

HETEROAROMATIC MODULATORS OF THE RETINOID-RELATED ORPHAN RECEPTOR GAMMA

FIELD OF THE INVENTION

- 5 This invention relates to compounds which are ROR-gamma ($\text{ROR}\gamma$) modulators, to intermediates for the preparation thereof, to said compounds for use in therapy and to pharmaceutical compositions comprising said compounds and to methods of treating diseases with said compounds.

10 BACKGROUND OF THE INVENTION

- The Retinoic acid-related orphan receptor (ROR) gene family is part of the nuclear hormone receptor super-family and consists of three members ROR alpha, ROR beta and ROR gamma ($\text{ROR}\alpha$, $\text{ROR}\beta$ and $\text{ROR}\gamma$). Each ROR gene is expressed in different isoforms; the isoforms differ in their pattern of tissue-specific expression and can regulate distinct physiological processes and target genes. More specifically two isoforms of $\text{ROR}\gamma$ have been identified; $\text{ROR}\gamma 1$ and $\text{ROR}\gamma 2$ (known as $\text{ROR}\gamma\text{t}$). $\text{ROR}\gamma 1$ is expressed in multiple tissues, such as heart, brain, kidney, lung, liver and muscle; whereas $\text{ROR}\gamma\text{t}$ is restricted to the cells of the immune system and is expressed in lymphoid organs, such as the thymus (Jetten, A. M.; Adv. Dev. Biol. (2006), 16, 313-355).
- 15 $\text{ROR}\gamma\text{t}$ has been shown to be crucial for the development of T helper 17 cells ($\text{T}_\text{H}17$ cells) (Ivanov et al., Cell (2006), 126, 1121-1133). $\text{T}_\text{H}17$ cells, which produce IL-17, IL-21 and IL-22, have an essential role in the development of many autoimmune and inflammatory disorders, such as multiple sclerosis, psoriasis and rheumatoid arthritis. (Betelli, E. et al., Nature Immunol. (2007), 8, 345-350; Fouser, L. et al. Immunol. Rev. (2008), 226, 87-102); suggesting that development of $\text{ROR}\gamma$ modulators may be beneficial for treatment of autoimmune and inflammatory diseases (Kojetin, D. et al.; Nature Rev Drug Discovery (2014) 13, 197-215).
- 20 Recently, Proof-of-Concept was shown with an oral $\text{ROR}\gamma\text{t}$ inhibitor (VTP 43742) in a Phase 2a clinical trial in psoriatic patients.
- 30 Several other compounds modulating $\text{ROR}\gamma\text{t}$ have been reported, for example; WO2014/086894 discloses 'Modulators of the retinoid-related orphan receptor gamma (ROR -gamma) for use in the treatment of autoimmune and inflammatory diseases.' WO2015/180612, WO2015/180613 and WO2015/180614 disclose novel retinoid-related orphan receptor gamma (ROR -gamma) modulators and their use in the treatment of autoimmune and inflammatory diseases.
- 35 Thus it is desirable to provide compounds that modulate the activity of $\text{ROR}\gamma$ for use in the treatment of autoimmune and inflammatory disorders.

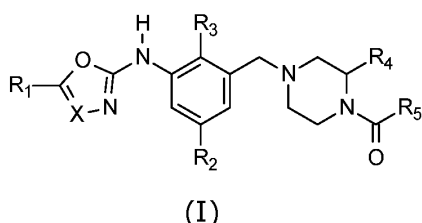
SUMMARY OF THE INVENTION

The inventors have surprisingly found that novel compounds of the present invention exhibit modulating effect on ROR-gamma and may be useful as therapeutic agents for diseases mediated by ROR-gamma, including autoimmune or inflammatory diseases such as psoriasis, psoriatic arthritis, multiple sclerosis, rheumatoid arthritis, Crohns disease, ulcerative colitis, alopecia areata, contact dermatitis, including irritative contact dermatitis and allergic contact dermatitis, spondyloarthritis; and cancers, including prostate cancer and non-small cell lung cancer.

- 10 Compounds of the present invention may have favourable pharmacokinetic and pharmacodynamic properties such as favourable oral bioavailability, solubility, absorption and metabolic stability or a favourable toxicity profile.

- 15 Compounds of the present invention may have low clearance in human liver microsomes thus making them suitable for oral use; or compounds of the present invention may have high clearance in human liver microsomes thus making them suitable for topical use as they may have reduced systemic side-effects while retaining the topical anti-inflammatory efficacy.

- 20 Accordingly, the present invention relates to a compound according to general formula (I)



wherein X represents N or CH;

- 25 R₁ is selected from the group consisting of -CN, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered)heterocycloalkyl, (5-6 membered)heteroaryl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (3-7 membered)heterocycloalkyl-(C₁-C₄)alkyl and (5-6 membered)heteroaryl-(C₁-C₄)alkyl, wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered)heterocycloalkyl, (5-6-membered)heteroaryl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (3-7 membered)heterocycloalkyl-(C₁-C₄)alkyl and (5-6 membered)heteroaryl-(C₁-C₄)alkyl is
- 30 optionally substituted with one or more substituents independently selected from R₆;

R₂ is selected from the group consisting of halogen, cyano, (C₁-C₄)alkyl and (C₃-C₇)cycloalkyl, wherein said (C₁-C₄)alkyl and (C₃-C₇)cycloalkyl is optionally substituted with one or more substituents independently selected from -OH and halogen;

R₃ is selected from the group consisting of halogen, cyano, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and (C₃-C₇)cycloalkyl;

- 5 R₄ is selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)haloalkyl;
R₅ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-
(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, (3-7 membered)heterocycloalkyl,
phenyl, (5-6 membered)heteroaryl and -OR_a; wherein said (C₁-C₆)alkyl, (C₃-
C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, (3-7
10 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and -OR_a is optionally
substituted with one or more substituents independently selected from R₇;

- R₆ represents the group consisting of -OH, -CN, halogen, =O, -S(O)₂R_b, -NR_cR_d, -
NR_cC(O)R_d, -C(O)NR_cR_d, -S(O)₂NR_cR_d, -NR_cS(O)₂R_b, -OR_b, -C(O)R_b, (C₁-C₄)alkyl,
15 hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, (3-7
membered)heterocycloalkyl and (5-6 membered)heteroaryl;

- R₇ represents the group consisting of -OH, -CN, halogen, (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl
and (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl-;

- 20 R_a represents (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl- or (C₃-C₇)-
cycloalkyl(C₁-C₆)alkyl;

- R_b represents (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl;

- 25 R_c and R_d each independently represents H, (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl;

or pharmaceutically acceptable salts, hydrates or solvates thereof.

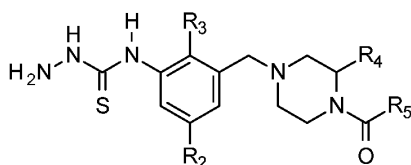
- 30 In another aspect, the invention relates to a compound of general formula (I) for use as
a medicament.

In yet another aspect, the invention relates to a compound of general formula (I) for use
in treatment of autoimmune or inflammatory diseases.

- 35 In yet another aspect, the invention relates to a pharmaceutical composition comprising
a compound according to general formula (I) together with a pharmaceutically
acceptable vehicle or excipient or pharmaceutically acceptable carrier(s).

In yet another aspect, the invention relates to a method of preventing, treating or ameliorating psoriasis, the method comprising administering to a person suffering from psoriasis an effective amount of one or more compounds according to general formula (I), optionally together with a pharmaceutically acceptable carrier or one or more excipients, optionally in combination with other therapeutically active compounds.

In another aspect the invention relates to a compound according to general formula (II), which is useful as intermediate for the preparation of a compound of general formula (I),



(II)

wherein

R_2 is selected from the group consisting of halogen, cyano, (C_1-C_4) alkyl and (C_3-C_7) cycloalkyl, wherein said (C_1-C_4) alkyl and (C_3-C_7) cycloalkyl is optionally substituted with one or more substituents independently selected from $-\text{OH}$ and halogen;

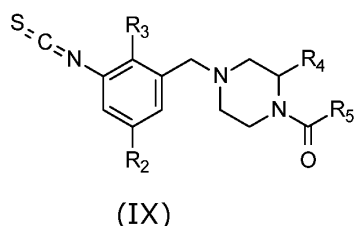
R_3 is selected from the group consisting of halogen, cyano, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl and (C_3-C_7) cycloalkyl;

R_4 is selected from the group consisting of (C_1-C_4) alkyl and (C_1-C_4) haloalkyl;

R_5 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl- (C_1-C_6) alkyl, (3-7 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and $-\text{OR}_a$; wherein said (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl- (C_1-C_6) alkyl, (3-7 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and $-\text{OR}_a$ is optionally substituted with one or more substituents independently selected from R_7 ;

R_7 represents the group consisting of $-\text{OH}$, $-\text{CN}$, halogen, (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl and (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl-.

In yet another aspect the invention relates to a compound according to general formula (IX), which is useful as intermediate for the preparation of a compound of general formula (I),



wherein

R₂ is selected from the group consisting of halogen, cyano, (C₁-C₄)alkyl and (C₃-C₇)cycloalkyl, wherein said (C₁-C₄)alkyl and (C₃-C₇)cycloalkyl is optionally substituted with one or more substituents independently selected from -OH and halogen;

R₃ is selected from the group consisting of halogen, cyano, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and (C₃-C₇)cycloalkyl;

R₄ is selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)haloalkyl;

R₅ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, (3-7 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and -OR_a; wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, (3-7 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and -OR_a is optionally substituted with one or more substituents independently selected from R₇;

R₇ represents the group consisting of -OH, -CN, halogen, (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl and (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl-.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "alkyl" is intended to indicate a radical obtained when one hydrogen atom is removed from a branched or linear hydrocarbon. Said alkyl comprises 1-6, preferably 1-4, such as 1-3, such as 2-3 or such as 1-2 carbon atoms. The term includes the subclasses normal alkyl (*n*-alkyl), secondary and tertiary alkyl, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*.-butyl, *tert*.-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl and isohexyl.

The term "alkylcycloalkyl" is intended to indicate an alkyl radical appended to the parent molecular moiety through a cycloalkyl group, as defined herein.

The term "(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl" is intended to indicate an "(C₁-C₆)alkyl radical appended to the parent molecular moiety through a (C₃-C₇)cycloalkyl group, as defined herein.

5

The term "alkylheteroaryl" is intended to indicate an alkyl radical appended to the parent molecular moiety through a heteroaryl group, as defined herein.

10 The term "alkylheterocycloalkyl" is intended to indicate an alkyl radical appended to the parent molecular moiety through a heterocycloalkyl group, as defined herein.

The terms "alkyloxy" and "alkoxy" are intended to indicate a radical of the formula -OR, wherein R is alkyl as indicated herein, wherein the alkyl group is appended to the parent molecular moiety through an oxygen atom, e.g. methoxy (-OCH₃), ethoxy (-OCH₂CH₃),
15 n-propoxy, isopropoxy, butoxy, *tert*-butoxy, and the like.

The term "aryl" is intended to indicate a radical of aromatic carbocyclic rings comprising 6-13 carbon atoms, such as 6-9 carbon atoms, such as 6 carbon atoms, in particular 5- or 6-membered rings, including fused carbocyclic rings with at least one aromatic ring. If
20 the aryl group is a fused carbocyclic ring, the point of attachment of the aryl group to the parent molecular moiety may be through an aromatic or through an aliphatic carbon atom within the aryl group. Representative examples of aryl include, but are not limited to phenyl, naphthyl, indenyl, indanyl, dihydronaphthyl, tetrahydronaphthyl and fluorenyl.

25 The term "cyano" is intended to indicate a -CN group attached to the parent molecular moiety through the carbon atom.

The term "cycloalkyl" is intended to indicate a saturated cycloalkane hydrocarbon radical, including polycyclic radicals such as bicyclic radicals, comprising 3-7 carbon
30 atoms, preferably 3-6 carbon atoms, such as 3-5 carbon atoms or such as 3-4 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

The term "cycloalkylalkyl" is intended to indicate a cycloalkyl radical appended to the parent molecular moiety through an alkyl group, as defined herein.

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The term "(C₃-C₇)cycloalkyl(C₁-C₄)alkyl" is intended to indicate a (C₃-C₇)cycloalkyl radical appended to the parent molecular moiety through an (C₁-C₄)alkyl group, as defined herein.

The term "(C₃-C₇)cycloalkyl(C₁-C₆)alkyl" is intended to indicate a (C₃-C₇)cycloalkyl radical appended to the parent molecular moiety through an (C₁-C₆)alkyl group, as defined herein.

- 5 The term "haloalkyl" is intended to indicate an alkyl group as defined herein substituted with one or more halogen atoms as defined herein, e.g. fluoro or chloro, such as difluoromethyl or trifluoromethyl.

- "(C₁-C₄)haloalkyl" is intended to indicate a (C₁-C₄)alkyl group as defined herein
10 substituted with one or more halogen atoms as defined herein, e.g. fluoro or chloro, such as difluoromethyl or trifluoromethyl.

The term "halogen" is intended to indicate a substituent from the 7th main group of the periodic table, such as fluoro, chloro and bromo.

- 15 The term "heteroaryl" is intended to indicate radicals of monocyclic heteroaromatic rings.

- The term "(5-6 membered)heteroaryl" is intended to indicate radicals of monocyclic heteroaromatic rings, comprising 5- or 6-membered rings, i.e. having a ring size of 5 or
20 6 atoms, which contain from 1-5 carbon atoms and from 1-5 heteroatoms selected from oxygen, sulphur and nitrogen, such as 1 heteroatom, such as 1-2 heteroatoms, such as 1-3 heteroatoms, such as 1-4 heteroatoms selected from oxygen, sulphur and nitrogen. The heteroaryl radical may be connected to the parent molecular moiety through a carbon atom or a nitrogen atom contained anywhere within the heteroaryl group.
- 25 Representative examples of (5-6 membered)heteroaryl groups include, but are not limited to furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl.

- 30 The term "(5 - membered)heteroaryl" is intended to indicate radicals of monocyclic heteroaromatic rings, comprising 5- membered rings, i.e. having a ring size of 5 atoms, which contain from 1-4 carbon atoms and from 1-4 heteroatoms selected from oxygen, sulphur and nitrogen, such as 1 heteroatom, such as 1-2 heteroatoms, such as 1-3 heteroatoms, such as 1-4 heteroatoms selected from oxygen, sulphur and nitrogen. The
35 heteroaryl radical may be connected to the parent molecular moiety through a carbon atom or a nitrogen atom contained anywhere within the heteroaryl group. Representative examples of (5-membered)heteroaryl groups include, but are not limited

to furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl.

- 5 The term "heteroarylalkyl" is intended to indicate a heteroaryl radical appended to the parent molecular moiety through an alkyl group, as defined herein.

The term "(5-6 membered)heteroaryl-(C₁-C₄)alkyl" is intended to indicate a "(5-6 membered)heteroaryl radical appended to the parent molecular moiety through an (C₁-
10 C₄)alkyl group, as defined herein.

The term "heterocycloalkyl" is intended to indicate a cycloalkane radical as described herein, wherein one or more carbon atoms are replaced by heteroatoms.

15 The term "(3-7 membered)heterocycloalkyl" is intended to indicate a cycloalkane radical as described herein, wherein one or more carbon atoms are replaced by heteroatoms, having a ring size of 3-7 atoms, comprising 1-6 carbon atoms, e.g. 2-5 or 2-4 carbon atoms, further comprising 1-6 heteroatoms, preferably 1, 2, or 3 heteroatoms, selected
20 from O, N, or S, such as 1 heteroatom or such as 1-2 heteroatoms selected from O, N, or S ; such as 4-membered heterocycloalkyl comprising 3 carbon atoms and 1 heteroatom selected from oxygen, nitrogen and sulphur; such as (5-6 membered)heterocycloalkyl comprising 3-5 carbon atoms and 1-2 heteroatoms selected from oxygen, nitrogen and sulphur, such as (5-membered)heterocycloalkyl comprising 4
25 carbon atoms and 1 heteroatom selected from oxygen, nitrogen and sulphur, such as (6-membered)heterocycloalkyl comprising 4-5 carbon atoms and 1-2 heteroatoms selected from oxygen, nitrogen and sulphur. The heterocycloalkyl radical may be connected to the parent molecular moiety through a carbon atom or a nitrogen atom contained anywhere within the heterocycloalkyl group. Representative examples of (3-7
30 membered)heterocycloalkyl groups include, but are not limited to azepanyl, azetidiny, aziridiny, dioxolanyl, dioxolyl, imidazolidiny, morpholiny, oxetanyl, piperaziny, piperidiny, pyrrolidiny tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, thietanyl.

- 35 The term "heterocycloalkylalkyl" is intended to indicate a heterocycloalkyl radical appended to the parent molecular moiety through an alkyl group, as defined herein.

The term "(3-7 membered)heterocycloalkyl-(C₁-C₄)alkyl" is intended to indicate a "(3-7 membered)heterocycloalkyl appended to the parent molecular moiety through an (C₁-C₄)alkyl group, as defined herein.

- 5 The term "hydrocarbon radical" is intended to indicate a radical containing only hydrogen and carbon atoms, it may contain one or more double and/or triple carbon-carbon bonds, and it may comprise cyclic moieties in combination with branched or linear moieties. Said hydrocarbon comprises 1-10 carbon atoms, and preferably comprises 1-8, e.g. 1-6, e.g. 1-4, e.g. 1-3, e.g. 1-2 carbon atoms. The term includes alkyl, alkenyl, 10 cycloalkyl, cycloalkenyl, alkynyl and aryl, as indicated herein.

- The number of carbon atoms in a hydrocarbon radical (e.g. alkyl and cycloalkyl, as indicated below) is indicated by the prefix "(C_a-C_b)", wherein a is the minimum number and b is the maximum number of carbons in the hydrocarbon radical. Thus, for example 15 (C₁-C₄)alkyl is intended to indicate an alkyl radical comprising from 1 to 4 carbon atoms, (C₁-C₆)alkyl is intended to indicate an alkyl radical comprising from 1 to 6 carbon atoms and (C₃-C₇)cycloalkyl is intended to indicate a cycloalkyl radical comprising from 3 to 7 carbon ring atoms.

- 20 The term "hydroxyalkyl" is intended to indicate an alkyl group as defined above substituted with one or more hydroxy, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl.

- 25 The term "oxo" is intended to indicate an oxygen atom which is connected to the parent molecular moiety via a double bond (=O).

- When two or more of the above defined terms are used in combination, such as arylalkyl, heteroarylalkyl, cycloalkylalkyl and the like, it is to be understood that the first mentioned radical is a substituent on the latter mentioned radical, where the point of 30 attachment to the parent molecular moiety is on the latter radical.

The group C(O) is intended to represent a carbonyl group (C=O)

- 35 If substituents are described as being independently selected from a group, each substituent is selected independent of the other. Each substituent may therefore be identical or different from the other substituent(s).

The term "optionally substituted" means "unsubstituted or substituted", and therefore the general formulas described herein encompasses compounds containing the specified optional substituent(s) as well as compounds that do not contain the optional substituent(s).

5

The term "pharmaceutically acceptable salt" is intended to indicate salts prepared by reacting a compound of formula I, which comprise a basic moiety, with a suitable inorganic or organic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, phosphoric, formic, acetic, 2,2-dichloroacetic, adipic, ascorbic, L-aspartic, L-glutamic, galactaric, lactic, maleic, L-malic, phthalic, citric, propionic, benzoic, glutaric, gluconic, D-glucuronic, methanesulfonic, salicylic, succinic, malonic, tartaric, benzenesulfonic, ethane-1,2-disulfonic, 2-hydroxy ethanesulfonic acid, toluenesulfonic, sulfamic, fumaric and ethylenediaminetetraacetic acid. Pharmaceutically acceptable salts of compounds of formula I comprising an acidic moiety may also be prepared by reaction with a suitable base such as sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, silver hydroxide, ammonia or the like, or suitable non-toxic amines, such as lower alkylamines, hydroxy-lower alkylamines, cycloalkylamines, or benzylamines, or L-arginine or L-lysine. Further examples of pharmaceutical acceptable salts are listed in Berge, S.M.; J. Pharm. Sci.; (1977), 66(1), 1-19, which is incorporated herein by reference.

20

The terms "ROR gamma" and "ROR γ " are used to describe ROR γ 1 and/or ROR γ t

The term "solvate" is intended to indicate a species formed by interaction between a compound, e.g. a compound of formula I, and a solvent, e.g. alcohol, glycerol or water, wherein said species are in an amorphous or in a crystalline form. When water is the solvent, said species is referred to as a hydrate.

25

The term "protic solvent" is intended to indicate a solvent which has an acidic hydrogen, such as water, or such as alcohols, e.g. methanol, ethanol or isopropanol.

30

The term "aprotic solvent" is intended to indicate a solvent which does not have an acidic hydrogen, such as for example dichloromethane, acetonitrile, dimethylformamide, dimethyl sulfoxide or acetone.

35

The term "treatment" as used herein means the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the delaying of the progression of the disease, disorder or condition, the

amelioration, alleviation or relief of symptoms and complications, and/or the cure or elimination of the disease, disorder or condition. The term may also include prevention of the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition or disorder and includes

5 the administration of the active compounds to prevent the onset of the symptoms or complications. Nonetheless, prophylactic (preventive) and therapeutic (curative) treatments are two separate aspects.

Unless otherwise indicated, all exact values provided herein are representative of

10 corresponding approximate values, e.g. exact exemplary values provided with respect to a particular measurement can be considered to also provide a corresponding approximate measurement, modified by "about" where appropriate.

All references, including publications, patent applications and patents, cited herein are

15 hereby incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference, regardless of any separately provided incorporation of particular documents made elsewhere herein.

20 Embodiments of the invention

In one or more embodiments of the invention X represents N.

In one or more embodiments of the invention X represents CH.

25

In one or more embodiments of the invention R₁ represents -CN, methyl, ethyl, propyl, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, oxazolidinyl, morpholinyl, piperidinyl, triazolyl, pyrrazolyl, isoxazolyl, thiadiazolyl or oxadiazolyl.

30 In one or more embodiments of the invention R₂ represents chloro, methyl or difluoromethyl.

In one or more embodiments of the invention R₃ represents methyl.

35

In one or more embodiments of the invention R₄ represents methyl.

In one or more embodiments of the invention R₅ represents phenyl, propyl, butyl, ethoxy, iso-propyloxy, tert-butyloxy, cyclopropyl, cyclobutyl, cyclopentyl, methylcyclopropyl or cyclobutylmethyl.

- 5 In one or more embodiments of the invention R₆ represents -OH, -CN, fluoro, -NH₂, =O, -S(O)₂CH₃, methyl, methoxy or hydroxymethyl.

In one or more embodiments of the invention R₇ represents fluoro or -OH.

- 10 In one or more embodiments of the invention the compound of general formula (I) is selected from the list consisting of
- 5-[[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazol-2-carbonitrile,
- 15 [(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,
- [(2S)-4-[[5-chloro-2-methyl-3-[(5-tetrahydrofuran-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,
- 20 [(2S)-4-[[5-chloro-2-methyl-3-[(5-tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone
- [(2S)-4-[[5-chloro-3-[(5-cyclopropyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,
- [(2S)-4-[[5-chloro-3-[[5-(1-hydroxycyclopropyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,
- 25 3-[[5-[[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazol-2-yl]propanenitrile,
- 3-[[5-[[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazol-2-yl]propanenitrile,
- 1-[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-2,2-difluoro-butan-1-one,
- 30 [(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-(2-fluorophenyl)methanone,
- [(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-(3,3-difluorocyclopentyl)methanone,
- (2S)-1-[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-
- 35 methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-2-methyl-butan-1-one,
- [(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-cyclobutyl-methanone,

- [(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-cyclopentyl-methanone,
cyclobutyl-[(2S)-4-[[2,5-dimethyl-3-[(5-methyl-1,3,4-oxadiazol-2-yl)amino]phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
- 5 2-[5-[3-[[[(3S)-4-(cyclobutanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-anilino]-1,3,4-oxadiazol-2-yl]acetonitrile,
2-[5-[3-[[[(3S)-4-(cyclopropanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-anilino]-1,3,4-oxadiazol-2-yl]acetonitrile,
2-[5-[3-[[[(3S)-4-(3,3-difluorocyclopentanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-anilino]-1,3,4-oxadiazol-2-yl]acetonitrile,
- 10 2-[5-[5-chloro-3-[[4-(cyclopentanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2-methyl-anilino]-1,3,4-oxadiazol-2-yl]acetonitrile,
cyclobutyl-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
- 15 cyclobutyl-[(2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
2,2-difluoro-1-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]butan-1-one,
cyclopropyl-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
- 20 [(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-(2-methylcyclopropyl)methanone,
cyclopentyl-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
- 25 (3,3-difluorocyclopentyl)-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
2-cyclobutyl-1-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]ethanone,
cyclobutyl-[(2S)-4-[[5-(difluoromethyl)-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
- 30 tert-butyl (2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
tert-butyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 35 tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(3-methyltriazol-4-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-methylpyrazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,

- tert-butyl (2S)-4-[[3-[(5-isoxazol-5-yl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(1,2,5-thiadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 5 tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(4-methyl-1,2,5-oxadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[2,5-dimethyl-3-[(5-methyl-1,3,4-oxadiazol-2-yl)amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(1S)-1-amino-2-hydroxy-ethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 10 isopropyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(1S)-1-aminopropyl]-1,3,4-oxadiazol-2-yl]amino]-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 15 isopropyl (2S)-4-[[5-chloro-3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(oxetan-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(1S,2R)-1-amino-2-hydroxy-propyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 20 isopropyl (2S)-4-[[3-[[5-(cyanomethyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-(difluoromethyl)-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 25 isopropyl (2S)-4-[[5-chloro-2-methyl-3-[(5-tetrahydropyran-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-3-[[5-(1-hydroxycyclopropyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-3-[[5-[1-(hydroxymethyl)cyclopropyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 30 isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(2,2,2-trifluoro-1-hydroxy-ethyl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(2-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 35 isopropyl (2S)-4-[[3-[[5-[(1S)-1-aminoethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-(difluoromethyl)-3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,

- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(5-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(5S)-2-oxooxazolidin-5-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 5 isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-[(2S)-4-oxoazetidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(4-methyl-1,2,5-oxadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3S)-morpholin-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate dihydrochloride,
- 10 isopropyl (2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2R)-3,3,3-trifluoro-2-hydroxy-propyl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 15 isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-oxo-4-piperidyl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-methylpyrazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(2S)-2-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 20 isopropyl (2S)-4-[[3-[[5-[(2R)-2-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(1S)-1-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 25 isopropyl (2S)-4-[[5-chloro-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate
- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2S)-1-methylsulfonylpyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 30 isopropyl (2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(5-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 35 isopropyl (2S)-4-[[3-[[5-[(1R)-1-aminoethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate
- 2,2,2-trifluoroethyl (2S)-4-[[5-chloro-3-[[5-(cyanomethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,

2,2,2-trifluoroethyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
ethyl (2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
5 isopropyl (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[5-chloro-2-methyl-3-[(5-morpholin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate and
tert-butyl (2S)-4-[[5-chloro-3-[[5-(hydroxymethyl)oxazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate
10

or pharmaceutically acceptable salts, hydrates or solvates thereof.

Any combination of two or more embodiments described herein is considered within the
15 scope of the present invention.

The present invention includes all embodiments wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are combined in any combination as anywhere described herein.

20 The compounds of formula I may be obtained in crystalline form either directly by concentration from an organic solvent or by crystallisation or recrystallisation from an organic solvent or mixture of said solvent and a cosolvent that may be organic or inorganic, such as water. The crystals may be isolated in essentially solvent-free form or as a solvate, such as a hydrate. The invention covers all crystalline forms, such as
25 polymorphs and pseudopolymorphs, and also mixtures thereof.
If nothing else is indicated the term 'solid' in the description of the examples means that the compound of the invention was prepared as a non-crystalline compound.

Compounds of formula I comprise asymmetrically substituted (chiral) carbon atoms
30 which give rise to the existence of isomeric forms, e.g. enantiomers and possibly diastereomers. The present invention relates to all such isomers, either in optically pure form or as mixtures thereof (e.g. racemic mixtures or partially purified optical mixtures). Pure stereoisomeric forms of the compounds and the intermediates of this invention may be obtained by the application of procedures known in the art. The various isomeric
35 forms may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. high pressure liquid chromatography using chiral stationary phases. Enantiomers may be separated from each other by selective crystallization of their diastereomeric salts which may be formed with optically active

acids. Optically purified compounds may subsequently be liberated from said purified diastereomeric salts. Enantiomers may also be resolved by the formation of diastereomeric derivatives. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Pure stereoisomeric forms may also be derived from the corresponding pure stereoisomeric forms of the appropriate starting materials, provided that the reaction occur stereoselectively or stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereoselective or stereospecific methods of preparation. These methods will advantageously employ chiral pure starting materials.

In the compounds of general Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of general Formula I. For example, different isotopic forms of hydrogen include ^1H , ^2H and ^3H and different isotopic forms of carbon include ^{12}C , ^{13}C and ^{14}C . Enriching for deuterium (^2H) may for example increase in-vivo half-life or reduce dosage regimens, or may provide a compound useful as a standard for characterization of biological samples. Isotopically enriched compounds within general formula I can be prepared by conventional techniques well known to a person skilled in the art or by processes analogous to those described in the general procedures and examples herein using appropriate isotopically enriched reagents and/or intermediates.

In one or more embodiments of the present invention, the compounds of general formula (I) as defined above are useful in therapy and in particular for use in the treatment of psoriasis.

In one or more embodiments of the present invention, the compounds of general formula (I) as defined above are useful in treatment of a disease, disorder or condition, which disease, disorder or condition is responsive of modulation of ROR-gamma.

In one or more embodiments of present invention provides a pharmaceutical composition comprising a compound according to general formula (I) together with one or more other therapeutically active compound(s) together with a pharmaceutically acceptable vehicle or excipient or pharmaceutically acceptable carrier(s).

In one or more embodiments of the present invention, the compounds of general formula (I) are useful in the manufacture of a medicament for the prophylaxis, treatment or amelioration of autoimmune or inflammatory diseases.

- 5 In one or more embodiments of the present invention, the compounds of general formula (I) are useful in the manufacture of a medicament for the prophylaxis, treatment or amelioration of psoriasis.

- 10 In one or more embodiments of the present invention, the compounds of general formula (I) are useful in a method of preventing, treating or ameliorating autoimmune or inflammatory diseases or conditions, the method comprising administering to a person suffering from at least one of said diseases an effective amount of one or more compounds according to according to general formula (I), optionally together with a pharmaceutically acceptable carrier or one or more excipients, optionally in combination
15 with other therapeutically active compounds.

- Besides being useful for human treatment, the compounds of the present invention may also be useful for veterinary treatment of animals including mammals such as horses, cattle, sheep, pigs, dogs, and cats.
20

Pharmaceutical Compositions of the Invention

- For use in therapy, compounds of the present invention are typically in the form of a pharmaceutical composition. The invention therefore relates to a pharmaceutical
25 composition comprising a compound of formula I, optionally together with one or more other therapeutically active compound(s), together with a pharmaceutically acceptable excipient, vehicle or carrier(s). The excipient must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

- 30 Conveniently, the active ingredient comprises from 0.0001-50 % by weight of the formulation.

- In the form of a dosage unit, the compound may be administered one or more times a
35 day at appropriate intervals, always depending, however, on the condition of the patient, and in accordance with the prescription made by the medical practitioner. Conveniently, a dosage unit of a formulation contain between 0.001 mg and 1000 mg, preferably between 0.01 mg and 250 mg, such as 50-200 mg of a compound of formula I.

A suitable dosage of the compound of the invention will depend, inter alia, on the age and condition of the patient, the severity of the disease to be treated and other factors well known to the practising physician. The compound may be administered either orally, parenterally, topically, transdermally or interdermally + other routes according to
5 different dosing schedules, e.g. daily, weekly or with monthly intervals. In general a single dose will be in the range from 0.001 to 400 mg/kg body weight. The compound may be administered as a bolus (i.e. the entire daily dose is administered at once) or in divided doses two or more times a day.

10 In the context of topical treatment it may be more appropriate to refer to a "usage unit", which denotes a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid, semisolid or liquid pharmaceutical diluents or carriers.

15 The term "usage unit" in connection with topical use means a unitary, i.e. a single dose, capable of being administered topically to a patient in an application per square centimetre of the treatment area of from 0.001 microgram to 1 mg and preferably from 0.05 microgram to 0.5 mg of the active ingredient in question.

20 It is also envisaged that in certain treatment regimes, administration with longer intervals, e.g. every other day, every week, or even with longer intervals may be beneficial.

25 If the treatment involves administration of another therapeutically active compound it is recommended to consult *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12th Ed., L. L. Brunton (Ed.), McGraw-Hill 2010, for useful dosages of said compounds.

30 The administration of a compound of the present invention with one or more other active compounds may be either concomitantly or sequentially.

The formulations include e.g. those in a form suitable for oral, rectal, parenteral (including subcutaneous, intraperitoneal, intramuscular, intraarticular and intravenous),
35 transdermal, intradermal, ophthalmic, topical, nasal, sublingual or buccal administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by but not restricted to any of the methods well known in the art of pharmacy,

e.g. as disclosed in Remington, *The Science and Practice of Pharmacy*, 22nd ed., 2013. All methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into
5 association with a liquid carrier, semisolid carrier or a finely divided solid carrier or combinations of these, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral and buccal administration may be
10 in the form of discrete units as capsules, sachets, tablets, chewing gum or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder, granules or pellets; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid, such as ethanol or glycerol; or in the form of a gel, a nano-
or microemulsion, an oil-in-water emulsion, a water-in-oil emulsion or other dispensing
15 systems. The oils may be edible oils, such as but not restricted to e.g. cottonseed oil, sesame oil, coconut oil or peanut oil. Suitable dispersing or suspending agents for aqueous suspensions include synthetic or natural surfactants and viscosifying agents such as but not restricted to tragacanth, alginate, acacia, dextran, sodium
carboxymethylcellulose, gelatin, methylcellulose, hydroxypropylmethylcellulose,
20 hydroxypropylcellulose, carbomers, polyvinylpyrrolidone, polysorbates, sorbitan fatty acid esters,. The active ingredients may also be administered in the form of a bolus, electuary or paste.

A tablet may be made by compressing, moulding or freeze drying the active ingredient
25 optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient(s) in a free-flowing form such as a powder or granules, optionally mixed by a binder and/or filler, such as e.g. lactose, glucose, mannitol starch, gelatine, acacia gum, tragacanth gum, sodium
alginate, calcium phosphates, microcrystalline cellulose, carboxymethylcellulose,
30 methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose, hydroxyethylcellulose, polyethylene glycol, waxes or the like; a lubricant such as e.g. sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride or the like; a disintegrating agent such as e.g. starch, methylcellulose, agar, bentonite, croscarmellose sodium, sodium starch glycollate, crospovidone or the
35 like or a dispersing agent, such as polysorbate 80. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and suitable carrier moistened with an inert liquid diluent. Freeze dried tablets may be

formed in a freeze-dryer from a solution of the drug substance. Suitable filler can be included.

5 Formulations for rectal administration may be in the form of suppositories in which the compound of the present invention is admixed with low melting point, water soluble or insoluble solids such as cocoa butter, hydrogenated vegetable oils, polyethylene glycol or fatty acids esters of polyethylene glycols, while elixirs may be prepared using myristyl palmitate.

10 Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredients, which is preferably isotonic with the blood of the recipient, e.g. isotonic saline, isotonic glucose solution or buffer solution. Furthermore, the formulation may contain cosolvent, solubilising agent and/or complexation agents. The formulation may be conveniently sterilised by for instance
15 filtration through a bacteria retaining filter, addition of sterilising agent to the formulation, irradiation of the formulation or heating of the formulation. Liposomal formulations as disclosed in e.g. Encyclopedia of Pharmaceutical Technology, vol.9, 1994, are also suitable for parenteral administration.

20 Alternatively, the compounds of formula I may be presented as a sterile, solid preparation, e.g. a freeze-dried powder, which is readily dissolved in a sterile solvent immediately prior to use.

Transdermal formulations may be in the form of a plaster, patch, microneedles,
25 liposomal or nanoparticulate delivery systems or other cutaneous formulations applied to the skin.

Formulations suitable ophthalmic administration may be in the form of a sterile aqueous preparation of the active ingredients, which may be in microcrystalline form, for
30 example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems e.g. as disclosed in Encyclopedia of Pharmaceutical Technology, vol.2, 1989, may also be used to present the active ingredient for ophthalmic administration.

35 Formulations suitable for topical, such as dermal, intradermal or ophthalmic administration include liquid or semi-solid preparations such as liniments, lotions, gels, applicants, sprays, foams, film forming systems, microneedles, micro- or nano-

emulsions, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops.

For topical administration, the compound of formula I may typically be present in an amount of from 0.001 to 20% by weight of the composition, such as 0.01% to about 10 %, but may also be present in an amount of up to about 100% of the composition.

Formulations suitable for nasal or buccal administration include powder, self-propelling and spray formulations, such as aerosols and atomisers. Such formulations are disclosed in greater detail in e.g. Modern Pharmaceutics, 2nd ed., G.S. Banker and C.T. Rhodes (Eds.), page 427-432, Marcel Dekker, New York; Modern Pharmaceutics, 3th ed., G.S. Banker and C.T. Rhodes (Eds.), page 618-619 and 718-721, Marcel Dekker, New York and Encyclopedia of Pharmaceutical Technology, vol. 10, J. Swarbrick and J.C. Boylan (Eds.), page 191-221, Marcel Dekker, New York.

In addition to the aforementioned ingredients, the formulations of a compound of formula I may include one or more additional ingredients such as diluents, buffers, flavouring agents, colourant, surface active agents, thickeners, penetration enhancing agents, solubility enhancing agents preservatives, e.g. methyl hydroxybenzoate (including anti-oxidants), emulsifying agents and the like.

When the active ingredient is administered in the form of salts with pharmaceutically acceptable non-toxic acids or bases, preferred salts are for instance easily water-soluble or slightly soluble in water, in order to obtain a particular and appropriate rate of absorption.

The pharmaceutical composition may additionally comprise one or more other active components conventionally used in the treatment of autoimmune or inflammatory diseases such as psoriasis, psoriatic arthritis, multiple sclerosis, rheumatoid arthritis, crohns disease, alopecia areata, contact dermatitis, spondyloarthritis; and cancers.

METHODS OF PREPARATION

The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of synthesis. The compounds of formula I may for example be prepared using the reactions and techniques outlined below together with methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to,

those described below. The reactions are carried out in solvents appropriate to the reagents and materials employed and suitable for the transformations being effected. Also, in the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction

5 temperature, duration of experiment and work-up procedures, are chosen to be conditions of standard for that reaction, which should be readily recognized by one skilled in the art. Not all compounds falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such

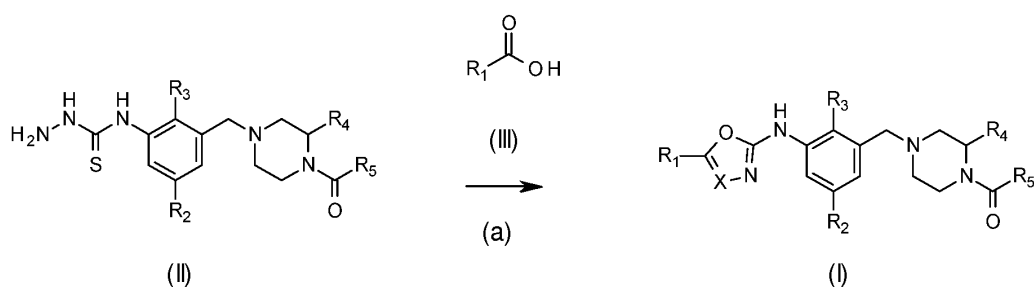
10 restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternative methods can be used. The compounds of the present invention or any intermediate may be purified if required using standard methods well known to a synthetic organist chemist, e.g. methods described in "Purification of Laboratory Chemicals", 6th ed. 2009, W. Amarego and C. Chai, Butterworth-Heinemann. Starting materials are either known compounds,

15 commercially available, or they may be prepared by routine synthetic methods well known to a person skilled in the art.

Synthetic routes

The following schemes illustrate the preparation of compounds of the formula (I), throughout which R₁, R₂, R₃, R₄, R₅ are as described above:

When X = N,



25 Scheme 1

Acids suitable for use as compound (III) are commercially available, are known in the literature or can be prepared by standard methods.

30 Step (a): Acid (III) is reacted with aminothiourethane (II) to give the compound of formula (I). This reaction is carried out by standard methods. Coupling may be undertaken by using either;

- (i) The acid chloride derivative of acid (III) + aminothiurea (II), with an excess of base in a suitable solvent, then desulfurative cyclisation with WSCDI or DCC in DCM, THF or DMSO with or without heating; or tosyl chloride and excess pyridine in THF at 65 °C
- 5 (ii) The acid (III) + aminothiurea (II), with WSCDI or DCC in DCM, THF or DMSO with or without heating; or tosyl chloride and excess pyridine in THF at 65 °C .

Typically the conditions are as follows:

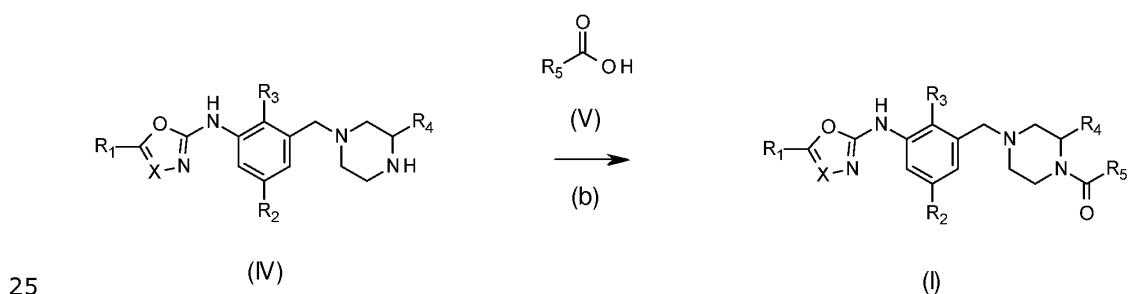
- 10 (i) acid chloride of acid (III) (generated in-situ or commercial), an excess of aminothiurea (II), optionally with an excess of tertiary amine such as TEA, Hünig's base or NMM, in DCM or THF, without heating for 1 to 24 hrs, then WSCDI in DCM or THF without heating for 1 to 16 hrs
- (ii) acid (III), WSCDI or DCC, aminothiurea (II), in THF, DCM without heating or in
15 DMSO at 60 °C for 1 to 16 hrs; or, acid (III), aminothiurea (II), with an excess of pyridine and tosyl chloride in THF at 65 °C for 1-2 hrs.

The preferred conditions are: 1.2 eq. acid (III), 1 eq. aminothiurea (II), 4 eq. WSCDI in DCM at room temperature for up to 16 hours.

20

Alternatively, when X = N or CH:

Compound (I) can be prepared as outlined in scheme 1.1



Scheme 1.1

- 30 Acids suitable for use as compound (V) are commercially available or known in the literature.

Step (b): Acid (V) is reacted with amine (IV) to give the compound of formula (I). This reaction is carried out by standard methods.

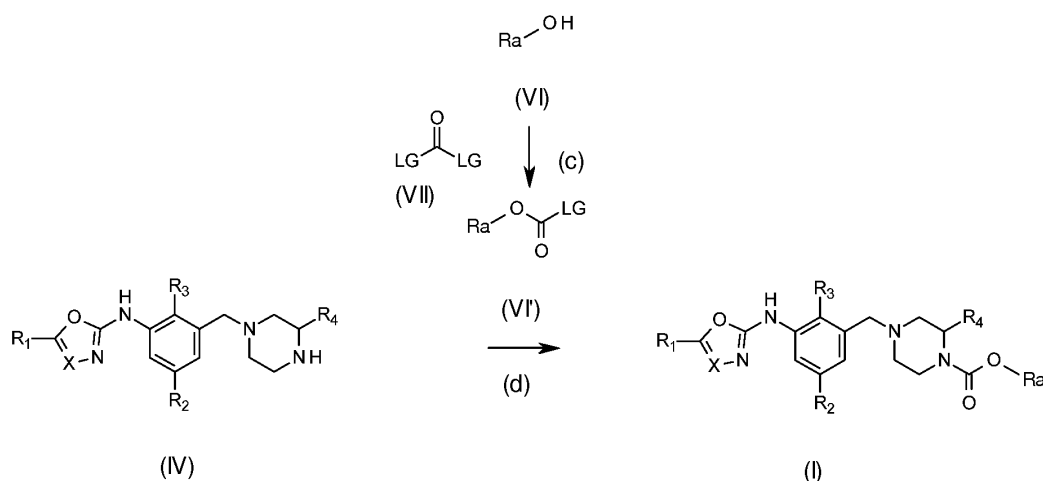
Coupling may be undertaken by using either;

- (i) The acid chloride derivative of acid (V) + amine (IV), with an excess of base in a suitable solvent, or
- (ii) acid (V), amine (IV), HATU with an excess of NMM, TEA, Hünig's base in THF or DMF at room temperature for 4 to 16 hrs; or acid (V), WSCDI /DCC and HOBT /HOAT, amine (IV), with an excess of NMM, TEA, Hünig's base in THF, DCM or EtOAc, at room temperature for 4 to 16 hrs.

The preferred conditions are: 1.0 eq. acid (V), 1.0 eq. amine (IV), 1.5 eq. HATU and an excess of in DMF at room temperature for up to 16 hours.

Alternatively, when X= N or CH and R₅ = ORa:

- Compound (I) can be prepared as outlined in scheme 1.2



Scheme 1.2

Alcohols suitable for use as compound (VI) are commercially available or are known in the literature.

LG represents a leaving group, typically chloro, compounds suitable for use as compound (VII) are known in the literature or commercially available.

Step (c): The alcohol (IV) is transformed in situ to the reactive intermediate (IV'), if LG is chloro then (IV') is a carbamoyl chloride.

Typical conditions are,

- (i) The alcohol (VI) in a suitable aprotic solvent with phosgene, triphosgene, diphosgene or CDI in the presence of a tertiary base, without heating for 1 to 24hr.

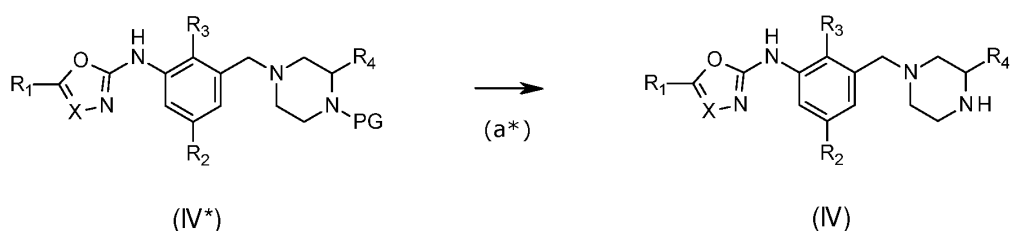
Preferred conditions are: The alcohol (VI) in DCM with triphosgene (0.4 eq) with Hunig's base (2 eq.), without heating for 2 hr.

Step (d): The reactive intermediate (VI') is reacted with amine (IV). Typical conditions are,

- (i) The reactive intermediate (IV') in a suitable aprotic solvent with amine (IV) in the presence of a tertiary base like NMM, Hunig's base, TEA without heating for 1 to 24hr.

Preferred conditions are: The reactive intermediate (VI') (1.3 eq.) with amine (IV) in with Hunig's base (3 eq) in DCM at low temperature for 2hr.

- 15 When X = N or CH,



Scheme 1.2*

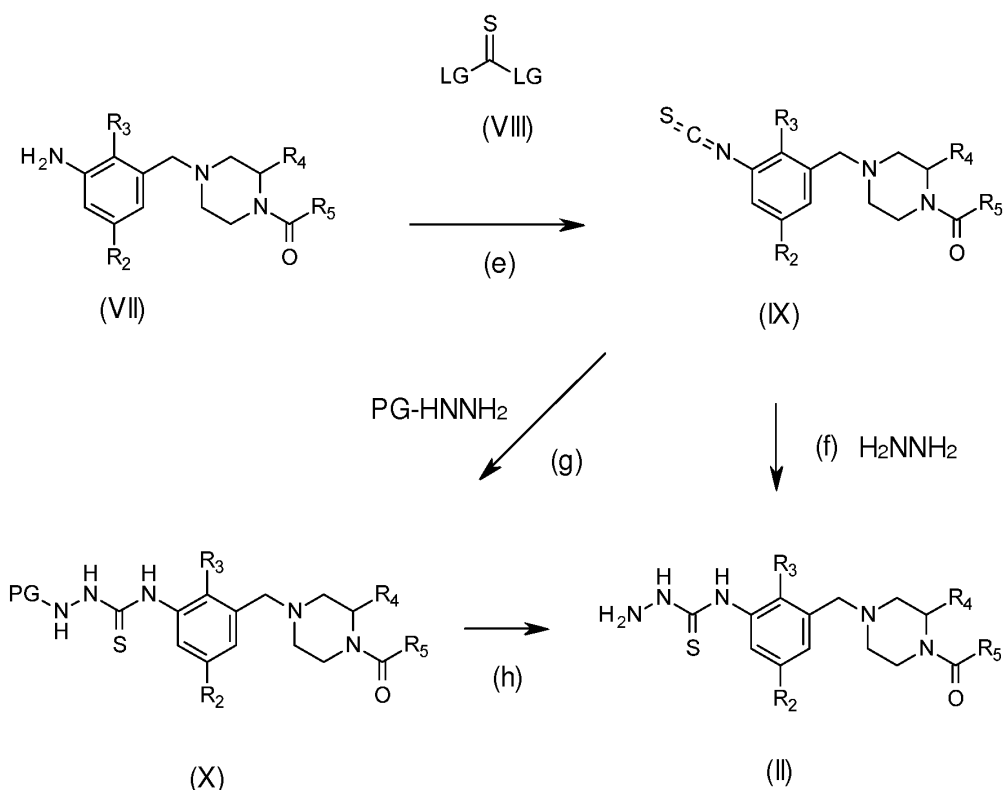
- 20 PG represents a suitable protecting group for nitrogen. Standard methodology for nitrogen protecting groups is used, described in for example "Greene's Protective Groups in Organic Synthesis" Fifth edition, Wiley, Ed. P. G. M. Wuts.

Those skilled in the art will appreciate that the compounds of formula (IV*) can have, but are not limited to, structures of the same formula as compound (I). (e.g. R₅ is O-

- 25 *tert*-butyl or O-benzyl)

Step (a*): Deprotection of compound (IX) is undertaken using standard methodology, as described in "Greene's Protective Groups in Organic Synthesis" Fifth edition, Wiley, Ed. P. G. M. Wuts.

- Preferred conditions are: when PG is Boc the is hydrogen chloride in a suitable solvent such as 1,4-dioxane at room temperature for 1-16 hours, or a solution of trifluoroacetic acid in dichloromethane for 1-2 hours.



Scheme 2

5

PG represents a suitable protecting group for nitrogen. Standard methodology for nitrogen protecting groups is used, such as that found in textbooks, e.g. "Greene's Protective Groups in Organic Synthesis" Fifth edition, Wiley, Ed. P. G. M. Wuts. LG represents a leaving group, typically chloro, compounds suitable for use as compound (VII) are known in the literature or commercially available.

Step (e): Amine (VII) is reacted with thiocarbonyl compounds (VIII) to give compounds of formula (IX). This reaction is carried out by standard methods.

Typical conditions are,

(i) Amine (II) in a suitable aprotic solvent with thiocarbonyl dichloride, optionally in the presence of base, without heating for 1-24 hrs.

(ii) Amine (II) in a suitable aprotic solvent with bis(2-pyridyloxy)methanethione and DMAP, without heating for 1-3hrs.

Preferred conditions are: The amine and thiocarbonyl dichloride (1 eq) in chloroform and aqueous sodium hydrogen carbonate without heating for 1 hr.

20

Step (f): Isothiocyanate (IX) is reacted with commercially available hydrazine compositions, such as hydrazine hydrate or hydrazine hydrochloride, to give compounds of formula (II). This reaction is carried out by standard methods.

Preferred conditions are: Isothiocyanate with hydrazine hydrate (1.05 eq) in CHCl_3 ,

5 without heating for 1-16 hrs.

Alternatively,

Compound (II) can be accessed via

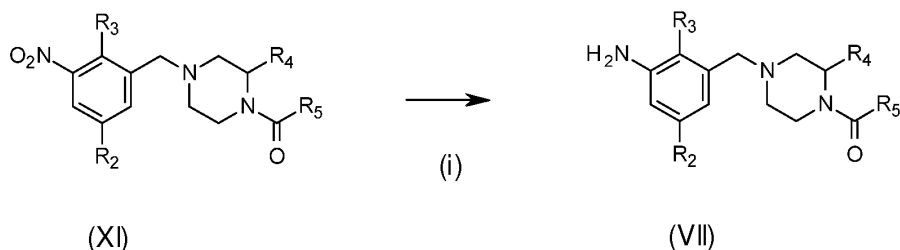
10 Step (g): Isothiocyanate (IX) is reacted with commercially available protected hydrazine to give compounds of formula (II). This reaction is carried out by standard methods.

Preferred conditions are: Isothiocyanate with hydrazine hydrate (1.05 eq) in CHCl_3 , without heating for 1-16 hrs.

15 Step (h): Deprotection of compound (IX) is undertaken using standard methodology, as described in "Greene's Protective Groups in Organic Synthesis" Fifth edition, Wiley, Ed. P. G. M. Wuts.

When PG is Boc the preferred method is hydrogen chloride in a suitable solvent such as 1,4-dioxane at room temperature for 1-16 hours, or a solution of trifluoroacetic acid in

20 dichloromethane for 1-2 hours.



Scheme 3

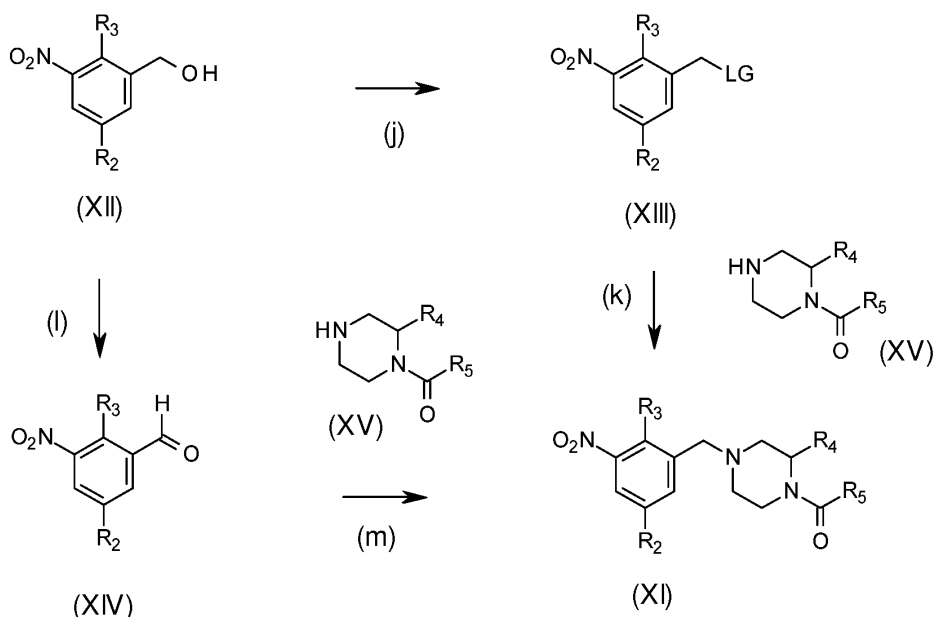
Step (i): Nitro compound (XI) is reacted under reducing conditions to give compounds of formula (VII). This reaction is carried out by standard methods.

Typical conditions are,

(i) Nitro compound (XI) and a suitable Pd catalyst in a protic solvent such as EtOH under a pressure of hydrogen gas, with heating for 4-24 hrs.

(ii) Nitro compound (XI) and Zn or Fe in AcOH with or without aprotic co-solvent without heating for 4-24 hrs.

Preferred conditions are: Nitro compound (XI) and Fe powder (2 eq) in AcOH without heating for 16 hrs.



Scheme 4

Step (j): Benzylic alcohol (XII) is reacted with a activating reagent to give compounds of
 5 the formula (XIII). If LG is a chloro, then (XIII) is a benzyl chloride. If LG is OSO_2CH_3 ,
 then (XIII) is a methanesulfonate.

Typical conditions are,

- (i) Benzylic alcohol (XII) and thionyl chloride in a suitable solvent such as THF or
 DMF, with a base such as TEA or Hunig's base with or without heating for 1- 24
 10 hrs.
- (ii) Benzylic alcohol (XII) and thionyl chloride in pyridine with or without heating for
 1- 24 hrs.
- (iii) Benzylic alcohol (XII) and methanesulfonyl chloride in a suitable aprotic solvent
 with a base such as TEA or Hunig's base without heating for 1- 24 hrs.

15 Preferred conditions are: Benzylic alcohol (XII), methanesulfonyl chloride (2 eq) and TEA
 (3 eq) in DCM at 0-5 °C.

Step (k): Benzylic chloride or methanesulfonate (XIII) is reacted with amine (XV) to give
 compounds of the formula (XI).

Typical conditions are,

- (i) Benzylic chloride (XIII), amine (XV) and TEA, Hunig's base, NMM or K_2CO_3 in
 suitable aprotic solvent, optionally with KI, with or without heating for 1-24 hrs.
- (ii) Benzylic methanesulfonate (XIII), amine (XV) and TEA, Hunig's base, NMM or
 20 K_2CO_3 in suitable aprotic solvent with or without heating for 1-24 hrs.

Preferred conditions are: Benzylic methanesulfonate (XIII), amine (XV), K_2CO_3 (3 eq) in MeCN from 0-75 °C for 16 hrs.

Alternatively

- 5 Compound (II) can be accessed via

Step (I): Benzylic alcohol (XII) is reacted to give compounds of the formula (XIV).

Typical conditions are,

- (i) Benzylic alcohol (XII) and MnO_2 in a suitable aprotic solvent with or without heating for 1-24 hrs.
- 10 (ii) Benzylic alcohol (XII), oxalyl chloride, DMSO and TEA in DCM at -78 °C.
- (iii) Benzylic alcohol (XII), PCC in a suitable aprotic solvent with or without heating for 1-24 hrs.

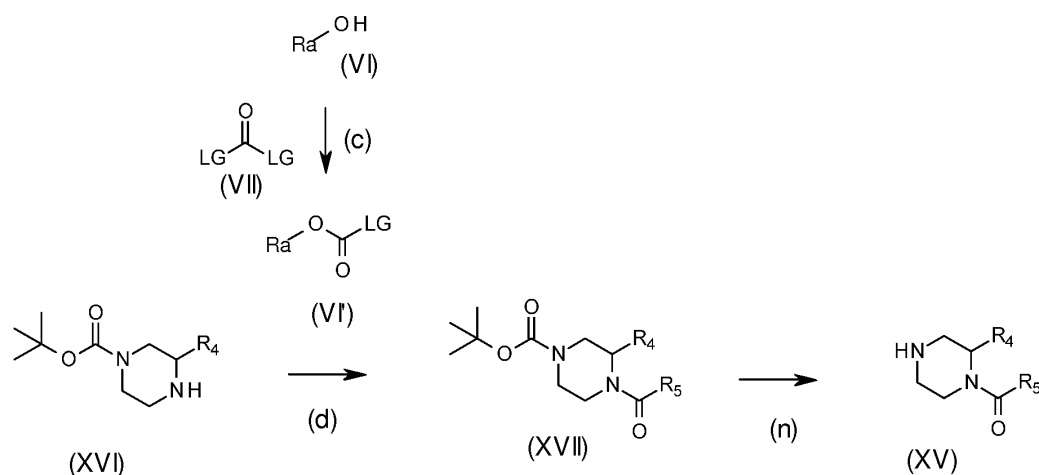
Preferred conditions are: Benzylic alcohol (XII) and PCC (1.3 eq) in DCM without heating for 3 hrs.

- 15 Step (m): Aldehyde (XIV) is reacted with amine (XV) to give compounds of formula (XI).

Typical conditions are,

- (i) Aldehyde (XIV), amine (XV), $Ti(OPr-i)_4$ and $NaBH_4$ in a protic solvent such as MeOH without heating for 1-24 hrs.
- (ii) Aldehyde (XIV), amine (XV) with $NaHB(OAc)_3$ in DCM without heating for 1-24
- 20 hrs.

Preferred conditions are: Aldehyde (XIV), amine (XV) (1.1 eq) and $NaHB(OAc)_3$ (2 eq) in DCM without heating for 4 hrs.



Scheme 5

- 25 LG represents a leaving group, typically chloro, compounds suitable for use as compound (VII) are known in the literature or commercially available.

Step (c): The alcohol (IV) is transformed in situ to the reactive intermediate (IV'), if LG is chloro then (IV') is a carbamoyl chloride.

Typical conditions are,

- 5 (i) The alcohol (VI) in a suitable aprotic solvent with phosgene, triphosgene, diphosgene or CDI in the presence of a tertiary base, without heating for 1 to 24hr.

Preferred conditions are: The alcohol (VI) in DCM with triphosgene (0.4 eq) with Hunig's base (2 eq.), without heating for 2 hr.

- 10 Step (d): The reactive intermediate (VI') is reacted with amine (XVI). Typical conditions are,

- (i) The reactive intermediate (IV') in a suitable aprotic solvent with amine (XVI) in the presence of a tertiary base like NMM, Hunig's base, TEA without heating for 1 to 24hr.

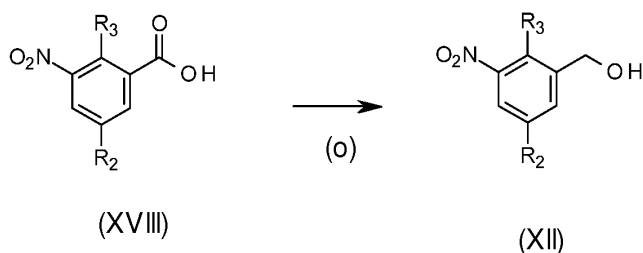
- 15 Preferred conditions are: The reactive intermediate (VI') (1.3 eq.) with amine (XVI) in with Hunig's base (3 eq) in DCM at low temperature for 2hr.

Step (n): Carbamate (XVII) is reacted to give compounds of the formula (XV)

Typical conditions are,

- 20 (i) Carbamate (XVII) in a solution of trifluoroacetic acid in dichloromethane for 1-2 hours.
(ii) Carbamate (XVII) and hydrogen chloride in either DCM or 1,4-dioxane for 1-16 hrs.

- Preferred conditions are: Carbamate (XVII) and an excess of HCl in 1,4-dioxane, without
25 heating for 16 hrs.



Scheme 6

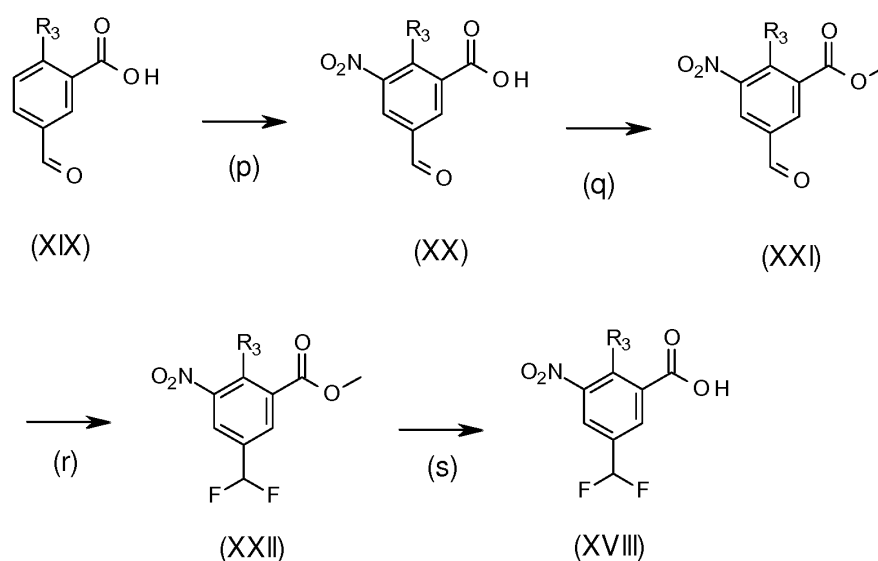
- Acids suitable for use as compounds (XVIII) are commercially available, known in the
30 literature or can be prepared from commercially available intermediates using methods outlined in, amongst others, Kuntz et al., J. Med. Chem (2016), 59, 1556-1564, Sun et al., PCT 2004073612, Jackson Bioorg Med Chem Lett. (2011), 21, 3227-3231, or defined as in Scheme 7.

Step (o): Acid (XVIII) is reacted to give compounds of the formula (XII).

Typical conditions are,

- (i) Acid (XVIII) and borane.tetrahydrofuran complex in suitable aprotic solvent such as THF with heating for 3-16 hrs.

(ii) Acid (XVIII) and LiAlH_4 in a suitable aprotic solvent without heating for 1-24 hrs.
Preferred conditions are: Acid (XVIII) and borane THF complex (3 eq) in THF with heat for 3 hrs.



Scheme 7

Step (p): Acid (XIX) is reacted to give compounds of formula (XX)

Typical conditions are,

- (i) Acid (XIX), $\text{c.H}_2\text{SO}_4$ and c.HNO_3 without heating for 1-3 hrs.
(ii) Acid (XIX), $\text{c.H}_2\text{SO}_4$ and KNO_3 with heating for 2-16 hrs.

Preferred conditions are: Acid (XIX) in $\text{c.H}_2\text{SO}_4$ with mixture of $\text{c.HNO}_3/\text{c.H}_2\text{SO}_4$ without heating for 1 hr.

Step (q): Acid (XX) is reacted to give compounds of formula (XXI)

Typical conditions are,

- (i) Acid (XX), TMSCHN_2 in a suitable aprotic solvent with MeOH and without heating for 2-16 hrs.
(ii) Acid (XX), MeI and K_2CO_3 or Na_2CO_3 in a suitable aprotic solvent without heating for 3-24 hrs.

Preferred conditions are: Acid (XX), MeI (2 eq) and K_2CO_3 (3 eq) in DMF at 0°C for 3 hrs.

Step (r): Aldehyde (XXI) is reacted to give compounds of formula (XXII)

Typical conditions are,

(i) Aldehyde (XXI) and DAST in a suitable solvent such as DCM without heating for 2-24 hrs

(ii) Aldehyde (XXI) and Deoxyfluor in a suitable solvent such as DCM, optionally with protic solvent such as EtOH, with or without heating.

Preferred conditions are: Aldehyde (XXI) and DAST (2 eq) in DCM without heating for 16 hrs.

Step (s): Ester (XXII) is reacted to give compounds of formula (XVIII)

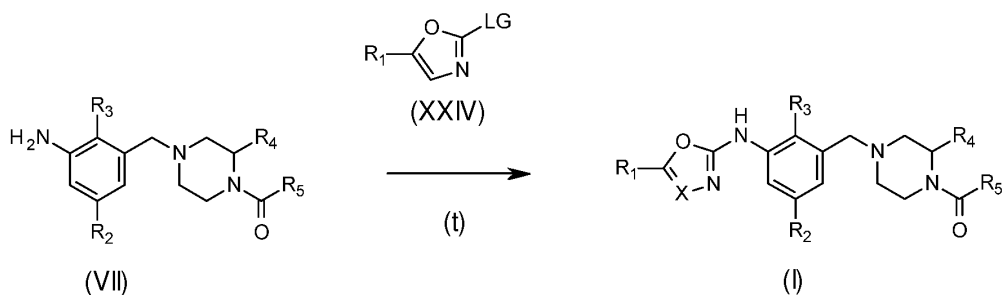
Deprotection of compound (XXII) is undertaken using standard methodology, as

described in "Greene's Protective Groups in Organic Synthesis" Fifth edition, Wiley, Ed. P. G. M. Wuts.

Preferred conditions are: Ester (XXII) with LiOH in aqueous THF without heating for 5 hrs.

The following scheme illustrates the preparation of compounds of the formula (XXIII) with R_1 , R_2 , R_3 , R_4 and R_5 as hereinbefore defined:

When $X = CH$,



Scheme 8

LG represents a leaving group, typically chloro, compounds suitable for use as compound (XXIV) are known in the literature or commercially available, or can be prepared from commercially available intermediates using methods outlined in the literature.

Step (t): Amine (VII) is reacted with oxazole (XXIV) to give compounds of formula (I')

When LG is chloro or bromo, typical conditions are,

(i) Amine (VII), oxazole (XXIV) in a suitable solvent with heating for 0.5-24 hrs.

(ii) Amine (VII), oxazole (XXIV) in a suitable aprotic solvent, with strong base such as NaH, with heating for 1-24 hrs.

When LG is sulfur, typical conditions are,

- (i) Amine (VII), oxazole (XXIV), POCl₃ or SOCl₂ with base such as TEA or pyridine with heating for 1-24 hrs.
- (ii) Amine (VII), oxazole (XXIV) with mcpba or Oxone in suitable solvent with heating for 1-24 hrs.
- 5 Preferred conditions are: LG is chloro: Amine (VII) and oxazole (XXIV) in IPA with microwave irradiation for 30 min.

GENERAL PROCEDURES, PREPARATIONS AND EXAMPLES

- ¹H nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz unless otherwise specified. Chemical shift values (δ , in ppm) are quoted relative to internal tetramethylsilane ($\delta = 0.00$) standards. The value of a multiplet, either defined doublet (d), triplet (t), quartet (q) or not (m) at the approximate midpoint is given unless a range is quoted. (br) indicates a broad peak, whilst (s) indicates a singlet. All NMR spectra are recorded in DMSO-d₆ unless another solvent is stated.
- 15 The organic solvents used were usually anhydrous. The solvent ratios indicated refer to vol:vol unless otherwise noted.

LCMS Method 1: KINETEX-1.7u XB-C18 column, 0.05% FA in water with acetonitrile

LCMS Method 2: ACQUITY UPLC BEH C18 column, 0.05% FA in water with acetonitrile

- 20 LCMS Method 3: Xbridge C18 column, 0.01M NH₄CO₃ in water with acetonitrile

UPLC-MS Method 4:

Column: Waters Acquity UPLC HSS T3 1.8 μ m, 2.1 x 50 mm.

Column temperature: 60°C.

- 25 UV: PDA 210-400 nm.

Injection volume: 2 μ l.

Eluents: A: 10 mM Ammonium acetate with 0.1% formic acid.

B: 100% Acetonitrile with 0.1% formic acid.

Gradient:	Time	A%	B%	Flow
30	0.0	95	5	1.2
	0.9	5	95	1.2
	0.91	5	95	1.3
	1.2	5	95	1.3
	1.21	5	95	1.2
35	1.4	95	5	1.2

MS: Electrospray switching between positive and negative ionisation.

Instruments: Waters Aquity UPLC, Waters SQD

UPLC-MS Method 5:

Column: Acquity UPLC HSS T3 1.8µm; 2.1 x 50mm

Flow: 0.7ml/min

Column temp: 40°C

5 Mobile phases: A: 10 mM Ammonium acetate + 0.1% formic acid

B: 100% Acetonitrile + 0.1% formic acid

UV: 240-400 nm

Injection volume: 2µl

Gradient:	Time	A%	B%
10	0.0	99% A	1% B
	0.5	94% A	6% B
	1.0	94% A	6% B
	2.6	5% A	95% B
	3.8	5% A	95% B
15	3.81	99% A	1% B
	4.8	99% A	1% B

UPLC (inlet method): XE Metode 7 CM

MS – method: PosNeg_50_1000

Instruments: Waters Acquity UPLC, Waters LCT Premier XE

20

UPLC-MS Method 6:

Column: Acquity UPLC HSS T3 1.8µm; 2.1 x 50mm

Flow: 0.7ml/min

Column temp: 30°C

25 Mobile phases: A: 10 mM Ammonium acetate + 0.1% formic acid

B: 100% Acetonitrile + 0.1% formic acid

UV: 240-400 nm

Injection volume: 1µl

Gradient:	Time	A%	B%
30	0.0	99% A	1% B
	0.5	94% A	6% B
	1.0	94% A	6% B
	2.6	5% A	95% B
	3.8	5% A	95% B
35	3.81	99% A	1% B

4.8 99% A 1% B

UPLC (inlet method): XEV Metode 1 CM

MS – method: Pos_50_1000 or Neg_50_1000

Instruments: Waters Acquity UPLC, Waters XEVO G2-XS QTof

5

Basic preparative HPLC conditions:

Column: XBridge Prep C18 5µm OBD, 19x150 mm

Eluents: Ammonium formate (50 mM)/acetonitrile, 10-100% acetonitrile

10 Flow: 30 mL/min

Acidic preparative HPLC conditions:

Column: XTerra® RP-18 5µm OBD, 19x150 mm

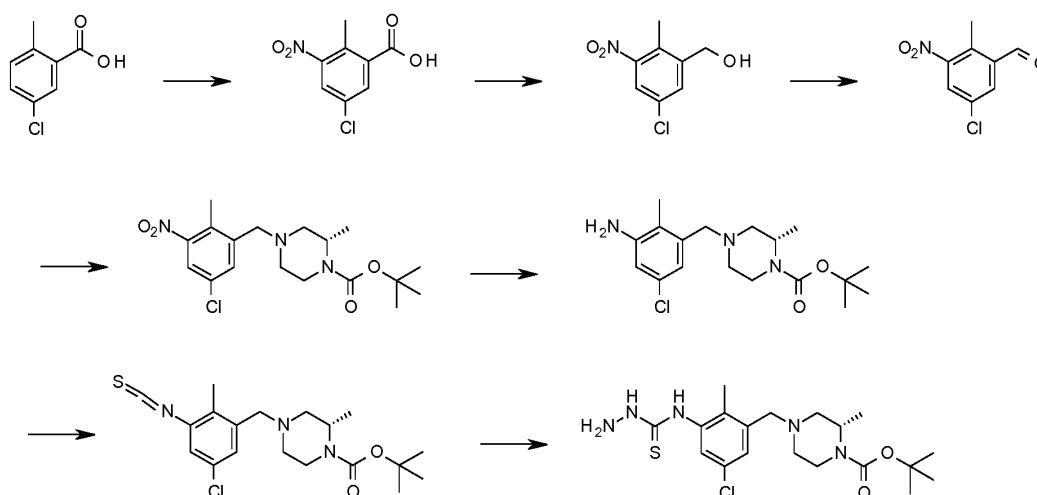
15 Eluents: 0.1% formic acid in water/acetonitrile, 10-100% acetonitrile

Flow: 30 mL/min

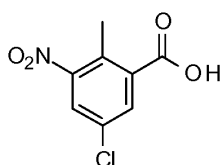
List of Abbreviations

	AcOH	acetic acid
20	CDI	1,1'-carbonyldiimidazole
	CHCl ₃	chloroform
	c.HNO ₃	concentrated nitric acid
	c.H ₂ SO ₄	concentrated sulfuric acid
	DAST	(diethylamino)sulfur trifluoride
25	DCC	dicyclohexylcarbodiimide
	DCM	dichloromethane
	Deoxyfluor	bis(2-methoxyethyl)aminosulfur trifluoride
	DMAP	<i>N,N</i> -dimethyl-4-pyridinamine
	DMF	dimethylformamide
30	DMSO	dimethylsulfoxide
	EtOAc	ethyl acetate
	EtOH	ethanol
	FA	Formic acid
	Fe	iron
35	HATU	<i>N,N,N',N'</i> -tetramethyl- <i>O</i> -(1 <i>H</i> -benzotriazol-1-yl)uronium hexafluorophosphate
	HCl	hydrogen chloride

	HOAT	1-hydroxy-7-azabenzotriazole
	HOBT	1-hydroxybenzotriazole
	Hunig's base	diisopropylethylamine
	IPA	propan-2-ol
5	K ₂ CO ₃	potassium carbonate
	KI	potassium iodide
	LiAlH ₄	lithium aluminium hydride
	LiOH	lithium hydroxide
	mcpba	3-chloroperbenzoic acid
10	MeCN	acetonitrile
	MeI	iodomethane
	MeOH	methanol
	NaBH ₄	sodium borohydride
	NaBH(OAc) ₃	sodium triacetoxyborohydride
15	Na ₂ CO ₃	sodium carbonate
	NaH	sodium hydride
	NMM	4-methylmorpholine
	Oxone	potassium peroxymonosulfate
	PCC	pyridinium chlorochromate
20	Pd	palladium
	POCl ₃	phosphorous oxychloride
	SOCl ₂	thionyl chloride
	TEA	triethylamine
	THF	tetrahydrofuran
25	Ti(OPr-i) ₄	titanium isopropoxide
	TMSCHN ₂	trimethylsilyldiazomethane
	TsCl	tosyl chloride
	WSCDI	3-(ethyliminomethyleneamino)-N,N-dimethyl- propan-1-amine hydrochloride
30	Zn	zinc



Scheme 9.1

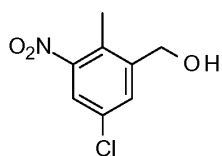
Preparation 1: 5-chloro-2-methyl-3-nitrobenzoic acid

5

5-Chloro-2-methylbenzoic acid (75.0 g, 439 mmol) was added portion-wise to conc. sulphuric acid (525 ml, 7 vol) at 0°C. After complete addition a solution of conc. nitric acid (41.1 g, 978 mmol, 67%) in conc. sulphuric acid (82.5 ml) was added drop-wise maintaining internal temperature at 0°C. On complete addition the reaction mixture was stirred for an additional 30 mins at 0°C. The mixture was poured onto ice/water and the precipitate was filtered, washed with water, dried and filtered to afford title compound as an off-white solid. (80.0 g, 84.4 %, as a mixture of isomers)

¹H NMR (400MHz, CDCl₃) δ = 8.18 (d, *J* = 2.4 Hz, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 2.66 (s, 3H). Peaks at 7.55 (d, *J* = 8.3 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 2.57 (s, 3H) relate to regioisomer. LCMS Method 1: *m/z* 214.03 [M-H⁺]; RT = 2.49 min.

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Preparation 2: (5-chloro-2-methyl-3-nitro-phenyl)methanol

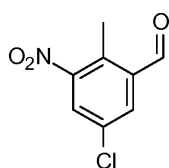
Borane tetrahydrofuran complex solution (1.11 L, 1.0 M in THF) was added to a solution of the acid from **Preparation 1** (80.0 g, 371 mmol) drop-wise at 0°C. On complete

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addition the reaction mixture was warmed to room temperature then stirred at reflux for 3 h. The reaction mixture was cooled to room temperature. Methanol was added drop-wise until evolution of gas subsided. The reaction mixture was stirred at reflux for 2 h. The cooled reaction mixture was poured into water (500 mL) and extracted with ethyl acetate (2 x 1000 mL). The combined ethyl acetate layers were dried over sodium sulphate and evaporated under reduced pressure to afford title compound as a pale brown solid. (75.0 g, 100%)

^1H NMR (400MHz, CDCl_3) δ = 7.71 (br d, $J=6.8$ Hz, 2H), 7.34-7.40 (m, 0.24H), 7.27-7.32 (m, 0.24H), 4.77 (s, 2H), 4.58 (s, 0.5H), 2.47 (s, 1H), 2.33 (s, 3H).

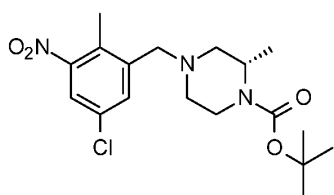
Preparation 3: 5-chloro-2-methyl-3-nitro-benzaldehyde



Pyridinium chlorochromate (104 g, 483 mmol) was slowly added to a stirred solution of alcohol from **Preparation 2** (75.0 g, 372 mmol) in dichloromethane (200 mL). The reaction mixture was stirred at room temperature for 3 h then filtered through Celite[®]. The solvent was removed under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-10% ethyl acetate in petroleum ether. Clean fractions were evaporated under reduced pressure to give the title compound as an off-white solid. (39.0 g, 52.5%)

^1H NMR (400MHz, CDCl_3) δ = 10.34 (s, 1H), 8.02 (d, $J=2.0$ Hz, 1H), 7.97 (d, $J=2.4$ Hz, 1H), 2.75 (s, 3H). LCMS Method 1: m/z 198.08 [$\text{M}-\text{H}^+$]; 82.8%; RT = 2.74 min.

Preparation 4: *tert*-butyl (2S)-4-[(5-chloro-2-methyl-3-nitro-phenyl)methyl]-2-methyl-piperazine-1-carboxylate



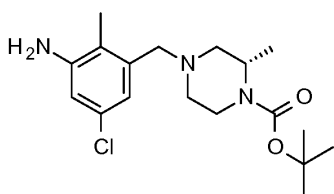
tert-Butyl (2S)-2-methylpiperazine-1-carboxylate (43.1 g, 215 mmol) was added to a solution of aldehyde from **Preparation 3** (39.0 g, 195 mmol) in dichloromethane (780 mL). The reaction mixture was stirred at room temperature for 10 min then sodium triacetoxyborohydride (83.1 g, 391 mmol) was added portion-wise. On complete addition the reaction mixture was stirred at room temperature for 4 h. The reaction

mixture was carefully quenched with water (200 mL) and extracted with dichloromethane (200 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure. Trituration of the crude product with n-pentane afforded the title compound as an off-white solid. (43.0 g, 57.3%)

- 5 ¹H NMR (300MHz, DMSO-*d*₆) δ = 7.92 (d, *J*=2.2 Hz, 1H), 7.68 (d, *J*=2.2 Hz, 1H), 4.09 (m, 1H), 3.67 (br d, *J*=13.1 Hz, 1H), 3.52 (s, 2H), 2.88-3.02 (m, 1H), 2.69 (br d, *J*=11.1 Hz, 1H), 2.57 (br d, *J*=11.3 Hz, 1H), 2.35 (s, 3H), 2.15 (dd, *J*=11.3, 3.6 Hz, 1H), 1.98 (td, *J*=11.7, 3.4 Hz, 1H), 1.39 (s, 9H), 1.13 (d, *J*=6.7 Hz, 3H). LCMS Method 1: *m/z* 384.66 [M+H⁺]; RT = 3.47 min.

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Preparation 5: *tert*-butyl (2*S*)-4-[(3-amino-5-chloro-2-methyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate

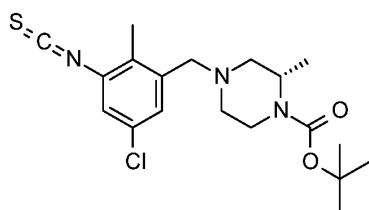


Iron powder (7.29 g, 130 mmol) was added to a solution of nitro compound from

- 15 **Preparation 4** (25.0 g, 65.3 mmol) in acetic acid (250 mL), portion-wise at room temperature. The reaction mixture was stirred for 16 h and then concentrated to low volume under reduced pressure. The crude product was diluted in dichloromethane (100 mL) and filtered through a pad of Celite®. The filtrate was concentrated and pH adjusted to pH 8 with saturated sodium hydrogen carbonate. The mixture was extracted with
- 20 dichloromethane (3 x 200 mL). The combined organic layer was dried over sodium sulphate and evaporated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 20-30% ethyl acetate in petroleum ether. Clean fractions were evaporated under reduced pressure to give the title compound as an off-white solid. (18.0 g, 78.1%)
- 25 ¹H NMR (400MHz, DMSO-*d*₆) δ = 6.59 (d, *J*=2.1 Hz, 1H), 6.47 (d, *J*=2.1 Hz, 1H), 5.10 (s, 2H), 4.07 (br s, 1H), 3.65 (br d, *J*=13.1 Hz, 1H), 3.21-3.31 (m, 2H), 2.91 (br t, *J*=11.4 Hz, 1H), 2.67 (br d, *J*=11.0 Hz, 1H), 2.56 (br d, *J*=11.3 Hz, 1H), 2.12 (s, 3H), 1.94-2.12 (m, 1H), 1.86 (td, *J*=11.6, 3.4 Hz, 1H), 1.39 (s, 9H), 1.11 (d, *J*=6.7 Hz, 3H). LCMS Method 1: *m/z* 354.27 [M+H⁺]; RT = 2.19 min.

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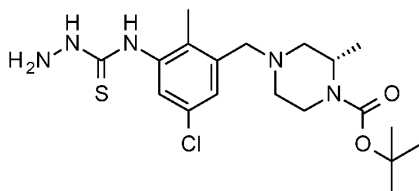
Preparation 6: *tert*-butyl (2*S*)-4-[(5-chloro-3-isothiocyanato-2-methyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate



Thiocarbonyl dichloride (0.17 mL, 2.12 mmol) was added drop-wise to a rapidly stirred mixture of the product from **Preparation 5** (750 mg, 2.12 mmol) in chloroform (70 mL) and saturated sodium hydrogen carbonate (70 mL). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure to afford title compound as off-white solid. (839 mg, 100%)

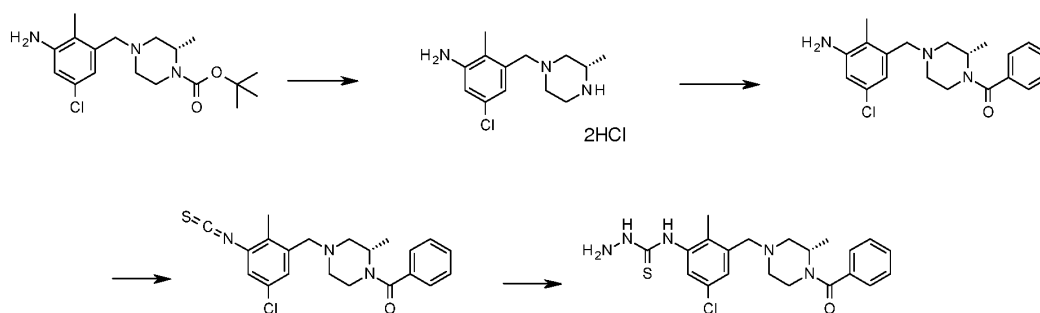
^1H NMR (300 MHz, CDCl_3) δ = 7.20 (d, J = 2.2 Hz, 1H), 7.16 (d, J = 2.2 Hz, 1H), 4.21 (s, 1H), 3.80 (d, J = 13.1 Hz, 1H), 3.36 (s, 2H), 3.05 (td, J = 12.7, 3.4 Hz, 1H), 2.67 (d, J = 11.0 Hz, 1H), 2.54 (d, J = 11.0 Hz, 1H), 2.34 (s, 3H), 2.20 (dd, J = 11.1, 3.9 Hz, 1H), 2.01 (d, J = 3.5 Hz, 1H), 1.46 (d, J = 0.6 Hz, 9H), 1.21 (d, J = 6.7 Hz, 3H). LCMS Method 4: m/z 396.2 [$\text{M}+\text{H}^+$]; RT = 1.15 min.

Preparation 7: *tert*-butyl (2S)-4-[[[3-(aminocarbamothioylamino)-5-chloro-2-methylphenyl]methyl]-2-methyl-piperazine-1-carboxylate



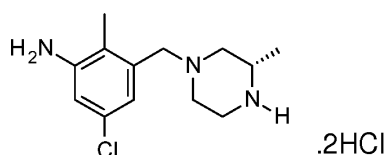
The thioisocyanate from **Preparation 6** (839 mg, 2.12 mmol), in chloroform (4 mL), was added to a solution of hydrazine hydrate (111 mg, 2.22 mmol) in chloroform (10 mL) over 10 min. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was evaporated under reduced pressure to afford title compound as pale yellow solid. (906 mg, 99%)

^1H NMR (300 MHz, CDCl_3) δ = 8.97 (s, 1H), 7.59 (s, 1H), 7.26 (1H), 7.23 (s, 1H), 4.20 (s, 1H), 4.01 (s, 2H), 3.80 (d, J = 13.1 Hz, 1H), 3.40 (s, 2H), 3.05 (td, J = 12.7, 3.4 Hz, 1H), 2.71 (d, J = 11.1 Hz, 1H), 2.57 (d, J = 11.1 Hz, 1H), 2.25 (s, 3H), 2.18 (d, J = 3.9 Hz, 1H), 2.01 (td, J = 11.7, 3.5 Hz, 1H), 1.46 (s, 9H), 1.21 (d, J = 6.7 Hz, 3H). LCMS Method 4: m/z 396.2 [$\text{M}+\text{H}^+$]; RT = 0.74 min.



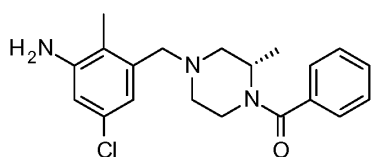
Scheme 9.2

- 5 **Preparation 8:** 5-chloro-2-methyl-3-[[[(3S)-3-methylpiperazin-1-yl]methyl]aniline dihydrochloride



- Hydrogen chloride (4M solution in 1,4-dioxane, 15 mL, 60 mmol) was added to a solution of the piperazine compound from **Preparation 5** (3.00 g, 8.48 mmol) in dichloromethane (30 mL) and stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure to afford title compound as a colourless solid that was used without any purification. (2.77 g, 100%) LCMS Method 4: m/z 254.2 $[M+H^+]$; RT = 0.42 min.

- 15 **Preparation 9:** [(2S)-4-[(3-amino-5-chloro-2-methyl-phenyl)methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone

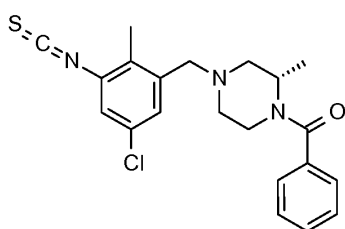


- Benzoic acid (561 mg, 4.59 mmol) was added to a solution of the amine from **Preparation 8** (1.50 g, 4.59 mmol) in ethyl acetate (25 mL). To this mixture was added triethylamine (3.84 mL, 27.6 mmol) and *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (1.83 g, 4.82 mmol). The resulting reaction mixture was stirred at room temperature for 16 h and then quenched with water and extracted with dichloromethane (2x 30 mL). The combined organic layers was dried over magnesium sulphate and evaporated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of

0-60% ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give the title compound as a colourless solid. (1.36 g, 83.0%)

¹H NMR (300 MHz, DMSO-d₆) δ = 7.42-7.45 (m, 3H), 7.32-7.35 (m, 2H), 6.59 (d, *J* = 2.2 Hz, 1H), 6.47 (d, *J* = 2.2 Hz, 1H), 5.10 (s, 2H), 3.10 (bs, 1H), 2.71 (d, *J* = 10.1 Hz, 1H), 2.61 (d, *J* = 7.3 Hz, 1H), 2.12 (dd, *J* = 11.3, 3.8 Hz, 1H), 2.01 (s, 3H), 1.95 (td, *J* = 11.7, 3.5 Hz, 1H), 1.22 (d, *J* = 6.7 Hz, 3H). LCMS Method 4: *m/z* 358.3 [M+H⁺]; RT = 0.42 min.

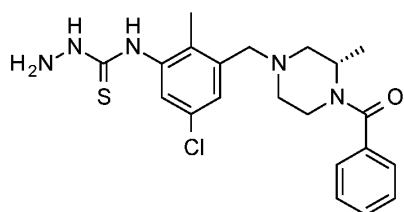
Preparation 10: [(2S)-4-[(5-chloro-3-isothiocyanato-2-methyl-phenyl)methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone



Using a procedure similar to that described for **Preparation 6**, but using the compound described in **Preparation 9** (675 mg, 1.89 mmol), the title compound was prepared as a yellow oil. (750 mg, 99%)

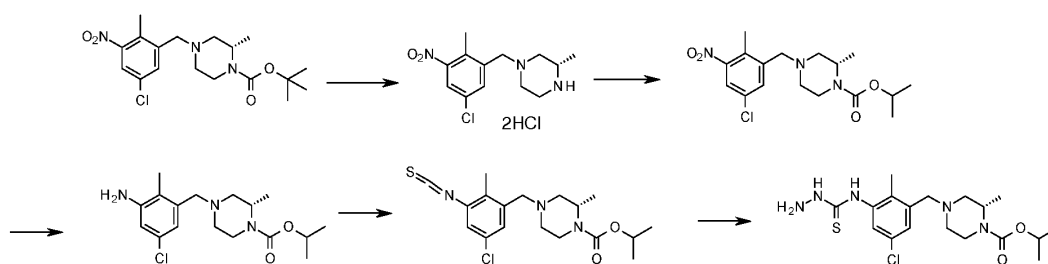
¹H NMR (300 MHz, CDCl₃) δ = 7.30 – 7.47 (m, 5H), 7.09 – 7.23 (m, 2H), 3.40 (s, 2H), 3.24 (s, 1H), 2.73 (s, 1H), 2.58 (s, 1H), 2.35 (s, 4H), 2.11 (d, *J* = 13.6 Hz, 1H), 1.33 (d, *J* = 6.8 Hz, 3H). LCMS Method 4: *m/z* 400.3 [M+H⁺]; RT = 1.04 min.

Preparation 11: 1-amino-3-[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl)methyl]-5-chloro-2-methyl-phenyl]thiourea



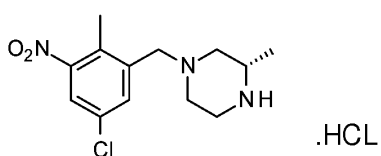
Using a procedure similar to that described for **Preparation 7**, but using the compound described in **Preparation 10** (550 mg, 1.37 mmol), the title compound was prepared as an off-white solid. (490 mg, 82%)

¹H NMR (300 MHz, CDCl₃) δ = 8.97 (s, 1H), 7.59 (s, 1H), 7.38 (tdd, *J* = 6.4, 2.8, 1.9 Hz, 5H), 7.20 (d, *J* = 2.2 Hz, 1H), 4.06 (d, *J* = 15.7 Hz, 2H), 3.43 (s, 2H), 3.23 (s, 1H), 2.76 (s, 1H), 2.63 (d, *J* = 11.4 Hz, 1H), 2.24 (s, 4H), 2.11 (d, *J* = 11.9 Hz, 1H), 1.32 (d, *J* = 6.7 Hz, 2H). LCMS Method 4: *m/z* 432.2 [M+H⁺]; RT = 0.64 min.



Scheme 9.3

Preparation 12: (3S)-1-[(5-chloro-2-methyl-3-nitro-phenyl)methyl]-3-methyl-piperazine hydrochloride

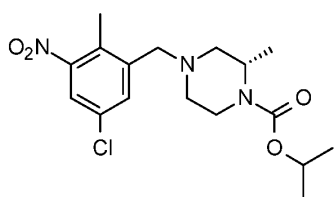


Hydrogen chloride (4M solution in 1,4-dioxane, 200 mL) was added to a solution of the piperazine compound from **Preparation 4** (15.0 g, 39.2 mmol) in 1,4-dioxane (45 mL) at 0°C. The resulting mixture was stirred at room temperature for 16 h before being concentrated under reduced pressure to afford title compound as a colourless solid. (12.5 g, 100%)

^1H NMR (300MHz, DMSO- d_6) δ = 7.86-8.17 (m, 2H), 5.46 (br s, 2H), 4.10 (br s, 2H), 3.57 (s, 3H), 3.25 (br s, 2H), 2.40 (s, 3H), 1.25 (br d, J =6.6 Hz, 3H).

LCMS Method 1: m/z 284, 17 [$\text{M}+\text{H}^+$]; RT = 2.04 min.

Preparation 13: isopropyl (2S)-4-[(5-chloro-2-methyl-3-nitro-phenyl)methyl]-2-methyl-piperazine-1-carboxylate

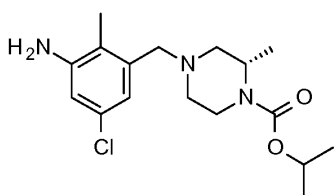


Isopropyl chloroformate (2M solution in toluene, 3.66 mmol) was added drop-wise to a solution of the amine from **Preparation 12** (900 mg, 2.81 mmol) and diisopropylethylamine (1.5 mL, 8.44 mmol) in dichloromethane (10 mL) at 0°C. The reaction mixture was stirred to room temperature over 2 h. The mixture was diluted with water (50 mL) and extracted with dichloromethane (2 x 50 mL). The combined organic layer was dried over sodium sulphate and evaporated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography

eluting with a gradient of 10-20% ethyl acetate in petroleum ether. Clean fractions were evaporated under reduced pressure to give the title compound as a colourless oil. (600 mg, 57.7%)

¹H NMR (300MHz, CDCl₃) δ = 7.69 (d, *J*=2.1 Hz, 1H), 7.53 (d, *J*=2.1 Hz, 1H), 4.92-4.96 (m, 1H), 4.28-4.31 (m, 1H), 3.85-3.88 (m, 1H), 3.46 (s, 2H), 3.10-3.14 (m, 1H), 2.70-2.73 (m, 1H), 2.52-2.57 (m, 1H), 2.44 (s, 3H), 2.21 – 2.31 (m, 1H), 2.01 – 2.15 (m, 1H), 1.24 (m, 9H). LCMS Method 1: *m/z* 370.62 [M+H⁺]; RT = 3.18 min.

Preparation 14: isopropyl (2S)-4-[(3-amino-5-chloro-2-methyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate

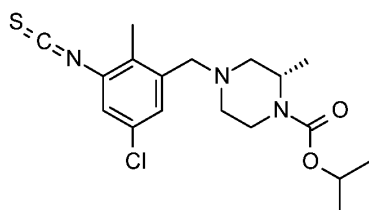


Using a procedure similar to that described for **Preparation 5** but using the nitro compound from **preparation 13** (3.30 g, 8.94 mmol), the title compound was prepared as a brown gum (2.60 g, 85.8%).

¹H NMR (400MHz, DMSO-*d*₆) δ = 6.59 (d, *J*=2.1 Hz, 1H), 6.47 (d, *J*=2.1 Hz, 1H), 5.10 (s, 2H), 4.75-4.79 (m, 1H), 4.11 (br s, 1H), 3.65-3.69 (m, 1H), 3.20-3.30 (m, 2H), 2.86-3.04 (m, 1H), 2.65-2.69 (m, 1H), 2.53-2.57 (m, 1H), 1.98-2.15 (m, 4H), 1.82-1.89 (m, 1H), 1.17 (d, *J*=6.1 Hz, 6H), 1.13 (d, *J*=6.7 Hz, 3H). LCMS Method 1: *m/z* 384. [M+H⁺]; 98.8%; RT = 2.05 min.

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Preparation 15: isopropyl (2S)-4-[(5-chloro-3-isothiocyanato-2-methyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate

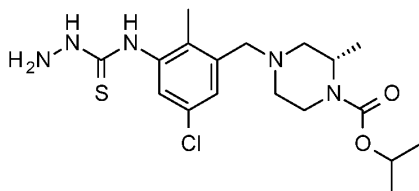


Using a procedure similar to that described for **Preparation 6**, but using the compound described in **Preparation 14** (1.00 g, 2.94 mmol), the title compound was prepared as a yellow oil. (1.11 g, 98.8%)

¹H NMR (300 MHz, CDCl₃) δ=7.20 (s, 1H), 7.17 (s, 1H), 4.92 (h, *J* = 6.2 Hz, 1H), 4.26 (s, 1H), 3.86 (d, *J* = 13.2 Hz, 1H), 3.37 (s, 2H), 3.08 (td, *J* = 12.7, 3.4 Hz, 1H), 2.68 (d, *J* = 11.0 Hz, 1H), 2.55 (d, *J* = 11.1 Hz, 1H), 2.34 (s, 3H), 2.28 – 2.13 (m, 1H), 2.03 (td,

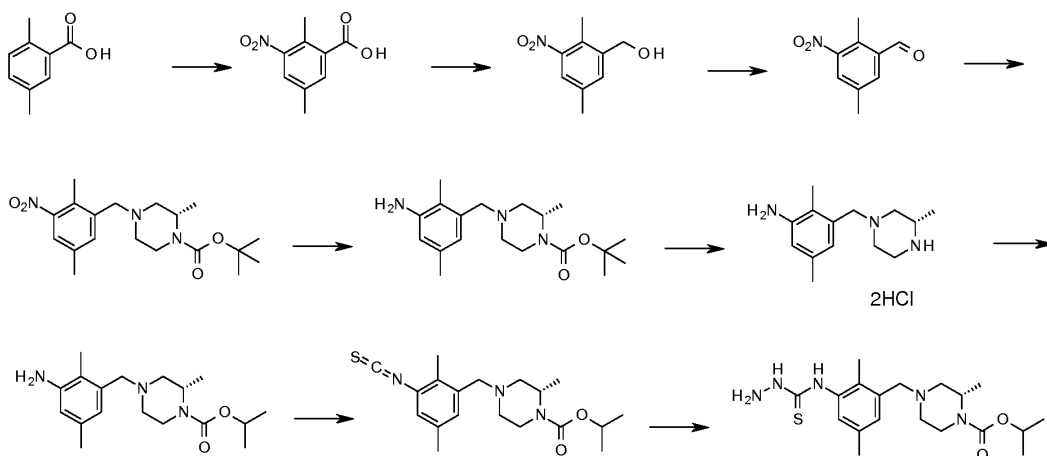
$J = 11.6, 3.5$ Hz, 1H), 1.24 (d, $J = 4.6$, Hz, 6H) overlapping 1.22 (d, $J = 6.5$, Hz, 3H).
LCMS Method 4: m/z 382.1 $[M+H^+]$; RT = 1.08 min.

Preparation 16: isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



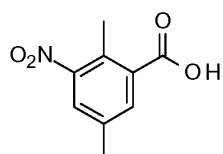
Using a procedure similar to that described for **Preparation 7**, but using the compound described in **Preparation 15** (1.11 g, 2.91 mmol), the title compound was prepared as a yellow oil. (869 mg, 72.2%)

^1H NMR (300 MHz, CDCl_3) δ = 7.59 (br s, 1H), 7.23 (s, 1H), 4.93 (p, $J = 6.2$ Hz, 1H), 4.25 (s, 1H), 4.04 (s, 2H), 3.85 (d, $J = 13.2$ Hz, 1H), 3.40 (s, 2H), 3.09 (td, $J = 12.9, 3.4$ Hz, 1H), 2.72 (d, $J = 10.9$ Hz, 1H), 2.58 (d, $J = 11.1$ Hz, 1H), 2.25 (s, 4H), 2.13 – 1.88 (m, 1H), 1.24 (d, $J = 4.6$, Hz, 6H) overlapping 1.22 (d, $J = 6.5$, Hz, 3H). LCMS Method 4: m/z 414.1 $[M+H^+]$; RT = 0.66 min.



Scheme 9.4

Preparation 17: 2,5-dimethyl-3-nitro-benzoic acid

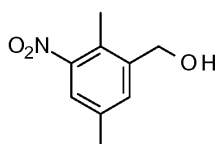


Using a procedure similar to that described for **Preparation 1**, but using 2,5-dimethylbenzoic acid (40.0g, 266 mmol), the title compound was prepared as an off-white solid (37.0 g, 71.1%, mixture of isomers).

^1H NMR (400MHz, acetone- d_6) δ = 7.89 (s, 1H), 7.79 (s, 1H), 2.54(s, 3H), 2.42 (s, 3H).

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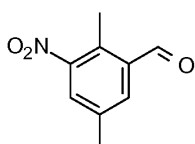
Preparation 18: (2,5-dimethyl-3-nitro-phenyl)methanol



Using a procedure similar to that described for **Preparation 2**, but using the acid from **Preparation 17** (37.0 g, 189 mmol), the title compound was prepared as a pale brown solid (15.9 g, 46.3%, mixture of isomers). Used directly without purification.

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Preparation 19: 2,5-dimethyl-3-nitro-benzaldehyde

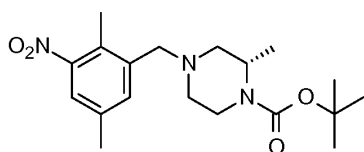


Using a procedure similar to that described for **Preparation 3**, but using the compound described in **Preparation 18** (12.0 g, 66.2 mmol), the title compound was prepared as an off white solid (10.5 g, 88.4%).

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^1H NMR (300 MHz, CDCl_3) δ = 10.35 (s, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 2.72 (s, 3H), 2.47 (s, 3H).

Preparation 20: *tert*-butyl (2S)-4-[(2,5-dimethyl-3-nitro-phenyl)methyl]-2-methyl-piperazine-1-carboxylate



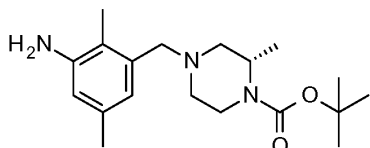
Using a procedure similar to that described for **Preparation 4**, but using the compound from **Preparation 19** (10.5 g, 56.6 mmol), the title compound was prepared as a colourless gum (11.5 g, 54.0%).

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^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ = 7.57 (s, 1H), 7.39 (s, 1H), 4.09 (br s, 1H), 3.64-3.67 (m, 1H), 3.40-3.53 (m, 2H), 2.86-2.99 (m, 1H), 2.67-2.69 (m, 1H), 2.57 (m, 1H), 2.25-

2.40 (m, 5H), 2.11-2.14 (m, 1H), 1.86-2.00 (m, 1H), 1.39 (s, 9H), 1.12 (d, $J=6.6$ Hz, 3H). LCMS Method 1: m/z 364.91 $[M+H^+]$; RT = 2.86 min.

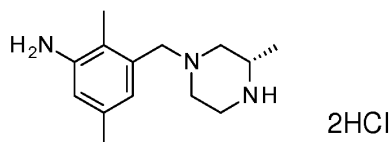
Preparation 21: *tert*-butyl (2S)-4-[(3-amino-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate



Using a procedure similar to that described for **Preparation 5**, but using the compound described in **Preparation 20** (11.5 g, 31.7 mmol), the title compound was prepared as an off-white solid. (9.90 g, 93.8%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 6.37 (s, 1H), 6.25 (s, 1H), 4.64 (br s, 2H), 4.06 (br s, 1H), 3.61-3.66 (m, 1H), 3.15-3.30 (m, 2H), 2.81-2.99 (m, 1H), 2.67 (br d, $J=10.8$ Hz, 1H), 2.57 (br d, $J=11.2$ Hz, 1H), 2.10 (s, 3H), 1.96-2.05 (m, 4H), 1.80 (td, $J=11.6$, 3.2 Hz, 1H), 1.38 (s, 9H), 1.10 (d, $J=6.8$ Hz, 3H). LCMS Method 1: m/z 334.15 $[M+H^+]$; RT = 1.93 min.

Preparation 22: 2,5-dimethyl-3-[[*(3S)*-3-methylpiperazin-1-yl]methyl]aniline dihydrochloride

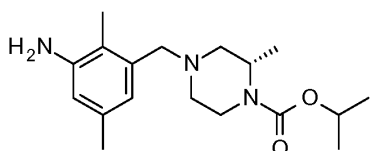


Using a procedure similar to that described for **Preparation 12**, but using the

compound described in **Preparation 21** (400 mg, 1.2 mmol) and replacing 1,4-dioxane with methanol as solvent, the title compound was prepared as an off-white solid taken directly into next step. (366 mg, 100%)

LCMS Method 4: m/z 232.2 $[M+H^+]$; RT = 0.31 min.

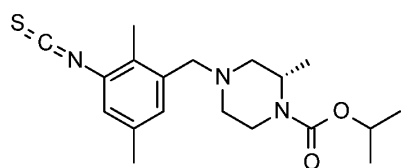
Preparation 23: isopropyl (2S)-4-[(3-amino-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate



Using a procedure similar to that described for **Preparation 13**, but using the compound described in **Preparation 22** (10.0 g, 32.6 mmol), the title compound was prepared as a brown oil. (5.60 g, 54.0%)

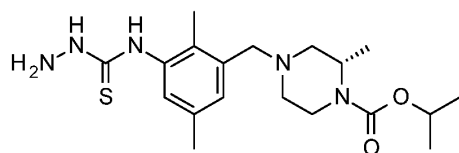
¹H NMR (500 MHz, DMSO-*d*₆) δ = 6.37 (s, 1H), 6.25 (s, 1H), 4.76 (quin, *J*=6.2 Hz, 1H), 4.65 (s, 2H), 4.10 (br s, 1H), 3.68 (br d, *J*=12.8 Hz, 1H), 3.20-3.30 (m, 2H), 2.87-2.98 (m, 1H), 2.68 (br d, *J*=11.0 Hz, 1H), 2.58 (br d, *J*=11.3 Hz, 1H), 2.10 (s, 3H), 1.96-2.05 (m, 4H), 1.82 (td, *J*=11.7, 3.4 Hz, 1H), 1.17 (d, *J*=6.3 Hz, 6H), 1.12 (d, *J*=6.7 Hz, 3H). LCMS Method 2: *m/z* 320.38 [M+H⁺]; RT = 1.24 min.

10 **Preparation 24:** isopropyl (2S)-4-[(3-isothiocyanato-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate



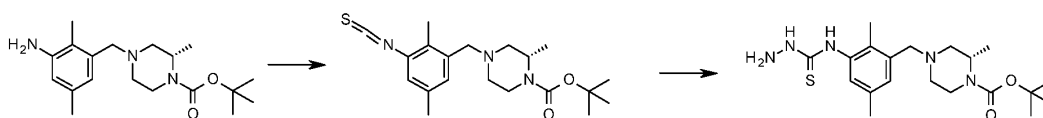
Using a procedure similar to that described for **Preparation 6**, but using the compound described in **Preparation 23** (3.52 g, 11.0 mmol), the title compound was prepared as a yellow oil and used directly in next step. (3.98 g, 100%) LCMS Method 4: *m/z* 362.2 [M+H⁺]; RT = 1.06 min.

Preparation 25: isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



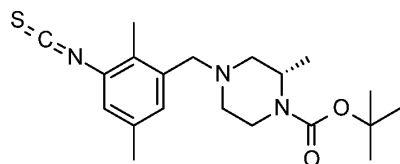
20 Using a procedure similar to that described for **Preparation 7**, but using the compound described in **Preparation 24** (3.98 g, 11.0 mmol), the title compound was prepared as a yellow oil. (3.17 g, 73.2%)

¹H NMR (600 MHz, CDCl₃) δ = 8.95 (s, 1H), 6.92-7.10 (m, 1H), 4.92 (p, *J* = 6.2 Hz, 1H), 4.24 (s, 1H), 4.05 (s, 1H), 3.84 (d, *J* = 13.2 Hz, 1H), 3.39 (s, 2H), 3.07 (td, *J* = 12.8, 3.5 Hz, 1H), 2.72 (d, *J* = 10.9 Hz, 1H), 2.58 (d, *J* = 11.3 Hz, 1H), 2.32 (s, 3H), 2.25 (s, 3H), 2.22 - 2.10 (m, 1H), 2.00 (td, *J* = 11.7, 3.6 Hz, 1H), 1.24 (dd, *J* = 6.2, 1.6 Hz, 6H), 1.21 (d, *J* = 6.7 Hz, 3H). LCMS Method 4: *m/z* 294.2 [M+H⁺]; RT = 0.50 min.



Scheme 9.5

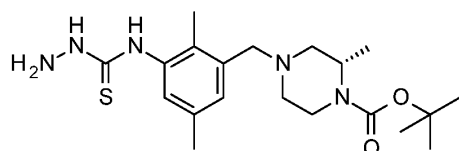
Preparation 26: *tert*-butyl (2S)-4-[(3-isothiocyanato-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate



Using a procedure similar to that described for **Preparation 6**, but using the compound described in **Preparation 21** (1.15 g, 3.45 mmol), the title compound was prepared as a yellow oil. (1.40 g, 100%)

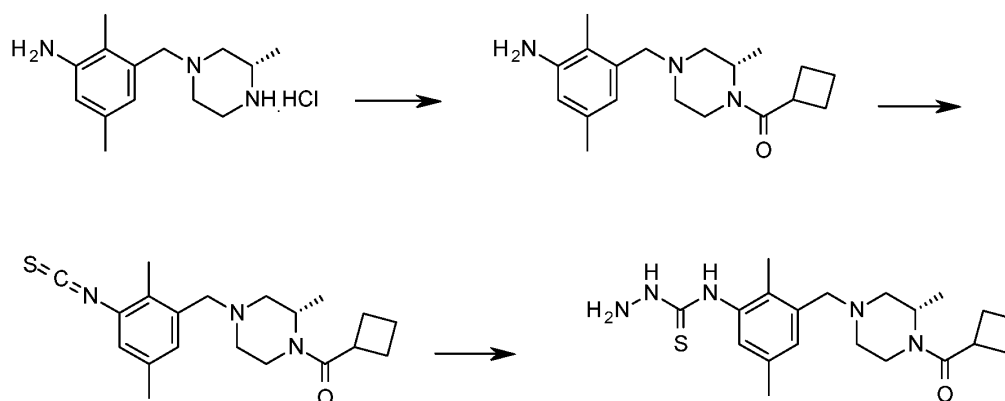
¹H NMR (300 MHz, CDCl₃) δ = 6.97 (m, 2H), 4.19 (s, 1H), 3.78 (d, *J* = 13.0 Hz, 1H), 3.44 – 3.24 (m, 2H), 3.03 (td, *J* = 12.7, 3.4 Hz, 1H), 2.66 (d, *J* = 11.2 Hz, 1H), 2.54 (d, *J* = 11.1 Hz, 1H), 2.35 (s, 3H), 2.28 (d, *J* = 0.8 Hz, 3H), 2.21 – 2.09 (m, 1H), 2.03 – 1.90 (m, 1H), 1.45 (s, 9H), 1.19 (d, *J* = 6.7 Hz, 3H). LCMS Method 4: *m/z* 376.2 [M+H⁺]; RT = 1.12 min.

Preparation 27: *tert*-butyl (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



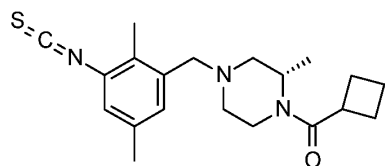
Using a procedure similar to that described for **Preparation 7**, but using the compound described in **Preparation 26** (1.40 g, 3.45 mmol), the title compound was prepared as a yellow oil. (1.50 g, 98.7%)

¹H NMR (300 MHz, DMSO-*d*₆) δ = 8.95 (s, 1H), 7.20 (s, 1H), 6.91 (s, 1H), 4.73 (s, 1H), 4.08 (s, 1H), 3.66 (d, *J* = 13.0 Hz, 1H), 2.92 (t, *J* = 12.1 Hz, 1H), 2.70 (d, *J* = 11.5 Hz, 1H), 2.59 (d, *J* = 11.4 Hz, 1H), 2.24 (s, 3H), 2.14 (s, 3H), 2.06 (dd, *J* = 11.1, 4.0 Hz, 1H), 1.95 – 1.81 (m, 1H), 1.39 (s, 9H), 1.12 (d, *J* = 6.7 Hz, 3H). LCMS Method 4: *m/z* 408.2 [M+H⁺]; RT = 0.54 min.



Scheme 9.6

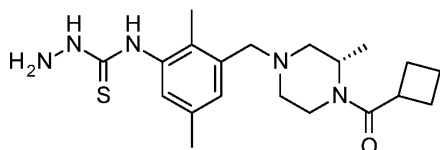
Preparation 28: cyclobutyl-[(2S)-4-[(3-isothiocyanato-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazin-1-yl]methanone



N,N,N',N'-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (478 mg, 1.26 mmol) was added to a solution of the product from **Preparation 22** (280 mg, 0.91 mmol), cyclobutane carboxylic acid (105 mg, 1.05 mmol) and triethylamine (0.73 mL, 5.24 mmol) in dichloromethane (3.0 mL) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water and extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over magnesium sulphate, filtered and evaporated under reduced pressure. The obtained residue (270 mg) was dissolved in chloroform (10 mL) and saturated sodium hydrogen carbonate (10 mL) added. The resulting mixture was rapidly stirred while thiocarbonyl dichloride (0.069 mL, 0.89 mmol) was added drop-wise. The reaction mixture was stirred at room temperature for 16 h before being extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure to afford title compound as off-white solid. (260 mg, 80%)

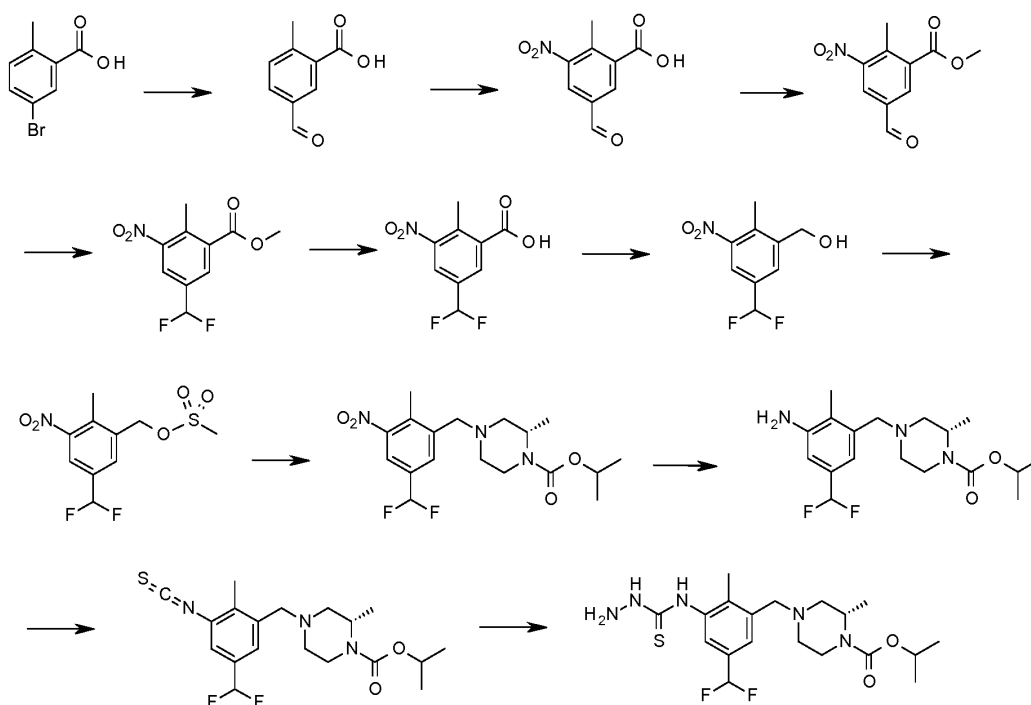
¹H NMR (600 MHz, CDCl₃) δ = 6.99 (s, 1H), 6.95 (s, 1H), 4.71 (s, 0.5H), 4.34-4.47 (m, 0.5H), 3.81-3.86 (m, 0.5H), 3.31-3.39 (m, 2.5H), 3.16-3.26 (m, 1.5H), 2.90 (td, *J* = 12.9, 3.5 Hz, 0.5H), 2.70 (dd, *J* = 32.9, 11.1 Hz, 1H), 2.59 (t, *J* = 12.1 Hz, 1H), 2.46 – 2.26 (m, 2H) covering 2.35 (s, 3H), 2.28 (s, 3H), 2.12 (qq, *J* = 12.4, 6.8, 5.2 Hz, 3H), 2.02 – 1.90 (m, 2H), 1.86 (tt, *J* = 12.4, 6.1 Hz, 1H), 1.31 – 1.14 (m, 3H). LCMS Method 4: *m/z* 358.2 [M+H⁺]; RT = 1.00 min.

Preparation 29: 1-amino-3-[3-[[[(3S)-4-(cyclobutanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-phenyl]thiourea



Using a procedure similar to that described for **Preparation 7**, but using the compound
5 described in **Preparation 28** (260 mg, 0.72 mmol), the title compound was prepared as
a colourless solid. (240 mg, 84.7%)

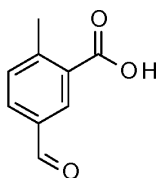
LCMS Method 4: m/z 390.2 $[M+H]^+$; RT = 0.46 min.



10

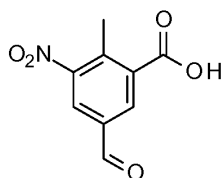
Scheme 9.7

Preparation 30: 5-formyl-2-methyl-benzoic acid



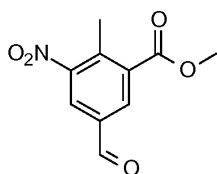
- n-Butyllithium (139 mL, 348 mmol, 2.5M solution in tetrahydrofuran) was added drop-wise to a solution of 5-bromo-2-methylbenzoic acid (30.0 g, 139 mmol) in tetrahydrofuran (300 mL) at -78°C. The resulting mixture was stirred for 1 h and then dimethylformamide (54.0 mL, 697 mmol) was added drop-wise and stirring continued for a further 1 h at -78°C. The reaction mixture was then poured onto aqueous hydrogen chloride solution (500 mL, 1M) and extracted with ethyl acetate (2 x 1000 mL). The combined organic layer was dried over sodium sulphate and evaporated under reduced pressure to afford title compound as yellow solid that was used in the next step without purification. (12.0 g, 52.4%)
- ¹H NMR (500 MHz, DMSO-*d*₆): δ = 13.16 (br s, 1H), 10.02 (s, 1H), 8.34 (d, *J*=1.8 Hz, 1H), 7.96 (dd, *J*=1.8, 7.9 Hz, 1H), 7.55 (d, *J*=7.9 Hz, 1H), 2.62 (s, 3H). LCMS Method 2: *m/z* 164.80 [M+H⁺]; RT = 1.43 min.

Preparation 31: 5-formyl-2-methyl-3-nitro-benzoic acid



- Using a procedure similar to that described for **Preparation 1**, but using the compound described in **Preparation 30** (42.0 g, 256 mmol), the title compound was prepared as an off-white solid. (32.0 g, 59.8%)
- ¹H NMR (300 MHz, DMSO-*d*₆): δ = 13.80 (br s, 1H), 10.07 (s, 1H), 8.49 (d, *J*=2.2 Hz, 2H), 2.61 (s, 3H). LCMS Method 1: *m/z* 208.32 [M-H⁺]; RT = 1.81 min.

Preparation 32: methyl 5-formyl-2-methyl-3-nitro-benzoate



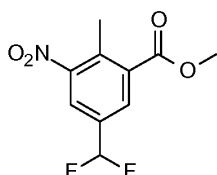
- Potassium carbonate (63.0 g, 459 mmol) was added portion-wise to a solution of product from **Preparation 31** (32.0 g, 153 mmol) in dimethylformamide (200 mL) at 0°C. The reaction mixture was stirred for 10 min before methyl iodide (33.9 mL, 306.2 mmol) was added drop-wise maintaining temperature around 0°C. The reaction was stirred for 3 h and allowed to reach to room temperature before being poured onto ice/water (500 mL) and extracted with ethyl acetate (2 x 1000 mL). The combined organic layer was dried over sodium sulphate and evaporated under reduced pressure to

afford title compound as a brown oil that was used in the next step without purification. (30.0 g, 87.8%)

^1H NMR (300 MHz, CDCl_3): δ = 10.05 (s, 1H), 8.50 (s, 1H), 8.32 (s, 1H), 3.99 (s, 3H), 2.73 (s, 3H). LCMS Method 2: m/z 222.19 [$\text{M}-\text{H}^+$]; RT = 2.33 min.

5

Preparation 33: methyl 5-(difluoromethyl)-2-methyl-3-nitro-benzoate

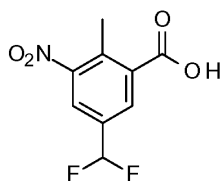


N,N-Diethylaminosulfur trifluoride (35.0 mL, 269 mmol) was added to a solution of product from **Preparation 32** (30.0g, 134 mmol) in dichloromethane at -10°C . The resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated sodium hydrogen carbonate solution (500 mL) and extracted with dichloromethane (2 x 1000 mL). The combined organic layers were washed with saturated brine (500 mL) then dried over sodium sulphate and evaporated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-10% ethyl acetate in petroleum ether. Clean fractions were evaporated under reduced pressure to give the title compound as an off-white solid. (20.0 g, 60.7%)

^1H NMR (400MHz, CDCl_3): δ = 8.15 (s, 1H), 8.00 (s, 1H), 6.87 - 6.52 (m, 1H), 3.97 (s, 3H), 2.68 (s, 3H).

20

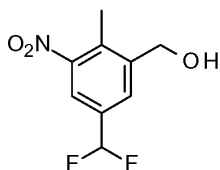
Preparation 34: 5-(difluoromethyl)-2-methyl-3-nitro-benzoic acid



Lithium hydroxide hydrate (22.7 g, 542 mmol) was added to a solution of product from **Preparation 33** (19.0 g, 77.5 mmol) in tetrahydrofuran (200 mL) and water (100 mL) portion-wise at room temperature. The reaction mixture was stirred for 5 h then neutralised with aqueous hydrogen chloride solution (1M). The precipitated solid was collected, washed with water and dried under reduced pressure to afford title compound as a colourless solid. (17.0 g, 94.9%)

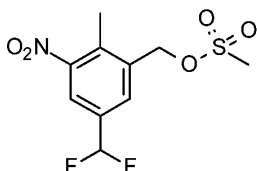
^1H NMR (300MHz, CDCl_3): δ = 8.30 (s, 1H), 8.04 (s, 1H), 6.95 - 6.50 (m, 1H), 2.74 (s, 3H). LCMS Method 2: m/z 230.10 [$\text{M}-\text{H}^+$]; RT = 1.76 min.

30

Preparation 35: [5-(difluoromethyl)-2-methyl-3-nitro-phenyl]methanol

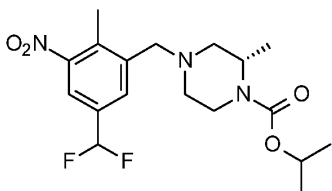
Using a procedure similar to that described for **Preparation 2**, but using the compound described in **Preparation 34** (17.0 g, 73.6 mmol), the title compound was prepared as an off-white solid. (16.0 g, 100%)

¹H NMR (500MHz, DMSO-*d*₆): δ = 7.97 (s, 1H), 7.92 (s, 1H), 7.31 - 6.99 (m, 1H), 5.58 (t, *J*=5.4 Hz, 1H), 4.64 (d, *J*=5.3 Hz, 2H), 2.33 (s, 3H). LCMS Method 2: *m/z* 215.71 [M-H⁺]; RT = 1.81 min.

Preparation 36: [5-(difluoromethyl)-2-methyl-3-nitro-phenyl]methyl methanesulfonate

Triethylamine (27.0 mL, 193 mmol) was added drop-wise to a solution of the product from **Preparation 35** (14.0 g, 64.5 mmol) in dichloromethane (10 mL) at 0°C. After 10 min, methanesulfonyl chloride (10.0 mL, 129 mmol) was added drop-wise maintaining temperature at 0°C. The reaction mixture was stirred for 2 h then diluted with water (200 mL) and extracted with dichloromethane (2 x 200 mL). The combined organic layer was dried over sodium sulphate and evaporated under reduced pressure to afford title compound as a brown oil. Used without further purification. (18.0 g, 94.5%)

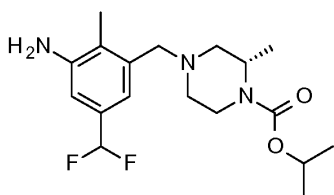
¹H NMR (400 MHz, CDCl₃): δ = 7.92 (s, 1H), 7.72 (s, 1H), 6.86 - 6.52 (m, 1H), 4.68 (s, 2H), 3.14 (s, 3H), 2.58 (s, 3H).

Preparation 37: isopropyl (2S)-4-[[5-(difluoromethyl)-2-methyl-3-nitro-phenyl]methyl]-2-methyl-piperazine-1-carboxylate

Potassium carbonate (10.8 g, 79.3 mmol) was added portion-wise to a solution of product from **Preparation 36** (7.80 g, 26.4 mmol) in acetonitrile (100 mL) at 0°C. Isopropyl (2S)-2-methylpiperazine-1-carboxylate hydrochloride from **Preparation 49** (5.04 g, 26.4 mmol) was added portion-wise at 0°C. The reaction mixture was warmed to 75°C and stirred for 16 h. The reaction mixture was quenched with water (200 mL) and extracted with ethyl acetate (2 x 300 mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-15% ethyl acetate in petroleum ether. Clean fractions were evaporated under reduced pressure to give the title compound as a brown gum. (8.0 g, 79.2%)

¹H NMR (500 MHz, CDCl₃): δ = 7.83 (s, 1H), 7.69 (s, 1H), 6.85 - 6.44 (m, 1H), 4.94-4.92 (m, 1H), 4.28 (br s, 1H), 3.88 (m, 1H), 3.53 (s, 2H), 3.12-3.10 (m, 1H), 2.70 (m, 1H), 2.56 (m, 1H), 2.52 (s, 3H), 2.27 (m, 1H), 2.12-2.10 (m, 1H), 1.27 - 1.22 (m, 9H). LCMS Method 2: *m/z* 386.37. [M+H⁺]; RT = 2.93 min.

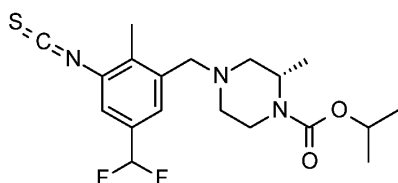
Preparation 38: isopropyl (2S)-4-[[3-amino-5-(difluoromethyl)-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



Using a procedure similar to that described for **Preparation 5**, but using the compound described in **Preparation 37** (8.0 g, 20.7 mmol), the title compound was prepared as a yellow gum. (6.40 g, 86.0%)

¹H NMR (400 MHz, DMSO-*d*₆): δ = 6.98 - 6.57 (m, 3H), 5.09 (s, 2H), 4.77 (m, 1H), 4.11 (br s, 1H), 3.69 (m, 1H), 3.34 (m, 2H), 3.02 - 2.88 (m, 1H), 2.68 (m, 1H), 2.57 (m, 1H), 2.12 - 2.02 (m, 4H), 1.9-1.86 (m, 1H), 1.19 - 1.08 (m, 9H). LCMS Method 3: *m/z* 356.2 [M+H⁺]; RT = 6.0 min.

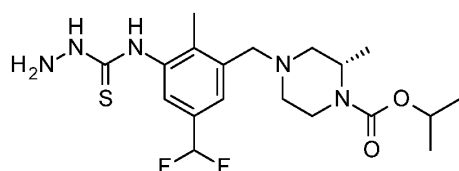
Preparation 39: isopropyl (2S)-4-[[5-(difluoromethyl)-3-isothiocyanato-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



Using a procedure similar to that described for **Preparation 6**, but using the compound described in **Preparation 38** (430 mg, 1.21 mmol), the title compound was prepared as a yellow oil. (447 mg, 92.9%)

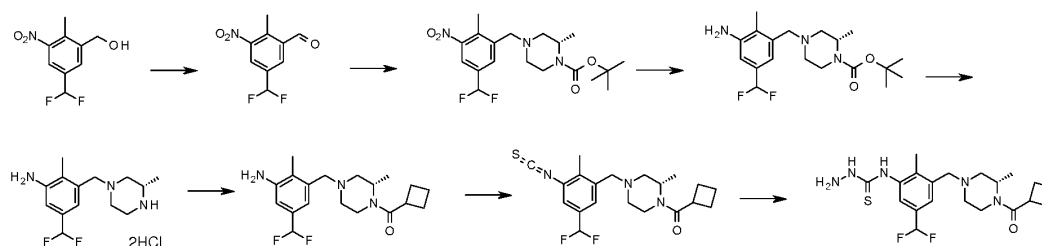
¹H NMR (300 MHz, CDCl₃): δ = 7.33 (s, 1H), 7.31 (s, 1H), 6.58 (t, *J* = 56.3 Hz, 1H), 4.92 (h, *J* = 6.2 Hz, 1H), 4.26 (s, 1H), 3.86 (d, *J* = 13.3 Hz, 1H), 3.44 (s, 2H), 3.09 (td, *J* = 12.7, 3.5 Hz, 1H), 2.68 (d, *J* = 11.0 Hz, 1H), 2.54 (d, *J* = 11.1 Hz, 1H), 2.43 (s, 3H), 2.22 (dd, *J* = 11.1, 3.9 Hz, 1H), 2.05 (td, *J* = 11.6, 3.5 Hz, 1H), 1.24 (d, *J* = 6.1 Hz, 6H) overlapping with 1.22 (d, *J* = 6.1 Hz, 3H). LCMS Method 4: *m/z* 398.2 [M+H⁺]; RT = 1.01 min.

Preparation 40: isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-5-(difluoromethyl)-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



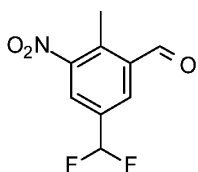
Using a procedure similar to that described for **Preparation 7**, but using the compound described in **Preparation 39** (447 mg, 1.12 mmol), the title compound was prepared as a yellow oil. (357 mg, 73.9%)

¹H NMR (300 MHz, CDCl₃) δ = 7.65 (br s, 1H), 7.39 (s, 1H), 6.63 (t, *J* = 56.6 Hz, 1H), 4.93 (hept, *J* = 6.2 Hz, 1H), 4.25 (s, 1H), 4.05 (s, 2H), 3.86 (d, *J* = 13.1 Hz, 1H), 3.48 (s, 2H), 3.09 (td, *J* = 12.8, 3.4 Hz, 1H), 2.72 (d, *J* = 11.1 Hz, 1H), 2.58 (d, *J* = 11.2 Hz, 1H), 2.33 (d, *J* = 1.4 Hz, 3H), 2.21 (dd, *J* = 11.2, 3.9 Hz, 1H), 2.13 – 1.94 (m, 1H), 1.24 (d, *J* = 6.1 Hz, 6H) overlapping with 1.22 (d, *J* = 6.1 Hz, 3H). LCMS Method 4: *m/z* 430.2 [M+H⁺]; RT = 0.62 min



Scheme 9.8

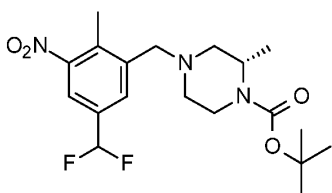
Preparation 41: 5-(difluoromethyl)-2-methyl-3-nitro-benzaldehyde



Using a procedure similar to that described for **Preparation 3**, but using the compound described in **Preparation 35** (1.0 g, 4.60 mmol), the title compound was prepared as an off white solid (500 mg, 50.5%).

- 5 ^1H NMR (300 MHz, CDCl_3) δ = 10.42 (s, 1H), 8.19 (s, 1H), 8.13 (s, 1H), 6.52-6.98 (m, 1H), 2.83 (s, 3H). LCMS Method 1: m/z 356.2 $[\text{M}+\text{H}^+]$; RT = 2.51 min.

Preparation 42: *tert*-butyl (2S)-4-[[5-(difluoromethyl)-2-methyl-3-nitrophenyl]methyl]-2-methyl-piperazine-1-carboxylate

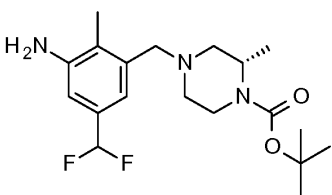


10

Using a procedure similar to that described for **Preparation 4**, but using the compound described in **Preparation 41** (600 mg, 2.79 mmol), the title compound was prepared as an off white solid (700 mg, 62.8%).

- 15 ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 7.99 (s, 1H), 7.81 (s, 1H), 6.95-7.27 (m, 1H), 4.08 - 4.10 (m, 1H), 3.67 - 3.70 (m, 1H), 3.58 (s, 2H), 2.91-3.02 (m, 1H), 2.69 - 2.71 (m, 1H), 2.55 - 2.58 (m, 1H), 2.43 (s, 3H), 2.14 - 2.18 (m, 1H), 1.98-2.04 (m, 1H), 1.39 (s, 9H), 1.14 (d, J = 6.4 Hz, 3H); LCMS Method 1: m/z 356.2 $[\text{M}+\text{H}^+]$; RT = 3.11 min.

- 20 **Preparation 43:** *tert*-butyl (2S)-4-[[3-amino-5-(difluoromethyl)-2-methylphenyl]methyl]-2-methyl-piperazine-1-carboxylate

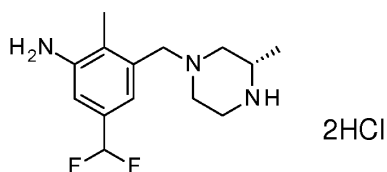


Using a procedure similar to that described for **Preparation 5**, but using the compound described in **Preparation 42** (7.0 g, 17.5 mmol), the title compound was prepared as a tacky yellow solid (5.1 g, 79%).

- 25 ^1H NMR (300 MHz, CDCl_3) δ = 6.80 (s, 1H), 6.77 (s, 1H), 6.40-6.64 (m, 1H), 4.18-4.20 (m, 1H), 3.76-3.80 (m, 3H), 3.36-3.45 (m, 2H), 3.00-3.06 (m, 1H), 2.68-2.70 (m, 1H),

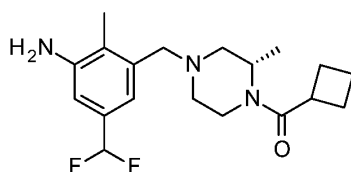
2.55-2.58 (m, 1H), 2.20 (s, 3H) 2.14-2.17 (m, 1H), 1.95-2.00 (m, 1H), 1.45 (s, 9H), 1.19 (d, $J = 6.7$ Hz, 3H). LCMS Method 2: m/z 270.2 $[M+H^+]$; RT = 1.57 min.

Preparation 44: 5-(difluoromethyl)-2-methyl-3-[[3-(3-methylpiperazin-1-yl)methyl]aniline dihydrochloride



Using a procedure similar to that described for **Preparation 8**, but using the compound described in **Preparation 43** (1.10 g, 2.98 mmol), the title compound was prepared as a colourless foam. (1.0 g, 100%) LCMS Method 4: m/z 270.2 $[M+H^+]$; RT = 0.37 min.

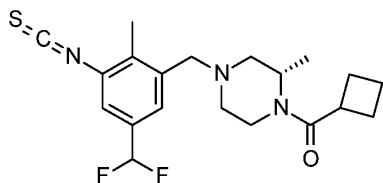
Preparation 45: [(2S)-4-[[3-amino-5-(difluoromethyl)-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-cyclobutyl-methanone



Using a procedure similar to that described for **Preparation 9**, but using the compound described in **Preparation 44** (1.10 g, 2.98 mmol) and cyclobutane carboxylic acid, the title compound was prepared as a yellow oil. (1.03 g, 98%)

^1H NMR (600 MHz, CDCl_3) δ = 6.79 (s, 1H), 6.77 (d, $J = 1.4$ Hz, 1H), 6.52 (t, $J = 56.8$ Hz, 1H), 4.71 (s, 0.5H), 4.36 (d, $J = 13.4$ Hz, 0.5H), 3.83 (s, 0.5H), 3.46 (dd, $J = 12.9$, 9.7 Hz, 1H), 3.35 (dd, $J = 15.1$, 11.3 Hz, 1.5H), 3.17-3.25 (m, 1.5H), 2.87-2.93 (m, 0.5H), 2.76 (s, 0.5H), 2.67-2.72 (m, 0.5H), 2.61 (dd, $J = 27.1$, 11.2 Hz, 1H), 2.38 – 2.43 (m, 0.5H), 2.25 – 2.35 (m, 1.5H), 2.19 (s, 3H), 2.05 – 2.17 (m, 3H), 1.90 – 2.01 (m, 2H), 1.81 – 1.89 (m, 1H), 1.19-1.27 (m, 3H). LCMS Method 4: m/z 352.2 $[M+H^+]$; RT = 0.58 min.

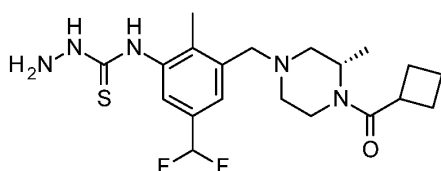
Preparation 46: cyclobutyl-[(2S)-4-[[5-(difluoromethyl)-3-isothiocyanato-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone



Using a procedure similar to that described for **Preparation 6**, but using the compound described in **Preparation 45** (550 mg, 1.56 mmol), the title compound was prepared as a yellow oil. (588 mg, 95%)

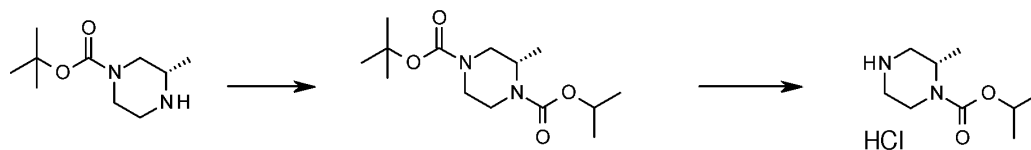
¹H NMR (600 MHz, CDCl₃) δ = 7.33 (s, 1H) overlapping with 7.31 (s, 1H), 6.58 (s, 1H), 4.74 (d, *J* = 5.8 Hz, 1H), 4.36-4.41 (m, 0.5H), 3.85 (s, 0.5H), 3.38-3.48 (m, 2.5H), 3.16-3.28 (m, 1.5H), 2.89-2.95 (m, 0.5H), 2.75 (d, 0.5H), 2.68 (d, 0.5H), 2.58 (dd, *J* = 21.4, 11.2 Hz, 1H), 2.43 (s, 3H) overlapping with 2.38-2.43 (m, 0.5H), 2.27 – 2.37 (m, 1.5H), 2.06 – 2.33 (m, 3H), 1.92-2.03 (m, 2H), 1.86 (d, *J* = 10.1 Hz, 1H), 1.25 (dd, *J* = 37.8, 6.8 Hz, 3H). LCMS Method 4: *m/z* 394.2 [M+H⁺]; RT = 0.95 min.

Preparation 47: 1-amino-3-[3-[[[(3S)-4-(cyclobutanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-5-(difluoromethyl)-2-methyl-phenyl]thiourea



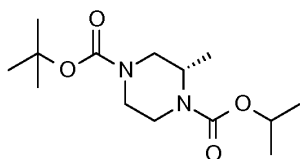
Using a procedure similar to that described for **Preparation 7**, but using the compound described in **Preparation 46** (588 mg, 1.19 mmol), the title compound was prepared as a yellow oil. (617 mg, 97%)

¹H NMR (600 MHz, CDCl₃) δ = 9.05 (s, 1H), 7.72 (s, 1H), 7.50 (s, 1H), 7.38 (s, 1H), 6.64 (t, *J* = 56.6 Hz, 1H), 4.72 (s, 0.5H), 4.38 (d, *J* = 13.4 Hz, 0.5H), 4.03 (s, 2H), 3.84 (s, 0.5H), 3.52 (dd, *J* = 13.4, 8.5 Hz, 1H), 3.36 – 3.44 (m, 1.5H), 3.17 – 3.28 (m, 1.5H), 2.93 (td, *J* = 12.9, 3.5 Hz, 0.5H), 2.71 – 2.80 (m, 1H), 2.62 (dd, *J* = 25.7, 11.2 Hz, 1H), 2.38 – 2.45 (m, 0.5H), 2.27 – 2.35 (m, 1.5H) overlapping 2.33 (s, 3H), 1.92 – 2.22 (m, 5H), 1.86 (t, *J* = 10.0 Hz, 1H), 1.17-1.30 (m, 3H). LCMS Method 4: *m/z* 426.3 [M+H⁺]; RT = 0.56 min.



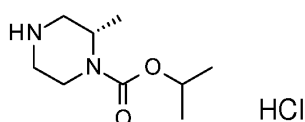
Scheme 9.9

Preparation 48: O4-*tert*-butyl O1-isopropyl (2S)-2-methylpiperazine-1,4-dicarboxylate

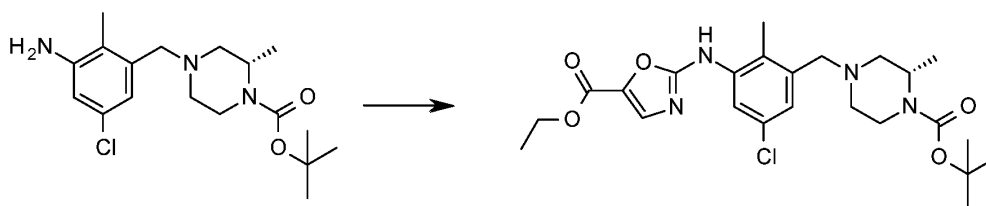


- Isopropyl chloroformate (39.0 mL, 78.0 mmol, 2M solution in toluene,) was added drop-wise to a solution of diisopropylethylamine (34.0 mL, 195 mmol) and *tert*-butyl (3*S*)-3-methylpiperazine-1-carboxylate (13.0 g, 65.0 mmol) in dichloromethane (130 mL) at 0°C. The reaction mixture was allowed to warm to room temperature over 2 h. The mixture was diluted with water (200 mL) and extracted with dichloromethane (2 x 200 mL). The combined organic layer was dried over sodium sulphate and evaporated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 20-50% ethyl acetate in petroleum ether. Clean fractions were evaporated under reduced pressure to give the title compound as a colourless oil. (12.0 g, 64.5%)
- ¹H NMR (400 MHz, CDCl₃): δ = 4.96 – 4.93 (m, 1H), 4.28 (m, 1H), 4.15 – 3.67 (m, 3H), 3.16 – 2.94 (m, 2H), 2.81 (m, 1H), 1.47 (s, 9H), 1.25 (d, *J*=6.2 Hz, 6H), 1.14 (d, *J*=6.7 Hz, 3H).

- Preparation 49:** isopropyl (2*S*)-2-methylpiperazine-1-carboxylate



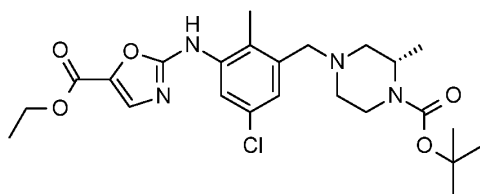
- Using a procedure similar to that described for **Preparation 8**, but using the compound described in **Preparation 48** (12.0 g, 41.9 mmol), the title compound was prepared as a colourless solid. (9.0 g, 96.4%)
- ¹H NMR (300 MHz, DMSO-*d*₆): δ = 9.52 (br s, 2H), 4.85 – 4.73 (m, 1H), 4.38 – 4.24 (m, 1H), 3.91 (m, 1H), 3.26 – 3.12 (m, 2H), 3.10 (s, 1H), 3.08 – 2.98 (m, 1H), 2.92 – 2.75 (m, 1H), 1.27 (d, *J*=7.0 Hz, 3H), 1.20 (d, *J*=6.2 Hz, 6H).



Scheme 9.10

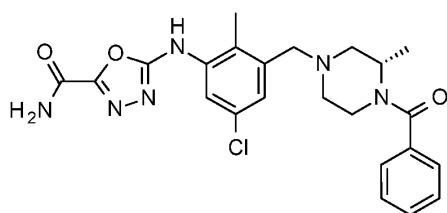
25

Preparation 50: ethyl 2-[3-[[3-(3*S*)-4-*tert*-butoxycarbonyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]oxazole-5-carboxylate



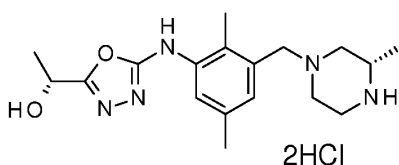
- Ethyl 2-chlorooxazole-5-carboxylate (372 mg, 2.12 mmol) was added to a solution of *tert*-butyl (2S)-4-[(3-amino-5-chloro-2-methyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 5** (500 mg, 1.41 mmol) in propan-2-ol (5.0 mL) and
- 5 stirred under microwave irradiation at 160°C for 30 min. The solvent was removed under reduced pressure and the obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 10-70% ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give title compound as colourless oil. (130 mg, 18.7%)
- 10 LCMS Method 4: m/z 493.3 $[M+H^+]$; RT = 0.94 min.

Preparation 51: 5-[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazole-2-carboxamide



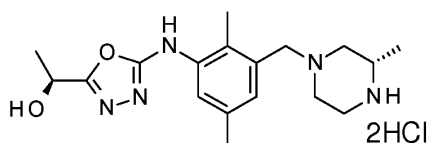
- 15 Oxamic acid (7.42 mg, 0.083 mmol) was added to a solution of product from **Preparation 11** (30.0 mg, 0.069 mmol) in dichloromethane (0.6 mL) followed by 3-(ethyliminomethyl)eneamino)-N,N-dimethyl-propan-1-amine hydrochloride (53.3 mg, 0.278 mmol). The reaction was stirred at room temperature for 1 h until complete. The reaction mixture was concentrated under reduced pressure then dissolved in
- 20 dimethylformamide (0.7 mL) and purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound (6.0 mg, 18.4%). LCMS Method 4: m/z 469.2 $[M+H^+]$; RT = 0.63 min.

- Preparation 52:** (1R)-1-[5-[2,5-dimethyl-3-[[[(3S)-3-methylpiperazin-1-yl]methyl]anilino]-1,3,4-oxadiazol-2-yl]ethanol dihydrochloride
- 25



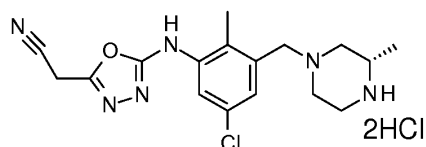
- 3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (423 mg, 2.21 mmol) was added to a solution of *tert*-butyl (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 27** (300 mg, 0.74 mmol) and (2R)-2-hydroxypropanoic acid (66.3 mg, 0.74 mmol) in dichloromethane (10.0 mL) at room temperature and stirred for 2 h. The mixture was concentrated under reduced pressure and the obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 30-100% ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give the *tert*-butyl carbamate intermediate as a colourless solid.
- Hydrogen chloride (4M in 1,4-dioxane, 1.0 mL) was added to a solution of the *tert*-butyl carbamate intermediate (75 mg, 0.17 mmol) in dichloromethane (3.0 mL) and stirred at room temperature for 2 hrs. Toluene (5 mL) was added and then the solvent was removed under reduced pressure to give title compound as colourless solid. (72 mg, 23%)
- LCMS Method 4: m/z 346.2 $[M+H^+]$; RT = 0.36 min.

Preparation 53: (1S)-1-[5-[2,5-dimethyl-3-[(3S)-3-methylpiperazin-1-yl]methyl]anilino]-1,3,4-oxadiazol-2-yl]ethanol dihydrochloride



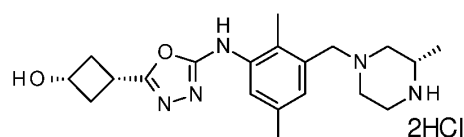
- 3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (715 mg, 3.75 mmol) was added to a solution of *tert*-butyl (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 27** (545 mg, 1.34 mmol) and (2S)-2-hydroxypropanoic acid (120 mg, 1.34 mmol) in dichloromethane (10.0 mL) at room temperature and stirred for 16 h. The mixture was diluted with water (5 mL) and extracted with dichloromethane (2 x 10 mL). The combined organic layer was dried over sodium sulphate and evaporated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-80% ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give the *tert*-butyl carbamate intermediate as a colourless solid. Hydrogen chloride (4M in 1,4-dioxane, 8.0 mL) was added to a solution of this intermediate material (280 mg, 0.63mmol) in 1,4-dioxane (4.0 mL) and stirred at room temperature for 4 hrs. The solvent was removed under reduced pressure to give title compound as colourless solid. (263 mg, 47%)
- LCMS Method 4: m/z 346.2 $[M+H^+]$; RT = 0.37 min.

Preparation 54: 2-[5-[5-chloro-2-methyl-3-[(3S)-3-methylpiperazin-1-yl]methyl]anilino]-1,3,4-oxadiazol-2-yl]acetonitrile dihydrochloride

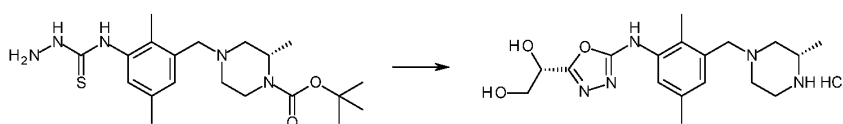


- 5 Using a procedure similar to that described for **Preparation 52**, but using 2-cyanoacetic acid instead of (2R)-2-hydroxypropanoic acid and the thiosemicarbazide from **Preparation 7** the title compound was prepared as a colourless solid. (112 mg, 61%)
LCMS Method 4: m/z 341.2 $[M+H^+]$; RT = 0.36 min.

- 10 **Preparation 55:** 3-[5-[2,5-dimethyl-3-[(3S)-3-methylpiperazin-1-yl]methyl]anilino]-1,3,4-oxadiazol-2-yl]cyclobutanol dihydrochloride



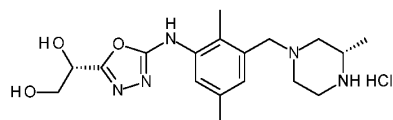
- Using a procedure similar to that described for **Preparation 52**, but using Cis-3-hydroxycyclobutanecarboxylic acid instead of (2R)-2-hydroxypropanoic acid the title compound was prepared as a colourless solid. (146 mg, 61%)
LCMS Method 4: m/z 372.2 $[M+H^+]$; RT = 0.36 min.



Scheme 9.11

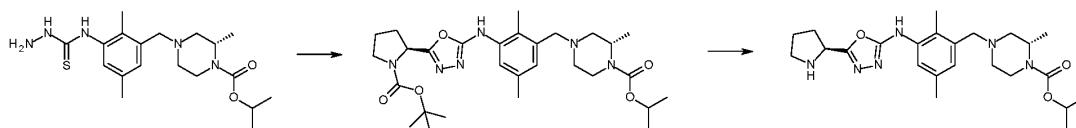
20

Preparation 56: (1S)-1-[5-[2,5-dimethyl-3-[(3S)-3-methylpiperazin-1-yl]methyl]anilino]-1,3,4-oxadiazol-2-yl]ethane-1,2-diol hydrochloride



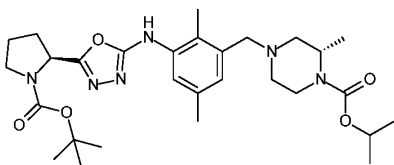
- 3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (846 mg, 4.42 mmol) was added to a solution of product from **Preparation 27** (600 mg, 1.47 mmol) and (4S)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (323 mg, 2.21 mmol) dissolved in dry dichloromethane (30 mL) and stirred at room temperature for 12

- h. The reaction mixture was quenched with water (30 mL) and extracted with dichloromethane (30 mL). The organic layer was collected and concentrated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-40% ethyl acetate in heptane.
- 5 Clean fractions were evaporated under reduced pressure to give the intermediate product as a colourless oil. (600 mg, 81.2 %) LCMS Method 4: m/z 502.4 $[M+H^+]$; RT = 0.77 min. Hydrogen chloride (4M solution in 1,4-dioxane, 2.99 mL, 12 mmol) was added to a solution of the intermediate in methanol (5 mL) and stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to afford title
- 10 compound as a colourless foam that was used without any purification. (476 mg, 100%) LCMS Method 4: m/z 362.3 $[M+H^+]$; RT = 0.33 min.

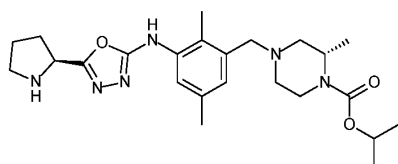


15 Scheme 9.12

Preparation 57: isopropyl (2S)-4-[[3-[[5-[(2S)-1-tert-butoxycarbonylpyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate

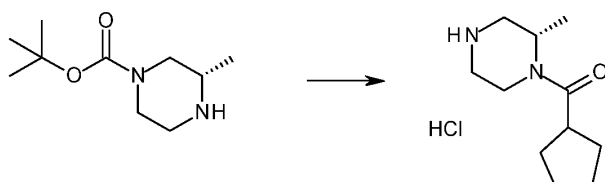


- 20 3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (450 mg, 2.34 mmol) was added to a solution of product from **Preparation 25** (264 mg, 0.67 mmol) and (2S)-1-tert-butoxycarbonylpyrrolidine-2-carboxylic acid (159 mg, 0.74 mmol) in dichloromethane (15 mL) and stirred at room temperature for 4.5 h. The mixture was concentrated to low volume and purified by silica gel (100-200 mesh)
- 25 column chromatography eluting with a gradient of 0-80% ethyl acetate in heptanes. Clean fractions were combined and evaporated under reduced pressure to give the title compound as a colourless solid. (292 mg, 78 %) LCMS Method 5: m/z 557.3 $[M+H^+]$; RT = 2.23 min.
- 30 **Preparation 58:** isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2S)-pyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate



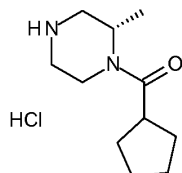
Hydrogen chloride (4M solution in 1,4-dioxane, 2.60 mL, 10.4 mmol) was added to a solution of the product from **Preparation 57** (290 mg, 0.52 mmol) in methanol (4 mL) and stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure then partitioned between dichloromethane and saturated aqueous NaHCO₃. The organic layer was washed with brine, then dried over Na₂SO₄, filtered and concentrated to dryness. The residue was taken up in DMSO and purified by basic preparative HPLC. Clean fractions were combined and evaporated under reduced pressure to give the title compound as a colourless solid. (224 mg, 94 %)

- ¹H NMR (600 MHz, DMSO-d₆) δ : 9.26 (s, 1H), 7.39 (d, J = 1.7 Hz, 1H), 6.83 (d, J = 1.7 Hz, 1H), 4.77 (hept, J = 6.2 Hz, 1H), 4.26 (dd, J = 8.1, 5.9 Hz, 1H), 4.12 (t, J = 5.7 Hz, 1H), 3.70 (dt, J = 13.1, 2.6 Hz, 1H), 3.38 (m, 2H), 2.95 (td, J = 12.9, 3.4 Hz, 1H), 2.88 (ddd, J = 10.0, 7.6, 5.7 Hz, 1H), 2.83 (dt, J = 9.9, 6.9 Hz, 1H), 2.71 (ddt, J = 11.2, 3.6, 1.9 Hz, 1H), 2.60 (dt, J = 11.2, 1.9 Hz, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 2.06 (m, 2H), 1.96 (m, 1H), 1.90 (td, J = 11.7, 3.5 Hz, 1H), 1.81 (dddd, J = 13.9, 12.0, 7.7, 5.9 Hz, 1H), 1.71 (m, 1H), 1.17 (dd, J = 6.3, 0.9 Hz, 6H), 1.13 (d, J = 6.7 Hz, 3H). LCMS Method 4: m/z 457.4 [M+H⁺]; RT = 0.45 min.



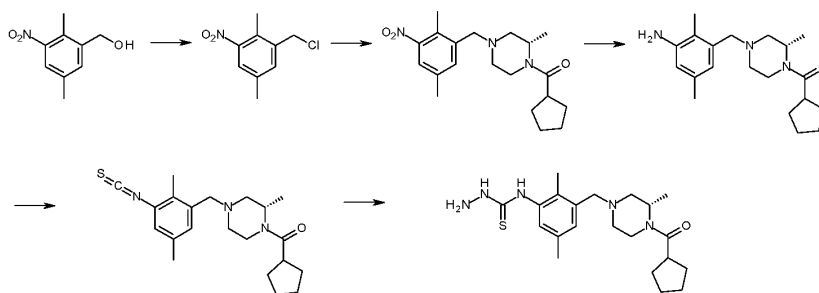
- Scheme 9.13

Preparation 59: cyclopentyl-[(2S)-2-methylpiperazin-1-yl]methanone hydrochloride



Cyclopentanecarbonyl chloride (12.3 mL, 101 mmol) was added dropwise to a solution of tert-butyl (3S)-3-methylpiperazine-1-carboxylate (18.4 g, 92 mmol) and triethylamine (46.1 mL, 243 mmol) in dichloromethane (270 mL) at 0°C. On complete addition the reaction mixture was stirred to room temperature over 2 h. The mixture was concentrated to dryness and the residue dissolved in ethyl acetate (150 ml) and washed

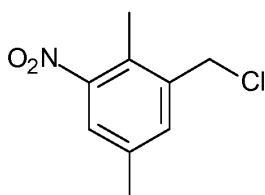
successively with 10% citric acid (aq), saturated NaHCO_3 (aq). The organic layer was filtered through a small plug of silica then concentrated *in vacuo* to leave crude intermediate material. This intermediate material (27.0 g) was dissolved in dichloromethane and using a procedure similar to that described for **Preparation 8**, the title compound was prepared as an off white solid (21.0 g, 95%). LCMS Method 4: m/z 197.2 $[\text{M}+\text{H}^+]$; RT = 0.35 min.



Scheme 9.14

10

Preparation 60: 1-(chloromethyl)-2,5-dimethyl-3-nitro-benzene

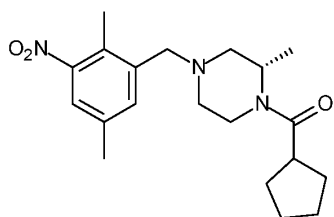


Methanesulfonyl chloride (3.3 mL, 42 mmol) was added to a solution of product from **Preparation 18** (5.1 g, 28 mmol) and triethylamine (7.9 mL, 56 mmol) in dichloromethane (25 mL) at room temperature and stirred for 72 h. The mixture was diluted with dichloromethane (25 mL) and washed successively with HCl (0.5 M aq, 5 mL), saturated NaHCO_3 (aq, 5 mL), water and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford the title compound as an off white solid. (5.6 g, 100%).

^1H NMR (600 MHz, CDCl_3) δ : 7.57 (d, J = 1.8 Hz, 1H), 7.37 (d, J = 1.8 Hz, 1H), 4.61 (s, 2H), 2.49 (s, 3H), 2.39 (s, 3H).

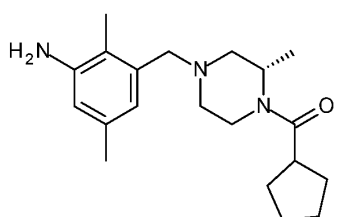
20

Preparation 61: cyclopentyl-[(2S)-4-[(2,5-dimethyl-3-nitro-phenyl)methyl]-2-methyl-2piperazin-1-yl]methanone



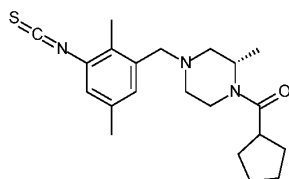
Potassium carbonate (12 g, 84 mmol) was added to a solution of product from **Preparation 60** (5.6 g, 28 mmol), product from **Preparation 59** (7.2 g, 31 mmol) and potassium iodide (0.23 g, 1.4 mmol) in dimethylformamide (20 mL) and stirred at room temperature for 18 h. The mixture was concentrated to dryness *in vacuo*. The residue was partitioned between dichloromethane (50 mL) and water (10 mL). The organic layer was collected, dried over Na₂SO₄, filtered and concentrated to dryness. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-40% ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give the title compound as a yellow oil (8.43 g, 84%). LCMS Method 4: m/z 360.3 [M+H⁺]; RT = 0.90 min.

Preparation 62: [(2S)-4-[(3-amino-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazin-1-yl]-cyclopentyl-methanone



Iron powder (19.6 g, 352 mmol) was added to a solution of product from **Preparation 61** (8.43 g, 23.4 mmol) in acetic acid (210 mL) and stirred at room temperature for 18 h. The mixture was filtered through a Celite[®] pad, washing the pad with methanol. The combined filtrate and methanol washings were concentrated to dryness. The crude residue was dissolved in water (20 mL) and basified to pH 12 with 4N NaOH (aq). The aqueous phase was extracted with dichloromethane (3 x 100 mL). The combined extracts were washed successively with saturated NaHCO₃ (aq) and brine, then dried over Na₂SO₄, filtered and concentrated *in vacuo* to leave the product as pale yellow oil (7.66 g, 99%). LCMS Method 4: m/z 330.3 [M+H⁺]; RT = 0.57 min.

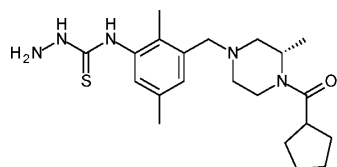
Preparation 63: cyclopentyl-[(2S)-4-[(3-isothiocyanato-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazin-1-yl]methanone



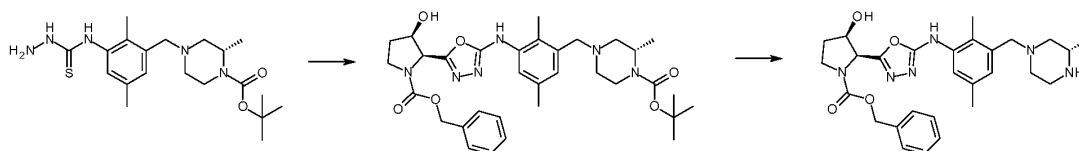
Using a procedure similar to that described for **Preparation 6**, but using the compound described in **Preparation 62** (6.00, 18.2 mmol), the title compound was prepared as a yellow oil (6.76 g, 99%). LCMS Method 4: m/z 330.3 $[M+H]^+$; RT = 1.05 min.

5

Preparation 64: 1-amino-3-[3-[[[(3S)-4-(cyclopentanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-phenyl]thiourea



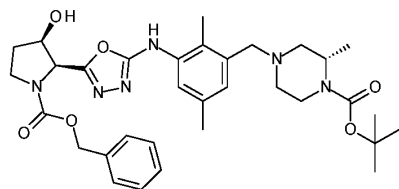
10 Using a procedure similar to that described for **Preparation 7**, but using the compound described in **Preparation 63** (6.00, 18.2 mmol), the title compound was prepared as a yellow oil (6.06 g, 82%). LCMS Method 4: m/z 330.3 $[M+H]^+$; RT = 0.54 min.



15

Scheme 9.15

Preparation 65: tert-butyl (2S)-4-[[[3-[[[5-[(2S,3R)-1-benzyloxycarbonyl-3-hydroxy-pyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate

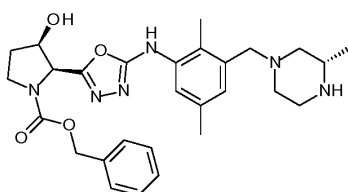


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Using a similar procedure to that described in **Example 31**, but using (2S,3R)-1-benzyloxycarbonyl-3-hydroxy-pyrrolidine-2-carboxylic acid (0.89 g, 3.36 mmol) and product from **Preparation 27** (1.14 g, 2.80 mmol). The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-100%

ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give the title compound as a colourless oil (0.85 g, 49%). LCMS Method 4: m/z 621.5 $[M+H]^+$; RT = 0.74 min.

- 5 **Preparation 66:** benzyl (2*S*,3*R*)-2-[5-[2,5-dimethyl-3-[[*(3S)*-3-methylpiperazin-1-yl]methyl]anilino]-1,3,4-oxadiazol-2-yl]-3-hydroxy-pyrrolidine-1-carboxylate



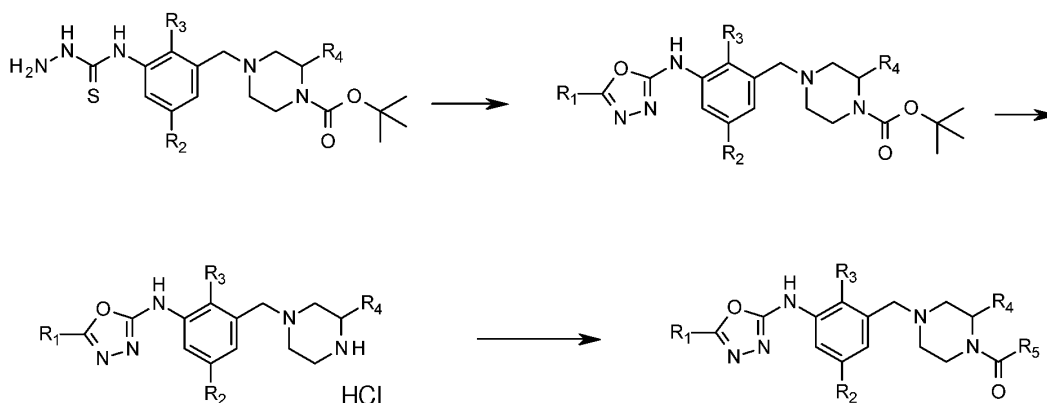
- Hydrogen chloride (4M solution in 1,4-dioxane, 6.85 mL, 27.3 mmol) was added to a solution of product from **Preparation 65** (0.85 g, 1.37 mmol) in methanol (5 mL) and stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure then azeotroped with toluene. The residue was purified by basic HPLC. Clean fractions were evaporated under reduced pressure to afford the title compound as a colourless solid. (443 mg, 62 %) LCMS Method 4: m/z 521.3 $[M+H]^+$; RT = 0.56 min.

15

General routes to exemplified compounds:

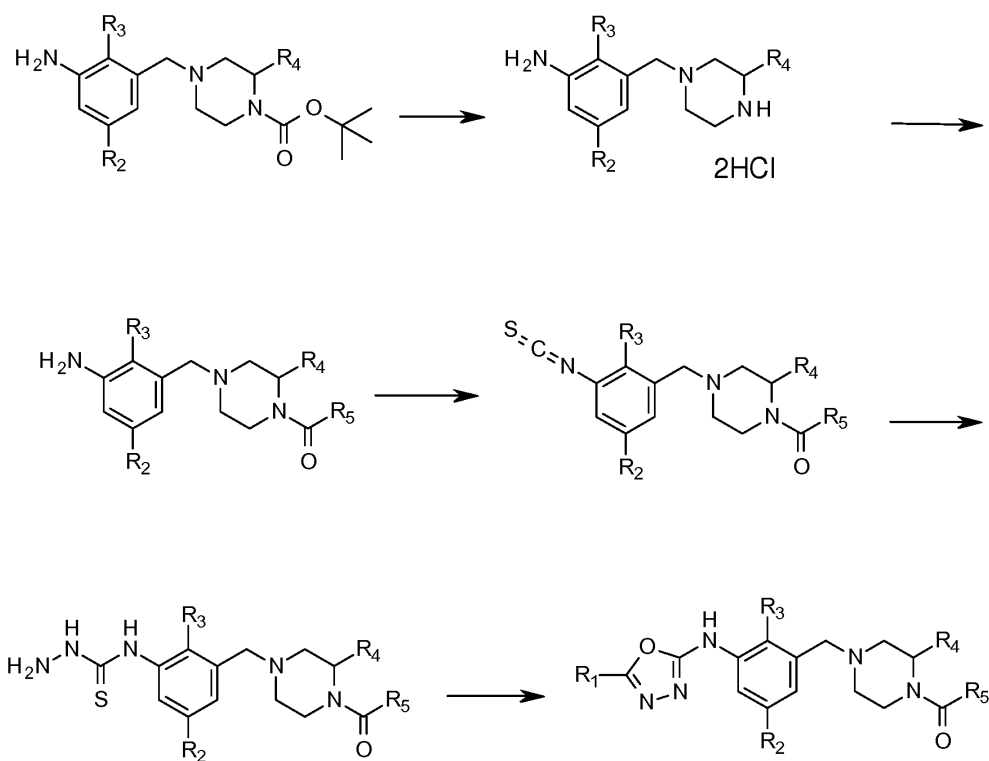
- All exemplified oxadiazole compounds can be accessed through either of the two general routes described in Scheme 10.1.

Route 1:



25 or,

Route 2:



5 Scheme 10.1

Those skilled in the art would recognize that R_1 and R_5 may carry protected functional groups that require additional, standard methodology, to deprotect said functionality. Such methodology for the removal of these protecting groups can for example be found in "Greene's Protective Groups in Organic Synthesis" Fifth edition, Wiley, Ed. P. G. M.

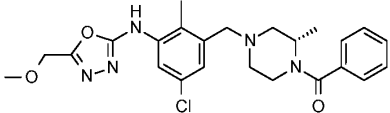
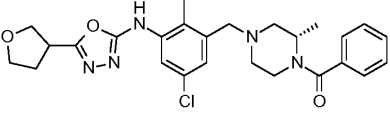
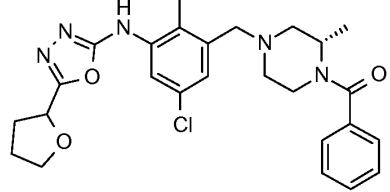
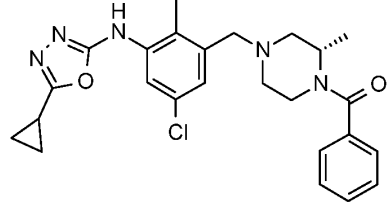
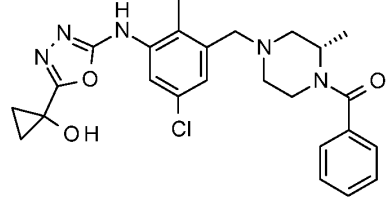
10 Wuts.

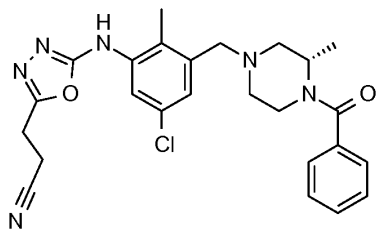
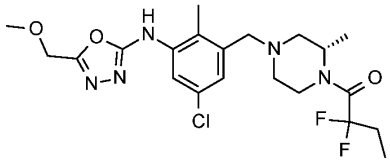
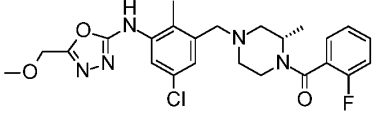
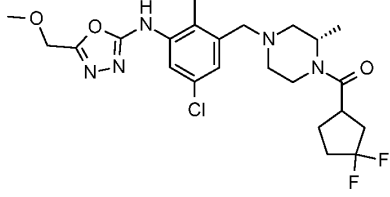
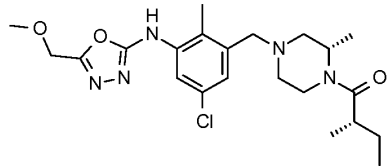
Exemplified compounds are shown in Table 1 below.

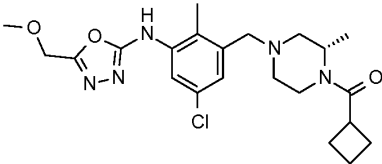
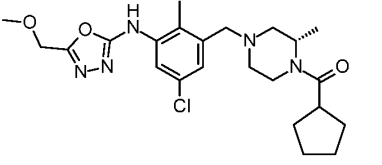
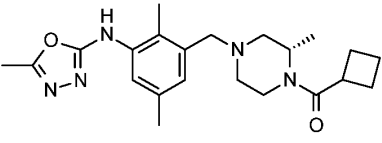
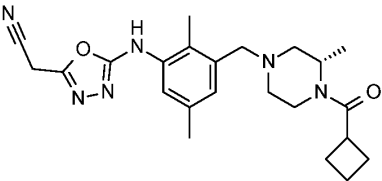
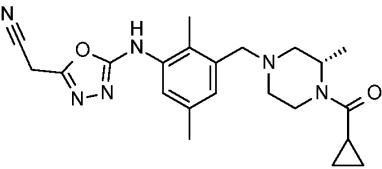
Specific preparation of selected compounds is described in Examples below.

Table 1

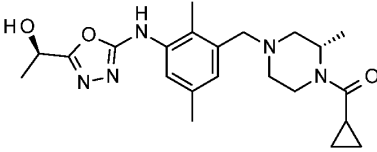
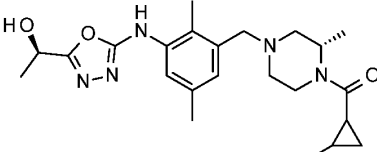
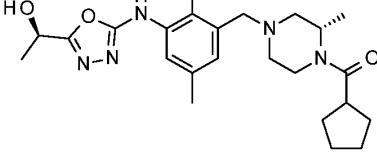
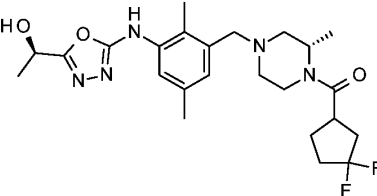
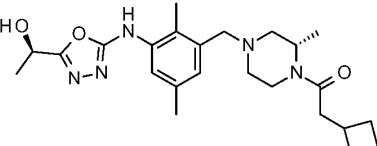
Example	Structure	Name	Mass ion	Rt
1		5-[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-]]methyl]-1,2,4-triazole	450.16	2.44

		methyl-anilino]-1,3,4-oxadiazole-2-carbonitrile		
2		[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone	469.19	2.21
3		[(2S)-4-[[5-chloro-2-methyl-3-[(5-tetrahydrofuran-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone	495.20	2.19
4		[(2S)-4-[[5-chloro-2-methyl-3-[(5-tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone	495.20	2.29
5		[(2S)-4-[[5-chloro-3-[(5-cyclopropyl-1,3,4-oxadiazol-2-yl)amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone	465.19	2.31
6		[(2S)-4-[[5-chloro-3-[[5-(1-hydroxycyclopropyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-	481.19	2.10

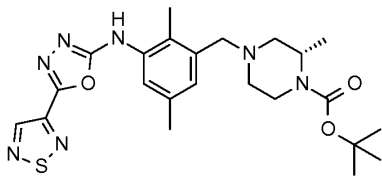
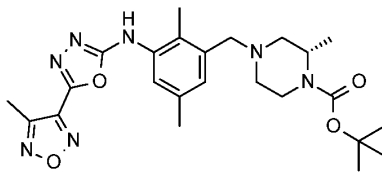
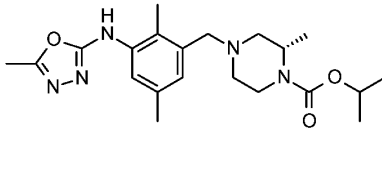
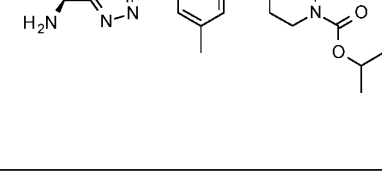
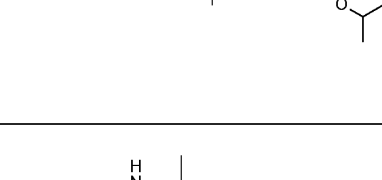
		methanone		
7		3-[5-[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazol-2-yl]propanenitrile	478.19	2.17
8		1-[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-2,2-difluoro-butan-1-one	471.18	2.44
9		[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-(2-fluorophenyl)methanone	487.18	2.27
10		[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-(3,3-difluorocyclopentyl)methanone	497.20	2.24
11		(2S)-1-[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]propan-1-one	449.22	2.17

		piperazin-1-yl]-2-methylbutan-1-one		
12		[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-cyclobutyl-methanone	447.20	2.11
13		[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-cyclopentyl-methanone	461.22	2.23
14		cyclobutyl-[(2S)-4-[[2,5-dimethyl-3-[(5-methyl-1,3,4-oxadiazol-2-yl)amino]phenyl]methyl]-2-methyl-piperazin-1-yl]methanone	398.25	1.80
15		2-[5-[3-[[[(3S)-4-(cyclobutanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethylanilino]-1,3,4-oxadiazol-2-yl]acetonitrile	422.24	1.82
16		2-[5-[3-[[[(3S)-4-(cyclopropanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethylanilino]-1,3,4-oxadiazol-2-yl]acetonitrile	408.22	1.72

17		2-[5-[3-[[[(3S)-4-(3,3-difluorocyclopentanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-anilino]-1,3,4-oxadiazol-2-yl]acetonitrile	472.24	1.94
18		2-[5-[5-chloro-3-[4-(cyclopentanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2-methyl-anilino]-1,3,4-oxadiazol-2-yl]acetonitrile	456.20	2.22
19		cyclobutyl-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone	428.26	1.75
20		cyclobutyl-[(2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone	428.26	1.75
21		2,2-difluoro-1-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]butan-1-one	451.24	1.99

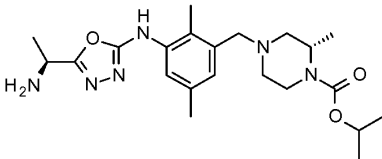
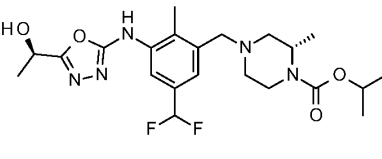
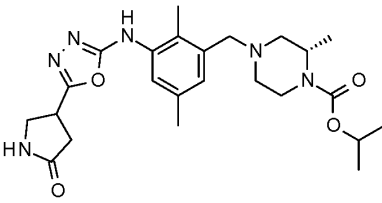
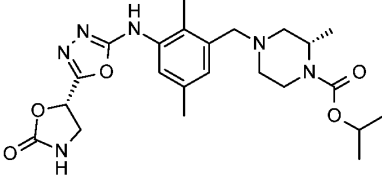
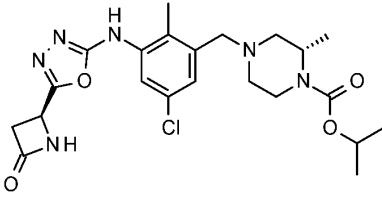
22		cyclopropyl-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone	413.24	1.66
23		[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-(2-methylcyclopropyl)methanone	428.27	1.74
24		cyclopentyl-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone	442.28	1.82
25		(3,3-difluorocyclopentyl)-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone	478.25	1.85
26		2-cyclobutyl-1-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]ethanone	442.28	1.83

27		cyclobutyl-[(2S)-4-[[5-(difluoromethyl)-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone	464.25	1.90
28		tert-butyl (2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	446.26	1.90
29		tert-butyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	471.28	1.91
30		tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(3-methyl-1H-1,2,4-triazol-4-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	483.27	2.06
31		tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-methylpyrazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	482.28	2.13
32		tert-butyl (2S)-4-[[3-[(5-isoxazol-5-yl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-	469.25	2.14

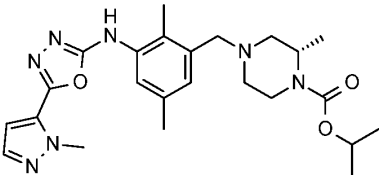
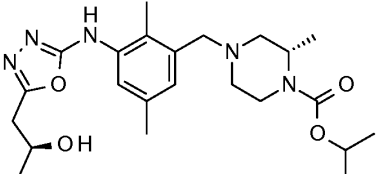
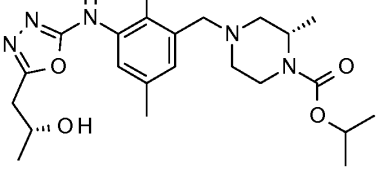
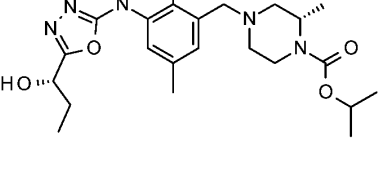
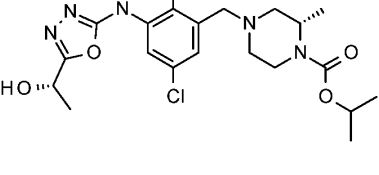
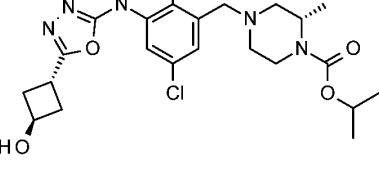
		carboxylate		
33		tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(1,2,5-thiadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	486.22	2.21
34		tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(4-methyl-1,2,5-oxadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	484.26	2.38
35		isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-methyl-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	402.24	1.89
36		isopropyl (2S)-4-[[3-[[5-[(1S)-1-amino-2-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	446.26	1.65
37		isopropyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	457.27	1.84
38		isopropyl (2S)-4-[[3-[[5-[(1S)-1-aminopropyl]-1,3,4-oxadiazol-2-yl]amino]-5-chloro-2-methyl-phenyl]methyl]-2-	465.23	1.91

		methyl-piperazine-1-carboxylate		
39		isopropyl (2S)-4-[[5-chloro-3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	452.21	2.06
40		isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(oxetan-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	463.20	2.17
41		isopropyl (2S)-4-[[3-[[5-[(1S,2R)-1-amino-2-hydroxy-propyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	461.29	1.68
42		isopropyl (2S)-4-[[3-[[5-(cyanomethyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	426.24	1.93
43		isopropyl (2S)-4-[[5-(difluoromethyl)-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	468.23	2.00

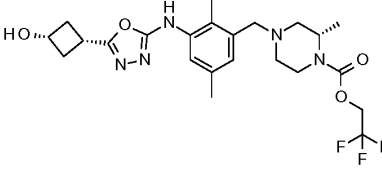
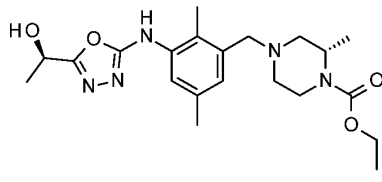
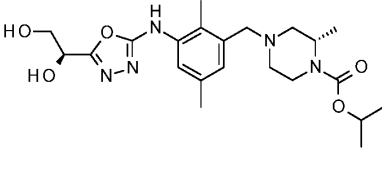
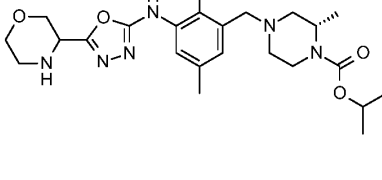
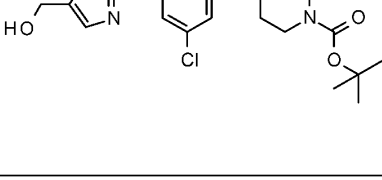
44		isopropyl (2S)-4-[[5-chloro-2-methyl-3-[(5-tetrahydropyran-3-yl-1,3,4-oxadiazol-2-yl)amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	491.23	2.35
45		isopropyl (2S)-4-[[5-chloro-3-[[5-(1-hydroxycyclopropyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	463.20	2.11
46		isopropyl (2S)-4-[[5-chloro-3-[[5-[1-(hydroxymethyl)cyclopropyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	477.21	2.13
47		isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(2,2,2-trifluoro-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	505.17	2.35
48		isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(2-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	490.21	2.01

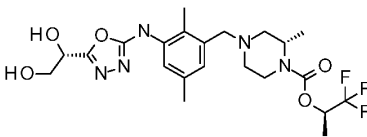
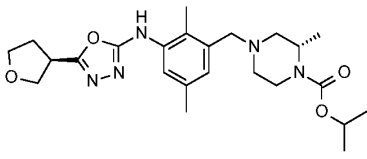
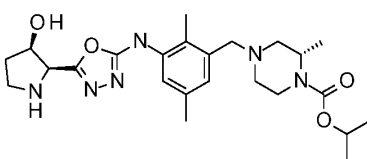
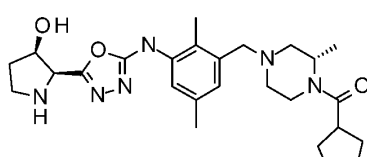
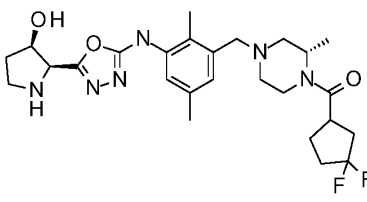
49		isopropyl (2S)-4-[[3-[[5-[(1S)-1-aminoethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	431.27	1.68
50		isopropyl (2S)-4-[[5-(difluoromethyl)-3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	468.23	2.00
51		isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(5-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	471.27	1.78
52		isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(5S)-2-oxooxazolidin-5-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	473.25	1.82
53		isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-[(2S)-4-oxoazetidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	476.19	2.04

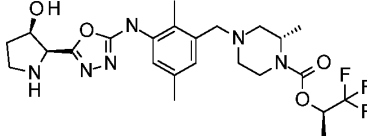
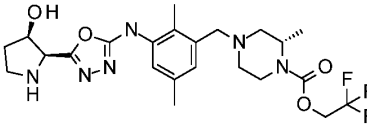
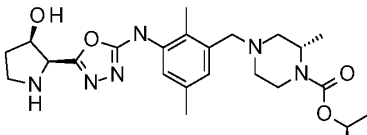
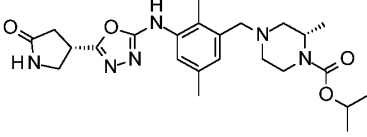
54		isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(4-methyl-1,2,5-oxadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	470.25	2.29
55		isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3S)-morpholin-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate dihydrochloride	473.28	1.72
56		isopropyl (2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	432.26	1.83
57		isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2R)-3,3,3-trifluoro-2-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	500.25	2.00
58		isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-oxo-4-piperidyl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	485.29	1.79

59		isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-methylpyrazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	468.27	2.05
60		isopropyl (2S)-4-[[3-[[5-[(2S)-2-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	446.28	1.83
61		isopropyl (2S)-4-[[3-[[5-[(2R)-2-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	446.28	1.83
62		isopropyl (2S)-4-[[3-[[5-[(1S)-1-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	446.28	1.89
63		isopropyl (2S)-4-[[5-chloro-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	451.20	2.08
64		isopropyl (2S)-4-[[5-chloro-3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-	477.21	2.07

		carboxylate		
65		isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2S)-1-methylsulfonylpyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	534.26	1.95
66		isopropyl (2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	432.26	1.83
67		isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(5-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	490.21	1.99
68		isopropyl (2S)-4-[[3-[[5-[(1R)-1-aminoethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	431.27	1.68
69		2,2,2-trifluoroethyl (2S)-4-[[5-chloro-3-[[5-(cyanomethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	486.14	2.39

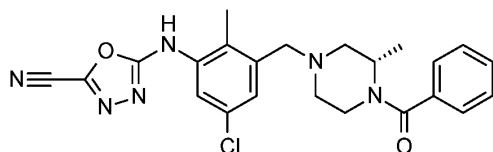
70		2,2,2-trifluoroethyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	497.22	1.96
71		ethyl (2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	417.24	1.73
72		isopropyl (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	448.25	1.74
73		isopropyl (2S)-4-[[5-chloro-2-methyl-3-[(5-morpholin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	492.22	1.90
74		<i>tert</i> -butyl (2S)-4-[[5-chloro-3-[[5-(hydroxymethyl)oxazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate		2.21

75		[(1R)-2,2,2-trifluoro-1-methyl-ethyl] (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	502.2	1.88 _a
76		isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3S)-tetrahydrofuran-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	458.2	1.92
77		isopropyl (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	473.2	1.67
78		cyclopentyl-[(2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-yl]methanone	483.3	1.63 _a
79		(3,3-difluorocyclopentyl)-[(2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-yl]methanone	519.3	0.55 _b

80		[(1R)-2,2,2-trifluoro-1-methyl-ethyl] (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	527.4	0.71 _b
81		2,2,2-trifluoroethyl (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	513.2	0.68 _b
82		[(1R)-1-methylpropyl] (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate	487.4	0.71 _b
83		isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3S)-5-oxopyrrolidin-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate	471.1	1.79

- RT quoted for UPLC-MS Method 5 unless a) UPLC-MS method 6 or b) UPLC-MS Method 4

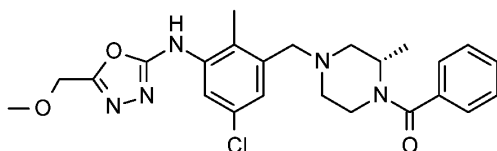
Example 1: 5-[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazole-2-carbonitrile



2,2,2-Trifluoroacetic anhydride (0.006 mL, 0.043mmol) was added to a solution of 5-[3-
 5 [[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazole-2-carboxamide from **Preparation 51** (4.0 mg, 0.008 mmol) and pyridine (0.014 mL, 0.17 mmol) in 1,4-dioxane (0.2 mL). After 2 h of stirring at room temperature a further aliquot of 2,2,2-trifluoroacetic anhydride (0.006 mL, 0.043mmol) was added. The reaction mixture was stirred for 4 h and then was concentrated under
 10 reduced pressure. The crude material was then dissolved in dimethylformamide (0.7 mL) and purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound (1.7 mg, 39%).

¹H NMR (600 MHz, DMSO-d₆) δ 7.70 (d, J = 2.3 Hz, 1H), 7.49 – 7.40 (m, 3H), 7.40 – 7.30 (m, 2H), 7.03 (d, J = 2.3 Hz, 1H), 3.42 (s, 2H), 2.74 (s, 1H), 2.23 (s, 3H), 2.21 –
 15 2.14 (m, 1H), 2.02 (td, J = 11.6, 3.4 Hz, 1H), 1.23 (d, J = 6.6 Hz, 3H). UPLC-MS Method 5: m/z 450.2 [M+H⁺]; RT = 2.44 min.

Example 2: [(2S)-4-[[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone



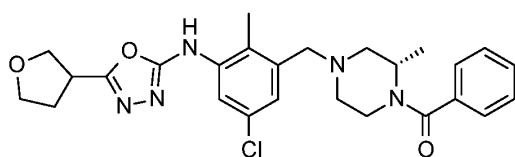
20 2-Methoxyacetyl chloride (7.91 mg, 0.073 mmol) was added to a solution of product from **Preparation 11** (30.0 mg, 0.069 mmol) and triethylamine (7.73 mg, 0.076 mmol) in tetrahydrofuran (2.0 mL) at 0°C. After 16 h at room temperature a further aliquot of both triethylamine (7.73 mg, 0.076 mmol) and 2-methoxyacetyl chloride (7.91 mg,
 25 0.073 mmol) were added. On completion the reaction mixture was filtered and concentrated under reduced pressure. The crude intermediate was dissolved in dichloromethane (3.0 mL) and to this added 3-(ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (26.6mg, 0.139 mmol). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced
 30 pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 35-100% ethyl acetate in heptane. Clean

fractions were evaporated under reduced pressure to give the title compound as a colourless solid. (7.0 mg, 21%)

¹H NMR (300 MHz, DMSO-*d*₆) δ 9.72 (s, 1H), 7.82 (d, 2.2 Hz, 1H), 7.44 (q, *J* = 2.8, 2.3 Hz, 3H), 7.35 (dd, *J* = 6.5, 3.2 Hz, 2H), 7.11 (d, *J* = 2.3 Hz, 1H), 4.53 (s, 2H), 3.45 (s, 2H), 3.33 (s, 3H), 3.14 (s, 3H), 2.73 (br s, 1H), 2.62 (d, *J* = 11.0 Hz, 1H), 2.25 (s, 3H), 2.18 (dd, *J* = 11.2, 3.8 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.23 (d, *J* = 6.3 Hz, 3H).

UPLC-MS Method 5: *m/z* [M+H⁺]; RT = 2.2 min

Example 3: [(2*S*)-4-[[5-chloro-2-methyl-3-[(5-tetrahydrofuran-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone

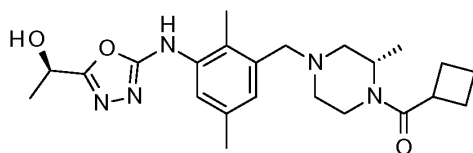


3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (14.2mg, 4 eq) was added to a solution of the product from **Preparation 11** (8.0 mg,) and tetrahydrofuran-3-carboxylic acid (2.58 mg, 1.2 eq) in dichloromethane (0.3 mL) and stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure then re-dissolved in dimethylformamide (0.3 mL) and purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound (0.8 mg, 9%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.59 (s, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 7.43 – 7.45 (m, 3H), 7.35 (ddd, *J* = 4.9, 3.7, 1.8 Hz, 2H), 7.09 (d, *J* = 2.3 Hz, 1H), 3.99 (dd, *J* = 8.6, 7.7 Hz, 1H), 3.83 – 3.89 (m, 2H), 3.77 (td, *J* = 8.0, 6.6 Hz, 1H), 3.65 (ddt, *J* = 8.8, 7.5, 5.7 Hz, 1H), 3.44 (s, 2H), 3.04-3.24 (br s, 1H), 2.73 (d, *J* = 14.6 Hz, 1H), 2.59 – 2.64 (m, 1H), 2.26-2.33 (m, 1H), 2.25 (s, 3H), 2.08-2.21 (m, 3H), 2.02 (td, *J* = 11.6, 3.3 Hz, 1H), 1.23 (d, *J* = 6.7 Hz, 3H).

UPLC-MS Method 5: *m/z* 496.2 [M+H⁺]; RT = 2.19 min.

Example 19: cyclobutyl-[(2*S*)-4-[[3-[[5-[(1*R*)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone



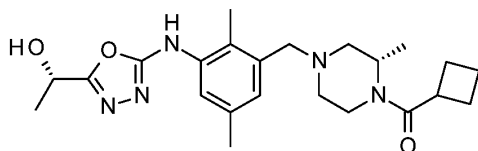
3-(ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (216 mg, 1.13 mmol) was added to a solution of 1-amino-3-[3-[(3*S*)-4-(cyclobutanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-phenyl]thiourea from **Preparation 29** (220

mg, 0.56 mmol) and (2R)-2-hydroxypropanoic acid (61.0 mg, 0.68 mmol) in dichloromethane (8.0 mL) at room temperature. The reaction was stirred for 1.5 h and then purified by automated silica gel chromatography. Clean fractions were evaporated under reduced pressure to give the title compound as an off-white solid (21.0 mg,

5 8.7%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.34 (s, 1H), 7.38 (s, 1H), 6.84 (s, 1H), 5.78 (d, *J* = 5.5 Hz, 1H), 4.79 (qd, *J* = 6.6, 5.3 Hz, 1H), 4.50 (s, 1H), 3.46 – 3.32 (m, 3H), 3.27 (dq, *J* = 16.9, 8.2 Hz, 1H), 3.08 (t, *J* = 12.0 Hz, 1H), 2.71 (dd, *J* = 24.2, 11.7 Hz, 2H), 2.60 (s, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 2.20 – 1.96 (m, 5H), 1.95 – 1.76 (m, 2H), 1.72 (d, *J* = 9.6 Hz, 1H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 1H), 1.08 (d, *J* = 6.7 Hz, 2H). UPLC-MS Method 5: RT = 1.75 min.

Example 20: cyclobutyl-[(2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone



15

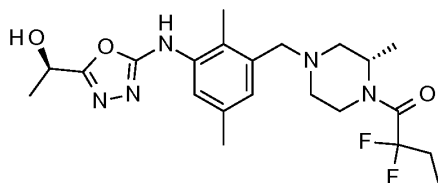
N,N,N',N'-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (136 mg, 0.36 mmol) was added to a solution of (1*S*)-1-[5-[2,5-dimethyl-3-[[[(3*S*)-3-methylpiperazin-1-yl]methyl]anilino]-1,3,4-oxadiazol-2-yl]ethanol hydrochloride from

Preparation 53 (100 mg, 0.24 mmol), cyclobutanecarboxylic acid (28.7 mg, 0.29 mmol) and diisopropylethylamine (0.21 mL, 1.20 mmol) in dimethylformamide (4.0 mL) and the resulting mixture was stirred at room temperature for 13 h. The reaction mixture was quenched with water and extracted with dichloromethane (2x 50 mL). The combined extracted organic layers were dried over sodium sulphate and then evaporated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-100% ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give the title compound as a colourless solid (25.0 mg, 24.5%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.34 (s, 1H), 7.38 (d, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H), 5.79 (d, *J* = 5.5 Hz, 1H), 4.85 – 4.70 (m, 1H), 4.09 (q, *J* = 5.9 Hz, 1H), 3.66 (dt, *J* = 13.1, 2.6 Hz, 1H), 3.39 (d, *J* = 13.0 Hz, 1H), 2.97 – 2.85 (m, 1H), 2.69 (ddt, *J* = 11.1, 3.5, 1.9 Hz, 1H), 2.59 (dt, *J* = 11.3, 1.9 Hz, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 2.07 (dd, *J* = 11.3, 3.9 Hz, 1H), 1.88 (td, *J* = 11.7, 3.5 Hz, 1H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H). UPLC-MS Method 5: RT = 1.75 min.

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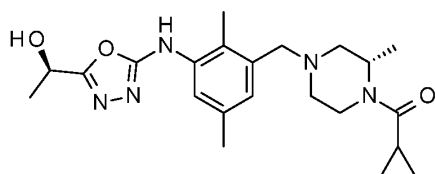
Example 21: 2,2-difluoro-1-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]butan-1-one



N,N,N',N'-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (8.7 mg, 0.023 mmol) was added to a solution of (1*R*)-1-[5-[2,5-dimethyl-3-[[[(3*S*)-3-methylpiperazin-1-yl]methyl]anilino]-1,3,4-oxadiazol-2-yl]ethanol hydrochloride from **Preparation 52** (8.0 mg, 0.019 mmol), 2,2-difluorobutanoic acid (2.37 mg, 0.019 mmol) and triethylamine (11.6 mg, 0.11 mmol) in dimethylformamide (0.5 mL). After 3 h stirring the reaction mixture was purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (0.8 mg, 9%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.35 (s, 1H), 7.40 (s, 1H), 6.85 (s, 1H), 5.79 (d, *J* = 5.5 Hz, 1H), 4.74 – 4.84 (m, 1H), 4.52 (s, 0.5H), 4.33 (s, 0.5H), 4.14 (d, *J* = 13.5 Hz, 0.5H), 3.88 (d, *J* = 13.7 Hz, 0.5H), 3.28-3.43 (m, 3H), 2.97 (t, *J* = 12.7 Hz, 0.5H), 2.80 (t, *J* = 15.3 Hz, 1H), 2.68 (d, *J* = 11.4 Hz, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 2.03-2.18 (m, 3.5H), 1.94 (dt, *J* = 28.0, 11.9 Hz, 1H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.23 (dd, *J* = 65.2, 6.6 Hz, 3H), 0.97 (q, *J* = 7.5 Hz, 3H). UPLC-MS Method 5: RT = 1.99 min.

Example 22: cyclopropyl-[(2*S*)-4-[[3-[[5-[(1*R*)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone

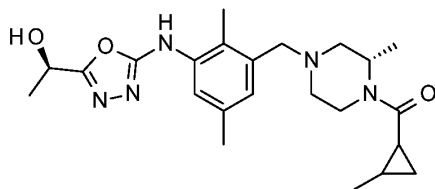


Using a procedure similar to that described for **Example 21**, but using cyclopropanecarboxylic acid (1.65 mg, 0.19 mmol) the title compound was prepared. After 3 h stirring the reaction mixture was purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (0.8 mg, 10%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.35 (s, 1H), 7.39 (s, 1H), 6.86 (m, 1H), 5.79 (d, *J* = 5.5 Hz, 1H), 4.74-4.82 (m, 1H), 4.49 (br s, 1H), 4.07 (br d, *J* = 39.4 Hz, 1H), 3.39 (q, *J* = 13.0 Hz, 2H), 2.76 (d, *J* = 10.8 Hz, 1H), 2.62 – 2.57 (m, 4H), 2.26 (s, 3H), 2.23 (s,

3H), 2.01-2.18 (m, 1H), 1.84-1.97 (m, 2H), 1.44 (d, $J = 6.6$ Hz, 3H), 1.05-1.30 (m, 3H), 0.68 (br d, $J = 9.5$ Hz, 4H). UPLC-MS Method 5: RT = 1.66 min.

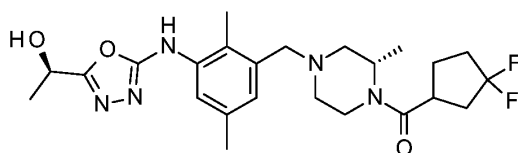
Example 23: [(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-(2-methylcyclopropyl)methanone



Using a procedure similar to that described for **Example 21**, but using 2-methylcyclopropanecarboxylic acid the title compound was prepared. After 3 h stirring the reaction mixture was purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (4.5 mg, 54%).

^1H NMR (600 MHz, DMSO- d_6) δ = 9.35 (s, 1H), 7.39 (s, 1H), 6.86 (s, 1H), 5.79 (d, $J = 5.5$ Hz, 1H), 4.78 (qd, $J = 6.6, 5.3$ Hz, 1H), 4.40-4.50 (m, 1H), 4.04 (d, $J = 47.1$ Hz, 1H), 3.39 (ddd, $J = 28.7, 13.0, 4.9$ Hz, 2H), 2.75 (d, $J = 10.7$ Hz, 1H), 2.58-2.69 (s, 1H), 2.26 (s, 3H), 2.22 (s, 3H), 1.80 – 2.20 (m, 2H), 1.65 (s, 1H), 1.44 (d, $J = 6.6$ Hz, 3H), 1.07-1.28 (m, 4H), 1.06 (d, $J = 3.5$ Hz, 3H), 0.52 (s, 1H). UPLC-MS Method 5: RT = 1.74 min.

Example 25: (3,3-difluorocyclopentyl)-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone

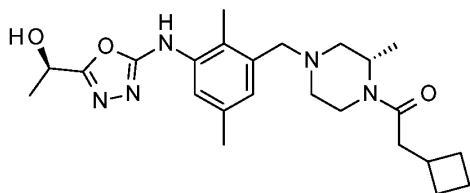


Using a procedure similar to that described for **Example 21**, but using 3,3-difluorocyclopentanecarboxylic acid the title compound was prepared. After 3 h stirring the reaction mixture was purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (5.7 mg, 63%).

^1H NMR (600 MHz, DMSO- d_6) δ = 9.35 (s, 1H), 7.39 (s, 1H), 6.85 (s, 1H), 5.79 (d, $J = 5.5$ Hz, 1H), 4.79 (qd, $J = 6.6, 5.4$ Hz, 1H), 4.53 (s, 0.5H), 4.14-4.21 (m, 1H), 3.71 (t, $J = 15.5$ Hz, 0.5H), 3.34-3.42 (m, 2H), 3.14-3.31 (m, 1.5H), 2.71-2.81 (m, 1.5H), 2.62 (d, $J = 6.6$ Hz, 1H), 2.28 – 2.44 (m, 0.5H), 2.25 (s, 3H), 2.22 (s, 3H), 1.98-2.15 (m,

4H), 1.89 – 1.99 (m, 1H), 1.77-1.85 (m, 1H), 1.63 – 1.75 (m, 0.5H), 1.44 (d, $J = 6.6$ Hz, 3H), 1.09 – 1.25 (m, 3H). UPLC-MS Method 5: RT = 1.75 min.

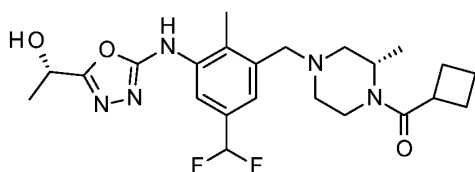
Example 26: 2-cyclobutyl-1-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]ethanone



Using a procedure similar to that described for **Example 21**, but using 2-cyclobutylacetic acid the title compound was prepared. After 3 h stirring the reaction mixture was purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (3.5 mg, 42%).

^1H NMR (600 MHz, DMSO- d_6) δ = 9.35 (s, 1H), 7.39 (d, $J = 1.8$ Hz, 1H), 6.85 (d, $J = 1.8$ Hz, 1H), 5.79 (d, $J = 5.5$ Hz, 1H), 4.79 (qd, $J = 6.6, 5.5$ Hz, 1H), 4.50 (s, 0.5H), 4.13 (d, $J = 13.3$ Hz, 0.5H), 4.06 (s, 0.5H), 3.62 (d, $J = 13.2$ Hz, 0.5H), 3.37 (q, 2H), 3.16 (t, $J = 12.6$ Hz, 1H), 2.72 (d, $J = 11.2$ Hz, 1.5H), 2.54 – 2.64 (m, 1.5H), 2.37-2.46 (m, 1H), 2.32 (dt, $J = 22.9, 7.9$ Hz, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 2.06-2.12 (m, 0.5H), 2.01 (s, 2.5H), 1.88-1.94 (m, 0.5H), 1.74-1.85 (m, 2.5H), 1.62 (dq, $J = 12.0, 8.5$ Hz, 2H), 1.44 (d, $J = 6.6$ Hz, 3H), 1.13 (dd, $J = 78.2, 6.6$ Hz, 3H). UPLC-MS Method 5: RT = 1.83 min.

Example 27: cyclobutyl-[(2S)-4-[[5-(difluoromethyl)-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone



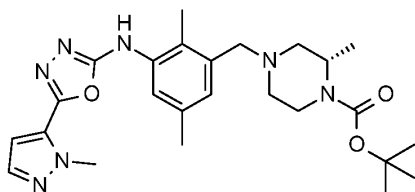
Using a procedure similar to that described for **Example 19**, but using 1-amino-3-[[[(3S)-4-(cyclobutanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-5-(difluoromethyl)-2-methyl-phenyl]thiourea from **Preparation 47** (300 mg, 0.2390 mmol) and (2S)-2-hydroxypropanoic acid the title compound was prepared as a colourless solid (40.0 mg, 15.3%).

^1H NMR (600 MHz, DMSO- d_6) δ = 9.61 (s, 1H), 7.91 (s, 1H), 7.23 (s, 1H), 7.00 (t, $J = 56.0$ Hz, 1H), 5.83 (d, $J = 5.4$ Hz, 1H), 4.81 (td, $J = 6.6, 5.5$ Hz, 1H), 4.51 (s, 0.5H),

4.16 (d, $J = 13.0$ Hz, 0.5H), 3.90 (s, 0.5H), 3.42-3.49 (m, 2.5H), 3.25-3.34 (m, 1H), 3.10 (m, 0.5H), 2.68-2.80 (m, 1.5H), 2.60 (m, 1H), 2.31 (s, 3H), 1.99-2.22 (m, 5H), 1.89 (qq, $J = 17.9, 9.5$ Hz, 2H), 1.73 (dd, $J = 12.1, 7.4$ Hz, 1H), 1.45 (d, $J = 6.6$ Hz, 3H), 1.15 (dd, $J = 55.9, 6.6$ Hz, 3H). UPLC-MS Method 5: RT = 1.90 min.

5

Example 31: *tert*-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-methylpyrazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate



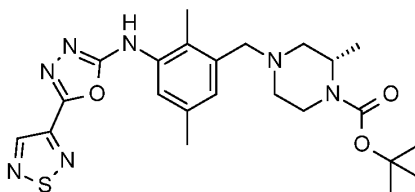
3-(ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride

10 was added to a solution of *tert*-butyl (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 27** (8.55 mg, 0.021 mmol) and 2-methylpyrazole-3-carboxylic acid (3.17 mg, 0.025 mmol) in dichloromethane (1.0 mL). After 3 h the reaction mixture was quenched with water (0.5 mL) and extracted with dichloromethane (2.0 mL). The organic layer was collected
15 and concentrated under reduced pressure. The residue was dissolved in dimethylformamide (0.4 mL) and purified basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (1.0 mg, 10%).

^1H NMR (600 MHz, DMSO- d_6) δ = 9.68 (s, 1H), 7.60 (d, $J = 2.0$ Hz, 1H), 7.44 (s, 1H),
20 6.89 (s, 1H), 6.74 (d, $J = 2.0$ Hz, 1H), 4.15 (s, 3H), 4.09 (s, 1H), 3.67 (d, $J = 13.2$ Hz, 2H), 3.36-3.47 (m, 2H), 2.91 (t, $J = 13.4$ Hz, 1H), 2.70 (d, $J = 11.2$ Hz, 1H), 2.60 (dd, $J = 11.5, 2.2$ Hz, 1H), 2.27 (s, 3H), 2.24 (s, 3H), 2.08 (dd, $J = 11.4, 3.8$ Hz, 1H), 1.89 (td, $J = 11.7, 3.5$ Hz, 1H), 1.39 (s, 9H), 1.12 (d, $J = 6.6$ Hz, 3H). UPLC-MS Method 5: RT = 2.13 min.

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Example 33: *tert*-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(1,2,5-thiadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate

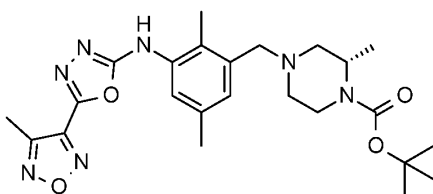


3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride was added
30 to a solution of *tert*-butyl (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-

phenyl)methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 27** (8.55 mg, 0.021 mmol) and 1,2,5-thiadiazole-3-carboxylic acid (3.25 mg, 0.025 mmol) in dichloromethane (1.0 mL). After 3 h the reaction mixture was quenched with water (0.5 mL) and extracted with dichloromethane (2.0 mL). The organic layer was collected and concentrated under reduced pressure. The residue was dissolved in dimethylformamide (0.4 mL) and purified basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (1.94 mg, 19%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.95 (s, 1H), 9.37 (s, 1H), 7.41 (s, 1H), 6.93 (s, 1H), 4.09 (s, 1H), 3.62 – 3.72 (m, 1H), 3.39 (q, *J* = 19.7 Hz, 2H), 2.93 (t, *J* = 12.6 Hz, 1H), 2.71 (d, *J* = 11.7 Hz, 1H), 2.60 (dt, *J* = 11.3, 1.9 Hz, 1H), 2.28 (s, 3H), 2.25 (s, 3H), 2.22 (d, *J* = 17.0 Hz, 1H), 2.09 (dd, *J* = 11.4, 4.0 Hz, 2H), 1.90 (td, *J* = 11.7, 3.5 Hz, 1H), 1.39 (s, 9H), 1.13 (d, *J* = 6.7 Hz, 3H). UPLC-MS Method 5: RT = 2.21 min.

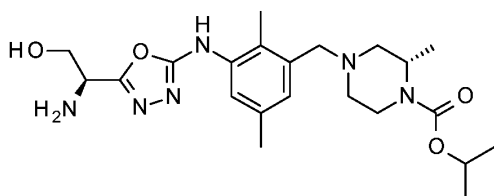
Example 34: *tert*-butyl (2*S*)-4-[[2,5-dimethyl-3-[[5-(4-methyl-1,2,5-oxadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl)methyl]-2-methyl-piperazine-1-carboxylate



3-(Ethyliminomethyleneamino)-*N,N*-dimethyl-propan-1-amine hydrochloride was added to a solution of *tert*-butyl (2*S*)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 27** (8.55 mg, 0.021 mmol) and 4-methyl-1,2,5-oxadiazole-3-carboxylic acid (3.20 mg, 0.025 mmol) in dichloromethane (1.0 mL). After 3 h the reaction mixture was quenched with water (0.5 mL) and extracted with dichloromethane (2.0 mL). The organic layer was collected and concentrated under reduced pressure. The residue was dissolved in dimethylformamide (0.4 mL) and purified basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (1.4 mg, 13%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 10.07 (s, 1H), 7.39 (s, 1H), 6.94 (s, 1H), 4.09 (s, 1H), 3.67 (d, *J* = 12.8 Hz, 1H), 3.36-3.44 (m, 2H), 2.91 (t, *J* = 13.1 Hz, 1H), 2.70 (d, *J* = 11.2 Hz, 1H), 2.64 (s, 3H), 2.60 (dt, *J* = 11.5, 2.0 Hz, 1H), 2.28 (s, 3H), 2.25 (s, 3H), 2.09 (dd, *J* = 11.3, 3.9 Hz, 1H), 1.90 (td, *J* = 11.7, 3.5 Hz, 1H), 1.39 (s, 9H), 1.12 (d, *J* = 6.7 Hz, 3H). UPLC-MS Method 5: RT = 2.38 min.

Example 36: isopropyl (2*S*)-4-[[3-[[5-[(1*S*)-1-amino-2-hydroxy-ethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate

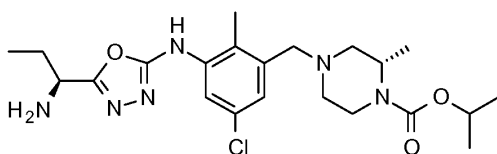


3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (73.1 mg, 0.38 mmol) was added to a solution of isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 25** (50.0 mg, 0.127 mmol) and (2S)-2-(tert-butoxycarbonylamino)-3-hydroxy-propanoic acid (28.7 mg, 0.14 mmol) in dichloromethane (3.0 mL) and stirred for 12 h. The reaction mixture was quenched with water (2.0 mL) and extracted with dichloromethane (5.0 mL). The organic layer was collected and concentrated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-90% ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give intermediate compound, isopropyl-(2S)-4-[[3-[[5-[(1S)-1-(tert-butoxycarbonylamino)-2-hydroxy-ethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate (33.0 mg, 0.60 mmol, 47.5%).

Hydrogen chloride (0.6 mL, 4M in dioxane) was added to a solution of intermediate isopropyl-(2S)-4-[[3-[[5-[(1S)-1-(tert-butoxycarbonylamino)-2-hydroxy-ethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate in dichloromethane (5.0 mL) and stirred for 1 h. The suspension was diluted with methanol and purified on 1g SCX column, eluting with methanol, then methanolic ammonia (2N). Clean fractions were evaporated under reduced pressure to give title compound as colourless solid (25.0 mg, 0.056 mmol, 44% overall).

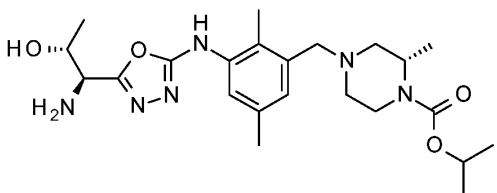
¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.30 (s, 1H), 7.39 (d, *J* = 1.6 Hz, 1H), 6.83 (d, *J* = 1.7 Hz, 1H), 5.01 (s, 1H), 4.77 (hept, *J* = 6.3 Hz, 1H), 4.12 (s, 1H), 4.01 (t, *J* = 5.9 Hz, 1H), 3.70 (dt, *J* = 12.9, 2.6 Hz, 1H), 3.63 (dd, *J* = 5.9, 2.4 Hz, 2H), 3.32-3.41 (m, 3H), 2.91-3.00 (m, 1H), 2.71 (ddt, *J* = 11.0, 3.3, 1.8 Hz, 1H), 2.60 (dt, *J* = 11.3, 1.9 Hz, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 2.08 (dd, *J* = 11.4, 3.9 Hz, 1H), 1.90 (td, *J* = 11.7, 3.6 Hz, 1H), 1.17 (dd, *J* = 6.2, 1.1 Hz, 6H), 1.13 (d, *J* = 6.8 Hz, 3H). UPLC-MS Method 5: RT = 1.68 min.

Example 38: isopropyl (2S)-4-[[3-[[5-[(1S)-1-aminopropyl]-1,3,4-oxadiazol-2-yl]amino]-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



- 3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (27.8 mg, 0.15 mmol) was added to a solution isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation**
- 5 **16** (15.0 mg, 0.036 mmol) and (2R)-2-(tert-butoxycarbonylamino)butanoic acid (7.73 mg, 0.038 mmol) in dichloromethane (1.0 mL) and stirred for 12 h. The reaction mixture was purified by silica gel (100-200 mesh) column chromatography eluting with of 33% ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give intermediate compound, isopropyl (2S)-4-[[3-[[5-[(1S)-1-(tert-
- 10 butoxycarbonylamino)propyl]-1,3,4-oxadiazol-2-yl]amino]-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate. (15 mg, 73%)
- Hydrogen chloride (0.6 mL, 4M in dioxane) was added to a solution of intermediate isopropyl (2S)-4-[[3-[[5-[(1S)-1-(tert-butoxycarbonylamino)propyl]-1,3,4-oxadiazol-2-yl]amino]-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate (15mg,
- 15 0.026mmol) in dichloromethane (1.0 mL) and stirred for 5 h. The reaction was evaporated under reduced pressure and the residue obtained was purified by silica gel (100-200 mesh) column chromatography eluting with dichloromethane/methanol/ammonia (95/5/0.5). Clean fractions were evaporated under reduced pressure to give title compound as colourless solid (7.0 mg, 57% overall).
- 20 ¹H NMR (300 MHz, DMSO-*d*₆) δ = 9.56 (s, 1H), 7.83 (d, *J* = 2.2 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 4.77 (hept, *J* = 6.1 Hz, 1H), 4.12 (s, 1H), 3.86 (t, *J* = 6.8 Hz, 1H), 3.71 (d, *J* = 12.8 Hz, 1H), 3.42 (s, 2H), 2.98 (dd, *J* = 13.0, 9.8 Hz, 1H), 2.71 (d, *J* = 11.3 Hz, 1H), 2.58 (d, *J* = 11.3 Hz, 1H), 2.24 (s, 3H), 2.11 (dd, *J* = 11.3, 3.8 Hz, 1H), 1.95 (td, *J* = 11.4, 3.2 Hz, 1H), 1.59-1.85 (m, 2H), 1.17 (d, *J* = 6.2 Hz, 6H), 1.14 (d, *J* = 6.7 Hz,
- 25 3H), 0.90 (t, *J* = 7.4 Hz, 3H). UPLC-MS Method 5: RT = 1.91 min.

Example 41: isopropyl (2S)-4-[[3-[[5-[(1S,2R)-1-amino-2-hydroxy-propyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate

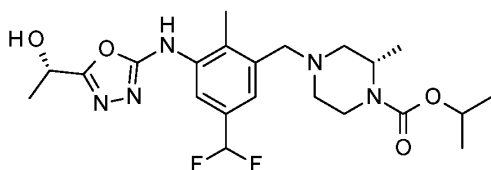


- 30 3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (73.1 mg, 0.38 mmol) was added to a solution of isopropyl (2S)-4-[[3-

(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 25** (50.0 mg, 0.127 mmol) and (2S,3R)-2-(tert-butoxycarbonylamino)-3-hydroxy-butanoic acid (30.6 mg, 0.14 mmol) in dichloromethane (5.0 mL) and stirred for 12 h. The reaction mixture was quenched with water (2.0 mL) and extracted with dichloromethane (5.0 mL). The organic layer was collected and concentrated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-90% ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give intermediate compound, isopropyl-(2S)-4-[[3-[[5-[(1S,2R)-1-(tert-butoxycarbonylamino)-2-hydroxy-propyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate (33.0 mg, 0.058 mmol, 46.3%). Hydrogen chloride (0.6 mL, 4M in dioxane) was added to a solution of the intermediate isopropyl-(2S)-4-[[3-[[5-[(1S,2R)-1-(tert-butoxycarbonylamino)-2-hydroxy-propyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate in dichloromethane and stirred for 12 h. The suspension was diluted with methanol and purified on 1g SCX column, eluting with methanol, then methanolic ammonia (2N). Clean fractions were evaporated under reduced pressure to give title compound as colourless solid (23.0 mg, 40% overall).

¹H NMR (600 MHz, DMSO-*d*₆) δ= 9.28 (s, 1H), 7.39 (d, *J* = 1.7 Hz, 1H), 6.83 (d, *J* = 1.7 Hz, 1H), 4.93 (s, 1H), 4.77 (hept, *J* = 6.2 Hz, 1H), 4.10-4.14 (m, 1H), 3.82 (q, *J* = 6.1 Hz, 1H), 3.79 (d, *J* = 5.5 Hz, 1H), 3.70 (dt, *J* = 13.0, 2.7 Hz, 1H), 3.36 (q, *J* = 15.7 Hz, 2H), 2.93-2.98 (m, 1H), 2.70 (ddt, *J* = 11.1, 3.4, 1.8 Hz, 1H), 2.59 (dt, *J* = 11.4, 1.8 Hz, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 2.08 (dd, *J* = 11.4, 3.8 Hz, 1H), 1.89 (td, *J* = 11.6, 3.5 Hz, 1H), 1.17 (dd, *J* = 6.3, 1.0 Hz, 6H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.2 Hz, 3H). UPLC-MS Method 5: RT = 1.68 min.

Example 43: isopropyl (2S)-4-[[5-(difluoromethyl)-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate

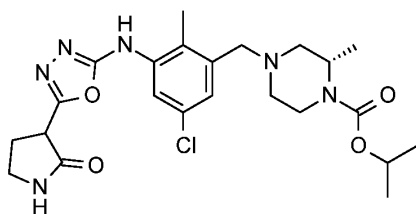


3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (78.1 mg, 0.41 mmol) was added to a solution of isopropyl (2S)-4-[[3(aminocarbamothioylamino)-5-(difluoromethyl)-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate **Preparation 40** (50.0 mg, 0.116 mmol) and (2S)-2-hydroxypropanoic acid (12.6 mg, 0.14mmol). After 5 h stirring the reaction mixture was purified by basic preparative

HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (16.0 mg, 29.4%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.63 (s, 1H), 7.90 (s, 1H), 7.24 (s, 1H), 7.00 (t, *J* = 56.0 Hz, 1H), 5.83 (d, *J* = 5.4 Hz, 1H) 4.72-4.88 (m, 2H), 4.12 (q, *J* = 6.5, 6.0 Hz, 1H),
5 3.72 (dt, *J* = 13.1, 2.7 Hz, 1H), 3.47 (s, 2H), 2.92-3.06 (m, 1H), 2.71 (ddt, *J* = 11.2, 3.5, 1.8 Hz, 1H), 2.59 (dt, *J* = 11.4, 2.0 Hz, 1H), 2.31 (d, *J* = 1.5 Hz, 3H), 2.12 (dd, *J* = 11.3, 3.9 Hz, 1H), 1.97 (td, *J* = 11.7, 3.5 Hz, 1H), 1.45 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 6.2 Hz, 6H), 1.14 (d, *J* = 6.7 Hz, 3H). UPLC-MS Method 5: RT = 2.00 min.

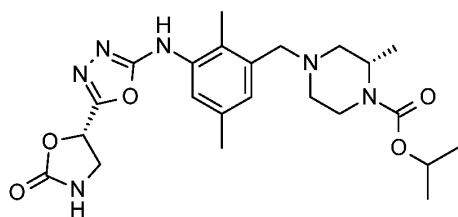
10 **Example 48:** isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(2-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate



3-(ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (14.8 mg, 0.077 mmol) was added to a solution of isopropyl (2S)-4-[[3-
15 (aminocarbamothioylamino)-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 16** (8.0 mg, 0.019 mmol) and 2-oxopyrrolidine-3-carboxylic acid (3.0 mg, 0.023 mmol) in dichloromethane (0.8 mL). After 5 h stirring the reaction mixture was purified by basic preparative HPLC. Clean fractions were
evaporated under reduced pressure to give title compound as a colourless solid (4.8 mg,
20 46%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.67 (s, 1H), 8.10 (s, 1H), 7.83 (d, *J* = 2.3 Hz, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 4.77 (hept, *J* = 6.3 Hz, 1H), 4.12 (s, 1H), 3.97 (t, *J* = 9.3 Hz, 1H), 3.59 – 3.77 (m, 1H), 3.42 (s, 2H), 2.98 (t, *J* = 12.5 Hz, 1H), 2.74 – 2.68 (m, 1H), 2.61 – 2.55 (m, 2H), 2.54 (s, 29H), 2.51 (s, 6H), 2.47 (ddd, *J* = 12.5, 7.8, 3.1 Hz, 1H),
25 2.41 – 2.32 (m, 1H), 2.11 (dd, *J* = 11.3, 3.9 Hz, 1H), 1.95 (td, *J* = 11.6, 3.5 Hz, 1H), 1.26 – 1.06 (m, 9H). UPLC-MS Method 5: RT = 2.01 min.

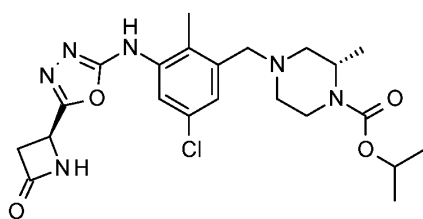
Example 52: isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(5S)-2-oxooxazolidin-5-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate



3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (195 mg, 1.02 mmol) was added to a solution of (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate (100 mg, 0.25 mmol) and (5S)-2-oxooxazolidine-5-carboxylic acid from **Preparation 25** (48.1 mg, 0.33 mmol) in dichloromethane (10 mL) and stirred at room temperature for 48 h. The reaction mixture was quenched with water (2.0 mL) and extracted with dichloromethane (5.0 mL). The organic layer was collected and concentrated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-90% ethyl acetate in heptane, then by acidic preparative HPLC to afford title compound as colourless solid (20.0 mg, 16.6%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.61 (s, 1H), 7.99 (s, 1H), 7.37 (d, *J* = 1.7 Hz, 1H), 6.88 (d, *J* = 1.8 Hz, 1H), 5.78 (dd, *J* = 9.2, 5.7 Hz, 1H), 4.77 (hept, *J* = 6.2 Hz, 1H), 4.12 (s, 1H), 3.88 (t, *J* = 9.3 Hz, 1H), 3.81 (dd, *J* = 9.3, 5.8 Hz, 1H), 3.70 (dt, *J* = 13.0, 2.7 Hz, 1H), 3.34-3.41 (m, 2H), 2.96 (td, *J* = 12.9, 3.3 Hz, 1H), 2.71 (ddt, *J* = 11.2, 3.7, 1.9 Hz, 1H), 2.59 (dt, *J* = 11.4, 1.8 Hz, 1H), 2.26 (s, 3H), 2.22 (s, 3H), 2.03-2.13 (m, 1H), 1.90 (td, *J* = 11.6, 3.5 Hz, 1H), 1.17 (dd, *J* = 6.3, 1.0 Hz, 6H), 1.13 (d, *J* = 6.7 Hz, 3H). UPLC-MS Method 5: RT = 1.82 min.

Example 53: isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-[(2S)-4-oxoazetidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate

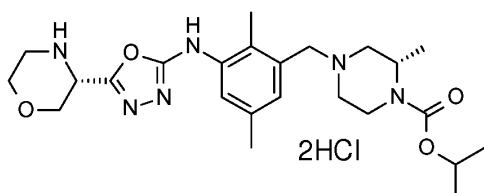


3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (18.5 mg, 0.097 mmol) was added to a solution of isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 16** (10.0 mg, 0.024 mmol) and 4-oxoazetidine-2-carboxylic acid (3.6 mg, 0.031 mmol) in dichloromethane (0.6 mL). After 2 h stirring the reaction mixture was purified by basic preparative HPLC. Clean fractions were

evaporated under reduced pressure to give title compound as a colourless solid (4.9 mg, 42%).

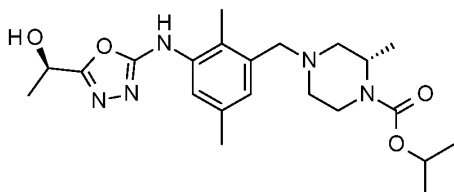
¹H NMR (300 MHz, DMSO-*d*₆) δ = 8.56 (s, 1H), 7.83 (d, *J* = 2.2 Hz, 1H), 7.07 (d, *J* = 2.3 Hz, 1H), 6.70 (br s, 1H), 4.74-4.82 (m, 2H), 4.13 (s, 1H), 3.71 (d, *J* = 12.8 Hz, 1H),
5 3.36-3.44 (m, 3H), 3.15 (dd, *J* = 14.8, 2.5 Hz, 1H), 2.91-3.07 (m, 1H), 2.71 (d, *J* = 11.1 Hz, 1H), 2.58 (d, *J* = 11.4 Hz, 1H), 2.24 (s, 3H), 2.02-2.17 (m, 1H), 1.95 (td, *J* = 11.5, 3.3 Hz, 1H), 1.17 (d, *J* = 6.2 Hz, 6H), 1.14 (d, *J* = 6.6 Hz, 3H). UPLC-MS Method 5: RT = 2.04 min.

10 **Example 55:** isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3S)-morpholin-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate dihydrochloride



3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (97.4 mg, 0.51 mmol) was added to a solution of (2S)-4-[[3-(aminocarbamothioylamino)-2,5-
15 dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 25** (50.0 mg, 0.127 mmol) and (3S)-4-tert-butoxycarbonylmorpholine-3-carboxylic acid (38.2 mg, 0.16 mmol) in dichloromethane (3.0 mL) and stirred for 2.5 h. The mixture was concentrated under reduced pressure and the obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 10-100% ethyl
20 acetate in heptane. Clean fractions were evaporated under reduced pressure to give intermediate compound tert-butyl 3-[5-[3-[[[(3S)-4-isopropoxycarbonyl-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-anilino]-1,3,4-oxadiazol-2-yl]morpholine-4-carboxylate (56.0 mg, 0.098 mmol, 77%). Hydrogen chloride (1.5 mL, 4M in dioxane) was added to a solution of intermediate tert-butyl 3-[5-[3-[[[(3S)-4-isopropoxycarbonyl-
25 3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-anilino]-1,3,4-oxadiazol-2-yl]morpholine-4-carboxylate (52.0 mg, 0.091 mmol) in dichloromethane (5.0 mL) and stirred for 3 h. Toluene (3.0 mL) was added and the solid was collected and dried under reduced pressure to give title compound as colourless salt. (52.0 mg, 0.091 mmol, 77% overall).
30 ¹H NMR (600 MHz, DMSO-*d*₆) δ = 10.59 (s, 1H), 10.42 (s, 1H), 10.22 (s, 1H), 9.86 (s, 1H), 7.51 (s, 1H), 7.45 (s, 1H), 4.88 (d, *J* = 7.7 Hz, 1H), 4.80 (hept, *J* = 6.3 Hz, 1H), 4.30-4.45 (m, 2H), 4.23 (dd, *J* = 12.4, 3.6 Hz, 1H), 3.89-4.02 (m, 3H), 3.84 (ddd, *J* = 12.3, 9.2, 2.8 Hz, 2H), 3.66-3.72 (m, 0.5H), 3.45-3.51 (m, 0.5H), 3.36 (s, 2H), 3.23 (d, *J* = 12.0 Hz, 2H), 3.13 (dd, *J* = 31.5, 12.5 Hz, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 6H). UPLC-MS Method 5: RT = 1.72 min.

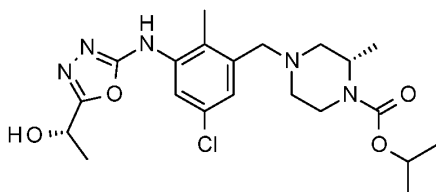
Example 56: isopropyl (2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



5 3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (219 mg, 1.14 mmol) was added to a solution of (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 25** (150 mg, 0.38 mmol) and (2R)-2-hydroxypropanoic acid (41.2 mg, 0.46 mmol) in dichloromethane (15 mL). After 1 h stirring the reaction mixture was purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (16.0 mg, 29.4%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.34 (s, 1H), 7.38 (s, 1H), 6.84 (s, 1H), 5.78 (d, *J* = 5.5 Hz, 1H), 4.74-4.82 (m, 2H), 4.12 (s, 1H), 3.70 (d, *J* = 12.9 Hz, 1H), 3.37 (q, *J* = 15.4 Hz, 2H), 2.95 (t, *J* = 12.2 Hz, 1H), 2.69-2.72 (m, 1H), 2.58-2.62 (m, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 2.08 (d, *J* = 8.2 Hz, 1H), 1.90 (td, *J* = 11.7, 3.5 Hz, 1H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.17 (dd, *J* = 6.2, 1.0 Hz, 6H), 1.13 (d, *J* = 6.7 Hz, 3H). UPLC-MS Method 5: RT = 1.83 min.

Example 63: isopropyl (2S)-4-[[5-chloro-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



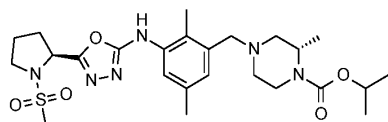
3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (14.8 mg, 0.077 mmol) was added to a solution of isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 16** (8.0 mg, 0.019 mmol) and (2S)-2-hydroxypropanoic acid (3.0 mg, 0.023 mmol) in dichloromethane (0.8 mL). After 5 h stirring the reaction mixture was purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (2.6 mg, 12%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.66 (s, 1H), 7.83 (d, *J* = 2.2 Hz, 1H), 7.10 (d, *J* = 2.3 Hz, 1H), 5.84 (d, *J* = 5.5 Hz, 1H), 4.80 – 4.85 (m, 1H), 4.77 (h, *J* = 6.3 Hz, 1H),

4.13 (s, 1H), 3.70 – 3.73 (m, 1H), 3.42 (s, 2H), 2.98 (t, $J = 12.4$ Hz, 1H), 2.71 (d, $J = 11.3$ Hz, 1H), 2.59 (dt, $J = 13.1, 2.7$ Hz, 1H), 2.24 (s, 3H), 2.11 (dd, $J = 11.4, 3.9$ Hz, 1H), 1.95 (td, $J = 11.7, 3.6$ Hz, 1H), 1.46 (d, $J = 6.6$ Hz, 3H), 1.17 (dd, $J = 6.2, 0.8$ Hz, 6H), 1.14 (d, $J = 6.7$ Hz, 3H). UPLC-MS Method 5: RT = 2.08 min.

5

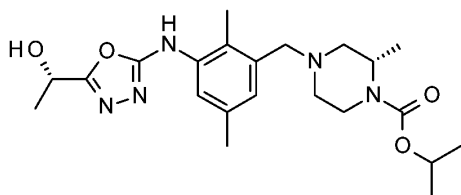
Example 65: isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2S)-1-methylsulfonylpyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate



10 Methanesulfonyl chloride (4.57 mg, 0.04 mmol) was added to a solution of pyrrolidine compound from **Preparation 58** (19.0 mg, 0.04 mmol) and diisopropylethylamine (0.04 mL, 0.21 mmol) in dimethylformamide (0.8 mL) and stirred at room temperature for 0.5 h. The mixture was purified directly by acidic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound. (4.3 mg, 24 %).

15 ^1H NMR (600 MHz, DMSO- d_6) δ = 9.40 (s, 1H), 7.39 (d, $J = 1.7$ Hz, 1H), 6.84 (d, $J = 1.7$ Hz, 1H), 5.03 (dd, $J = 8.2, 4.0$ Hz, 1H), 4.77 (hept, $J = 6.2$ Hz, 1H), 4.12 (dq, $J = 10.7, 6.2$ Hz, 1H), 3.70 (dt, $J = 13.1, 2.7$ Hz, 1H), 3.40 (m, 4H), 3.02 (s, 3H), 2.96 (td, $J = 12.9, 3.4$ Hz, 1H), 2.71 (ddt, $J = 11.1, 3.6, 1.9$ Hz, 1H), 2.60 (dt, $J = 11.2, 1.8$ Hz, 1H), 2.29 (m, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 2.11 (m, 2H), 2.01 (m, 2H), 1.90 (td, $J = 11.7, 3.5$ Hz, 1H), 1.17 (dd, $J = 6.2, 1.0$ Hz, 6H), 1.13 (d, $J = 6.7$ Hz, 3H). UPLC-MS
20 Method 5: m/z 535.3 [$M+H^+$]; RT = 1.95 min.

Example 66: isopropyl (2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



25

3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (292 mg, 1.52 mmol) was added to a solution of (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 25** (200 mg, 0.51 mmol) and (2S)-2-hydroxypropanoic acid (50.0 mg, 0.56 mmol) in
30 dichloromethane.(5 mL). After 3 h the reaction mixture was quenched with water (2.0 mL) and extracted with dichloromethane (5.0 mL). The organic layer was collected and

concentrated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-85% ethyl acetate in heptanes. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid. (124 mg, 56.6%) NMR and MS data as shown below.

5

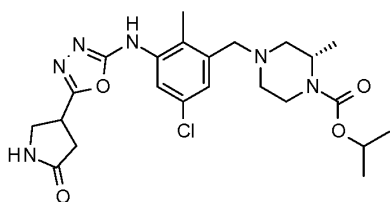
Alternative preparation

3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (11.7 g, 60.9 mmol) was added to a solution of (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 25** (6.00 g, 15.2 mmol) and (2S)-2-hydroxypropanoic acid (2.20 g, 24.1 mmol) in acetonitrile (15 mL) at 0°C. The reaction mixture was stirred at room temperature for 48 h. Lithium hydroxide solution (91.5 mL, 1.0 M) was added to the reaction mixture and stirred for 10 min. To the reaction mixture was added water (100 mL) followed by acetic acid (5.23 mL, 91.5 mmol). The mixture was reduced to low volume *in vacuo*. The aqueous residue was neutralised with saturated NaHCO₃ (aq) and extracted with ethyl acetate (3 x 250 mL). The combined organic layers were washed with saturated brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 20-100% ethyl acetate in heptanes. Clean fractions were evaporated under reduced pressure to give title compound as a colourless non-crystalline solid. (3.05 g, 46.4%) This obtained material (2.58 g, 5.98 mmol) was dissolved in diethyl ether (25.8 mL, 10 mL/g). The mixture was left to crystallize over 12 h. The crystals were collected and dried *in vacuo* to give the title material as a crystalline solid. (2.31 g, melting point 120-121 °C, 89.5%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.34 (s, 1H), 7.38 (d, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H), 5.79 (d, *J* = 5.5 Hz, 1H), 4.69-4.78 (m, 2H), 4.12 (s, 1H), 3.70 (dt, *J* = 13.0, 2.7 Hz, 1H), 3.33 – 3.43 (m, 2H), 2.90-3.02 (m, 1H), 2.71 (ddt, *J* = 11.1, 3.6, 1.9 Hz, 1H), 2.60 (dt, *J* = 11.2, 2.0 Hz, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 2.08 (dd, *J* = 11.3, 3.8 Hz, 1H), 1.90 (td, *J* = 11.7, 3.5 Hz, 1H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.17 (dd, *J* = 6.2, 1.0 Hz, 6H), 1.13 (d, *J* = 6.7 Hz, 3H). UPLC-MS Method 5: RT = 1.83 min.

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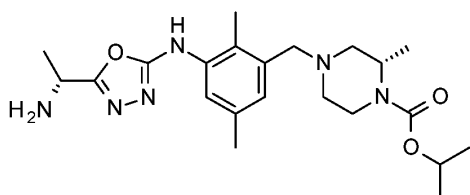
Example 67: isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(5-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate



3-(ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (14.8 mg, 0.077 mmol) was added to a solution of isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 16** (8.0 mg, 0.019 mmol) and 2-oxopyrrolidine-4-carboxylic acid (3.0 mg, 0.023 mmol) in dichloromethane (0.8 mL). After 5 h stirring the reaction mixture was purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (2.6 mg, 27%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.62 (s, 1H), 7.81-7.85 (m, 2H), 7.09 (d, *J* = 2.3 Hz, 1H), 4.77 (hept, *J* = 6.3 Hz, 1H), 4.13 (s, 1H), 3.88 (dddd, *J* = 9.5, 8.3, 6.8, 5.7 Hz, 1H), 3.69-3.73 (m, 1H), 3.63 – 3.67 (m, 1H), 3.46 – 3.54 (m, 1H), 3.42 (s, 2H), 2.98 (t, *J* = 12.4 Hz, 1H), 2.71 (d, *J* = 11.4 Hz, 1H), 2.56 – 2.66 (m, 3H), 2.24 (s, 3H), 2.11 (dd, *J* = 11.4, 3.9 Hz, 1H), 1.95 (td, *J* = 11.6, 3.5 Hz, 1H), 1.17 (dd, *J* = 6.2, 0.9 Hz, 6H), 1.14 (d, *J* = 6.8 Hz, 3H). UPLC-MS Method 5: RT = 1.99 min.

Example 68: isopropyl (2S)-4-[[3-[[5-[(1R)-1-aminoethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



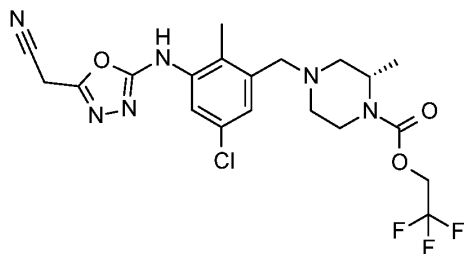
3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (46.4 mg, 0.24 mmol) was added to a solution of (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate from **Preparation 25** (32.0 mg, 0.08 mmol) and (2R)-2-(tert-butoxycarbonylamino)propanoic acid (16.9 mg, 0.09 mmol) in dichloromethane (3.0 mL) and stirred for 2.5 h. The reaction mixture was quenched with water (2.0 mL) and extracted with dichloromethane (5.0 mL). The organic layer was collected and concentrated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-70% ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give intermediate compound isopropyl (2S)-4-[[3-[[5-[(1R)-1-(tert-butoxycarbonylamino)ethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate (21.0 mg, 0.04 mmol, 48.7%). Hydrogen chloride (0.6 mL, 4M in dioxane) was added to a solution of the intermediate isopropyl (2S)-4-[[3-[[5-[(1R)-1-(tert-butoxycarbonylamino)ethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate (21.0 mg, 0.04 mmol) in dichloromethane (5.0 mL) and stirred for 2 h. The resulting suspension was diluted with

methanol and purified on 1g SCX column, eluting with methanol followed by methanolic ammonia (2N). Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (16.0 mg, 0.037 mmol, 93.9%).

¹H NMR (300 MHz, CDCl₃) δ = 7.53 (d, *J* = 1.7 Hz, 1H), 6.97-7.04 (m, 1H), 6.75 (d, *J* = 1.7 Hz, 1H), 5.04 (d, *J* = 8.6 Hz, 1H), 4.77 – 4.97 (m, 2H), 4.17 (s, 1H), 3.76 (d, *J* = 13.1 Hz, 1H), 3.32 (s, 2H), 2.98 (td, *J* = 12.7, 3.4 Hz, 1H), 2.64 (d, *J* = 11.3 Hz, 1H), 2.50 (dt, *J* = 11.0, 1.8 Hz, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 2.09 (dd, *J* = 11.2, 3.9 Hz, 1H), 1.85 – 1.96 (m, 1H), 1.50 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.2 Hz, 6H), 1.12 (d, *J* = 6.7 Hz, 3H). UPLC-MS Method 5: RT = 1.68 min.

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Example 69: 2,2,2-trifluoroethyl (2S)-4-[[5-chloro-3-[[5-(cyanomethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate

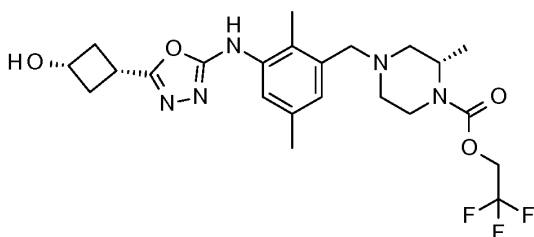


2,2,2-trifluoroethyl carbonochloridate (4.12 mg, 0.025 mmol) was added to a solution of 2-[5-[5-chloro-2-methyl-3-[[[(3S)-3-methylpiperazin-1-yl]methyl]anilino]-1,3,4-oxadiazol-2-yl]acetonitrile dihydrochloride from **Preparation 54** (10.0 mg, 0.023 mmol) and triethylamine (0.016 mL, 0.115 mmol) in dichloromethane (0.7 mL). The reaction was complete after 1h. The reaction mixture was evaporated under reduced pressure then diluted with dimethylformamide (0.4 mL). To this was added lithium hydroxide solution (0.03mL, 1N) and the reaction was stirred for 1 h. The reaction was purified by basic HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (0.8 mg, 8%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.81 (s, 1H), 7.77 (d, *J* = 2.2 Hz, 1H), 7.14 (d, *J* = 2.2 Hz, 1H), 4.65-4.76 (m, 2H), 4.50 (s, 2H), 4.15 (s, 1H), 3.73 (d, *J* = 13.1 Hz, 1H), 3.44 (s, 2H), 3.09 (s, 1H), 2.75 (d, *J* = 11.4 Hz, 1H), 2.61-2.64 (m, 1H), 2.25 (s, 3H), 2.16 (dd, *J* = 11.5, 3.9 Hz, 1H), 2.00 (td, *J* = 11.8, 3.5 Hz, 1H), 1.18 (d, *J* = 6.8 Hz, 3H). UPLC-MS Method 5: RT = 2.39 min.

Example 70: 2,2,2-trifluoroethyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate

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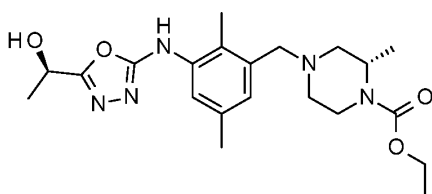


A solution of 2,2,2-trifluoroethyl carbonochloridate in dichloromethane (0.15 mL, 0.18 M, 0.027 mmol) was added to a solution of 3-[5-[2,5-dimethyl-3-[[[(3S)-3-methylpiperazin-1-yl]methyl]anilino]-1,3,4-oxadiazol-2-yl]cyclobutanol dihydrochloride from

- 5 **Preparation 55** (12.0 mg, 0.027 mmol) and triethylamine (0.03 mL, 0.22 mmol) in dichloromethane (0.8 mL). The resulting mixture was stirred for 30 min, a further aliquot of 2,2,2-trifluoroethyl carbonochloridate in dichloromethane (0.15 mL, 0.18 M, 0.027 mmol) was added and stirring continued. After 1 h the reaction mixture was
- 10 evaporated under reduced pressure then diluted with dimethylformamide (0.6 mL) and purified by basic HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (1.0 mg, 11%).

- ¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.23 (s, 1H), 7.41 (s, 1H), 6.83 (s, 1H), 5.31 (d, *J* = 6.5 Hz, 1H), 4.64-4.77 (m, 2H), 4.06-4.15 (m, 2H), 3.72 (d, *J* = 13.1 Hz, 1H), 3.38 (q, *J* = 12.8 Hz, 2H), 3.04 (td, *J* = 10.8, 10.1, 5.7 Hz, 2H), 2.73-2.76 (m, 1H), 2.63 (dt, *J* = 11.1, 1.7 Hz, 1H), 2.54-2.61 (m, 2H), 2.25 (s, 3H), 2.21 (s, 3H), 2.06-2.13 (m, 3H), 1.94 (td, *J* = 11.7, 3.6 Hz, 1H), 1.17 (d, *J* = 6.7 Hz, 3H). UPLC-MS Method 5: RT = 1.96 min.

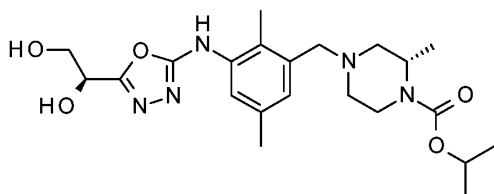
- Example 71:** ethyl (2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



- Ethyl carbonochloridate in dichloromethane (0.024 mL, 0.024 mmol) was added to a solution of (1R)-1-[5-[2,5-dimethyl-3-[[[(3S)-3-methylpiperazin-1-yl]methyl]anilino]-1,3,4-oxadiazol-2-yl]ethanol dihydrochloride from **Preparation 52** (10.0 mg, 0.024
- 25 mmol) and triethylamine (14.5 mg, 0.143 mmol) in dichloromethane (0.7 mL). After 2h the reaction mixture was evaporated under reduced pressure and then diluted with dimethylformamide (0.6 mL) and purified by basic HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (0.5 mg, 5%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 7.38 (d, *J* = 1.7 Hz, 1H), 6.84 (d, *J* = 1.6 Hz, 1H), 5.84 (s, 1H), 4.78 (q, *J* = 6.6 Hz, 1H), 4.10-4.15 (m, 1H), 4.03 (qq, *J* = 10.8, 7.1 Hz, 2H), 3.71 (d, *J* = 13.0 Hz, 1H), 2.93-3.02 (m, 1H), 2.71 (d, *J* = 12.0 Hz, 1H), 2.56 – 2.66 (m, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 2.08 (dd, *J* = 11.3, 3.9 Hz, 1H), 1.99 (dt, *J* = 18.9, 7.0 Hz, 1H), 1.90 (td, *J* = 11.7, 3.5 Hz, 1H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 6.7 Hz, 3H). UPLC-MS Method 5: RT = 1.73 min.

Example 72: isopropyl (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



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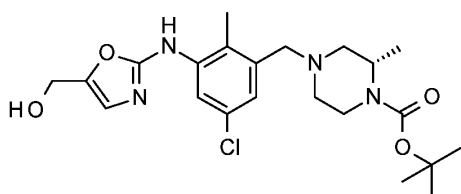
3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (29.2 mg, 0.15 mmol) was added to a solution of isopropyl(2S)-4-[[3(aminocarbamoethioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate (20.0 mg, 0.051 mmol) and 4S)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid **Preparation 25** (8.17mg, 0.056 mmol) dissolved in dry dichloromethane (5 mL) and stirred at room temperature for 12 h. The reaction mixture was quenched with water (2.0 mL) and extracted with dichloromethane (5.0 mL). The organic layer was collected and concentrated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 10-100% ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give intermediate compound isopropyl (2S)-4-[[3-[[5-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate (22.0 mg, 0.045 mmol, 88.8%). Hydrogen chloride (0.6 mL, 4M in dioxane) was added to a solution of the intermediate isopropyl-(2S)-4-[[3-[[5-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate (22.0 mg, 0.045 mmol, 88.8%) in dichloromethane (5.0 mL). After 1 h the solvent was removed under reduced pressure and the residue was dissolved in toluene and evaporated under reduced pressure (2 x 20 mL). The crude product was purified by basic HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless solid (9.0 mg, 39.5%).

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¹H NMR (600 MHz, DMSO-*d*₆) δ = 7.39 (d, *J* = 1.7 Hz, 1H), 6.84 (d, *J* = 1.7 Hz, 1H), 5.92 (s, 1H), 4.98 (s, 1H), 4.77 (h, *J* = 6.3 Hz, 1H), 4.61 (t, *J* = 6.7 Hz, 1H), 4.12 (dt, *J* = 11.5, 4.6 Hz, 1H), 3.70 (dt, *J* = 13.1, 2.6 Hz, 1H), 3.65 (d, *J* = 6.6 Hz, 2H), 3.39 (m,

2H), 2.93-2.98 (m, 1H), 2.65 – 2.75 (m, 1H), 2.60 (dt, $J = 11.2, 1.9$ Hz, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 2.02-2.12 (m, 1H), 1.90 (td, $J = 11.7, 3.5$ Hz, 1H), 1.17 (d, $J = 6.2$ Hz, 6H), 1.13 (d, $J = 6.7$ Hz, 3H). UPLC-MS Method 5: RT = 1.74 min.

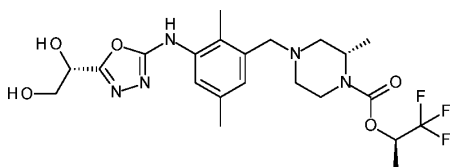
- 5 **Example 74:** *tert*-butyl (2S)-4-[[5-chloro-3-[[5-(hydroxymethyl)oxazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



Lithium aluminium hydride (2.3 M in THF, 0.026 mL, 0.061 mmol) was added to a solution of ethyl 2-[3-[[[(3S)-4-*tert*-butoxycarbonyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]oxazole-5-carboxylate **Preparation 50** (130 mg, 0.26 mmol) in tetrahydrofuran at 0°C. After 1h of stirring the mixture was quenched with water and extracted with ethyl acetate (3x 10 mL). The organic phase was washed with brine and water, dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by basic HPLC. Clean fractions were evaporated under reduced pressure to give title compound (4.0 mg, 21.8%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.22 (s, 1H), 7.97 (d, $J = 2.2$ Hz, 1H), 7.01 (d, $J = 2.2$ Hz, 1H), 6.78 (s, 1H), 5.19 (t, $J = 5.4$ Hz, 1H), 4.37 (d, $J = 4.7$ Hz, 2H), 4.09 (m, 1H), 3.67 (dt, $J = 13.1, 2.7$ Hz, 1H), 3.44 – 3.36 (m, 2H), 2.93 (t, $J = 12.2$, 1H), 2.69 (dp, $J = 11.2, 1.9$ Hz, 1H), 2.58 (dt, $J = 11.3, 1.9$ Hz, 1H), 2.22 (s, 3H), 2.09 (dd, $J = 11.3, 3.9$ Hz, 1H), 1.92 (td, $J = 11.6, 3.5$ Hz, 1H), 1.39 (s, 9H), 1.13 (d, $J = 6.7$ Hz, 3H). UPLC-MS Method 5: RT = 2.21 min.

- 25 **Example 75:** [(1R)-2,2,2-trifluoro-1-methyl-ethyl] (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate

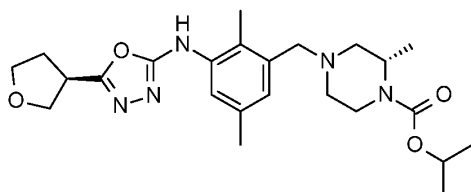


Bis(trichloromethyl) carbonate (150 mg, 0.49 mmol) was added to a solution of (2R)-1,1,1-trifluoropropan-2-ol (160 mg, 1.40mmol) and triethylamine (0.17 mL, 1.20 mmol) in dichloromethane (6.0 mL) at 0°C. On complete addition the reaction mixture was warmed to room temperature over 4 hr, whereupon the complete reaction mixture was

added to a solution of product from **Preparation 56** (476 mg, 1.20 mmol) and triethylamine (1.67 mL, 12.0 mmol) in dimethylformamide (20 mL) at room temperature. The reaction was stirred for 18 h then the solvent was removed *in vacuo*. The residue was dissolved in water (40 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-100% ethyl acetate in heptane. Clean fractions were evaporated under reduced pressure to give the title compound as a colourless non-crystalline solid (140 mg, 23.3%).

¹H NMR (600 MHz, DMSO-d₆) δ = 9.35 (s, 1H), 7.40 (s, 1H), 6.85 (s, 1H), 5.91 (d, *J* = 5.2 Hz, 1H), 5.33 (p, *J* = 6.7 Hz, 1H), 4.96 (t, *J* = 6.0 Hz, 1H), 4.61 (td, *J* = 6.6, 5.2 Hz, 1H), 4.15 (s, 1H), 3.70 (d, *J* = 13.2 Hz, 1H), 3.65 (t, *J* = 6.3 Hz, 2H), 3.33-3.45 (m, 2H), 3.05 (bs, 1H), 2.72-2.77 (m, 1H), 2.64 (d, *J* = 11.4 Hz, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 2.13 (d, *J* = 11.5 Hz, 1H), 1.89-1.97 (m, 1H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.16 (d, *J* = 6.7 Hz, 3H). UPLC-MS Method 6: *m/z* 502.2 [M+H⁺]; RT = 1.88 min.

Example 76: isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3R)-tetrahydrofuran-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate



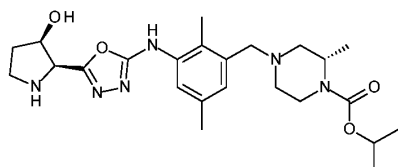
3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (29.2 mg, 0.15 mmol) was added to a solution of product from **Preparation 25** (15.0 mg, 0.04 mmol) and (3R)-tetrahydrofuran-3-carboxylic acid (6.20 mg, 0.05 mmol) in dichloromethane at room temperature. The mixture was stirred for 1 h then concentrated to dryness *in vacuo*. The residue was re-dissolved in 1,4-dioxan (0.5 mL) and lithium hydroxide solution added (0.2 mL, 1.0 M). The mixture was stirred for 0.5 h. The reaction mixture was purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give title compound as a colourless oil (16 mg, 91%).

¹H NMR (600 MHz, DMSO-d₆) δ : 7.39 (s, 1H), 6.83 (s, 1H), 4.77 (hept, *J* = 6.2 Hz, 1H), 4.11 (hept, *J* = 8.9, 6.6 Hz, 1H), 3.97 (dd, *J* = 8.6, 7.6 Hz, 1H), 3.84 (ddd, *J* = 10.8, 8.3, 5.8 Hz, 2H), 3.77 (td, *J* = 7.9, 6.6 Hz, 1H), 3.70 (dt, *J* = 12.9, 2.6 Hz, 1H), 3.62 (ddt, *J* = 8.9, 7.6, 5.8 Hz, 1H), 3.34-3.41 (m, 2H), 2.95 (m, 1H), 2.70 (ddt, *J* = 11.1, 3.4, 1.8 Hz, 1H), 2.59 (dt, *J* = 11.2, 1.8 Hz, 1H), 2.25-2.31 (m, 1H), 2.24 (s, 3H), 2.20

(s, 3H), 2.15 (ddt, $J = 12.4, 7.7, 6.2$ Hz, 1H), 2.06- 2.10 (m, 1H), 1.89 (td, $J = 11.7, 3.5$ Hz, 1H), 1.17 (dd, $J = 6.2, 1.1$ Hz, 6H), 1.13 (d, $J = 6.7$ Hz, 3H). UPLC-MS Method 5: m/z 458.2 $[M+H^+]$; RT = 1.92 min.

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Example 77: isopropyl (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate

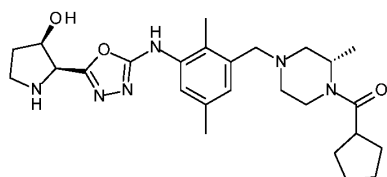


3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (1.0 g, 5.0 mmol) was added to a solution of product from **Preparation 25** (500 mg, 1.0 mmol) and (2S,3R)-1-tert-butoxycarbonyl-3-hydroxy-pyrrolidine-2-carboxylic acid (300 mg, 1.0 mmol) in dichloromethane (40 mL) and stirred at room temperature for 1.5h. The mixture was concentrated to dryness *in vacuo*. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-100% ethyl acetate in heptanes. Clean fractions were combined and concentrated *in vacuo* to leave intermediate product as colourless oil. LCMS Method 4: m/z 473.4 $[M+H^+]$; RT = 0.68 min.

Hydrogen chloride (4M solution in 1,4-dioxane, 2.27 mL, 9.08 mmol) was added to a solution of this piperazine intermediate (520 mg, 0.91 mmol) in methanol (2 mL) and stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-100% ethyl acetate in heptanes. Fractions were pooled and concentrated *in vacuo* and the residue obtained was re-purified by basic HPLC (10-100% MeCN). Clean fractions were combined and evaporated under reduced pressure to give the title compound as a colourless non-crystalline solid. (208 mg, 48.4 %)

^1H NMR (600 MHz, DMSO- d_6) δ : 9.23 (s, 1H), 7.41 (s, 1H), 6.82 (s, 1H), 4.98 (d, $J = 4.9$ Hz, 1H), 4.77 (hept, $J = 6.3$ Hz, 1H), 4.35 (p, $J = 5.4$ Hz, 1H), 4.17 (d, $J = 5.7$ Hz, 1H), 4.12 (d, $J = 6.4$ Hz, 1H), 3.69 (m, 1H), 3.32-3.42 (m, 2H), 3.09 (ddd, $J = 9.9, 8.1, 5.8$ Hz, 1H), 2.95 (m, 1H), 2.82 (ddd, $J = 9.9, 8.1, 6.3$ Hz, 1H), 2.71 (d, $J = 10.6$ Hz, 1H), 2.60 (dt, $J = 11.2, 1.7$ Hz, 1H), 2.24 (s, 3H), 2.21 (s, 3H), 2.08 (dd, $J = 11.4, 3.9$ Hz, 1H), 1.96 (ddt, $J = 12.2, 8.0, 6.0$ Hz, 1H), 1.89 (td, $J = 11.7, 3.5$ Hz, 1H), 1.77 (dddd, $J = 12.6, 8.0, 6.3, 4.9$ Hz, 1H), 1.17 (d, $J = 6.2$ Hz, 6H), 1.13 (d, $J = 6.7$ Hz, 3H). LCMS Method 5: m/z 473.2 $[M+H^+]$; RT = 1.67 min.

Example 78: cyclopentyl-[(2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone

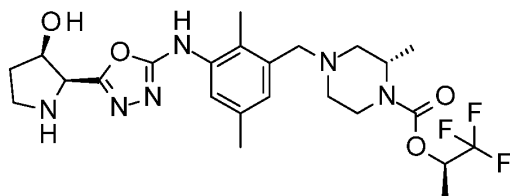


3-(Ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (1.21 g, 6.30 mmol) was added to a solution of product from **Preparation 64** (635 mg, 1.58 mmol) and (2S,3R)-1-tert-butoxycarbonyl-3-hydroxy-pyrrolidine-2-carboxylic acid (437 mg, 1.89 mmol) in dichloromethane (10 mL) and stirred at room temperature for 2 h. The reaction mixture was quenched with aqueous brine (10 mL) and extracted with dichloromethane (40 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was dissolved in 2M AcOH/MeOH and loaded onto 10g SCX cartridge. Washed with methanol then eluted with 2N NH₃/MeOH. Relevant fractions were combined and concentrated *in vacuo*. The residue was re-purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-20% of a 4% methanolic ammonia solution in ethyl acetate. Relevant fractions were combined and concentrated *in vacuo* to leave the intermediate material as a colourless oil (724 mg, 1.24 mmol, 78%). LCMS Method 4: m/z 473.4 [M+H⁺]; RT = 0.67 min.

Trifluoroacetic acid (4.0 mL, 52.2 mmol) was added to a solution of this intermediate (724 mg, 1.24 mmol) in acetonitrile (4.0 mL) and stirred for 1 h, then concentrated to dryness. The residue was dissolved in 2M AcOH/MeOH and loaded onto 10g SCX cartridge. Washed with methanol then eluted with 2N ammonia in methanol. Relevant fractions were combined and concentrated *in vacuo*. The residue was dissolved in acetonitrile and purified by basic preparative HPLC. Clean fractions were evaporated under reduced pressure to give the title compound (349 mg, 58.2 %).

¹H NMR (600 MHz, DMSO-d₆) δ : 9.23 (s, 1H), 7.41 (s, 1H), 6.82 (s, 1H), 4.99 (d, J = 4.9 Hz, 1H), 4.54 (d, J = 7.4 Hz, 0.5H), 4.35 (p, J = 5.3 Hz, 1H), 4.20 (m, 0.5H) overlapping 4.17 (d, J = 5.7 Hz, 1H), 3.73 (d, J = 13.3 Hz, 0.5H), 3.16 (t, J = 12.6 Hz, 0.5H), 3.09 (ddd, J = 10.0, 8.1, 5.7 Hz, 1H), 2.91 (q, J = 7.1 Hz, 1H), 2.83 (ddd, J = 10.0, 8.2, 6.3 Hz, 1H), 2.77 (m, 0.5H) overlapping 2.73 (d, J = 11.0 Hz, 1H), 2.63 (m, 1H), 2.25 (s, 3H), 2.23 (s, 3H), 2.04 (m, 1H), 1.96 (ddt, J = 12.3, 8.2, 6.0 Hz, 1H), 1.86 (m, 0.5H), 1.77 (dddd, J = 12.8, 8.1, 6.3, 4.9 Hz, 1H), 1.70 (m, 2H), 1.57 (m, 3H), 1.50 (m, 2H), 1.15 (dd, J = 82.7, 6.6 Hz, 3H).). LCMS Method 6: m/z 483.3 [M+H⁺]; RT = 1.63 min.

Example 80: [(1R)-2,2,2-trifluoro-1-methyl-ethyl] (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate



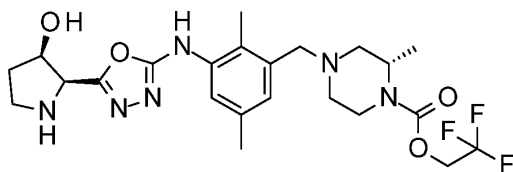
5

Using a procedure similar to that described in **Example 75**, but using the product from **Preparation 66** (30.0 mg, 0.06 mmol) and (2R)-1,1,1-trifluoropropan-2-ol (24.0 mg, 0.21 mmol), the intermediate compound was prepared. The crude intermediate product was purified by basic HPLC. The clean fractions were combined and concentrated *in vacuo* to leave the intermediate product as a colourless foam (17.0 mg, 44%). 10% palladium on carbon (4.0 mg, 0.04 mmol) was added to a solution of the isolated intermediate (17.0 mg, 0.026 mmol) in ethanol (2 mL) under an atmosphere of hydrogen and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was filtered through a Celite[®] pad and concentrated *in vacuo*. The obtained residue was dissolved in methanol and purified by basic HPLC. The clean fractions were combined and concentrated *in vacuo* to leave the title product as a colourless non-crystalline solid (8.0 mg, 62%).

¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.23 (s, 1H), 7.41 (d, *J* = 1.7 Hz, 1H), 6.82 (d, *J* = 1.7 Hz, 1H), 5.33 (hept, *J* = 6.8 Hz, 1H), 4.98 (d, *J* = 4.9 Hz, 1H), 4.35 (p, *J* = 5.3 Hz, 1H), 4.17 (d, *J* = 5.7 Hz, 1H) overlapping 4.14 (d, *J* = 9.2 Hz, 1H), 3.70 (d, *J* = 13.1 Hz, 1H), 3.41 (d, *J* = 13.0 Hz, 1H), 3.36 (m, 2H), 3.09 (ddd, *J* = 10.0, 8.1, 5.7 Hz, 1H), 3.05 (m, 1H), 2.82 (ddd, *J* = 10.0, 8.1, 6.3 Hz, 1H), 2.74 (ddt, *J* = 11.2, 3.5, 1.8 Hz, 1H), 2.63 (m, 1H), 2.24 (s, 3H), 2.22 (s, 3H), 2.12 (dd, *J* = 12.0, 4.0 Hz, 1H), 1.95 (m, 2H), 1.77 (dddd, *J* = 12.8, 8.1, 6.2, 4.8 Hz, 1H), 1.35 (dd, *J* = 6.6 Hz, 3H), 1.16 (d, *J* = 6.7 Hz, 3H). UPLC-MS Method 4: RT = 0.71 min.

Example 81: 2,2,2-trifluoroethyl (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate

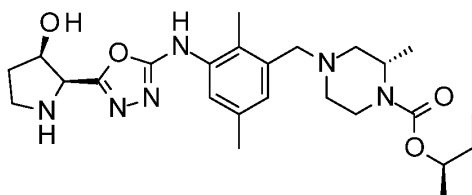
30



Using a procedure as described in **Example 80**, using the product from **Preparation 66** (29.0 mg, 0.06 mmol) and 2,2,2-trifluoroethanol (70.0 mg, 0.7 mmol), followed by the intermediate deprotection with palladium on carbon and basic HPLC purification, the title

- 5 compound was isolated as a colourless non-crystalline solid. (4.0 mg, 14% overall)
 ^1H NMR (600 MHz, DMSO- d_6) δ = 9.22 (s, 1H), 7.41 (d, J = 1.7 Hz, 1H), 6.82 (d, J = 1.7 Hz, 1H), 4.97 (d, J = 4.8 Hz, 1H), 4.68 (m, 2H), 4.35 (p, J = 5.4 Hz, 1H), 4.17 (d, J = 5.7 Hz, 1H), 3.72 (d, J = 13.0 Hz, 1H), 3.38 (d, J = 4.9 Hz, 1H), 3.36 (m, 2H), 3.09 (ddd, J = 9.8, 8.0, 5.6 Hz, 1H), 2.80 (m, 2H), 2.64 (d, J = 11.3 Hz, 1H), 2.24 (s, 3H),
 10 2.22 (s, 3H), 2.12 (dd, J = 11.4, 3.8 Hz, 1H), 1.95 (m, 2H), 1.77 (m, 1H), 1.17 (d, J = 6.7 Hz, 3H). UPLC-MS Method 4: RT = 0.68 min.

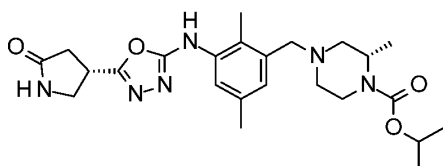
Example 82: [(1R)-1-methylpropyl] (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-
 15 carboxylate



Using a procedure as described in **Example 80**, using the product from **Preparation 66** (30.0 mg, 0.06 mmol) and (2R)-butan-2-ol (90.0 mg, 1.21 mmol), followed by the intermediate deprotection with palladium on carbon and basic HPLC purification, the title

- 20 compound was isolated as a colourless non-crystalline solid. (4.0 mg, 14% overall)
 ^1H NMR (600 MHz, DMSO- d_6) δ = 9.23 (s, 1H), 7.41 (d, J = 1.7 Hz, 1H), 6.82 (d, J = 1.7 Hz, 1H), 4.98 (d, J = 4.8 Hz, 1H), 4.61 (hept, J = 6.2 Hz, 1H), 4.35 (p, J = 5.3 Hz, 1H), 4.17 (d, J = 5.8 Hz, 1H), 4.14 (t, J = 5.6 Hz, 1H), 3.71 (dt, J = 13.0, 2.7 Hz, 1H), 3.40 (m, 2H), 3.09 (ddd, J = 10.1, 8.1, 5.8 Hz, 1H), 2.96 (m, 1H), 2.82 (ddd, J = 10.0,
 25 8.2, 6.3 Hz, 1H), 2.71 (m, 1H), 2.60 (dt, J = 11.1, 1.9 Hz, 1H), 2.24 (s, 3H), 2.22 (s, 3H), 2.08 (dd, J = 11.3, 3.9 Hz, 1H), 1.96 (m, 1H), 1.89 (td, J = 11.7, 3.5 Hz, 1H), 1.77 (dddd, J = 12.7, 8.1, 6.3, 4.9 Hz, 1H), 1.51 (m, 2H), 1.14 (m, 6H), 0.85 (t, J = 7.4 Hz, 3H). UPLC-MS Method 4: RT = 0.71 min.

Example 83: isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3S)-5-oxopyrrolidin-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate



Using a procedure similar to that described for **Example 3**, but with the product from

- 5 **Preparation 27** (750 mg, 1.91 mmol) and (3S)-5-oxopyrrolidine-3-carboxylic acid (295 mg, 2.29 mmol) the title compound was prepared. The obtained residue was purified by silica gel (100-200 mesh) column chromatography eluting with a gradient of 0-15% methanol in ethyl acetate. Clean fractions were evaporated under reduced pressure to give title compound as a colourless non-crystalline solid (700 mg, 78%). The obtained
- 10 product (15 mg) was dissolved in ethyl acetate (0.1 mL) which crystallized immediately. The crystalline material was collected and dried under pressure, before being used to seed the remaining product (650 mg) in ethyl acetate (5 mL). The precipitated material was collected and dried under pressure to give the title compound as a crystalline solid. (625 mg, melting point 169-170°C, 93 %)
- 15 ¹H NMR (600 MHz, DMSO-*d*₆) δ = 9.33 (s, 1H), 7.80 (s, 1H), 7.39 (d, *J* = 1.7 Hz, 1H), 6.84 (d, *J* = 1.7 Hz, 1H), 4.77 (hept, *J* = 6.3 Hz, 1H), 4.11 (m, 1H), 3.85 (m, 1H), 3.70 (dt, *J* = 13.0, 2.6 Hz, 1H), 3.63 (m, 1H), 3.45 (dd, *J* = 9.7, 5.7 Hz, 1H), 3.38 (m, 2H), 2.95 (td, *J* = 12.9, 3.3 Hz, 1H), 2.70 (dp, *J* = 11.2, 1.8 Hz, 1H), 2.59 (m, 2H), 2.46 (dd, *J* = 16.5, 6.7 Hz, 1H), 2.24 (s, 3H), 2.21 (s, 3H), 2.08 (dd, *J* = 11.3, 3.9 Hz, 1H), 1.90
- 20 (td, *J* = 11.7, 3.5 Hz, 1H), 1.17 (dd, *J* = 6.2, 1.0 Hz, 6H), 1.12 (d, *J* = 6.7 Hz, 3H).
UPLC-MS Method 5: RT = 1.79 min.

25 ROR-gamma binding assay

- This assay is used to evaluate the binding affinity of compounds to the ligand-binding pocket of the human RORγ nuclear receptor based on displacement of a radio-ligand. The EC₅₀ values are calculated using a four parameter fit. Compounds binding with high
- 30 affinity to RORγ will have low EC₅₀ values.

- The assay is a Scintillation Proximity Assay (SPA) that involves competition between an unlabeled test compound and tritium-labeled 25-hydroxycholesterol for binding to RORγT ligand binding domain (LBD) protein immobilized on the surface of SPA beads.
- 35 These beads contain a scintillant that emits light if excited by a radioactive particle, and

this light is detected using a scintillation counter. In this assay, tritium-labelled 25-hydroxycholesterol is used as radiotracer.

400 nL of titrated test and reference compounds in DMSO were transferred by the Echo
5 liquid handling system to a 384-well assay plate followed by addition of 5 μ L [3H]-25-Hydroxycholesterol (Perkin Elmer) and 35 μ L diluted ROR γ T LBD protein with the following amino acid sequence (HIS-FLG-tag): MAHHHHHHGS DYKDDDDKGS SGASLTEIEH LVQSVCKSYR ETCQLRLEDL LRQRSNIFSR EEVTGYQRKS MWEMWERCAH HLTEAIQYVV EFAKRLSGFM ELCQNDQIVL LKAGAMEVVL VRMCRAYNAD NRTVFFEGKY
10 GGMELFRALG CSELISSIFD FSHLSALHF SEDEIALYTA LVLINAHPRG LQEKRKVEQL QYNLELAFHH HLCKTHRQSI LAKLPPKGKL RSLCSQHVER LQIFQHLHPI VVQAAFPPLY KELFSTETES PVGLSK (Purchased from Proteros Biostructures GmbH).

After 30 min of preincubation, 40 μ L of HIS-TAG PVT SPA beads (Perkin Elmer) were added. The plates were then incubated for minimum 4 hours at room temperature in
15 darkness before measuring the SPA signal using a MicroBeta plate scintillation counter. Final assay conditions were: 50 mM HEPES pH 7.4, 150 mM NaCl, 5 mM MgCl₂, 0.1% BSA, 4 μ g/well HIS-TAG PVT SPA Beads, 30 ng/well ROR γ T LBD (equal to a final concentration of 12 nM), 15 nM [3H]-25-Hydroxycholesterol, 0.5 % DMSO and varying concentrations of test compound in a total volume of 80 μ L/well. EC₅₀ values were
20 calculated using a 4-parameter non-linear regression curve-fitting model. The exemplified compounds were tested in the ROR-gamma binding assay. Results are shown in Table 2.

Human PBMC IL-17A assay

25 This assay measures the IL-17A inhibitory potential of test compounds in Human peripheral mononuclear cells.
Peripheral blood mononuclear cells (PBMC) were isolated from human buffy coats using density grade centrifugation (Lymphoprep, Medinor), washed twice in PBS and frozen at -150°C for later use.
30 Test compounds were diluted in DMSO and 70 nL of titrated test and reference compounds were transferred by the Echo liquid handling system to a 384-well assay plate in to give a final concentration of 0.1% DMSO in the wells.
The PBMC were thawed, washed and suspended in RPMI-1640 supplemented with pen/strep, glutamax and 10 % bovine calf serum. The cells were mixed with
35 antiCD3/antiCD28-coated beads (1 cells pr one bead) (Milteney T-cell expansion kit), and immediately thereafter the cells were pipetted to the plate at 130,000c/well. The plate was incubated for 3 days in humidified air/CO₂ (95%/5%) On day 3 the level of IL-17A in the culture supernatant is measured using alpha-LISA kit (Perkin Elmer). Cell

viability was measured by adding 6 μ L per well Prestoblu[®] (Life Technologies) and incubating for 2 hours followed by fluorescent measurement (Ex535/Em615). EC₅₀ values were calculated using a 4-parameter non-linear regression curve-fitting model. Donors may be pre-screened in order to select PBMC with a high secretion of IL-17A.

- 5 The exemplified compounds were tested in the Human PBMC IL-17A assay. Results are shown in Table 2.

Human whole blood IL-17A assay

- 10 The EC₅₀ value reported from this assay is a measure of the potency of the tested compound in inhibiting IL-17A levels in the blood after three days of incubation. Test compounds were diluted in DMSO and 80 nL of titrated compound is transferred by the Echo liquid handling system to a 384-well assay plate to give a final concentration of 0.1% DMSO in the wells.
- 15 Freshly drawn human peripheral blood stabilized with heparin was diluted 1:1 with X-vivo 15 medium (Lonza) added pen/strep and glutamax. Staphylococcus enterotoxin B (Sigma) at 300 ng/mL was added to the diluted blood just prior to pipetting into wells, 80 μ L per well. The plates were incubated for 3 days at 37°C in humidified air/CO₂ (95%/5%). After 3 days of incubation, the level of IL-17A was measured using an alpha-
- 20 LISA kit (Perkin Elmer). EC₅₀ values were calculated using a 4-parameter non-linear regression curve-fitting model. The exemplified compounds were tested in the Human whole blood IL-17A assay. Results are shown in Table 2.

25

Human liver microsomes (HLM) assay

- Compounds of the invention were tested in the Human liver microsomes (HLM) assay. Incubations of test compounds in DMSO, diluted with phosphate buffer, pH 7.4, at 0.5
- 30 μ M were carried out with human liver microsomes (0.5 mg/mL). The percentage of organic solvent in the incubations was 1%. The human liver microsomal suspension in phosphate buffer was mixed with NADPH (1 mM) and preheated to 37 °C before test compound was added. Aliquots were taken at 0, 5, 10, 20, 30 and 40 minutes, and reactions were terminated by addition of cold acetonitrile containing analytical internal
- 35 standard (IS).

The results were expressed as apparent clearance (Cl_{app}) (mL/min/kg) and hepatic extraction ratio (E_h) (%) calculated from the elimination rate constant (k) (min⁻¹) of test

compound depletion. Apparent clearance is a measure of compound elimination from the liver.

Table 2

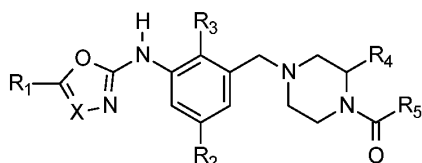
Example	ROR-gamma binding (nM)	Human PBMC IL-17a (nM)	Human Whole blood IL-17A (nM)
1	40.2	3,030	NT
2	29	137	454
3	22.3	51.1	204
4	29.9	34.7	428
5	22.6	69.7	385
6	31.7	234	504
7	33	49.8	219
8	69	251	497
9	23.5	99.3	254
10	45.4	173	296
11	28.1	92.6	132
12	40.4	128	302
13	14.7	48.9	112
14	61.1	185	372
15	63.8	101	421
16	223	237	206
17	54.5	230	131
18	21.2	69.8	203
19	92.3	117	216
20	113	189	259
21	71.7	180	251
22	169	254	355
23	125	368	238
24	38.6	35.9	112
25	159	258	191
26	58.2	91.3	119
27	95.9	425	457

28	35.5	107	NT
29	37.8	117	422
30	31.2	93.6	239
31	32.4	63.5	231
32	26.4	101	392
33	23.3	45.2	126
34	24.6	24.8	83.7
35	33.9	106	499
36	84.1	366	451
37	40.8	43.7	426
38	49.7	58.5	403
39	29.2	38.2	377
40	21.2	212	365
41	91.1	215	373
42	48	34.2	359
43	53.9	63.5	332
44	22.7	26	330
45	42	39.9	330
46	37.1	103	322
47	26.6	63.2	307
48	37.2	191	296
49	90.5	218	275
50	31.6	86.5	272
51	64.4	216	266
52	42.1	134	256
53	68.2	93.9	247
54	16.3	28.1	176
55	39	62.3	36.8
56	36.5	51.9	92.2
57	23.8	46.5	96.7
58	54.4	373	215
59	25.7	123	211
60	38.3	106	195

61	42.3	106	101
62	20.7	67.6	103
63	34.8	62.1	187
64	50.6	131	191
65	47.9	58.7	107
66	54.8	77.6	140
67	62.2	47.2	597
68	103	182	552
69	70	308	NT
70	52.2	78.5	227
71	62	223	307
72	81.6	262	258
73	55.9	59.8	270
74	71.8	408	946
75	32.4	52.9	158
76	25.6	60.5	112
77	61.2	180	368
78	72.5	95.9	157
79	274	1,220	3,530
80	22.3	70	NT
81	110	1,520	NT
82	32	46	NT
83	67	123	240

The following are further embodiments of the invention:

Embodiment 1. A compound according to general formula (I)



(I)

wherein X represents N or CH;

R₁ is selected from the group consisting of -CN, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered)heterocycloalkyl, (5-6 membered)heteroaryl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (3-7 membered)heterocycloalkyl-(C₁-C₄)alkyl and (5-6 membered)heteroaryl-(C₁-C₄)alkyl, wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered)heterocycloalkyl, (5-6 membered)heteroaryl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (3-7 membered)heterocycloalkyl-(C₁-C₄)alkyl and (5-6 membered)heteroaryl-(C₁-C₄)alkyl is optionally substituted with one or more substituents independently selected from R₆;

R₂ is selected from the group consisting of halogen, cyano, (C₁-C₄)alkyl and (C₃-C₇)cycloalkyl, wherein said (C₁-C₄)alkyl and (C₃-C₇)cycloalkyl is optionally substituted with one or more substituents independently selected from -OH and halogen;

R₃ is selected from the group consisting of halogen, cyano, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and (C₃-C₇)cycloalkyl;

R₄ is selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)haloalkyl;

R₅ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, (3-7 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and -OR_a; wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, (3-7 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and -OR_a is optionally substituted with one or more substituents independently selected from R₇;

R₆ represents the group consisting of -OH, -CN, halogen, =O, -S(O)₂R_b, -NR_cR_d, -NR_cC(O)R_d, -C(O)NR_cR_d, -S(O)₂NR_cR_d, -NR_cS(O)₂R_b, -OR_b, -C(O)R_b, (C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered)heterocycloalkyl and (5-6 membered)heteroaryl;

R₇ represents the group consisting of -OH, -CN, halogen, (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl and (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl;

R_a represents (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl- or (C₃-C₇)cycloalkyl(C₁-C₆)alkyl;

R_b represents (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl;

R_c and R_d each independently represents H, (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl;

or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 2. The compound according to embodiment 1 wherein X represents N.

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Embodiment 3. The compound according to any one of embodiments 1-2 wherein R_1 is selected from the group consisting of -CN, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (3-7 membered)heterocycloalkyl and 5-membered heteroaryl wherein said (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (3-7 membered)heterocycloalkyl and 5-membered heteroaryl is optionally substituted with one or more substituents independently selected from R_6 .

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Embodiment 4. The compound according to any one of embodiments 1-3 wherein R_1 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (3-7 membered)heterocycloalkyl, wherein said (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (3-7 membered)heterocycloalkyl is optionally substituted with one or more substituents independently selected from R_6 ; wherein R_6 represents the group consisting of -OH, halogen, =O, $-S(O)_2R_b$, $-NR_cR_d$, and $-OR_b$; R_b represents methyl or ethyl; R_c and R_d independently represents hydrogen, methyl or ethyl.

15

Embodiment 5. The compound according to any one of embodiments 1-4 wherein R_1 is selected from the group consisting of (3-7 membered)heterocycloalkyl, wherein said (3-7 membered)heterocycloalkyl is optionally substituted with one or more substituents independently selected from R_6 ; wherein R_6 represents $-S(O)_2R_b$ and R_b represents (C_1-C_4) alkyl.

25

Embodiment 6. The compound according to any one of embodiments 1-5 wherein R_1 is selected from the group consisting of (C_1-C_4) alkyl, wherein said (C_1-C_4) alkyl is optionally substituted with one or more -OH.

Embodiment 7. The compound according to any one of embodiments 1-6 wherein R_1 is selected from (5-6 membered)heteroaryl, wherein said (5-6-membered)heteroaryl is optionally substituted with one or more substituents independently selected from (C_1-C_4) alkyl.

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Embodiment 8. The compound according to any one of embodiments 1-7 wherein R_1 is selected from (3-7 membered)heterocycloalkyl, wherein said (3-7 membered)heterocycloalkyl is optionally substituted with one or more substituents independently selected from (C_1-C_4) alkyl.

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Embodiment 9. The compound according to any one of embodiments 1-8 wherein R₁ represents cyclopropyl, cyclobutyl, oxetanyl, azetidiny and pyrrolidinyl, wherein said cyclopropyl, cyclobutyl, oxetanyl, azetidiny and pyrrolidinyl is optionally substituted
5 with one or more -OH or =O.

Embodiment 10. The compound according to any one of embodiments 1-9 wherein R₁ is selected from the group consisting of (C₁-C₄)alkyl and pyrrolidinyl, wherein said (C₁-C₄)alkyl and pyrrolidinyl is optionally substituted with one or more -OH.
10

Embodiment 11. The compound according to any one of embodiments 1-10 wherein R₁ is selected from the group consisting of methyl, ethyl, propyl and pyrrolidinyl, wherein said methyl, ethyl, propyl and pyrrolidinyl is optionally substituted with one or more -OH.
15

Embodiment 12. The compound according to any one of embodiments 1-11 wherein R₁ represents -CN, methyl, ethyl, propyl, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, oxazolidinyl, morpholinyl, piperidinyl, triazolyl, pyrrazolyl, isoxazolyl, thiadiazolyl or oxadiazolyl, wherein said
20 methyl, ethyl, propyl, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, oxazolidinyl, morpholinyl, piperidinyl, triazolyl, pyrrazolyl, isoxazolyl, thiadiazolyl or oxadiazolyl is optionally substituted with one or more -OH, -S(O)₂CH₃, -NH₂, -CN, =O, fluoro, methyl, methoxy or hydroxymethyl,

Embodiment 13. The compound according to any one of embodiments 1-12 wherein R₂ is selected from the group consisting of halogen and (C₁-C₄)alkyl, wherein said (C₁-C₄)alkyl is optionally substituted with one or more substituents independently selected from halogen.
25

Embodiment 14. The compound according to any one of embodiments 1-13 wherein R₂ represents (C₁-C₄)alkyl.
30

Embodiment 15. The compound according to any one of embodiments 1-14 wherein R₂ represents methyl.
35

Embodiment 16. The compound according to any one of embodiments 1-15 wherein R₂ and R₃ both represent methyl.

Embodiment 17. The compound according to any one of embodiments 1-16 wherein each of R₂, R₃ and R₄ represent methyl.

Embodiment 18. The compound according to any one of embodiments 1-17 wherein X
5 represents N and each of R₂, R₃ and R₄ represent methyl.

Embodiment 19. The compound according to any one of embodiments 1-18 wherein R₂ represents chloro or difluoromethyl.

10 Embodiment 20. The compound according to any one of embodiments 1-19 wherein R₂ represents chloro, methyl or difluoromethyl.

Embodiment 21. The compound according to any one of embodiments 1- 20 wherein R₃ represents (C₁-C₄)alkyl.

15 Embodiment 22. The compound according to any one of embodiments 1-21 wherein R₃ represents methyl.

Embodiment 23. The compound according to embodiments 1-22 wherein R₄ represents
20 (C₁-C₄)alkyl.

Embodiment 24. The compound according to any one of embodiments 1-23 wherein R₄ represents methyl.

25 Embodiment 25. The compound according to any one of embodiments 1-24 wherein R₅ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, phenyl and -OR_a; wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, phenyl and -OR_a is optionally substituted with one or more substituents
30 independently selected from R₇.

Embodiment 26. The compound according to any one of embodiments 1-25 wherein R₅ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl and -OR_a; wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl and -OR_a is
35 optionally substituted with one or more substituents independently selected from R₇; wherein R₇ represent halogen and R_a represents (C₁-C₆)alkyl.

Embodiment 27. The compound according to any one of embodiments 1-26 wherein R_5 is selected from the group consisting of (C_1-C_6) alkyl and $-OR_a$; wherein said (C_1-C_6) alkyl and $-OR_a$ is optionally substituted with one or more substituents independently selected from R_7 ; wherein R_a represents (C_1-C_6) alkyl and R_7 represent halogen.

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Embodiment 28. The compound according to any one of embodiments 1-27 wherein R_5 is selected from the group consisting of (C_1-C_6) alkyl and $-OR_a$; wherein said (C_1-C_6) alkyl and $-OR_a$ is optionally substituted with one or more fluoro and wherein R_a represents ethyl, propyl or isopropyl.

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Embodiment 29. The compound according to any one of embodiments 1-28 wherein R_5 represents phenyl; wherein said phenyl is optionally substituted with one or more substituents independently selected from R_7 .

15 Embodiment 30. The compound according to any one of embodiments 1-29 wherein R_5 represents phenyl; wherein said phenyl is optionally substituted with one or more halogen.

Embodiment 31. The compound according to any one of embodiments 1-30 wherein R_5 represents cyclopentyl; wherein said cyclopentyl is optionally substituted with one or more fluoro.

Embodiment 32. The compound according to any one of embodiments 1-31 wherein R_5 represents phenyl, propyl, butyl, ethoxy, iso-propyloxy, tert-butyloxy, cyclopropyl, cyclobutyl, cyclopentyl, methylcyclopropyl or cyclobutylmethyl.

Embodiment 33. The compound according to any one of embodiments 1-32 wherein R_5 represents phenyl, propyl, butyl, ethoxy, iso-propyloxy, tert-butyloxy, cyclopropyl, cyclobutyl, cyclopentyl, methylcyclopropyl or cyclobutylmethyl; wherein said phenyl, propyl, butyl, ethoxy, iso-propyloxy, tert-butyloxy, cyclopropyl, cyclobutyl, cyclopentyl, methylcyclopropyl or cyclobutylmethyl is optionally substituted with one or more fluoro.

Embodiment 34. The compound according to any one of embodiments 1-33 wherein R_6 represents the group consisting of $-OH$, $-CN$, halogen, $=O$, $-S(O)_2R_b$, $-NR_cR_d$, $-OR_b$, (C_1-C_4) alkyl and hydroxy (C_1-C_4) alkyl.

Embodiment 35. The compound according to any one of embodiments 1-34 wherein R_6 represents $-OH$, $-CN$, fluoro, $-NH_2$, $=O$, $-S(O)_2CH_3$, methyl, methoxy or hydroxymethyl.

Embodiment 36. The compound according to any one of embodiments 1-35 wherein R₆ represents -OH.

- 5 Embodiment 37. The compound according to any one of embodiments 1-36 wherein R₇ represents halogen.

Embodiment 38. The compound according to any one of embodiments 1-37 wherein R₇ represents fluoro.

10

Embodiment 39. The compound according to any one of embodiments 1-38 wherein R₇ represents fluoro or -OH.

- Embodiment 40. The compound according to any one of embodiments 1-39 wherein R_a
15 represents (C₁-C₆)alkyl optionally substituted with one or more halogen.

Embodiment 41. The compound according to any one of embodiments 1-40 wherein R_b represents (C₁-C₆)alkyl.

- 20 Embodiment 42. The compound according to any one of embodiments 1-41 wherein R_b represents methyl.

Embodiment 43. The compound according to any one of embodiments 1-42 wherein R_c and R_d each independently represents H or (C₁-C₆)alkyl.

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Embodiment 44. The compound according to any one of embodiments 1-43 wherein R_c and R_d each independently represents H or methyl.

- Embodiment 45. The compound according to any one of embodiments 1-44 wherein R₁
30 is selected from the group consisting of (C₁-C₄)alkyl and pyrrolidinyl, wherein said (C₁-C₄)alkyl and pyrrolidinyl is optionally substituted with one or more -OH; and wherein R₂ represents halogen or (C₁-C₄)alkyl which is optionally substituted with one or more halogen; R₃ represents (C₁-C₄)alkyl; R₄ represents (C₁-C₄)alkyl; R₅ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl and -OR_a; wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl and -OR_a is optionally
35 substituted with one or more substituents independently selected from R₇; wherein R₇

represent halogen and R_a represents (C_1-C_6) alkyl and X represents N; or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 46. The compound according to any one of embodiments 1-45 wherein R_1 is selected from the group consisting of (C_1-C_4) alkyl and pyrrolidinyl, wherein said (C_1-C_4) alkyl and pyrrolidinyl is optionally substituted with one or more -OH; wherein X represents N; wherein each of R_2 , R_3 and R_4 represent methyl; and wherein R_5 is selected from the group consisting of (C_1-C_6) alkyl and $-OR_a$, said (C_1-C_6) alkyl and $-OR_a$ optionally being substituted with one or more substituents independently selected from R_7 and wherein R_7 represents fluoro and R_a represents ethyl, propyl or isopropyl, or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 47. The compound according to any one of embodiments 46 wherein R_1 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (3-7 membered)heterocycloalkyl, wherein said (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (3-7 membered)heterocycloalkyl is optionally substituted with one or more substituents independently selected from R_6 ; wherein R_6 represents the group consisting of -OH, halogen, =O, $-S(O)_2R_b$, $-NR_cR_d$, and $-OR_b$; R_b represents methyl or ethyl; R_c and R_d independently represents hydrogen, methyl or ethyl; and wherein R_2 represents halogen or (C_1-C_4) alkyl which is optionally substituted with one or more halogen; R_3 represents (C_1-C_4) alkyl; R_4 represents (C_1-C_4) alkyl; R_5 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl- (C_1-C_6) alkyl and $-OR_a$; wherein said (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl- (C_1-C_6) alkyl and $-OR_a$ is optionally substituted with one or more substituents independently selected from R_7 ; wherein R_7 represent halogen and R_a represents (C_1-C_6) alkyl and X represents N; or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 48. The compound according to any one of embodiments 1-47 wherein R_1 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (3-7 membered)heterocycloalkyl, wherein said (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (3-7 membered)heterocycloalkyl is optionally substituted with one or more substituents independently selected from R_6 ; wherein R_6 represents the group consisting of -OH, halogen, =O, $-S(O)_2R_b$, $-NR_cR_d$, and $-OR_b$; R_b represents methyl or ethyl; R_c and R_d independently represents hydrogen, methyl or ethyl; and wherein R_2 represents (C_1-C_4) alkyl which is optionally substituted with one or more halogen; R_3 represents (C_1-C_4) alkyl; R_4 represents (C_1-C_4) alkyl; R_5 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl- (C_1-C_6) alkyl

and -OR_a; wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl and -OR_a is optionally substituted with one or more substituents independently selected from R₇; wherein R₇ represent halogen and R_a represents (C₁-C₆)alkyl and X represents N; or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 49. The compound according to any one of embodiments 1-48 wherein R₁ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered)heterocycloalkyl, wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered)heterocycloalkyl is optionally substituted with one or more substituents independently selected from R₆; wherein R₆ represents the group consisting of -OH, halogen, =O, -NH₂ and -OR_b; R_b represents methyl or ethyl; and wherein R₂ represents (C₁-C₄)alkyl which is optionally substituted with one or more halogen; R₃ represents (C₁-C₄)alkyl; R₄ represents (C₁-C₄)alkyl; R₅ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl and -OR_a; wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl and -OR_a is optionally substituted with one or more substituents independently selected from R₇; wherein R₇ represent halogen and R_a represents (C₁-C₆)alkyl and X represents N; or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 50. The compound according to any one of embodiments 1-49 wherein R₁ is selected from the group consisting of -CN, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered) heterocycloalkyl and 5- membered heteroaryl wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered) heterocycloalkyl and 5-membered heteroaryl is optionally substituted with one or more substituents independently selected from R₆; R₆ represents the group consisting of -OH, halogen, =O, -S(O)₂R_b, -NR_cR_d, and -OR_b; R_b represents (C₁-C₄)alkyl; R_c and R_d independently represents H or (C₁-C₆)alkyl; and wherein R₂ represents halogen or (C₁-C₄)alkyl which is optionally substituted with one or more halogen; R₃ represents (C₁-C₄)alkyl; R₄ represents (C₁-C₄)alkyl; X represents N; R₅ represents phenyl; wherein said phenyl is optionally substituted with one or more substituents independently selected from R₇; wherein R₇ represents CN, halogen or (C₁-C₄)alkyl, or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 51. The compound according to any one of embodiments 1-50 wherein R₁ is selected from (5-membered)heteroaryl, wherein said (5-membered)heteroaryl is optionally substituted with one or more substituents independently selected from (C₁-C₄)alkyl; and wherein R₂ represents halogen or (C₁-C₄)alkyl which is optionally

substituted with one or more halogen; R_3 represents (C_1-C_4) alkyl; R_4 represents (C_1-C_4) alkyl; R_5 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl- (C_1-C_6) alkyl and $-OR_a$; wherein said (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl- (C_1-C_6) alkyl and $-OR_a$ is optionally substituted with one or more substituents independently selected from R_7 ; wherein R_7 represent halogen; R_a represents (C_1-C_6) alkyl and wherein X represents N_x or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 52. The compound according to any one of embodiments 1-51 wherein R_1 is selected from the group consisting of (3-7 membered)heterocycloalkyl, wherein said (3-7 membered)heterocycloalkyl is optionally substituted with one or more substituents independently selected from R_6 ; wherein R_6 represents $-S(O)_2R_b$ and R_b represents (C_1-C_4) alkyl; and wherein R_2 represents halogen or (C_1-C_4) alkyl which is optionally substituted with one or more halogen; R_3 represents (C_1-C_4) alkyl; R_4 represents (C_1-C_4) alkyl; R_5 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl- (C_1-C_6) alkyl and $-OR_a$; wherein said (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl- (C_1-C_6) alkyl and $-OR_a$ is optionally substituted with one or more substituents independently selected from R_7 ; wherein R_7 represent halogen; R_a represents (C_1-C_6) alkyl and wherein X represents N_x or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 53. A compound according to any one of embodiments 1-52 selected from the list consisting of

5-[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazole-2-carbonitrile,

[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,

[(2S)-4-[[5-chloro-2-methyl-3-[(5-tetrahydrofuran-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,

[(2S)-4-[[5-chloro-2-methyl-3-[(5-tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,

[(2S)-4-[[5-chloro-3-[(5-cyclopropyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,

[(2S)-4-[[5-chloro-3-[[5-(1-hydroxycyclopropyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,

3-[5-[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazol-2-yl]propanenitrile,

- 3-[5-[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazol-2-yl]propanenitrile,
1-[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-2,2-difluoro-butan-1-one,
5 [(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-(2-fluorophenyl)methanone,
[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-(3,3-difluorocyclopentyl)methanone,
(2S)-1-[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-
10 methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-2-methyl-butan-1-one,
[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-cyclobutyl-methanone,
[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-cyclopentyl-methanone,
15 cyclobutyl-[(2S)-4-[[2,5-dimethyl-3-[(5-methyl-1,3,4-oxadiazol-2-yl)amino]phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
2-[5-[3-[[[(3S)-4-(cyclobutanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-anilino]-1,3,4-oxadiazol-2-yl]acetonitrile,
2-[5-[3-[[[(3S)-4-(cyclopropanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-
20 anilino]-1,3,4-oxadiazol-2-yl]acetonitrile,
2-[5-[3-[[[(3S)-4-(3,3-difluorocyclopentanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-anilino]-1,3,4-oxadiazol-2-yl]acetonitrile,
2-[5-[5-chloro-3-[[4-(cyclopentanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2-methyl-anilino]-1,3,4-oxadiazol-2-yl]acetonitrile,
25 cyclobutyl-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
cyclobutyl-[(2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
2,2-difluoro-1-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-
30 dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]butan-1-one,
cyclopropyl-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-(2-methylcyclopropyl)methanone,
35 cyclopentyl-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
(3,3-difluorocyclopentyl)-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,

- 2-cyclobutyl-1-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]ethanone,
cyclobutyl-[(2S)-4-[[5-(difluoromethyl)-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
- 5 tert-butyl (2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
tert-butyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(3-methyltriazol-4-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 10 tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-methylpyrazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
tert-butyl (2S)-4-[[3-[[5-(isoxazol-5-yl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 15 tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(1,2,5-thiadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(4-methyl-1,2,5-oxadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(5-methyl-1,3,4-oxadiazol-2-yl)amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 20 isopropyl (2S)-4-[[3-[[5-[(1S)-1-amino-2-hydroxy-ethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 25 isopropyl (2S)-4-[[3-[[5-[(1S)-1-aminopropyl]-1,3,4-oxadiazol-2-yl]amino]-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[5-chloro-3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(oxetan-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 30 isopropyl (2S)-4-[[3-[[5-[(1S,2R)-1-amino-2-hydroxy-propyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[3-[[5-(cyanomethyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 35 isopropyl (2S)-4-[[5-(difluoromethyl)-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(tetrahydropyran-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,

- isopropyl (2S)-4-[[5-chloro-3-[[5-(1-hydroxycyclopropyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-3-[[5-[1-(hydroxymethyl)cyclopropyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 5 isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(2,2,2-trifluoro-1-hydroxy-ethyl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(2-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(1S)-1-aminoethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 10 isopropyl (2S)-4-[[5-(difluoromethyl)-3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(5-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 15 isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(5S)-2-oxooxazolidin-5-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-[(2S)-4-oxoazetidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(4-methyl-1,2,5-oxadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 20 isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3S)-morpholin-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate dihydrochloride,
- isopropyl (2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 25 isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2R)-3,3,3-trifluoro-2-hydroxy-propyl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-oxo-4-piperidyl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-methylpyrazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 30 isopropyl (2S)-4-[[3-[[5-[(2S)-2-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(2R)-2-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 35 isopropyl (2S)-4-[[3-[[5-[(1S)-1-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,

- isopropyl (2S)-4-[[5-chloro-3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2S)-1-methylsulfonylpyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 5 isopropyl (2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(5-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(1R)-1-aminoethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 10 2,2,2-trifluoroethyl (2S)-4-[[5-chloro-3-[[5-(cyanomethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 2,2,2-trifluoroethyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 15 ethyl (2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-2-methyl-3-[(5-morpholin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 20 *tert*-butyl (2S)-4-[[5-chloro-3-[[5-(hydroxymethyl)oxazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- [(1R)-2,2,2-trifluoro-1-methyl-ethyl] (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 25 isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3R)-tetrahydrofuran-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- cyclopentyl-[(2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
- 30 (3,3-difluorocyclopentyl)-[(2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
- [(1R)-2,2,2-trifluoro-1-methyl-ethyl] (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-
- 35 carboxylate,
- 2,2,2-trifluoroethyl (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,

[(1R)-1-methylpropyl] (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate and

isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3S)-5-oxopyrrolidin-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,

or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 54. The compound according to any one of the embodiments 1-53 selected from

[(1R)-2,2,2-trifluoro-1-methyl-ethyl] (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate, or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 55. The compound according to any one of the embodiments 1-54 wherein said compound is [(1R)-2,2,2-trifluoro-1-methyl-ethyl] (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate.

Embodiment 56. The compound according to any one of the embodiments 1-53 selected from isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3R)-tetrahydrofuran-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate, or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 57. The compound according to any one of the embodiments 1-53 or 56 wherein said compound is isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3R)-tetrahydrofuran-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate.

Embodiment 58. The compound according to any one of the embodiments 1-53 selected from isopropyl (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate, or pharmaceutically acceptable salts, hydrates or solvates thereof.

Embodiment 59. The compound according to any one of the embodiments 1-53 or 58 wherein said compound is isopropyl (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate.

Embodiment 60. The compound according to any one of embodiments 1-53 wherein said compound is [(1R)-2,2,2-trifluoro-1-methyl-ethyl] (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate, or pharmaceutically acceptable salts thereof.

5

Embodiment 61. The compound according to any one of embodiments 1-53 wherein said compound is isopropyl (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate, or pharmaceutically acceptable salts thereof.

10

Embodiment 62. The compound according to any one of embodiments 1-53 wherein said compound is isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2S)-1-methylsulfonylpyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate, or pharmaceutically acceptable salts thereof.

15

Embodiment 63. The compound according to any one of embodiments 1-53 wherein said compound is cyclopentyl-[(2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone, or pharmaceutically acceptable salts thereof.

20

Embodiment 64. The compound according to any one of the embodiments 1-63 selected from isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2S)-1-methylsulfonylpyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate or pharmaceutically acceptable salts, hydrates or solvates thereof.

25

Embodiment 65. The compound according to any one of the embodiments 1-63 wherein said compound is isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2S)-1-methylsulfonylpyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate.

30

Embodiment 66. The compound according to any one of the embodiments 1-63 selected from cyclopentyl-[(2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone or pharmaceutically acceptable salts, hydrates or solvates thereof.

35

Embodiment 67. The compound according to any one of the embodiments 1-63 wherein said compound is cyclopentyl-[(2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-

oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone.

5 Embodiment 68. A compound according to any one of embodiments 1-67 for use as a medicament.

Embodiment 69. A compound according to any one of embodiments 1-67 for use in treatment of autoimmune or inflammatory diseases.

10 Embodiment 70. The compound for use according to embodiment 69 wherein the autoimmune or inflammatory diseases is selected from psoriasis, psoriatic arthritis, multiple sclerosis, rheumatoid arthritis, Crohns disease, ulcerative colitis, alopecia areata, contact dermatitis, including irritative contact dermatitis and allergic contact dermatitis, spondyloarthritis.

15 Embodiment 71. A compound according to any one of embodiments 1-67 for use in treatment cancers, including prostate cancer and non-small cell lung cancer.

20 Embodiment 72. The compound for use according to embodiments 69-70 wherein the autoimmune or inflammatory diseases is psoriasis.

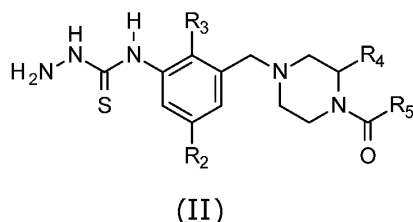
25 Embodiment 73. A pharmaceutical composition comprising a compound according to any one of embodiments 1-67 together with a pharmaceutically acceptable vehicle or excipient or pharmaceutically acceptable carrier(s).

Embodiment 74. The pharmaceutical composition according to embodiment 1-73 together with one or more other therapeutically active compound(s).

30 Embodiment 75. A method of preventing, treating or ameliorating psoriasis, the method comprising administering to a person suffering from psoriasis an effective amount of one or more compounds according to any one of embodiments 1-67, optionally together with a pharmaceutically acceptable carrier or one or more excipients, optionally in combination with other therapeutically active compounds.

35 Embodiment 76. A compound according to any one of embodiments 1-67 for use in treatment of a disease, disorder or condition, which disease, disorder or condition is responsive of modulation of RORgamma.

Embodiment 77. A compound according to general formula (II)



wherein

5 R_2 is selected from the group consisting of halogen, cyano, (C_1-C_4) alkyl and (C_3-C_7) cycloalkyl, wherein said (C_1-C_4) alkyl and (C_3-C_7) cycloalkyl is optionally substituted with one or more substituents independently selected from $-OH$ and halogen;

10 R_3 is selected from the group consisting of halogen, cyano, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl and (C_3-C_7) cycloalkyl;

R_4 is selected from the group consisting of (C_1-C_4) alkyl and (C_1-C_4) haloalkyl;

15 R_5 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl- (C_1-C_6) alkyl, (3-7 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and $-OR_a$; wherein said (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl- (C_1-C_6) alkyl, (3-7 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and $-OR_a$ is optionally substituted with one or more substituents independently selected from R_7 ;

20 R_7 represents the group consisting of $-OH$, $-CN$, halogen, (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl and (C_1-C_6) alkyl- (C_3-C_7) cycloalkyl-.

Embodiment 78. The compound according to embodiment 77 wherein R_2 is selected from the group consisting of halogen and (C_1-C_4) alkyl, wherein said (C_1-C_4) alkyl is optionally substituted with one or more substituents independently selected from halogen;

R_3 is selected from (C_1-C_4) alkyl;

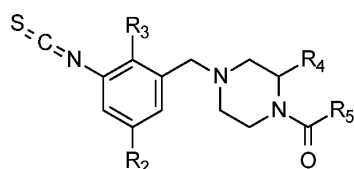
30 R_4 is selected from the group (C_1-C_4) alkyl;

R_5 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, phenyl and $-OR_a$; wherein said (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, phenyl and $-OR_a$ is optionally substituted with one or more substituents independently selected from halogen

Embodiment 79. The compound according to embodiments 77-78, said compound being selected from the list consisting of

- 5 *tert*-butyl (2S)-4-[[3-(aminocarbamothioylamino)-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
 1-amino-3-[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-phenyl]thiourea,
 isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
 10 isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
tert-butyl (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
 1-amino-3-[3-[[[(3S)-4-(cyclobutanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-phenyl]thiourea,
 15 isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-5-(difluoromethyl)-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
 1-amino-3-[3-[[[(3S)-4-(cyclobutanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-5-(difluoromethyl)-2-methyl-phenyl]thiourea,
 20 1-amino-3-[3-[[[(3S)-4-(cyclopentanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-phenyl]thiourea.

Embodiment 80. A compound according to general formula (IX)



(IX)

25

wherein

R₂ is selected from the group consisting of halogen, cyano, (C₁-C₄)alkyl and (C₃-C₇)cycloalkyl, wherein said (C₁-C₄)alkyl and (C₃-C₇)cycloalkyl is optionally substituted with one or more substituents independently selected from -OH and halogen;

30

R₃ is selected from the group consisting of halogen, cyano, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and (C₃-C₇)cycloalkyl;

R₄ is selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)haloalkyl;

R₅ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, (3-7 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and -OR_a; wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, (3-7 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and -OR_a is optionally substituted with one or more substituents independently selected from R₇;

R₇ represents the group consisting of -OH, -CN, halogen, (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl and (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl-.

Embodiment 81. The compound according to embodiment 80 wherein R₂ is selected from the group consisting of halogen and (C₁-C₄)alkyl, wherein said (C₁-C₄)alkyl is optionally substituted with one or more substituents independently selected from halogen;

R₃ is selected from (C₁-C₄)alkyl;

R₄ is selected from the group (C₁-C₄)alkyl;

R₅ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, phenyl and -OR_a; wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, phenyl and -OR_a is optionally substituted with one or more substituents independently selected from halogen

Embodiment 82. The compound according to embodiments 80-81, said compound being selected from the list consisting of

tert-butyl (2S)-4-[(5-chloro-3-isothiocyanato-2-methyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate,

[(2S)-4-[(5-chloro-3-isothiocyanato-2-methyl-phenyl)methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,

isopropyl (2S)-4-[(5-chloro-3-isothiocyanato-2-methyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate,

isopropyl (2S)-4-[(3-isothiocyanato-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate,

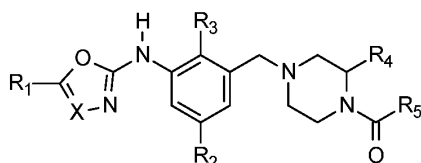
tert-butyl (2S)-4-[(3-isothiocyanato-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate,

cyclobutyl-[(2S)-4-[(3-isothiocyanato-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazin-1-yl]methanone,

- isopropyl (2S)-4-[[5-(difluoromethyl)-3-isothiocyanato-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- cyclobutyl-[(2S)-4-[[5-(difluoromethyl)-3-isothiocyanato-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
- 5 cyclopentyl-[(2S)-4-[(3-isothiocyanato-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazin-1-yl]methanone.

CLAIMS

1. A compound according to general formula (I)



(I)

wherein X represents N or CH;

- 5 R₁ is selected from the group consisting of -CN, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered)heterocycloalkyl, (5-6 membered)heteroaryl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (3-7 membered)heterocycloalkyl-(C₁-C₄)alkyl and (5-6 membered)heteroaryl-(C₁-C₄)alkyl, wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered)heterocycloalkyl, (5-6 membered)heteroaryl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (3-7 membered)heterocycloalkyl-(C₁-C₄)alkyl and (5-6 membered)heteroaryl-(C₁-C₄)alkyl is optionally substituted with one or more substituents independently selected from R₆;

- 15 R₂ is selected from the group consisting of halogen, cyano, (C₁-C₄)alkyl and (C₃-C₇)cycloalkyl, wherein said (C₁-C₄)alkyl and (C₃-C₇)cycloalkyl is optionally substituted with one or more substituents independently selected from -OH and halogen;

R₃ is selected from the group consisting of halogen, cyano, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and (C₃-C₇)cycloalkyl;

- 20 R₄ is selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)haloalkyl;

- R₅ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, (3-7 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and -OR_a; wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, (3-7 membered)heterocycloalkyl, phenyl, (5-6 membered)heteroaryl and -OR_a is optionally substituted with one or more substituents independently selected from R₇;

- R₆ represents the group consisting of -OH, -CN, halogen, =O, -S(O)₂R_b, -NR_cR_d, -NR_cC(O)R_d, -C(O)NR_cR_d, -S(O)₂NR_cR_d, -NR_cS(O)₂R_b, -OR_b, -C(O)R_b, (C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered)heterocycloalkyl and (5-6 membered)heteroaryl;

R₇ represents the group consisting of -OH, -CN, halogen, (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl and (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl-;

5 R_a represents (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl- or (C₃-C₇)cycloalkyl(C₁-C₆)alkyl;

R_b represents (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl;

10 R_c and R_d each independently represents H, (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl;
or pharmaceutically acceptable salts, hydrates or solvates thereof.

2. The compound according to claim 1 wherein X represents N.

15 3. The compound according to any one of claims 1-2 wherein R₁ is selected from the group consisting of -CN, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered) heterocycloalkyl and 5-membered heteroaryl wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (3-7 membered) heterocycloalkyl and 5-membered heteroaryl is optionally substituted with one or more substituents independently selected from R₆.

20

4. The compound according to any one of claims 1-3 wherein R₂ represents chloro, methyl or difluoromethyl.

25 5. The compound according to any one of claims 1-4 wherein R₃ represents methyl.

25

6. The compound according to any one of claims 1-5 wherein R₄ represents methyl.

7. The compound according to any one of claims 1-6 wherein R₅ represents (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, phenyl or -OR_a; wherein said (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, phenyl or -OR_a is optionally substituted with one or more substituents independently selected from R₇.

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8. The compound according to any one of claims 1-7 wherein R₆ represents -OH, -CN, 35 halogen, =O, -S(O)₂R_b, -NR_cR_d, -OR_b, (C₁-C₄)alkyl or hydroxy(C₁-C₄)alkyl.

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9. The compound according to any one of claims 1-8 wherein R₇ represents halogen.

10. The compound according to any one of claims 1-9 wherein R_a represents (C₁-C₆)alkyl.
11. The compound according to any one of claims 1-10 wherein R_b represents (C₁-C₆)alkyl.
12. The compound according to any one of claims 11 wherein R_c and R_d each independently represents H or (C₁-C₆)alkyl.
13. A compound according to any one of claims 1-12 selected from the list consisting of
- 5-[[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazol-2-carbonitrile,
- [(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,
- [(2S)-4-[[5-chloro-2-methyl-3-[(5-tetrahydrofuran-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,
- [(2S)-4-[[5-chloro-2-methyl-3-[(5-tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone
- [(2S)-4-[[5-chloro-3-[(5-cyclopropyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,
- [(2S)-4-[[5-chloro-3-[[5-(1-hydroxycyclopropyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,
- 3-[[5-[[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazol-2-yl]propanenitrile,
- 3-[[5-[[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-anilino]-1,3,4-oxadiazol-2-yl]propanenitrile,
- 1-[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-2,2-difluoro-butan-1-one,
- [(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-(2-fluorophenyl)methanone,
- [(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-(3,3-difluorocyclopentyl)methanone,
- (2S)-1-[(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-2-methyl-butan-1-one,
- [(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-cyclobutyl-methanone,
- [(2S)-4-[[5-chloro-3-[[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]-cyclopentyl-methanone,

- cyclobutyl-[(2S)-4-[[2,5-dimethyl-3-[(5-methyl-1,3,4-oxadiazol-2-yl)amino]phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
2-[5-[3-[[[(3S)-4-(cyclobutanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-anilino]-1,3,4-oxadiazol-2-yl]acetonitrile,
- 5 2-[5-[3-[[[(3S)-4-(cyclopropanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-anilino]-1,3,4-oxadiazol-2-yl]acetonitrile,
2-[5-[3-[[[(3S)-4-(3,3-difluorocyclopentanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-anilino]-1,3,4-oxadiazol-2-yl]acetonitrile,
2-[5-[5-chloro-3-[[4-(cyclopentanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2-methyl-
- 10 anilino]-1,3,4-oxadiazol-2-yl]acetonitrile,
cyclobutyl-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
cyclobutyl-[(2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
- 15 2,2-difluoro-1-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]butan-1-one,
cyclopropyl-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-
- 20 phenyl]methyl]-2-methyl-piperazin-1-yl]-(2-methylcyclopropyl)methanone,
cyclopentyl-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
(3,3-difluorocyclopentyl)-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
- 25 2-cyclobutyl-1-[(2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]ethanone,
cyclobutyl-[(2S)-4-[[5-(difluoromethyl)-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
tert-butyl (2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-
- 30 dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
tert-butyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(3-methyltriazol-4-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 35 tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-methylpyrazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
tert-butyl (2S)-4-[[3-[[5-(isoxazol-5-yl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,

- tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(1,2,5-thiadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- tert-butyl (2S)-4-[[2,5-dimethyl-3-[[5-(4-methyl-1,2,5-oxadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 5 isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-methyl-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(1S)-1-amino-2-hydroxy-ethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 10 isopropyl (2S)-4-[[3-[[5-[(1S)-1-aminopropyl]-1,3,4-oxadiazol-2-yl]amino]-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 15 isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(oxetan-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(1S,2R)-1-amino-2-hydroxy-propyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-(cyanomethyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 20 isopropyl (2S)-4-[[5-(difluoromethyl)-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(tetrahydropyran-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 25 isopropyl (2S)-4-[[5-chloro-3-[[5-(1-hydroxycyclopropyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-3-[[5-[1-(hydroxymethyl)cyclopropyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(2,2,2-trifluoro-1-hydroxy-ethyl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 30 isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(2-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[3-[[5-[(1S)-1-aminoethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- 35 isopropyl (2S)-4-[[5-(difluoromethyl)-3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(5-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,

- isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(5S)-2-oxooxazolidin-5-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-[(2S)-4-oxoazetidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
5 isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(4-methyl-1,2,5-oxadiazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3S)-morpholin-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate dihydrochloride,
isopropyl (2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-
10 dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2R)-3,3,3-trifluoro-2-hydroxy-propyl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-oxo-4-piperidyl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
15 isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-(2-methylpyrazol-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[3-[[5-[(2S)-2-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[3-[[5-[(2R)-2-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-
20 dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[3-[[5-[(1S)-1-hydroxypropyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[5-chloro-3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
25 isopropyl (2S)-4-[[5-chloro-3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate
isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2S)-1-methylsulfonylpyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[3-[[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-
30 dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[5-chloro-2-methyl-3-[[5-(5-oxopyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[3-[[5-[(1R)-1-aminoethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate
35 2,2,2-trifluoroethyl (2S)-4-[[5-chloro-3-[[5-(cyanomethyl)-1,3,4-oxadiazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
2,2,2-trifluoroethyl (2S)-4-[[3-[[5-(3-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,

- ethyl (2S)-4-[[3-[[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
5 isopropyl (2S)-4-[[5-chloro-2-methyl-3-[(5-morpholin-3-yl)-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
tert-butyl (2S)-4-[[5-chloro-3-[[5-(hydroxymethyl)oxazol-2-yl]amino]-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
[(1R)-2,2,2-trifluoro-1-methyl-ethyl] (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
10 isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3R)-tetrahydrofuran-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
15 cyclopentyl-[(2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
(3,3-difluorocyclopentyl)-[(2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
20 [(1R)-2,2,2-trifluoro-1-methyl-ethyl] (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
2,2,2-trifluoroethyl (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
25 [(1R)-1-methylpropyl] (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate
and
isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(3S)-5-oxopyrrolidin-3-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
30
or pharmaceutically acceptable salts, hydrates or solvates thereof.

14. The compound according to any one of claims 1-13 wherein said compound is [(1R)-2,2,2-trifluoro-1-methyl-ethyl] (2S)-4-[[3-[[5-[(1S)-1,2-dihydroxyethyl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
35
or pharmaceutically acceptable salts thereof.

15. The compound according to any one of claims 1-13 wherein said compound is isopropyl (2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate, or pharmaceutically acceptable salts thereof.

5

16. The compound according to any one of claims 1-13 wherein said compound is isopropyl (2S)-4-[[2,5-dimethyl-3-[[5-[(2S)-1-methylsulfonylpyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]phenyl]methyl]-2-methyl-piperazine-1-carboxylate, or pharmaceutically acceptable salts thereof.

10

17. The compound according to any one of claims 1-13 wherein said compound is cyclopentyl-[(2S)-4-[[3-[[5-[(2S,3R)-3-hydroxypyrrolidin-2-yl]-1,3,4-oxadiazol-2-yl]amino]-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone, or pharmaceutically acceptable salts thereof.

15

18. A compound according to any one of claims 1-17 for use as a medicament.

19. A compound according to any one of claims 1-17 for use in treatment of autoimmune or inflammatory diseases.

20

20. The compound according to claim 19 for use in the treatment of psoriasis.

21. A pharmaceutical composition comprising a compound according to any one of claims 1-17 together with a pharmaceutically acceptable vehicle or excipient or pharmaceutically acceptable carrier(s).

25

22. The pharmaceutical composition according to claim 21 together with one or more other therapeutically active compound(s).

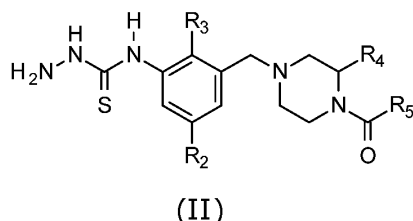
30

23. A method of preventing, treating or ameliorating psoriasis, the method comprising administering to a person suffering from psoriasis an effective amount of one or more compounds according to any one of claims 1-17, optionally together with a pharmaceutically acceptable carrier or one or more excipients, optionally in combination with other therapeutically active compounds.

35

24. A compound according to any one of claims 1-17 for use in treatment of a disease, disorder or condition, which disease, disorder or condition is responsive of modulation of RORgamma.

25. A compound according to general formula (II)



wherein

5

R_2 is selected from the group consisting of halogen and (C_1-C_4) alkyl, wherein said (C_1-C_4) alkyl is optionally substituted with one or more substituents independently selected from halogen;

10 R_3 is selected from (C_1-C_4) alkyl;

R_4 is selected from the group (C_1-C_4) alkyl;

15 R_5 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, phenyl and -OR_a; wherein said (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, phenyl and -OR_a is optionally substituted with one or more substituents independently selected from halogen.

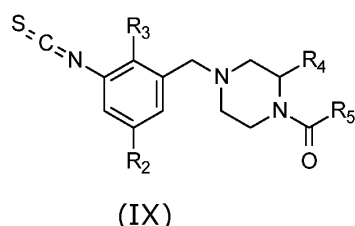
Claim 26. The compound according to claim 25, said compound being selected from the list consisting of

- 20 *tert*-butyl (2S)-4-[[3-(aminocarbamothioylamino)-5-chloro-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
 1-amino-3-[3-[[[(3S)-4-benzoyl-3-methyl-piperazin-1-yl]methyl]-5-chloro-2-methyl-phenyl]thiourea,
 isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-5-chloro-2-methyl-phenyl]methyl]-2-
 25 methyl-piperazine-1-carboxylate,
 isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
tert-butyl (2S)-4-[[3-(aminocarbamothioylamino)-2,5-dimethyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
 30 1-amino-3-[3-[[[(3S)-4-(cyclobutanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-phenyl]thiourea,
 isopropyl (2S)-4-[[3-(aminocarbamothioylamino)-5-(difluoromethyl)-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,

1-amino-3-[3-[[[(3S)-4-(cyclobutanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-5-(difluoromethyl)-2-methyl-phenyl]thiourea,
1-amino-3-[3-[[[(3S)-4-(cyclopentanecarbonyl)-3-methyl-piperazin-1-yl]methyl]-2,5-dimethyl-phenyl]thiourea.

5

27. A compound according to general formula (IX)



wherein

10

R_2 is selected from the group consisting of halogen and (C_1-C_4) alkyl, wherein said (C_1-C_4) alkyl is optionally substituted with one or more substituents independently selected from halogen;

15

R_3 is selected from (C_1-C_4) alkyl;

R_4 is selected from the group (C_1-C_4) alkyl;

20 R_5 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, phenyl and $-OR_a$; wherein said (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, phenyl and $-OR_a$ is optionally substituted with one or more substituents independently selected from halogen.

Claim 28. The compound according to claim 27, said compound being selected from the
25 list consisting of

tert-butyl (2S)-4-[(5-chloro-3-isothiocyanato-2-methyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate,
[(2S)-4-[(5-chloro-3-isothiocyanato-2-methyl-phenyl)methyl]-2-methyl-piperazin-1-yl]-phenyl-methanone,
30 isopropyl (2S)-4-[(5-chloro-3-isothiocyanato-2-methyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate,
isopropyl (2S)-4-[(3-isothiocyanato-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate,

- tert*-butyl (2S)-4-[(3-isothiocyanato-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazine-1-carboxylate,
cyclobutyl-[(2S)-4-[(3-isothiocyanato-2,5-dimethyl-phenyl)methyl]-2-methyl-piperazin-1-yl]methanone,
- 5 isopropyl (2S)-4-[[5-(difluoromethyl)-3-isothiocyanato-2-methyl-phenyl]methyl]-2-methyl-piperazine-1-carboxylate,
cyclobutyl-[(2S)-4-[[5-(difluoromethyl)-3-isothiocyanato-2-methyl-phenyl]methyl]-2-methyl-piperazin-1-yl]methanone,
cyclopentyl-[(2S)-4-[(3-isothiocyanato-2,5-dimethyl-phenyl)methyl]-2-methyl-
- 10 piperazin-1-yl]methanone.