USE OF SIGMA LIGANDS IN OPIOID-INDUCED HYPERALGESIA

FIELD OF THE INVENTION

The present invention relates to the use of sigma receptor ligands in the prevention and/or treatment of opioid-induced hyperalgesia (OIH) associated to opioid therapy, including the combination of opioids with a sigma receptor ligand for the treatment and/or prevention of OIH.

BACKGROUND

Opioids and opiates are potent analgesics widely used in clinical practice. Opiates refer to alkaloids extracted from poppy pods (Opium Poppy; Papaver Somniferum) and their semi-synthetic counterparts which bind to the opioid receptors. Basically to be called an opiate one has to either be a natural opioid receptor agonist or start the refining process with one of the natural alkaloid molecules. Once chemically altered, such as the process of converting morphine into heroin, the drug is then labeled as a semi-synthetic opiate or semi-synthetic opioid − the terms can be used interchangeably. Semi-synthetic opiates (or semi-synthetic opioids) include heroin (diamorphine), oxycodone, hydrocodone, dihydrocodiene, hydromorphone, oxymorphone, buprenorphine and etorphine. In contrast, opioid is a blanket term used for any drug which binds to the opioid receptors. Opioids include all of the opiates as well as any synthesized drug that bind to opioid receptors. Synthetic opioids include methadone, pethidine, fentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, tramadol, tapentadol and loperamide.

Opioid and opiates drugs are classified typically by their binding selectivity in respect of the cellular and differentiated tissue receptors to which specific the drug binds as a ligand. There are 3 well-defined or "classical" types of opioid receptor: mu (μ), delta (δ), and kappa (κ). More recently, cDNA encoding an "orphan" receptor named ORL1 (opioid receptor-like) was identified which has a high degree of homology to the "classical" opioid receptors. All the opioid receptors are G-protein coupled receptors and possess the same general structure: an extracellular N-terminal region, seven transmembrane domains and an intracellular C-terminal tail structure. Pharmacological

evidence supporting for subtypes of each receptor and other types of novel, less well-characterised opioid receptors have also been postulated. The well-known opioid analgesics bind to and activate selectively the opioid mu receptors; that is, they act as agonists at mu opioid receptors.The sigma receptor, however, is not regarded as an opioid receptor.

Opioid analgesics are recommended for the management of moderate to severe pain including that which occurs following surgery and trauma and in many patients with cancer. Apart from pain relief, opioid analgesics also produce a range of common well-known side effects (e.g., sedation, emesis, constipation, respiratori depression, dependence).

In addition to the afore-mentioned side-effects, it has been appreciated more recently that opioid analgesics may also activate a pro-nociceptive mechanism resulting in the phenomenon of opioid-induced hyperalgesia (OIH) [also called opioid-induced abnormal pain sensitivity]. OIH is a recognized complication of opioid therapy characterized by enhanced pain sensitivity. Somewhat paradoxically, opioid therapy aiming at alleviating pain may render patients more sensitive to pain and potentially may aggravate their preexisting pain. In fact, OIH should be considered in the differential when opioid therapy fails. Hence, any apparent decrease in opioid analgesic effectiveness may be due at least in part to the presence of OIH rather than reflecting a worsening of the disease state and/or the development of pharmacological tolerance.

As disclosed in the art (Sandford,M. et al.; Pain Physician 2009; 12:679-684) the existence of OIH is proved by basic science evidence (Mao,J.; Pain 2002; 100:213-217) and by clinical evidence (Guignard,B. et al.; Anesthesiology 2000; 93:409-417 and Angst, M.S. et al.; Anesthesiology 2006; 104:570-587). Additionally there are neurobiological mechanisms discussed for OIH involving the central glutaminergic system, the spinal dynorphins or the descending facilitation.

OIH is evidenced by individuals taking opioids, which can develop an increasing sensitivity to noxious stimuli (hyperalgesia), even evolving a painful response to previously non-noxious stimuli (allodynia). Increased pain in OIH may result from one or more of the following: pain in the absence of a noxious stimulus (spontaneous pain), increased duration of pain in response to brief stimulation (ongoing pain or hyperpathia), reduced pain threshold (allodynia), increased responsiveness to suprathreshold stimulation (hyperalgesia), spread of pain and hyperalgesia to uninjured

tissue (referred pain and secondary hyperalgesia), and abnormal sensations (e.g., dysesthesia, paresthesia).

OIH is a phenomenon often associated with the long term use of opioids, but some studies have demonstrated that this effect can also occur after only a single dose of opioids (E. Celerier et al., J. Neurosci. 21, 4074–4080 (2001)). Thus, OIH occurs following both acute and chronic opioid administration. In this way, OIH is a less recognized side effect of chronic opioid therapy. However, it is becoming more prevalent as the number of patients receiving opioids for chronic pain increases (Trescot,A.M. et al.; Pain Physician 2008; 11:S12-S16).

Increases in pain intensity can occur upon discontinuation of opioid therapy but such an abnormal increased pain sensitivity including hyperalgesia or allodynia can occur also in the absence of overt opioid withdrawal in subjects that have been administered opioid drugs.

The cellular mechanisms underpinning OIH have been proposed to be in common with those of neuropathic pain and analgesic tolerance involving augmented glutamatergic signaling and persistent activation of the *N*-methyl-D-aspartate (NMDA)-nitric oxide synthase (NOS)-nitric oxide (NO) signaling cascade.

Another mechanism proposed to underpin opioid-induced excitatory signaling involves stimulation of adenylate cyclase formation via G_5-coupled opioid receptors that opposes inhibition of adenylate cyclise formation via $G_{i/o}$-coupled opioid receptors to attenuate levels of pain relief (Smith,M.T.; Acute Pain 2008; 10:199-200).

It is known that the combination of opioid analgesics with agents that block excitatory opioid signaling pathways can improve pain relief. Some strategies include combining opioid analgesics with NMDA-receptor antagonists, such as low dose ketamine, and more recently, clinical trials have investigated combinations of ultra-low dose naltrexone (non-selective opioid antagonist) and opioid agonists such as morphine and oxycodone to selective block signaling via G_5-coupled opioid receptors (Smith,M.T.; Acute Pain; 2008;10; 199-200) that are useful in the prevention and/or treatment of opioid-induced hyperalgesia.

Sigma receptors are non-opioid receptors of great interest in pharmacology. 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. 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.

It has been reported that some sigma receptor ligands (i.e., haloperidol) in combination with opioids are capable of modulating the analgesic effect of opioids (both kappa and mu opiods) in models of acute thermal nociceptive tests (i.e., radiant heat tail-flick test) in mice (Mei J and Pasternak GW, Sigma 1 receptor modulation of opioid analgesia in the mouse, J Pharmacol Exp Ther. 2002, 300(3):1070-1074) and rats (Chien CC and Pasternak GW, Sigma antagonists potentiate opioid analgesia in rats, Neurosci Lett. 1995, 190(2):137-139). Recently it has been shown that some sigma-1 receptor antagonists potentiate opioid analgesia in models of acute thermal nociceptive pain and that this potentiation of analgesia is not accompanied by potentiation of opioid side effects (i.e., dependence) (WO 2009/130310). However, no information is available regarding inhibition of OIH by sigma-1 receptor ligands.

The treatment of OIH can be time-consuming and, at times, impractical. Weaning patients from high dose opioids usually requires time and patience. While reducing the opioid dose, patients may experience transient increases in pain or exacerbation of pain and the hyperalgesic effect may not be mitigated until a certain critical dose of opioid is reached.

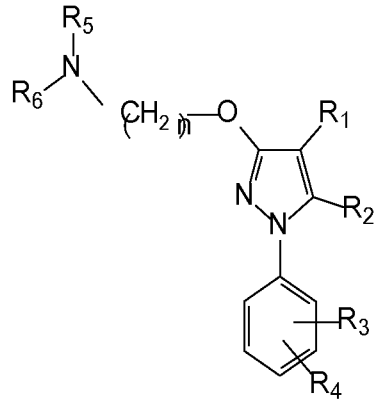
Breaking the cycle of OIH is an attractive course of action for the interventional pain specialist. Thus, there is still a need for substances that could be used as an adjuvant to opioid therapy for the prevention and/or treatment of the associated OIH.

BRIEF DESCRIPTION OF THE INVENTION

The present invention relates to the use of a sigma ligand as adjuvant in the opioid therapy of pain for the prevention and/or treatment of OIH associated to said opioid therapy. This benefit of the invention is more evident when the sigma ligand is specifically a sigma-1 receptor antagonist, preferably in the form of a (neutral) antagonist, an inverse agonist or a partial antagonist.

Therefore, one aspect of the present invention relates to a sigma ligand for use in the prevention and/or treatment of OIH associated to opioid therapy.

In a preferred embodiment, said sigma ligand has the general formula (I):



(I)

wherein

R_1 is selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, and halogen;

R_2 is selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, and halogen;

R_3 and R_4 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic

heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, -CN, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, and halogen, or together they form an optionally substituted fused ring system;

R_5 and **R_6** are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, -CN, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, and halogen, or together form, with the nitrogen atom to which they are attached, a substituted or unsubstituted, aromatic or non-aromatic heterocyclyl group;

n is selected from 1, 2, 3, 4, 5, 6, 7 and 8;

t is 1,2 or 3;

R_8 and **R_9** are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, and halogen;

or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof.

Another aspect of this invention refers to the use of sigma ligand as defined above for the manufacture of a medicament for the prevention and/or treatment of OIH associated to opioid therapy.

Another aspect of the invention is a method of treatment of a patient suffering from OIH associated to opioid therapy, which comprises administering to the patient in need of such a treatment or prophylaxis a therapeutically effective amount of a sigma ligand as defined above.

Another aspect of the invention refers to a combination of at least one sigma ligand as defined above and at least one opioid or opiate compound for simultaneous, separate or sequential administration, for use in the prevention and/or treatment of opioid-induced hyperalgesia associated to opioid therapy.

These aspects and preferred embodiments thereof are additionally also defined in the claims.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Schematic representation of experimental protocol nº 1 (co-administration studies in the perioperative period) showing the time course for the assessment of mechanical sensitization induced by plantar incision. The opioid ligand was administered immediatly after the surgery in three consecutive intraperitoneally injections (every 15 minutes). Paradigm 1 corresponds to a single administration of the sigma receptor ligand immediately before surgery and hence before opioid injection whereas Paradigm 2 corresponds to a single administration of the sigma receptor ligand immediately after the last opioid injection. The experimental protocol nº 1 represents a preventive approach as the sigma ligand is administered in the periooperative period (before-Paradigm 1 or immediately after-Paradigm 2 the opioid administration), long before hyperalgesia develops.

Figure 2: It shows the effect of Remifentanil (opioid receptor agonist) and compound nº 63 (sigma antagonist) approached by Paradigm 1 according to experimental protocol nº 1 (co-administration studies in the perioperative period).

Figure 3: It shows the effect of Remifentanil (opioid receptor agonist) and compound nº 63 (sigma antagonist) approached by Paradigm 2 according to experimental protocol nº 1 (co-administration studies in the perioperative period).

Figures 2 and 3 show that administration of the sigma ligand in the perioperative period inhibits the development of mechanical allodynia when administered both before (Paradigm 1) and after (Paradigm 2) opiod administration. At 40 and 80 mg/kg the sigma ligand (compound nº 63) inhibits allodynia secondary to both surgery and opioid (Remifentanil) use (i.e., OIH). When compound nº 63 is administered at the dose of 20 mg/kg OIH is selectively blocked.

Figure 4: It shows the effect of Morphine (opioid receptor agonist) and compound nº 63 (sigma antagonist) approached by Paradigm 2 according to experimental protocol nº 1 (co-administration studies in the perioperative period). Similar to previous figures showing the effect on Remifentanil use, the sigma ligand (compound nº 63) also inhibits allodynia secondary to surgery and OIH when Morphine was used.

Figure 5: It shows the effect of Morphine (opioid receptor agonist) and BD-1063 (sigma antagonist) approached by Paradigm 2 according to experimental protocol nº 1 (co-administration studies in the perioperative period). The sigma ligand BD-1063 at 80 mg/kg also inhibits the development of OIH when Morphine was used.

Figure 6: Schematic representation of experimental protocol nº 3 (co-administration studies in naïve rats) showing the time course for the assessment of Mechanical Sensitization (i.e., OIH) induced by opioids.

Figure 7: It shows the effect of Remifentanil (opioid ligand) and compound nº 63 (sigma antagonist) according to experimental protocol nº 3 (co-administration studies in naïve rats). The figure 7 shows the inhibitory effect of compound nº 63 on remifentanil-induced hyperalgesia. The inhibitory effect on OIH is clear at 20 and 40 mg/kg.

Figure 8: It shows the effect of Remifentanil (opioid ligand) and compound BD-1063 (sigma antagonist) according to experimental protocol nº 3 (co-administration studies in naïve rats). Similar to compound nº 63, BD-1063 is able to inhibit OIH (i.e., remifentanil-induced hyperalgesia) when administered at 40 mg/kg.

Figure 9: It shows the effect of Morphine (opioid ligand) and compound BD-1063 (sigma antagonist) according to experimental protocol nº 3 (co-administration studies in naïve rats). Not only remifentanil- but also morphine-induced hyperalgesia is inhibited by the sigma ligand BD-1063 when co-administered to naïve rats at 40 mg/kg together with the opioid.

Figure 10: It shows the effect of Fentanyl (opioid receptor agonist) and compound nº 63 (sigma antagonist) approached by Paradigm 2 according to experimental protocol nº 1 (co-administration studies in the perioperative period).

Figure 11: It shows the effect of Sufentanil (opioid receptor agonist) and compound nº 63 (sigma antagonist) approached by Paradigm 2 according to experimental protocol nº 1 (co-administration studies in the perioperative period).

Figure 12: Schematic representation of experimental protocol nº 2 (OIH precipitated by naloxone).

Figure 13: It shows the effect of Remifentanil (opioid receptor agonist) and compound nº 63 (sigma antagonist) according to experimental protocol nº 2 (OIH precipitated by naloxone).

Figure 14: It shows the effect of Morphine (opioid receptor agonist) and compound nº 63 (sigma antagonist) according to experimental protocol nº 2 (OIH precipitated by naloxone).

Figure 15: It shows the effect of Fentanyl (opioid receptor agonist) and compound nº 63 (sigma antagonist) according to experimental protocol nº 2 (OIH precipitated by naloxone).

Figure 16: It shows the effect of Sufentanil (opioid receptor agonist) and compound nº 63 (sigma antagonist) according to experimental protocol nº 2 (OIH precipitated by naloxone).

DETAILED DESCRIPTION OF THE INVENTION

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

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting of 1 to 12 carbon atoms, containing no unsaturation, and which is attached to the rest of the molecule by a single bond, e. g., methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, etc. Alkyl radicals may be optionally substituted by one or more substituents such as aryl, halo, hydroxy, alkoxy, carboxy, cyano, carbonyl, acyl, alkoxycarbonyl, amino, nitro, mercapto, alkylthio, etc. Preferred alkyl radicals have from 1 to 6 carbon atoms. If substituted by aryl, it corresponds to an "Arylalkyl" radical, such as benzyl or phenethyl. If substituted by heterocyclyl, it corresponds to a “Heterocyclylalkyl” radical.

“Alkenyl” refers to a straight or branched hydrocarbon chain radical consisting of 2 to 12 carbon atoms, containing at least one unsaturation, and which is attached to the rest of the molecule by a single bond. Alkenill radicals may be optionally substituted by one or more substituents such as aryl, halo, hydroxy, alkoxy, carboxy, cyano, carbonyl,

acyl, alkoxycarbonyl, amino, nitro, mercapto, alkylthio, etc. Preferred alkenyl radicals have from 2 to 6 carbon atoms.

"Cycloalkyl" refers to a stable 3-to 10-membered monocyclic or bicyclic radical which is saturated or partially saturated, and which consist solely of carbon and hydrogen atoms, such as cyclohexyl or adamantyl. Unless otherwise stated specifically in the specification, the term "cycloalkyl" is meant to include cycloalkyl radicals which are optionally substituted by one or more substituents such as alkyl, halo, hydroxy, amino, cyano, nitro, alkoxy, carboxy, alkoxycarbonyl, etc.

"Aryl" refers to single and multiple aromatic ring radicals, including multiple ring radicals that contain separate and/or fused aryl groups. Typical aryl groups contain from 1 to 3 separated or fused rings and from 6 to about 18 carbon ring atoms, such as phenyl, naphthyl, indenyl, fenanthryl or anthracyl radical. The aryl radical may be optionally substituted by one or more substituents such as hydroxy, mercapto, halo, alkyl, phenyl, alkoxy, haloalkyl, nitro, cyano, dialkylamino, aminoalkyl, acyl, alkoxycarbonyl, etc.

“Heterocyclyl” refers to a stable 3-to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, preferably a 4-to 8-membered ring with one or more heteroatoms, more preferably a 5-or 6-membered ring with one or more heteroatoms. It may be aromatic or not aromatic. For the purposes of this invention, the heterocycle may be a monocyclic, bicyclic or tricyclic ring system, which may include fused ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidised; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated or aromatic. Examples of such heterocycles include, but are not limited to, azepines, benzimidazole, benzothiazole, furan, isothiazole, imidazole, indole, piperidine, piperazine, purine, quinoline, thiadiazole, tetrahydrofuran, coumarine, morpholine; pyrrole, pyrazole, oxazole, isoxazole, triazole, imidazole, etc.

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above, e. g., methoxy, ethoxy, propoxy, etc.

"Amino" refers to a radical of the formula $-NH_2$, $-NHR_a$ or $-NR_aR_b$, optionally quaternized, e.g., methylamino, ethylamino, dimethylamino, diethylamino, propylamino, etc.

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

References herein to substituted groups in the compounds of the present invention refer to the specified moiety that may be substituted at one or more available positions by one or more suitable groups, e. g., halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; alkanoyl such as a C_{1-6} alkanoyl group such as acyl and the like; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms and more preferably 1-3 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon or from 2 to about 6 carbon atoms; alkoxy groups having one or more oxygen linkages and from 1 to about 12 carbon atoms or 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; carbocylic aryl having 6 or more carbons, particularly phenyl or naphthyl and aralkyl such as benzyl. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

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

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

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

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

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

(H. Bundgaard ed., 1985, Harwood Academic Publishers) and Krogsgaard-Larsen et al. "Textbook of Drug design and Discovery" Taylor & Francis (April 2002).

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

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

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

The sigma ligands, in particular 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.

As noted previously, the term “pharmaceutically acceptable salts, solvates, prodrugs” refers to any salt, solvate, or any other compound which, upon administration to the recipient is capable of providing (directly or indirectly) a compound as described herein. However, it will be appreciated that non-pharmaceutically acceptable salts, solvates and prodrugs also fall within the scope of the invention since those may be useful in the preparation of pharmaceutically acceptable salts, solvates and prodrugs. The preparation of salts, solvates and prodrugs can be carried out by methods known in the art.

As used herein, the terms “treat”, “treating” and “treatment” include the eradication, removal, reversion, alleviation, modification, or control of opioid-induced hyperalgesia (OIH).

As used herein, the terms “prevention”, “preventing”, “preventive” “prevent” and prophylaxis refer to the capacity of a therapeutic to avoid, minimize or difficult the onset or development of a disease or condition before its onset, in this case opioid-induced hyperalgesia (OIH).

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

As used herein, the terms “sigma ligand” or “sigma receptor ligand” refer to any compound binding to the sigma receptor. As stated previously, the sigma ligand is preferebly a sigma receptor antagonist in the form of a (neutral) antagonist, an inverse agonist or a partial antagonist.

An “agonist" is defined as a compound that binds to a receptor and has an intrinsic effect, and thus, increases the basal activity of a receptor when it contacts the receptor.

An "antagonist" is defined as a compound that competes with an agonist or inverse agonist for binding to a receptor, thereby blocking the action of an agonist or inverse agonist on the receptor. However, an antagonist (also known as a "neutral" antagonist) has no effect on constitutive receptor activity. Antagonists mediate their effects by binding to the active site or to allosteric sites on receptors, or they may interact at unique binding sites not normally involved in the biological regulation of the receptor's activity. Antagonist activity may be reversible or irreversible depending on the longevity of the antagonist–receptor complex, which, in turn, depends on the nature of antagonist receptor binding.

A “partial antagonist” is defined as a compound that binds to the receptor and generates an antagonist response; however, a partial antagonist does not generate the full antagonist response. Partial antagonists are weak antagonists, thereby blocking partially the action of an agonist or inverse agonist on the receptor.

An "inverse agonist" is defined as a compound that produces an effect opposite to that of the agonist by occupying the same receptor and, thus, decreases the basal activity of a receptor (i.e., signalling mediated by the receptor). Such compounds are also known as negative antagonists. An inverse agonist is a ligand for a receptor that causes the receptor to adopt an inactive state relative to a basal state occurring in the absence of any ligand. Thus, while an antagonist can inhibit the activity of an agonist, an inverse agonist is a ligand that can alter the conformation of the receptor in the absence of an agonist.

“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)). Pharmacological data based on ligand binding studies, anatomical distribution and biochemical features distinguish at least two subtypes of σ receptors (R. Quiron et al., Trends Pharmacol. Sci. 13, 85-86 (1992); M.L.Leitner, Eur. J. Pharmacol. 259, 65-69 (1994); S.B. Hellewell and W.D. Bowen; Brain Res. 527, 244-253 (1990)) (G. Ronsisvalle et al. Pure Appl. Chem. 73, 1499-1509 (2001)). The protein sequences of the sigma receptors (Sigma 1 (σ1) and Sigma 2 (σ2)) are known in the art (e.g. Prasad, P.D. et al., J. Neurochem. 70 (2), 443-451 (1998)). They show a very high affinity to various analgesics (e.g. pentazocine).

"Compound/s binding to the sigma receptor" or "sigma ligand" as used in this application is/are defined as a compound having an IC_{50} value of ≤ 5000 nM, more preferably ≤ 1000 nM, more preferably ≤ 500 nM on the sigma receptor. More preferably, the IC_{50} value is ≤ 250 nM. More preferably, the IC_{50} value is ≤ 100 nM. Most preferably, the IC_{50} value is ≤ 50 nM. The half maximal inhibitory concentration (IC50) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function. The IC50 is the concentration of competing ligand which displaces 50% of the specific binding of the radioligand. Additionally, the wording "Compound/s binding to the sigma receptor", as used in the present application is defined as having at least ≥50% displacement using 10 nM radioligand specific for the sigma receptor (e.g. preferably [^{3}H]-(+) pentazocine) whereby the sigma receptor may be any sigma receptor subtype. Preferably, said compounds bind to the sigma-1 receptor subtype.

Compounds binding to the sigma receptor, generally also referred to as sigma ligands, are well known in the art. Many of them are encompassed by the "Compound/s binding to the sigma receptor" definition above. Although there are many known uses for sigma ligands, such as antipsychotic drugs, anxiolytics, antidepressants, stroke treatment, antiepileptic drugs and many other indications, including anti-migraine and general pain, there is no mention in the art of these compounds as useful for the treatment of opioid-induced hyperalgesia (OIH) associated to opioid therapy.

Table 1 lists some sigma ligands known in the art (i.e. having an IC_{50} ≤ 5000 nM). Some of these compounds may bind to the sigma-1 and/or to the sigma-2 receptor. These sigma ligands also include their respective salts, bases, and acids.

Table 1

(-)-Cyanopindolol hemifumarate	Cutamesine hydrochloride
(-)-(1R,2S)-cis-N-[2-(3,4-Dichlorophenyl)ethyl]-2-pyrrolidinocyclohexylamine	Cyclobenzaprine HCl
(-)-1-[1-(3-Chlorophenyl)pyrrolidin-2-ylmethyl]-4-(2-phenylethyl)piperazine	Cycloheximide

(-)-Sparteine sulfate pentahydrate	Cyproheptadine HCl
(+)-Himbacine	Darrow Red HCl
(±)-1-Cyclohexyl-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)propyl]piperazine	Demecarium Bromide
(1S,5R)-3-[2-(2-Adamantyl)ethyl]-1,8,8-trimethyl-3-azabicyclo[3.2.1]octane hydrochloride	Denatonium Benzoate
(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin-1-Yl)-Ethyl Ester	Deptropine Citrate
(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)-Carbamic Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester	Desloratadine
(4aalpha,8aalpha)-6-(4-Fluorophenyl)-2-(4-pyridylmethyl)-6-hydroxydecahydroisoquinoline; (4a,8a-cis)-6-(4-Fluorophenyl)-2-(pyridin-4-ylmethyl)perhydroisoquinolin-6-ol	Dexbrompheniramine Maleate
(4aalpha,8abeta)-2-Benzyl-6-(4-fluorophenyl)-6-hydroxydecahydroisoquinoline	Dexchlorpheniramine Maleate
(6aR,9R)-5-Bromo-7-methyl-N-(2-propynyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide	Dexfenfluramine HCl
(S)-(-)-N-(2-Amino-3-phenylpropyl)-2-(3,4-dichlorophenyl)-N-methylacetamide hydrochloride	Dicyclomine HCl
(S)-Methamphetamine HCl	Diethylpropion HCl
[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 1-(3-Benzyloxy-4-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester	Dimethisoquin HCl

[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 2-(Tert-Butoxycarbonyl-Naphthalen-1-Ylmethyl-Amino)-Ethyl Ester	Dimetindene Maleate
[4-(4-Ethyl-3,5-Dimethyl-Pyrazol-1-Yl)-Phenyl]-[4-(3-Phenyl-Allyl)-Piperazin-1-Yl]-Methanone	Diphemanil Methylsulfate
1-(1,2-Diphenylethyl)Piperidine Maleate, (+/-)	Diphenidol HCl
1-(1,4-Ethano-1,2,3,4-tetrahydro-2-naphthylmethyl)-4-methylpiperazine hydrate; 1-(Benzobicyclo[2.2.2]octen-2-ylmethyl)-4-methylpiperazine hydrate	Diphenoxylate HCl
1-(1-Adamantyl)-2-[4-(2H-naphtho[1,8-cd]isothiazol-2-ylmethyl)piperidin-1-yl]ethanone S,S-dioxide hydrochloride	Diphenylpyraline HCl
1-(1-Naphthyl)Piperazine HCl	Dipropyldopamine HBr
1-(2-Benzyloxyethyl)-4-(3-phenylpropyl)piperazine dihydrochloride	Doxepin HCl
1-(2-Phenylethyl)piperidine oxalate	Dyclonine HCl
1-(3-Chlorophenyl)Piperazine HCl	Ebastine
1-(3-Chlorothien-2-yl)-2-[4-(4-fluorobenzyl)piperidin-1-yl]ethanol	Econazole Nitrate
1-(4-Bromo-Benzenesulfonyl)-4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine	Epinastine HCl
1-(4-Chloro-3-hydroxyphenyl)-2-[4-(4-fluorobenzyl)piperidin-1-yl]ethanol	Ethaverine HCl
1-(4-Chlorophenyl)-3-(hexahydroazepin-1-ylmethyl)pyrrolidin-2-one	Ethopropazine HCl
1-(4-Chlorophenyl)-3(R)-[4-(2-methoxyethyl)-1-piperazinylmethyl]pyrrolidin-2-one (-)-D-	Eticlopride HCl, S(-)-

tartrate	
1-(4-Chlorophenyl)-3(R)-[4-(2-methoxyethyl)piperazin-1-ylmethyl]pyrrolidin-2-one dihydrochloride	Etofenamate
1'-(4-Fluorobenzyl)-1,3-dihydrospiro[2-benzofuran-1,4'-piperidine]	Etonitazenyl Isothiocyanate
1-(4-Fluorophenyl)-4-[4-(5-fluoro-2-pyrimidinyl)-1-piperazinyl]butan-1-ol hydrochloride	Femoxetine HCl
1-(4-Fluorophenyl)-4-[4-(5-fluoropyrimidin-2-yl)piperazin-1-yl]butan-1-ol; 1-[4-(4-Fluorophenyl)-4-hydroxybutyl]-4-(5-fluoropyrimidin-2-yl)piperazine	Fenfluramine HCl
1'-(4-Phenylbutyl)spiro[1,3-dihydroisobenzofuran-1,4'-piperidine]	Fenticonazole Nitrate
1-(Cyclobutylmethyl)-2-[3-phenyl-2(E)-propenyl]pyrrolidine hydrochloride	Fipexide HCl
1-(Cyclohexylmethyl)-3'-methoxy-5'-phenyl-4',5'-dihydro-3'H-spiro[piperidine-4,1'-pyrano[4,3-c]pyrazole]	Flavoxate HCl
1-(Cyclopropylmethyl)-4-[2-(4-fluorophenyl)-2-oxoethyl]piperidine hydrobromide	Flunarizine diHCl
1,4-Bis[spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl]butane	Fluoxetine Related Compound B
1-[(1R,3R)-2,2-Dimethyl-3-(2-phenoxyethyl)cyclobutylmethyl]piperidine	Fluperlapine
1-[2-(3,4-Dichlorophenyl)ethyl]-3-(pyrrolidin-1-yl)piperidine	Fluphenazine Decanoate DiHCl
1-[2-(3,4-Dichlorophenyl)ethyl]-4-(3-phenylpropyl)piperazine	Fluphenazine Enanthate DiHCl

1-[2-(3,4-Dichlorophenyl)ethyl]-4-methylpiperazine	Fluphenazine HCl
1-[2-(4-Fluorophenyl)ethyl]-4,4-dimethylhexahydroazepine hydrochloride	Fluphenazine N-Mustard DiHCl
1-[2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylsulfanyl]ethyl]piperidine oxalate	Flurazepam Related Compound C
1-[2-Benzyloxy-1(R)-phenylethyl]-4-cyclohexylpiperazine dihydrochloride	Fluspirilene
1-[3-(2-Oxo-3-phenylimidazolin-1-yl)propyl]spiro[piperidine-4,1'(3H)-isobenzofuran] hydrochloride; 1-Phenyl-3-[3-[spiro[piperidine-4,1'(3H)-isobenzofuran]-1-yl]propyl]imidazolin-2-one hydrochloride	GBR 12783 DiHCl
1-[3-(3,4-Dimethoxyphenyl)propyl]-4-(4-phenylbutyl)perhydro-1,4-diazepine dihydrochloride	GBR 12909 DiHCl
1-[3-(4-Chlorophenoxy)propyl]-4-methylpiperidine hydrochloride	GBR 13069 DiHCl
1-[3-(4-Phenyl-2H-1,2,3-triazol-2-yl)propyl]piperidine	GBR-12935 DiHCl
1-[4-(6-Methoxynaphthalen-1-yl)butyl]-3,3-dimethylpiperidine hydrochloride	GR 89696 Fumarate
1-[4-[2-[1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yloxy]ethyl]piperazin-1-yl]ethanone oxalate	Guanabenz Acetate
11-[5-(4-Fluorophenyl)-5-oxopentyl]-5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[b]indole	Guanadrel Sulfate
1-Benzyl-3beta-[3-(cyclopropylmethoxy)propyl]-2alpha,3alpha,4beta-trimethylpiperidine	Halofantrine HCl

1-Benzyl-3-methoxy-3',4'-dihydrospiro(piperidine-4,1'-thieno[3,2-c]pyrane)	HEAT HCl
1'-Benzyl-3-methoxy-4-phenyl-3,4-dihydrospiro[furo[3,4-c]pyrazole-1,4'-piperidine]	Hexylcaine HCl
1-Benzyl-4-(4-fluorophenoxymethyl)piperidine	Hycanthone
1-Benzyl-4-[2-(4-fluorophenyl)-2-oxoethyl]piperidine maleate	Hydroxychloroquine Sulfate
1-Benzyl-4-[3-phenyl-2(E)-propenyloxymethyl]piperidine hydrochloride	IBZM, S(-)-
1-Benzyl-4-[4-(4-fluorophenyl)-3-cyclohexen-1-yl]piperazine dihydrochloride hemihydrate	ICI-199,441 HCl
1'-Benzylspiro[1,2,3,4-tetrahydronaphthalene-1,4'-piperidine]	Ifenprodil Tartrate
1'-Benzylspiro[indane-1,4'-piperidine]	Indatraline HCl
1'-Butyl-3-Methoxy-4-phenyl-3,4-dihydrospiro[furo[3,4-c]pyrazole-1,4'-piperidine]	Iofetamine HCl
1-Cyclohexyl-4-(3-phenoxypropyl)piperazine dihydrochloride	Isamoltane Hemifumarate
1-Hydroxy-1'-(2-phenylethyl)spiro[1,2,3,4-tetrahydronaphthalene-2,4'-piperidine] hydrochloride	Isoxsuprine HCl
1-Methyl-4-[2-(4-phenylpiperidin-1-yl)ethyl]-4,5,6,7-tetrahydro-1H-indazole oxalate	Ketotifen Fumarate Salt
1-Phenyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1-propanone oxime oxalate	L-693,403 Maleate

1-Phenyl-4-(pyrrolidin-1-ylmethyl)-1,4,6,7-tetrahydropyrano[4,3-c]pyrazole	L-741,626
2-(2-{[1-(3-Chloro-Benzyl)-Pyrrolidin-3-Yl]-Methyl-Carbamoyl}-2-Methyl-Propyl)-4,6-Dimethyl-Benzoic Acid	L-741,742 HCl
2-(3,4-Dichlorophenyl)-N-methyl-N-[2-(1,2alpha,3alpha,4beta-tetramethylpiperidin-3beta-yl)ethyl]acetamide	L-745,870 TriHCl
2-(Cyclohexylmethylaminomethyl)-8-methoxy-3,4-dihydro-2H-1-benzopyran hydrochloride	Levetimide HCl, R(-)
2(S)-[(3aS,6aR)-5-Butyl-4-oxo-1,2,3,3a,4,6a-hexahydrocyclopenta[c]pyrrol-2-yl]propionic acid ethyl ester	Levobunolol HCl
2-[2-[5-Methyl-1-(2-naphthyl)-1H-pyrazol-3-yloxy]ethylamino]ethanol hydrochloride	Lidoflazine
2-[2-[N-(Cyclobutylmethyl)-N-methylamino]ethyl]-1,2,3,4-tetrahydronaphthalen-2-one	Lobeline HCl
2-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propoxy]-9H-carbazole	lomerizine diHCl
2-[4-(4-Methoxybenzyl)piperazin-1-ylmethyl]-4H-1-benzopyran-4-one	Loxapine Succinate
2-[N-[2-(3,4-Dichlorophenyl)ethyl]-N-methylaminomethyl]-1-ethylpyrrolidine	LY-53,857 Maleate
2-Benzyl-3,4,8-trimethyl-2-azabicyclo[2.2.2]octane-6-carboxylic acid ethyl ester	Maprotiline HCl
2-Butyl-2,3,4,4a,9,9a-hexahydro-1H-indeno[2,1-c]pyridine	Mazindol
2-Chloro-11-(4-	MDL 12,330A HCl

Methylpiperazino)Dibenz[B,F]Oxepin Maleate	
3-(1-Benzyl-2r,3c,4t-trimethylpiperidin-3t-yl)propionic acid ethyl ester hydrochloride	Mebhydroline 1,5-naphthalendisulfonate Salt
3-(3-Chloro-4-cyclohexylphenyl)-1-(hexahydroazepin-1-yl)-1(Z)-propene hydrochloride; 1-[3-(3-Chloro-4-cyclohexylphenyl)-2(Z)-propenyl]hexahydroazepine hydrochloride	Meclizine HCl
3-(4-Methylphenyl)-5-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)isoxazole oxalate	Mefloquine HCl
3-(N-Benzyl-N-methylamino)-1-(4-nitrophenyl)piperidine	Meprylcaine HCl
3,3'-Diethylthiacarbocyanine Iodide	Mesoridazine Besylate
3-[1-(Benzocyclobutan-1-ylmethyl)piperidin-4-yl]-6-fluoro-1,2-benzisoxazole	Metaphit Methanesulfonate
3-[2-(2-Adamantyl)ethyl]-3-azabicyclo[3.2.2]nonane	Metaphit
3-[3-(4-Methylphenyl)isoxazol-5-yl]-1-propyl-1,2,5,6-tetrahydropyridine	Methantheline Bromide
3a,6-Epoxy-2-[2-(4-fluorophenyl)ethyl]-2,3,3a,6,7,7a-hexahydro-1H-isoindole	Methdilazine
3a,6-Epoxy-2-[2-(4-fluorophenyl)ethyl]perhydroisoindole	Methiothepin Mesylate
3-Mercapto-2-Methylpropanoic Acid 1,2-Diphenylethylamine Salt	Methixene HCl
3-Phenyl-1-(1-propyl-1,2,5,6-tetrahydro-3-pyridyl)-1-propanone oxime monohydrochloride	Methylene Violet 3Rax HCl
3-Quinuclidinyl Benzilate	Metipranolol

3-Tropanyl-3,5-Dichlorobenzoate	Mianserin HCl
3-Tropanyl-Indole-3-Carboxylate HCl	Miconazole
4-(1H-Indol-4-Yl)-Piperazine-1-Carboxylic Acid 2-(5-Bromo-2-Ethoxy-Phenylamino)-Cyclohexylmethyl Ester	ML-9 HCl
4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine-1-Carboxylic Acid 2-Thiophen-2-Yl-Ethyl Ester	Morantel Hydrogen L-Tartrate
4-(3,5-Dimethoxy-Phenyl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-Benzyl)-Piperidin-2-Ylmethyl Ester	MR 16728 HCl
4-(3-Nitro-5-Sulfamoyl-Thiophen-2-Yl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-5-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester	MT-210
4-(4-Benzylpiperazin-1-ylmethyl)-7-methoxy-2H-1-benzopyran-2-one	N-(2-Adamantyl)-N-[2-(2-adamantyl)ethyl]-N-methylamine hydrochloride
4-(4-Bromophenyl)-5-[2-(dihexylamino)ethyl]thiazol-2-amine dihydrochloride	N-[1-(2-Indanyl)piperidin-4-yl]-N-methylcarbamic acid isobutyl ester fumarate
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	N-[1-[4-Methoxy-3-(2-phenylethoxy)benzyl]-4-methylpentyl]-N-propylamine
4-(4-Methylphenyl)-1-(3-morpholinopropyl)-1,2,3,6-tetrahydropyridine	N-[2-(3,4-Dichlorophenyl)ethyl]-N-ethyl-N-[2-(1-pyrrolidinyl)ethyl]amine
4-(5-Trifluoromethyl-Pyridin-2-Yl)-Piperazine-1-Carboxylic Acid Pent-2-Ynyl Ester	N-[2-(3,4-Dichlorophenyl)ethyl]-N-methyl-N-(2-pyrrolidinoethyl)amine dihydrobromide
4-(Dimethylamino)-1-phenylcyclohexanol	N-[4-[4-(Diethylamino)piperidin-1-yl]phenyl]methanesulfonamide
4,7-Epoxy-2-[2-(4-fluorophenyl)ethyl]-2,3,3a,4,7,7a-hexahydro-1H-isoindole	N1-(1-Adamantyl)-N2-(2-methylphenyl)acetamidine
4-[1-(3-[18F]fluoropropyl)piperidin-4-	N1-[2-(3,4-Dichlorophenyl)ethyl]-N1,N2,N2-

ylmethoxy]benzonitrile	trimethyl-1,2-ethanediamine
4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl]-2-hydroxy-4-oxobut-2-enoic acid	Nafronyl Oxalate Salt
4-[1-(4-Fluorophenyl)-1-hydroxymethyl]-1-[3-(4-fluorophenoxy)propyl]piperidine	Naftifine
4-[2-(Dipropylamino)ethyl]-2-(2-phenylethoxy)anisole hydrochloride	Naftopidil diHCl
4-[2-(Dipropylamino)ethyl]-5,8-dimethylcarbazole hydrochloride	Naltriben Mesylate
4-[2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl]morpholine	NE-100
4-[2-[1-(Cyclopropylmethyl)piperidin-4-yl]acetyl]benzonitrile fumarate	Nefazodone
4-[4-(N-Benzyl-N-methylamino)piperidin-1-yl]benzonitrile	N-Ethyl-N-[2-(1-piperidinyl)ethyl]-N-[2-[4-(trifluoromethoxy)phenyl]ethyl]amine
4-[N-[2-[N'-(4-Fluorobenzyl)-N'-methylamino]ethyl]-N-methylamino]-1-(4-fluorophenyl)-1-butanone dihydrochloride	Nicergoline
4-Benzyl-1-[4-(4-fluorophenyl)-4-hydroxybutyl]piperidine hydrochloride	Niguldipine HCl, (+/-)-
4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-2-Trifluoromethoxy-Benzenesulfonamide	Nisoxetine HCl
4'-Chloro-3-Alpha-(Diphenylmethoxy)Tropane HCl	NP-07
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-10-Yl)-Propyl]-Piperazin-1-Yl}-Ethyl Ester	Nylidrin HCl
4-Methoxy-1-[2-(4-phenylpiperazin-1-yl)ethyl]-	Octoclothepin Maleate, (±)-

6H-dibenzo[b,d]pyran hydrochloride	
4-Methoxy-N-[1-(7-Methoxy-Benzo[1,3]Dioxol-5-Ylmethyl)-Pyrrolidin-3-Yl]-Benzenesulfonamide	Oxamniquine
4-Phenyl-1-(3-phenylpropyl)-4-(pyrrolidin-1-ylcarbonyl)piperidine	Oxamniquine Related Compound A
5-(2-Pyrrolidinoethyl)-4-(2,4,6-trimethoxyphenyl)thiazole-2-amine dihydrochloride	Oxamniquine Related Compound B
5-(N-Ethyl-N-Isopropyl)-Amiloride	Oxatomide
6-[1-Hydroxy-2-[4-(2-phenylethyl)piperidin-1-yl]ethyl]-1,2,3,4-tetrahydroquinolin-2-one	Oxiconazole Nitrate
6-[2-(4-Benzylpiperidin-1-yl)ethyl]-3-methylbenzothiazol-2(3H)-one	Panamesine hydrochloride
6-[2-[4-(2-Phenylethyl)piperidin-1-yl]ethyl]-1,2,3,4-tetrahydroquinolin-2-one	Panaxatriol
6-[3-(Morpholin-4-yl)propyl]benzothiazol-2(3H)-one	PAPP
6-[6-(4-Hydroxypiperidin-1-yl)hexyloxy]-3-methyl-2-phenyl-4H-1-benzopyran-4-one	Paroxetine
7-(4-Methoxyphenyl)-4-[4-(4-pyridyl)butyl]hexahydro-1,4-thiazepine	Paxilline
7-[3-[4-(4-Fluorobenzoyl)piperidin-1-yl]propoxy]-4H-1-benzopyran-4-one hydrochloride	p-Chlorobenzhydrylpiperazine
9-[4-({[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl}amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide	Penbutolol Sulfate
9-Hydroxy-2,3,6,7,7a,8,12b,12c-octahydro-	Pentamidine Isethionate

1H,5H-naphtho[1,2,3-ij]quinolizine	
Acetophenazine Maleate	Pergolide Methanesulfonate
Acrinol	Perospirone
Ajmaline	Phenamil Methanesulfonate
Alaproclate HCl	Phenosafranin HCl
Aloe-Emodin	Piboserod
Alprenolol D-Tartrate Salt Hydrate	Pimozide
Alprenolol HCl	Pinacyanol Chloride
AMI-193	Pindobind, (+/-)-
Aminobenztropine	Piperacetazine
Amiodarone HCl	Piperidolate HCl
Amodiaquine HCl	Pirenperone
Amorolfine HCl	PPHT HCl, (±)-
Amoxapine	Prenylamine Lactate Salt
AN2/AVex-73; AE-37; ANAVEX 2-73; N-(2,2-Diphenyltetrahydrofuran-3-ylmethyl)-N,N-dimethylamine	Pridinol Methanesulfonate Salt
Anavex 1-41; AE-14; N-(5,5-Diphenyltetrahydrofuran-3-ylmethyl)-N,N-dimethylamine hydrochloride	Procyclidine HCl
Anavex 19-144; AE-37met; AN19/AVex-144	Proflavine Hemisulfate Salt
Anavex 7-1037	Propafenone HCl
Anisotropine Methylbromide	Proparacaine HCl
Anpirtoline	Propiomazine
ARC 239 DiHCl	Protokylol

Auramine O HCl	Protriptyline HCl
Azaperone	Pyrilamine Maleate
Azatadine Maleate	Pyrimethamine
Azelastine HCl	Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-2-Ylmethyl] Ester 2-Benzyl Ester
Bamethan sulfate	Pyrvinium Pamoate
BD 1008 DiHBr	Quetiapine Fumarate
BD-1063	Quinacrine HCl
Benextramine TetraHCl	Quinaldine Red
Benfluorex HCl	Quipazine Dimaleate
Benidipine HCl	Quipazine, 6-Nitro-, Maleate
Benoxathian HCl	Raloxifene
Benproperine Phosphate	Rimantadine HCl
Benzododecinium bromide	Rimcazole hydrochloride
Benzphetamine HCl	Risperidone
Benztropine Mesylate	Ritanserin
Bephenium Hydroxynaphthoate	Ritodrine HCl
Bepridil HCl	RS 23597-190 HCl
Berberine chloride	RS 67333 HCl
Betaxolol HCl	RS 67506 HCl
Bifemelane	Safranin O HCl
BMY 7378 DiHCl	Salmeterol
Bopindolol Malonate	SB203186

BP 554 Maleate	SCH-23390 HCl, R(+)-
Bromhexine HCl	Sertaconazole Nitrate
Bromodiphenhydramine HCl	Sertindole
Bromperidol	Sertraline
Brompheniramine Maleate	Sibutramine HCl
BTCP HCl	Siramesine hydrochloride
Buclizine HCl	SKF-525A HCl
Buflomedil HCl	SKF-96365 HCl
Bupropion HCl	SNC 121
Buspirone HCl	Spiperone HCl
Butacaine Sulfate	T-226296
Butaclamol HCl, (±)-	Tegaserod Maleate
Butenafine HCl	Terbinafine HCl
Butoconazole Nitrate	Terconazole
BW 723C86 HCl	Terfenadine
Carbetapentane Citrate	Terfenadine Related Compound A
Carbinoxamine Maleate	Tetrindole Mesylate
Carpipramine DiHCl DiH2O	Thiethylperazine Malate
Carvedilol	Thioperamide Maleate
Cephapirin Benzathine	Thioproperazine
CGS-12066A Maleate	Thioridazine
Chloroprocaine HCl	Thiothixene
Chlorpheniramine Maleate	Thiothixene, (E)-

Chlorphenoxamine HCl	Thonzonium Bromide
Chlorprothixene	Tioconazole Related Compound A
Cinanserin HCl	TMB-8 HCl
Cinnarizine	Tolterodine L-Tartrate
Cirazoline HCl	Toremifene Citrate
Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidinyl)Cyclohexamine DiHBr	Tramazoline HCl
Cis(Z)-Flupentixol DiHCl	Trans-U-50488 Methanesulfonate, (±)-
cis-2-(Cyclopropylmethyl)-7-(4-fluorobenzoyl)perhydropyrido[1,2-a]pyrazine	Tridihexethyl Chloride
cis-2-[4-(Trifluoromethyl)benzyl]-3a,4,7,7a-tetrahydroisoindoline	Trifluoperazine HCl
Cisapride Hydrate	Trifluperidol HCl
Citalopram HBr	Trihexyphenidyl HCl
Clemastine Fumarate	Trimeprazine Hemi-L-Tartrate
Clemizole HCl	Trimipramine Maleate
Clenbuterol HCl	Tripelennamine HCl
Clidinium Bromide	Triprolidine HCl
Clobenpropit 2HBr	Triprolidine HCl Z Isomer
Clofazimine	Tropanyl 3,5-Dimethylbenzoate
Clofilium Tosylate	Tropine 2-(4-Chlorophenoxy)Butanoate, Maleate
Clomiphene Citrate	U-50488 HCl, (-)-
Clomiphene Related Compound A	U-62066

Clomipramine	UH 232 Maleate, (+)-
Cloperastine HCl	Vesamicol HCl
Clorgyline HCl	Vinpocetine
Clozapine	W-7 HCl
Conessine	WB-4101 HCl

Preferably, the table above includes also reduced haloperidol. Reduced haloperidol is an active metabolite of haloperidol that is produced in humans, shows a high affinity (in the low nanomolar range) for sigma-1 receptors, and produces an irreversible blockade of sigma-1 receptors both in experimental animals and human cells.

Examples of well known methods of producing a prodrug of a given acting compound are known to those skilled in the art (e.g. in Krogsgaard-Larsen et al., Textbook of Drug design and Discovery, Taylor & Francis (April 2002)).

In a preferred embodiment, the sigma ligand in the context of the present invention has the general formula (I) as depicted above.

In a preferred embodiment, R_1 in the compounds of formula (I) is selected from H, -COR_8, and substituted or unsubstituted alkyl. More preferably, R_1 is selected from H, methyl and acetyl. A more preferred embodiment is when R_1 is H.

In another preferred embodiment, R_2 in the compounds of formula (I) represents H or alkyl, more preferably methyl.

In yet another preferred embodiment of the invention, R_3 and R_4 in the compounds of formula (I) are situated in the meta and para positions of the phenyl group, and preferably, they are selected independently from halogen and substituted or unsubstituted alkyl.

In an especially preferred embodiment of the invention, in the compounds of formula (I) both R_3 and R_4 together with the phenyl group form an optionally substituted fused ring system (for example, a substituted or unsubstituted aryl group or a substituted or unsubsituted, aromatic or non-aromatic heterocyclyl group may be fused), more preferably, a naphthyl ring system.

Also in the compounds of formula (I), embodiments where n is selected from 2, 3, 4 are preferred in the context of the present invention, more preferably n is 2.

Finally, in another embodiment it is preferred in the compounds of formula (I) that R_5 and R_6 are, each independently, C_{1-6} alkyl, or together with the nitrogen atom to which they are attached form a substituted or unsubstituted heterocyclyl group a, in particular a group chosen among morpholinyl, piperidinyl, and pyrrolidinyl group. More preferably, R_5 and R_6 together form a morpholine-4-yl group.

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

[1] 4-{2-(1-(3,4-dichlorophenyl)-5-methyl-1H pyrazol-3-yloxy)ethyl}morpholine

[2] 2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]-N,N-diethylethanamine

[3] 1-(3,4-Dichlorophenyl)-5-methyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole

[4] 1-(3,4-Dichlorophenyl)-5-methyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole

[5] 1-{2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}piperidine

[6] 1-{2-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}-1H-imidazole

[7] 3-{1-[2-(1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy)ethyl]piperidin-4-yl}-3H-imidazo[4,5-b]pyridine

[8]1-{2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}-4-methylpiperazine

[9] Ethyl 4-{2-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}piperazine carboxylate

[10] 1-(4-(2-(1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy)ethyl)piperazin-1-yl)ethanone

[11] 4-{2-[1-(4-Methoxyphenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}morpholine

[12] 1-(4-Methoxyphenyl)-5-methyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole

[13] 1-(4-Methoxyphenyl)-5-methyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole

[14] 1-[2-(1-(4-Methoxyphenyl)-5-methyl-1H-pyrazol-3-yloxy)ethyl]piperidine

[15] 1-{2-[1-(4-Methoxyphenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}-1H-imidazole

[16] 4-{2-[1-(3,4-Dichlorophenyl)-5-phenyl-1H-pyrazol-3-yloxy]ethyl}morpholine

[17] 1-(3,4-Dichlorophenyl)-5-phenyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole

[18] 1-(3,4-Dichlorophenyl)-5-phenyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole

[19] 1-{2-[1-(3,4-Dichlorophenyl)-5-phenyl-1H-pyrazol-3-yloxy]ethyl}piperidine

[20] 1-{2-[1-(3,4-Dichlorophenyl)-5-phenyl-1H-pyrazol-3-yloxy]ethyl}-1H-imidazole

[21]2-{2-[1-(3,4-dichlorophenyl)-5-phenyl-1H-pyrazol-3-yloxy]ethyl}-1,2,3,4-tetrahydroisoquinoline

[22] 4-{4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}morpholine

[23] 1-(3,4-Dichlorophenyl)-5-methyl-3-[4-(pyrrolidin-1-yl)butoxy]-1H-pyrazole

[24] 1-{4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}piperidine

[25]1-{4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-4-methylpiperazine

[26] 1-{4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-1H-imidazole

[27] 4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]-N,N-diethylbutan-1-amine

[28]1-{4-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-4-phenylpiperidine

[29] 1-{4-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-6,7-dihydro-1H-indol-4(5H)-one

[30] 2-{4-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-1,2,3,4-tetrahydroisoquinoline

[31] 4-{2-[1-(3,4-dichlorophenyl)-5-isopropyl-1H-pyrazol-3-yloxy]ethyl}morpholine

[32]2-[1-(3,4-Dichlorophenyl)-5-isopropyl-1H-pyrazol-3-yloxy]-N,N-diethylethanamine

[33] 1-(3,4-Dichlorophenyl)-5-isopropyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole

[34] 1-(3,4-Dichlorophenyl)-5-isopropyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole

[35] 1-{2-[1-(3,4-Dichlorophenyl)-5-isopropyl-1H-pyrazol-3-yloxy]ethyl}piperidine

[36] 2-{2-[1-(3,4-dichlorophenyl)-5-isopropyl-1H-pyrazol-3-yloxy]ethyl}-1,2,3,4-tetrahydroisoquinoline

[37] 4-{2-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]ethyl}morpholine

[38] 2-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy] N,N-diethylethanamine

[39] 1-(3,4-dichlorophenyl)-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole

[40] 1-{2-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]ethyl}piperidine

[41] 1-(3,4-dichlorophenyl)-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole

[42]1-{2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}piperazine

[43] 1-{2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}pyrrolidin-3-amine

[44]4-{2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]ethyl}morpholine

[45]4-{2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]ethyl}morpholine

[46]2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]-N,N-diethylethanamine

[47] 1-(3,4-Dichlorophenyl)-4,5-dimethyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole

[48] 1-(3,4-Dichlorophenyl)-4,5-dimethyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole

[49] 1-{2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]ethyl}piperidine

[50] 4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}morpholine

[51](2S,6R)-4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}-2,6-dimethylmorpholine

[52] 1-{4-[1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}piperidine

[53] 1-(3,4-Dichlorophenyl)-3-[4-(pyrrolidin-1-yl)butoxy]-1H-pyrazole

[55] 4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N,N-diethylbutan-1-amine

[56] N-benzyl-4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N-methylbutan-1-amine

[57]4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N-(2-methoxyethyl)-N-methylbutan-1-amine

[58] 4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}thiomorpholine

[59]1-[1-(3,4-Dichlorophenyl)-5-methyl-3-(2-morpholinoethoxy)-1H-pyrazol-4-yl]ethanone

[60]1-{1-(3,4-dichlorophenyl)-5-methyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazol-4-yl}ethanone

[61] 1-{1-(3,4-dichlorophenyl)-5-methyl-3-[2-(piperidin-1-yl)ethoxy]-1H-pyrazol-4-yl}ethanone

[62] 1-{1-(3,4-dichlorophenyl)-3-[2-(diethylamino)ethoxy]-5-methyl-1H-pyrazol-4-yl}ethanone

[63] 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine

[64] N,N-Diethyl-2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethanamine

[65] 1-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}piperidine

[66] 5-Methyl-1-(naphthalen-2-yl)-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole

or their pharmaceutically acceptable salts, isomers, prodrugs or solvates.

In a more preferred variant of the invention, the sigma ligand of formula (I) is 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine. This particular compound is designated in the examples of the present invention as compound 63.

The compounds of formula (I) and their salts or solvates can be prepared as disclosed in the previous application WO2006/021462.

As stated previously, one aspect of this invention refers to the use of sigma ligand as defined above for the manufacture of a medicament for the prevention and/or treatment of OIH associated to opioid therapy.

According to the IASP “hyperalgesia” is defined as “an increased response to a stimulus which is normally painful” (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 211).

As noted previously, opioid-induced hyperalgesia or opioid-induced abnormal pain sensitivity is a phenomenon associated with the use of opioids such as morphine, hydrocodone, remifentanyl, oxycodone or methadone. Individuals taking opioids can develop an increasing sensitivity to noxious stimuli, even evolving a painful response to previously non-noxious stimuli (allodynia). Some studies demonstrated that this effect occurs not only after long use of opioids but also after only a single high dose of opioids. Although tolerance and opioid-induced hyperalgesia both result in a similar need for dose escalation, they are nevertheless caused by two distinct mechanisms. The similar net effect makes the two phenomena difficult to distinguish in a clinical setting. Under chronic opioid treatment, a particular individual's requirement for dose escalation may be due to tolerance (desensitization of antinociceptive mechanisms), opioid-induced hyperalgesia (sensitization of pronociceptive mechanisms), or a combination of both. Identifying the development of hyperalgesia is of great clinical importance since patients receiving opioids to relieve pain may paradoxically experience more pain as a result of treatment. Whereas increasing the dose of opioid can be an effective way to overcome tolerance, doing so to compensate for opioid-induced hyperalgesia may worsen the patient's condition by increasing sensitivity to pain while escalating physical dependence. If an individual is taking opioids for a chronic pain condition, and cannot achieve effective pain relief despite increases in dose, they may be experiencing opioid-induced hyperalgesia.

The invention is also directed to a combination of at least one sigma ligand as defined above and at least one opioid or opiate compound for simultaneous, separate or sequential administration, for use in the prevention and/or treatment of opioid-induced hyperalgesia associated to opioid therapy. Compounds that bind to the opioid receptor within the scope of the present invention include natural opiates, such as morphine, codeine and thebaine; semi-synthetic opiates, derived from the natural opioids, such as hydromorphone, hydrocodone, oxycodone, oxymorphone, desomorphine, diacetylmorphine, nicomorphine, dipropanoylmorphine, benzylmorphine and ethylmorphine; fully synthetic opioids, such as fentanyl, pethidine, methadone, tramadol and propoxyphene; and endogenous opioid peptides, produced naturally in the body, such as endorphins, enkephalins, dynorphins, and endomorphins and their analogues. Preferably, the combination according to this invention comprises morphine or its analogues.

The combination of the invention may be formulated for its simultaneous separate or sequential administration, with at least a pharmaceutically acceptable carrier, additive, adjuvant or vehicle. This has the implication that the combination of the two active compounds may be administered:

a) As a combination that is being part of the same medicament formulation, the two active compounds being then administered always simultaneously.

b) As a combination of two units, each with one of the active substances giving rise to the possibility of simultaneous, sequential or separate administration. In a particular embodiment, the sigma ligand is independently administered from the opioid or opiate (i.e in two units) but at the same time. In another particular embodiment, the sigma ligand is administered first, and then the opioid or opiate is separately or sequentially administered. In yet another particular embodiment, the opioid or opiate is administered first, and then the sigma ligand is administered, separately or sequentially, as defined.

The auxiliary materials or additives of a pharmaceutical composition according to the present invention (i.e. a composition comprising at least one sigma ligand or a composition comprising at least one sigma ligand and at least one opioid or opiate compound) can be selected among carriers, excipients, support materials, lubricants, fillers, solvents, diluents, colorants, flavour conditioners such as sugars, antioxidants, binders, adhesives, disintegrants, anti-adherents, glidants 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.

The pharmaceutical composition in accordance with the invention can be adapted to any form of administration, be it orally or parenterally, for example pulmonar, nasally, rectally and/or intravenously. Therefore, the formulation in accordance with the invention may be adapted for topical or systemic application, particularly for dermal, transdermal, subcutaneous, intramuscular, intra-articular, intraperitoneal, intravenous, intra-arterial, intravesical, intraosseous, intracavernosal, pulmonary, buccal, sublingual, ocular, intravitreal, intranasal, percutaneous, rectal, vaginal, oral, epidural, intrathecal, intraventricular, intracerebral, intracerebroventricular, intracisternal,

intraspinal, perispinal, intracranial, delivery via needles or catheters with or without pump devices, or other application routes.

Suitable preparations for oral applications are tablets, pills, caplets, gel caps, chewing gums, capsules, granules, drops or syrups.

Suitable preparations for parenteral applications are solutions, suspensions, reconstitutable dry preparations, aerosols or sprays.

The composition of the invention may be formulated as deposits in dissolved form or in patches, for percutaneous application.

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

Suitable form of rectal application is by means of suppositories.

Moreover, the composition may be presented in a form suitable for once daily, weekly, or monthly administration.

Accordingly, in another aspect the invention provides a method of treatment of a patient, notably a human, suffering from OIH associated to opioid therapy, which comprises administering to the patient in need of such a treatment or prophylaxis a therapeutically effective amount of a sigma ligand as defined above.

In certain embodiments, hyperalgesia is suppressed, ameliorated and/or prevented. In certain embodiments, the sigma ligand can be administered prior to an activity likely to result in hyperalgelsia, i.e. opioid administration. For example, the formulation can be administered 30 minutes, 1 hour, 2 hours, 5 hours, 10 hours, 15 hours, 24 hours or even more, such as 1 day, several days, or even a week, two weeks, three weeks, or more prior to the activity likely to result in hyperalgelsia, i.e. prior to opioid administration. In other embodiments, the sigma ligand can be administered during and/or after the administration of the opioid. In some instances, the sigma ligand is administered 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours, 30 hours, 36 hours, or more, after the administration of the opioid.

In one embodiment of the invention it is preferred that the sigma ligand is used in therapeutically effective amounts. The physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with

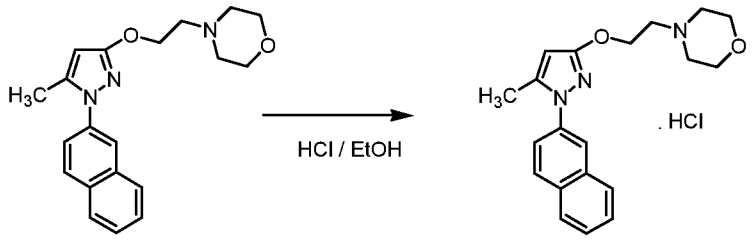
the patient under treatment, the age of the patient, the type of condition being treated. He will generally wish to initiate treatment with small dosages substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached. When the composition is administered orally, larger quantities of the active agent will be required to produce the same effect as a smaller quantity given parenterally. The compounds are useful in the same manner as comparable therapeutic agents and the dosage level is of the same order of magnitude as is generally employed with these other therapeutic agents.

For example, the dosage regime that must be administered to the patient will depend on the patient's weight, the type of application, the condition and severity of the disease. A preferred dosage regime of comprises an administration of a compound according the present invention within a range of 0.01 to 300 mg/kg, more preferably 0.01 to 100 mg/kg, and most preferable 0.01 to 50 mg/kg.

The following examples are merely illustrative of certain embodiments of the invention and cannot be considered as restricting it in any way.

Examples

Example 1. Synthesis of 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine (compound 63) and its hydrochloride salt



Compound 63 **Compound 63·HCl**

Compound 63 can be can be prepared as disclosed in the previous application WO2006/021462. Its hydrochloride can be obtained according the following procedure:

Compound 63 (6,39 g) was dissolved in ethanol saturated with HCl, the mixture was stirred then for some minutes and evaporated to dryness. The residue was crystallized

from isopropanol. The mother liquors from the first crystallization afforded a second crystallization by concentrating. Both crystallizations taken together yielded 5.24 g (63 %) of the corresponding hydrochloride salt (m.p. = 197-199 ºC).

^{1}H-NMR (DMSO-d_6) δ ppm: 10,85 (bs, 1H), 7,95 (m, 4H), 7,7 (dd, J=2,2, 8,8 Hz, 1H), 7,55 (m, 2H), 5,9 (s, 1H), 4,55 (m, 2H), 3,95 (m, 2H), 3,75 (m, 2H), 3,55-3,4 (m, 4H), 3,2 (m, 2H), 2,35 (s, 3H).

HPLC purity: 99.8%.

Example 2: Modulation on Mechanical Sensitization induced by opioid administration in operated (plantar incision) and naïve rats: effect of sigma antagonists

Plantar incision surgery

The incisional pain model was adapted from Brennan et al. (1996). The induction of anaesthesia in rats was performed with 3% isofluoran for veterinary use, employing an Ohmeda vaporizer and an anaesthesia chamber. Anaesthesia was kept during the surgical operation by a tube which directs the isofluran vapours to the animal's snout. Once the rats were anaesthetised, they were laid down in a prone position and their right hindpaws were cleaned out with alcohol.

Then, a skin incision in the hind paw of about 10 mm was made by means of a scalpel, starting about 5 mm from the heel and extending toward the toes. Fascia was located and by means of curve scissors muscle was elevated and a longitudinal incision of about 5 mm was made, thus the muscle origin and insertion remained intact. Therefore, both superficial (skin) and deep (muscle) tissues and nerves were injured. The skin of the paw was stitched with a suturing stitch with breaded silk (3.0) and the wound was cleaned out with iodinated povidone.

Behavioural test

Mechanical allodynia was tested using von Frey filaments: Animals were placed in methacrylate cylinders on an elevated surface, with metallic mesh floor perforated in order to apply the filaments. After an acclimation period of about 30 minutes within the

cylinders, both hindpaws were stimulated (the injured and the non-injured paw, serving the latter as control), starting with the lowest force filament (0.4 g) and reaching a 15 g filament. The animal's response to pain was manifested by the withdrawal of the paw as a consequence of the painful stimulus caused by a filament. The pressure (force in grams) threshold eliciting the withdrawal of the paw was recorded.

Experimental protocol 1: Coadministration studies in operated rats

The effect of opioids (morphine, remifentanil, fentanyl or sufentanil) and sigma antagonists (compound 63 or BD-1063) in operated rats were evaluated in a co-treatment paradigm as follows: the opioid drug is administrated through the intraperitoneal route in three consecutive administrations: at the time of surgery, 15 minutes later and 30 minutes after surgery. The sigma antagonist is administrated only once either 30 minutes before surgery (paradigm 1) or 30 minutes after surgery (paradigm 2). Figure 1 is a schematic representation showing the time course for the two paradigms followed in experimental protocol nº 1.

The doses of remifentanil per administration were 0.066 mg/kg each time (0.2 mg/kg total). The doses of morphine were 3.3 mg/kg each time (10 mg/kg in total). The doses of fentanyl per administration were 0.16 mg/kg each time (0.48 mg/kg total). The doses of sufentanil per administration were 0.05 mg/kg each time (0.15 mg/kg total). The doses used for the single administration of sigma antagonist (BD-1063 and compound 63) were 20, 40 and 80 mg/kg.

Assessment of mechanical allodynia was done 4, 24, 48, 72 and 96 hours after surgery. Additional evaluations were performed on days 5, 6, 7 and 8 after surgery when coadministration of compound 63 and opioids were assessed. The results are shown in Figures 2-5 and 10-11.

As expected, the plantar incision surgery produced a significant decrease of the mechanical sensitization threshold as measured with the von Frey filaments application (tactile allodynia for 2 days; figures 2-5) in control rats (vehicle group) that almost recovered their normal threshold at day 3-4. Opioid administration (remiphentanyl in figures 2 and 3; morphine in figures 4 and 5; fentanyl in figure 10; sufentanil in figure 11) initially induced an analgesic effect 4 hours after operation. However, the analgesic effect disappeared 24 hours later and consecutive daily measurements of paw

withdrawal showed an enhancement of tactile allodynia (that is OIH) respect to vehicle treatment that is evidenciable from day 3 to day 6-7.

Administration of 20 mg/kg of compound nº 63 during the perioperative period on day 0 strongly reduced the enhancement of allodynia induced by perioperative remiphentanyl (figures 2 and 3), morphine (figure 4), fentanyl (figure 10) and sufentanil (figure 11) administration. Furthermore, 40 and 80 mg/kg of compound nº 63 also inhibit dose-dependently the decrease of the mechanical sensitization threshold induced by the surgery.

Administration of 80 mg/kg of BD-1063 during the perioperative period on day 0 strongly reduced the enhancement of allodynia induced by perioperative morphine (figure 5) administration.

Altogether, data obtained following this experimental approach (perioperative co-administration of sigma ligands and opioids) indicate that sigma ligands are able to prevent the development of OIH.

Experimental protocol 2: OIH precipitated by naloxone

In the previous study (experimental protocol 1), it has been shown that the perioperative administration of morphine, fentanyl, sufentanil or remifentanil enhances the extent and duration of postoperative pain (hyperalgesia). In contrast, the co-administration of compound nº 63 inhibits dose-dependently the development of OIH. To further study the effect on OIH, the mechanical threshold in these opioid-treated rats was evaluated by administering naloxone since naloxone-precipitated opioid abstinence is associated with an enhancement of reflex responses to noxious stimulation (hyperalgesia).

Thus, when rats had recovered their pre-drug nociceptive threshold value after the opioid or co-administration treatment (21 days later), the ability of naloxone to precipitate hyperalgesia in rats was tested by measuring the withdrawal responses using the von Frey filaments._Figure 12 is a schematic representation showing the time course for experimental protocol nº 2.

The long lasting effects of morphine, remifentanil, fentanyl and sufentanil, and the effects of compound nº 63 co-administration on pharmacological effects of the opioids

were studied following this protocol. In particular, the treatment schedule was as follows: morphine (3.3 mg/kg), remifentanil (0.2 mg/kg), fentanyl (0.16 mg/kg), sufentanil (0.05 mg/kg) or vehicle was injected three times every 15 min starting at the time of plantar incision. The single injection of compound nº 63 was co-administered with the last dose of opioid. At the end of these experiments, on day 21, all rats received a naloxone injection (2 mg/kg), and the nociceptive threshold was measured 1, 24 and 48 hours later (see Figures 13-16).

As shown above in experimental protocol 1, the nociceptive threshold was returned to basal 10 days after opioids administrations. The injection of naloxone on day 21 (11 days after the animals had completely recovered their pre-drug nociceptive threshold value) induced a significant decrease in the nociceptive threshold below the basal value. On the other hand, no significant effect of naloxone was observed in vehicle saline-treated rats. Moreover, naloxone was also unable to precipitate hyperalgesia when it was injected on day 21 in opioid-treated rats that had been co-administrated with 80 mg/kg of compound nº 63 (20 and 40 mg/kg produced an attenuation of naloxone-precipitated hyperalgesia) (see Figures 13-16).

Experimental protocol 3: Coadministration studies in naïve rats.

The effect of opioids (morphine or remiphentanyl) and sigma antagonists (compound 63 or BD-1063) in naïve rats was evaluated in a co-treatment paradigm by intraperitoneal administration at the same time (figure 6).

Naïve rats were administrated with 0.3 mg/kg of remifentanil or 10 mg/kg of morphine. The doses of BD-1063 or compound nº 63 were 20, 40 and 80 mg/kg.

Assessment of mechanical allodynia was done 4, 24, 48 and 72 hours after surgery. The results are shown in Figures 7-9.

Opioid administration to naïve rats produces, 24 hours after, a significant decrease of the mechanical threshold (that is OIH) as measured with the von Frey filaments application (tactile allodynia for 2 days; figures 7-9). Three days later rats recovered their normal threshold.

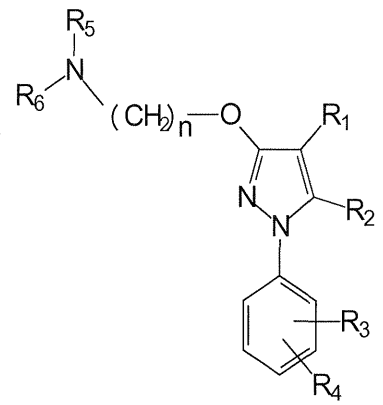
Compound nº 63 coadministration reduces dose-dependently the enhancement of allodynia induced by remifentanil administration (figure 7).

BD-1063 coadministration also reduces the enhancement of allodynia induced by remifentanil (figure 8) and morphine (figure 9) administration.

Altogether, data obtained following this experimental approach (co-administration of sigma ligands and opioids to naïve rats) indicate that opioids induce OIH, evidenciable from day 1-2 after opioid administration, and that the co-administration of sigma ligands prevents the development of OIH.

CLAIMS

1. Use of a sigma ligand in the manufacture of a medicament for the treatment of opioid-induced hyperalgesia associated to opioid therapy, wherein the sigma ligand has the general formula (I):



(I)

wherein

R_1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and -COR_8,;

R_2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and phenyl;

R_3 and **R_4** are independently selected from the group consisting of hydrogen, -OR_8, and halogen, or together they form a fused naphthyl ring system;

R_5 and **R_6** are independently selected from substituted or unsubstituted C_1-C_6 alkyl, or together form, with the nitrogen atom to which they are attached, a substituted or unsubstituted, 5-6 membered aromatic or non-aromatic heterocyclyl group containing one to five heteroatoms selected form the group consisting of nitrogen, oxygen and sulphur, optionally fused to a 6-membered carbocyclic ring; wherein the substituent is selected from C_1-C_3 alkyl, -COR_8, phenyl;

n is selected from 2, 3, and 4;

R_8 is C_1-C_6 alkyl,;

or a pharmaceutically acceptable salt or stereoisomer thereof.

2. Use of a sigma ligand according to claim 1, wherein the sigma ligand is selected from the group consisting of a sigma receptor antagonist, preferably selected from a neutral antagonist, an inverse agonist, or a partial antagonist.
3. Use of a sigma ligand according to claim 1 or 2, wherein R_2 is H or C_1-C_6 alkyl.
4. Use of a sigma ligand according to any of claims 1 to 3, wherein R_3 and R_4 together form a fused naphthyl ring system.
5. Use of a sigma ligand according to any of claims 1 to 4, wherein R_5 and R_6 together form a morpholine-4-yl group.
6. Use of a sigma ligand according to claim 1, which is selected from the group consisting of:

4-{2-(1-(3,4-dichlorophenyl)-5-methyl-1H pyrazol-3-yloxy)ethyl}morpholine,

2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]-N,N-diethylethanamine,

1-(3,4-Dichlorophenyl)-5-methyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,

1-(3,4-Dichlorophenyl)-5-methyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole,

1-{2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}piperidine,

1-{2-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}-1H-imidazole,

1-{2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}-4-methylpiperazine,

1-(4-(2-(1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy)ethyl)piperazin-1-yl)ethanone,

4-{2-[1-(4-Methoxyphenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}morpholine,

1-(4-Methoxyphenyl)-5-methyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,

1-(4-Methoxyphenyl)-5-methyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole,

1-[2-(1-(4-Methoxyphenyl)-5-methyl-1H-pyrazol-3-yloxy)ethyl]piperidine,

1-{2-[1-(4-Methoxyphenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}-1H-imidazole,

4-{2-[1-(3,4-Dichlorophenyl)-5-phenyl-1H-pyrazol-3-yloxy]ethyl}morpholine,

1-(3,4-Dichlorophenyl)-5-phenyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,

1-(3,4-Dichlorophenyl)-5-phenyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole,

1-{2-[1-(3,4-Dichlorophenyl)-5-phenyl-1H-pyrazol-3-yloxy]ethyl}piperidine,

1-{2-[1-(3,4-Dichlorophenyl)-5-phenyl-1H-pyrazol-3-yloxy]ethyl}-1H-imidazole,

4-{4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}morpholine,

1-(3,4-Dichlorophenyl)-5-methyl-3-[4-(pyrrolidin-1-yl)butoxy]-1H-pyrazole,

1-{4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}piperidine,

1-{4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-4-methylpiperazine,

1-{4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-1H-imidazole,

4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]-N,N-diethylbutan-1-amine,

1-{4-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-4-phenylpiperidine,

4-{2-[1-(3,4-dichlorophenyl)-5-isopropyl-1H-pyrazol-3-yloxy]ethyl}morpholine,

2-[1-(3,4-Dichlorophenyl)-5-isopropyl-1H-pyrazol-3-yloxy]-N,N-diethylethanamine,

1-(3,4-Dichlorophenyl)-5-isopropyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,

1-(3,4-Dichlorophenyl)-5-isopropyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole,

1-{2-[1-(3,4-Dichlorophenyl)-5-isopropyl-1H-pyrazol-3-yloxy]ethyl}piperidine,

4-{2-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]ethyl}morpholine,

2-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy] N,N-diethylethanamine,

1-(3,4-dichlorophenyl)-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,

1-{2-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]ethyl}piperidine,

1-(3,4-dichlorophenyl)-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole,

1-{2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}piperazine,

4-{2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]ethyl}morpholine,

4-{2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]ethyl}morpholine,

2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]-N,N-diethylethanamine,

1-(3,4-Dichlorophenyl)-4,5-dimethyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,

1-(3,4-Dichlorophenyl)-4,5-dimethyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole,

1-{2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]ethyl}piperidine,

4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}morpholine,

(2S,6R)-4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}-2,6-dimethylmorpholine,

1-{4-[1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}piperidine,

1-(3,4-Dichlorophenyl)-3-[4-(pyrrolidin-1-yl)butoxy]-1H-pyrazole,

4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N,N-diethylbutan-1-amine,

N-benzyl-4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N-methylbutan-1-amine,

4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N-(2-methoxyethyl)-N-methylbutan-1-amine,

4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}thiomorpholine,

1-[1-(3,4-Dichlorophenyl)-5-methyl-3-(2-morpholinoethoxy)-1H-pyrazol-4-yl]ethanone,

1-{1-(3,4-dichlorophenyl)-5-methyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazol-4-yl}ethanone,

1-{1-(3,4-dichlorophenyl)-5-methyl-3-[2-(piperidin-1-yl)ethoxy]-1H-pyrazol-4-yl}ethanone,

1-{1-(3,4-dichlorophenyl)-3-[2-(diethylamino)ethoxy]-5-methyl-1H-pyrazol-4-yl}ethanone,

4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine,

N,N-Diethyl-2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethanamine,

1-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}piperidine, and

5-Methyl-1-(naphthalen-2-yl)-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,

or a pharmaceutically acceptable salt thereof.

7. Use of a sigma ligand according to any of claims 1 to 6, wherein the sigma ligand is 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine, or a pharmaceutically acceptable salt or stereoisomer thereof.

8. Use of a sigma ligand according to claim 7, wherein the sigma ligand is 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine hydrochloride.

9. Use of a combination of at least one sigma ligand as defined in any preceding claim and at least one opioid or opiate compound for simultaneous, separate or sequential administration, in the manufacture of a medicament forthe treatment of opioid-induced hyperalgesia associated to opioid therapy.

10. Use of a sigma ligand in the manufacture of a medicament for the treatment of opioid-induced hyperalgesia associated to opioid therapy, wherein the sigma ligand is selected from the group consisting of
3-{1-[2-(1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy)ethyl]piperidin-4-yl}-3H-imidazo[4,5-b]pyridine,
Ethyl 4-{2-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}piperazine carboxylate,
2-{2-[1-(3,4-dichlorophenyl)-5-phenyl-1H-pyrazol-3-yloxy]ethyl}-1,2,3,4-tetrahydroisoquinoline,
1-{4-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-6,7-dihydro-1H-indol-4(5H)-one,
2-{4-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-1,2,3,4-tetrahydroisoquinoline,
2-{2-[1-(3,4-dichlorophenyl)-5-isopropyl-1H-pyrazol-3-yloxy]ethyl}-1,2,3,4-tetrahydroisoquinoline, and
1-{2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}pyrrolidin-3-amine,
or a pharmaceutically acceptable salt thereof.