SIGMA LIGANDS FOR USE IN THE PREVENTION AND/OR TREATMENT OF POSTOPERATIVE PAIN

FIELD OF THE INVENTION

The present invention relates to the use of sigma receptor ligands in the prevention and/or treatment of pain developed as a consequence of surgery.

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. Pain can be classified based on temporal, aetiological or physiological criteria. When pain is classified by time, it can be acute or chronic. Aetiological classifications of pain are malignant or non-malignant. A third classification is physiological, which includes nociceptive pain (results from detection by specialized transducers in tissues attached to A-delta and C-fibres), that can be divided into somatic and visceral types of pain, and neuropathic pain (results from irritation or damage to the nervous system), that can be divided into peripheral and central neuropathic pain. Pain is a normal physiological reaction of the somatosensory system to noxious stimulation which alerts the individual to actual or potential tissue damage. It serves a protective function of informing us of injury or disease, and usually remits when healing is complete or the condition is cured. However, pain may result from a pathological state characterized by one or more of the following: pain in the absence of a noxious stimulus (spontaneous pain), increased duration of 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).

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 anesthetics, 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 anesthetics (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" (interchangeably termed “post-operative”, "post-incisional" or "posttraumatic pain") refers to pain arising or resulting from an external trauma or injury 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). 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). Infections and/or physical or chemical injuries affecting the wound area can exacerbate and prolong post-surgical pain. 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 resting (also known as spontaneous, persistent or ongoing) pain and evoked pain (pain

evoked by stimulation). Evoked pain can be classified as 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). Stimuli can be thermal or mechanical (tactile) in nature. Mechanical and/or thermal allodynia and/or hyperalgesia can occur in the primary wound area (i.e., primary allodynia or hyperalgesia) or expand to adjacent and surrounding areas that become sensitized (i.e., secondary allodynia or hyperalgesia). Therefore, the pain is characterized by thermal hypersensitivity, mechanical hypersensitivity and/or resting pain (e.g. pain in the absence of external stimuli). Hyperpathia, characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. Hyperpathia may occur with allodynia, hyperesthesia, hyperalgesia, or dysesthesia, and faulty identification and localization of the stimulus, delay, radiating sensation, and after-sensation may be present, and the pain is often explosive in character. 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). Further, the pain can be acute or chronic. Acute pain results from the external trauma (cut, puncture, incision, tear, or wound), including that arising from all surgical procedures, and can be mild and last seconds, minutes or hours, or it can be severe and last for weeks or months. In most cases, acute pain does not last longer than three months, and it disappears when the underlying cause of pain (e.g., the wound) has been cured or has healed. Unrelieved acute pain, however, might lead to chronic pain. Chronic pain (also known as persistent pain) usually lasts longer than three months, beyond the healing period of tissue damage. Chronic pain normally originates with the initial trauma/injury but persists despite the fact that the injury has healed and no new tissue injury occurs. Pain signals remain active in the nervous system for weeks, months, or years. Physical effects include tense muscles, limited mobility, sleep disturbances and changes in appetite. Emotional effects include depression, anger, anxiety and fear of re-injury. Such emotional effects can hinder a person's ability to return to normal work or leisure activities. Post-surgical pain can also be divided into "superficial" and "deep", and deep pain into "deep somatic" and "visceral". Superficial pain comes from the damaged skin or superficial tissues and is sharp, well-defined and clearly localized. Deep somatic pain comes from injured ligaments, tendons, bones, blood vessels, fasciae and muscles, and is dull, aching, poorly-localized. Visceral pain originates in the injured viscera (organs) and is usually more aching or cramping than somatic pain. Visceral pain may be well-localized, but often it is extremely difficult to locate, and

several visceral regions produce "referred" pain when injured, where the sensation is located in an area completely unrelated to the site of injury. Post-surgical pain can also be neuropathic (i.e., neuropathic pain) in nature as the nervous system becomes injured. Peripheral neuropathic pain occurs when the lesion affects the peripheral nervous system (e.g., peripheral nerves, nerve roots and/or ganglia) and thus peripheral neuropathy takes place. Nerve damage by surgery can also result in nerve inflammation (neuritis) and neuralgia (pain in the distribution of the nerves). Central neuropathic pain may occur when the lesion affects the central nervous system (e.g., brain, cerebellum, spinal cord). Pain can result from neuroma (also known as "pseudoneuroma") formation (e.g., traumatic neuroma following nerve injury as a result of surgery) that typically occurs at the end of injured nerve fibres as a form of ineffective, unregulated nerve regeneration commonly near a scar, either superficially (skin, subcutaneous fat) or deep (e.g., after a cholecystectomy). Pain from deafferentation can also occur if injured or axotomized nerve fibres degenerate thus completely or partially interrupting afferent nerve impulses. Causalgia, 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 can also happen. In fact, pain can arise from any tissue or part of the body where external trauma or injury 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) occurs. Finally, pain can differ in quantity (e.g., mild, moderate, severe) and quality (e.g., aching, burning, tingling, electrical, stabbing), it can include abnormal sensations (e.g., dysesthesia, paresthesia) and it can be continuous, intermittent or oscillating in intensity.

Different animal models and studies on postoperative incisional pain are reported in the state of the art (T.J. Brennan et al. Pain 1996, 64, 493-501; P.K. Zahn et al. Regional Anesthesia and Pain Medicine 2002, Vol. 27, No 5 (September-October), 514-516).

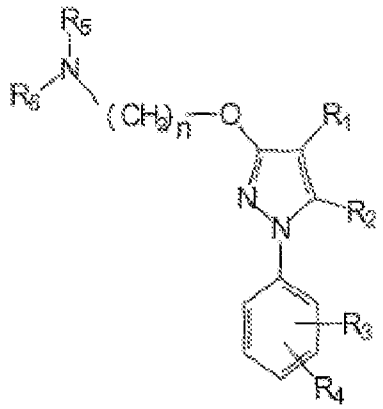
Finally, it is important to emphasize that there is a need to provide a new form of prevention and/or treatment of post-surgical acute and chronic pain, allodynia, hyperalgesia and abnormal sensations secondary to nerve (peripheral neuropathy) and tissue (superficial and deep somatic and visceral) injury developing during and/or after surgery.

BRIEF DESCRIPTION OF THE INVENTION

The inventors of the present invention have surprisingly found and demonstrated that the administration of sigma receptor ligands is highly effective for preventing or treating the pain associated to a surgery. This benefit of the invention is more evident when the sigma ligand is specifically a sigma 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 pain developed as a consequence of surgery.

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



(I)

wherein

$\mathbf{R_1}$ 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 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;

$\mathbf{R_2}$ 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, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, and 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, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, and 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, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, and halogen, or together form, with the nitrogen atom to which they are attached, a substituted or unsubstituted, aromatic or non-aromatic heterocyclyl group;

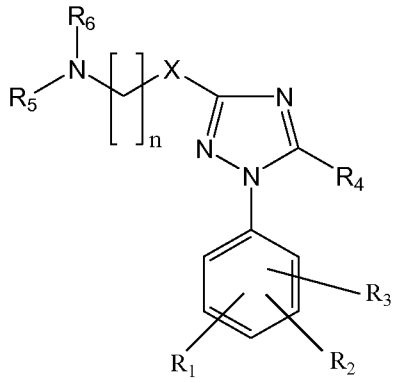
n is selected from 1, 2, 3, 4, 5, 6, 7 and 8;

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.

In another preferred embodiment, the sigma ligand has the general formula (II):



(II)

wherein

R_1, R_2 and R_3 are independently selected from hydrogen, halogen, hydroxyl, alcoxyl, substituted or unsubstituted alkyl, cyano, NR^aR^b, $NHCONR^c$, $NHSO_2R^d$, COOH, $COOR^e$, wherein R^a is hydrogen or alkyl and R^b, R^c, R^d and R^e are independently an alkyl;

R_4 is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted, aromatic or non-aromatic heterocyclyl;

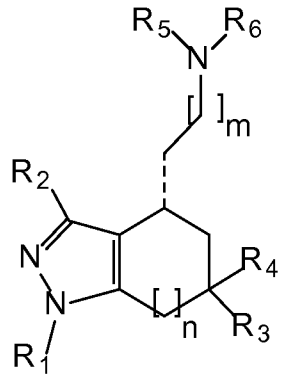
R_5 and R_6 are independently a substituted or unsubstituted alkyl or form, together with the nitrogen atom to which they are attached, a substituted or unsubstituted, aromatic or non-aromatic heterocyclyl group;

X is selected from –S-, -SO-, $-SO_2-$ and O; and

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

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

In still another preferred embodiment, the sigma ligand has the general formula (III):



(III)

wherein

R_1 is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, and substituted or unsubstituted heterocyclylalkyl;

R_2 is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted arylalkyl, and substituted or unsubstituted heterocyclylalkyl;

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, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl and substituted or unsubstituted heterocyclylalkyl or, together, R_3 and R_4 form a 3 to 6 substituted or unsubstituted member ring;

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, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl and substituted or unsubstituted heterocyclylalkyl or, R_5 and R_6 together, form a substituted or unsubstituted, aromatic or non-aromatic heterocyclyl having 3 to 7 atoms in the ring;

n is selected from 0, 1 and 2;

m is selected from 0, 1, 2, 3 and 4;
the dotted line ----- is either a single or a double bond;
with the proviso that when R_1 is phenyl, R_2 is H, the dotted line ------ is a double bond, m is 1, and R_5 and R_6 form a 2,5-dioxopyrrolidine or a 5-ethoxy,2-oxo-pyrrolidine; then R_3 and R_4 are not both at the same time H or methyl;
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 pain developed as a consequence of surgery.

Another aspect of the invention 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 sigma ligand as defined above.

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

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Treatment approach in mechanical allodynia. Results obtained with a known Sigma ligand (BD-1063) administered intraperitoneally 30 min before mechanical allodynia was assessed in the ipsilateral (operated) hindpaw of rats [0h: surgery; 3.5h: administration i.p. of the compound; 4h: mechanical allodynia assessment; *: significant differences ($p<0.05$); ns: non-significant differences ($p>0.05$); n=10].

Figure 2: Treatment approach in mechanical allodynia. Results obtained with compound 63 administered intraperitoneally 30 min before mechanical allodynia was assessed in the ipsilateral (operated) hindpaw of rats [0h: surgery; 3.5h: administration i.p. of the compound; 4h: mechanical allodynia assessment; *: significant differences ($p<0.05$); ns: non-significant differences ($p>0.05$); n=10].

Figure 3: Treatment vs preventive approach in mechanical allodynia. Comparative results of mechanical allodynia obtained with sodium diclofenac, commonly used for

the post-surgical pain treatment, administered before (prevention) and after (treatment) surgery in the ipsilateral (operated) hindpaw of rats [-10 min: administration i.p. of the compound (preventive); 0h: surgery; 3h: administration i.p. of the compound (treatment); 4h: mechanical allodynia assessment; *: significant differences ($p<0.05$); ns: non-significant differences ($p>0.05$); n=10].

Figure 4: Treatment vs preventive approach in mechanical allodynia. Comparative results of mechanical allodynia for BD-1063 and compound 63 administered before (prevention) and after (treatment) surgery in the ipsilateral (operated) hindpaw of rats [-10 min: administration i.p. of the compound (preventive); 0h: surgery; 3.5h: administration i.p. of the compound (treatment); 4h: mechanical allodynia assessment; *: significant differences ($p<0.05$); ns: non-significant differences ($p>0.05$); n=10].

Figure 5: Treatment vs preventive approach in thermal hyperalgesia. Comparative results of thermal hyperalgesia obtained with sodium diclofenac, commonly used for the post-surgical pain treatment, administered before (prevention) and after (treatment) surgery in the ipsilateral (operated) hindpaw of rats [-10 min: administration i.p. of the compound (preventive); 0h: surgery; 3h: administration i.p. of the compound (treatment); 4h: thermal hyperalgasia assessment; *: significant differences ($p<0.05$); ns: non-significant differences ($p>0.05$); n=10].

Figure 6: Treatment vs preventive approach in thermal hyperalgesia. Comparative results of thermal hyperalgesia for compound 63 administered before (prevention) and after (treatment) surgery in the ipsilateral (operated) hindpaw of rats [-10 min: administration i.p. of the compound (preventive); 0h: surgery; 3.5h: administration i.p. of the compound (treatment); 4h: thermal hyperalgasia assessment; *: significant differences ($p<0.05$); ns: non-significant differences ($p>0.05$); n=10].

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”.

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 formulae (I), (II) or (III), 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, in particular the compounds of formulae (I), (II) or (III), 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 “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 acute and chronic pain induced by a surgical operation, including superficial and/or deep pain secondary to surgical tissue injury, and peripheral neuropathic pain, neuralgia, allodynia, causalgia, hyperalgesia, hyperesthesia, hyperpathia, dysesthesia, paresthesia, neuritis or neuropathy, secondary to surgical nerve injury.

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. 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 prevention and/or treatment of pain developing as a consequence of surgery.

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	Desloratadine

Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester	
(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-tartrate	Eticlopride HCl, S(-)-
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-Methylpiperazino)Dibenz[B,F]Oxepin Maleate	MDL 12,330A HCl
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-ylmethoxy]benzonitrile	N1-[2-(3,4-Dichlorophenyl)ethyl]-N1,N2,N2-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-1H,5H-naphtho[1,2,3-ij]quinolizine	Pentamidine Isethionate
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 Drugdesign 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

[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.

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

In another embodiment of the invention, it is preferred that in the compound of formula (II), at least one of R_1 to R_3 is hydrogen. In another embodiment of the invention, it is preferred that in the compound of formula (II), at least one of R_1 to R_3 is halogen. In another embodiment, it is preferred that two of R_1 to R_3 are hydrogen or halogen, the last being preferably chloride.

In another embodiment, R_4 in the compounds of formula (II) is preferably a lower alkyl, more preferably is methyl.

In one embodiment in the compounds of formula (II) R_5 and R_6 are independently an alkyl, more preferably a C_1-C_6 alkyl, even more preferably ethyl or isopropyl.

In another embodiment in the compounds of formula (II) R_5 and R_6 form, together with the nitrogen to which they are attached, a substituted or unsubstituted heterocyclyl group, preferably selected from pyrrolidine, piperidine, azepane and morpholine.

Further, in a preferred embodiment in the compounds of formula (II) n is 1, 2, 3, 4 or 5.

Preferred compounds of formula (II) are the following:

[67] 4-[2-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazole-3-ylthioethyl]morpholine;

[68] 1-[2-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazole-3-yl-thioethyl]piperidine;

[69] 1-[2-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazole-3-yl-thioethyl]pyrrolidine;

[70] 2-[2-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazole-3-yl-thio]-N,N-diisopropyl ethanamine;

[71] 2-[1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazole-3-yl-thio]-N,N-diethyl ethanamine;

[72] 1-[2-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-thio)ethyl]azepane;

[73] 4-[3-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)propyl] morpholine;

[74] 1-[3-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-thio)propyl]-4-pyrrolidine;

[75] 1-[3-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)propyl]-4-phenylpiperidine;

[76] 1-[4-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-thio)butyl]-4-phenylpiperidine;

[77] 4-[4-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-thio)butyl]morpholine;

[78] 1-[5-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)pentyl]piperidine;

[79] 4-[5-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)pentyl] morpholine;

[80] 1-[5-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)pentyl]pyrrolidine;

[81] 1-[2-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-sulfinyl)ethyl] pyrrolidine;

[82] 4-[2-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-sulfinyl)-ethyl]-morpholine;

[83] 2-[2-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylsulfinyl]-N,N-diisopropylethanamine;

[84] 1-[4-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylsulfinyl)butyl]-4-phenylpiperidine;

[85] 1-[2-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylsulfonyl]ethylpyrrolidine;

[86] 2-[1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-sulfonyl]-N,N-diethylethanamine;

[87] 4-[4-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-sulfonyl)-butyl] morpholine;

[88] 1-[2-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yloxy)ethyl]piperidine;

[89] 2-[1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yloxy]-N,N-diethylethanamine;

[90] 1-[2-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yloxy)ethyl]pyrrolidine;

[91] 4-[2-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yloxy)ethyl]morpholine;

[92] 2-(5-methyl-1-phenyl-1H-1,2,4-triazol-3-yloxy)-N,N-diethylethanamine;

[93] 1-[2-(5-methyl-1-phenyl-1H-1,2,4-triazol-3-yloxy)ethyl]pyrrolidine;

[94] 4-[2-(5-methyl-1-phenyl-1H-1,2,4-triazol-3-yloxy)ethyl]morpholine;

[95] 1-[2-(5-methyl-1-phenyl-1H-1,2,4-triazol-3-yloxy)ethyl]piperidine;

[96] 4-[4-(5-methyl-1-phenyl-1H-1,2,4-triazol-3-yloxy)butyl]morpholine;

[97] 1-[2-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)ethyl]-4-methylpiperidine;

[98] 4-[2-(5-methyl-1-phenyl-1H-1,2,4-triazol-3-ylthio)ethyl]morpholine;

[99] 4-[2-(1-(4-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)ethyl]morpholine;

[100] N-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)ethyl]-N,N-diisopropylpropan-2-amine;

[101] 1-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)ethyl]piperidine;

[102] 4-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)ethyl]morpholine;

[103] 4-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)ethyl]pyrrolidine;

[104] 2-[1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio]-N,N-diethylethanamine;

[105] 4-[1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio]-N,N-diethylbutan-1-amine;

[106] 1-[4-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)butyl]piperidine;

[107] 1-[4-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)butyl]pyrrolidine;

[108] 2-[1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylsulfinyl]-N,N-diethylethanamine;

[109] 1-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-sulfinyl)ethyl]pyrrolidine

[110] 1-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-sulfinyl)ethyl]morpholine

[111] 1-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-sulfinyl)ethyl]-N,N-diethylamine;

[112] 1-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-sulfonyl)ethyl]pyrrolidine

[113] 1-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-sulfonyl)ethyl]-N,N-diisopropilamine;

[114] 1-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-sulfonyl)ethyl]-N,N-diethylamine;

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

Additionally, in another preferred embodiment of the invention the compound of formula (II) is an oxalic salt thereof.

Preferred salts of the compounds of formula II are the following:

[115] 4-[2-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazole-3-ylthio ethyl]morpholine oxalate;

[116] 1-[2-(3,4-dichlorophenyl)-5-methyl-1H-1.2.4-triazole-3-yl-thio)ethyl]piperidine oxalate;

[117] 1-[2-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazole-3-yl-thio ethyl]pyrrolidine oxalate;

[118] 2-[2-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazole-3-yl-thio]-N,N-diisopropyl ethanamine oxalate;

[119] 2-[1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazole-3-yl-thio]-N,N-diethyl ethanamine oxalate;

[120] 1-[2-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-thio)ethyl]azepane oxalate;

[121] 4-[3-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)propyl] morpholine oxalate;

[122] 1-[3-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-thio)propyl] pyrrolidine oxalate;

[123] 1-[3-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)propyl]-4-phenylpiperidine oxalate;

[124] 1-[4-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-thio)butyl]-4-phenylpiperidine oxalate;

[125] 4-[4-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yl-thio)butyl]morpholine oxalate;

[126] 1-[5-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)pentyl]piperidine oxalate;

[127] 4-[5-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)pentyl] morpholine oxalate;

[128] 1-[5-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)pentyl]pyrrolidine oxalate;

[129] 4-[2-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-yloxy)ethyl]morpholine oxalate;

[130] 4-[2-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazole-3-ylthio) ethyl]morpholine hydrochloride.

[131] 1-[2-(1-(3,4-dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)ethyl]-4-methyl piperidinium oxalate;

[132] 4-[2-(5-methyl-1-phenyl-1H-1,2,4-triazol-3-ylthio)ethyl]morpholinium oxalate;

[133] 4-[2-(1-(4-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)ethyl]morpholinium oxalate;

[134] N-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)ethyl]-N,N-diisopropylpropan-2-aminium oxalate

[135] 1-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)ethyl]piperidinium oxalate

[136] 4-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)ethyl]morpholinium oxalate;

[137] 4-[2-(1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio)ethyl]pyrrolidinium oxalate

[138] 2-[1-(3-chlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylthio]-N,N-diethylethan aminium oxalate.

In a more preferred variant of the invention, the sigma ligand of formula (II) is 4-[2-(3,4-dichlorophenyl)-5-methyl-1*H*-1,2,4-triazole-3-ylthio ethyl] morpholine oxalate.

The compounds of formula (II) can be prepared as disclosed in the previous application WO2008/055932.

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

In another embodiment of the invention, it is preferred that in the compound of formula (III) R_2 is preferably hydrogen or alkyl; more preferably hydrogen.

In the compound of formula (III) it is also preferred that m is 1 or 2, and also that n is 0 or 1.

Moreover, in the compound of formula (III) it is also preferred that R_3 and R_4 are either hydrogen or alkyl; more preferred either hydrogen or methyl; and most preferred both are hydrogen.

Further, it is preferred that in the compound of formula (III) R_1 is selected from the group formed by substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl and substituted or unsubstituted aryl; more preferred substituted or unsubstituted alkyl, unsubstituted cycloalkyl, unsubstituted aryl and aromatic heterocyclic; and most preferred, methyl, t-butyl, cyclohexyl and phenyl.

Moreover, it is also preferred that R_5 and R_6 together form a substituted or unsubstituted heterocyclyl having 3 to 7 atoms in the ring, in particular morpholin-4-yl, 2,6-dimethylmorpholin-4-yl, piperidin-1-yl, 4-phenylpiperidin-1-yl, 3-phenylpiperidin-1-yl, 4-benzylpiperazin-1-yl, 4-phenyl-piperazin-1-yl, 2-[spiro [isobenzofuran-1(3H),4'-piperidin]-1'-yl, azepan-1-yl, 1,2,3,4-tetrahidro-isoquinolin-2-yl, pyrrolidin-1-yl, 3-phenyl-

pyrrolidin-1-yl, isoindolin-2-yl or imidazol-1-yl; especially when R_2 is hydrogen, m is 1 and n is 1; more especially when R_3 and R_4 are both hydrogen; and even more especially when R_1 is substituted or unsubstituted phenyl. Good results are obtained when R_5 is benzyl and R_6 is methyl.

The above embodiments and preferences for R_1 to R_6, n, m and the dotted line ----- can be combined to give further preferred compounds.

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

[139] 4,5,6,7-tetrahydro-4-(2-(morpholin-4-yl)ethyl)-1-phenyl-1H-indazole,

[140] 4,5,6,7-tetrahydro-4-(2-(morpholin-4-yl)ethyl)-1-phenyl-1H-indazole oxalate,

[141] 1-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-4-(2-(4-phenylpiperidin-1-yl)ethyl)-1H-indazole,

[142] 1-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-4-(2-(4-phenylpiperidin-1-yl)ethyl)-1H-indazole oxalate,

[143] (E)-4,5,6,7-tetrahydro-4-(2-(morpholin-4-yl)ethylidene)-1-phenyl-1H-indazole,

[144] 1-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-4-(2-(morpholin-4-yl)ethyl)-1H-indazole,

[145] 1-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-4-(2-(morpholin-4-yl)ethyl)-1H-indazole oxalate,

[146] 4,5,6,7-tetrahydro-1-phenyl-4-(2-(4-phenylpiperidin-1-yl)ethyl)-1H-indazole,

[147] 4,5,6,7-tetrahydro-1-phenyl-4-(2-(4-phenylpiperidin-1-yl)ethyl)-1H-indazole oxalate,

[148] 4-(2-(4-benzylpiperazin-1-yl)ethyl)-4,5,6,7-tetrahydro-1-phenyl-1H-indazole,

[149] 4,5,6,7-tetrahydro-1-phenyl-4-(2-[spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl] ethyl)-1H-indazole,

[150] 4,5,6,7-tetrahydro-1-phenyl-4-(2-[spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl] ethyl)-1H-indazole oxalate,

[151] 4,5,6,7-tetrahydro-1-phenyl-4-(2-(piperidin-1-yl)ethyl)-1H-indazole,

[152] 4,5,6,7-tetrahydro-1-phenyl-4-(2-(piperidin-1-yl)ethyl)-1H-indazole oxalate,

[153] (E)-4-(2-(azepan-1-yl)ethylidene)-4,5,6,7-tetrahydro-1-phenyl-1H-indazole,

[154] (E)-4-(2-(azepan-1-yl)ethylidene)-4,5,6,7-tetrahydro-1-phenyl-1H-indazole oxalate,

[155] (E)-4,5,6,7-tetrahydro-1-phenyl-4-(2-(4-phenylpiperidin-1-yl)ethylidene)-1H-indazole,

[156] (E)-4,5,6,7-tetrahydro-1-phenyl-4-(2-[spiro[isobenzofuran-1(3H),4'-piperi din]-1'-yl] ethylidene)-1H-indazole,

[157] (E)-4,5,6,7-tetrahydro-1-phenyl-4-(2-[spiro[isobenzofuran-1(3H),4'-piperi din]-1'-yl] ethylidene)-1H-indazole oxalate,

[158] (E)-4,5,6,7-tetrahydro-1-phenyl-4-(2-(4-phenylpiperazin-1-yl)ethylidene)-1H-indazole,

[159] 1,2,3,4-tetrahydro-2-((E)-2-(6,7-dihydro-1-phenyl-1H-indazol-4(5H)-ylide ne)ethyl)isoquinoline,

[160] 1,2,3,4-tetrahydro-2-((E)-2-(6,7-dihydro-1-phenyl-1H-indazol-4(5H)-ylide ne)ethyl)isoquinoline oxalate,

[161] (E)-4,5,6,7-tetrahydro-1-phenyl-4-(2-(3-phenylpiperidin-1-yl)ethylidene)-1H-indazole,

[162] (E)-4,5,6,7-tetrahydro-1-phenyl-4-(2-(3-phenylpyrrolidin-1-yl)ethylidene)-1H-indazole

[163] (E)-4,5,6,7-tetrahydro-1-phenyl-4-(2-(3-phenylpyrrolidin-1-yl)ethylidene)-1H-indazole oxalate,

[164] (E)-4,5,6,7-tetrahydro-4-(2-(isoindolin-2-yl)ethylidene)-1-phenyl-1H-indazole,

[165] (E)-4,5,6,7-tetrahydro-1-phenyl-4-(2-(piperidin-1-yl)ethylidene)-1H-indazole,

[166] 1-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1H-indazole,

[167] 1-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1H-indazole oxalate,

[168] 1,4,5,6-tetrahydro-4-(2-(morpholin-4-yl)ethyl)-1-phenylcyclopenta[c]pyrazole,

[169] 1,4,5,6-tetrahydro-4-(2-(morpholin-4-yl)ethyl)-1-phenylcyclopenta[c]pyrazole oxalate,

[170] 4,5,6,7-tetrahydro-1-phenyl-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1H-indazole,

[171] 4,5,6,7-tetrahydro-1-phenyl-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1H-indazole oxalate,

[172] 2-(2-(1,4,5,6-tetrahydro-1-phenylcyclopenta[c]pyrazol-4-yl)ethyl)isoindoline,

[173] 2-(2-(1,4,5,6-tetrahydro-1-phenylcyclopenta[c]pyrazol-4-yl)ethyl)isoindoline oxalate,

[174] 1,4,5,6-tetrahydro-1-phenyl-4-(2-(4-phenylpiperidin-1-yl)ethyl)cyclopenta[c] pyrazole,

[175] 1,4,5,6-tetrahydro-1-phenyl-4-(2-(piperidin-1-yl)ethyl)cyclopenta[c]pyrazole,

[176] 1,4,5,6-tetrahydro-1-phenyl-4-(2-(4-phenylpiperazin-1-yl)ethyl)cyclopenta [c]pyrzole,

[177] 1,4,5,6-tetrahydro-1-phenyl-4-(2-(pyrrolidin-1-yl)ethyl)cyclopenta[c]pyrazole,

[178] 1,4,5,6-tetrahydro-1-phenyl-4-(2-(pyrrolidin-1-yl)ethyl)cyclopenta[c]pyrazole oxalate,

[179] 4-(2-(4-benzylpiperazin-1-yl)ethyl)-1,4,5,6-tetrahydro-1-phenylcyclopenta [c]pyrazole,

[180] 4-(2-(4-benzylpiperazin-1-yl)ethyl)-1,4,5,6-tetrahydro-1-phenylcyclopenta [c]pyrazole dioxalate,

[181] 1,2,3,4-tetrahydro-2-(2-(1,4,5,6-tetrahydro-1-phenylcyclopenta[c]pyrazol-4-yl)ethyl) isoquinoline,

[182] 1,2,3,4-tetrahydro-2-(2-(1,4,5,6-tetrahydro-1-phenylcyclopenta[c]pyrazol-4-yl)ethyl) isoquinoline oxalate,

[183] 4-(2-(1H-imidazol-1-yl)ethyl)-1,4,5,6-tetrahydro-1-phenylcyclopenta [c]pyrazole,

[184] cis-1,4,5,6-tetrahydro-4-(2-(2,6-dimethylmorpholin-4-yl)ethyl)-1-phenyl cyclopenta[c]pyrazole,

[185] cis-1,4,5,6-tetrahydro-4-(2-(2,6-dimethylmorpholin-4-yl)ethyl)-1-phenyl cyclopenta [c]pyrazole oxalate,

[186] cis-4,5,6,7-tetrahydro-4-(2-(2,6-dimethylmorpholin-4-yl)ethyl)-1-phenyl-1H-indazole,

[187] cis-4,5,6,7-tetrahydro-4-(2-(2,6-dimethylmorpholin-4-yl)ethyl)-1-phenyl-1H-indazole oxalate,

[188] 1,4,5,6-tetrahydro-1-phenyl-4-(2-[spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl]-ethyl)cyclopenta[c]pyrazole,

[189] 1,4,5,6-tetrahydro-1-phenyl-4-(2-[spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl]-ethyl)cyclopenta[c]pyrazole oxalate,

[190] N-benzyl-2-(1,4,5,6-tetrahydro-1-phenylcyclopenta[c]pyrazol-4-yl)-N-methyl-ethanamine,

[191] diastereomeric mixture of 1,4,5,6-tetrahydro-1-phenyl-4-(2-(3-phenylpiperidin-1-yl)ethyl)cyclopenta[c]pyrazole,

[192] N-benzyl-2-(4,5,6,7-tetrahydro-1-phenyl-1H-indazol-4-yl)-N-methylethanamine,

[193] 4,5,6,7-tetrahydro-4-(2-(isoindolin-2-yl)ethyl)-1-phenyl-1H-indazole,

[194] 4,5,6,7-tetrahydro-4-(2-(isoindolin-2-yl)ethyl)-1-phenyl-1H-indazole oxalate,

[195] 4,5,6,7-tetrahydro-1-methyl-4-(2-(4-phenylpiperidin-1-yl)ethyl)-1H-indazole,

[196] 4,5,6,7-tetrahydro-1-methyl-4-(2-(4-phenylpiperidin-1-yl)ethyl)-1H-indazole oxalate,

[197] 4,5,6,7-tetrahydro-4-(2-(isoindolin-2-yl)ethyl)-1-methyl-1H-indazole,

[198] 4,5,6,7-tetrahydro-4-(2-(isoindolin-2-yl)ethyl)-1-methyl-1H-indazole oxalate,

[199] N-benzyl-2-(4,5,6,7-tetrahydro-1-methyl-1H-indazol-4-yl)-N-methylethanamine,

[200] N-benzyl-2-(4,5,6,7-tetrahydro-1-methyl-1H-indazol-4-yl)-N-methylethanamine oxalate,

[201] 4,5,6,7-tetrahydro-1-methyl-4-(2-(morpholin-4-yl)ethyl)-1H-indazole,

[202] 4,5,6,7-tetrahydro-1-methyl-4-(2-(morpholin-4-yl)ethyl)-1H-indazole oxalate,

[203] 1-(4-fluorophenyl)-4,5,6,7-tetrahydro-4-(2-(morpholin-4-yl)ethyl)-1H-indazole,

[204] 1-(4-fluorophenyl)-4,5,6,7-tetrahydro-4-(2-(morpholin-4-yl)ethyl)-1H-indazole oxalate,

[205] cis-1-(4-fluorophenyl)-4,5,6,7-tetrahydro-4-(2-(2,6-dimethylmorpholin-4-yl)ethyl)-1H-indazole,

[206] cis-1-(4-fluorophenyl)-4,5,6,7-tetrahydro-4-(2-(2,6-dimethylmorpholin-4-yl)ethyl)-1H-indazole oxalate,

[207] N-benzyl-2-(1-(4-fluorophenyl)-4,5,6,7-tetrahydro-1H-indazol-4-yl)-N-methyl-ethanamine,

[208] 1-(4-fluorophenyl)-4,5,6,7-tetrahydro-4-(2-(isoindolin-2-yl)ethyl)-1H-indazole,

[209] 1-(4-fluorophenyl)-4,5,6,7-tetrahydro-4-(2-(isoindolin-2-yl)ethyl)-1H-indazole oxalate,

[210] 1-(4-fluorophenyl)-4,5,6,7-tetrahydro-4-(2-(4-phenylpiperidin-1-yl)ethyl)-1H-indazole,

[211] (+)-4,5,6,7-tetrahydro-4-(2-(morpholin-4-yl)ethyl)-1-phenyl-1H-indazole,

[212] (+)-4,5,6,7-tetrahydro-4-(2-(morpholin-4-yl)ethyl)-1-phenyl-1H-indazole oxalate,

[213] (-)-4,5,6,7-tetrahydro-4-(2-(morpholin-4-yl)ethyl)-1-phenyl-1H-indazole,

[214] (-)-4,5,6,7-tetrahydro-4-(2-(morpholin-4-yl)ethyl)-1-phenyl-1H-indazole oxalate,

[215] (E)-4,5,6,7-tetrahydro-4-(2-(morpholin-4-yl)ethylidene)-1-phenyl-1H-indazole oxalate,

[216] (E)-4,5,6,7-tetrahydro-1-phenyl-4-(2-(piperidin-1-yl)ethylidene)-1H-indazole oxalate,

[217] (E)-N-benzyl-2-(6,7-dihydro-1-phenyl-1H-indazol-4(5H)-ylidene)-N-methyl-ethanamine,

[218] (E)-N-benzyl-2-(6,7-dihydro-1-phenyl-1H-indazol-4(5H)-ylidene)-N-methyl-ethanamine oxalate,

[219] (E)-4,5,6,7-tetrahydro-4-(2-(cis-2,6-dimethylmorpholin-4-yl)ethylidene)-1-phenyl-1H-indazole,

[220] (E)-4,5,6,7-tetrahydro-4-(2-(cis-2,6-dimethylmorpholin-4-yl)ethylidene)-1-phenyl-1H-indazole oxalate,

[221] (E)-1-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-4-(2-(cis-2,6-dimethylmorpholino-4-yl)- ethylidene)-1H-indazole,

[222] (E)-1-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-4-(2-(cis-2,6-dimethyl-morpholino-4-yl) ethylidene)-1H-indazole oxalate,

[223] (E)-1-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-4-(2-(morpholino-4-yl)ethylidene)-1H-indazole,

[224] (E)-1-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-4-(2-(morpholino-4-yl)-ethylidene)-1H-indazole oxalate,

[225] (E)-1-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-4-(2-(piperidin-1-yl)ethylidene)-1H-indazole,

[226] (E)-1-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-4-(2-(piperidin-1-yl)- ethylidene)-1H-indazole oxalate,

[227] (E)-4-(2-(N,N-diethylamino)ethylidene)- 4,5,6,7-tetrahydro-1-phenyl-1H-indazole,

[228] (E)-4-(2-(N,N-diethylamino)ethylidene)- 4,5,6,7-tetrahydro-1-phenyl-1H-indazole oxalate,

[229] (E)-4-(2-(4-cyclohexylpiperazin-1-yl)ethylidene)-4,5,6,7-tetrahydro-1-phenyl-1H-indazole,

[230] (E)-4,5,6,7-tetrahydro-4-(2-(4-methylpiperidin-1-yl)ethylidene)-1-phenyl-1H-indazole,

[231] 4,5,6,7-tetrahydro-4-(2-(4-methylpiperidin-1-yl)ethyl)-1-phenyl-1H-indazole,

[232] 4,5,6,7-tetrahydro-4-(2-(4-methylpiperidin-1-yl)ethyl)-1-phenyl-1H-indazole oxalate,

[233] 1,4,5,6-tetrahydro-1-phenyl-4-(2-(piperidin-1-yl)ethyl)cyclopenta[c]pyrazole oxalate,

[234] 1,4,5,6-tetrahydro-1-phenyl-4-[2-(thiomorpholin-4-yl)ethyl]cyclopenta[c]pyrazole,

[235] 1,4,5,6-tetrahydro-1-phenyl-4-[2-(thiomorpholin-4-yl)ethyl]cyclopenta[c]pyrazole oxalate,

[236] 1,4,5,6-tetrahydro-4-(2-(4-methylpiperidin-1-yl)ethyl)-1-phenylcyclopenta [c]pyrazole,

[237] 1,4,5,6-tetrahydro-4-(2-(4-methylpiperidin-1-yl)ethyl)-1-phenylcyclopenta [c]pyrazole oxalate,

[238] 1,4,5,6-tetrahydro-4-(2-(4-methylpiperazin-1-yl)ethyl)-1-phenylcyclopenta [c]pyrazole,

[239] 4-(2-(4-cyclohexylpiperazin-1-yl)ethyl)-1,4,5,6-tetrahydro-1-phenylcyclopenta[c] pyrazole,

[240] 4-(2-(azepan-1-yl)ethyl)-4,5,6,7-tetrahydro-1-phenyl-1H-indazole,

[241] N-benzyl-2-(1-tert-butyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-N-methylethan amine,

[242] 1-tert-butyl-4,5,6,7-tetrahydro-4-(2-(4-phenylpiperidin-1-yl)ethyl)-1H-indazole,

[243] 1-tert-butyl-4,5,6,7-tetrahydro-4-(2-(4-phenylpiperidin-1-yl)ethyl)-1H-indazole oxalate,

[244] (-)-N-bencyl-2-(4,5,6,7-tetrahydro-1-methyl-1H-indazol-4-yl)-N-methylethan amine,

[245] (+)-N-bencyl-2-(4,5,6,7-tetrahydro-1-methyl-1H-indazol-4-yl)-N-methylethan amine,

[246] N-(2-(4,5,6,7-tetrahydro-1-methyl-1H-indazol-4-yl)ethyl)-N-methylcyclohe xanamine,

[247] 4,5,6,7-tetrahydro-4-(2-(4-hydroxy-4-phenylpiperidin-1-yl)ethyl)-1-methyl-1H-indazole,

[248] 4,5,6,7-tetrahydro-1-methyl-4-(2-(4-phenylpiperidin-1-yl)ethyl)-1H-indazole,

[249] N-benzyl-2-(4,5,6,7-tetrahydro-1-methyl-1H-indazol-4-yl)-N-methylethanamine,

[250] 4,5,6,7-tetrahydro-1-phenyl-4-(2-[spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl]-ethyl)-1H-indazole.

Although the oxalates are listed, other pharmaceutically acceptable salts also form part of this group of preferred compounds.

In a more preferred variant of the invention, the sigma ligand of formula (III) are selected from:

[251] 4-(2-(1-(4-fluorophenyl)-4,5,6,7-tetrahydro-1H-indazol-4-yl)ethyl)morpholine oxalate;

[252] 4-(1-(2-(1-methyl)-4,5,6,7-tetrahydro-1H-indazol-4-yl)ethyl)piperidin-4-yl) benzonitrile oxalate; and

[253] 1-(4-(7-((5-bromothiophen-2-yl)methyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-ylamino)phenyl)ethyl acetate.

The compounds of formula (III) can be prepared as disclosed in the previous application WO2006/021463.

In a particular embodiment of the present invention, the pain developed as a consequence of surgery is superficial and/or deep pain and for example is peripheral neuropathic pain, with neuralgia, allodynia, causalgia, hyperalgesia, hyperesthesia and/or hyperpathia.

In another aspect of the present invention, the pain developed as a consequence of surgery as defined herein before is accompanied by neuropathy and/or neuritis. More preferably, the pain is thermal 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 "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 "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 "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).

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 the pain developed as a consequence to surgery.

The auxiliary materials or additives of a pharmaceutical composition according to the present invention 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 comprising the sigma ligand 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 suffering from post-surgical pain, or likely to suffer pain as a result of a surgical operation, which comprises administering to the patient in need of such a treatment or prophylaxis a therapeutically effective amount of a sigma ligand at the appropriate treatment frequency as defined above.

In some embodiments, the post-surgical pain includes one or more of: allodynia, hyperalgesia, 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. Additional aspects of the subject methods include methods of ameliorating and/or preventing the development or progression of post-surgical pain by administering the subject sigma ligands. In certain embodiments, the sigma ligand can be administered prior to an activity likely to result in external trauma, wound or incision, such as surgery. For example, the emulsion 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 external trauma, wound or incision, such as prior to surgery. In other embodiments, the sigma ligand can be administered during and/or after surgery or activity that resulted in external trauma, wound or incision. 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 surgery, or activity that resulted in external trauma, wound or incision.

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 pain 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

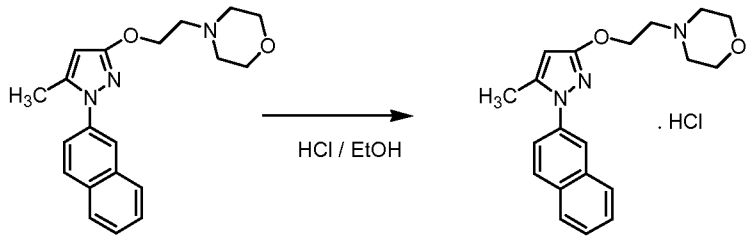
administered orally, larger quantities of the active agent will be required to produce the same effect as a smaller quantity given parenterally. The compounds are useful in the same manner as comparable therapeutic agents and the dosage level is of the same order of magnitude as is generally employed 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°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

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 longitudal 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.

PLANTAR INICISION – MECHANICAL ALLODYNIA

Treatment:

Figure 1: Results obtained with a known Sigma ligand (BD-1063) administered intraperitoneally 30 min before mechanical allodynia was assessed in the ipsilateral (operated) hindpaw of rats.

Figure 2: Results obtained with compound 63 administered intraperitoneally 30 min before mechanical allodynia was assessed in the ipsilateral (operated) hindpaw of rats.

Prevention/Treatment comparison:

Figure 3: Comparative results of mechanical allodynia obtained with sodium diclofenac, commonly used for the post-surgical pain treatment, administered before (prevention) and after (treatment) surgery in the ipsilateral (operated) hindpaw of rats.

Figure 4: Comparative results of mechanical allodynia for BD-1063 and compound 63 administered before (prevention) and after (treatment) surgery in the ipsilateral (operated) hindpaw of rats.

PLANTAR INICISION – THERMAL HYPERALGESIA

Prevention/Treatment comparison:

Figure 5: Comparative results of thermal hyperalgesia obtained with sodium diclofenac, commonly used for the post-surgical pain treatment, administered before (prevention) and after (treatment) surgery in the ipsilateral (operated) hindpaw of rats.

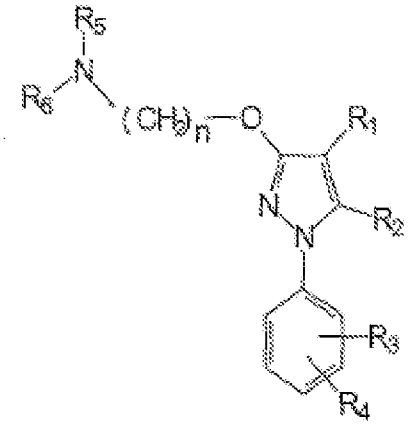
Figure 6: Comparative results of thermal hyperalgesia for compound 63 administered before (prevention) and after (treatment) surgery in the ipsilateral (operated) hindpaw of rats.

The main issue observed in thermal hyperalgesia is the same as for the previous test described (mechanical allodynia).

Sigma ligands are effective against post-operative pain by reducing both mechanical allodynia and thermal hyperalgesia. It is important to note that activity is seen both when administered before (prevention) and after (treatment) surgery and that, in contrast to diclofenac (Figure 3 and 5), the potency increases when the compound was administered before the surgery (Figure 4 and 6).

CLAIMS

1. A sigma ligand for use in the prevention and/or treatment of pain developed as a consequence of surgery.
2. Sigma ligand according to claim 1, wherein the pain is selected from acute and/or chronic pain developed as a consequence of surgery, especially superficial and/or deep pain secondary to surgical tissue injury, and/or neuropathic pain, neuralgia, allodynia, causalgia, hyperalgesia, hyperesthesia, hyperpathia, neuritis or neuropathy secondary to surgical procedure.
3. Sigma ligand according to claims 1 or 2, which is selected from a sigma receptor antagonist preferably selected from a neutral antagonist, an inverse agonist or a partial antagonist.
4. Sigma ligand according to any preceding claim, having the general formula (I):



(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 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 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, -$N=CR_8R_9$, and 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, -$N=CR_8R_9$, and 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, -$N=CR_8R_9$, 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.

5. Sigma ligand according to claim 4, wherein R_1 is selected from H, -COR_8 and substituted or unsubstituted alkyl.

6. Sigma ligand according to claims 4 or 5, wherein R_2 is H or alkyl.

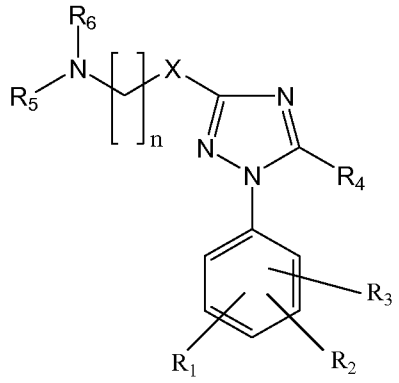
7. Sigma ligand according to any of claims 4 to 6, wherein R_3 and R_4 together form a fused naphthyl ring system.

8. Sigma ligand according to any of claims 4 to 7, wherein R_5 and R_6 together form a morpholine-4-yl group.

9. Sigma ligand according to any of claims 4 to 8, wherein the sigma ligand is 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof.

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

11. Sigma ligand according to any of claims 1 to 3, having the general formula (II):



(II)

wherein

R_1, **R_2** and **R_3** are independently selected from hydrogen, halogen, hydroxyl, alcoxyl, substituted or unsubstituted alkyl, cyano, NR^aR^b, $NHCONR^c$, $NHSO_2R^d$, COOH, $COOR^e$, wherein R^a is hydrogen or alkyl and R^b, R^c, R^d and R^e are independently an alkyl;

R_4 is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted, aromatic or non-aromatic heterocyclyl;

R_5 and **R_6** are independently a substituted or unsubstituted alkyl or form, together with the nitrogen atom to which they are attached, a substituted or unsubstituted, aromatic or non-aromatic heterocyclyl group;

X is selected from –S-, -SO-, $-SO_2-$ and O; and

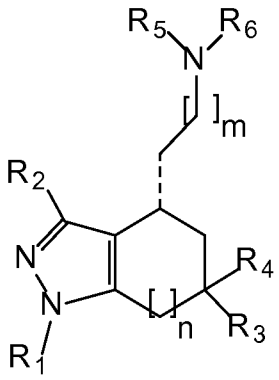
n is an integer selected from 1, 2, 3, 4, 5, 6, 7 and 8,

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

12. Sigma ligand according to claim 11, wherein at least one of R_1 to R_3 is hydrogen or halogen.

13. Sigma ligand according to claims 11 or 12, wherein R_4 is an alkyl.

14. Sigma ligand according to any of claims 1 to 3, having the general formula (III):



(III)

wherein

R_1 is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, and substituted or unsubstituted heterocyclylalkyl;

R_2 is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted arylalkyl, and substituted or unsubstituted heterocyclylalkyl;

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, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl and substituted or unsubstituted heterocyclylalkyl or, together, R_3 and R_4 form a 3 to 6 substituted or unsubstituted member ring;

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, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl and substituted or unsubstituted heterocyclylalkyl or, R_5 and R_6 together, form a substituted or unsubstituted heterocyclyl having 3 to 7 atoms in the ring;

n is selected from 0, 1 and 2;

m is selected from 0, 1, 2, 3 and 4;

the dotted line ----- is either a single or a double bond;

with the proviso that when R_1 is phenyl, R_2 is H, the dotted line ------ is a double bond, m is 1, and R_5 and R_6 form a 2,5-dioxopyrrolidine or a 5-ethoxy,2-oxo-pyrrolidine; then R_3 and R_4 are not both at the same time H or methyl;

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

15. Sigma ligand according to claim 14, wherein R_4 is hydrogen or alkyl.

16. Use of a sigma ligand as defined in any of claims 1 to 15 for the manufacture of a medicament for the prevention and/or treatment of pain developed as a consequence of surgery.

17. 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 sigma ligand as defined in any of claims 1 to 15.