically acceptable salt thereof.

370. The compound according to any one of the preceding items, wherein R¹¹



is , or a pharmaceutically acceptable salt thereof.

5 371. The compound according to any one of the preceding items, wherein R³³ is pyrrolidinyl optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂, or a pharmaceutically acceptable salt thereof.

10 372. The compound according to any one of the preceding items, wherein R³³ is pyrrolidinyl optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F, or a pharmaceutically acceptable salt thereof.

15 373. The compound according to any one of the preceding items, wherein R³³ is pyrrolidinyl substituted with one or more F, or a pharmaceutically acceptable salt thereof.

20 374. The compound according to any one of the preceding items, wherein R³³ is pyrrolidinyl substituted with one or more C₁₋₃ alkyl optionally substituted with one or more F, or a pharmaceutically acceptable salt thereof.

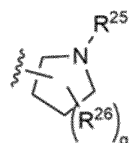
375. The compound according to any one of the preceding items, wherein R³³ is pyrrolidinyl substituted with one or more -CH₃, or a pharmaceutically acceptable salt thereof.

25 376. The compound according to any one of the preceding items, wherein R³³ is pyrrolidinyl substituted with one or more -CF₃, or a pharmaceutically acceptable salt thereof.

30 377. The compound according to any one of the preceding items, wherein R¹¹ is pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of C₁₋₃ alkyl, halogen, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, or a pharmaceutically acceptable salt thereof.

378. The compound according to any one of the preceding items, wherein R¹¹ is pyrrolidinyl optionally substituted with one or more substituents individually selected from C₁₋₃ alkyl and halogen, or a pharmaceutically acceptable salt thereof.

5 379. The compound according to any one of the preceding items, wherein R³³ is of Formula (XIV):



Formula (XIV)

wherein

10 R²⁵ is H or C₁₋₃ alkyl;

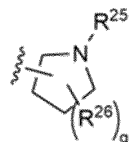
R²⁶ is individually halogen, such as F, C₁₋₃ alkyl, or C₁₋₃ haloalkyl, such as CF₃;

and

q is 0, 1 or 2,

or a pharmaceutically acceptable salt thereof.

15 380. The compound according to any one of the preceding items, wherein R¹¹ is of Formula (XIV):



Formula (XIV)

wherein

20 R²⁵ is H or C₁₋₃ alkyl;

R²⁶ is individually halogen, such as F, C₁₋₃ alkyl, or C₁₋₃ haloalkyl, such as CF₃;

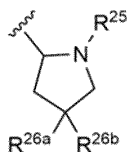
and

q is 0, 1 or 2,

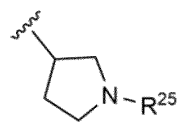
or a pharmaceutically acceptable salt thereof.

25 The compound according to any one of items 379 or 380, wherein R²⁵ is H or C₁₋₃ alkyl; R²⁶ is halogen, such as F, or C₁₋₃ alkyl; and q is 0, 1 or 2, or a pharmaceutically acceptable salt thereof.

381. The compound according to any one of the preceding items, wherein R³³ is of Formula (XIVa) or Formula (XIVb):



Formula (XIVa)



Formula (XIVb)

wherein

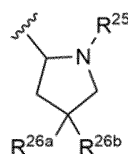
5 R^{25} is H or C_{1-3} alkyl;

R^{26a} is H or F; and

R^{26b} is H or F;

or a pharmaceutically acceptable salt thereof.

382. The compound according to any one of the preceding items, wherein R^{11}
10 is of Formula (XIVa):



Formula (XIVa)

wherein

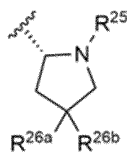
15 R^{25} is H or C_{1-3} alkyl;

R^{26a} is H or F; and

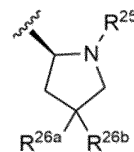
R^{26b} is H or F;

or a pharmaceutically acceptable salt thereof.

383. The compound according to any one of the preceding items, wherein the
moiety of Formula (XIVa) is of Formula (XIVa-1) or Formula (XIVa-2):



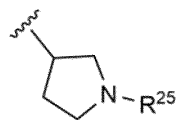
Formula (XIVa-1)



Formula (XIVa-2)

or a pharmaceutically acceptable salt thereof.

384. The compound according to any one of the preceding items, wherein R^{11}
25 is of Formula (XIVb):



Formula (XIVb)

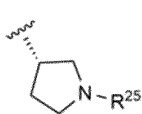
wherein

R^{25} is H or C_{1-3} alkyl;

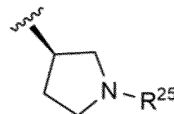
5

or a pharmaceutically acceptable salt thereof.

385. The compound according to any one of the preceding items, wherein the moiety of Formula (XIVb) is of Formula (XIVb-1) or Formula (XIVb-2) :



Formula (XIVb-1)



Formula (XIVb-2)

10

or a pharmaceutically acceptable salt thereof.

386. The compound according to any one of the preceding items, wherein R^{25} is H, or a pharmaceutically acceptable salt thereof.

15

387. The compound according to any one of the preceding items, wherein R^{25} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.

388. The compound according to any one of the preceding items, wherein R^{25} is CH_3 , or a pharmaceutically acceptable salt thereof.

389. The compound according to any one of the preceding items, wherein q is 0, or a pharmaceutically acceptable salt thereof.

20

390. The compound according to any one of the preceding items, wherein q is 1, or a pharmaceutically acceptable salt thereof.

391. The compound according to any one of the preceding items, wherein q is 2, or a pharmaceutically acceptable salt thereof.

25

392. The compound according to any one of the preceding items, wherein R^{26a} is F, or a pharmaceutically acceptable salt thereof.

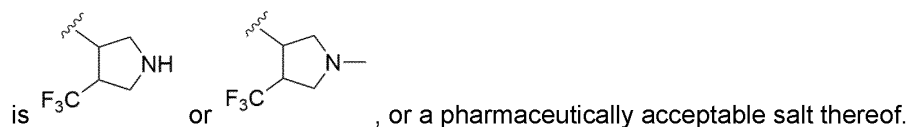
393. The compound according to any one of the preceding items, wherein R^{26b} is F, or a pharmaceutically acceptable salt thereof.

394. The compound according to any one of the preceding items, wherein R^{26a} is F and R^{26b} is F, or a pharmaceutically acceptable salt thereof.

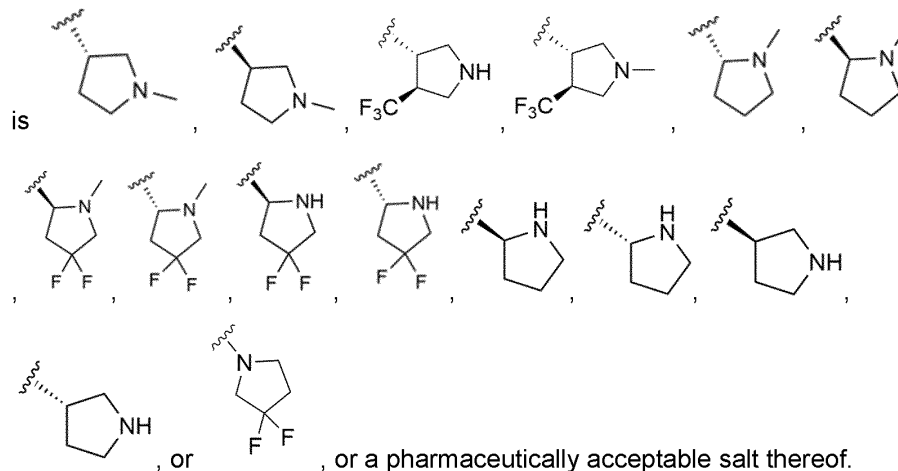
395. The compound according to any one of the preceding items, wherein R^{26a} is F and R^{26b} is H, or a pharmaceutically acceptable salt thereof.

396. The compound according to any one of the preceding items, wherein R^{26a} is H and R^{26b} is F, or a pharmaceutically acceptable salt thereof.

5 397. The compound according to any one of the preceding items, wherein R^{33}

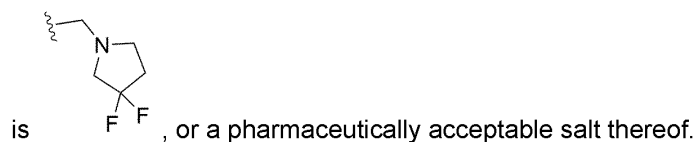


398. The compound according to any one of the preceding items, wherein R^{33}

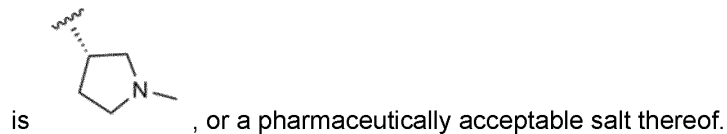


10

399. The compound according to any one of the preceding items, wherein R^{11}

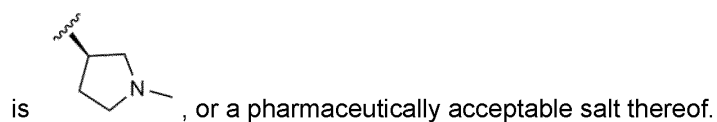


400. The compound according to any one of the preceding items, wherein R^{11}

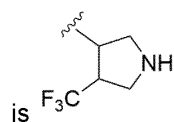


15

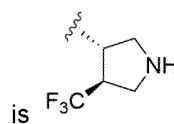
401. The compound according to any one of the preceding items, wherein R^{11}



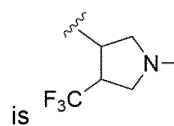
402. The compound according to any one of the preceding items, wherein R¹¹



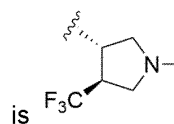
403. The compound according to any one of the preceding items, wherein R¹¹



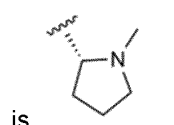
5 404. The compound according to any one of the preceding items, wherein R¹¹



405. The compound according to any one of the preceding items, wherein R¹¹

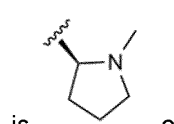


406. The compound according to any one of the preceding items, wherein R¹¹

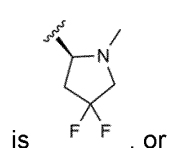


10

407. The compound according to any one of the preceding items, wherein R¹¹

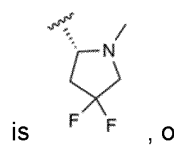


408. The compound according to any one of the preceding items, wherein R¹¹

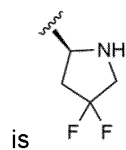


15

409. The compound according to any one of the preceding items, wherein R¹¹

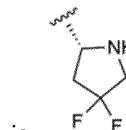


410. The compound according to any one of the preceding items, wherein R¹¹



is , or a pharmaceutically acceptable salt thereof.

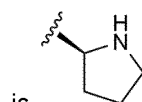
411. The compound according to any one of the preceding items, wherein R¹¹



is , or a pharmaceutically acceptable salt thereof.

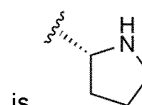
5 412. The compound according to any one of the preceding items, wherein R¹¹ is pyrrolidinyl, or a pharmaceutically acceptable salt thereof.

413. The compound according to any one of the preceding items, wherein R¹¹



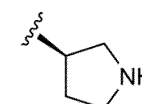
is , or a pharmaceutically acceptable salt thereof.

414. The compound according to any one of the preceding items, wherein R¹¹



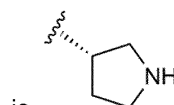
10 is , or a pharmaceutically acceptable salt thereof.

415. The compound according to any one of the preceding items, wherein R¹¹ is



, or a pharmaceutically acceptable salt thereof.

416. The compound according to any one of the preceding items, wherein R¹¹



15 is , or a pharmaceutically acceptable salt thereof.

417. The compound according to any one of the preceding items, wherein R³³ is tetrahydrofuranyl optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂, or a pharmaceutically acceptable salt thereof.

20

418. The compound according to any one of the preceding items, wherein R³³ is tetrahydrofuranyl, or a pharmaceutically acceptable salt thereof.

419. The compound according to any one of the preceding items, wherein R^{11} is tetrahydrofuranyl, or a pharmaceutically acceptable salt thereof.

420. The compound according to any one of the preceding items, wherein R^{33} is tetrahydrofuran-2-yl, or a pharmaceutically acceptable salt thereof.

5 421. The compound according to any one of the preceding items, wherein R^{33}

is  or , or a pharmaceutically acceptable salt thereof.

422. The compound according to any one of the preceding items, wherein R^{11} is tetrahydrofuran-2-yl, or a pharmaceutically acceptable salt thereof.

423. The compound according to any one of the preceding items, wherein R^{11}

10 is , or a pharmaceutically acceptable salt thereof.

424. The compound according to any one of the preceding items, wherein R^{11}

is , or a pharmaceutically acceptable salt thereof.

425. The compound according to any one of the preceding items, wherein R^{33} is morpholinyl optionally substituted with one or more substituents individually selected from halogen; C_{1-3} alkoxy optionally substituted with one or more F; C_{1-3} alkyl optionally substituted with one or more F; NH_2 ; $N(H)(CH_3)$; and $N(CH_3)_2$, or a pharmaceutically acceptable salt thereof.

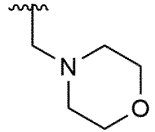
15

426. The compound according to any one of the preceding items, wherein R^{33} is morpholinyl, or a pharmaceutically acceptable salt thereof.

20

427. The compound according to any one of the preceding items, wherein R^{33} is N-morpholinyl, or a pharmaceutically acceptable salt thereof.

428. The compound according to any one of the preceding items, wherein R^{11}

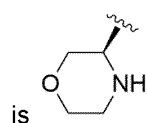
is , or a pharmaceutically acceptable salt thereof.

429. The compound according to any one of the preceding items, wherein R^{11} is morpholinyl optionally substituted with C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.

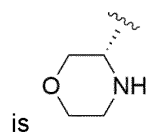
25

430. The compound according to any one of the preceding items, wherein R^{11} is morpholinyl, or a pharmaceutically acceptable salt thereof.

431. The compound according to any one of the preceding items, wherein R¹¹



432. The compound according to any one of the preceding items, wherein R¹¹

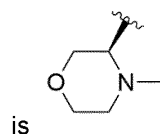


5 433. The compound according to any one of the preceding items, wherein R¹¹ is morpholinyl substituted with C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

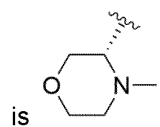
434. The compound according to any one of the preceding items, wherein R¹¹ is morpholinyl substituted with CH₃, or a pharmaceutically acceptable salt thereof.

10

435. The compound according to any one of the preceding items, wherein R¹¹



436. The compound according to any one of the preceding items, wherein R¹¹



15

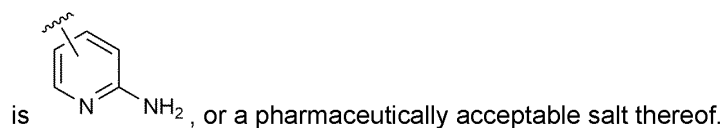
437. The compound according to any one of the preceding items, wherein R³³ is pyridinyl optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂, or a pharmaceutically acceptable salt thereof.

20

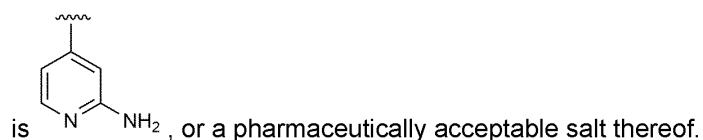
438. The compound according to any one of the preceding items, wherein R³³ is pyridinyl optionally substituted with one or more NH₂, or a pharmaceutically acceptable salt thereof.

439. The compound according to any one of the preceding items, wherein R³³ is pyridinyl substituted with NH₂, or a pharmaceutically acceptable salt thereof.

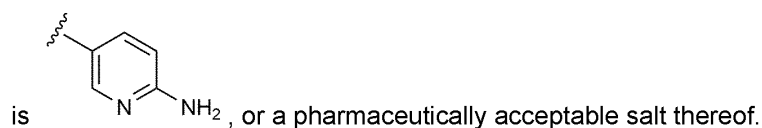
440. The compound according to any one of the preceding items, wherein R³³



441. The compound according to any one of the preceding items, wherein R³³



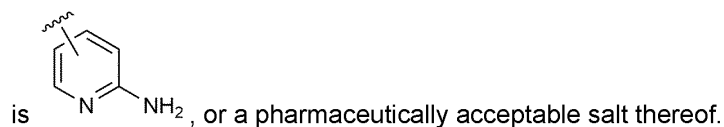
5 442. The compound according to any one of the preceding items, wherein R³³



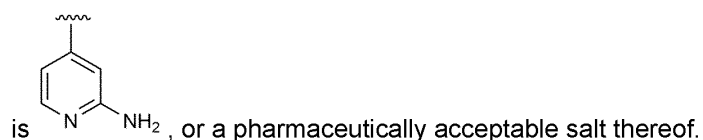
443. The compound according to any one of the preceding items, wherein R¹¹
is pyridinyl optionally substituted with one or more NH₂, or a pharmaceutically
acceptable salt thereof.

10 444. The compound according to any one of the preceding items, wherein R¹¹
is pyridinyl substituted with NH₂, or a pharmaceutically acceptable salt thereof.

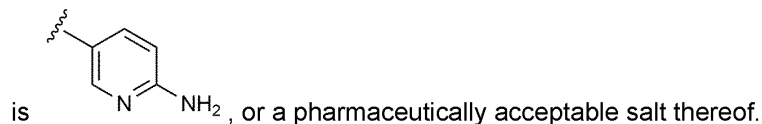
445. The compound according to any one of the preceding items, wherein R¹¹



446. The compound according to any one of the preceding items, wherein R¹¹



15 447. The compound according to any one of the preceding items, wherein R¹¹



448. The compound according to any one of the preceding items, wherein R³³
is C₁₋₃ alkyl optionally substituted with one or more substituents individually
20 selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋

₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂, or a pharmaceutically acceptable salt thereof.

449. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, C₁₋₃ alkoxy, morpholinyl, azetidiny, -O-azetidiny, and -O-oxetany, and said azetidiny is optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
450. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(CH₃)₂, N(H)(CH₃), C₁₋₃ alkoxy, and morpholinyl, or a pharmaceutically acceptable salt thereof.
451. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl optionally substituted with one or more substituents individually selected from the group consisting of NH₂, N(CH₃)₂, N(H)(CH₃) and C₁₋₃ alkoxy, or a pharmaceutically acceptable salt thereof.
452. The compound according to any one of the preceding items, wherein R³³ is C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
453. The compound according to any one of the preceding items, wherein R³³ is CH₃, or a pharmaceutically acceptable salt thereof.
454. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
455. The compound according to any one of the preceding items, wherein R¹¹ is CH₃, or a pharmaceutically acceptable salt thereof.
456. The compound according to any one of the preceding items, wherein R³³ is NH₂, or a pharmaceutically acceptable salt thereof.
457. The compound according to any one of the preceding items, wherein R³³ is N(H)(CH₃), or a pharmaceutically acceptable salt thereof.
458. The compound according to any one of the preceding items, wherein R³³ is N(CH₃)₂, or a pharmaceutically acceptable salt thereof.
459. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl substituted with one or more N(CH₃)₂, or a pharmaceutically acceptable salt thereof.

460. The compound according to any one of the preceding items, wherein R^{11} is C_{1-3} alkyl substituted with one or more NH_2 , or a pharmaceutically acceptable salt thereof.
- 5 461. The compound according to any one of the preceding items, wherein R^{11} is $-CH_2NH_2$, or a pharmaceutically acceptable salt thereof.
462. The compound according to any one of the preceding items, wherein R^{11} is $-CH_2-N(H)(CH_3)$, or a pharmaceutically acceptable salt thereof.
463. The compound according to any one of the preceding items, wherein R^{11} is $-CH_2N(CH_3)_2$, or a pharmaceutically acceptable salt thereof.
- 10 464. The compound according to any one of the preceding items, wherein R^{11} is C_{1-3} alkyl substituted with one or more C_{1-3} alkoxy, or a pharmaceutically acceptable salt thereof.
465. The compound according to any one of the preceding items, wherein R^{11} is $-CH_2OCH_3$, or a pharmaceutically acceptable salt thereof.
- 15 466. The compound according to any one of the preceding items, wherein R^{11} is $-OCH_3$, or a pharmaceutically acceptable salt thereof.
467. The compound according to any one of the preceding items, wherein R^{33} is C_{1-3} alkyl optionally substituted with one or more F, or a pharmaceutically acceptable salt thereof.
- 20 468. The compound according to any one of the preceding items, wherein R^{33} is CF_3 , or a pharmaceutically acceptable salt thereof.
469. The compound according to any one of the preceding items, wherein R^{33} is CHF_2 , or a pharmaceutically acceptable salt thereof.
- 25 470. The compound according to any one of the preceding items, wherein R^{11} is $-CH_2-O-CF_3$, or a pharmaceutically acceptable salt thereof.
471. The compound according to any one of the preceding items, wherein R^{11} is $-CH_2-O-CHF_2$, or a pharmaceutically acceptable salt thereof.
472. The compound according to any one of the preceding items, wherein R^{11} is CHF_2 , or a pharmaceutically acceptable salt thereof.
- 30 473. The compound according to any one of the preceding items, wherein R^{11} is C_{1-3} alkyl substituted with morpholinyl, or a pharmaceutically acceptable salt thereof.
474. The compound according to any one of the preceding items, wherein R^{11} is C_1 alkyl substituted with morpholinyl, or a pharmaceutically acceptable salt thereof.
- 35

475. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl substituted with azetidiny, wherein the azetidiny is optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
- 5 476. The compound according to any one of the preceding items, wherein R¹¹ is C₁ alkyl substituted with azetidiny, wherein the azetidiny is optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
- 10 477. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl substituted with azetidiny, or a pharmaceutically acceptable salt thereof.
478. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl substituted with azetidiny, wherein the azetidiny is substituted with one or more halogens, or a pharmaceutically acceptable salt thereof.
- 15 479. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl substituted with azetidiny, wherein the azetidiny is substituted with one or more F, or a pharmaceutically acceptable salt thereof.
- 20 480. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl substituted with azetidiny, wherein the azetidiny is substituted with one or two F, or a pharmaceutically acceptable salt thereof.
481. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl substituted with -O-azetidiny, wherein the azetidiny is optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
- 25 482. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl substituted with -O-azetidiny, or a pharmaceutically acceptable salt thereof.
483. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl substituted with -O-azetidiny, wherein the azetidiny is optionally substituted with C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
- 30 484. The compound according to any one of the preceding items, wherein R¹¹ is C₁₋₃ alkyl substituted with -O-azetidiny, wherein the azetidiny is optionally substituted with CH₃, or a pharmaceutically acceptable salt thereof.

485. The compound according to any one of the preceding items, wherein R^{11} is C_{1-3} alkyl substituted with -O-oxetanyl, or a pharmaceutically acceptable salt thereof.
- 5 486. The compound according to any one of the preceding items, wherein R^{33} is C_{1-3} alkoxy optionally substituted with one or more substituents individually selected from halogen; C_{1-3} alkoxy optionally substituted with one or more F; C_{1-3} alkyl optionally substituted with one or more F; NH_2 ; $N(H)(CH_3)$; and $N(CH_3)_2$, or a pharmaceutically acceptable salt thereof.
- 10 487. The compound according to any one of the preceding items, wherein R^{33} is C_{1-3} alkoxy, or a pharmaceutically acceptable salt thereof.
488. The compound according to any one of the preceding items, wherein R^{33} is $-OCH_3$, or a pharmaceutically acceptable salt thereof.
489. The compound according to any one of the preceding items, wherein R^{11} is C_{1-3} alkoxy, or a pharmaceutically acceptable salt thereof.
- 15 490. The compound according to any one of the preceding items, wherein R^{11} is $-OCH_3$, or a pharmaceutically acceptable salt thereof.
491. The compound according to any one of the preceding items, wherein R^{33} is C_{3-6} cycloalkyl optionally substituted with one or more substituents individually selected from halogen; C_{1-3} alkoxy optionally substituted with one or more F; C_{1-3} alkyl optionally substituted with one or more F; NH_2 ; $N(H)(CH_3)$; and $N(CH_3)_2$, or a pharmaceutically acceptable salt thereof.
- 20 492. The compound according to any one of the preceding items, wherein R^{33} is C_{3-6} cycloalkyl, or a pharmaceutically acceptable salt thereof.
493. The compound according to any one of the preceding items, wherein R^{33} is C_{3-6} cycloalkyl substituted with one or more substituents individually selected from halogen; C_{1-3} alkoxy optionally substituted with one or more F; and C_{1-3} alkyl optionally substituted with one or more F, or a pharmaceutically acceptable salt thereof.
- 25 494. The compound according to any one of the preceding items, wherein R^{33} is C_{3-6} cycloalkyl substituted with one or more substituents selected from halogen, and C_{1-3} alkoxy, or a pharmaceutically acceptable salt thereof.
- 30 495. The compound according to any one of the preceding items, wherein R^{33} is C_{3-6} cycloalkyl substituted with one or more F, or a pharmaceutically acceptable salt thereof.

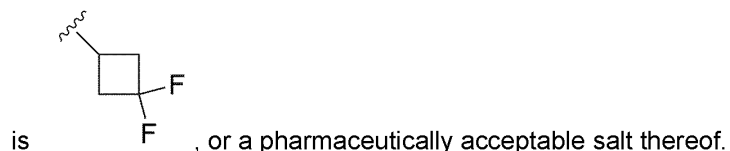
496. The compound according to any one of the preceding items, wherein R^{11} is C_{3-6} cycloalkyl substituted with C_{1-3} alkoxy, or a pharmaceutically acceptable salt thereof.

5 497. The compound according to any one of the preceding items, wherein R^{11} is C_{3-6} cycloalkyl substituted with $-OCH_3$, or a pharmaceutically acceptable salt thereof.

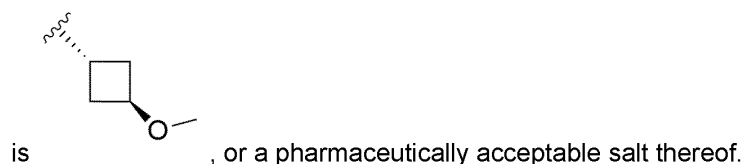
498. The compound according to any one of the preceding items, wherein the C_{3-6} cycloalkyl is C_{3-5} cycloalkyl, or a pharmaceutically acceptable salt thereof.

10 499. The compound according to any one of the preceding items, wherein the C_{3-5} cycloalkyl is cyclobutyl, or a pharmaceutically acceptable salt thereof.

500. The compound according to any one of the preceding items, wherein R^{33}



501. The compound according to any one of the preceding items, wherein R^{33}



15 502. The compound according to any one of the preceding items, wherein R^{11} is C_{3-5} cycloalkyl is optionally substituted with one or more substituents selected from halogen, and C_{1-3} alkoxy, or a pharmaceutically acceptable salt thereof.

20 503. The compound according to any one of the preceding items, wherein R^{11} is C_{3-5} cycloalkyl is optionally substituted with one or more halogen, such as F, or a pharmaceutically acceptable salt thereof.

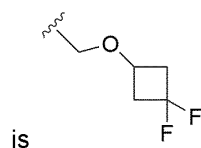
504. The compound according to any one of the preceding items, wherein R^{11} is C_{3-5} cycloalkyl is optionally substituted with C_{1-3} alkoxy, such as $-OCH_3$, or a pharmaceutically acceptable salt thereof.

25 505. The compound according to any one of the preceding items, wherein the C_{3-5} cycloalkyl is cyclobutyl, or a pharmaceutically acceptable salt thereof.

506. The compound according to any one of the preceding items, wherein R^{11}

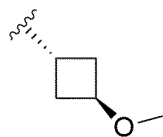


507. The compound according to any one of the preceding items, wherein R^{11}



is , or a pharmaceutically acceptable salt thereof.

508. The compound according to any one of the preceding items, wherein R^{11}



is , or a pharmaceutically acceptable salt thereof.

509. The compound according to any one of the preceding items, wherein R^{33} is C_{3-6} cycloalkyl, or a pharmaceutically acceptable salt thereof.

510. The compound according to any one of the preceding items, wherein R^{33} is cyclopropyl, or a pharmaceutically acceptable salt thereof.

511. The compound according to any one of the preceding items, wherein R^{11} is C_{3-5} cycloalkyl, or a pharmaceutically acceptable salt thereof.

512. The compound according to any one of the preceding items, wherein R^{11} is cyclopropyl, or a pharmaceutically acceptable salt thereof.

513. The compound according to any one of the preceding items, wherein R^{12} is H, or a pharmaceutically acceptable salt thereof.

514. The compound according to any one of the preceding items, wherein R^{12} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.

515. The compound according to any one of the preceding items, wherein R^{12} is CH_3 , or a pharmaceutically acceptable salt thereof.

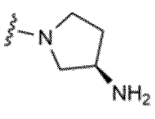
516. The compound according to any one of the preceding items, wherein R^{13} is $N(H)(CH_3)$, or a pharmaceutically acceptable salt thereof.

517. The compound according to any one of the preceding items, wherein R^{13} is pyrrolidinyl optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH_2 , $N(H)(CH_3)$, $N(CH_3)_2$ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, or a pharmaceutically acceptable salt thereof.

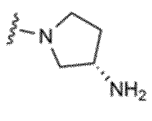
518. The compound according to any one of the preceding items, wherein R^{13} is pyrrolidinyl substituted with one or more substituents individually selected from the group consisting of halogen, NH_2 , $N(H)(CH_3)$, and $N(CH_3)_2$, or a pharmaceutically acceptable salt thereof.

519. The compound according to any one of the preceding items, wherein R¹³ is pyrrolidinyl optionally substituted with NH₂, N(H)(CH₃), or N(CH₃)₂, or a pharmaceutically acceptable salt thereof.

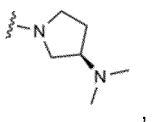
520. The compound according to any one of the preceding items, wherein R¹³

5 is , or a pharmaceutically acceptable salt thereof.

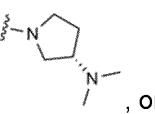
521. The compound according to any one of the preceding items, wherein R¹³

is , or a pharmaceutically acceptable salt thereof.

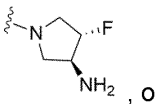
522. The compound according to any one of the preceding items, wherein R¹³

10 is , or a pharmaceutically acceptable salt thereof.

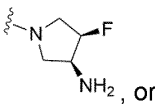
523. The compound according to any one of the preceding items, wherein R¹³

is , or a pharmaceutically acceptable salt thereof.

524. The compound according to any one of the preceding items, wherein R¹³

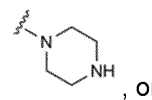
is , or a pharmaceutically acceptable salt thereof.

525. The compound according to any one of the preceding items, wherein R¹³

15 is , or a pharmaceutically acceptable salt thereof.

526. The compound according to any one of the preceding items, wherein R¹³ is piperazinyl, or a pharmaceutically acceptable salt thereof.

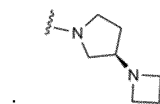
527. The compound according to any one of the preceding items, wherein R¹³

20 is , or a pharmaceutically acceptable salt thereof.

528. The compound according to any one of the preceding items, wherein R¹³ is pyrrolidinyl optionally substituted with azetidiny, and the azetidiny is

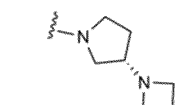
optionally substituted with one or more halogens, or a pharmaceutically acceptable salt thereof.

529. The compound according to any one of the preceding items, wherein R^{13}



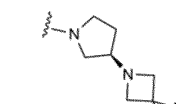
is , or a pharmaceutically acceptable salt thereof.

530. The compound according to any one of the preceding items, wherein R^{13}



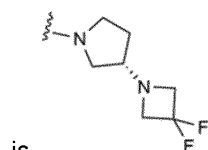
is , or a pharmaceutically acceptable salt thereof.

531. The compound according to any one of the preceding items, wherein R^{13}



is , or a pharmaceutically acceptable salt thereof.

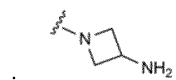
532. The compound according to any one of the preceding items, wherein R^{13}



is , or a pharmaceutically acceptable salt thereof.

533. The compound according to any one of the preceding items, wherein R^{13} is azetidynyl optionally substituted with NH_2 , or a pharmaceutically acceptable salt thereof.

534. The compound according to any one of the preceding items, wherein R^{13}



is , or a pharmaceutically acceptable salt thereof.

535. The compound according to any one of the preceding items, wherein R^{13} is NH_2 , $N(H)(CH_3)$, or $N(CH_3)_2$, or a pharmaceutically acceptable salt thereof.

536. The compound according to any one of the preceding items, wherein R^{13} is linked to R^9 , R^{10} , R^{17} , or R^{18} to form a ring together with the intervening atoms, and R^{13} is $-N(R^{28})-$, wherein R^{28} is H or C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.

537. The compound according to any one of the preceding items, wherein R^{13} is linked to R^9 , R^{10} , R^{17} , or R^{18} to form a ring together with the intervening atoms, and R^{13} is $-N(CH_3)-$, or a pharmaceutically acceptable salt thereof.
538. The compound according to any one of the preceding items, wherein R^{14} is $N(H)(C(O)CH_3)$, or a pharmaceutically acceptable salt thereof.
539. The compound according to any one of the preceding items, wherein R^{15} is H, or a pharmaceutically acceptable salt thereof.
540. The compound according to any one of the preceding items, wherein R^{16} is H, or a pharmaceutically acceptable salt thereof.
541. The compound according to any one of the preceding items, wherein R^{16} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
542. The compound according to any one of the preceding items, wherein R^{16} is CH_3 , or a pharmaceutically acceptable salt thereof.
543. The compound according to any one of the preceding items, wherein R^{17} is H, or a pharmaceutically acceptable salt thereof.
544. The compound according to any one of the preceding items, wherein R^{17} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
545. The compound according to any one of the preceding items, wherein R^{17} is CH_3 , or a pharmaceutically acceptable salt thereof.
546. The compound according to any one of the preceding items, wherein R^{17} is C_{1-3} alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
547. The compound according to any one of the preceding items, wherein R^{17} is halogen, such as F, or a pharmaceutically acceptable salt thereof.
548. The compound according to any one of the preceding items, wherein R^{18} is H, or a pharmaceutically acceptable salt thereof.
549. The compound according to any one of the preceding items, wherein R^{18} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
550. The compound according to any one of the preceding items, wherein R^{18} is CH_3 , or a pharmaceutically acceptable salt thereof.
551. The compound according to any one of the preceding items, wherein R^{18} is C_{1-3} alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
552. The compound according to any one of the preceding items, wherein R^{18} is halogen, such as F, or a pharmaceutically acceptable salt thereof.

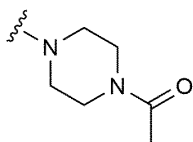
553. The compound according to any one of the preceding items, wherein R¹⁹ is H, or a pharmaceutically acceptable salt thereof.
554. The compound according to any one of the preceding items, wherein R¹⁹ is C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
- 5 555. The compound according to any one of the preceding items, wherein R¹⁹ is C₁₋₃ alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
556. The compound according to any one of the preceding items, wherein R¹⁹ is halogen, such as F, or a pharmaceutically acceptable salt thereof.
- 10 557. The compound according to any one of the preceding items, wherein R²⁰ is H, or a pharmaceutically acceptable salt thereof.
558. The compound according to any one of the preceding items, wherein R²⁰ is C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
559. The compound according to any one of the preceding items, wherein R²⁰ is CH₃, or a pharmaceutically acceptable salt thereof.
- 15 560. The compound according to any one of the preceding items, wherein R²⁰ is C₁₋₃ alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
561. The compound according to any one of the preceding items, wherein R²⁰ is halogen, such as F, or a pharmaceutically acceptable salt thereof.
- 20 562. The compound according to any one of the preceding items, wherein R²¹ is H, or a pharmaceutically acceptable salt thereof.
563. The compound according to any one of the preceding items, wherein R²¹ is C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
- 25 564. The compound according to any one of the preceding items, wherein R²¹ is CH₃, or a pharmaceutically acceptable salt thereof.
565. The compound according to any one of the preceding items, wherein R²¹ is C₁₋₃ alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
- 30 566. The compound according to any one of the preceding items, wherein R²¹ is halogen, such as F, or a pharmaceutically acceptable salt thereof.
567. The compound according to any one of the preceding items, wherein R²² is H, or a pharmaceutically acceptable salt thereof.
- 35 568. The compound according to any one of the preceding items, wherein R²² is C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

569. The compound according to any one of the preceding items, wherein R^{22} is CH_3 , or a pharmaceutically acceptable salt thereof.
570. The compound according to any one of the preceding items, wherein R^{22} is C_{1-3} alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
571. The compound according to any one of the preceding items, wherein R^{22} is halogen, such as F, or a pharmaceutically acceptable salt thereof.
572. The compound according to any one of the preceding items, wherein R^{23} is H, or a pharmaceutically acceptable salt thereof.
573. The compound according to any one of the preceding items, wherein R^{23} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
574. The compound according to any one of the preceding items, wherein R^{23} is a bond and R^{15} is C_{1-3} alkanediyl and R^{23} is linked to R^{15} to form a 4 or 5 membered ring, or a pharmaceutically acceptable salt thereof.
575. The compound according to any one of the preceding items, wherein R^{24} is CH_3 , or a pharmaceutically acceptable salt thereof.
576. The compound according to any one of the preceding items, wherein more than two of X^2 , X^5 and X^6 are bonds, or a pharmaceutically acceptable salt thereof.
577. The compound according to any one of the preceding items, wherein the azetidiny is azetidin-1-yl, or a pharmaceutically acceptable salt thereof.
578. The compound according to any one of the preceding items, wherein the azetidiny is azetidin-2-yl, or a pharmaceutically acceptable salt thereof.
579. The compound according to any one of the preceding items, wherein the azetidiny is azetidin-3-yl, or a pharmaceutically acceptable salt thereof.
580. The compound according to any one of the preceding items, wherein the morpholiny is morpholin-4-yl, or a pharmaceutically acceptable salt thereof.
581. The compound according to any one of the preceding items, wherein the morpholiny is morpholin-3-yl, or a pharmaceutically acceptable salt thereof.
582. The compound according to any one of the preceding items, wherein the pyrrolidiny is pyrrolidin-1-yl, or a pharmaceutically acceptable salt thereof.
583. The compound according to any one of the preceding items, wherein the pyrrolidiny is pyrrolidin-2-yl, or a pharmaceutically acceptable salt thereof.
584. The compound according to any one of the preceding items, wherein the pyrrolidiny is pyrrolidin-3-yl, or a pharmaceutically acceptable salt thereof.

585. The compound according to any one of the preceding items, wherein the oxetanyl is oxetan-2-yl, or a pharmaceutically acceptable salt thereof.

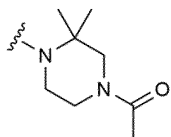
586. The compound according to any one of the preceding items, wherein the oxetanyl is oxetan-3-yl, or a pharmaceutically acceptable salt thereof.

5 587. The compound according to any one of the preceding items, wherein R⁴



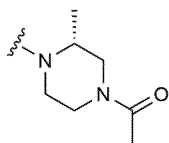
is , or a pharmaceutically acceptable salt thereof.

588. The compound according to any one of the preceding items, wherein R⁴



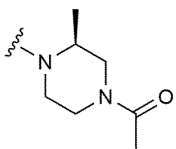
is , or a pharmaceutically acceptable salt thereof.

589. The compound according to any one of the preceding items, wherein R⁴



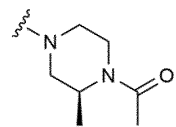
10 is , or a pharmaceutically acceptable salt thereof.

590. The compound according to any one of the preceding items, wherein R⁴



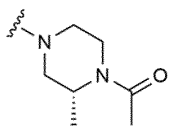
is , or a pharmaceutically acceptable salt thereof.

591. The compound according to any one of the preceding items, wherein R⁴



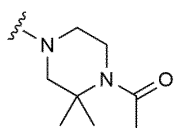
is , or a pharmaceutically acceptable salt thereof.

15 592. The compound according to any one of the preceding items, wherein R⁴



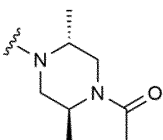
is , or a pharmaceutically acceptable salt thereof.

593. The compound according to any one of the preceding items, wherein R⁴



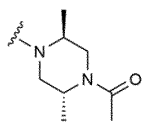
is , or a pharmaceutically acceptable salt thereof.

594. The compound according to any one of the preceding items, wherein R⁴



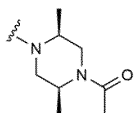
is , or a pharmaceutically acceptable salt thereof.

5 595. The compound according to any one of the preceding items, wherein R⁴



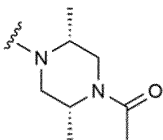
is , or a pharmaceutically acceptable salt thereof.

596. The compound according to any one of the preceding items, wherein R⁴



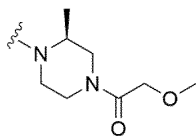
is , or a pharmaceutically acceptable salt thereof.

597. The compound according to any one of the preceding items, wherein R⁴



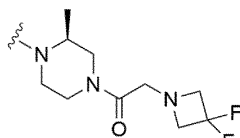
10 is , or a pharmaceutically acceptable salt thereof.

598. The compound according to any one of the preceding items, wherein R⁴



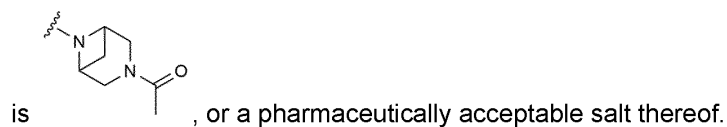
is , or a pharmaceutically acceptable salt thereof.

599. The compound according to any one of the preceding items, wherein R⁴

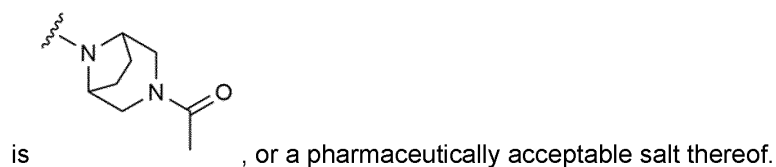


is , or a pharmaceutically acceptable salt thereof.

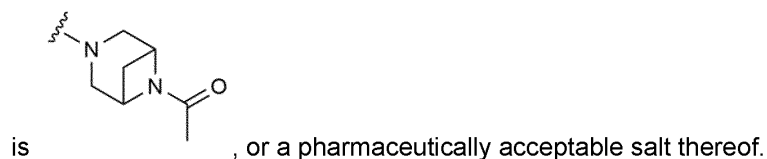
600. The compound according to any one of the preceding items, wherein R⁴



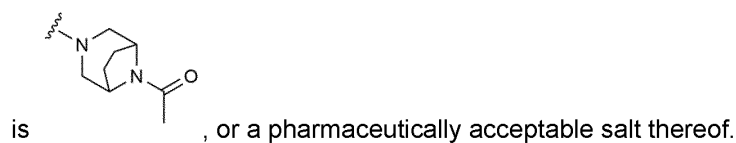
601. The compound according to any one of the preceding items, wherein R⁴



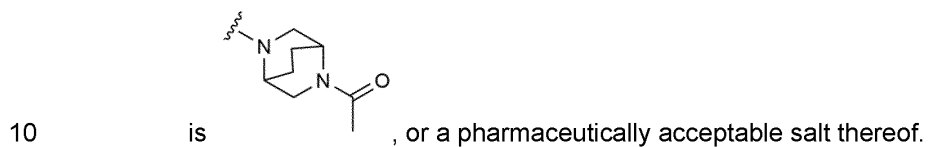
5 602. The compound according to any one of the preceding items, wherein R⁴



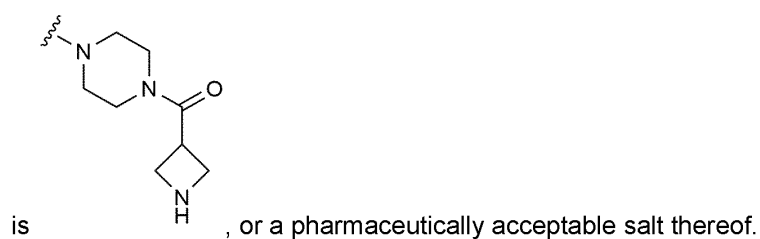
603. The compound according to any one of the preceding items, wherein R⁴



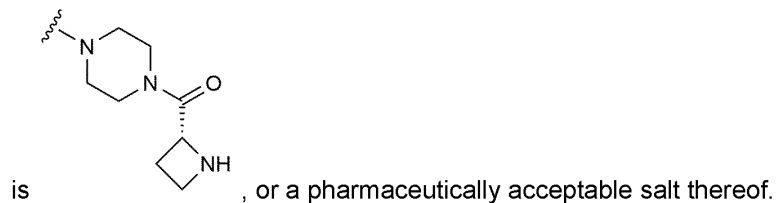
604. The compound according to any one of the preceding items, wherein R⁴



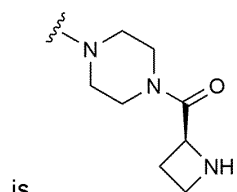
605. The compound according to any one of the preceding items, wherein R⁴



606. The compound according to any one of the preceding items, wherein R⁴

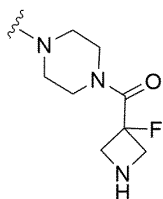


607. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

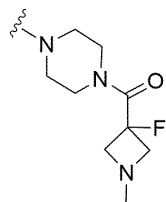
608. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

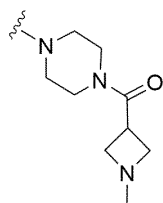
5

609. The compound according to any one of the preceding items, wherein R⁴



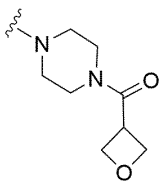
is , or a pharmaceutically acceptable salt thereof.

610. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

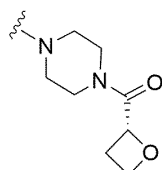
611. The compound according to any one of the preceding items, wherein R⁴



10

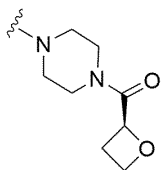
is , or a pharmaceutically acceptable salt thereof.

612. The compound according to any one of the preceding items, wherein R⁴



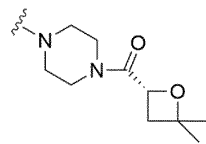
is , or a pharmaceutically acceptable salt thereof.

613. The compound according to any one of the preceding items, wherein R⁴



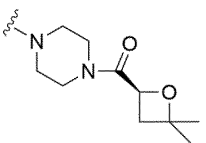
is , or a pharmaceutically acceptable salt thereof.

5 614. The compound according to any one of the preceding items, wherein R⁴



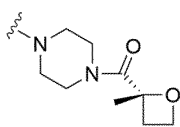
is , or a pharmaceutically acceptable salt thereof.

615. The compound according to any one of the preceding items, wherein R⁴



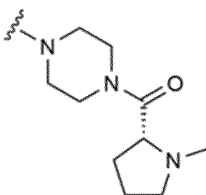
is , or a pharmaceutically acceptable salt thereof.

616. The compound according to any one of the preceding items, wherein R⁴



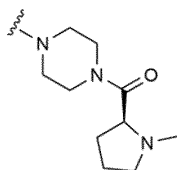
10 is , or a pharmaceutically acceptable salt thereof.

617. The compound according to any one of the preceding items, wherein R⁴



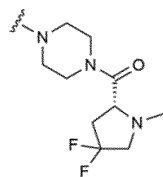
is , or a pharmaceutically acceptable salt thereof.

618. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

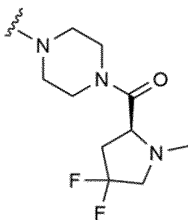
619. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

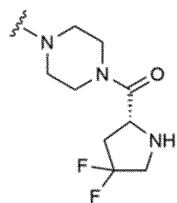
5

620. The compound according to any one of the preceding items, wherein R⁴



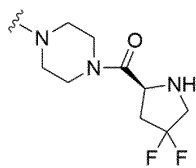
is , or a pharmaceutically acceptable salt thereof.

621. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

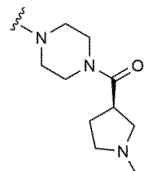
622. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

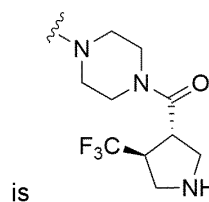
10

623. The compound according to any one of the preceding items, wherein R⁴



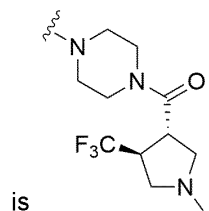
is , or a pharmaceutically acceptable salt thereof.

624. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

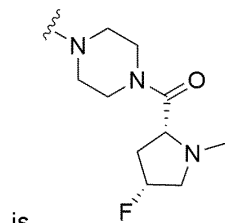
625. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

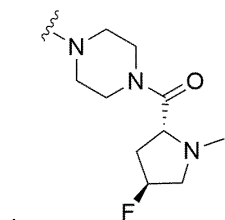
5

626. The compound according to any one of the preceding items, wherein R⁴



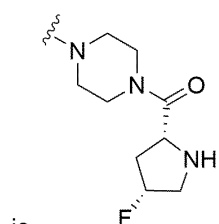
is , or a pharmaceutically acceptable salt thereof.

627. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

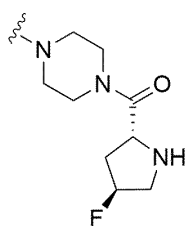
628. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

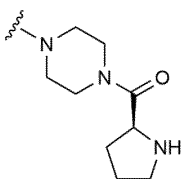
10

629. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

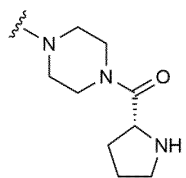
630. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

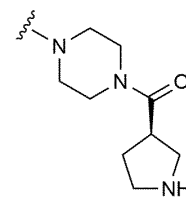
5

631. The compound according to any one of the preceding items, wherein R⁴



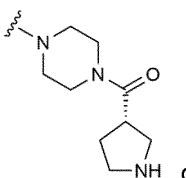
is , or a pharmaceutically acceptable salt thereof.

632. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

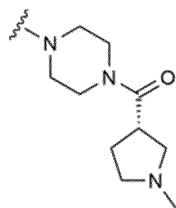
633. The compound according to any one of the preceding items, wherein R⁴



10

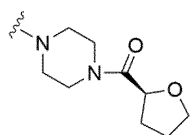
is , or a pharmaceutically acceptable salt thereof.

634. The compound according to any one of the preceding items, wherein R⁴



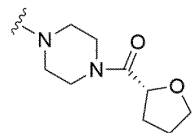
is , or a pharmaceutically acceptable salt thereof.

635. The compound according to any one of the preceding items, wherein R⁴



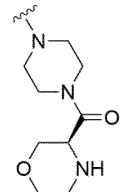
is , or a pharmaceutically acceptable salt thereof.

5 636. The compound according to any one of the preceding items, wherein R⁴



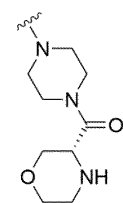
is , or a pharmaceutically acceptable salt thereof.

637. The compound according to any one of the preceding items, wherein R⁴



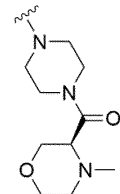
is , or a pharmaceutically acceptable salt thereof.

638. The compound according to any one of the preceding items, wherein R⁴



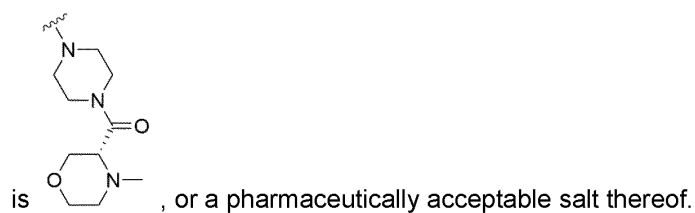
10 is , or a pharmaceutically acceptable salt thereof.

639. The compound according to any one of the preceding items, wherein R⁴

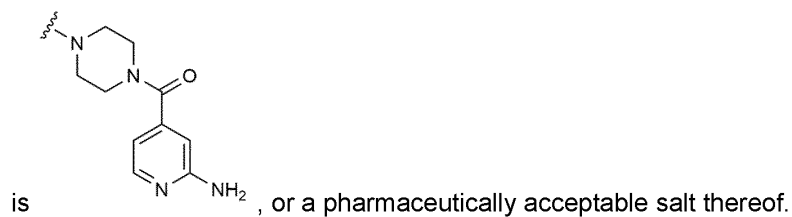


is , or a pharmaceutically acceptable salt thereof.

640. The compound according to any one of the preceding items, wherein R⁴

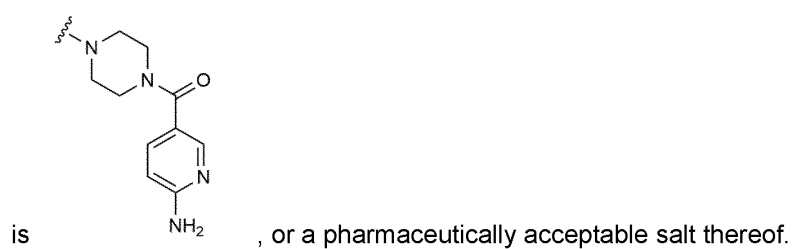


641. The compound according to any one of the preceding items, wherein R⁴

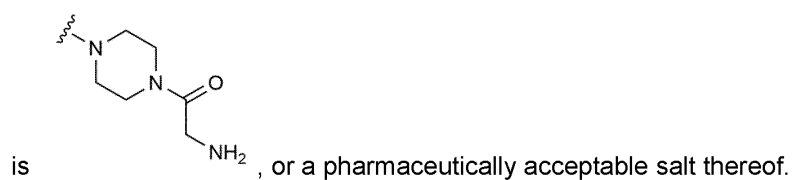


5

642. The compound according to any one of the preceding items, wherein R⁴

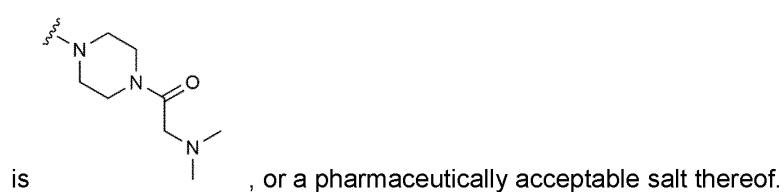


643. The compound according to any one of the preceding items, wherein R⁴

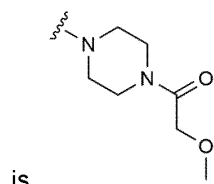


10

644. The compound according to any one of the preceding items, wherein R⁴

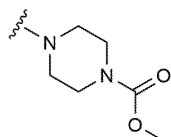


645. The compound according to any one of the preceding items, wherein R⁴



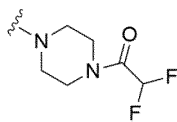
is , or a pharmaceutically acceptable salt thereof.

646. The compound according to any one of the preceding items, wherein R⁴



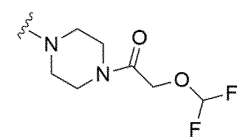
is , or a pharmaceutically acceptable salt thereof.

5 647. The compound according to any one of the preceding items, wherein R⁴



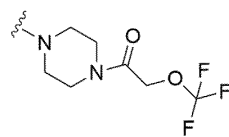
is , or a pharmaceutically acceptable salt thereof.

648. The compound according to any one of the preceding items, wherein R⁴



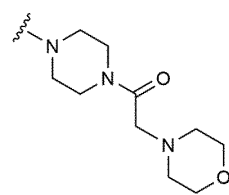
is , or a pharmaceutically acceptable salt thereof.

649. The compound according to any one of the preceding items, wherein R⁴



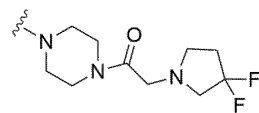
10 is , or a pharmaceutically acceptable salt thereof.

650. The compound according to any one of the preceding items, wherein R⁴



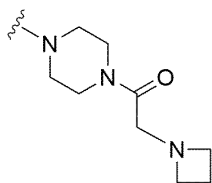
is , or a pharmaceutically acceptable salt thereof.

651. The compound according to any one of the preceding items, wherein R⁴



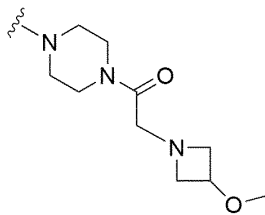
is , or a pharmaceutically acceptable salt thereof.

652. The compound according to any one of the preceding items, wherein R⁴



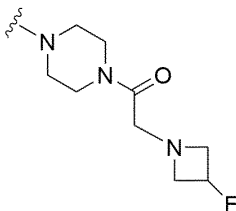
is , or a pharmaceutically acceptable salt thereof.

653. The compound according to any one of the preceding items, wherein R⁴



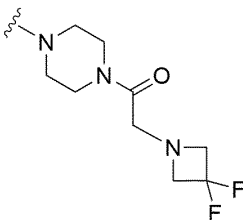
is , or a pharmaceutically acceptable salt thereof.

5 654. The compound according to any one of the preceding items, wherein R⁴



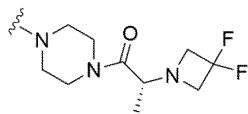
is , or a pharmaceutically acceptable salt thereof.

655. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

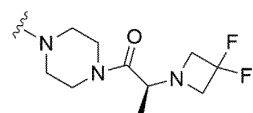
656. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

10

657. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

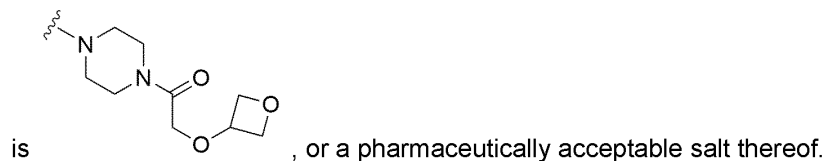
658. The compound according to any one of the preceding items, wherein R⁴



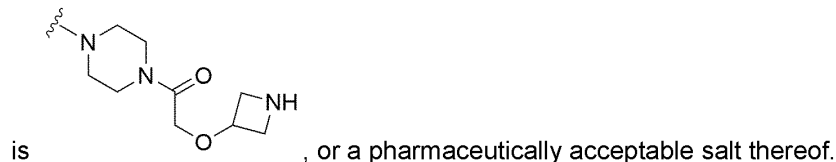
659. The compound according to any one of the preceding items, wherein R⁴



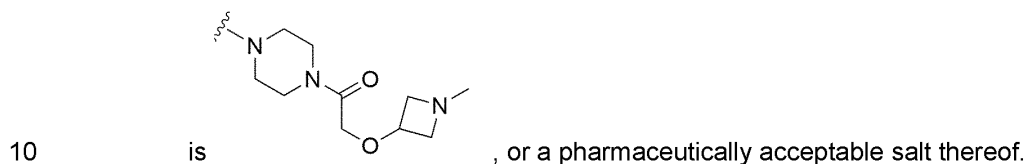
5 660. The compound according to any one of the preceding items, wherein R⁴



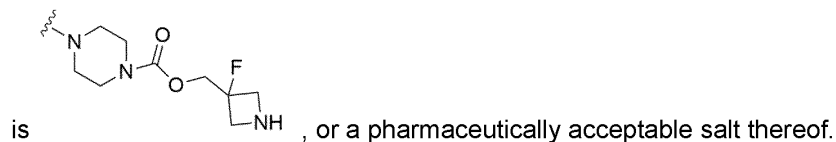
661. The compound according to any one of the preceding items, wherein R⁴



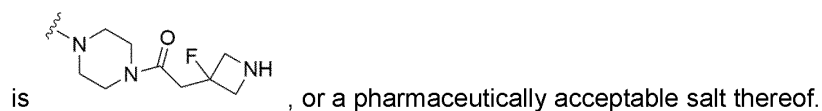
662. The compound according to any one of the preceding items, wherein R⁴



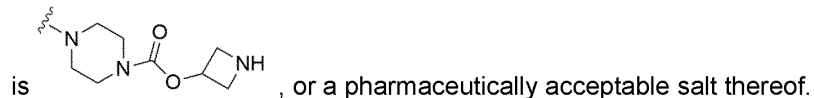
663. The compound according to any one of the preceding items, wherein R⁴



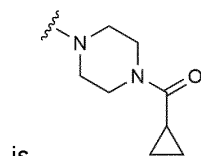
664. The compound according to any one of the preceding items, wherein R⁴



15 665. The compound according to any one of the preceding items, wherein R⁴

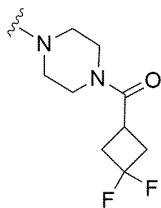


666. The compound according to any one of the preceding items, wherein R⁴



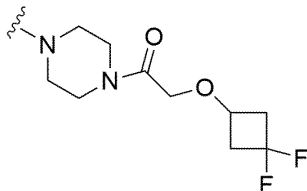
is , or a pharmaceutically acceptable salt thereof.

667. The compound according to any one of the preceding items, wherein R⁴



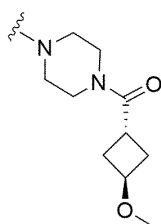
is , or a pharmaceutically acceptable salt thereof.

5 668. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

669. The compound according to any one of the preceding items, wherein R⁴

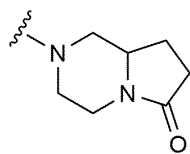


is , or a pharmaceutically acceptable salt thereof.

670. The compound according to any one of the preceding items, wherein R⁴

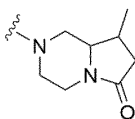
10

is



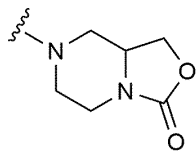
, or a pharmaceutically acceptable salt thereof.

671. The compound according to any one of the preceding items, wherein R⁴



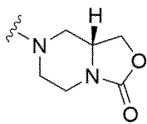
is , or a pharmaceutically acceptable salt thereof.

672. The compound according to any one of the preceding items, wherein R⁴



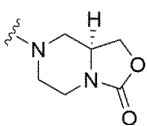
is , or a pharmaceutically acceptable salt thereof.

673. The compound according to any one of the preceding items, wherein R⁴



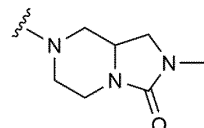
is , or a pharmaceutically acceptable salt thereof.

5 674. The compound according to any one of the preceding items, wherein R⁴



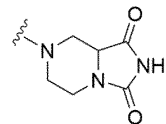
is , or a pharmaceutically acceptable salt thereof.

675. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

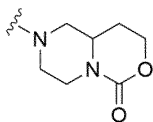
676. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

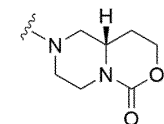
10

677. The compound according to any one of the preceding items, wherein R⁴



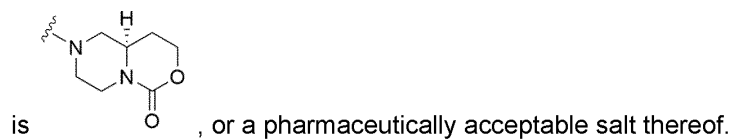
is , or a pharmaceutically acceptable salt thereof.

678. The compound according to any one of the preceding items, wherein R⁴

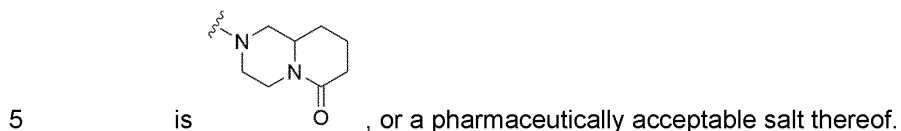


is , or a pharmaceutically acceptable salt thereof.

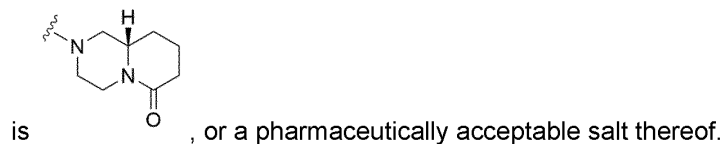
679. The compound according to any one of the preceding items, wherein R⁴



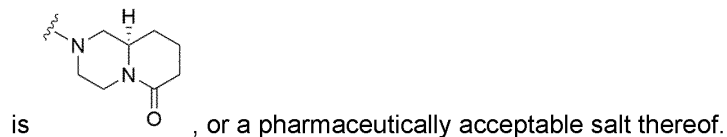
680. The compound according to any one of the preceding items, wherein R⁴



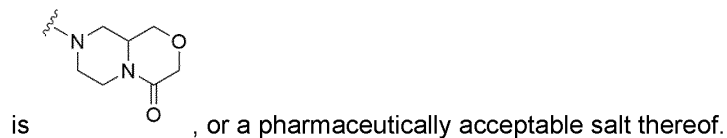
681. The compound according to any one of the preceding items, wherein R⁴



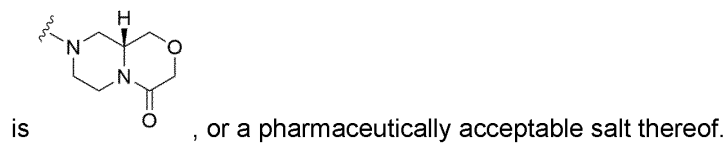
682. The compound according to any one of the preceding items, wherein R⁴



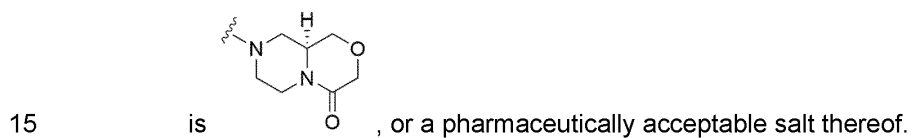
10 683. The compound according to any one of the preceding items, wherein R⁴



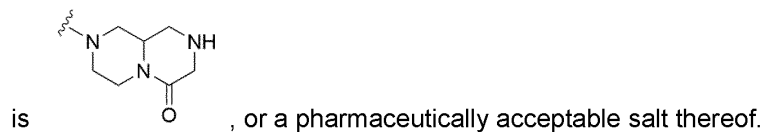
684. The compound according to any one of the preceding items, wherein R⁴



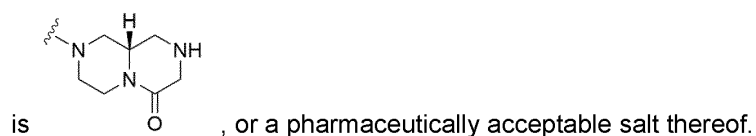
685. The compound according to any one of the preceding items, wherein R⁴



686. The compound according to any one of the preceding items, wherein R⁴



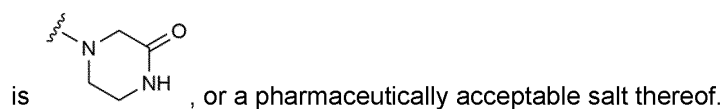
687. The compound according to any one of the preceding items, wherein R⁴



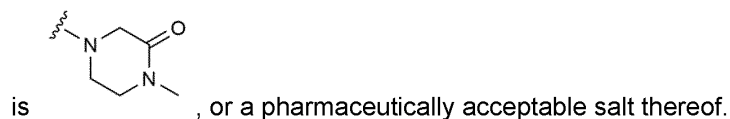
5 688. The compound according to any one of the preceding items, wherein R⁴



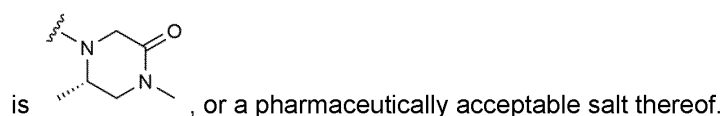
689. The compound according to any one of the preceding items, wherein R⁴



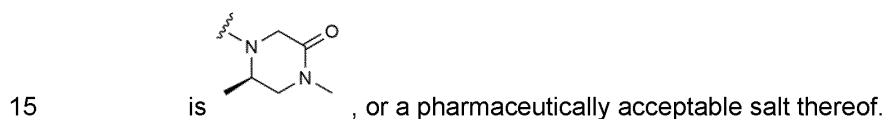
10 690. The compound according to any one of the preceding items, wherein R⁴



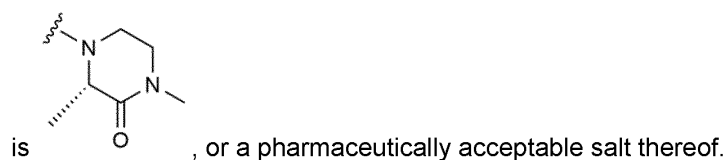
691. The compound according to any one of the preceding items, wherein R⁴



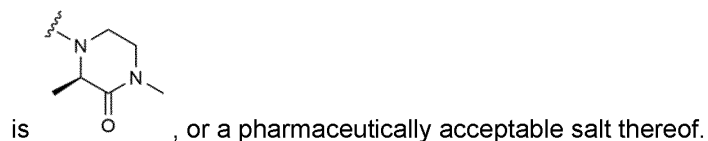
692. The compound according to any one of the preceding items, wherein R⁴



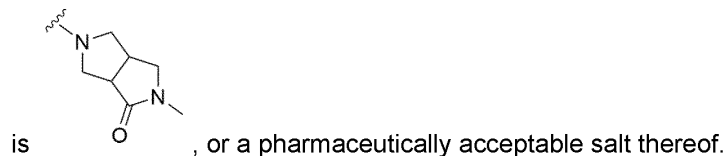
693. The compound according to any one of the preceding items, wherein R⁴



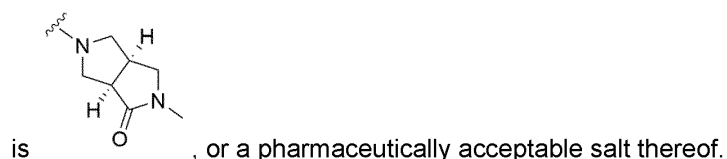
694. The compound according to any one of the preceding items, wherein R⁴



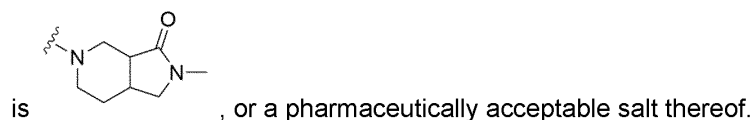
695. The compound according to any one of the preceding items, wherein R⁴



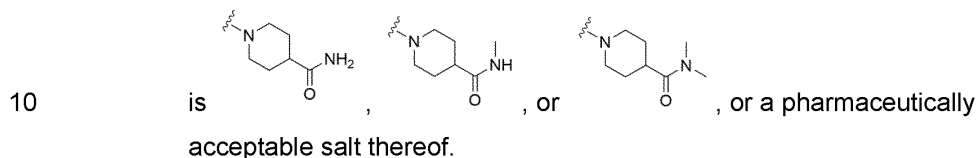
5 696. The compound according to any one of the preceding items, wherein R⁴



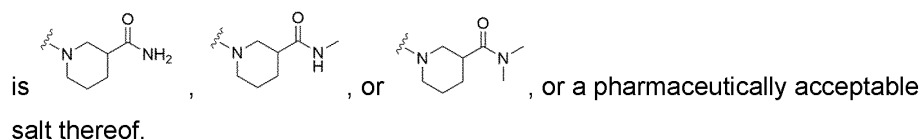
697. The compound according to any one of the preceding items, wherein R⁴



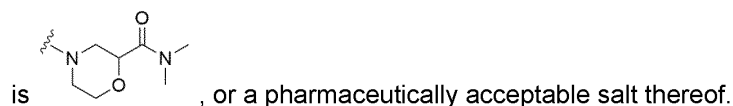
698. The compound according to any one of the preceding items, wherein R⁴



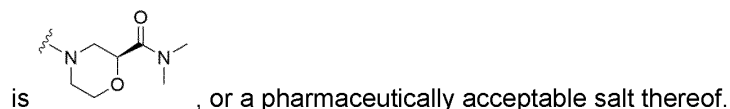
699. The compound according to any one of the preceding items, wherein R⁴



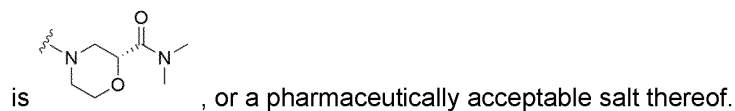
15 700. The compound according to any one of the preceding items, wherein R⁴



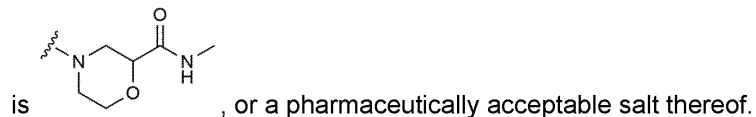
701. The compound according to any one of the preceding items, wherein R⁴



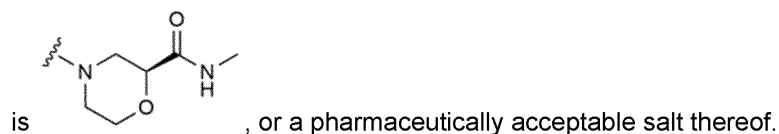
702. The compound according to any one of the preceding items, wherein R⁴



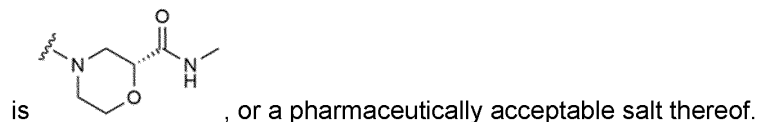
703. The compound according to any one of the preceding items, wherein R⁴



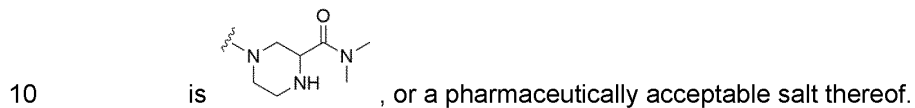
5 704. The compound according to any one of the preceding items, wherein R⁴



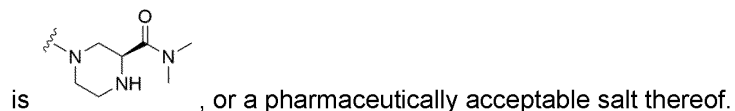
705. The compound according to any one of the preceding items, wherein R⁴



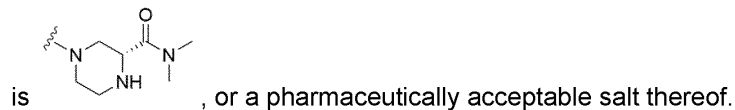
706. The compound according to any one of the preceding items, wherein R⁴



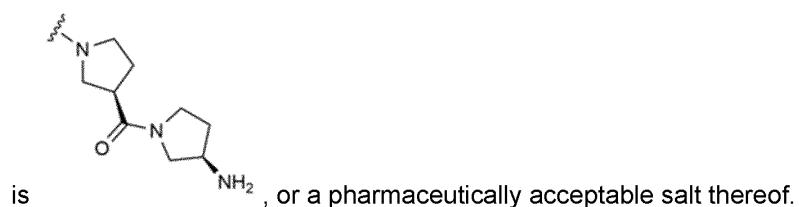
707. The compound according to any one of the preceding items, wherein R⁴



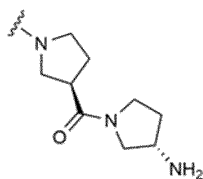
708. The compound according to any one of the preceding items, wherein R⁴



15 709. The compound according to any one of the preceding items, wherein R⁴

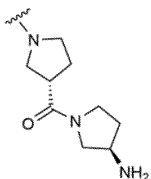


710. The compound according to any one of the preceding items, wherein R⁴



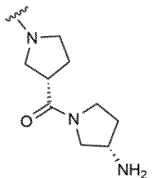
is , or a pharmaceutically acceptable salt thereof.

711. The compound according to any one of the preceding items, wherein R⁴



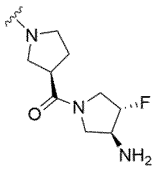
is , or a pharmaceutically acceptable salt thereof.

5 712. The compound according to any one of the preceding items, wherein R⁴



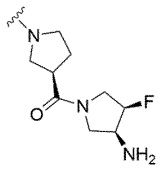
is , or a pharmaceutically acceptable salt thereof.

713. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

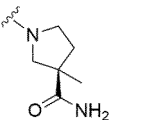
714. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

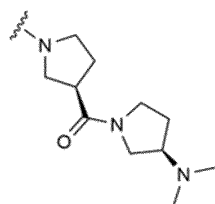
10

715. The compound according to any one of the preceding items, wherein R⁴



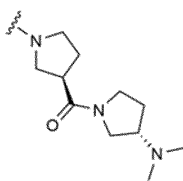
is , or a pharmaceutically acceptable salt thereof.

716. The compound according to any one of the preceding items, wherein R⁴



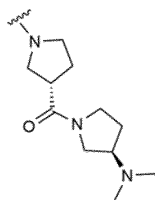
is , or a pharmaceutically acceptable salt thereof.

717. The compound according to any one of the preceding items, wherein R⁴



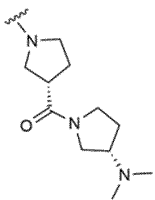
is , or a pharmaceutically acceptable salt thereof.

5 718. The compound according to any one of the preceding items, wherein R⁴



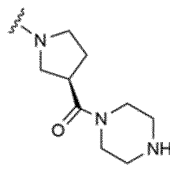
is , or a pharmaceutically acceptable salt thereof.

719. The compound according to any one of the preceding items, wherein R⁴



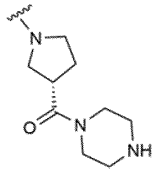
is , or a pharmaceutically acceptable salt thereof.

720. The compound according to any one of the preceding items, wherein R⁴



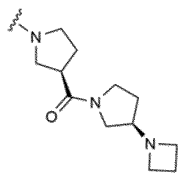
is , or a pharmaceutically acceptable salt thereof.

721. The compound according to any one of the preceding items, wherein R⁴



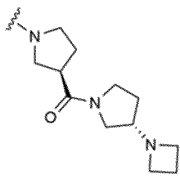
is , or a pharmaceutically acceptable salt thereof.

722. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

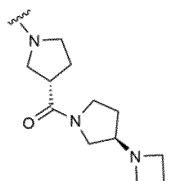
723. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

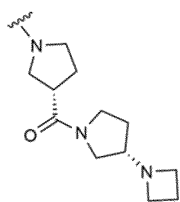
5

724. The compound according to any one of the preceding items, wherein R⁴



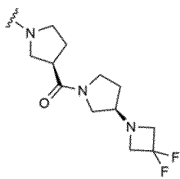
is , or a pharmaceutically acceptable salt thereof.

725. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

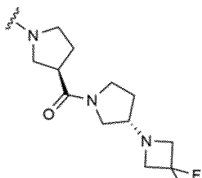
726. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

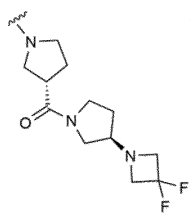
10

727. The compound according to any one of the preceding items, wherein R⁴



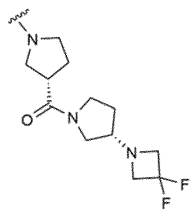
is , or a pharmaceutically acceptable salt thereof.

728. The compound according to any one of the preceding items, wherein R⁴



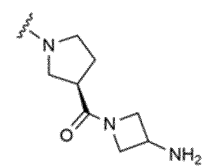
is , or a pharmaceutically acceptable salt thereof.

729. The compound according to any one of the preceding items, wherein R⁴



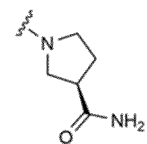
is , or a pharmaceutically acceptable salt thereof.

5 730. The compound according to any one of the preceding items, wherein R⁴



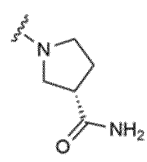
is , or a pharmaceutically acceptable salt thereof.

731. The compound according to any one of the preceding items, wherein R⁴



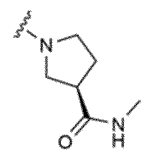
is , or a pharmaceutically acceptable salt thereof.

The compound according to any one of the preceding items, wherein R⁴ is



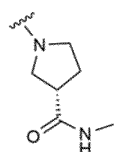
is , or a pharmaceutically acceptable salt thereof.

10 732. The compound according to any one of the preceding items, wherein R⁴



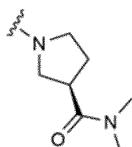
is , or a pharmaceutically acceptable salt thereof.

733. The compound according to any one of the preceding items, wherein R⁴



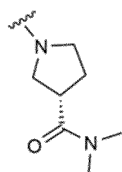
is , or a pharmaceutically acceptable salt thereof.

734. The compound according to any one of the preceding items, wherein R⁴



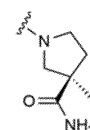
is , or a pharmaceutically acceptable salt thereof.

5 735. The compound according to any one of the preceding items, wherein R⁴



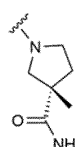
is , or a pharmaceutically acceptable salt thereof.

736. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

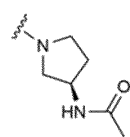
737. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

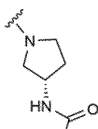
10

738. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

739. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

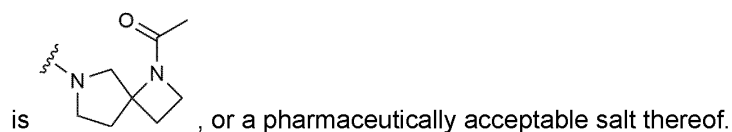
740. The compound according to any one of the preceding items, wherein R⁴



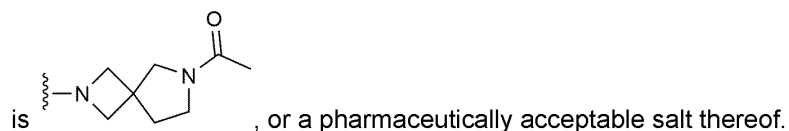
741. The compound according to any one of the preceding items, wherein R⁴



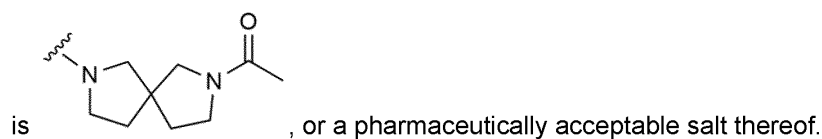
5 742. The compound according to any one of the preceding items, wherein R⁴



743. The compound according to any one of the preceding items, wherein R⁴

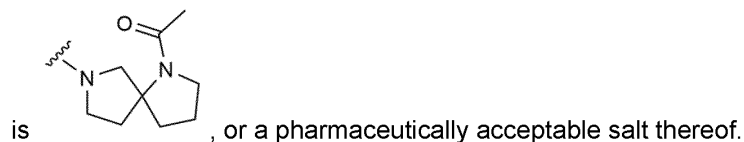


744. The compound according to any one of the preceding items, wherein R⁴

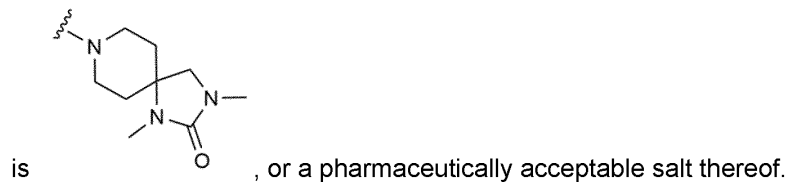


10

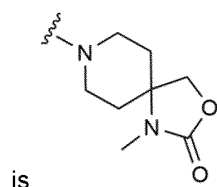
745. The compound according to any one of the preceding items, wherein R⁴



746. The compound according to any one of the preceding items, wherein R⁴

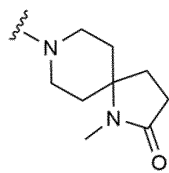


747. The compound according to any one of the preceding items, wherein R⁴



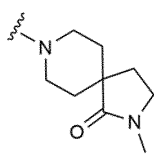
is , or a pharmaceutically acceptable salt thereof.

748. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

5 749. The compound according to any one of the preceding items, wherein R⁴



is , or a pharmaceutically acceptable salt thereof.

750. The compound according to any one of the preceding items, wherein the compound is not a compound selected from the group consisting of:

- 10 (3a*R*,7a*R*)-2-[(4-Fluoro-1*H*-indol-2-yl)carbonyl]hexahydropyrano[3,4-*c*]pyrrole-7a(1*H*)-carboxamide;
- (4,5-dichloro-1*H*-indol-2-yl)(3-(pyrrolidine-1-carbonyl)piperidin-1-yl)methanone;
- (4a*R*,7a*S*)-1-[(4,5-Dichloro-1*H*-indol-2-yl)carbonyl]octahydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one;
- (4-chloro-1*H*-indol-2-yl)(4-(cyclobutanecarbonyl)piperazin-1-yl)methanone;
- 15 (4-chloro-5-methyl-1*H*-indol-2-yl)(4-(cyclopropanecarbonyl)-2,2-dimethylpiperazin-1-yl)methanone;
- (4-fluoro-1*H*-indol-2-yl)(3-(pyrrolidine-1-carbonyl)piperidin-1-yl)methanone;
- [2-(cyclopropylcarbonyl)-4-morpholinyl](4,5-dichloro-1*H*-indol-2-yl)-methanone;
- [2-(cyclopropylcarbonyl)-4-morpholinyl](4-fluoro-1*H*-indol-2-yl)-methanone;
- 20 [4-[(6-bromo-4-fluoro-1*H*-indol-2-yl)carbonyl]-2-morpholinyl]cyclopropyl-methanone;
- 1-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-3-methyl-3-pyrrolidinecarboxamide;
- 1-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-3-piperidinecarboxamide;
- 1-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-3-pyrrolidinecarboxamide;
- 25 1-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-*N*-methyl-3-piperidinecarboxamide;

- 1-[(4-bromo-1*H*-indol-2-yl)carbonyl]-3-methyl-3-pyrrolidinecarboxamide;
1-[(4-bromo-1*H*-indol-2-yl)carbonyl]-3-piperidinecarboxamide;
1-[(4-bromo-1*H*-indol-2-yl)carbonyl]-*N*-methyl-3-piperidinecarboxamide;
1-[(4-fluoro-1*H*-indol-2-yl)carbonyl]-*N*-methyl-3-piperidinecarboxamide;
5 1-[(6-bromo-4-fluoro-1*H*-indol-2-yl)carbonyl]-3-methyl-3-pyrrolidinecarboxamide;
1-[(6-bromo-4-fluoro-1*H*-indol-2-yl)carbonyl]-3-piperidinecarboxamide;
1-[(6-bromo-4-fluoro-1*H*-indol-2-yl)carbonyl]-*N*-methyl-3-piperidinecarboxamide;
1-[4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1-piperazinyl]-2,2-dimethyl-1-propanone;
10 1-[4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1-piperazinyl]-2-methoxyethanone;
1-[4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1-piperazinyl]-2-methyl-1-propanone;
1-[4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1-piperazinyl]ethanone;
1-[4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-3,3-dimethyl-1-piperazinyl]ethanone;
1-[4-[(4-chloro-1*H*-indol-2-yl)carbonyl]-1-piperazinyl]ethanone;
15 2-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
2-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
2-[(4-bromo-1*H*-indol-2-yl)carbonyl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
20 2-[(4-chloro-1*H*-indol-2-yl)carbonyl]-7-(2-hydroxyethyl)-2,7-diazaspiro[4.5]decan-6-one;
2-[(4-fluoro-1*H*-indol-2-yl)carbonyl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
2-[(6-bromo-4-fluoro-1*H*-indol-2-yl)carbonyl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
25 2-amino-1-[4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1-piperazinyl]-ethanone;
4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1-(1-methylethyl)-2-piperazinone;
4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-1,6-dimethyl-2-piperazinone;
4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-2-piperazinone;
4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-3,3-dimethyl-2-piperazinone;
30 4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-3-propyl-2-piperazinone;
4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-*N*-methyl-2-morpholinecarboxamide;
4-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]octahydro-2(1*H*)-quinoxalinone;
7-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-2,7-diazaspiro[4.4]nonan-3-one;
7-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]hexahydroimidazo[1,5-*a*]pyrazin-3(2*H*)-
35 one;

- 7-[(4-chloro-1*H*-indol-2-yl)carbonyl]hexahydro-3*H*-oxazolo[3,4-*a*]pyrazin-3-one;
7-[(4-chloro-5-fluoro-1*H*-indol-2-yl)carbonyl]-2,7-diazaspiro[4.4]nonan-3-one;
rel-(3*aR*,7*aR*)-2-[(4-Fluoro-1*H*-indol-2-yl)carbonyl]hexahydropyrano[3,4-
c]pyrrole-7*a*(1*H*)-carboxamide;
5 *rel*-(3*R*,4*R*)-1-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-4-methyl-3-
pyrrolidinecarboxamide;
rel-(3*R*,4*R*)-1-[(4-bromo-1*H*-indol-2-yl)carbonyl]-4-methyl-3-
pyrrolidinecarboxamide; and
rel-(3*R*,4*R*)-1-[(6-bromo-4-fluoro-1*H*-indol-2-yl)carbonyl]-4-methyl-3-
10 pyrrolidinecarboxamide,
or a pharmaceutically acceptable salt thereof.
751. The compound according to any one of the preceding items, wherein the
compound is selected from the group consisting of:
- 4-(3,4,5-trichloro-1*H*-indole-2-carbonyl)piperazin-2-one;
15 1-(4-(4,5-dichloro-1*H*-indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one;
1-[(2*R*)-4-(4,5-dichloro-1*H*-indole-2-carbonyl)-2-methyl-piperazin-1-yl]ethanone;
1-[4-(4,5-dichloro-1*H*-indole-2-carbonyl)-2,2-dimethyl-piperazin-1-yl]ethanone;
1-[3-(4,5-dichloro-1*H*-indole-2-carbonyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]ethanone;
1-[4-(4,5-dichloro-1*H*-indole-2-carbonyl)piperazin-1-yl]ethanone;
20 1-[(3*S*)-4-(4,5-dichloro-1*H*-indole-2-carbonyl)-3-methyl-piperazin-1-yl]ethanone;
1-[4-(4-chloro-5-fluoro-1*H*-indole-2-carbonyl)piperazin-1-yl]-2-
(dimethylamino)ethanone;
1-(4-(4,5-dichloro-1*H*-indole-2-carbonyl)-3,3-dimethylpiperazin-1-yl)ethan-1-one;
2-amino-1-[4-(4-chloro-5-fluoro-1*H*-indole-2-carbonyl)piperazin-1-yl]ethanone;
25 2-amino-1-[4-(4,5-dichloro-1*H*-indole-2-carbonyl)piperazin-1-yl]ethanone;
(3*R*)-1-(4,5-dichloro-1*H*-indole-2-carbonyl)pyrrolidine-3-carboxamide;
4-(4,5-dichloro-1*H*-indole-2-carbonyl)piperazin-2-one;
4-(4,5-dichloro-1*H*-indole-2-carbonyl)-1-methyl-piperazin-2-one;
4-(4,5-dichloro-6-fluoro-1*H*-indole-2-carbonyl)piperazin-2-one;
30 4-(4-chloro-5-fluoro-1*H*-indole-2-carbonyl)piperazin-2-one;
(3*R*)-1-[(4,5-dichloro-1*H*-indol-2-yl)carbonyl]-*N*-methylpyrrolidine-3-carboxamide;
4-(4-chloro-1*H*-indole-2-carbonyl)piperazin-2-one;
1-[4-(4,5-dichloro-1*H*-indole-2-carbonyl)piperazin-1-yl]-2-methoxy-ethanone;
1-(4-(4-chloro-5-fluoro-1*H*-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
35 1-[4-(4-chloro-5-fluoro-1*H*-indole-2-carbonyl)piperazin-1-yl]-2-methoxy-ethanone;

- 4-(4,5-dichloro-7-fluoro-1H-indole-2-carbonyl)piperazin-2-one;
4-(4,5-dichloro-3-fluoro-1H-indole-2-carbonyl)piperazin-2-one;
(S)-(4,5-dichloro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
[4-(azetidine-3-carbonyl)piperazin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone;
5 (4,5-dichloro-1H-indol-2-yl)-[4-[(3R)-pyrrolidine-3-carbonyl]piperazin-1-yl]methanone;
[4-[(2S)-azetidine-2-carbonyl]piperazin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone;
(4,5-dichloro-1H-indol-2-yl)-[4-[(2S)-pyrrolidine-2-carbonyl]piperazin-1-yl]methanone;
(4-(cyclopropanecarbonyl)piperazin-1-yl)(4,5-dichloro-1H-indol-2-yl)methanone;
(4-(2-aminoisonicotinoyl)piperazin-1-yl)(4,5-dichloro-1H-indol-2-yl) methanone;
10 ((R)-3-aminopyrrolidin-1-yl)((R)-1-(4,5-dichloro-1H-indole-2-carbonyl) pyrrolidin-3-yl)methanone;
[(3R)-3-(3-aminoazetidine-1-carbonyl)pyrrolidin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone;
[(3R)-3-[(3S)-3-aminopyrrolidine-1-carbonyl]pyrrolidin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone;
15 N-[1-(4-acetamidophenyl)sulfonyl-4-piperidyl]-3,5-dimethyl-1H-pyrrole-2-carboxamide;
(R)-N-(1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidin-3-yl)acetamide;
(R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpyrrolidine-3-carboxamide;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
20 2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one;
7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one;
methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate;
25 (S)-1-(4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one;
4-(4,5-dichloro-1H-indole-2-carbonyl)-N-methylmorpholine-2-carboxamide;
1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-3,3-dimethylpiperazin-1-yl)ethan-1-one;
(S)-1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-2-methylpiperazin-1-yl)ethan-1-one;
(S)-1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidine-3-carboxamide;
30 (R)-1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one;
1-(3-(4,5-dichloro-1H-indole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl)ethan-1-one;
1-(5-(4,5-dichloro-1H-indole-2-carbonyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)ethan-1-one;
1-(6-(4,5-dichloro-1H-indole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)ethan-1-one;
35 one;

- 1-((2S,5R)-4-(4,5-dichloro-1H-indole-2-carbonyl)-2,5-dimethylpiperazin-1-yl)ethan-1-one;
(R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-N,N-dimethylpyrrolidine-3-carboxamide;
1-(8-(4,5-dichloro-1H-indole-2-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)ethan-1-one;
5 (S)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one;
(S)-4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,5-dimethylpiperazin-2-one;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one;
10 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
2-amino-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
(R)-(4,5-dichloro-1H-indol-2-yl)(4-prolylpiperazin-1-yl)methanone;
(S)-(4-chloro-5-fluoro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
15 (R)-azetidin-2-yl(4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl)methanone;
((R)-3-aminopyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone;
(3,4-dichloro-5-fluoro-1H-indol-2-yl)((3R)-3-(3-(dimethylamino)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)methanone;
20 ((R)-3-aminopyrrolidin-1-yl)((R)-1-(4-chloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone;
(3-(azetidin-1-yl)pyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone;
(3,4-dichloro-5-fluoro-1H-indol-2-yl)((3R)-3-(3-(3,3-difluoroazetidin-1-yl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)methanone;
25 (2-amino-4-pyridyl)-[4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl]methanone;
1-(6-(4,5-dichloro-1H-indole-2-carbonyl)-2,6-diazaspiro[3.4]octan-2-yl)ethan-1-one;
1-(6-(4,5-dichloro-1H-indole-2-carbonyl)-1,6-diazaspiro[3.4]octan-1-yl)ethan-1-one;
1-(7-(4,5-dichloro-1H-indole-2-carbonyl)-1,7-diazaspiro[4.4]nonan-1-yl)ethan-1-one;
30 1-(2-(4,5-dichloro-1H-indole-2-carbonyl)-2,6-diazaspiro[3.4]octan-6-yl)ethan-1-one;
1-(7-(4,5-dichloro-1H-indole-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)ethan-1-one;
8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methyl-2,8-diazaspiro[4.5]decan-1-one;
8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1-methyl-1,8-diazaspiro[4.5]decan-2-one;
35 one;

- 8-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)-1-methyl-3-oxa-1,8-diazaspiro[4.5]decan-2-one;
- 8-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)-1,3-dimethyl-1,3,8-triazaspiro[4.5]decan-2-one;
- 5 (S)-4-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)-1,3-dimethylpiperazin-2-one;
- (S)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
- (3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(methyl-D-prolyl)piperazin-1-yl)methanone;
- (R)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(4,4-difluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- 10 1-yl)methanone;
- 7-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)-2-methylhexahydroimidazo[1,5-a]pyrazin-3(2*H*)-one;
- (R)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- 15 (S)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(1-methylpyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
- (4-(6-aminonicotinoyl)piperazin-1-yl)(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)methanone;
- (S)-2-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydropyrrolo[1,2-a]pyrazin-6(2*H*)-one;
- 20 (R)-2-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydropyrrolo[1,2-a]pyrazin-6(2*H*)-one;
- (R)-7-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydro-3*H*-oxazolo[3,4-a]pyrazin-3-one;
- (S)-7-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydro-3*H*-oxazolo[3,4-a]pyrazin-3-one;
- 25 1-(4-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl) piperazin-1-yl)-2-morpholinoethan-1-one;
- (4-(2-aminoisonicotinoyl) piperazin-1-yl) (3,4-dichloro-5-fluoro-1*H*-indol-2-yl) methanone;
- 30 1-(4-(3,4-dichloro-1*H*-indole-2-carbonyl) piperazin-1-yl)-2-methoxyethan-1-one;
- (S)-2-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl) hexahydropyrrolo[1,2-a] pyrazin-6(2*H*)-one;
- (R)-2-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl) hexahydropyrrolo[1,2-a] pyrazin-6(2*H*)-one;
- 35 2-amino-1-(4-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;

- (R)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-propylpiperazin-1-yl)methanone;
((3S,4R)-3-amino-4-fluoropyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone;
(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((3S,4S)-4-(trifluoromethyl)pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
5 azetidin-3-yl(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)methanone;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(3-fluoroazetidine-3-carbonyl)piperazin-1-yl)methanone;
((3S,4S)-3-amino-4-fluoropyrrolidin-1-yl)(®-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl) pyrrolidine-3-yl)methanone;
10 (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl) (4-(morpholine-3-carbonyl) piperazin-1-yl) methanone;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(morpholine-3-carbonyl)piperazin-1-yl)methanone;
(S)-azetidin-2-yl(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)methanone;
15 (R)-azetidin-2-yl(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)methanone;
(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4R)-4-fluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
20 (4-(2-aminoisonicotinoyl) piperazin-1-yl) (4-chloro-3,5-difluoro-1H-indol-2-yl) methanone;
(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl) (4-(4,4-difluoropyrrolidine-2-carbonyl) piperazin-1-yl) methanone;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl) (4-(4,4-difluoropyrrolidine-2-carbonyl) piperazin-1-yl) methanone;
25 2-(azetidin-3-yloxy)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-propylpiperazin-1-yl)methanone;
30 (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-propylpiperazin-1-yl)methanone;
((R)-3-aminopyrrolidin-1-yl) ((R)-1-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl) pyrrolidin-3-yl) methanone;
1-(4-(3-chloro-4-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-2-one;

- 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-morpholinoethan-1-one;
- 5 (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(oxetane-3-carbonyl)piperazin-1-yl)methanone;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(3,3-difluorocyclobutane-1-carbonyl)piperazin-1-yl)methanone;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-((1R,3R)-3-methoxycyclobutane-1-carbonyl)piperazin-1-yl)methanone;
- 10 1-(4-(3-chloro-4,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone;
- 15 2-(azetidin-1-yl)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(1-methylazetidine-3-carbonyl)piperazin-1-yl)methanone;
(3aR,6aR)-5-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-
- 20 methylhexahydropyrrolo[3,4-c]pyrrol-1(2H)-one;
2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(methyl-L-prolyl)piperazin-1-yl)methanone;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(methyl-D-prolyl)piperazin-1-yl)methanone;
- 25 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
(S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-methoxyethan-1-one;
2-(azetidine-1-yl)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
- 30 (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4-methylmorpholine-3-carbonyl)piperazin-1-yl)methanone;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4-methylmorpholine-3-carbonyl)piperazin-1-yl)methanone;
2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)octahydro-6H-pyrido[1,2-a]pyrazin-6-one;

- 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-methoxyazetidin-1-yl)ethan-1-one;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-1-yl)ethan-1-one;
5 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-methoxyazetidin-1-yl)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-1-yl)ethan-1-one;
10 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(oxetan-3-yloxy)ethan-1-one;
15 (R)-7-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one;
(S)-7-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one;
(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4S)-4-fluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
20 5-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methyloctahydro-3H-pyrrolo[3,4-c]pyridine-3-one;
(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((3S,4S)-1-methyl-4-(trifluoromethyl)pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
25 (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4R)-4-fluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(3-fluoro-1-methylazetidine-3-carbonyl)piperazin-1-yl)methanone;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-((1-methylazetidin-3-yl)oxy)ethan-1-one;
30 (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;

- (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4S)-4-fluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
(3-fluoroazetidin-3-yl)methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate;
- 5 azetidin-3-yl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl) piperazine-1-carboxylate;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(oxetan-3-yloxy)ethan-1-one;
8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one;
- 10 7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)tetrahydroimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione;
2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-8-methylhexahydropyrrolo[1,2-a]pyrazin-6(2H)-one;
2-(azetidin-3-yloxy)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
- 15 (3aR,6aR)-5-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-2-methylhexahydropyrrolo[3,4-c]pyrrol-1(2H)-one;
2-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one;
- 20 (R)-2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one;
(S)-2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-((1-methylazetidin-3-yl)oxy)ethan-1-one;
- 25 8-(3,4-dichloro-5-fluoro-1 H-indole-2-carbonyl)octahydro-4 H-pyrazino[1,2- a]pyrazin-4-one;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-3-yl)ethan-1-one;
- 30 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoropyrrolidin-1-yl)ethan-1-one;
(S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-
- 35 difluorocyclobutoxy)ethan-1-one;

- (R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-(methoxymethyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
(S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)propan-1-one;
- 5 (R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)propan-1-one;
(S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoro-2-methylazetidin-1-yl)ethan-1-one;
(R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoro-2-methylazetidin-1-yl)ethan-1-one;
- 10 4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylmorpholine-2-carboxamide;
(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone;
- 15 4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylpiperazine-2-carboxamide;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-dimethyloxetane-2-carbonyl)piperazin-1-yl)methanone;
- 20 (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-dimethyloxetane-2-carbonyl)piperazin-1-yl)methanone;
(S)-8-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one;
(R)-8-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one;
- 25 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2,2-difluoroethan-1-one;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(2-methyloxetane-2-carbonyl)piperazin-1-yl)methanone;
- 30 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(trifluoromethoxy)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(difluoromethoxy)ethan-1-one;
(S)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N-methylpiperazine-2-carboxamide;

- (S)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylpiperazine-2-carboxamide;
1-(4-(3,4-dichloro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
- 5 (R)-(4-chloro-3-fluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone;
1-(4-(4-chloro-3-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
1-(4-(4-chloro-3-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
- (R)-(4-chloro-3-fluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone;
- 10 (R)-(3,4-dichloro-1 H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone;
(S)-1-(4-(3,4-dichloro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-methoxyethan-1-one; and
- (R)-(3,4-dichloro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone, or a pharmaceutically acceptable salt thereof.
- 15 752. The compound according to any one of the preceding items, or a pharmaceutically acceptable salt thereof, wherein the compound is a $K_v1.3$ potassium channel inhibitor.
753. A pharmaceutical composition comprising a compound according to any one of the preceding items, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.
- 20 754. The compound according to any one of items 1 to 752, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 753, for use as a medicament.
755. The compound according to any one of items 1 to 752, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 753, for use in the treatment of a disease or medical condition where inhibition of $K_v1.3$ potassium channel is beneficial.
- 25 756. The compound according to any one of items 1 to 752, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 753, for use in the treatment of a neurodegenerative disease.
- 30 757. The compound or composition for use according to item 756, wherein said neurodegenerative disease is selected from the group consisting of a tauopathy, a TDP-43 proteinopathy, a synucleinopathy, dementia, amyloidosis, a demyelinating disorder of the CNS, a demyelinating disorder of the PNS, a
- 35

Leukoencephalopathy, a leukodystrophy, a transmissible spongiform encephalopathy (TSE) and a lysosomal storage disorder (LSD).

- 5 758. The compound according to any one of items 1 to 752, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 753, for use in the treatment of a neurodegenerative disease selected from the group consisting of Alzheimer's disease, Frontotemporal lobar degeneration (FTLD), frontotemporal dementia (FTD), Parkinson's disease, Nasu-Hakola disease, FTLD-like syndrome, Huntington disease, Amyotrophic lateral sclerosis, multiple sclerosis, Guillain-Barre syndrome, chronic
- 10 inflammatory demyelinating polyneuropathies, Charcot-Marie-Tooth disease, prion disease and stroke.
- 15 759. The compound according to any one of items 1 to 752, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 753, for use in the treatment of a disease selected from the group consisting of rheumatoid arthritis (RA), neuropathic pain, inflammatory pain, CNS complications of COVID-19 infection, post-COVID-19 conditions, Chronic Traumatic Encephalopathy, HIV-Associated Neurocognitive Disorder (HAND), Traumatic Brain Injury, Epilepsy, Autoimmune Encephalitis, Bipolar disorder, major depression disorder(MDD) and Schizophrenia.
- 20 760. The compound according to any one of items 1 to 752, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 753, for use in the treatment of a disease selected from the group consisting of Psoriasis, Atopic dermatitis, Celiac Disease, Lupus, Type 1 diabetes, Sjogren's syndrome, Vasculitis, IBD, Crohn's disease, Graves' disease, Hashimoto's thyroiditis, Myasthenia gravis and Scleroderma.
- 25 761. The compound according to any one of items 1 to 752, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 753, for use in the treatment of a condition selected from the group consisting of cancer, an immunological disorder, a central nervous system disorder, an inflammatory disorder, a gastroenterological disorder, a metabolic disorder, a cardiovascular disorder, and a kidney disease.
- 30 762. The compound for use according to item 761, wherein the immunological disorder is transplant rejection or an autoimmune disease.

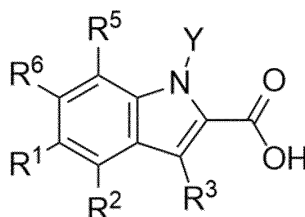
763. The compound for use according to item 761, wherein the autoimmune disease is rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, or type I diabetes mellitus.
- 5 764. The compound for use according to item 761, wherein the central nervous system disorder is Alzheimer's disease.
765. The compound for use according to item 761, wherein the inflammatory disorder is an inflammatory skin condition, arthritis, psoriasis, spondylitis, parodontitis, or an inflammatory neuropathy.
- 10 766. The compound for use according to item 761, wherein the gastroenterological disorder is an inflammatory bowel disease.
767. The compound for use according to item 761, wherein the metabolic disorder is obesity or type II diabetes mellitus.
768. The compound for use according to item 761, wherein the kidney disease is chronic kidney disease, nephritis, or chronic renal failure.
- 15 769. The compound for use according to item 761, wherein the condition is selected from the group consisting of cancer, transplant rejection, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, type I diabetes mellitus, Alzheimer's disease, inflammatory skin condition, inflammatory neuropathy, psoriasis, spondylitis, parodontitis, Crohn's disease, ulcerative
- 20 colitis, obesity, type II diabetes mellitus, ischemic stroke, chronic kidney disease, nephritis, chronic renal failure, and a combination thereof.
770. The compound or composition for use according to any one of items 754 to 769, wherein said compound is administered in an amount of about 0.01 mg/kg to about 100 mg/kg bodyweight/day.
- 25 771. The compound or composition for use according to any one of items 754 to 770, wherein said compound is administered via enteral delivery, oral delivery, topical delivery, parenteral delivery, intravenous delivery, intradermal delivery, intramuscular delivery, intrathecal delivery, colonic delivery, rectal delivery, or intraperitoneal delivery.
- 30 772. A method of blocking $K_v1.3$ potassium channel in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one compound according to any one of items 1 to 752 or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of the pharmaceutical composition of item 753.

773. The method according to any one of the preceding items, wherein the subject is a mammal, such as human.

774. A method for manufacturing the compound of Formula (I) according to any one of items 1 to 1 to 752.

5 775. The method according to item 774, wherein said method comprising the steps of:

a. providing a compound of Formula (SI),



Formula (SI)

10

wherein

R¹ is halogen or H;

R² is halogen;

R³ is H or halogen;

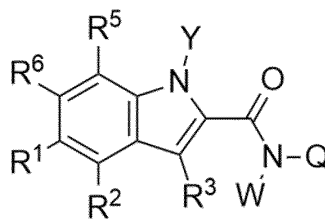
R⁵ is H or halogen;

15

R⁶ is H or halogen; and

Y is H or a protecting group;

b. reacting the compound of step a) with $\text{H}-\text{N}^{\text{Q}}\text{W}$, wherein $\text{N}^{\text{Q}}\text{W}$ is R⁴ or a precursor for R⁴, to generate the compound of Formula (SII):



Formula (SII)

20

wherein

R¹ is halogen or H;

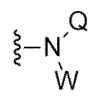
R² is halogen;

R³ is H or halogen;

R⁵ is H or halogen;

R⁶ is H or halogen;

Y is a H or a protecting group; and

 is R⁴ or a precursor for R⁴.

5 776. The method according to item 775, wherein Y is a protecting group (e.g. SEM) and the method further includes a step subsequent to step b) wherein the protecting group in position Y is removed.

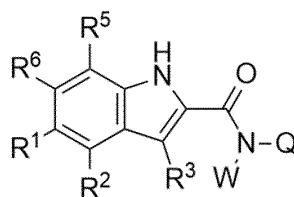
777. The method according to item 775, wherein Y is H.

10 778. The method according to any one of items 775 to 777, wherein  is R⁴.

779. The method according to any one of items 775 to 777, wherein  is a precursor for R⁴ and the method further includes a step subsequent to step b) wherein the precursor for R⁴ is modified to R⁴.

780. The method according to item 775, wherein Y is a protecting group and

15  is a precursor for R⁴, and step b) is followed by step c-1), wherein the protecting group in position Y is removed to generate the compound of Formula (SIII):



Formula (SIII)

20 and step c-1) is followed by step c-2), wherein  is modified to R⁴ to generate the compound of Formula (I).

781. The method according to item 780, wherein step c-1) and step c-2) occur simultaneously.

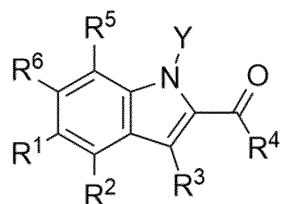
782. The method according to item 775, wherein Y is a protecting group and



is a precursor for R⁴, and step b) is followed by step d-1), wherein



is modified to R⁴ to generate the compound of Formula (SIV):



Formula (SIV)

and step d-1) is followed by step d-2), wherein the protecting group in position Y is removed, and the compound of Formula (I) is generated.

783. The method according to item 782, wherein step d-1) and step d-2) occur simultaneously.

784. The method according to any one of items 775 to 783, wherein R³ in Formula (SI) is H.

785. The method according to any one of items 775 to 783, wherein R³ in Formula (SI) is H and step a) includes introducing a halogen in position R³ of the compound of Formula (SI) via a halogenation reaction.

Examples

Abbreviations

1. Ac = Acetyl
2. AcO = Acetate
3. ACN = Acetonitrile
4. Ar = Aryl
5. Boc = *tert*-Butoxycarbonyl
6. Bu = Butyl
7. CBZ = Benzyloxycarbonyl
8. COMU = (1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate

9. DABCO = 1,4-Diazabicyclo[2.2.2]octane
10. DCM = Dichloromethane
11. DIPEA = Diisopropylethylamine
12. DMAP = 4-dimethylamino pyridine
5 13. DMF = *N,N*-Dimethylformamide
14. DMSO = Dimethylsulphoxide
15. ELSD = Evaporative light scattering detector
16. EDC = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
17. Et₂O = Diethyl ether
10 18. gm = grams
19. HEX = n-hexane
20. HPLC = high pressure liquid chromatography
21. HOBt = 1-Hydroxybenzotriazole
22. LCMS = Liquid chromatography mass spectrometry
15 23. Me = Methyl
24. Min = minutes
25. Mg = milligram
26. NCS = *N*-Chlorosuccinimide
27. NMI = *N*-Methylimidazole
20 28. NMR = Nuclear magnetic resonance
29. Ph = Phenyl
30. RT = Retention time
31. rt = room temperature
32. SEM = 2-(Trimethylsilyl)ethoxymethyl
25 33. Selecfluor™ = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane
bis(tetrafluoroborate)
34. TCFH = Chloro-*N,N,N',N'*-tetramethylformamidium hexafluorophosphate
35. TFA = Trifluoroacetic acid
36. THF = Tetrahydrofuran
30 37. TLC = thin layer chromatography

¹H NMR Spectroscopy:

¹H NMR was recorded at 400MHz, on a Bruker Advance, II & III spectrometer using solvents from Merck Laboratories. Chemical shifts (δ, ppm) are reported relative to the solvent peak (CDCl₃: 7.25, DMSO-*d*₆: 2.50). Proton resonances are annotated as:

chemical shift (δ), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant (J , Hz), and number of protons.

General Hydrolysis Condition:

- 5 To a stirred solution of carboxylic ester (1 equiv.) in THF-H₂O (2:1, 3.0 mL/mmol) was added LiOH.H₂O (1.2-2 equiv.) and stirred at rt for 6-16 h. The reaction was monitored by LCMS or, TLC. After completion, reaction mixture was concentrated under reduced pressure, diluted with 1N HCl and extracted with organic solvent and concentrated. In case of precipitation, solid was filtered, washed with organic solvent and dried. Finally, 10 crude material was triturated with pentane or, Et₂O to get solid compound.

General Amidation Condition:

- Condition-A:** To a stirred solution of carboxylic acid (1 equiv.) in DMF (3.0 mL/mmol) was added DIPEA (3 equiv. or, 5 equiv. for SM containing HCl salt) followed by EDC.HCl 15 (1.5 equiv.) and HOBt (1.5 equiv.) and stirred at rt for 30 minutes. Thereafter, amine (1.2-2 equiv.) was added into the reaction mixture and allowed to stir at rt for 16 h. After completion (monitored by TLC or, LCMS), the reaction mixture was subjected to usual work-up. It was diluted with organic solvent (EtOAc/DCM) and H₂O and taken in a separatory funnel. The organic layer was separated and aq. layer was back extracted 20 with organic solvent three times. The combined organic layer was washed with H₂O, brine and dried over anhyd. Na₂SO₄. Then, it was filtered and the filtrate was evaporated to dryness under reduced pressure to afford the crude compound, which was purified by reverse phase prep. HPLC or, combiflash chromatography.

- Condition-B:** To a stirred solution of carboxylic acid (1 equiv.) in DMF (3.0 mL/mmol) was added DIPEA (3 equiv. or, 5 equiv. for SM containing HCl salt) followed by HATU 25 (1.5 equiv.) and stirred at rt for 30 minutes. Thereafter, amine (1.2-2 equiv.) was added into the reaction mixture and allowed to stir at rt for 16 h. After completion (monitored by TLC or, LCMS), the reaction mixture was subjected to usual work-up. It was diluted with organic solvent (EtOAc/DCM) and H₂O and taken in a separatory funnel. The organic 30 layer was separated and aq. layer was back extracted with organic solvent three times. The combined organic layer was washed with H₂O, brine and dried over anhyd. Na₂SO₄. Then, it was filtered and the filtrate was evaporated to dryness under reduced pressure to afford the crude compound, which was purified by reverse phase prep. HPLC or, combiflash chromatography.

- Condition-C:** To an ice cold stirred solution of acid (1 equiv) in acetonitrile (0.03 mmol/ml) was added TCFH (1.1 equiv) followed by NMI (5 equiv.) and the resulting reaction mixture was stirred for 30 minutes before addition of amine (1.1 equiv.). The reaction was continued at rt and monitored by LCMS/TLC. The reaction mixture was
- 5 diluted with ethyl acetate and washed with saturated aqueous NaHCO₃ solution. The aqueous part was back extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure and the crude material was purified by RP-prep HPLC or, combiflash chromatography.
- 10 **Condition-D:** To a stirred solution of carboxylic acid (1 equiv.) in DMF (3.0 mL/mmol) was added DIPEA (3 equiv. or, 5 equiv. for SM containing HCl salt) followed by COMU (1.5 equiv.) and stirred at rt for 30 minutes. Thereafter, amine (1.2-2 equiv.) was added into the reaction mixture and allowed to stir at rt for 16 h. After completion (monitored by
- 15 TLC or, LCMS), the reaction mixture was subjected to usual work-up. It was diluted with organic solvent (EtOAc/DCM) and H₂O and taken in a separatory funnel. The organic layer was separated and aq. layer was back extracted with organic solvent three times. The combined organic layer was washed with H₂O, brine and dried over anhyd. Na₂SO₄. Then, it was filtered and the filtrate was evaporated to dryness under reduced pressure to afford the crude compound, which was purified by reverse phase prep. HPLC or,
- 20 combiflash chromatography.

General Reductive amination Condition:

- Condition-A:** To a stirred solution of corresponding amine (1 eq) in methanol(1 mmol/ml), formaldehyde solution (6eq,37 wt. % in H₂O) was added followed by addition
- 25 of catalytic AcOH(0.01 eq) and then reaction mixture was allowed to stir at RT for 10 min. NaCNBH₃ (5eq) was then added and allowed to stir at RT for 3 hr. After completion (monitored by TLC or, LCMS), the reaction mixture was quenched with cold water and the organic layer was extracted by using ethyl acetate. The organic layer was separated, and aq. layer was back extracted with organic solvent three times. The combined organic
- 30 layer was washed with H₂O, brine and dried over anhydrous Na₂SO₄. It was then filtered and the filtrate was evaporated to dryness under reduced pressure to afford the crude compound, which was purified by reverse phase prep. HPLC or, combiflash chromatography.

- 35 **Reverse Phase Prep. HPLC Purification Method:**

Unless stated otherwise, purifications were carried out on a WATERS auto purification instrument operating at ambient temperature and flow rate of 16.0 mL/min.

Method-A: Column name: YMC-Actus Triart C18 (250 x 20 mm, 5 μ). Mobile phase: A= 20 mM NH₄HCO₃ in water, B= ACN; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 60% A and 40% B in 3 min., then to 25% A and 75% B in 24 min., then to 5% A and 95% B in 25 min., held this composition upto 27 min. for column washing, then returned to initial composition in 28 min. and held till 30 min.

Method-B: Column name: Hydrosphare C18 (250 x 20 mm, 5 μ). Mobile phase: A = 0.1% Formic acid in water, B= ACN; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then 80% A and 20% B in 3 min, then to 55% A and 45% B in 20 min., then to 5% A and 95% B in 21 min., held this composition up to 22 min. for column washing, then returned to initial composition in 23 min. and held till 25 min.

Method-C: Column name: X-bridge C18 prep OBD (250 x 19mm, 5 μ). Mobile phase: A= 20mM NH₄HCO₃ in water, B=MeOH; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 40% A and 60% B in 4 min., then to 10% A and 90% B in 24 min., then to 5% A and 95% B in 25 min., held this composition up to 28 min. for column washing, then returned to initial composition in 29 min. and held till 32 mins.

Method-D: Column name: YMC-Triart C18 (250 x 20mm, 5 μ). Mobile phase: A= 20mM NH₄HCO₃ in water, B= ACN; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 50% A and 50% B in 3 min., then to 20% A and 80% B in 24 min., then to 5% A and 95% B in 25 min., held this composition up to 28 min. for column washing, then returned to initial composition in 29 min. and held till 32 mins.

Method-E: Column name: YMC-Actus Triart C18 (250 x 20mm, 5 μ). Mobile phase: A= 20mM NH₄HCO₃ in water, B= ACN; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 65% A and 35% B in 5 min., then to 30% A and 70% B in 30 min., then to 5% A and 95% B in 31 min., held this composition up to 33 min. for column washing, then returned to initial composition in 34 min. and held till 36 mins.

Method-F: Column name: - YMC Triart C18 (250 x 20mm, 5 μ). Mobile phase: A= 20mM NH₄HCO₃ in water, B= ACN; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 70% A and 30% B in 3 min., then to 40% A and 60% B in 24 min., then to 5% A and 95% B in 25 min., held this composition up to 28 min. for column washing, then returned to initial composition in 29 min. and held till 32 mins.

Method-G: Column name: YMC Triart C18 (250 x 20mm, 5 μ). Mobile phase: A= 20mM NH₄HCO₃ in water, B= ACN; Gradient Profile: Mobile phase initial composition of 80%

A and 20% B, then to 55% A and 45% B in 3 min., then to 20% A and 80% B in 24 min., then to 5% A and 95% B in 25 min., held this composition up to 28 min. for column washing, then returned to initial composition in 29 min. and held till 32 mins.

5 **Method-H:** Column name: YMC Triart C18 (250 x 20mm, 5 μ). Mobile phase: A= 20mM NH₄HCO₃ in water, B= ACN; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 60% A and 40% B in 3 min., then to 30% A and 70% B in 25 min., then to 5% A and 95% B in 26 min., held this composition up to 29 min. for column washing, then returned to initial composition in 30 min. and held till 33 mins.

10 **Method-I:** Column name: Chromcore 120 C18 (250 x 21.2mm, 5 μ). Mobile phase: A= 20mM NH₄HCO₃ in water, B= ACN; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 60% A and 40% B in 3 min., then to 25% A and 75% B in 24 min., then to 5% A and 95% B in 25 min., held this composition up to 27 min. for column washing, then returned to initial composition in 28 min. and held till 30 mins.

15 **Method-J:** Column name: YMC-Actus C18 (250 x 20 mm, 5 μ). Mobile phase: A = ACN, B=20mM NH₄HCO₃ in water; Gradient Profile: Mobile phase initial composition of 30% A and 70% B, then 45% A and 55% B in 3 min, then to 56.9% A and 43.1% B in 12 min., then to 100% A and 0% B in 12.5 min., held this composition up to 16 min. for column washing, then returned to initial composition in 17 min. and held till 20 min.

20 **Method-K:** Column name: - YMC Triart C18 (250 x 20mm, 5 μ). Mobile phase: A= 20mM NH₄HCO₃ in water, B= ACN; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 80% A and 20% B in 3 min., then to 40% A and 60% B in 24 min., then to 5% A and 95% B in 25 min., held this composition up to 28 min. for column washing, then returned to initial composition in 29 min. and held till 32 mins.

25 **Method-L:** Column name: Kinetex C18 (250 x 21.2 mm, 5 μ). Mobile phase: A = 20mM NH₄HCO₃ in water, B= ACN; Gradient Profile: Mobile phase initial composition of 70% A and 30% B, then 70% A and 30% B in 3 min, then to 30% A and 70% B in 20 min., then to 5% A and 95% B in 21 min., held this composition up to 22 min. for column washing, then returned to initial composition in 23 min. and held till 25 min.

30 **Method-M:** Column name: YMC Actus Triart C18 (250 x 20mm, 5 μ). Mobile phase: A= 20mM NH₄HCO₃ in water, B= ACN; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 70% A and 30% B in 3 min., then to 30% A and 70% B in 20 min, then to 0% A and 100% B in 21 min., held this composition up to 24 min. for column washing, then returned to initial composition in 25 min. and held till 28 mins.

35 **Method-N:** Column name: YMC-Actus Triart C18 (250 x 20mm, 5 μ). Mobile phase: A= 20mM NH₄HCO₃ in water, B=ACN; Gradient Profile: Mobile phase initial composition of

70% A and 30% B, then to 45% A and 55% B in 3 min., then to 10% A and 90% B in 24 min., then to 5% A and 95% B in 25 min., held this composition up to 28 min for column washing, then returned to initial composition in 29 min. and held till 32 mins.

5 **Method-O:** Column name: Xterra C18 (250 x 19 mm, 10 μ). Mobile phase: A = 20mM NH₄HCO₃ in water, B= ACN; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then 70% A and 30% B in 3 min, then to 40% A and 60% B in 20 min., then to 5% A and 95% B in 21 min., held this composition up to 22 min. for column washing, then returned to initial composition in 23 min. and held till 25 min.

10 **Method-P:** Column name: Xterra C18 (250 x 19 mm, 10 μ). Mobile phase: A = 0.1% Formic acid in water, B=Methanol; Gradient Profile: Mobile phase initial composition of 60% A and 40% B, then 40% A and 60% B in 3 min, then to 10% A and 90% B in 20 min., then to 5% A and 95% B in 21 min., held this composition up to 22 min. for column washing, then returned to initial composition in 23 min. and held till 25 min.

15 **Method-Q:** Column name: YMC-Actus C18 (250 x 20 mm, 5 μ). Mobile phase: A = 20mM NH₄HCO₃ in water, B= ACN; Gradient Profile: Mobile phase initial composition of 70% A and 30% B, then 50% A and 50% B in 3 min, then to 20% A and 80% B in 20 min., then to 5% A and 95% B in 21 min., held this composition up to 22 min. for column washing, then returned to initial composition in 23 min. and held till 25 min.

20 **Method-R:** Preparative HPLC was done in Gilson auto purification instrument equipped with UV Detector set to 220nm. Column name: Chromcore 120 C18 (250 x 21.2 mm, 5 μ) operating at ambient temperature and flow rate of 18 ml/min. Mobile phase: A =20 mM NH₄HCO₃ in water, Mobile phase: B= ACN; Gradient Profile: Mobile phase initial composition of 65% A and 35% B, held it up to 3 min, then to 25% A and 75% B in 22 min, then to 5% A and 95% B in 22.5 min, held this composition up to 25 min. for column washing, then returned to initial composition in 25.5 min. and held till 28 min.

25 **Method-S:** Column name: Chromcore 120 C18 (250 x 21.2 mm, 5 μ). Mobile phase: A =20 mM NH₄HCO₃ in water, Mobile phase: B= ACN; Gradient Profile: Mobile phase initial composition of 40% A and 60% B, held this composition up to 3 min, then to 10% A and 90% B in 18 min, then to 5% A and 95% B in 18.5 min held this composition up to 19 min. for column washing, then returned to initial composition in 19.5 min. and held till 25 min.

30 **Method-T:** Column name: Xterra C18 (250 x 19 mm, 10 μ). Mobile phase: A = 20mM NH₄HCO₃ in water, B=ACN; Gradient Profile: Mobile phase initial composition of 70% A and 30% B, then 50% A and 50% B in 3 min, then to 20% A and 80% B in 20 min., then

to 5% A and 95% B in 21 min., held this composition up to 22 min. for column washing, then returned to initial composition in 23 min. and held till 25 min.

Method-U: Column name: -ChromCore Polar C18 (250 x 21.2mm, 5 μ) Mobile phase: A= 20mM NH₄HCO₃ in water, B=MeOH; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 65% A and 35% B in 5 min., then to 40% A and 60% B in 30 min., then to 5% A and 95% B in 31 min., held this composition up to 34 min. for column washing, then returned to initial composition in 35 min. and held till 38 mins.

Method-V: Preparative HPLC was done in AGILENT-1260 instrument with PDA detector set to multiple-wavelength UV (200-400nm) detection. Column name: YMC Actus triart C18 (250 x 20 mm, 5 μ). Mobile phase: A= 20 mM ammonium bicarbonate in water, B= Acetonitrile. Gradient profile: Mobile phase initial composition of 70% A and 30% B, then to 60% A and 40% B in 3 min, then to 45% A and 55% B in 18 min, then 5% A and 95% B in 20 min, held in this composition upto 24 min for column washing, then returned to initial composition in 25 min and held till 26 min.

Method-W: Column name: Hydrosphere C18 (250 x 20 mm, 5 μ). Mobile phase: A = 0.1% Formic acid in water, B=Acetonitrile; Gradient Profile: Mobile phase initial composition of 70% A and 30% B, then 50% A and 50% B in 3 min, then to 20% A and 80% B in 20 min., then to 5% A and 95% B in 21 min., held this composition up to 22 min. for column washing, then returned to initial composition in 23 min. and held till 25 min.

Method-X: Column name: - xterra C18 (250 x 19mm, 10 μ) Mobile phase: A= 0.1% Formic Acid in water, B=Methanol; Gradient Profile: Mobile phase initial composition of 50% A and 50% B, then to 25% A and 75% B in 22 min , then to 5% A and 95% B in 23 min., held this composition up to 25 min for column washing, then returned to initial composition in 26 min. and held till 28 mins.

Method-Y: Column name: Hydrosphere C18 (250 x 20 mm, 5 μ). Mobile phase: A = 10mM Ammonium Acetate in water, B=Acetonitrile; Gradient Profile: Mobile phase initial composition of 60% A and 40% B, then 20% A and 80% B in 20 min, then to 5% A and 95% B in 21 min., held this composition up to 22 min. for column washing, then returned to initial composition in 23 min. and held till 25 min.

Method-Z: Column name: Xbridge C18 (250 x 19 mm, 5 μ) Mobile phase: A = 20mM Ammonium Bicarbonate in water, B=Acetonitrile; Gradient Profile: Mobile phase initial composition of 70% A and 30% B, then 70% A and 30% B in 3 min, then to 45% A and 55% B in 20 min., then to 5% A and 95% B in 21 min., held this composition up to 22

min. for column washing, then returned to initial composition in 23 min. and held till 25 min.

5 **Method-AA:** Column name: - Hydrosphere C18 (250 x 20 mm, 5 μ m). Mobile phase: A= water, B=Acetonitrile; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 75% A and 25% B in 5 min., then to 50% A and 50% B in 30 min., then to 5% A and 95% B in 31 min., held this composition up to 34 min. for column washing, then returned to initial composition in 35 min. and held till 38 mins.

10 **Method-AB:** Column name: - Sunfire C18 (19 x 150mm, 10 μ). Mobile phase: A= 0.1% Formic acid in water, B=Acetonitrile; Gradient Profile: Mobile phase initial composition of 90% A and 10% B, then to 90% A and 10% B in 3 min, then to 65% A and 35% B in 22 min, then to 0% A and 100% B in 23 min., held this composition up to 25 min. for column washing, then returned to initial composition in 26 min. and held till 28 mins.

15 **Method-AC:** Column name: - Hydrosphere C18 (250 x 20mm, 5 μ) Mobile phase: A= 10mM Ammonium acetate in water, B=Acetonitrile; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 70% A and 30% B in 3 min., then to 40% A and 60% B in 22 min, then to 0% A and 100% B in 23 min., held this composition up to 25 min. for column washing, then returned to initial composition in 26 min. and held till 28 mins.

20 **Method-AD:** Column name: - Luna Omega C8 (250 x 21.2mm, 5 μ). Mobile phase: A= 10mM Ammonium acetate in water, B=Acetonitrile; Gradient Profile: Mobile phase initial composition of 45% A and 55% B, then to 35% A and 65% B in 22 min, then to 0% A and 100% B in 23 min., held this composition up to 25 min. for column washing, then returned to initial composition in 26 min. and held till 28 mins.

25 **Method-AE:** Column name: - Gemini NX C18 (250 x 21.2 mm, 5 μ) Mobile phase: A= 20mM Ammonium bicarbonate in water, B=Acetonitrile; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 70% A and 30% B in 3 min., then to 50% A and 50% B in 18 min, then to 0% A and 100% B in 19 min., held this composition up to 21 min. for column washing, then returned to initial composition in 23 min. and held till 25 mins.

30 **Method-AF:** Column name: - Hydrosphere C18 (250 x 20mm, 5 μ). Mobile phase: A= 10Mm NH₄OAc in water, B=Acetonitrile; Gradient Profile: Mobile phase initial composition of 90% A and 10% B, then to 70% A and 30% B in 3 min., then to 20% A and 70% B in 25 min., then to 5% A and 95% B in 28 min. held this composition up to 29 min. for column washing, then returned to initial composition in 30 min. and held till 33 mins.

35

Method-AG: Column name: - Luna C8(250 x 21.2mm, 5 μ). Mobile phase: A= 0.1 % Formic acid in water, B=Acetonitrile; Gradient Profile: Mobile phase initial composition of 90% A and 10% B, then to 55% A and 45% B in 22 min , then to 5% A and 95% B in 23 min., held this composition up to 25 min for column washing, then returned to initial composition in 26 min. and held till 28 mins.

Method-AH: Column name: - XBRIDGE C18 OBD (250 x 19mm, 10 μ). Mobile phase: A= 20mM Ammonium Bicarbonate in water, B=Acetonitrile; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 70% A and 30% B in 3 min., then to 40% A and 60% B in 25 min., then to 5% A and 95% B in 28 min. held this composition up to 29 min. for column washing, then returned to initial composition in 30 min. and held till 33 mins.

Chiral SFC prep. purification:

Method-A: SFC prep has been completed in Pic Solution 175 instrument equipped with Knauer UV Detector 40D by using Chiralpak-IG (21.0 mm x 250mm), 5 μ Column operating at 35°C temperature, maintaining flow rate of 70 ml/min, using 65% CO₂ in super critical state & 35% of 100% Methanol as Mobile phase. Run this isocratic mixture up to 10.0 minutes and also maintained the isobaric condition of 120 bar at 289 nm wavelength.

Method-B: SFC prep has been completed on Waters SFC150 instrument equipped with Waters 2489 UV/Visible Detector by using Chiralpak IG(30.0 mm x 250 mm), 5 μ Column operating at 35 °C temperature, maintaining flow rate of 100 ml/min, using 60% CO₂ in super critical state and 40% [0.1% Methanolic NH₃ in Methanol) as Mobile phase, Run this isocratic mixture up to 9.0 minutes and also maintained the isobaric condition of 120 bar at 290 nm wavelength.

Method-C: SFC prep has been on Waters SFC150 instrument equipped with Waters 2489 UV/Visible Detector by using Chiralpak-IG (30.0 mm x 250 mm), 5 μ Column operating at 35 °C temperature, maintaining flow rate of 100 ml/min, using 60% CO₂ in super critical state & 40% of (0.3% Methanolic NH₃ in Methanol) as Mobile phase. Run this isocratic mixture up to 15.0 minutes and maintained the isobaric condition of 120 bar at 220 nm wavelength.

Method-D: SFC prep has been on Waters SFC150 instrument equipped with Waters 2489 UV/Visible Detector by using Chiralpak IC(30.0 mm x 250mm), 5 μ Column operating at 35 °C temperature, maintaining flow rate of 100 ml/min ,using 70% CO₂ in super critical state & 30% [MeOH : ACN (1:1)) as Mobile

phase, Run this isocratic mixture up to 15.0 minutes and also maintained the isobaric condition of 100 bar at 288 nm wavelength.

LCMS/UPLC Methods:

- 5 **Method-A (UV 260 and 220 nm):** Column: Xbridge C18 column (3.5 μ m, 50 x 3 mm). Mobile phase: 95% [5 mM NH₄OAc in water] and 5% [5 mM NH₄OAc in ACN: Water (90:10)] held for 0.75 min, then 85% [5 mM NH₄OAc in water] and 15% [5 mM NH₄OAc in ACN: Water (90:10)] in 1.25 min further 70% [5 mM NH₄OAc in water] and 30% [5 mM NH₄OAc in ACN: Water (90:10)] in 2.50 min, and finally 2% [5 mM NH₄OAc in water] and 98% [5 mM NH₄OAc in ACN: Water (90:10)] in 3.75 min, held this mobile phase composition up to 4.25 min and finally back to initial condition in 4.50 min and held this composition up to 5.10 min).
- 10 **Method B (UV 260 and 220 nm):** Column: Waters Acquity UPLC BEH C8 (2.1 x 50 mm, 1.7 micron). Mobile phase: 95% [0.05% HCOOH in water] and 5% [0.05% HCOOH in ACN: Water (90:10)] held for 0.75 min, then to 75% [0.05% HCOOH in water] and 25% [0.05% HCOOH in ACN: Water (90:10)] in 1.5 min, further to 5% [0.05% HCOOH in water] and 95% [0.05% HCOOH in ACN: Water (90:10)] in 3.00 min, held this mobile phase composition up to 4.00 min and finally back to initial condition in 4.50 min and held this composition up to 5.10 min).
- 15 **Method C (UV 260 and 220 nm):** Column: YMC TRIART C18 (33 x 2.1 mm, 3 μ). Mobile phase: 98% [0.05% HCOOH in water] and 2% [ACN] held for 0.75 min, then to 90% [0.05% HCOOH in water] and 10% [ACN] in 1.0 min, further to 2% [0.05% HCOOH in water] and 98% [ACN] in 2.0 min, held this mobile phase composition up to 2.25 min and finally back to initial condition in 3.0 min). Flow =1.5 ml/min.
- 20 **Method D (UV 260 and 220 nm):** Column: Xbridge C18 (4.6 x 50 mm, 5 μ). Mobile phase: 90 % [10 mM NH₄OAc in Water] and 10 % [ACN] to 70% [10 mM NH₄OAc in Water] and 30% [ACN] in 1.5 min, further to 10% [10 mM NH₄OAc in Water] and 90% [ACN] in 3.00 min, held this mobile phase composition up to 4.00 min and finally back to initial condition in 5.00 min. Flow =1.20 ml/min.
- 25 **Method E (UV 260 and 220 nm):** Column: Waters Acquity UPLC BEH C8 (2.1 x 50 mm, 1.7 μ). Mobile phase: 90% [0.05% HCOOH in water] and 10% [0.05% HCOOH in ACN: Water (90:10)] held for 0.75 min, then to 50% [0.05% HCOOH in water] and 50% [0.05% HCOOH in ACN: Water (90:10)] in 1.0 min, further to 2% [0.05% HCOOH in water] and 98% [0.05% HCOOH in ACN: Water (90:10)] in 2.0 min, held this mobile phase
- 30

composition up to 2.25 min and finally back to initial condition in 2.60 min and held this composition up to 3.00 min). Flow =0.80 ml/min.

Method-F (UV 260 and 220 nm): Column: Xbridge C18 column (3.5 µm, 50 x 3 mm).

Mobile phase: 95% [5 mM NH₄OAc in water] and 5% [5 mM NH₄OAc in ACN: Water

5 (90:10)] held for 0.75 min, then to 70% [5 mM NH₄OAc in water] and 30% [5 mM NH₄OAc in ACN: Water (90:10)] in 1.00 min, and finally 2% [5 mM NH₄OAc in water] and 98% [5 mM NH₄OAc in ACN: Water (90:10)] in 2.00 min, held this mobile phase composition up to 2.50 min and finally back to initial condition in 2.75 min and held this composition up to 3.0 min). Flow rate-1.20 ml/min.

10 **Method G (ELSD):** Column: Waters Acquity UPLC BEH C8 (2.1 x 50 mm, 1.7 µ).

Mobile phase: 90% [0.05% HCOOH in water] and 10% [0.05% HCOOH in ACN: Water (90:10)] held for 0.75 min, then to 50% [0.05% HCOOH in water] and 50% [0.05%

HCOOH in ACN: Water (90:10)] in 1.0 min, further to 2% [0.05% HCOOH in water] and 98% [0.05% HCOOH in ACN: Water (90:10)] in 2.0 min, held this mobile phase

15 composition up to 2.25 min and finally back to initial condition in 2.60 min and held this composition up to 3.00 min). Flow =0.80 ml/min.

Method H (UV 260 and 220 nm): Column: Xbridge C18 column (3.5 µm, 50 x 3 mm).

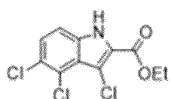
Mobile phase: 98% [5 mM NH₄OAc in water] and 2% [5 mM NH₄OAc in ACN: Water (90:10)] held for 1.00 min, then 50% [5 mM NH₄OAc in water] and 50% [5 mM

20 NH₄OAc in ACN: Water (90:10)] in 5.00 min and finally 2% [5 mM NH₄OAc in water] and 98% [5 mM NH₄OAc in ACN: Water (90:10)] in 8.00 min, held this mobile phase composition up to 10.00 min and finally back to initial condition in 12.00 min and held this composition up to 12.10 min).

25 Preparations

Preparation 1: Synthesis of 3,4,5-trichloro-1H-indole-2-carboxylic acid

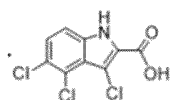
Step-1: Synthesis of ethyl 3,4,5-trichloro-1H-indole-2-carboxylate



To a stirred solution of ethyl 4,5-dichloro-1H-indole-2-carboxylate (400.0 mg, 1.55
30 mmol) in CH₃CN (5.0 mL) was added NCS (311.0 mg, 2.33 mmol) and stirred at 80 °C for 16 h. After completion (monitored by LCMS), the reaction mixture was concentrated

under reduced pressure to get crude compound. It was purified by combiflash chromatography (eluent gradient: 10-20% EtOAc in hexane) to obtain ethyl 3,4,5-trichloro-1*H*-indole-2-carboxylate (240.0 mg, 53%) as a white sticky solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.66 (s, 1H), 7.51 (d, *J* = 8.85 Hz, 1H), 7.47 (d, *J* = 8.85 Hz, 1H), 5 4.39 (q, *J* = 6.9 Hz, 2H), 1.36 (t, *J* = 6.9 Hz, 3H).

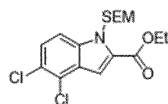
Step-2: Synthesis of 3,4,5-trichloro-1*H*-indole-2-carboxylic acid



Hydrolysis of ethyl 3,4,5-trichloro-1*H*-indole-2-carboxylate (200 mg, 0.775 mmol) was
10 done following general hydrolysis condition. **Yield:** 97%. ¹H NMR (400 MHz, DMSO-*d*₆):
δ 12.57 (s, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H). LCMS (Method-A): RT
1.04 min; 262.0 [M-H]⁻.

Preparation 2: tert-butyl 4-(4,5-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-
15 indole-2-carbonyl)piperazine-1-carboxylate

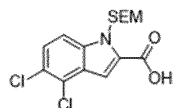
Step-1: Synthesis of ethyl 4,5-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-2-carboxylate



To a stirred solution of ethyl 4,5-dichloro-1*H*-indole-2-carboxylate (1.3 g, 5.03 mmol) in THF was added NaH (109.0 mg, 4.53 mmol, 60% in mineral oil) portion wise at 0 °C followed by SEM-chloride (1.07 mL, 6.03 mmol) dropwise and stirred at rt for 2 h. After completion (monitored by LCMS or, TLC), the reaction mixture was quenched with ice water and extracted with ethyl acetate (3 x 50.0 mL). The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to crude get crude compound, which was purified by combiflash column chromatography (eluent gradient: 12-15% EtOAc in hexane) to obtain ethyl 4,5-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-2-carboxylate (1.2 g, 56%) as colourless oil. ¹H NMR (400 MHz, DMSO-*d*₆): 7.39 (m, 2H), 7.38 (s, 1H),

5.98 (s, 2H), 4.38 (q, $J = 7.1$ Hz, 2H), 3.50 (t, $J = 8.1$ Hz, 2H), 1.43 (t, $J = 4.8$ Hz, 3H), 0.83 (t, $J = 8.1$ Hz, 2H), -0.09 (s, 9H).

Step-2: Synthesis of 4,5-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-2-carboxylic acid



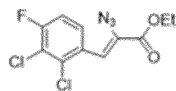
Hydrolysis of ethyl 4,5-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-2-carboxylate (1.2 gm, 3.34 mmol) was done following general hydrolysis condition to get 1.3 g (crude) of title compound. The crude material was pure enough to be used in the next step without further purification. ^1H NMR (400 MHz, DMSO- d_6): 13.45 (brs, 1H), 7.73 (d, $J = 8.9$ Hz, 1H), 7.54 (d, $J = 8.9$ Hz, 1H), 7.25 (s, 1H), 5.60 (s, 2H), 3.44 (t, $J = 7.8$ Hz, 2H), 0.77 (t, $J = 7.8$ Hz, 2H), -0.13 (s, 9H). LCMS (Method-D): RT 1.01 min; 358.2 [M-H] $^-$.

Step-3: Synthesis of *tert*-butyl 4-(4,5-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-2-carbonyl)piperazine-1-carboxylate

Amidation of 4,5-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-2-carboxylic acid (500 mg, 1.393 mmol) and *N*-*boc* piperazine (142 mg, 1.67 mmol) was done following general amidation condition-B. Resulting crude compound was purified by silica gel column chromatography (eluent gradient: 25-30% EtOAc in hexane) to get the title compound (700 mg, 95%). ^1H NMR (400 MHz, DMSO- d_6): 7.36-7.31 (m, 2H), 6.68 (s, 1H), 5.62 (s, 2H), 3.75-3.65 (m, 4H), 3.51-3.40 (m, 6H), 1.47 (s, 9H), 0.83 (t, $J = 8.3$ Hz, 2H), -0.07 (s, 9H).

Preparation 3: Synthesis of 4,5-dichloro-6-fluoro-1*H*-indole-2-carboxylic acid

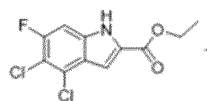
Step-1: Synthesis of ethyl (Z)-2-azido-3-(2,3-dichloro-4-fluorophenyl)acrylate



To a stirred solution of 2,3-dichloro-4-fluorobenzaldehyde (1.5 g, 7.82 mmol) in ethanol (25.0 mL) was added NaH (0.56 mg, 23.44 mmol, 60% in mineral oil) portionwise at -30 °C. After 30 minutes, a solution of ethyl 2-azidoacetate (4.03 g, 31.26 mmol) in ethanol

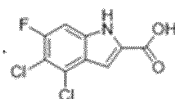
(15.0 mL) was added dropwise through a dropping funnel. The reaction mixture was stirred at 15 °C for 6 h. After completion (monitored by TLC and LCMS), the reaction mixture was quenched with aq. NH₄Cl solution and extracted with ethyl acetate (3 x 50.0 mL). The combined organic layer was washed with H₂O, followed by brine, and dried over anhyd. Na₂SO₄ then filtered. The filtrate was evaporated under reduced pressure to get crude product, which was purified by combiflash chromatography using a gradient elution with hexane to afford ethyl (Z)-2-azido-3-(2,3-dichloro-4-fluorophenyl)acrylate (1.0 g, 40%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.17 (dd, *J* = 5.9, 9.2 Hz, 1H), 7.55 (t, *J* = 8.8 Hz, 1H), 7.03 (s, 1H), 4.36 (q, *J* = 7.0 Hz, 2H), 1.32 (t, *J* = 7.0 Hz, 3H).

Step-2: Synthesis of ethyl 4,5-dichloro-6-fluoro-1*H*-indole-2-carboxylate



A stirred solution of ethyl (Z)-2-azido-3-(2,3-dichloro-4-fluorophenyl)acrylate (600.0 mg, 3.13 mmol) in xylene (7.0 mL) was heated at 140 °C for 2 h. After completion (monitored by TLC), the reaction mixture was concentrated under reduced pressure to get crude which was triturated with pentane to afford ethyl 4,5-dichloro-6-fluoro-1*H*-indole-2-carboxylate (290.0 mg, 33%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.56 (s, 1H), 7.41 (d, *J* = 9.1 Hz, 1H), 7.14 (s, 1H), 4.37 (q, *J* = 6.7 Hz, 2H), 1.34 (t, *J* = 6.9 Hz, 3H). LCMS (Method-C): RT 2.01 min; 276.0 [M+H]⁺.

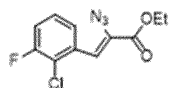
Step-3: Synthesis of 4,5-dichloro-6-fluoro-1*H*-indole-2-carboxylic acid



Hydrolysis of ethyl 4,5-dichloro-6-fluoro-1*H*-indole-2-carboxylate (180.0 mg, 0.66 mmol) was done following general hydrolysis condition to get title compound as yellow solid. Yield: 98% (160 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.75 (brs, 1H), 7.32 (d, *J* = 10.5 Hz), 6.63 (s, 1H). LCMS (Method-D): RT 2.57 min; 246.2 [M-H]⁻.

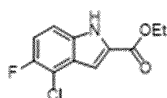
Preparation 4: 4-chloro-5-fluoro-1*H*-indole-2-carboxylic acid

Step-1: Synthesis of ethyl (Z)-2-azido-3-(2-chloro-3-fluorophenyl)acrylate



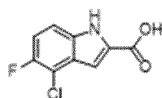
Under argon atmosphere to an ice cold stirred solution of NaOEt (1.1 g, 16.3 mmol) in EtOH (20 mL) was added a solution of 2-chloro-3-fluorobenzaldehyde (2.5 g, 18.11 mmol) and ethyl 2-azidoacetate (3.05 mL, 19.9 mmol) in ethanol dropwise. The resulting reaction mixture was stirred at rt. for 16 h. After completion (monitored by ¹H-NMR), ethanol was removed under reduced pressure at ambient temperature. After usual work-up using EtOAc-H₂O, the resulting crude material was purified by combiflash chromatography using hexane as an eluent to afford title compound as a white solid (585 mg, 13%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.18 (dd, *J* = 6.1, 13.7 Hz, 1H), 7.06 (s, 1H), 6.99 (t, *J* = 8.8 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

Step-2: Synthesis of ethyl 4-chloro-5-fluoro-1*H*-indole-2-carboxylate



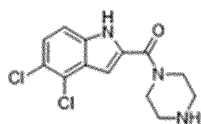
The title compound was synthesized as yellow solid (324 mg, 90%) from ethyl (*Z*)-2-azido-3-(2-chloro-3-fluorophenyl)acrylate (400 mg, 1.49 mmol) following the method described in Step-4 (Scheme-8). ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.37 (s, 1H), 7.47-7.41 (m, 1H), 7.31 (t, *J* = 9.6 Hz, 1H), 7.13 (s, 1H), 4.35 (q, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H). LCMS (Method-C): RT 1.87 min; 241.9 [M+H]⁺.

Step-3: Synthesis of 4-chloro-5-fluoro-1*H*-indole-2-carboxylic acid



Hydrolysis of ethyl 4-chloro-5-fluoro-1*H*-indole-2-carboxylate (372 mg, 1.54 mmol) was done following general hydrolysis condition to get title compound (80%, 264 mg) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.08 (s, 1H), 12.24 (s, 1H), 7.47-7.40 (m, 1H), 7.23 (t, *J* = 9.5 Hz, 1H), 7.08 (s, 1H). LCMS (Method-C): RT 2.04 min; 212 [M-H]⁻.

Preparation 5: Synthesis of (4,5-dichloro-1*H*-indol-2-yl)(piperazin-1-yl)methanone



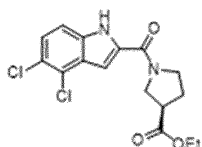
Step-1: 4,5-dichloro-2-(piperazine-1-carbonyl)-1*H*-indole

Amidation of 4,5-dichloro-1*H*-indole-2-carboxylic acid and piperazine was done following general amidation condition-B. Purification was done by combiflash chromatography

(eluent gradient: 25-31% EtOAc in hexane). Yield: 60%. ¹H NMR (400 MHz, DMSO-d₆): 8.20 (brs, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 3.93 (brs, 2H), 3.64 – 3.51 (m, 2H), 3.22-3.06 (m, 4H). LCMS (Method-A): RT 1.59 min; 298.09 [M+H]⁺.

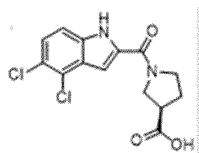
5 **Preparation 6: Synthesis of (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidine-3-carboxylic acid:**

Step-1: Synthesis of ethyl (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidine-3-carboxylate



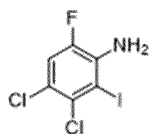
10 Amidation of 4,5-dichloro-1H-indole-2-carboxylic acid (1.1 g, 4.804 mmol) and ethyl (R)-pyrrolidine-3-carboxylate (949 mg, 5.285 mmol) was done following amidation condition-A. The crude material was purified by combiflash column chromatography (eluent gradient: 65-75% EtOAc in hexane) to afford the title compound (900.0 mg, 52.7%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 12.13 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.38 (d, J = 8.6 Hz, 1H), 6.93 (s, 1H), 4.18 – 4.07 (m, 2H), 4.03 – 3.99 (m, 1H), 3.95–3.90 (m, 1H), 3.80-3.73 (m, 1H), 3.65–3.59 (m, 1H), 3.30 – 3.10 (m, 1H), 2.41–2.01 (m, 2H), 1.19 (t, J = 8 Hz, 3H). LCMS (Method-C): RT 1.82 min; 355.0 [M+H]⁺.

20 **Step-2:** Synthesis of (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidine-3-carboxylic acid

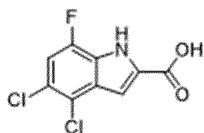


25 Hydrolysis of ethyl (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidine-3-carboxylate (700 mg, 1.977 mmol) was done following general hydrolysis condition to get title compound (400 mg, 61.8%) as an off-white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 12.61 (s, 1H), 12.14 (s, 1H), 7.44 (d, J = 8.50 Hz, 1H), 7.38 (d, J = 8.50 Hz, 1H), 6.94 (s, 1H), 4.07-4.02 (m, 1H), 3.93-3.77 (m, 1H), 3.75-3.71 (m, 1H), 3.62-3.60 (m, 1H), 3.25-3.12 (m, 1H), 2.27-2.09 (m, 2H). LCMS (Method-C): RT 1.59 min; 326.9 [M+H]⁺.

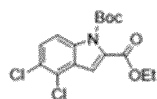
Preparation 7: Synthesis of 4,5-dichloro-7-fluoro-1H-indole-2-carboxylic acid

Step-1: Synthesis of 3,4-dichloro-6-fluoro-2-iodoaniline

To a stirred solution of 4,5-dichloro-2-fluoroaniline (250.0 mg, 1.40 mmol) in ethanol (15.0 ml) was added silver sulfate (436.0 mg, 1.4 mmol) followed by addition of iodine (177.0 mg, 1.40 mmol) portion wise and stirred at RT for 16h. The reaction was monitored by LCMS. The reaction mixture was concentrated and crude was purified by column chromatography using gradient elution of 5 – 10% ethyl acetate in hexane to afford titled compound (100.0 mg, 23%) as sticky gum. ¹H NMR (400 MHz, DMSO-d₆): δ 7.65 (d, J = 10.8 Hz, 1H), 5.66 (s, 2H).

Step-2: 4,5-dichloro-7-fluoro-1H-indole-2-carboxylic acid

To a sealed tube a solution of 3,4-dichloro-6-fluoro-2-iodoaniline (100.0 mg, 0.33 mmol) and 2-oxopropanoic acid (58.0 mg, 0.66 mmol) in DMF (1.0 ml). Reaction mixture was purged with an argon balloon for 10 minutes. DABCO (74.0 mg, 0.66 mmol) and Pd(OAc)₂ (29.0 mg, 0.13 mmol) were added under purging and heated to 115 °C for 16 h. The reaction was monitored by LCMS. After completion, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (150.0 mL). Combined organic part was dried over anhydrous sodium sulfate and concentrated to get title compound (248.0 mg, 73%) and used for next step without further purification. LCMS (Method-D): RT 1.49 min; 246.0 [M-H]⁻.

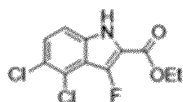
Preparation 8: Synthesis of 4,5-dichloro-3-fluoro-1H-indole-2-carboxylic acid**Step-1: Synthesis of 1-(tert-butyl) 2-ethyl 4,5-dichloro-1H-indole-1,2-dicarboxylate**

To a stirred solution of ethyl 4,5-dichloro-1H-indole-2-carboxylate (200.0 mg, 0.78 mmol) in ACN (5.0 mL) was added Boc-anhydride (0.21 ml, 0.93 mmol) followed by DMAP (10 mg, 0.077 mmol) and stirred at rt for 16 h. The reaction was monitored by LCMS. The reaction mixture was concentrated in vacuo to crude residue, which was then purified by

combiflash chromatography using gradient elution of 5 – 10% ethyl acetate in hexane to afford titled compound (190.0 mg, 60%) as a colorless oil, ¹H NMR (400 MHz, DMSO-d₆): δ 7.53 (d, J = 8.95 Hz, 1H), 7.68 (d, J = 8.95 Hz, 1H), 7.27 (s, 1H), 4.35 (q, J = 7.06 Hz, 2H), 1.58 (s, 9H), 1.33 (t, J = 8.06 Hz, 3H). LCMS (Method-D): RT 2.32 min; 302.21 [M+H]⁺.

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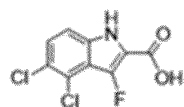
Step-2: Synthesis of ethyl 4,5-dichloro-3-fluoro-1H-indole-2-carboxylate



To a stirred solution of 1-(tert-butyl) 2-ethyl 4,5-dichloro-1H-indole-1,2-dicarboxylate (600.0 mg, 1.68 mmol) in DCM was added 1-fluoro-2,6-dichloropyridinium triflate (1.0 g, 3.18 mmol) and stirred at 40 °C for 16 h. The reaction was monitored by LCMS. The crude was then filtered and concentrated and purified by combiflash chromatography using gradient elution of 5 – 10% ethyl acetate in hexane to afford the titled compound (200.0 mg, 49%) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆): δ 12.25 (s, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 2H). LCMS (Method-D): RT 2.10 min; 274.08 [M-H]⁻.

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Step-3: Synthesis of 4,5-dichloro-3-fluoro-1H-indole-2-carboxylic acid

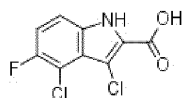


To a stirred sol of ethyl 4,5-dichloro-3-fluoro-1H-indole-2-carboxylate (200.0 mg, 0.72 mmol) in THF-H₂O (3.0 mL) was added LiOH.H₂O (92.0 mg, 2.17 mmol) and stirred at 40 °C for 16h. The reaction was monitored by LCMS. The reaction mixture was concentrated in vacuo to afford the title compound as a lithium salt of the corresponding acid (130.0 mg, 72%) as off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 6.96 (d, J = 8.50 Hz, 1H), 6.70 (d, J = 8.50 Hz, 1H). LCMS (Method-D): RT 1.44 min; 245.99 [M-H]⁻.

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25 Preparation 9: Synthesis of 3,4-dichloro-5-fluoro-1H-indole-2-carboxylic acid

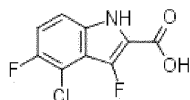
Step 1: Synthesis of 3,4-dichloro-5-fluoro-1H-indole-2-carboxylic acid



To a stirred solution of 4-chloro-5-fluoro-1H-indole-2-carboxylic acid (Preparation 4, 3.0 g, 14.1 mmol) in ACN (40.0 mL) was added NCS (2.26 g, 16.90 mmol) and heated to

60°C for 3 hrs. The reaction was monitored by TLC. The reaction was filtered and the filtrate was concentrated to get crude compound. The crude was then purified by combiflash to afford desired product (1.2 g, 35%) as off white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.70 (brs, 1H), 12.48 (s, 1H), 7.44 (dd, J= 9.0, 4.2 Hz, 1 H), 7.35 (t, J = 9.5 Hz, 1H), LCMS: 246.0 [M-H]⁻.

Preparation 10: Synthesis of 3,5-fluoro-5-chloro-1H-indole-2-carboxylic acid

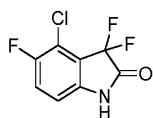


Protocol 1

In a sealed tube, to a solution of 4-chloro-5-fluoro-1H-indole-2-carboxylic acid (Preparation 4, 2.5 g, 11.73 mmol) in dry ACN (25 mL) was added Selectfluor (4.57 g, 12.91 mmol) and the resulting suspension was stirred for 16 hours at rt. The crude material was diluted with ethyl acetate and washed subsequently with water and brine. After drying over anhydrous sodium sulfate, the organic layer was filtered and concentrated under reduced pressure. The crude material was triturated with ether-pentane and used in the next step without further purification (~1:1 ratio of desired product and unreacted starting material as observed by ¹H-NMR).

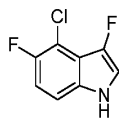
Protocol 2

Step-1: 4-chloro-3,3,5-trifluoroindolin-2-one:



To a stirred solution 4-chloro-5-fluoro-2,3-dihydro-1H-indole-2,3-dione (14.0 g, 70.15 mmol) in DCM (160.0 mL) was added DAST (23.167 mL, 175.38 mmol) at 0 °C under N₂ atmosphere. The reaction mixture (suspension) was stirred for 6 h at rt. By this time suspension turned into solution. The reaction mixture was poured into saturated aq. NaHCO₃ solution (200.0 mL) and extracted with DCM (3 x 200.0 mL). The combined organic layer was washed with brine, dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by combiflash chromatography (0 – 5% EtOAc-Hex) to give 3,3-difluoroindolin-2-one (8.5 g, 49%) as redish solid.

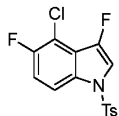
Step-2: 4-Chloro-3,5-difluoro-1H-indole:



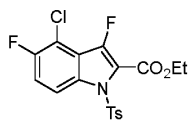
To a stirred solution of 4-chloro-3,3,5-trifluoro-2,3-dihydro-1H-indol-2-one (10.0 g, 45.13 mmol) in dry THF (150.0 mL) was added BH₃.DMS (2M in THF, 67.5 mL, 135.39 mmol) dropwise under nitrogen at 0 °C. The reaction mixture was stirred at room temperature for 3 h. After completion (monitored by TLC), the reaction mixture was quenched with 10% aq. citric acid solution (till gas evolution ceased), diluted with water and extracted with EtOAc (3 x 200.0 mL). Combined organic layer was washed with water (2 x 200.0 mL) and brine (200.0 mL). The organic layer was then dried over anhyd. Na₂SO₄, filtered and filtrate was evaporated under reduced pressure to provide crude compound. The resulting crude was purified by combiflash chromatography (eluent: 10% ethyl acetate in hexane) to afford 4-chloro-3,5-difluoro-1H-indole (6 g, 71%) as brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ 11.28 (brs, 1H), 7.52 (t, J = 2.6 Hz, 1H), 7.36 - 7.32 (m, 1 H), 7.15 (t, J = 9.4 Hz, 1H). LCMS (Method C): RT 2.19 min; 186.01 [M-H]⁻.

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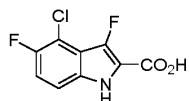
Step-3: 4-Chloro-3,5-difluoro-1-tosyl-1H-indole:



To a stirred solution of 4-chloro-3,5-difluoro-1H-indole (3.6 g, 19.19 mmol) in dry DMF (40.0 mL) was added NaH (1.0 g, 21.11 mmol, 60% in mineral oil) portionwise at 0 °C over a period of 10 minutes. The mixture was stirred at same for 15 minutes. *p*-TsCl (5.4 g, 28.79 mmol) was added, and the mixture was stirred at rt for 2 h. After completion (monitored by TLC), the reaction mixture was quenched with satd. cold aq. NH₄Cl solution and subjected to usual work-up. The reaction mixture was diluted with EtOAc (100.0 mL) and H₂O (100.0 mL) and taken in a separatory funnel. The organic layer was separated and aq. layer was back extracted with EtOAc (3 x 100.0 mL). The combined organic layer was washed with H₂O, brine and then dried over anhyd. Na₂SO₄. Then, organic part was filtered and the filtrate was evaporated to dryness under reduced pressure to get crude compound, which was purified using silica gel column chromatography (eluent: 25% ethyl acetate in hexane) to get 4-chloro-3,5-difluoro-1-(4-methyl-1-sulfonylphenyl)-1H-indole (4.8 g, 73%) as white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.17 (s, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 7.9 Hz, 2 H), 7.48 (t, J = 9.5 Hz, 1H), 7.41 (d, J = 7.8 Hz, 2H), 2.34 (s, 3H).

Step-4: Ethyl 4-chloro-3,5-difluoro-1-tosyl-1*H*-indole-2-carboxylate:

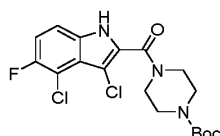
n-Butyllithium (2.5 M in hexane, 6.4 mL) was added dropwise to a stirred solution of 4-chloro-3,5-difluoro-1-[(4-methylbenzene)sulfonyl]-1*H*-indole (5.0 g, 14.63 mmol) in dry THF (80 mL) at -78 °C. The resulting mixture was stirred at same temperature for 30 minutes. Thereafter, ethyl chloroformate (1.67 mL, 17.56 mmol) was added dropwise into the reaction mixture at -78 °C. After 10 minutes, cooling bath was removed and the mixture warmed to rt. After 2-3 h, the reaction mixture was quenched with satd. aq. NH₄Cl solution and extracted with EtOAc (3 x 100.0 mL). The combined organic layer was washed with H₂O (100.0 mL), brine and then dried over anhyd. Na₂SO₄. Organic part was then filtered and the filtrate was evaporated to dryness under reduced pressure. The resulting crude was purified by combiflash chromatography (eluent: 5% ethyl acetate in hexane) to get ethyl 4-chloro-3,5-difluoro-1-tosyl-1*H*-indole-2-carboxylate (4.2 g, 69%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.07 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.63 (t, *J* = 9.5 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 1H), 4.42 (q, *J* = 7.0 Hz, 2H), 1.98 (s, 3H), 1.35 (t, *J* = 7.0 Hz, 3H). LCMS (Method C): RT 2.56 min; 414.1 [M+H]⁺.

Step-5: 4-Chloro-3,5-difluoro-1*H*-indole-2-carboxylic acid:

To a stirred solution of ethyl 4-chloro-3,5-difluoro-1-tosyl-1*H*-indole-2-carboxylate (4.2 g, 10.149 mmol) in THF-H₂O mixture (80.0 mL, 1:3 ratio) was added LiOH·H₂O (4.26 g, 101.493 mmol). The resulting mixture was stirred for 6 h at 60 °C. After completion (monitored by TLC), THF was evaporated from the reaction mixture under reduced pressure. The aqueous layer was washed with EtOAc (100.0 mL) to eliminate any non-polar impurity. Then, pH of the aqueous layer was adjusted to ~4-5 with 6N HCl. The resulting solution was then extracted with EtOAc (3 x 100.0 mL). The combined organic layer was washed with brine and dried over anhyd. Na₂SO₄, filtered and the filtrate was evaporated to dryness under reduced pressure to provide 4-chloro-3,5-difluoro-1*H*-indole-2-carboxylic acid (2.0 g, 85%) as grey solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.53 (brs, 1H), 12.03 (s, 1H), 7.48 - 7.32 (m, 2H). LCMS (Method A): RT 2.36 min; 230.2 [M-H]⁻.

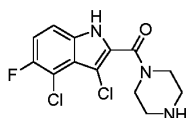
Preparation 11: Synthesis of (3,4-dichloro-5-fluoro-1H-indol-2-yl)(piperazin-1-yl)methanone:

Step 1: Synthesis of tert-butyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate



To a stirred solution of 3,4-dichloro-5-fluoro-1H-indole-2-carboxylic acid (1.0 g, 4.03 mmol) in DMF (10.0 ml) was added DIPEA (2.1 ml, 12.10) at 0°C followed by addition of EDCI (927.0 mg, 4.84 mmol) and HOBt (654.0 mg, 4.84 mmol). After 30 minutes at 0°C tert-butyl piperazine-1-carboxylate (901.0 mg, 4.84 mmol) was added and stirred for 16h. The reaction mixture was quenched in ice cold water (30.0 ml) and extracted with ethyl acetate (2 X 40.0 ml). Combined organic was washed with brine solution (20.0 ml), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to crude product was purified using column chromatography (50-70% ethyl acetate in hexane) to afford tert-butyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate (900.0 mg, 54%) as yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 12.41 (bs, 1H), 7.41 (dd, J = 8.9 Hz, 4.1 Hz, 1H) 7.23 (t, J = 9.4 Hz, 1H), 3.64 (brs, 2H), 3.41 - 3.26 (m, 6H), 2.50 (s, 9H). LCMS (Method A): RT 2.03 min; 414.19 [M-H]⁻.

Step 2: Synthesis of (4-chloro-3,5-difluoro-1H-indol-2-yl)(piperazin-1-yl) methanone

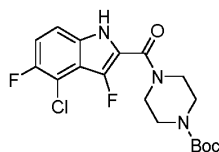


To a stirred solution of tert-butyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate (600.0 mg, 1.44 mmol) in DCM (5.0 mL) was added TFA (1.1 ml, 14.41 mmol). at 0°C over a period of 30 minutes. Reaction mixture was allowed to come at RT and stirred at same for 3h. Reaction mixture was concentrated to dryness. Crude was diluted with methanol (100 ml) and pH was adjusted to 8 by adding freshly dried Amberlyst A21 resin, filtered, concentrated and crude was purified using SCX column, concentrated and was triturated with pentane to provide (4-chloro-3,5-difluoro-1H-indol-2-yl)(piperazin-1-yl) methanone (400 mg, 88%) as white solid. ¹H NMR (400 MHz, DMSO-d₆, 100 °C) δ 12.38 (bs, 1H), 7.40 (dd, J = 8.8 Hz, 4.0 Hz, 1H) 7.27 (t, J =

9.6 Hz, 1H), 3.55 - 3.47 (m, 4H), 3.78-3.76 (m, 4H). LCMS (Method B): RT 2.25 min; 316.2 [M+H]⁺.

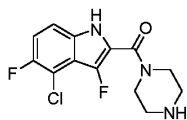
Preparation 12: Synthesis of (4-chloro-3,5-difluoro-1H-indol-2-yl)(piperazin-1-yl)methanone:

Step 1: Synthesis of tert-butyl tert-butyl 4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl) piperazine-1-carboxylate



To a stirred solution of 4-chloro-3,5-difluoro-1H-indole-2-carboxylic acid (35.0 g, 151.13 mmol) in DMF (350.0 ml) was added DIPEA (131.0 ml, 755.67 mmol) at 0°C followed by addition of EDCI (37.5 g, 196.47 mmol) and HOBT (26.5 g, 196.47 mmol). After 30 minutes at 0 °C tert-butyl piperazine-1-carboxylate (34.0 g, 181.36 mmol) was added and stirred for 16h. Reaction mixture was quenched in ice cold water (500.0 ml) and extracted with ethyl acetate (2 X 800.0 ml). Combined organic was washed with brine solution (500.0 ml), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Crude product was purified using column chromatography (80-100% ethyl acetate in hexane) to get tert-butyl 4-[(4-chloro-3,5-difluoro-1H-indol-2-yl)carbonyl] piperazine-1-carboxylate (40.0 g, 66.2%) as yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 11.95 (brs, 1H), 7.39 – 7.35 (m, 1H), 7.29 (t, J = 9.2 Hz, 1H), 3.61 (brs, 4H), 3.42 (brs, 4H). LCMS (Method A): RT 3.00 min; 398.2 [M-H]⁻.

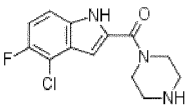
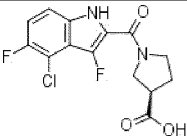
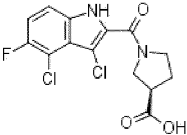
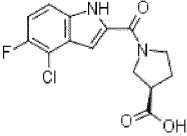
Step 2: Synthesis of (4-chloro-3,5-difluoro-1H-indol-2-yl)(piperazin-1-yl) methanone

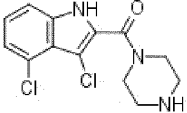
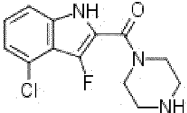
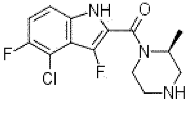


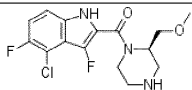
To a stirred solution of tert-butyl 4-[(4-chloro-3,5-difluoro-1H-indol-2-yl)carbonyl] piperazine-1-carboxylate (48.0 g, 120.05 mmol) in DCM (500.0 ml) was added TFA (92.0 ml, 1200.54 mmol) at 0°C over a period of 30 minutes. Reaction mixture was allowed to come at RT and stirred at same for 3h. Reaction mixture was concentrated to dryness. Crude was diluted with methanol (100 ml) and pH was adjusted to -8 by adding freshly dried Amberlyst A21 resin, filtered, concentrated and crude was purified using SCX column, concentrated and was triturated with pentane to get 4-chloro-3,5-difluoro-2-[(piperazin-1-yl)carbonyl]-1H-indole (30.2 g, 83.9%) as off white solid. ¹H NMR (400

MHz, DMSO-d₆) δ 11.93 (brs, 1H), 7.34 – 7.33 (m, 1H), 7.27 (t, J = 9.3 Hz, 1H), 3.53 (brs, 4H), 2.75 - 2.72 (m, 4H). LCMS (Method A): RT 2.17 min; 300.1 [M+H]⁺.

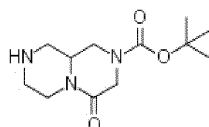
The following intermediates were made using similar methods to those described above.

Preparation no.	Structure	Name	Purification method	LCMS	¹ H NMR
13		(4-chloro-5-fluoro-1H-indol-2-yl)(piperazin-1-yl)methanone	Purified by trituration	Method C: RT 1.24 min; 283.3 [M+H] ⁺ .	(400 MHz, DMSO-d ₆) δ 12.05 (s, 1H), 7.41 (dd, J = 3.6, 8.8 Hz, 1H), 7.2265 (t, J = 9.4 Hz, 1H), 6.80 (s, 1H), 3.72 (brs, 4H) 2.88 – 2.84 (m, 4H).
14		(<i>R</i>)-1-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)pyrrolidine-3-carboxylic acid	Trituration with ether and pentane.	Method D: RT 2.54 min; 327 [M-H] ⁻	
15		(<i>R</i>)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidine-3-carboxylic acid	Combi flash chromatography (eluent gradient: 10% MeOH in DCM)	Method C: RT 1.54 min; 344.98 [M+H] ⁺ .	(400 MHz, DMSO-d ₆) δ 12.37 (s, 1H), 7.39 (m, 1H), 7.28 (t, J = 9.2 Hz, 1H), 3.72 – 3.66 (m, 2H), 3.59 – 3.55 (m, 2H) 3.18 – 3.09 (m, 1H), 2.19 – 2.05 (s, 2H).
16		(<i>R</i>)-1-(4-chloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidine-3-carboxylic acid	Combi flash chromatography (eluent gradient: 10% MeOH in DCM)	Method C: RT 1.70 min; 311.3 [M+H] ⁺ .	400 MHz, DMSO-d ₆) δ 12.63 (brs, 1H), 12.04 (s, 1H), 7.43 (dd, J = 7.8, 3.7 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 4.06 – 4.03 (m, 1H), 4.01 (brs, 1H)

					3.93 – 3.92 (m, 1H), 3.77 – 3.74 (m, 1H), 3.22 – 3.13 (m, 1H), 2.32 – 2.16 (m, 2H).
17		(3,4-dichloro-1H-indol-2-yl)(piperazin-1-yl)methanone	Method-AF	Method A: RT 2.16 min; 298.2 [M+H] ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 12.28 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 7.68 Hz, 1H), 7.15 (d, J = 7.44 Hz, 1H), 3.62–3.50 (m, 4H), 2.90 (s, 4H)
18		(4-chloro-3-fluoro-1H-indol-2-yl)(piperazin-1-yl)methanone	Combi flash chromatography (eluent gradient: 10% MeOH in DCM)	Method A: RT 1.07 min; 280.1 [M-H] ⁻	¹ H NMR (401 MHz, DMSO-d ₆) δ 7.33 (dd, J = 1.7, 8.2 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 7.4 Hz, 1H), 3.65 – 3.47 (m, 4H), 2.80 – 2.70 (m, 4H).
19		(S)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(2-methylpiperazin-1-yl)methanone	Method AH	Method H: RT 4.43 min; 330.0 [M+H] ⁺	¹ H NMR (401 MHz, DMSO-d ₆ , 100 °C) δ 13.38 – 10.68 (m, 1H), 7.40 (dd, J = 4.0, 8.8 Hz, 1H), 7.20 (t, J = 9.6 Hz, 1H), 4.20 (s, 1H), 3.66 (d, J = 11.6 Hz, 1H), 3.28 – 3.12 (m, 1H), 2.96 – 2.79 (m, 3H), 2.79 – 2.69 (m, 1H), 2.68 – 2.53 (m, 1H), 1.31

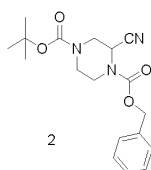
					(d, $J = 6.8$ Hz, 3H).
20		(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(2-(methoxymethyl)piperazin-1-yl)methanone	Method AH	Method A: RT 2.30 min; 344.2 [M+H] ⁺ .	¹ H NMR (401 MHz, DMSO-d ₆ , 100 °C) δ 10.66 – 10.06 (m, 1H), 7.42 – 7.30 (m, 1H), 7.20 (t, $J = 9.6$ Hz, 1H), 4.42 – 4.21 (m, 1H), 3.86 (d, $J = 13.3$ Hz, 1H), 3.76 – 3.59 (m, 2H), 3.25 (s, 3H), 3.23 – 3.11 (m, 1H), 3.06 – 3.01 (m, 1H), 2.95 – 2.89 (m, 1H), 2.80 (dd, $J = 4.0, 12.8$ Hz, 1H), 2.70 – 2.56 (m, 1H).

Preparation 21: Synthesis of tert-butyl 6-oxo-octahydro-1H-pyrazino[1,2-a]piperazine-2-carboxylate



5

Step-1: Synthesis of 1-benzyl 4-tert-butyl 2-cyanopiperazine-1,4-dicarboxylate:



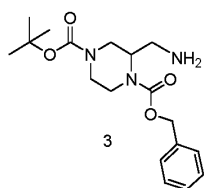
To stirred solution of tert-butyl 3-cyanopiperazine-1-carboxylate (1.6 gm, 7.574 mmol, 1.0 eq.) in THF (5 ml) and H₂O (5 ml) (1:1) was added Na₂CO₃ (1.606 gm, 15.147 mmol, 2.0 eq.) at RT under N₂ atmosphere. Then CBZ Chloride (1.3 ml, 9.088 mmol, 1.2 eq.) was added at 0°C under N₂ atmosphere. Then reaction mixture was stirred for overnight at

10

RT. LCMS and TLC of reaction mixture shows formation of desired product Then reaction mixture was extracted with EA and washed with water and dried over Na_2SO_4 which was concentrated to get crude product, which was purified by Combi-Flash Chromatography (eluted with 15-20% EA-HEX solvent system) to afford 1-benzyl 4-tert-butyl 2-cyanopiperazine-1,4-dicarboxylate (2.5 gm, 96 %) as off white solid.

5 LCMS: m/z $[\text{M}+\text{H}]^+ = 346.2$ (calc. $m/z = 346.17$); RT = 2.02 min.

Step-2: Synthesis of 1-benzyl 4-tert-butyl 2-(aminomethyl)piperazine-1,4-dicarboxylate:



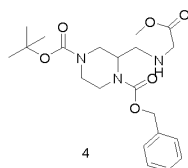
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To stirred solution of 1-benzyl 4-tert-butyl 2-cyanopiperazine-1,4-dicarboxylate (3 gm, 8.686 mmol, 1.0 eq.) in MeOH (50 ml) was degassed under N_2 atmosphere. Then Raney Ni was added under degassing condition and after degassing aqueous ammonia (2 ml) was added. Then reaction mixture was degassed one time in per shaker. Then reaction mixture was stirred for overnight at 50 PSI under H_2 atmosphere. LCMS and TLC of reaction mixture shows formation of desired Product. Then reaction mixture was filtered through celite bed and concentrated to get 1-benzyl 4-tert-butyl 2-(aminomethyl)piperazine-1,4-dicarboxylate (2.7 gm, 89 %) as gummy colourless liquid.

15 LCMS: m/z $[\text{M}+\text{H}]^+ = 350.3$ (calc. $m/z = 350.2$); RT = 1.60 min.

20

Step-3: Synthesis of 1-benzyl 4-tert-butyl 2-[(2-methoxy-2-oxoethyl)amino]methyl)piperazine-1,4-dicarboxylate :



To stirred solution of 1-benzyl 4-tert-butyl 2-(aminomethyl)piperazine-1,4-dicarboxylate (2.7 gm, 7.727 mmol, 1.0 eq.) in THF (25 ml) was added TEA (2.2 ml, 15.45 mmol, 2.0 eq.) under inert atmosphere. Then reaction mixture was reflux for overnight at 80°C under inert atmosphere. LCMS of reaction mixture shows formation of desired product. Then reaction mixture was extracted with EA and washed with water and dried over Na_2SO_4 which was concentrated and purified by combi-flash Chromatography (eluted with 30-35

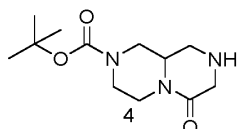
25

% EA-Hex solvent system) to afford 1-benzyl 4-tert-butyl 2-[[2-methoxy-2-oxoethyl)amino)methyl]piperazine-1,4-dicarboxylate (2.2 gm, 70%) as colourless gummy liquid.

LCMS: m/z $[M+H]^+ = 422.6$ (calc. $m/z = 422.22$); RT = 3.30 min.

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Step-4: Synthesis of tert-butyl 6-oxo-octahydro-1H-pyrazino[1,2-a]piperazine-2-carboxylate :

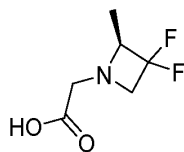


To a stirred solution of 1-benzyl 4-tert-butyl 2-[[2-methoxy-2-oxoethyl)amino)methyl]piperazine-1,4-dicarboxylate (110mg, 0.261 mmol, 1.0 eq.) in MeOH (6 ml) in 100 ml autoclave vessel, then reaction mixture was degassed under argon atmosphere. Then Pd/C (100mg, w/w) was added in reaction mixture, then reaction mixture was degassed and purged with H₂ 3 times. The reaction mixture was stirred at 50 °C for 16 hr under a H₂ atmosphere. TLC and LCMS of reaction mixture shows formation of desired product. Upon completion, then reaction mixture was filtered through celite bed and filtrate part was evaporated to give crude product which was purified by Combi-flash chromatography (eluted with 1 % MeOH-DCM solvent system) to afford tert-butyl 6-oxo-octahydro-1H-pyrazino[1,2-a]piperazine-2-carboxylate as a colourless gummy liquid (50 mg, 75%).

LCMS: m/z $[M+H]^+ = 256.1$ (calc. $m/z = 256.16$); RT = 2.30 min.

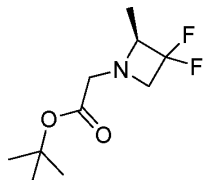
¹H NMR (400 MHz, DMSO-d₆, 100 °C : δ 4.39-4.36 (m, 1H), 3.89-3.83 (m, 1H), 3.34-3.32 (m, 1H), 3.24 (s, 2H), 3.12-3.07 (m, 1H), 2.77-2.50 (m, 4H), 1.41 (s, 9H), 1.27 (s, 2H).

Preparation 22: Synthesis of (S)-2-(3,3-difluoro-2-methylazetidin-1-yl)acetic acid:



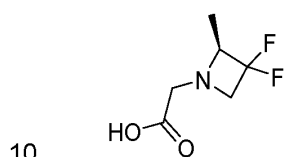
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Step 1: Synthesis of tert-butyl (S)-2-(3,3-difluoro-2-methylazetidin-1-yl)acetate



A slurry of (2S)-3,3-difluoro-2-methylazetidin-1-ium hydrochloride (150.0 mg, 1.04 mmol) and tert-butyl 2-bromoacetate (223.0 mg, 1.14 mmol) in DMF (3.0 mL) was stirred for 5 min, treated with KI (198.0 mg, 1.19 mmol) and stirred at RT for 16 h. EtOAc (10.0 mL) was added to the reaction mixture, washed with saturated aq NH₄Cl, water, and brine. The organics were dried (Na₂SO₄) and concentrated *in vacuo* to provide tert-butyl (S)-2-(3,3-difluoro-2-methylazetidin-1-yl)acetate (200.0 mg, crude), which was used in the next step without further purification. LCMS (Method A): RT 1.88 min; 222.09 [M+H]⁺.

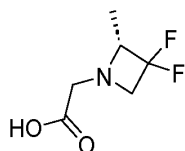
Step 2: Synthesis of (S)-2-(3,3-difluoro-2-methylazetidin-1-yl)acetic acid



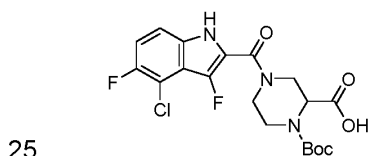
To a stirred solution of tert-butyl 2-[(SR)-3,3-difluoro-2-methylazetidin-1-yl]acetate (200.0 mg, crude) in DCM (5.0 ml) was added TFA (0.4 mL) and stirred at RT for 4h. The reaction mixture was concentrated, triturated with pentane and dried *in vacuo* to get (S)-2-(3,3-difluoro-2-methylazetidin-1-yl)acetic acid as TFA salt (175.0 mg, crude) which was used in next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 4.65 - 4.53 (m, 1H), 4.14 – 3.97 (m, 2H), 3.37 (s, 2H), 1.42 (d, *J* = 12.0 Hz, 3H).

Preparation 23: Synthesis of (R)-2-(3,3-difluoro-2-methylazetidin-1-yl)acetic acid:

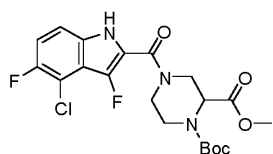
Same as Preparation 22, starting from (2R)-3,3-difluoro-2-methylazetidin-1-ium hydrochloride :



Preparation 24: Synthesis of 1-(tert-butoxycarbonyl)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl) piperazine-2-carboxylic acid:

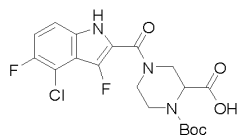


Step-1: 1-(tert-butyl) 2-methyl 4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazine-1,2-dicarboxylate



Amidation of 4-chloro-3,5-difluoro-1H-indole-2-carboxylic acid (500.0 mg, 2.16 mmol) and 1-(tert-butyl) 2-methyl piperazine-1,2-dicarboxylate (633.0 mg, 2.59 mmol) was done following amidation condition-A. The crude material was purified by combiflash column chromatography (eluent gradient: 20-30% EtOAc in hexane) to afford 1-(tert-butyl) 2-methyl 4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl) piperazine-1,2-dicarboxylate (820.0 mg, 83%) as a brown oil. LCMS (Method-H): RT 9.37 min; 458.2 [M+H]⁺.

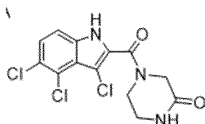
Step-2: 1-(tert-butoxycarbonyl)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazine-2-carboxylic acid



To a stirred solution of 1-(tert-butyl) 2-methyl 4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl) piperazine-1,2-dicarboxylate (820.0 mg, 1.79 mmol) in THF-Water (2:1, 10.0 mL) was added LiOH.H₂O (151.0 mg, 3.58 mmol) and stirred at rt for 16h. The reaction was monitored by LCSM, concentrated under reduced pressure, diluted with 1N HCl and extracted with EA (2 x 15.0 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to afford t1-(tert-butoxycarbonyl)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl) piperazine-2-carboxylic acid (680.0 mg, 85%) as a yellow sticky oil. ¹H NMR (400 MHz, DMSO-d₆) δ 12.97 (bs, 1H), 12.00 (bs, 1H), 7.36 - 7.26 (m, 2H) 4.66 - 4.59 (m, 1H), 4.01 (d, *J* = 12.5 Hz, 1H), 3.83 (d, *J* = 11.9 Hz, 1H), 3.32 (m, 2H merged with solvent peak) 3.22 - 3.11 (m, 2H), 1.42 (s, 9H). LCMS (Method A): RT 3.01 min; 444.0 [M+H]⁺.

Example 1

Synthesis of 4-(3,4,5-trichloro-1H-indole-2-carbonyl)piperazin-2-one

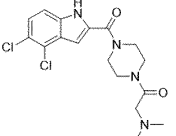
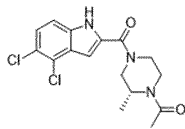
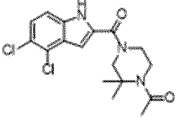
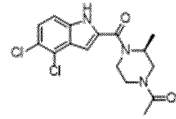
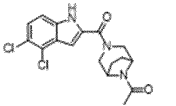


Step-1: Synthesis of 4-(3,4,5-trichloro-1H-indole-2-carbonyl)piperazin-2-one): Amidation of 3,4,5-trichloro-1H-indole-2-carboxylic acid (280 mg, 1.05 mmol, Preparation 1) and piperazin-2-one (127 mg, 1.27 mmol) was done following general condition-A to afford title compound (38 mg, 10%) as an off-white solid. Purification was done by reverse phase prep. HPLC following method A. ¹H NMR (400 MHz, DMSO-d₆): δ 12.49 (s, 1H), 8.19 (brs, 1H), 7.44 (s, 2H), 4.14 - 4.063 (m, 2H), 3.83 - 3.63 (m, 2H), 3.32 - 3.27 (m, 2H). LCMS (Method-A): RT 3.26 min; 344.0 [M-H]⁻.

Examples 2-20

Examples 2-20 were synthesized using conditions described in the general methods using the appropriate indole (described in the preparation section or commercially available) (Table 1).

Table 1

Ex. No.	Structure	Indole starting material	Amide coupling partner	Name	Amide bond formation method
2		Preparation 5	CAS# 1118-68-9	1-(4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one	B
3		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 1033709-36-2	1-[(2R)-4-(4,5-dichloro-1H-indole-2-carboxylic acid)-2-methyl-piperazin-1-yl]ethanone	B
4		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 1266872-99-4	1-[4-(4,5-dichloro-1H-indole-2-carboxylic acid)-2,2-dimethyl-piperazin-1-yl]ethanone	B
5		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 612493-89-7	1-[(3S)-4-(4,5-dichloro-1H-indole-2-carboxylic acid)-3-methyl-piperazin-1-yl]ethanone	B
6		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 67572-28-5	1-[3-(4,5-dichloro-1H-indole-2-carboxylic acid)-3,8-diazabicyclo[3.2.1]octan-8-yl]ethanone	B

7		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 848488-76-6	(3R)-1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidine-3-carboxamide	B
8		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 67572-28-5	4-(4,5-dichloro-1H-indole-2-carbonyl)piperazine-2-one	B
9		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 59702-07-7	4-(4,5-dichloro-1H-indole-2-carbonyl)-1-methyl-piperazine-2-one	B
10		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 13889-98-0	1-[4-(4,5-dichloro-1H-indole-2-carbonyl)piperazine-1-yl]ethanone	B
11		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 67572-28-5	4-(4,5-dichloro-6-fluoro-1H-indole-2-carbonyl)piperazine-2-one	B
12		Preparation 4	CAS# 67572-28-5	4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazine-2-one	B
13		Preparation 6	CAS# 1160161-52-3	(3R)-1-[(4,5-dichloro-1H-indol-2-yl)carbonyl]-N-methylpyrrolidine-3-carboxamide	B
14		4-chloro-1H-indole-2-carboxylic acid	CAS# 67572-28-5	4-(4-chloro-1H-indole-2-carbonyl)piperazine-2-one	B
15		Preparation 5	CAS# 625-45-6	1-[4-(4,5-dichloro-1H-indole-2-carbonyl)piperazine-1-yl]-2-methoxyethanone	B
16		Preparation 4	CAS# 13889-98-0	1-(4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-yl)ethan-1-one	B

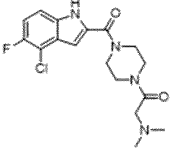
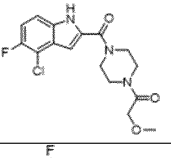
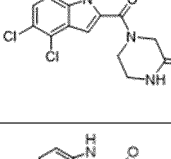
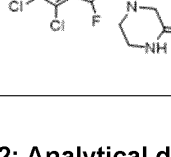
17		Preparation 4	CAS# 1118-68-9	1-[4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl]-2-(dimethylamino)ethanone	B
18		Preparation 4	CAS# 625-45-6	1-[4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl]-2-methoxyethanone	B
19		Preparation 7	CAS# 67572-28-5	4-(4,5-dichloro-7-fluoro-1H-indole-2-carbonyl)piperazin-2-one	A
20		Preparation 9	CAS# 67572-28-5	4-(4,5-dichloro-3-fluoro-1H-indole-2-carbonyl)piperazin-2-one	B

Table 2: Analytical data for Examples 2-20

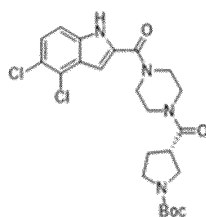
Example number	¹ H-NMR	Purification method	LCMS
2	(400 MHz, DMSO-d ₆): δ 12.30 – 12.10 (m, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.86 (s, 1H), 4.06 – 3.44 (m, 8H), 2.15 – 1.84 (m, 1H), 0.76 (t, J = 8.1 Hz, 4H).	Reverse phase prep. HPLC (Method-A)	Method-A: RT 2.66 min; 364.1 [M-H] ⁻
3	(400 MHz, DMSO-d ₆ , 100 °C) δ 12.18 – 11.44 (m, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 6.80 (s, 1H), 4.54 – 4.35 (m, 1H), 4.27 (d, J = 10.0 Hz, 1H), 4.17 – 4.11 (m, 1H), 4.08 – 3.87 (m, 1H), 3.41 (dd, J = 3.6, 13.2 Hz, 1H), 3.35 – 3.16 (m, 2H), 2.03 (s, 3H), 1.15 (d, J = 6.8 Hz, 3H).	Reverse phase Prep. HPLC: Method-C 100% ee	Method-A: RT 2.58 min; 306.0 [M-H] ⁻ .
4	(400 MHz, DMSO-d ₆ , 100 °C) δ 12.27 – 11.42 (m, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.7 Hz, 1H), 6.90 (s, 1H), 3.95 – 3.84 (m, 2H), 3.81 – 3.73 (m, 4H), 2.03 (s, 3H), 1.43 (s, 6H).	Reverse phase Prep. HPLC: Method-D	Method-A: RT 2.55 min; 368.1 [M+H] ⁺ .
5	(400 MHz, DMSO-d ₆ , 100 °C) δ 11.95 – 11.44 (m, 1H), 7.42 (dd, J = 3.6, 8.8 Hz, 1H), 7.17 (t, J = 9.2 Hz, 1H), 6.74 (s, 1H), 4.01 – 3.90 (m, 2H), 3.57 – 3.43 (m, 3H), 3.31 (s, 3H), 2.00 – 1.84 (m, 2H), 1.65 – 1.48 (m, 2H).	Reverse phase Prep. HPLC: Method-E 97.8% ee	Method-A: RT 2.42 min; 352.1 [M-H] ⁻ .
6	(400 MHz, DMSO-d ₆ , 100 °C) δ 12.14 – 11.33 (m, 1H), 7.44 (d, J = 8.8 Hz,	Reverse phase Prep. HPLC:	Method-B:

	1H), 7.34 (d, J = 8.4 Hz, 1H), 6.78 (s, 1H), 4.69 – 4.30 (m, 2H), 4.23 (d, J = 12.8 Hz, 2H), 3.53 – 3.10 (m, 2H), 2.04 (s, 3H), 2.00 – 1.79 (m, 2H), 1.76 – 1.61 (m, 2H).	Method-R	RT 2.67 min; 366.1 [M+H] ⁺ .
7	(400 MHz, DMSO-d ₆ , 100 °C) δ 12.23 – 11.48 (m, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.27 – 6.96 (m, 1H), 6.91 (s, 1H), 6.86 – 6.58 (m, 1H), 4.22 – 3.53 (m, 4H), 3.27 – 3.02 (m, 1H), 2.29 – 1.94 (m, 2H).	Reverse phase Prep. HPLC: Method-F 100% ee	Method-A: RT 2.31 min; 324.1 [M-H] ⁻ .
8	(400 MHz, DMSO-d ₆) δ 12.46 – 11.48 (m, 1H), 8.05 – 7.75 (m, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 6.88 (s, 1H), 4.26 (s, 2H), 3.91 (t, J = 5.6 Hz, 2H), 3.41 – 3.30 (m, 2H).	Reverse phase Prep. HPLC: Method-A	Method-A: RT 2.314 min; 310.0 [M-H] ⁻ .
9	(400 MHz, DMSO-d ₆ , 100 °C) δ 12.37 – 11.61 (m, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 6.89 (s, 1H), 4.32 (s, 2H), 4.03 – 3.96 (m, 2H), 3.54 – 3.38 (m, 2H), 2.91 (s, 3H).	Reverse phase Prep. HPLC: Method-J	Method-A: RT 2.38 min; 324.0 [M-H] ⁻ .
10	(400 MHz, DMSO-d ₆) δ 12.18 (s, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 6.84 (s, 1H), 4.00 – 3.63 (m, 4H), 3.62 – 3.49 (m, 4H), 2.04 (s, 3H).	Combiflash chromatography: Eluent gradient- 24-32% EtOAc in hexane	Method-A: RT 2.40 min; 338.1 [M-H] ⁻ .
11	(400 MHz, DMSO-d ₆): δ 12.19 – 11.74 (m, 1H), 7.97 – 7.70 (m, 1H), 7.40 (d, J = 9.2 Hz, 1H), 6.90 (s, 1H), 4.26 (s, 2H), 3.91 (t, J = 5.6 Hz, 2H), 3.35 (t, J = 6.0 Hz, 2H).	reverse phase prep. HPLC (Method-H)	(Method-A): RT 2.41 min; 328.0 [M-H] ⁻ .
12	(400 MHz, DMSO-d ₆): δ 12.22 – 11.98 (m, 1H), 8.20 (s, 1H), 7.42 (dd, J = 3.9, 9.2 Hz, 1H), 7.25 (t, J = 9.4 Hz, 1H), 6.92 (s, 1H), 4.96 – 4.06 (m, 2H), 4.10 – 3.78 (m, 2H), 3.14 – 2.79 (m, 1H).	reverse phase prep. HPLC (Method-F)	LCMS (Method-A): RT 2.23 min; 294.1 [M-H] ⁻ .
13	(400 MHz, DMSO-d ₆ , 100 °C): δ 11.94 – 11.71 (m, 1H), 7.79 – 7.54 (m, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 6.90 (s, 1H), 4.12 – 3.55 (m, 4H), 3.09 – 3.02 (m, 1H), 2.71-2.60 (m, 3H), 2.30 – 1.98 (m, 2H).	reverse phase prep. HPLC (Method-M)	LCMS (Method-B): RT 2.75 min; 338.1 [M-H] ⁻ .
14	(400 MHz, DMSO-d ₆): δ 12.02 (s, 1H), 8.20 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 6.89 (s, 1H), 4.56 – 4.14 (m, 2H), 3.92 (s, 2H), 3.30 (s, 2H).	reverse phase prep. HPLC (Method-K),	(Method-A): RT 2.14 min; 276.0 [M-H] ⁻ .
15	(400 MHz, DMSO-d ₆) δ 12.36 – 11.99 (m, 1H), 7.43 (d, J = 8.7 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.84 (s, 1H), 4.12 (s, 2H), 3.87 – 3.69 (m, 4H), 3.65 – 3.47 (m, 4H), 3.30 (s, 3H).	Reverse phase Prep. HPLC: Method-H	Method-B: RT 2.64 min; 368.1 [M+H] ⁺ .

16	(400 MHz, DMSO-d ₆) δ 11.75 (s, 1H), 7.44 (dd, J = 3.6, 8.8 Hz, 1H), 7.19 (t, J = 9.6 Hz, 1H), 6.82 (s, 1H), 3.81 – 3.73 (m, 4H), 3.63 – 3.56 (m, 4H), 2.04 (s, 3H).	Reverse phase prep. HPLC (Method-A)	(Method-A): RT 2.31 min; 324.1 [M+H] ⁺ .
17	(400 MHz, DMSO-d ₆) δ 12.07 (s, 1H), 7.41 (dd, J = 3.8, 8.8 Hz, 1H), 7.23 (t, J = 9.1 Hz, 1H), 6.86 (s, 1H), 3.94 – 3.62 (m, 6H), 3.56 (s, 2H), 3.10 (s, 2H), 2.19 (s, 6H).	Reverse phase Prep. HPLC: Method-E	Method-A: RT 2.14 min; 367.1 [M+H] ⁺ .
18	(400 MHz, DMSO-d ₆) δ 12.07 (s, 1H), 7.42 (dd, J = 3.8, 8.8 Hz, 1H), 7.23 (t, J = 9.3 Hz, 1H), 6.86 (s, 1H), 4.12 (s, 2H), 3.90 – 3.65 (m, 4H), 3.64 – 3.45 (m, 4H), 3.31 (s, 3H merged with solvent peak).	Reverse phase Prep. HPLC: Method-E	Method-A: RT 2.30 min; 352.1 [M-H] ⁻ .
19	(400 MHz, DMSO-d ₆ , 100 °C) δ 12.76 – 12.10 (m, 1H), 7.99 – 7.70 (m, 1H), 7.31 (d, J = 10.0 Hz, 1H), 6.90 (s, 1H), 4.21 (s, 2H), 3.85 (t, J = 5.2 Hz, 2H), 3.38 – 3.30 (m, 2H).	reverse phase prep. HPLC (Method-A)	(Method-A): RT 2.39 min; 328.0 [M-H] ⁻ .
20	(400 MHz, DMSO-d ₆) δ 12.70 – 11.59 (m, 1H), 8.16 (s, 1H), 7.36 (s, 2H), 4.31 – 4.04 (m, 2H), 3.82 (t, J = 5.3 Hz, 2H), 3.31 – 3.20 (m, 2H).	reverse phase prep. HPLC (Method-E)	(Method-A): RT 2.34 min; 328.0 [M-H] ⁻ .

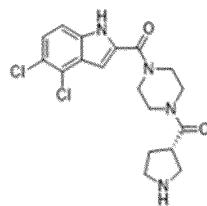
Example 21**Synthesis of (S)-(4,5-dichloro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone**

- 5 **Step-1:** Synthesis of tert-butyl(S)-3-(4-(4,5-dichloro-1H-indole-2-carbonyl)piperazine-1-carbonyl)pyrrolidine-1-carboxylate



- 10 Amidation of (4,5-dichloro-1H-indol-2-yl)(piperazin-1-yl)methanone (Preparation 5) and (S)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid was done following general condition-B. Crude material was used in the next step without further purification. Yield: 55% (crude). LCMS (Method-E): RT 2.58 min; 495.2 [M+H]⁺.

Step-2: Synthesis of (S)-(4,5-dichloro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone



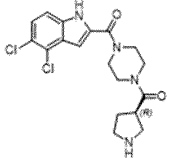
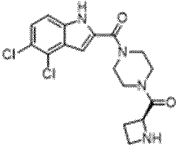
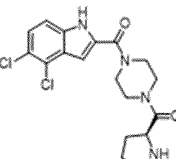
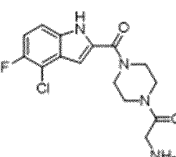
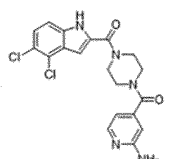
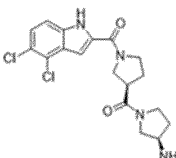
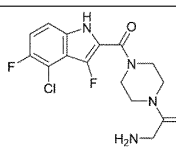
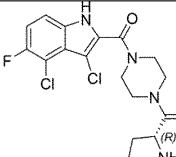
To a stirred solution of tert-butyl(S)-3-(4-(4,5-dichloro-1H-indole-2-carbonyl)piperazine-1-carbonyl) pyrrolidine-1-carboxylate (130 mg, 0.263 mmol) in DCM (5 mL), was added 4M HCl in dioxane (2 mL). The resulting solution was stirred at rt for 16 h. After the completion of the reaction which was monitored by LCMS, the reaction mixture was evaporated under reduced pressure to get the crude product. It was purified by reverse phase prep. HPLC (Method-A) to afford (S)-4-(4,5-dichloro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone, (40.0 mg, 38%, 96.6% ee) as a white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 7.43 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 6.83 (s, 1H), 3.79 - 3.75 (m, 4H), 3.65 - 3.59 (m, 4H), 3.21 - 3.19 (m, 1H), 3.05 - 3.01 (m, 1H), 2.97 - 2.93 (m, 1H), 2.87 - 2.81 (m, 2H), 1.95 - 1.90 (m, 1H), 1.86 - 1.81 (m, 1H) ppm. LCMS (Method B): RT 3.26 min; 395.2 [M+H]⁺.

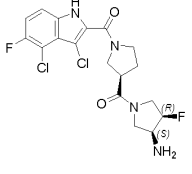
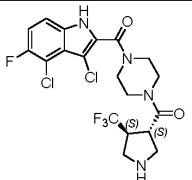
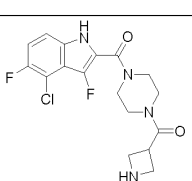
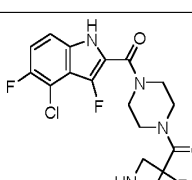
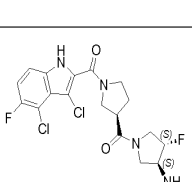
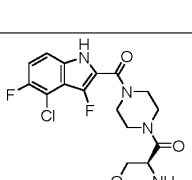
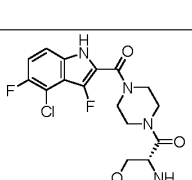
Examples 22-48

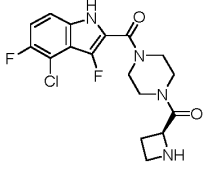
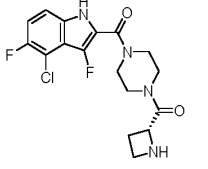
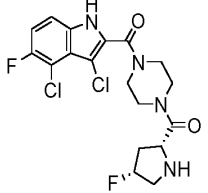
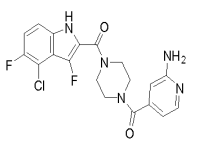
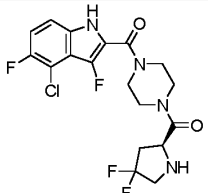
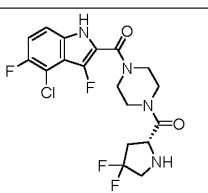
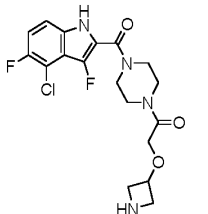
Examples 22-48 were made following similar methods described for Example 21 using the appropriate indole derivative.

Table 3

Ex.#	Structure	Indole Starting Material	Amide coupling partner	Name	Amide bond formation method
22		Preparation 5	CAS# 4530-20-5	2-amino-1-[4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl]ethanone	B
23		Preparation 5	CAS# 142253-55-2	[4-(azetidine-3-carbonyl)piperazin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone	B

24		Preparation 5	CAS# 72925-16-7	(4,5-dichloro-1H-indol-2-yl)-[4-[(3R)-pyrrolidine-3-carbonyl]piperazin-1-yl]methanone	B
25		Preparation 5	CAS# 51077-14-6	[4-[(2S)-azetidine-2-carbonyl]piperazin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone	B
26		Preparation 5	CAS# 15761-39-4	(4,5-dichloro-1H-indol-2-yl)-[4-[(2S)-pyrrolidine-2-carbonyl]piperazin-1-yl]methanone	B
27		Preparation 13	CAS# 4530-20-5	2-amino-1-[4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl]ethanone	B
28		Preparation 5	CAS# 365412-92-6	(4-(2-aminoisonicotinoyl)piperazin-1-yl)(4,5-dichloro-1H-indol-2-yl)methanone	A
29		Preparation 6	CAS# 122536-77-0	((R)-3-aminopyrrolidin-1-yl)((R)-1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone	B
30		Preparation 12	CAS# 4530-20-5	2-amino-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one	C
31		Preparation 11	CAS# 37784-17-1	(R)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-prolylpiperazin-1-yl)methanone	C

32		Preparation 15	CAS# 1033718-89-6	((3S,4R)-3-amino-4-fluoropyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone	A
33		Preparation 11	CAS# 1212064-03-3	(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((3S,4S)-4-(trifluoromethyl)pyrrolidine-3-carbonyl)piperazin-1-yl)methanone	A
34		Preparation 12	CAS# 142253-55-2	azetidin-3-yl(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)methanone	A
35		Preparation 12	CAS# 1126650-67-6	(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(3-fluoroazetidine-3-carbonyl)piperazin-1-yl)methanone	C
36		Preparation 15	CAS# 213388-72-8	((3S,4S)-3-amino-4-fluoropyrrolidin-1-yl)(®-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidine-3-yl)methanone	A
37		Preparation 12	CAS# 783350-37-8	S-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(morpholine-3-carbonyl)piperazin-1-yl)methanone	A
38		Preparation 12	CAS# 869681-70-9	®-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(morpholine-3-carbonyl)piperazin-1-yl)methanone	A

39		Preparation 12	CAS# 51077-14-6	(S)-azetidin-2-yl(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)methanone	A
40		Preparation 12	CAS# 228857-58-7	(R)-azetidin-2-yl(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)methanone	A
41		Preparation 11	CAS# 681128-51-8	(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4R)-4-fluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone	A
42		Preparation 12	CAS# 365412-92-6	(4-(2-aminoisonicotinoyl)piperazin-1-yl)(4-chloro-3,5-difluoro-1H-indol-2-yl)methanone	A
43		Preparation 12	CAS# 203866-15-3	(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone	A
44		Preparation 12	CAS# 536747-87-2	(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone	A
45		Preparation 12	CAS# 889952-83-4	2-(azetidin-3-yloxy)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one	A

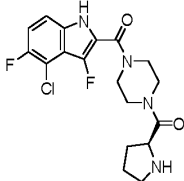
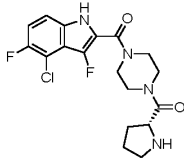
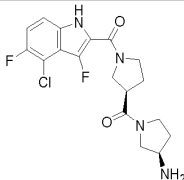
46		Preparation 12	CAS# 15761-39-4	(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-prolylpiperazin-1-yl)methanone	A
47		Preparation 12	CAS# 37784-17-1	(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-prolylpiperazin-1-yl)methanone	A
48		Preparation 14	CAS# 122536-77-0	((R)-3-aminopyrrolidin-1-yl) ((R)-1-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone	A

Table 4: Analytical data for Examples 22-48

Ex. No.	¹ H-NMR	Purification method	LCMS
22	(400 MHz, DMSO-d ₆) δ 8.26 (s, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 6.85 (s, 1H), 3.96 – 3.70 (m, 4H), 3.69 – 3.48 (m, 8H).	Reverse phase Prep. HPLC: Method-B	Method-D: RT 2.17 min; 355.0 [M+H] ⁺ .
23	(400 MHz, DMSO-d ₆) δ 12.31 – 11.98 (m, 1H), 7.47 – 7.34 (m, 2H), 6.84 (s, 1H), 4.13 – 3.83 (m, 5H), 3.84 – 3.69 (m, 4H), 3.66 – 3.54 (m, 2H), 3.47 – 3.34 (m, 2H).	Reverse phase Prep. HPLC: Method-D	Method-A: RT 2.17 min; 381.1 [M+H] ⁺ .
24	(400 MHz, DMSO-d ₆ , 100 °C) δ 7.45 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.82 (s, 1H), 3.82 – 3.72 (m, 4H), 3.68 – 3.59 (m, 4H), 3.16 (td, J = 6.9, 11.6, 12.7 Hz, 2H), 3.00 – 2.70 (m, 5H), 2.04 – 1.72 (m, 2H).	Reverse phase Prep. HPLC: Method-D	Method-B: RT 2.30 min; 395.2 [M+H] ⁺ .
25	(400 MHz, DMSO-d ₆ , 100 °C) δ 12.76 – 10.75 (m, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 6.81 (s, 1H), 4.39 (t, J = 6.4, 8.4 Hz, 1H), 3.92 – 3.69 (m, 4H), 3.63 – 3.45 (m, 4H), 3.44 – 3.29 (m, 2H), 2.65 – 2.53 (m, 1H), 2.42 – 2.29 (m, 1H).	Reverse phase Prep. HPLC: Method-E	Method-A: RT 2.22 min; 381.0 [M+H] ⁺ .

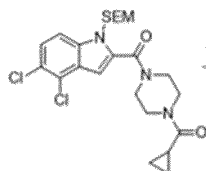
26	(400 MHz, DMSO- d_6) δ 12.40 – 12.06 (m, 1H), 8.36 (s, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 6.85 (s, 1H), 3.98 – 3.53 (m, 9H), 3.04 – 2.95 (m, 1H), 2.67 – 2.60 (m, 1H), 2.11 – 1.95 (m, 1H), 1.79 – 1.49 (m, 3H).	Reverse phase Prep. HPLC: Method-F	Method-A: RT 2.25 min; 395.1 [M+H] ⁺ .
27	(400 MHz, DMSO- d_6 , 100 °C) δ 7.44 (dd, J = 4.4, 8.8 Hz, 1H), 7.19 (t, J = 9.2 Hz, 1H), 6.82 (s, 1H), 3.78 (t, J = 5.2 Hz, 4H), 3.66 – 3.54 (m, 4H), 3.40 (s, 2H).	Reverse phase Prep. HPLC: Method-E	Method-A: RT 2.07 min; 337.1 [M-H] ⁻ .
28	¹ H NMR (400 MHz, DMSO- d_6): δ 12.17 (s, 1H), 8.07 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.85 (s, 1H), 6.45 (d, J = 8.6 Hz, 1H), 6.41 (s, 2H), 4.10 – 3.68 (m, 4H), 3.68 – 3.60 (m, 4H).	Reverse phase Prep. HPLC: Method-F	Method-A: RT 2.35 min; 418.0 [M+H] ⁺ .
29	¹ H NMR (400 MHz, DMSO- d_6 , 100 °C) δ 7.47 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.90 (s, 1H), 4.12 – 3.59 (m, 6H), 3.62 – 3.40 (m, 3H), 3.41 – 3.13 (m, 3H), 2.30 – 1.85 (m, 3H), 1.75 – 1.48 (m, 1H).	Reverse phase Prep. HPLC: Method-F	Method-B: RT 2.16 min; 395.1 [M+H] ⁺ .
30	¹ H NMR (400 MHz, DMSO- d_6 , 100 °C) δ 7.43 – 7.35 (m, 1H), 7.23 (t, J = 9.2 Hz, 1H), 3.74 – 3.49 (m, 8H), 3.40 (s, 2H).	Method A	Method C: RT 3.95 min; 357.1 [M+H] ⁺ .
31	¹ H NMR (400 MHz, DMSO- d_6 , 100 °C) δ 8.13 (brs, 1H), 7.47 – 7.39 (m, 1H), 7.24 (t, J = 9.2 Hz, 1H), 4.08 – 4.00 (m, 1H), 3.76 – 3.47 (m, 8H), 3.13 – 3.02 (m, 1H), 2.88 – 2.78 (m, 1H), 2.19 – 1.98 (m, 1H), 1.87 – 1.59 (m, 3H).	Method A	Method A: RT 2.27 min; 413.2 [M+H] ⁺ .
32	¹ H NMR (400 MHz, DMSO- d_6) δ 7.45 – 7.37 (m, 1H), 7.22 (t, J = 9.4 Hz, 1H), 5.07 – 4.78 (m, 1H), 3.85 – 3.46 (m, 9H), 3.36 – 3.08 (m, 2H), 2.26 – 1.95 (m, 3H).	Method Z	Method A: RT 2.05 min; 431.3 [M+H] ⁺ .
33	¹ H NMR (400 MHz, DMSO- d_6 , 100 °C) δ 12.24 (brs, 1H), 7.51 – 7.35 (m, 1H), 7.22 (t, J = 9.2 Hz, 1H), 3.78 – 3.53 (m, 6H), 3.50 – 3.12 (m, 4H), 2.97 – 2.81 (m, 3H), 2.85 – 2.74 (m, 1H).	Method Y	Method A: RT 2.79 min; 495.2 [M+H] ⁺ .
34	¹ H NMR (400 MHz, DMSO- d_6 , 100 °C) δ 7.41 – 7.37 (m, 1H), 7.24 (t, J = 9.4 Hz, 1H), 3.73 (s, 3H), 3.62 – 3.56 (m, 4H), 3.52 – 3.43 (m, 5H). NB: Two aliphatic protons merged with solvent peak.	Method M	Method A: RT 2.11 min; 383.2 [M+H] ⁺ .
35	¹ H NMR (400 MHz, DMSO- d_6 , 100 °C) δ 11.92 (brs, 1H), 8.12 (s, 1H), 7.43 – 7.36	Method AA	Method A: RT 2.27 min;

	(m, 1H), 7.24 (t, $J = 9.6$ Hz, 1H), 4.15 (dd, $J = 10.7, 21.2$ Hz, 2H), 3.84 (dd, $J = 10.7, 23.3$ Hz, 2H), 3.74 – 3.46 (m, 8H).		399.2 [M-H] ⁻ .
36	¹ H NMR (400 MHz, DMSO- d_6 , 100 °C) δ 13.95 – 10.07 (m, 1H), 7.45 – 7.36 (m, 1H), 7.22 (t, $J = 9.2$ Hz, 1H), 5.15 – 4.68 (m, 1H), 3.97 – 3.40 (m, 8H), 3.37 – 3.07 (m, 2H), 2.25 – 1.92 (m, 2H).	Method Z	Method A: RT 2.27 min; 399.2 [M-H] ⁻ .
37	¹ H NMR (401 MHz, DMSO- d_6 , 100 °C) δ 11.57 (s, 1H), 7.38 (d, $J = 8$ Hz, 1H), 7.22 (t, $J = 9.6$ Hz, 1H), 3.95 (s, 1H), 3.78 (d, $J = 8.8, 1$ Hz), 3.65 (s, 8H), 3.75 (t, $J = 10.4$ Hz, 2H), 2.84 (s, 2H)	Method AC	Method A: RT 2.25 min; 412.1 [M+H] ⁺ .
38	¹ H NMR (401 MHz, DMSO- d_6 , 100 °C) δ 11.60 (s, 1H), 7.37 (d, $J = 6.96$ Hz, 1H), 7.29 (t, $J = 9.52$ Hz, 1H), 3.77 (d, $J = 8.72$ Hz, 2H), 3.65 (s, 8H), 3.37 (t, $J = 10.8$ Hz, 2H), 2.82 (d, $J = 10$ Hz, 2H)	Method AB	Method A: RT 2.25 min; 412.1 [M+H] ⁺ .
39	¹ H NMR (401 MHz, DMSO- d_6 , 100 °C) δ 8.18 (s, 1H), 7.37 (s, 1H), 7.24 (s, 1H), 4.42 (s, 1H), 3.64 (s, 4H), 3.50 (s, 2H), 2.84 (s, 2H), 2.67-2.32 (m, 2H)	Method AB	Method A RT 2.21 min; 383.2 [M+H] ⁺ .
40	¹ H NMR (401 MHz, DMSO- d_6 , 100 °C) δ 8.20 (s, 1H), 7.38 (d, $J = 9.2$ Hz, 1H), 7.24 (t, $J = 18.8$ Hz, 1H), 4.41 (t, $J = 14$ Hz, 1H), 3.64 (s, 4H), 3.50(s, 4H), 3.36 (dd, $J = 15.2$ Hz, 7.6 Hz), 2.66-2.32 (m, 2H)	Method AB	Method A RT 2.21 min; 383.2 [M+H] ⁺ .
41	¹ H NMR (400 MHz, DMSO- d_6 , 100 °C) δ 12.09 (s, 1H), 7.43 (dd, $J = 8.8$ Hz, 4 Hz, 1H), 7.23 (t, $J = 9.2$ Hz, 1H), 5.25 (s, 1H), 5.11 (s, 1H), 3.89 (t, $J = 6.4$ Hz, 1H), 3.26 (s, 7H), 3.23-2.96 (m, 1H), 2.78-2.50-2.33(m, 2H), 2.40-2.309 (m, 1H), 1.97-1.85(m, 2H)	Method A	Method A RT 2.38 min; 431.2[M+H] ⁺
42	¹ H NMR (401 MHz, DMSO- d_6 ,) δ 11.96(s, 1H), 7.96 (d, $J = 5.2$ Hz, 1H), 7.37 (d, $J = 6.4$ Hz, 1H), 7.29 (t, $J = 9.4$ Hz, 1H), 6.47 (d, $J = 4.8$ Hz, 1H), 6.40(s, 1H), 6.13 (s, 2H), 3.70-3.63 (m, 6H), 3.40-3.35 (m, 2H)	Method AE	Method A: RT 2.36 min; 420.2[M+H] ⁺ .
43	¹ H NMR (400 MHz, DMSO- d_6 ,) δ 11.96(s, 1H), 7.38-7.35(m, 1H), 7.29 (t, $J = 9.4$ Hz, 1H), 4.23 (t, $J = 7.6$ Hz, 1H), 3.65-3.56 (m, 8H), 3.26 -3.17 (m, 2H), 3.04-2.94 (m, 1H), 2.43-2.32 (m, 1H)	Method AE	Method A: RT 2.54 min; 433.2[M+H] ⁺ .
44	¹ H NMR (400 MHz, DMSO- d_6 ,) δ 11.95(s, 1H), 7.37(m, 1H), 7.29 (t, $J = 9.4$ Hz, 1H), 4.23 (t, 1H), 3.65-3.56 (m, 8H), 3.23 -3.16 (m, 1H), 3.04-2.97 (m, 1H), 2.43-2.32 (m, 2H)	Method AE	Method H: RT 5.07 min; 433.2[M+H] ⁺

45	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.31 (s, 1H), 7.32-7.29 (m, 2H), 4.34-4.32 (m, 1H), 4.21 (s, 2H) 3.78-3.73 (m, 2H), 3.65-3.63 (m, 6H), 3.54-3.47 (m, 2H), 3.47-3.34 (m, 2H).	Method AB	Method A: RT 2.13 min; 413.2 [M+H] ⁺ .
46	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , at 100 °C) δ 8.16 (s, 1H), 7.39 (d, J=6.8Hz, 1H), 7.29 (t, J=9.6 Hz, 1H), 3.91 (m, 1H), 3.67-3.61 (m, 8H), 2.74 (brs, 1H), 2.01 (brs, 1H), 1.70-1.68 (m, 1H), 1.68 (brs, 3H).	Method AC	Method C: RT 2.13 min; 397.2 [M+H] ⁺ .
47	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , at 100 °C) δ 8.13 (s, 1H), 7.39 (d, J=6.8Hz, 1H), 7.29 (t, J=9.6 Hz, 1H), 3.91 (m, 1H), 3.67-3.61 (m, 8H), 3.02-3. (m, 1H), 2.74 (brs, 1H), 2.01 (brs, 1H), 1.68 (brs, 3H).	Method AC	Method C: RT 2.15 min; 397.2 [M+H] ⁺ .
48	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ 7.39-7.37 (m, 1H), 7.25-7.20 (m, 1H), 3.85-3.76 (m, 3H), 3.66 -3.64 (m, 2H), 3.52-3.46 (m, 2H), 3.31-3.15 (m, 2H), 2.17 (bs, 1H), 2.06-2.02 (m, 3H), 1.66-1.56 (bs, 2H)	Method A	Method B: RT 2.51 min; 397.2 [M+H] ⁺ .

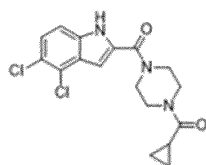
Example 49**Synthesis of (4-(cyclopropanecarbonyl)piperazin-1-yl)(4,5-dichloro-1H-indol-2-yl)methanone**

- 5 **Step-1:** Synthesis of (4-(cyclopropanecarbonyl)piperazin-1-yl)(4,5-dichloro-1-((2-(trimethyl silyl)ethoxy)methyl)-1H-indol-2-yl)methanone



- Amidation of (4,5-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indol-2-yl)(piperazin-1-yl)methanone hydrochloride (273 mg, 0.64 mmol, Preparation 2) and
 10 cyclopropanecarboxylic acid (50 mg, 0.581 mmol) was done following general condition-B to get the title compound (150.0 mg, 52%). Crude compound was pure enough to be used in the next step without further purification. LCMS (Method-D): RT 4.02 min; 496.1 [M+H]⁺.

- Step-2:** Synthesis of (4-(cyclopropanecarbonyl)piperazin-1-yl)(4,5-dichloro-1H-indol-2-yl)methanone
 15



To a stirred solution of (4-(cyclopropanecarbonyl)piperazin-1-yl)(4,5-dichloro-1-((2-(trimethylsilyl) ethoxy)methyl)-1H-indol-2-yl)methanone (150.0 mg, 0.35 mmol) in DCM (3.0 mL) was added TFA (0.05 mL, 0.70 mmol) at 0 °C and stirred at rt for 12 h. After completion (monitored by LCMS), the reaction mixture was concentrated under reduced pressure. The resulting crude material was dissolved in methanol (2 mL) and added Amberlyst-A21 till the solution become basic and stirred for 15 minutes at rt. The reaction mixture was filtered and filtrate was concentrated. The resulting crude was purified by reverse phase prep. HPLC (Method-A) to afford (4-(cyclopropanecarbonyl)piperazin-1-yl)(4,5-dichloro-1H-indol-2-yl)methanone (12.0 mg, 10 %) as white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 12.30 – 12.10 (m, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.86 (s, 1H), 4.06 – 3.44 (m, 8H), 2.15 – 1.84 (m, 1H), 0.76 (t, J = 8.1 Hz, 4H). LCMS (400 MHz, DMSO-d₆): δ 12.30 – 12.10 (m, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.86 (s, 1H), 4.06 – 3.44 (m, 8H), 2.15 – 1.84 (m, 1H), 0.76 (t, J = 8.1 Hz, 4H). (Method-A): RT 2.66 min; 364.1 [M-H]⁻.

Examples 50-52

Examples 50-52 were made using similar methods to those described for Example 49 (Table 5)

Table 5

Example number	Structure	Name	Amide bond formation method
50		[(3R)-3-(3-aminoazetidine-1-carbonyl)pyrrolidin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone	B
51		[(3R)-3-[(3S)-3-aminopyrrolidine-1-carbonyl]pyrrolidin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone	B

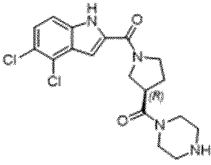
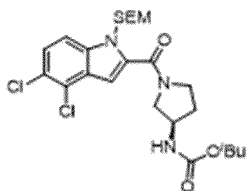
52		N-[1-(4-acetamidophenyl)sulfonyl-4-piperidyl]-3,5-dimethyl-1H-pyrrole-2-carboxamide	B
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Table 6: Analytical data for Examples 50-52

Example number	¹ H-NMR	Purification method	LCMS
50	(400 MHz, DMSO-d ₆ , 100 °C) δ 12.18 – 11.55 (m, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 6.90 (s, 1H), 4.55 – 3.32 (m, 9H), 3.17 – 3.08 (m, 1H), 2.24 – 1.97 (m, 2H), 1.90 (s, 2H).	Reverse phase Prep. HPLC: Method-I 92.6% ee	Method-B: RT 2.28 min; 381.2 [M+H] ⁺ .
51	(400 MHz, DMSO-d ₆ , 100 °C) δ 7.47 (d, J = 7.2 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 6.90 (s, 1H), 4.17 – 3.64 (m, 5H), 3.63 – 3.28 (m, 5H), 3.16 (dt, J = 5.5, 17.5 Hz, 1H), 2.30 – 1.87 (m, 3H), 1.82 – 1.53 (m, 2H).	Reverse phase Prep. HPLC: Method-C 100% ee	Method-A: RT 2.21 min; 395.1 [M+H] ⁺ .
52	(400 MHz, DMSO-d ₆ , 100 °C) δ 12.27 – 11.35 (m, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.90 (s, 1H), 4.01 – 3.68 (m, 4H), 3.56 – 3.37 (m, 5H), 2.82 – 2.65 (m, 4H), 2.30 – 2.01 (m, 2H).	Reverse phase Prep. HPLC: Method-A 91% ee	Method-A: RT 2.25 min; 395.1 [M+H] ⁺ .

Example 535 **(R)-N-(1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidin-3-yl)acetamide:**

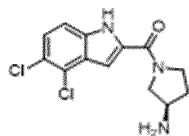
Step-1: Synthesis of tert-butyl (R)-(1-(4,5-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-2-carbonyl)pyrrolidin-3-yl)carbamate



10 Amidation of 4,5-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-2-carboxylic acid (200 mg, 0.557 mmol, Preparation 2) and tert-butyl (R)-pyrrolidin-3-ylcarbamate (123.6 mg, 0.669 mmol) was done following amidation condition-B to afford the title

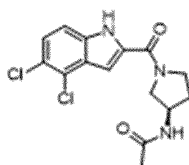
compound (250 mg, crude). The crude compound was used in the next step without further purification. LCMS (Method-B): RT 3.97 min; 528.3 [M+H]⁺.

Step-2: Synthesis of (R)-(3-aminopyrrolidin-1-yl)(4,5-dichloro-1H-indol-2-yl)methanone



5 The title compound was synthesized from tert-butyl (R)-(1-(4,5-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-2-carbonyl)pyrrolidin-3-yl)carbamate (130 mg, 0.247 mmol) following the deprotection procedure described in Example 21. The crude material was purified by reverse phase prep. HPLC (Method-O) to afford desired product, (36 mg, 50%, 98.8% ee) as an off-white solid. ¹H NMR (400 MHz, DMSO-d₆, 100 °C): δ 7.46 (d, J = 9.2 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.90 (s, 1H), 4.25 – 3.25 (m, 5H), 2.21 – 1.95 (m, 1H), 1.88 – 1.60 (m, 1H). LCMS (Method-B): RT 2.21 min; 298.1 [M+H]⁺.

Step-3: Synthesis of (R)-N-(1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidin-3-yl)acetamide

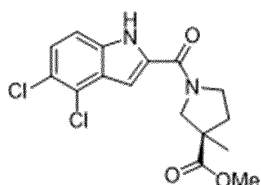


15 To a stirred solution of (R)-(3-aminopyrrolidin-1-yl)(4,5-dichloro-1H-indol-2-yl)methanone (250.0 mg, 0.842 mmol) in DCM was added Et₃N (0.351 mL, 2.527 mmol) at 0 °C and stirred for 10 min. Thereafter, acetyl chloride (0.089 mL, 1.26 mmol) was added dropwise into the reaction mixture at same temperature and stirred at rt for 3 h. After completion (monitored by LCMS), the reaction mixture was quenched with water and extracted with 10% MeOH in DCM (3 x 50 mL). The combined organic layer was washed with water followed by brine, dried over anhyd. Na₂SO₄ and then filtered. The filtrate was evaporated under reduced pressure. The resulting crude material was purified by reverse phase prep. HPLC (Method-P) to afford title compound, (40 mg, 14%, 100% ee) as an off-white solid. ¹H NMR (400 MHz, DMSO-d₆, 100 °C): δ 12.41 – 11.33 (m, 1H), 7.95 – 7.78 (m, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.90 (s, 1H), 4.34 (q, J = 5.6 Hz, 1H), 4.08 – 3.69 (m, 3H), 3.66 – 3.51 (m, 1H), 2.29 – 2.10 (m, 1H), 2.03 – 1.86 (m, 1H), 1.83 (s, 3H). (Method-B): RT 2.53 min; 340.2 [M+H]⁺.

30

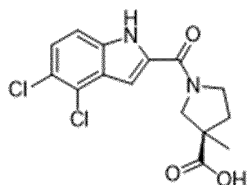
Example 54**Synthesis of (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpyrrolidine-3-carboxamide**

Step-1: Synthesis of methyl (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpyrrolidine-3-carboxylate



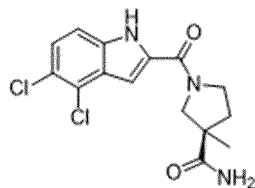
Amidation of 4,5-dichloro-1H-indole-2-carboxylic acid (120 mg, 0.524 mmol) and methyl (R)-3-methylpyrrolidine-3-carboxylate (82 mg, 0.576 mmol) was done following amidation condition-A. Resulting crude was purified by combiflash column chromatography (eluent gradient: 55%-60% EtOAc in hexane) to afford the title compound (150 mg, 80.58%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 12.13 (s, 1H), 7.48 – 7.35 (m, 2H), 6.95 (d, J = 10.4 Hz, 1H), 4.27 (d, J = 10.4 Hz, 1H), 4.11 – 3.86 (m, 1H), 3.77 (d, J = 10.5 Hz, 1H), 3.67 (d, J = 9.4 Hz, 3H), 3.45 (d, J = 12.2 Hz, 1H), 2.44 – 2.23 (m, 1H), 2.11 – 1.82 (m, 1H), 1.36 (s, 3H). LCMS (Method-F): RT 2.00 min; 355.1 [M+H]⁺.

Step-2: Synthesis of (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpyrrolidine-3-carboxylic acid



Hydrolysis of methyl (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpyrrolidine-3-carboxylate (100 mg, 0.282 mmol) was done following general hydrolysis condition to get title compound (90 mg, 93.38%) as a white solid. LCMS (Method-F): RT 1.48 min; 341.1 [M+H]⁺.

Step-3: Synthesis of (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpyrrolidine-3-carboxamide



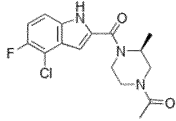
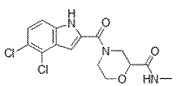
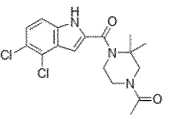
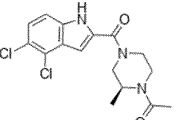
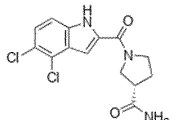
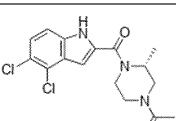
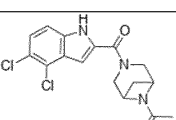
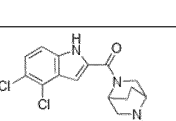
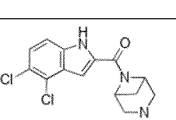
Amidation of (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpyrrolidine-3-carboxylic acid (90 mg, 0.265 mmol) with ammonium chloride (71 mg, 1.324 mmol) was done following amidation condition-A. The resulting crude material was purified by reverse phase prep. HPLC (Method-A) to afford title compound (20 mg, 22.2%, 100% ee) as a white solid. ¹H NMR (400 MHz, DMSO-d₆, 100 °C): δ 12.00 – 11.68 (m, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.22 – 6.55 (m, 3H), 4.44 – 3.32 (m, 4H), 2.45 – 2.30 (m, 1H), 2.03 – 1.71 (m, 1H), 1.33 (s, 3H). LCMS (Method-A): RT 2.36 min; 340.1 [M+H]⁺.

Examples 55-74

Examples 55-74 were synthesized using similar conditions to those described for Example 1 using the appropriate indole acid (described in the preparation section or commercially available) and in the general methods (Table 7).

Table 7

Ex. No.	Structure	Indole starting material	Amide coupling partner	Name	Amide bond formation method
55		Preparation 9	CAS# 13889-98-0	1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one	A
56		Preparation 9	CAS# 117810-52-3	2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro pyrrolo[1,2-a]pyrazin-6(2H)-one	A
57		Preparation 9	CAS# 937047-42-2	7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one	A
58		Preparation 9	CAS# 50606-31-0	methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate	A

59		Preparation 4	CAS# 612493-89-7	(S)-1-(4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one	B
60		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 135072-21-8	4-(4,5-dichloro-1H-indole-2-carbonyl)-N-methylmorpholine-2-carboxamide	B
61		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 1266867-75-7	1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-3,3-dimethylpiperazin-1-yl)ethan-1-one	B
62		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 211748-76-4	(S)-1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-2-methylpiperazin-1-yl)ethan-1-one	B
63		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 573704-64-0	(S)-1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidine-3-carboxamide	C
64		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 849149-47-9	(R)-1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one	B
65		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 1474024-25-3	1-(3-(4,5-dichloro-1H-indole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl)ethan-1-one	B
66		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 1541190-23-1	1-(5-(4,5-dichloro-1H-indole-2-carbonyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)ethan-1-one	B
67		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 1310717-00-0	1-(6-(4,5-dichloro-1H-indole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)ethan-1-one	B

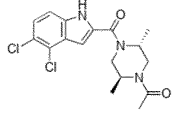
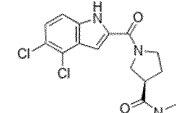
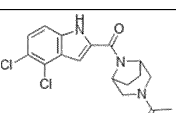
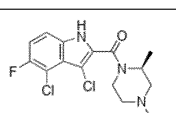
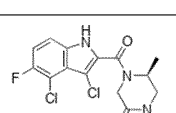
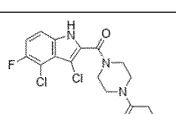
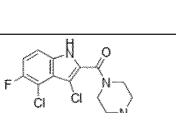
68		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 309915-46-6	1-((2S,5R)-4-(4,5-dichloro-1H-indole-2-carbonyl)-2,5-dimethylpiperazin-1-yl)ethan-1-one	B
69		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 1033705-59-7	(R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-N,N-dimethylpyrrolidine-3-carboxamide	B
70		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 1146852-27-8	1-(8-(4,5-dichloro-1H-indole-2-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)ethan-1-one	B
71		Preparation 9	CAS# 612493-89-7	(S)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one	C
72		Preparation 9	CAS# 1068149-94-9	(S)-4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,5-dimethylpiperazine-2-one	C
73		Preparation 11	CAS# 1118-68-9	1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one	B
74		Preparation 11	CAS# 625-45-6	1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one	B

Table 8: Analytical data for Examples 55-74

Ex. No.	¹ H-NMR	Purification method	LCMS
55	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 7.42 (dd, <i>J</i> = 4.1, 9.0 Hz, 1H), 7.23 (t, <i>J</i> = 9.4 Hz, 1H), 3.64 – 3.47 (m, 8H), 2.03 (s, 3H).	Method B	Method B: RT 2.59 min; 358.2 [M+H] ⁺ .
56	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.62 – 11.60 (m, 1H), 7.42 (dd, <i>J</i> = 3.6, 8.8 Hz, 1H), 7.23 (t, <i>J</i> = 9.2 Hz, 1H), 4.43 – 4.00 (m, 2H), 3.94 (d, <i>J</i> = 13.2 Hz, 1H), 3.67 – 3.55 (m, 1H), 2.90 – 2.78 (m, 3H),	Method A	Method A: RT 2.37 min; 369.9 [M+H] ⁺ .

	2.38 – 2.23 (m, 2H), 2.22 – 2.08 (m, 1H), 1.75 – 1.50 (m, 1H).		
57	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.71 – 11.07 (m, 1H), 7.43 (dd, <i>J</i> = 4.0, 9.0 Hz, 1H), 7.24 (t, <i>J</i> = 9.6 Hz, 1H), 4.39 (t, <i>J</i> = 8.8 Hz, 1H), 4.30 – 4.04 (m, 2H), 4.03 – 3.95 (m, 1H), 3.95 – 3.83 (m, 1H), 3.79 – 3.66 (m, 1H), 3.14 – 2.98 (m, 3H).	Method A	Method A: RT 2.42 min; 370.0 [M-H] ⁻ .
58	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.48 – 11.78 (m, 1H), 7.41 (dd, <i>J</i> = 3.6, 8.8 Hz, 1H), 7.22 (t, <i>J</i> = 9.2 Hz, 1H), 3.66 (s, 3H), 3.62 – 3.39 (m, 8H).	Method C	Method A: RT 2.63 min; 374.0 [M+H] ⁺ .
59	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.06 – 11.44 (m, 1H), 7.43 (dd, <i>J</i> = 4.0, 8.8 Hz, 1H), 7.18 (t, <i>J</i> = 9.6 Hz, 1H), 6.80 (s, 1H), 4.79 – 4.56 (m, 1H), 4.30 – 4.15 (m, 1H), 3.57 – 3.27 (m, 1H), 3.03 – 2.79 (m, 4H), 2.05 (s, 3H), 1.25 (d, <i>J</i> = 6.4 Hz, 3H).	Method D	Method B: RT 2.61 min; 338.2 [M+H] ⁺ .
60	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.89 (s, 1H), 7.65 – 7.51 (m, 1H), 7.45 (d, <i>J</i> = 8.8 Hz, 1H), 7.35 (d, <i>J</i> = 8.4 Hz, 1H), 6.84 (s, 1H), 4.43 (d, <i>J</i> = 13.2 Hz, 1H), 4.15 (d, <i>J</i> = 13.6 Hz, 1H), 4.07 – 3.95 (m, 3H), 3.73 – 3.62 (m, 1H), 3.43 – 3.23 (m, 2H), 2.67 (d, <i>J</i> = 4.0 Hz, 3H).	Method B	Method A: RT 2.35 min; 356.0 [M+H] ⁺ .
61	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.38 – 11.49 (m, 1H), 7.42 (d, <i>J</i> = 8.8 Hz, 1H), 7.33 (d, <i>J</i> = 8.0 Hz, 1H), 6.74 (s, 1H), 4.11 – 3.88 (m, 2H), 3.76 – 3.44 (m, 4H), 2.11 – 1.97 (m, 3H), 1.62 – 1.42 (m, 6H).	Method B	Method B: RT 2.66 min; 368.1 [M+H] ⁺ .
62	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.49 – 11.15 (m, 0H), 7.45 (d, <i>J</i> = 8.8 Hz, 1H), 7.34 (d, <i>J</i> = 8.8 Hz, 1H), 6.81 (s, 1H), 4.54 – 4.36 (m, 1H), 4.30 – 4.23 (m, 1H), 4.14 (d, <i>J</i> = 13.2 Hz, 1H), 4.08 – 3.89 (m, 1H), 3.46 – 3.36 (m, 1H), 3.34 – 3.18 (m, 2H), 2.04 (s, 3H), 1.15 (d, <i>J</i> = 6.4 Hz, 3H).	Method E	Method B: RT 2.66 min; 352.1 [M-H] ⁻ .
63	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.20 – 11.39 (m, 1H), 7.46 (d, <i>J</i> = 8.4 Hz, 1H), 7.34 (d, <i>J</i> = 8.8 Hz, 1H), 6.90 (s, 1H), 4.28 – 3.48 (m, 4H), 2.24 – 2.02 (m, 2H). NB: NH ₂ and one aliphatic proton merged with solvent peak	Method D	Method A: RT 2.38 min; 326.1 [M+H] ⁺ .
64	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.39 – 11.56 (m, 1H), 7.44 (d, <i>J</i> = 8.4 Hz, 1H), 7.34 (d, <i>J</i> = 8.8 Hz, 1H), 6.79 (s, 1H), 4.67 (s, 1H), 4.30 – 4.17 (m, 1H), 4.14 – 3.62 (m, 2H), 3.55 – 3.29 (m, 1H), 2.82 – 2.52 (m, 2H), 2.05 (s, 3H), 1.46 – 1.10 (m, 3H).	Method F	Method B: RT 2.95 min; 354.23 [M+H] ⁺ .

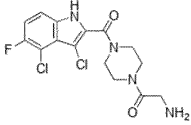
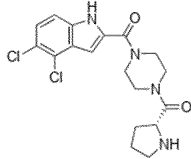
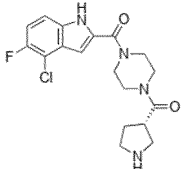
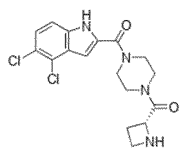
65	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.02 – 11.63 (m, 1H), 7.46 (t, <i>J</i> = 8.8 Hz, 1H), 7.35 (d, <i>J</i> = 8.7 Hz, 1H), 7.04 – 6.87 (m, 1H), 4.93 – 4.69 (m, 1H), 4.62 – 4.26 (m, 1H), 4.32 – 3.88 (m, 2H), 3.89 – 3.68 (m, 2H), 3.59 (d, <i>J</i> = 13.2 Hz, 1H), 1.95 (s, 2H), 1.87 (s, 1H), 1.61 (t, <i>J</i> = 8.4 Hz, 1H).	Method G	Method A: RT 2.39 min; 350.1 [M-H]-.
66	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.17 – 11.50 (m, 1H), 7.46 (d, <i>J</i> = 8.8 Hz, 1H), 7.35 (d, <i>J</i> = 8.4 Hz, 1H), 6.89 (s, 1H), 4.76 – 4.68 (m, 2H), 4.21 (s, 1H), 4.09 – 3.64 (m, 2H), 3.55 (q, <i>J</i> = 12.7 Hz, 1H), 2.04 (s, 3H), 1.95 (s, 1H), 1.93 – 1.80 (m, 3H).	Method G	Method A: RT 2.44 min; 364.1 [M-H]-.
67	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.02 – 11.69 (m, 1H), 7.51 – 7.42 (m, 1H), 7.39 – 7.33 (m, 1H), 7.01 – 6.89 (m, 1H), 5.00 – 4.67 (m, 1H), 4.64 – 4.36 (m, 1H), 4.28 – 3.87 (m, 2H), 3.86 – 3.69 (m, 2H), 3.66 – 3.52 (m, 1H), 2.81 (q, <i>J</i> = 6.9 Hz, 1H), 1.96 (s, 2H), 1.61 (t, <i>J</i> = 8.8 Hz, 1H).	Method B	Method A: RT 2.36 min; 350.1 [M-H]-.
68	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.15 – 11.56 (m, 1H), 7.44 (d, <i>J</i> = 8.8 Hz, 1H), 7.34 (d, <i>J</i> = 8.4 Hz, 1H), 6.75 (s, 1H), 4.86 – 4.54 (m, 1H), 4.44 – 3.88 (m, 2H), 3.74 – 3.34 (m, 2H), 3.22 – 3.00 (m, 1H), 2.24 – 1.88 (m, 3H), 1.57 – 0.93 (m, 6H).	Method B	Method A: RT 2.55 min; 366.1 [M-H]-.
69	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.31 – 11.37 (m, 1H), 7.47 (d, <i>J</i> = 8.8 Hz, 1H), 7.34 (d, <i>J</i> = 8.8 Hz, 1H), 6.90 (s, 1H), 4.14 – 3.63 (m, 4H), 3.62 – 3.40 (m, 1H), 2.32 – 1.95 (m, 2H). NB: Isopropyl proton merged with solvent peak	Method B	Method A: RT 2.58 min; 354.1 [M+H]+.
70	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , D ₂ O) δ 7.48 – 7.34 (m, 2H), 6.92 (s, 1H), 4.89 – 4.63 (m, 2H), 4.23 (d, <i>J</i> = 12.9 Hz, 1H), 3.87 – 3.74 (m, 1H), 3.58 – 3.26 (m, 1H), 2.95 – 2.74 (m, 1H), 2.03 (s, 3H), 1.98 – 1.68 (m, 3H), 1.63 – 1.48 (m, 1H).	Method B	Method A: RT 2.46 min; 364.1 [M-H]-.
71	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , D ₂ O) δ 7.42 (dd, <i>J</i> = 4.0, 9.0 Hz, 1H), 7.27 (t, <i>J</i> = 9.2 Hz, 1H), 3.68 – 3.60 (m, 2H), 3.59 – 3.49 (m, 2H), 3.40 – 3.05 (m, 4H), 2.47 – 2.30 (m, 8H), 2.29 – 1.82 (m, 4H).	Method F	Method B: RT 2.72 min; 372.2 [M+H]+.
72	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 13.45 – 11.00 (m, 1H), 7.43 (dd, <i>J</i> = 3.6, 8.8 Hz, 1H), 7.23 (t, <i>J</i> = 9.6 Hz, 1H), 4.53 – 4.37 (m, 1H), 4.24 (d, <i>J</i> = 18.0 Hz, 1H), 3.95 (d, <i>J</i> = 18.0 Hz, 1H), 3.71 (dd, <i>J</i> = 4.0, 12.4 Hz, 1H), 3.20 (d, <i>J</i> = 12.8 Hz, 1H), 2.92 (s, 3H), 1.29 (d, <i>J</i> = 6.4 Hz, 3H).	Method A	Method B: RT 2.41 min; 356.0 [M-H]-.

73	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.58 – 11.75 (m, 1H), 7.42 (dd, <i>J</i> = 4.4, 9.2 Hz, 1H), 7.23 (t, <i>J</i> = 9.2 Hz, 1H), 3.73 – 3.47 (m, 8H), 3.12 (s, 2H), 2.54 – 2.34 (m, 6H).	Method B	Method A: RT 2.27 min; 401.1 [M+H] ⁺ .
74	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.25 – 11.76 (m, 1H), 7.42 (dd, <i>J</i> = 4.0, 9.2 Hz, 1H), 7.22 (t, <i>J</i> = 9.6 Hz, 1H), 4.10 (s, 2H), 3.58 (s, 8H), 3.33 (s, 3H).	Method B	Method A: RT 2.38 min; 388.0 [M+H] ⁺ .

Examples 75-78

Examples 75-78 were made using similar methods described for Example 21 (Table 9)

Table 9

Ex. No.	Structure	Indole starting material	Amide coupling partner	Name	Amide bond formation method
75		Preparation 11	CAS# 4530-20-5	2-amino-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one	B
76		Preparation 5	CAS# 37784-17-1	(R)-(4,5-dichloro-1H-indol-2-yl)(4-propylpiperazin-1-yl)methanone	A
77		Preparation 13	CAS# 140148-70-5	(S)-(4-chloro-5-fluoro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone	B
78		Preparation 5	CAS# 228857-58-7	(R)-azetidin-2-yl(4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl)methanone	B

5

Table 10: Analytical data for Examples 75-78

Ex. No.	¹ H-NMR	Purification method	LCMS
75	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 7.42 (dd, <i>J</i> = 3.6, 8.8 Hz, 1H), 7.23 (t, <i>J</i> = 9.2 Hz, 1H), 3.64 – 3.48 (m, 8H), 3.40 (s, 2H).	Method A	Method B: RT 2.28 min;

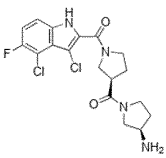
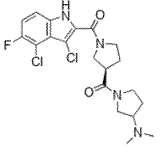
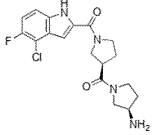
			373.2 [M+H] ⁺ .
76	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 7.45 (d, <i>J</i> = 8.4 Hz, 1H), 7.35 (d, <i>J</i> = 8.8 Hz, 1H), 6.82 (s, 1H), 3.91 – 3.82 (m, 1H), 3.83 – 3.73 (m, 4H), 3.70 – 3.59 (m, 4H), 2.79 – 2.69 (m, 1H), 2.09 – 1.92 (m, 2H), 1.78 – 1.57 (m, 4H).	Method D	Method B: RT 2.33 min; 395.3 [M+H] ⁺ .
77	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 7.44 (dd, <i>J</i> = 4.0, 8.8 Hz, 1H), 7.20 (t, <i>J</i> = 10.0 Hz, 1H), 6.83 (s, 1H), 3.81 – 3.73 (m, 4H), 3.68 – 3.60 (m, 4H), 3.20 – 3.07 (m, 1H), 2.95 – 2.73 (m, 2H), 2.51 – 2.32 (m, 3H), 2.00 – 1.78 (m, 2H).	Method D	Method B: RT 2.00 min; 379.3 [M+H] ⁺ .
78	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.70 – 10.42 (m, 1H), 7.45 (d, <i>J</i> = 8.8 Hz, 1H), 7.34 (d, <i>J</i> = 8.7 Hz, 1H), 6.81 (s, 1H), 4.40 (t, <i>J</i> = 7.8 Hz, 1H), 3.88 – 3.69 (m, 4H), 3.65 – 3.47 (m, 4H), 3.38 (q, <i>J</i> = 8.0 Hz, 2H), 2.65 – 2.57 (m, 2H), 2.44 – 2.33 (m, 1H).	Method D	Method C: RT 4.35 min; 381.0 [M+H] ⁺ .

Examples 79-83

Examples 79-83 were made using similar methods described for Examples 1 and 21 (Table 11)

5

Table 11

Ex. No.	Structure	Indole starting material	Amide coupling partner	Name	Amide bond formation method
79		Preparation 15	CAS# 122536-77-0	((R)-3-aminopyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone	B
80		Preparation 15	CAS# 69478-75-7	(3,4-dichloro-5-fluoro-1H-indol-2-yl)((3R)-3-(3-(dimethylamino)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)methanone	B
81		Preparation 16	CAS# 122536-77-0	((R)-3-aminopyrrolidin-1-yl)((R)-1-(4-chloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone	B

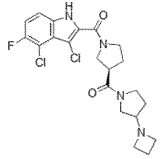
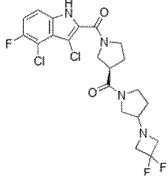
82		Preparation 15	CAS# 1018443-34-9	(3-(azetidin-1-yl)pyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone	B
83		Preparation 15	CAS# 1784688-01-2	(3,4-dichloro-5-fluoro-1H-indol-2-yl)((3R)-3-(3-(3,3-difluoroazetidin-1-yl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)methanone	B

Table 12: Analytical data for Examples 79-83

Ex. No.	¹ H-NMR	Purification method	LCMS
79	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 7.41 (dd, <i>J</i> = 4.0, 9.1 Hz, 1H), 7.22 (t, <i>J</i> = 9.2 Hz, 1H), 3.82 – 3.42 (m, 7H), 3.43 – 3.08 (m, 3H), 2.25 – 1.94 (m, 3H), 1.94 – 1.55 (m, 2H).	Method A	Method A: RT 2.19 min; 413.0 [M+H] ⁺ .
80	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , D ₂ O) δ 7.42 (dd, <i>J</i> = 4.0, 9.0 Hz, 1H), 7.27 (t, <i>J</i> = 9.2 Hz, 1H), 3.68 – 3.60 (m, 2H), 3.59 – 3.49 (m, 2H), 3.40 – 3.05 (m, 4H), 2.47 – 2.30 (m, 8H), 2.29 – 1.82 (m, 4H).	Method B	Method A: RT 2.36 min; 441.1 [M+H] ⁺ .
81	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.71 – 11.04 (m, 1H), 3.00 – 2.92 (m, 16H), 7.46 (dd, <i>J</i> = 4.0, 9.0 Hz, 1H), 7.19 (t, <i>J</i> = 9.6 Hz, 1H), 6.90 (s, 1H), 3.81 (dd, <i>J</i> = 36.5, 77.4 Hz, 5H), 3.60 – 3.42 (m, 2H), 3.41 – 3.26 (m, 2H), 3.25 – 3.12 (m, 1H), 3.10 – 3.00 (m, 1H), 2.30 – 2.18 (m, 1H), 2.15 – 1.85 (m, 2H), 1.87 – 1.43 (m, 2H).	Method D	Method A: RT 2.11 min; 379.1 [M+H] ⁺ .
82	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.44 – 11.50 (m, 1H), 7.40 (dd, <i>J</i> = 3.2, 8.4 Hz, 1H), 7.21 (t, <i>J</i> = 8.8 Hz, 1H), 3.84 – 3.47 (m, 5H), 3.41 – 3.18 (m, 3H), 3.20 – 3.06 (m, 4H), 2.95 – 2.72 (m, 1H), 2.24 – 2.11 (m, 1H), 2.10 – 1.49 (m, 6H).	Method A	Method A: RT 2.34 min; 453.1 [M+H] ⁺ .
83	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.62 – 11.30 (m, 1H), 7.40 (dd, <i>J</i> = 4.0, 8.8 Hz, 1H), 7.20 (t, <i>J</i> = 9.2 Hz, 1H), 3.86-3.47 (m, 9H), 3.48 – 3.04 (m, 5H), 2.26 – 2.11 (m, 1H), 2.09 – 1.41 (m, 3H).	Method A	Method A: RT 2.53 min; 489.0 [M+H] ⁺ .

Examples 84-88

5 Examples 84-88 were made using similar methods described for Example 1 (Table 13)

Table 13

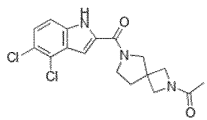
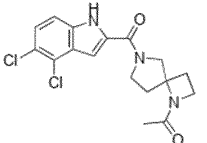
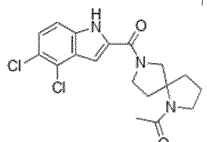
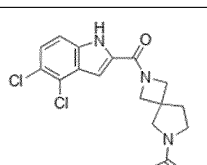
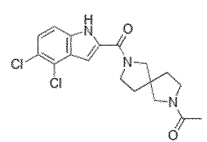
Ex. No.	Structure	Indole starting material	Amide coupling partner	Name	Amide bond formation method
84		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 1474026-88-4	1-(6-(4,5-dichloro-1H-indole-2-carboxyl)-2,6-diazaspiro[3.4]octan-2-yl)ethan-1-one	A
85		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 2445251-08-9	1-(6-(4,5-dichloro-1H-indole-2-carboxyl)-1,6-diazaspiro[3.4]octan-1-yl)ethan-1-one	B
86		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 1400797-53-6	1-(7-(4,5-dichloro-1H-indole-2-carboxyl)-1,7-diazaspiro[4.4]nonan-1-yl)ethan-1-one	B
87		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 1422067-02-4	1-(2-(4,5-dichloro-1H-indole-2-carboxyl)-2,6-diazaspiro[3.4]octan-6-yl)ethan-1-one	A
88		4,5-dichloro-1H-indole-2-carboxylic acid	CAS# 1181335-25-0	1-(7-(4,5-dichloro-1H-indole-2-carboxyl)-2,7-diazaspiro[4.4]nonan-2-yl)ethan-1-one	A

Table 14: Analytical data for Examples 84-88

Example number	¹ H-NMR	Purification method	LCMS
84	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.05 – 11.60 (m, 1H), 7.47 (d, <i>J</i> = 8.8 Hz, 1H), 7.35 (d, <i>J</i> = 8.8 Hz, 1H), 6.95 (s, 1H), 4.34 – 3.49 (m, 8H), 2.28 – 2.07 (m, 2H), 1.77 (s, 3H).	Method D	Method A: RT 2.45 min; 366.1 [M+H] ⁺ .
85	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.99 – 11.58 (m, 1H), 7.47 (d, <i>J</i> = 8.8 Hz, 1H), 7.35 (d, <i>J</i> = 8.8 Hz, 1H), 6.90 (s, 1H), 4.25 (s, 1H), 4.19 – 3.59 (m, 5H),	Method H	Method B: RT 2.69 min; 366.1 [M+H] ⁺ .

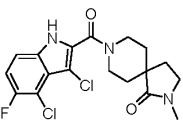
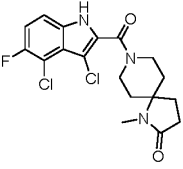
	2.75 – 2.57 (m, 1H), 2.45 – 2.02 (m, 3H), 1.74 (s, 3H).		
86	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.08 – 11.31 (m, 1H), 7.46 (d, <i>J</i> = 8.8 Hz, 1H), 7.34 (d, <i>J</i> = 9.2 Hz, 1H), 6.87 (s, 1H), 4.55 – 4.25 (m, 1H), 4.19 – 3.89 (m, 1H), 3.84 – 3.40 (m, 4H), 2.09 – 1.91 (m, 6H), 1.93 – 1.82 (m, 2H), 1.82 – 1.63 (m, 1H).	Method I	Method B: RT 2.68 min; 380.2 [M+H] ⁺ .
87	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.14 – 11.59 (m, 1H), 7.47 (d, <i>J</i> = 8.8 Hz, 1H), 7.36 (d, <i>J</i> = 8.4 Hz, 1H), 6.80 (s, 1H), 4.63 – 4.08 (m, 4H), 3.70 (s, 1H), 3.60 – 3.50 (m, 2H), 3.44 – 3.34 (m, 1H), 2.27 – 2.06 (m, 2H), 1.95 (s, 3H).	Method D	Method A: RT 2.51 min; 366.1 [M+H] ⁺ .
88	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.05 – 11.33 (m, 1H), 7.47 (d, <i>J</i> = 8.0 Hz, 1H), 7.35 (d, <i>J</i> = 8.4 Hz, 1H), 6.94 (s, 1H), 3.97 – 3.62 (m, 3H), 3.61 – 3.29 (m, 5H), 2.26 – 1.72 (m, 7H).	Method F	Method A: RT 2.45 min; 380.0 [M+H] ⁺ .

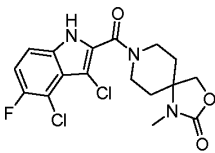
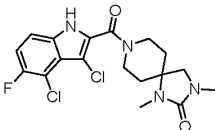
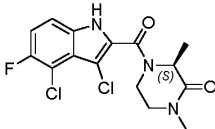
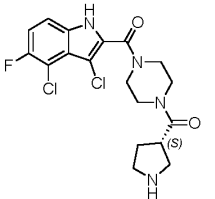
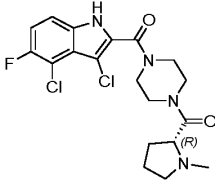
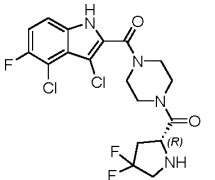
Examples 89-141

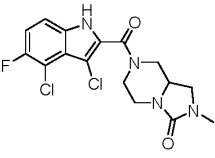
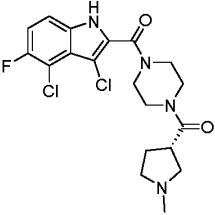
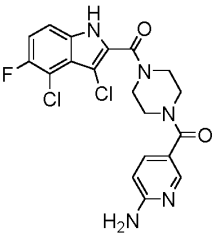
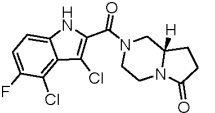
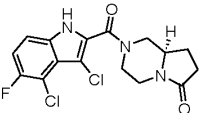
Examples 89-141 were synthesized using similar conditions to those described for

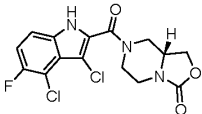
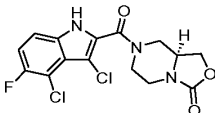
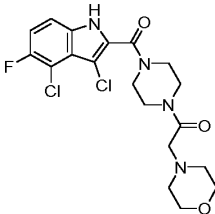
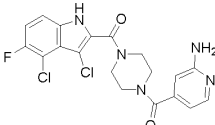
5 Examples 1 and 21 using the appropriate indole starting material (described in the Preparation section or commercially available) (Table 15).

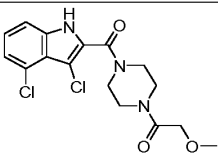
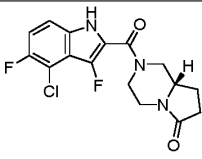
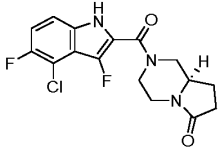
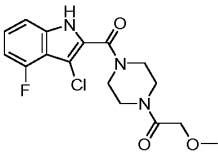
Table 15

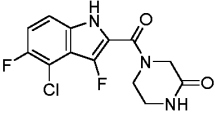
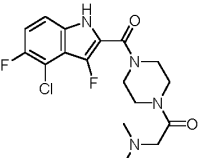
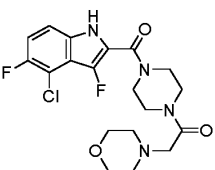
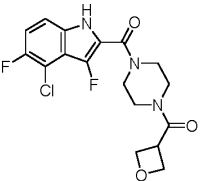
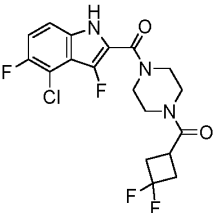
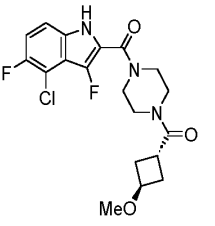
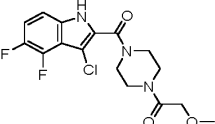
Ex. No.	Indole starting material	Structure	Amide coupling partner	Name	Amide bond formation method
89	Preparation 9		CAS# 546093-44-1	8-(3,4-dichloro-5-fluoro-1 <i>H</i> -indole-2-carbonyl)-2-methyl-2,8-diazaspiro[4.5]decan-1-one	C
90	Preparation 9		CAS# 1380300-63-9	8-(3,4-dichloro-5-fluoro-1 <i>H</i> -indole-2-carbonyl)-1-methyl-1,8-diazaspiro[4.5]decan-2-one	A

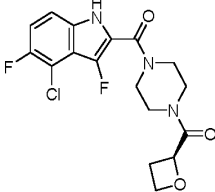
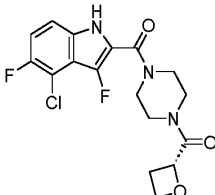
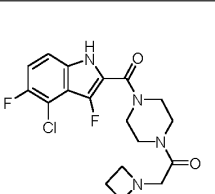
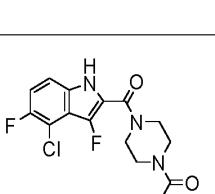
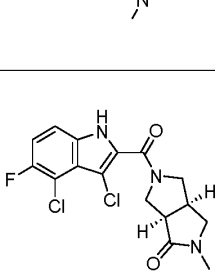
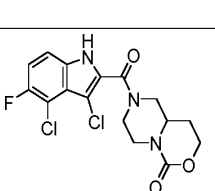
91	Preparation 9		CAS# 1556317-01-1	8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1-methyl-3-oxa-1,8-diazaspiro[4.5]decan-2-one	C
92	Preparation 9		CAS# 2580216-80-2	8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,3-dimethyl-1,3,8-triazaspiro[4.5]decan-2-one	A
93	Preparation 9		CAS# 1240300-34-8	(S)-4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,3-dimethylpiperazin-2-one	C
94	Preparation 11		CAS# 140148-70-5	(S)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone	B
95	Preparation 11		CAS# 58123-62-9	(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(methyl-D-propyl)piperazin-1-yl)methanone	B
96	Preparation 11		CAS# 536747-87-2	(R)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(4,4-difluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone	B

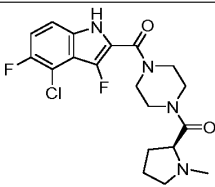
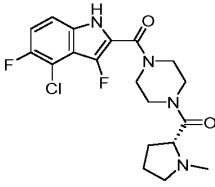
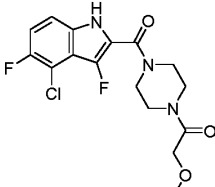
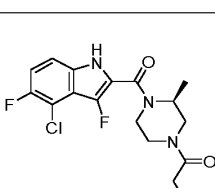
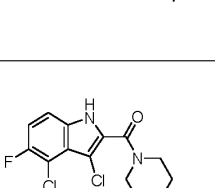
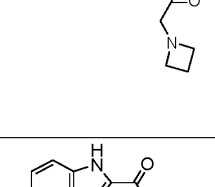
				razin-1-yl)methanone	
97	Preparation 9		CAS# 1256815-08-3	7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methylhexahydroimidazo[1,5-a]pyrazin-3(2H)-one	C
98	Preparation 11		CAS# 952484-58-1	(S)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(1-methylpyrrolidine-3-carbonyl)piperazin-1-yl)methanone	B
99	Preparation 11		CAS# 231958-14-8	(4-(6-aminonicotinoyl)piperazin-1-yl)(3,4-dichloro-5-fluoro-1H-indol-2-yl)methanone	C
100	Preparation 9		CAS# 151763-88-1	(S)-2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one Absolute stereochemistry not determined, assigned arbitrarily	A
101	Preparation 9		CAS# 151763-89-2	(R)-2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one	A

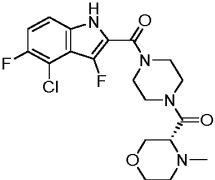
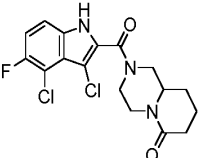
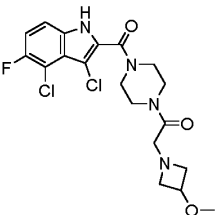
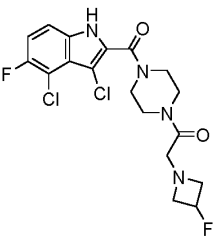
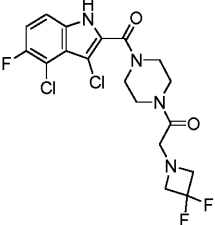
				o[1,2-a]pyrazin-6(2 <i>H</i>)-one Absolute stereochemis try not determined, assigned arbitrarily	
102	Preparation 9		CAS# 909187-55-9	(<i>R</i>)-7-(3,4-dichloro-5-fluoro-1 <i>H</i> -indole-2-carbonyl)hexahydro-3 <i>H</i> -oxazolo[3,4-a]pyrazin-3-one Absolute stereochemis try not determined, assigned arbitrarily	C
103	Preparation 9		CAS# 958693-53-3	(<i>S</i>)-7-(3,4-dichloro-5-fluoro-1 <i>H</i> -indole-2-carbonyl)hexahydro-3 <i>H</i> -oxazolo[3,4-a]pyrazin-3-one Absolute stereochemis try not determined, assigned arbitrarily	C
104	Preparation 11		CAS# 3235-69-6	1-(4-(3,4-dichloro-5-fluoro-1 <i>H</i> -indole-2-carbonyl)piperazin-1-yl)-2-morpholinoethan-1-one	A
105	Preparation 11		CAS# 365412-92-6	(4-(2-aminoisonicotinoyl)piperazin-1-	C

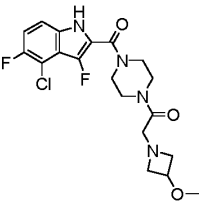
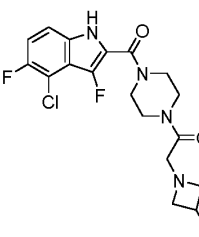
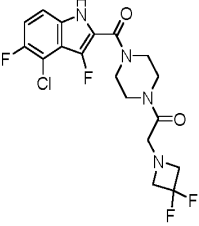
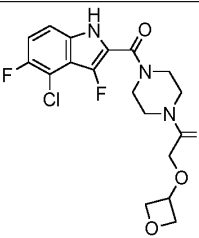
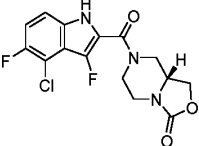
				yl) (3,4-dichloro-5-fluoro-1H-indol-2-yl) methanone	
106	Preparation 17		CAS# 95550-06-4	1-(4-(3,4-dichloro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one	A
107	Preparation 10		CAS# 151763-88-1	(S)-2-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one Absolute stereochemistry not determined, assigned arbitrarily	A
108	Preparation 10		CAS# 151763-89-2	(R)-2-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one Absolute stereochemistry not determined, assigned arbitrarily	A
109	3-chloro-4-fluoro-1H-indole-2-carboxylic acid		CAS# 95550-06-4	1-(4-(3-chloro-4-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one	A

110	Preparation 10		CAS# 5625-67-2	4-(4-chloro-3,5-difluoro-1 <i>H</i> -indole-2-carbonyl)piperazin-2-one	C
111	Preparation 12		CAS# 1118-68-9	1-(4-(4-chloro-3,5-difluoro-1 <i>H</i> -indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one	C
112	Preparation 12		CAS# 3235-69-6	1-(4-(4-chloro-3,5-difluoro-1 <i>H</i> -indole-2-carbonyl)piperazin-1-yl)-2-morpholinoethan-1-one	C
113	Preparation 12		CAS# 114012-41-8	(4-chloro-3,5-difluoro-1 <i>H</i> -indol-2-yl)(4-(oxetane-3-carbonyl)piperazin-1-yl)methanone	B
114	Preparation 12		CAS# 107496-54-8	(4-chloro-3,5-difluoro-1 <i>H</i> -indol-2-yl)(4-(3,3-difluorocyclobutane-1-carbonyl)piperazin-1-yl)methanone	A
115	Preparation 12		CAS# 1408076-05-0	(4-chloro-3,5-difluoro-1 <i>H</i> -indol-2-yl)(4-((1 <i>R</i> ,3 <i>R</i>)-3-methoxycyclobutane-1-carbonyl)piperazin-1-yl)methanone	B
116	Similar method to preparation 9 starting from ethyl		CAS# 625-45-6	1-(4-(3-chloro-4,5-difluoro-1 <i>H</i> -indole-2-carbonyl)piperazin-1-yl)ethan-1-one	B

	4,5-difluoro-1 <i>H</i> -indole-2-carboxylate			razin-1-yl)-2-methoxyethan-1-one	
117	Preparation 12		CAS# 2241107-29-7	(<i>S</i>)-(4-chloro-3,5-difluoro-1 <i>H</i> -indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone	A
118	Preparation 12		CAS# 2200583-25-9	(<i>R</i>)-(4-chloro-3,5-difluoro-1 <i>H</i> -indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone	A
119	Preparation 12		CAS# 1008304-81-1	2-(azetidin-1-yl)-1-(4-(4-chloro-3,5-difluoro-1 <i>H</i> -indole-2-carbonyl)piperazin-1-yl)ethan-1-one	A
120	Preparation 12		CAS# 875629-26-8	(4-chloro-3,5-difluoro-1 <i>H</i> -indol-2-yl)(4-(1-methylazetidin-3-carbonyl)piperazin-1-yl)methanone	C
121	Preparation 9		CAS# 1422134-66-4	(3 <i>aR</i> ,6 <i>aR</i>)-5-(3,4-dichloro-5-fluoro-1 <i>H</i> -indole-2-carbonyl)-2-methylhexahydroindolopyrrolo[3,4- <i>c</i>]pyrrol-1(2 <i>H</i>)-one	C
122	Preparation 9		CAS# 1423117-10-5	2-(3,4-dichloro-5-fluoro-1 <i>H</i> -indole-2-carbonyl)hexahydroindolopyrrolo[3,4- <i>c</i>]pyrrol-1(2 <i>H</i>)-one	A

				ahydro- 2 <i>H</i> ,6 <i>H</i> - pyrazino[1,2- c][1,3]oxazin- 6-one	
123	Preparation 12		CAS# 475-11-6	(4-chloro-3,5- difluoro-1 <i>H</i> - indol-2-yl)(4- (methyl-L- propyl)piperaz- in-1- yl)methanone	A
124	Preparation 12		CAS# 58123- 62-9	(4-chloro-3,5- difluoro-1 <i>H</i> - indol-2-yl)(4- (methyl-D- propyl)piperaz- in-1- yl)methanone	A
125	Preparation 12		CAS# 625-45-6	1-(4-(4- chloro-3,5- difluoro-1 <i>H</i> - indole-2- carbonyl)pipe- razin-1-yl)-2- methoxyetha- n-1-one	A
126	Preparation 10		CAS# 1568225- 99-9	(<i>S</i>)-1-(4-(4- chloro-3,5- difluoro-1 <i>H</i> - indole-2- carbonyl)-3- methylpiper- azin-1-yl)-2- methoxyetha- n-1-one	A
127	Preparation 11		CAS# 1008304- 81-1	2- (3,3-difluoro- 1-yl)-1-(4- (3,4-dichloro- 5-fluoro-1 <i>H</i> - indole-2- carbonyl) piperazin-1- yl) ethan-1- one	A
128	Preparation 12		CAS# 1315051- 74-1	(<i>S</i>)-(4-chloro- 3,5-difluoro- 1 <i>H</i> -indol-2-yl) (4-(4- methylmorph- oline-3-	A

				carbonyl) piperazin-1-yl) methanone	
129	Preparation 12		CAS# 1821837-71-1	(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4-methylmorpholine-3-carbonyl)piperazin-1-yl)methanone	A
130	Preparation 9		CAS# 151665-85-9	2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)octahydro-6H-pyrido[1,2-a]pyrazin-6-one	A
131	Preparation 11		CAS# 1781971-45-6	1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-methoxyazetidin-1-yl)ethan-1-one	A
132	Preparation 11		CAS# 2243503-23-1	1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-1-yl)ethan-1-one	A
133	Preparation 11		CAS# 1420271-48-2	1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one	A

				in-1-yl)ethan-1-one	
134	Preparation 12		CAS# 1781971-45-6	1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)pyrrolidin-1-yl)-2-(3-methoxyazetidin-1-yl)ethan-1-one	A
135	Preparation 12		CAS# 2243503-23-1	1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)pyrrolidin-1-yl)-2-(3-fluoroazetidin-1-yl)ethan-1-one	A
136	Preparation 12		CAS# 1420271-48-2	1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)pyrrolidin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one	A
137	Preparation 12		CAS# 1557814-84-2	1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)pyrrolidin-1-yl)-2-(oxetan-3-yloxy)ethan-1-one	A
138	Preparation 10		CAS# 909187-55-9	7-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one	A

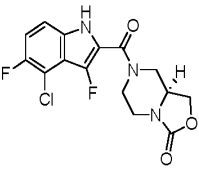
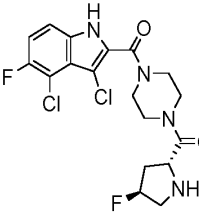
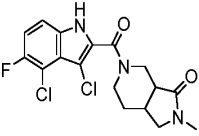
139	Preparation 10		CAS# 958693-53-3	(S)-7-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one	A
140	Preparation 11		CAS# 203866-13-1	(3,4-dichloro-5-fluoro-1H-indol-2-yl)((2R,4S)-4-fluoropyrrolidin-2-carbonyl)piperazin-1-ylmethanone	A
141	Preparation 9		CAS# 1242336-75-9	5-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methyloctahydro-3H-pyrrolo[3,4-c]pyridine-3-one	A

Table 16: Analytical data for Examples 89-141

Ex. No.	¹ H-NMR	Purification method	LCMS
89	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.10 (brs, 1H), 7.40 (dd, <i>J</i> = 4.0, 8.9 Hz, 1H), 7.22 (t, <i>J</i> = 9.2 Hz, 1H), 4.12 – 3.80 (m, 2H), 3.35 – 3.24 (m, 4H), 2.75 (s, 3H), 2.07 – 1.95 (m, 2H), 1.83 – 1.71 (m, 2H), 1.51 – 1.43 (m, 2H).	Method J	Method A: RT 2.44 min; 398.1 [M+H] ⁺ .
90	¹ H NMR (400 MHz, DMSO) δ 12.39 (brs, 1H), 7.47 – 7.39 (m, 1H), 7.33 – 7.24 (m, 1H), 4.55 – 4.50 (m, 1H), 3.65 – 3.60 (m, 1H), 2.99 – 2.60 (m, 1H), 2.61 – 2.56 (m, 3H), (2.62 – 2.61 (m, 2H), 2.00 – 2.01 (m, 2H), 2.02 – 1.84 (m, 2H), 1.85 – 1.77 (m, 3H)	Method A	Method A: RT 2.62 min; 396.2 [M-H] ⁻ .
91	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.06 (brs, 1H), 7.46 – 7.39 (m, 1H), 7.23 (t, <i>J</i> = 9.4 Hz, 1H), 4.27 (s, 2H), 4.12 – 4.08 (m, 2H), 3.16 – 3.05 (m, 2H), 2.69 (s, 3H), 1.97 – 1.85 (m, 2H), 1.67 (d, <i>J</i> = 13.0 Hz, 2H).	Method B	Method B: RT 2.41 min; 398.1 [M-H] ⁻ .
92	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.03 (brs, 1H), 7.46 – 7.38 (m, 1H), 7.23 (t,	Method H	Method A:

	$J = 9.4$ Hz, 1H), 4.11-4.07 (m, 2H), 3.12 (t, $J = 13.3$ Hz, 2H), 2.97 (s, 2H), 2.70 (s, 3H), 2.61 (s, 3H) 1.98 – 1.81 (m, 2H), 1.56 (d, $J = 12.9$ Hz, 2H).		RT 2.50 min; 411.1 [M-H] ⁻ .
93	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.44 (brs, 1H), 7.44 (dd, $J = 9.0, 4.0$ Hz, 1H), 7.30 (t, $J = 9.4$ Hz, 1H), 4.80 – 4.76 (m, 1H), 4.01 – 3.44 (m, 3H), 3.28 – 3.23 (m, 1H), 2.88 (s, 3H), 1.42 (s, 3H).	Method A	Method B: RT 2.73 min; 358.2 [M+H] ⁺ .
94	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 7.31 (dd, $J = 4.1, 8.8$ Hz, 1H), 6.99 (t, $J = 9.3$ Hz, 1H), 3.58 (s, 6H), 3.20 – 3.03 (m, 3H), 2.93 – 2.69 (m, 6H), 1.92 – 1.71 (m, 2H).	Method D	Method B: RT 2.11 min; 413.2 [M+H] ⁺ .
95	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.01 (brs, 1H), 7.46 – 7.38 (m, 1H), 7.23 (t, $J = 9.6$ Hz, 1H), 3.67 (s, 4H), 3.57 (s, 4H), 3.24 – 3.22 (m, 1H), 2.94 (s, 3H), 2.05 (s, 2H), 1.91– 1.79 (m, 4H).	Method B	Method B: RT 2.22 min; 427.0 [M+H] ⁺ .
96	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.00 (brs, 1H), 7.46 – 7.39 (m, 1H), 7.24 (t, $J = 9.3$ Hz, 1H), 4.28 – 4.19 (m, 1H), 3.63 – 3.60 (m, 8H), 3.28 – 3.17 (m, 1H), 3.11 – 3.03 (m, 2H), 3.02 – 2.98 (m, 2H), 2.44 – 2.36 (m, 1H), two-protons merged with solvent peak.	Method G	Method A: RT 2.50 min; 449.0 [M+H] ⁺ .
97	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.05 (brs, 1H), 7.42 (dd, $J = 4.0, 9.0$ Hz, 1H), 7.23 (t, $J = 9.6$ Hz, 1H), 4.30 – 3.90 (m, 2H), 3.75 – 3.58 (m, 2H), 3.40 (t, $J = 8.8$ Hz, 1H), 3.07 – 3.00 (m, 1H), 2.96 – 2.84 (m, 2H), 2.70 (s, 3H).	Method A	Method A: RT 2.43 min; 385.1 [M+H] ⁺ .
98	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.179 (s, 1H, formate), 7.43 (dd, $J = 4.0, 9.0$ Hz, 1H), 7.23 (t, $J = 9.6$ Hz, 1H), 3.58 (brs, 6H), 3.27 – 3.25 (m, 1H), 2.96 – 2.75 (m, 2H), 2.60 – 2.49 (m, 3H), 2.41 (s, 1H), 2.14 (s, 3H), 2.15 – 1.96 (m, 2H).	Method F	Method A: RT 2.23 min; 312.1 [M-H] ⁻ .
99	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 8.08 (s, 1H), 7.48 (d, $J = 8.7$ Hz, 1H), 7.45 – 7.39 (m, 1H), 7.23 (t, $J = 9.4$ Hz, 1H), 6.49 (d, $J = 8.7$ Hz, 1H), 6.04 (s, 2H), 3.62 (s, 8H).	Method D	Method A: RT 2.33 min; 436.1 [M+H] ⁺ .
100	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.02 (brs, 1H), 7.47 – 7.39 (m, 1H), 7.23 (t, $J = 9.6$ Hz, 1H), 4.38 – 4.01 (m, 2H), 3.98 – 3.89 (m, 1H), 3.69 – 3.50 (m, 1H), 3.09 – 3.00 (m, 1H), 2.86 (d, $J = 13.3$ Hz, 2H), 2.38 – 2.22 (m, 2H), 2.21 – 2.08 (m, 1H), 1.72 – 1.54 (m, 1H).	Method K Chiral Purification method (SFC): Method A	Method A: RT 2.40 min; 368.1 [M-H] ⁻ .
101	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.20 (brs, 1H), 7.47-7.39 (m, 1H), 7.23 (t, J	Method K	Method A:

	= 9.6 Hz, 1H), 4.34 – 4.00 (m, 2H), 3.98 – 3.89 (m, 1H), 3.71 – 3.52 (m, 1H), 2.92 – 2.77 (m, 3H), 2.38 – 2.22 (m, 2H), 2.21 – 2.08 (m, 1H), 1.72 – 1.54 (m, 1H).		RT 1.69 min; 370.1 [M+H] ⁺ .
102	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.41 (brs, 1H), 7.43 (dd, <i>J</i> = 9.0, 4.0 Hz, 1H), 7.30 (t, <i>J</i> = 9.2 Hz, 1H), 4.70 – 4.24 (m, 2H), 3.91 – 3.62 (m, 5H), 3.26 – 3.14 (m, 1H), 3.04 (t, <i>J</i> = 12.0 Hz, 1H).	Method K Chiral Purification method (SFC): Method B	Method A: RT 2.47 min; 372.1 [M+H] ⁺ .
103	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.41 (brs, 1H), 7.43 (dd, <i>J</i> = 9.0, 4.1 Hz, 1H), 7.29 (t, <i>J</i> = 9.2 Hz, 1H), 4.46 (t, <i>J</i> = 64.8 Hz, 2H), 4.16 – 3.58 (m, 5H), 3.28 – 3.13 (m, 1H), 3.03 (t, <i>J</i> = 11.4 Hz, 1H).	Method K Chiral Purification method (SFC): Method B	Method A: RT 2.48 min; 372.1 [M+H] ⁺ .
104	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.39 (brs, 1H), 7.42 (dd, <i>J</i> = 8 Hz, <i>J</i> = 4 Hz 1H), 7.28 (t, <i>J</i> = 12 Hz, 1H), 3.63-3.55 (m, 12H), 3.17 (brs, 2H), 2.40-2.32 (m, 4H)	Method E	Method B: RT 2.31 min; 443.4 [M+H] ⁺ .
105	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.07 (brs, 1H), 7.97 (d, <i>J</i> = 4 Hz, 1H), 7.41 (dd, <i>J</i> = 8 Hz, <i>J</i> = 3.6 Hz, 1H), 7.22 (t, <i>J</i> = 8 Hz, 1H), 6.49-6.45 (m, 2H), 5.81 (brs, 2H), 3.60-3.57 (m, 8H),	Method E	Method B: RT 2.59 min; 436.2 [M+H] ⁺ .
106	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 7.35 (d, <i>J</i> = 8 Hz, 1H), 7.08 (d, <i>J</i> = 7.6 Hz, 1H), 7.01 (d, <i>J</i> = 7.6 Hz, 1H), 4.10 (s, 2H), 3.60-3.53 (m, 8H), 3.32 (s, 3H).	Method E	Method H: RT 2.38 min; 370.2 [M+H] ⁺ .
107	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.84 (brs, 1H), 7.38 (d, <i>J</i> = 6.8 Hz, 1H), 7.23 (t, <i>J</i> = 9.6 Hz, 1H), 4.49 - 4.45 (m, 2H), 4.14 - 4.12 (m, 1H), 3.92 (d, <i>J</i> = 10.4 Hz, 1H), 3.58 - 5.59 (m, 1H), 2.79 (t, <i>J</i> = 9.6 Hz, 2H), 2.32 - 2.26 (m, 2H), 2.12-2.07 (m, 1H), 1.23 - 1.11 (m, 1H).	Chiral Purification method (SFC): Method C	Method H: RT 2.36 min; 352.2 [M-H] ⁻ .
108	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.96 (brs, 1H), 7.35 (d, <i>J</i> = 6.8 Hz, 1H), 7.24 (t, <i>J</i> = 9.6 Hz, 1H), 4.49 - 4.45 (m, 2H), 4.14 - 4.12 (m, 1H), 3.92 (d, <i>J</i> = 10.4 Hz, 1H), 3.58 - 5.59 (m, 1H), 2.79 (t, <i>J</i> = 9.6 Hz, 2H), 2.32 - 2.26 (m, 2H), 2.12 - 2.07 (m, 1H), 1.23 - 1.11 (m, 1H).	Chiral Purification method (SFC): Method C	Method H: RT 2.36 min; 352.2 [M-H] ⁻ .

109	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.3 (brs, 1H), 7.31 – 7.17 (m, 2H), 6.95 – 6.86 (m, 1H), 4.12 (s, 2H), 3.82 – 3.41 (m, 8H), 3.29 (s, 3H).	Method C	Method A: RT 2.29 min; 354.2 [M+H] ⁺ .
110	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.5 (brs, 1H), 8.18 (s, 1H), 7.42 – 7.34 (m, 1H), 7.30 (t, <i>J</i> = 9.2 Hz, 1H), 4.14 (s, 2H), 3.80 (t, <i>J</i> = 5.4 Hz, 2H), 3.33 – 3.23 (m, 2H).	Method O	Method A: RT 2.23 min; 312.1 [M-H] ⁻ .
111	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.94 (brs, 1H), 7.40 – 7.34 (m, 1H), 7.29 (t, <i>J</i> = 9.3 Hz, 1H), 3.71 – 3.58 (m, 6H), 3.58 – 3.48 (m, 2H), 3.10 (s, 2H), 2.19 (s, 6H).	Method C	Method A: RT 2.23 min; 383.2 [M-H] ⁻ .
112	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.51 (m, 1H), 7.43 – 7.36 (m, 1H), 7.29 – 7.19 (m, 1H), 3.84 – 3.49 (m, 12H), 3.20 (s, 2H), 2.49 – 2.35 (m, 4H).	Method A	Method A: RT 2.44 min; 427.2 [M+H] ⁺ .
113	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.76 – 11.40 (m, 1H), 7.43 – 7.35 (m, 1H), 7.23 (t, <i>J</i> = 9.2 Hz, 1H), 4.72 (d, <i>J</i> = 7.6 Hz, 4H), 4.21 – 4.09 (m, 1H), 3.76 – 3.21 (m, 8H).	Method U	Method A: RT 2.34 min; 382.2 [M-H] ⁻ .
114	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.10 (brs, 1H), 7.42 – 7.34 (m, 1H), 7.28 (t, <i>J</i> = 9.2 Hz, 1H), 3.67 – 3.53 (m, 6H), 3.53 – 3.45 (m, 2H), 2.88 – 2.74 (m, 4H).	Method D	Method A: RT 2.67 min; 416.2 [M-H] ⁻ .
115	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.01 (brs, 1H), 7.41 – 7.34 (m, 1H), 7.31 (t, <i>J</i> = 9.1 Hz, 1H), 3.88 – 3.78 (m, 1H), 3.71 – 3.47 (m, 6H), 3.46 – 3.38 (m, 2H), 3.31 – 3.22 (m, 1H), 3.11 (s, 3H), 2.44 – 2.36 (m, 2H), 2.18 – 2.04 (m, 2H).	Method V	Method A: RT 2.50 min; 412.2 [M+H] ⁺ .
116	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 7.25 (d, <i>J</i> = 4.4 Hz, 2H), 4.10 (s, 2H), 3.64 – 3.53 (m, 8H), 3.33 (s, 3H).	Method Y	Method A: RT 2.33 min; 372.2 [M+H] ⁺ .
117	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.51 (m, 1H), 7.43 – 7.35 (m, 1H), 7.23 (t, <i>J</i> = 9.6 Hz, 1H), 5.41 (t, <i>J</i> = 7.2 Hz, 1H), 4.57 (q, <i>J</i> = 7.2 Hz, 1H), 4.50 – 4.41 (m, 1H), 3.69 – 3.62 (m, 4H), 3.56 – 3.50 (m, 4H), 2.94 – 2.72 (m, 2H).	Method X	Method A: RT 2.35 min; 382.2 [M-H] ⁻ .
118	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.50 (brs, 1H), 7.43 – 7.34 (m, 1H), 7.23 (t, <i>J</i> = 9.6 Hz, 1H), 5.41 (t, <i>J</i> = 7.6 Hz, 1H), 4.62	Method Q	Method A: RT 2.36 min; 384.1 [M+H] ⁺ .

	– 4.52 (m, 1H), 4.49 – 4.39 (m, 1H), 3.86 – 3.32 (m, 8H), 2.94 – 2.69 (m, 2H).		
119	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.92 (brs, 1H), 7.39 – 7.31 (m, 1H), 7.27 (t, <i>J</i> = 9.2 Hz, 1H), 3.73 – 3.41 (m, 11H), 3.19 (t, <i>J</i> = 7.2 Hz, 3H), 2.05 – 1.91 (m, 2H).	Method V	Method A: RT 2.18 min; 397.2 [M+H] ⁺ .
120	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.50 (brs, 1H), 7.43 – 7.35 (m, 1H), 7.23 (t, <i>J</i> = 9.2 Hz, 1H), 3.76 – 3.59 (m, 4H), 3.58 – 3.32 (m, 7H), 3.16 (s, 2H), 2.20 (s, 3H).	Method C	Method A: RT 2.17 min; 397.2 [M+H] ⁺ .
121	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.82 (m, 1H), 7.44 – 7.36 (m, 1H), 7.22 (t, <i>J</i> = 9.4 Hz, 1H), 3.91 – 3.69 (m, 3H), 3.62 – 3.54 (m, 1H), 3.43 – 3.34 (m, 1H), 3.19 – 3.06 (m, 3H), 2.76 (s, 3H).	Method E	Method A: RT 2.37 min; 370.1 [M+H] ⁺ .
122	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.82 (m, 1H), 7.47 – 7.39 (m, 1H), 7.24 (t, <i>J</i> = 9.4 Hz, 1H), 4.31 – 3.88 (m, 6H), 3.63 – 3.52 (m, 1H), 3.13 (t, <i>J</i> = 12.5 Hz, 1H), 2.92 – 2.87 (m, 1H), 2.20 – 2.11 (m, 1H), 1.84 – 1.72 (m, 1H).	Method W	Method B: RT 2.65 min; 386.17 [M+H] ⁺ .
123	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆) δ 11.95 (s, 1H), 7.38 (d, <i>J</i> = 6.44 Hz, 1H), 7.30 (d, <i>J</i> = 9.6 Hz, 1H), 3.80 – 3.47 (m, 9H), 3.16 (s, 1H), 2.97 (s, 1H), 2.24 (s, 3H), 2.08 (s, 1H), 1.74 (s, 1H)	Method AB	Method A: RT 2.25 min; 411.2 [M+H] ⁺ .
124	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 8.23 (s, 1H), 7.38 (d, <i>J</i> = 9.2 Hz, 1H), 7.23 (t, <i>J</i> = 9.6 Hz, 1H), 3.67 (d, <i>J</i> = 10.2 Hz, 6H), 3.25 (d, <i>J</i> = 6.4 Hz 4H), 2.50(s, 4H), 2.30 (d, <i>J</i> =16.8 Hz,3H), 2.07-1.79 (m, 4H)	Method AB	Method A RT 2.21 min; 411.2 [M+H] ⁺ .
125	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.58 (s, 1H), 7.38 (d, <i>J</i> = 8.8 Hz, 1H), 4.11 (s, 2H), 3.66-3.56 (m, 8H), 2.50(s, 4H), 3.34 (s, 3H)	Method AB	Method A RT 2.38 min; 371 [M+H] ⁺ .
126	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.95 (s, 1H), 7.32 (s, 1H), 7.26(s, 1H) 4.11 (s, 2H), 3.66-3.56 (m, 8H), 2.50(s, 4H), 3.34 (s, 3H)	Method AC	Method A RT 2.44 min; 386.2[M+H] ⁺ .
127	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.28 (s, 1H), 7.41 (dd, <i>J</i> =4.0Hz, 3.6 Hz, 1H), 7.21 (t, <i>J</i> =9.2Hz, 1H), 3.49(m, 8H), 3.32-3.23(m, 2H), 3.16(t, <i>J</i> =6.6 Hz, 4H), 1.96(t, <i>J</i> =6.6 Hz, 2H)	Method AE	Method A: RT 2.24 min; 413.2[M+H] ⁺ .
128	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.96(s, 1H), 7.38-7.36 (m, 1H), 7.29 (t, <i>J</i> = 9.6 Hz,	Method AE	Method A: RT 2.33 min;

	1H), 3.89(t, 2H), 3.72 – 3.55 (m, 9H), 3.47(t, J=10.6 Hz, 1H), 3.20 (d, J=9.2 Hz, 1H), 2.77 (d, J=11.6 Hz, 1H), 2.19 – 2.16 (m, 4H).		427.2[M+H] ⁺ .
129	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.95(s, 1H), 7.37 (d, J = 6.4 Hz, 1H), 7.29 (t, J = 9.4 Hz, 1H), 3.93-3.89 (m, 2H), 3.72-3.44(m, 10H), 3.20(d, J=7.6 Hz, 1H), 2.77(d, J=11.6 Hz, 1H), 2.22-2.16 (m, 4H).	Method AE	Method B: RT 2.36 min; 427.2[M+H] ⁺ .
130	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.09 (s, 1H), 7.41(dd, J=4.8 Hz, J= 8.8 Hz, 1H), 7.22 (t, 9.2, 1H), 4.50 (d, J=12 Hz, 1H), 4.06 (brs, 2H), 3.47 (t, 1H), 2.99 (m, 1H), 2.92-2.89 (m, 1H), 2.70-2.67 (m, 1H), 2.28-2.27 (m, 2H), 1.95(m, 1H), 1.78 (m, 1H), 1.66(m, 1H), 1.52-1.44 (m, 1H)	Method AB	Method A: RT 2.48 min; 384.1[M+H] ⁺
131	¹ H NMR (400 MHz, MeOD) δ 7.35 (dd, J = 3.88 Hz, 3.96 Hz, 1H), 7.16 (t, J = 9.44 Hz, 1H), 4.10-4.07 (m, 1H), 3.79-3.47 (m, 12H), 3.30-3.25 (m, 3H), 3.16-3.12 (m, 2H)	Method A	Method A: RT 2.39 min; 443.2 [M+H] ⁺ .
132	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.89 (bs, 1H), 7.44-7.42 (m, 1H), 7.26-7.21 (m, 1H), 5.24-5.09 (m, 1H), 3.64-3.60 (m, 4H), 3.60-3.49 (m, 5H), 3.39-3.32 (m, 3H), 3.23-3.17 (m, 2H)	Method AB	Method C: RT 6.96 min; 431.2 [M+H] ⁺ .
133	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.34 (bs, 1H), 7.44-7.41 (m, 1H), 7.31-7.26 (m, 1H), 3.68-3.51 (m, 6H), 3.51-3.32 (m, 8H)	Method A	Method A: RT 2.60 min; 449.2 [M+H] ⁺ .
134	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.62 (bs, 1H), 7.38-7.37 (m, 1H), 7.24 (t, J = 9.2 Hz, 1H), 4.01-3.99 (m, 1H), 3.64-3.58 (m, 10H), 3.54 (s, 2H), 3.18 (m, 2H), 2.99 (s, 3H)	Method A	Method A: RT 2.26 min; 427 [M+H] ⁺ .
135	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.54 (bs, 1H), 7.39-7.37 (m, 1H), 7.26-7.21 (m, 1H), 5.24-5.09 (m, 1H), 3.65-3.57 (m, 10H), 3.39 (s, 2H), 3.30-3.24 (m, 2H)	Method A	Method A: RT 2.36 min; 415 [M+H] ⁺ .
136	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.95 (bs, 1H), 7.39-7.37 (m, 1H), 7.29 (t, J = 9.64 Hz, 1H), 3.71-3.60 (m, 8H), 3.53-3.50 (m, 6H)	Method A	Method A: RT 2.50 min; 433 [M+H] ⁺ .
137	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.95 (s, 1H), 7.37-7.32 (m, 1H), 7.32-7.29 (m, 1H), 4.65-4.58 (m, 3H), 4.48-4.45 (m, 2H), 4.23 (s, 2H), 3.64-3.53 (m, 4H), 3.53-3.47 (m, 4H)	Method AD	Method C: RT 4.62 min; 414.2 [M+H] ⁺ .
138	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , at 100 °C) δ 11.66 (brs, 1H), 7.39 (d, J=6.8Hz, 1H), 7.24 (t, J=9.6 Hz, 1H), 4.42-4.35 (m, 2H), 4.22	Chiral Purification	Method C: RT 2.45 min; 354.1 [M-H] ⁻ .

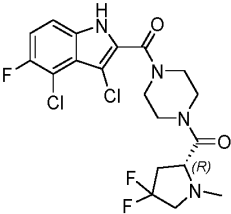
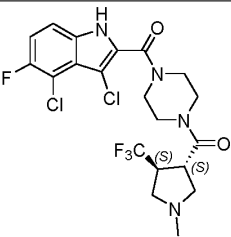
	(d, J=8Hz, 1H), 4.02 (t, J=8.8Hz, 1H), 3.91-3.89 (m, 1H), 3.72 (t, J=9.2Hz, 1H), 3.095-3.075 (m, 3H).	method (SFC):	
		Method A	
139	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , at 100 °C) δ 11.58 (brs, 1H), 7.39 (d, J=6.8Hz, 1H), 7.24 (t, J=9.6 Hz, 1H), 4.42-4.35 (m, 2H), 4.22 (d, J=8Hz, 1H), 4.02 (t, J=8.8Hz, 1H), 3.91-3.89 (m, 1H), 3.72 (t, J=9.2Hz, 1H), 3.095-3.075 (m, 3H).	Chiral Purification method (SFC):	Method C: RT 2.45 min; 354.1 [M-H] ⁻ .
		Method A	
140	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , at 100 °C) δ 12.01 (brs, 1H), 7.43 (dd, J1=4Hz, J2=4Hz, 1H), 7.23 (t, J=9.6 Hz, 1H), 5.25 (d, J=55.6 Hz, 1H), 4.13 (t, J=8.8Hz, 1H), 3.62-3.60 (m, 8H), 3.16-3.07 (m, 2H), 2.18-2.01 (m, 2H).	Method A	Method B: RT 2.09 min; 431.2 [M+H] ⁺ .
141	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , at 100 °C) δ 12.03 (brs, 1H), 7.43 (dd, J1=4Hz, J2=4Hz, 1H), 7.21 (t, J=9.6 Hz, 1H), 4.05 (brs, 1H), 3.86 (s, 1H), 3.50 (brs, 2H), 3.12-3.06 (m, 2H), 2.76 (s, 3H), 2.66-2.61 (m, 2H), 1.92-1.88 (m, 1H), 1.25-1.21 (m, 1H).	Method A	Method C: RT 2.45 min; 384.2 [M+H] ⁺ .

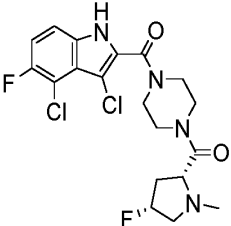
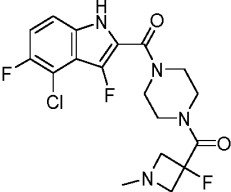
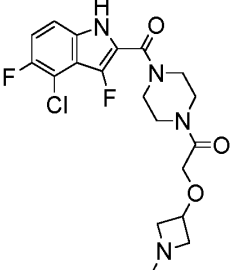
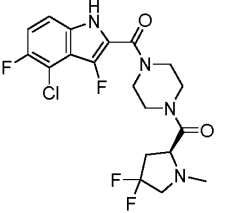
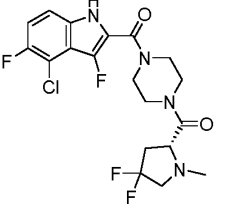
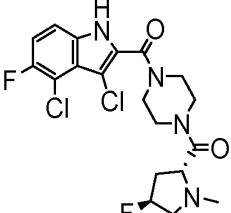
Examples 142-149

Examples 142-149 were made using general reductive amination condition A

5

Table 17: Examples 142-149

Ex. No.	Starting material	Structure	Name	Reductive amination method
142	Example 98		(<i>R</i>)-(3,4-dichloro-5-fluoro-1 <i>H</i> -indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone	A
143	Example 33		(3,4-dichloro-5-fluoro-1 <i>H</i> -indol-2-yl)(4-((3 <i>S</i> ,4 <i>S</i>)-1-methyl-4-(trifluoromethyl)pyrrolidine-3-carbonyl)piperazin-1-yl)methanone	A

144	Example 41		(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4R)-4-fluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone	A
145	Example 35		(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(3-fluoro-1-methylazetidine-3-carbonyl)piperazin-1-yl)methanone	A
146	Example 45		1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-((1-methylazetidin-3-yl)oxy)ethan-1-one	A
147	Example 43		(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone	A
148	Example 44		(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone	A
149	Example 140		(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4S)-4-fluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone	A

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Table 18: Analytical data for Examples 142-149

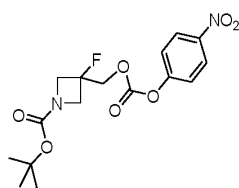
Example number	¹ H-NMR	Purification method	LCMS
142	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆) δ 12.36 (brs, 1H), 7.43 (dd, <i>J</i> = 4.0, 9.0 Hz, 1H), 7.29 (t, <i>J</i> = 9.6 Hz, 1H), 3.73 – 3.63 (m, 6H), 3.50 (m, 2H), 3.36 – 3.33 (m, 1H), 2.67 (m, 1H), 2.54 – 2.50 (m, 2H), 2.38 – 2.33 (m, 1H), 2.28 (s, 3H).	Method G	Method B: RT 2.74 min; 463.3 [M+H] ⁺ .
143	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.91 (brs, 1H), 7.47 – 7.39 (m, 1H), 7.23 (t, <i>J</i> = 9.2 Hz, 1H), 3.80 – 3.50 (m, 8H), 3.49 – 3.33 (m, 1H), 3.18 – 3.00 (m, 1H), 2.97 – 2.84 (m, 1H), 2.73 (d, <i>J</i> = 6.4 Hz, 2H), 2.42 (t, <i>J</i> = 8.1 Hz, 1H), 2.26 (s, 3H).	Method Y	Method A: RT 2.33 min; 372.2 [M+H] ⁺ .
144	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.02 (s, 1H), 7.42 (dd, <i>J</i> = 8.8 Hz, 4 Hz, 1H), 7.28 (t, <i>J</i> = 9.2 Hz, 1H), 5.23 (s, 1H), 5.09 (s, 1H), 3.70-3.58 (m, 8H), 3.21-2.97 (m, 2H), 2.66-2.55 (m, 1H), 2.40-2.32 (m, 2H), 2.27 (s, 3H), 2.05-1.95 (m, 2H) F120	Method A	Method A RT 2.44 min; 445.2 [M+H] ⁺
145	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.96 (s, 1H), 7.39-7.37 (m, 1H), 7.32-7.27 (m, 1H), 3.77-3.60 (m, 8H), 3.43-3.41 (m, 3H), 3.35-3.29 (m, 1H), 2.28 (s, 3H)	Method AE	Method A: RT 2.41 min; 415.2 [M+H] ⁺ .
146	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.37-7.32 (m, 1H), 7.29-7.27 (m, 1H), 4.12-4.06 (m, 3H), 3.64-3.53 (m, 4H), 3.53-3.48 (m, 6H), 2.81-2.73 (m, 2H), 2.22 (s, 3H).	Method AB	Method C: RT 4.02 min; 427.2 [M+H] ⁺ .
147	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.83 (bs, 1H), 7.39-7.36 (m, 1H), 7.32-7.27 (m, 1H), 3.76-3.48 (m, 8H), 3.48-3.34 (m, 1H), 3.32-3.30 (m, 1H), 2.79-2.66 (m, 1H), 2.63-2.56 (m, 1H), 2.37-2.36 (m, 1H), 2.28 (s, 3H).	Method AC	Method A: RT 2.52 min; 447.2 [M+H] ⁺ .
148	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.78 (bs, 1H), 7.39-7.36 (m, 1H), 7.32-7.29 (m, 1H), 3.78-3.59 (m, 8H), 3.54-3.49 (m, 1H), 3.40-3.35 (m, 1H), 2.79-2.69 (m, 1H), 2.66-2.60 (m, 1H), 2.38-2.33 (m, 1H), 2.28 (s, 3H).	Method AC	Method A: RT 2.52 min; 447.2 [M+H] ⁺ .
149	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , at 100 °C) δ 12.03 (brs, 1H), 7.43 (dd, <i>J</i> ₁ =4Hz, <i>J</i> ₂ =4Hz, 1H), 7.22 (t, <i>J</i> =9.6	Method A	Method C: RT 2.45 min; 445.2 [M+H] ⁺ .

	Hz, 1H), 5.25 (d, J=55.6, 1H), 3.81 (t, J=8.8Hz, 1H), 3.66-3.58 (m, 8H), 3.39-3.28 (m, 1H), 2.70-2.67 (m, 1H), 2.35 (s, 3H), 2.22-2.15 (m, 2H).		
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Example 150**Synthesis of (3-fluoroazetidin-3-yl)methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate**

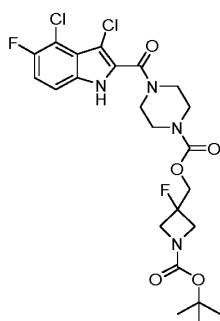
5

Step-1: Tert-butyl 3-fluoro-3-(((4-nitrophenoxy)carbonyl)oxy)methyl)azetidine-1-carboxylate



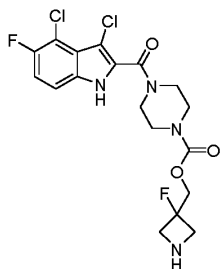
- 10 To a stirred solution of the tert-butyl 3-fluoro-3-(hydroxymethyl)azetidine-1-carboxylate (459.0 mg, 2.24 mmol) in dry DCM (5.0 mL) at 0°C was added TEA (0.9 mL, 6.7 mmol) and 4-nitrophenyl carbonochloridate (450.0 mg, 2.24 mmol). The reaction mixture was stirred at RT for 2 h, added sat aq NaHCO₃ (10.0 mL) and DCM (10.0 mL). The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄, filtered and
- 15 concentrated under reduced pressure to provide the crude product which was purified by silica gel column chromatography (10% EtOAc/Hexane) to provide tert-butyl 3-fluoro-3-(((4-nitrophenoxy) carbonyl)oxy)methyl)azetidine-1-carboxylate. (450 mg, 54%) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.11 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.59 (dd, *J* = 9.6 Hz, 2.1 Hz, 1H), 6.93 (d, *J* = 7.0, 2.1 Hz, 1H), 4.64
- 20 (d, *J* = 22.9 Hz, 2H), 4.18 -4.11 (m, 2H), 4.05 - 3.96 (m, 2H), 1.39 (s, 9H).

Step-2: (1-(tert-butoxycarbonyl)-3-fluoroazetidin-3-yl)methyl-4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate



Under argon atmosphere to a stirred solution of tert-butyl 3-fluoro-3-((((4-nitrophenoxy)carbonyl)oxy)methyl)azetidine-1-carboxylate (420.0 mg, 1.13 mmol) in dry DCM (5.0 mL) at 0 °C was added TEA (0.5 mL, 3.4 mmol) followed (3,4-dichloro-5-fluoro-1H-indol-2-yl)(piperazin-1-yl)methanone (357 mg, 1.13 mmol). After completion (Monitored by LCMS), the reaction mixture was diluted with DCM (5.0 mL) and washed with cold water. The aqueous part was back extracted with ethyl acetate (2 x 10.0 mL) and the combiner organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to provide the crude product as (1-(tert-butoxycarbonyl)-3-fluoroazetidin-3-yl)methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl) piperazine-1-carboxylate (250 mg, 40%), which was used for next step without further purification. (Method-C): RT 1.86 min; 447.14 [M+H]⁺.

Step-3: (3-fluoroazetidin-3-yl)methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate



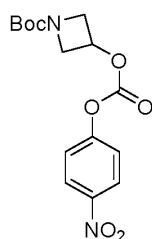
A solution of (1-(tert-butoxycarbonyl)-3-fluoroazetidin-3-yl)methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate (250.0 mg, 0.45 mmol) in DCM (2.0 mL) was treated with TFA (0.34 mL) and stirred at RT for 2 h. The solvent was removed *in vacuo* and the crude was dissolved in DCM, washed with sat aq NaHCO₃, brine, dried (MgSO₄), and concentrated. The resulting material was purified by reverse phase prep HPLC (Method H) to provide (3-fluoroazetidin-3-yl)methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate (100.0 mg, 49%)

as a white solid. ^1H NMR (401 MHz, $\text{DMSO}-d_6$) δ 12.26 (brs, 1H), 7.42 (dd, J = 4.0, 9.0 Hz, 1H), 7.28 (t, J = 9.2 Hz, 1H), 4.41 (s, 1H), 4.35 (s, 1H), 3.80 – 3.36 (m, 13H). LCMS (Method-A): RT 2.33 min; 447.2 $[\text{M}+\text{H}]^+$.

5 **Example 151**

Synthesis of azetidin-3-yl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl) piperazine-1-carboxylate

Step-1: Synthesis of tert-butyl 3-(((4-nitrophenoxy)carbonyl)oxy)azetidine-1-carboxylate

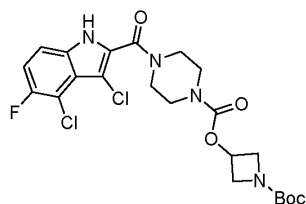


10

To a stirred solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (500.0 mg, 2.89 mmol) in dry DCM (10.0 mL) at 0°C was added TEA (1.2 mL, 8.66 mmol) and 4-nitrophenyl carbonochloridate (581.8 mg, 2.89 mmol). The reaction mixture was stirred at RT for 2 h, added sat aq NaHCO_3 (10.0 mL) and DCM (10.0 mL). The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to provide the crude product which was purified by silica gel column chromatography (10% EtOAc/Hexane) to provide tert-butyl 3-(((4-nitrophenoxy)carbonyl)oxy)azetidine-1-carboxylate. (450 mg, 54%) as a brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.33 (dd, J = 7.0, 2.0 Hz, 1H), 8.11 (dd, J = 7.0, 2.1 Hz, 1H), 7.59 (dd, J = 9.6 Hz, 2.1 Hz, 1H), 6.93 (d, J = 7.0, 2.1 Hz, 1H), 5.24 - 5.06 (m, 1H), 4.24 - 4.13 (m, 2H), 4.04 - 3.83 (m, 2H), 1.38 (s, 9H).

20

Step-2: Synthesis of 1-(tert-butoxycarbonyl)azetidin-3-yl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate

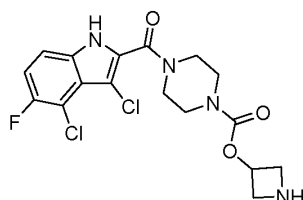


25

Under argon atmosphere to a stirred solution of tert-butyl 3-(((4-nitrophenoxy)carbonyl)oxy)azetidine-1-carboxylate ((250.0 mg, 0.73 mmol) in dry DCM

(5.0 mL) at 0 °C was added TEA (0.31 ml, 2.21 mmol) followed (3,4-dichloro-5-fluoro-1H-indol-2-yl)(piperazin-1-yl)methanone (232.93 mg, 0.737mmol). After completion (Monitored by LCMS), the reaction mixture was diluted with DCM (5.0 mL) and washed with cold water. The aqueous part was back extracted with ethyl acetate (2 x 10.0 mL) and the combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to provide the crude 1-(tert-butoxycarbonyl)azetidin-3-yl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate (125.0 mg, 33%), which was used for next step without further purification. (Method-A): RT 2.71 min; 515.2 [M+H]⁺.

Step-3: Synthesis of (3-fluoroazetidin-3-yl)methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl) piperazine-1-carboxylate



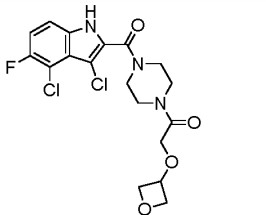
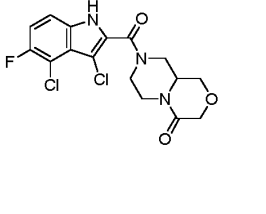
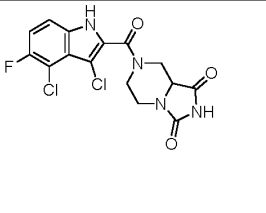
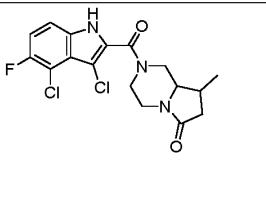
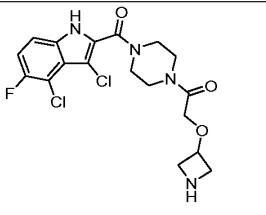
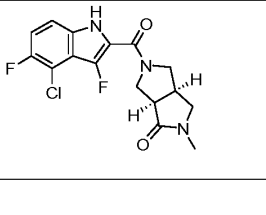
A solution of 1-(tert-butoxycarbonyl)azetidin-3-yl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl) piperazine-1-carboxylate ((125.0 mg, 0.24 mmol)) in DCM (2.0 mL) was treated with TFA (0.37 mL) and stirred at RT for 2 h. The solvent was removed *in vacuo* and the crude was dissolved in DCM, washed with sat aq NaHCO₃, brine, dried (MgSO₄), and concentrated. The resulting material was purified by reverse phase prep HPLC (Method H) to provide azetidin-3-yl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate (40.0 mg, 99%) as a off white solid. ¹H NMR (401 MHz, DMSO-*d*₆) δ 12.26 (brs, 1H), 7.42 (dd, *J* = 4.0, 9.0 Hz, 1H), 7.28 (t, *J* = 9.2 Hz, 1H), 4.41 (s, 1H), 4.35 (s, 1H), 3.80 – 3.36 (m, 13H). LCMS (Method A): RT 2.27 min; 415.2 [M+H]⁺.

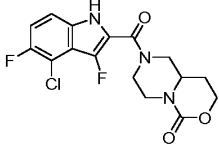
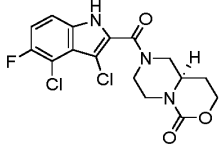
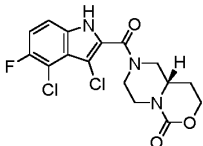
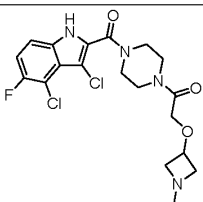
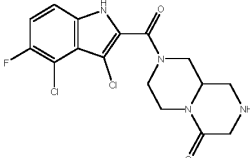
Example 152-194

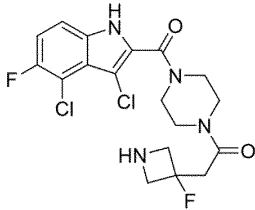
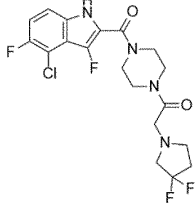
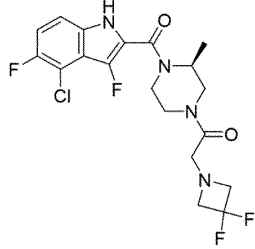
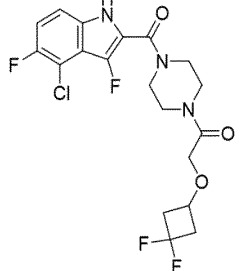
Examples 152-194 were made using similar methods to previous examples (Table 19):

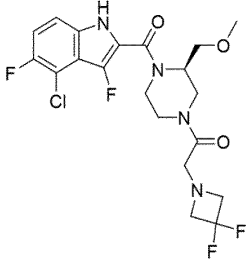
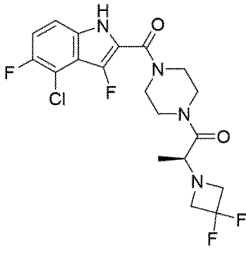
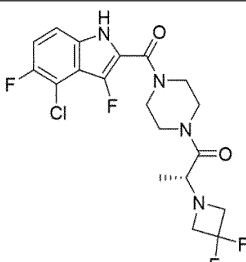
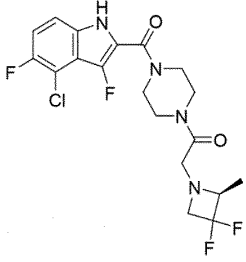
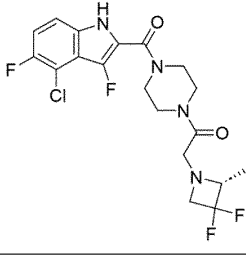
Table 19

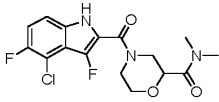
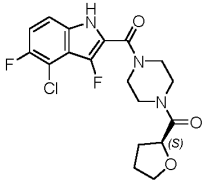
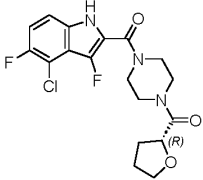
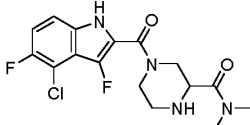
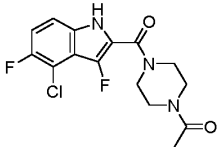
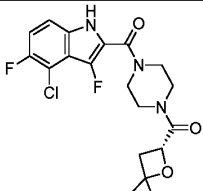
Ex. No.	Structure	Indole starting material	Amide coupling partner	Name	Amide bond formation method
152		Preparation 11	CAS#	1-(4-(3,4-dichloro-5-	A

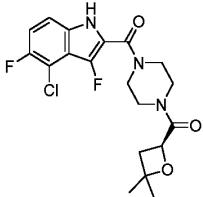
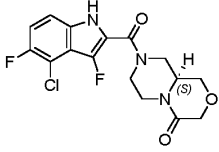
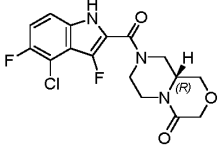
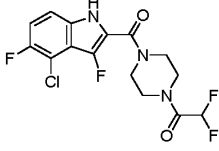
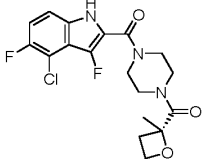
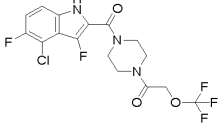
			1557814-84-2	fluoro-1H-indole-2-carbonyl)pyrrolidin-1-yl)-2-(oxetan-3-yloxy)ethan-1-one	
153		Preparation 9	CAS# 908066-25-1	8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydroindolo[2,1-c][1,4]oxazin-4(3H)-one	A
154		Preparation 9	CAS# 1251729-84-6	7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)tetrahydroimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione	C
155		Preparation 9	CAS# 1934501-43-5	2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-8-methylhexahydroindolo[1,2-a]pyrazine-6(2H)-one	A
156		Preparation 11	CAS# 889952-83-4	2-(azetidin-3-yloxy)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-1-yl)ethan-1-one	A
157		Preparation 10	CAS# 1779821-12-3	(3aR,6aR)-5-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-2-methylhexahydroindolo[1,2-a]pyrazine-6(2H)-one	A

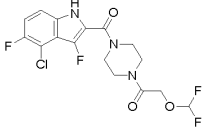
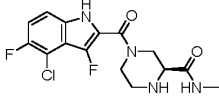
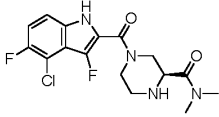
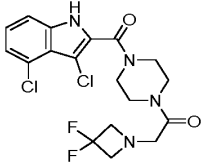
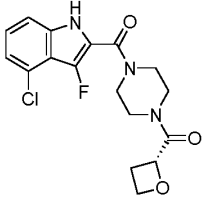
				ydopyrrolo[3,4-c]pyrrol-1(2H)-one	
158		Preparation 10	CAS# 1423117-10-5	2-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one	C
159		Preparation 9	CAS# 1423117-10-5	(R)-2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one	A
160		Preparation 9	CAS# 1423117-10-5	(S)-2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one	A
161		Example 156	N-methylation	1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-((1-methylazetidin-3-yl)oxy)ethan-1-one	A
162		Preparation 9	Preparation 23	8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)octahydro-4H-pyrazino[1,2-a]pyrazin-4-one	A

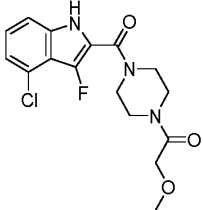
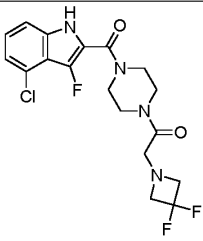
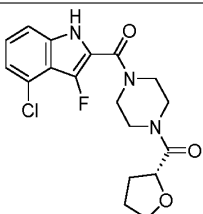
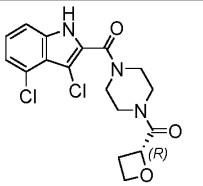
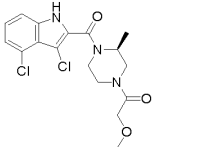
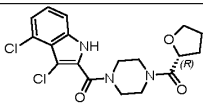
163		Preparati on 11	CAS# 1408074-68- 9	1-(4-(3,4- dichloro-5- fluoro-1H- indole-2- carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-3-yl)ethan-1-one	A
164		Preparati on 12	CAS# 1627953-21- 2	1-(4-(4- chloro-3,5- difluoro-1H- indole-2- carbonyl)piperazin-1-yl)-2-(3,3-difluoropyrrolidin-1-yl)ethan-1-one	A
165		Preparati on 19	CAS# 1420271-48- 2	(S)-1-(4-(4- chloro-3,5- difluoro-1H- indole-2- carbonyl)-3- methylpiperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one	A
166		Preparati on 12	CAS# 2228736-84- 1	1-(4-(4- chloro-3,5- difluoro-1H- indole-2- carbonyl)piperazin-1-yl)-2-(3,3-difluorocyclobutoxy)ethan-1-one	A

167		Preparati on 20	CAS# 1420271-48- 2	(R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-(methoxymethyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one	A
168		Preparati on 12	CAS# 2089669-22- 5	(S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)propan-1-one	A
169		Preparati on 12	CAS# 2089669-22- 5	(R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)propan-1-one	A
170		Preparati on 12	Preparation 22	(S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoro-2-methylazetidin-1-yl)ethan-1-one	A
171		Preparati on 12	Preparation 23	(R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoro-2-ethylazetidin-1-yl)ethan-1-one	A

				methylazetidin-1-yl)ethan-1-one	
172		Preparation 10	CAS# 135072-23-0	4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylmorpholine-2-carboxamide	B
173		Preparation 12	CAS # 87392-07-2	(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone	A
174		Preparation 12	CAS# 87392-05-0	(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone	A
175		Preparation 24	CAS# 506-59-2	4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylpiperazine-2-carboxamide	A
176		Preparation 10	CAS# 13889-98-0	1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one	A
177		Preparation 12	CAS# 2167330-95-0	(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-dimethyloxetane-2-carbonyl)piperazin-1-yl)methanone	A

				razin-1-yl)methanone	
178		Preparati on 12	CAS# 2167330-95-0	(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-dimethyloxetan-2-carbonyl)piperazin-1-yl)methanone	A
179		Preparati on 10	CAS# 930783-26-9	(S)-8-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydroindolo[2,1-c][1,4]oxazin-4(3H)-one	D
180		Preparati on 10	930783-25-8	(R)-8-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydroindolo[2,1-c][1,4]oxazin-4(3H)-one	D
181		Preparati on 12	Difluoroacetic acid	1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2,2-difluoroethan-1-one	A
182		Preparati on 12	CAS# 2306255-43-4	(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(2-methyloxetan-2-carbonyl)piperazin-1-yl)methanone	A
183		Preparati on 12	CAS# 55276-43-2	1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)methanone	A

				razin-1-yl)-2-(trifluoromethoxy)ethan-1-one	
184		Preparati on 12	CAS# 1089695-61-3	1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)pipe razin-1-yl)-2-(difluoromethoxy)ethan-1-one	A
185		Preparati on 24	CAS# 593-51-1	(S)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N-methylpiperazine-2-carboxamide	A
186		Preparati on 24	CAS# 506-59-2	(S)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylpiperazine-2-carboxamide	A
187		Preparati on 17	CAS# 1420271-48-2	1-(4-(3,4-dichloro-1H-indole-2-carbonyl)pipe razin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one	A
188		Preparati on 18	CAS# 2200583-25-9	(R)-4-(4-chloro-3-fluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)pipe razin-1-yl)methanone	A

189		Preparation on 18	CAS# 625-45-6	1-(4-(4-chloro-3-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one	A
190		Preparation on 18	CAS# 1420271-48-2	1-(4-(4-chloro-3-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one	A
191		Preparation on 18	CAS# 87392-05-0	(R)-(4-chloro-3-fluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone	A
192		Preparation on 17	CAS# 2200583-25-9	(R)-(3,4-dichloro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone	A
193		Similar method to Preparations 17 and 19	CAS# 625-45-6	(S)-1-(4-(3,4-dichloro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-methoxyethan-1-one	A
194		Preparation on 17	CAS# 87392-05-0	(R)-(3,4-dichloro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone	A

Analytical data for Examples 152-194

Table 20:

Ex. No.	¹ H-NMR	Purification method	LCMS
152	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.36 (s, 1H), 7.44-7.40 (m, 1H), 7.30-7.25 (m, 1H), 4.65-4.56 (m, 3H) 4.47-4.44 (m, 2H), 4.22 (s, 2H), 3.66-3.45 (m, 8H)	Method G	Method A: RT 2.59 min; 430.2 [M+H] ⁺ .
153	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆ , 100°C) δ 12.11 (m, 1H), 7.47 – 7.39 (m, 1H), 7.23 (t, <i>J</i> = 10.0 Hz, 1H), 4.50 – 4.42 (m, 1H), 4.26 – 3.95 (m, 4H), 3.77 – 3.52 (m, 2H), 3.13 – 3.00 (m, 2H), 2.80 (t, <i>J</i> = 12.0 Hz, 1H).	Method B	Method B: RT 2.65 min; 384.09 [M-H] ⁻ .
154	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.34 (brs, 2H), 7.48 – 7.40 (m, 1H), 7.26 (t, <i>J</i> = 9.2 Hz, 1H), 4.38 – 4.22 (m, 1H), 4.21 – 4.12 (m, 1H), 4.12 – 4.01 (m, 1H), 4.00 – 3.92 (m, 1H), 3.27 – 3.09 (m, 2H), 3.08 – 3.00 (m, 1H).	Method E	Method A: RT 2.36 min; 383.1 [M-H] ⁻ .
155	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.12 (brs, 1H), 7.43 (dd, <i>J</i> = 4.1, 8.9 Hz, 1H), 7.23 (t, <i>J</i> = 9.2 Hz, 1H), 4.48 – 4.22 (m, 1H), 4.23 – 3.85 (m, 3H), 3.71 – 3.54 (m, 1H), 3.31 – 3.13 (m, 1H), 2.84 (p, <i>J</i> = 11.6 Hz, 2H), 2.18 – 1.87 (m, 1H), 1.11 (d, <i>J</i> = 6.6 Hz, 2H), 1.01 (d, <i>J</i> = 7.0 Hz, 2H)	Method C	Method A: RT 2.54 min; 384.1 [M+H] ⁺ .
156	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 7.46 – 7.38 (m, 1H), 7.23 (t, <i>J</i> = 9.5 Hz, 1H), 4.35 – 4.26 (m, 1H), 4.10 (s, 2H), 3.64 – 3.49 (m, 9H), 3.43 (t, <i>J</i> = 7.2 Hz, 2H), 3.36 – 3.07 (m, 2H).	Method A	Method A: RT 2.18 min; 429.1 [M+H] ⁺ .
157	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.52 (brs, 1H), 7.42 – 7.33 (m, 1H), 7.24 (t, <i>J</i> = 9.5 Hz, 1H), 4.06 – 3.86 (m, 2H), 3.86 – 3.76 (m, 1H), 3.59 (dd, <i>J</i> = 6.5, 10.3 Hz, 1H), 3.48 (dd, <i>J</i> = 6.3, 12.2 Hz, 1H), 3.19 (d, <i>J</i> = 10.0 Hz, 1H), 3.16 – 3.04 (m, 2H), 2.76 (s, 3H).	Method D	Method A: RT 2.31 min; 354.2 [M+H] ⁺ .
158	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.51 (brs, 1H), 7.43 – 7.35 (m, 1H), 7.24 (t, <i>J</i> = 9.2 Hz, 1H), 4.26 – 4.12 (m, 5H), 3.67 – 3.48 (m, 1H), 3.25 – 3.09 (m, 1H), 2.99 – 2.85 (m, 2H), 2.26 – 2.09 (m, 1H), 1.91 – 1.66 (m, 1H).	Method Q	Method B: RT 2.78 min; 386.26 [M+H] ⁺ .
159	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 12.56 (brs, 1H), 7.47 – 7.39 (m, 1H), 7.25 (t, <i>J</i> = 9.4 Hz, 1H), 4.41 – 3.91 (m, 5H), 3.73 – 3.45 (m, 1H), 3.18 – 3.07 (m, 1H), 3.01 – 2.84 (m, 2H), 2.29 – 1.99 (m, 1H), 1.88 – 1.67 (m, 1H).	Method Q	Method B: RT 2.78 min; 386.26 [M+H] ⁺ .
160	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆) δ 12.41 (brs, 1H), 7.47 – 7.36 (m, 1H), 7.29 (t, <i>J</i> = 9.5 Hz, 1H), 4.66 – 3.93 (m, 3H), 3.88 – 3.44 (m, 2H), 3.23 – 2.71 (m, 2H), 2.29 – 1.95 (m, 2H), 1.92 – 1.58 (m, 2H).	Method Q Chiral: Method D	Method H: RT 4.61 min; 386.21 [M+H] ⁺ .
161	¹ H NMR (401 MHz, DMSO- <i>d</i> ₆ , 100 °C) δ 11.52 (m, 1H), 7.49 – 7.35 (m, 1H), 7.22 (t, <i>J</i> = 9.6 Hz,	Method A	Method B: RT 2.37 min;

	1H), 4.10 (s, 3H), 3.65 – 3.51 (m, 8H), 3.47 (t, $J = 6.0$ Hz, 2H), 2.86 (d, $J = 7.0$ Hz, 2H), 2.24 (s, 3H).		443.32 [M+H] ⁺ .
162	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 12.03 (1H, brs), 7.44-7.40 (m, 1H), 7.26-7.21 (m, 1H), 4.49 (d, $J = 13.2$, 1H), 4.05 (brs, 1H), 3.47 (s, 1H), 3.27 (s, 1H), 3.12-3.09 (m, 2H), 2.72-2.62 (m, 2H)	Method K	Method B: RT 2.26 min; 385.23 [M+H] ⁺ .
163	¹ H NMR (400 MHz, DMSO-d ₆ – 100 °C) δ 8.13 (s, 1H, formate peak), 7.47 – 7.39 (m, 1H), 7.24 (t, $J = 9.4$ Hz, 1H), 3.92 – 3.71 (m, 4H), 3.59 (s, 8H), 3.12 – 3.07 (m, 1H), 3.06 – 3.01 (m, 1H). NB: N-H proton is absent in the NMR.	Method A	Method A: RT 1.55 min; 431.1 [M+H] ⁺ .
164	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.63 (s, 1H), 7.38-7.26 (m, 1H), 7.24-7.21 (m, 1H), 3.66-3.61 (m, 8H), 3.42 (s, 2H), 3.06-2.99 (m, 2H), 2.85 (s, 2H), 2.33-2.21 (m, 2H)	Method N	Method A: RT 2.63 min; 447.2 [M+H] ⁺ .
165	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 11.60 (s, 1H), 7.39-7.36 (m, 1H), 7.23 (t, $J = 9.2$ Hz, 1H), 4.52 (s, 1H) 4.07-3.96 (m, 3H), 3.73-3.67 (m, 4H), 3.57-3.46 (m, 2H), 3.36-3.33 (m, 1H) 3.01-2.97 (m, 2H), 1.27-1.21 (m, 3H).	Method AB	Method B: RT 2.44 min; 447.2 [M+H] ⁺ .
166	DMSO-d ₆ , 100 °C) δ 11.60 (m, 1H), 7.43 – 7.35 (m, 1H), 7.24 (t, $J = 9.4$ Hz, 1H), 4.18 (s, 2H), 4.16 – 4.06 (m, 1H), 3.70 – 3.63 (m, 4H), 3.60 – 3.53 (m, 4H), 2.95 – 2.80 (m, 2H), 2.65 – 2.52 (m, 2H).	Method N	Method A: RT 2.64 min; 448.2 [M+H] ⁺ .
167	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 11.49 (brs, 1H), 7.39 – 7.34 (m, 1H), 7.22 (t, 1H), 4.53 – 4.49 (m, 1H), 4.37 – 3.89 (m, 4H), 3.71 (t, $J = 12.5$ Hz, 4H), 3.60 – 3.42 (m, 4H), 3.35 – 3.28 (m, 1H), 3.25 (s, 3H), 2.99 – 2.94 (m, 1H).	Method N	Method A: RT 2.53 min; 477.2 [M+H] ⁺ .
168	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.9 (s, 1H), 7.36-7.35 (m, 1H), 7.27-7.23 (m, 1H), 3.72-3.62 (m, 12H), 3.59-3.51 (m, 1H), 1.10 (d, $J = 6.4$ Hz, 3H)	Combi-column purification (eluted at 55-60 % Hex-EA) followed by chiral purification through Method D	Method A: RT 2.39 min; 447.3 [M+H] ⁺ .
169	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.94 (s, 1H), 7.33-7.32 (m, 1H), 7.21-7.17 (m, 1H), 3.72-3.59 (m, 12H), 3.56-3.53 (m, 1H), 1.10 (d, $J = 6.4$ Hz, 3H)	Combi-column purification (eluted at 55-60 % Hex-EA) followed	Method A: RT 2.39 min; 447.3 [M+H] ⁺ .

		by chiral purification through Method D	
170	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 11.51 (brs, 1H), 8.46 (brs, 1H, formate), 7.38 (d, J = 8.8, 1H) – 7.22 (t, J = 9.6 Hz, 1H), 3.86 – 3.76 (m, 1H), 3.68 – 3.56 (m, 8H), 3.52 – 3.37 (m, 2H), 1.19 – 1.13 (m, 3H). One proton merged with solvent peak.	Method N	Method A: RT 2.42 min; 447.30 [M+H] ⁺ .
171	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.96 (brs, 1H), 7.42 – 7.34 (m, 1H), 7.29 (t, J = 9.4 Hz, 1H), 3.85 – 3.74 (m, 1H), 3.73 – 3.43 (m, 10H), 3.42 – 3.34 (m, 2H), 1.12 (d, J = 6.3 Hz, 3H).	Method N	Method A: RT 2.60 min; 447.2 [M+H] ⁺ .
172	¹ H NMR (401 MHz, DMSO- d ₆ , 100°C) δ 11.95 (s, 1H), 7.38-7.36 (m, 1H), 7.31-7.26 (m, 1H), 4.31-4.29 (m, 1H), 4.12 (s, 1H), 3.93-3.84 (m, 2H) 3.67-3.62 (m, 1H), 3.41 (s, 1H), 3.01 (s, 1H), 2.66 (s, 3H), 2.50 (s, 3H).	Method F	Method B: RT 2.60 min; 372.2 [M+H] ⁺ .
173	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.94 (brs, 1H), 7.42 – 7.34 (m, 1H), 7.29 (t, J = 9.4 Hz, 1H), 4.70 (t, J = 6.7 Hz, 1H), 3.84 – 3.69 (m, 2H), 3.69 – 3.48 (m, 8H), 2.14 – 1.94 (m, 2H), 1.91 – 1.76 (m, 2H).	Method D	Method A: RT 2.47 min; 398.2 [M+H] ⁺ .
174	¹ H NMR (401 MHz, DMSO-d ₆ , 100°C) δ 11.76 – 11.42 (m, 1H), 7.43 – 7.37 (m, 1H), 7.23 (t, J = 9.2 Hz, 1H), 4.67 (t, J = 6.4 Hz, 1H), 3.89 – 3.72 (m, 2H), 3.73 – 3.54 (m, 8H), 2.22 – 1.79 (m, 4H).	Method AF	Method A: RT 2.30 min; 398.2 [M+H] ⁺ .
175	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 11.91 (brs, 1H), 7.37 – 7.32 (m, 1H), 7.26 (t, J = 9.4 Hz, 1H), 4.38 – 4.34 (m, 1H), 4.13 – 4.08 (m, 1H), 3.67 – 3.63 (m, 1H), 3.13 – 2.92 (m, 6H), 2.83 – 2.79 (m, 4H), 2.46 – 2.23 (m, 1H)	Method C	Method A: RT 2.29 min; 371.2 [M+H] ⁺ .
176	¹ H NMR (401 MHz, DMSO-d ₆) δ 11.96 (brs, 1H), 7.38 – 7.36 (m, 1H), 7.29 (t, J = 9.4 Hz, 1H), 3.66 – 3.54 (m, 8H), 2.04 (s, 3H).	Method I	Method A: RT 2.59 min; 342.2 [M+H] ⁺ .
177	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.91 (s, 1H), 7.38-7.36 (m, 1H), 7.31-7.27 (m, 1H), 5.19-5.16 (m, 1H), 3.62-3.58 (m, 6H), 3.41-3.32 (s, 3H), 2.62-2.50 (m, 2H), 1.41 (s, 3H), 1.29-2.24 (m, 3H)	Combi- column purification (eluted at 40-	Method A: RT 2.56 min; 410.2 [M-H].

		45% Hex-EA) followed by chiral purification through Method E	
178	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.86 (s, 1H), 7.36-7.35 (m, 1H), 7.29-7.28 (m, 1H), 5.19-5.15 (m, 1H), 3.62-3.57 (m, 6H), 3.41-3.39 (s, 2H), 2.58-2.54 (m, 1H), 1.41 (s, 3H), 1.29 (s, 3H)	Combi-column purification (eluted at 40-45% Hex-EA) followed by chiral purification through Method E	Method A: RT 2.50 min; 412.2 [M+H] ⁺ .
179	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 11.52 (brs, 1H), 7.40 – 7.36 (m, 1H), 7.24 (t, J = 9.5 Hz, 1H), 4.47 (d, J = 13.4 Hz, 1H), 4.25 – 4.20 (m, 2H), 4.10 – 4.02 (m, 3H), 3.67 – 3.63 (m, 2H), 3.19 – 3.08 (m, 2H), 2.87 – 2.76 (m, 1H).	Method Q	Method C: RT 5.13 min; 370.2 [M+H] ⁺ .
180	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 11.61 (m, 1H), 7.43 – 7.36 (m, 1H), 7.25 (t, J = 9.5 Hz, 1H), 4.47 (d, J = 13.3 Hz, 1H), 4.26 – 4.18 (m, 2H), 4.10 – 4.00 (m, 3H), 3.68 – 3.59 (m, 2H), 3.19 – 3.08 (m, 1H), 3.05 – 2.96 (m, 1H), 2.81 (t, J = 12.5 Hz, 1H).	Method AG	Method A: RT 2.37 min; 370.1 [M+H] ⁺ .
181	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.97 (brs, 1H), 7.43 – 7.35 (m, 1H), 7.30 (t, J = 9.4 Hz, 1H), 6.94 – 6.58 (m, 1H), 3.70 (s, 4H), 3.66 – 3.56 (m, 4H).	Method D	Method B: RT 2.78 min; 378.2 [M+H] ⁺ .
182	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.95 (s, 1H), 7.36 (d, J- 4Hz, 1H), 7.29 (t, J-9.6 Hz, 1H), 4.42-4.38 (m, 1H), 4.30-4.25 (m, 1H), 3.62 (m, 6H), 3.52 (m, 2H), 3.06-3.00 (q, 1H), 2.49-2.41 (m, 1H), 1.58 (s, 3H)	Combi-column purification (eluted at 50-55% Hex-EA)	Method A: RT 2.70 min; 396.2 [M-H] ⁻ .
183	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.96 (brs, 1H), 7.42 – 7.25 (m, 2H), 4.98 (s, 2H), 3.68 – 3.60 (m, 4H), 3.59 – 3.54 (m, 2H), 3.47 – 3.43 (m, 2H).	Method AF	Method B: RT 2.89 min; 426.2 [M+H] ⁺ .
184	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 11.66 – 11.26 (m, 1H), 7.43 – 7.34 (m, 1H), 7.23 (t, J = 9.4 Hz, 1H), 6.66 (s, 1H), 4.64 (s, 2H), 3.72 – 3.65 (m, 4H), 3.60 – 3.53 (m, 4H).	Method Q	Method A: RT 2.52 min; 406.2 [M+H] ⁺ .

185	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 10.71 (m, 1H), 7.59 (s, 1H), 7.44 – 7.32 (m, 1H), 7.22 (t, J = 9.4 Hz, 1H), 4.08 (d, J = 8.7 Hz, 1H), 3.82 (d, J = 12.8 Hz, 1H), 3.28 – 3.21 (m, 1H), 2.78 – 2.69 (m, 1H), 2.64 (d, J = 4.4 Hz, 3H), 2.53 (s, 3H).	Method C	Method A: RT 2.22 min; 357.2 [M+H] ⁺ .
186	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 11.51 (m, 1H), 7.44 – 7.31 (m, 1H), 7.21 (t, J = 9.6 Hz, 1H), 4.20 – 4.00 (m, 1H), 4.00 – 3.85 (m, 1H), 3.76 – 3.63 (m, 1H), 3.29 – 3.03 (m, 4H), 2.96 – 2.60 (m, 6H).	Method C	Method A: RT 2.29 min; 371.2 [M+H] ⁺ .
187	¹ H NMR (400 MHz, DMSO-d ₆ , 20 °C) δ 12.26 (s, 1H), 7.41-7.39 (m, 1H), 7.20-7.19 (m, 1H), 7.16-7.14 (m, 1H), 3.67 (t, J=12.8 Hz, 4H), 3.51 (s, 10H).	Method K	Method B: RT 2.53 min; 431.2 [M+H] ⁺ .
188	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 11.85 (s, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 5.42 (t, J = 7.7 Hz, 1H), 4.53 (q, J = 6.4 Hz, 1H), 4.47 – 4.33 (m, 1H), 3.77 – 3.51 (m, 6H), 3.44 – 3.36 (m, 2H), 2.89 – 2.73 (m, 2H).	Method AF	Method A: RT 2.34 min; 364.1 [M-H] ⁻ .
189	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.86 (s, 1H), 7.41 – 7.31 (m, 1H), 7.23 (t, J = 8.1 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 4.13 (s, 2H), 3.72 – 3.45 (m, 8H), 3.30 (s, 3H).	Method I	Method A: RT 2.29 min; 352.2 [M-H] ⁻ .
190	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.83 (s, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 3.77 – 3.58 (m, 8H), 3.57 – 3.45 (m, 6H).	Method C	Method A: RT 2.44 min; 415.2 [M+H] ⁺ .
191	¹ H NMR (401 MHz, DMSO-d ₆) δ 11.84 (s, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 4.70 (t, J = 6.0 Hz, 1H), 3.89 – 3.44 (m, 10H), 2.12 – 1.95 (m, 2H), 1.90 – 1.76 (m, 2H).	Method Q	Method C: RT 2.76 min; 380.2 [M+H] ⁺ .
192	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 11.87 (s, 1H), 7.42-7.40 (m, 1H), 7.22-7.18 (m, 1H), 7.15-7.13 (m, 1H), 5.42-5.38 (m, 1H), 4.59-4.53 (m, 1H), 4.46-4.41 (m, 1H), 3.58-3.52 (m, 8H), 2.90-2.76 (m, 2H)	Method AD	Method B: RT 2.78 min; 382.2 [M+H] ⁺ .
193	¹ H NMR (400 MHz, DMSO-d ₆ , 100 °C) δ 11.87 (s, 1H), 7.41 (d, J=8Hz, 1H), 7.22-7.18 (m, 1H), 7.15-7.13 (m, 1H), 4.41 (s, 1H), 4.15-4.03 (m, 6H), 3.33-3.29 (m, 4H), 2.99 (s, 1H), 1.27-1.20 (m, 3H)	Method F	Method B: RT 2.80 min; 384.2 [M+H] ⁺ .
194	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.75 (s, 1H), 7.42-7.41 (m, 1H), 7.23-7.21 (m, 1H), 7.19-7.13	Method Z	Method A: RT 2.42 min;

	(m, 1H), 4.68-6.64 (m, 1H), 3.83-3.75 (m, 2H), 3.62-3.59 (m, 8H), 2.15-2.11 (m, 1H), 2.03-1.98 (m, 1H), 1.92-1.84 (m, 2H)		396.2 [M+H] ⁺ .
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Example 195 – Biological Evaluation

Cell Culture Conditions

5 CHO DUKx/hKv1.3 FL (clone 4) cells are cultured in MEM Alpha, nucleosides, GlutaMAX Supplement supplemented with 5 mL of 100X Penicillin/Streptomycin, 10 mL of 50 mg/mL of G418 (final concentration 1 mg/mL) and 50 mL of Fetal Bovine Serum (final concentration 10%).

Experimental protocol

10 CHO DUKx/hKv1.3 FL cells are seeded 48 hours before experiment, at a concentration of 2.4 million cells onto a T225 flask (Corning® cell culture flasks, cat CC431082). Just before the experiments cells are washed twice with D-PBS w/o Ca²⁺/Mg²⁺ (Euroclone cat. ECB4004L) and detached from the flask with Detachin Cell Detachment Solution (Genlantis cat. T100100). Cells are then re-suspended in the suspension solution: 25
15 mL EX-CELL ACF CHO medium (Sigma cat. C5467); 0.625 mL HEPES (Sigma cat. H0887); 0.25 mL of 100x Penicillin/Streptomycin (Euroclone cat. ECB3001D) and placed on the QPatch 48X (Sophion Bioscience, Denmark).

Compound dilution for QPatch assay

20 The dilutions from 1000x concentrated dose-response curve (100% DMSO) are performed in the extracellular solution (for composition see below) right before the experiment; 0.5 µL of the 1000x solution are added in single glass-insert vials (4050FB-917 0.5mL Glass Flat Bottom Vials, LABORATORY SUPPLY DISTRIBUTORS, CORP BIOTECH SOLUTIONS) pre-filled with 500 µL of the extracellular solution (final
25 %DMSO is 0.1%).

Compounds are tested at QPatch 48X in cumulative dose-response at four concentrations according to client request.

PAP-1 (5-(4-Phenoxybutoxy)psoralen; Sigma cat. P6124, stock solution 10 mM in DMSO) is used as reference blocker.

30 Patch clamp analysis – QPatch 48X

In order to directly monitor the block of human Kv1.3 channel, an electrophysiological assay is developed and implemented on the QPatch48X automated electrophysiology instrument, using the single-hole QPlates (dedicated plate with internal glass-coated

flow channel structure, enablingishes and application of multiple concentrations/compounds per well, minimize absorption of compounds).

5 All the experiments are performed at room temperature using the voltage-clamp mode in the whole cell configuration and data are sampled at 5 KHz. The outward currents are recorded in an extracellular solution containing: NaCl 145mM, KCl 5mM, MgCl2 1mM, CaCl2 2mM, HEPES 10mM, and glucose 10mM, pH 7.4, whereas the intracellular solution contains KCl 20mM, KF 120mM, HEPES 10mM, EGTA 10mM, pH 10 7.2. After establishment of the seal and the passage in the whole cell configuration, the cells are held at -90mV and the potassium current is evoked using the following voltage protocol, applied every 15 sec. (40ms step at -90mV; 200ms step at +30mV; and back to -90mV), in the absence and in the presence of the compounds under investigation at increasing concentrations. Finally, the reference blocker PAP-1 (1 µM) is added as 15 positive control (blocking Kv1.3 current).

Both the outward peak current and the area under curve (charge) during the 200ms depolarizing pulse are analyzed. The averaged steady-state currents and charge level at the end of the compound application are measured and normalized to the maximum 20 current response in the vehicle period. To obtain the IC50 values, the normalized data are plotted against the respective antagonist concentrations on a logarithmic scale and fitted with the following equation (in-built PRISM GraphPad software):
$$Y=100/(1+10^{((LogIC50-X)*HillSlope)})$$

X: log of concentration
25 Y: normalized response, 100% down to 0%, decreasing as X increases.
LogIC50: same log units as X
HillSlope: slope factor or hill slope, unitless
All data are expressed as mean ± S.E.
For any given compound, the resulting IC50 value is provided only when the % of 30 inhibition at the highest tested concentration is greater than 50%.

The IC50 values measured in this assay for the exemplified compounds is set out in the table below:

Example Number	IC50	Example Number	IC50	Example Number	IC50
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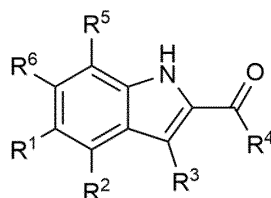
1	A	2	B	3	C
4	C	5	C	6	C
7	C	8	B	9	C
10	B	11	C	12	B
13	C	14	C	15	B
16	B	17	B	18	B
19	C	20	B	21	B
22	B	23	B	24	B
25	B	26	B	27	B
28	B	29	B	30	A
31	A	32	B	33	B
34	A	35	A	36	B
37	A	38	A	39	A
40	A	41	A	42	A
43	A	44	A	45	A
46	A	47	A	48	A
49	B	50	C	51	C
52	C	53	D	54	C
55	A	56	B	57	B
58	B	59	C	60	C
61	C	62	D	63	D
64	D	65	D	66	D
67	D	68	D	69	D
70	D	71	B	72	C
73	A	74	A	75	A
76	B	77	B	78	B
79	A	80	A	81	C
82	B	83	C	84	D
85	D	86	D	87	D
88	D	89	C	90	C
91	C	92	C	93	C
94	A	95	A	96	B
97	A	98	A	99	A
100	A	101	A	102	A
103	A	104	A	105	A
106	A	107	A	108	A
109	C	110	A	111	A
112	A	113	A	114	B
115	A	116	C	117	A
118	A	119	A	120	A
121	A	122	A	123	A
124	A	125	A	126	A
127	A	128	A	129	A
130	B	131	A	132	A
133	A	134	A	135	A
136	A	137	A	138	A
139	A	140	A	141	B
142	B	143	B	144	A
145	A	146	A	147	A
148	A	149	B	150	A
151	A	152	A	153	A

154	A	155	A	156	A
157	A	158	A	159	A
160	A	161	A	162	A
163	A	164	A	165	A
166	A	167	A	168	A
169	A	170	A	171	A
172	A	173	A	174	A
175	A	176	A	177	A
178	A	179	A	180	A
181	A	182	A	183	A
184	A	185	A	186	A
187	A	188	A	189	A
190	A	191	A	192	A
193	A	194	A		

wherein “A” denotes an IC₅₀ value <100 nM, “B” denotes an IC₅₀ value between 100 nM and 300 nM, “C” denotes an IC₅₀ between 300 and 1000 nM, “D” denotes an IC₅₀ greater than 1000 nM.

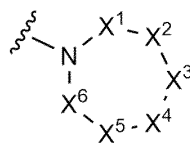
Claims

1. A compound of Formula (I),



Formula (I)

- 5 wherein
 R¹ is halogen or H;
 R² is halogen;
 R³ is halogen;
 R⁵ is H or halogen;
 10 R⁶ is H or halogen;
 R⁴ is of Formula (II):



Formula (II)

- wherein
 15 X¹ is C(R⁷)(R⁸);
 X² is C(R⁹)(R¹⁰) or a bond;
 X³ is N(C(O)R¹¹), C(R¹²)(C(O)R¹³), C(R¹⁴)(R¹⁵) or N(R¹⁶);
 X⁴ is C(R¹⁷)(R¹⁸), O or C(O);
 X⁵ is C(R¹⁹)(R²⁰) or a bond;
 20 X⁶ is a bond or C(R²¹)(R²²);
 wherein R⁹ and R¹¹, R⁹ and R¹³, R¹⁰ and R¹¹, R¹⁰ and R¹³, R¹³ and R¹⁷, R¹³ and
 R¹⁸, or R¹⁴ and R¹⁵ are optionally joined together to form a ring together with the
 intervening atom(s);
 R⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen,
 25 such as F;
 R⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F or C₁₋₃ alkoxy, or halogen,
 such as F;

R⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, halogen, such as F, or -C(O)N(R³¹)(R³²), wherein R³¹ is H or C₁₋₃ alkyl and R³² is H or C₁₋₃ alkyl, or when R⁹ is linked to R¹¹ or R¹³ to form a ring, then R⁹ is a bond, -C(O)- or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R¹⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 halogens, halogen, such as F, , or -C(O)N(R³¹)(R³²), wherein R³¹ is H or C₁₋₃ alkyl and R³² is H or C₁₋₃ alkyl, or when R¹⁰ is linked to R¹¹ or R¹³ to form a ring, then R¹⁰ is a bond, -C(O)- or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R¹¹ is -X¹³-R³³;

X¹³ is a bond, C₁₋₃ alkanediyl optionally substituted with C₁₋₃ alkyl, -O-, or C₁₋₃ alkanediyl-O-;

R³³ is selected from the group consisting of C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₁₋₃ alkoxy, pyridinyl, azetidiny, pyrrolidinyl, oxetanyl, tetrahydrofuranyl, and morpholinyl, each of which is optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂;

or when R¹¹ is linked to R⁹ or R¹⁰ to form a ring, then R¹¹ is -O-, -N(R²⁸)-, or C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl, wherein one methylene group of the C₁₋₃ alkanediyl is optionally replaced by -O- or -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

R¹² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein

- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂, N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
- said azetidiny optionally substituted with NH₂;

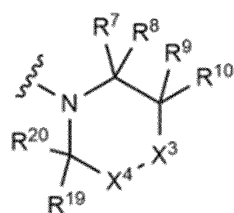
or when R¹³ is linked to R⁹, R¹⁰, R¹⁷, or R¹⁸ to form a ring, then R¹³ is -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),

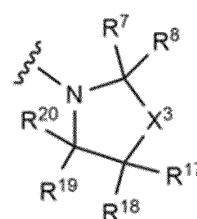
wherein

X⁷ is a bond or C₁₋₃ alkanediyl;
R²⁴ is C₁₋₃ alkyl; and
R²³ is H or C₁₋₃ alkyl, and R¹⁵ is H or C₁₋₃ alkyl,
or R²³ is a bond or C₁₋₃ alkanediyl, and R¹⁵ is a bond or C₁₋₃ alkanediyl
5 and R²³ is linked to R¹⁵ to form a ring;
or R¹⁴ is -X⁹C(O)X¹¹-, R¹⁵ is a bond or C₁₋₃ alkanediyl, and X¹¹ is linked to R¹⁵ to
form a ring,
wherein
X⁹ is a bond or -N(R²⁹)-;
10 R²⁹ is C₁₋₃ alkyl;
X¹¹ is -O-, C₁₋₃ alkanediyl, or -N(R³⁰)-; and
R³⁰ is C₁₋₃ alkyl;
R¹⁶ is H or C₁₋₃ alkyl;
R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or
15 when R¹⁷ is linked to R¹³ to form a ring, then R¹⁷ is a bond or a C₁₋₃ alkanediyl
optionally substituted with 1 to 3 substituents individually selected from halogen
and C₁₋₃ alkyl;
R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or
when R¹⁸ is linked to R¹³ to form a ring, then R¹⁸ is a bond or a C₁₋₃ alkanediyl
20 optionally substituted with 1 to 3 substituents individually selected from halogen
and C₁₋₃ alkyl;
R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
R²¹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
25 R²² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
any two of R⁷, R⁸, R⁹, R¹⁰, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, and R²² are optionally linked
together to form a ring;
with the proviso that when X⁴ is O, then X³ is C(R¹²)C(O)R¹³ and R¹³ is NH₂,
N(H)(CH₃) or N(CH₃)₂;
30 with the proviso that when X³ is N(R¹⁶), then X⁴ is C(O),
with the proviso that when X⁴ is C(O), then X³ is N(R¹⁶), and
with the proviso that when X² is a bond, then X³ is C(R¹²)(C(O)R¹³) or
C(R¹⁴)(R¹⁵),
or a pharmaceutically acceptable salt thereof.

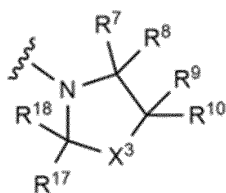
2. The compound according to claim 1, wherein R¹ is halogen, or a pharmaceutically acceptable salt thereof.
3. The compound according to any one of the preceding claims, wherein R⁵ is H and R⁶ is H, or a pharmaceutically acceptable salt thereof.
- 5 4. The compound according to any one of the preceding claims, wherein R¹ is F or Cl, R² is F or Cl, R³ is F or Cl, R⁵ is H, and R⁶ is H, or a pharmaceutically acceptable salt thereof.
5. The compound according to any one of the preceding claims, wherein R⁴ is of Formula (XXIV), Formula (XXV), Formula (XXVI) or Formula (XXVII):



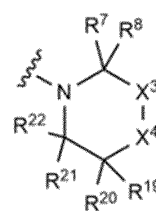
Formula (XXIV)



Formula (XXV)

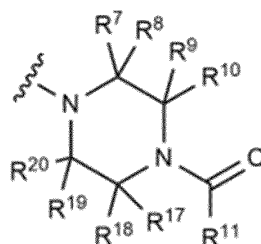


Formula (XXVI)



Formula (XXVII)

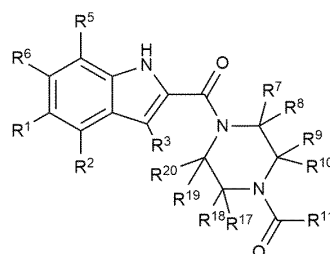
- 10 or a pharmaceutically acceptable salt thereof.
6. The compound according to any one of the preceding claims, wherein R⁴ is of Formula (III):



Formula (III)

- 15 or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 1, wherein the compound is of Formula (LVII),

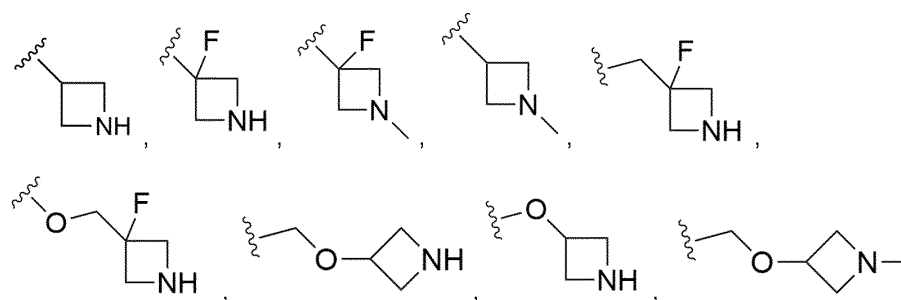


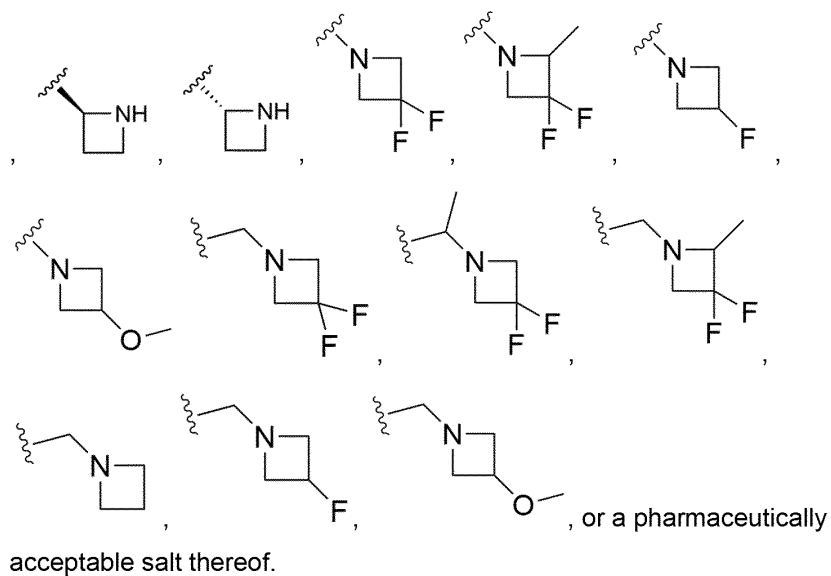
Formula (LVII)

- 5 wherein
- R¹ is halogen or H;
- R² is halogen;
- R³ is halogen;
- R⁵, R⁶, R⁸, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H;
- 10 wherein R⁹ and R¹¹ or R¹⁰ and R¹¹ are optionally joined together via R³³ to form a ring together with the intervening atoms;
- R⁷ is H or C₁₋₃ alkyl optionally substituted with 1 to 3 F;
- R¹⁰ is H, or when R¹⁰ is linked to R¹¹ to form a ring, then R¹⁰ is a bond or a C₁₋₃ alkanediyl;
- 15 R⁹ is H, or when R⁹ is linked to R¹¹ to form a ring, then R⁹ is a bond or a C₁₋₃ alkanediyl;
- R¹¹ is -X¹³-R³³;
- X¹³ is a bond, C₁₋₃ alkanediyl optionally substituted with C₁₋₃ alkyl, -O-, or C₁₋₃ alkanediyl-O-; and
- 20 R³³ is C₁₋₃ alkyl, azetidiny, pyrrolidinyl, oxetanyl, and tetrahydrofuranyl, each of which is optionally substituted with one or more F; or when R¹¹ is linked to R⁹ or R¹⁰ via R³³ to form a ring, then R³³ is a bond or a C₁₋₃ alkanediyl, or a pharmaceutically acceptable salt thereof.
8. The compound according to any one of claims 1 to 6, wherein R³³ is azetidiny
- 25 optionally substituted with one or more substituents selected from halogen, C₁₋₃ alkoxy, and C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
9. The compound according to any one of claims 1 to 6, wherein R³³ is oxetanyl, or a pharmaceutically acceptable salt thereof.
10. The compound according to any one of claims 1 to 6, wherein R³³ is pyrrolidinyl
- 30 optionally substituted with one or more substituents individually selected from

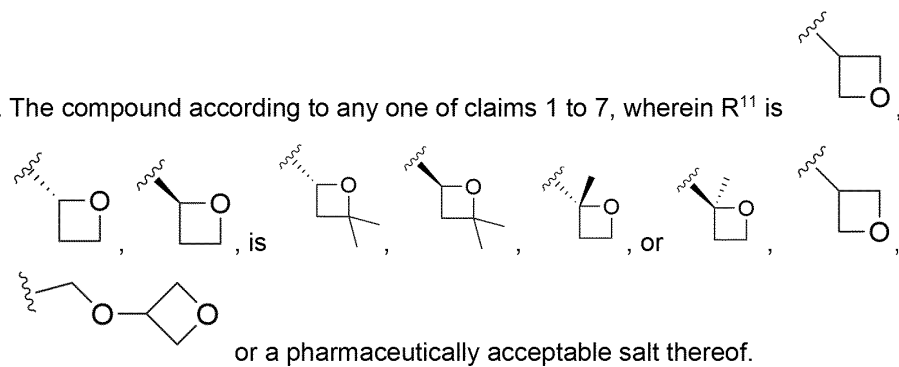
halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F, or a pharmaceutically acceptable salt thereof.

11. The compound according to any one of claims 1 to 6, wherein R³³ is tetrahydrofuranyl, or a pharmaceutically acceptable salt thereof.
12. The compound according to any one of claims 1 to 6, wherein R³³ is morpholinyl optionally substituted with C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
13. The compound according to any one of claims 1 to 6, wherein R³³ is pyridinyl optionally substituted with one or more substituents individually selected from NH₂; N(H)(CH₃); and N(CH₃)₂, or a pharmaceutically acceptable salt thereof.
14. The compound according to any one of claims 1 to 6, wherein R³³ is C₁₋₃ alkyl optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂, or a pharmaceutically acceptable salt thereof.
15. The compound according to any one of claims 1 to 6, wherein R³³ is C₁₋₃ alkoxy, or a pharmaceutically acceptable salt thereof.
16. The compound according to any one of claims 1 to 6, wherein R³³ is C₃₋₆ cycloalkyl optionally substituted with one or more substituents individually selected from halogen; C₁₋₃ alkoxy optionally substituted with one or more F; C₁₋₃ alkyl optionally substituted with one or more F; NH₂; N(H)(CH₃); and N(CH₃)₂, or a pharmaceutically acceptable salt thereof.
17. The compound according to any one of the preceding claims, wherein X¹³ is bond, -CH₂-, -C(H)(CH₃)-, -O-, or -CH₂O-, or a pharmaceutically acceptable salt thereof.
18. The compound according to any one of claims 1 to 7, wherein R¹¹ is

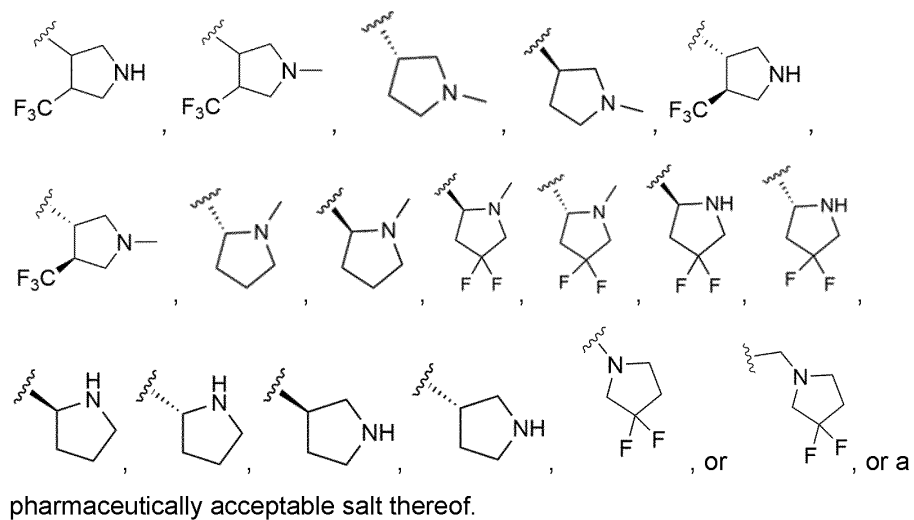




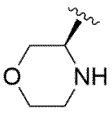
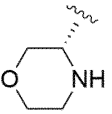
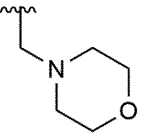
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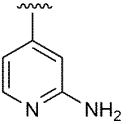
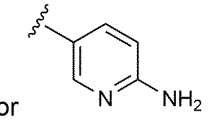
19. The compound according to any one of claims 1 to 7, wherein R¹¹ is20. The compound according to any one of claims 1 to 7, wherein R¹¹ is

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21. The compound according to any one of claims 1 to 7, wherein R¹¹ is  or , or a pharmaceutically acceptable salt thereof.

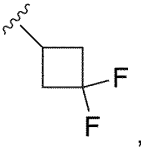
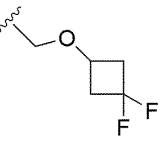
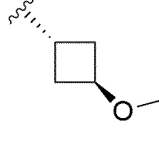
22. The compound according to any one of claims 1 to 7, wherein R¹¹ is , , or , or a pharmaceutically acceptable salt thereof.

23. The compound according to any one of claims 1 to 7, wherein R¹¹ is  or , or a pharmaceutically acceptable salt thereof.

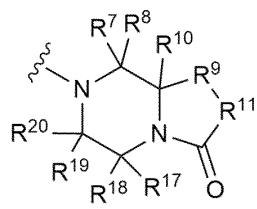
24. The compound according to any one of claims 1 to 7, wherein R¹¹ is CH₃, -CH₂NH₂, -CH₂-N(H)(CH₃), -CH₂N(CH₃)₂, is -OCH₃, -CH₂-O-CF₃, -CH₂-O-CHF₂, or CHF₂, or a pharmaceutically acceptable salt thereof.

25. The compound according to any one of claims 1 to 7, wherein R¹¹ is -OCH₃, or a pharmaceutically acceptable salt thereof.

26. The compound according to any one of claims 1 to 7, wherein R¹¹ is

cyclopropyl, cyclobutyl, , , or , or a pharmaceutically acceptable salt thereof.

27. The compound according to any one of claims 1 to 4, wherein R⁴ is of Formula (LI):



Formula (LI)

wherein

R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

R^9 is a bond, $-C(O)-$ or a C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{11} is $-O-$, $-N(R^{28})-$, or C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl, wherein one methylene group of the C_{1-3} alkanediyl is optionally replaced by $-O-$ or $-N(R^{28})-$, wherein R^{28} is H or C_{1-3} alkyl;

R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

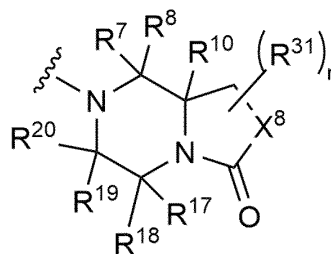
R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

and

R^{28} is H or C_{1-3} alkyl,

or a pharmaceutically acceptable salt thereof.

28. The compound according to any one of claims 1 to 4, wherein R^4 is of Formula (XX):



Formula (XX)

wherein

R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen;
 R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen;
 R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen;
 R^{17} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen;
 R^{18} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen;
 R^{19} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen;
 R^{20} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen;;
 R^{31} is individually halogen or C_{1-3} alkyl;

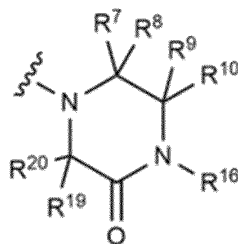
r is 0, 1, 2, 3 or 4;

X^8 is $-CH_2-$, $-O-$ or $-N(R^{28})-$; and

R^{28} is H or C_{1-3} alkyl,

or a pharmaceutically acceptable salt thereof.

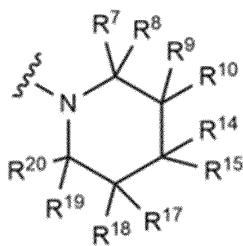
29. The compound according to any one of claims 1 to 5, wherein R^4 is of Formula (XXXIV):



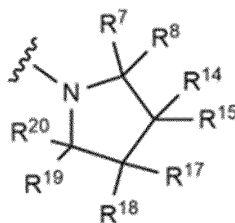
Formula (XXXIV)

or a pharmaceutically acceptable salt thereof.

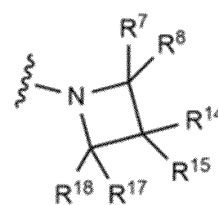
30. The compound according to any one of claims 1 to 5, wherein R^4 is of Formula (XXXV), Formula (XXXVI), Formula (XXXVII):



Formula (XXXV)



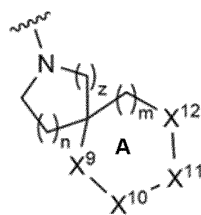
Formula (XXXVI)



Formula (XXXVII)

or a pharmaceutically acceptable salt thereof.

31. The compound according to any one of any one of claims 1 to 5, wherein R^4 is of Formula (XIX):



Formula (XIX)

wherein

X⁹ is a bond or -N(R²⁹)-;

5 R²⁹ is C₁₋₃ alkyl;

X¹⁰ is -C(O)-, -CH₂-, or a bond;

X¹¹ is -O-, -CH₂-, or -N(R³⁰)-;

R³⁰ is C₁₋₃ alkyl;

X¹² is -N(C(O)R²⁴)- or a bond;

10 m is 1 or 2;

n is 0 or 1; and

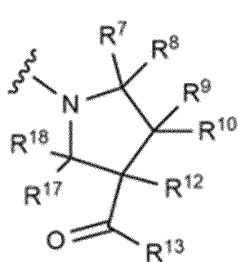
z is 1 or 2;

with the proviso that when X¹⁰ is -C(O)-, then X¹² is a bond;

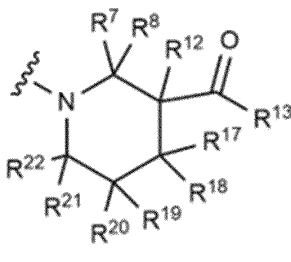
with the proviso that when X¹⁰ is -CH₂- or a bond, then X¹² is -N(C(O)R²⁴)-; and

15 with the proviso that ring A is a 4 to 6 membered ring, or a pharmaceutically acceptable salt thereof.

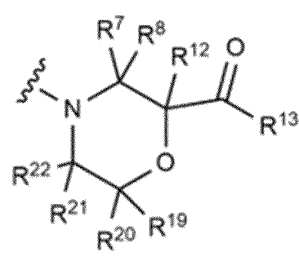
32. The compound according to any one of claims 1 to 5, wherein R⁴ is of Formula (XXXVIII), Formula (XXXIX), or Formula (XL):



Formula (XXXVIII)



Formula (XXXIX)

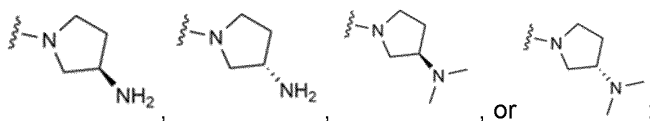


Formula (XL)

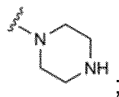
or a pharmaceutically acceptable salt thereof.

20 33. The compound according to claim 32, wherein R¹³ is selected from the group consisting of:

- pyrrolidinyl optionally substituted with NH_2 , $\text{N(H)(CH}_3\text{)}$, or $\text{N(CH}_3\text{)}_2$, such as

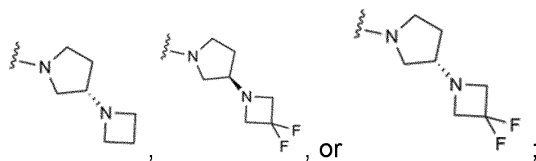
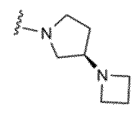


- piperazinyl, such as
- pyrrolidinyl optionally substituted with azetidiny, wherein the azetidiny is

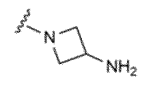


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optionally substituted with one or more halogens, such as



- azetidiny optionally substituted with NH_2 , such as
- NH_2 ;
- $\text{N(H)(CH}_3\text{)}$; and
- $\text{N(CH}_3\text{)}_2$,



10

or a pharmaceutically acceptable salt thereof.

34. The compound according to claim 1, wherein the compound is:

4-(3,4,5-trichloro-1H-indole-2-carbonyl)piperazin-2-one;

4-(4,5-dichloro-3-fluoro-1H-indole-2-carbonyl)piperazin-2-one;

15 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;

2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one;

7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one;

20 methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate;

1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-3,3-dimethylpiperazin-1-yl)ethan-1-one;

(S)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one;

(S)-4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,5-dimethylpiperazin-2-one;

- 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
2-amino-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
5 ((R)-3-aminopyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone;
(3,4-dichloro-5-fluoro-1H-indol-2-yl)((3R)-3-(3-(dimethylamino)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)methanone;
(3-(azetidin-1-yl)pyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone;
10 (3,4-dichloro-5-fluoro-1H-indol-2-yl)((3R)-3-(3-(3,3-difluoroazetidin-1-yl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)methanone;
(2-amino-4-pyridyl)-[4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl]methanone;
8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methyl-2,8-diazaspiro[4.5]decan-1-one;
15 one;
8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1-methyl-1,8-diazaspiro[4.5]decan-2-one;
8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1-methyl-3-oxa-1,8-diazaspiro[4.5]decan-2-one;
20 8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,3-dimethyl-1,3,8-triazaspiro[4.5]decan-2-one;
(S)-4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,3-dimethylpiperazin-2-one;
(S)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
25 (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(methyl-D-prolyl)piperazin-1-yl)methanone;
(R)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(4,4-difluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methylhexahydroimidazo[1,5-a]pyrazin-3(2H)-one;
30 (R)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
(S)-(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-(1-methylpyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
(4-(6-aminonicotinoyl)piperazin-1-yl)(3,4-dichloro-5-fluoro-1H-indol-2-yl)methanone;

- (S)-2-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
(*R*)-2-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
5 (*R*)-7-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydro-3*H*-oxazolo[3,4-*a*]pyrazin-3-one;
(*S*)-7-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydro-3*H*-oxazolo[3,4-*a*]pyrazin-3-one;
10 1-(4-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl) piperazin-1-yl)-2-morpholinoethan-1-one;
(4-(2-aminoisonicotinoyl) piperazin-1-yl) (3,4-dichloro-5-fluoro-1*H*-indol-2-yl) methanone;
1-(4-(3,4-dichloro-1*H*-indole-2-carbonyl) piperazin-1-yl)-2-methoxyethan-1-one;
(*S*)-2-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl) hexahydropyrrolo[1,2-*a*] pyrazin-6(2*H*)-one;
15 (*R*)-2-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl) hexahydropyrrolo[1,2-*a*] pyrazin-6(2*H*)-one;
2-amino-1-(4-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
(*R*)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-prolylpiperazin-1-yl)methanone;
20 ((3*S*,4*R*)-3-amino-4-fluoropyrrolidin-1-yl)((*R*)-1-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)pyrrolidin-3-yl)methanone;
(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-((3*S*,4*S*)-4-(trifluoromethyl)pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
azetidin-3-yl(4-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl)piperazin-1-yl)methanone;
25 (4-chloro-3,5-difluoro-1*H*-indol-2-yl)(4-(3-fluoroazetidine-3-carbonyl)piperazin-1-yl)methanone;
((3*S*,4*S*)-3-amino-4-fluoropyrrolidin-1-yl)(®-1-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl) pyrrolidine-3-yl)methanone;
(*S*)-(4-chloro-3,5-difluoro-1*H*-indol-2-yl) (4-(morpholine-3-carbonyl) piperazin-1-yl) methanone;
30 (*R*)-(4-chloro-3,5-difluoro-1*H*-indol-2-yl)(4-(morpholine-3-carbonyl)piperazin-1-yl)methanone;
(*S*)-azetidin-2-yl(4-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl)piperazin-1-yl)methanone;

- (R)-azetidin-2-yl(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)methanone;
(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4R)-4-fluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- 5 (4-(2-aminoisonicotinoyl) piperazin-1-yl) (4-chloro-3,5-difluoro-1H-indol-2-yl) methanone;
(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl) (4-(4,4-difluoropyrrolidine-2-carbonyl) piperazin-1-yl) methanone;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl) (4-(4,4-difluoropyrrolidine-2-carbonyl) piperazin-1-yl) methanone;
- 10 2-(azetidin-3-yloxy)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-propylpiperazin-1-yl)methanone;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-propylpiperazin-1-yl)methanone;
- 15 ((R)-3-aminopyrrolidin-1-yl) ((R)-1-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl) pyrrolidin-3-yl) methanone;
1-(4-(3-chloro-4-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-2-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-
- 20 (dimethylamino)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-morpholinoethan-1-one;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(oxetane-3-carbonyl)piperazin-1-yl)methanone;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(3,3-difluorocyclobutane-1-carbonyl)piperazin-1-yl)methanone;
- 25 (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-((1R,3R)-3-methoxycyclobutane-1-carbonyl)piperazin-1-yl)methanone;
1-(4-(3-chloro-4,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone;
- 30 (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone;
2-(azetidin-1-yl)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;

- (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(1-methylazetidine-3-carbonyl)piperazin-1-yl)methanone;
(3aR,6aR)-5-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methylhexahydropyrrolo[3,4-c]pyrrol-1(2H)-one;
- 5 2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(methyl-L-prolyl)piperazin-1-yl)methanone;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(methyl-D-prolyl)piperazin-1-yl)methanone;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
- 10 (S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-methoxyethan-1-one;
2-(4-(azetidine-1-yl)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4-methylmorpholine-3-carbonyl)piperazin-1-yl)methanone;
- 15 (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4-methylmorpholine-3-carbonyl)piperazin-1-yl)methanone;
2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)octahydro-6H-pyrido[1,2-a]pyrazin-6-one;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-methoxyazetidin-1-yl)ethan-1-one;
- 20 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-1-yl)ethan-1-one;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
- 25 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-methoxyazetidin-1-yl)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-1-yl)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
- 30 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(oxetan-3-yloxy)ethan-1-one;
(R)-7-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one;

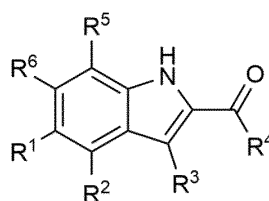
- (S)-7-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one;
- (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4S)-4-fluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- 5 5-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methyloctahydro-3H-pyrrolo[3,4-c]pyridine-3-one;
- (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((3S,4S)-1-methyl-4-(trifluoromethyl)pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
- (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4R)-4-fluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- 10 (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(3-fluoro-1-methylazetidine-3-carbonyl)piperazin-1-yl)methanone;
- 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-((1-methylazetidin-3-yl)oxy)ethan-1-one;
- 15 (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4S)-4-fluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- 20 (3-fluoroazetidin-3-yl)methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate;
- azetidin-3-yl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl) piperazine-1-carboxylate;
- 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(oxetan-3-yloxy)ethan-1-one;
- 25 8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one;
- 7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)tetrahydroimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione;
- 30 2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-8-methylhexahydropyrrolo[1,2-a]pyrazin-6(2H)-one;
- 2-(azetidin-3-yloxy)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
- (3aR,6aR)-5-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-2-
- 35 methylhexahydropyrrolo[3,4-c]pyrrol-1(2H)-one;

- 2-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one;
(R)-2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one;
- 5 (S)-2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-((1-methylazetidin-3-yl)oxy)ethan-1-one;
8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)octahydro-4H-pyrazino[1,2-a]pyrazin-4-one;
- 10 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-3-yl)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoropyrrolidin-1-yl)ethan-1-one;
- 15 (S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluorocyclobutoxy)ethan-1-one;
- (R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-(methoxymethyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
- 20 (S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)propan-1-one;
(R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)propan-1-one;
- 25 (S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoro-2-methylazetidin-1-yl)ethan-1-one;
(R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoro-2-methylazetidin-1-yl)ethan-1-one;
- 4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylmorpholine-2-carboxamide;
- 30 (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone;
- 4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylpiperazine-2-carboxamide;
- 35 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;

- (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-dimethyloxetane-2-carbonyl)piperazin-1-yl)methanone;
(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-dimethyloxetane-2-carbonyl)piperazin-1-yl)methanone;
- 5 (S)-8-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one;
(R)-8-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2,2-difluoroethan-1-one;
- 10 (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(2-methyloxetane-2-carbonyl)piperazin-1-yl)methanone;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(trifluoromethoxy)ethan-1-one;
- 15 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(difluoromethoxy)ethan-1-one;
(S)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N-methylpiperazine-2-carboxamide;
(S)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylpiperazine-2-carboxamide;
- 20 1-(4-(3,4-dichloro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
(R)-(4-chloro-3-fluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone;
1-(4-(4-chloro-3-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
1-(4-(4-chloro-3-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
- 25 (R)-(4-chloro-3-fluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone;
(R)-(3,4-dichloro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone;
(S)-1-(4-(3,4-dichloro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-methoxyethan-1-one; and
- 30 (R)-(3,4-dichloro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone,

or a pharmaceutically acceptable salt thereof.

35. The compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein the compound is a K_v1.3 potassium channel inhibitor.
36. A pharmaceutical composition comprising a compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.
37. The compound according to any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 36, for use as a medicament.
38. The compound according to any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 36, for use in the treatment of a disease or medical condition where inhibition of K_v1.3 potassium channel is beneficial.
39. A compound of Formula (I):



Formula (I)

wherein

R¹ is halogen or H;

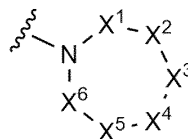
R² is halogen;

R³ is H or halogen;

R⁵ is H or halogen;

R⁶ is H or halogen;

R⁴ is of Formula (II):



Formula (II)

wherein

X¹ is C(R⁷)(R⁸);

X² is C(R⁹)(R¹⁰) or a bond;

X^3 is $N(C(O)R^{11})$, $C(R^{12})(C(O)R^{13})$, $C(R^{14})(R^{15})$ or $N(R^{16})$;

X^4 is $C(R^{17})(R^{18})$, O or $C(O)$;

X^5 is $C(R^{19})(R^{20})$ or a bond;

X^6 is a bond or $C(R^{21})(R^{22})$;

5 wherein R^9 and R^{11} , R^9 and R^{13} , R^{10} and R^{11} , R^{10} and R^{13} , R^{13} and R^{17} , R^{13} and R^{18} , or R^{14} and R^{15} are optionally joined together to form a ring together with the intervening atom(s);

R^7 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

10 R^8 is H, C_{1-3} alkyl optionally substituted with 1 to 3 F or C_{1-3} alkoxy, or halogen, such as F;

R^9 is H, C_{1-3} alkyl optionally substituted with 1 to 3 halogens, halogen, such as F, or $-C(O)N(R^{31})(R^{32})$, wherein R^{31} is H or C_{1-3} alkyl and R^{32} is H or C_{1-3} alkyl, or when R^9 is linked to R^{11} or R^{13} to form a ring, then R^9 is a bond, $-C(O)-$ or a

15 C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

R^{10} is H, C_{1-3} alkyl optionally substituted with 1 to 3 halogens, halogen, such as F, or $-C(O)N(R^{31})(R^{32})$, wherein R^{31} is H or C_{1-3} alkyl and R^{32} is H or C_{1-3} alkyl, or when R^{10} is linked to R^{11} or R^{13} to form a ring, then R^{10} is a bond, $-C(O)-$ or a

20 C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl;

R^{11} is $-X^{13}-R^{33}$;

X^{13} is a bond, C_{1-3} alkanediyl optionally substituted with C_{1-3} alkyl, $-O-$, or C_{1-3} alkanediyl- $O-$;

25 R^{33} is selected from the group consisting of C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, pyridinyl, azetidiny, pyrrolidinyl, oxetanyl, tetrahydrofuranyl, and morpholinyl, each of which is optionally substituted with one or more substituents individually selected from halogen; C_{1-3} alkoxy optionally substituted with one or more F; C_{1-3} alkyl optionally substituted with one or more F; NH_2 ; $N(H)(CH_3)$; and $N(CH_3)_2$;

30 or when R^{11} is linked to R^9 or R^{10} to form a ring, then R^{11} is $-O-$, $-N(R^{28})-$, or C_{1-3} alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C_{1-3} alkyl, wherein one methylene group of the C_{1-3} alkanediyl is optionally replaced by $-O-$ or $-N(R^{28})-$, wherein R^{28} is H or C_{1-3} alkyl;

35 R^{12} is H, C_{1-3} alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R¹³ is selected from the group consisting of NH₂, N(H)(CH₃), N(CH₃)₂, pyrrolidinyl, azetidiny, and piperazinyl, wherein

- said pyrrolidinyl is optionally substituted with one or more substituents individually selected from the group consisting of halogen, NH₂,
5 N(H)(CH₃), N(CH₃)₂ and azetidiny, and said azetidiny is optionally substituted with one or more halogens, and
- said azetidiny optionally substituted with NH₂;

or when R¹³ is linked to R⁹, R¹⁰, R¹⁷, or R¹⁸ to form a ring, then R¹³ is -N(R²⁸)-, wherein R²⁸ is H or C₁₋₃ alkyl;

10 R¹⁴ is -X⁷N(R²³)(C(O)R²⁴),

wherein

X⁷ is a bond or C₁₋₃ alkanediyl;

R²⁴ is C₁₋₃ alkyl; and

R²³ is H or C₁₋₃ alkyl, and R¹⁵ is H or C₁₋₃ alkyl,

15 or R²³ is a bond or C₁₋₃ alkanediyl, and R¹⁵ is a bond or C₁₋₃ alkanediyl and R²³ is linked to R¹⁵ to form a ring;

or R¹⁴ is -X⁹C(O)X¹¹-, R¹⁵ is a bond or C₁₋₃ alkanediyl, and X¹¹ is linked to R¹⁵ to form a ring,

wherein

20 X⁹ is a bond or -N(R²⁹)-;

R²⁹ is C₁₋₃ alkyl;

X¹¹ is -O-, C₁₋₃ alkanediyl, or -N(R³⁰)-; and

R³⁰ is C₁₋₃ alkyl;

R¹⁶ is H or C₁₋₃ alkyl;

25 R¹⁷ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or when R¹⁷ is linked to R¹³ to form a ring, then R¹⁷ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

30 R¹⁸ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F; or when R¹⁸ is linked to R¹³ to form a ring, then R¹⁸ is a bond or a C₁₋₃ alkanediyl optionally substituted with 1 to 3 substituents individually selected from halogen and C₁₋₃ alkyl;

R¹⁹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R²⁰ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

35 R²¹ is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;

R²² is H, C₁₋₃ alkyl optionally substituted with 1 to 3 F, or halogen, such as F;
any two of R⁷, R⁸, R⁹, R¹⁰, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, and R²² are optionally linked
together to form a ring;

with the proviso that when X⁴ is O, then X³ is C(R¹²)C(O)R¹³ and R¹³ is NH₂,
N(H)(CH₃) or N(CH₃)₂;

with the proviso that when X³ is N(R¹⁶), then X⁴ is C(O),

with the proviso that when X⁴ is C(O), then X³ is N(R¹⁶), and

with the proviso that when X² is a bond, then X³ is C(R¹²)(C(O)R¹³) or
C(R¹⁴)(R¹⁵),

or a pharmaceutically acceptable salt thereof, for use in the treatment of a
disease or medical condition where inhibition of K_v1.3 potassium channel is
beneficial.

40. The compound for use according to claim 39, wherein R¹ is halogen, and R³ is
halogen.

41. The compound for use according to claim 39, wherein the compound is:

4-(3,4,5-trichloro-1H-indole-2-carbonyl)piperazin-2-one;

1-(4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one;

1-[(2R)-4-(4,5-dichloro-1H-indole-2-carbonyl)-2-methyl-piperazin-1-yl]ethanone;

1-[4-(4,5-dichloro-1H-indole-2-carbonyl)-2,2-dimethyl-piperazin-1-yl]ethanone;

1-[3-(4,5-dichloro-1H-indole-2-carbonyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]ethanone;

1-[4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl]ethanone;

1-[(3S)-4-(4,5-dichloro-1H-indole-2-carbonyl)-3-methyl-piperazin-1-yl]ethanone;

1-[4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl]-2-

(dimethylamino)ethanone;

1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-3,3-dimethylpiperazin-1-yl)ethan-1-one;

2-amino-1-[4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl]ethanone;

2-amino-1-[4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl]ethanone;

(3R)-1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidine-3-carboxamide;

4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-2-one;

4-(4,5-dichloro-1H-indole-2-carbonyl)-1-methyl-piperazin-2-one;

4-(4,5-dichloro-6-fluoro-1H-indole-2-carbonyl)piperazin-2-one;

4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-2-one;

(3R)-1-[(4,5-dichloro-1H-indol-2-yl)carbonyl]-N-methylpyrrolidine-3-carboxamide;

4-(4-chloro-1H-indole-2-carbonyl)piperazin-2-one;

- 1-[4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl]-2-methoxy-ethanone;
1-(4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
1-[4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl]-2-methoxy-ethanone;
4-(4,5-dichloro-7-fluoro-1H-indole-2-carbonyl)piperazin-2-one;
5 4-(4,5-dichloro-3-fluoro-1H-indole-2-carbonyl)piperazin-2-one;
(S)-(4,5-dichloro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
[4-(azetidine-3-carbonyl)piperazin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone;
(4,5-dichloro-1H-indol-2-yl)-[4-[(3R)-pyrrolidine-3-carbonyl]piperazin-1-yl]methanone;
[4-[(2S)-azetidine-2-carbonyl]piperazin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone;
10 (4,5-dichloro-1H-indol-2-yl)-[4-[(2S)-pyrrolidine-2-carbonyl]piperazin-1-yl]methanone;
(4-(cyclopropanecarbonyl)piperazin-1-yl)(4,5-dichloro-1H-indol-2-yl)methanone;
(4-(2-aminoisonicotinoyl)piperazin-1-yl)(4,5-dichloro-1H-indol-2-yl) methanone;
((R)-3-aminopyrrolidin-1-yl)((R)-1-(4,5-dichloro-1H-indole-2-carbonyl) pyrrolidin-3-yl)methanone;
15 [(3R)-3-(3-aminoazetidine-1-carbonyl)pyrrolidin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone;
[(3R)-3-[(3S)-3-aminopyrrolidine-1-carbonyl]pyrrolidin-1-yl]-(4,5-dichloro-1H-indol-2-yl)methanone;
N-[1-(4-acetamidophenyl)sulfonyl-4-piperidyl]-3,5-dimethyl-1H-pyrrole-2-carboxamide;
20 (R)-N-(1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidin-3-yl)acetamide;
(R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpyrrolidine-3-carboxamide;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one;
25 7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one;
methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate;
(S)-1-(4-(4-chloro-5-fluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one;
4-(4,5-dichloro-1H-indole-2-carbonyl)-N-methylmorpholine-2-carboxamide;
30 1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-3,3-dimethylpiperazin-1-yl)ethan-1-one;
(S)-1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-2-methylpiperazin-1-yl)ethan-1-one;
(S)-1-(4,5-dichloro-1H-indole-2-carbonyl)pyrrolidine-3-carboxamide;
(R)-1-(4-(4,5-dichloro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one;
1-(3-(4,5-dichloro-1H-indole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl)ethan-1-
35 one;

- 1-(5-(4,5-dichloro-1H-indole-2-carbonyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)ethan-1-one;
1-(6-(4,5-dichloro-1H-indole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)ethan-1-one;
1-((2S,5R)-4-(4,5-dichloro-1H-indole-2-carbonyl)-2,5-dimethylpiperazin-1-yl)ethan-1-one;
5 (R)-1-(4,5-dichloro-1H-indole-2-carbonyl)-N,N-dimethylpyrrolidine-3-carboxamide;
1-(8-(4,5-dichloro-1H-indole-2-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)ethan-1-one;
(S)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)ethan-1-one;
10 (S)-4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-1,5-dimethylpiperazin-2-one;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
2-amino-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
15 (R)-(4,5-dichloro-1H-indol-2-yl)(4-prolylpiperazin-1-yl)methanone;
(S)-(4-chloro-5-fluoro-1H-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
(R)-azetidin-2-yl(4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl)methanone;
((R)-3-aminopyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone;
20 (3,4-dichloro-5-fluoro-1H-indol-2-yl)((3R)-3-(3-(dimethylamino)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)methanone;
((R)-3-aminopyrrolidin-1-yl)((R)-1-(4-chloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone;
25 (3-(azetidin-1-yl)pyrrolidin-1-yl)((R)-1-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)pyrrolidin-3-yl)methanone;
(3,4-dichloro-5-fluoro-1H-indol-2-yl)((3R)-3-(3-(3,3-difluoroazetidin-1-yl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)methanone;
(2-amino-4-pyridyl)-[4-(4,5-dichloro-1H-indole-2-carbonyl)piperazin-1-yl]methanone;
30 1-(6-(4,5-dichloro-1H-indole-2-carbonyl)-2,6-diazaspiro[3.4]octan-2-yl)ethan-1-one;
1-(6-(4,5-dichloro-1H-indole-2-carbonyl)-1,6-diazaspiro[3.4]octan-1-yl)ethan-1-one;
1-(7-(4,5-dichloro-1H-indole-2-carbonyl)-1,7-diazaspiro[4.4]nonan-1-yl)ethan-1-one;
1-(2-(4,5-dichloro-1H-indole-2-carbonyl)-2,6-diazaspiro[3.4]octan-6-yl)ethan-1-one;
1-(7-(4,5-dichloro-1H-indole-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)ethan-1-one;

- 8-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)-2-methyl-2,8-diazaspiro[4.5]decan-1-one;
- 8-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)-1-methyl-1,8-diazaspiro[4.5]decan-2-one;
- 5 8-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)-1-methyl-3-oxa-1,8-diazaspiro[4.5]decan-2-one;
- 8-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)-1,3-dimethyl-1,3,8-triazaspiro[4.5]decan-2-one;
- (*S*)-4-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)-1,3-dimethylpiperazin-2-one;
- 10 (*S*)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
- (3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(methyl-D-prolyl)piperazin-1-yl)methanone;
- (*R*)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(4,4-difluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- 15 7-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)-2-methylhexahydroimidazo[1,5-*a*]pyrazin-3(2*H*)-one;
- (*R*)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- (*S*)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-(1-methylpyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
- 20 (4-(6-aminonicotinoyl)piperazin-1-yl)(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)methanone;
- (*S*)-2-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
- (*R*)-2-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one;
- 25 (*R*)-7-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydro-3*H*-oxazolo[3,4-*a*]pyrazin-3-one;
- (*S*)-7-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)hexahydro-3*H*-oxazolo[3,4-*a*]pyrazin-3-one;
- 30 1-(4-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl) piperazin-1-yl)-2-morpholinoethan-1-one;
- (4-(2-aminoisonicotinoyl) piperazin-1-yl) (3,4-dichloro-5-fluoro-1*H*-indol-2-yl) methanone;
- 1-(4-(3,4-dichloro-1*H*-indole-2-carbonyl) piperazin-1-yl)-2-methoxyethan-1-one;

- (S)-2-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl) hexahydropyrrolo[1,2-*a*] pyrazin-6(2*H*)-one;
(*R*)-2-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl) hexahydropyrrolo[1,2-*a*] pyrazin-6(2*H*)-one;
- 5 2-amino-1-(4-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
(*R*)-(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-prolylpiperazin-1-yl)methanone;
((3*S*,4*R*)-3-amino-4-fluoropyrrolidin-1-yl)((*R*)-1-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl)pyrrolidin-3-yl)methanone;
(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-((3*S*,4*S*)-4-(trifluoromethyl)pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
- 10 azetidin-3-yl(4-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl)piperazin-1-yl)methanone;
(4-chloro-3,5-difluoro-1*H*-indol-2-yl)(4-(3-fluoroazetidine-3-carbonyl)piperazin-1-yl)methanone;
((3*S*,4*S*)-3-amino-4-fluoropyrrolidin-1-yl)(®-1-(3,4-dichloro-5-fluoro-1*H*-indole-2-carbonyl) pyrrolidine-3-yl)methanone;
- 15 (*S*)-(4-chloro-3,5-difluoro-1*H*-indol-2-yl) (4-(morpholine-3-carbonyl) piperazin-1-yl) methanone;
(*R*)-(4-chloro-3,5-difluoro-1*H*-indol-2-yl)(4-(morpholine-3-carbonyl)piperazin-1-yl)methanone;
- 20 (*S*)-azetidin-2-yl(4-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl)piperazin-1-yl)methanone;
(*R*)-azetidin-2-yl(4-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl)piperazin-1-yl)methanone;
(3,4-dichloro-5-fluoro-1*H*-indol-2-yl)(4-((2*R*,4*R*)-4-fluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- 25 (4-(2-aminoisonicotinoyl) piperazin-1-yl) (4-chloro-3,5-difluoro-1*H*-indol-2-yl) methanone;
(*S*)-(4-chloro-3,5-difluoro-1*H*-indol-2-yl) (4-(4,4-difluoropyrrolidine-2-carbonyl) piperazin-1-yl) methanone;
- 30 (*R*)-(4-chloro-3,5-difluoro-1*H*-indol-2-yl) (4-(4,4-difluoropyrrolidine-2-carbonyl) piperazin-1-yl) methanone;
2-(azetidin-3-yloxy)-1-(4-(4-chloro-3,5-difluoro-1*H*-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
- 35 (*S*)-(4-chloro-3,5-difluoro-1*H*-indol-2-yl)(4-prolylpiperazin-1-yl)methanone;
(*R*)-(4-chloro-3,5-difluoro-1*H*-indol-2-yl)(4-prolylpiperazin-1-yl)methanone;

- ((R)-3-aminopyrrolidin-1-yl) ((R)-1-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl) pyrrolidin-3-yl) methanone;
1-(4-(3-chloro-4-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-2-one;
5 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(dimethylamino)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-morpholinoethan-1-one;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(oxetane-3-carbonyl)piperazin-1-yl)methanone;
10 (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(3,3-difluorocyclobutane-1-carbonyl)piperazin-1-yl)methanone;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-((1R,3R)-3-methoxycyclobutane-1-carbonyl)piperazin-1-yl)methanone;
1-(4-(3-chloro-4,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
15 (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone;
2-(azetidin-1-yl)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-
20 1-one;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(1-methylazetidine-3-carbonyl)piperazin-1-yl)methanone;
(3aR,6aR)-5-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methylhexahydropyrrolo[3,4-c]pyrrol-1(2H)-one;
25 2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(methyl-L-prolyl)piperazin-1-yl)methanone;
(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(methyl-D-prolyl)piperazin-1-yl)methanone;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
30 (S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-methoxyethan-1-one;
2-(azetidine-1-yl)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4-methylmorpholine-3-carbonyl)piperazin-
35 1-yl)methanone;

- (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl) (4-(4-methylmorpholine-3-carbonyl) piperazin-1-yl) methanone;
- 2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)octahydro-6H-pyrido[1,2-a]pyrazin-6-one;
- 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-methoxyazetidin-1-yl)ethan-1-one;
- 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-1-yl)ethan-1-one;
- 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
- 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-methoxyazetidin-1-yl)ethan-1-one;
- 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-1-yl)ethan-1-one;
- 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
- 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(oxetan-3-yloxy)ethan-1-one;
- (R)-7-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one;
- (S)-7-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one;
- (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4S)-4-fluoropyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- 5-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-2-methyloctahydro-3H-pyrrolo[3,4-c]pyridine-3-one;
- (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((3S,4S)-1-methyl-4-(trifluoromethyl)pyrrolidine-3-carbonyl)piperazin-1-yl)methanone;
- (3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4R)-4-fluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- (4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(3-fluoro-1-methylazetidine-3-carbonyl)piperazin-1-yl)methanone;
- 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-((1-methylazetidin-3-yl)oxy)ethan-1-one;
- (S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;

- (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
(3,4-dichloro-5-fluoro-1H-indol-2-yl)(4-((2R,4S)-4-fluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)methanone;
- 5 (3-fluoroazetidin-3-yl)methyl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazine-1-carboxylate;
azetidin-3-yl 4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl) piperazine-1-carboxylate;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(oxetan-3-yloxy)ethan-1-one;
- 10 8-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one;
7-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)tetrahydroimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione;
2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)-8-methylhexahydropyrrolo[1,2-a]pyrazin-
- 15 6(2H)-one;
2-(azetidin-3-yloxy)-1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
(3aR,6aR)-5-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-2-methylhexahydropyrrolo[3,4-c]pyrrol-1(2H)-one;
- 20 2-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one;
(R)-2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-6-one;
(S)-2-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)hexahydro-2H,6H-pyrazino[1,2-
- 25 c][1,3]oxazin-6-one;
1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-((1-methylazetidin-3-yl)oxy)ethan-1-one;
8-(3,4-dichloro-5-fluoro-1 H-indole-2-carbonyl)octahydro-4 H-pyrazino[1,2- a]pyrazin-4-one;
- 30 1-(4-(3,4-dichloro-5-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3-fluoroazetidin-3-yl)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoropyrrolidin-1-yl)ethan-1-one;
(S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-(3,3-
- 35 difluoroazetidin-1-yl)ethan-1-one;

- 1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluorocyclobutoxy)ethan-1-one;
(R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-3-(methoxymethyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
- 5 (S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)propan-1-one;
(R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)propan-1-one;
(S)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoro-2-
- 10 methylazetidin-1-yl)ethan-1-one;
(R)-1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoro-2-methylazetidin-1-yl)ethan-1-one;
4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylmorpholine-2-carboxamide;
(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-
- 15 yl)methanone;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone;
4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylpiperazine-2-carboxamide;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)ethan-1-one;
- 20 (R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-dimethyloxetane-2-carbonyl)piperazin-1-yl)methanone;
(S)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(4,4-dimethyloxetane-2-carbonyl)piperazin-1-yl)methanone;
(S)-8-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydropyrazino[2,1-c][1,4]oxazin-
- 25 4(3H)-one;
(R)-8-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2,2-difluoroethan-1-
- 30 one;
(R)-(4-chloro-3,5-difluoro-1H-indol-2-yl)(4-(2-methyloxetane-2-carbonyl)piperazin-1-yl)methanone;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-
- 35 (trifluoromethoxy)ethan-1-one;
1-(4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-
- (difluoromethoxy)ethan-1-one;

- (S)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N-methylpiperazine-2-carboxamide;
(S)-4-(4-chloro-3,5-difluoro-1H-indole-2-carbonyl)-N,N-dimethylpiperazine-2-carboxamide;
1-(4-(3,4-dichloro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
5 (R)-(4-chloro-3-fluoro-1H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone;
1-(4-(4-chloro-3-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-methoxyethan-1-one;
1-(4-(4-chloro-3-fluoro-1H-indole-2-carbonyl)piperazin-1-yl)-2-(3,3-difluoroazetidin-1-yl)ethan-1-one;
10 (R)-(4-chloro-3-fluoro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone;
(R)-(3,4-dichloro-1 H-indol-2-yl)(4-(oxetane-2-carbonyl)piperazin-1-yl)methanone;
(S)-1-(4-(3,4-dichloro-1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)-2-methoxyethan-1-one; or
15 (R)-(3,4-dichloro-1H-indol-2-yl)(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methanone,
or a pharmaceutically acceptable salt thereof.
42. The compound for use according to any one of claims 38 to 41, wherein the disease or medical condition is a neurodegenerative disease.
- 20 43. The compound for use according to any one of claims 38 to 41, wherein the disease or medical condition is Multiple Sclerosis, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease
44. The compound for use according to claim 42, wherein the neurodegenerative disease is a tauopathy, a TDP-43 proteinopathy, a synucleinopathy, dementia,
25 amyloidosis, a demyelinating disorder of the CNS, a demyelinating disorder of the PNS, a Leukoencephalopathy, a leukodystrophy, a transmissible spongiform encephalopathy (TSE), or a lysosomal storage disorder (LSD).
45. The compound for use according to claim 42, wherein the neurodegenerative disease is Alzheimer's disease, Frontotemporal lobar degeneration (FTLD),
30 frontotemporal dementia (FTD), Parkinson's disease, Nasu-Hakola disease, FTLD-like syndrome, Huntington disease, Amyotrophic lateral sclerosis, multiple sclerosis, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathies, Charcot-Marie-Tooth disease, prion disease or stroke.
46. The compound for use according to any one of claims 38 to 41, wherein the
35 disease or medical condition is rheumatoid arthritis (RA), neuropathic pain,

inflammatory pain, CNS complications of COVID-19 infection, post-COVID-19 conditions, Chronic Traumatic Encephalopathy, HIV-Associated Neurocognitive Disorder (HAND), Traumatic Brain Injury, Epilepsy, Autoimmune Encephalitis, Bipolar disorder, major depression disorder(MDD) or Schizophrenia.

- 5 47. The compound for use according to any one of claims 38 to 41, wherein the disease or medical condition is Psoriasis, Atopic dermatitis, Celiac Disease, Lupus, Type 1 diabetes, Sjogren's syndrome, Vasculitis, IBD, Crohn's disease, Graves' disease, Hashimoto's thyroiditis, Myasthenia gravis or Scleroderma.
- 10 48. The compound for use according to any one of claims 38 to 41, wherein the disease or medical condition is cancer; an immunological disorder, such as transplant rejection or an autoimmune disease, for example rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, or type I diabetes mellitus; a central nervous system disorder, such as Alzheimer's disease; an inflammatory disorder, such as an inflammatory skin condition, arthritis,
- 15 psoriasis, spondylitis, parodontitis, or an inflammatory neuropathy; a gastroenterological disorder, such as an inflammatory bowel disease; a metabolic disorder, such as obesity or type II diabetes mellitus; a cardiovascular disorder; or a kidney disease, such as chronic kidney disease, nephritis, or chronic renal failure.
- 20 49. The compound for use according to any one of claims 38 to 41, wherein the condition is selected from the group consisting of cancer, transplant rejection, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, type I diabetes mellitus, Alzheimer's disease, inflammatory skin condition,
- 25 inflammatory neuropathy, psoriasis, spondylitis, parodontitis, Crohn's disease, ulcerative colitis, obesity, type II diabetes mellitus, ischemic stroke, chronic kidney disease, nephritis, chronic renal failure, and a combination thereof.
- 30 50. Use of a compound, or a pharmaceutically acceptable salt thereof, as defined in any one of claims 20 to 22 for the manufacture of a medicament for treatment of disease or medical condition where inhibition of K_v1.3 potassium channel is beneficial.
51. A method for treatment of a disease or medical condition where inhibition of K_v1.3 potassium channel is beneficial comprising administering a compound, or a pharmaceutically acceptable salt thereof, as defined in any one of claims 38 to 41 to a subject in need thereof.

52. A method of blocking K_v1.3 potassium channel in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one as defined in any one of claims 38 to 41, or a pharmaceutically acceptable salt thereof.
- 5 53. The method according to any one of claims 52 or 53, wherein the subject is a mammal, such as human.