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(54) **IMIDAZO[2,1-b]THIAZOLE DERIVATIVES, THEIR PREPARATION AND USE AS MEDICAMENTS**

IMIDAZO[1,2-b]THIAZOL-DERIVATE, DEREN HERSTELLUNG UND VERWENDUNG ALS ARZNEIMITTEL

DÉRIVÉS D'IMIDAZO[2,1-b]THIAZOLE, LEUR PRÉPARATION ET LEUR UTILISATION COMME MÉDICAMENTS

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EP-A2- 0 141 072 WO-A1-2007/098961
WO-A2-2009/040552

• **SCRIBNER A ET AL: "Synthesis and biological activity of anticoccidial agents: 5,6-Diarylimidazo[2,1-b][1,3]thiazoles", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 18, no. 19, 1 October 2008 (2008-10-01), pages 5263-5267, XP025433914, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2008.08.063 [retrieved on 2008-08-22]**

EP 2 870 164 B1

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Description**FIELD OF THE INVENTION**

5 [0001] The present invention relates to new imidazo[2,1-b]thiazole derivatives having a great affinity for sigma receptors, especially sigma-1 receptors, as well as to the process for the preparation thereof, to compositions comprising them, and to their use as medicaments.

BACKGROUND OF THE INVENTION

10 [0002] 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 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 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 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.

[0003] "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 opioid, NMDA, dopaminergic, and other known neurotransmitter or hormone receptor families (G. Ronsisvalle et al. Pure Appl. Chem. 73, 1499-1509 (2001)).

25 [0004] 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. Haloperidol has similar affinities for both subtypes.

[0005] 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 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. The sigma-1 receptor is of great interest in pharmacology in view of its possible physiological role in processes related to analgesia, anxiety, addiction, amnesia, depression, schizophrenia, stress, neuroprotection and psychosis [Kaiser et al (1991) Neurotransmissions 7 (1): 1-5], [Walker, J.M. et al, Pharmacological Reviews, 1990, 42, 355] and [Bowen W.D. (2000) Pharmaceutica Acta Helvetiae 74: 211-218].

30 [0006] The Sigma-2 receptor is also expressed in numerous adult mammal tissues (e.g. nervous system, immune system, endocrine system, liver, kidney). Sigma-2 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

35 als can be used in the signaling route for normal cells and/or in induction of apoptosis.

[0007] Agonists of Sigma-2 receptors induce changes in cell morphology, apoptosis in several types of cell lines and regulate the expression of p-glycoprotein mRNA, so that they are potentially useful as antineoplastic agents for treatment of cancer. In fact, Sigma-2 receptor agonists have been observed to induce apoptosis in mammary tumour cell lines resistant to common antineoplastic agents that damage DNA. In addition, agonists of Sigma-2 receptors enhance the cytotoxic effects of these antineoplastic agents at concentrations in which the agonist is not cytotoxic.

[0008] Thus, agonists of Sigma-2 receptors 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.

40 [0009] Antagonists of Sigma-2 receptors can prevent the irreversible motor side effects caused by typical neuroleptic agents. In fact, it has been found that antagonists of Sigma-2 receptors 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.

55 [0010] 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 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.

[0011] In view of the potential therapeutic applications of agonists or antagonists of the sigma receptor, a great effort has been directed to find selective ligands. Different sigma receptor ligands have been reported.

[0012] For instance, the international patent application WO2007/098961 describes 4,5,6,7 tetrahydrobenzo[b]thiophene derivatives having pharmacological activity towards the sigma receptor.

[0013] Spiro[benzopyran] or spiro[benzofuran] derivatives were also disclosed in EP1847542 as well as pyrazole derivatives (EP1634873) with pharmacological activity on sigma receptors.

[0014] WO2009071657 also reports tricyclic triazolic compounds having good activity towards sigma receptors.

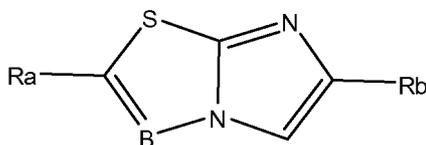
[0015] Some imidazo[2,1-b]thiazole derivatives with therapeutic activity have been disclosed so far in the prior art. For instance document WO 2009040552 imidazothiadiazoles for treating cancer via inhibition of protein kinases. CA 1053239 also discloses some imidazo[2,1-b]thiazole derivatives with antihyperglycaemic activity. WO2005079735 and US 20060156484 teaches among other compounds imidazo[2,1-b]thiazole derivatives although as dyeing agents for keratin. EP0141072 teaches imidazothiadiazoles as antihypertensive diuretic and uricosuric agents. Also Scribner et al. [Bioorganic & Medicinal Chemistry Letters 18 (2008):5263-5267] discloses 5, 6 diarylimidazo[2,1-b][1,3]thiazoles as anticoccidial agents. However, none of these references discloses the imidazo[2,1-b]thiazole derivatives of the present invention. In addition none of these references suggest that imidazo[2,1-b]thiazole derivatives can be active towards sigma receptors.

[0016] Nevertheless, there is still a need to find compounds having pharmacological activity towards the sigma receptor, being both effective and selective, and having good "drugability" properties, i.e. good pharmaceutical properties related to administration, distribution, metabolism and excretion.

SUMMARY OF THE INVENTION

[0017] The present invention discloses novel compounds with great affinity to sigma receptors which might be used for the treatment of sigma related disorders or diseases.

[0018] Specifically, it is an object of the present invention novel imidazo[2,1-b]thiazole derivatives of general formula (I):



(I)

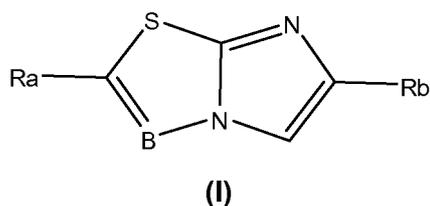
[0019] Another object of the invention is the different processes for preparation of compounds of general formula (I).

[0020] Another object of the invention refers to the use of such compounds of general formula (I) for the treatment or prophylaxis of sigma receptor mediated diseases or conditions, especially sigma-1 mediated diseases or conditions. Within the group of diseases or conditions mediated by the sigma receptor for which the compounds of the invention are effective diarrhea, 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, ischemic stroke, epilepsy, stroke, stress, cancer, psychotic conditions, in particular depression, anxiety or schizophrenia; inflammation or autoimmune diseases, may be cited. Compounds of the invention are very good and are especially effective for the treatment and prophylaxis of pain, especially neuropathic pain, inflammatory pain or other pain conditions involving allodynia and/or hyperalgesia.

[0021] It is also an object of the invention pharmaceutical compositions comprising one or more compounds of general formula (I) with at least one pharmaceutically acceptable excipient. 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.

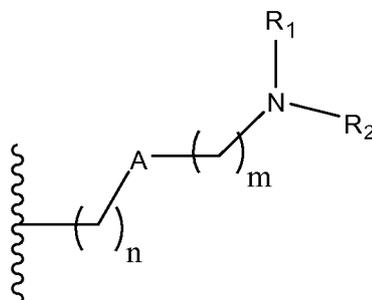
DETAILED DESCRIPTION OF THE INVENTION

[0022] The invention first relates to a compound of general formula (I):



where

15 R_a and R_b independently represent a 5 or 6-membered aryl radical optionally substituted by a halogen or a branched or unbranched, saturated alkyl radical C_{1-6} ; a 5 or 6-membered heteroaryl radical having at least one heteroatom selected from N, O or S as ring member, optionally substituted by a halogen or a branched or unbranched, saturated alkyl radical C_{1-6} ; or the following moiety:



with the proviso that one of R_a and R_b represents this moiety and the other one represents 5 or 6-membered aryl radical optionally substituted by a halogen or a branched or unbranched, saturated alkyl radical C_{1-6} ; or a 5 or 6-membered heteroaryl radical having at least one heteroatom selected from N, O or S as ring member, optionally substituted by a halogen or a branched or unbranched, saturated alkyl radical C_{1-6}

35 **A** is a C or O;

B is a C or N;

40 R_1 and R_2 independently represent a H; or R_1 and R_2 together with the bridging N form an 5 to 7-membered heterocyclic ring which can have at least one additional heteroatom selected from N, O or S and that can be optionally substituted by a branched or unbranched, saturated or unsaturated, aliphatic radical C_{1-10} or by an aryl radical optionally substituted by an alkyl C_{1-6} , a halogen or an OH group;

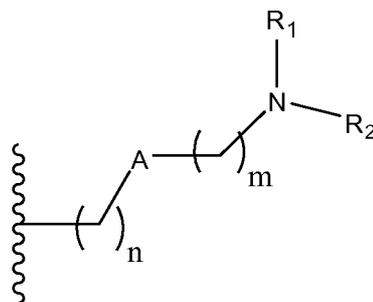
45 **n** is 0, 1 or 2;

m is 0, 1, 2, 3 or 4;

with the proviso that when A is O m is different from 0; and

50 with the proviso that when B represents a C and R_b represents a phenyl substituted by a halogen, R_a cannot represent the moiety:

55

5
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with R_1 and R_2 together with the bridging N forming a piperazine,
or a pharmaceutically acceptable salt, enantiomer and geometric/diastereoisomeric isomer or solvate thereof.

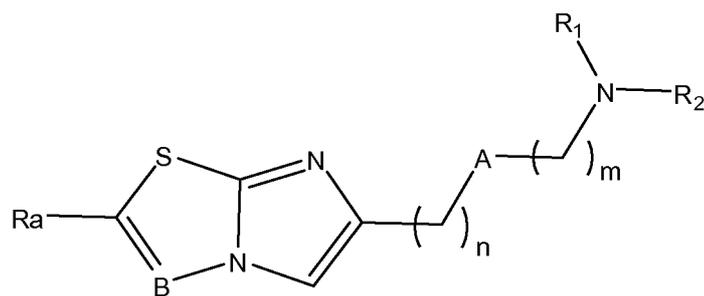
- 15 **[0023]** "Halogen" or "halo" as referred in the present invention represent fluorine, chlorine, bromine or iodine.
- [0024]** "Alkyl radicals", as referred to in the present invention, are saturated aliphatic radicals. They may be linear or branched. C_{1-6} alkyl as expressed in the present invention means an alkyl radical of 1, 2, 3, 4, 5 or 6 carbon atoms.
- 20 **[0025]** An "aryl radical", as referred to in the present invention, is understood as meaning ring systems with at least one aromatic ring but without heteroatoms even in only one of the rings. These aryl radicals may optionally be mono- or polysubstituted by substituents independently selected from a C_{1-6} alkyl group, -, -F, -Cl, -I, -Br, - -OH, . Preferred examples of aryl radicals include but are not restricted to phenyl, naphthyl, fluoranthenyl, fluorenyl, tetralinyl or indanyl or anthracenyl radicals, which may optionally be mono- or polysubstituted, if not defined otherwise.
- 25 **[0026]** A "heteroaryl radical", is understood as meaning heterocyclic ring systems which have at least one aromatic ring and may optionally contain one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur and may optionally be mono- or polysubstituted by substituents independently selected from a C_{1-6} alkyl group, F, Cl, I, Br, OH, . Preferred examples of heteroaryls include but are not restricted to furan, benzofuran, thiophene, benzothio-
ophene, pyrrole, pyridine, pyrimidine, pyridazine, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, benzothiazole, triazole, pyrazole, isoxazole, indole, benzotriazole, benzodioxolane, benzodioxane, benzimidazole, car-
bazole and quinazoline.
- 30 **[0027]** The term "condensed" according to the present invention means that a ring or ring-system is attached to another ring or ring-system, whereby the terms "annulated" or "annelated" are also used by those skilled in the art to designate this kind of attachment.
- [0028]** The term "ring system" according to the present invention refers to ring systems comprising saturated, unsatu-
rated or aromatic carbocyclic ring systems which contain optionally at least one heteroatom as ring member and which
35 are optionally at least mono-substituted. Said ring systems may be condensed to other carbocyclic ring systems such as aryl groups, naphthyl groups, heteroaryl groups, cycloalkyl groups, etc.
- [0029]** "Cyclyl groups/radicals" or "cyclic systems", as defined in the present invention, comprise any saturated, un-
saturated or aromatic carbocyclic ring systems which contain optionally at least one heteroatom as ring member and
40 which are optionally at least mono-substituted. Cyclyl groups or cyclic systems preferably comprise aryl, heteroaryl, cyclyl, heterocyclyl and/or spiro ring systems.
- [0030]** "Heterocyclyl groups/radicals" or "heterocyclic ring or systems", as defined in the present invention, comprise any saturated, carbocyclic ring systems which are optionally at least mono-substituted and which contain at least one heteroatom as ring member. Preferred heteroatoms for these heterocyclyl groups are N, S or O. Preferred substituents for heterocyclyl radicals, according to the present invention, are F, Cl, Br, I, phenyl and/or C_{1-6} alkyl.
- 45 **[0031]** The term "salt" is to be understood as meaning any form of the active compound according to the invention in which this assumes an ionic form or is charged and is coupled with a counter-ion (a cation or anion) or is in solution. By this are also to be understood complexes of the active compound with other molecules and ions, in particular complexes which are complexed via ionic interactions.
- [0032]** The term "physiologically acceptable salt" or "pharmaceutically acceptable salt" is understood in particular, in
50 the context of this invention, as salt (as defined above) formed either with a physiologically tolerated acid, that is to say salts of the particular active compound with inorganic or organic acids which are physiologically tolerated -especially if used on humans and/or mammals - or with at least one, preferably inorganic, cation which are physiologically tolerated - especially if used on humans and/or mammals. Examples of physiologically tolerated salts of particular acids are salts of:
55 of: hydrochloric acid, hydrobromic acid, sulfuric acid, hydrobromide, monohydrobromide, monohydrochloride or hydrochloride, methiodide, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, hippuric acid picric acid and/or aspartic acid. Examples of physiologically tolerated salts of particular bases are salts of alkali metals and alkaline earth metals and with NH_4 .
- [0033]** The term "solvate" is to be understood as meaning any form of the active compound according to the invention

in which this compound has attached to it via noncovalent binding another molecule (most likely a polar solvent) especially including hydrates and alcoholates, e.g. methanolate.

The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted in vivo to the compounds of the invention. Such derivatives would readily occur to those skilled in the art, and include, depending on the functional groups present in the molecule and without limitation, the following derivatives of the compounds of the invention: esters, amino acid esters, phosphate esters, metal salts sulfonate esters, carbamates, and amides. Examples of well known methods of producing a prodrug of a given acting compound are known to those skilled in the art and can be found e.g. in Krogsgaard-Larsen et al. "Textbook of Drug design and Discovery" Taylor & Francis (april 2002).

[0034] Particularly favored prodrugs are those that increase the bioavailability of the compounds when such compounds are administered to a patient (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species. Prodrugs are not part of the invention.

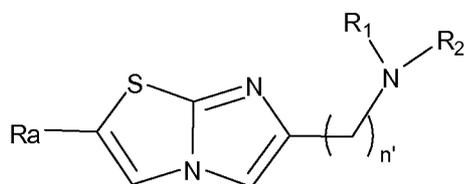
[0035] In a particular and preferred embodiment of the invention the compounds of the invention have a general formula (Ia):



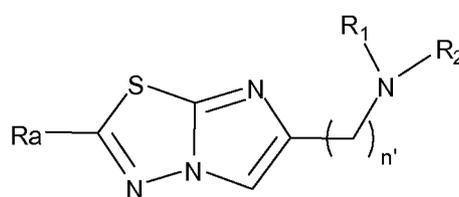
(Ia)

where R_a , R_1 , R_2 , A , B , n and m have the same meaning as for general formula (I).

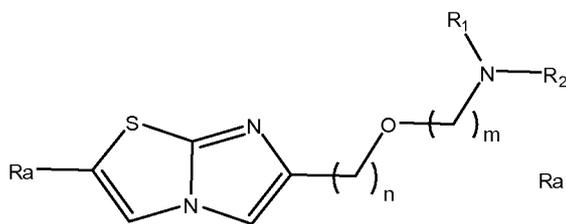
[0036] In a yet more particular embodiment, compounds of the invention have a general formula I selected from (Iaa), (Iab), (Iac) or (Iad):



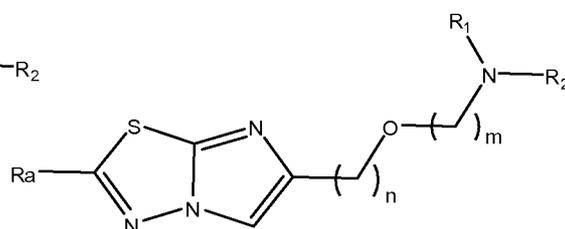
(Iaa)



(Iab)



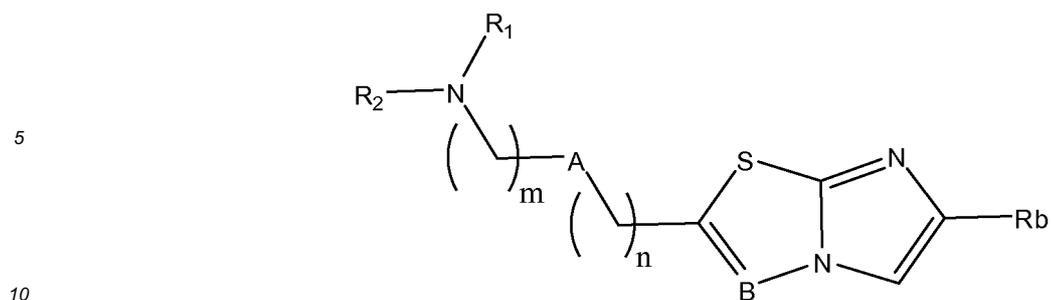
(Iac)



(Iad)

where R_a , R_1 , R_2 , n and m have the same meaning as for general formula (I) and n' are 1 or 2.

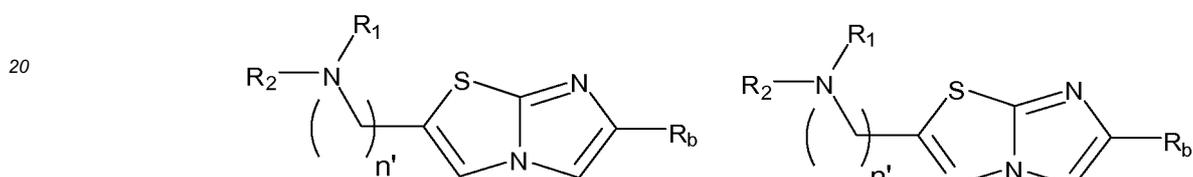
[0037] In another particular and preferred embodiment of the invention the compounds may have a general formula (Ib):



(Ib)

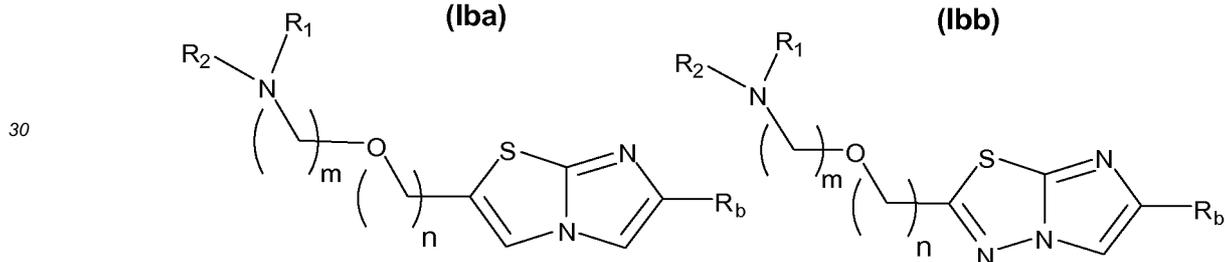
15 where R_b , R_1 , R_2 , A , B , n and m have the same meaning as for general formula (I).

[0038] A still more particular embodiment is represented by compounds of general formula (Iba), (Ibb), (Ibc) or (Ibd):



(Iba)

(Ibb)

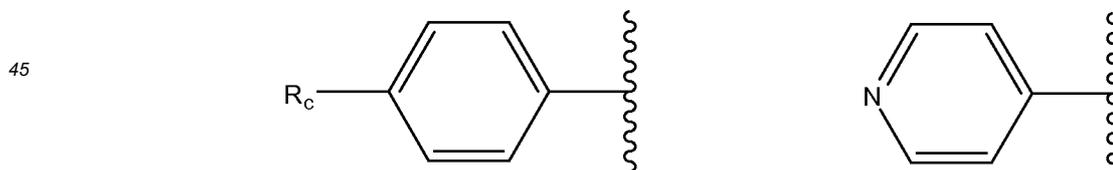


(Ibc)

(Ibd)

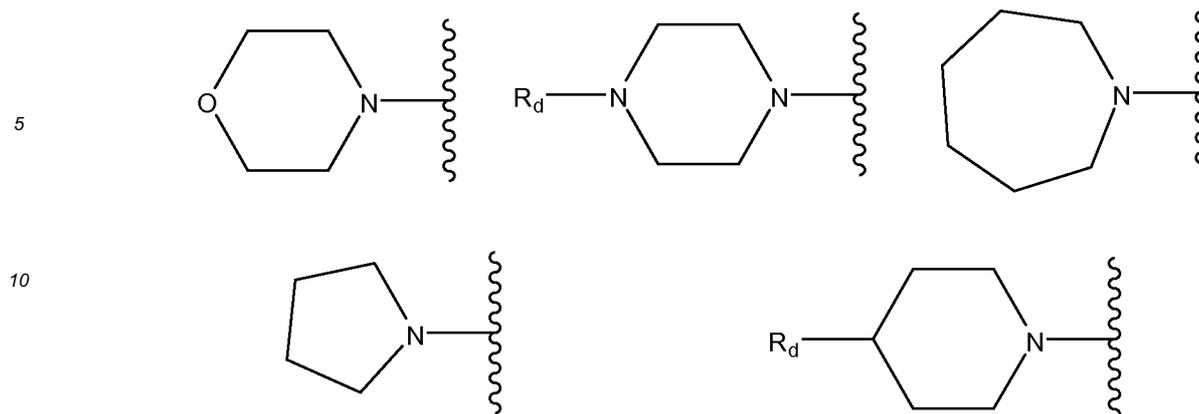
40 where R_b , R_1 , R_2 , n and m have the same meaning as for general formula (I) and n' is 1 or 2.

[0039] In another preferred embodiment of the invention, R_a or R_b in either compounds of formula (I), (Ia) or (Ib) may represent a group selected from:



50 where R_c represents H, a C_{1-6} alkyl, a halogen or an $-OR'$ group where R' represents a linear or branched C_{1-6} -alkyl group.

[0040] In yet another preferred embodiment of the invention R_1 and R_2 together with the bridging N form a group selected from:



where R_d represents a H, a C_{1-6} alkyl or a phenyl group optionally substituted by a C_{1-6} alkyl, a halogen or an -OH group.

[0041] In a particular and preferred embodiment **A** is C and m and n are both 0 for compounds of formula (I), (Ia) or (Ib).

[0042] In another particular and preferred embodiment of compounds of formula (I), (Ia) or (Ib) **A** is O, n is 1 and m is 2.

[0043] In preferred variants of the invention, the sigma ligand of formula (I) is selected from:

20

[1] 4-((2-phenylimidazo[2,1-*b*]thiazol-6-yl)methyl)morpholine maleate,

[2] 6-((4-methylpiperazin-1-yl)methyl)-2-(pyridin-4-yl)imidazo[2,1-*b*]thiazole maleate,

25

[3] 6-(2-(4-methylpiperazin-1-yl)ethyl)-2-phenylimidazo[2,1-*b*]thiazole maleate,

[4] 6-((2-(azepan-1-yl)ethoxy)methyl)-2-phenylimidazo[2,1-*b*][1,3,4]thiadiazole maleate,

30

[5] 2-((4-methylpiperazin-1-yl)methyl)-6-phenylimidazo[2,1-*b*]thiazole maleate,

[6] 6-(azepan-1-ylmethyl)-2-phenylimidazo[2,1-*b*]thiazole maleate,

[7] 6-((4-methylpiperazin-1-yl)methyl)-2-phenylimidazo[2,1-*b*]thiazole maleate,

35

[8] 4-(2-((2-phenylimidazo[2,1-*b*]thiazol-6-yl)methoxy)ethyl)morpholine maleate,

[9] 6-((2-(azepan-1-yl)ethoxy)methyl)-2-phenylimidazo[2,1-*b*]thiazole maleate,

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[10] 2-phenyl-6-((2-(pyrrolidin-1-yl)ethoxy)methyl)imidazo[2,1-*b*]thiazole maleate,

[11] 6-((4-methylpiperazin-1-yl)methyl)-2-phenylimidazo[2,1-*b*][1,3,4]thiadiazole maleate,

[12] 2-(azepan-1-ylmethyl)-6-phenylimidazo[2,1-*b*]thiazole maleate,

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[13] 2-(4-fluorophenyl)-6-((4-methylpiperazin-1-yl)methyl)imidazo[2,1-*b*]thiazole maleate,

[14] 3-(1-((2-phenylimidazo[2,1-*b*]thiazol-6-yl)methyl)piperidin-4-yl)phenol maleate

[0044] 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 centers 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.

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[0045] 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 amine-imine, amide-imidic acid, keto-enol, lactam-lactim, etc.

[0046] 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.

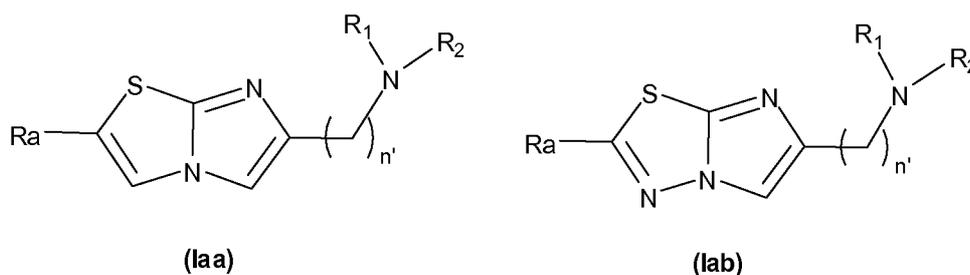
[0047] The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents 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.

[0048] In another aspect, the invention refers to the processes for obtaining the compounds of general formula (I). Four different procedures have been developed for obtaining all the compound derivatives of the invention, herein the procedures will be explained below in methods A to D.

METHOD A

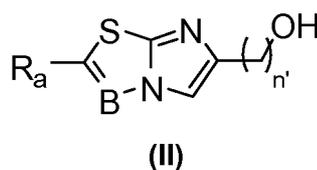
[0049] Method A represents the process for preparing compounds of general formula (Ia) and formula (Ib), that is, compounds of formula (I) where B can be C or N but A represents a C and n is always 1 or 2.

[0050] The process for the preparation of a compound of general formula (Ia) or (Ib) according to method A:



where R_a , R_1 and R_2 have the same meanings as for formula (I) and n' is 1 or 2, the process comprises:

a) the reaction between a compound of general formula (II):



where B is a C or a N, with a sulphonide halide such as methanesulphonide chloride, and

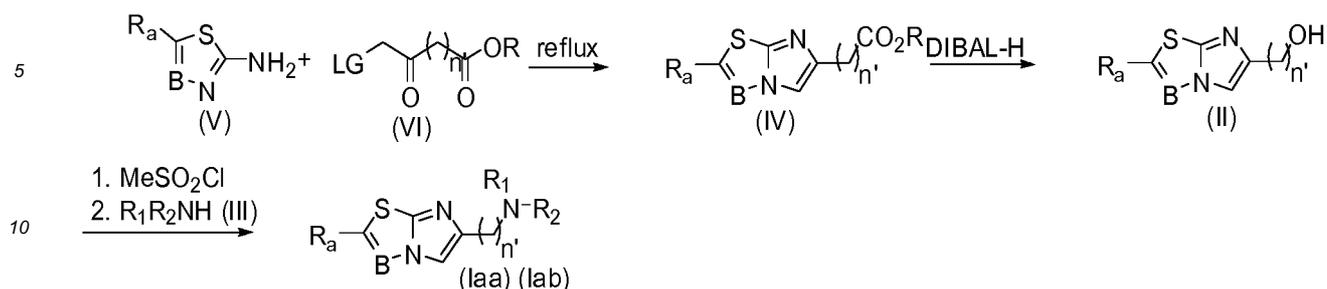
b) the reaction between the resulting compound with a compound of general formula (III):



the reactions being carried out in the presence of a base such as triethylamine in a suitable organic solvent such as dichloromethane.

[0051] The general route for the synthesis of compounds of formula (Ia) and (Ib) by method A is represented in scheme 1:

Scheme 1



15 **[0052]** Compounds of formula (Iaa) and (Iab) as expressed in scheme 1 are prepared by a nucleophilic substitution between a compound of formula (II), converted to the corresponding mesylate by treatment with methanesulfonyl chloride, and a convenient substituted amine (III). This reaction is conducted in the presence of a base such as triethylamine and in a suitable solvent such as CH₂Cl₂ at room temperature.

20 **[0053]** In turn, compounds of formula (II) are obtained by reduction of compounds of formula (IV) by methods generally known by the skilled in the art (Bioorg. Med. Chem. Lett. 2008, 18, 5263).

[0054] Amines (III) are commercially available.

[0055] Compounds of formula (IV) are obtained by condensation between compounds of formula (V) and compounds of formula (VI) by methods generally known by the skilled in the art (J. Med. Chem. 2009, 52, 1275; WO2007019344).

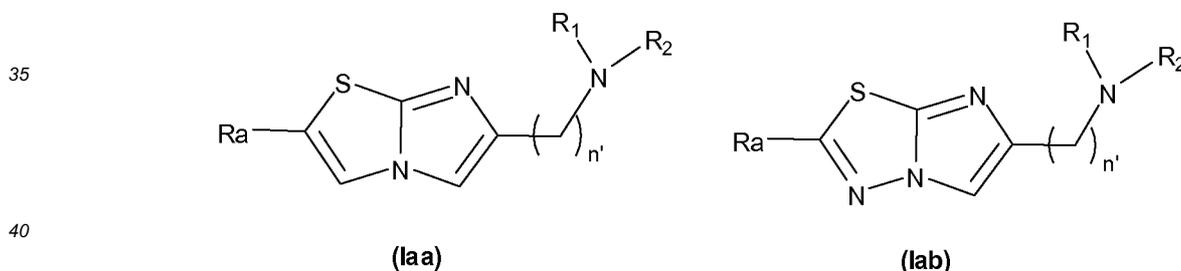
[0056] Compounds (V) are commercially available or obtained by reaction between a convenient substituted acetaldehyde and thiourea as described in WO2008144767.

25 **[0057]** Oxoacid derivatives (VI) are commercially available.

METHOD B

30 **[0058]** Method B represents a different process for preparing compounds of general formula (Iaa) and formula (Iab), that is, compounds of formula (Ia) where B can be C or N but A represents a C and n is always 1 or 2.

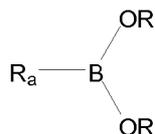
[0059] Method B represents a process for the preparation of a compound of general formula (Iaa) or (Iab):



45 where R_a, R₁ and R₂ have the same meanings as for formula (I) and n' is 1 or 2, the process comprising the reaction between a compound of general formula (VII):



55 where X represents a halogen and B a C or a N, and a compound of general formula (VIII):

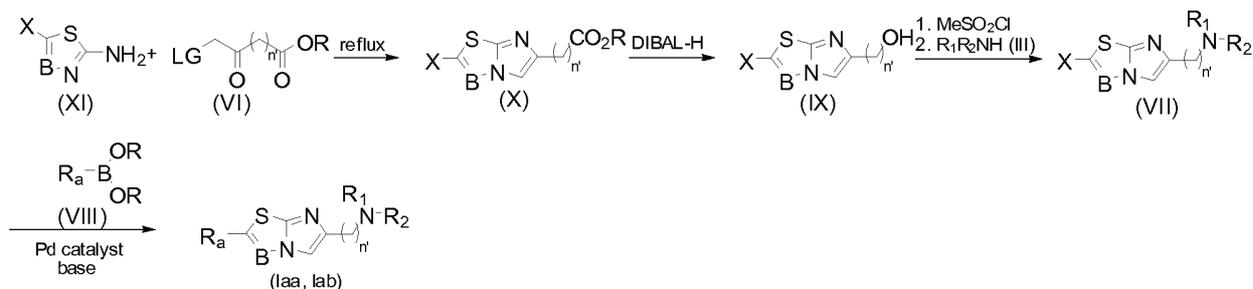


(VIII)

where each **R** represent independently represent a hydrogen, a C₁₋₆ alkyl or both R together with the bridging boron form a boronic cyclic ester such as a boronic acid pinacol ester in the presence of a suitable catalyst, such as a palladium catalyst, and a base such as potassium carbonate, phosphate hydroxide or alkoxides in an organic reaction-inert solvent such as THF, DMSO, DMF, diethyl ether or ethanol..

[0060] The general route for the synthesis of compounds of formula (Iaa) and (Iab) by method B is represented in scheme 2:

Scheme 2



[0061] Compounds of formula (Iaa) and (Iab) are obtained by a Suzuki coupling of a compound of formula (VII) with organoboronic acid derivatives (VIII) in the presence of a palladium catalyst, a base and a suitable solvent. This reaction is conducted in a reaction-inert solvent, such as tetrahydrofuran (THF), dimethylsulfoxide (DMSO), dimethylformamide (DMF), diethyl ether, ethanol, etc. The palladium catalyst may be selected from a Pd(II) or Pd(0) catalyst, e. g. Pd(OAc)₂, Pd(PPh₃)₄ or Pd/C. The base that is involved in the coordination sphere of the palladium and in the acceleration of the transmetalation step may be selected from a negatively charged base, such as sodium or potassium carbonate, phosphate, hydroxide, alkoxides, etc.

[0062] In turn, compounds of formula (VII) are obtained by nucleophilic substitution between a compound of formula (IX), converted to the corresponding mesylate by treatment with methanesulfonyl chloride, and a convenient substituted amine (III). This reaction is conducted in the presence of a base such as triethylamine and in a suitable solvent such as CH₂Cl₂ at room temperature.

Organoboronic acid derivatives (VIII) are commercially available

[0063] Compounds of formula (IX) are obtained by reduction of compounds of formula (X) by methods generally known by the skilled in the art (Bioorg. Med. Chem. Lett. 2008, 18, 5263).

Amines (III) are commercially available.

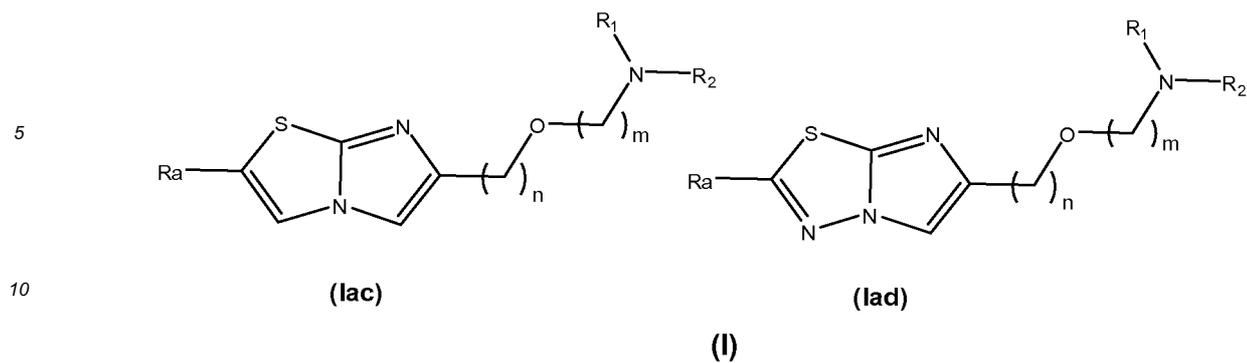
[0064] Compounds of formula (X) are obtained by condensation between compounds of formula (XI) and compounds of formula (VI) by methods generally known by the skilled in the art (J. Med. Chem. 2009, 52, 1275; WO2007019344).

[0065] Compounds (XI) and oxoacid derivatives (VI) are commercially available.

METHOD C

[0066] **Method C** represents the process for preparing compounds of general formula (Iac) and formula (Iad), that is, compounds of formula (Ia) where B can be C or N but A represents an O.

[0067] The process for the preparation of a compound of general formula (Iac) or (Iad) by method C:



where R_a , R_1 , R_2 , n and m have the same meanings as for formula (I), comprises the reaction between a compound of general formula (II):

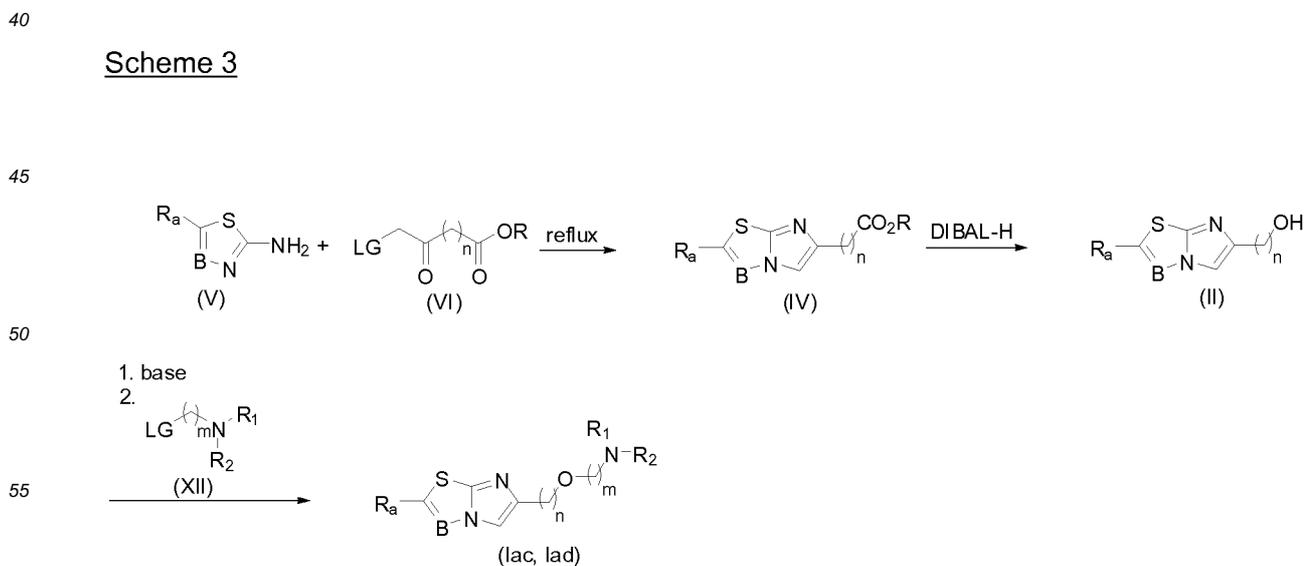


where B is C or a N, and a compound of general formula (XII):



where LG is a suitable leaving group, preferably a halogen, in the presence of a base in an organic solvent.

[0068] The general route for the synthesis of compounds of formula (Iac) and (Iad) by method C is represented in scheme 3:



[0069] Compounds of general formula (Iac) and formula (Iad) are obtained by reaction of a compound of formula (II) with a compound of formula (XII) in the presence of a base and a suitable solvent; where LG represents a leaving group that may be selected from a halide, e.g. bromide or chloride, or an arylsulfonyl group, e.g. mesylate, triflate, or tosylate, and the like. This reaction is conducted under phase transfer conditions. The base is strong enough to detract a hydrogen from the hydroxyl group, for example a negatively charged base, such as sodium or potassium carbonate, phosphate, hydroxide, alkoxides, etc.

[0070] Compounds of formula (II) are obtained by reduction of compounds of formula (IV) by methods generally known by the skilled in the art (Bioorg. Med. Chem. Lett. 2008, 18, 5263).

[0071] Compounds of formula (XII) are commercially available.

[0072] Compounds of formula (IV) are obtained by condensation between compounds of formula (V) and compounds of formula (VI) by methods generally known by the skilled in the art (J. Med. Chem. 2009, 52, 1275; WO2007019344).

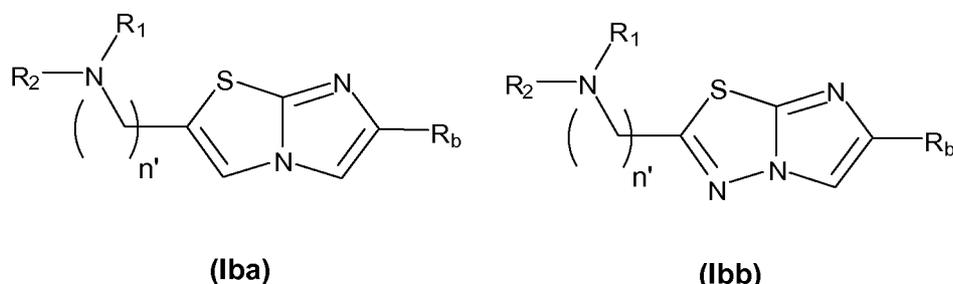
[0073] Compounds (V) are commercially available or obtained by reaction between a convenient substituted acetaldehyde and thiourea as described in WO2008144767.

[0074] Oxoacid derivatives (VI) are commercially available.

METHOD D

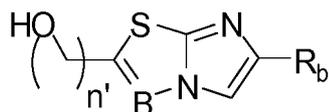
[0075] Method D represents the process for preparing compounds of general formula (Iba) and formula (Ibb), that is, compounds of formula (Ib) where B can be C or N but A represents a C and n is always 1 or 2.

[0076] Method B is represents a process for the preparation of a compound of general formula (Iba) or (Ibb):



where R_b , R_1 and R_2 have the same meanings as for formula (I) and n' is 1 or 2, the process comprising:

a) the reaction between a compound of general formula (XIII):



(XIII)

where B is C or N, with a sulphonide halide such as methansulphonidde chloride,

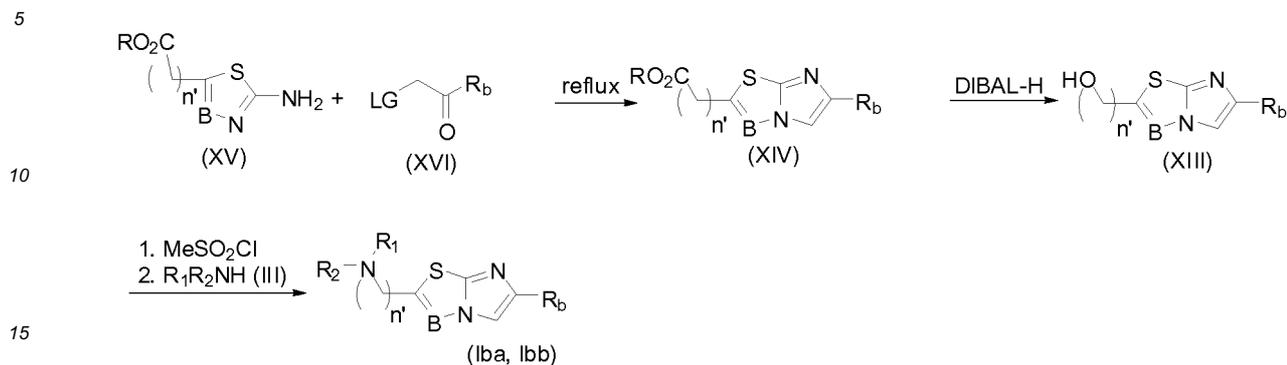
b) the reaction of the resulting compound with a compound of general formula (III):



the reactions being carried out in the presence of a base such as triethylamine in an organic solvent such as dichloromethane.

[0077] The general route for the synthesis of compounds of formula (Iba) and (Ibb) by method D is represented in scheme 4:

Scheme 4



[0078] Compounds of formula (Iba) and (Ibb) are prepared by nucleophilic substitution between a compound of formula (XIII), converted to the corresponding mesylate by treatment with methanesulfonyl chloride, and a convenient substituted amine (III). This reaction is conducted in the presence of a base such as triethylamine and in a suitable solvent such as CH₂Cl₂ at room temperature.

[0079] In turn, compounds of formula (XIII) are obtained by reduction of compounds of formula (XIV) by methods generally known by the skilled in the art (Bioorg. Med. Chem. Lett. 2008, 18, 5263).

[0080] Amines (III) are commercially available.

[0081] Compounds of formula (XIV) are obtained by condensation between compounds of formula (XV) and compounds of formula (XVI) by methods generally known by the skilled in the art (Bioorg. Med. Chem. Lett. 2008, 18, 5263; J. Med. Chem. 2009, 52, 1275; WO2007019344).

[0082] Compounds (XV) and arylketones (XVI) are commercially available.

[0083] An additional aspect of the invention relates to the therapeutic use of the compounds of general formula (I). As mentioned above, compounds of general formula (I) show a strong affinity to sigma receptors and can behave as agonists, antagonists, inverse agonists, partial antagonists or partial agonists thereof. Therefore, compounds of general formula (I) are useful as medicaments.

[0084] They are suitable for the treatment and the prophylaxis of disorders and diseases mediated by sigma receptors, especially, sigma-1 receptors. In this sense, compounds of formula (I) are very good anxiolytic and immunosuppressant and are very useful in the treatment and prophylaxis of 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, ischemic stroke, epilepsy, stroke, stress, cancer, psychotic conditions, in particular depression, anxiety or schizophrenia; inflammation or autoimmune diseases.

[0085] The compounds of formula (I) are especially suited for the treatment of pain, especially neuropathic pain, inflammatory pain or other pain conditions involving allodynia and/or hyperalgesia. PAIN is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 210). Even though pain is always subjective its causes or syndromes can be classified.

[0086] In a preferred embodiment compounds of the invention are used for the treatment and prophylaxis of allodynia and more specifically mechanical or thermal allodynia.

[0087] In another preferred embodiment compounds of the invention are used for the treatment and prophylaxis of hyperalgesia.

[0088] In yet another preferred embodiment compounds of the invention are used for the treatment and prophylaxis of neuropathic pain and more specifically for the treatment and prophylaxis of hyperpathia.

[0089] A related aspect of the invention refers to the use of compounds of formula (I) for the manufacture of a medicament for the treatment of disorders and diseases mediated by sigma receptors, as explained before.

Another aspect of the invention is a pharmaceutical composition which comprises at least a compound of general formula (I) or a pharmaceutically acceptable salt, prodrug, isomer or solvate thereof, and at least a pharmaceutically acceptable carrier, additive, adjuvant or vehicle.

[0090] The pharmaceutical composition of the invention can be formulated as a medicament in different pharmaceutical forms comprising at least a compound binding to the sigma receptor and optionally at least one further active substance

and/or optionally at least one auxiliary substance.

[0091] The auxiliary substances or additives can be selected among carriers, excipients, support materials, lubricants, fillers, solvents, diluents, colorants, flavour conditioners such as sugars, antioxidants and/or agglutinants. In the case of suppositories, this may imply waxes or fatty acid esters or preservatives, emulsifiers and/or carriers for parenteral application. The selection of these auxiliary materials and/or additives and the amounts to be used will depend on the form of application of the pharmaceutical composition.

[0092] The pharmaceutical composition in accordance with the invention can be adapted to any form of administration, be it orally or parenterally, for example pulmonarily, nasally, rectally and/or intravenously.

[0093] Preferably, the composition is suitable for oral or parenteral administration, more preferably for oral, intravenous, intraperitoneal, intramuscular, subcutaneous, intrathecal, rectal, transdermal, transmucosal or nasal administration.

[0094] The composition of the invention can be formulated for oral administration in any form preferably selected from the group consisting of tablets, drageés, capsules, pills, chewing gums, powders, drops, gels, juices, syrups, solutions and suspensions.

[0095] The composition of the present invention for oral administration may also be in the form of multiparticulates, preferably microparticles, microtablets, pellets or granules, optionally compressed into a tablet, filled into a capsule or suspended in a suitable liquid. Suitable liquids are known to those skilled in the art.

[0096] Suitable preparations for parenteral applications are solutions, suspensions, reconstitutable dry preparations or sprays.

[0097] The compounds of the invention can be formulated as deposits in dissolved form or in patches, for percutaneous application.

[0098] Skin applications include ointments, gels, creams, lotions, suspensions or emulsions.

[0099] The preferred form of rectal application is by means of suppositories.

[0100] The respective medicament may - depending on its route of administration - also contain one or more auxiliary substances known to those skilled in the art. The medicament according to the present invention may be produced according to standard procedures known to those skilled in the art.

[0101] The daily dosage for humans and animals may vary depending on factors that have their basis in the respective species or other factors, such as age, sex, weight or degree of illness and so forth. The daily dosage for humans may preferably be in the range from 1 to 2000, preferably 1 to 1500, more preferably 1 to 1000 milligrams of active substance to be administered during one or several intakes per day.

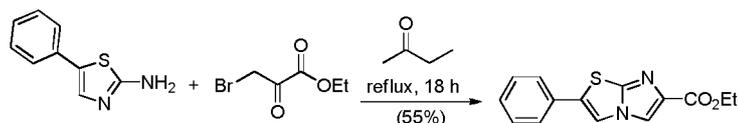
[0102] The following examples are merely illustrative of certain embodiments of the invention.

EXAMPLES

Example 1 (Method A): Synthesis of 4-((2-phenylimidazo[2,1-b]thiazol-6-yl)methyl)morpholine maleate

a) Synthesis of ethyl 2-phenylimidazo[2,1-b]thiazole-6-carboxylate

[0103]



[0104] A solution of 5-phenylthiazol-2-amine (5.0 g, 28.37 mmol) and ethyl bromopiruvate (5.3 mL, 42.56 mmol) in methyl ethyl ketone (250 mL) was refluxed overnight under argon atmosphere. The reaction mixture was evaporated to dryness. The crude product was purified by silica gel column chromatography (CH₂Cl₂: MeOH mixtures of increasing polarity as eluent) to afford the desired product (4.24 g, 55%).

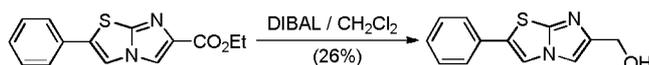
¹H-NMR (DMSO-d₆, 300 MHz) δ: 8.45 (s, 1 H), 8.39 (s, 1 H), 7.66 (m, 2H), 7.52-7.42 (m, 3H), 4.26 (d, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H) ppm.

EL-MS *m/z*: 272.1 (M).

b) Synthesis of (2-phenylimidazo[2,1-b]thiazol-6-yl)methanol

[0105]

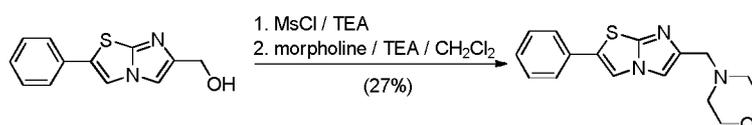
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5 **[0106]** A solution of DIBAL (1.0 M in CH₂Cl₂, 46.7 mL, 46.7 mmol) was added to a solution of ethyl 2-phenylimidazo[2,1-*b*]thiazole-6-carboxylate (4.2 g, 15.57 mmol) in CH₂Cl₂ (130 mL) cooled to 0 °C under argon atmosphere. The resulting mixture was stirred for 2 h. The reaction mixture was diluted with water and filtered through Celite®. The layers were separated and the organic phase, was dried over Na₂SO₄, and evaporated to dryness. The crude product was purified by silica gel column chromatography (CH₂Cl₂:MeOH mixtures of increasing polarity as eluent) to afford the desired product (929 mg, 26%).
 10 ¹H-NMR (DMSO-d₆, 400 MHz) δ: 8.39 (s, 1H), 7.60 (m, 3H), 7.46 (t, *J* = 8Hz, 2H), 7.37 (t, *J* = 8 Hz, 1 H), 5.07 (t, *J* = 5.8 Hz, 1 H), 4.45 (d, *J* = 4.8 Hz, 2H) ppm.
 EL-MS *m/z*: 230.1 (M).

15 **c) Synthesis of 4-((2-phenylimidazo[2,1-*b*]thiazol-6-yl)methyl) morpholine maleate**

[0107]

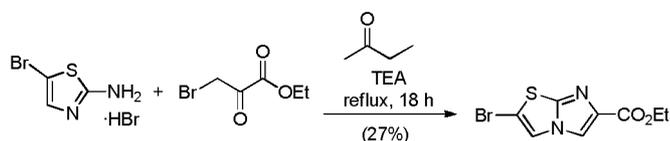


20 **[0108]** Methanesulfonyl chloride (0.1 mL, 0.99 mmol) and triethylamine (0.14 mL, 0.99 mmol) were added to a solution of (2-phenylimidazo[2,1-*b*]thiazol-6-yl)methanol (228 mg, 0.99 mmol) in CH₂Cl₂ (15 mL) cooled to 0 °C under argon atmosphere. The resulting mixture was stirred for 15 minutes. The reaction mixture was diluted with brine and extracted with CH₂Cl₂. The organic extract was dried with Na₂SO₄ and evaporated to dryness. To a solution of the previous residue in CH₂Cl₂ (8 mL), morpholine (0.082 mL, 0.94 mmol) and triethylamine (0.13 mL, 0.94 mmol) was added. The resulting mixture was stirred overnight. The reaction mixture was diluted with water and extracted with CH₂Cl₂. The organic extract was dried with Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (CH₂Cl₂:MeOH mixtures of increasing polarity as eluent) to afford the desired product (80 mg, 27%). The product was converted into the corresponding maleate salt by adding maleic acid (26 mg, 0.22 mmol) in acetone (0.35 mL), followed by filtration of the resulting solid and drying under vacuum.
 25 ¹H-NMR (CDCl₃, 400 MHz) δ: 8.49 (s, 1H), 7.90 (m, 1H), 7.63 (m, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 6.04 (s, 2H), 3.65 (m, 2H), 3.31 (m, 8H) ppm.
 30 ESI(+)-HRMS: 300.1164 [M+H]⁺.

Example 2 (Method B): Synthesis of 6-((4-methylpiperazin-1-yl)methyl)-2-(pyridin-4-yl)imidazo[2,1-*b*]thiazole maleate

40 **a) Synthesis of ethyl 2-bromoimidazo[2,1-*b*]thiazole-6-carboxylate**

[0109]

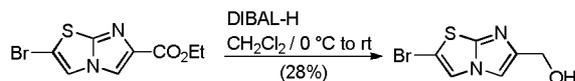


45 **[0110]** A mixture of 5-bromothiazol-2-amine hydrobromide (5.0 g, 19.23 mmol), ethyl bromopiruvate (3.6 mL, 28.85 mmol) and triethylamine (4.0 mL, 28.85 mmol) in methyl ethyl ketone (200 mL) was refluxed overnight under argon atmosphere. The reaction mixture was evaporated to dryness. The crude product was purified by silica gel column chromatography (hexane:EtOAc mixtures of increasing polarity as eluent) to afford the desired product (1.46 g, 27%).
 50 ¹H-NMR (DMSO-d₆, 300 MHz) δ: 8.34 (s, 1 H), 8.25 (s, 1 H), 4.25 (q, *J* = 6.9 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H) ppm.
 55 EI-MS *m/z*: 273.9 (M).

b) Synthesis of (2-bromoimidazo[2,1-b]thiazol-6-yl)methanol

[0111]

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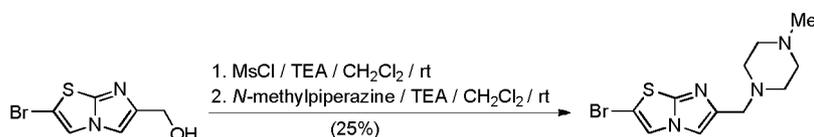
[0112] A solution of DIBAL (1.0 M in CH_2Cl_2 , 15.8 mL, 15.81 mmol) was added to a solution of ethyl 2-bromoimidazo[2,1-b]thiazole-6-carboxylate (1.45 g, 5.27 mmol) in CH_2Cl_2 (100 mL) under argon atmosphere. The resulting mixture was stirred for 4 h. The reaction mixture was diluted with water and filtered through Celite®. The layers were separated and the organic phase, was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography (CH_2Cl_2 : MeOH mixtures of increasing polarity as eluent) to afford the desired product (341 mg, 28%).

$^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz) δ : 8.18 (s, 1 H), 7.58 (s, 1 H), 5.06 (t, $J=6.4$ Hz, 1 H), 4.41 (d, $J=4.4$ Hz, 2H) ppm. EI-MS m/z : 231.9 (M).

c) Synthesis of 2-bromo-6-((4-methylpiperazin-1-yl)methyl)imidazo[2,1-b]thiazole

[0113]

20



[0114] Methanesulfonyl chloride (0.16 mL, 1.44 mmol) and triethylamine (0.2 mL, 1.44 mmol) was added to a solution of (2-bromoimidazo[2,1-b]thiazol-6-yl)methanol (335 mg, 1.44 mmol) in CH_2Cl_2 (8 mL) under argon atmosphere. The resulting mixture was stirred for 15 minutes. The reaction mixture was diluted with brine and extracted with CH_2Cl_2 . The organic extract was dried with Na_2SO_4 and evaporated to dryness. To a solution of the previous residue in CH_2Cl_2 (8 mL), *N*-methylpiperazine (0.16 mL, 1.44 mmol) and triethylamine (0.2 mL, 1.44 mmol) was added. The resulting mixture was stirred for 20 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 . The organic extract was dried with Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography (EtOAc/ NH_3 : MeOH mixtures of increasing polarity as eluent) to afford the desired product (114 mg, 25%).

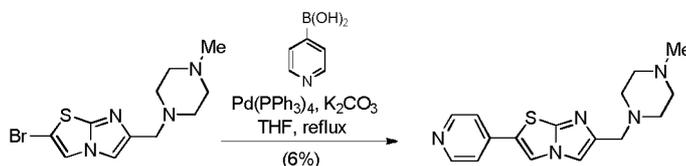
$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 7.43 (s, 1 H), 7.32 (s, 1 H), 3.58 (s, 2H), 2.58 (m, 4H), 2.48 (m, 4H), 2.28 (s, 3H) ppm. EI-MS m/z : 314.0 (M).

d) Synthesis of 6-((4-methylpiperazin-1-yl)methyl)-2-(pyridin-4-yl)imidazo[2,1-b]thiazole maleate

40

[0115]

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[0116] A mixture of 2-bromo-6-((4-methylpiperazin-1-yl)methyl)imidazo[2,1-b]thiazole (86 mg, 0.27 mmol), $\text{Pd}(\text{PPh}_3)_4$ (79 g, 0.07 mmol), 4-pyridineboronic acid (43 mg, 0.3 mmol) and 2 M solution of K_2CO_3 (0.7 mL) in THF (7 mL) was refluxed with stirring for 1 day under argon atmosphere. The reaction mixture was poured into water and extracted with 1 N HCl. The aqueous layers were basified with 2N NaOH and extracted with EtOAc. The organic layers were dried with Na_2SO_4 and evaporated to dryness. Purification of the residue by silica gel column chromatography (EtOAc/ NH_3 : MeOH mixtures of increasing polarity as eluent) afforded the desired product (5 mg, 6%). The product was converted into the corresponding maleate salt by adding maleic acid (1.0 equiv) in acetone, followed by filtration of the resulting solid and drying under vacuum.

$^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz) δ : 8.75 (s, 1H), 8.64 (d, $J=6.4$ Hz, 2H), 7.77 (m, 1H), 7.61 (d, $J=6$ Hz, 2H), 6.03 (s, 2H),

3.65 (m, 2H), 3.30 (m, 4H), 3.03 (m, 4H), 2.71 (m, 3H) ppm.

ESI(+)-HRMS: 314.1434 [M+H]⁺.

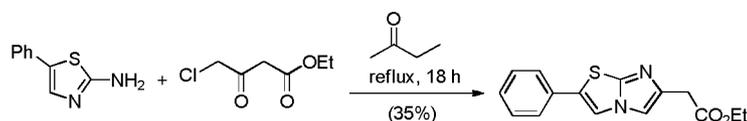
Example 3 (Method A): Synthesis of 6-(2-(4-methylpiperazin-1-yl)ethyl)-2-phenylimidazo[2,1-b]thiazole maleate

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a) Synthesis of ethyl 2-(2-phenylimidazo[2,1-b]thiazol-6-yl)acetate

[0117]

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[0118] A mixture of 5-phenylthiazol-2-amine (500 mg, 2.84 mmol) and ethyl 4-chloro-3-oxobutanoate (0.58 mL, 4.26 mmol) in methyl ethyl ketone (50 mL) was refluxed overnight under argon atmosphere. The reaction mixture was evaporated to dryness. The crude product was purified by silica gel column chromatography (CH₂Cl₂:MeOH mixtures of increasing polarity as eluent) to afford the desired product (272 mg, 35%).

20

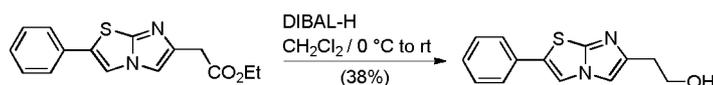
¹H-NMR (DMSO, 400 MHz) δ: 8.40 (s, 1H), 7.65 (s, 1H), 7.60 (m, 2H), 7.47 (m, 2H), 7.38 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.67 (s, 2H), 1.19 (t, J = 7 Hz, 3H) ppm.

EI-MS *m/z*: 286.1 (M).

b) Synthesis of 2-(2-phenylimidazo[2,1-b]thiazol-6-yl)ethanol

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[0119]



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[0120] A solution of DIBAL (1.0 M in CH₂Cl₂, 5.1 mL, 5.1 mmol) was added to a solution of ethyl 2-(2-phenylimidazo[2,1-b]thiazol-6-yl)acetate (486 mg, 1.7 mmol) in CH₂Cl₂ (10 mL) under argon atmosphere. The resulting mixture was stirred for 5 h. The reaction mixture was diluted with water and filtered through Celite®. The layers were separated and the organic phase was dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (CH₂Cl₂:MeOH mixtures of increasing polarity as eluent) to afford the desired product (156 mg, 38%).

35

¹H-NMR (DMSO, 400 MHz) δ: 8.37 (s, 1H), 7.60 (m, 2H), 7.52 (s, 1H), 7.46 (m, 2H), 7.36 (m, 1H), 4.60 (t, J = 5.6 Hz, 1H), 3.66 (m, 2H), 2.72 (t, J = 6.8 Hz, 2H) ppm.

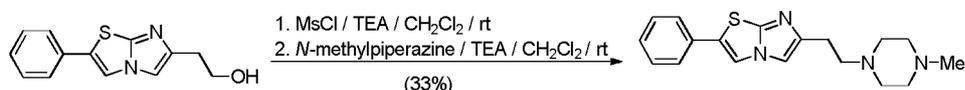
EI-MS *m/z*: 244.1 (M).

40

c) Synthesis of 6-(2-(4-methylpiperazin-1-yl)ethyl)-2-phenylimidazo[2,1-b]thiazole maleate

[0121]

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[0122] Methanesulfonyl chloride (0.048 mL, 0.62 mmol) and triethylamine (0.087 mL, 0.62 mmol) was added to a solution of 2-(2-phenylimidazo[2,1-b]thiazol-6-yl)ethanol (152 mg, 0.62 mmol) in CH₂Cl₂ (3 mL) cooled to 0 °C under argon atmosphere. The resulting mixture was stirred for 15 minutes. The reaction mixture was diluted with brine and extracted with CH₂Cl₂. The organic extract was dried with Na₂SO₄ and evaporated to dryness. To a solution of the previous residue in CH₂Cl₂ (3 mL), *N*-methylpiperazine (0.07 mL, 0.62 mmol) and triethylamine (0.087 mL, 0.62 mmol) was added. The resulting mixture was stirred overnight. The reaction mixture was diluted with water and extracted with CH₂Cl₂. The organic extract was dried with Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (CH₂Cl₂:MeOH mixtures of increasing polarity as eluent) to afford the desired product (68 mg, 33%). The product was converted into the corresponding maleate salt by adding maleic acid (24 mg, 0.21 mmol) in acetone (0.4 mL), followed by filtration of the resulting solid and drying under vacuum.

55

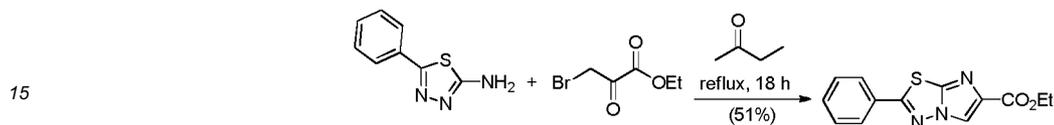
EP 2 870 164 B1

¹H-NMR (DMSO-d₆, 400 MHz) δ: 8.39 (s, 1 H), 7.56 (m, 3H), 7.46 (m, 2H), 7.38 (m, 1 H), 6.12 (s, 2H), 3.30 (m, 8H), 2.82 (m, 4H), 2.66 (m, 4H) ppm.
ESI(+)-HRMS: 327.1644 [M+H]⁺.

5 **Example 4 (Method C): Synthesis of 6-((2-(azepan-1-yl)ethoxy)methyl)-2-phenylimidazo[2,1-b][1,3,4]thiadiazole maleate**

a) Synthesis of ethyl 2-phenylimidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate

10 [0123]



20 [0124] A mixture of 5-phenyl-1,3,4-thiadiazol-2-amine (489 mg, 2.76 mmol) and ethyl bromopiruvate (0.58 mL, 4.14 mmol) in methyl ethyl ketone (25 mL) was refluxed overnight under argon atmosphere. The reaction mixture was evaporated to dryness. The crude product was purified by silica gel column chromatography (CH₂Cl₂:MeOH mixtures of increasing polarity as eluent) to afford the desired product (386 g, 51%).

¹H-NMR (DMSO-d₆, 400 MHz) δ: 8.86 (s, 1H), 7.95 (m, 2H), 7.64-7.59 (m, 3H), 4.28 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7 Hz, 3H) ppm.

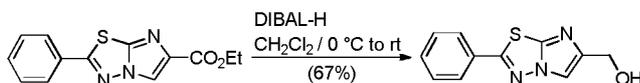
EI-MS *m/z*: 273.1 (M).

25

b) Synthesis of (2-phenylimidazo[2,1-b][1,3,4]thiadiazol-6-yl)methanol

[0125]

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35 [0126] A solution of DIBAL (1.0 M in CH₂Cl₂, 7.6 mL, 7.58 mmol) was added to a solution of ethyl 2-phenylimidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (691 g, 2.53 mmol) in CH₂Cl₂ (50 mL) under argon atmosphere. The resulting mixture was stirred for 3 h. The reaction mixture was diluted with water and filtered through Celite[®]. The layers were separated and the organic phase was dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (CH₂Cl₂: MeOH mixtures of increasing polarity as eluent) to afford the desired product (393 mg, 67%).

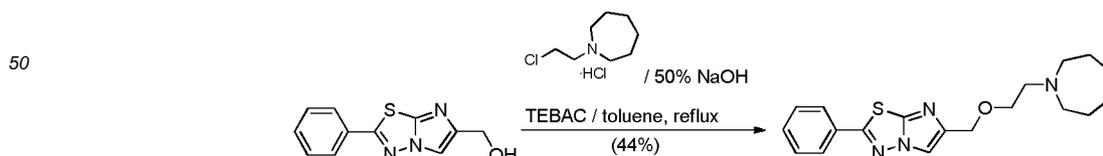
40 ¹H-NMR (DMSO-d₆, 400 MHz) δ: 8.01 (s, 1 H), 7.90 (m, 2H), 7.59-7.56 (m, 3H), 5.17 (t, J = 5.6 Hz, 1 H), 4.47 (d, J = 5.6 Hz, 2H) ppm.

EI-MS *m/z*: 231.0 (M).

c) Synthesis of 6-((2-(azepan-1-yl)ethoxy)methyl)-2-phenylimidazo[2,1-b][1,3,4]thiadiazole maleate

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[0127]



55 [0128] 1-(2-Chloroethyl)azepane hydrochloride (514 mg, 2.59 mmol), 50% NaOH (10.4 mL, 12.97 mmol), and a catalytic amount of benzyltriethylammonium chloride were added to a solution of (2-phenylimidazo[2,1-b][1,3,4]thiadiazol-6-yl)methanol (120 mg, 0.52 mmol) in toluene (3 mL) under argon atmosphere. The resulting mixture was refluxed for 6 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were dried with Na₂SO₄

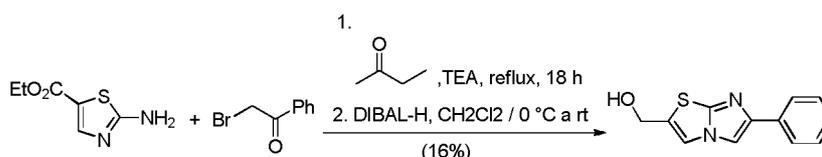
and evaporated to dryness. The crude product was purified by silica gel column chromatography (EtOAc:MeOH mixtures of increasing polarity as eluent) to afford the desired product (393 mg, 67%). The product was converted into the corresponding maleate salt by adding maleic acid (27 mg, 0.23 mmol) in acetone (0.25 mL), followed by filtration of the resulting solid and drying under vacuum.

¹H-NMR (DMSO-d₆, 300 MHz) δ: 9.24 (s, 1H), 8.27 (s, 1H), 7.94 (m, 2H), 7.62 (m, 3H), 6.00 (s, 2H), 4.55 (s, 2H), 3.78 (t, *J* = 5.1 Hz, 2H), 3.31 (m, 6H), 1.76 (m, 4H), 1.59 (m, 4H) ppm.
ESI(+)-HRMS: 357.1746 [M+H]⁺.

Example 5 (Method D): Synthesis of 2-((4-methylpiperazin-1-yl)methyl)-6-phenylimidazo[2,1-b]thiazole maleate

a) Synthesis of (6-phenylimidazo[2,1-b]thiazol-2-yl)methanol

[0129]

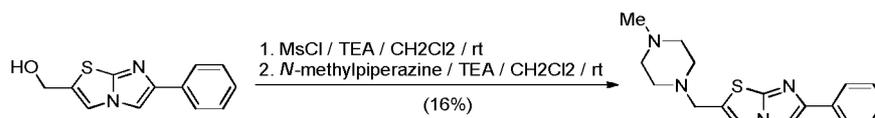


[0130] A mixture of ethyl 2-aminothiazole-5-carboxylate (500 mg, 2.9 mmol) and 2-bromoacetophenone (869 mg, 4.35 mmol) in methyl ethyl ketone (50 mL) was refluxed for 1 day under argon atmosphere. The reaction mixture was evaporated to dryness. To a solution of the previous residue in CH₂Cl₂ (65 mL), a solution of DIBAL (1.0 M in CH₂Cl₂, 12.1 mL, 12.18 mmol) was added. The resulting mixture was stirred for 2 h. The reaction mixture was diluted with water and filtered through Celite®. The layers were separated and the organic phase was dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (EtOAc: MeOH mixtures of increasing polarity as eluent) to afford the desired product (298 mg, 16%).

¹H-NMR (DMSO-d₆, 400 MHz) δ: 8.15 (s, 1 H), 7.83 (m, 3H), 7.37 (m, 2H), 7.23 (tt, *J* = 7.2, 1.4 Hz, 1 H), 5.66 (t, *J* = 5.8 Hz, 1 H), 4.58 (dd, *J* = 5.6, 1.2 Hz, 2H) ppm.
EI-MS *m/z*: 230.1 (M).

b) Synthesis of 2-((4-methylpiperazin-1-yl)methyl)-6-phenylimidazo[2,1-b]thiazole maleate

[0131]



[0132] Methanesulfonyl chloride (0.1 mL, 1.29 mmol) and triethylamine (0.18 mL, 1.29 mmol) was added to a suspension of (6-phenylimidazo[2,1-b]thiazol-2-yl)methanol (298 mg, 1.29 mmol) in CH₂Cl₂ (4 mL) cooled to 0 °C under argon atmosphere. The resulting mixture was stirred for 15 minutes. The reaction mixture was diluted with brine and extracted with CH₂Cl₂. The organic extract was dried with Na₂SO₄ and evaporated to dryness. To a solution of the previous residue in CH₂Cl₂ (3 mL), *N*-methylpiperazine (0.17 mL, 1.55 mmol) and triethylamine (0.22 mL, 1.55 mmol) was added. The resulting mixture was stirred overnight. The reaction mixture was diluted with water and extracted with CH₂Cl₂. The organic extract was dried with Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography (EtOAc/NH₃:MeOH mixtures of increasing polarity as eluent) to afford the desired product (13 mg, 16%). The product was converted into the corresponding maleate salt by adding maleic acid (5 mg, 0.04 mmol) in acetone, followed by filtration of the resulting solid and drying under vacuum.

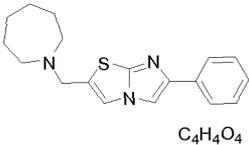
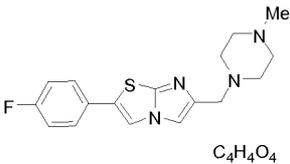
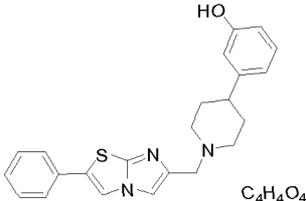
¹H-NMR (DMSO-d₆, 300 MHz) δ: 8.17 (s, 1 H), 7.92 (s, 1 H), 7.79 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1 H), 6.03 (s, 2H), 3.75 (s, 2H), 3.31 (m, 4H), 3.04 (m, 4H), 2.78 (s, 3H) ppm.

ESI(+)-HRMS: 313.1481 [M+H]⁺.

[0133] Further compounds of the invention are the examples shown in the following table:

Example	Structure	Method	Name	NMR
5 6		A	6-(Azepan-1-ylmethyl)-2-phenylimidazo[2,1-b]thiazole maleate	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 8.51 (s, 1H), 7.97 (s, 1H), 7.63 (m, 2H), 7.49 (t, J= 7.6 Hz, 2H), 7.42 (t, J= 7.4 Hz, 1H), 6.06 (s, 2H), 4.34 (s, 2H), 3.37 (m, 4H), 3.19 (m, 2H), 1.79 (m, 3H), 1.60 (m, 3H) ppm.
15 7		A	6-((4-Methylpiperazin-1-yl)methyl)-2-phenylimidazo[2,1-b]thiazole maleate	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 8.43 (s, 1H), 7.71 (s, 1H), 7.61 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 6.01 (s, 2H), 3.66 (m, 2H), 3.31 (m, 4H), 3.00 (m, 4H), 2.66 (m, 3H) ppm.
20 25 8		C	4-(2-((2-Phenylimidazo[2,1-b]thiazol-6-yl)methoxy)ethyl)morpholine maleate	¹ H-NMR (DMSO-d ₆ , 300 MHz) δ: 8.40 (s, 1H), 7.80 (s, 1H), 7.62 (d, J= 7.8 Hz, 2H), 7.48 (t, J= 7.5 Hz, 2H), 7.39 (m, 1H), 6.04 (s, 2H), 4.52 (s, 2H), 3.76 (m, 6H), 3.23 (m, 3H), 3.15 (m, 3H) ppm.
30 35 9		C	6-((2-(Azepan-1-yl)ethoxy)methyl)-2-phenylimidazo[2,1-b]thiazole maleate	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 9.29 (s, 1H), 8.45 (s, 1H), 7.81 (s, 1H), 7.62 (d, J= 7.6 Hz, 2H), 7.48 (t, J= 7.4 Hz, 2H), 7.39 (t, J= 7.4 Hz, 1H), 6.01 (s, 2H), 4.53 (s, 2H), 3.77 (t, J= 5 Hz, 2H), 3.31 (m, 6H), 1.76 (m, 4H), 1.59 (m, 4H) ppm.
40 45 10		C	2-Phenyl-6-((2-(pyrrolidin-1-yl)ethoxy)methyl)imidazo[2,1-b]thiazole maleate	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 9.49 (s, 1H), 8.44 (s, 1H), 7.81 (s, 1H), 7.62 (m, 2H), 7.47 (m, 2H), 7.38 (m, 1H), 6.03 (s, 2H), 4.54 (s, 2H), 3.73 (m, 2H), 3.49 (m, 2H), 3.31 (m, 2H), 3.02 (m, 2H), 1.96 (m, 2H), 1.87 (m, 2H) ppm.
50 11		A	6-((4-Methylpiperazin-1-yl)methyl)-2-phenylimidazo[2,1-b][1,3,4]thiadiazole maleate	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 8.16 (s, 1H), 7.92 (m, 2H), 7.60 (m, 3H), 6.07 (s, 2H), 3.66 (m, 2H), 3.31 (m, 4H), 3.04 (m, 4H), 2.72 (m, 3H) ppm.

(continued)

Example	Structure	Method	Name	NMR
12		D	2-(Azepan-1-ylmethyl)-6-phenylimidazo[2,1-b]thiazole maleate	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 8.28 (s, 1H), 8.13 (s, 1H), 7.82 (d, J= 7.2 Hz, 2H), 7.40 (t, J= 7.6 Hz, 2H), 7.27 (t, J= 7.8 Hz, 1H), 6.09 (s, 2H), 4.55 (m, 2H), 3.31 (m, 4H), 1.76 (m, 4H), 1.61 (m, 4H) ppm.
13		B	2-(4-Fluorophenyl)-6-((4-methylpiperazin-1-yl)methyl)imidazo[2,1-b]thiazole maleate	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 8.40 (s, 1H), 7.72 (s, 1H), 7.66 (m, 2H), 7.33 (t, J= 8.8 Hz, 2H), 6.12 (s, 2H), 3.69 (m, 2H), 3.30 (m, 6H), 3.06 (m, 2H), 2.69 (m, 3H) ppm.
14		B	3-(1-((2-Phenylimidazo[2,1-b]thiazol-6-yl)methyl)piperidin-4-yl)phenol maleate	¹ H-NMR (DMSO-d ₆ , 400 MHz) δ: 9.65 (s, 1H), 9.33 (s, 1H), 8.52 (s, 1H), 8.00 (s, 1H), 7.64 (d, J= 7.6 Hz, 2H), 7.50 (t, J= 7.8 Hz, 1H), 7.43 (m, 1H), 7.10 (t, J= 7.8 Hz, 1H), 6.60 (m, 3H), 6.05 (s, 2H), 4.53 (s, 2H), 4.35 (s, 1H), 3.56 (d, J= 11.6 Hz, 2H), 3.08 (m, 2H), 2.65 (m, 1H), 1.93 (m, 2H), 1.82 (m, 2H) ppm.

BIOLOGICAL ACTIVITY

Pharmacological study

[0134] Brain membrane preparation and binding assays for the σ 1-receptor were performed as described (DeHaven-Hudkins, D. L., L.C. Fleissner, and F. Y. Ford-Rice, 1992, Characterization of the binding of [³H](+)-pentazocine to σ recognition sites in guinea pig brain, Eur. J. Pharmacol. 227, 371-378) with some modifications. Guinea pig brains were homogenized in 10 vols. (w/v) of Tris-HCl 50 mM 0.32 M sucrose, pH 7.4, with a Kinematica Polytron PT 3000 at 15000 r.p.m. for 30 s. The homogenate was centrifuged at 1000g for 10 min at 4°C and the supernatants collected and centrifuged again at 48000g for 15 min at 4°C. The pellet was resuspended in 10 volumes of Tris-HCl buffer (50 mM, pH 7.4), incubated at 37°C for 30 min, and centrifuged at 48000g for 20 min at 4°C. Following this, the pellet was re-suspended in fresh Tris-HCl buffer (50 mM, pH 7.4) and stored on ice until use.

[0135] The radioligand used was [³H]-(+)-pentazocine at 5.0 nM and the final volume was 200 μ l. The incubation was initiated with the addition of 100 μ l of membrane at a final tissue concentration of approximately 5 mg tissue net weight/mL and the incubation time was 150 min at 37 °C. After incubation, the membranes were collected onto pretreated glass fiber filterplate (MultiScreen-FC, Millipore), with polyethylenimine 0.1 %. The filters were washed two times with 200 μ l of washing buffer (50 mM Tris Cl, pH = 7.4) and then 25 μ l of Ecoscint H liquid scintillation cocktail were added. Microplates were allowed to set for several hours and then quantified by liquid scintillation spectrophotometry (1450 Microbeta, Wallac). Nonspecific binding was determined with 1 μ M haloperidol.

[0136] Some of the results obtained are shown in table (I).

Table (I)

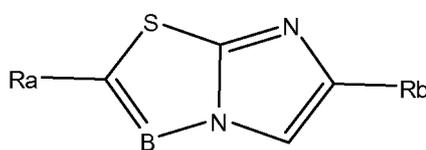
Compound	K _i σ 1 (nM)
4	168

(continued)

Compound	$K_i \sigma 1$ (nM)
6	16
7	56
9	40
10	190
11	260
12	100
13	210

Claims

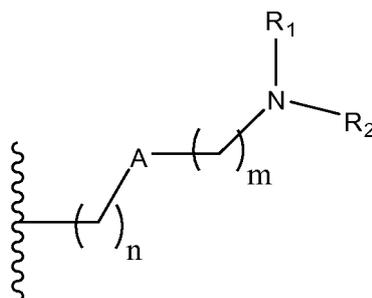
1. A compound of general formula (I):



(I)

where

R_a and R_b independently represent a 5 or 6-membered aryl radical optionally substituted by a halogen or a branched or unbranched, saturated alkyl radical C_{1-6} ; a 5 or 6-membered heteroaryl radical having at least one heteroatom selected from N, O or S as ring member, optionally substituted by a halogen or a branched or unbranched, saturated alkyl radical C_{1-6} ; or the following moiety:



with the proviso that one of R_a and R_b represents this moiety and the other one represents 5 or 6-membered aryl radical optionally substituted by a halogen or a branched or unbranched, saturated alkyl radical C_{1-6} ; or a 5 or 6-membered heteroaryl radical having at least one heteroatom selected from N, O or S as ring member, optionally substituted by a halogen or a branched or unbranched, saturated alkyl radical C_{1-6}

A is a C or O;

B is a C or N;

R_1 and R_2 independently represent a H, or R_1 and R_2 together with the bridging N form an 5 to 7-membered heterocyclic ring which can have at least one additional heteroatom selected from N, O or S and that can be optionally substituted by a branched or unbranched, saturated alkyl radical C_{1-6} or by an aryl radical optionally substituted by an alkyl C_{1-6} , a halogen or an OH group;

n is 0, 1 or 2;

m is 0, 1, 2, 3 or 4;

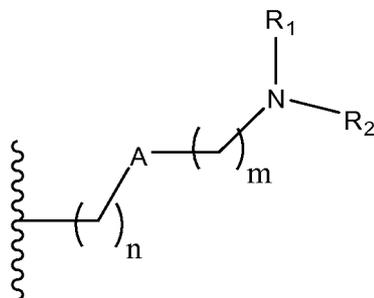
with the proviso that when A is O m is different from 0; and

with the proviso that when B represents a C and R_b represents a phenyl substituted by a halogen, R_a cannot represent the moiety:

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with R_1 and R_2 together with the bridging N forming a piperazine,

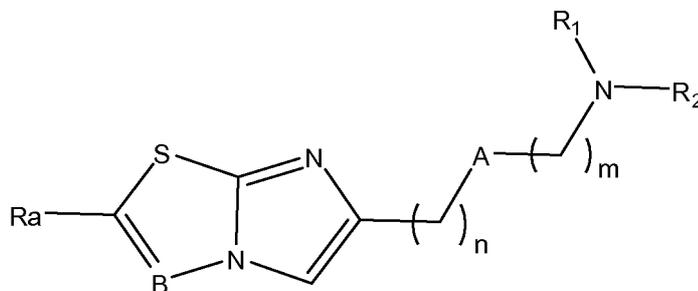
or a pharmaceutically acceptable salt, enantiomer and geometric/diastereoisomeric isomer or solvate thereof.

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2. A compound according to claim 1 having general formula (Ia):

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(Ia)

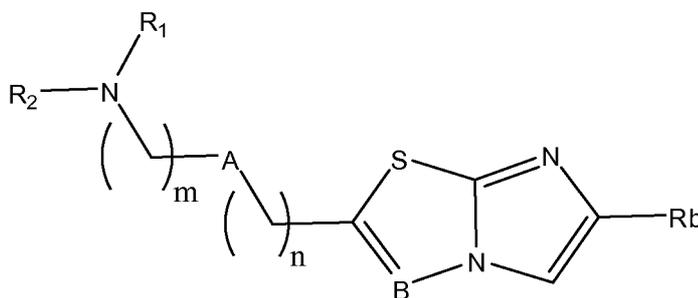
where R_a , R_1 , R_2 , A , B , n and m have the same meaning as in claim 1.

3. A compound according to claim 1 having general formula (Ib):

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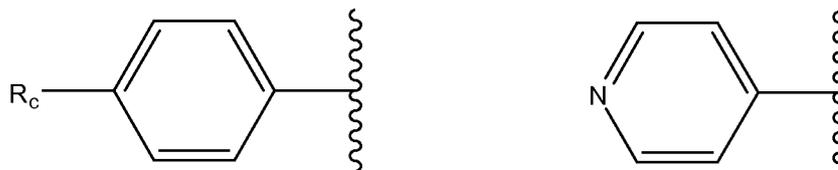


(Ib)

where R_b , R_1 , R_2 , A , B , n and m have the same meaning as in claim 1.

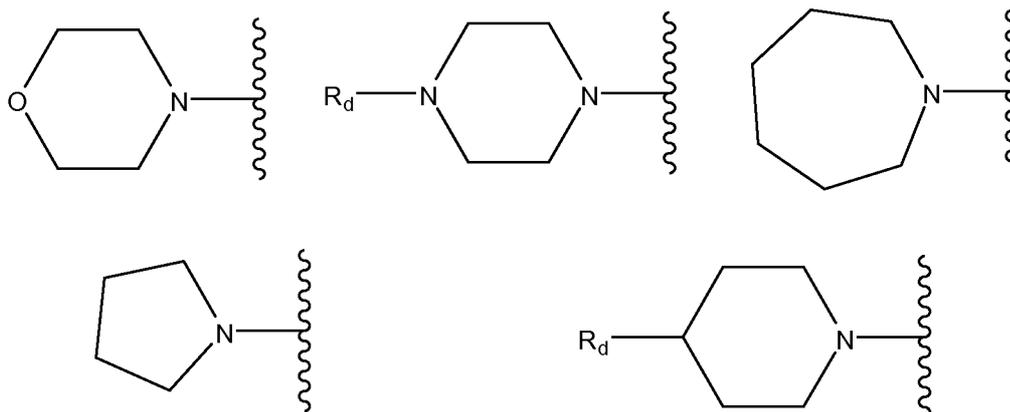
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4. A compound according to any of claim 1 to 3 where R_a or R_b represents a group selected from:



where R_c represents H, a C₁₋₆ alkyl, a halogen or an -OR' group where R' represents a linear or branched C₁₋₆-alkyl group.

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5. A compound according to any of claims 1 to 4 where R₁ and R₂ together with the bridging N form a group selected from:



where R_d represents a H, a C₁₋₆ alkyl or a phenyl group optionally substituted by a C₁₋₆ alkyl, a halogen or an -OH group.

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6. A compound according to any of claims 1 to 5 where A is C and m and n are both 0.
7. A compound according to any of claims 1 to 5 where A is O, n is 1 and m is 2
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8. A compound according to any of claims 1-7 selected from the group consisting of:

- 40
- [1] 4-((2-phenylimidazo[2,1-*b*]thiazol-6-yl)methyl)morpholine maleate,
 - [2] 6-((4-methylpiperazin-1-yl)methyl)-2-(pyridin-4-yl)imidazo[2,1-*b*]thiazole maleate,
 - [3] 6-(2-(4-methylpiperazin-1-yl)ethyl)-2-phenylimidazo[2,1-*b*]thiazole maleate,
 - [4] 6-((2-(azepan-1-yl)ethoxy)methyl)-2-phenylimidazo[2,1-*b*][1,3,4]thiadiazole maleate,
 - [5] 2-((4-methylpiperazin-1-yl)methyl)-6-phenylimidazo[2,1-*b*]thiazole maleate,
 - [6] 6-(azepan-1-ylmethyl)-2-phenylimidazo[2,1-*b*]thiazole maleate,
 - [7] 6-((4-methylpiperazin-1-yl)methyl)-2-phenylimidazo[2,1-*b*]thiazole maleate,
 - [8] 4-(2-((2-phenylimidazo[2,1-*b*]thiazol-6-yl)methoxy)ethyl)morpholine maleate,
 - [9] 6-((2-(azepan-1-yl)ethoxy)methyl)-2-phenylimidazo[2,1-*b*]thiazole maleate,
 - [10] 2-phenyl-6-((2-(pyrrolidin-1-yl)ethoxy)methyl)imidazo[2,1-*b*]thiazole maleate,
 - [11] 6-((4-methylpiperazin-1-yl)methyl)-2-phenylimidazo[2,1-*b*][1,3,4]thiadiazole maleate,
 - [12] 2-(azepan-1-ylmethyl)-6-phenylimidazo[2,1-*b*]thiazole maleate,
 - [13] 2-(4-fluorophenyl)-6-((4-methylpiperazin-1-yl)methyl)imidazo[2,1-*b*]thiazole maleate,
 - [14] 3-(1-((2-phenylimidazo[2,1-*b*]thiazol-6-yl)methyl)piperidin-4-yl)phenol maleate
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or a pharmaceutically acceptable salt or solvate thereof.

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9. A compound according to any of claims 1 to 8 for use as a medicament.
10. A compound according to any of claims 1 to 8 for its use in the treatment or prophylaxis of a sigma receptor mediated disease or condition.

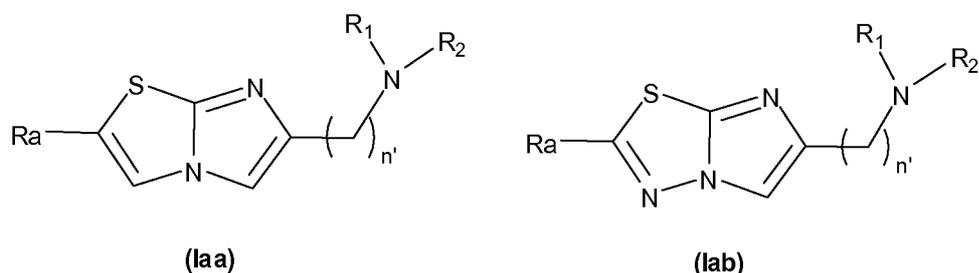
11. A compound for use according to claim 10 wherein the disease or condition is pain, especially neuropathic pain, inflammatory pain or other pain conditions involving allodynia and/or hyperalgesia.

12. A compound for use according to claim 11 wherein the allodynia is mechanical allodynia or thermal allodynia.

13. A compound for use according to claim 11 wherein the neuropathic pain is hyperpathia.

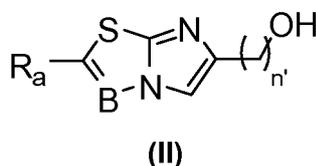
14. A compound for use according to claim 10 wherein the disease is diarrhea, lipoprotein disorders, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, obesity, migraine, arthritis, hypertension, arrhythmia, ulcer, glaucoma, learning, memory and attention deficits, cognition disorders, neurodegenerative diseases, demyelinating diseases, addiction to drugs and chemical substances including cocaine, amphetamine, ethanol and nicotine; tardive dyskinesia, epilepsy, stroke, stress, cancer, psychotic conditions, in particular depression, anxiety or schizophrenia; inflammation or autoimmune diseases.

15. A process for the preparation of a compound of general formula (Iaa) or (Iab):



where R_a , R_1 and R_2 have the same meanings as in claim 1 and n' is 1 or 2, the process comprising:

a) the reaction between a compound of general formula (II):



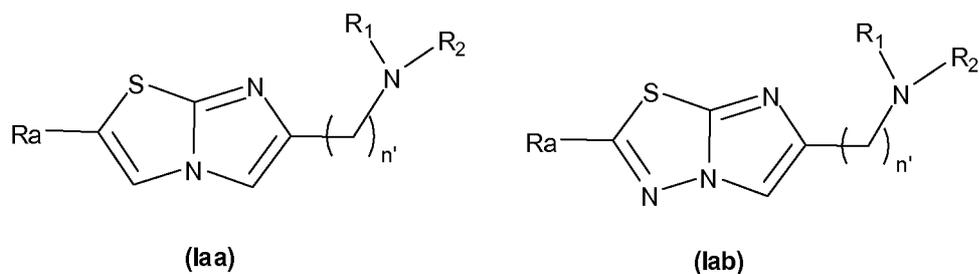
where B is a C or a N, with a sulphonide halide, and

b) the reaction of the resulting compound with a compound of general formula (III):



the reactions being carried out in the presence of a base in an organic solvent.

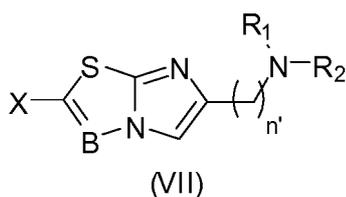
16. A process for the preparation of a compound of general formula (Iaa) or (Iab):



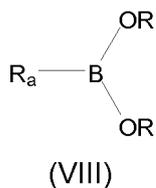
where R_a , R_1 and R_2 have the same meanings as in claim 1 and n' is 1 or 2, the process comprising the reaction

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between a compound of general formula (VII):

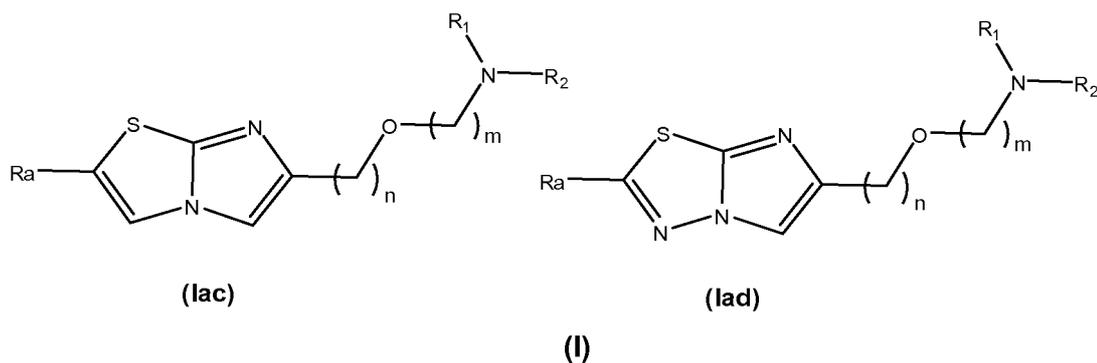


10 where **X** represents a halogen an **B** a C or a N, and a compound of general formula (VIII):

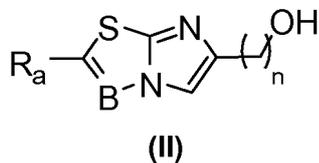


20 where each **R** independently represents a hydrogen, a C₁₋₆ alkyl or both R together with the bridging boron form a boronic cyclic ester such as a boronic acid pinacol ester, in the presence of a suitable catalyst and a base in an organic solvent.

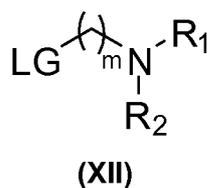
25 17. A process for the preparation of a compound of general formula (Iac) or (Iad):



40 where **R_a**, **R₁**, **R₂**, **n** and **m** have the same meanings as in claim 1, the process comprising the reaction between a compound of general formula (II):



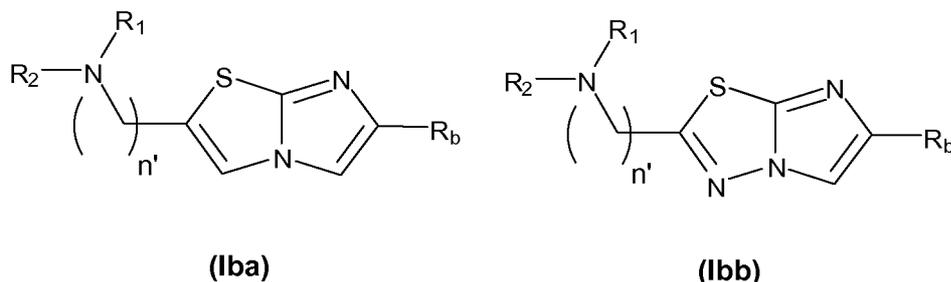
50 where **B** is C or a N, and a compound of general formula (XII):



where LG is a suitable leaving group, preferably a halogen, in the presence of a base in an organic solvent.

18. A process for the preparation of a compound of general formula (Iba) or (Ibb):

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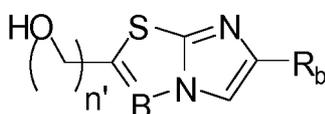


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where R_b , R_1 and R_2 have the same meanings as in claim 1 and n' is 1 or 2, the process comprising:

a) the reaction between a compound of general formula (XIII):

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(XIII)

where B is C or N, with a sulphonide halide and

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b) the reaction of the resulting compound with a compound of general formula (III):



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the reactions being carried out in the presence of a base in an organic solvent.

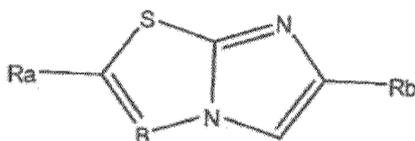
19. A pharmaceutical composition comprising a compound of general formula (I) according to any of claims 1 to 7 or a pharmaceutically acceptable salt, enantiomer and geometric/diastereoisomeric isomer or solvate thereof, and at least a pharmaceutically acceptable carrier, additive, adjuvant or vehicle.

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Patentansprüche

1. Verbindung der allgemeinen Formel (I):

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(I)

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wobei

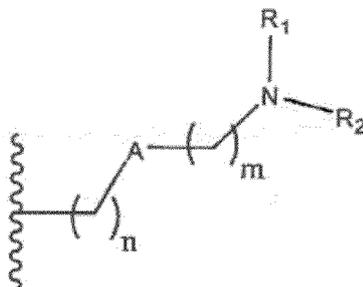
R_a und R_b unabhängig für Folgendes stehen: einen fünf- oder sechsgliedrigen Arylrest, der gegebenenfalls mit einem Halogen oder einem verzweigten oder unverzweigten, gesättigten C_{1-6} -Alkylrest substituiert ist; einen

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fünf- oder sechsgliedrigen Heteroarylrest, der wenigstens ein Heteroatom, das aus N, O oder S ausgewählt ist, als Ringelement aufweist und gegebenenfalls mit einem Halogen oder einem verzweigten oder unverzweigten, gesättigten C₁₋₆-Alkylrest substituiert ist; oder die folgende Struktureinheit:

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mit der Maßgabe, dass eines von R_a und R_b für diese Struktureinheit steht und das andere für einen fünf- oder sechsgliedrigen Arylrest, der gegebenenfalls mit einem Halogen oder einem verzweigten oder unverzweigten, gesättigten C₁₋₆-Alkylrest substituiert ist, einen fünf- oder sechsgliedrigen Heteroarylrest, der wenigstens ein Heteroatom, das aus N, O oder S ausgewählt ist, als Ringelement aufweist und gegebenenfalls mit einem Halogen oder einem verzweigten oder unverzweigten, gesättigten C₁₋₆-Alkylrest substituiert ist, steht;

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A = C oder O ist;

B = C oder N ist;

R₁ und R₂ unabhängig für ein H stehen, oder R₁ und R₂ zusammen mit dem verbrückenden N einen fünf- bis siebengliedrigen heterocyclischen Ring bilden, der wenigstens ein zusätzliches Heteroatom, das aus N, O oder S ausgewählt ist, aufweisen kann und der gegebenenfalls mit einem verzweigten oder unverzweigten, gesättigten C₁₋₆-Alkylrest oder mit einem Arylrest, der gegebenenfalls mit einem C₁₋₆-Alkyl, einem Halogen oder einer OH-Gruppe substituiert sein kann, substituiert sein kann;

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n = 0, 1 oder 2 ist;

m = 0, 1, 2, 3 oder 4 ist;

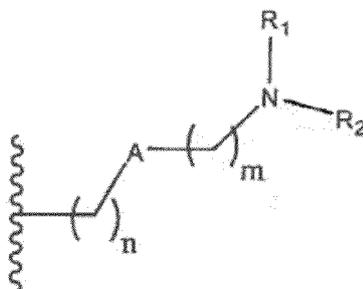
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mit der Maßgabe, dass dann, wenn A = O ist, dann m von 0 verschieden ist; und

mit der Maßgabe, dass dann, wenn B für ein C steht und R_b für ein mit einem Halogen substituiertes Phenyl steht, dann R_a nicht für die Struktureinheit:

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stehen kann, wobei R₁ und R₂ zusammen mit dem verbrückenden N ein Piperazin bilden;

oder ein pharmazeutisch annehmbares Salz, Enantiomer und geometrisches/diastereomeres Isomer oder Solvat davon.

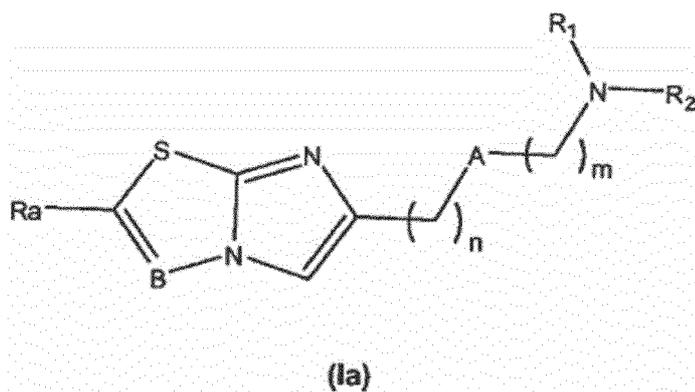
2. Verbindung gemäß Anspruch 1 mit der allgemeinen Formel (Ia):

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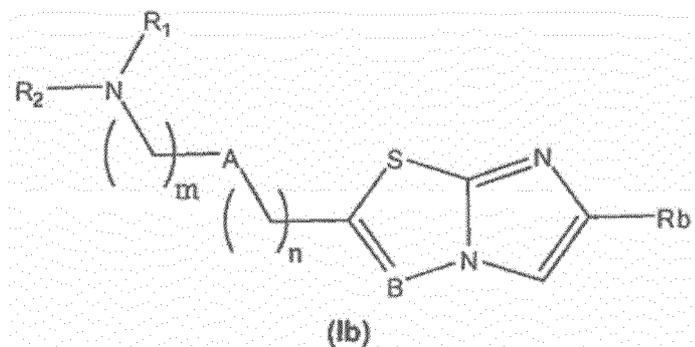
wobei R_a , R_1 , R_2 , A, B, n und m dasselbe wie in Anspruch 1 bedeuten.

3. Verbindung gemäß Anspruch 1 mit der allgemeinen Formel (Ib):

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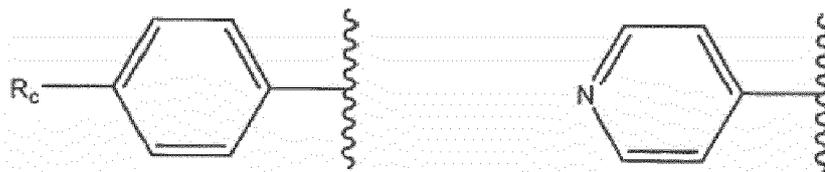


wobei R_b , R_1 , R_2 , A, B, n und m dasselbe wie in Anspruch 1 bedeuten.

4. Verbindung gemäß einem der Ansprüche 1 bis 3, wobei R_a oder R_b für eine Gruppe steht, die aus

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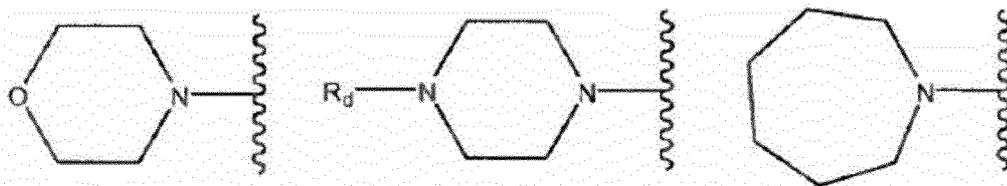
ausgewählt ist, wobei R_c für H, ein C_{1-6} -Alkyl, ein Halogen oder eine $-OR'$ -Gruppe steht, wobei R' für eine lineare oder verzweigte C_{1-6} -Alkylgruppe steht.

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5. Verbindung gemäß einem der Ansprüche 1 bis 4, wobei R_1 und R_2 zusammen mit dem verbrückenden N eine Gruppe bilden, die aus

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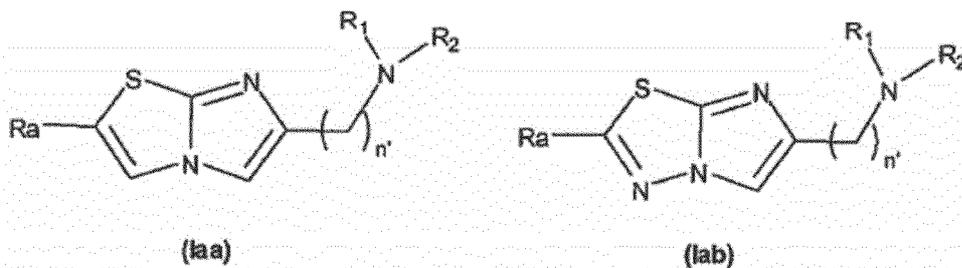
ausgewählt ist, wobei R_d für H, ein C_{1-6} -Alkyl oder eine Phenylgruppe, die gegebenenfalls mit einem C_{1-6} -Alkyl, einem Halogen oder einer -OH-Gruppe substituiert ist, steht.

6. Verbindung gemäß einem der Ansprüche 1 bis 5, wobei $A = C$ ist und m und n beide = 0 sind.
7. Verbindung gemäß einem der Ansprüche 1 bis 5, wobei $A = O$ ist, $n = 1$ ist und $m = 2$ ist.
8. Verbindung gemäß einem der Ansprüche 1 bis 7, die aus der Gruppe ausgewählt ist, die aus Folgenden besteht:

- [1] 4-((2-Phenylimidazo[2,1-b]thiazol-6-yl)methyl)morpholinmaleat,
 [2] 6-((4-Methylpiperazin-1-yl)methyl)-2-(pyridin-4-yl)imidazo[2,1-b]thiazolmaleat,
 [3] 6-(2-(4-Methylpiperazin-1-yl)ethyl)-2-phenylimidazo[2,1-b]thiazolmaleat,
 [4] 6-((2-(Azepan-1-yl)ethoxy)methyl)-2-phenylimidazo[2,1-b][1,3,4]-thiadiazolmaleat,
 [5] 2-((4-Methylpiperazin-1-yl)methyl)-6-phenylimidazo[2,1-b]thiazolmaleat,
 [6] 6-(Azepan-1-ylmethyl)-2-phenylimidazo[2,1-b]thiazolmaleat,
 [7] 6-((4-Methylpiperazin-1-yl)methyl)-2-phenylimidazo[2,1-b]thiazolmaleat,
 [8] 4-(2-((2-Phenylimidazo[2,1-b]thiazol-6-yl)methoxy)ethyl)morpholinmaleat,
 [9] 6-((2-(Azepan-1-yl)ethoxy)methyl)-2-phenylimidazo[2,1-b]thiazolmaleat,
 [10] 2-Phenyl-6-((2-(pyrrolidin-1-yl)ethoxy)methyl)imidazo[2,1-b]thiazolmaleat,
 [11] 6-((4-Methylpiperazin-1-yl)methyl)-2-phenylimidazo[2,1-b][1,3,4]-thiadiazolmaleat,
 [12] 2-(Azepan-1-ylmethyl)-6-phenylimidazo[2,1-b]thiazolmaleat,
 [13] 2-(4-Fluorphenyl)-6-((4-methylpiperazin-1-yl)methyl)imidazo[2,1-b]thiazolmaleat,
 [14] 3-(1-((2-Phenylimidazo[2,1-b]thiazol-6-yl)methyl)piperidin-4-yl)-phenolmaleat

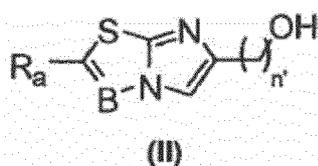
oder ein pharmazeutisch annehmbares Salz oder Solvat davon.

9. Verbindung gemäß einem der Ansprüche 1 bis 8 zur Verwendung als Medikament.
10. Verbindung gemäß einem der Ansprüche 1 bis 8 zur Verwendung bei der Behandlung oder Prophylaxe einer durch Sigma-Rezeptor vermittelten Krankheit oder Zustand.
11. Verbindung zur Verwendung gemäß Anspruch 10, wobei es sich bei der Krankheit oder dem Zustand um Schmerzen, insbesondere neuropathischen Schmerzen, Entzündungsschmerzen oder andere Schmerzzustände, die Allodynie und/oder Hyperalgesie beinhalten, handelt.
12. Verbindung zur Verwendung gemäß Anspruch 11, wobei es sich bei der Allodynie um mechanische Allodynie oder thermische Allodynie handelt.
13. Verbindung zur Verwendung gemäß Anspruch 11, wobei es sich bei den neuropathischen Schmerzen um Hyperpathie handelt.
14. Verbindung zur Verwendung gemäß Anspruch 10, wobei es sich bei der Krankheit um Diarrhöe, Lipoproteinstörungen, Hyperlipidämie, Hypertriglyceridämie, Hypercholesterinämie, Adipositas, Migräne, Arthritis, Bluthochdruck, Arrhythmie, Ulkus, Glaukom, Defizite beim Lernen, Gedächtnis und Aufmerksamkeit, Kognitionsstörungen, neurodegenerative Krankheiten, demyelinisierende Krankheiten, Sucht nach Drogen und chemischen Substanzen einschließlich Kokain, Amphetamin, Ethanol und Nicotin, tardive Dyskinesie, Epilepsie, Schlaganfall, Stress, Krebs, psychotische Zustände, insbesondere Depression, Angstzustände oder Schizophrenie, Entzündung oder Autoimmunkrankheiten handelt.
15. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (Iaa) oder (Iab):



wobei R_a , R_1 und R_2 dasselbe wie in Anspruch 1 bedeuten und $n' = 1$ oder 2 ist, wobei das Verfahren umfasst:

a) die Reaktion zwischen einer Verbindung der allgemeinen Formel (II):



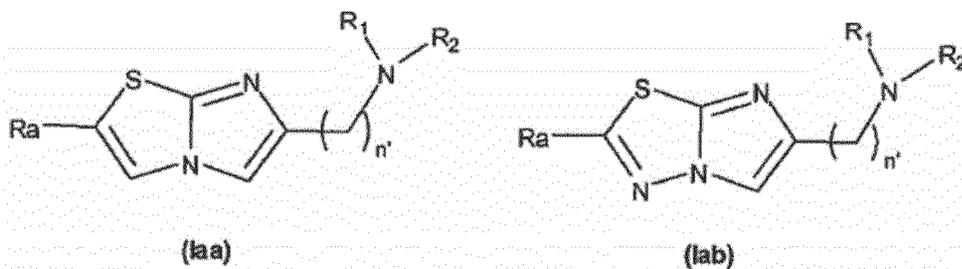
wobei $B = C$ oder N ist, und einem Sulfonidhalogenid und

b) die Reaktion der resultierenden Verbindung mit einer Verbindung der allgemeinen Formel (III):



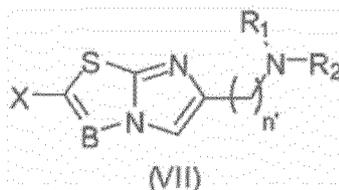
wobei die Reaktionen in Gegenwart einer Base in einem organischen Lösungsmittel durchgeführt werden.

16. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (Ia) oder (Ib):



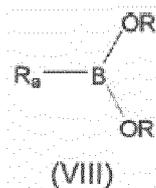
wobei R_a , R_1 und R_2 dasselbe wie in Anspruch 1 bedeuten und $n' = 1$ oder 2 ist, wobei das Verfahren umfasst:

die Reaktion zwischen einer Verbindung der allgemeinen Formel (VII):



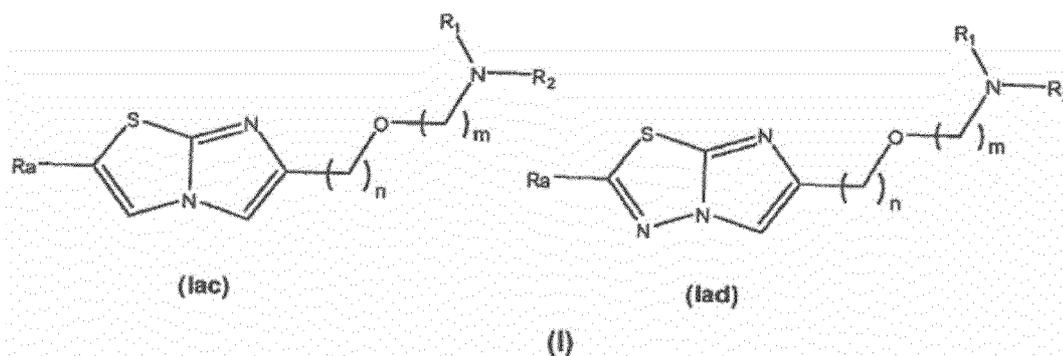
wobei X für ein Halogen steht und $B = C$ oder N ist, und einer Verbindung der allgemeinen Formel (VIII):

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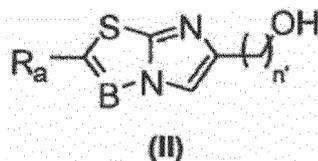


wobei R jeweils unabhängig für Wasserstoff oder ein C₁₋₆-Alkyl steht oder beide R zusammen mit dem verbrückenden Bor einen cyclischen Boronsäureester, wie einen Boronsäurepinakolester, bilden, in Gegenwart eines geeigneten Katalysators und einer Base in einem organischen Lösungsmittel.

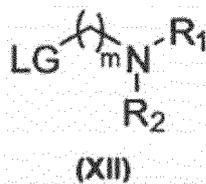
17. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (Iac) oder (Iad):



wobei R_a, R₁, R₂, n und m dasselbe wie in Anspruch 1 bedeuten, wobei das Verfahren die Reaktion zwischen einer Verbindung der allgemeinen Formel (II):

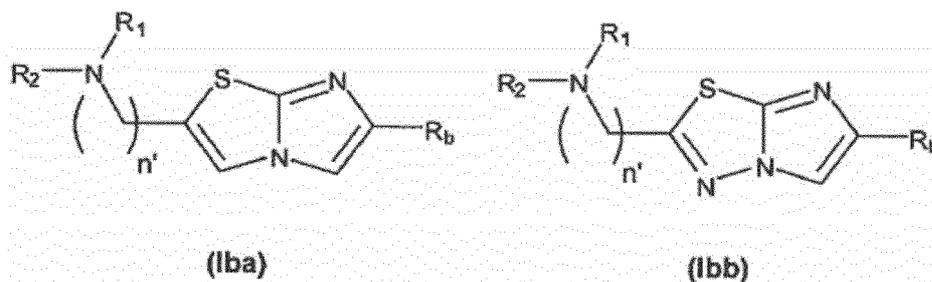


wobei B = C oder N ist, und einer Verbindung der allgemeinen Formel (XII):



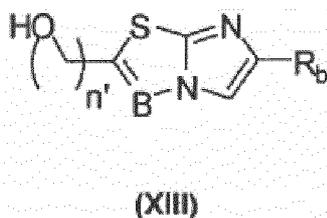
wobei LG eine geeignete Abgangsgruppe, vorzugsweise ein Halogen, ist, in Gegenwart einer Base in einem organischen Lösungsmittel umfasst.

18. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (Iba) oder (Ibb):



wobei R_b , R_1 und R_2 dasselbe wie in Anspruch 1 bedeuten und $n' = 1$ oder 2 ist, wobei das Verfahren umfasst:

15 a) die Reaktion zwischen einer Verbindung der allgemeinen Formel (XIII):



25 wobei $B = C$ oder N ist, mit einem Sulfonylhalogenid und

b) die Reaktion der resultierenden Verbindung mit einer Verbindung der allgemeinen Formel (III):

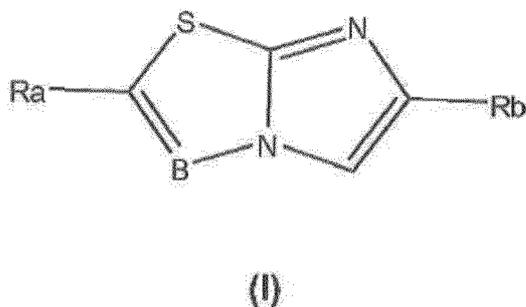


wobei die Reaktionen in Gegenwart einer Base in einem organischen Lösungsmittel durchgeführt werden.

35 **19.** Pharmazeutische Zusammensetzung, die eine Verbindung der allgemeinen Formel (I) gemäß einem der Ansprüche 1 bis 7 oder ein pharmazeutisch annehmbares Salz, Enantiomer und geometrisches/diastereomeres Isomer oder Solvat davon und wenigstens einen pharmazeutisch annehmbaren Träger, Additiv, Adjuvans oder Trägerstoff umfasst.

Revendications

40 **1.** Composé de formule générale (I)



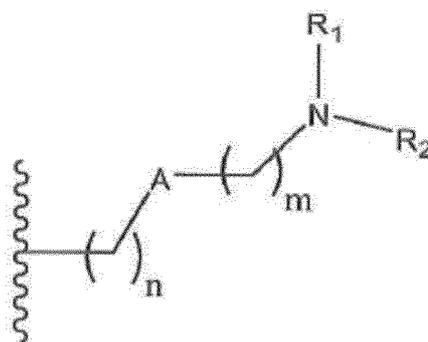
dans laquelle

55 R_a et R_b représentent indépendamment un radical aryle de 5 ou 6 chaînons éventuellement substitué par un atome d'halogène ou un radical alkyle en C_1 à C_6 saturé, ramifié ou non ramifié ; un radical hétéroaryle de 5 ou 6 chaînons ayant au moins un hétéroatome choisi parmi N, O ou S comme élément du cycle, éventuellement substitué par un atome d'halogène ou un radical alkyle en C_1 à C_6 saturé, ramifié ou non ramifié; ou la fraction

suivante :

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à condition que l'un des R_a et R_b représente cette fraction et l'autre représente un radical aryle de 5 ou 6 chaînons éventuellement substitué par un atome d'halogène ou un radical alkyle en C_1 à C_6 saturé, ramifié ou non ramifié ; ou un radical hétéroaryle de 5 ou 6 chaînons ayant au moins un hétéroatome choisi parmi N, O ou S comme élément du cycle, éventuellement substitué par un atome d'halogène ou un radical alkyle en C_1 à C_6 saturé, ramifié ou non ramifié,

20

A est un atome de C ou O;

B est un atome de C ou N;

R_1 et R_2 représentent indépendamment un atome d'hydrogène, ou R_1 et R_2 conjointement avec l'atome d'azote formant un pont forment un cycle hétérocyclique de 5 à 7 chaînons qui peut avoir au moins un hétéroatome supplémentaire choisi parmi N, O ou S et qui peut être éventuellement substitué par un radical alkyle en C_1 à C_6 saturé, ramifié ou non ramifié ou par un radical aryle éventuellement substitué par un groupe alkyle en C_1 à C_6 , un atome d'halogène ou un groupe OH;

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n est 0, 1 ou 2;

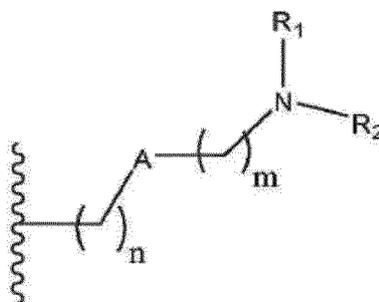
m est 0, 1, 2, 3 ou 4;

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à condition que si A est 0, m soit différent de 0 ; et à condition que si B représente un atome de carbone et R_b représente un groupe phényle substitué par un atome d'halogène, R_a ne puisse pas représenter la fraction :

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R_1 et R_2 formant conjointement avec l'atome d'azote formant un pont, un groupe pipérazine, ou sel, énantiomère et isomère géométrique/ diastéréomérique ou solvate pharmaceutiquement acceptables de celui-ci

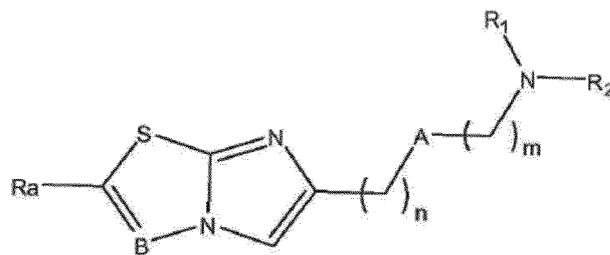
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2. Composé selon la revendication 1, ayant la formule générale (1a) :

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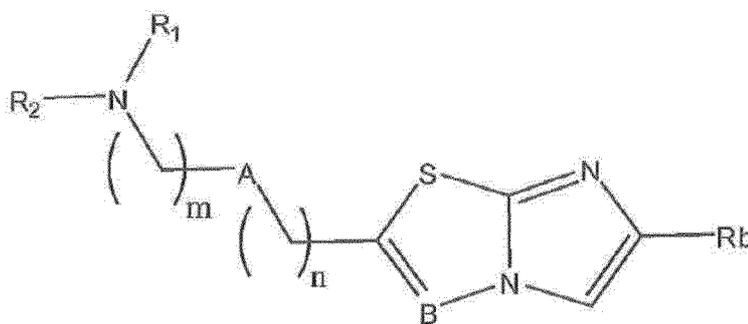
(Ia)

dans laquelle R_a , R_1 , R_2 , A, B, n et m ont la même signification que dans la revendication 1.

15

3. Composé selon la revendication 1 ayant une formule générale (Ib) :

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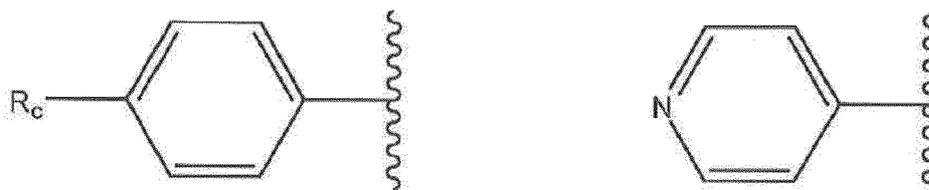
(Ib)

dans laquelle R_b , R_1 , R_2 , A, B, n et m ont la même signification que dans la revendication 1.

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4. Composé selon l'une quelconque des revendications 1 à 3, où R_a ou R_b représente un groupe choisi parmi :

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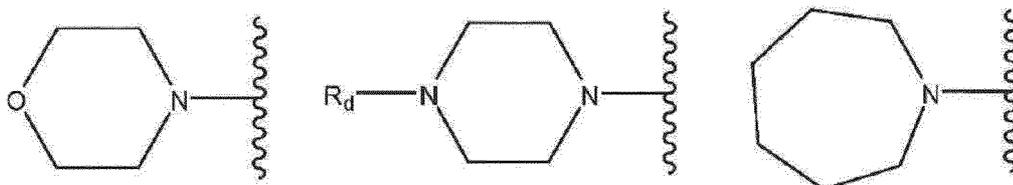


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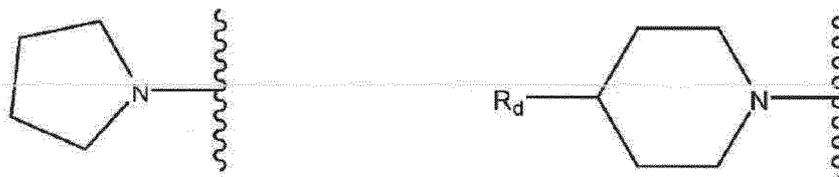
où R_c représente H, un groupe alkyle en C_1 à C_6 , un atome d'halogène ou un groupe $-OR'$, où R' représente un groupe alkyle en C_1 à C_6 linéaire ou ramifié.

5. Composé selon l'une quelconque des revendications 1 à 4, où R_1 et R_2 conjointement avec l'atome d'azote formant un pont forment un groupe choisi parmi :

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où R_d représente un atome d'hydrogène, un groupe alkyle en C_1 à C_6 ou un groupe phényle éventuellement substitué par un groupe alkyle en C_1 à C_6 , un atome d'halogène ou un groupe -OH.

6. Composé selon l'une quelconque des revendications 1 à 5, où A est un atome de C et m et n sont tous deux 0.

7. Composé selon l'une quelconque des revendications 1 à 5, où A est 0, n est 1 et m est 2.

8. Composé selon l'une quelconque des revendications 1 à 7, choisi dans le groupe constitué du :

- [1] maléate de 4-((2-phénylimidazo[2,1-b]thiazol-6-yl)méthyl)morpholine,
- [2] maléate de 6-((4-méthylpipérazin-1-yl)méthyl)-2-(pyridin-4-yl)imidazo[2,1-b]thiazole,
- [3] maléate de 6-(2-(4-méthylpipérazin-1-yl)éthyl)-2-phénylimidazo[2,1-b]thiazole,
- [4] maléate de 6-((2-(azépan-1-yl)éthoxy)méthyl)-2-phénylimidazo[2,1-b][1,3,4]thiazole,
- [5] maléate de 2-((4-méthylpipérazin-1-yl)méthyl)-6-phénylimidazo[2,1-b]thiazole,
- [6] maléate de 6-(azépan-1-ylméthyl)-2-phénylimidazo[2,1-b]thiazole,
- [7] maléate de 6-((4-méthylpipérazin-1-yl)méthyl)-2-phénylimidazo[2,1-b]thiazole,
- [8] maléate de 4-(2-((2-phénylimidazo[2,1-b]thiazol-6-yl)méthoxy)éthyl)morpholine,
- [9] maléate de 6-((2-(azépan-1-yl)éthoxy)méthyl)-2-phénylimidazo[2,1-b]thiazole,
- [10] maléate de 2-phényl-6-((2-(pyrrolidin-1-yl)éthoxy)méthyl)imidazo[2,1-b]thiazole,
- [11] maléate de 6-((4-méthylpipérazin-1-yl)méthyl)-2-phénylimidazo[2,1-b][1,3,4]thiazole,
- [12] maléate de 2-(azépan-1-ylméthyl)-6-phénylimidazo[2,1-b]thiazole,
- [13] maléate de 2-(4-fluorophényl)-6-((4-méthylpipérazin-1-yl)méthyl)imidazo[2,1-b]thiazole,
- [14] maléate de 3-(1-((2-phénylimidazo[2,1-b]thiazol-6-yl)méthyl)pipéridin-4-yl)phénol

ou un sel ou solvate pharmaceutiquement acceptable de ceux-ci.

9. Composé selon l'une quelconque des revendications 1 à 8 pour une utilisation comme médicament.

10. Composé selon l'une quelconque des revendications 1 à 8 pour son utilisation dans le traitement ou la prophylaxie d'une maladie ou d'une affection médiée par un récepteur sigma.

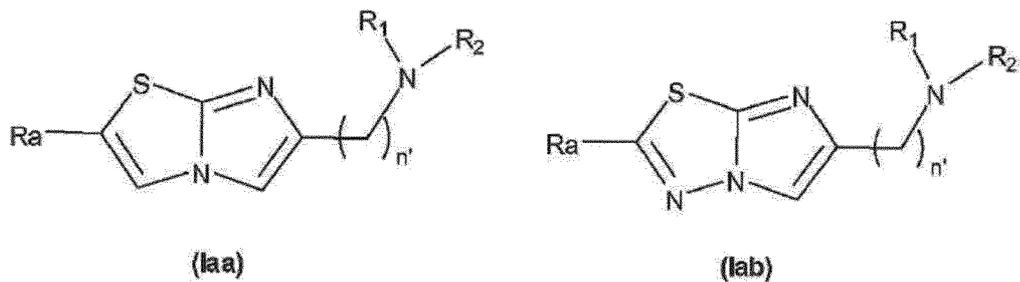
11. Composé pour son utilisation selon la revendication 10, dans lequel la maladie ou l'affection est une douleur, en particulier, une douleur neuropathique, une douleur inflammatoire ou d'autres affections douloureuses comprenant une allodynie et/ou une hyperalgésie.

12. Composé pour son utilisation selon la revendication 11, dans lequel l'allodynie est une allodynie mécanique ou une allodynie thermique.

13. Composé pour une utilisation selon la revendication 11, dans lequel la douleur neuropathique est l'hyperpathie.

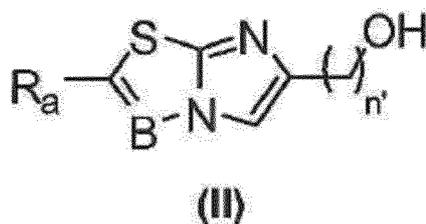
14. Composé pour une utilisation selon la revendication 10, dans lequel la maladie est la diarrhée, les troubles lipoprotéiques, l'hyperlipidémie, l'hyper-triglycéridémie, l'hypercholestérolémie, l'obésité, la migraine, l'arthrite, l'hypertension, l'arythmie, l'ulcère, le glaucome, les déficits de l'apprentissage, de la mémoire et de l'attention, les troubles cognitifs, les maladies neurodégénératives, les maladies démyélinisantes, l'addiction aux médicaments ou aux substances chimiques comprenant la cocaïne, les amphétamines, l'éthanol et la nicotine ; la dyskinésie tardive, l'épilepsie, l'AVC, le stress, le cancer, les troubles psychotiques, en particulier, la dépression, l'anxiété ou la schizophrénie ; les maladies inflammatoires ou auto-immunes.

15. Procédé pour la préparation d'un composé de formule générale (Iaa) ou (Iab) :



où R_a , R_1 et R_2 ont les mêmes significations que dans la revendication 1 et n' est 1 ou 2, le procédé comprenant :

a) la réaction entre un composé de formule générale (II) :

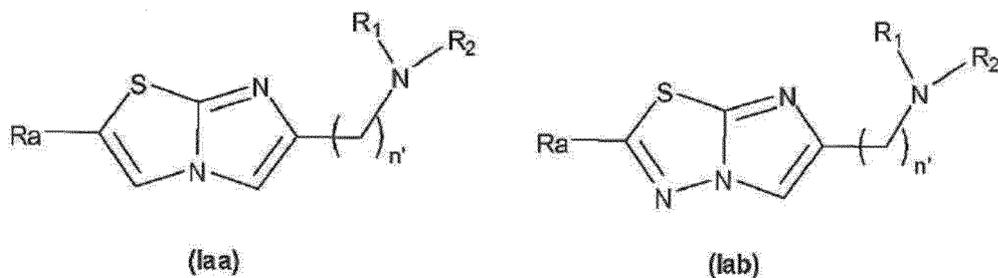


25 où B est un atome de carbone ou d'azote, avec un halogénure de sulfonyde, et
b) la réaction du composé obtenu avec un composé de formule générale (III) :

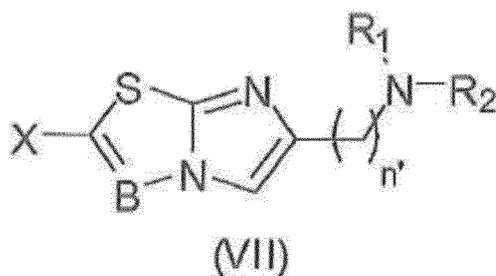


les réactions étant réalisées en présence d'une base dans un solvant organique.

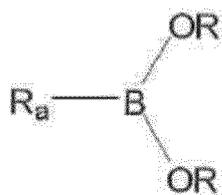
16. Procédé pour la préparation d'un composé de formule générale (Ia) ou (Ib) :



45 où R_a , R_1 et R_2 ont les mêmes significations que dans la revendication 1 et n' est 1 ou 2, le procédé comprenant la réaction entre un composé de formule générale (VII) :



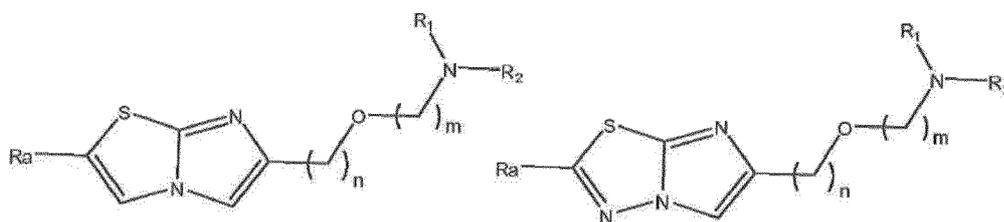
où X représente un atome d'halogène, de B, C ou N, et un composé de formule générale (VIII) :



(VIII)

où chaque R représente indépendamment un atome d'hydrogène, un groupe alkyle en C₁ à C₆ ou les deux R conjointement avec l'atome de bore formant un pont, forment un ester cyclique boronique tel qu'un ester de pinacol d'acide boronique, en présence d'un catalyseur approprié et d'une base dans un solvant organique.

17. Procédé pour la préparation d'un composé de formule générale (Iac) ou (Iad) :

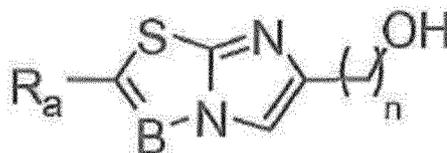


(Iac)

(Iad)

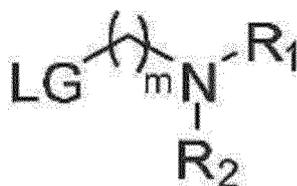
(I)

où R_a, R₁ et R₂, n et m ont les mêmes significations que dans la revendication 1, le procédé comprenant la réaction entre un composé de formule générale (II) :



(II)

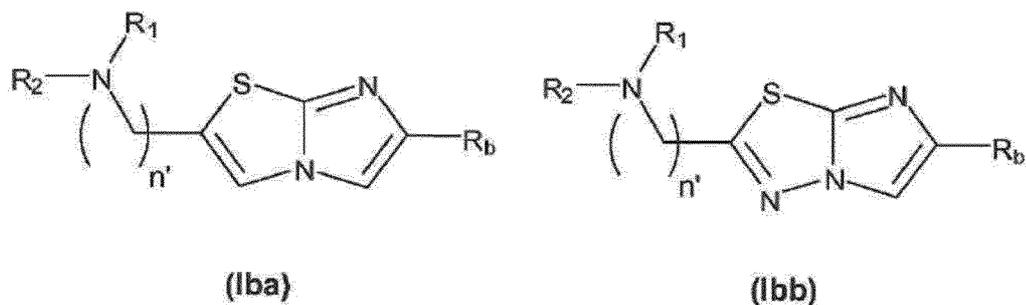
où B est un atome de C ou N, et un composé de formule générale (XII) :



(XII)

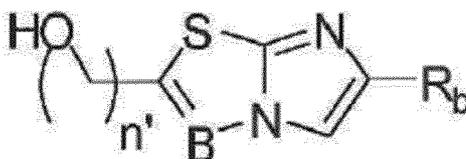
où LG est un groupe partant approprié, de préférence un atome d'halogène, en présence d'une base dans un solvant organique.

18. Procédé pour la préparation d'un composé de formule générale (Iba) ou (Ibb) :



où R_b , R_1 et R_2 ont les mêmes significations que dans la revendication 1 et n' est 1 ou 2, le procédé comprenant :

15 a) la réaction entre un composé de formule générale (XIII) :



où B est C ou N, avec un halogénure de sulfonide et

b) la réaction du composé obtenu avec un composé de formule générale (III) :



les réactions étant réalisées en présence d'une base dans un solvant organique.

35 **19.** Composition pharmaceutique comprenant un composé de formule générale (I) selon l'une quelconque des revendications 1 à 7 ou un sel, énantiomère et isomère géométrique/diastéréomérique ou solvate pharmaceutiquement acceptable de celui-ci, et au moins un support, additif, adjuvant ou véhicule pharmaceutiquement acceptable.

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REFERENCES CITED IN THE DESCRIPTION

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