USE OF SIGMA LIGANDS IN DIABETES TYPE-2 ASSOCIATED PAIN

FIELD OF THE INVENTION

The present invention refers to the use of compounds binding to the sigma receptor for the production of a medicament for the prevention and/or treatment of pain and pain-related symptoms associated to diabetes type-2.

BACKGROUND

Diabetes is a metabolic disorder caused by interaction of genetic, environmental, immunological, as well as life-style factors. The World Health Organization estimates that 366 million people worldwide will suffer from diabetes by year 2030 [Wild S. et al., Diabetes Care 2004, 27, 1047-1053].

According to the American Diabetes Association (ADA; http://www.diabetes.org/home.jsp) four major categories of diabetes have been identified including:

- Type 1 diabetes mellitus: The body's fails to produce insulin.
- Type 2 diabetes mellitus: Results from insulin resistance, combined with relative insulin deficiency.
- Gestational diabetes: Occurs during pregnancy.
- Impaired glucose tolerance (i.e. prediabetes): When a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 diabetes.

Diabetic neuropathy comprises a number of conditions affecting peripheral nerves. It is the most common of the long-term diabetic complications. In fact, diabetic neuropathy is now the most common neuropathy in industrialized countries and may be the most common in the world. The prevalence of sensory neuropathic symptoms, particularly pain, is about 30% among patients with diabetes. Moreover, the prevalence of diabetic neuropathy increases with age, from about 5% in patients between the ages of 20 and 29 to approximately 44% in those between the ages of 70 and 79, and with duration of disease, particularly after 20 years. Prevalence is also higher in patients with poor

glycemic control. The most prominent manifestations of diabetic neuropathy are pain and trophic ulcers (e.g., diabetic foot ulcers), both of which are associated with considerable morbidity and disability [Said G. Advanced Studies in Medicine 2001, 1 (11), 457-459].

Peripheral neuropathy can result in a loss of sensation that can lead to neuropathic ulcers, and this is a leading cause of amputation [Poncelet A.N., Geriatrics. 2003, 58(6), 16-8, 24-5, 30; Vileikyte L. Diabetes Metab. Res. Rev. 2004, 20 Suppl 1, S13-18].

Diabetic peripheral neuropathy (DPN, also called distal symmetric neuropathy or sensorimotor neuropathy or diabetic polyneuropathy) is one of the most common complications of both type 1 and type 2 diabetes. In a population-based study [Abbott C.A. et al., Diabet. Med. 2002, 19: 377–384], 22% of the diabetic cohort had peripheral neuropathy that was graded as either moderate or severe. Long-standing peripheral neuropathic pain associated with peripheral neuropathy occurs in one of six diabetic subjects [Daousi C. et al., Diabet. Med. 2004, 21, 976-982].

Most preclinical studies evaluating treatment options for DPN have been carried out in streptozotocin-induced diabetic rodents, which resemble type-1 diabetes. However there is evidence that the etiology and pathology of diabetic neuropathy in type-1 and type-2 diabetes may be different [Sima A.A., Front. Biosci. 2008, 13, 4809-4816].

Research using type-2 diabetic animal models has also been carried out, but less frequently than type-1 [Sima A.A. et al., Diabetología 2000, 43, 786-793; Li F. et al., Neurobiol. Dis. 2006, 22, 669-676; Oltman C.L. et al., Am. J. Physiol. Endocrinol. Metabol. 2005, 289, E113-E122].

Zucker diabetic fatty (ZDF) rat was first described by Shaw et al. [Proc. Soc. Exp. Biol. Med. 1983, 173(1), 68-75] and Friedman et al. [Am. J. Physiol. 1991, 261(6 Pt 1), E782-E788]. Male obese ZDF (fa/fa or ZDF7Drt-fa; Charles River) are homozygous for a missense mutation causing a nonfunctional leptin receptor (fa/fa). ZDF rats develop obesity, initial hyperinsulinemia (insulin resistance) and then overt diabetes at 8-10 weeks of age [Cheng D. et al., Diabetes Obes. Metab. 2005, 7, 307-317]. Several papers have described neurological abnormalities, including slowed conduction velocity and alterations in sensory testing [Li F. et al., Neurobiol. Dis. 2006, 22, 669-676; Oltman C.L. et al., Diabetes Obes. Metab. 2008, 10, 64-74 among others].

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.

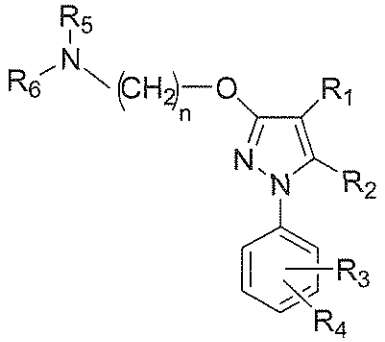
BRIEF DESCRIPTION OF THE INVENTION

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 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 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 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 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).

Figure 3b: Effect of the chronic treatment with example 1 on mechanical stimulation using repeated stimulus (steps) applying innocuous force (Constant suprathreshold pressure; Step)

Figure 3c: Effect of the chronic treatment with example 1 on mechanical stimulation using repeated stimulus (steps) applying nocive force (Constant supramaximal pressure; Nocive Step).

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. Alkenyl 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 oxidized; 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 having one or more (e.g., 1, 2, 3 or 4) oxygen linkages and from 1 to about 12 carbon atoms or preferably 1 to about 6 carbon atoms, e. g., methoxy, ethoxy, propoxy, etc.

"Aryloxy" refers to a radical of formula –O-aryl, where aryl is as previously defined. Some examples of aryloxy compounds are –O-phenyl, –O-p-tolyl, -O-m-tolyl, -O-o-tolyl or –O-naphtyl.

"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 (e.g., 1, 2, 3 or 4)

available positions by one or more suitable groups, e. g., halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; acyl, such as alkanoyl, e.g. a C_{1-6} alkanoyl group, 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 (e.g., 1, 2, 3 or 4) unsaturated linkages and from 2 to about 12 carbon or from 2 to about 6 carbon atoms; alkoxy groups having one or more (e.g., 1, 2, 3 or 4) 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 (e.g., 1, 2, 3 or 4) 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 (e.g., 1, 2, 3 or 4) 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 (e.g., 1, 2, 3 or 4) 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 (e.g., 1, 2, 3 or 4) 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 compounds of the present invention are preferably in neutral form, the form of a base or acid, in the form of a salt, preferably a physiologically acceptable salt, in the form of a solvate or of a polymorph and/or in the form of in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, and/or in any mixing ratio.

The term "salt" is to be understood as meaning any form of the active compound according to the invention in which this assumes an ionic form or is charged and is coupled with a counter-ion (a cation or anion) or is in solution. By this are also to be understood complexes of the active compound with other molecules and ions, in particular complexes which are complexed via ionic interactions. The definition includes in particular physiologically acceptable salts; this term must be understood as equivalent to "pharmacologically acceptable salts" or "pharmaceutically acceptable salts".

The term "physiologically acceptable salt" or "pharmaceutically acceptable salt" is understood in particular, in the context of this invention, as salt (as defined above) formed either with a physiologically tolerated acid, that is to say salts of the particular active compound with inorganic or organic acids which are physiologically tolerated - especially if used on humans and/or mammals - or with at least one, preferably inorganic, cation which are physiologically tolerated - especially if used on humans and/or mammals. Examples of physiologically tolerated salts of particular acids are salts of: hydrochloric acid, hydrobromic acid, sulfuric acid, hydrobromide, monohydrobromide, monohydrochloride or hydrochloride, methiodide, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, hippuric acid picric acid and/or aspartic acid. Examples of physiologically tolerated salts of particular bases are salts of alkali metals and alkaline earth metals and with NH_4.

The term "solvate" according to this invention is to be understood as meaning any form of the active compound according to the invention in which this compound has attached to it via non-covalent binding another molecule (most likely a polar solvent) especially including hydrates and alcoholates, e.g. methanolate.

Any compound that is a prodrug of a sigma ligand, in particular a prodrug of a compound of formula (I) is also within the scope of the invention. The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted in vivo to the compounds of the invention. Examples of prodrugs include, but are not limited to derivatives 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), "Design and Applications of Prodrugs" (H. Bundgaard ed., 1985, Harwood Academic Publishers) and Krogsgaard-Larsen et al. "Textbook of Drug design and Discovery" Taylor & Francis (April 2002).

The compounds of the present invention represented by the above described formula (I) may include enantiomers depending on the presence of chiral centres or isomers

depending on the presence of multiple bonds (e.g. Z, E). The single isomers, enantiomers or diastereoisomers and mixtures thereof fall 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 formula (I) or their salts or solvates, are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. Purity levels for the drug substance are preferably above 50%, more preferably above 70%, most preferably above 90%. In a preferred embodiment it is above 95% of the compound of formula (I), or of its salts, solvates or prodrugs.

As noted previously, the term "pharmaceutically acceptable salts, solvates, prodrugs" refers to any salt, solvate, or any other compound which, upon administration to the recipient is capable of providing (directly or indirectly) a compound as described herein. However, it will be appreciated that non-pharmaceutically acceptable salts, solvates and prodrugs also fall within the scope of the invention since those may be useful in the preparation of pharmaceutically acceptable salts, solvates and prodrugs. The preparation of salts, solvates and prodrugs can be carried out by methods known in the art.

As used herein, the terms "treat", "treating" and "treatment" include in general the eradication, removal, reversion, alleviation, modification, or control of pain and pain-related symptoms associated to diabetes type-2.

As used herein, the terms "prevention", "preventing", "preventive", "prevent" and prophylaxis refer to the capacity of a given substance to avoid, minimize or difficult the onset or development of a pain and pain-related symptoms associated to diabetes type-2 before its onset.

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]. Even though pain is always subjective its causes or syndromes can be classified.

The term "pain" as used in the present invention refers to type-2 diabetes-associated pain.

"Type-2 diabetes-associated pain", as defined in the present invention, preferably includes any form and type of pain/pain syndromes which are related to diabetes type-2. 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 optionally diabetic foot problems.

The term "derived from", as defined in the present invention, has the same meaning as the terms "caused by" and/or "associated with", thereby referring to the consequences of the pathological process/es of diabetes which result in pain.

In a preferred embodiment of the invention said diabetic neuropathy preferably comprises autonomic neuropathy, sensorimotor neuropathy, distal symmetric sensorimotor neuropathy, focal and multifocal neuropathies and/or sensorimotor polyneuropathy.

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]. Even though allodynia is commonly recognized as a symptom of neuropathic pain, this is not always necessarily the case so that allodynia not connected to neuropathic pain can occur, though rendering allodynia in some areas broader than neuropathic pain.

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

In a preferred embodiment of the invention said type-2 diabetes-associated pain is allodynia. According to one more particular embodiment, said allodynia is mechanical allodynia. According to another more particular embodiment, said allodynia is thermal allodynia.

In another preferred embodiment of the invention said type-2 diabetes-associated pain is hyperalgesia. According to one more particular embodiment, said hyperalgesia is mechanical hyperalgesia. According to another more particular embodiment, said hyperalgesia is thermal hyperalgesia.

In another preferred embodiment of the invention said type-2 diabetes-associated pain is hyperpathia.

According to the IASP "neuropathy" is defined as "a primary lesion or dysfunction in the nervous system" [IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 211]. Neuropathic pain may have central or peripheral origin.

In a preferred embodiment of the present invention said type-2 diabetes-associated pain is derived from neuropathy. According to one more particular embodiment, said type-2 diabetes-associated pain is derived from peripheral neuropathy. According to another more particular embodiment, said type-2 diabetes-associated pain is derived from central neuropathy.

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].

In a preferred embodiment of the invention said type-2 diabetes-associated pain derives from neuritis.

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].

In a preferred embodiment of the invention said type-2 diabetes-associated pain is identified as neuralgia.

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

In a preferred aspect of the present invention said type-2 diabetes-associated pain is identified as causalgia.

As used herein, the terms "sigma ligand" or "sigma receptor ligand" refer to any compound binding to the sigma receptor.

Said compounds binding to the sigma receptor as defined herein, may be antagonists, inverse agonists, agonists, partial antagonists and/or partial agonists.

The sigma ligand according to the present invention is preferably a sigma receptor antagonist in the form of a (neutral) antagonist, an inverse agonist or a partial antagonist.

In a highly preferred embodiment of the present invention said compounds bind to the sigma-1 receptor.

In a possible embodiment of the present invention the compound binding to the sigma receptor as defined herein is acting on the sigma receptor as a mixed agonist/antagonist.

In another embodiment of the invention the compound binding to the sigma receptor as defined herein is acting on the sigma receptor as an antagonist.

In another embodiment of the invention the compound binding to the sigma receptor as defined herein is acting on the sigma receptor-1 as an antagonist.

In another embodiment of the invention the compound binding to the sigma receptor as defined herein is acting on the sigma receptor as an inverse agonist.

In another embodiment of the invention the compound binding to the sigma receptor as defined herein is acting on the sigma receptor as a partial antagonist.

In another possible embodiment of the invention the compound binding to the sigma receptor as defined herein is acting on the sigma receptor as an agonist.

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.

A "partial agonist" is defined as a compound which possesses affinity for a receptor, but unlike a full agonist, will elicit only a small degree of the pharmacological response peculiar to the nature of the receptor involved, even if a high proportion of receptors are occupied by the compound.

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., signaling 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. 2001, 73, 1499-1509]. Pharmacological data based on ligand binding studies, anatomical distribution and biochemical features distinguish at least two subtypes of sigma (σ) receptors [R. Quiron et al., Trends Pharmacol. Sci. 1992, 13, 85-86; M.L.Leitner, Eur. J. Pharmacol. 1994, 259, 65-69; S.B. Hellewell and W.D. Bowen; Brain Res., 1990, 527, 244-253; G. Ronsisvalle et al. Pure Appl. Chem. 2001, 73, 1499-1509]. The protein sequence of the sigma 1 receptor (σ1) is known in the art [e.g. Prasad, P.D. et al., J. Neurochem. 1998, 70, 443-451]. They show a very high affinity to various analgesics (e.g. pentazocine).

"Compound/s binding to the sigma receptor" or "sigma ligand/s" 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. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function. The IC_{50} is the concentration of competing ligand which displaces 50% of the specific binding of the radioligand. 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 [3H]-(+) 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 treatment of pain associated to diabetes type-2.

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 Drug design 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 unsubstituted, aromatic or non-aromatic heterocyclyl group may be fused to phenyl group), 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, 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 additional preferred embodiments, the preferences described above for the different substituents are combined. The present invention is also directed to such combinations of preferred substitutions in the formula (I) above.

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

[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 their pharmaceutically acceptable salts, isomers, prodrugs or solvates.

In a preferred embodiment 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 n° 61.

In a more preferred embodiment, the sigma ligand of formula (I) is the 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine hydrochloride. This particular compound is designated in the examples of the present invention as example n° 1.

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

As stated previously, one aspect of this invention refers to the use of a sigma ligand as defined above for the manufacture of a medicament for the treatment and/or prevention of pain associated to type-2 diabetes.

A further aspect of the present invention relates to a medicament or composition in different pharmaceutical forms comprising at least a compound binding to the sigma receptor (preferably a compound of formula (I)), optionally at least one further active substance and at least one pharmaceutically acceptable excipient for use in the treatment and/or prevention of pain associated to type-2 diabetes.

Preferably, the medicament is suitable for oral or parenteral administration, more preferably for oral, intravenous, intraperitoneal, intramuscular, subcutaneous, intrathekal, rectal, transdermal, transmucosal or nasal administration.

Medicaments for oral administration are preferably selected from the group consisting of tablets, drageés, capsules, powders, drops, gels, juices, sirups, solutions and suspensions.

The medicament of the present invention for oral administration may also be in the form of multiparticulates, preferably microparticles, microtablets, pellets or granules,

optionally compressed into a tablet, filled into a capsule or suspended in a suitable liquid. Suitable liquids are known to those skilled in the art.

The respective medicament may - depending on its route of administration - also contain one or more excipients known to those skilled in the art. The medicament according to the present invention may be produced according to standard procedures known to those skilled in the art.

The term "excipient" refers to components of a drug compound other than the active ingredient (definition obtained from the European Medicines Agency- EMA). They preferably include a "carrier, adjuvant and/or vehicle". Carriers are forms to which substances are incorporated to improve the delivery and the effectiveness of drugs. Drug carriers are used in drug-delivery systems such as the controlled-release technology to prolong *in vivo* drug actions, decrease drug metabolism, and reduce drug toxicity. Carriers are also used in designs to increase the effectiveness of drug delivery to the target sites of pharmacological actions (*U.S. National Library of Medicine. National Institutes of Health*). Adjuvant is a substance added to a drug product formulation that affects the action of the active ingredient in a predictable way. Vehicle is an excipient or a substance, preferably without therapeutic action, used as a medium to give bulk for the administration of medicines (Stedman's Medical Spellchecker, © 2006 Lippincott Williams & Wilkins). Such pharmaceutical carriers, adjuvants or vehicles can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like, excipients, disgregants, wetting agents or diluents. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. The selection of these excipients and the amounts to be used will depend on the form of application of the pharmaceutical composition.

The daily dosage for humans and animals may vary depending on factors that have their basis in the respective species or other factors, such as age, sex, weight or degree of illness and so forth. The daily dosage for humans may preferably be in the range from 1 to 2000, preferably 1 to 1500, more preferably 1 to 1000 milligrams of active substance to be administered during one or several intakes per day.

The invention also provides a combination of at least one sigma ligand as defined above 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.

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.

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

All experimental protocols were performed in strict accordance with the EC regulation for care and use of experimental animals (86/609/EEC). Studies were performed with male ZDF (Zucker Diabetic Fatty) rats (ZDF/Gmi, fa/fa) obtained from Charles Rivers Genetic Models Inc. 6 week old rats were housed in groups of two in standard transparent cages, under a 12 light-dark cycle, and animals were maintained on Purina 5008 (16.7 kcal% fat) diet and sterile tap water, available *ad libitum*. Nonfasting blood glucose levels and body weight were regularly monitored.

2. TREATMENTS

2.1. Acute treatments

Acute example 1: animals received one injection (0.5 ml) of example 1 (64 mg/kg i.p.) 30 minutes before behavioral testing (n = 8).

Control: animals received one vehicle injection (0.5 ml) (0.001% acetic acid solution diluted in physiological saline) 30 minutes before behavioral testing (n = 8).

2.2. Chronic treatments

Chronic example 1: animals received one injection (0.5 ml) of example 1 (25 mg/kg BID, for 14 days) (n = 8). Behavioral tests were performed once a week during the treatment, and one week after the last administration they were sacrificed and electrophysiological and cardiovascular experiments were carried out.

Chronic vehicle: animals receiving a vehicle injection (0.5 ml i.p. BID for 14 days) (n = 8). Behavioral tests were performed once a week during the treatment, and after the last in vivo determination animal were sacrificed and electrophysiological and cardiovascular experiments were carried on.

3. PROCEDURES

3.1. Behavioral tests

Plantar test: Thermal (heat) hyperalgesia (heat-nociception) was tested using a 37370 plantar test apparatus (Ugo Basile, Comerio VA, Italy). The withdrawal latency from a focused beam of radiant heat applied to the mid plantar surface of the hindpaws was recorded. The intensity of light was adjusted at the start of the experiment such that the control average baseline latencies were about 8 s and a cut-off latency of 30 s was imposed. The withdrawal latency of each paw was measured and the mean value was

used for data analysis. The antihyperalgesic effect of the treatment was evidenced as an increase in the withdrawal latency respect to control baseline latencies.

Von Frey test: Mechanical allodynia was assessed using an electronic Von Frey apparatus (EVF3, Bioseb, BP89, Chaville Cedez, France). Rats were placed individually on an elevated iron mesh floor, covered by a transparent plastic cage and were allowed to adapt to the testing environment for at least 15 minutes. The test was done by applying the von Frey filament through the mesh floor to the plantar surface of each hindpaw.

The test was performed three times with approximately 3 min interval between trials. The mean of the three trials was used for data analysis. Mechanical allodynia was defined as a significant decrease in the pressure threshold evoking withdrawal of the hindpaw mechanically stimulated. The upper cut-off limit was 50 g.

Spontaneous locomotor activity: it was evaluated using individual photocell activity chambers (Cibertec, Spain). Rats were placed in the recording chambers (55x40 cm, spacing between beams 3 cm) 50 min after drug administration, and the number of interruptions of photocell beams was recorded over a 30-min period.

3.2 Skin – nerve preparation and electrophysiological recordings

In order to minimize pain or discomfort, animals were killed by cervical dislocation. The saphenous nerve and its innervating territory on the hairy hindpaw skin were subcutaneously dissected and excised. The skin was pinned, corium-side up, in an organ bath, and superfused (16 ml/min) with synthetic interstitial fluid (SIF) [(in mM): 108, NaCl; 3.5, KCl; 0.7, $MgSO_4$; 26, $NaHCO_3$; 1.7, NaH_2PO_4; 1.5, $CaCl_2$; 9.6, sodium gluconate; 5.5, glucose; 7.6, sucrose)], which was saturated with carbogen (95% O_2-5% CO_2), maintained at a temperature of 32±0.5 °C and a pH of 7.38. The saphenous nerve was drawn through a hole into a recording chamber, placed on a small mirror and covered with a layer of paraffin oil. Neuronal activity was recorded using gold-wire electrodes. Small filaments of the nerve were repeatedly split with sharpened forceps until a single unit activity could be recorded from them. The evoked action potentials were amplified, filtered, and led to an oscilloscope and audiomonitor and sent to a PC, through an analog-digital converter, where they were sampled online via a data acquisition system (Microstar DAP 3000a board and SPIKE/SPIDI software package (C. Forster, University of Erlangen- Nurnberg, Germany)). Spikes were later analyzed offline using the SPIDI software.

Units were first identified by manual probing of the skin with a blunt glass rod that exerts a pressure of more than 500 mN to search for their receptive field (RF). Only units responding to this stimulus were then studied in detail. In order to characterize the units, we assessed their conduction velocity (CV) by electrically stimulating the RF with supramaximal square-wave pulses (pulse width, 0.5 ms; train frequency, 0.2 Hz; variable intensity) with a Teflon-coated steel microneurography electrode (shaft diameter 1 mm, bare tip diameter 5-10 µm impedance 1-5 MΩ); an indifferent electrode was placed nearby in the organ bath. The CV of a unit was estimated using the distance and conduction delay between the recording and stimulating electrodes placed on the receptive field.

Once a single unit was identified, it was left to a control period of 1 min in order to record spontaneous activity, defined as a discharge rate ≥ 1 spike/min and then, mechanical stimulation was applied with a stimulator with plastic cylindrical probe (flat tip; diameter: 1 mm, Cibertec®) that was perpendicularly placed with a micromanipulator on the most sensitive spot of the skinny RF of the unit. Each stimulus began with an adaptation period of 3 s in which the probe of the stimulator was touching the skin but not delivered any pressure.

After the offset of any stimuli, the probe was lifted off the tissue and in order to avoid fibers' damage (desensitization) time interval between two consecutive stimuli along the protocol was 5 min. The stimulation protocol was as follows:

First, the electromechanical threshold of the units, defined as the pressure that evoked the first spike that was followed by another spike within the next 8 mN increment (modified from: Suzuki et al., Neurosci. Res. 2002, 43, 171-178), was determined by application of a ramp-pressure stimulation (constantly increasing stimulus from 0 to 200 mN [Schlegel T. et al., Neurosci. Lett. 2004, 361, 163-167] with a speed of 8 mN/s). For units that showed spontaneous discharges during the 30 s preceding the ramp force stimulus onset, the mean discharge rate in those 30 s was calculated (basal activity, impulses/s (imp/s)) and the threshold was determined as the lowest force at which the instantaneous frequency of spikes continuously exceeded the mean basal activity +SD.

Second, 8 stimuli of constant suprathreshold pressure (~threshold+40 mN, step-pressure stimulation) were delivered for 5 s.

Finally, to explore the thermal sensitivity of the units, when the mechanical stimulation protocol was finished, the response to cold (~11 °C) and noxious heat (~52 °C) were

checked by bolus application of a 1 ml of SIF solution at icecold and heat temperatures to the receptive field which was isolated by a selfsealing metal ring (1 cm diameter) and the bath solution inside the ring was removed with a syringe. The temperature reached within the ring was measured with a thermocouple gently placed inside and almost touching the skin. A true cold or heat discharges were scored when the unit discharged at least three action potentials during the application and control applications of fluid at 32 °C did not evoke a discharge. The responses to cold and heat stimuli are only qualitatively reported. The interval between the cold and heat applications was of 5 min.

This study is focused only on those mechanically sensitive afferents units who's CVs were in the myelinated Aδ-fiber range. In agreement with other studies in the rat, units conducting from 2.5 to 24.0 m/s were considered as Aδ. None of the fibers presented a CV>13.5 m/s, that has been considered the limit to distinguish between Aδ- and Aβ-fibers.

To analyze the mechanical response to the step-pressure stimulation and in order to avoid pressure fluctuations, the spikes elicited by the first and last seconds of each stimulus were not included in the total spike counting.

4. DATA AND STATISTICAL ANALYSIS

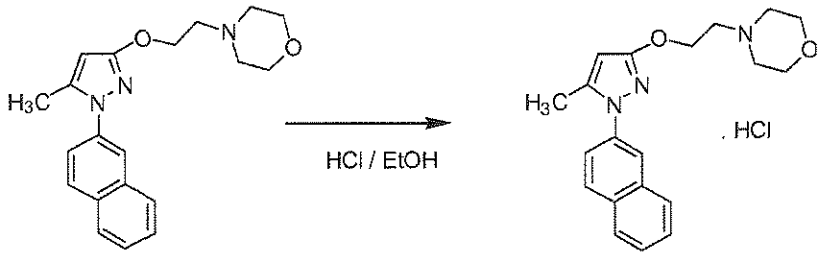
Plantar test results are expressed as the percentage of the mean of thermal latency obtained from both hindpaws.

Von Frey test results are expressed as the percentage of the mean of mechanical threshold obtained from both hindpaws.

Spontaneous locomotor activity is expressed as the percentage of the mean number of crossings of the photocell beams over 30 minutes.

Data are expresses as mean + standard error mean (SEM). Statistical analysis of drug effects for significant differences between multiple groups were performed by analysis of variance (ANOVA), followed, when appropriate, by post-hoc Newman-Keuls test or Bonferroni Test. $P < 0.05$ was considered as statistically significant.

Example 1. Synthesis of 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine (compound 61) and its hydrochloride salt



Compound 61 **Compound 61·HCl**

Compound 61 can be can be prepared as disclosed in the previous application WO2006/021462. Its hydrochloride can be obtained according the following procedure:

Compound 61 (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. Effect of the acute treatment with Example 1 on nociception and motility (Figure 1)

Nociception and motility of ZDF rats aged 7 weeks (before neuropathy), 13 weeks (after neuropathy was developed) and the effect induced by one i.p. administration of example 1 (64 mg/kg) or vehicle are shown in Figures 1a-1c. Control values are normalized (control groups = 100) in order to simplify the comparison. Statistical differences have been calculated using Bonferroni's Multiple Comparison Test post-two way ANOVA and are labeled as follows: * vs. corresponding group of week 7; # vs. corresponding group of week 13; + vs. vehicle (week 13).

ZDF rats showed mean blood glucose concentration (mg/dL) on week 7 of 91.8± 8.6 for the group of rats assigned to receive treatment with example 1 and of 84.4±7 for those assigned to be treated with the vehicle. Six weeks later (week 13) glucose levels were already significantly higher in both groups 414.3±46.2% and 412.9±18.9%, respectively.

The ZDF rats developed significant thermal hyperalgesia (Figure 1a) and mechanical allodynia (Figure 1b) by the 13th week and acute i.p. treatment with example 1 at 64 mg/kg restored baseline values found at the 7th week (before the development of type-2 diabetes and thus type-2 diabetic neuropathy and pain).

Example 1 at dose of 64 mg/kg i.p. administered 30 minutes before tests in ZDF rats *significantly increased the latency to hindpaw withdrawal (i.e., reversed thermal* hyperalgesia) in response to thermal stimulation: 25.5±9.1% for Example 1-treated compared to 12.6±6.9% for vehicle-treated animals (Figure 1a).

With respect to mechanical allodynia, the pressure threshold evoking withdrawal response was reduced in ZDF rats aged 13 weeks (29.2 ±3.1% reduction in the group assigned to be treated with vehicle and 26.1±4.5 reduction in the group assigned to be treated with Example 1) when compared with values recorded in rats aged 7 weeks. The threshold was significantly increased (i.e., the mechanical allodynia was reversed) by treatment with compound example 1, returning to basal values found by week 7 (Figure 1b).

The spontaneous locomotor activity was not significantly different in none of the analyzed groups (Figure 1c).

Example 3. Effect of the chronic treatment with example 1 on nociception and motility (Figure 2)

Nociception and motility of ZDF rats aged 7 weeks (before neuropathy), 13 weeks (after neuropathy was developed) and the effect induced by i.p. administration of example 1 (25 mg/kg) or vehicle twice a day during 14 days (week 13 to 15) are shown in Figures 2a-2c. Control values are normalized (control groups = 100) in order to simplify the comparison. Statistical differences have been calculated using Bonferroni's Multiple Comparison Test post-two way ANOVA and are labeled as follows: * vs.

corresponding group of week 7; # vs. corresponding group of week 13; + vs. vehicle (week 13).

The compound example 1 (25 mg/kg i.p, BID) was administered for 14 days and the effect of this treatment on nociception and on spontaneous motility was 14 days after the first injection. Treatment began on week 13, when neuropathy was already developed.

After 14 days of example 1 administration, thermal hyperalgesia (Figure 2a) and mechanical allodynia (Figure 2b) were completely reversed and the recorded values were similar to those obtained before neuropathy was developed (7 weeks of age).

There were no differences in spontaneous locomotor activity between pretreatment values and those recorded on example 1 or vehicle-treated groups (Figure 2c).

Example 4. Effect of the chronic treatment with example 1 on peripheral electrophysiological recordings (Figure 3)

The effect of the chronic treatment with example 1 on the electrophysiological response of nociceptors is shown in Figures 3a-3c. Tissues were obtained from Wistar rats (non-diabetic rats) and from ZDF rats after i.p. administration of example 1 (25 mg/kg) or vehicle BID for 14 days. Statistical differences are calculated using Bonferroni's Multiple Comparison Test post-two way ANOVA and are labeled as + for example 1 vs. vehicle.

In the vehicle-treated group of ZDF rats there was a significant increase of the peripheral electrophysiological response to mechanical stimulation as seen in all stimulation protocols (Figures 3a-3c) when compared with responses recorded in control Wistar (non-diabetic) rats.

Example 1 administered at 25 mg/kg i.p, BID, for 14 days to ZDF rats reduced the threshold of response to the mechanical stimulation and increased the electrophysiological response (total number of spikes) evoked by mechanical stimulation in comparison with vehicle-treated ZDF rats (Figures 3a to 3c).

From the above experimental data it can be concluded that:

a) The ZDF rats developed mechanical allodynia and thermal hyperalgesia, these modifications are considered reliable signs of peripheral neuropathy.

b) The single administration of the example 1 (64 mg/kg, i.p.) reversed the changes in the thresholds for mechanical allodynia and thermal hyperalgesia. Values recorded after example 1 administration were similar to those obtained before the development of neuropathy.

c) No tolerance to the antiallodynic and antihyperalgesic effects exerted by compound Example 1 developed following chronic treatment at a dose of 25 mg/kg for 14 days, twice a day.

d) The inhibitory effects exerted by Example 1 on mechanical allodynia and thermal hyperalgesia were not masked by unspecific effects on locomotor activity.

e) The mechanical allodynia in the behavioral tests correlates with the electrophysiological hyperreactivity recorded on Aδ-fibres in response to mechanical stimulation. Accordingly, the inhibitory effect of compound Example 1 on mechanical allodynia in behavioral tests correlates with a reduction of the hyperreactivity in response to mechanical stimulation found in electrophysiological recordings.

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.