SIGMA LIGANDS FOR POTENTIATING THE ANALGESIC EFFECT OF OPIOIDS AND OPIATES IN POST-OPERATIVE PAIN AND ATTENUATING THE DEPENDENCY THEREOF

FIELD OF THE INVENTION

The present invention relates to use of sigma receptor ligands for potentiating the analgesic effect of opioids and opiates and for decreasing the dependence thereof and to a combination of a sigma ligand and opioids or opiates for use in the treatment of pain. In particular, the present invention refers to the potentiation of opioid and opiate analgesia in relation to the treatment and/or prevention of post-operative pain.

BACKGROUND

The treatment of pain conditions is of great importance in medicine. There is currently a world-wide need for additional pain therapy. The pressing requirement for a specific treatment of pain conditions is documented in the large number of scientific works that have appeared recently in the field of applied analgesics.

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). Although it is a complex process influenced by both physiological and psychological factors and is always subjective, its causes or syndromes can be classified. Some of the most relevant pain subtypes are neuropathic pain, allodynia, hyperalgesia, and peripheral neuropathy.

Over twenty million patients have surgical procedures each year. Postsurgical pain (interchangeably termed, post-incisional pain), or pain that occurs after surgery or traumatic injury, is a serious and often intractable medical problem. Pain is usually localized within the vicinity of the surgical site. Post-surgical pain can have two clinically important aspects, namely resting pain, or pain that occurs when the patient is not moving and mechanical pain which is exacerbated by movement (coughing/sneezing, getting out of bed, physiotherapy, etc.). The major problem with post-surgical pain management for major surgery is that the drugs currently used have a variety of prominent side effects that delay recovery, prolong hospitalization and subject certain vulnerable patient groups to the risk of serious complications.

The three major classes of pharmaceutical drugs used to treat post-surgical pain are the opioid analgesics, local anaesthetics, and the non-steroidal anti-inflammatory drugs (NSAID). Two of these classes of drugs, the opioid analgesics and NSAIDs, are typically administered systemically while the local anaesthetics (e.g. channel blockers) are administered non-systemically during surgery.

The systemic administration of drugs to relieve pain after surgery is frequently inadequate. For example, systemic administration of opioids after surgery may cause nausea, the inhibition of bowel function, urinary retention, inhibition of pulmonary function, cardiovascular effects, and sedation.

"Post-surgical pain" is interchangeable with "post-incisional" or "posttraumatic pain" and refers to pain arising or resulting from an external trauma such as a cut, puncture, incision, tear, or wound into tissue of an individual (including those that arise from all surgical procedures, whether invasive or non-invasive), i.e. to pain developed as a consequence of surgery. As used herein, "post-surgical pain" does not include pain that occurs without an external physical trauma. In some embodiments, post-surgical pain is internal or external pain, and the wound, cut, trauma, tear or incision may occur accidentally (as with a traumatic wound) or deliberately (as with a surgical incision). As used herein, "pain" includes nociception and the sensation of pain, and pain can be assessed objectively and subjectively, using pain scores and other methods, e.g., with protocols well-known in the art. Post-surgical pain, as used herein, includes allodynia (i.e., pain due to a stimulus that does not normally provoke pain) and hyperalgesia (i.e., increased response to a stimulus that is normally painful), which can in turn, be thermal or mechanical (tactile) in nature. Therefore, the pain is characterized by thermal sensitivity, mechanical sensitivity and/or resting pain (e.g. persistent pain in the absence of external stimuli). Further, the pain can be primary (e.g., resulting directly from the pain-causing event) or secondary pain (e.g., pain associated with, but not directly resulting, from the pain-causing event).
Different animal models and studies on postoperative incisional pain the same are reported in the state of the art (T.J. Brennan et al. Pain 1996, 64, 493-501; P.K. Zahn et al. Regional Anaesthesia and Pain Medicine 2002, Vol. 27, No 5 (September-October), 514-516).

Opioids and opiates are potent analgesics widely used in clinical practice. Opioid and opiates drugs are classified typically by their binding selectivity in respect of the cellular

and differentiated tissue receptors to which specific drug specie binds as a ligand. These receptors include mu (μ), delta (δ), kappa (κ) and the nociceptive receptors.

The well-known narcotic opiates, such as morphine and its analogs, are selective for the opioid mu receptors. Mu receptors mediate analgesia, respiratory depression, and inhibition of gastrointestinal transit. Kappa receptors mediate analgesia and sedation. However, despite their good activity as analgesics, opioids and opiates have the drawback of causing dependence.

Sigma receptors are non-opiaceous type of receptors of great interest in pharmacology due to their role in analgesia related processes. 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 ligands in combination with opioids or opiates are capable of modulating the analgesic effect thereof. It is known, for example, that haloperidol potentiates the activity of different opioids and opiates such as morphine, DADL or bremazocine [Chichenkov, O. N. et al: Effect of haloperidol on the analgesic activity of intracisternally and intrathecally injected opiate agonists, Farmakologiya i Toksikologiya (Moscow) (1985), 48(4), 58-61]. Chien C. et al. also referred the synergistic effect of the combination of haloperidol and morphine [Selective antagonism of opioid analgesia by a sigma system, J Pharmacol Exp Ther (1994), 271, 1583-1590 and Sigma antagonists potentiate opioid analgesia in rats, Neurosci Lett (1995), 190, 137-139] and Marazzo A. et al taught the capacity of the sigma ligand (+)-MR200 to modulate κ-opioid receptor mediated analgesia. Mei J. et al confirmed the importance of sigma-1 receptors as a modulatory system on the analgesic activity of opioid drugs [Sigma1 receptor modulation of opioid analgesia in the mouse, J Pharmacol Exp Ther (2002), 300(3), 1070-1074]. Notwithstanding, in all of this cases the problem of dependence induced by opioids and opiates remain to be present.

One of the pharmacological approaches to solve the problem of opioid and opiate dependence has been the co-administration of opioids or opiates and sigma ligands. For instance, sigma-1 receptor agonist SA4503 has been shown to have a modulatory

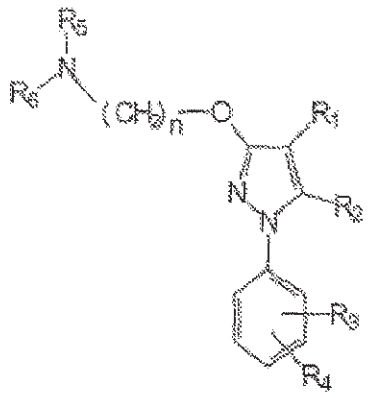
effect on addiction to morphine [Nomura, M. et al: Studies on drug dependence (Rept. 322): Attenuation of morphine- and psychostimulants-induced place preference by sigma1 receptor agonist SA4503, 72nd Annual Meeting of the Japanese Pharmacological Society (Sapporo, Japan-March 1999)]. Also, sigma-1 agonist DHEA has shown some capacity to attenuate the development of morphine dependence [Noda, Y. et al: A neuroactive steroid, dehydroepiandrosterone sulfate, attenuates the development of morphine dependence: an association with sigma1 receptors, 31st Annual Meeting of the Society of Neuroscience (San Diego-Nov 2001)]. EP1130018 teaches the use of sigma ligands for the treatment of drug addiction to morphine, cocaine and methamphetamine. However, none of these approaches show an enhancement of the analgesic effect of morphine.

Therefore, there is a need to provide new treatments for post-surgical pain which reduce side effects shown by known drugs.

BRIEF DESCRIPTION OF THE INVENTION

The inventors of the present invention have found and demonstrated that the administration of some specific sigma receptor ligands in conjunction with an opioid or opiate may surprisingly potentiate synergistically the analgesic effects of the latter, while decreasing their associated dependence.

Therefore, disclosed is a combination for simultaneous, separate or sequential administration comprising at least one sigma ligand of formula (I), or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, and at least one opioid or opiate, for use in the prevention and/or treatment of pain developed as a consequence of surgery



(I)

wherein,

R_1 is selected from the group formed by 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, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

R_2 is selected from the group formed by 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, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

R_3 and R_4 are independently selected from the group formed by 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, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen, or together they form an optionally substituted fused ring system;

R_5 and R_6 are independently selected from the group formed by 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, -$N=CR_8R_9$, or halogen;

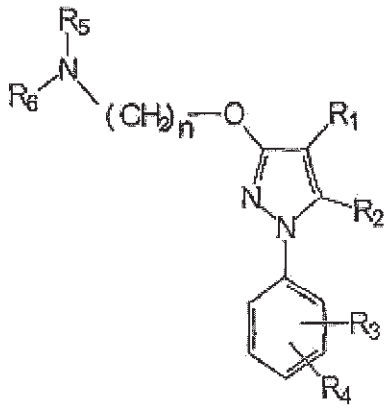
or together form, with the nitrogen atom to which they are attached, a substituted or unsubstituted, aromatic or non-aromatic heterocyclyl group;

n is selected from 1, 2, 3, 4, 5, 6, 7 or 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, or halogen.

In one aspect, the present invention provides use of a combination for simultaneous, separate or sequential administration comprising at least one sigma ligand of formula (I), or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, and at least one opioid or opiate selected from the group consisting of morphine, tramadol, sufentanil, remifentanil, fentanyl, tapentadol, oxycodone, and buprenorphine or an analogue thereof, for the manufacture of a medicament for the prevention and/or treatment of pain developed as a consequence of surgery



(I)

wherein,

R_1 is selected from the group formed by 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, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

R_2 is selected from the group formed by 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, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

R_3 and R_4 are independently selected from the group formed by 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, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen, or together they form an optionally substituted fused ring system;

R_5 and R_6 are independently selected from the group formed by 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, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or 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 or 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, or halogen

Also disclosed is the sigma ligand of formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, for use in potentiating the analgesic effects of an opioid or opiate and/or attenuating dependency thereof when said opioid or opiate is used in the prevention and/or treatment of pain developed as a consequence of surgery.

Also disclosed is the sigma ligand of formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, for use in potentiating the analgesic effects of an opioid or opiate when said opioid or opiate is used in the prevention and/or treatment of pain developed as a consequence of surgery.

In another aspect, the present invention provides use of a sigma ligand of formula (I) as disclosed herein, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, for the manufacture of a medicament for potentiating the analgesic effect of an opioid or opiate selected from the group consisting of morphine, tramadol, sufentanil, remifentanil, fentanyl, tapentadol, oxycodone, and buprenorphine or an analogue thereof, when said opioid or opiate is used in the prevention and/or treatment of pain developed as a consequence of surgery.

Also disclosed is the sigma ligand of formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, for use in attenuating dependency of an opioid or opiate when said opioid or opiate is used in the prevention and/or treatment of pain developed as a consequence of surgery.

Also disclosed is the use of the combiniation, for simultaneous, separate or sequential administration, comprising at least one sigma ligand of formula

(I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, and at least one opioid or opiate for manufacturing a medicament for the prevention and/or treatment of pain developed as a consequence of surgery.

Also disclosed is the use of a sigma ligand of formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof for manufacturing a medicament for potentiating the analgesic effects of an opioid or opiate and/or attenuating dependency thereof in relation to the prevention and/or treatment of pain developed as a consequence of surgery.

Also disclosed is a method of treatment of a patient suffering from pain developed as a consequence of surgery, or likely to suffer pain as a result of a surgical treatment, which comprises administering to the patient in need of such a treatment or prophylaxis a therapeutically effective amount of a combination comprising at least sigma ligand of formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, and an opioid or opiate.

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

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Potentiation of morphine analgesia (0.625 mg/kg) by compound 63 (10, 20, 40 and 80 mg/kg) in a mechanical allodynia rat model. n=10, #: $p < 0.05$; ns: $p > 0.05$ Dunnett, compound 63 + M vs. Morphine; **: $p < 0.01$; ***: $p > 0.001$ t-Student, compound 63 + M vs. compound 63.

Figure 2: Potentiation of morphine analgesia (0.625 mg/kg) by compound 63 (10, 20, 40 and 80 mg/kg) in a thermal hyperalgesia rat model. n=10, #: $p < 0.05$; ns: $p > 0.05$ Dunnett, compound 63 + M vs. Morphine; **: $p < 0.01$; ***: $p > 0.001$ t-Student, compound 63 + M vs. compound 63.

Figure 3: Potentiation of tramadol analgesia (1.25 mg/kg) by compound 63 (5, 10, 20, and 40 mg/kg) in a mechanical allodynia rat model. n=10, #: $p < 0.05$; ns: $p > 0.05$ Dunnett, compound 63 + T vs. Tramadol; **: $p < 0.01$; ***: $p > 0.001$ t-Student, compound 63 + T vs. compound 63.

Figure 4: Potentiation of tramadol analgesia (1.25 mg/kg) by compound 63 (5, 10, 20, and 40 mg/kg) in thermal hyperalgesia rat model. n=10, #: $p < 0.05$;

ns: p > 0.05 Dunnett, compound 63 + T vs. Tramadol; **: p < 0.01; ***: p > 0.001 t-Student, compound 63 + T vs. compound 63.

Figure 5: Potentiation of morphine analgesia (0.625 mg/kg) by compound 63 (10, 20, 40 and 80 mg/kg) in a mechanical allodynia rat model. *: p < 0.05 (Dunnett); ns (no significant): p > 0.05 (Dunnett).

Figure 6: Potentiation of tramadol analgesia (1.25 mg/kg) by compound 63 (5, 10, 20 and 40 mg/kg) in a mechanical allodynia rat model. *: p < 0.05 (Dunnett); ns (no significant): p > 0.05 (Dunnett).

Figure 7: Potentiation of sufentanil analgesia (0.003 mg/kg) by compound 63 (5, 10, 20 and 40 mg/kg) in a mechanical allodynia rat model. *: p < 0.05 (Dunnett); ns (no significant): p > 0.05 (Dunnett).

Figure 8: Potentiation of remifentanil analgesia (0.01 mg/kg) by compound 63 (2.5, 5, 10, 20, 40 and 80 mg/kg) in a mechanical allodynia rat model. *: p < 0.05 (Dunnett); ns (no significant): p > 0.05 (Dunnett).

Figure 9: Potentiation of fentanyl analgesia (0.01 mg/kg) by compound 63 (10, 20, 40 and 80 mg/kg) in a mechanical allodynia rat model. *: p < 0.05 (Dunnett); ns (no significant): p > 0.05 (Dunnett).

Figure 10: Potentiation of tapentadol analgesia (1.25 mg/kg) by compound 63 (5, 10, 20 and 40 mg/kg) in a mechanical allodynia rat model. *: p < 0.05 (Dunnett); ns (no significant): p > 0.05 (Dunnett).

Figure 11: Potentiation of oxycodone analgesia (0.039 mg/kg) by compound 63 (2.5, 5, 10, 20 and 40 mg/kg) in a mechanical allodynia rat model. *: p < 0.05 (Dunnett); ns (no significant): p > 0.05 (Dunnett).

Figure 12: Potentiation of buprenorphine analgesia (0.0015 mg/kg) by compound 63 (5, 10, 20 and 40 mg/kg) in a mechanical allodynia rat model. *: p < 0.05 (Dunnett); ns (no significant): p > 0.05 (Dunnett).

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 carbon and hydrogen atoms, containing no unsaturation, having one to eight carbon atoms, 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. If substituted by aryl we have an "alkylaryl" radical, such as benzyl and phenethyl. If substituted by heterocyclyl we have an "heterocyclylalkyl" radical.

"Alkenyl" refers to an alkyl radical having at least 2 C atoms and having one or more unsaturated bonds. In a particular embodiment the alkenyl group has two to eight carbon atoms. In a particular embodiment, the alkenyl group is vinyl, 1-methyl-ethenyl, 1-propenyl, 2-propenyl, or butenyl.

"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 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. Analogously, "aryloxy" refers to a radical of the formula $-OR_c$ where R_c is an aryl radical as defined above, e. g., phenoxy.

"Amino" refers to a radical of the formula $-NH_2$, $-NHR_a$ or $-NR_aR_b$, optionally quaternized. In an embodiment of the invention each of R_a and R_b is independently selected from an alkyl radical as defined above.

"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 C1-6 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.

"Opioids" and "opiates" refer to compounds that bind to opioid receptors. 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 sufentanil, remifentanil, fentanyl,

pethidine, methadone, tapentadol, tramadol and propoxyphene; and endogenous opioid peptides, produced naturally in the body, such as endorphins, enkephalins, dynorphins, and endomorphins and their analogs.

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".

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

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

Furthermore, any compound referred to herein may exist as tautomers. Specifically, the term tautomer refers to one of two or more structural isomers of a compound that exist

in equilibrium and are readily converted from one isomeric form to another. Common tautomeric pairs are 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 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 used herein, the terms "treat", "treating" and "treatment" include the eradication, removal, reversion, alleviation, modification, or control of pain induced by a surgical operation, after the pain onset.

As used herein, the terms "prevention", "preventing", "preventive" "prevent" and "prophylaxis" refer to the capacity of a therapeutic to avoid, minimize or difficult the onset or development of a disease or condition before its onset, in this case pain induced by a surgical operation.

Therefore, by "treating" or "treatment" and/or "preventing" or "prevention", as a whole, is meant at least a suppression or an amelioration of the symptoms associated with the condition afflicting the subject, where suppression and amelioration are used in a broad sense to refer to at least a reduction in the magnitude of a parameter, e.g., symptom associated with the condition being treated, such as pain. 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 pain induced by a surgical operation, particularly, peripheral

neuropathic pain, allodynia, causalgia, hyperalgesia, hyperesthesia, hyperpathia, neuralgia, neuritis or neuropathy.

As used herein, the term "potentiating the analgesic effect of an opioid or opiate" refer to the increase in the affectivity of the analgesic effect of said opioids or opiates produced by sigma ligands of formula (I). In an embodiment of the invention said potentiating effect induces an increase in the analgesic effect of opioids by a factor of 1.2, 1.5, 2, 3, 4 or more, even in some case by a factor of 14 or 15, when compared, with the opioids or opiates, or with the sigma ligand of formula (I) when administered in isolation. The measurement can be done following any known method in the art. In an embodiment of the invention, the sigma ligand of formula (I) potentiates the analgesic effect of an opioid or opiate by a factor of at least 1.2 when measured in a mechanical allodynia rat model or in a in a thermal hyperalgesia rat model. In a further embodiment, said factor is of at least 1.5, 2, 3, 4 or more, even in some case by a factor of 14 or 15.

As used herein, the term "decreasing the dependency induced by an opioid or opiate" refer to the amelioration, decrease or reduction of the dependency of the patient from said opioids or opiates produced by sigma ligands of formula (I). In an embodiment of the invention said decreasing effect induces a reduction in the dependency from opioids by a factor of 1.2, 1.5, 2, 3, 4 or more, even in some case by a factor of 14 or 15, when compared, with the opioids or opiates when administered in isolation. The measurement can be done following any known method in the art. In an embodiment of the invention, the sigma ligand of formula (I) reduces the dependency of the patient from said opioid or opiate by a factor of at least 1.2 when measured with the place conditioning paradigm model. In a further embodiment, said factor is of at least 1.5, 2, 3, 4 or more, even in some case by a factor of 14 or 15.

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, $C_{1\text{-}6}$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,

[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 and its pharmaceutically acceptable salts, solvates or prodrug thereof is performed.

In a 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 or a salt thereof.

Preferably, the compound of formula I used is 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine hydrochloride.

These particular compounds are designated in the examples of the present invention as compounds 63 (and a salt thereof).

A preferred embodiment of the present invention comprises the use of a combination of 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine hydrochloride and an opioid or opiate selected from the group consisting of morphine, tramadol, sufentanil, remifentanil, fentanyl, tapentadol, oxycodone, and buprenorphine. In a preferred embodiment of the present invention, the opiate utilized is morphine or its analogs. In another preferred embodiment of the present invention, the opioid utilized is tramadol or its analogs. In another preferred embodiment of the present invention, the opioid utilized is sufentanil or its analogs. In another preferred embodiment of the present invention, the opioid utilized is remifentanil or its analogs. In another preferred embodiment of the present invention, the opioid utilized is fentanyl or its analogs. In another preferred

embodiment of the present invention, the opioid utilized is tapentadol or its analogs. In another preferred embodiment of the present invention, the opioid utilized is oxycodone or its analogs. In another preferred embodiment of the present invention, the opioid utilized is buprenorphine or its analogs.

Analogs of these opioids or opiates are known to the skilled person and refer in general to any compound structurally derived from them including their pharmaceutically acceptable salts, isomers, prodrugs or solvates. Thus, a "morphine analog" may be any compound structurally derived from morphine as, for instance, those disclosed in EP0975648. Particular analogs of morphine include hydromorphone, dihydromorphine, oxymorphone, desomorphine, diacetylmorphine, nicomorphine, dipropanoylmorphine, benzylmorphine and ethylmorphine.

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

The present invention refers also to the use of pharmaceutical compositions comprising the sigma ligands of formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, and opioids or opiates combined jointly or separately with at least a pharmaceutically acceptable carrier, additive, adjuvant or vehicle.

The auxiliary materials or additives can be selected among carriers, excipients, support materials, lubricants, fillers, solvents, diluents, colorants, flavor 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.

The pharmaceutical composition used according to the present invention can be adapted to any form of administration, be it orally or parenterally, for example pulmonarily, nasally, rectally and/or intravenously. Therefore, the formulation according to the present invention may be adapted for topical or systemic application, particularly for dermal, subcutaneous, intramuscular, intra-articular, intraperitoneal, pulmonary, buccal, sublingual, nasal, percutaneous, vaginal, oral or parenteral application. The preferred form of rectal application is by means of suppositories.

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

The combination 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.

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

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 sigma ligand of formula (I) and the opioid or opiate may be administered:

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

b) As a combination of two units, each with one of them giving rise to the possibility of simultaneous, sequential or separate administration. In a particular embodiment, the sigma ligand of formula (I) 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 of formula (I) 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 of formula (I) is administered, separately or sequentially, as defined.

In a particular embodiment of the present invention, the pain developed as a consequence of surgery is peripheral neuropathic pain, allodynia, causalgia, hyperalgesia, hyperesthesia, hyperpathia, neuralgia, neuritis or neuropathy. More preferably, the pain is hyperalgesia or mechanical allodynia.

"Neuropathic pain" is defined by the IASP as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 210). For the purpose of this invention this term is to be treated as synonymous to "Neurogenic Pain" which is defined by the IASP as "pain initiated or caused by a primary lesion, dysfunction or transitory perturbation in the

peripheral or central nervous system". Neuropathic pain according to this invention is restricted to the neuropathic pain resulting from a surgery.

According to the IASP "peripheral neuropathic pain" is defined as "a pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system" and "peripheral neurogenic pain" is defined as "a pain initiated or caused by a primary lesion, dysfunction or transitory perturbation in the peripheral nervous system" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 213).

According to the IASP "allodynia" is defined as "a pain due to a stimulus which does not normally provoke pain" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 210).

According to the IASP "causalgia" is defined as "a syndrome of sustained burning pain, allodynia and hyperpathia after a traumatic nerve lesion, often combined with vasomotor and sudomotor dysfunction and later trophic changes" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 210).

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).

According to the IASP "hyperesthesia" is defined as "increased sensitivity to stimulation, excluding the senses" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 211).

According to the IASP "hyperpathia" is defined as "a painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212).

The IASP draws the following difference between "allodynia", "hyperalgesia" and "hyperpathia" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212):

Allodynia	Lowered threshold	Stimulus and response mode differ
Hyperalgesia	Increased response	Stimulus and response rate are the same

Hyperpathia	Raised threshold Increased response	Stimulus and response rate may be the same or different

According to the IASP "neuralgia" is defined as "pain in the distribution of a nerve or nerves" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212).

According to the IASP "neuritis" is defined as "inflammation of a nerve or nerves" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212).

According to the IASP "neuropathy/neuritis" is defined as "a disturbance of function or pathological change in a nerve: in one nerve mononeuropathy, in several nerves mononeuropthy multiplex, if diffuse and bilateral, polyneuropathy" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212).

In some embodiments, the post-surgical pain includes one or more of: thermally induced pain, mechanically induced pain, or resting pain. For instance, post-surgical pain can include mechanically induced pain and/or resting pain. In some cases, the post-surgical pain includes resting pain.

In certain embodiments, allodynia is suppressed, ameliorated and/or prevented, and in some embodiments, hyperalgesia is suppressed, ameliorated and/or prevented. In some instances, the pain is chronic pain. In other cases, the pain is at, proximal and/or near to one or more site(s) of external trauma, wound or incision. In certain embodiments, the combination of the sigma ligand of formula (I) and the opioid or opiate can be administered prior to an activity likely to result in external trauma, wound or incision, such as surgery. For example, the combination of the sigma ligand of formula (I) and the opioid or opiate 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 external trauma, wound or incision, such as prior to surgery. In other embodiments, the combination of the sigma ligand of formula (I) and the opioid or opiate can be administered during and/or after surgery or activity that resulted in external trauma, wound or incision. In some instances, the combination of the sigma ligand of formula (I) and the opioid or opiate 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 surgery, or activity that resulted in external trauma, wound or incision.

In one embodiment of the invention it is preferred that the sigma ligand of formula (I) 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 and weight of the patient, the type of pain being treated, its severity. 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.

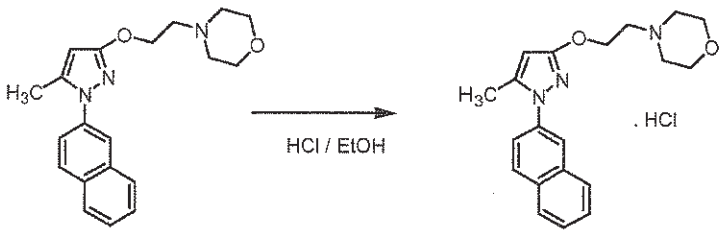
According to the present invention the dosage of the opioid or opiate can be reduced when combined with a sigma ligand of formula (I), and therefore attaining the same analgesic effect with a reduced dosage, and thus attenuating dependency. The sigma ligands of formula (I) may induce an increase in the analgesic effect of opioids of a factor of 1.2, 1.5, 2, 3, 4 or more, even in some case by a factor of 14 or 15. For example, in the case of the mechanical allodynia test with morphine, the increase observed with 10mg of compound 63 was from 2.7% to 29.1% (see figure 1). Other dosages in the same test have reached increases from 14.7% to 56.3, 44.0% to 83.0% or 41.0% to 93.8%.

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 comprises an administration of a compound of formula I within a range of 0.5 to 100 mg/kg and of the opioid or opiate from 0.15 to 15 mg/kg. The administration may be performed once or in several occasions.

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°C.)

^{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. Assessment of analgesic activity against post-operative pain in rats: Enhanced synergistic effect of compound 63, opioids and opiate in the treatment of post-operative pain

a) General protocol for the assessment of analgesia in the treatment post-operative pain

The induction of anaesthesia in rats was performed with 3% isofluran 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 hindpaw 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 povidone.

The assessment was performed always 4 hours after the surgery (plantar incision), 30 or 60 minutes after the administration of said product. Two types of analysis were carried out:

- 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.
- The thermal hyperalgesia was tested using a Ugo Basile plantar test: Animals were placed in the methacrylate cages of said apparatus, having a crystal floor. The acclimatation period within the cages was about 10 minutes. The thermal stimulus came from a lamp moving below the crystal floor and which was applied to both paws, with a minimum interval of 1 minute between both stimulations in order to avoid learning behaviours. The rat was able to withdraw the paw freely when it feels the pain produced by the heat coming from the lamp; then it is switched off and the latency time to the withdrawal response is recorded in seconds. In order to avoid hurting the animal's paw, the lamp was automatically switched off after 32 seconds.

b) Opiate: Morphine

The efficacy of morphine and compound 63 in rats was evaluated separately as follows: 1) morphine was administered at a constant dose of 0.625 mg/kg and 2) compound 63 was administered at different doses (10, 20, 40 and 80 mg/kg). Both administrations were performed 3.5 hours after surgery.

Subsequently, the efficacy of the combined use of morphine and compound 63 was assayed at different doses of compound 63 (10, 20, 40 and 80 mg/kg), while the morphine dose remained constant (0.625 mg/kg). The administrations were performed simultaneously 3.5 hours after surgery.

The treated subjects were tested according to the mechanical allodynia and thermal hyperalgesia protocols above. Compound 63 enhances morphine analgesia in the treatment of post-operative pain under both protocols. See Figures 1, 2 and 5.

c) Opioid: Tramadol

The efficacy of tramadol and compound 63 in rats was evaluated separately as follows: 1) tramadol was administered at a constant dose of 1.25 mg/kg and 2) compound 63 was administered at different doses (10, 20, 40, and 80 mg/kg). Both administrations were performed 3.5 hours after surgery.

Subsequently, the efficacy of the combined use of tramadol and compound 63 was assayed at different doses of compound 63 (5, 10, 20, and 40 mg/kg), while the tramadol dose remained constant (1.25 mg/kg). The administrations were performed simultaneously 3.5 hours after surgery.

The treated subjects were tested according to the mechanical allodynia and thermal hyperalgesia protocols above. Compound 63 enhances tramadol analgesia in the treatment of post-operative pain under both protocols. See Figures 3, 4, and 6.

d) Opioid: Sufentanil

The efficacy of sufentanil and compound 63 in rats was evaluated separately as follows: 1) sufentanil was administered at a constant dose of 0.003 mg/kg and 2) compound 63 was administered at different doses (10, 20, 40 and 80 mg/kg). Both administrations were performed 3.5 hours after surgery.

Subsequently, the efficacy of the combined use of sufentanil and compound 63 was assayed at different doses of compound 63 (5, 10, 20 and 40 mg/kg), while the sufentanil dose remained constant (0.003 mg/kg). The administrations were performed simultaneously 3.5 hours after surgery.

The treated subjects were tested according to the mechanical allodynia protocol above. Compound 63 enhances sufentanil analgesia in the treatment of post-operative pain under said protocol. See Figure 7.

e) Opioid: Remifentanil

The efficacy of remifentanil and compound 63 in rats was evaluated separately as follows: 1) remifentanil was administered at a constant dose of 0.01 mg/kg and 2) compound 63 was administered at different doses (10, 20, 40 and 80 mg/kg). Both administrations were performed 3.5 hours after surgery.

Subsequently, the efficacy of the combined use of remifentanil and compound 63 was assayed at different doses of compound 63 (2.5, 5, 10, 20, 40 and 80 mg/kg), while the remifentanil dose remained constant (0.01 mg/kg). The administrations were performed simultaneously 3.5 hours after surgery.

The treated subjects were tested according to the mechanical allodynia protocol above. Compound 63 enhances remifentanil analgesia in the treatment of post-operative pain under said protocol. See Figure 8.

f) Opioid: Fentanyl

The efficacy of fentanyl and compound 63 in rats was evaluated separately as follows: 1) fentanyl was administered at a constant dose of 0.01 mg/kg and 2) compound 63 was administered at different doses (10, 20, 40 and 80 mg/kg). Both administrations were performed 3.5 hours after surgery.

Subsequently, the efficacy of the combined use of fentanyl and compound 63 was assayed at different doses of compound 63 (10, 20, 40 and 80 mg/kg), while the fentanyl dose remained constant (0.01 mg/kg). The administrations were performed simultaneously 3.5 hours after surgery.

The treated subjects were tested according to the mechanical allodynia protocol above. Compound 63 enhances fentanyl analgesia in the treatment of post-operative pain under said protocol. See Figure 9.

g) Opioid: Tapentadol

The efficacy of tapentadol and compound 63 in rats was evaluated separately as follows: 1) tapentadol was administered at a constant dose of 1.25 mg/kg and 2) compound 63 was administered at different doses (10, 20, 40 and 80 mg/kg). Both administrations were performed 3.5 hours after surgery.

Subsequently, the efficacy of the combined use of tapentadol and compound 63 was assayed at different doses of compound 63 (5, 10, 20 and 40 mg/kg), while the

tapentadol dose remained constant (1.25 mg/kg). The administrations were performed simultaneously 3.5 hours after surgery.

The treated subjects were tested according to the mechanical allodynia protocol above. Compound 63 enhances tapentadol analgesia in the treatment of post-operative pain under said protocol. See Figure 10.

h) Opioid: Oxycodone

The efficacy of oxycodone and compound 63 in rats was evaluated separately as follows: 1) oxycodone was administered at a constant dose of 0.039 mg/kg and 2) compound 63 was administered at different doses (10, 20, 40 and 80 mg/kg). Both administrations were performed 3.5 hours after surgery.

Subsequently, the efficacy of the combined use of oxycodone and compound 63 was assayed at different doses of compound 63 (2.5, 5, 10, 20 and 40 mg/kg), while the oxycodone dose remained constant (0.039 mg/kg). The administrations were performed simultaneously 3.5 hours after surgery.

The treated subjects were tested according to the mechanical allodynia protocol above. Compound 63 enhances oxycodone analgesia in the treatment of post-operative pain under said protocol. See Figure 11.

i) Opioid: Buprenorphine

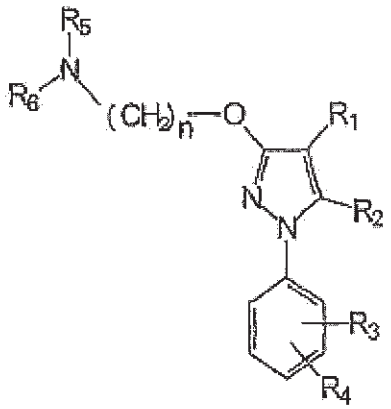
The efficacy of buprenorphine and compound 63 in rats was evaluated separately as follows: 1) buprenorphine was administered at a constant dose of 0.0015 mg/kg and 2) compound 63 was administered at different doses (10, 20, 40 and 80 mg/kg). Both administrations were performed 3.5 hours after surgery.

Subsequently, the efficacy of the combined use of buprenorphine and compound 63 was assayed at different doses of compound 63 (5, 10, 20 and 40 mg/kg), while the buprenorphine dose remained constant (0.0015 mg/kg). The administrations were performed simultaneously 3.5 hours after surgery.

The treated subjects were tested according to the mechanical allodynia protocol above. Compound 63 enhances buprenorphine analgesia in the treatment of post-operative pain under said protocol. See Figure 12.

CLAIMS

1. Use of a combination for simultaneous, separate or sequential administration comprising at least one sigma ligand of formula (I), or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, and at least one opioid or opiate selected from the group consisting of morphine, tramadol, sufentanil, remifentanil, fentanyl, tapentadol, oxycodone, and buprenorphine or an analogue thereof, for the manufacture of a medicament for the prevention and/or treatment of pain developed as a consequence of surgery



(I)

wherein,

R_1 is selected from the group formed by 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, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

R_2 is selected from the group formed by 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, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

R_3 and R_4 are independently selected from the group formed by 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, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen, or together they form an optionally substituted fused ring system;

R_5 and R_6 are independently selected from the group formed by 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, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or 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 or 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, or halogen.

2. Use of a combination according to claim 1 wherein R_1 is selected from H, $-COR_8$, or substituted or unsubstituted alkyl.

3. Use of a combination according to claim 1 or 2 wherein R_2 is H or alkyl.

4. Use of a combination according to any of the preceding claims wherein R_3 and R_4 are situated in the meta and para positions of the phenyl group.

5. Use of a combination according to any of the preceding claims wherein R_3 and R_4 are independently selected from halogen, or substituted or unsubstituted alkyl.

6. Use of a combination according to any of claims 1-3 where R_3 and R_4 together form a fused naphthyl ring system.

7. Use of a combination according to any of the preceding claims wherein n is selected from 2, 3, 4.

8. Use of a combination according to any of the preceding claims wherein R_5 and R_6 together form a morpholine-4-yl group.

9. Use of a combination according to claim 1 wherein compound 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,

[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 its pharmaceutically acceptable salts, solvates or a prodrug thereof.

10. Use of a combination according to any of the preceding claims wherein the combination comprises 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine hydrochloride.

11. Use of a combination according to claim 1 wherein the combination comprises 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine hydrochloride and an opioid or opiate selected from the group consisting of morphine, tramadol, sufentanil, remifentanil, fentanyl, tapentadol, oxycodone, and buprenorphine.

12. Use of a sigma ligand of formula (I) as defined in any of claims 1-9, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, for the manufacture of a medicament for potentiating the analgesic effect of an opioid or opiate selected from the group consisting of morphine, tramadol, sufentanil, remifentanil, fentanyl, tapentadol, oxycodone, and buprenorphine or an analogue thereof, when said opioid or opiate is used in the prevention and/or treatment of pain developed as a consequence of surgery.