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(54) **OPTIONALLY FUSED HETEROCYCLYL-SUBSTITUTED DERIVATIVES OF PYRIMIDINE USEFUL FOR THE TREATMENT OF INFLAMMATORY, METABOLIC, ONCOLOGIC AND AUTOIMMUNE DISEASES**

ZUR BEHANDLUNG VON ENTZÜNDLICHEN, METABOLISCHEN, ONKOLOGISCHEN UND AUTOIMMUNERKRANKUNGEN GEEIGNETE HETEROCYCL-SUBSTITUIERTE GEGEBENENFALLS KONDENSIERTE PYRIMDINDERIVTE

DERIVES DE PYRIMIDINE EVENTUELLEMENT CONDENSEE SUBSTITUEE PAR UN HETEROCYCLE UTILES DANS LE TRAITEMENT DE MALADIES INFLAMMATOIRES, METABOLIQUES, ONCOLOGIQUES ET AUTO-IMMUNES

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(73) Proprietor: **Nuevolution A/S**
2100 Copenhagen (DK)

(72) Inventors:
- **SCHRØDER GLAD, Sanne**
2750 Ballerup (DK)
- **BIRKEBÆK JENSEN, Kim**
2610 Rødovre (DK)
- **GRØN NØRAGER, Niels**
2200 Copenhagen N (DK)
- **SARVARY, Ian**
SE-21851 Klagshamn (SE)
- **VESTERGAARD, Mikkel**
2670 Greve (DK)
- **HAAHR GOULIAEV, Alex**
3670 Veksø Sjælland (DK)
- **TEUBER, Lene**
3500 Værløse (DK)
- **STASI, Luigi Piero**
20900 Monza (IT)

(74) Representative: **Aamand, Jesper L. et al**
Jesper Levin A/S
Jægersborg Allé 93
2820 Gentofte (DK)

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- None

Description

Field

[0001] 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

[0002] 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.

[0003] Examples of nuclear receptors include the nucelar 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.

[0004] RORs consist of three members, namely ROR alpha (RORα), ROR beta (R0Rβ) and ROR gamma (RORγ or RORc).

[0005] RORα is expressed in many tissues such as cerebellar Purkinje cells, the liver, thymus, skeletal muscle, skin, lung, adipose tissue and kidney.

[0006] RORy also has a broad expression pattern and was the most recently discovered of the three members. To date, five splice variants have been recorded for RORy coding for two different protein isoforms: RORγ1 and RORy2 (RORy2 is also known as RORyt). Generally RORy is used to describe RORγ1 and/or RORyt. RORγ1 is expressed in many tissues and is predominantly expressed in the kidneys, liver, and skeletal muscle. In contrast, expression of RORyt is restricted to lymphoid organs such as the thymus. RORyt has been identified as a key regulator of Th17 cell differentiation. Th17 cells are a subset of T helper cells which preferentially produce the cytokines IL-17A, IL-17F, IL-21 and IL-22. Th17 cells and their products have been shown to be associated with the pathology of many human inflammatory and autoimmune disorders.

[0007] There is thus evidence that RORα and RORy play a role in the pathogenesis of many diseases.

[0008] It would be desirable to provide compounds that modulate the activity of RORα and/or RORy for use in treating inflammatory, metabolic and autoimmune diseases.

Summary

[0009] In one aspect provided herein are compounds of Formula (I)

Formula (I)

or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, and stereoisomers thereof, wherein:

Y is NR or O;

R is hydrogen or substituted or unsubstituted C_{1-4} alkyl;
R_1 is selected from the group consisting of hydrogen, -OH, halogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, and substituted or unsubstituted C_{2-4} alkenyl;
R_2 is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, -CN, and -OH ;
or R and R_2 are combined to form a substituted or unsubstituted fused ring;
R_3 is selected from the group consisting of hydrogen, halogen, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, oxo, $-C(=O)R_{10}$;
R_{4a} is selected from the group consisting of hydrogen, halogen, -OH, -CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_3-C_6 cycloalkyl,
substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_{1-6} alkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroaryl-C_{1-6} alkyl;
R_{4b} is selected from the group consisting of hydrogen, halogen, oxo, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, and $-C(=O)R_{10}$;
R_5 is selected from the group consisting of $-(CR_8R_9)pOR_{12}$, $-(CR_8R_9)p-CR_{13}R_{14}R_{15}$,$-(CR_8R_9)p-C(=O)OR_7$, and $-(CR_8R_9)p-C(=O)NR_8R_9$;
n, m, and p are integers independently selected from the group consisting of 0, 1, 2, 3 and 4;
R_{6a}, R_{6b} are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{2-9} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, or R_{6a} and R_{6b} are taken together to form an oxo group or a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl, or R_{6a} and R_{13} are taken together to form a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-5} heteroalicyclyl;
R_7, R_8, R_9, and R_{12}, are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl;
R_{10} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, -OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, and C_{3-7} cycloalkyl;
R_{13} is absent, or selected from the group consisting of hydrogen, -OH, -CN, fluorine, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, and $-(CR_8R_9)p-C(=O)OR_7$, $-(CR_8R_9)p-SO_2R_7$ and $-(CR_8R_9)p-C(=O)NR_8R_9$;
R_{14} and R_{15} are independently selected from the group consisting of hydrogen, and substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl; or
R_{14} and R_{15} are combined to form a ring system selected from the group consisting of substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{2-9} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;
B is a ring system selected from the group consisting of aryl, heteroaryl, and bicyclic heteroalicyclyl, provided that it is not 5,6-dichloro-1H-benzo[d]imidazol-2-yl when R_1 and R_2 both are hydrogen;
C is a ring system selected from C_{2-9} heteroalicyclyl ;
wherein B is attached to a carbon atom adjacent the N atom of ring system C; and
with the proviso the compound is not:

[0010] According to a further aspect, R and R_2 are combined to form a fused ring. In another aspect, R_5 is $-(CR_8R_9)p-$

$C(=O)OR_7$, or $-(CR_8R_9)p-C(=O)NR_8R_9$. Alternatively, R_5 is $-(CR_8R_9)p-CR_{13}R_{14}R_{15}$ wherein R_{14} and R_{15} are combined to form a ring system.

[0011] According to another aspect, there is provided a pharmaceutical composition comprising a compound of the herein above described type and at least one pharmaceutical acceptable excipient.

[0012] According to yet another aspect, the herein above described compound or pharmaceutical composition are for use in therapy.

[0013] According to another aspect, the herein above described compound or pharmaceutical composition are for use in the treatment and/or prevention of inflammatory, metabolic and autoimmune diseases or disorders.

[0014] In another aspect, the herein above described compound or pharmaceutical composition are for modulating the activity of a retinoic acid receptor-related orphan receptor (ROR).

[0015] Further, advantageous features of various embodiments are defined in the dependent claims and within the detailed description below.

Detailed description of preferred embodiments

Definitions

[0016] 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.

[0017] As used herein, any "R" group(s) such as, without limitation, R_1, R_2, R_3, R_4, R_5, R_8, R_9, and R_{10}, represent substituents that can be attached to the indicated atom. A non-limiting list of R groups includes but is not limited to hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, and heteroalicyclyl. If two "R" groups are covalently bonded to the same atom or to adjacent 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:

[0018] 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.

[0019] Whenever a group is described as being "unsubstituted or substituted," if 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-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof.

[0020] When a substituent on a group is deemed to be "substituted," the substitutent itself is substituted with one or more of the indicated substitutents. 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) individually and 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-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, 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, 3rd Ed., John Wiley & Sons, New York, NY, 1999.

[0021] 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 "C_1 to C_6 alkyl" group refers to all alkyl groups having from 1 to 6 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$-, $CH_3CH(CH)_3CH_2$- , $CH_3CH(CH)_3CH_2$- and $(CH_3)_3C$-. If no "m" and "n" are designated with regard to a group, the broadest range described in these definitions is to be assumed.

[0022] As used herein, "alkyl" refers to a straight or branched hydrocarbon chain group 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 "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms, such as "C_{1-6}". 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 "C_1-C_4 alkyl," "C_{1-4} alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" or "C_{1-4} 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, iso-propyl, 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, 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, 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-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof.

[0023] As used herein, "alkenyl" refers to an alkyl group that contains in the straight or 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 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, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)alkyl, hydroxy, oxo, alkoxy, mercapto, alkylthio, cyano, halogen, nitro, haloalkyl, haloalkoxy, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof.

[0024] 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 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.

[0025] As used herein, "hetero" may be attached to a group and refers to one or more 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.

[0026] 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, 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 replace may be in the middle or at the end of the alkyl group. Examples of heteroalkyl include, but are not limited to, -S-alkyl, -O-alkyl, -NH-alkyl, -alkylene-O-alkyl, etc

[0027] 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-electron system. 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, 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-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, 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.

[0028] 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. Examples of monocyclic "heteroaryl" include, but are not limited to, furan, thiophene, phthalazine, pyrrole, oxazole, 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, 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-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. When substituted, substituents on a heteroayl group may form a non-aromatic ring fused to the aryl group, including a cycloalkyl, cycloalkenyl, cycloalkynyl, and heterocyclyl.

[0029] 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.

[0030] 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.

[0031] 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 carbon atoms. The alkylene may also be a medium size alkylene having 1 to 10 carbon atoms, such as "C_{1-6}" The alkylene could also be a lower alkylene having 1 to 4 carbon atoms. The alkylene may be designated as "C_1-C_4 alkylene", "C_{1-4} alkylene" or similar designations. Non-limiting examples include, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), and butylene ($-(CH_2)_4-$) groups. In the case of methylene, the two connected fragments are connected to the same carbon atom. A lower alkylene group may be substituted.

[0032] 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 replaced with the same or different heteroatoms selected from oxygen, sulfur and nitrogen. Examples of heteroalkylene include, but not limited to $-CH_2-O-$, $-CH_2-CH_2-O-$, $-CH_2-CH_2-CH_2-O-$, $-CH_2-NH-$, $-CH_2-CH_2-NH-$, $-CH_2-CH_2-CH_2-NH-$, $-CH_2-CH_2-NH-CH_2-$, $-O-CH_2-CH_2-O-CH_2-CH_2-O-$, $-O-CH_2-CH_2-O-CH_2-CH_2-$, and the like.

[0033] As used herein, "alkylidene" refers to a divalent group, such as =CR'R", which is attached to one carbon of another group, forming a double bond. Alkylidene groups include, but are not limited to, methylidene ($=CH_2$) and ethylidene ($=CHCH_3$). 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.

[0034] As used herein, "alkoxy" refers to the group -OR wherein R is an alkyl, e.g. methoxy, ethoxy, n-propoxy, cyclopropoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, amoxy, tert-amoxy and the like. An alkoxy may be substituted.

[0035] 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-methylethylmercapto (isopropylmercapto), n-butylmercapto, iso-butylmercapto, sec-butylmercapto, tert-butylmercapto, and the like. An alkylthio may be substituted.

[0036] 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.

[0037] 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-pentenyloxy, tert-pentenyloxy, and the like. The alkenyloxy may be substituted.

[0038] 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.

[0039] As used herein, "cycloalkyl" refers to a completely saturated (no double bonds) 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 C_3 to C_{10}, such as from C_3 to C_6. 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, 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.

[0040] As used herein, "cycloalkenyl" refers to a cycloalkyl group that contains one or 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 connetected together in a fused, bridged or spiro-connected fashion. Cycloalkenyl groups may range from C_3 to C_{10}, such as from C_5 to C_{10}. 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.

[0041] As used herein, "cycloalkynyl" refers to a cycloalkyl group that contains one or 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 C_8 to C_{12}. 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.

[0042] 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 C_2 to C_{10}, in some embodiments it may range from C_2 to C_9, and in other embodiments it may range from C_2 to C_8. 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 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 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, isothiocyanato, nitro, silyl, haloalkyl, 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, imidazolinyl, morpholinyl, oxetanyl, oxiranyl, piperidinyl N-Oxide, piperidinyl, piperazinyl, pyrrolidinyl, pyranyl, 4-piperidonyl, pyrazolidinyl, 2-oxopyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone. When substituted, substituents on a heteroalicyclyl group may form an aromatic ring fused to the heteroalicyclyl group, including an aryl and a heteroaryl.

[0043] 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. 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.

[0044] 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.

[0045] 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. In some cases, the alkylene group is a lower alkylene group.

[0046] As used herein, "halo" or "halogen" refers to F (fluoro), Cl (chloro), Br (bromo) or I (iodo).

[0047] 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, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl and 1-chloro-2-fluoromethyl, 2-fluoroisobutyl. A haloalkyl may be substituted.

[0048] 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.

[0049] 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, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl, as defined herein. An O-carboxy may be substituted.

[0050] 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.

[0051] A "trihalomethanesulfonyl" group refers to an "X_3CSO_2-" group" wherein X is a halogen.

[0052] 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.

[0053] A "nitro" group refers to a "$-NO_2$" group

[0054] A "cyano" group refers to a "-CN" group.

[0055] A "cyanato" group refers to an "-OCN" group.

[0056] An "isocyanato" group refers to a "-NCO" group.

[0057] A "thiocyanato" group refers to a "-SCN" group.

[0058] A "carbonyl" group refers to a "-C(=O)-" group.

[0059] A "thiocarbonyl" group refers to a "-C(=S)-" group.

[0060] An "oxo" group refers to a " =O " group.

[0061] A "hydroxy" group or "hydroxyl" group refers to an "-OH" group.

[0062] An "isothiocyanato" group refers to an " -NCS" group.

[0063] 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.

[0064] A "sulfonyl" group refers to an "SO_2R" group in which R can be the same as defined with respect to O-carboxy. A sulfonyl may be substituted.

[0065] An "S-sulfonamido" group refers to a "-$SO_2NR_AR_B$" 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 C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl substituted or unsubstituted heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A S-sulfonamido may be substituted.

[0066] An "N-sulfonamido" group refers to a "$RSO_2N(R_A)$-" 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.

[0067] A "trihalomethanesulfonamido" group refers to an "$X_3CSO_2N(R)$-" group with X as halogen and R can be the same as defined with respect to O-carboxy. A trihalomethanesulfonamido may be substituted.

[0068] 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 C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl substituted or unsubstituted heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A C-amido may be substituted.

[0069] 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.

[0070] 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.

[0071] A lower alkoxyalkyl refers to an alkoxy group connected via a lower alkylene group. A lower alkoxyalkyl may be substituted.

[0072] An "amine" or "amino" refers to "RNH_2" (a primary amine), "R_2NH" (a secondary amine), "R_3N" (a tertiary amine). An amino group may be substituted.

[0073] A lower aminoalkyl refers to an amino group connected via a lower alkylene group. A lower aminoalkyl may be substituted.

[0074] 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).

[0075] 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)).

[0076] As employed herein, the following terms have their accepted meaning in the chemical literature.

$CDCl_3$	deuterated chloroform
DCM	dichloromethane or CH_2Cl_2
DIPEA	N,N-diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
h	hour(s)
MeOH	methanol
TFA	trifluoroacetic acid

[0077] 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 enatiomerically 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 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.

[0078] 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.

[0079] 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 forms unless the context clearly dictates otherwise.

[0080] 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, 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, 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 tosylates.

[0081] Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent of water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

[0082] "Anti-drug" refers to a compound or composition acting against or opposing illicit drugs or their use. Compounds of the present application may act as anti-drugs.

[0083] 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 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.

[0084] An "agonist" is defined as a compound that increases the basal activity of a receptor (i.e. signal transduction mediated by the receptor).

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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 particular, humans.

[0089] 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.

[0090] 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.

[0091] As used herein, a "diluent" refers to an ingredient in a pharmaceutical composition 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 saline that mimics the composition of human blood.

[0092] 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.

[0093] 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.

[0094] "Ligand" is intended to include any substance that interacts with a receptor.

[0095] "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 receptor 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.

[0096] 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.

[0097] 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.

[0098] 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.

Compounds

[0099] According to one aspect compounds of Formula (I)

Formula (I)

or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, and stereoisomers thereof, wherein:

Y is NR or O;
R is hydrogen or substituted or unsubstituted C_{1-4} alkyl;
R_1 is selected from the group consisting of hydrogen, -OH, halogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, and substituted or unsubstituted C_{2-4} alkenyl;
R_2 is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, -CN, and -OH ;

or R and R_2 are combined to form a substituted or unsubstituted fused ring;
R_3 is selected from the group consisting of hydrogen, halogen, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, oxo, $-C(=O)R_{10}$;
R_{4a} is selected from the group consisting of hydrogen, halogen, -OH, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_{1-6} alkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroaryl-C_{1-6} alkyl;
R_{4b} is selected from the group consisting of hydrogen, halogen, oxo, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, and - $C(=O)R_{10}$;
R_5 is selected from the group consisting of $-(CR_8R_9)pOR_{12}$, $-(CR_8R_9)p-CR_{13}R_{14}R_{15}$, $-(CR_8R_9)p-C(=O)OR_7$, and $-(CR_8R_9)p-C(=O)NR_8R_9$;
n, m, and p are integers independently selected from the group consisting of 0, 1, 2, 3 and 4;
R_{6a}, R_{6b} are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{2-9} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, or R_{6a} and R_{6b} are taken together to form an oxo group or a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl, or R_{6a} and R_{13} are taken together to form a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-5} heteroalicyclyl;
R_7, R_8, R_9, and R_{12}, are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl;
R_{10} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, -OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, and C_{3-7} cycloalkyl;
R_{13}, if not to be taken together with R_{6a}, is absent, or selected from the group consisting of hydrogen, -OH, -CN substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, and-$(CR_8R_9)p-C(=O)OR_7$, $-(CR_8R_9)p-SO_2R_7$ and $-(CR_8R_9)p-C(=O)NR_8R_9$;
R_{14} and R_{15} are independently selected from the group consisting of hydrogen, and substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl; or
R_{14} and R_{15} are combined to form a ring system selected from the group consisting of substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{2-9} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;
B is a ring system selected from the group consisting of aryl, heteroaryl, and bicyclic heteroalicyclyl, provided that it is not 5,6-dichloro-1H-benzo[d]imidazol-2-yl when R_1 and R_2 both are hydrogen;
C is a ring system selected from C_{2-9} heteroalicyclyl;
wherein B is attached to a carbon atom adjacent the N atom of ring system C; and with the proviso the compound is not:

are provided.

[0100] As with any group of structurally related compounds which possess a particular utility, certain embodiments of variables of the compounds of Formula (I) may be particularly useful in their end use application.

[0101] In some embodiments of the compounds of Formula (I), R and R_2 in combination with the pyrimidine ring form a ring system selected from pyrrolo[2,3-d]pyrimidine and 6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine. The ring system may be pyrrolo[2,3-d]pyrimidine.

[0102] In some embodiments according to Formula (I) B is a ring system selected from the group consisting of aryl, heteroaryl, and bicyclic heteroalicyclyl, provided that it is not 5,6-dichloro-1H-benzo[d]imidazole-2-yl; i.e.

[0103] In some further embodiments according to Formula (I), B is a ring system selected from the group consisting of aryl, monocyclic heteroaryl, and bicyclic heteroalicyclyl.In some embodiments of the compounds of Formula (I), R and R_2 in combination with the pyrimidine ring form a pyrrolo[2,3-d]pyrimidine or 6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine. The compounds of Formula (I) may also have the Formula (IIa):

Formula (IIa)

wherein R_{4e} and R_{4d} are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, and -OH. In preferred compounds of Formula (IIa), R_{4e} and R_{4d} may be independently selected from the group consisting of hydrogen, methyl, and fluorine.

[0104] Embodiment disclosed herein below in relation to various groups, rings and substituents of compounds of Formula (I) are, as indicated, equally applicable to compounds of any one of the Formulae (IIa-IIe) provided below herein, provided that the relevant group, integer, ring and/or substituent is present in the Formula of concern, as readily appreciated by the skilled person.

[0105] According to another embodiment, the compounds of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe) as disclosed herein below, have R_5 being -(CR_8R_9)p-C(=O)OR_7 or -(CR_8R_9)p-C(=O)NR_8R_9, unless otherwise specified. In an alternative embodiment, the compounds of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe) have R_5 being -$(CR_8R_9)_pOR_{12}$. In these embodiments, R_7, R_8, R_9, and R_{12} are independently selected of each other from hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted aryl-C_{1-6} alkyl and substituted or unsubstituted aryl. Preferred groups of R_7, R_8, R_9, and R_{12} are selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, and aryl, while even more preferred groups are selected from hydrogen, methyl, ethyl and tert-butyl. The integer p is preferably selected from 0, 1 or 2. In some embodiments, p is 0.

[0106] According to yet another embodiment, R_5 is -(CR_8R_9)p-$CR_{13}R_{14}R_{15}$. In this embodiment it is preferred that R_{14} and R_{15} are combined to form a ring system. Further, the integer "p" may be 0 (zero), or 1. While it is not intended that the ring system be particular limited, preferred ring systems are selected from the group consisting of substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{3-7} cycloalkenyl, substituted or unsubstituted C_{2-6} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. For example, R_{14} and R_{15} may be combined to form a ring system selected from the group consisting of phenyl, naphthyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, thietanyl, pyrrolyl, pyrazolyl imidazolyl, pyrrolidinyl, imidazolinyl, pyrazolidinyl, thiazolidinyl, isothiazolidinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxathianyl, thiazolyl, isothiazolyl,

pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxolanyl, dioxanyl, furyl, dihydrofuranyl, furazanyl, tetrahydrofuryl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, dithiolanyl, dithianyl, thiopyranyl, thianyl, thienyl, oxetanyl, quinolyl, isoquinolyl, indolyl, iso-indolyl, and tetrahydrothienyl, any of which may be substituted or unsubstituted. Preferably, R_{14} and R_{15} are combined to form a ring system selected from the group consisting of cycloheptyl, cyclohexyl, cyclopentyl, dioxanyl, furyl, imidazolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, oxetanyl, oxathianyl, phenyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolidinyl, pyrrolyl, tetrahydrofuryl, tetrahydropyranyl, tetrazolyl, thianyl, thiazolyl, thienyl, thiomorpholinyl, thiopyryl, and triazolyl, all of which may be unsubstituted or substituted. Some embodiments relate to the ring system formed being phenyl, pyridyl, cyclopentyl, cyclohexyl, piperidyl, pyrrolidinyl, oxetanyl, and tetrahydropyranyl, all which may be substituted by $(CH_2)_q(R_{5a})$ as defined herein. Some embodiments relate to the ring system being phenyl, pyridyl, piperidinyl oxetanyl, or cyclohexyl. In embodiments wherein R_{14} and R_{15} are combined to form an aromatic ring system, R_{13} is absent.

[0107] In a further embodiment, the ring system formed by the combination of R_{14} and R_{15} is substituted with $-(CH_2)q(R5_a)$ wherein R_{5A} is independently selected from the group consisting of $-CH_2COOR_{20}$, $-CH_2CONR_{21}R_{22}$, -CN, C_{1-6} alkyl, $-CH_2$-imidazolyl,$-CH_2-SO_2R_{20}$, $-CH_2C(CH_3)_2(OR_{20})$, $-OCH_3$, $-CH_2$-triazolyl, $-CF_3$, dimethyl substituted-imidazolyl-2,4-dione, $-CH_2-SO_2NR_{21}R_{22}$, morpholinyl, -C(=O)-morpholinyl, piperidyl-CH_2OR_{20}, $-OCH_2$-tetrahydrofuryl, piperazinonyl, piperidinyl-$CONR_{21}R_{22}$, -OH,$-CONR_{21}R_{22}$, $-CH(OR_{20})CH_3$, $-COOR_{20}$, $-CH_2$-pyrrolidyl, C_{1-6} alkylene-OH, cyclopentyl, pyrrolidonyl, tetrazolyl, $-CH_2$- tetrazolyl, $-CH_2OR_{20}$, acyl, $-SOR_{20}$, $-SO_2R_{20}$, $-COR_{20}$,$-NR_{21}SO_2R_{20}$, $-SO_2NR_{21}R_{22}$, and halogen;

R_{20}, R_{21}, and R_{22} are independently of each other selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, -CN, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted C_{2-6} heteroalicyclyl; and
q is an integer selected from 0, 1 or 2.

[0108] Of course the ring system formed by the combination of R_{14} and R_{15} may, in alternative embodiments, be substituted with groups other than $-(CH_2)q(R5_a)$.

[0109] According to some embodiments, R_{13} is selected from the group consisting of hydrogen, -CN, CH_3, fluorine, -OH, $-CH_2OH$, $-OCH_3$, $-CH_2CH_2OH$, $-CO_2H$, $-CO_2-C_{1-4}$ alkyl, $-CH_2SO_2R_{20}$ and $-CONR_8R_9$ wherein R_8 and R_9 are independently of each other selected from hydrogen, C_{1-4} alkyl and C_{1-4} aminoalkyl or R_8 and R_9 are combined to form a C_2-C_6 heteroalicyclyl. Some embodiments relate to R_{13} taken together with R_{6a} to form a ring system selected from the group consisting of substituted or unsubstituted C_{3-6} cycloalkyl and substituted or unsubstituted C_{2-5} heteroalicyclyl.

[0110] According to some embodiments, R_{13} is absent or hydrogen.

[0111] In some embodiments of the compounds of Formula (I), Y is NR. Further, while R may be selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} hydroxyalkyl. In one embodiment R is hydrogen.

[0112] According to some embodiments, R_1 is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy. R_1 may thus include C_{1-4} haloalkyl and C_{1-4} hydroxyalkyl groups. In some embodiments, R_1 is hydrogen or CF_3.

[0113] According to some embodiments, R_2 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} hydroxyalkyl. In some embdoiments, R_2 is a halogen such as fluorine.

[0114] In some embodiments, the compounds of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein may have an R_3 group selected from hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, oxo, C_{1-4} alkoxy and C_{1-4} haloalkoxy, unless otherwise specified. According to one embodiment R_3 is selected from the group consisting of hydrogen, methyl, fluorine, chlorine and oxo. In some embodiments, R_3 is hydrogen.

[0115] In some compounds of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein the integer m is selected from 2, 3, or 4, and at least two of the R_3 groups present are bound to the same atom of ring system C. This embodiment provides compounds with one or two geminally substituted atoms that are part of ring system C. In some embodiments, R_3 is flouro, such as geminally arranged fluoro atoms.

[0116] According to some embodiments of the compounds of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein, R_{4a} is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_1-C_6 alkoxy, C_{1-6} haloalkoxy, heteroaryl and aryl. In some embdoiments R_{4a} groups are selected from the group consisting of methyl, ethyl, propyl, iso-propyl, *tert*-butyl, chlorine, bromine, fluorine, methoxy, ethoxy, C_{1-2} haloalkyl, C_{1-2} haloalkoxy and triazolyl. In some embodiments R_{4a} groups are $-CF_3$, $-CF_2CF_3$, $-CHF_2$, $-OCF_3$, $-OCF_2CF_3$, and $-OCHF_2$. In some embodiments R_{4a} is selected from the group consisting of isopropyl, halogen, ethoxy, CF_3, $-OCF_3$.

[0117] In some embodiments, wherein the ring system B is 6-membered aryl or heteroaryl, R_{4a} is arranged in the para- or meta-position, in relation to the the carbon carrying ring system C.

[0118] According to some embodiments, R_{4b} is selected from hydrogen, oxo, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}

hydroxyalkyl, C_1-C_4 alkoxy, and C_{1-4} haloalkoxy. In this embodiment, R_{4b} may be further selected from methyl, ethyl, propyl, iso-propyl, *tert*-butyl, chlorine, bromine, fluorine, methoxy, ethoxy, -OH, C_{1-2} haloalkyl, and C_{1-2} haloalkoxy. Examples of R_{4b} groups comprise $-CF_3$, , $-CHF_2$, $-OCF_3$, , and $-OCHF_2$. In some embodiments R_{4b} is hydrogen.

[0119] Some embodiments relate to R_{4a} being selected from the group consisting of methyl, ethyl, propyl, iso-propyl, tert-butyl, chlorine, bromine, fluorine, methoxy, ethoxy, C_{1-2} haloalkyl, C_{1-2} haloalkoxy, and triazolyl arranged in the above mentioned para- or meta-position, and R_{4b} being hydrogen.

[0120] In some embodiments of the compounds of of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein, R_{6a} is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, and substituted or unsubstituted aryl, or R_{6a} and R_{13} are taken together to form a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl. Further examples of R_{6a} are selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and aryl. It is preferred however, that R_{6a} is hydrogen.

[0121] According to some embodiments, R_{6b} is selected from hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted aryl-C_{1-6} alkyl, substituted or unsubstituted C_{2-9} heteroalicyclyl-C_{1-6} alkyl, and substituted or unsubstituted aryl in the compounds of Formula (I). Thus, R_{6b} may be hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_1-C_6 alkoxy, C_{1-6} haloalkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl-, aryl-C_{1-6} alkyl-, C_{2-9} heteroalicyclyl-C_{1-4} alkyl-, C_{1-6}-alkoxyaryl-, haloaryl, and aryl. Particular examples of compounds of Formula (I) have an R_{6b} group selected from hydrogen, $-(CH_2)C(CH_3)_3$, $-(CH_2)CONH_2$, phenyl, phenyl substituted with 1 to 3 halogens, $-CH(CH_3)OC(CH_3)_3$, $-CH_2$-phenyl-OCH_3, -phenyl-OCH_3, $-CH_2$-pyridyl, CH_2-cyclohexyl-CH_2CO_2H, $-CH_2$-cyclohexyl-CH_2CONH_2,CH_2-cyclohexyl-CH_2-tetrazolyl, $-CH_2$-cyclohexyl-CH_2OH, $-CH_2$-cyclohexyl-$NHSO_2CH_3$,$-CH_2$-cyclohexyl-$NHSO_2CH_2CF_3$, $-CH_2$-cyclohexyl-CH_2CN, $-CH_2$-phenyl-CH_2CO_2H,$-CH_2$-phenyl-CH_2CONH_2, $-CH_2$-phenyl-$CH_2CONH_2CH_3$, $-CH_2$-phenyl-CH_2-tetrazolyl,$-CH_2$-phenyl-$CONH_2$, $-CH_2$-phenyl-SO_2NH-cyclopropyl, $-CH_2$-phenyl-SO_2CH_3, $-CH_2$-phenyl-$NHSO_2CF_3$, $-CH_2$-phenyl-$NHSO_2CH_3$, $-CH_2$-phenyl-$NHSO_2CHF_2$, $-CH_2$-pyridyl-CH_3, $-CH_2$-pyridyl-SO_2CH_3, $-CH_2$-pyridyl-CH_2CONH_2, $-CH_2$-pyrimidyl-$NHSO_2CH_3$,$-CH_2$-piperidyl-$COCH_3$, $-CH_2$-piperidyl-SO_2CH_3, $-CH_2$-piperidyl-SO_2CF_3, $-CH_2$-thienyl-CH_2CO_2H, $-CH_2$-cyclobutyl-CH_2CO_2H, $-CH_2$-cyclobutyl-CH_2CONH_2, $-CH_2$-cyclobutyl-CO_2H, $-CH_2$-cyclobutyl-$CONH_2$, $-CH_2$-tetrahydrothiopyryl, $-CH_2$-cyclopentyl, $-CH_2$-cyclohexyl, $-CH_2$-tetrahydrofuranyl, $-CH_2$-tetrahydropyranyl, $-CH_2$-oxetanyl, and $-CH_2$-pyranyl.

[0122] Some embodiments relate to R_{6a} and R_{6b} being taken together to form a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted C_{2-9} heteroalicyclyl.

[0123] Ring system B in compounds of of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein is not intended to be particularly limited, unless otherwise indicated. In some embodiments, ring system B is a mono- or bicyclic aryl, a mono- or bicyclic heteroaryl, or a bicyclic heteroalicyclyl. Further, ring system B may be a monocyclic heteroalicyclyl. Ring system B may, but need not, be substituted with at least one of R_{4a} or R_{4b} that is a non-hydrogen substituent. Compounds of of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein, may also have a ring system B that is a monocyclic, 6-membered aryl or heteroaryl substituted with R_{4a}. In some embodiments ring system B is selected from the group consisting of phenyl, pyridyl, pyridazinyl, pyrimidinyl, naphthyl and furanyl, such as from the group consisting of phenyl, pyridyl, and pyrimidinyl. Some embodiments ring system B is selected from the group consisting of phenyl, and pyridyl. In some embodiments, n is an integer selected from 1, 2, 3 and 4. Alternatively, n may be 0 meaning that R_{4a} will be the only substituent on ring system B.

[0124] In some embodiments, the ring B is a bicyclic ring system, such as bicyclic aryl, bicyclic heteroaryl, or bicyclic heteroalicyclyl ring systems, e.g. benzazepine, benzazocines, benzimidazole, benzimidazoline, benzodioxin, benzodioxole, benzofuran, benzoisothiazole, benzothiadiazine, benzothiadiazole, benzothiazepine, benzothiazine, benzothiazole, benzothiophene, benzotriazole, benzoxadiazole, benzoxathiole, benzoxazepine, benzoxazine, benzoxazole, benzisoxazole, benzodioxole, chromane, chromene, coumarin, cyclopentapyridine, cyclopentapyrimidine, diazanaphthalene, dioxolopyridine, dioxolopyrimidine, dihydrobenzodioxine, dihydrobenzooxathiine, furofuran, furopyridine, furopyridine, furopyrimidine, imidazopyridine, imidazopyrimidines, indane, indazole, indene, indole, indoline, indolizines, isobenzofuran, isochromenes, isoindole, isoindoline, isoquinoline, naphthalene, naphthyridine, oxathiolopyridine, oxathiolopyrimidine, oxazolopyridine, oxazolopyrimidine, pteridine, purine, pyranopyridine, pyranopyrimidine, pyrazolodiazepines, pyrazolopyridine, pyrazolopyrimidine, pyridobenzthiazine, pyridodiazepene, pyridooxazine, pyridopyrazine, pyridopyrimidine, pyridothiazine, pyrimidooxazine, pyrimidopyrimidine, pyrimidothiazine, pyrrolizine, pyrroloimidazole, pyrrolopyrazine, pyrrolopyridine, pyrrolopyrimidine, quinazoline, quinoline, quinolone, quinolizidine, quinoxaline, tetralin, thiazolopyridine, thiazolopyrimidine, thienodiazepine, thienopyridine, thienopyrimidine, thiochromane, thiochromene, thiopyranopyridine, thiopyranopyrimidine, triazolopyridazine, triazolopyridine or triazolopyrimidine, all of which may be unsubstituted or substituted.

[0125] Like ring system B, the ring system C in compounds of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein, is not intended to be particularly limited in scope, unless otherwise specified. According to one embodiment, ring system C is a C_{2-9} heteroalicyclylIn some embodiments ring system C is

a 4-7-membered heteroalicyclyl. For example, ring system C may be pyrrolidinyl or morpholinyl.

[0126] The integer values of n and m may take any particular combination. In one embodiment, m is 1 or 2. Further, m may be 0 (zero) meaning that the ring system C is unsubstituted. In another embodiment, n is an integer selected from 1, 2, 3 and 4. Alternatively, n may be 0 meaning that R_{4a} will be the only substituent on ring system B. Alternatively, n may be 0 and R_{4a} hydrogen, i.e. the ring system B is unsubstituted.

[0127] According to yet another embodiment, the compounds of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein, have R_5 being $-(CR_8R_9)p-C(=O)NR_8R_9$; R_8 and R_9 are independently of each other selected from H and substituted or unsubstituted C_{1-6} alkyl; p is 0; and R_{6b} is hydrogen or $-(CH_2)C(CH_3)_3$.

[0128] Compounds disclosed herein may also comprise compounds of Formula (IIb):

Formula (IIb)

wherein:

C is a pyrrolidine ring or a morpholine ring;

R1 is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; some compounds of Formula (IIb) have an R1 that is hydrogen or $-CF_3$;

R_3 is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-4} alkyl, and halogen;

R_{4a} is selected from the group consisting of hydrogen, halogen, -OH, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_{1-6} alkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaryl-C_{1-6} alkyl; some compounds of Formula (IIb) have an R_{4a} that is selected from the group consisting of halogen, $-CF_3$, $-OCF_3$, iso-propyl, tert-butyl, - C_{1-6} alkoxy, C_{1-6} alkoxy substituted with one or more halogens, and phenyl;

R_{4b} is independently selected from the group consisting of hydrogen, halogen,-OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy,$-C(=O)R_{10}$;

R_5 is selected from the group consisting of substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{3-7} cycloalkenyl, substituted or unsubstituted C_{2-6} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

R_{6a} are R_{6b} are independently selected from the group consisting of hydrogen and substituted or unsubstituted C_{1-6} alkyl; and

m is an integer independently selected from the group consisting of 1, 2, and 3; and

n is an integer independently selected from the group consisting of 1, 2, 3, and 4.

[0129] In compounds of Formula (IIb), R_5 may be selected from the group consisting of substituted or unsubstituted C_{4-7} cycloalkyl, substituted or unsubstituted C_{6-12} membered aryl, substituted or unsubstituted 4-membered heteroali-

cyclyl, substituted or unsubstituted 5-membered heteroaryl, substituted or unsubstituted 5-membered heteroalicyclyl, substituted or unsubstituted 6-membered heteroaryl, a substituted or unsubstituted 6-membered heteroalicyclyl, substituted or unsubstituted 7-membered heteroaryl, and a substituted or unsubstituted 7-membered heteroalicyclyl. Thus, R_5 may be selected from the group consisting of phenyl, naphthyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, thietanyl, pyrrolyl, pyrazoleyl imidazolyl, pyrrolidinyl, imidazolinyl, pyrazolidinyl, thiazolidinyl, isothiazolidinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxathianyl thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxolanyl, dioxanyl, furyl, dihydrofuranyl, furazanyl, tetrahydrofuryl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, dithiolanyl, dithianyl, thiopyranyl, thianyl, thienyl, oxetanyl, quinolyl, isoquinolyl, indolyl, iso-indolyl, and tetrahydrothienyl, any of which may be substituted or unsubstituted. Especially, R_5 may be selected from the group consisting of cycloheptyl, cyclohexyl, cyclopentyl, dioxanyl, furyl, imidazolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, oxetanyl, oxathianyl, phenyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolidinyl, pyrrolyl, tetrahydrofuryl, tetrahydropyranyl, tetrazolyl, thianyl, thiazolyl, thienyl, thiomorpholinyl, thiopyryl, and triazolyl, any of which may be substituted or unsubstituted.

[0130] If substituted, R_5 may be substituted with $-(CH_2)q(R5_a)$, wherein R_{5a} is independently selected from the group consisting of $-CH_2COOR_{20}$, $-CH_2CONR_{21}R_{22}$, oxo, -CN, $-CH_2$-CN, C_{1-6} alkyl, $-CH_2$-imidazolyl, $-CH_2-SO_2R_{20}$, $-CH_2C(CH_3)_2(OR_{20})$,$-OR_{20}$, $-CH_2$-triazolyl, $-CF_3$, dimethyl substituted-imidazolyl-2,4-dione, $-CH_2-SO_2NR_{21}R_{22}$, morpholinyl, -C(=O)-morpholinyl, piperidyl-CH_2OR_{20}, $-OCH_2$-tetrahydrofuryl, piperazinonyl, piperidinyl-$CONR_{21}R_{22}$, -OH, $-CONR_{21}R_{22}$,$-CH(OR_{20})CH_3$, $-COOR_{20}$, $-CH_2$-pyrrolidyl, C_{1-6} alkylene-OH, cyclopentyl, pyrrolidonyl, , $-NR_{21}SO_2R_{20}$, tetrazolyl, $-CH_2$-tetrazolyl, $-CH_2OR_{20}$, acyl, $-SOR_{20}$, $-SO_3R_{20}$, $-SO_2R_{20}$, $-SO_2NR_{21}R_{22}$, and halogen;

R_{20}, R_{21}, and R_{22} are independently of each other selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, -CN, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted C_{2-6} heteroalicyclyl; and
q is an integer selected from 0, 1 or 2.

[0131] Further, R_5 may be selected from the group consisting of unsubstituted aryl, unsubstituted heteroaryl, aryl substituted with one or more C_{1-6} alkoxy, aryl substituted with $-CH_2COOC_{1-6}$ alkyl, aryl substituted with $-CH_2CONH-(C_{1-6}$ alkyl), aryl substituted with $CH_2CON(C_{1-6}$ alkyl$)_2$, $-(CH_2)-C(=O)OR_7$, $-C(=O)OR_7$, $-(CH_2)-C(=O)NR_8R_9$ or$-C(=O)NR_8R_9$, heteroaryl substituted with $-(CH_2)-C(=O)NR_8R_9$ or SO_2R_7, and C_{2-9} heteroalicyclyl substituted with $-(CH_2)-C(=O)NR_8R_9$ or SO_2R_7;
R_7, R_8, and R_9 are independently selected from the group consisting of hydrogen, unsubstituted C_{1-6} alkyl, and C_{1-6} alkylene substituted with furanyl.

[0132] Compounds disclosed herein may also comprise compounds of Formula (IIc):

Formula (IIc)

wherein:

R_3 is hydrogen, fluorine or methyl;
R_{4a} is selected from the group consisting of hydrogen, fluorine, chlorine,$-C(CH_3)_3$, $-CH_2(CH_3)_2$, $-CF_3$, $-OCH_3$, $-OC(CH_3)_3$, and $-OCF_3$;
R_{4b} is selected from the group consisting of hydrogen, fluorine, chlorine, and - OCH_3;
m and n are integers independently selected from 1 or 2;
Y is OR_7 or NR_8R_9;

R_7, R_8, and R_9 are independently selected from H and C_{1-6} alkyl; and
B is selected from the group consisting of phenyl, pyridyl, pyrimidinyl, 2-benzothiazolyl, quinolinyl, and 1,4-benzodioxanyl; and
C is pyrrolidinyl or morpholinyl.

[0133] Compounds disclosed herein may also comprise compounds of Formula (IId):

Formula (IId)

wherein:

B is selected from phenyl, pyridyl and pyrimidyl;
C is pyrrolidinyl or morpholinyl;
R_{4a} is a substituent arrange in para- or meta-position compared to the carbon atom in the ring system C, and selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl (for example $-CF_3$), C_{1-4} haloalkoxy (for example $-OCF_3$), and heteroaryl;
R_5 is a ring selected from the group consisting of phenyl, pyrimidinyl, pyridyl, pyridinyl-N-oxide, cyclohexyl, pyrrolyl, pyrazolyl, furanyl, pyrrolidonyl, tetrahydrofuranyl, tetrahydropyranyl, benzopyrrolidonyl, cyclobutyl, oxetanyl, tetrahydrothiophenyl, tetrahydro-2*H*-thiopyranyl, cyclopentyl, cycloheptanyl, tetrahydrothiophenyl-1,1-dioxide, tetrahydro-2*H*-thiopyranyl-1,1-dioxide, 1,4-oxathianyl-4,4-dioxide, and piperidinyl, any of which may be unsubstituted or substituted with $(R5_b)t$;
R_{5b}, when present, is independently selected from the group consisting of-CH_2COOR_{20}, $-CH_2CONR_{21}R_{22}$, oxo, -CN, $-CH_2$-CN, $-C_{1-6}$ alkyl, $-CH_2$-imidazolyl,$-CH_2-SO_2R_{20}$, $-CH_2C(CH_3)_2(OR_{20})$, $-OR_{20}$, $-CH_2$-triazolyl, $-CF_3$, dimethyl substituted-imidazolidinyl-2,4-dione, $-CH_2-SO_2NR_{21}R_{22}$, morpholinyl, -C(=O)-morpholinyl, piperazinonyl, piperidinyl-$CONR_{21}R_{22}$, -OH, $-COR_{20}$, $-CONR_{21}R_{22}$, $-CH(OR_{20})CH_3$,$-COOR_{20}$, $-CH_2$-pyrrolidonyl, $-C_{1-6}$-alkylene-OH, -cyclopentyl, -pyrrolidonyl, -tetrazolyl, $-CH_2$-triazolyl, $-CH_2OR_{20}$, -acyl, $-SOR_{20}$, $-SO_2R_{20}$, $-SO_2NR_{21}R_{22}$, $-NR_{21}SO_2R_{20}$, and halogen;
R_{20}, R_{21}, and R_{22} are independently selected from H, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{3-6}$ cycloalkyl, and $-C_{1-6}$ heteroalicyclyl; and
t is an integer selected from 1 or 2.

[0134] Compounds disclosed herein may also comprise compounds of Formula (IIe):

(IIe),

or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, and stereoisomers thereof, wherein:

n, p and v are an integer selected from 0,1 and 2;
R is hydrogen or C_{1-4} alkyl;
R_1 is selected from the group consisting of hydrogen, -OH, halogen, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy;
R_2 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} hydroxyalkyl; or R and R_2 are combined to form a fused ring;
R_3 is selected from the group consisting of hydrogen, halogen, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, oxo, and $-C(=O)R_{10}$;
R_{4a} is selected from the group consisting of hydrogen, halogen, -OH, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_{1-6} alkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroaryl-C_{1-6} alkyl;
R_{4b} is selected from the group consisting of hydrogen, oxo, halogen, -OH, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy,$-C(=O)R_{10}$;
R_{5a} is selected from the group consisting of hydrogen, halogen, oxo, -CN, -OH, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, , substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_{1-6} alkyl, substituted or unsubstituted C_2-C_8 heteroalicyclyl, substituted or unsubstituted C_2-C_8 heteroalicyclyl-C_{1-6} alkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaryl-C_{1-6} alkyl,$-(CH_2)_qCO_2R_{20}$, $-(CH_2)_q-CONR_{20}R_{21}$, $-(CH_2)_q-SOR_{20}$, $-(CH_2)_q-SO_2R_{20}$, $-(CH_2)_q-SO_2NR_{21}R_{22}$, and $-(CH_2)_qNR_{21}SO_2R_{20}$;
q is an integer selected from 0 or 1;
R_{20}, R_{21}, and R_{22} are independently of each other selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, -CN, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-6} heteroalicyclyl, or R_{21} and R_{22} are combined to form a C_{3-6} cycloalkyl;
R_{6a}, R_{6b} are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{2-9} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, or R_{6a} and R_{6b} are taken together to form and oxo group or a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2*9} heteroalicyclyl, or R_{6a} and R_{13} are taken together to form a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-5} heteroalicyclyl;
R_7, R_8, and R_9 are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl;
R_{10} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, -OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, and C_{3-7} cycloalkyl;
R_{13}, if not to be taken together with R_{6a}, is absent, or selected from the group consisting of hydrogen, -CN, -OH, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6}

alkoxy, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, and-(CR_8R_9)p-$C(=O)OR_7$, -(CR_8R_9)p-SO_2R_7 and -(CR_8R_9)p-$C(=O)NR_8R_9$;
B is a ring system selected from the group consisting of aryl, heteroaryl, and, C_2-C_9 bicyclic heteroalicyclyl;
D is a ring system selected from the group consisting of aryl, heteroaryl, C_{3-8} cycloalkyl and, C_2-C_9 heteroalicyclyl,
C is a ring system selected from C_{2-9} heteroalicyclyl, and
with the proviso the compound is not:

[0135] Some embodiments relates to the compound according to Formula (IIe) wherein

R_3 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, oxo, C_{1-4} alkoxy and C_{1-4} haloalkoxy;
R_{4a} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, and heteroaryl;
R_{4b} is selected from the group consisting of hydrogen, oxo, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy;
R_{6a} is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;
R_{6b} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} haloalkoxy, aryl- C_{1-6} alkyl, substituted or unsubstituted C_{2-9} heteroalicyclyl-C_{1-6} alkyl, and substituted or unsubstituted aryl;
or R_{6a} and R_{6b} are taken together to form and oxo group or a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl,
or R_{6a} and R_{13} are taken together to form a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-5} heteroalicyclyl;

[0136] In some embodiments the compounds of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein, B is aryl or heteroaryl, for example phenyl, pyridyl, pyrazolyl, pyridazinyl, pyrimidinyl, naphthyl and furanyl, unless otherwise specified. Some embodiments relates to B being phenyl, pyrimidyl or pyridyl.
[0137] In some embodiments the compounds of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein, B is a 6-membered aryl substituted with R_{4a} in the *para*-position or meta-position, a 6-membered heteroaryl substituted with R_{4a} in the *para*-position or meta-position, or a 5-membered heteroaryl substituted with R_{4a} in 2- or 3-position, unless otherwise specified. In some embodiments the 6-membered aryl is phenyl and the 6-membered heteroaryl is pyridyl or pyrimidinyl. Some embodiments relate to R_{4a} being selected from the group consisting of halogen, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_1-C_4 alkoxy, C_{1-4} haloalkoxy and heteroaryl, for example isopropyl, -CN, ethoxy, CF_3, and -OCF_3. Some embodiments relate to R_{4b} being selected from the group consisting of hydrogen, oxo, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_1-C_4 alkoxy, C_{1-4} haloalkoxy, and heteroaryl. Some embodiments relate to R_{4a} being selected from the group consisting of halogen,-CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_1-C_4 alkoxy, and C_{1-4} haloalkoxy, for example isopropyl, ethoxy, -CF_3, -CHF_2, -OCF_3, and -$OCHF_2$ and R_{4b} being selected from the group consisting of hydrogen, halogen, and -OH.
[0138] In some embodiments the compounds of Formulae (IIe), D is selected from the group consisting of aryl, such as phenyl; heteroaryl, such as pyridyl, and pyrimidyl; C_{3-8} cycloalkyl, such as cyclohexyl; and C_{2-8} heteroalicyclyl, such as piperidyl, tetrahydro-2H-pyranyl, thiopyranyl, tetrahydro-2H-thiopyranyl, tetrahydro-2H-thiopyranyl-1,1-dioxide, pyrrolidinyl, thianyl and oxetanyl, all which may be substituted with one or more R_{5a}. Some embodiments relates to R_{5a} being selected from hydrogen, C_{1-6} alkyl, such as methyl and ethyl; C_{1-6} hydroxyalkyl, such as methanol and ethanol; -$(CH_2)_q$-CN; -$(CH_2)_q$-CO_2R_{20}; -$(CH_2)_q$-C_{1-6} alkoxy, such as methoxy and ethoxy and methoxyethyl; oxo, -$(CH_2)_q$-heter-

oaryl, such as -$(CH_2-)_q$-tetrazolyl, -$(CH_2-)_q$-imidazolyl, -$(CH_2-)_q$-triazolyl; -$(CH_2-)_q$-$CONR_{20}R_{21}$; -$(CH_2-)_q$-COR_{20}; -$(CH_2-)_q$-SO_2R_{20}; -$(CH_2-)_q$-$NR_{21}SOR_{20}$; and -$(CH_2-)_q$-$SO_2NR_{21}R_{22}$;

R_{20}, R_{21}, and R_{22} are independently of each other selected from the group consisting of hydrogen, -OH, substituted or unsubstituted C_{1-6} alkyl, -CN, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-6} heteroalicyclyl, or R_{21} and R_{22} are combined to form a C_{3-6} cycloalkyl; and
q is an integer selected from 0 or 1.

[0139] As for any given group disclosed herein,the ring system D may comprise further hydrogen(s) than the one(s) provided by R_{5a} being hydrogen.
[0140] In some embodiments R_{20}, R_{21}, and R_{22} are independently of each other selected from the group consisting of hydrogen, methyl, ethyl, cyclopropyl, -CF_3, and-CHF_2,
[0141] In some embodiments the compunds of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein, R_{13} is absent, or selected from the group consisting of hydrogen, -OH, -CN, C_{1-4} hydroxyalkyl, C_{1-6} haloalkyl, -$(CH_2-)_qCO_2H$ -$(CH_2-)_q$-SO_2R_{20}, -$(CH_2-)_q$-$NR_{21}SO_2R_{20}$ and C_{1-6} alkoxy, or R_{13} combined with the atom to which it is attached and an adjacent R_{5a} to form a C_{3-5} cycloalkyl, or C_{2-4} heteroalicyclyl.
[0142] In some embodiments the compounds of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein, R_{6a} is hydrogen, or combined with R_{5a}, R_{6b} or R_{13} to form ring system such as a C_{3-6} cycloalkyl or C_{2-5}-heteroalicyclyl; R_{6b} is hydrogen or absent. In some embodiments both R_{6a} and R_{6b} are hydrogen.
[0143] In some embodiments the compounds according to Formula (IIe)

R is hydrogen; R_2 is selected from Cl or F; or R and R_2 are combined to form a pyrrolo[2,3-d]pyrimidine, 6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;
m is an integer selected from 0,1 and 2;
n is an integer selected from 0 and 1;
v is an integer selected from 0 and 1;
R_3 is hydrogen or fluoro
B is aryl or heteroaryl, for example phenyl, pyridyl, pyrazolyl, pyridazinyl, pyrimidinyl, naphthyl or furanyl;
C is C_{2-9} heteroalicyclyl, for example pyrrolidinyl or morpholinyl;
R_{4a} is selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_1-C_4 alkoxy, C_{1-4} haloalkoxy and heteroaryl, for example -CF_3, -CHF_2, -OCF_3,-$OCHF_2$, and triazolyl;
R_{4b} is selected from the group consisting of hydrogen, -OH, oxo, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_1-C_4 alkoxy, C_{1-4} haloalkoxy, and heteroaryl.

[0144] D is selected from the group consisting of aryl, such as phenyl; heteroaryl, such as pyridyl, and pyrimidyl; C_{3-8} cycloalkyl, such as cyclopentyl and cyclohexyl; and C_{2-8} heteroalicyclyl, such as a mono-cyclic or a bridged C_{2-8} heteroalicyclyl, such as piperidyl, tetrahydro-2H-pyranyl , thiopyranyl, tetrahydro-2H-thiopyranyl, tetrahydro-2H-thiopyranyl-1,1-dioxide, oxetanyl, tropanyl, and pyrrolidinyl, all which may be substituted with one or more R_{5a};

R_{5a} is selected from halogen, C_{1-6} alkyl, such as methyl and ethyl; C_{1-6} hydroxyalkyl, such as methanol and ethanol; C_{1-6} haloalkyl, such as -CF_3, -$(CH_2)_q$-CN; -$(CH_2)_q$-acyl; -$(CH_2)_q$-C_{1-6} alkoxy, such as methoxy and ethoxy and methoxyethyl;-$(CH_2)_q$-heteroaryl, such as -$(CH_2-)_q$-tetrazolyl, -$(CH_2-)_q$-imidazolyl, -$(CH_2-)_q$-triazolyl; -$(CH_2-)_q$-$CONR_{20}R_{21}$; -$(CH_2-)_q$-COR_{20}; -$(CH_2-)_q$-SO_2R_{20}; -$(CH_2-)_q$-$NR_{21}SOR_{20}$;-$(CH_2-)_q$- $SO_2NR_{21}R_{22}$;

R_{20}, R_{21}, and R_{22} are independently of each other selected from the group consisting of hydrogen, -OH, substituted or unsubstituted C_{1-6} alkyl, -CN, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-6} heteroalicyclyl, or R_{21} and R_{22} are combined to form a C_{3-6} cycloalkyl; and

q is an integer selected from 0 or 1;

R_{13} is absent, or selected from the group consisting of hydrogen, -OH,-CN, C_{1-4} hydroxyalkyl, C_{1-6} haloalkyl, -$(CH_2-)_q$-SO_2R_{20}, -$(CH_2-)_q$-$NR_{21}SO_2R_{20}$ and C_{1-6} alkoxy, or R_{13} combined with the atom to which it is attached and an adjacent R_{5a} to form a C_{3-5} cycloalkyl, or C_{2-4} heteroalicyclyl; In some embodiments R_{13} is absent or hydrogen.

[0145] R_{6a} is hydrogen, or combined with R_{5a}, R_{6b} or R_{13} to form ring system such as a C_{3-6} cycloalkyl or C_{2-5}-heteroalicyclyl; R_{6b} is hydrogen or absent; for example both R_{6a} and R_{6b} are hydrogen.
[0146] In such an embodiment, B may be phenyl or pyridyl. Further, B may be phenyl with R_{4a} in the *para*-position or

meta-position, or a 6-membered heteroaryl substituted with R_{4a} in the *para*-position or *meta*-position, or a 5-membered heteroaryl substituted with R_{4a} in 2- or 3-position, wherein R_{4a} is selected from a group other than hydrogen.

[0147] According to one aspect disclosed herein are compounds of Formula (X)

Formula (X)

or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, and stereoisomers thereof, wherein:

Y_1 is NR or O;
Y_2 is N or C;
R is hydrogen or substituted or unsubstituted C_{1-4} alkyl;
R_1 is selected from the group consisting of hydrogen, -OH, halogen, -CN,-NO_2, -NH_2, alkylamino, amide, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, carbonyl, thisocarbonyl, C amido, N amido, S-sulfonamido, N sulfonamide, silyl, sulfenyl, sulfinyl, sulfonyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy,substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_{3-9} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{2-9} heteroaliyclyl;
R_2 is selected from the group consisting of hydrogen, -OH, halogen, -CN, - NO_2, -NH_2, alkylamino, amide, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, carbonyl, thisocarbonyl, C amido, N amido, S-sulfonamido, N sulfonamide, silyl, sulfenyl, sulfinyl, sulfonyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy,substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_{3-9} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{2-9} heteroaliyclyl;
or R and R_2 are combined to form a fused ring;
R_{4a} is selected from the group consisting of hydrogen, halogen, -OH, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_{1-6} alkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaryl-C_{1-6} alkyl;
R_3 and R_{4b} are independently selected from the group consisting of hydrogen, halogen, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, -C(=O)R_{10};
R_5 is selected from the group consisting of -(CR_8R_9)pOR_{12}, -(CR_8R_9)p-$CR_{13}R_{14}R_{15}$, -(CR_8R_9)p-C(=O)OR_7, and -(CR_8R_9)p-C(=O)NR_8R_9;
n, m, and p are integers independently selected from the group consisting of 0, 1, 2, 3 and 4;
R_{6a}, R_{6b} are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkynyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{2-9} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;
R_7, R_8, R_9, and R_{12}, are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl;
R_{10} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, -NH_2,-NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, and C_{3-7} cycloalkyl;
R_{13} is absent, or selected from the group consisting of hydrogen, -OH, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{3-8}

cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, and -$(CR_8R_9)_p$-C(=O)OR_7, and-$(CR_8R_9)_p$-C(=O)NR_8R_9; R_{14} and R_{15} are independently selected from the group consisting of hydrogen, and substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted C_{2-9} heteroalicyclyl; or R_{14} and R_{15} are combined to form a ring system selected from the group consisting of substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl substituted or unsubstituted C_{2-9} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;
A, B and C are independently of each other a ring system selected from the group consisting of aryl, heteroaryl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, and C_{2-9} heteroaliyclyl. -

[0148] In a related embodiment A is selected from the group consisting of phenyl, pyridyl, pyrrolyl, furyl, pyranyl, thiopyranyl, thienyl, pyrazinyl, pyrimidinyl, triazinyl, naphthyl, indolyl, iso-indolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, and oxazolyl. In yet a related embodiment A is selected from the group consisting of phenyl, pyridyl, pyrimidinyl, and wherein R_1 is arranged in position 1 of the 6 membered ring, R_1 is arranged in position 4 of the 6 membered ring, Y_1 arranged in position 3 of the 6 membered ring, Y_2 arranged in position 5 of the 6 membered ring.In a related embodiment R_1 is selected from the group consisting of hydrogen, -OH, halogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, and substituted or unsubstituted C_{2-4} alkenyl; and R_2 is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, -CN, -OH and -NO_2; or R and R_2 are combined to form a fused ring;

[0149] In yet a related embodiment B is a ring system selected from the group consisting of aryl, heteroaryl, and bicyclic heteroalicyclyl; C is a ring system selected from the group consisting of C_{2-9} heteroalicyclyl and heteroaryl; wherein B is attached to a carbon atom adjacent the N atom of ring system C.

[0150] In some embodiments whenever a halogen is specified as a substituent the halogen is selected from fluoro or chloro.

Brief description of the drawings

[0151]

Figure 1 illustrates the TAMRA-labelled probe.
Figure 2 illustrates the characterisation of the Fluorescence Polarization (FP) assay with the TAMRA-labelled probe used in the FP assay.
Figure 3 depicts the assay results of example no. **89** in (A) Fluorescence Polarization Assay, (B) RORy Reporter Assay (Gal4), and (C) Th17 Assay. Specific examples of compounds are disclosed in Table 1 below.

Table 1. Example Compounds by Structure and Name.

Ex. No.	Structure	Name
4		3-[[2-[4-[2-(4-phenylphenyl)pyrrolidin-1-yl] pyrrolo[2,3-d]pyrimidin-7-yl]butanoylamino] methyl]furan-2-carboxamide

(continued)

Ex. No.	Structure	Name
5		(2R)-2-[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide or (2R)-2-[[5-fluoro-6-[(2S)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide
6		(2R)-4,4-dimethyl-2-[[6-[2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] pentanamide
9		(2R)-2-[[6-[2-(1,3-benzothiazol-2-yl)pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]-3-(2,4,5-trifluorophenyl)propanamide
11		(2R)-2-[[6-[2-(2,4-dichlorophenyl)pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide

(continued)

Ex. No.	Structure	Name
13		(2R)-2-[[5-fluoro-2-(trifluoromethyl)-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide
14		(2R)-4,4-dimethyl-2-[[5-methyl-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]pentanamide
15		(2R)-2-[[2,5-dimethyl-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide
16		5-fluoro-N-(3-methoxy-1,3-dimethyl-butyl)-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
17		(2R)-2-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-3-(4-methoxyphenyl)propanamide

(continued)

Ex. No.	Structure	Name
18		(2R)-2-[[5-fluoro-6-[4-methyl-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide
19		(2R)-2-[[6-[2-(4-tert-butylphenyl)pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide
20		(2R)-2-[[5-fluoro-6-[3-[4-(trifluoromethyl)phenyl]morpholin-4-yl]pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide
21		N-(3,3-dimethylbutyl)-5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
23		(2R)-2-[[5-fluoro-6-[2-(6-quinolyl)pyrrolidin-1-yl] pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide
24		(2R)-2-[[6-[2-(2,3-dihydro-1,4-benzodioxin-6-yl) pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide
29		(2R)-2-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]-3-(4-methoxyphenyl)propan-1-ol
30		(2R)-2-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]-4,4-dimethyl-pentan-1-ol

(continued)

Ex. No.	Structure	Name
31		(2R)-2-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]-methyl-amino]-N, 4,4-trimethyl-pentanamide
32		2-[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]acetic acid
33		(2R)-2-[[5-fluoro-6-[4-methyl-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-yl]amino]-4-methyl-pentanoic acid
34		(2R)-2-[[5-fluoro-6-[4-methyl-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-yl]amino]-4-methyl-pentanamide

(continued)

Ex. No.	Structure	Name
35		(2R)-2-[[6-[2-[2-chloro-4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl] amino]-4,4-dimethyl-pentanamide
36		(2R)-2-[[6-[2-[2-chloro-4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl] amino]-4,4-dimethyl-pentanoic acid
37		(2R)-2-[[5-fluoro-6-[4-methyl-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-yl]amino]-3-(4-fluorophenyl) propanamide
38		(2R)-2-[[5-fluoro-6-[3-methyl-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide

(continued)

Ex. No.	Structure	Name
39		(2R)-2-[[3-fluoro-2-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]-4-pyridyl]amino]-4,4-dimethyl-pentanamide
40		2-[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]acetamide
41		5-fluoro-N-(1-methyl-2-tetrahydropyran-4-yl-ethyl)-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
42		(2R)-2-[[5-fluoro-6-[2-[5-(trifluoromethyl)-2-pyridyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide
43		(2R)-2-[[6-[2-(4-tert-butoxyphenyl)pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide

(continued)

Ex. No.	Structure	Name
44		4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] benzoic acid
45		3-[[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]methyl]-5,5-dimethyl-imidazolidine-2,4-dione
46		[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]methanesulfonamide
48		5-fluoro-N-[[4-(trifluoromethyl)phenyl]methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
51		(2R)-3-tert-butoxy-2-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]butanamide
52		(2R)-2-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-3-tetrahydropyran-4-yl-propanamide
53		N-[(3,4-dimethoxyphenyl)methyl]-5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
54		N-[(2,3-dimethoxyphenyl)methyl]-5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
55		N-[1-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl) propyl]-5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
56		5-fluoro-N-[(4-morpholinophenyl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
57		[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]-morpholino- methanone
58		[1-[5-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]-2-pyridyl]-4-piperidyl]methanol

(continued)

Ex. No.	Structure	Name
59		5-fluoro-N-[[4-(tetrahydrofuran-2-ylmethoxy) phenyl]methyl]-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
60		4-[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]piperazin-2-one
61		1-[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]piperidine-3-carboxamide
62		(2R)-2-[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide or (2R)-2-[[5-fluoro-6-[(2S)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide

(continued)

Ex. No.	Structure	Name
63		(2R)-2-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]-3-(2-oxopyrrolidin-3-yl)propanamide
64		N-[(1R)-3,3-dimethyl-1-morpholin-2-yl-butyl]-5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
65		(2R)-2-[[5-fluoro-6-[2-[2-methoxy-4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide
66		3-fluoro-N-[(6-methyl-3-pyridyl)methyl]-4-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyridin-2-amine
67		1-[(3,4-dimethoxyphenyl)methyl]-4-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrrolo[2,3-b]pyridine

(continued)

Ex. No.	Structure	Name
68		(2R)-2-[[5-fluoro-6-[3-[4-(trifluoromethoxy) phenyl]morpholi n-4-yl]pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide
69		7-[(3,4-dimethoxyphenyl)methyl]-4-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrrolo[2,3-d]pyrimidine
70		methyl 2-[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]phenyl]acetate
71		1-[2-[(1R)-1-[[5-fluoro-6-[2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-3,3-dimethyl-butyl]morpholin-4-yl]ethanone
72		(2R)-2-[[5-fluoro-6-[2-[3-fluoro-4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-yl]amino]-4,4-dimethyl-pentanamide

(continued)

Ex. No.	Structure	Name
73		5-fluoro-4-[2-[3-fluoro-4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]-6-[(6-methyl-3-pyridyl)methoxy] pyrimidine
74		5-fluoro-4-[(6-methyl-3-pyridyl)methoxy]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidine
77		(2R)-2-[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]oxy-4-methyl-pentanamide or (2R)-2-[5-fluoro-6-[(2S)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-yl]oxy-4-methyl-pentanamide
78		(2R)-2-[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]oxy-4-methyl-pentanamide or (2R)-2-[5-fluoro-6-[(2S)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-yl]oxy-4-methyl-pentanamide

(continued)

Ex. No.	Structure	Name
79		2-[4-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]oxymethyl]phenyl] acetic acid
80		(2R)-2-[5-fluoro-6-[5-[4-(trifluoromethyl)phenyl] pyrazol-1-yl]pyrimidin-4-yl]oxy-4-methyl-pentanamide
81		2-[4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]phenyl]acetic acid
83		2-[4-[[5-fluoro-6-[[4-(trifluoromethyl)phenyl] methylamin o]pyrimidin-4-yl]oxymethyl]phenyl] acetic acid
84		2-[4-[[5-fluoro-6-[2-[6-(trifluoromethyl)-3-pyridyl] pyrrolidin-1-yl]pyrimidin-4-yl]oxymethyl]phenyl] acetamide

(continued)

Ex. No.	Structure	Name
85		2-[4-[[4-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrrolo[2,3-d]pyrimidin-7-yl]methyl]phenyl] acetic acid
86		2-[5-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]oxymethyl] pyrimidin-2-yl]acetamide
87		2-[5-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] pyrimidin-2-yl]acetamide
88		4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] benzonitrile
89		5-fluoro-N-[(6-methyl-3-pyridyl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
90		5-fluoro-6-[2-(4-methoxyphenyl)pyrrolidin-1-yl]-N-[(6-methyl-3-pyridyl)methyl]pyrimidin-4-amine
91		2-[4-[[[5-fluoro-6-[3-[4-(trifluoromethoxy)phenyl] morpholi n-4-yl]pyrimidin-4-yl]amino]methyl] phenyl]acetic acid
93		5-fluoro-N-[(4-methylcyclohexyl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
94		5-fluoro-N-[[4-(imidazol-1-ylmethyl)phenyl] methyl]-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
95		5-fluoro-N-[[4-(methylsulfonylmethyl)phenyl] meth yl]-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
96		5-fluoro-N-[(6-methyl-3-pyridyl)methyl]-6-[5-[4-(trifluoromethyl)phenyl]triazol-1-yl] pyrimidin-4-amine
97		5-fluoro-N-[(6-methyl-3-pyridyl)methyl]-6-[2-[4-(trifluoromethoxy)phenyl]pyrrolidin -1-yl] pyrimidin-4-amine
98		1-[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]-2-methyl-propan-2-ol

(continued)

Ex. No.	Structure	Name
99		5-fluoro-N-[(2-methoxy-6-methyl-3-pyridyl) methyl]-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
100		5-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] pyridin-2-ol
104		2-[1-[5-fluoro-6-[(6-methyl-3-pyridyl) methylamino]pyrimidin-4-yl]pyrrolidin-2-yl]-5-(trifluoromethyl)phenol

(continued)

Ex. No.	Structure	Name
105		5-fluoro-N-[(1-methylpyrrol-3-yl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
106		5-fluoro-N-[(1-methylpyrazol-4-yl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
107		5-fluoro-N-[(5-methyl-2-furyl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
108		5-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] pyrrolidin-2-one
109		4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-yl]amino]methyl]-1-methyl-pyrrolidin-2-one
110		5-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]-N, N-dimethyl-tetrahydrofuran-2-carboxamide
111		5-fluoro-N-[(4-methoxytetrahydropyran-4-yl) methyl]-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
112		1-[6-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]-2-methyl-3-pyridyl]ethanol
113		5-fluoro-N-[(2-methoxy-4-pyridyl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
114		5-fluoro-N-[(6-methoxy-3-pyridyl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
115		5-fluoro-N-[[4-(1,2,4-triazol-1-ylmethyl)phenyl] methyl]-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
116		5-fluoro-N-[(6-methoxy-3-pyridyl)methyl]-N-methyl-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
117		2-[4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]phenyl]acetic acid
118		2-[4-[[[5-fluoro-6-[(2S)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]phenyl]acetic acid
119		2-[4-[[[5-fluoro-6-[3-[4-(trifluoromethyl)phenyl] morpholin-4-yl]pyrimidin-4-yl]amino]methyl] phenyl]acetic acid
120		4-[2-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]ethyl] benzoic acid

(continued)

Ex. No.	Structure	Name
121		[3-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]pyrrolidin-1-yl]-(4-pyridyl)methanone
122		5-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] indolin-2-one
123		5-fluoro-N-[3-methyl-1-(1H-tetrazol-5-yl)butyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
124		1-[[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]methyl]pyr rolidin-2-one
126		5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]-N-[[6-(trifluoromethyl)-3-pyridyl] methyl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
128		2-[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]ethanol
129		4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] tetrahydropyran-4-ol
130		1-cyclopentyl-4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-yl]amino]methyl]pyrrolidin-2-one
131		5-fluoro-N- [(4-methoxy-2-pyridyl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
132		5-fluoro-N-[(6-methyl-2-pyridyl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
134		9-[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]-3,9-diazaspiro[4.5]decan-2-one
135		4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]-methyl-amino]methyl]-1-methyl-pyrrolidin-2-one
136		N-[(5-ethyl-2-pyridyl)methyl]-5-fluoro-N-methyl-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
137		1-[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]pyrrolidin-2-one
138		5-fluoro-N-[[4-(1H-tetrazol-5-yl)phenyl]methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
139		N-benzyl-5-fluoro-6-[2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
140		5-fluoro-N-(4-pyridylmethyl)-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
141		5-fluoro-N-(3-pyridylmethyl)-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
142		N-[(3,5-dimethoxyphenyl)methyl]-5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
143		1-[3-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]pyrrolidin-2-one
144		3-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]-N-methyl-benzamide
145		3-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]-N, N-dimethyl-benzamide
146		5-fluoro-N-[[3-(1,2,4-triazol-1-ylmethyl)phenyl] methyl]-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
147		5-fluoro-N-[[3-(methoxymethyl)phenyl]methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
148		2-[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] cyclohexyl]acetic acid
150		5-fluoro-6-[2-(5-methyl-2-furyl)pyrrolidin-1-yl]-N-[(6-methyl-3-pyridyl)methyl]pyrimidin-4-amine
151		N-(cyclobutylmethyl)-5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
152		5-fluoro-N-[(1-methylcyclobutyl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
154		5-fluoro-N-(tetrahydrofuran-3-ylmethyl)-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
155		5-fluoro-N-(tetrahydropyran-2-ylmethyl)-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
159		5-fluoro-N-(tetrahydrothiophen-2-ylmethyl)-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
161		5-fluoro-N-[(4-methyltetrahydropyran-4-yl) methyl]-6-[(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
164		5-fluoro-N-(tetrahydrothiopyran-4-ylmethyl)-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
165		3-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]tetrahydrothiophen -3-ol

(continued)

Ex. No.	Structure	Name
166		N-[(4,4-dimethylcyclohexyl)methyl]-5-fluoro-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
167		1-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]cycloheptanol
168		5-fluoro-N-[(2-methoxycyclohexyl)methyl]-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
169		4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]tetrahydrothiopyra n-4-ol
170		N-[(1,1-dioxothiolan-2-yl)methyl]-5-fluoro-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
175		N-[(2-tert-butyltetrahydropyran-3-yl)methyl]-5-fluoro-6-[(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
178		5-fluoro-N-[(4-isopropylcyclohexyl)methyl]-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
181		5-fluoro-N-(tetrahydrofuran-2-ylmethyl)-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
182		4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]benzenesulfonami de

(continued)

Ex. No.	Structure	Name
183		N-[(6-chloro-3-pyridyl)methyl]-5-fluoro-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
184		N-[(1,1-dioxothiolan-3-yl)methyl]-5-fluoro-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
185		5 -fluoro-N-(3 -thienylmethyl)-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
186		5-fluoro-N-(tetrahydropyran-3-ylmethyl)-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
188		5-fluoro-N-[[1-(methoxymethyl)cyclobutyl] methyl] -6-[(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
189		2-[4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]phenyl]-N-methyl-acetamide
190		5-fluoro-N-[[4-(1H-tetrazol-5-ylmethyl) cyclohexyl]methyl]-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
191		1-[4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]-1-piperidyl]ethanone

(continued)

Ex. No.	Structure	Name
192		2-[4-[[[5-fluoro-6-[2-[4-(trifluoromethoxy)phenyl] pyrrolidin -1-yl]pyrimidin-4-yl]amino]methyl] phenyl]acetic acid
193		5-fluoro-N-[(1 -oxidopyridin-1-ium-3-yl)methyl]-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
194		5-fluoro-N-[(1-oxidopyridin-1-ium-4-yl)methyl]-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
195		2-[4-[[4-[(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrrolo[2,3-d]pyrimidin-7-yl] methyl]phenyl] acetic acid
196		2-[4-[[4-[(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrrolo[2,3-d]pyrimidin-7-yl] methyl]phenyl]acetamide

(continued)

Ex. No.	Structure	Name
197		5-fluoro-N-[(1-methylsulfonyl-4-piperidyl) methyl]-6-[(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
198		5-fluoro-N-[(3-methyloxetan-3-yl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
199		5-fluoro-N-[(2-methyltetrahydrofuran-2-yl) methyl]-6-[(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
200		2-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]cyclohexanol
201		5-fluoro-N-[(2-methyltetrahydrothiophen-2-yl) methyl]-6-[(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
202		N-[(4,4-dioxo-1,4-oxathian-2-yl)methyl]-5-fluoro-6-[(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
203		5-fluoro-N-(2-thienylmethyl)-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
204		2-[4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]phenyl]acetamide
205		2-[4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]cyclohexyl]acetic acid
206		2-[4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]cyclohexyl]acetam ide
207		2-[5-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]-2-thienyl]acetic acid

(continued)

Ex. No.	Structure	Name
208		5-fluoro-N-(tetrahydropyran-4-ylmethyl)-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
209		5-fluoro-N-[(6-methyl-3-pyridyl)methyl]-6-[2-methyl-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
210		5-fluoro-6-[(2R)-2-[2-fluoro-4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]-N-[(6-methyl-3-pyridyl) methyl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
211		5-fluoro-N-[(6-methyl-3-pyridyl)methyl]-6-[4-methyl-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
212		5-fluoro-6-[4-methoxy-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]-N-[(6-methyl-3-pyridyl) methyl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
213		5-fluoro-N-[(5-methyloxazol-2-yl)methyl]-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
214		5-(((5-fluoro-6-(2-(4-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrimidin-4-yl)amino)methyl)-1,3,4-oxadiazol-2-ol

(continued)

Ex. No.	Structure	Name
215		5-fluoro-N-[1-(5-methyl-1,2,4-oxadiazol-3-yl) propyl]-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-amine
216		5-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] isoxazol-3-ol
217		[3-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]phenyl]methanol

(continued)

Ex. No.	Structure	Name
218		N-(cyclopentylmethyl)-5-fluoro-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
219		5-fluoro-N-[(4-methylsulfonylphenyl)methyl]-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine
220		3-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]tetrahydrofuran-3-ol

(continued)

Ex. No.	Structure	Name
221		2-[4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]tetrahydropyran-4-yl]ethanol
222		N-[(1,1-dioxothian-4-yl)methyl]-5-fluoro-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine
223		4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]-1,1-dioxo-thian-4-ol
224		N-cyclopropyl-4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-yl]amino]methyl]benzenesulfonamide

(continued)

Ex. No.	Structure	Name
225		[4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]cyclohexyl]metha nol
226		4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]benzamide
227		[4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]phenyl]methanol

(continued)

Ex. No.	Structure	Name
228		[3-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]oxetan-3-yl]methanol
229		2-[4-[[[5-fluoro-6-[2-methyl-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]phenyl]acetamide
230		2-[4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethoxy) phenyl]morpholi n-4-yl]pyrimidin-4-yl]amino] methyl]phenyl]acetamide

(continued)

Ex. No.	Structure	Name
231		2-[4-[[[6-[4,4-difluoro-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl] amino]methyl]phenyl]acetamide
232		2-[4-[[[5-fluoro-6-[(2R)-2-[2-fluoro-4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-yl] amino]methyl]phenyl]acetamide
233		1-[4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]-1-piperidyl]ethanone
234		4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]-1,1-dioxo-thian-4-ol

(continued)

Ex. No.	Structure	Name
235		5-fluoro-N-[(3-methyloxetan-3-yl)methyl]-6-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl]pyrimidin-4-amine
236		N-cyclopropyl-4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl]pyrimidin-4-yl]amino]methyl]benzenesulfonamide
237		5-fluoro-N-[(1-methylsulfonyl-4-piperidyl)methyl]-6-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
238		3-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]tetrahydrofuran-3-ol
239		2-[4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]tetrahydropyran-4-yl]ethanol
240		5-fluoro-N-[[4-(methylsulfonylmethyl) tetrahydropyran-4-yl]methyl]-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl] pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
241		2-[4-[[[5-fluoro-6-[(2R,4R)-4-fluoro-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]phenyl]acetamide AND 2-[4-[[[5-fluoro-6-[(2S,4S)-4-fluoro-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]phenyl]acetamide
242		2-[4-[[[5-fluoro-6-[(2S,4R)-4-fluoro-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]phenyl]acetamide AND 2-[4-[[[5-fluoro-6-[(2R,4S)-4-fluoro-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]phenyl]acetamide

(continued)

Ex. No.	Structure	Name
243		2-[4-[[[5-fluoro-6-[(3 S)-3-[4-(trifluoromethoxy) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]cyclohexyl]acetic acid
244		2-[4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]phenyl]-N-methyl-acetamide
245		2-[4-[[[5-fluoro-6-[(3 S)-3-[4-(trifluoromethoxy) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]cyclohexyl]acetamide
246		5-fluoro-N-[[4-(1H-tetrazol-5-ylmethyl)phenyl] methyl]-6-[(3S)-3-[4-(trifluoromethoxy)phenyl] morpholin-4-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
247		5-fluoro-N-(tetrahydropyran-4-ylmethyl)-6-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl]pyrimidin-4-amine
248		2-[4-[[[5-fluoro-6-[4-methyl-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]phenyl]acetamide
249		1-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]cyclopentanecarboxamide
250		1-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]-N,N-dimethyl-cyclopentanecarboxamide

(continued)

Ex. No.	Structure	Name
251		N-[2-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]cyclopentyl]methanesulfonamide
252		2-[4-[[4-[(3S)-3-[4-(trifluoromethoxy)phenyl] morpholin-4-yl]pyrrolo[2,3-d]pyrimidin-7-yl] methyl]phenyl]acetamide
253		5-fluoro-N-[[4-(methylsulfonylmethyl) tetrahydropy ran-4-yl]methyl]-6-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl] pyrimidin-4-amine
254		methyl 4-[[[5-fluoro-6-[3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]tetrahydropyran-4-carboxylate

(continued)

Ex. No.	Structure	Name
255		4-[[[5-fluoro-6-[(3 S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]tetrahydropyran-4-carboxamide
256		N-(2-aminoethyl)-4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl] pyrimidin-4-yl]amino]methyl]tetrahydropyran-4-carboxamide
257		4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]tetrahydropyran-4-carbonitrile

(continued)

Ex. No.	Structure	Name
258		2-[4-[[[5-fluoro-6-[(3S)-3-[2-fluoro-4-(trifluoromethoxy)phenyl]morpholin-4-yl]pyrimidin-4-yl]amino]methyl]phenyl]acetamide
259		6-[4,4-difluoro-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]-5-fluoro-N-(tetrahydropyran-4-ylmethyl)pyrimidin-4-amine
260		6-[4,4-difluoro-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]-5-fluoro-N-[[4-(methylsulfonylmethyl)tetrahydropyran-4-yl]methyl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
261		[3-[[[6-[4,4-difluoro-2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino] methyl]oxetan-3-yl]methanol
262		1-[4-fluoro-4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl] pyrimidin-4-yl]amino]methyl]-1-piperidyl] ethanone
263		5-fluoro-6-[(3S)-3-[4-(trifluoromethyl)phenyl] morpholin-4-yl]-N-[[1-(trifluoromethylsulfonyl)-4-piperidyl]methyl]pyrimidin-4-amine
264		5-fluoro-N-[(4-fluorotetrahydropyran-4-yl) methyl]-6-[(3S)-3-[4-(trifluoromethyl)phenyl] morpholin-4-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
265		2-[4-[[4-[(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidin-1-yl]-5,6-dihydropyrrolo[2,3-d] pyrimidin-7-yl]methyl]phenyl]acetamide
266		5-fluoro-N-[(4-fluoro-1-methylsulfonyl-4-piperidyl)methyl]-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-amine
267		N-[4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethoxy) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]cyclohexyl]methanesulfonamide
268		4-[[[5-fluoro-6-[3-[4-(trifluoromethyl)phenyl] morpholin-4-yl]pyrimidin-4-yl]amino]methyl] tetrahydropyran-4-carboxylic acid

(continued)

Ex. No.	Structure	Name
273		N-cyclopropyl-4-[[[5-fluoro-6-(3-phenylmorpholin-4-yl)pyrimidin-4-yl]amino] methyl]benzenesulfonamide
274		5-fluoro-N-[(1-methylsulfonyl-4-piperidyl) methyl]-6-(3-phenylmorpholin-4-yl)pyrimidin-4-amine
276		2-[4-[[[5-fluoro-6-(3-phenylmorpholin-4-yl) pyrimidin-4-yl]amino]methyl]phenyl]acetic acid
279		2-[4-[[[5-fluoro-6-(2-phenylpyrrolidin-1-yl) pyrimidin-4-yl]amino]methyl]phenyl]acetamide

(continued)

Ex. No.	Structure	Name
280		2-[4-[[[5-fluoro-6-[4-oxo-2-[4-(trifluoromethyl) phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino] methyl]phenyl]acetamide
282		2-[5-[[[5-fluoro-6-(3-phenylmorpholin-4-yl) pyrimidin-4-yl]amino]methyl]-2-thienyl]acetic acid
283		2-[5-[[[5-fluoro-6-(3-phenylmorpholin-4-yl) pyrimidin-4-yl]amino]methyl]-2-thienyl] acetamide

(continued)

Ex. No.	Structure	Name
284		2-[4-[[4-(3-phenylmorpholin-4-yl)pyrrolo[2,3-d] pyrimidin-7-yl]methyl]phenyl]acetamide
285		2,2,2-trifluoro-N-[4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethoxy)phenyl]morpholi n-4-yl] pyrimidin-4-yl]amino]methyl]cyclohexyl]ethane sulfonamide
286		4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]-N-methyl-tetrahydropyran-4-carboxamide
287		2-[4-[[[5-fluoro-6-[(3 S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]cyclohexyl]acetonitrile
288		5-fluoro-N-[[4-(1H-tetrazol-5-ylmethyl) cyclohexyl]methyl]-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-amine

(continued)

Ex. No.	Structure	Name
290		(3S)-4-[7-[(1-methylsulfonyl-4-piperidyl)methyl] pyrrolo[2,3-d]pyrimidin-4-yl]-3-[4-(trifluoromethoxy)phenyl]morpholine
291		1,1,1-trifluoro-N-[4-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl] pyrimidin-4-yl]amino]methyl]phenyl] methanesulfonamide
292		N-cyano-2-[4-[[[5-fluoro-6-[3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]phenyl]acetamide

(continued)

Ex. No.	Structure	Name
293		5-fluoro-N-[(6-methylsulfonyl-3-pyridyl)methyl]-6-[(3S)-3-[4-(trifluoromethyl)phenyl]morpholin-4-yl]pyrimidin-4-amine
294		N-(2,2-dimethyl-4-methylsulfonyl-butyl)-5-fluoro-6-[(3S)-3-[4-(trifluoromethyl)phenyl] morpholin-4-yl]pyrimidin-4-amine
295		2-[[[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]-2-methyl-cyclohexanol
296		[1-[[[5-fluoro-6-[(3 S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]amino] methyl]cyclopropyl]methanol

(continued)

Ex. No.	Structure	Name
297		N-[1-[5-fluoro-6-[(3S)-3-[4-(trifluoromethyl) phenyl]morpholin-4-yl]pyrimidin-4-yl]-4-piperidyl]methanesulfonamide
299		2-[4-[[[6-[2-(1,3-benzodioxol-5-yl)pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]methyl]phenyl] acetamide
300		2-[4-[[[5-fluoro-6-[2-(4-hydroxyphenyl) pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]acetamide
301		2-[4-[[[6-[2-(4-ethoxyphenyl)pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]methyl]phenyl] acetamide
302		2-[4-[[[5-fluoro-6-[2-(p-tolyl)pyrrolidin-1-yl] pyrimidin-4-yl]amino]methyl]phenyl]acetamide
303		2-[4-[[[5-fluoro-6-[2-(4-isopropylphenyl) pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]acetamide

(continued)

Ex. No.	Structure	Name
304		2-[4-[[[5-fluoro-6-[2-(3-methoxyphenyl) pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]acetamide
305		2-[4-[[[6-[2-(3-bromophenyl)pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]methyl]phenyl] acetamide
306		2-[4-[[[6-[2-(3-chlorophenyl)pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]methyl]phenyl] acetamide
307		2-[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl] azetidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]acetamide
308		2-[4-[[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]-1-piperidyl]pyrimidin-4-yl]amino]methyl]phenyl] acetamide

(continued)

Ex. No.	Structure	Name
309		5-fluoro-N-[(4-methylsulfonylmorpholin-2-yl) methyl]-6-[(3S)-3-[4-(trifluoromethyl)phenyl] morpholin-4-yl]pyrimidin-4-amine
310		2-[4-[[[6-[2-(1,3-benzothiazol-2-yl)pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]methyl]phenyl] acetamide
311		2-[4-[[[5-fluoro-6-[2-(1-naphthyl)pyrrolidin-1-yl] pyrimidin-4-yl]amino]methyl]phenyl]acetamide
312		2-[4-[[[5-fluoro-6-[2-(2-naphthyl)pyrrolidin-1-yl] pyrimidin-4-yl]amino]methyl]phenyl]acetamide
313		2-[4-[[[5-fluoro-6-[2-(5-methyl-2-furyl)pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]phenyl] acetamide
314		2-[4-[[[5-fluoro-6-[2-(5-methyl-1,2,4-oxadiazol-3-yl)pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl] phenyl]acetamide

(continued)

Ex. No.	Structure	Name
315		2-[4-[[[5-fluoro-6-[2-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]phenyl]acetamide
316		2-[4-[[[6-[2-(5-ethyl-2-furyl)pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]methyl]phenyl]acetamide
317		2-[4-[[[6-[2-(1,3-dimethylpyrazol-4-yl)pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]methyl]phenyl]acetamide
318		2-[4-[[[6-[2-(2,4-dimethoxyphenyl)pyrrolidin-1-yl]-5-fluoro-pyrimidin-4-yl]amino]methyl]phenyl]acetamide
319		4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]benzenesulfonic acid
320		4-[[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]-N-(2-methoxyethyl)benzenesulfonamide

(continued)

Ex. No.	Structure	Name
323		2-[4-[[[5-fluoro-6-[2-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]methyl]phenyl]acetamide
324		2-[1-[5-fluoro-6-[(1-methylsulfonyl-4-piperidyl)methylamino]pyrimidin-4-yl]pyrrolidin-2-yl]-5-(trifluoromethyl)phenol
325		(2R)-2-[[5-fluoro-6-[(2R)-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-4,4-dimethyl-pentanoic acid
326		2-[4-[[4-[(3S)-3-[6-(trifluoromethyl)-3-pyridyl]morpholin-4-yl]pyrrolo[2,3-d]pyrimidin-7-yl]methyl]phenyl]acetamide

(continued)

Ex. No.	Structure	Name
327		5-fluoro-N-[(1-methylsulfonylpyrrolidin-3-yl) methyl]-6-[(3S)-3-[4-(trifluoromethyl)phenyl] morpholin-4-yl]pyrimidin-4-amine
328		2-[4-[[4-[(3S)-3-[5-(trifluoromethyl)-2-pyridyl] morpholin-4-yl]pyrrolo[2,3-d]pyrimidin-7-yl] methyl]phenyl]acetamide
329		(3S)-4-[7-[(6-methylsulfonyl-3-pyridyl)methyl] pyrrolo[2,3-d]pyrimidin-4-yl]- 3-[4-(trifluoromethoxy)phenyl]morpholine

(continued)

Ex. No.	Structure	Name
330		(3S)-4-[7-[(5-methylsulfonyl-2-pyridyl) methyl] pyrrolo[2,3-d]pyrimidin-4-yl]-3-[4-(trifluoromethoxy)phenyl] morpholine

Pharmaceutical Compositions

[0152] 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 compound of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), as disclosed herein. The compounds of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), 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 compound of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe). Acceptable carriers or diluents, as well as other additives to be combined with a compound of Formula (I), compounds of Formula (IIa), and compounds of any one of Formulae (IIb-IIe), 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 Sciences, 18th Ed., Mack Publishing Co., Easton, PA (1990).

[0153] 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 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.

[0154] 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.

[0155] The term "carrier" defines a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example 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.

[0156] The term "physiologically acceptable" defines a carrier or diluent that does not abrogate the biological activity and properties of the compound.

[0157] 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.

[0158] 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, including depot injections, osmotic pumps, pills, transdermal (including electrotransport) patches, and the like, for prolonged and/or timed, pulsed administration at a predetermined rate.

[0159] The pharmaceutical compositions may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tabletting processes.

[0160] 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 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.

[0161] 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 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 solution, Ringer's solution, or physiological saline buffer. If desired, absorption enhancing preparations (for example, liposomes), may be utilized.

[0162] For transmucosal administration, penetrants appropriate to the barrier to be permeated may be used in the formulation.

[0163] 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.

[0164] 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, hydroxypropylmethylcellulose, 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.

[0165] 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.

[0166] For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

[0167] 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.

[0168] 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.

[0169] 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 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.

[0170] Such suitable pharmaceutical formulations for intraocular delivery are most often and preferably formulated to be sterile, isotonic and buffered for stability and comfort. Pharmaceutical compositions for intranasal delviery 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), 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 include glycerin and water.

[0171] 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.

[0172] In addition to the formulations described previously, the compounds may also be 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.

[0173] 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.

[0174] 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.

[0175] 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.

[0176] 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.

Uses

[0177] 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 RORα, RORβ and/or RORγ (RORc) receptor. Modulators of RORγ have been reviewed by B. Fauber and S. Magnuson in J. Med. Chem., February 6, 2014. Examples of RORγ receptors are RORγ1 and RORγt 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 RORγ receptor to a larger extent than they modulate the activity of RORα and/or RORβ receptors.

[0178] The compounds or pharmaceutical compositions disclosed herein may also be used to modulate the activity of regulatory T cells (Tregs).

[0179] The compounds or pharmaceutical compositions disclosed herein may also be used to modulate the activity of cells producing IL17 in a RORγt dependent manner, for example, $\gamma\delta$T cells, Th17 cells and ILC3 cells.

[0180] 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.

[0181] 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. Examples of such diseases or disorders are inflammatory, metabolic, oncologic and autoimmune diseases or disorders mediated or affected by IL17 and/or RORγ (RORc). The role of RORγ in the pathogenesis of autoimmune or inflammatory diseases has been disclosed in Immunity 2007, 26, 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.

[0182] More specific examples of diseases or disorders include asthma, 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, cystic fibrosis, lung allograph rejection, multiple sclerosis, rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, 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, neuromyelitis optica, Myasthenia Gravis, Guillain-Barre syndrome, Graves' disease, scleritis, obesity, obesity-induced insulin resistance and type II diabetes and cancer.

[0183] More specifically, compounds or pharmaceutical compositions having an antagonistic or inverse agonistic effect on RORγ may be used to reduce levels of IL17 and/or other gene products, such as interleukins, and cytokines, regulated RORγ. This may for example be in subjects suffering from for example, asthma, 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, cystic fibrosis, lung allograph rejection, multiple sclerosis, rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, 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, neuromyelitis optica, Myasthenia Gravis, Guillain-Barre syndrome, Graves' disease, scleritis, obesity, obesity-induced insulin resistance and type II diabetes.

[0184] Conversely, compounds or pharmaceutical compositions having an agonistic effect on RORγ may be used to increase IL17 levels. Increasing IL17 levels may be particularly useful in immune compromised conditions or boosting the immune system response for example during infections and in cancer.

Methods of Administration

[0185] 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 though 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, 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; (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 (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.

[0186] 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.

[0187] 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.

[0188] 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.

[0189] 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", with particular reference to Ch. 1, p. 1).

[0190] 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 ED_{50} or ID_{50} values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

[0191] 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 administrated 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.

[0192] 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 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 a week or more, or for months or years.

[0193] 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 on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

[0194] 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%.

[0195] 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.

[0196] 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.

[0197] 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, 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 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.

[0198] 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.

General remarks

[0199] 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 invention. Rather, the invention is limited only by the accompanying claims and other embodiments than the specific above are equally possible within the scope of these appended claims.

[0200] 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 com-

bined, 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.

Experimental

[0201] The following examples are mere examples and should by no mean be interpreted to limit the scope of the invention. Rather, the invention is limited only by the accompanying claims.

General Chemical Procedures

[0202] Unless otherwise stated, starting materials were obtained from commercial suppliers, such as (but not limited to); ABchem, ABCR, Alfa Aesar, Anaspec, Anichem, Apollo Scientific, ASDI-Inter, Asiba Pharmatech, Astatech, Bachem, Chem-Impex, ChemCollect, Chembridge, Combi-Blocks, Enamine, 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. N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and dichloromethane (DCM) were dried over molecular sieves. Analytical HPLC was performed on a Waters Acquity system using a C18 reverse phase column (Merck Chromolith Speedrod RP-18E) with a linear gradient of the binary solvent system water/acetonitrile/formic acid (A: 100/0/0.1% and B: 0/100/0.1%) with a flow rate of 3.0 mL/min and UV detection at 254 nm at room temperature, combined with MS detection on a Waters Micromass QZ Quadrupole Mass Spectrometer instrument using electron spray ionization, or on a Shimadzu Nexera X2 system using a C18 reverse phase column (Acquity UPLC BEH C18 1.7μm, 2.1 x 50 mm), with a linear gradient of the binary solvent system water/methanol/formic acid (A: 100/0/0.1% and B: 0/100/0.1%) with a flow rate of 0.78 mL/min and UV detection at 254 nm, combined with MS detecting on a Shimadzu LCMS-2020 Spectrometer instrument using electron spray ionization. Preparative HPLC was performed on a Waters Acquity system using a C18 reverse phase column (Supelco ASCENTIS C18 581358-U, 15 cm x 21.2 mm), with a linear gradient of the binary solvent system water/acetonitrile/formic acid (A: 100/0/0.1% and B: 0/100/0.1%) with a flow rate of 15 mL/min and UV detection at 254 nm, combined with MS detection on a Waters Micromass QZ Quadrupole Mass Spectrometer instrument using electron spray ionization. Chiral resolution was performed on a Lux Cellulose2 (250 x 21 mm) column using a mobile phase of 0.2% diethyamine in hexane/ethanol, with a flow of 20 mL/min and UV detection at 290 nm. ^{1}H NMR spectra were recorded on a Bruker Avance 300 spectrometer (at 300 MHz), using CD_3OD, $CDCl_3$, DMSO-d_6 or C_6D_6 solvents. Chemical shifts are reported in ppm (δ) using residual solvent as an internal standard; $CDCl_3$: 7.26 ppm; CD_3OD: 3.31; DMSO-d6: 2.50 ppm. Coupling constants (J) are given in Hz.

Synthetic Methods

[0203] The compounds disclosed herein may be made by one of the following four general methods. Further, additional guidance for preparing building blocks to be used in providing compounds disclosed herein is present in the co-pending international application PCT/EP2015/067692 also claiming priority from SE 1450920-2 and SE 1451406-1.

General Method 1

[0204]

[0205] A fluorenylmethyloxycarbonyl (Fmoc) protected amino acid was coupled to a Rink resin to produce **1a** using the coupling reagents 1-hydroxy-7-azabenzotriazol (HOAt) and *N,N'*-diisopropylcarbodiimide (DIC) in the presence of a suitable base, e.g. ethyldiisopropylamine (DIPEA), in DCM/DMF (e.g. in a 1:1 ratio). The mixture was agitated at a suitable temperature until complete conversion of the starting materials was observed, typically overnight at room temperature (i.e. 20-25 °C). The Fmoc group was removed from **1a** by treatment with a base, e.g. 20% piperidine in DMF for 30 minutes at room temperature, to yield **1b.** An aromatic fluorinated building block, e.g. 4,5,6-trifluoro-pyrimidine, was coupled to a compound containing a free amino group in a nucleophilic aromatic substitution reaction to produce **1c.** The reaction may for example be done by addition of DIPEA in dimethyl sulfoxide (DMSO) followed by agitation overnight at room temperature. An aromatic nucleophilic substitution reaction was subsequently performed by addition of a compound containing a free amine to **1c,** in the presence of a suitable base, to yield **1d.** An example the addition of 4-methyl-2-[4-(trifluoromethyl)phenyl]pyrrolidine and DIPEA in DMSO, followed by agitation overnight at elevated temperature, e.g. 80-100 °C. The desired compound **1e** was obtained by cleavage from the resin upon treatment of **1d** with an acid, e.g. 2,2,2-trifluoroethanoic acid (TFA) as an 80% solution in DCM upon stirring for 1 hour at room temperature. The obtained mixture was concentrated in vacuo and purification by e.g. flash column chromatography (CC) using an appropriate eluent combination on a suitable column material, e.g. heptane/EtOAc on silica gel.

*Use of General Method 1 to Prepare Example No. **37**:*

[0206]

37

[0207] A rink amide resin (0.88 g, 0.68 mmol/g, 0.6 mmol) was swelled in dry DMF (8 mL) for 15 minutes. The resin was drained and treated twice with 20% piperidine in DMF (2 x 8 mL) for 30 minutes each. The resin was drained and washed with DMF (3 x 8 mL), methanol (2 x 8 mL), DMF (2 x 8 mL) and DCM (3 x 8 mL). The resin was swelled in dry DCM (8 mL) for 15 minutes and drained. A solution of (2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-(4-fluorophenyl)propanoic acid (0.49 g, 1.2 mol) and 1-hydroxy-7-azabenzotriazol (0.16 mg, 1.2 mmol) dissolved in DMF/DCM (1:1, 8 mL) was added, followed by DIPEA (0.31 mL, 3.6 mmol) and DIC (0.19 mL, 1.2 mmol). The reaction was agitated at room temperature overnight, drained and washed with DMF (3 x 8 mL), MeOH (2 x 8 mL), DMF (2 x 8 mL) and DCM (3 x 8 mL). The resin was swelled in dry DCM (8 mL) for 15 minutes and drained. A solution of acetic anhydride (0.57 mL, 6 mmol) and pyridine (0.97 mL, 12 mmol) dissolved in DCM (8 mL) was added and the mixture was agitated at room temperature for 1 hour. The resin was drained and washed with DCM (3 x 8 mL), DMF (3 x 8 mL) and DCM (3 x 8 mL). The resin was swelled in dry DMSO (8 mL) for 15 minutes and drained. A solution of 4,5,6-trifluoro-pyrimidine (0.16 g, 1.2 mmol) in dry DMSO (6 mL) was added, followed by DIPEA (0.26 mL, 3.0 mmol). The mixture was agitated overnight at room temperature, drained and washed with DCM (3 x 8 mL), DMF (3 x 8 mL) and DCM (3 x 8 mL). The resin was swelled in dry DMSO (8 mL) for 15 minutes and drained. A solution of 4-methyl-2-[4-(trifluoromethyl)phenyl]pyrrolidine (0.28, 1.2 mmol) in dry DMSO (6 mL) was added, followed by DIPEA (0.26 mL, 3.0 mmol). The mixture was agitated overnight at 80°C, drained and washed with DCM (3 x 8 mL), DMF (3 x 8 mL) and DCM (3 x 8 mL). The resin was swelled in dry DCM (8 mL) for 15 minutes and drained. A solution of 80% TFA in dry DCM (8 mL) was added and the mixture was agitated for 1 hour. The filtrate was collected and the treatment repeated once. The resin was washed with acetonitrile (ACN, 8 mL) and the filtrated collected. The pooled filtrates were concentrated in vacuo and purified by flash CC (eluent: DCM/MeOH, on silica gel) yielding (2R)-2-[[5-fluoro-6-[4-methyl-2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]amino]-3-(4-fluorophenyl)propanamide **37** (37 mg, 12% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70-7.55 (m, 2H), 7.50-7.45 (s, 1H), 7.43-7.36 (m, 2H), 7.33-7.23 (m, 2H), 7.10-7.00 (m, 2H), 5.22-5.18 (m, 1H), 4.67-4.55 (m, 1H), 4.02-3.92 (m, 1H), 3.43-3.38 (m, 1H), 3.05-2.96 (m, 1H), 2.57-2.52 (m, 1H), 2.31-2.28 (m, 1H), 1.35-1.29 (m, 1H), 1.02 (d, J = 6.1 Hz, 3H). *m/z* 506 (M+H).

[0208] General method 1 was used to prepare the following example numbers using the shown starting materials:

Ex. No.	Fmoc protected amino acid	Aromatic fluorinated building block	Free amine
5	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	2-[4-(trifluoromethyl)phenyl] pyrrolidine
6	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,6-difluoropyrimidine	2-[4-(trifluoromethyl) phenyl]pyrrolidine
9	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-(2,4,5-trifluorophenyl)propanoic acid	4,5,6-trifluoropyrimidine	2-pyrrolidin-2-yl-1,3-benzothiazole
11	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	2-(2,4-dichlorophenyl)pyrrolidine

(continued)

Ex. No.	Fmoc protected amino acid	Aromatic fluorinated building block	Free amine
13	9H-fluoren-9-ylmethyl N-[(1R)-1-carbamoyl-3,3-dimethylbutyl]carbamate	4,5,6-trifluoro-2-(trifluoromethyl) pyrimidine	2-[4-(trifluoromethyl)phenyl] pyrrolidine
14	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,6-difluoro-5-methylpyrimidine	2-[4-(trifluoromethyl)phenyl] pyrrolidine
15	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,6-difluoro-2,5-dimethyl-pyrimidine	2-[4-(trifluoromethyl)phenyl] pyrrolidine
17	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-(4-methoxyphenyl)propanoic acid	4,5,6-trifluoropyrimidine	2-[4-(trifluoromethyl)phenyl] pyrrolidine

(continued)

Ex. No.	Fmoc protected amino acid	Aromatic fluorinated building block	Free amine
18	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	4-methyl-2-[4-(trifluoromethyl)phenyl] pyrrolidine
19	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	2-(4-tert-butylphenyl)pyrrolidine
20	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	3-[4-(trifluoromethyl)phenyl] morpholine
23	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	6-pyrrolidin-2-ylquinoline

(continued)

Ex. No.	Fmoc protected amino acid	Aromatic fluorinated building block	Free amine
24	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	2-(2,3-dihydro-1,4-benzodioxin-6-yl) pyrrolidine
34	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-methyl-pentanoic acid	4,5,6-trifluoropyrimidine	4-methyl-2-[4-(trifluoromethyl)phenyl] pyrrolidine
35	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	2-[2-chloro-4-(trifluoromethyl)phenyl] pyrrolidine
37	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-(4-fluorophenyl)propanoic acid	4,5,6-trifluoropyrimidine	4-methyl-2-[4-(trifluoromethyl)phenyl] pyrrolidine

(continued)

Ex. No.	Fmoc protected amino acid	Aromatic fluorinated building block	Free amine
38	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	3-methyl-2-[4-(trifluoromethyl)phenyl] pyrrolidine
39	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	2,3,4-trifluoropyridine	2-[4-(trifluoromethyl)phenyl] pyrrolidine
42	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	2-pyrrolidin-2-yl-5-(trifluoromethyl) pyridine
43	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	2-pyrrolidin-2-yl-5-(trifluoromethyl) pyridine
51			

(continued)

Ex. No.	Fmoc protected amino acid	Aromatic fluorinated building block	Free amine
	(2R)-3-tert-butoxy-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoic acid	4,5,6-trifluoropyrimidie	2-[4-(trifluoromethyl)phenyl] pyrrolidine
52	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamno)-3-tetrahydropyran-4-yl-propanoic acid	4,5,6-trifluoropyrimidine	2-[4-(trifluoromethyl)phenyl] pyrrolidine
62	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	2-[4-(trifluoromethyl)phenyl] pyrrolidine
63	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-(2-oxopyrrolidin-3-yl)propanoic acid	4,5,6-trifluoropyrimidine	2-[4-(trifluoromethyl)phenyl] pyrrolidine
65	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	2-[2-methoxy-4-(trifluoromethyl) phenyl]pyrrolidine

(continued)

Ex. No.	Fmoc protected amino acid	Aromatic fluorinated building block	Free amine
68	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	3-[4-(trifluoromethoxy)phenyl] morpholine
72	(2R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine	2-[3-fluoro-4-(trifluoromethyl)phenyl] pyrrolidine
77	(2R)-2-hydroxy-4-methyl-pentanoic acid	4,5,6-trifluoropyrimidine	2-[4-(trifluoromethyl)phenyl] pyrrolidine
78	(2R)-2-hydroxy-4-methyl-pentanoic acid	4,5,6-trifluoropyrimidine	2-[4-(trifluoromethyl)phenyl] pyrrolidine

General Method 2:

[0209]

[0210] A halogenated pyrrolopyrimidine **2b,** e.g. 6-chloro-7-deazapurine, was *N*-alkylated by addition of an alkyl halide **2a,** e.g. 4-(bromomethyl)-1,2-dimethoxybenzene, and an appropriate base in a suitable solvent, e.g. cesium carbonate in dry dioxane or sodium hydride in dry tetrahydrofuran. The mixture was stirred at room temperature until completion of reaction, typically overnight. The reaction may for example be monitored by thin layer chromatography. The reaction may for example be monitored by thin layer chromatography. The desired product was obtained upon work-up, e.g. by extraction with EtOAc, washing with water at a suitable pH and brine, drying over an appropriate drying agent, e.g. Na_2SO_4, and purification by flash column chromatrography (CC) using an appropriate eluent combination on a suitable column material, e.g. heptane/EtOAc or DCM/MeOH on silica gel, or recrystallization from a suitable solvent or solvent mixture, e.g. toluene/heptane. Nucleophilic aromatic substitution of the halogen on intermediate **2c** was achieved upon addition of a building block containing a free amino group, e.g. 2-(4-trifluoromethyl-phenyl)-pyrrolidine, and a suitable base in an appropriate solvent, e.g. cesium carbonate in dry DMSO. The reaction was achieved by microwave irradiation at elevated temperatures for a period of time, e.g. at 100-150 °C for 1 hour. The reaction may for example be monitored by thin layer chromatography. The desired compound **2d** was obtained upon work-up, for example by extraction with EtOAc, washing with water at a suitable pH and brine, drying over an appropriate drying agent, e.g. Na_2SO_4, and purification by flash column chromatrography (CC) using an appropriate eluent combination on a suitable column material, e.g. heptane/EtOAc or DCM/MeOH on silica gel, or recrystallization from a suitable solvent or solvent mixture, e.g. toluene/heptane.

Use of General Method 2 to Prepare Example No. ***69:***

[0211]

69

[0212] 6-Chloro-7-deazapurine (77 mg, 0.5 mmol) and 4-(bromomethyl)-1,2-dimethoxy-benzene (127 mg, 0.55 mmol) were dissolved in dry dioxane (5 mL) and cesium carbonate (325 mg, 1.0 mmol) was added. The mixture was stirred overnight at room temperature, concentrated in vacuo, redissolved in water, extracted with EtOAc, washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by flash CC (eluent: DCM/MeOH, on silica gel) yielding 4-chloro-7-(3,4-dimethoxybenzyl)-7H-pyrrolo[2,3-d]pyrimidine (65 mg, 43% yield).

[0213] 4-Chloro-7-(3,4-dimethoxybenzyl)-7H-pyrrolo[2,3-d]pyrimidine (63 mg, 0.21 mmol) and 2-(4-trifluoromethyl-phenyl)-pyrrolidine (45 mg, 0.21 mmol) were dissolved in dry DMSO (4 mL). Cesium carbonate (137 mg, 0.42 mmol) was added, and the mixture was heated at 150 °C for 30 minutes in a microwave reactor. The mixture was poured onto 3M aq. calcium chloride, extracted with EtOAc, washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by preparative HPLC yielding 7-[(3,4-dimethoxyphenyl)methyl]-4-[2-[4-(trifluor-omethyl)phenyl]pyrrolidin-1-yl]pyrrolo[2,3-d]pyrimidine **69** (9 mg, 9% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.64 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.22 (s, 1H), 6.97 (s, 1H), 6.84 (d, J = 8.3 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 5.62 (s, 1H), 5.22 (s, 2H), 4.30-3.81 (m, 3H), 3.68 (s, 6H), 2.22-1.71 (m, 4H). *m/z* 483 (M+H).

[0214] General method 2 was used to prepare the following example numbers using the shown starting materials:

Ex. No.	Halogenated pyrrolopyrimidine	Alkyl halide	Free amine
4			

(continued)

Ex. No.	Halogenated pyrrolopyrimidine	Alkyl halide	Free amine
	4-chloro-7H-pyrrolo[2,3-d] pyrimidine	3-[(2-bromobutanoylamino)methyl] furan-2-carboxylic acid	2-(4-phenylphenyl)pyrrolidine
67	4-chloro-1H-pyrrolo[2,3-b] pyridine	4-(bromomethyl)-1,2-dimethoxy-benzene	2-[4-(trifluoromethyl)phenyl] pyrrolidine
69	4-chloro-7H-pyrrolo[2,3-d] pyrimidine	4-(bromomethyl)-1,2-dimethoxy-benzene	2-[4-(trifluoromethyl)phenyl] pyrrolidine
85	4-chloro-7H-pyrrolo[2,3-d] pyrimidine	2-[4-(bromomethyl)phenyl] acetic acid	2-[4-(trifluoromethyl)phenyl] pyrrolidine
195	4-chloro-7H-pyrrolo[2,3-d] pyrimidine	2-[4-(bromomethyl)phenyl]acetic acid	(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidine
196	4-chloro-7H-pyrrolo[2,3-d] pyrimidine	2-[4-(chloromethyl)phenyl] acetamide	(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidine

(continued)

Ex. No.	Halogenated pyrrolopyrimidine	Alkyl halide	Free amine
252	4-chloro-7H-pyrrolo[2,3-d] pyrimidine	2-[4-(chloromethyl)phenyl] acetamide	(3S)-3-[4-(trifluoromethoxy) phenyl]morpholine
265	4-chloro-6,7-dihydro-5H-pyrrolo [2,3-d]pyrimidine	2-[4-(chloromethyl)phenyl] acetamide	(2R)-2-[4-(trifluoromethyl) phenyl]pyrrolidine
284	4-chloro-7H-pyrrolo[2,3-d] pyrimidine	2-[4-(chloromethyl)phenyl] acetamide	3-phenylmorpholine
290	4-chloro-7H-pyrrolo[2,3-d] pyrimidine	4-(bromomethyl)-1-methylsulfonyl-piperidine	(3S)-3-[4-(trifluoromethoxy) phenyl]morpholine
326	4-chloro-7H-pyrrolo[2,3-d] pyrimidine	2-[4-(chloromethyl)phenyl] acetamide	(3S)-3-[6-(trifluoromethyl)-3-pyridyl]morpholine

(continued)

Ex. No.	Halogenated pyrrolopyrimidine	Alkyl halide	Free amine
328	4-chloro-7H-pyrrolo[2,3-d] pyrimidine	2-[4-(chloromethyl)phenyl] acetamide	(3S)-3-[5-(trifluoromethyl)-2-pyridyl]morpholine
329	4-chloro-7H-pyrrolo[2,3-d] pyrimidine	5-(chloromethyl)-2-methylsulfonyl-pyridine	(3S)-3-[4-(trifluoromethoxy) phenyl]morpholine
330	4-chloro-7H-pyrrolo[2,3-d] pyrimidine	2-(chloromethyl)-5-methylsulfonyl-pyridine	(3S)-3-[4-(trifluoromethoxy) phenyl]morpholine

Synthesis of selected alkyl halide

2-[4-(Chloromethyl)phenyl]acetamide

[0215] To a solution of 2-(4-(hydroxymethyl) phenyl) acetic acid (20 g, 120.48 mmol) in MeOH: toluene (1: 1) (200 mL) at 0°C was added trimethylsilyldiazomethane ($TMSCHN_2$, 27.51 g, 240 mmol), and the mixture was stirred at room temperature for 16 hours. After completion, the solvent was evaporated and the crude compound was purified by flash CC (Eluent: EtOAc/pet ether, on silica gel) to afford methyl 2-(4-(hydroxymethyl) phenyl) acetate (Compound-2) (18 g, 83 %) as an off white solid.

[0216] To a solution of methyl 2-(4-(hydroxymethyl) phenyl) acetate (3.4 g, 1.87 mmol) in MeOH (10 vol) was added aqueous NH_3 (34 ml), and the mixture was heated at 90°C for 16 hours in a sealed tube. After completion, the reaction mixture was allowed to room temperature, filtered and concentrated in vacuo to afford 2-(4-(hydroxymethyl) phenyl) acetamide (1.1 g, 35 %) as an off white solid.

[0217] To a solution of 2-(4-(hydroxymethyl) phenyl) acetamide (2 g, 12.12 mmol), Et_3N (5.1 mL, 36.36 mmol) in DMF (20 mL) was added methane sulfonyl chloride (1.5 mL, 18.18 mmol), and the mixture was stirred at room temperature for 3 hours. After completion, the reaction mixture was poured into ice water and filtered the solid to afford 2-(4-(chloromethyl) phenyl) acetamide (1.2 g, 54 %) as an off white solid.

General Method 3

[0218]

[0219] A compound containing a free amino or hydroxyl group **3a,** e.g. 1-tetrahydropyran-4-ylpropan-2-amine, was coupled to a fluorinated aromatic compound **3b,** e.g. 4,5,6-trifluoro-pyrimidine, upon treatment with a suitable base in an appropriate solvent, e.g. DIPEA or cesium carbonate in dry DMSO or dioxane. Conversion to **3c** was typically achieved after stirring at room temperature overnight. The reaction may for example be monitored by thin layer chromatography. The reaction may for example be monitored by thin layer chromatography. The desired product was obtained upon work-up, e.g. by extraction with EtOAc, washing with water at a suitable pH and brine, drying over an appropriate drying agent, e.g. Na_2SO_4, and purification by flash column chromatrography (CC) using an appropriate eluent combination on a suitable column material, e.g. heptane/EtOAc or DCM/MeOH on silica gel, or recrystallization from a suitable solvent or solvent mixture, e.g. toluene/heptane. Subsequent nucleophilic aromatic substitution of **3c** with a building block containing a free amino or hydroxyl group can be achieved upon treatment with a suitable base in an appropriate solvent. An example of such treatment is cesium carbonate in dry DMSO, heated under microwave irradiation during a period of time, e.g. at 80-150 °C for 1 hour. The reaction may for example be monitored by thin layer chromatography. The desired compound **3d** was obtained upon work-up, for example by extraction with EtOAc, washing with water at a suitable pH and brine, drying over an appropriate drying agent, e.g. Na_2SO_4, and purification by flash column chromatrography (CC) using an appropriate eluent combination on a suitable column material, e.g. heptane/EtOAc or DCM/MeOH on silica gel, or recrystallization from a suitable solvent or solvent mixture, e.g. toluene/heptane.

Use of General Method 3 to Prepare Example No. ***41:***

[0220]

41

[0221] 4,5,6-Trifluoro-pyrimidine (0.27 g, 2.0 mmol) and 2-(4-trifluoromethylphenyl)-pyrrolidine (0.43 g, 2.0 mmol) were dissolved in dry DMSO (4 mL) and DIPEA (0.7 mL, 4.0 mmol) was added. The reaction was stirred at room temperature overnight, poured into 3M aq. calcium chloride, extracted with EtOAc, washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by flash CC (eluent: DCM/MeOH, on silica gel) yielding 4,5-difluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidine (0.58 g, 88% yield).

[0222] 4,5-difluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidine (0.33 g, 1.0 mmol) and 1-tetrahydropyran-4-ylpropan-2-amine hydrochloride (0.18 g, 1.0 mmol) were dissolved in dry DMSO (2 mL) and cesium carbonate (0.65 g, 2.0 mmol) was added. The reaction was heated in a microwave reactor for 1 hour at 100 °C, poured into 3M aq. calcium chloride, extracted with EtOAc, washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by flash CC (eluent: DCM/MeOH, on silica gel), yielding 5-fluoro-N-(1-methyl-2-tetrahydropyran-4-yl-ethyl)-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-amine **41** (205 mg, 45% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0Hz, 2H), 5.40 (d, J = 7.8 Hz, 1H), 4.28-4.24 (m, 2H), 4.05-4.00 (m, 1H), 4.00-3.91 (m, 2H), 3.86-3.79 (m, 1H), 3.39-3.25 (m, 2H), 2.39-2.25 (m, 1H), 1.99-1.83 (m, 3H), 1.76-1.64 (m, 2H), 1.41-1.18 (m, 7H). *m/z* 453 (M+H).

[0223] General method 3 was used to prepare the following example numbers using the shown starting materials:

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
16	2-[4-(trifluoromethyl)phenyl] pyrrolidine	4-methoxy-4-methyl-pentan-2-amine	4,5,6-trifluoropyrimidine
21	2-[4-(trifluoromethyl)phenyl] pyrrolidine	3,3-dimethylbutan-1-amine	4,5,6-trifluoropyrimidine
29	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(2R)-2-amino-3-(4-methoxyphenyl)propan-1-ol	4,5,6-trifluoropyrimidine
30	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(2R)-2-amino-4,4-dimethyl-pentan-1-ol	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
31	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(2R)-N,4,4-trimethyl-2-(methylamino) pentanamide	4,5,6-trifluoropyrimidine
33	4-methyl-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(2R)-2-amino-4-methyl-pentanoic acid	4,5,6-trifluoropyrimidine
36	2-[2-chloro-4-(trifluoromethyl)phenyl] pyrrolidine	(2R)-2-amino-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine
41	2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-tetrahydropyran-4-ylpropan-2-amine	4,5,6-trifluoropyrimidine
44	2-[4-(trifluoromethyl)phenyl] pyrrolidine	4-(aminomethyl)benzoic acid	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
45	2-[4-(trifluoromethyl)phenyl] pyrrolidine	3-[[4-(aminomethyl)phenyl]me thyl]-5,5-dimethyl-imidazolidine-2,4-dione	4,5,6-trifluoropyrimidine
46	2-[4-(trifluoromethyl)phenyl] pyrrolidine	[4-(aminomethyl)phenyl]me thanesulfonamide	4,5,6-trifluoropyrimidine
48	2-[4-(trifluoromethyl)phenyl] pyrrolidine	[4-(trifluoromethyl)phenyl] methanamine	4,5,6-trifluoropyrimidine
53	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(3,4-dimethoxyphenyl)methanamine	4,5,6-trifluoropyrimidine
54	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(2,3-dimethoxyphenyl)methanamine	4,5,6-trifluoropyrimidine
55	2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl) propan-1-amine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
56	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(4-morpholinophenyl)methanamine	4,5,6-trifluoropyrimidine
57	2-[4-(trifluoromethyl)phenyl] pyrrolidine	[4-(aminomethyl)phenyl]-morpholino-methanone	4,5,6-trifluoropyrimidine
58	2-[4-(trifluoromethyl)phenyl] pyrrolidine	[1-[5-(aminomethyl)-2-pyridyl]-4-piperidyl] methanol	4,5,6-trifluoropyrimidine
59	2-[4-(trifluoromethyl)phenyl] pyrrolidine	[4-(tetrahydrofuran-2-ylmethoxy)phenyl] methanamine	4,5,6-trifluoropyrimidine
60	2-[4-(trifluoromethyl)phenyl] pyrrolidine	4-[4-(aminomethyl)phenyl]piperazin-2-one	4,5,6-trifluoropyrimidine
61	2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-[4-(aminomethyl)phenyl]piperidine-3-carboxamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
64	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 (1R)-3,3-dimethyl-1-morpholin-2-yl-butan-1-amine	 4,5,6-trifluoropyrimidine
66	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 (6-methyl-3-pyridyl)methanamine	 2,3,4-trifluoropyridine
70	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 methyl 2-[4-(aminomethyl)phenyl]ac etate	 4,5,6-trifluoropyrimidine
71	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 1-[2-[(1R)-1-amino-3,3-dimethylbutyl] morpholin-4-yl]ethanone	 4,5,6-trifluoropyrimidine
73	 2-[3-fluoro-4-(trifluoromethyl)phenyl] pyrrolidine	 (6-methyl-3-pyridyl)methanol	 4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
74	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(6-methyl-3-pyridyl)methanol	4,5,6-trifluoropyrimidine
80	5-[4-(trifluoromethyl)phenyl]-1H-pyrazole	(2R)-2-hydroxy-4-methyl-pentanamide	4,5,6-trifluoropyrimidine
88	2-[4-(trifluoromethyl)phenyl] pyrrolidine	4-(aminomethyl)benzonitrile	4,5,6-trifluoropyrimidine
89	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(6-methyl-3-pyridyl)methanamine	4,5,6-trifluoropyrimidine
90	2-(4-methoxyphenyl)pyrrolidine	(6-methyl-3-pyridyl)methanamine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
93	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(4-methylcyclohexyl)methanamine	4,5,6-trifluoropyrimidine
94	2-[4-(trifluoromethyl)phenyl] pyrrolidine	[4-(imidazol-1-ylmethyl)phenyl]methanamine	4,5,6-trifluoropyrimidine
95	2-[4-(trifluoromethyl)phenyl] pyrrolidine	[4-(methylsulfonylmethyl)phenyl] methanamine	4,5,6-trifluoropyrimidine
96	5-[4-(trifluoromethyl)phenyl]-1H-triazole	(6-methyl-3-pyridyl)methanamine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
97	2-[4-(trifluoromethoxy)phenyl] pyrrolidine	(6-methyl-3-pyridyl)methanamine	4,5,6-trifluoropyrimidine
98	2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-[4-(aminomethyl)phenyl]-2-methyl-propan-2-ol	4,5,6-trifluoropyrimidine
99	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(2-methoxy-6-methyl-3-pyridyl)methanamine	4,5,6-trifluoropyrimidine
100	2-[4-(trifluoromethyl)phenyl] pyrrolidine	5-(aminomethyl)pyridin-2-ol	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
104	 2-pyrrolidin-2-yl-5-(trifluoromethyl) phenol	 (6-methyl-3-pyridyl)methanamine	 4,5,6-trifluoropyrimidine
105	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 (1-methylpyrrol-3-yl)methanamine	 4,5,6-trifluoropyrimidine
106	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 (1-methylpyrazol-4-yl)methanamine	 4,5,6-trifluoropyrimidine
107	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 (5-methyl-2-furyl)methanamine	 4,5,6-trifluoropyrimidine
108	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 5-(aminomethyl)pyrrolidin-2-one	 4,5,6-trifluoropyrimidine
109	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 4-(aminomethyl)-1-methyl-pyrrolidin-2-one	 4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
110	2-[4-(trifluoromethyl)phenyl] pyrrolidine	5-(aminomethyl)-N,N-dimethyltetrahydrofuran-2-carboxamide	4,5,6-trifluoropyrimidine
111	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(4-methoxytetrahydropyran-4-yl) methanamine	4,5,6-trifluoropyrimidine
112	2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-[6-(aminomethyl)-2-methyl-3-pyridyl] ethanol	4,5,6-trifluoropyrimidine
113	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(2-methoxy-4-pyridyl)methanamine	4,5,6-trifluoropyrimidine
114	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(6-methoxy-3-pyridyl)methanamine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
115	2-[4-(trifluoromethyl)phenyl] pyrrolidine	[4-(1,2,4-triazol-1-ylmethyl)phenyl] methanamine	4,5,6-trifluoropyrimidine
116	2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-(6-methoxy-3-pyridyl)-N-methyl-methanamine	4,5,6-trifluoropyrimidine
120	2-[4-(trifluoromethyl)phenyl] pyrrolidine	4-(2-aminoethyl)benzoic acid	4,5,6-trifluoropyrimidine
121	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(3-aminopyrrolidin-1-yl)-(4-pyridyl) methanone	4,5,6-trifluoropyrimidine
122	2-[4-(trifluoromethyl)phenyl] pyrrolidine	5-(aminomethyl)indolin-2-one	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
123	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 3-methyl-1-(1H-tetrazol-5-yl)butan-1-amine	 4,5,6-trifluoropyrimidine
124	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 1-[4-(aminomethyl)phenyl]me thyl]pyrrolidin-2-one	 4,5,6-trifluoropyrimidine
126	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 [6-(trifluoromethyl)-3-pyridyl]methanamine	 4,5,6-trifluoropyrimidine
128	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 2-[4-(aminomethyl)phenyl]ethanol	 4,5,6-trifluoropyrimidine
129	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 4-(aminomethyl)tetrahydropyran-4-ol	 4,5,6-trifluoropyrimidine
130	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 4-(aminomethyl)-1-cyclopentyl-pyrrolidin-2-one	 4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
131	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(4-methoxy-2-pyridyl)methanamine	4,5,6-trifluoropyrimidine
132	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(6-methyl-2-pyridyl)methanamine	4,5,6-trifluoropyrimidine
134	2-[4-(trifluoromethyl)phenyl] pyrrolidine	3,9-diazaspiro[4.5]decan-2-one	4,5,6-trifluoropyrimidine
135	2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-methyl-4-(methylaminomethyl)pyr rolidin-2-one	4,5,6-trifluoropyrimidine
136	2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-(5-ethyl-2-pyridyl)-N-methyl-methanamine	4,5,6-trifluoropyrimidine
137	2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-[4-(aminomethyl)phenyl]py rrolidin-2-one	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
138	2-[4-(trifluoromethyl)phenyl] pyrrolidine	[4-(1H-tetrazol-5-yl)phenyl]methanamine	4,5,6-trifluoropyrimidine
139	2-[4-(trifluoromethyl)phenyl] pyrrolidine	phenylmethanamine	4,5,6-trifluoropyrimidine
140	2-[4-(trifluoromethyl)phenyl] pyrrolidine	4-pyridylmethanamine	4,5,6-trifluoropyrimidine
141	2-[4-(trifluoromethyl)phenyl] pyrrolidine	3-pyridylmethanamine	4,5,6-trifluoropyrimidine
142	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(3,5-dimethoxyphenyl)methanamine	4,5,6-trifluoropyrimidine
143	2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-[3-(aminomethyl)phenyl]pyrrolidin-2-one	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
144	2-[4-(trifluoromethyl)phenyl] pyrrolidine	3-(aminomethyl)-N-methyl-benzamide	4,5,6-trifluoropyrimidine
145	2-[4-(trifluoromethyl)phenyl] pyrrolidine	3-(aminomethyl)-N,N-dimethyl-benzamide	4,5,6-trifluoropyrimidine
146	2-[4-(trifluoromethyl)phenyl] pyrrolidine	[3-(1,2,4-triazol-1-ylmethyl)phenyl] methanamine	4,5,6-trifluoropyrimidine
147	2-[4-(trifluoromethyl)phenyl] pyrrolidine	[3-(methoxymethyl)phenyl] methanamine	4,5,6-trifluoropyrimidine
148	2-[4-(trifluoromethyl)phenyl] pyrrolidine	2-[4-(aminomethyl)cyclohexy l]acetic acid	4,5,6-trifluoropyrimidine
150	(6-methyl-3-pyridyl)methanamine	2-(5-methyl-2-furyl)pyrrolidine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
151	2-[4-(trifluoromethyl)phenyl] pyrrolidine	cyclobutylmethanamine	4,5,6-trifluoropyrimidine
152	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(1-methylcyclobutyl)methanamine	4,5,6-trifluoropyrimidine
154	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	tetrahydrofuran-3-ylmethanamine	4,5,6-trifluoropyrimidine
155	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	tetrahydropyran-2-ylmethanamine	4,5,6-trifluoropyrimidine
159	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	tetrahydrothiophen-2-ylmethanamine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
161	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(4-methyltetrahydropyran-4-yl)methanamine	4,5,6-trifluoropyrimidine
164	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	tetrahydrothiopyran-4-ylmethanamine	4,5,6-trifluoropyrimidine
165	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	3-(aminomethyl)tetrahydro thiophen-3-ol	4,5,6-trifluoropyrimidine
166	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(4,4-dimethylcyclohexyl)meth anamine	4,5,6-trifluoropyrimidine
167	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-(aminomethyl)cycloheptanol	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
168	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(2-methoxycyclohexyl)methanamine	4,5,6-trifluoropyrimidine
169	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	4-(aminomethyl)tetrahydro thiopyran-4-ol	4,5,6-trifluoropyrimidine
170	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(1,1-dioxothiolan-2-yl)methanamine	4,5,6-trifluoropyrimidine
175	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(2-tert-butyltetrahydropyran-3-yl) methanamine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
178	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(4-isopropylcyclohexyl)methanamine	4,5,6-trifluoropyrimidine
181	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	tetrahydrofuran-2-ylmethanamine	4,5,6-trifluoropyrimidine
182	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	4-(amino methyl)benzenesulfonamide	4,5,6-trifluoropyrimidine
183	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(6-chloro-3-pyridyl)methanamine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
184	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(1,1-dioxothiolan-3-yl)methanamine	4,5,6-trifluoropyrimidine
185	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	3-thienylmethanamine	4,5,6-trifluoropyrimidine
186	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	tetrahydropyran-3-ylmethanamine	4,5,6-trifluoropyrimidine
188	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	[1-(methoxymethyl)cyclobutyl]methanamine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
189	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	2-[4-(aminomethyl)phenyl]-N-methyl-acetamide	4,5,6-trifluoropyrimidine
190	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	[4-(1H-tetrazol-5-ylmethyl)cyclohexyl] methanamine	4,5,6-trifluoropyrimidine
191	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-[4-(aminomethyl)-1-piperidyl]ethanone	4,5,6-trifluoropyrimidine
193	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(1-oxidopyridin-1-ium-3-yl)methanamine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
194	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(1-oxidopyridin-1-ium-4-yl)methanamine	4,5,6-trifluoropyrimidine
197	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(1-methylsulfonyl-4-piperidyl)methanamine	4,5,6-trifluoropyrimidine
198	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(3-methyloxetan-3-yl)methanamine	4,5,6-trifluoropyrimidine
199	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(2-methyltetrahydrofuran-2-yl)methanamine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
200	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	2-(aminomethyl)cyclohexanol	4,5,6-trifluoropyrimidine
201	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(2-methyltetrahydrothiophen-2-yl) methanamine	4,5,6-trifluoropyrimidine
202	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(4,4-dioxo-1,4-oxathian-2-yl)methanamine	4,5,6-trifluoropyrimidine
203	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	2-thienylmethanamine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
208	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	tetrahydropyran-4-ylmethanamine	4,5,6-trifluoropyrimidine
209	2-methyl-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(6-methyl-3-pyridyl)methanamine	4,5,6-trifluoropyrimidine
210	(2R)-2-[2-fluoro-4-(trifluoromethyl) phenyl] pyrrolidine	(6-methyl-3-pyridyl)methanamine	4,5,6-trifluoropyrimidine
211	4-methyl-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(6-methyl-3-pyridyl)methanamine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
212	4-methoxy-2-[4-(trifluoromethyl) phenyl] pyrrolidine	(6-methyl-3-pyridyl)methanamine	4,5,6-trifluoropyrimidine
213	2-[4-(trifluoromethyl)phenyl] pyrrolidine	(5-methyloxazol-2-yl)methanamine	4,5,6-trifluoropyrimidine
214	2-[4-(trifluoromethyl)phenyl] pyrrolidine	5-(aminomethyl)-1,3,4-oxadiazol-2-ol	4,5,6-trifluoropyrimidine
215	2-[4-(trifluoromethyl)phenyl] pyrrolidine	1-(5-methyl-1,2,4-oxadiazol-3-yl)propan-1-amine	4,5,6-trifluoropyrimidine
216	2-[4-(trifluoromethyl)phenyl] pyrrolidine	5-(aminomethyl)isoxazol-3-ol	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
217	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	[3-(aminomethyl)phenyl]methanol	4,5,6-trifluoropyrimidine
218	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	cyclopentylmethanamine	4,5,6-trifluoropyrimidine
219	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(4-methylsulfonylphenyl)methanamine	4,5,6-trifluoropyrimidine
220	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	3-(aminomethyl)tetrahydro furan-3-ol	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
221	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	2-[4-(aminomethyl)tetrahydro pyran-4-yl] ethanol	4,5,6-trifluoropyrimidine
222	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(1,1-dioxothian-4-yl)methanamine	4,5,6-trifluoropyrimidine
223	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	4-(aminomethyl)-1,1-dioxo-thian-4-ol	4,5,6-trifluoropyrimidine
224	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	4-(aminomethyl)-N-cyclopropyl-benzenesulfonamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
225	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	[4-(aminomethyl)cyclohexyl]methanol	4,5,6-trifluoropyrimidine
226	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	4-(aminomethyl)benzamide	4,5,6-trifluoropyrimidine
227	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	[4-(aminomethyl)phenyl]methanol	4,5,6-trifluoropyrimidine
228	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	[3-(aminomethyl)oxetan-3-yl]methanol	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
229	2-methyl-2-[4-(trifluoromethyl)phenyl] pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
230	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
231	4,4-difluoro-2-[4-(trifluoromethyl) phenyl] pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
232	(2R)-2-[2-fluoro-4-(trifluoromethyl) phenyl] pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
233	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	1-[4-(aminomethyl)-1-piperidyl]ethanone	4,5,6-trifluoropyrimidine
234	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	4-(aminomethyl)-1,1-dioxo-thian-4-ol	4,5,6-trifluoropyrimidine
235	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	(3-methyloxetan-3-yl)methanamine	4,5,6-trifluoropyrimidine
236	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	4-(aminomethyl)-N-cyclopropyl-benzenesulfonamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
237	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	(1-methylsulfonyl-4-piperidyl)methanamine	4,5,6-trifluoropyrimidine
238	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	3-(aminomethyl)tetrahydrofuran-3-ol	4,5,6-trifluoropyrimidine
239	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	2-[4-(aminomethyl)tetrahydropyran-4-yl] ethanol	4,5,6-trifluoropyrimidine
240	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	[4-(methylsulfonylmethyl)tetrahydropyran-4-yl]methanamine	4,5,6-trifluoropyrimidine
241			

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
	4-methyl-2-[4-(trifluoromethyl)phenyl] pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
242	4-methyl-2-[4-(trifluoromethyl)phenyl] pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
243	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	2-[4-(aminomethyl)cyclohexyl]acetic acid	4,5,6-trifluoropyrimidine
244	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
245	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	2-[4-(aminomethyl)cyclohexyl]acetamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
246	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	[4-(1H-tetrazol-5-ylmethyl)phenyl] methanamine	4,5,6-trifluoropyrimidine
247	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	tetrahydropyran-4-ylmethanamine	4,5,6-trifluoropyrimidine
248	4-methyl-2-[4-(trifluoromethyl)phenyl] pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
249	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	1-(aminomethyl)cyclopentanecarboxamide	4,5,6-trifluoropyrimidine
250	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	1-(aminomethyl)-N,N-dimethyl-cyclopentanecarboxamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
251	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	N-[2-(aminomethyl)cyclopen tyl] methanesulfonamid e	4,5,6-trifluoropyrimidine
253	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	[4-(methylsulfonylmethyl) tetrahydropyran-4-yl]methanamine	4,5,6-trifluoropyrimidine
254	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	methyl 4-(aminomethyl)tetrahydropyran-4-carboxylate	4,5,6-trifluoropyrimidine
255	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	4-(aminomethyl)tetrahydropyran-4-carboxamide	4,5,6-trifluoropyrimidine
256	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	N-(2-aminoethyl)-4-(aminomethyl) tetrahydropyran-4-carboxamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
257	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	4-(aminomethyl)tetrahydropyran-4-carbonitrile	4,5,6-trifluoropyrimidine
258	(3S)-3-[2-fluoro-4-(trifluoromethoxy) phenyl]morpholine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
259	4,4-difluoro-2-[4-(trifluoromethyl) phenyl]pyrrolidine	tetrahydropyran-4-ylmethanamine	4,5,6-trifluoropyrimidine
260	4,4-difluoro-2-[4-(trifluoromethyl) phenyl]pyrrolidine	[4-(methylsulfonylmethyl) tetrahydropyran-4-yl]methanamine	4,5,6-trifluoropyrimidine
261	4,4-difluoro-2-[4-(trifluoromethyl) phenyl]pyrrolidine	[3-(aminomethyl)oxetan-3-yl]methanol	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
262	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	1-[4-(aminomethyl)-4-fluoro-1-piperidyl] ethanone	4,5,6-trifluoropyrimidine
263	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	[1-(trifluoromethylsulfonyl)-4-piperidyl] methanamine	4,5,6-trifluoropyrimidine
264	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	(4-fluorotetrahydropyran-4-yl)methanamine	4,5,6-trifluoropyrimidine
266	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	(4-fluoro-1-methylsulfonyl-4-piperidyl) methanamine	4,5,6-trifluoropyrimidine
267	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	N-[4-(aminomethyl)cyclohexyl] methanesulfonamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
268	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	4-(aminomethyl)tetrahydropyran-4-carboxylic acid	4,5,6-trifluoropyrimidine
273	3-phenylmorpholine	4-(aminomethyl)-N-cyclopropyl-benzenesulfonamide	4,5,6-trifluoropyrimidine
274	3-phenylmorpholine	(1-methylsulfonyl-4-piperidyl)methanamine	4,5,6-trifluoropyrimidine
276	3-phenylmorpholine	2-[4-(aminomethyl)phenyl]acetic acid	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
279	2-phenylpyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
280	5-[4-(trifluoromethyl)phenyl]pyrrolidin-3-one	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
282	3-phenylmorpholine	2-[5-(aminomethyl)-2-thienyl]acetic acid	4,5,6-trifluoropyrimidine
283	3-phenylmorpholine	2-[5-(aminomethyl)-2-thienyl]acetamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
285	(3S)-3-[4-(trifluoromethoxy)phenyl] morpholine	AND Enantiomer N-[4-(aminomethyl)cyclohex yl]-2,2,2-trifluoro-ethanesulfonamide	4,5,6-trifluoropyrimidine
286	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	4-(aminomethyl)-N-methyltetrahydropyran-4-carboxamide	4,5,6-trifluoropyrimidine
287	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	2-[4-(aminomethyl)cyclohexyl]acetonitrile	4,5,6-trifluoropyrimidine
288	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	[4-(1H-tetrazol-5-ylmethyl)cyclohexyl] methanamine	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
291	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	N-[4-(aminomethyl)phenyl]-1,1,1-trifluoro-methanesulfonamide	4,5,6-trifluoropyrimidine
292	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	2-[4-(aminomethyl)phenyl]-N-cyano-acetamide	4,5,6-trifluoropyrimidine
293	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	(6-methylsulfonyl-3-pyridyl)methanamine	4,5,6-trifluoropyrimidine
294	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	2,2-dimethyl-4-methylsulfonyl-butan-1-amine	4,5,6-trifluoropyrimidine
295			

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	2-(aminomethyl)-2-methyl-cyclohexanol	4,5,6-trifluoropyrimidine
296	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	[1-(aminomethyl)cyclopropyl]methanol	4,5,6-trifluoropyrimidine
297	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	N-(4-piperidyl)methanesulfonamide	4,5,6-trifluoropyrimidine
299	2-(1,3-benzodioxol-5-yl)pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
300	4-pyrrolidin-2-ylphenol	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
301	2-(4-ethoxyphenyl)pyrrolidine	2-[4-(aminomethyl)phenyl] acetamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
302	2-(p-tolyl)pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
303	2-(4-isopropylphenyl)pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
304	2-(3-methoxyphenyl)pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
305	2-(3-bromophenyl)pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
306	2-(3-chlorophenyl)pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
307	2-[4-(trifluoromethyl)phenyl]azetidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
308	2-[4-(trifluoromethyl)phenyl] piperidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
309	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	(4-methylsulfonylmorphol in-2-yl) methanamine	4,5,6-trifluoropyrimidine
310	2-pyrrolidin-2-yl-1,3-benzothiazole	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
311	2-(1-naphthyl)pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
312	2-(2-naphthyl)pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
313	2-(5-methyl-2-furyl)pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
314	5-methyl-3-pyrrolidin-2-yl-1,2,4-oxadiazole	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
315	2-methyl-5-pyrrolidin-2-yl-1,3,4-oxadiazole	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
316	2-(5-ethyl-2-furyl)pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
317	1,3-dimethyl-4-pyrrolidin-2-yl-pyrazole	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
318	2-(2,4-dimethoxyphenyl)pyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine
319	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	4-(aminomethyl)benzene sulfonic acid	4,5,6-trifluoropyrimidine
320	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	4-(aminomethyl)-N-(2-methoxyethyl) benzenes ulfonamide	4,5,6-trifluoropyrimidine
321	2-benzylpyrrolidine	2-[4-(aminomethyl)phenyl]acetamide	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Free amine or alcohol (2)	Fluorinated aromatic compound
324	2-pyrrolidin-2-yl-5-(trifluoromethyl) phenol	(1-methylsulfonyl-4-piperidyl)methanamine	4,5,6-trifluoropyrimidine
325	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	(2R)-2-amino-4,4-dimethyl-pentanoic acid	4,5,6-trifluoropyrimidine
327	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	(1-methylsulfonylpyrrolidin-3-yl) methanamine	4,5,6-trifluoropyrimidine

Synthesis of selected amines

[4-(1H-Tetrazol-5-ylmethyl)cyclohexyl]methanamine

[0224] To 4-[(tert-butoxycarbonylamino)methyl]cyclohexanecarboxylic acid (0.84 g, 3.2 mmol) was added slowly solution of a BH_3-THF solution in THF (16 mL, 1M). The reaction was allowed to stir for 2.5 hours, concentrated in vacuo, and the residue was redissolved and stirred with an aq. sodium hydroxide solution (1M, 30 mL) for 20 min. Ethyl acetate was added, and the mixture was allowed to stir for another 10 min. The phases were separated and the EtOAc phase was concentrated in vacuo and the crude product thereof was purified by flash CC (eluent: EtOAc/heptane, on silica gel) yielding tert-butyl N-[[4 (hydroxymethyl)cyclohexyl]methyl]carbamate (0.76 g, quant yield).

[0225] Tert-butyl N-[[4-(hydroxymethyl)cyclohexyl]methyl]carbamate (0.60 g, 2.5 mmol) was dissolved in DCM (20 mL) and Et3N (1mL) and then methanesulfonyl chloride was the added to the solution. The reaction was stirred over night at room temperature whereafter concentration under reduced pressure yielded a solid that was mixed with water and EtOAc. The EtOAc phase was separated and washed with brine and dried over sodium sulfate. Filtration and concentration in vacuo of the EtOAC phase gave a solid that was dissolved dry DMSO (10 mL). Potassium cyanide (0.36 g, 5.5 mmol) was added and the reaction was heated to 90 °C for 4 hours. The crude reaction was poured into water and the resulting mixture was extracted with EtOAc. The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by flash CC (eluent: EtOAc/heptane, on silica gel) yielding tert-butyl N-[[4-(cyanomethyl)cyclohexyl]methyl]carbamate (0.57 g, 88% yield).

[0226] To a solution of tert-butyl N-[[4-(cyanomethyl)cyclohexyl]methyl]carbamate (160 mg, 0.60 mmol) in nitrobenzene

was added triethylammonium chloride (160 mg, 1.2 mmol) and sodium azide (91 mg, 1.4 mmol). The resulting mixture was heated to 105 °C for 11 hours using microwave irradiation. Some more sodium azide (40 mg, 0.7 mmol) was added and the reaction was heated for another 45 min at 105 °C with microwave irradiation. The reaction was extracted with water and the water phase was washed with ether, made acidic with 1M HCl and extracted with EtOAc. The EtOAc phase was dried using sodium sulfate, filtered and concentrated in vacuo and finally purified by flash CC (eluent: EtOAc/heptane, on silica gel) yielding tert-butyl N-[[4-(1H-tetrazol-5-ylmethyl)cyclohexyl]methyl]carbamate (33 mg, 18% yield).

[0227] Tert-butyl N-[[4-(4-(1 H-tetrazol-5 -ylmethyl)cyclohexyl]methyl] carbamate (33 mg, 0.11 mmol) was dissolved in DCM (2 mL), TFA (1 mL) was added, and the reaction was stirred for 2 hours. Concentration of the reaction mixture yielded [4-(1H-tetrazol-5-ylmethyl)cyclohexyl]methylammonium 2,2,2-trifluoroacetate that was used without further purification. Using an extra equivalent of the base in the General Method 3 gave [4-(1H-tetrazol-5-ylmethyl)cyclohexyl]methanamine in situ during the reaction.

1-Oxidopyridin-1-ium-3-yl)methanamine

[0228] Tert-butyl N-(3-pyridylmethyl)carbamate (1.7 g, 8.4 mmol) was dissolved in DCM, meta-chloroperbenzoic acid (6.1 g, 25 mmol, 70%) was added, and the reaction was stirred at room temperature for 3 hours. After concentration in vacuo, the crude product was purified by flash CC (eluent: EtOAc/heptane followed by EtOAc/MeOH/ammounium hydroxide, on silica gel) to yield tert-butyl N-[(1-oxidopyridin-1-ium-3-yl)methyl]carbamate (1.9 g, 97% yield).

[0229] Tert-butyl N-[(1-oxidopyridin-1-ium-3-yl)methyl]carbamate (1.9 g, 8.2 mmol) was dissolved in DCM (2 mL) followed by the addition of TFA . The reaction was heated to reflux overnight. After concentration in vacuo the residue was dissolved in a mixture of MEOH and DCM and the solution was then stirred together with Amberlite IRA-67 free base (7 g, washed and dried) for 30 min. The mixture was filtered with DCM and MeOH. Concentration of the filtrate gave 1-oxidopyridin-1-ium-3-yl)methanamine_(0.91 g, 91 % yield).

1-Oxidopyridin-1-ium-4-yl)methanamine

[0230] Tert-butyl N-(4-pyridylmethyl)carbamate (100 mg, 0.48 mmol) was dissolved in DCM, meta-chloroperbenzoic acid (350 mg, 2.2 mmol, 70%) was added, and the reaction was stirred at room temperature for 4 hours. After concentration in vacuo the crude product was purified by flash CC (eluent: EtOAc/heptane followed by ethyl acetate/MeOH/ammounium hydroxide, on silica gel) to yield tert-butyl N-[(1-oxidopyridin-1-ium-4-yl)methyl]carbamate.

[0231] Tert-butyl N-[(1-oxidopyridin-1-ium-4-yl)methyl]carbamate (80 mg, 0.64 mmol) was dissolved in DCM followed by the addition of TFA (0.19 mL). The reaction was heated to 60 °C by mircrowave irradiation for 30 min. After cooling, the solution was then stirred together with Amberlite IRA-67 free base (0.5 g, washed and dried) for 30 min. The mixture was filtered with DCM and MeOH. Concentration of the filtrate yielded 1-oxidopyridin-1-ium-4-yl)methanamine (48 mg, 61% yield).

1-[4-(Aminomethyl)-4-fluoro-1-piperidyl]ethanone

[0232] Tert-butyl N-[(4-fluoro-4-piperidyl)methyl]carbamate (232 mg, 1 mmol) was dissolved in 4 mL DCM and trimethylamine (TEA, 160μL, 1.1 mmol) was added. The mixture was cooled to 0°C and acetyl chloride (80 μL, 1.1 mmol) was added. The mixture was stirred for 1 hour while returning to room temperature. The mixture was poured into H_2O, extracted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated in vacuo and purified by flash CC (eluent: Heptane/EtOAc, on silica gel) yielding tert-butyl N-[(1-acetyl-4-fluoro-4-piperidyl)methyl]carbamate. The pruduct was dissolved in 2 mL DCM and a solution of 4M HCl in dioxane (2 mL) was added. The mixture was stirred overnight at room temperature. The mixture was concentrated, and the crude 1-[4-(aminomethyl)-4-fluoro-1-piperidyl]ethanone hydrocloride was used in the next step without further purification (180 mg, 86%).

(4-Fluoro-1-methylsulfonyl-4-piperidyl)methanamine

[0233] Tert-butyl N-[(4-fluoro-4-piperidyl)methyl]carbamate (232 mg, 1 mmol) was dissolved in 4 mL DCM and TEA (160μL, 1.1 mmol) was added. The mixture was cooled to 0°C and methanesulfonyl chloride (90 μL, 1.1 mmol) was added. The mixture was stirred for 1 hour while returning to room temperature. The mixture was poured into H_2O, extracted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated in vacuo and purified by flash CC (eluent: Heptane/EtOAc) yielding tert-butyl N-[(4-fluoro-1-methylsulfonyl-4-piperidyl)methyl]carbamate. The product was dissolved in 2 mL DCM and a solution of 4M HCl in dioxane (2 mL) was added. The mixture was stirred overnight at room temperature. The mixture was concentrated, and the crude (4-fluoro-1-methylsulfonyl-4-piperidyl)methanamine hydrochloride was used in the next step without further purification (162 mg, 61%).

N-[4-(aminomethyl)cyclohexyl]methanesulfonamide

[0234] To a solution of tert-butyl (((trans)-4-aminocyclohexyl)methyl)carbamate (2 g, 8.77 mmol) in CH_2Cl_2 (20 mL) at -78°C was added DIPEA (2.26 g, 17.54 mmol), methane sulfonyl chloride (1 g, 8.77 mmol), and the mixture was stirred at room temperature for 4 hours. After completion, the reaction mixture was poured into ice water and extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with water (2 x 20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. The crude compound was purified by flash CC (eluent: DCM/MeOH, on silica gel) to afford tert-butyl (((trans)-4-(methylsulfonamido)cyclohexyl)methyl)carbamate (230 mg) as yellow liquid.

[0235] To a solution of tert-butyl (((trans)-4-(methylsulfonamido) cyclohexyl)methyl) carbamate (0.23 g, 0.751 mmol) in dioxane (1 mL) was added 4 N HCl in dioxane (2.3 mL), and the mixture was stirred at room temperature for 3 hours. After completion, the reaction mixture was evaporated to afford N-((trans)-4-(aminomethyl)cyclohexyl)methanesulfonamide (140 mg, 91 %) as an off white solid.

N-[4-(aminomethyl)phenyl]-1,1,1-trifluoro-methanesulfonamide

[0236] To a solution of tert-butyl 4-aminobenzylcarbamate (2 g, 9.0 mmol) in CH_2Cl_2 (20 mL) at -78°C was added Et_3N (1.8 g, 18.01 mmol), trifluoromethanesulfonic anhydride (2.54 g, 9.0 mmol), and the mixture was stirred at room temperature for 16 hours. After completion, the reaction mixture was diluted with CH_2Cl_2 (75 mL) and washed with saturated aq. $NaHCO_3$ (40 mL), water (40 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. The crude compound was purified by flash CC (Eluent: EtOAc/Pet ether, on silica gel) to afford tert-butyl 4-(trifluoromethylsulfonamido) benzylcarbamate (1.3 g, 41 %) as pale yellow solid. N-[4-(aminomethyl)phenyl]-1,1,1-trifluoro-methanesulfonamide was isolated after BOC deprotection, as described for tert-butyl (((trans)-4-(methylsulfonamido) cyclohexyl)methyl) carbamate.

[0237] 2-[4-(aminomethyl)phenyl]-N-cyano-acetamide 2-[4-[(tert-butoxycarbonylamino)methyl]phenyl]acetic acid (265 mg, 1.0 mmol), [dimethylamino(triazolo[4,5-b]pyridin-3-yloxy)methylene]-dimethyl-ammonium hexafluorophosphate (HATU, 380 mg, 1.0 mmol) and cyanamide (42 mg, 1.0 mmol) were dissolved in 5 mL dry DMF, and DIPEA (0.35 mL, 2.0 mmol) was added. The mixture was stirred at room temperature for 4 hours, poured into H_2O, extracted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated in vacuo and purified by flash CC (eluent: DCM/MeOH, on silica gel) yielding tert-butyl tert-butyl N-[[4-[2-(cyanoamino)-2-oxo-ethyl]phenyl]methyl]carbamate. The pruduct was dissolved in 2 mL DCM and a solution of 4M HCl in dioxane (2 mL) was added. The mixture was stirred overnight at room temperature, concentrated, and the crude 2-[4-(aminomethyl)phenyl]-N-cyano-acetamide hydrochloride was used in the next step without further purification (120 mg, 53%).

General Method 4

[0238]

4b **4a**

4c

[0239] The initial two steps of general method 4 may be performed in accordance with general method 3. The methyl ester **4a** was subsequently hydrolyzed to yield **4b,** e.g. by treatment with 1M lithium hydroxide in an appropriate solvent combination, e.g. water/tetrahydrofuran/methanol (e.g. in a ratio of 1:1:1). Hydrolysis was typically achieved after stirring at room temperature overnight. The reaction may for example be monitored by thin layer chromatography The reaction may for example be monitored by thin layer chromatography. The desired product was obtained upon work-up, e.g. by extraction with EtOAc, washing with water at a suitable pH and brine, drying over an appropriate drying agent, e.g. Na_2SO_4, and purification by flash column chromatrography (CC) using an appropriate eluent combination on a suitable column material, e.g. heptane/EtOAc or DCM/MeOH on silica gel, or recrystallization from a suitable solvent or solvent mixture, e.g. toluene/heptane. Amide analogues **4c** were prepared by treatment of **4b** with ammonium chloride, HOAt, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) and DIPEA in an appropriate solvent, e.g. DMF, followed by stirring at room temperature overnight. The reaction may for example be monitored by thin layer chromatography. The desired compound **4c** was obtained upon work-up, for example by extraction with EtOAc, washing with water at a suitable pH and brine, drying over an appropriate drying agent, e.g. Na_2SO_4, and purification by flash column chromatrography (CC) using an appropriate eluent combination on a suitable column material, e.g. heptane/EtOAc or DCM/MeOH on silica gel, or recrystallization from a suitable solvent or solvent mixture, e.g. toluene/heptane.

Use of General Method 4 to Prepare Example No. ***86:***

[0240]

86

[0241] Methyl 2-[5-(hydroxymethyl)pyrimidin-2-yl]acetate (0.36 g, 2.0 mmol) and 4,5,6-trifluoro-pyrimidine (0.27 g, 2.0 mmol) were dissolved in dry DMSO (4 mL) and DIPEA (0.7 mL, 4.0 mmol) was added. The reaction was stirred at room temperature overnight, poured into 3M aq. calcium chloride, extracted with EtOAc, washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by flash CC (eluent: DCM/MeOH, on silica gel) yielding methyl 2-[5-[(5,6-difluoropyrimidin-4-yl)oxymethyl]pyrimidin-2-yl]acetate (0.39 g, 66 % yield).

[0242] Methyl 2-[5-[(5 ,6-difluoropyrimidin-4-yl)oxymethyl]pyrimidin-2-yl] acetate (0.30 g, 1.0 mmol) and 2-(4-trifluor-omethyl-phenyl)-pyrrolidine (0.22 g, 1.0 mmol) were dissolved in dry DMSO (2 mL) and cesium carbonate (0.65 g, 2.0 mmol) was added. The reaction was heated in a microwave reactor for 1 hour at 100 °C, poured into 3M aq. calcium chloride, extracted with EtOAc, washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by flash CC (eluent: DCM/MeOH, on silica gel) yielding methyl 2-[5-[[5-fluoro-6-[2-[4-(trifluor-omethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]oxymethyl]pyrimidin-2-yl]acetate (0.24 g, 49% yield).

[0243] Methyl 2-[5-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]oxymethyl]pyrimidin-2-yl]acetate (0.20 g, 0.41 mmol) was dissolved in 2M aq. lithium hydroxide/tetrahydrofuran/methanol (1:1:1, 10 mL) and stirred at room temperature overnight. The solvents were removed in vacuo and the residue purified by preparative HPLC yielding 2-[5-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]oxymethyl]pyrimidin-2-yl]acetic acid (0.15 g, 76% yield).

[0244] 2-[5-[[5-Fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]oxymethyl]pyrimidin-2-yl]acetic acid (0.12 g, 0.25 mmol), ammonium chloride (14 mg, 0.25 mmol), HOAt (31 mg, 0.25 mmol), EDC (39 mg, 0.25 mmol) and DIPEA (45 μL, 0.25 mmol) were dissolved in dry DMF (2 mL), and the reaction was stirred at room temperature overnight. The mixture was concentrated in vacuo, redissolved in EtOAc, washed with sat. aq. potassium carbonate, aq. potassium bisulfate (10%) and brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash CC (eluent: eluent: DCM/MeOH, on silica gel) yielding 2-[5-[[5-fluoro-6-[2-[4-(trifluoromethyl)phenyl]pyrrolidin-1-yl]pyrimidin-4-yl]oxymethyl]pyrimidin-2-yl]acetamide **86** (68 mg, 56% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.02 (s, 1H), 7.94 - 7.83 (m, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 5.32 (d, J = 7.7 Hz, 1H), 4.02-3.96 (m, 1H), 3.81 - 3.52 (m, 4H), 2.38 - 2.19 (m, 1H), 1.97 - 1.71 (m, 3H). *m/z* 477 (M+H).

[0245] General method 4 was used to prepare the following example numbers using the shown starting materials:

Ex. No.	Free amine or alcohol (1)	Methyl ester	Fluorinated aromatic compound
32	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 methyl 2-[4-(aminomethyl)phenyl] acetate	 4,5,6-trifluoropyrimidine
40	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 methyl 2-[4-(aminomethyl)phenyl] acetate	 4,5,6-trifluoropyrimidine
79	 2-[4-(trifluoromethyl)phenyl] pyrrolidine	 methyl 2-[4-(hydroxymethyl)phenyl] acetate	 4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Methyl ester	Fluorinated aromatic compound
81	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	methyl 2-[4-(aminomethyl)phenyl] acetate	4,5,6-trifluoropyrimidine
83	[4-(trifluoromethyl)phenyl] methanamine	methyl 2-[4-(hydroxymethyl)phenyl] acetate	4,5,6-trifluoropyrimidine
84	5-pyrrolidin-2-yl-2-(trifluoromethyl) pyridine	methyl 2-[4-(hydroxymethyl)phenyl] acetate	4,5,6-trifluoropyrimidine
86	2-[4-(trifluoromethyl)phenyl] pyrrolidine	methyl 2-[5-(hydroxymethyl)pyrimidin-2-yl]acetate	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Methyl ester	Fluorinated aromatic compound
87	2-[4-(trifluoromethyl)phenyl] pyrrolidine	methyl 2-[5-(aminomethyl)pyrimidin-2-yl]acetate	4,5,6-trifluoropyrimidine
91	3-[4-(trifluoromethoxy)phenyl] morpholine	methyl 2-[4-(aminomethyl)phenyl] acetate	4,5,6-trifluoropyrimidine
117	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	methyl 2-[4-(aminomethyl)phenyl] acetate	4,5,6-trifluoropyrimidine
118	(2S)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	methyl 2-[4-(aminomethyl)phenyl] acetate	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Methyl ester	Fluorinated aromatic compound
119	3-[4-(trifluoromethyl)phenyl] morpholine	methyl 2-[4-(aminomethyl)phenyl] acetate	4,5,6-trifluoropyrimidine
192	2-[4-(trifluoromethoxy)phenyl] pyrrolidine	methyl 2-[4-(aminomethyl)phenyl] acetate	4,5,6-trifluoropyrimidine
204	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	methyl 2-[4-(aminomethyl)phenyl] acetate	4,5,6-trifluoropyrimidine
205	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	methyl 2-[4-(aminomethyl)cyclohexyl] acetate	4,5,6-trifluoropyrimidine
206	(3S)-3-[4-(trifluoromethyl)phenyl] morpholine	methyl 2-[4-(aminomethyl)cyclohexyl] acetate	4,5,6-trifluoropyrimidine

(continued)

Ex. No.	Free amine or alcohol (1)	Methyl ester	Fluorinated aromatic compound
207	(2R)-2-[4-(trifluoromethyl)phenyl] pyrrolidine	methyl 2-[5-(aminomethyl)-2-thienyl] acetate	4,5,6-trifluoropyrimidine

Table of ^{1}H NMR and MS Data for example compounds.

Ex. No.	^{1}H NMR or MS Data
4	m/z 589 (M+H)
5	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.9 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.46 (s, 1H), 5.41 (d, *J* = 7.9 Hz, 1H), 5.24 (s, 1H), 4.69 (s, 1H), 4.58 (s, 1H), 4.08 - 3.99 (m, 1H), 3.83 - 3.72 (m, 1H), 2.36 (dt, *J* = 15.4, 5.7 Hz, 1H), 2.05 (dd, *J* = 14.6, 3.6 Hz, 1H), 2.01 - 1.86 (m, 3H), 1.50 (dd, *J* = 14.7, 8.7 Hz, 1H), 0.96 (s, 9H).
6	^{1}H NMR (300 MHz, CD_3OD) δ 8.23 (s, 1H), 8.06 - 7.92 (m, 1H), 7.75 - 7.55 (m, 2H), 7.48 - 7.29 (m, 2H), 5.44 - 4.98 (m, 2H), 4.50 - 4.21 (m, 1H), 3.95 - 3.48 (m, 3H), 2.62 - 2.42 (m, 1H), 2.11 - 1.90 (m, 3H), 0.94 (s, 9H).
9	m/z 517 (M+H)
11	m/z 454 (M+H)
13	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.2, 3.3 Hz, 2H), 7.31 (dd, *J* = 8.0, 3.3 Hz, 2H), 5.46 - 5.30 (m, 1H), 4.69 - 4.51 (m, 1H), 4.17 - 4.00 (m, 1H), 3.91 - 3.77 (m, 1H), 2.54 - 2.25 (m, 1H), 2.12 - 1.87 (m, 4H), 1.64 - 1.46 (m, 1H), 1.04 - 0.77 (m, 9H).
14	m/z 450 (M+H)
15	m/z 464 (M+H)
16	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.8 Hz, 1H), 7.65 - 7.50 (m, 2H), 7.35 - 7.28 (m, 2H), 5.62 - 5.47 (m, 1H), 5.42 (t, *J* = 8.8 Hz, 1H), 4.22 - 3.94 (m, 2H), 3.89 - 3.66 (m, 1H), 2.49 - 2.28 (m, 1H), 2.05 - 1.82 (m, 3H), 1.81 - 1.55 (m, 4H), 1.26 (dd, *J* = 6.3, 0.8 Hz, 3H), 1.23 - 1.15 (m, 4H), 1.11 (s, 2H).
17	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 3.2, 1.8 Hz, 1H), 7.63 - 7.52 (m, 2H), 7.35 - 7.25 (m, 2H), 7.23 - 7.11 (m, 2H), 6.90 - 6.76 (m, 2H), 5.41 (d, *J* = 8.0 Hz, 1H), 5.12 - 4.96 (m, 1H), 4.83 - 4.66 (m, 1H), 4.12 - 3.98 (m, 1H), 3.79 (s, 3H), 3.20 - 2.98 (m, *J* = 6.7 Hz, 2H), 2.46 - 2.27 (m, 1H), 2.04 - 1.83 (m, 3H).
18	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.71 - 7.55 (m, 3H), 7.42 (t, *J* = 9.0 Hz, 2H), 7.15 (s, 1H), 6.89 (d, *J* = 6.9 Hz, 1H), 6.63 - 6.49 (m, 1H), 5.29 - 5.17 (m, 1H), 4.53 - 4.39 (m, 1H), 4.17 - 3.90 (m, 1H), 3.42 (t, *J* = 10.0 Hz, 2H), 2.66 - 2.53 (m, 1H), 2.41 - 2.18 (m, 1H), 1.75 - 1.54 (m, 2H), 1.42 - 1.28 (m, 1H), 1.10 - 0.99 (m, 3H), 0.85 (dd, *J* = 8.4, 3.7 Hz, 9H).
19	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.75 (dd, *J* = 6.4, 1.9 Hz, 1H), 7.30 (dd, *J* = 8.1, 6.1 Hz, 2H), 7.18 -7.01 (m, 3H), 6.87 (d, *J* = 14.0 Hz, 1H), 6.55 - 6.44 (m, 1H), 5.30 (d, *J* = 7.2 Hz, 1H), 4.46 (qd, *J* = 9.1, 3.4 Hz, 1H), 3.99 - 3.89 (m, 1H), 3.73 - 3.60 (m, 1H), 2.34 - 2.19 (m, 1H), 1.91 - 1.50 (m, 5H), 1.31 - 1.17 (m, 9H).

(continued)

Ex. No.	^{1}H NMR or MS Data
20	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 - 7.83 (m, 1H), 7.71 (dd, *J* = 8.4, 2.5 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.22 (s, 1H), 6.93 (d, *J* = 6.6 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 5.46 (d, *J* = 3.3 Hz, 1H), 4.58 - 4.45 (m, 1H), 4.35 - 4.26 (m, 1H), 4.07 - 3.81 (m, 3H), 3.73 - 3.60 (m, 1H), 3.50 - 3.38 (m, 1H), 1.81 - 1.55 (m, 2H), 0.88 (d, *J* = 3.6 Hz, 9H).
21	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 2H), 5.41 (d, *J* = 8.2 Hz, 1H), 4.44 (s, 1H), 4.12 - 3.96 (m, 1H), 3.88 - 3.69 (m, 1H), 3.53 - 3.31 (m, 2H), 2.48 - 2.28 (m, 1H), 2.06 - 1.81 (m, 3H), 1.56 - 1.40 (m, 2H), 0.95 (s, 9H).
23	m/z 437 (M+H)
24	m/z 444 (M+H)
29	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74 - 7.59 (m, 3H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 8.0 Hz, 2H), 6.78 (dd, *J* = 8.4, 6.2 Hz, 2H), 6.46 - 6.31 (m, 1H), 5.34 (d, *J* = 7.7 Hz, 1H), 4.72 (t, *J* = 5.3 Hz, 1H), 4.21 - 4.07 (m, 1H), 4.02 - 3.86 (m, 1H), 3.68 (s, 3H), 2.88 - 2.58 (m, 2H), 2.41 - 2.21 (m, 1H), 1.98 - 1.68 (m, 3H), 1.05 (t, *J* = 7.0 Hz, 1H).
30	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.77 - 7.58 (m, 3H), 7.46 - 7.32 (m, 2H), 6.29 (d, *J* = 8.6 Hz, 1H), 5.41 - 5.29 (m, 1H), 4.70 - 4.53 (m, 1H), 4.24 - 4.08 (m, 1H), 4.02 - 3.88 (m, 1H), 3.76 - 3.60 (m, 1H), 2.44 - 2.23 (m, 1H), 2.01 - 1.70 (m, 3H), 1.55 - 1.33 (m, 2H), 0.90 - 0.78 (m, 9H).
31	m/z 482 (M+H)
32	^{1}H NMR (300 MHz, CD_3OD) δ 7.72 (s, 1H), 7.60 (d, *J*= 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.32 - 7.17 (m, 4H), 5.49 - 5.37 (m, 1H), 4.61 - 4.45 (m, 2H), 4.13 - 3.96 (m, 1H), 3.90 - 3.72 (m, 1H), 3.57 (s, 2H), 2.54 - 2.35 (m, 1H), 2.08 - 1.85 (m, 3H).
33	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 - 7.75 (m, 1H), 7.54 (d, *J*= 8.3 Hz, 2H), 7.32 (dd, *J* = 8.4, 2.8 Hz, 2H), 5.27 (t, *J* = 8.4 Hz, 1H), 4.93 - 4.79 (m, 1H), 4.66 - 4.48 (m, 1H), 4.21 - 4.04 (m, 1H), 3.53 - 3.38 (m, 1H), 2.68 - 2.51 (m, 1H), 2.48 - 2.27 (m, 1H), 1.90 - 1.57 (m, 3H), 1.12 (d, *J* = 6.4 Hz, 3H), 1.01 - 0.84 (m, 6H).
34	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 - 7.77 (m, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 5.27 (t, *J* = 8.7 Hz, 1H), 4.91 - 4.73 (m, 1H), 4.64 - 4.47 (m, 1H), 4.24 - 4.02 (m, 1H), 3.46 (t, *J* = 10.4 Hz, 1H), 2.71 - 2.50 (m, 1H), 2.46 - 2.29 (m, 1H), 1.89 - 1.58 (m, 3H), 1.17 - 1.04 (m, 3H), 1.01 - 0.90 (m, 6H).
35	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 5.7, 1.9 Hz, 1H), 7.70 - 7.64 (m, 1H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.21 (dd, *J* = 8.1, 5.4 Hz, 1H), 5.59 - 5.44 (m, 1H), 4.76 - 4.68 (m, 1H), 4.64 - 4.50 (m, 1H), 3.89 - 3.74 (m, 1H), 2.52 - 2.36 (m, 1H), 2.13 - 1.80 (m, 4H), 1.58 - 1.43 (m, 1H), 1.02 - 0.89 (m, 9H).
36	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 4.1 Hz, 1H), 7.67 (s, 1H), 7.45 (t, *J* = 6.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 5.72 - 5.60 (m, 1H), 4.83 - 4.70 (m, 1H), 4.61 - 4.46 (m, 1H), 4.16 - 4.02 (m, 1H), 3.92 - 3.74 (m, 1H), 2.53 - 2.36 (m, 1H), 2.12 - 1.81 (m, 4H), 1.62 - 1.47 (m, 1H), 1.03 - 0.93 (m, 9H).
37	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70 - 7.55 (m, 3H), 7.52 - 7.45 (m, 1H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.35 - 7.20 (m, 2H), 7.08 - 6.99 (m, 2H), 5.29 - 5.10 (m, 1H), 3.48 - 3.37 (m, 1H), 2.98 (t, *J* = 11.9 Hz, 2H), 2.34 - 2.20 (m, 1H), 1.41 - 1.21 (m, 1H), 1.10 - 0.94 (m, 3H).
38	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 - 7.85 (m, 1H), 7.62 - 7.50 (m, 2H), 7.35 - 7.29 (m, 1H), 7.26 - 7.17 (m, 1H), 5.33 - 5.23 (m, 1H), 4.15 (t, *J* = 9.9 Hz, 1H), 4.03 - 3.88 (m, 1H), 3.83 - 3.70 (m, 1H), 1.77 - 1.62 (m, 3H), 1.19 (d, *J* = 6.6 Hz, 2H), 1.01 - 0.87 (m, 12H).
39	m/z 453 (M+H)
40	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.23 - 7.08 (m, 4H), 6.92 - 6.75 (m, 1H), 5.37 (d, *J* = 7.9 Hz, 1H), 4.56 - 4.37 (m, 2H), 4.05 - 3.86 (m, 1H), 3.78 - 3.61 (m, 1H), 3.31 - 3.27 (m, 2H), 2.46 - 2.22 (m, 2H), 1.97 - 1.70 (m, 3H).

(continued)

Ex. No.	^{1}H NMR or MS Data
41	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (S, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J*= 8.6 Hz, 2H), 5.40 (d, *J* = 7.9 Hz, 1H), 4.25 (s, 2H), 4.07 - 3.97 (m, 1H), 3.91 (dd, *J* = 11.1, 4.3 Hz, 2H), 3.83 - 3.71 (m, 1H), 3.39 - 3.26 (m, 2H), 2.42 - 2.30 (m, 1H), 2.03 - 1.85 (m, 3H), 1.69 (d, *J* = 13.0 Hz, 2H), 1.49 - 1.20 (m, 4H), 1.19 - 1.13 (m, 3H).
42	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 - 8.77 (m, 1H), 8.11 (d, J = 8.1 Hz, 1H), 8.05 (d, *J* = 6.2 Hz, 1H), 7.62 - 7.55 (m, 1H), 5.59 (s, 1H), 4.67 - 4.58 (m, 1H), 4.07 (t, *J* = 9.7 Hz, 1H), 3.92 - 3.81 (m, 1H), 2.56 (s, 1H), 2.21 - 1.95 (m, 4H), 1.89 - 1.73 (m, 2H), 0.97 - 0.87 (m, 9H).
43	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 6.4, 2.0 Hz, 1H), 7.03 (dd, *J* = 8.6, 4.2 Hz, 2H), 6.93 - 6.86 (m, 2H), 6.52 (s, 1H), 5.35 (s, 1H), 5.22 (s, 1H), 4.61 (s, 1H), 4.58 - 4.48 (m, 1H), 3.98 (s, 1H), 3.73 (t, *J* = 7.3 Hz, 1H), 2.38 - 2.22 (m, 1H), 2.06 (dt, *J* = 14.5, 3.0 Hz, 1H), 1.98 - 1.88 (m, 3H), 1.53 - 1.42 (m, 1H), 1.32 (dd, *J* = 5.6, 1.2 Hz, 9H), 0.93 (dd, *J* = 17.0, 3.0 Hz, 9H).
44	m/z 461 (M+H)
45	m/z 557 (M+H)
46	m/z 510 (M+H)
48	m/z 485 (M+H)
51	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 5.3, 2.0 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.26 (s, 2H), 6.23 (s, 1H), 5.45 - 5.31 (m, 2H), 5.18 (dd, *J* = 7.6, 2.3 Hz, 1H), 4.54 - 4.45 (m, 1H), 4.14 - 3.99 (m, 2H), 3.84 - 3.73 (m, 1H), 2.45 - 2.31 (m, 1H), 2.04 - 1.85 (m, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.16 (d, *J* = 22.8 Hz, 9H).
52	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, *J* = 8.6 Hz, 1H), 7.66 (dd, *J* = 8.5, 2.7 Hz, 2H), 7.46 - 7.39 (m, 2H), 7.34 - 7.29 (m, 1H), 6.95 (d, *J* = 11.9 Hz, 1H), 6.77 (d, *J* = 20.9 Hz, 1H), 5.38 (s, 1H), 4.52 - 4.37 (m, 1H), 3.97 (d, *J* = 8.1 Hz, 1H), 3.83 - 3.67 (m, 3H), 3.29 - 3.09 (m, 2H), 2.40 - 2.30 (m, 1H), 1.98 - 1.74 (m, 3H), 1.73 - 1.46 (m, 5H), 1.25 - 1.05 (m, 2H).
53	m/z 477 (M+H)
54	m/z 477 (M+H)
55	m/z 517 (M+H)
56	m/z 502 (M+H)
57	m/z 530 (M+H)
58	m/z 531 (M+H)
59	m/z 517 (M+H)
60	m/z 515 (M+H)
61	m/z 543 (M+H)
62	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.9 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.46 (s, 1H), 5.41 (d, *J* = 7.9 Hz, 1H), 5.24 (s, 1H), 4.69 (s, 1H), 4.58 (s, 1H), 4.08 - 3.99 (m, 1H), 3.83 - 3.72 (m, 1H), 2.36 (dt, *J* = 15.4, 5.7 Hz, 1H), 2.05 (dd, *J* = 14.6, 3.6 Hz, 1H), 2.01 - 1.86 (m, 3H), 1.50 (dd, *J* = 14.7, 8.7 Hz, 1H), 0.96 (s, 9H).
63	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J*= 5.1, 2.0 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J*= 8.3 Hz, 2H), 6.92 (d, *J*= 22.7 Hz, 1H), 6.71 (d, *J* = 3.7 Hz, 1H), 6.41 (s, 0H), 5.61 (d, *J* = 8.8 Hz, 1H), 5.47 - 5.29 (m, 2H), 4.81 - 4.56 (m, 1H), 4.09 - 3.98 (m, 1H), 3.84 - 3.71 (m, 1H), 3.44 - 3.28 (m, 2H), 2.59 - 2.47 (m, 1H), 2.46 - 2.29 (m, 2H), 2.25 - 2.10 (m, 1H), 2.09 - 1.81 (m, 6H).
64	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.73 (dd, *J*= 7.1, 2.0 Hz, 1H), 7.64 (t, *J* = 7.3 Hz, 2H), 7.41 (dd, *J* = 7.8, 3.7 Hz, 2H), 6.51 - 6.22 (m, 1H), 5.35 (d, *J*= 7.5 Hz, 1H), 4.21 (s, 1H), 3.96 (s, 1H), 3.69 (d, *J* = 10.0 Hz, 2H), 3.35 (s, 1H), 3.27 - 3.05 (m, 1H), 2.69 (d, *J* = 11.7 Hz, 1H), 2.64 - 2.52 (m, 2H), 2.42 - 2.14 (m, 3H), 1.99 - 1.71 (m, 3H), 1.51 (d, *J* = 11.3 Hz, 1H), 1.47 - 1.32 (m, 1H), 0.79 (dd, *J* = 9.0, 4.2 Hz, 9H).

(continued)

Ex. No.	^{1}H NMR or MS Data
65	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 6.8, 1.7 Hz, 1H), 7.15 - 6.99 (m, 3H), 6.44 (s, 1H), 5.60 (d, *J* = 8.1 Hz, 1H), 5.20 (s, 1H), 4.66 - 4.51 (m, 2H), 4.02 (s, 1H), 3.93 (d, *J* = 2.4 Hz, 3H), 3.75 (t, *J* = 8.8 Hz, 1H), 2.30 (t, *J* = 7.3 Hz, 1H), 2.09 - 2.02 (m, 1H), 1.90 (dt, *J* = 27.6, 9.5 Hz, 3H), 1.47 (M, 1H), 0.93 (d, *J* = 17.1 Hz, 9H).
66	m/z 431 (M+H)
67	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.76 (d, *J*= 5.6 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 7.7 Hz, 2H), 7.17 (d, *J* = 3.4 Hz, 1H), 6.96 (s, 1H), 6.82 (dd, J = 8.0, 1.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.44 (s, 1H), 5.90 (d, *J* = 5.6 Hz, 1H), 5.31 (d, *J* = 8.3 Hz, 1H), 5.26 - 5.14 (m, 2H), 4.19 - 4.02 (m, 1H), 3.92 - 3.76 (m, 1H), 3.70 - 3.63 (m, 6H), 2.47 - 2.37 (m, 1H), 2.09 - 1.79 (m, 3H).
68	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J*= 1.7 Hz, 1H), 7.58 - 7.47 (m, 2H), 7.22 - 7.13 (m, 2H), 6.36 (s, 1H), 5.57 (s, 1H), 5.29 (s, 1H), 4.89 (d, *J* = 7.5 Hz, 1H), 4.68 - 4.58 (m, 1H), 4.42 - 4.31 (m, 1H), 4.08 - 3.90 (m, 3H), 3.84 - 3.69 (m, 1H), 3.50 - 3.35 (m, 1H), 2.15 - 2.02 (m, 1H), 1.64 - 1.56 (m, 1H), 0.99 (s, 9H).
69	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.71 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J*= 8.1 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.21 - 7.10 (m, 5H), 5.37 (d, *J* = 7.9 Hz, 1H), 4.55 - 4.38 (m, 2H), 4.05 - 3.87 (m, 1H), 3.81 - 3.65 (m, 1H), 3.64 - 3.53 (m, 5H), 2.39 - 2.21 (m, 1H), 1.99 - 1.67 (m, 3H).
70	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.71 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.21 - 7.10 (m, 5H), 5.37 (d, *J* = 7.9 Hz, 1H), 4.55 - 4.38 (m, 2H), 4.05 - 3.87 (m, 1H), 3.81 - 3.65 (m, 1H), 3.64 - 3.53 (m, 5H), 2.39 - 2.21 (m, 1H), 1.99 - 1.67 (m, 3H).
71	m/z 538 (M+H)
72	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 5.4 Hz, 1H), 7.52 (q, *J* = 7.2 Hz, 1H), 7.10 - 6.97 (m, 2H), 6.41 (s, 1H), 5.36 (s, 1H), 5.22 (s, 1H), 4.70 (s, 1H), 4.58 (s, 1H), 4.03 (s, 1H), 3.78 (d, *J* = 10.8 Hz, 1H), 2.37 (s, 1H), 2.10 - 1.86 (m, 4H), 1.52 - 1.46 (m, 1H), 1.26 (s, 1H), 0.95 (d, *J*= 11.6 Hz, 8H).
73	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 2.4 Hz, 1H), 7.96 (s, 1H), 7.66 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 11.0 Hz, 1H), 5.44 - 5.32 (m, 3H), 4.06 (dt, *J* = 6.8, 3.9 Hz, 1H), 3.86 - 3.76 (m, 1H), 2.55 (s, 3H), 2.45 - 2.32 (m, 1H), 2.07 - 1.87 (m, 3H).
74	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 2.4 Hz, 1H), 7.95 (s, 1H), 7.65 (dd, *J* = 7.9, 2.6 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.28 (s, 2H), 7.14 (d, *J* = 7.8 Hz, 1H), 5.46 - 5.31 (m, 3H), 4.12 - 4.02 (m, 1H), 3.86 - 3.77 (m, 1H), 2.55 (s, 3H), 2.43 - 2.32 (m, 1H), 2.03 - 1.87 (m, 3H).
77	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 9.8 Hz, 4H), 6.10 (s, 1H), 5.46 (dt, *J* = 8.1, 3.4 Hz, 2H), 5.30 (s, 1H), 4.15 - 4.01 (m, 1H), 3.92 - 3.75 (m, 1H), 2.47 - 2.31 (m, 1H), 2.07 - 1.72 (m, 7H), 1.02 - 0.86 (m, 6H).
78	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.56 (d, *J*= 8.3 Hz, 2H), 7.26 (d, 4H), 6.17 (s, 1H), 5.53 - 5.32 (m, 3H), 4.09 (s, 1H), 3.91 - 3.78 (m, 1H), 2.48 - 2.31 (m, 1H), 2.08 - 1.48 (m, 7H), 0.92 (dd, *J* = 7.8, 6.1 Hz, 6H).
79	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J*= 8.1 Hz, 4H), 5.47 - 5.30 (m, 3H), 4.13 - 4.01 (m, 1H), 3.88 - 3.75 (m, 1H), 3.65 (s, 2H), 2.44 - 2.31 (m, 1H), 2.04 - 1.85 (m, 3H).
80	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 0.3H), 8.77 - 8.73 (m, 0.64H), 8.69 (d, *J* = 2.9 Hz, 0.63H), 8.53 (s, 0.57H), 8.19 (dd, *J* = 8.1, 2.5 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 0.68H), 7.33 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.22 (s, 0.67H), 5.81 (d, *J* = 6.0 Hz, 0.36H), 5.31 (dd, *J* = 9.6, 3.7 Hz, 0.71H), 4.27 - 4.20 (m, 0.42H), 1.95 - 1.79 (m, 2H), 1.79 - 1.66 (m, 1H), 1.59 - 1.51 (m, 1H), 1.01 - 0.89 (m, 6H). Note: Due to the presence of isomers the protons were integrated in decimals
81	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.31 - 7.21 (m, 6H), 5.41 (d, *J* = 7.9 Hz, 1H), 4.93 (s, 1H), 4.66 - 4.50 (m, 2H), 4.10 - 3.98 (m, 1H), 3.86 - 3.72 (m, 1H), 3.63 (s, 2H), 2.49 - 2.29 (m, 1H), 2.03 - 1.84 (m, 3H).

(continued)

Ex. No.	^{1}H NMR or MS Data
83	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.46 (dd, *J* = 8.3, 2.2 Hz, 4H), 7.37 - 7.29 (m, 2H), 5.46 (s, 2H), 4.79 (d, *J* = 6.1 Hz, 2H), 3.68 (s, 2H).
84	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.74 - 8.60 (m, 1H), 8.01 - 7.84 (m, 2H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.95 - 6.73 (m, 1H), 5.44 (d, *J* = 7.7 Hz, 1H), 5.40 - 5.24 (m, 2H), 4.17 - 3.95 (m, 1H), 3.86 - 3.67 (m, 1H), 3.36 (s, 2H), 2.46 - 2.29 (m, 1H), 2.04 - 1.76 (m, 3H).
85	^{1}H NMR (300 MHz, DMSO-d_6) δ 12.19 (s, 1H), 8.07 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.16 (s, 5H), 6.80 - 6.55 (m, 1H), 5.61 (d, *J* = 7.8 Hz, 1H), 5.44 - 5.19 (m, 2H), 4.32 - 4.05 (m, 1H), 4.05 - 3.78 (m, 1H), 3.50 (s, 2H), 2.44 - 2.27 (m, 1H), 2.12 - 1.70 (m, 3H).
86	^{1}H NMR (300 MHz, CD_3OD) δ 8.02 (dd, *J* = 2.3, 1.2 Hz, 1H), 7.93 - 7.85 (m, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.32 (d, *J* = 7.7 Hz, 1H), 4.81 (d, *J* = 4.9 Hz, 2H), 4.04 - 3.92 (m, 1H), 3.72 - 3.55 (m, 3H), 2.40 - 2019 (m, 1H), 1.95 - 1.70 (m, 3H).
87	^{1}H NMR (300 MHz, CD_3OD) δ 7.92 (s, 1H), 7.84 - 7.79 (m, 1H), 7.65 (t, *J* = 1.6 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.34 - 5.26 (m, 1H), 4.39 - 4.25 (m, 2H), 4.00 - 3.87 (m, 1H), 3.77 - 3.60 (m, 3H), 2.40 - 2.23 (m, 1H), 1.96 - 1.73 (m, 3H).
88	^{1}H NMR (300 MHz, CD_3OD) δ 7.70 (t, *J* = 1.7 Hz, 1H), 7.67 - 7.56 (m, 4H), 7.45 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 5.47 - 5.39 (m, 1H), 4.63 (s, 2H), 4.13 - 4.00 (m, 1H), 3.86 - 3.73 (m, 1H), 2.51 - 2.35 (m, 1H), 2.06 - 1.84 (m, 3H).
89	^{1}H NMR (300 MHz, CD_3OD) δ 8.35 (d, *J* = 2.2 Hz, 1H), 7.78 - 7.70 (m, 1H), 7.65 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 5.48 - 5.36 (m, 1H), 4.55 (d, *J* = 3.5 Hz, 2H), 4.13 - 3.95 (m, 1H), 3.89 - 3.70 (m, 1H), 2.47 (s, 3H), 2.46 - 2.31 (m, 1H), 2.04 - 1.81 (m, 3H).
90	^{1}H NMR (300 MHz, CD_3OD) δ 8.39 - 8.30 (m, 1H), 7.74 (d, *J* = 1.7 Hz, 1H), 7.63 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.07 - 7.01 (m, 2H), 6.84 - 6.77 (m, 2H), 5.36 - 5.24 (m, 1H), 4.53 (d, *J* = 3.8 Hz, 2H), 4.05 - 3.92 (m, 1H), 3.75 - 3.64 (m, 5H), 2.47 (s, 3H), 2.36 - 2.23 (m, 1H), 1.95 - 1.82 (m, 3H).
91	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (s, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.63 (q, *J* = 4.5 Hz, 1H), 7.53 - 7.47 (m, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.25 - 7.14 (m, 4H), 5.42 (s, 1H), 4.58 - 4.44 (m, 2H), 4.28 (dd, *J* = 12.1, 2.3 Hz, 1H), 4.01 - 3.81 (m, 3H), 3.65 (td, *J* = 11.2, 2.9 Hz, 2H), 3.51 (s, 2H), 3.30 - 3.24 (m, 1H).
93	^{1}H NMR (300 MHz, CD_3OD) δ 7.72 (t, *J* = 2.0 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 5.44 - 5.37 (m, 1H), 4.10 - 3.99 (m, 1H), 3.84 - 3.72 (m, 1H), 3.31 - 3.25 (m, 1H), 3.16 (dd, *J* = 7.0, 5.2 Hz, 1H), 2.51 - 2.34 (m, 1H), 2.04 - 1.84 (m, 3H), 1.81 - 1.65 (m, 3H), 1.48 - 1.38 (m, 2H), 1.38 - 1.21 (m, 2H), 1.00 - 0.82 (m, 6H).
94	^{1}H NMR (300 MHz, CD_3OD) δ 7.70 (s, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J*= 8.1 Hz, 2H), 7.28 (d, *J*= 8.2 Hz, 2H), 7.16 (d, *J*= 8.2 Hz, 2H), 7.06 (s, 1H), 6.96 (s, 1H), 5.44 - 5.38 (m, 1H), 4.55 (d, *J* = 4.7 Hz, 2H), 4.10 - 3.98 (m, 1H), 3.85 - 3.69 (m, 1H), 2.49 - 2.32 (m, 1H), 2.03 - 1.82 (m, 3H).
95	^{1}H NMR (300 MHz, CD_3OD) δ 7.72 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.43 - 7.29 (m, 6H), 5.46 - 5.39 (m, 1H), 4.65 - 4.52 (m, 2H), 4.37 (s, 2H), 4.11 - 4.00 (m, 1H), 3.80 (dtd, *J*= 10.4, 7.5, 2.8 Hz, 1H), 2.83 (s, 3H), 2.52 - 2.35 (m, 1H), 2.07 - 1.85 (m, 3H).
96	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.46 (s, 1H), 8.90 (t, *J* = 5.9 Hz, 1H), 8.47 (d, *J* = 2.5 Hz, 1H), 8.38 (d, *J* = 1.2 Hz, 1H), 8.27 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 2H), 7.66 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 4.67 (d, *J* = 5.9 Hz, 2H), 2.44 (s, 3H).
97	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (d, *J* = 2.2 Hz, 1H), 7.73 (d, *J* = 2.0 Hz, 1H), 7.53 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.44 - 7.34 (m, 1H), 7.33 - 7.22 (m, 4H), 7.14 (d, *J* = 7.9 Hz, 1H), 5.38 - 5.28 (m, 1H), 4.52 - 4.36 (m, 2H), 4.00 - 3.86 (m, 1H), 3.71 - 3.62 (m, 1H), 2.40 (s, 3H), 2.36 - 2.25 (m, 1H), 2.01 - 1.66 (m, 3H).

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Ex. No.	^{1}H NMR or MS Data
98	^{1}H NMR (300 MHz, CD_3OD) δ 7.72 (d, *J* = 1.7 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.25 - 7.09 (m, 4H), 5.51 - 5.37 (m, 1H), 4.63 - 4.46 (m, 2H), 4.12 - 4.00 (m, 1H), 3.86 - 3.73 (m, 1H), 2.72 (s, 2H), 2.54 - 2.38 (m, 1H), 2.04 - 1.86 (m, 3H), 1.15 (s, 6H).
99	^{1}H NMR (300 MHz, CD_3OD) δ 7.69 (t, *J* = 1.4 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.39 - 7.31 (m, 3H), 6.66 (d, *J* = 7.3 Hz, 1H), 5.40 (d, *J* = 7.7 Hz, 1H), 4.45 (s, 2H), 4.09 - 3.98 (m, 1H), 3.92 (d, *J* = 1.2 Hz, 3H), 3.85 - 3.69 (m, 1H), 2.50 - 2.33 (m, 4H), 2.05 - 1.81 (m, 3H).
100	m/z 434 (M+H)
104	^{1}H NMR (300 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.33 (d, *J* = 2.2 Hz, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.53 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.44 - 7.29 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.11 - 6.96 (m, 3H), 5.46 (d, *J* = 7.9 Hz, 1H), 4.51 - 4.33 (m, 2H), 4.04 - 3.86 (m, 1H), 3.76 - 3.56 (m, 1H), 2.40 (s, 3H), 2.31 - 2.10 (m, 1H), 2.01 - 1.83 (m, 1H), 1.83 - 1.60 (m, 2H).
105	m/z 420 (M+H)
106	m/z 421 (M+H)
107	m/z 421 (M+H)
108	m/z 424 (M+H)
109	m/z 438 (M+H)
110	m/z 482 (M+H)
111	m/z 455 (M+H)
112	m/z 476 (M+H)
113	^{1}H NMR (300 MHz, CD_3OD) δ 7.99 (dd, *J* = 5.3, 1.0 Hz, 1H), 7.71 (t, *J* = 1.3 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 6.86 (dt, *J* = 5.4, 1.2 Hz, 1H), 6.67 (s, 1H), 5.43 (d, *J* = 7.8 Hz, 1H), 4.63 - 4.46 (m, 2H), 4.13 - 3.98 (m, 1H), 3.90 - 3.75 (m, 4H), 2.52 - 2.35 (m, 1H), 2.06 - 1.84 (m, 3H).
114	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.05 (dd, *J* = 2.4, 0.8 Hz, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.67 - 7.60 (m, 2H), 7.59 (d, *J* = 2.5 Hz, 0H), 7.39 (d, *J* = 8.2 Hz, 3H), 6.73 (dd, *J* = 8.5, 0.8 Hz, 1H), 5.36 (d, *J* = 7.8 Hz, 1H), 4.48 - 4.32 (m, 2H), 3.98 - 3.90 (m, 1H), 3.79 (s, 3H), 3.76 - 3.62 (m, 1H), 2.38 - 2.26 (m, 1H), 1.97 - 1.71 (m, 3H).
115	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.62 (s, 1H), 7.94 (s, 1H), 7.71 - 7.61 (m, 3H), 7.46 - 7.35 (m, 3H), 7.30 - 7.13 (m, 4H), 5.35 (s, 3H), 4.54 - 4.33 (m, 2H), 3.98 - 3.89 (m, 1H), 3.77 - 3.61 (m, 1H), 2.42 - 2.27 (m, 1H), 1.95 - 1.70 (m, 3H).
116	^{1}H NMR (300 MHz, CD_3OD) δ 7.97 (s, 1H), 7.77 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.48 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 1H), 5.46 - 5.34 (m, 1H), 4.55 (q, *J* = 15.5 Hz, 2H), 4.11 - 3.97 (m, 1H), 3.86 (s, 3H), 3.85 - 3.68 (m, 1H), 2.95 (d, *J* = 3.7 Hz, 3H), 2.50 - 2.34 (m, 1H), 2.02 - 1.80 (m, 3H).
117	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.31 - 7.21 (m, 6H), 5.41 (d, *J* = 7.9 Hz, 1H), 4.93 (s, 1H), 4.66 - 4.50 (m, 2H), 4.10 - 3.98 (m, 1H), 3.86 - 3.72 (m, 1H), 3.63 (s, 2H), 2.49 - 2.29 (m, 1H), 2.03 - 1.84 (m, 3H).
118	m/z 475 (M+H)
119	^{1}H NMR (300 MHz, DMSO-d_6) δ 12.25 (s, 1H), 7.84 (d, *J* = 1.7 Hz, 1H), 7.75 - 7.56 (m, 5H), 7.27 - 7.11 (m, 4H), 5.46 (s, 1H), 4.51 (d, *J* = 6.1 Hz, 2H), 4.30 (dd, *J* = 12.1, 2.3 Hz, 1H), 4.08 - 3.81 (m, 4H), 3.66 (td, *J* = 11.0, 2.9 Hz, 1H), 3.51 (s, 2H).
120	m/z 475 (M+H)
121	m/z 501 (M+H)
122	m/z 472 (M+H)
123	m/z 465 (M+H)

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Ex. No.	^{1}H NMR or MS Data
124	m/z 514 (M+H)
126	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (s, 1H), 7.95 - 7.89 (m, 1H), 7.82 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.54 (t, *J* = 6.0 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 5.37 (d, *J* = 8.0 Hz, 1H), 4.69 - 4.49 (m, 2H), 4.06 - 3.91 (m, 1H), 3.80 - 3.63 (m, 1H), 2.39 - 2.26 (m, 1H), 2.02 - 1.70 (m, 3H).
128	m/z 461 (M+H)
129	m/z 441 (M+H)
130	m/z 492 (M+H)
131	m/z 448 (M+H)
132	m/z 432 (M+H)
134	m/z 464 (M+H)
135	m/z 452 (M+H)
136	m/z 460 (M+H)
137	m/z 500 (M+H)
138	m/z 485 (M+H)
139	m/z 417 (M+H)
140	m/z 418 (M+H)
141	m/z 418 (M+H)
142	m/z 477 (M+H)
143	m/z 500 (M+H)
144	m/z 474 (M+H)
145	m/z 488 (M+H)
146	m/z 498 (M+H)
147	m/z 461 (M+H)
148	m/z 481 (M+H)
150	m/z 368 (M+H)
151	m/z 495 (M+H)
152	m/z 409 (M+H)
154	m/z 411 (M+H)
155	m/z 425 (M+H)
159	m/z 427 (M+H)
161	m/z 439 (M+H)
164	m/z 441 (M+H)
165	m/z 443 (M+H)
166	m/z 451 (M+H)
167	m/z 453 (M+H)
168	m/z 453 (M+H)
169	m/z 457 (M+H)
170	m/z 459 (M+H)

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Ex. No.	^{1}H NMR or MS Data
175	m/z 481 (M+H)
178	m/z 465 (M+H)
181	m/z 411 (M+H)
182	m/z 496 (M+H)
183	m/z 452 (M+H)
184	m/z 459 (M+H)
185	m/z 423 (M+H)
186	m/z 425 (M+H)
188	m/z 439 (M+H)
189	m/z 488 (M+H)
190	^{1}H NMR (300 MHz, CD_3OD) δ 7.71 (s (br), 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 5.41 (d, *J* = 7.9 Hz, 1H), 4.14 - 3.96 (m, 1H), 3.87-3.72 (m, 1H), 3.28 - 3.06 (m, 2H), 2.82 (d, *J* = 6.8 Hz, 2H), 2.57 - 2.33 (m, 1H), 2.07-1.85 (m, 3H), 1.85 - 1.63 (m, 5H), 1.63-1.42 (m, 1H), 1.17 - 0.81 (m, 4H).
191	^{1}H NMR (300 MHz, CD_3OD) δ 7.73 (s (br), Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 5.41 (d, *J* = 7.9 Hz, 2H), 4.56 - 4.42 (m, 1H), 4.19 - 3.99 (m, 1H), 3.90 (d, *J* = 13.8 Hz, 1H), 3.85-3.3.73 (m, 1H), 3.30 - 3.15 (m, 2H), 3.13-3.0 (m, 1H), 2.66-2.52 (m, 1H), 2.52 - 2.36 (m, 1H), 2.08 (s (br), 3H), 2.05 - 1.68 (m, 6H), 1.33 - 0.98 (m, 2H).
192	^{1}H NMR (300 MHz, $cdcl_3$) δ 7.96 (d, *J* = 1.8 Hz, 2H), 7.25 (d, *J* = 4.5 Hz, 11H), 7.20 - 7.09 (m, 4H), 5.38 (d, J = 7.9 Hz, 1H), 4.94 (s, 1H), 4.58 (t, *J* = 6.0 Hz, 2H), 4.02 (s, 1H), 3.82 - 3.70 (m, 1H), 3.63 (s, 2H), 2.40 - 2.29 (m, 1H), 2.00 - 1.84 (m, 3H).
193	^{1}H NMR (300 MHz, C_6D_6) δ 8.11 (d, *J* = 2.0 Hz, 1H), 8.04 (s, 1H), 7.64 (d, *J* = 6.4 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.55 (d, *J* = 7.8 Hz, 1H), 6.11 (dd, *J* = 7.9, 6.4 Hz, 1H), 5.84 - 5.74 (m, 1H), 5.18 (d, *J* = 7.9 Hz, 1H), 4.20 - 3.99 (m, 2H), 3.92 - 3.75 (m, 1H), 3.64 - 3.46 (m, 1H), 1.89 - 1.68 (m, 1H), 1.48 - 1.28 (m, 3H).
194	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.13 - 8.07 (m, 2H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.69 - 7.62 (m, 2H), 7.51 - 7.44 (m, 1H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.27 - 7.20 (m, 2H), 5.38 (d, *J* = 7.8 Hz, 2H), 4.43 (t, *J* = 5.5 Hz, 2H), 4.04 - 3.91 (m, 2H), 3.77 - 3.65 (m, 2H), 2.40 - 2.30 (m, 1H), 1.94 - 1.75 (m, 4H).
195	^{1}H NMR (300 MHz, DMSO-d_6) δ 12.19 (s, 1H), 8.07 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.16 (s, 5H), 6.80 - 6.55 (m, 1H), 5.61 (d, *J* = 7.8 Hz, 1H), 5.44 - 5.19 (m, 2H), 4.32 - 4.05 (m, 1H), 4.05 - 3.78 (m, 1H), 3.50 (s, 2H), 2.44 - 2.27 (m, 1H), 2.12 - 1.70 (m, 3H).
196	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.20 (s, 1H), 6.71 (d, *J* = 8.1 Hz, 2H), 6.53 (d, *J* = 8.1 Hz, 2H), 6.35 (d, *J* = 8.0 Hz, 2H), 6.24 (d, *J* = 7.9 Hz, 2H), 6.13 (s, 1H), 5.60 (s, 1H), 4.78 (d, *J* = 7.9 Hz, 1H), 4.55 - 4.35 (m, 2H), 3.43 - 3.27 (m, 1H), 3.21 - 3.03 (m, 1H), 1.74 - 1.52 (m, 1H), 1.26 - 1.02 (m, 3H).
197	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.73 (s, 1H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.43 - 7.34 (m, 2H), 6.89 (s, 1H), 5.47 - 5.23 (m, 1H), 4.07 - 3.88 (m, 1H), 3.76 - 3.63 (m, 1H), 3.57 - 3.46 (m, 2H), 3.27 - 3.06 (m, 2H), 2.81 (s, 3H), 2.67 - 2.54 (m, 2H), 2.42 - 2.27 (m, 1H), 2.01 - 1.56 (m, 5H), 1.27 - 1.01 (m, 3H).
198	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.9 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.41 (d, *J* = 7.9 Hz, 1H), 4.80 (s, 1H), 4.52 (dd, *J* = 6.1, 2.1 Hz, 2H), 4.38 (d, *J* = 6.0 Hz, 2H), 4.08 - 3.97 (m, 1H), 3.79-3.70 (m, 1H), 3.68 (dd, *J* = 13.7, 6.3 Hz, 1H), 3.58 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.39 - 2.36 (m, 1H), 1.97 - 1.89 (m, 3H), 1.32 (s, 3H).
199	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 9.3 Hz, 2H), 5.40 (d, *J* = 7.7 Hz, 1H), 4.92 (s, 1H), 4.03-4.01 (m, 1H), 3.89 - 3.72 (m, 3H), 3.52-.3.44 (m, 2H), 2.39 - 2.35 (m, 1H), 2.00 - 1.73 (m, 6H), 1.73 - 1.58 (m, 1H), 1.20 (d,*J* = 3.0 Hz, 3H).

(continued)

Ex. No.	^{1}H NMR or MS Data
200	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (t, *J* = 2.2 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 5.38 (t, *J* = 7.5 Hz, 1H), 4.99 (s, 1H), 4.76 (s, 1H), 4.00 (s, 1H), 3.84 - 3.59 (m, 3H), 3.00 - 2.90 (m, 1H), 2.3-2.32 (m, 1H), 2.01 - 1.81 (m, 4H), 1.77 - 1.51 (m, 3H), 1.50 - 1.33 (m, 3H), 1.32 - 1.21 (m, 2H).
201	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 1.8 Hz, 1H), 7.55 (dd, *J* = 8.4, 2.2 Hz, 2H), 7.30 (dd, *J* = 8.5, 2.2 Hz, 2H), 5.41 (d, *J* = 7.2 Hz, 1H), 5.06 (s, 1H), 4.04 (s, 1H), 3.77 (td, *J* = 7.5, 3.2 Hz, 1H), 3.57 (dd, *J* = 6.1, 3.9 Hz, 1H), 3.01 - 2.80 (m, 2H), 2.37 (td, *J* = 9.6, 8.8, 4.5 Hz, 1H), 2.13 - 2.00 (m, 2H), 2.00 - 1.79 (m, 4H), 1.73 - 1.68 (m, 1H), 1.42 (s, 3H).
202	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.9 Hz, 1H), 7.55 (d, *J* = 7.8Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 5.40 (d, *J* = 7.8 Hz, 1H), 4.77 (s, 1H), 4.57 - 4.42 (m, 1H), 4.21 - 4.09 (m, 2H), 4.02 - 4.01 (m, 1H), 3.85 - 3.50 (m, 3H), 3.26 - 3.13 (m, 2H), 2.38 - 2.35 (m, 1H), 2.20 - 2.05 (m, 2H), 1.97-1.89 (m, 3H).
203	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 1.9 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.29 - 7.26 (m, 2H), 7.20 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.98 (d, *J* = 3.3 Hz, 1H), 6.94-6.92 (m, 1H), 5.40 (d, *J* = 8.0 Hz, 1H), 4.90 - 4.66 (m, 2H), 4.03-4.01 (m, 1H), 3.80 - 3.75 (m, 1H), 2.37 - 2.35 (m, 1H), 2.00 - 1.82 (m, 3H).
204	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.84 (d, *J* = 1.7 Hz, 1H), 7.75 - 7.55 (m, 5H), 7.41 (s, 1H), 7.25 - 7.13 (m, 4H), 6.83 (s, 1H), 5.45 (s, 1H), 4.50 (d, *J* = 6.1 Hz, 2H), 4.29 (dd, *J* = 12.2, 2.3 Hz, 1H), 4.04 - 3.78 (m, 3H), 3.75 - 3.59 (m, 1H).
205	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.59 (d, *J* = 1.4 Hz, 4H), 5.53 (s, 1H), 4.81 (s, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.07 - 3.88 (m, 3H), 3.83 - 3.71 (m, 1H), 3.54 - 3.15 (m, 3H), 2.25 (d, *J* = 6.5 Hz, 2H), 1.91 - 1.80 (m, 5H), 1.09 - 0.99 (m, 4H).
206	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.7 Hz, 1H), 7.62 - 7.55 (m, 4H), 5.52 (s, 1H), 5.40 - 5.21 (m, 2H), 4.80 (s, 1H), 4.33 (dd, *J* = 11.9, 2.4 Hz, 1H), 4.06 - 3.89 (m, 3H), 3.83 - 3.72 (m, 1H), 3.48 - 3.35 (m, 1H), 3.32 (t, *J* = 6.4 Hz, 2H), 2.10 (d, *J* = 6.8 Hz, 2H), 1.90 - 1.78 (m, 5H), 1.52 - 1.41 (m, 1H), 1.02 (q, *J* = 10.5, 10.1 Hz, 4H).
207	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 8.9 Hz, 2H), 6.80 (dd, *J* = 20.3, 3.4 Hz, 2H), 5.42 (d, *J* = 7.8 Hz, 1H), 5.06 (s, 1H), 4.83 - 4.50 (m, 2H), 4.05 (m, 1H), 3.80 (s, 3H), 2.38 (q, *J* = 7.5 Hz, 1H), 2.01 - 1.87 (m, 3H).
208	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 1.9 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.34 - 7.21 (m, 2H), 5.40 (d, *J* = 7.8 Hz, 1H), 4.61 (s, 1H), 4.07 - 3.90 (m, 3H), 3.85 - 3.69 (m, 1H), 3.43 - 3.22 (m, 4H), 2.46 - 2.30 (m, 1H), 2.03 - 1.71 (m, 4H), 1.71 - 1.47 (m, 2H), 1.41 - 1.17 (m, 3H).
209	^{1}H NMR (300 MHz, CD_3OD) δ 8.35 (s, 1H), 7.72 - 7.60 (m, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.43 (d, *J*= 8.3 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 1H), 4.55 (s, 2H), 4.10 - 3.95 (m, 2H), 2.50 (s, 3H), 2.28 - 2.13 (m, 1H), 2.12 - 1.83 (m, 6H).
210	m/z 450 (M+H)
211	m/z 446 (M+H)
212	m/z 462 (M+H)
213	m/z 422 (M+H)
214	m/z 425 (M+H)
215	m/z 451 (M+H)
216	m/z 424 (M+H)
217	m/z 447 (M+H)
218	m/z 409 (M+H)
219	m/z 495 (M+H)

(continued)

Ex. No.	^{1}H NMR or MS Data
220	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 1.8 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.61 (s, 1H), 5.41 (d, *J* = 7.9 Hz, 1H), 5.05 (s, 1H), 4.09 - 3.70 (m, 5H), 3.64 - 3.54 (m, 3H), 2.46 - 2.30 (m, 1H), 2.05 - 1.86 (m, 5H).
221	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 5.40 (d, *J* = 7.9 Hz, 1H), 5.07 (s, 1H), 4.03 - 4.00 (m, 1H), 3.82 - 3.72 (m, 6H), 3.65 - 3.57 (m, 3H), 3.50 (dd, *J* = 14.1, 6.8 Hz, 1H), 2.43 - 2.31 (m, 1H), 1.98 - 1.90 (m, 3H), 1.64 (t, *J* = 5.8 Hz, 2H), 1.59 - 1.42 (m, 4H).
222	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 3H), 5.39 (d, *J* = 8.1 Hz, 1H), 4.68 (s, 1H), 4.04 - 4.01 (m, 1H), 3.81 - 3.72 (m, 1H), 3.43 - 3.33 (m, 2H), 3.09-3.05 (m, 2H), 2.94 (t, *J* = 12.5 Hz, 2H), 2.39 - 2.34 (m, 1H), 2.15 (d, *J* = 10.4 Hz, 2H), 1.97-1.85 (m, 6H).
223	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 1.7 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.28 (s, 2H), 6.57 (s, 1H), 5.41 (d, *J* = 7.8 Hz, 1H), 4.95 (s, 1H), 4.05 (s, 1H), 3.79 (d, *J* = 7.9 Hz, 1H), 3.59 - 3.26 (m, 4H), 2.86 (d, *J* = 13.5 Hz, 2H), 2.39 (t, *J* = 7.2 Hz, 1H), 2.21 - 1.74 (m, 6H).
224	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 1.9 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 5.46 - 5.33 (m, 1H), 4.94 (s, 1H), 4.80 - 4.62 (m, 3H), 4.05 - 4.01 (m, 1H), 3.80 - 3.78 (m, 1H), 2.41 - 2.36 (m, 1H), 2.23 - 2.21 (m, 1H), 1.99 - 1.91 (m, 3H), 0.70 - 0.54 (m, 4H).
225	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 5.47 (d, *J* = 7.9 Hz, 1H), 4.16 - 4.05 (m, 1H), 3.92 - 3.79 (m, 1H), 3.49 - 3.23 (m, 3H), 2.49 - 2.34 (m, 1H), 2.12 - 1.58 (m, 9H), 1.25 (s, 1H), 1.14 - 0.79 (m, 4H).
226	m/z 460 (M+H)
227	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.33 - 7.19 (m, 6H), 5.37 (d, *J* = 7.8 Hz, 1H), 4.59 (s, 2H), 4.55 (d, *J* = 6.0 Hz, 2H), 4.07 - 3.94 (m, 1H), 3.83 - 3.68 (m, 1H), 2.46 - 2.25 (m, 1H), 2.03 - 1.80 (m, 3H).
228	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 1.8 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 5.44 - 5.24 (m, 2H), 4.89 (s, 1H), 4.46 - 4.31 (m, 4H), 4.10 - 3.96 (m, 1H), 3.86 - 3.66 (m, 5H), 2.46 - 2.28 (m, 1H), 2.04 - 1.85 (m, 3H).
229	^{1}H NMR (300 MHz, CD_3OD) δ 7.61 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 4.53 (s, 2H), 4.10 - 3.96 (m, 2H), 3.48 (s, 2H), 2.26 - 2.10 (m, 1H), 2.09 - 1.82 (m, 6H).
230	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 1.7 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.30 - 7.24 (m, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 5.53 (s, 1H), 5.32 (s, 2H), 5.03 (s, 1H), 4.67 (d, *J* = 5.7 Hz, 2H), 4.38 - 4.29 (m, 1H), 4.05 - 3.90 (m, 3H), 3.77 (td, *J* = 11.2, 2.8 Hz, 1H), 3.58 (s, 2H), 3.48 - 3.39 (m, 1H).
231	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 1.8 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 7.4 Hz, 2H), 5.88 - 5.49 (m, 1H), 5.31 (s, 2H), 4.94 (s, 1H), 4.72 - 4.50 (m, 2H), 4.31 (q, *J* = 13.0 Hz, 1H), 4.19 (q, *J* = 12.6 Hz, 1H), 3.57 (s, 2H), 3.16 - 2.77 (m, 1H), 2.58 - 1.97 (m, 1H).
232	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.9 Hz, 1H), 7.34 - 7.28 (m, 4H), 7.25 - 7.17 (m, 3H), 5.60 (d, *J* = 8.2 Hz, 1H), 5.30 (s, 2H), 4.85 (s, 1H), 4.72 - 4.39 (m, 2H), 4.20 - 3.95 (m, 1H), 3.90 - 3.73 (m, 1H), 3.57 (s, 2H), 2.55 - 2.22 (m, 1H), 2.11 - 1.75 (m, 3H).
233	^{1}H NMR (300 MHz, CD_3OD) δ 7.86 (s, 1H), 7.65 - 7.56 (m, 4H), 5.45 (s, 1H), 4.60 - 4.46 (m, 1H), 4.30 (dd, *J* = 12.0, 2.8 Hz, 1H), 4.04 - 3.84 (m, 4H), 3.84 - 3.69 (m, 1H), 3.50 - 3.36 (m, 2H), 2.83 (s, 2H), 2.36 (t, *J* = 8.1 Hz, 1H), 2.13 - 2.06 (m, 3H), 1.96 - 1.69 (m, 3H), 1.33 - 0.98 (m, 2H).
234	^{1}H NMR (300 MHz, CD_3OD) δ 7.88 (s, 1H), 7.63 (d, *J* = 1.1 Hz, 4H), 5.53 - 5.47 (m, 1H), 4.34 (dd, *J* = 12.1, 2.5 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 1H), 4.06 - 3.88 (m, 3H), 3.85 - 3.70 (m, 1H), 3.52 (s, 2H), 3.50 - 3.36 (m, 2H), 2.97 - 2.86 (m, 2H), 2.15 - 2.02 (m, 4H).

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Ex. No.	^{1}H NMR or MS Data
235	^{1}H NMR (300 MHz, CD_3OD) δ 7.86 (s, 1H), 7.67 - 7.58 (m, 4H), 5.49 - 5.44 (m, 1H), 4.62 (d, *J* = 5.9 Hz, 2H), 4.36 - 4.26 (m, 3H), 4.05 - 3.87 (m, 3H), 3.84 - 3.71 (m, 1H), 3.61 (s, 2H), 3.50 - 3.38 (m, 1H), 1.33 (s, 3H).
236	^{1}H NMR (300 MHz, CD_3OD) δ 7.67 - 7.58 (m, 3H), 7.41 (s, 4H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.34 - 5.23 (m, 1H), 4.51 (s, 2H), 4.12 (dd, *J* = 12.0, 2.6 Hz, 1H), 3.83 - 3.65 (m, 3H), 3.56 (td, *J* = 10.8, 2.8 Hz, 1H), 3.29 - 3.16 (m, 1H), 1.96 - 1.88 (m, 1H), 0.34 - 0.22 (m, 4H).
237	^{1}H NMR (300 MHz, CD_3OD) δ 7.86 (s, 1H), 7.66 - 7.59 (m, 4H), 5.47 - 5.42 (m, 1H), 4.30 (dd, *J* = 12.0, 2.9 Hz, 1H), 4.04 - 3.86 (m, 3H), 3.84 - 3.68 (m, 3H), 3.50 - 3.38 (m, 1H), 2.81 (s, 3H), 2.76 - 2.63 (m, 2H), 2.02 (d, *J* = 0.9 Hz, 1H), 1.92 - 1.67 (m, 3H), 1.38 - 1.19 (m, 3H).
238	m/z 443 (M+H)
239	m/z 485 (M+H)
240	m/z 517 (M+H)
241	m/z 492 (M+H)
242	m/z 492 (M+H)
243	m/z 513 (M+H)
244	m/z 504 (M+H)
245	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 1.6 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 5.50 (s, 1H), 5.41 - 5.18 (m, 2H), 4.81 (s, 1H), 4.33 (d, *J* = 11.8 Hz, 1H), 4.06 - 3.88 (m, 3H), 3.82 - 3.71 (m, 1H), 3.47 - 3.26 (m, 3H), 2.11 (d, *J* = 608 Hz, 2H), 1.91 - 1.73 (m, 5H), 1.03 (q, *J* = 10.3, 9.7 Hz, 4H).
246	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 1.6 Hz, 1H), 7.58 - 7.46 (m, 2H), 7.27 - 7.10 (m, 6H), 5.56 (s, 1H), 5.36 (m, 1H), 4.59 (d, *J* = 5.7 Hz, 2H), 4.35 (dd, *J* = 12.0, 2.0 Hz, 1H), 4.24 (s, 2H), 4.08 - 3.89 (m, 3H), 3.77 (td, *J* = 11.2, 2.7 Hz, 1H), 3.49 (s, 1H), 3.43 (m, 1H).
247	^{1}H NMR (300 MHz, CD_3OD) δ 7.85 (s, 1H), 7.61 (s, 4H), 5.44 (t, *J* = 3.1 Hz, 1H), 4.29 (dd, *J* = 12.1, 2.9 Hz, 2H), 4.00 - 3.86 (m, 4H), 3.84 - 3.72 (m, 1H), 3.50 - 3.26 (m, 5H), 1.96 - 1.79 (m, 1H), 1.71 - 1.62 (m, 2H), 1.37 - 1.20 (m, 2H).
248	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 1.8 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.36 - 7.27 (m, 4H), 7.23 (d, *J* = 8.1 Hz, 2H), 5.28-5.24 (m, 3H), 4.82 (m, 2H), 4.60 (dd, *J* = 10.3, 5.7 Hz, 2H), 4.08 (m, 1H), 3.57 (s, 2H), 3.45 (t, *J* = 10.3 Hz, 1H), 2.64 - 2.51 (m, 1H), 2.36 (m, 1H), 1.52 - 1.40 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H).
249	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.6 Hz, 1H), 7.58 (s, 4H), 5.94 (s, 1H), 5.51 (d, *J* = 17.3 Hz, 2H), 5.39 - 5.17 (m, 1H), 4.39 - 4.28 (m, 1H), 4.07 - 3.85 (m, 4H), 3.85 - 3.69 (m, 1H), 3.66 (d, *J* = 6.0 Hz, 2H), 3.51 - 3.30 (m, 1H), 1.98-1.94 (m, 2H), 1.88 - 1.66 (m, 6H).
250	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 1.6 Hz, 1H), 7.58 (s, 4H), 5.50 (s, 2H), 4.32 (dd, *J* = 12.1, 2.3 Hz, 1H), 4.09 - 3.86 (m, 3H), 3.82 - 3.68 (m, 1H), 3.63 (d, *J* = 5.8 Hz, 2H), 3.48 - 3.30 (m, 1H), 3.00 (s, 6H), 2.28 - 1.92 (m, 2H), 1.94 - 1.75 (m, 6H).
251	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.58 (s, 4H), 5.65-5.39 (m, 2H), 4.63 (d, *J* = 8.1 Hz, 1H), 4.39 - 4.28 (m, 1H), 4.08 - 3.69 (m, 5H), 3.61 - 3.24 (m, 4H), 2.98 (d, *J* = 2.2 Hz, 3H), 2.33 - 1.80 (m, 3H), 1.83 - 1.58 (m, 3H).
252	^{1}H NMR (300 MHz, CDC13): δ 8.46 (s, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.28 - 7.18 (m, 6H), 6.97 (d, *J* = 3.7 Hz, 1H), 6.44 (d, *J* = 3.7 Hz, 1H), 6.05 (s, 1H), 5.44 - 5.35 (m, 3H), 4.55 - 451 (m, 2H), 4.13 - 08 (m, 2H), 3.86 - 3.72 (m, 1H), 3.60 - 155 (m, 3H).
253	^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, *J* = 1.7 Hz, 1H), 7.59 (s, 4H), 5.78 (m, 1H), 5.55 (s, 1H), 4.35 (dd, *J* = 12.0, 2.2 Hz, 1H), 4.09 - 3.83 (m, 7H), 3.82 - 3.65 (m, 3H), 3.48 - 3.35 (m, 1H), 3.13 (s, 2H), 3.00 (s, 3H), 1.87 - 1.60 (m, 4H).

(continued)

Ex. No.	^{1}H NMR or MS Data
254	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 1.7 Hz, 1H), 7.59 (s, 4H), 5.54 (s, 1H), 5.02 (m, 1H), 4.37-4.32 (m, 1H), 4.04-3.76 (m, 6H), 3.73-3.55 (m, 5H), 3.55-3.41 (m, 3H), 2.14-2.09 (m, 2H), 1.65-1.55 (m, 2H).
255	^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 1.8 Hz, 1H), 7.59 (s, 4H), 5.88 (s, 1H), 5.55 (s, 1H), 5.43 (s, 1H), 5.22 (q, *J* = 5.5 Hz, 1H), 4.37-4.33 (m, 1H), 4.04-4.63 (m, 10H), 3.46-3.37 (m, 1H), 2.06 (m, 2H), 1.75-1.66 (m, 2H).
256	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.96 - 7.84 (m, 2H), 7.84 - 7.75 (m, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 6.87 (s, 1H), 5.44 (s, 1H), 4.37 - 4.04 (m, 3H), 4.04 - 3.81 (m, 4H), 3.61 (dd, *J* = 42.7, 13.3 Hz, 5H), 3.40 - 3.21 (m, 4H), 2.82 (d, *J* = 6.2 Hz, 2H), 1.95 (d, *J* = 13.7 Hz, 2H), 1.48 (t, *J* = 11.0 Hz, 2H).
257	^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, *J* = 1.7 Hz, 1H), 7.60 (s, 4H), 5.59 (s, 1H), 5.07 (s, 1H), 4.39-4.35 (m, 1H), 4.04-3.93 (m, 5H), 3.80-3.64 (m, 5H), 3.48-3.38 (m, 1H), 1.89-1.54 (m, 4H).
258	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 1.6 Hz, 1H), 7.58 (t, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.26 (s, 2H), 7.00-6.93 (m, 2H), 5.61 (s, 1H), 5.33 (s, 2H), 5.02 (s, 1H), 4.70 - 4.61 (m, 2H), 4.20-4.16 (m, 1H), 4.06-3.96 (m, 3H), 3.81-3.75 (m, 1H), 3.62 - 3.55 (m, 3H).
259	^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 1.8 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 5.60 (m, 1H), 4.73 (s, 1H), 4.32-4.16 (m, 2H), 3.99-3.94 (m, 2H), 3.40-3.30 (m, 4H), 2.94-2.87 (m, 1H), 2.41-2.35 (m, 1H), 1.82 (m, 1H), 1.66-1.62 (m, 2H), 1.40-1.26 (m, 2H).
260	^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J* = 1.8 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.66-5.58 (m, 2H), 4.31-4.15 (m, 2H), 4.06-3.86 (m, 4H), 3.70-3.66 (m, 2H), 3.09 (s, 2H), 2.98-2.86 (m, 4H), 2.40-2.34 (m, 1H), 1.80-1.54 (m, 4H), 1.11 - 0.95 (m, 1H).
261	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 1.6 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 5.60 (m, 1H), 5.01 (m, 1H), 4.93 (t, *J* = 7.3 Hz, 1H), 4.44-4.32 (m, 4H), 4.29-4.15 (m, 2H), 3.86-3.80 (m, 2H), 3.71 (d, *J* = 7.1 Hz, 2H), 2.94-2.86 (m, 1H), 2.45-2.34 (m, 1H).
262	^{1}H NMR (300 MHz, CD_3OD) δ 7.86 (s, 1H), 7.70 - 7.55 (s,4H), 5.47 (s, 1H), 4.38 - 4.25 (m, 2H), 4.05 - 3.86 (m, 3H), 3.86 - 3.55 (m, 4H), 3.53 - 3.30 (m, 3H), 2.10 (s, 3H), 1.96 - 1.48 (m, 4H).
263	^{1}H NMR (300 MHz, CD_3OD) δ 7.86 (s, 1H), 7.67 - 7.61 (m, 4H), 5.45 (s, 1H), 4.31 (dd, *J* = 12.0, 2.8 Hz, 2H), 4.05 - 3.88 (m, 5H), 3.85 - 3.72 (m, 1H), 3.51 - 3.35 (m, 2H), 3.16 - 3.01 (m, 2H), 1.95 - 1.81 (m, 3H), 1.38 - 1.20 (m, 2H).
264	^{1}H NMR (300 MHz, CD_3OD) δ 7.87 (t, *J* = 1.3 Hz, 1H), 7.67 - 7.61 (m, 4H), 5.47 (s, 1H), 4.06 - 3.89 (m, 3H), 3.86 - 3.63 (m, 7H), 3.49 - 3.38 (m, 1H), 1.92 - 1.69 (m, 4H).
265	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 7.6 Hz, 2H), 5.39 (d, *J* = 8.0 Hz, 1H), 5.31 (s, 2H), 4.56-4.44 (m, 2H), 4.01 (t, *J* = 9.8 Hz, 1H), 3.79-3.77 (m, 1H), 3.56 (s, 2H), 3.28-3.10 (m, 3H), 2.91 - 2.63 (m, 1H), 2.35 (m, 1H), 1.96-1.90 (m, 3H).
266	^{1}H NMR (300 MHz, CD_3OD) δ 7.87 (s, 1H), 7.71 - 7.56 (m, 4H), 5.48 (s, 1H), 4.33 (d, *J* = 11.9 Hz, 2H), 4.06 - 3.85 (m, 3H), 3.85 - 3.53 (m, 5H), 3.52 - 3.30 (m, 2H), 2.85 (s, 3H), 2.05 - 1.63 (m, 4H).
267	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 1.5 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 5.51 (s, 1H), 4.79 (d, *J* = 2.9 Hz, 1H), 4.33 (dd, *J* = 1.7, 12.0 Hz, 1H), 4.18 (br d, *J* = 7.8 Hz, 1H), 4.05 - 3.90 (m, 3H), 3.76 (dt, *J* = 3.2, 11.4 Hz, 1H), 3.48 - 3.23 (m, 4H), 2.98 (s, 3H), 2.11 (d, *J* = 10.3 Hz, 2H), 1.89 (br d, *J* = 12.7 Hz, 2H), 1.59 - 1.49 (m, 1H), 1.33 - 1.19 (m, 3H), 1.12 (m, 2H).
268	m/z 485 (M+H)
273	m/z 484 (M+H)
274	m/z 450 (M+H)
276	m/z 423 (M+H)
279	m/z 406 (M+H)

(continued)

Ex. No.	^{1}H NMR or MS Data
280	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 4H), 7.26 - 7.21 (m, 2H), 5.99 (d, *J* = 9.3 Hz, 1H), 5.33 (br s, 2H), 4.99 (m, 1H), 4.69 - 4.56 (m, 2H), 4.38 - 4.20 (m, 2H), 3.57 (s, 2H), 3.22 (dd, *J* = 9.5, 18.3 Hz, 1H), 2.62 - 2.57 (m, 1H).
282	m/z 429 (M+H)
283	m/z 428 (M+H)
284	m/z 428 (M+H)
285	^{1}H NMR (300 MHz, CDCl3) δ 7.98 (d, *J* = 1.7 Hz, 1H), 7.55 - 7.47 (m, 2H), 7.17 (dq, *J* = 8.9, 1.0 Hz, 2H), 5.51 (d, *J* = 2.8 Hz, 1H), 4.87 (s, 1H), 4.54 (d, *J* = 8.0 Hz, 1H), 4.33 (dd, *J* = 12.1, 2.1 Hz, 1H), 4.04 - 3.91 (m, 3H), 3.89 - 3.64 (m, 3H), 3.49 - 3.26 (m, 4H), 2.19 - 2.06 (m, 2H), 1.97 - 1.84 (m, 2H), 1.65-1.45 (m, 1H), 1.38 - 1.20 (m, 2H), 1.20 - 1.01 (m, 2H).
286	^{1}H NMR (300 MHz, CD_3OD) δ 7.86 (d, *J* = 1.6 Hz, 1H), 7.66 - 7.60 (m, 4H), 5.44 (t, *J* = 3.1 Hz, 1H), 4.31 (dd, *J* = 12.1, 2.9 Hz, 1H), 4.06 - 3.74 (m, 7H), 3.61 (d, *J* = 2.0 Hz, 2H), 3.53 - 3.39 (m, 3H), 2.67 (s, 3H), 2.14 - 1.99 (m, 2H), 1.72 - 1.54 (m, 2H).
287	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.84 (d, *J* = 1.8 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.12 (s, 1H), 5.44 - 5.39 (m, 1H), 4.27 (dd, *J* = 12.1, 2.5 Hz, 1H), 3.89 (m, 3H), 3.72 - 3.60 (m, 1H), 3.41 - 3.25 (m, 2H), 3.20 - 3.12 (m, 2H), 2.41 (d, *J* = 6.5 Hz, 2H), 1.80 - 1.67 (m, 4H), 1.60 - 1.43 (m, 2H), 1.07 - 0.80 (m, 4H).
288	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.83 (d, *J* = 1.8 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.15 - 7.06 (m, 1H), 5.41 (s, 1H), 4.27 (dd, *J* = 12.1, 2.5 Hz, 1H), 3.99 - 3.80 (m, 3H), 3.71 - 3.60 (m, 1H), 3.39 - 3.25 (m, 2H), 3.18 - 3.11 (m, 2H), 2.75 (d, *J* = 6.7 Hz, 2H), 1.75 - 1.57 (m, 5H), 1.57 - 1.41 (m, 1H), 1.03 - 0.79 (m, 4H).
290	^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.21 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 3.9 Hz, 1H), 6.54 (d, *J* = 2.9 Hz, 1H), 5.93 (s, 1H), 4.53 (d, *J* = 13.2 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.14 - 4.05 (m, 2H), 4.00 - 3.91 (m, 2H), 3.66 (dt, *J* = 2.7, 11.6 Hz, 1H), 3.57 - 3.43 (m, 3H), 2.81 (s, 3H), 2.69 - 2.55 (m, 2H), 1.97 (m, 1H), 1.54 (br d, *J* = 11.2 Hz, 2H), 1.32 - 1.19 (m, 2H).
291	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.56 (s, 4H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 5.53 (s, 1H), 5.15 - 5.06 (m, 1H), 4.58 (d, *J* = 5.4 Hz, 2H), 4.32 (d, *J* = 12.2 Hz, 1H), 4.03 - 3.86 (m, 3H), 3.80 - 3.70 (m, 1H), 3.40 (t, *J* = 10.5 Hz, 1H), 2.60 (s, 1H).
292	^{1}H NMR (300 MHz, CD_3OD) δ 7.85 (d, *J* = 1.6 Hz, 1H), 7.67 - 7.62 (m, 4H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 5.51 - 5.44 (m, 1H), 4.62 (s, 2H), 4.33 (dd, *J* = 12.1, 2.8 Hz, 1H), 4.07 - 3.89 (m, 3H), 3.85 - 3.75 (m, 1H), 3.66 (s, 2H), 3.53 - 3.37 (m, 1H).
293	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 8.00 - 7.92 (m, 2H), 7.60 (s, 4H), 5.60 (s, 1H), 5.22 (s, 1H), 4.81 (d, *J* = 5.9 Hz, 2H), 4.38 (dd, *J* = 2.0, 12.2 Hz, 1H), 4.09 - 3.99 (m, 2H), 3.95 (d, *J* = 11.2 Hz, 1H), 3.78 (dt, *J* = 2.7, 11.4 Hz, 1H), 3.44 (ddd, *J* = 3.4, 11.0, 13.9 Hz, 1H), 3.22 (s, 3H).
294	m/z 505 (M+H)
295	m/z 469 (M+H)
296	m/z 427 (M+H)
297	m/z 504 (M+H)
299	m/z 450 (M+H)
300	m/z 422 (M+H)
301	m/z 450 (M+H)
302	m/z 420 (M+H)
303	m/z 448 (M+H)
304	m/z 436 (M+H)

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Ex. No.	^{1}H NMR or MS Data
305	m/z 485 (M+H)
306	m/z 440 (M+H)
307	m/z 460 (M+H)
308	m/z 488 (M+H)
309	m/z 520 (M+H)
310	m/z 463 (M+H)
311	m/z 456 (M+H)
312	m/z 456 (M+H)
313	m/z 410 (M+H)
314	m/z 412 (M+H)
315	m/z 412 (M+H)
316	m/z 424 (M+H)
317	m/z 424 (M+H)
318	m/z 466 (M+H)
319	m/z 497 (M+H)
320	m/z 554 (M+H)
323	m/z 490 (M+H)
324	m/z 518 (M+H)
325	m/z 455 (M+H)
326	^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.40 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.69 - 7.60 (m, 1H), 7.25 - 7.17 (m, 4H), 6.95 (d, *J* = 3.7 Hz, 1H), 6.42 (d, *J* = 3.7 Hz, 1H), 6.21 (s, 1H), 5.40 (s, 2H), 5.33 (br s, 2H), 4.49 (d, *J* = 12.5 Hz, 1H), 4.39 (d, *J* = 12.8 Hz, 1H), 4.18 - 4.05 (m, 2H), 3.90 - 3.76 (m, 1H), 3.68 - 3.58 (m, 1H), 3.56 (s, 2H).
327	m/z 504 (M+H)
328	^{1}H NMR (300 MHz, $CDCl_3$): δ 8.91 (s, 1H), 8.38 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.25 - 7.16 (m, 4H), 6.91 (d, *J* = 3.7 Hz, 1H), 6.35 (d, *J* = 3.7 Hz, 1H), 5.96 (s, 1H), 5.47 - 5.29 (m, 4H), 4.93 (d, *J* = 11.3 Hz, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.04 (dd, *J* = 3.7, 11.3 Hz, 2H), 3.88 - 3.62 (m, 2H), 3.55 (s, 2H).
329	m/z 534 (M+H)
330	m/z 534 (M+H)

Biological evaluation

[0246] The activity of the compounds was evaluated using a Fluorescence Polarization (FP) Assay and, in most cases, a Th17 Assay and/or RORγ Reporter assay (also referred to as Gal4 assay). The FP assay is an in vitro assay monitoring binding within the ligand binding pocket. The RORγ and the Th17 assays are both cell-based assays monitoring functional activity of the compound assayed.

Fluorescence Polarization (FP) Assay

[0247] A buffer containing 10 mM Hepes, 150 mM NaCl, 1 mM DTT, 0.05% Pluronic F-127 detergent (all from Sigma), and 100 nM human RORγt (Ligand Binding Domain obtained from Crelux (Planegg, Germany), batch no PC5032-1) was complemented with 1 μl test compounds diluted in 100% DMSO. The total volume was 25 μl, in a black Perkin Elmer OptiPlate. As negative control, 1 μl DMSO was used. Samples were incubated at room temperature for 30 min,

followed by addition 5 μl of probe diluted in assay buffer to a concentration of 125 nM (final concentration of probe is 25 nM). The probe is a fluorescently labeled (TAMRA) RORyt ligand identified by Nuevolution with a total molecular weight of 910 g/mole as shown in Graph A in figure 1. Graph (B) in figure 2 shows the polarization signal rises with increasing concentration of human RORyt (LBD), using 50 nM TAMRA-labelled probe concentration. Graph (C) of figure 2 shows the RORyt inhibitor SR2211 (1,1,1,3,3,3-hexafluoro-2-(2-fluoro-4'-((4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)-[1,1'-biphenyl]-4-yl)propan-2-ol; see Kumar et al, ACS Chem. Biol., 2012, 7 (4), pp 672-677) inhibits the probe from binding RORyt with an IC50 of 0.36 μM, which is close to the value reported in the literature. The plate was incubated for 10 min at room temperature and fluorescence polarization was read using an Envision 2102 plate reader (Perkin Elmer) with the TAMRA FP optical module installed.

Th17 Assay

[0248] Human peripheral blood mononuclear cells (PBMCs) were isolated from buffy coats of healthy human volunteers using the Ficoll paque PLUS kit (GE Healthcare, cat no 17-1440-02), as instructed by the manufacturer. Naive CD4+ T cells were isolated with Naive CD4+ T cell kit, human (Milteny Biotec, cat no 130-094-131). The following modifications were made to the manufacturer's protocol: 1) Incubation with Biotin-Antibody Cocktail and Anti-Biotin MicroBeads was prolonged to 30 minutes, and 2) Cells were washed with 40 mL of Miltenyi buffer. Differentiation of Th17 cells in anti-CD3 (BD Pharmingen, 5 μg/ml) coated 96-well plates (400,000 cells/well, 160 μl RPMI 1640 + 10 % Fetal Bovine Serum) containing 5 μg/ml anti-CD28 (BD Pharmingen), 10 ng/ml IL-2 (R&D Systems), 2.5 ng/ml TGFβ-1 (R&D Systems), 20 ng/ml IL-1β (R&D Systems), 20 ng/ml IL-6 (R&D Systems), 30 ng/ml IL-23 (R&D Systems), 2.5 μg/ml anti-IL-4 (R&D Systems) and 1 μg/ml anti-IFNy (R&D Systems) and with test compound during the entire differentiation (or vehicle, 0.1% DMSO for control). Test compounds were tested in triplicates, diluted 1000-fold in medium (final DMSO concentration is 0.1%). Incubated for seven days at 37°C, 5 % CO_2, 95% humidity, and 2-fluoro-4'-[[4-(4-pyridinylmethyl)-1-piperazinyl]methyl]-α,α-bis(trifluoromethyl)-[1,1'-biphenyl]-4-methanol (SR2211 Calbiochem, Cat. No. 557353) was used as positive control. As negative control, cells were differentiated into Th0 using 5 μg/ml anti-CD28 (BD Pharmingen), 10 ng/ml IL-2 (R&D Systems), 2 μg/ml anti-IL4 (R&D Systems) and 2 μg/ml anti-IFNy (R&D Systems) are negative control. IL-17 levels in supernatants were measured with ELISA (R&D Systems).

RORγ *Reporter Assay (Gal4)*

[0249] Cell-based RORγ functional assays were performed using a commercially available assay product (INDIGO Biosciences, State College, PA, USA; product #IB04001). The RORγ reporter cells are HEK293t cells transfected with one vector that provides high level constitutive expression of a hybrid protein comprised of the yeast Gal4-DNA binding domain fused to the ligand binding domain of human RORγ, and a second vector comprising the firefly luciferase cDNA functionally linked to the upstream activation sequence (UAS) of yeast Gal4. A suspension of RORγ Reporter Cells was prepared using the protocol and culture medium provided in the kit product, and 100 μl of the Reporter Cell suspension was then dispensed into wells of a white, collagen-treated, 96-well assay plate. Concentrated stocks of test compounds were prepared in DMSO, then further diluted using media provided in the kit to generate '2x-concentration' treatment media. 100 μl of medium for each respective treatment concentration dispensed into triplicate assay wells, thereby combining with the reporter cells. All media formulations contained 10% charcoal stripped Fetal Bovine Serum, but are otherwise proprietary to INDIGO Biosciences. Final treatment concentrations for each test compound were 1,000 nM and 100 nM, each with 0.1% residual DMSO. Separate control treatments were media supplemented with vehicle only (0.1% DMSO) to determine the constitutive level of RORγ activity in the reporter cells, and the reference inverse-agonist ursolic acid (f.c. 6,000 nM to 8.2 nM in 3-fold decrements) to establish a positive control inverse-agonist dose response. Assay plates were placed in a 37°C, 5% CO_2, 85% humidity incubator for 24 hour. Treatment media were then discarded, 100 μl of luciferase detection reagent was added to each well, and relative light units (RLUs) were quantified from each assay well using a plate reading luminometer. Values of average RLU +/- standard deviation were computed for all treatment sets, followed by the calculations of fold-reduction: [Average $RLU_{Vehicle}$ / Average $RLU_{Test\ Cmpd}$]. Percent-reduction of RORγ activity in response to respective test compound treatments was calculated: [100*(1-[Ave $RLU_{Test\ Cmpd}$ / Ave $RLU_{Vehicle}$)] where the theoretical minimum reduction (0% reduction) derives from Vehicle treatment only, no treatment compound.

[0250] In some aspects it may be of interest to provide compounds with selective modulation of RORγ for example compounds that are selective to RORγ over RORα, compounds that are selective for RORγ versus RORβ, and compounds that are selective for RORγ versus BOTH RORα and RORβ. It may also be of interest to provide compounds that are selective for RORγ versus further nuclear hormone receptors such as CAR1, FXR, GR, LXRα, LXRβ, PPARα, PXR, RARα, RXRα, TRα, VDR. It is apparent to those skilled in the art that these nuclear hormone receptors are merely examples, and that selectivity against other nuclear receptors may also be of interest. It may for example be of interest to provide compounds that modulate RORγ and one or more further nuclear hormone receptors, as well as compounds

that modulate both RORγ and RORα, or RORγ and RORβ. It may also be of interest to provide compounds that modulate RORγ and BOTH RORα and RORβ, as well as compounds that modulate both RORγ and one or more further nuclear hormone receptors such as CAR1, FXR, GR, LXRα, LXRβ, PPARα, PXR, RARα, RXRα, TRα, VDR. It is apparent to those skilled in the art that these nuclear hormone receptors are merely examples, and that modulation of even other nuclear receptors may also be of interest. By substituting the ligand binding domain of another nuclear hormone receptor for the ligand binding domain of RORγ, the reporter assay (Gal4) may be modified to provide activity data for compounds against said other nuclear hormone receptor. Those skilled in the art know how to accomplish such modification. By comparing activity against RORγ to activity against another nuclear hormone receptor in this assay, the selectivity of a compound towards RORγ versus said other nuclear hormone receptor can be established. A compound may be said to be selective for RORγ versus another nuclear hormone receptor if the activity of the compound against RORγ is greater than 5, 10, 20, or 100 fold higher for RORγ than for said other nuclear receptor. The compound(s) or pharmaceutical composition(s) described herein may modulate the activity of an RORγ receptor to a larger extent than it modulates the activity of RORα and/or RORβ receptors.

[0251] The results of the Fluorescence Polarization (FP) Assay, Th17 Assay, and RORγ Reporter (Gal4) Assay are shown in Tables 2-5 below.

Table 2. Activity Data of Example Compounds obtained from the Fluorescence Polarization (FP) Assay.

Example. No.	FP activity range (nM)	Example. No.	FP activity range (nM)
4	<500	**188**	<500
5	<500	**189**	<500
6	<10000	**190**	<500
9	<500	**191**	<500
11	<500	**192**	<500
13	<10000	**193**	<10000
14	<10000	**194**	<2000
15	<10000	**195**	<500
17	<500	**196**	<500
18	<500	**197**	<500
19	<500	**198**	<500
20	<2000	**199**	<1000
21	<10000	**200**	<1000
23	<500	**201**	<500
24	<500	**202**	<10000
26	<500	**203**	<2000
29	<1000	**204**	<500
30	<500	**205**	<500
31	<10000	**206**	<1000
32	<500	**207**	<500
33	<10000	**208**	<500
34	<1000	**209**	<1000
35	<500	**210**	<1000
36	<2000	**211**	<1000
37	<1000	**212**	<10000
38	<2000	**213**	<10000
39	<10000	**214**	<10000

(continued)

Example. No.	FP activity range (nM)	Example. No.	FP activity range (nM)
40	<1000	**215**	<10000
41	<2000	**216**	<10000
42	<2000	**217**	<10000
43	<1000	**218**	<10000
44	<10000	**219**	<10000
45	<10000	**220**	<500
46	<1000	**221**	<500
48	<2000	**222**	<2000
51	<1000	**223**	<500
52	<2000	**224**	<500
53	<1000	**225**	<500
54	<1000	**226**	<10000
55	<10000	**227**	<500
56	<2000	**228**	<500
57	<10000	**229**	<500
58	<10000	**230**	<500
59	<10000	**231**	<500
60	<2000	**232**	<500
61	<10000	**233**	<500
62	<500	**234**	<1000
63	<2000	**235**	<2000
64	<2000	**236**	<500
65	<500	**237**	<500
66	<2000	**238**	<10000
67	<2000	**239**	<500
68	<2000	**240**	<500
69	<1000	**241**	<1000
70	<2000	**242**	<2000
71	<10000	**243**	<500
72	<1000	**244**	<2000
73	<2000	**245**	<1000
74	<2000	**246**	<500
79	<500	**247**	<10000
81	<500	**248**	<1000
85	<500	**249**	<10000
88	<500	**250**	<10000
89	<500	**251**	<10000
90	<1000	**252**	<500

(continued)

Example. No.	FP activity range (nM)	Example. No.	FP activity range (nM)
91	<500	**253**	<1000
93	<500	**254**	<500
94	<500	**255**	<2000
95	<1000	**256**	<10000
97	<1000	**257**	<500
98	<1000	**258**	<500
100	<2000	**259**	<500
105	<10000	**260**	<500
106	<10000	**261**	<1000
107	<10000	**262**	<1000
108	<10000	**263**	<500
109	<2000	**264**	<500
110	<10000	**265**	<500
111	<500	**266**	<500
113	<500	**267**	<500
114	<1000	**268**	<10000
115	<500	**273**	<500
116	<1000	**274**	<2000
117	<500	**276**	<2000
118	<10000	**278**	<500
119	<1000	**280**	<500
120	<10000	**282**	<10000
122	<10000	**283**	<1000
123	<10000	**284**	<500
126	<2000	**285**	<500
128	<500	**286**	<2000
129	<500	**287**	<500
130	<10000	**288**	<500
131	<2000	**290**	<500
132	<10000	**291**	<1000
134	<10000	**292**	<500
135	<10000	**293**	<1000
136	<2000	**294**	<10000
137	<10000	**295**	<500
138	<500	**296**	<10000
139	<2000	**297**	<10000
140	<500	**299**	<1000
141	<2000	**300**	<10000

(continued)

Example. No.	FP activity range (nM)	Example. No.	FP activity range (nM)
142	<2000	**301**	<500
143	<2000	**302**	<500
144	<10000	**303**	<500
145	<10000	**304**	<500
146	<2000	**305**	<500
147	<2000	**306**	<500
148	<1000	**307**	<2000
150	<10000	**308**	<10000
151	<10000	**309**	<2000
152	<500	**310**	<500
154	<500	**311**	<500
155	<10000	**312**	<500
159	<2000	**313**	<500
161	<500	**314**	<10000
164	<500	**315**	<10000
165	<500	**316**	<500
166	<500	**317**	<10000
167	<500	**318**	<500
168	<500	**319**	<500
169	<500	**320**	<500
170	<10000	**323**	<500
175	<10000	**324**	<500
178	<500	**325**	<1000
181	<10000	**326**	<500
182	<500	**327**	<1000
183	<500	**328**	<500
184	<500	**329**	<2000
185	<1000	**330**	<2000
186	<500		

Table 3. Activity Data of Example Compounds obtained from the Th17 Assay.

Example. No.	Th17 activity range @ 1 μM (% inhibition)	Example. No.	Th17 activity range @ 1 μM (% inhibition)
6	>20	**67**	>80
13	>20	**77**	>50
16	>0	**78**	>50
18	>80	**79**	>50
19	>80	**80**	>50

(continued)

Example. No.	Th17 activity range @ 1 μM (% inhibition)	Example. No.	Th17 activity range @ 1 μM (% inhibition)
29	>50	**81**	>80
30	>50	**83**	>20
33	>20	**85**	>80
35	>50	**88**	>80
36	>50	**89**	>20
38	>50	**91**	>80
40	>80	**94**	>80
62	>80		

Table 4. Activity Data of Example Compounds obtained from the RORγ Reporter Assay (Gal4) at 1μM.

Example. No.	Gal4 activity range @ 1 μM (% inhibition)	Example. No.	Gal4 activity range @ 1 μM (% inhibition)
14	>0	**220**	>80
17	>80	**221**	>80
20	>50	**222**	>80
30	>80	**223**	>80
31	>0	**224**	>80
39	>20	**225**	>80
42	>20	**226**	>50
43	>80	**227**	>80
51	>80	**228**	>80
52	>80	**229**	>80
53	>20	**230**	>80
54	>50	**231**	>80
56	>20	**232**	>80
60	>20	**233**	>80
62	>80	**234**	>50
63	>20	**235**	>50
64	>20	**236**	>80
65	>20	**237**	>80
66	>50	**238**	>50
67	>80	**239**	>80
68	>80	**240**	>80
69	>50	**245**	>80
72	>80	**246**	>80
73	>20	**247**	>80
74	>80	**248**	>80

(continued)

Example. No.	Gal4 activity range @ 1 μM (% inhibition)	Example. No.	Gal4 activity range @ 1 μM (% inhibition)
79	>50	**252**	>80
81	>80	**253**	>80
84	>20	**254**	>80
85	>80	**255**	>50
86	>20	**257**	>80
87	>20	**258**	>80
89	>80	**259**	>80
90	>20	**260**	>80
91	>80	**261**	>80
93	>50	**262**	>50
94	>80	**263**	>80
95	>80	**264**	>80
96	>20	**265**	>80
97	>80	**266**	>80
98	>80	**267**	>80
99	>50	**273**	>80
100	>20	**274**	>50
104	>20	**276**	>20
106	>20	**279**	>50
107	>0	**280**	>20
109	>20	**282**	>0
110	>0	**283**	>20
111	>80	**284**	>50
112	>20	**285**	>20
113	>80	**286**	>20
114	>80	**287**	>80
115	>80	**288**	>80
116	>50	**290**	>80
117	>80	**291**	>50
118	>20	**292**	>20
119	>80	**295**	>80
121	>50	**299**	>80
123	>20	**300**	>20
124	>20	**301**	>80
126	>50	**302**	>50
190	>80	**303**	>80
191	>80	**304**	>80

(continued)

Example. No.	Gal4 activity range @ 1 μM (% inhibition)	Example. No.	Gal4 activity range @ 1 μM (% inhibition)
197	>80	**305**	>80
198	>80	**306**	>80
199	>80	**307**	>50
200	>80	**308**	>50
201	>80	**313**	>80
202	>50	**316**	>80
203	>50	**318**	>20
204	>80	**319**	>0
205	>80	**320**	>80
206	>80	**323**	>80
207	>80	**324**	>80
208	>80	**326**	>80
209	>50	**327**	>80
210	>80	**328**	>80
211	>50		

Table 5. Activity Data of Example Compounds obtained from the RORγ Reporter Assay (Gal4) at 0.1 μM.

Example. No.	Gal4 activity range @ 0.1 μM (% inhibition)	Example. No.	Gal4 activity range @ 0.1 μM (% inhibition)
73	>0	**227**	>80
89	>20	**228**	>20
90	>0	**229**	>50
91	>20	**230**	>50
93	>0	**231**	>50
94	>80	**232**	>50
95	>20	**233**	>20
96	>0	**234**	>0
97	>20	**235**	>0
98	>20	**236**	>80
99	>20	**237**	>80
104	>0	**238**	>0
111	>50	**239**	>20
112	>0	**240**	>80
113	>50	**245**	>20
114	>20	**246**	>20
115	>50	**247**	>20
116	>20	**248**	>20

(continued)

Example. No.	Gal4 activity range @ 0.1 μM (% inhibition)	Example. No.	Gal4 activity range @ 0.1 μM (% inhibition)
117	>50	**252**	>80
118	>0	**253**	>50
119	>20	**254**	>50
121	>20	**255**	>20
123	>0	**257**	>50
126	>20	**258**	>80
128	>50	**259**	>50
129	>50	**260**	>50
131	>20	**261**	>20
140	>20	**262**	>20
148	>50	**263**	>50
152	>0	**264**	>20
161	>20	**265**	>80
164	>20	**266**	>80
165	>50	**267**	>80
167	>0	**273**	>20
168	>50	**274**	>20
169	>0	**276**	>0
182	>50	**279**	>20
183	>50	**280**	>0
185	>50	**282**	>0
186	>0	**283**	>0
188	>0	**284**	>20
189	>20	**285**	>0
190	>80	**286**	>20
191	>50	**287**	>50
192	>50	**288**	>80
195	>80	**290**	>50
196	>80	**291**	>0
197	>80	**292**	>0
198	>20	**295**	>20
199	>20	**299**	>0
200	>20	**300**	>20
201	>0	**301**	>50
202	>0	**302**	>20
203	>0	**303**	>80
204	>50	**304**	>20

(continued)

Example. No.	Gal4 activity range @ 0.1 μM (% inhibition)	Example. No.	Gal4 activity range @ 0.1 μM (% inhibition)
205	>50	**305**	>50
206	>20	**306**	>50
207	>20	**307**	>20
208	>50	**308**	>20
209	>20	**313**	>20
210	>50	**316**	>20
211	>0	**318**	>20
220	>20	**320**	>80
221	>50	**323**	>80
222	>20	**324**	>50
223	>50	**326**	>50
224	>80	**327**	>20
225	>80	**328**	>80

[0252] As can be seen from the tables above, the compounds were found to show beneficial activity across the assays. Figure 3 graphically illustrates the assay results of example no. **89.**

[0253] According to an embodiment, compounds having inhibition values of greater than 80% in both an RORγ Reporter Assay (Gal4) and a Th17 Assay are disclosed herein. According to an embodiment the compounds have inhibition values of greater than 80% in both a RORγ Reporter Assay (Gal4) and a Th17 Assay, and a FP activity range less than 1000nM, such as less than 500nM.

[0254] According to an embodiment the compounds are having inhibition values of greater than 80% in at least one of a RORγ Reporter Assay (Gal4) and a Th17 Assay. According to an embodiment the compounds have inhibition values of greater than 80% in at least one of a RORγ Reporter Assay (Gal4) and a Th17 Assay, and a FP activity range less than 1000nM, such as less than 500nM.

[0255] According to an embodiment the compounds are having inhibition values of greater than 50% in both an RORγ Reporter Assay (Gal4) and a Th17 Assay. According to an embodiment the compounds have inhibition values of greater than 50% in both a RORγ Reporter Assay (Gal4) and a Th17 Assay, and a FP activity range less than 1000nM, such as less than 500nM.

[0256] According to an embodiment the compounds are having inhibition values of greater than 50% in at least one of a RORγ Reporter Assay (Gal4) and a Th17 Assay. According to an embodiment the compounds have inhibition values of greater than 50% in at least one of a RORγ Reporter Assay (Gal4) and a Th17 Assay, and a FP activity range less than 2000nM, such as less than 1000nM, such as less than 500nM.

[0257] According to an embodiment the compounds are having inhibition values of greater than 20% in both an RORγ Reporter Assay (Gal4) and a Th17 Assay. According to an embodiment the compounds have inhibition values of greater than 20% in both a RORγ Reporter Assay (Gal4) and a Th17 Assay, and a FP activity range less than 2000nM, such as less than 1000nM, such as less than 500nM.

[0258] According to an embodiment the compounds are having inhibition values of greater than 50% in a RORγ Reporter Assay (Gal4) at 1μM and inhibition values of greater than 20% in a RORγ Reporter Assay (Gal4) at 0.1 uM. According to an embodiment the compounds are having inhibition values of greater than 50% in a RORγ Reporter Assay (Gal4) at 1μM and inhibition values of greater than 20% in a RORγ Reporter Assay (Gal4) at 0.1μM, and a FP activity range less than 2000nM, such as less than 1000nM, such as less than 500nM.

[0259] According to an embodiment the compounds are having inhibition values of greater than 20% in at least one of a RORγ Reporter Assay (Gal4) and a Th17 Assay. According to an embodiment the compounds have inhibition values of greater than 20% in at least one of a RORγ Reporter Assay (Gal4) and a Th17 Assay, and a FP activity range less than 2000nM, such as less than 1000nM, such as less than 500nM.

Experimental Autoimmune Encephalomyelitis (EAE) study

[0260] EAE is an animal model for multiple sclerosis used to evaluate the efficacy of test compounds. EAE was induced at WuXi AppTec (Shanghai) in female C57BL/6 mice obtained from SLAC Laboratories, Shanghai by injection of 100 μl (100 μg MOG_{35-55} peptide in complete Freund's adjuvant containing 200 μg M.tuberculosis/mouse) emulsion (with a 25-G needle) subcutaneously in the shaved back of the mouse. Each mouse was also given 200 ng PTX in 200 μl of PBS by intraperitoneal injection at 0 and 48 hours after immunization. For treatment, compound or vehicle (2% DMSO, 10% HP-β-CD in MilliQ water) was given orally twice daily at various doses selected from 3, 10, and 30 mg/kg, beginning at the day of EAE induction. Treatment lasted for 25 days, and the animals were scored daily for EAE symptoms using the following scoring system: 0, Normal mouse; no overt signs of disease; 1, Limp tail or hind limb weakness but not both; 2 Limp tail and hind limb weakness; 3 Partial hind limb paralysis; 4 Complete hind limb paralysis; 5 Moribund state; death by EAE: sacrifice for humane reasons. The clinical score can be expressed as the mean score for each treatment group +/- S.E.M.

[0261] Results:_Example 204 was tested in the EAE study at 10 and 30 mg/kg. Example 204 was shown to delay onset and lower clinical score at both doses.

Collagen-induced Arthritis (CIA) study

[0262] Collagen-induced arthritis is an animal model of rheumatoid arthritis used to evaluate the efficacy of test compounds. CIA was induced at Washington Biotechnology Inc. (Baltimore) in male DBA/1J mice (Jackson Laboratories) by subcutaneous injection at the base of the tail with 50 μl of a bovine collagen/complete Freund's adjuvant emulsion. After 21 days, the mice were further boosted by a further subcutaneous injection of 50 μl of a collagen/incomplete Freund's adjuvant emulsion. For treatment, compound or vehicle (2% DMSO, 10% HP-β-CD in MilliQ water) was given orally twice daily at various doses selected from 3, 10, 30 mg/kg, beginning at the day of CIA induction (Prophylactic setting), or after disease initiation (at day 27, therapeutic setting).Treatment lasted until day 41, and the animals were scored three times weekly. Each paw was scored and the sum of all four scores was recorded as the Arthritic Index (AI). The maximum possible AI was 16. 0 = no visible effects of arthritis; 1 = edema and/or erythema of one digit; 2 = edema and/or erythema of 2 joints; 3 = edema and/or erythema of more than 2 joints; 4 = severe arthritis of the entire paw and digits including limb deformation and ankylosis of the joint. The Arthritis Index for each treatment can be expressed as the mean score for each treatment group +/- S.E.M.

[0263] Results:_Example 204 was tested in the CIA study at 10 and 30 mg/kg in prophylactic setting and at 30 mg/kg in therapeutic setting. Example 204 was shown to significantly reduce disease severity at both prophylactic doses. Example 204 was shown to arrest disease development in the therapeutic setting.

[0264] In summary, compounds disclosed herein have been found to at least modulate the activity of RORγ. 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.

Claims

1. A compound of Formula (I)

Formula (I)

or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, and stereoisomers thereof, wherein:

Y is NR or O;
R is hydrogen or substituted or unsubstituted C_{1-4} alkyl;
R_1 is selected from the group consisting of hydrogen, -OH, halogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, and substituted or unsubstituted C_{2-4} alkenyl;
R_2 is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, -CN, and -OH;
or R and R_2 are combined to form a substituted or unsubstituted fused ring;
R_3 is selected from the group consisting of hydrogen, halogen, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, oxo, $-C(=O)R_{10}$;
R_{4a} is selected from the group consisting of hydrogen, halogen, -OH, -CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_{1-6} alkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroaryl-C_{1-6} alkyl;
R_{4b} is selected from the group consisting of hydrogen, halogen, oxo, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, and - $C(=O)R_{10}$;
R_5 is selected from the group consisting of $-(CR_8R_9)pOR_{12}$, $-(CR_8R_9)p-CR_{13}R_{14}R_{15}$, $-(CR_8R_9)p-C(=O)OR_7$, and $-(CR_8R_9)p-C(=O)NR_8R_9$;
n, m, and p are integers independently selected from the group consisting of 0, 1, 2, 3 and 4;
R_{6a}, R_{6b} are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{2-9} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, or R_{6a} and R_{6b} are taken together to form an oxo group or a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl, or R_{6a} and R_{13} are taken together to form a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-5} heteroalicyclyl;
R_7, R_8, R_9, and R_{12}, are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl;
R_{10} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, -OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, and C_{3-7} cycloalkyl;
R_{13} is absent, or selected from the group consisting of hydrogen, -OH, -CN, fluorine, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, and $-(CR_8R_9)p-C(=O)OR_7$, $-(CR_8R_9)p-SO_2R_7$ and $-(CR_8R_9)p-C(=O)NR_8R_9$;
R_{14} and R_{15} are independently selected from the group consisting of hydrogen, and substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl; or R_{14} and R_{15} are combined to form a ring system selected from the group consisting of substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{2-9} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;
B is a ring system selected from the group consisting of aryl, heteroaryl, and bicyclic heteroalicyclyl, provided that it is not 5,6-dichloro-1H-benzo[d]imidazol-2-yl when R_1 and R_2 both are hydrogen;
C is a ring system selected from C_{2-9} heteroalicyclyl;
wherein B is attached to a carbon atom adjacent the N atom of ring system C; and
with the proviso the compound is not:

2. The compound according to claim 1, wherein R and R_2 in combination with the pyrimidine ring of formula (I) form a pyrrolo[2,3-d]pyrimidine or 6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine; or the compound is a compound of Formula (IIa):

Formula (IIa)

wherein:

R_{4e} and R_{4d} are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, and -OH; or
R_{4e} and R_{4d} are independently selected from the group consisting of hydrogen, methyl, and fluorine.

3. The compound according to any one of claims 1 to 2, wherein R_5 is - $(CR_8R_9)p$-$C(=O)OR_7$, or -$(CR_8R_9)p$-$C(=O)NR_8R_9$; or - $(CR_8R_9)_pOR_{12}$; or -$(CR_8R_9)p$-$CR_{13}R_{14}R_{15}$.

4. The compound according to claim 3, wherein R_{14} and R_{15} are combined to form a ring system selected from the group consisting of substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{3-7} cycloalkenyl, substituted or unsubstituted C_{2-6} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; or

R_{14} and R_{15} are combined to form a ring system selected from the group consisting of substituted or unsubstituted C_{4-7} cycloalkyl, substituted or unsubstituted C_{6-12} membered aryl, substituted or unsubstituted 4-membered heteroalicyclyl, substituted or unsubstituted 5-membered heteroaryl, substituted or unsubstituted 5-membered heteroalicyclyl, substituted or unsubstituted 6-membered heteroaryl, a substituted or unsubstituted 6-membered heteroalicyclyl, substituted or unsubstituted 7-membered heteroaryl, and a substituted or unsubstituted 7-membered heteroalicyclyl; or
R_{14} and R_{15} are combined to form a ring system selected from the group consisting of phenyl, naphthyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, thietanyl, pyrrolyl, pyrazoleyl imidazolyl, pyrrolidinyl, imidazolinyl, pyrazolidinyl, thiazolidinyl, isothiazolidinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxathianyl thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxolanyl, dioxanyl, furyl, dihydrofuranyl, furazanyl, tetrahydrofuryl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, dithiolanyl, dithianyl, thiopyranyl, thianyl, thienyl, oxetanyl, quinolyl,

isoquinolyl, indolyl, iso-indolyl, and tetrahydrothienyl, any of which may be substituted or unsubstituted.

5. The compound according to claim 4, wherein the ring system formed by the combination of R_{14} and R_{15} is substituted with $-(CH_2)q(R_{5a})$ wherein R_{5a} is independently selected from the group consisting of $-CH_2COOR_{20}$, $-CH_2CONR_{21}R_{22}$, oxo, -CN, $-CH_2$-CN, C_{1-6} alkyl, $-CH_2$-imidazolyl, $-CH_2-SO_2R_{20}$, $-CH_2C(CH_3)_2(OR_{20})$,$-OR_{20}$, $-CH_2$-triazolyl, $-CF_3$, dimethyl substituted-imidazolyl-2,4-dione, $-CH_2-SO_2NR_{21}R_{22}$, morpholinyl, -C(=O)-morpholinyl, piperidyl-CH_2OR_{20}, $-OCH_2$-tetrahydrofuryl, piperazinonyl, piperidinyl-$CONR_{21}R_{22}$, -OH, $-CONR_{21}R_{22}$,$-CH(OR_{20})CH_3$, $-COOR_{20}$, $-CH_2$-pyrrolidyl, C_{1-6} alkylene-OH, cyclopentyl, pyrrolidonyl, , $-NR_{21}SO_2R_{20}$, tetrazolyl, $-CH_2$-tetrazolyl, $-CH_2OR_{20}$, acyl, $-SOR_{20}$, $-SO_3R_{20}$, $-SO_2R_{20}$, $-SO_2NR_{21}R_{22}$, and halogen;

R_{20}, R_{21}, and R_{22} are independently of each other selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, -CN, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted C_{2-6} heteroalicyclyl; and
q is an integer selected from 0, 1 or 2.

6. The compound according to any one of claims 3 to 5, wherein R_{13} is absent or selected from the group consisting of hydrogen, -CN, $-CH_3$, fluorine, -OH, $-CH_2OH$, $-OCH_3$, $-CH_2CH_2OH$, $-CO_2H$, $-CO_2-C_{1-4}$-alkyl and $-CONR_8R_9$ wherein R_8 and R_9 are independently of each other selected from hydrogen, C_{1-4} alkyl, C_{1-4} aminoalkyl, or R_8 and R_9 are combined to form a C_2-C_6 heteroalicyclyl.

7. The compound according to any one of claims 1 to 6, wherein Y is NR, and

R is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} hydroxyalkyl; or
R is hydrogen.

8. The compound according to any one of claims 1 to 7, wherein R_1 is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; or

R_1 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} hydroxyalkyl; or
R_1 is hydrogen or $-CF_3$.

9. The compound according to any one of claims 1 to 8, wherein R_2 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} hydroxyalkyl; or

R_2 is halogen; or
R_2 is fluorine.

10. The compound according to any one of claims 1 to 9, wherein R_3 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, oxo, C_{1-4} alkoxy and C_{1-4} haloalkoxy; or

R_3 is selected from the group consisting of hydrogen, methyl, fluorine, chlorine, and oxo; and/or
whenever m is an integer selected from 2, 3, or 4, at least two of the R_3 groups present are bound to the same atom of ring system C.

11. The compound according to any one of claims 1 to 10, wherein R_{4a} is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, -CN, C_1-C_6 alkoxy, C_{1-6} haloalkoxy, C_3-C_5 cycloalkyl, heteroaryl and aryl; or

R_{4a} is selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_1-C_4 alkoxy, C_{1-4} haloalkoxy, and heteroaryl; or
R_{4a} is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, tert-butyl, chlorine, fluorine, methoxy, ethoxy, C_{1-2} haloalkyl, C_{1-2} haloalkoxy, and triazolyl; or
R_{4a} is selected from the group consisting of $-CF_3$, $-CHF_2$, $-OCF_3$, and $-OCHF_2$.

12. The compound according to any one of claims 1 to 11, wherein R_{4b} is selected from the group consisting of hydrogen, oxo, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_1-C_4 alkoxy, and C_{1-4} haloalkoxy; or

R_{4b} is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, tert-butyl, chlorine, fluorine, methoxy,

ethoxy, -OH, C_{1-2} haloalkyl, and C_{1-2} haloalkoxy; or
R_{4b} is selected from the group consisting of $-CF_3$, $-CF_2CF_3$, $-CHF_2$, $-OCF_3$,$-OCF_2CF_3$, and $-OCHF_2$.

13. The compound according to any one of claims 1 to 12, wherein R_{6a} is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, and substituted or unsubstituted aryl; or

R_{6a} and R_{13} are taken together to form a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl, or R_{6a} and R_{6b} are taken together to form a ring system selected from substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{2-9} heteroalicyclyl; or
R_{6a} is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and aryl; or
R_{6a} is hydrogen.

14. The compound according to any one of claims 1 to 13, wherein R_{6b} is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted aryl-C_{1-6} alkyl, substituted or unsubstituted C_{2-9} heteroalicyclyl-C_{1-6} alkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted aryl; or

R_{6b} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_1-C_6 alkoxy, C_{1-6} haloalkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl; or R_{6b} is selected from the group consisting of $-(CH_2)_q$-C_{3-6} cycloalkyl, $-(CH_2)_q$-aryl, $-(CH_2)_q$-C_{2-9} heteroalicyclyl, $-(CH_2)_q$-heteroaryl, which may be substituted by one or more substituent selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{3-5} cycloalkyl, $-(CH_2)_q$-$CONR_{23}R_{24}$, $-(CH_2)_q$-SO_2R_{23}, $-(CH_2)_q$-$NR_{23}SO_2R_{24}$ and $-(CH_2)_q$-SO_2NR_{23},
R_{23}, and R_{24} are independently of each other selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, -CN, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted C_{2-6} heteroalicyclyl; and
q is an integer selected from 0, or 1; or
R_{6b} is selected from the group consisting of hydrogen, $-(CH_2)C(CH_3)_3$,$-(CH_2)CONH_2$, phenyl, phenyl substituted with 1 to 3 halogens, $-CH(CH_3)OC(CH_3)_3$,$-CH_2$-phenyl-OCH_3, -phenyl-OCH_3, -CH2-pyridyl, CH_2-cyclohexyl-CH_2CO_2H, $-CH_2$-cyclohexyl-CH_2CONH_2,CH_2-cyclohexyl-CH_2-tetrazolyl, $-CH_2$-cyclohexyl-CH_2OH,$-CH_2$-cyclohexyl-$NHSO_2CH_3$, $-CH_2$-cyclohexyl-$NHSO_2CH_2CF_3$, -CH2-cyclohexyl-CH_2CN, $-CH_2$-phenyl-CH_2CO_2H, $-CH_2$-phenyl-CH_2CONH_2, $-CH_2$-phenyl-$CH_2CONH_2CH_3$, $-CH_2$-phenyl-CH_2-tetrazolyl, $-CH_2$-phenyl-$CONH_2$, -CH2-phenyl-SO_2NH-cyclopropyl, $-CH_2$-phenyl-SO_2CH_3, $-CH_2$-phenyl-$NHSO_2CF_3$, -CH2-phenyl-$NHSO_2CH_3$, $-CH_2$-phenyl-$NHSO_2CHF_2$, $-CH_2$-pyridyl-CH_3, $-CH_2$-pyridyl-SO_2CH_3,$-CH_2$-pyridyl-CH_2CONH_2, $-CH_2$-pyrimidyl-$NHSO_2CH_3$, $-CH_2$-piperidyl-$COCH_3$, $-CH_2$-piperidyl-SO_2CH_3, $-CH_2$-piperidyl-SO_2CF_3, $-CH_2$-thienyl-CH_2CO_2H, -CH2-cyclobutyl-CH_2CO_2H, $-CH_2$-cyclobutyl-CH_2CONH_2, $-CH_2$-cyclobutyl-CO_2H, $-CH_2$-cyclobutyl-$CONH_2$, $-CH_2$-tetrahydrothiopyryl, $-CH_2$-cyclopentyl, -CH2-cyclohexyl, $-CH_2$-tetrahydrofuranyl, -CH2-tetrahydropyranyl, $-CH_2$-oxetanyl, and $-CH_2$-pyranyl; or
R_{6b} is hydrogen or $-(CH_2)C(CH_3)_3$.

15. The compound according to any one of claims 1 to 14, wherein R_7, R_8, R_9, and R_{12} are independently selected of each other from hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted aryl-C_{1-6} alkyl, substituted or unsubstituted heteroaryl-C_{1-6} alkyl and substituted or unsubstituted aryl; or

R_7, Rs, R_9, and R_{12} are independently of each other selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, and aryl; or
R_7, R_8, R_9, and R_{12} are independently of each other selected from hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} hydroxyalkyl; or
R_7, R_8, R_9, and R_{12} are independently of each other selected from hydrogen, methyl, ethyl and tert-butyl.

16. The compound according to any one of claims 1 to 15, wherein ring system B is aryl or heteroaryl; and/or

ring system B has at least one of R_{4a} or R_{4b} present and other than hydrogen; or
ring system B is a 6-membered aryl having R_{4a} in the *para*-position or meta-position to ring system C, 6-membered heteroaryl having R_{4a} in the *para*-position or meta-position to ring system C, or 5-membered heteroaryl having R_{4a} in 2- or 3-position.

17. The compound according to any one of claims 1 to 16, wherein
ring system B is selected from the group consisting of phenyl, pyridyl, pyrazolyl, pyridazinyl, pyrimidinyl, naphthyl and furanyl.

18. The compound according to any one of claims 1 to 17, wherein ring system C is a 4-7-membered heteroalicyclyl; or

ring system C is selected from the group consisting of a 5-membered heteroalicyclyl, and 6-membered heteroalicyclyl; or
ring system C is selected from the group consisting of pyrrolidinyl, piperidyl, azetidinyl and morpholinyl.

19. The compound according to any one of claims 1 to 18, wherein m is an integer selected from the group consisting of 1, 2, 3 and 4; or
m is 1 or 2.

20. The compound according to any one of claims 1 to 19, wherein n is an integer selected from the group consisting of 1, 2, 3 and 4; or
n is 0 and/or m is 0.

21. The compound according to any one of claims 1 to 20, wherein p is an integer selected from 0, 1 or 2; or
p is 0.

22. The compound according to claim 1, selected from the group consisting of:

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23. A compound according to any one of claims 1-22 or pharmaceutical composition thereof comprising at least one acceptable excipient, for use in the treatment and/or prevention of inflammatory, metabolic and autoimmune diseases or disorders; or
for use in the treatment of a disease or disorder selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), bronchitis, atherosclerosis, helicobacter pylori infection, allergic diseases including allergic rhinitis, allergic conjunctivitis and uvetis, sprue and food allergy, atopic dermatitis, cystic fibrosis, lung allograph rejection, multiple sclerosis, rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, steatosis, steatohepatitis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), lupus erythematosus, Hashimoto's disease, pancreatisis, autoimmune diabetes, autoimmune ocular disease, ulcerative colitis, colitis, Crohn's disease, inflammatory bowel disease (IBD), inflammatory

bowel syndrome (IBS), Sjögren's syndrome, optic neuritis, type I diabetes, neuromyelitis optica, Myastehnia Gravis, Guillain-Barre syndrome, Graves' disease, scleritis, obesity, obesity-induced insulin resistance and type II diabetes, and cancer.

24. The compound, pharmaceutically acceptable salts, hydrates, solvates, polymorphs, and stereoisomers thereof according to claim 1, wherein

R_{4a} is selected from the group consisting of hydrogen, halogen, -OH, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_{1-6} alkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroaryl-C_{1-6} alkyl; and/or
R_{13} is absent, or selected from the group consisting of hydrogen, -OH, -CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, and -(CR_8R_9)p-C(=O)OR_7, -(CR_8R_9)p-SO_2R_7 and -(CR_8R_9)p-C(=O)NR_8R_9.

Patentansprüche

1. Substanz gemäß Formel (I)

Formel (I)

oder pharmazeutisch verträglichen Salzen, Hydraten, Solvaten, Polymorphen, und Stereoisomeren davon, wobei:

Y NR oder O ist;
R Wasserstoff oder substituiertes oder unsubstituiertes C_{1-4}-Alkyl ist;
R_1 ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, -OH, Halogen, substituiertem oder unsubstituiertem C_{1-4}-Alkyl, substituiertem oder unsubstituiertem C_{1-4}-Alkox, und substituierte oder unsubstituierte C_{1-4}-Alkenyl;
R_2 ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Halogen, substituiertem oder unsubstituiertem C_{1-4}-Alkyl, substituiertem oder unsubstituiertem C_{1-4}-Alkoxy, -CN, und -OH;
oder R und R_2 zu einem substituierten oder unsubstituierten fusionierten ring kombiniert sind;
R_3 ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Halogen, -OH, substituiertem oder unsubstituiertem C_{1-4}-Alkyl, substituiertem oder unsubstituiertem C_{1-4}-Alkox, Oxo, -C(=O)R_{10};
R_{4a} ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Halogen, -OH, -CN, substituiertem oder unsubstituiertem C_{1-6}-Alkyl, substituiertem oder unsubstituiertem C_{1-6}-Alkoxy, substituiertem oder unsubstituiertem C_{1-6}-Alkenyl, substituiertem oder unsubstituiertem C_{1-6}-Cycloalkenyl, substituiertem oder unsubstituiertem Aryl, substituiertem oder unsubstituiertem Aryl-C_{1-6}-Alkyl, substituiertem oder unsubstituiertem Heteroaryl, und substituiertem oder unsubstituiertem Heteroaryl-C_{1-6}-Alkyl;
R_{4b} ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Halogen, Oxo, -OH, substituiertem oder unsubstituiertem C_{1-4}-Alkyl, substituiertem oder unsubstituiertem C_{1-4}-Alkoxy, und -C(=O)R_{10};
R_5 ausgewählt ist aus der Gruppe bestehend aus -(CR_8R_9)pOR_{12}, -(CR_8R_9)p-$CR_{13}R_{14}R_{15}$, -(CR_8R_9)p-C(=O)OR_7, and -(CR_8R_9)p-C(=O)NR_8R_9;
n, m und p Ziffern sind, die voneinander unabhängig ausgewählt aus der Gruppe bestehend aus 0, 1, 2, 3 und 4;
R_{6a}, R_{6b} voneinander unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, substituiertem oder unsubstituiertem C_{1-6}-Alkyl, substituiertem oder unsubstituiertem C_{1-6}-Alkenyl, substituiertem oder unsubstituiertem C_{2-6}-Alkynyl, substituiertem oder unsubstituiertem C_{1-6}-Alkoxy, substituiertem oder

unsubstituiertem C_{1-6}-Heteroalkyl, substituiertem oder unsubstituiertem C_{3-8}-Cycloalkyl, substituiertem oder unsubstituiertem C_{3-8}-Cycloalkenyl, substituiertem oder unsubstituiertem C_{2-9}-heteroalicyclyl, substituiertem oder unsubstituiertem Aryl, und substituiertem oder unsubstituiertem Heteroaryl, oder R_{6a} und R_{6b} sind gemeinsam entnommen aus einer Oxo-Gruppe oder aus einem Ringsystem ausgewählt aus substituiertem oder unsubstituiertem C_{3-6}-Cycloalkyl, und substituiertem oder unsubstituiertem C_{2-9}-Heteroalicyclyl, oder R_{6a}, R_{13} sind formen gemeinsam ein Ringsystem ausgewählt aus der Gruppe umfassend substituiertem oder unsubstituiertem C_{3-6}-Cycloalkyl, und substituiertem oder unsubstituiertem C_{2-5}-Heteroalicyclyl;

R_7, R_8, R_9, and R_{12} voneinander unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, substituiertem oder unsubstituiertem C_{1-6}-Alkyl, substituiertem oder unsubstituiertem C_{3-6}-Cycloalkyl, und substituiertem oder unsubstituiertem C_{2-9}-Heteroalicyclyl;

R_{10} ausgewählt ist aus der Gruppe bestehend aus C_{1-6}-Alkyl, C_{1-6}-Alkoxy, -OH, $-NH_2$,-NH(C_{1-6}-Alkyl), -N(C_{1-6}-Alkyl)$_2$, und C_{3-7}-Cycloalkyl;

R_{13} nicht vorhanden ist oder ausgewählt ist aus der Gruppe bestehen aus Wasserstoff, -OH, -CN, Fluor, substituiertem oder unsubstituiertem C_{1-6}-Alkyl, substituiertem oder unsubstituiertem C_{1-6}-Alkenyl, substituiertem oder unsubstituiertem C_{1-6}-Alkoxy, substituiertem oder unsubstituiertem C_{3-8}-Cycloalkyl, substituiertem oder unsubstituiertem C_{3-8}-Cycloalkenyl, und $-(CR_8R_9)p-C(=O)OR_7$, $-(CR_8R_9)p-SO_2R_7$ and $-(CR_8R_9)p-C(=O)NR_8R_9$;

R_{14} und R_{15} voneinander unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, und substituiertem oder unsubstituiertem C_{1-6}-Alkyl, substituiertem oder unsubstituiertem C_{3-6}-Cycloalkyl, und substituiertem oder unsubstituiertem C_{2-9}-Heteroalicyclyl; oder

R_{14} and R_{15} zu einem Ringsystem kombiniert sind, ausgewählt aus der Gruppe bestehend aus substituiertem oder unsubstituiertem C_{3-8}-Cycloalkyl, substituiertem oder unsubstituiertem C_{3-8}-Cycloalkenyl, substituiertem oder unsubstituiertem C_{2-9}-Heteroalicyclyl, substituiertem oder unsubstituiertem Aryl, und substituiertem oder unsubstituiertem Heteroaryl;

B ein Ringsystem ist, ausgewählt aus der Gruppe bestehend aus Aryl, Heteroaryl, und bizyklischem Heteroalicyclyl, vorausgesetzt, dass es nicht 5,6-dichloro-1 H-benzo[d]imidazol-2-yl ist wenn sowohl R_1 als auch R_2 Wasserstoff sind;

C ein Ringsystem ist, ausgewählt aus C_{2-9}-Heteroalicycly;

wobei B mit einem Kohlenstoffatom verbunden ist, das neben dem Stickstoffatom des Ringsystems C ist; und

mit der Bedingung das die Substanz nicht: ist.

2. Substanz nach Anspruch 1, wobei R and R_2 in Kombination mit dem Pyrimidinring der Formel (I) ein Pyrrolo[2,3-d]Pyrimidin oder 6,7-dihydro-5Hpyrrolo[2,3-d]Pyrimidin formen; oder die Substanz ist eine Substanz der Formul (IIa):

Formel (IIa)

wobei:

R_{4e} and R_{4d} voneinander unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, substituiertem oder unsubstituiertem C_{1-4}-Alkyl, substituiertem oder unsubstituiertem C_{1-4}-Alkoxy, und -OH; oder
R_{4e} and R_{4d} voneinander unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Methyl, und Fluor.

3. Substanz nach einem der Ansprüche 1 oder 2, wobei R_5-(CR_8R_9)p-C(=O)OR_7, or - (CR_8R_9)p-C(=O)NR_8R_9 ist; or -(CR_8R_9)pOR_{12} ist; oder -(CR_8R_9)p-$CR_{13}R_{14}R_{15}$ ist.

4. Substanz nach Anspruch 3, wobei R_{14} and R_{15} zu einem Ringsystem kombiniert sind, ausgewählt aus der Gruppe bestehend aus substituiertem oder unsubstituiertem C_{3-7}-Cycloalkyl, substituiertem oder unsubstituiertem C_{3-7}-Cycloalkenyl, substituiertem oder unsubstituiertem C_{2-6}Heteroalicyclyl, substituiertem oder unsubstituiertem Aryl, und substituiertem oder unsubstituiertem Heteroaryl; oder

R_{14} und R_{15} kombiniert sind zu einem Ringsystem ausgewählt aus der Gruppe bestehend aus substituiertem oder unsubstituiertem C_{4-7}-Cycloalkyl, substituiertem oder unsubstituiertem C_{6-12}-Aryl, substituiertem oder unsubstituiertem 4-Heteroalicyclyl, substituiertem oder unsubstituiertem 5-Heteroaryl, substituiertem oder unsubstituiertem 5-Heteroalicyclyl, substituiertem oder unsubstituiertem 6-Heteroaryl, einem substituiertem oder unsubstituiertem 6-Heteroalicyclyl, substituiertem oder unsubstituiertem 7-Heteroaryl, und einem substituiertem oder unsubstituiertem 7-Heteroalicyclyl; oder
R_{14} and R_{15} kombiniert sind zu einem Ringsystem ausgewählt aus der Gruppe bestehend Phenyl, Naphthyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Cycloheptyl, Azetidinyl, Thietanyl, Pyrrolyl, Pyrazoleyl Imidazolyl, Pyrrolidinyl, Imidazolinyl, Pyrazolidinyl, Thiazolidinyl, Isothiazolidinyl, Triazolyl, Tetrazolyl, Oxazolyl, Isoxazolyl, Oxadiazolyl, Oxathianyl Thiazolyl, Isothiazolyl, Pyridyl, Pyridazinyl, Pyrazinyl, Pyrimidinyl, Triazinyl, Piperidinyl, Piperazinyl, Morpholinyl, Thiomorpholinyl, Dioxolanyl, Dioxanyl, Furyl, Dihydrofuranyl, Furazanyl, Tetrahydrofuryl, Pyranyl, Tetrahydropyranyl, Tetrahydrothiopyranyl, Dithiolanyl, Dithianyl, Thiopyranyl, Thianyl, Thienyl, Oxetanyl, Quinolyl, Isoquinolyl, Indolyl, Iso-Indolyl, und Tetrahydrothienyl, wobei jeder der vorgenannten Stoffe substituiert oder unsubstituiert sein kann.

5. Substanz nach Anspruch 4, wobei das Ringsystem, geformt durch die Kombination von R_{14} und R_{15}, substituiert ist mit -(CH_2)q(R_{5a}) wobei R_{5a} unabhängig ausgewählt ist aus der Gruppe bestehend aus -CH_2COOR_{20}, -$CH_2CONR_{21}R_{22}$, oxo, -CN, -CH_2-CN, C_{1-6}-Alkyl, -CH_2-Imidazolyl, -CH_2-SO_2R_{20}, -$CH_2C(CH_3)_2(OR_{20})$, -OR_{20}, -CH_2-Triazolyl, -CF_3, Dimethyl substituiertem Imidazolyl-2,4-dione, -CH_2-$SO_2NR_{21}R_{22}$, Morpholinyl, -C(=O)-Morpholinyl, Piperidyl-CH_2OR_{20}, -OCH_2-Tetrahydrofuryl, Piperazinonyl, Piperidinyl-$CONR_{21}R_{22}$, -OH, -$CONR_{21}R_{22}$, -$CH(OR_{20})CH_3$, -$COOR_{20}$, -CH_2-Pyrrolidyl, C_{1-6}-Alkylene-OH, Cyclopentyl, Pyrrolidonyl, - $NR_{21}SO_2R_{20}$, Tetrazolyl, -CH_2-Tetrazolyl, -CH_2OR_{20}, Acyl, -SOR_{20}, -sO_3R_{20}, -SO_2R_{20}, - $SO_2NR_{21}R_{22}$, and Halogen;

R_{20}, R_{21}, und R_{22} unabhängig voneinander ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, substituiertem oder unsubstituiertem C_{1-6}-Alkyl, -CN, substituiertem oder unsubstituiertem C_{3-6}-Cycloalkyl, substituiertem oder unsubstituiertem C_{2-6}-Heteroalicyclyl;
und q ist eine Ziffer ausgewählt aus der Gruppe umfassend 0, 1 oder 2.

6. Substanz nach einem der Ansprüche 3-5, wobei R_{13} nicht vorhanden ist oder ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, -CN, -CH_3, Fluor, -OH, -CH_2OH, -OCH_3, - CH_2CH_2OH, -CO_2H, -CO_2-C_{1-4}-Alkyl and -$CONR_8R_9$, wobei R_8 und Rg unabhängig voneinander ausgewählt sind aus Wasserstoff, C_{1-4}-Akyl, C_{1-4}-Aminoalkyl, oder R_8 and R_9 zu C_2-C_6-Heteroalicyclyl kombiniert sind.

7. Substanz nach einem der Ansprüche 1 bis 6, wobei Y NR ist, und R ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, C_{1-4}-Alkyl, C_{1-4}-Haloalkyl und C_{1-4}-Hydroxyalkyl; oder
Wasserstoff ist.

8. Substanz nach einem der Ansprüche 1 bis 7, wobei R_1 ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Halogen, substituiertem oder unsubstituiertem C_{1-4}-Alkyl, und substituiertem oder unsubstituiertem C_{1-4}-Alkoxy; oder

R_1 ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Halogen, C_{1-4}-Alkyl, C_{1-4}-Haloalkyl, und C_{1-4}-Hydroxyalkyl; oder
R_1 Wasserstoff oder -CF_3 ist.

9. Substanz nach einem der Ansprüche 1 bis 8, wobei R_2 ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Halogen, C_{1-4}-Alkyl, C_{1-4}-Haloalkyl, und C_{1-4}-Hydroxyalkyl; oder

R_2 Halogen ist;
R_2 Fluorine ist.

10. Substanz nach einem der Ansprüche 1 bis 9, wobei R_3 ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Halogen, C_{1-4}-Alkyl, C_{1-4}-Haloalkyl, und C_{1-4}-Hydroxyalkyl, Oxo, C_{1-4}-Alkoxy and C_{1-4}-Haloalkoxy; oder

R_3 ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Methyl, Fluor, Chlor, und Oxo; und/oder immer wenn m eine Ziffer aus der Gruppe 2, 3 oder 4 ist, mindestens zwei der vorhandenen R_3-Gruppen an dasselbe Atom des Ringsystems C gebunden sind.

11. Substanz nach einem der Ansprüche 1 bis 10, wobei R_{4a} ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Halogen, C_{1-6}-Alkyl, C_{1-6}-Haloalkyl, C_{1-6}-Hydroxyalkyl, -CN, C_1-C_6-Alkoxy, C_{1-6}-Haloalkoxy, C_3-C_5-Cycloalkyl, Heteroaryl und Aryl; or

R_{4a} ausgewählt ist aus der Gruppe bestehend aus Halogen, C_{1-4}-Alkyl, C_{1-4}-Haloalkyl, C_1-C_4-Alkoxy, C_{1-4}-Haloalkoxy, und Heteroaryl; oder
R_{4a} ausgewählt ist aus der Gruppe bestehend aus Methyl, Ethyl, Propyl, Iso-Propyl, tert-Butyl, Chlor, Fluor, Methoxy, Ethoxy, C_{1-2}-Haloalkyl, C_{1-2}-Haloalkoxy, und Triazolyl; oder
R_{4a} ausgewählt ist aus der Gruppe bestehend aus $-CF_3$, $-CHF_2$, $-OCF_3$, and $-OCHF_2$.

12. Substanz nach einem der Ansprüche 1 bis 11, wobei R_{4b} ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Oxo, Halogenm, C_{1-4}-Alkyl, C_{1-4}-Haloalkyl, C_{1-4}-Hydroxyalkyl, C_{1-4}-Alkoxy, und C_{1-4}-Haloalkoy; oder

R_{4b} ausgewählt ist aus der Gruppe bestehend aus Methyl, Ethyl, Propyl, iso-Propyl, tert-Butyl, Chlor, Flour, Methoxy, Ethoxy, -OH, C_{1-2}-Haloalkyl, und C_{1-2}-Haloalkoxy; oder
R_{4b} ausgewählt ist aus der Gruppe bestehend aus $-CF_3$, $-CF_2CF_3$, $-CHF_2$, $-OCF_3$, - OCF_2CF_3, and $-OCHF_2$.

13. Substanz nach einem der Ansprüche 1 bis 12, wobei R_{6a} ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Halogen, substituiertem oder unsubstituiertem C_{1-6}-Alkyl, substituiertem oder unsubstituiertem C_{1-6}-Alkoxy, und substituiertem oder unsubstituiertem Aryl; oder

R_{6a} und R_{13} gemeinsam ein Ringsystem formen, ausgewählt aus der Gruppe bestehend aus substituiertem oder unsubstituiertem C_{3-6}-Cycloalkyl, und substituiertem oder unsubstituiertem C_{2-9}-Heteroalicyclyl, oder R_{6a} und R_{6b} ar formen gemeinsam ein Ringsystem ausgewählt aus substituiertem oder unsubstituiertem C_{3-6}-Cycloalkyl, und substituiertem oder unsubstituiertem C_{2-9}-Heteroalicyclyl; oder
R_{6a} ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Halogen, C_{1-6}-Alkyl, C_{1-6}-Haloalkyl, C_{1-6}-Hydroxyalkyl, C_{1-6}-Alkoxy, C_{1-6}-Haloalkoxy, und Aryl; oder
R_{6a} ist Wasserstoff hydrogen.

14. Substanz nach einem der Ansprüche 1 bis 13, wobei R_{6a} ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, substituiertem oder unsubstituiertem C_{1-6}-Alkyl, substituiertem oder unsubstituiertem C_{1-6}-Alkoxy, substituiertem oder unsubstituiertem Aryl-C_{1-6}-Alkyl, substituiertem oder unsubstituiertem C_{2-9}-Heteroalicyclyl-C_{1-6}-Alkyl, substituiertem oder unsubstituiertem Heteroaryl, und substituiertem oder unsubstituiertem Aryl; oder

R_{6a} ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, C_{1-6}-Alkyl, C_{1-6}-Haloalkyl, C_{1-6}-Hydroxyalkyl, C_1-C_6-Aalkoxy, C_{1-6}-Haloalkoxy, C_{1-6}-Alkoxy-C_{1-6}-Alkyl; oder R_{6b} ausgewählt ist aus der Gruppe bestehend aus $-(CH_2)q$-C_{3-6}-Cycloalkyl, $-(CH_2)q$-Aryl, $-(CH_2)q$-C_{2-9}-Heteroalicyclyl, $-(CH_2)q$-Heteroaryl, welches durch einen oder mehrere Substituenten substituiert sein kann, wobei der Substituent ausgewählt ist aus der Gruppe bestehend aus Halogen, C_{1-4}-Alkyl, C_{1-4}-Haloalkyl, C_{1-4}-Alkoxy, C_{3-5}-Cycloalkyl, $-(CH_2)q$-$CONR_{23}R_{24}$, $-(CH_2)q$-SO_2R_{23}, $-(CH_2)q$-$NR_{23}SO2R_{24}$ and $-(CH_2)q$-SO_2NR_{23},
R_{23} und R_{24} unabhängig voneinander ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, substituiertem oder unsubstituiertem C_{1-6}-Alkyl, -CN, substituiertem oder unsubstituiertem C_{3-6}-Cycloalkyl, substituiertem oder unsubstituiertem $C2_{-6}$-Heteroalicyclyl; und
q eine Ziffer 0 oder 1 ist; oder
R_{6b} ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, $-(CH_2)C(CH_3)_3$, - $(CH_2)CONH_2$, Phenyl, Phenyl

substituiert mit 1 bis 3 Halogenen, $-CH(CH_3)OC(CH_3)_3$, $-CH_2$-phenyl-OCH_3, -phenyl-OCH_3, $-CH_2$-pyridyl, CH_2-cyclohexyl-CH_2CO_2H, $-CH_2$-cyclohexyl-CH_2CONH_2, CH_2-cyclohexyl-CH_2-tetrazolyl, $-CH_2$-cyclohexyl-CH_2OH, $-CH_2$-cyclohexyl-$NHSO_2CH_3$, $-CH_2$-cyclohexyl-$NHSO_2CH_2CF_3$, $-CH_2$-cyclohexyl-CH_2CN, $-CH_2$-phenyl-CH_2CO_2H, $-CH_2$-phenyl-CH_2CONH_2, $-CH_2$-phenyl-$CH_2CONH_2CH_3$, $-CH_2$-phenyl-CH_2-tetrazolyl, $-CH_2$-phenyl-$CONH_2$, - CH_2-phenyl-SO_2NH-cyclopropyl, $-CH_2$-phenyl-SO_2CH_3, -CH2-phenyl-$NHSO_2CF_3$, $-CH_2$-phenyl-$NHSO_2CH_3$, $-CH_2$-phenyl-$NHSO_2CHF_2$, $-CH_2$-pyridyl-CH_3, $-CH_2$-pyridyl-SO_2CH_3, $-CH_2$-pyridyl-CH_2CONH_2, $-CH_2$-pyrimidyl-$NHSO_2CH_3$, $-CH_2$-piperidyl-$COCH_3$, $-CH_2$-piperidyl-SO_2CH_3, $-CH_2$-piperidyl-SO_2CF_3, $-CH_2$-thienyl-CH_2CO_2H, $-CH_2$-cyclobutyl-CH_2CO_2H, $-CH_2$-cyclobutyl-CH_2CONH_2, $-CH_2$-cyclobutyl-CO_2H, $-CH_2$-cyclobutyl-$CONH_2$, $-CH_2$-tetrahydrothiopyryl, $-CH_2$-cyclopentyl, $-CH_2$-cyclohexyl, $-CH_2$-tetrahydrofuranyl, $-CH_2$-tetrahydropyranyl, $-CH_2$-oxetanyl, and - CH_2-pyranyl; oder
R_{6b} Wasserstoff $-(CH_2)C(CH_3)_3$ oder ist.

15. Substanz nach einem der Ansprüche 1 bis 14, wobei R_7, R_8, R_9, und R_{12} unabhängig voneinander ausgewählt sind aus Wasserstoff; unsubstituiertem C_{1-6}-Alkyl, substituiertem oder unsubstituiertem Aryl-C_{1-6}-Alkyl, substituiertem oder unsubstituiertem C_{1-6}-Heteroaryl-C_{1-6}-Alkyl, substituiertem oder unsubstituiertem Aryl; oder

R_7, R_8, R_9, and R_{12} unabhängig voneinander ausgewählt sind aus Wasserstoff, C_{1-6}-Alkyl, C_{1-6}-Haloalkyl, C_{1-6}-Hydroxyalkyl, und Aryl; oder
R_7, R_8, R_9, and R_{12} unabhängig voneinander ausgewählt sind aus Wasserstoff, C_{1-4}-Alkyl, C_{1-4}-Haloalkyl, und C_{1-4}-Hydroxyalkyl; oder
R_7, R_8, R_9, and R_{12} unabhängig voneinander ausgewählt sind aus Wasserstoff, Methyl, Ethyl und tert-Butyl.

16. Substanz nach einem der Ansprüche 1 bis 15, wobei das Ringsystem B Aryl oder Heteroaryl ist; und/oder

das Ringsystem B mindestens einen des Paares R_{4a} oder R_{4b} aufweist, welches dann nicht Wasserstoff ist; oder
das Ringsystem B ein 6-Aryl mit einem R_{4a} ist, das in para-Position oder *meta*-Position zu Ringsystem C ist, 6- Heteroaryl einem R_{4a} ist, das in para-Position oder *meta*-Position zu Ringsystem C ist, oder 5- Heteroaryl mit einem R_{4a} ist, das in 2- oder 3-Position ist.

17. Substanz nach einem der Ansprüche 1 bis 16, wobei das Ringsystem B ausgewählt ist aus der Gruppe bestehend aus Phenyl, Pyridyl, Pyrazolyl, Pyridazinyl, Pyrimidinyl, Naphthyl and Furanyl.

18. Substanz nach einem der Ansprüche 1 bis 17, wobei das Ringsystem C ein 4-7-Heteroalicyclyl ist; oder

das Ringsystem C ausgewählt ist aus der Gruppe bestehend aus einem 5-Heteroalicyclyl, und einem 6-Heteroalicyclyl; oder
das Ringsystem C ausgewählt ist aus der Gruppe bestehend aus Pyrrolidinyl, Piperidyl, Azetidinyl und Morpholinyl.

19. Substanz nach einem der Ansprüche 1 bis 18, wobei m eine Ziffer ist, ausgewählt aus 1, 2, 3 und 4; oder m 1 oder 2 ist.

20. Substanz nach einem der Ansprüche 1 bis 19, wobei n eine Ziffer ist, ausgewählt aus 1, 2, 3 und 4; oder n 0 ist und/oder m 0 ist.

21. Substanz nach einem der Ansprüche 1 bis 20, wobei p eine Ziffer ist, ausgewählt aus 0, 1 oder 2; oder p 0 ist.

22. Substanz nach der Anspruch 1, ausgewählt aus der Gruppe bestehend aus:

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23. Substanz nach einem der Ansprüche 1-22 oder die Substanz umfassende pharmazeutische Zusammensetzung, umfassend mindestens einen verträglichen Hilfsstoff, zur Verwendung bei der Behandlung und/oder zur Prävention von Entzündungs-, Stoffwechsel- oder Autoimmunkrankheiten oder -Störungen; oder
zur Verwendung bei der Behandlung einer Krankheit, ausgewählt aus der Gruppe bestehend aus Asthma, chronic obstructive pulmonary disease (COPD), Bronchitis, Atherosklerose, Infektion mit Helicobacter pylori, allergische

Krankheiten einschließlich allergische Rhinitis, allergische Konjunktivitis and Uveitis, Zöliakie, atopische Dermatitis, zystische Fibrose, lung allograph rejection, multiple Sklerose, Rheumatoide Arthritis, juvenile rheumatoide Arthritis, Osteoarthritis, Spondylitis ankylosans, Psoriasis, Psoriasis-Arthritis, Steatosis, Steatohepatitis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), Lupus erythematodes, Hashimoto-Krankheit, Pankreatitis, autoimmune Diabetes, autoimmune Augenkrankheit, Colitis ulcerosa, Colitis, Morbus Crohn, inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), Sjögren-Syndrom, Neuritis nervi optici, Typ I Diabetes, Neuromyelitis-optica-Spektrum-Erkrankungen, Myastehnia Gravis, Guillain-Barre syndrome, Basedow-Krankheit, Skleritis, Fettleibigkeit, fettleibigkeitsinduzierte Insulinresistenz und Typ II Diabetes, und Krebs.

24. Substanz, pharmazeutisch verträgliche Salze, Hydrate, Solvates, Polymorphe, und daraus aufgebaute Stereoisomere nach Anspruch 1, wobei

R_{4a} ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Halogen, -OH, substituiertem oder unsubstituiertem C_{1-6}-Alkyl, substituiertem oder unsubstituiertem C_1-C_6-Alkoxy, substituiertem oder unsubstituiertem C_{1-6}-Alkenyl, substituiertem oder unsubstituiertem C_3-C_6-Cycloalkyl, substituiertem oder unsubstituiertem Aryl, substituiertem oder unsubstituiertem Aryl-C_{1-6}-Alkyl, substituiertem oder unsubstituiertem Heteroaryl, und substituiertem oder unsubstituiertem Heteroaryl-C_{1-6}-Alkyl; und/oder
R_{13} ist nicht vorhanden, oder ausgewählt aus der Gruppe bestehend aus Wasserstoff, - OH, -CN, substituiertem oder unsubstituiertem C_{1-6}-Alkyl, substituiertem oder unsubstituiertem C_{1-6}-Alkenyl, substituiertem oder unsubstituiertem C_{1-6}-Alkoxy, substituiertem oder unsubstituiertem C_{3-8}-Cycloalkyl, substituiertem oder unsubstituiertem C_{3-8}-Cycloalkenyl, und $-(CR_8R_9)p-C(=O)OR_7$, $-(CR_8R_9)p-SO_2R_7$ and $-(CR_8R_9)p-C(=O)NR_8R_9$.

Revendications

1. Composé de Formule (I)

Formule (I)

ou sels, hydrates, solvates, polymorphes et stéréoisomères pharmaceutiquement acceptables de celui-ci, formule dans laquelle :

Y est NR ou O ;
R est hydrogène ou alkyle en C_{1-4} substitué ou non substitué ;
R_1 est choisi dans le groupe consistant en hydrogène, -OH, halogène, alkyle en C_{1-4} substitué ou non substitué, alcoxy en C_{1-4} substitué ou non substitué et alcényle en C_{2-4} substitué ou non substitué ;
R_2 est choisi dans le groupe consistant en hydrogène, halogène, alkyle en C_{1-4} substitué ou non substitué, alcoxy en C_{1-4} substitué ou non substitué, -CN et -OH ;
ou R et R_2 sont combinés pour former un cycle fusionné substitué ou non substitué ;
R_3 est choisi dans le groupe consistant en hydrogène, halogène, -OH, alkyle en C_{1-4} substitué ou non substitué, alcoxy en C_{1-4} substitué ou non substitué, oxo, $-C(=O)R_{10}$;
R_{4a} est choisi dans le groupe consistant en hydrogène, halogène, -OH, -CN, alkyle en C_{1-6} substitué ou non

substitué, alcoxy en C_{1-6} substitué ou non substitué, alcényle en C_{1-6} substitué ou non substitué, cycloalkyle en C_{3-6} substitué ou non substitué, aryle substitué ou non substitué, aryl-alkyle en C_{1-6} substitué ou non substitué, hétéroaryle substitué ou non substitué et hétéroaryl-alkyle en C_{1-6} substitué ou non substitué ;

R_{4b} est choisi dans le groupe consistant en hydrogène, halogène, oxo, -OH, alkyle en C_{1-4} substitué ou non substitué, alcoxy en C_{1-4} substitué ou non substitué et $-C(=O)R_{10}$;

R_5 est choisi dans le groupe consistant en - (CR_8R_9) pOR_{12}, - (CR_8R_9) p-$CR_{13}R_{14}R_{15}$, - (CR_8R_9) p-C (=O)OR_7 et - (CR_8R_9) p-C (=O) NR_8R_9 ;

n, m et p sont des entiers choisis indépendamment dans le groupe consistant en 0, 1, 2, 3 et 4 ;

R_{6a}, R_{6b} sont indépendamment choisis dans le groupe consistant en hydrogène, halogène, alkyle en C_{1-6} substitué ou non substitué, alcényle en C_{1-6} substitué ou non substitué, alcynyle en C_{2-6} substitué ou non substitué, alcoxy en C_{1-6} substitué ou non substitué, hétéroalkyle en C_{1-6} substitué ou non substitué, cycloalkyle en C_{3-8} substitué ou non substitué, cycloalcényle en C_{3-8} substitué ou non substitué, hétéroalicyclyle en C_{2-9} substitué ou non substitué, aryle substitué ou non substitué et hétéroaryle substitué ou non substitué, ou R_{6a} et R_{6b} sont pris conjointement pour former un groupe oxo ou un système cyclique choisi parmi cycloalkyle en C_{3-6} substitué ou non substitué et hétéroalicyclyle en C_{2-9} substitué ou non substitué, ou R_{6a} et R_{13} sont pris conjointement pour former un système cyclique choisi parmi cycloalkyle en C_{3-6} substitué ou non substitué et hétéroalicyclyle en C_{2-5} substitué ou non substitué ;

R_7, R_9, R_9 et R_{12} sont indépendamment choisis dans le groupe consistant en hydrogène, alkyle en C_{1-6} substitué ou non substitué, cycloalkyle en C_{3-6} substitué ou non substitué et hétéroalicyclyle en C_{2-9} substitué ou non substitué ;

R_{10} est choisi dans le groupe consistant en alkyle en C_{1-6}, alcoxy en C_{1-6}, -OH, $-NH_2$, -NH(alkyle en C_{1-6}) , -N (alkyle en $C_{1-6})_2$ et cycloalkyle en C_{3-7} ;

R_{13} est absent ou choisi dans le groupe consistant en hydrogène, -OH, -CN, fluor, alkyle en C_{1-6} substitué ou non substitué, alcényle en C_{1-6} substitué ou non substitué, alcoxy en C_{1-6} substitué ou non substitué, cycloalkyle en C_{3-8} substitué ou non substitué, cycloalcényle en C_{3-8} substitué ou non substitué et $-(CR_8R_9)p-C(=O)OR_7$, $-(CR_8R_9)p-SO_2R_7$ et - (CR_8R_9) p-C (=O) NR_8R_9 ;

R_{14} et R_{15} sont indépendamment choisis dans le groupe consistant en hydrogène et alkyle en C_{1-6} substitué ou non substitué, cycloalkyle en C_{3-6} substitué ou non substitué et hétéroalicyclyle en C_{2-9} substitué ou non substitué ; ou

R_{14} et R_{15} sont combinés pour former un système cyclique choisi dans le groupe consistant en cycloalkyle en C_{3-8} substitué ou non substitué, cycloalcényle en C_{3-8} substitué ou non substitué, hétéroalicyclyle en C_{2-9} substitué ou non substitué, aryle substitué ou non substitué et hétéroaryle substitué ou non substitué ;

B est un système cyclique choisi dans le groupe consistant en aryle, hétéroaryle et hétéroalicyclyle bicyclique, à condition qu'il ne soit pas le 5,6-dichloro-1H-benzo[d]imidazol-2-yle lorsque R_1 et R_2 sont tous deux hydrogène ;

C est un système cyclique choisi parmi hétéroalicyclyle en C_{2-9} ;

où B est attaché à un atome de carbone adjacent à l'atome de N du système cyclique C ; et

à condition que le composé ne soit pas :

.

2. Composé selon la revendication 1, dans lequel R et R_2 en combinaison avec le cycle pyrimidine de formule (I) forment une pyrrolo[2,3-d]pyrimidine ou une 6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine ; ou le composé est un composé de Formule (IIa) :

Formule (IIa)

dans laquelle :

R_{4e} et R_{4d} sont indépendamment choisis dans le groupe consistant en hydrogène, halogène, alkyle en C_{1-4} substitué ou non substitué, alcoxy en C_{1-4} substitué ou non substitué et -OH ; ou
R_{4e} et R_{4d} sont indépendamment choisis dans le groupe consistant en hydrogène, méthyle et fluor.

3. Composé selon l'une quelconque des revendications 1 et 2, dans lequel R_5 est - (CR_8R_9) p-C (=O) OR_7, ou - (CR_8R_9) p-C(=O) NR_8R_9 ; ou - $(CR_8R_9)_pOR_{12}$; ou - (CR_8R_9)p-$CR_{13}R_{14}R_{15}$.

4. Composé selon la revendication 3, dans lequel R_{14} et R_{15} sont combinés pour former un système cyclique choisi dans le groupe consistant en cycloalkyle en C_{3-7} substitué ou non substitué, cycloalcényle en C_{3-7} substitué ou non substitué, hétéroalicyclyle en C_{2-6} substitué ou non substitué, aryle substitué ou non substitué et hétéroaryle substitué ou non substitué ; ou

R_{14} et R_{15} sont combinés pour former un système cyclique choisi dans le groupe consistant en cycloalkyle en C_{4-7} substitué ou non substitué, aryle en C_{6-12} substitué ou non substitué, hétéroalicyclyle à 4 chaînons substitué ou non substitué, hétéroaryle à 5 chaînons substitué ou non substitué, hétéroalicyclyle à 5 chaînons substitué ou non substitué, hétéroaryle à 6 chaînons substitué ou non substitué, hétéroalicyclyle à 6 chaînons substitué ou non substitué, hétéroaryle à 7 chaînons substitué ou non substitué et hétéroalicyclyle à 7 chaînons substitué ou non substitué ; ou
R_{14} et R_{15} sont combinés pour former un système cyclique choisi dans le groupe consistant en phényle, naphtyle, cyclopropyle, cyclobutyle, cyclopentyle, cyclohexyle, cycloheptyle, azétidinyle, thiétanyle, pyrrolyle, pyrazolyle, imidazolyle, pyrrolidinyle, imidazolinyle, pyrazolidinyle, thiazolidinyle, isothiazolidinyle, triazolyle, tétrazolyle, oxazolyle, isoxazolyle, oxadiazolyle, oxathianyle, thiazolyle, isothiazolyle, pyridyle, pyridazinyle, pyrazinyle, pyrimidinyle, triazinyle, pipéridinyle, pipérazinyle, morpholinyle, thiomorpholinyle, dioxolanyle, dioxanyle, furyle, dihydrofuranyle, furazanyle, tétrahydrofuryle, pyranyle, tétrahydropyranyle, tétrahydrothiopyranyle, dithiolanyle, dithianyle, thiopyranyle, thianyle, thiényle, oxétanyle, quinolyle, isoquinolyle, indolyle, iso-indolyle et tétrahydrothiényle, dont chacun peut être substitué ou non substitué.

5. Composé selon la revendication 4, dans lequel le système cyclique formé par la combinaison de R_{14} et R_{15} est substitué par -$(CH_2)q(R_{5a})$ dans lequel R_{5a} est indépendamment choisi dans le groupe consistant en -CH_2COOR_{20}, -$CH_2CONR_{21}R_{22}$, oxo, -CN, -CH_2-CN, alkyle en C_{1-6}, -CH_2-imidazolyle, -CH_2-SO_2R_{20}, -$CH_2C(CH_3)_2(OR_{20})$, -OR_{20}, -CH_2-triazolyle, -CF_3, imidazolyl substitué par diméthyle-2,4-dione, -CH_2-$SO_2NR_{21}R_{22}$, morpholinyle, -C(=O)-morpholinyle, pipéridyl-CH_2OR_{20}, -OCH_2-tétrahydrofuryle, pipérazinonyle, pipéridinyl-$CONR_{21}R_{22}$, -OH, -$CONR_{21}R_{22}$, -CH $(OR_{20})CH_3$, -$COOR_{20}$, -CH_2-pyrrolidyle, alkylène en C_{1-6}-OH, cyclopentyle, pyrrolidonyle, -$NR_{21}SO_2R_{20}$, tétrazolyle, -CH_2-tétrazolyle, -CH_2OR_{20}, acyle, -SOR_{20}, -SO_3R_{20}, -SO_2R_{20}, -$SO_2NR_{21}R_{22}$ et halogène ;

R_{20}, R_{21} et R_{22} sont indépendamment l'un de l'autre choisis dans le groupe consistant en hydrogène, alkyle en C_{1-6} substitué ou non substitué, -CN, cycloalkyle en C_{3-6} substitué ou non substitué, hétéroalicyclyle en C_{2-6} substitué ou non substitué ; et
q est un entier choisi parmi 0, 1 ou 2.

6. Composé selon l'une quelconque des revendications 3 à 5, dans lequel R_{13} est absent ou choisi dans le groupe consistant en hydrogène, -CN, $-CH_3$, fluor, -OH, $-CH_2OH$, $-OCH_3$, $-CH_2CH_2OH$, $-CO_2H$, $-CO_2$-alkyle en C_{1-4} et $-CONR_8R_9$ où R_8 et R_9 sont indépendamment l'un de l'autre choisis parmi hydrogène, alkyle en C_{1-4}, aminoalkyle en C_{1-4}, ou R_8 et R_9 sont combinés pour former un hétéroalicyclyle en C_{2-6}.

7. Composé selon l'une quelconque des revendications 1 à 6, dans lequel Y est NR, et

R est choisi dans le groupe consistant en hydrogène, alkyle en C_{1-4}, haloalkyle en C_{1-4} et hydroxyalkyle en C_{1-4} ; ou
R est hydrogène.

8. Composé selon l'une quelconque des revendications 1 à 7, dans lequel R_1 est choisi dans le groupe consistant en hydrogène, halogène, alkyle en C_{1-4} substitué ou non substitué et alcoxy en C_{1-4} substitué ou non substitué ; ou

R_1 est choisi dans le groupe consistant en hydrogène, halogène, alkyle en C_{1-4}, haloalkyle en C_{1-4} et hydroxyalkyle en C_{1-4} ; ou
R_1 est hydrogène ou $-CF_3$.

9. Composé selon l'une quelconque des revendications 1 à 8, dans lequel R_2 est choisi dans le groupe consistant en hydrogène, halogène, alkyle en C_{1-4}, haloalkyle en C_{1-4} et hydroxyalkyle en C_{1-4} ; ou

R_2 est halogène ; ou
R_2 est fluor.

10. Composé selon l'une quelconque des revendications 1 à 9, dans lequel R_3 est choisi dans le groupe consistant en hydrogène, halogène, alkyle en C_{1-4}, haloalkyle en C_{1-4}, hydroxyalkyle en C_{1-4}, oxo, alcoxy en C_{1-4} et haloalcoxy en C_{1-4} ; ou

R_3 est choisi dans le groupe consistant en hydrogène, méthyle, fluor, chlore et oxo ; et/ou
chaque fois que m est un entier choisi parmi 2, 3 ou 4, au moins deux des groupes R_3 présents sont liés au même atome de système cyclique C.

11. Composé selon l'une quelconque des revendications 1 à 10, dans lequel R_{4a} est choisi dans le groupe consistant en hydrogène, halogène, alkyle en C_{1-6}, haloalkyle en C_{1-6}, hydroxyalkyle en C_{1-6}, -CN, alcoxy en C_1-C_6, haloalcoxy en C_{1-6}, cycloalkyle en C_3-C_5, hétéroaryle et aryle ; ou

R_{4a} est choisi dans le groupe consistant en halogène, alkyle en C_{1-4}, haloalkyle en C_{1-4}, alcoxy en C_{1-4}, haloalcoxy en C_{1-4}, et hétéroaryle ; ou
R_{4a} est choisi dans le groupe consistant en méthyle, éthyle, propyle, iso-propyle, tert-butyle, chlore, fluor, méthoxy, éthoxy, haloalkyle en C_{1-2}, haloalcoxy en C_{1-2} et triazolyle ; ou
R_{4a} est choisi dans le groupe consistant en $-CF_3$, $-CHF_2$, $-OCF_3$ et $-OCHF_2$.

12. Composé selon l'une quelconque des revendications 1 à 11, dans lequel R_{4b} est choisi dans le groupe consistant en hydrogène, oxo, halogène, alkyle en C_{1-4},haloalkyle en C_{1-4}, hydroxyalkyle en C_{1-4}, alcoxy en C_1-C_4 et haloalcoxy en C_{1-4} ; ou

R_{4b} est choisi dans le groupe consistant en méthyle, éthyle, propyle, iso-propyle, tert-butyle, chlore, fluor, méthoxy, éthoxy, -OH, haloalkyle en C_{1-2} et haloalcoxy en C_{1-2} ; ou
R_{4b} est choisi dans le groupe consistant en $-CF_3$, $-CF_2CF_3$, $-CHF_2$, $-OCF_3$, $-OCF_2CF_3$ et $-OCHF_2$.

13. Composé selon l'une quelconque des revendications 1 à 12, dans lequel R_{6a} est choisi dans le groupe consistant en hydrogène, halogène, alkyle en C_{1-6} substitué ou non substitué, alcoxy en C_{1-6} substitué ou non substitué et aryle substitué ou non substitué ; ou

R_{6a} et R_{13} sont pris conjointement pour former un système cyclique choisi parmi cycloalkyle en C_{3-6} substitué ou non substitué et hétéroalicyclyle en C_{2-9} substitué ou non substitué, ou R_{6a} et R_{6b} sont pris conjointement pour former un système cyclique choisi parmi cycloalkyle en C_{3-6} substitué ou non substitué et hétéroalicyclyle en C_{2-9} substitué ou non substitué ; ou

R_{6a} est choisi dans le groupe consistant en hydrogène, halogène, alkyle en C_{1-6}, haloalkyle en C_{1-6}, hydroxyalkyle en C_{1-6}, alcoxy en C_{1-6}, haloalcoxy en C_{1-6} et aryle ; ou
R_{6a} est hydrogène.

14. Composé selon l'une quelconque des revendications 1 à 13, dans lequel R_{6b} est choisi dans le groupe consistant en hydrogène, alkyle en C_{1-6} substitué ou non substitué, alcoxy en C_{1-6} substitué ou non substitué, aryl-alkyle en C_{1-6} substitué ou non substitué, hétéroalicyclyl en C_{2-9}-alkyle en C_{1-6} substitué ou non substitué, hétéroaryle substitué ou non substitué et aryle substitué ou non substitué ; ou

R_{6b} est choisi dans le groupe consistant en hydrogène, alkyle en C_{1-6}, haloalkyle en C_{1-6}, hydroxyalkyle en C_{1-6}, alcoxy en C_{1-6}, haloalcoxy en C_{1-6}, alcoxy en C_{1-6}-alkyle en C_{1-6} ; ou R_{6b} est choisi dans le groupe consistant en - $(CH_2)_q$-cycloalkyle en C_{3-6}, - $(CH_2)_q$-aryle, - $(CH_2)_q$-hétéroalicyclyle en C_{2-9}, - $(CH_2)_q$-hétéroaryle, qui peuvent être substitués par un ou plusieurs substituants choisis dans le groupe consistant en halogène, alkyle en C_{1-4}, haloalkyle en C_{1-4}, alcoxy en C_{1-4}, cycloalkyle en C_{3-5}, - $(CH_2)_q$-$CONR_{23}R_{24}$, - $(CH_2)_q$-SO_2R_{23}, - $(CH_2)_q$-$NR_{23}SO_2R_{24}$ et - $(CH_2)_q$-SO_2NR_{23} ,
R_{23} et R_{24} sont indépendamment l'un de l'autre choisis dans le groupe consistant en hydrogène, alkyle en C_{1-6} substitué ou non substitué, -CN, cycloalkyle en C_{3-6} substitué ou non substitué, hétéroalicyclyle en C_{2-6} substitué ou non substitué ; et
q est un nombre entier choisi parmi 0 ou 1 ; ou
R_{6b} est choisi dans le groupe consistant en hydrogène, - $(CH_2)C(CH_3)_3$, - $(CH_2)CONH_2$, phényle, phényle substitué par 1 à 3 halogènes, -$CH(CH_3)OC(CH_3)_3$, -CH_2-phényl-OCH_3, -phényl-OCH_3, -CH_2-pyridyle, CH_2-cyclohexyl-CH_2CO_2H, -CH_2-cyclohexyl-CH_2CONH_2, CH_2-cyclohexyl-CH_2-tétrazolyle, -CH_2-cyclohexyl-CH_2OH, -CH_2-cyclohexyl-$NHSO_2CH_3$, -CH_2-cyclohexyl-$NHSO_2CH_2CF_3$, -CH_2-cyclohexyl-CH_2CN, -CH_2-phényl-CH_2CO_2H, -CH_2-phényl-CH_2CONH_2, -CH_2-phényl-$CH_2CONH_2CH_3$, -CH_2-phényl-CH_2-tétrazolyle, -CH_2-phényl-$CONH_2$, -CH_2-phényl-SO_2NH-cyclopropyle, -CH_2-phényl-SO_2CH_3, -CH_2-phényl-$NHSO_2CF_3$, -CH_2-phényl-$NHSO_2CH_3$, -CH_2-phényl-$NHSO_2CHF_2$, -CH_2-pyridyl-CH_3, -CH_2-pyridyl-SO_2CH_3, -CH_2-pyridyl-CH_2CONH_2, -CH_2-pyrimidyl-$NHSO_2CH_3$, -CH_2-pipéridyl-$COCH_3$, -CH_2-pipéridyl-SO_2CH_3, -CH_2-pipéridyl-SO_2CF_3, -CH_2-thiényl-CH_2CO_2H, -CH_2-cyclobutyl-CH_2CO_2H, -CH_2-cyclobutyl-CH_2CONH_2, -CH_2-cyclobutyl-CO_2H, -CH_2-cyclobutyl-$CONH_2$, -CH_2-tétrahydrothiopyryle, -CH_2-cyclopentyle, -CH_2-cyclohexyle, -CH_2-tétrahydrofuranyle, -CH_2-tétrahydropyranyle, -CH_2-oxétanyle et -CH_2-pyranyle ; ou
R_{6b} est hydrogène ou -$(CH_2)C(CH_3)_3$.

15. Composé selon l'une quelconque des revendications 1 à 14, dans lequel R_7, R_9, R_9 et R_{12} sont choisis indépendamment l'un de l'autre parmi hydrogène, alkyle en C_{1-6} substitué ou non substitué, aryl-alkyle en C_{1-6} substitué ou non substitué, hétéroaryl-alkyle en C_{1-6} substitué ou non substitué et aryle substitué ou non substitué ; ou

R_7, R_9, R_9 et R_{12} sont indépendamment l'un de l'autre choisis parmi hydrogène, alkyle en C_{1-6}, haloalkyle en C_{1-6}, hydroxyalkyle en C_{1-6} et aryle ; ou
R_7, R_9, R_9 et R_{12} sont indépendamment l'un de l'autre choisis parmi hydrogène, alkyle en C_{1-4}, haloalkyle en C_{1-4} et hydroxyalkyle en C_{1-4} ; ou
R_7, R_9, R_9 et R_{12} sont indépendamment l'un de l'autre choisis parmi hydrogène, méthyle, éthyle et tert-butyle.

16. Composé selon l'une quelconque des revendications 1 à 15, dans lequel le système cyclique B est aryle ou hétéroaryle ; et / ou

le système cyclique B a au moins l'un de R_{4a} ou R_{4b} présent et autre qu'hydrogène ; ou
le système cyclique B est un aryle à 6 chaînons ayant R_{4a} en position *para* ou en position *méta* par rapport au système cyclique C, un hétéroaryle à 6 chaînons ayant R_{4a} en position *para* ou en position *méta* par rapport au système cyclique C, ou un hétéroaryle à 5 chaînons ayant R_{4a} en position 2 ou 3.

17. Composé selon l'une quelconque des revendications 1 à 16, dans lequel
le système cyclique B est choisi dans le groupe consistant en phényle, pyridyle, pyrazolyle, pyridazinyle, pyrimidinyle, naphtyle et furanyle.

18. Composé selon l'une quelconque des revendications 1 à 17, dans lequel le système cyclique C est un hétéroalicyclyle à 4-7 chaînons ; ou

le système cyclique C est choisi dans le groupe consistant en un hétéroalicyclyle à 5 chaînons et un hétéroa-

licyclyle à 6 chaînons ; ou
le système cyclique C est choisi dans le groupe consistant en pyrrolidinyle, pipéridyle, azétidinyle et morpholinyle.

19. Composé selon l'une quelconque des revendications 1 à 18, dans lequel m est un entier choisi dans le groupe consistant en 1, 2, 3 et 4 ; ou
m est 1 ou 2.

20. Composé selon l'une quelconque des revendications 1 à 19, dans lequel n est un entier choisi dans le groupe consistant en 1, 2, 3 et 4 ; ou
n est 0 et/ou m est 0.

21. Composé selon l'une quelconque des revendications 1 à 20, dans lequel p est un entier choisi parmi 0, 1 ou 2 ; ou
p est 0.

22. Composé selon la revendication 1, choisi dans le groupe consistant en :

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23. Composé selon l'une quelconque des revendications 1 à 22 ou composition pharmaceutique de celui-ci comprenant au moins un excipient acceptable, pour une utilisation dans le traitement et / ou la prévention de maladies ou troubles inflammatoires, métaboliques et auto-immuns ; ou
pour une utilisation dans le traitement d'une maladie ou trouble choisi dans le groupe consistant en l'asthme, la bronchopneumopathie chronique obstructive (COPD), la bronchite, l'athérosclérose, l'infection par helicobacter pylori, les maladies allergiques comprenant la rhinite allergique, la conjonctivite allergique et l'uvéite, la sprue et l'allergie alimentaire, la dermatite atopique, la mucoviscidose, le rejet d'allogreffe pulmonaire, la sclérose en plaques, la polyarthrite rhumatoïde, la polyarthrite rhumatoïde juvénile, l'arthrose, la spondylarthrite ankylosante, le psoriasis, le rhumatisme psoriasique, la stéatose, la stéatohépatite, la stéatose hépatique non alcoolique (NAFLD), la stéatohépatite non alcoolique (NASH), le lupus érythémateux, la maladie de Hashimoto, la pancréatite, le diabète auto-immun, une maladie oculaire auto-immune, la colite ulcéreuse, la colite, la maladie de Crohn, une maladie inflammatoire de l'intestin (IBD), le syndrome inflammatoire de l'intestin (IBS), le syndrome de Sjögren, la névrite optique, le diabète de type I, la neuromyélite optique, la myasthénie grave, le syndrome de Guillain-Barré, la maladie de Graves, la sclérite, l'obésité, la résistance à l'insuline induite par l'obésité et le diabète de type II, et le cancer.

24. Composé, sels, hydrates, solvates, polymorphes et stéréoisomères pharmaceutiquement acceptables de celui-ci selon la revendication 1, où

R_{4a} est choisi dans le groupe consistant en hydrogène, halogène, -OH, alkyle en C_{1-6} substitué ou non substitué, alcoxy en C_1-C_6 substitué ou non substitué, alcényle en C_{1-6} substitué ou non substitué, cycloalkyle en C_3-C_6 substitué ou non substitué, aryle substitué ou non substitué, aryl-alkyle en C_{1-6} substitué ou non substitué, hétéroaryle substitué ou non substitué et hétéroaryl-alkyle en C_{1-6} substitué ou non substitué ; et / ou
R_{13} est absent ou choisi dans le groupe consistant en hydrogène, -OH, -CN, alkyle en C_{1-6} substitué ou non substitué, alcényle en C_{1-6} substitué ou non substitué, alcoxy en C_{1-6} substitué ou non substitué, cycloalkyle en C_{3-8} substitué ou non substitué, cycloalcényle en C_{3-8} substitué ou non substitué et - (CR_8R_9) p-C (=O) OR_7, - (CR_8R_9)p-SO_2R_7 et - (CR_8R_9) p-C (=O) NR_8R_9.

A

Figure 1

B
mP
200
150
100
50
0
0 nM
100 nM
250 nM
hRORγt
C
% of max
100
50
0
-10
-9
-8
-7
-6
-5
-4
Log [M]
SR2211
IC50 = 0.36 μM

Figure 2

A
% of max
100
80
60
40
20
0
IC50 = 0.8 µM
-9
-8
-7
-6
-5
-4
Log [M]
B
% inhibition
100
80
60
40
20
0
1µM
10µM
C
% inhibition
100
50
0
IC50 = 0.7 µM
-8
-7
-6
-5
Log [M]

Figure 3

REFERENCES CITED IN THE DESCRIPTION

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