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(54) Title: COMPOUNDS ACTIVE TOWARDS NUCLEAR RECEPTORS

(57) Abstract: Disclosed are compounds active towards nuclear receptors, pharmaceutical compositions containing the compounds and use of the compounds in therapy.



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COMPOUNDS ACTIVE TOWARDS NUCLEAR RECEPTORS

Field

5 Aspects and embodiments described herein relate to compounds active towards nuclear receptors, pharmaceutical compositions comprising the compounds, and methods of treating inflammatory, metabolic, oncologic and autoimmune diseases or disorders using the compounds.

Background

10 Nuclear receptors are a family of transcription factors involved in the regulation of physiological functions, such as cell differentiation, embryonic development, and organ physiology. Nuclear receptors have also been identified as important pathological regulators in diseases such as cancer, diabetes, and autoimmune disorders.

Examples of nuclear receptors include the nuclear retinoic acid receptor-related orphan receptors (RORs). RORs contain four principal domains: an N-terminal A/B domain, a DNA-binding domain, a hinge domain and a ligand binding domain. Binding of ligands to the ligand-binding domain is believed to cause conformational changes in the domain resulting in downstream actions. Different isoforms exist and these isoforms differ in their N-terminal A/B domain only (Jetten, 2009, Nuclear Receptor Signaling).

20 RORs consist of three members, namely ROR alpha (ROR α or RORa), ROR beta (ROR β or RORb) and ROR gamma (ROR γ or RORc).

ROR α is expressed in many tissues such as cerebellar Purkinje cells, the liver, thymus, skeletal muscle, skin, lung, adipose tissue and kidney. ROR α regulates neuronal cell development, bone metabolism, and arteriosclerosis (Jetten, 2009, Nuclear Receptor Signaling). Additionally, ROR α plays a role in the immune responses, such as in the regulation interleukin (IL) 17A expression in T helper (Th) 17 cells and the function of T regulatory (Treg) cells (Castro PLOS 2017; Malhotra 2018).

30 ROR β exhibits a restriction pattern of expression limited to certain regions of brain (cerebral cortex, thalamus, hypothalamus and pineal gland) as well as retina (Jetten, 2009, Nuclear Receptor Signaling). ROR β has been related to epilepsy and together with RORa also to bipolar disease (Rudolf 2016; Lai 2015).

ROR γ shows a broad expression pattern and was the most recently discovered of the three members. To date two different protein isoforms have been recorded: ROR γ 1 and ROR γ 2 (ROR γ 2 is also known as ROR γ t). Generally ROR γ is used to describe ROR γ 1 and/or ROR γ t. ROR γ 1 is expressed in many tissues and is predominantly expressed in the kidneys, liver, and skeletal muscle. In contrast, expression of ROR γ t is restricted to some cell types of the immune system and to lymphoid organs such as the thymus and secondary lymphoid tissues (Hirose 1994; Jetten, 2009, Nuclear Receptor Signaling).

ROR γ t has been identified as a key regulator of Th17 cell differentiation and IL-17 production by $\gamma\delta$ T cells, Th17 cells, T cytotoxic (Tc) 17 cells and innate lymphoid cells type 3 (ILC3) cells (Gaffen 2014). Th17 cells are a subset of T helper cells which preferentially produce the cytokines IL-17A, IL-17F, IL-21 and IL-22 (Castro PLOS
 5 2017). T cells lacking ROR γ t failed to differentiate into Th17 cells even under Th17-polarizing culture conditions, while over-expression of ROR γ t in naïve CD4+ T cells was sufficient to accelerate the expression of Th17-related cytokines and chemokines (Gaffen 2014, Nat Rev Immunol; Yang 2014, Trend Pharmacol Sci). IL-23 is a vital checkpoint
 10 in the generation, maintenance and activation of pathogenic Th17 cells. In response to IL-23 signals, ROR γ t cooperates with a network of transcription factors (STAT3, IRF4 and BATF) to initiate the complete differentiation program of Th17 cells (Gaffen 2014, Nat Rev Immunol).

Th17 cells and IL-17 immune response have been shown to be associated with the pathology of many human inflammatory and autoimmune disorders. Therapeutic
 15 strategies targeting the IL-23–IL-17 axis are being developed in many autoimmune diseases, and some of them have already demonstrated to provide clinical efficacy some diseases (Patel 2015; Krueger 2018 Exp Dermatol) .

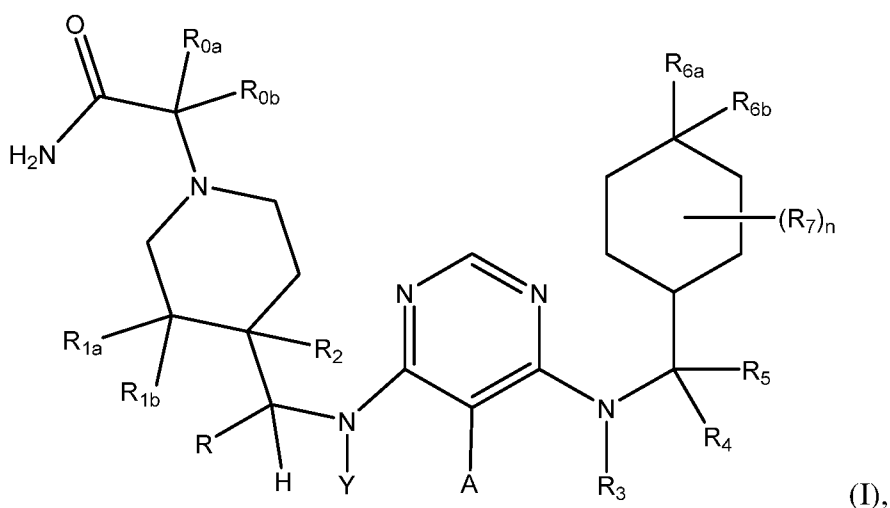
There is thus evidence that ROR α , ROR β and ROR γ play a role in the pathogenesis of many diseases.

20 It would be desirable to provide compounds that modulate the activity of ROR α and/or ROR γ for use in treating inflammatory, metabolic and autoimmune diseases.

WO2016020288 and WO2016020295 describe compounds that modulate the activity or ROR γ receptors. However, a need still exists for potent ROR γ modulators having improved physico-chemical properties.

25 Summary

In one aspect provided herein are compounds of Formula (I)



a stereoisomer thereof, or a pharmaceutically acceptable salt of the compound or stereoisomer, wherein:

n is selected from the group consisting of 0, 1 and 2;

R is selected from the group consisting of hydrogen, C₁₋₆ alkyl and C₁₋₄ hydroxyalkyl;

5 A is fluoro and Y is hydrogen; or

Y and A are taken together with the atoms to which they are attached to form a 5-membered heteroaryl or heteroalicycyl ring system optionally substituted with 1 or 2 substituents selected from halogen, cyano, or C₁₋₄ alkyl;

10 R_{0a} and R_{0b} independently are selected from the group consisting of hydrogen, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, and C₁₋₄ haloalkyl;

R_{1a} and R_{1b} are independently selected from the group consisting of hydrogen, hydroxyl, amino, halogen, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, and C₁₋₄ haloalkyl;

15 R₂ is selected from the group consisting of hydrogen, hydroxyl, amino, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, -C(=O)OH, -C(=O)NH₂, -C(=O)O-C₁₋₄ alkyl, and substituted or unsubstituted heteroaryl;

R₃ is selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, C₃₋₇ cycloalkyl, and C₃₋₇ cycloalkenyl; or

R₃ and R₄ are taken together with the atoms to which they are attached to form a substituted or unsubstituted 4-6 membered heteroalicyclic ring system ;

20 R₄ is hydrogen or C₁₋₄ alkyl, provided R₃ and R₄ are not taken together with the atoms to which they are attached to form a substituted or unsubstituted 4-6 membered heteroalicyclic ring system; or R₄ and R₅ are taken together with the carbon atom to which they are attached to form a C₃₋₄ cycloalkyl;

25 R₅ is absent; or selected from the group consisting of hydrogen and C₁₋₄ alkyl, provided R₄ and R₅ are not taken together with the carbon atom to which they are attached to form a C₃₋₄ cycloalkyl;

R_{6a} and R_{6b} are independently selected from the group consisting of hydrogen, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyhaloalkyl, C₁₋₄

alkoxy, C₁₋₄ haloalkoxy, and substituted or unsubstituted heteroaryl, and whenever n is 0 then at least one of R_{6a} and R_{6b} is selected from the group consisting of cyano, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyhaloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, and substituted or unsubstituted heteroaryl; or

- 5 R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form a 3-6 membered alicyclic or a 3-6 membered heteroalicyclic ring system comprising 1-3 heteroatoms selected from S, O, or N, optionally substituted with one to three halogen atoms; and
- 10 R₇ is selected from the group consisting of hydroxyl, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy.

In one aspect provided herein are pharmaceutical compositions comprising a compound of Formula (I) or a stereoisomer thereof, or a pharmaceutically acceptable salt of the compound or stereoisomer and at least one pharmaceutical acceptable

15 excipient.

In one aspect provided herein are compounds of Formula (I) or a stereoisomer thereof, or a pharmaceutically acceptable salt of the compound or stereoisomer, or pharmaceutical compositions thereof for use in treatment and/or prevention of a disease or disorder or a symptom thereof selected from the group consisting of asthma, acne,

20 chronic obstructive pulmonary disease (COPD), bronchitis, atherosclerosis, helicobacter pylori infection, allergic diseases including allergic rhinitis, allergic conjunctivitis and uveitis, sprue and food allergy, atopic dermatitis, lichen planus, cystic fibrosis, lung allograft rejection, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, ichthyoses, bullous

25 diseases, hidradenitis suppurativa, steatosis, steatohepatitis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), lupus erythematosus, Hashimoto's disease, pancreatitis, autoimmune diabetes, autoimmune ocular disease, ulcerative colitis, colitis, Crohn's disease, inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), Sjogren's syndrome, optic neuritis, type I diabetes,

30 neuromyelitis optica, Myastehnia Gravis, Guillain-Barre syndrome, Graves' disease, scleritis, obesity, obesity-induced insulin resistance, type II diabetes, and cancer.

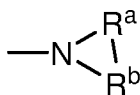
Further, advantageous features of various embodiments are defined in the dependent claims and within the detailed description below.

Detailed description of preferred embodiments

Definitions

5 Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

10 As used herein, any “R” group(s) such as, without limitation, R, R₁, R₂, R₃, R₄, R₅, R₈, R₉, and R₁₀, represent substituents that can be attached to the indicated atom. Examples of R groups includes but is not limited to hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, and heteroalicyclyl. If two “R” groups are covalently bonded to the same atom or to adjacent
15 atoms, then they may be “taken together” or “combined” as defined herein to form a cycloalkyl, aryl, heteroaryl or heteroalicyclyl group. For example, without limitation, if R_a and R_b of an NR_aR_b group are indicated to be “taken together” or “combined”, it means that they are covalently bonded to one another at their terminal atoms to form a ring that includes the nitrogen:



20

As readily recognized by the skilled person, any given group disclosed herein may comprise further hydrogen(s) than the one(s) provided by a R-group, being hydrogen, attached to the group.

Whenever a group is described as being “unsubstituted or substituted,” if
25 substituted, the substituent(s) (which may be present one or more times, such as 1, 2, 3 or 4 times) are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-
30 sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, hydroxyalkyl, hydroxyhaloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino

groups, and the protected derivatives thereof. When a substituent on a group is deemed to be “substituted,” the substituent itself is substituted with one or more of the indicated substituents. When the referenced substituent is substituted, it is meant that one or more hydrogen atoms on the referenced substituent may be replaced with a group(s)
5 individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclic, aralkyl, heteroaralkyl, (heteroalicyclic)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl,
10 hydroxyalkyl, hydroxyhaloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references Greene and Wuts, *Protective Groups in Organic Synthesis*,
15 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is hereby incorporated by reference in its entirety.

As used herein, “C_m to C_n,” “C_m-C_n” or “C_{m-n}” in which “m” and “n” are integers refers to the number of carbon atoms in the relevant group. That is, the group can contain from “m” to “n”, inclusive, carbon atoms. Thus, for example, a “C₁ to C₆ alkyl” group
20 refers to all alkyl groups having from 1 to 6 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-, CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)-, CH₃CH(CH₃)₃CH₂- , CH₃CH(CH₃)₃CH₂- and (CH₃)₃C-. If no “m” and “n” are designated with regard to a group, the broadest range described in these definitions is to be assumed.

As used herein, “alkyl” refers to a straight or branched hydrocarbon chain group
25 that is fully saturated (no double or triple bonds). The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as “1 to 20” refers to each integer in the given range; *e.g.*, “1 to 20 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term
30 “alkyl” where no numerical range is designated). The alkyl group may also be an alkyl having 1 to 10 carbon atoms, such as “C₁₋₆”. The alkyl group could also be a lower alkyl having 1 to 4 carbon atoms. The alkyl group of the compounds may be designated as “C₁-C₄ alkyl,” “C₁₋₄ alkyl” or similar designations. By way of example only, “C₁-C₄

alkyl” or “C₁₋₄ alkyl” indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, 5 hexyl, and the like. When substituted, the substituent group(s) is(are) one or more group(s) individually and independently selected from alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, heteroaralkyl, (heteroalicycyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-10 sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, hydroxyalkyl, hydroxyhaloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethane-sulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof.

As used herein, “alkenyl” refers to an alkyl group that contains in the straight or 15 branched hydrocarbon chain one or more double bonds. If more than one double bond is present, the double bonds may be conjugated or not conjugated. The alkenyl group may have 2 to 20 carbon atoms (whenever it appears herein, a numerical range such as “2 to 20” refers to each integer in the given range; *e.g.*, “2 to 20 carbon atoms” means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, *etc.*, up to 20 and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated). When substituted, the substituent group(s) is(are) one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, heteroaralkyl, (heteroalicycyl)alkyl, hydroxy, oxo, alkoxy, 25 mercapto, alkylthio, cyano, halogen, nitro, haloalkyl, hydroxyalkyl, hydroxyhaloalkyl, haloalkoxy, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof.

As used herein, “alkynyl” refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more triple bonds. The alkynyl group may have 2 to 30 20 carbon atoms (whenever it appears herein, a numerical range such as “2 to 20” refers to each integer in the given range; *e.g.*, “2 to 20 carbon atoms” means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of

the term “alkynyl” where no numerical range is designated). An alkynyl group may be unsubstituted or substituted. When substituted, the substituent(s) may be selected from the same groups disclosed above with regard to alkenyl group substitution.

As used herein, “hetero” may be attached to a group and refers to one or more
5 carbon atom(s) and the associated hydrogen atom(s) in the attached group have been independently replaced with the same or different heteroatoms selected from nitrogen, oxygen, phosphorus and sulfur.

As used herein, “heteroalkyl,” by itself or in combination with another term, refers to a straight or branched alkyl group consisting of the stated number of carbon atoms,
10 where one or more carbon atom(s), such as 1, 2, 3 or 4 carbon atom(s), and the associated hydrogen atom(s) have been independently replaced with the same or different heteroatoms selected from nitrogen, oxygen and sulfur. The carbon atom(s) being replaced may be in the middle or at the end of the alkyl group. Examples of heteroalkyl include C₁₋₆ heteroalkyl wherein one or more of the carbon atom(s) has been replaced by
15 a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, examples are, -S-alkyl, -O-alkyl, -NH-alkyl, -alkylene-O-alkyl, etc. A heteroalkyl may be substituted.

As used herein, “aryl” refers to a carbocyclic (all carbon) ring or two or more fused rings (rings that share two adjacent carbon atoms) that have a fully delocalized pi-
20 electron system. In some embodiments described herein the aryl group is a C₁₋₁₀ aryl, which may be substituted or unsubstituted. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted. When substituted, hydrogen atoms are replaced by substituent group(s) that is(are) one or more group(s) independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl,
25 cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, heteroaralkyl, (heteroalicycyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, hydroxyalkyl, hydroxyhaloalkyl, haloalkoxy, trihalomethanesulfonyl,
30 trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. When substituted, substituents on an aryl group may form a non-aromatic ring fused to the aryl group, including a cycloalkyl, cycloalkenyl, cycloalkynyl, and heterocyclyl.

As used herein, “heteroaryl” refers to a monocyclic or multicyclic aromatic ring system (a ring system with fully delocalized pi-electron system), in which at least one of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. In some embodiments described herein the heteroaryl includes, but is not limited to, C₆₋₁₀ heteroaryl, wherein one to four carbon atoms is/are replaced by one to four heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. Examples of monocyclic “heteroaryl” include, but are not limited to, furan, thiophene, phthalazine, pyrrole, oxazole, oxadiazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, tetrazole, and triazine. Examples of multicyclic “heteroaryl” include, but are not limited to, quinoline, isoquinoline, quinazoline, quinoxaline, indole, purines, benzofuran, benzothiophene, benzopyranones (e.g. coumarin, chromone, and isocoumarin). A heteroaryl may be substituted. When substituted, hydrogen atoms are replaced by substituent group(s) that is(are) one or more group(s) independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, heteroaralkyl, (heteroalicycyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, hydroxyalkyl, hydroxyhaloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. When substituted, substituents on a heteroaryl group may form a non-aromatic ring fused to the aryl group, including a cycloalkyl, cycloalkenyl, cycloalkynyl, and heterocyclyl.

An “aralkyl” or “arylalkyl” is an aryl group connected, as a substituent, via an alkylene group. The alkylene and aryl group of an aralkyl may be substituted. Examples include but are not limited to benzyl, substituted benzyl, 2-phenylethyl, 3-phenylpropyl, and naphthylalkyl. In some cases, the alkylene group is a lower alkylene group.

A “heteroaralkyl” or “heteroarylalkyl” is heteroaryl group connected, as a substituent, via an alkylene group. The alkylene and heteroaryl group of heteroaralkyl may be substituted. Examples include but are not limited to 2-thienylmethyl, 3-thienylmethyl, furylmethyl, thienylethyl, pyrrolylalkyl, pyridylalkyl, isoxazolylalkyl,

pyrazolylalkyl and imidazolylalkyl, and their substituted as well as benzo-fused analogs. In some cases, the alkylene group is a lower alkylene group.

An “alkylene” is a straight-chained tethering group, forming bonds to connect molecular fragments via their terminal carbon atoms. The alkylene may have 1 to 20
5 carbon atoms. The alkylene may also be an alkylene having 1 to 10 carbon atoms, such as “C₁₋₆”. The alkylene could also be a lower alkylene having 1 to 4 carbon atoms. The alkylene may be designated as “C₁₋₄ alkylene”, “C₁₋₄ alkylene” or similar designations. Non-limiting examples include, methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), and butylene (-(CH₂)₄-) groups. In the case of methylene, the two
10 connected fragments are connected to the same carbon atom. A lower alkylene group may be substituted.

As used herein, “heteroalkylene” by itself or in combination with another term refers to an alkylene group consisting of the stated number of carbon atoms in which one or more of the carbon atoms, such as 1, 2, 3 or 4 carbon atom(s), are independently
15 replaced with the same or different heteroatoms selected from oxygen, sulfur and nitrogen. Examples of heteroalkylene include, but not limited to -CH₂-O-, -CH₂-CH₂-O-, -CH₂-CH₂-CH₂-O-, -CH₂-NH-, -CH₂-CH₂-NH-, -CH₂-CH₂-CH₂-NH-, -CH₂-CH₂-NH-CH₂-, -O-CH₂-CH₂-O-CH₂-CH₂-O-, -O-CH₂-CH₂-O-CH₂-CH₂-, and the like.

As used herein, “alkylidene” refers to a divalent group, such as =CR'R'', which
20 is attached to one carbon of another group, forming a double bond. Alkylidene groups include, but are not limited to, methyldiene (=CH₂) and ethyldiene (=CHCH₃). As used herein, “arylalkylidene” refers to an alkylidene group in which either R' or R'' is an aryl group. An alkylidene group may be substituted.

As used herein, “alkoxy” refers to the group -OR wherein R is an alkyl, e.g.
25 methoxy, ethoxy, n-propoxy, cyclopropoxy, 1-methylethoxy (isopropoxy), n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, amoxy, tert-amoxy and the like. An alkoxy may be substituted.

As used herein, “alkylthio” refers to the formula -SR wherein R is an alkyl is defined as above, e.g. methylmercapto, ethylmercapto, n-propylmercapto, 1-
30 methylethylmercapto (isopropylmercapto), n-butylmercapto, iso-butylmercapto, sec-butylmercapto, tert-butylmercapto, and the like. An alkylthio may be substituted.

As used herein, “aryloxy” and “arylthio” refers to RO- and RS-, in which R is an aryl as defined above, e.g., phenoxy, naphthalenyloxy, azulenyloxy, anthracenyloxy,

naphthalenylthio, phenylthio and the like. Both an aryloxy and arylthio may be substituted.

As used herein, “alkenyloxy” refers to the formula –OR wherein R is an alkenyl as defined above, e.g., vinyloxy, propenyloxy, n-butenyloxy, iso-butenyloxy, sec-
5 pentenyloxy, tert-pentyloxy, and the like. The alkenyloxy may be substituted.

As used herein, “acyl” refers to a hydrogen, alkyl, alkenyl, alkynyl, or aryl connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl, and acryl. An acyl may be substituted.

As used herein, “cycloalkyl” refers to a completely saturated (no double bonds)
10 mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro-connected fashion. Cycloalkyl groups may range from C₃ to C₁₀, such as from C₃ to C₆. A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. If substituted,
15 the substituent(s) may be an alkyl or selected from those indicated above with regard to substitution of an alkyl group unless otherwise indicated. When substituted, substituents on a cycloalkyl group may form an aromatic ring fused to the cycloalkyl group, including an aryl and a heteroaryl.

As used herein, “cycloalkenyl” refers to a cycloalkyl group that contains one or
20 more double bonds in the ring although, if there is more than one, they cannot form a fully delocalized pi-electron system in the ring (otherwise the group would be “aryl,” as defined herein). When composed of two or more rings, the rings may be connected together in a fused, bridged or spiro-connected fashion. Cycloalkenyl groups may range from C₃ to C₁₀, such as from C₃ to C₈ or from C₅ to C₁₀. For example, C₃₋₈ cycloalkenyl
25 includes C₄₋₈ cycloalkenyl, C₅₋₈ cycloalkenyl or C₆₋₈ cycloalkenyl. A cycloalkenyl group may be unsubstituted or substituted. When substituted, the substituent(s) may be an alkyl or selected from the groups disclosed above with regard to alkyl group substitution unless otherwise indicated. When substituted, substituents on a cycloalkenyl group may form an aromatic ring fused to the cycloalkenyl group, including an aryl and a heteroaryl.

As used herein, “cycloalkynyl” refers to a cycloalkyl group that contains one or
30 more triple bonds in the ring. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro-connected fashion. Cycloalkynyl groups may range from C₈ to C₁₂. A cycloalkynyl group may be unsubstituted or substituted. When

substituted, the substituent(s) may be an alkyl or selected from the groups disclosed above with regard to alkyl group substitution unless otherwise indicated. When substituted, substituents on a cycloalkynyl group may form an aromatic ring fused to the cycloalkynyl group, including an aryl and a heteroaryl.

5 As used herein, “heteroalicyclic” or “heteroalicyclyl” refers to a 3- to 18 membered ring which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. The heteroalicyclic or heteroalicyclyl groups may range from C₂ to C₁₀, in some embodiments it may range from C₂ to C₉, and in other embodiments it may range from C₂ to C₈. In some embodiments

10 The “heteroalicyclic” or “heteroalicyclyl” may be monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may be joined together in a fused, bridged or spiro-connected fashion; and the nitrogen, carbon and sulfur atoms in the “heteroalicyclic” or “heteroalicyclyl” may be oxidized; the nitrogen may be quaternized; and the rings may also contain one or more double bonds provided that they do not form a fully delocalized

15 pi-electron system throughout all the rings, examples are 2H-benzo[b][1,4]oxazin-3(4H)-one, 3,4-dihydroquinolin-2(1H)-one, 1,2,3,4-tetrahydroquinoline, 3,4-dihydro-2H-benzo[b][1,4]oxazine, 2,3-dihydrobenzo[d]oxazole, 2,3-dihydro-1H-benzo[d]imidazole, indoline, and 1,3-dihydro-2H-benzo[d]imidazol-2-one, and benzo[d]oxazol-2(3H)-one. Heteroalicyclyl groups may be unsubstituted or substituted. When substituted, the

20 substituent(s) may be one or more groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, C-amido, N-amido, S-sulfonamido, N-sulfonamido, isocyanato, thiocyanato,

25 isothiocyanato, nitro, silyl, haloalkyl, hydroxyalkyl, hydroxyhaloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Examples of such “heteroalicyclic” or “heteroalicyclyl” include but are not limited to, azepinyl, dioxolanyl, imidazolanyl, morpholanyl, oxetanyl, oxiranyl, piperidinyl *N*-Oxide, piperidinyl,

30 piperazinyl, pyrrolidinyl, pyranyl, 4-piperidonyl, pyrazolidinyl, 2-oxopyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiamorpholanyl, thiamorpholanyl sulfoxide, and thiamorpholanyl sulfone. When substituted, substituents on a heteroalicyclyl group may

form an aromatic ring fused to the heteroalicycyl group, including an aryl and a heteroaryl.

A “(cycloalkyl)alkyl” is a cycloalkyl group connected, as a substituent, via an alkylene group. The alkylene and cycloalkyl of a (cycloalkyl)alkyl may be substituted.
5 Examples include but are not limited cyclopropylmethyl, cyclobutylmethyl, cyclopropylethyl, cyclopropylbutyl, cyclobutylethyl, cyclopropylisopropyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, cycloheptylmethyl, and the like. In some cases, the alkylene group is a lower alkylene group.

10 A “(cycloalkenyl)alkyl” is a cycloalkenyl group connected, as a substituent, via an alkylene group. The alkylene and cycloalkenyl of a (cycloalkenyl)alkyl may be substituted. In some cases, the alkylene group is a lower alkylene group.

A “(cycloalkynyl)alkyl” is a cycloalkynyl group connected, as a substituent, via an alkylene group. The alkylene and cycloalkynyl of a (cycloalkynyl)alkyl may be substituted.
15 substituted. In some cases, the alkylene group is a lower alkylene group.

As used herein, “halo” or “halogen” refers to F (fluoro), Cl (chloro), Br (bromo) or I (iodo).

As used herein, “haloalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include but are not limited to,
20 chloromethyl, fluoromethyl, difluoromethyl, fluoroethyl, difluoroethyl, trifluoromethyl, 1,1,1,3,3,3-hexafluoropropan-2-yl, 1-chloro-2-fluoromethyl and 2-fluoroisobutyl. A haloalkyl may be substituted or unsubstituted, and some embodiments relate to a haloalkyl having 1 to 10 carbon atoms, such as C₁₋₆ haloalkyl.

As used herein, “hydroxyhaloalkyl” refers to a haloalkyl group in which one or
25 more of the hydrogen atoms are replaced by hydroxyl. Such substituted “hydroxyhaloalkyl” groups include but are not limited to 1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl and 1,1-difluoro-2-hydroxyethyl. Some embodiments relate to a hydroxyhaloalkyl having 1 to 10 carbon atoms, such as C₁₋₆ hydroxyhaloalkyl. Other embodiments relate to C₁₋₄ hydroxyhaloalkyl.

30 As used herein, “haloalkoxy” refers to a RO-group in which R is a haloalkyl group. Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy and 1-chloro-2-fluoromethoxy, 2-fluoroisobutyoxy. A haloalkoxy may be substituted.

As used herein, the term “hydroxyalkyl” refers to an alkyl group in which one of more of the hydrogen atoms are replaced by a hydroxyl group. Such groups include but are not limited to hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl and hydroxyhexyl. A hydroxyalkyl group may be substituted or
 5 unsubstituted, and some embodiments relate to a hydroxyalkyl having 1 to 10 carbon atoms, such as C₁₋₆ hydroxyalkyl or C₁₋₄ hydroxyalkyl.

An “O-carboxy” group refers to a “RC(=O)O-” group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, or (heteroalicycyl)alkyl, as defined herein. An O-
 10 carboxy may be substituted.

A “C-carboxy” group refers to a “-C(=O)OR” group in which R can be the same as defined with respect to O-carboxy. A C-carboxy may be substituted.

A “trihalomethanesulfonyl” group refers to an “X₃CSO₂-” group” wherein X is a halogen.

15 A dashed bond, --- , represents an optional unsaturation between the atoms forming the bond. This bond may be unsaturated (e.g. C=C, C=N, C=O) or saturated (e.g. C-C, C-N, C-O). When a dashed bond is present in a ring system it may form part of an aromatic ring system.

As used herein, a straight (unwedged) bolded or hashed bond, — or |||| , refers
 20 to relative stereochemistry inclusive of all possible stereoisomers at that position.

As used herein, and unless otherwise indicated, a wedged-bond (bolded, hashed, or otherwise), — , = , or |||| , refers to absolute stereochemistry referring to the particular stereoisomer as depicted at that position.

A “nitro” group refers to a “-NO₂” group
 25 A “cyano” group refers to a “-CN” group.
 A “cyanato” group refers to an “-OCN” group.
 An “isocyanato” group refers to a “-NCO” group.

A “thiocyanato” group refers to a “-SCN” group.
 A “carbonyl” group refers to a “-C(=O)-“ group.
 30 A “thiocarbonyl” group refers to a “-C(=S)-“ group.

An “oxo” group refers to a “=O” group.

A “hydroxy” group or “hydroxyl” group refers to an “-OH” group.

An “isothiocyanato” group refers to an “-NCS” group.

A “sulfinyl” group refers to an “-S(=O)-R” group in which R can be the same as defined with respect to O-carboxy. A sulfinyl may be substituted.

A “sulfonyl” group refers to an “SO₂R” group in which R can be the same as defined with respect to O-carboxy. A sulfonyl may be substituted.

5 An “S-sulfonamido” group refers to a “-SO₂NR_AR_B” group in which R_A and R_B indendently of each other can be the same as defined with respect to the R group as defined for O-carboxy, or combined to form a ring system selected from the group consisting of substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted C₃₋₈ cycloalkenyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted C₃₋₈ cycloalkenyl substituted or unsubstituted heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A S-sulfonamido may be substituted.

An “N-sulfonamido” group refers to a “RSO₂N(R_A)-“ group in which R and R_A indendently of each other can be the same as defined with respect to the R group as defined for O-carboxy. An N-sulfonamido may be substituted.

15 A “trihalomethanesulfonamido” group refers to an “X₃CSO₂N(R)-“ group with X as halogen and R can be the same as defined with respect to O-carboxy. A trihalomethanesulfonamido may be substituted.

A “C-amido” group refers to a “-C(=O)NR_AR_B” group in which R_A and R_B indendently of each other can be the same as defined with respect to the R group as defined for O-carboxy, or combined to form a ring system selected from the group consisting of substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted C₃₋₈ cycloalkenyl, substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted C₃₋₈ cycloalkenyl substituted or unsubstituted heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A C-amido may be substituted.

25 An “N-amido” group refers to a “RC(=O)NR_A-“ group in which R and R_A indendently of each other can be the same as defined with respect to the R group as defined for O-carboxy. An N-amido may be substituted.

An “ester” refers to a “-C(=O)OR” group in which R can be the same as defined with respect to O-carboxy. An ester may be substituted.

30 A lower alkoxyalkyl refers to an alkoxy group connected via a lower alkylene group. A lower alkoxyalkyl may be substituted.

An “amine” or “amino” refers to “RNH₂” (a primary amine), “R₂NH” (a secondary amine), “R₃N” (a tertiary amine). An amino group may be substituted.

A lower aminoalkyl refers to an amino group connected via a lower alkylene group. A lower aminoalkyl may be substituted.

Any unsubstituted or monosubstituted amine group on a compound herein can be converted to an amide, any hydroxyl group can be converted to an ester and any carboxyl group can be converted to either an amide or ester using techniques well-known to those skilled in the art (see, for example, Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999).

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (See, *Biochem.* 11:942-944 (1972)).

List of abbreviations

	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
15	MeOH	methanol
	EtOH	ethanol
	THF	tetrahydrofuran
	DCM	dichloromethane, methylene chloride
	DCE	1,2-dichloroethane
20	LRMS	low resolution mass spectrometry
	HPLC	high pressure liquid chromatography
	Prep-HPLC	preparative high pressure liquid chromatography
	h	hour
	min	minutes
25	EA	ethyl acetate
	EDC·HCl	3-((ethylimino)methyleneamino)- <i>N,N</i> -dimethylpropan-1-aminium chloride
	DIEA	diisopropylethyamine
	TEA	triethylamine
30	TFA	trifluoroacetic acid
	HCl	hydrochloric acid, hydrogen chloride
	HOBt	1-hydroxybenzotriazole hydrate
	HOAt	1-hydroxy-7-azabenzotriazole

	HATU	1-[bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxid hexafluorophosphate
	DMAP	4-(dimethylamino)pyridine
	DAST	(diethylamino)sulfur trifluoride
5	DMP	Dess-Martin Periodinane, 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1 <i>H</i>)-one
	TBAF	tetrabutylammonium fluoride trihydrate
	TBDMSCl	<i>tert</i> -butyldimethylsilyl chloride
	MsCl	methanesulfonyl chloride
10	TsCl	4-toluenesulfonyl chloride
	NAS	nucleophilic aromatic substitution
	<i>n</i> BuLi	<i>n</i> -Butyllithium
	<i>i</i> Pr	isopropyl
	DIAD	Diisopropyl azodicarboxylate
15	Boc	<i>tert</i> -Butyloxycarbonyl
	Flash CC	Flash Column Chromatography
	on	overnight
	rt	room temperature
	aq	aqueous
20	ND	Not Determined
	Cbz	Carboxybenzyl
	Hex	hexane
	Hept	heptane
	DEA	diethylamine
25	PE	petroleum ether
	DAD	Diode Array Detctor
	TOF	Time of Flight
	IPA	isopropanol
	Pg	Protective group
30	lg	Leaving group
	atm	atmosphere
	“	enantiomerically enriched (in certain chemical structures “
	”	denotes enantiomerically enriched)

(the * symbol is used in the experimental part indicating mixture of isomers, We think it should be changed by another symbol to avoid confusion with the * recited in the names.)

5 It is understood that, in any compound disclosed herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure or be stereoisomeric mixtures. Further, compounds provided herein may be scalemic mixtures. In addition, it is understood that in any compound having one or more double bond(s) generating
10 geometrical isomers that can be defined as E or Z each double bond may independently be E or Z or a mixture thereof. Likewise, all tautomeric forms are also intended to be included.

As used herein, the term “rac” refers to “racemic”, “racemate”, etc., as is understood by one of ordinary skill in the art. For example, a racemate comprises a
15 mixture of enantiomers of a chiral molecule in equivalent amounts. Typically, a racemate does not exhibit optical activity.

As used herein, the term “rel” refers to the relative, but not absolute, configuration of a stereogenic center with respect to any other stereogenic center within the same compound, as is understood by one of ordinary skill in the art.

20 As used herein, "tautomer" and “tautomeric” refer to alternate forms of a compound disclosed herein that differ in the position of a proton. Non-limiting examples include enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH- moiety and a ring =N- moiety such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

25 It is understood that isotopes may be present in the compounds described herein. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound described herein a hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic
30 forms unless the context clearly dictates otherwise.

As used herein, reference to an element, whether by description or chemical structure, encompasses all isotopes of that element unless otherwise described. By way of example, the term “hydrogen” or “H” in a chemical structure as used herein is

understood to encompass, for example, not only ^1H , but also deuterium (^2H), tritium (^3H), and mixtures thereof unless otherwise denoted by use of a specific isotope. Other specific non-limiting examples of elements for which isotopes are encompassed include carbon, phosphorous, iodine, and fluorine.

5 As used herein, “pharmaceutically acceptable salt” refers to a salt of a compound that does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reaction of a compound disclosed herein with an acid or base. Base-formed salts include, without limitation, ammonium salt (NH_4^+); alkali metal, such as, without limitation, sodium or potassium, salts; alkaline earth, such as,
10 without limitation, calcium or magnesium, salts; salts of organic bases such as, without limitation, dicyclohexylamine, piperidine, piperazine, methylpiperazine, N-methyl-D-glucamine, diethylamine, ethylenediamine, tris(hydroxymethyl)methylamine; and salts with the amino group of amino acids such as, without limitation, arginine and lysine. Useful acid-based salts include, without limitation, acetates, adipates, aspartates,
15 ascorbates, benzoates, butyrates, caparate, caproate, caprylate, camsylates, citrates, decanoates, formates, fumarates, gluconates, glutarate, glycolates, hexanoates, laurates, lactates, maleates, nitrates, oleates, oxalates, octanoates, propanoates, palmitates, phosphates, sebacates, succinates, stearates, sulfates, sulfonates, such as methanesulfonates, ethanesulfonates, p-toluenesulfonates, salicylates, tartrates, and
20 tosylates.

 As used herein, to “modulate” the activity of a receptor means either to activate it, i.e., to increase its cellular function over the base level measured in the particular environment in which it is found, or deactivate it, i.e., decrease its cellular function to less than the measured base level in the environment in which it is found and/or render it
25 unable to perform its cellular function at all, even in the presence of a natural binding partner. A natural binding partner is an endogenous molecule that is an agonist for the receptor.

 An “agonist” is defined as a compound that increases the basal activity of a receptor (i.e. signal transduction mediated by the receptor).

30 As used herein, “partial agonist” refers to a compound that has an affinity for a receptor but, unlike an agonist, when bound to the receptor it elicits only a fractional degree of the pharmacological response normally associated with the receptor even if a large number of receptors are occupied by the compound.

An “inverse agonist” is defined as a compound, which reduces, or suppresses the basal activity of a receptor, such that the compound is not technically an antagonist but, rather, is an agonist with negative intrinsic activity.

5 As used herein, “antagonist” refers to a compound that binds to a receptor to form a complex that does not give rise to any response, as if the receptor was unoccupied. An antagonist attenuates the action of an agonist on a receptor. An antagonist may bind reversibly or irreversibly, effectively eliminating the activity of the receptor permanently or at least until the antagonist is metabolized or dissociates or is otherwise removed by a physical or biological process.

10 As used herein, a “subject” refers to an animal that is the object of treatment, observation or experiment. “Animal” includes cold- and warm-blooded vertebrates and invertebrates such as birds, fish, shellfish, reptiles and, in particular, mammals. “Mammal” includes, without limitation, mice; rats; rabbits; guinea pigs; dogs; cats; sheep; goats; cows; horses; primates, such as monkeys, chimpanzees, and apes, and, in
15 particular, humans.

As used herein, a “patient” refers to a subject that is being treated by a medical professional such as an M.D. or a D.V.M. to attempt to cure, or at least ameliorate the effects of, a particular disease or disorder or to prevent the disease or disorder from occurring in the first place.

20 As used herein, a “carrier” refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

As used herein, a “diluent” refers to an ingredient in a pharmaceutical composition
25 that lacks pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered
30 saline that mimics the composition of human blood.

As used herein, an “excipient” refers to an inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability,

binding ability, lubrication, disintegrating ability etc., to the composition. A “diluent” is a type of excipient.

A "receptor" is intended to include any molecule present inside or on the surface of a cell that may affect cellular physiology when it is inhibited or stimulated by a ligand. Typically, a receptor comprises an extracellular domain with ligand-binding properties, a transmembrane domain that anchors the receptor in the cell membrane, and a cytoplasmic domain that generates a cellular signal in response to ligand binding ("signal transduction"). A receptor also includes any intracellular molecule that in response to ligation generates a signal. A receptor also includes any molecule having the characteristic structure of a receptor, but with no identifiable ligand. In addition, a receptor includes a truncated, modified, mutated receptor, or any molecule comprising partial or all of the sequences of a receptor.

"Ligand" is intended to include any substance that interacts with a receptor.

"Selective" or "selectivity" is defined as a compound's ability to generate a desired response from a particular receptor type, subtype, class or subclass while generating less or little response from other receptor types. "Selective" or "selectivity" of one or more particular subtypes of a compound means a compound's ability to increase the activity of the subtypes while causing less, little or no increase in the activity of other subtypes.

As used herein, "coadministration" of pharmacologically active compounds refers to the delivery of two or more separate chemical entities, whether in vitro or in vivo. Coadministration means the simultaneous delivery of separate agents; the simultaneous delivery of a mixture of agents; as well as the delivery of one agent followed by delivery of a second agent or additional agents. Agents that are coadministered are typically intended to work in conjunction with each other.

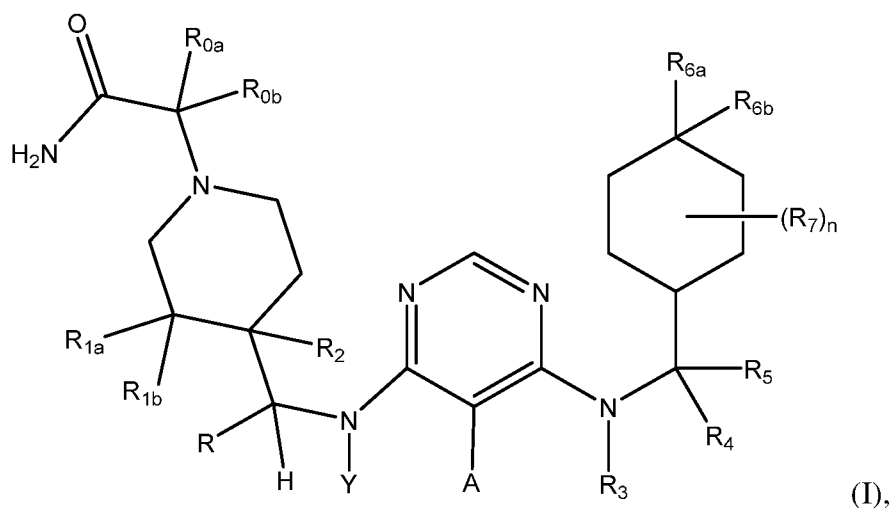
The term "an effective amount" as used herein means an amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation or palliation of the symptoms of the disease being treated.

When used herein, “prevent/preventing” should not be construed to mean that a condition and/or a disease never might occur again after use of a compound or pharmaceutical composition according to embodiments disclosed herein to achieve prevention. Further, the term should neither be construed to mean that a condition not

might occur, at least to some extent, after such use to prevent said condition. Rather, “prevent/preventing” is intended to mean that the condition to be prevented, if occurring despite such use, will be less severe than without such use.

5 Compounds

In some embodiments, the present disclosure relates to compounds, stereoisomers, and salts of compounds and stereoisomers of Formula (I):



- 10 a stereoisomer thereof, or a pharmaceutically acceptable salt of the compound or stereoisomer, wherein:

n is selected from the group consisting of 0, 1 and 2;

R is selected from the group consisting of hydrogen, C₁₋₆ alkyl and C₁₋₄ hydroxyalkyl;

A is fluoro and Y is hydrogen; or

- 15 Y and A are taken together with the atoms to which they are attached to form a 5-membered heteroaryl or heteroalicyclic ring system optionally substituted with 1 or 2 substituents selected from halogen, cyano, or C₁₋₄ alkyl;

R_{0a} and R_{0b} independently are selected from the group consisting of hydrogen, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, and C₁₋₄ haloalkyl;

- 20 R_{1a} and R_{1b} are independently selected from the group consisting of hydrogen, hydroxyl, amino, halogen, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, and C₁₋₄ haloalkyl;

R₂ is selected from the group consisting of hydrogen, hydroxyl, amino, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, -C(=O)OH, -C(=O)NH₂, -C(=O)O-C₁₋₄ alkyl, and substituted or unsubstituted heteroaryl;

R₃ is selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, C₃₋₇ cycloalkyl, and C₃₋₇ cycloalkenyl; or

R₃ and R₄ are taken together with the atoms to which they are attached to form a substituted or unsubstituted 4-6 membered heteroalicyclic ring system;

R₄ is hydrogen or C₁₋₄ alkyl, provided R₃ and R₄ are not taken together with the atoms to which they are attached to form a substituted or unsubstituted 4-6 membered heteroalicyclic ring system; or R₄ and R₅ are taken together with the carbon atom to which they are attached to form a C₃₋₄ cycloalkyl;

R₅ is absent; or selected from the group consisting of hydrogen and C₁₋₄ alkyl, provided R₄ and R₅ are not taken together with the carbon atom to which they are attached to form a C₃₋₄ cycloalkyl;

R_{6a} and R_{6b} are independently selected from the group consisting of hydrogen, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyhaloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, and substituted or unsubstituted heteroaryl, and whenever n is 0 then at least one of R_{6a} and R_{6b} is selected from the group consisting of cyano, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyhaloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, and substituted or unsubstituted heteroaryl; or

R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form a 3-6 membered alicyclic or a 3-6 membered heteroalicyclic ring system comprising 1-3 heteroatoms selected from S, O, or N, optionally substituted with one to three halogen atoms; and

R₇ is selected from the group consisting of hydroxyl, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy.

In some embodiments disclosed herein, A is fluoro and Y is hydrogen. In some embodiments disclosed herein, Y and A are taken together with the atoms to which they are attached to form a 5-membered heteroaryl or heteroalicyclic ring system optionally substituted with 1 or 2 substituents selected from halogen, cyano, or C₁₋₄ alkyl.

herein, R_{0b} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, and C_{1-4} haloalkyl.

In some embodiments disclosed herein, R_{0a} is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2F$, and $-CHF_2$; and R_{0b} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, and C_{1-4} haloalkyl. In some embodiments disclosed herein, R_{0a} and R_{0b} both are hydrogen.

In some embodiments disclosed herein, at least one of R_{1a} , R_{1b} and R_2 is not hydrogen.

In some embodiments disclosed herein, R_{1a} is selected from the group consisting of hydrogen, hydroxyl, amino, halogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, and C_{1-4} haloalkyl. In some embodiments disclosed herein, R_{1a} is hydrogen. In some embodiments disclosed herein, R_{1a} is hydroxyl. In some embodiments disclosed herein, R_{1a} is amino. In some embodiments disclosed herein, R_{1a} is halogen. In some embodiments disclosed herein, R_{1a} is C_{1-4} alkyl. In some embodiments disclosed herein, R_{1a} is C_{1-4} hydroxyalkyl. In some embodiments disclosed herein, R_{1a} is C_{1-4} haloalkyl. In some embodiments, R_{1a} is hydroxyl or hydrogen. In some embodiments disclosed herein, R_{1a} is selected from the group consisting of hydroxyl, halogen, and C_{1-4} haloalkyl. In some embodiments disclosed herein, R_{1a} is selected from the group consisting of hydroxyl, fluoro and $-CF_3$.

In some embodiments disclosed herein, R_{1b} is selected from the group consisting of hydrogen, hydroxyl, amino, halogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, and C_{1-4} haloalkyl. In some embodiments disclosed herein, R_{1b} is hydrogen. In some embodiments disclosed herein, R_{1b} is hydroxyl. In some embodiments disclosed herein, R_{1b} is amino. In some embodiments disclosed herein, R_{1b} is halogen. In some embodiments disclosed herein, R_{1b} is C_{1-4} alkyl. In some embodiments disclosed herein, R_{1b} is C_{1-4} hydroxyalkyl. In some embodiments disclosed herein, R_{1b} is C_{1-4} haloalkyl. In some embodiments disclosed herein, R_{1b} is selected from the group consisting of hydrogen, halogen, and C_{1-4} alkyl. In some embodiments, R_{1b} is selected from the group consisting of hydrogen, fluoro, and methyl.

In some embodiments disclosed herein, R_{1a} is selected from the group consisting of hydroxyl, halogen, and C₁₋₄ haloalkyl and R_{1b} is selected from the group consisting of hydrogen, halogen, and C₁₋₄ alkyl. In some embodiments disclosed herein, R_{1a} is selected from the group consisting of hydroxyl, fluoro and -CF₃ and R_{1b} is selected from the group consisting of hydrogen, fluoro, and methyl. In some embodiments disclosed
5 herein, R_{1a} is hydrogen or hydroxyl and R_{1b} is hydrogen.

In some embodiments disclosed herein, R₂ is selected from the group consisting of hydrogen, hydroxyl, amino, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄
10 hydroxyalkyl, -C(=O)OH, -C(=O)NH₂, -C(=O)O-C₁₋₄ alkyl, and substituted or unsubstituted heteroaryl. In some embodiments disclosed herein, R₂ is hydrogen. In some embodiments disclosed herein, R₂ is hydroxyl. In some embodiments disclosed herein, R₂ is amino. In some embodiments disclosed herein, R₂ is cyano. In some
15 embodiments disclosed herein, R₂ is halogen. In some embodiments disclosed herein, R₂ is C₁₋₄ alkyl. In some embodiments disclosed herein, R₂ is C₁₋₄ haloalkyl. In some embodiments disclosed herein, R₂ is C₁₋₄ hydroxyalkyl. In some embodiments disclosed herein, R₂ is -C(=O)OH. In some embodiments disclosed herein, R₂ is -
C(=O)NH₂. In some embodiments disclosed herein, R₂ is -C(=O)O-C₁₋₄ alkyl. In some
20 embodiments disclosed herein, R₂ is substituted or unsubstituted heteroaryl. In some
embodiments disclosed herein, R₂ is substituted heteroaryl. In some embodiments
disclosed herein, R₂ is unsubstituted heteroaryl.

In some embodiments disclosed herein, R₂ is hydrogen, halogen, hydroxyl, cyano, C₁₋₄
alkyl, C₁₋₄ hydroxyalkyl, or -C(=O)O-C₁₋₄ alkyl. In some embodiments disclosed
25 herein, R₂ is hydrogen, halogen, hydroxyl, cyano, methyl, ethyl, -CH₂OH, -CH₂CH₂OH,
or -C(=O)O-C₁₋₂ alkyl. In some embodiments disclosed herein, R₂ is hydrogen,
halogen, hydroxyl, or C₁₋₄ hydroxyalkyl. In some embodiments disclosed herein, R₂ is
hydrogen, fluoro, hydroxyl, or -CH₂OH. In some embodiments disclosed herein, R₂ is
hydrogen or hydroxyl. In some embodiments disclosed herein, R₂ is hydrogen. In some
30 embodiments disclosed herein, R₂ is hydroxyl.

In some embodiments disclosed herein, R₂ is hydrogen and R_{1a} is hydroxyl. In some
embodiments disclosed herein, R₂ is hydroxyl and R_{1a} is hydroxyl.

- In some embodiments disclosed herein, R₃ is selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, C₃₋₇ cycloalkyl, and C₃₋₇ cycloalkenyl. In some embodiments disclosed herein, R₃ is C₁₋₄ alkyl. In some
5 embodiments disclosed herein, R₃ is C₁₋₄ alkenyl. In some embodiments disclosed herein, R₃ is C₁₋₄ haloalkyl. In some embodiments disclosed herein, R₃ is C₁₋₄ hydroxyalkyl. In some embodiments disclosed herein, R₃ is C₃₋₇ cycloalkyl. In some embodiments disclosed herein, R₃ is C₃₋₇ cycloalkenyl.
- 10 In some embodiments disclosed herein, R₃ is C₁₋₄ alkyl or C₃₋₇ cycloalkyl. In some embodiments disclosed herein, R₃ is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, cyclopropyl or cyclobutyl. In some embodiments disclosed herein, R₃ is methyl, ethyl, cyclopropyl, or cyclobutyl. In some embodiments disclosed herein, R₃ is ethyl or cyclobutyl. In some embodiments disclosed herein, R₃ is ethyl.
15
- In some embodiments disclosed herein, R₄ is hydrogen or C₁₋₄ alkyl. In some embodiments disclosed herein, R₄ is hydrogen. In some embodiments disclosed herein, R₄ is C₁₋₄ alkyl. In some embodiments disclosed herein, R₄ is methyl.
- In some embodiments disclosed herein, R₅ is absent. In some embodiments disclosed
20 herein, R₅ is hydrogen or C₁₋₄ alkyl. In some embodiments disclosed herein, R₅ is hydrogen. In some embodiments disclosed herein, R₅ is C₁₋₄ alkyl. In some embodiments disclosed herein, R₅ is methyl.
- In some embodiments disclosed herein, R₄ and R₅ are taken together with the carbon
25 atom to which they are attached to form a C₃₋₄ cycloalkyl. In some embodiments disclosed herein, R₄ and R₅ are taken together with the carbon atom to which they are attached to form a cyclopropyl. In some embodiments disclosed herein, R₄ and R₅ are taken together with the carbon atom to which they are attached to form a cyclobutyl.
- In some embodiments disclosed herein, each of R₄ and R₅ independently is hydrogen or
30 C₁₋₄ alkyl, or R₄ and R₅ are taken together with the carbon atom to which they are attached to form a C₃₋₄ cycloalkyl. In some embodiments disclosed herein, each of R₄ and R₅ independently is hydrogen or methyl, or R₄ and R₅ are taken together with the carbon atom to which they are attached to form a cyclopropyl.

In some embodiments disclosed herein, R₄ and R₅ are hydrogen.

In some embodiments disclosed herein, R₃ and R₄ are taken together with the atoms to
5 which they are attached to form a substituted or unsubstituted 4-6 membered
heteroalicyclic ring system. In some embodiments disclosed herein, the heteroalicyclic
ring system comprising R₃ and R₄ is a 4 membered heteroalicyclic. In some
embodiments disclosed herein, the heteroalicyclic ring system comprising R₃ and R₄ is a
10 5 membered heteroalicyclic. In some embodiments disclosed herein, the heteroalicyclic
ring system comprising R₃ and R₄ is a 6 membered heteroalicyclic. In some
embodiments disclosed herein, the heteroalicyclic ring system comprising R₃ and R₄ is
unsubstituted. In some embodiments disclosed herein, the heteroalicyclic ring system
comprising R₃ and R₄ is substituted with one or two substituents selected from halogen,
hydroxyl, and C₁₋₄ alkyl. In some embodiments disclosed herein, R³ and R⁴, taken
15 together with the atoms to which they are attached, form a 4-6 membered
heteroalicyclic ring comprising a double bond, and R⁵ is absent.

In some embodiments disclosed herein, the heteroalicyclic ring system comprising R₃
and R₄ is azetidiny, pyrrolidinyl, morpholinyl, piperidinyl, 2-azabicyclo[3.1.0]hexanyl,
20 or 3-azabicyclo[3.1.0]hexanyl; wherein the heteroalicyclic ring system is optionally
substituted with one or two substituents selected from halogen and methyl, and
whenever the heteroalicyclic ring system is substituted or unsubstituted 2-
azabicyclo[3.1.0]hexanyl then R₅ is absent. In some embodiments disclosed herein, the
heteroalicyclic ring system comprising R₃ and R₄ is unsubstituted azetidiny,
25 unsubstituted pyrrolidinyl, unsubstituted morpholinyl, unsubstituted piperidinyl, 2-
azabicyclo[3.1.0]hexanyl, or unsubstituted 3-azabicyclo[3.1.0]hexanyl. In some
embodiments disclosed herein, the heteroalicyclic ring system comprising R₃ and R₄ is
azetidiny, pyrrolidinyl, morpholinyl, piperidinyl, 2-azabicyclo[3.1.0]hexanyl, or 3-
azabicyclo[3.1.0]hexanyl; wherein the heteroalicyclic ring system is substituted with
30 one or two substituents selected from halogen and methyl. In some embodiments
disclosed herein, the heteroalicyclic ring system is substituted or unsubstituted 2-
azabicyclo[3.1.0]hexanyl and R₅ is absent. In some embodiments disclosed here, the
heteroalicyclic ring system is substituted 2-azabicyclo[3.1.0]hexanyl and R₅ is absent.

In some embodiments disclosed here, the heteroalicyclic ring system is unsubstituted 2-azabicyclo[3.1.0]hexanyl and R₅ is absent.

5 In some embodiments disclosed herein, the heteroalicyclic ring system comprising R₃ and R₄ is morpholinyl optionally substituted with one or two substituents selected from halogen and methyl, and R₅ is hydrogen. In some embodiments disclosed herein, the heteroalicyclic ring system comprising R₃ and R₄ is unsubstituted morpholinyl, and R₅ is hydrogen.

10 In some embodiments disclosed herein, R_{6a} is selected from the group consisting of hydrogen, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyhaloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, and substituted or unsubstituted heteroaryl. In some embodiments disclosed herein, R_{6a} is hydrogen. In some
15 R_{6a} is halogen. In some embodiments disclosed herein, R_{6a} is C₁₋₄ alkyl. In some embodiments disclosed herein, R_{6a} is C₁₋₄ hydroxyalkyl. In some embodiments disclosed herein, R_{6a} is C₁₋₄ haloalkyl. In some embodiments disclosed herein, R_{6a} is C₁₋₄ hydroxyhaloalkyl. In some embodiments disclosed herein, R_{6a} is C₁₋₄ alkoxy. In some
20 R_{6a} is substituted or unsubstituted heteroaryl. In some embodiments disclosed herein, R_{6a} is substituted heteroaryl. In some embodiments disclosed herein, R_{6a} is unsubstituted heteroaryl. In some embodiments disclosed herein, R_{6a} is hydrogen, halogen, C₁₋₄ haloalkyl, or C₁₋₄ haloalkoxy. In some embodiments disclosed herein, R_{6a} is hydrogen, C₁₋₄ haloalkyl, or C₁₋₄ haloalkoxy. In some embodiments disclosed herein,
25 R_{6a} is hydrogen, -CF₃, -CH₂F, -CCH₃F₂, -OCF₃, or -OCHF₂.

In some embodiments disclosed herein, R_{6b} is selected from the group consisting of hydrogen, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyhaloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, and substituted or unsubstituted heteroaryl. In some
30 R_{6b} is cyano. In some embodiments disclosed herein, R_{6b} is halogen. In some embodiments disclosed herein, R_{6b} is C₁₋₄ alkyl. In some embodiments disclosed herein, R_{6b} is C₁₋₄ hydroxyalkyl. In some embodiments disclosed herein, R_{6b} is C₁₋₄ haloalkyl. In some embodiments disclosed herein, R_{6b} is C₁₋

4 hydroxyhaloalkyl. In some embodiments disclosed herein, R_{6b} is C₁₋₄ alkoxy. In some
embodiments disclosed herein, R_{6b} is C₁₋₄ haloalkoxy. In some embodiments disclosed
herein, R_{6b} is substituted or unsubstituted heteroaryl. In some embodiments disclosed
herein, R_{6b} is substituted heteroaryl. In some embodiments disclosed herein, R_{6b} is
5 unsubstituted heteroaryl. In some embodiments disclosed herein, R_{6b} is hydrogen,
halogen, C₁₋₄ haloalkyl, or C₁₋₄ haloalkoxy.

In some embodiments disclosed herein, R_{6a} is hydrogen, -CF₃, -CH₂F, -CCH₃F₂, -OCF₃,
or -OCHF₂, and R_{6b} is hydrogen. In some embodiments disclosed herein, R_{6a} is -CF₃,
and R_{6b} is hydrogen. In some embodiments disclosed herein, n is 0 and at least one of
10 R_{6a} and R_{6b} is selected from the group consisting of cyano, halogen, C₁₋₄ alkyl, C₁₋₄
haloalkyl, C₁₋₄ hydroxyhaloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy,
substituted or unsubstituted heteroaryl; or R_{6a} and R_{6b} are taken together with the carbon
atom to which they are attached to form a 3-6 membered alicyclic or a 3-6 membered
heteroalicyclic ring system comprising 1-3 heteroatoms selected from S, O, or N,
15 optionally substituted with one to three halogen atoms. In some embodiments disclosed
herein, whenever n is 0 then at least one of R_{6a} and R_{6b} is selected from the group
consisting of cyano, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyhaloalkyl, C₁₋₄
hydroxyalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, substituted or unsubstituted heteroaryl.

In some embodiments disclosed herein, R_{6a} and R_{6b} are taken together with the carbon
20 atom to which they are attached to form a 3-6 membered alicyclic or a 3-6 membered
heteroalicyclic ring system comprising 1-3 heteroatoms selected from S, O, or N,
optionally substituted with one to three halogen atoms. In some embodiments disclosed
herein, R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached
to form a 3-6 membered alicyclic ring system, optionally substituted with one to three
25 halogen atoms. In some embodiments disclosed herein, R_{6a} and R_{6b} are taken together
with the carbon atom to which they are attached to form a 3-6 membered heteroalicyclic
ring system comprising 1-3 heteroatoms selected from S, O, or N, optionally substituted
with one to three halogen atoms. In some embodiments disclosed herein, R_{6a} and R_{6b}
are taken together with the carbon atom to which they are attached to form a 3-4
30 membered alicyclic ring system, optionally substituted by one to three fluoro, or a 4-5
heteroalicyclic ring system, comprising one, two, or three heteroatoms selected from O
and N. In some embodiments disclosed herein, R_{6a} and R_{6b} are taken together with the

carbon atom to which they are attached to form a 3-4 membered alicyclic ring system, optionally substituted by one to three fluoro. In some embodiments disclosed herein, R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form an unsubstituted 3-4 membered alicyclic ring system. In some embodiments disclosed
5 herein, R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form a 3-4 membered alicyclic ring system substituted by one to three fluoro. In some embodiments disclosed herein, R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form a 4-5 heteroalicyclic ring system, comprising one, two, or three heteroatoms selected from O and N. In some embodiments disclosed
10 herein, R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form an oxetanyl or a cyclopropyl optionally substituted with one or two fluoro.

In some embodiments disclosed herein, R_{6a} and R_{6b} are each independently hydrogen, halogen, C₁₋₄ haloalkyl, or C₁₋₄ haloalkoxy, or R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form a 3-6 membered heteroalicyclic or a 3-6
15 membered alicyclic ring system, optionally substituted by one to three halogen atoms.

In some embodiments disclosed herein, R_{6a} is hydrogen, -CF₃, -CH₂F, -CCH₃F₂, -OCF₃, or -OCHF₂, and R_{6b} is hydrogen; or R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form a 3-4 membered alicyclic ring system, optionally
20 substituted by one to three fluoro, or a 4-5 heteroalicyclic ring system, comprising one, two, or three heteroatoms selected from O and N. In some embodiments disclosed herein, R_{6a} is -CF₃, and R_{6b} is hydrogen; or R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form an oxetanyl or a cyclopropyl optionally substituted with one or two fluoro. In some embodiments disclosed herein, at least one
25 of R_{6a} and R_{6b} is substituted or unsubstituted heteroaryl. In some embodiments disclosed herein, at least one of R_{6a} and R_{6b} is heteroaryl substituted with C₁₋₄ alkyl.

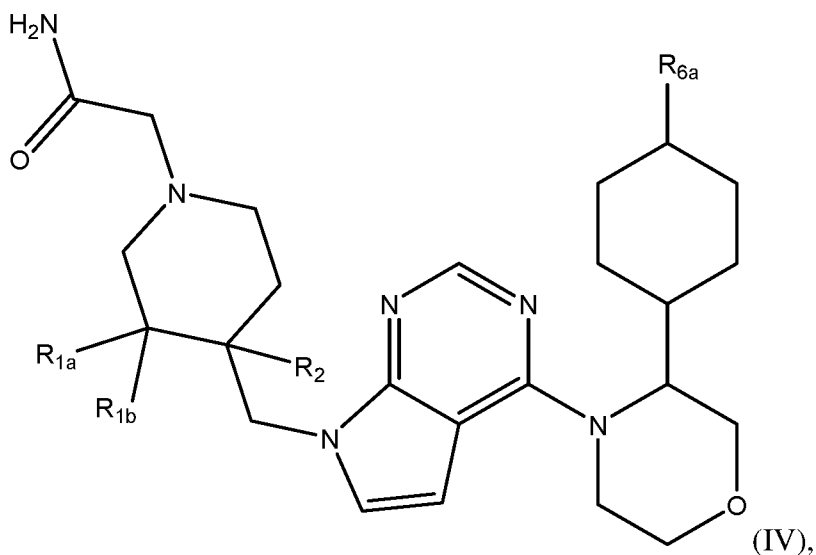
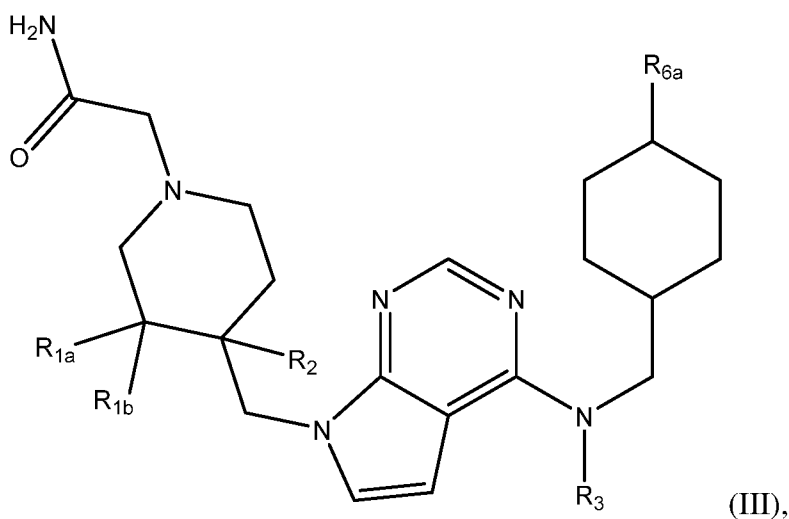
In some embodiments disclosed herein, n is 0 or 1. In some embodiments disclosed herein, n is 0. In some embodiments disclosed herein, n is 1.

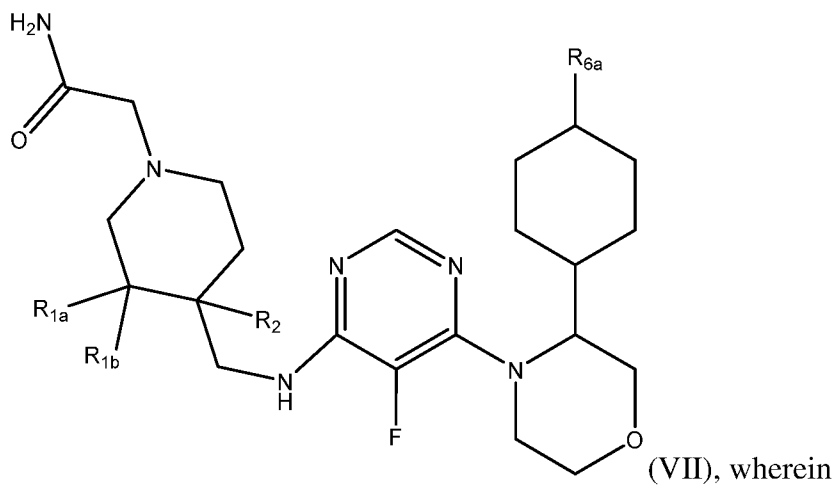
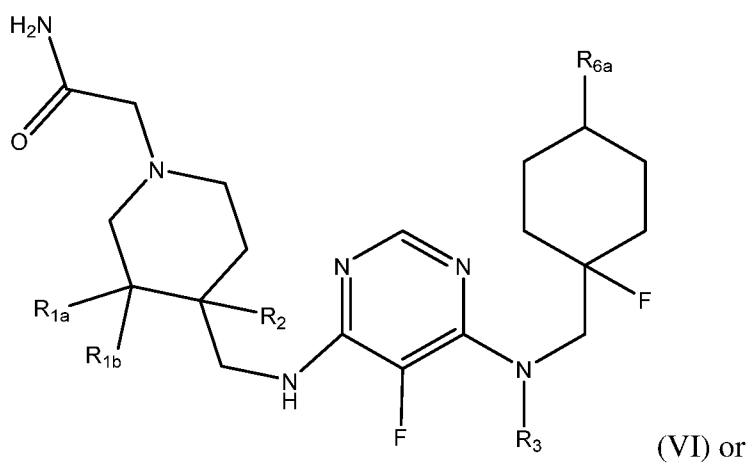
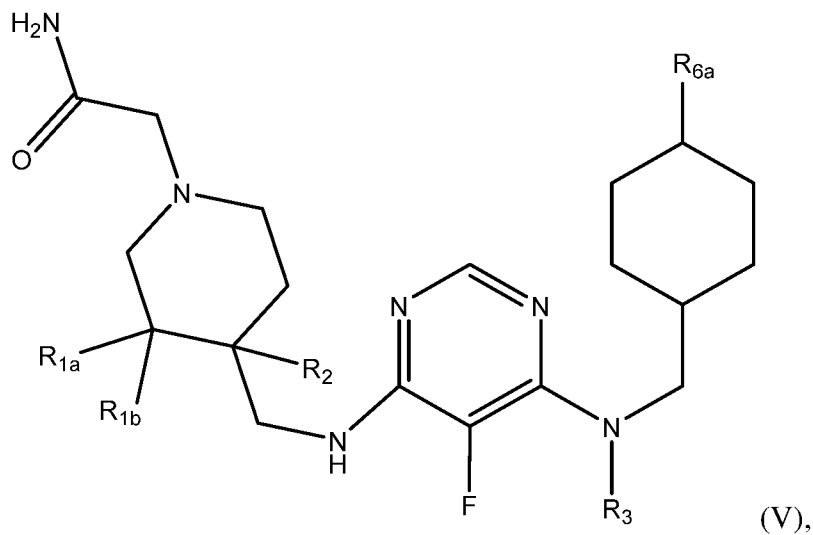
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In some embodiments disclosed herein, R₇ is selected from the group consisting of hydroxyl, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy. In some embodiments disclosed herein, R₇ is hydroxyl. In some

embodiments disclosed herein, R₇ is cyano. In some embodiments disclosed herein, R₇ is halogen. In some embodiments disclosed herein, R₇ is C₁₋₄ alkyl. In some embodiments disclosed herein, R₇ is C₁₋₄ haloalkyl. In some embodiments disclosed herein, R₇ is C₁₋₄ hydroxyalkyl. In some embodiments disclosed herein, R₇ is C₁₋₄ alkoxy. In some embodiments disclosed herein, R₇ is C₁₋₄ haloalkoxy. In some embodiments disclosed herein, R₇ is hydroxyl, cyano, halogen, C₁₋₄ haloalkyl, or C₁₋₄ haloalkoxy. In some embodiments disclosed herein, R₇ is halogen, hydroxyl, cyano, -CF₃, -OCHF₂, -CHF₂ or -OCF₃.

10 The compound, stereoisomer, or salt according to claim 1, wherein the compound has the structure





- R_{1a} is hydrogen, fluoro or hydroxyl;
- 5 R_{1b} is hydrogen or fluoro;
- R₂ is hydrogen or hydroxyl
- R₃ is methyl, ethyl, cyclopropyl or cyclobutyl;
- R_{6a} is -CF₃; and provided at least one of R_{1a}, R_{1b} and R₂ is not hydrogen.

In some embodiments disclosed herein, R_{0a} and R_{0b} are both hydrogen; R_{1a} and R_{1b} are independently hydrogen or hydroxy; R₂ is selected from the group consisting of hydrogen and hydroxyl; R is hydrogen; Y is hydrogen and A is fluoro; or Y and A are taken together with the atoms to which they are attached and the pyrimidine ring of
 5 formula (I) to form an unsubstituted pyrrolo[2,3-d]pyrimidine; R₃ is selected from the group consisting of methyl, ethyl, cyclopropyl and cyclobutyl, and R₄ and R₅ are hydrogen; or R₃ and R₄ are taken together with the atoms to which they are attached to form an unsubstituted morpholinyl, and R₅ is hydrogen; n is 0; or n is 1 and R₇ is a fluoro; R_{6a} is -CF₃, and R_{6b} is hydrogen; or R_{6a} and R_{6b} are taken together with the
 10 carbon atom to which they are attached to form an oxetanyl or a cyclopropyl substituted by two fluoro.

In one embodiment, the compound, salt, stereoisomer, or salt of the stereoisomer of Formula (I) is selected from the group consisting of:

rel-2-((3*R*,4*R*)-4-(((6-(((1,1-Difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-
 15 fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
 2-((3*R**,4*R**)-4-(((5-fluoro-6-(methyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)pyrimidin-4-yl)amino)methyl)-3-
 hydroxypiperidin-1-yl)acetamide,
 2-((3*R**,4*R**)-4-(((6-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-
 20 fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
 2-((3*R**,4*R**)-4-(((6-(cyclopropyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-
 hydroxypiperidin-1-yl)acetamide,
 2-((3*RS*,4*RS*)-4-(((6-(cyclobutyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-
 25 5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
rel-2-((3*R*,4*R*)-4-(((6-(((2-oxaspiro[3.5]nonan-7-yl)methyl)(ethyl)amino)-5-
 fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
rel-2-((3*R*,4*R*)-4-(((6-(ethyl((1-fluoro-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-
 fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
 30 2-(4-(((5-fluoro-6-((3*S*)-3-(4-(trifluoromethyl)cyclohexyl)morpholino)pyrimidin-4-
 yl)amino)methyl)piperidin-1-yl)acetamide,
 2-((3*RS*,4*RS*)-4-((4-(Ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-
 pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide,

2-((3*R**,4*R**)-4-((4-(Ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide,

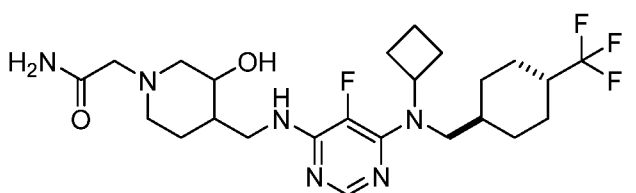
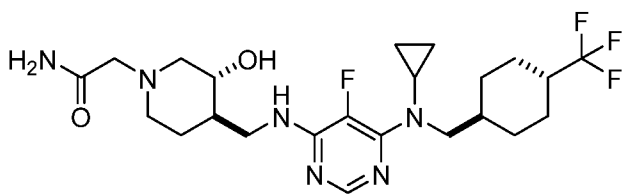
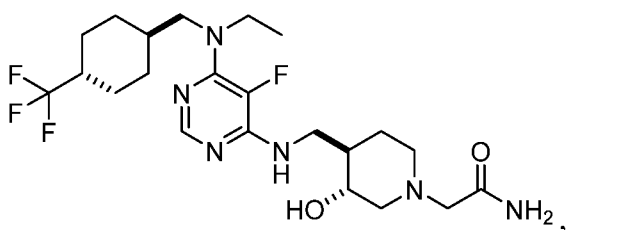
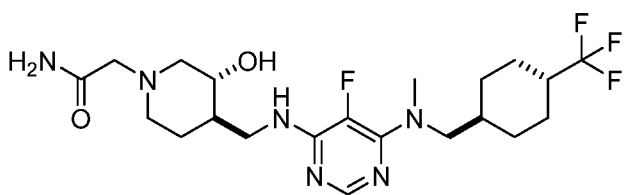
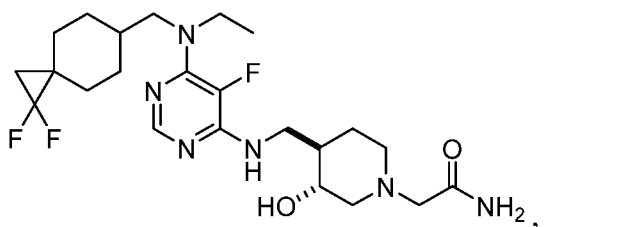
2-((3*RS*,4*RS*)-4-((4-(cyclobutyl(((1*r*,4*S*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide,

5 2-((3*R**,4*R**)-4-(((6-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide, and

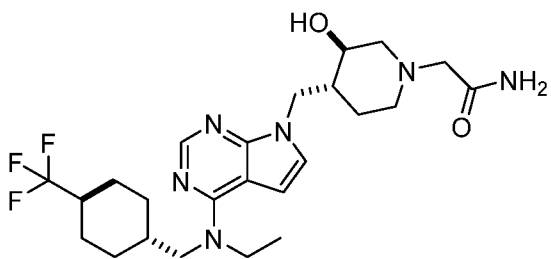
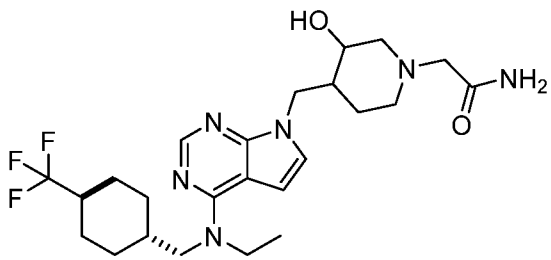
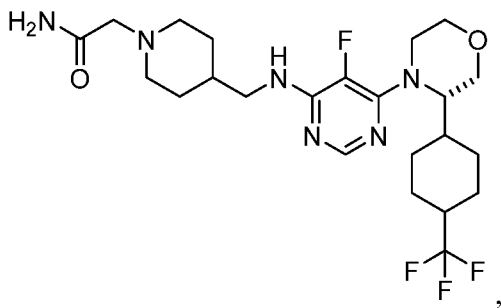
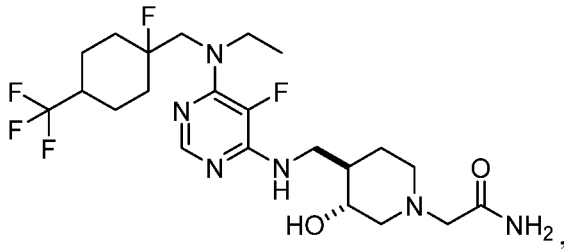
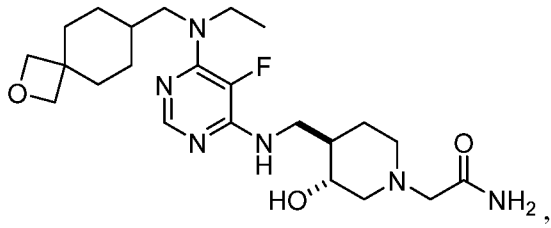
2-((3*R**,4*R**)-4-((4-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide.

In one embodiment, the compound, salt, stereoisomer, or salt of the stereoisomer of

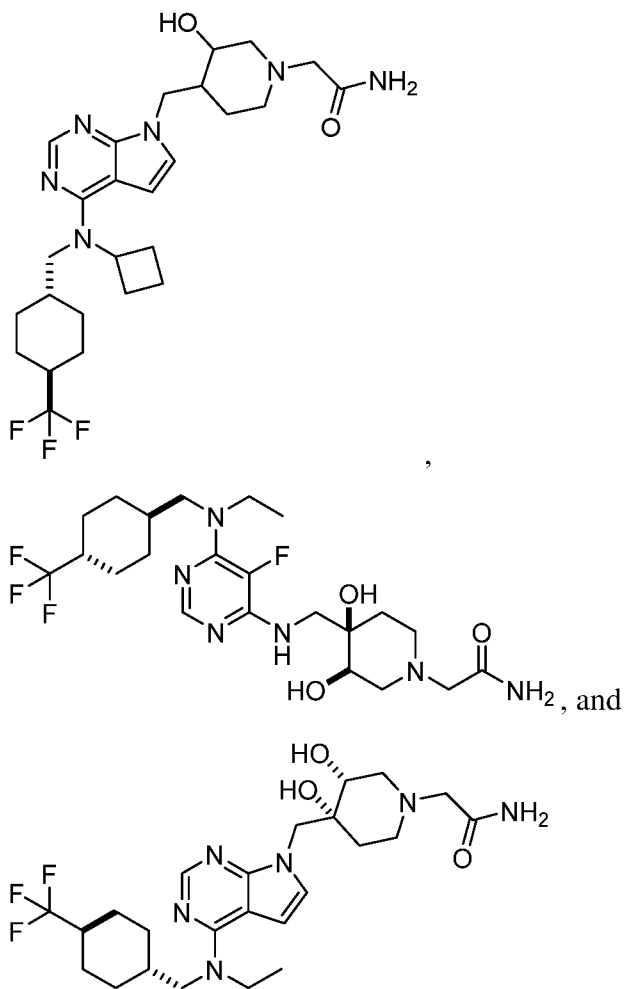
10 Formula (I) is selected from the group consisting of:



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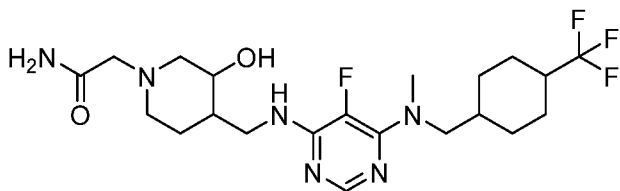
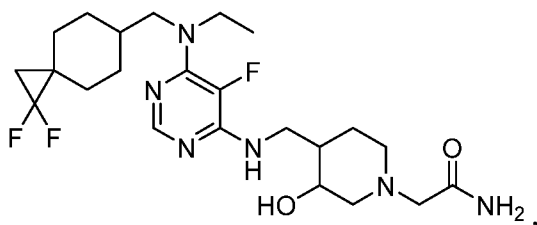


- 5 In one embodiment, the compound, salt, stereoisomer, or salt of the stereoisomer of Formula (I) is selected from the group consisting of:
- 2-(4-(((6-(((1,1-Difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 2-(4-(((5-fluoro-6-(methyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)pyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 10 2-(4-(((6-(ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 2-(4-(((6-(cyclopropyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 15 2-(4-(((6-(cyclobutyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 2-(4-(((6-(((2-oxaspiro[3.5]nonan-7-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,

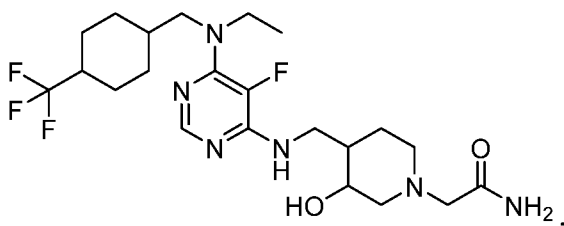
- 2-(4-(((6-(ethyl((1-fluoro-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
 2-(4-(((5-fluoro-6-(3-(4-(trifluoromethyl)cyclohexyl)morpholino)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)acetamide,
 5 2-(4-((4-(Ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide,
 2-(4-((4-(Ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide,
 2-(4-((4-(cyclobutyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide,
 10 2-(4-(((6-(ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide, and
 2-(4-((4-(ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide.

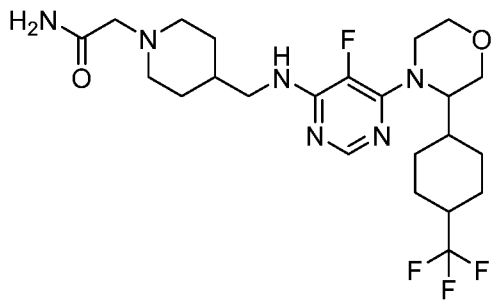
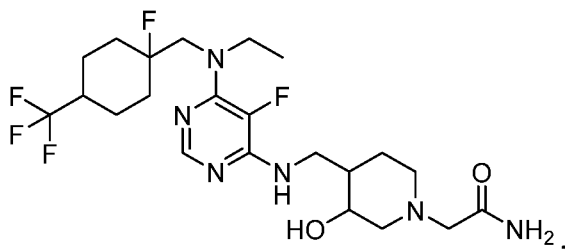
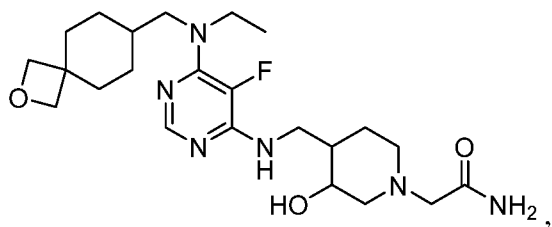
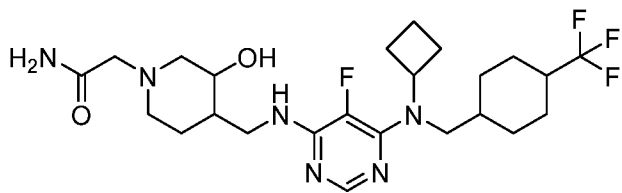
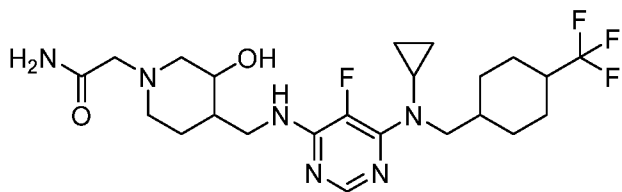
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In one embodiment, the compound, salt, stereoisomer, or salt of the stereoisomer of Formula (I) is selected from the group consisting of:

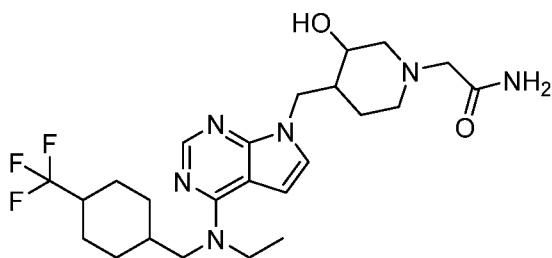


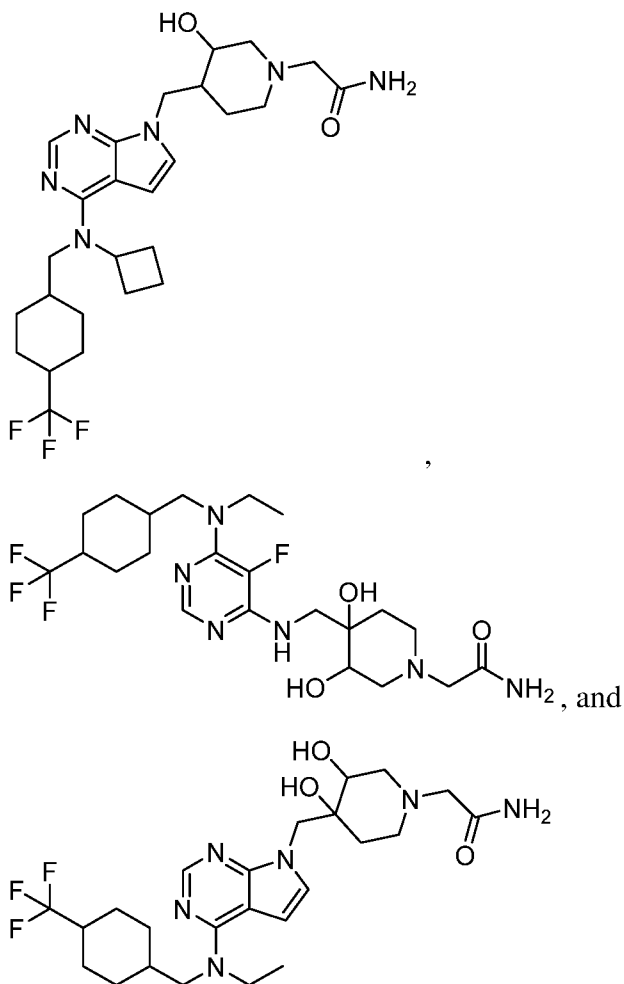
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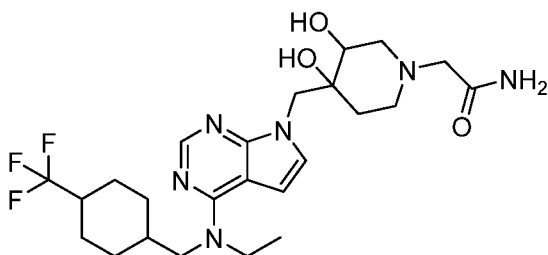
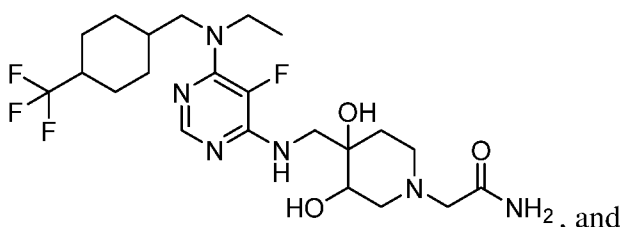
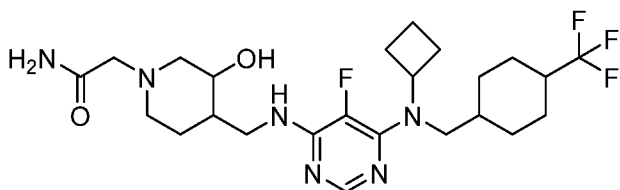
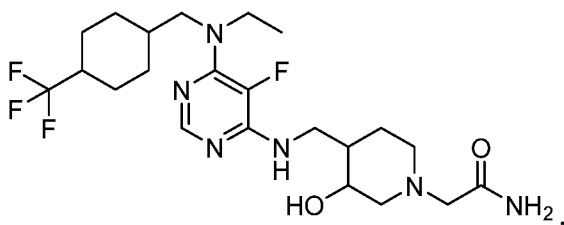


- 5 In one embodiment, the compound, salt, stereoisomer, or salt of the stereoisomer of Formula (I) is selected from the group consisting of:
- 2-((3*R**,4*R**)-4-(((6-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 2-((3*RS*,4*RS*)-4-(((6-(cyclobutyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 10 2-((3*R**,4*R**)-4-(((6-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide, and
- 2-((3*R**,4*R**)-4-(((4-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide.

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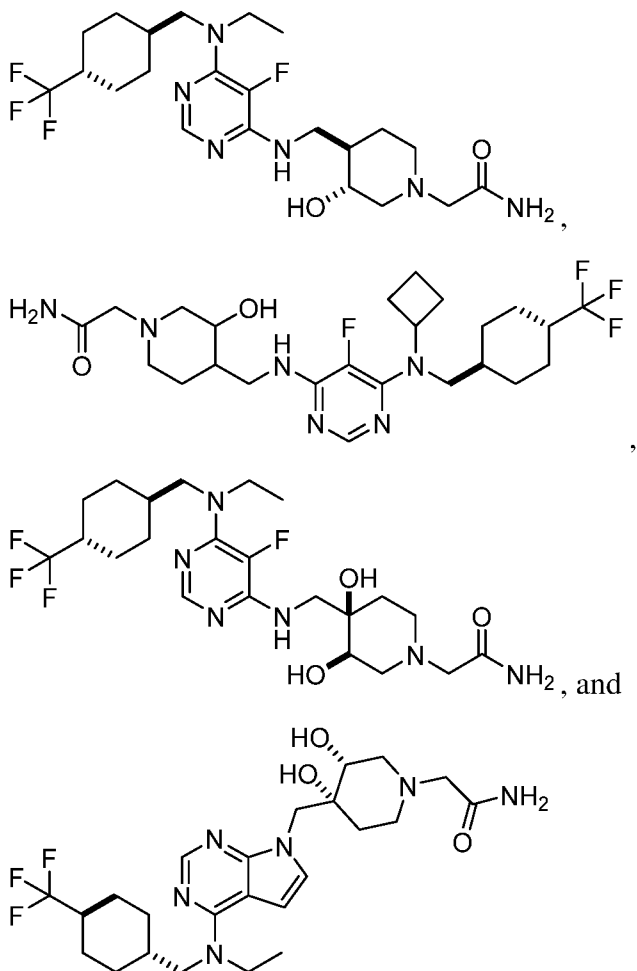
In one embodiment, the compound, salt, stereoisomer, or salt of the stereoisomer of Formula (I) is selected from the group consisting of:

- 2-(4-(((6-(ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
 2-(4-(((6-(cyclobutyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
 5 2-(4-(((6-(ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide, and
 2-(4-((4-(ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide.
- 10 In one embodiment, the compound, salt, stereoisomer, or salt of the stereoisomer of Formula (I) is selected from the group consisting of:



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In one embodiment, the compound, salt, stereoisomer, or salt of the stereoisomer of Formula (I) is selected from the group consisting of:



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In some embodiments whenever a halogen is specified as a substituent the halogen is selected from fluoro or chloro.

Embodiments and particular disclosures used herein are to illustrate different alternatives of the disclosure and embodiments may be combined with other applicable

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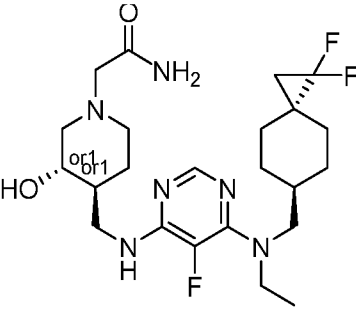
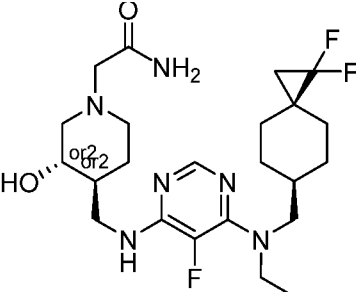
embodiments.

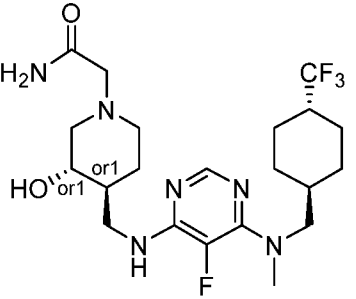
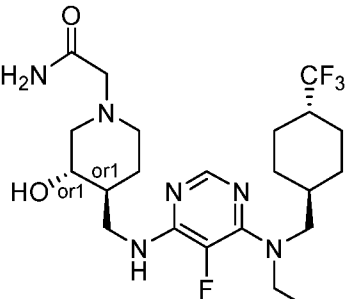
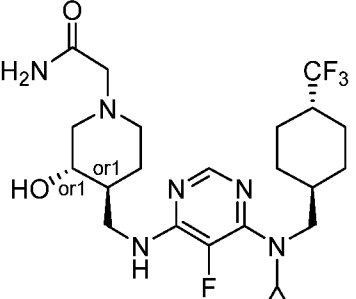
Specific examples of compounds are disclosed in Table 1 below.

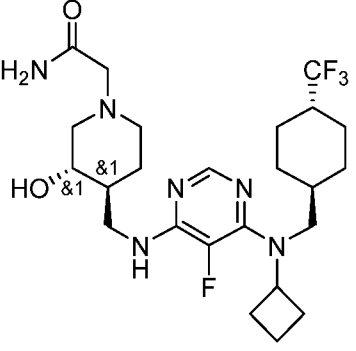
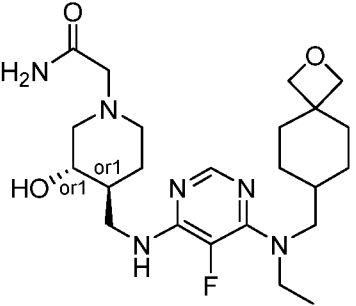
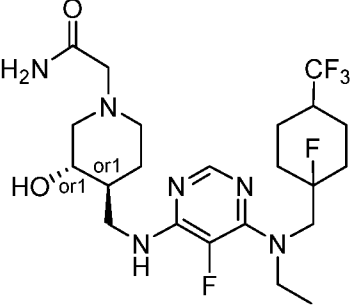
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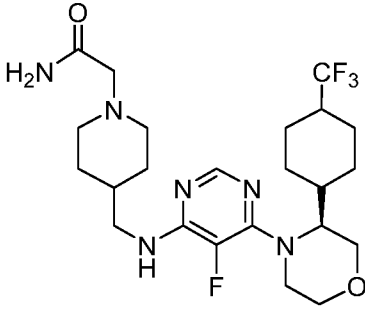
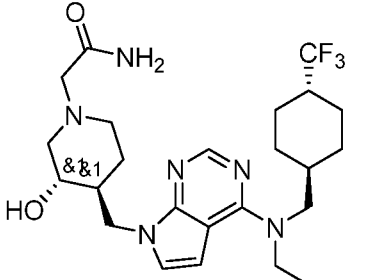
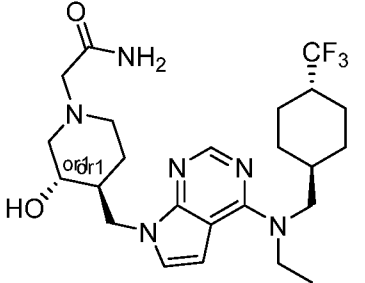
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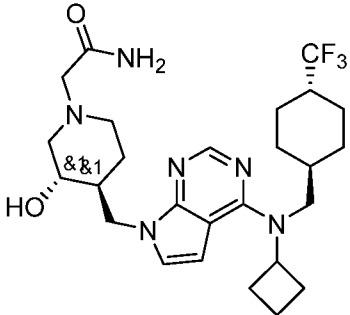
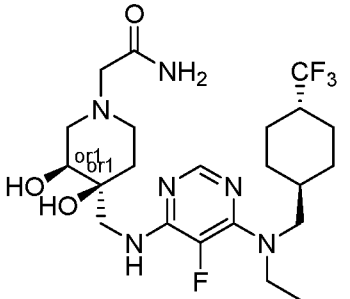
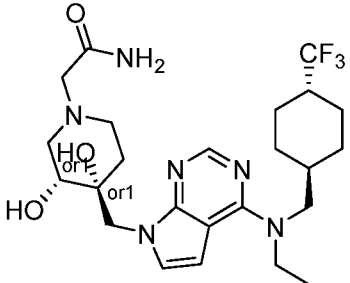
Table 1. Example compounds by Structure and Name.

Example	Structure	Name
A6-1-1-1		<i>rel</i> -2-((3 <i>R</i> ,4 <i>R</i>)-4-(((6-(((1,1-Difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 1 st eluting isomer
A6-1-1-2		<i>rel</i> -2-((3 <i>R</i> ,4 <i>R</i>)-4-(((6-(((1,1-Difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 2 nd eluting isomer
A6-1-2-1		<i>rel</i> -2-((3 <i>R</i> ,4 <i>R</i>)-4-(((6-(((1,1-Difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 1 st eluting isomer
A6-1-2-2		<i>rel</i> -2-((3 <i>R</i> ,4 <i>R</i>)-4-(((6-(((1,1-Difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 2 nd eluting isomer

A6-2-1		2-((3 <i>R</i> *,4 <i>R</i> *)-4-(((5-fluoro-6-(methyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)pyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 1 st eluting isomer
A6-2-2		2-((3 <i>R</i> *,4 <i>R</i> *)-4-(((5-fluoro-6-(methyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)pyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 2 nd eluting isomer
A6-3-1		2-((3 <i>R</i> *,4 <i>R</i> *)-4-(((6-(ethyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 1 st eluting isomer
A6-3-2		2-((3 <i>R</i> *,4 <i>R</i> *)-4-(((6-(ethyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 2 nd eluting isomer
A6-4-1		2-((3 <i>R</i> *,4 <i>R</i> *)-4-(((6-(cyclopropyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 1 st eluting isomer
A6-4-2		2-((3 <i>R</i> *,4 <i>R</i> *)-4-(((6-(cyclopropyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 2 nd eluting isomer

A6-5		2-((3 <i>RS</i> ,4 <i>RS</i>)-4-(((6-(cyclobutyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide
A6-6-1		<i>rel</i> -2-((3 <i>R</i> ,4 <i>R</i>)-4-(((6-(((2-oxaspiro[3.5]nonan-7-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 1 st eluting isomer
A6-6-2		<i>rel</i> -2-((3 <i>R</i> ,4 <i>R</i>)-4-(((6-(((2-oxaspiro[3.5]nonan-7-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 2 nd eluting isomer
A6-7-1		<i>rel</i> -2-((3 <i>R</i> ,4 <i>R</i>)-4-(((6-(ethyl((1-fluoro-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 1 st eluting isomer
A6-7-2		<i>rel</i> -2-((3 <i>R</i> ,4 <i>R</i>)-4-(((6-(ethyl((1-fluoro-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 2 nd eluting isomer

A6-8-1		2-(4-(((5-fluoro-6-((3 <i>S</i>)-3-(4-(trifluoromethyl)cyclohexyl)morpholin-4-yl)amino)methyl)piperidin-1-yl)acetamide 1 st eluting isomer
A6-8-2		2-(4-(((5-fluoro-6-((3 <i>S</i>)-3-(4-(trifluoromethyl)cyclohexyl)morpholin-4-yl)amino)methyl)piperidin-1-yl)acetamide 2 nd eluting isomer
B6-1		2-((3 <i>RS</i> ,4 <i>RS</i>)-4-((4-(Ethyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide
B6-1-1		2-((3 <i>R</i> [*] ,4 <i>R</i> [*])-4-((4-(Ethyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide 1 st eluting isomer
B6-1-2		2-((3 <i>R</i> [*] ,4 <i>R</i> [*])-4-((4-(Ethyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide 2 nd eluting isomer

B6-2		2-((3 <i>RS</i> ,4 <i>RS</i>)-4-((4-(cyclobutyl(((1 <i>r</i> ,4 <i>S</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide
AD-6-1		2-((3 <i>R</i> *,4 <i>R</i> *)-4-(((6-(ethyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide 1 st eluting isomer
AD-6-2		2-((3 <i>R</i> *,4 <i>R</i> *)-4-(((6-(ethyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide 2 nd eluting isomer
BD-5-1-1		2-((3 <i>R</i> *,4 <i>R</i> *)-4-((4-(ethyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide 1 st eluting isomer
BD-5-1-2		2-((3 <i>R</i> *,4 <i>R</i> *)-4-((4-(ethyl(((1 <i>r</i> ,4 <i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide 2 nd eluting isomer

In a related aspect there is provided a prodrug of a compound of Formula (I) as described herein.

The compounds of the present disclosure are active, e.g. having a ROR_y Gal4 < 5 1000 nM, such as < 500 nM, such as < 100 nM.

According to an embodiment, compounds having $IC_{50} < 1000$ nM values in the Gal4 assay are disclosed herein.

According to another preferred embodiment, compounds having $IC_{50} < 500$ nM values in the Gal4 assay are disclosed herein.

5 According to another more preferred embodiment, compounds having $IC_{50} < 100$ nM values in the Gal4 assay are disclosed herein.

Pharmaceutical Compositions

In another aspect, the present disclosure relates to a pharmaceutical composition
10 comprising physiologically acceptable surface active agents, carriers, diluents, excipients, smoothing agents, suspension agents, film forming substances, and coating assistants, or a combination thereof; and a compound as disclosed herein, .e.g., a compound of Formulae (I), (II), (III), (IV), (V), (VI), and (VII) as disclosed herein, or a salt, stereoisomer, or salt of a stereoisomer thereof. The compound of Formulae (I), (II), (III),
15 (IV), (V), (VI), and (VII) included in the pharmaceutical composition may also be any compound of the preferred embodiments described above. In another aspect, the present disclosure relates to a pharmaceutical composition comprising physiologically acceptable surface active agents, carriers, diluents, excipients, smoothing agents, suspension agents, film forming substances, and coating assistants, or a combination thereof; and a
20 compound of any one of Formulae (I), (II), (III), (IV), (V), (VI), and (VII) as disclosed herein. Acceptable carriers or diluents, as well as other additives to be combined with one or more compound(s) of Formula (I), (II), (III), (IV), (V), (VI), and (VII) as disclosed herein to provide a pharmaceutical composition, for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical
25 Sciences, 18th Ed., Mack Publishing Co., Easton, PA (1990), which is incorporated herein by reference in its entirety. Preservatives, stabilizers, dyes, sweeteners, fragrances, flavoring agents, taste masking agents, and the like may be provided in the pharmaceutical composition. For example, sodium benzoate, ascorbic acid and esters of p-hydroxybenzoic acid may be added as preservatives. In addition, antioxidants and
30 suspending agents may be used. In various embodiments, alcohols, esters, sulfated aliphatic alcohols, and the like may be used as surface active agents; sucrose, glucose, lactose, starch, crystallized cellulose, mannitol, light anhydrous silicate, magnesium

aluminate, magnesium methasilicate aluminate, synthetic aluminum silicate, calcium carbonate, sodium acid carbonate, calcium hydrogen phosphate, calcium carboxymethyl cellulose, and the like may be used as excipients; magnesium stearate, talc, hardened oil and the like may be used as smoothing agents; coconut oil, olive oil, sesame oil, peanut oil, soya may be used as suspension agents or lubricants; cellulose acetate phthalate as a derivative of a carbohydrate such as cellulose or sugar, or methylacetate-methacrylate copolymer as a derivative of polyvinyl may be used as suspension agents; and plasticizers such as ester phthalates and the like may be used as suspension agents.

The term “pharmaceutical composition” refers to a mixture of a compound disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, injection, aerosol, parenteral, and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Similar, pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic bases, such as ammonia, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, and the like.

The term “carrier” defines a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example, and without limitation dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

The term “diluent” defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the salt conditions of human blood. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

The term “physiologically acceptable” defines a carrier or diluent that does not abrogate the biological activity and properties of the compound.

The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other

active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

5 Suitable routes of administration may, for example, include oral, rectal, transmucosal, topical, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections. The compounds can also be administered in sustained or controlled release dosage forms,
10 including depot injections, osmotic pumps, pills, transdermal (including electrotransport) patches, and the like, for prolonged and/or timed, pulsed administration at a predetermined rate.

 The pharmaceutical compositions may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making,
15 levigating, emulsifying, encapsulating, entrapping or tableting processes.

 Pharmaceutical compositions for use as described herein may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon
20 the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

 Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or
25 as emulsions. Suitable excipients are, for example, water, saline, dextrose, mannitol, lactose, lecithin, albumin, sodium glutamate, cysteine hydrochloride, and the like. In addition, if desired, the injectable pharmaceutical compositions may contain minor amounts of nontoxic auxiliary substances, such as wetting agents, pH buffering agents, and the like. Physiologically compatible buffers include, but are not limited to, Hanks's
30 solution, Ringer's solution, or physiological saline buffer. If desired, absorption enhancing preparations (for example, liposomes), may be utilized.

 For transmucosal administration, penetrants appropriate to the barrier to be permeated may be used in the formulation.

Pharmaceutical formulations for parenteral administration, *e.g.*, by bolus injection or continuous infusion, include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or other organic oils such as soybean, grapefruit or almond oils, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds disclosed herein to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent

mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use as described herein are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Further disclosed herein are various pharmaceutical compositions well known in the pharmaceutical art for uses that include intraocular, intranasal, and intraauricular delivery. Suitable penetrants for these uses are generally known in the art. Topical ophthalmic compositions may be formulated as a solution in water buffered at a pH of 5.0 to 8.0. Other ingredients that may be desirable to use in the ophthalmic preparations include preservatives (such as benzalkonium chloride, stabilized oxychloro complex, which is sold as Purite™, or stabilized chlorine dioxide), cosolvents (such as polysorbate 20, 60 and 80, Pluronic® F-68, F-84 and P-103, cyclodextrin, or Solutol) and viscosity-

building agents (such as polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, or hydroxypropyl cellulose). The compounds disclosed herein may also be used in an intraocular implant as described in U.S. Patent 7,931,909 which is hereby incorporated
5 by reference. Pharmaceutical compositions for intraocular delivery include aqueous ophthalmic solutions of the active compounds in water-soluble form, such as eyedrops, or in gellan gum (Shedden et al., *Clin. Ther.*, 23(3):440-50 (2001)) or hydrogels (Mayer et al., *Ophthalmologica*, 210(2):101-3 (1996)); ophthalmic ointments; ophthalmic suspensions, such as microparticulates, drug-containing small polymeric particles that are
10 suspended in a liquid carrier medium (Joshi, A., *J. Ocul. Pharmacol.*, 10(1):29-45 (1994)), lipid-soluble formulations (Alm et al., *Prog. Clin. Biol. Res.*, 312:447-58 (1989)), and microspheres (Mordenti, *Toxicol. Sci.*, 52(1):101-6 (1999)); and ocular inserts. All of the above-mentioned references, are incorporated herein by reference in their entireties. Such suitable pharmaceutical formulations for intraocular delivery are
15 most often and preferably formulated to be sterile, isotonic and buffered for stability and comfort. Pharmaceutical compositions for intranasal delivery may also include drops and sprays often prepared to simulate in many respects nasal secretions to ensure maintenance of normal ciliary action. As disclosed in Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, PA (1990), which is incorporated herein by reference in its
20 entirety, and well-known to those skilled in the art, suitable formulations are most often and preferably isotonic, slightly buffered to maintain a pH of 5.5 to 6.5, and most often and preferably include antimicrobial preservatives and appropriate drug stabilizers. Pharmaceutical formulations for intraauricular delivery include suspensions and ointments for topical application in the ear. Common solvents for such aural formulations
25 include glycerin and water.

The compounds disclosed herein may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be
30 formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion

exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For hydrophobic compounds, a suitable pharmaceutical carrier may be a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. A common cosolvent system used is the VPD co-solvent system, which is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of POLYSORBATE 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

Agents intended to be administered intracellularly may be administered using techniques well known to those of ordinary skill in the art. For example, such agents may be encapsulated into liposomes. All molecules present in an aqueous solution at the time of liposome formation are incorporated into the aqueous interior. The liposomal contents are both protected from the external micro-environment and, because liposomes fuse with cell membranes, are efficiently delivered into the cell cytoplasm. The liposome may be coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the desired organ. Alternatively, small hydrophobic organic molecules may be directly administered intracellularly.

Additional therapeutic or diagnostic agents may be incorporated into the pharmaceutical compositions. Alternatively or additionally, pharmaceutical compositions may be combined with other compositions that contain other therapeutic or diagnostic agents.

5

Combinations

The compounds disclosed herein may also be combined with other active compounds in the treatment and/or prevention of inflammatory, metabolic, oncologic and autoimmune diseases or disorders or a symptom thereof.

10

The combinations provided herein comprise the compounds disclosed herein and one or more additional active substances, such as:

- 15 a) Corticosteroids, such as prednisone, methylprednisolone or betamethasone;
- b) Immunosuppressants, such as cyclosporine, tacrolimus, methotrexate, hydroxyurea, mycophenolate mofetil, mycophenolic acid, sulfasalazine, 6-thioguanine or azathioprine;
- c) Fumaric acid esters, such as dimethyl fumarate;
- 20 d) Dihydroorotate dehydrogenase (DHODH) inhibitors such as leflunomide;
- e) Retinoids, such as acitretin or isotretinoin;
- f) Anti-inflammatories such as apremilast, crisaborole, celecoxib, diclofenac, aceclofenac, aspirin or naproxen;
- 25 g) JAK inhibitors such as tofacitinib, baricitinib, upadacitinib, ruxolitinib or delgocitinib;
- h) Antibiotics such as gentamicin;
- i) Anti-cancer agents such as lenalidomide, pomalidomide, pembrolizumab, nivolumab, daratumumab, bortezomib, carfilzomib, ixazomib, bendamustine or ventoclast;
- 30 j) T-cell blockers such as alefacept or efalizumab;
- k) Tumor necrosis factor-alpha (TNF-alpha) blockers such as etanercept, adalimumab, infliximab, golimumab, certolizumab pegol;

- l) interleukin 12/23 blockers such as ustekinumab;
- m) IL-23 blockers such as risankizumab, guselkumab or tildrakizumab;
- n) anti-IL4/IL13 antagonist such as dupilumab, lebrikizumab or tralokinumab;
- 5 o) IL-1 β blockers such as canakinumab;
- p) IL-alpha blockers such as bermekimab;
- q) CD6 blockers such as itolizumab;
- r) IL-36R blockers such as BI-655130 or bimekizumab;
- s) IL-6 antagonist such as tocilizumab;
- 10 t) Calcineurin inhibitors such as pimecrolimus, tacrolimus or cyclosporine;
- u) Phototherapy agents commonly employed in phototherapy such as psoralen, methoxypsoralen or 5-methoxypsoralen + UVA (PUVA) or treatment with UVB (with or without tar);
- 15 v) Fixed combinations of corticosteroids and vitamin D derivatives;
- w) Fixed combinations of corticosteroids and retinoids;
- x) Corticosteroid tapes; and
- y) one or more agents selected from the group consisting of BMS986165, PF-06700841, PF-06826647, piclidenoson, tepilamide fumarate, LYC-30937, LEO-
 20 32731, BI-730357, PRCL-02, LNP-1955, GSK-2982772, CBP-307, KD-025, MP-1032, petesicatib, JTE-451, Hemay-005, SM-04755, EDP-1815, BI-730460, SFA-002 ER, JNJ-3534, SAR-441169, BOS-172767, SCD-044, ABBV-157, BAY-1834845, AUR-101, R-835, PBF-1650, RTA-1701, AZD-0284, mirikizumab, CD20 antagonist, salicylic acid, coal tar, Mical-1, DUR-928, AM-001, BMX-010, TA-102, SNA-125, brepocitinib
 25 tosylate, pegcantratinib, ESR-114, NP-000888, SM-04755, BOS-475, SB-414, LEO-134310, CBS-3595, PF-06763809, XCUR-17 or BTX-1308.

The active compounds in the combination, i.e the compounds disclosed herein, and the other optional active compounds may be administered together in the same
 30 pharmaceutical composition or in different compositions intended for separate, simultaneous, concomitant or sequential administration by the same or a different route.

Uses

The compounds or pharmaceutical compositions disclosed herein as described above may be used to modulate the activity of a retinoic acid receptor-related orphan receptor (ROR), such as a ROR α , ROR β and/or ROR γ receptor. Modulators of ROR γ have been reviewed by B. Fauber and S. Magnuson in *J. Med. Chem.*, February 6, 2014, and Pandya et al in *J. Med. Chem.* 2018, 61, 24, 10976-10995 which hereby are incorporated by reference in its entirety. Examples of ROR γ receptors are ROR γ 1 and ROR γ t receptors. The compounds or pharmaceutical compositions as described above may also display selective modulation of a particular ROR receptor relative to a different ROR receptor. For example, according to some embodiments disclosed herein some compounds or pharmaceutical compositions modulate the activity of an ROR γ receptor to a larger extent than they modulate the activity of ROR α and/or ROR β receptors.

The compounds or pharmaceutical compositions disclosed herein may also be used to modulate the activity of cells producing IL-17A in a ROR γ t dependent manner, for example, $\gamma\delta$ T cells, Th17 cells, Tc17 cells and ILC3 cells. The compounds or pharmaceutical compositions disclosed herein may also be used to inhibit ROR γ t function upon IL-23 stimulation, which in turn negatively impacts on the differentiation and expansion of pathogenic Tc17 and Th17.

Publications providing useful background information are *Arthritis & Rheumatism*, 2014, 66, 579-588; *Curr Top Microbial Immun*, 2014, 378, 171-182; *Drug Disc. Today*, 2014, May; *Nature Rev. Drug Disc.* 2012, 11, 763-776, and *Nature Rev. Drug Disc.*, 2014, 13, 197-216, all of which are hereby incorporated by reference in their entirety.

The compounds or pharmaceutical compositions as described herein and above may also be used in therapy or may be used to treat inflammatory, metabolic, oncologic and autoimmune diseases or disorders or a symptom thereof. Examples of such diseases or disorders are inflammatory, metabolic, oncologic and autoimmune diseases or disorders mediated or affected by IL-17A and/or ROR γ . The role of ROR γ in the pathogenesis of autoimmune or inflammatory diseases has been disclosed in *Immunity* 2007, 26(5), 643-654; *Nat. Rev. Immunol.* 2006, 6, 205-217; *J. Immunol.* 2009, 183, 7169-7177; *Brain Pathol.* 2004, 14, 164-174; *Brain* 2007, 130, 1089-1104; and *Nat Rev. Immunol.* 2008, 8, 183-192 all of which are hereby incorporated by reference in their entirety.

More specific examples of diseases or disorders, or a symptom thereof include asthma, acne, chronic obstructive pulmonary disease (COPD), bronchitis, atherosclerosis, helicobacter pylori infection, allergic diseases including allergic rhinitis, allergic conjunctivitis and uveitis, sprue and food allergy, atopic dermatitis, lichen planus, cystic
5 fibrosis, lung allograft rejection, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, ichthyoses, bullous diseases, hidradenitis suppurativa, steatosis, steatohepatitis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), lupus erythematosus, Hashimoto's disease, pancreatitis, autoimmune diabetes, autoimmune
10 ocular disease, ulcerative colitis, colitis, Crohn's disease, inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), Sjogren's syndrome, optic neuritis, type I diabetes, neuromyelitis optica, Myasthenia Gravis, Guillain-Barre syndrome, Graves' disease, scleritis, obesity, obesity-induced insulin resistance, type II diabetes and cancer.

More preferably, the diseases or disorders, or a symptom thereof include acne,
15 atopic dermatitis, lichen planus, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, ichthyoses, bullous diseases, hidradenitis suppurativa, ulcerative colitis, colitis, Crohn's disease, inflammatory bowel disease (IBD) and lupus erythematosus.

An example of a symptom is a physical or mental feature which is regarded as
20 indicating a condition of disease, particularly such a feature that is apparent to the patient, e.g. treating or preventing a symptom is not considered disease-modifying but preventing or alleviating one or more symptoms commonly experience in connection with such a disease.

More specifically, compounds or pharmaceutical compositions having an
25 antagonistic or inverse agonistic effect on ROR γ may be used to reduce levels of IL-17A and/or other gene products, such as interleukins, and cytokines, regulated ROR γ . This may for example be in subjects suffering from for example, asthma, acne, chronic obstructive pulmonary disease (COPD), bronchitis, atherosclerosis, helicobacter pylori infection, allergic diseases including allergic rhinitis, allergic conjunctivitis and uveitis,
30 sprue and food allergy, atopic dermatitis, lichen planus, cystic fibrosis, lung allograft rejection, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, ichthyoses, bullous diseases, hidradenitis suppurativa, ankylosing spondylitis, psoriasis, psoriatic arthritis, steatosis, steatohepatitis, non-alcoholic fatty

liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), lupus erythematosus, Hashimoto's disease, pancreatitis, autoimmune diabetes, autoimmune ocular disease, ulcerative colitis, colitis, Crohn's disease, inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), Sjogren's syndrome, optic neuritis, type I diabetes, 5 neuromyelitis optica, Myasthenia Gravis, Guillain-Barre syndrome, Graves' disease, scleritis, obesity, obesity-induced insulin resistance and type II diabetes.

Conversely, compounds or pharmaceutical compositions having an agonistic effect on ROR γ may be used to increase IL-17A levels. Increasing IL-17A levels may be particularly useful in immune compromised conditions or boosting the immune system 10 response for example during infections and in cancer.

The compounds described herein may be used in the manufacture of a medicament for the treatment and/or prevention of inflammatory, metabolic, oncologic and autoimmune diseases or disorders or a symptom thereof.

Methods of Administration

15 The compounds or pharmaceutical compositions may be administered to the patient by any suitable means. Non-limiting examples of methods of administration include, among others, (a) administration through oral pathways, which administration includes administration in capsule, tablet, granule, spray, syrup, or other such forms; (b) administration through non-oral pathways such as rectal, vaginal, intraurethral, 20 intraocular, intranasal, or intraauricular, which administration includes administration as an aqueous suspension, an oily preparation or the like or as a drip, spray, suppository, salve, ointment or the like; (c) administration via injection, subcutaneously, intraperitoneally, intravenously, intramuscularly, intradermally, intraorbitally, intracapsularly, intraspinally, intrasternally, or the like, including infusion pump delivery; 25 (d) administration locally such as by injection directly in the renal or cardiac area, e.g., by depot implantation, by intratumoral injection, or by intra-lymph node injection; (e) administration topically; as well as as well as (f) administration to cells *ex vivo* followed by insertion of said cells into the patient; as deemed appropriate by those of skill in the art for bringing the compound disclosed herein into contact with living tissue.

30 Pharmaceutical compositions suitable for administration include compositions where the active ingredients are contained in an amount effective to achieve its intended purpose. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including

mammal, e.g. human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

As will be readily apparent to one skilled in the art, the useful *in vivo* dosage to be administered and the particular mode of administration will vary depending upon the age, weight and mammalian species treated, the particular compounds employed, and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine pharmacological methods. Typically, human clinical applications of products are commenced at lower dosage levels, with dosage level being increased until the desired effect is achieved. Alternatively, acceptable *in vitro* studies can be used to establish useful doses and routes of administration of the compositions identified by the present methods using established pharmacological methods.

In non-human animal studies, applications of potential products are commenced at higher dosage levels, with dosage being decreased until the desired effect is no longer achieved or adverse side effects disappear. The dosage may range broadly, depending upon the desired effects and the therapeutic indication.

Typically, dosages may be between about 10 microgram/kg and 100 mg/kg body weight, preferably between about 100 microgram/kg and 10 mg/kg body weight. Alternatively dosages may be based and calculated upon the surface area of the patient, as understood by those of skill in the art.

The exact formulation, route of administration and dosage for the pharmaceutical compositions disclosed herein can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl *et al.* 1975, in "The Pharmacological Basis of Therapeutics", which is hereby incorporated herein by reference in its entirety, with particular reference to Ch. 1, p. 1). Typically, the dose range of the composition administered to the patient can be from about 0.5 to 1000 mg/kg of the patient's body

weight. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the patient. In instances where human dosages for compounds have been established for at least some condition, those same dosages may be used, or dosages that are between about 0.1% and 500%, more preferably between about 25% and 250% of the established human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compounds, a suitable human dosage can be inferred from ED₅₀ or ID₅₀ values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

10 It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps the dose frequency will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

20 Although the exact dosage will be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an adult human patient may be, for example, an oral dose of between 0.1 mg and 2000 mg of each active ingredient, preferably between 1 mg and 500 mg, e.g. 5 to 200 mg. An ocular eye drop may range in concentration between 0.005 and 5 percent. In one embodiment, an eye drop may range between 0.01 and 1 percent, or between 0.01 and 0.3 percent in another embodiment. In other embodiments, an intravenous, subcutaneous, or intramuscular dose of each active ingredient of between 0.01 mg and 100 mg, preferably between 0.1 mg and 60 mg, e.g. 1 to 40 mg is used. In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. In some 25 30 embodiments, the composition is administered 1 to 4 times per day. Alternatively, the compositions disclosed herein may be administered by continuous intravenous infusion, preferably at a dose of each active ingredient up to 1000 mg per day. As will be understood by those of skill in the art, in certain situations it may be necessary to

administer the compounds disclosed herein in amounts that exceed, or even far exceed, the above-stated, preferred dosage range or frequency in order to effectively and aggressively treat particularly aggressive diseases or infections. In some embodiments, the compounds will be administered for a period of continuous therapy, for example for
5 a week or more, or for months or years.

Dosage amount and interval may be adjusted individually to provide plasma or tissue levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data. Dosages necessary to achieve the MEC will depend
10 on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

15 In cases of local or *ex vivo* administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

The amount of composition administered may be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

20 Compounds disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be established by determining *in vitro* toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals,
25 or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, or monkeys, may be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as *in vitro* methods, animal models, or human clinical trials. Recognized *in vitro* models exist for nearly every class of condition, including but not
30 limited to cancer, cardiovascular disease, and various immune dysfunction. Similarly, acceptable animal models may be used to establish efficacy of chemicals to treat such conditions. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, and route of

administration, and regime. Of course, human clinical trials can also be used to determine the efficacy of a compound in humans.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound disclosed herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

15 *General remarks*

As described above with reference to specific illustrative embodiments, it is not intended to be limited to the specific form set forth herein. Any combination of the above mentioned embodiments should be appreciated as being within the scope of the disclosure. Rather, the disclosure is limited only by the accompanying claims and other embodiments than the specific above are equally possible within the scope of these appended claims.

In the claims, the term “comprises/comprising” does not exclude the presence of other species or steps. Additionally, although individual features may be included in different claims, these may possibly advantageously be combined, and the inclusion in different claims does not imply that a combination of features is not feasible and/or advantageous. In addition, singular references do not exclude a plurality. The terms “a”, “an”, “first”, “second” etc. do not preclude a plurality. The phrases “at least one” or “one or more” refer to 1 or a number greater than 1, such as to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

Whenever a chemical name or structure has been given it has been generated by conventional means or by means of a suitable software. Names for the compounds were generated with ChemDraw Professional, version 17.1.0.105 (19).

In the present disclosure, in the drawings of the structures, the labels “or1”, “or2”, “&1”, or “&2” at each stereogenic center specify the “stereochemical group” to which the center belongs.

In the case of the “or” groups, the meaning is a structure that represents one stereoisomer that has either the “stereochemical group” as drawn ((R, S), for instance) or the stereoisomer in which the stereogenic centers of the group have the opposite configuration (S, R).

In the case of the “&” groups, & in combination with the number given (e.g. &1) indicate a mixture of the marked asymmetrically substituted atoms. When the numbering pools several asymmetrically substituted atoms together this displays their configuration relative to each other. If they are displayed as (R,S) the opposite configuration (S,R) is also present for the specified pooled group.

In the present disclosure, the symbol “ ^ ” specifies enantiomerically enriched. Any compound or intermediate synthesized in an enantiomerically enriched manner and where no chiral separation has been performed is identified with “ ^ ”.

Experimental

The following examples are mere examples and should by no means be interpreted to limit the scope of the disclosure. Rather, the disclosure is limited only by the accompanying claims.

General Chemical Procedures

General

Unless otherwise stated, starting materials were obtained from commercial suppliers, such as (but not limited to); AbBchem, ABCR, Alfa Aesar, Anaspec, Anichem, Apollo Scientific, ASDI-Inter, Asiba Pharmatech, Astatech, ArkPharm, Bachem, Chem-Impex, ChemCollect, Chembridge, Combi-Blocks, Enamine, FCH, Fluka, Fluorochem, Frontier Scientific, HDH Pharma, InFarmatik, InterBioScreen, Life Chemicals, Manchester organics, Matrix, MercaChem, NetChem, Oakwood Chemical, PepTech, Pharmcore, PrincetonBio, Sigma-Aldrich, TRC, Tyger Scientific and Ukrorgsyn, and were used without further purification. Solvents such as DMF, DMSO and DCM, etc were used directly or dried over molecular sieves.

Equipment

NMR

¹H NMR spectra were recorded on the following; Bruker Avance 300 spectrometer (at 300 MHz), Bruker Avance III 400 spectrometer (at 400 MHz), Bruker Avance Neo (400 MHz), Bruker Avance III 600 (at 600 MHz), Varian VNMR spectrometer (at 400 MHz) using CD₃OD, CDCl₃ or DMSO-*d*₆ solvents. Chemical shifts are reported in ppm (δ) using residual solvent as an internal standard; CDCl₃: 7.26 ppm; CD₃OD: 3.31; DMSO-*d*₆: 2.50 ppm. Coupling constants (*J*) are given in Hz.

Analytical U/HPLC

The following equipment was used for analytical U/HPLC:

Waters Acquity system equipped with an Acquity BEH C18 (1.7μm, 2.1 x 50 mm) with a linear gradient of a binary solvent system using a flow rate of 0.5 mL/min and DAD at ambient temperature, combined with MS detection SQD I.

Agilent Infinity I/II -TOF6230B /CLND Antek 8060 equipped with Acquity BEH C18 (1.7μm, 2.1 x 50 mm) with a linear gradient of a binary solvent system using a flow rate of 0.75 mL/min combined with DAD.

Agilent 1200series-1260 Infinity equipped with a Waters XBridge C18 (5μm, 4.6 x 50 mm) with a linear gradient of a binary solvent system using a flow rate of 1.5 mL/min and UV detection at 214 nm or 254 nm, combined with MS detection (Agilent).

Shimadzu Nexera equipped with a Waters XBridge C18 (5μm, 4.6 x 50 mm) with a linear gradient of a binary solvent system using a flow rate of 1.5 mL/min and UV detection at 214 nm or 254 nm, combined with MS detection (Shimadzu).

Waters Acquity system equipped with an Acquity BEH C18 (1.7μm, 2.1 x 50 mm) with a linear gradient of a binary solvent system using a flow rate of 0.65 mL/min and DAD at ambient temperature, combined with MS detection Waters spectrometer.

Preparative HPLC

The following equipment was used for Prep-HPLC:

Waters Acquity system equipped with a Supelco DISCOVERY C18 (5μm, 25 cm x 21.2 mm), with a linear gradient of a binary solvent system using a flow rate of 45 mL/min and UV detection at 254 nm, combined with MS detection on a Waters Micromass ZQ Quadrupole MS.

Shimadzu Nexera X2 equipped with a Merck Chromolith SpeedROD RP-18E (5μm, 10 x 100 mm) with a linear gradient of a binary solvent system using a flow rate between 4 and 7 mL/min and UV detection at 254 nm, combined with MS detecting on a Shimadzu LCMS-2020.

Waters Masslynx system equipped with a Waters XBridge C18 column (5 μ m, 19 x 150 mm) with a linear gradient of a binary solvent system using a flow rate of 15 mL/min and UV detection at 214 nm or 254 nm, combined with MS detection (Waters).

5 Gilson GX-281 TRILUTION equipped with a Phenomenex Gemini NX-C18 column (5 μ m, 21.2 x 150 mm) with a linear gradient of a binary solvent system using a flow rate of 15 mL/min and UV detection at 214 nm or 254 nm, combined with MS detection (Waters).

The following linear gradients have been used:

HCO₂H - (H₂O/CH₃CN/HCO₂H (100/0/0.1% to 0/100/0.1%))
 10 NH₄OAc – (H₂O/CH₃CN/NH₄OAc (100/0/0.02% to 0/100/0.02%))
 TFA – (H₂O/CH₃CN/TFA (100/0/0.1% to 0/100/0.1%))
 NH₄HCO₃ – (H₂O/CH₃CN/NH₄HCO₃ (100/0/0.1% to 0/100/0.1%))
 NH₄OH – (H₂O/CH₃CN/NH₄OH (100/0/0.1% to 0/100/0.1%))
 HCO₂ NH₄ – (H₂O/50%MeOH+50%CH₃CN/HCO₂H/NH₃ (95/5/0.05%/0.01% to
 15 5/95/0.05%/0.01%))

Flash CC was most often performed on an Isolera® automated systems. Flash CC and Prep TLC were performed employing SiO₂, if not otherwise mentioned. However, C18 columns have also been employed (using a gradient of water-acetonitrile/MeOH (1:1), with or without 0.1% v/v ammonium formate in both phases,
 20 from 0% to 100% acetonitrile/MeOH (1:1)).

Analytical Chiral Chromatography

Was performed on a Waters UPC2 system coupled to a DAD detector and a Waters QDa MS detector, equipped with a chiral column with gradient elution using a flow rate of 1 mL/min. The available chiral columns were CHIRALPAK (3 μ m, 4.6 x
 25 100 mm) IA, IB, IC and ID and Trefoil AMY1 (2.5 μ m, 2.1 x 150 mm).

The following linear gradients have been used for analytical UPC2:

CO₂/MeOH/DEA (99/1/0.2% to 60/40/0.2%))
 CO₂/EtOH/DEA (99/1/0.2% to 60/40/0.2%))
 CO₂/IPA/DEA (99/1/0.2% to 60/40/0.2%))

30 Preparative Chiral Chromatography

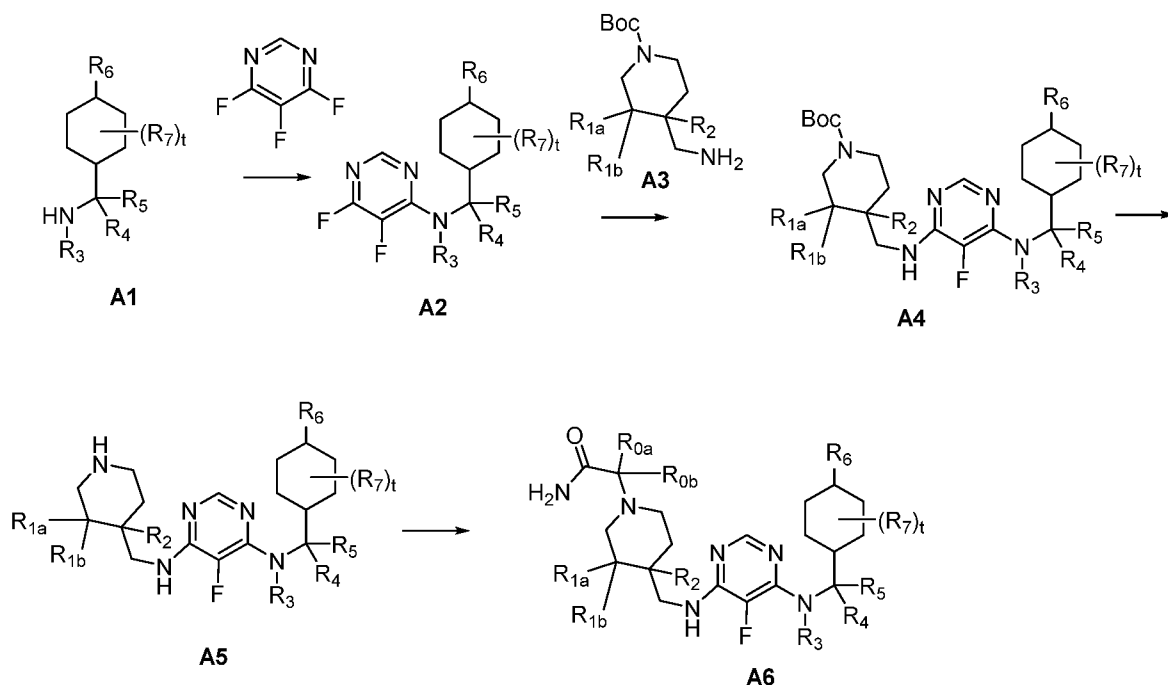
Before chiral separation, compounds were purified by the standards methods previously described using the appropriate solvents.

Preparative chiral separations were performed either on a Gilson (306, GX-281 trilution, 156-UV/Vis, Waters 3100 MSD), or a Waters SFC-80, equipped with a chiral column with the solvents specified using flow rates between 10-50 mL/min (only 50 g/min for SCF) and detection at either 214 or 230 nm; The available chiral columns were Reprisil AMS (5 μ m, 20mm x 250mm), Lux C2 (5 μ m, 21.2mm x 250mm), Lux C4 (5 μ m, 21.2mm x 250mm), Chiralpak[®] column IA, IB, IC, ID, IF or IG (5 μ m, 20mm x 250mm) or Chiralcel[®] OJ-H or OD-H. Exact column and elution conditions used for each compound are described in the experimental part.

Synthetic Methods

The compounds disclosed herein may be synthesized by one of the following methods

General Method A - Synthesis from Boc-protected piperidines



The secondary amine A1 was reacted with 4,5,6-trifluoropyrimidine (at ambient temperature or slightly above, 30 °C) together with a suitable base (such as; DIEA, TEA or K₂CO₃) at rt. After the reaction was deemed complete the intermediate A2 was worked up and purified by chromatography (Flash CC or HPLC) or used as the crude. Intermediate A2, a base (such as; DIEA, TEA or Cs₂CO₃) and the primary amine A3 were thereafter dissolved in a solvent (such as DMSO or DMSO-water, water, water-ethanol mixtures) and the temperature was increased to 70 – 100 °C on, or until the reaction was considered complete. Workup and purification then gave Intermediate A4, which was

subjected to de-protection. The intermediate from the following Boc-deprotection A5 was most often used directly, as the corresponding pyridinium salt (HCl or TFA), in the alkylation with 2-bromoacetamide and a suitable base, such as DIEA or K₂CO₃.

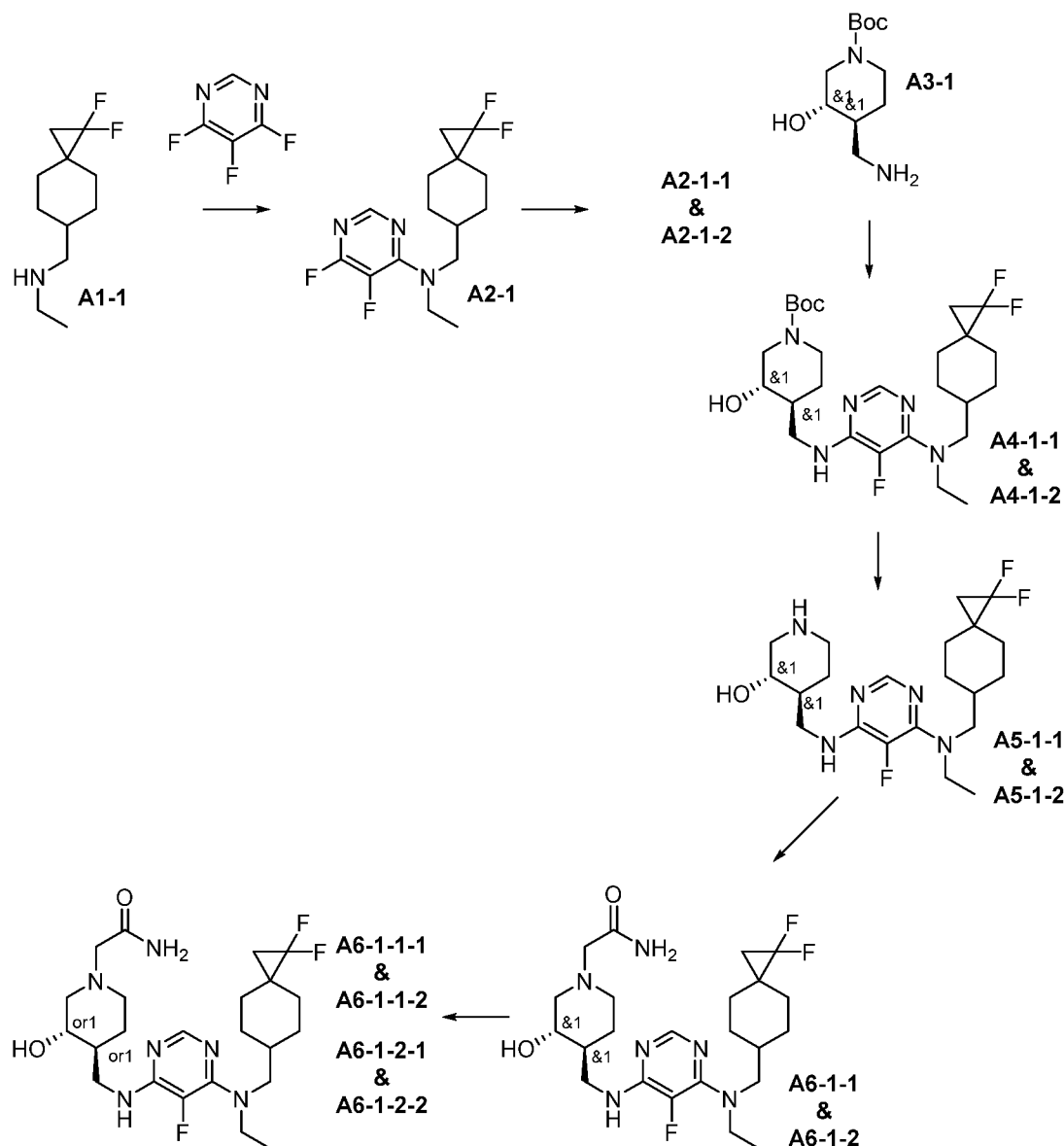
The products A6 were first purified by chromatographic methods (to ensure pure products and to isolate possible diastereomers).

In the cases when the products (or intermediates) were stereoisomers they were often (but not always) subjected to chiral chromatography, to obtain the single stereoisomers as end products.

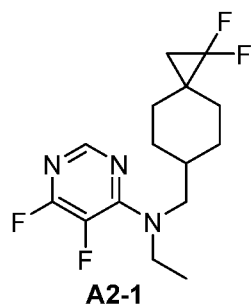
All the compounds in Table A have been synthesized employing this methodology, in ranges from 2 μmol up to ca 1 mol scale.

Example A6-1

Synthesis and isolation of the 4 stereoisomers of *rel*-2-((3*R*,4*R*)-4-(((6-(((1,1-difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)-methyl)-3-hydroxypiperidin-1-yl)acetamide, A6-1-1-1, A6-1-1-2, A6-1-2-1 and A6-1-2-2.



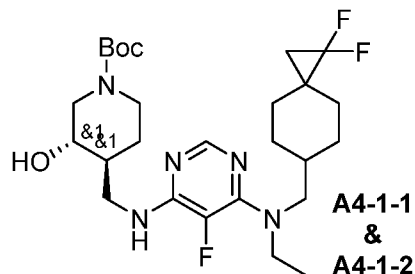
Synthesis of *N*-((1,1-difluorospiro[2.5]octan-6-yl)methyl)-*N*-ethyl-5,6-difluoropyrimidin-4-amine, A2-1, and separation of the stereoisomers A2-1-1 & A2-1-2.



- 5 4,5,6-trifluoropyrimidine (673 mg, 5.0 mmol) and DIEA (1.8 g, 14.1 mmol) were added to a solution of A1-1 (1.1 g, crude) in DMSO (10 mL). The reaction was stirred at ambient temperature on, poured into water (20 mL) and extracted with EA (3 x 20 mL). The combined EA phase was washed with brine (20 mL), dried (Na₂SO₄), filtered and

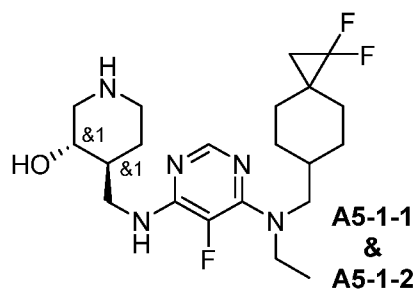
concentrated *in vacuo*. The residue was purified by Flash CC (PE:EA=15:1) to afford the desired product A2-1. After Prep HPLC (CHIRALPAK IC, Hex:IPA= 98:2) two stereoisomers A2-1-1 and A2-1-2 were obtained. MS Calcd (calculated): 317; MS Found: 318 ([M+H]⁺).

- 5 Synthesis of *rac-tert-butyl (3R,4R)-4-(((6-(((1,1-difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidine-1-carboxylate*, A4-1-1 and A4-1-2.



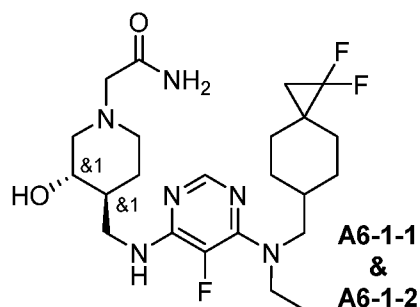
- A3-1 (243 mg, 1.1 mmol) and DIEA (275 mg, 2.1 mmol) were in turn added to a solution of A2-1-1 (223 mg, 0.7 mmol) and the reaction was stirred at 95 °C for 3h. Thereafter H₂O (20 mL) was added and the mixture was extracted with EA (3 x 20 mL). The EA phase was washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to yield crude A4-1-1, which was used without further purification. MS Calcd.: 527; MS Found: 528 ([M+H]⁺). A2-1-2 (525 mg, 1.7 mmol) was treated as outlined for A2-1-1 to yield A4-1-2. MS Calcd.: 527; MS Found: 528 ([M+H]⁺).
- 10
- 15

Synthesis of *rac-(3R,4R)-4-(((6-(((1,1-difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)piperidin-3-ol*, A5-1-1 and A5-1-2.



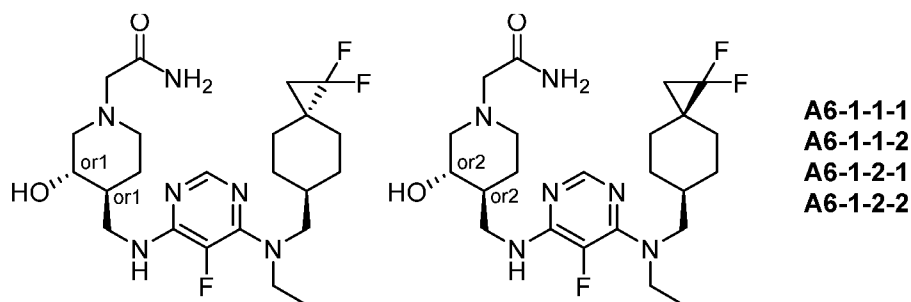
- A4-1-1 (461 mg) was dissolved in HCl/EA (10 mL). The reaction was stirred at ambient temperature for 2h and then concentrated *in vacuo* yield crude A5-1-1, which was used without further purification. MS Calcd.: 427; MS Found: 428 ([M+H]⁺). A4-1-2 (920 mg) was treated as outlined for A4-1-1 to yield crude A5-1-2. MS Calcd.: 427; MS Found: 428 ([M+H]⁺).
- 20

Synthesis of *rac*-2-((3*R*,4*R*)-4-(((6-(((1,1-difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide, A6-1-1 and A6-1-2.



- 5 2-Bromoacetamide (195 mg, 1.4 mmol) and K₂CO₃ (485 mg, 3.5 mmol) were added to a solution of A5-1-1 (440 mg, crude) in DMF (12 mL). The reaction was stirred at 35 °C for 3h. The mixture was poured into H₂O (20 mL), extracted with EA (3 x 20 mL). The combined organic phase was washed with brine (20 mL), and dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was by Flash CC (DCM:MeOH=20:1) to
- 10 yield A6-1-1. 2-Bromoacetamide (457 mg, 3.3 mmol), and K₂CO₃ (1.1 g, 8.3 mmol) were added to a solution of A5-1-2 (910 mg, crude) in DMF (12 mL) and the reaction was stirred at 35 °C for 3h. Then mixture was poured into H₂O (20 mL), extracted with EA (3 x 20 mL). The combined organic phase was washed with brine (20 mL), dried (Na₂SO₄) filtered and concentrated *in vacuo*. The residue was purified by Flash CC
- 15 (DCM:MeOH=20:1) to yield A6-1-2.

rel-2-((3*R*,4*R*)-4-(((6-(((1,1-Difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide, A6-1-1-1, A6-1-1-2, A6-1-2-1 and A6-1-2-2.

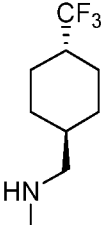
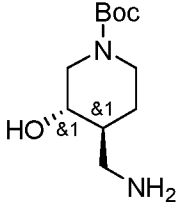
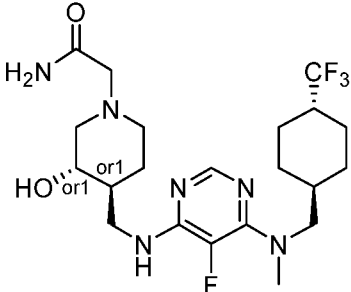
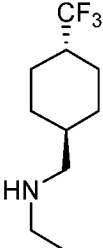
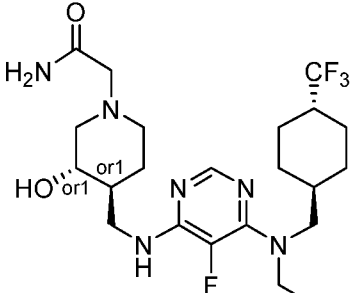


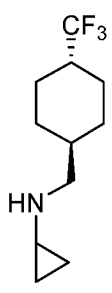
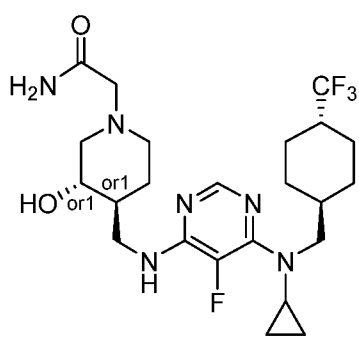
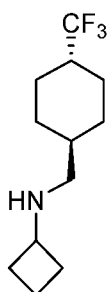
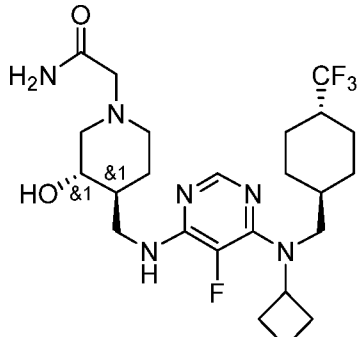
- 20 A6-1-1 (160 mg, 0.33 mmol) was subjected to Chiral-HPLC (CHIRALPAK ID, Hex:EtOH:DEA=70:30:0.3) to yield A6-1-1-1 (1st eluting isomer) and A6-1-1-2 (2nd eluting isomer). A6-1-2 (346mg, 0.72 mmol) was subjected to Chiral-HPLC

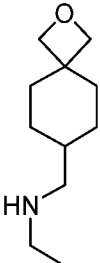
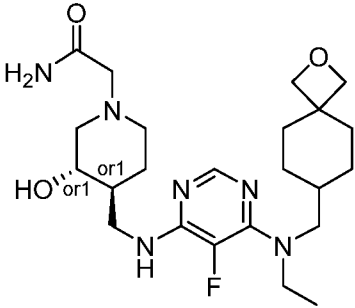
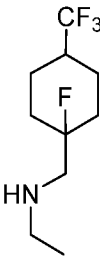
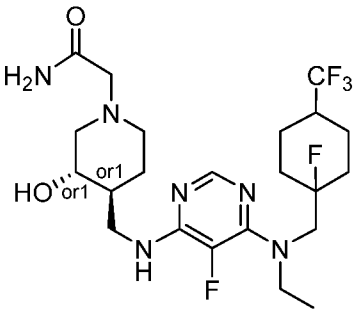
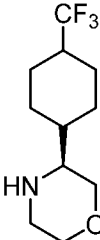
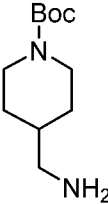
(CHIRALPAK ID, Hex:EtOH:DEA=60:40:0.3) to yield A6-1-2-1 (1st eluting isomer) and A6-1-2-2 (2nd eluting isomer).

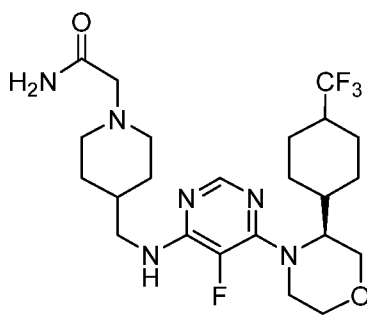
The following compounds in Table A were prepared according to the General Method A.

5 Table A:

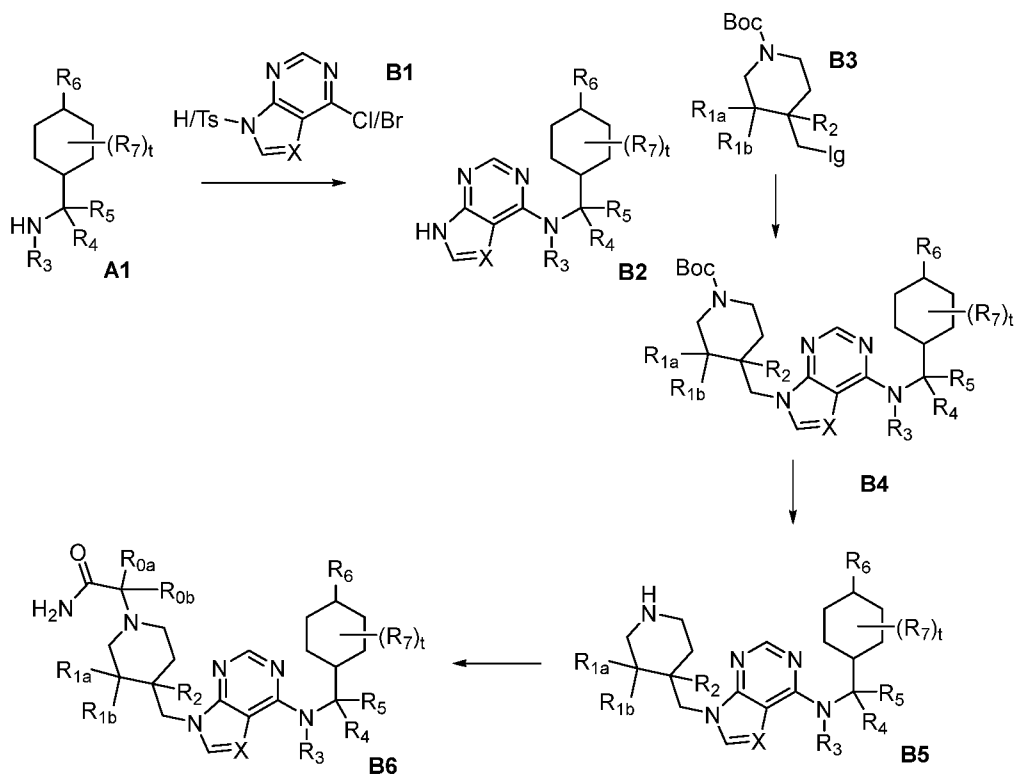
<p>A1 A1-2</p>  <p><i>N</i>-methyl-1-((1<i>r</i>,4<i>r</i>)-4-(trifluoromethyl)cyclohexyl)methanamine</p>	<p>A3 A3-1</p>  <p><i>rac</i>-<i>tert</i>-butyl (3<i>R</i>,4<i>R</i>)-4-(aminomethyl)-3-hydroxypiperidine-1-carboxylate</p>	<p>A6 A6-2-1</p>  <p>2-(((3<i>R</i>[*],4<i>R</i>[*])-4-(((5-fluoro-6-(methyl((1<i>r</i>,4<i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)pyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 1st eluting isomer</p>
<p>A1-2</p>	<p>A3-1</p>	<p>A6-2-2</p> <p>2-(((3<i>R</i>[*],4<i>R</i>[*])-4-(((5-fluoro-6-(methyl((1<i>r</i>,4<i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)pyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 2nd eluting isomer</p>
<p>A1-3</p>  <p><i>N</i>-(((1<i>r</i>,4<i>r</i>)-4-(trifluoromethyl)cyclohexyl)methyl)ethanamine</p>	<p>A3-1</p>	<p>A6-3-1</p>  <p>2-(((3<i>R</i>[*],4<i>R</i>[*])-4-(((6-(ethyl((1<i>r</i>,4<i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 1st eluting isomer</p>
<p>A1-3</p>	<p>A3-1</p>	<p>A6-3-2</p> <p>2-(((3<i>R</i>[*],4<i>R</i>[*])-4-(((6-(ethyl((1<i>r</i>,4<i>R</i>)-4-(trifluoromethyl)cyclohexyl)methyl)amino</p>

)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 2 nd eluting isomer
A1-4  N-(((1r,4r)-4-(trifluoromethyl)cyclohexyl)methyl)cyclopropanamine	A3-1	A6-4-1  2-(((3R*,4R*)-4-(((6-(cyclopropyl(((1r,4R)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 1 st eluting isomer
A1-4	A3-1	A6-4-2 2-(((3R*,4R*)-4-(((6-(cyclopropyl(((1r,4R)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 2 nd eluting isomer
A1-5  N-(((1r,4r)-4-(trifluoromethyl)cyclohexyl)methyl)cyclobutanamine	A3-1	A6-5  2-(((3RS,4RS)-4-(((6-(cyclobutyl(((1r,4R)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide
A1-6	A3-1	A6-6-1

 <p>N-((2-oxaspiro[3.5]nonan-7-yl)methyl)ethanamine</p>		 <p><i>rel</i>-2-((3<i>R</i>,4<i>R</i>)-4-(((6-(((2-oxaspiro[3.5]nonan-7-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 1st eluting isomer</p>
A1-6	A3-1	<p>A6-6-2 <i>rel</i>-2-((3<i>R</i>,4<i>R</i>)-4-(((6-(((2-oxaspiro[3.5]nonan-7-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 2nd eluting isomer</p>
<p>A1-7</p>  <p>N-((1-fluoro-4-(trifluoromethyl)cyclohexyl)methyl)ethanamine</p>	A3-1	<p>A6-7-1</p>  <p><i>rel</i>-2-((3<i>R</i>,4<i>R</i>)-4-(((6-(ethyl((1-fluoro-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 1st eluting isomer</p>
A1-7	A3-1	<p>A6-7-2 <i>rel</i>-2-((3<i>R</i>,4<i>R</i>)-4-(((6-(ethyl((1-fluoro-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide 2nd eluting isomer</p>
<p>A1-8</p> 	<p>A3-2</p> 	A6-8-1

(3S)-3-(4-(trifluoromethyl)cyclohexyl)morpholine	tert-butyl 4-(aminomethyl)piperidine-1-carboxylate	 2-(4-(((5-fluoro-6-((3S)-3-(4-(trifluoromethyl)cyclohexyl)morpholino)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)acetamide 1 st eluting isomer
A1-8	A3-2	A6-8-2 2-(4-(((5-fluoro-6-((3S)-3-(4-(trifluoromethyl)cyclohexyl)morpholino)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)acetamide 2 nd eluting isomer

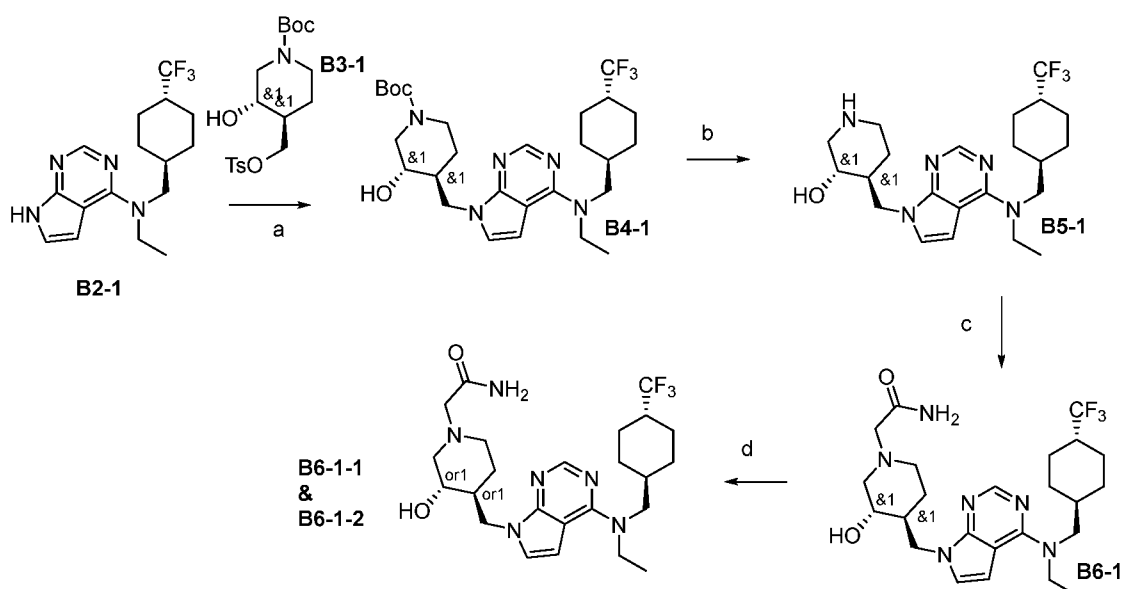
General method B- Synthesis from Boc-protected piperidines.



The secondary amine, A1, was reacted with B1, in a suitable solvent (such as DMF, DMSO, EtOH, BuOH, water) together with a suitable base (such as; DIEA, TEA or K₂CO₃) at an elevated temperature (80-130 °C) in a sealed vessel and often (but not always) with an additive (such as KI). After the reaction was deemed complete the

intermediate B2 was isolated. When B1 was protected, the tosyl group was thereafter removed using K_2CO_3 or NaOH at a slightly elevated temperature (typically 50 °C). B2 was then reacted together with the Boc protected piperidine B3, in a suitable solvent (such as DMF, DMSO, EtOH, BuOH, water) together with a suitable base (such as; Cs₂CO₃, DIEA, TEA or K₂CO₃). B4 was then deprotected using an acid (such as HCl or TFA) in a suitable solvent at room temperature. B5 was most often used directly, as the corresponding pyridinium salt (HCl or TFA), in the alkylation with the corresponding 2-haloacetamides and a suitable base, such as DIEA, TEA, Cs₂CO₃ or K₂CO₃. The products B6 were first purified by chromatographic methods (to ensure pure products and to isolate possible diastereomers). In the cases when the B6 products were racemic (or diastereomeric) they were often (but not always) subjected to chiral resolution (by chromatography) to obtain the single stereoisomers as the end products.

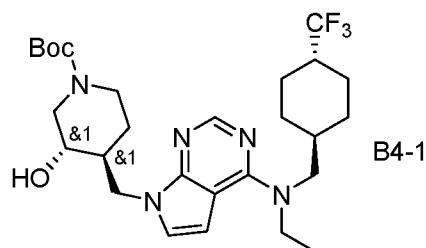
Example B6-1-1 and B6-1-2



15 a) NaH, THF. b) TFA, DCM. c) 2-Bromoacetamide, K₂CO₃, DMF. d)
CHIRALPAK IC (Hex:EtOH:DEA=40:60:0.3).

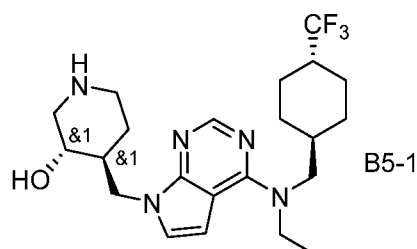
Scheme B6-1

tert-Butyl (3*RS*,4*RS*)-4-((4-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)-methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3-hydroxypiperidine-1-
20 carboxylate, B4-1.



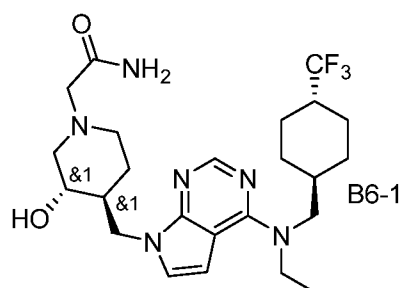
Cs_2CO_3 (757 mg, 0.23 mmol) and B2-1 (250 mg, 0.77 mmol) were added to a solution of B3-1 (356 mg, 0.92 mmol) in DMF (10 mL) and the reaction was heated to 40 °C for 5 h. Then H_2O (100 mL) was added and the mixture was extracted with EA (3 x 80 ml). The combined organic fraction was washed with H_2O (60 mL), brine (60 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by Flash CC (MeOH:DCM = 1:10) to yield B4-1. LCMS: MS Calcd.: 539; MS Found: 540 ($[\text{M}+\text{H}]^+$).

(3*RS*,4*RS*)-4-((4-(Ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)piperidin-3-ol, B5-1.



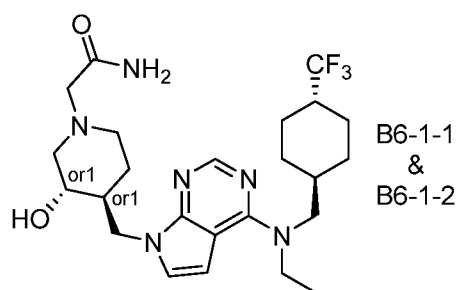
TFA (3 mL) was added to a solution of B4-1 (240 mg, 0.45 mmol) in DCM (3 mL). The reaction was stirred at room temperature for 1 h. The solution was concentrated *in vacuo* to yield crude B5-1 that was used without further purification. LCMS: MS Calcd.: 439; MS Found: 440 ($[\text{M}+\text{H}]^+$).

2-((3*RS*,4*RS*)-4-((4-(Ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide, B6-1.



A mixture of crude B5-1 (290 mg, 0.45 mmol), K₂CO₃ (184 mg, 1.34 mmol) and 2-bromoacetamide (74 mg, 0.53 mmol) in DMF (5 mL) was stirred at 25 °C for 16 h. Then H₂O (40 mL) was added and the resulting mixture was extracted with EA (3 x 40 mL). The combined organic fraction was washed with H₂O (30 mL), brine (30 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by Flash CC (MeOH:DCM =1:10) to obtain B6-1.

2-((3*R**,4*R**)-4-((4-(Ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)-amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide, B6-1-1 and B6-1-2.



10

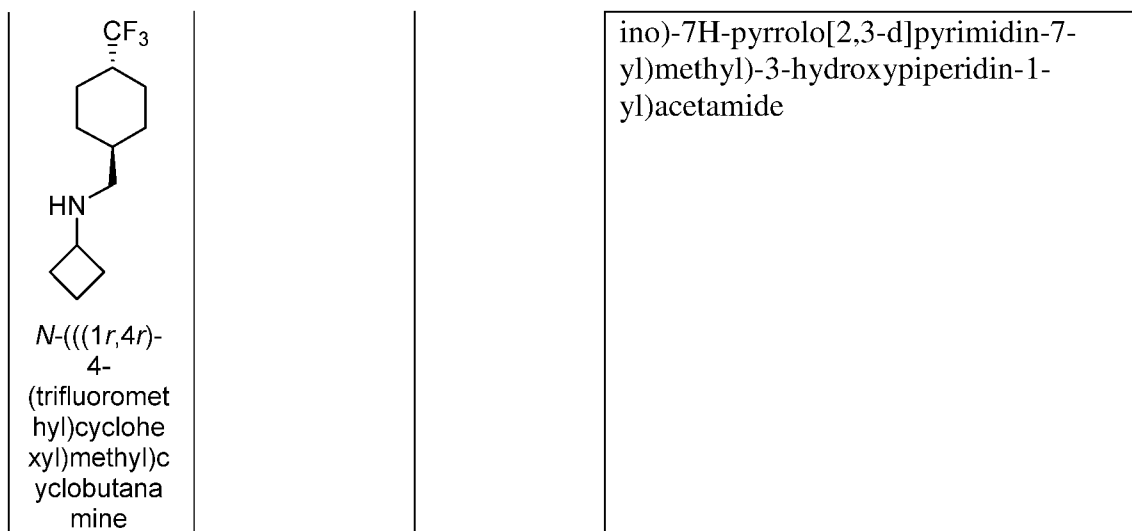
Chiral chromatography (CHIRALPAK IC (Hex:EtOH:DEA=40:60:0.3) of B6-1 gave B6-1-1 (1st eluting isomer) and B6-1-2 (2nd eluting isomer).

The following compounds in Table B were synthesized following general method B using the disclosed starting materials

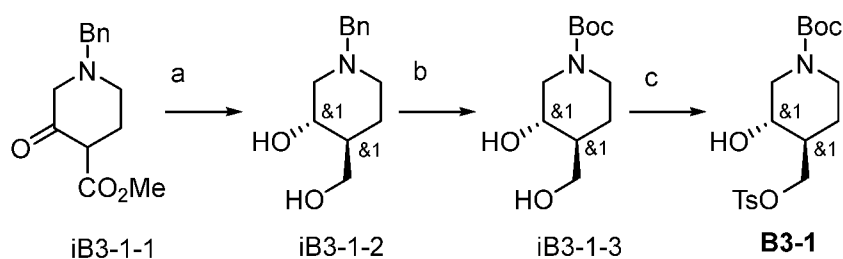
15

Table B:

A1	B2	B3	B6
A1-5	<p>4-chloro-7-tosyl-7<i>H</i>-pyrrolo[2,3-<i>d</i>]pyrimidine</p>	<p>B3-1</p>	<p>B6-2</p> <p>2-((3<i>RS</i>,4<i>RS</i>)-4-((4-(cyclobutyl(((1<i>r</i>,4<i>S</i>)-4-(trifluoromethyl)cyclohexyl)methyl)am</p>



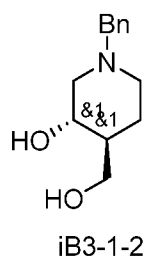
Synthesis of B3-1



a) NaBH₄, EtOH. b) Pd/C, (Boc)₂O, MeOH. c) TsCl, Et₃N, DCM.

Scheme B3-1

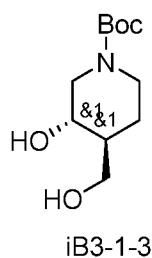
5 *rac*-(3*R*,4*R*)-1-Benzyl-4-(hydroxymethyl)piperidin-3-ol, iB3-1-2.



NaBH₄ (1.3 g, 33.6 mmol) was added in portions to a 0 °C suspension of methyl 1-benzyl-3-oxopiperidine-4-carboxylate (5 g, 16.8 mmol) in MeOH (50 mL). Then the reaction was warmed slowly to rt and stirred for 6h. The reaction was then

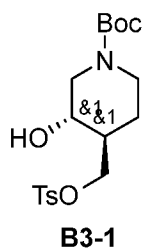
10 quenched with NH₄Cl (aq, sat, 30 ml) and H₂O (70 ml). The mixture was extracted with EA (2 x 100 ml) and combined organic fraction was washed with H₂O (100 ml), brine (100 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by Prep-HPLC to obtain iB3-1-2. LCMS: MS Calcd.: 221; MS Found: 222 ([M+H]⁺).

rac-tert-Butyl (3*R*,4*R*)-3-hydroxy-4-(hydroxymethyl)piperidine-1-carboxylate, iB3-1-3.



Pd/C (150 mg, 10%) and Boc₂O (946 mg, 4.3 mmol) were added to a suspension of B2 (800 mg, 3.62 mmol) in MeOH (20 mL) and the reaction was stirred at rt for 18h under H₂ (1 atm). The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by Flash CC (MeOH:DCM=1:20) to yield iB3-1-3. LCMS: MS Calcd.: 231; MS Found: 176 ([M-56+H]⁺).

rac-tert-Butyl (3*R*,4*R*)-3-hydroxy-4-((tosyloxy)methyl)piperidine-1-carboxylate), B3-1.

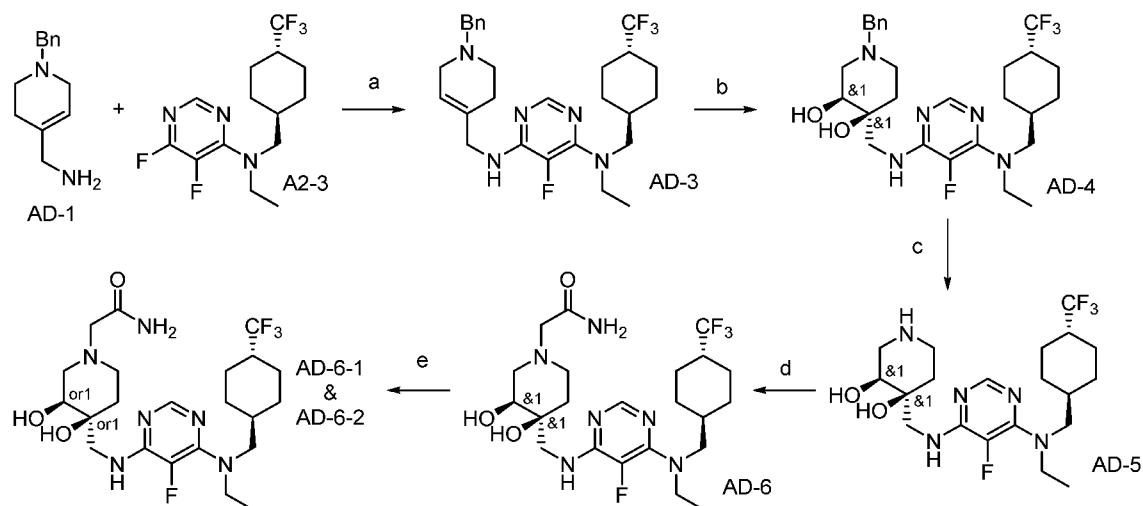


A solution of TsCl (717 mg, 3.8 mmol) in DCM (2 ml) was added to a 0 °C solution of iB3-1-3 (790 mg, 3.42 mmol) and Et₃N (1 g, 10.3 mmol) in DCM (10 ml). The reaction was then slowly warmed to rt and stirred for 20h. The reaction was quenched with H₂O (40 mL), and the mixture extracted with EA (3 x 50 ml). The combined organic layer was washed with H₂O (40 mL), brine (40 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by Flash CC (EA:PE=1:10) to obtain B3-1. LCMS: MS Calcd.: 385; MS Found: 286 ([M-101+H]⁺).

Diol ligands have also been synthesized, via route A or B.

Diol Route-A:

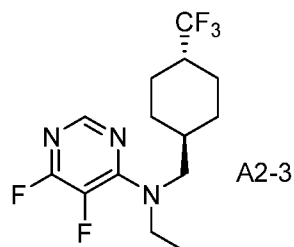
Synthesis of 2-((3*R**,4*R**)-4-(((6-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide, AD-6-1 and AD-6-2



- 5 a) DMSO, DIEA. b) Sharpless dihydroxylation. c) Pd/C, H₂ MeOH. d) 2-Bromoacetamide, K₂CO₃, DMF, Chiral separation (CHIRALPAK IG, Hex:EtOH:DEA=60:40:0.3).

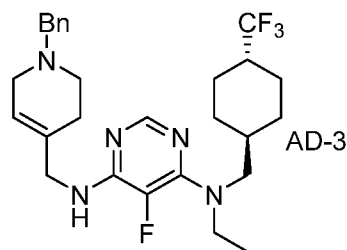
Scheme AD-6

- 10 *N*-Ethyl-5,6-difluoro-*N*-(((1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl)methyl)pyrimidin-4-amine, A2-3



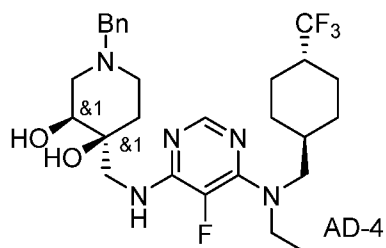
A2-3 was synthesized as outlined in General Method A, using 4,5,6-trifluoropyrimidine and A1-3.

- 15 *N*⁴-((1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)-*N*⁶-ethyl-5-fluoro-*N*⁶-(((1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl)methyl)pyrimidine-4,6-diamine AD-3



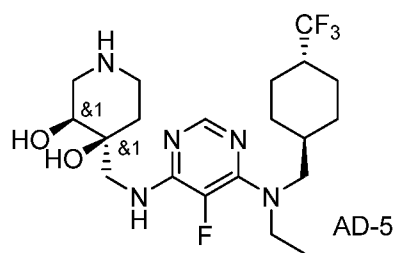
A solution of (1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methanamine--*N*-ethyl-5,6-difluoro-*N*-(((1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl)methyl)pyrimidin-4-amine AD-1 (800 mg, 2.91 mmol), *N*-ethyl-5,6-difluoro-*N*-(((1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl)methyl)pyrimidin-4-amine AD-2 (940 mg, 2.91 mmol) and DIEA (1.9 g, 14.6 mmol) in DMSO (20 mL) heated to 90 ° in a microwave reactor on. Thereafter, H₂O (50 mL) was added and the mixture was extracted with EA (3 x 20 mL). The combined organic layer was washed with brine (3 x 20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by Flash CC (EA:PE=1:2 to MeOH:DCM=1:30) to afford AD-3. LCMS: MS Calcd.: 505; MS Found: 506 ([M+H]⁺).

(3*RS*,4*RS*)-1-Benzyl-4-(((6-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)-methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)piperidine-3,4-diol, AD-4



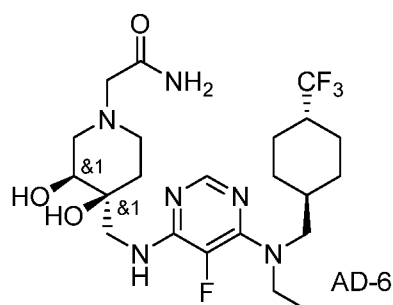
AD-3 (700 mg, 1.4 mmol) was dissolved in *t*-BuOH/H₂O (10 mL/10 mL) cooled to 0 °C and then K₃Fe(CN)₆ (1.4 g, 4.16 mmol), K₂CO₃ (574 mg, 4.16 mmol), (DHQ)₂PHAL (33 mg, 0.04 mmol), K₂OsO₂(OH)₄ (16 mg, 0.04 mmol) and MeSO₂NH₂ (132 mg, 1.39 mmol) were added. The reaction was stirred at rt on. Then sodium nitrite (10 g) and H₂O (20 mL) were added and the mixture was stirred for another 1h. The resulting mixture was extracted with DCM (3 x 20 mL). The combined organic layer was washed with brine and concentrated *in vacuo*. The residue was purified by Flash CC (EA:PE=1:2 to 1:1) to yield AD-4. LCMS: MS Calcd.: 539; MS Found: 540 ([M+H]⁺).

(3*RS*,4*RS*)-4-(((6-(Ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)-amino)-5-fluoropyrimidin-4-yl)amino)methyl)piperidine-3,4-diol, AD-5



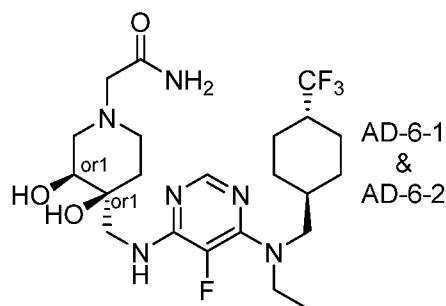
Pd/C (300 mg, 10 %) was added to a solution of AD-4 (560 mg, 1.0 mmol) in MeOH (10 mL) the reaction was stirred at r.t under H₂ (1 atm) on. The mixture was filtered and concentrated *in vacuo* to afford AD-5. LCMS: MS Calcd.: 449; MS Found: 450 ([M+H]⁺).

2-(((3*RS*,4*RS*)-4-(((6-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)-amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydropiperidin-1-yl)acetamide, AD-6.



K₂CO₃ (1.1 g, 8.00 mmol) and 2-bromoacetamide (221 mg, 1.60 mmol) were added to a solution of AD-5 (360 mg, 0.8 mmol) in DMF (10 mL) and the reaction was stirred at 25 °C for 2 h. Thereafter, H₂O (50 mL) was added and the mixture was extracted with EA (3 x 20 mL). The combined organic phase was washed with brine (3 x 15 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by Prep-TLC (MeOH:DCM=1:10) to afford AD-6. LCMS: MS Calcd.: 506; MS Found: 507 ([M+H]⁺).

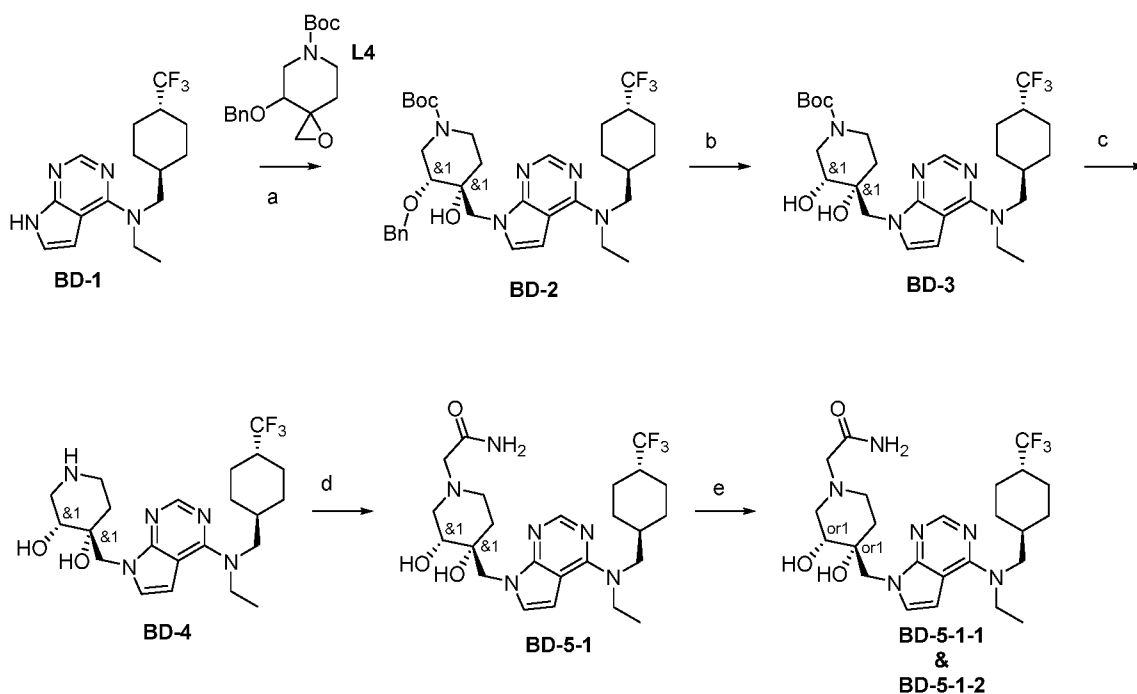
Isolation of the two stereoisomers 2-(((3*R**,4*R**)-4-(((6-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydropiperidin-1-yl)acetamide, AD-6-1 and AD-6-2



Chiral Separation (CHIRALPAK IG (Hex:EtOH:DEA=40:60:0.3) of AD-6 gave AD-6-1 (, 1st eluting isomer) and AD-6-2 (2nd eluting isomer).

Diol Route-B:

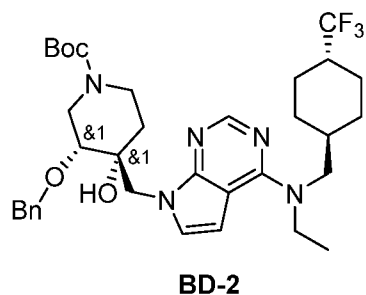
- 5 Synthesis of 2-((3*R**,4*R**)-4-((4-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide, BD-5-1-1 and BD-5-1-2



- a) NaH, DMF. b) Pd/C, NH₄CO₂H, MeOH. c) TFA, DCM. d) 2-Bromoacetamide, K₂CO₃, DMF. e) Chiral chromatography, IC (Hex:EtOH:DEA=40:60:0.3).

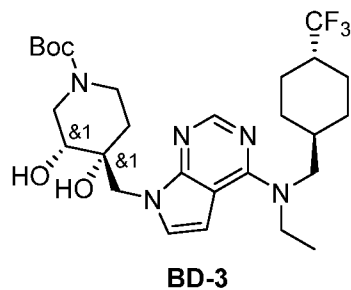
Scheme BD-5-1

tert-Butyl (3*RS*,4*RS*)-3-(benzyloxy)-4-((4-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)-cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-4-hydroxy-piperidine-1-carboxylate



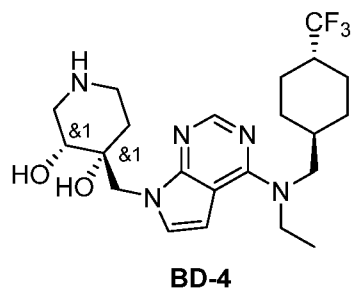
Under N₂ atmosphere NaH (75 mg, 1.86 mmol) was added to a solution of AD-2 (300 mg, 0.93 mmol) in dry DMF (20 mL), after 30 min a solution of BD-1 (443 mg, 1.39 mmol) in dry DMF (4 mL) was dropwise added and the reaction was stirred at 60 °. The reaction was quenched with NH₄Cl (aq, sat, 40 mL) and extracted with EA (3 x 20 mL). The combined organic fraction was washed with brine (3 x 15 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by Flash CC (EA:PE=1:5 to 1:4) to yield BD-2. LCMS: MS Calcd.: 645; MS Found: 646 ([M+H]⁺).

tert-Butyl (3*RS*,4*RS*)-4-((4-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3,4-dihydropiperidine-1-carboxylate



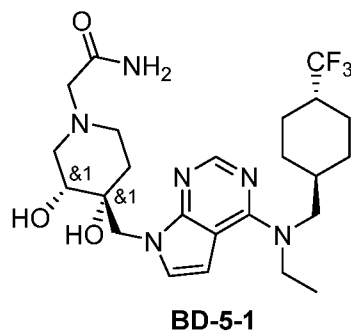
A mixture of BD-2 (750 mg, 0.93 mmol) in MeOH (20 mL), NH₄CO₂H (1.4 g, 22.32 mmol) and Pd/C (500 mg, 10%) was refluxed on. Then the mixture was filtered and concentrated *in vacuo* to give crude BD-3. LCMS: MS Calcd.: 555; MS Found: 556 ([M+H]⁺).

(3*RS*,4*RS*)-4-((4-(Ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)piperidine-3,4-diol, BD-4.



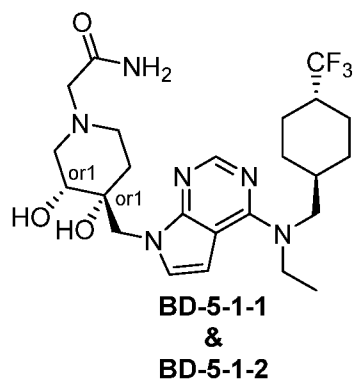
BD-3 (413 mg, 0.74 mmol) was stirred at rt for 1h in a mixture of in TFA (4 mL) and DCM (10 mL). Then mixture was concentrated *in vacuo* to give the crude product BD-4, that was used without further purification. LCMS: MS Calcd.: 455; MS Found:456 ([M+H]⁺).

2-((3*RS*,4*RS*)-4-((4-(Ethyl((1*r*,4*R*)-4-(trifluoromethyl)-cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide), BD-5



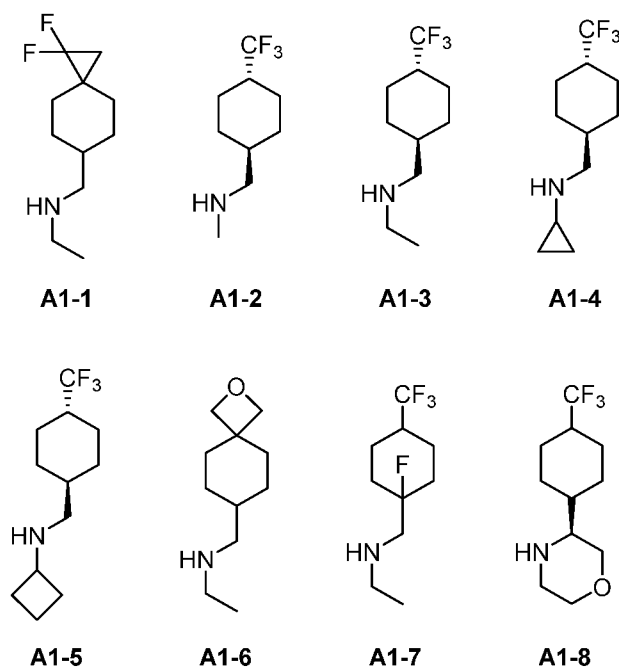
10 K_2CO_3 (1.0g, 7.40 mmol) and 2-bromoacetamide (205mg, 1.48mmol) were added to a solution of crude BD-4 (785mg) in DMF (10mL). The reaction was stirred at rt for 2 h. Thereafter H_2O (50mL) was added and the mixture was extracted with EA (3 x 30mL). The combined organic phase was washed with brine (3 x 20mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by Prep-TLC
15 (MeOH:DCM=1:10) to give two stereo isomers BD-5-1 and BD-5-2.

Separation and isolation of the stereoisomers 2-((3*R*^{*},4*R*^{*})-4-((4-(ethyl((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide, BD-5-1-1 and BD-5-1-2

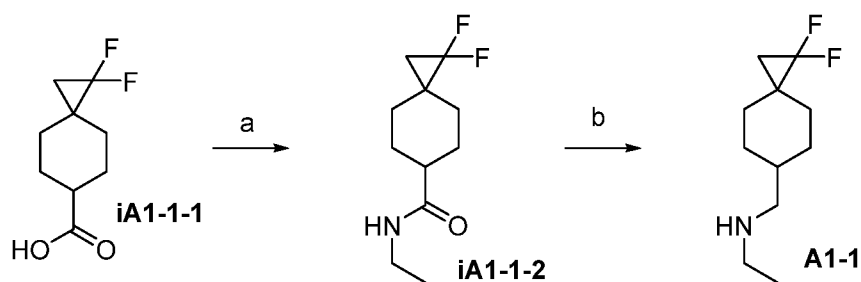


BD-5-1 was separated by chiral HPLC (CHIRALPAK IG, Hex:EtOH:DEA=40:60:0.3) to give the stereoisomers BD-5-1-1 (1st eluting isomer,) and BD-5-1-2 (2nd eluting isomer).

5 Synthesis of A1 building blocks:

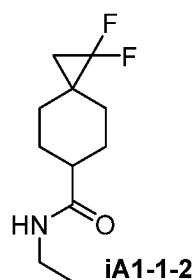


Synthesis of *N*-((1,1-difluorospiro[2.5]octan-6-yl)methyl)ethanamine, A1-1

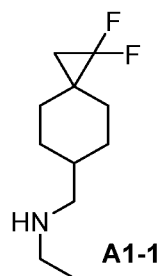


a) EtNH₂, DIEA, HATU. b) BH₃·THF.

Scheme A1-1

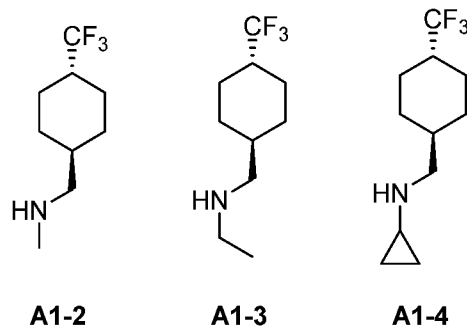
Synthesis of *N*-ethyl-1,1-difluorospiro[2.5]octane-6-carboxamide, iA1-1-2

DIEA (1.8 g, 14.1 mmol) and HATU (2.1 g, 5.6 mmol) were added to a
 5 solution of 1,1-difluorospiro[2.5]octane-6-carboxylic acid (890 mg, 4.7 mmol) in DMF
 (10 mL). The reaction was stirred at 30 °C for 30min, and then ethylamine (2M in THF,
 7 mL). The reaction was stirred at 30 °C on, diluted with water (20 mL), extracted with
 EA (3 x 20 mL), washed with brine and dried over Na₂SO₄. The organic solution was
 concentrated *in vacuo* to yield crude iA1-1-2 that was used without further purification.
 10 MS Calcd.: 217; MS Found: 218 ([M+H]⁺).

Synthesis of *N*-((1,1-difluorospiro[2.5]octan-6-yl)methyl)ethanamine, A1-1

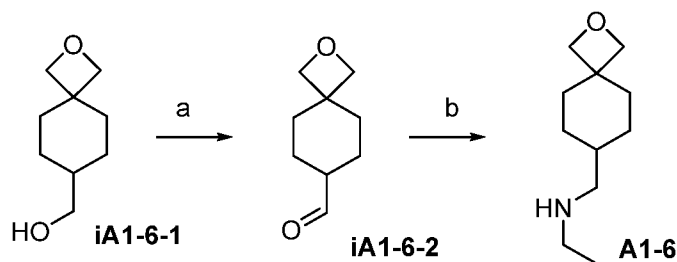
Under a N₂ atmosphere BH₃·THF (1M, 18 mL) was added portion wise to a
 solution of crude iA1-1-2 (1.5 g) in THF (15 mL). The reaction was refluxed overnight,
 15 cooled by an ice bath, and quenched by adding MeOH (4 mL), followed by 1N HCl (4
 mL), and the mixture was then stirred at 50 °C for 30 min and thereafter concentrated *in vacuo*.
 The residue was taken into sat K₂CO₃ (20 mL), extracted with DCM (3 x 20
 mL), washed with brine (20 mL) and dried over Na₂SO₄. The organic solution was
 filtered and concentrated *in vacuo* to afford crude A1-1, that was used without further
 20 purification. MS Calcd.: 203; MS Found: 204 ([M+H]⁺).

Synthesis of *N*-methyl-1-((1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl)methanamine (A1-2), *N*-(((1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl)methyl)ethanamine (A1-3) and *N*-(((1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl)methyl)cyclopropanamine (A1-4).



- 5 These intermediates were synthesized according to the synthesis of A1-1 but using 2-((1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl)acetic acid instead of iA-1-1 together with either; methylamine hydrochloride, ethylamine or cyclopropylamine, respectively.

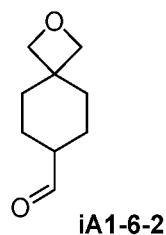
Synthesis of *N*-((2-oxaspiro[3.5]nonan-7-yl)methyl)ethanamine, A1-6.



- 10 a) Dess-Martin oxidation. b) EtNH₂, MgSO₄, NaBH₄, MeOH.

Scheme A1-6

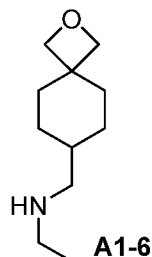
2-Oxaspiro[3.5]nonane-7-carbaldehyde, iA1-6-2.



- 15 Dess-Martin periodinane (956 mg, 2.25 mmol) was added to a ice cooled solution of (2-oxaspiro[3.5]nonan-7-yl)methanol (320 mg, 2.05 mmol) in DCM (10 ml) and the reaction was stirred at rt for 2.5 hours. The mixture was adjusted with NaHCO₃ (aq) to pH= 7 - 8, extracted with DCM (2 x 50 mL), dried (Na₂SO₄) and concentrated *in*

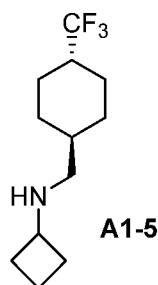
vacuo to yield iA1-6-2. ¹H-NMR (400MHz, CDCl₃): δ 9.61 (d, *J* = 0.8 Hz, 1H), 4.37 (d, *J* = 5.2 Hz, 4H), 2.20 (m, 1H), 2.13-2.03 (m, 2H), 1.88-1.84 (m, 2H), 1.59-1.52 (m, 2H), 1.40-1.36 (m, 2H).

N-(2-Oxaspiro[3.5]nonan-7-ylmethyl)ethanamine, A1-6.



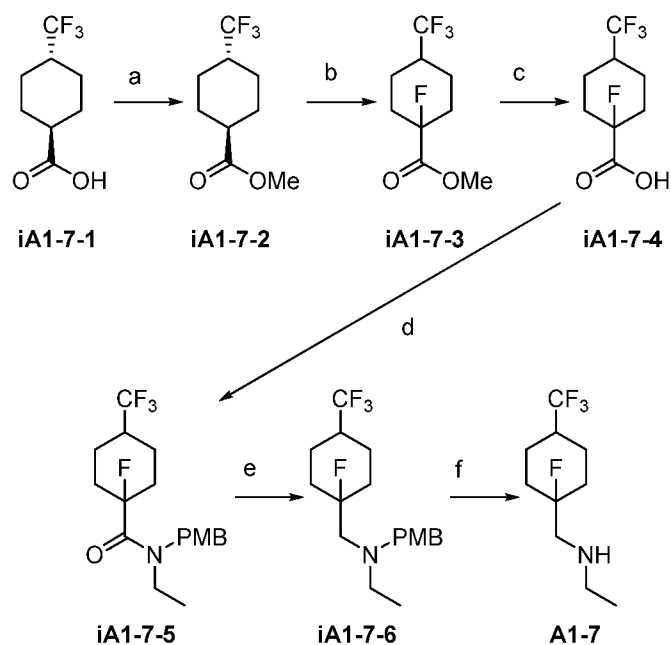
A mixture of iA1-6-2 (310 mg, 2 mmol), MeOH (10 mL), MgSO₄ (1 g) and ethanamine (2 mL, 2 mol/L) was stirred at rt overnight. Then NaBH₄ (133 mg, 3.5 mmol) was added and the reaction was stirred for another 2h at rt. Thereafter H₂O was added, and the mixture was extracted with EA (3 x 50 mL), dried (Na₂SO₄) and
 10 concentrated *in vacuo* to yield A1-6. ¹H-NMR (400 MHz, CDCl₃): δ 4.40 (s, 2H), 4.33 (s, 2H), 2.65-2.59 (m, 2H), 2.42 (d, *J* = 6.8 Hz, 2H), 2.13 (d, *J* = 13.2 Hz, 2H), 1.7-1.68 (m, 2H), 1.44-1.639 (m, 2H), 1.37 (d, *J* = 3.6Hz, 1H), 1.10 (t, *J* = 7.2Hz, 3H).

Synthesis of *N*-(((1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl)methyl)cyclobutan-amine, A1-5.



A1-5 was synthesized according to the synthesis of A1-6 but using DMSO/oxalyl chloride oxidation (Swern) instead of Dess-Martin oxidation, followed by reductive amination with cyclobutylamine. LCMS: MS Calcd.: 235; MS Found: 236 ([M+H]⁺).

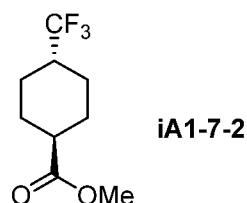
20 Synthesis of *N*-((1-fluoro-4-(trifluoromethyl)cyclohexyl)methyl)ethanamine, A1-7.



a) SOCl_2 , MeOH. b) LDA, N-Fluorobenzenesulfonimide. c) KOH, EtOH. d) N-(4-methoxybenzyl)ethanamine, HATU, DIEA, DMF. e) $\text{BH}_3 \cdot \text{THF}$. f) H_2 , Pd/C, MeOH.

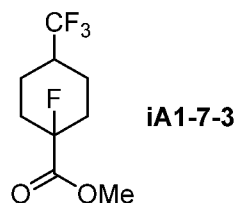
Scheme A1-7

5 4-Trifluoromethyl-cyclohexanecarboxylic acid methyl ester, iA1-7-2.



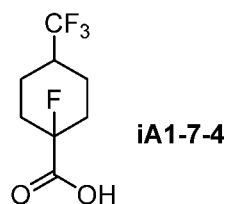
Under a N_2 atmosphere SOCl_2 (12.2 g, 102 mmol) was dropwise added to a 0 °C solution of (1r,4r)-4-(trifluoromethyl)cyclohexane-1-carboxylic acid (10 g, 51 mmol) in MeOH (200 mL). The reaction was stirred at rt on. The reaction was then concentrated *in vacuo* and water (200 mL) was added. The mixture was extracted with DCM (2 x 200 mL) and the combined organic phase was washed with sat NaHCO_3 (100 ml), brine (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield iA1-7-2 that was used without further purification.

1-Fluoro-4-trifluoromethyl-cyclohexanecarboxylic acid methyl ester, iA1-7-3.



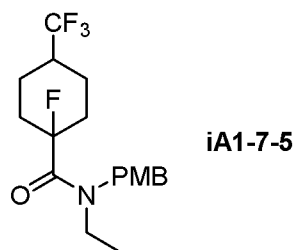
Under a N₂ atmosphere LDA (2.0M, 5.5 ml) was added dropwise to a solution of iA1-7-2 (2.1 g, 10 mmol) in THF (30 mL) at -70 °C and the reaction was stirred at this temperature for 1h. Thereafter, a solution of N-fluorobenzenesulfonimide (3.2 g, 10 mmol) in THF (5 mL) was added dropwise. The resulting mixture was slowly warmed to rt and stirred for another 16h. The reaction was quenched with sat NH₄Cl (20 mL). Water (60 mL) was added and the mixture was extracted with DCM (2 x 50 mL). The combined organic layer was washed with water (40 mL), brine (40 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified Flash CC (EA:PE=1:10) to yield iA1-7-3.

1-Fluoro-4-trifluoromethyl-cyclohexanecarboxylic acid, iA1-7-4.

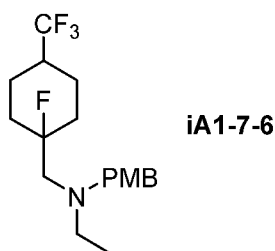


KOH (164 mg, 2.9 mmol) was added to a solution of iA1-7-2 (500 mg, 2.19 mmol) in EtOH (9 mL) and H₂O (3 ml) at rt and the reaction was stirred at rt for 18h. Water (50 mL) was added and the mixture was washed with EA (2 x 50 mL). The aqueous phase was acidified with HCl (1M) to pH=2 and extracted with DCM (2 x 50 mL), The combined organic layer was washed with H₂O (40 mL), brine (40 mL), dried over Na₂SO₄ and filtered. Concentration *in vacuo* gave crude iA1-7-4 that was used without further purification.

1-Fluoro-4-trifluoromethyl-cyclohexanecarboxylic acid ethyl-(4-methoxybenzyl)-amide iA1-7-5.

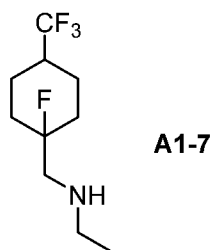


- DIEA (541 mg, 4.2 mmol), ethyl-(4-methoxy-benzyl)-amine (416 mg, 2.52 mmol) and HATU (960 mg, 2.52 mmol) were in turn added to a solution of iA1-7-4 (450 mg, 2.1 mmol) in DMF (10 mL). Then the reaction was stirred at room
- 5 temperature for 5h and then water (50 mL) was added. The mixture was extracted with EA (2 x 50 mL). The combined organic phase was washed with H₂O (30 mL), brine (30 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by Flash CC (EA:PE=1:1) to yield iA1-7-5. LCMS: MS Calcd.: 361; MS Found: 362 ([M+H]⁺).
- 10 Ethyl-(1-fluoro-4-trifluoromethyl-cyclohexylmethyl)-(4-methoxy-ben-zyl)-amine, iA1-7-6



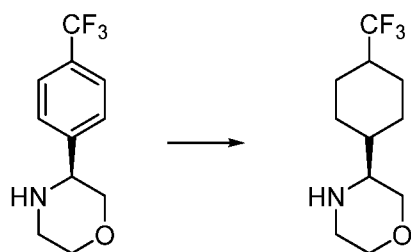
- A solution BH₃·THF (2.0 M in THF, 3.5 ml) in was added to a 0 °C solution of iA1-7-5 (510 mg, 1.41 mmol) (10 mL) ant the reaction was heated to 65 °C for 18 h.
- 15 The reaction was quenched with MeOH (5 mL) and extracted with DCM (2 x 50 mL). The combined organic layer was washed with water (40 mL) and brine (40 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by Flash CC (EA:PE=1:10) to yield iA1-7-6. LCMS: MS Calcd.: 347; MS Found: 348 ([M+H]⁺).

Ethyl-(1-fluoro-4-trifluoromethyl-cyclohexylmethyl)-amine, A1-7.



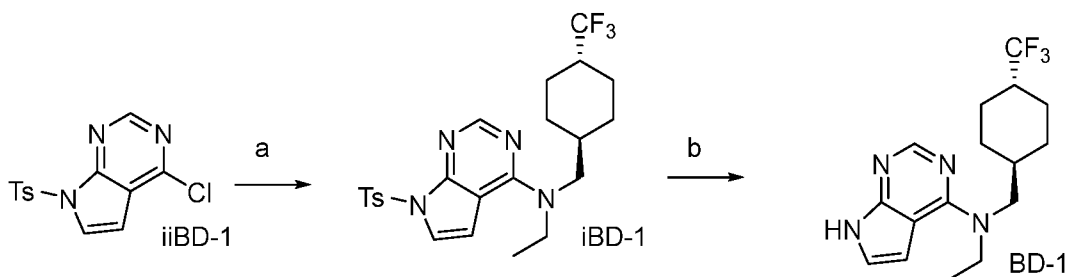
Pd/C (100 mg, 10%) was added to a solution of iA1-6-1 (350 mg, 0.99 mmol) in MeOH (5 mL) and stirred at 25 °C under H₂ (1 atm) for 20 h. Thereafter, the mixture was filtered and concentrated *in vacuo*. The residue was purified using Flash CC (EA:PE=1:2) to obtain A1-7. LCMS: MS Calcd.: 227; MS Found: 228 ([M+H]⁺).

Synthesis of (3*S*)-3-(4-(trifluoromethyl)cyclohexyl)morpholine, A1-8.



A mixture of (S)-3-(4-(trifluoromethyl)phenyl)morpholine (1.5 g, 5.6 mmol), RuCl₃·H₂O (635 mg, 2.8 mmol) and trioctylamine (0.49 mL, 1.1 mmol) was subjected to H₂ under pressure (700 psi) at 60 °C for 140 h. Thereafter, the reaction mixture was filtered through celite, concentrated *in vacuo*, 2M NaOH was added and the resulting mixture was extracted with EA (2 x 30 mL). The combined EA phase was dried (Na₂SO₄) filtered and concentrated *in vacuo*. The residue was purified by Flash CC (MeOH:DCM=1:10) to yield A1-8. LCMS: MS Calcd.: 237; MS Found: 238 ([M+H]⁺).

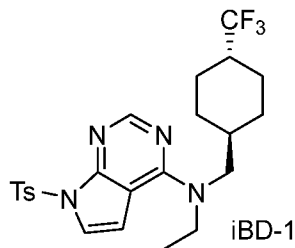
N-Ethyl-*N*-(((1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine, BD-1



a) TEA, A1-1, KI, H₂O. b) K₂CO₃, MeOH.

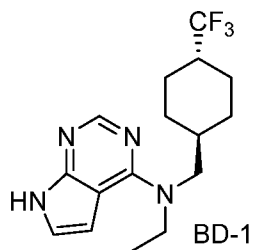
Scheme BD-1

N-Ethyl-7-tosyl-*N*-(((1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine, iBD-1.



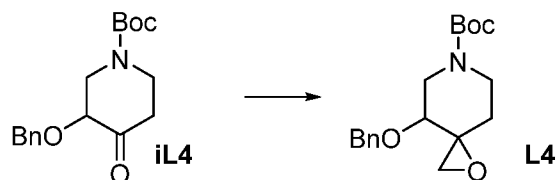
- 5 4-Chloro-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.2 g, 3.9 mmol), A1-3 (810 mg, 3.9 mmol), H₂O (5 mL), TEA (5mL) and KI (650 mg, 1.9 mmol) were mixed together in a sealed vial at 130 °C on. The reaction was allowed to cool and then extracted with EA (3 x 15 mL). The combined organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by Flash CC (PE:EA= 10:1 to 5:1) yield iBD-1 .
- 10

N-Ethyl-*N*-(((1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine, BD-1.



- 15 K₂CO₃ (3.4 g, 18.3 mmol) was added to a solution of iBD-1 (1.1 g, 2.2 mmol) in MeOH (10 mL). The reaction was then stirred at 50 °C for 4h. After cooling to ambient temperature, the reaction was extracted with EA (3 x 15 mL). The combined EA phase was dried (Na₂SO₄), filtered and concentrated *in vacuo* to yield crude BD-1 that was used without further purification. LCMS: MS Calcd.: 326; MS Found: 327 ([M+H]⁺).

- 20 Synthesis of *tert*-butyl 4-(benzyloxy)-1-oxa-6-azaspiro[2.5]octane-6-carboxylate, L4



a) NaH, Me₃SI, DMF.

Scheme L4

Under a N₂ atmosphere NaH (283 mg, 7.1 mmol, 60%) was added to a 0 °C
 5 solution of trimethylsulfonium iodide (1.44 g, 7.1 mmol) in dry DMF (20 mL) and the
 reaction was allowed to stir for 30 min. Thereafter, a solution of (tert-butyl 3-
 (benzyloxy)-4-oxopiperidine-1-carboxylate) (1.8 g, 5.9 mmol) in dry DMF (5 mL) was
 added slowly and then stirred at rt on. The reaction was quenched with NH₄Cl (sat aq 50
 mL) and the mixture was extracted with EA (3 x 15 mL). The combined organic layer
 10 was washed with brine (2 x 10 mL), dried (Na₂SO₄) filtered, concentrated *in vacuo* to
 yield crude L4 that was used without further purification. LCMS: MS Calcd.: 319; MS
 Found: 342 ([M+Na]⁺).

Analytical table 1:

Patent example	¹ H-NMR	prep HPLC method	analytical HPLC method	MS Calc./MS Observed:	chiral HPLC method
A6-1-1-1	¹ H-NMR (400 MHz, CDCl ₃): δ 7.89 (d, <i>J</i> = 1.6 Hz, 1H), 6.94 (s, 1H), 5.91 (s, 1H), 5.38-2.42 (m, 1H), 4.87-4.92 (m, 1H), 4.09-4.17 (m, 1H), 3.50-3.61 (m, 2H), 3.31-3.45 (m, 3H), 3.02-3.12 (m, 4H), 2.85-2.89 (m, 1H), 2.10-2.24 (m, 2H), 1.76-1.79 (m, 3H), 1.54-1.66 (m, 6H), 1.40-1.43 (m, 1H), 1.15-1.19 (t, <i>J</i> = 7.2 Hz, 3H), 1.06-1.14 (m, 2H), 1.00-1.04 (t, <i>J</i> = 8.4 Hz, 2H).	Flash CC (DCM: MeOH= 20:1)	NH4Ac	485	ID (Hex:EtOH:D EA=70:30:0.3)
A6-1-1-2	¹ H-NMR (400 MHz, CDCl ₃): δ 7.89 (d, <i>J</i> = 1.6 Hz, 1H), 6.94 (s, 1H), 5.91 (s, 1H), 5.39-5.40 (m, 1H), 4.87-4.92 (m, 1H), 4.09-4.17 (m, 1H), 3.49-3.61 (m, 2H), 3.31-3.45 (m, 3H), 3.02-3.12 (m, 4H), 2.85-2.89 (m, 1H), 2.10-2.24	Flash CC (DCM: MeOH= 20:1)	NH4Ac	485	ID (Hex:EtOH:D EA=70:30:0.3)

	(m, 2H), 1.76-1.79 (m, 3H), 1.54-1.66 (m, 6H), 1.37-1.43 (m, 1H), 1.15-1.19 (t, $J = 7.2$ Hz, 3H), 1.06-1.14 (m, 2H), 1.00-1.04 (t, $J = 8.8$ Hz, 2H).				
A6-1-2-1	¹ H-NMR (400 MHz, CDCl ₃): δ 7.89 (d, $J = 2.0$ Hz, 1H), 6.93 (s, 1H), 5.89 (s, 1H), 5.48-5.50 (m, 1H), 4.90-4.93 (m, 1H), 4.09-4.15 (m, 1H), 3.33-3.60 (m, 5H), 3.02-3.13 (m, 4H), 2.85-2.88 (m, 1H), 2.10-2.24 (m, 2H), 1.75-1.79 (m, 3H), 1.53-1.68 (m, 4H), 1.38-1.42 (m, 3H), 1.00-1.22 (m, 5H), 0.95-1.00 (t, $J = 8.4$ Hz, 2H).	Flash CC (DCM: MeOH=20:1)	NH4Ac	485	ID (Hex:EtOH:D EA=60:40:0.3)
A6-1-2-2	¹ H-NMR (400 MHz, CDCl ₃): δ 7.89 (d, $J = 1.6$ Hz, 1H), 6.93 (s, 1H), 5.89 (s, 1H), 5.46-5.47 (m, 1H), 4.88-4.93 (m, 1H), 4.09-4.16 (m, 1H), 3.31-3.61 (m, 5H), 3.02-3.13 (m, 4H), 2.85-2.88 (m, 1H), 2.09-2.24 (m, 2H), 1.75-1.81 (m, 3H), 1.53-1.68 (m, 4H), 1.38-1.42 (m, 3H), 1.08-1.22 (m, 5H), 0.95-1.00 (t, $J = 8.4$ Hz, 2H).	Flash CC (DCM: MeOH=20:1)	NH4Ac	485	ID (Hex:EtOH:D EA=60:40:0.3)
A6-2-1	¹ H-NMR (400 MHz, MeOH-d ₄) δ 7.68 (d, $J = 1.2$ Hz, 1 H), 3.55-3.50 (m, 1H), 3.38-3.29 (m, 4 H), 3.05 (d, $J = 3.6$ Hz, 3 H), 2.95-2.88 (m, 3 H), 2.76-2.73 (m, 1 H), 2.06-1.95 (m, 3 H), 1.94-1.84 (m, 2 H), 1.73-1.63 (m, 4 H), 1.42-1.37 (m, 2 H), 1.25-1.15 (m, 2 H), 0.99-0.93 (m, 2 H)		NH4HC O3	MS Calcd.: 490; MS Found: 491	OJ (Hex: EtOH=85:15)
A6-2-2	¹ H-NMR (400 MHz, MeOH-d ₄) δ 7.68 (d, $J = 1.2$ Hz, 1 H), 3.55-3.50 (m, 1H), 3.39-3.29 (m, 4 H), 3.05 (d, $J = 3.2$ Hz, 3 H), 2.97-2.89 (m, 3 H), 2.77-2.74 (m, 1 H), 2.07-1.95 (m, 3 H), 1.94-1.84 (m, 2 H), 1.73-1.64 (m, 4 H), 1.43-1.36 (m, 2 H), 1.25-1.15 (m, 2 H), 0.80-0.78 (m, 2 H)		NH4HC O3	MS Calcd.: 490; MS Found: 491	OJ (Hex: EtOH=85:15)
A6-3-1	¹ H-NMR (400 MHz MeOH-d ₄) δ 7.68 (d, $J = 4$ Hz, 1H), 3.44-3.57 (m, 3H), 3.25-3.39	NH4HC O3	HN4HO Ac	MS Calcd.: 490; MS	

	(m, 4H), 2.86-2.95(m, 3H), 2.74 (d, $J=12$ Hz, 1H), 1.84-2.06 (m, 5H), 1.73-1.76 (m, 2H), 1.60-1.65 (m, 2H), 1.37-1.42 (m, 2H), 1.13-1.24 (m, 3H), 1.04-1.08 (t, $J=8$ Hz 3H), 0.90-0.98 (m, 2H).			Found: 491	
A6-3-2	¹ HNMR (400 MHz MeOH-d ₄) δ 7.67 (d, $J=4$ Hz, 1H), 3.44-3.56 (m, 3H), 3.29-3.39 (m, 4H), 2.87-2.97(m, 3H), 2.74 (d, $J=12$ Hz, 1H), 1.95-2.05 (m, 3H), 1.84-1.87 (m, 2H), 1.73-1.76 (m, 2H), 1.60-1.66 (m, 2H), 1.37-1.43 (m, 2H), 1.13-1.24 (m, 3H), 1.04-1.08 (t, $J=8$ Hz 3H), 0.90-0.98 (m, 2H).	NH ₄ HC O ₃	HN ₄ HO Ac	MS Calcd.: 490; MS Found: 491	
A6-4-1	¹ HNMR (400 MHz CDCl ₃) δ 7.92 (d, $J = 1.2$ Hz, 1H), 6.94 (s, 1H), 5.85 (s, 1H), 5.48-5.49 (m, 1H), 5.95-5.05 (m, 1H), 4.09-4.17 (m, 1H), 3.43-3.49 (m, 2H), 3.32-3.37 (m, 1H), 3.03-3.15 (m, 4H), 2.86-2.95 (m, 2H), 2.11-2.24 (m, 2H), 1.94-1.98 (m, 3H), 1.82-1.86 (m, 2H), 1.53-1.69 (m, 5H), 1.40-1.46 (m, 1H), 1.25-1.34 (m, 3H), 0.92-1.02 (m, 2H), 0.79-0.85 (m, 2H), 0.64-0.66 (m, 2H).	NH ₄ HC O ₃	HN ₄ HO Ac	MS Calcd.: 502; MS Found: 503	ID (Hex:EtOH:D EA=80:20:0.3)
A6-4-2	¹ HNMR (400 MHz CDCl ₃) δ 7.92 (d, $J = 1.2$ Hz, 1H), 6.94 (s, 1H), 5.85 (s, 1H), 5.41-5.43 (m, 1H), 5.95-5.05 (m, 1H), 4.10-4.17 (m, 1H), 3.43-3.50 (m, 2H), 3.33-3.37 (m, 1H), 3.03-3.15 (m, 4H), 2.86-2.95 (m, 2H), 2.11-2.24 (m, 2H), 1.94-1.97 (m, 3H), 1.76-1.86 (m, 2H), 1.53-1.65 (m, 5H), 1.39-1.46 (m, 1H), 1.25-1.34 (m, 3H), 0.92-1.02 (m, 2H), 0.79-0.86 (m, 2H), 0.64-0.66 (m, 2H).	NH ₄ HC O ₃	HN ₄ HO Ac	MS Calcd.: 502; MS Found: 503	ID (Hex:EtOH:D EA=80:20:0.3)
A6-5	¹ H NMR (400 MHz, Chloroform-d) δ 0.75 – 0.94 (m, 2H), 1.14 – 1.23 (m, 3H), 1.32 – 1.36 (m, 2H), 1.55 – 1.67 (m, 3H), 1.72 (d, $J = 12.3$ Hz, 2H), 1.82 – 2.26 (m, 10H), 2.80 (d, $J = 11.3$ Hz,			517.0	

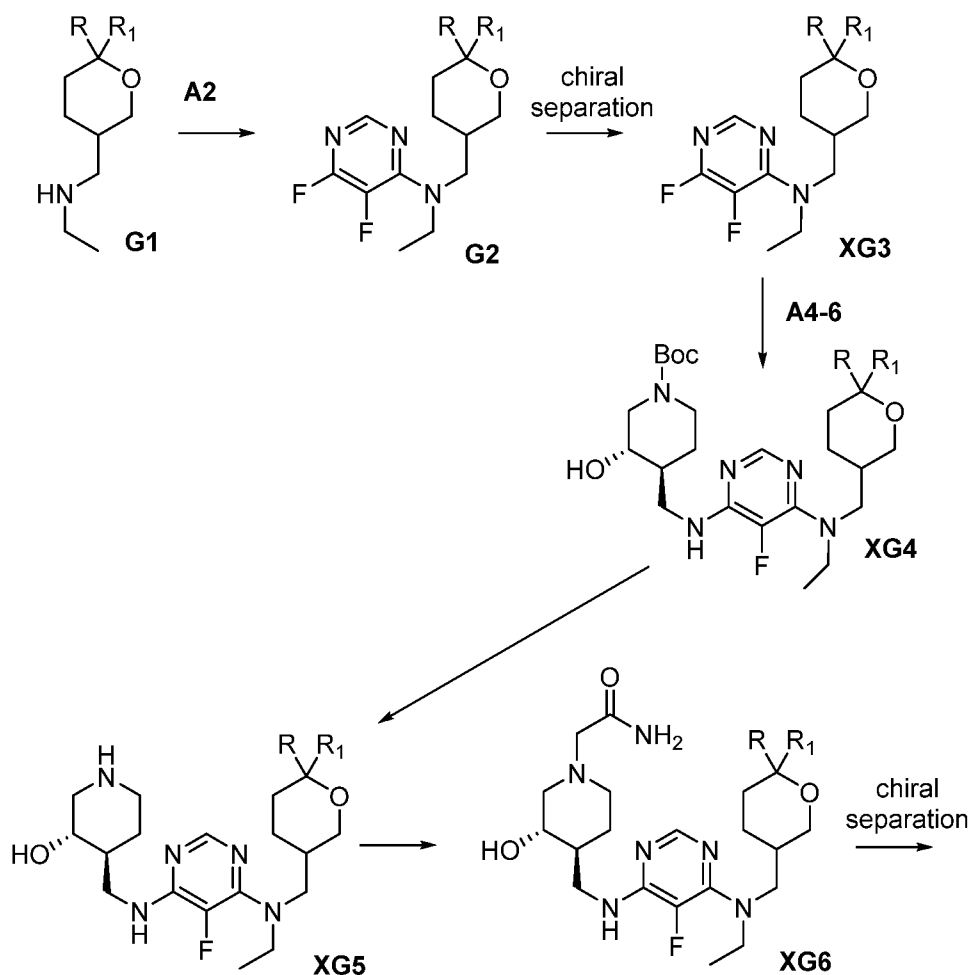
	1H), 2.92 – 3.10 (m, 3H), 3.27 (dd, $J = 10.0, 5.5$ Hz, 1H), 3.34 (d, $J = 7.2$ Hz, 1H), 4.06 (ddd, $J = 15.1, 7.8, 3.2$ Hz, 1H), 4.35 – 4.46 (m, 1H), 4.86 (s, 1H), 5.27 (s, 1H), 6.85 (s, 1H), 7.85 (d, $J = 1.5$ Hz, 1H).				
A6-6-1	¹ H NMR (400MHz, CDCl ₃) δ 7.88 (d, $J = 1.6$ Hz, 1H), 6.93 (s, 1H), 5.65 (d, $J = 2.8$ Hz, 1H), 4.88 (s, 1H), 4.41 (s, 2H), 4.33-4.14 (m, 2H), 4.15-4.09 (m, 1H), 3.58-3.47 (m, 2H), 3.37-3.30 (m, 3H), 3.11-3.03 (m, 4H), 2.86 (d, $J = 12.0$ Hz, 1H), 2.21-2.11 (m, 4H), 1.72-1.51 (m, 4H), 1.4-1.35 (m, 4H), 1.20-1.14 (m, 3H), 0.98-0.93 (m, 3H).		NH4HC O3	MS Calcd.: 464; MS Found: 465	IG (Hex:EtOH:D EA=50:50:0.5)
A6-6-2	¹ H NMR (400MHz, CDCl ₃) δ 7.87 (d, $J = 1.6$ Hz, 1H), 6.92 (s, 1H), 5.41(d, $J = 2.8$ Hz, 1H), 4.88 (s, 1H), 4.41 (s, 2H), 4.33 (s, 2H), 4.19-4.05 (m, 1H), 3.58-3.47 (m, 5H), 3.11-3.02 (m, 3H), 2.87-2.85 (m, 1H), 2.23-2.10 (m, 4H), 1.65-1.53(m, 4H), 1.41-1.35 (m, 3H), 1.25 (s, 1H), 1.16 (t, $J = 7.2$ Hz, 3H), 0.98-0.89(m, 2H).		NH4HC O3	MS Calcd.: 464; MS Found: 465	IG (Hex:EtOH:D EA=50:50:0.5)
A6-7-1	¹ H NMR (400 MHz, MeOH- <i>d</i> ₄) δ 8.16 (s, 1H), 7.49 (d, $J = 10.0$ Hz, 1H), 7.40 – 7.37 (m, 2H), 7.19 (d, $J = 3.6$ Hz, 1H), 6.49 (d, $J = 3.6$ Hz, 1H), 5.13 (s, 2H), 4.44 (d, $J = 14.4$ Hz, 1H), 4.20 (d, $J = 14.4$ Hz, 1H), 3.90 (q, $J = 7.2$ Hz, 2H), 3.55 (dd, $J = 10.0$ Hz, 4.4 Hz, 1H), 2.96 (s, 2H), 2.74 – 2.70 (m, 1H), 2.53 – 2.51 (m, 1H), 2.44 – 2.35 (m, 2H), 1.68 – 1.60 (m, 1H), 1.43 – 1.40 (m, 1H), 1.35 (t, $J = 7.2$ Hz, 3H).	Prep- TLC (MeOH: DCM=1 :20)	NH4HO Ac	MS Calcd.: 508; MS Found: 509	IG (Hex:EtOH:D EA=60:40:0.3)

A6-7-2	¹ H NMR (400 MHz, MeOH- <i>d</i> ₄) δ 8.16 (s, 1H), 7.49 (d, <i>J</i> = 10.4Hz, 1H), 7.40 – 7.37 (m, 2H), 7.19 (d, <i>J</i> = 3.6 Hz, 1H), 6.49 (d, <i>J</i> = 3.6 Hz, 1H), 5.13 (s, 2H), 4.44 (d, <i>J</i> = 14.4 Hz, 1H), 4.20 (d, <i>J</i> = 14.4 Hz, 1H), 3.90 (q, <i>J</i> = 7.2 Hz, 2H), 3.55 (dd, <i>J</i> = 10.4Hz, 4.8Hz, 1H), 2.96 (s, 2H), 2.74 – 2.70 (m, 1H), 2.53 – 2.51 (m, 1H), 2.44 – 2.35 (m, 2H), 1.68 – 1.60 (m, 1H), 1.43 – 1.40 (m, 1H), 1.35 (t, <i>J</i> = 7.2 Hz, 3H).	Prep-TLC (MeOH:DCM=1:20)	NH ₄ HOAc	MS Calcd.: 508; MS Found: 509	IG (Hex:EtOH:D EA=60:40:0.3)
A6-8-1	¹ H NMR (400 MHz, CDCl ₃): δ 7.93 (s, 1H), 7.07 (s, 1H), 5.50 (s, 1H), 4.74 (s, 1H), 4.13-4.10 (m, 1H), 4.02-3.99 (m, 2H), 3.88-3.85 (m, 1H), 3.61-3.55 (m, 2H), 3.37-3.29 (m, 3H), 2.98 (s, 2H), 2.92-2.89 (m, 2H), 2.19-2.13 (m, 3H), 2.02-1.93 (m, 4H), 1.80-1.74 (m, 2H), 1.62-1.57 (m, 1H), 1.38-1.26 (m, 5H), 1.06-0.89 (m, 2H).	NH ₄ HCO ₃	TFA	MS Calcd.: 502; MS Found: 503	
A6-8-2	¹ H NMR (400 MHz, CDCl ₃): δ 7.93 (s, 1H), 7.07 (s, 1H), 5.50 (s, 1H), 4.74 (s, 1H), 4.13-4.10 (m, 1H), 4.02-3.99 (m, 2H), 3.88-3.85 (m, 1H), 3.61-3.55 (m, 2H), 3.37-3.29 (m, 3H), 2.98 (s, 2H), 2.92-2.89 (m, 2H), 2.19-2.13 (m, 3H), 2.02-1.93 (m, 4H), 1.80-1.74 (m, 2H), 1.62-1.57 (m, 1H), 1.38-1.26 (m, 5H), 1.06-0.89 (m, 2H).	NH ₄ HCO ₃	TFA	MS Calcd.: 502; MS Found: 503	
B6-1-1	¹ H NMR (400 MHz, CD ₃ OD- <i>d</i> ₄) δ 8.02 (s, 1H), 7.01 (d, <i>J</i> = 3.6 Hz, 1H), 6.45 (d, <i>J</i> = 3.6 Hz, 1H), 4.29 – 4.18 (m, 2H), 3.74 (q, <i>J</i> = 7.2 Hz, 2H), 3.53 (d, <i>J</i> = 7.2 Hz, 2H), 3.32 – 3.26 (m, 1H), 2.95 – 2.90 (m, 1H), 2.88 (s, 2H), 2.68 (d, <i>J</i> = 11.2 Hz, 1H), 2.04 – 1.91 (m, 3H), 1.87 – 1.77 (m, 5H), 1.66 – 1.59 (m, 1H), 1.43 – 1.39 (m, 1H), 1.31 – 1.27 (m, 2H), 1.25 – 1.14 (m, 4H), 1.10 – 1.01 (m, 2H).	Flash CC (MeOH:DCM =1:10)	NH ₄ Ac	497	IC (Hex:EtOH:D EA=40:60:0.3)

B6-1-2	¹ H NMR (400 MHz, CD ₃ OD- <i>d</i> 4) δ 8.04 (s, 1H), 7.02 (d, <i>J</i> = 3.6 Hz, 1H), 6.47 (d, <i>J</i> = 3.6 Hz, 1H), 4.30 – 4.19 (m, 2H), 3.75 (q, <i>J</i> = 6.8 Hz, 2H), 3.55 (d, <i>J</i> = 6.8 Hz, 2H), 3.34 – 3.28 (m, 1H), 2.98 – 2.91 (m, 3H), 2.71 (d, <i>J</i> = 11.2 Hz, 1H), 2.06 – 1.95 (m, 3H), 1.89 – 1.79 (m, 5H), 1.68 – 1.61 (m, 1H), 1.45 – 1.41 (m, 1H), 1.33 – 1.29 (m, 2H), 1.27 – 1.15 (m, 4H), 1.12 – 1.03 (m, 2H).	Flash CC (MeOH: DCM =1:10)	NH4Ac	497	IC (Hex:EtOH:D EA=40:60:0.3)
B6-2	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 1.04 (m, 2H), 1.25 (m, 2H), 1.43 (ddd, <i>J</i> = 20.9, 10.6, 6.7 Hz, 2H), 1.57 (m, 4H), 1.68 – 1.88 (m, 6H), 1.95 (d, <i>J</i> = 11.4 Hz, 2H), 2.08 – 2.27 (m, 4H), 2.28 – 2.48 (m, 2H), 2.83 (d, <i>J</i> = 11.1 Hz, 1H), 2.90 – 3.12 (m, 3H), 3.68 (t, <i>J</i> = 7.3 Hz, 1H), 3.77 (dd, <i>J</i> = 14.7, 2.1 Hz, 1H), 4.87 (ddd, <i>J</i> = 13.5, 10.6, 2.8 Hz, 2H), 5.26 (brs, 1H), 6.48 (d, <i>J</i> = 3.6 Hz, 1H), 6.75 (brs, 1H), 6.84 (d, <i>J</i> = 3.6 Hz, 1H), 8.26 (s, 1H).	523		523	
AD-6-1	¹ H NMR (400 MHz, CDCl ₃): δ 7.87 (s, 1H), 6.95 (br s, 1H), 5.66 (br s, 1H), 5.41 (br s, 1H), 4.98 (br s, 1H), 3.74-3.69 (m, 1H), 3.59-3.51 (m, 3H), 3.41-3.36 (m, 3H), 3.16-3.11 (m, 1H), 3.03 (s, 2H), 2.78-2.74 (m, 1H), 2.59-2.56 (m, 2H), 2.44 (t, <i>J</i> = 10.8 Hz, 1H), 2.01-1.96 (m, 3H), 1.86-1.83 (m, 2H), 1.78-1.65 (m, 3H), 1.34-1.25 (m, 2H), 1.17 (t, <i>J</i> = 6.8 Hz, 3H), 1.05-0.96 (m, 2H)	Prep- TLC (MeOH: DCM=1 :10)	HN4HO Ac	MS Calcd.: 506; MS Found: 507	IG (Hex:EtOH:D EA=60:40:0.3)
AD-6-2	¹ H NMR (400 MHz, CDCl ₃): δ 7.86 (s, 1H), 6.94 (br s, 1H), 5.61 (br s, 1H), 5.40 (br s, 1H), 4.96 (br s, 1H), 3.73-3.68 (m, 1H), 3.57-3.50 (m, 3H), 3.40-3.34 (m, 3H), 3.15-3.10 (m, 1H), 3.02 (s, 2H), 2.77-2.73 (m, 1H), 2.58-2.55 (m, 2H), 2.43 (t, <i>J</i> = 10.4 Hz, 1H), 2.00-1.95 (m, 3H), 1.85-	Prep- TLC (MeOH: DCM=1 :10)	HN4HO Ac	MS Calcd.: 506; MS Found: 507	IG (Hex:EtOH:D EA=60:40:0.3)

	1.82 (m, 2H), 1.77-1.64 (m, 3H), 1.33-1.24 (m, 2H), 1.16 (t, $J = 6.8$ Hz, 3H), 1.04-0.95 (m, 2H)				
BD-5-1-1	^1H NMR (400 MHz, CDCl_3): δ 8.22 (s, 1H), 6.85 (s, 1H), 6.79 (br s, 1H), 6.43 (s, 1H), 5.62 (br s, 1H), 4.46 (d, $J = 14.4$ Hz, 1H), 3.83-3.71 (m, 3H), 3.63-3.56 (m, 2H), 3.32-3.28 (m, 1H), 2.99 (s, 2H), 2.74-2.70 (m, 1H), 2.58-2.56 (m, 2H), 2.46 (t, $J = 10.8$ Hz, 1H), 2.03-1.85 (m, 6H), 1.75-1.63 (m, 3H), 1.34-1.25 (m, 6H), 1.15-1.06 (m, 2H).	Prep-TLC (MeOH:DCM=1:10)	NH4Ac	513	IG (Hex:EtOH:D EA=40:60:0.3)
BD-5-1-2	^1H NMR (400 MHz, CDCl_3): δ 8.22 (s, 1H), 6.85 (s, 1H), 6.80 (br s, 1H), 6.43 (s, 1H), 5.65 (br s, 1H), 4.46 (d, $J = 14.8$ Hz, 1H), 3.83-3.71 (m, 3H), 3.63-3.57 (m, 2H), 3.32-3.28 (m, 1H), 2.99 (s, 2H), 2.74-2.71 (m, 1H), 2.59-2.57 (m, 2H), 2.46 (t, $J = 10.8$ Hz, 1H), 2.04-1.85 (m, 6H), 1.75-1.63 (m, 3H), 1.34-1.25 (m, 6H), 1.15-1.06 (m, 2H).	Prep-TLC (MeOH:DCM=1:10)	NH4Ac	513	IG (Hex:EtOH:D EA=40:60:0.3)

General Method G – Cyclic alkoxy substituted secondary amines



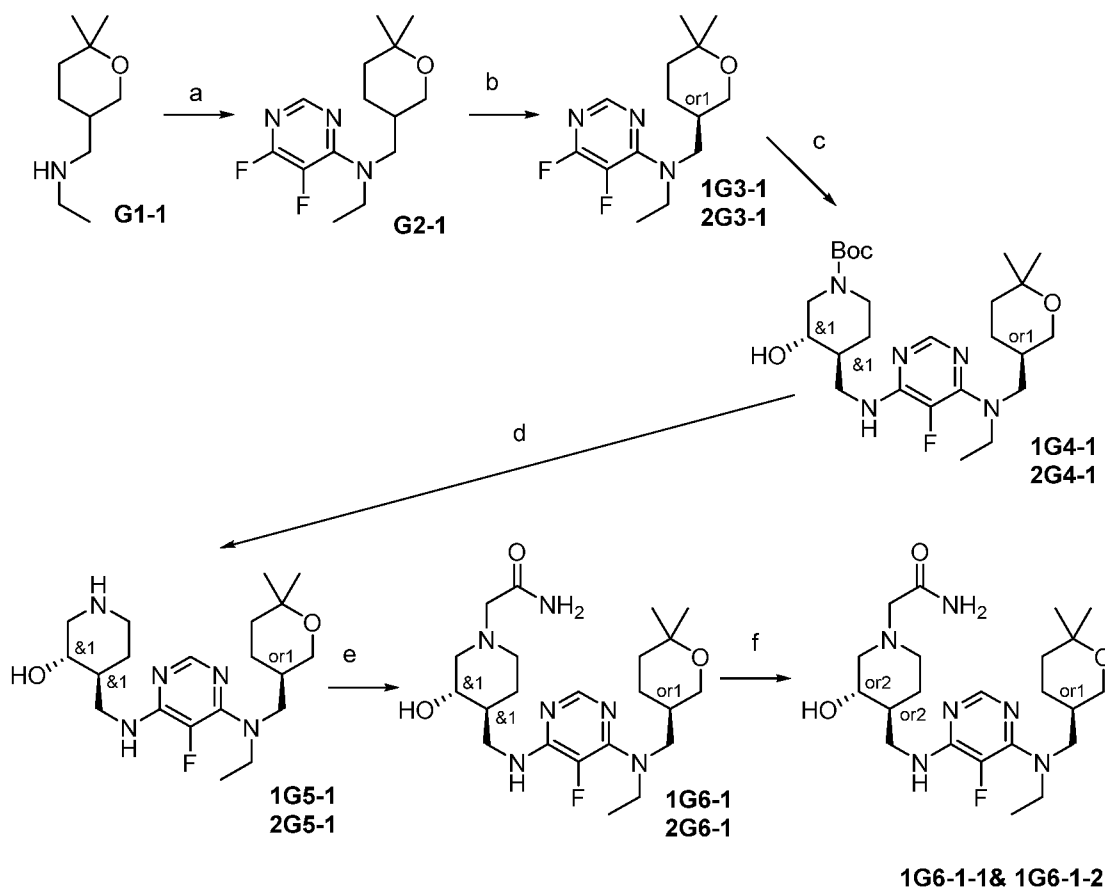
General Scheme G

The secondary amine G1 was reacted with A2 (at ambient temperature or slightly above, 30 °C) together with a suitable base (such as; DIEA, TEA or K₂CO₃) at 5 rt. After the reaction was deemed complete the intermediate G2 was worked up and purified by chromatography (Flash CC or HPLC). The stereoisomers of G3, were then, if possible, isolated.

These separated stereo isomers, XG3 (denoted 1G3, 2G3 and so on) were then 10 reacted with the primary amine A4 as to give XG4. After boc-deprotection XG5, and thereafter subjected to alkylation with 2-bromoacetamide to produce XG6. The stereoisomeric mixtures XG6 were then subjected to chiral resolution (chromatography) in order to isolate as many stereo isomers as possible.

Example G6-1

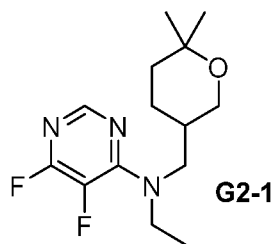
15 Synthesis and isolation of the four stereo isomers of G6-1



a) DMSO, DIEA, **A2-1**. b) Chiral separation. c) **A4-6**, DMSO, DIEA. d) TFA, DCM. e) Cs_2CO_3 , DMF. f) Chiral Separation.

Scheme G6-1

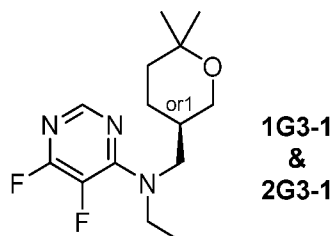
- 5 Synthesis of *N*-((6,6-dimethyltetrahydro-2*H*-pyran-3-yl)methyl)-*N*-ethyl-5,6-difluoropyrimidin-4-amine, G2-1. and separation of the stereoisomers *rel*-(*R*)-*N*-((6,6-dimethyltetrahydro-2*H*-pyran-3-yl)methyl)-*N*-ethyl-5,6-difluoropyrimidin-4-amine, 1G2-1 and 2G2-1



- 10 A mixture of G1-1 (340 mg, 1.98 mmol), 4, 5, 6-trifluoropyrimidine (318 mg, 2.38 mmol), DIEA (510 mg, 3.96 mmol) and DMSO (20 mL) was stirred at rt overnight. Then H₂O (50 mL) was added and the mixture was extracted with DCM (50

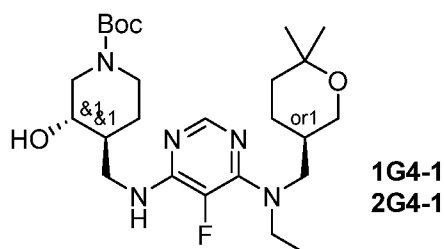
mL x 2). The combined organic phase was washed with H₂O, brine, dried (Na₂SO₄) and contracted. The residue was purified by Flash CC (PE:EA=10:1to5:1) to give G2-1. MS Calcd.: 285; MS Found: 286 ([M+H]⁺).

5 Separation and isolation of the stereoisomers *rel*-(*R*)-*N*-((6,6-dimethyltetrahydro-2*H*-pyran-3-yl)methyl)-*N*-ethyl-5,6-difluoropyrimidin-4-amine, 1G2-1 and 2G2-1



G2-1 was subjected to chiral chromatography to give 1G2-1 (240 mg, 1st eluting isomer) and 2G2-1 (230 mg, 2nd eluting isomer).

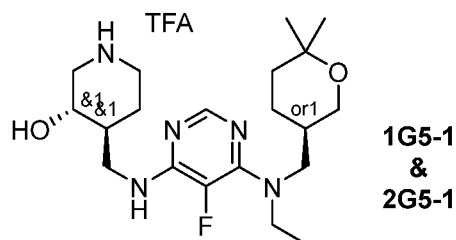
10 Synthesis of *tert*-butyl (3*RS*,4*RS*)-4-(((6-(((*S**)-6,6-dimethyltetrahydro-2*H*-pyran-3-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidine-1-carboxylate, 1G4-1 and 2G4-1



15 A mixture of 1G3-1 (110 mg, 0.39 mmol), XYZ (105 mg, 0.46 mmol), DIEA (118 mg, 0.91 mmol) and DMSO (10 mL) was stirred at 80 °C on. Thereafter the reaction was cooled to rt, washed with H₂O and extracted with EA (20 mL). The organic phase was washed with brine, dried (Na₂SO₄) and contracted to afford 1G4-1. MS Calcd.: 495; MS Found: 496 ([M+H]⁺).

20 A mixture of 2G3-1 (97 mg, 0.34 mmol), XYZ (92 mg, 0.40 mmol), DIEA (103 mg, 0.80 mmol) and DMSO (10 mL) was stirred at 80 °C on. Thereafter the reaction was cooled to rt, washed with H₂O and extracted with EA (20 mL). The organic phase was washed with brine, dried (Na₂SO₄) and contracted to afford 2G4-1. MS Calcd.: 495; MS Found: 496 ([M+H]⁺).

Synthesis of (3*RS*,4*RS*)-4-(((6-(((*S*^{*})-6,6-dimethyltetrahydro-2*H*-pyran-3-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-ium trifluoroacetate, 1G5-1 and 2G5-1.

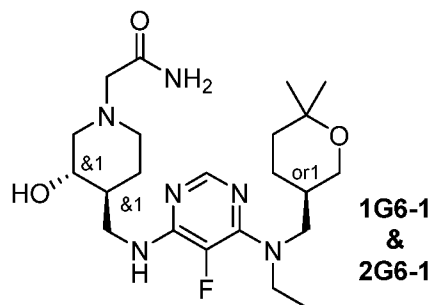


5 A mixture of 1G4-1 (170 mg, 0.34 mmol), DCM (3 mL) and TFA (3 mL) was stirred at rt for 2 hours and thereafter contracted to afford 1G5-1. MS Calcd.: 395; MS Found: 396 ([M+H]⁺).

A mixture of 2G4-1 (166 mg, 0.33 mmol), DCM (3 mL) and TFA (3 mL) was stirred at rt for 2 hours and contracted to afford 2G5-1. MS Calcd.: 395; MS Found: 396 ([M+H]⁺).

10

Synthesis of 2-(((3*RS*,4*RS*)-4-(((6-(((*S*^{*})-6,6-dimethyltetrahydro-2*H*-pyran-3-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide, 1G6-1 and 2G6-1.

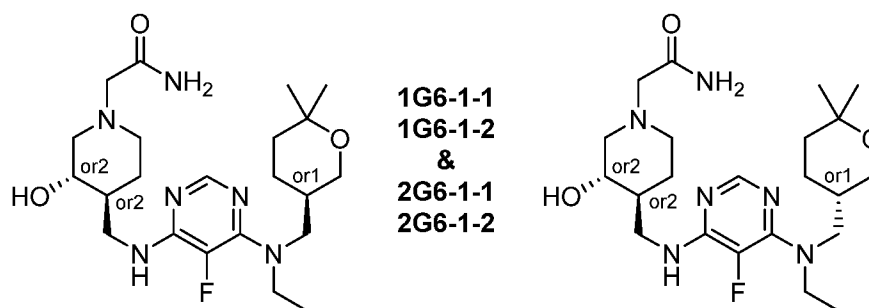


15 A mixture of 1G5-1 (174 mg, 0.34mmol), DMF (7 mL), K₂CO₃ (141 mg, 1.02 mmol) and 2-bromoacetamide (56.6 mg, 0.41 mmol) was stirred at rt on. Water was added and the mixture was extracted EA. The organic phase was dried (Na₂SO₄) filtered and concentrated *in vacuo*. The residue was thereafter purified by Flash CC (DCM:MeOH=30:1to10:1) to afford 1G6-1. A mixture of 2G5-1 (170 mg, 0.33 mmol),

20 DMF (7 mL), K₂CO₃ (136 mg, 0.99 mmol) and 2-bromoacetamide (55.3 mg, 0.41 mmol) was stirred at rt on. Water was added and the mixture was extracted EA. The

organic phase was dried (Na₂SO₄) filtered and concentrated *in vacuo*. The residue was thereafter purified by Flash CC (DCM:MeOH=30:1 to 10:1) to afford 2G6-1.

Isolation of the 4 stereoisomers *rel*-2-((3*R*,4*R*)-4-(((6-(((*S*)-6,6-dimethyltetrahydro-2*H*-pyran-3-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide and *rel*-2-((3*R*,4*R*)-4-(((6-(((*R*)-6,6-dimethyltetrahydro-2*H*-pyran-3-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide, 1G6-1-1, 1G6-1-2, 2G6-1-1 and 2G6-1-2.



Subsequent chiral chromatography 1G6-1 gave 1G6-1-1 (1st eluting peak,) and 1G6-1-2 (2nd eluting peak,).

Subsequent chiral chromatography of 2G6-1 gave two stereoisomers 2G6-1-1 (1st eluting peak,) and 2G6-1-2 (2nd eluting peak,).

The following compounds in Table 3 have been synthesized according to General Method G.

Table 3:

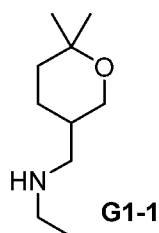
G1	XG6
G1-2 N-((6-(trifluoromethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)methyl)ethanamine	1&2G6-2-1 <i>rel</i> -2-((3 <i>R</i> ,4 <i>R</i>)-4-(((3-(ethyl((6-(trifluoromethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)methyl)amino)-2-fluorophenyl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide

G1-2	1&2G6-2-2&3* rel-2-((3R,4R)-4-(((3-(ethyl((6-(trifluoromethyl)tetrahydro-2H-pyran-3-yl)methyl)amino)-2-fluorophenyl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide *mixture of two stereoisomers
G1-2	1&2G6-2-4 rel-2-((3R,4R)-4-(((3-(ethyl((6-(trifluoromethyl)tetrahydro-2H-pyran-3-yl)methyl)amino)-2-fluorophenyl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide
G1-2	3G6-2-1 rel-2-((3R,4R)-4-(((3-(ethyl((6-(trifluoromethyl)tetrahydro-2H-pyran-3-yl)methyl)amino)-2-fluorophenyl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide
G1-2	3G6-2-2 rel-2-((3R,4R)-4-(((3-(ethyl((6-(trifluoromethyl)tetrahydro-2H-pyran-3-yl)methyl)amino)-2-fluorophenyl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide
G1-2	4G6-2-1 rel-2-((3R,4R)-4-(((3-(ethyl((6-(trifluoromethyl)tetrahydro-2H-pyran-3-yl)methyl)amino)-2-fluorophenyl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide
G1-2	4G6-2-2 rel-2-((3R,4R)-4-(((3-(ethyl((6-(trifluoromethyl)tetrahydro-2H-pyran-3-yl)methyl)amino)-2-fluorophenyl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide

In the 1st chiral purification the 1st and 2nd eluting isomers were not separated. In the second chiral purification the 2nd and 3rd eluting isomers, from the mixture of the 1st and 2nd eluting isomers, were not separated.

5 Synthesis of G1-1

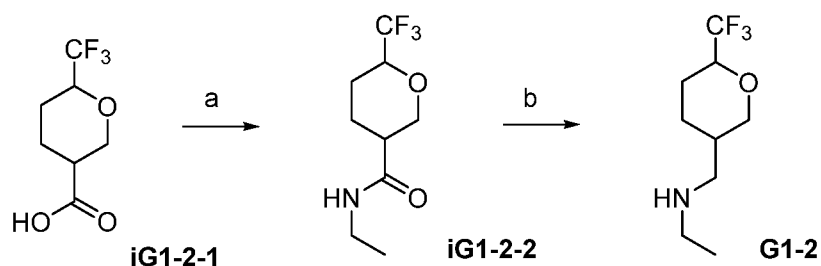
Synthesis of *N*-((6,6-dimethyltetrahydro-2*H*-pyran-3-yl)methyl)ethanamine, G1-1.



A mixture of 6,6-dimethyltetrahydro-2*H*-pyran-3-carbaldehyde (360 mg, 2.53 mmol), MeOH (10 mL), MgSO₄ (1 g) and ethanamine (2 mL, 2 mol/L) was stirred at rt on. Then NaBH₄ (96 mg, 2.53 mmol) was added and the reaction was stirred at rt for 2h.

The reaction was quenched with NH_4Cl and H_2O , extracted with EA (2x50 mL). The combined organic phase was washed with H_2O and brine, dried (Na_2SO_4) and finally concentrated *in vacuo* to afford G1-1. MS Calcd.: 171; MS Found: 172 ($[\text{M}+\text{H}]^+$).

5 Synthesis of *N*-((6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)methyl)ethanamine, G1-2.

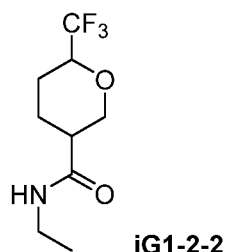


a) EtNH, HATU, DIEA. b) $\text{BH}_3 \cdot \text{THF}$.

iG1-3-1 was prepared according to Claremon, D., et al WO 2017024018 A1

Scheme G1-3

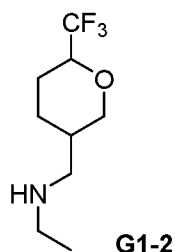
10 Synthesis of *N*-ethyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-carboxamide, iG1-2-2



TEA (1.2 g, 7.5 mmol) and HATU (2.1 g, 5.6 mmol) were added to a solution of 6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-carboxylic acid (740 mg, 3.7 mmol) in THF (10 mL). After stirring the reaction at 30 °C for 30 min ethylamine (2M in THF, 3.7 mL) was added and the reaction was stirred at 30 °C on. H_2O (20 mL) was added and the mixture was extracted with EA (3 x 20 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield crude iG1-2-2. MS Calcd.: 225; MS Found: 226 ($[\text{M}+\text{H}]^+$).

15

20 Synthesis of *N*-((6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)methyl)ethanamine, G1-2.



Under a N₂ atmosphere BH₃·THF (15 mL, 14.9 mmol) was added in portions to a solution of crude iG1-2-2 (1.5 g) in THF (10 mL) and the reaction was stirred at reflux on. The reaction was then cooled to 0 °C (ice-bath) and then MeOH (2 mL), followed by HCl (2 mL, 1M), were added. After concentration Na₂CO₃ (sat, 20 mL) was added to the residue and the mixture was extracted with EA (3 x 20 mL). The combined organic phase was washed with brine (20 mL), dried (Na₂SO₄). The organic solution was filtered and concentrated *in vacuo* to afford crude 2-5 that was used without further purification. MS Calcd.: 211; MS Found: 212 ([M+H]⁺).

10 Analytical table 2.

Patent example	¹ H-NMR	prep HPLC method	analytical HPLC method	MS (observed)	chiral separation method
1G6-1-1	¹ H-NMR (400MHz, CDCl ₃): δ 7.88 (d, <i>J</i> = 2.0 Hz, 1H), 6.96 (s, 1H), 5.88 (s, 1H), 5.34 (d, <i>J</i> = 2.4 Hz, 1H), 4.87 (s, 1H), 4.17-4.10 (m, 1H), 3.70-3.30 (m, 6H), 3.10-3.02 (m, 3H), 2.86 (d, <i>J</i> = 10.8 Hz, 1H), 2.23-2.10 (m, 2H), 1.96-1.95 (m, 1H), 1.71-1.67 (m, 1H), 1.58-1.47 (m, 5H), 1.45-1.36 (m, 3H), 1.20-1.15 (m, 9H).	Flash CC (DCM:MeOH=30:1 to 10:1)	NH ₄ OAc	453	ID (CO ₂ :IPA:DEA=60:40:0.3)
1G6-1-2	¹ H-NMR (400MHz, CDCl ₃): δ 7.88 (d, <i>J</i> = 2.0 Hz, 1H), 6.95 (s, 1H), 5.88 (s, 1H), 5.34 (d, <i>J</i> = 2.4 Hz, 1H), 4.87 (s, 1H), 4.12-4.10 (m, 1H), 3.69-3.32 (m, 6H), 3.11-3.02	Flash CC (DCM:MeOH=30:1 to 10:1)	NH ₄ OAc	453	ID (CO ₂ :IPA:DEA=60:40:0.3)

	(m, 3H), 2.87 (d, $J = 1.6$ Hz, 1H), 2.20-2.10 (m, 2H), 1.70-1.62 (m, 1H), 1.55-1.51 (m, 5H), 1.46-1.37 (m, 3H), 1.20-1.15 (m, 9H).				
2G6-1-1	1H-NMR (400MHz, CDCl ₃) δ 7.88 (d, $J = 1.6$ Hz, 1H), 6.96 (d, $J = 3.2$ Hz, 1H), 5.42 (d, $J = 2.0$ Hz, 1H), 4.87 (s, 1H), 4.16-4.11 (m, 1H), 3.70-3.65 (m, 1H), 3.58-3.48 (m, 2H), 3.42-3.38 (m, 2H), 3.35-3.30 (m, 1H), 3.10-3.02 (m, 3H), 2.86 (d, $J = 12.0$ Hz, 1H), 2.20-2.10 (m, 2H), 1.96 (s, 1H), 1.71-1.58 (m, 6H), 1.45-1.37 (m, 3H), 1.23-1.15 (m, 9H)	Flash CC (DCM:Me OH=30:1 to 10:1)	TFA	453	IA (CO ₂ :Me OH:DEA =60:40:0.3)
2G6-1-2	1H-NMR (400MHz, CDCl ₃) δ 7.88 (d, $J = 1.6$ Hz, 1H), 6.96 (d, $J = 3.2$ Hz, 1H), 5.45(d, $J = 2.0$ Hz, 1H), 4.89 (t, $J = 7.6$ Hz, 1H), 4.15-4.05 (m, 1H), 3.69-3.65 (m, 1H), 3.57-3.49 (m, 2H), 3.42-3.39 (m, 2H), 3.36-3.30 (m, 1H), 3.11-3.00 (m, 3H), 2.86 (d, $J = 10.8$ Hz, 1H), 2.23-2.10 (m, 2H), 1.95 (d, $J = 6.4$ Hz, 1H), 1.70-1.58 (m, 6H), 1.45-1.36 (m, 3H), 1.20-1.15 (m, 9H)	Flash CC (DCM:Me OH=30:1 to 10:1)	NH ₄ OAc	453	IA (CO ₂ :Me OH:DEA =60:40:0.3)
1&2G6-2-1	1H-NMR (400 MHz, CDCl ₃): δ 7.88 (d, $J = 1.6$ Hz, 1H), 6.94 (s, 1H), 5.83 (s, 1H), 5.38-5.42 (m, 1H), 4.90-4.95 (m, 1H), 4.10-4.17 (m, 1H), 3.95-3.99 (m, 1H), 3.60-3.85 (m, 4H), 3.42-3.50 (m, 2H), 3.29-3.35 (m, 1H), 3.02-3.13 (m, 4H), 2.85-2.89 (m, 1H), 2.11-2.24 (m, 2H), 2.04-2.08 (m, 1H), 1.82-1.87 (m, 2H), 1.50-1.81 (m, 2H), 1.37-1.44 (m, 1H), 1.26-1.33 (m, 2H), 1.17-1.25 (t, $J = 6.8$ Hz, 3H)	Flash CC (DCM:Me OH=20:1)	NH ₄ OAc	493	IG (Hex:EtO H:DEA= 50:50:0.3)

1&2G6-2-2&3**	1H-NMR (400 MHz, CDCl ₃): δ 7.88 (d, J = 1.6 Hz, 1H), 6.94 (s, 1H), 5.83 (s, 1H), 5.45-5.50 (m, 1H), 4.90-4.95 (m, 1H), 4.08-4.14 (m, 1H), 3.95-3.99 (m, 1H), 3.74-3.82 (m, 2H), 3.60-3.68 (m, 2H), 3.45-3.55 (m, 2H), 3.29-3.36 (m, 1H), 3.02-3.13 (m, 4H), 2.85-2.89 (m, 1H), 2.10-2.24 (m, 2H), 2.04-2.08 (m, 1H), 1.50-1.89 (m, 4H), 1.32-1.44 (m, 1H), 1.26-1.33 (m, 2H), 1.18-1.22 (t, J = 7.2 Hz, 3H)	Flash CC (DCM:Me OH=20:1)	NH ₄ OAc	493	IG (Hex:EtO H:DEA=50:50:0.3)
1&2G6-2-4	1H-NMR (400 MHz, CDCl ₃): δ 7.88 (d, J = 1.6 Hz, 1H), 6.93 (s, 1H), 5.83 (s, 1H), 5.34-5.38 (m, 1H), 4.90-4.95 (m, 1H), 4.10-4.17 (m, 1H), 3.95-3.99 (m, 1H), 3.60-3.85 (m, 4H), 3.42-3.49 (m, 2H), 3.29-3.35 (m, 1H), 3.02-3.12 (m, 4H), 2.85-2.89 (m, 1H), 2.11-2.24 (m, 2H), 2.04-2.08 (m, 1H), 1.82-1.87 (m, 2H), 1.53-1.81 (m, 2H), 1.37-1.44 (m, 1H), 1.26-1.33 (m, 2H), 1.17-1.25 (t, J = 6.8 Hz, 3H)	Flash CC (DCM:Me OH=20:1)	NH ₄ OAc	493	IG (Hex:EtO H:DEA=50:50:0.3)
3G6-2-1	1H-NMR (400 MHz, CDCl ₃): δ 7.88 (d, J = 1.6 Hz, 1H), 6.94 (s, 1H), 5.77 (s, 1H), 5.34-5.38 (m, 1H), 4.90-4.95 (m, 1H), 4.05-4.17 (m, 2H), 3.64-3.70 (m, 1H), 3.47-3.56 (m, 2H), 3.23-3.45 (m, 4H), 3.02-3.13 (m, 4H), 2.85-2.89 (m, 1H), 2.08-2.24 (m, 3H), 1.96-2.00 (m, 1H), 1.84-1.89 (m, 1H), 1.54-1.67 (m, 2H), 1.37-1.44 (m, 1H), 1.23-1.33 (m, 2H), 1.16-1.21 (t, J = 6.8 Hz, 3H)	Flash CC (DCM:Me OH=20:1)	NH ₄ OAc	493	ID (Hex:IPA :DEA=40 :60:0.3)

3G6-2-2	1H-NMR (400 MHz, CDC13): δ 7.88 (d, J = 1.6 Hz, 1H), 6.94 (s, 1H), 5.77 (s, 1H), 5.37-5.41 (m, 1H), 4.90-4.95 (m, 1H), 4.04-4.15 (m, 2H), 3.64-3.69 (m, 1H), 3.41-3.54 (m, 3H), 3.23-3.34 (m, 3H), 3.02-3.13 (m, 4H), 2.85-2.89 (m, 1H), 2.10-2.24 (m, 3H), 1.95-1.99 (m, 1H), 1.84-1.89 (m, 1H), 1.5-1.67 (m, 2H), 1.40-1.43 (m, 1H), 1.23-1.33 (m, 2H), 1.16-1.21 (t, J = 6.8 Hz, 3H)	Flash CC (DCM:Me OH=20:1)	NH ₄ OAc	493	ID (Hex:IPA :DEA=40 :60:0.3)
4G6-2-1	1H-NMR (400 MHz, CDC13): δ 7.88 (d, J = 2.0 Hz, 1H), 6.95 (s, 1H), 5.77 (s, 1H), 5.42-5.44 (m, 1H), 4.90-4.95 (m, 1H), 4.05-4.17 (m, 2H), 3.64-3.70 (m, 1H), 3.47-3.56 (m, 2H), 3.23-3.45 (m, 4H), 3.02-3.13 (m, 4H), 2.85-2.89 (m, 1H), 2.08-2.24 (m, 3H), 1.96-2.00 (m, 1H), 1.84-1.89 (m, 1H), 1.54-1.67 (m, 2H), 1.37-1.44 (m, 1H), 1.22-1.33 (m, 2H), 1.16-1.21 (t, J = 6.8 Hz, 3H)	Flash CC, (DCM:Me OH=20:1)	NH ₄ OAc	493	IA (Hex:EtO H:DEA= 60:40:0.3)
4G6-2-2	1H-NMR (400 MHz, CDC13): δ 7.88 (d, J = 2.0 Hz, 1H), 6.94 (s, 1H), 5.77 (s, 1H), 5.42-5.44 (m, 1H), 4.90-4.95 (m, 1H), 4.05-4.17 (m, 2H), 3.64-3.70 (m, 1H), 3.41-3.54 (m, 3H), 3.23-3.34 (m, 3H), 3.02-3.13 (m, 4H), 2.85-2.89 (m, 1H), 2.08-2.24 (m, 3H), 1.96-1.99 (m, 1H), 1.84-1.89 (m, 1H), 1.53-1.67 (m, 2H), 1.37-1.44 (m, 1H), 1.22-1.33 (m, 2H), 1.16-1.21 (t, J = 6.8 Hz, 3H)	Flash CC, (DCM:Me OH=20:1)	NH ₄ OAc	493	IA (Hex:EtO H:DEA= 60:40:0.3)

Biological evaluation

The activity of the compounds was evaluated using a ROR γ Reporter assay (also referred to as Gal4 assay). The Gal4 and the Th17 assays (another suitable assay) are both cell-based assays monitoring functional activity of the compound assayed.

Compounds disclosed herein have also been evaluated in a mouse in vivo pharmacodynamic model (anti-CD3-induced plasma IL-17A).

ROR γ Reporter Assay (Gal4)

5 The HEK293 cell line is co-transfected transiently with two plasmids, one with the ROR γ ligand-binding domain fused to galactose-responsive transcription factor (Gal4), and the other with the luciferase reporter gene and Gal binding sites (UAS). This construction allows to determine the ROR γ activity in a cellular system through the measurement of luminescence.

10 A suspension of ROR γ reporter cells was dispensed into plates and cultured 2 h at 37°C and 5% CO₂. Media formulation consisted in DMEM/F-12 medium (Gibco) supplemented with 10% heat inactivated FBS (Sigma-Aldrich), non-essential aminoacids (Sigma-Aldrich), 2 mM Glutamax (Gibco) and 100 U/mL penicillin (Sigma-Aldrich). Dose-response curves with compounds were prepared in 100%
15 DMSO and further diluted 100-fold in culture medium. Compound solutions were added to the plate containing cells (final DMSO concentration of 0.1%) and incubated for 24 h at 37°C and 5% CO₂. Luciferase detection reagent was added to each well, and relative light units (RLUs) were quantified from each assay well using a plate reading luminometer.

20 Values of average RLU \pm S.D. were computed for all treatment sets, followed by the calculations of percent-reduction of ROR γ activity in response to respective test compound. The following formula was used: activity = 100 * [1 - [x test compound/average vehicle where the theoretical minimum reduction (0% reduction)]. For all experiments, the activity values were plotted versus compound concentrations
25 in one single plot and adjusted to a four-parameter logistic curve to obtain the absolute IC₅₀ value along with the 95% confidence interval. These calculations were performed in excel-fit software using X-204 model curve.

The results of ROR γ Reporter (Gal4) Assay are shown in the Table 2 below.

Table 2: ROR γ Reporter Assay (Gal4)		
Patent Example		IC ₅₀ (nM)
A6-1-1-1		35
A6-1-1-2		44
A6-1-2-1		49
A6-1-2-2		ND
A6-2-1		57
A6-2-2		85
A6-3-1		8,1
A6-3-2		14
A6-4-1		31
A6-4-2		33
A6-5		17
A6-6-1		690
A6-6-2		980
A6-7-1		43
A6-7-2		69
A6-8-1		ND
A6-8-2		480
B6-1-1		ND
B6-1-2		ND
B6-2		ND
AD-6-1		1,2
AD-6-2		15
BD-5-1-1		3,3
BD-5-1-2		4,3

As can be seen from the Table 2 above, the compounds of the present disclosure were found to show beneficial activity across the ROR γ Reporter (Gal4) Assay.

According to an embodiment, compounds having $IC_{50} < 1000$ nM values in the ROR γ Reporter Assay (Gal4) are disclosed herein.

According to another preferred embodiment compounds having $IC_{50} < 500$ nM values in the ROR γ Reporter Assay (Gal4) are disclosed herein.

5 According to another more preferred embodiment compounds having $IC_{50} < 100$ nM values in the ROR γ Reporter Assay (Gal4) are disclosed herein.

In vivo IL-17A induction in anti-CD3 model in mice

Male C57BL/6JRj mice (7 week old) were purchased from Janvier Labs and housed at the animal facilities of Almirall throughout the study. Animals were allowed to
10 condition for 5 days in their new environment at $22^{\circ}C \pm 2^{\circ}C$, $55\% \pm 10\%$ relative humidity and 12 h:12 h light:dark cycles. Animals were housed in polycarbonate cages, with free access to water and non-purified stock diet (2014 Teklad Global 14% Protein Rodent Maintenance Diet, Envigo) during the full course of the studies. Care of animals was undertaken in compliance with the European Committee Directive 2010/63/EU, and
15 the Catalan and Spanish law. All procedures were performed according to the ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments) and with approval from the Animal Experimentation Ethical Committee of Almirall (Barcelona, Spain).

Mice were injected intraperitoneally with 7.5 μ g of anti-CD3e (Clone 145-2C11 from Pharmingen BD) at 0 h (day 0) and 48 h (day 3) time-points. The non-induced-group were
20 injected with PBS instead of anti-CD3e. At study completion (4 h after anti-CD3e injection), animals were anaesthetized with isofluorane (Baxter) and 0.5-1 mL blood samples were drawn by intracardiac puncture in heparinized tubes. Plasma samples were stored at $-80^{\circ}C$ for subsequent analysis.

Test compounds were freshly suspended in sterile 0.5% methylcellulose 0.1% tween-80
25 solution (10 mL/kg body weight). Compounds administered by oral gavage according to the selected dosing and body weight; control animals received an equivalent volume of vehicle. Treatments were given twice daily from day 0 to day 3, last administration was done 1 h before anti-CD3e injection.

Plasma levels of IL-17A were measured by ELISA (R&D Systems) according to the
30 manufacturer's instruction. Results were calculated as the percentage of reduction of plasma IL-17A versus the difference between non-induced and anti-CD3e induced groups through the formula: inhibition = $100 * [1 - ((x - \text{mean non-induced}) / (\text{mean control vehicle} - \text{mean non-induced}))]$. The IL-17A inhibition for each treatment can be expressed

as the mean for each treatment group \pm S.E.M. Statistical analysis of data were conducted with one-way ANOVA followed by Dunnett's multiple comparisons test when appropriate. Differences were considered significant when $p \leq 0.05$.

Results:

Compound	Inhibition of IL-17A (%) at 3 mg/kg
AD-6-1	95%

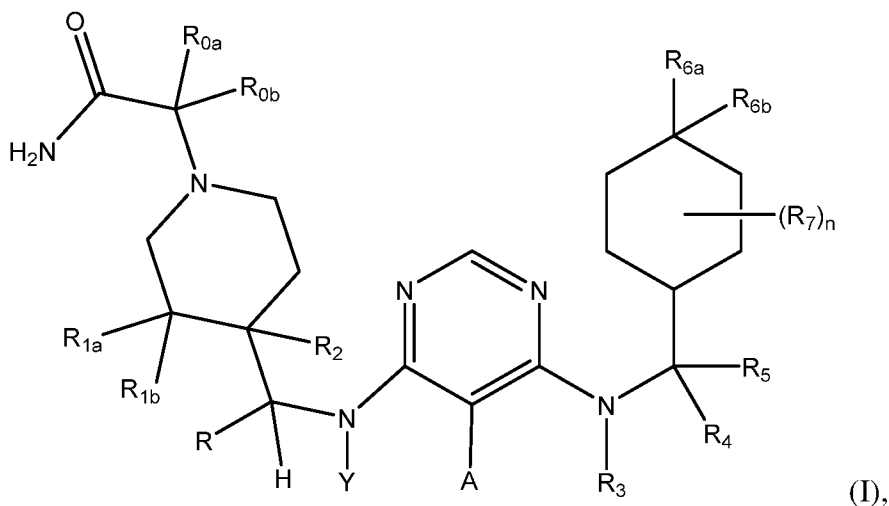
5

In summary, compounds disclosed herein have been found to at least modulate the activity of ROR γ . Compounds disclosed herein are active, e.g. having a Gal4 < 1000 nM, such as < 500 nM, such as < 100 nM.

10 Additionally it has been found that compounds disclosed herein have in vivo usefulness, and could consequently be useful in treating inflammatory, metabolic and autoimmune diseases or symptoms thereof.

CLAIMS

1. A compound according to Formula (I)



- 5 a stereoisomer thereof, or a pharmaceutically acceptable salt of the compound or stereoisomer, wherein:
- n is selected from the group consisting of 0, 1 and 2;
- R is selected from the group consisting of hydrogen, C₁₋₆ alkyl and C₁₋₄ hydroxyalkyl;
- A is fluoro and Y is hydrogen; or
- 10 Y and A are taken together with the atoms to which they are attached to form a 5-membered heteroaryl or heteroalicycyl ring system optionally substituted with 1 or 2 substituents selected from halogen, cyano, or C₁₋₄ alkyl;
- R_{0a} and R_{0b} independently are selected from the group consisting of hydrogen, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, and C₁₋₄ haloalkyl;
- 15 R_{1a} and R_{1b} are independently selected from the group consisting of hydrogen, hydroxyl, amino, halogen, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, and C₁₋₄ haloalkyl;
- R₂ is selected from the group consisting of hydrogen, hydroxyl, amino, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, -C(=O)OH, -C(=O)NH₂, -C(=O)O-C₁₋₄ alkyl, and substituted or unsubstituted heteroaryl;
- 20 R₃ is selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, C₃₋₇ cycloalkyl, and C₃₋₇ cycloalkenyl; or

R₃ and R₄ are taken together with the atoms to which they are attached to form a substituted or unsubstituted 4-6 membered heteroalicyclic ring system ;

R₄ is hydrogen or C₁₋₄ alkyl, provided R₃ and R₄ are not taken together with the atoms to which they are attached to form a substituted or unsubstituted 4-6 membered
5 heteroalicyclic ring system; or R₄ and R₅ are taken together with the carbon atom to which they are attached to form a C₃₋₄ cycloalkyl;

R₅ is absent; or selected from the group consisting of hydrogen and C₁₋₄ alkyl, provided R₄ and R₅ are not taken together with the carbon atom to which they are attached to form a C₃₋₄ cycloalkyl;

10 R_{6a} and R_{6b} are independently selected from the group consisting of hydrogen, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyhaloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, and substituted or unsubstituted heteroaryl, and whenever n is 0 then at least one of R_{6a} and R_{6b} is selected from the group consisting of cyano, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyhaloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxy, C₁₋₄
15 haloalkoxy, and substituted or unsubstituted heteroaryl; or

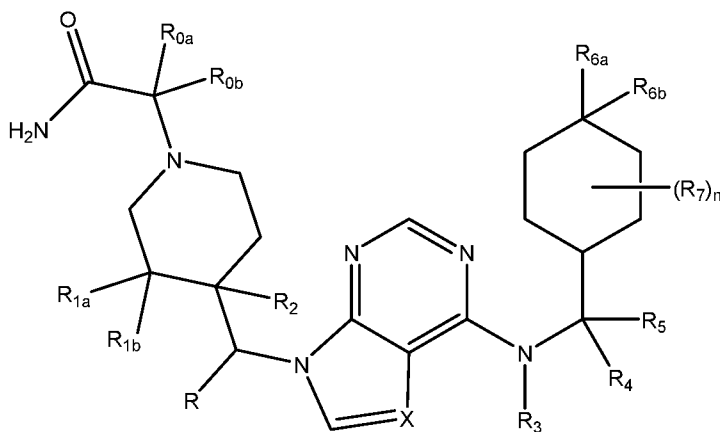
R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form a 3-6 membered alicyclic or a 3-6 membered heteroalicyclic ring system comprising 1-3 heteroatoms selected from S, O, or N, optionally substituted with one to three halogen atoms; and

20

R₇ is selected from the group consisting of hydroxyl, cyano, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy.

2. The compound, stereoisomer, or salt according to claim 1, wherein A is
25 fluoro and Y is hydrogen.

3. The compound, stereoisomer, or salt according to claim 1, having the following formula:



(II), wherein

X is $\text{-CR}_8\text{-}$ or -N- , and R_8 is selected from the group consisting of hydrogen, halogen, cyano, and C_{1-4} alkyl.

- 5 4. The compound, stereoisomer, or salt according to claim 3, wherein X is -CR_8 and R_8 is selected from the group consisting of hydrogen, cyano and fluoro; or X is -N- .
5. The compound, stereoisomer, or salt according to claim 3 or 4, wherein X
- 10 is -CH- .
6. The compound, stereoisomer, or salt according to any one of claims 1-5, wherein R_{0a} is selected from the group consisting of hydrogen, methyl, $\text{-CH}_2\text{OH}$, $\text{-CH}_2\text{CH}_2\text{OH}$, $\text{-CH}_2\text{F}$, and -CHF_2 ; and R_{0b} is selected from the group consisting of
- 15 hydrogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, and C_{1-4} haloalkyl.
7. The compound, stereoisomer, or salt according to any one of claims 1-6, wherein R_{0a} and R_{0b} are both hydrogen.
- 20 8. The compound, stereoisomer, or salt according to any one of claims 1-7, wherein at least one of R_{1a} , R_{1b} and R_2 is not hydrogen.
9. The compound, stereoisomer, or salt according to any one of claims 1-8, wherein R_{1a} is selected from the group consisting of hydroxyl, fluoro and -CF_3 and R_{1b}
- 25 is selected from the group consisting of hydrogen, fluoro, and methyl.

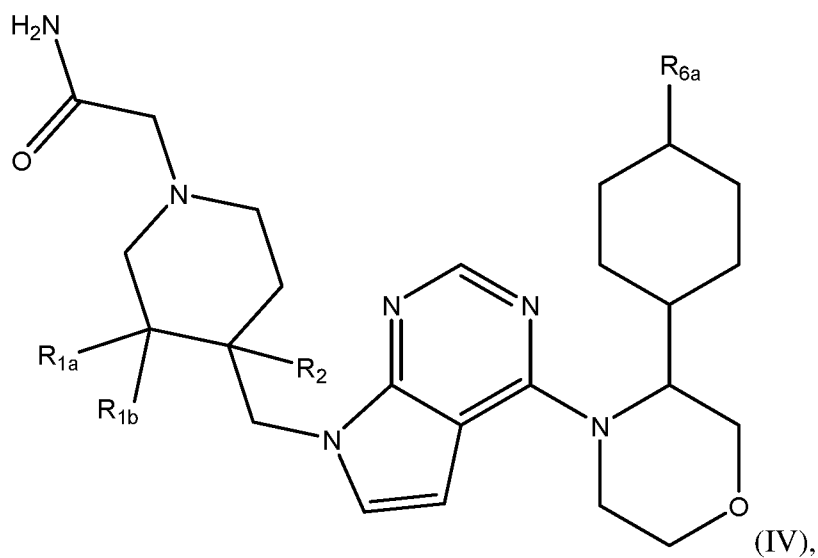
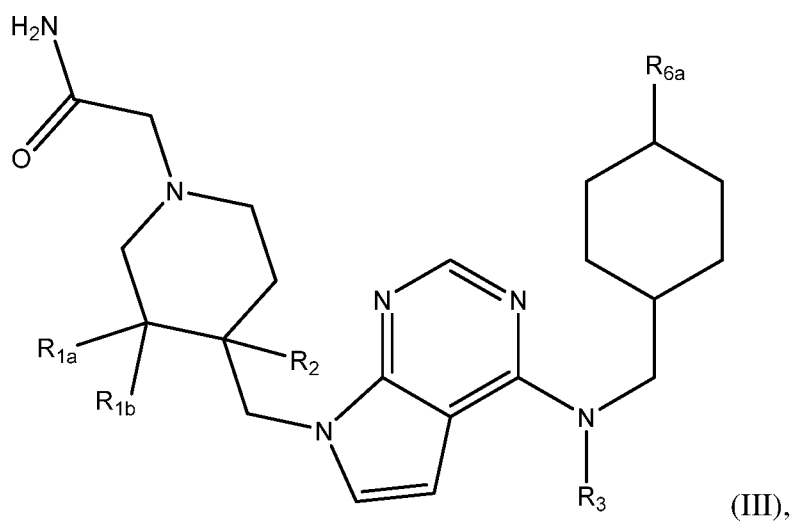
10. The compound, stereoisomer, or salt according to any one of claims 1-9, wherein R_{1a} is hydroxyl or hydrogen.
11. The compound, stereoisomer, or salt according to any one of claims 1-10,
5 wherein R_{1b} is hydrogen.
12. The compound, stereoisomer, or salt according to any one of claims 1-11, wherein R_2 is hydrogen, halogen, hydroxyl, cyano, methyl, ethyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OH}$ or $-\text{C}(=\text{O})\text{O}-\text{C}_{1-2}$ alkyl.
10
13. The compound, stereoisomer, or salt according to any one of claims 1-12, wherein R_2 is hydrogen, fluoro, hydroxyl, or $-\text{CH}_2\text{OH}$.
14. The compound, stereoisomer, or salt according to any one of claims 1-13,
15 wherein R_2 is hydrogen or hydroxyl.
15. The compound, stereoisomer, or salt according to any one of claims 1-14, wherein R_2 is hydrogen.
- 20 16. The compound, stereoisomer, or salt according to any one of claims 1-14, wherein R_2 is hydroxyl.
17. The compound, stereoisomer, or salt according to any one of claims 1-16, wherein R_3 is methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl,
25 cyclopropyl or cyclobutyl.
18. The compound, stereoisomer, or salt according to any one of claims 1-17, wherein R_3 is methyl, ethyl, cyclopropyl, or cyclobutyl.
- 30 19. The compound, stereoisomer, or salt according to any one of claims 1-18, wherein R_3 is ethyl or cyclobutyl.

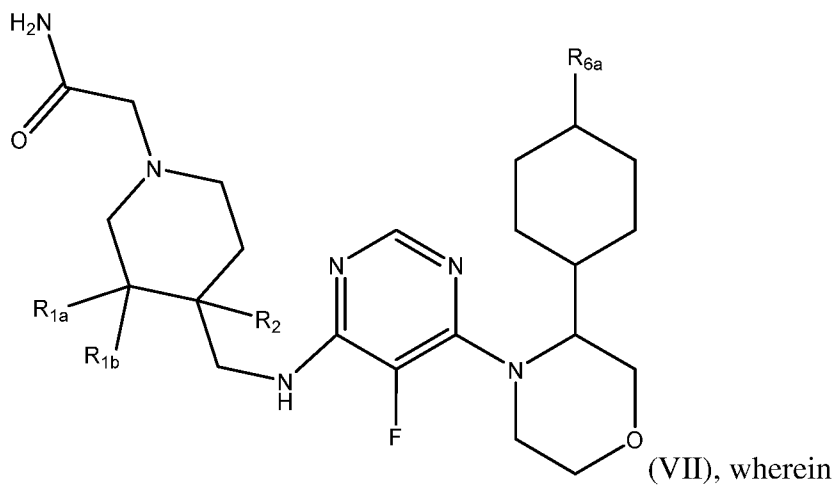
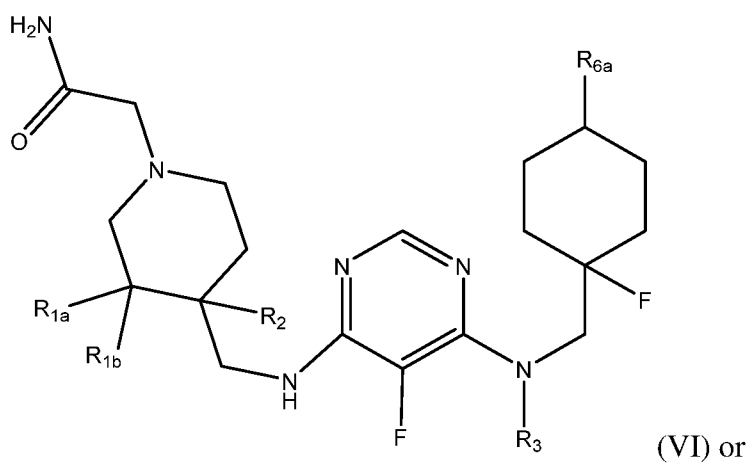
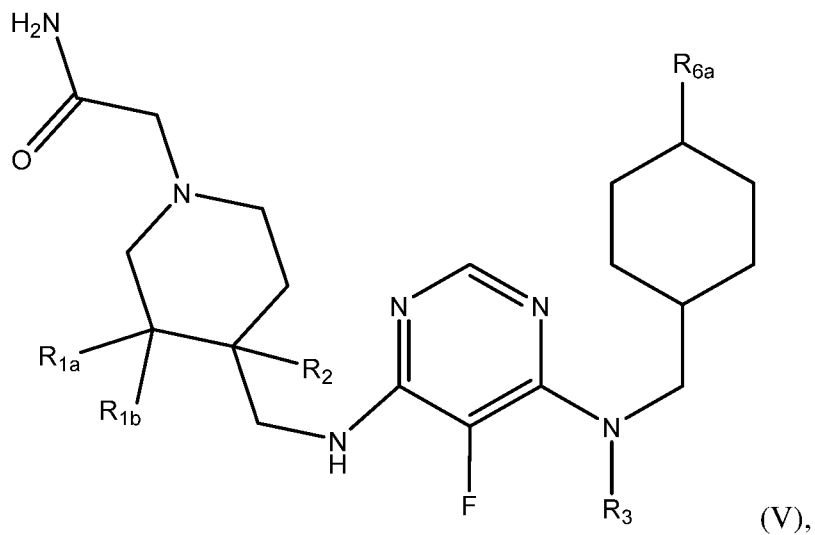
20. The compound, stereoisomer, or salt according to any one of claims 1-19, wherein R₃ is ethyl.
21. The compound, stereoisomer, or salt according to any one of claims 1-20,
5 wherein each of R₄ and R₅ independently is hydrogen or methyl, or R₄ and R₅ are taken together with the carbon atom to which they are attached to form a cyclopropyl.
22. The compound, stereoisomer, or salt according to any one of claims 1-21,
10 wherein R₄ and R₅ are hydrogen.
23. The compound, stereoisomer, or salt according to any one of claims 1-16,
15 wherein the heteroalicyclic ring system comprising R₃ and R₄ is a 4 membered heteroalicyclic ring system, 5 membered heteroalicyclic ring system, or 6 membered heteroalicyclic ring system; wherein the heteroalicyclic ring system is optionally substituted with one or two substituents selected from halogen, hydroxyl, and C₁₋₄ alkyl.
24. The compound, stereoisomer, or salt according to claim 23, wherein the heteroalicyclic ring system comprising R₃ and R₄ is azetidiny, pyrrolidinyl, morpholinyl, piperidinyl, 2-azabicyclo[3.1.0]hexanyl, or 3-azabicyclo[3.1.0]hexanyl;
20 wherein the heteroalicyclic ring system is optionally substituted with one or two substituents selected from halogen and methyl, and whenever the heteroalicyclic ring system is substituted or unsubstituted 2-azabicyclo[3.1.0]hexanyl then R₅ is absent.
25. The compound, stereoisomer, or salt according to any one of claims 23-24,
25 wherein the heteroalicyclic ring system comprising R₃ and R₄ is morpholinyl optionally substituted with one or two substituents selected from halogen and methyl, and R₅ is hydrogen.
26. The compound, stereoisomer, or salt according to any one of claims 23-25,
30 wherein the heteroalicyclic rings system comprising R₃ and R₄ is unsubstituted morpholinyl, and R₅ is hydrogen.

27. The compound, stereoisomer, or salt according to any one of claims 1-26, wherein R_{6a} and R_{6b} are each independently hydrogen, halogen, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy, or R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form a 3-6 membered heteroalicyclic or a 3-6 membered alicyclic ring system, optionally substituted by one to three halogen atoms.
28. The compound, stereoisomer, or salt according to any one of claims 1-27, wherein R_{6a} is hydrogen, $-CF_3$, $-CH_2F$, $-CCH_3F_2$, $-OCF_3$, or $-OCHF_2$, and R_{6b} is hydrogen; or R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form a 3-4 membered alicyclic ring system, optionally substituted by one to three fluoro, or a 4-5 heteroalicyclic ring system, comprising one, two, or three heteroatoms selected from O and N.
29. The compound, stereoisomer, or salt according to any one of claims 1-28, wherein R_{6a} is $-CF_3$, and R_{6b} is hydrogen; or R_{6a} and R_{6b} are taken together with the carbon atom to which they are attached to form an oxetanyl or a cyclopropyl optionally substituted with one or two fluoro.
30. The compound, stereoisomer, or salt according to any one of claims 1-26, wherein at least one of R_{6a} and R_{6b} is substituted or unsubstituted heteroaryl.
31. The compound, stereoisomer, or salt according to claim 30, wherein at least one of R_{6a} and R_{6b} is heteroaryl substituted with C_{1-4} alkyl.
32. The compound, stereoisomer, or salt according to any one of claims 1-31, wherein n is 0 or 1.
33. The compound, stereoisomer, or salt according to any one of claims 1-32, wherein n is 1.
34. The compound, stereoisomer, or salt according to any one of claims 1-33, wherein R_7 is halogen, hydroxyl, cyano, $-CF_3$, $-OCHF_2$, $-CHF_2$ or $-OCF_3$.

35. The compound, stereoisomer, or salt according to any one of claims 1-32, wherein n is 0.

36. The compound, stereoisomer, or salt according to claim 1, wherein the
5 compound has the structure





R_{1a} is hydrogen, fluoro or hydroxyl;

5 R_{1b} is hydrogen or fluoro;

R₂ is hydrogen or hydroxyl

R₃ is methyl, ethyl, cyclopropyl or cyclobutyl;

R_{6a} is -CF₃; and provided at least one of R_{1a}, R_{1b} and R₂ is not hydrogen.

37. The compound, stereoisomer, or salt according to claim 36, wherein R_{1a} is hydrogen or hydroxyl and R_{1b} is hydrogen.

5

38. The compound, stereoisomer, or salt according to claims 36 or 37, wherein R₂ is hydrogen or hydroxyl.

39. The compound, stereoisomer, or salt according to claim 38, wherein R₂ is hydroxyl.

10

40. The compound, stereoisomer, or salt according to claim 38, wherein R₂ is hydrogen.

41. The compound, stereoisomer, or salt according to claim 37, wherein R₂ is hydrogen and R_{1a} is hydroxyl.

15

42. The compound, stereoisomer, or salt according to claim 37, wherein R₂ is hydroxyl and R_{1a} is hydroxyl.

20

43. The compound, stereoisomer, or salt according to any one of claims 36-42, wherein R₃ is ethyl.

44. The compound, stereoisomer, or salt according to claim 1, wherein:

25 R_{0a} and R_{0b} are both hydrogen;

R_{1a} and R_{1b} are independently hydrogen or hydroxyl;

R₂ is selected from the group consisting of hydrogen and hydroxyl;

R is hydrogen;

Y is hydrogen and A is fluoro; or

30 Y and A are taken together with the atoms to which they are attached and the pyrimidine ring of formula (I) to form an unsubstituted pyrrolo[2,3-d]pyrimidine;

R₃ is selected from the group consisting of methyl, ethyl, cyclopropyl and cyclobutyl, and

R₄ and R₅ are hydrogen; or

R₃ and R₄ are taken together with the atoms to which they are attached to form an unsubstituted morpholinyl, and R₅ is hydrogen;

n is 0; or n is 1 and R₇ is a fluoro;

R_{6a} is -CF₃, and R_{6b} is hydrogen; or R_{6a} and R_{6b} are taken together with the carbon atom
5 to which they are attached to form an oxetanyl or a cyclopropyl substituted by two fluoro.

45. The compound, stereoisomer, or salt according to claim 1, selected from the group consisting of:

- 10 *rel*-2-((3*R*,4*R*)-4-(((6-(((1,1-Difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
2-((3*R**,4*R**)-4-(((5-fluoro-6-(methyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)pyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 15 2-((3*R**,4*R**)-4-(((6-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
2-((3*R**,4*R**)-4-(((6-(cyclopropyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 20 2-((3*RS*,4*RS*)-4-(((6-(cyclobutyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
rel-2-((3*R*,4*R*)-4-(((6-(((2-oxaspiro[3.5]nonan-7-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
rel-2-((3*R*,4*R*)-4-(((6-(ethyl((1-fluoro-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-
25 fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
2-4-(((5-fluoro-6-((3*S*)-3-(4-(trifluoromethyl)cyclohexyl)morpholino)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)acetamide,
2-((3*RS*,4*RS*)-4-(((4-(Ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide,

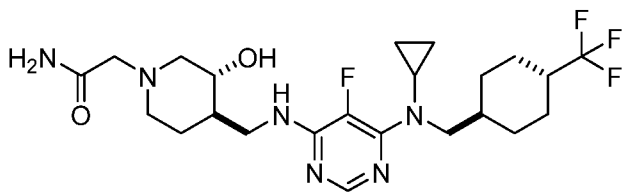
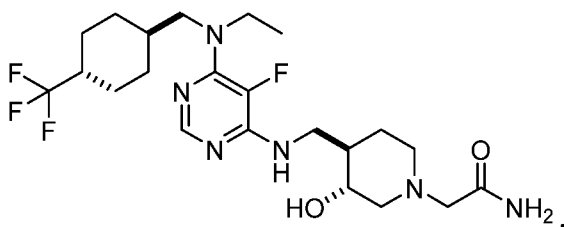
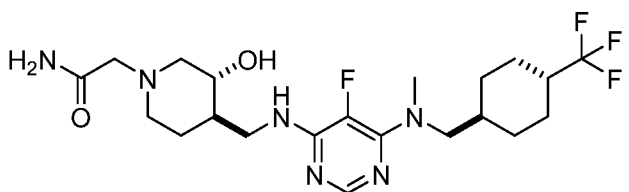
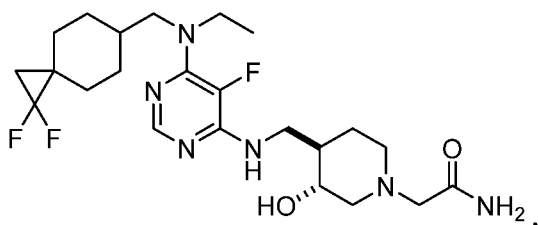
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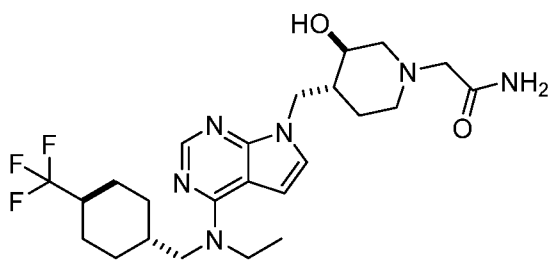
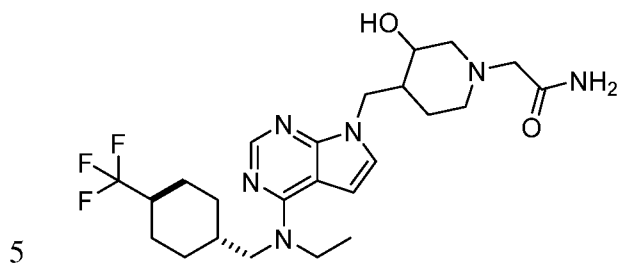
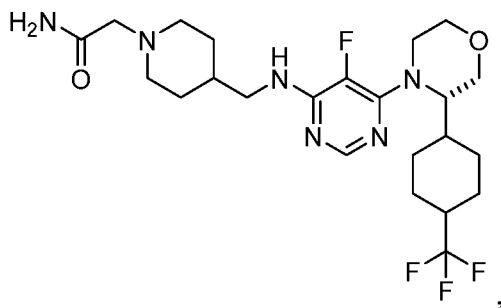
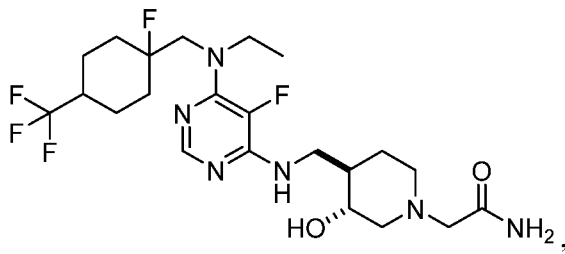
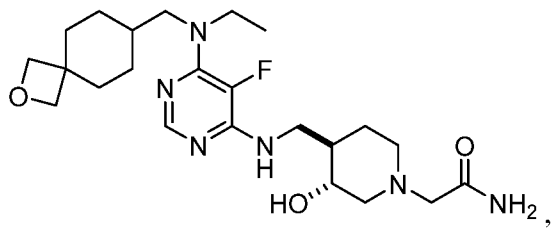
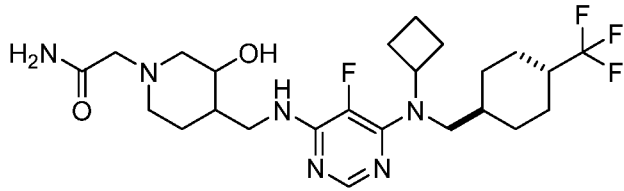
2-((3*RS*,4*RS*)-4-((4-(cyclobutyl(((1*r*,4*S*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide,

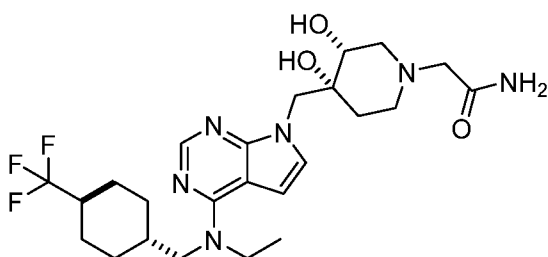
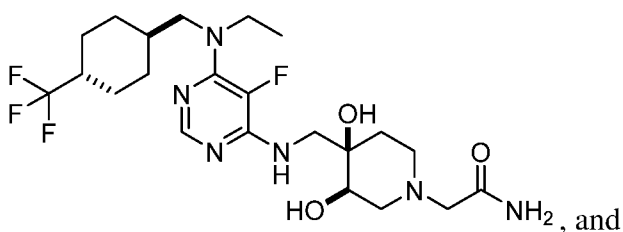
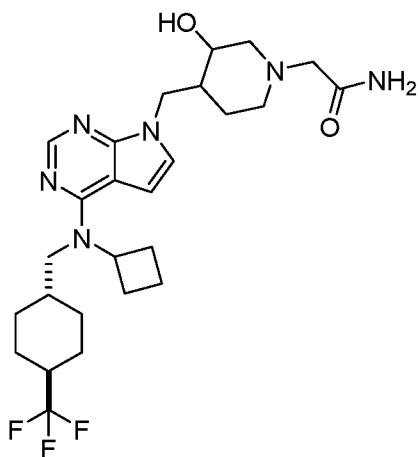
5 2-((3*R**,4*R**)-4-(((6-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide, and

2-((3*R**,4*R**)-4-((4-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide.

46. The compound, stereoisomer, or salt according to claim 1, selected from
10 the group consisting of:







- 5 47. The compound, stereoisomer, or salt according to claim 1, selected from the group consisting of:

2-(4-(((6-(((1,1-Difluorospiro[2.5]octan-6-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,

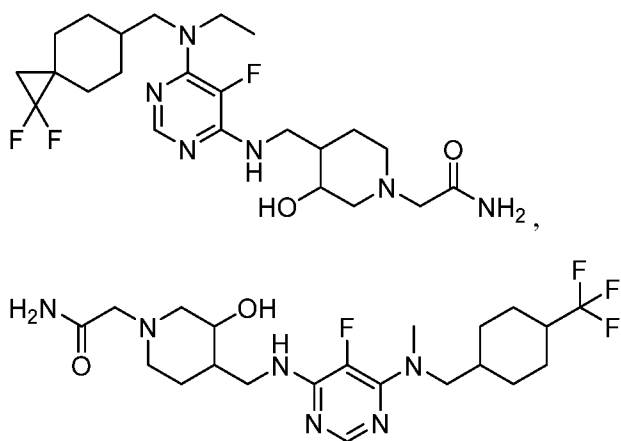
- 10 2-(4-(((5-fluoro-6-(methyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)pyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,

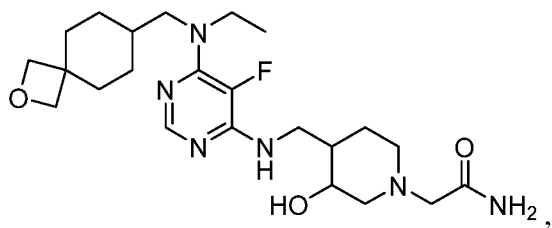
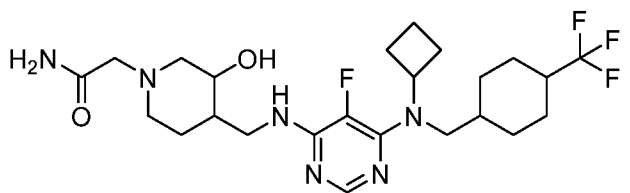
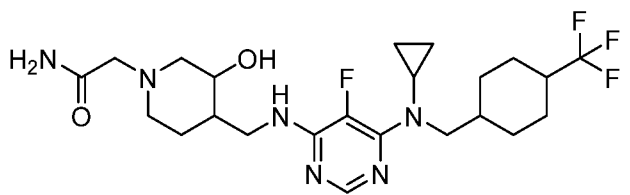
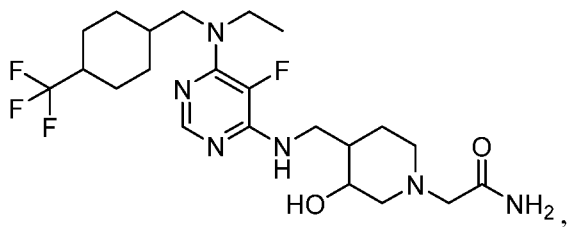
2-(4-(((6-(ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,

- 15 2-(4-(((6-(cyclopropyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,

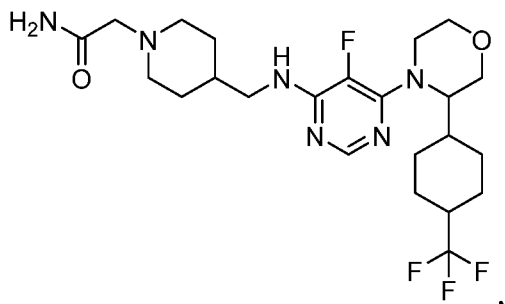
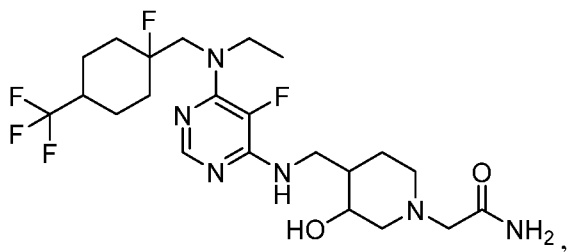
- 2-(4-(((6-(cyclobutyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 2-(4-(((6-(((2-oxaspiro[3.5]nonan-7-yl)methyl)(ethyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 5 2-(4-(((6-(ethyl((1-fluoro-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 2-(4-(((5-fluoro-6-(3-(4-(trifluoromethyl)cyclohexyl)morpholino)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)acetamide,
- 2-(4-(((4-(Ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-
10 *d*]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 2-(4-(((4-(Ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-
d]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 2-(4-(((4-(cyclobutyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-
d]pyrimidin-7-yl)methyl)-3-hydroxypiperidin-1-yl)acetamide,
- 15 2-(4-(((6-(ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide, and
- 2-(4-(((4-(ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-
d]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide.

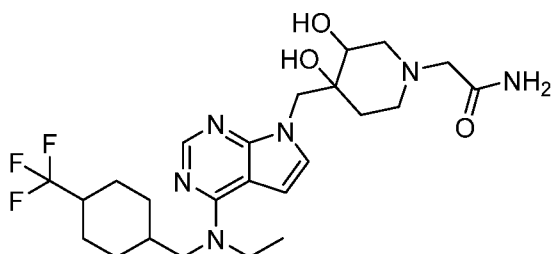
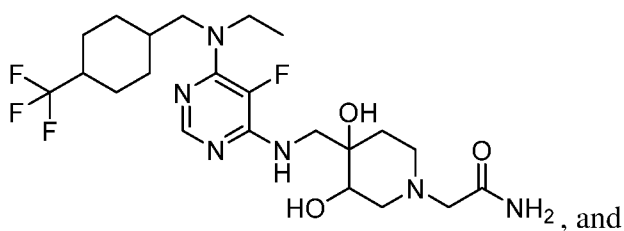
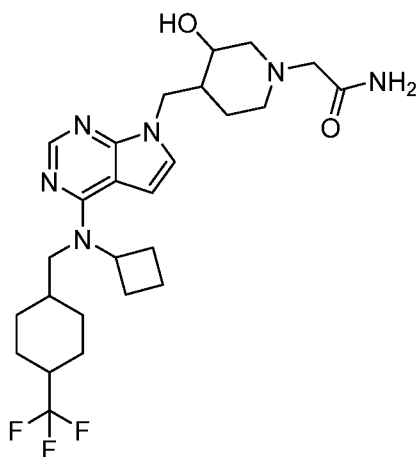
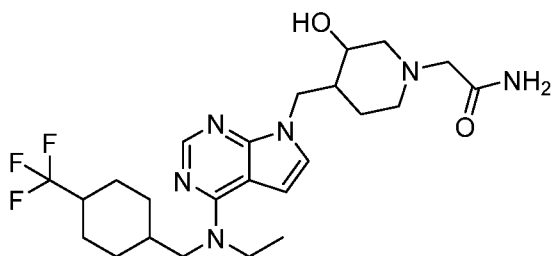
48. The compound, stereoisomer, or salt according to claim 1, selected from
20 the group consisting of:





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49. The compound, stereoisomer, or salt according to claim 1, selected from the group consisting of:

- 2-((3*R**,4*R**)-4-(((6-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide, 2-((3*RS*,4*RS*)-
- 10 4-(((6-(cyclobutyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,

2-((3*R**,4*R**)-4-(((6-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide, and

2-((3*R**,4*R**)-4-(((4-(ethyl(((1*r*,4*R*)-4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide.

5 50. The compound, stereoisomer, or salt according to claim 1, selected from the group consisting of:

2-(4-(((6-(ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,

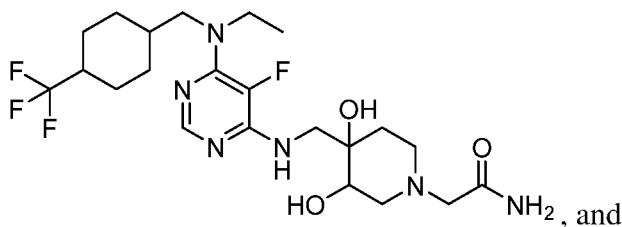
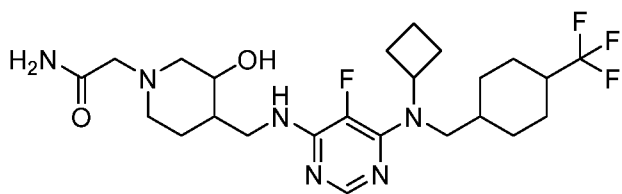
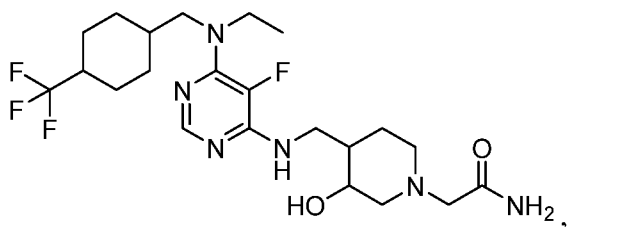
2-(4-(((6-(cyclobutyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-10 4-yl)amino)methyl)-3-hydroxypiperidin-1-yl)acetamide,

2-(4-(((6-(ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-5-fluoropyrimidin-4-yl)amino)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide, and

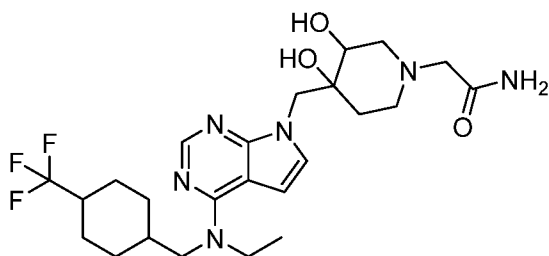
2-(4-(((4-(ethyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl)-3,4-dihydroxypiperidin-1-yl)acetamide.

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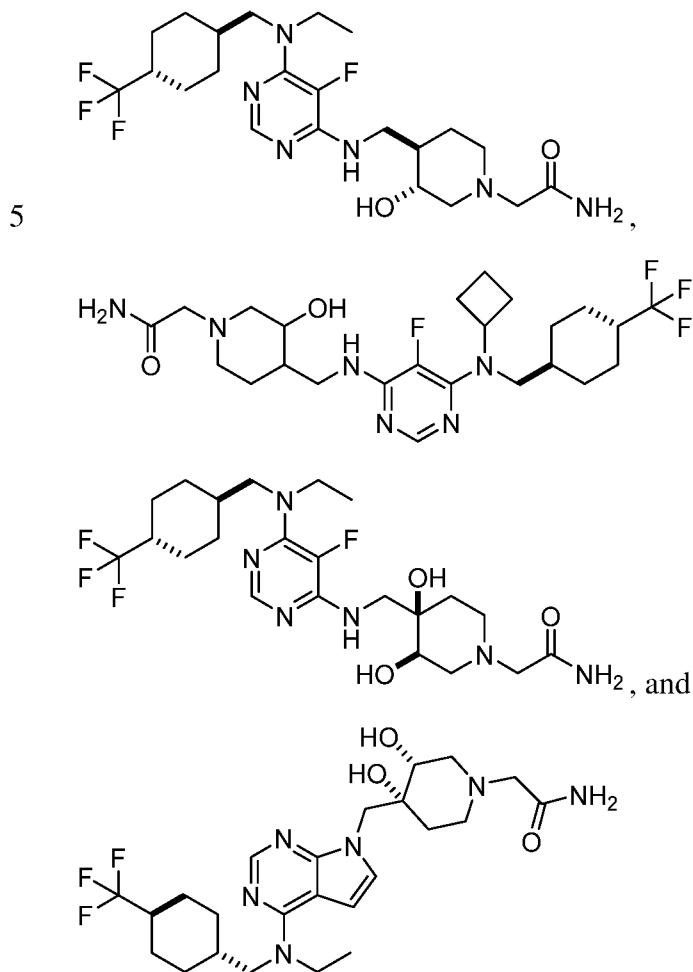
51. The compound, stereoisomer, or salt according to claim 1, selected from the group consisting of:



20



52. The compound, stereoisomer, or salt according to claim 1, selected from the group consisting of:



10 53. A pharmaceutical composition comprising a compound, stereoisomer, or salt according to any one of claims 1-52 and at least one pharmaceutical acceptable excipient.

15 54. A compound, stereoisomer, or salt according to any one of claims 1-52 or a pharmaceutical composition according to claim 53, for use as a medicament.

55. A compound, stereoisomer, or salt according to any one of claims 1-52 or a pharmaceutical composition according to claim 53, for use in the treatment and/or prevention of an inflammatory, metabolic, oncologic or autoimmune disease.

5

56. A method of treating an inflammatory, metabolic, oncologic or autoimmune disease in a subject suffering therefrom, the method comprising: administering to the subject a compound, stereoisomer, or salt according to any one of claims 1-52 or a pharmaceutical composition according to claim 53.

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57. The compound, stereoisomer, or salt or pharmaceutical composition for use according to claim 53 or the method of claim 56 wherein the disease is selected from the group consisting of asthma, acne, chronic obstructive pulmonary disease (COPD), bronchitis, atherosclerosis, helicobacter pylori infection, allergic diseases including allergic rhinitis, allergic conjunctivitis and uveitis, sprue and food allergy, atopic dermatitis, lichen planus, cystic fibrosis, lung allograft rejection, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, ichthyoses, bullous diseases, hidradenitis suppurativa, steatosis, steatohepatitis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), lupus erythematosus, Hashimoto's disease, pancreatitis, autoimmune diabetes, autoimmune ocular disease, ulcerative colitis, colitis, Crohn's disease, inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), Sjogren's syndrome, optic neuritis, type I diabetes, neuromyelitis optica, Myastehnia Gravis, Guillain-Barre syndrome, Graves' disease, scleritis, obesity, obesity-induced insulin resistance, type II diabetes, and cancer.

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58. The compound, stereoisomer, or salt or pharmaceutical composition according to claim 55 or method of claim 56, wherein the disease is selected from the group consisting of acne, atopic dermatitis, lichen planus, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, ichthyoses, bullous diseases, hidradenitis suppurativa, ulcerative colitis, colitis, Crohn's disease, inflammatory bowel disease (IBD) and lupus erythematosus.

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57. A combination product comprising (i) at least one compound, stereoisomer, or salt according to any one of claims 1-52 and (ii) one or more active ingredients selected from the group consisting of:
- 5 a) Corticosteroids, such as prednisone, methylprednisolone or beta-methasone;
 - b) Immunosuppressants, such as cyclosporine, tacrolimus methotrexate, hydroxyurea, mycophenolate mofetil, mycophenolic acid, sulfasalazine, 6-thioguanine or azathioprine;
 - 10 c) Fumaric acid esters, such as dimethyl fumarate;
 - d) Dihydroorotate dehydrogenase (DHODH) inhibitors such as leflunomide;
 - e) Retinoids, such as acitretin or isotretinoin;
 - f) Anti-inflammatories such as apremilast, crisaborole, celecoxib, diclofenac, aceclofenac, aspirin or naproxen;
 - 15 g) JAK inhibitors such as tofacitinib, baricitinib, upadacitinib, ruxolitinib or delgocitinib;
 - h) Antibiotics such as gentamicin;
 - i) Anti-cancer agents such as lenalidomide, pomalidomide, pembrolizumab, nivolumab, daratumumab, bortezomib, carfilzomib, ixazomib,
 - 20 bendamustine or ventoclast;
 - j) T-cell blockers such as alefacept or efalizumab;
 - k) Tumor necrosis factor-alpha (TNF-alpha) blockers such as etanercept, adalimumab, infliximab, golimumab, certolizumab pegol;
 - l) interleukin 12/23 blockers such as ustekinumab;
 - 25 m) IL-23 blockers such as risankizumab, guselkumab or tildrakizumab;
 - n) anti-IL4/IL13 antagonist such as dupilumab, lebrikizumab or tralokinumab;
 - o) IL-1 β blockers such as canakinumab;
 - p) IL-alpha blockers such as bermekimab;
 - 30 q) CD6 blockers such as itolizumab;
 - r) IL-36R blockers such as BI-655130 or bimekizumab;
 - s) IL-6 antagonist such as tocilizumab;
 - t) Calcineurin inhibitors such as pimecrolimus, tacrolimus or cyclosporine;

- u) Phototherapy agents commonly employed in phototherapy such as psoralen, methoxypsoralen or 5-methoxypsoralen + UVA (PUVA) or treatment with UVB (with or without tar);
- v) Fixed combinations of corticosteroids and vitamin D derivatives;
- 5 w) Fixed combinations of corticosteroids and retinoids;
- x) Corticosteroid tapes; and
- y) one or more agents selected from the group consisting of BMS986165, PF-06700841, PF-06826647, piclidenoson, tepilamide fumarate, LYC-30937, LEO-32731, BI-730357, PRCL-02, LNP-1955, GSK-2982772, CBP-307, KD-025, MP-1032, 10 petesicatib, JTE-451, Hemay-005, SM-04755, EDP-1815, BI-730460, SFA-002 ER, JNJ-3534, SAR-441169, BOS-172767, SCD-044, ABBV-157, BAY-1834845, AUR-101, R-835, PBF-1650, RTA-1701, AZD-0284, mirikizumab, CD20 antagonist, salicylic acid, coal tar, Mical-1, DUR-928, AM-001, BMX-010, TA-102, SNA-125, brepocitinib tosylate, pegcantratinib, ESR-114, NP-000888, SM-04755, BOS-475, SB-15 414, LEO-134310, CBS-3595, PF-06763809, XCUR-17 and BTX-1308.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/052702

A. CLASSIFICATION OF SUBJECT MATTER
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 C07D405/14 C07D413/14
 ADD.
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
 C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2016/020295 A1 (NUEVOLUTION AS [DK]) 11 February 2016 (2016-02-11) cited in the application claims 1,63-69	1-58

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search 8 June 2021	Date of mailing of the international search report 17/06/2021
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Fanni, Stefano
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