

TREM2 modulators

Technical field

The present invention relates to compounds useful for modulating Triggering Receptor Expressed on Myeloid Cells-2 ("TREM2"). The invention also relates to the compounds
5 for use in treatment of conditions related to loss of function of TREM2, such as neurodegenerative diseases, and to pharmaceutical compositions comprising the compounds.

10 Background

Triggering receptor expressed on myeloid cells-2 (TREM2) is a transmembrane receptor belonging to the immunoglobulin superfamily and is encoded by the TREM2 gene, which maps to human chromosome 6p21. TREM2 consists of an extracellular part that includes a single immunoglobulin domain and a short ectodomain, a single
15 transmembrane helix and a short cytosolic tail (Colonna, M. et al. (2016))).

Insight to the role of TREM2 is provided by its restricted expression pattern. It is expressed exclusively on myeloid lineage cells, such as macrophages, microglia, dendritic cells and osteoclasts. It plays a role in tissue maintenance, as a sensor of
20 pathology and inducer of innate immune signalling in specific tissues. In the brain TREM2 is exclusively expressed in microglia and is functionally required e.g. in phagocytosis of cellular debris, but has also been assigned roles in restricting inflammation as well as promoting cell survival (Deczkowska, A. et al. (2020)).

25 TREM2 has a wide range of ligands such as bacterial anionic molecules/endotoxins, phospholipids incl phosphatidylserine, lipoproteins and apolipoproteins incl ApoE, as well as oligomeric A β (Hammond, T. R. (2019)).

Signaling via TREM2 is well described through co-receptor DAP12. The adaptor
30 molecule DAP 12 is expressed as a homodimer at the surface of a variety of cells participating in the innate immune response, including microglia, macrophages, granulocytes, NK cells, and dendritic cells. After ligation of TREM2, ITAM (immunoreceptor tyrosine-based activation motif) tyrosine phosphorylation of DAP12 by SRC-family kinases drive the recruitment and activation of the Syk kinase and/or
35 ZAP70 kinase. Downstream of TREM2/DAP12/Syk several signaling pathways have

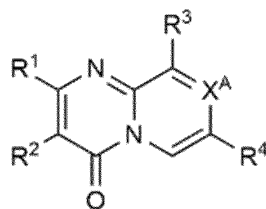
been described involved in cell survival, cell activation and differentiation, and in the control of the actin cytoskeleton.

- 5 Proteolytic cleavage of the ectodomain of TREM2 by metalloproteinases, including ADAM10 and ADAM17 and possibly matrix metalloproteinases, leads to the shedding of soluble TREM2 (sTREM2), which can be detected in human cerebrospinal fluid (CSF). sTREM2 has been suggested as a potential biomarker for microglia activity in early-stage Alzheimer's disease (Suárez-Calvet, M. et al. (2016)).
- 10 Deficiency of either TREM2 or DAP12 leads to a blunted microglial response to pathological agents. The impact of TREM2-deficiency in vitro has been shown in the context of stimulation with typical TLR ligands, such as LPS. Loss-of-function genetic variants of TREM2 are associated with neurodegenerative diseases and supports a central role of microglial function in disease pathogenesis. Homozygous loss-of-
- 15 function TREM2 variants cause Nasu-Hakola disease (Yamazaki, K. et al. (2015); Paloneva BM, J. et al. (2001); Ulrich J.D. et al. (2017)), whereas heterozygous loss-of-function TREM2 variants are associated with an increased risk for several neurological and neurodegenerative disorders such as Alzheimer's disease (AD), Frontotemporal lobar degeneration (FTLD), Parkinson's disease, FTLD-like syndrome, and
- 20 Amyotrophic lateral sclerosis (ALS). The most prevalent mutation associated with AD is the loss-of-function mutation R47H, which has been shown to abrogate ligand binding and phagocytosis (Atagi, Y. et al. (2015); Kleinberger, G. et al (2014)).
- 25 Neurodegenerative disorders that may be treated by modulation of TREM2 activity and/or signaling include, but is not limited to, Alzheimer's disease (AD), Frontotemporal lobar degeneration (FTLD), FTLD-like syndrome, Parkinson's disease, Huntington disease, Nasu-Hakola disease (also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy), Multiple sclerosis (MS), Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathies, Charcot-Marie-Tooth disease and Amyotrophic lateral sclerosis (ALS). Thus, there is a high and unmet
- 30 medical need for TREM2 modulators to address these indications.

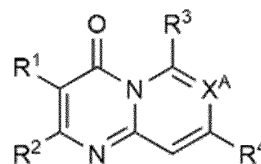
Summary

The present invention relates to compounds that modulates TREM2.

In one aspect, the present invention relates to a compound of Formula IA or Formula IB:



Formula IA



Formula IB

wherein

5 X^A is N or C(R⁵);

R^5 is H;

R^1 is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, and H, wherein the C₁₋₆ alkyl or C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R⁶;

10 R^2 is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, halogen and H, wherein the C₁₋₆ alkyl or C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R⁹;

R^3 is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₈ spiroalkyl, C₅₋₈ tricycloalkyl, C₅₋₈ bicycloalkyl cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl, 5-membered heteroaryl, azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, and -OCH₂-(C₃₋₆ cycloalkyl),

wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₈ spiroalkyl, C₅₋₈ bicycloalkyl, C₅₋₈ tricycloalkyl, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl or 5-membered heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy and CN;

wherein one methylene group of the C₃₋₆ cycloalkyl is optionally replaced with -O- or -N(R¹⁰)-;

25 R^{10} is selected from the group consisting of H, C₁₋₃ alkyl and -C(O)C₁₋₃ alkyl;

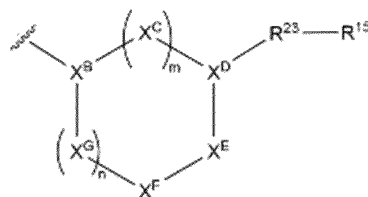
and wherein the azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, or -OCH₂-(C₃₋₆ cycloalkyl) is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy and C₁₋₃ haloalkoxy;

R^6 is individually selected from the group consisting of $-O-C_{1-6}$ alkyl, C_{3-6} cycloalkyl and halogen;

R^9 is selected from the group consisting of $-O-C_{1-6}$ alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl and phenyl, wherein the phenyl is optionally substituted with 1 to 5 substituents

5 individually selected from $-O-C_{1-6}$ alkyl;

R^4 is of Formula II:



Formula II

wherein

10 X^B is N or $C(R^{11})$;

R^{11} is selected from the group consisting of H, C_{1-3} alkyl, $-OH$, $-O-C_{1-3}$ alkyl and halogen;

X^C is $C(R^{12})(R^{13})$;

R^{12} is individually H, C_{1-3} alkyl or a bond;

15 wherein when R^{12} is a bond then R^{11} is C_{1-3} alkyl, and R^{11} and R^{12} are linked together to form a 3-5 membered ring;

R^{13} is individually H or C_{1-3} alkyl;

X^D is $C(R^{14})$ or N;

R^{14} is H or C_{1-3} alkyl;

20 R^{23} is a bond, $-O-$ or C_{1-6} hydrocarbon chain wherein one methylene group is optionally replaced with $-O-$;

R^{15} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, diC_{1-3} alkylamino, $-C(O)-O-(C_{1-6}$ alkyl), C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, phenyl, $-O$ -phenyl, 5-membered heteroaryl, $-O$ -(5-membered heteroaryl), 6-membered heteroaryl and $-O$ -(6-membered heteroaryl), wherein

(a) the C_{3-6} cycloalkyl or C_{3-6} heterocycloalkyl is optionally substituted with 1 to 3 substituents independently selected from oxo ($=O$), C_{1-3} alkoxy and halogen;

30 (b) the phenyl, $-O$ -phenyl, 5-membered heteroaryl, $-O$ -(5-membered heteroaryl), 6-membered heteroaryl or $-O$ -(6-membered heteroaryl) is optionally substituted with 1 to 3 substituents independently selected

- from the group consisting of halogen, C₁₋₆ alkyl, -O-C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -(C₁₋₃ alkyl)O(C₁₋₃ alkyl), -CN, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl and C₃₋₆ heterocycloalkyl, wherein the C₁₋₆ alkyl or C₁₋₆ haloalkyl of subsection (b) are optionally substituted with -OH, and
- wherein the C₃₋₆ heterocycloalkyl of subsection (b) is optionally substituted with 1 to 3 substituents individually selected from the group consisting of halogen, C₁₋₃ alkyl and -C(O)O(C₁₋₆ alkyl);
- (c) the C₁₋₆ alkyl is optionally substituted with 1 to 3 substituents independently selected from -N(H)C(O)R²⁴, -oxo (=O), -O-C₁₋₃ alkyl and -N(R²⁵)(R²⁶);
- R²⁴ is C₁₋₆ alkyl or aryl, wherein the C₁₋₆ alkyl is optionally substituted with C₁₋₃ alkoxy or halogen;
- R²⁵ is H or C₁₋₃ alkyl;
- R²⁶ is H or C₁₋₃ alkyl;
- X^E is C(R¹⁶)(R¹⁷), O, NR¹⁸ or a bond;
- R¹⁶ is H or F;
- R¹⁷ is H or F;
- R¹⁸ is H, C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl, -C(O)-C₃₋₆ cycloalkyl or C₁₋₆ haloalkyl, wherein the C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl or -C(O)-C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 substituents independently selected from halogen and C₁₋₃ alkoxy;
- X^F is C(R¹⁹)(R²⁰);
- R¹⁹ is H, halogen or C₁₋₃ alkyl;
- R²⁰ is H, halogen or C₁₋₃ alkyl;
- wherein when R¹⁹ and R²⁰ are C₁₋₃ alkyl, then R¹⁹ and R²⁰ are optionally linked together to form a 3-6 membered ring; and/or
- wherein when R¹⁹ and R²⁰ are C₁₋₃ alkyl, then one methylene group is optionally replaced with -O- or -N(R²⁷)-, wherein R²⁷ is selected from the group consisting of H, C₁₋₃ alkyl and -C(O)C₁₋₃ alkyl;
- X^G is individually C(R²¹)(R²²) or C(O);
- R²¹ is individually H, C₁₋₃ alkyl or a bond;
- wherein when R²¹ is a bond then R¹⁹ is C₁₋₃ alkyl, n is 1, and R²¹ and R¹⁹ are linked together to form a 3-5 membered ring;
- R²² is individually H or C₁₋₃ alkyl;
- m is 0, 1 or 2; and

n is 0, 1 or 2,
or a pharmaceutically acceptable salt thereof.

5 In one aspect, the present invention relates a compound of Formula IA or Ib as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease associated with loss-of-function of TREM2, such as a neurodegenerative disease.

Definitions

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

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 $\pm 0.5\%$.

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

The terms “C₁₋₃ alkyl”, “C₁₋₅ alkyl” and “C₁₋₆ alkyl” as used herein refer to a straight or branched hydrocarbon chains containing from 1 to 3, 1 to 5, and 1 to 6 carbon atoms, respectively. Representative examples of C₁₋₃ alkyl, C₁₋₅ 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.

30 The term “C₂₋₄ alkenyl” as used herein refers to a saturated hydrocarbon containing 2 to 4 carbon atoms having at least one carbon-carbon double bond. Alkenyl groups include both straight and branched moieties. Representative examples of C₂₋₄ alkenyl include, but are not limited to, 1-propenyl, 2-propenyl, 2-methyl -2 -propenyl, and butenyl.

35 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.

The terms "diC₁₋₃ alkylamino" as used herein refer to -NR^{*}R^{**}, wherein R^{*} and R^{**} independently represent a C₁₋₃ alkyl as defined herein. Representative examples of diC₁₋₃ alkylamino include, but are not limited to, -N(CH₃)₂, -N(CH₂CH₃)₂, -
5 N(CH₃)(CH₂CH₃), -N(CH₂CH₂CH₃)₂ and -N(CH(CH₃)₂)₂.

The term "C₁₋₃ alkoxy" and "C₁₋₆ alkoxy" as used herein refer to -OR[#], wherein R[#] represents a C₁₋₃ alkyl and C₁₋₆ alkyl group, respectively, as defined herein. Representative examples of C₁₋₃ alkoxy and C₁₋₆ alkoxy include, but are not limited to,
10 methoxy, ethoxy, propoxy, iso-propoxy, and butoxy.

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.

15 The term "halo" as used herein as a prefix to another term for a chemical group refers to a modification of the chemical group, wherein one or more hydrogen atoms are substituted with a halogen as defined herein. The halogen is independently selected at each occurrence. For example, the term "C₁₋₆ haloalkyl" refers to a C₁₋₆ alkyl as defined herein, wherein one or more hydrogen atoms are substituted with a halogen.
20 Representative examples of C₁₋₆ haloalkyl include, but are not limited to, -CH₂F, -CHF₂, -CF₃, -CHFCl, -CH₂CF₃, -CFHCF₃, -CF₂CF₃, -CH(CF₃)₂, -CF(CHF₂)₂, and -CH(CH₂F)(CF₃). Further, the term "C₁₋₆ haloalkoxy" for example refers to a C₁₋₆ alkoxy as defined herein, wherein one or more hydrogen atoms are substituted with a halogen. Representative examples of C₁₋₆ haloalkoxy include, but are not limited to, -
25 OCH₂F, -OCHF₂, -OCF₃, -OCHFCl, -OCH₂CF₃, -OCFHCF₃, -OCF₂CF₃, -OCH(CF₃)₂, -OCF(CHF₂)₂, and -OCH(CH₂F)(CF₃).

The term "CN" is used herein to indicate a cyano group ($\text{—C}\equiv\text{N}$).

30 The term "5-membered heteroaryl" or "6-membered heteroaryl" as used herein refers to a 5 or 6-membered carbon ring with two or three double bonds containing one ring heteroatom selected from N, S, and O and optionally one or two further ring N atoms instead of the one or more ring carbon atom(s). Representative examples of a 5-membered heteroaryl include, but are not limited to, furyl, imidazolyl, pyrazolyl,
35 isoxazolyl, isothiazolyl, oxadiazolyl, and oxazolyl. Representative examples of a 6-

membered heteroaryl include, but are not limited to, pyridyl, pyrimidyl, pyrazyl, and pyridazyl.

5 The term “C₃₋₆ heterocycloalkyl” as used herein refers to a saturated carbocyclic molecule wherein the cyclic framework has 3 to 6 carbons and wherein one or more carbon atoms are substituted with heteroatom(s) selected from N, O, and S. In some embodiments, a “C₃₋₆ heterocycloalkyl” refers to a saturated carbocyclic molecule wherein the cyclic framework has 3 to 6 carbons and wherein one carbon atom is substituted with a heteroatom selected from N, O, and S. If the C₃₋₆ heterocycloalkyl group is a C₆ heterocycloalkyl, one or two carbon atoms are substituted with a heteroatom independently selected from N, O, and S. Representative examples of C₃₋₆ heterocycloalkyl include, but are not limited to, aziridinyl, azetidiny, oxetanyl, pyrrolidinyl, piperazinyl, morpholinyl, and thiomorpholinyl.

15 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.

25 The term “C₅₋₈ tricycloalkyl” as used herein refers a tricyclic ring system, wherein all three cycloalkyl rings share the same two ring atoms. Representative examples of C₅₋₈ tricycloalkyl include, but are not limited to, tricyclo[1.1.1.0^{1,3}]pentanyl, tricyclo[2.1.1.0^{1,4}]hexanyl, tricyclo [3.1.1.0^{1,5}]hexanyl and tricyclo[3.2.1.0^{1,5}]octanyl.

30 The term “C₅₋₈ bicycloalkyl” as used herein refers a bicyclic ring system, wherein both cycloalkyl rings share the same two ring atoms. The term “C₅₋₈ bicycloalkyl” includes bridged bicyclic compounds, i.e. wherein the two rings share three or more atoms, separating the two bridgehead atoms by a bridge containing at least one atom. For example, the term “C₅₋₈ bicycloalkyl” includes bicyclo[1.1.1]pentyl. For example, the

term “C₅₋₈ bicycloalkyl” includes



The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic or bicyclic ring systems having a total of 4 to 14 ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term "aryl" may be used interchangeably with the term "aryl ring". In certain embodiments of the present invention, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl," as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

The terms "heteroaryl" and "heteroar-", used alone or as part of a larger moiety, e.g., "heteroaralkyl" or "heteroaralkoxy" refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" in the context of "heteroaryl" particularly includes, but is not limited to, nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indoliziny, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar-", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnoliny, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinoliziny, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinoliny, tetrahydroisoquinoliny, and pyrido[2,3-*b*]-1,4-oxazin- 3(4*H*)-one. A heteroaryl group may be monocyclic or bicyclic. A heteroaryl ring may include one or more oxo (=O) or thioxo (=S) substituent. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

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 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.

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.

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).

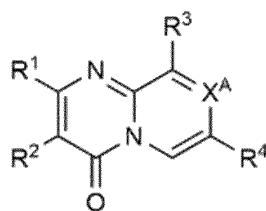
The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

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.

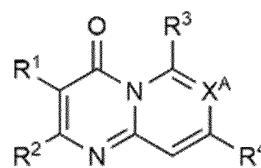
Pharmaceutically acceptable salts are well known in the art.

Detailed description

In one aspect, the present invention relates to a compound of Formula IA or Formula IB:



Formula IA



Formula IB

wherein

X^A is N or C(R^5);

R^5 is H;

5 R^1 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and H, wherein the C_{1-6} alkyl or C_{3-6} cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R^6 ;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, halogen and H, wherein the C_{1-6} alkyl or C_{3-6} cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R^9 ;

10 R^3 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{5-8} spiroalkyl, C_{5-8} tricycloalkyl, C_{5-8} bicycloalkyl cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl, 5-membered heteroaryl, azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, and $-OCH_2-(C_{3-6} \text{ cycloalkyl})$,

15 wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-8} spiroalkyl, C_{5-8} bicycloalkyl, C_{5-8} tricycloalkyl, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl or 5-membered heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl and CN, wherein one methylene group of the C_{3-6} cycloalkyl is optionally replaced with $-O-$ or $-N(R^{10})-$;

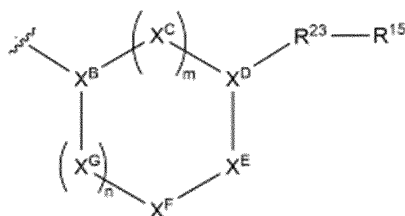
20 R^{10} is selected from the group consisting of H, C_{1-3} alkyl and $-C(O)C_{1-3}$ alkyl;

and wherein the azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, or $-OCH_2-(C_{3-6} \text{ cycloalkyl})$ is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy and C_{1-3} haloalkoxy;

25 R^6 is individually selected from the group consisting of $-O-C_{1-6}$ alkyl, C_{3-6} cycloalkyl and halogen;

R^9 is selected from the group consisting of $-O-C_{1-6}$ alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl and phenyl, wherein the phenyl is optionally substituted with 1 to 5 substituents individually selected from $-O-C_{1-6}$ alkyl;

R^4 is of Formula II:



Formula II

wherein

X^B is N or $C(R^{11})$;

R^{11} is selected from the group consisting of H, C_{1-3} alkyl, $-OH$, $-O-C_{1-3}$ alkyl and halogen;

X^C is $C(R^{12})(R^{13})$;

R^{12} is individually H, C_{1-3} alkyl or a bond;

wherein when R^{12} is a bond then R^{11} is C_{1-3} alkyl, and R^{11} and R^{12} are linked together to form a 3-5 membered ring;

R^{13} is individually H or C_{1-3} alkyl;

X^D is $C(R^{14})$ or N;

R^{14} is H or C_{1-3} alkyl;

R^{23} is a bond, $-O-$ or C_{1-6} hydrocarbon chain wherein one methylene group is optionally replaced with $-O-$;

R^{15} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, diC_{1-3} alkylamino, $-C(O)-O-(C_{1-6}$ alkyl), C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, phenyl, $-O$ -phenyl, 5-membered heteroaryl, $-O$ -(5-membered heteroaryl), 6-membered heteroaryl and $-O$ -(6-membered heteroaryl), wherein

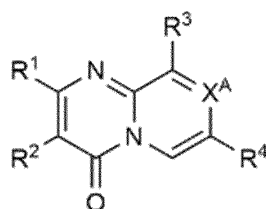
(a) the C_{3-6} cycloalkyl or C_{3-6} heterocycloalkyl is optionally substituted with 1 to 3 substituents independently selected from oxo ($=O$), C_{1-3} alkoxy and halogen;

(b) the phenyl, $-O$ -phenyl, 5-membered heteroaryl, $-O$ -(5-membered heteroaryl), 6-membered heteroaryl or $-O$ -(6-membered heteroaryl) is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, C_{1-6}

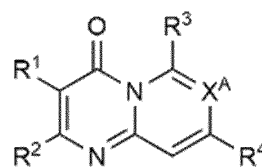
- haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -(C₁₋₃ alkyl)O(C₁₋₃ alkyl), -CN, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl and C₃₋₆ heterocycloalkyl, wherein the C₁₋₆ alkyl or C₁₋₆ haloalkyl of subsection (b) are optionally substituted with -OH, and
- 5 wherein the C₃₋₆ heterocycloalkyl of subsection (b) is optionally substituted with 1 to 3 substituents individually selected from the group consisting of halogen, C₁₋₃ alkyl and -C(O)O(C₁₋₆ alkyl);
- (c) the C₁₋₆ alkyl is optionally substituted with 1 to 3 substituents independently selected from -N(H)C(O)R²⁴, -oxo (=O), -O-C₁₋₃ alkyl
- 10 and -N(R²⁵)(R²⁶);
- R²⁴ is C₁₋₆ alkyl or aryl, wherein the C₁₋₆ alkyl is optionally substituted with C₁₋₃ alkoxy or halogen;
- R²⁵ is H or C₁₋₃ alkyl;
- R²⁶ is H or C₁₋₃ alkyl;
- 15 X^E is C(R¹⁶)(R¹⁷), O, NR¹⁸ or a bond;
- R¹⁶ is H or F;
- R¹⁷ is H or F;
- R¹⁸ is H, C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl, -C(O)-C₃₋₆ cycloalkyl or C₁₋₆ haloalkyl, wherein the C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl or -C(O)-C₃₋₆ cycloalkyl is optionally substituted with 1 to 3
- 20 substituents independently selected from halogen and C₁₋₃ alkoxy;
- X^F is C(R¹⁹)(R²⁰);
- R¹⁹ is H, halogen or C₁₋₃ alkyl;
- R²⁰ is H, halogen or C₁₋₃ alkyl;
- wherein when R¹⁹ and R²⁰ are C₁₋₃ alkyl, then R¹⁹ and R²⁰ are optionally
- 25 linked together to form a 3-6 membered ring; and/or
- wherein when R¹⁹ and R²⁰ are C₁₋₃ alkyl, then one methylene group is optionally replaced with -O- or -N(R²⁷)-, wherein R²⁷ is selected from the group consisting of H, C₁₋₃ alkyl and -C(O)C₁₋₃ alkyl;
- X^G is individually C(R²¹)(R²²) or C(O);
- 30 R²¹ is individually H, C₁₋₃ alkyl or a bond;
- wherein when R²¹ is a bond then R¹⁹ is C₁₋₃ alkyl, n is 1, and R²¹ and R¹⁹ are linked together to form a 3-5 membered ring;
- R²² is individually H or C₁₋₃ alkyl;
- m is 0, 1 or 2; and
- 35 n is 0, 1 or 2,

or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention relates to a compound of Formula IA or Formula IB:



Formula IA



Formula IB

5

wherein

X^A is N or C(R⁵);

R⁵ is H;

10 R¹ is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, and H, wherein the C₁₋₆ alkyl or C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R⁶;

R² is selected from the group consisting of C₁₋₆ alkyl, C₃₋₆ cycloalkyl, halogen and H, wherein the C₁₋₆ alkyl or C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R⁹;

15 R³ is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₈ spiroalkyl, C₅₋₈ tricycloalkyl, C₅₋₈ bicycloalkyl cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl, 5-membered heteroaryl, azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, and -OCH₂-(C₃₋₆ cycloalkyl),

20 wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₈ spiroalkyl, C₅₋₈ bicycloalkyl, C₅₋₈ tricycloalkyl, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl or 5-membered heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy and CN;

25 wherein one methylene group of the C₃₋₆ cycloalkyl is optionally replaced with -O- or -N(R¹⁰)-;

R¹⁰ is selected from the group consisting of H, C₁₋₃ alkyl and -C(O)C₁₋₃ alkyl;

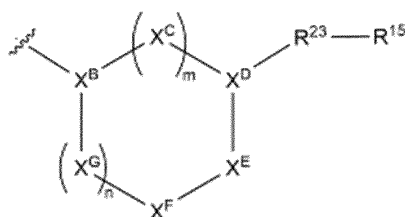
and wherein the azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, or -OCH₂-(C₃₋₆ cycloalkyl) is optionally substituted

with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy and C₁₋₃ haloalkoxy;

R⁶ is individually selected from the group consisting of -O-C₁₋₆ alkyl, C₃₋₆ cycloalkyl and halogen;

5 R⁹ is selected from the group consisting of -O-C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl and phenyl, wherein the phenyl is optionally substituted with 1 to 5 substituents individually selected from -O-C₁₋₆ alkyl;

R⁴ is of Formula II:



Formula II

wherein

X^B is N or C(R¹¹);

R¹¹ is selected from the group consisting of H, C₁₋₃ alkyl, -OH, -O-C₁₋₃ alkyl and halogen;

15 X^C is C(R¹²)(R¹³);

R¹² is individually H, C₁₋₃ alkyl or a bond;

wherein when R¹² is a bond then R¹¹ is C₁₋₃ alkyl, and R¹¹ and R¹² are linked together to form a 3-5 membered ring;

R¹³ is individually H or C₁₋₃ alkyl;

20 X^D is C(R¹⁴) or N;

R¹⁴ is H or C₁₋₃ alkyl;

R²³ is a bond, -O- or C₁₋₆ hydrocarbon chain wherein one methylene group is optionally replaced with -O-;

25 R¹⁵ is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, diC₁₋₃ alkylamino, -C(O)-O-(C₁₋₆ alkyl), C₃₋₆ cycloalkyl, C₃₋₆ heterocycloalkyl, phenyl, -O-phenyl, 5-membered heteroaryl, -O-(5-membered heteroaryl), 6-membered heteroaryl and -O-(6-membered heteroaryl), wherein

(a) the C₃₋₆ cycloalkyl or C₃₋₆ heterocycloalkyl is optionally substituted with 1 to 3 substituents independently selected from oxo (=O), C₁₋₃ alkoxy and halogen;

30

- (b) the phenyl, -O-phenyl, 5-membered heteroaryl, -O-(5-membered heteroaryl), 6-membered heteroaryl or -O-(6-membered heteroaryl) is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl, -O-C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -(C₁₋₃ alkyl)O(C₁₋₃ alkyl), -CN, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl and C₃₋₆ heterocycloalkyl, wherein the C₁₋₆ alkyl or C₁₋₆ haloalkyl of subsection (b) are optionally substituted with -OH, and wherein the C₃₋₆ heterocycloalkyl of subsection (b) is optionally substituted with 1 to 3 substituents individually selected from the group consisting of halogen, C₁₋₃ alkyl and -C(O)O(C₁₋₆ alkyl);
- (c) the C₁₋₆ alkyl is optionally substituted with 1 to 3 substituents independently selected from -N(H)C(O)R²⁴, -oxo (=O), -O-C₁₋₃ alkyl and -N(R²⁵)(R²⁶);
- R²⁴ is C₁₋₆ alkyl or aryl, wherein the C₁₋₆ alkyl is optionally substituted with C₁₋₃ alkoxy or halogen;
- R²⁵ is H or C₁₋₃ alkyl;
- R²⁶ is H or C₁₋₃ alkyl;
- X^E is C(R¹⁶)(R¹⁷), O, NR¹⁸ or a bond;
- R¹⁶ is H or F;
- R¹⁷ is H or F;
- R¹⁸ is H, C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl, -C(O)-C₃₋₆ cycloalkyl or C₁₋₆ haloalkyl, wherein the C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl or -C(O)-C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 substituents independently selected from halogen and C₁₋₃ alkoxy;
- X^F is C(R¹⁹)(R²⁰);
- R¹⁹ is H, halogen or C₁₋₃ alkyl;
- R²⁰ is H, halogen or C₁₋₃ alkyl;
- wherein when R¹⁹ and R²⁰ are C₁₋₃ alkyl, then R¹⁹ and R²⁰ are optionally linked together to form a 3-6 membered ring; and/or
- wherein when R¹⁹ and R²⁰ are C₁₋₃ alkyl, then one methylene group is optionally replaced with -O- or -N(R²⁷)-, wherein R²⁷ is selected from the group consisting of H, C₁₋₃ alkyl and -C(O)C₁₋₃ alkyl;
- X^G is individually C(R²¹)(R²²) or C(O);
- R²¹ is individually H, C₁₋₃ alkyl or a bond;

wherein when R^{21} is a bond then R^{19} is C_{1-3} alkyl, n is 1, and R^{21} and R^{19} are linked together to form a 3-5 membered ring;

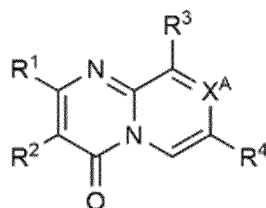
R^{22} is individually H or C_{1-3} alkyl;

m is 0, 1 or 2; and

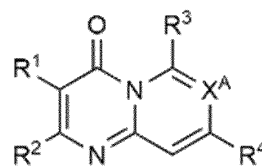
5 n is 0, 1 or 2,

or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention relates to a compound of Formula IA or Formula IB:



Formula IA



Formula IB

10

wherein

X^A is N or $C(R^5)$;

R^5 is H;

15 R^1 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and H, wherein the C_{1-6} alkyl or C_{3-6} cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R^6 ;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and H, wherein the C_{1-6} alkyl or C_{3-6} cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R^9 ;

20 R^3 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{5-8} spiroalkyl, C_{5-8} tricycloalkyl, C_{5-8} bicycloalkyl cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl, 5-membered heteroaryl, azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, and $-OCH_2-(C_{3-6} \text{ cycloalkyl})$,

25 wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-8} spiroalkyl, C_{5-8} bicycloalkyl, C_{5-8} tricycloalkyl, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl or 5-membered heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and CN;

wherein one methylene group of the C₃₋₆ cycloalkyl is optionally replaced with -O- or -N(R¹⁰)-;

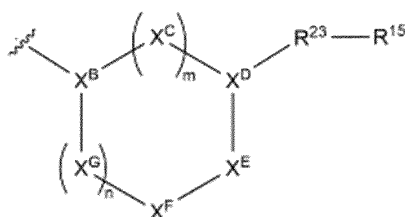
R¹⁰ is selected from the group consisting of H, C₁₋₃ alkyl and -C(O)C₁₋₃ alkyl;

5 and wherein the azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, or -OCH₂-(C₃₋₆ cycloalkyl) is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy and C₁₋₃ haloalkoxy;

10 R⁶ is individually selected from the group consisting of -O-C₁₋₆ alkyl, C₃₋₆ cycloalkyl and halogen;

R⁹ is selected from the group consisting of -O-C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl and phenyl, wherein the phenyl is optionally substituted with 1 to 5 substituents individually selected from -O-C₁₋₆ alkyl;

R⁴ is of Formula II:



Formula II

wherein

X^B is N or C(R¹¹);

18 R¹¹ is selected from the group consisting of H, C₁₋₃ alkyl, -OH, -O-C₁₋₃ alkyl and halogen;

X^C is C(R¹²)(R¹³);

R¹² is individually H, C₁₋₃ alkyl or a bond;

wherein when R¹² is a bond then R¹¹ is C₁₋₃ alkyl, and R¹¹ and R¹² are linked together to form a 3-5 membered ring;

22 R¹³ is individually H or C₁₋₃ alkyl;

X^D is C(R¹⁴) or N;

R¹⁴ is H or C₁₋₃ alkyl;

R²³ is a bond, -O- or C₁₋₆ hydrocarbon chain wherein one methylene group is optionally replaced with -O-;

30 R¹⁵ is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, diC₁₋₃ alkylamino, -C(O)-O-(C₁₋₆ alkyl), C₃₋₆ cycloalkyl, C₃₋₆ heterocycloalkyl, phenyl, -O-phenyl, 5-

membered heteroaryl, -O-(5-membered heteroaryl), 6-membered heteroaryl and -O-(6-membered heteroaryl), wherein

- (a) the C₃₋₆ cycloalkyl or C₃₋₆ heterocycloalkyl is optionally substituted with 1 to 3 substituents independently selected from oxo (=O), C₁₋₃ alkoxy and halogen;
- (b) the phenyl, -O-phenyl, 5-membered heteroaryl, -O-(5-membered heteroaryl), 6-membered heteroaryl or -O-(6-membered heteroaryl) is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl, -O-C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -(C₁₋₃ alkyl)O(C₁₋₃ alkyl), -CN, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl and C₃₋₆ heterocycloalkyl, wherein the C₁₋₆ alkyl or C₁₋₆ haloalkyl of subsection (b) are optionally substituted with -OH, and wherein the C₃₋₆ heterocycloalkyl of subsection (b) is optionally substituted with 1 to 3 substituents individually selected from the group consisting of halogen, C₁₋₃ alkyl and -C(O)O(C₁₋₆ alkyl);
- (c) the C₁₋₆ alkyl is optionally substituted with 1 to 3 substituents independently selected from -N(H)C(O)R²⁴, -oxo (=O), -O-C₁₋₃ alkyl and -N(R²⁵)(R²⁶);
- R²⁴ is C₁₋₆ alkyl or aryl, wherein the C₁₋₆ alkyl is optionally substituted with C₁₋₃ alkoxy or halogen;
- R²⁵ is H or C₁₋₃ alkyl;
- R²⁶ is H or C₁₋₃ alkyl;
- X^E is C(R¹⁶)(R¹⁷), O, NR¹⁸ or a bond;
- R¹⁶ is H or F;
- R¹⁷ is H or F;
- R¹⁸ is H, C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl, -C(O)-C₃₋₆ cycloalkyl or C₁₋₆ haloalkyl, wherein the C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl or -C(O)-C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 substituents independently selected from halogen and C₁₋₃ alkoxy;
- X^F is C(R¹⁹)(R²⁰);
- R¹⁹ is H, halogen or C₁₋₃ alkyl;
- R²⁰ is H, halogen or C₁₋₃ alkyl;
- wherein when R¹⁹ and R²⁰ are C₁₋₃ alkyl, then R¹⁹ and R²⁰ are optionally linked together to form a 3-6 membered ring; and/or

wherein when R^{19} and R^{20} are C_{1-3} alkyl, then one methylene group is optionally replaced with $-O-$ or $-N(R^{27})-$, wherein R^{27} is selected from the group consisting of H, C_{1-3} alkyl and $-C(O)C_{1-3}$ alkyl;

X^G is individually $C(R^{21})(R^{22})$ or $C(O)$;

5 R^{21} is individually H, C_{1-3} alkyl or a bond;

wherein when R^{21} is a bond then R^{19} is C_{1-3} alkyl, n is 1, and R^{21} and R^{19} are linked together to form a 3-5 membered ring;

R^{22} is individually H or C_{1-3} alkyl;

m is 0, 1 or 2; and

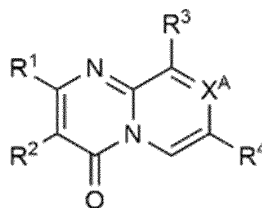
10 n is 0, 1 or 2,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is of Formula IA. In some embodiments, the compound is of Formula IB.

15

In one aspect, the present invention relates to a compound of Formula IA:



Formula IA

wherein

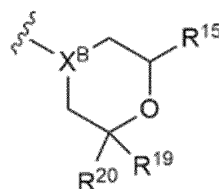
20 R^1 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and H;

R^2 is selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl and H;

R^3 is phenyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl;

X^A is N or C(H);

25 R^4 is of Formula XXVI:



Formula XXVI

wherein

X^B is N or C(H);

R¹⁵ is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl,

5 C₁₋₆ haloalkyl, -CN, and C₃₋₆ cycloalkyl;

R¹⁹ is H, halogen or C₁₋₃ alkyl; and

R²⁰ is H, halogen or C₁₋₃ alkyl;

or a pharmaceutically acceptable salt thereof.

10 In some embodiments, X^A is N. In some embodiments, X^A is C(R⁵) and R⁵ is H.

In some embodiments, the compound is of Formula IA and X^A is N. In some embodiments, the compound is of Formula IA and X^A is C(R⁵) and R⁵ is H. In some embodiments, the compound is of Formula IB and X^A is C(R⁵) and R⁵ is H.

15

In some embodiments, R¹ is C₁₋₆ alkyl optionally substituted with 1 to 3 individually selected substituents R⁶. In some embodiments, R¹ is C₁₋₃ alkyl. In some embodiments, R¹ is -CH₃. In some embodiments, R¹ is C₁₋₆ alkyl substituted with 1 to 3 individually selected substituents R⁶. In some embodiments, R¹ is C₁₋₃ alkyl substituted with 1 to 3 individually selected substituents R⁶. In some embodiments, R⁶ is halogen. In some
20 embodiments, R⁶ is F. In some embodiments, R¹ is C₁₋₆ haloalkyl. In some embodiments, R¹ is C₁₋₃ haloalkyl. In some embodiments, R¹ is -CF₃.

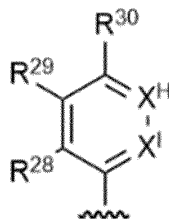
25

In some embodiments, R² is C₁₋₆ alkyl optionally substituted with 1 to 3 individually selected substituents R⁹. In some embodiments, R² is C₁₋₃ alkyl optionally substituted with 1 to 3 individually selected substituents R⁹. In some embodiments, R² is -CH₃. In some embodiments, R² is halogen. In some embodiments, R² is Cl. In some embodiments, R² is F.

30

In some embodiments, R³ is phenyl optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy and CN. In some embodiments, R³ is phenyl optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, and CN. In some embodiments, R³ is 6-membered heteroaryl optionally

substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl and CN. In some embodiments, R³ is of Formula III:



Formula III

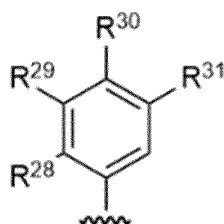
- 5 wherein
 X^H is C(R³¹) or N;
 X^I is C(R³²) or N;
 R²⁸ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy or CN;
 R²⁹ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy or CN;
 10 R³⁰ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy or CN;
 R³¹ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy or CN; and
 R³² is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy or CN.

In some embodiments, R³ is of Formula III, wherein

- 15 X^H is C(R³¹) or N;
 X^I is C(R³²) or N;
 R²⁸ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl or CN;
 R²⁹ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl or CN;
 R³⁰ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl or CN;
 20 R³¹ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl or CN; and
 R³² is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl or CN.

In some embodiments, X^H is C(R³¹). In some embodiments, X^H is N. In some
 embodiments, X^I is C(R³²), or a pharmaceutically acceptable salt thereof. In some
 25 embodiments, X^I is N. In some embodiments, X^H is C(R³¹), and X^I is C(R³²), or a
 pharmaceutically acceptable salt thereof. In some embodiments, X^H is N, and X^I is
 C(R³²). In some embodiments, X^H is C(R³¹), and X^I is N. In some embodiments, R³¹ is
 H.

In some embodiments, R^3 is of Formula IV:



Formula IV

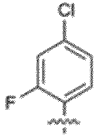
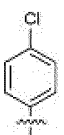
wherein

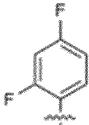
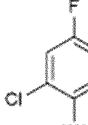
- 5 R^{28} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN;
 R^{29} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN;
 R^{30} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN; and
 R^{31} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN.
- 10 In some embodiments, R^3 is of Formula IV wherein
 R^{28} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN;
 R^{29} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN;
 R^{30} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN; and
 R^{31} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN.

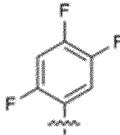
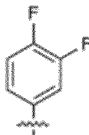
15

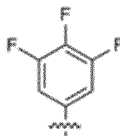
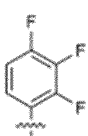
In some embodiments, R^{28} is H. In some embodiments, R^{28} is halogen. In some embodiments, R^{28} is F or Cl. In some embodiments, R^{28} is C_{1-3} alkyl, such as $-CH_3$. In some embodiments, R^{28} is CN. In some embodiments, R^{29} is H. In some embodiments, R^{29} is halogen. In some embodiments, R^{29} is F. In some embodiments, R^{30} is halogen.

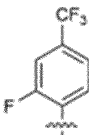
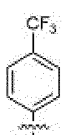
- 20 In some embodiments, R^{30} is F or Cl. In some embodiments, R^{30} is C_{1-3} alkyl, such as $-CH_3$. In some embodiments, R^{30} is C_{1-3} haloalkyl, such as $-CF_3$. In some embodiments, R^{30} is C_{1-3} haloalkyl, such as $-CHF_2$. In some embodiments, R^{30} is CN. In some embodiments, R^{30} is C_{1-3} alkoxy, such as $-OCH_3$. In some embodiments, R^{31} is H. In some embodiments, R^{31} is halogen. In some embodiments, R^{31} is F. In some

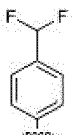
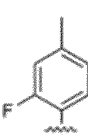
- 25 In some embodiments, R^3 is . In some embodiments, R^3 is . In some

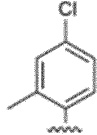
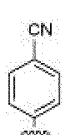
embodiments, R^3 is . In some embodiments, R^3 is . In some

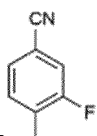
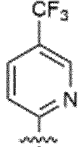
embodiments, R^3 is . In some embodiments, R^3 is . In some

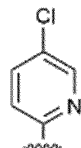
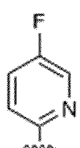
embodiments, R^3 is . In some embodiments, R^3 is . In some

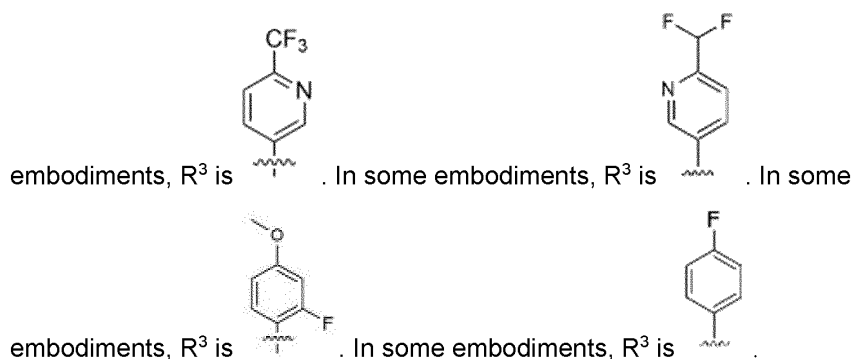
embodiments, R^3 is . In some embodiments, R^3 is . In some

5 embodiments, R^3 is . In some embodiments, R^3 is . In some

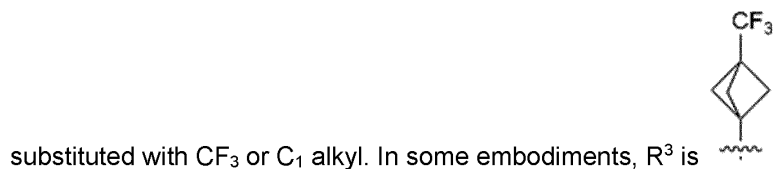
embodiments, R^3 is . In some embodiments, R^3 is . In some

embodiments, R^3 is . In some embodiments, R^3 is . In some

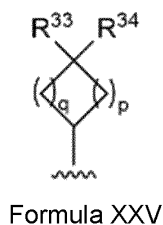
embodiments, R^3 is . In some embodiments, R^3 is . In some



In some embodiments, R^3 is C_{5-8} bicycloalkyl optionally substituted with 1 to 4
5 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl
and C_{1-3} haloalkyl. In some embodiments, R^3 is bicyclo[1.1.1]pentyl optionally



In some embodiments, R^3 is C_{3-6} cycloalkyl optionally substituted with 1 to 4
10 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl
and C_{1-3} haloalkyl. In some embodiments, R^3 is of Formula XXV:



wherein

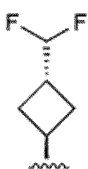
15 R^{33} is H, halogen, C_{1-3} alkyl and C_{1-3} haloalkyl;
 R^{34} is H, halogen, C_{1-3} alkyl and C_{1-3} haloalkyl;
 q is 1, 2 or 3; and
 p is 1, 2 or 3.

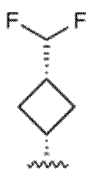
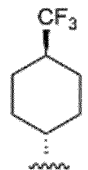
20 In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, p is
1. In some embodiments, p is 2. In some embodiments, R^{33} is H. In some
embodiments, R^{33} is halogen, such as F. In some embodiments, R^{33} is C_{1-3} alkyl, such

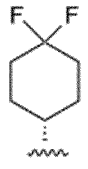
as $-\text{CH}_3$. In some embodiments, R^{33} is C_{1-3} haloalkyl, such as $-\text{CF}_3$ or $-\text{CHF}_2$. In some embodiments, R^{34} is H. In some embodiments, R^{34} is halogen, such as F. In some embodiments, R^{34} is C_{1-3} alkyl, such as $-\text{CH}_3$. In some embodiments, R^{34} is C_{1-3}

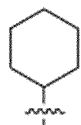
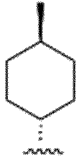
haloalkyl, such as $-\text{CF}_3$ or $-\text{CHF}_2$. In some embodiments, R^3 is . In some

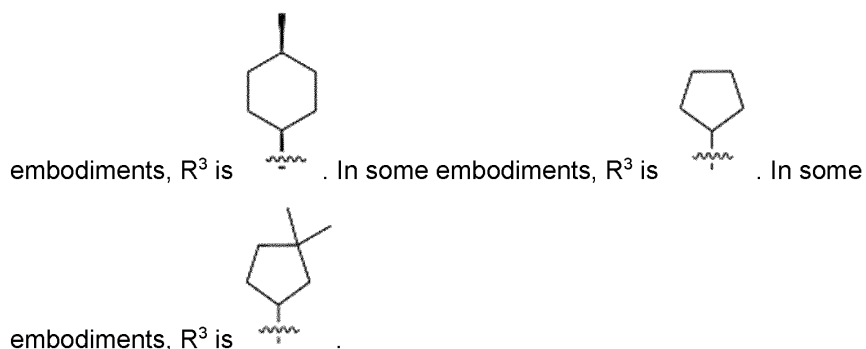
embodiments, R^3 is . In some embodiments, R^3 is . In some

embodiments, R^3 is . In some embodiments, R^3 is . In some

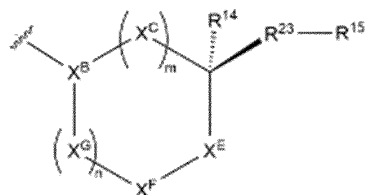
embodiments, R^3 is . In some embodiments, R^3 is . In some

embodiments, R^3 is . In some embodiments, R^3 is . In some

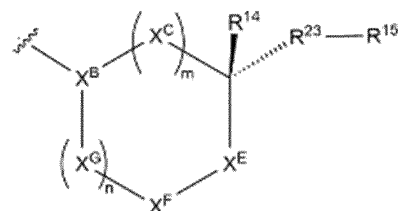
embodiments, R^3 is . In some embodiments, R^3 is . In some



5 In some embodiments, X^D is $C(R^{14})$. In some embodiments, R^4 is of Formula IIA. In some embodiments, R^4 is of Formula IIB.

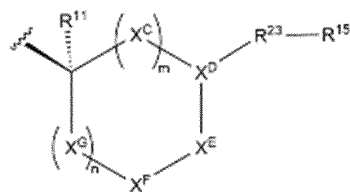


Formula IIA

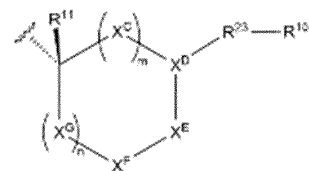


Formula IIB

In some embodiments, X^B is $C(R^{11})$. In some embodiments, R^4 is of Formula IIC. In some embodiments, R^4 is of Formula IID.



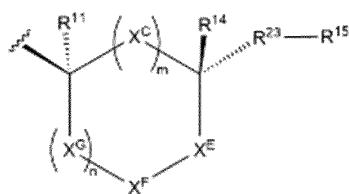
Formula IIC



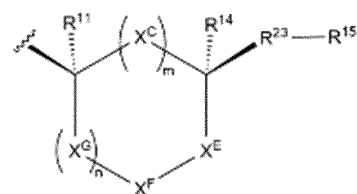
Formula IID

10

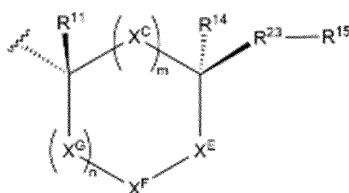
In some embodiments, X^B is $C(R^{11})$ and X^D is $C(R^{14})$. In some embodiments, R^4 is of Formula IIE. In some embodiments, R^4 is of Formula IIF. In some embodiments, R^4 is of Formula IIG. In some embodiments, R^4 is of Formula IIH.



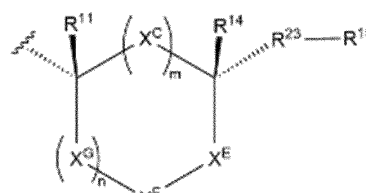
Formula IIE



Formula IIF



Formula IIG



Formula IIH

In some embodiments, R^4 is a 6-membered ring. In some embodiments, X^E is O, $C(R^{16})(R^{17})$ or NR^{18} ; m is 1; and n is 1. In some embodiments, X^B is N; X^C is $C(R^{12})(R^{13})$; X^D is $C(R^{14})$; X^E is O; X^F is $C(R^{19})(R^{20})$; X^G is $C(R^{21})(R^{22})$; m is 1; and n is 1.

- 5 In some embodiments, X^B is $C(R^{11})$; X^C is $C(R^{12})(R^{13})$; X^D is $C(R^{14})$; X^E is O; X^F is $C(R^{19})(R^{20})$; X^G is $C(R^{21})(R^{22})$; m is 1; and n is 1. In some embodiments, X^B is N; X^C is $C(R^{12})(R^{13})$; X^D is $C(R^{14})$; X^E is NR^{18} ; X^F is $C(R^{19})(R^{20})$; X^G is $C(R^{21})(R^{22})$; m is 1; and n is 1. In some embodiments, X^B is N; X^C is $C(R^{12})(R^{13})$; X^D is $C(R^{14})$; X^E is $C(R^{16})(R^{17})$; X^F is $C(R^{19})(R^{20})$; X^G is $C(R^{21})(R^{22})$; m is 1; and n is 1.

10

In some embodiments, X^B is N. In some embodiments, X^B is $C(R^{11})$. In some embodiments, R^{11} is H. In some embodiments, R^{11} is C_{1-3} alkyl.

15

In some embodiments, X^C is $C(R^{12})(R^{13})$. In some embodiments, R^{12} is individually H. In some embodiments, R^{12} is individually C_{1-3} alkyl. In some embodiments, R^{12} is a bond and R^{11} is C_{1-3} alkyl, and R^{11} and R^{12} are linked together to form a 3-5 membered ring. In some embodiments, R^{13} is individually H. In some embodiments, R^{13} is individually C_{1-3} alkyl.

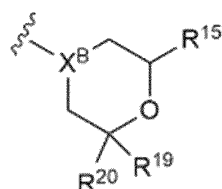
20

In some embodiments, X^D is $C(R^{14})$. In some embodiments, X^D is N. In some embodiments, R^{14} is H. In some embodiments, R^{14} is C_{1-3} alkyl.

In some embodiments, when X^B is N, then X^D is $C(R^{14})$.

In some embodiments, R^{23} is a bond.

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



Formula XXVI

wherein

X^B is N or C(H);

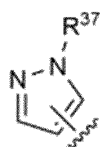
R^{15} is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl,

C_{1-6} haloalkyl, -CN, and C_{3-6} cycloalkyl;

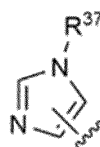
R^{19} is H, halogen or C_{1-3} alkyl; and

R^{20} is H, halogen or C_{1-3} alkyl.

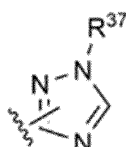
In some embodiments, R^{15} is a 5-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, -O- C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -(C_{1-3} alkyl)O(C_{1-3} alkyl), -CN, and halogen. In some embodiments, R^{15} is selected from the group consisting of Formula V, Formula VI, Formula VII, Formula VIII, Formula IX, Formula X, Formula XI, and Formula XII:



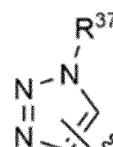
Formula V



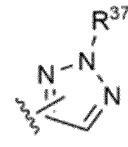
Formula VI



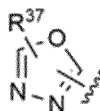
Formula VII



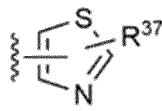
Formula VIII



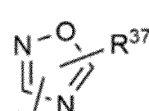
Formula IX



Formula X



Formula XI



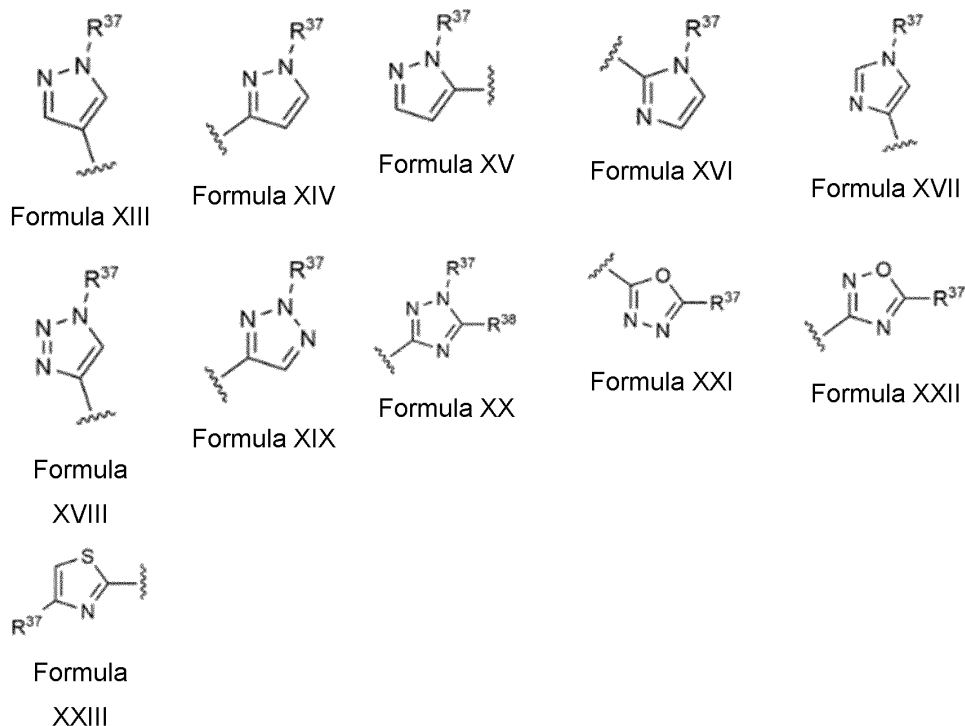
Formula XII

wherein R^{37} is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, -O- C_{1-6} alkyl, H, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -(C_{1-3} alkyl)O(C_{1-3} alkyl), -CN, and halogen. In some embodiments, R^{15} is of Formula V. In some embodiments, R^{15} is of

Formula VI. In some embodiments, R^{15} is of Formula VII. In some embodiments, R^{15} is of Formula VIII. In some embodiments, R^{15} is of Formula IX. In some embodiments, R^{15} is of Formula X. In some embodiments, R^{15} is of Formula XI. In some embodiments, R^{15} is of Formula XII.

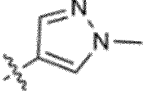
5

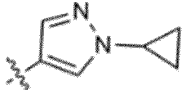
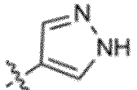
In some embodiments, R^{15} is selected from the group consisting of Formula XIII, Formula XIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XIX, Formula XX, Formula XXI, Formula XXII, and Formula XXIII:

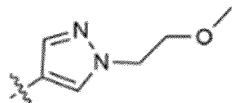
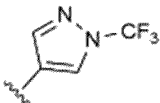


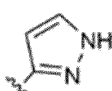
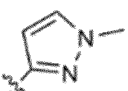
wherein R^{37} and R^{38} are independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, $-O-C_{1-6}$ alkyl, H, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-(C_{1-3}$ alkyl)O(C_{1-3} alkyl), -CN, and halogen. In some embodiments, R^{15} is Formula XIII. In some embodiments, R^{15} is Formula XIV. In some embodiments, R^{15} is Formula XV. In some embodiments, R^{15} is Formula XVI. In some embodiments, R^{15} is Formula XVII. In some embodiments, R^{15} is Formula XVIII. In some embodiments, R^{15} is Formula XIX. In some embodiments, R^{15} is Formula XX. In some embodiments, R^{15} is Formula XXI. In some embodiments, R^{15} is Formula XXII. In some embodiments, R^{15} is Formula XXIII.

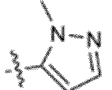
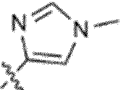
In some embodiments, R^{37} is C_{1-3} alkyl. In some embodiments, R^{37} is CH_3 . In some embodiments, R^{37} is C_{3-6} cycloalkyl. In some embodiments, R^{37} is C_3 cycloalkyl.

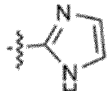
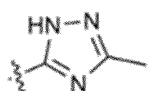
In some embodiments, R^{15} is . In some embodiments, R^{15} is

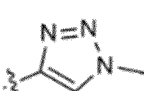
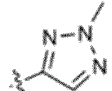
5 . In some embodiments, R^{15} is . In some embodiments,

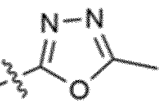
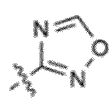
R^{15} is . In some embodiments, R^{15} is . In some

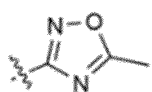
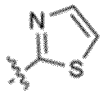
embodiments, R^{15} is . In some embodiments, R^{15} is . In some

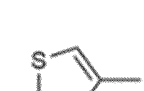
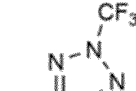
embodiments, R^{15} is . In some embodiments, R^{15} is . In some

embodiments, R^{15} is . In some embodiments, R^{15} is . In some

10 . In some embodiments, R^{15} is . In some

embodiments, R^{15} is . In some embodiments, R^{15} is . In some

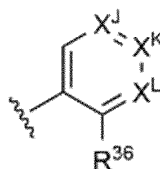
embodiments, R^{15} is . In some embodiments, R^{15} is . In some

embodiments, R^{15} is . In some embodiments, R^{15} is . In some

In some embodiments, R^{15} is a 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, $-O-C_{1-6}$ alkyl, H, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-(C_{1-3} \text{ alkyl})O(C_{1-3} \text{ alkyl})$, $-CN$, and halogen.

5

In some embodiments, R^{15} is of Formula XXIV:

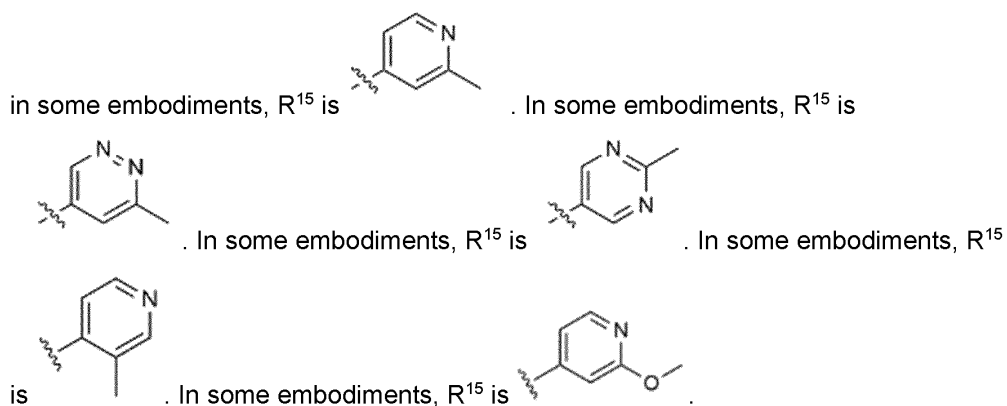


Formula XXIV

wherein

- 10 X^J is N or CH;
 X^K is N or $C(R^7)$;
 X^L is N or $C(R^8)$;
 R^7 is C_{1-3} alkyl;
 R^8 is C_{1-3} alkyl; and
 15 R^{36} is H or C_{1-3} alkyl.

- In some embodiments, X^J is CH. In some embodiments, X^K is N. In some embodiments, X^K is $C(R^7)$. In some embodiments, R^7 is $-CH_3$. In some embodiments, X^L is N. In some embodiments, X^L is $C(R^8)$. In some embodiments, R^8 is $-CH_3$. In some
 20 embodiments, R^{36} is H. In some embodiments, R^{36} is C_{1-3} alkyl. In some embodiments, R^{36} is $-CH_3$. In some embodiments, at least one of X^J , X^K , and X^L is N. In some embodiments, one of X^J , X^K , and X^L is N. In some embodiments, two of X^J , X^K , and X^L are N.



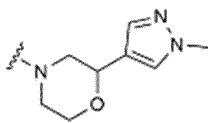
- 5 In some embodiments, X^E is C(R¹⁶)(R¹⁷). In some embodiments, X^E is O. In some embodiments, X^E is NR¹⁸. In some embodiments, X^E is a bond.

- In some embodiments, R¹⁹ is H. In some embodiments, R¹⁹ is halogen. In some
embodiments, R¹⁹ is F. In some embodiments, R¹⁹ is C₁₋₃ alkyl. In some embodiments,
10 R¹⁹ is CH₃. In some embodiments, R²⁰ is H. In some embodiments, R²⁰ is halogen. In
some embodiments, R²⁰ is F. In some embodiments, R²⁰ is C₁₋₃ alkyl. In some
embodiments, R²⁰ is CH₃. In some embodiments, R¹⁹ and R²⁰ are C₁₋₃ alkyl, and R¹⁹
and R²⁰ are optionally linked together to form a 3-6 membered ring.

- 15 In some embodiments, X^G is C(R²¹)(R²²). In some embodiments, X^G is C(O). In some
embodiments, R²¹ is H. In some embodiments, R²² is H

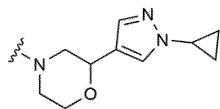
- In some embodiments, m is 1. In some embodiments, m is 0. In some embodiments, m
is 2.

- 20 In some embodiments, n is 1. In some embodiments, n is 0. In some embodiments, n is
2.

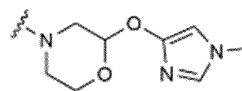


In some embodiments, R⁴ is

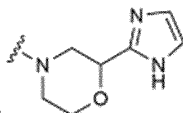
. In some embodiments, R⁴ is



. In some embodiments, R⁴ is

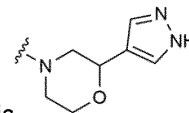


. In some

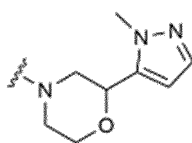


embodiments, R⁴ is

. In some embodiments, R⁴ is

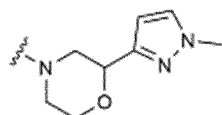


. In



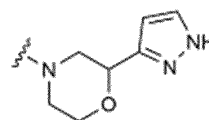
some embodiments, R⁴ is

. In some embodiments, R⁴ is

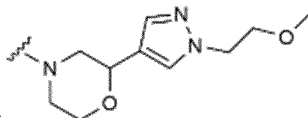


5

. In some embodiments, R⁴ is

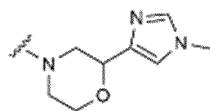


. In some

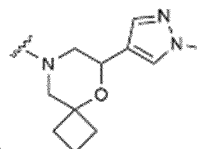


embodiments, R⁴ is

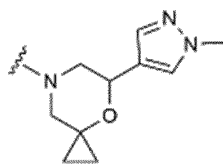
. In some embodiments, R⁴ is



. In some embodiments, R⁴ is

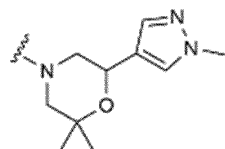


. In some

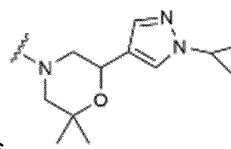


embodiments, R⁴ is

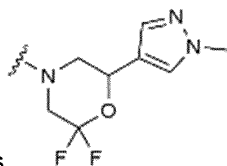
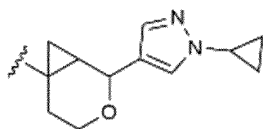
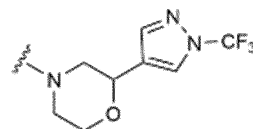
. In some embodiments, R⁴ is



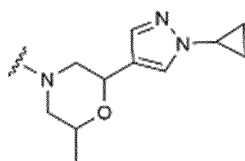
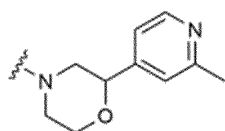
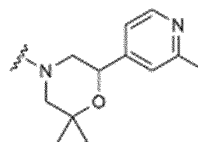
. In some embodiments, R⁴ is



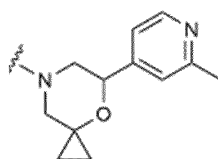
. In some

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

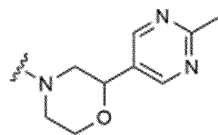
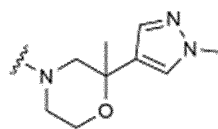
. In some

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

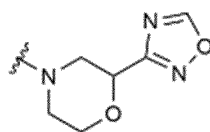
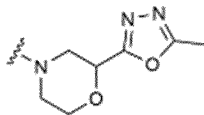
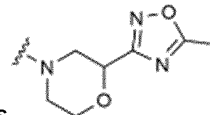
. In some



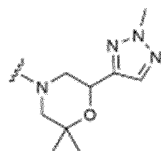
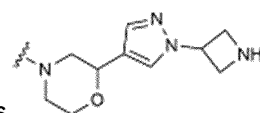
5

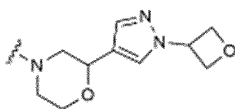
embodiments, R⁴ is. In some embodiments, R⁴ is. In some embodiments, R⁴ is

. In some

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

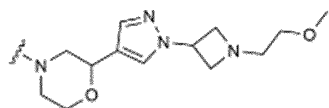
. In some

embodiments, R⁴ is. In some embodiments, R⁴ is

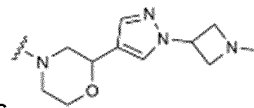


. In some embodiments, R⁴ is

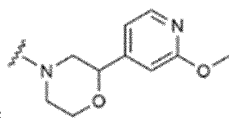
. In some embodiments, R⁴ is



. In some embodiments, R⁴ is

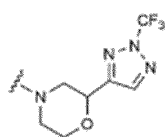


. In

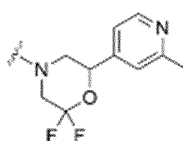


some embodiments, R⁴ is

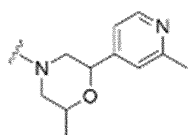
. In some embodiments, R⁴ is



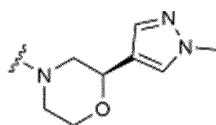
. In some embodiments, R⁴ is



. In some embodiments,

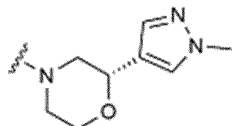


5 R⁴ is

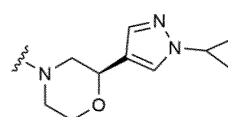


In some embodiments, R⁴ is

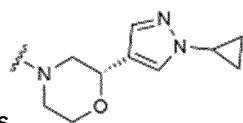
. In some embodiments, R⁴ is



. In some embodiments, R⁴ is

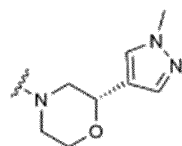


. In some

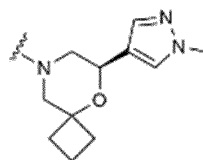


embodiments, R⁴ is

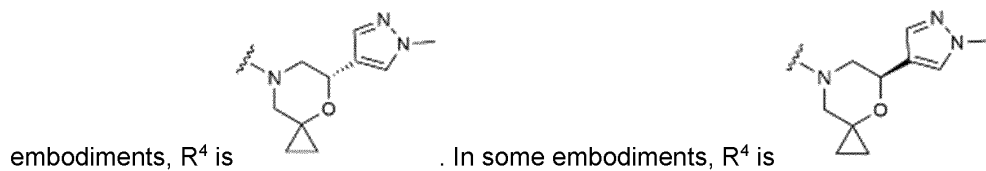
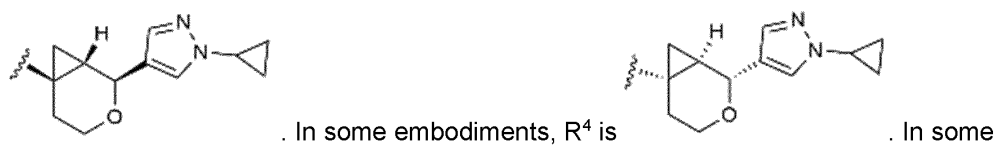
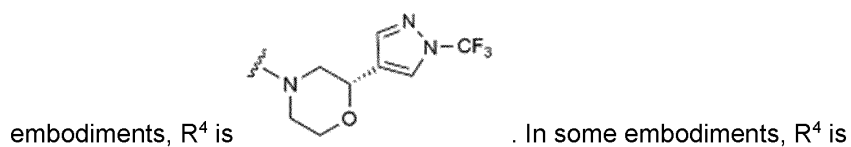
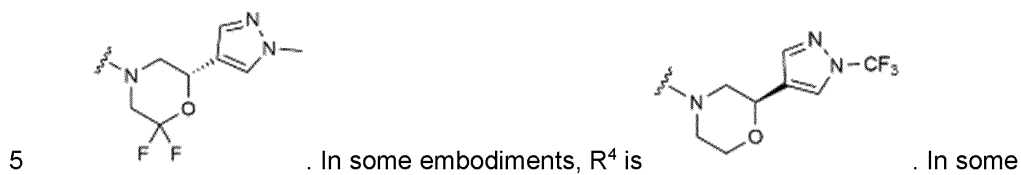
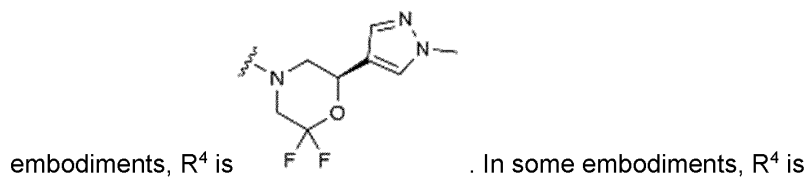
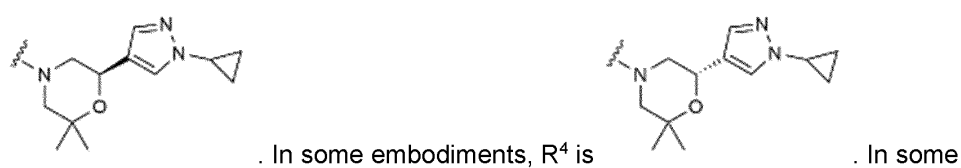
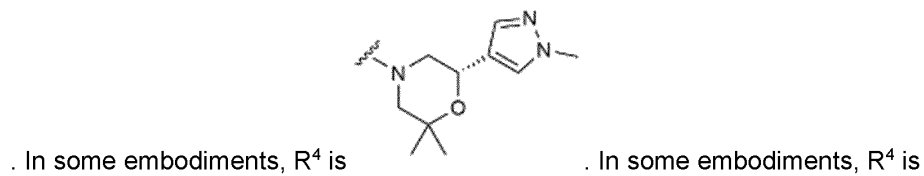
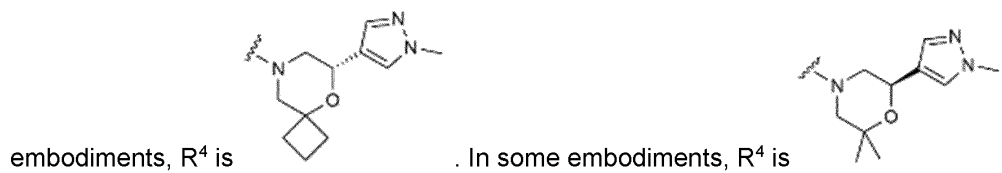
. In some embodiments, R⁴ is

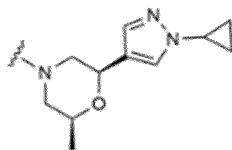


. In some embodiments, R⁴ is



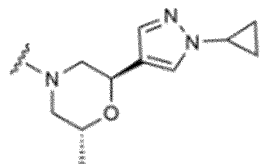
. In some



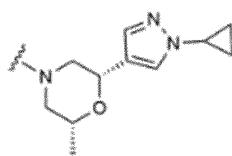
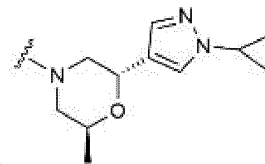


. In some embodiments, R⁴ is

. In some embodiments, R⁴ is

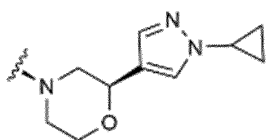


. In some embodiments, R⁴ is

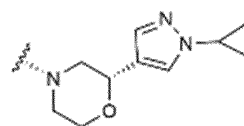


In some embodiments, R⁴ is

. In some embodiments, R⁴ is



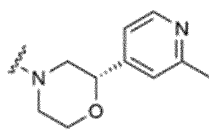
. In some embodiments, R⁴ is



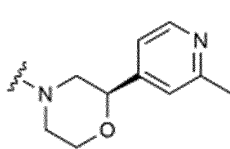
. In some

5

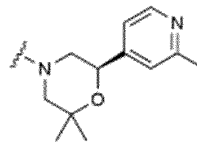
embodiments, R⁴ is



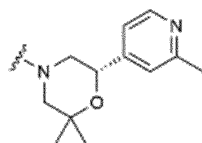
. In some embodiments, R⁴ is



. In some embodiments, R⁴ is

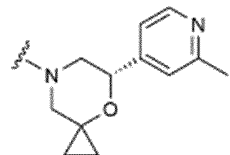


. In some

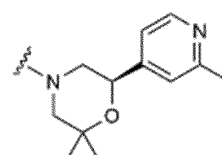


embodiments, R⁴ is

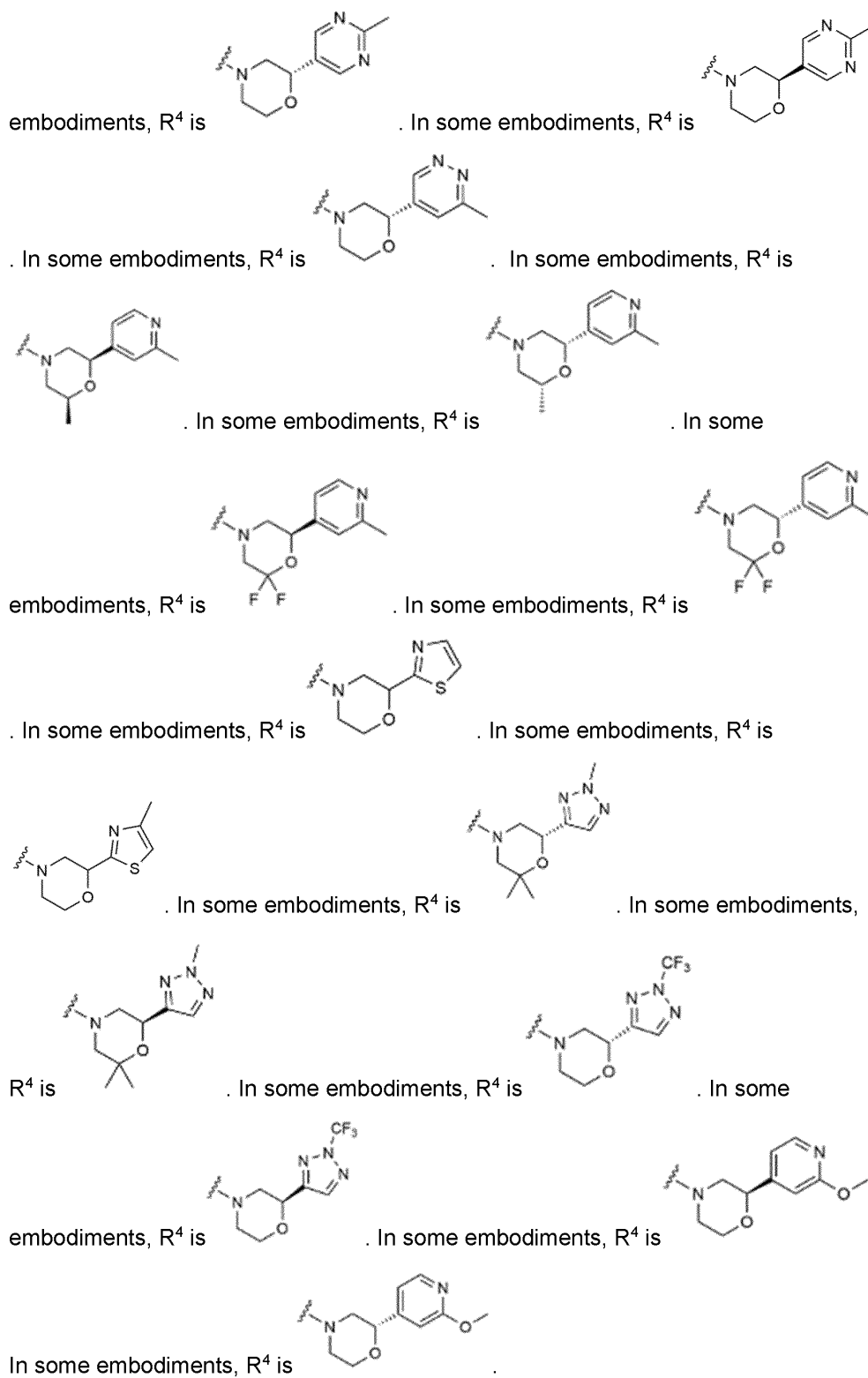
. In some embodiments, R⁴ is

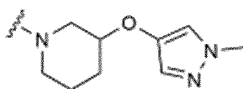


. In some embodiments, R⁴ is



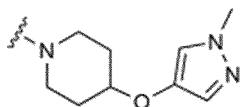
. In some



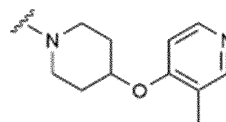


In some embodiments, R⁴ is

. In some embodiments, R⁴ is

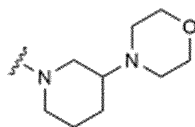


. In some embodiments, R⁴ is

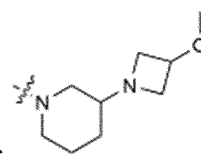


. In some

embodiments, R⁴ is

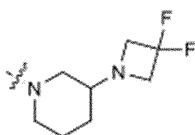


. In some embodiments, R⁴ is

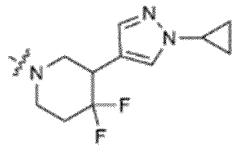


5

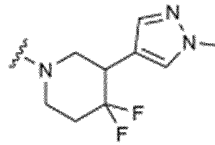
In some embodiments, R⁴ is



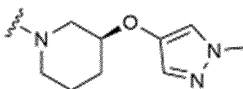
. In some embodiments, R⁴ is



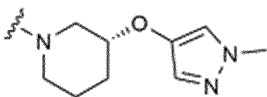
. In some embodiments, R⁴ is



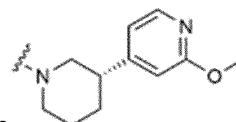
In some embodiments, R⁴ is



. In some embodiments, R⁴ is



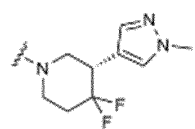
. In some embodiments, R⁴ is



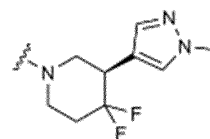
. In some

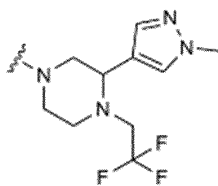
10

embodiments, R⁴ is



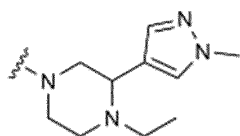
. In some embodiments, R⁴ is



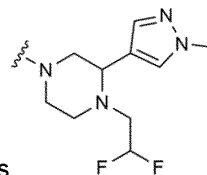


In some embodiments, R⁴ is

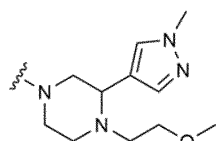
. In some embodiments, R⁴ is



. In some embodiments, R⁴ is

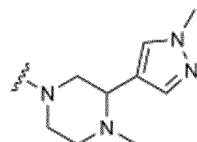
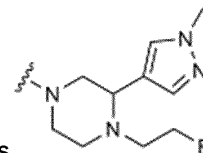


. In some



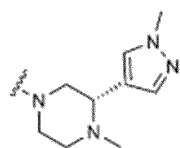
embodiments, R⁴ is

. In some embodiments, R⁴ is



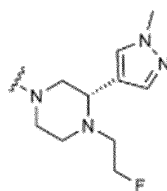
. In some embodiments, R⁴ is

. In some embodiments, R⁴ is

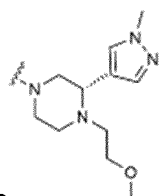


5

. In some embodiments, R⁴ is

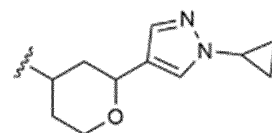
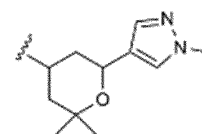


. In some



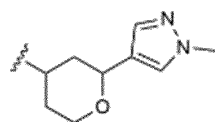
embodiments, R⁴ is

. In some embodiments, R⁴ is

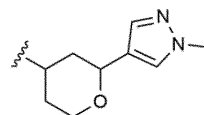


In some embodiments, R⁴ is

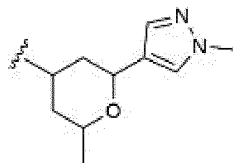
. In some embodiments, R⁴ is



. In some embodiments, R⁴ is

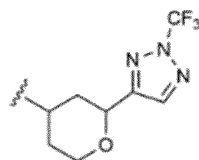


. In some

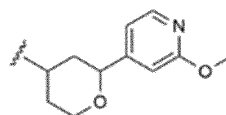


embodiments, R⁴ is

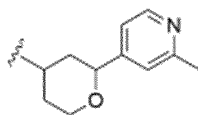
. In some embodiments, R⁴ is



. In some embodiments, R⁴ is

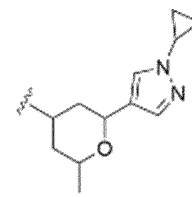


. In some

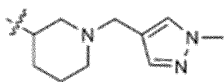


embodiments, R⁴ is

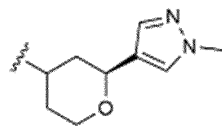
. In some embodiments, R⁴ is



In some embodiments, R⁴ is

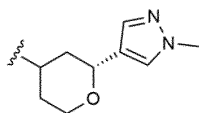


5

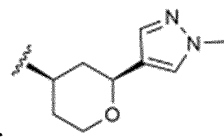


In some embodiments, R⁴ is

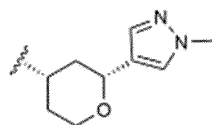
. In some embodiments, R⁴ is



. In some embodiments, R⁴ is

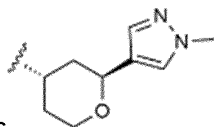
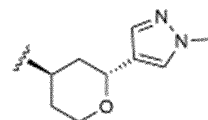


. In some



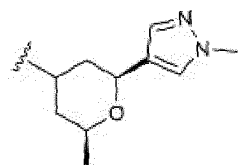
embodiments, R⁴ is

. In some embodiments, R⁴ is

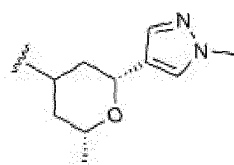


In some embodiments, R⁴ is

. In some embodiments, R⁴ is

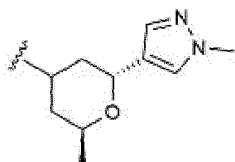


. In some embodiments, R⁴ is

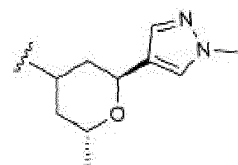


. In some

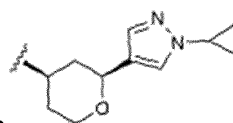
embodiments, R⁴ is



. In some embodiments, R⁴ is

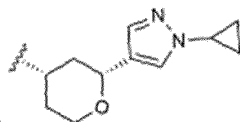


. In some embodiments, R⁴ is

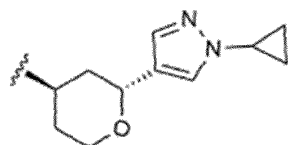


. In some

embodiments, R⁴ is

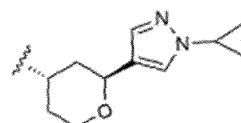


. In some embodiments, R⁴ is



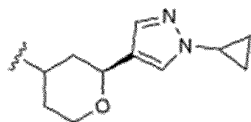
5

. In some embodiments, R⁴ is

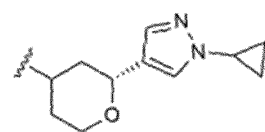


. In some

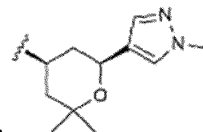
embodiments, R⁴ is



. In some embodiments, R⁴ is

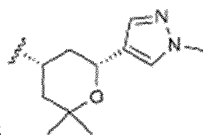


. In some embodiments, R⁴ is

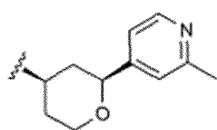


. In some

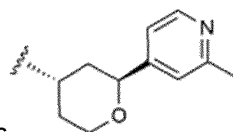
embodiments, R⁴ is



. In some embodiments, R⁴ is

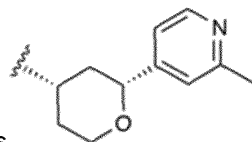


. In some embodiments, R⁴ is

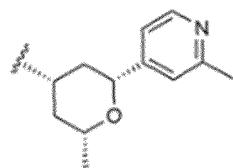


. In some

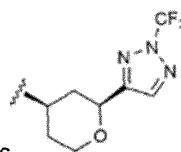
embodiments, R⁴ is



. In some embodiments, R⁴ is

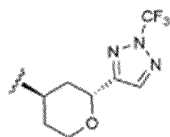


. In some embodiments, R⁴ is

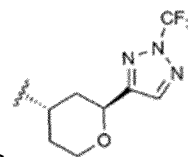


. In some

embodiments, R⁴ is



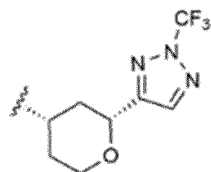
. In some embodiments, R⁴ is



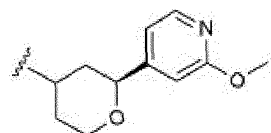
. In

5

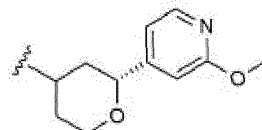
some embodiments, R⁴ is



. In some embodiments, R⁴ is

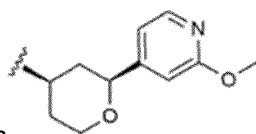


. In some embodiments, R⁴ is

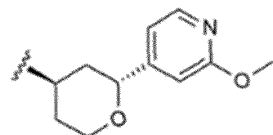


. In

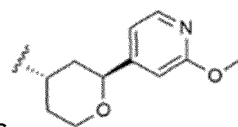
some embodiments, R⁴ is



. In some embodiments, R⁴ is

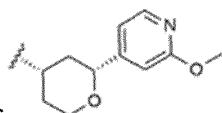


. In some embodiments, R⁴ is

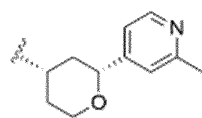


. In some

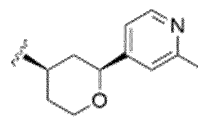
embodiments, R⁴ is



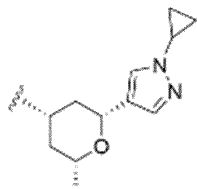
. In some embodiments, R⁴ is



. In some embodiments, R^4 is

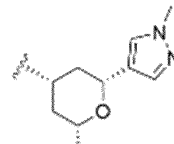


. In some



embodiments, R^4 is

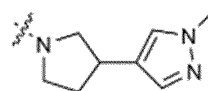
. In some embodiments, R^4 is



5 In some embodiments, R^4 is a 5-membered ring. In some embodiments, m is 1; X^E is a bond; and n is 1.

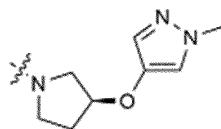
In some embodiments, X^B is N; X^C is CH_2 ; m is 1; X^D is C(H); X^E is a bond; X^F is C(H_2);

X^G is C(H_2); and n is 1. In some embodiments, R^4 is

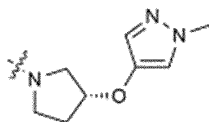


. In some

embodiments, R^4 is

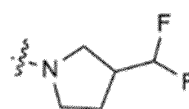


. In some embodiments, R^4 is



10

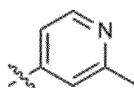
. In some embodiments, R^4 is

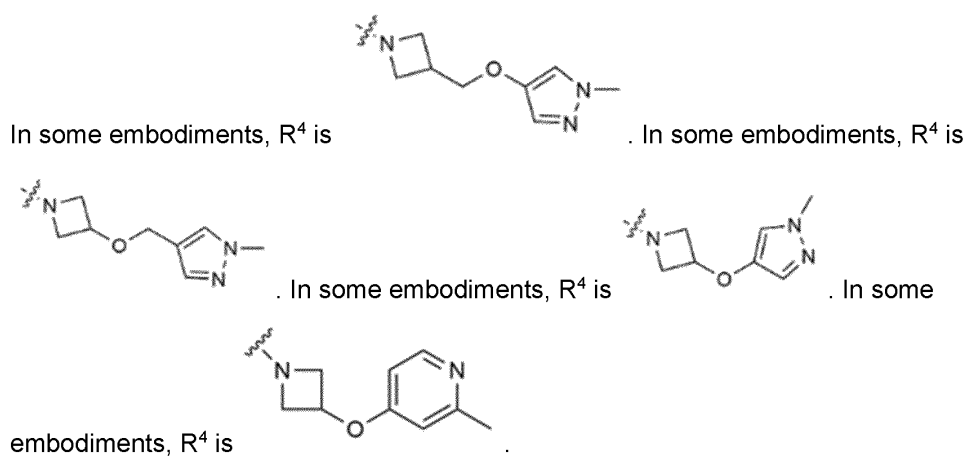


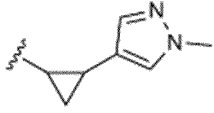
In some embodiments, R^4 is a 4-membered ring. In some embodiments, m is 1; X^E is a bond; and n is 0.

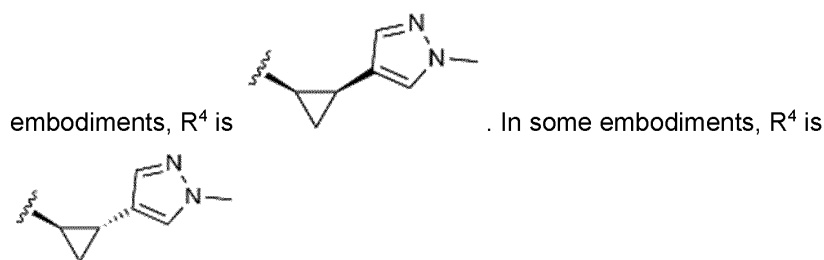
15 In some embodiments, X^B is N; X^C is CH_2 ; m is 1; X^D is C(H); X^E is a bond; X^F is C(H_2); and n is 0. In some embodiments, X^B is N; X^C is CH_2 ; m is 1; X^D is C(H); X^E is a bond;

X^F is C(H_2); n is 0; and R^{15} is





- 5 In some embodiments, R^4 is a 3-membered ring. In some embodiments, m is 0; X^E is a bond; and n is 0. In some embodiments, X^B is C(H); m is 0; X^D is C(H); X^E is a bond; X^F is C(H₂); and n is 0. In some embodiments, R^4 is . In some



10

In some embodiments, the compound is of Formula IA, wherein:

R^1 is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl and H;

R^2 is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halogen and H;

R^3 is phenyl is optionally substituted with 1 to 3 substituents independently selected

- 15 from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl and CN, wherein one methylene group of the C₁₋₃ alkyl is optionally replaced with -O-;

X^A is N or CH;

X^B is N or CH;

X^C is C(H)₂;

- 20 X^D is C(H);

X^E is O;

X^F is $C(R^{19})(R^{20})$, wherein each R^{19} and R^{20} are individually selected as H or CH_3 ;

X^G is $C(H)_2$;

m is 1;

n is 1;

5 R^{23} is a bond; and

R^{15} is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, -CN, and C_{3-6} cycloalkyl, or a pharmaceutically acceptable salt thereof.

10

In some embodiments, the compound is of Formula IA, wherein:

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and H;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, and H;

R^3 is phenyl is optionally substituted with 1 to 3 substituents independently selected

15 from the group consisting of halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl;

X^A is CH;

X^B is N;

X^C is $C(H)_2$;

X^D is $C(H)$;

20 X^E is O;

X^F is $C(H)_2$;

X^G is $C(H)_2$;

m is 1;

n is 1;

25 R^{23} is a bond; and

R^{15} is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, -CN, and C_{3-6} cycloalkyl, or a pharmaceutically acceptable salt thereof.

30

In some embodiments, the compound is of Formula IA and wherein:

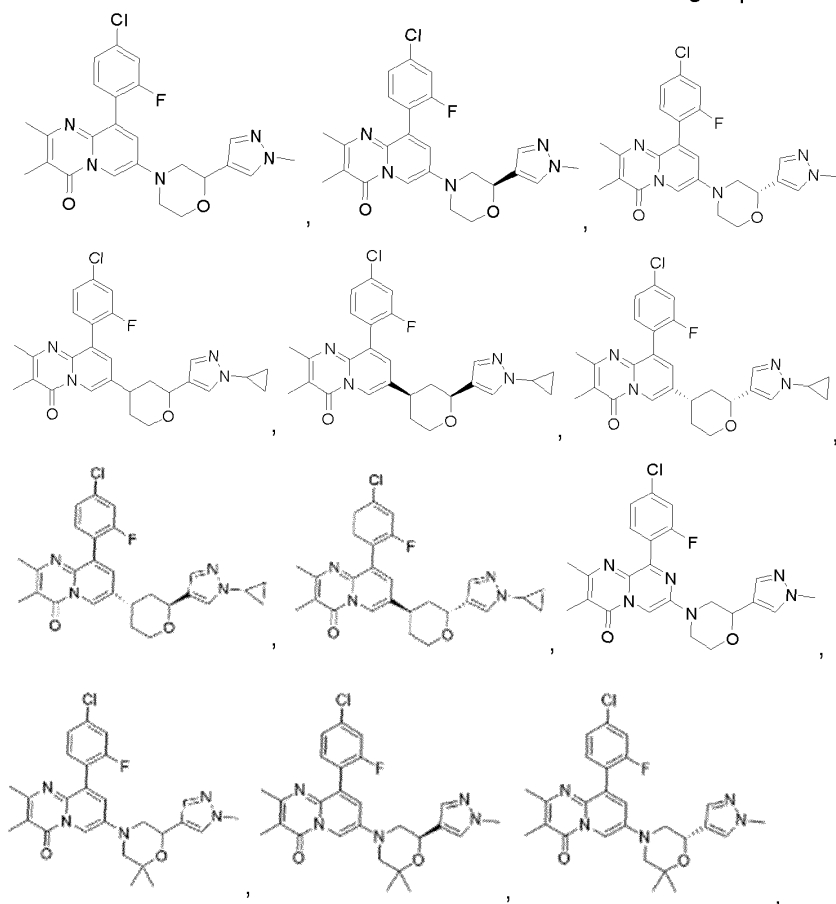
R^1 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and H;

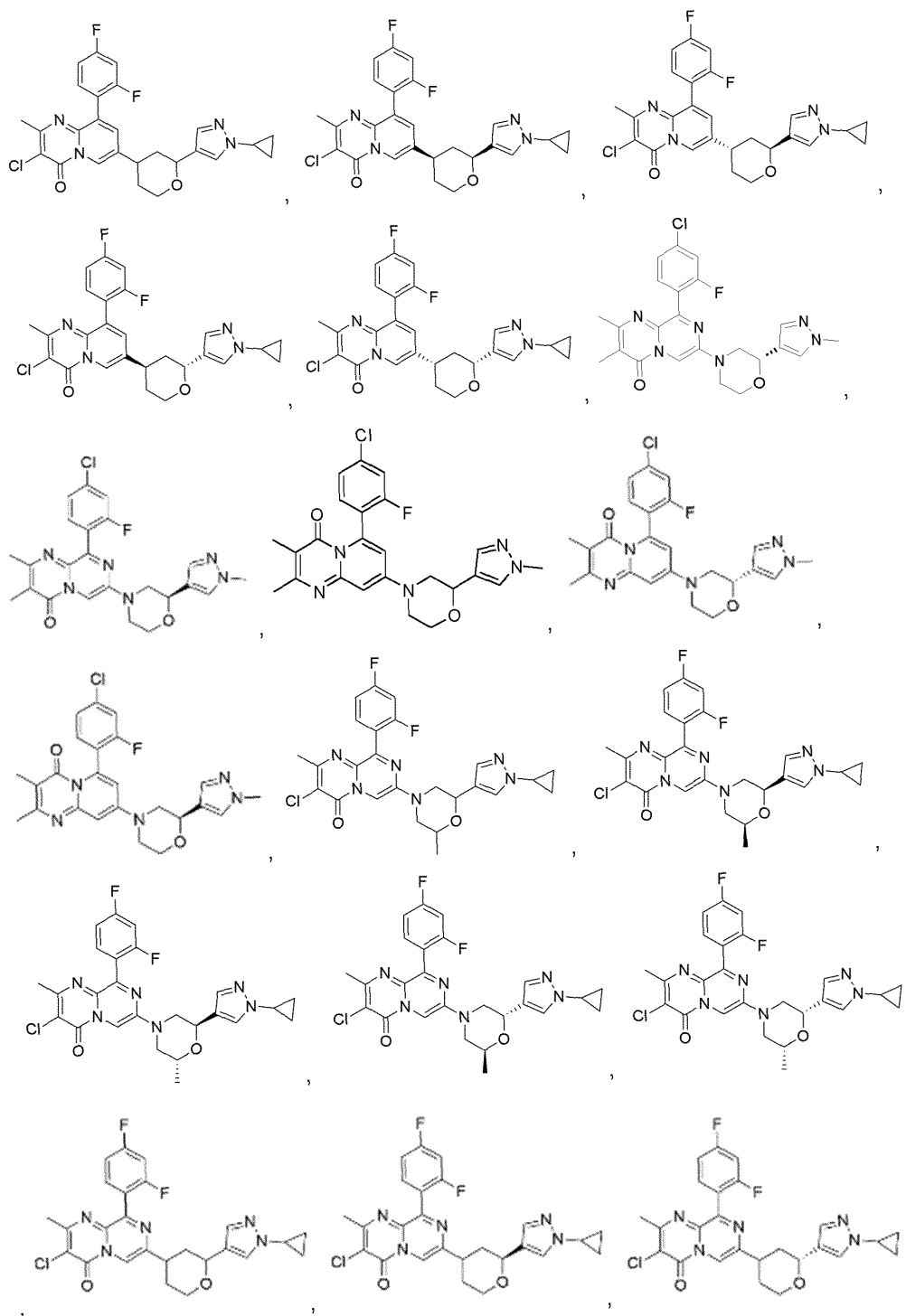
R^2 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, and H;

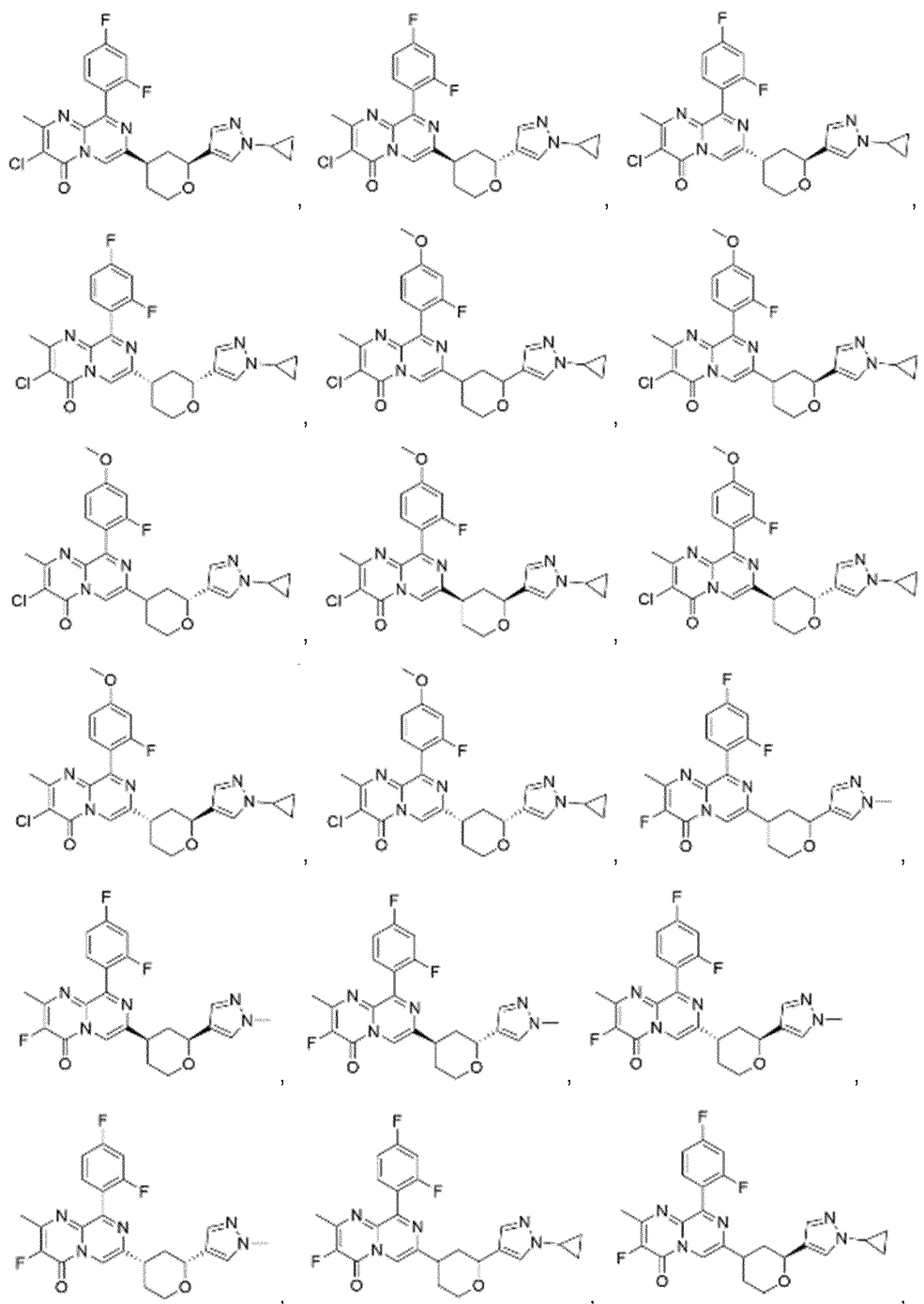
R^3 is phenyl is optionally substituted with 1 to 3 substituents independently selected

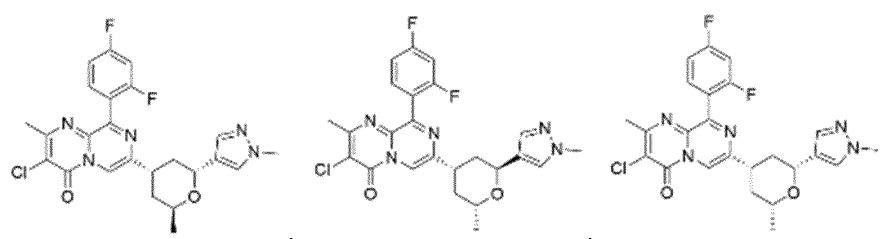
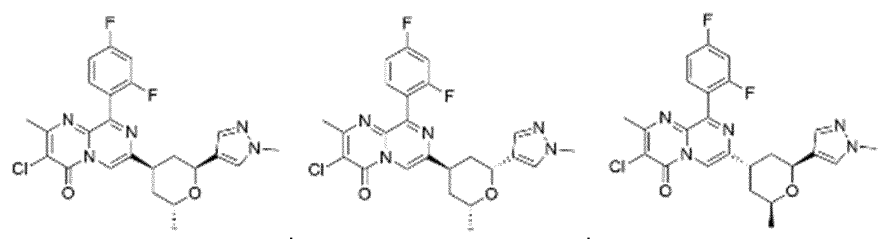
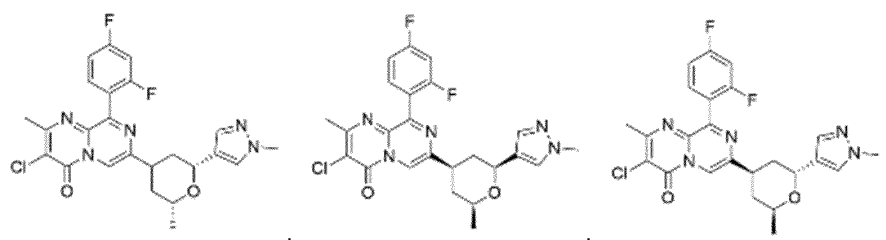
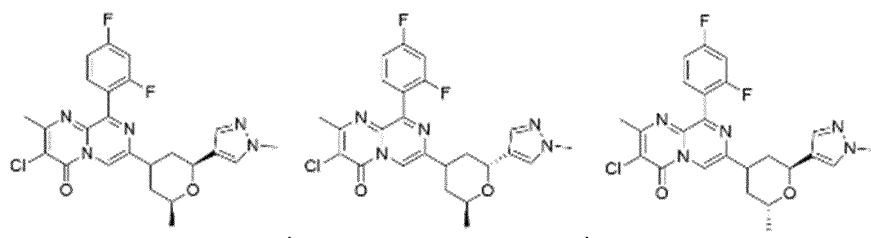
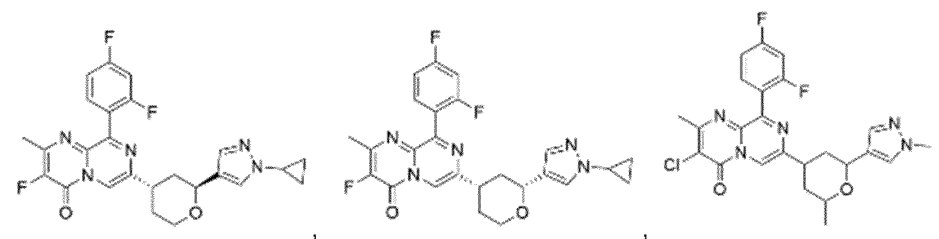
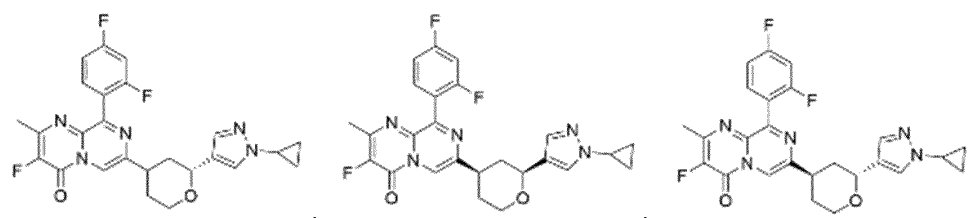
35 from the group consisting of halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl;

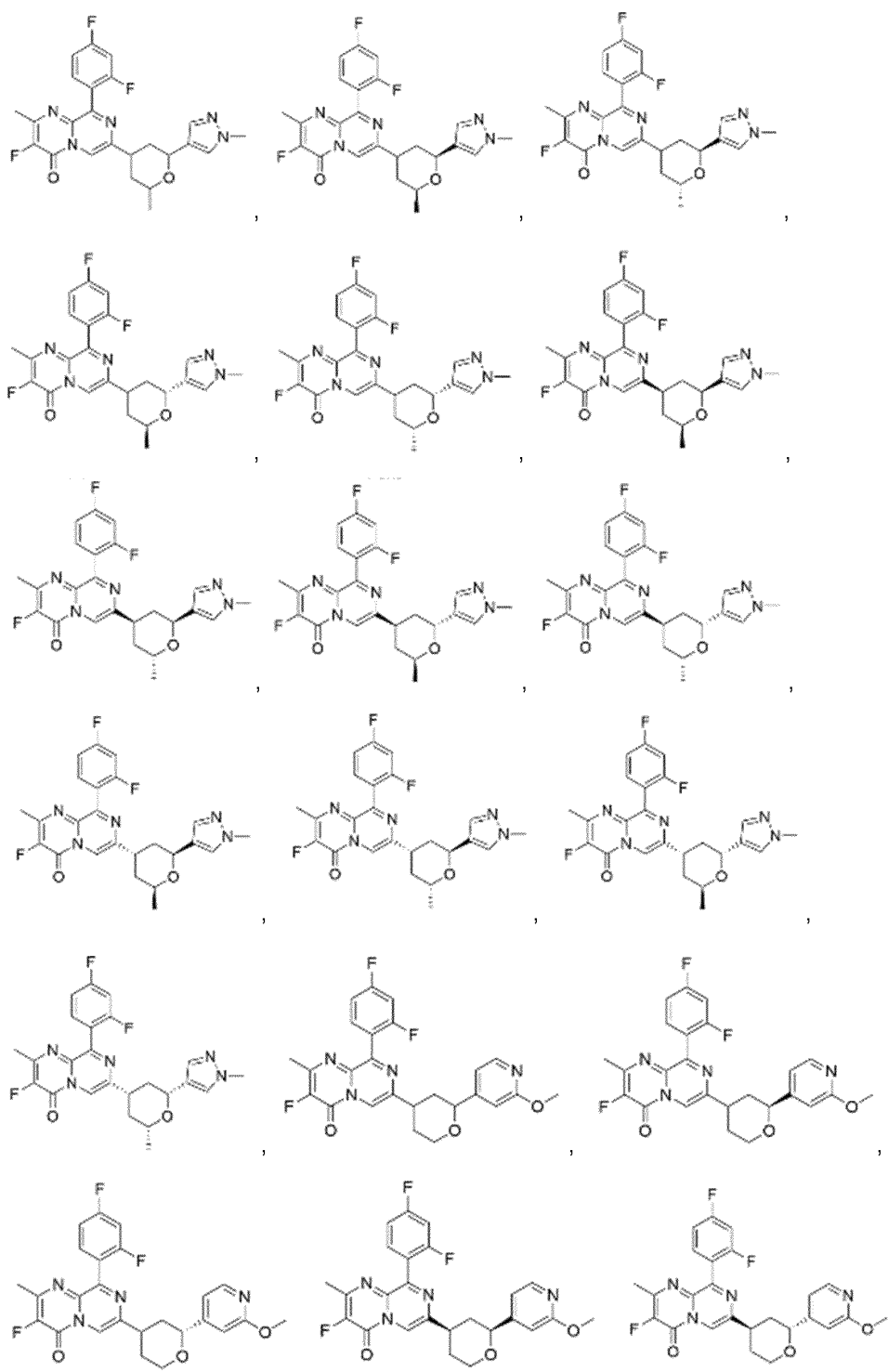
- X^A is N;
 X^B is C(H);
 X^C is C(H)₂;
 X^D is C(H);
5 X^E is O;
 X^F is C(H)₂;
 X^G is C(H)₂;
m is 1;
n is 1;
10 R^{23} is a bond; and
 R^{15} is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -CN, and C₃₋₆ cycloalkyl.
- 15 In some embodiments, the compound is selected from the group consisting of:

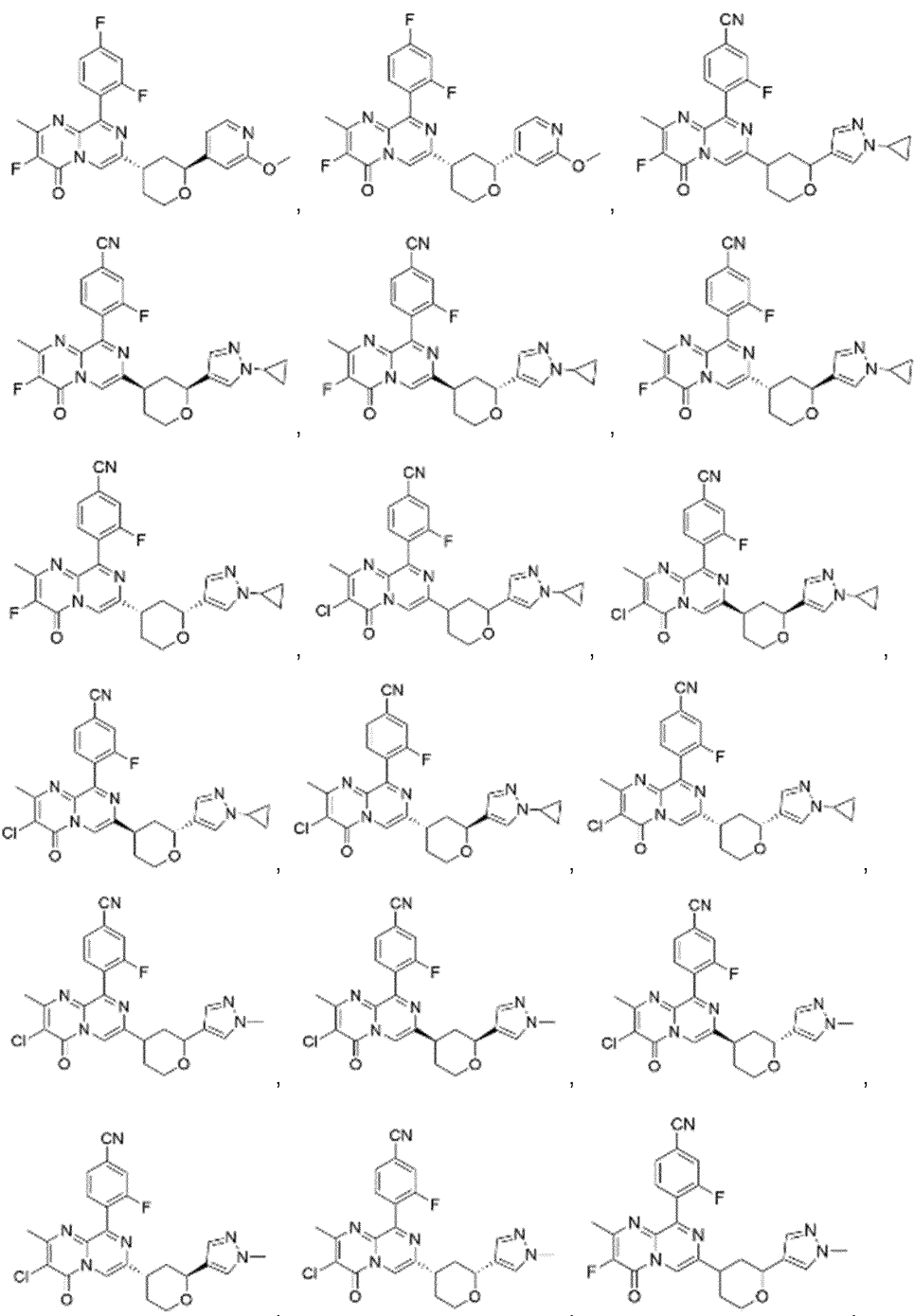


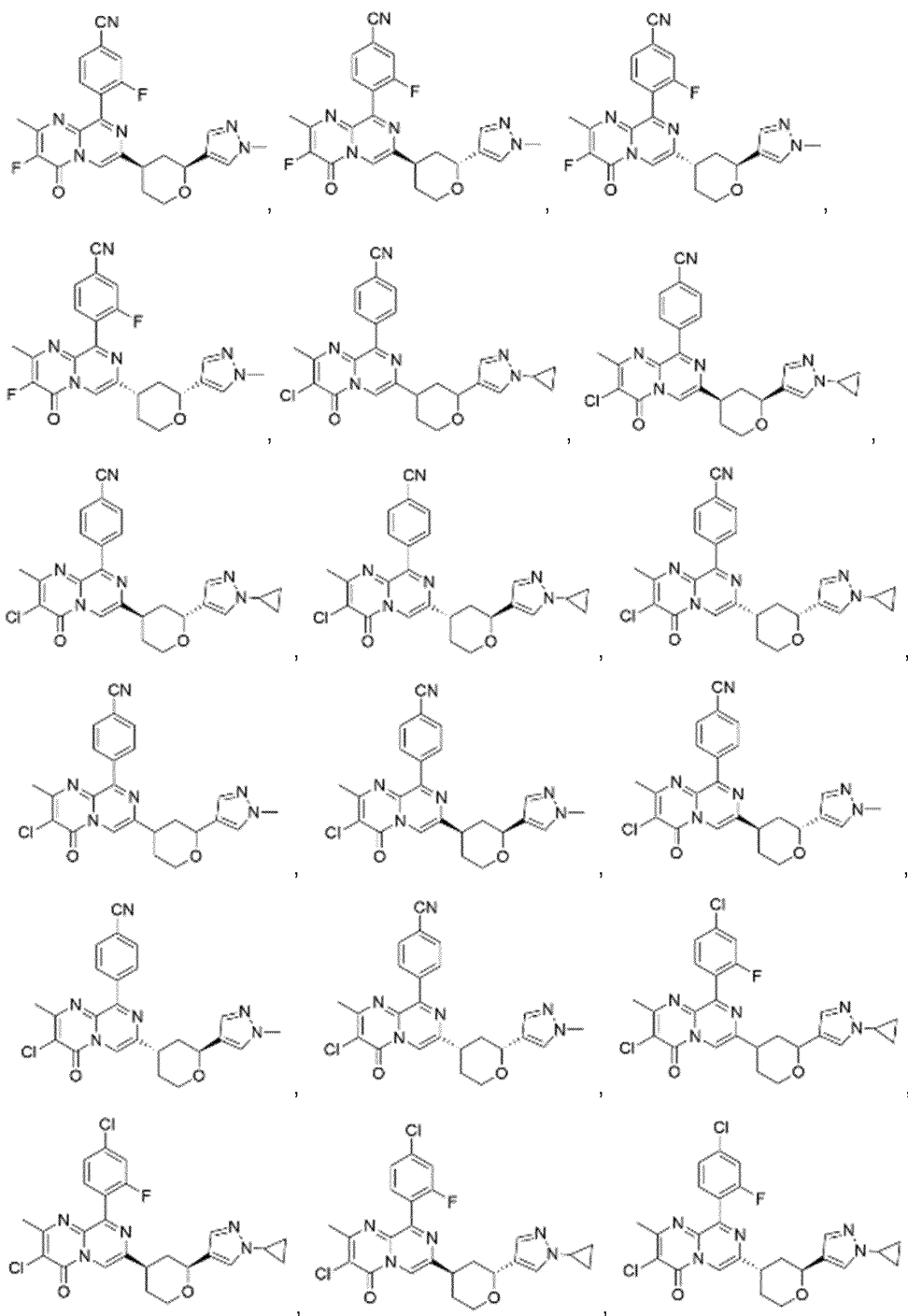


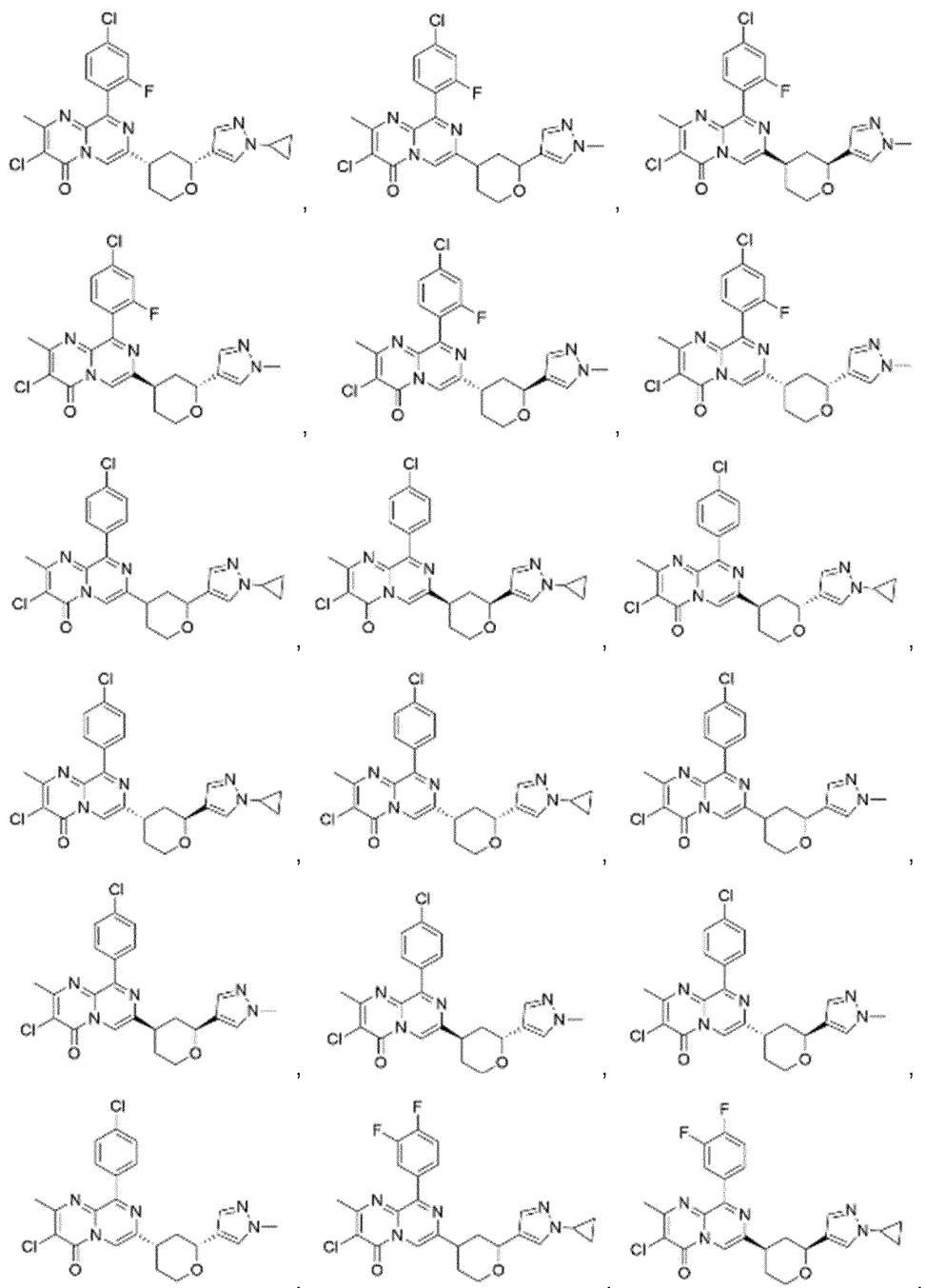


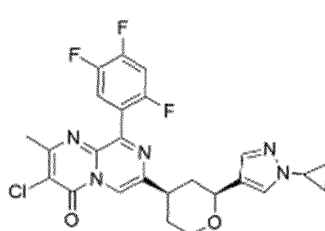
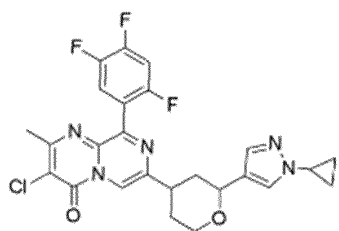
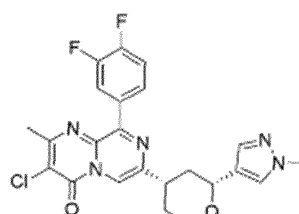
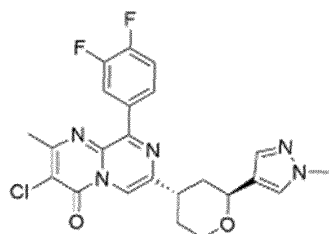
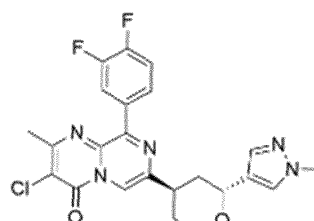
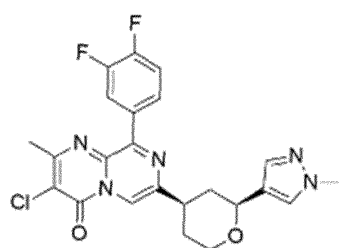
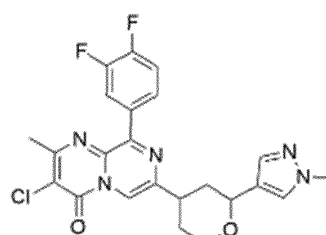
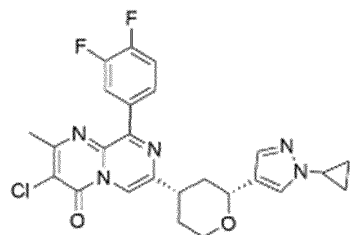
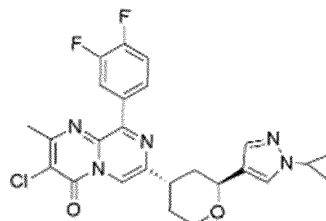
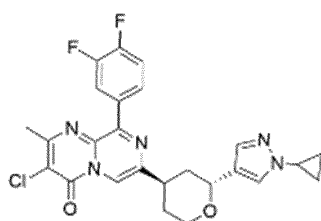




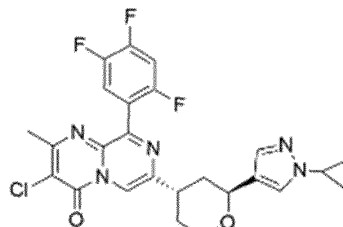
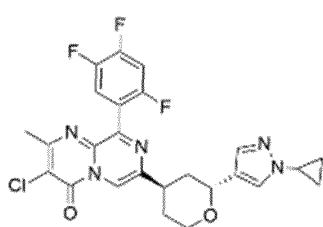


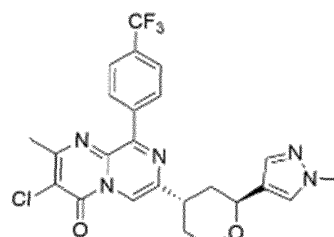
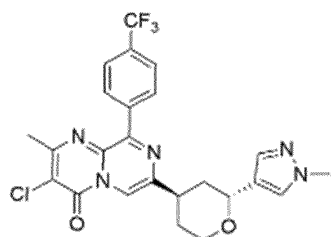
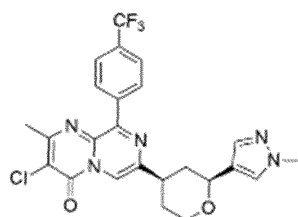
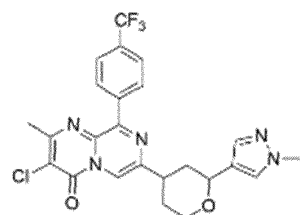
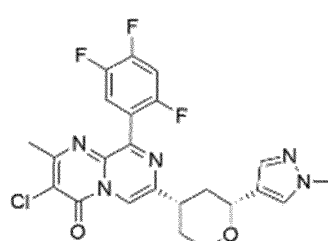
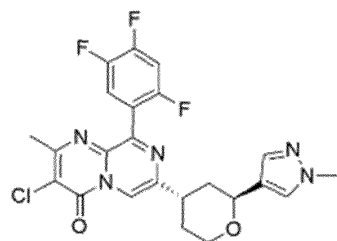
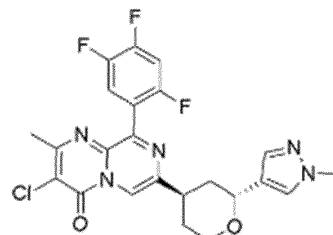
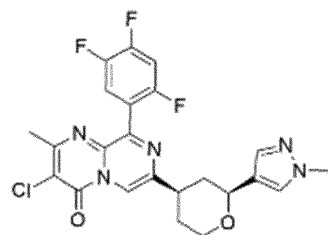
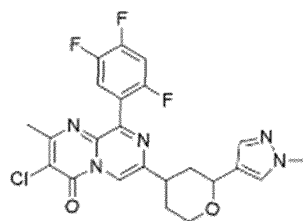
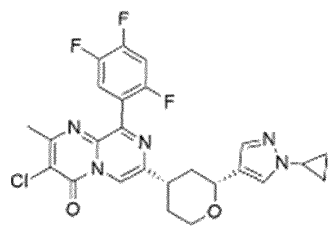




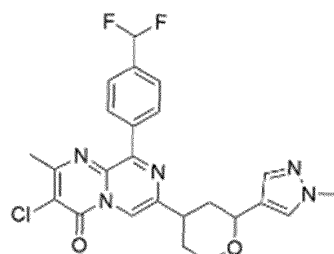
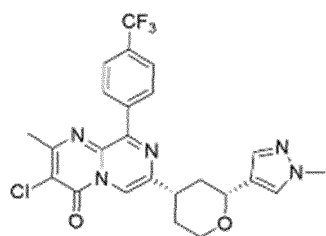


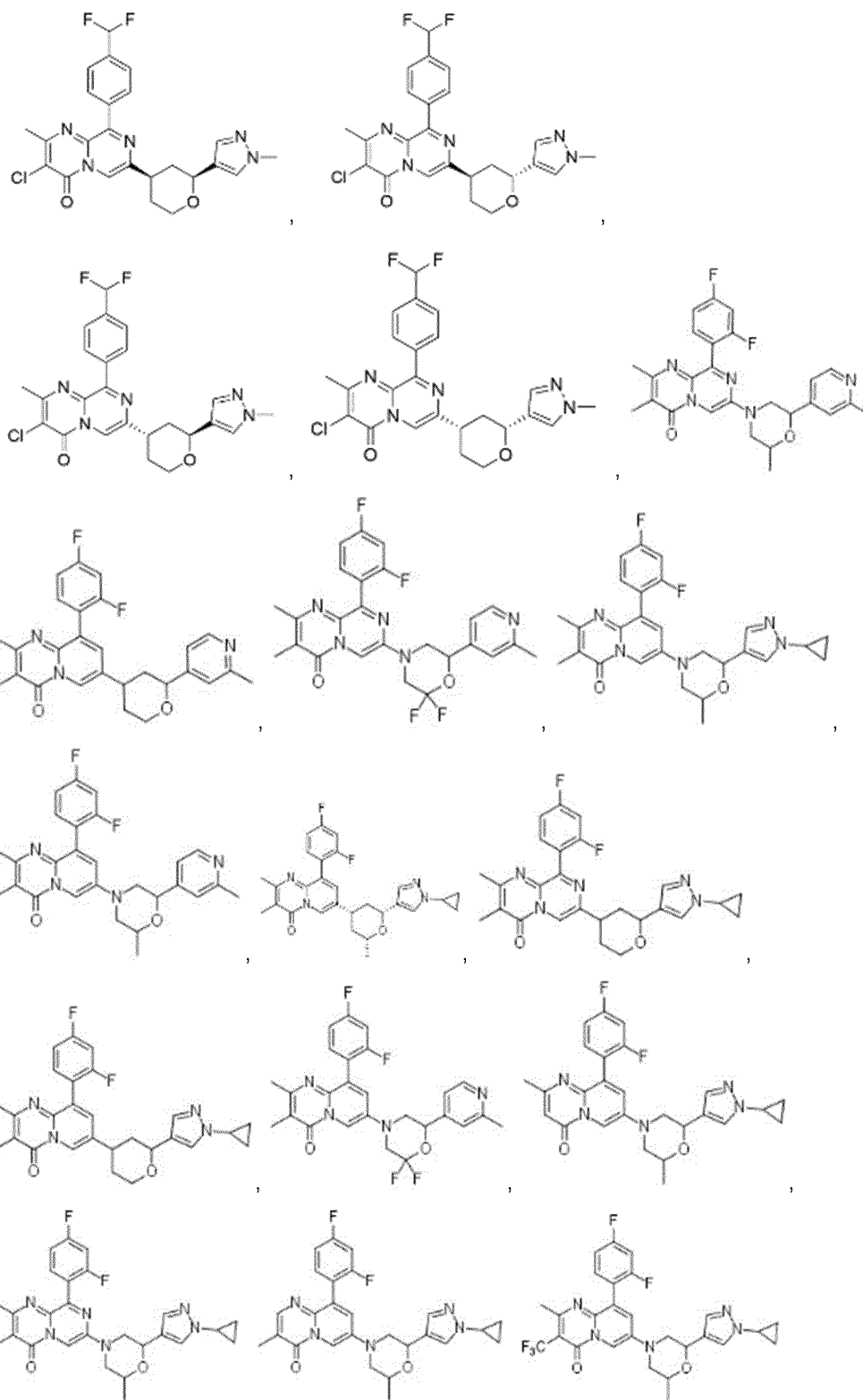
5

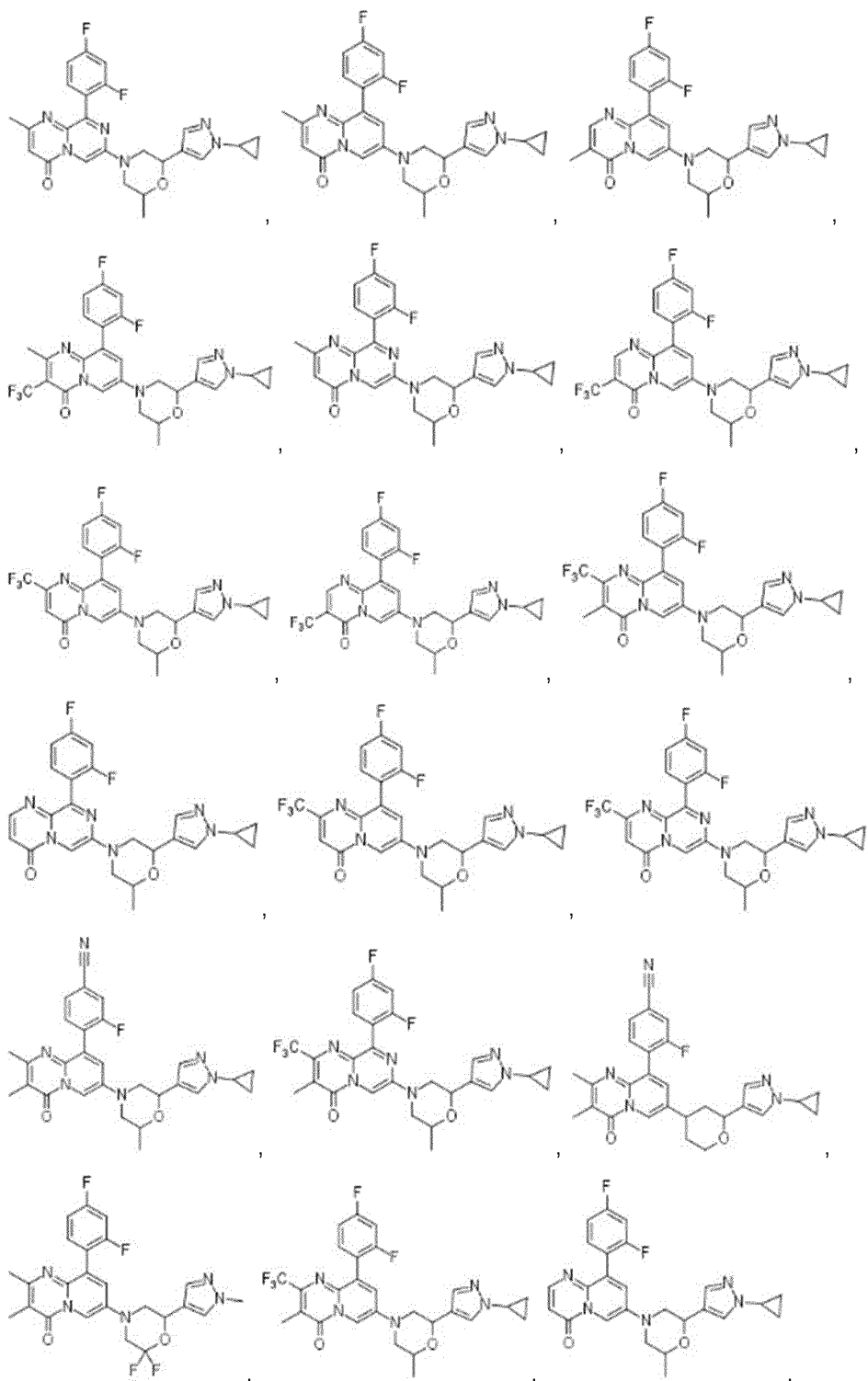


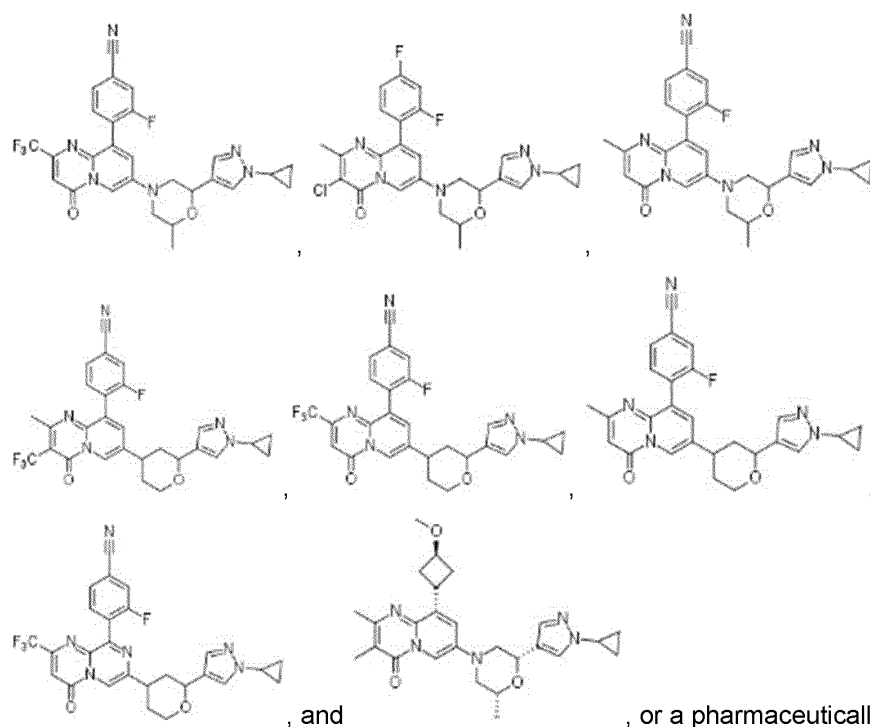


5









, and , or a pharmaceutically acceptable salt thereof.

5

In some embodiments, the compound is 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(4-chloro-2-fluorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(4-chloro-2-fluorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-9-(4-chloro-2-fluorophenyl)-7-(2,2-dimethyl-6-(1-methyl-1H-pyrazol-4-

10

15

20

yl)morpholino)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-9-(4-chloro-2-fluorophenyl)-7-(2,2-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)morpholino)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

5 embodiments, the compound is (S)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 6-(4-chloro-2-fluorophenyl)-2,3-dimethyl-8-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

10 embodiments, the compound is 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)-6-methylmorpholino)-9-(2,4-difluorophenyl)-2,3-dimethyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-((2R,6S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)-6-methylmorpholino)-9-(2,4-difluorophenyl)-2,3-dimethyl-4H-pyrazino[1,2-a]pyrimidin-4-

15 one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-((2R,6R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)-6-methylmorpholino)-9-(2,4-difluorophenyl)-2,3-dimethyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-((2R,6R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)-6-methylmorpholino)-9-(2,4-difluorophenyl)-2,3-dimethyl-4H-pyrazino[1,2-a]pyrimidin-4-

20 one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-((2S,6R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)-6-methylmorpholino)-9-(2,4-difluorophenyl)-2,3-dimethyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

25 embodiments, the compound is 3-chloro-7-((2S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

30 embodiments, the compound is 3-chloro-7-((2R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-

35 a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-7-((2R,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-7-((2S,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2-fluoro-4-methoxyphenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-7-((2S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2-fluoro-4-methoxyphenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-7-((2R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2-fluoro-4-methoxyphenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2-fluoro-4-methoxyphenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-7-((2R,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2-fluoro-4-methoxyphenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-7-((2S,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2-fluoro-4-methoxyphenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2-fluoro-4-methoxyphenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-3-fluoro-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 7-((2S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-3-fluoro-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a

pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-((2R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-3-fluoro-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-3-fluoro-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-((2R,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-3-fluoro-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-((2S,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-3-fluoro-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-3-fluoro-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-(2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-(2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2S,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2R,6S)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2R,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2S,4R,6S)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2S,4R,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-
((2R,4R,6S)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-
pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-
5 ((2R,4R,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-
pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2S,4S,6S)-
2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-
a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
10 embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2S,4S,6R)-
2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-
a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2R,4S,6S)-
2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-
15 a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-
((2R,4S,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-
pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-7-(2-(2-methoxypyridin-
20 4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a
pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-
(2,4-difluorophenyl)-3-fluoro-7-((2S)-2-(2-methoxypyridin-4-yl)tetrahydro-2H-pyran-4-
yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt
thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-7-
25 ((2R)-2-(2-methoxypyridin-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-
a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-7-((2S,4R)-2-(2-
methoxypyridin-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-
one, or a pharmaceutically acceptable salt thereof. In some embodiments, the
30 compound is 9-(2,4-difluorophenyl)-3-fluoro-7-((2R,4R)-2-(2-methoxypyridin-4-
yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a
pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-
(2,4-difluorophenyl)-3-fluoro-7-((2S,4S)-2-(2-methoxypyridin-4-yl)tetrahydro-2H-pyran-
4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt
35 thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-7-

((2R,4S)-2-(2-methoxypyridin-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-3-fluoro-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some
5 embodiments, the compound is 4-(7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-3-fluoro-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some
10 embodiments, the compound is 4-(7-((2R,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-3-fluoro-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some
15 embodiments, the compound is 4-(7-((2S,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-3-fluoro-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some
20 embodiments, the compound is 4-(7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-3-fluoro-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some
25 embodiments, the compound is 4-(3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some
30 embodiments, the compound is 4-(3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some
35 embodiments, the compound is 4-(3-chloro-7-((2R,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 4-(3-chloro-7-((2S,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 4-(3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 4-(3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-2-methyl-7-((2R,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-2-methyl-7-((2S,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-7-((2R,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-7-((2S,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-2-methyl-7-((2R,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 4-(3-chloro-2-methyl-7-((2S,4S)-2-(1-methyl-1H-pyrazol-4-

yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-7-((2R,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-7-((2S,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-((2R,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-((2S,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a

pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-7-((2R,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-7-((2S,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-2-methyl-7-((2R,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-2-methyl-7-((2S,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-((2R,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-((2S,4S)-2-(1-cyclopropyl-1H-pyrazol-4-

yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
5 embodiments, the compound is 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
10 embodiments, the compound is 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-((2R,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-((2S,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
15 embodiments, the compound is 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
20 embodiments, the compound is 3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-((2R,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
25 embodiments, the compound is 3-chloro-7-((2S,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
30 embodiments, the compound is 3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
35 embodiments, the compound is 3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-((2R,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-((2S,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-((2R,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-((2S,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-((2R,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable

salt thereof. In some embodiments, the compound is 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-((2S,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2R,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2S,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-(2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2S,6S)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2R,6S)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2S,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2R,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2S,4R,6S)-

2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2R,4R,6S)-
2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-
5 a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2S,4R,6R)-
2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-
a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2R,4R,6R)-
10 2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-
a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2S,4S,6S)-
2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-
a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
15 embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2R,4S,6S)-
2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-
a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2S,4S,6R)-
2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-
20 a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2R,4S,6R)-
2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-
a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
embodiments, the compound is 3-fluoro-4-(3-fluoro-2-methyl-7-(2-(1-methyl-1H-
25 pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-
yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments,
the compound is 3-fluoro-4-(3-fluoro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-
yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a
pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-
30 fluoro-4-(3-fluoro-2-methyl-7-((2R,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-
pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically
acceptable salt thereof. In some embodiments, the compound is 3-fluoro-4-(3-fluoro-2-
methyl-7-((2S,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-
pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt
35 thereof. In some embodiments, the compound is 3-fluoro-4-(3-fluoro-2-methyl-7-

((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (S)-6-(4-chloro-2-fluorophenyl)-2,3-dimethyl-8-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is (R)-6-(4-chloro-2-fluorophenyl)-2,3-dimethyl-8-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-

yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-methyl-6-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-[2,2-difluoro-6-(2-methyl-4-pyridyl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-methyl-6-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-[(2R,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-[2,2-difluoro-6-(2-methyl-4-pyridyl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
5 embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some
10 embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt
15 thereof. In some embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically
20 acceptable salt thereof. In some embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-(trifluoromethyl)pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile, or a pharmaceutically acceptable salt thereof. In some
25 embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile, or a pharmaceutically acceptable salt thereof. In
30 some embodiments, the compound is 7-[2,2-difluoro-6-(1-methylpyrazol-4-yl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)pyrido[1,2-

a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-4-oxo-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2-methyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-methyl-4-oxo-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-4-oxo-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-methyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-4-oxo-2-(trifluoromethyl)pyrazino[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(3-methoxycyclobutyl)-2,3-dimethyl-7-[rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 9-(3-methoxycyclobutyl)-2,3-dimethyl-7-[rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-

((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

5 embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

10 embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

15 embodiments, the compound is 3-chloro-9-(4-chlorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

20 embodiments, the compound is 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

25 embodiments, the compound is 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

30 embodiments, the compound is 3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

35 embodiments, the compound is 3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some

embodiments, the compound is 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-

yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile, 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 the working examples herein. In some embodiments the compound of the present invention is selected from any of the intermediate compounds, or a pharmaceutically acceptable salt thereof of any one of the intermediates designated I-1 to I-13 herein.

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 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, 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 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 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 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.

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

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
5 comprises a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient and/or diluent.

While a compound as disclosed herein for use in therapy may be administered in the
10 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 pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

15 In some embodiments, the invention provides pharmaceutical compositions comprising a compound as disclosed herein or a pharmaceutically acceptable salt thereof, 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
20 formulation and not harmful to the recipient thereof. Examples of excipients and their use may be found in Remington's Pharmaceutical Sciences 20th Edition (Lippincott Williams & Wilkins, 2000).

A therapeutic amount or therapeutically effective amount or dose refers to that amount
25 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, increase survival time or rate, diminish symptoms, make an injury, disease, or condition
30 (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
pharmacological procedures in cell cultures or experimental animals. The dose ratio
35 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 compound as disclosed herein is in the range of about 0.01 mg/kg to about 100 mg/kg bodyweight/day.

5

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 form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

10

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, enteral delivery, oral delivery, topical delivery, parenteral delivery, intravenous delivery, intradermal delivery, intramuscular delivery, intrathecal delivery, colonic delivery, rectal delivery, or intraperitoneal delivery.

15

Biological activity

As demonstrated in Example 32 compounds of the present invention are capable of modulating TREM2. Thus, in some embodiments, the compound of the present invention is a TREM2 modulator, such as a TREM2 agonist. The assay described in Example 32 may be used to assess and characterize a compound's ability to act as an agonist of TREM2. In some embodiments the compounds of the present invention are useful for the activation of TREM2. In some embodiments the compounds of the present invention activates TREM2. In some embodiments the compounds of the present invention enhances TREM2 activity. In some embodiments, a compound of the present invention induces phosphorylation of a kinase that interacts with the TREM2/DAP12 signalling complex, such as, but not limited to, Syk, ZAP70, PI3K, Erk, AKT and GSK3b. In some embodiments the compounds of the present invention enhances or activates TREM2 signalling through DAP12. In some embodiments the compounds of the present invention enhances or activates TREM2-induced phosphorylation levels of the Syk kinase. In some embodiments, a compound of the present invention induces or enhances phosphorylation of Syk if the level of Syk phosphorylation in a sample treated with the compound is increased by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100% or more as compared to a control value; such as is

20

25

30

35

increased by at least 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, or more as compared to a control value.

5 The potency of compounds of the present invention are in some embodiments expressed as EC₅₀ corresponding to the concentration of compound able to activate the phospho-Syk AlphaScreen signal to 50% of the maximal response. In some
embodiments the compounds of the present invention has an EC₅₀ value of less than 1000 nM, such as an EC₅₀ value between 100 nM and 1000 nM, such as an EC₅₀
value between 10 nM and 100 nM, such as an an EC₅₀ value between 1 nM and 10
10 nM, such as an EC₅₀ value <1 nM.

In some embodiments the compounds of the present invention are capable of increasing the expression of one or more TREM2 regulated genes. In some
embodiments the compounds of the present invention increases the expression of one
15 or more TREM2 regulated genes. In some embodiments the compounds of the present invention are capable or increasing one or more TREM2 regulated genes selected from the group consisting of CXCL10, CCL2, CST7 and TMEM119 (see Example 205). In some embodiments the compounds of the present invention increases expression levels, such as brain expression levels, of one or more TREM2 regulated genes
20 selected from the group consisting of CXCL10, CCL2, CST7 and TMEM119.
In some embodiments, a compound of the present invention increases expression levels, such as brain expression levels, if the level expression of the gene in a sample treated with the compound is increased by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least
25 100% or more as compared to a control value; such as is increased by at least 1.5-fold, 2-fold, 2.5-fold, 3-fold, 3.5-fold, 4-fold, 5-fold, or more as compared to a control value (e.g. untreated control/vehicle).

Medical use

30 Being modulators of TREM2, the compounds of the present invention 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, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of a condition associated with a loss of function of TREM2. In one aspect, the present invention relates to a compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of a condition associated with a mutation in TREM2.
- 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.
- In some embodiments, a compound as described herein is used in treating a neurodegenerative disease that is characterized by a loss of function of TREM2. In some embodiments, a compound as described herein is used in treating a neurodegenerative disease that is characterized by a mutation in TREM2.
- In one aspect, the present invention relates to a method for enhancing or increasing TREM2 activity in a subject in need thereof, such as in a subject having a neurodegenerative disease, said method comprising administering to the subject a compound, or a pharmaceutically acceptable salt thereof, as defined herein.
- In one aspect, the present invention relates to method for one or more of i) enhancing or activating TREM2 signaling through DAP12, ii) inducing phosphorylation of a kinase that interacts with the TREM2/DAP12 signaling complex, such as, but not limited to, Syk, ZAP70, PI3K, Erk, AKT and GSK3b, iii) enhancing TREM2-induced phosphorylation levels of the Syk kinase, iv) increasing the expression levels, such as brain expression levels, of one or more TREM2 regulated genes, and/or v) increasing the expression levels, such as brain expression levels, of one or more TREM2 regulated genes selected from the group consisting of CXCL10, CCL2, CST7 and TMEM119; in a subject in need thereof, such as in a subject having a neurodegenerative disease, said method comprising administering to the subject a compound, or a pharmaceutically acceptable salt thereof, as defined herein.
- 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

encephalopathy (CTE), Progressive supranuclear palsy, Corticobasal degeneration, diffuse neurofibrillary tangles with calcification (DNCT), Frontotemporal dementia (FTD), and FTD with parkinsonism-17 (FTD with parkinsonism linked to chromosome 17; FTDP-17).

5

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.

10

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).

15

20

25

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).

30

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, dementia with lewy bodies, prion disease dementia, argyrophilic grain dementia, 15 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 disorders, nutritional deficiencies, infections, immune disorders, liver or kidney failure, 20 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 disorder is a leukodystrophic or dysmyelinating disorder, such as selected from the 35 group consisting of CNS neuropathies such as vitamin B12 deficiency, central pontine

myelinolysis, myelopathies such as tabes dorsalis (syphilitic myelopathy), leukoencephalopathies and leukodystrophies.

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 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 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 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 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 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 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 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 retinal degeneration (e.g., macular degeneration).
- 10 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 some embodiments the neurodegenerative disease is a Leukoencephalopathy selected from the group consisting of Progressive multifocal leukoencephalopathy, Toxic
- 15 leukoencephalopathy, Leukoencephalopathy with vanishing white matter, Leukoencephalopathy with neuroaxonal spheroids, Reversible posterior leukoencephalopathy syndrome, Megalencephalic leukoencephalopathy with subcortical cysts, and Hypertensive leukoencephalopathy. In some embodiments, the neurodegenerative disease is ALSP (Adult-onset leukoencephalopathy with axonal
- 20 spheroids and pigmented glia).
- In some embodiments the neurodegenerative disease is selected from the group consisting of cerebral autosomal dominant arteriopathy with subcortical infarcts or leukoencephalopathy; cerebral autosomal recessive arteriopathy with subcortical
- 25 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).
- 30 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 as globoid cell leukodystrophy), Krabbe disease, Canavan disease, X-linked adrenoleukodystrophy, Alexander disease, hypomyelinating leukodystrophy type 7 (4H
- 35 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). 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).

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.

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.

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.

In some embodiments, the subject is a mammal, such as a human.

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.

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 associated with dysfunction of Colony stimulating factor 1 receptor (CSF1R, also known as macrophage colony-stimulating factor receptor / M-CSFR, or cluster of differentiation 115 / CD115). In some embodiments the disease or disorder associated with dysfunction of CSF1R is a neurodegenerative disease associated with dysfunction of CSF1R.

In some embodiments the disease or disorder is caused by a heterozygous CSF1R mutation, a homozygous CSF1R mutation, a splice mutation in the csf1r gene, a missense mutation in the csf1r gene, a mutation in the catalytic kinase domain of CSF1R, a mutation in an immunoglobulin domain of CSF1R, a mutation in the
5 ectodomain of CSF1R, a loss-of-function mutation in CSF1R. In some embodiments the disease or disorder result from a change (e.g. increase, decrease or cessation) in the activity of CSF1R and/or a decrease or cessation in the activity of CSF1R.

10 In some embodiments the neurodegenerative disease associated with dysfunction of CSF1R is a Leukoencephalopathy.

In some embodiments the neurodegenerative disease associated with dysfunction of CSF1R is selected from the group consisting of:

adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP),
CSF1R-related leukoencephalopathy,
15 hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS),
pigmentary orthochromatic leukodystrophy (POLD),
pediatric-onset leukoencephalopathy,
congenital absence of microglia,
brain abnormalities neurodegeneration and dysosteosclerosis (BANDDOS), and
20 Cerebral autosomal dominant arteriopathy with subcortical infarcts and
leukoencephalopathy (CADASIL).

In some embodiments the neurodegenerative disease is a condition associated with dysfunction of ATP- binding cassette transporter 1 (ABCD1).
25

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*.

30 In some embodiments the LSD is a 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
35

(globoid cell leukodystrophy), metachromatic leukodystrophy (MLD), Niemann-Pick disease (Types A, B and C), Sandhoff disease, Farmer disease, multiple sulfatase deficiency and Tay-Sachs disease.

5 In some embodiments the LSD is a mucopolysaccharidosis, such as a mucopolysaccharidosis 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.

10 In some embodiments the LSD is selected from the group consisting of 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
15 disorder of the bones and/or joints. In some embodiments said disease or disorder is 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 autism spectrum
20 disorders, autism and Aspergers syndrome.

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
25 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).

30 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).

35

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
5 bowel conditions including Inflammatory bowel disease (IBD).

A reduction in the functional levels of TREM2 results in dysregulation of lipid metabolism. 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
10 dysregulated lipid metabolism. In certain embodiments, the dysregulated lipid metabolism comprises increased intracellular and/or extracellular accumulation of one or more lipids. In some embodiments said dysregulated lipid metabolism is atherosclerosis.

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 metabolic syndrome and conditions associated with metabolic syndrome, such as obesity, type 2 diabetes, atherosclerosis, alcoholic and non-alcoholic fatty liver disease, and alcoholic and non-alcoholic steatohepatitis,

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 Amyloidosis, including AL amyloidosis (immunoglobulin light chain amyloidosis), AA amyloidosis (secondary amyloidosis), familial amyloidosis, familial systemic amyloidosis, Wild-type amyloidosis (senile systemic amyloidosis) and Localized amyloidosis.
25

In some embodiments, the neurodegenerative disease is Alzheimer's disease. In some embodiments, the neurodegenerative disease is Nasu-Hakola disease. In some
30 embodiments, the neurodegenerative disease is frontotemporal dementia. In some embodiments, the method comprises administering to the subject a compound as described herein, or a pharmaceutical composition comprising a compound as described herein.

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

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 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.

10 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
15 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
20 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
25 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
30 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
35 or sequentially in separate unit dosage forms or together in a single unit dosage form.

Methods of manufacturing

Generally, the compounds of Formula IA and Formula IB as described herein may be synthesised according to the following Schemes:

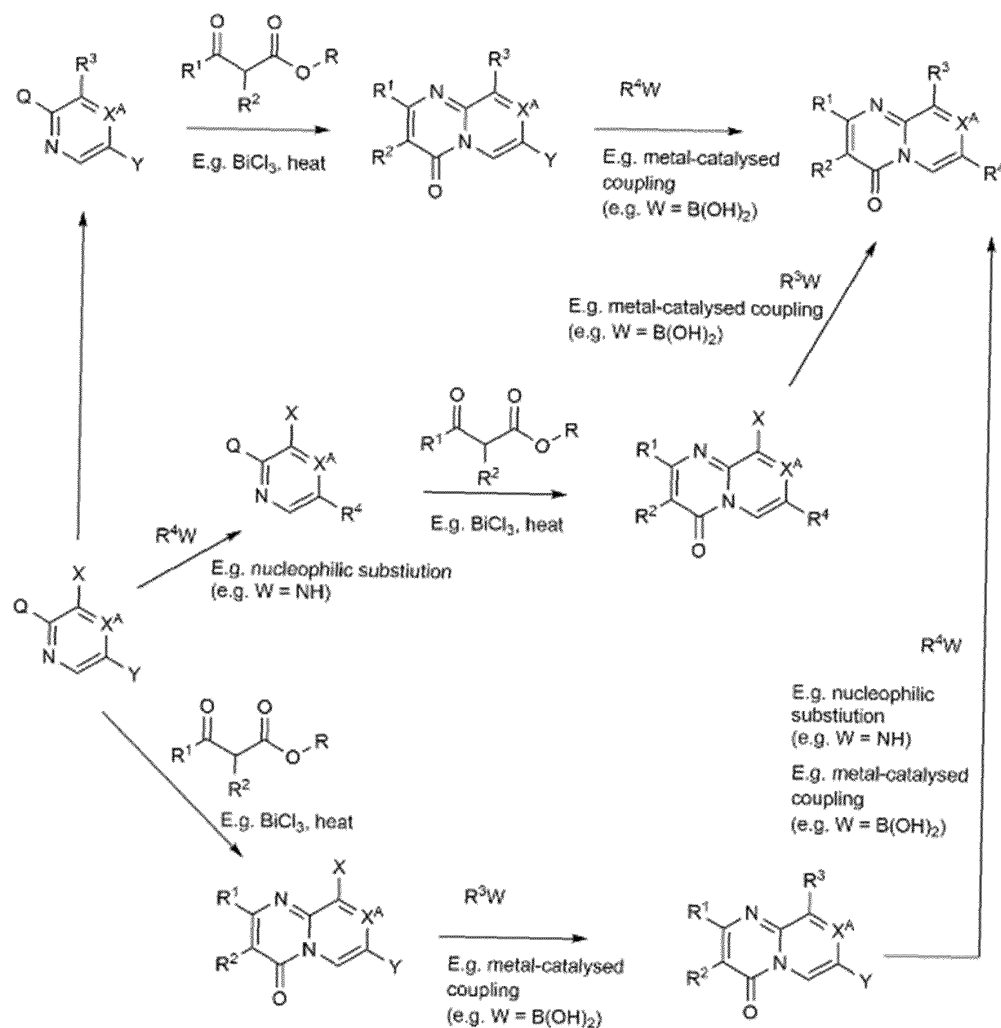
5

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.

10

As shown in Scheme 1, a suitably substituted pyridine or pyrazine can be functionalised in many ways to deliver the desired compounds. For example, the R³ group can be introduced first via a cross coupling reaction which is then followed by cyclisation (where Q = NH₂) with a keto ester R¹C(O)CHR²CO₂R and then a further substitution or cross coupling reaction. Alternatively, R⁴ can be introduced first via nucleophilic substitution or cross coupling followed by cyclisation and then finally cross coupling to introduce R³. In a further alternative, cyclisation occurs first, then R³ is introduced via cross coupling and then finally R⁴ via a second cross coupling reaction or via a nucleophilic displacement.

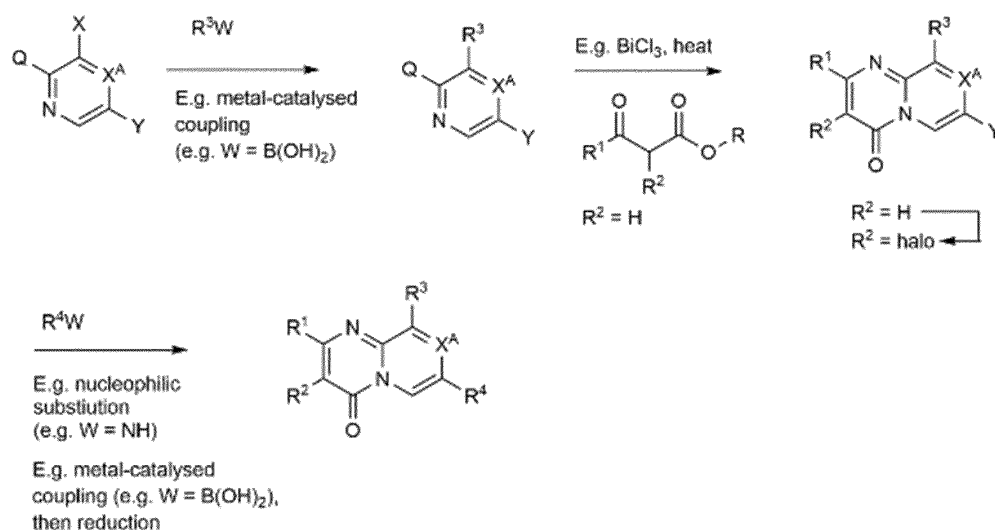
20



Scheme 1. Examples of synthetic routes for compounds of Formula IA. Q is NH2 or NO2; X is halogen; Y is halogen; R is alkyl; and X^A , R^1 , R^2 , R^3 and R^4 are as defined herein.

5

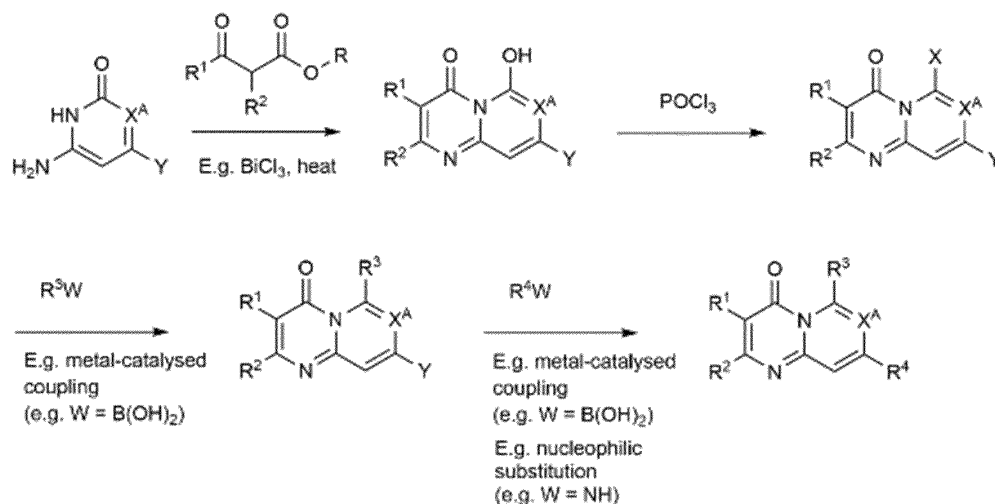
Other examples can be made as shown in Scheme 2. In some cases cyclisation is performed with $R^2 = H$, which is then converted to a halogen using a suitable halogenating reagent such as NIS or Selectfluor.



Scheme 2. Examples of synthetic routes for compounds of Formula IA. Q is NH₂; X is halogen; Y is halogen; R is alkyl; and X^A, R¹, R², R³ and R⁴ are as defined herein.

- 5 Further examples can be made as shown in Scheme 3. An amino-pyridone or pyrimidonone is cyclised with a keto ester R¹C(O)CHR²CO₂R. Activation, for example using POCl₃ is followed by introduction of R³ via a metal-catalysed cross coupling reaction and R⁴ is incorporated using a second cross coupling reaction or a nucleophilic displacement.

10



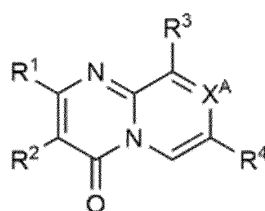
Scheme 3. Examples of synthetic routes for compounds of Formula IB. X is halogen; Y is halogen; R is alkyl; and X^A, R¹, R², R³ and R⁴ are as defined herein.

In schemes 1 and 2, when W is NH in R⁴W, then said N atom is part of the R⁴ group, i.e. X^B is N.

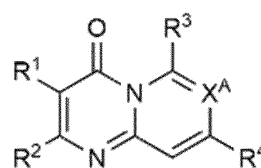
5

Items

1. A compound of Formula IA or Formula IB:



Formula IA



Formula IB

wherein

10

X^A is N or C(R⁵);

R⁵ is H;

R¹ is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, and H, wherein the C₁₋₆ alkyl or C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R⁶;

15

R² is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, halogen and H, wherein the C₁₋₆ alkyl or C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R⁹;

R³ is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₈ spiroalkyl, C₅₋₈ tricycloalkyl, C₅₋₈ bicycloalkyl cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl, 5-membered heteroaryl, azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, and -OCH₂-(C₃₋₆ cycloalkyl),

20

wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₈ spiroalkyl, C₅₋₈ bicycloalkyl, C₅₋₈ tricycloalkyl, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl or 5-membered heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl and CN, wherein one methylene group of the C₃₋₆ cycloalkyl is optionally replaced with -O- or -N(R¹⁰)-;

25

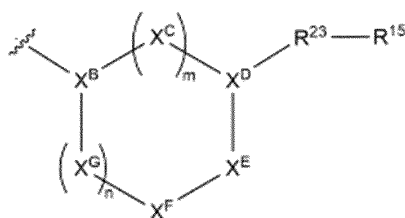
R^{10} is selected from the group consisting of H, C_{1-3} alkyl and $-C(O)C_{1-3}$ alkyl;

and wherein the azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, or $-OCH_2-(C_{3-6}$ cycloalkyl) is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy and C_{1-3} haloalkoxy;

R^6 is individually selected from the group consisting of $-O-C_{1-6}$ alkyl, C_{3-6} cycloalkyl and halogen;

R^9 is selected from the group consisting of $-O-C_{1-6}$ alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl and phenyl, wherein the phenyl is optionally substituted with 1 to 5 substituents individually selected from $-O-C_{1-6}$ alkyl;

R^4 is of Formula II:



Formula II

wherein

X^B is N or $C(R^{11})$;

R^{11} is selected from the group consisting of H, C_{1-3} alkyl, $-OH$, $-O-C_{1-3}$ alkyl and halogen;

X^C is $C(R^{12})(R^{13})$;

R^{12} is individually H, C_{1-3} alkyl or a bond;

wherein when R^{12} is a bond then R^{11} is C_{1-3} alkyl, and R^{11} and R^{12} are linked together to form a 3-5 membered ring;

R^{13} is individually H or C_{1-3} alkyl;

X^D is $C(R^{14})$ or N;

R^{14} is H or C_{1-3} alkyl;

R^{23} is a bond, $-O-$ or C_{1-6} hydrocarbon chain wherein one methylene group is optionally replaced with $-O-$;

R^{15} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, diC_{1-3} alkylamino, $-C(O)-O-(C_{1-6}$ alkyl), C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, phenyl, $-O$ -phenyl, 5-membered heteroaryl, $-O$ -(5-membered heteroaryl), 6-membered heteroaryl and $-O$ -(6-membered heteroaryl), wherein

- (a) the C₃₋₆ cycloalkyl or C₃₋₆ heterocycloalkyl is optionally substituted with 1 to 3 substituents independently selected from oxo (=O), C₁₋₃ alkoxy and halogen;
- (b) the phenyl, -O-phenyl, 5-membered heteroaryl, -O-(5-membered heteroaryl), 6-membered heteroaryl or -O-(6-membered heteroaryl) is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl, -O-C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -(C₁₋₃ alkyl)O(C₁₋₃ alkyl), -CN, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl and C₃₋₆ heterocycloalkyl, wherein the C₁₋₆ alkyl or C₁₋₆ haloalkyl of subsection (b) are optionally substituted with -OH, and wherein the C₃₋₆ heterocycloalkyl of subsection (b) is optionally substituted with 1 to 3 substituents individually selected from the group consisting of halogen, C₁₋₃ alkyl and -C(O)O(C₁₋₆ alkyl);
- (c) the C₁₋₆ alkyl is optionally substituted with 1 to 3 substituents independently selected from -N(H)C(O)R²⁴, -oxo (=O), -O-C₁₋₃ alkyl and -N(R²⁵)(R²⁶);
- R²⁴ is C₁₋₆ alkyl or aryl, wherein the C₁₋₆ alkyl is optionally substituted with C₁₋₃ alkoxy or halogen;
- R²⁵ is H or C₁₋₃ alkyl;
- R²⁶ is H or C₁₋₃ alkyl;
- X^E is C(R¹⁶)(R¹⁷), O, NR¹⁸ or a bond;
- R¹⁶ is H or F;
- R¹⁷ is H or F;
- R¹⁸ is H, C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl, -C(O)-C₃₋₆ cycloalkyl or C₁₋₆ haloalkyl, wherein the C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl or -C(O)-C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 substituents independently selected from halogen and C₁₋₃ alkoxy;
- X^F is C(R¹⁹)(R²⁰);
- R¹⁹ is H, halogen or C₁₋₃ alkyl;
- R²⁰ is H, halogen or C₁₋₃ alkyl;
- wherein when R¹⁹ and R²⁰ are C₁₋₃ alkyl, then R¹⁹ and R²⁰ are optionally linked together to form a 3-6 membered ring; and/or

wherein when R^{19} and R^{20} are C_{1-3} alkyl, then one methylene group is optionally replaced with $-O-$ or $-N(R^{27})-$, wherein R^{27} is selected from the group consisting of H, C_{1-3} alkyl and $-C(O)C_{1-3}$ alkyl;

X^G is individually $C(R^{21})(R^{22})$ or $C(O)$;

5 R^{21} is individually H, C_{1-3} alkyl or a bond;

wherein when R^{21} is a bond then R^{19} is C_{1-3} alkyl, n is 1, and R^{21} and R^{19} are linked together to form a 3-5 membered ring;

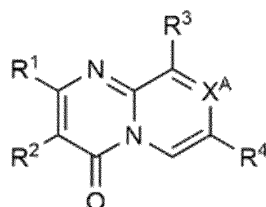
R^{22} is individually H or C_{1-3} alkyl;

m is 0, 1 or 2; and

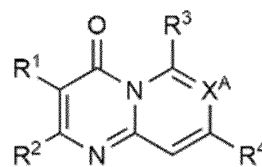
10 n is 0, 1 or 2,

or a pharmaceutically acceptable salt thereof.

2. A compound of Formula IA or Formula IB:



Formula IA



Formula IB

15 wherein

X^A is N or $C(R^5)$;

R^5 is H;

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and H, wherein the C_{1-6} alkyl or C_{3-6} cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R^6 ;

20

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen and H, wherein the C_{1-6} alkyl or C_{3-6} cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R^9 ;

25

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{5-8} spiroalkyl, C_{5-8} tricycloalkyl, C_{5-8} bicycloalkyl cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl, 5-membered heteroaryl, azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, and $-OCH_2-(C_{3-6}$ cycloalkyl),

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-8} spiroalkyl, C_{5-8} bicycloalkyl, C_{5-8} tricycloalkyl, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl or 5-membered heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen,

5

C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl and CN, wherein one methylene group of the C_{3-6} cycloalkyl is optionally replaced with $-O-$ or $-N(R^{10})-$;

R^{10} is selected from the group consisting of H, C_{1-3} alkyl and $-C(O)C_{1-3}$ alkyl;

and wherein the azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, or $-OCH_2-(C_{3-6} \text{ cycloalkyl})$ is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy and C_{1-3} haloalkoxy;

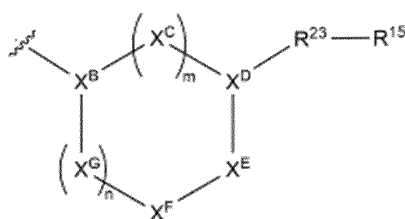
10

R^6 is individually selected from the group consisting of $-O-C_{1-6}$ alkyl, C_{3-6} cycloalkyl and halogen;

15

R^9 is selected from the group consisting of $-O-C_{1-6}$ alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl and phenyl, wherein the phenyl is optionally substituted with 1 to 5 substituents individually selected from $-O-C_{1-6}$ alkyl;

R^4 is of Formula II:



20

Formula II

wherein

X^B is N or $C(R^{11})$;

R^{11} is selected from the group consisting of H, C_{1-3} alkyl, $-OH$, $-O-C_{1-3}$ alkyl and halogen;

25

X^C is $C(R^{12})(R^{13})$;

R^{12} is individually H, C_{1-3} alkyl or a bond;

wherein when R^{12} is a bond then R^{11} is C_{1-3} alkyl, and R^{11} and R^{12} are linked together to form a 3-5 membered ring;

R^{13} is individually H or C_{1-3} alkyl;

30

X^D is $C(R^{14})$ or N;

R^{14} is H or C_{1-3} alkyl;

R^{23} is a bond, -O- or C_{1-6} hydrocarbon chain wherein one methylene group is optionally replaced with -O-;

R^{15} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, diC_{1-3} alkylamino, -C(O)-O-(C_{1-6} alkyl), C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, phenyl, -O-phenyl, 5-membered heteroaryl, -O-(5-membered heteroaryl), 6-membered heteroaryl and -O-(6-membered heteroaryl), wherein

(a) the C_{3-6} cycloalkyl or C_{3-6} heterocycloalkyl is optionally substituted with 1 to 3 substituents independently selected from oxo (=O), C_{1-3} alkoxy and halogen;

(b) the phenyl, -O-phenyl, 5-membered heteroaryl, -O-(5-membered heteroaryl), 6-membered heteroaryl or -O-(6-membered heteroaryl) is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, -O- C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -(C_{1-3} alkyl)O(C_{1-3} alkyl), -CN, C_{2-4} alkenyl, C_{3-6} cycloalkyl and C_{3-6} heterocycloalkyl, wherein the C_{1-6} alkyl or C_{1-6} haloalkyl of subsection (b) are optionally substituted with -OH, and

wherein the C_{3-6} heterocycloalkyl of subsection (b) is optionally substituted with 1 to 3 substituents individually selected from the group consisting of halogen, C_{1-3} alkyl and -C(O)O(C_{1-6} alkyl);

(c) the C_{1-6} alkyl is optionally substituted with 1 to 3 substituents independently selected from -N(H)C(O) R^{24} , -oxo (=O), -O- C_{1-3} alkyl and -N(R^{25})(R^{26});

R^{24} is C_{1-6} alkyl or aryl, wherein the C_{1-6} alkyl is optionally substituted with C_{1-3} alkoxy or halogen;

R^{25} is H or C_{1-3} alkyl;

R^{26} is H or C_{1-3} alkyl;

X^E is C(R^{16})(R^{17}), O, NR^{18} or a bond;

R^{16} is H or F;

R^{17} is H or F;

R^{18} is H, C_{1-6} alkyl, -C(O)- C_{1-6} alkyl, -C(O)- C_{3-6} cycloalkyl or C_{1-6} haloalkyl, wherein the C_{1-6} alkyl, -C(O)- C_{1-6} alkyl or -C(O)- C_{3-6} cycloalkyl is optionally substituted with 1 to 3 substituents independently selected from halogen and C_{1-3} alkoxy;

X^F is C(R^{19})(R^{20});

R^{19} is H, halogen or C_{1-3} alkyl;

R^{20} is H, halogen or C_{1-3} alkyl;

wherein when R^{19} and R^{20} are C_{1-3} alkyl, then R^{19} and R^{20} are optionally linked together to form a 3-6 membered ring; and/or

5 wherein when R^{19} and R^{20} are C_{1-3} alkyl, then one methylene group is optionally replaced with $-O-$ or $-N(R^{27})-$, wherein R^{27} is selected from the group consisting of H, C_{1-3} alkyl and $-C(O)C_{1-3}$ alkyl;

X^G is individually $C(R^{21})(R^{22})$ or $C(O)$;

R^{21} is individually H, C_{1-3} alkyl or a bond;

10 wherein when R^{21} is a bond then R^{19} is C_{1-3} alkyl, n is 1, and R^{21} and R^{19} are linked together to form a 3-5 membered ring;

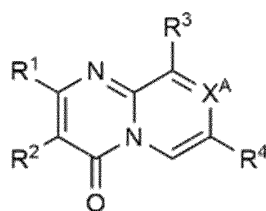
R^{22} is individually H or C_{1-3} alkyl;

m is 0, 1 or 2; and

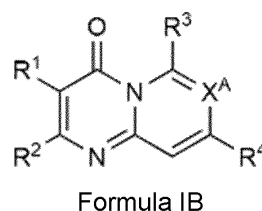
n is 0, 1 or 2,

15 or a pharmaceutically acceptable salt thereof.

3. A compound of Formula IA or Formula IB:



Formula IA



Formula IB

wherein

X^A is N or $C(R^5)$;

20 R^5 is H;

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and H, wherein the C_{1-6} alkyl or C_{3-6} cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R^6 ;

25 R^2 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and H, wherein the C_{1-6} alkyl or C_{3-6} cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R^9 ;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{5-8} spiroalkyl, C_{5-8} tricycloalkyl, C_{5-8} bicycloalkyl cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl, 5-membered heteroaryl,

azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, and $-\text{OCH}_2-(\text{C}_{3-6} \text{ cycloalkyl})$,

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-8} spiroalkyl, C_{5-8} bicycloalkyl, C_{5-8} tricycloalkyl, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl or 5-membered heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl, C_{1-3} haloalkyl and CN;

wherein one methylene group of the C_{3-6} cycloalkyl is optionally replaced with $-\text{O}-$ or $-\text{N}(\text{R}^{10})-$;

R^{10} is selected from the group consisting of H, C_{1-3} alkyl and $-\text{C}(\text{O})\text{C}_{1-3}$ alkyl;

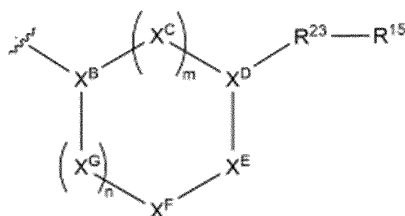
and wherein the azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, or $-\text{OCH}_2-(\text{C}_{3-6} \text{ cycloalkyl})$ is optionally substituted with 1 to 4 substituents independently selected from the group consisting

of halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy and C_{1-3} haloalkoxy;

R^6 is individually selected from the group consisting of $-\text{O}-\text{C}_{1-6}$ alkyl, C_{3-6} cycloalkyl and halogen;

R^9 is selected from the group consisting of $-\text{O}-\text{C}_{1-6}$ alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl and phenyl, wherein the phenyl is optionally substituted with 1 to 5 substituents individually selected from $-\text{O}-\text{C}_{1-6}$ alkyl;

R^4 is of Formula II:



Formula II

wherein

X^B is N or $\text{C}(\text{R}^{11})$;

R^{11} is selected from the group consisting of H, C_{1-3} alkyl, $-\text{OH}$, $-\text{O}-\text{C}_{1-3}$ alkyl and halogen;

X^C is $\text{C}(\text{R}^{12})(\text{R}^{13})$;

R^{12} is individually H, C_{1-3} alkyl or a bond;

wherein when R^{12} is a bond then R^{11} is C_{1-3} alkyl, and R^{11} and R^{12} are linked together to form a 3-5 membered ring;

R^{13} is individually H or C_{1-3} alkyl;

X^D is $C(R^{14})$ or N;

R^{14} is H or C_{1-3} alkyl;

5 R^{23} is a bond, -O- or C_{1-6} hydrocarbon chain wherein one methylene group is optionally replaced with -O-;

R^{15} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, di C_{1-3} alkylamino, -C(O)-O-(C_{1-6} alkyl), C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, phenyl, -O-phenyl, 5-membered heteroaryl, -O-(5-membered heteroaryl), 6-membered heteroaryl and -O-(6-membered heteroaryl), wherein

10 (a) the C_{3-6} cycloalkyl or C_{3-6} heterocycloalkyl is optionally substituted with 1 to 3 substituents independently selected from oxo (=O), C_{1-3} alkoxy and halogen;

(b) the phenyl, -O-phenyl, 5-membered heteroaryl, -O-(5-membered heteroaryl), 6-membered heteroaryl or -O-(6-membered heteroaryl) is
15 optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, -O- C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -(C_{1-3} alkyl)O(C_{1-3} alkyl), -CN, C_{2-4} alkenyl, C_{3-6} cycloalkyl and C_{3-6} heterocycloalkyl,
wherein the C_{1-6} alkyl or C_{1-6} haloalkyl of subsection (b) are optionally
20 substituted with -OH, and

wherein the C_{3-6} heterocycloalkyl of subsection (b) is optionally substituted with 1 to 3 substituents individually selected from the group consisting of halogen, C_{1-3} alkyl and -C(O)O(C_{1-6} alkyl);

(c) the C_{1-6} alkyl is optionally substituted with 1 to 3 substituents
25 independently selected from -N(H)C(O) R^{24} , -oxo (=O), -O- C_{1-3} alkyl and -N(R^{25})(R^{26});

R^{24} is C_{1-6} alkyl or aryl, wherein the C_{1-6} alkyl is optionally substituted with C_{1-3} alkoxy or halogen;

R^{25} is H or C_{1-3} alkyl;

30 R^{26} is H or C_{1-3} alkyl;

X^E is $C(R^{16})(R^{17})$, O, NR^{18} or a bond;

R^{16} is H or F;

R^{17} is H or F;

R^{18} is H, C_{1-6} alkyl, -C(O)- C_{1-6} alkyl, -C(O)- C_{3-6} cycloalkyl or C_{1-6} haloalkyl,
35 wherein the C_{1-6} alkyl, -C(O)- C_{1-6} alkyl or -C(O)- C_{3-6} cycloalkyl is optionally

substituted with 1 to 3 substituents independently selected from halogen and C₁₋₃ alkoxy;

X^F is C(R¹⁹)(R²⁰);

R¹⁹ is H, halogen or C₁₋₃ alkyl;

5 R²⁰ is H, halogen or C₁₋₃ alkyl;

wherein when R¹⁹ and R²⁰ are C₁₋₃ alkyl, then R¹⁹ and R²⁰ are optionally linked together to form a 3-6 membered ring; and/or

wherein when R¹⁹ and R²⁰ are C₁₋₃ alkyl, then one methylene group is optionally replaced with -O- or -N(R²⁷)-, wherein R²⁷ is selected from the group consisting of H, C₁₋₃ alkyl and -C(O)C₁₋₃ alkyl;

10

X^G is individually C(R²¹)(R²²) or C(O);

R²¹ is individually H, C₁₋₃ alkyl or a bond;

wherein when R²¹ is a bond then R¹⁹ is C₁₋₃ alkyl, n is 1, and R²¹ and R¹⁹ are linked together to form a 3-5 membered ring;

15

R²² is individually H or C₁₋₃ alkyl;

m is 0, 1 or 2; and

n is 0, 1 or 2,

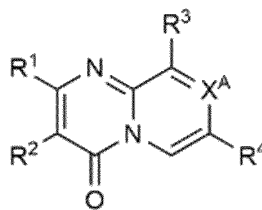
or a pharmaceutically acceptable salt thereof.

4. The compound according to item 1, wherein the compound is of Formula IA, or a pharmaceutically acceptable salt thereof.

20

5. The compound according to item 1, wherein the compound is of Formula IB, or a pharmaceutically acceptable salt thereof.

6. A compound of Formula IA:



Formula IA

25

wherein

R¹ is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl and H;

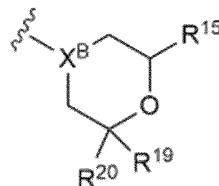
R² is selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl and H;

30

R³ is phenyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, and C₁₋₃ haloalkyl;

X^A is N or C(H);

R^4 is of Formula XXVI:

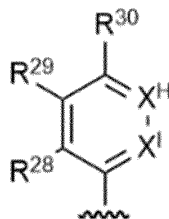


Formula XXVI

- 5 wherein
- X^B is N or C(H);
- R^{15} is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -CN, and C_{3-6} cycloalkyl;
- 10 R^{19} is H, halogen or C_{1-3} alkyl; and
- R^{20} is H, halogen or C_{1-3} alkyl;
- or a pharmaceutically acceptable salt thereof.
7. The compound according to any one of the preceding items, wherein X^A is N, or a pharmaceutically acceptable salt thereof.
- 15 8. The compound according to any one of the preceding items, wherein X^A is C(R^5) and R^5 is H, or a pharmaceutically acceptable salt thereof.
9. The compound according to item 1, wherein the compound is of Formula IA and X^A is N, or a pharmaceutically acceptable salt thereof.
10. The compound according to item 1, wherein the compound is of Formula IA and
- 20 X^A is C(R^5) and R^5 is H, or a pharmaceutically acceptable salt thereof.
11. The compound according to item 1, wherein the compound is of Formula IB and X^A is C(R^5) and R^5 is H, or a pharmaceutically acceptable salt thereof.
12. The compound according to any one of the preceding items, wherein R^1 is C_{1-6} alkyl optionally substituted with 1 to 3 individually selected substituents R^6 , or a
- 25 pharmaceutically acceptable salt thereof.
13. The compound according to any one of the preceding items, wherein R^1 is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
14. The compound according to any one of the preceding items, wherein R^1 is -CH₃, or a pharmaceutically acceptable salt thereof.
- 30 15. The compound according to any one of the preceding items, wherein R^1 is C_{1-6} alkyl substituted with 1 to 3 individually selected substituents R^6 , or a pharmaceutically acceptable salt thereof.

16. The compound according to any one of the preceding items, wherein R^1 is C_{1-3} alkyl substituted with 1 to 3 individually selected substituents R^6 , or a pharmaceutically acceptable salt thereof.
17. The compound according to any one of the preceding items, wherein R^6 is
5 halogen, or a pharmaceutically acceptable salt thereof.
18. The compound according to any one of the preceding items, wherein R^6 is F, or a pharmaceutically acceptable salt thereof.
19. The compound according to any one of the preceding items, wherein R^1 is C_{1-6} haloalkyl, or a pharmaceutically acceptable salt thereof.
- 10 20. The compound according to any one of the preceding items, wherein R^1 is C_{1-3} haloalkyl, or a pharmaceutically acceptable salt thereof.
21. The compound according to any one of the preceding items, wherein R^1 is -
 CF_3 , or a pharmaceutically acceptable salt thereof.
22. The compound according to any one of the preceding items, wherein R^2 is C_{1-6}
15 alkyl optionally substituted with 1 to 3 individually selected substituents R^9 , or a pharmaceutically acceptable salt thereof.
23. The compound according to any one of the preceding items, wherein R^2 is C_{1-3} alkyl optionally substituted with 1 to 3 individually selected substituents R^9 , or a pharmaceutically acceptable salt thereof.
- 20 24. The compound according to any one of the preceding items, wherein R^2 is -
 CH_3 , or a pharmaceutically acceptable salt thereof.
25. The compound according to any one of the preceding items, wherein R^2 is
halogen, or a pharmaceutically acceptable salt thereof.
26. The compound according to any one of the preceding items, wherein R^2 is Cl,
25 or a pharmaceutically acceptable salt thereof.
27. The compound according to any one of the preceding items, wherein R^2 is F, or
a pharmaceutically acceptable salt thereof.
28. The compound according to any one of the preceding items, wherein R^3 is
phenyl optionally substituted with 1 to 4 substituents independently selected
30 from the group consisting of halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl and
CN, or a pharmaceutically acceptable salt thereof.
29. The compound according to any one of the preceding items, wherein R^3 is 6-
membered heteroaryl optionally substituted with 1 to 4 substituents
independently selected from the group consisting of halogen, C_{1-3} alkyl, C_{1-3}
35 haloalkyl and CN, or a pharmaceutically acceptable salt thereof.

30. The compound according to any one of the preceding items, wherein R^3 is of Formula III:



Formula III

5 wherein

X^H is $C(R^{31})$ or N;

X^I is $C(R^{32})$ or N;

R^{28} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN;

R^{29} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN;

10 R^{30} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN;

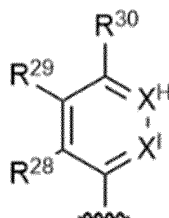
R^{31} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN; and

R^{32} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN,

or a pharmaceutically acceptable salt thereof.

31. The compound according to any one of the preceding items, wherein R^3 is of Formula III:

15



Formula III

wherein

X^H is $C(R^{31})$ or N;

20 X^I is $C(R^{32})$ or N;

R^{28} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN;

R^{29} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN;

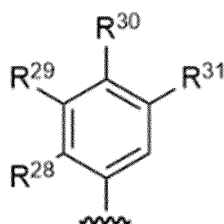
R^{30} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN;

R^{31} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN; and

25 R^{32} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN,

or a pharmaceutically acceptable salt thereof.

32. The compound according to any one of items 30 to 31, wherein X^H is $C(R^{31})$, or a pharmaceutically acceptable salt thereof.
33. The compound according to any one of items 30 to 31, wherein X^H is N, or a pharmaceutically acceptable salt thereof.
- 5 34. The compound according to any one of the preceding items, wherein X^I is $C(R^{32})$, or a pharmaceutically acceptable salt thereof.
35. The compound according to any one of the preceding items, wherein X^I is N, or a pharmaceutically acceptable salt thereof.
- 10 36. The compound according to any one of the preceding items, wherein X^H is $C(R^{31})$, and X^I is $C(R^{32})$, or a pharmaceutically acceptable salt thereof.
37. The compound according to any one of the preceding items, wherein X^H is N, and X^I is $C(R^{32})$, or a pharmaceutically acceptable salt thereof.
38. The compound according to any one of the preceding items, wherein X^H is $C(R^{31})$, and X^I is N, or a pharmaceutically acceptable salt thereof.
- 15 39. The compound according to any one of the preceding items, wherein R^{31} is H, or a pharmaceutically acceptable salt thereof.
40. The compound according to any one of the preceding items, wherein R^3 is of Formula IV:



Formula IV

20 wherein

R^{28} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN;

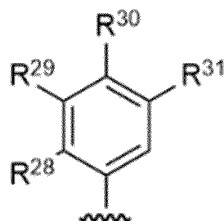
R^{29} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN;

R^{30} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN; and

25 R^{31} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy or CN,

or a pharmaceutically acceptable salt thereof.

41. The compound according to any one of the preceding items, wherein R^3 is of Formula IV:



Formula IV

wherein

R²⁸ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl or CN;

5 R²⁹ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl or CN;

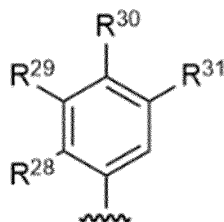
R³⁰ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl or CN; and

R³¹ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl or CN,

or a pharmaceutically acceptable salt thereof.

42. The compound according to any one of the preceding items, wherein R³ is of

10 Formula IV:



Formula IV

wherein

R²⁸ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, or C₁₋₃ alkoxy;

15 R²⁹ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy or CN;

R³⁰ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy or CN; and

R³¹ is H, halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy or CN,

or a pharmaceutically acceptable salt thereof.

43. The compound according to any one of the preceding items, wherein R²⁸ is H,

20 or a pharmaceutically acceptable salt thereof.

44. The compound according to any one of the preceding items, wherein R²⁸ is

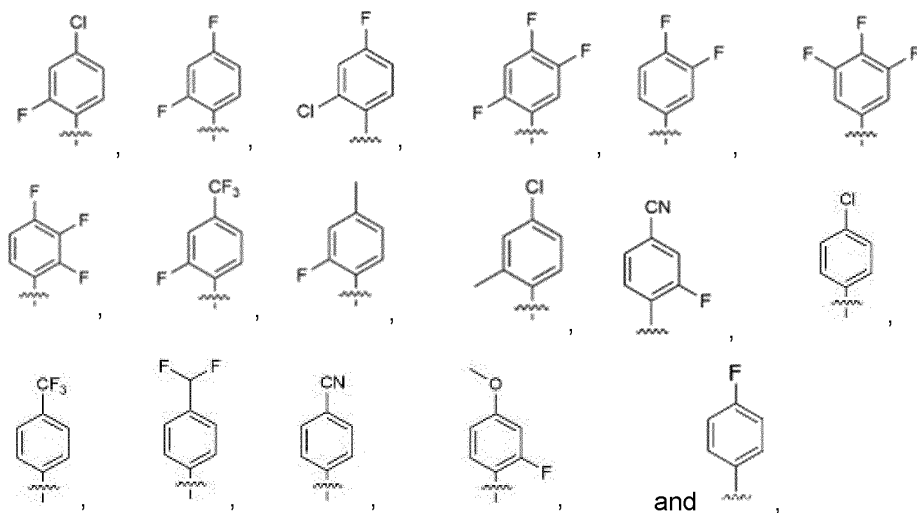
halogen, or a pharmaceutically acceptable salt thereof.

45. The compound according to any one of the preceding items, wherein R²⁸ is F or

Cl, or a pharmaceutically acceptable salt thereof.

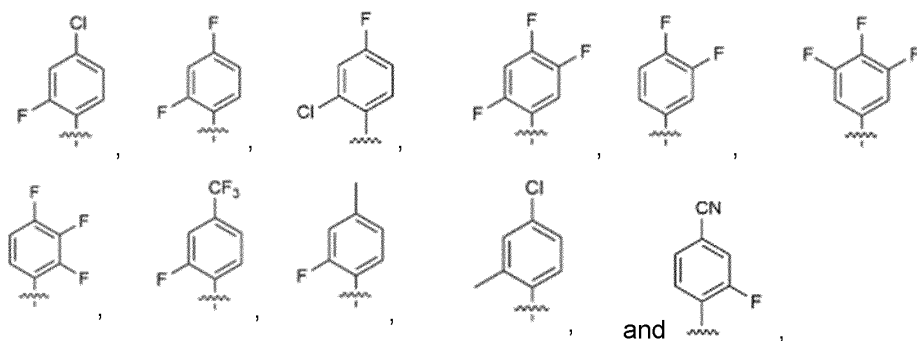
46. The compound according to any one of the preceding items, wherein R^{28} is F, or a pharmaceutically acceptable salt thereof.
47. The compound according to any one of the preceding items, wherein R^{28} is Cl, or a pharmaceutically acceptable salt thereof.
- 5 48. The compound according to any one of the preceding items, wherein R^{28} is C_{1-3} alkyl, such as $-CH_3$, or a pharmaceutically acceptable salt thereof.
49. The compound according to any one of the preceding items, wherein R^{28} is CN, or a pharmaceutically acceptable salt thereof.
- 10 50. The compound according to any one of the preceding items, wherein R^{29} is H, or a pharmaceutically acceptable salt thereof.
51. The compound according to any one of the preceding items, wherein R^{29} is halogen, or a pharmaceutically acceptable salt thereof.
52. The compound according to any one of the preceding items, wherein R^{29} is F, or a pharmaceutically acceptable salt thereof.
- 15 53. The compound according to any one of the preceding items, wherein R^{30} is halogen, or a pharmaceutically acceptable salt thereof.
54. The compound according to any one of the preceding items, wherein R^{30} is F or Cl, or a pharmaceutically acceptable salt thereof.
- 20 55. The compound according to any one of the preceding items, wherein R^{30} is C_{1-3} alkyl, such as $-CH_3$, or a pharmaceutically acceptable salt thereof.
56. The compound according to any one of the preceding items, wherein R^{30} is C_{1-3} alkoxy, such as $-OCH_3$, or a pharmaceutically acceptable salt thereof.
57. The compound according to any one of the preceding items, wherein R^{30} is C_{1-3} haloalkyl, such as $-CF_3$, or a pharmaceutically acceptable salt thereof.
- 25 58. The compound according to any one of the preceding items, wherein R^{30} is C_{1-3} haloalkyl, such as $-CHF_2$, or a pharmaceutically acceptable salt thereof.
59. The compound according to any one of the preceding items, wherein R^{30} is CN, or a pharmaceutically acceptable salt thereof.
- 30 60. The compound according to any one of the preceding items, wherein R^{31} is H, or a pharmaceutically acceptable salt thereof.
61. The compound according to any one of the preceding items, wherein R^{31} is halogen, or a pharmaceutically acceptable salt thereof.
62. The compound according to any one of the preceding items, wherein R^{31} is F, or a pharmaceutically acceptable salt thereof.

63. The compound according to any one of the preceding items, wherein R^3 is selected from the group consisting of:



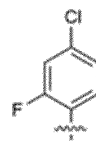
or a pharmaceutically acceptable salt thereof.

64. The compound according to any one of the preceding items, wherein R^3 is selected from the group consisting of:



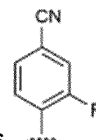
or a pharmaceutically acceptable salt thereof.

65. The compound according to any one of the preceding items, or a



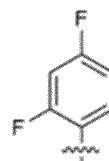
pharmaceutically acceptable salt thereof, wherein R^3 is

66. The compound according to any one of the preceding items, or a



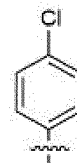
pharmaceutically acceptable salt thereof, wherein R^3 is

67. The compound according to any one of the preceding items, or a



pharmaceutically acceptable salt thereof, wherein R^3 is

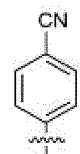
68. The compound according to any one of the preceding items, or a



pharmaceutically acceptable salt thereof, wherein R^3 is

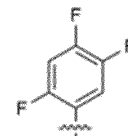
5

69. The compound according to any one of the preceding items, or a



pharmaceutically acceptable salt thereof, wherein R^3 is

70. The compound according to any one of the preceding items, or a

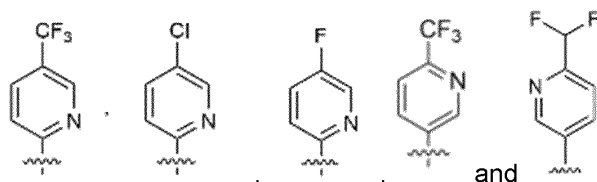


pharmaceutically acceptable salt thereof, wherein R^3 is

71. The compound according to any one of the preceding items, or a

10

pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of:



and

72. The compound according to any one of the preceding items, wherein R^3 is C_{5-8}

bicycloalkyl optionally substituted with 1 to 4 substituents independently

15

selected from the group consisting of halogen, C_{1-3} alkyl and C_{1-3} haloalkyl, or a pharmaceutically acceptable salt thereof.

73. The compound according to any one of the preceding items, wherein R^3 is

bicyclo[1.1.1]pentyl optionally substituted with CF_3 or C_1 alkyl, or a

pharmaceutically acceptable salt thereof.

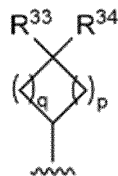
74. The compound according to any one of the preceding items, wherein R^3 is



, or a pharmaceutically acceptable salt thereof.

75. The compound according to any one of the preceding items, wherein R^3 is C_{3-6} cycloalkyl optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl and C_{1-3} haloalkyl, or a pharmaceutically acceptable salt thereof.

76. The compound according to any one of the preceding items, wherein R^3 is of Formula XXV:



Formula XXV

wherein

R^{33} is H, halogen, C_{1-3} alkyl and C_{1-3} haloalkyl;

R^{34} is H, halogen, C_{1-3} alkyl and C_{1-3} haloalkyl;

q is 1, 2 or 3; and

p is 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

77. The compound according to any one of the preceding items, wherein q is 1, or a pharmaceutically acceptable salt thereof.

78. The compound according to any one of the preceding items, wherein q is 2, or a pharmaceutically acceptable salt thereof.

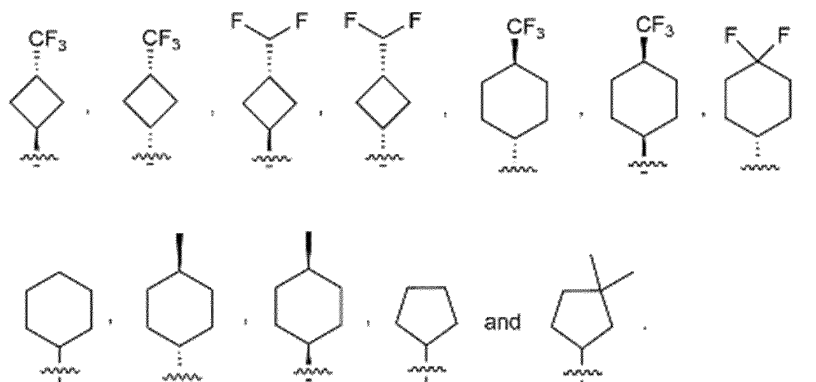
79. The compound according to any one of the preceding items, wherein p is 1, or a pharmaceutically acceptable salt thereof.

80. The compound according to any one of the preceding items, wherein p is 2, or a pharmaceutically acceptable salt thereof.

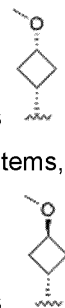
81. The compound according to any one of the preceding items, wherein R^{33} is H, or a pharmaceutically acceptable salt thereof.

82. The compound according to any one of the preceding items, wherein R^{33} is halogen, such as F, or a pharmaceutically acceptable salt thereof.

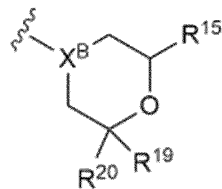
83. The compound according to any one of the preceding items, wherein R^{33} is C_{1-3} alkyl, such as $-CH_3$, or a pharmaceutically acceptable salt thereof.
84. The compound according to any one of the preceding items, wherein R^{33} is C_{1-3} haloalkyl, such as $-CF_3$ or $-CHF_2$, or a pharmaceutically acceptable salt thereof.
85. The compound according to any one of the preceding items, wherein R^{34} is H, or a pharmaceutically acceptable salt thereof.
86. The compound according to any one of the preceding items, wherein R^{34} is halogen, such as F, or a pharmaceutically acceptable salt thereof.
87. The compound according to any one of the preceding items, wherein R^{34} is C_{1-3} alkyl, such as $-CH_3$, or a pharmaceutically acceptable salt thereof.
88. The compound according to any one of the preceding items, wherein R^{34} is C_{1-3} haloalkyl, such as $-CF_3$ or $-CHF_2$, or a pharmaceutically acceptable salt thereof.
89. The compound according to any one of the preceding items, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of:



90. The compound according to any one of the preceding items, or a pharmaceutically acceptable salt thereof, wherein R^3 is
91. The compound according to any one of the preceding items, or a pharmaceutically acceptable salt thereof, wherein R^3 is



92. The compound according to any one of the preceding items, wherein R^4 is of Formula XXVI:



Formula XXVI

5 wherein

X^B is N or C(H);

R^{15} is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -CN, and C_{3-6} cycloalkyl;

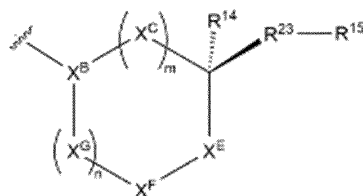
10 R^{19} is H, halogen or C_{1-3} alkyl; and

R^{20} is H, halogen or C_{1-3} alkyl;

or a pharmaceutically acceptable salt thereof.

93. The compound according to any one of the preceding items, wherein X^D is C(R^{14}), or a pharmaceutically acceptable salt thereof.

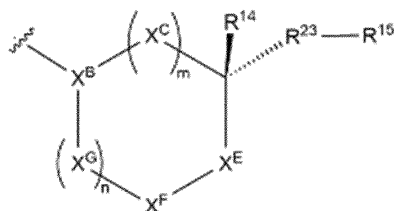
15 94. The compound according to any one of the preceding items, wherein R^4 is of Formula IIA,



Formula IIA

or a pharmaceutically acceptable salt thereof.

20 95. The compound according to any one of the preceding items, wherein R^4 is of Formula IIB,

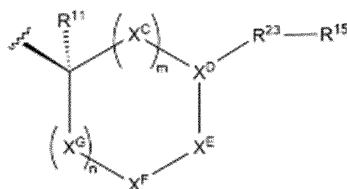


Formula IIB

or a pharmaceutically acceptable salt thereof.

96. The compound according to any one of the preceding items, wherein X^B is $C(R^{11})$, or a pharmaceutically acceptable salt thereof.

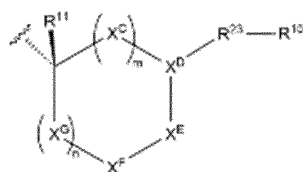
97. The compound according to any one of the preceding items, wherein R^4 is of
5 Formula IIC,



Formula IIC

or a pharmaceutically acceptable salt thereof.

98. The compound according to any one of the preceding items, wherein R^4 is of
10 Formula IID,

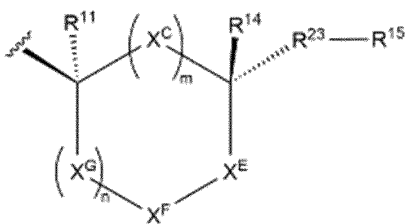


Formula IID

or a pharmaceutically acceptable salt thereof.

99. The compound according to any one of the preceding items, wherein X^B is
15 $C(R^{11})$ and X^D is $C(R^{14})$, or a pharmaceutically acceptable salt thereof.

100. The compound according to any one of the preceding items, wherein R^4 is of Formula IIE,

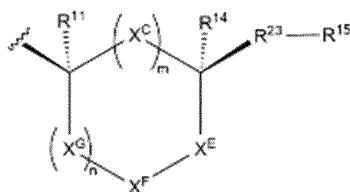


Formula IIE

or a pharmaceutically acceptable salt thereof.

101. The compound according to any one of the preceding items, wherein R^4 is of Formula IIF,

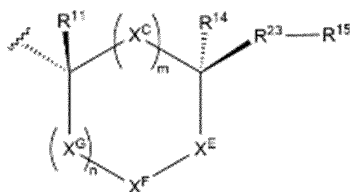
20



Formula IIF

or a pharmaceutically acceptable salt thereof.

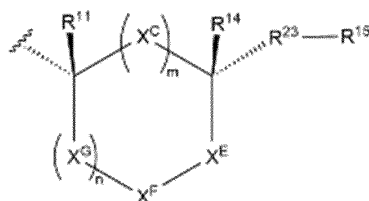
102. The compound according to any one of the preceding items, wherein R^4 is of Formula IIG,



Formula IIG

or a pharmaceutically acceptable salt thereof.

103. The compound according to any one of the preceding items, wherein R^4 is of Formula IIH,



Formula IIH

or a pharmaceutically acceptable salt thereof.

104. The compound according to any one of the preceding items, wherein R^4 is a 6-membered ring, or a pharmaceutically acceptable salt thereof.

105. The compound according to any one of the preceding items, wherein X^E is O, $C(R^{16})(R^{17})$ or NR^{18} ; m is 1; and n is 1, or a pharmaceutically acceptable salt thereof.

106. The compound according to any one of the preceding items, wherein X^B is N; X^C is $C(R^{12})(R^{13})$; X^D is $C(R^{14})$; X^E is O; X^F is $C(R^{19})(R^{20})$; X^G is $C(R^{21})(R^{22})$; m is 1; and n is 1, or a pharmaceutically acceptable salt thereof.

107. The compound according to any one of the preceding items, wherein X^B is $C(R^{11})$; X^C is $C(R^{12})(R^{13})$; X^D is $C(R^{14})$; X^E is O; X^F is $C(R^{19})(R^{20})$; X^G is $C(R^{21})(R^{22})$; m is 1; and n is 1, or a pharmaceutically acceptable salt thereof.

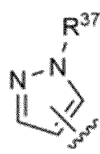
108. The compound according to any one of the preceding items, wherein X^B is N; X^C is $C(R^{12})(R^{13})$; X^D is $C(R^{14})$; X^E is NR^{18} ; X^F is $C(R^{19})(R^{20})$; X^G is $C(R^{21})(R^{22})$; m is 1; and n is 1, or a pharmaceutically acceptable salt thereof.
109. The compound according to any one of the preceding items, wherein X^B is N; X^C is $C(R^{12})(R^{13})$; X^D is $C(R^{14})$; X^E is $C(R^{16})(R^{17})$; X^F is $C(R^{19})(R^{20})$; X^G is $C(R^{21})(R^{22})$; m is 1; and n is 1, or a pharmaceutically acceptable salt thereof.
110. The compound according to any one of the preceding items, wherein X^B is N, or a pharmaceutically acceptable salt thereof.
111. The compound according to any one of the preceding items, wherein X^B is $C(R^{11})$, or a pharmaceutically acceptable salt thereof.
112. The compound according to any one of the preceding items, wherein R^{11} is H, or a pharmaceutically acceptable salt thereof.
113. The compound according to any one of the preceding items, wherein R^{11} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
114. The compound according to any one of the preceding items, wherein X^C is $C(R^{12})(R^{13})$, or a pharmaceutically acceptable salt thereof.
115. The compound according to any one of the preceding items, wherein R^{12} is individually H, or a pharmaceutically acceptable salt thereof.
116. The compound according to any one of the preceding items, wherein R^{12} is individually C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
117. The compound according to any one of the preceding items, wherein R^{12} is a bond and R^{11} is C_{1-3} alkyl, and R^{11} and R^{12} are linked together to form a 3-5 membered ring, or a pharmaceutically acceptable salt thereof.
118. The compound according to any one of the preceding items, wherein R^{13} is individually H, or a pharmaceutically acceptable salt thereof.
119. The compound according to any one of the preceding items, wherein R^{13} is individually C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
120. The compound according to any one of the preceding items, wherein X^D is $C(R^{14})$, or a pharmaceutically acceptable salt thereof.
121. The compound according to any one of the preceding items, wherein X^D is N, or a pharmaceutically acceptable salt thereof.
122. The compound according to any one of the preceding items, wherein R^{14} is H, or a pharmaceutically acceptable salt thereof.
123. The compound according to any one of the preceding items, wherein R^{14} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.

124. The compound according to any one of the preceding items, wherein when X^B is N, then X^D is $C(R^{14})$, or a pharmaceutically acceptable salt thereof.

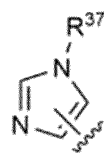
125. The compound according to any one of the preceding items, wherein R^{23} is a bond, or a pharmaceutically acceptable salt thereof.

5 126. The compound according to any one of the preceding items, wherein R^{15} is a 5-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, - $O-C_{1-6}$ alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-(C_{1-3} \text{ alkyl})O(C_{1-3} \text{ alkyl})$, -CN, and halogen, or a pharmaceutically acceptable salt thereof.

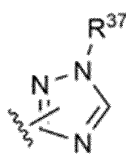
10 127. The compound according to any one of the preceding items, wherein R^{15} is selected from the group consisting of Formula V, Formula VI, Formula VII, Formula VIII, Formula IX, Formula X, Formula XI, and Formula XII:



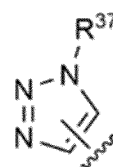
Formula V



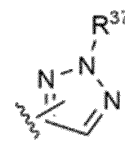
Formula VI



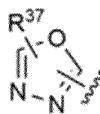
Formula VII



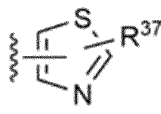
Formula VIII



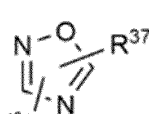
Formula IX



Formula X



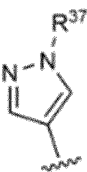
Formula XI



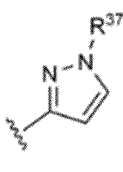
Formula XII

wherein R^{37} is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, - $O-C_{1-6}$ alkyl, H, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-(C_{1-3} \text{ alkyl})O(C_{1-3} \text{ alkyl})$, -CN, and halogen, or a pharmaceutically acceptable salt thereof.

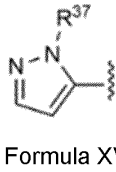
128. The compound according to any one of the preceding items, wherein R^{15} is selected from the group consisting of Formula XIII, Formula XIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XIX, Formula XX, Formula XXI, Formula XXII, and Formula XXIII:



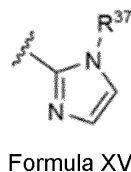
Formula XIII



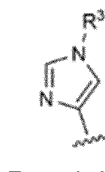
Formula XIV



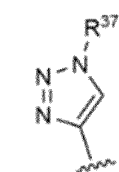
Formula XV



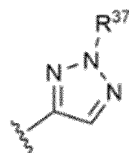
Formula XVI



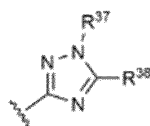
Formula XVII



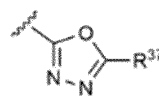
Formula XVIII



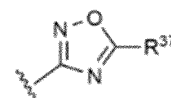
Formula XIX



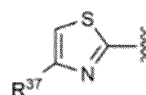
Formula XX



Formula XXI



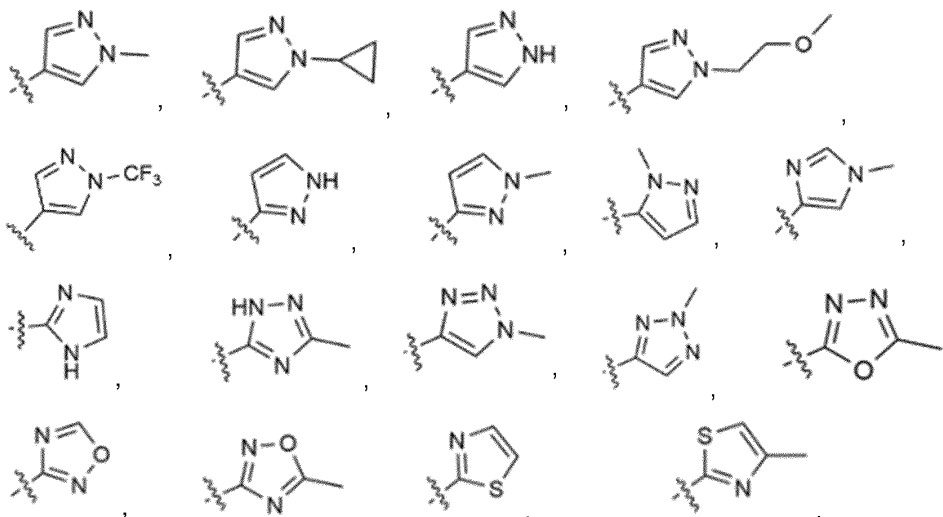
Formula XXII

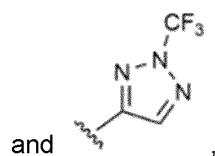


Formula XXIII

wherein R^{37} and R^{38} are independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, $-O-C_{1-6}$ alkyl, H, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-(C_{1-3} \text{ alkyl})O(C_{1-3} \text{ alkyl})$, $-CN$, and halogen, or a pharmaceutically acceptable salt thereof.

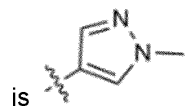
- 5 129. The compound according to any one of the preceding items, wherein R^{37} is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
130. The compound according to any one of the preceding items, wherein R^{37} is CH_3 , or a pharmaceutically acceptable salt thereof.
- 10 131. The compound according to any one of the preceding items, wherein R^{37} is C_{3-6} cycloalkyl, or a pharmaceutically acceptable salt thereof.
132. The compound according to any one of the preceding items, wherein R^{37} is C_3 cycloalkyl, or a pharmaceutically acceptable salt thereof.
133. The compound according to any one of the preceding items, wherein R^{15} is selected from the group consisting of:





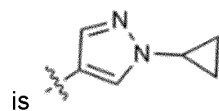
or a pharmaceutically acceptable salt thereof.

134. The compound according to any one of the preceding items, wherein R¹⁵



or a pharmaceutically acceptable salt thereof.

5 135. The compound according to any one of the preceding items, wherein R¹⁵



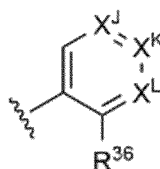
or a pharmaceutically acceptable salt thereof.

136. The compound according to any one of the preceding items, wherein R¹⁵

is a 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of C₁₋₆ alkyl, C₃₋₆ cycloalkyl, -O-C₁₋₆ alkyl, H, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -(C₁₋₃ alkyl)O(C₁₋₃ alkyl), -CN, and halogen, or a pharmaceutically acceptable salt thereof.

10

137. The compound according to any one of the preceding items, wherein R¹⁵ is of Formula XXIV:



15

Formula XXIV

wherein

X^J is N or CH;

X^K is N or C(R⁷);

20

X^L is N or C(R⁸);

R⁷ is C₁₋₃ alkyl;

R⁸ is C₁₋₃ alkyl; and

R³⁶ is H or C₁₋₃ alkyl,

or a pharmaceutically acceptable salt thereof.

138. The compound according to any one of the preceding items, wherein X^J is CH, or a pharmaceutically acceptable salt thereof.

139. The compound according to any one of the preceding items, wherein X^K is N, or a pharmaceutically acceptable salt thereof.

5 140. The compound according to any one of the preceding items, wherein X^K is C(R⁷), or a pharmaceutically acceptable salt thereof.

141. The compound according to any one of the preceding items, wherein R⁷ is -CH₃, or a pharmaceutically acceptable salt thereof.

10 142. The compound according to any one of the preceding items, wherein X^L is N, or a pharmaceutically acceptable salt thereof.

143. The compound according to any one of the preceding items, wherein X^L is C(R⁸), or a pharmaceutically acceptable salt thereof.

144. The compound according to any one of the preceding items, wherein R⁸ is -CH₃, or a pharmaceutically acceptable salt thereof.

15 145. The compound according to any one of the preceding items, wherein R³⁶ is H, or a pharmaceutically acceptable salt thereof.

146. The compound according to any one of the preceding items, wherein R³⁶ is C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

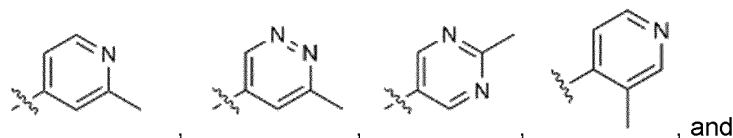
20 147. The compound according to any one of the preceding items, wherein R³⁶ is -CH₃, or a pharmaceutically acceptable salt thereof.

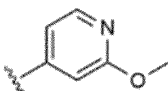
148. The compound according to any one of the preceding items, wherein at least one of X^J , X^K , and X^L is N, or a pharmaceutically acceptable salt thereof.

149. The compound according to any one of the preceding items, wherein one of X^J , X^K , and X^L is N, or a pharmaceutically acceptable salt thereof.

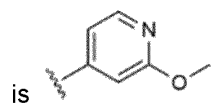
25 150. The compound according to any one of the preceding items, wherein two of X^J , X^K , and X^L are N, or a pharmaceutically acceptable salt thereof.

151. The compound according to any one of the preceding items, wherein R¹⁵ is selected from the group consisting of



30 , or a pharmaceutically acceptable salt thereof.

152. The compound according to any one of the preceding items, wherein R¹⁵



is , or a pharmaceutically acceptable salt thereof.

153. The compound according to any one of the preceding items, wherein X^E is C(R¹⁶)(R¹⁷), or a pharmaceutically acceptable salt thereof.

5 154. The compound according to any one of the preceding items, wherein X^E is O, or a pharmaceutically acceptable salt thereof.

155. The compound according to any one of the preceding items, wherein X^E is NR¹⁸, or a pharmaceutically acceptable salt thereof.

10 156. The compound according to any one of the preceding items, wherein X^E is a bond, or a pharmaceutically acceptable salt thereof.

157. The compound according to any one of the preceding items, wherein R¹⁹ is H, or a pharmaceutically acceptable salt thereof.

158. The compound according to any one of the preceding items, wherein R¹⁹ is halogen, or a pharmaceutically acceptable salt thereof.

15 159. The compound according to any one of the preceding items, wherein R¹⁹ is F, or a pharmaceutically acceptable salt thereof.

160. The compound according to any one of the preceding items, wherein R¹⁹ is C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

20 161. The compound according to any one of the preceding items, wherein R¹⁹ is CH₃, or a pharmaceutically acceptable salt thereof.

162. The compound according to any one of the preceding items, wherein R²⁰ is H, or a pharmaceutically acceptable salt thereof.

163. The compound according to any one of the preceding items, wherein R²⁰ is halogen, or a pharmaceutically acceptable salt thereof.

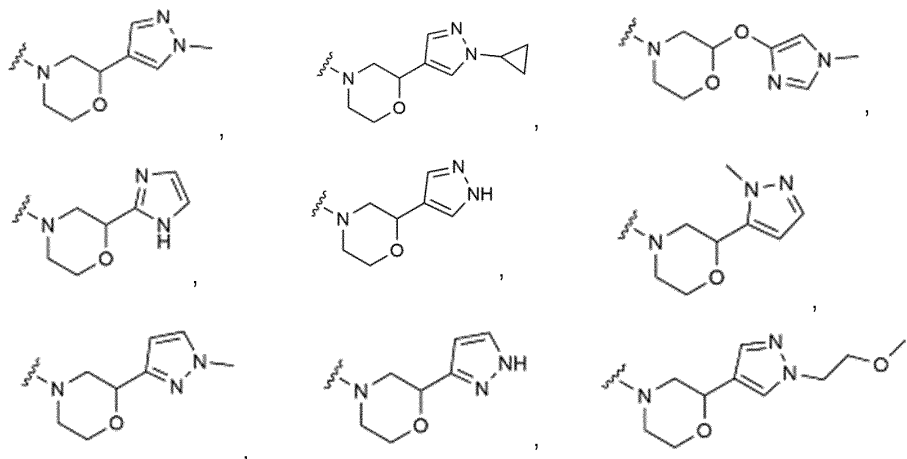
25 164. The compound according to any one of the preceding items, wherein R²⁰ is F, or a pharmaceutically acceptable salt thereof.

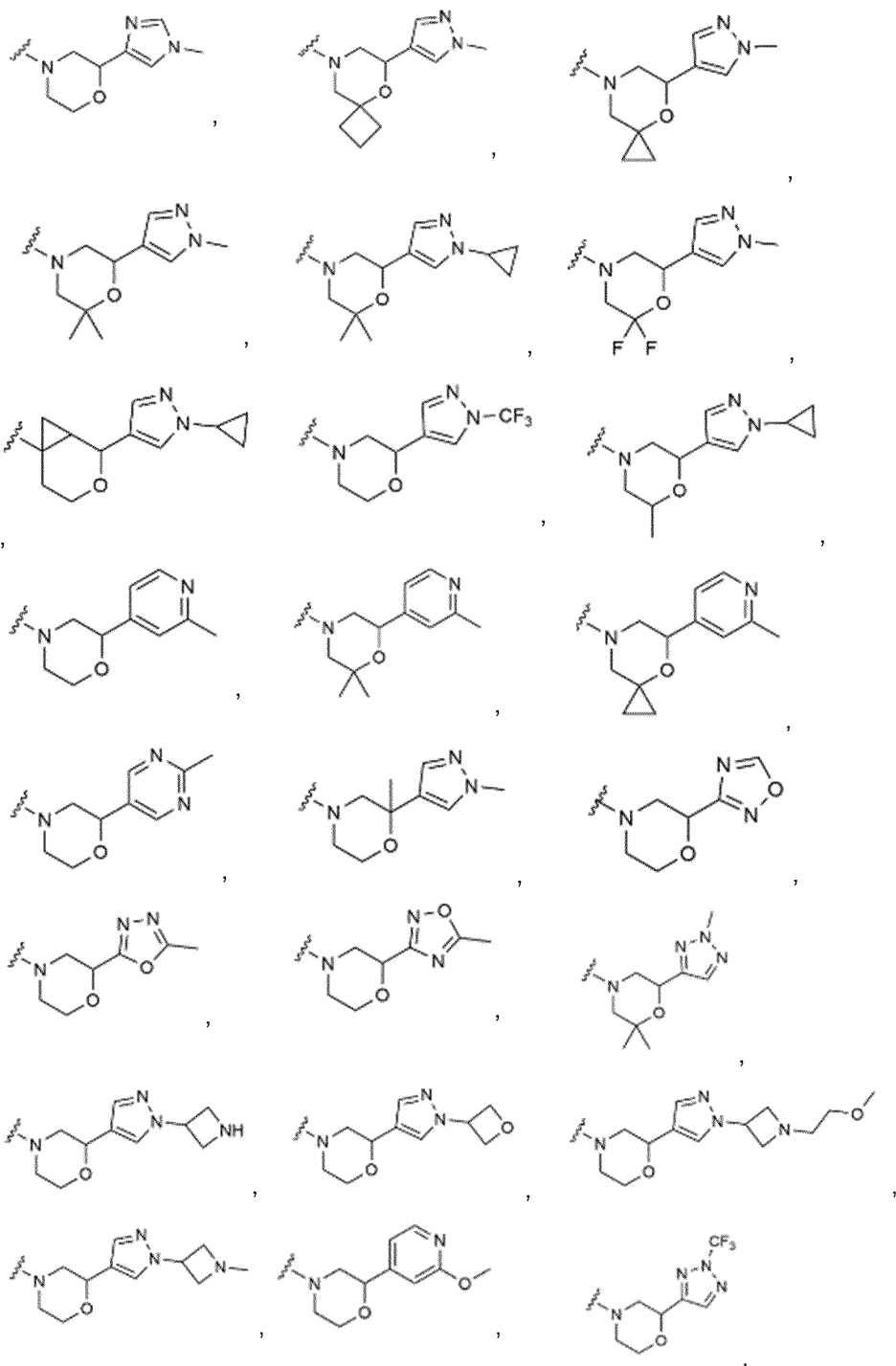
165. The compound according to any one of the preceding items, wherein R²⁰ is C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

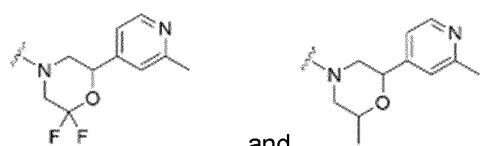
30 166. The compound according to any one of the preceding items, wherein R²⁰ is CH₃, or a pharmaceutically acceptable salt thereof.

167. The compound according to any one of the preceding items, wherein R¹⁹ and R²⁰ are C₁₋₃ alkyl, and R¹⁹ and R²⁰ are optionally linked together to form a 3-6 membered ring, or a pharmaceutically acceptable salt thereof.

168. The compound according to any one of the preceding items, wherein X^G is $C(R^{21})(R^{22})$, or a pharmaceutically acceptable salt thereof.
169. The compound according to any one of the preceding items, wherein X^G is $C(O)$, or a pharmaceutically acceptable salt thereof.
- 5 170. The compound according to any one of the preceding items, wherein R^{21} is H, or a pharmaceutically acceptable salt thereof.
171. The compound according to any one of the preceding items, wherein R^{22} is H, or a pharmaceutically acceptable salt thereof.
172. The compound according to any one of the preceding items, wherein m is 1, or a pharmaceutically acceptable salt thereof.
- 10 173. The compound according to any one of the preceding items, wherein m is 0, or a pharmaceutically acceptable salt thereof.
174. The compound according to any one of the preceding items, wherein m is 2, or a pharmaceutically acceptable salt thereof.
- 15 175. The compound according to any one of the preceding items, wherein n is 1, or a pharmaceutically acceptable salt thereof.
176. The compound according to any one of the preceding items, wherein n is 0, or a pharmaceutically acceptable salt thereof.
177. The compound according to any one of the preceding items, wherein n is 2, or a pharmaceutically acceptable salt thereof.
- 20 178. The compound according to any one of the preceding items, wherein R^4 is selected from the group consisting of:

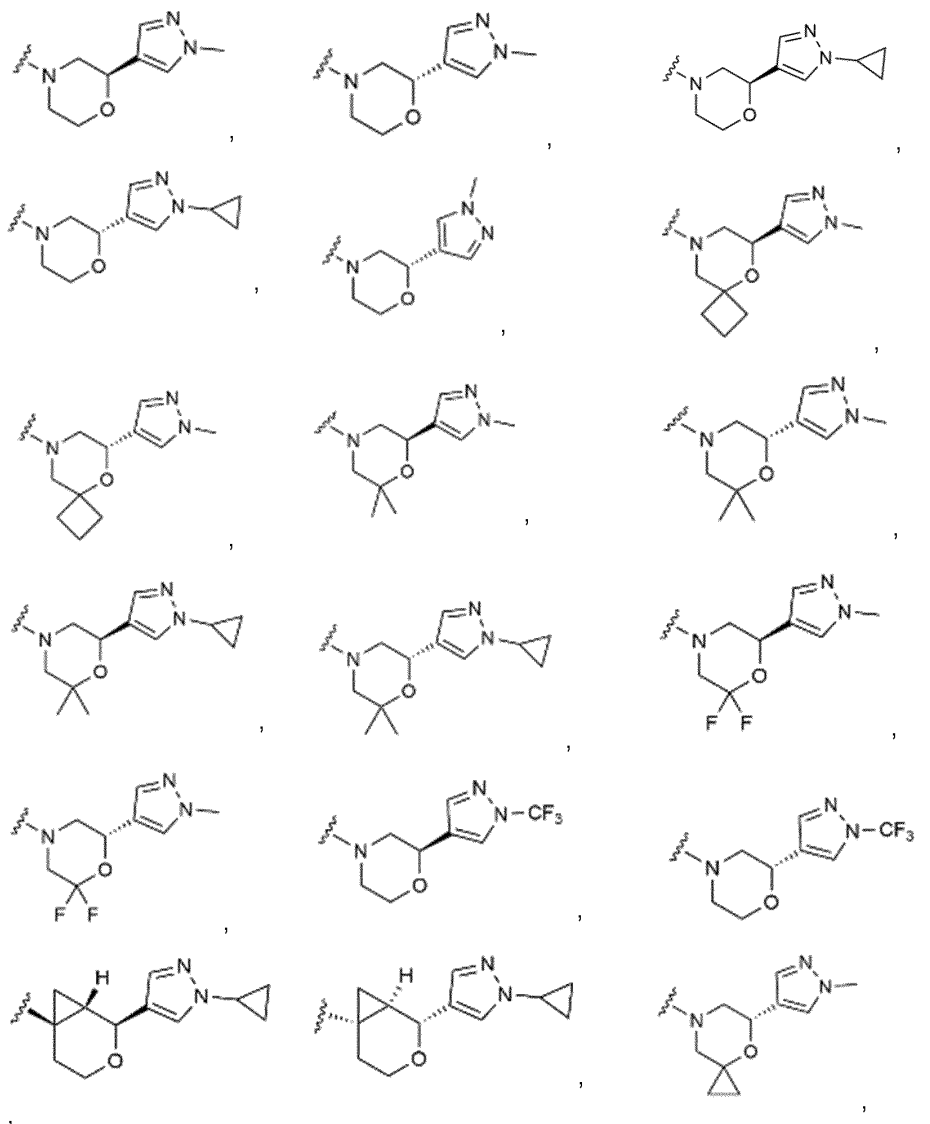


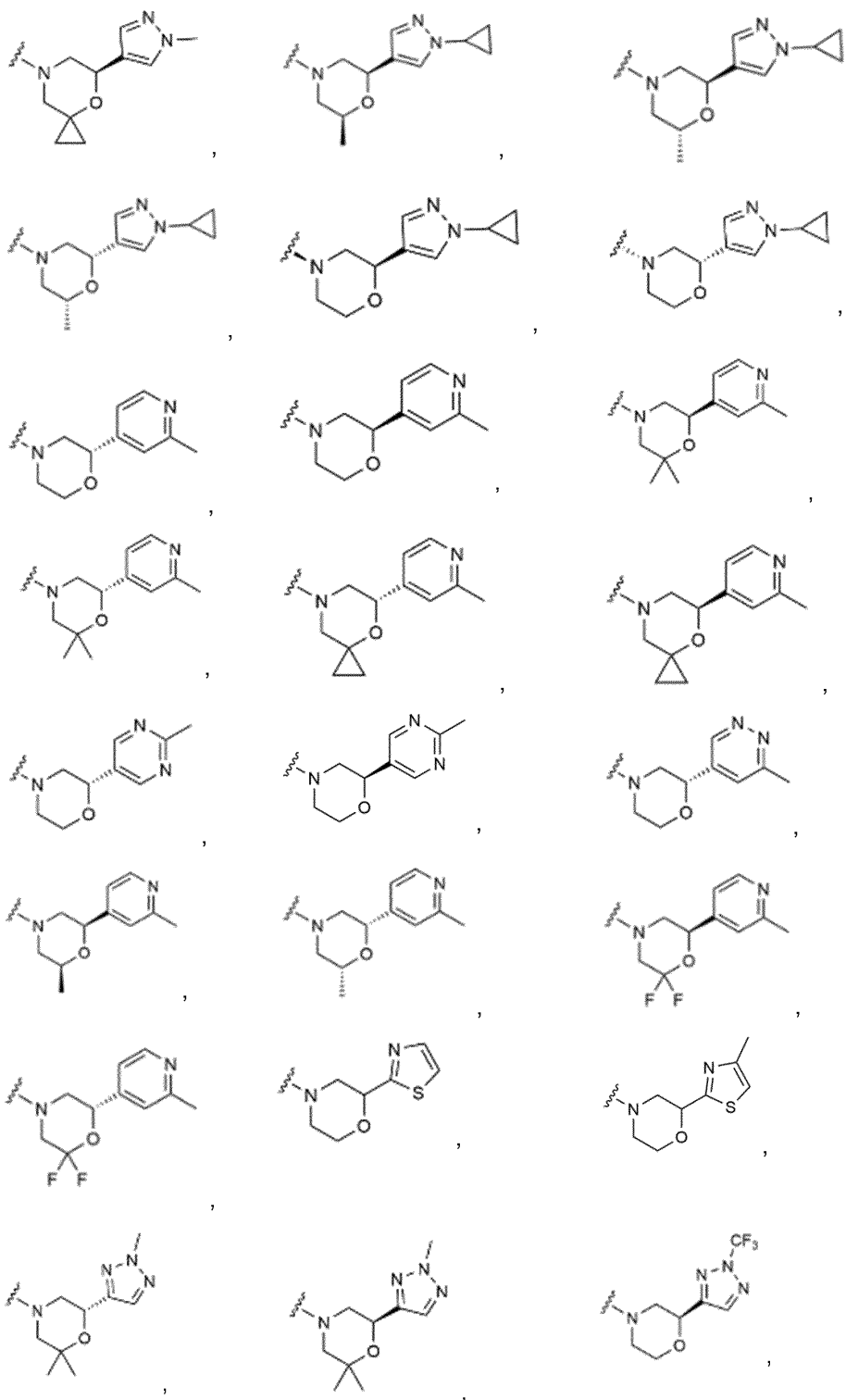




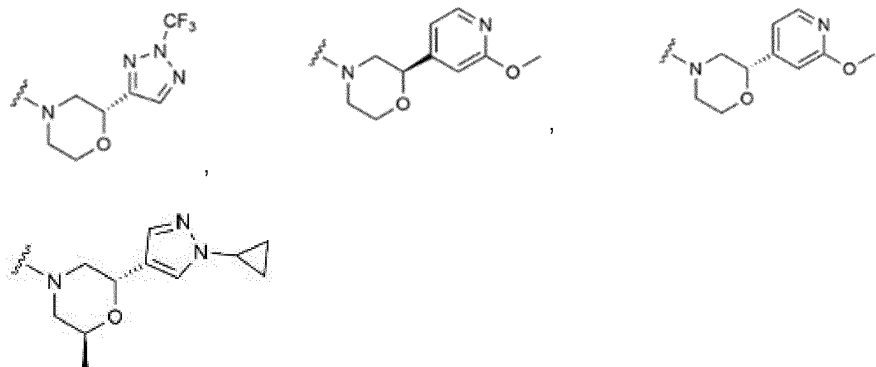
or a pharmaceutically acceptable salt thereof.

179. The compound according to any one of the preceding items, wherein R^4 is selected from the group consisting of:





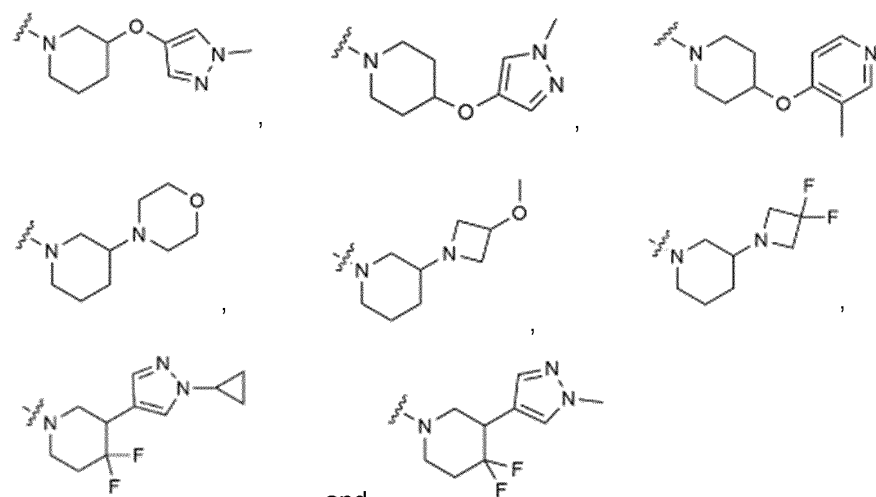
130



and

or a pharmaceutically acceptable salt thereof.

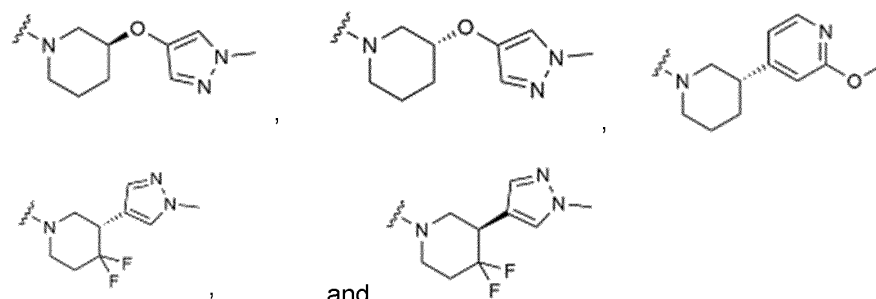
180. The compound according to any one of the preceding items, wherein R^4 is selected from the group consisting of:



and

or a pharmaceutically acceptable salt thereof.

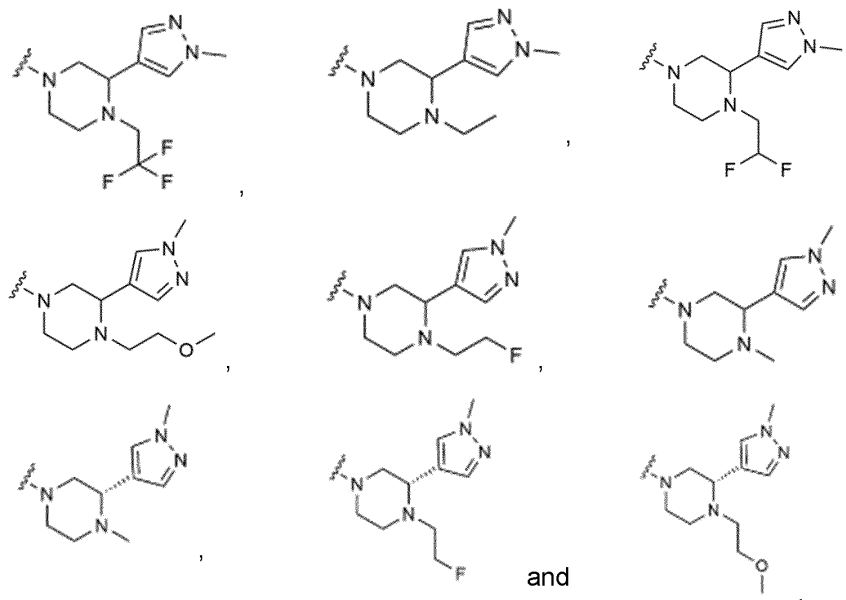
5 181. The compound according to any one of the preceding items, wherein R^4 is selected from the group consisting of:



and

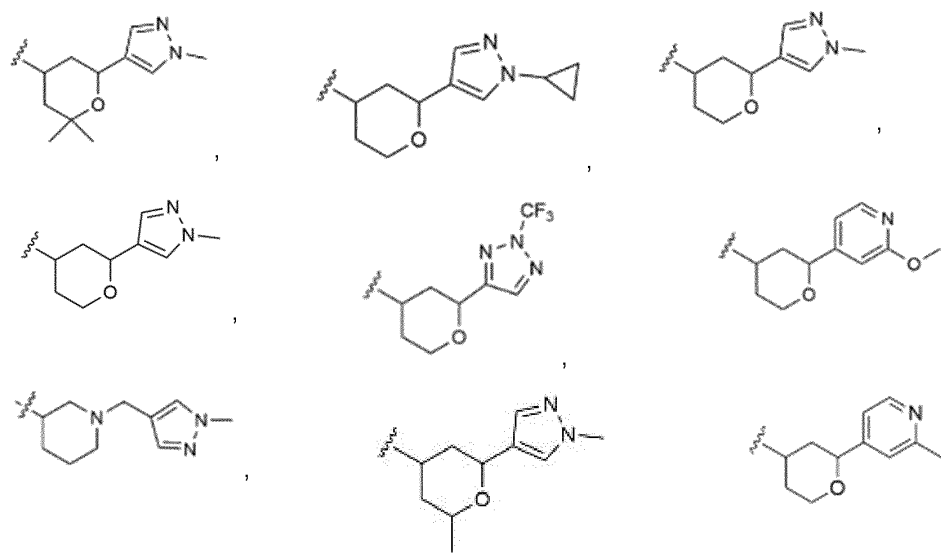
or a pharmaceutically acceptable salt thereof.

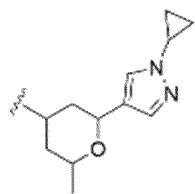
182. The compound according to any one of the preceding items, wherein R⁴ is selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

- 5 183. The compound according to any one of the preceding items, wherein R⁴ is selected from the group consisting of:

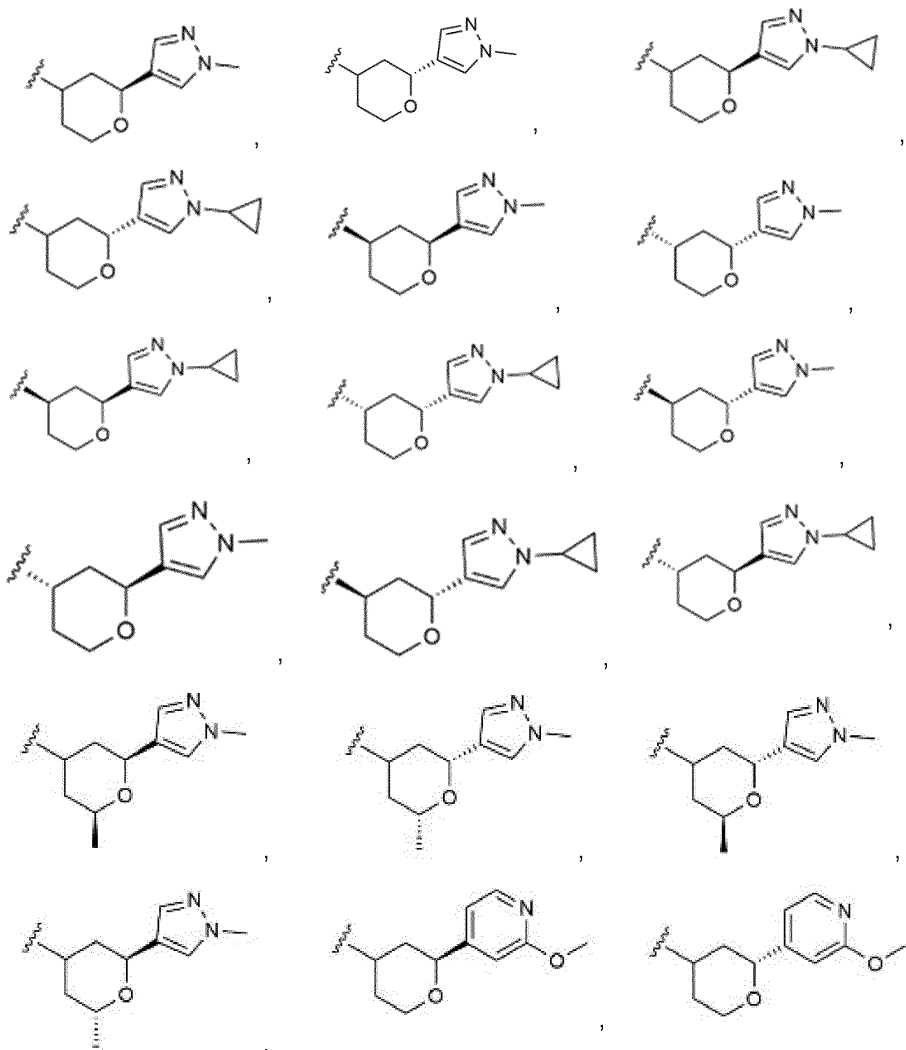


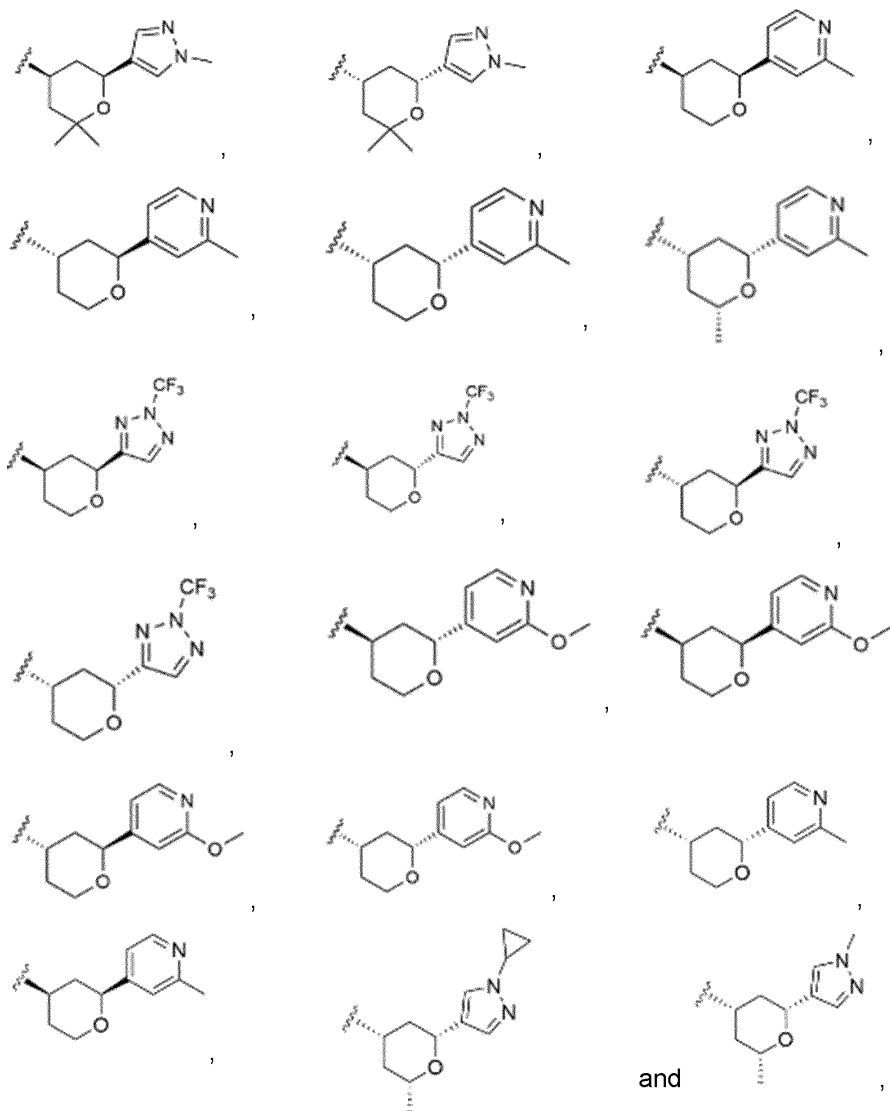


and

or a pharmaceutically acceptable salt thereof.

184. The compound according to any one of the preceding items, wherein R^4 is selected from the group consisting of:





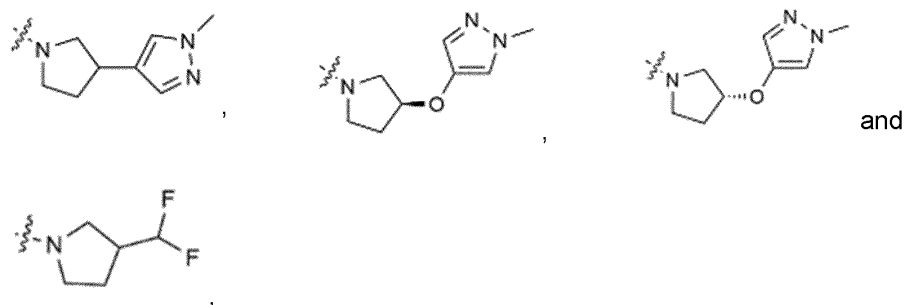
or a pharmaceutically acceptable salt thereof.

185. The compound according to any one of the preceding items, wherein R^4 is a 5-membered ring, or a pharmaceutically acceptable salt thereof.

186. The compound according to any one of the preceding items, wherein m is 1; X^E is a bond; and n is 1, or a pharmaceutically acceptable salt thereof.

187. The compound according to any one of the preceding items, wherein X^B is N; X^C is CH_2 ; m is 1; X^D is C(H); X^E is a bond; X^F is $C(H_2)$; X^G is $C(H_2)$; and n is 1, or a pharmaceutically acceptable salt thereof.

188. The compound according to any one of the preceding items, wherein R^4 is selected from the group consisting of:



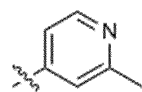
or a pharmaceutically acceptable salt thereof.

189. The compound according to any one of the preceding items, wherein R^4 is a 4-membered ring, or a pharmaceutically acceptable salt thereof.

190. The compound according to any one of the preceding items, wherein m is 1; X^E is a bond; and n is 0, or a pharmaceutically acceptable salt thereof.

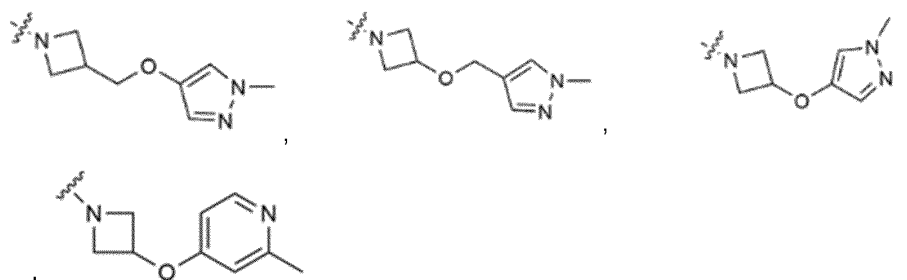
191. The compound according to any one of the preceding items, wherein X^B is N; X^C is CH_2 ; m is 1; X^D is C(H); X^E is a bond; X^F is $C(H_2)$; and n is 0, or a pharmaceutically acceptable salt thereof.

192. The compound according to any one of the preceding items, wherein X^B is N; X^C is CH_2 ; m is 1; X^D is C(H); X^E is a bond; X^F is $C(H_2)$; n is 0; and R^{15} is



, or a pharmaceutically acceptable salt thereof.

193. The compound according to any one of the preceding items, wherein R^4 is selected from the group consisting of:



and

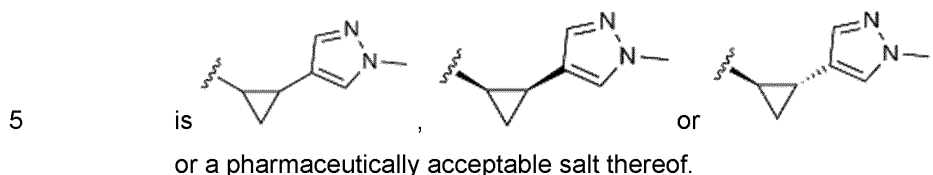
or a pharmaceutically acceptable salt thereof.

194. The compound according to any one of the preceding items, wherein R^4 is a 3-membered ring, or a pharmaceutically acceptable salt thereof.

195. The compound according to any one of the preceding items, wherein m is 0; X^E is a bond; and n is 0, or a pharmaceutically acceptable salt thereof.

196. The compound according to any one of the preceding items, wherein X^B is C(H); m is 0; X^D is C(H); X^E is a bond; X^F is C(H₂); and n is 0, or a pharmaceutically acceptable salt thereof.

197. The compound according to any one of the preceding items, wherein R^4



198. The compound according to any one of the preceding items, wherein the compound is of Formula IA and wherein

R^1 is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl and H;

10 R^2 is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halogen and H;

R^3 is phenyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl and CN, wherein one methylene group of the C₁₋₃ alkyl is optionally replaced with -O-;

X^A is N or CH;

X^B is N or CH;

X^C is C(H)₂;

X^D is C(H);

20 X^E is O;

X^F is C(R¹⁹)(R²⁰), wherein each R¹⁹ and R²⁰ are individually selected as H or CH₃;

X^G is C(H)₂;

m is 1;

25 n is 1;

R^{23} is a bond; and

R^{15} is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, -CN, and C₃₋₆ cycloalkyl, or a pharmaceutically acceptable salt thereof.

30

199. The compound according to any one of the preceding items, wherein the compound is of Formula IA and wherein

R^1 is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl and H;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, and H;
 R^3 is phenyl is optionally substituted with 1 to 3 substituents independently
selected from the group consisting of halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl;

X^A is CH;

5 X^B is N;

X^C is $C(H)_2$;

X^D is $C(H)$;

X^E is O;

X^F is $C(H)_2$;

10 X^G is $C(H)_2$;

m is 1;

n is 1;

R^{23} is a bond; and

R^{15} is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted
15 with 1 to 3 substituents independently selected from the group consisting of
halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -CN, and C_{3-6} cycloalkyl.

200. The compound according to any one of the preceding items, wherein the
compound is of Formula IA and wherein

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and H;

20 R^2 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, and H;

R^3 is phenyl is optionally substituted with 1 to 3 substituents independently
selected from the group consisting of halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl;

X^A is N;

X^B is $C(H)$;

25 X^C is $C(H)_2$;

X^D is $C(H)$;

X^E is O;

X^F is $C(H)_2$;

X^G is $C(H)_2$;

30 m is 1;

n is 1;

R^{23} is a bond; and

R^{15} is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted
with 1 to 3 substituents independently selected from the group consisting of
35 halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -CN, and C_{3-6} cycloalkyl.

201. The compound according to any one of the preceding items, wherein the compound is selected from the group consisting of:

- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one;
- 5 (R)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one;
- (S)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one;
- 10 9-(4-chloro-2-fluorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 15 (R)-9-(4-chloro-2-fluorophenyl)-7-(2,2-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)morpholino)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one;
- (S)-9-(4-chloro-2-fluorophenyl)-7-(2,2-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)morpholino)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one;
- (S)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 20 6-(4-chloro-2-fluorophenyl)-2,3-dimethyl-8-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-chloro-2-fluorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 25 3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-chlorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-chlorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 30 3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;

- 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 5 4-(3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile;
- 4-(3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile;
- 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-
- 10 (2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 4-(3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile;
- 15 4-(3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile;
- 9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-methyl-6-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-(2-methyl-4-pyridyl)tetrahydropyran-4-
- 20 yl]pyrido[1,2-a]pyrimidin-4-one;
- 7-[2,2-difluoro-6-(2-methyl-4-pyridyl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 25 9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-methyl-6-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 7-[(2R,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-
- 30 dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 7-[2,2-difluoro-6-(2-methyl-4-pyridyl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 5 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-pyrido[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrazino[1,2-a]pyrimidin-4-one;
- 10 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one;
- 15 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)pyrazino[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-(trifluoromethyl)pyrazino[1,2-a]pyrimidin-4-one;
- 20 4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrazino[1,2-a]pyrimidin-4-one;
- 25 4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
- 7-[2,2-difluoro-6-(1-methylpyrazol-4-yl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)pyrido[1,2-a]pyrimidin-4-one;
- 30 4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-4-oxo-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
- 3-chloro-7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one;

- 4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2-methyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
- 4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-methyl-4-oxo-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
- 5 4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-4-oxo-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
- 4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-methyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
- 4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-4-oxo-2-(trifluoromethyl)pyrazino[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
- 10 9-(3-methoxycyclobutyl)-2,3-dimethyl-7-[rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(3-methoxycyclobutyl)-2,3-dimethyl-7-[rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 15 3-chloro-9-(4-chloro-2-fluorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-chloro-2-fluorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 20 3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-chlorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 25 3-chloro-9-(4-chlorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-chlorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-chlorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 30 3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;

- 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 5 3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 10 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 4-(3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile;
- 15 4-(3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile;
- 4-(3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile;
- 4-(3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile;
- 20 3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 25 3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 4-(3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile;
- 30 4-(3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile;
- 4-(3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile; and

4-(3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile,
or a pharmaceutically acceptable salt thereof.

- 5 202. The compound according to any one of the preceding items, or a pharmaceutically acceptable salt thereof, wherein the compound is a TREM2 modulator, such as a TREM2 activator, such as a TREM2 agonist.
- 10 203. The compound according to any one of the preceding items, or a pharmaceutically acceptable salt thereof, wherein the compound enhances or activates TREM2 signaling through DAP12; and/or wherein the compound induces phosphorylation of a kinase that interacts with the TREM2/DAP12 signaling complex, such as, but not limited to, Syk, ZAP70, PI3K, Erk, AKT and GSK3b; and/or wherein the compound enhances TREM2-induced phosphorylation levels of the Syk kinase.
- 15 204. The compound according to any one of the preceding items, or a pharmaceutically acceptable salt thereof, wherein the compound increases the expression of one or more TREM2 regulated genes, such as wherein the compound increases the expression of one or more TREM2 regulated genes selected from the group consisting of CXCL10, CCL2, CST7 and TMEM119.
- 20 205. 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.
- 25 206. The compound according to any one of items 1 to 204, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 205, for use as a medicament.
- 30 207. The compound according to any one of items 1 to 204, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 205, for use in the treatment of a condition associated with a loss of function of TREM2, such as for use in the treatment of a condition associated with a mutation of TREM2.
- 35 208. The compound according to any one of items 1 to 204, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 205, for use in the treatment of a neurodegenerative disease.
209. The compound or composition for use according to item 208, 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 Leukoencephalopathy, a leukodystrophy, a transmissible spongiform encephalopathy (TSE) and a lysosomal storage disorder (LSD).

210. The compound according to any one of items 1 to 204, or a
5 pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 205, 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
10 lateral sclerosis, multiple sclerosis, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathies, Charcot-Marie-Tooth disease, prion disease and stroke.
211. The compound according to any one of items 1 to 204, or a
15 pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 205, for use in the treatment of a disease selected from the group consisting of arthritis, rheumatoid arthritis, pyle disease, osteoporosis, osteopetrosis, osteosclerosis, skeletal dysplasia, dysosteoplasia, autism
20 spectrum disorders, autism and Aspergers syndrome, traumatic brain injuries (TBI), spinal cord injuries, muscular dystrophy, myotonic dystrophy, inclusion-body myositis, systemic lupus erythematosus (SLE), RA, gout, bowel conditions, Inflammatory bowel disease (IBD), metabolic syndrome, obesity, type 2 diabetes, atherosclerosis, alcoholic and non-alcoholic fatty liver disease, alcoholic and non-alcoholic steatohepatitis, Amyloidosis.
212. The compound or composition for use according to any one of items 206
25 to 211, wherein said compound is administered in an amount of about 0.01 mg/kg to about 100 mg/kg bodyweight/day.
213. The compound or composition for use according to any one of items 206
30 to 211, 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.
214. A method for treatment of a condition associated with a loss of function of TREM2, such as a neurodegenerative disease, said method comprising administering a therapeutically effective amount of a compound according to

any one of items 1 to 204, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 205, to a subject in need thereof.

215. Use of a compound according to any one of items 1 to 204, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 205, for the manufacture of a medicament for the treatment of a condition associated with a loss of function of TREM2, such as a neurodegenerative disease.
216. A method of enhancing or increasing TREM2 activity, such as a method of one or more of i) enhancing or activating TREM2 signaling through DAP12, ii) inducing phosphorylation of a kinase that interacts with the TREM2/DAP12 signaling complex, such as, but not limited to, Syk, ZAP70, PI3K, Erk, AKT and GSK3b, iii) enhancing TREM2-induced phosphorylation levels of the Syk kinase, iv) increasing the expression levels, such as brain expression levels, of one or more TREM2 regulated genes, and/or v) increasing the expression levels, such as brain expression levels, of one or more TREM2 regulated genes selected from the group consisting of CXCL10, CCL2, CST7 and TMEM119; in a subject in need thereof, such as in a subject having a neurodegenerative disease, said method comprising administering to the subject a compound, or a pharmaceutically acceptable salt thereof, according to any one of items 1 to 204.

Abbreviations

25	DCM	Dichloromethane
	PIDA	Phenyl iodine(III) diacetate
	HPLC	High performance liquid chromatography
	MeCN	Acetonitrile
	MeOH	Methanol
30	EtOH	Ethanol
	THF	Tetrahydrofuran
	DMF	Dimethyl formamide
	TFA	Trifluoroacetic Acid
	DIPEA	Diisopropylethylamine
35	EtOAc	Ethyl acetate
	NBS	N-bromo succinimide

	NCS	N-chloro succinimide
	Pd/C	Palladium on carbon
	NaOAc	Sodium acetate
	AcOH	Acetic acid
5	NaHCO ₃	Sodium bicarbonate
	NH ₄ OAc	Ammonium acetate
	NiCl ₂ ·6H ₂ O	Nickel chloride; hexahydrate
	DMAP	4-Dimethylaminopyridine
	Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
10	Pd(tBu ₃ P) ₂	Bis(tri- <i>tert</i> -butylphosphine)palladium(0)
	PdCl ₂ (dppf)	[1,1'-Bis(diphenylphosphino) ferrocene]dichloropalladium(II)
	RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
	Xanthphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
	Me ₂ NH ₂ ·HCl	Methylamine hydrochloride
15	HATU	1-[Bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxid hexafluorophosphate
	NH ₄ OAc	Ammonium acetate
	RuPhos-	
20	Pd-G3	(2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate
	rt	Room temperature
	Rt	Retention time
	SFC	Supercritical fluid chromatography
	Prep HPLC	Preparative high performance liquid chromatography
25	NP	Normal phase
	mL	millilitre
	mg	milligram
	g	gram
	mmol	millimole
30	mol	mole

LCMS conditions:**Condition A**

LCMS Column- Acquity BEH C18 (50 x 2.1 mm, 1.7u), Initially (90% [0.05% HCOOH in water] and 10% [0.05% HCOOH in CH₃CN: water (90:10)] is held up to 0.75 min, then

to 50% [0.05% HCOOH in water] and 50% [0.05% HCOOH in CH₃CN: water (90:10)] in 1.00 min, then to 2% [0.05% HCOOH in water] and 98% [0.05% HCOOH in CH₃CN: water (90:10)] in 2.00 min held this mobile phase composition up to 2.25 min and finally back to initial condition in 2.60 min and held up to 3.00 min). Flow: 0.60 ml/min.

5

Condition B

Column -Xbridge C18 (4.6 x 50 mm, 5 u) mobile phase: 90 % [10 mM Ammonium Acetate in Water] and 10 % [CH₃CN] to 70% [10 mM Ammonium Acetate in Water] and 30% [CH₃CN] in 1.5 min, further to 10% [10 mM Ammonium Acetate in Water] and 90% [CH₃CN] 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

10

Condition C

LCMS Column- Acquity BEH C8 (50 x 2.1 mm, 1.7u), Initially (95% [0.05% HCOOH in water] and 5% [0.05% HCOOH in CH₃CN: water (90:10)] is held up to 0.75 min, then to 75% [0.05% HCOOH in water] and 25% [0.05% HCOOH in CH₃CN: water (90:10)] in 1.50 min, then to 5% [0.05% HCOOH in water] and 95% [0.05% HCOOH in CH₃CN: 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 up to 5.10 min). Flow: 0.80 ml/min.

15

20

Condition D

Column- Xbridge C18 column (3.5 µm, 50 x 3 mm), (initially 95% [5 mM NH₄OAc in water] and 5% [5 mM NH₄OAc in ACN: Water (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: 1.20 ml/min.

25

Condition E

Column- YMC Triart C18 (33 x 2.1 mm, 3u), (initially 98% [0.05% HCOOH in water] and 2% [0.05% HCOOH in ACN: Water (90:10)] held for 0.75 min, then to 90% [0.05% HCOOH in water] and 10% [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 2.00 min, held this mobile phase composition up to 2.50 min and finally back to initial condition in 4.90 min and held this composition up to 3.0 min). Flow: 1.0 ml/min.

30

35

Reverse Phase Prep-Purification method:

Unless stated otherwise, preparative HPLC was done on Waters auto purification instrument operating at ambient temperature and flow rate of 16 mL/min

5 Prep-A

Column name: YMC-Actus C18 (250 x 20 mm, 5 μ). Mobile phase: A = 20mM Ammonium bicarbonate in water, B = Acetonitrile; Gradient Profile: Mobile phase initial composition of 60% A and 40% B, then 40% A and 60% 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

15 Prep-B

Column name: Chromcore C18 (250 x 21.2 mm, 5 μ). Mobile phase: A = 20mM Ammonium Bicarbonate in water, B=Acetonitrile:Methanol(50:50); Gradient Profile: Mobile phase initial composition of 60% A and 40% B, then 35% A and 65% B in 3 min, then to 5% A and 95% 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 Prep-C

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 45% A and 55% 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 Prep-D

Column name: CHROMCORE 120 C18, 5 μ m (21.2 x 250mm). Mobile phase: A=Acetonitrile, B = 20mM Ammonium Bicarbonate in water; Gradient Profile: Mobile phase initial composition of 30% A and 70% B, then 50% A and 50% B in 3 min, then to 61.6% A and 38.4% B in 14 min., then to 100% A and 0% B in 14.1 min., held this composition up to 18 min. for column washing, then returned to initial composition in 18.1 min. and held till 21 min.

35

SFC methods:

SFC condition -1: Chiral separation of was done by running sample in Waters Thar SFC-80 instrument equipped with UV Detector 40D by using CHIRALPAK-IG (30.0 mm x 250mm), 5 μ Column operating at 35 °C temperature, maintaining flow rate of 70 ml/min, using 60% CO₂ in super critical state & 40% of (100% MeOH) as Mobile phase, run this isocratic mixture upto 10.0 minutes and also maintained the isobaric condition of 110 bar at 220 nm wavelength.

SFC condition -2: SFC PREP PURIFICATION of CR635-22308-31-P (T.N-86) is running on PIC SOLUTIONS-175 instrument equipped with Knauer 40D Detector by using I CELLULOSE J(30.0 mm x 250mm), 5 μ Column operating at 35 °C temperature, maintaining flow rate of 80 ml/min ,using 60% CO₂ in super critical state & 40%[100% MeOH] as Mobile phase, Run this isocratic mixture up to 14.0 minutes and also maintained the isobaric condition of 100 bar at 275nm wavelength

Normal Phase Chiral Prep Methods:**NP Chiral Method 1:**

Chiral separation was done on Agilent 1200 series instrument. Column name: CHIRALPAK IG (250 X 4.6 mm) 5 μ . Operating at ambient temperature and flow rate is 1.0 mL/min. Mobile phase was mixture of 50% Hexane ,25% Ethyl alcohol and 25% Dichloromethane ,IP amine 0.1%, held this isocratic mixture run upto 25 min with wavelength of 296 nm.

NP Chiral Method 2:

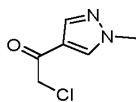
Chiral separation was done on Agilent 1200 series instrument. Column name: CHIRALPAK IG (250 X 21 mm) 5 μ . Operating at ambient temperature and flow rate is 21.0 mL/min. Mobile phase was mixture of 60% Hexane, 20% Dichloromethane and 20% Ethyl alcohol , held this isocratic mixture run upto 25 min with wavelength of 260 nm.

NP Chiral Method 3:

Chiral separation was done on Agilent 1200 series instrument. Column name: CHIRALPAK IG (250 X 21 mm) 5 μ . Operating at ambient temperature and flow rate is 21.0 mL/min. Mobile phase was a mixture of 70% Hexane, 15% DCM and 15% EtOH, held this isocratic mixture run up to 20min with wavelength of 308nm.

NP Chiral Method 4:

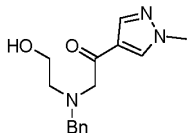
Chiral separation was done on Agilent 1200 series instrument. Column name: CHIRALPAK IC (250 X 20 mm) 5u. Operating at ambient temperature and flow rate is 18.0 mL/min. Mobile phase was mixture of 50% Hexane, 25% Dichloromethane and 25% Ethyl alcohol, held this isocratic mixture run up-to 25 min with wavelength of 328 nm.

Synthesis of intermediates:**10 Synthesis of 2-(1-methyl-1H-pyrazol-4-yl)morpholine (Intermediate I-1)****Step-1 - Preparation of 2-chloro-1-(1-methyl-1H-pyrazol-4-yl)ethan-1-one:**

In an oven-dried two neck round-bottom flask 4-bromo-1-methyl-1H-pyrazole (10 g, 62.2 mmol) was dissolved in dry THF (100 mL) and cooled to -78 °C. n-BuLi (40 mL, 93.2 mmol; 2.3 M in hexane) was slowly added to it under argon atmosphere and reaction was continued for at -78 °C for 1 h. A solution of 2-chloro-N-methoxy-N-methylacetamide (13 g, 93.2 mmol) in THF (40 mL) was then slowly added to it and reaction was prolonged for another one hour at 78 °C. After completion, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and followed by extracted with ethyl acetate. The combined organic layer was dried over MgSO₄ and concentrated into vacuo. The crude was purified by column chromatography on silica gel (100-200 mesh size) using 20-50% ethyl acetate in hexane to afford 2-chloro-1-(1-methyl-1H-pyrazol-4-yl)ethan-1-one (3.5 g, 35.5% yield) as off-white solid.

¹H NMR (400 MHz, DMSO D₆) δ 8.46 (s, 1H), 7.99 (s, 1H), 4.81 (s, 2H), 3.88 (s, 3H).

LCMS Condition A: Rt = 1.48 min. m/z 159.02 [M+H]⁺.

Step-2 - Preparation of 2-(benzyl(2-hydroxyethyl)amino)-1-(1-methyl-1H-pyrazol-4-yl)ethan-1-one:

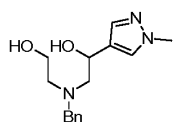
To a suspension of 2-chloro-1-(1-methyl-1H-pyrazol-4-yl)ethan-1-one (5 g, 31.6 mmol) in acetonitrile (50 mL) was added 2-(benzylamino)ethan-1-ol (5.7 g, 38.3 mmol) and

potassium carbonate (8.8 g, 63.2 mmol) and heated the reaction mixture at 60 °C for 16 h. After completion excess solvent was removed under reduced pressure and the residue was with cold water and followed by extracted with ethyl acetate. Combined organic layer was dried over sodium sulphate and concentrated into vacuo to obtain the crude. The crude was purified by column chromatography on silica gel (100-200 mesh size) using 40-60% ethyl acetate in hexane to afford 2-(benzyl(2-hydroxyethyl)amino)-1-(1-methyl-1H-pyrazol-4-yl)ethan-1-one (6 g, 69.5% yield) as yellow oil.

1H NMR (400 MHz, DMSO D6) δ 8.38 (s, 1H), 7.92 (s, 1H), 7.56-7.27 (m, 5H), 4.44 (t, J = 5.04 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.51-3.48 (m, 2H), 2.61 (t, J = 6.32 Hz, 2H),

LCMS Condition A: Rt = 0.46 min. m/z 274.3 [M+H]⁺.

Step-3 - Preparation of 2-(benzyl(2-hydroxyethyl)amino)-1-(1-methyl-1H-pyrazol-4-yl)ethan-1-ol:

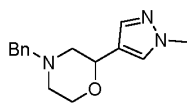


To a stirred solution of 2-(benzyl(2-hydroxyethyl)amino)-1-(1-methyl-1H-pyrazol-4-yl)ethan-1-one (5 g, 18.3 mmol) was in dry Methanol and cooled the reaction mixture at 0 °C. NaBH₄ (1.4 g, 3.7 mmol) was added to it portion-wise for 10 min and reaction was kept stirring for 15 min at 0 °C. Reaction was then warm to room temperature for 2 h. The reaction mixture was quenched with cold water and followed by extracted with dichloromethane. Combined organic layer was dried over sodium sulphate and concentrated into vacuo and purified by column chromatography on silica gel (100-200 mesh size) using 5% methanol in dichloromethane to afford 2-(benzyl(2-hydroxyethyl)amino)-1-(1-methyl-1H-pyrazol-4-yl)ethan-1-ol (3.0 g, 59.5% yield) as yellow sticky oil.

1H NMR (400 MHz, DMSO D6) δ 7.47 (s, 1H), 7.35-7.29 (m, 5H), 7.26 (s, 1H). 4.76 (d, J = 3.52 Hz, 1H), 4.62-4.58 (M, 1H), 4.38 (t, J = 5.36 Hz, 1H), 3.75 (s, 3H), 3.69 (d, J = 9.08 Hz, 2H), 3.48-3.4 (m, 2H), 2.63-2.54 (m, 3H).

LCMS Condition A: Rt = 0.39 min. m/z 276.3 [M+H]⁺.

Step-4 - Preparation of 4-benzyl-2-(1-methyl-1H-pyrazol-4-yl)morpholine (as HCl salt):



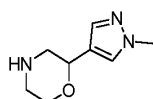
A mixture of afford 2-(benzyl(2-hydroxyethyl)amino)-1-(1-methyl-1H-pyrazol-4-yl)ethan-1-ol (2 g, 7.27 mmol) and aqueous HCl (6N, 20.0 mL) was heated to reflux for 2 h. The reaction mixture was evaporated under reduced pressure and the residue was washed with ether and dried under vacuum to afford 4-benzyl-2-(1-methyl-1H-pyrazol-4-yl)morpholine, HCl salt (1.7 g, 90.8% yield) as yellow sticky solid.

This material was forwarded for the next step without further purification.

¹H NMR (400 MHz, DMSO D6) δ 12.05 (bs, 1H), 7.76 (s, 1H), 7.68-7.63 (m, 2H), 7.46-7.43 (m, 3H), 7.41 (s, 1H), 4.95 (d, J = 10.0 Hz, 1H), 4.34 (s, 2H), 4.08-4.0 (m, 2H), 3.78 (s, 3H), 3.32 (d, J = 11.8 Hz, 1H), 3.21 (d, J = 12.12 Hz, 1H), 3.15-3.07 (m, 2H).

LCMS Condition A: Rt = 0.40 min. m/z 258.3 [M+H]⁺.

Step-5 - Preparation of 2-(1-methyl-1H-pyrazol-4-yl)morpholine, HCl salt (Intermediate-I-1):



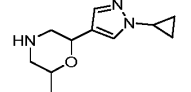
An ethanolic (50 mL) solution of 4-benzyl-2-(1-methyl-1H-pyrazol-4-yl)morpholine (2 g, 7.8 mmol) was taken in a par-autoclave vessel (100 mL) and purged it with argon. Pd(OH)₂ (0.5 g; 10% w/w) was added to it and reaction mixture was hydrogenated (30 psi) for 18 h at rt. The reaction mixture was filtered through a pad of celite and washed with ethanol. Evaporation of the solvent under reduced pressure afforded 2-(1-methyl-1H-pyrazol-4-yl)morpholine, HCl salt (1.2 g, 92.2% yield) as sticky solid.

¹H NMR (400 MHz, DMSO D6) δ 9.82 (bs, 1H), 9.64 (bs, 1H), 7.77 (s, 1H), 7.45 (s, 1H), 4.75 (d, J = 9.68 Hz, 1H), 3.98-3.86 (m, 2H), 3.78 (s, 3H), 3.31 (d, J = 11.32 Hz, 1H), 3.31 (d, J = 11.32 Hz, 1H), 3.18 3.31 (d, J = 11.36 Hz, 1H), 3.15-2.85 (m, 2H).

LCMS Condition A: Rt = 0.70 min. m/z 168.1 [M+H]⁺.

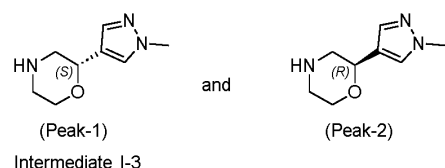
The intermediates I-2 & I-14 were synthesized using similar procedures described for Intermediate I-1 in 1-5 steps.

Intermediates #	Structure	Name	LCMS/NMR	Description
I-2		2,2-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)morpholine (HCl salt)	Condition B: Rt = 1.24 min. m/z 196.23 [M+H] ⁺	Yellow gum

I-14		2-(1-cyclopropyl-1H-pyrazol-4-yl)-6-methylmorpholine	Condition B: Rt = 0.44 min. m/z 208.23 [M+H] ⁺	Light yellow gum
-------------	---	--	--	------------------

Synthesis of (S)-2-(1-methyl-1H-pyrazol-4-yl)morpholine, HCl salt (Intermediate I-3)

Step-1 - Chiral separation of (S)-2-(1-methyl-1H-pyrazol-4-yl)morpholine, HCl salt (Intermediate I-3) and (R)-2-(1-methyl-1H-pyrazol-4-yl)morpholine:



Chiral separation of 2-(1-methyl-1H-pyrazol-4-yl)morpholine (3 g, 0.086 mmol) was done by SFC (SFC condition-1) to afford (S)-2-(1-methyl-1H-pyrazol-4-yl)morpholine (730.2 mg, 24.3% yield; eluted first, assigned as Intermediate I-3 (Peak-1) as light yellow gum and (R)-2-(1-methyl-1H-pyrazol-4-yl)morpholine (762.3 mg, 25.4% yield eluted later, assigned as Peak-2 as light yellow gum. Stereochemistry of both peaks were assigned based on the report in WO 2021226135.

Intermediate I-3 (Peak1): ¹H NMR (400 MHz, DMSO-d₆) δ 9.82 (brs, 1H), 9.64 (brs, 1H), 7.77 (s, 1H), 7.45 (s, 1H), 4.75 (d, J = 9.68 Hz, 1H), 3.98-3.86 (m, 2H), 3.78 (s, 3H), 3.31 (d, J = 11.32 Hz, 1H), 3.31 (d, J = 11.32 Hz, 1H), 3.18 3.31 (d, J = 11.36 Hz, 1H), 3.15-2.85 (m, 2H).

LCMS Condition A: Rt = 0.70 min. m/z 168.1 [M+H]⁺.

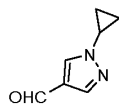
Peak-2: ¹H NMR (400 MHz, DMSO-d₆) δ 9.82 (brs, 1H), 9.64 (brs, 1H), 7.77 (s, 1H), 7.45 (s, 1H), 4.75 (d, J = 9.68 Hz, 1H), 3.98-3.86 (m, 2H), 3.78 (s, 3H), 3.31 (d, J = 11.32 Hz, 1H), 3.31 (d, J = 11.32 Hz, 1H), 3.18 3.31 (d, J = 11.36 Hz, 1H), 3.15-2.85 (m, 2H).

LCMS Condition A: Rt = 0.70 min. m/z 168.1 [M+H]⁺.

Analytical chiral HPLC: CHIRALPAK AD-H (4.6 x 250 mm), 5μ Mobile Phase: 0.5%DEA in EtOH Flow Rate: 4.0 ml/min. Solubility: MeOH, Rt = 2.4 min for Peak1 and Rt = 3.02 min for Peak2.

Synthesis of 1-cyclopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyran-2-yl)-1H-pyrazole (Intermediate I-4)

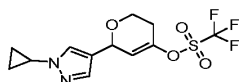
Step-1 - Preparation of 1-cyclopropyl-1H-pyrazole-4-carbaldehyde:



To a stirred solution of 1H-pyrazole-4-carbaldehyde (5 g, 52.1 mmol) in DCE (200 mL) were added cyclopropyl boronic acid (8.9 g, 104.2 mmol), 2,2'-bipyridyl (8.9 g, 57.3 mmol) and sodium carbonate (15.8 g, 114.6 mmol) under oxygen atmosphere. Copper acetate (10.4 g, 57.3 mmol) was added to the reaction mixture. Resulting mixture was heated to 70 °C for 16 h. Reaction mixture was filtered through a short pad of celite, washed with methanol and concentrated under reduced pressure. Crude residue was extracted with ethyl acetate, washed with brine, dried over sodium sulphate, and concentrated under reduced pressure. Crude product was purified by combi-flash chromatography (10% ethyl acetate-hexane) to afford 1-cyclopropyl-1H-pyrazole-4-carbaldehyde (6 g, 84.1% yield) as colourless liquid.

LCMS Condition A: Rt = 0.93 min. m/z 137.2 [M+H]⁺.

Step-2 - Preparation of 6-(1-cyclopropyl-1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate:

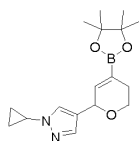


To a stirred solution of 1-cyclopropyl-1H-pyrazole-4-carbaldehyde (3.5 g, 25.7 mmol) in DCM (80 mL) at 0 °C was added but-3-yn-1-ol (3.2 ml, 38.6 mmol) followed by addition of triflic acid (5.7 mL, 64.3 mmol). Resulting mixture was stirred at rt for 3 h. Reaction mixture was quenched with saturated aqueous sodium bicarbonate solution, extracted with DCM, and concentrated under reduced pressure. Crude material was purified by column chromatography (20-40% ethyl acetate in hexane) to afford 6-(1-cyclopropyl-1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate (3 g, 34.2% yield) as brown gum.

¹H NMR (400 MHz, DMSO-d₆) δ 7.74 (s, 1H), 7.36 (s, 1H), 6.20 (s, 1H), 5.32 (s, 1H), 3.91-3.64 (m, 3H), 2.49-2.42 (m, 2H), 1.11-0.88 (m, 4H).

LCMS Condition B: Rt = 3.35 min. m/z 339 [M+H]⁺

Step-3 - Preparation of 1-cyclopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyran-2-yl)-1H-pyrazole (Intermediate I-4) :



To a stirred solution of 6-(1-cyclopropyl-1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate (1 g, 2.96 mmol) and Bis(pinacolato)diboron (1.2 g, 4.4 mmol) in 1,4-dioxane (15 mL) were added potassium acetate (1.2 g, 11.8 mmol) and degassed with argon. PdCl₂(dppf). DCM (0.2 g, 0.3 mmol) was added under inert atmosphere. Resulting mixture was heated at 80 °C for 2 h. Reaction mixture was diluted with ethyl acetate, filtered through a short pad of celite and washed with ethyl acetate. Combined organic layer was concentrated under reduced pressure and crude product was purified by column chromatography (30% ethyl acetate in hexane) to afford 1-cyclopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyran-2-yl)-1H-pyrazole (0.5 g, 53% yield) as solid.

LCMS Condition B : Rt = 3.19 min. m/z 317 [M+H]⁺.

Following intermediates I-5 and I-6 were synthesized using similar procedures described for Intermediate I-4 two steps (step-2 & 3) using corresponding commercial aldehyde and alkyne.

Intermediates #	Structure	Name	SM1	SM2
I-5		1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyran-2-yl)-1H-pyrazole	1-methyl-1H-pyrazole-4-carbaldehyde	but-3-yn-1-ol
I-6		2-methoxy-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyran-2-yl)pyridine	2-methoxyisonicotinaldehyde	but-3-yn-1-ol

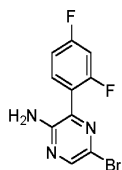
The following table describes analytical data analysis and yield information of intermediates I-5 & I-6.

Intermediates #	LCMS/NMR	Description	Yield%
I-5	LCMS Condition D : Rt = 3.07 min. m/z 291.2 [M+H] ⁺ .	Yellow gum	46.2

I-6	LCMS Condition D : Rt = 3.07 min. m/z 318.2 [M+H] ⁺ .	Brown gum	50.7
-----	---	-----------	------

Synthesis of 7-bromo-3-chloro-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one (Intermediate I-7):

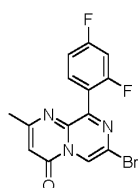
5 Step-1- Preparation of 5-bromo-3-(2,4-difluorophenyl)pyrazin-2-amine:



To a stirred suspension of 3,5-dibromopyrazin-2-amine (10 g, 39.5 mmol) and (2,4-difluorophenyl)boronic acid (6.2 g, 39.5 mmol) in toluene (225 mL), ethanol (50 mL) and water (40 mL) was added K₃PO₄ (16.8 g, 17.1 mmol) and purged with argon. Pd(PPh₃)₄ (2.1 g, 1.9 mmol) was added under inert atmosphere. Resulting mixture was heated at 100 °C for 16 h. Reaction mixture was then passed through a short pad of celite and washed with ethyl acetate. Organic layer was dried over sodium sulphate, filtered, and concentrated under reduced pressure. Crude product was purified by combi flash chromatography (5-15% ethyl acetate-hexane) to afford 5-bromo-3-(2,4-difluorophenyl)pyrazin-2-amine (8 g, 70.7% yield) as yellow solid.

LCMS Condition A: Rt = 2.04 min. m/z 286.01 [M+H]⁺

Step-2 - Preparation of 7-bromo-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one:



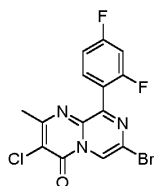
To a stirred solution of 5-bromo-3-(2,4-difluorophenyl)pyrazin-2-amine (1.0 g, 3.5 mmol) and methyl 3-oxobutanoate (2.0 g, 17.5 mmol) in diphenyl ether (6 mL) was added BiCl₃ (662 mg, 2.1 mmol) in portion at RT under nitrogen atmosphere. The reaction mixture was stirred at 150 °C for 4 h. The reaction mixture was diluted with DCM (30 mL), and it was quenched with cold saturated sodium bicarbonate solution (25 mL). Reaction mass was filtered over celite pad, and the organic layer was washed with saturated sodium bicarbonate solution and brine, dried over anhydrous Na₂SO₄, and then evaporated

under reduced pressure to get the crude. Crude product was purified by combi flash (2-10% ethyl acetate in hexane) to get 7-bromo-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one (300 mg, 24.3% yield) as off-white solid.

LCMS Condition A: Rt = 2.32 min. m/z 352.3 [M+H]⁺

5

Step-3 - Preparation of 7-bromo-3-chloro-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one (Intermediate I-7):



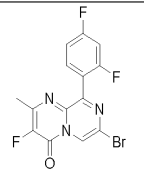
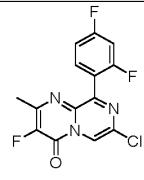
To a stirred solution of 7-bromo-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one (700 mg, 2 mmol) in DMF (10 mL) was added NCS (398.2 mg, 3 mmol) at room temperature. Resulting mixture was heated at 90 °C for 16 h. Reaction mixture was poured into cold water and extracted with ethyl acetate. Combined organic layer was dried over sodium sulphate, filtered, and concentrated under reduced pressure. Crude product was purified by combi flash chromatography (5% ethyl acetate-hexane) to afford 7-bromo-3-chloro-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one (450 mg, 58.6% yield) as yellow solid.

15

LCMS Condition A: Rt = 2.33 min. m/z 386.04 [M+H]⁺

20

Following intermediates I-8 to I-12 were synthesized by using similar procedures described for Intermediate I-7

Intermediates #	Structure	Name	Starting materials	Remarks
I-8		7-bromo-9-(2,4-difluorophenyl)-3-fluoro-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	Same SMs of I-7 used in the 3 steps	At step-3, fluorination was done using selectfluor, MeCN, 75 °C, 3h condition.
I-9		7-chloro-9-(2,4-difluorophenyl)-3-fluoro-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	At Step-1: 3-bromo-5-chloropyrazin-2-amine was used.	At step-3, fluorination was done using selectfluor, MeCN, 75 °C, 3h condition.

I-10		7-bromo-3-chloro-9-(2-fluoro-4-methoxyphenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	At Step-1: (2-fluoro-4-methoxyphenyl)boronic acid was used.	
I-11		4-(7-bromo-3-fluoro-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile	At Step-1: (2-fluoro-4-cyanophenyl)boronic acid was used.	At step-3, fluorination was done using selectfluor, MeCN, 75 °C, 3h condition.
I-12		7-bromo-3-chloro-9-(2,4-difluorophenyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	SM used at Step-1: 3,5-dibromopyridin-2-amine. Remaining all same.	At step-3, chlorination was done using NCS, PIDA, DCM, 40 °C, 16h condition.

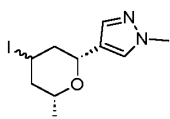
The following table describes analytical data analysis and yield information of intermediates I-8 to I-12.

Intermediates #	LCMS/NMR	Description	Yield%
I-8	Condition A: Rt = 2.09 min. m/z 370.3 [M+H] ⁺	Off-white solid	43
I-9	Condition A: Rt = 2.13 min. m/z 326.3 [M+H] ⁺	Off-white solid	40
I-10	Condition A: Rt = 2.21 min. m/z 398.2 [M+H] ⁺	White solid	46
I-11	Condition A: Rt = 2.15 min. m/z 333.2 [M+H] ⁺	Off-white solid	51
I-12	Condition A: Rt = 2.35 min. m/z 387.3 [M+H] ⁺	Off-white solid	38

5

Synthesis of 4-((2R,6R)-4-iodo-6-methyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazole (Intermediate I-13):

Step-1 – Preparation of 4-((2R,6R)-4-iodo-6-methyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazole (Intermediate I-13):



10

To a stirred solution of 1-methyl-1H-pyrazole-4-carbaldehyde (1 g, 9.1 mmol), (2R)-pent-4-en-2-ol (0.93 g, 10.8 mmol) and tetrabutylammonium iodide (2.1 g, 10.9 mmol) in DCM (20 mL) was added trimethylsilyl trifluoromethanesulfonate (2 mL, 10.8 mmol) dropwise at rt and stirred for 16 h. After completion, reaction mixture was concentrated under reduced pressure, diluted with saturated Na₂S₂O₃ solution, and extracted with EtOAc. Combined organic part was washed with water, brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Crude product was purified by combi flash column chromatography eluted at (50% EA in Hexane) to afford 4-((2R,6R)-4-iodo-6-methyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazole (0.7 g, 25% yield) as light-yellow liquid.

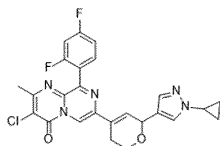
LCMS Condition A: Rt = 2.01 min. m/z 307.13 [M+H]⁺.

Synthesis of Examples

Examples 1 to 8

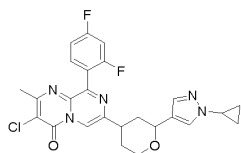
Example 1: 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one

Step-1 - Preparation of 3-chloro-7-(6-(1-cyclopropyl-1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one:



To a stirred solution of 7-bromo-3-chloro-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one **[I-7]** (500 mg, 1.3 mmol) and 1-cyclopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyran-2-yl)-1H-pyrazole **[I-4]** (817.9 mg, 2.6 mmol) in 1,4-dioxane (10 mL), and water (2.5 mL) was added K₃PO₄ (822.6 mg, 3.9 mmol) and purged with argon. Pd-118 (42.1 mg, 0.06 mmol) was added under inert atmosphere. Resulting mixture was heated at 90 °C for 0.5 h. Reaction mixture was then passed through a short pad of celite and washed with ethyl acetate. Organic layer was dried over sodium sulphate, filtered, and concentrated under reduced pressure. Crude product was purified by combi flash chromatography (40-60% ethyl acetate-hexane) to afford 3-chloro-7-(6-(1-cyclopropyl-1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one (300 mg, 46.7% yield) as light yellow solid. LCMS Condition A: Rt = 3.33 min. m/z 496.13 [M+H]⁺

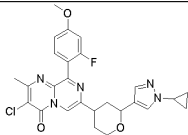
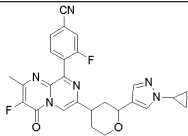
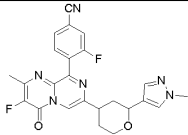
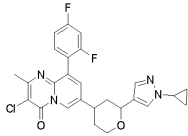
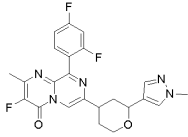
Step-2 - Preparation of 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one:



- 5 To a degassed solution 3-chloro-7-(6-(1-cyclopropyl-1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one (200 mg, 0.4 mmol) in THF (20 mL) NaOAc (66 mg, 0.8 mmol) and acetic acid (0.05 mL, 0.8 mmol) were added and stirred for 10 min under inert atmosphere. Pd(OH)₂ on carbon (20%, 84.7 mg) was added and degassed again. The resulting mixture was stirred under
- 10 hydrogen balloon pressure at rt for 3 h. Reaction mixture was filtered through a short pad of celite and washed with ethyl acetate. Combined filtrate was concentrated under reduced pressure and crude product was purified by prep-HPLC (Prep-B) to afford 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one (104 mg, 51.2% yield) as
- 15 off-white solid.
- ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.58 (s, 1H), 7.75-7.72 (m, 2H), 7.43 (t, *J*=10.0 Hz, 1H), 7.37 (s, 1H), 7.27 (t, *J*= 8.4 Hz, 1H), 4.45 (d, *J*=11.2 Hz, 1H), 4.09 - 4.06 (m, 1H), 3.69 - 3.63 (m, 2H), 3.28-3.27 (m, 1H), 2.45 (s, 3H), 2.11 (d, *J*= 11.6 Hz, 1H), 1.87 - 1.77 (m, 3H), 1.00 - 0.98 (m, 2H), 0.91 - 0.89 (m, 2H).
- 20 LCMS Condition C: Rt = 3.02 min. *m/z* 498.39 [M+H]⁺

Examples 2-8 were synthesized by using similar procedures described for Example 1.

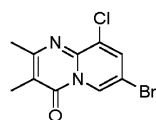
Ex. No.	Structure	Name	Step-1 SMs and remarks	Purification method (Step-2)
2		7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-3-fluoro-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	I-8 & I-4.	Prep-B method
3		9-(2,4-difluorophenyl)-3-fluoro-7-(2-(2-methoxyphenyl)-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	I-9 & I-6	Prep-A method

		yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one		
4		3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2-fluoro-4-methoxyphenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	I-10 & I-4	Prep-B method
5		4-(7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-3-fluoro-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile	I-11 & I-4	Prep-C method
6		3-fluoro-4-(3-fluoro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile	I-11 & I-5	Prep-C method
7		3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	I-12 & I-4	Prep-C method
8		9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one	I-9 & I-5	Prep-B method

The following table describes analytical data analysis and yield information of examples 2-8.

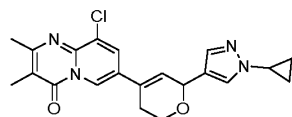
Ex. No.	¹ H-NMR	LCMS	Description	Yield %
2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.57 (s, 1H), 7.75-7.70 (m, 2H), 7.43 (t, <i>J</i> = 9.2 Hz, 1H), 7.37 (s, 1H), 7.26 (t, <i>J</i> =7.6 Hz, 1H), 4.44 (d, <i>J</i> =10.8 Hz, 1H), 4.08 - 4.06 (m, 1H), 3.69 - 3.63 (m, 2H), 3.28-3.27 (m, 1H), 2.37 (s, 3H), 2.14-2.11 (m, 1H), 1.90 - 1.76 (m, 3H), 0.98 - 0.96 (m, 2H), 0.93 - 0.89 (m, 2H).	Condition A: Rt = 3.05 min. m/z 482.42 [M+H] ⁺	White solid	37
3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.57 (s, 1H), 8.10 (d, <i>J</i> =5.2 Hz, 1H), 7.73-7.67 (m, 1H), 7.42 (d, <i>J</i> =10.0 Hz, 1H), 7.25 (t, <i>J</i> =8.4 Hz, 1H), 6.97 (d, <i>J</i> =4.8 Hz, 1H), 6.77 (s, 1H), 4.54 (d, <i>J</i> =10.8 Hz, 1H), 4.22 - 4.19 (m, 1H), 3.82 (s, 3H), 3.69 - 3.63 (m, 2H), 3.74-3.69 (m, 1H), 3.38-3.37 (m, 1H), 2.37 (s, 3H), 2.21-2.18 (m, 1H), 1.92 - 1.86 (m, 2H), 1.67-1.58 (m, 1H).	Condition A: Rt = 3.19 min. m/z 483.4 [M+H] ⁺	White solid	42
4	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.53 (s, 1H), 7.72 (s, 1H), 7.62 (t, <i>J</i> =8.4 Hz, 1H), 7.37 (s, 1H), 7.00-6.92 (m, 2H), 4.45 (d, <i>J</i> =10.8 Hz, 1H), 4.08 - 4.06 (m, 1H), 3.86 (s, 3H), 3.69 - 3.63 (m, 2H), 3.28-3.27 (m, 1H), 2.55 (s, 3H), 2.14-2.11 (m, 1H), 1.87 - 1.77 (m, 3H), 0.98 - 0.96 (m, 2H), 0.91 - 0.89 (m, 2H).	Condition A: Rt = 2.93 min. m/z 510.4 [M+H] ⁺	White solid	38
5	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (s, 1H), 8.05 (d, <i>J</i> =10.0 Hz, 1H), 7.89-7.83 (m, 2H), 7.72 (s, 1H), 7.37 (s, 1H), 4.45 (d, <i>J</i> =10.8 Hz, 1H), 4.09 - 4.05 (m, 1H), 3.69 - 3.63 (m, 2H), 3.28-3.27 (m, 1H), 2.36 (s, 3H), 2.14-2.11 (m, 1H), 1.87 - 1.77 (m, 3H), 0.98 - 0.96 (m, 2H), 0.92 - 0.89 (m, 2H).	Condition A: Rt = 2.77 min. m/z 489.36 [M+H] ⁺	White solid	43
6	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (s, 1H), 8.04 (d, <i>J</i> =10.0 Hz, 1H), 7.89-7.83 (m, 2H), 7.64 (s, 1H), 7.36 (s, 1H), 4.46 (d, <i>J</i> =10.8 Hz, 1H), 4.09 - 4.05 (m, 1H), 3.77 (s, 3H), 3.69 - 3.64 (m, 1H), 3.36-3.34 (m, 1H), 2.36 (s, 3H), 2.14-2.11 (m, 1H), 1.90 - 1.76 (m, 3H).	Condition A: Rt = 2.71 min. m/z 463.37 [M+H] ⁺	White solid	29
7	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.83 (d, <i>J</i> =1.2 Hz, 1H), 8.11 (d, <i>J</i> =1.2 Hz, 1H), 7.73 (s, 1H), 7.63-7.57 (m, 1H), 7.42-7.37 (m, 2H), 7.25-7.20 (m, 1H), 4.42 (d, <i>J</i> =9.6 Hz, 1H), 4.09-4.05 (m, 1H), 3.67-	Condition C: Rt = 2.98min. m/z 497.44 [M+H] ⁺	Off-white solid	38

	3.62 (m, 2H), 3.23-3.21 (m, 1H), 2.40 (s, 3H), 2.13-2.09 (m, 1H), 1.88-1.75 (m, 3H), 0.98-0.95 (m, 2H), 0.93-0.91 (m, 2H).			
8	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.57 (s, 1H), 7.76-7.70 (m, 1H), 7.64 (s, 1H), 7.46-7.40 (m, 1H), 7.37 (s, 1H), 7.29-7.24 (m, 1H), 4.46 (d, J=10.8 Hz, 1H), 4.09-4.06 (m, 1H), 3.77 (s, 3H), 3.70-3.64 (m, 1H), 3.31-3.25 (m, 1H), 2.37 (s, 3H), 2.14-2.07 (m, 1H), 1.91-1.77 (m, 3H).	Condition C: Rt = 2.79 min. m/z 456.37 [M+H] ⁺ .	White solid	42

Example 9**9-(4-chloro-2-fluorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one:****5 Step-1 - Preparation of 7-bromo-9-chloro-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one**

In a sealed tube, 5-bromo-3-chloropyridin-2-amine (1 gm, 4.8 mmol), methyl 2-methyl-3-oxobutanoate (0.6 ml, 4.8 mmol) and BiCl₃ (76 mg, 0.2 mmol) were mixed. The resulting mixture was heated at 130 °C for 16 h. Reaction mixture was then diluted with DCM, washed with NaHCO₃ solution, brine, dried over sodium sulphate, filtered, and concentrated under reduced pressure. Crude product was purified by combi flash chromatography (5% methanol-DCM) to get 7-bromo-9-chloro-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (1.4 g, yield 57.7 %) as orange solid.

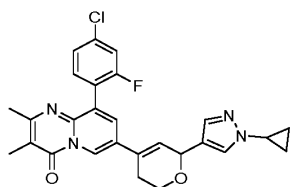
LCMS Condition A: Rt = 1.96 min. m/z 288.98 [M+H]⁺

Step-2 - Preparation of 9-chloro-7-(6-(1-cyclopropyl-1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a suspension of 7-bromo-9-chloro-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (650 mg, 2.3 mmol) and 1-cyclopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyran-2-yl)-1H-pyrazole [**I-4**] (2.1 gm, 6.8 mmol) in 1,4-dioxane (30 mL) and water (8 mL) was added K₃PO₄ (958.5 mg, 4.5 mmol) and purged the reaction

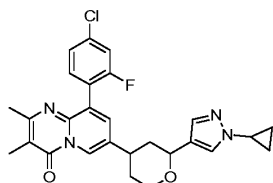
mixture with argon for 5 min. Pd118 (73.7 mg, 0.11 mmol) was then added to it under inert atmosphere. Resulting mixture was heated at 90 °C for 4 h. Reaction mixture was then passed through a short bed of celite and washed with ethyl acetate. dried over sodium sulphate, filtered and concentrated under reduced pressure. Crude product was purified by combi flash chromatography (50-95% ethyl acetate-hexane) to get 9-chloro-7-(6-(1-cyclopropyl-1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (700 mg, 78.1% yield) as yellowish solid.
LCMS Condition A: Rt = 1.87 min. m/z 397.28 [M+H]⁺.

Step-3 - Preparation of 9-(4-chloro-2-fluorophenyl)-7-(6-(1-cyclopropyl-1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one



To a stirred solution of 9-chloro-7-(6-(1-cyclopropyl-1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (400 mg, 1 mmol) and (4-chloro-2-fluorophenyl)boronic acid (263 mg, 1.5 mmol) in 1,4-dioxane (16 mL) and water (4 mL) was added K₃PO₄ (428 mg, 2 mmol) and purged the reaction mixture with argon for 5 min. Pd118 (32.9 mg, 0.05 mmol) was then added to it under inert atmosphere. Resulting mixture was heated at 90 °C for 2 h. Reaction mixture was then passed through a short bed of celite and washed with ethyl acetate. dried over sodium sulphate, filtered, and concentrated under reduced pressure. Crude product was purified by combi flash chromatography (50-95% ethyl acetate-hexane) to get grey solid 9-(4-chloro-2-fluorophenyl)-7-(6-(1-cyclopropyl-1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (250 mg, 50.4% yield) as grey solid.
LCMS Condition A: Rt = 2.01 min. m/z 491.4 [M+H]⁺.

Step-4 - Preparation of 9-(4-chloro-2-fluorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (Example 9)



- To a degassed solution 9-(4-chloro-2-fluorophenyl)-7-(6-(1-cyclopropyl-1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (100 mg, 0.2 mmol) was dissolved in 1,4-Dioxane (20 mL) was added sodium acetate (60 mg) and acetic acid (0.05 mL) stirred for 10 min under inert atmosphere. Pd(OH)₂ on carbon (20%, 40 mg) was added and degassed again. Resulting mixture was stirred under hydrogen balloon pressure at rt for 3 h. The reaction mixture was filtered through a short pad of celite and washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure. The crude material was purified by reverse phase prep HPLC to afford 9-(4-chloro-2-fluorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (55 mg, 54.7% yield) as white solid.
- ¹H NMR (400 MHz, DMSO-d₆) δ 8.81 (s, 1H), 7.72 (s, 1H), 7.57-7.55 (m, 2H), 7.41-7.39 (m, 2H), 4.45-4.42 (m, 1H), 4.08-4.05 (m, 1H), 3.67-3.64 (m, 2H), 3.19-3.11 (m, 1H), 2.28 (s, 3H), 2.13-2.09 (m, 4H), 1.87-1.74 (m, 3H), 0.97-0.91 (m, 4H).
- LCMS Condition A: Rt = 2.20 min. m/z 493.23[M+H]⁺.

The following table describes information regarding separation of enantiomers Example 1A/1B to 9A/9B

Target #	Structure	Name	Starting material	Chiral Separation method
Ex. 1A (Peak-1)		3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 1	NP Chiral Method 2
Ex. 1B (Peak-2)		3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one		Peak 1 & Peak 2 Absolute stereochemistry unknown, arbitrary assignment
Ex. 2A (Peak-1)		7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-3-fluoro-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 2	SFC condition-2

		methyl-4H-pyrazino[1,2-a]pyrimidin-4-one		Peak 1 & Peak 2 Absolute stereochemistry unknown, arbitrary assignment
Ex. 2B (Peak-2)		7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-3-fluoro-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one		
Ex. 3A (Peak-1)		9-(2,4-difluorophenyl)-3-fluoro-7-((2R,4S)-2-(2-methoxypyridin-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one		NP Chiral Method 2
Ex. 3B (Peak-2)		9-(2,4-difluorophenyl)-3-fluoro-7-((2S,4R)-2-(2-methoxypyridin-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 3	Peak 1 & Peak 2 Absolute stereochemistry unknown, arbitrary assignment
Ex. 4A (Peak-1)		3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2-fluoro-4-methoxyphenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one		NP Chiral Method 4
Ex. 4B (Peak-2)		3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2-fluoro-4-methoxyphenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 4	Peak 1 & Peak 2 Absolute stereochemistry unknown, arbitrary assignment
Ex. 5A (Peak-1)		4-(7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-3-fluoro-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile		SFC condition-2
Ex. 5B (Peak-2)		4-(7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-3-fluoro-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile	Example 5	Peak 1 & Peak 2 Absolute stereochemistry unknown, arbitrary assignment
Ex. 6A (Peak-1)		3-fluoro-4-(3-fluoro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile	Example 6	SFC condition-2

Ex. 6B (Peak-2)		3-fluoro-4-(3-fluoro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile		Peak 1 & Peak 2 Absolute stereochemistry unknown, arbitrary assignment
Ex. 7A (Peak-1)		3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	Example 7	NP Chiral Method 2 Peak 1 & Peak 2 Absolute stereochemistry unknown, arbitrary assignment
Ex. 7B (Peak-2)		3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one		
Ex. 8A (Peak-1)		9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 8	SFC condition -2 Peak 1 & Peak 2 Absolute stereochemistry unknown, arbitrary assignment
Ex. 8B (Peak-2)		9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one		
Ex. 9A (Peak-1)		9-(4-chloro-2-fluorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one	Example 9	NP Chiral Method 1 Peak 1 & Peak 2 Absolute stereochemistry unknown, arbitrary assignment
Ex. 9B (Peak-2)		9-(4-chloro-2-fluorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one		

Following table describes analytical data analysis and yield information of examples 1A/1B to examples 9A/9B.

Target #	1H-NMR	LCMS	Analytical chiral	Description	Yield %
----------	--------	------	-------------------	-------------	---------

			HPLC		
Ex. 1A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 7.75-7.72 (m, 2H), 7.43 (t, <i>J</i> =10.0 Hz, 1H), 7.37 (s, 1H), 7.27 (t, <i>J</i> =8.4 Hz, 1H), 4.45 (d, <i>J</i> =11.2 Hz, 1H), 4.09 - 4.06 (m, 1H), 3.69 - 3.63 (m, 2H), 3.28-3.27 (m, 1H), 2.45 (s, 3H), 2.11 (d, <i>J</i> =11.6 Hz, 1H), 1.87 - 1.77 (m, 3H), 1.00 - 0.98 (m, 2H), 0.91 - 0.89 (m, 2H).	Condi on C: Rt = 3.02 min. m/z 498.39 [M+H] ⁺	Analytical chiral HPLC by SFC: I- Cellulose J (250X4.6) mm, 5μ solvent: 0.3% IPamine in MeOH Flow Rate = 5 ml/min.using 50% CO ₂ Solubility: MeOH, Rt = 3.1 min for Peak 1 and Rt = 4.59 min for Peak 2.	White solid	22
Ex. 1B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 7.75-7.72 (m, 2H), 7.43 (t, <i>J</i> =10.0 Hz, 1H), 7.37 (s, 1H), 7.27 (t, <i>J</i> =8.4 Hz, 1H), 4.45 (d, <i>J</i> =11.2 Hz, 1H), 4.09 - 4.06 (m, 1H), 3.69 - 3.63 (m, 2H), 3.28-3.27 (m, 1H), 2.45 (s, 3H), 2.11 (d, <i>J</i> =11.6 Hz, 1H), 1.87 - 1.77 (m, 3H), 1.00 - 0.98 (m, 2H), 0.91 - 0.89 (m, 2H).	Condi on C: Rt = 3.02 min. m/z 498.39 [M+H] ⁺		White solid	22
Ex. 2A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.57 (s, 1H), 7.75-7.70 (m, 2H), 7.43 (t, <i>J</i> =9.2 Hz, 1H), 7.37 (s, 1H), 7.26 (t, <i>J</i> =7.6 Hz, 1H), 4.44 (d, <i>J</i> =10.8 Hz, 1H), 4.08 - 4.06 (m, 1H), 3.69 - 3.63 (m, 2H), 3.28-3.27 (m, 1H), 2.37 (s, 3H), 2.14-2.11 (m, 1H), 1.90 - 1.76 (m, 3H), 0.98 - 0.96 (m, 2H), 0.93 - 0.89 (m, 2H).	Condi on A: Rt = 3.05 min. m/z 482.42 [M+H] ⁺	Analytical chiral HPLC: CHIRALPAK IC (250X4.6) mm, 5μ M.P.- Hexane/EA/Et OH/IPamine 50/25/25/0.1 Flow Rate - 1.0 ml/min. Solubility: MeOH, Rt = 9.93 min for Peak 1 and Rt = 14.27 min for Peak 2.	White solid	22
Ex. 2B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.57 (s, 1H), 7.75-7.70 (m, 2H), 7.43 (t, <i>J</i> =9.2 Hz, 1H), 7.37 (s, 1H), 7.26 (t, <i>J</i> =7.6 Hz, 1H), 4.44 (d, <i>J</i> =10.8 Hz, 1H), 4.08 - 4.06 (m, 1H), 3.69 - 3.63 (m, 2H), 3.28-3.27 (m, 1H), 2.37 (s, 3H), 2.14-2.11 (m, 1H), 1.90 - 1.76 (m, 3H), 0.98 - 0.96 (m, 2H), 0.93 - 0.89 (m, 2H).	Condi on A: Rt = 3.05 min. m/z 482.42 [M+H] ⁺		White solid	21
Ex. 3A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.57 (s, 1H), 8.10 (d, <i>J</i> =5.2 Hz, 1H), 7.73-7.67 (m, 1H),	Condi on A: Rt = 3.19	Analytical chiral HPLC: CHIRALPAK	White solid	25

	7.42 (d, $J=10.0$ Hz, 1H), 7.25 (t, $J=8.4$ Hz, 1H), 6.97 (d, $J=4.8$ Hz, 1H), 6.77 (s, 1H), 4.54 (d, $J=10.8$ Hz, 1H), 4.22 - 4.19 (m, 1H), 3.82 (s, 3H), 3.69 - 3.63 (m, 2H), 3.74-3.69 (m, 1H), 3.38-3.37 (m, 1H), 2.37 (s, 3H), 2.21-2.18 (m, 1H), 1.92 - 1.86 (m, 2H). 1.67-1.58 (m, 1H).	min. m/z 483.4 [M+H] ⁺	IG (250X4.6) mm, 5 μ M.P.-Hexane/EA/EtOH/IPAmine 50/25/25/0.1 Flow Rate - 1.0 ml/min. Solubility: MeOH, R_t = 6.93 min for Peak 1 and R_t = 7.87 min for Peak 2.		
Ex. 3B (Peak-2)	¹ H NMR (400 MHz, DMSO- d_6) δ 8.57 (s, 1H), 8.10 (d, $J=5.2$ Hz, 1H), 7.73-7.67 (m, 1H), 7.42 (d, $J=10.0$ Hz, 1H), 7.25 (t, $J=8.4$ Hz, 1H), 6.97 (d, $J=4.8$ Hz, 1H), 6.77 (s, 1H), 4.54 (d, $J=10.8$ Hz, 1H), 4.22 - 4.19 (m, 1H), 3.82 (s, 3H), 3.69 - 3.63 (m, 2H), 3.74-3.69 (m, 1H), 3.38-3.37 (m, 1H), 2.37 (s, 3H), 2.21-2.18 (m, 1H), 1.92 - 1.86 (m, 2H). 1.67-1.58 (m, 1H).	Condition A: R_t = 3.19 min. m/z 483.4 [M+H] ⁺		White solid	27
Ex. 4A (Peak-1)	¹ H NMR (400 MHz, DMSO- d_6) δ 8.53 (s, 1H), 7.72 (s, 1H), 7.62 (t, $J=8.4$ Hz, 1H), 7.37 (s, 1H), 7.00-6.92 (m, 2H), 4.45 (d, $J=10.8$ Hz, 1H), 4.08 - 4.06 (m, 1H), 3.86 (s, 3H), 3.69 - 3.63 (m, 2H), 3.28-3.27 (m, 1H), 2.55 (s, 3H), 2.14-2.11 (m, 1H), 1.87 - 1.77 (m, 3H), 0.98 - 0.96 (m, 2H), 0.91 - 0.89 (m, 2H).	Condition A: R_t = 2.93 min. m/z 510.4 [M+H] ⁺	Analytical chiral HPLC: CHIRALPAK IC (250X4.6) mm, 5 μ M.P.-Hexane/DCM/EtOH/IPAmine 20/40/40/0.1 Flow Rate - 1.0 ml/min. Solubility: MeOH, R_t = 5.89 min for Peak 1 and R_t = 7.05 min for Peak 2.	White solid	24
Ex. 4B (Peak-2)	¹ H NMR (400 MHz, DMSO- d_6) δ 8.53 (s, 1H), 7.72 (s, 1H), 7.62 (t, $J=8.4$ Hz, 1H), 7.37 (s, 1H), 7.00-6.92 (m, 2H), 4.45 (d, $J=10.8$ Hz, 1H), 4.08 - 4.06 (m, 1H), 3.86 (s, 3H), 3.69 - 3.63 (m, 2H), 3.28-3.27 (m, 1H), 2.55 (s, 3H), 2.14-2.11 (m, 1H), 1.87 - 1.77 (m, 3H), 0.98 - 0.96 (m, 2H), 0.91 - 0.89 (m, 2H).	Condition A: R_t = 2.93 min. m/z 510.4 [M+H] ⁺		White solid	22
Ex. 5A (Peak-1)	¹ H NMR (400 MHz, DMSO- d_6) δ 8.61 (s, 1H), 8.05 (d, $J=10.0$ Hz, 1H), 7.89-7.83 (m, 2H), 7.72 (s, 1H), 7.37 (s, 1H), 4.45 (d, $J=10.8$ Hz, 1H), 4.09 - 4.05 (m, 1H), 3.69 - 3.63 (m, 2H), 3.28-3.27 (m, 1H), 2.36 (s,	Condition A: R_t = 2.77 min. m/z 489.36 [M+H] ⁺	Analytical chiral HPLC by SFC: I-Cellulose J (250X4.6) mm, 5 μ solvent: 0.3% IPAmine	White solid	24

	3H), 2.14-2.11 (m, 1H), 1.87 - 1.77 (m, 3H), 0.98 - 0.96 (m, 2H), 0.92 - 0.89 (m, 2H).		in MeOH Flow Rate – 5 ml/min.using 50% CO2		
Ex. 5B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (s, 1H), 8.05 (d, <i>J</i> =10.0 Hz, 1H), 7.89-7.83 (m, 2H), 7.72 (s, 1H), 7.37 (s, 1H), 4.45 (d, <i>J</i> =10.8 Hz, 1H), 4.09 - 4.05 (m, 1H), 3.69 - 3.63 (m, 2H), 3.28-3.27 (m, 1H), 2.36 (s, 3H), 2.14-2.11 (m, 1H), 1.87 - 1.77 (m, 3H), 0.98 - 0.96 (m, 2H), 0.92 - 0.89 (m, 2H).	Condition A: Rt = 2.77 min. m/z 489.36 [M+H] ⁺	Solubility: MeOH, Rt = 3.36 min for Peak 1 and Rt = 4.49 min for Peak 2.	White solid	22
Ex. 6A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (s, 1H), 8.04 (d, <i>J</i> =10.0 Hz, 1H), 7.89-7.83 (m, 2H), 7.64 (s, 1H), 7.36 (s, 1H), 4.46 (d, <i>J</i> =10.8 Hz, 1H), 4.09 - 4.05 (m, 1H), 3.77 (s, 3H), 3.69 - 3.64 (m, 1H), 3.36-3.34 (m, 1H), 2.36 (s, 3H), 2.14-2.11 (m, 1H), 1.90 - 1.76 (m, 3H).	Condition A: Rt = 2.71 min. m/z 463.37 [M+H] ⁺	Analytical chiral HPLC by SFC: I-Cellulose J (250X4.6) mm, 5μ solvent: 0.3% IPamine in MeOH Flow Rate – 5 ml/min.using 50% CO2	White solid	28
Ex. 6B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (s, 1H), 8.04 (d, <i>J</i> =10.0 Hz, 1H), 7.89-7.83 (m, 2H), 7.64 (s, 1H), 7.36 (s, 1H), 4.46 (d, <i>J</i> =10.8 Hz, 1H), 4.09 - 4.05 (m, 1H), 3.77 (s, 3H), 3.69 - 3.64 (m, 1H), 3.36-3.34 (m, 1H), 2.36 (s, 3H), 2.14-2.11 (m, 1H), 1.90 - 1.76 (m, 3H).	Condition A: Rt = 2.71 min. m/z 463.37 [M+H] ⁺	Solubility: MeOH, Rt = 2.99 min for Peak 1 and Rt = 3.59 min for Peak 2.	White solid	28
Ex. 7A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.83 (d, <i>J</i> =1.2 Hz, 1H), 8.11 (d, <i>J</i> =1.2 Hz, 1H), 7.73 (s, 1H), 7.63-7.57 (m, 1H), 7.42-7.37 (m, 2H), 7.25-7.20 (m, 1H), 4.42 (d, <i>J</i> =9.6 Hz, 1H), 4.09-4.05 (m, 1H), 3.67-3.62 (m, 2H), 3.23-3.21 (m, 1H), 2.40 (s, 3H), 2.13-2.09 (m, 1H), 1.88-1.75 (m, 3H), 0.98-0.95 (m, 2H), 0.93-0.91 (m, 2H).	Condition C: Rt = 2.98 min. m/z 497.44 [M+H] ⁺ .	Analytical chiral HPLC: CHIRALPAK IG (250X4.6) mm, 5μ M.P.-Hexane/EA/Et OH/IPAmine 50/25/25/0.1 Flow Rate - 1.0 ml/min.	White solid	29
Ex. 7B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.83 (d, <i>J</i> =1.2 Hz, 1H), 8.11 (d, <i>J</i> =1.2 Hz, 1H), 7.73 (s, 1H), 7.63-7.57 (m, 1H), 7.42-7.37 (m, 2H), 7.25-7.20 (m, 1H), 4.42 (d, <i>J</i> =9.6 Hz, 1H), 4.09-4.05 (m, 1H), 3.67-3.62 (m, 2H), 3.23-3.21 (m, 1H),	Condition C: Rt = 2.98 min. m/z 497.44 [M+H] ⁺ .	Solubility: MeOH, Rt = 11.26 min for Peak 1 and Rt = 14.5 min for Peak 2.	White solid	32

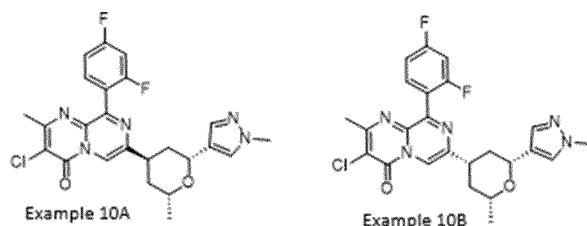
	2.40 (s, 3H), 2.13-2.09 (m, 1H), 1.88-1.75 (m, 3H), 0.98-0.95 (m, 2H), 0.93-0.91 (m, 2H).				
Ex. 8A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.57 (s, 1H), 7.76-7.70 (m, 1H), 7.64 (s, 1H), 7.46-7.40 (m, 1H), 7.37 (s, 1H), 7.29-7.24 (m, 1H), 4.46 (d, J=10.8 Hz, 1H), 4.09-4.06 (m, 1H), 3.77 (s, 3H), 3.70-3.64 (m, 1H), 3.31-3.25 (m, 1H), 2.37 (s, 3H), 2.14-2.07 (m, 1H), 1.91-1.77 (m, 3H).	Condition C: Rt = 2.79 min. m/z 456.37 [M+H] ⁺ .	Analytical chiral HPLC by SFC: I-Cellulose J (250X4.6) mm, 5μ solvent: 0.3% IPamine in MeOH Flow Rate - 5	White solid	26
Ex. 8B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.57 (s, 1H), 7.76-7.70 (m, 1H), 7.64 (s, 1H), 7.46-7.40 (m, 1H), 7.37 (s, 1H), 7.29-7.24 (m, 1H), 4.46 (d, J=10.8 Hz, 1H), 4.09-4.06 (m, 1H), 3.77 (s, 3H), 3.70-3.64 (m, 1H), 3.31-3.25 (m, 1H), 2.37 (s, 3H), 2.14-2.07 (m, 1H), 1.91-1.77 (m, 3H).	Condition C: Rt = 2.79 min. m/z 456.37 [M+H] ⁺ .	ml/min.using 60% CO ₂ Solubility: MeOH, Rt = 2.45 min for Peak 1 and Rt = 2.81 min for Peak 2.	White solid	24
Ex. 9A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.81 (s, 1H), 7.72 (s, 1H), 7.57-7.55 (m, 2H), 7.41-7.39 (m, 2H), 4.45-4.42 (m, 1H), 4.08-4.05 (m, 1H), 3.67-3.64 (m, 2H), 3.19-3.11 (m, 1H), 2.28 (s, 3H), 2.13-2.09 (m, 4H), 1.87-1.74 (m, 3H), 0.97-0.91 (m, 4H).	Condition C: Rt = 3.02 min. m/z 493.3 [M+H] ⁺ .	Analytical chiral HPLC: CHIRALPAK IG (250X4.6) mm, 5μ M.P.-Hexane/EA/Et OH/IPAmine 50/25/25/0.1	White solid	27
Ex. 9B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.81 (s, 1H), 7.72 (s, 1H), 7.57-7.55 (m, 2H), 7.41-7.39 (m, 2H), 4.45-4.42 (m, 1H), 4.08-4.05 (m, 1H), 3.67-3.64 (m, 2H), 3.19-3.11 (m, 1H), 2.28 (s, 3H), 2.13-2.09 (m, 4H), 1.87-1.74 (m, 3H), 0.97-0.91 (m, 4H).	Condition C: Rt = 3.02 min. m/z 493.3 [M+H] ⁺ .	Flow Rate - 1.0 ml/min. Solubility: MeOH, Rt = 7.86 min for Peak 1 and Rt = 10.29 min for Peak 2.	White solid	26

Example 10A and Example 10B:

Synthesis of 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2*R*,4*R*,6*R*)-2-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)tetrahydro-2*H*-pyran-4-yl)-4*H*-pyrazino[1,2-*a*]pyrimidin-4-one and 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2*R*,4*S*,6*R*)-2-methyl-6-(1-

methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one:

Step-1 - Preparation of 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2R,4R,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one (example 10A) and 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2R,4S,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one (example 10B)



To a stirred solution of 7-bromo-3-chloro-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one **[I-7]** (180 mg, 0.47 mmol), 4-((2R,6R)-4-iodo-6-methyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazole **[I-13]** (239.4 mg, 0.8 mmol) in DMA (6 mL) were added TBAI (257 mg, 0.7 mmol), Zinc (60 mg, 0.9 mmol). The reaction mass was degassed with argon for over 10 minutes. Nickel (II) chloride ethylene glycol dimethyl ether complex (102 mg, 0.47 mmol), 4,4'-Di-tert-butyl-2,2'-bipyridyl (187 mg, 0.7 mmol) were then added to the reaction mixture. Resulting mixture was heated at 100 °C for 16 h. Reaction mixture was diluted with ethyl acetate, filtered through a short pad of celite and washed with ethyl acetate. Combined organic part was washed with water, brine, dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude material was purified by combi flash chromatography (40% ethyl acetate in hexane) followed by diastereomer separation by reverse phase prep HPLC (Prep-A method) to afford 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2R,4R,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one [example 10A] (4.2 mg, 2% yield) and 3-chloro-9-(2,4-difluorophenyl)-2-methyl-7-((2R,4S,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one [example 10B] (13.2 mg, 6% yield) both as off white solid. Stereochemistry of both peaks were assigned arbitrarily.

Example 10A: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.64 (s, 1H), 7.80-7.74 (m, 1H), 7.58 (s, 1H), 7.47-7.42 (m, 1H), 7.31-7.26 (m, 2H), 4.65 (d, J=10.8 Hz, 1H), 3.93-3.89 (m, 1H),

3.77 (s, 3H), 3.59-3.58 (m, 1H), 2.47 (s, 3H), 2.37-2.32 (m, 1H), 2.23-2.20 (m, 1H), 2.07-2.06 (m, 1H), 1.78-1.72 (m, 1H), 1.12-1.11 (m, 3H).

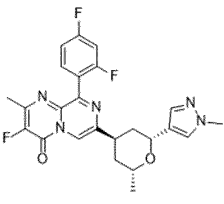
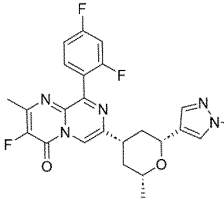
Condition C: Rt = 2.97 min. m/z 486.33 [M+H]⁺

Example 10B: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.57 (s, 1H), 7.74-7.73 (m, 1H), 7.64 (s, 1H), 7.39-7.43 (m, 1H), 7.37 (s, 1H), 7.31-7.26 (m, 1H), 4.52 (d, J=10.0 Hz, 1H), 3.77 (s, 3H), 3.76-3.75 (m, 1H), 3.35-3.34 (m, 1H), 2.47 (s, 3H), 2.07-2.06 (m, 1H), 1.98-1.97 (m, 1H), 1.77-1.75 (m, 1H), 1.50-1.49 (m, 1H), 1.23-1.22 (m, 3H).

Condition C: Rt = 2.99 min. m/z 486.33 [M+H]⁺

10 **Example 11**

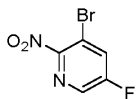
Examples 11A and 11B were synthesized by using similar procedure described for Example 10A & 10B in one step and stereochemistry of both peaks were assigned in a similar fashion to Example 10A & 10B

Ex. No.	Structure	Name	Step-1 SMS and remarks	Purification method (Step-2)
11A		9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2R,4R,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one	I-9 & I-13.	Column purification followed by diastereomer separation by reverse phase prep HPLC using Prep-B method
11B		9-(2,4-difluorophenyl)-3-fluoro-2-methyl-7-((2R,4S,6R)-2-methyl-6-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one		

15 The following table describes analytical data analysis and yield information of examples 11A and 11B.

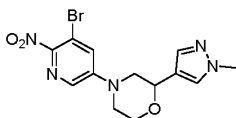
Ex. No.	¹ H-NMR	LCMS	Description	Yield %
---------	--------------------	------	-------------	---------

11A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.63 (s, 1H), 7.79-7.73 (m, 1H), 7.58 (s, 1H), 7.47-7.41 (m, 1H), 7.31-7.25 (m, 2H), 4.65 (d, J=10.4 Hz, 1H), 3.94-3.90 (m, 1H), 3.77 (s, 3H), 3.59-3.57 (m, 1H), 2.38 (s, 3H), 2.34-2.32 (m, 1H), 2.23-2.20 (m, 1H), 2.08-2.01 (m, 1H), 1.78-1.70 (m, 1H), 1.12-1.11 (m, 3H).	Condition C: Rt = 3.02 min. m/z 470.3 [M+H] ⁺	White solid	4
11B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.56 (s, 1H), 7.75-7.69 (m, 1H), 7.65 (s, 1H), 7.46-7.40 (m, 1H), 7.37 (s, 1H), 7.29-7.24 (m, 1H), 4.51 (d, J=10.0 Hz, 1H), 3.77 (s, 3H), 3.76-3.75 (m, 1H), 3.33-3.31 (m, 1H), 2.49 (s, 3H), 2.11-2.07 (m, 1H), 1.97-1.94 (m, 1H), 1.80-1.71 (m, 1H), 1.50-1.44 (m, 1H), 1.19-1.18 (m, 3H).	Condition C: Rt = 3.04 min. m/z 470.3 [M+H] ⁺	White solid	14

Example 12**9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one****5 Step-1 - Preparation of 3-bromo-5-fluoro-2-nitropyridine:**

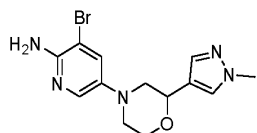
Potassium persulfate (10.2 g, 37.7 mmol) was added to sulfuric acid (10.7 mL) and the resulting mixture was stirred at rt for 10 min. It was cooled to 0 °C and 3-bromo-5-fluoropyridin-2-amine (1.8 g, 9.4 mmol) was added. Reaction mixture continued to stir at 0 °C for 1.5 h. Reaction mixture was poured slowly into crushed ice, neutralized with aq. NH₃, extracted with ethyl acetate. The combined organic layer was dried over sodium sulphate, filtered and evaporated under reduced pressure. Crude product was purified by combi flash chromatography (30-40% ethyl acetate-hexane) to get 3-bromo-5-fluoro-2-nitropyridine (1 g, 48.1% yield) as brown solid.

15 ¹H NMR (400 MHz, DMSO D6) δ 8.72 (m, 2 H)

Step-2 - Preparation of 4-(5-bromo-6-nitropyridin-3-yl)-2-(1-methyl-1H-pyrazol-4-yl)morpholine:

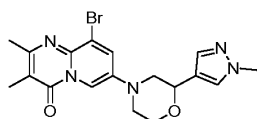
- To a stirred solution of 2-(1-methyl-1H-pyrazol-4-yl)morpholine [I-1](HCl salt, 113.4 mg, 0.7 mmol) in DMSO (2 mL) was added DIPEA (0.3 mL, 1.8 mmol) at RT and stirred for 15 min. To it was added 3-bromo-5-fluoro-2-nitropyridine (100 mg, 0.5 mmol) at RT. Resulting mixture was stirred at RT for 3h. Reaction mixture was poured slowly into ice cold water, extracted with ethyl acetate. Combined organic layer was washed with brine, dried over sodium sulphate, filtered and evaporated under reduced pressure. Crude product was purified by combi flash chromatography (80-90% ethyl acetate-hexane) to get 4-(5-bromo-6-nitropyridin-3-yl)-2-(1-methyl-1H-pyrazol-4-yl)morpholine (140 mg, 84.1% yield) as yellow solid.
- LCMS Condition B: Rt = 1.86 min. m/z 368.3 [M+H]⁺.

Step-3 - Preparation of 3-bromo-5-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)pyridin-2-amine:



- To a stirred solution of 4-(5-bromo-6-nitropyridin-3-yl)-2-(1-methyl-1H-pyrazol-4-yl)morpholine (166 mg, 0.5 mmol) in ethanol (2 mL) was added SnCl₂·2H₂O (1 g, 4.5 mmol) at RT. Resulting mixture was heated at 80 °C for 2 h. Reaction mixture was quenched with water, extracted with DCM. Combined organic layer was washed with brine, dried over sodium sulphate, filtered and evaporated under reduced pressure. Crude product was purified by combi flash chromatography (5% methanol-DCM) to get 3-bromo-5-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)pyridin-2-amine (100 mg, 65.4% yield) as brown solid.
- LCMS Condition A: Rt = 1.56 min. m/z 338.3 [M+H]⁺.

- Step-4 - Preparation of 9-bromo-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one:**

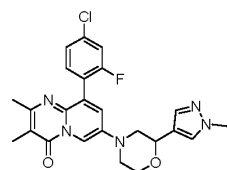


- In a sealed tube, 3-bromo-5-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)pyridin-2-amine (70 mg, 0.2 mmol), methyl 2-methyl-3-oxobutanoate (53.9 mg, 0.4 mmol) and BiCl₃ (6.5 mg, 0.02 mmol) were mixed. The resulting mixture was heated at 130 °C for 16 h. Reaction mixture was then diluted with DCM, washed with NaHCO₃ solution, brine, dried

over sodium sulphate, filtered, and evaporated under reduced pressure. Crude product was purified by combi flash chromatography (5% methanol-DCM) to get 9-bromo-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one (40 mg, 46.2% yield) as yellow solid..

5 LCMS Condition A: Rt = 1.89 min. m/z 418.3 [M+H]⁺.

Step-5 - Preparation of 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one [Example 12]:



10 To a stirred solution of 9-bromo-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one (160 mg, 0.4 mmol) and (4-chloro-2-fluorophenyl)boronic acid (80.1 mg, 0.5 mmol) in 1,4-dioxane (6 mL) and water (2 mL) was added sodium carbonate (81.1 mg, 0.8 mmol) and degassed with argon. PdCl₂(dppf) (27.9 mg, 0.04 mmol) was added under inert atmosphere. The
15 resulting mixture was heated at 60 °C for 3 h. Reaction mixture was diluted with ethyl acetate, filtered through a short pad of celite and washed with ethyl acetate. Combined organic part was washed with water, brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Crude mass was purified by reverse phase prep HPLC (prep-A method) to afford 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one (38 mg,
20 21.3% yield) as yellow solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.09 (s, 1H), 7.72 (s, 1H), 7.57 – 7.53 (m, 2H), 7.45 (s, 1H),

7.42 – 7.39 (m, 1H), 4.63– 4.61 (m, 1H), 4.05– 4.03 (m, 1H), 3.85 – 3.79 (m, 5H), 3.59 –
25 3.56 (m, 1H), 2.89 – 2.84 (m, 1H), 2.79 – 2.67 (m, 1H), 2.26 (s, 3H), 2.12 (s, 3H).

LCMS Condition C: Rt = 2.84 min. m/z 468.2 [M+H]⁺.

Examples 13 and 14

Examples 13 and 14 were synthesized using similar procedure described for Example
30 12.

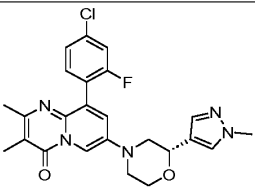
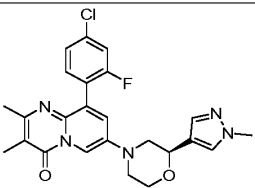
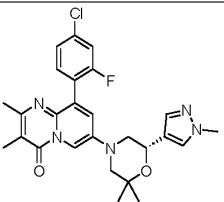
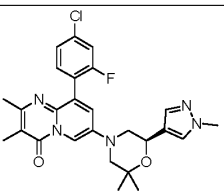
Ex. No.	Structure	Name	Starting materials	Remarks
---------	-----------	------	--------------------	---------

13		9-(4-chloro-2-fluorophenyl)-7-(2,2-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)morpholino)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one	Step-1: Same as example 12 Step-2: I-2 instead of I-1 Step-3, 4 & 5: Same as example 12	
14		3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)-6-methylmorpholino)-9-(2,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	I-7 & I-14	Step-5: Modified condition used: NaOtBu (2 eq), RuPhosPdG 3 (0.05 eq), RuPhos (0.05 eq), PhMe, 80 °C, 3 h

The following table describes analytical data analysis and yield information of examples 13 and 14.

Ex. No.	¹ H-NMR	LCMS	Description	Yield %
13	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.26 (s, 1H), 8.06 (s, 1H), 7.69 (s, 1H), 7.57-7.53 (m, 2H), 7.43-7.40 (m, 2H), 4.89 (d, <i>J</i> =10.0 Hz, 1H), 3.80-3.76 (m, 4H), 3.57 (d, <i>J</i> =11.6 Hz, 1H), 2.64-2.56 (m, 2H), 2.25 (s, 3H), 2.12 (s, 3H), 1.39 (s, 3H), 1.24 (s, 3H).	LCMS Condition K: Rt = 3.02 min. m/z 496.3 [M+H] ⁺ .	Yellow solid	39
14	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.05 (s, 1H), 7.85 (s, 1H), 7.77-7.71 (m, 1H), 7.47 (s, 1H), 7.45-7.39 (m, 1H), 7.28-7.24 (m, 1H), 4.62 (d, <i>J</i> =8.8 Hz, 1H), 4.14-4.05 (m, 2H), 3.85-3.83 (m, 1H), 3.71-3.65 (m, 1H), 2.89 (t, <i>J</i> =12.0 Hz, 1H), 2.66-2.50 (m, 1H), 2.43 (s, 3H), 1.22 (d, <i>J</i> =6.4 Hz, 3H), 1.01-0.97 (m, 2H), 0.95-0.90 (m, 2H).	LCMS Condition K: Rt = 3.14 min. m/z 513.44 [M+H] ⁺ .	Yellow solid	43

Chiral separation details of Example 12A-12B to 13A-13B are captured in following table:

Ex. No.	Structure	Name	Starting material	Chiral Separation method
12A (Peak-1)		(S)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one	Example 12	NP Chiral Method 2 Peak 1 & Peak 2 - Actual stereochemistry unknown, arbitrary assignment of stereochemistry.
12B (Peak-2)		(R)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one		
13A (Peak-1)		(S)-9-(4-chloro-2-fluorophenyl)-7-(2,2-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)morpholino)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one	Example 13	NP Chiral Method 3 Peak 1 & Peak 2 - Actual stereochemistry unknown, arbitrary assignment of stereochemistry.
13B (Peak-2)		(R)-9-(4-chloro-2-fluorophenyl)-7-(2,2-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)morpholino)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one		

Following table describes analytical data analysis and yield information of examples 12A/12B and 13A/13B

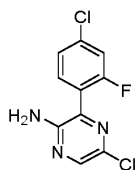
Ex. No.	HNMR	LCMS	Analytical chiral HPLC	Description	Yield (%)
12A (Peak 1)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.09 (s, 1H), 7.72 (s, 1H), 7.57-7.53 (m, 2H), 7.45 (s, 1H), 7.42-7.39 (m, 1H), 4.63-4.61 (m, 1H), 4.05-4.03 (m, 1H), 3.85-3.79 (m, 5H), 3.59-3.56 (m, 1H), 2.89-2.84 (m, 1H), 2.79-2.67	LCMS Condition C: Rt = 2.84 min. m/z 468.2 [M+H] ⁺ .	CHIRALPAK IG (250X4.6)mm, 5μm M.P.- Hexane/DCM /EtOH/IPAmine 50/25/25/0.1	Off white solid	60.4

	(m, 1H), 2.26 (s, 3H), 2.12 (s, 3H).		Flow Rate - 1.0 ml/min		
12B (Peak 2)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.09 (s, 1H), 7.72 (s, 1H), 7.57–7.53 (m, 2H), 7.45 (s, 1H), 7.42–7.39 (m, 1H), 4.63–4.61 (m, 1H), 4.05–4.03 (m, 1H), 3.85–3.79 (m, 5H), 3.59–3.56 (m, 1H), 2.89–2.84 (m, 1H), 2.79–2.67 (m, 1H), 2.26 (s, 3H), 2.12 (s, 3H).	LCMS Condition C: Rt = 2.84 min. m/z 468.2 [M+H] ⁺ .	Solubility: MeOH Rt = 8.94 min for Peak 1 and Rt = 10.29 min for Peak 2.	Off white solid	58.3
13A (Peak 1)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.26 (s, 1H), 8.06 (s, 1H), 7.69 (s, 1H), 7.57–7.53 (m, 2H), 7.43–7.40 (m, 2H), 4.89 (d, J=10.0 Hz, 1H), 3.80–3.76 (m, 4H), 3.57 (d, J=11.6 Hz, 1H), 2.64–2.56 (m, 2H), 2.25 (s, 3H), 2.12 (s, 3H), 1.39 (s, 3H), 1.24 (s, 3H).	LCMS Condition K: Rt = 3.02 min. m/z 496.3 [M+H] ⁺ .	Analytical chiral HPLC: Chiralpak IG (4.6 x 250 mm), 5μ ARD/K/ Mobile Phase : Hexane/DCM /EtOH/IPAmine : 50/25/25/0.1 Flow Rate : 1.0 ml/min	Yellow solid	34.5
13B (Peak 2)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.26 (s, 1H), 8.06 (s, 1H), 7.69 (s, 1H), 7.57–7.53 (m, 2H), 7.43–7.40 (m, 2H), 4.89 (d, J=10.0 Hz, 1H), 3.80–3.76 (m, 4H), 3.57 (d, J=11.6 Hz, 1H), 2.64–2.56 (m, 2H), 2.25 (s, 3H), 2.12 (s, 3H), 1.39 (s, 3H), 1.24 (s, 3H). LCMS Condition K: Rt = 3.02 min. m/z 496.3 [M+H] ⁺ .	LCMS Condition K: Rt = 3.02 min. m/z 496.3 [M+H] ⁺ .	Solubility : MeOH; Rt = 5.75 min for Peak 1 and Rt = 6.36 min for Peak 2	Yellow solid	31.4

Example 15

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrazino[1,2-a]pyrimidin-4-one:

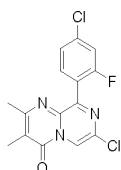
5 **Step-1 - Preparation of 5-chloro-3-(4-chloro-2-fluorophenyl)pyrazin-2-amine:**



To a stirred solution of 3-bromo-5-chloropyrazin-2-amine (1 g, 4.8 mmol) and (4-chloro-2-fluorophenyl)boronic acid (752.8 mg, 4.3 mmol) in 1,4-dioxane (100 mL) and water (20 mL) was added sodium carbonate (762.6 mg, 7.2 mmol) and degassed with argon. PdCl₂(dppf) (350.7 mg, 0.5 mmol) was added under inert atmosphere. The resulting mixture was heated at 60 °C for 3 h. Reaction mixture was diluted with ethyl acetate, filtered through a short pad of celite and washed with ethyl acetate. Combined organic part was washed with water, brine, dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. Crude mass was purified by combi flash chromatography (45% ethyl acetate in hexane) to afford 5-chloro-3-(4-chloro-2-fluorophenyl)pyrazin-2-amine (691 mg, 56.2% yield) as yellow solid.

LCMS Condition A: Rt = 2.07 min. m/z 302.3 [M+H]⁺.

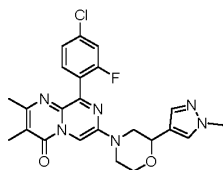
Step-2 - Preparation of 7-chloro-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-4H-pyrazino[1,2-a]pyrimidin-4-one



To a stirred mixture of 3-bromo-5-chloropyrazin-2-amine (247.9 mg, 0.9 mmol) and methyl 2-methyl-3-oxobutanoate (250 mg, 1.9 mmol) was added BiCl₃ (30.2 mg, 1.9 mmol). Resulting mixture was heated at 170 °C for 6 h. The reaction mixture was quenched with ice cold sodium bicarbonate solution, extracted with ethyl acetate, dried over sodium sulphate and concentrated. Crude mass was purified by combi flash chromatography using 10% - 20% ethyl acetate in hexane on silica gel to afford 7-chloro-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-4H-pyrazino[1,2-a]pyrimidin-4-one (70 mg, 20.7% yield) as brown solid.

LCMS Condition C: Rt = 2.44 min. m/z 338.3 [M+H]⁺.

Step-3 - Preparation of 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrazino[1,2-a]pyrimidin-4-one [Example 15]:



To a stirred solution of 2-(1-methyl-1H-pyrazol-4-yl)morpholine **[I-1]** (HCl salt, 148.3 mg, 0.9 mmol) in DMSO (3 mL) was added DIPEA (0.6 mL, 3.5 mmol) at rt and stirred for 15 min. To it was added 7-chloro-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-4H-pyrazino[1,2-a]pyrimidin-4-one (150 mg, 0.4 mmol) at rt. Resulting mixture was heated at 110 °C for 16 h. Reaction mixture was concentrated under reduced pressure. Crude mass was purified by reverse phase preparative HPLC (Prep-A method) to afford 8-(4-chloro-2-fluorophenyl)-2,3-dimethyl-6-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)pyrimido[5,4-d]pyrimidin-4(3H)-one (10 mg, 4.9% yield) as yellow solid.

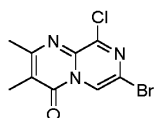
¹H NMR (400 MHz, DMSO D₆) δ 8.01 (s, 1H), 7.75 (s, 1H), 7.73-7.69 (m, 1H), 7.63-7.61 (m, 1H), 7.46-7.44 (m, 2H), 4.63-4.61 (m, 1H), 4.06-4.03 (m, 2H), 3.81-3.74 (m, 4H), 2.99-2.89 (m, 3H), 2.32 (s, 3H), 2.17 (s, 3H).

LCMS Condition C: Rt = 2.91 min. m/z 469.3 [M+H]⁺.

Example 16

(S)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrazino[1,2-a]pyrimidin-4-one

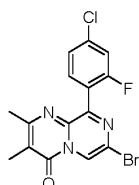
Step-1 - Preparation of 7-bromo-9-chloro-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one:



To a stirred mixture of 3-bromo-5-chloropyrazin-2-amine (500 mg, 2.39 mmol) and methyl 2-methyl-3-oxobutanoate (624 mg, 4.8 mmol) was added BiCl₃ (75 mg, 0.24 mmol). Resulting mixture was heated at 130 °C for 16 h. The reaction mixture was quenched with ice cold sodium bicarbonate solution, extracted with ethyl acetate, dried over sodium sulphate and concentrated. Crude mass was purified by combi flash chromatography using 30% - 40% ethyl acetate in hexane on silica gel to afford 7-bromo-9-chloro-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (250 mg, 36.2% yield) as yellow gummy mass.

LCMS Condition C: Rt = 1.98 min. m/z 288.1 [M+H]⁺.

Step-2 - Preparation of 7-bromo-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one:

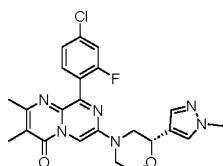


5 To a stirred solution of 7-bromo-9-chloro-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (100 mg, 0.3 mmol) in 1,4-dioxane-water (10 mL, 9:1) were added (4-chloro-2-fluorophenyl)boronic acid (54 mg, 0.3 mmol), Na₂CO₃ (55 mg, 0.5 mmol). The resulting mixture was degassed with argon and Pd(dppf)Cl₂ (25 mg, 0.04 mmol) was added. The resulting mixture was heated at 60 °C for 2 h. After completion, reaction mixture was

10 passed through a pad of celite and washed with ethyl acetate and concentrated. Crude product was purified by combi flash chromatography using 10% - 20% ethyl acetate in hexane on silica gel to afford 7-bromo-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (50 mg, 37.2% yield) as yellow gummy mass. LCMS Condition C: Rt = 2.29 min. m/z 382.0 [M+H]⁺.

15

Step-3 - Preparation of (S)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrazino[1,2-a]pyrimidin-4-one (Example-16)



20 To a stirred solution of 7-bromo-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (100 mg 0.3 mmol) in toluene (10 mL) were added (S)-2-(1-methyl-1H-pyrazol-4-yl)morpholine [I-3] (35 mg, 0.21 mmol), sodium tert-butoxide (75 mg 0.8 mmol) and Ru-Phos (6 mg, 0.01 mmol). The resulting mixture was degassed with argon and Ru-Phos-Pd-G3 (11 mg, 0.06 mmol) was added. The resulting mixture was heated at 80 °C for 1 h. After completion, reaction mixture was passed through celite bed and

25 washed with DCM and concentrated. Crude product was purified by reverse phase preparative HPLC (Prep-B method) to afford (S)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrazino[1,2-a]pyrimidin-4-one (17 mg, 14.2% yield) as yellow solid.

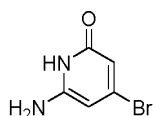
¹H NMR (400 MHz, DMSO-d₆) δ 8.01 (s, 1H), 7.75 (s, 1H), 7.71 (t, *J*=8.0 Hz, 1H), 7.62-7.59 (dd, *J*=9.6 Hz, *J*= 1.6 Hz, 1H), 7.46 (s, 1H), 7.44 (d, *J*=2.0 Hz, 1H), 4.63-4.60 (dd, *J*=10.4 Hz, *J*= 2.4 Hz, 1H), 4.03 (d, *J*=12.0 Hz, 2H), 3.86 (d, *J*=12.0 Hz, 1H), 3.80 (s, 3H), 3.76-3.74 (m, 1H), 3.01-2.89 (m, 2H), 2.32 (s, 3H), 2.16 (s, 3H).

5 LCMS Condition K: *R*_t = 2.90 min. *m/z* 469.3 [M+H]⁺.

Example 17

6-(4-chloro-2-fluorophenyl)-2,3-dimethyl-8-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one

10 **Step-1 - Preparation of 6-amino-4-bromopyridin-2(1H)-one:**

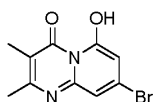


To a stirred solution of 4-bromopyridine-2,6-diamine (2 g, 10.6 mmol) in 50 % aqueous sulphuric acid (20 mL) was heated at 100 °C for 5 h. Reaction mixture was quenched with crushed ice and neutralized with sodium bicarbonate. The solid was precipitated out, filtered, washed with water, and dried to have 6-amino-4-bromopyridin-2(1H)-one (1.7 g, 84.1% yield) as brown solid.

15

LCMS Condition C: *R*_t = 0.78 min. *m/z* 189.1 [M+H]⁺.

20 **Step-2 - Preparation of 8-bromo-6-hydroxy-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one:**

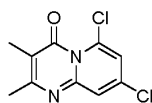


To a stirred mixture of 6-amino-4-bromopyridin-2(1H)-one (250 mg, 1.32 mmol) and methyl 2-methyl-3-oxobutanoate (343 mg, 2.6 mmol) was added BiCl₃ (41 mg, 0.13 mmol). Resulting mixture was heated at 130 °C for 16 h. The reaction mixture was quenched with ice cold sodium bicarbonate solution, extracted with DCM, dried over sodium sulphate and concentrated. Crude mass was purified by combi flash chromatography using 30% - 50% DCM in ethyl acetate on silica gel to afford 8-bromo-6-hydroxy-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (250 mg, 70% yield) as yellow gummy mass.

25

30 LCMS Condition C: *R*_t = 1.55 min. *m/z* 269.1 [M+H]⁺.

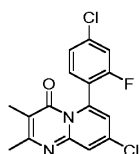
Step-3 - Preparation of 6,8-dichloro-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one:



To a stirred solution of 8-bromo-6-hydroxy-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (350 mg, 1.3 mmol) in POCl₃ (12 mL) was added DIPEA (1.2 mL, 6.5 mmol) at 0 °C. Resulting mixture was stirred at 100 °C for 16 h. Crude reaction mixture was evaporated to dryness and purified by combi flash chromatography using 10% - 30% ethyl acetate in hexane on silica gel to afford 6,8-dichloro-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (200 mg, 63.2% yield) as brown solid.

LCMS Condition C: Rt = 2.00 min. m/z 243.2 [M+H]⁺.

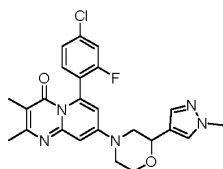
Step-4 - Preparation of 8-chloro-6-(4-chloro-2-fluorophenyl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one:



To a stirred solution of 6,8-dichloro-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (100 mg, 0.41 mmol) in 1,4-dioxane-water (10 mL, 9:1) were added (4-chloro-2-fluorophenyl)boronic acid (64 mg, 0.4 mmol), Na₂CO₃ (87 mg, 0.82 mmol). The resulting mixture was degassed with argon and Pd(dppf)Cl₂ (30 mg, 0.04 mmol) was added. The resulting mixture was heated at 80 °C for 16 h. After completion, the reaction mixture was passed through a pad of celite and washed with ethyl acetate. The crude reaction mixture was extracted with ethyl acetate, dried over sodium sulphate, concentrated and purified by combi flash chromatography using 20% - 30% ethyl acetate in hexane on silica gel to afford 8-chloro-6-(4-chloro-2-fluorophenyl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (40 mg, 28.7% yield) as brown solid. [structure was confirmed by 2D NMR].

LCMS Condition C: Rt = 2.35 min. m/z 337.2 [M+H]⁺.

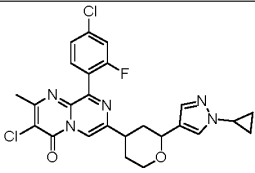
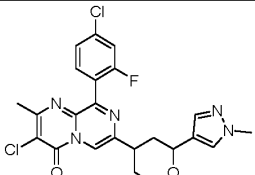
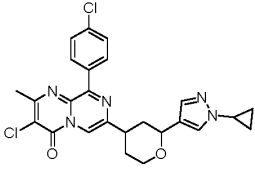
Step-5 - Preparation of 6-(4-chloro-2-fluorophenyl)-2,3-dimethyl-8-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one (Example-72):



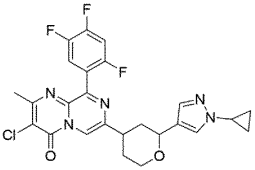
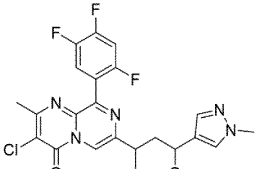
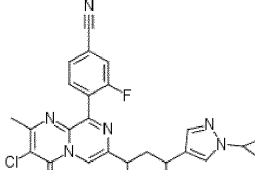
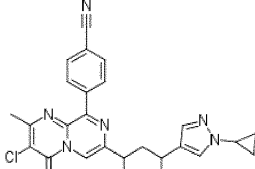
- To a stirred solution of 8-chloro-6-(4-chloro-2-fluorophenyl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (80 mg 0.24 mmol) in toluene (10 mL) were added 2-(1-methyl-1H-pyrazol-4-yl)morpholine **[I-1]** (40 mg, 0.24 mmol), sodium tert-butoxide (75 mg 0.8 mmol) and Ruphos(6 mg, 0.01 mmol). The resulting mixture was degassed with argon and Ru-Phos-Pd-G3 (10 mg, 0.01 mmol) was added. The resulting mixture was heated at 80 °C for 16 h. After completion, the reaction mixture was passed through celite bed and washed with DCM and concentrated. Crude product was purified by reverse phase preparative HPLC to afford 6-(4-chloro-2-fluorophenyl)-2,3-dimethyl-8-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one (8 mg, 7% yield) as white solid.
- ¹H NMR (400 MHz, DMSO-d₆) δ 7.32 (s, 1H), 7.50-7.46 (m, 2H), 7.37-7.30 (m, 2H), 7.02 (s, 1H), 6.70 (d, *J*= 1.6 Hz, 1H), 4.51 (d, *J*=10.0 Hz, 1H), 4.14 (brs, 1H), 3.99-3.91 (m, 2H), 3.80 (s, 3H), 3.69 (t, *J*= 11.6 Hz, 1H), 3.08 (m, 1H), 2.99-2.94 (m, 1H), 2.26 (s, 3H), 1.87 (s, 3H).
- LCMS Condition K: Rt = 2.38 min. m/z 468.3 [M+H]⁺.

Examples 18 to 31

Examples 18-31 were synthesized by using similar procedures described for Example 1 in two steps.

Ex. No.	Structure	Name	Step-1 SMs and remarks	Purification method (Step-2)
18		3-chloro-9-(4-chloro-2-fluorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	I-14 and I-5	Prep-A method
19		3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one	I-14 and I-6	Prep-A method
20		3-chloro-9-(4-chlorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	I-15 and I-5	Prep-A method

21		3-chloro-9-(4-chlorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one	I-15 and I-6	Prep-A method
22		3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one	I-16 and I-6	Prep-A method
23		3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one	I-17 and I-6	Prep-A method
24		3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	I-18 and I-5	Prep-A method
25		3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one	I-18 and I-6	Prep-A method
26		4-(3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile	I-19 and I-5	Prep-A method
27		4-(3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile	I-20 and I-5	Prep-A method

28		3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one	I-21 and I-5	Prep-A method
29		3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one	I-21 and I-6	Prep-A method
30		4-(3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile	I-19 and I-6	Prep-A method
31		4-(3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile	I-20 and I-6	Prep-A method

The following table describes analytical data analysis and yield information of examples 18-29.

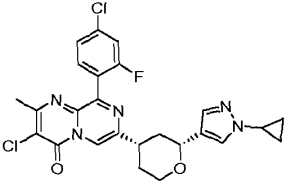
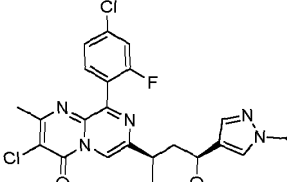
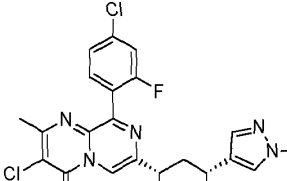
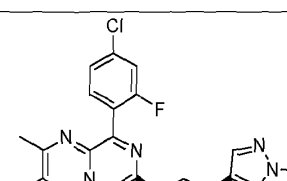
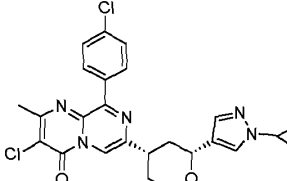
Ex. No.	¹ H-NMR	LCMS	Description	Yield%
18	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 7.72-7.68 (m, 2H), 7.62 (d, J=10.0 Hz, 1H), 7.47 (d, J=8.0 Hz, 1H), 7.36 (s, 1H), 4.48-4.46 (m, 1H), 4.08-4.06 (m, 1H), 3.69-3.64 (m, 2H), 3.32-3.31 (m, 1H), 2.47 (s, 3H), 2.14-2.11 (m, 1H), 1.90-1.80 (m, 3H), 0.98-0.97 (m, 2H), 0.91-0.89 (m, 2H).	Condition A : Rt = 3.25 min. m/z 514.2 [M+H] ⁺	White solid	24
19	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 7.72-7.68 (m, 1H), 7.64-7.62 (m, 2H), 7.47 (d, J=8.0 Hz, 1H), 7.36 (s, 1H), 4.49-4.46 (m, 1H), 4.10-4.06 (m, 1H), 3.77 (s, 3H), 3.70-3.64 (m, 1H), 3.29-3.28 (m, 1H), 2.47 (s, 3H), 2.14-2.11 (m, 1H), 1.90-1.80 (m, 3H).	Condition A : Rt = 3.02 min. m/z 488.3 [M+H] ⁺	White solid	20
20	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.54 (s, 1H), 8.21 (d, J=8.8 Hz, 2H), 7.37	Condition A : Rt =	White solid	21

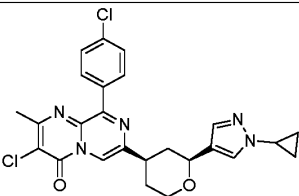
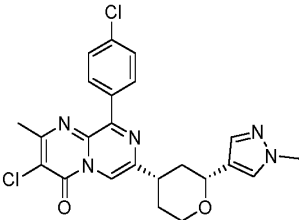
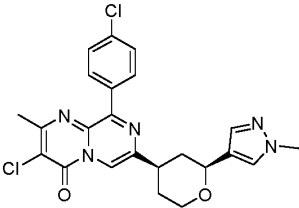
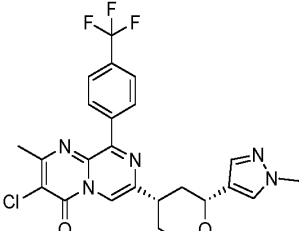
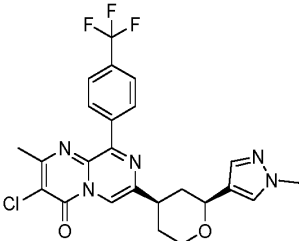
	(s, 1H), 7.60 (d, J=8.8 Hz, 2H), 7.38 (s, 1H), 4.49-4.47 (m, 1H), 4.10-4.08 (m, 1H), 3.68-3.63 (m, 2H), 3.32-3.31 (m, 1H), 2.55 (s, 3H), 2.16-2.13 (m, 1H), 1.90-1.84 (m, 3H), 1.01-0.97 (m, 2H), 0.93-0.89 (m, 2H).	3.23 min. m/z 496.3 [M+H] ⁺		
21	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.54 (s, 1H), 8.21 (d, J=8.8 Hz, 2H), 7.65-7.60 (m, 3H), 7.38 (s, 1H), 4.50-4.48 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H), 3.72-3.67 (m, 1H), 3.32-3.28 (m, 1H), 2.66 (s, 3H), 2.16-2.13 (m, 1H), 1.89-1.83 (m, 3H).	Condition A : Rt = 3.04 min. m/z 470.3 [M+H] ⁺	White solid	17
22	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 8.33 (d, J=8.0 Hz, 2H), 7.90 (d, J=8.4 Hz, 2H), 7.65 (s, 1H), 7.38 (s, 1H), 4.50-4.48 (m, 1H), 4.10-4.08 (m, 1H), 3.77 (s, 3H), 3.70-3.68 (m, 1H), 3.35-3.31 (m, 1H), 2.54 (s, 3H), 2.16-2.13 (m, 1H), 1.90-1.84 (m, 3H).	Condition A : Rt = 3.27 min. m/z 504.2 [M+H] ⁺	White solid	23
23	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.56 (s, 1H), 8.26 (d, J=8.0 Hz, 2H), 7.73 (d, J=7.6 Hz, 2H), 7.66 (s, 1H), 7.38 (s, 1H), 7.29-7.01 (m, 1H), (m, 1H), 4.51-4.48 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H), 3.72-3.69 (m, 1H), 3.33-3.31 (m, 1H), 2.54 (s, 3H), 2.16-2.13 (m, 1H), 1.90-1.82 (m, 3H).	Condition A : Rt = 2.96 min. m/z 486.3 [M+H] ⁺	White solid	26
24	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.55 (s, 1H), 8.31-8.26 (m, 1H), 8.12-8.10 (m, 1H), 7.73 (s, 1H), 7.65-7.58 (m, 1H), 7.38 (s, 1H), 4.49-4.47 (m, 1H), 4.11-4.08 (m, 1H), 3.71-3.63 (m, 2H), 3.29-3.27 (m, 1H), 2.57 (s, 3H), 2.17-2.14 (m, 1H), 1.90-1.81 (m, 3H), 0.99-0.98 (m, 2H), 0.94-0.90 (m, 2H).	Condition A : Rt = 3.11 min. m/z 498.3 [M+H] ⁺	White solid	22
25	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.55 (s, 1H), 8.31-8.26 (m, 1H), 8.12-8.11 (m, 1H), 7.67-7.58 (m, 2H), 7.39 (s, 1H), 4.50-4.48 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H), 3.72-3.66 (m, 1H), 3.32-3.26 (m, 1H), 2.56 (s, 3H), 2.16-2.13 (m, 1H), 1.89-1.82 (m, 3H).	Condition A : Rt = 2.99 min. m/z 472.3 [M+H] ⁺	Yellow solid	21
26	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.62 (s, 1H), 8.05 (d, J=9.6 Hz, 1H), 7.87-7.86 (m, 2H), 7.72 (s, 1H), 7.36 (s, 1H), 4.47-4.45 (m, 1H), 4.08-4.06 (m, 1H), 3.69-3.63 (m, 2H), 3.37-3.34 (m, 1H), 2.46 (s, 3H), 2.14-2.11 (m, 1H), 1.90-1.79 (m, 3H), 0.98-0.96 (m, 2H), 0.92-0.89 (m, 2H).	Condition A : Rt = 6.06 min. m/z 505.3 [M+H] ⁺	Yellow solid	23

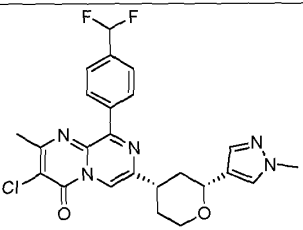
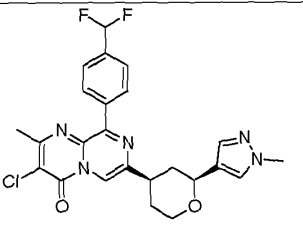
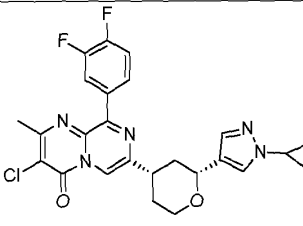
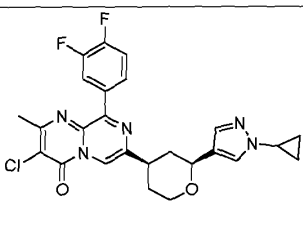
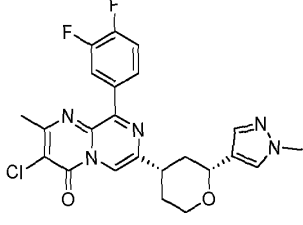
27	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 8.30 (d, J=8.4 Hz, 2H), 8.00 (d, J=8.4 Hz, 2H), 7.73 (s, 1H), 7.38 (s, 1H), 4.48-4.46 (m, 1H), 4.10-4.07 (m, 1H), 3.71-3.62 (m, 2H), 3.33-3.28 (m, 1H), 2.53 (s, 3H), 2.16-2.12 (m, 1H), 1.90-1.84 (m, 3H), 0.98-0.96 (m, 2H), 0.92-0.89 (m, 2H).	Condition A : Rt = 3.08 min. m/z 487.3 [M+H] ⁺	White solid	20
28	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.59 (s, 1H), 7.78-7.72 (m, 3H), 7.37 (s, 1H), 4.47-4.45 (m, 1H), 4.08-4.06 (m, 1H), 3.66-3.63 (m, 2H), 3.27-3.24 (m, 1H), 2.45 (s, 3H), 2.14-2.10 (m, 1H), 1.88-1.80 (m, 3H), 0.98-0.96 (m, 2H), 0.91-0.89 (m, 2H).	Condition A : Rt = 3.06 min. m/z 516.3 [M+H] ⁺	White solid	21
29	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.59 (s, 1H), 7.83-7.72 (m, 2H), 7.64 (s, 1H), 7.36 (s, 1H), 4.48-4.46 (m, 1H), 4.09-4.08 (m, 1H), 3.77 (s, 3H), 3.69-3.64 (m, 1H), 3.36-3.35 (m, 1H), 2.46 (s, 3H), 2.13-2.07 (m, 1H), 1.89-1.79 (m, 3H).	Condition A : Rt = 2.96 min. m/z 490.3 [M+H] ⁺	Yellow solid	20
30	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (s, 1H), 8.05 (d, J=9.6 Hz, 1H), 7.87-7.86 (m, 2H), 7.63 (s, 1H), 7.36 (s, 1H), 4.49-4.46 (m, 1H), 4.07-4.04 (m, 1H), 3.77 (s, 3H), 3.36-3.34 (m, 2H), 2.44 (s, 3H), 2.13-2.09 (m, 1H), 1.86-1.77 (m, 3H).	Condition A : Rt = 2.84 min. m/z 479.3 [M+H] ⁺	Yellow solid	59
31	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 8.30 (d, J=8.4 Hz, 2H), 8.01 (d, J=8.4 Hz, 2H), 7.65 (s, 1H), 7.38 (s, 1H), 4.51-4.48 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H), 3.71-3.69 (m, 2H), 2.44 (s, 3H), 2.13-2.09 (m, 1H), 1.86-1.77 (m, 3H).	Condition A : Rt = 2.69 min. m/z 461.3 [M+H] ⁺	Yellow solid	25

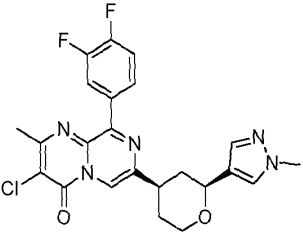
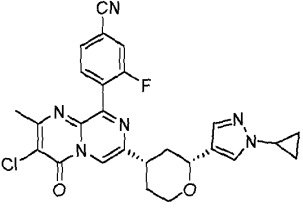
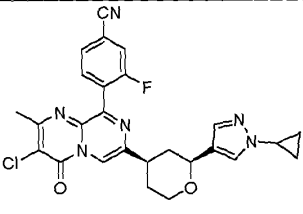
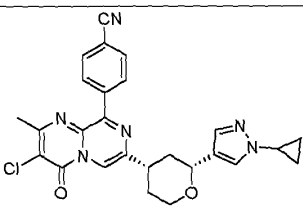
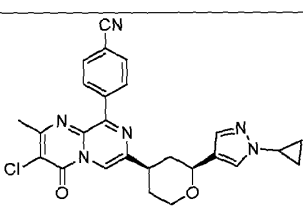
The following table describes information regarding separation of enantiomers Example 18A/18B to 29A/29B

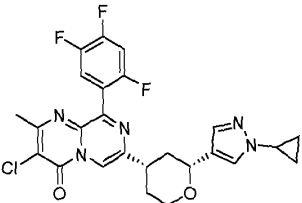
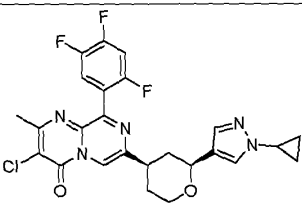
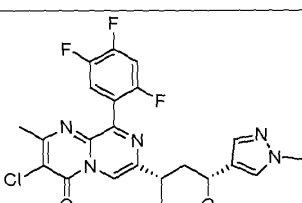
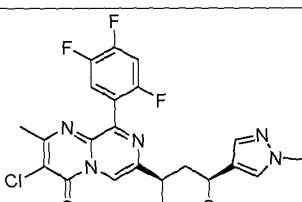
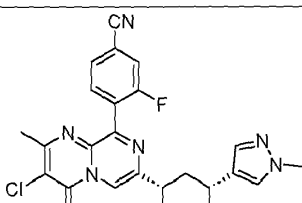
Target#	Structure	Name	Starting material	Chiral Separation method
---------	-----------	------	-------------------	--------------------------

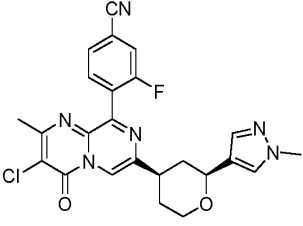
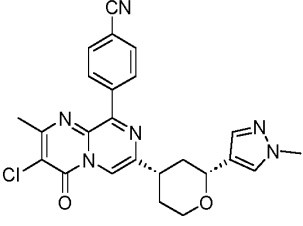
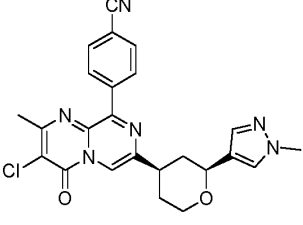
Ex. 18A (Peak -1)		3-chloro-9-(4-chloro-2-fluorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 18	NP Chiral Method 5 Peak 1 & Peak 2 - Actual stereochemistry unknown, arbitrary assignment of stereochemistry.
Ex. 18B (Peak -2)		3-chloro-9-(4-chloro-2-fluorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one		
Ex. 19A (Peak -1)		3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 19	NP Chiral Method 5 Peak 1 & Peak 2 - Actual stereochemistry unknown, arbitrary assignment of stereochemistry.
Ex. 19B (Peak -2)		3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one		
Ex. 20A (Peak -1)		3-chloro-9-(4-chlorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 20	SFC condition-2 Peak 1 & Peak 2 - Actual stereochemistry

		pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one		y unknown, arbitrary assignment of stereochemistry.
Ex. 20B (Peak -2)		3-chloro-9-(4-chlorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one		
Ex. 21A (Peak -1)		3-chloro-9-(4-chlorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 21	NP Chiral Method 4 Peak 1 & Peak 2 - Actual stereochemistry unknown, arbitrary assignment of stereochemistry
Ex. 21B (Peak -2)		3-chloro-9-(4-chlorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one		
Ex. 22A (Peak -1)		3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 22	NP Chiral Method 5 Peak 1 & Peak 2 - Actual stereochemistry unknown, arbitrary assignment of stereochemistry
Ex. 22B (Peak -2)		3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one		

		pyrazino[1,2-a]pyrimidin-4-one		
Ex. 23A (Peak -1)		3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 23	NP Chiral Method 5 Peak 1 & Peak 2 - Actual stereochemistry unknown, arbitrary assignment of stereochemistry
Ex. 23B (Peak -2)		3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one		
Ex. 24A (Peak -1)		3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 24	SFC condition -2 Peak 1 & Peak 2 - Actual stereochemistry unknown, arbitrary assignment of stereochemistry
Ex. 24B (Peak -2)		3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one		
Ex. 25A (Peak -1)		3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one	Example 25	SFC condition-2 Peak 1 & Peak 2 - Actual stereochemistry unknown, arbitrary assignment of

Ex. 25B (Peak -2)		3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one		stereochemistr y.
Ex. 26A (Peak -1)		4-(3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile	Example 26	SFC condition- 2 Peak 1 & Peak 2 - Actual stereochemistr y unknown, arbitrary assignment of stereochemistr y.
Ex. 26B (Peak -2)		4-(3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile		
Ex. 27A (Peak -1)		4-(3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile	Example 27	NP Chiral Method 4 Peak 1 & Peak 2 - Actual stereochemistr y unknown, arbitrary assignment of stereochemistr y
Ex. 27B (Peak -2)		4-(3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile		

Ex. 28A (Peak -1)		3-chloro-7- ((2R,4S)-2-(1- cyclopropyl-1H- pyrazol-4- yl)tetrahydro-2H- pyran-4-yl)-2- methyl-9-(2,4,5- trifluorophenyl)-4H- pyrazino[1,2- a]pyrimidin-4-one	Example 28	SFC condition- 2 Peak 1 & Peak 2 - Actual stereochemistr y unknown, arbitrary assignment of stereochemistr y
Ex. 28B (Peak -2)		3-chloro-7- ((2S,4R)-2-(1- cyclopropyl-1H- pyrazol-4- yl)tetrahydro-2H- pyran-4-yl)-2- methyl-9-(2,4,5- trifluorophenyl)-4H- pyrazino[1,2- a]pyrimidin-4-one		
Ex. 29A (Peak -1)		3-chloro-2-methyl- 7-((2R,4S)-2-(1- methyl-1H-pyrazol- 4-yl)tetrahydro-2H- pyran-4-yl)-9- (2,4,5- trifluorophenyl)-4H- pyrazino[1,2- a]pyrimidin-4-one	Example 29	SFC condition- 2 Peak 1 & Peak 2 - Actual stereochemistr y unknown, arbitrary assignment of stereochemistr y
Ex. 29B (Peak -2)		3-chloro-2-methyl- 7-((2S,4R)-2-(1- methyl-1H-pyrazol- 4-yl)tetrahydro-2H- pyran-4-yl)-9- (2,4,5- trifluorophenyl)-4H- pyrazino[1,2- a]pyrimidin-4-one		
Ex. 30A (Peak -1)		4-(3-chloro-2- methyl-7-((2R,4S)- 2-(1-methyl-1H- pyrazol-4- yl)tetrahydro-2H- pyran-4-yl)-4-oxo- 4H-pyrazino[1,2- a]pyrimidin-9-yl)-3- fluorobenzonitrile	Example 30	NP Chiral Method 6 Peak 1 & Peak 2 - Actual stereochemistr y unknown, arbitrary assignment of

Ex. 30B (Peak -2)		4-(3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile		stereochemistry
Ex. 31A (Peak -1)		4-(3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile	Example 31	NP Chiral Method 7 Peak 1 & Peak 2 - Actual stereochemistry unknown, arbitrary assignment of stereochemistry
Ex. 31B (Peak -2)		4-(3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile		

Following table describes analytical data analysis and yield information of examples 18A/18B to examples 29A/29B:

Target#	¹ H-NMR	LCMS	Analytical chiral HPLC	Description	Yield%
Ex. 18A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 7.72-7.68 (m, 2H), 7.62 (d, J=10.0 Hz, 1H), 7.47 (d, J=8.0 Hz, 1H), 7.36 (s, 1H), 4.48-4.46 (m, 1H), 4.08-4.06 (m, 1H), 3.69-3.64 (m, 2H), 3.32-3.31 (m, 1H), 2.47 (s, 3H), 2.14-2.11 (m, 1H), 1.90-1.80 (m, 3H), 0.98-0.97 (m, 2H), 0.91-0.89 (m, 2H).	Condition A : Rt = 3.25 min. m/z 514.2 [M+H] ⁺	Analytical chiral HPLC: CHIRALPA K IC (250X4.6)mm, 5μm M.P.-Hexane/DCM/EtOH/IPA : 20/40/40/0.1 Flow Rate - 1.0 ml/min	White solid	31
Ex. 18B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 7.72-7.68 (m, 2H), 7.62 (d, J=10.0 Hz, 1H), 7.47 (d, J=8.0 Hz, 1H), 7.36 (s, 1H), 4.48-4.46 (m, 1H), 4.08-	Condition A : Rt = 3.25 min. m/z	Solubility: MeOH; Rt = 7.70 min for Peak 1 and Rt =	White solid	30

	4.06 (m, 1H), 3.69-3.64 (m, 2H), 3.32-3.31 (m, 1H), 2.47 (s, 3H), 2.14-2.11 (m, 1H), 1.90-1.80 (m, 3H), 0.98-0.97 (m, 2H), 0.91-0.89 (m, 2H).	514.2 [M+H] ⁺	9.59 min for Peak 2		
Ex. 19A (Peak-1)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.58 (s, 1H), 7.72-7.68 (m, 1H), 7.64-7.62 (m, 2H), 7.47 (d, J=8.0 Hz, 1H), 7.36 (s, 1H), 4.49-4.46 (m, 1H), 4.10-4.06 (m, 1H), 3.77 (s, 3H), 3.70-3.64 (m, 1H), 3.29-3.28 (m, 1H), 2.47 (s, 3H), 2.14-2.11 (m, 1H), 1.90-1.80 (m, 3H).	Condition A : Rt = 3.02 min. m/z 488.3 [M+H] ⁺	Analytical chiral HPLC: CHIRALPA K IC (250X4.6) mm, 5μ M.P.- Hexane/EA/ EtOH/IPamine : 50/25/25/0.1 Flow Rate - 1.0 ml/min	White solid	17
Ex. 19B (Peak-2)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.58 (s, 1H), 7.72-7.68 (m, 1H), 7.64-7.62 (m, 2H), 7.47 (d, J=8.0 Hz, 1H), 7.36 (s, 1H), 4.49-4.46 (m, 1H), 4.10-4.06 (m, 1H), 3.77 (s, 3H), 3.70-3.64 (m, 1H), 3.29-3.28 (m, 1H), 2.47 (s, 3H), 2.14-2.11 (m, 1H), 1.90-1.80 (m, 3H).	Condition A : Rt = 3.02 min. m/z 488.3 [M+H] ⁺	Solubility: MeOH; Rt = 12.01 min for Peak 1 and Rt = 15.34 min for Peak 2	White solid	18
Ex. 20A (Peak-1)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.54 (s, 1H), 8.21 (d, J=8.8 Hz, 2H), 7.37 (s, 1H), 7.60 (d, J=8.8 Hz, 2H), 7.38 (s, 1H), 4.49-4.47 (m, 1H), 4.10-4.08 (m, 1H), 3.68-3.63 (m, 2H), 3.32-3.31 (m, 1H), 2.55 (s, 3H), 2.16-2.13 (m, 1H), 1.90-1.84 (m, 3H), 1.01-0.97 (m, 2H), 0.93-0.89 (m, 2H).	Condition A : Rt = 3.23 min. m/z 496.3 [M+H] ⁺	Analytical chiral HPLC by SFC: I-Cellulose J (250X4.6) mm, 5μ solvent: 0.3% IPamine in MeOH Flow Rate – 5	White solid	24
Ex. 20B (Peak-2)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.54 (s, 1H), 8.21 (d, J=8.8 Hz, 2H), 7.37 (s, 1H), 7.60 (d, J=8.8 Hz, 2H), 7.38 (s, 1H), 4.49-4.47 (m, 1H), 4.10-4.08 (m, 1H), 3.68-3.63 (m, 2H), 3.32-3.31 (m, 1H), 2.55 (s, 3H), 2.16-2.13 (m, 1H), 1.90-1.84 (m, 3H), 1.01-0.97 (m, 2H), 0.93-0.89 (m, 2H).	Condition A : Rt = 3.23 min. m/z 496.3 [M+H] ⁺	ml/min. using 60% CO ₂ ; Solubility: MeOH; Rt = 4.22 min for Peak 1 and Rt = 6.71 min for Peak 2	White solid	23
Ex. 21A (Peak-1)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.54 (s, 1H), 8.21 (d,	Condition	Analytical chiral HPLC:	White solid	30

	J=8.8 Hz, 2H), 7.65-7.60 (m, 3H), 7.38 (s, 1H), 4.50-4.48 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H), 3.72-3.67 (m, 1H), 3.32-3.28 (m, 1H), 2.66 (s, 3H), 2.16-2.13 (m, 1H), 1.89-1.83 (m, 3H).	A : Rt = 3.04 min. m/z 470.3 [M+H] ⁺	CHIRALPA K IC (250X4.6)m m,5μ M.P.- Hexane/EA/ EtOH/IPAmine : 30/35/35/0.1		
Ex. 21B (Peak-2)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.54 (s, 1H), 8.21 (d, J=8.8 Hz, 2H), 7.65-7.60 (m, 3H), 7.38 (s, 1H), 4.50-4.48 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H), 3.72-3.67 (m, 1H), 3.32-3.28 (m, 1H), 2.66 (s, 3H), 2.16-2.13 (m, 1H), 1.89-1.83 (m, 3H).	Condition A : Rt = 3.04 min. m/z 470.3 [M+H] ⁺	Flow Rate - 1.0 ml/min. Solubility: MeOH; Rt = 8.54 min for Peak 1 and Rt = 11.10 min for Peak 2	White solid	29
Ex. 22A (Peak-1)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.58 (s, 1H), 8.33 (d, J=8.0 Hz, 2H), 7.90 (d, J=8.4 Hz, 2H), 7.65 (s, 1H), 7.38 (s, 1H), 4.50-4.48 (m, 1H), 4.10-4.08 (m, 1H), 3.77 (s, 3H), 3.70-3.68 (m, 1H), 3.35-3.31 (m, 1H), 2.54 (s, 3H), 2.16-2.13 (m, 1H), 1.90-1.84 (m, 3H).	Condition A : Rt = 3.27 min. m/z 504.2 [M+H] ⁺	Analytical chiral HPLC: CHIRALPA K IC (4.6 x 250 mm),5μ ARD/K/7788 Mobile Phase: Hexane/DC M/EtOH/IPA	White solid	26
Ex. 22B (Peak-2)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.58 (s, 1H), 8.33 (d, J=8.0 Hz, 2H), 7.90 (d, J=8.4 Hz, 2H), 7.65 (s, 1H), 7.38 (s, 1H), 4.50-4.48 (m, 1H), 4.10-4.08 (m, 1H), 3.77 (s, 3H), 3.70-3.68 (m, 1H), 3.35-3.31 (m, 1H), 2.54 (s, 3H), 2.16-2.13 (m, 1H), 1.90-1.84 (m, 3H).	Condition A : Rt = 3.27 min. m/z 504.2 [M+H] ⁺	mine : 20/40/40/0.1 Flow Rate : 1.0 ml/min Solubility : MeOHRt = 7.29 min for Peak 1 and Rt = 9.05 min for Peak 2	White solid	25
Ex. 23A (Peak-1)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.56 (s, 1H), 8.26 (d, J=8.0 Hz, 2H), 7.73 (d, J=7.6 Hz, 2H), 7.66 (s, 1H), 7.38 (s, 1H), 7.29-7.01 (m, 1H), 4.51-4.48 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H), 3.72-3.69 (m, 1H), 3.33-3.31 (m, 1H), 2.54 (s, 3H), 2.16-2.13 (m, 1H), 1.90-1.82 (m, 3H).	Condition A : Rt = 2.96 min. m/z 486.3 [M+H] ⁺	Analytical chiral HPLC: CHIRALPA K IC (250X4.6)m m,5μ M.P.- Hexane/EA/ EtOH/IPAmine : 50/25/25/0.1 Flow Rate - 1.0 ml/min,	White solid	32
Ex. 23B (Peak-2)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.56 (s, 1H), 8.26 (d,	Condition		White solid	33

	J=8.0 Hz, 2H), 7.73 (d, J=7.6 Hz, 2H), 7.66 (s, 1H), 7.38 (s, 1H), 7.29-7.01 (m, 1H), 4.51-4.48 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H), 3.72-3.69 (m, 1H), 3.33-3.31 (m, 1H), 2.54 (s, 3H), 2.16-2.13 (m, 1H), 1.90-1.82 (m, 3H).	A : Rt = 2.96 min. m/z 486.3 [M+H] ⁺	Solubility: MeOH; Rt = 13.79 min for Peak 1 and Rt = 18.44 min for Peak 2		
Ex. 24A (Peak-1)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.55 (s, 1H), 8.31-8.26 (m, 1H), 8.12-8.10 (m, 1H), 7.73 (s, 1H), 7.65-7.58 (m, 1H), 7.38 (s, 1H), 4.49-4.47 (m, 1H), 4.11-4.08 (m, 1H), 3.71-3.63 (m, 2H), 3.29-3.27 (m, 1H), 2.57 (s, 3H), 2.17-2.14 (m, 1H), 1.90-1.81 (m, 3H), 0.99-0.98 (m, 2H), 0.94-0.90 (m, 2H).	Condition A : Rt = 3.11 min. m/z 498.3 [M+H] ⁺	Analytical chiral HPLC by SFC: I-Cellulose J (250X4.6) mm, 5μ solvent: 0.3% IPamine in MeOH Flow Rate – 5	White solid	24
Ex. 24B (Peak-2)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.55 (s, 1H), 8.31-8.26 (m, 1H), 8.12-8.10 (m, 1H), 7.73 (s, 1H), 7.65-7.58 (m, 1H), 7.38 (s, 1H), 4.49-4.47 (m, 1H), 4.11-4.08 (m, 1H), 3.71-3.63 (m, 2H), 3.29-3.27 (m, 1H), 2.57 (s, 3H), 2.17-2.14 (m, 1H), 1.90-1.81 (m, 3H), 0.99-0.98 (m, 2H), 0.94-0.90 (m, 2H).	Condition A : Rt = 3.11 min. m/z 498.3 [M+H] ⁺	ml/min. using 60% CO ₂ ; Solubility: MeOH; Solubility: MeOH; Rt = 4.40 min for Peak 1 and Rt = 6.75 min for Peak 2	White solid	25
Ex. 25A (Peak-1)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.55 (s, 1H), 8.31-8.26 (m, 1H), 8.12-8.11 (m, 1H), 7.67-7.58 (m, 2H), 7.39 (s, 1H), 4.50-4.48 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H), 3.72-3.66 (m, 1H), 3.32-3.26 (m, 1H), 2.56 (s, 3H), 2.16-2.13 (m, 1H), 1.89-1.82 (m, 3H).	Condition A : Rt = 2.99 min. m/z 472.3 [M+H] ⁺	Analytical chiral HPLC by SFC: I-Cellulose J (250X4.6) mm, 5μ solvent: 0.3% IP amine in MeOH Flow Rate – 5 ml/min. using 60% CO ₂ ; Solubility: MeOH; Rt = 2.48 min for Peak 1 and Rt =	Yellow solid	21
Ex. 25B (Peak-2)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.55 (s, 1H), 8.31-8.26 (m, 1H), 8.12-8.11 (m, 1H), 7.67-7.58 (m, 2H), 7.39 (s, 1H), 4.50-4.48 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H), 3.72-3.66 (m, 1H), 3.32-3.26 (m, 1H),	Condition A : Rt = 2.99 min. m/z 472.3 [M+H] ⁺	Flow Rate – 5 ml/min. using 60% CO ₂ ; Solubility: MeOH; Rt = 2.48 min for Peak 1 and Rt =	Yellow solid	20

	2.56 (s, 3H), 2.16-2.13 (m, 1H), 1.89-1.82 (m, 3H).		3.38 min for Peak 2		
Ex. 26A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.62 (s, 1H), 8.05 (d, J=9.6 Hz, 1H), 7.87-7.86 (m, 2H), 7.72 (s, 1H), 7.36 (s, 1H), 4.47-4.45 (m, 1H), 4.08-4.06 (m, 1H), 3.69-3.63 (m, 2H), 3.37-3.34 (m, 1H), 2.46 (s, 3H), 2.14-2.11 (m, 1H), 1.90-1.79 (m, 3H), 0.98-0.96 (m, 2H), 0.92-0.89 (m, 2H).	Condition A : Rt = 6.06 min. m/z 505.3 [M+H] ⁺	Analytical chiral HPLC by SFC: I-Cellulose J (250X4.6) mm, 5μ solvent: 0.3% IPamine in MeOH Flow Rate –	Yellow solid	33
Ex. 26B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.62 (s, 1H), 8.05 (d, J=9.6 Hz, 1H), 7.87-7.86 (m, 2H), 7.72 (s, 1H), 7.36 (s, 1H), 4.47-4.45 (m, 1H), 4.08-4.06 (m, 1H), 3.69-3.63 (m, 2H), 3.37-3.34 (m, 1H), 2.46 (s, 3H), 2.14-2.11 (m, 1H), 1.90-1.79 (m, 3H), 0.98-0.96 (m, 2H), 0.92-0.89 (m, 2H).	Condition A : Rt = 6.06 min. m/z 505.3 [M+H] ⁺	5 ml/min. using 60% CO ₂ ; Solubility: MeOH; Rt = 2.59 min for Peak 1 and Rt = 3.81 min for Peak 2	Yellow solid	34
Ex. 27A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 8.30 (d, J=8.4 Hz, 2H), 8.00 (d, J=8.4 Hz, 2H), 7.73 (s, 1H), 7.38 (s, 1H), 4.48-4.46 (m, 1H), 4.10-4.07 (m, 1H), 3.71-3.62 (m, 2H), 3.33-3.28 (m, 1H), 2.53 (s, 3H), 2.16-2.12 (m, 1H), 1.90-1.84 (m, 3H), 0.98-0.96 (m, 2H), 0.92-0.89 (m, 2H).	Condition A : Rt = 3.08 min. m/z 487.3 [M+H] ⁺	Analytical chiral HPLC: Chiralpak IC (4.6 x 250 mm), 5μ ARD/K/7788 Mobile Phase: Hexane/DCM/EtOH/IPA : mine	White solid	10
Ex. 27B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 8.30 (d, J=8.4 Hz, 2H), 8.00 (d, J=8.4 Hz, 2H), 7.73 (s, 1H), 7.38 (s, 1H), 4.48-4.46 (m, 1H), 4.10-4.07 (m, 1H), 3.71-3.62 (m, 2H), 3.33-3.28 (m, 1H), 2.53 (s, 3H), 2.16-2.12 (m, 1H), 1.90-1.84 (m, 3H), 0.98-0.96 (m, 2H), 0.92-0.89 (m, 2H).	Condition A : Rt = 3.08 min. m/z 487.3 [M+H] ⁺	20/40/40/0.1 Flow Rate : 1.0 ml/min Solubility : MeOH; Rt = 10.85 min for Peak 1 and Rt = 14.58 min for Peak 2	White solid	10
Ex. 28A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.59 (s, 1H), 7.78-7.72 (m, 3H), 7.37 (s, 1H), 4.47-4.45 (m, 1H), 4.08-4.06 (m, 1H), 3.66-3.63 (m, 2H), 3.27-3.24 (m, 1H),	Condition A : Rt = 3.06 min. m/z	Analytical chiral HPLC by SFC: I-Cellulose J (250X4.6) mm, 5μ	White solid	15

	2.45 (s, 3H), 2.14-2.10 (m, 1H), 1.88-1.80 (m, 3H), 0.98-0.96 (m, 2H), 0.91-0.89 (m, 2H).	516.3 [M+H] +	solvent: 0.3% IPamine in MeOH		
Ex. 28B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.59 (s, 1H), 7.78-7.72 (m, 3H), 7.37 (s, 1H), 4.47-4.45 (m, 1H), 4.08-4.06 (m, 1H), 3.66-3.63 (m, 2H), 3.27-3.24 (m, 1H), 2.45 (s, 3H), 2.14-2.10 (m, 1H), 1.88-1.80 (m, 3H), 0.98-0.96 (m, 2H), 0.91-0.89 (m, 2H).	Condi tion A : Rt = 3.06 min. m/z 516.3 [M+H] +	Flow Rate – 5 ml/min.usin g 60% CO ₂ ; Solubility: MeOH; Rt = 2.74 min for Peak 1 and Rt = 4.01 min for Peak 2	White solid	16
Ex. 29A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.59 (s, 1H), 7.83-7.72 (m, 2H), 7.64 (s, 1H), 7.36 (s, 1H), 4.48-4.46 (m, 1H), 4.09-4.08 (m, 1H), 3.77 (s, 3H), 3.69-3.64 (m, 1H), 3.36-3.35 (m, 1H), 2.46 (s, 3H), 2.13-2.07 (m, 1H), 1.89-1.79 (m, 3H).	Condi tion A : Rt = 2.96 min. m/z 490.3 [M+H] +	Analytical chiral HPLC by SFC: I- Cellulose J (250X4.6) mm, 5μ solvent: 0.3% IPamine in MeOH	Yellow solid	17
Ex. 29B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.59 (s, 1H), 7.83-7.72 (m, 2H), 7.64 (s, 1H), 7.36 (s, 1H), 4.48-4.46 (m, 1H), 4.09-4.08 (m, 1H), 3.77 (s, 3H), 3.69-3.64 (m, 1H), 3.36-3.35 (m, 1H), 2.46 (s, 3H), 2.13-2.07 (m, 1H), 1.89-1.79 (m, 3H).	Condi tion A : Rt = 2.96 min. m/z 490.3 [M+H] +	Flow Rate – 5 ml/min.usin g 60% CO ₂ ; Solubility: MeOH; Rt = 3.63 min for Peak 1 and Rt = 4.73 min for Peak 2	Yellow solid	18
Ex. 30A (Peak-1)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (s, 1H), 8.05 (d, J=9.6 Hz, 1H), 7.87-7.86 (m, 2H), 7.63 (s, 1H), 7.36 (s, 1H), 4.49-4.46 (m, 1H), 4.07-4.04 (m, 1H), 3.77 (s, 3H), 3.36-3.34 (m, 2H), 2.44 (s, 3H), 2.13-2.09 (m, 1H), 1.86-1.77 (m, 3H).	Condi tion A : Rt = 2.84 min. m/z 479.3 [M+H] +	Analytical chiral HPLC: Chiralpak IG (4.6 x 250 mm), 5μ ARD/K/7788 Mobile Phase: Hexane/EA/ EtOH/IPami ne : 50/25/25/0.1	Yellow solid	31
Ex. 30B (Peak-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (s, 1H), 8.05 (d, J=9.6 Hz, 1H), 7.87-7.86 (m, 2H), 7.63 (s, 1H), 7.36 (s, 1H), 4.49-4.46 (m, 1H), 4.07-4.04 (m, 1H),	Condi tion A : Rt = 2.84 min. m/z	Flow Rate : 1.0 ml/min Solubility : MeOH; Rt =	Yellow solid	27

	3.77 (s, 3H),3.36-3.34 (m, 2H),2.44 (s, 3H), 2.13-2.09 (m, 1H), 1.86-1.77 (m, 3H).	479.3 [M+H] ⁺	12.33 min for Peak 1 and Rt = 13.3 min for Peak 2		
Ex. 31A (Peak-1)	1H NMR (400 MHz, DMSO-d6) δ 8.58 (s, 1H), 8.30 (d, J=8.4 Hz, 2H), 8.01 (d, J=8.4 Hz, 2H), 7.65 (s, 1H), 7.38 (s, 1H), 4.51-4.48 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H), 3.71-3.69 (m, 2H), 2.44 (s, 3H), 2.13-2.09 (m, 1H), 1.86-1.77 (m, 3H).	Condition A : Rt = 2.69 min. m/z 461.3 [M+H] ⁺	Analytical chiral HPLC: UNICHIRAL CND (250X4.6)m m,5μ Mobile Phase: Hexane//Et OH/MeOH/I	Yellow solid	34
Ex. 31B (Peak-2)	1H NMR (400 MHz, DMSO-d6) δ 8.58 (s, 1H), 8.30 (d, J=8.4 Hz, 2H), 8.01 (d, J=8.4 Hz, 2H), 7.65 (s, 1H), 7.38 (s, 1H), 4.51-4.48 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H), 3.71-3.69 (m, 2H), 2.44 (s, 3H), 2.13-2.09 (m, 1H), 1.86-1.77 (m, 3H).	Condition A : Rt = 2.69 min. m/z 461.3 [M+H] ⁺	PAmine : 20/40/40/0.1 Flow Rate : 1.0 ml/min Solubility : MeOH; Rt = 16.83 min for Peak 1 and Rt = 20.67 min for Peak 2	Yellow solid	26

Example 32 – Biological assay

Human TREM2, in vitro Measurement of Triggering Receptor Expressed on Myeloid Cells 2 activity using cellular phosphorylation of Spleen Tyrosine Kinase (“Syk”) Assay

5 Cell line:

HEK-293 cells were co-transfected with separate plasmids encoding TREM2 and DAP12 to generate a stable cell line. After antibiotic selection, functional clone pool analysis and two successive limiting dilutions, the final clone

10 “HEK293/DAP12+TREM2” underwent a qPCR analysis and a pharmacological validation.

Assay

15 TREM2 signaling through DAP12 was monitored in the HEK293/DAP12+TREM2 stable cell line by measuring the phosphorylation levels of the Syk kinase using the commercially available AlphaLISA SureFire Ultra p-SYK (Tyr525/526) Assay Kit (PerkinElmer #ALSU-PSYK), based on the Perkin Elmer AlphaScreen/AlphaLISA technology.

Compounds are transferred to the test plate and tested in full dose response, 8 concentrations in quadruplicate data points. Compound serial dilutions were performed at Cybi-Felix instrument in 100% DMSO and the dose response curves were assembled in automated fashion in 384MPT at Hamilton STARlet instrument. All the stock solutions were prepared at 20 mM in 100% DMSO. For compounds testing, the starting concentration was 100 μ M, dilution steps 1:6. A different concentration's range was adapted for compound's activity based on the preliminary results. Finally, a 384MPT reformatted for all compounds at 8 concentrations, quadruplicates, was used as "mother to child" process with a CyBi®-Well dispenser in which 1 μ L of each compound was moved into a destination plate pre-filled with 65.6 μ L of EMEM cell culture medium (BIOHITTAKER_cat.BE12-125F), thus obtaining 3x concentrated compounds working solution. In columns 1-2 and 23-24 the control wells were added. In particular, dose response curves of a reference control agonist were included in column 1 and 24 as reference control agonist (Reference control agonists used include Human TREM2 polyclonal Antibody AF1828: R&D Systems; Human TREM2 monoclonal Antibody MAB1828: R&D Systems). The dose response curves were tested starting at 30 μ M, dilution step 1:6. Both "source" compound plate and "destination" compound plate were barcoded and a relationship between the two plates was thus generated.

HEK293/DAP12+TREM2 cells were cultured in EMEM medium supplemented with IX Penicillin/Streptomycin (BIOHITTAKER_cat.DE17-602E), ULTRAGLUTAMINE I 200mM, 10% Fetal Bovine Serum plus antibiotics referred to as "HEK293 Culture Medium". The day before the experiment, cells were detached by gentle wash with DPBS, followed by 5 min incubation at 37°C with Trypsin solution. Cells were then diluted in HEK293 Culture Medium without antibiotics, counted and seeded into 384-well poly-D-Lysine coated microplates black/clear bottom (GREINER 781946) at a density of 10,000 cells/well in 25 μ L/well by the use of a MATRIX WellMate dispenser. Plates were placed into a humidified cell culture incubator at 37°C with 5% CO₂ until the experimental day. 20-24 hours after seeding mature medium was removed and replaced with 10 μ L/well of EMEM cell medium supplemented with 0.1% Pluronic F-68 non-ionic surfactant (Thermofisher, 24040032), referred to as "Assay Buffer", using the CyBi®-Well instrument. Then 5 μ L/well of Assay Buffer containing 3X concentrated test compounds or the reference control agonist (in 0.5 % final DMSO concentration) were added to the cells with the CyBi®-Well instrument. Cell plates were incubated for 30 min into a humidified cell culture incubator at 37°C with 5% CO₂, then the medium was

removed by manually discard. 20 µL/well of lysis buffer were dispensed using the CyBi®-Well instrument and plates were incubated for 10 min at room temperature on a plate shaker (350rpm). Then, 10 µL/well of lysate were transferred to the Alpha plates. The CyBi®-Well instrument was used to dispense 5 µL/well of AlphaLISA Acceptor

5 Bead Solution in IX Immunoassay buffer (Perkin Elmer AL000F). Then the plates were sealed with Heat sealing foil, shaken for 2 minutes (350 rpm) and incubated for 1 hour at room temperature. Following the incubation with the AlphaLISA Acceptor Bead Solution, the CyBi®-Well instrument was used to dispense 5 µL/well of AlphaLISA Donor Bead Solution in IX Immunoassay buffer. The plates were sealed with Heat

10 sealing foil, shaken for 2 minutes (350 rpm) and then incubated for 1 hour at room temperature. At the end of the incubation an AlphaLISA signal was acquired from the donor and acceptor beads using the Pherastar FSX instrument, a high throughput multi-modal microplate reader calibrated to the plate type with the AlphaLISA mirror and filter-set in 384-well mode, 680-615 nanometer excitation wavelength. The total

15 integration time was 0,60 seconds with a 0,30 second excitation time and a gain of 3600.

Data analysis was performed with Genedata Screener® software and reported compounds activity as % effect in relation to the normalization standards. The AlphaScreen Signal was normalized versus Neutral Controls (Assay buffer plus 0.5%

20 DMSO final conc.) and Stimulator Controls (EC₁₀₀ of the reference control agonist in Assay buffer plus 0.5% DMSO final conc.) in order to obtain the Activity[%] for each well. The normalization places the compound activity values on an equivalent scale and makes them comparable across plates or different compound batches. Therefore, the compound activity values were scaled (based on the two references) to a common

25 range (two-point normalization). The following equation was used by the software to normalize the signal values to the desired signal range:

$$N(x) = CR + [(x - < cr >) / (< sr > - < cr >)] \cdot (SR - CR)$$

where: x is the signal value of a well; < cr > is the median of the signal values for the Central Reference wells of a plate (median of Neutral Controls); < sr > is the

30 median of the signal values for the Scale Reference wells of a plate (median of Stimulator Controls); CR is the desired median normalized value for the Central Reference (0) and SR is the desired median normalized value for the Scale Reference (100).

The final equation to calculate the Activity% can be simplified as follow:

% Activity = 100 · (x - <NeutralControls>) / (<StimulatorControls> - <NeutralControls>)
where full activation corresponds to % Activity = 100.

The fitting of the dose-response curve of each test compound is performed in the Analyzer module of the Screener software on the normalized values and applying the “smart fit” strategy. This strategy allowed an automatic selection between the “Constant Fit” and the “Hill Fit” model calculating which fit model best matched the experimental data. The Constant Fit was applied when no change of activity was detected across the measured concentrations, and the corresponding compounds were further classified as “inactive”. The Hill Fit was applied when the observed activity significantly changed with the compound concentration. In case of Hill Fit, Hill equation was used to determine the concentration at which activity reaches 50% of maximum level, i.e., AC₅₀.

$$Y = S_0 + ((S_{inf} - S_0) / (1 + (10^{LogAC50} / 10^X)^n))$$

where X is Log10 of compound concentration.

The equation has four parameters:

- Zero Activity (S₀) - Activity level at zero concentration of test compound;
- Infinite Activity (S_{inf}) - Activity level at infinite concentration of test compound;
- AC₅₀ - Concentration at which activity reaches 50% of maximum level. This term corresponds to EC₅₀ in this assay;
- Hill coefficient (n) - Measure of the slope at AC₅₀.

The potency of the test compounds was expressed as EC₅₀ corresponding to the test compound concentration able to activate the phospho-Syk AlphaScreen signal to 50% of the maximal response.

The EC₅₀ values measured in this assay for the exemplified compounds is set out in the table below:

Example	EC ₅₀	E _{max}
1A	B	++
1B	C	+
2A	D	+
2B	B	++
3A	B	++
3B	C	+

4A	D	+
4B	C	++
5A	B	++
5B	C	+
6A	C	+
6B	D	+
7A	D	+
7B	B	++
8A	C	+
8B	D	+
9A	C	+
9B	B	++
10A	C	++
10B	B	++
11A	C	+
11B	C	++
12A	B	++
12B	C	+
13A	B	++
13B	C	+
14	A	++
15	B	++
16	B	++
17	B	++
18A	C	+
18B	A	++
19A	C	+
19B	B	++
20A	A	++
20B	C	+
21A	C	+
21B	A	++
22A	C	+
22B	A	++

23A	C	+
23B	B	++
24A	B	++
24B	C	++
25A	B	++
25B	C	+
26A	B	++
26B	D	+
27A	C	+
27B	B	++
28A	A	++
28B	B	+
29A	B	++
29B	C	+
30A	B	++
30B	C	+
31A	B	++
31B	C	+

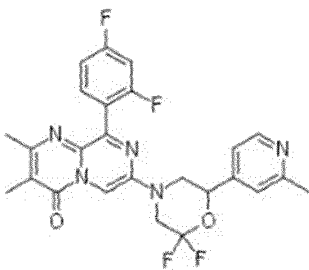
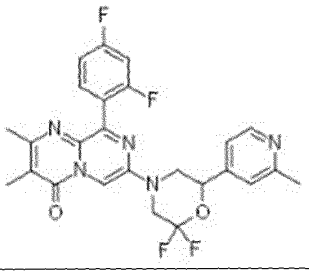
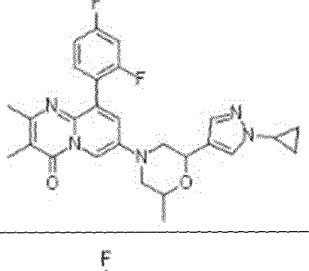
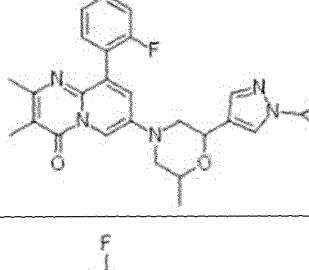
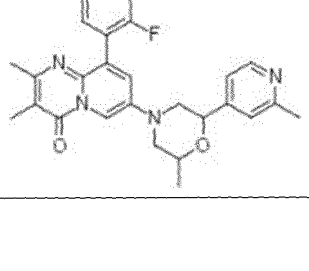
wherein "A" denotes an EC₅₀ value <10 nM, "B" denotes an EC₅₀ value between 10 nM and 100 nM, "C" denotes an EC₅₀ value between 100 and 1000 nM, "D" denotes an EC₅₀ value greater than 1000 nM. Regarding E_{max} values, "+" denotes < 75%, "++" denotes 75-110% and "+++" denotes >110% maximal response relative to the maximal response of the reference agonist (8-(4-chloro-2-fluorophenyl)-2,3-dimethyl-6-[(2S)-2-(1-methyl-1H-pyrazol-4-yl)morpholin-4-yl]-3H,4H-[1,3]diazino[5,4-d]pyrimidin-4-one).

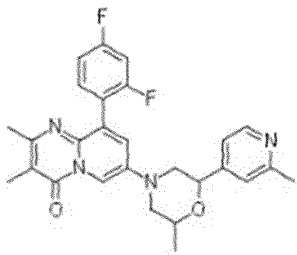
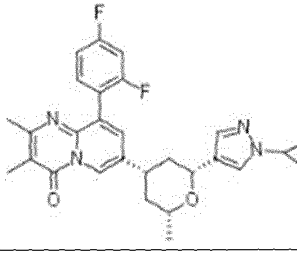
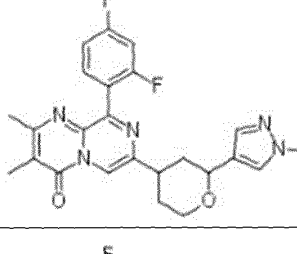
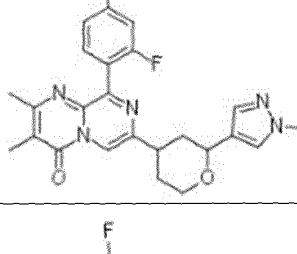
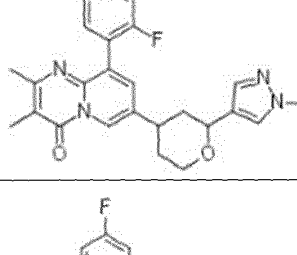
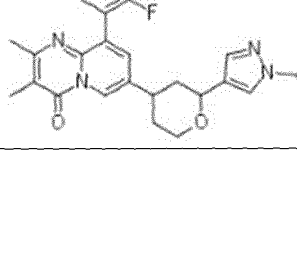
Examples 33 to 71

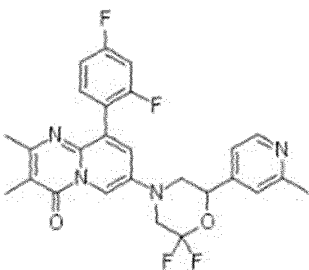
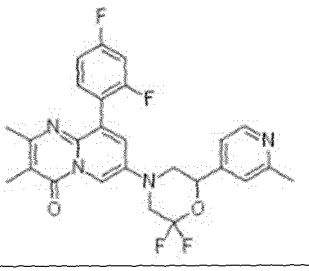
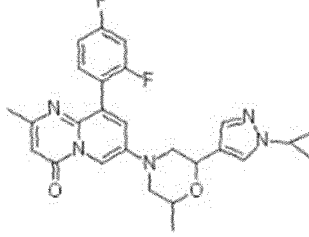
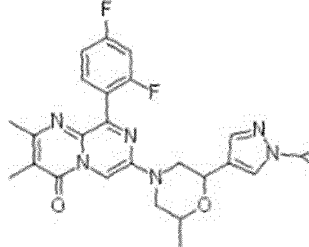
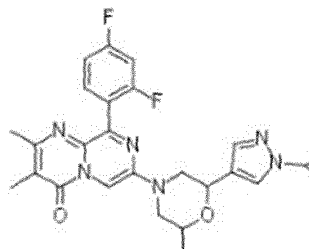
The following additional examples were made using similar methods to those described for previous examples, and were assessed in the biological assay described in Example 32.

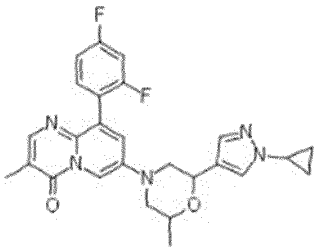
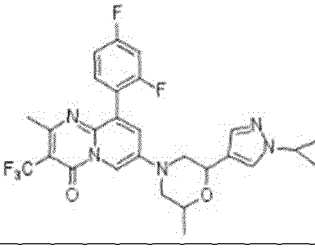
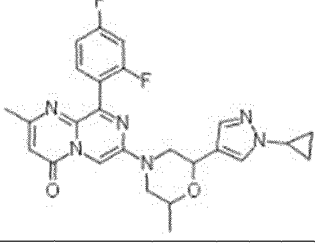
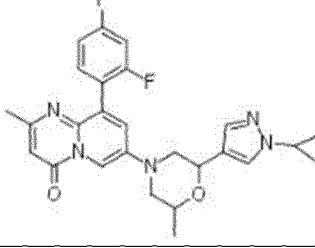
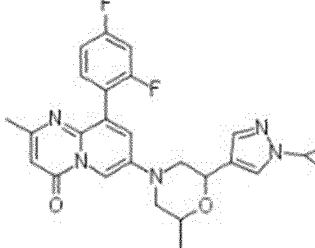
5

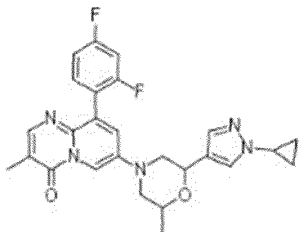
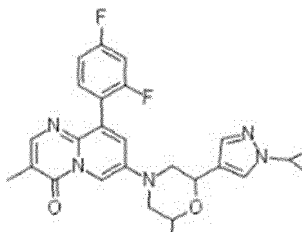
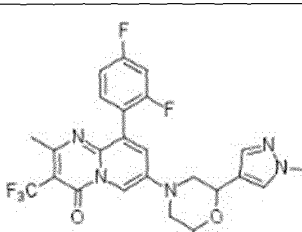
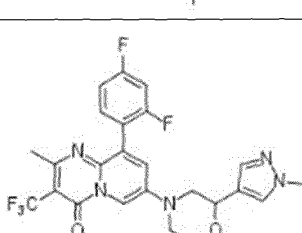
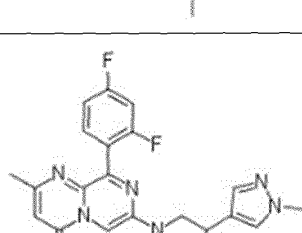
Ex.	Structure	Name	EC ₅₀	E _{max}
33A		9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-methyl-6-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one Peak 1	A	++
33B		9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-methyl-6-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one Peak 2	C	+
34A		9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one Peak 1	B	+
34B		9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one Peak 2	A	+++

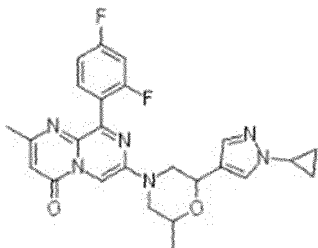
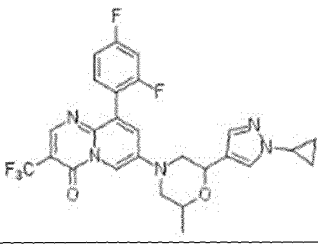
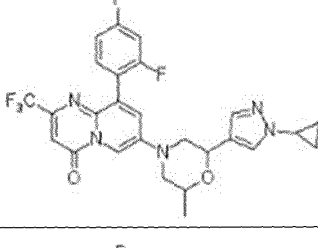
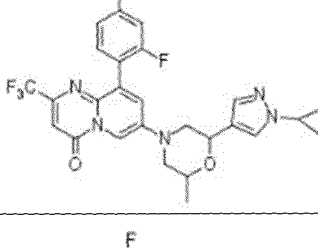
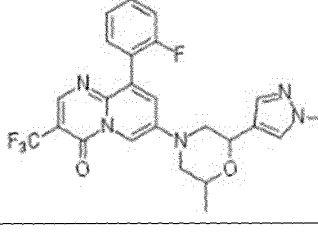
35A		7-[2,2-difluoro-6-(2-methyl-4-pyridyl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one Peak 1	A	++
35B		7-[2,2-difluoro-6-(2-methyl-4-pyridyl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one Peak 2	C	+
36A		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one Peak 1	B	++
36B		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one Peak 2	C	+
37A		9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-methyl-6-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one Peak 1	B	++

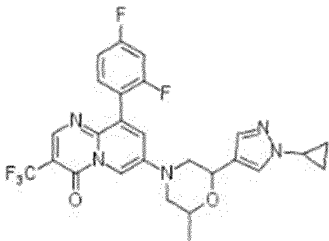
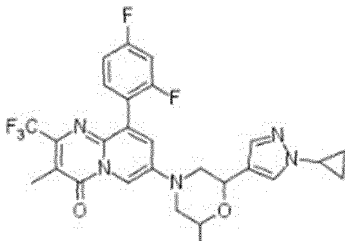
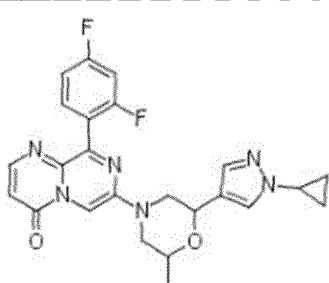
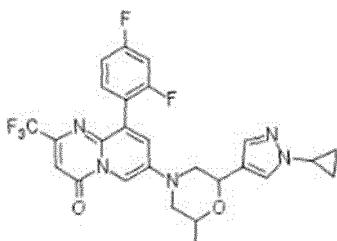
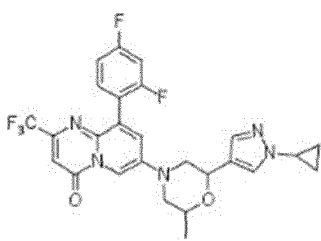
37B		9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-methyl-6-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one Peak 2	B	+
38		7-[(2R,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one	B	++
39A		7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one Peak 1	A	**
39B		7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one Peak 2	B	++
40A		7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one Peak 1	B	++
40B		7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one Peak 2	B	+

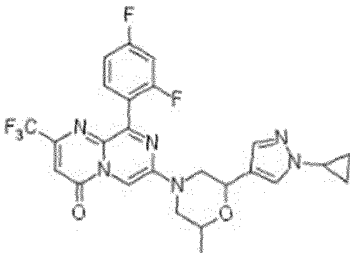
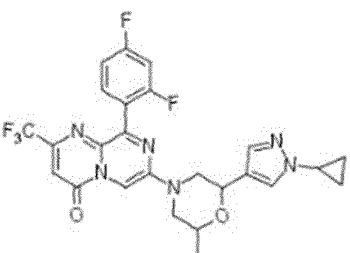
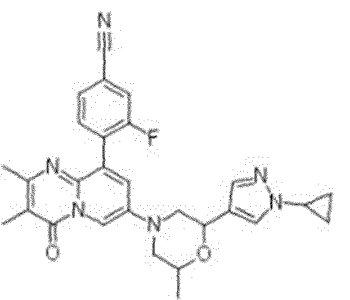
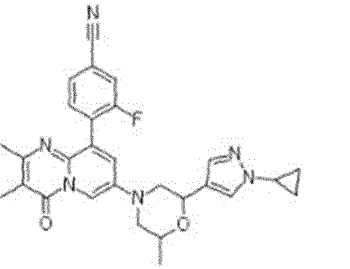
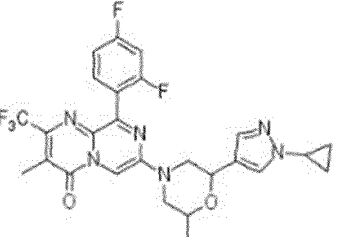
41A		7-[2,2-difluoro-6-(2-methyl-4-pyridyl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one Peak 1	A	++
41B		7-[2,2-difluoro-6-(2-methyl-4-pyridyl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one Peak 2	B	+
42		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one	C	+
43A		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one Peak 1	A	++
43B		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one Peak 2	B	++

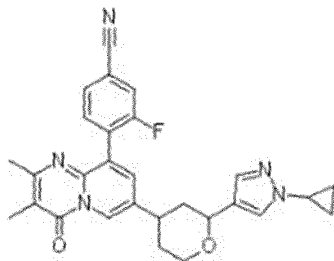
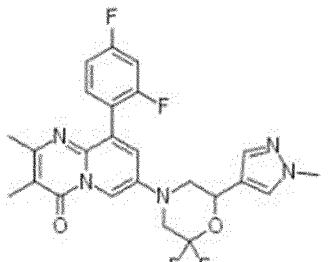
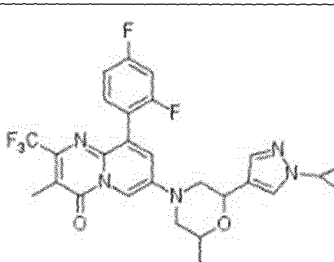
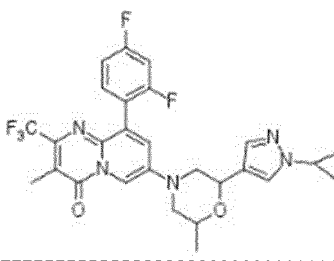
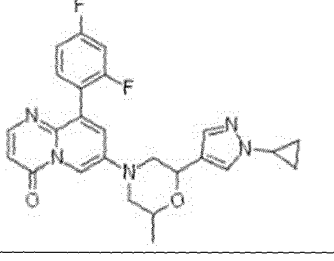
44		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-pyrido[1,2-a]pyrimidin-4-one	B	+
45		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one	C	+
46		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrazino[1,2-a]pyrimidin-4-one	C	+
47A	 Peak 1	7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one Peak 1	C	+
47B	 Peak 2	7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one Peak 2	D	+

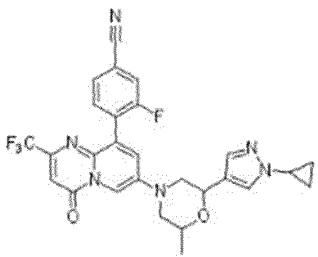
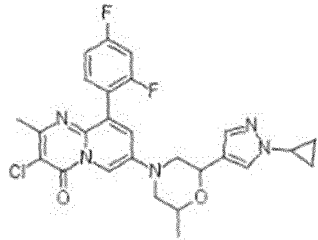
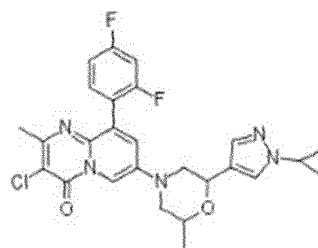
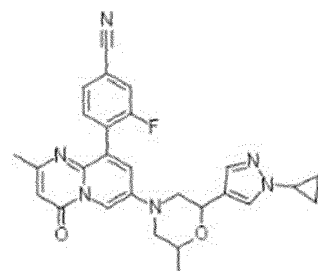
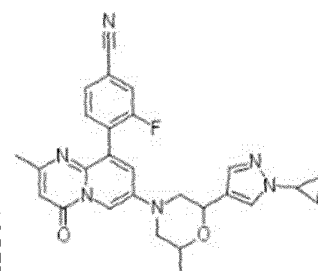
48A		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-pyrido[1,2-a]pyrimidin-4-one Peak 1	B	++
48B		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-pyrido[1,2-a]pyrimidin-4-one Peak 2	C	+
49A		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one Peak 1	B	++
49B		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one Peak 2	C	+
50A		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrazino[1,2-a]pyrimidin-4-one Peak 1	B	++

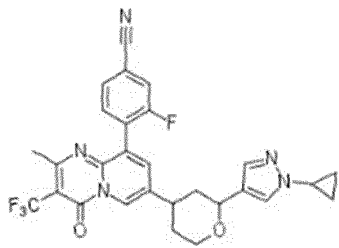
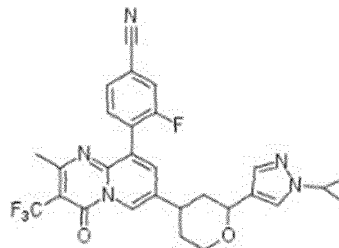
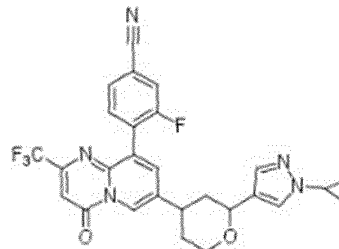
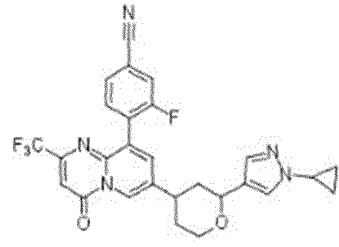
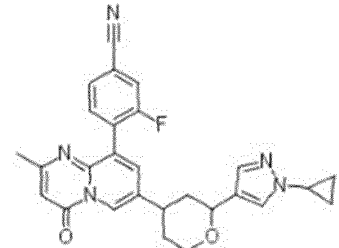
50B		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrazino[1,2-a]pyrimidin-4-one Peak 2	C	+
51		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one	D	+
52A		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one Peak 1	B	++
52B		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one Peak 2	B	++
53A		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one Peak 1	D	+

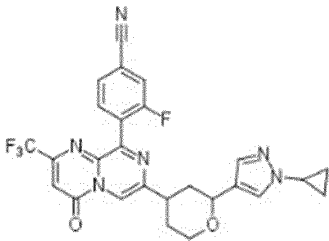
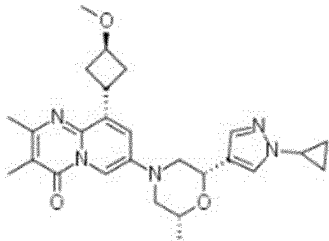
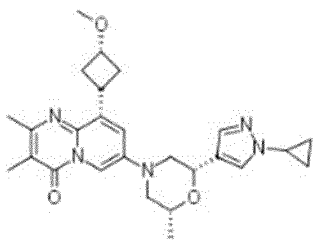
53B		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one Peak 2	D	+
54		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one	A	++
55		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)pyrazino[1,2-a]pyrimidin-4-one	C	+
56A		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one Peak 1	B	+
56B		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one Peak 2	C	+

57A		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-(trifluoromethyl)pyrazino[1,2-a]pyrimidin-4-one Peak 1	B	++
57B		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-(trifluoromethyl)pyrazino[1,2-a]pyrimidin-4-one Peak 2	C	+
58A		4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluorobenzonitrile Peak 1	B	++
58B		4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluorobenzonitrile Peak 2	D	+
59		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrazino[1,2-a]pyrimidin-4-one	A	++

60		4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluorobenzonitrile	C	+
61		7-[2,2-difluoro-6-(1-methylpyrazol-4-yl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one	A	++
62A		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one Peak 1	A	++
62B		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one Peak 2	B	++
63		7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)pyrido[1,2-a]pyrimidin-4-one	D	+

64		4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-4-oxo-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluorobenzonitrile	C	++
65A		3-chloro-7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one Peak 1	C	+
65B		3-chloro-7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one Peak 2	B	++
66A		4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2-methyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluorobenzonitrile Peak 1	C	+
66B		4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2-methyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluorobenzonitrile Peak 2	D	+

67A		4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-methyl-4-oxo-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluorobenzonitrile Peak 1	D	+
67B		4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-methyl-4-oxo-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluorobenzonitrile Peak 2	C	+
68A		4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-4-oxo-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluorobenzonitrile Peak 1	D	+
68B		4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-4-oxo-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluorobenzonitrile Peak 2	C	++
69		4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-methyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluorobenzonitrile	D	+

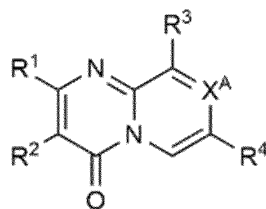
70		4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-4-oxo-2-(trifluoromethyl)pyrazino[1,2-a]pyrimidin-9-yl]-3-fluorobenzonitrile	C	++
71A		9-(3-methoxycyclobutyl)-2,3-dimethyl-7-[rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one	B	+
71B		9-(3-methoxycyclobutyl)-2,3-dimethyl-7-[rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one	B	+

References

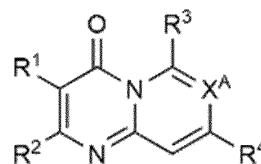
- 5 Colonna, M. et al. (2016) *Nat Rev Neurosci* 17, 201–207
- Deczkowska, A. et al. (2020) *Perspective*, 181, 6, 1207-1217
- Hammond, T. R. (2019) *Immunity*, 50, 4 5955-974
- Suárez-Calvet, M. et al. (2016) *EMBO Mol Med*, 8, 466-476
- Yamazaki, K. et al. (2015) *Clinical psychopharmacology and neuroscience : the official scientific journal of the Korean College of Neuropsychopharmacology*, 13(3), 324–326
- 10 Paloneva BM, J. et al. (2001) *Neurology*, 56 (11) 1552-1558;
- Ulrich J.D. et al. (2017) *Neuron.*, 19;94(2):237-248)
- Atagi, Y. et al. (2015) *J Biol Chem.*, 290(43), 26043-50
- Kleinberger, G. et al (2014) *Sci Transl Med.*, 2, 6 (243):243

Claims

1. A compound of Formula IA or Formula IB:



Formula IA



Formula IB

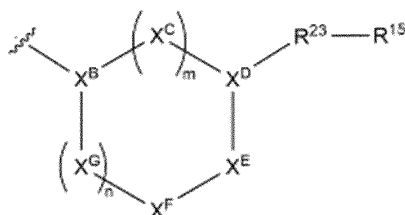
wherein

- 5 X^A is N or C(R⁵);
 R^5 is H;
 R^1 is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, and H, wherein the C₁₋₆ alkyl or C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R⁶;
10 R^2 is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, halogen and H, wherein the C₁₋₆ alkyl or C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 individually selected substituents R⁹;
 R^3 is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₈ spiroalkyl, C₅₋₈ tricycloalkyl, C₅₋₈ bicycloalkyl cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl, 5-membered heteroaryl, azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, and -OCH₂-(C₃₋₆ cycloalkyl),
15 wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₈ spiroalkyl, C₅₋₈ bicycloalkyl, C₅₋₈ tricycloalkyl, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, phenyl, 6-membered heteroaryl or 5-membered heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl and CN, wherein one methylene group of the C₃₋₆ cycloalkyl is optionally replaced with -O- or -N(R¹⁰)-;
20 R¹⁰ is selected from the group consisting of H, C₁₋₃ alkyl and -C(O)C₁₋₃ alkyl;
and wherein the azetidine-1-yl, pyrrolidine-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, piperidine-1-yl, or -OCH₂-(C₃₋₆ cycloalkyl) is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy and C₁₋₃ haloalkoxy;

R^6 is individually selected from the group consisting of $-O-C_{1-6}$ alkyl, C_{3-6} cycloalkyl and halogen;

R^9 is selected from the group consisting of $-O-C_{1-6}$ alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl and phenyl, wherein the phenyl is optionally substituted with 1 to 5 substituents individually selected from $-O-C_{1-6}$ alkyl;

R^4 is of Formula II:



Formula II

wherein

X^B is N or $C(R^{11})$;

R^{11} is selected from the group consisting of H, C_{1-3} alkyl, $-OH$, $-O-C_{1-3}$ alkyl and halogen;

X^C is $C(R^{12})(R^{13})$;

R^{12} is individually H, C_{1-3} alkyl or a bond;

wherein when R^{12} is a bond then R^{11} is C_{1-3} alkyl, and R^{11} and R^{12} are linked together to form a 3-5 membered ring;

R^{13} is individually H or C_{1-3} alkyl;

X^D is $C(R^{14})$ or N;

R^{14} is H or C_{1-3} alkyl;

R^{23} is a bond, $-O-$ or C_{1-6} hydrocarbon chain wherein one methylene group is optionally replaced with $-O-$;

R^{15} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, diC_{1-3} alkylamino, $-C(O)-O-(C_{1-6}$ alkyl), C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, phenyl, $-O$ -phenyl, 5-membered heteroaryl, $-O$ -(5-membered heteroaryl), 6-membered heteroaryl and $-O$ -(6-membered heteroaryl), wherein

(a) the C_{3-6} cycloalkyl or C_{3-6} heterocycloalkyl is optionally substituted with 1 to 3 substituents independently selected from oxo ($=O$), C_{1-3} alkoxy and halogen;

(b) the phenyl, $-O$ -phenyl, 5-membered heteroaryl, $-O$ -(5-membered heteroaryl), 6-membered heteroaryl or $-O$ -(6-membered heteroaryl) is optionally substituted with 1 to 3 substituents independently selected

from the group consisting of halogen, C₁₋₆ alkyl, -O-C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -(C₁₋₃ alkyl)O(C₁₋₃ alkyl), -CN, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl and C₃₋₆ heterocycloalkyl, wherein the C₁₋₆ alkyl or C₁₋₆ haloalkyl of subsection (b) are optionally substituted with -OH, and

5 wherein the C₃₋₆ heterocycloalkyl of subsection (b) is optionally substituted with 1 to 3 substituents individually selected from the group consisting of halogen, C₁₋₃ alkyl and -C(O)O(C₁₋₆ alkyl);

(c) the C₁₋₆ alkyl is optionally substituted with 1 to 3 substituents

10 independently selected from -N(H)C(O)R²⁴, -oxo (=O), -O-C₁₋₃ alkyl and -N(R²⁵)(R²⁶);

R²⁴ is C₁₋₆ alkyl or aryl, wherein the C₁₋₆ alkyl is optionally substituted with C₁₋₃ alkoxy or halogen;

R²⁵ is H or C₁₋₃ alkyl;

15 R²⁶ is H or C₁₋₃ alkyl;

X^E is C(R¹⁶)(R¹⁷), O, NR¹⁸ or a bond;

R¹⁶ is H or F;

R¹⁷ is H or F;

R¹⁸ is H, C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl, -C(O)-C₃₋₆ cycloalkyl or C₁₋₆ haloalkyl, wherein the C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl or -C(O)-C₃₋₆ cycloalkyl is optionally substituted with 1 to 3 substituents independently selected from halogen and C₁₋₃ alkoxy;

20 X^F is C(R¹⁹)(R²⁰);

R¹⁹ is H, halogen or C₁₋₃ alkyl;

25 R²⁰ is H, halogen or C₁₋₃ alkyl;

wherein when R¹⁹ and R²⁰ are C₁₋₃ alkyl, then R¹⁹ and R²⁰ are optionally linked together to form a 3-6 membered ring; and/or

wherein when R¹⁹ and R²⁰ are C₁₋₃ alkyl, then one methylene group is optionally replaced with -O- or -N(R²⁷)-, wherein R²⁷ is selected from the group consisting of H, C₁₋₃ alkyl and -C(O)C₁₋₃ alkyl;

30 X^G is individually C(R²¹)(R²²) or C(O);

R²¹ is individually H, C₁₋₃ alkyl or a bond;

wherein when R²¹ is a bond then R¹⁹ is C₁₋₃ alkyl, n is 1, and R²¹ and R¹⁹ are linked together to form a 3-5 membered ring;

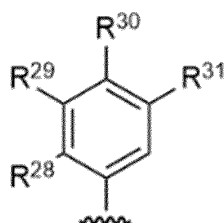
35 R²² is individually H or C₁₋₃ alkyl;

m is 0, 1 or 2; and

n is 0, 1 or 2,

or a pharmaceutically acceptable salt thereof.

- 5 2. The compound according to claim 1, wherein R^3 is of Formula IV:



Formula IV

wherein

R^{28} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN;

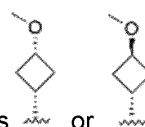
10 R^{29} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN;

R^{30} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN; and

R^{31} is H, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl or CN,

or a pharmaceutically acceptable salt thereof.

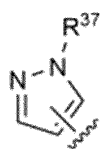
- 15 3. The compound according to claim 1, wherein R^3 is C_{3-6} cycloalkyl optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl and CN, or a pharmaceutically acceptable salt thereof.



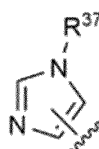
- 20 4. The compound according to claim 3, wherein R^3 is  or , or a pharmaceutically acceptable salt thereof.
- 20 5. The compound according to any one of the preceding claims, wherein X^B is $C(R^{11})$; X^C is $C(R^{12})(R^{13})$; X^D is $C(R^{14})$; X^E is O; X^F is $C(R^{19})(R^{20})$; X^G is $C(R^{21})(R^{22})$; m is 1; and n is 1, or a pharmaceutically acceptable salt thereof.
- 25 6. The compound according to any one of claims 1 to 4, wherein X^B is N; X^C is $C(R^{12})(R^{13})$; X^D is $C(R^{14})$; X^E is O; X^F is $C(R^{19})(R^{20})$; X^G is $C(R^{21})(R^{22})$; m is 1; and n is 1, or a pharmaceutically acceptable salt thereof.
- 25 7. The compound according to any one of the preceding claims, wherein R^{15} is a 5-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, -

O-C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -(C₁₋₃ alkyl)O(C₁₋₃ alkyl), -CN, and halogen, or a pharmaceutically acceptable salt thereof.

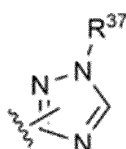
8. The compound according to any one of the preceding claims, wherein R¹⁵ is selected from the group consisting of Formula V, Formula VI, Formula VII, Formula VIII, Formula IX, Formula X, Formula XI, and Formula XII:



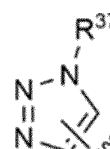
Formula V



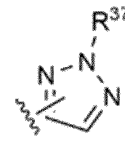
Formula VI



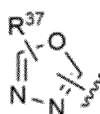
Formula VII



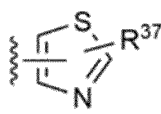
Formula VIII



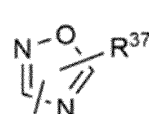
Formula IX



Formula X



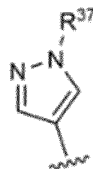
Formula XI



Formula XII

wherein R³⁷ is selected from the group consisting of C₁₋₆ alkyl, C₃₋₆ cycloalkyl, -O-C₁₋₆ alkyl, H, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -(C₁₋₃ alkyl)O(C₁₋₃ alkyl), -CN, and halogen, or a pharmaceutically acceptable salt thereof.

9. The compound according to any one of the preceding claims, wherein R¹⁵ is of Formula XIII:

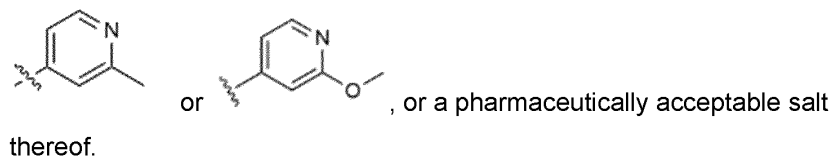


Formula XIII

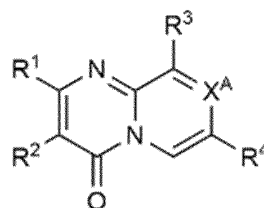
wherein R³⁷ and is selected from the group consisting of C₁₋₆ alkyl, C₃₋₆ cycloalkyl, -O-C₁₋₆ alkyl, H, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -(C₁₋₃ alkyl)O(C₁₋₃ alkyl), -CN, and halogen, or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 9, wherein R³⁷ is C₁₋₃ alkyl, such as CH₃, or C₃₋₆ cycloalkyl, such as C₃ cycloalkyl, or a pharmaceutically acceptable salt thereof.

11. The compound according to any one of the claims 1 to 6, wherein R¹⁵ is



12. The compound according to claim 1, wherein the compound is of Formula IA:



Formula IA

wherein

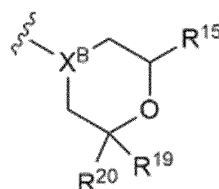
R¹ is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl and H;

R² is selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl and H;

R³ is phenyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃ alkyl, and C₁₋₃ haloalkyl;

X^A is N or C(H);

R⁴ is of Formula XXVI:



Formula XXVI

wherein

X^B is N or C(H);

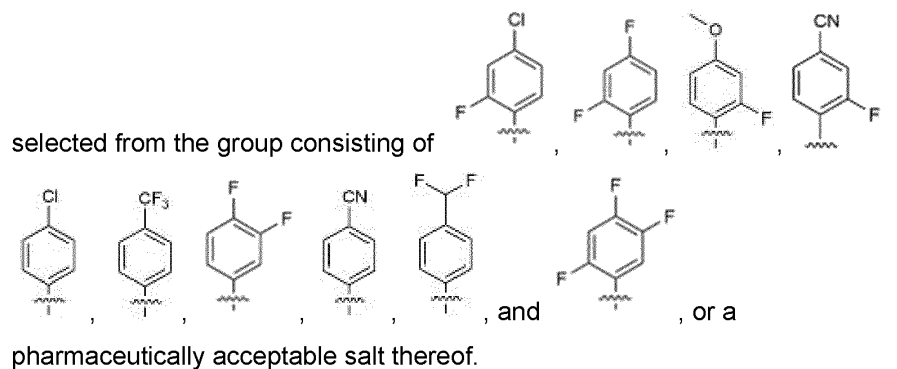
R¹⁵ is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -CN, and C₃₋₆ cycloalkyl;

R¹⁹ is H, halogen or C₁₋₃ alkyl; and

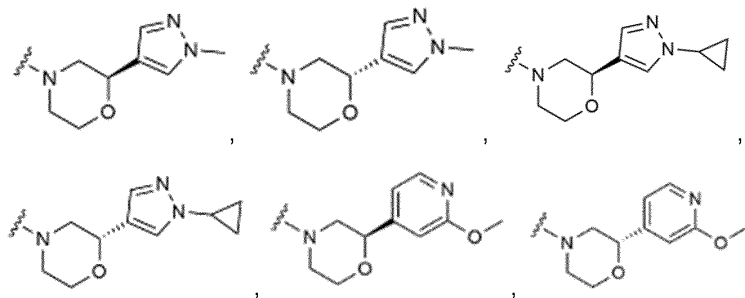
R²⁰ is H, halogen or C₁₋₃ alkyl;

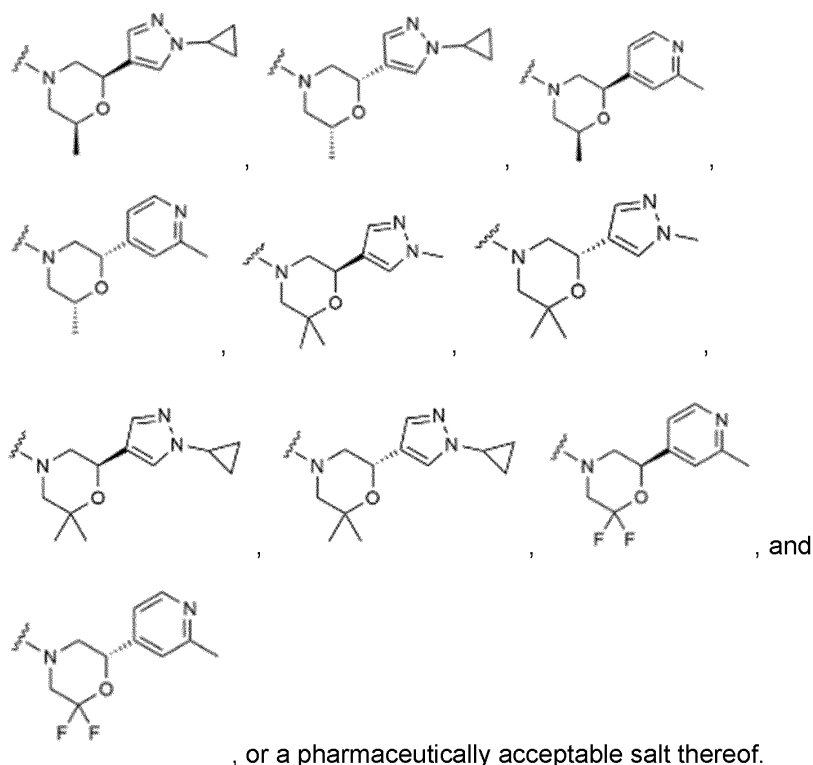
or a pharmaceutically acceptable salt thereof.

13. The compound according to any one of the preceding claims, wherein X^A is N, or a pharmaceutically acceptable salt thereof.
14. The compound according to any one of the preceding claims, wherein X^A is C(H), or a pharmaceutically acceptable salt thereof.
- 5 15. The compound according to any one of claims 1 to 4 or 7 to 14, wherein X^B is N, or a pharmaceutically acceptable salt thereof.
16. The compound according to any one of claims 1 to 4 or 7 to 14, wherein X^B is C(H), or a pharmaceutically acceptable salt thereof.
17. The compound according to any one of the preceding claims, wherein R^1 is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
- 10 18. The compound according to any one of the preceding claims, wherein R^2 is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
19. The compound according to any one of claims 1 to 17, wherein R^2 is halogen, such as Cl, or a pharmaceutically acceptable salt thereof.
- 15 20. The compound according to any one of claims 1, 2, to 5 to 19, wherein R^3 is

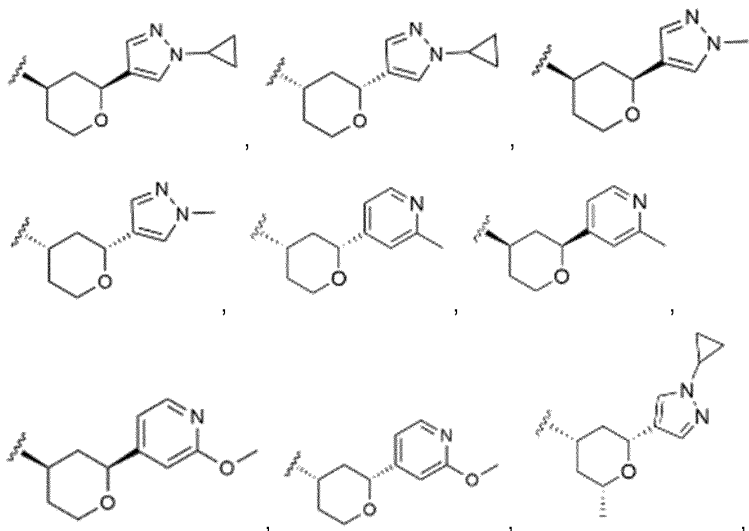


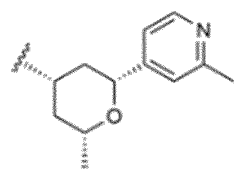
- 20 21. The compound according to any one of claims 1 to 4, 12 to 14, or 17 to 20, wherein R^4 is selected from the group consisting of:



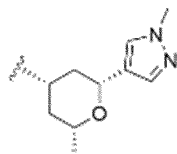


- 5 22. The compound according to any one of claims 1 to 4, 12 to 14, or 17 to 20, wherein R^4 is selected from the group consisting of:





, and



, or a pharmaceutically acceptable

salt thereof.

23. The compound according to claim 1, wherein the compound is of Formula IA

5

and wherein

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and H;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and H;

R^3 is phenyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl;

10

X^A is CH;

X^B is N;

X^C is $C(H)_2$;

X^D is $C(H)$;

X^E is O;

15

X^F is $C(H)_2$;

X^G is $C(H)_2$;

m is 1;

n is 1;

R^{23} is a bond; and

20

R^{15} is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -CN, and C_{3-6} cycloalkyl, or a pharmaceutically acceptable salt thereof.

24. The compound according to claim 1, wherein the compound is of Formula IA

25

and wherein

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and H;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and H;

R^3 is phenyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl;

30

X^A is N;

X^B is $C(H)$;

X^C is $C(H)_2$;

X^D is C(H);

X^E is O;

X^F is C(H)₂;

X^G is C(H)₂;

5 m is 1;

n is 1;

R²³ is a bond; and

R¹⁵ is 5-membered heteroaryl or 6-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of
10 halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -CN, and C₃₋₆ cycloalkyl,
or a pharmaceutically acceptable salt thereof.

25. The compound according to claim 1, wherein the compound is selected from the group consisting of:

- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-
15 4H-pyrido[1,2-a]pyrimidin-4-one;
(R)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one;
(S)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one;
20 9-(4-chloro-2-fluorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-
25 4H-pyrazino[1,2-a]pyrimidin-4-one;
(R)-9-(4-chloro-2-fluorophenyl)-7-(2,2-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)morpholino)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one;
(S)-9-(4-chloro-2-fluorophenyl)-7-(2,2-dimethyl-6-(1-methyl-1H-pyrazol-4-yl)morpholino)-2,3-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one;
30 (S)-9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrazino[1,2-a]pyrimidin-4-one;
6-(4-chloro-2-fluorophenyl)-2,3-dimethyl-8-(2-(1-methyl-1H-pyrazol-4-yl)morpholino)-4H-pyrido[1,2-a]pyrimidin-4-one;
35 3-chloro-9-(4-chloro-2-fluorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;

- 3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-chlorophenyl)-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 5 3-chloro-9-(4-chlorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 10 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 15 4-(3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile;
- 4-(3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile;
- 3-chloro-7-(2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 20 3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 4-(3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile;
- 25 4-(3-chloro-2-methyl-7-(2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile;
- 9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-methyl-6-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 30 7-[2,2-difluoro-6-(2-methyl-4-pyridyl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

- 9-(2,4-difluorophenyl)-2,3-dimethyl-7-[2-methyl-6-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 7-[(2R,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 5 7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 7-[2,2-difluoro-6-(2-methyl-4-pyridyl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 10 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 15 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-pyrido[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-methyl-pyrazino[1,2-a]pyrimidin-4-one;
- 20 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one;
- 25 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)pyrazino[1,2-a]pyrimidin-4-one;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-2-(trifluoromethyl)pyrazino[1,2-a]pyrimidin-4-one;
- 30 4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
- 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrazino[1,2-a]pyrimidin-4-one;

- 4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
7-[2,2-difluoro-6-(1-methylpyrazol-4-yl)morpholin-4-yl]-9-(2,4-difluorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 5 7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-difluorophenyl)pyrido[1,2-a]pyrimidin-4-one;
4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-4-oxo-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
3-chloro-7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-9-(2,4-
- 10 difluorophenyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one;
4-[7-[2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2-methyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-methyl-4-oxo-3-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
- 15 4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-4-oxo-2-(trifluoromethyl)pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-methyl-4-oxo-pyrido[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
4-[7-[2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-4-oxo-2-
- 20 (trifluoromethyl)pyrazino[1,2-a]pyrimidin-9-yl]-3-fluoro-benzonitrile;
9-(3-methoxycyclobutyl)-2,3-dimethyl-7-[rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
9-(3-methoxycyclobutyl)-2,3-dimethyl-7-[rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 25 3-chloro-9-(4-chloro-2-fluorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
3-chloro-9-(4-chloro-2-fluorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 30 3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
3-chloro-9-(4-chloro-2-fluorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
3-chloro-9-(4-chlorophenyl)-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;

- 3-chloro-9-(4-chlorophenyl)-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-chlorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 5 3-chloro-9-(4-chlorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(4-(trifluoromethyl)phenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 10 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(4-(difluoromethyl)phenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 15 3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(3,4-difluorophenyl)-2-methyl-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 20 3-chloro-9-(3,4-difluorophenyl)-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 4-(3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile;
- 25 4-(3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile;
- 4-(3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile;
- 4-(3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile;
- 30 3-chloro-7-((2R,4S)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 3-chloro-7-((2S,4R)-2-(1-cyclopropyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-2-methyl-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;

- 3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-9-(2,4,5-trifluorophenyl)-4H-pyrazino[1,2-a]pyrimidin-4-one;
- 5 4-(3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile;
4-(3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)-3-fluorobenzonitrile;
4-(3-chloro-2-methyl-7-((2R,4S)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile; and
- 10 4-(3-chloro-2-methyl-7-((2S,4R)-2-(1-methyl-1H-pyrazol-4-yl)tetrahydro-2H-pyran-4-yl)-4-oxo-4H-pyrazino[1,2-a]pyrimidin-9-yl)benzonitrile,
or a pharmaceutically acceptable salt thereof.
26. The compound according to any one of the preceding claims, or a
15 pharmaceutically acceptable salt thereof, wherein the compound is a TREM2 modulator, such as a TREM2 activator, such as a TREM2 agonist.
27. 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.
- 20 28. The compound according to any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 27, for use as a medicament.
29. The compound according to any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 27, for use in the treatment of a condition associated with a loss of function of TREM2, such as for use in the treatment of a condition associated with a
25 mutation of TREM2.
30. The compound according to any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 27, for use in the treatment of a neurodegenerative disease.
- 30 31. The compound or composition for use according to claim 30, 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

Leukoencephalopathy, a leukodystrophy, a transmissible spongiform encephalopathy (TSE) and a lysosomal storage disorder (LSD).

- 5 32. The compound according to any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 27, 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 inflammatory demyelinating polyneuropathies, Charcot-Marie-Tooth disease, prion disease and stroke.
- 10 33. The compound according to any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 27, for use in the treatment of a disease selected from the group consisting of
- 15 arthritis, rheumatoid arthritis, pyle disease, osteoporosis, osteopetrosis, osteosclerosis, skeletal dysplasia, dysosteoplasia, autism spectrum disorders, autism and Aspergers syndrome, traumatic brain injuries (TBI), spinal cord injuries, muscular dystrophy, myotonic dystrophy, inclusion-body myositis, systemic lupus erythematosus (SLE), RA, gout, bowel conditions, Inflammatory
- 20 bowel disease (IBD), metabolic syndrome, obesity, type 2 diabetes, atherosclerosis, alcoholic and non-alcoholic fatty liver disease, alcoholic and non-alcoholic steatohepatitis, Amyloidosis.
- 25 34. A method for treatment of a condition associated with a loss of function of TREM2, such as a neurodegenerative disease, said method comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 27, to a subject in need thereof.
- 30 35. Use of a compound according to any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 27, for the manufacture of a medicament for the treatment of a condition associated with a loss of function of TREM2, such as a neurodegenerative disease.
- 35 36. A method of enhancing or increasing TREM2 activity, such as a method of one or more of i) enhancing or activating TREM2 signaling through DAP12, ii) inducing phosphorylation of a kinase that interacts with the TREM2/DAP12

signaling complex, such as, but not limited to, Syk, ZAP70, PI3K, Erk, AKT and GSK3b, iii) enhancing TREM2-induced phosphorylation levels of the Syk kinase, iv) increasing the expression levels, such as brain expression levels, of one or more TREM2 regulated genes, and/or v) increasing the expression

5 levels, such as brain expression levels, of one or more TREM2 regulated genes selected from the group consisting of CXCL10, CCL2, CST7 and TMEM119; in a subject in need thereof, such as in a subject having a neurodegenerative disease, said method comprising administering to the subject a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to

10 26.