

2-AZETIDINYL-7-METHYL-8-OXO-6-(TRIFLUOROMETHYL)-7,8-DIHYDROPYRIMIDO[5,4-D]PYRIMIDINE DERIVATIVES
DERIVATIVES AS TREM2 MODULATORS FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

Technical field

The present invention relates to compounds useful for modulating Triggering Receptor
5 Expressed on Myeloid Cells-2 ("TREM2"). The invention also relates to the compounds
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)).

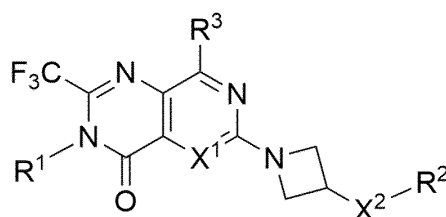
25 Neurodegenerative disorders that may be treated by modulation of TREM2 activity and/or signaling include, but is not limited to, Alzheimer's disease (AD), Frontotemporal lobar degeneration (FTLD), FTLD-like syndrome, Parkinson's disease, Huntington disease, Nasu-Hakola disease (also known as polycystic 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.

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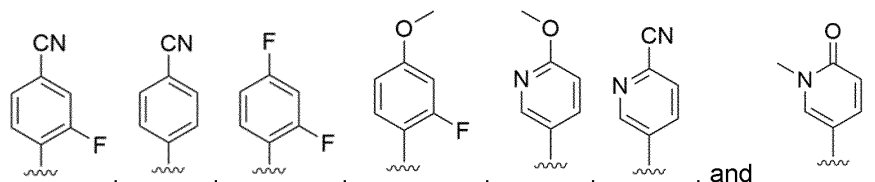
In one aspect, the present invention relates to a compound of Formula (I):



Formula (I)

wherein:

- 5 **X¹** is N or C(H);
X² is O, CH₂ or N(R⁴);
R⁴ is H or C₁₋₃ alkyl;
R¹ is C₁₋₃ alkyl;
R² is selected from the group consisting of pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl,
 10 pyrimidinyl, and 1,3,4-thiadiazolyl, each of which is optionally substituted with 1 to 3
 individually selected substituents R⁵;
R⁵ is individually selected from the group consisting of C₁₋₃ alkyl optionally substituted
 with C₃₋₅ cycloalkyl and/or 1 to 3 F; C₁₋₃ alkoxy optionally substituted with 1 to 3 F; C₃₋₅
 cycloalkyl; CN; and halogen; and
 15 **R³** is selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

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

Definitions

- 25 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 $\pm 0.5\%$.

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

- 10 The terms “C₁₋₃ alkyl”, “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.

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

- 20 The term “C₁₋₃ alkoxy” 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, methoxy, ethoxy, propoxy, iso-propoxy, and butoxy.

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

- 30 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.

- 35 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, -OCH₂F, -OCHF₂, -OCF₃, -OCHFCl, -OCH₂CF₃, -OCFHCF₃, -OCF₂CF₃, -OCH(CF₃)₂, -OCF(CHF₂)₂, and -OCH(CH₂F)(CF₃).

5

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

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.

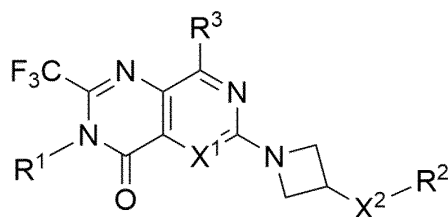
The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

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.

30

Detailed description

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



Formula (I)

wherein:

X^1 is N or C(H);

5 X^2 is O, CH_2 or $N(R^4)$;

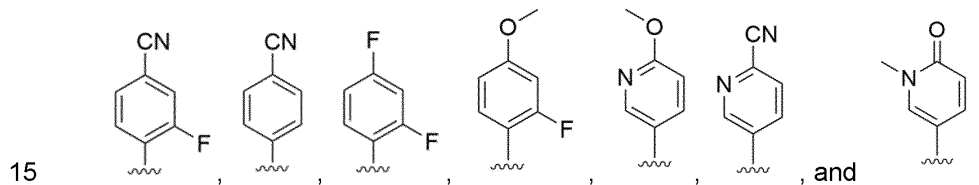
R^4 is H or C_{1-3} alkyl;

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

R^2 is selected from the group consisting of pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, and 1,3,4-thiadiazolyl, each of which is optionally substituted with 1 to 3
10 individually selected substituents R^5 ;

R^5 is individually selected from the group consisting of C_{1-3} alkyl optionally substituted with C_{3-5} cycloalkyl and/or 1 to 3 F; C_{1-3} alkoxy optionally substituted with 1 to 3 F; C_{3-5} cycloalkyl; CN; and halogen; and

R^3 is selected from the group consisting of:



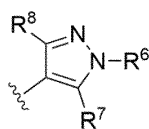
or a pharmaceutically acceptable salt thereof.

In some embodiments, X^1 is N. In some embodiments X^1 is C(H).

20 In some embodiments, X^2 is O. In some embodiments, X^2 is CH_2 . In some embodiments, X^2 is $N(R^4)$, and R^4 is H or C_{1-3} alkyl. In some embodiments, R^4 is H. In some embodiments, R^4 is C_{1-3} alkyl. In some embodiments, R^4 is CH_3 . In some embodiments, X^2 is N(H). In some embodiments, X^2 is $N(CH_3)$.

25 In some embodiments, R^1 is CH_3 .

- In some embodiments, R² is pyrazolyl optionally substituted with 1 to 3 individually selected substituents R⁵. In some embodiments, R² is pyridinyl optionally substituted with 1 to 3 individually selected substituents R⁵. In some embodiments, R² is pyrazinyl optionally substituted with 1 to 3 individually selected substituents R⁵. In some
- 5 embodiments, R² is pyridazinyl, optionally substituted with 1 to 3 individually selected substituents R⁵. In some embodiments, R² is pyrimidinyl, optionally substituted with 1 to 3 individually selected substituents R⁵. In some embodiments, R² is 1,3,4-thiadiazolyl, optionally substituted with 1 to 3 individually selected substituents R⁵.
- 10 In some embodiments, R⁵ is C₁₋₃ alkyl. In some embodiments, R⁵ is CH₃. In some embodiments, R⁵ is CH₂CH₃. In some embodiments, R⁵ is CH₂CH₂CH₃. In some embodiments, R⁵ is CH₂(CH₃)₂. In some embodiments, R⁵ is C₁₋₃ alkyl substituted with 1 to 3 F. In some embodiments, R⁵ is CH₃ substituted with 1 to 3 F. In some
- 15 embodiments, R⁵ is CF₃. In some embodiments, R⁵ is CHF₂. In some embodiments, R⁵ is CH₂CH₃ substituted with 1 to 3 F. In some embodiments, R⁵ is CH₂CF₃. In some embodiments, R⁵ is CH₂CHF₂. In some embodiments, R⁵ is C₁₋₃ alkoxy. In some embodiments, R⁵ is -OCH₃. In some embodiments, R⁵ is C₁₋₃ alkoxy substituted with 1 to 3 F. In some embodiments, R⁵ is -OCH₃. In some embodiments, R⁵ is -OCHF₂. In
- 20 some embodiments, R⁵ is C₁₋₃ alkyl substituted with C₃₋₅ cycloalkyl. In some embodiments, R⁵ is -CH₂-cyclopropyl. In some embodiments, R⁵ is C₃₋₅ cycloalkyl. In some embodiments, R⁵ is cyclopropyl. In some embodiments, R⁵ is cyclobutyl. In some embodiments, R⁵ is cyclopentyl. In some embodiments, R⁵ is CN. In some
- 25 embodiments, R⁵ is halogen. In some embodiments, R⁵ is Cl.
- 25 In some embodiments, R² is of Formula (II):



Formula (II)

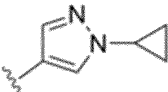
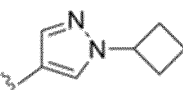
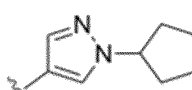
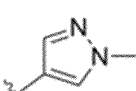
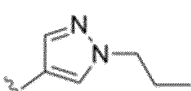
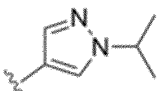
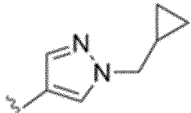
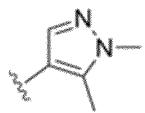
wherein

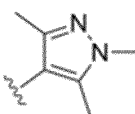
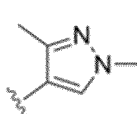
- R⁶ is selected from the group consisting of H; C₁₋₃ alkyl optionally substituted with C₃₋₅ cycloalkyl and/or 1 to 3 F; C₁₋₃ alkoxy optionally substituted with 1 to 3 F; and C₃₋₅ cycloalkyl;
- 30 R⁷ is H, C₁₋₃ alkyl or halogen; and
- R⁸ is H, C₁₋₃ alkyl or halogen.

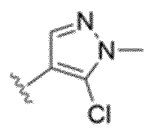
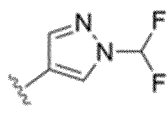
In some embodiments, R^6 is H. In some embodiments, R^6 is C_{1-3} alkyl. In some
embodiments, R^6 is CH_3 . In some embodiments, R^6 is $-(CH_2)_2CH_3$. In some
embodiments, R^6 is $-C(H)(CH_3)_2$. In some embodiments, R^6 is C_{1-3} alkyl substituted with
5 1 to 3 F. In some embodiments, R^6 is CH_3 substituted with 1 to 3 F. In some
embodiments, R^6 is CHF_2 . In some embodiments, R^6 is CH_2CH_3 substituted with 1 to 3
F. In some embodiments, R^6 is CH_2CF_3 . In some embodiments, R^6 is CH_2CHF_2 . In
some embodiments, R^6 is C_{1-3} alkyl substituted with C_{3-5} cycloalkyl. In some
embodiments, R^6 is $-CH_2$ -cyclopropyl. In some embodiments, R^6 is C_{3-5} cycloalkyl. In
10 some embodiments, R^6 is cyclopropyl. In some embodiments, R^6 is cyclobutyl. In some
embodiments, R^6 is cyclopentyl.

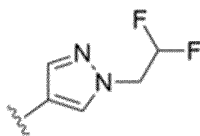
In some embodiments, R^7 is H. In some embodiments, R^7 is C_{1-3} alkyl. In some
embodiments, R^7 is CH_3 .

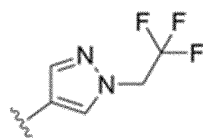
15 In some embodiments, R^8 is H. In some embodiments, R^8 is C_{1-3} alkyl. In some
embodiments, R^8 is CH_3 . In some embodiments, R^8 is halogen. In some embodiments,
 R^8 is Cl.

In some embodiments, R^2 is . In some embodiments, R^2 is
. In some embodiments, R^2 is . In some
20 embodiments, R^2 is . In some embodiments, R^2 is . In
some embodiments, R^2 is . In some embodiments, R^2 is
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is . In some embodiments, R² is . In some embodiments,

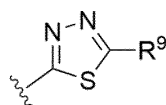
R² is . In some embodiments, R² is . In some

embodiments, R² is . In some embodiments, R² is



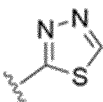
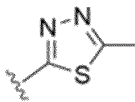
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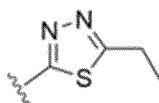
In some embodiments, R² is of Formula (III):



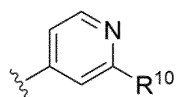
Formula (III)

10 wherein R⁹ is H or C₁₋₃ alkyl.

In some embodiments, R² is . In some embodiments, R² is . In

some embodiments, R² is .

In some embodiments, R² is of Formula (IV):

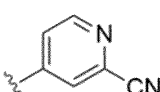
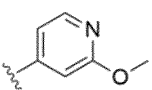
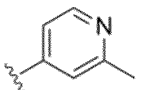
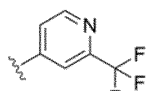
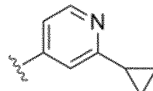
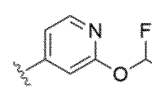
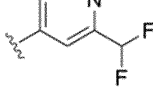


Formula (IV)

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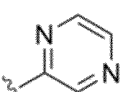
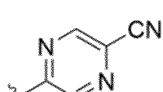
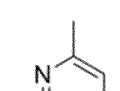
wherein R^{10} is selected from the group consisting of H; C_{1-3} alkyl optionally substituted with 1 to 3 F; C_{1-3} alkoxy optionally substituted with 1 to 3 F; CN; and C_{3-5} cycloalkyl.

In some embodiments, R^{10} is CN. In some embodiments, R^{10} is C_{1-3} alkyl. In some
 5 embodiments, R^{10} is CH_3 . In some embodiments, R^{10} is C_{1-3} alkyl substituted with 1 to 3 F. In some embodiments, R^{10} is CF_3 . In some embodiments, R^{10} is CHF_2 . In some
 embodiments, R^{10} is C_{1-3} alkoxy. In some embodiments, R^{10} is $-OCH_3$. In some
 embodiments, R^{10} is C_{1-3} alkoxy substituted with 1 to 3 F. In some embodiments, R^{10} is
 10 $-OCHF_2$. In some embodiments, R^{10} is C_{3-5} cycloalkyl. In some embodiments, R^{10} is
 cyclopropyl.

In some embodiments, R^2 is . In some embodiments, R^2 is
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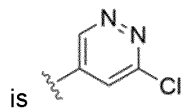
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In some embodiments, R^2 is pyrazinyl optionally substituted with CN. In some
 embodiments, R^2 is pyrazinyl optionally substituted with C_{1-3} alkyl. In some
 embodiments, R^2 is pyrazinyl optionally substituted with CH_3 .

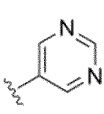
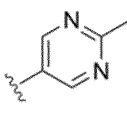
In some embodiments, R^2 is . In some embodiments, R^2 is .
 In some embodiments, R^2 is .

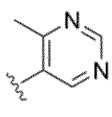
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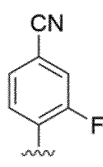
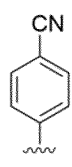
In some embodiments, R^2 is pyridazinyl optionally substituted with halogen. In some embodiments, R^2 is pyridazinyl optionally substituted with Cl. In some embodiments, R^2

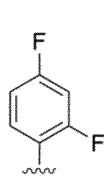
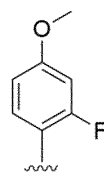


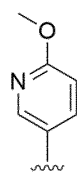
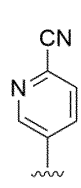
- 5 In some embodiments, R^2 is pyrimidinyl optionally substituted with C_{1-3} alkyl. In some embodiments, R^2 is pyrimidinyl optionally substituted with CH_3 .

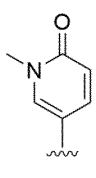
In some embodiments, R^2 is . In some embodiments, R^2 is . In

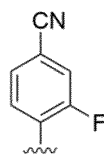
some embodiments, R^2 is .

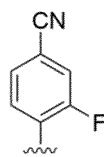
- 10 In some embodiments, R^3 is . In some embodiments, R^3 is . R^3 is

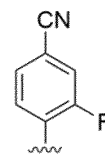
. In some embodiments, R^3 is . In some embodiments, R^3 is

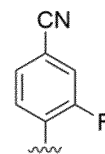
. R^3 is .

In some embodiments, R^3 is .

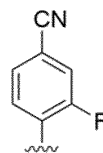


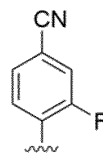
In some embodiments, X^1 is N and R^3 is . In some embodiments, X^1 is N and

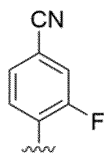


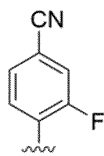
R^1 is CH_3 . In some embodiments, X^1 is N, R^1 is CH_3 , and R^3 is . In some embodiments, X^1 is N and X^2 is O. In some embodiments, X^2 is O and R^2 is pyrazolyl optionally substituted with 1 to 3 individually selected substituents R^5 . In some

5 individually selected substituents R^5 . In some embodiments, X^1 is N, X^2 is O and R^2 is pyrazolyl optionally substituted with 1 to 3 individually selected substituents R^5 . In some embodiments, X^1 is N and R^1 is CH_3 . In



some embodiments, X^1 is N, R^1 is CH_3 , and R^3 is , In some embodiments, X^1



is N, R^1 is CH_3 , R^3 is , X^2 is O, and R^2 is pyrazolyl optionally substituted with 1 to 3 individually selected substituents R^5 .

10

In some embodiments, the compound is 4-(2-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((1,3,4-thiadiazol-2-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some

15 embodiments, the compound is 3-fluoro-4-(7-methyl-2-(3-((5-methyl-1,3,4-thiadiazol-2-yl)oxy)azetidin-1-yl)-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments,

20 the compound is 4-(2-(3-((5-ethyl-1,3,4-thiadiazol-2-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-fluoro-4-(7-methyl-8-oxo-2-(3-(pyrazin-2-yloxy)azetidin-1-yl)-6-(trifluoromethyl)-7,8-

dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-fluoro-4-(7-methyl-2-(3-(6-methylpyrazin-2-yl)oxy)azetidin-1-yl)-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some

5 embodiments, the compound is 5-((1-(4-(4-cyano-2-fluorophenyl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-2-yl)azetidin-3-yl)oxy)pyrazine-2-carbonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((1,5-dimethyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a

10 pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((3,5-dimethyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((1,3-dimethyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-

15 dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-fluoro-4-(2-(3-((1-isopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-fluoro-4-(7-methyl-8-oxo-2-(3-((1-propyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-

20 d]pyrimidin-4-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((5-chloro-1-methyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In

25 some embodiments, the compound is 4-(2-(3-((1-(difluoromethyl)-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((1-(cyclopropylmethyl)-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-

30 d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((1-(cyclobutyl)-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((1-(2,2-difluoroethyl)-1H-pyrazol-4-

35 yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-

d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((1-cyclopentyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In

5 some embodiments, the compound is 3-fluoro-4-(7-methyl-8-oxo-2-(3-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-((1-(4-(4-cyano-2-fluorophenyl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-2-yl)azetidin-3-

10 yl)oxy)picolinonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-fluoro-4-(2-(3-((2-methoxypyridin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((2-cyclopropylpyridin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-

15 (trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((2-(difluoromethyl)pyridin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((2-

20 (difluoromethoxy)pyridin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-fluoro-4-(7-methyl-8-oxo-6-(trifluoromethyl)-2-(3-((2-(trifluoromethyl)pyridin-4-yl)oxy)azetidin-1-yl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(2-(3-((6-chloropyridazin-4-

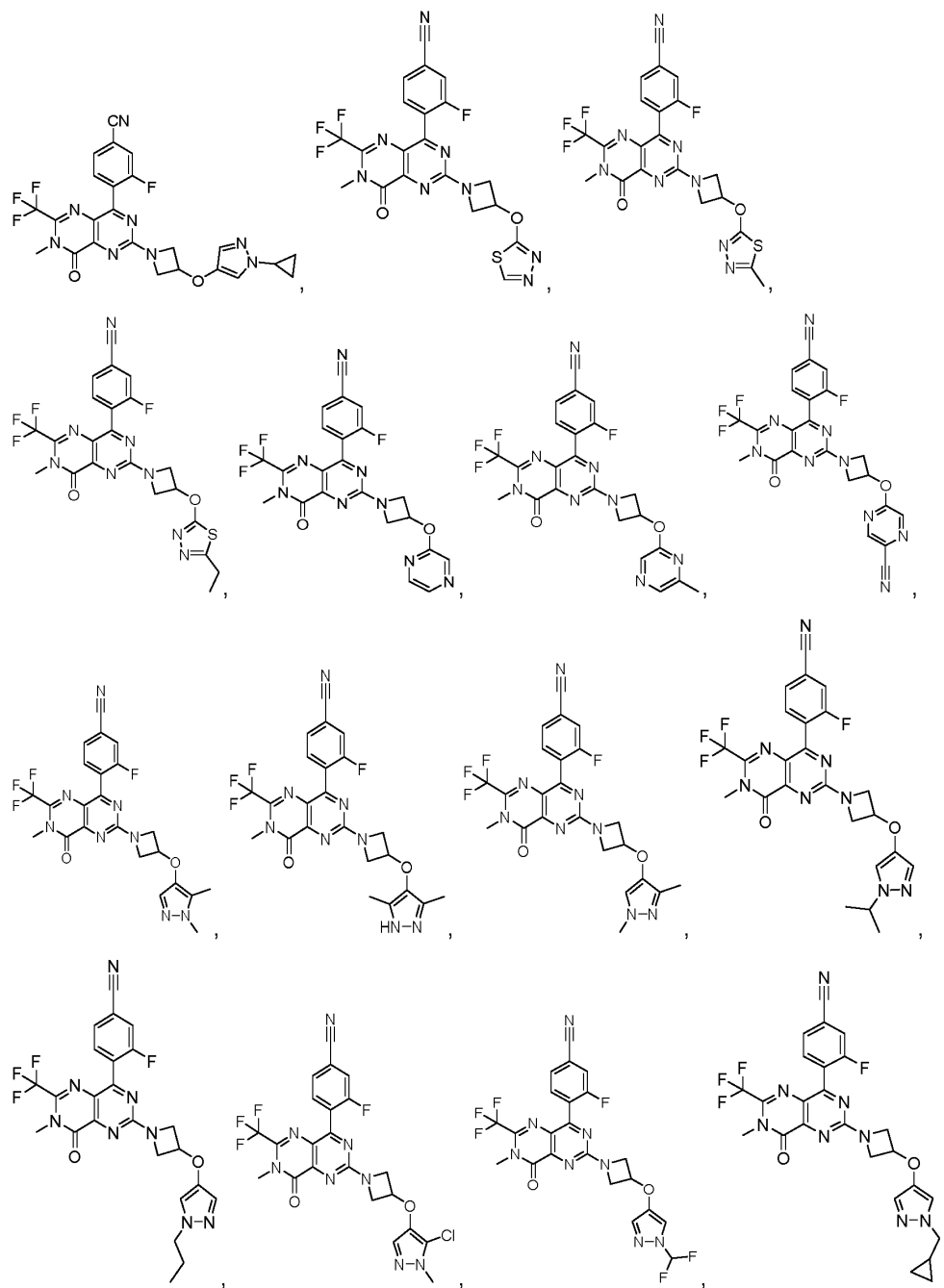
25 yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-fluoro-4-(7-methyl-8-oxo-2-(3-(pyrimidin-5-yloxy)azetidin-1-yl)-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-

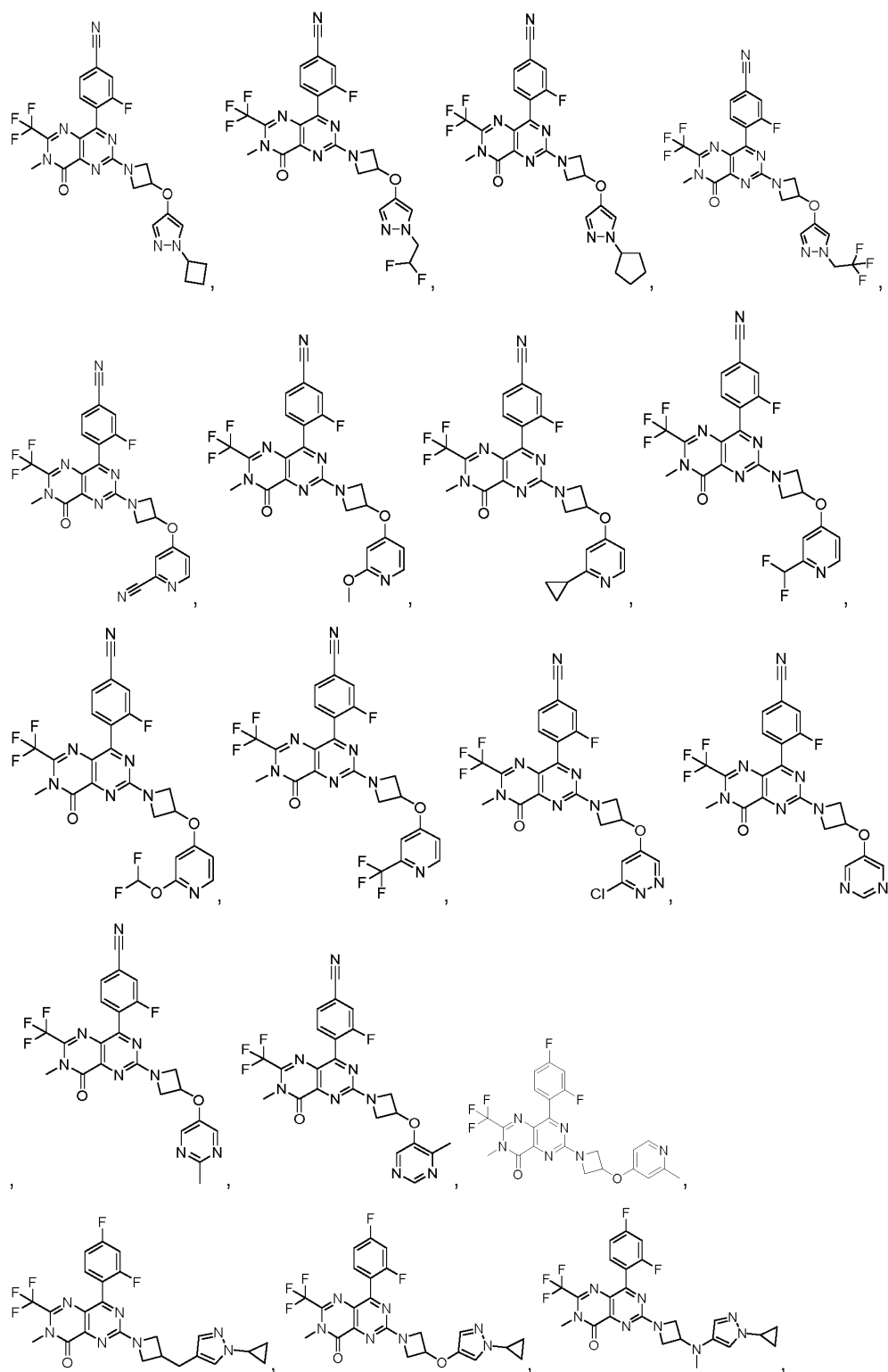
30 yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-fluoro-4-(7-methyl-2-(3-((2-methylpyrimidin-5-yl)oxy)azetidin-1-yl)-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 3-fluoro-4-(7-methyl-2-(3-((4-methylpyrimidin-5-yl)oxy)azetidin-1-yl)-8-oxo-6-

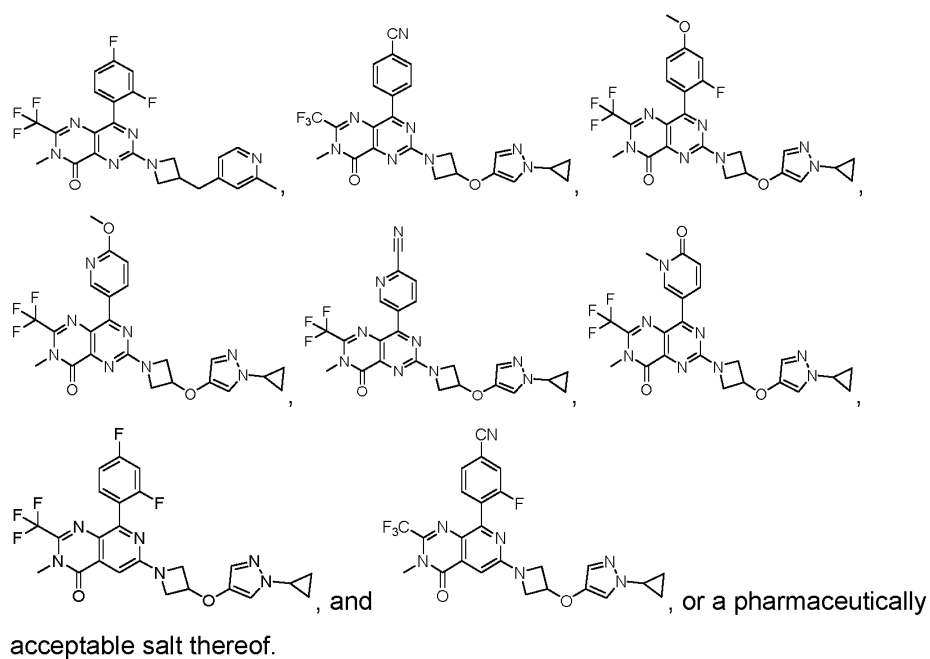
35 (trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile, or a

pharmaceutically acceptable salt thereof. In some embodiments, the compound is 8-(2,4-difluorophenyl)-3-methyl-6-(3-((2-methylpyridin-4-yl)oxy)azetidin-1-yl)-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)methyl)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one, or a pharmaceutically acceptable salt thereof. In some
5 embodiments, the compound is 6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is
10 6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)(methyl)amino)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 8-(2,4-difluorophenyl)-3-methyl-6-(3-((2-methylpyridin-4-yl)methyl)azetidin-1-yl)-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one, or a pharmaceutically acceptable
15 salt thereof. In some embodiments, the compound is 4-(2-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(2-fluoro-4-methoxyphenyl)-3-methyl-2-
20 (trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(6-methoxypyridin-3-yl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one, or a pharmaceutically acceptable salt thereof. In some
25 embodiments, the compound is 5-(2-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)picolinonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-3-methyl-8-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the
30 compound is 6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is 4-(6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-3-methyl-4-oxo-2-(trifluoromethyl)-3,4-dihydropyrido[3,4-d]pyrimidin-8-yl)-3-fluorobenzonitrile, or a pharmaceutically
35 acceptable salt thereof.

In one aspect, the present invention relates to a compound selected from the group consisting of:

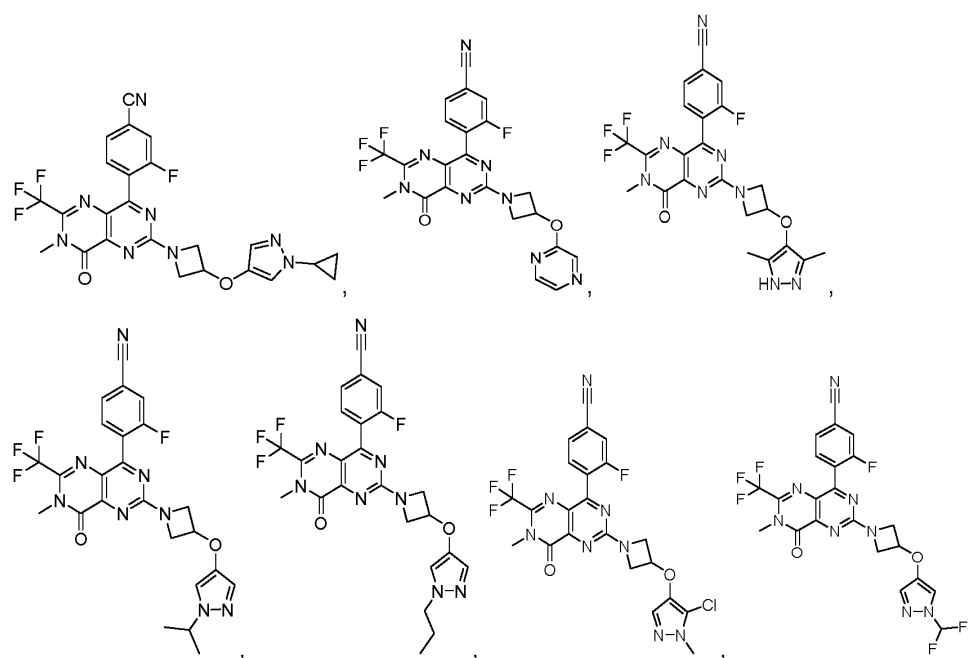


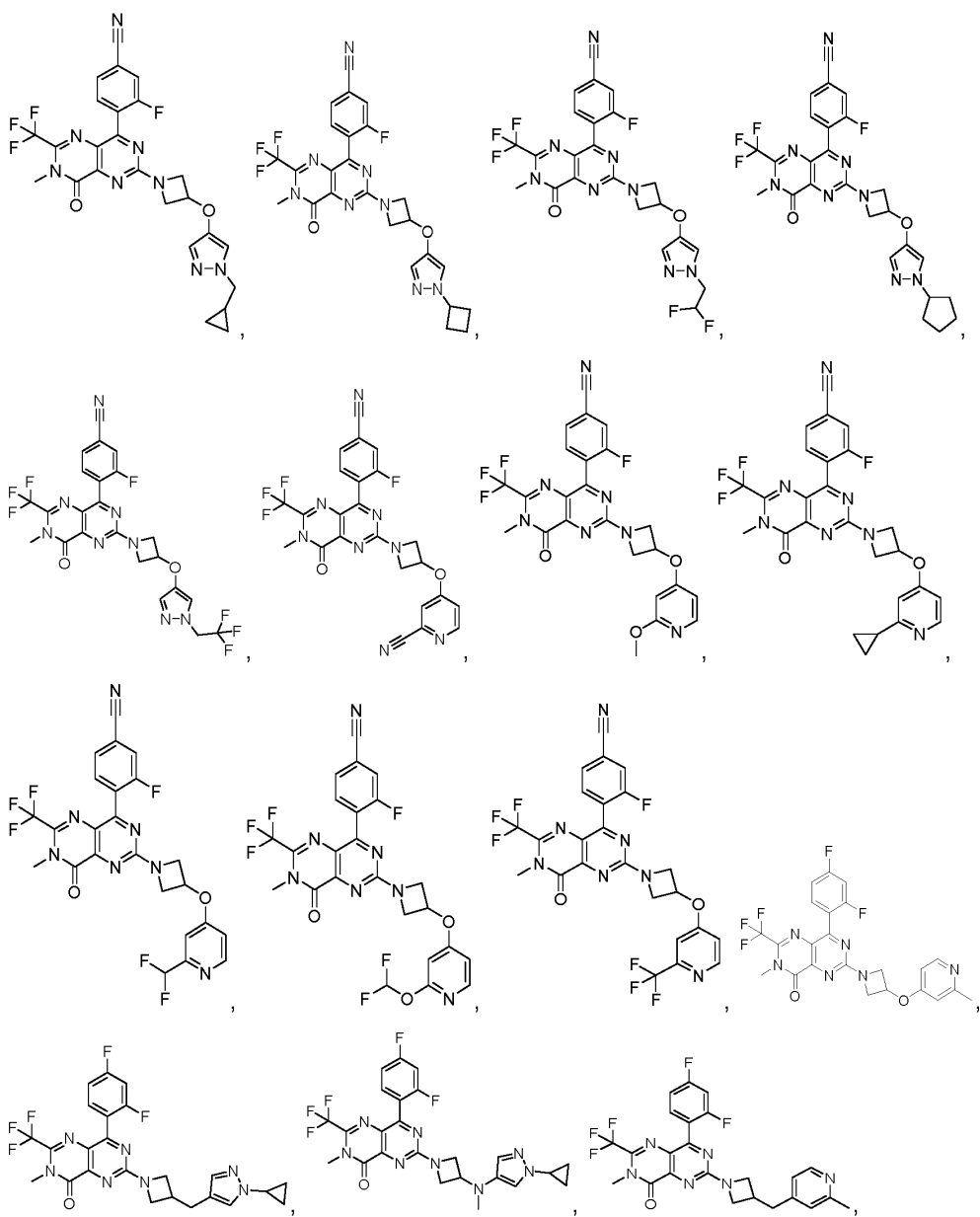


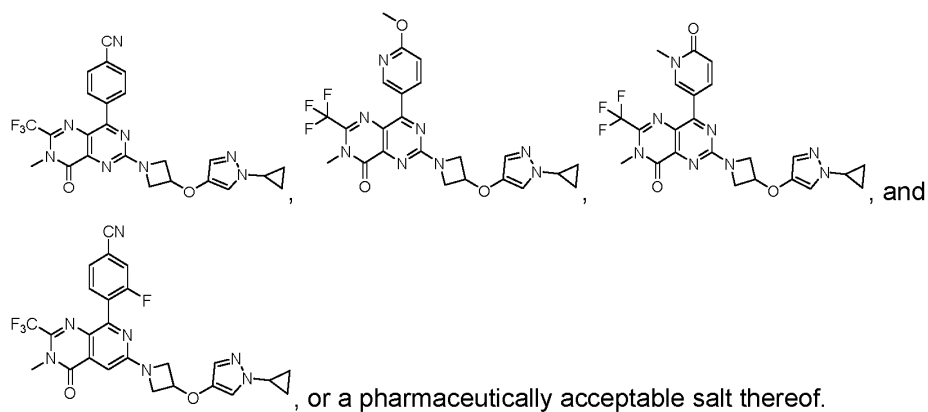


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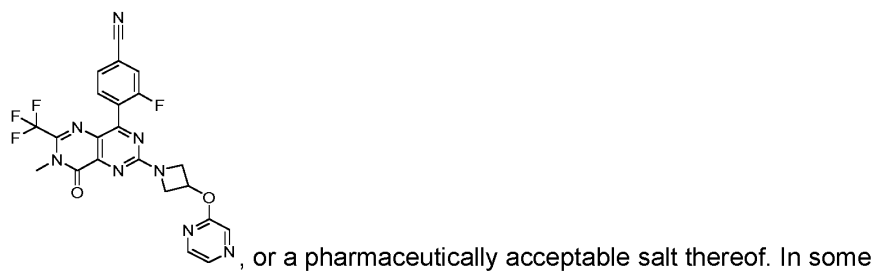
In one aspect, the present invention relates to a compound selected from



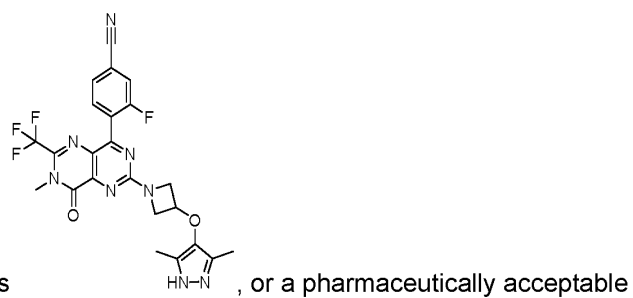


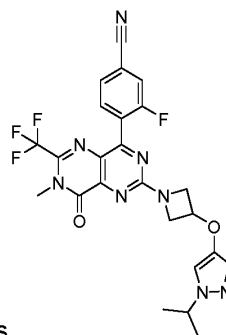


In some embodiments, the compound is
 5 pharmaceutically acceptable salt thereof. In some embodiments, the compound is

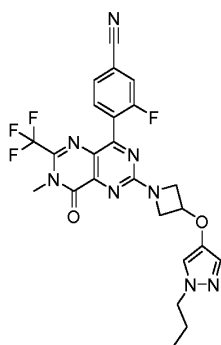


embodiments, the compound is

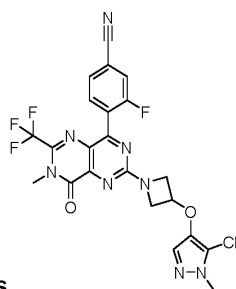




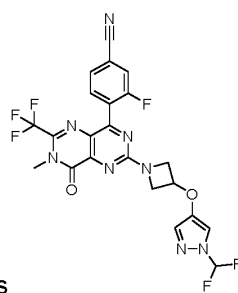
salt thereof. In some embodiments, the compound is
pharmaceutically acceptable salt thereof. In some embodiments, the compound is



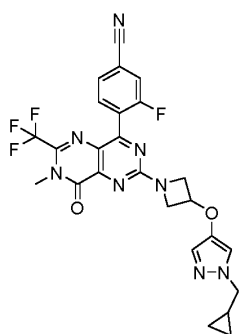
, or a pharmaceutically acceptable salt thereof. In some



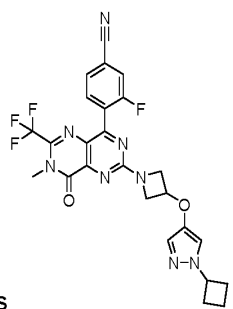
embodiments, the compound is
, or a pharmaceutically acceptable



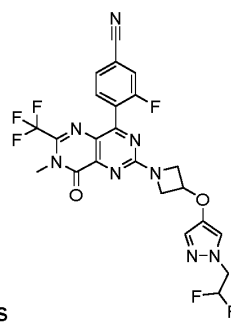
5 salt thereof. In some embodiments, the compound is
pharmaceutically acceptable salt thereof. In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof. In some

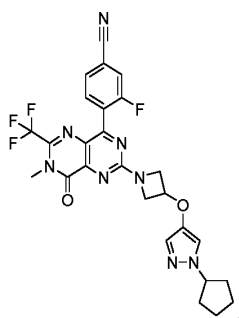


embodiments, the compound is

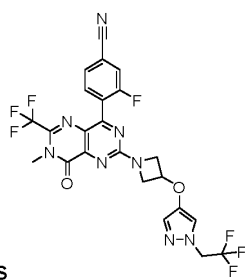


salt thereof. In some embodiments, the compound is

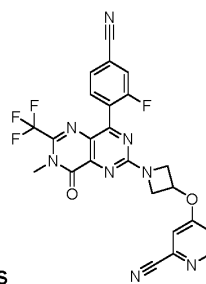
pharmaceutically acceptable salt thereof. In some embodiments, the compound is



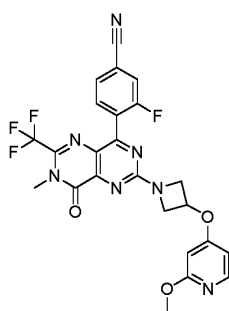
5, or a pharmaceutically acceptable salt thereof. In some



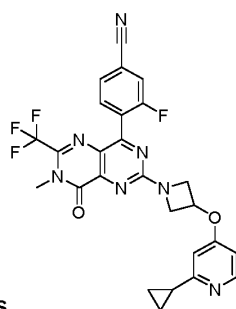
embodiments, the compound is , or a pharmaceutically acceptable



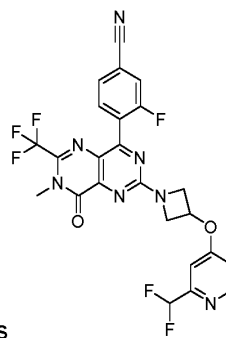
salt thereof. In some embodiments, the compound is pharmaceutically acceptable salt thereof. In some embodiments, the compound is



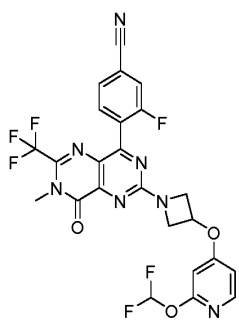
, or a pharmaceutically acceptable salt thereof. In some



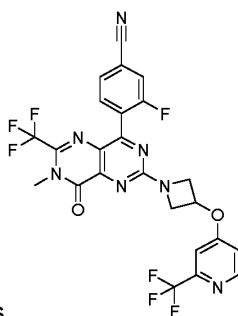
5 embodiments, the compound is , or a pharmaceutically acceptable



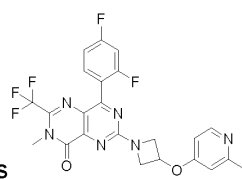
salt thereof. In some embodiments, the compound is
pharmaceutically acceptable salt thereof. In some embodiments, the compound is



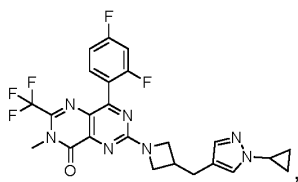
, or a pharmaceutically acceptable salt thereof. In some



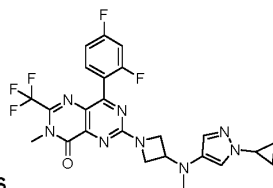
embodiments, the compound is
, or a pharmaceutically acceptable

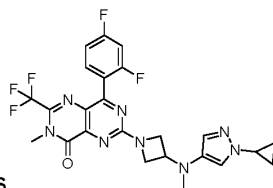


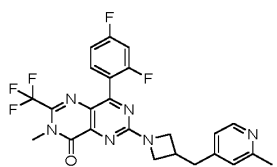
5 salt thereof. In some embodiments, the compound is
pharmaceutically acceptable salt thereof. In some embodiments, the compound is



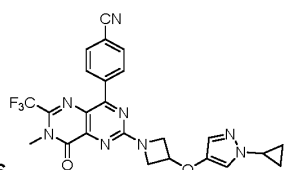
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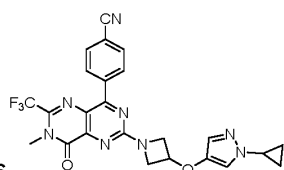


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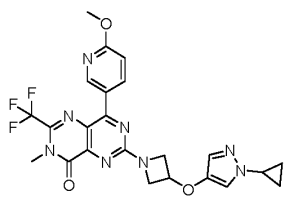


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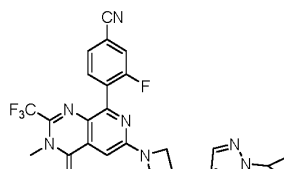


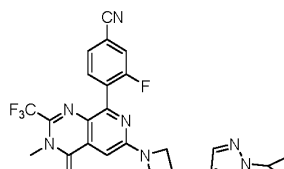
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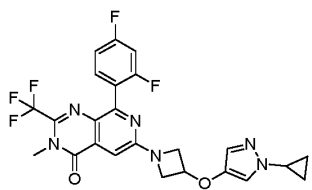
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, or a pharmaceutically acceptable salt thereof. In some



embodiments, the compound is , or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

10

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.

10 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).

20 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, described in the example section disclosed herein. In some embodiments the compound of the present invention is selected from any of the intermediate compounds, or a pharmaceutically acceptable salt thereof, disclosed in any one of examples 1 to 41 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 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.

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

10 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
15 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).

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

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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.

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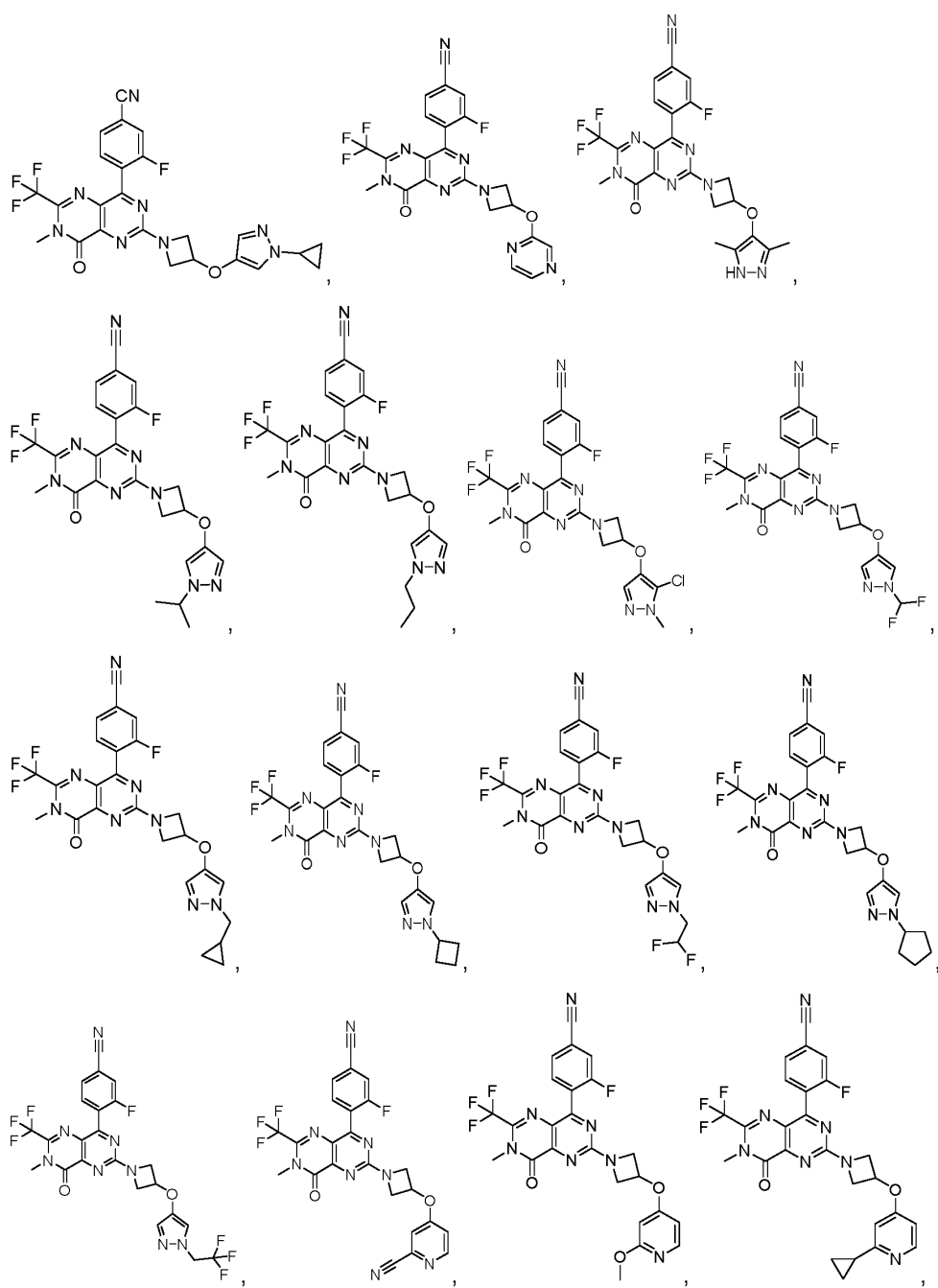
To administer refers to a method of delivering agents, compounds, or compositions to the desired site of biological action. These methods include, but are not limited to, enteral delivery, oral delivery, topical delivery, parenteral delivery, intravenous delivery, intradermal delivery, intramuscular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

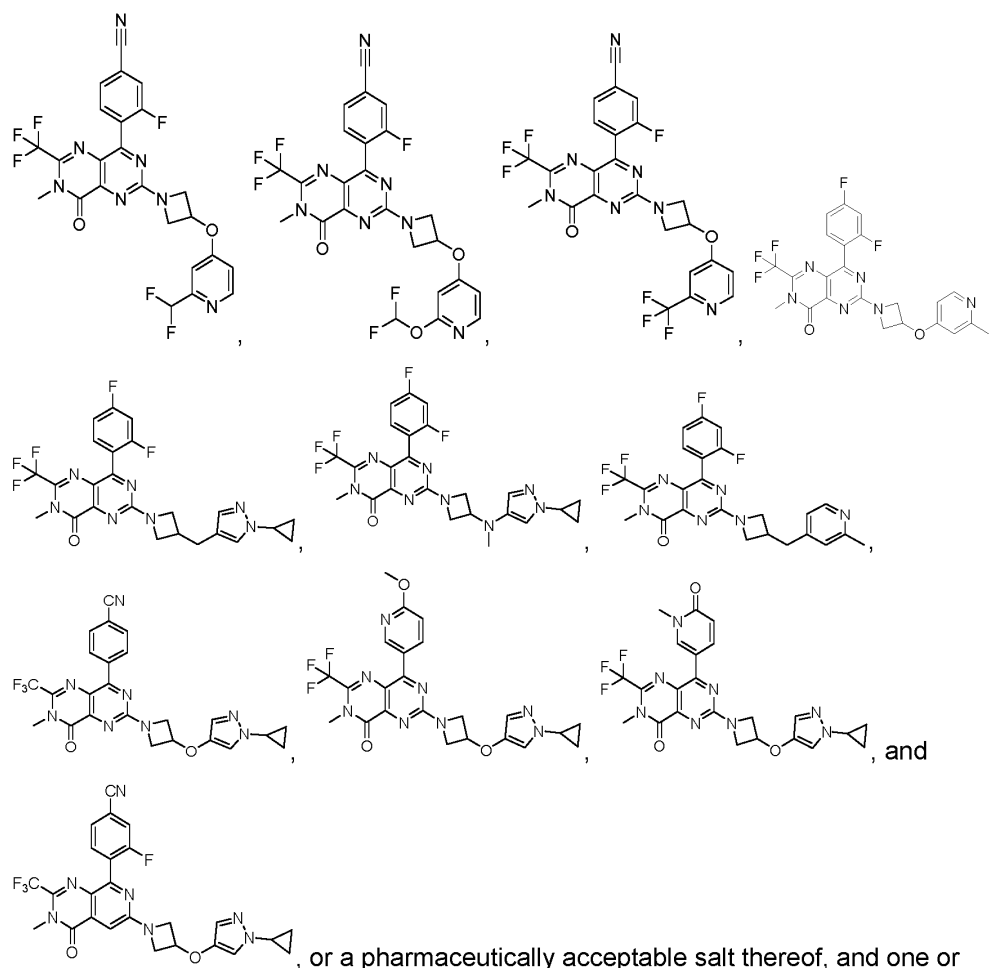
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In some embodiments, the compound of the present invention is suitable for use as a pharmaceutical agent. Hence, in some embodiments, the compound has suitable pharmacological activity, such as target efficacy, affinity and/or selectivity. In some
15 embodiments, the compound has suitable Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties. For example, in some embodiments, the compound has acceptable levels of off-target effects, including low hERG channel (human Ether-à-go-go-Related Gene) inhibition, low off-target toxicity, genotoxicity, carcinogenicity, and/or hepatotoxicity. In some embodiments, the compound
20 demonstrates suitable pharmacokinetics, such as bioavailability, half-life, and/or clearance. In some embodiments, the compound demonstrates suitable pharmacodynamics, such as efficacy and/or potency. In some embodiments, the compound demonstrates chemical stability and/or metabolic stability. Said parameters may be assessed by conventional *in vitro* tests, animal studies and/or clinical trials
25 known by the skilled person. In some embodiments, the compound demonstrates suitable characteristics for oral formulation using pharmaceutically acceptable excipients. For example, the compound demonstrates suitable solubility in relevant media.

30

In one aspect, the present invention relates to a pharmaceutical composition comprising a compound selected from





5 more pharmaceutically acceptable carriers, excipients and/or diluents.

Biological activity

As demonstrated in Example 42 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

10 Example 42 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

15 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 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.

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 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 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. In some embodiments the compounds of the present invention increases 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 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 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

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,
5 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.

In one aspect, the present invention relates to a compound, or a pharmaceutically
10 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
15 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
20 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
25 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,
30 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
35 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.

5 In some embodiments, the neurodegenerative disease is a tauopathy. Tautopathies 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, 10 diffuse neurofibrillary tangles with calcification (DNTC), Frontotemporal dementia (FTD), and FTD with parkinsonism-17 (FTD with parkinsonism linked to chromosome 17; FTDP-17).

15 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.

20 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), 25 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 30 pathology, including Alzheimer's disease (AD) and Chronic traumatic encephalopathy (CTE).

35 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).

5

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.

10

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).

15

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,

20

dementia with lewy bodies, prion disease dementia, argyrophilic grain dementia, dementia pugilistica, Guadeloupean parkinsonism with dementia, neurofibrillary tangle-predominant dementia, tangle only dementia, Down's syndrome, semantic dementia, familial British dementia, familial Danish dementia, and other dementias caused by another medical condition such as brain tumors, subdural hematoma, endocrine disorders, nutritional deficiencies, infections, immune disorders, liver or kidney failure, metabolic disorders such as Kufs disease, some leukodystrophies, some neurological disorders such as epilepsy, and multiple sclerosis.

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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).

35

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 inflammatory demyelinating diseases. In some embodiments, the demyelinating disorder is a leukodystrophic or dysmyelinating disorder, such as selected from the group consisting of CNS neuropathies such as vitamin B12 deficiency, central pontine myelinolysis, myelopathies such as tabes dorsalis (syphilitic myelopathy), leukoencephalopathies and leukodystrophies.

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).

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 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 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 infarcts and leukoencephalopathy; and retinal vasculopathy with cerebral leukoencephalopathy (or cerebroretinal vasculopathy).

In some embodiments the neurodegenerative disease is a leukodystrophy. In some embodiments the neurodegenerative disease is vanishing white matter disease (VWM).

Leukodystrophies are a group of rare, genetic disorders that affect the white matter of the brain. In some embodiments the neurodegenerative disease is a leukodystrophy selected from the group consisting of metachromatic leukodystrophy (MLD, also known as globoid cell leukodystrophy), Krabbe disease, Canavan disease, X-linked
5 adrenoleukodystrophy, Alexander disease, hypomyelinating leukodystrophy type 7 (4H syndrome), Pelizaeus-Merzbacher disease, cerebrotendineous xanthomatosis and leukoencephalopathy with vanishing white matter. In some embodiments the neurodegenerative disease is adult-onset autosomal dominant leukodystrophy (ADLD). In some embodiments the neurodegenerative disease is X-linked
10 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
15 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
20 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
25 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.

30 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
35 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 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.

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,
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
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).

In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of a lysosomal storage disorder (LSD). Most lysosomal storage disorders cause progressive neurodegeneration leading to early death.

In some embodiments the LSD is a lipidoses, such as a lipidoses selected from the group consisting of cholesteryl ester storage disease, fucosidosis, Schindler disease and Wolman disease.

5 In some embodiments the LSD is a sphingolipidoses, such as a sphingolipidoses selected from the group consisting of Fabry disease, Gaucher disease, Krabbe disease (globoid cell leukodystrophy), metachromatic leukodystrophy (MLD), Niemann-Pick disease (Types A, B and C), Sandhoff disease, Farmer disease, multiple sulfatase deficiency and Tay-Sachs disease.

10

In some embodiments the LSD is a mucopolysaccharidoses, such as a mucopolysaccharidoses selected from the group consisting of Hunter syndrome, Hurler syndrome, Hurler-Scheie syndrome, Scheie syndrome, Sanfilippo syndrome (A, B, C, D), Morquio syndrome, Maroteaux-Lamy syndrome, Sly syndrome and Natowicz syndrome.

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In some embodiments the LSD is selected from the group consisting of Batten disease, cyctinosis, Danon disease and Pompe disease.

20

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

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In one aspect, the present invention relates to the compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of autism spectrum disorders, autism and Aspergers syndrome.

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

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

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

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 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.

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,

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.

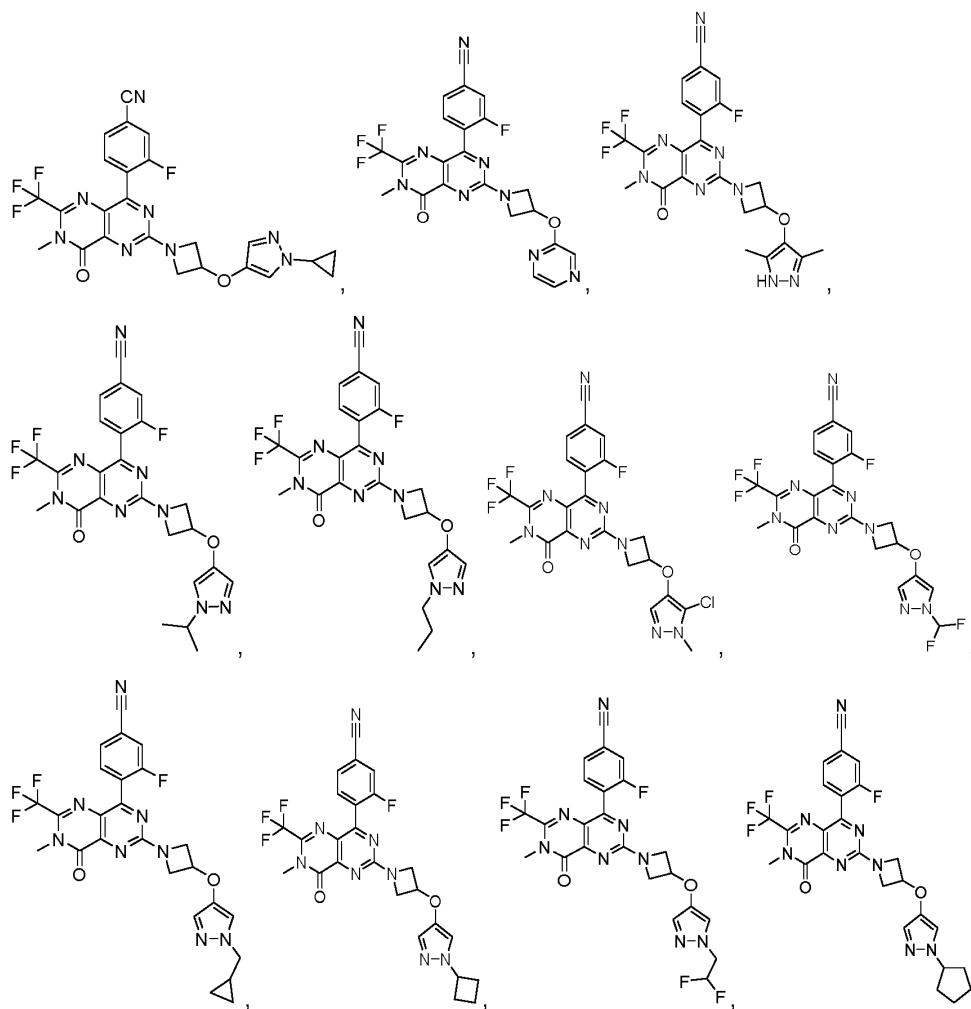
In some embodiments, the neurodegenerative disease is Alzheimer's disease. In some embodiments, the neurodegenerative disease is Nasu-Hakola disease. In some embodiments, the neurodegenerative disease is frontotemporal dementia. In some

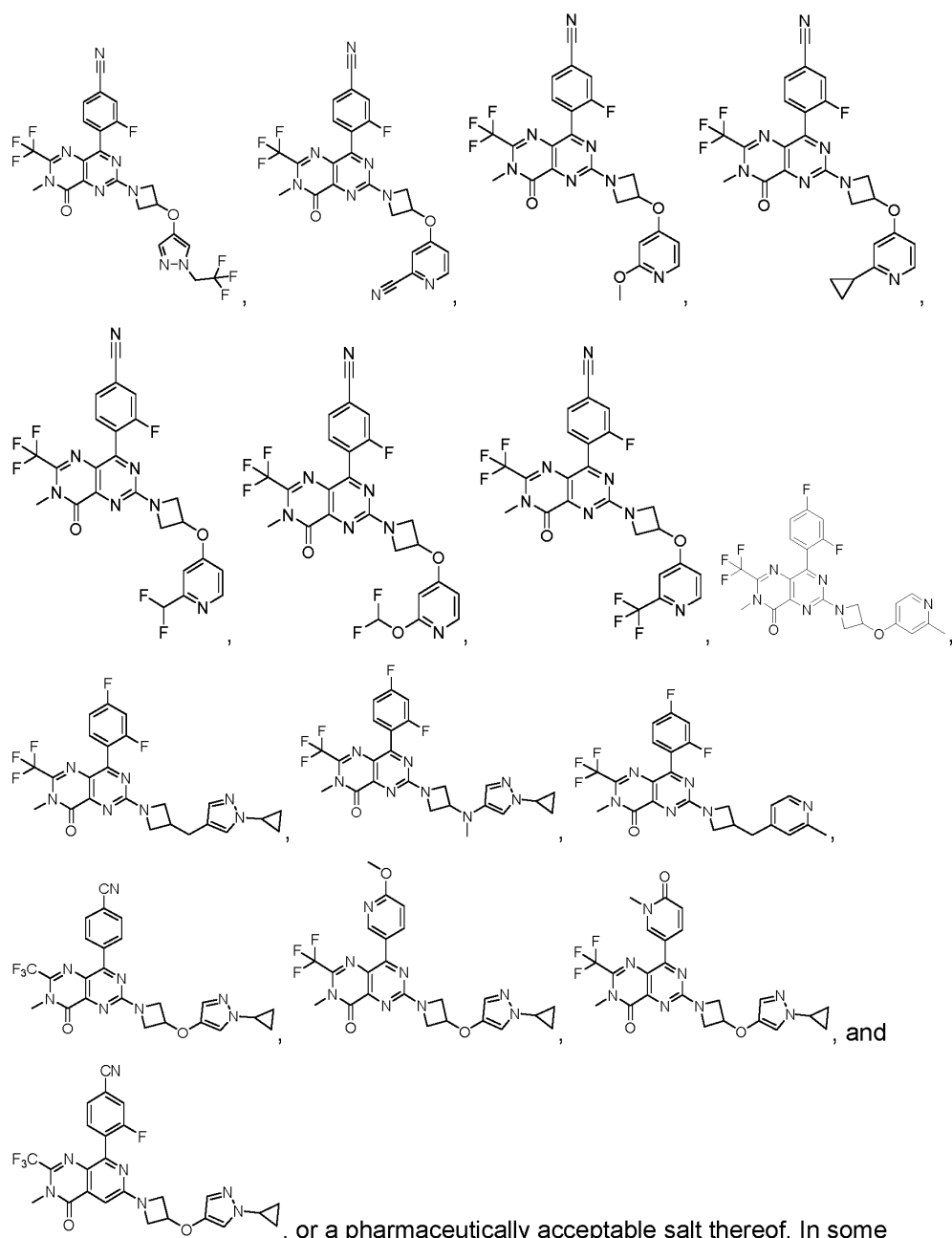
embodiments, the method comprises administering to the subject a compound as described herein, or a pharmaceutical composition comprising a compound as described herein.

- 5 The compounds of the present invention may be used to treat an animal patient belonging to any classification. Examples of such animals include mammals such as humans, rodents, dogs, cats, zoo animals and farm animals. In some embodiments, the subject referred to herein is a mammal, such as a human.
- 10 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.
- 15 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
- 20 condition, being treated." In some embodiments, a provided combination, or composition thereof, is administered in combination with another therapeutic agent. In some embodiments, the present invention provides a method of treating a disclosed disease or condition comprising administering to a patient in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof,
- 25 and co-administering simultaneously or sequentially an effective amount of one or more additional therapeutic agents. In some embodiments, the method includes co-administering one or more additional therapeutic agent. Examples of therapeutic agents the combinations of the present invention may also be combined with include, without limitation: treatments for Parkinson's disease, rheumatoid arthritis, Alzheimer's
- 30 disease, Nasu- Hakola disease, frontotemporal dementia, multiple sclerosis, prion disease, or stroke. In some embodiments, the therapeutic agents the combinations of the present invention may also be combined with include, without limitation: treatments for a disease selected from the group consisting of a tauopathy, a TDP-43 proteinopathy, a synucleinopathy, dementia, amyloidosis, a demyelinating disorder of
- 35 the CNS, a demyelinating disorder of the PNS, a Leukoencephalopathy, a

leukodystrophy, a transmissible spongiform encephalopathy (TSE) and a lysosomal storage disorder (LSD). As used herein, the term “combination,” “combined,” and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with the present invention. For example, a combination of the
5 present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form.

In one aspect, the present invention relates to a method of treating a condition associated with a loss of function of TREM2 comprising administering to a subject a
10 therapeutically effective amount of a compound selected from





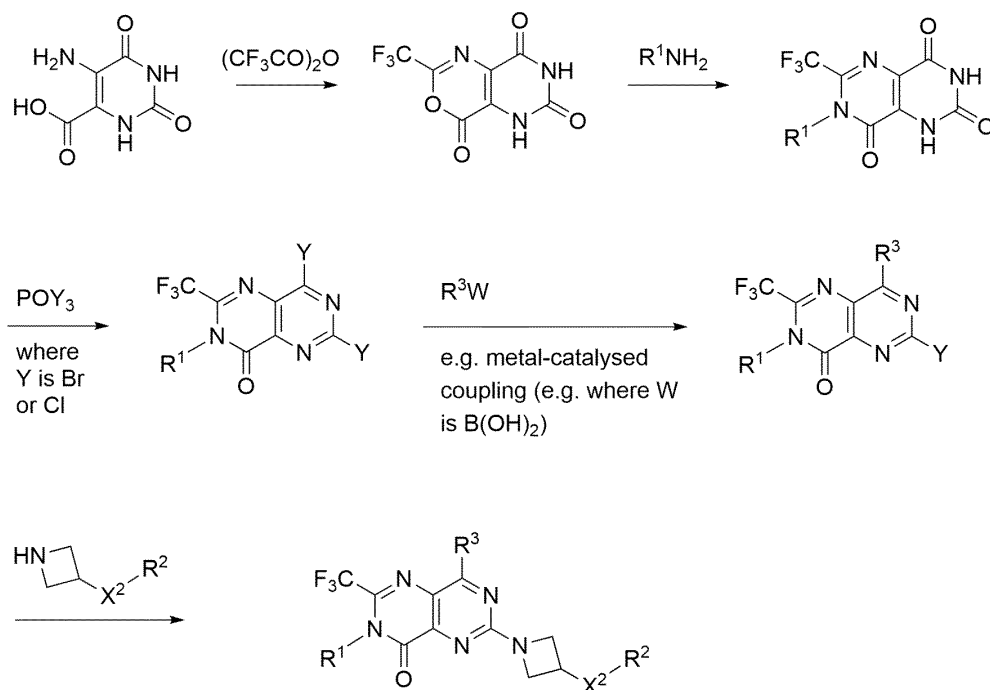
Charcot-Marie-Tooth disease, prion disease and stroke. In some embodiments, the neurodegenerative disease is Alzheimer's Disease.

Methods of manufacturing

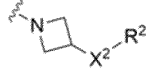
5 Compounds of the present invention may be prepared according to any conventional methods of chemical synthesis known by the skilled person, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods known by the skilled artisan from commercially available chemicals. The end products of the
10 reactions described herein may be isolated by conventional technique such as extraction, crystallisation, distillation, chromatography etc.

Generally, the compounds of Formula (I) as described herein may be synthesised according to the following schemes. All starting materials are either commercially
15 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.

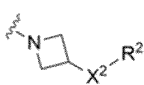
20 Scheme 1A:



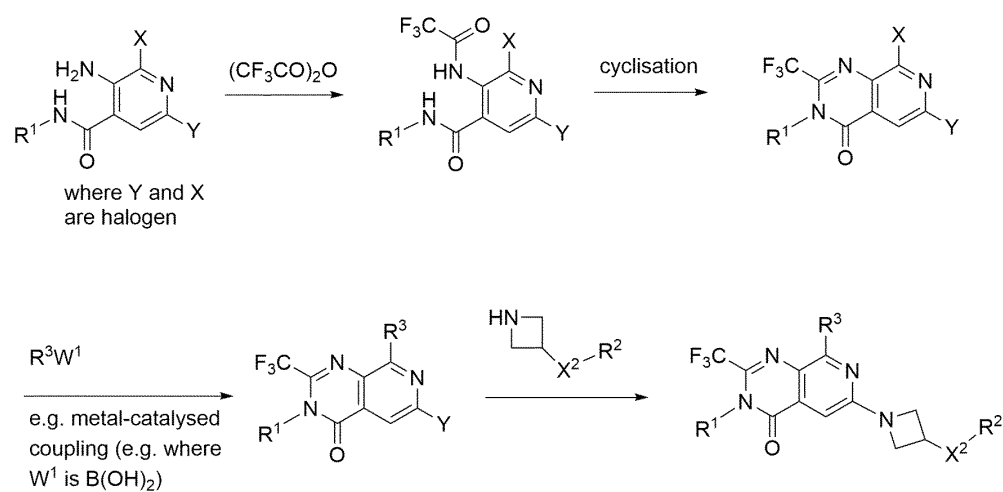
As shown in Scheme 1A, (CF₃CO)₂O is condensed with 5-amino-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid to form a 2-substituted pyrimido[5,4-d][1,3]oxazine-4,6,8-trione. Addition and cyclisation with R¹NH₂ affords the [1,3]diazino[5,4-d]pyrimidine-2,4,8-trione. Activation with POCl₃ or POBr₃ for example affords the 6,8-dihalo-pyrimido[5,4-d][1,3]diazin-4-one where Y is a Cl or Br leaving group. The R³ substituent is added via cross-coupling reaction, for example where W is a boronic acid, boronate ester or other organometallic coupling reagent such as

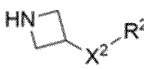
organomagnesium, organotin or organozinc reagent. The  substituent may then subsequently be introduced via a nucleophilic displacement reaction.

In Scheme 1B, (CF₃CO)₂O is reacted with a 3-amino-2,6-dihalo-1,2,3,6-tetrahydropyridin-4-carboxamide. Cyclisation forms a 6,8-dihalo-2,3-disubstituted pyridopyrimidinone, the R³ substituent is added via cross-coupling reaction, for example where W¹ is a boronic acid, boronate ester or other organometallic coupling reagent such as organomagnesium, organotin or

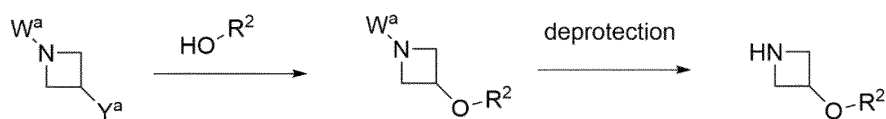
organozinc reagent. The  substituent may then subsequently be introduced via a nucleophilic displacement reaction or metal-catalysed coupling.

Scheme 1B:



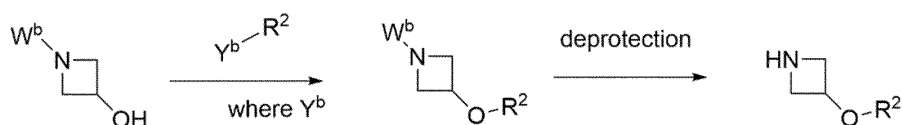
In Schemes 2A to D, different methods for the synthesis of , wherein X^2 and R^2 are as defined herein, are described.

Scheme 2A:



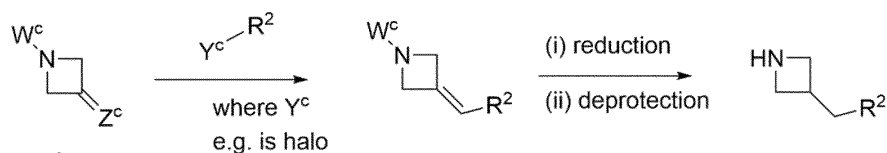
where W^a e.g. is Boc
and Y^a e.g. is halo

Scheme 2B:



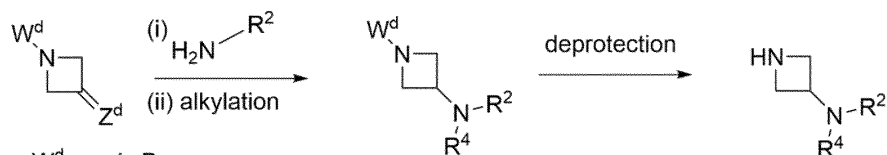
where W^b e.g. is Boc

Scheme 2C:



where W^c e.g. is Boc
and Z^c e.g. is O or CH_2

Scheme 2D:



where W^d e.g. is Boc
and Z^d e.g. is O

5 In Scheme 2A, a N-protected (e.g. with Boc) 3-halo-substituted azetidine undergoes a nucleophilic substitution reaction with a hydroxy-substituted R^2 substituent, deprotection then affords the substituted NH azetidine which is used as described in Scheme 1A and B.

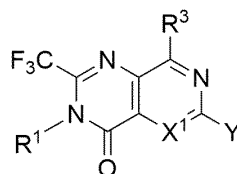
In Scheme 2B, a N-protected (e.g. with Boc) 3-hydroxy-substituted azetidine undergoes a nucleophilic substitution reaction with a halo-substituted R^2 substituent, deprotection

then affords the substituted NH azetidine which is used as described in Scheme 1A and B.

In Scheme 2C, a protected azetidine substituted with a carbonyl or methylene group is
 5 reacted with a halo-substituted R^2 substituent to form a substituted methylene intermediate. Reduction and deprotection then affords the substituted NH azetidine which is used as described in Scheme 1A and B.

In Scheme 2D, a protected azetidine substituted with a carbonyl group undergoes a
 10 reductive amination with an amino-substituted R^2 , the intermediate secondary amine is then alkylated to introduce R^4 . Deprotection then affords the substituted NH azetidine which is used as described in Scheme 1A and B.

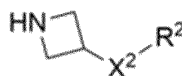
In one aspect, the present invention relates to a method for synthesizing a compound
 15 of Formula (I) as defined herein comprising one or more of the steps described above. In one aspect, the present invention relates to a method for manufacturing a compound of Formula (I) as defined herein, said method comprising the step of reacting a compound of Formula (SI):



20

Formula (SI)

wherein R^1 , R^3 , and X^1 are as defined herein and Y is Br or Cl,
 with a compound of Formula (SII):



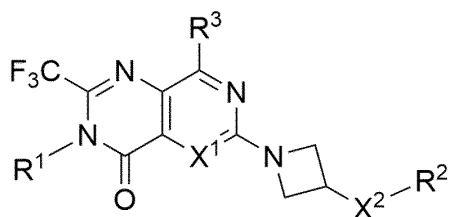
25

Formula (SII)

wherein X^2 and R^2 are as defined herein,
 to generate the compound of Formula (I).

Items

30 1. A compound of Formula (I):



Formula (I)

wherein:

X^1 is N or C(H);

5 X^2 is O, CH_2 or $N(R^4)$;

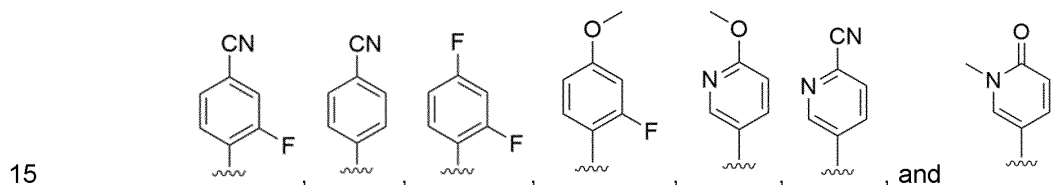
R^4 is H or C_{1-3} alkyl;

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

10 R^2 is selected from the group consisting of pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, and 1,3,4-thiadiazolyl, each of which is optionally substituted with 1 to 3 individually selected substituents R^5 ;

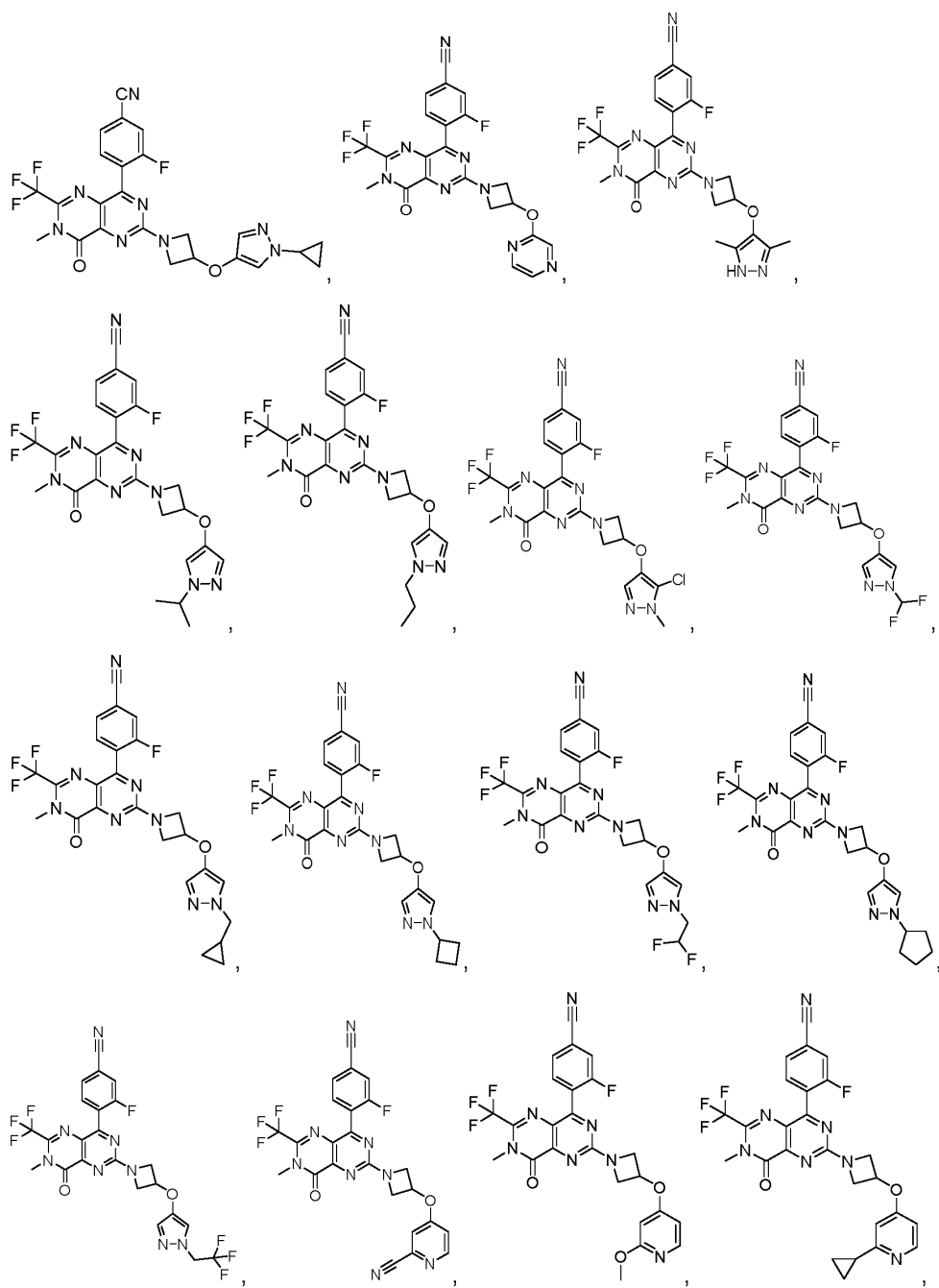
R^5 is individually selected from the group consisting of C_{1-3} alkyl optionally substituted with C_{3-5} cycloalkyl and/or 1 to 3 F; C_{1-3} alkoxy optionally substituted with 1 to 3 F; C_{3-5} cycloalkyl; CN; and halogen; and

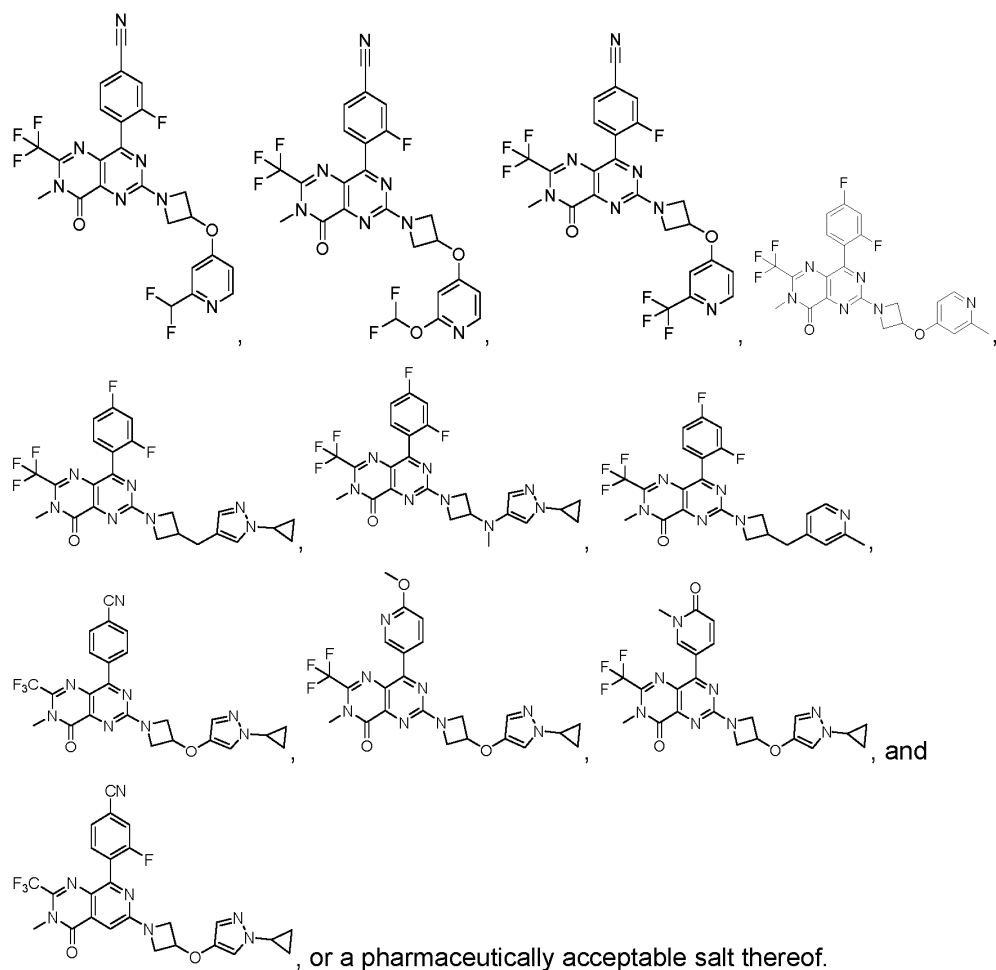
R^3 is selected from the group consisting of:



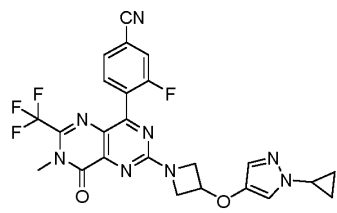
or a pharmaceutically acceptable salt thereof.

2. The compound according to item 1, wherein the compound is selected from





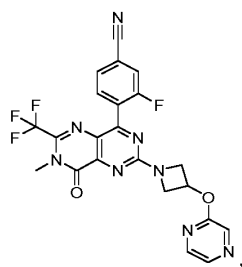
- 5 3. A pharmaceutical composition comprising a compound of item 2, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.
4. The compound according to item 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

- 10 5. A pharmaceutical composition comprising a compound of item 4, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

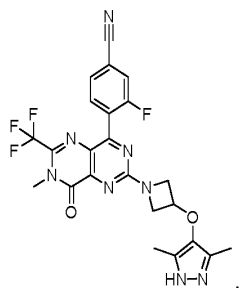
6. The compound according to item 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a compound of item 6, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

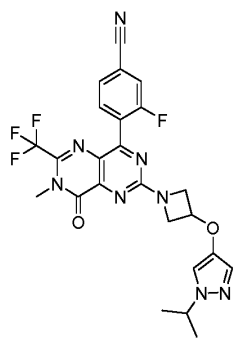
8. The compound according to item 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a compound of item 8, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

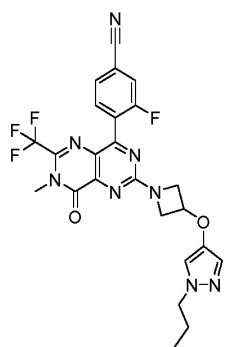
10. The compound according to item 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound of item 10, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

12. The compound according to item 1, wherein the compound is

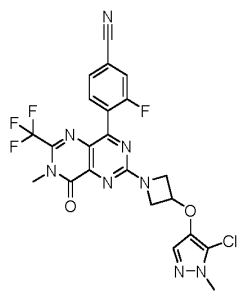


, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound of item 12, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

5

14. The compound according to item 1, wherein the compound is

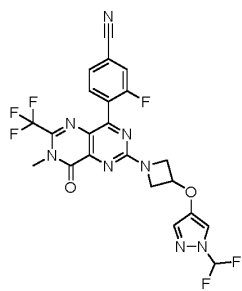


, or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising a compound of item 14, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

10

16. The compound according to item 1, wherein the compound is

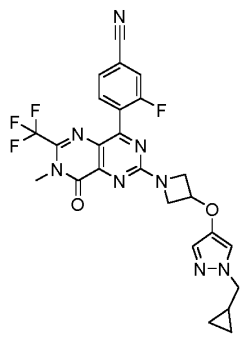


, or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising a compound of item 16, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

15

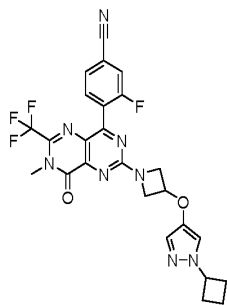
18. The compound according to item 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a compound of item 18, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

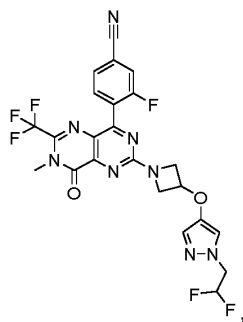
20. The compound according to item 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a compound of item 20, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

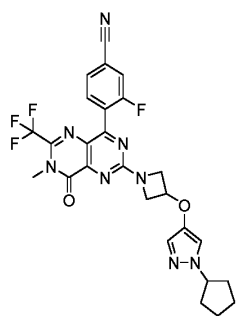
22. The compound according to item 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising a compound of item 22, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

24. The compound according to item 1, wherein the compound is

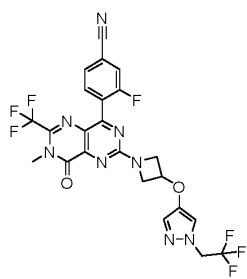


, or a pharmaceutically acceptable salt thereof.

25. A pharmaceutical composition comprising a compound of item 24, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

5

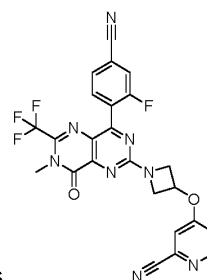
26. The compound according to item 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

27. A pharmaceutical composition comprising a compound of item 26, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

10

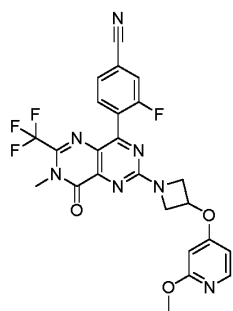


28. The compound according to item 1, wherein the compound is
, or a pharmaceutically acceptable salt thereof.

29. A pharmaceutical composition comprising a compound of item 28, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

15

30. The compound according to item 1, wherein the compound is

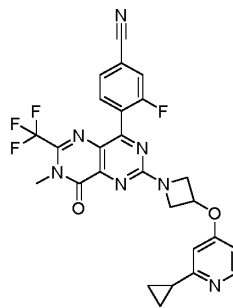


, or a pharmaceutically acceptable salt thereof.

31. A pharmaceutical composition comprising a compound of item 30, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

5

32. The compound according to item 1, wherein the compound is

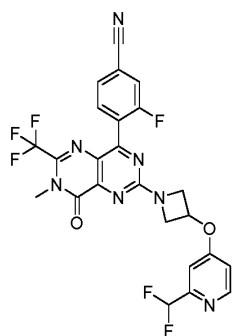


, or a pharmaceutically acceptable salt thereof.

33. A pharmaceutical composition comprising a compound of item 32, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

10

34. The compound according to item 1, wherein the compound is

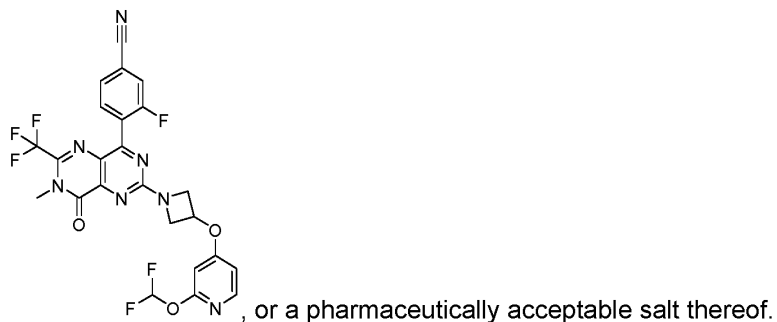


, or a pharmaceutically acceptable salt thereof.

35. A pharmaceutical composition comprising a compound of item 34, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

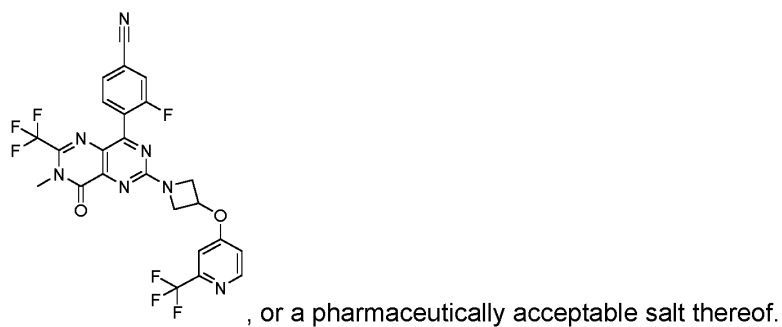
15

36. The compound according to item 1, wherein the compound is



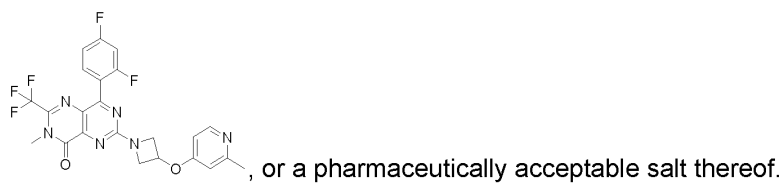
37. A pharmaceutical composition comprising a compound of item 36, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

38. The compound according to item 1, wherein the compound is



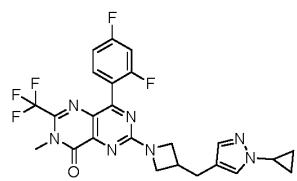
39. A pharmaceutical composition comprising a compound of item 38, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

40. The compound according to item 1, wherein the compound is



41. A pharmaceutical composition comprising a compound of item 40, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

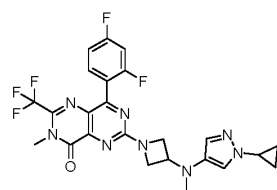
42. The compound according to item 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

43. A pharmaceutical composition comprising a compound of item 42, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

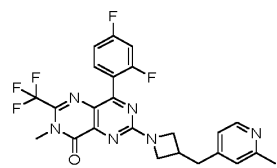
44. The compound according to item 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

45. A pharmaceutical composition comprising a compound of item 44, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

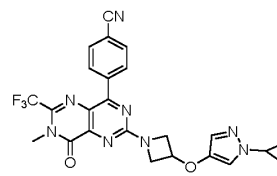
46. The compound according to item 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

47. A pharmaceutical composition comprising a compound of item 46, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

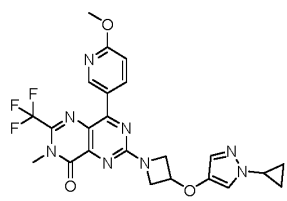
48. The compound according to item 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

49. A pharmaceutical composition comprising a compound of item 48, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

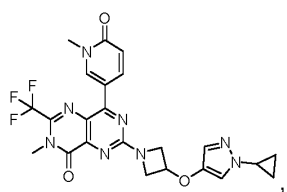
50. The compound according to item 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

51. A pharmaceutical composition comprising a compound of item 50, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

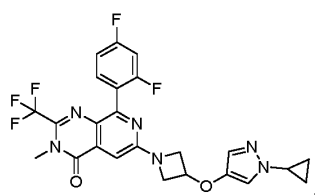
52. The compound according to item 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

53. A pharmaceutical composition comprising a compound of item 52, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

54. The compound according to item 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

55. A pharmaceutical composition comprising a compound of item 54, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.

56. A method of treating a condition associated with a loss of function of TREM2 comprising administering to a subject a therapeutically effective amount of a compound of item 1, or a pharmaceutically acceptable salt thereof.

57. The method of item 56, wherein the condition is a neurodegenerative disease.

58. The method of item 57, wherein the neurodegenerative disease is 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, stroke, and traumatic brain injuries (TBI).

59. The method of item 57, wherein the neurodegenerative disease is Alzheimer's Disease.

5

Examples

Abbreviations

10

Ac	:	Acetyl
aq.	:	Aqueous
dba	:	dibenzylideneacetone
DCM	:	Dichloromethane
15 DIPEA	:	Diisopropylethylamine
DMAP	:	4-Dimethylaminopyridine
DMF	:	Dimethyl formamide
DMSO	:	Dimethylsulfoxide
Dppf	:	1,1'-Bis(diphenylphosphino)ferrocene
20 EtOAc	:	Ethyl acetate
eq.	:	equivalents
g	:	gram(s)
h	:	hour(s)
HATU	:	1-[Bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5-
25 <i>b</i>]pyridinium 3-oxid hexafluorophosphate		
HPLC	:	High performance liquid chromatography
LCMS	:	Liquid chromatography-mass spectrometry
MeOH	:	Methanol
Me ₂ NH ₂ ·HCl	:	Methylamine hydrochloride
30 mg	:	milligrams
min	:	minutes
mmol	:	millimole
mL	:	millilitre
mm	:	millimeter
35 MS	:	mass spectra
m/z	:	mass divided by charge number

	NH ₄ OAc	:	Ammonium acetate
	NBS	:	N-bromo succinimide
	NMR	:	Nuclear magnetic resonance
	rt	:	Room temperature
5	Rt	:	Retention time
	RuPhos	:	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
	sat.	:	saturated
	THF	:	Tetrahydrofuran
	TFA	:	Trifluoroacetic Acid
10	Xanphos	:	(9,9-Dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane)

LCMS conditions

15 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.

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

30 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.

Condition D

Column- Xbridge C18 column (3.5 μ m, 50 x 3 mm),(initially 95% [5 mM NH₄OAc in water] and 5% [5 mM NH₄OAc in CH₃CN: Water (90:10)] held for 0.75 min, then to 70% [5 mM NH₄OAc in water] and 30% [5 mM NH₄OAc in CH₃CN: Water (90:10)] in 1.00 min, and finally 2% [5 mM NH₄OAc in water] and 98% [5 mM NH₄OAc in CH₃CN: 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.

Condition E

Column- YMC Triart C18 (33 x 2.1 mm, 3 μ), (initially 98% [0.05% HCOOH in water] and 2% [0.05% HCOOH in CH₃CN: Water (90:10)] held for 0.75 min, then to 90% [0.05% HCOOH in water] and 10% [0.05% HCOOH in CH₃CN: Water (90:10)] in 1.0 min, further 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 2.50 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.

Reverse Phase Prep-Purification method:

Prep-A

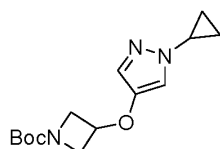
Preparative HPLC was done on Waters auto purification instrument. Column name: LONG-YMC,C18(20 X 250 mm),5 μ m operating at ambient temperature and flow rate of 16 mL/min. Mobile phase: A=Acetonitrile, B = 10mM Ammonium Acetate in water; Gradient Profile: Mobile phase initial composition of 30% A and 70% B, then 45% A and 55% B in 3 min, then to 78% A and 22% B in 18 min., then to 100% A and 0% B in 19 min., held this composition up to 21.5 min. for column washing, then returned to initial composition in 22 min. and held till 24 min.

Prep-B

Preparative HPLC was done on Waters auto purification instrument. Column name: YMC-Actus C18 (250 x 20 mm, 5 μ) operating at ambient temperature and flow rate of 16 mL/min. 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.

Synthesis of intermediates:**Preparation of 4-(azetidin-3-yloxy)-1-cyclopropyl-1H-pyrazole (Intermediate I-1)**

5

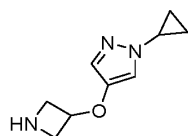
Step-1**Preparation of tert-butyl 3-[(1-cyclopropyl-1H-pyrazol-4-yl)oxy]azetidine-1-carboxylate:**

10 To a stirred solution of 1-cyclopropyl-1H-pyrazol-4-ol (2 g, 18.35 mmol) in DMF (40 mL) was added Cs_2CO_3 (9.50 g, 27.5 mmol) followed by tert-butyl 3-iodoazetidine-1-carboxylate (7.75 g, 27.5 mmol) and the resulting mixture was heated at 70 °C for 16h. The reaction mixture was diluted with ethyl acetate. Combined organic part was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Crude mass was purified by column chromatography (50% ethyl acetate-hexane) to afford tert-butyl 3-[(1-cyclopropyl-1H-pyrazol-4-yl)oxy]azetidine-1-carboxylate (3.5 g, 68.3% yield) as yellowish liquid.

15

1H NMR (400 MHz, DMSO D_6) δ 7.50 (1H, s), 7.16 (1H, s), 4.70-4.67 (1H, m), 4.20-4.16 (2H, t), 3.74 (2H, d, $J=4$ MHz), 1.19 (9H, m), 0.99-0.93 (2H, m), 0.92-0.87 (2H, m); LCMS Condition E: R_t = 3.16 min. m/z 280.1 $[\text{M}+\text{H}]^+$.

20

Step-2**Preparation of 4-(azetidin-3-yloxy)-1-cyclopropyl-1H-pyrazole, TFA salt:**

25

To a stirred solution of tert-butyl 3-[(1-cyclopropyl-1H-pyrazol-4-yl)oxy]azetidine-1-carboxylate (500 mg, 0.307 mmol, 1 equiv.) in DCM (10 mL) and was cooled to 0 °C. TFA (1.5 mL) was added drop wise. The reaction was gradually warmed to room temperature and stir for 1h. The reaction was concentrated under reduced pressure

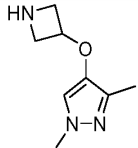
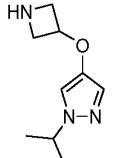
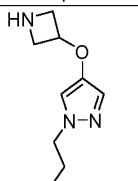
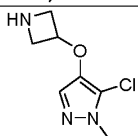
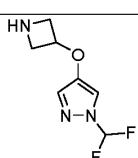
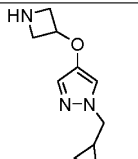
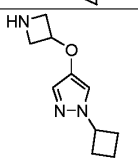
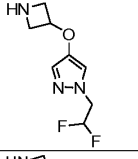
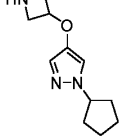
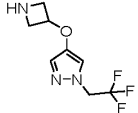
and washed with ether to afford 4-(azetidin-3-yloxy)-1-cyclopropyl-1H-pyrazole as TFA salt. as yellowish sticky liquid.

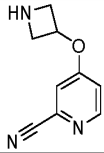
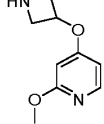
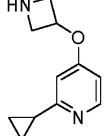
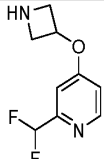
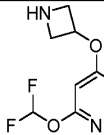
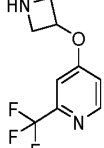
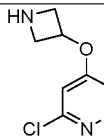
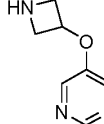
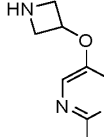
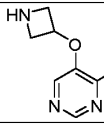
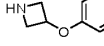
¹H NMR (400 MHz, DMSO D6) δ 7.57 (1H, s), 7.21 (1H, s), 4.78-4.74 (1H, m), 4.35 (2H, dd, J=16 Hz, J=4 Hz), 3.95 (2H, d, J=4 Hz), 3.62-3.57 (1H, m), 0.99-0.93 (2H, m), 0.92-0.89 (2H, m).

Intermediates I-2 to I-28 were synthesized by using similar procedures as used to make Intermediate I-1.

10

Structure	Intermediate Number	Name	Starting alcohol	LCMS/NMR
	I-2	2-(azetidin-3-yloxy)-1,3,4-thiadiazole	1,3,4-thiadiazol-2-ol	LCMS Condition A: Rt = 0.26 min. m/z 158.0 [M+H] ⁺ .
	I-3	2-(azetidin-3-yloxy)-5-methyl-1,3,4-thiadiazole	5-methyl-1,3,4-thiadiazol-2-ol	LCMS Condition A: Rt = 0.17 min. m/z 171.95 [M+H] ⁺ .
	I-4	2-(azetidin-3-yloxy)-5-ethyl-1,3,4-thiadiazole	5-ethyl-1,3,4-thiadiazol-2-ol	LCMS Condition A: Rt = 0.3 min. m/z 186.02 [M+H] ⁺ .
	I-5	2-(azetidin-3-yloxy)pyrazine	Pyrazin-2-ol	LCMS Condition A: Rt = 0.25 min. m/z 152.12 [M+H] ⁺ .
	I-6	2-(azetidin-3-yloxy)-6-methylpyrazine	6-methylpyrazin-2-ol	LCMS Condition A: Rt = 0.3 min. m/z 166.1 [M+H] ⁺ .
	I-7	4-(azetidin-3-yloxy)-1,5-dimethyl-1H-pyrazole	1,5-dimethyl-1H-pyrazol-4-ol	LCMS Condition A: Rt = 0.15 min. m/z 168.2 [M+H] ⁺ .
	I-8	4-(azetidin-3-yloxy)-3,5-dimethyl-1H-pyrazole	3,5-dimethyl-1H-pyrazol-4-ol	LCMS Condition A: Rt = 0.17 min. m/z 168.1 [M+H] ⁺ .

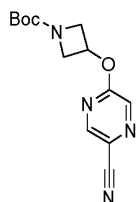
	I-9	4-(azetidin-3-yloxy)-1,3-dimethyl-1H-pyrazole	1,3-dimethyl-1H-pyrazol-4-ol	LCMS Condition A: Rt = 0.26 min. m/z 168.2 [M+H] ⁺ .
	I-10	4-(azetidin-3-yloxy)-1-isopropyl-1H-pyrazole	1-isopropyl-1H-pyrazol-4-ol	LCMS Condition A: Rt = 0.34 min. m/z 182.19 [M+H] ⁺ .
	I-11	4-(azetidin-3-yloxy)-1-propyl-1H-pyrazole	1-propyl-1H-pyrazol-4-ol	LCMS Condition A: Rt = 0.50 min. m/z 182.2 [M+H] ⁺ .
	I-12	4-(azetidin-3-yloxy)-5-chloro-1-methyl-1H-pyrazole	5-chloro-1-methyl-1H-pyrazol-4-ol	LCMS Condition A: Rt = 0.39 min. m/z 188.1 [M+H] ⁺ .
	I-13	4-(azetidin-3-yloxy)-1-(difluoromethyl)-1H-pyrazole	1-(difluoromethyl)-1H-pyrazol-4-ol	LCMS Condition A: Rt = 0.34 min. m/z 190.12 [M+H] ⁺ .
	I-14	4-(azetidin-3-yloxy)-1-(cyclopropylmethyl)-1H-pyrazole	1-(cyclopropylmethyl)-1H-pyrazol-4-ol	LCMS Condition A: Rt = 0.43 min. m/z 194.2 [M+H] ⁺ .
	I-15	4-(azetidin-3-yloxy)-1-cyclobutyl-1H-pyrazole	1-cyclobutyl-1H-pyrazol-4-ol	LCMS Condition A: Rt = 0.47 min. m/z 194.1 [M+H] ⁺ .
	I-16	4-(azetidin-3-yloxy)-1-(2,2-difluoroethyl)-1H-pyrazole	1-(2,2-difluoroethyl)-1H-pyrazol-4-ol	LCMS Condition A: Rt = 0.26 min. m/z 204.1 [M+H] ⁺ .
	I-17	4-(azetidin-3-yloxy)-1-cyclopentyl-1H-pyrazole	1-cyclopentyl-1H-pyrazol-4-ol	LCMS Condition A: Rt = 0.89 min. m/z 208.2 [M+H] ⁺ .
	I-18	4-(azetidin-3-yloxy)-1-(2,2,2-trifluoroethyl)-1H-pyrazole	1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-ol	LCMS Condition A: Rt = 0.44 min. m/z 222.1 [M+H] ⁺ .

	I-19	4-(azetidin-3-yloxy)picolinonitrile	4-hydroxypicolonitrile	LCMS Condition A: Rt = 0.2 min. m/z 176.0 [M+H] ⁺ .
	I-20	4-(azetidin-3-yloxy)-2-methoxypyridine	2-methoxypyridin-4-ol	LCMS Condition A: Rt = 0.21 min. m/z 181.19 [M+H] ⁺ .
	I-21	4-(azetidin-3-yloxy)-2-cyclopropylpyridine	2-cyclopropylpyridin-4-ol	LCMS Condition A: Rt = 0.26 min. m/z 191.1 [M+H] ⁺ .
	I-22	4-(azetidin-3-yloxy)-2-(difluoromethyl)pyridine	2-(difluoromethyl)pyridin-4-ol	LCMS Condition A: Rt = 0.30 min. m/z 201.2 [M+H] ⁺ .
	I-23	4-(azetidin-3-yloxy)-2-(difluoromethoxy)pyridine	2-(difluoromethoxy)pyridin-4-ol	LCMS Condition A: Rt = 0.74 min. m/z 217.05 [M+H] ⁺ .
	I-24	4-(azetidin-3-yloxy)-2-(trifluoromethyl)pyridine	2-(trifluoromethyl)pyridin-4-ol	LCMS Condition A: Rt = 0.40 min. m/z 219.17 [M+H] ⁺ .
	I-25	5-(azetidin-3-yloxy)-3-chloropyridazine	6-chloropyridazin-4-ol	LCMS Condition A: Rt = 0.25 min. m/z 186.2 [M+H] ⁺ .
	I-26	5-(azetidin-3-yloxy)pyrimidine	pyrimidin-5-ol	LCMS Condition A: Rt = 0.21 min. m/z 152.13 [M+H] ⁺ .
	I-27	5-(azetidin-3-yloxy)-2-methylpyrimidine	2-methylpyrimidin-5-ol	LCMS Condition A: Rt = 0.24 min. m/z 166.2 [M+H] ⁺ .
	I-28	5-(azetidin-3-yloxy)-4-methylpyrimidine	4-methylpyrimidin-5-ol	LCMS Condition A: Rt = 0.27 min. m/z 166.1 [M+H] ⁺ .
	I-29	4-(azetidin-3-yloxy)-2-methylpyridine	2-methylpyridin-4-ol	LCMS Condition A: Rt = 0.20 min. m/z 165.1 [M+H] ⁺ .

**Synthesis of tert-butyl 3-((5-cyanopyrazin-2-yl)oxy)azetidine-1-carboxylate
(Intermediate I-30):**

5 Step-1

Preparation of tert-butyl 3-((5-cyanopyrazin-2-yl)oxy)azetidine-1-carboxylate:

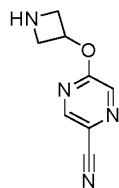


To a stirred solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (150 mg, 0.86 mmol) in DMF (5 mL) was added NaH (31 mg, 1.3 mmol; 60% assay) at 0 °C and stirred at for 10 min. Then 5-chloropyrazine-2-carbonitrile (140 mg, 1.3 mmol) was added to the reaction mixture and resulting mixture was stirred at rt for 16h. The reaction mixture was diluted with ethyl acetate. Combined organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Crude mass was purified by column chromatography (50% ethyl acetate-hexane) to afford tert-butyl tert-butyl 3-((5-cyanopyrazin-2-yl)oxy)azetidine-1-carboxylate (120 mg, 50 % yield) as yellowish liquid.

¹H NMR (400 MHz, DMSO D6) δ 7.83 (1H, s), 7.54 (1H, s), 5.39-5.38 (m, 1H), 4.30-4.26 (m, 2H), 3.91-3.89(m, 2H), 1.38 (s, 6H)

Step-2

Preparation of 5-(azetidin-3-yloxy)pyrazine-2-carbonitrile, TFA salt:



To a stirred solution of tert-butyl 3-((5-cyanopyrazin-2-yl)oxy)azetidine-1-carboxylate (500 mg, 0.307 mmol, 1 equiv.) in DCM (10 mL) and was cooled to 0 °C. TFA (1.5 mL) was added drop wise. The reaction was gradually warmed to room temperature and stir for 1h. The reaction was concentrated under reduced pressure and washed with ether

to afford 5-(azetidin-3-yloxy)pyrazine-2-carbonitrile as TFA salt. as yellowish sticky liquid.

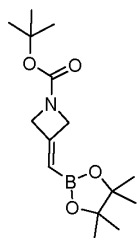
LCMS Condition E: Rt = 0.2 min. m/z 177.01 [M+H]⁺.

5

Synthesis of 4-(azetidin-3-ylmethyl)-1-cyclopropyl-1H-pyrazole, TFA salt (Intermediate I-31):

Step-1

10 **Preparation of tert-butyl 3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)azetidine-1-carboxylate:**



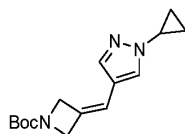
To a stirred solution of 2,2,6,6-Tetramethylpiperidine (247 mg, 1.75 mmol) in THF (10 mL) at -30 °C was added n-BuLi (0.8 mL, 2.5 M in Hexane, 1.75 mmol) and stirred it for 30 minutes. The reaction mixture was cooled to -78 °C and added bis[(pinacolato)boryl]methane (391 mg, 1.46 mmol) and stirred at same temperature for 30 minutes. Then added tert-butyl 3-oxoazetidine-1-carboxylate (250 mg, 1.46 mmol) to the reaction mixture and allowed to warm up to room temperature and stirred for 16 h. The reaction mixture was quenched with ice-cold ammonium chloride solution, extracted ethyl acetate and concentrated under reduced pressure. Crude mass was purified by column chromatography (35% ethyl acetate-hexane) to afford tert-butyl 3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)azetidine-1-carboxylate (250 mg, 58% yield) as liquid.

LCMS Condition B ; Rt = 3.87 min.m/z 296.3 [M+H]⁺.

25

Step-2

Preparation of tert-butyl 3-((1-cyclopropyl-1H-pyrazol-4-yl) methylene) azetidine-1-carboxylate:

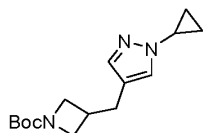


To a stirred solution of tert-butyl 3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)azetidine-1-carboxylate (173 mg, 0.588 mmol) and 4-bromo-1-cyclopropyl-1H-pyrazole (110 mg, 0.588 mmol) in dioxane (6 mL) and water (2 mL) was added potassium carbonate (162 mg, 1.27 mmol) and degassed with argon. PdCl₂(dppf) (43 mg, 0.059 mmol) was added under inert atmosphere. The resulting mixture was heated at 90 °C for 2h. 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 brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Crude mass was purified by column chromatography (silica gel; 35% ethyl acetate-hexane) to afford tert-butyl 3-(1-cyclopropyl-1H-pyrazol-4-yl)methylene)azetidine-1-carboxylate (70 mg, 43% yield) as liquid.

LCMS Condition A: Rt = 1.87 min.m/z 276.3 [M+H]⁺

Step-3

Preparation of tert-butyl 3-((1-cyclopropyl-1H-pyrazol-4-yl)methyl)azetidine-1-carboxylate

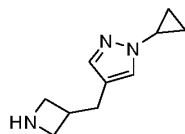


To a stirred solution of tert-butyl 3-((1-cyclopropyl-1H-pyrazol-4-yl)methylene)azetidine-1-carboxylate 70 mg, 0.25 mmol) in ethanol (5.0 mL) was added Pd/C (20 mg, 10 % on charcoal) under nitrogen atmosphere. The reaction mixture was stirred at rt for 4 h under hydrogen balloons pressure. The reaction was filtered through a pad of celite bed, washed with ethyl acetate and concentrated under reduced pressure to afford tert-butyl 3-((1-cyclopropyl-1H-pyrazol-4-yl)methyl)azetidine-1-carboxylate (60 mg, 85% yield) as liquid.

LCMS Condition : B ; Rt = 3.21 min.m/z 278.3 [M+H]⁺

Step-4

Preparation of 4-(azetidin-3-ylmethyl)-1-cyclopropyl-1H-pyrazole, TFA salt:



To a stirred solution of tert-butyl 3-((1-cyclopropyl-1H-pyrazol-4-yl)methyl)azetidine-1-carboxylate (400 mg, 1.54 mmol.) in DCM (10 mL) and was cooled to 0 °C. TFA (1.5 mL) was added drop wise and stirred at rt for 1h. The reaction mixture was

5 concentrated under vacuo and washed with ether to afford 4-(azetidin-3-ylmethyl)-1-cyclopropyl-1H-pyrazole as TFA salt. as yellowish sticky liquid.

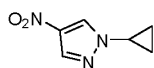
LCMS Condition: B; Rt = 1.27 min.m/z 178.1 [M+H]⁺

Synthesis of N-(azetidin-3-yl)-1-cyclopropyl-N-methyl-1H-pyrazol-4-amine

10 (Intermédiaire I-32):

Step-1

Preparation of 1-cyclopropyl-4-nitro-1H-pyrazole:



15

To a stirred solution of 4-nitro-1H-pyrazole (5 g, 44.20 mmol) in dichloroethane (200 mL) were added cyclopropyl boronic acid (7.59 g, 88 mmol), 2,2'-bipyridyl (7.59 g, 48.63 mmol) and sodium carbonate (13.37 g, 137 mmol) under oxygen atmosphere. Finally, copper acetate (8.86 g, 48.63 mmol) was added to the reaction mixture.

20 Resulting mixture was heated to 65 °C for 16 h. Reaction mixture was filtered through a pad of celite bed, washed with methanol and concentrated under reduced pressure.

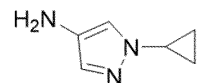
The crude residue was extracted with ethyl acetate, washed with brine, dried over sodium sulphate and concentrated. Crude product was purified by combi-flash chromatography (silica gel; 10% ethyl acetate-hexane) to afford 1-cyclopropyl-4-nitro-1H-pyrazole (3 g, 44 % yield) as colourless liquid.

25

LCMS Condition : A ; Rt = 1.68 min.m/z 153.1 [M+H]⁺

Step-2

Preparation of 1-cyclopropyl-1H-pyrazol-4-amine:



30

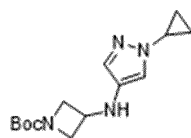
To a stirred solution of 1-cyclopropyl-4-nitro-1H-pyrazole (5 g, 18.7 mmol) in EtOAc-

ethanol mixture (50.0 mL; 1:1) was added Pd/C (1.6 g, 10 % on charcoal) under nitrogen atmosphere. Finally, under vacuum condition the reaction mixture was charged with hydrogen gas pressure. The resulting reaction mixture was stirred at room temperature for 2 h. The reaction was filtered through a pad of celite bed, washed with ethyl acetate and concentrated under reduced pressure to afford 1-cyclopropyl-1H-pyrazol-4-amine (2.4 g, 70% yield) as liquid.

1H NMR (400 MHz, DMSO D6) δ 7.00 (s, 1H), 6.86 (s, 1H), 3.86 (brs, 2H), 3.51-3.45 (m, 1H), 0.91-0.78 (m, 4H).

Step-3

Preparation of tert-butyl 3-((1-cyclopropyl-1H-pyrazol-4-yl)amino)azetidine-1-carboxylate:

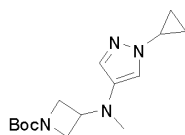


To a stirred solution of 1-cyclopropyl-1H-pyrazol-4-amine (94 mg, 0.764 mmol) and tert-butyl 3-oxoazetidine-1-carboxylate (392 mg, 2.29 mmol) and acetic acid (0.2 mL) in methanol (4 mL) was added sodium cyanoborohydride (240 mg, 3.82 mmol). Resulting mixture was heated at 50 °C for 2h. After completion of reaction it was quenched with water and extracted with DCM and concentrated, the crude mass was purified by column chromatography (silica gel; 10% ethyl acetate-hexane) to get tert-butyl 3-((1-cyclopropyl-1H-pyrazol-4-yl)amino)azetidine-1-carboxylate (40 mg, 19 % yield) as yellow gummy mass.

LCMS Condition : A ; Rt = 1.81 min.m/z 279.3 [M+H]⁺

Step-4

Preparation of tert-butyl 3-((1-cyclopropyl-1H-pyrazol-4-yl)(methyl)amino)azetidine-1-carboxylate:

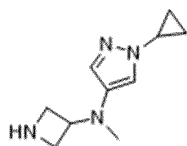


To a stirred solution of tert-butyl 3-((1-cyclopropyl-1H-pyrazol-4-yl)amino)azetidine-1-carboxylate (650 mg, 2.335 mmol) and HCHO (1.6 mL, 7.0 mmol) and acetic acid (1 mL) in methanol (20 mL) was added sodium cyanoborohydride (733 mg, 11.67 mmol)

portion wise. Resulting mixture was heated at 50 °C for 2h. After completion of reaction it was quenched with water and extracted with DCM and concentrated, the crude mass was purified by combi-flash chromatography (silica gel; 40% ethyl acetate-hexane) to get tert-butyl 3-((1-cyclopropyl-1H-pyrazol-4-yl)(methyl)amino)azetidine-1-carboxylate (550 mg, 80.56 % yield) as yellow gummy mass.

LCMS Condition : A ; Rt = 1.75 min.m/z 293.3 [M+H]⁺

Preparation of N-(azetidin-3-yl)-1-cyclopropyl-N-methyl-1H-pyrazol-4-amine, TFA salt:



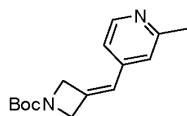
To a stirred solution of tert-butyl 3-((1-cyclopropyl-1H-pyrazol-4-yl)(methyl)amino)azetidine-1-carboxylate (100 mg, 0.342 mmol.) in DCM (10 mL) and was cooled to 0 °C. TFA (0.5 mL) was added drop wise. The reaction mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure and crude was washed with ether to afford N-(azetidin-3-yl)-1-cyclopropyl-N-methyl-1H-pyrazol-4-amine (80 mg, 76 % yield) as TFA salt.

LCMS Condition : B ; Rt = 1.06 min.m/z 193.3 [M+H]⁺

Synthesis of 4-(azetidin-3-ylmethyl)-2-methylpyridine, TFA salt (Intermediate I-33):

Step-1

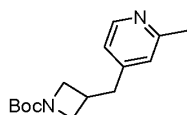
Preparation of tert-butyl 3-[(2-methylpyridin-4-yl)methylene]azetidine-1-carboxylate :



To a stirred solution of 4-Bromo-2-methylpyridine (500 mg, 2.941 mmol) in acetonitrile (4 ml) under nitrogen atmosphere were added tert-butyl 3-methyleneazetidine-1-carboxylate (1.5 g, 8.824 mmol) and triethyl amine (0.686 mL, 8.824 mmol) and degassed under nitrogen atmosphere. Pd(t-Bu₃P)₂ (75 mg, 0.147 mmol) was added under nitrogen atmosphere. The resulting mixture was heated at 80°C for 4 h. The reaction mixture was filtered through celite bed and filtrate was evaporated under

reduced pressure. Crude mass was purified by combi-flash chromatography (silica gel; 50% ethyl acetate-hexane) to get tert-butyl 3-[(2-methylpyridin-4-yl)methylidene]azetidine-1-carboxylate (140 mg, 18.28% yield) as sticky liquid. LCMS Condition : B ; Rt = 1.66 min. m/z 261.2 [M+H]⁺.

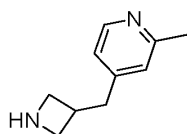
5

Step-2**Preparation of tert-butyl 3-[(2-methylpyridin-4-yl)methyl]azetidine-1-carboxylate :**

To a stirred solution of tert-butyl 3-[(2-methylpyridin-4-yl)methylidene]azetidine-1-carboxylate (140 mg, 0.461 mmol) in EtOAc (10 mL) was added Pd/C (50 mg, 10 % on charcoal) under nitrogen atmosphere. Finally, under vacuum condition the reaction mixture was charged with hydrogen gas pressure. The resulting reaction mixture was stirred at room temperature for 3 h. The reaction was filtered through a pad of celite bed, washed with ethyl acetate and concentrated under reduced pressure to afford tert-butyl 3-[(2-methylpyridin-4-yl)methyl]azetidine-1-carboxylate (100 mg, 82% yield) as liquid.

15

LCMS Condition A : Rt = 2.88 min. m/z 263.2 [M+H]⁺.

Step-3**Preparation of 4-(azetidin-3-ylmethyl)-2-methylpyridine:**

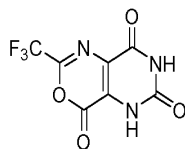
To a stirred solution of afford tert-butyl 3-[(2-methylpyridin-4-yl)methyl]azetidine-1-carboxylate (100 mg, 0.57 mmol.) in DCM (10 mL) and was cooled to 0 °C. TFA (1 mL) was added drop wise and stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure and crude was washed with ether to afford 4-(azetidin-3-ylmethyl)-2-methylpyridine (55 mg, 89% yield) as TFA salt. as sticky liquid.

25

LCMS Condition B: Rt = 1.80 min. m/z 163.2 [M+H]⁺.

Synthesis of 4-(2-chloro-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-**dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile (Intermediate I-34):**

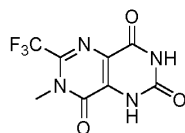
30

Step-1**Preparation of 2-(trifluoromethyl)-4H-pyrimido[5,4-d][1,3]oxazine-4,6,8(5H,7H)-trione:**

- 5 To a stirred solution of 5-amino-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid (50 g, 292.21 mmol) was added trifluoroacetic anhydride (490 mL, 3.5 mol) in drop wise at 0 °C. Resulting mixture was heated at 120 °C for 16 h under autoclave. It was cooled to ambient temperature and concentrated under reduced pressure. The crude product was triturated with DCM and dried to afford 2-(trifluoromethyl)-4H-pyrimido[5,4-d][1,3]oxazine-4,6,8(5H,7H)-trione (50 g, 68.63% yield) as brown solid.
- 10 ¹H NMR (400 MHz, DMSO-D₆) δ 9.96-9.88 (s, 1H), 8.82 (d, J=7.6 Hz, 1H), 8.82 (d, J=6.8 Hz, 1H).

Step-2

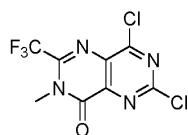
- 15 **Preparation of 7-methyl-6-(trifluoromethyl)-1,7-dihydropyrimido[5,4-d]pyrimidine-2,4,8(3H)-trione:**



- 20 To a stirred solution of 2-(trifluoromethyl)-4H-pyrimido[5,4-d][1,3]oxazine-4,6,8(5H,7H)-trione (50 g, 202 mmol) in acetic acid (1.1 L) was added sodium acetate (16 g, 202 mmol) followed by added MeNH₂.HCl [134 g, 2.02 mol] at rt. Resulting mixture was heated at 120 °C for 16h. The mixture was cooled to rt and concentrated under reduced pressure. The residue was diluted with water and precipitate thus formed was collected and dried. It was then triturated with diethyl ether, ethyl acetate successively and dried under high vacuum to afford 7-methyl-6-(trifluoromethyl)-1,7-dihydropyrimido[5,4-d]pyrimidine-2,4,8(3H)-trione (25 g, 48.0% yield) as light brown solid.
- 25 LCMS Condition A: Rt = 1.14 min. m/z 262.1 [M+H]⁺

Step-3

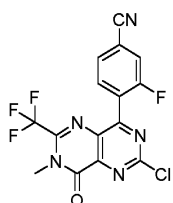
Preparation of 6,8-dichloro-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one:



To a stirred solution of 7-methyl-6-(trifluoromethyl)-1,7-dihydropyrimido[5,4-d]pyrimidine-2,4,8(3H)-trione (10 g, 38 mmol) in POCl₃ (160 mL, 1.7 mol), DIPEA (26 mL, 152 mmol) was added drop wise at 0°C. Resultant mixture was stirred at rt for 15 min and then heated to 100°C for 16h. The mixture was cooled to rt and concentrated under reduced pressure. The residue was cooled to 0°C, quenched with saturated aqueous NaHCO₃ solution and extracted 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 column chromatography (silica gel; 50% ethyl acetate-hexane) to afford 6,8-dichloro-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one (7 g, 61 % yield) as yellow solid. LCMS Condition A: Rt = 3.26 min. m/z 299.0 [M+H]⁺

Step-4

Preparation of 4-(2-chloro-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile:



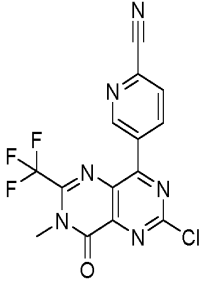
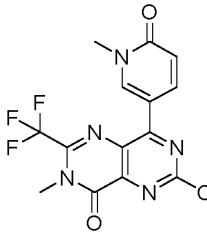
To a stirred solution of 6,8-dichloro-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one (500 mg, 1.672 mmol) and 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (620 mg, 2.5 mmol) in toluene (6 mL) and water (2 mL) was added 2M aqueous sodium carbonate (710 mg, 6.70 mmol; 2M solution in water) solution and degassed with argon. PdCl₂(dppf) (136 mg, 0.167 mmol) was added under inert atmosphere. The resulting mixture was stirred for 3h. 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 column chromatography (35% ethyl acetate-hexane) to afford 4-(2-chloro-7-

methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile (250 mg, 39 % yield) as white solid.

Condition A: Rt = 3.21 min. m/z 384.13 [M+H]⁺

- 5 The following intermediates were synthesized by using similar procedures described for Intermediate I-34 (Step 4)

Structure	Name	SM1	SM2	Intermediate Number
	6-chloro-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	6,8-dichloro-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	2, 4 difluorophenyl boronic acid (1.0 eq)	I-35
	4-(2-chloro-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile	6,8-dichloro-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	4-cyano phenyl boronic acid (1.0 eq)	I-36
	6-chloro-8-(2-fluoro-4-methoxyphenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	6,8-dichloro-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	2-fluoro-4-methoxyphenyl boronic acid (1 eq)	I-37
	6-chloro-8-(6-methoxypyridin-3-yl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	6,8-dichloro-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	(6-methoxypyridin-3-yl)boronic acid (1 eq)	I-38

	5-(2-chloro-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)picolinonitrile	6,8-dichloro-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile (1 eq)	I-39
	6-chloro-3-methyl-8-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	6,8-dichloro-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (1 eq)	I-40

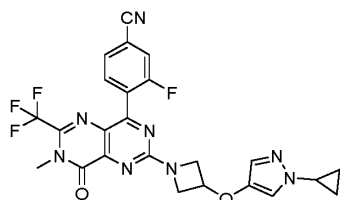
The following table describes analytical data analysis and yield information of intermediates I-34 to I-40.

Intermediate number	LCMS/NMR	Description	Yield%
I-34	Condition A : Rt = 2.22 min. m/z 377.1 [M+H] ⁺	White solid	43.0
I-35	Condition A : Rt = 2.14 min. m/z 366.1 [M+H] ⁺	White solid	50.0
I-36	Condition A : Rt = 2.07 min. m/z 384.0 [M+H] ⁺	White solid	34.0
I-37	Condition A: Rt = 2.15 min. m/z 366.2 [M+H] ⁺	White solid	39.0
I-38	Condition A: Rt = 1.99 min. m/z 372.25 [M+H] ⁺	White solid	35.0
I-39	Condition A: Rt = 1.88 min. m/z 367.22 [M+H] ⁺	White solid	38.0
I-40	Condition A: Rt = 2.00 min. m/z 371.1 [M+H] ⁺	White solid	25.0

Synthesis of Examples

Examples 1-39

Example 1: 4-(2-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile



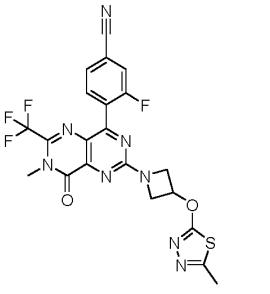
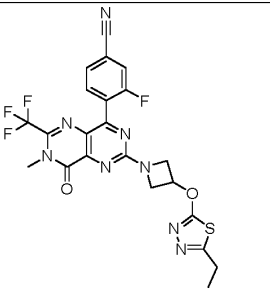
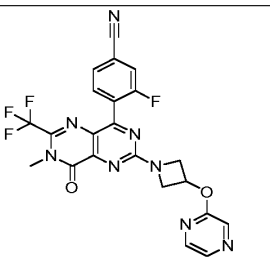
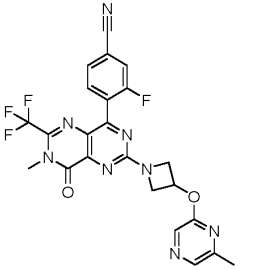
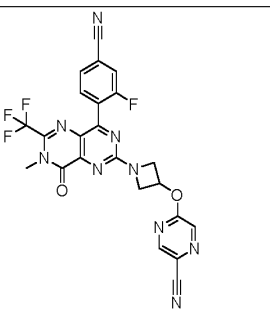
- 5 To a stirred solution of 4-(2-chloro-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile (200 mg, 0.52 mmol) in DMSO (4 mL) was added 4-(azetidin-3-yloxy)-1-cyclopropyl-1H-pyrazole (140 mg, 0.77 mmol) and followed by DIPEA (0.37 mL, 0.2 mmol) at rt and stirred for 1h. Reaction mixture was directly submitted for reverse phase preparative HPLC (Prep-A)
- 10 to afford 4-(2-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile (70 mg, 25% yield) as yellow solid.

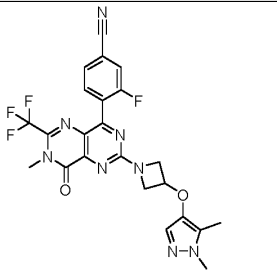
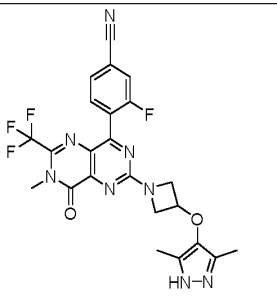
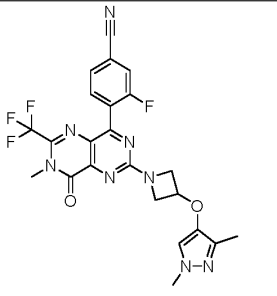
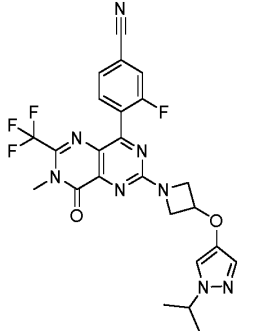
- ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.06 (d, J=9.6 Hz, 1H), 7.90-7.88 (m, 1H), 7.84-7.81(m, 1H), 7.58 (s, 1H), 7.23 (s, 1H), 4.92-4.89 (m, 1H), 4.60 (brs, 2H), 4.16-4.12 (m, 2H), 3.62- 3.58 (m, 1H), 3.55 (s, 3H), 1.0-0.96 (m, 2H), 0.92-0.88 (m, 2H).
- Condition A : Rt = 2.84 min. m/z 527.45 [M+H]⁺

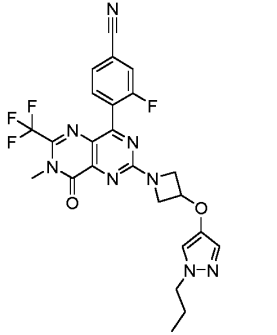
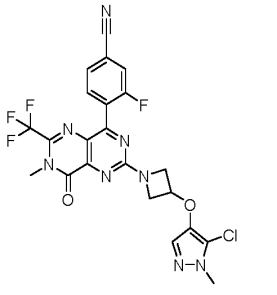
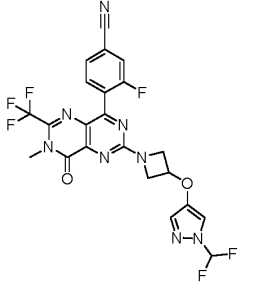
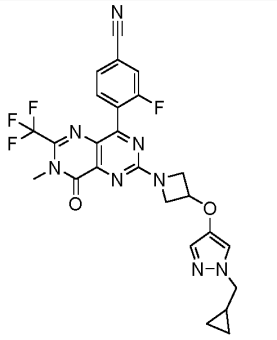
Examples 2-39 were synthesised using similar protocols as described for Example 1.

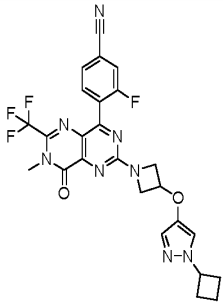
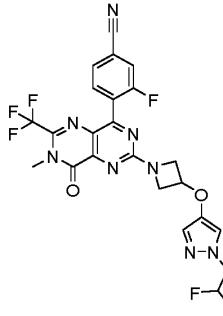
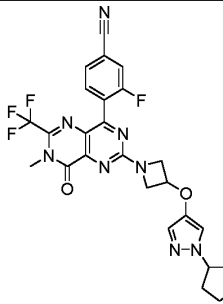
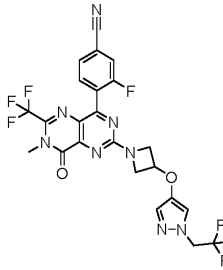
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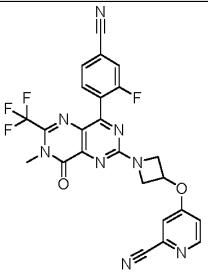
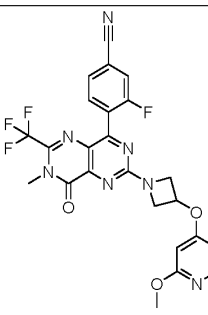
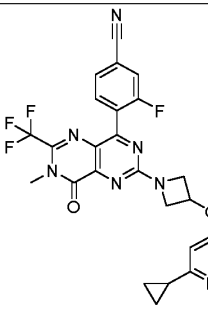
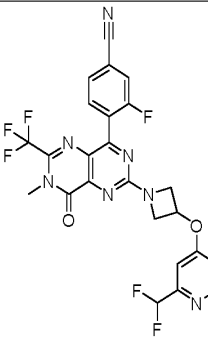
Ex. No.	Structure	Name	SM-1	SM-2	Purification method (Prep-HPLC)
2		4-(2-(3-((1,3,4-thiadiazol-2-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-2	Prep-B

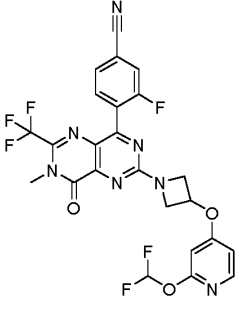
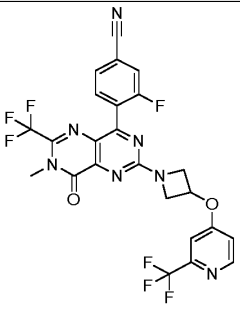
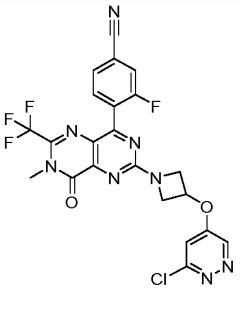
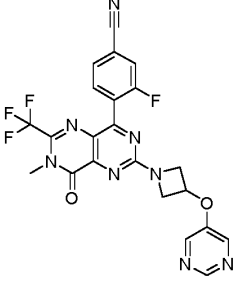
3		3-fluoro-4-(7-methyl-2-(3-((5-methyl-1,3,4-thiadiazol-2-yl)oxy)azetidin-1-yl)-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile	I-34	I-3	Prep-A
4		4-(2-(3-((5-ethyl-1,3,4-thiadiazol-2-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-4	Prep-A
5		3-fluoro-4-(7-methyl-8-oxo-2-(3-(pyrazin-2-yloxy)azetidin-1-yl)-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile	I-34	I-5	Prep-A
6		3-fluoro-4-(7-methyl-2-(3-((6-methylpyrazin-2-yl)oxy)azetidin-1-yl)-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile	I-34	I-6	Prep-A
7		5-((1-(4-(4-cyano-2-fluorophenyl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-2-yl)azetidin-3-yl)oxy)pyrazine-2-carbonitrile	I-34	I-30	Prep-A

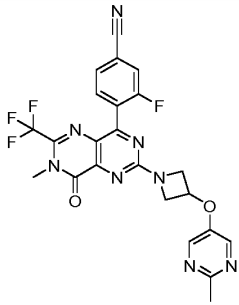
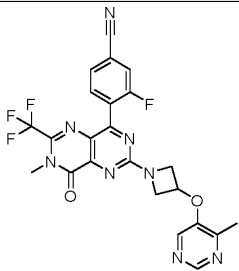
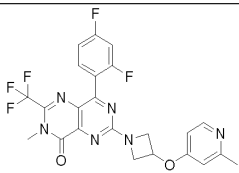
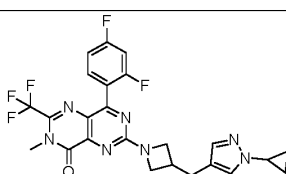
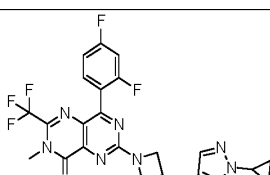
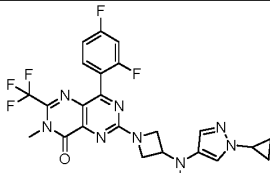
8		4-(2-(3-((1,5-dimethyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-7	Prep-A
9		4-(2-(3-((3,5-dimethyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-8	Prep-A
10		4-(2-(3-((1,3-dimethyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-9	Prep-A
11		3-fluoro-4-(2-(3-((1-isopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile	I-34	I-10	Prep-A

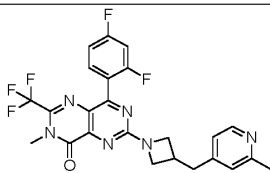
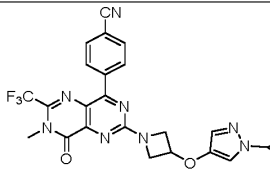
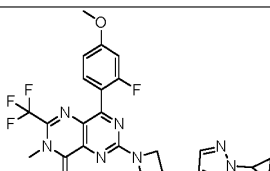
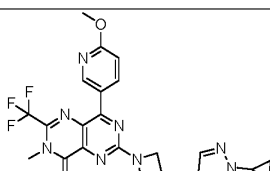
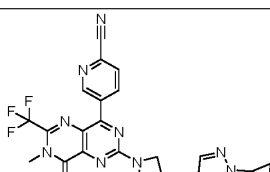
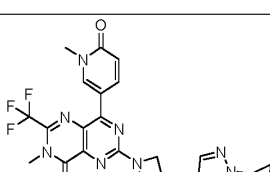
12		3-fluoro-4-(7-methyl-8-oxo-2-((1-propyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-ylbenzonitrile	I-34	I-11	Prep-A
13		4-(2-(3-((5-chloro-1-methyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-12	Prep-B
14		4-(2-(3-((1-(difluoromethyl)-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-13	Prep-A
15		4-(2-(3-((1-(cyclopropylmethyl)-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-14	Prep-A

16		4-(2-(3-((1-cyclobutyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-15	Prep-B
17		4-(2-(3-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-16	Prep-A
18		4-(2-(3-((1-cyclopentyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-17	Prep-A
19		3-fluoro-4-(7-methyl-8-oxo-2-(3-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile	I-34	I-18	Prep-A

20		4-((1-(4-(4-cyano-2-fluorophenyl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-2-yl)azetidin-3-yl)oxy)picolinonitrile	I-34	I-19	Prep-A
21		3-fluoro-4-(2-(3-((2-methoxypyridin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile	I-34	I-20	Prep-B
22		4-(2-(3-((2-cyclopropylpyridin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-21	Prep-A
23		4-(2-(3-((2-(difluoromethyl)pyridin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-22	Prep-A

24		4-(2-(3-((2-(difluoromethoxy)pyridin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-23	Prep-A
25		3-fluoro-4-(7-methyl-8-oxo-6-(trifluoromethyl)-2-(3-((2-(trifluoromethyl)pyridin-4-yl)oxy)azetidin-1-yl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile	I-34	I-24	Prep-A
26		4-(2-(3-((6-chloropyridazin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile	I-34	I-25	Prep-A
27		3-fluoro-4-(7-methyl-8-oxo-2-(3-(pyrimidin-5-yloxy)azetidin-1-yl)-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile	I-34	I-26	Prep-B

28		3-fluoro-4-(7-methyl-2-(3-((2-methylpyrimidin-5-yl)oxy)azetidin-1-yl)-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile	I-34	I-27	Prep-A
29		3-fluoro-4-(7-methyl-2-(3-((4-methylpyrimidin-5-yl)oxy)azetidin-1-yl)-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile	I-34	I-28	Prep-A
30		8-(2,4-difluorophenyl)-3-methyl-6-(3-((2-methylpyridin-4-yl)oxy)azetidin-1-yl)-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	I-35	I-29	Prep-A
31		6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)methyl)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	I-35	I-31	Prep-A
32		6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	I-35	I-1	Prep-A
33		6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)(methyl)amino)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	I-35	I-32	Prep-A

		do[5,4-d]pyrimidin-4(3H)-one			
34		8-(2,4-difluorophenyl)-3-methyl-6-((2-methylpyridin-4-yl)methyl)azetidin-1-yl)-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	I-35	I-33	Prep-A
35		4-(2-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile	I-36	I-1	Prep-A
36		6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(2-fluoro-4-methoxyphenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	I-37	I-1	Prep-A
37		6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(6-methoxypyridin-3-yl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one	I-38	I-1	Prep-A
38		5-(2-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)picolinonitrile	I-39	I-1	Prep-A
39		6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-3-methyl-8-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(trifluoromethyl)pyrimi	I-40	I-1	Prep-A

		do[5,4-d]pyrimidin-4(3H)-one			
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The following table describes analytical data analysis and yield information of examples 2-39.

Ex. No.	¹ H-NMR	LCMS	Description	Yield%
2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.67 (s, 1H), 8.07 (d, J=10.0 Hz, 1H), 7.99-7.88 (m, 1H), 7.84-7.81(m, 1H), 5.38-5.37 (m, 1H); 4.64 (t, J=8.0 Hz, 2H), 4.40 (brs, 3H), 3.56 (s, 3H).	Condition A : Rt = 2.84 min. m/z 505.34 [M+H] ⁺	Yellow solid	42.0
3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.07 (d, J=9.6 Hz, 1H), 7.90-7.80 (m, 2H), 5.35-5.33 (m, 1H); 4.64 (brs, 2H), 4.39 (brs, 2H), 3.56 (s, 3H), 2.43 (s, 3H).	Condition A: Rt = 2.89 min. m/z 519.34 [M+H] ⁺	Yellow solid	38.0
4	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.07 (d, J=9.6 Hz, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.82 (t, J=7.2 Hz, 1H), 5.33 (t, J=7.6 Hz, 1H), 4.62-4.60 (m, 2H), 4.41 (brs, 2H), 3.56 (s, 3H), 2.80-2.74 (m, 2H), 1.18 (t, J=7.2 Hz, 3H).	Condition A : Rt = 3.02 min. m/z 533.33 [M+H] ⁺	Yellow solid	36.0
5	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.43 (s, 1H), 8.29 (s, 1H), 8.24 (s, 1H), 8.06 (d, J=9.2 Hz, 1H), 7.90-7.83 (m, 2H), 5.56 (brs, 1H), 4.68-4.66 (m, 2H), 4.27-4.25 (m, 2H), 3.56 (s, 3H), 2.80-2.74 (m, 2H), 1.18 (t, J=7.2 Hz, 3H).	Condition A : Rt = 2.90 min. m/z 499.34 [M+H] ⁺	Yellow solid	34.0
6	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.20 (d, J=9.6 Hz, 2H), 8.07 (d, J=9.6 Hz, 1H), 7.90-7.81 (m, 2H), 5.52 (brs, 1H), 4.68-4.66 (m, 2H), 4.25-4.23 (m, 2H), 3.56 (s, 3H), 2.42 (s, 3H).	Condition A : Rt = 2.99 min. m/z 513.37 [M+H] ⁺	Yellow solid	41.0
7	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.88 (s, 1H), 8.59 (s, 1H), 8.07 (d, J=9.6 Hz, 1H), 7.90-7.81 (m, 2H), 5.63 (brs, 1H), 4.69-4.66 (m, 2H), 4.32-4.30 (m, 2H), 3.56 (s, 3H).	Condition A : Rt = 2.98 min. m/z 524.32 [M+H] ⁺	Yellow solid	39.0
8	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.06 (d, J=9.6 Hz, 1H), 7.90 (d, J=8.0 Hz, 1H), 7.83 (t, J=7.2 Hz, 1H), 7.21 (s, 1H), 4.92-4.91 (m, 1H), 4.56 (t, J=9.2 Hz, 2H), 4.17-4.14 (m, 2H), 3.66 (s, 3H), 3.56 (s, 3H), 2.15 (s, 3H).	Condition A : Rt = 2.87 min. m/z 515.42 [M+H] ⁺	Yellow solid	42.0
9	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.94 (s, 1H), 8.09 (d, J=9.6 Hz, 1H), 7.90-7.81(m, 2H), 4.85 (brs, 1H), 4.48 (brs,	Condition A : Rt = 2.76 min. m/z	White solid	40.0

	2H), 4.17-4.15(m, 2H), 3.56 (s, 3H), 2.10 (s, 6H).	515.42 [M+H] ⁺		
10	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.07 (d, J=9.2 Hz, 1H), 7.90-7.81 (m, 2H), 4.86-4.85 (m, 1H), 4.58-4.56 (m, 2H), 4.16 (t, J=3.6 Hz, 2H), 3.66 (s, 3H), 3.56 (s, 3H), 2.05 (s, 3H).	Condition A : Rt = 2.87 min. m/z 515.38 [M+H] ⁺	Yellow solid	44.0
11	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.06 (d, J=9.6 Hz, 1H), 7.90 (d, J=8.0 Hz, 1H), 7.83 (t, J=7.2 Hz, 1H), 7.58 (s, 1H), 7.22 (s, 1H), 4.92-4.91 (m, 1H), 4.60 (brs, 2H), 4.39-4.32 (m, 2H), 4.17-4.14 (m, 2H), 3.56 (s, 3H), 1.36 (d, J=6.8 Hz, 6H).	Condition A : Rt = 3.00 min. m/z 529.41 [M+H] ⁺	Yellow solid	37.0
12	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.06 (d, J=9.6 Hz, 1H), 7.90-7.81 (m, 2H), 7.55 (s, 1H), 7.23 (s, 1H), 4.92-4.91 (m, 1H), 4.60 (brs, 2H), 4.16-4.14 (m, 2H), 3.95-3.92 (m, 2H), 3.56 (s, 3H), 1.76-1.71 (m, 2H), 0.80 (t, J=7.2 Hz, 3H).	Condition A : Rt = 3.02 min. m/z 529.45 [M+H] ⁺	Yellow solid	41.0
13	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.07 (d, J=10.0 Hz, 1H), 7.91-7.81(m, 2H), 7.50 (s, 1H), 5.03-5.01 (m, 1H), 4.60 (brs, 2H), 4.20-4.18 (m, 2H), 3.75 (s, 3H), 3.56 (s, 3H).	Condition A : Rt = 3.01 min. m/z 535.34 [M+H] ⁺	Yellow solid	39.0
14	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.09-8.05 (m, 2H), 7.90-7.81(m, 2H), 7.70-7.53 (m, 2H), 5.04-5.01 (m, 1H), 4.65 (brs, 2H), 4.19-4.17 (m, 2H), 3.56 (s, 3H).	Condition A : Rt = 3.00 min. m/z 537.36 [M+H] ⁺	Yellow solid	42.0
15	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.09-8.07 (m, 1H), 7.91-7.81 (m, 2H), 7.58 (s, 1H), 7.24 (s, 1H), 4.93 (t, J=3.6 Hz, 1H), 4.60 (brs, 2H), 4.17-4.14 (m, 2H), 3.84 (d, J=7.2 Hz, 2H), 3.55 (s, 3H), 1.20-1.18 (m, 1H), 0.51-0.48 (m, 2H), 0.35-0.32 (m, 2H).	Condition A : Rt = 3.00 min. m/z 541.39 [M+H] ⁺	Yellow solid	35.0
16	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.06 (d, J=9.6 Hz, 1H), 7.90-7.81 (m, 2H), 7.65 (s, 1H), 7.26 (s, 1H), 4.92-4.91 (m, 1H), 4.73-4.61 (m, 3H), 4.17-4.14 (m, 2H), 3.56 (s, 3H), 2.43-2.32 (m, 4H), 1.78-1.69 (m, 2H).	Condition A : Rt = 3.07 min. m/z 541.45 [M+H] ⁺	Yellow solid	44.0
17	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.06 (d, J=9.6 Hz, 1H), 7.90-7.81(m, 2H), 7.60 (s, 1H), 7.38 (s, 1H), 6.45-6.18 (m, 1H), 4.95 (brs, 1H), 4.60-4.45 (m, 4H), 4.17-4.14(m, 2H), 3.55 (s, 3H).	Condition A : Rt = 2.98 min. m/z 551.39 [M+H] ⁺	Yellow solid	41.0
18	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.06 (d, J=9.6 Hz, 1H), 7.90-7.81 (m, 2H), 7.58 (s, 1H), 7.23 (s, 1H), 4.92-4.91 (m, 1H),	Condition A : Rt = 3.06 min. m/z	Yellow solid	37.0

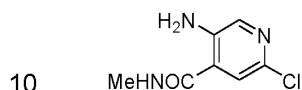
	4.60-4.53 (m, 3H), 4.16-4.13 (m, 2H), 3.55 (s, 3H), 2.04-1.98 (m, 2H), 1.89-1.85 (m, 2H), 1.76-1.74 (m, 2H), 1.62-1.59 (m, 2H).	555.42 [M+H] ⁺		
19	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.09 (d, J=9.6 Hz, 1H), 7.88-7.83 (m, 2H), 7.66 (s, 1H), 7.45 (s, 1H), 5.01-4.96 (m, 3H), 4.60 (brs, 2H), 4.18-4.15 (m, 2H), 3.56 (s, 3H).	Condition A : Rt = 3.01 min. m/z 569.37 [M+H] ⁺	Yellow solid	38.0
20	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.59 (d, J=5.6 Hz, 1H), 8.07 (d, J=9.6 Hz, 1H), 7.91-7.81 (m, 2H), 7.70 (d, J=2.4 Hz, 1H), 7.31-7.29 (m, 1H), 5.41-5.36 (m, 1H), 4.77-4.75 (m, 2H), 4.25-4.22 (m, 2H), 3.56 (s, 3H).	Condition A : Rt = 2.93 min. m/z 523.33 [M+H] ⁺	Yellow solid	47.0
21	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.07 (d, J=8.8 Hz, 1H), 8.01 (d, J=6.0 Hz, 1H), 7.90-7.81 (m, 2H), 6.62-6.60 (m, 1H), 6.28 (d, J=2.0 Hz, 1H), 5.28 (brs, 1H), 4.73 (m, 2H), 4.20-4.16 (m, 2H), 3.81 (s, 3H), 3.56 (s, 3H).	Condition A : Rt = 2.91 min. m/z 528.35 [M+H] ⁺	Yellow solid	45.0
22	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.22 (d, J=5.6 Hz, 1H), 8.07 (d, J=9.6 Hz, 1H), 7.90-7.82 (m, 2H), 6.83 (d, J=2.0 Hz, 1H), 6.70-6.68 (m, 1H), 5.29 (brs, 1H), 4.75-4.73 (m, 2H), 4.20-4.18 (m, 2H), 3.56 (s, 3H), 2.09-2.05 (m, 1H), 0.91-0.90 (m, 4H).	Condition A : Rt = 2.57 min. m/z 538.43 [M+H] ⁺	Yellow solid	44.0
23	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.54 (d, J=5.6 Hz, 1H), 8.07 (d, J=10.0 Hz, 1H), 7.91-7.82 (m, 2H), 7.21 (d, J=2.4 Hz, 1H), 7.14-7.12 (m, 1H), 7.05-6.77 (m, 1H), 5.40-5.36 (m, 1H), 4.76-4.75 (m, 2H), 4.25-4.22 (m, 2H), 3.56 (s, 3H).	Condition A : Rt = 3.00 min. m/z 548.38 [M+H] ⁺	Yellow solid	39.0
24	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.12-8.07 (m, 2H), 7.91-7.35 (m, 3H), 6.89 (dd, J=5.6 Hz, J=2.0 Hz, 1H), 6.62 (d, J=2.0 Hz, 1H), 5.34-5.33 (m, 1H), 4.75-4.74 (m, 2H), 4.23-4.20 (m, 2H), 3.56 (s, 3H).	Condition A : Rt = 3.11 min. m/z 564.39 [M+H] ⁺	Yellow solid	45.0
25	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.62 (d, J=5.6 Hz, 1H), 8.07 (d, J=8.8 Hz, 1H), 7.91-7.81 (m, 2H), 7.42 (d, J=2.4 Hz, 1H), 7.27-7.25 (m, 1H), 5.45-5.43 (m, 1H), 4.77-4.75 (m, 2H), 4.26-4.24 (m, 2H), 3.56 (s, 3H).	Condition A : Rt = 3.07 min. m/z 566.32 [M+H] ⁺	Yellow solid	42.0
26	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.07 (s, 1H), 8.07 (d, J=9.6 Hz, 1H), 7.91-7.81 (m, 2H), 7.48 (s, 1H), 5.43-5.42 (m, 1H), 4.77-4.75 (m, 2H), 4.29-4.27 (m, 2H), 3.56 (s, 3H).	Condition A : Rt = 2.85 min. m/z 533.31 [M+H] ⁺	Yellow solid	38.0

27	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.89 (s, 1H), 8.56 (s, 1H), 8.07 (d, J=9.6 Hz, 1H), 7.91-7.82 (m, 2H), 5.39-5.37(m, 1H), 4.76-4.75 (m, 2H), 4.27-4.25 (m, 2H), 3.56 (s, 3H).	Condition A : Rt = 2.77 min. m/z 499.34 [M+H] ⁺	Yellow solid	40.0
28	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.42 (brs, 2H), 8.07 (d, J=10.0 Hz, 1H), 7.90-7.81 (m, 2H), 5.33-5.32(m, 1H), 4.73-4.72 (m, 2H), 4.24-4.22 (m, 2H), 3.56 (s, 3H), 2.57 (s, 3H).	Condition A : Rt = 2.77 min. m/z 513.37 [M+H] ⁺	Yellow solid	46.0
29	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.70 (s, 1H), 8.29 (s, 1H), 8.07 (d, J=10.0 Hz, 1H), 7.91-7.82 (m, 2H), 5.37-5.36(m, 1H), 4.76-4.75 (m, 2H), 4.28-4.24 (m, 2H), 3.56 (s, 3H), 2.57 (s, 3H).	Condition A : Rt = 2.82 min. m/z 513.37 [M+H] ⁺	Yellow solid	42.0
30	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.27 (d, J = 5.2 Hz, 1H), 7.75-7.69 (m, 1H), 7.45 (t, J=9.2 Hz, 1H), 7.28 (d, J=8.4 Hz, 1H), 6.79 (s, 1H), 6.75 (d, J=5.2 Hz, 1H), 5.27(s, 1H), 4.73 (t, J=9.6 Hz, 2H), 4.17 (d, J= 8.0 Hz, 2H), 3.56 (s, 3H), 2.42 (s, 3H).	Condition A : Rt = 2.62 min. m/z 505.4 [M+H] ⁺	Yellow solid	59.0
31	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.71-7.66 (m, 1H), 7.63 (s, 1H), 7.44 (t, J = 10.4 Hz, 1H), 7.29-7.25 (m, 2H), 4.29 (t, J= 8.0 Hz, 2H), 3.88 (s, 2h), 3.64-3.59 (m, 1H), 3.55 (s, 3H), 2.90 (t, J= 6.4 Hz, 1H), 2.27(d, 8.4 Hz, 2H), 0.96-0.94 (m, 2H), 0.91-0.89 (m, 2H).	Condition A: Rt = 3.13 min. m/z 518.4 [M+H] ⁺	Yellow solid	45
32	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.74-7.68 (m, 1H), 7.58 (s, 1H), 7.48-7.42 (m, 1H), 7.30-7.26 (m, 1H), 7.23 (s, 1H), 4.92-4.90 (m, 1H), 4.62-4.58 (m, 2H), 4.15-4.12 (m, 2H), 3.63- 3.59 (m, 1H), 3.56 (s, 3H), 1.0-0.96 (m, 2H), 0.93-0.88 (m, 2H).	Condition A : Rt = 3.13 min. m/z 520.4 [M+H] ⁺	Yellow solid	48
33	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.74-7.68 (m, 1H), 7.45(t,J=9.6 Hz, 1H), 7.35 (s, 1H), 7.28 (t, J=8.8 Hz, 1H), 7.16 (s, 1H), 4.40 -4.38 (m, 2H), 4.12-4.09 (m, 2H), 4.01 (t, J=5.6 Hz, 1H), 3.60-3.55 (m, 4H), 2.61 (s, 3H), 1.0-0.96 (m, 2H), 0.93-0.88 (m, 2H).	Condition A : Rt = 3.06 min. m/z 533.4 [M+H] ⁺	Yellow solid	10.0
34	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.30 (d, J=4.8 Hz, 1H), 7.67-7.65 (m, 1H), 7.42-7.41 (m, 1H), 7.25 -7.24 (m, 1H), 7.12 (s, 1H), 7.05 (d, 4.8 Hz, 1H), 4.26 (t, J= 8.4 Hz, 2H), 3.92 (t, J=8.8 Hz, 2H), 3.52 (s, 3H), 2.94-2.92 (m, 1H), 2.94 (d, J= 7.6 Hz, 2H), 2.41 (s, 3H).	Condition A : Rt = 2.64 min. m/z 503.4 [M+H] ⁺	Yellow solid	19.0
35	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.34 (d, J=8.4 Hz, 1H), 8.03 (d, J=8.4 Hz, 1H), 7.60 (s, 1H), 7.24 (s, 1H), 4.93 (brs, 1H),	Condition A : Rt = 2.99 min. m/z	Yellow solid	27.0

	4.65-4.61 (m, 2H), 4.16 (brs, 2H), 3.62-3.60 (m, 1H), 3.57 (s, 3H), 1.0-0.98 (m, 2H), 0.93-0.90 (m, 2H).	509.43 [M+H] ⁺		
36	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.62-7.59 (m, 2H), 7.23 (s, 1H), 7.00-6.94 (m, 2H), 4.93-4.90 (m, 1H), 4.61-4.57 (m, 2H), 4.14-4.11 (m, 2H), 3.86 (s, 3H), 3.63-3.58 (m, 1H), 3.57 (s, 3H), 0.99-0.95 (m, 2H), 0.93-0.88 (m, 2H).	Condition A : Rt = 3.11 min. m/z 532.38 [M+H] ⁺	Yellow solid	30.0
37	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.19 (d, J=2.4 Hz, 1H), 8.58-8.7.56 (dd, J=8.8 Hz, J=2.4 Hz, 1H), 7.57 (s, 1H), 7.21 (s, 1H), 6.97 (d, J=8.8 Hz, 1H), 4.90-4.89 (m, 1H), 4.61-4.57 (m, 2H), 4.14-4.12 (m, 2H), 3.92 (s, 3H), 3.60-3.57 (m, 1H), 3.55 (s, 3H), 0.98-0.94 (m, 2H), 0.91-0.88 (m, 2H).	Condition A : Rt = 3.06 min. m/z 515.38 [M+H] ⁺	Yellow solid	34.0
38	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.49 (s, 1H), 8.77 (d, J=8.0 Hz, 1H), 8.26 (d, J=8.0 Hz, 1H), 7.60 (s, 1H), 7.24 (s, 1H), 4.96-4.93 (m, 1H), 4.64 (brs, 2H), 4.19-4.18 (m, 2H), 3.61-3.58 (m, 4H), 1.00-0.98 (m, 2H), 0.92-0.90 (m, 2H).	Condition A : Rt = 3.03 min. m/z 510.40 [M+H] ⁺	Yellow solid	30.0
39	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.22 (d, J=2.4 Hz, 1H), 8.44-8.41 (m, 1H), 7.59 (s, 1H), 7.24 (s, 1H), 6.53 (d, J=9.6 Hz, 1H), 4.92-4.91 (m, 1H), 4.62-4.58 (m, 2H), 4.15-4.13 (m, 2H), 3.62-3.54 (m, 7H), 1.00-0.98 (m, 2H), 0.92-0.90 (m, 2H).	Condition A : Rt = 2.59 min. m/z 515.42 [M+H] ⁺	Yellow solid	40.0

Example 40

6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-
5 2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one

Step-1**Preparation of 5-amino-2-chloro-N-methylisonicotinamide:**

To a stirred solution of 5-amino-2-chloroisonicotinic acid (20 g, 116.3 mmol) in DMF (250 mL) at 0 °C was added MeNH₂·HCl (9.4 g, 139.5 mmol) followed by HATU (53 g, 139.5 mmol) and DIPEA (70.8 mL, 406.9 mmol). Resulting mixture was stirred at room

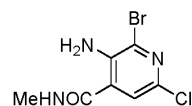
temperature for 16 h. After completion, reaction mixture was quenched with water, extracted with ethyl acetate, washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. Crude product was purified by combi-flash chromatography (silica gel; 50-60% ethyl acetate-hexane) to get 5-amino-2-chloro-N-methylisonicotinamide (18.0 g, 83.72%) as pale-yellow solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.59 (s, 1H), 7.91 (s, 1H), 7.45 (s, 1H), 6.54 (br s, 2H), 2.72 (s, 3H).

LCMS Condition A : Rt = 1.92 min. m/z 186.2 [M+H]⁺.

Step-2

Preparation of 3-amino-2-bromo-6-chloro-N-methylisonicotinamide:



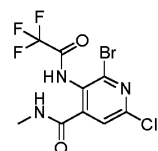
To a stirred solution of 5-amino-2-chloro-N-methylisonicotinamide (17 g, 91.8 mmol) in DMF (100.0 mL) was added NBS (16.3 g, 91.9 mmol) at 0 °C. Resulting mixture was heated at 80 °C for 2 h. Reaction mixture was quenched with crushed ice, extracted with ethyl acetate, washed with brine, dried over sodium sulphate, filtered and evaporated under reduced pressure. Crude product was purified by combi-flash chromatography (silica gel; 25-30% ethyl acetate-hexane) to get (11.0 g, 45.2% yield) as pale-yellow solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.76 (s, 1H), 7.62 (s, 1H), 6.52 (s, 2H), 2.74 (s, 3H).

LCMS Condition G : Rt = 2.78 min. m/z 266.2 [M+H]⁺.

Step-3

Preparation of 2-bromo-6-chloro-N-methyl-3-(2,2,2-trifluoroacetamido)isonicotinamide:

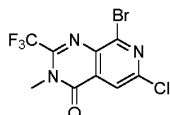


To a stirred solution of 3-amino-2-bromo-6-chloro-N-methylpyridine-4-carboxamide (3.8 g, 14.36 mmol) in THF (30.0 ml) were added pyridine (3.47 ml, 43.09 mmol) and DMAP (350 mg, 2.87 mmol) successively. Finally the reaction mixture cooled to 0°C and Trifluoro acetic anhydride (6.03 mL, 43.09 mmol) was added dropwise to the reaction mixture. Then it was stirred at RT for 2h. The reaction mixture was quenched with cold water, extracted with ethyl acetate, washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. Crude product was purified by combi-flash chromatography (silica gel; 30-40% ethyl acetate-hexane) to get 2-bromo-6-chloro-N-methyl-3-(2,2,2-trifluoroacetamido)isonicotinamide (2.6 g, 50%) as grey solid mass.

LCMS Condition A : Rt = 2.21 min. m/z 362.1 [M+H]⁺.

Step-4

Preparation of 8-bromo-6-chloro-3-methyl-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one:

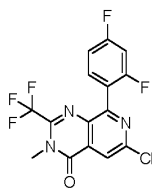


To a stirred mixture of 2-bromo-6-chloro-N-methyl-3-(2,2,2-trifluoroacetamido)isonicotinamide (2.2 g, 6.10 mmol) in acetic acid (30.0 mL) was added sodium acetate (750 mg, 9.15 mmol). Resulting mixture was heated at 120 °C for 16 h. The reaction mixture was evaporated to dryness and quenched with sat. sodium bicarbonate solution and extracted with 10% MeOH-DCM mixture. Combined organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure. Crude mass was purified by combi flash chromatography (30-40% ethyl acetate-hexane) to afford 8-bromo-6-chloro-3-methyl-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one (1.2 g, 57 % yield) as brown solid.

LCMS Condition A : Rt = 1.89 min. m/z 342.27 [M+H]⁺.

Step-5

Preparation of 6-chloro-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one:



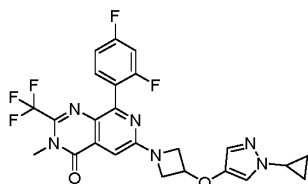
To a stirred solution of 8-bromo-6-chloro-3-methyl-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one (500 mg, 1.46 mmol) and corresponding 2,4-difluoro phenyl boronic acid (230 mg, 1.46 mmol) in dioxane (15 mL) and water (5 mL) was added sodium carbonate (3 mmol) and degassed with argon. PdCl₂(dppf).DCM (120 mg, 0.14 mmol) was added under inert atmosphere. The resulting mixture was heated at 90°C for 3h. 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 column chromatography (35% ethyl acetate-hexane) to afford 6-chloro-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one (250 mg, 45 % yield) as white solid.

LCMS Condition A : Rt = 2.46 min. m/z 376.2 [M+H]⁺.

Step-6

Preparation of 6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one

:



To a stirred solution of 6-chloro-8-(2,4-difluorophenyl)-3-methyl-2 (trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one (100 mg, 0.26 mmol) and 4-(azetidin-3-yloxy)-1-cyclopropyl-1H-pyrazole (71 mg, 0.40 mmol) in toluene (4 mL) degassed with argon was added sodium tertiary butoxide (51 mg, 0.53 mmol) and RuPhos (6.21 mg, 0.01 mmol) and RuPhos-Pd-G3 (11 mg, 0.01 mmol). The resulting mixture was heated at 100 °C for 12 h. Reaction mixture was diluted with DCM, filtered through a short pad of celite and washed with ethyl acetate. Combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced

pressure. Crude was purified by Prep-HPLC (Prep-A) to afford 6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one (25 mg; 18 %yield) as yellow solid.

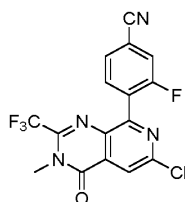
5 ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65-7.59 (m, 1H), 7.57 (s, 1H), 7.40-7.35 (m, 1H), 7.25-7.20 (m, 2H), 6.96 (s, 1H), 4.94-4.91 (m, 1H), 4.52-4.48 (m, 2H), 4.08-4.04 (m, 2H), 3.62- 3.58 (m, 1H), 3.55 (s, 3H), 1.0-0.97 (m, 2H), 0.93-0.89 (m, 2H).
Condition A : Rt = 3.48 min. m/z 519.2 [M+H]⁺

10 **Example 41**

Synthesis of 4-(6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-3-methyl-4-oxo-2-(trifluoromethyl)-3,4-dihydropyrido[3,4-d]pyrimidin-8-yl)-3-fluorobenzonitrile

Step-1

15 **Preparation of 4-(6-chloro-3-methyl-4-oxo-2-(trifluoromethyl)-3,4-dihydropyrido[3,4-d]pyrimidin-8-yl)-3-fluorobenzonitrile:**



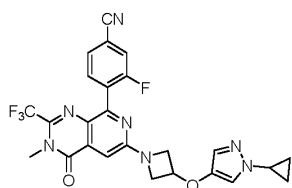
Synthesis of 4-(6-chloro-3-methyl-4-oxo-2-(trifluoromethyl)-3,4-dihydropyrido[3,4-d]pyrimidin-8-yl)-3-fluorobenzonitrile was done using 8-bromo-6-chloro-3-methyl-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one (white solid; 60% yield) and 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile according to the similar protocol mentioned in 38 (Step-5).

25 LCMS Condition A : Rt = 3.38 min. m/z 383.08 [M+H]⁺.

Step-2

Preparation of 4-(6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-3-methyl-4-oxo-2-(trifluoromethyl)-3,4-dihydropyrido[3,4-d]pyrimidin-8-yl)-3-fluorobenzonitrile :

30



To a stirred solution of 4-(6-chloro-3-methyl-4-oxo-2-(trifluoromethyl)-3,4-dihydropyrido[3,4-d]pyrimidin-8-yl)-3-fluorobenzonitrile (100 mg, 0.26 mmol) and 4-
 5 (azetidin-3-yloxy)-1-cyclopropyl-1H-pyrazole (56 mg, 0.31 mmol) in toluene (5 mL) degassed with argon was added Caesium carbonate (186 mg, 0.57 mmol) and Xanthphos (15 mg, 0.026 mmol) and Pd₂(dba)₃ (23 mg, 0.026 mmol). The resulting mixture was heated at 80 °C for 2 h. Reaction mixture was diluted with DCM, filtered through a short pad of celite and washed with ethyl acetate. Combined organic
 10 layer was washed with water, brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Crude was purified by Prep-HPLC(Prep-A) to afford 4-(6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-3-methyl-4-oxo-2-(trifluoromethyl)-3,4-dihydropyrido[3,4-d]pyrimidin-8-yl)-3-fluorobenzonitrile (25 mg, 18 % yield) as yellow solid.

15 ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.99 (d, J=9.6 Hz, 1H), 7.82 (d, J=7.6 Hz, 1H), 7.76 (t, J=7.2 Hz, 1H), 7.57 (s, 1H), 7.22 (s, 1H), 7.01 (s, 1H), 4.92 (brs, 1H), 4.50 (t, J=9.2 Hz, 2H), 4.08-4.05 (m, 2H), 3.62-3.57 (m, 1H), 3.55 (s, 3H), 0.98-0.97 (m, 2H), 0.93-0.89 (m, 2H).

20 Condition A : Rt = 3.09 min. m/z 526.40 [M+H]⁺

Example 42 – Biological evaluation

Human TREM2, in vitro Measurement of Triggering Receptor Expressed on Myeloid Cells 2 activity using cellular phosphorylation of Spleen Tyrosine Kinase ("Syk") Assay

25 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

30 "HEK293/DAP12+TREM2" underwent a qPCR analysis and a pharmacological validation.

Assay

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
5 (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
10 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
15 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 (BIOWHITTAKER_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
20 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
25 was thus generated.

HEK293/DAP12+TREM2 cells were cultured in EMEM medium supplemented with IX Penicillin/Streptomycin (BIOWHITTAKER_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
30 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 μ L/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 μ L/well of lysate were transferred to the Alpha plates. The CyBi®-Well instrument was used to dispense 5 μ L/well of AlphaLISA Acceptor 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 μ L/well of AlphaLISA Donor Bead Solution in IX Immunoassay buffer. The plates were sealed with Heat 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 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% 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 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; $\langle cr \rangle$ is the median of the signal values for the Central Reference wells of a plate (median of Neutral Controls); $\langle sr \rangle$ is the 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:

$$\% \text{ Activity} = 100 \cdot (x - \langle \text{NeutralControls} \rangle) / (\langle \text{StimulatorControls} \rangle - \langle \text{NeutralControls} \rangle)$$

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., AC_{50} .

$$Y = S_0 + ((S_{inf} - S_0) / (1 + (10^{\text{Log}AC_{50}} / 10^X)^n))$$

where X is Log10 of compound concentration.

The equation has four parameters:

- Zero Activity (S_0) - Activity level at zero concentration of test compound;
- Infinite Activity (S_{inf}) - Activity level at infinite concentration of test compound;
- AC_{50} - Concentration at which activity reaches 50% of maximum level. This term corresponds to EC_{50} in this assay;
- Hill coefficient (n) - Measure of the slope at AC_{50} .

The potency of the test compounds was expressed as EC_{50} corresponding to the test compound concentration able to activate the phospho-Syk AlphaScreen signal to 50% of the maximal response.

The EC_{50} values measured in this assay for the exemplified compounds is set out in the table below:

Example	EC ₅₀	E _{max}
1	A	++
2	D	+
3	C	+
4	C	+
5	B	+
6	C	+
7	C	+
8	C	+
9	C	++
10	C	+
11	B	++
12	C	++
13	C	++
14	B	++
15	B	+++
16	B	++
17	C	++
18	A	++
19	B	++
20	B	++
21	A	++
22	B	++
23	B	++
24	B	++
25	B	++
26	C	+
27	C	+
28	C	+
29	C	+
30	B	++
31	C	++
32	B	+

33	C	++
34	B	+
35	B	++
36	C	+
37	C	++
38	C	++
39	C	++
40	C	+
41	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).

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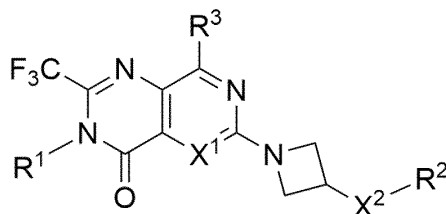
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Claims

1. A compound of Formula (I):



Formula (I)

5 wherein:

X^1 is N or C(H);

X^2 is O, CH₂ or N(R⁴);

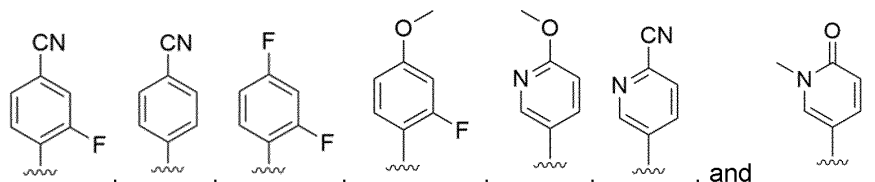
R⁴ is H or C₁₋₃ alkyl;

R¹ is C₁₋₃ alkyl;

10 R² is selected from the group consisting of pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, and 1,3,4-thiadiazolyl, each of which is optionally substituted with 1 to 3 individually selected substituents R⁵;

R⁵ is individually selected from the group consisting of C₁₋₃ alkyl optionally substituted with C₃₋₅ cycloalkyl and/or 1 to 3 F; C₁₋₃ alkoxy optionally substituted with 1 to 3 F; C₃₋₅ cycloalkyl; CN; and halogen; and

15 R³ is selected from the group consisting of:



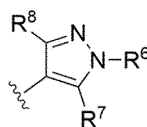
or a pharmaceutically acceptable salt thereof.

- 20 2. The compound according to claim 1, wherein X^1 is N, or a pharmaceutically acceptable salt thereof.
3. The compound according to claim 1, wherein X^1 is C(H), or a pharmaceutically acceptable salt thereof.
- 25 4. The compound according to any one of the preceding claims, wherein X^2 is O, or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of the preceding claims, wherein X^2 is CH_2 , or a pharmaceutically acceptable salt thereof.
6. The compound according to any one of the preceding claims, wherein X^2 is $N(R^4)$, and R^4 is H or C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
- 5 7. The compound according to any one of the preceding claims, wherein R^4 is H, or a pharmaceutically acceptable salt thereof.
8. The compound according to any one of the preceding claims, wherein R^4 is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
9. The compound according to any one of the preceding claims, wherein R^4 is CH_3 , or a pharmaceutically acceptable salt thereof.
- 10 10. The compound according to any one of the preceding claims, wherein X^2 is $N(H)$, or a pharmaceutically acceptable salt thereof.
11. The compound according to any one of the preceding claims, wherein X^2 is $N(CH_3)$, or a pharmaceutically acceptable salt thereof.
- 15 12. The compound according to any one of the preceding claims, wherein R^1 is CH_3 , or a pharmaceutically acceptable salt thereof.
13. The compound according to any one of the preceding claims, wherein R^2 is pyrazolyl optionally substituted with 1 to 3 individually selected substituents R^5 , or a pharmaceutically acceptable salt thereof.
- 20 14. The compound according to any one of the preceding claims, wherein R^2 is pyridinyl optionally substituted with 1 to 3 individually selected substituents R^5 , or a pharmaceutically acceptable salt thereof.
- 25 15. The compound according to any one of the preceding claims, wherein R^2 is pyrazinyl optionally substituted with 1 to 3 individually selected substituents R^5 , or a pharmaceutically acceptable salt thereof.
16. The compound according to any one of the preceding claims, wherein R^2 is pyridazinyl, optionally substituted with 1 to 3 individually selected substituents R^5 , or a pharmaceutically acceptable salt thereof.
- 30 17. The compound according to any one of the preceding claims, wherein R^2 is pyrimidinyl, optionally substituted with 1 to 3 individually selected substituents R^5 , or a pharmaceutically acceptable salt thereof.

18. The compound according to any one of the preceding claims, wherein R^2 is 1,3,4-thiadiazolyl, optionally substituted with 1 to 3 individually selected substituents R^5 , or a pharmaceutically acceptable salt thereof.
19. The compound according to any one of the preceding claims, wherein R^5 is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
20. The compound according to any one of the preceding claims, wherein R^5 is CH_3 , or a pharmaceutically acceptable salt thereof.
21. The compound according to any one of the preceding claims, wherein R^5 is CH_2CH_3 , or a pharmaceutically acceptable salt thereof.
22. The compound according to any one of the preceding claims, wherein R^5 is $CH_2CH_2CH_3$, or a pharmaceutically acceptable salt thereof.
23. The compound according to any one of the preceding claims, wherein R^5 is $CH_2(CH_3)_2$, or a pharmaceutically acceptable salt thereof.
24. The compound according to any one of the preceding claims, wherein R^5 is C_{1-3} alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
25. The compound according to any one of the preceding claims, wherein R^5 is CH_3 substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
26. The compound according to any one of the preceding claims, wherein R^5 is CF_3 , or a pharmaceutically acceptable salt thereof.
27. The compound according to any one of the preceding claims, wherein R^5 is CHF_2 , or a pharmaceutically acceptable salt thereof.
28. The compound according to any one of the preceding claims, wherein R^5 is CH_2CH_3 substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
29. The compound according to any one of the preceding claims, wherein R^5 is CH_2CF_3 , or a pharmaceutically acceptable salt thereof.
30. The compound according to any one of the preceding claims, wherein R^5 is CH_2CHF_2 , or a pharmaceutically acceptable salt thereof.
31. The compound according to any one of the preceding claims, wherein R^5 is C_{1-3} alkoxy, or a pharmaceutically acceptable salt thereof.
32. The compound according to any one of the preceding claims, wherein R^5 is $-OCH_3$, or a pharmaceutically acceptable salt thereof.
33. The compound according to any one of the preceding claims, wherein R^5 is C_{1-3} alkoxy substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
34. The compound according to any one of the preceding claims, wherein R^5 is $-OCH_3$, or a pharmaceutically acceptable salt thereof.

35. The compound according to any one of the preceding claims, wherein R^5 is -
OCHF₂, or a pharmaceutically acceptable salt thereof.
36. The compound according to any one of the preceding claims, wherein R^5 is C₁₋₃
alkyl substituted with C₃₋₅ cycloalkyl, or a pharmaceutically acceptable salt
thereof.
37. The compound according to any one of the preceding claims, wherein R^5 is -
CH₂-cyclopropyl, or a pharmaceutically acceptable salt thereof.
38. The compound according to any one of the preceding claims, wherein R^5 is C₃₋₅
cycloalkyl, or a pharmaceutically acceptable salt thereof.
39. The compound according to any one of the preceding claims, wherein R^5 is
cyclopropyl, or a pharmaceutically acceptable salt thereof.
40. The compound according to any one of the preceding claims, wherein R^5 is
cyclobutyl, or a pharmaceutically acceptable salt thereof.
41. The compound according to any one of the preceding claims, wherein R^5 is
cyclopentyl, or a pharmaceutically acceptable salt thereof.
42. The compound according to any one of the preceding claims, wherein R^5 is CN,
or a pharmaceutically acceptable salt thereof.
43. The compound according to any one of the preceding claims, wherein R^5 is
halogen, or a pharmaceutically acceptable salt thereof.
44. The compound according to any one of the preceding claims, wherein R^5 is Cl,
or a pharmaceutically acceptable salt thereof.
45. The compound according to any one of the preceding claims, wherein R^2 is of
Formula (II):



Formula (II)

wherein

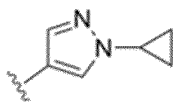
R^6 is selected from the group consisting of H; C₁₋₃ alkyl optionally substituted
with C₃₋₅ cycloalkyl and/or 1 to 3 F; C₁₋₃ alkoxy optionally substituted with 1 to 3
F; and C₃₋₅ cycloalkyl;

R^7 is H, C₁₋₃ alkyl or halogen; and

R^8 is H, C₁₋₃ alkyl or halogen,
or a pharmaceutically acceptable salt thereof.

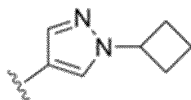
46. The compound according to any one of the preceding claims, wherein R^6 is H, or a pharmaceutically acceptable salt thereof.
47. The compound according to any one of the preceding claims, wherein R^6 is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
- 5 48. The compound according to any one of the preceding claims, wherein R^6 is CH_3 , or a pharmaceutically acceptable salt thereof.
49. The compound according to any one of the preceding claims, wherein R^6 is - $(CH_2)_2CH_3$, or a pharmaceutically acceptable salt thereof.
50. The compound according to any one of the preceding claims, wherein R^6 is - $C(H)(CH_3)_2$, or a pharmaceutically acceptable salt thereof.
- 10 51. The compound according to any one of the preceding claims, wherein R^6 is C_{1-3} alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
52. The compound according to any one of the preceding claims, wherein R^6 is CH_3 substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
- 15 53. The compound according to any one of the preceding claims, wherein R^6 is CHF_2 , or a pharmaceutically acceptable salt thereof.
54. The compound according to any one of the preceding claims, wherein R^6 is CH_2CH_3 substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
55. The compound according to any one of the preceding claims, wherein R^6 is CH_2CF_3 , or a pharmaceutically acceptable salt thereof.
- 20 56. The compound according to any one of the preceding claims, wherein R^6 is CH_2CHF_2 , or a pharmaceutically acceptable salt thereof.
57. The compound according to any one of the preceding claims, wherein R^6 is C_{1-3} alkyl substituted with C_{3-5} cycloalkyl, or a pharmaceutically acceptable salt thereof.
- 25 58. The compound according to any one of the preceding claims, wherein R^6 is - CH_2 -cyclopropyl, or a pharmaceutically acceptable salt thereof.
59. The compound according to any one of the preceding claims, wherein R^6 is C_{3-5} cycloalkyl, or a pharmaceutically acceptable salt thereof.
- 30 60. The compound according to any one of the preceding claims, wherein R^6 is cyclopropyl, or a pharmaceutically acceptable salt thereof.
61. The compound according to any one of the preceding claims, wherein R^6 is cyclobutyl, or a pharmaceutically acceptable salt thereof.
- 35 62. The compound according to any one of the preceding claims, wherein R^6 is cyclopentyl, or a pharmaceutically acceptable salt thereof.

63. The compound according to any one of the preceding claims, wherein R^7 is H, or a pharmaceutically acceptable salt thereof.
64. The compound according to any one of the preceding claims, wherein R^7 is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
- 5 65. The compound according to any one of the preceding claims, wherein R^7 is CH_3 , or a pharmaceutically acceptable salt thereof.
66. The compound according to any one of the preceding claims, wherein R^8 is H, or a pharmaceutically acceptable salt thereof.
67. The compound according to any one of the preceding claims, wherein R^8 is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.
- 10 68. The compound according to any one of the preceding claims, wherein R^8 is CH_3 , or a pharmaceutically acceptable salt thereof.
69. The compound according to any one of the preceding claims, wherein R^8 is halogen, or a pharmaceutically acceptable salt thereof.
- 15 70. The compound according to any one of the preceding claims, wherein R^8 is Cl, or a pharmaceutically acceptable salt thereof.
71. The compound according to any one of the preceding claims, wherein R^2 is



, or a pharmaceutically acceptable salt thereof.

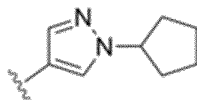
72. The compound according to any one of the preceding claims, wherein R^2 is



20

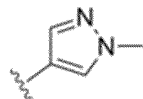
, or a pharmaceutically acceptable salt thereof.

73. The compound according to any one of the preceding claims, wherein R^2 is



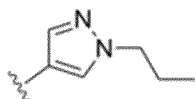
, or a pharmaceutically acceptable salt thereof.

74. The compound according to any one of the preceding claims, wherein R^2 is



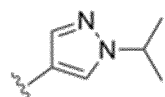
, or a pharmaceutically acceptable salt thereof.

75. The compound according to any one of the preceding claims, wherein R² is



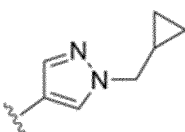
, or a pharmaceutically acceptable salt thereof.

76. The compound according to any one of the preceding claims, wherein R² is



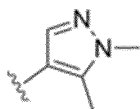
, or a pharmaceutically acceptable salt thereof.

5 77. The compound according to any one of the preceding claims, wherein R² is



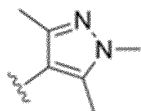
, or a pharmaceutically acceptable salt thereof.

78. The compound according to any one of the preceding claims, wherein R² is



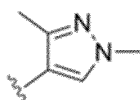
, or a pharmaceutically acceptable salt thereof.

79. The compound according to any one of the preceding claims, wherein R² is



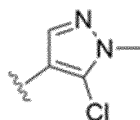
10 , or a pharmaceutically acceptable salt thereof.

80. The compound according to any one of the preceding claims, wherein R² is



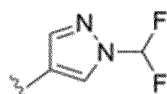
, or a pharmaceutically acceptable salt thereof.

81. The compound according to any one of the preceding claims, wherein R² is



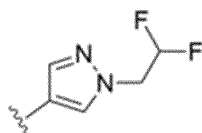
, or a pharmaceutically acceptable salt thereof.

82. The compound according to any one of the preceding claims, wherein R² is



, or a pharmaceutically acceptable salt thereof.

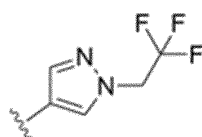
83. The compound according to any one of the preceding claims, wherein R² is



, or a pharmaceutically acceptable salt thereof.

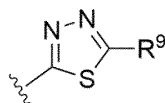
5

84. The compound according to any one of the preceding claims, wherein R² is



, or a pharmaceutically acceptable salt thereof.

85. The compound according to any one of the preceding claims, wherein R² is of Formula (III):

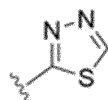


10

Formula (III)

wherein R⁹ is H or C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

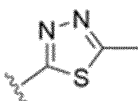
86. The compound according to any one of the preceding claims, wherein R² is



, or a pharmaceutically acceptable salt thereof.

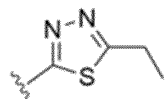
15

87. The compound according to any one of the preceding claims, wherein R² is



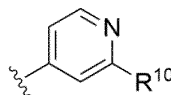
, or a pharmaceutically acceptable salt thereof.

88. The compound according to any one of the preceding claims, wherein R² is



, or a pharmaceutically acceptable salt thereof.

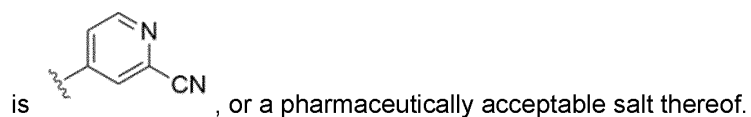
89. The compound according to any one of the preceding claims, wherein R² is of Formula (IV):



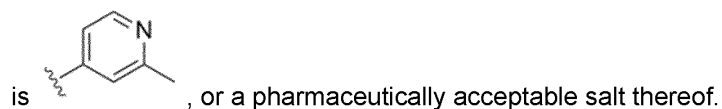
Formula (IV)

- 5 wherein R¹⁰ is selected from the group consisting of H; C₁₋₃ alkyl optionally substituted with 1 to 3 F; C₁₋₃ alkoxy optionally substituted with 1 to 3 F; CN; and C₃₋₅ cycloalkyl, or a pharmaceutically acceptable salt thereof.
90. The compound according to any one of the preceding claims, wherein R¹⁰ is CN, or a pharmaceutically acceptable salt thereof.
- 10 91. The compound according to any one of the preceding claims, wherein R¹⁰ is C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.
92. The compound according to any one of the preceding claims, wherein R¹⁰ is CH₃, or a pharmaceutically acceptable salt thereof.
93. The compound according to any one of the preceding claims, wherein R¹⁰ is C₁₋₃ alkyl substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
- 15 94. The compound according to any one of the preceding claims, wherein R¹⁰ is CF₃, or a pharmaceutically acceptable salt thereof.
95. The compound according to any one of the preceding claims, wherein R¹⁰ is CHF₂, or a pharmaceutically acceptable salt thereof
- 20 96. The compound according to any one of the preceding claims, wherein R¹⁰ is C₁₋₃ alkoxy, or a pharmaceutically acceptable salt thereof.
97. The compound according to any one of the preceding claims, wherein R¹⁰ is -OCH₃, or a pharmaceutically acceptable salt thereof.
98. The compound according to any one of the preceding claims, wherein R¹⁰ is C₁₋₃ alkoxy substituted with 1 to 3 F, or a pharmaceutically acceptable salt thereof.
- 25 99. The compound according to any one of the preceding claims, wherein R¹⁰ is -OCHF₂, or a pharmaceutically acceptable salt thereof
100. The compound according to any one of the preceding claims, wherein R¹⁰ is C₃₋₅ cycloalkyl, or a pharmaceutically acceptable salt thereof.
- 30 101. The compound according to any one of the preceding claims, wherein R¹⁰ is cyclopropyl, or a pharmaceutically acceptable salt thereof.

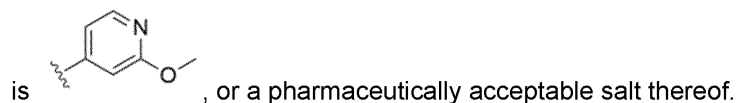
102. The compound according to any one of the preceding claims, wherein R²



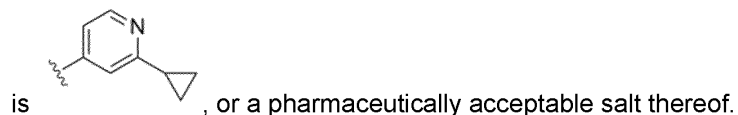
103. The compound according to any one of the preceding claims, wherein R²



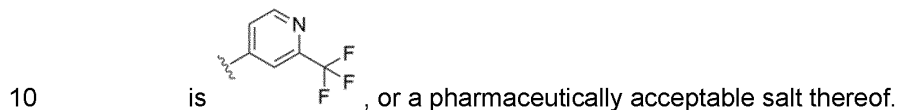
5 104. The compound according to any one of the preceding claims, wherein R²



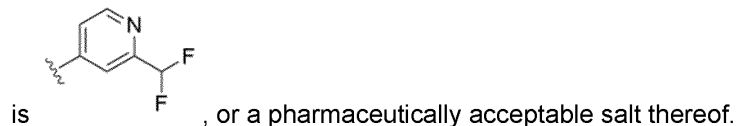
105. The compound according to any one of the preceding claims, wherein R²



106. The compound according to any one of the preceding claims, wherein R²



107. The compound according to any one of the preceding claims, wherein R²



108. The compound according to any one of the preceding claims, wherein R²

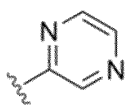


15 109. The compound according to any one of the preceding claims, wherein R² is pyrazinyl optionally substituted with CN, or a pharmaceutically acceptable salt thereof.

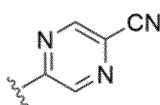
20 110. The compound according to any one of the preceding claims, wherein R² is pyrazinyl optionally substituted with C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

111. The compound according to any one of the preceding claims, wherein R² is pyrazinyl optionally substituted with CH₃, or a pharmaceutically acceptable salt thereof.

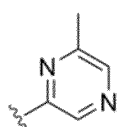
112. The compound according to any one of the preceding claims, wherein R²

5 is , or a pharmaceutically acceptable salt thereof.

113. The compound according to any one of the preceding claims, wherein R²

is , or a pharmaceutically acceptable salt thereof.

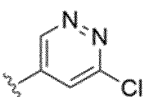
114. The compound according to any one of the preceding claims, wherein R²

10 is , or a pharmaceutically acceptable salt thereof.

115. The compound according to any one of the preceding claims, wherein R² is pyridazinyl optionally substituted with halogen, or a pharmaceutically acceptable salt thereof.

116. The compound according to any one of the preceding claims, wherein R² is pyridazinyl optionally substituted with Cl, or a pharmaceutically acceptable salt thereof.

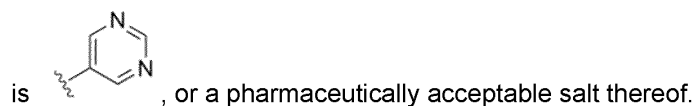
117. The compound according to any one of the preceding claims, wherein R²

is , or a pharmaceutically acceptable salt thereof.

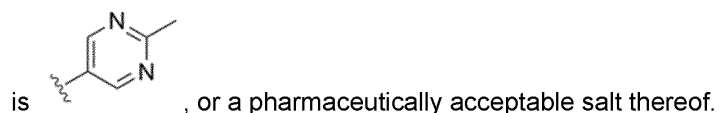
118. The compound according to any one of the preceding claims, wherein R² is pyrimidinyl optionally substituted with C₁₋₃ alkyl, or a pharmaceutically acceptable salt thereof.

119. The compound according to any one of the preceding claims, wherein R² is pyrimidinyl optionally substituted with CH₃, or a pharmaceutically acceptable salt thereof.

120. The compound according to any one of the preceding claims, wherein R²



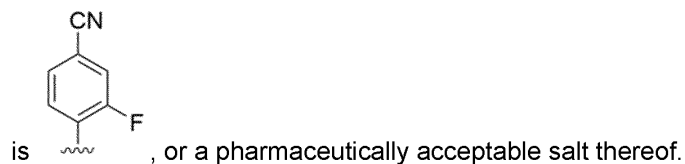
121. The compound according to any one of the preceding claims, wherein R²



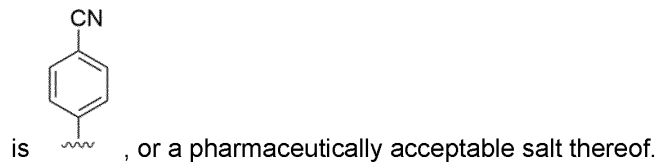
5 122. The compound according to any one of the preceding claims, wherein R²



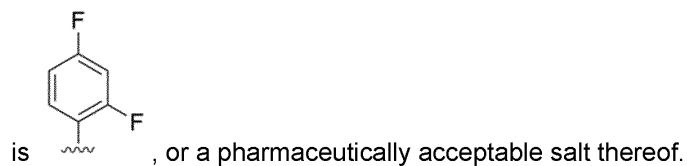
123. The compound according to any one of the preceding claims, wherein R³



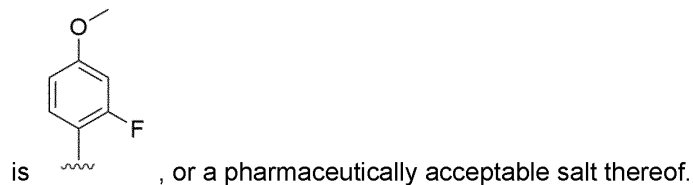
10 124. The compound according to any one of the preceding claims, wherein R³



125. The compound according to any one of the preceding claims, wherein R³

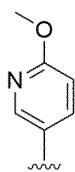


126. The compound according to any one of the preceding claims, wherein R³



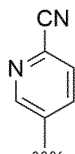
15

127. The compound according to any one of the preceding claims, wherein R³



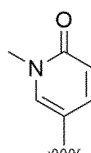
is , or a pharmaceutically acceptable salt thereof.

128. The compound according to any one of the preceding claims, wherein R³



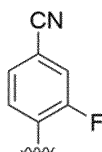
is , or a pharmaceutically acceptable salt thereof.

5 129. The compound according to any one of the preceding claims, wherein R³



is , or a pharmaceutically acceptable salt thereof.

130. The compound according to any one of the preceding claims, wherein X¹

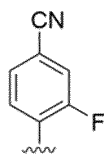


is N and R³ is .

131. The compound according to any one of the preceding claims, wherein X¹

10 is N and R¹ is CH₃.

132. The compound according to any one of the preceding claims, wherein X¹



is N, R¹ is CH₃, and R³ is .

133. The compound according to any one of the preceding claims, wherein X¹

is N and X² is O.

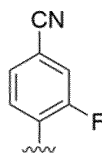
15 134. The compound according to any one of the preceding claims, wherein X²

is O and R² is pyrazolyl optionally substituted with 1 to 3 individually selected substituents R⁵.

135. The compound according to any one of the preceding claims, wherein X¹ is N, X² is O and R² is pyrazolyl optionally substituted with 1 to 3 individually selected substituents R⁵.

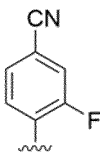
136. The compound according to any one of the preceding claims, wherein X¹ is N and R¹ is CH₃.

137. The compound according to any one of the preceding claims, wherein X¹



is N, R¹ is CH₃, and R³ is

138. The compound according to any one of the preceding claims, wherein X¹



is N, R¹ is CH₃, R³ is , X² is O, and R² is pyrazolyl optionally substituted with 1 to 3 individually selected substituents R⁵.

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

4-(2-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;

4-(2-(3-((1,3,4-thiadiazol-2-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;

3-fluoro-4-(7-methyl-2-(3-((5-methyl-1,3,4-thiadiazol-2-yl)oxy)azetidin-1-yl)-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile;

4-(2-(3-((5-ethyl-1,3,4-thiadiazol-2-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;

3-fluoro-4-(7-methyl-8-oxo-2-(3-(pyrazin-2-yloxy)azetidin-1-yl)-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile;

3-fluoro-4-(7-methyl-2-(3-((6-methylpyrazin-2-yl)oxy)azetidin-1-yl)-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile;

5-((1-(4-(4-cyano-2-fluorophenyl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-2-yl)azetidin-3-yl)oxy)pyrazine-2-carbonitrile;

4-(2-(3-((1,5-dimethyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;

- 4-(2-(3-((3,5-dimethyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;
- 4-(2-(3-((1,3-dimethyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;
- 5 3-fluoro-4-(2-(3-((1-isopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile;
- 3-fluoro-4-(7-methyl-8-oxo-2-(3-((1-propyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile;
- 4-(2-(3-((5-chloro-1-methyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;
- 10 4-(2-(3-((1-(difluoromethyl)-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;
- 4-(2-(3-((1-(cyclopropylmethyl)-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;
- 15 4-(2-(3-((1-cyclobutyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;
- 4-(2-(3-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;
- 20 4-(2-(3-((1-cyclopentyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;
- 3-fluoro-4-(7-methyl-8-oxo-2-(3-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile;
- 25 4-((1-(4-(4-cyano-2-fluorophenyl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-2-yl)azetidin-3-yl)oxy)picolinonitrile;
- 3-fluoro-4-(2-(3-((2-methoxypyridin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile;
- 4-(2-(3-((2-cyclopropylpyridin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;
- 30 4-(2-(3-((2-(difluoromethyl)pyridin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;
- 4-(2-(3-((2-(difluoromethoxy)pyridin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;

- 3-fluoro-4-(7-methyl-8-oxo-6-(trifluoromethyl)-2-(3-((2-(trifluoromethyl)pyridin-4-yl)oxy)azetidin-1-yl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile;
4-(2-(3-((6-chloropyridazin-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-3-fluorobenzonitrile;
- 5 3-fluoro-4-(7-methyl-8-oxo-2-(3-(pyrimidin-5-yloxy)azetidin-1-yl)-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile;
3-fluoro-4-(7-methyl-2-(3-((2-methylpyrimidin-5-yl)oxy)azetidin-1-yl)-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile;
3-fluoro-4-(7-methyl-2-(3-((4-methylpyrimidin-5-yl)oxy)azetidin-1-yl)-8-oxo-6-
- 10 (trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile;
8-(2,4-difluorophenyl)-3-methyl-6-(3-((2-methylpyridin-4-yl)oxy)azetidin-1-yl)-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one;
6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)methyl)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one;
- 15 6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one;
6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)(methyl)amino)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one;
8-(2,4-difluorophenyl)-3-methyl-6-(3-((2-methylpyridin-4-yl)methyl)azetidin-1-yl)-2-
- 20 2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one;
4-(2-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)benzonitrile;
6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(2-fluoro-4-methoxyphenyl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one;
- 25 6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(6-methoxypyridin-3-yl)-3-methyl-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one;
5-(2-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-7-methyl-8-oxo-6-(trifluoromethyl)-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)picolinonitrile;
6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-3-methyl-8-(1-methyl-6-
- 30 oxo-1,6-dihydropyridin-3-yl)-2-(trifluoromethyl)pyrimido[5,4-d]pyrimidin-4(3H)-one;
6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-8-(2,4-difluorophenyl)-3-methyl-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one; and
4-(6-(3-((1-cyclopropyl-1H-pyrazol-4-yl)oxy)azetidin-1-yl)-3-methyl-4-oxo-2-
- 35 (trifluoromethyl)-3,4-dihydropyrido[3,4-d]pyrimidin-8-yl)-3-fluorobenzonitrile,

or a pharmaceutically acceptable salt thereof.

140. The compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein the compound is a TREM2 modulator, such as a TREM2 activator, such as a TREM2 agonist.

5 141. The compound according to any one of the preceding claims, 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
10 GSK3b; and/or wherein the compound enhances TREM2-induced phosphorylation levels of the Syk kinase.

142. The compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein the compound increases the expression of one or more TREM2 regulated genes, such as wherein the
15 compound increases the expression of one or more TREM2 regulated genes selected from the group consisting of CXCL10, CCL2, CST7 and TMEM119.

143. A pharmaceutical composition comprising a compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and
20 one or more pharmaceutically acceptable carriers, excipients and/or diluents.

144. The compound according to any one of claims 1 to 142, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 143, for use as a medicament.

25 145. The compound according to any one of claims 1 to 142, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 143, 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
30 associated with a mutation of TREM2.

146. The compound according to any one of claims 1 to 142, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 143, for use in the treatment of a neurodegenerative disease.

147. The compound according to any one of claims 1 to 142, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 143, for use in the treatment of a neurodegenerative disease selected from the group consisting of a tauopathy, a TDP-43 proteinopathy, a synucleinopathy, dementia, amyloidosis, a demyelinating disorder of the CNS, a demyelinating disorder of the PNS, a Leukoencephalopathy, a leukodystrophy, a transmissible spongiform encephalopathy (TSE) and a lysosomal storage disorder (LSD).
148. The compound according to any one of claims 1 to 142, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 143, 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, stroke, and traumatic brain injuries (TBI).
149. The compound according to any one of claims 1 to 142, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 143, 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 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.
150. The compound for use according to any one of claims 144 to 149, wherein said compound is administered in an amount of about 0.01 mg/kg to about 100 mg/kg bodyweight/day.
151. The compound for use according to any one of claims 144 to 149, 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.

- 5 152. 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 142, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 143, to a subject in need thereof.
- 10 153. Use of a compound according to any one of claims 1 to 142, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 143, 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.
- 15 154. 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 claims 1 to 142.
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