In the pathological course of type-2 diabetes often further complications may arise such as peripheral vascular disease, diabetic neuropathy, diabetic foot problems, diabetic retinopathy and nephropathy. At least some of these complications may cause light, moderate or severe pain symptoms which represent a big problem for the many patients suffering from this disease.

About one-half of patients suffering from type-2 diabetes evidence peripheral polyneuropathy (DPN). This chronic disease is not benign and patients with type-2 diabetes suffer from numerous microvascular and macrovascular complications which cause morbidity and mortality.

The consequences of sensory neuropathy include altered perception of thermal, tactile and vibratory stimuli, involving pain-related symptoms that range from hyperalgesia and allodynia to hypoalgesia [Vinik A. et al., Nature Clinical Practice Endocrinology & Metabolism, 2006, 2, 2-13].

In summary, DPN represents a diffuse symmetric and length-dependent injury to peripheral nerves that has major implications for quality of life (QOL), morbidity, and cost from a public health perspective [Boulton A.J. et al., Diabetes Care 2005, 28, 956–962; Gordois A. et al., Diabetes Care 2003, 26, 1790–1795]. DPN affects 16% of patients with diabetes; it is frequently unreported (12.5%) and more frequently untreated or inadequately treated (39%) [Daousi C. et al., Diabet. Med. 2004, 21, 976–982]. DPN presents an ongoing management problem for patients, caregivers, and physicians. Therefore, there is a need to find new ways for the treatment of type-2 diabetes-associated pain.

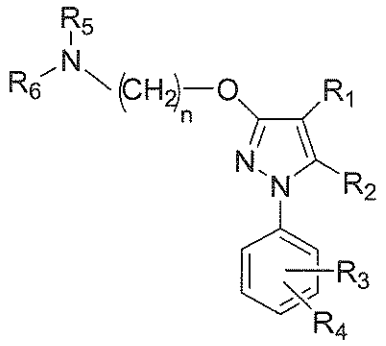
BRIEF DESCRIPTION OF THE INVENTION

The present invention solves the aforementioned need since it relates to the new use of compounds binding to the sigma receptor for the production of a medicament for the treatment and/or prevention of type-2 diabetes-associated pain as well as pain-related symptoms associated to type-2 diabetes, preferably type-2 diabetes-associated neuropathic pain.

Therefore, one aspect of the present invention relates to the use of a sigma ligand for the manufacture of a medicament for treatment and/or prevention of type-2 diabetes-associated pain, wherein the sigma ligand is 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine or a pharmaceutically acceptable salt thereof. Also disclosed is a sigma ligand for the use in the treatment and/or prevention of pain associated to type-2 diabetes and related symptoms. Preferably, said type-2 diabetes-associated pain derives from diabetic

neuropathy, diabetic retinopathy, diabetic amyotrophy, gastroparesis, diabetic diarrhea, charcot joint, neuropathy of the bladder, diabetic nephropathy and/or diabetic foot problems.

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



(I)

wherein

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

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

R_3 and R_4 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, -

NO_2, -N=CR_8R_9, and halogen, or together they form an optionally substituted fused ring system;

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

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

t is 1,2 or 3;

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

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

Also disclosed is~~Another aspect of this invention refers to~~ the use of a sigma ligand, preferably a sigma ligand of formula (I), or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, for the manufacture of a medicament for the treatment and/or prevention of type-2 diabetes-associated pain and related symptoms.

Also disclosed~~Another aspect of the invention~~ is a method for the treatment and/or prophylaxis of type-2 diabetes-associated pain and related symptoms, which comprises administering to the patient in need of such a treatment or prophylaxis a therapeutically effective amount of a sigma ligand, preferably a sigma ligand of formula (I), or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof.

Also disclosed is~~Another aspect of the invention refers to~~ a medicament or pharmaceutical composition comprising at least one sigma ligand and at least one pharmaceutically acceptable

excipient for use in the treatment and/or prevention of type-2 diabetes-associated pain and related symptoms.

Another aspect of the invention refers to the use of a combination of at least one sigma ligand as defined above and at least one further active substance for the manufacture of a medicament for the treatment and/or prevention of type-2 diabetes-associated pain, wherein the at least one further active substance is selected from the group consisting of oxycodone, tramadol, tapentadol, morphine, hydrocodone, codeine, buprenorfine, fentanyl, remifentanyl, sufentanyl, pregabalin, gabapentin, retigabine, duloxetine, amitriptyline, venlafaxine, ibuprofen, diclofenac, naproxen, aspirin, desketoprofen, ketoprofen, celecoxib, clonidine, ketamine and memantine. Also disclosed is a combination of at least one sigma ligand and at least one further active substance for use in the treatment and/or prevention of type-2 diabetes-associated signs and symptoms, including pain.

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

BRIEF DESCRIPTION OF THE FIGURES

Figure 1a: Effect of the acute treatment with example 1 on thermal hyperalgesia. Bars show the mean % ±SEM of modification of the thermal latency (plantar test).

Figure 1b: Effect of the acute treatment with example 1 on mechanical allodynia. Bars show the mean % ±SEM of modification of the threshold of response to mechanical stimulation (Von Frey test).

Figure 1c: Effect of the acute treatment with example 1 on spontaneous locomotor activity. Bars show the mean % ±SEM of modification of the total number of crosses (spontaneous motility).

Figure 2a: Effect of the chronic treatment with example 1 on thermal hyperalgesia. Bars show the mean % ±SEM of modification of the thermal latency (plantar test).

Figure 2b: Effect of the chronic treatment with example 1 on mechanical allodynia. Bars show the mean % ±SEM of modification of the threshold of response to mechanical stimulation (Von Frey test).

Figure 2c: Effect of the chronic treatment with example 1 on spontaneous locomotor activity Bars show the mean % ±SEM of modification of the total number of crosses (spontaneous motility).

Figure 3a: Effect of the chronic treatment with example 1 on mechanical stimulation of increasing force (Electromechanical threshold; Ramp).

The term "further active substance" refers to any active substance or active pharmaceutical ingredient (API) other than a sigma ligand. According to a preferred embodiment, the "further active substance" is selected from:

- Opioids: more preferably oxycodone, tramadol, tapentadol, morphine, hydrocodone, codeine, buprenorfine, fentanyl, remifentanyl or sufentanyl; even more preferably oxycodone, tramadol, tapentadol, morphine or hydrocodone;
- Anti-epileptics: more preferably pregabalin, gabapentin or retigabine;
- Antidepressants: more preferably duloxetine, amitriptyline or venlafaxine;
- Conventional analgesics: more preferably ibuprofen, diclofenac, naproxen, aspirin, desketoprofen or ketoprofen;
- Selective COX-2 inhibitors: more preferably celecoxib;
- α_2-adrenergics: more preferably clonidine; and/or
- NMDA inhibitors: more preferably ketamine or memantine.

Another aspect of the invention is a method of treatment of a patient, notably a human, suffering type-2 diabetes-associated pain, or likely to suffer pain as a result of type-2 diabetes, 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.

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

Examples

1. MATERIALS AND METHODS

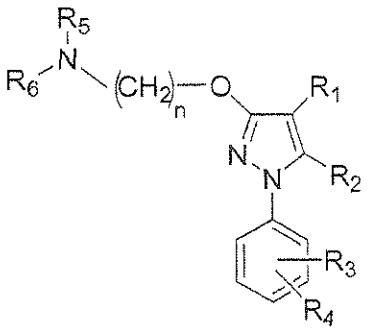
1.1. Drugs

The example 1 was dissolved in physiological saline (0.9%) and pH was corrected to 5 with NaOH. The compound was administered by the intraperitoneal (i.p.) route. The doses of drug employed in the present study were 64 mg/kg i.p. for acute administration and 25 mg/kg i.p. twice a day (BID) for the chronic treatment during 14 days. The compound and the saline (vehicle) adjusted at pH 5, were administered in a volume of 0.5 ml.

1.2. Animals

CLAIMS

1. Use of a sigma ligand for the manufacture of a medicament for treatment and/or prevention of type-2 diabetes-associated pain,
wherein the sigma ligand has the general formula (I):



(I)

wherein

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

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

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

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

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

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

t is 1,2 or 3;

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

wherein the substituted groups are substituted at one or more available positions by one or more groups selected from the group consisting of halogen; cyano; hydroxyl; nitro; azido; acyl; carboxamido; alkyl; alkenyl; alkynyl; alkoxy; aryloxy; alkylthio; alkylsulfinyl; alkylsulfonyl; aminoalkyl; carbocyclic aryl and aralkyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. Use of a sigma ligand according to claim 1, wherein the type-2 diabetes-associated pain is derived from diabetic neuropathy, diabetic retinopathy, diabetic amyotrophy, gastroparesis, diabetic diarrhea, charcot joint, neuropathy of the bladder, diabetic nephropathy and/or diabetic foot problems.

3. Use of a sigma ligand according to any of claims 1 or 2, which is selected from a sigma receptor antagonist preferably selected from a neutral antagonist, an inverse agonist and 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 claim 1, which is selected from the group consisting of:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[45] 2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]-N,N-diethylethanamine

[46] 1-(3,4-Dichlorophenyl)-4,5-dimethyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole

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

[48] 1-{2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]ethyl}piperidine

[49] 4-{4-[1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}morpholine

[50] (2S,6R)-4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}-2,6-dimethyl morpholine

[51] 1-{4-[1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}piperidine

[52] 1-(3,4-Dichlorophenyl)-3-[4-(pyrrolidin-1-yl)butoxy]-1H-pyrazole

[53] 4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N,N-diethylbutan-1-amine

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

[55] 4-[1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yloxy]-N-(2-methoxyethyl)-N-methylbutan-1-amine

[56] 4-{4-[1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}thiomorpholine

[57] 1-[1-(3,4-Dichlorophenyl)-5-methyl-3-(2-morpholinoethoxy)-1H-pyrazol-4-yl] ethanone

[58] 1-{1-(3,4-Dichlorophenyl)-5-methyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazol-4-yl} ethanone

[59] 1-{1-(3,4-Dichlorophenyl)-5-methyl-3-[2-(piperidin-1-yl)ethoxy]-1H-pyrazol-4-yl} ethanone

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

[61] 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine

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

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

[64] 5-Methyl-1-(naphthalen-2-yl)-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole

or a pharmaceutically acceptable salt or solvate thereof.

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

10. Use of a sigma ligand according to claim 9, which is 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine hydrochloride.

11. Use of a combination of at least one sigma ligand as defined in any of claims 1 to 10 and at least one further active substance for the manufacture of a medicament for the treatment and/or prevention of type-2 diabetes-associated pain, wherein the at least one further active substance is selected from the group consisting of oxycodone, tramadol, tapentadol, morphine, hydrocodone, codeine, buprenorfine, fentanyl, remifentanyl, sufentanyl, pregabalin, gabapentin, retigabine, duloxetine,

amitriptyline, venlafaxine, ibuprofen, diclofenac, naproxen, aspirin, desketoprofen, ketoprofen, celecoxib, clonidine, ketamine and memantine.

CLAIMS

1. Use of a sigma ligand for the manufacture of a medicament for treatment and/or prevention of type-2 diabetes-associated pain,
   wherein the sigma ligand is 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine or a pharmaceutically acceptable salt thereof.

2. Use of a sigma ligand according to claim 1, wherein the type-2 diabetes-associated pain is derived from diabetic neuropathy, diabetic retinopathy, diabetic amyotrophy, gastroparesis, diabetic diarrhea, charcot joint, neuropathy of the bladder, diabetic nephropathy and/or diabetic foot problems.

3. Use of a sigma ligand according to any of claims 1 or 2 , which is 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine hydrochloride.

4. Use of a combination of at least one sigma ligand as defined in any of claims 1 to 3 and at least one further active substance for the manufacture of a medicament for the treatment and/or prevention of type-2 diabetes-associated pain, wherein the at least one further active substance is selected from the group consisting of oxycodone, tramadol, tapentadol, morphine, hydrocodone, codeine, buprenorfine, fentanyl, remifentanyl, sufentanyl, pregabalin, gabapentin, retigabine, duloxetine, amitriptyline, venlafaxine, ibuprofen, diclofenac, naproxen, aspirin, desketoprofen, ketoprofen, celecoxib, clonidine, ketamine and memantine.