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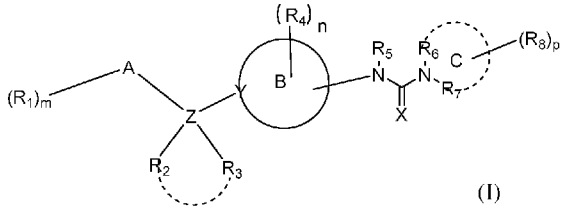
(54) Title: NOVEL COMPOUNDS AS ROR-GAMMA MODULATORS



(I)

(57) Abstract: The present invention provides compounds which are modulators of RORγ and their use for the treatment of diseases or conditions mediated by RORγ. Further, the present invention relates to processes of preparing such compounds, their tautomeric forms, deuterated form, novel intermediates involved in their synthesis, their pharmaceutically acceptable salts, methods for using such compounds and pharmaceutical compositions containing them. formula (I)

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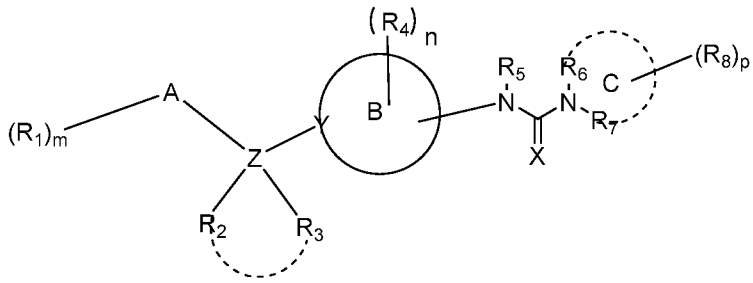
NOVEL COMPOUNDS AS ROR-GAMMA MODULATORS

FIELD OF THE INVENTION

The present invention provides compounds which are modulators of RORγ (**ROR-GAMMA**) and their use for the treatment of diseases or conditions mediated by RORγ. Further, the present invention relates to processes of preparing such compounds, their tautomeric forms, novel intermediates involved in their synthesis, their pharmaceutically acceptable salts, methods for using such compounds and pharmaceutical compositions containing them.



formula (I)

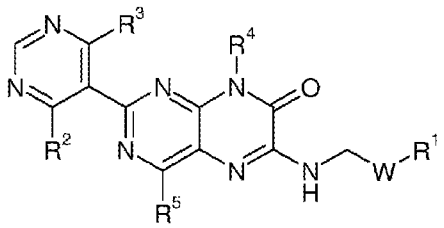
BACKGROUND TO THE INVENTION

There has been rapid advancement in the biological roles played by nuclear receptors. Nuclear receptors are involved in regulation of key physiological functions and have been identified as the key regulators in metabolic diseases, cancer and autoimmune disorders. The Retinoic acid receptor-related orphan receptor γ known as RORγ belonging to the nuclear receptor superfamily (Hirose, T.; Smith, R. J.; Biochem. Biophys. Res. Commun. 1994, 205, 1976–1983). Till date there are three sub-types of ROR`s which is classified as RORα, RORβ and RORγ. Like other nuclear receptors, structure ROR`s consists of four distinct functional regions called N-terminal A/B domain, DNA binding domain (DBD) or C domain, a hinge domain and The E domain or ligand binding domain (LBD).Two isoforms RORγ1 and RORγ2 (which is also called as RORγt) have been identified which differ in N-terminal sequences (He, Y.-W.; Deftos, M. L.; Ojala, Immunity 1998, 9,797-806). Tissue distribution of RORγt isoform is restricted to lymphoid organs, such as the thymus. The isoform RORγt plays important role in the development and regulation of the immune system as it has been identified as a key regulator of T helper cells (TH17 cell) differentiation (Ivanov, I. I.;

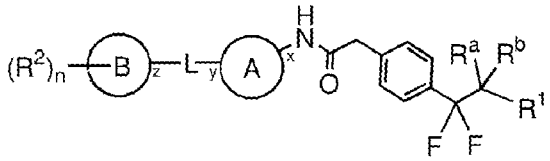
McKenzie, B. S.; Zhou, L.; Cell 2006, 126, 1121–1133). Th17 is the IL-17 producing CD4+ Th subset and are key drivers of chronic inflammation in autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, irritable bowel diseases, psoriasis, psoriatic arthritis (Jetten (2009) Nucl. RecepL Signal. 7: e003; Manel et al. (2008) Nat. Immunol. 9:641-649). Mouse autoimmune disease models like experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA) have demonstrated the role of TH17 in autoimmune diseases. RORγ is central transcription factor driving Th17 differentiation.

In light of the role of RORγ in the pathogenesis of autoimmune disease, development of ligands which can modulate RORγ activity could lead to specific therapies for diseases mediated by RORγ.

WO2017058831 "Pteridine derivatives as modulators of ror gamma" by Boehringer has been disclosed with following general structure.

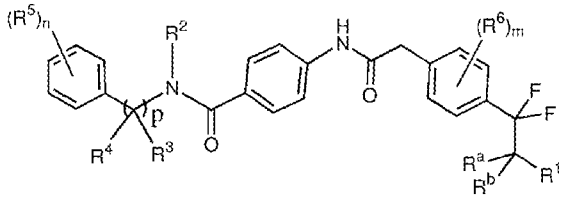


Glenmark disclosed aryl and heteroaryl ether compounds with following general structure as ROR gamma modulators in WO2017051319

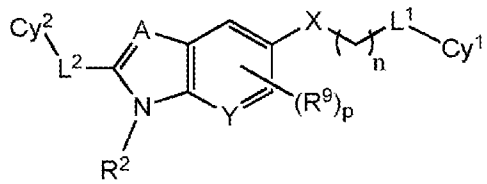


Eli Lilly discloses dihydrospiro piperidine-thienopyran-carboxamide compounds useful for inhibiting ROR-gamma-t and their preparation in the patent application US20170066781

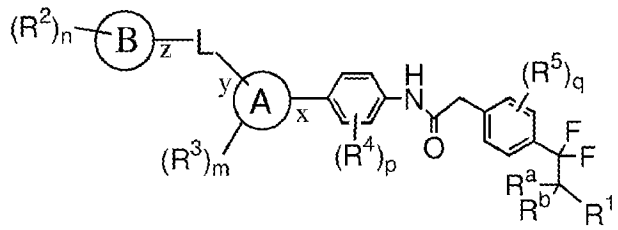
Glenmark disclosed preparation of carbocyclic compounds as ROR gamma modulators in WO2017037595 having the following general formula



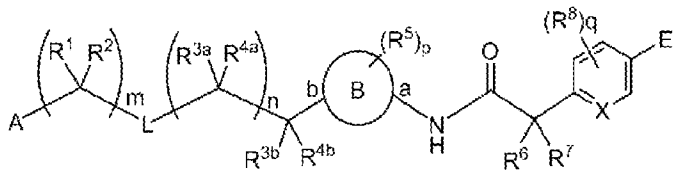
Vitae Pharmaceutical claims preparation of ROR-gamma modulators in patent application WO 2017024018 with following structure



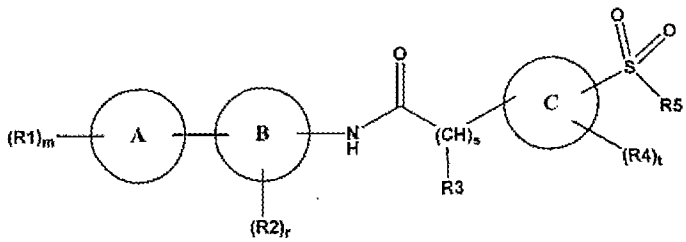
Glenmark in its patent application WO2017021879, has disclosed preparation of certain ROR gamma modulators having the following general formula.



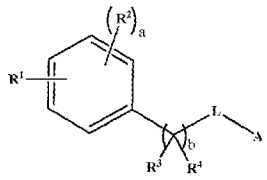
Shionogi patent application titled" Preparation of amide compounds having RORγt inhibitory effect", WO2017010399 describes compounds with the following general structure.



Glaxo Pharmaceuticals disclosed novel RORγ modulator and their use in treatment of disease mediated by RORγ, having the following formula in patent application WO 2013029338

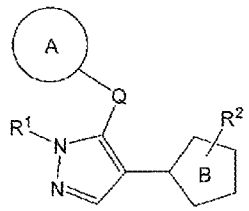


Piramal enterprises describes certain ROR gamma modulators and uses thereof with following general structure in patent application WO2015145371



Formula I

Takeda Pharmaceuticals disclosed novel RORγ modulators and their use in the treatment of disease mediated by RORγ, having following formula in patent application WO2013018395.



Though a number of different approaches in terms of different scaffolds, molecular formulae, none of these molecules have advanced far in the clinics. There is therefore an huge unmet need for providing novel compounds which are modulators of RORγ. We herein disclose novel compounds of formula (I) useful as RORγ modulator which may have a beneficial effect in the treatment of autoimmune or inflammatory diseases such as multiple sclerosis, rheumatoid arthritis, irritable bowel diseases, psoriasis, psoriatic arthritis which are mediated by RORγ, and methods for their preparation.

SUMMARY OF THE INVENTION

The invention provides compounds which are modulators of RORγ and their use for the treatment of autoimmune or inflammatory diseases such as multiple sclerosis, rheumatoid arthritis, irritable bowel diseases, psoriasis, psoriatic arthritis which are mediated by RORγ. The novel compounds are defined by the general formula (I) as given below. The compounds of the present invention are useful in the treatment of the human or animal body by regulation of RORγ receptor gene expression. The compounds of this invention are therefore suitable for the treatment/mitigation/regulation or prophylaxis of number autoimmune or inflammatory diseases.

EMBODIMENTS OF THE INVENTION

The main objective of the present invention is to provide novel compounds of general formula (I), their tautomeric forms, novel intermediates involved in their synthesis, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures suitable for the treatment of autoimmune or inflammatory diseases such as multiple sclerosis, rheumatoid arthritis, irritable bowel diseases, psoriasis, psoriatic arthritis.

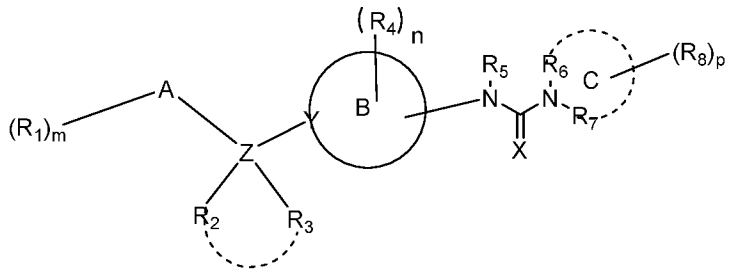
In an embodiment is provided a process for the preparation of novel compounds of general formula (I), their tautomeric forms, novel intermediates involved in their synthesis, their pharmaceutically acceptable salts, pharmaceutically acceptable solvates and pharmaceutical compositions containing them.

In another embodiment is provided pharmaceutical compositions containing compounds of general formula (I), their tautomeric forms, their pharmaceutically acceptable salts, solvates and their mixtures having pharmaceutically acceptable carriers, solvents, diluents, excipients and other media normally employed in their manufacture.

In a further another embodiment is provided the use of the novel compounds of the present invention for the treatment of autoimmune diseases, by administering a therapeutically effective & non-toxic amount of the compound of formula (I), or their pharmaceutically acceptable compositions to the mammals.

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (I),



formula (I)

Wherein

'A' represents either a bond, or the groups selected from -CN, -COOH, optionally substituted groups selected from (C_1-C_8)alkyl, (C_3-C_6)cycloalkyl, aryl, heteroaryl or heterocyclyl groups. In an embodiment A may be absent.

Ring 'B' represents aryl, heteroaryl or heterocyclyl wherein 'Y' represents C or N;

'Z' represents either a bond or the atoms C, or -N. In an embodiment Z may be absent.

When 'Z' represents C or N, R_2 and R_3 are each independently selected from the group comprising of hydrogen, hydroxyl, haloalkyl, optionally substituted groups selected from (C_1-C_8)alkyl, (C_1-C_8)alkoxy, (C_3-C_6)cycloalkyl, benzyl or carbocyclic group or R_2 and R_3 together with the atom to which they are attached may form a 3- to 10- membered carbocyclic ring system having optionally one or more than one heteroatoms;

R_5 represents hydrogen, optionally substituted (C_1-C_8)alkyl, (C_1-C_8)alkoxy, (C_3-C_6)cycloalkyl;

X represents -O, NR' wherein R' is hydrogen, CN, NO_2, OR" or optionally substituted (C_1-C_8)alkyl wherein R" is hydrogen, haloalkyl, optionally substituted (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl groups;

R_6 and R_7 are each independently selected from the group comprising of hydrogen, optionally substituted groups selected from (C_1-C_8)alkyl, aryl, heteroaryl, heterocyclyl or In an embodiment R_6 and R_7 together with the atom to which they are attached to form a heterocyclic, bridged or spiro ring system 'C' having optionally one or more than one heteroatoms;

In a preferred embodiment, the heterocyclyl group may be selected from heterocyclic ring is selected from aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, 2-oxopiperidinyl, 4-oxopiperidinyl, 2-oxopiperazinyl, 3-oxopiperazinyl, morpholinyl, thiomorpholinyl, 2-oxomorpholinyl, azepinyl, diazepinyl, oxapinyl, thiazepinyl, oxazolidinyl, thiazolidinyl;

Each of R_1, R_4 and R_8 at each occurrence is independently selected from the group comprising of hydrogen, halogen, hydroxy, cyano, oxo, halo(C_1-C_8)alkyl, optionally substituted (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_6)cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroaralkyl, heterocyclylalkyl, cycloalkanylalkyl, alkylsulfonyloxy, $-COR_a$, $-COOR_a$, $-OR_a$, $-S(O)_tR_a$, $-S(O)_tNR_a$, $-NR_aR_b$, $-CONR_aR_b$, $-N(R_a)COR_b$, $-N(R_a)COOR_b$, $-OCH_2COR_a$, $-N(R_a)CH_2COR_b$, $-N(R_a)CONR_aR_b$, $-S(O)_tNR_aR_b$, $-N(R_a)S(O)_tR_b$ groups;

'm', 'n' and 'p' represent integers from 0-2;

Each of R_a and R_b at each occurrence are independently selected from the group comprising of hydrogen, haloalkyl, optionally substituted groups selected from (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8) cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl groups; or wherever feasible, R_a and R_b together with the atom to which they are attached may form an optionally substituted 5- to 10- membered carbocyclic ring optionally containing 0-2 additional heteroatoms selected from –O-, -NR_9- or $S(O)_t$; wherein, R_9 represents hydrogen, optionally substituted groups selected from (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_8)haloalkyl; 't' represents integers from 1-2;

When any of above defined group is substituted the substitutions on them may be selected from hydrogen, hydroxy, cyano, halo, oxo, imino, haloalkyl, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroaralkyl, heterocyclylalkyl, alkylsulfonyloxy, -COR_a, -$COOR_a$, -OR_a, -$S(O)_tR_a$, -NR_aR_b, -$CONR_aR_b$, -$N(R_a)COR_b$, -$N(R_a)COOR_b$, -OCH_2COR_a, -$N(R_a)CH_2COR_b$, -$N(R_a)CONR_aR_b$, -$SO_2NR_aR_b$, -$N(R_a)SO_2R_b$ derivatives; wherein, R_a and R_b are as defined earlier;

In a preferred embodiment, the groups referred to above may comprise of:

- "Alkyl" by itself or as part of another substituent, means, unless otherwise stated, a straight- or branched-chain, fully saturated aliphatic hydrocarbon radical having the number of carbon atoms designated. For example, "C_{1-6}alkyl" refers to a hydrocarbon radical, either straight- or branched-chain, that contains from 1 to 6 carbon atoms and that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Alkyl includes branched-chain isomers of straight-chain alkyl groups, such as isopropyl, t-butyl, isobutyl, sec-butyl, and the like. Representative alkyl groups include straight- and branched-chain alkyl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. Further representative alkyl groups include straight and branched chain alkyl groups having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms.
- the "alkenyl" group used either alone or in combination with other radicals, is selected from a radical containing from two to eight carbons, more preferably groups selected from vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and the like; the "alkenyl" group includes dienes and trienes of straight and branched chains;

- the “alkynyl” group used either alone or in combination with other radicals, is selected from a linear or branched radical containing two to eight carbon atoms, more preferably thienyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, and the like. The term “alkynyl” includes di- and tri-ynes;
- the “cycloalkyl”, or “alicyclic” group used either alone or in combination with other radicals, is selected from a cyclic radical containing three to six carbons, more preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like;
- the “alkoxy” group used either alone or in combination with other radicals, is selected from groups containing an alkyl radical, as defined above, attached directly to an oxygen atom, more preferably groups selected from methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy, pentyloxy, hexyloxy, and the like;
- "Halo" or "halogen" by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl", are meant to include an alkyl in which one or more hydrogen is replaced by halogen atoms that can be the same or different, in a number ranging from one up to the maximum number of halogens permitted e.g. for alkyl, (2m'+l), where m' is the total number of carbon atoms in the alkyl group. For example, the term "halo$C_{1\text{-}8}$alkyl" is meant to include difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. Additionally, term "haloalkoxy" refers to an alkoxy radical substituted with one or more halogen atoms. In one group of embodiments, the haloalkyl and haloalkoxy groups have from one to five or from one to three halogen atoms. Examples of haloalkoxy groups include difluoromethoxy and trifluoromethoxy.
- the “aryl” or “aromatic” group used either alone or in combination with other radicals, is selected from a suitable aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused, more preferably the groups are selected from phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl, and the like;
- As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 4 to 7-membered monocyclic or 7 to 14-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or aromatic, and which consists of carbon atoms & also contains from 1 to 3 hetero atoms independently selected from

the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The term heterocycle as used in the specification includes both aromatic and non-aromatic single or fused cyclic system containing at least one heteroatom selected from N, O and S. The nitrogen and sulfur hetero atoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. A skilled person is well aware of the terms "heterocycle" or "heterocyclic system" and the present invention encompasses all such variations, alterations of definitions which are within the scope of such a skilled person. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. In a further optional embodiment, nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these hetero atoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5 to 7 membered monocyclic or bicyclic or 7 to 14 membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. Also included are fused ring, bridged bicyclic heterocycles, Spiro-compounds containing, for example, the above heterocycles.

- As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable monocyclic or bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycle include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin);
- the “cycloalkanylalkyl” group used either alone or in combination with other radicals, is selected from groups containing a cycloalkyl radical, as defined above, attached directly to an alkyl radical, as define above;
- the “heteroaryl” or “heteroaromatic” group used either alone or in combination with other radicals, is selected from suitable single or fused mono, bi or tricyclic aromatic

heterocyclic radicals containing one or more hetero atoms selected from O, N or S, more preferably the groups are selected from pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, isothiazolyl, imidazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, benzofuranyl, benzothienyl, indolinyl, indolyl, azaindolyl, azaindolinyl, pyrazolopyrimidinyl, azaquinazolinyl, pyridofuranyl, pyridothienyl, thienopyrimidyl, quinolinyl, pyrimidinyl, pyrazolyl, quinazolinyl, pyridazinyl, triazinyl, benzimidazolyl, benzotriazolyl, phthalazynil, naphthylidinyl, purinyl, carbazolyl, phenothiazinyl, phenoxazinyl, benzoxazolyl, benzothiazolyl and the like;

- the "aralkyl" group used either alone or in combination with other radicals, is selected from groups containing an aryl radical, as defined above, attached directly to an alkyl radical, as define above, more preferably groups selected from benzyl, phenethyl, and the like;
- the "heterocyclylalkyl" group used either alone or in combination with other radicals, is selected from groups containing an heterocyclyl radical, as defined above, attached directly to an alkyl radical, as define above;
- the "heteroaralkyl" group used either alone or in combination with other radicals, is selected from groups containing an heteroaryl radical, as defined above, attached directly to an alkyl radical, as define above;
- the term "alkylsulfonyloxy" represents R_xSO_2-group attached to an oxygen atom, such that oxygen acts as the point of attachment. R_x represents alkyl group;
- the "oxo" and "imino" group used either alone or in combination with other groups represents radical of formula -C=O or -C=NH respectively.
- The term "substituted," as used herein, means that any one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. The term "substituted," as used herein, means that any one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound.
- Compounds of formula (I) may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of formula (I), either as single species or mixtures thereof.

- Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.
- Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of formula (I).

List of Abbreviation

DMF: Dimethyl formamide

DCM: Dichloromethane

EDAC.HCl: N-(3-Dimethyl aminopropyl)-N'-ethyl carbodiimide hydrochloride,

HOBT: 1-Hydroxy benzotriazole

TFA: Trifluoro acetic acid

DCC: Dicyclohexylcarbodiimide

DIPEA: Disopropyl ethyl amine

EtOAc: Ethyl acetate

h: Hour(s)

rt : room temperature

min: Minute(s)

t_{Ret}: Retention time

HCl: Hydrochloric acid

RT: Room temperature [25-30 ^{0}C]

Cs_2CO_3: Cesium carbonate

TEA: Triethyl amine

HBTU : *N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate

Instrument details

Mass spectrum was recorded on LC-MS 2010-A Shimadzu.

HPLC purity was determined by using Agilent 1100 instrument.

HPLC Column: YMC J Sphere C18 (150X4.6 mm)4µ

Mobile phase: 0.05 % TFA in water: ACN gradient.

Flow rate: 1.0 ml/min.

Wave length: UV at 220 nm.

UPLC was determined on Acquity Ultra performance instrument.

UPLC Column: BEHC18 (2.1x100mm)1.7 µ

Mobile phase: 0.05 % TFA in water: ACN gradient.

Flow rate: 0.04 ml/min

NMR spectrum: Bruker Advance 400 MHz

Suitable groups and substituents on the groups may be selected from those described anywhere in the specification.

Preferred compounds according to the present invention include but are not limited to:

1-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-3-(4-(ethylsulfonyl)phenyl)urea;

1-(3,5-dichloro-4-(1-(5-(2,3-difluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-3-(4-(ethylsulfonyl)phenyl)urea;

1-(3,5-dichloro-4-(1-(5-(2,4-difluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-3-(4-(ethylsulfonyl)phenyl)urea;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-5-(ethylsulfonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide;

N-(3,5-dichloro-4-morpholinophenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-methyl-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-isopropyl-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(Ethylsulfonyl)-N-(4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-3,5-dimethylphenyl)piperazine-1-carboxamide;

N-(3,5-difluoro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperidine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)-1,4-diazepane-1-carboxamide;

N-(3,5-dichloro-4-((5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)methyl)phenyl)-4-(ethylsulfonyl) piperazine-1-carboxamide;

N-(3,5-dichloro-4-(2,3-dihydrospiro[indene-1,4'-piperidin]-1'-yl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(methylsulfonyl)piperazine-1-carboxamide;

N-(3-chloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(isopropylsulfonyl)piperazine-1-carboxamide;

2-(4-((3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl) carbamoyl) piperazin-1-yl)acetic acid;

Ethyl-2-(4-((3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)carbamoyl) piperazin-1-yl)acetate;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperidine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-6-(ethylsulfonyl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxamide;

1-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)thiazol-2-yl)cyclopropyl)phenyl)urea;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)thiazol-2-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-morpholinophenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)thiazol-2-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-(trifluoromethyl)cyclohexyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(2,3-difluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-6-(ethylsulfonyl)-2,6-diazaspiro[3.3]heptane-2-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4,4-difluorocyclohexyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

N-(2,6-dichloro-3'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(2,6-dichloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(2,6-dichloro-3'-methyl-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(2,6-dichloro-2'-methoxy-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(2,6-dichloro-4'-hydroxy-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(2,6-dichloro-3'-cyano-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-*N*-(3,5-dichloro-4-(1-(5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-cyanophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

N-(3-chloro-5-fluoro-4-(1-(5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(cyclopropylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(2-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)propan-2-yl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(2-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)propan-2-yl)phenyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-difluoro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-((5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)methyl)phenyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-((5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)methyl)phenyl)-4-(ethylsulfonyl) piperazine-1-carboxamide;

N-(3,5-dichloro-4-(2-oxopyridin-1(2H)-yl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)-3,5-dimethylpiperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonamido)piperidine-1-carboxamide;

N-(3-chloro-4-(1-(5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-5-fluorophenyl)-4-(cyclopropylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

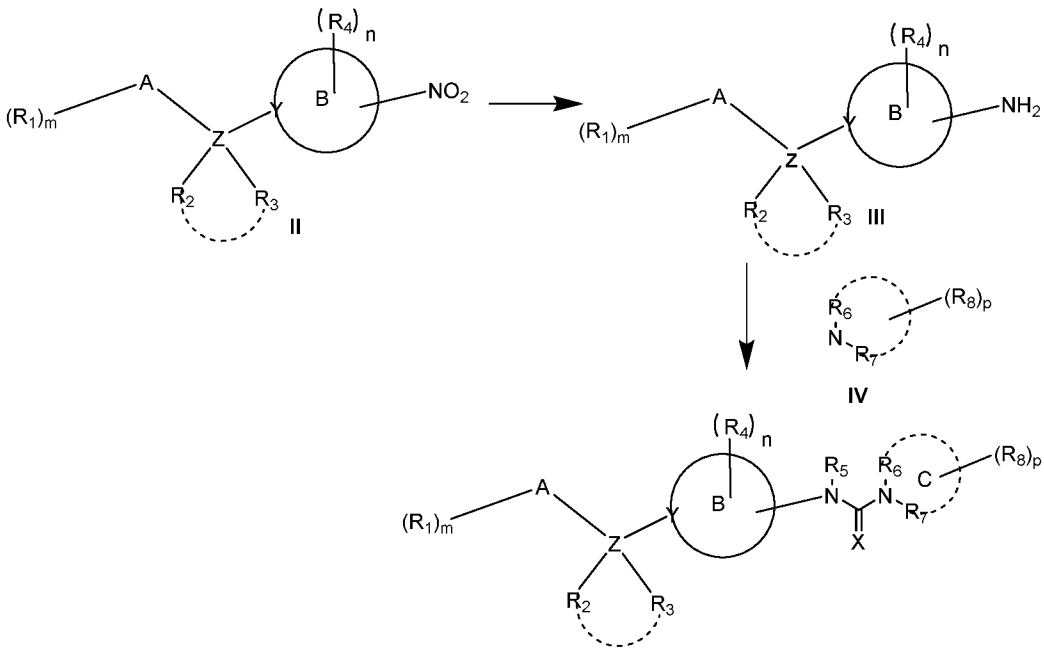
N-(3-chloro-4-(1-(5-(4-cyanophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-5-fluorophenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3-chloro-5-fluoro-4-(1-(5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(2,6-dichloro-3'-methoxy-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

The compounds of the present invention may be prepared using the methods described below, together with conventional techniques known to those skilled in the art of organic synthesis or variation thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to those described below, where all symbols are as defined earlier.

General Scheme 1: Synthesis of compounds of general formula (I)



formula (I)

Nitro compound **[II]** on reduction with suitable reducing agents such as Pd/C, H_2(g), RaneyNi, $FeCl_3$, NH_4Cl, $SnCl_2$ in solvents selected from MeOH, EtOH, and the like resulted in amine compound **[III].** Amine compound of formula **[III]** on coupling with suitable acid derivative **[IV]** in presence of phosgene and the like in solvent selected from DCM, DMF and the like, afforded compound of formula **[I].**

The compound of formula **[II]** and **[IV]** can be synthesized as per the general procedures known in the art along with suitable variations as are well known to a skilled person, in the art such as following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis; Wiley & Sons: New York, Volumes 1-21; R. C. LaRock, Comprehensive Organic Transformations, 2.nd edition Wiley-VCH, New York 1999; Comprehensive Organic Synthesis, B. Trost and I. Fleming (Eds.) vol. 1-9 Pergamon, Oxford, 1991; Comprehensive Heterocyclic Chemistry, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1984, vol. 1-9; Comprehensive Heterocyclic Chemistry II, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1996, vol. 1-1 1 ; and Organic Reactions, Wiley & Sons: New York, 1991, Volumes 1–40, to name some of the known literature processes, each of which are incorporated by reference herein.

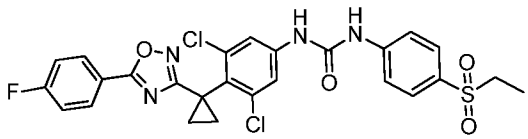
Unless otherwise specified, 1H NMR spectral data given in the examples are recorded using a 400 MHz spectrometer (Bruker Topspin 3.5) and reported in δ scale. Tetra methyl silane is used as the internal standard.

The pharmaceutically acceptable salts forming a part of this invention may be prepared by treating the compound of formula **(I)** with suitable acids in suitable solvents by processes known in the art.

The invention is further exemplified by the following examples below, which provides some of the several preferred embodiments of the present invention. These examples are provided merely as representative embodiments and should not be construed to limit the scope of the invention in any way.

Example 1

Preparation of 1-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-3-(4-(ethylsulfonyl)phenyl)urea

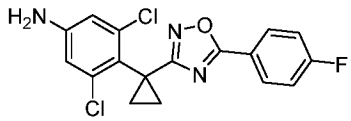


4-(ethylsulfonyl) aniline (50.9 mg, 0.275 mmol) and triethyl amine (0.042 ml, 0.302 mmol) were dissolved in CH_2Cl_2 (5 mL) with stirring at -78°C. To this mixture triphosgene (32.6 mg, 0.110 mmol) dissolved in CH_2Cl_2 (5 mL) was added dropwise at -78° C. The reactants were then warmed to 0°C and stirred for 30 min. Thereafter the reactants and reaction products were cooled to 0°C. 3,5-dichloro-4-(1-(5-(4-

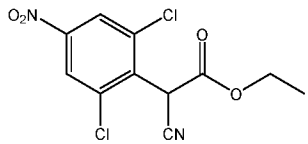
fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)aniline (100 mg, 0.275 mmol) dissolved in CH_2Cl_2 (5 mL) and triethyl amine (0.042 ml, 0.302 mmol) were added slowly and the resulting reaction mixture was further stirred at room temperature for 12h.The reaction was then quenched with the addition of HCl solution (1M,15 mL). The organic layer was collected from the reaction mixture and the remaining aqueous layer was further extracted with ethyl acetate. The obtained organic layers were pooled and washed with saturated NaCl solution. The organic layer was separated and dried over anhydrous sodium sulfate. The solvents were removed on rotatory evaporator to get crude product, which was purified by flash chromatography using mobile phase (EtOAc: Hexane /7:3) to get 58 mg of yellow colored solid product

^{1}HNMR (DMSO-d_6): 9.47 (s, 1H), 9.24 (s, 1H),8.13-8.10 (m, 2H), 7.79 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.65 (s, 2H), 7.47-7.43 (m, 2H), 3.22 (q, J_1= 7.2 Hz, J_2 = 2.0 Hz ,2H), 1.98-1.89 (m, 2H), 1.59-1.56 (m, 2H), 1.08 (t, J = 7.2 Hz, 3H).

Synthesis of intermediate: 3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl) cyclopropyl)aniline

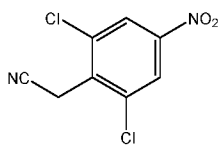


Step 1: ethyl 2-cyano-2-(2,6-dichloro-4-nitrophenyl)acetate



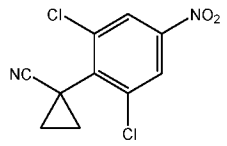
To a stirred solution of 1,2,3-trichloro-5-nitrobenzene (50 g, 221 mmol) and cesium carbonate (151 g, 464 mmol) in DMF (200 mL) was added ethyl cyano acetate (28.3 mL, 265 mmol) at 10-20^{o}C. Reaction mixture was heated at 70-75^{o}C for 1 h before it was cooled and dumped in to 2N 200 mL HCl solution. Solid obtained was filtered to get title product as brown solid. ^{1}HNMR (DMSO-d_6): 8.47 (s, 2H), 6.54 (s, 1H), 4.28 (q, J = 6.8 Hz, 2H), 1.23 (t, J = 6.8 Hz, 3H).

Step 2: 2-(2,6-dichloro-4-nitrophenyl)acetonitrile



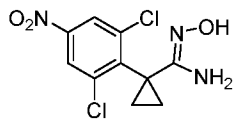
To a stirred solution of product of step 1 ethyl 2-cyano-2-(2,6-dichloro-4-nitrophenyl)acetate (52 g, 172 mmol) in DMSO (12 mL) and water (4.5 mL) was added lithium chloride (9.46 g, 223 mmol) at 25-30° C. The reaction mixture was heated at 165° C for 1h. The reaction mixture was cooled and dumped in to ice cold water. Solid obtained was filtered to get 25 g title compound. ^{1}HNMR (DMSO-d_6): 8.42 (s, 2H), 4.31 (s, 2H).

Step 3: Preparation of 1-(2,6-dichloro-4-nitrophenyl)cyclopropane-1-carbonitrile



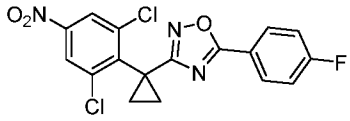
To a stirred solution of product of step 2, 2-(2,6-dichloro-4-nitrophenyl)acetonitrile (4.0 g, 17.31 mmol) in acetonitrile (40 mL) was added ethylene dibromide (4.48 ml, 51.9 mmol) followed by tetra butyl ammonium bromide (5.58 g, 17.31 mmol). To this was added 8 mL 50 % NaOH solution at 25-30°C and reaction mixture was stirred at 70-75°C for 12 h. The reaction mixture was poured in to water and extracted with EtOAc. The organic layer was separated, washed with water, dried over sodium sulfate and solvents were removed on rotatory evaporator to get crude product, which was purified by column chromatography (4% EtOAc in hexane) to get titled product. ^{1}HNMR (DMSO-d_6): 8.42 (s, 2H), 2.06-2.03 (m, 2H), 1.57-1.53 (m, 2H).

Step 4: 1-(2,6-dichloro-4-nitrophenyl)-N'-hydroxycyclopropane-1-carboximidamide



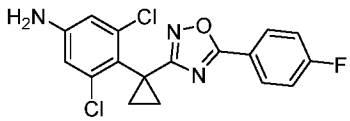
To a stirred solution of 1-(2,6-dichloro-4-nitrophenyl)cyclopropane-1-carbonitrile (5 g, 19.45 mmol) in rectified spirit (50 mL) was added hydroxyl amine hydrochloride (3.38 g, 48.6 mmol) and K_2CO_3 (6.72 g, 48.6 mmol) at 25-30°C. The reaction mixture was refluxed for 16 h. The progress of reaction was monitored by TLC. The reaction mixture was diluted with water and precipitated solid was filtered to get title product. ^{1}HNMR (DMSO-d_6): 9.26 (s, 1H), 8.19 (s, 2H), 5.16 (s, 2H), 1.74-1.70 (m, 2H), 1.08-1.05 (m, 2H).

Step 5: 3-(1-(2,6-dichloro-4-nitrophenyl)cyclopropyl)-5-(4-fluorophenyl)-1,2,4-oxadiazole



To a stirred solution of 4-fluorobenzoic acid (0.560 g, 4 mmol), HOBT (0.857 g, 5.60 mmol) in DMF (30 mL) was added EDC: HCl (1.073 g, 5.60 mmol) and stirred at 25-30° C over a period of 15 min.. To this was added product of step 4 (1.16 g, 4 mmol) and stirred at 110°C over a period of 16 h. The progress of reaction was monitored by TLC. The reaction mixture was poured in water and extracted with EtOAc. The organic layer was washed with water followed by sodium bicarbonate solution. The organic layer was separated, dried over sodium sulfate and solvents were removed to get crude product, which was column purified using mobile phase (0-3% EtOAc: Hexane) to get title product. ^{1}HNMR (DMSO-d_6): 8.38 (s, 2H), 8.13 (dd, J = 5.2 and 8.8 Hz, 2H), 7.46 (t, 2H), 2.01 (bd, 2H), 1.65 (bd, 2H).

Step 6: 3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)aniline

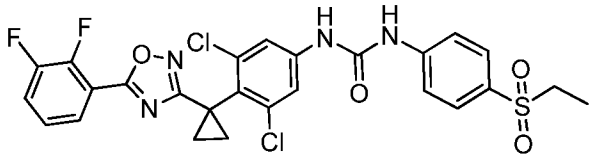


To a stirred solution of product of step 5 (140 mg, 0.355 mmol) in ethyl acetate (5 mL) was added stannous chloride dihydrate (401 mg, 1.776 mmol) and stirred at 25-30° C for 3 h. The progress of reaction was monitored by TLC. The reaction mixture was diluted with EtOAc, basified with aq. ammonia and passed through celite using buchner funnel. The organic layer was separated, solvents were removed on rotatory evaporator to get title product. ^{1}HNMR (DMSO-d_6): 8.12-8.08 (m, 2H), 7.46-7.42 (m, 2H), 6.63 (s, 2H), 5.72 (s, 2H), 1.82-1.79 (m, 2H), 1.45-1.42 (m, 2H).

Using appropriate starting materials and suitable modifications of the process described in **example 1**, including suitable addition and/or deletion of steps as may be necessary, well within the scope of a person skilled in the art, the following compounds were prepared in an analogues manner.

Example 2

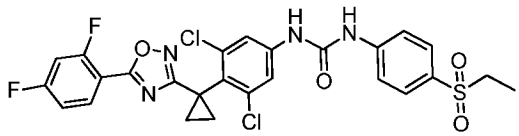
Preparation of 1-(3,5-dichloro-4-(1-(5-(2,3-difluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-3-(4-(ethylsulfonyl)phenyl)urea



^{1}HNMR (DMSO-d_6): 9.49 (s, 1H), 9.28 (s, 1H),7.90 -7.80 (m, 1H), 7.81 -7.78 (m, 3H), 7.72 (d, J = 8.8 Hz, 2H), 7.65 (s, 2H), 7.45-7.44(m, 1H), 7.37-7.34 (m, 1H), 3.23 (q, J_1= 7.2 Hz, J_2 = 2.8 Hz ,2H), 1.98-1.88 (m, 2H), 1.59-1.56(m, 2H), 1.09 (t, J = 7.2 Hz, 3H).

Example 3

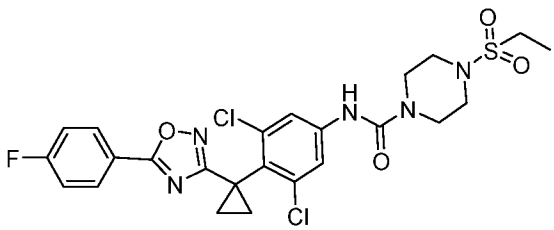
Preparation of 1-(3,5-dichloro-4-(1-(5-(2,4-difluorophenyl)-1,2,4-oxadiazol-3-l)cyclopropyl)phenyl)-3-(4-(ethylsulfonyl)phenyl)urea



^{1}HNMR (DMSO-d_6): 9.50 (s, 1H), 9.28 (s, 1H),8.18-8.12 (m, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.65 (s, 2H), 7.63-7.58 (m, 1H), 7.37-7.34 (m, 1H), 3.22 (q, J_1= 7.2 Hz, J_2 = 2.0 Hz ,2H), 1.91-1.88 (m, 2H), 1.57-1.54(m, 2H), 1.09 (t, J = 7.2 Hz, 3H).

Example 4

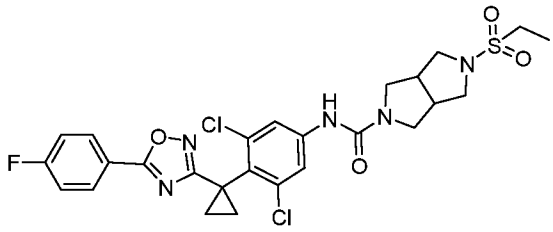
***N*-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}HNMR (DMSO-d_6): δ 8.99 (s, 1H), 8.09–8.12 (m, 2H), 7.66 (s, 2H), 7.42-7.47 (m, 2H), 3.50-3.56 (m, 4H), 3.20-3.29 (m, 4H), 3.06-3.11 (m, 2H), 1.86-1.90 (m, 2H), 1.50-1.54 (m, 2H), 1.27-1.29 (m, 3H).

Example 5

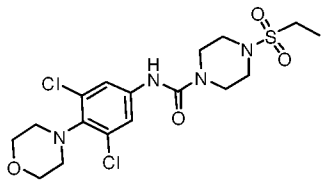
N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-5-(ethylsulfonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide



^{1}HNMR ($CDCl_3$): δ 8.08–8.12 (m, 2H), 7.49 (s, 2H), 7.17-7.21 (m, 2H), 6.35 (s, 1H), 3.73-3.78 (m, 2H), 3.67-3.69 (m, 2H), 3.41-3.45 (m, 2H), 3.03-3.10 (m, 4H), 1.97-2.01 (m, 2H), 1.52-1.37 (m, 2H), 1.03-1.07 (m, 3H),.

Example 6

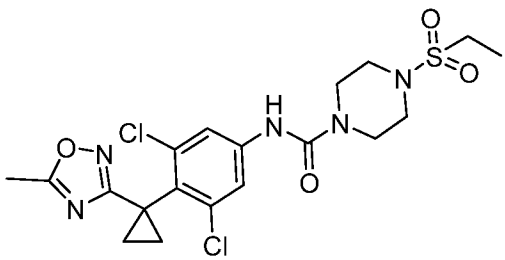
N-(3,5-dichloro-4-morpholinophenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide



^{1}HNMR (DMSO-d_6): δ 8.86 (s, 1H), 7.58 (s, 2H), 3.66-3.68 (m, 4H), 3.50-3.53 (m, 4H), 3.17-3.20 (m, 4H), 3.05-3.10 (m, 8H), 1.19-1.23 (brt, 3H).

Example 7

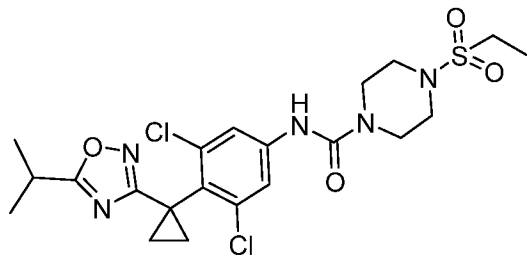
N-(3,5-dichloro-4-(1-(5-methyl-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d*6): δ8.97 (s, 1H), 7.63 (s, 2H), 3.53 (t, 4H), 3.21-3.19 (m, 4H), 3.09-3.07 (m, 2H), 1.74 (m, 2H), 1.44 (m, 2H), 1.21, (t, J = 7.6 Hz 3H)

Example 8

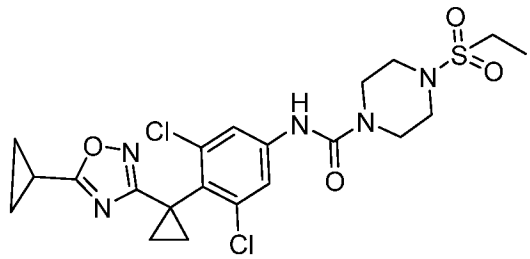
***N*-(3,5-dichloro-4-(1-(5-isopropyl-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d*6): δ8.98 (s, 1H), 7.63 (s, 2H), 3.55 – 3.52 (m, 4H), 3.22 – 3.20 (m, 4H), 3.09 – 3.07 (m, 2H), 1.75 (m, 2H), 1.44 (m, 2H), 1.28 – 1.26 (d, *J* = 87.2 Hz, 6H), 1.23 – 1.19 (m, 3H).

Example 9

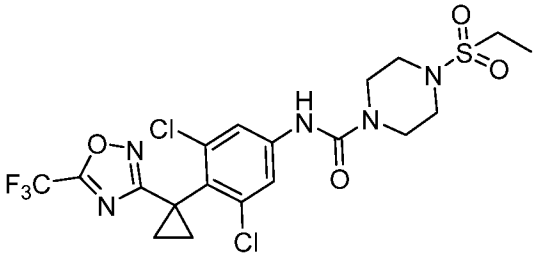
***N*-(3,5-dichloro-4-(1-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*: δ8.96 (s, 1H), 7.62 (s, 2H), 3.53 – 3.52 (m, 4H), 3.20 (m, 4H), 3.09 – 3.07 (m, 2H), 1.72 – 1.71 (m, 2H), 1.41 (m, 2H), 1.23 – 1.17 (m, 6H).

Example 10

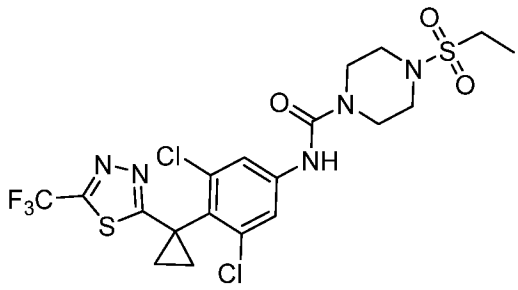
***N*-(3,5-dichloro-4-(1-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*: δ9.03 (s, 1H), 7.68 (s, 2H), 3.56 – 3.55 (m, 4H), 3.23 – 3.20 (m, 4H), 3.10 – 3.07 (q, 2H), 1.88 – 1.85 (m, 2H), 1.64 – 1.60 (m, 2H), 1.22 (t, 3H)

Example 11

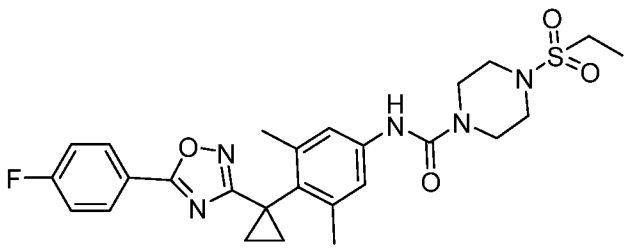
***N*-(3,5-dichloro-4-(1-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*) δ9.08 (s, 1H), 7.73 (s, 2H), 3.53-3.55 (m, 4H), 3.21-3.22(m, 4H), 3.08-3.19 (m, 2H), 2.12-2.13(m, 2H), 1.77-1.78 (m, 2H), 1.20-1.23(m, 3H)

Example 12

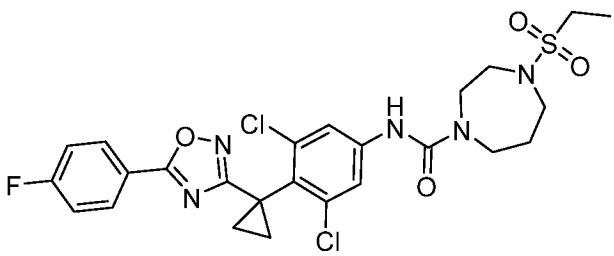
4-(Ethylsulfonyl)-N-(4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-3,5-dimethylphenyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.53 (s, 1H), 8.12-8.08 (m, 2H), 7.46-7.42 (m, 2H), 7.13 (s, 2H), 3.51 (t, *J* = 4.8 Hz, 4H), 3.20 (t, J = 4.8 Hz, 4H), 3.09 (q, J = 7.2 Hz, 2H), 2.26 (s, 6H), 1.75-1.72 (m, 2H), 1.32-1.29 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H)

Example 13

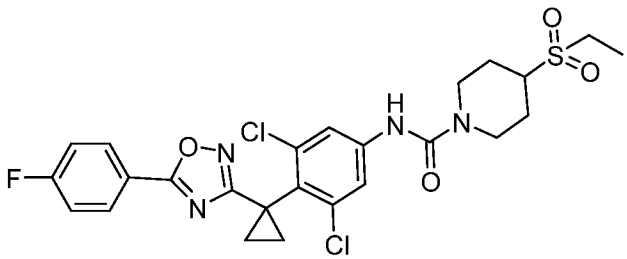
***N*-(3,5-difluoro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*: δ9.03 (s, 1H), 8.08-8.11 (m, 2H), 7.44 (t, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 10.8 Hz, 2H), 3.53-3.55 (m, 4H), 3.21-3.22(m, 4H), 3.06-3.12 (m, 2H), 1.71 (d, *J* = 6.8 Hz, 2H), 1.42(d, *J* = 6.0 Hz, 2H), 1.15-1.24(m, 3H)

Example 14

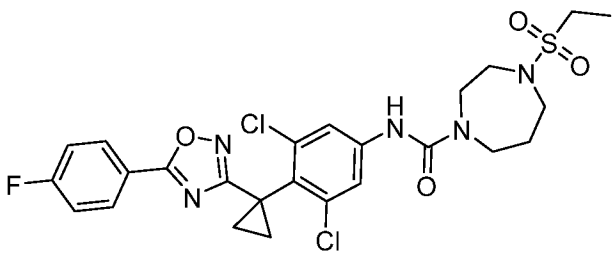
***N*-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperidine-1-carboxamide**



^{1}H NMR ($CDCl_3$, 400 MHz): δ7.87-7.89 (m, 1H), 7.77-7.80 (m, 1H), 7.48-7.53 (m, 3H), 7.26-7.30 (m, 1H), 6.42 (s, 1H), 4.42-4.44 (brd, 2H), 4.32-4.34 (brd, 1H), 4.12-4.14 (brd, 2H), 3.96-3.99 (brd, 2H), 2.99-3.06 (m, 4H), 1.98-2.02 (m, 2H),1.67-1.72 (m, 1H), 1.35-1.42 (m, 2H).

Example 15

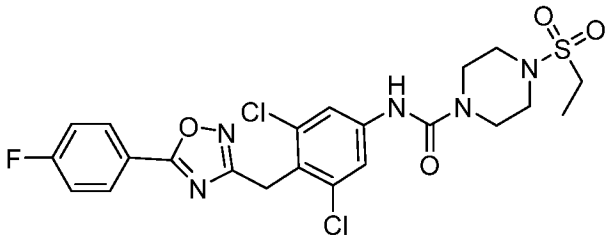
***N*-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)-1,4-diazepane-1-carboxamide**



^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.67 (s, 1H), 8.14-8.10 (m, 2H), 7.73 (s, 2H), 7.48-7.44 (m, 2H), 3.61-3.59 (m, 4H), 3.45-3.30 (m, 4H), 3.08 (q, J = 7.2 Hz, 2H), 1.89-1.81 (m, 4H), 1.54-1.52 (m, 2H), 1.18 (t, J = 7.2 Hz, 3H).

Example 16

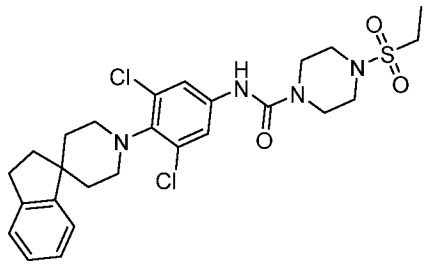
***N*-(3,5-dichloro-4-((5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)methyl)phenyl)-4-(ethylsulfonyl) piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*) δ8.98 (s, 1H), 8.12 (dd, *J* = 8.4 Hz & 5.6 Hz, 2H), 7.68 (s, 1H), 7.45 (m, 2H), 4.35 (s, 2H), 3.54 (s, 4H), 3.08 (m, 2H), 1.22 (m, 5H).

Example 17

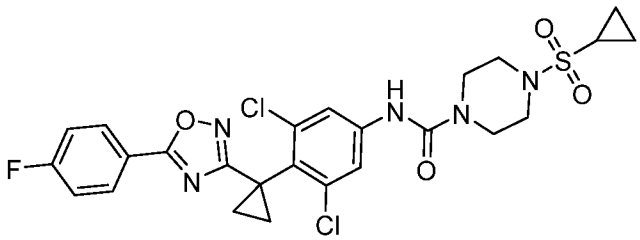
***N*-(3,5-dichloro-4-(2,3-dihydrospiro[indene-1,4'-piperidin]-1'-yl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.84 (s, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 2.4 Hz, 1H), 7.23-7.13 (m, 4H), 3.53-3.44 (m, 6H), 3.31-3.11 (m, 4H), 3.08 (q, J = 7.2 Hz, 2H), 2.90-2.85 (m, 4H), 2.06 (t, J = 7.6 Hz, 2H), 1.95-1.92 (m, 2H), 1.51-1.48 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H).

Example 18

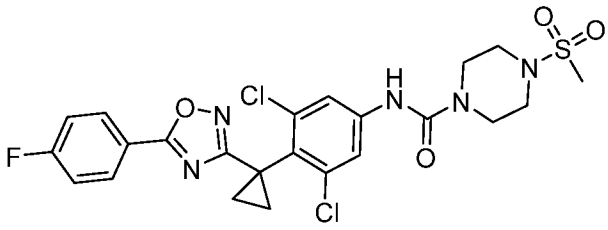
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.02 (s, 1H), 8.13-8.09 (m, 2H), 7.67 (s, 2H), 7.47-7.42 (m, 2H), 3.53 (t, J = 4.8 Hz, 4H), 3.22 (t, J = 4.8 Hz, 4H), 2.66-2.60 (m, 1H), 1.88 (q, J = 4.8 Hz, 2H), 1.54 (q, J = 4.8 Hz, 2H), 1.02-0.96 (m, 4H)

Example 19

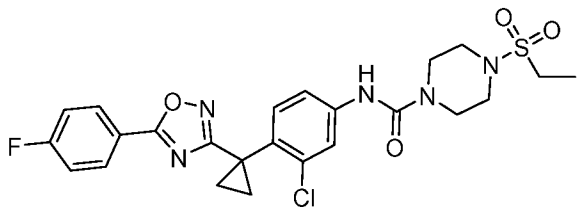
***N*-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(methylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.02 (s, 1H), 8.12-8.08 (m, 2H), 7.67 (s, 2H), 7.47-7.42 (m, 2H), 3.58 (t, J = 4.8 Hz, 4H), 3.15 (t, J = 4.8 Hz, 4H), 2.90 (s, 3H), 1.90-1.87 (m, 2H), 1.54-1.51 (m, 2H).

Example 20

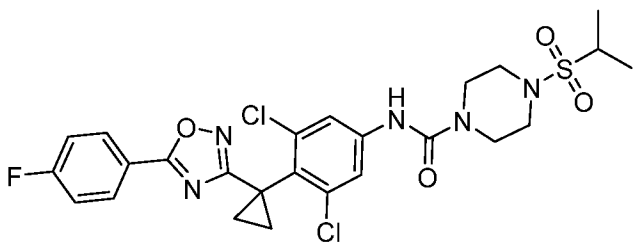
***N*-(3-chloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.80 (s, 1H), 8.12-8.09 (m, 2H), 7.67 (d, J = 2.8 Hz, 1H), 7.52 (dd, J = 2.4 & 8.8 Hz, 1H), 7.46-7.42 (m, 2H), 7.34 (d, J = 8.4 Hz, 1H), 3.53 (t, J = 4.4 Hz, 4H), 3.18 (t, J = 4.4 Hz, 4H), 3.07 (q, J = 7.2 Hz, 2H), 1.73 (q, J = 4.8 Hz, 2H), 1.41 (q, J = 4.8 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H)

Example 21

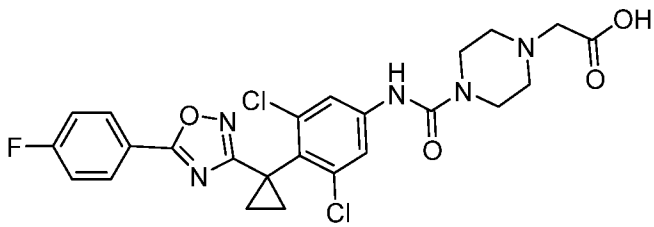
***N*-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(isopropylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.99 (s, 1H), 8.14-8.10 (m, 2H), 7.67 (s, 2H), 7.48-7.44 (m, 2H), 3.52 (t, J = 4.8 Hz, 4H), 3.42-3.39 (m, 1H), 3.29 (t, J = 4.8 Hz, 4H), 1.91-1.88 (m, 2H), 1.55-1.52 (m, 2H), 1.25 (d, J =6.8 Hz, 6H)

Example 22

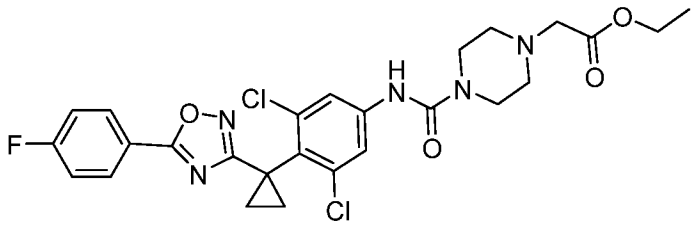
2-(4-((3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl) phenyl) carbamoyl) piperazin-1-yl)acetic acid



^{1}H NMR (DMSO-d_6, 400 MHz, δ): 8.87-8.92 (brd, 1H), 8.12-8.21 (brd, 2H), 7.68-7.79 (brd, 2H), 7.46 -7.54 (brd, 2H), 3.10-3.60 (brm, 8H), 2.70 (brs, 2H), 1.99 (brs, 2H), 1.53 (brs, 2H).

Example 23

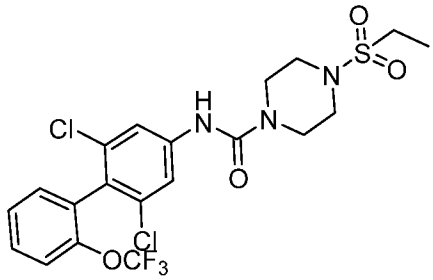
Ethyl-2-(4-((3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl) cyclopropyl)phenyl)carbamoyl) piperazin-1-yl)acetate



^{1}H NMR (DMSO-d_6, 400 MHz, δ): 8.91(s, 1H), 8.09-8.12 (m, 2H), 7.66 (s, 2H), 7.42-7.47 (m, 2H), 4.11-4.13 (brd, 2H), 3.32-3.58 (m, 8H), 2.66 (brs, 2H), 1.88-1.90 (m, 2H), 1.50-1.53 (m, 2H), 1.17-1.22 (m, 3H).

Example 24

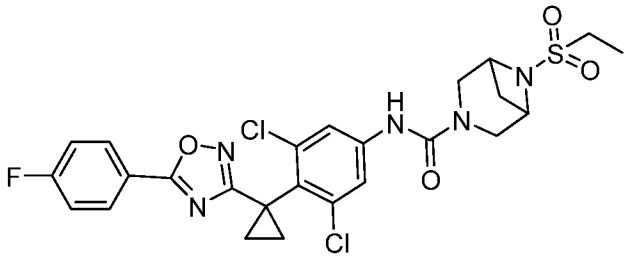
N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperidine-1-carboxamide



^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.46–7.52 (m, 3H), 7.36–7.40 (m, 2H), 7.27-7.29 (m, 1H), 6.53 (s, 1H), 3.62-3.65 (brt, 4H), 3.38-3.41 (brt, 4H), 2.98-3.04 (m, 2H), 1.41 (t, *J* = 7.4 Hz, 3H)

Example 25

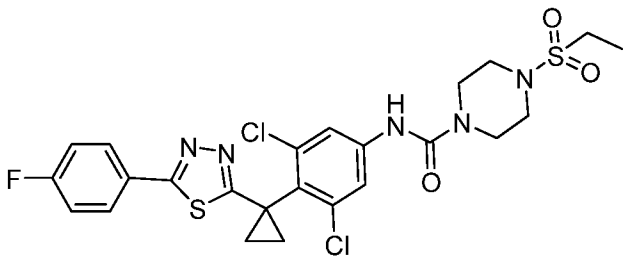
***N*-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-6-(ethylsulfonyl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxamide**



1H NMR ($CDCl_3$, 400 MHz, δ): 7.88–7.90 (m, 1H), 7.78–7.81 (m, 1H), 7.47-7.53 (m, 1H), 7.41 (m, 2H), 7.30-7.31 (m, 1H), 6.76 (m, 1H), 4.23-4.27 (brd, 2H), 2.92-3.07 (m, 5H), 2.14-2.18 (m, 2H), 1.99-2.02 (m, 2H), 1.86-1.90 (m, 2H), 1.41-1.44 (m, 4H)

Example 26

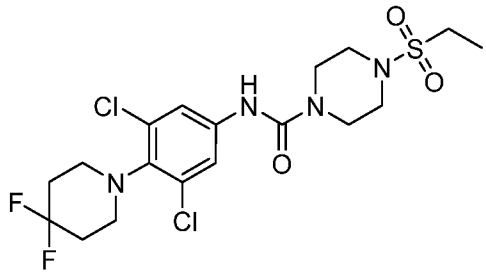
***N*-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)thiazol-2-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.83-7.86 (m, 2H), 7.45 (s, 2H), 7.23 (s, 1H), 7.11-7.16 (m, 2H), 4.10-4.16 (m, 4H), 3.59-3.61 (m, 4H), 2.92-3.01 (m, 2H), 2.00-2.11 (m, 2H), 1.70-1.77 (m, 2H), 1.32-1.39 (m, 3H).

Example 27

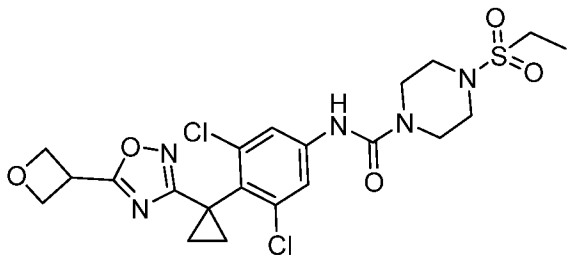
***N*-(3,5-dichloro-4-morpholinophenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*): δ8.57 (s, 1H), 7.59 (s, 2H), 3.51-3.53 (m, 4H), 3.16-3.19 (m, 8H), 3.08-3.10 (m, 2H), 1.90-2.20 (m, 4H), 1.22 (t, 3H)

Example 28

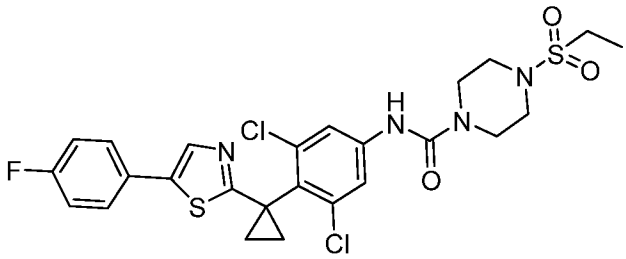
***N*-(3,5-dichloro-4-(1-(5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.36 (s, 2H), 6.80 (s, 1H), 3.79-3.85 (m, 1H), 3.56-3.61 (m, 8 H), 3.32-3.35 (m, 4H), 2.97-3.03 (m, 2H), 1.91-1.94 (m, 2H), 1.51-1.53 (m, 2H), 1.39-1.42 (t, 3H).

Example 29

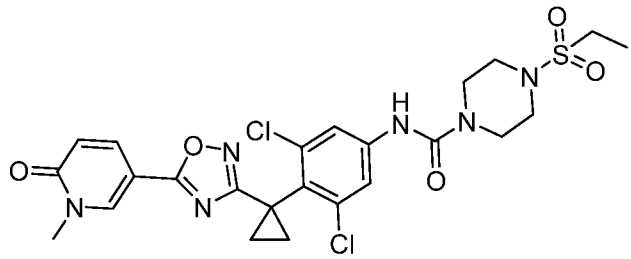
***N*-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)thiazol-2-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.72 (s, 1H), 7.51 (d, 2H), 7.28-7.46 (m, 2H), 6.91 (m, 2H), 3.61-3.65 (m, 4H), 2.98-3.04 (m,2H), 2.09-2.12 (m, 2H), 1.62-1.65 (m, 2H), 1.37-1.44 (m, 3H).

Example 30

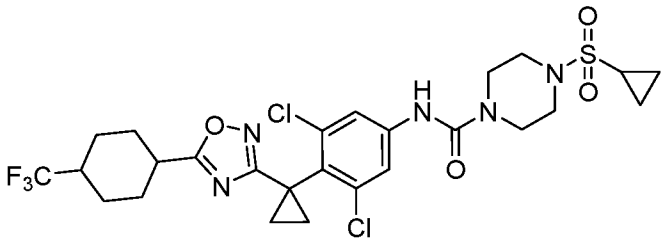
N-(3,5-dichloro-4-(1-(5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-d6, 400 MHz, δ): 9 (s, 1H), 8.68 (d, *J* = 2.8 Hz, 1H), 7.87 (d, *J* = 9.6 & 2.4 Hz, 1H), 7.66 (s, 2H), 6.53 (d, *J* = 9.2 Hz, 1H), 3.54 (brd, 7H), 3.20-3.23 (brt, 4 H), 3.07–3.13 (q, *J* = 7.4 Hz, 2H), 1.84-1.87 (m, 2H), 1.49-1.52 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H).

Example 31

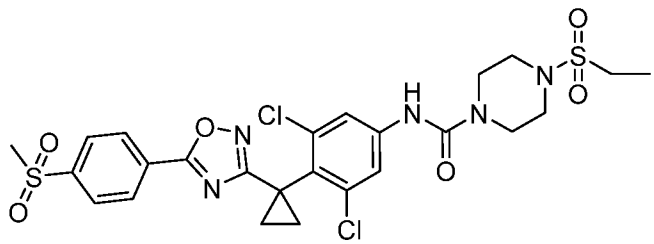
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-(trifluoromethyl)cyclohexyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide



^{1}H NMR ($CDCl_3$):δ7.36 (s, 2H), 6.8 (s, 1H), 3.6 - 3.57 (m, 4H), 3.35 - 3.32 (m, 4H), 2.90-2.84 (m, 1H), 2.30 - 2.13 (m, 6H),1.92 - 1.89 (m, 2H), 1.68 - 1.64(m, 2H), 1.52-1.45 (m, 4H), 1.27-1.19 (m, 4H).

Example 32

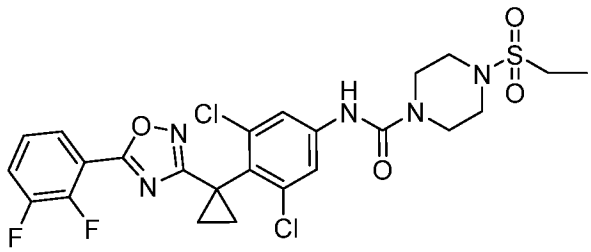
***N*-(3,5-dichloro-4-(1-(5-(4-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl) cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



1H NMR (DMSO-d6, δ): 9.02 (s, 1H), 8.30 (d, *J* = 8.4 Hz, 2H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.68 (s, 2H), 3.57 – 3.54 (m, 4H), 3.22 – 3.21 (m, 4H), 3.11 – 3.09 (m, 2H), 1.92-1.91 (m, 2H), 1.57-1.56 (m, 2H), 1.25-1.21 (t, *J* = 7.6 Hz, 3H)

Example 33

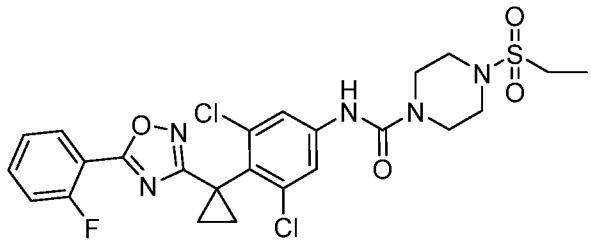
N-(3,5-dichloro-4-(1-(5-(2,3-difluorophenyl)-1,2,4-oxadiazol-3-yl) cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*): δ 9.02 (s, 1H), 7.89 - 7.70 (m, 2H), 7.68 (s, 2H), 7.3 - 7.5 (m, 1H), 3.57 – 3.54 (m, 4H), 3.23 – 3.21 (m, 4H), 3.13 – 3.07 (m, 2H), 1.91 - 1.88 (m, 2H), 1.57 - 1.54 (m, 2H), 1.24 - 1.21 (t, *J* = 7.6 Hz, 3H).

Example 34

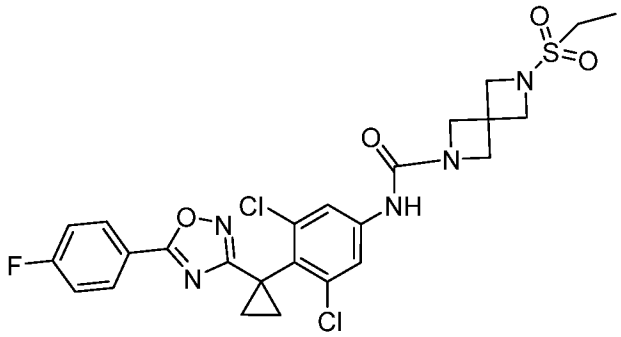
***N*-(3,5-dichloro-4-(1-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*) δ 9.02 (s, 1H), 8.09 - 8.06 (m, 1H), 7.79 - 7.74 (m, 1H), 7.68 (s, 2H), 7.53 -7.43 (m, 2H), 3.56 – 3.54 (m, 4H), 3.23 – 3.21 (m, 4H), 3.13 – 3.09 (m, 2H), 1.91 - 1.88 (m, 2H), 1.56 – 1.53 (m, 2H), 1.24 – 1.21 (t, 3H).

Example 35

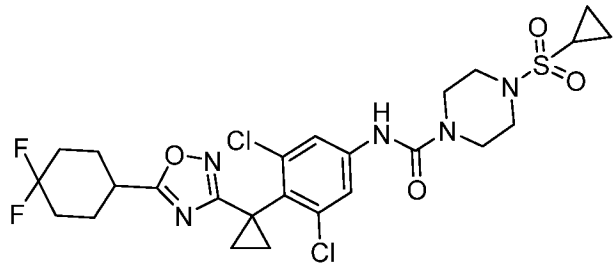
***N*-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-6-(ethylsulfonyl)-2,6-diazaspiro[3.3]heptane-2-carboxamide**



1H NMR ($CDCl_3$, 400 MHz, δ): 8.13-8.17 (m, 2H), 7.22-7.30 (m, 4H), 3.85-3.87 (brd, 2H), 3.72-3.74 (brt, 4H), 3.58-3.59 (brd, 2H), 2.97-3.00 (m, 2H), 2.06-2.07 (brt, 2H), 1.57-1.62 (brs, 2H), 1.35-1.39 (t, 3H)

Example 36

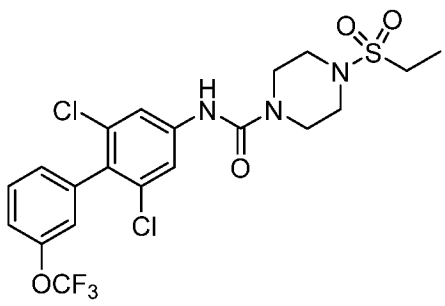
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4,4-difluorocyclohexyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.36 (brd, 2H), 6.97 (s, 1H), 3.57-3.59 (m, 4H), 3.31-3.33 (m, 4 H), 2.90-3.0 (m, 1H), 2.19-2.29 (m, 5H), 1.89-2.07 (m, 5H), 1.49-1.61 (m, 2H), 1.26-1.30 (m, 1H), 1.18-1.21 (m, 2H), 1.03-1.06 (m, 2H).

Example 37

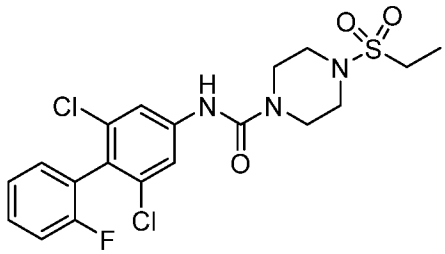
***N*-(2,6-dichloro-3'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl) piperazine-1-carboxamide**



1H NMR (DMSO-*d6*: δ 9.03 (s, 1H), 7.74 (s, 2H), 7.69-7.59 (m, 1H), 7.41-7.38 (m, 1H), 7.31-7.27(m, 1H), 3.57-3.54 (m, 4H), 3.23-3.21 (m, 4H), 3.10-3.08 (m, 2H), 1.24-1.20 (t, *J*=7.4Hz, 3H

Example 38

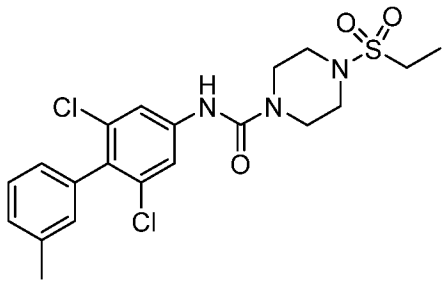
N-(2,6-dichloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*): δ8.97 (s, 1H), 7.63 (s, 2H), 3.53 (t, 4H), 3.21-3.19 (m, 4H), 3.09-3.07 (m, 2H), 1.74 (m, 2H), 1.44 (m, 2H), 1.21, (t, *J* = 7.6 Hz 3H)

Example 39

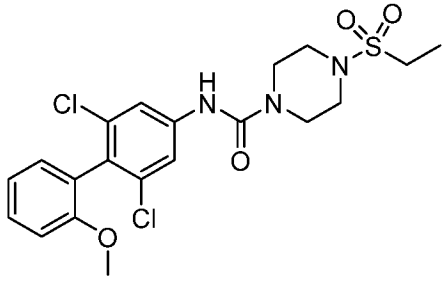
***N*-(2,6-dichloro-3'-methyl-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



1H NMR (DMSO-*d6*: δ 9.02 (s, 1H), 7.72 (s, 2H), 7.35-7.33 (m, 1H), 7.23-7.21 (m, 1H), 7.04-7.00 (m, 2H), 3.57-3.55 (m, 4H), 3.23-3.21 (m, 4H), 3.13-3.07 (m, 2H), 2.35(s, 3H), 1.23 (t, *J*=7.4Hz, 3H).

Example 40

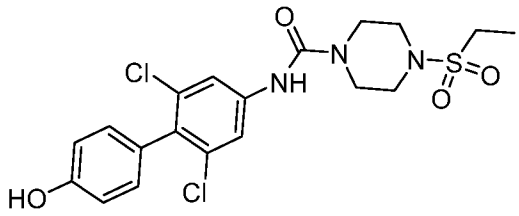
***N*-(2,6-dichloro-2'-methoxy-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*: δ8.99 (s, 1H), 7.67 (s, 2H), 7.42-7.38 (m, 1H), 7.12-7.10 (m, 1H), 7.09-7.00(m, 2H), 3.71(s, 3H), 3.56-3.55 (m, 4H), 3.23-3.21 (m, 4H), 3.13-3.07(m, 2H), 1.23 (t, *J*=7.4Hz, 3H).

Example 41

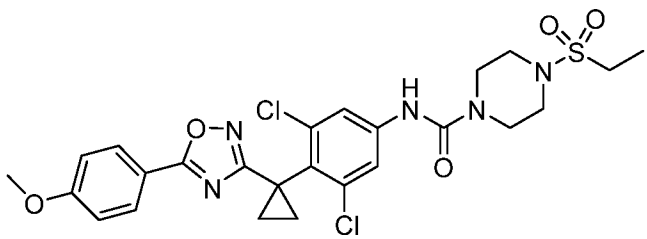
***N*-(2,6-dichloro-4'-hydroxy-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*):δ9.59 (s, 1H), 8.98(s, 1H), 7.70(s, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 3.55-3.54 (m, 4H), 3.23-3.22 (m, 4H), 3.11-3.09 (m, 2H), 1.23 (t, *J*=7.4Hz, 3H).

Example 42

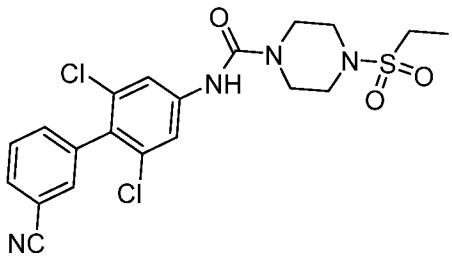
***N*-(3,5-dichloro-4-(1-(5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl) cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*): δ9.01 (s, 1H), 7.99 (d, *J*= 8.8Hz, 2H), 7.66 (s, 2H), 7.14 (d, *J*= 8.4 Hz, 2H), 3.86 (s, 3H), 3.55-3.53 (m, 4H), 3.25-3.22 (m, 4H), 3.11-3.07 (m, 2H), 1.87 (m, 2H), 1.51(m, 2H), 1.23 (t, *J*=7.4Hz, 3H).

Example 43

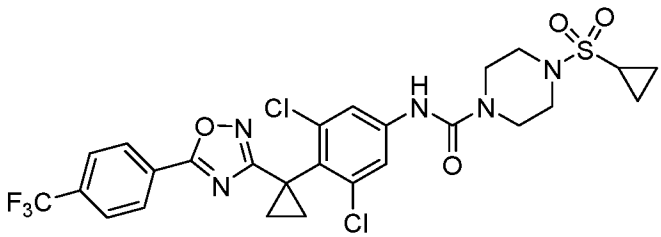
***N*-(2,6-dichloro-3'-cyano-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-d6, δ): 9.08(s, 1H), 7.92-7.90 (m, 1H), 7.83 (s, 1H), 7.76-7.63 (m, 2H), 7.20-7.10(m, 2H), 3.58-3.55 (m, 4H), 3.24-3.21 (m, 4H), 3.13-3.08 (m, 2H), 1.23 (t, *J*=7.4Hz, 3H)

Example 44

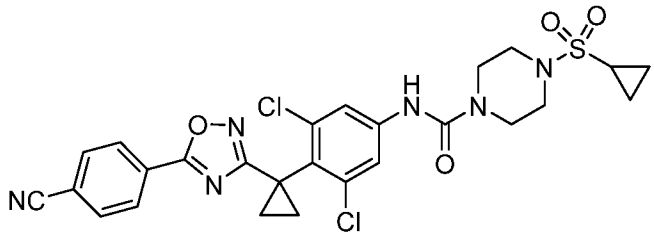
4-(cyclopropylsulfonyl)-*N*-(3,5-dichloro-4-(1-(5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*) δ 9.04 (s, 1H), 8.26 (d, *J*=8.4Hz, 2H), 7.99 (d, *J*=8.0Hz, 2H), 7.68 (s, 2H), 3.59-3.57 (m, 4H), 3.24-3.22 (m, 4H), 2.68-2.65(m, 1H), 1.93-1.90 (m, 2H), 1.58-1.55 (m, 2H), 1.02-0.96 (m, 4H).

Example 45

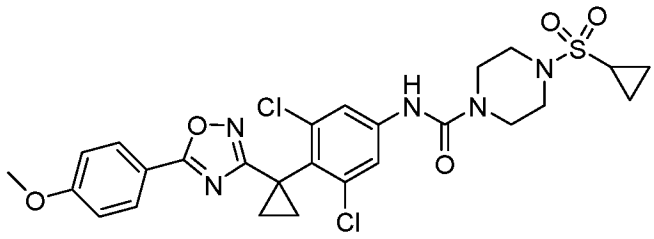
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-cyanophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6)*, δ9.04 (s, 1H), 8.22 (d, *J* = 8.8 Hz, 2H), 8.09 (d, *J*=8.8Hz, 2H), 7.68 (s, 2H), 3.59-3.56 (m, 4H), 3.24-3.22 (m, 4H), 2.67-2.65 (m, 1H), 1.93-1.90 (m, 2H), 1.58-1.56 (m, 2H), 1.1- 0.95 (m, 4H)

Example 46

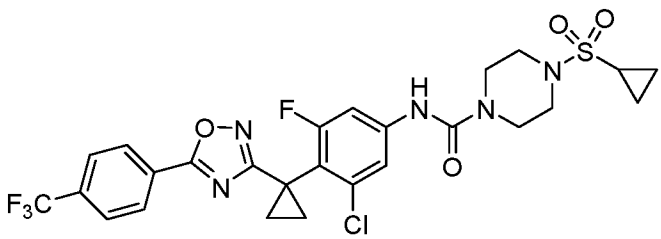
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*): δ9.03 (s, 1H), 7.99 (d, *J*=9.2Hz, 2H), 7.67 (s, 2H), 7.14 (d, *J*=8.8Hz, 2H), 3.86 (s, 3H), 3.59-3.56 (m, 4H), 3.24-3.22 (m, 4H), 2.67-2.65(m, 1H), 1.88-1.87 (m, 2H), 1.51-1.50 (m, 2H), 1.02-0.95(m, 4H).

Example 47

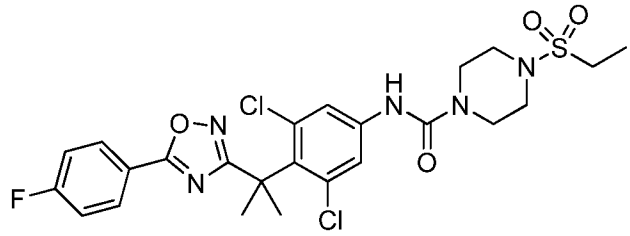
***N*-(3-chloro-5-fluoro-4-(1-(5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(cyclopropylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*) δ9.06 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J*=8.0Hz, 2H), 7.51-7.4 (m, 2H), 3.59-3.56 (m, 4H), 3.25-3.22 (m, 4H), 2.67-2.65 (m, 1H), 1.90-1.85 (m, 2H), 1.60-1.50 (m, 2H), 1.02-1.96 (m, 4H)

Example 48

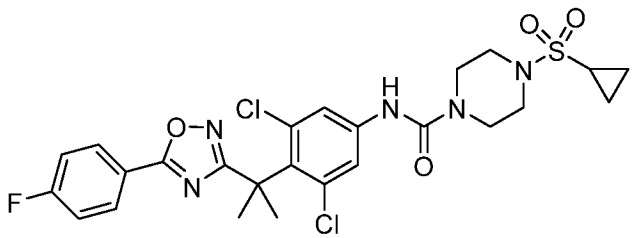
N-(3,5-dichloro-4-(2-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)propan-2-yl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6* :) δ8.97 (s, 1H), 8.16-8.13 (m, 2H), 7.61 (s, 2H), 7.47-7.42 (m, 2H), 3.55-3.52 (m, 4H), 3.21-3.20 (m, 4H), 3.10-3.08 (m, 2H), 1.94 (s, 6H), 1.22 (t, *J*=7.4Hz, 3H)

Example 49

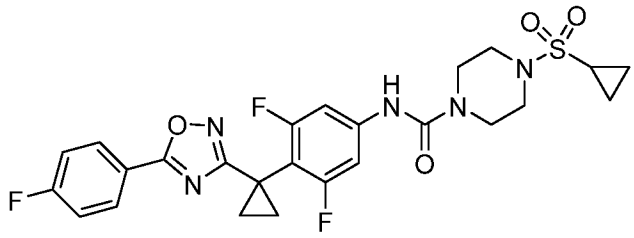
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(2-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)propan-2-yl)phenyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*): δ8.99 (s, 1H), 8.16-8.13 (m, 2H), 7.61 (s, 2H), 7.47-7.42 (m, 2H), 3.57-3.54 (m, 4H), 3.23-3.20 (m, 4H), 2.68-2.65(m, 1H), 1.94 (s, 6H), 1.01-0.95 (m, 4H).

Example 50

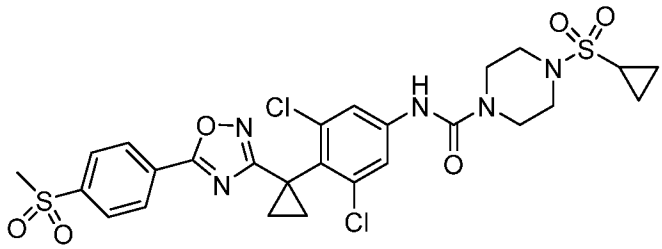
4-(cyclopropylsulfonyl)-N-(3,5-difluoro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*):δ9.07 (s, 1H), 8.12-8.09 (m, 2H), 7.48-7.43 (m, 2H), 7.27 (d, *J*=10.8Hz, 2H), 3.59-3.56 (m, 4H), 3.24-3.22 (m, 4H), 2.67-2.63 (m, 1H), 1.73-1.70 (m, 2H), 1.45-1.42 (m, 2H),

Example 51

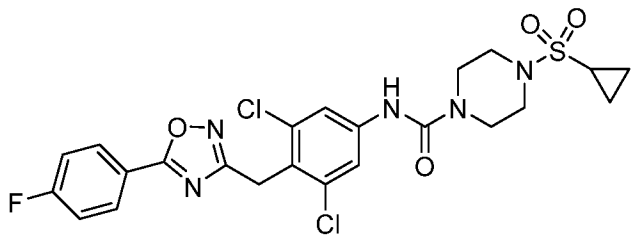
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide



1H NMR (DMSO-*d6*): δ 9.04 (s, 1H), 8.31-8.29 (m, 2H), 8.15 (d, *J*=8.4Hz, 2H), 7.68(s, 2H), 3.59-3.57 (m, 4H), 3.32(s, 3H), 3.24-3.22 (m, 4H), 2.67-2.66 (m, 1H), 1.92 (m, 2H), 1.57-1.55 (m, 2H), 1.02-0.95(m, 4H).

Example 52

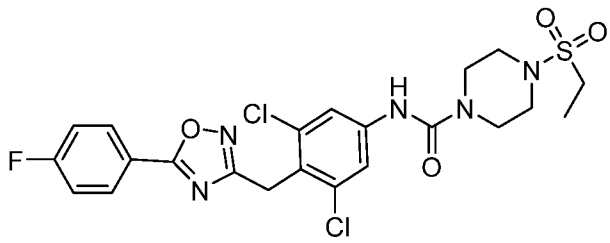
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-((5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)methyl)phenyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*) δ 9.02 (s, 1H), 8.16-8.12 (m, 2H), 7.69 (s, 2H), 7.49-7.44 (m, 2H), 4.36(s, 2H), 3.58-3.56 (m, 4H), 3.24-3.21 (m, 4H), 2.67-2.64 (m, 1H), 1.01-0.94 (m, 4H)

Example 53

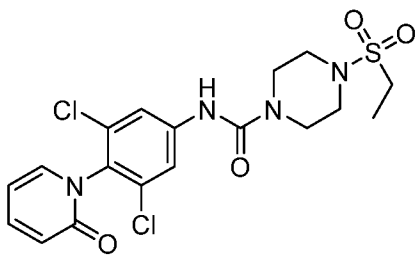
N-(3,5-dichloro-4-((5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)methyl)phenyl)-4-(ethylsulfonyl) piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*): δ8.98 (s, 1H), 8.12 (dd, *J* = 8.4 Hz & 5.6 Hz, 2H), 7.68 (s, 1H), 7.45 (m, 2H), 4.35 (s, 2H), 3.54 (s, 4H), 3.08 (m, 2H), 1.22 (m, 5H)

Example 54

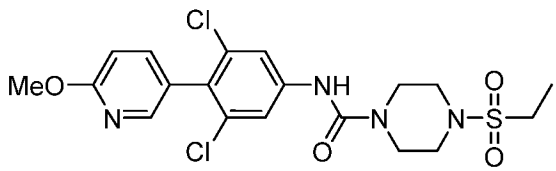
***N*-(3,5-dichloro-4-(2-oxopyridin-1(2H)-yl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*): δ9.12 (s, 1H), 7.77 (s, 2H), 7.57 – 7.50 (m, 2H), 6.52 (d, *J* = 9.2 Hz, 1H), 6.35 (t, *J* = 6.8 Hz & 13.6 Hz, 1H), 3.56 (t, 4H), 3.22 (t, 4H), 3.10 (q, 2H), 1.22 (t, 3H)

Example 55

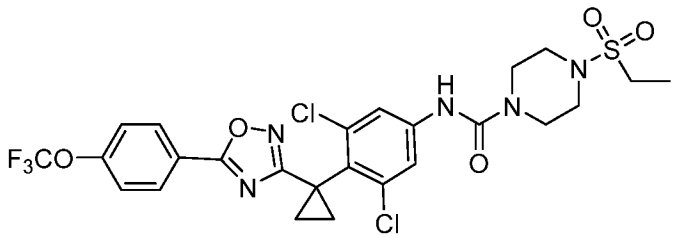
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*): δ9.05 (s, 1H), 8.06 (dd, *J*= 2.4 Hz & 0.8 Hz, 1H), 7.75 (s, 2H), 7.63 (dd, *J*= 8.4 & 2.4 Hz, 1H), 6.92 (dd, *J*= 8.8 Hz & 0.8 Hz, 1H), 3.56 (m, 4H), 3.22 (m, 4H), 3.11 (q, 2H), 1.21 (t, 3H).

Example 56

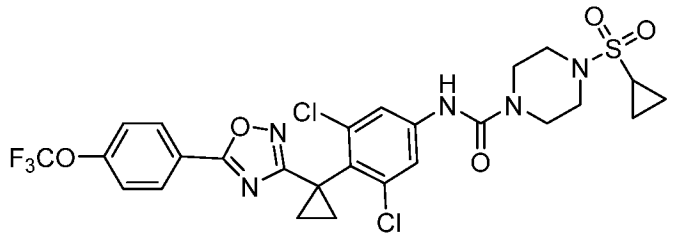
***N*-(3,5-dichloro-4-(1-(5-(4-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl) cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*): δ9.02 (s, 1H), 8.19 – 8.16 (m, 2H), 7.68 (s, 2H), 7.61 (d, *J* = 8 Hz, 2H), 3.57 – 3.28 (m, 4H), 3.28 – 3.13 (m, 4H), 3.1 – 3.07 (q, 2H), 1.9 (m, 2H), 1.59 (m, 2H), 1.54 (t, 3H).

Example 57

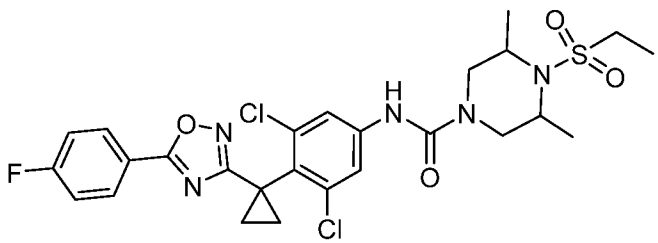
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*): δ 9.04 (s, 1H), 8.18 (d, *J* = 9.2 Hz, 2H), 7.68 (s, 2H), 7.62 (d, *J* = 8 Hz, 2H), 3.59 – 3.56 (m, 4H), 3.24 – 3.22 (m, 4H), 1.90 (m, 2H), 1.55 (m, 2H), 1.1 (m, 2H), 0.96 (m, 2H)

Example 58

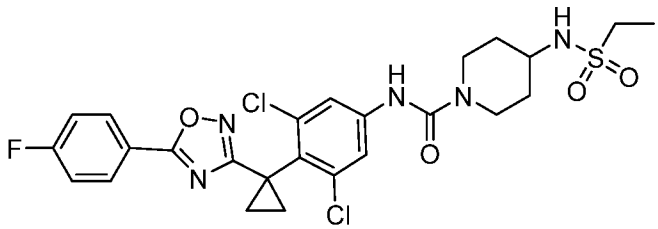
N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)-3,5-dimethylpiperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*): δ8.86 (s, 1H), 8.14 – 8.10 (m, 2H), 7.73 (s, 2H), 7.48 – 7.44 (t, 2H), 4.07 – 3.96 (d, 2H), 3.95 – 3.93 (m, 4H), 3.16 – 3.08 (m, 4H), 1.91 – 1.88 (m, 2H), 1.55 – 1.52 (m, 2H), 1.28 – 1.26 (d, 6H), 1.23 – 1.21 (t, 3H)

Example 59

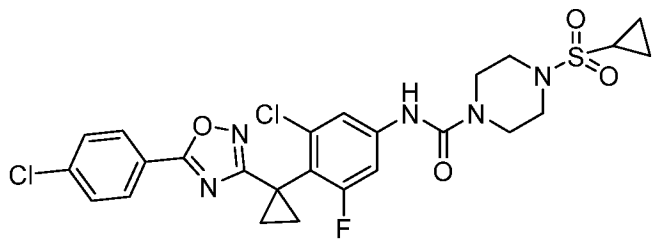
***N*-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonamido)piperidine-1-carboxamide**



^{1}H NMR (DMSO-*d6*):δ8.90 (s, 1H), 8.12 (dd, *J* = 8.8 Hz & 5.2 Hz, 2H), 7.67 (s, 2H), 7.46 (t, 2H), 7.19 (d, *J* = 8 Hz, 1H), 4.0 (m, 2H), 3.04 – 3.02 (m, 2H), 2.94 (m, 2H), 1.89 – 1.87 (m, 4H), 1.54 (m, 2H), 1.4 (m, 2H), 1.23 – 1.19 (m, 5H)

Example 60

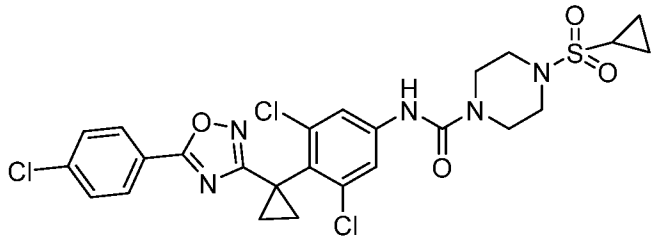
***N*-(3-chloro-4-(1-(5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-5-fluorophenyl)-4-(cyclopropylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*): δ9.05 (s, 1H), 8.04-8.06 (m, 2H), 7.68-7.69 (m, 2H), 7.42-7.50 (m, 2H), 3.56-3.59 (m, 4H), 3.22-3.33 (m, 4H), 1.88-1.99 (m, 1H), 1.52-1.54 (m, 2H), 1.24-1.25 (m, 2H), 1.11-1.19 (m, 2H), 0.96-1.10 (m, 2H).

Example 61

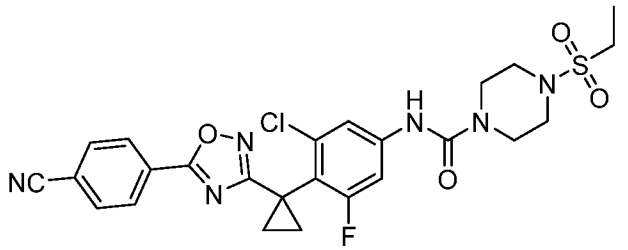
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*): δ9.03 (s, 1H), 8.05-8.07 (m, 2H), 7.67-7.70 (m, 4H), 3.56-3.59 (m, 4H), 3.22-3.34 (m, 4H), 1.89-1.99 (m, 2H), 1.54-1.55 (m, 2H), 1.14-1.18 (m, 1H), 100-1.02 (m, 2H), 0.96-1.01 (m, 3H).

Example 62

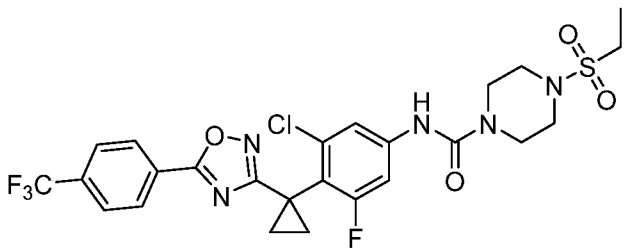
***N*-(3-chloro-4-(1-(5-(4-cyanophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-5-fluorophenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*): δ9.04 (s, 1H), 8.21-8.22 (m, 2H), 8.19-8.20 (m, 2H), 8.07-8.09 (m, 2H), 3.54-3.57 (m, 4H), 3.21-3.33 (m, 4H), 3.09-3.22 (m, 2H), 1.81-1.83 (m, 2H), 1.23-1.25 (m, 2H), 1.21-1.23 (t, 3H).

Example 63

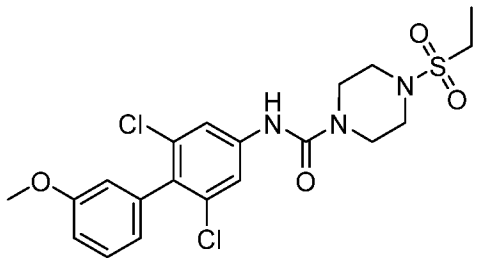
***N*-(3-chloro-5-fluoro-4-(1-(5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



1H NMR (DMSO-*d6*): δ9.04 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 9.2 Hz, 2H), 7.46-7.51 (m, 1H), 7.43-7.46 (m, 1H), 3.54-3.57 (m, 4H), 3.33-3.38 (m, 4H), 3.07-3.13 (m, 2H), 1.67-1.77 (m, 2H), 1.45-1.56(m, 2H), 1.27 (t, 3H).

Example 64

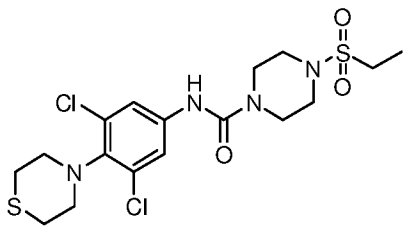
N-(2,6-dichloro-3'-methoxy-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide



^{1}H NMR (DMSO-*d6*): δ9.02 (s, 1H), 7.22 (s, 2H), 7.37 (d, *J* = 8 Hz, 1H), 6.80-6.99 (m, 1H), 6.77-6.78 (m, 2H), 3.77 (s, 3H), 3.55 – 3.57 (m, 4H), 3.33 – 3.38 (m, 4H), 3.07-3.13 (m, 2H), 1.20-1.24 (m, 3H)

Example 65

***N*-(3,5-dichloro-4-thiomorpholinophenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide**



^{1}H NMR (DMSO-*d6*): δ8.60 (s, 1H), 7.57 (s, 2H), 3.50 – 3.51 (m, 4H), 3.27 – 3.32 (m, 6H), 3.19 – 3.26 (m, 6H), 3.07-3.09 (m, 2H), 1.21 (t, *J* = 7.4 Hz , 3H).

The following compounds can be synthesized in the analogous manner as described above -

(*R*)-*N*-(3,5-dichloro-4-(methyl(1-(o-tolyl)ethyl)carbamoyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

(*R*)-4-(ethylsulfonyl)-*N*-(4-(methyl(1-(o-tolyl)ethyl)carbamoyl)phenyl)piperazine-1-carboxamide;

(*R*)-4-(ethylsulfonyl)-N-(4-(methyl(1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)phenyl)piperazine-1-carboxamide;

(*R*)-N-(3,5-dichloro-4-(methyl(1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

(*R*)-4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(methyl(1-(o-tolyl)ethyl)carbamoyl)phenyl)piperazine-1-carboxamide;

N-(1-((2,2-difluorobenzo[d][1,3]dioxol-4-yl)methyl)-2-(trifluoromethyl)-1H-benzo[d]imidazol-5-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(1-((2,2-difluorobenzo[d][1,3]dioxol-4-yl)methyl)-2-(trifluoromethyl)-1H-benzo[d]imidazol-5-yl)piperazine-1-carboxamide;

Activity data:

***In-vitro* Activity:**

5XRORE based Luciferase assay:

Human RORγt (*h*RORγt) inhibitors were screened in RORE (RORγt Response Element) based Luciferase assay by transient transfection of 5X RORE (5 tandem repeats of RORγt Response Element) and full length human RORγt together in COS-7 cells. COS-7 cells were maintained as monolayer in complete DMEM (High Glucose) medium in presence of 2mM Glutamin and 1X Sodium Pyruvate. Day before transfection, 15000 cells were seeded in 96 well cell culture plate in 100µl antibiotic free medium and incubated at 37 ^{0}C in 5% CO_2 containing humidified chamber O/N. Prior to transfection, cells were fed with fresh complete growth medium and incubated until the addition of transfection complex. Transfection complex for the required numbers of wells were prepared from pGL2-promoter-5XRORE-Luc plasmid, pcDNA3.1 (+)-*h*RORγt expression plasmid, pβ-GAL plasmid (transfection control), and Lipofectamine 3000 (Invitrogen). 50µl of transfection complex were added in 100µl of complete medium to respective wells, mixed gently and plate was incubated for 5-6 h at 37^{0}C in 5% CO_2 containing humidified chamber. After 5 h of transfection, content of the wells were aspirated and cells were treated with increasing concentration of RORγt inverse agonist in medium devoid of serum with a final DMSO concentration of 0.2% for 18-20 h at 37^{0}C in 5% CO_2 containing humidified chamber. Next day, cells were lysed and the lysates were assayed for luciferase and β-GAL activity using Promega's luciferase assay system and an in-house made β-GAL assay buffer respectively. Luciferase signals were normalized with β-GAL and % activity was determined with respect to that of 10 nM control ligand.

RORγt inhibitory activity displayed by compounds of the present invention in the form of % inhibition at 100 nM concentration was found to be very good. IC_{50} of

selected compounds were then determined by nonlinear regression analysis of % activity, plotted against compound concentration (Table 1).

Human IL-17 inhibition assay:

Peripheral blood mononuclear cells (PBMCs) were isolated from healthy volunteers and subjected to T cell polarization assay. Two million PBMCs were placed on anti-CD3 (Biolegend, US) coated 96-well plates and 1µg/mL of anti-CD28 (Biolegend, US) was added along with RORγt inhibitors or the vehicle control and incubated at 37^0C and 5% CO_2 for 72 h. At the end of incubation time, the supernatant was collected and analyzed for secreted IL-17 using sandwich enzyme immunoassay (Mabtech AB, Sweden). The results were analyzed using Graphpad Prism and the half-maximal inhibitory concentrations (IC_{50}) of the test compounds were derived (Table 1).

Table 1: IC_{50} values of selected compounds in luciferase and IL-17 assay.

Example	Luc IC_{50} (nM)	IL17 IC_{50} (nM)
4	28	61
11	29	-
15	108	-
18	21	7
21	54	-
22	62	-
25	7.2	-
26	111	-
32	35	239
43	40	29
45	25	496
47	23	-
48	4	53
49	21	-
58	105	-
62	41	-
66	83	26
67	78	-

In-vivo Activity:

Effect in mouse model of EAE:

EAE was induced in C57BL/6 wild-type mice by s.c. injection at four sites on the back with 200 µg/mouse MOG peptide in an emulsion with IFA supplemented with 5 mg/ml Mycobacterium tuberculosis, strain H37Ra. Pertussis toxin dissolved in PBS was injected i.p. at 200 ng/mouse at the time of immunization (Day 0) and 48 h later. Mice were scored daily on a scale of 0–5. 0, no clinical disease; 1, limp/flaccid tail; 2, moderate hind-limb weakness; 3, complete paralysis of hind-limbs; 4, complete hind-limb paralysis with partial forelimb paralysis; 5, death. All mice were 6–10 weeks of age when experiments were performed. Test compounds or its vehicle was administered per oral from day 0 to day 20.

Selected compounds have shown ~70% inhibition of clinical score when given orally at 50 mg/kg BID.

Effect in Collagen-Induced Arthritis model

Male DBA1j (8 to 12-weeks old) mice were injected s.c with native bovine type II collagen (Chondrex, Redmond, WA), mixed with complete Freund's adjuvant at the ratio of 2:1, on days 0 and 21 at the base of the tail. Animals were observed for clinical score and assigned to different groups of similar score. Mice were then dosed and determined for clinical scores for 3 weeks. The degree of arthritis was determined based on a clinical score of 0–4 per paw and summed for all four paws.

Selected compounds has shown ~60% reduction in clinical score when given orally at 30 mg/kg BID.

Effect in Imiquimod induced psoriasis model

C57BL/6j Male mice (8-10 week-old at study initiation) were treated with imiquimod (IMQ) cream (5%) or petroleum (non-inflammatory inert cream). Mice were anesthetized before applying IMQ cream on to the skin. Test compounds or its vehicle was administered per oral one hour before the IMQ application. Treatment started at day 0 and continued twice a day for 6 days. The mice were scored daily for skin erythema and scaling. Ear thickness was measured daily using an engineer's caliper (Incyte) before the application of IMQ.

Selected compounds has shown 40% reduction in ear weight when given orally at 30 mg/kg BID.

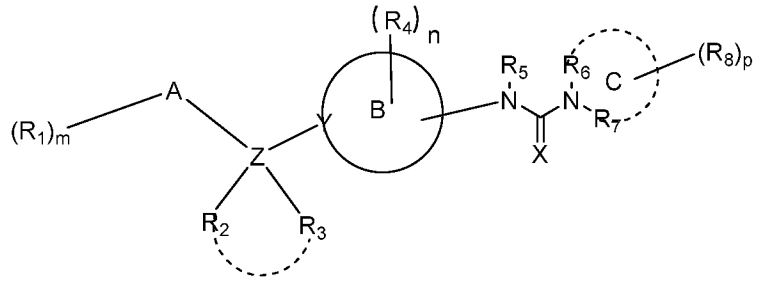
The pharmaceutical composition is provided by employing conventional techniques. Preferably the composition is in unit dosage form containing an effective amount of the active component, that is, the compounds of formula (I) according to this invention.

The quantity of active component, that is, the compounds of formula (I) according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In one of the embodiments, the present invention of formula (I) can be co-administered in combination with one or more suitable pharmaceutically active agents. In a particular embodiment, the pharmaceutical compositions of the invention can be co-administered with or can include one or more other therapeutic compounds or adjuvants, such as but not limited to other (1) TNF-a Inhibitors; (2) non-selective COX-1/COX-2 inhibitors; (3) COX-2 inhibitors (4) other agents for inflammatory and autoimmune disease including glucocorticoids, methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporine, tacrolimus, penicillamine, bucillamine, actarit, mizoribine, lobenzarit, ciclesonide, hydroxychloroquin, d-penicillamine, aurothiomalate, auranofin or parenteral or oral gold, cyclophosphamide, Lymphostate-B, BAFF/APRIL inhibitors and CTLA-4-Ig or mimetic thereof, (5) leukotriene biosynthesis inhibitors, 5-lipoxygenase inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist; (6) LTD4 receptor antagonist; (7) PDE4 inhibitors; (8) antihistamine HI receptor antagonists; (9) a1 and a2-adrenoceptor agonist; (10) anticholinergic agents; (11) β-adrenoceptor agonist (12) insulin-like growth factor type I (IGF-I) mimetic; (13) glucocorticosteroids; (14) kinase inhibitors such as inhibitors of Janus kinases (JAK 1 and/or JAK2 and/or JAK3 and/or TYK2), p38 MAPK and IKK2; (15) B-cell targeting biologies such as rituximab; (16) selective costimulation modulators such as abatacept; (17) interleukine inhibitors, such as IL-1 inhibitor anakinra, IL-6 inhibitor tocilizumab, and IL12/IL23 inhibitor ustekinumab. The compounds of the invention could also be combined with anti-IL17 antibodies to obtain additive/synergistic response for the treatment of inflammatory and autoimmune diseases.

We Claim:

1. Compound having the structure of general formula (**I**)



formula (I)

Wherein 'A' represents either a bond or the group selected from -CN, -COOH, optionally substituted groups selected from (C_1-C_8)alkyl, (C_3-C_6)cycloalkyl, aryl, heteroaryl or heterocyclyl or 'A' may be absent;

Ring 'B' is selected from aryl, heteroaryl or heterocyclyl wherein 'Y' is selected from C or N;

'Z' represents either a bond or the atoms C, -N, or 'Z' may be absent;

When 'Z' represents C or N, R_2 and R_3 are each independently selected from the group comprising of hydrogen, hydroxyl, haloalkyl, optionally substituted groups selected from (C_1-C_8)alkyl, (C_1-C_8)alkoxy, (C_3-C_6)cycloalkyl, benzyl or carbocyclic group or R_2 and R_3 together with the atom to which they are attached may form a 3- to 10- membered carbocyclic ring system having optionally one or more than one heteroatoms;

R_5 represents hydrogen, optionally substituted groups selected from (C_1-C_8)alkyl, (C_1-C_8)alkoxy, (C_3-C_6)cycloalkyl;

X represents -O, NR' wherein R' is hydrogen, CN, NO_2, OR" or optionally substituted (C_1-C_8)alkyl wherein R" is hydrogen, haloalkyl, optionally substituted (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl groups;

R_6 and R_7 are each independently selected from the group comprising of hydrogen, optionally substituted groups selected from (C_1-C_8)alkyl, aryl, heteroaryl, heterocyclyl or R_6 and R_7 together with the atom to which they are attached may form a heterocyclic, bridged or spiro ring system 'C' having optionally one or more than one heteroatoms;

Each of R_1, R_4 and R_8 at each occurrence is independently selected from the group comprising of hydrogen, halogen, hydroxy, cyano, oxo, halo(C_1-C_8)alkyl, optionally substituted (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_6)cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroaralkyl, heterocyclylalkyl, cycloalkanylalkyl, alkylsulfonyloxy, -COR_a, -$COOR_a$, -OR_a, -$S(O)_tR_a$, -$S(O)_tNR_a$, -NR_aR_b, -$CONR_aR_b$, -$N(R_a)COR_b$, -$N(R_a)COOR_b$, -OCH_2COR_a, -$N(R_a)CH_2COR_b$, -$N(R_a)CONR_aR_b$, -$S(O)_tNR_aR_b$, -$N(R_a)S(O)_tR_b$ groups;

'm', 'n' and 'p' represent integers from 0-2;

Each of R_a and R_b at each occurrence are independently selected from the group comprising of hydrogen, haloalkyl, optionally substituted groups selected from (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8) cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl groups; or wherever feasible, R_a and R_b together with the atom to which they are attached may form an optionally substituted 5- to 10- membered carbocyclic ring optionally containing 0-2 additional heteroatoms selected from –O-, -NR_9- or $S(O)_t$; wherein, R_9 represents hydrogen, optionally substituted groups selected from (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_8)haloalkyl; 't' represents integers from 1-2.

2. The compound as claimed in claim 1, wherein when ring 'C' represents a heterocyclyl group, the heterocyclyl group may be selected from single or fused mono or bicyclic non-aromatic groups containing one or more hetero atoms selected from O, N or S.

3. The compound as claimed in claim 2, wherein the heterocyclyl group is selected from aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, 2-oxopiperidinyl, 4-oxopiperidinyl, 2-oxopiperazinyl, 3-oxopiperazinyl, morpholinyl, thiomorpholinyl, 2-oxomorpholinyl, azepinyl, diazepinyl, oxapinyl, thiazepinyl, oxazolidinyl, thiazolidinyl.

4. The compound as claimed in claim 1, wherein heteroaryl group is selected from pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, isothiazolyl, imidazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, benzofuranyl,

benzothienyl, indolinyl, indolyl, azaindolyl, azaindolinyl, pyrazolopyrimidinyl, azaquinazolinyl, pyridofuranyl, pyridothienyl, thienopyrimidyl, quinolinyl, pyrimidinyl, pyrazolyl, quinazolinyl, pyridazinyl, triazinyl, benzimidazolyl, benzotriazolyl, phthalazynil, naphthylidinyl, purinyl, carbazolyl, phenothiazinyl, phenoxazinyl, benzoxazolyl, benzothiazolyl.

5. The compound as claimed in claim 1, wherein when any of the above group is substituted the substitution on the substituted groups is selected from hydrogen, hydroxy, cyano, halo, oxo, imino, haloalkyl, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_5\text{-}C_8)$cycloalkenyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroaralkyl, heterocyclylalkyl, alkylsulfonyloxy, $-COR_a$, $-COOR_a$, $-OR_a$, $-S(O)_tR_a$, $-NR_aR_b$, $-CONR_aR_b$, $-N(R_a)COR_b$, $-N(R_a)COOR_b$, $-OCH_2COR_a$, $-N(R_a)CH_2COR_b$, $-N(R_a)CONR_aR_b$, $-SO_2NR_aR_b$, $-N(R_a)SO_2R_b$ derivatives; wherein, R_a and R_b are as defined in claim 1.

6. A compound as claimed in claim 1 selected from the group comprising of:

1-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-3-(4-(ethylsulfonyl)phenyl)urea;
1-(3,5-dichloro-4-(1-(5-(2,3-difluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-3-(4-(ethylsulfonyl)phenyl)urea;
1-(3,5-dichloro-4-(1-(5-(2,4-difluorophenyl)-1,2,4-oxadiazol-3-l)cyclopropyl)phenyl)-3-(4-(ethylsulfonyl)phenyl)urea;
N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;
N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-5-(ethylsulfonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide;
N-(3,5-dichloro-4-morpholinophenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;
N-(3,5-dichloro-4-(1-(5-methyl-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;
N-(3,5-dichloro-4-(1-(5-isopropyl-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(Ethylsulfonyl)-N-(4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-3,5-dimethylphenyl)piperazine-1-carboxamide;

N-(3,5-difluoro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperidine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)-1,4-diazepane-1-carboxamide;

N-(3,5-dichloro-4-((5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)methyl)phenyl)-4-(ethylsulfonyl) piperazine-1-carboxamide;

N-(3,5-dichloro-4-(2,3-dihydrospiro[indene-1,4'-piperidin]-1'-yl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(methylsulfonyl)piperazine-1-carboxamide;

N-(3-chloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(isopropylsulfonyl)piperazine-1-carboxamide;

2-(4-((3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl) carbamoyl) piperazin-1-yl)acetic acid;

Ethyl-2-(4-((3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)carbamoyl) piperazin-1-yl)acetate;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperidine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-6-(ethylsulfonyl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)thiazol-2-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-morpholinophenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)thiazol-2-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-(trifluoromethyl)cyclohexyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(2,3-difluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;
N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-6-(ethylsulfonyl)-2,6-diazaspiro[3.3]heptane-2-carboxamide;
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4,4-difluorocyclohexyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;
N-(2,6-dichloro-3'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;
N-(2,6-dichloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;
N-(2,6-dichloro-3'-methyl-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;
N-(2,6-dichloro-2'-methoxy-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;
N-(2,6-dichloro-4'-hydroxy-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;
N-(3,5-dichloro-4-(1-(5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;
N-(2,6-dichloro-3'-cyano-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;
4-(cyclopropylsulfonyl)-*N*-(3,5-dichloro-4-(1-(5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;
4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-cyanophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

N-(3-chloro-5-fluoro-4-(1-(5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(cyclopropylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(2-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)propan-2-yl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(2-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)propan-2-yl)phenyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-difluoro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-((5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)methyl)phenyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-((5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)methyl)phenyl)-4-(ethylsulfonyl) piperazine-1-carboxamide;

N-(3,5-dichloro-4-(2-oxopyridin-1(2H)-yl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)-3,5-dimethylpiperazine-1-carboxamide;

N-(3,5-dichloro-4-(1-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonamido)piperidine-1-carboxamide;

N-(3-chloro-4-(1-(5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-5-fluorophenyl)-4-(cyclopropylsulfonyl)piperazine-1-carboxamide;

4-(cyclopropylsulfonyl)-N-(3,5-dichloro-4-(1-(5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)piperazine-1-carboxamide;

N-(3-chloro-4-(1-(5-(4-cyanophenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-5-fluorophenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3-chloro-5-fluoro-4-(1-(5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(2,6-dichloro-3'-methoxy-[1,1'-biphenyl]-4-yl)-4-(ethylsulfonyl)piperazine-1-carboxamide;

N-(3,5-dichloro-4-thiomorpholinophenyl)-4-(ethylsulfonyl)piperazine-1-carboxamide.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (**I**) as claimed in any of the preceding claims and optionally one or more pharmaceutically acceptable carriers, diluents or excipients.

8. A method of treating diseases medicated by the RORγ which comprising administering to a patient in need thereof an effective amount of a compound of Formula (**I**) as claimed in any of the preceding claims or its suitable pharmaceutical composition.

9. The use of compounds of formula **(I)** or its pharmaceutical compositions as claimed in any of the preceding claim suitable for treatment of diseases wherein the RORγ has a pathophysiological function.

10. The pharmaceutical composition as claimed in claim 4 in combination with suitable (1) TNF-a Inhibitors; (2) non-selective COX-1/COX-2 inhibitors; (3) COX-2 inhibitors (4) and other agents suitable for inflammatory and autoimmune disease including glucocorticoids, methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporine, tacrolimus, penicillamine, bucillamine, actarit, mizoribine, lobenzarit, ciclesonide, hydroxychloroquin, d-penicillamine, aurothiomalate, auranofin or parenteral or oral gold, cyclophosphamide, lymphostate-B, BAFF/APRIL inhibitors and CTLA-4-Ig or mimetic thereof, (5) leukotriene biosynthesis inhibitors, 5-lipoxygenase inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist; (6) LTD4 receptor antagonist; (7) PDE4 inhibitors; (8) antihistamine HI receptor antagonists; (9) a1 and a2-adrenoceptor agonist; (10) anticholinergic agents; (11) β-adrenoreceptor agonist (12) insulin-like growth factor type I (IGF-I) mimetic; (13) glucocorticosteroids; (14) kinase inhibitors selected from inhibitors of Janus kinases (JAK 1 and/or JAK2 and/or JAK3 and/or TYK2), p38 MAPK and IKK2; (15) B-cell targeting biologies such as rituximab; (16) selective costimulation modulators such as abatacept; (17) interleukine inhibitors, selected from IL-1 inhibitor anakinra, IL-6 inhibitor tocilizumab, and IL12/IL23 inhibitor ustekinumab.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/057777

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D271/06 C07D285/08 C07D295/15 C07D413/04 C07D487/04
C07D487/08 A61K31/4245 A61P3/00 A61P35/00 A61P37/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/159233 A1 (GLENMARK PHARMACEUTICALS SA [CH]) 22 October 2015 (2015-10-22) claim 1	6-10
A	WO 2013/029338 A1 (GLAXO GROUP LTD [GB]; WANG YONGHUI [CN]; CAI WEI [CN]; LIU QIAN [CN];) 7 March 2013 (2013-03-07) cited in the application claim 1	6-10
A	WO 2016/039408 A1 (TAKEDA PHARMACEUTICAL [JP]) 17 March 2016 (2016-03-17) claim 1 examples & EP 3 192 791 A1 (TAKEDA PHARMACEUTICALS CO [JP]) 19 July 2017 (2017-07-19)	6-10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2018	28/02/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bérillon, Laurent

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/057777

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-5(completely); 7-10(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation of Box II.2

Claims Nos.: 1-5(completely); 7-10(partially)

In the general formula (I) of present claim 1 the moieties A and Z can be a bond, the substituents R1 and R8 can be H and m and p can be 0. It follows that compounds having a B ring (whose definition is very broad) substituted by a urea group fall within the claimed scope such as known 1-phenyl urea, 1-3-diphenylurea, 1-phenyl-3-(2-pyridyl)urea, 1-(N-phenylcarbamoyl)piperidine etc. The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of claims 1-5 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search. The search was restricted to compounds of formula 6, compositions thereof and use thereof.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2017/057777

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015159233 A1	22-10-2015	AU 2015248466 A1	15-09-2016
		CA 2940264 A1	22-10-2015
		CN 106232582 A	14-12-2016
		EA 201691491 A1	28-02-2017
		JP 2017513850 A	01-06-2017
		KR 20160146701 A	21-12-2016
		PE 13992016 A1	14-01-2017
		PH 12016502045 A1	09-01-2017
		SG 11201607518R A	28-10-2016
		US 2017022195 A1	26-01-2017
		WO 2015159233 A1	22-10-2015
WO 2013029338 A1	07-03-2013	NONE	
WO 2016039408 A1	17-03-2016	CA 2961033 A1	17-03-2016
		EP 3192791 A1	19-07-2017
		JP WO2016039408 A1	22-06-2017
		US 2017253591 A1	07-09-2017
		WO 2016039408 A1	17-03-2016