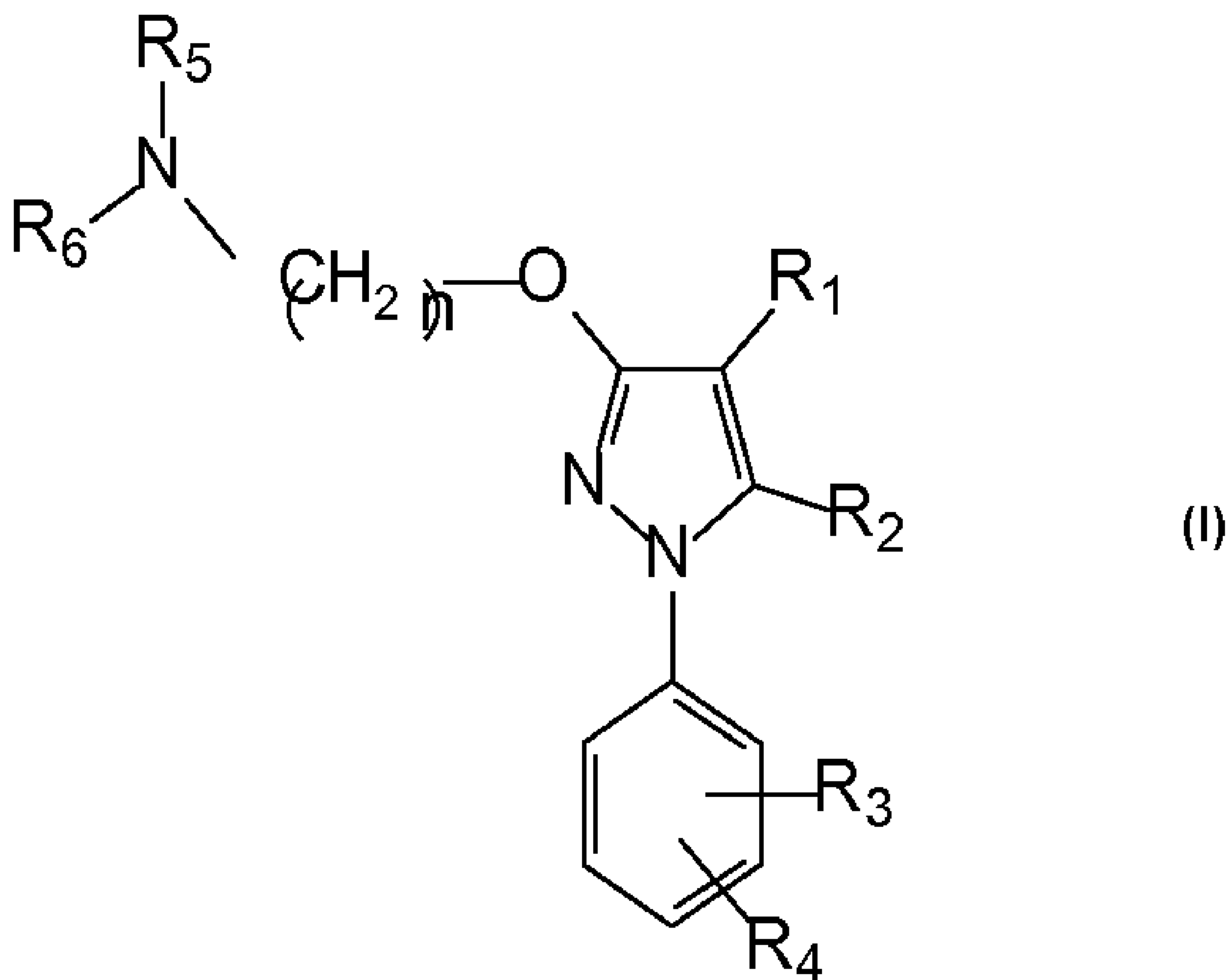




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 (71) Demandeur/Applicant:
 LABORATORIOS DEL DR. ESTEVE, S.A., ES
 (72) Inventeurs/Inventors:
 VELA HERNANDEZ, JOSE MIGUEL, ES;
 CODONY-SOLER, XAVIER, ES;
 ZAMANILLO-CASTANEDO, DANIEL, ES
 (74) Agent: BORDEN LADNER GERVAIS LLP

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 (54) Title: SIGMA LIGANDS FOR THE PREVENTION AND/OR TREATMENT OF EMESIS INDUCED BY CHEMOTHERAPY OR RADIOTHERAPY



(57) Abrégé/Abstract:

The invention refers to the use of a sigma ligand, preferably a sigma ligand of formula (I), to prevent or treat emesis induced by a chemotherapeutic agent or radioactivity, especially emesis induced by taxanes, vinca alkaloids or platin chemotherapeutic drugs.

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(71) Applicant (for all designated States except US): **LABORATORIOS DEL DR. ESTEVE, S.A.** [ES/ES]; Avda. Mare de Déu de Montserrat, 221, E-08041 Barcelona (ES).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **VELA HERNÁNDEZ, José Miguel** [ES/ES]; Rambla Badal nº 153, 8º, 3ª, E-08028 Barcelona (ES). **CODONY-SOLER, Xavier** [ES/ES]; C/Sant Joan, 7 2º 1ª, E-08301 Mataró - Barcelona (ES). **ZAMANILLO-CASTANEDO, Daniel** [ES/ES]; Avda. Mare de Déu de Montserrat, 252, 5º- 2ª, E-08041 Barcelona (ES).(74) Agent: **BERNARDO NORIEGA, Francisco**; ABG Patentes, S.L., Avenida de Burgos, 16D, Edificio Euro-mor, E-28036 Madrid (ES).

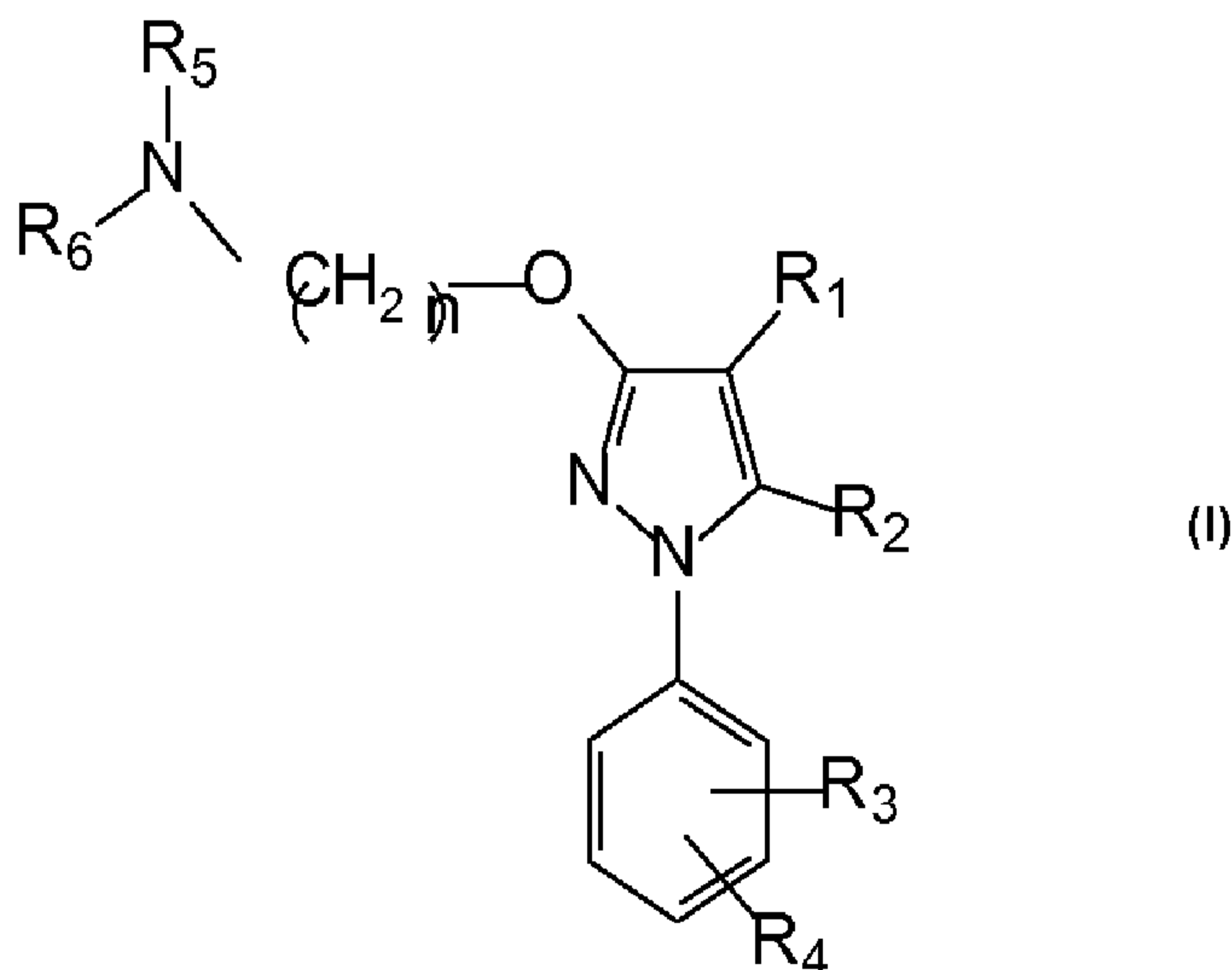
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(54) Title: SIGMA LIGANDS FOR THE PREVENTION AND/OR TREATMENT OF EMESIS INDUCED BY CHEMOTHERAPY OR RADIOTHERAPY



(57) Abstract: The invention refers to the use of a sigma ligand, preferably a sigma ligand of formula (I), to prevent or treat emesis induced by a chemotherapeutic agent or radioactivity, especially emesis induced by taxanes, vinca alkaloids or platinum chemotherapeutic drugs.

SIGMA LIGANDS FOR THE PREVENTION AND/OR TREATMENT OF EMESIS INDUCED BY CHEMOTHERAPY OR RADIOTHERAPY

FIELD OF THE INVENTION

5 The present invention relates to the use of sigma receptor ligands in the prevention and/or treatment of emesis resulting from chemotherapy or radiotherapy. The present invention also refers to a combination of a sigma receptor ligand and a chemotherapeutic agent, for its use in the prevention and/or treatment of cancer while preventing or reducing emesis developing as a consequence of chemotherapy or
10 radiotherapy.

BACKGROUND

Cancer and its associated therapies are some of the biggest health concerns in the world. The two main forms of treatment for cancer are chemotherapy and radiotherapy.

15 Chemotherapy, in combination with or as an alternative to surgery, is the method of choice in most cases for controlling or helping patients struck by carcinomas. Chemotherapy is defined as the use of chemical substances to treat disease and, in the sense of this invention, refers primarily to the use of cytotoxic or cytostatic drugs, called chemotherapeutic drugs, to treat cancer. In general it is a systemic treatment.
20 Chemotherapy in cancer treatment consists of a personalized combination of potent chemotherapy drugs, designed to slow rapid cancer tumor growth, shrink tumors, kill cancer cells, and prevent the spread of cancer. The chemotherapeutic drugs prevent cells from replicating in the typical, out-of-control manner in which cancer cells divide.

Radiotherapy (or radiation therapy), on the other hand, involves the targeted use of
25 ionizing radiation in cancer treatment. Radiotherapy is also commonly used in combination with other methods such as chemotherapy.

Anti-cancer therapy, such as the use of radiation or the administration of chemotherapeutic agents, is associated with Adverse Events including radio and chemotherapy-associated toxicities. Such toxicities and/or side-effects can materially
30 offset or limit the potential benefits to the patient undergoing treatment, for example, resulting in treatment delays, treatment interruptions, dose modifications, dose schedule modifications, or even complete cessation of treatment. Thus, in addition to

their adverse pharmacological affects, the development of said toxicities can limit or curtail the effectiveness of the primary treatment of the patient's cancer or preclude it all together. Cessation, interruption, or delays in patient treatment, or reducing the dosage of chemotherapeutic therapy or the fractions of radiotherapy, for example, may
5 be detrimental to a subject's chances of long-term survival or control of the cancer, since such alterations in the treatment can allow the progression of cancer within the subject.

Emesis is a well-known and frequent side-effect of cancer chemotherapeutic agents, such as cisplatin, as well as of radiotherapy. It causes serious problems, and in some
10 patients emesis is so severe that therapy must be discontinued. Anti-emetic agents are therefore often administered in order to alleviate this side-effect of the cancer chemotherapeutic agent or radiation. The anti-emetic agents employed are usually benzamide derivatives, such as metoclopramide, which have dopamine antagonist activity. In view of their dopamine antagonist activity benzamide derivatives such as
15 metoclopramide themselves exhibit serious and undesirable side- effects, such as extra-pyramidal effects, i.e. tardive dyskinesia, acute dystonia, akathisia and tremor. Other anti-emetic drugs include 5-HT3 antagonists, e.g., ondansetron; corticosteroids, e.g., dexamethasone; and NK1 antagonists, e.g., aprepitant. These treatments fail to adequately address the needs of the patient. Serious side effects that may occur due to
20 the use of antiemetics include fever, hearing loss, extreme nausea, constipation, ringing ears, severe stomach pain, severe vomiting, heartburn and unusual weight gain. Allergic reaction marked by swelling of the face or throat may also occur as a result of using antiemetics. Other less-serious side effects that may occur as a result of using antiemetics include darkening of the stool or tongue, drowsiness, dry mouth, mild
25 nausea, stomach pain and headache.

Several reports on the drawbacks of anti-emetic drugs have been published. Although there is no consensus on the severity of said drawbacks such as the side effects, it is commonly agreed that they must be mitigated. In this sense, J. Raynov [Archive of Oncology 2001; 9(3):151-3] studies the side effects and reactions caused by
30 antiemetics in patients under chemotherapy treatment and concludes that the most common side effects (extrapyramidal reactions, headache, constipation...) are usually mild and controlled by symptomatic treatment, but they have to be identified by the medical staff and the patients.

The efficacy and adverse effects of known antiemetics (droperidol, ondasetron, hyoscine TTS, tropisetron, metoclopramide, propofol, promethazine) during Patient-Controlled Analgesia Therapy, a highly emetogenic treatment, has also been evaluated [Martin R. Tramèr et al. (*Anaesth Analg* 1999; 88: 1354-61)]. Although the results must
5 be confirmed and completed, the authors state regarding droperidol that the risk of adverse effects is dose-depededent. Likewise, 5-HT₃ receptor antagonists (ondasetron, tropisetron) shown no evidence of any antinausea effect.

On another front, it is known in the art that neuropathic pain, allodynia, hyperalgesia,
10 and especially, peripheral neuropathy, develop in a considerable number of cases as a result of chemotherapy. These are very specific symptoms arising from the neurotoxicity of the chemotherapeutic drug. The treatment of these symptoms is crucial for preserving the quality of life of the afflicted patients (Mielke et al., *Eur. J. Cancer*, 2006, 42(1), 24-30; Park et al., *Curr. Med. Chem.*, 2008, 15(29), 3081-94; Argyriou et
15 al., *Blood*, 2008, 112(5), 1593-9). Unfortunately, an effective treatment for chemotherapy-induced peripheral neuropathy has yet to be found (Wolf et al., *Eur. J. Cancer*, 2008, 44(11), 1507-15). WO 2009/103487 and co-pending application EP 09382144.5 relates to the use of sigma receptor ligands in the prevention or treatment of pain resulting from chemotherapy.

20

In view of the above, an effective treatment for emesis that minimizes or eliminates one or more of this side effect of currently available cancer therapies is highly desirable. Therefore, there is an urgent need to provide a new form of treatment and/or prevention for the emesis associated to chemotherapy or radiotherapy. Preferably, the
25 therapy should also be useful for treating and/or preventing other conditions developed as result of chemotherapy or radiotherapy, such as pain induced by chemo- or radiotherapy.

BRIEF DESCRIPTION OF THE INVENTION

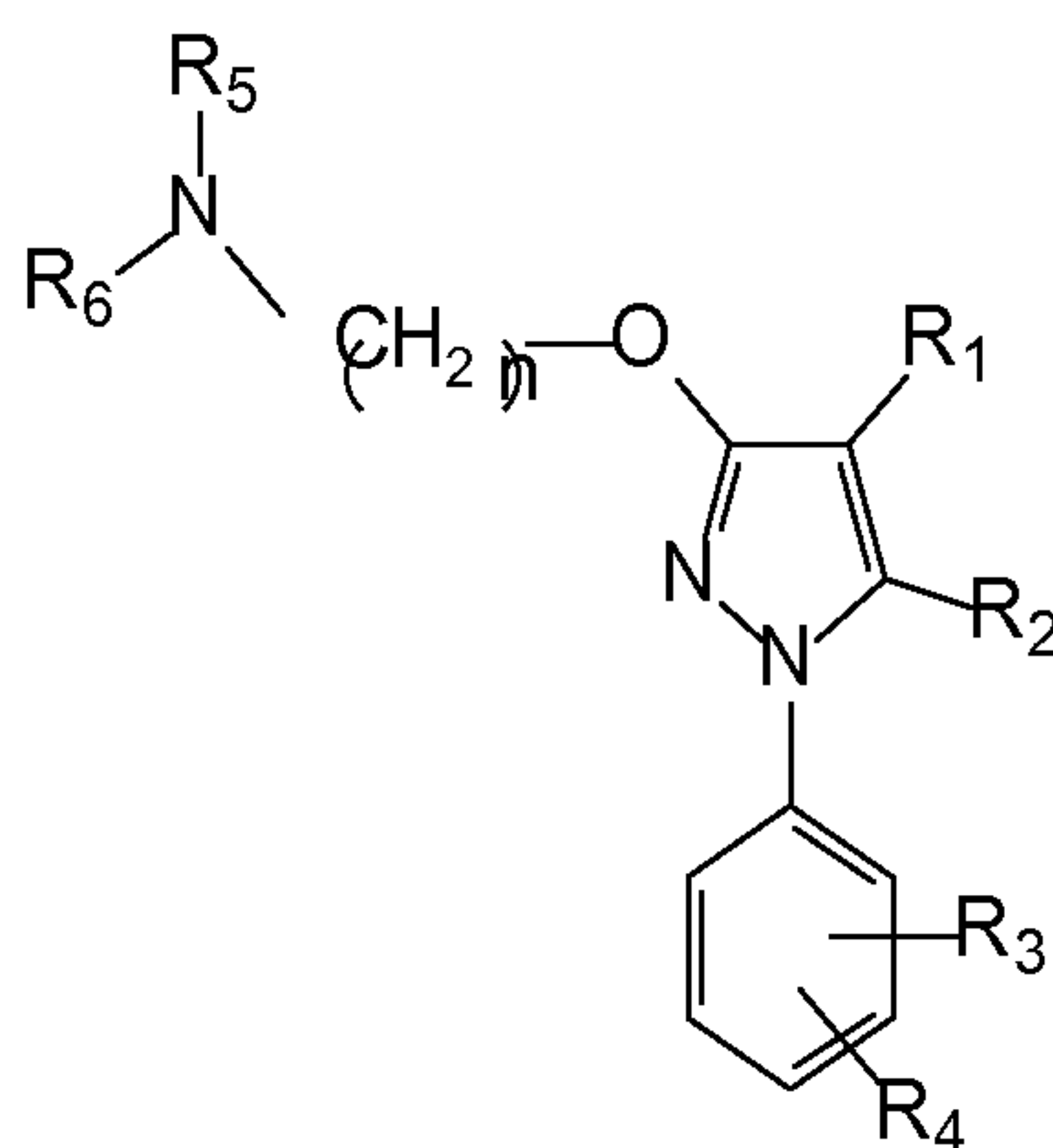
30 The inventors of the present invention have surprisingly found and demonstrated for the first time that the administration of sigma receptor ligands is highly effective for preventing or treating the emesis developing as a consequence of chemotherapy or radiotherapy. Even more surprisingly, this invention demonstrates that the co-

administration of these sigma ligands and a chemotherapeutic drug prevents the emesis frequently associated to chemotherapy or radiotherapy. This benefit of the invention is more evident when the sigma ligand is specifically a sigma receptor antagonist in the form of a (neutral) antagonist, an inverse agonist or a partial antagonist. An additional advantage and relating to WO 2009/103487 and the co-pending application EP 09382144.5 is the use of the sigma ligands, at the same time, in the prevention and/or treatment of pain induced by chemotherapy or radiotherapy. Accordingly, sigma ligands are useful against the two main concerns relating to chemotherapy and radiotherapy: pain and emesis induced.

10

Therefore, one aspect of the present invention relates to a sigma ligand for use in the prevention and/or treatment of emesis induced by chemotherapy or radiotherapy.

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



15

(I)

wherein

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

20

R₂ is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR₈, -C(O)OR₈, -C(O)NR₈R₉, -CH=NR₈, -CN, -OR₈, -OC(O)R₈, -S(O)_t-R₈, -NR₈R₉, -NR₈C(O)R₉, -NO₂, -N=CR₈R₉, and halogen;

R₃ and **R₄** are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR₈, -C(O)OR₈, -C(O)NR₈R₉, -CH=NR₈, -CN, -OR₈, -OC(O)R₈, -S(O)_t-R₈, -NR₈R₉, -NR₈C(O)R₉, -NO₂, -N=CR₈R₉, and halogen, or together they form an optionally substituted fused ring system;

R₅ and **R₆** are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR₈, -C(O)OR₈, -C(O)NR₈R₉, -CH=NR₈, -CN, -OR₈, -OC(O)R₈, -S(O)_t-R₈, -NR₈R₉, -NR₈C(O)R₉, -NO₂, -N=CR₈R₉, 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;

R₈ and **R₉** 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.

Another aspect of this invention refers to the use of a sigma receptor ligand as defined above for the manufacture of a medicament for the prevention and/or treatment of emesis induced by chemotherapy or radiotherapy.

Another aspect of the invention refers to a combination of at least one sigma ligand
5 as defined above and at least one chemotherapeutic drug for use in the treatment of cancer and simultaneous prevention and/or treatment of emesis induced by chemotherapy or radiotherapy.

Another aspect of the invention relates to the use of a combination as defined above for the manufacture of a medicament for the treatment of cancer and
10 simultaneous prevention and/or treatment of emesis induced by chemotherapy or radiotherapy.

Another aspect of the invention is a method of treatment of a patient, notably a human, suffering from emesis induced by chemotherapy or radiotherapy, or likely to suffer emesis as a result of a chemotherapeutic or radiotherapeutic treatment, which
15 comprises administering to the patient in need of such a treatment or prophylaxis a therapeutically effective amount of a sigma ligand as defined above.

In a particular embodiment, sigma ligands are useful at the same time against the two main concerns relating to chemotherapy and radiotherapy: pain and emesis induced. Accordingly, a combination comprising at least a sigma ligand and at least one
20 chemotherapeutic drug may be indicated for the treatment of cancer and simultaneous prevention and/or treatment of emesis and pain induced by chemotherapy or radiotherapy.

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

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1: Mean number of emetic events per 1-hour epoch after Cisplatin administration (Mean + sem, n=4); vehicle vs compound 63 (80 mg/kg, 9 treatments)

30 The following abbreviations are used in the figures:

(R + E): retchings and expulsions

Mean: arithmetic mean

Sem: standard error of the mean

n=4: number of animals per group

5 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, alkoxy-carbonyl, 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 "Heterocyclalkyl" 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, alkoxy-carbonyl, 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, alkoxy-carbonyl, 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, alkoxy-carbonyl, etc.

"Heterocyclyl" refers to a stable 3-to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, preferably a 4-to 8-membered ring with one or more heteroatoms, more preferably a 5-or 6-membered ring with one or more heteroatoms. It may be aromatic or not aromatic. For the purposes of this invention, the heterocycle may be a monocyclic, bicyclic or tricyclic ring system, which may include fused ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidised; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated or aromatic. Examples of such heterocycles include, but are not limited to, azepines, benzimidazole, benzothiazole, furan, isothiazole, imidazole, indole, piperidine, piperazine, purine, quinoline, thiadiazole, tetrahydrofuran, coumarine, morpholine; pyrrole, pyrazole, oxazole, isoxazole, triazole, imidazole, etc.

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above, e. g., methoxy, ethoxy, propoxy, etc.

"Aryloxy" refers to a radical of the formula $-OR_a$ where R_a is an aryl radical as defined above, e. g., phenoxy, naphthoxy, etc.

"Amino" refers to a radical of the formula $-NH_2$, $-NHR_a$ or $-NR_aR_b$, optionally quaternized, wherein R_a and R_b are independently an alkyl or aryl radical as defined above, e.g., methylamino, ethylamino, dimethylamino, diethylamino, propylamino, phenylamino, etc.

"Halogen", "halo" or "hal" refers to bromo, chloro, iodo or fluoro.

References herein to substituted groups in the compounds of the present invention refer to the specified moiety that may be substituted at one or more available positions by one or more suitable groups, e. g., halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; alkanoyl such as a C_{1-6} alkanoyl group such as acyl and the like; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms and more preferably 1-3 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon or from 2 to about 6 carbon atoms; alkoxy groups having one or more oxygen linkages and from 1 to about 12 carbon atoms or 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties

having one or more thioether linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; carbocyclic aryl having 6 or more carbons, particularly phenyl or naphthyl and aralkyl such as benzyl. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

The term "salt" must be understood as any form of an active compound used in accordance with this invention in which said compound is in ionic form or is charged and coupled to a counter-ion (a cation or anion) or is in solution. This definition also includes quaternary ammonium salts and complexes of the active molecule with other molecules and ions, particularly, complexes formed via ionic interactions. The definition includes in particular physiologically acceptable salts; this term must be understood as equivalent to "pharmacologically acceptable salts" or "pharmaceutically acceptable salts".

The term "pharmaceutically acceptable salts" in the context of this invention means any salt that is tolerated physiologically (normally meaning that it is not toxic, particularly, as a result of the counter-ion) when used in an appropriate manner for a treatment, applied or used, particularly, in humans and/or mammals. These physiologically acceptable salts may be formed with cations or bases and, in the context of this invention, are understood to be salts formed by at least one compound used in accordance with the invention – normally an acid (deprotonated)– such as an anion and at least one physiologically tolerated cation, preferably inorganic, particularly when used on humans and/or mammals. Salts with alkali and alkali earth metals are preferred particularly, as well as those formed with ammonium cations (NH_4^+). Preferred salts are those formed with (mono) or (di)sodium, (mono) or (di)potassium, magnesium or calcium. These physiologically acceptable salts may also be formed with anions or acids and, in the context of this invention, are understood as being salts formed by at least one compound used in accordance with the invention – normally protonated, for example in nitrogen – such as a cation and at least one physiologically tolerated anion, particularly when used on humans and/or mammals. This definition

specifically includes in the context of this invention a salt formed by a physiologically tolerated acid, i.e. salts of a specific active compound with physiologically tolerated organic or inorganic acids – particularly when used on humans and/or mammals. Examples of this type of salts are those formed with: hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid or citric acid.

The term “solvate” in accordance with this invention should be understood as meaning any form of the active compound in accordance with the invention in which said compound is bonded by a non-covalent bond to another molecule (normally a polar solvent), including especially hydrates and alcoholates, like for example, methanolate. A preferred solvate is the hydrate.

The compounds of the invention may be in crystalline form either as free compounds or as solvates and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art. Suitable solvates are pharmaceutically acceptable solvates. In a particular embodiment the solvate is a hydrate.

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 and metabolites of the compounds of formula I that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Preferably, prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by Burger “Medicinal Chemistry and Drug Discovery 6th ed. (Donald J. Abraham ed., 2001, Wiley), “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).

Any compound referred to herein is intended to represent such specific compound as well as certain variations or forms. In particular, compounds referred to herein may have asymmetric centres and therefore exist in different enantiomeric or diastereomeric

forms. Thus, any given compound referred to herein is intended to represent any one of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, and mixtures thereof. Likewise, stereoisomerism or geometric isomerism about the double bond is also possible, therefore in some cases the molecule could exist as (E)-isomer or (Z)-isomer (trans and cis isomers). If the molecule contains several double bonds, each double bond will have its own stereoisomerism, that could be the same as, or different to, the stereoisomerism of the other double bonds of the molecule. Furthermore, compounds referred to herein may exist as atropisomers. All the stereoisomers including enantiomers, diastereoisomers, geometric isomers and atropisomers of the compounds referred to herein, and mixtures thereof, are considered within the scope of the present invention.

Furthermore, any compound referred to herein may exist as tautomers. Specifically, the term tautomer refers to one of two or more structural isomers of a compound that exist in equilibrium and are readily converted from one isomeric form to another. Common tautomeric pairs are amine-imine, amide-imidic acid, keto-enol, lactam-lactim, etc.

Unless otherwise stated, the compounds of the invention are also meant to include isotopically-labelled forms i.e. compounds which differ only in the presence of one or more isotopically-enriched atoms. For example, compounds having the present structures except for the replacement of at least one hydrogen atom by a deuterium or tritium, or the replacement of at least one carbon by ^{13}C - or ^{14}C -enriched carbon, or the replacement of at least one nitrogen by ^{15}N -enriched nitrogen are within the scope of this invention.

The sigma ligands, in particular the compounds of 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.

- 5 As used herein in regards to emesis, the terms “treat”, “treating” and “treatment” include the eradication, removal, reversion, alleviation, modification, or control of emesis induced by chemotherapy or radiotherapy.

As used herein, the terms “prevention”, “preventing”, “preventive”, “prevent” and prophylaxis refer to the capacity of a therapeutic to avoid, minimize or difficult the onset
10 or development of a disease or condition before its onset, in this case emesis induced by chemotherapy or radiotherapy.

The above terms “treat” and the like as well as “prevent” and the like are also used with respect to the other diseases referred to in the present invention, i.e. cancer and pain.

As used herein, the terms “chemotherapy” or “chemotherapeutic drug” refer broadly to
15 the use of a chemical drug for the treatment of cancer, tumors or malign neoplasia. Examples of chemical drugs used to treat cancer are cytostatic and cytotoxic drugs, but not limited only to these.

“Developing as a consequence of chemotherapy” or “resulting from chemotherapy” according to this invention is defined as: a) developing after or with at the beginning of
20 chemotherapy and b) thus coinciding with or following the use of a chemotherapeutic drug. Therefore, the symptom to be treated is likely to be caused by or is due to the toxicity, cytotoxicity or especially, the peripheral neurotoxicity, of the chemotherapeutic drug.

As used herein, the terms “radiotherapy” or “radiation therapy” refer broadly to the use
25 of ionizing radiation in cancer treatment to control malignant cell. It includes its use for curative, adjuvant or palliative purposes.

“Developing as a consequence of radiotherapy” or “resulting from radiotherapy” according to this invention is defined as developing after or with at the beginning of radiotherapy.

30 As mentioned above, chemo- and radiotherapy can be combined and therefore the emesis and/or pain resulting in such cases may be due to the action of one or both the chemotherapeutic drug and the radiation.

As used herein, the terms "emetic syndrome", "emetic condition", "vomiting", "nausea" and "emesis" are interchangeable and intended to have the same meaning. Emetic syndromes are those characterized by the reflexive act of ejecting the contents of the stomach through the mouth, or the feeling that such a reflexive action is likely to occur. Emetic conditions are often associated with chemotherapeutic treatment (chemotherapy-induced nausea and vomiting (CINV)) or surgery (post-operative nausea and vomiting (PONV)).

According to general knowledge chemotherapy-induced nausea and emesis (vomiting) (CINV) can be classified as follows:

- 10 ○ Acute nausea and emesis which occurs during first 24 hours (day 1) after chemotherapy drug administration;
- Delayed nausea and emesis which occurs from 24 hours after chemotherapy drug administration and may persist during some days (days 2 to 5); and
- 15 ○ Anticipatory nausea and emesis which occurs prior to a chemotherapy drug administration as result of classical conditioning (also known as Pavlovian or respondent conditioning).

Emetic syndromes resulting from radiotherapeutic treatment can be classified analogously.

For bibliographic references relating to the emesis classification, see for example:
20 Herrstedt J, Koeller JM, Roila F. Acute emesis: moderately emetogenic chemotherapy. *Supp Care Cancer*. **2005**; 13: 97–103; Roila F, Warr D, Clark-Snow RA. Delayed emesis: moderately emetogenic chemotherapy. *Supp Care Cancer*. **2005**; 13: 104 – 8; Aapro M, Molassiotis A, Olver I. Anticipatory nausea and vomiting. *Supp Care Cancer*. **2005**; 13: 117– 21.

25 Delayed nausea and emesis, which may appear even in the absence of acute nausea and emesis, remain important targets for improved therapeutic intervention (Grunberg SM, Deuson RR, Mavros P, et al.; *Cancer*; 100 (10); 2261-8, **2004**).

According to the present invention, acute emesis occurs within about 16 hours of receiving chemotherapy, and delayed emesis occurs between about 18 hours and
30 about 72 hours of receiving chemotherapy.

The term "cancer symptom burden" is used as a measure of a cancer subject's quality of life or the amount of amelioration of advanced cancer symptoms. A subject's cancer

symptom burden may be measured by the Anderson Symptom Assessment System (ASAS).

The severity of overall cancer symptom burden or emetic conditions can be characterized by a number of scales that are known in the art. For example, the
5 Anderson Symptom Assessment System (ASAS) is a modified form of the Edmonton Symptom Assessment System that includes an assessment of pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep and feeling of wellbeing (see, Palmer et al. (2005) *J. Pain and Symptom Management* 6:565-571). ASAS requires patients to identify the severity of each of these symptoms on a 0-10
10 scale, with 0=none (or best), and 10=most (or worst imaginable). A subject ASAS score is the sum total of their numerical answers for the ten symptoms.

Alternatively, the Hesketh scale can be used to classify the acute emetogenicity of cancer chemotherapy (Hesketh et al. (1997) *J. Clin. Oncology* 15:103-109). The Hesketh scale sets forth five levels of emetogenicity. Level 1 consists of agents that are
15 nonemetogenic; Level 2 consists of agents that cause vomiting in 10-30% of patients; Level 3 consists of agents that are moderately emetogenic with 30-60% of patients experiencing emesis; Level 4 consists of agents that produce emesis in 60-90% of patients; and Level 5 consists of agents that cause vomiting in >90% of patients.

20 As used herein, the terms "sigma ligand" or "sigma receptor ligand" refer to any compound binding to the sigma receptor. As stated previously, the sigma ligand is preferably a sigma receptor antagonist in the form of a (neutral) antagonist, an inverse agonist or a partial antagonist.

An "agonist" is defined as a compound that binds to a receptor and it has an intrinsic
25 effect, and thus, increases the basal activity of a receptor when it contacts the receptor. An "antagonist" is defined as a compound that competes with an agonist or inverse agonist for binding to a receptor, thereby blocking the action of an agonist or inverse agonist on the receptor. However, an antagonist (also known as a "neutral" antagonist) has no effect on constitutive receptor activity. Antagonists mediate their effects by
30 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.

- 5 An "inverse agonist" is defined as a compound that produces an effect opposite to that of the agonist by occupying the same receptor and, thus, decreases the basal activity of a receptor (i.e., signalling mediated by the receptor). Such compounds are also known as negative antagonists. An inverse agonist is a ligand for a receptor that causes the receptor to adopt an inactive state relative to a basal state occurring in the
10 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,
15 NMDA, dopaminergic, and other known neurotransmitter or hormone receptor families" (G. Ronsisvalle et al. Pure Appl. Chem. 73, 1499-1509 (2001)). Pharmacological data based on ligand binding studies, anatomical distribution and biochemical features distinguish at least two subtypes of σ receptors (R. Quiron et al., Trends Pharmacol. Sci. 13, 85-86 (1992); M.L. Leitner, Eur. J. Pharmacol. 259, 65-69 (1994); S.B. Hellewell
20 and W.D. Bowen; Brain Res. 527, 244-253 (1990)) (G. Ronsisvalle et al. Pure Appl. Chem. 73, 1499-1509 (2001)). The protein sequences of the sigma receptors (Sigma 1 (σ_1) and Sigma 2 (σ_2)) are known in the art (e.g. Prasad, P.D. et al., J. Neurochem. 70 (2), 443-451 (1998)). They show a very high affinity to various analgesics (e.g. pentazocine).

25

"Compound/s binding to the sigma receptor" or "sigma ligand" as used in this application is/are defined as a compound having an IC_{50} value of ≤ 5000 nM, more preferably ≤ 1000 nM, more preferably ≤ 500 nM on the sigma receptor. More preferably, the IC_{50} value is ≤ 250 nM. More preferably, the IC_{50} value is ≤ 100 nM.
30 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 $\geq 50\%$ 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
5 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,
10 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 the symptoms of emesis developing as a consequence of chemotherapy or radiotherapy.

15 Table 1 lists some sigma ligands known in the art (i.e. having an $\text{IC}_{50} \leq 5000$ nM). Some of these compounds may bind to the sigma-1 and/or to the sigma-2 receptor. These sigma ligands also include their respective salts, bases, and acids.

Table 1

(-)-Cyanopindolol hemifumarate	Cutamesine hydrochloride
(-)-(1R,2S)-cis-N-[2-(3,4-Dichlorophenyl)ethyl]-2-pyrrolidinocyclohexylamine	Cyclobenzaprine HCl
(-)-1-[1-(3-Chlorophenyl)pyrrolidin-2-ylmethyl]-4-(2-phenylethyl)piperazine	Cycloheximide
(-)-Sparteine sulfate pentahydrate	Cyproheptadine HCl
(+)-Himbacine	Darrow Red HCl
(±)-1-Cyclohexyl-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)propyl]piperazine	Demecarium Bromide
(1S,5R)-3-[2-(2-Adamantyl)ethyl]-1,8,8-trimethyl-3-azabicyclo[3.2.1]octane hydrochloride	Denatonium Benzoate
(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin-1-Yl)-Ethyl Ester	Deptropine Citrate

(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)-Carbamic Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester	Desloratadine
(4aalpha,8aalpha)-6-(4-Fluorophenyl)-2-(4-pyridylmethyl)-6-hydroxydecahydroisoquinoline; (4a,8a-cis)-6-(4-Fluorophenyl)-2-(pyridin-4-ylmethyl)perhydroisoquinolin-6-ol	Dexbrompheniramine Maleate
(4aalpha,8abeta)-2-Benzyl-6-(4-fluorophenyl)-6-hydroxydecahydroisoquinoline	Dexchlorpheniramine Maleate
(6aR,9R)-5-Bromo-7-methyl-N-(2-propynyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide	Dexfenfluramine HCl
(S)-(-)-N-(2-Amino-3-phenylpropyl)-2-(3,4-dichlorophenyl)-N-methylacetamide hydrochloride	Dicyclomine HCl
(S)-Methamphetamine HCl	Diethylpropion HCl
[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 1-(3-Benzyloxy-4-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester	Dimethisoquin HCl
[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 2-(Tert-Butoxycarbonyl-Naphthalen-1-Ylmethyl-Amino)-Ethyl Ester	Dimetindene Maleate
[4-(4-Ethyl-3,5-Dimethyl-Pyrazol-1-Yl)-Phenyl]-[4-(3-Phenyl-Allyl)-Piperazin-1-Yl]-Methanone	Diphemanil Methylsulfate
1-(1,2-Diphenylethyl)Piperidine Maleate, (+/-)	Diphenidol HCl
1-(1,4-Ethano-1,2,3,4-tetrahydro-2-naphthylmethyl)-4-methylpiperazine hydrate; 1-(Benzobicyclo[2.2.2]octen-2-ylmethyl)-4-methylpiperazine hydrate	Diphenoxylate HCl
1-(1-Adamantyl)-2-[4-(2H-naphtho[1,8-cd]isothiazol-2-ylmethyl)piperidin-1-yl]ethanone S,S-dioxide hydrochloride	Diphenylpyraline HCl
1-(1-Naphthyl)Piperazine HCl	Dipropyldopamine HBr
1-(2-Benzyloxyethyl)-4-(3-	Doxepin HCl

phenylpropyl)piperazine dihydrochloride	
1-(2-Phenylethyl)piperidine oxalate	Dyclonine HCl
1-(3-Chlorophenyl)Piperazine HCl	Ebastine
1-(3-Chlorothien-2-yl)-2-[4-(4-fluorobenzyl)piperidin-1-yl]ethanol	Econazole Nitrate
1-(4-Bromo-Benzenesulfonyl)-4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine	Epinastine HCl
1-(4-Chloro-3-hydroxyphenyl)-2-[4-(4-fluorobenzyl)piperidin-1-yl]ethanol	Ethaverine HCl
1-(4-Chlorophenyl)-3-(hexahydroazepin-1-ylmethyl)pyrrolidin-2-one	Ethopropazine HCl
1-(4-Chlorophenyl)-3(R)-[4-(2-methoxyethyl)-1-piperazinylmethyl]pyrrolidin-2-one (-)-D-tartrate	Eticlopride HCl, S(-)-
1-(4-Chlorophenyl)-3(R)-[4-(2-methoxyethyl)piperazin-1-ylmethyl]pyrrolidin-2-one dihydrochloride	Etofenamate
1'-(4-Fluorobenzyl)-1,3-dihydrospiro[2-benzofuran-1,4'-piperidine]	Etonitazenyl Isothiocyanate
1-(4-Fluorophenyl)-4-[4-(5-fluoro-2-pyrimidinyl)-1-piperazinyl]butan-1-ol hydrochloride	Femoxetine HCl
1-(4-Fluorophenyl)-4-[4-(5-fluoropyrimidin-2-yl)piperazin-1-yl]butan-1-ol; 1-[4-(4-Fluorophenyl)-4-hydroxybutyl]-4-(5-fluoropyrimidin-2-yl)piperazine	Fenfluramine HCl
1'-(4-Phenylbutyl)spiro[1,3-dihydroisobenzofuran-1,4'-piperidine]	Fenticonazole Nitrate
1-(Cyclobutylmethyl)-2-[3-phenyl-2(E)-propenyl]pyrrolidine hydrochloride	Fipexide HCl
1-(Cyclohexylmethyl)-3'-methoxy-5'-phenyl-4',5'-dihydro-3'H-spiro[piperidine-4,1'-pyrano[4,3-c]pyrazole]	Flavoxate HCl
1-(Cyclopropylmethyl)-4-[2-(4-fluorophenyl)-2-oxoethyl]piperidine hydrobromide	Flunarizine diHCl
1,4-Bis[spiro[isobenzofuran-1(3H),4'-	Fluoxetine Related Compound B

piperidin]-1'-yl]butane	
1-[(1R,3R)-2,2-Dimethyl-3-(2-phenoxyethyl)cyclobutylmethyl]piperidine	Fluperlapine
1-[2-(3,4-Dichlorophenyl)ethyl]-3-(pyrrolidin-1-yl)piperidine	Fluphenazine Decanoate DiHCl
1-[2-(3,4-Dichlorophenyl)ethyl]-4-(3-phenylpropyl)piperazine	Fluphenazine Enanthate DiHCl
1-[2-(3,4-Dichlorophenyl)ethyl]-4-methylpiperazine	Fluphenazine HCl
1-[2-(4-Fluorophenyl)ethyl]-4,4-dimethylhexahydroazepine hydrochloride	Fluphenazine N-Mustard DiHCl
1-[2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-1,2,4-triazol-3-ylsulfanyl]ethyl]piperidine oxalate	Flurazepam Related Compound C
1-[2-Benzyloxy-1(R)-phenylethyl]-4-cyclohexylpiperazine dihydrochloride	Fluspirilene
1-[3-(2-Oxo-3-phenylimidazolin-1-yl)propyl]spiro[piperidine-4,1'(3H)-isobenzofuran] hydrochloride; 1-Phenyl-3-[3-[spiro[piperidine-4,1'(3H)-isobenzofuran]-1-yl]propyl]imidazolin-2-one hydrochloride	GBR 12783 DiHCl
1-[3-(3,4-Dimethoxyphenyl)propyl]-4-(4-phenylbutyl)perhydro-1,4-diazepine dihydrochloride	GBR 12909 DiHCl
1-[3-(4-Chlorophenoxy)propyl]-4-methylpiperidine hydrochloride	GBR 13069 DiHCl
1-[3-(4-Phenyl-2H-1,2,3-triazol-2-yl)propyl]piperidine	GBR-12935 DiHCl
1-[4-(6-Methoxynaphthalen-1-yl)butyl]-3,3-dimethylpiperidine hydrochloride	GR 89696 Fumarate
1-[4-[2-[1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yloxy]ethyl]piperazin-1-yl]ethanone oxalate	Guanabenz Acetate
11-[5-(4-Fluorophenyl)-5-oxopentyl]-5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[b]indole	Guanadrel Sulfate
1-Benzyl-3beta-[3-(cyclopropylmethoxy)propyl]-	Halofantrine HCl

2alpha,3alpha,4beta-trimethylpiperidine	
1-Benzyl-3-methoxy-3',4'-dihydrospiro(piperidine-4,1'-thieno[3,2-c]pyrane)	HEAT HCl
1'-Benzyl-3-methoxy-4-phenyl-3,4-dihydrospiro[furo[3,4-c]pyrazole-1,4'-piperidine]	Hexylcaine HCl
1-Benzyl-4-(4-fluorophenoxymethyl)piperidine	Hycanthone
1-Benzyl-4-[2-(4-fluorophenyl)-2-oxoethyl]piperidine maleate	Hydroxychloroquine Sulfate
1-Benzyl-4-[3-phenyl-2(E)-propenyloxymethyl]piperidine hydrochloride	IBZM, S(-)-
1-Benzyl-4-[4-(4-fluorophenyl)-3-cyclohexen-1-yl]piperazine dihydrochloride hemihydrate	ICI-199,441 HCl
1'-Benzylspiro[1,2,3,4-tetrahydronaphthalene-1,4'-piperidine]	Ifenprodil Tartrate
1'-Benzylspiro[indane-1,4'-piperidine]	Indatraline HCl
1'-Butyl-3-Methoxy-4-phenyl-3,4-dihydrospiro[furo[3,4-c]pyrazole-1,4'-piperidine]	lofetamine HCl
1-Cyclohexyl-4-(3-phenoxypropyl)piperazine dihydrochloride	Isamoltane Hemifumarate
1-Hydroxy-1'-(2-phenylethyl)spiro[1,2,3,4-tetrahydronaphthalene-2,4'-piperidine] hydrochloride	Isoxsuprine HCl
1-Methyl-4-[2-(4-phenylpiperidin-1-yl)ethyl]-4,5,6,7-tetrahydro-1H-indazole oxalate	Ketotifen Fumarate Salt
1-Phenyl-3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)-1-propanone oxime oxalate	L-693,403 Maleate
1-Phenyl-4-(pyrrolidin-1-ylmethyl)-1,4,6,7-tetrahydropyrano[4,3-c]pyrazole	L-741,626
2-(2-[[1-(3-Chloro-Benzyl)-Pyrrolidin-3-Yl]-Methyl-Carbamoyl]-2-Methyl-Propyl)-4,6-Dimethyl-Benzoic Acid	L-741,742 HCl
2-(3,4-Dichlorophenyl)-N-methyl-N-[2-(1,2alpha,3alpha,4beta-tetramethylpiperidin-	L-745,870 TriHCl

3beta-yl)ethyl]acetamide	
2-(Cyclohexylmethylaminomethyl)-8-methoxy-3,4-dihydro-2H-1-benzopyran hydrochloride	Levetimide HCl, R(-)
2(S)-[(3aS,6aR)-5-Butyl-4-oxo-1,2,3,3a,4,6a-hexahydrocyclopenta[c]pyrrol-2-yl]propionic acid ethyl ester	Levobunolol HCl
2-[2-[5-Methyl-1-(2-naphthyl)-1H-pyrazol-3-yloxy]ethylamino]ethanol hydrochloride	Lidoflazine
2-[2-[N-(Cyclobutylmethyl)-N-methylamino]ethyl]-1,2,3,4-tetrahydronaphthalen-2-one	Lobeline HCl
2-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propoxy]-9H-carbazole	lomerizine diHCl
2-[4-(4-Methoxybenzyl)piperazin-1-ylmethyl]-4H-1-benzopyran-4-one	Loxapine Succinate
2-[N-[2-(3,4-Dichlorophenyl)ethyl]-N-methylaminomethyl]-1-ethylpyrrolidine	LY-53,857 Maleate
2-Benzyl-3,4,8-trimethyl-2-azabicyclo[2.2.2]octane-6-carboxylic acid ethyl ester	Maprotiline HCl
2-Butyl-2,3,4,4a,9,9a-hexahydro-1H-indeno[2,1-c]pyridine	Mazindol
2-Chloro-11-(4-Methylpiperazino)Dibenz[B,F]Oxepin Maleate	MDL 12,330A HCl
3-(1-Benzyl-2r,3c,4t-trimethylpiperidin-3t-yl)propionic acid ethyl ester hydrochloride	Mebhydroline 1,5-naphthalendisulfonate Salt
3-(3-Chloro-4-cyclohexylphenyl)-1-(hexahydroazepin-1-yl)-1(Z)-propene hydrochloride; 1-[3-(3-Chloro-4-cyclohexylphenyl)-2(Z)-propenyl]hexahydroazepine hydrochloride	Meclizine HCl
3-(4-Methylphenyl)-5-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)isoxazole oxalate	Mefloquine HCl
3-(N-Benzyl-N-methylamino)-1-(4-nitrophenyl)piperidine	Meprylcaine HCl
3,3'-Diethylthiacarbocyanine Iodide	Mesoridazine Besylate

3-[1-(Benzocyclobutan-1-ylmethyl)piperidin-4-yl]-6-fluoro-1,2-benzisoxazole	Metaphit Methanesulfonate
3-[2-(2-Adamantyl)ethyl]-3-azabicyclo[3.2.2]nonane	Metaphit
3-[3-(4-Methylphenyl)isoxazol-5-yl]-1-propyl-1,2,5,6-tetrahydropyridine	Methantheline Bromide
3a,6-Epoxy-2-[2-(4-fluorophenyl)ethyl]-2,3,3a,6,7,7a-hexahydro-1H-isoindole	Methdilazine
3a,6-Epoxy-2-[2-(4-fluorophenyl)ethyl]perhydroisoindole	Methiothepin Mesylate
3-Mercapto-2-Methylpropanoic Acid 1,2-Diphenylethylamine Salt	Methixene HCl
3-Phenyl-1-(1-propyl-1,2,5,6-tetrahydro-3-pyridyl)-1-propanone oxime monohydrochloride	Methylene Violet 3Rax HCl
3-Quinuclidinyl Benzilate	Metipranolol
3-Tropanyl-3,5-Dichlorobenzoate	Mianserin HCl
3-Tropanyl-Indole-3-Carboxylate HCl	Miconazole
4-(1H-Indol-4-yl)-Piperazine-1-Carboxylic Acid 2-(5-Bromo-2-Ethoxy-Phenylamino)-Cyclohexylmethyl Ester	ML-9 HCl
4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine-1-Carboxylic Acid 2-Thiophen-2-yl-Ethyl Ester	Morantel Hydrogen L-Tartrate
4-(3,5-Dimethoxy-Phenyl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-Benzyl)-Piperidin-2-ylmethyl Ester	MR 16728 HCl
4-(3-Nitro-5-Sulfamoyl-Thiophen-2-yl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-5-Methoxy-Benzyl)-Piperidin-3-ylmethyl Ester	MT-210
4-(4-Benzylpiperazin-1-ylmethyl)-7-methoxy-2H-1-benzopyran-2-one	N-(2-Adamantyl)-N-[2-(2-adamantyl)ethyl]-N-methylamine hydrochloride
4-(4-Bromophenyl)-5-[2-(dihexylamino)ethyl]thiazol-2-amine dihydrochloride	N-[1-(2-Indanyl)piperidin-4-yl]-N-methylcarbamic acid isobutyl ester fumarate
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	N-[1-[4-Methoxy-3-(2-phenylethoxy)benzyl]-4-methylpentyl]-N-propylamine

4-(4-Methylphenyl)-1-(3-morpholinopropyl)-1,2,3,6-tetrahydropyridine	N-[2-(3,4-Dichlorophenyl)ethyl]-N-ethyl-N-[2-(1-pyrrolidinyl)ethyl]amine
4-(5-Trifluoromethyl-Pyridin-2-Yl)-Piperazine-1-Carboxylic Acid Pent-2-Ynyl Ester	N-[2-(3,4-Dichlorophenyl)ethyl]-N-methyl-N-(2-pyrrolidinoethyl)amine dihydrobromide
4-(Dimethylamino)-1-phenylcyclohexanol	N-[4-[4-(Diethylamino)piperidin-1-yl]phenyl]methanesulfonamide
4,7-Epoxy-2-[2-(4-fluorophenyl)ethyl]-2,3,3a,4,7,7a-hexahydro-1H-isoindole	N1-(1-Adamantyl)-N2-(2-methylphenyl)acetamide
4-[1-(3-[¹⁸ F]fluoropropyl)piperidin-4-ylmethoxy]benzotrile	N1-[2-(3,4-Dichlorophenyl)ethyl]-N1,N2,N2-trimethyl-1,2-ethanediamine
4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl)-2-hydroxy-4-oxobut-2-enoic acid	Nafronyl Oxalate Salt
4-[1-(4-Fluorophenyl)-1-hydroxymethyl]-1-[3-(4-fluorophenoxy)propyl]piperidine	Naftifine
4-[2-(Dipropylamino)ethyl]-2-(2-phenylethoxy)anisole hydrochloride	Naftopidil diHCl
4-[2-(Dipropylamino)ethyl]-5,8-dimethylcarbazole hydrochloride	Naltriben Mesylate
4-[2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl]morpholine	NE-100
4-[2-[1-(Cyclopropylmethyl)piperidin-4-yl]acetyl]benzotrile fumarate	Nefazodone
4-[4-(N-Benzyl-N-methylamino)piperidin-1-yl]benzotrile	N-Ethyl-N-[2-(1-piperidinyl)ethyl]-N-[2-[4-(trifluoromethoxy)phenyl]ethyl]amine
4-[N-[2-[N'-(4-Fluorobenzyl)-N'-methylamino]ethyl]-N-methylamino]-1-(4-fluorophenyl)-1-butanone dihydrochloride	Nicergoline
4-Benzyl-1-[4-(4-fluorophenyl)-4-hydroxybutyl]piperidine hydrochloride	Niguldipine HCl, (+/-)-
4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-2-Trifluoromethoxy-Benzenesulfonamide	Nisoxetine HCl
4'-Chloro-3-Alpha-(Diphenylmethoxy)Tropane HCl	NP-07
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-	Nylidrin HCl

10-Yl)-Propyl]-Piperazin-1-Yl}-Ethyl Ester	
4-Methoxy-1-[2-(4-phenylpiperazin-1-yl)ethyl]-6H-dibenzo[b,d]pyran hydrochloride	Octoclothebin Maleate, (±)-
4-Methoxy-N-[1-(7-Methoxy-Benzo[1,3]Dioxol-5-Ylmethyl)-Pyrrolidin-3-Yl]-Benzenesulfonamide	Oxamniquine
4-Phenyl-1-(3-phenylpropyl)-4-(pyrrolidin-1-ylcarbonyl)piperidine	Oxamniquine Related Compound A
5-(2-Pyrrolidinoethyl)-4-(2,4,6-trimethoxyphenyl)thiazole-2-amine dihydrochloride	Oxamniquine Related Compound B
5-(N-Ethyl-N-Isopropyl)-Amiloride	Oxatomide
6-[1-Hydroxy-2-[4-(2-phenylethyl)piperidin-1-yl]ethyl]-1,2,3,4-tetrahydroquinolin-2-one	Oxiconazole Nitrate
6-[2-(4-Benzylpiperidin-1-yl)ethyl]-3-methylbenzothiazol-2(3H)-one	Panamesine hydrochloride
6-[2-[4-(2-Phenylethyl)piperidin-1-yl]ethyl]-1,2,3,4-tetrahydroquinolin-2-one	Panaxatriol
6-[3-(Morpholin-4-yl)propyl]benzothiazol-2(3H)-one	PAPP
6-[6-(4-Hydroxypiperidin-1-yl)hexyloxy]-3-methyl-2-phenyl-4H-1-benzopyran-4-one	Paroxetine
7-(4-Methoxyphenyl)-4-[4-(4-pyridyl)butyl]hexahydro-1,4-thiazepine	Paxilline
7-[3-[4-(4-Fluorobenzoyl)piperidin-1-yl]propoxy]-4H-1-benzopyran-4-one hydrochloride	p-Chlorobenzhydrylpiperazine
9-[4-({[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl}amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide	Penbutolol Sulfate
9-Hydroxy-2,3,6,7,7a,8,12b,12c-octahydro-1H,5H-naphtho[1,2,3-ij]quinolizine	Pentamidine Isethionate
Acetophenazine Maleate	Pergolide Methanesulfonate
Acrinol	Perospirone
Ajmaline	Phenamyl Methanesulfonate

Alaproclate HCl	Phenosafranin HCl
Aloe-Emodin	Piboserod
Alprenolol D-Tartrate Salt Hydrate	Pimozide
Alprenolol HCl	Pinacyanol Chloride
AMI-193	Pindobind, (+/-)-
Aminobenzotropine	Piperacetazine
Amiodarone HCl	Piperidolate HCl
Amodiaquine HCl	Pirenperone
Amorolfine HCl	PPHT HCl, (±)-
Amoxapine	Prenylamine Lactate Salt
AN2/AVex-73; AE-37; ANAVEX 2-73; N-(2,2-Diphenyltetrahydrofuran-3-ylmethyl)-N,N-dimethylamine	Pridinol Methanesulfonate Salt
Anavex 1-41; AE-14; N-(5,5-Diphenyltetrahydrofuran-3-ylmethyl)-N,N-dimethylamine hydrochloride	Procyclidine HCl
Anavex 19-144; AE-37met; AN19/AVex-144	Proflavine Hemisulfate Salt
Anavex 7-1037	Propafenone HCl
Anisotropine Methylbromide	Proparacaine HCl
Anpirtoline	Propiomazine
ARC 239 DiHCl	Protokylol
Auramine O HCl	Protriptyline HCl
Azaperone	Pyrilamine Maleate
Azatadine Maleate	Pyrimethamine
Azelastine HCl	Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-2-Ylmethyl] Ester 2-Benzyl Ester
Bamethan sulfate	Pyrvinium Pamoate
BD 1008 DiHBr	Quetiapine Fumarate
BD-1063	Quinacrine HCl

Benextramine TetraHCl	Quinaldine Red
Benfluorex HCl	Quipazine Dimaleate
Benidipine HCl	Quipazine, 6-Nitro-, Maleate
Benoxathian HCl	Raloxifene
Benproperine Phosphate	Rimantadine HCl
Benzododecinium bromide	Rimcazole hydrochloride
Benzphetamine HCl	Risperidone
Benztropine Mesylate	Ritanserlin
Bephenium Hydroxynaphthoate	Ritodrine HCl
Bepriidil HCl	RS 23597-190 HCl
Berberine chloride	RS 67333 HCl
Betaxolol HCl	RS 67506 HCl
Bifemelane	Safranin O HCl
BMY 7378 DiHCl	Salmeterol
Bopindolol Malonate	SB203186
BP 554 Maleate	SCH-23390 HCl, R(+)-
Bromhexine HCl	Sertaconazole Nitrate
Bromodiphenhydramine HCl	Sertindole
Bromperidol	Sertraline
Brompheniramine Maleate	Sibutramine HCl
BTCP HCl	Siramesine hydrochloride
Buclizine HCl	SKF-525A HCl
Buflomedil HCl	SKF-96365 HCl
Bupropion HCl	SNC 121
Buspirone HCl	Spiiperone HCl
Butacaine Sulfate	T-226296
Butaclamol HCl, (±)-	Tegaserod Maleate

Butenafine HCl	Terbinafine HCl
Butoconazole Nitrate	Terconazole
BW 723C86 HCl	Terfenadine
Carbetapentane Citrate	Terfenadine Related Compound A
Carbinoxamine Maleate	Tetrindole Mesylate
Carpipramine DiHCl DiH ₂ O	Thiethylperazine Malate
Carvedilol	Thioperamide Maleate
Cephapirin Benzathine	Thiopropazine
CGS-12066A Maleate	Thioridazine
Chlorprocaine HCl	Thiothixene
Chlorpheniramine Maleate	Thiothixene, (E)-
Chlorphenoxamine HCl	Thonzonium Bromide
Chlorprothixene	Tioconazole Related Compound A
Cinanserin HCl	TMB-8 HCl
Cinnarizine	Tolterodine L-Tartrate
Cirazoline HCl	Toremifene Citrate
Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidinyl)Cyclohexamine DiHBr	Tramazoline HCl
Cis(Z)-Flupentixol DiHCl	Trans-U-50488 Methanesulfonate, (±)-
cis-2-(Cyclopropylmethyl)-7-(4-fluorobenzoyl)perhydropyrido[1,2-a]pyrazine	Tridihexethyl Chloride
cis-2-[4-(Trifluoromethyl)benzyl]-3a,4,7,7a-tetrahydroisoindoline	Trifluoperazine HCl
Cisapride Hydrate	Trifluoperidol HCl
Citalopram HBr	Trihexyphenidyl HCl
Clemastine Fumarate	Trimeprazine Hemi-L-Tartrate
Clemizole HCl	Trimipramine Maleate
Clenbuterol HCl	Tripelennamine HCl

Clidinium Bromide	Triprolidine HCl
Clobenpropit 2HBr	Triprolidine HCl Z Isomer
Clofazimine	Tropanyl 3,5-Dimethylbenzoate
Clofilium Tosylate	Tropine 2-(4-Chlorophenoxy)Butanoate, Maleate
Clomiphene Citrate	U-50488 HCl, (-)-
Clomiphene Related Compound A	U-62066
Clomipramine	UH 232 Maleate, (+)-
Cloperastine HCl	Vesamicol HCl
Clorgyline HCl	Vinpocetine
Clozapine	W-7 HCl
Conessine	WB-4101 HCl

Preferably, the table above also includes reduced haloperidol. Reduced haloperidol is an active metabolite of haloperidol that is produced in humans, shows a high affinity (in the low nanomolar range) for sigma-1 receptors, and produces an irreversible blockade of sigma-1 receptors both in experimental animals and human cells.

Examples of well known methods of producing a prodrug of a given acting compound are known to those skilled in the art (e.g. in Krosgaard-Larsen et al., Textbook of Drug Design and Discovery, Taylor & Francis (April 2002)).

10

Preferably 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 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.

15

In another preferred embodiment, R_2 represents H or alkyl, more preferably methyl.

In yet another preferred embodiment of the invention, R₃ and R₄ 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, both R₃ and R₄ 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), more preferably, a naphthyl ring system.

Also, 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 that R₅ and R₆ are, each independently, C₁₋₆alkyl, or together with the nitrogen atom to which they are attached form a substituted or unsubstituted heterocyclyl group a, in particular a group chosen among morpholinyl, piperidinyl, and pyrrolidinyl group. More preferably, R₅ and R₆ 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 combination of the invention encompasses a sigma ligand of formula (I) 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
- 5 [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
- 10 [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
- 15 [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
- 20 [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-
- 25 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
- 5 [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
- 10 [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] 4-{2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]ethyl}morpholine
- [46] 2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]-N,N-diethylethanamine
- 15 [47] 1-(3,4-Dichlorophenyl)-4,5-dimethyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole
- [48] 1-(3,4-Dichlorophenyl)-4,5-dimethyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole
- [49] 1-{2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]ethyl}piperidine
- [50] 4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}morpholine
- [51] (2S,6R)-4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}-2,6-
- 20 dimethylmorpholine
- [52] 1-{4-[1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}piperidine
- [53] 1-(3,4-Dichlorophenyl)-3-[4-(pyrrolidin-1-yl)butoxy]-1H-pyrazole
- [55] 4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N,N-diethylbutan-1-amine
- [56] N-benzyl-4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N-methylbutan-1-amine
- 25 [57] 4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N-(2-methoxyethyl)-N-methylbutan-1-amine
- [58] 4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}thiomorpholine

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

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

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

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

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

10 [64] N,N-Diethyl-2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethanamine

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

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

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

15 In a more preferred variant of the invention, the sigma ligand of formula (I) is 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine. This particular compound is designated in the examples of the present invention as compound 63.

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

20

As defined previously, "chemotherapeutic drugs" in the sense of this invention are compounds used in chemotherapy, especially those that impair mitosis (cell division) by targeting fast-dividing cells effectively. As these drugs cause damage to cells, they are termed cytotoxic. Some drugs cause cells to undergo apoptosis (so-called "cell suicide").

25

In a preferred embodiment of the invention, the chemotherapeutic drug is selected from drugs derived from platin, especially the platin-derivatives cisplatin, carboplatin and oxaliplatin; plant alkaloids and terpenes (terpenoids).

30 "Plant alkaloids" (and terpenoids) are alkaloids derived from plants that block cell division by preventing microtubule function. Since microtubules are vital for cell

division, their inhibition also arrests cell mitosis. The main examples of plant alkaloids are vinca alkaloids and taxanes.

“Vinca alkaloids” bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules (M phase of the cell cycle). They are derived from the Madagascar periwinkle, *Catharanthus roseus* (formerly known as *Vinca rosea*). The vinca alkaloids include Vincristine, Vinblastine, Vinorelbine, and Vindesine.

“Taxanes” are derived from the Pacific yew tree, *Taxus brevifolia*. Taxanes enhance the stability of microtubules, preventing the separation of chromosomes during anaphase. Preferred taxanes in this invention include Paclitaxel and Docetaxel.

10 Examples of chemotherapeutic drugs (by their trademarks) that can induce emesis that can be prevented or treated with sigma ligands are:

13-cis-Retinoic Acid, 2-CdA, 2-Chlorodeoxyadenosine, 5-fluorouracil 5-FU, 6-Mercaptopurine, 6-MP, 6-TG 6-Thioguanine, Abraxane, Accutane®, Actinomycin-D, Adriamycin®, Adrucil®, Agrylin®, Ala-Cort®, Aldesleukin, Alemtuzumab, ALIMTA, Alitretinoin, Alkaban-A Q®, Alkeran®, All-transretinoic acid, Alpha interferon, Altretamine, Amethopterin, Amifostine, Aminoglutethimide, Anagrelide, Anandron®, Anastrozole, Arabinosylcytosine, Ara-C, Aranesp®, Aredia®, Arimidex®, Aromasin®, Arranon®, Arsenic trioxide, Asparaginase, ATRA, Avastin®, Azacitidine, BCG, BCNU, Bevacizumab, Bexarotene, BEXXAR®, Bicalutamide, BiCNU, Blenoxane®, Bleomycin, Bortezomib, Busulfan, Busulfex®, C225, Calcium Leucovorin, Campath®, Camptosar®, Camptothecin-11, Capecitabine, Carac TM, Carboplatin, Carmustine, Carmustine wafer, Casodex®, CC-5013, CCNU (o), CDDP (t), CeeNU (t), Cerubidine (t), cetuximab, Chlorambucil, Cisplatin, Citrovorum Factor, Cladribine, Cortisone, Cosmegen (t), CPT-11 (o), Cyclophosphamide, Cytadren (t), Cytarabine, Cytarabine liposomal, Cytosar-U (t), Cytoxan®, Dacarbazine, Dactinomycin, Darbepoetin alfa, Daunomycin, Daunorubicin, Daunorubicin hydrochloride (t), Daunorubicin liposomal, DaunoXome (t), Decadron, Delta-Cortef (t), Deltasone (t), Denileukin, diftitox, DepoCyt (t), Dexamethasone, Dexamethasone acetate, dexamethasone sodium phosphate, Dexasone (t), Dexrazoxane, DHAD (o), DIC (t), Diodex (t), Docetaxel, Doxil (t), Doxorubicin, Doxorubicin liposomal, Droxia (t), DTIC, DTIC-Dome (t), Duralone (t), Efudex (t), Eligard (t), Ellence (t), Eloxatin (t), Elspar (t), Emcyt (t), Epirubicin, Epoetin alfa, Erbitux, Erlotinib, Erwinia L-asparaginase (t), Estramustine, Ethyol, Etopophos (t), Etoposide, Etoposide phosphate (t), Eulexin (t), Evista (t), Exemestane, Fareston (t), Faslodex (t), Femara®, Filgrastim, Floxuridine, Fludara (t), Fludarabine, Fluoroplex (t),

Fluorouracil, Fluorouracil (cream), Fluoxymesterone, Flutamide, Folinic Acid (o), FUDR
 (t), Fulvestrant, G-CSF (t), Gefitinib, Gemcitabine, Gemtuzumab ozogamicin, Gemzar
 (t), Gleevec™, Gliadel wafer (t), GM-CSF (o), Goserelin, granulocyte - colony
 stimulating factor (t), Granulocyte macrophage colony stimulating factor (o), Halotestin
 5 (t), Herceptin (t), Hexadrol (t), Hexalen (t), Hexamethylmelamine (t), HMM (t), Hycamtin
 (t), Hydrea (t), Hydrocort Acetate (t), Hydrocortisone, Hydrocortisone sodium
 phosphate, Hydrocortisone sodium succinate, Hydrocortone phosphate (t),
 Hydroxyurea, Ibritumomab, Ibritumomab Tiuxetan, Idamycin®, Idarubicin Ifex®, IFN-
 alpha, Ifosfamide, IL-11, IL-2, Imatinib mesylate, Imidazole Carboxamide, Interferon
 10 alfa, Interferon Alfa-2b (PEG conjugate) (o), Interleukin - 2 (t), Interleukin-11 (o), Intron
 A® (interferon alfa-2b), Iressa®, Irinotecan, Isotretinoin, Kidrolase (t), Lanacort (t), L-
 asparaginase (t), LCR (o), Lenalidomide (Lenolidamide), Letrozole, Leucovorin,
 Leukeran (t), Leukine (t), Leuprolide, Leurocristine (o), Leustatin (t), Liposomal Ara-C
 (t), Liquid Pred (t), Lomustine, L-PAM (o), L-Sarcosine (o), Lupron (t), Lupron Depot (t),
 15 Matulane (t), Maxidex (t), Mechlorethamine, Mechlorethamine Hydrochloride,
 Medralone (t), Medrol®, Megace (t), Megestrol, Megestrol Acetate (o), Melphalan,
 Mercaptopurine, Mesna, Mesnex (t), Methotrexate, Methotrexate Sodium (o),
 Methylprednisolone, Meticorten (t), Mitomycin, Mitomycin-C (o), Mitoxantrone, M-
 Prednisol (t), MTC (o), MTX (o), Mustargen (t), Mustine, Mutamycin (t), Myleran (t),
 20 Mylocel (t), Mylotarg (t), Navelbine (t), Nelarabine, Neosar (t), Neulasta (t), Neumega
 (t), Neupogen (t), Nexavar®, Nilandron (t), Nilutamide, Nipent®, Nitrogen Mustard (o),
 Novaldex (t), Novantrone (t), Octreotide, Octreotide acetate (o), Oncospar (t), Oncovin
 (t), Ontak (t), Onxal (t), Oprevelkin, Orapred (t), Orasone (t), Oxaliplatin, Paclitaxel,
 Paclitaxel Protein-bound, Pamidronate, Panretin (t), Paraplatin (t), Pediapred (t), PEG
 25 Interferon, Pegaspargase, Pegfilgrastim, PEG-INTRON (t), PEG-L-asparaginase,
 Pemetrexed, Pentostatin, Phenylalanine Mustard (o), Platinol (t), Platinol-AQ (t),
 Prednisolone, Prednisone, Prelone (t), Procarbazine, PROCRIT®, Proleukin (t),
 Prolifeprospan 20 with Carmustine implant (t), Purinethol (t), Raloxifene, Revlimid®,
 Rheumatrex (t), Rituxan (t), Rituximab, Roferon-A®, (interferon alfa-2a) Rubex (t),
 30 Rubidomycin hydrochloride (t), Sandostatin®, Sandostatin LAR (t), Sargramostim,
 Solu-Cortef (t), Solu-Medrol (t), Sorafenib, STI-571, Streptozocin, SU11248, Sunitinib,
 Sutent®, Tamoxifen, Tarceva®, Targretin (t), Taxol®, Taxotere (t), Temodar®,
 Temozolomide, Teniposide, TESPAs (o), Thalidomide, Thalomid®, TheraCys (t),
 Thioguanine, Thioguanine Tabloid (t), Thiophosphoamide (o), Thioplex (t), Thiotepa,
 35 TICE®, Toposar (t), Topotecan, Toremifene, Tositumomab, Trastuzumab, Tretinoin,

Trexall (t), Trisenox (t), TSPA (o), VCR (o), Velban (t), Velcade ®, VePesid (t), Vesanoid (t), Viadur (t), Vidaza (t), Vinblastine, Vinblastine Sulfate (o), Vincasar Pfs (t), Vincristine, Vinorelbine, Vinorelbine tartrate (o), VLB (o), VM-26 (o), VP-16 (t), Vumon (t), Xeloda ®, Xyotax, Zanosar (t), Zevalin TM, Zinecard (t), Zoladex ®, Zoledronic acid, and Zometa ®.

Another drugs used in cancer-therapy (mostly as chemotherapeutics) are:

(as trademarks): Aldara, Alimta, Androcur, Arimidex, Borea, Caelyx, Campto, Casodex, Decapeptyl, Eloxatin, Eutirox, Faslodex, Femara, Gemzar, Gonapeptyl, Grisetin, Herceptin, Isovorin, Lysodren, Megefren, Metvix, Navelbine, Novaldex, Novantrone, Paraplatin, Procrin, Prostacur, Suprefact, Tamoxifeno Funk, Taxol, Taxotere, Testex, Elmu/Prolongatum, Tomudex, Utefos, Vepesid, Xeloda, Zoladex;

(as active compounds): Anastrozole, Bicalutamide, Busereline, Capecetabine, Cisplatin, Carboplatin, Desoxorubicin, Docetaxel, Etoposid, Fulvestrant, Gemcitabine, Gosereline, Irinotecan, Letrozole, Leuproreline, Megestrol, Mitotane, Mitoxantrone, Oxaliplatin, Paclitaxel, Pemetrexed, Raltitrexed, Tamoxiphen, Tegafur, Triptoreline, Vincristine, Vinblastine, Vinorelbine, and Vindesine.

In a preferred embodiment of the invention, the chemotherapeutic drug is selected from taxanes, vinca alkaloids and drugs derived from platinum. Preferably, the chemotherapeutic drug is selected from paclitaxel, oxaliplatin and vincristine.

In a more preferred embodiment of the invention, the chemotherapeutic drug is Paclitaxel. Paclitaxel (Taxol®) is one of the most effective and commonly used antineoplastic drugs for the treatment of solid tumours.

In another more preferred embodiment of the invention, the chemotherapeutic drug is Oxaliplatin.

In another more preferred embodiment of the invention, the chemotherapeutic drug is Vincristine.

Preferred combinations of the invention comprise the combination of 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine (compound 63) with a chemotherapeutic drug selected from Paclitaxel, Oxaliplatin and Vincristine.

More preferred combinations of the invention comprise the combination of 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine with Paclitaxel and the

combination of 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine with Oxaliplatin.

The combination of the invention may be formulated for its simultaneous, separate or sequential administration, with at least a pharmaceutically acceptable carrier, additive, 5 adjuvant or vehicle. This has the implication that the combination of the two active compounds may be administered:

- as a combination that is being part of the same medicament formulation, the two active compounds being then administered always simultaneously.
- as a combination of two units, each with one of the active substances giving 10 rise to the possibility of simultaneous, sequential or separate administration.

In a particular embodiment, the sigma ligand is independently administered from the chemotherapeutic drug (i.e in two units) but at the same time.

In another particular embodiment, the sigma ligand is administered first, and then the chemotherapeutic drug is separately or sequentially administered.

15 These particular ways of administration are preferably used to prevent the emesis developing as a consequence of chemotherapy.

In yet another particular embodiment, the chemotherapeutic drug is administered first, and then the sigma ligand is administered, separately or sequentially, as defined.

This particular way of administration is preferably used to treat the emesis developing 20 as a consequence of chemotherapy.

The auxiliary materials or additives can be selected among carriers, excipients, support materials, lubricants, fillers, solvents, diluents, colorants, flavour conditioners such as sugars, antioxidants and/or agglutinants. In the case of suppositories, this may imply waxes or fatty acid esters or preservatives, emulsifiers and/or carriers for 25 parenteral application. The selection of these auxiliary materials and/or additives and the amounts to be used will depend on the form of application of the pharmaceutical composition.

The pharmaceutical combination in accordance with the invention can be adapted to any form of administration, be it orally or parenterally, for example pulmonar, nasally, 30 rectally and/or intravenously. Therefore, the formulation in accordance with the invention may be adapted for topical or systemic application, particularly for dermal,

subcutaneous, intramuscular, intra-articular, intraperitoneal, pulmonary, buccal, sublingual, nasal, percutaneous, vaginal, oral or parenteral application.

Suitable preparations for oral applications are tablets, pills, chewing gums, capsules, granules, drops or syrups.

- 5 Suitable preparations for parenteral applications are solutions, suspensions, reconstitutable dry preparations or sprays.

The combination of the invention may be formulated as deposits in dissolved form or in patches, for percutaneous application.

Skin applications include ointments, gels, creams, lotions, suspensions or emulsions.

- 10 Suitable form of rectal application is by means of suppositories.

As mentioned above, the combination of at least one sigma ligand (such as a compound of general formula (I)) and at least one chemotherapeutic drug is suited for its use in the treatment of cancer and simultaneous prevention and/or treatment of emesis induced by chemotherapy. This combination could be administered simultaneously, separately or sequentially. Nevertheless, as chemotherapy is usually combined with radiotherapy, the combination is also useful for the treatment of cancer and simultaneous prevention and/or treatment of emesis resulting from radiotherapy.

15 In a particular embodiment, the sigma ligand according to the present invention is used in the prevention of emesis induced by chemotherapy or radiotherapy. In another particular embodiment, the sigma ligand according to the present invention is used in the treatment of emesis induced by chemotherapy or radiotherapy.

In a particular embodiment, the sigma ligand according to the present invention is used in the prevention of acute emesis induced by chemotherapy or radiotherapy. In another particular embodiment, the sigma ligand according to the present invention is used in the treatment of acute emesis induced by chemotherapy or radiotherapy.

25 In a particular embodiment, the sigma ligand according to the present invention is used in the prevention of delayed emesis induced by chemotherapy or radiotherapy. In another particular embodiment, the sigma ligand according to the present invention is used in the treatment of delayed emesis induced by chemotherapy or radiotherapy.

30

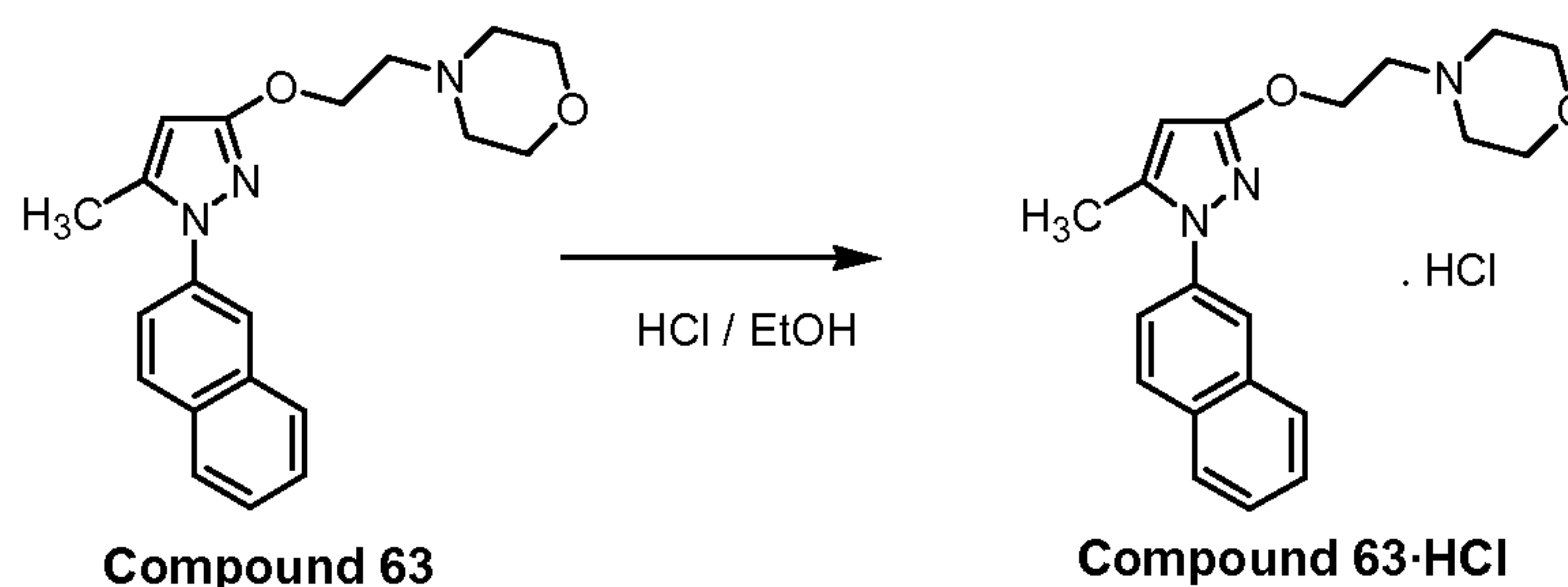
In a particular embodiment, the combination according to the present invention is used in the treatment of cancer and simultaneous prevention of emesis induced by chemotherapy or radiotherapy. In another particular embodiment, the combination according to the present invention is used in the treatment of cancer and simultaneous
5 treatment of emesis induced by chemotherapy or radiotherapy.

As note previously, in a particular embodiment, sigma ligands (such as compounds of general formula (I)) are useful at the same time against the two main concerns relating to chemotherapy and radiotherapy: pain and emesis induced. Hence, a combination according to the present invention comprising at least a sigma ligand (such as a
10 compound of general formula (I)) and at least one chemotherapeutic drug for simultaneous, separate or sequential administration, may be indicated for the treatment of cancer and simultaneous prevention and/or treatment of emesis and pain induced by chemotherapy or radiotherapy.

In one embodiment of the invention it is preferred that the sigma ligand is used in
15 therapeutically effective amounts. The physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the patient under treatment, the age of the patient, the type of cancer and emesis being treated. He will generally wish to initiate treatment with small dosages substantially less
20 than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached. When the composition is administered orally, larger quantities of the active agent will be required to produce the same effect as a smaller quantity given parenterally. The compounds are useful in the same manner as comparable therapeutic agents and the dosage level is of the same
25 order of magnitude as is generally employed with these other therapeutic agents.

For example, the dosage regime that must be administered to the patient will depend on the patient's weight, the type of application, the condition and severity of the disease. A preferred dosage regime of comprises an administration of a compound of
30 formula (I) within a range of 0.5 to 100 mg/kg and of the chemotherapeutic drug from 0.15 to 15 mg/kg and it is administered daily in one or several doses.

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

Examples**Example 1. Synthesis of 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine (compound 63) and its hydrochloride salt**

5

Compound 63 can be prepared as disclosed in the previous application WO2006/021462. Its hydrochloride can be obtained according the following procedure:

Compound 63 (6,39 g) was dissolved in ethanol saturated with HCl, the mixture was stirred then for some minutes and evaporated to dryness. The residue was crystallized from isopropanol. The mother liquors from the first crystallization afforded a second crystallization by concentrating. Both crystallizations taken together yielded 5,24 g (63 %) of the corresponding hydrochloride salt (m.p. = 197-199°C.)

¹H-NMR (DMSO-d₆) δ ppm: 10,85 (bs, 1H), 7,95 (m, 4H), 7,7 (dd, J=2,2, 8,8 Hz, 1H), 7,55 (m, 2H), 5,9 (s, 1H), 4,55 (m, 2H), 3,95 (m, 2H), 3,75 (m, 2H), 3,55-3,4 (m, 4H), 3,2 (m, 2H), 2,35 (s, 3H).

HPLC purity: 99.8%.

Example 2. Assessment of the antimimetic properties of compound 63

The antiemetic properties of compound 63 were assessed in combination with intraperitoneal administration of the chemotherapeutic agent cisplatin in the conscious, unrestrained ferret (*Mustela putorius furo*). Figure 1 shows these results.

Chemotherapeutic agents including cisplatin elicit an immediate emetic response on the day of therapy, that is, acute emesis, and also protracted nausea and vomiting lasting up to 5 days thereafter, that is, delayed emesis. Cisplatin damages the gastrointestinal epithelium and triggers acute emesis through stimulation of 5-HT₃

25

receptors in abdominal afferent fibers, whereas the precise mechanism of delayed emesis has not been fully revealed. In the prevention of acute emesis, 5-HT₃-receptor antagonists are effective in both animals and humans. In contrast, the incidence of delayed emesis is not sufficiently reduced by 5-HT₃-receptor antagonists. Recent studies have suggested the involvement of substance P and NK1 receptors in the generation of delayed emesis following the treatment with chemotherapeutic agents

2.1 Procedures

At least 12 days before their first treatment, ferrets were surgically implanted with telemetry devices. Individual body weights were recorded before treatment, at the time of telemetry device implantation, one day before the initiation of treatment and after completion of the treatment session, at the time of euthanasia, for each animal respectively.

The animals were treated according to the following schedule:

Group	Description	Animal number	Dose level (mg/kg)	Dose volume (mL/kg)	Dose concentration (mg/mL)	Administration per day	Number of days of treatment
A	Vehicle (0.9 % NaCl)	1 to 4	0	2	0	3	3
B	High dose	5 to 8	80	2	40	1	1
C	Low dose	9 to 12	40	2	20	3	3
D	High dose	13 to 16	80	2	40	3	3

Group A, B, C and D animals were administered by the intraperitoneal route.

Animals were dosed and monitored as follows:

Day no.	Group	Animal numbers
0 to 3	A, B, C and D	1 and 2; 5 and 6; 9 and 10; 13 and 14
7 to 10	A, B, C and D	3 and 4; 7 and 8; 11 and 12; 15 and 16

In all groups (including group A), on days 0 and 7, cisplatin was administered at the dose level of 5 mg/kg intraperitoneally (5 mL/kg) on fasted animals.

In all groups, on days 0 and 7, the first treatment with the vehicle or the test item was administered 1 hour prior to cisplatin treatment.

Moreover, in group B, only one administration of test item was done (1 hour before cisplatin) whereas in groups A, C, and D, eight additional administrations were performed every 8 hours for 3 days.

Body temperature, abdominal pressure and activity of the abdominal muscle (EMG) were recorded in treated animals, on day 0 and day 7, respectively, starting approximately 1 hour before the first administration of the vehicle and the test item and for at least 72 hours following the first administration of the vehicle and the test item.

After the last scheduled measurement, animals were euthanized without necropsy.

2.2 Test system

Species/strain: Domestic ferret (*Mustela putorius furo*), descended and neutered.

Supplier: Marshall Bioresources, 5800 Lake Bluff Road, North Rose NY 14516 USA.

Number of animals in the study: 20 males.

Age at initiation of test: At least 19 weeks.

Body weight range at initiation of treatment (day 0 or 7): 1.0 to 1.5 kg.

Justification: the ferret is considered as the gold standard species for emesis screening.

2.3 Animal husbandry

Housing: One room for the acclimatization period and another

room for the test period (dosing and emesis observation), in an air-conditioned building (Building G7):

Temperature: 19 to 25 °C,
Relative humidity: ≥ 35 %,
Air changes: Minimum 10 air changes per hour,
Lighting cycle: 12 hours light (artificial) / 12 hours dark.

Environmental conditions (within target ranges through the test)

The normal dark cycle was interrupted (for up to 1 hour) to allow the +16h, +40h and +64h treatments and the other scheduled procedures. These differences were considered not to have affected the health of the animals or the outcome of the study.

Caging: Animals were housed in 4 plastic cages (1100 x 730 x 650 mm each). Each cage was connected by tubes to the other cages allowing the animals to exert their natural burrowing activity during the pretest period.
From the night before the first treatment onwards, animals were housed singly in plastic cage (900 x 520 x 520 mm).

Bedding: Dust free and irradiated wood shaving (LAB SHAVING) made from coniferous tree wood. From 03 August 2009 (day 6), the bedding was sterilised instead of being irradiated.

Diet:

Ferret complete diet (Diet F, Dietex).

Quantity distributed: approximately
100 g diet/animal/day.

Diet was distributed twice per day (approximately 50 g at each distribution) during pretest.

From the evening of the day before the first treatment, diet was distributed once per day (approximately 100 g). On days -1 and 6, treated animals received 150 g of diet (50 g the morning then 100 g at the end of the day).

Animals were fasted for approximately 1 hour before the first administration of the vehicle, the test item and the positive control on day 0 or day 7.

After telemetry device implantation, all animals received twice daily and during 3 days, 10 mL of a liquid food supplement (Fortol® C+, Intervet SA).

Water:

Softened and filtered (0.2 µm) mains drinking water was available *ad libitum* (via bowls). Water is analysed twice a year for chemical and bacterial contaminants by Laboratoire Santé Environnement Hygiène de Lyon, France.

2.4 Pre-treatment procedures

Animal health procedure:

By supplier, all animals received a standard vaccination (rabies and distemper) and were descented and castrated (surgeries on 12, 20 and 22 May, 03 and 24 June 2009).

All animals received a clinical inspection for ill-health on arrival. During the acclimatisation period, animals were observed daily for clinical signs, and at least

twice daily (at the beginning and at the end of the normal working day) for mortality/morbidity.

Acclimatisation period: At least 20 days between animal arrival and the start of treatment.

Body weight: Animals were weighed on arrival (data are maintained in the raw data of the study), on the day of implantation, on the day before allocation during the acclimatisation period, on the day before treatment and on the day of euthanasia.

Animal identification: Animals were identified by microchip implants (Electronic Laboratory Animal Monitoring System, Bio Medic Data Systems), inserted in the inter-scapular region by supplier on 04 or 30 June 2009.

Allocation to treatment groups: Performed at random.

2.5 Animal preparation

Telemetry implantation procedures:

At least 12 days before their first treatment, all animals were implanted with a telemetry
5 device.

Surgical procedures

24 hours before surgical procedures, animals received antibiotherapy with long acting amoxicilline (Clamoxyl® LA, Pfizer Italia SRL, 10 mg/kg, intramuscular).

Animals were anaesthetised with an intramuscular injection of ketamine hydrochloride
10 (Imalgène 500®, Merial SAS; 10 mg/kg) and xylazine hydrochloride (Rompun® 2 %, kvp Kiel; 2 mg/kg). The hair on the abdomen was clipped. During surgery, the level of anaesthesia was maintained with gaseous anaesthetic (1 to 3 % isoflurane in oxygen). The transmitter body was implanted under aseptic conditions into the abdominal cavity.
15 Electromyographic (EMG) activity of the abdominal muscle was monitored by implanting the 2 biopotential leads (leads that extend out of the device body and

consist of a helix of medical grade stainless steel wire inserted into a silicone tubing) into the left rectus abdominis muscle.

The abdominal pressure developed during abdominal muscles contractions of retching and/or expulsions was measured with the pressure catheter (polyurethane tubing that
5 extends out of the device body) positioned intraperitoneally.

Post-surgical procedures

- Antibiotic prophylaxis with long-acting amoxicilline (Clamoxyl® LA, Pfizer Italia SRL, 10 mg/kg, intramuscular), once approximately 24 hours after surgical procedures,
- Analgesic prophylaxis with tolfenamic acid (Tolfédine 4 %®, Laboratoire Vétoquinol
10 SA, 4 mg/kg; intramuscular), once just after implantation and once 48 hours later.

2.6 Administration of compound 63 and vehicle

Route: Intraperitoneal.

Method of administration: Bolus injection using a sterile syringe and needle introduced intraperitoneally into the pelvic area.

Frequency: Groups A, C and D: one administration every 8 hours during 3 days (day 0 to 3 and day 7 to 10); for a total of 9 administrations (“multiple dose regimen”),

Group B: one administration on day 0 or 7 (“single dose”).

Volume of administration: 2 mL/kg.

Individual dose volumes were calculated using the latest recorded body weight.

Rationale for the choice of the route of administration: the intraperitoneal route was selected as a route of administration allowing a good plasma exposure.

2.7 Administration of emetogenic item

Route:	Intraperitoneal.
Method of administration:	Bolus injection using a sterile syringe and needle introduced intraperitoneally into the pelvic area.
Frequency:	One administration for each animal, on day 0 or 7, one hour after the first treatment with the test item
Volume of administration:	5 mL/kg. Individual dose volumes were calculated using the latest recorded body weight.

2.8 Data evaluation

2.8.1 Characterization of emesis from telemetry signals

- 5 Emesis is characterized by rhythmic abdominal contractions that are either associated with oral expulsion of solid or liquid material from the gastrointestinal tract, that is vomiting, or not associated with the passage of material, that is retching movements. The characteristic pattern of the abdominal pressure and of the electromyographic activity of the abdominal wall during the vomiting reflex was used to characterize the
- 10 emetogenic properties of the test item and the emetic response (time-course).

When judged necessary to allow a better evaluation, raw EMG signals were filtered, rectified and integrated.

2.8.2 Emetic episodes evaluation

- 15 For emetic episodes evaluation, retching and expulsion events were considered together.

For each animal, the number of retchings and expulsions per 1-hour epoch after cisplatin administration were determined.

Cisplatin-induced emesis was divided in two distinct phases:

- 20 – the acute phase from 0 to 16 hours after cisplatin administration,

- the delayed phase from 18 to 72 hours after cisplatin administration.

For each animal, the total number of retchings and expulsions was determined for the acute and the delayed phases.

The results are expressed as arithmetic mean \pm standard error of the mean (s.e.m.).

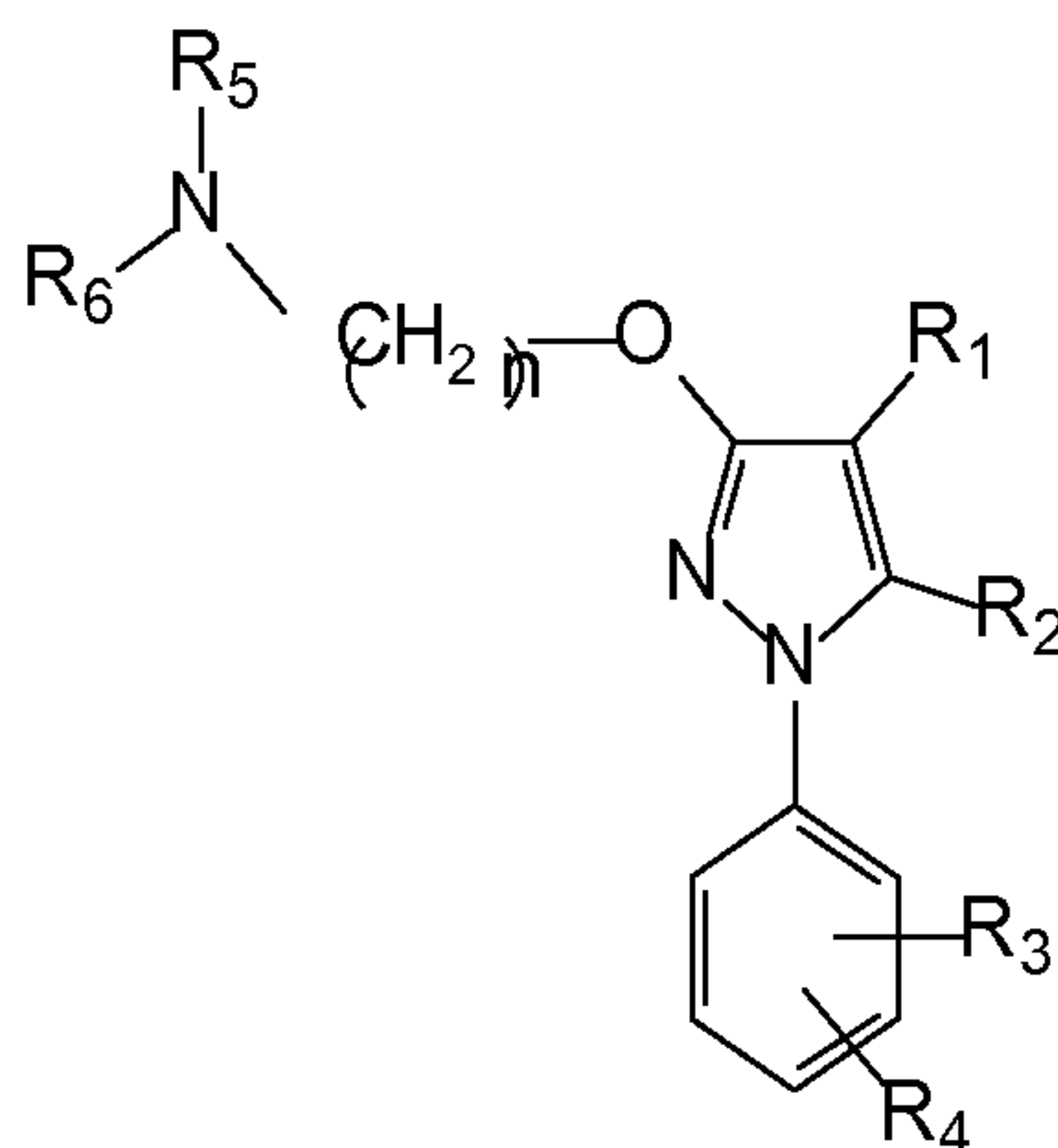
- 5 For evaluation of the antiemetic properties of the test item compound 63, the cisplatin-induced emesis was divided in two distinct phases the acute phase from 0 to 16 hours and the delayed phase from 18 to 72 hours.

Results

- 10 With the administration of compound 63, 80 mg/kg, multiple dose regimen (9 treatments), the number of emetic events during the delayed phase was markedly decreased, with a maximum total number of 39 EE between 62 and 63 hours (Figure 1).

CLAIMS

1. A sigma ligand for use in the prevention and/or treatment of chemotherapy or radiotherapy-induced emesis.
2. Sigma ligand according to claim 1, having the general formula (I):



5

(I)

wherein

R₁ is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR₈, -C(O)OR₈, -C(O)NR₈R₉, -CH=NR₈, -CN, -OR₈, -OC(O)R₈, -S(O)_t-R₈, -NR₈R₉, -NR₈C(O)R₉, -NO₂, -N=CR₈R₉, and halogen;

15

R₂ is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR₈, -C(O)OR₈, -C(O)NR₈R₉, -CH=NR₈, -CN, -OR₈, -OC(O)R₈, -S(O)_t-R₈, -NR₈R₉, -NR₈C(O)R₉, -NO₂, -N=CR₈R₉, and halogen;

20

R₃ and **R₄** are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl,

25

5 substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR₈, -C(O)OR₈, -C(O)NR₈R₉, -CH=NR₈, -CN, -OR₈, -OC(O)R₈, -S(O)_t-R₈, -NR₈R₉, -NR₈C(O)R₉, -NO₂, -N=CR₈R₉, and halogen, or together they form an optionally substituted fused ring system;

10 **R**₅ and **R**₆ are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, aromatic or non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR₈, -C(O)OR₈, -C(O)NR₈R₉, -CH=NR₈, -CN, -OR₈, -OC(O)R₈, -S(O)_t-R₈, -NR₈R₉, -NR₈C(O)R₉, -NO₂, -N=CR₈R₉, and halogen, or together form, with the nitrogen atom to which they are attached, a substituted or unsubstituted, aromatic or non-aromatic heterocyclyl group;

15

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

t is 1,2 or 3;

20 **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.

- 25
3. Sigma ligand according to claim 2, wherein R₁ is selected from H, -COR₈ and substituted or unsubstituted alkyl.
 4. Sigma ligand according to any of claims 2 or 3, wherein R₂ is H or alkyl.
 5. Sigma ligand according to any of claims 2 to 4, wherein R₃ and R₄ together form a fused naphthyl ring system.
 6. Sigma ligand according to any of claims 2 to 5, wherein R₅ and R₆ together form a morpholine-4-yl group.
 7. Sigma ligand according to any preceding claim, which is selected from the group consisting of:
- 30

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

- 2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]-N,N-diethylethanamine,
1-(3,4-Dichlorophenyl)-5-methyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,
1-(3,4-Dichlorophenyl)-5-methyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole,
1-{2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}piperidine,
5 1-{2-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}-1H-imidazole,
3-{1-[2-(1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy)ethyl]piperidin-4-yl}-3H-
imidazo[4,5-b]pyridine,
1-{2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}-4-methylpiperazine,
Ethyl 4-{2-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}piperazine
10 carboxylate,
1-(4-(2-(1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy)ethyl)piperazin-1-
yl)ethanone,
4-{2-[1-(4-Methoxyphenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}morpholine,
1-(4-Methoxyphenyl)-5-methyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,
15 1-(4-Methoxyphenyl)-5-methyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole,
1-[2-(1-(4-Methoxyphenyl)-5-methyl-1H-pyrazol-3-yloxy)ethyl]piperidine,
1-{2-[1-(4-Methoxyphenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}-1H-imidazole,
4-{2-[1-(3,4-Dichlorophenyl)-5-phenyl-1H-pyrazol-3-yloxy]ethyl}morpholine,
1-(3,4-Dichlorophenyl)-5-phenyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,
20 1-(3,4-Dichlorophenyl)-5-phenyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole,
1-{2-[1-(3,4-Dichlorophenyl)-5-phenyl-1H-pyrazol-3-yloxy]ethyl}piperidine,
1-{2-[1-(3,4-Dichlorophenyl)-5-phenyl-1H-pyrazol-3-yloxy]ethyl}-1H-imidazole,
2-{2-[1-(3,4-dichlorophenyl)-5-phenyl-1H-pyrazol-3-yloxy]ethyl}-1,2,3,4-
tetrahydroisoquinoline,
25 4-{4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}morpholine,
1-(3,4-Dichlorophenyl)-5-methyl-3-[4-(pyrrolidin-1-yl)butoxy]-1H-pyrazole,
1-{4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}piperidine,
1-{4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-4-methylpiperazine,

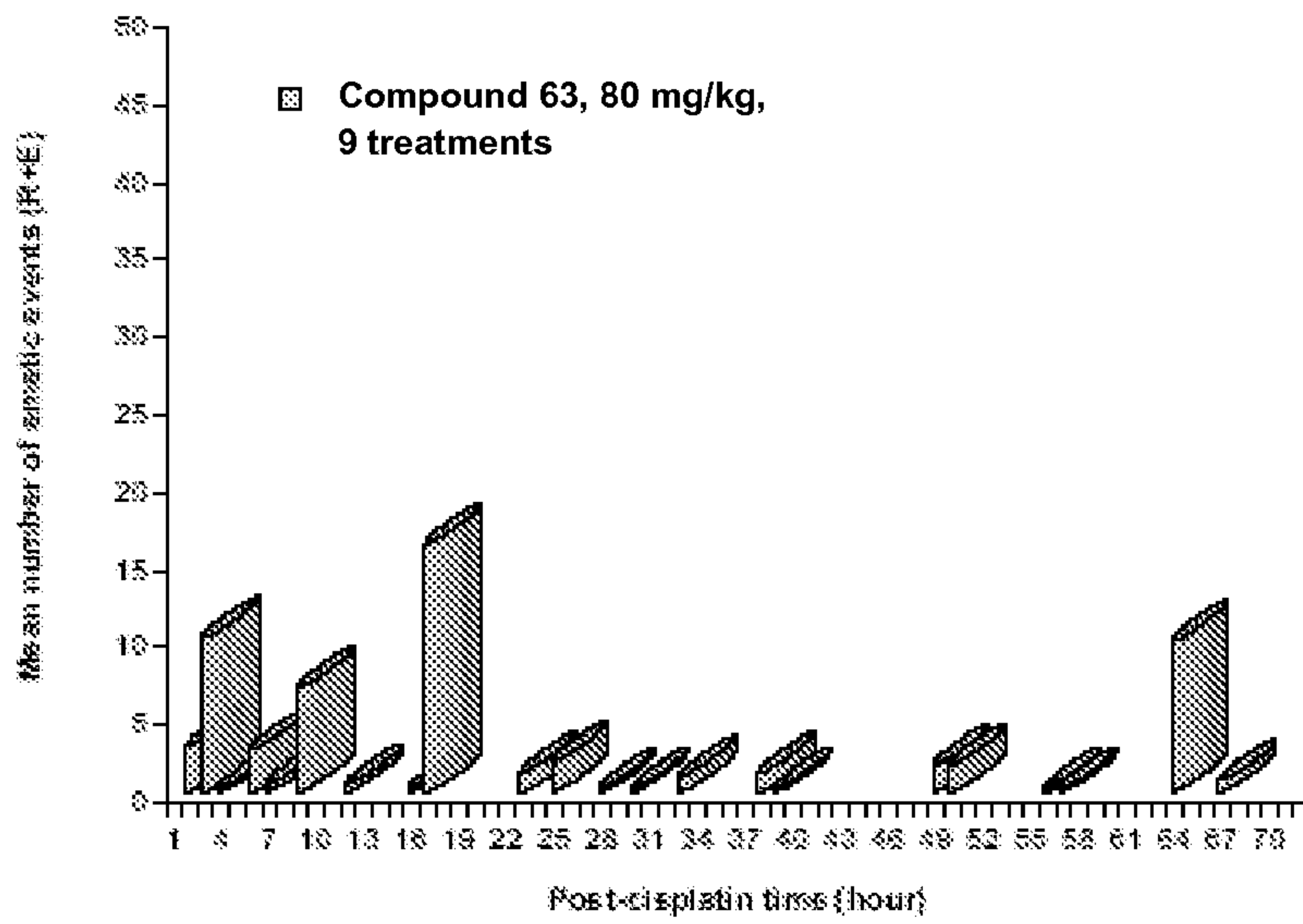
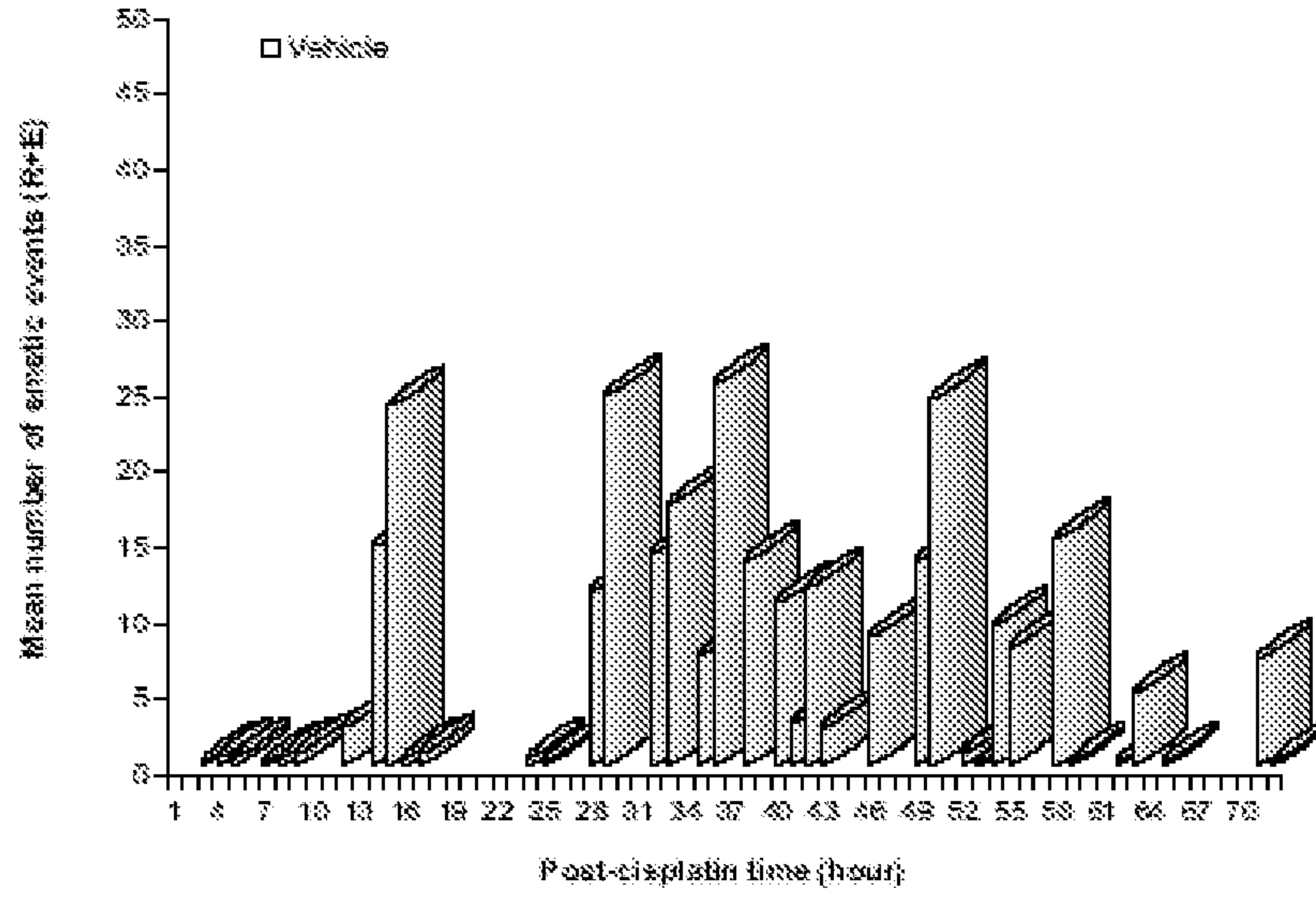
- 1-{4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-1H-imidazole,
4-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]-N,N-diethylbutan-1-amine,
1-{4-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-4-phenylpiperidine,
1-{4-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-6,7-dihydro-1H-indol-
5 4(5H)-one,
2-{4-[1-(3,4-dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]butyl}-1,2,3,4-
tetrahydroisoquinoline,
4-{2-[1-(3,4-dichlorophenyl)-5-isopropyl-1H-pyrazol-3-yloxy]ethyl}morpholine,
2-[1-(3,4-Dichlorophenyl)-5-isopropyl-1H-pyrazol-3-yloxy]-N,N-diethylethanamine,
10 1-(3,4-Dichlorophenyl)-5-isopropyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,
1-(3,4-Dichlorophenyl)-5-isopropyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole,
1-{2-[1-(3,4-Dichlorophenyl)-5-isopropyl-1H-pyrazol-3-yloxy]ethyl}piperidine,
2-{2-[1-(3,4-dichlorophenyl)-5-isopropyl-1H-pyrazol-3-yloxy]ethyl}-1,2,3,4-
tetrahydroisoquinoline,
15 4-{2-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]ethyl}morpholine,
2-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy] N,N-diethylethanamine,
1-(3,4-dichlorophenyl)-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,
1-{2-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]ethyl}piperidine,
1-(3,4-dichlorophenyl)-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole,
20 1-{2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}piperazine,
1-{2-[1-(3,4-Dichlorophenyl)-5-methyl-1H-pyrazol-3-yloxy]ethyl}pyrrolidin-3-amine,
4-{2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]ethyl}morpholine,
4-{2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]ethyl}morpholine,
2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]-N,N-diethylethanamine,
25 1-(3,4-Dichlorophenyl)-4,5-dimethyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,
1-(3,4-Dichlorophenyl)-4,5-dimethyl-3-[3-(pyrrolidin-1-yl)propoxy]-1H-pyrazole,
1-{2-[1-(3,4-Dichlorophenyl)-4,5-dimethyl-1H-pyrazol-3-yloxy]ethyl}piperidine,

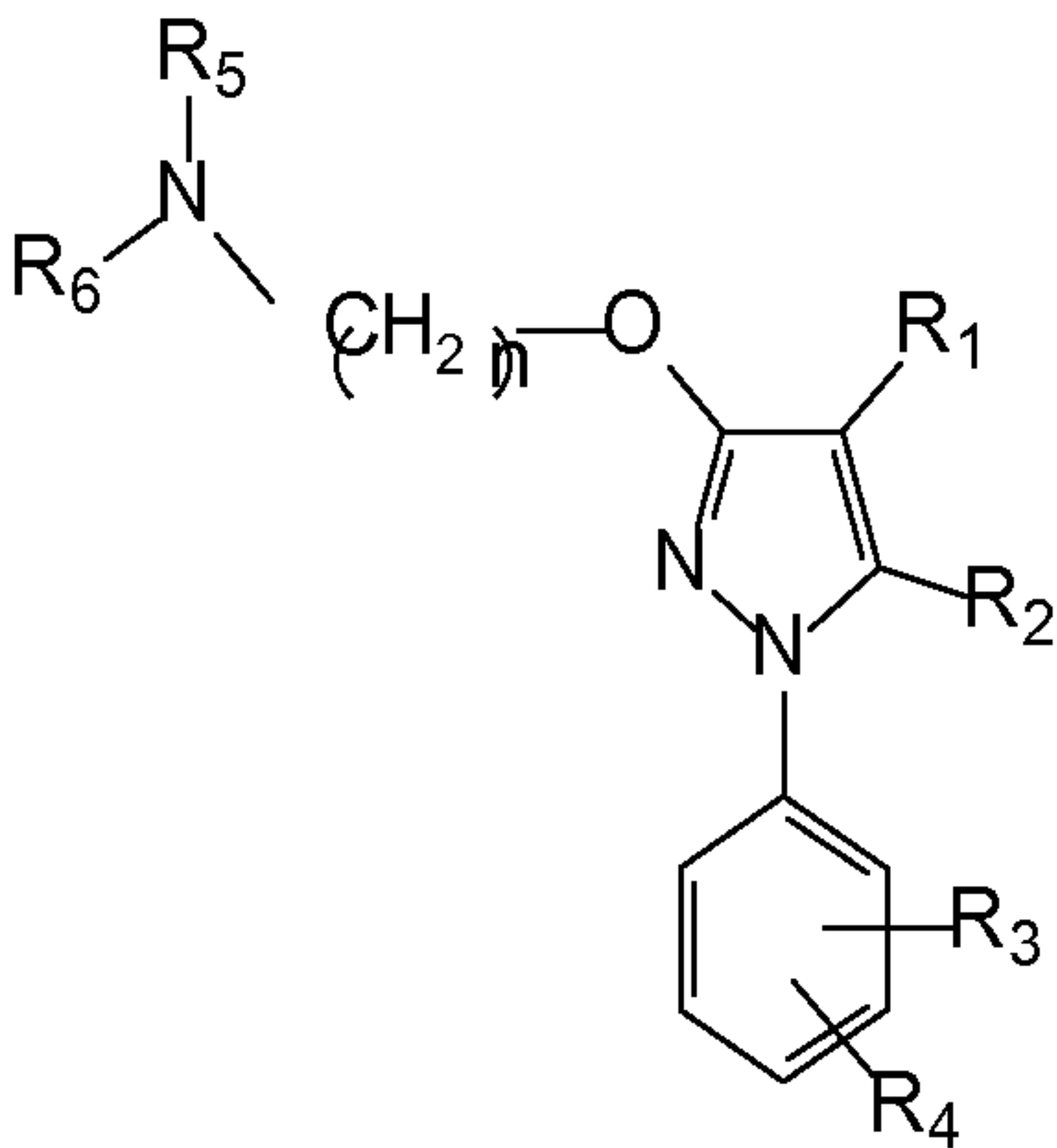
- 4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}morpholine,
 (2S,6R)-4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}-2,6-dimethylmorpholine,
 1-{4-[1-(3,4-Dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}piperidine,
 1-(3,4-Dichlorophenyl)-3-[4-(pyrrolidin-1-yl)butoxy]-1H-pyrazole,
- 5 4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N,N-diethylbutan-1-amine,
 N-benzyl-4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N-methylbutan-1-amine,
 4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]-N-(2-methoxyethyl)-N-methylbutan-1-amine,
 4-{4-[1-(3,4-dichlorophenyl)-1H-pyrazol-3-yloxy]butyl}thiomorpholine,
- 10 1-[1-(3,4-Dichlorophenyl)-5-methyl-3-(2-morpholinoethoxy)-1H-pyrazol-4-yl]ethanone,
 1-{1-(3,4-dichlorophenyl)-5-methyl-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazol-4-yl}ethanone,
 1-{1-(3,4-dichlorophenyl)-5-methyl-3-[2-(piperidin-1-yl)ethoxy]-1H-pyrazol-4-yl}ethanone,
- 15 1-{1-(3,4-dichlorophenyl)-3-[2-(diethylamino)ethoxy]-5-methyl-1H-pyrazol-4-yl}ethanone,
 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine,
 N,N-Diethyl-2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethanamine,
 1-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}piperidine, and
- 20 5-Methyl-1-(naphthalen-2-yl)-3-[2-(pyrrolidin-1-yl)ethoxy]-1H-pyrazole,
 or a pharmaceutically acceptable salt, prodrug or solvate thereof.
8. Sigma ligand according to any preceding claim, wherein the sigma ligand is 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine or a pharmaceutically acceptable salt, prodrug or solvate thereof.
- 25 9. Sigma ligand according to any preceding claim for the simultaneous prevention and/or treatment of chemotherapy or radiotherapy-induced emesis and pain.
10. Combination of at least one sigma ligand as defined in any of claims 1 to 9 and at least one chemotherapeutic drug for simultaneous, separate or sequential

administration, for use in the treatment of cancer and simultaneous prevention and/or treatment of emesis induced by chemotherapy or radiotherapy.

- 5
11. Combination according to claim 10, wherein the chemotherapeutic drug is selected from the group formed by taxanes, vinca alkaloids and drugs derived from platinum.
12. Combination according to claim 11, wherein the chemotherapeutic drug is selected from paclitaxel, oxaliplatin and vincristine.
13. Combination according to any of claims 10 to 12, comprising 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine and paclitaxel
- 10 14. Combination according to any of claims 10 to 12, comprising 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine and oxaliplatin
15. Combination according to any of claims 10 to 12, comprising 4-{2-[5-Methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl} morpholine and vincristine.

FIGURE 1





(I)