



(43) International Publication Date
5 February 2015 (05.02.2015)

(51) International Patent Classification:

C07C 217/44 (2006.01) A61K 31/13 (2006.01)
C07D 401/12 (2006.01) A61K 31/415 (2006.01)
C07D 413/12 (2006.01) A61K 31/435 (2006.01)
C07D 211/14 (2006.01) A61P 25/00 (2006.01)
C07D 295/096 (2006.01)

(21) International Application Number:

PCT/EP2014/066223

(22) International Filing Date:

29 July 2014 (29.07.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

13382310.4 30 July 2013 (30.07.2013) EP

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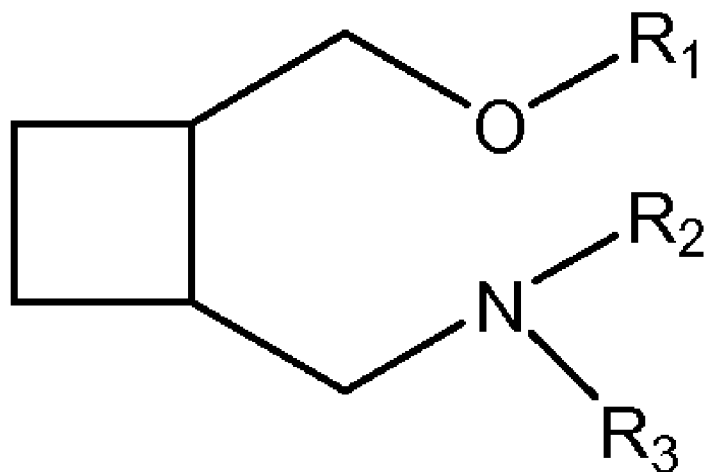
(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: 1,2-DISUBSTITUTED CYCLOBUTYL COMPOUNDS



(I)

(57) Abstract: The invention refers to com-
pounds of general formula (I) wherein the vari-
ables take various meanings, pharmaceutical
compositions containing them and their use in
medicine, particularly in pain therapy.



1,2-DISUBSTITUTED CYCLOBUTYL COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to compounds, pharmaceutical compositions
5 containing them and their use in medicine, particularly in pain therapy.

BACKGROUND

The search for new therapeutic agents has been greatly aided in recent years
by better understanding of the structure of proteins and other biomolecules associated
10 with target diseases. One important class of these proteins are the sigma (σ) receptors,
cell surface receptors of the central nervous system (CNS) which may be related to the
dysphoric, hallucinogenic and cardiac stimulant effects of opioids. From studies of the
biology and function of sigma receptors, evidence has been presented that sigma
receptor ligands may be useful in the treatment of psychosis and movement disorders
15 such as dystonia and tardive dyskinesia, and motor disturbances associated with
Huntington's chorea or Tourette's syndrome and in Parkinson's disease (Walker, J.M.
et al, Pharmacological Reviews, 1990, 42, 355). It has been reported that the known
sigma receptor ligand rimcazole clinically shows effects in the treatment of psychosis
(Snyder, S.H., Largent, B.L. J. Neuropsychiatry 1989, 1, 7). The sigma binding sites
20 have preferential affinity for the dextrorotatory isomers of certain opiate
benzomorphans, such as SKF-10047, (+)-cyclazocine, and (+)-pentazocine and also
for some narcoleptics such as haloperidol.

"The sigma receptor/s" as used in this application is/are well known and defined
using the following citation: This binding site represents a typical protein different from
25 opioid, NMDA, dopaminergic, and other known neurotransmitter or hormone receptor
families (G. Ronsisvalle et al. Pure Appl. Chem. 73, 1499-1509 (2001)).

The sigma receptor has at least two subtypes, which may be discriminated by
stereoselective isomers of these pharmacoactive drugs. SKF-10047 has nanomolar
affinity for the sigma 1 (σ -1) site, and has micromolar affinity for the sigma 2 (σ -2) site.
30 Haloperidol has similar affinities for both subtypes.

The Sigma-1 receptor is a non-opiaceous type receptor expressed in numerous
adult mammal tissues (e.g. central nervous system, ovary, testicle, placenta, adrenal
gland, spleen, liver, kidney, gastrointestinal tract) as well as in embryo development
from its earliest stages, and is apparently involved in a large number of physiological
35 functions. Its high affinity for various pharmaceuticals has been described, such as for
SKF-10047, (+)-pentazocine, haloperidol and rimcazole, among others, known ligands
with analgesic, anxiolytic, antidepressive, anti-amnesic, antipsychotic and
neuroprotective activity. Sigma-1 receptor is of great interest in pharmacology in view
of its possible physiological role in processes related to analgesia, anxiety, addiction,
40 amnesia, depression, schizophrenia, stress, neuroprotection, psychosis and mood
disorders [Kaiser et al (1991) Neurotransmissions 7 (1): 1-5], [Walker, J.M. et al,

Pharmacological Reviews, 1990, 42, 355], [Bowen W.D. (2000) Pharmaceutica Acta Helvetiae 74: 211-218] and Hayashi, T. et al, Drugs of the Future 2009, 34 (2), 137].

The Sigma-2 receptor is also expressed in numerous adult mammal tissues (e.g. nervous system, immune system, endocrine system, liver, kidney). Sigma-2
5 receptors can be components in a new apoptosis route that may play an important role in regulating cell proliferation or in cell development. This route seems to consist of Sigma-2 receptors joined to intracellular membranes, located in organelles storing calcium, such as the endoplasmic reticulum and mitochondria, which also have the ability to release calcium from these organelles. The calcium signals can be used in the
10 signaling route for normal cells and/or in induction of apoptosis.

Sigma-2 receptor ligands, specially agonists, can be used as antineoplastic agents at doses inducing apoptosis or at sub-toxic doses in combination with other antineoplastic agents to revert the resistance to the drug, thereby allowing using lower doses of the antineoplastic agent and considerably reducing its adverse effects.

15 Additionally, Sigma-2 receptor ligands, specially antagonists, can be useful as agents for improving the weakening effects of delayed dyskinesia appearing in patients due to chronic treatment of psychosis with typical antipsychotic drugs, such as haloperidol. Sigma-2 receptors also seem to play a role in certain degenerative disorders in which blocking these receptors could be useful.

20 Endogenous sigma ligands are not known, although progesterone has been suggested to be one of them. Possible sigma-site-mediated drug effects include modulation of glutamate receptor function, neurotransmitter response, neuroprotection, behavior, and cognition (Quirion, R. et al. Trends Pharmacol. Sci., 1992, 13:85-86). Most studies have implied that sigma binding sites (receptors) are plasmalemmal
25 elements of the signal transduction cascade. Drugs reported to be selective sigma ligands have been evaluated as antipsychotics (Hanner, M. et al. Proc. Natl. Acad. Sci., 1996, 93:8072-8077). The existence of sigma receptors in the CNS, immune and endocrine systems have suggested a likelihood that it may serve as link between the three systems.

30 In view of the potential therapeutic applications of agonists or antagonists of the sigma receptor, a great effort has been directed to find effective ligands. Different sigma receptor ligands have been reported.

For instance, WO2007/098961A1 describes 4,5,6,7-
35 tetrahydrobenzo[b]thiophene derivatives having pharmacological activity towards the sigma receptor.

Spiro[benzopyran] and spiro[benzofuran] derivatives with pharmacological activity on sigma receptors are disclosed in WO2007/121976A1.

Pyrazole derivatives presenting a pyrazole group condensed with a cycloalkyl
40 ring have been also reported as sigma ligands in WO2006/021463A1.

WO2008/055932A1 and WO2008/055933A1 deal with 1,2,4- and 1,2,3-triazole compounds, respectively, having activity towards sigma receptors.

WO2009/071657A1 also reports tricyclic triazolic compounds having activity towards sigma receptors.

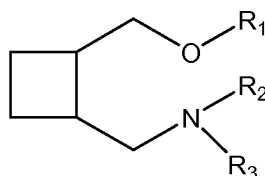
5 WO2008/015266A1 discloses cyclobutyl compounds with sigma receptor binding.

In spite of this background, there is still a need to find further compounds that have pharmacological activity towards the sigma receptor, preferably being both effective and selective as well as having potentially good "drugability" properties, i.e. good pharmaceutical properties related to administration, distribution, metabolism and excretion.

BRIEF DESCRIPTION OF THE INVENTION

15 The present invention discloses novel 1,2-disubstituted cyclobutyl compounds with great affinity to sigma receptors which might be used for the treatment and/or prophylaxis of sigma related disorders or diseases.

Specifically, it is an object of the present invention a compound of general formula (I), or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof:



20

(I)

wherein

R₁ is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, and substituted or unsubstituted non-aromatic heterocyclylalkyl;

R₂ and **R₃**, identical or different, are selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted alkenyl;

30

or

R_2 and R_3 form together with the bridging nitrogen atom to which they are attached a substituted or unsubstituted non-aromatic heterocyclyl.

Another object of the invention refers to different processes for the preparation of a compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof.

Another object of the invention refers to a medicament or pharmaceutical composition comprising at least one compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof and at least one pharmaceutically acceptable excipient.

Another object of the invention refers to a compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, for use as a medicament, particularly for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition.

Another object of the invention refers to the use of a compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, in the manufacture of a medicament for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition.

Another object of the invention refers to a method for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition, the method comprising administering to the subject in need of such a treatment or prophylaxis a therapeutically effective amount of a compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof.

In one embodiment, said sigma receptor-mediated disease or condition is specifically a sigma-1 mediated disease or condition. Within the group of diseases or conditions mediated by sigma receptor for which the compounds of the invention are useful, the following may be cited: pain, diarrhoea, lipoprotein disorders, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, obesity, migraine, arthritis, hypertension, arrhythmia, ulcer, glaucoma, learning, memory and attention deficits, cognition disorders, neurodegenerative diseases, demyelinating diseases, addiction to drugs and chemical substances including cocaine, amphetamine, ethanol and nicotine; tardive dyskinesia, stroke including ischemic stroke, epilepsy, stress, cancer, psychotic conditions, in particular depression, anxiety or schizophrenia; inflammation or autoimmune diseases. According to one preferred embodiment, the compounds of the invention are used for the treatment and/or prophylaxis of pain, especially neuropathic pain, inflammatory pain or other pain conditions involving allodynia and/or hyperalgesia.

According to one preferred embodiment, the compounds of this invention effectively and selectively inhibit the Sigma-1 receptor. According to one more preferred embodiment, the compounds of the present invention are selective Sigma-1 antagonists.

These aspects and preferred embodiments thereof are additionally also defined hereinafter in the detailed description, as well as in the claims.

DETAILED DESCRIPTION OF THE INVENTION

5 In the context of the present invention, the following terms have the meaning detailed below.

"Alkyl" refers to a straight or branched hydrocarbon chain radical containing no unsaturation, and which is attached to the rest of the molecule by a single bond. Typical alkyl groups have from 1 to about 12, 1 to about 8, or 1 to about 6 carbon atoms, e. g., methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, etc. If substituted by cycloalkyl, it corresponds to a "cycloalkylalkyl" radical, such as cyclopropyl methyl. If substituted by aryl, it corresponds to an "arylalkyl" radical, such as benzyl, benzhydryl or phenethyl. If substituted by heterocyclyl, it corresponds to a "heterocyclylalkyl" radical.

15 "Alkenyl" refers to a straight or branched hydrocarbon chain radical containing at least two carbon atoms and at least one unsaturation, and which is attached to the rest of the molecule by a single bond. Typical alkenyl radicals have from 2 to about 12, 2 to about 8 or 2 to about 6 carbon atoms. In a particular embodiment, the alkenyl group is vinyl, 1-methyl-ethenyl, 1-propenyl, 2-propenyl, or butenyl.

20 "Alkynyl" refers to a straight or branched hydrocarbon chain radical containing at least two carbon atoms and at least one carbon-carbon triple bond, and which is attached to the rest of the molecule by a single bond. Typical alkynyl radicals have from 2 to about 12, 2 to about 8 or 2 to about 6 carbon atoms. In a particular embodiment, the alkynyl group is ethynyl, propynyl (e.g. 1-propynyl, 2-propynyl), or butynyl (e.g. 1-butynyl, 2-butynyl, 3-butynyl).

25 "Cycloalkyl" refers to an alicyclic hydrocarbon. Typical cycloalkyl radicals contain from 1 to 4 separated and/or fused rings and from 3 to about 18 carbon atoms, preferably from 3 to 10 carbon atoms, such as cyclopropyl, cyclohexyl or adamantyl. In a particular embodiment, the cycloalkyl radical contains from 3 to about 6 carbon atoms.

30 "Aryl" refers to single and multiple ring radicals, including multiple ring radicals that contain separate and/or fused aryl groups. Typical aryl groups contain from 1 to 3 separated and/or fused rings and from 6 to about 18 carbon ring atoms, preferably from 6 to about 14 carbon ring atoms, such as phenyl, naphthyl, biphenyl, indenyl, fenanthryl or anthracyl radical.

35 "Heteroaryl" refers to heteroaromatic groups containing from 1 to 3 separated and/or fused rings and from 3 to about 18 ring atoms. Preferably heteroaromatic groups contain from 5 to about 10 ring atoms. Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolyl including 8-quinolyl, isoquinolyl, pyridyl, pyrazinyl, pyrazolyl, pyrimidinyl, furyl, pyrrolyl,

40

thienyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, imidazolyl, indolyl, isoindolyl, indazolyl, indoliziny, phthalazinyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, pyridazinyl, triazinyl, cinnolinyl, benzimidazolyl, benzofuranyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazoliny, quinoxaliny, naphthyridiny, and furopyridiny.

“Non-aromatic Heterocyclyl” refers to heteroalicyclic groups containing from 1 to 3 separated and/or fused rings and from 3 to about 18 ring atoms. Preferably heteroalicyclic groups contain from 5 to about 10 ring atoms. Suitable heteroalicyclic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., pyrrolidiny, tetrahydrofuryl, dihydrofuryl, tetrahydrothienyl, tetrahydrothiopyranyl, piperidyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidiny, oxepanyl, thiepanyl, azepiny, oxazepiny, diazepiny, thiazepiny, 1,2,3,6-tetrahydropyridyl, 2-pyrroliny, 3-pyrroliny, indoliny, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazoliny, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, pyrazolidiny, imidazoliny, imidazolidiny, 3-azabicyclo[3.1.0]hexyl, 3-azabicyclo[4.1.0]heptyl, 3H-indolyl, and quinoliziny.

The groups above mentioned may be substituted at one or more available positions by one or more suitable groups such as OR', =O, SR', SOR', SO₂R', OSO₂R', OSO₃R', NO₂, NHR', N(R')₂, =N-R', N(R')COR', N(COR')₂, N(R')SO₂R', N(R')C(=NR')N(R')R', N₃, CN, halogen, COR', COOR', OCOR', OCOOR', OCONHR', OCON(R')₂, CONHR', CON(R')₂, PO(OR')₂, PO(OR')R', C₁-C₁₂ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, aryl, heteroaryl and non-aromatic heterocyclic group, wherein each of the R' groups is independently selected from the group consisting of hydrogen, OH, NH₂, SH, CN, halogen, COH, COalkyl, COOH, C₁-C₁₂ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, aryl, heteroaryl and non-aromatic heterocyclic group.

“Halogen”, “halo” or “hal” refers to bromo, chloro, iodo or fluoro.

The term “salt” must be understood as any form of a compound used in accordance with this invention in which said compound is in ionic form or is charged and coupled to a counter-ion (a cation or anion) or is in solution. This definition also includes quaternary ammonium salts and complexes of the molecule with other molecules and ions, particularly, complexes formed via ionic interactions. The definition includes in particular physiologically acceptable salts; this term must be understood as equivalent to “pharmacologically acceptable salts” or “pharmaceutically acceptable salts”.

The term “pharmaceutically acceptable salts” in the context of this invention means any salt that is tolerated physiologically (normally meaning that it is not toxic, particularly, as a result of the counter-ion) when used in an appropriate manner for a treatment, applied or used, particularly, in humans and/or mammals. These physiologically acceptable salts may be formed with cations or bases and, in the context of this invention, are understood to be salts formed by at least one compound used in accordance with the invention –normally an acid (deprotonated)– such as an

anion and at least one physiologically tolerated cation, preferably inorganic, particularly when used on humans and/or mammals. Salts with alkali and alkali earth metals are preferred particularly, as well as those formed with ammonium cations (NH_4^+). Preferred salts are those formed with (mono) or (di)sodium, (mono) or (di)potassium, magnesium or calcium. These physiologically acceptable salts may also be formed with anions or acids and, in the context of this invention, are understood as being salts formed by at least one compound used in accordance with the invention – normally protonated, for example in nitrogen – such as a cation and at least one physiologically tolerated anion, particularly when used on humans and/or mammals. This definition specifically includes in the context of this invention a salt formed by a physiologically tolerated acid, i.e. salts of a specific active compound with physiologically tolerated organic or inorganic acids – particularly when used on humans and/or mammals. Examples of this type of salts are those formed with: hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid or citric acid.

The term “solvate” in accordance with this invention should be understood as meaning any form of the compound in accordance with the invention in which said compound is bonded by a non-covalent bond to another molecule (normally a polar solvent), including especially hydrates and alcoholates, like for example, methanolate. A preferred solvate is the hydrate.

Any compound that is a prodrug of a compound of formula (I) is also within the scope of the invention. The term “prodrug” is used in its broadest sense and encompasses those derivatives that are converted in vivo to the compounds of the invention. Examples of prodrugs include, but are not limited to, derivatives and metabolites of the compounds of formula (I) that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Preferably, prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by Burger “Medicinal Chemistry and Drug Discovery 6th ed. (Donald J. Abraham ed., 2001, Wiley) and “Design and Applications of Prodrugs” (H. Bundgaard ed., 1985, Harwood Academic Publishers).

Any compound referred to herein is intended to represent such specific compound as well as certain variations or forms. In particular, compounds referred to herein may have asymmetric centres and therefore exist in different enantiomeric or diastereomeric forms. Thus, any given compound referred to herein is intended to represent any one of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, and mixtures thereof. Likewise, stereoisomerism or geometric isomerism about the double bond is also possible, therefore in some cases the molecule could exist as (E)-isomer or (Z)-isomer (trans and cis isomers). If the molecule contains several double bonds, each double bond will have its own

stereoisomerism, that could be the same as, or different to, the stereoisomerism of the other double bonds of the molecule. Furthermore, compounds referred to herein may exist as atropisomers. All the stereoisomers including enantiomers, diastereoisomers, geometric isomers and atropisomers of the compounds referred to herein, and mixtures thereof, are considered within the scope of the present invention.

Furthermore, any compound referred to herein may exist as tautomers. Specifically, the term tautomer refers to one of two or more structural isomers of a compound that exist in equilibrium and are readily converted from one isomeric form to another. Common tautomeric pairs are enamine-imine, amide-imidic acid, keto-enol, lactam-lactim, etc.

Unless otherwise stated, the compounds of the invention are also meant to include isotopically-labelled forms i.e. compounds which differ only in the presence of one or more isotopically-enriched atoms. For example, compounds having the present structures except for the replacement of at least one hydrogen atom by a deuterium or tritium, or the replacement of at least one carbon by ^{13}C - or ^{14}C -enriched carbon, or the replacement of at least one nitrogen by ^{15}N -enriched nitrogen are within the scope of this invention.

The compounds formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. Purity levels for the drug substance are preferably above 50%, more preferably above 70%, most preferably above 90%. In a preferred embodiment it is above 95% of the compound of formula (I), or of its salts, solvates or prodrugs.

As used herein, the terms "treat", "treating" and "treatment" include the eradication, removal, reversion, alleviation, modification, or control of a disease or condition after its onset.

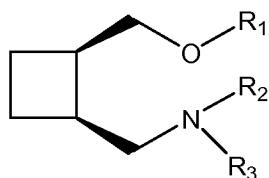
As used herein, the terms "prevention", "preventing", "preventive" "prevent" and "prophylaxis" refer to the capacity of a therapeutic to avoid, minimize or difficult the onset or development of a disease or condition before its onset.

Therefore, by "treating" or "treatment" and/or "preventing" or "prevention", as a whole, is meant at least a suppression or an amelioration of the symptoms associated with the condition afflicting the subject, where suppression and amelioration are used in a broad sense to refer to at least a reduction in the magnitude of a parameter, e.g., symptom associated with the condition being treated. As such, the method of the present invention also includes situations where the condition is completely inhibited, e.g., prevented from happening, or stopped, e.g., terminated, such that the subject no longer experiences the condition.

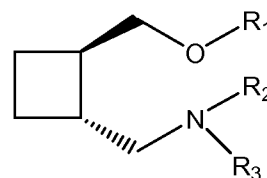
The inventors of the present invention have observed that 1,2-disubstituted cyclobutyl compounds with general formula (I) as defined above unexpectedly show an affinity for Sigma-1 receptor ranging from good to excellent. These compounds are

therefore particularly suitable as pharmacologically active agents in medicaments for the prophylaxis and/or treatment of disorders or diseases related to Sigma receptors, preferably related to Sigma-1 receptor.

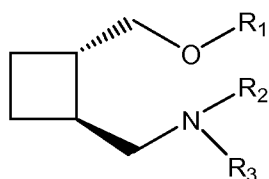
All the diastereoisomers of general formula (I), as depicted below are included
5 within the scope of the invention.



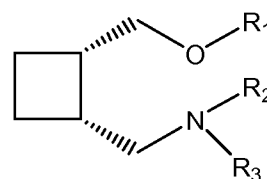
(Ia)



(Ib)



(Ic)



(Id)

In a preferred embodiment the compounds of the invention are compounds according to general formula (Ia).

In another preferred embodiment the compounds of the invention are compounds according to general formula (Ib).

10 In another preferred embodiment the compounds of the invention are compounds according to general formula (Ic).

In another preferred embodiment the compounds of the invention are compounds according to general formula (Id).

15 In a particular embodiment, R₁ in the compounds of general formula (I) is selected from the group consisting of substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

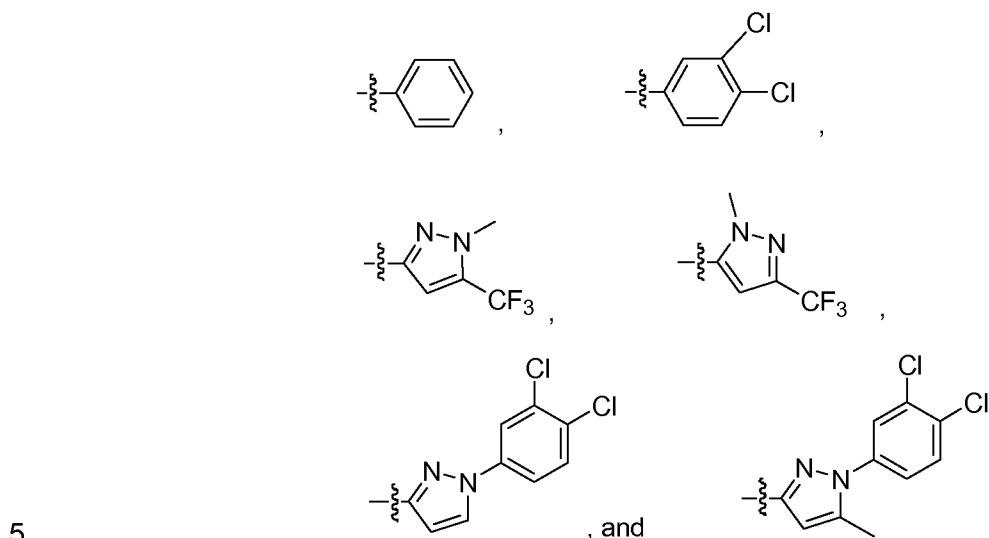
In a more particular embodiment, R₁ is selected from the group consisting of substituted or unsubstituted C₆-C₁₄ aryl and substituted or unsubstituted 5- to 10-membered heteroaryl.

20 In preferred variants of the invention, R₁ is substituted or unsubstituted C₆-C₁₄ aryl, more preferably substituted or unsubstituted phenyl. Preferred substituents for the aryl groups representing R₁ are halogen such as chloro.

In preferred variants of the invention, R₁ is substituted or unsubstituted 5- to 10-membered heteroaryl (i.e. an heteroaromatic group), more preferably substituted or
25 unsubstituted pyrazole. Preferred substituents for the heterocyclyl groups representing R₁ are halogen (preferably chloro), methyl, trifluoromethyl, optionally substituted aryl

(preferably phenyl, which may be optionally substituted for instance with halogen such as chloro).

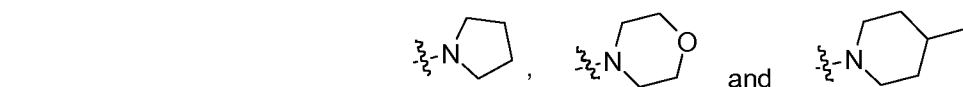
In a particular embodiment, R₁ in the compounds of general formula (I) is selected from the group consisting of:



10 In a particular embodiment R₂ and R₃ are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, and substituted or unsubstituted cycloalkyl, or R₂ and R₃ together with the bridging nitrogen atom form a substituted or unsubstituted non-aromatic heterocyclyl.

15 In a more particular embodiment, R₂ and R₃ are independently selected from the group consisting of hydrogen and substituted or unsubstituted C₁-C₆ alkyl, or R₂ and R₃ together with the bridging nitrogen atom form a substituted or unsubstituted 5- to 10-membered non-aromatic heterocyclyl, preferably a substituted or unsubstituted 5-, 6- or 7-membered non-aromatic heterocyclyl.

20 Preferably, R₂ and R₃ are independently selected from the group consisting of hydrogen and substituted or unsubstituted methyl or ethyl, or R₂ and R₃ together with the bridging nitrogen atom form a substituted or unsubstituted pyrrolidinyl, morpholinyl or piperidinyl, Particular heterocyclyl radicals formed by R₂ and R₃ together with the bridging nitrogen atom are pyrrolidinyl, morpholinyl and 4-methylpiperidinyl. Thus, in a particular embodiment, R₂ and R₃ in the compounds of general formula (I) together with the bridging nitrogen atom form a non-aromatic heterocyclyl selected from the group consisting of:



In additional preferred embodiments, the preferences described above for the different substituents are combined. The present invention is also directed to such combinations of preferred substitutions in the formula (I) above.

Particular individual compounds of the invention falling under formula (I) include the compounds listed below:

- [1] 1-(((1S,2R)-2-(Phenoxymethyl)cyclobutyl)methyl)pyrrolidine
- [2] 4-(((1S,2R)-2-(Phenoxymethyl)cyclobutyl)methyl)morpholine
- 5 [3] 4-methyl-1-(((1S,2R)-2-(Phenoxymethyl)cyclobutyl)methyl)piperidine
- [4] 1-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)pyrrolidine
- [5] 4-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)morpholine
- [6] 1-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)-4-methylpiperidine
- 10 [7] 4-Methyl-1-(((1S,2R)-2-(((1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)piperidine
- [8] 4-Methyl-1-(((1S,2R)-2-(((1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)methyl)piperidine
- [9] 1-Methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole
- 15 [10] 4-(((1S,2R)-2-(((1-Methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine
- [11] 1-Methyl-5-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-3-(trifluoromethyl)-1H-pyrazole
- 20 [12] 4-(((1S,2R)-2-(((1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)methyl)morpholine
- [13] 1-(3,4-Dichlorophenyl)-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole
- [14] 4-(((1S,2R)-2-(((1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine
- 25 [15] 1-(3,4-Dichlorophenyl)-5-methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole
- [16] 4-(((1S,2R)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine
- 30 [17] 4-(((1S,2R)-2-(Phenoxymethyl)cyclobutyl)methyl)morpholine hydrochloride
- [18] 1-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)pyrrolidine hydrochloride
- [19] 4-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)morpholine hydrochloride
- 35 [20] 1-(((1S,2R)-2-((3,4-dichlorophenoxy)methyl)cyclobutyl)methyl)-4-methylpiperidine hydrochloride
- [21] 1-Methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride

- [22] 4-(((1S,2R)-2-(((1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine hydrochloride
- [23] 1-Methyl-5-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-3-(trifluoromethyl)-1H-pyrazole hydrochloride
- 5 [24] 4-(((1S,2R)-2-(((1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)methyl)morpholine hydrochloride
- [25] 1-(3,4-Dichlorophenyl)-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole hydrochloride
- [26] 4-(((1S,2R)-2-(((1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine hydrochloride
- 10 [27] 1-(3,4-Dichlorophenyl)-5-methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole hydrochloride
- [28] 1-(3,4-Dichlorophenyl)-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole
- 15 [29] 1-(3,4-Dichlorophenyl)-5-methyl-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole
- [30] 4-(((1R,2R)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine
- [31] 1-Methyl-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole
- 20 [32] 1-Methyl-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride
- [33] 1-Methyl-3-(((1S,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole
- 25 [34] 1-Methyl-3-(((1S,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride
- [35] 1-Methyl-3-(((1S,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole
- [36] 4-(((1S,2S)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine
- 30 [37] N,N-Diethyl-N-(((1S,2S)-2-(phenoxy)methyl)cyclobutyl)methyl)ethanamine
- [38] 1-methyl-3-(((1S,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride
- 35 [39] N,N-Diethyl-N-(((1S,2S)-2-(phenoxy)methyl)cyclobutyl)methyl)ethanamine hydrochloride

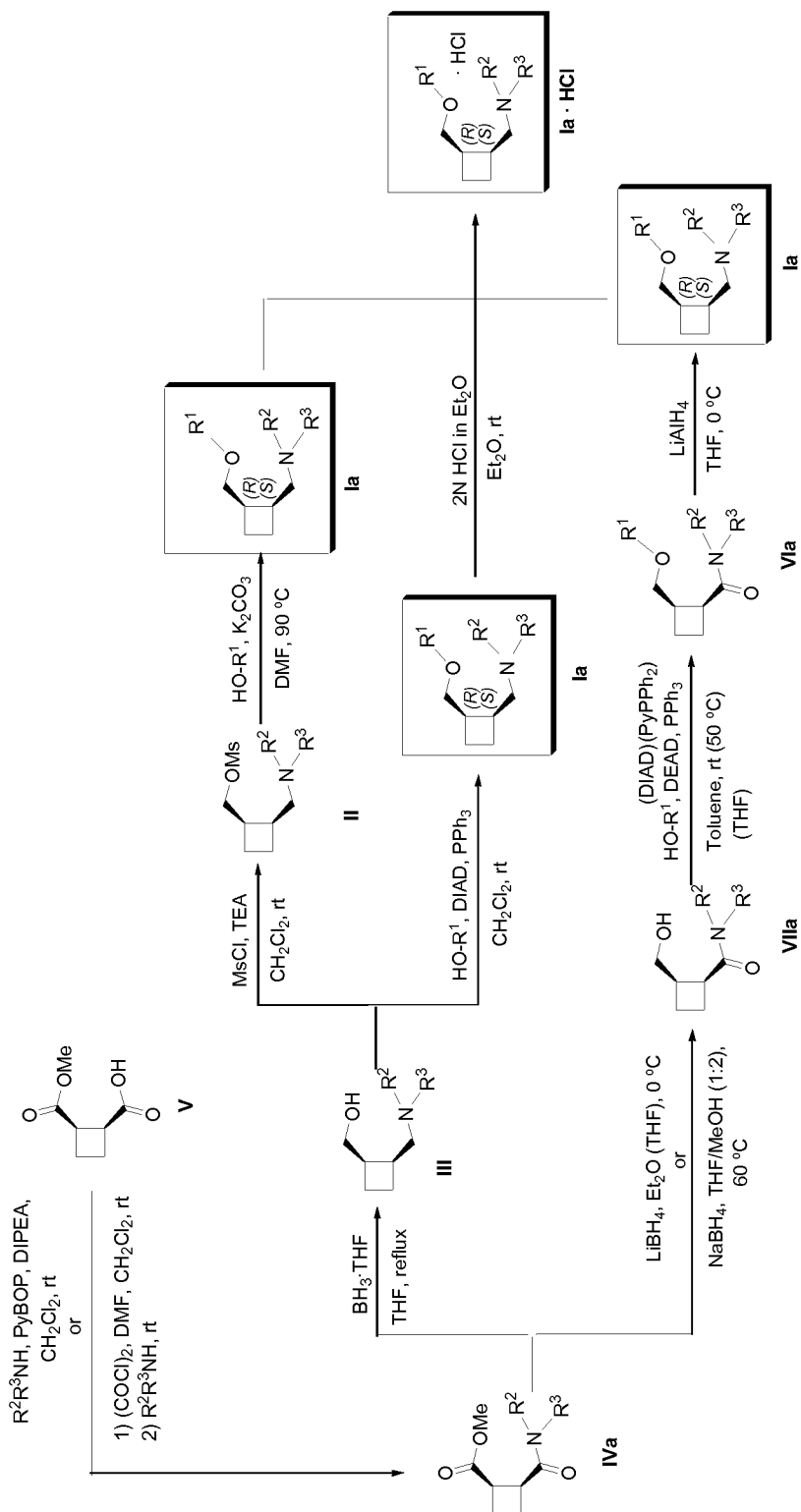
or a solvate or prodrug thereof as well as any pharmaceutically acceptable salt of the free-base compounds.

The compounds of general formula (I) and the corresponding diastereoisomers above disclosed (Ia, Ib, Ic and/or Id) can be obtained by available synthetic procedures. For instance, they can be prepared in accordance with the following general procedures.

5

Synthesis of (R,S)-stereoisomers: Compounds of general formula (Ia) (Scheme 1)

Scheme 1



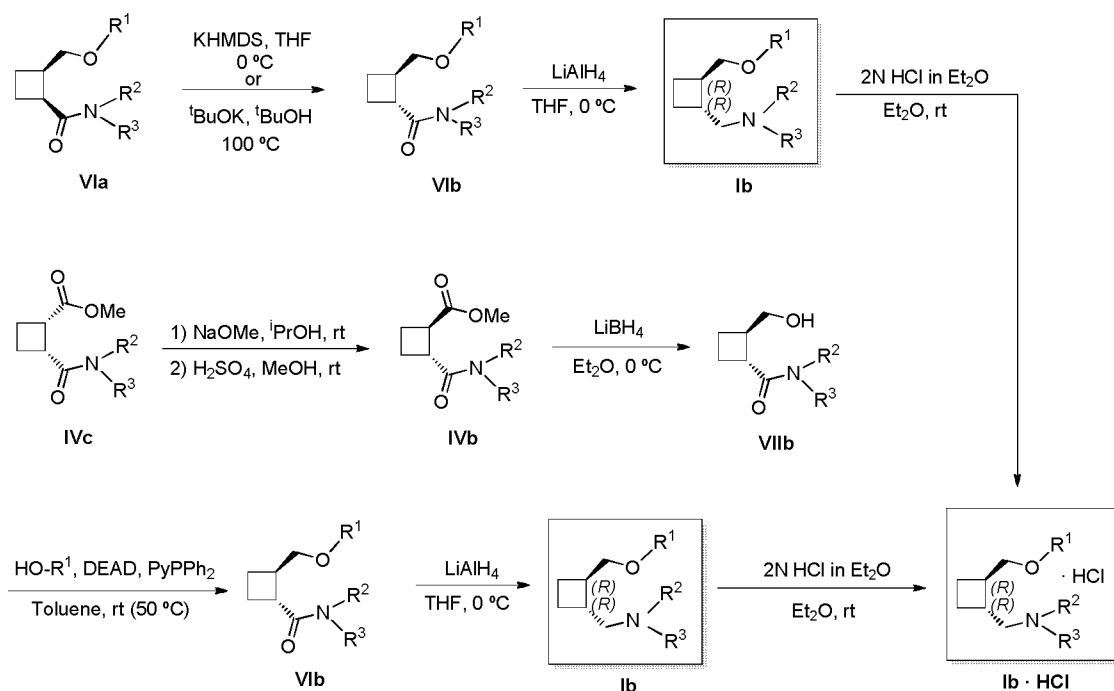
Compounds of general formula **(Ia)** can be prepared through reactions of mesylates **II** with aromatic alcohols R^1OH in the presence of potassium carbonate as a base and DMF (dimethylformamide) as a solvent. In turn, mesylates can be prepared by reaction of alcohols **III** with mesyl chloride and triethylamine. Alcohols **III** come from total reduction of compounds **IVa** with BH_3 in refluxing THF (tetrahydrofuran). Compound **IVa** is prepared from half ester **V**, which is synthesized according to S. Izquierdo, F. Rúa, A. Sbai, T. Parella, Á. Álvarez-Larena, V. Branchadell, R. M. Ortuño, *J. Org. Chem.* **2005**, *70*, 7963-7971. Compound **IVa** is obtained from **V** by standard peptide coupling procedures, i.e., reaction with a secondary amine R^2R^3NH in the presence of PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate) and DIPEA (*N,N*-diisopropylethylamine) or, alternatively, via acyl chloride prepared by reaction of **V** with oxalyl chloride and in situ reaction with the amine.

Alternatively, compounds of general formula **(Ia)** can be synthesized via a Mitsunobu reaction between alcohols **III** and an aromatic alcohol R^1OH in the presence of DIAD (diisopropyl azodicarboxylate) and PPh_3 .

A third alternative route to synthesize compounds of general formula **(Ia)** consists in reduction of amides **VIa** with $LiAlH_4$ in THF at 0 °C. Amides **VIa** come from Mitsunobu reaction of alcohols **VIIa** with aromatic alcohols R^1OH in the presence of DIAD/ $PyPPh_2$ ($PyPPh_2$: 2-pyridyldiphenylphosphine) or DEAD/ PPh_3 (DEAD: diethyl azodicarboxylate). Alcohols **VIIa** are prepared by selective reduction of the methyl ester **IVa** by using $LiBH_4$ in Et_2O or THF at 0 °C, or $NaBH_4$ in THF-MeOH.

Synthesis of (R,R)-stereoisomers: Compounds of general formula (Ib) (Scheme 2)

Scheme 2

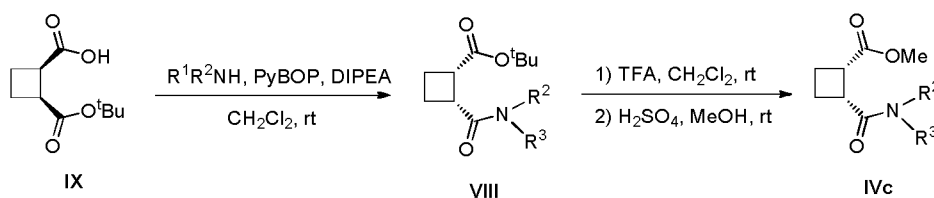


Compounds of general formula (**Ib**) result from reduction of amides **Vlb** with LiAlH₄. Amides **Vlb** are obtained through epimerization of **Vla** by using KHMDS (potassium hexamethyldisilazane) in THF at 0 °C or ^tBuOK in ^tBuOH at 100 °C.

Alternatively, compounds of general formula (**Ib**) can be prepared through the reduction of amides **Vlb** with LiAlH₄ in THF at 0 °C. Compounds **Vlb** result from Mitsunobu reaction of alcohols **VIIb** with aromatic alcohols R¹OH in the presence of DEAD and PyPPh₂. Alcohols **VIIb** result from selective reduction of the methyl ester in **IVb** with LiBH₄ in Et₂O at 0 °C. Compound **IVb** is prepared through epimerization of **IVc** with MeONa in ⁱPrOH followed by treatment with H₂SO₄ in MeOH.

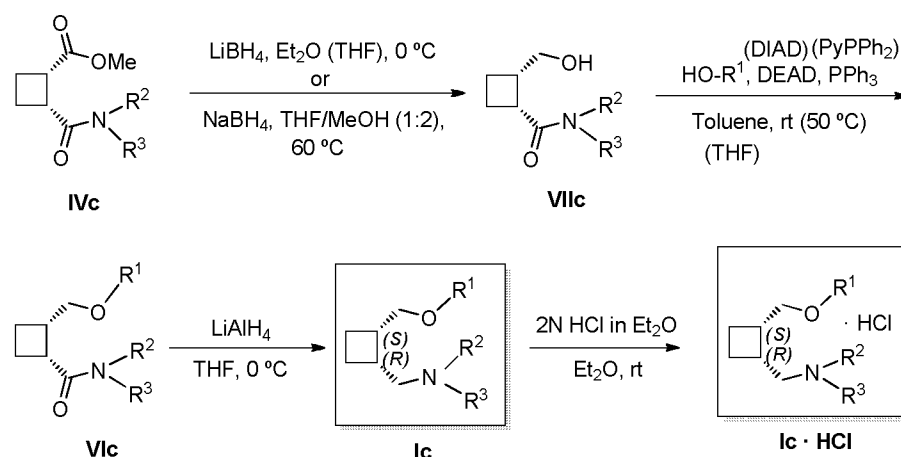
Compound **IVc** is synthesized from amino ester **VIII** (Scheme 3) by elimination of the *tert*-butyl ester with TFA (trifluoroacetic acid) and subsequent Fisher esterification of the resulting acid with MeOH and H₂SO₄. Compound **VIII** is obtained by peptide coupling of R¹R²NH secondary amines (PyBOP, DIPEA) with acid **IX**, which is prepared as previously described in S. Izquierdo, F. Rúa, A. Sbai, T. Parella, Á. Álvarez-Larena, V. Branchadell, R. M. Ortuño, *J. Org. Chem.* **2005**, *70*, 7963-7971.

Scheme 3



Synthesis of (S,R)-stereoisomers: Compounds of general formula (Ic) (Scheme 4)

Scheme 4



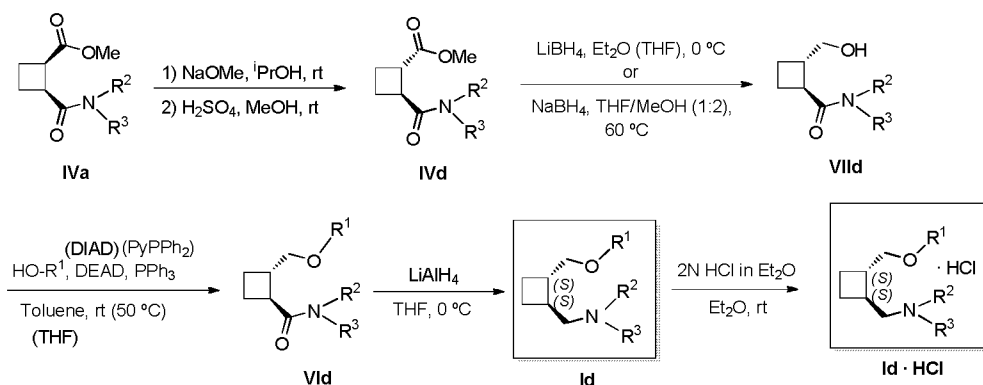
5

This route is similar to one of the synthetic pathways in Scheme 1 to prepare compounds of general formula (Ia). Compounds of general formula (Ic) result from reduction of amides VIc with LiAlH₄ in THF at 0 °C. Amides VIc are obtained through Mitsunobu reaction of alcohols VIc with aromatic alcohol R¹OH in the presence of DIAD/PyPPh₂ or DEAD/PPh₃. Alcohols VIc are prepared by selective reduction of the methyl ester IVc by using LiBH₄ in Et₂O or THF at 0 °C, or NaBH₄ in THF-MeOH.

10

Synthesis of (S,S)-stereoisomers: Compounds of general formula (Id) (Scheme 5)

Scheme 5



15

The synthesis is similar than that depicted in Scheme 2 for (*R,R*)-compounds **lb**. Compounds of general formula (**ld**) can be prepared through the reduction of amides **Vld** with LiAlH₄ in THF at 0 °C. Compounds **Vld** result from Mitsunobu reaction of alcohols **Vlld** with aromatic alcohol R¹OH, in the presence of DEAD and PyPPh₂.
5 Alcohols **Vlld** result from selective reduction of the methyl ester in **IVd** with LiBH₄ in Et₂O at 0 °C. Compound **IVd** is prepared through epimerization of **IVa** with MeONa in ⁱPrOH followed by treatment with H₂SO₄ in MeOH.

10 Additionally, the processes defined above may include the transformation of any compound (starting, intermediate or final) in a salt thereof. In a particular embodiment the processes further comprise the transformation of the compound of general formula (I) or its corresponding diastereoisomers (Ia, Ib, Ic and/or Id) obtained in a salt thereof such as the HCl salt. For example, the hydrochloride salts **Ia·HCl**, **Ib·HCl**, **Ic·HCl** and **Id·HCl** can be prepared by treatment of the corresponding amines with 2N HCl in Et₂O.

15 It is also an object of the invention to provide medicaments or pharmaceutical compositions comprising at least one compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, and at least one pharmaceutically acceptable excipient.

20 The term "excipient" refers to components of a drug compound other than the active ingredient (definition obtained from the European Medicines Agency- EMA). They preferably include a "carrier, adjuvant and/or vehicle". Carriers are forms to which substances are incorporated to improve the delivery and the effectiveness of drugs. Drug carriers are used in drug-delivery systems such as the controlled-release technology to prolong in vivo drug actions, decrease drug metabolism, and reduce drug toxicity. Carriers are also used in designs to increase the effectiveness of drug delivery to the target sites of pharmacological actions (U.S. National Library of Medicine. National Institutes of Health). Adjuvant is a substance added to a drug product formulation that affects the action of the active ingredient in a predictable way. Vehicle is an excipient or a substance, preferably without therapeutic action, used as a medium
25 to give bulk for the administration of medicines (Stedman's Medical Spellchecker, © 2006 Lippincott Williams & Wilkins). Such pharmaceutical carriers, adjuvants or vehicles can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like, excipients, disgregants, wetting agents or diluents. Suitable
30 pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. The selection of these excipients and the amounts to be used will depend on the form of application of the pharmaceutical composition.

40 The pharmaceutical compositions in accordance with the invention can be adapted in order to be administered by any route of administration, be it orally or parenterally, such as pulmonarily, nasally, rectally and/or intravenously. Therefore, the formulation in accordance with the invention may be adapted for topical or systemic application, particularly for dermal, subcutaneous, intramuscular, intra-articular,

intraperitoneal, pulmonary, buccal, sublingual, nasal, percutaneous, vaginal, oral or parenteral application. The preferred form of rectal application is by means of suppositories.

5 Suitable preparations for oral applications are tablets, pills, chewing gums, capsules, granules, drops or syrups. Suitable preparations for parenteral applications are solutions, suspensions, reconstitutable dry preparations or sprays.

The pharmaceutical composition of the invention may be formulated as deposits in dissolved form or in patches, for percutaneous application. Skin applications include ointments, gels, creams, lotions, suspensions or emulsions.

10 Another aspect of the invention is a method for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition, the method comprising administering to the subject in need of such a treatment or prophylaxis a therapeutically effective amount of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof.

15 Generally an effective administered amount of a compound used in the invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated, or the age, weight or mode of administration. However, active compounds will typically be administered once or more times a day, for example 1, 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.1 to 500
20 mg/kg/day.

Having described the present invention in general terms, it will be more easily understood by reference to the following examples which are presented as an illustration and are not intended to limit the present invention.

25 **Examples**

Synthesis of (R,S)-stereoisomers: Compounds of general formula (Ia)

According to the synthetic pathway disclosed in Scheme n° 1:

30 Half-ester **V** was prepared according to the previous procedure published in: S. Izquierdo, F. Rúa, A. Sbai, T. Parella, Á. Álvarez-Larena, V. Branchadell, R. M. Ortuño, *J. Org. Chem.* **2005**, *70*, 7963-7971.

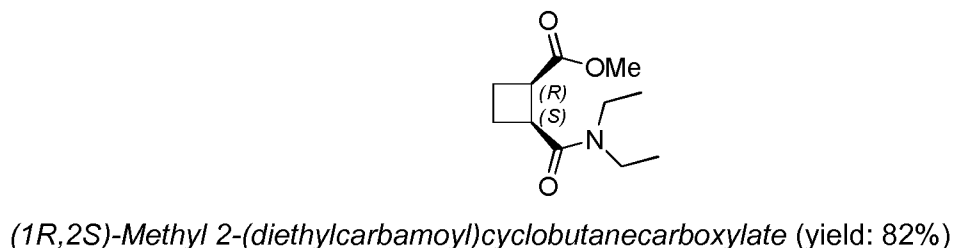
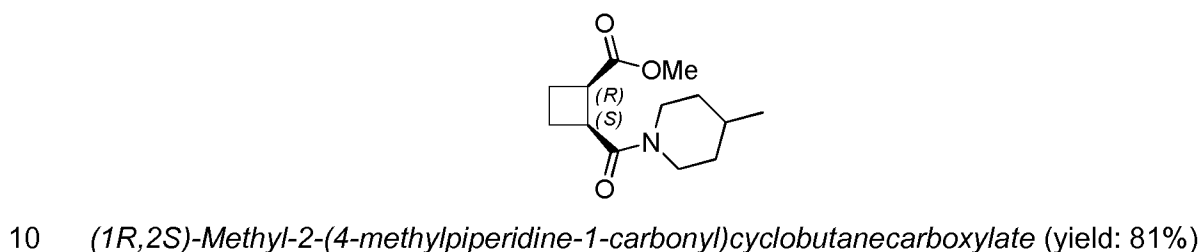
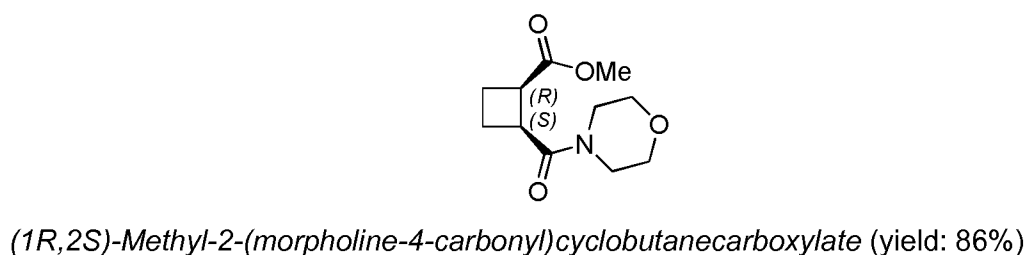
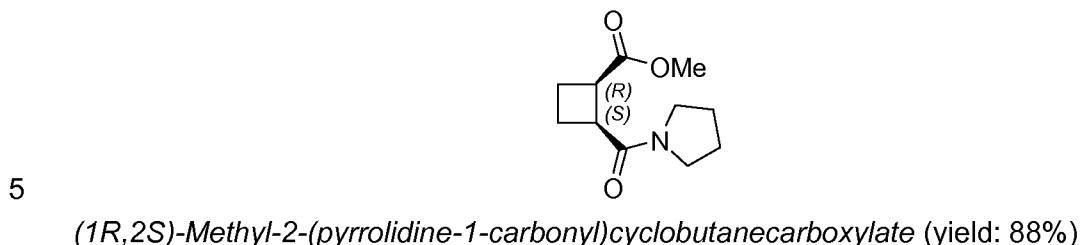
Coupling of the amine via acid chloride: Compounds IVa.

35 Under N₂ atmosphere, half-ester is dissolved in dichloromethane (0.1 M) at room temperature, followed by the addition of oxalyl chloride (1.1 eq., 2M in CH₂Cl₂) and a few drops DMF. The resulting mixture is stirred for 2 h and then pyrrolidine (3.0 eq.) is added. The reaction is allowed to evolve overnight.

After the specified time, HCl 2M (3.0 eq.) is added and the solution is stirred for 20 min. Then, more dichloromethane and water are added and the phases are

separated. The organic phase is washed with saturated aqueous solution of NaHCO_3 and brine, dried and evaporated under reduced pressure, to afford the final products as oils. (yield: 81-88%).

According to this procedure, the following compounds **IVa** were synthesized:

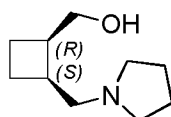


Reduction of IVa with borane: synthesis of amino alcohols III.

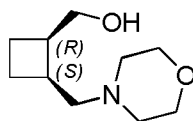
15 Amido ester **IVa** is dissolved in THF (0.5 M) and borane in THF solution (6 eq) is added slowly via syringe. Then the system is heated to reflux. After TLC completion (2-4 hour), the system is cooled at room temperature and MeOH is added very slowly. The crude is evaporated and washed with CH_2Cl_2 , AcOEt and water. The organic layer is dried over MgSO_4 and the solvents are removed to afford the corresponding

20 amino alcohols **III** as colourless oils. (yield: 66-70%)

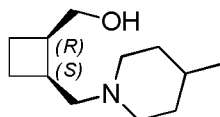
According to this procedure, the following compounds **III** were synthesized:



((1*R*,2*S*)-2-(Pyrrolidin-1-ylmethyl)cyclobutyl)methanol (yield: 70%)



((1*R*,2*S*)-2-(Morpholinomethyl)cyclobutyl)methanol (yield: 69%)



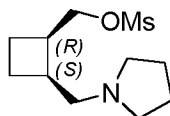
5 ((1*R*,2*S*)-2-((4-Methylpiperidin-1-yl)methyl)cyclobutyl)methanol (yield: 66%)

Mesylation of alcohols III: synthesis of mesylates II.

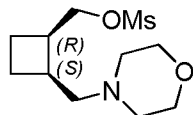
The corresponding alcohol is dissolved in dichloromethane (0.1 M) and the solution cooled down to 0°C with an ice bath. Then, are sequentially added triethylamine (2.0 eq.), DMAP (0.2 eq.) and, dropwise, MsCl (2.0 eq.). The mixture is stirred at this temperature for 2 h, when TLC analysis showed totally consumption of the starting material.

At this moment, water is added and the phases separated, extracting the aqueous phase with more dichloromethane. The whole organic layers are dried and evaporated under reduced pressure to afford the corresponding mesylates, which were used in the next step without further purification.

According to this procedure, the following compounds II were synthesized:

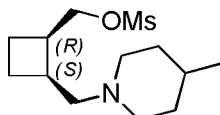


((1*R*,2*S*)-2-(Pyrrolidin-1-ylmethyl)cyclobutyl)methyl methanesulfonate



20

((1*R*,2*S*)-2-(Morpholinomethyl)cyclobutyl)methyl methanesulfonate



((1*R*,2*S*)-2-((4-Methylpiperidin-1-yl)methyl)cyclobutyl)methyl methanesulfonate

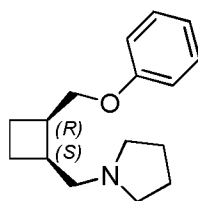
25 ***S_N2* reaction of mesylates II with phenol: synthesis of compounds of general formula (Ia) (Examples 1-3).**

Mesyate II is dissolved in DMF (0.1 M) under nitrogen atmosphere and aromatic alcohol (2.0 eq.) and potassium carbonate (3.0 eq.) are added. The mixture is

heated to 80°C and stirred overnight. Next day, water is added and the aqueous phase extracted with diethyl ether. The whole organic layers are dried and evaporated under reduced pressure to afford crude oil. Purification was achieved by flash column chromatography on silica gel providing compounds (**1a**) as colourless oils (Examples 1-3). (yield: 44-53%)

According to this procedure, the following compounds of general formula (**1a**) were synthesized:

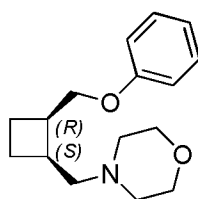
Example 1



1-(((1S,2R)-2-(Phenoxymethyl)cyclobutyl)methyl)pyrrolidine (yield: 53%)

¹H NMR (360 MHz, CDCl₃) δ 7.30 (m, 2H), 6.94 (m, 3H), 4.04 (t, J = 7.0 Hz, 2H), 2.86 (d, J = 10.0 Hz, 2H), 2.77 (m, 2H), 2.55 (t, J = 7.5 Hz, 2H), 2.14 (m, 2H), 2.03 (m, 2H), 1.91 (m, 2H), 1.76 (m, 4H).

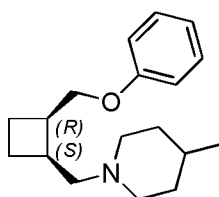
Example 2



4-(((1S,2R)-2-(Phenoxymethyl)cyclobutyl)methyl)morpholine (yield: 44%)

¹H NMR (360 MHz, CDCl₃) δ 7.28 (dd, J = 8.6, 7.5 Hz, 2H), 6.99 – 6.82 (m, 3H), 4.16 (dd, J = 9.3, 6.8 Hz, 1H), 4.01 (dd, J = 9.4, 6.4 Hz, 1H), 3.67 (t, J = 4.7 Hz, 4H), 2.81 (dd, J = 5.1, 2.9 Hz, 2H), 2.64 (dd, J = 12.3, 6.4 Hz, 1H), 2.52 – 2.29 (m, 4H), 2.24 – 2.02 (m, 2H), 1.82 (dd, J = 8.6, 3.8 Hz, 2H).

Example 3



4-Methyl-1-(((1S,2R)-2-(phenoxymethyl)cyclobutyl)methyl)piperidine (yield: 51%)

$^1\text{H NMR}$ (360 MHz, CDCl_3) δ 7.30 (m, 2H), 6.94 (m, 3H), 4.19 (dd, $J = 9.0, 6.0$ Hz, 1H), 4.03 (dd, $J = 9.0, 6.0$ Hz, 1H), 2.82 (m, 4H), 2.63 (dd, $J = 12.0, 6.0$ Hz, 1H), 2.14 (m, 2H), 1.91 (m, 4H), 1.61 (m, 2H), 1.26 (m, 3H), 0.92 (d, $J = 6.0$ Hz, 3H).

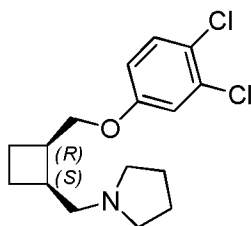
5 **Mitsunobu reaction: synthesis of compounds of general formula (Ia) (Examples 4-8)**

Starting primary alcohol, the corresponding ArOH (1.2 eq) and triphenylphosphine (1.5 eq) are dissolved in toluene (0.12 mM) under nitrogen atmosphere and the reaction is cooled to 0 °C with an ice bath. After five minutes of stirring, a 40% solution of DEAD (diethyl azodicarboxylate) in toluene (1.5 eq) is added dropwise during 10 minutes and the mixture is heated to 50 °C and stirred for 2 h. The reaction can also be carried out with DIAD (diisopropyl azodicarboxylate) as the azoderivative, and in dichloromethane or THF as the solvent.

Once the reaction has come to an end, the crude mixture is set inside the fridge overnight and the resulting white precipitate is filtered off. The filtrate is evaporated under reduced pressure and the remaining orange oil is purified by flash column chromatography in silica gel (hexanes/EtOAc 6:1 to 3:1) affording the desired products as colourless oils (yield: 56-77%).

According to this procedure, the following compounds of general formula (Ia) were synthesized:

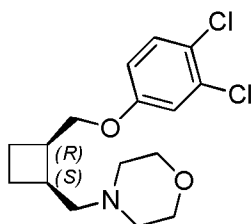
Example 4



1-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)pyrrolidine (yield: 73%)

25 $^1\text{H NMR}$ (360 MHz, CDCl_3) δ 7.32 (d, $J = 8.8$ Hz, 1H), 7.00 (s, 1H), 6.76 (d, $J = 8.8$ Hz, 1H), 3.99 (t, $J = 6.2$ Hz, 2H), 2.90 (d, $J = 9.3$ Hz, 2H), 2.79 (s, 2H), 2.57 (t, $J = 7.3$ Hz, 2H), 2.23 – 2.03 (m, 4H), 1.88 (dt, $J = 12.7, 6.4$ Hz, 2H), 1.75 (s, 4H).

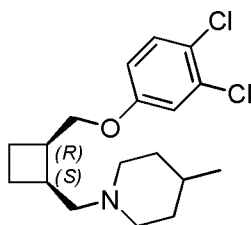
Example 5



4-(((1*S*,2*R*)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)morpholine (yield: 77%)

¹H NMR (360 MHz, CDCl₃) δ 7.34 (d, J = 8.9 Hz, 1H), 7.02 (d, J = 2.8 Hz, 1H), 6.78 (dd, J = 8.9, 2.9 Hz, 1H), 4.31 – 4.02 (m, 4H), 3.74 – 3.60 (m, 2H), 3.37 (dd, J = 11.5, 6.5 Hz, 1H), 3.09 (dd, J = 12.8, 4.3 Hz, 1H), 2.97 – 2.59 (m, 6H), 2.22 (ddd, J = 20.1, 10.6, 4.5 Hz, 2H), 2.08 (dd, J = 16.2, 6.3 Hz, 1H), 1.72 (t, J = 10.1 Hz, 1H).

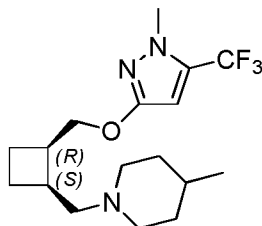
Example 6



1-(((1*S*,2*R*)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)-4-methylpiperidine (yield: 69%)

¹H NMR (250 MHz, CDCl₃) δ 7.33 (d, J = 8.9 Hz, 1H), 7.02 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 8.9, 2.9 Hz, 1H), 4.08 (ddd, J = 41.3, 9.2, 6.5 Hz, 2H), 2.82 (dd, J = 12.2, 9.7 Hz, 4H), 2.58 (dd, J = 12.4, 6.2 Hz, 1H), 2.31 (dd, J = 12.5, 7.2 Hz, 1H), 2.14 (dt, J = 9.5, 5.1 Hz, 2H), 1.99 – 1.72 (m, 4H), 1.60 (d, J = 12.6 Hz, 2H), 1.29 (m, 4H), 0.91 (d, J = 6.0 Hz, 3H).

Example 7



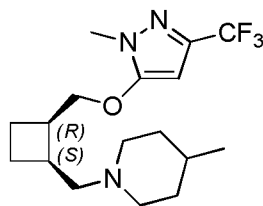
4-Methyl-1-(((1*S*,2*R*)-2-(((1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)piperidine (yield: 71%)

¹H NMR (360 MHz, Acetone-*d*₆) δ 6.22 (d, J = 10.8 Hz, 1H), 4.52 – 4.37 (m, 1H), 4.30 (dt, J = 10.5, 6.5 Hz, 1H), 3.86 (d, J = 4.2 Hz, 3H), 3.38 – 3.10 (m, 4H), 3.10 – 2.66 (m, 5H), 2.33 – 2.10 (m, 3H), 1.71 (dd, J = 11.5, 4.5 Hz, 2H), 1.67 – 1.42 (m, 4H), 0.97 (d, J = 5.6 Hz, 3H).

25

Example 8

25



4-Methyl-1-(((1S,2R)-2-(((1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)methyl)piperidine (yield: 56%)

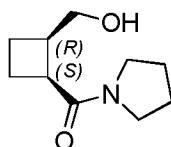
¹H NMR (250 MHz, CDCl₃) δ 5.86 (s, 1H), 4.44 – 4.20 (m, 2H), 3.73 (s, 3H), 3.09 – 2.91 (m, 4H), 2.79 (dd, J = 12.9, 4.7 Hz, 2H), 2.52 – 2.30 (m, 1H), 2.30 – 2.16 (m, 2H), 2.16 – 1.93 (m, 2H), 1.77 (t, J = 9.8 Hz, 2H), 1.65 – 1.50 (m, 3H), 1.28 (s, 3H).

Selective ester reduction of IVa with LiBH₄: hydroxy amides VIIa

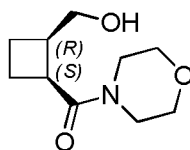
Starting amido-ester is dissolved in diethyl ether (0.1 M) under N₂ atmosphere and the solution is cooled to 0 °C with an ice bath. Then, a 2M solution of LiBH₄ in THF (1.5 eq.) is added dropwise and the mixture is stirred for 1 h, allowing it to reach room temperature.

At this time, a saturated aqueous solution of NH₄Cl is added carefully to quench the reaction, and the biphasic system is stirred for 30 min. Then, phases are separated and the aqueous layer is extracted three times with further EtOAc. After this, the whole organic phases are dried and evaporated under reduced pressure and the remaining oily crude is further purified with flash column chromatography in silica gel (hexanes/EtOAc 1:1) to yield the hydroxyl amides VIIa as colourless oils (yield: 82–87 %).

According to this procedure, the following compounds VIIa were synthesized:



((1S,2R)-2-(Hydroxymethyl)cyclobutyl)(pyrrolidin-1-yl)methanone (yield: 87%)

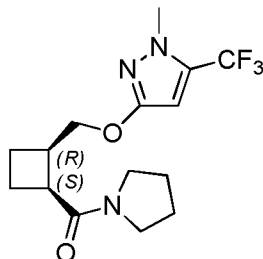


25

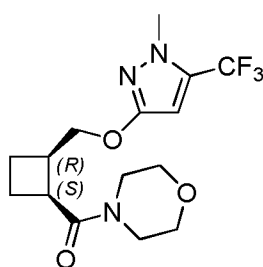
((1S,2R)-2-(Hydroxymethyl)cyclobutyl)(morpholino)methanone (yield: 82%)

Mitsunobu reaction: compounds VIa.

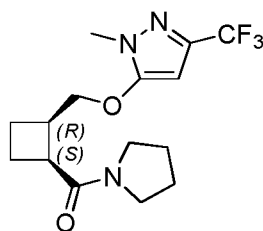
The procedure has been described above for examples 4-8 (yield: 52-81%). Accordingly, the following amidoethers **Via** were synthesized:



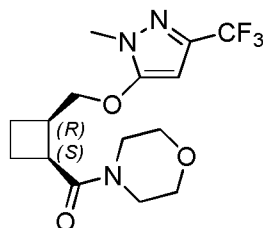
- 5 ((1S,2R)-2-(((1-Methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)(pyrrolidin-1-yl)methanone (yield: 81%)



- 10 ((1S,2R)-2-(((1-Methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)(morpholino)methanone (yield: 77%)

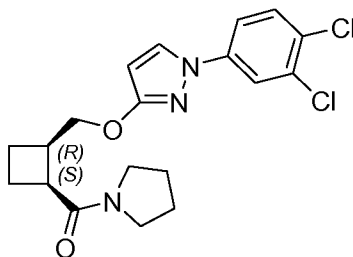


- 15 ((1S,2R)-2-(((1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)(pyrrolidin-1-yl)methanone (yield: 52%)

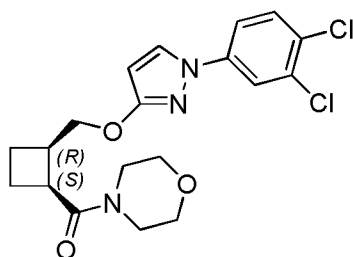


- 15 ((1S,2R)-2-(((1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)(morpholino)methanone (yield: 56%)

27

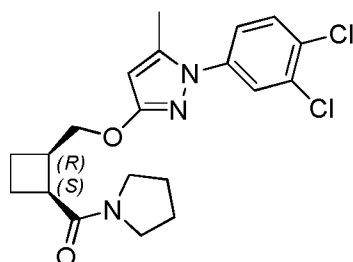


((1*S*,2*R*)-2-(((1-(3,4-Dichlorophenyl)-1*H*-pyrazol-3-yl)oxy)methyl)cyclobutyl) (pyrrolidin-1-yl)methanone (yield: 73%)

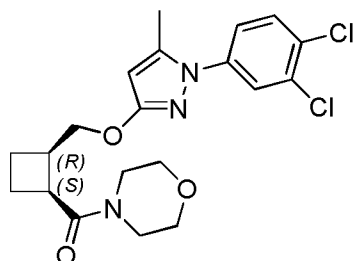


5

((1*S*,2*R*)-2-(((1-(3,4-Dichlorophenyl)-1*H*-pyrazol-3-yl)oxy)methyl)cyclobutyl) (morpholino)methanone (yield: 77%)



10 ((1*S*,2*R*)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1*H*-pyrazol-3-yl)oxy)methyl)cyclobutyl)(pyrrolidin-1-yl)methanone (yield: 69%)



15 ((1*S*,2*R*)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1*H*-pyrazol-3-yl)oxy)methyl)cyclobutyl)(morpholino)methanone (yield: 72%)

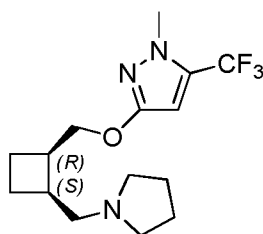
Reduction of VIa with LiAlH₄: compounds of general formula (Ia) (Examples 9-16)

Starting material is dissolved in THF (0.1 M) under N₂ atmosphere and the mixture is cooled to 0 °C with an ice bath. Then, LiAlH₄ (2.0 eq, 2.0 M in THF) is added dropwise to the solution and stirred for 30 minutes to 1h.

At 0 °C, water (1 ml/g LiAlH₄) is added very slowly and stirred for 15 min. Then, a 10% solution of NaOH (2 ml/g LiAlH₄) is introduced and stirred for further 15 min. and finally, more water (3 ml/g LiAlH₄) is added. The resulting aluminium salts are filtered off by passing them through a pressed pad of Celite®, rinsing with EtOAc. Then, to the filtrate is added more water and the aqueous phase is extracted with EtOAc three times. The whole organic phases are dried and evaporated under reduced pressure to furnish the desired amino ethers **1a** (Examples **9-16**) as colourless oils (yield: 85-97%).

According to this procedure, the following compounds of general formula (**1a**) were synthesized:

Example 9



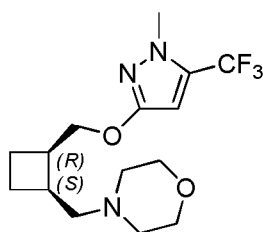
15

1-Methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole (yield: 97%)

¹H NMR (360 MHz, CDCl₃) δ 5.97 (s, 1H), 4.28 (dd, *J* = 9.9, 7.2 Hz, 1H), 4.15 (dd, *J* = 10.0, 6.7 Hz, 1H), 3.80 (s, 3H), 2.79 (m, 2H), 2.71 (dd, *J* = 12.7, 3.7 Hz, 1H), 2.50 (s br, 5H), 2.10 (m, 2H), 1.95 – 1.81 (m, 1H), 1.75 (s br, 5H).

20

Example 10



25

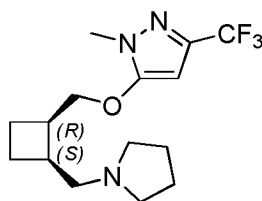
4-(((1S,2R)-2-(((1-Methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine (yield: 94%)

¹H NMR (360 MHz, CDCl₃) δ 5.97 (s, 1H), 4.22 (ddd, *J* = 53.1, 9.9, 6.8 Hz, 2H), 3.81 (s, 3H), 3.73 – 3.58 (m, 4H), 2.87 – 2.66 (m, 2H), 2.59 (dd, *J* = 12.3, 6.2 Hz, 1H), 2.48 – 2.27 (m, 5H), 2.19 – 1.98 (m, 2H), 1.92 – 1.65 (m, 2H).

30

Example 11

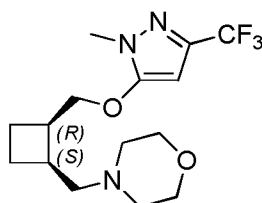
29



1-Methyl-5-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-3-(trifluoromethyl)-1H-pyrazole (yield: 86%)

¹H NMR (360 MHz, CDCl₃) δ 5.74 (s, 1H), 4.24 (dd, *J* = 9.5, 6.9 Hz, 1H), 4.09 (dd, *J* = 9.4, 7.0 Hz, 1H), 3.64 (s, 3H), 2.87 – 2.60 (m, 3H), 2.40 (s br, 5H), 2.17 – 2.06 (m, 3H), 1.77 – 1.72 (m, 1H), 1.69 (s br, 4H).

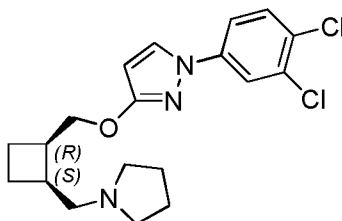
Example 12



4-(((1S,2R)-2-(((1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)methyl)morpholine (yields: 85%)

¹H NMR (360 MHz, CDCl₃) δ 5.82 (s, 1H), 4.38 – 4.09 (m, 4H), 3.76 – 3.60 (m, 5H), 3.38 (d, *J* = 4.6 Hz, 1H), 3.06 (dd, *J* = 12.7, 4.3 Hz, 1H), 2.90 (d, *J* = 11.8 Hz, 3H), 2.79 (dd, *J* = 12.6, 8.0 Hz, 1H), 2.67 (td, *J* = 13.6, 3.1 Hz, 2H), 2.31 – 2.16 (m, 2H), 2.03 (s, 1H), 1.74 (s, 2H).

Example 13

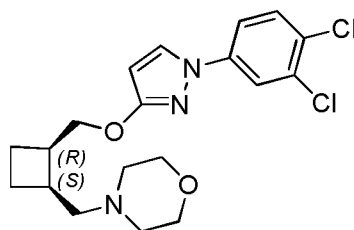


1-(3,4-Dichlorophenyl)-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole (yield: 95%)

¹H NMR (360 MHz, MeOD-*d*₄) δ 7.73 (dd, *J* = 25.4, 2.2 Hz, 2H), 7.52 – 7.37 (m, 2H), 5.92 (d, *J* = 2.5 Hz, 1H), 4.37 (ddd, *J* = 48.0, 10.1, 7.2 Hz, 2H), 2.99 – 2.70 (m, 3H), 2.65 – 2.46 (m, 5H), 2.14 (dt, *J* = 6.5, 4.7 Hz, 2H), 1.93 (t, *J* = 6.2 Hz, 1H), 1.78 (s, 5H).

25 Example 14

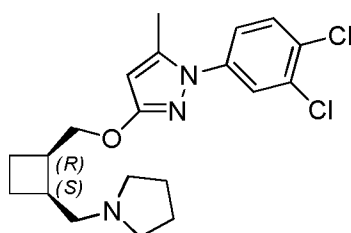
30



4-(((1S,2R)-2-(((1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine (yield: 92%)

- 5 $^1\text{H NMR}$ (360 MHz, CDCl_3) δ 8.09 (d, $J = 2.7$ Hz, 1H), 7.89 (d, $J = 2.4$ Hz, 1H), 7.59 (dt, $J = 20.4, 5.6$ Hz, 2H), 5.98 (d, $J = 2.6$ Hz, 1H), 4.47 (dd, $J = 10.3, 7.2$ Hz, 1H), 4.31 (dd, $J = 10.3, 6.2$ Hz, 1H), 3.72 – 3.59 (m, 4H), 2.93 – 2.68 (m, 3H), 2.50 (d, $J = 2.0$ Hz, 4H), 2.25 – 2.04 (m, 2H), 1.98 – 1.76 (m, 2H).

Example 15

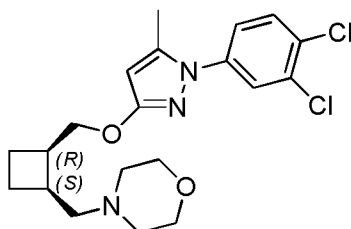


10

1-(3,4-Dichlorophenyl)-5-methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole (yield: 91%)

- 15 $^1\text{H NMR}$ (360 MHz, CDCl_3) δ 7.58 (d, $J = 2.4$ Hz, 1H), 7.47 (d, $J = 8.6$ Hz, 1H), 7.28 (dd, $J = 8.5, 2.6$ Hz, 1H), 5.65 (s, 1H), 4.34 (dd, $J = 10.1, 7.3$ Hz, 1H), 4.20 (dd, $J = 10.1, 7.1$ Hz, 1H), 2.88 – 2.64 (m, 3H), 2.54 (d, $J = 9.0$ Hz, 1H), 2.47 (s br, 4H), 2.30 (s, 3H), 2.10 (td, $J = 7.7, 2.4$ Hz, 2H), 1.95 – 1.81 (m, 1H), 1.73 (s br, 5H).

Example 16



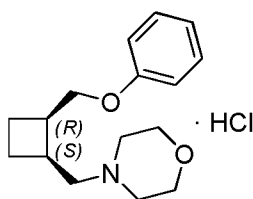
- 20 4-(((1S,2R)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine (yield: 93%)

- 25 $^1\text{H NMR}$ (360 MHz, CDCl_3) δ 7.58 (d, $J = 2.2$ Hz, 1H), 7.48 (d, $J = 8.6$ Hz, 1H), 7.28 (dd, $J = 9.6, 3.1$ Hz, 1H), 5.66 (s, 1H), 4.36 (dd, $J = 9.9, 7.3$ Hz, 1H), 4.20 (dd, $J = 9.9, 6.8$ Hz, 1H), 3.67 (s br, 4H), 2.84 – 2.72 (m, 2H), 2.68 – 2.55 (m, 1H), 2.40 (s br, 5H), 2.31 (s, 3H), 2.14 (m, 2H), 1.79 (m, 2H).

General procedure for the formation of hydrochlorides *la*·HCl (Examples 17-27)

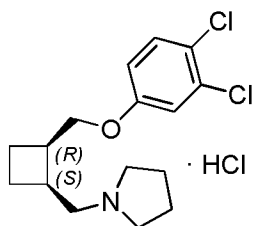
Free amine derivative **la** is dissolved in diethyl ether (0.2 mM) and a 2N solution of HCl in diethyl ether is added (1.5 eq.), under N₂ atmosphere, and the mixture is stirred for 2h. Then, the white solid is filtered and washed with more diethyl ether and pentane, and the white solid is dried under vacuum to afford the corresponding hydrochloride salts **la**·HCl as white solids (Examples 17-27) (yield: 60-98%).

According to this procedure, the following salts **la**·HCl were synthesized:

10 **Example 17**

4-(((1S,2R)-2-(Phenoxy)methyl)cyclobutyl)methyl)morpholine hydrochloride (yield: 89%)

¹H NMR (360 MHz, MeOD-*d*₄) δ 7.30 (dd, J = 8.7, 7.4 Hz, 2H), 7.03 – 6.90 (m, 3H), 4.35 – 4.18 (m, 1H), 4.14 – 3.94 (m, 3H), 3.78 (d, J = 11.9 Hz, 2H), 3.42 (dd, J = 20.6, 15.2 Hz, 4H), 3.22 – 2.90 (m, 4H), 2.28 (dd, J = 8.3, 5.0 Hz, 2H), 2.21 – 2.07 (m, 1H), 1.91 – 1.71 (m, 1H).

Example 18

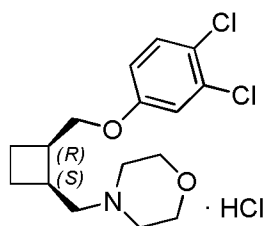
20 1-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)pyrrolidine hydrochloride (yield: 87%)

¹H NMR (360 MHz, CDCl₃) δ 7.33 (d, J = 8.0 Hz, 1H), 6.97 (s, 1H), 6.74 (d, J = 6.4 Hz, 1H), 4.00 (s, 2H), 3.78 (s, 2H), 2.85 (s, 2H), 2.42 (s, 2H), 2.29 (s, 4H), 2.18 (s, 6H), 1.90 (s, 2H).

25

Example 19

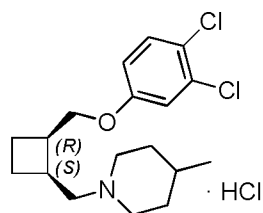
32



4-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)morpholine hydrochloride (yield: 91%)

- ¹H NMR (360 MHz, MeOD-*d*₄) δ 7.39 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 10.4 Hz, 1H), 6.90 (t, *J* = 7.8 Hz, 1H), 4.37 – 3.99 (m, 3H), 3.71 (s, 3H), 3.37 (s, 1H), 3.08 (d, *J* = 12.9 Hz, 1H), 2.93 – 2.60 (m, 6H), 2.18 (s, 2H), 1.88 (d, *J* = 55.2 Hz, 1H), 1.73 (s, 1H).

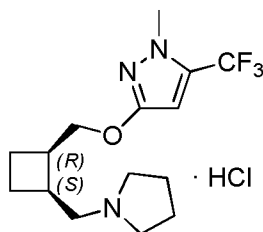
Example 20



- 10 1-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)-4-methylpiperidine hydrochloride (yield: 79%)

- ¹H NMR (360 MHz, CDCl₃) δ 7.37 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.21 – 3.99 (m, 2H), 3.48 (dd, *J* = 17.8, 10.9 Hz, 3H), 3.25 (d, *J* = 12.6 Hz, 1H), 2.98 (s, 2H), 2.59 (dd, *J* = 26.2, 11.3 Hz, 2H), 2.42 – 1.90 (m, 7H), 1.79 (d, *J* = 12.2 Hz, 3H), 1.59 (s, 1H), 1.05 (d, *J* = 6.4 Hz, 3H).

Example 21



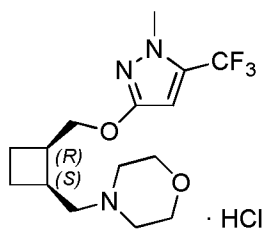
- 20 1-Methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride (yield: 98%)

- ¹H NMR (360 MHz, MeOD-*d*₄) δ 6.24 (s, 1H), 4.37 (dd, *J* = 10.3, 9.0 Hz, 1H), 4.24 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.83 (s, 3H), 3.62 (m, 2H), 3.43 (dd, *J* = 12.8, 5.3 Hz, 1H), 3.35 (d, *J* = 8.5 Hz, 1H), 3.06 (dd, *J* = 17.1, 9.0 Hz, 2H), 2.94 (dd, 2H), 2.23 (t, *J* = 8.2 Hz, 2H), 2.17 – 1.95 (m, 5H), 1.73 (t, *J* = 11.7 Hz, 1H).

25

Example 22

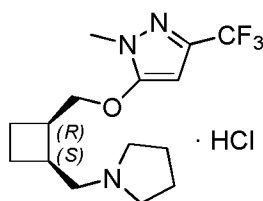
33



4-(((1S,2R)-2-(((1-Methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine hydrochloride (yield: 96%)

¹H NMR (360 MHz, MeOD-*d*₄) δ 6.25 (s, 1H), 4.32 (ddd, *J* = 15.6, 10.6, 7.1 Hz, 2H), 4.03 (d, *J* = 12.8 Hz, 2H), 3.83 (s, 5H), 3.43 (dd, *J* = 13.1, 5.6 Hz, 3H), 3.15 (t, *J* = 11.7 Hz, 2H), 3.09 – 3.00 (m, 1H), 2.97 (dd, *J* = 7.8, 3.9 Hz, 1H), 2.33 – 2.19 (m, 2H), 2.19 – 2.06 (m, 1H), 1.75 (dd, *J* = 14.2, 6.7 Hz, 1H).

Example 23



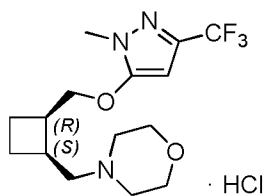
10

1-Methyl-5-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-3-(trifluoromethyl)-1H-pyrazole hydrochloride (yield: 60%)

¹H NMR (360 MHz, MeOD-*d*₄) δ 6.12 (s, 1H), 4.47 – 4.35 (m, 1H), 4.27 (dd, *J* = 9.5, 5.3 Hz, 1H), 3.92 – 3.75 (m, 2H), 3.70 (s, 3H), 3.64 (s br, 3H), 3.45 (d, *J* = 6.4 Hz, 2H), 3.05 (m, 5H), 2.33 – 1.96 (m, 8H), 1.83 (m, 1H).

15

Example 24



20

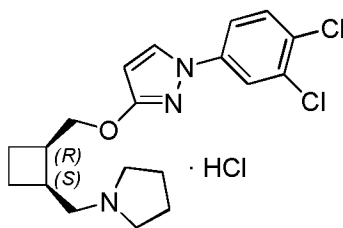
4-(((1S,2R)-2-(((1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)methyl)morpholine hydrochloride (yield: 67%)

¹H NMR (360 MHz, MeOD-*d*₄) δ 6.10 (d, *J* = 8.5 Hz, 1H), 4.39 (dd, *J* = 32.3, 24.2 Hz, 2H), 4.09 - 3.91 (m, 2H), 3.80 (dd, *J* = 11.4, 8.3 Hz, 2H), 3.70 (s, 4H), 3.50 - 3.41 (m, 3H), 3.25 – 3.05 (m, 3H), 2.90 (dd, *J* = 8.1, 3.8 Hz, 2H), 2.37 – 2.06 (m, 3H), 1.81 (d, *J* = 38.5 Hz, 1H).

25

Example 25

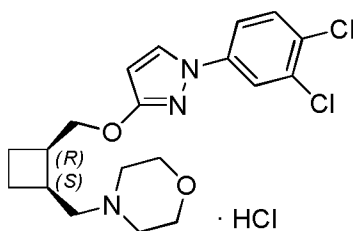
34



1-(3,4-Dichlorophenyl)-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole hydrochloride (yield: 85%)

¹H NMR (360 MHz, MeOD-*d*₄) δ 8.15 (d, *J* = 2.6 Hz, 1H), 7.93 (d, *J* = 2.3 Hz, 1H), 7.63 (dt, *J* = 19.3, 5.6 Hz, 2H), 6.07 (d, *J* = 2.6 Hz, 1H), 4.60 – 4.27 (m, 2H), 3.65 (s, 2H), 3.57 – 3.36 (m, 2H), 3.05 (d, *J* = 33.4 Hz, 4H), 2.40 – 2.22 (m, 2H), 2.13 (dd, *J* = 24.7, 18.0 Hz, 5H), 1.82 (d, *J* = 10.2 Hz, 1H).

Example 26



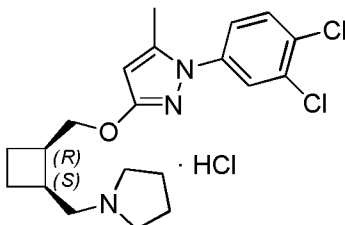
10

4-(((1S,2R)-2-(((1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine hydrochloride (yield: 92%)

¹H NMR (360 MHz, MeOD-*d*₄) δ 8.15 (d, *J* = 2.4 Hz, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.62 (dt, *J* = 20.8, 5.5 Hz, 2H), 6.07 (d, *J* = 2.4 Hz, 1H), 4.55 – 4.33 (m, 2H), 4.04 (d, *J* = 13.1 Hz, 2H), 3.85 (dd, *J* = 20.3, 11.9 Hz, 2H), 3.47 (d, *J* = 12.6 Hz, 3H), 3.39 (d, *J* = 8.3 Hz, 1H), 3.24 – 2.94 (m, 4H), 2.37 – 2.10 (m, 3H), 1.81 (t, *J* = 9.9 Hz, 1H).

15

Example 27



20 1-(3,4-Dichlorophenyl)-5-methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole hydrochloride (yield: 88%)

¹H NMR (360 MHz, MeOD-*d*₄) δ 7.71 (d, *J* = 2.3 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.45 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.90 (s, 1H), 4.47 – 4.35 (m, 1H), 4.28 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.74 – 3.55 (m, 2H), 3.47 (dd, *J* = 12.7, 5.6 Hz, 1H), 3.41 – 3.34 (m, 1H), 3.17 – 2.86 (m, 4H), 2.35 (s, 3H), 2.23 (m, 2H), 2.14 (m, 3H), 2.08 – 1.96 (m, 2H), 1.77 (m, 1H).

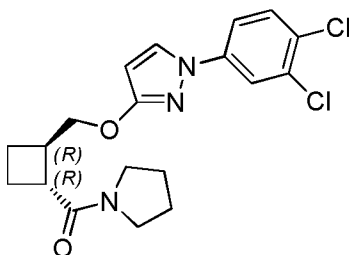
25

Synthesis of (R,R)-stereoisomers: Compounds of general formula (Ib)**According to the synthetic pathway disclosed in Scheme n° 2:****Epimerization of cis-amides VIa: trans-amides VIb**5 **Method A: KHMDS as a base**

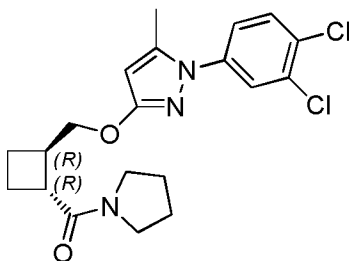
The starting material is dissolved in THF under nitrogen atmosphere and once the system is cooled to 0 °C a solution of potassium hexamethyldisilazide (0.5 M in toluene, 1.5 eq.) is added dropwise. Immediately, the cooling bath is removed and the mixture is stirred at room temperature for 1 h.

10 Water is added to quench the reaction along with dichloromethane (several). The organic phase is then washed with more water and brine, affording a yellowish oil that consists in a mixture *cis/trans* 10/90. In order to separate both diastereoisomers, a flash column chromatography in silica gel (hexanes/EtOAc 2:1) is carried out, obtaining the desired *trans* diastereoisomers **VIb** as colourless oils (yield: 80-85%).

15 Accordingly, the following compounds **VIb** were synthesized:



20 *((1R,2R)-2-(((1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)(pyrrolidin-1-yl)methanone* (yield: 80%)



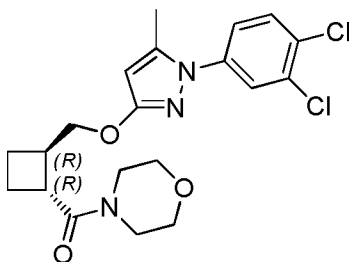
((1R,2R)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)(pyrrolidin-1-yl)methanone (yield: 85%)

25 **Method B: KO^tBu/^tBuOH as a base**

The corresponding amido-ether is dissolved in tert-butanol (0.05 M) and four equivalents of KO^tBu are added. The reaction system is heated to 100°C and stirred for 5 hours, observing no presence of starting material in TLC.

A little bit of water is added and volatiles are removed under reduced pressure. The oily crude is then partitioned between water and EtOAc and the phases are separated. The organic phase is dried and evaporated under vacuum affording a yellowish oil that consists in a mixture *cis/trans* 10/90. In order to separate both diastereoisomers, a flash column chromatography in silica gel (hexanes/EtOAc 2:1) is carried out, obtaining the desired *trans* diastereoisomer **Vib** as a colourless oil (yield: 62%).

Accordingly, the following compound **Vib** was synthesized:



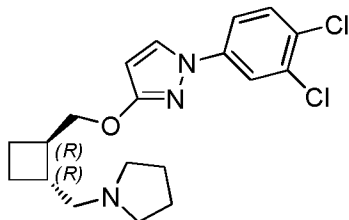
((1R,2R)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)(morpholino)methanone (yield: 62%)

Reduction of amides **Vib to compounds of general formula (**Ib**) (Examples 28-30).**

Reduction was achieved following the same procedure as described for examples 9-16 to afford amino ethers **Ib** as colourless oils (Examples 28-30).

According to this procedure, the following compounds of general formula (**Ib**) were synthesized:

Example 28

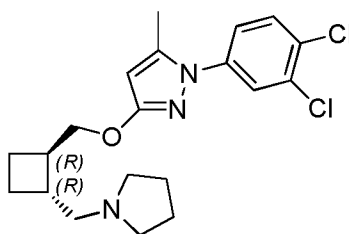


1-(3,4-Dichlorophenyl)-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole (yield: 87%)

$^1\text{H NMR}$ (360 MHz, CDCl_3) δ 7.75 (d, $J = 2.1$ Hz, 1H), 7.68 (d, $J = 2.5$ Hz, 1H), 7.49 – 7.38 (m, 2H), 5.92 (d, $J = 2.5$ Hz, 1H), 4.22 (d, $J = 3.8$ Hz, 2H), 2.73 (d, $J = 6.8$ Hz, 1H), 2.56 – 2.36 (m, 7H), 2.18 – 1.97 (m, 2H), 1.89 – 1.61 (m, 6H).

Example 29

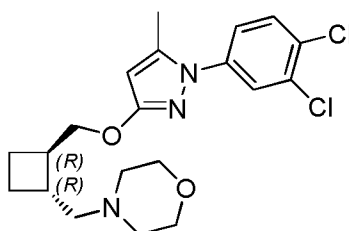
37



1-(3,4-Dichlorophenyl)-5-methyl-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole (yield: 94%)

¹H NMR (360 MHz, CDCl₃) δ 7.58 (d, *J* = 2.5 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 7.28 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.66 (s, 1H), 4.14 (dd, *J* = 5.7, 2.2 Hz, 2H), 2.70 (d, *J* = 8.9 Hz, 1H), 2.48 (s br, 4H), 2.43 – 2.35 (m, 2H), 2.30 (s, 3H), 2.09 (m, 1H), 2.05 – 1.92 (m, 1H), 1.75 (s br, 5H), 1.70 – 1.58 (m, 1H).

Example 30



10

4-(((1R,2R)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine (yield: 82%)

¹H NMR (360 MHz, CDCl₃) δ 7.57 (d, *J* = 2.4 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 7.31 – 7.24 (dd, *J* = 8.6, 2.4 Hz, 1H), 5.65 (s, 1H), 4.13 (d, *J* = 5.7 Hz, 2H), 3.68 (t, *J* = 4.6 Hz, 4H), 2.56 (dd, *J* = 11.2, 4.5 Hz, 1H), 2.49 – 2.33 (m, 6H), 2.30 (s, 3H), 2.14 – 1.93 (m, 2H), 1.87 – 1.72 (m, 1H), 1.72 – 1.55 (m, 1H).

15

Epimerization of *cis*-amides IVc: *trans*-amides IVb.

Starting material **IVc** is dissolved in ⁱPrOH (0.05 M) and sodium methoxide (10 eq.) is added at room temperature, all in one portion. After 2 h., a TLC analysis shows totally conversion of the product as a carboxylate, due to saponification carried out after epimerization.

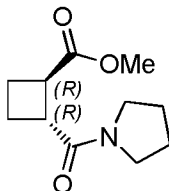
The solution is acidified to pH=2 with a 2N solution of HCl, and dichloromethane is added. Then, the phases are separated, and the aqueous is washed with more dichloromethane. The whole organic layers are dried and evaporated under reduced pressure, affording *trans*-carboxylic acid as colourless oil, which is used in the next step without further purification.

The crude obtained in the first step is dissolved in methanol (0.1 M), and sulfuric acid (1.1 eq.) is added dropwise. The reaction mixture is stirred at room temperature overnight.

30

Volatiles are removed under vacuum and dichloromethane is added. The organic layer is washed with water (slightly basic) and brine, dried and evaporated under reduced pressure to afford the desired *trans* amido-ester **IVb** as a colourless oil. (yield: 90 %).

- 5 Accordingly, the following compound **IVb** was synthesized:

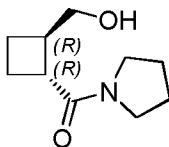


(1*R*,2*R*)-Methyl 2-(pyrrolidine-1-carbonyl)cyclobutanecarboxylate (yield: 90%)

10 **Reduction of amides *IVb*: alcohols *VIIb*.**

Reduction was achieved as described above for compounds **IVa**, affording alcohols **VIIb** as a colourless oils. (yield: 84%)

Accordingly, the following compound **VIIb** was synthesized:

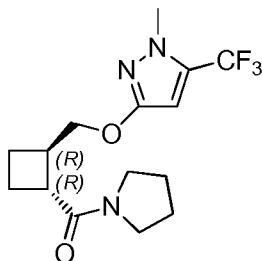


- 15 ((1*R*,2*R*)-2-(Hydroxymethyl)cyclobutyl)(pyrrolidin-1-yl)methanone (yield: 84%)

Mitsunobu reaction of alcohols *VIIb*: compounds *VIIb*.

This reaction was carried out as described above for compounds **VIa** affording the amido ether **VIIb** as a colourless oil. (yield: 68%)

- 20 According to this procedure, the following compound **VIIb** was synthesized:



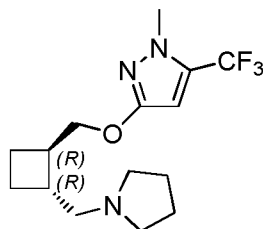
((1*R*,2*R*)-2-(((1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)oxy)methyl)cyclobutyl)(pyrrolidin-1-yl)methanone (yield: 68%)

- 25 **Reduction of *VIIb*: compounds of general formula (Ib) (Example 31) and their hydrochloride salts (Example 32).**

This reaction was carried out as described above for examples 9-16, affording **1b** as a colourless oil (Example 31) which was transformed into its hydrochloride salt **1b-HCl** (Example 32), obtained as a white solid, following the same procedure described for examples 17-27.

5 Accordingly, compound **1b** and its salt **1b-HCl** were synthesized:

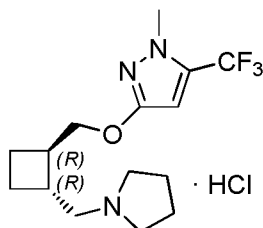
Example 31



10 *1-Methyl-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole* (yield: 96%)

¹H NMR (250 MHz, CDCl₃) δ 5.98 (s, 1H), 4.10 (d, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 2.99 – 2.35 (m, 8H), 2.21 – 1.69 (m, 8H).

Example 32



15 *1-Methyl-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride* (yield: 90%)

20 ¹H NMR (250 MHz, MeOD-*d*₄) δ 6.20 (s, 1H), 4.15 (qd, *J* = 10.3, 5.8 Hz, 2H), 3.82 (s, 3H), 3.74 – 3.55 (m, 2H), 3.50 – 3.21 (m, 2H), 3.16 – 2.97 (m, 2H), 2.63 (dt, *J* = 15.1, 8.3 Hz, 2H), 2.29 – 1.79 (m, 8H).

Synthesis of amides IVc

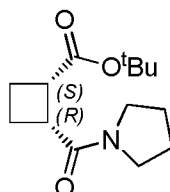
According to synthetic pathway described in Scheme 3:

25 *Synthesis of amido esters VIII*

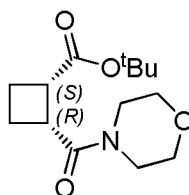
Free carboxylic acid **IX**, prepared according to the methods previously described in S. Izquierdo, F. Rúa, A. Sbai, T. Parella, Á. Álvarez-Larena, V. Branchadell, R. M. Ortuño, *J. Org. Chem.* **2005**, *70*, 7963-7971, is dissolved in dichloromethane (0.05 M) and PyBOP (1.5 eq.) and DIPEA (2 eq.) are added. After

stirring for 10 minutes, pyrrolidine (2 eq.) is added and the system allowed to stir for 24 h. At this time, the solvent is removed in vacuo and the crude oil is purified by flash column chromatography through Celite® in silica gel (hexanes/EtOAc 2:1) to afford the corresponding amido esters **VIII** as yellowish oils. (yield: 85-99 %).

5 According to this procedure, the following compounds **VIII** were synthesized:



(1*S*,2*R*)-*tert*-Butyl 2-(pyrrolidine-1-carbonyl)cyclobutanecarboxylate (yield: 99%)



10

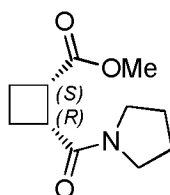
(1*S*,2*R*)-*tert*-Butyl 2-(morpholine-4-carbonyl)cyclobutanecarboxylate (yield: 85%)

Synthesis of amido esters **IVc**.

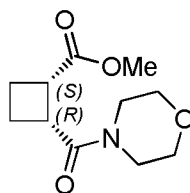
15 Starting amido-ester **VIII** is dissolved in TFA/DCM (1/1, 0,05 M). After 1 h stirring at room temperature, the solvent is removed and the residue taken up in toluene and evaporated again to yield the free carboxylic acid as colourless oil. (yield: quantitative)

20 The crude obtained in the first step is dissolved in methanol (0.1 M), and sulfuric acid (1.1 eq.) is added dropwise. The reaction mixture is stirred at room temperature overnight. Volatiles are removed under vacuum and dichloromethane is added. The organic layer is washed with water (slightly basic) and brine, dried and evaporated under reduced pressure to afford the desired amide methyl esters **IVc** as colourless oils. (yield: 99%).

25 According to this procedure, the following compounds **IVc** were synthesized:



(1*S*,2*R*)-Methyl 2-(pyrrolidine-1-carbonyl)cyclobutanecarboxylate (yield: 99%)



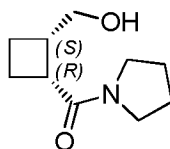
(1*S*,2*R*)-Methyl 2-(morpholine-4-carbonyl)cyclobutanecarboxylate (yield: 99%)

5 **Synthesis of (S,R)-stereoisomers: Compounds of general formula (Ic)**

According to the synthetic pathway disclosed in Scheme n° 4:

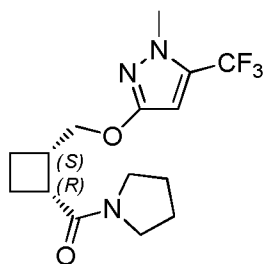
All procedures are similar to those already described for the preparation of enantiomeric compounds of general formula (Ia).

10 Accordingly, hydroxy amides **VIc**, ethers **VIc** and compounds of general formula (Ic) (Example 33) as well as its hydrochloride salt **Ic·HCl** (Example 34) were synthesized.



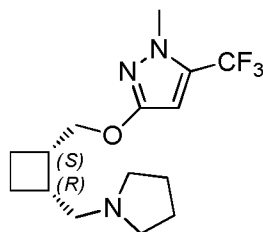
((1*R*,2*S*)-2-(Hydroxymethyl)cyclobutyl)(pyrrolidin-1-yl)methanone (yield: 83%)

15



((1*R*,2*S*)-2-(((1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)oxy)methyl)cyclobutyl)(pyrrolidin-1-yl)methanone (yield: 72%)

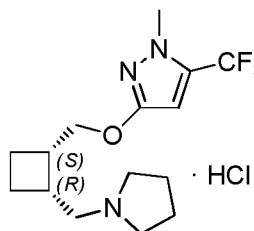
20 **Example 33**



1-Methyl-3-(((1*S*,2*R*)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1*H*-pyrazole (yield: 94%)

¹H NMR (360 MHz, CDCl₃) δ 5.97 (s, 1H), 4.28 (dd, *J* = 9.9, 7.2 Hz, 1H), 4.15 (dd, *J* = 10.0, 6.7 Hz, 1H), 3.80 (s, 3H), 2.79 (m, 2H), 2.71 (dd, *J* = 12.7, 3.7 Hz, 1H), 2.50 (s br, 5H), 2.10 (m, 2H), 1.95 – 1.81 (m, 1H), 1.75 (s br, 5H).

Example 34



1-Methyl-3-(((1*S*,2*R*)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1*H*-pyrazole hydrochloride (yield: 89%)

¹H NMR (360 MHz, MeOD-*d*₄) δ 6.24 (s, 1H), 4.37 (dd, *J* = 10.3, 9.0 Hz, 1H), 4.24 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.83 (s, 3H), 3.62 (m, 2H), 3.43 (dd, *J* = 12.8, 5.3 Hz, 1H), 3.35 (d, *J* = 8.5 Hz, 1H), 3.06 (dd, *J* = 17.1, 9.0 Hz, 2H), 2.94 (dd, 2H), 2.23 (t, *J* = 8.2 Hz, 2H), 2.17 – 1.95 (m, 5H), 1.73 (t, *J* = 11.7 Hz, 1H).

Synthesis of (S,S)-stereoisomers: Compounds of general formula (Id)

According to the synthetic pathway disclosed in Scheme n° 5:

Epimerization of *cis*-ester IVa: Synthesis of *trans*-ester IVd.

Starting material **IVa** is dissolved in ⁱPrOH (0.05 M), and sodium methoxide (10 eq.) is added at room temperature, all in one portion. After 2 h., a TLC analysis shows totally conversion of the product to a carboxylate, due to saponification carried out after epimerization.

The solution is acidified to pH=2 with a 2N solution of HCl, and several dichloromethane is added. Then, the phases are separated, and the aqueous is washed with more dichloromethane. The whole organic layers are dried and evaporated under reduced pressure, affording *trans*-carboxylic acid as colourless oil, which is used in the next step without further purification.

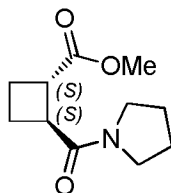
The crude obtained in the first step is dissolved in methanol (0.1 M), and sulfuric acid (1.1 eq.) is added dropwise. The reaction mixture is stirred at room temperature overnight.

Volatiles are removed under vacuum and dichloromethane is added. The organic layer is washed with water (slightly basic) and brine, dried and evaporated

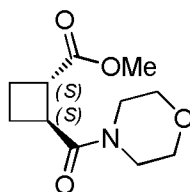
under reduced pressure to afford the desired *trans* amido-esters **IVd** as colourless oils.
(yield: 84-95 %)

Accordingly, the following compounds **IVd** were synthesized:

5

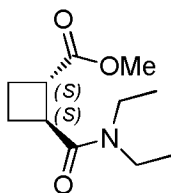


(1S,2S)-Methyl 2-(pyrrolidine-1-carbonyl)cyclobutanecarboxylate (yield: 95%)



(1S,2S)-Methyl 2-(morpholine-4-carbonyl)cyclobutanecarboxylate (yield: 84%)

10

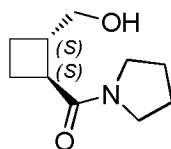


(1S,2S)-Methyl 2-(diethylcarbamoyl)cyclobutanecarboxylate (yield: 86%)

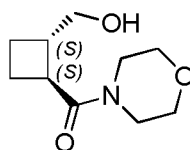
Selective reduction of the ester group in **IVd** was achieved as described above for compounds VIIa, affording hydroxy amides **VIIId**.

15

Accordingly, the following hydroxyl amides **VIIId** were synthesized:

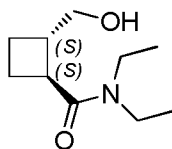


((1S,2S)-2-(Hydroxymethyl)cyclobutyl)(pyrrolidin-1-yl)methanone (yield: 86%)



20 *((1S,2S)-2-(Hydroxymethyl)cyclobutyl)(morpholino)methanone* (yield: 83%)

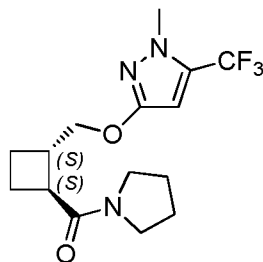
44



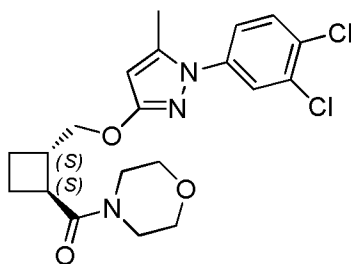
(1S,2S)-N,N-Diethyl-2-(hydroxymethyl)cyclobutanecarboxamide (yield: 84%)

- 5 **Mitsunobu reaction** of these alcohols with phenols R¹OH was carried out following the same procedure described above for compounds VIa, producing amido ethers **VId** as colourless oils.

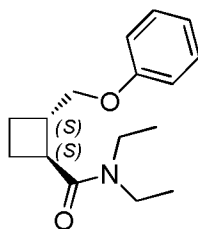
According to this procedure, the following amido ethers **VId** were synthesized:



- 10 ((1S,2S)-2-(((1-Methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)(pyrrolidin-1-yl)methanone (yield: 74%)



- 15 ((1S,2S)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)(morpholino)methanone (yield: 69%)

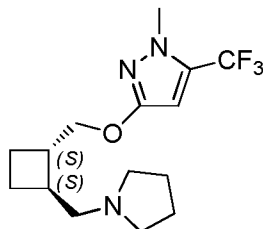


(1S,2S)-N,N-Diethyl-2-(phenoxy)methyl)cyclobutanecarboxamide (yield: 78%)

Finally, **reduction of amides Vld** with LiAlH_4 as described above for examples 9-16, allowed us to obtain compounds of general formula (**Id**) (**Examples 35-37**) as colourless oils. Hydrochloride salts **Id·HCl** (**Examples 38 and 39**) were also prepared as white solids, using the same procedure performed for examples 17-27.

5 Accordingly, the following compounds of general formula (**Id**) and their hydrochloride salt **Id·HCl** were synthesized:

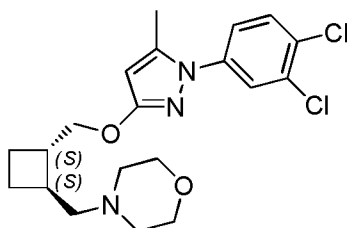
Example 35



10 *1-Methyl-3-(((1S,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole* (yield: 90%)

$^1\text{H NMR}$ (250 MHz, CDCl_3) δ 5.98 (s, 1H), 4.10 (d, $J = 7.1$ Hz, 2H), 3.81 (s, 3H), 2.99 – 2.35 (m, 8H), 2.21 – 1.69 (m, 8H).

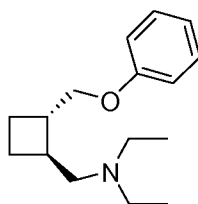
Example 36



15 *4-(((1S,2S)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine* (yield: 86%)

20 $^1\text{H NMR}$ (360 MHz, CDCl_3) δ 7.57 (d, $J = 2.4$ Hz, 1H), 7.47 (d, $J = 8.6$ Hz, 1H), 7.31 – 7.24 (dd, $J = 8.6, 2.4$ Hz, 1H), 5.65 (s, 1H), 4.13 (d, $J = 5.7$ Hz, 2H), 3.68 (t, $J = 4.6$ Hz, 4H), 2.56 (dd, $J = 11.2, 4.5$ Hz, 1H), 2.49 – 2.33 (m, 6H), 2.30 (s, 3H), 2.14 – 1.93 (m, 2H), 1.87 – 1.72 (m, 1H), 1.72 – 1.55 (m, 1H).

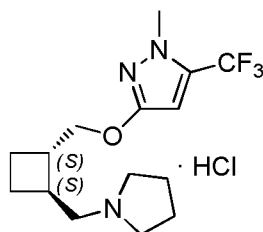
Example 37



25 *N,N-Diethyl-N-(((1S,2S)-2-(phenoxy)methyl)cyclobutyl)methyl)ethanamine* (yield: 81%)

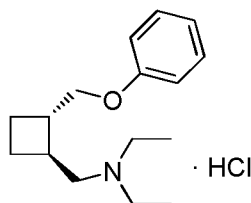
$^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.33 – 7.21 (m, 2H), 6.90 (dd, $J = 7.7, 6.6$ Hz, 3H), 3.94 (d, $J = 3.7$ Hz, 2H), 2.71 (dd, $J = 11.2, 6.4$ Hz, 1H), 2.57 (dd, $J = 14.0, 7.0$ Hz, 5H), 2.40 (dd, $J = 13.6, 6.5$ Hz, 2H), 2.20 – 1.97 (m, 4H), 1.74 (dd, $J = 26.2, 10.4$ Hz, 2H), 1.04 (d, $J = 7.2$ Hz, 6H).

5

Example 38

1-Methyl-3-(((1S,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride (yield: 92%)

10 $^1\text{H NMR}$ (250 MHz, $\text{MeOD-}d_4$) δ 6.20 (s, 1H), 4.15 (qd, $J = 10.3, 5.8$ Hz, 2H), 3.82 (s, 3H), 3.74 – 3.55 (m, 2H), 3.50 – 3.21 (m, 2H), 3.16 – 2.97 (m, 2H), 2.63 (dt, $J = 15.1, 8.3$ Hz, 2H), 2.29 – 1.79 (m, 8H).

Example 39

15

N,N-Diethyl-N-(((1S,2S)-2-(phenoxymethyl)cyclobutyl)methyl)ethanamine hydrochloride (yield: 78%)

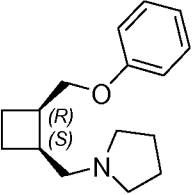
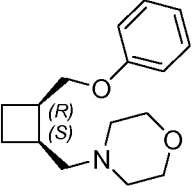
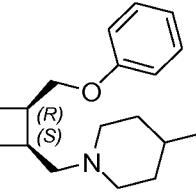
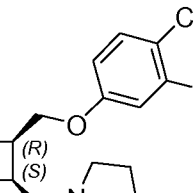
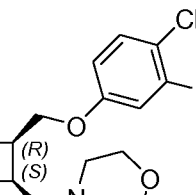
20 $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.38 – 7.22 (m, 2H), 6.96 (dd, $J = 8.1, 3.2$ Hz, 3H), 4.03 (qd, $J = 9.6, 5.9$ Hz, 2H), 3.43 – 3.36 (m, 1H), 3.23 (q, $J = 7.3$ Hz, 5H), 2.78 – 2.55 (m, 2H), 2.26 (m, 1H), 2.19 – 2.04 (m, 1H), 1.93 (m, 2H), 1.34 (t, $J = 7.3$ Hz, 6H).

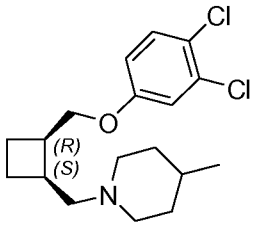
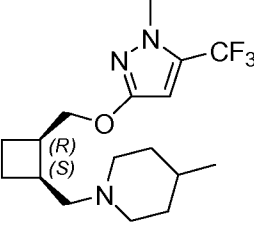
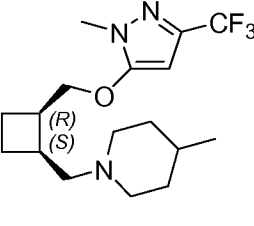
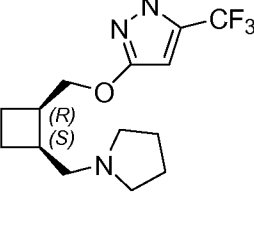
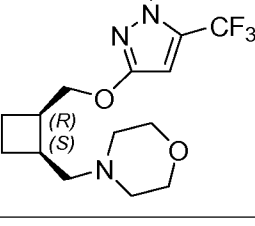
Particular compounds of general formula (I) are listed in table (I) below.

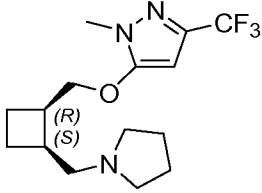
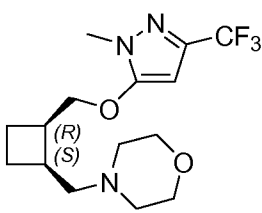
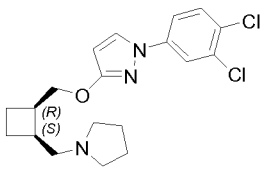
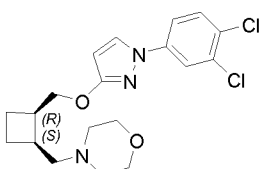
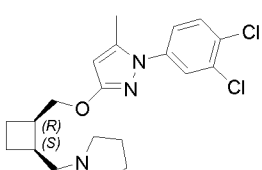
Table I

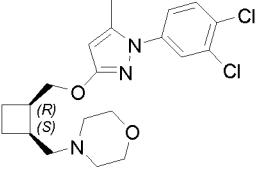
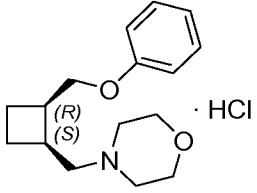
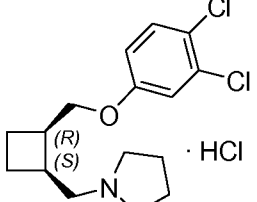
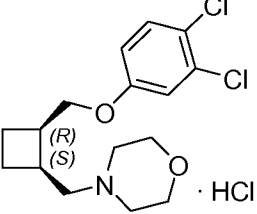
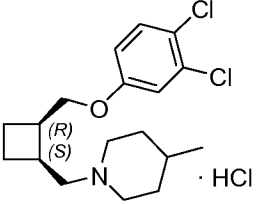
25

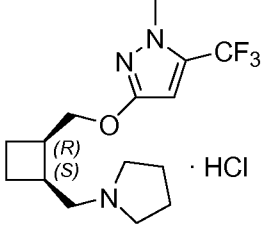
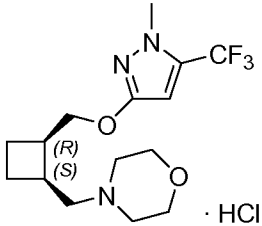
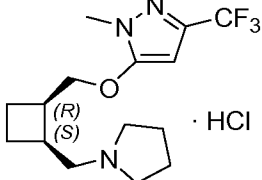
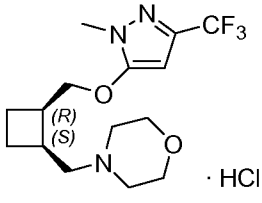
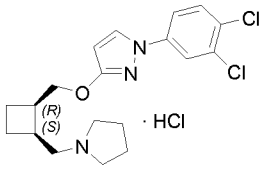
STRUCTURE	Example N°	NAME	NMR
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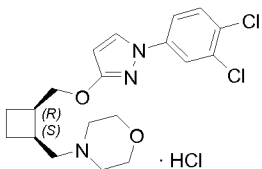
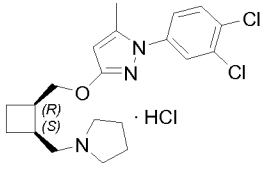
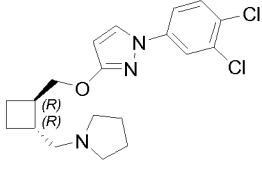
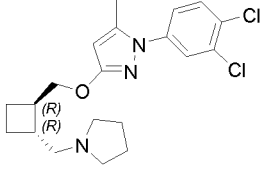
	1	<p>1-(((1S,2R)-2-(phenoxy)methyl)cyclobutyl)methylpyrrolidine</p>	<p>¹H NMR (360 MHz, CDCl₃) δ 7.30 (m, 2H), 6.94 (m, 3H), 4.04 (t, J = 7.0 Hz, 2H), 2.86 (d, J = 10.0 Hz, 2H), 2.77 (m, 2H), 2.55 (t, J = 7.5 Hz, 2H), 2.14 (m, 2H), 2.03 (m, 2H), 1.91 (m, 2H), 1.76 (m, 4H).</p>
	2	<p>4-(((1S,2R)-2-(phenoxy)methyl)cyclobutyl)methylmorpholine</p>	<p>¹H NMR (360 MHz, CDCl₃) δ 7.28 (dd, J = 8.6, 7.5 Hz, 2H), 6.99 – 6.82 (m, 3H), 4.16 (dd, J = 9.3, 6.8 Hz, 1H), 4.01 (dd, J = 9.4, 6.4 Hz, 1H), 3.67 (t, J = 4.7 Hz, 4H), 2.81 (dd, J = 5.1, 2.9 Hz, 2H), 2.64 (dd, J = 12.3, 6.4 Hz, 1H), 2.52 – 2.29 (m, 4H), 2.24 – 2.02 (m, 2H), 1.82 (dd, J = 8.6, 3.8 Hz, 2H).</p>
	3	<p>4-methyl-1-(((1S,2R)-2-(phenoxy)methyl)cyclobutyl)methylpiperidine</p>	<p>¹H NMR (360 MHz, CDCl₃) δ 7.30 (m, 2H), 6.94 (m, 3H), 4.19 (dd, J = 9.0, 6.0 Hz, 1H), 4.03 (dd, J = 9.0, 6.0 Hz, 1H), 2.82 (m, 4H), 2.63 (dd, J = 12.0, 6.0 Hz, 1H), 2.14 (m, 2H), 1.91 (m, 4H), 1.61 (m, 2H), 1.26 (m, 3H), 0.92 (d, J = 6.0 Hz, 3H).</p>
	4	<p>1-(((1S,2R)-2-((3,4-dichlorophenoxy)methyl)cyclobutyl)methyl)pyrrolidine</p>	<p>¹H NMR (360 MHz, CDCl₃) δ 7.32 (d, J = 8.8 Hz, 1H), 7.00 (s, 1H), 6.76 (d, J = 8.8 Hz, 1H), 3.99 (t, J = 6.2 Hz, 2H), 2.90 (d, J = 9.3 Hz, 2H), 2.79 (s, 2H), 2.57 (t, J = 7.3 Hz, 2H), 2.23 – 2.03 (m, 4H), 1.88 (dt, J = 12.7, 6.4 Hz, 2H), 1.75 (s, 4H).</p>
	5	<p>4-(((1S,2R)-2-((3,4-dichlorophenoxy)methyl)cyclobutyl)methyl)morpholine</p>	<p>¹H NMR (360 MHz, CDCl₃) δ 7.34 (d, J = 8.9 Hz, 1H), 7.02 (d, J = 2.8 Hz, 1H), 6.78 (dd, J = 8.9, 2.9 Hz, 1H), 4.31 – 4.02 (m, 4H), 3.74 – 3.60 (m, 2H), 3.37 (dd, J = 11.5, 6.5 Hz, 1H), 3.09 (dd, J = 12.8, 4.3 Hz, 1H), 2.97 – 2.59 (m, 6H), 2.22 (ddd, J = 20.1, 10.6, 4.5 Hz, 2H), 2.08 (dd, J = 16.2, 6.3 Hz, 1H), 1.72 (t, J = 10.1 Hz, 1H).</p>

	6	1-(((1S,2R)-2-((3,4-dichlorophenoxy)methyl)cyclobutyl)methyl)-4-methylpiperidine	¹ H NMR (250 MHz, CDCl ₃) δ 7.33 (d, J = 8.9 Hz, 1H), 7.02 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 8.9, 2.9 Hz, 1H), 4.08 (ddd, J = 41.3, 9.2, 6.5 Hz, 2H), 2.82 (dd, J = 12.2, 9.7 Hz, 4H), 2.58 (dd, J = 12.4, 6.2 Hz, 1H), 2.31 (dd, J = 12.5, 7.2 Hz, 1H), 2.14 (dt, J = 9.5, 5.1 Hz, 2H), 1.99 – 1.72 (m, 4H), 1.60 (d, J = 12.6 Hz, 2H), 1.29 (m, 4H), 0.91 (d, J = 6.0 Hz, 3H).
	7	4-methyl-1-(((1S,2R)-2-(((1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)piperidine	¹ H NMR (360 MHz, Acetone- <i>d</i> ₆) δ 6.22 (d, J = 10.8 Hz, 1H), 4.52 – 4.37 (m, 1H), 4.30 (dt, J = 10.5, 6.5 Hz, 1H), 3.86 (d, J = 4.2 Hz, 3H), 3.38 – 3.10 (m, 4H), 3.10 – 2.66 (m, 5H), 2.33 – 2.10 (m, 3H), 1.71 (dd, J = 11.5, 4.5 Hz, 2H), 1.67 – 1.42 (m, 4H), 0.97 (d, J = 5.6 Hz, 3H).
	8	4-methyl-1-(((1S,2R)-2-(((1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)methyl)piperidine	¹ H NMR (250 MHz, CDCl ₃) δ 5.86 (s, 1H), 4.44 – 4.20 (m, 2H), 3.73 (s, 3H), 3.09 – 2.91 (m, 4H), 2.79 (dd, J = 12.9, 4.7 Hz, 2H), 2.52 – 2.30 (m, 1H), 2.30 – 2.16 (m, 2H), 2.16 – 1.93 (m, 2H), 1.77 (t, J = 9.8 Hz, 2H), 1.65 – 1.50 (m, 3H), 1.28 (s, 3H).
	9	1-methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole	¹ H NMR (360 MHz, CDCl ₃) δ 5.97 (s, 1H), 4.28 (dd, J = 9.9, 7.2 Hz, 1H), 4.15 (dd, J = 10.0, 6.7 Hz, 1H), 3.80 (s, 3H), 2.79 (m, 2H), 2.71 (dd, J = 12.7, 3.7 Hz, 1H), 2.50 (s br, 5H), 2.10 (m, 2H), 1.95 – 1.81 (m, 1H), 1.75 (s br, 5H).
	10	4-(((1S,2R)-2-(((1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine	¹ H NMR (360 MHz, CDCl ₃) δ 5.97 (s, 1H), 4.22 (ddd, J = 53.1, 9.9, 6.8 Hz, 2H), 3.81 (s, 3H), 3.73 – 3.58 (m, 4H), 2.87 – 2.66 (m, 2H), 2.59 (dd, J = 12.3, 6.2 Hz, 1H), 2.48 – 2.27 (m, 5H), 2.19 – 1.98 (m, 2H), 1.92 – 1.65 (m, 2H).

	11	1-methyl-5-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-3-(trifluoromethyl)-1H-pyrazole	¹ H NMR (360 MHz, CDCl ₃) δ 5.74 (s, 1H), 4.24 (dd, J = 9.5, 6.9 Hz, 1H), 4.09 (dd, J = 9.4, 7.0 Hz, 1H), 3.64 (s, 3H), 2.87 – 2.60 (m, 3H), 2.40 (s br, 5H), 2.17 – 2.06 (m, 3H), 1.77 – 1.72 (m, 1H), 1.69 (s br, 4H).
	12	4-(((1S,2R)-2-(((1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)methyl)morpholine	¹ H NMR (360 MHz, CDCl ₃) δ 5.82 (s, 1H), 4.38 – 4.09 (m, 4H), 3.76 – 3.60 (m, 5H), 3.38 (d, J = 4.6 Hz, 1H), 3.06 (dd, J = 12.7, 4.3 Hz, 1H), 2.90 (d, J = 11.8 Hz, 3H), 2.79 (dd, J = 12.6, 8.0 Hz, 1H), 2.67 (td, J = 13.6, 3.1 Hz, 2H), 2.31 – 2.16 (m, 2H), 2.03 (s, 1H), 1.74 (s, 2H).
	13	1-(3,4-dichlorophenyl)-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole	¹ H NMR (360 MHz, MeOD-d ₄) δ 7.73 (dd, J = 25.4, 2.2 Hz, 2H), 7.52 – 7.37 (m, 2H), 5.92 (d, J = 2.5 Hz, 1H), 4.37 (ddd, J = 48.0, 10.1, 7.2 Hz, 2H), 2.99 – 2.70 (m, 3H), 2.65 – 2.46 (m, 5H), 2.14 (dt, J = 6.5, 4.7 Hz, 2H), 1.93 (t, J = 6.2 Hz, 1H), 1.78 (s, 5H).
	14	4-(((1S,2R)-2-(((1-(3,4-dichlorophenyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine	¹ H NMR (360 MHz, CDCl ₃) δ 8.09 (d, J = 2.7 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.59 (dt, J = 20.4, 5.6 Hz, 2H), 5.98 (d, J = 2.6 Hz, 1H), 4.47 (dd, J = 10.3, 7.2 Hz, 1H), 4.31 (dd, J = 10.3, 6.2 Hz, 1H), 3.72 – 3.59 (m, 4H), 2.93 – 2.68 (m, 3H), 2.50 (d, J = 2.0 Hz, 4H), 2.25 – 2.04 (m, 2H), 1.98 – 1.76 (m, 2H).
	15	1-(3,4-dichlorophenyl)-5-methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole	¹ H NMR (360 MHz, CDCl ₃) δ 7.58 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.28 (dd, J = 8.5, 2.6 Hz, 1H), 5.65 (s, 1H), 4.34 (dd, J = 10.1, 7.3 Hz, 1H), 4.20 (dd, J = 10.1, 7.1 Hz, 1H), 2.88 – 2.64 (m, 3H), 2.54 (d, J = 9.0 Hz, 1H), 2.47 (s br, 4H), 2.30 (s, 3H), 2.10 (td, J = 7.7, 2.4 Hz, 2H), 1.95 – 1.81 (m, 1H), 1.73 (s br, 5H).

	16	4-(((1S,2R)-2-(((1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine	¹ H NMR (360 MHz, CDCl ₃) δ 7.58 (d, <i>J</i> = 2.2 Hz, 1H), 7.48 (d, <i>J</i> = 8.6 Hz, 1H), 7.28 (dd, <i>J</i> = 9.6, 3.1 Hz, 1H), 5.66 (s, 1H), 4.36 (dd, <i>J</i> = 9.9, 7.3 Hz, 1H), 4.20 (dd, <i>J</i> = 9.9, 6.8 Hz, 1H), 3.67 (s br, 4H), 2.84 – 2.72 (m, 2H), 2.68 – 2.55 (m, 1H), 2.40 (s br, 5H), 2.31 (s, 3H), 2.14 (m, 2H), 1.79 (m, 2H).
	17	4-(((1S,2R)-2-(phenoxy)methyl)cyclobutyl)methyl)morpholine hydrochloride	¹ H NMR (360 MHz, MeOD- <i>d</i> ₄) δ 7.30 (dd, <i>J</i> = 8.7, 7.4 Hz, 2H), 7.03 – 6.90 (m, 3H), 4.35 – 4.18 (m, 1H), 4.14 – 3.94 (m, 3H), 3.78 (d, <i>J</i> = 11.9 Hz, 2H), 3.42 (dd, <i>J</i> = 20.6, 15.2 Hz, 4H), 3.22 – 2.90 (m, 4H), 2.28 (dd, <i>J</i> = 8.3, 5.0 Hz, 2H), 2.21 – 2.07 (m, 1H), 1.91 – 1.71 (m, 1H).
	18	1-(((1S,2R)-2-((3,4-dichlorophenoxy)methyl)cyclobutyl)methyl)pyrrolidine hydrochloride	¹ H NMR (360 MHz, CDCl ₃) δ 7.33 (d, <i>J</i> = 8.0 Hz, 1H), 6.97 (s, 1H), 6.74 (d, <i>J</i> = 6.4 Hz, 1H), 4.00 (s, 2H), 3.78 (s, 2H), 2.85 (s, 2H), 2.42 (s, 2H), 2.29 (s, 4H), 2.18 (s, 6H), 1.90 (s, 2H).
	19	4-(((1S,2R)-2-((3,4-dichlorophenoxy)methyl)cyclobutyl)methyl)morpholine hydrochloride	¹ H NMR (360 MHz, MeOD- <i>d</i> ₄) δ 7.39 (d, <i>J</i> = 8.8 Hz, 1H), 7.13 (d, <i>J</i> = 10.4 Hz, 1H), 6.90 (t, <i>J</i> = 7.8 Hz, 1H), 4.37 – 3.99 (m, 3H), 3.71 (s, 3H), 3.37 (s, 1H), 3.08 (d, <i>J</i> = 12.9 Hz, 1H), 2.93 – 2.60 (m, 6H), 2.18 (s, 2H), 1.88 (d, <i>J</i> = 55.2 Hz, 1H), 1.73 (s, 1H).
	20	1-(((1S,2R)-2-((3,4-dichlorophenoxy)methyl)cyclobutyl)methyl)-4-methylpiperidine hydrochloride	¹ H NMR (360 MHz, CDCl ₃) δ 7.37 (d, <i>J</i> = 8.8 Hz, 1H), 7.03 (d, <i>J</i> = 2.4 Hz, 1H), 6.79 (dd, <i>J</i> = 8.8, 2.4 Hz, 1H), 4.21 – 3.99 (m, 2H), 3.48 (dd, <i>J</i> = 17.8, 10.9 Hz, 3H), 3.25 (d, <i>J</i> = 12.6 Hz, 1H), 2.98 (s, 2H), 2.59 (dd, <i>J</i> = 26.2, 11.3 Hz, 2H), 2.42 – 1.90 (m, 7H), 1.79 (d, <i>J</i> = 12.2 Hz, 3H), 1.59 (s, 1H), 1.05 (d, <i>J</i> = 6.4 Hz, 3H).

	21	1-methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride	¹ H NMR (360 MHz, MeOD- <i>d</i> ₄) δ 6.24 (s, 1H), 4.37 (dd, <i>J</i> = 10.3, 9.0 Hz, 1H), 4.24 (dd, <i>J</i> = 10.4, 4.8 Hz, 1H), 3.83 (s, 3H), 3.62 (m, 2H), 3.43 (dd, <i>J</i> = 12.8, 5.3 Hz, 1H), 3.35 (d, <i>J</i> = 8.5 Hz, 1H), 3.06 (dd, <i>J</i> = 17.1, 9.0 Hz, 2H), 2.94 (dd, 2H), 2.23 (t, <i>J</i> = 8.2 Hz, 2H), 2.17 – 1.95 (m, 5H), 1.73 (t, <i>J</i> = 11.7 Hz, 1H).
	22	4-(((1S,2R)-2-(((1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine hydrochloride	¹ H NMR (360 MHz, MeOD- <i>d</i> ₄) δ 6.25 (s, 1H), 4.32 (ddd, <i>J</i> = 15.6, 10.6, 7.1 Hz, 2H), 4.03 (d, <i>J</i> = 12.8 Hz, 2H), 3.83 (s, 5H), 3.43 (dd, <i>J</i> = 13.1, 5.6 Hz, 3H), 3.15 (t, <i>J</i> = 11.7 Hz, 2H), 3.09 – 3.00 (m, 1H), 2.97 (dd, <i>J</i> = 7.8, 3.9 Hz, 1H), 2.33 – 2.19 (m, 2H), 2.19 – 2.06 (m, 1H), 1.75 (dd, <i>J</i> = 14.2, 6.7 Hz, 1H).
	23	1-methyl-5-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-3-(trifluoromethyl)-1H-pyrazole hydrochloride	¹ H NMR (360 MHz, MeOD- <i>d</i> ₄) δ 6.12 (s, 1H), 4.47 – 4.35 (m, 1H), 4.27 (dd, <i>J</i> = 9.5, 5.3 Hz, 1H), 3.92 – 3.75 (m, 2H), 3.70 (s, 3H), 3.64 (s br, 3H), 3.45 (d, <i>J</i> = 6.4 Hz, 2H), 3.05 (m, 5H), 2.33 – 1.96 (m, 8H), 1.83 (m, 1H).
	24	4-(((1S,2R)-2-(((1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)methyl)morpholine hydrochloride	¹ H NMR (360 MHz, MeOD- <i>d</i> ₄) δ 6.10 (d, <i>J</i> = 8.5 Hz, 1H), 4.39 (dd, <i>J</i> = 32.3, 24.2 Hz, 2H), 4.09 – 3.91 (m, 2H), 3.80 (dd, <i>J</i> = 11.4, 8.3 Hz, 2H), 3.70 (s, 4H), 3.50 – 3.41 (m, 3H), 3.25 – 3.05 (m, 3H), 2.90 (dd, <i>J</i> = 8.1, 3.8 Hz, 2H), 2.37 – 2.06 (m, 3H), 1.81 (d, <i>J</i> = 38.5 Hz, 1H).
	25	1-(3,4-dichlorophenyl)-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole hydrochloride	¹ H NMR (360 MHz, MeOD- <i>d</i> ₄) δ 8.15 (d, <i>J</i> = 2.6 Hz, 1H), 7.93 (d, <i>J</i> = 2.3 Hz, 1H), 7.63 (dt, <i>J</i> = 19.3, 5.6 Hz, 2H), 6.07 (d, <i>J</i> = 2.6 Hz, 1H), 4.60 – 4.27 (m, 2H), 3.65 (s, 2H), 3.57 – 3.36 (m, 2H), 3.05 (d, <i>J</i> = 33.4 Hz, 4H), 2.40 – 2.22 (m, 2H), 2.13 (dd, <i>J</i> = 24.7, 18.0 Hz, 5H), 1.82 (d, <i>J</i> =

			10.2 Hz, 1H).
	26	4-(((1S,2R)-2-(((1-(3,4-dichlorophenyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine hydrochloride	¹ H NMR (360 MHz, MeOD- <i>d</i> ₄) δ 8.15 (d, <i>J</i> = 2.4 Hz, 1H), 7.91 (d, <i>J</i> = 2.2 Hz, 1H), 7.62 (dt, <i>J</i> = 20.8, 5.5 Hz, 2H), 6.07 (d, <i>J</i> = 2.4 Hz, 1H), 4.55 – 4.33 (m, 2H), 4.04 (d, <i>J</i> = 13.1 Hz, 2H), 3.85 (dd, <i>J</i> = 20.3, 11.9 Hz, 2H), 3.47 (d, <i>J</i> = 12.6 Hz, 3H), 3.39 (d, <i>J</i> = 8.3 Hz, 1H), 3.24 – 2.94 (m, 4H), 2.37 – 2.10 (m, 3H), 1.81 (t, <i>J</i> = 9.9 Hz, 1H).
	27	1-(3,4-dichlorophenyl)-5-methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole hydrochloride	¹ H NMR (360 MHz, MeOD- <i>d</i> ₄) δ 7.71 (d, <i>J</i> = 2.3 Hz, 1H), 7.66 (d, <i>J</i> = 8.7 Hz, 1H), 7.45 (dd, <i>J</i> = 8.6, 2.3 Hz, 1H), 5.90 (s, 1H), 4.47 – 4.35 (m, 1H), 4.28 (dd, <i>J</i> = 10.5, 5.2 Hz, 1H), 3.74 – 3.55 (m, 2H), 3.47 (dd, <i>J</i> = 12.7, 5.6 Hz, 1H), 3.41 – 3.34 (m, 1H), 3.17 – 2.86 (m, 4H), 2.35 (s, 3H), 2.23 (m, 2H), 2.14 (m, 3H), 2.08 – 1.96 (m, 2H), 1.77 (m, 1H).
	28	1-(3,4-dichlorophenyl)-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole	¹ H NMR (360 MHz, CDCl ₃) δ 7.75 (d, <i>J</i> = 2.1 Hz, 1H), 7.68 (d, <i>J</i> = 2.5 Hz, 1H), 7.49 – 7.38 (m, 2H), 5.92 (d, <i>J</i> = 2.5 Hz, 1H), 4.22 (d, <i>J</i> = 3.8 Hz, 2H), 2.73 (d, <i>J</i> = 6.8 Hz, 1H), 2.56 – 2.36 (m, 7H), 2.18 – 1.97 (m, 2H), 1.89 – 1.61 (m, 6H).
	29	1-(3,4-dichlorophenyl)-5-methyl-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole	¹ H NMR (360 MHz, CDCl ₃) δ 7.58 (d, <i>J</i> = 2.5 Hz, 1H), 7.47 (d, <i>J</i> = 8.6 Hz, 1H), 7.28 (dd, <i>J</i> = 8.7, 2.5 Hz, 1H), 5.66 (s, 1H), 4.14 (dd, <i>J</i> = 5.7, 2.2 Hz, 2H), 2.70 (d, <i>J</i> = 8.9 Hz, 1H), 2.48 (s br, 4H), 2.43 – 2.35 (m, 2H), 2.30 (s, 3H), 2.09 (m, 1H), 2.05 – 1.92 (m, 1H), 1.75 (s br, 5H), 1.70 – 1.58 (m, 1H).

	30	4-(((1R,2R)-2-(((1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine	¹ H NMR (360 MHz, CDCl ₃) δ 7.57 (d, <i>J</i> = 2.4 Hz, 1H), 7.47 (d, <i>J</i> = 8.6 Hz, 1H), 7.31 – 7.24 (dd, <i>J</i> = 8.6, 2.4 Hz, 1H), 5.65 (s, 1H), 4.13 (d, <i>J</i> = 5.7 Hz, 2H), 3.68 (t, <i>J</i> = 4.6 Hz, 4H), 2.56 (dd, <i>J</i> = 11.2, 4.5 Hz, 1H), 2.49 – 2.33 (m, 6H), 2.30 (s, 3H), 2.14 – 1.93 (m, 2H), 1.87 – 1.72 (m, 1H), 1.72 – 1.55 (m, 1H).
	31	1-methyl-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole	¹ H NMR (250 MHz, CDCl ₃) δ 5.98 (s, 1H), 4.10 (d, <i>J</i> = 7.1 Hz, 2H), 3.81 (s, 3H), 2.99 – 2.35 (m, 8H), 2.21 – 1.69 (m, 8H).
	32	1-methyl-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride	¹ H NMR (250 MHz, MeOD- <i>d</i> ₄) δ 6.20 (s, 1H), 4.15 (qd, <i>J</i> = 10.3, 5.8 Hz, 2H), 3.82 (s, 3H), 3.74 – 3.55 (m, 2H), 3.50 – 3.21 (m, 2H), 3.16 – 2.97 (m, 2H), 2.63 (dt, <i>J</i> = 15.1, 8.3 Hz, 2H), 2.29 – 1.79 (m, 8H).
	33	1-methyl-3-(((1S,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole	¹ H NMR (360 MHz, CDCl ₃) δ 5.97 (s, 1H), 4.28 (dd, <i>J</i> = 9.9, 7.2 Hz, 1H), 4.15 (dd, <i>J</i> = 10.0, 6.7 Hz, 1H), 3.80 (s, 3H), 2.79 (m, 2H), 2.71 (dd, <i>J</i> = 12.7, 3.7 Hz, 1H), 2.50 (s br, 5H), 2.10 (m, 2H), 1.95 – 1.81 (m, 1H), 1.75 (s br, 5H).
	34	1-methyl-3-(((1S,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride	¹ H NMR (360 MHz, MeOD- <i>d</i> ₄) δ 6.24 (s, 1H), 4.37 (dd, <i>J</i> = 10.3, 9.0 Hz, 1H), 4.24 (dd, <i>J</i> = 10.4, 4.8 Hz, 1H), 3.83 (s, 3H), 3.62 (m, 2H), 3.43 (dd, <i>J</i> = 12.8, 5.3 Hz, 1H), 3.35 (d, <i>J</i> = 8.5 Hz, 1H), 3.06 (dd, <i>J</i> = 17.1, 9.0 Hz, 2H), 2.94 (dd, 2H), 2.23 (t, <i>J</i> = 8.2 Hz, 2H), 2.17 – 1.95 (m, 5H), 1.73 (t, <i>J</i> = 11.7 Hz, 1H).

	35	1-methyl-3-(((1S,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole	¹ H NMR (250 MHz, CDCl ₃) δ 5.98 (s, 1H), 4.10 (d, <i>J</i> = 7.1 Hz, 2H), 3.81 (s, 3H), 2.99 – 2.35 (m, 8H), 2.21 – 1.69 (m, 8H).
	36	4-(((1S,2S)-2-(((1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine	¹ H NMR (360 MHz, CDCl ₃) δ 7.57 (d, <i>J</i> = 2.4 Hz, 1H), 7.47 (d, <i>J</i> = 8.6 Hz, 1H), 7.31 – 7.24 (dd, <i>J</i> = 8.6, 2.4 Hz, 1H), 5.65 (s, 1H), 4.13 (d, <i>J</i> = 5.7 Hz, 2H), 3.68 (t, <i>J</i> = 4.6 Hz, 4H), 2.56 (dd, <i>J</i> = 11.2, 4.5 Hz, 1H), 2.49 – 2.33 (m, 6H), 2.30 (s, 3H), 2.14 – 1.93 (m, 2H), 1.87 – 1.72 (m, 1H), 1.72 – 1.55 (m, 1H).
	37	N,N-diethyl-N-(((1S,2S)-2-(phoxymethyl)cyclobutyl)methyl)ethanamine	¹ H NMR (250 MHz, CDCl ₃) δ 7.33 – 7.21 (m, 2H), 6.90 (dd, <i>J</i> = 7.7, 6.6 Hz, 3H), 3.94 (d, <i>J</i> = 3.7 Hz, 2H), 2.71 (dd, <i>J</i> = 11.2, 6.4 Hz, 1H), 2.57 (dd, <i>J</i> = 14.0, 7.0 Hz, 5H), 2.40 (dd, <i>J</i> = 13.6, 6.5 Hz, 2H), 2.20 – 1.97 (m, 4H), 1.74 (dd, <i>J</i> = 26.2, 10.4 Hz, 2H), 1.04 (d, <i>J</i> = 7.2 Hz, 6H).
	38	1-methyl-3-(((1S,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride	¹ H NMR (250 MHz, MeOD- <i>d</i> ₄) δ 6.20 (s, 1H), 4.15 (qd, <i>J</i> = 10.3, 5.8 Hz, 2H), 3.82 (s, 3H), 3.74 – 3.55 (m, 2H), 3.50 – 3.21 (m, 2H), 3.16 – 2.97 (m, 2H), 2.63 (dt, <i>J</i> = 15.1, 8.3 Hz, 2H), 2.29 – 1.79 (m, 8H).
	39	N,N-diethyl-N-(((1S,2S)-2-(phoxymethyl)cyclobutyl)methyl)ethanamine hydrochloride	¹ H NMR (250 MHz, CDCl ₃) δ 7.38 – 7.22 (m, 2H), 6.96 (dd, <i>J</i> = 8.1, 3.2 Hz, 3H), 4.03 (qd, <i>J</i> = 9.6, 5.9 Hz, 2H), 3.43 – 3.36 (m, 1H), 3.23 (q, <i>J</i> = 7.3 Hz, 5H), 2.78 – 2.55 (m, 2H), 2.26 (m, 1H), 2.19 – 2.04 (m, 1H), 1.93 (m, 2H), 1.34 (t, <i>J</i> = 7.3 Hz, 6H).

BIOLOGICAL ACTIVITY**Pharmacological study**Human Sigma 1 receptor radioligand assay

- 5 To investigate binding properties of sigma 1 receptor ligands to human sigma 1 receptor, transfected HEK-293 membranes and [³H](+)-pentazocine (Perkin Elmer, NET-1056), as the radioligand, were used. The assay was carried out with 7 µg of membrane suspension, 5 nM of [³H](+)-pentazocine in either absence or presence of either buffer or 10 µM Haloperidol for total and non-specific binding, respectively.
- 10 Binding buffer contained Tris-HCl 50 mM at pH 8. Plates were incubated at 37 °C for 120 minutes. After the incubation period, the reaction mix was then transferred to MultiScreen HTS, FC plates (Millipore), filtered and plates were washed 3 times with ice-cold 10 mM Tris-HCL (pH 7.4). Filters were dried and counted at approximately 40% efficiency in a MicroBeta scintillation counter (Perkin-Elmer) using EcoScint liquid
- 15 scintillation cocktail.

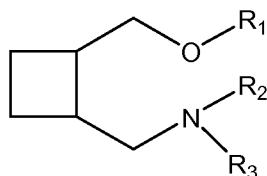
Some of the results obtained are shown in table (II) below:

Table II

Ex	Ki (nM)	Ex	Ki (nM)
1	7.1	25	20.4
3	2.8	26	13.4
13	16.5	27	72.5
15	50.3	28	104.4
16	178.3	29	113.2
17	33.9	30	578.3
18	2.3	32	17.2
19	3.7	34	28.3
20	4.8	36	465.3
21	19.1	38	75.8
22	5.6	39	39.9
23	30.1		

CLAIMS

1. A compound of general formula (I), or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof:



5

(I)

wherein

R₁ is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, and substituted or unsubstituted non-aromatic heterocyclylalkyl;

R₂ and **R₃**, identical or different, are selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted alkenyl;

or

R₂ and **R₃** form together with the bridging nitrogen atom to which they are attached a substituted or unsubstituted non-aromatic heterocyclyl.

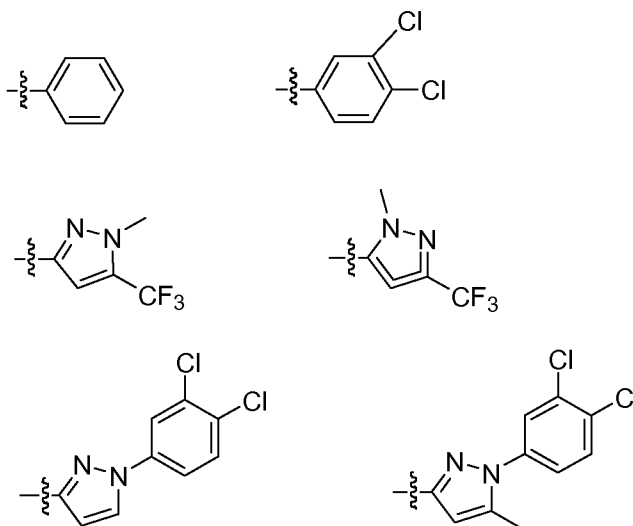
2. The compound according to claim 1, wherein **R₁** is selected from the group consisting of substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

3. The compound according to claim 2, wherein **R₁** is selected from substituted or unsubstituted C₆-C₁₄ aryl or substituted or unsubstituted 5- to 10-membered heteroaryl.

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4. The compound according to claim 3, wherein **R₁** is selected from the group consisting of:

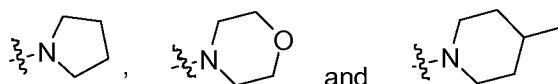
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5. The compound according to any one of claims 1 to 4, wherein R₂ and R₃ are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, and substituted or unsubstituted cycloalkyl, or R₂ and R₃ together with the bridging nitrogen atom form a substituted or unsubstituted non-aromatic heterocyclyl.

6. The compound according to claim 5, wherein R₂ and R₃ together with the bridging nitrogen atom form a substituted or unsubstituted 5- to 10-membered non-aromatic heterocyclyl.

7. The compound according to claim 6, wherein R₂ and R₃ together with the bridging nitrogen atom form a non-aromatic heterocyclyl selected from the group consisting of:



8. A compound according to any one of claims 1 to 7, which is selected from:

- 20 [1] 1-(((1S,2R)-2-(Phenoxymethyl)cyclobutyl)methyl)pyrrolidine
 [2] 4-(((1S,2R)-2-(Phenoxymethyl)cyclobutyl)methyl)morpholine
 [3] 4-methyl-1-(((1S,2R)-2-(Phenoxymethyl)cyclobutyl)methyl)piperidine
 [4] 1-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)pyrrolidine
 [5] 4-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)morpholine

- [6] 1-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)-4-methylpiperidine
- [7] 4-Methyl-1-(((1S,2R)-2-(((1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)piperidine
- 5 [8] 4-Methyl-1-(((1S,2R)-2-(((1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)methyl)piperidine
- [9] 1-Methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole
- [10] 4-(((1S,2R)-2-(((1-Methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine
- 10 [11] 1-Methyl-5-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-3-(trifluoromethyl)-1H-pyrazole
- [12] 4-(((1S,2R)-2-(((1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)methyl)morpholine
- 15 [13] 1-(3,4-Dichlorophenyl)-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole
- [14] 4-(((1S,2R)-2-(((1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine
- [15] 1-(3,4-Dichlorophenyl)-5-methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole
- 20 [16] 4-(((1S,2R)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine
- [17] 4-(((1S,2R)-2-(Phenoxymethyl)cyclobutyl)methyl)morpholine hydrochloride
- [18] 1-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)pyrrolidine hydrochloride
- 25 [19] 4-(((1S,2R)-2-((3,4-Dichlorophenoxy)methyl)cyclobutyl)methyl)morpholine hydrochloride
- [20] 1-(((1S,2R)-2-((3,4-dichlorophenoxy)methyl)cyclobutyl)methyl)-4-methylpiperidine hydrochloride
- 30 [21] 1-Methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride
- [22] 4-(((1S,2R)-2-(((1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine hydrochloride
- [23] 1-Methyl-5-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-3-(trifluoromethyl)-1H-pyrazole hydrochloride
- 35 [24] 4-(((1S,2R)-2-(((1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)oxy)methyl)cyclobutyl)methyl)morpholine hydrochloride

- [25] 1-(3,4-Dichlorophenyl)-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole hydrochloride
- [26] 4-(((1S,2R)-2-(((1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine hydrochloride
- 5 [27] 1-(3,4-Dichlorophenyl)-5-methyl-3-(((1R,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole hydrochloride
- [28] 1-(3,4-Dichlorophenyl)-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole
- [29] 1-(3,4-Dichlorophenyl)-5-methyl-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-1H-pyrazole
- 10 [30] 4-(((1R,2R)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine
- [31] 1-Methyl-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole
- 15 [32] 1-Methyl-3-(((1R,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride
- [33] 1-Methyl-3-(((1S,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole
- [34] 1-Methyl-3-(((1S,2R)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride
- 20 [35] 1-Methyl-3-(((1S,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole
- [36] 4-(((1S,2S)-2-(((1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yl)oxy)methyl)cyclobutyl)methyl)morpholine
- 25 [37] N,N-Diethyl-N-(((1S,2S)-2-(phenoxy)methyl)cyclobutyl)methyl)ethanamine
- [38] 1-methyl-3-(((1S,2S)-2-(pyrrolidin-1-ylmethyl)cyclobutyl)methoxy)-5-(trifluoromethyl)-1H-pyrazole hydrochloride
- [39] N,N-Diethyl-N-(((1S,2S)-2-(phenoxy)methyl)cyclobutyl)methyl)ethanamine hydrochloride
- 30 or a solvate or prodrug thereof as well as any pharmaceutically acceptable salt of the free-base compounds.

9. A pharmaceutical composition comprising at least one compound of general formula (I) as defined in any one of claims 1 to 8, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof and a pharmaceutically acceptable excipient.
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10. A compound of general formula (I) as defined in any one of claims 1 to 8, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, for use as a medicament.
- 5 11. The compound for use according to claim 10, wherein the medicament is for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition.
- 10 12. The compound for use according to claim 11, wherein the sigma receptor-mediated disease or condition is selected from pain; diarrhoea; lipoprotein disorders; hyperlipidemia; hypertriglyceridemia; hypercholesterolemia; obesity; migraine; arthritis; hypertension; arrhythmia; ulcer; glaucoma; learning, memory and attention deficits; cognition disorders; neurodegenerative diseases; demyelinating diseases; addiction to drugs and chemical substances; tardive dyskinesia; stroke; epilepsy; stress; cancer; psychotic conditions; inflammation and autoimmune diseases.
- 15 13. The compound for use according to claim 12, wherein the pain is selected from neuropathic pain, inflammatory pain or other pain conditions involving allodynia and/or hyperalgesia.
- 20 14. The compound for use according to claim 12, wherein the addiction to drugs and chemical substances is selected from addiction to cocaine, amphetamine, ethanol or nicotine;
- 25 wherein the stroke is ischemic stroke; and
wherein the psychotic conditions are selected from depression, anxiety or schizophrenia.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/066223

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07C217/44 C07D401/12 C07D413/12 C07D211/14 C07D295/096
 A61K31/13 A61K31/415 A61K31/435 A61P25/00
 ADD.
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
 C07C C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/015266 A1 (ESTEVE LABOR DR [ES]; CUBERES ALTISEN MARIA ROSA [ES]; CORBERA ARJONA) 7 February 2008 (2008-02-07) cited in the application abstract claim 1 ----- -/--	1-14

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 24 September 2014	Date of mailing of the international search report 07/10/2014
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Fitz, Wolfgang
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/066223

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>TORRES E ET AL: "Synthesis and structural study of novel dimethylcyclobutyl beta-peptides", TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 65, no. 29-30, 18 July 2009 (2009-07-18), pages 5669-5675, XP026714613, ISSN: 0040-4020, DOI: 10.1016/J.TET.2009.05.039 [retrieved on 2009-05-23] chart 1 schemes 1 and 2</p> <p style="text-align: center;">-----</p>	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/066223

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008015266 A1	07-02-2008	CA 2660028 A1	07-02-2008
		CN 101563332 A	21-10-2009
		EP 2066648 A1	10-06-2009
		JP 2009545625 A	24-12-2009
		US 2010105680 A1	29-04-2010
		WO 2008015266 A1	07-02-2008
