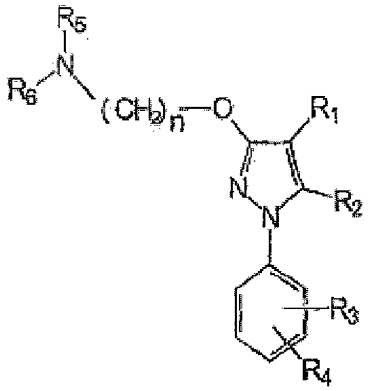
The inventors of the present invention have surprisingly found and demonstrated that the administration of sigma receptor ligands is highly effective for preventing or treating the pain associated to a surgery. This benefit of the invention is more evident when the sigma ligand is specifically a sigma receptor antagonist, preferably in the form of a (neutral) antagonist, an inverse agonist or a partial antagonist.

In one aspect, the present invention provides use of a sigma ligand for the manufacture of a medicament for the prevention and/or treatment of pain developed as a consequence of surgery, wherein the sigma ligand has 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;

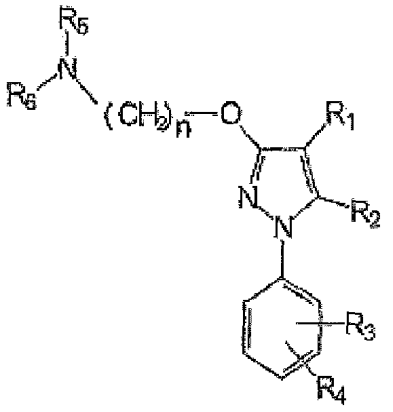
t is 1,2 or 3;

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.

Disclosed is a sigma ligand for use in the prevention and/or treatment of pain developed as a consequence of surgery.

In a preferred example, said sigma ligand has 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;

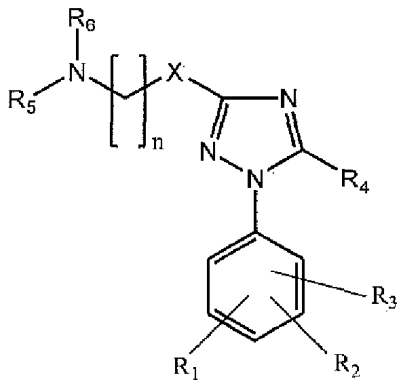
n is selected from 1, 2, 3, 4, 5, 6, 7 and 8;

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.

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

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.

Also disclosed is 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.

Also disclosed is a method of treatment of a patient suffering from pain developed as a consequence of surgery, or likely to suffer pain as a result of a surgical treatment, which comprises administering to the patient in need of such a treatment or prophylaxis a therapeutically effective amount of a sigma ligand as defined above.

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

BRIEF DESCRIPTION OF THE FIGURES

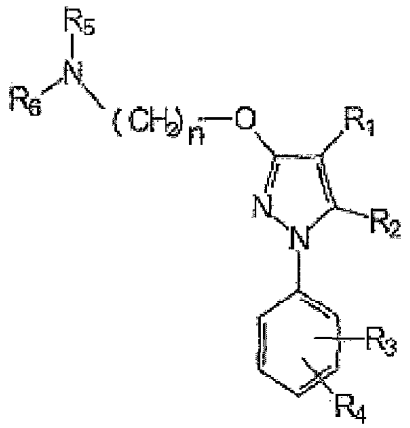
Figure 1: Treatment approach in mechanical allodynia. Results obtained with a known Sigma ligand (BD-1063) administered intraperitoneally 30 min before mechanical allodynia was assessed in the ipsilateral (operated) hindpaw of rats [0h: surgery; 3.5h: administration i.p. of the compound; 4h: mechanical 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)

CLAIMS

1. Use of a sigma ligand for the manufacture of a medicament for the prevention and/or treatment of pain developed as a consequence of surgery, wherein the sigma ligand has 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.

2. Use of a 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. Use of a 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. Use of a sigma ligand according to any of claims 1 to 3, wherein R_1 is selected from H, $-COR_8$ and substituted or unsubstituted alkyl.
5. Use of a sigma ligand according to any of claims 1 to 4, wherein R_2 is H or alkyl.
6. Use of a sigma ligand according to any of claims 1 to 5, wherein R_3 and R_4 together form a fused naphthyl ring system.
7. Use of a sigma ligand according to any of claims 1 to 6, wherein R_5 and R_6 together form a morpholine-4-yl group.
8. Use of a sigma ligand according to any of claims 1 to 7, 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.
9. Use of a sigma ligand according to any of claims 1 to 7, wherein the sigma ligand is 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine hydrochloride.