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

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

BRIEF DESCRIPTION OF THE INVENTION

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

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

R_5 and R_6 are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

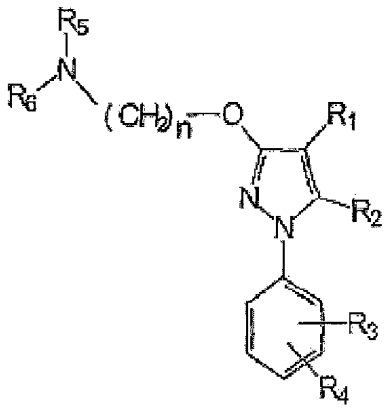
or together form, with the nitrogen atom to which they are attached, a substituted or unsubstituted, aromatic or non-aromatic heterocyclyl group;

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

t is 1,2 or 3;

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

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



(I)

wherein,

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

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

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

R_5 and R_6 are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, -CN, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

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

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

t is 1,2 or 3;

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

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

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

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

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE FIGURES

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

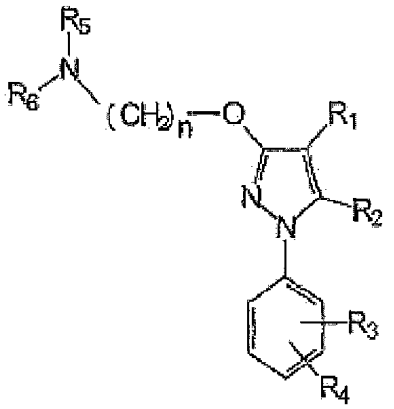
Figure 2: Potentiation of morphine analgesia (0.625 mg/kg) by compound 63 (10, 20, 40 and 80 mg/kg) in a thermal hyperalgesia rat model. n=10, #: $p < 0.05$; ns: $p > 0.05$ Dunnett, compound 63 + M vs. Morphine; **: $p < 0.01$; ***: $p > 0.001$ t-Student, compound 63 + M vs. compound 63.

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

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

CLAIMS

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



(I)

wherein,

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

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

or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

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

R_5 and R_6 are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

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

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

t is 1,2 or 3;

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

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

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

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

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

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

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

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

9. Use of a combination according to claim 1 wherein compound of formula I is selected from:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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