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(54) Title: USE OF COMPOUNDS BINDING TO THE SIGMA RECEPTOR LIGANDS FOR THE TREATMENT OF NEUROPATHIC PAIN DEVELOPING AS A CONSEQUENCE OF CHEMOTHERAPY

(57) Abstract: The present invention refers to the use of compounds binding to the sigma receptor for the treatment or prevention of neuropathic pain resulting from chemotherapy.



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**Use of compounds binding to the sigma receptor ligands for
the treatment of neuropathic pain developing as a
consequence of chemotherapy**

Field of the invention

- 5 The present invention refers to the use of compounds binding to the sigma receptor for the treatment or prevention of neuropathic pain resulting from chemotherapy.

Background of the invention

10 The treatment of pain conditions is of great importance in medicine. There is currently a world-wide need for additional pain therapy. The pressing requirement for a specific treatment of pain conditions is documented in the large number of scientific works that have appeared recently in the field of applied analgesics.

15 PAIN is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 210). Although pain is always subjective, its causes or syndromes can be classified. The most relevant pain subtypes discussed in this invention are neuropathic pain, allodynia, hyperalgesia, and especially, peripheral neuropathy.

20 On the other hand, cancer and its associated therapies are some of the biggest health concerns in the world. 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.

25 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 drugs, called chemotherapeutic drugs, to treat cancer. 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.

Peripheral neurotoxicity is a clinically significant complication of cancer chemotherapy. For several of the most effective drugs (e.g. taxanes, vinca alkaloids, cisplatin, bortezomib, thalidomide and lenolidamide), neurotoxicity is dose-limiting and sometimes forces the termination of otherwise successful therapy (Polomano and Bennett, 2001; Park et al., 2008). Since these drugs are the treatment of choice for a multitude of hematologic malignancies and solid tumours, hundred of thousands of patients are affected each year. Sensory abnormalities from antineoplastic-evoked neurotoxicity range from mild paresthesiae or dysesthesiae in many patients, and in some, in chronic painful peripheral neuropathy (Quasthoff and Hartung, 2002). The occurrence and severity of the neuropathy is dependent on single dose intensity, duration of treatment, cumulative dose, prior or concurrent treatment with other neuropathic drugs and co-existing conditions such as diabetes and alcohol abuse (Alberts et al., 1995; Postma et al., 1995; Forsyth et al., 1997; Quasthoff and Hartung, 2002). It is known in the art that neuropathic pain, allodynia, hyperalgesia, 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., 2006; Park et al., 2008; Argyriou et al., 2008). Unfortunately, an effective treatment for chemotherapy-induced peripheral neuropathy has yet to be found (Wolf et al., 2008).

Therefore, the objective of the present invention is to provide a new form of treatment for neuropathic pain, allodynia, hyperalgesia, and especially, peripheral neuropathy, developing as a consequence of chemotherapy.

This invention demonstrates surprisingly that the administration of a compound binding to the sigma receptor is highly effective for the treatment of neuropathic pain, allodynia or hyperalgesia developing after chemotherapy. 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. Even more surprisingly this invention demonstrates that the co-administration of a sigma

ligand and a chemotherapeutic drug prevents the pain onset frequently associated to chemotherapy.

5 The present invention relates to the use of a compound binding to the sigma receptor for the production of a medicament for the treatment of pain developing as a consequence of chemotherapy. The present invention also relates to the use of a compound binding to the sigma receptor for the production of a medicament for the prevention or treatment of pain developing as a consequence of chemotherapy. Preferably, the pain to be treated is neuropathic pain, allodynia or hyperalgesia. More preferably, the pain to be treated is peripheral neuropathic pain, allodynia, causalgia, 10 hyperalgesia, hyperesthesia, hyperpathia, neuralgia, neuritis or neuropathy.

In one preferred embodiment of the invention, the compound binding to the sigma receptor is used for the prevention of the development of pain developing as a consequence of chemotherapy.

15 In another preferred embodiment of the invention, the compound binding to the sigma receptor is used for the treatment of pain developing as a consequence of chemotherapy.

"Chemotherapy", in the sense of this invention, is defined as the use of a chemotherapeutic drug for the treatment of cancer, tumors or malign neoplasia.

20 "Developing as a consequence of chemotherapy" according to this invention is defined as: a) developing after or with at the beginning of 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.

25 "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"). Preferred chemotherapeutic drugs in the sense of this invention are drugs derived

from platin, especially the platin-derivatives cisplatin, carboplatin and oxaliplatin; plant alkaloids and terpenes (terpenoids). Further preferred chemotherapeutic drugs in the sense of this invention are bortezomib, thalidomide and its derivatives, especially lenolidamide.

- 5 “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.

10 “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.

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

Examples of chemotherapeutic drugs (by their trademarks), including paclitaxel (Taxol®), Iressa, Gefintinib and Xyotax 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, 20 Adriamycin®, Aducan®, Agrylin®, Ala-Cort®, Aldesleukin, Alemtuzumab, ALIMTA, Alitretinoin, Alkaban-AQ®, 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, 25 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, 30 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,
 5 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),
 10 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),
 15 Granulocyte macrophage colony stimulating factor (o), Halotestin (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,
 20 Ifosfamide, IL-11, IL-2, Imatinib mesylate, Imidazole Carboxamide, Interferon 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
 25 (t), Liquid Pred (t), Lomustine, L-PAM (o), L-Sarcosyl (o), Lupron (t), Lupron Depot
 (t), 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-
 30 Prednisol (t), MTC (o), MTX (o), Mustargen (t), Mustine, Mutamycin (t), Myleran (t),
 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 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 ®,
 5 Proleukin (t), Prolifeprospan 20 with Carmustine implant (t), Purinethol (t), Raloxifene,
 Revlimid ®, Rheumatrex (t), Rituxan (t), Rituximab, Roferon-A®, (interferon alfa-2a)
 Rubex (t), 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
 10 (t), Temodar ®, Temozolomide, Teniposide, TESPAs (o), Thalidomide, Thalomid ®,
 TheraCys (t), Thioguanine, Thioguanine Tabloid (t), Thiophosphoamide (o), Thioplex
 (t), Thiotepa, 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
 15 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,
 20 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,
 25 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.

Paclitaxel (Taxol®) is one of the most effective and commonly used antineoplastic
 30 drugs for the treatment of solid tumours. It has two serious side effects,

myelosuppression and peripheral neurotoxicity. The granulocyte colony-stimulating factor effectively counteracts the neutropenia in most patients. However, there are no acceptable therapies to prevent or minimize the nerve damage, making neurotoxicity a significant dose-limiting side effect (Rowinsky et al., 1993a, b; Wasserheit et al., 1996; Gordon et al., 1997; Mielke et al., 2006). Paclitaxel-induced neurotoxicity typically presents as a sensory neuropathy, with the most common complaints being numbness, tingling, burning pain and cold allodynia (Rowinsky et al., 1993a; Chaudhry et al., 1994; Forsyth et al., 1997; Dougherty et al., 2004). Sensory symptoms usually start symmetrically in the feet, but sometimes appear simultaneously in both hands and feet (Rowinsky et al., 1993a; Quasthoff and Hartung, 2002; Mielke et al., 2006). A clinically significant number of patients with paclitaxel-induced neuropathy experience neuropathic pain. For example, in a study of 27 patients treated with paclitaxel doses of 135, 175 and 250-300 mg/m², neuropathic symptoms occurred in 50, 79 and 100% of patients, progressing to dose-limiting neurotoxicity in 0, 21 and 71% of patients, respectively (Postma et al., 1995).

“Neuropathic pain” is defined by the IASP as “pain initiated or caused by a primary lesion or dysfunction in the nervous system” (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 210). For the purpose of this invention this term is to be treated as synonymous to “Neurogenic Pain” which is defined by the IASP as “pain initiated or caused by a primary lesion, dysfunction or transitory perturbation in the peripheral or central nervous system”. Neuropathic pain according to this invention is restricted to the neuropathic pain resulting from chemotherapy, meaning caused by the use of a chemotherapeutic drug in chemotherapy. The most likely cause of this pain is the chemotherapeutic drug neurotoxicity, and more specifically, its peripheral neurotoxicity.

According to the IASP “allodynia” is defined as “a pain due to a stimulus which does not normally provoke pain” (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 210). According to the IASP “peripheral neuropathic pain” is defined as “a pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system” and “peripheral neurogenic pain” is defined as “a pain initiated or caused by a primary lesion, dysfunction or transitory perturbation in the peripheral

nervous system" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 213).

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

According to the IASP "hyperalgesia" is defined as "an increased response to a stimulus which is normally painful" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 211).

According to the IASP "hyperesthesia" is defined as "increased sensitivity to stimulation, excluding the senses" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 211).

According to the IASP "hyperpathia" is defined as "a painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212).

The IASP draws the following difference between "allodynia", "hyperalgesia" and "hyperpathia" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212):

Allodynia	Lowered threshold	Stimulus and response mode differ
Hyperalgesia	Increased response	Stimulus and response rate are the same
Hyperpathia	Raised threshold Increased response	Stimulus and response rate may be the same or different

According to the IASP "neuralgia" is defined as "pain in the distribution of a nerve or nerves" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212).

According to the IASP "neuritis" is defined as "inflammation of a nerve or nerves" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212).

- 5 According to the IASP "neuropathy/neuritis" is defined as "a disturbance of function or pathological change in a nerve: in one nerve mononeuropathy, in several nerves mononeuropathy multiplex, if diffuse and bilateral, polyneuropathy" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212).

10 "The sigma receptor/s" as used in this application is/are well known and defined using the following citation: "this binding site represents a typical protein different from opioid, NMDA, dopaminergic, and other known neurotransmitter or hormone receptor families" (G. Ronsisvalle et al. Pure Appl. Chem. 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 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
20 affinity to various analgesics (e.g. pentazocine).

"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.
25 Most preferably, the IC_{50} value is ≤ 50 nM. 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 receptor subtype.

Compounds binding to the sigma receptor, generally also referred to as sigma ligands, are well known in the art. Many of them are encompassed by the "Compound/s binding to the sigma receptor" definition above. Although there are many known uses for sigma ligands, such as antipsychotic drugs, anxiolytics, antidepressants, stroke treatment, antiepileptic drugs and many other indications, including anti-migraine and general pain, there is no mention in the art of these compounds as useful for the treatment of the symptoms of pain developing as a consequence of chemotherapy.

Table 1 lists some sigma ligands known in the art (i.e. having an $IC_{50} \leq 5000$ 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	(-)-SPARTEINE SULFATE PENTAHYDRATE
(+)-HIMBACINE	(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin-1-Yl)-Ethyl Ester
(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)-Carbamic Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester	(S)-Methamphetamine HCl
[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 1-(3-Benzoyloxy-4-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester	[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 2-(Tert-Butoxycarbonyl-Naphthalen-1-Ylmethyl-Amino)-Ethyl Ester
[4-(4-Ethyl-3,5-Dimethyl-Pyrazol-1-Yl)-Phenyl]-[4-(3-Phenyl-Allyl)-Piperazin-1-	1-(1,2-Diphenylethyl)Piperidine Maleate, (+/-)

YI]-Methanone	
1-(1-Naphthyl)Piperazine HCl	1-(3-Chlorophenyl)Piperazine HCl
1-(4-Bromo-Benzenesulfonyl)-4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine	2-(2-{[1-(3-Chloro-Benzyl)-Pyrrolidin-3-YI]-Methyl-Carbamoyl}-2-Methyl-Propyl)-4,6-Dimethyl-Benzoic Acid
2-Chloro-11-(4-Methylpiperazino)Dibenz[B,F]Oxepin Maleate	3,3'-Diethylthiacarbocyanine Iodide
3-Mercapto-2-Methylpropanoic Acid 1,2-Diphenylethylamine Salt	3-Quinuclidinyl Benzilate
3-Tropanyl-3,5-Dichlorobenzoate	3-Tropanyl-Indole-3-Carboxylate HCl
4-(1H-Indol-4-YI)-Piperazine-1-Carboxylic Acid 2-(5-Bromo-2-Ethoxy-Phenylamino)-Cyclohexylmethyl Ester	4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine-1-Carboxylic Acid 2-Thiophen-2-YI-Ethyl Ester
4-(3,5-Dimethoxy-Phenyl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-Benzyl)-Piperidin-2-Ylmethyl Ester	4-(3-Nitro-5-Sulfamoyl-Thiophen-2-YI)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-5-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	4-(5-Trifluoromethyl-Pyridin-2-YI)-Piperazine-1-Carboxylic Acid Pent-2-Ynyl Ester
4,4'-Bis[4-(P-Chlorophenyl)-4-Hydroxypiperidino]Butyrophenone	4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl)-2-hydroxy-4-oxobut-2-enoic acid

4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-YI]-2-Trifluoromethoxy-Benzenesulfonamide	4'-Chloro-3-Alpha-(Diphenylmethoxy)Tropane HCl
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-10-YI)-Propyl]-Piperazin-1-YI}-Ethyl Ester	4-Methoxy-N-[1-(7-Methoxy-Benzo[1,3]Dioxol-5-Ylmethyl)-Pyrrolidin-3-YI]-Benzenesulfonamide
5-(N-Ethyl-N-Isopropyl)-Amiloride	7-Hydroxy-DPAT HBr, (±)-
8-Hydroxy-DPAT HBr, (R)-(+)-	8-Hydroxy-DPAT HBr, S(-)-
9-[4-({[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl}amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide	Acepromazine Maleate
Acetophenazine Maleate	Acrinol
Ajmaline	Alaproclate HCl
Aloe-Emodin	Alprenolol D-Tartrate Salt Hydrate
Alprenolol HCl	AMI-193
Aminobenzotropine	Amiodarone HCl
Amodiaquine HCl	Amorolfine HCl
Amoxapine	Anileridine HCl
Anisotropine Methylbromide	Anpirtoline

ARC 239 DiHCl	Astemizole
Auramine O HCl	Azaperone
Azatadine Maleate	Azelastine HCl
Bamethan sulfate	BD 1008 DiHBr
BD-1047	BD-1063
Benextramine TetraHCl	Benfluorex HCl
Benidipine HCl	Benoxathian HCl
Benoxinate HCl	Benperidol
Benproperine Phosphate	Benzododecinium bromide
Benzphetamine HCl	Benztropine Mesylate
Benzydamine HCl	Bephenium Hydroxynaphthoate
Bepidil HCl	Berberine chloride
Betaxolol HCl	Bifemelane
BMY 7378 DiHCl	Bopindolol Malonate
BP 554 Maleate	Bromhexine HCl
Bromodiphenhydramine HCl	Bromperidol
Brompheniramine Maleate	BTCP HCl

Bucizine HCl	Buflomedil HCl
Bupropion HCl	Buspirone HCl
Butacaine Sulfate	Butaclamol HCl, (±)-
Butenafine HCl	Butoconazole Nitrate
BW 723C86 HCl	Carbetapentane Citrate
Carbinoxamine Maleate	Carpipramine DiHCl DiH ₂ O
Carvedilol	Cephapirin Benzathine
CGS-12066A Maleate	Chloroprocaine HCl
Chloroquine Phosphate	Chlorpheniramine Maleate
Chlorphenoxamine HCl	Chlorpromazine HCl
Chlorprothixene	Cinanserin HCl
Cinnarizine	Cirazoline HCl
Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidinyl)Cyclohexamine DiHBr	Cis(Z)-Flupentixol DiHCl
Cisapride Hydrate	Citalopram HBr
Clebopride Maleate Salt	Clemastine Fumarate
Clemizole HCl	Clenbuterol HCl

Clidinium Bromide	Clobenpropit 2HBr
Clofazimine	Clofilium Tosylate
Clomiphene Citrate	Clomiphene Related Compound A
Clomipramine	Cloperastine HCl
Clorgyline HCl	Clozapine
CONESSINE	Cyclizine
Cyclobenzaprine HCl	Cycloheximide
Cyproheptadine HCl	Darrow Red HCl
Demecarium Bromide	Denatonium Benzoate
Deptropine Citrate	Desloratadine
Dexbrompheniramine Maleate	Dexchlorpheniramine Maleate
Dexfenfluramine HCl	Dibucaine HCl
Dicyclomine HCl	Diethylpropion HCl
Dimethisoquin HCl	Dimetindene Maleate
Diphepanil Methylsulfate	Diphenidol HCl
Diphenoxylate HCl	Diphenylpyraline HCl
Dipropyldopamine HBr	Dobutamine HCl

Donepezil HCl	Doxepin HCl
Droperidol	Duloxetine
Dyclonine HCl	Ebastine
Econazole Nitrate	Epinastine HCl
Ethaverine HCl	Ethopropazine HCl
Eticlopride HCl, S(-)-	Etofenamate
Etonitazenyl Isothiocyanate	Femoxetine HCl
Fenfluramine HCl	Fentanyl Citrate
Fenticonazole Nitrate	Fipexide HCl
Flavoxate HCl	Flunarizine diHCl
Fluoxetine Related Compound B	Fluperlapine
Fluphenazine Decanoate DiHCl	Fluphenazine Enanthate DiHCl
Fluphenazine HCl	Fluphenazine N-Mustard DiHCl
Flurazepam Related Compound C	Fluspirilene
Fluvoxamine Maleate	GBR 12783 DiHCl
GBR 12909 DiHCl	GBR 13069 DiHCl
GBR-12935 DiHCl	GR 89696 Fumarate

Guanabenz Acetate	Guanadrel Sulfate
Guanethidine Sulfate	Halofantrine HCl
Haloperidol	HEAT HCl
Hexylcaine HCl	Hycanthone
Hydroxychloroquine Sulfate	Hydroxyzine HCl
Hyoscyamine Sulfate	IBZM, S(-)-
ICI-199,441 HCl	Ifenprodil Tartrate
Imipramine HCl	Indatraline HCl
Iofetamine HCl	Irinotecan HCl
Isamoltane Hemifumarate	Isopromethazine HCl
Isoxsuprine HCl	Ketanserin L-Tartrate
Ketoconazole	Ketotifen Fumarate Salt
L-693,403 Maleate	L-741,626
L-741,742 HCl	L-745,870 TriHCl
Labetalol HCl	Levetimide HCl, R(-)
Levobunolol HCl	Lidoflazine
Lisuride Hydrogen Maleate, R(+)-	Lobeline HCl

Iomerizine diHCl	Loperamide HCl
Loxapine Succinate	LY-53,857 Maleate
Maprotiline HCl	Mazindol
MDL 12,330A HCl	Mebhydroline 1,5-naphthalendisulfonate Salt
Meclizine HCl	Mefloquine HCl
Meprylcaine HCl	Mesoridazine Besylate
Metaphit Methanesulfonate	Metergoline
Methantheline Bromide	Methdilazine
Methiothepin Mesylate	Methixene HCl
Methoctramine	Methotrimeprazine Maleate
Methylene Violet 3Rax HCl	Metipranolol
Mexiletine HCl	Mianserin HCl
Miconazole	ML-9 HCl
Morantel Hydrogen L-Tartrate	MR 16728 HCl
N-(2-Chloroethyl)-N-Ethyl-2-Bromobenzylamine HCl	N'-[2-(Benzo[1,2,5]Thiadiazole-4-Sulfonylamino)-Acetyl]-Hydrazinecarboxylic Acid 2-(2-{4-[(4-Chloro-Phenyl)-Phenyl-Methyl]-

	Piperazin-1-Yl}-Ethoxy)-Ethyl Ester
Nafronyl Oxalate Salt	Naftifine
Naftopidil diHCl	Naltriben Mesylate
NAN-190 HBr	NE-100
Nefazodone	Nefopam HCl
Nicardipine HCl	Nicergoline
Niguldipine HCl, (+/-)-	Nisoxetine HCl
Nortriptyline HCl	Nylidrin HCl
OctoclothePIN Maleate, (±)-	Orphenadrine Citrate
Oxamniquine	Oxamniquine Related Compound A
Oxamniquine Related Compound B	Oxatomide
Oxiconazole Nitrate	Oxybutynin HCl
Panaxatriol	PAPP
Paroxetine	Paxilline
p-Chlorobenzhydrylpiperazine	Penbutolol Sulfate
Pentamidine Isethionate	Pentazocine, (±)-
Pergolide Methanesulfonate	Perhexiline Maleate Salt

Perospirone	Perphenazine
Perphenazine Sulfoxide	Phenamil Methanesulfonate
Phencyclidine HCl	Phenosafranin HCl
Phenoxybenzamine HCl	Phenyltoloxamine Citrate Salt
Piboserod	Pimozide
Pinacyanol Chloride	Pindobind, (+/-)-
Piperacetazine	Piperazine-1,4-Dicarboxylic Acid Benzyl Ester 2-[4-(4-Dimethylamino- Benzyl)-Piperazin-1-Yl]-Ethyl Ester
Piperidolate HCl	Pirenperone
PPHT HCl, (±)-	Pramoxine HCl
Prenylamine Lactate Salt	Pridinol Methanesulfonate Salt
Prochlorperazine Maleate	Procyclidine HCl
Proflavine Hemisulfate Salt	Progesterone
Promazine HCl	Promethazine HCl
Propafenone HCl	Proparacaine HCl
Propericyazine	Propiomazine
Propranolol HCl	Protokylol

Protriptyline HCl	Pyrilamine Maleate
Pyrimethamine	Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-2-Ylmethyl] Ester 2-Benzyl Ester
Pyrvinium Pamoate	Quetiapine Fumarate
Quinacrine HCl	Quinaldine Red
Quipazine Dimaleate	Quipazine, 6-Nitro-, Maleate
Raloxifene	Rimantadine HCl
Risperidone	Ritanserlin
Ritodrine HCl	RS 23597-190 HCl
RS 67333 HCl	RS 67506 HCl
Safranin O HCl	Salmeterol
SB203186	SCH-23390 HCl, R(+)-
Sertaconazole Nitrate	Sertindole
Sertraline	Sibutramine HCl
SKF-525A HCl	SKF-96365 HCl
SNC 121	Spiperone HCl
Sufentanil	T-226296

Tamoxifen Citrate	Tamsulosin HCl
Tegaserod Maleate	Terbinafine HCl
Terconazole	Terfenadine
Terfenadine Related Compound A	Tetracaine HCl
Tetrindole Mesylate	Thiethylperazine Malate
Thioperamide Maleate	Thiopropazine
Thioridazine	Thiothixene
Thiothixene, (E)-	Thonzonium Bromide
Tioconazole Related Compound A	TMB-8 HCl
Tolterodine L-Tartrate	Toremifene Citrate
Tramazoline HCl	Trans-U-50488 Methanesulfonate, (±)-
Trazodone HCl	Tridihexethyl Chloride
Trifluoperazine HCl	Trifluoperidol HCl
Triflupromazine HCl	Trihexyphenidyl HCl
Trimebutine	Trimeprazine Hemi-L-Tartrate
Trimipramine Maleate	Tripelennamine HCl
Tripolidine HCl	Tripolidine HCl Z Isomer

Tropanyl 3,5-Dimethylbenzoate	Tropine 2-(4-Chlorophenoxy)Butanoate, Maleate
U-50488 HCl, (-)-	U-62066
UH 232 Maleate, (+)-	Vecuronium Bromide
Verapamil HCl	Verapamil Related Compound B
Vesamicol HCl	Vinpocetine
W-7 HCl	WB-4101 HCl
Xylazine	Xylometazoline HCl

Preferably, the table above includes also 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.

- 5 Table 2 lists some sigma ligands known in the art (i.e. having an $IC_{50} \leq 250$ nM)) that show an affinity to the sigma receptor higher than the compounds listed in Table 1. 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 2

(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin-1-Yl)-Ethyl Ester	(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)-Carbamic Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl)-2-hydroxy-4-oxobut-2-enoic acid

4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-YI]-2-Trifluoromethoxy-Benzenesulfonamide	4'-Chloro-3-Alpha-(Diphenylmethoxy)Tropane HCl
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-10-YI)-Propyl]-Piperazin-1-YI}-Ethyl Ester	Acetophenazine Maleate
Aminobenzotropine	Amiodarone HCl
Amodiaquine HCl	Amorolfine HCl
Anileridine HCl	Astemizole
Azaperone	Azelastine HCl
BD 1008 DiHBr	BD-1047
BD-1063	Benextramine TetraHCl
Benfluorex HCl	Benoxathian HCl
Benperidol	Benproperine Phosphate
Benzododecinium bromide	Benztropine Mesylate
Bepriidil HCl	Berberine chloride
Bifemelane	BP 554 Maleate
Bromhexine HCl	Bromodiphenhydramine HCl

Bromperidol	Buflomedil HCl
Butacaine Sulfate	Butaclamol HCl, (±)-
Butenafine HCl	Carbetapentane Citrate
Carpipramine DiHCl DiH ₂ O	Cinnarizine
Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidinyl)Cyclohexamine DiHBr	Cis(Z)-Flupentixol DiHCl
Cisapride Hydrate	Clofilium Tosylate
Clomiphene Citrate	Clomiphene Related Compound A
Clomipramine	Cloperastine HCl
Clorgyline HCl	Cyclobenzaprine HCl
Cyproheptadine HCl	Demecarium Bromide
Deptropine Citrate	Dibucaine HCl
Dicyclomine HCl	Diphenylpyraline HCl
Donepezil HCl	Doxepin HCl
Dyclonine HCl	Femoxetine HCl
Flunarizine diHCl	Fluphenazine Decanoate DiHCl
Fluphenazine Enanthate DiHCl	Fluphenazine HCl

Fluphenazine N-Mustard DiHCl	GBR 12783 DiHCl
GBR 12909 DiHCl	GBR 13069 DiHCl
GBR-12935 DiHCl	Haloperidol
HEAT HCl	Hexylcaine HCl
Hydroxyzine HCl	Ifenprodil Tartrate
Isopromethazine HCl	Isoxsuprine HCl
L-693,403 Maleate	L-741,626
L-741,742 HCl	L-745,870 TriHCl
Lidoflazine	Lobeline HCl
Iomerizine diHCl	Loperamide HCl
LY-53,857 Maleate	Metergoline
Methdilazine	Methixene HCl
Metipranolol	ML-9 HCl
MR 16728 HCl	Naftifine
Naftopidil diHCl	NAN-190 HBr
Nicardipine HCl	Nylidrin HCl
OctoclothePIN Maleate, (±)-	Oxamniquine Related Compound A

Oxybutynin HCl	PAPP
Penbutolol Sulfate	Pentazocine, (±)-
Perphenazine	Phenoxybenzamine HCl
Pimozide	Piperidolate HCl
PPHT HCl, (±)-	Prenylamine Lactate Salt
Prochlorperazine Maleate	Promazine HCl
Proparacaine HCl	Protriptyline HCl
Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-2-Ylmethyl] Ester 2-Benzyl Ester	Pyrvinium Pamoate
Raloxifene	Ritanserlin
RS 67333 HCl	RS 67506 HCl
Salmeterol	Sertindole
Sertraline	SKF-525° HCl
Tamoxifen Citrate	Tegaserod Maleate
Terbinafine HCl	Terconazole
Thioridazine	Toremifene Citrate
TMB-8 HCl	Trifluoperidol HCl

Trifluoperazine HCl	Trimeprazine Hemi-L-Tartrate
Triflupromazine HCl	Tripelennamine HCl
Trimipramine Maleate	Verapamil HCl
U-50488 HCl, (-)-	Xylazine
WB-4101 HCl	

Preferably, the table above includes also 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.

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

10 In this application "about" means "approximately", and illustratively, the use of the term "about" indicates that dosages slightly outside the cited ranges may also be effective and safe, and such dosages are also encompassed by the scope of the present claims.

15 Compounds that are "administered together with compounds binding to the sigma receptor" or "in combination with compounds binding to the sigma receptor" may be administered as part of the same composition, or may be administered separately, at the same or at separate times, in the same therapeutic regimen.

In connection with this invention "neutral form" refers either to a non-ionic form or to a neutrally net charged form, for example a Zwitter-Ion at its isoelectric point.

The term "salt" according to this invention is to be understood as meaning any form of the active compound according to the invention in which this compound assumes

an ionic form or is charged and, if applicable, is also coupled to a counter-ion (a cation or anion). By "salt" is should also be understood complexes of the active compound with other molecules and ions, and in particular complexes which are formed via ionic interactions. Preferred examples of salts include those formed by acetate, mono-trifluoroacetate, acetate ester salt, citrate, formate, picrate, hydrobromide, monohydrobromide, monohydrochloride or hydrochloride ions and molecules.

The term "physiologically acceptable salt" in the context of this invention is understood as meaning a salt of at least one of the compounds according to the invention which are physiologically tolerated by humans and/or mammals.

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

The term "treatment" or "to treat" in the context of this specification means administration of a compound or formulation according to the invention to prevent, ameliorate or eliminate one or more symptoms associated with neuropathic pain, hyperalgesia and/or allodynia.

Furthermore, the terms "to treat" or "treatment" according to this invention include the treatment of symptoms of neuropathic pain, hyperalgesia and/or allodynia, the prevention or the prophylaxis of the symptoms of neuropathic pain, hyperalgesia and/or allodynia, as well as the prevention or prophylaxis of the causes of the neuropathic pain, hyperalgesia and/or allodynia symptoms.

According to the various embodiments of the invention, the compounds binding to the sigma receptor or the pharmaceutical compositions comprising them, may be administered, in unit dosage form, intestinally, enterally, parenterally or topically, orally, subcutaneously, intranasally, by inhalation, by oral absorption, intravenously, intramuscularly, percutaneously, intraperitoneally, rectally, intravaginally, transdermally, sublingually, buccally, orally transmucosally. Administrative dosage forms may include the following: tablets, capsules, dragees, lozenges, patches,

pastilles, gels, pastes, drops, aerosols, pills, powders, liquors, suspensions, emulsions, granules, ointments, creams, suppositories, freeze-dried injections, injectable compositions, in food supplements, nutritional and food bars, syrups, drinks, liquids, cordials etc, which could be regular preparation, delayed-released preparation, controlled-released preparation and various micro-granule delivery system, in food supplements, nutritional and food bars, syrups, drinks, liquids, cordials. In case of tablet, various carriers known in the art may be used, e.g. diluent and resorbent such as starch, dextrin, calcium sulfate, kaolin, microcrystalline cellulose, aluminium silicate, etc; wetting agent and adhesives such as water, glycerin, polyethylene glycol, ethanol, propanol, starch mucilage, dextrin, syrup, honey, glucose solution, acacia, gelatin, carboxymethylcellulose sodium, shellac, methylcellulose, potassium phosphate, polyvinylpyrrolidone, etc; disintegrating agent, such as dried starch, alginate, agar powder, laminaran, sodium bicarbonate and citric acid, calcium carbonate, polyoxyethylene sorbitol aliphatic ester, lauryl sodium sulfate, methylcellulose, ethylcellulose, lactose, sucrose, maltose, mannitol, fructose, various disaccharides and polysaccharides etc; disintegration inhibiting agent, such as sucrose, tristearin, cacao butter, hydrogenated oil, etc; absorption accelerator, such as quaternary ammonium salt, lauryl sodium sulfate, etc; lubricant, such as talc, silica, corn starch, stearate, boric acid, fluid wax, polyethylene, etc. The tablet may be further formulated into coated tablet, e.g. sugar-coated tablet, film-coated tablet, enteric-coated tablet, or double-layer tablet and multi-layer tablet. In the case of pill, various carriers known in the art may be used, e.g. diluent and resorbent, such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oil, polyvinylpyrrolidone, kaolin, talc, etc; adhesives, such as acacia, bassora gum, gelatin, ethanol, honey, liquid sugar, rice paste or flour paste, etc; disintegrating agent, such as agar powder, dried starch, alginate, lauryl sodium sulfate, methylcellulose, ethylcellulose. In case of suppository, various carriers known in the art may be used, e.g. polyethylene, lecithin, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semi-synthetic glyceride, etc. In the case of capsule, it may be prepared by mixing said compound binding to the sigma-receptor as active ingredient with the above mentioned carriers, followed by placing the mixture into a hard gelatin capsule or soft capsule. Also, said compound binding to the sigma-receptor may be applied in the following dosage forms: microcapsules, suspension in an aqueous phase, hard capsule, or injection. In the case of injection, such as liquor,

emulsion, freeze-dried injection, and suspension, all the dilutents common in the art may be used, e.g. water, ethanol, polyethylene glycol, propylene glycol, oxyethylated isostearyl alcohol, polyoxidated isostearyl alcohol, polyoxyethylene sorbitol aliphatic ester, etc. In addition, in order to obtain isotonic injection, a suitable amount of sodium chloride, glucose or glycerin may be added into the preparation, as well as regular cosolvent, buffer, pH adjusting agent, etc. In addition, coloring agent, antiseptic, perfume, correctives, food sweetening agent or other materials may be added to the pharmaceutical preparation if necessary.

In certain embodiments of the invention a formulation or pharmaceutical composition may contain an active ingredient (a compound binding to the sigma receptor) as well as optionally at least one auxiliary material and/or additive. In other embodiments of the invention the formulation or pharmaceutical composition may contain optionally one or more additional active ingredients.

In certain embodiments of the invention the auxiliary material and/or additive can be specifically selected from conserving agents, emulsifiers and/or carriers for parenteral application. The selection of these auxiliary materials and/or additives and of the amounts to be used depends upon how the pharmaceutical composition is to be applied. Examples of these include parenteral formulations such as intravenous subcutaneous or intramuscular application formulations, which could also be applied by other administration routes.

In certain embodiments of the invention the routes of administration of the compound binding to the sigma receptor include intramuscular injection, intravenous injection, subcutaneous injection, sublingual, bucal, patch through skin, oral ingestion, implantable osmotic pump, collagen implants, aerosols or suppository.

In alternative embodiments of the invention the compounds binding to the sigma receptor may be administered in a schedule of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty or more doses per day, alone or in combination with other medications, over range of time periods including but not limited to periods of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen,

sixteen, eighteen, twenty, twenty four, thirty, or more days; or over a period of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, sixteen, eighteen, twenty, twenty four, thirty, thirty six, forty eight, sixty, seventy two, eighty four or more months.

- 5 In some embodiments of the invention the effectiveness of a course of treatment of one, two, three, four, five or more doses or one, two or three days may last for up to about five, ten, fifteen, twenty, twenty five or thirty. In other embodiments of the invention dosing is only performed once every day or once every two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, sixteen, eighteen,
10 twenty, twenty four, thirty or more days.

According to the present disclosure, the dosage of the compound binding to the sigma receptor depends on a variety of factors, including the nature and severity of the diseases, the sex, age, weight and individual reaction of the subject, the particular compound employed, the route and frequency of administration, etc. Said
15 compounds binding to the sigma receptor or the pharmaceutical compositions comprising them may be administered in single or divided dosage form, e.g. one to four doses per day. Those skilled in the art will readily understand and implement the changes to the treatment methods exemplified herein that are necessary or desirable to reflect varied therapeutic requirements.

- 20 In a highly preferred embodiment of the invention the neuropathic pain is peripheral.

According to the IASP "peripheral neuropathic pain" is defined as "a pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system" and "peripheral neurogenic pain" is defined as "a pain initiated or caused by a primary lesion, dysfunction or transitory perturbation in the peripheral nervous system" (IASP,
25 Classification of chronic pain, 2nd Edition, IASP Press (2002), 213).

In another preferred embodiment of the invention the neuropathic pain is allodynia.

According to the IASP "allodynia" is defined as "a pain due to a stimulus which does not normally provoke pain" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 210).

In another preferred embodiment of the invention the neuropathic pain is causalgia.

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

- 10 In another preferred embodiment of the invention the neuropathic pain is hyperalgesia.

According to the IASP "hyperalgesia" is defined as "an increased response to a stimulus which is normally painful" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 211).

- 15 In another preferred embodiment of the invention the neuropathic pain is hyperesthesia.

According to the IASP "hyperesthesia" is defined as "increased sensitivity to stimulation, excluding the senses" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 211).

In another preferred embodiment of the invention the neuropathic pain is hyperpathia.

- 20 According to the IASP "hyperpathia" is defined as "a painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212).

- 25 The IASP draws the following difference between "allodynia", "hyperalgesia" and "hyperpathia" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212):

Allodynia	Lowered threshold	Stimulus and response mode differ
Hyperalgesia	Increased response	Stimulus and response rate are the same
Hyperpathia	Raised threshold Increased response	Stimulus and response rate may be the same or different

In another preferred embodiment of the invention the neuropathic pain is neuralgia.

According to the IASP "neuralgia" is defined as "pain in the distribution of a nerve or nerves" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212).

5 In another preferred embodiment of the invention the neuropathic pain is neuritis.

According to the IASP "neuritis" is defined as "inflammation of a nerve or nerves" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212).

In another preferred embodiment of the invention the neuropathic pain is neuropathy/neuritis.

10 According to the IASP "neuritis" is defined as "a disturbance of function or pathological change in a nerve: in one nerve mononeuropathy, in several nerves mononeuropthy multiplex, if diffuse and bilateral, polyneuropathy" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212).

15 In another preferred embodiment of the invention the neuropathic pain is orofacial pain.

Another aspect of the present invention relates to the use of a compound binding to the sigma receptor, optionally in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable mixing ratio; in neutral form, 5 in the form of an acid or base or in the form of a salt, especially a physiologically acceptable salt, or in the form of a solvate, especially a hydrate for the treatment of allodynia developing as a consequence of chemotherapy.

Another aspect of the present invention relates to the use of a compound binding to the sigma receptor, optionally in the form of its racemate, pure stereoisomers, 10 especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable mixing ratio; in neutral form, in the form of an acid or base or in the form of a salt, especially a physiologically acceptable salt, or in the form of a solvate, especially a hydrate for the production of a medicament for the treatment of hyperalgesia developing as a consequence of 15 chemotherapy.

In a highly preferred embodiment of the invention at least one chemotherapeutic agent used in chemotherapy is selected from a platin-derivative, a vinca alkaloid or a taxane. In another highly preferred embodiment of the invention at least one chemotherapeutic agent used in chemotherapy is selected from a platin-derivative, a 20 vinca alkaloid, a taxane, bortezomib, thalidomide or its derivatives.

In a highly preferred embodiment of the invention at least one chemotherapeutic agent used in chemotherapy is selected from the group consisting of cisplatin, carboplatin and oxaliplatin; vincristine, vinblastine, vinorelbine and vindesine; 25 paclitaxel and docetaxel. In another highly preferred embodiment of the invention at least one chemotherapeutic agent used in chemotherapy is selected from the group consisting of cisplatin, carboplatin and oxaliplatin; vincristine, vinblastine, vinorelbine and vindesine; paclitaxel and docetaxel; bortezomib; thalidomide and lenolidamide.

Preferably, at least one chemotherapeutic agent used in chemotherapy is cisplatin.

Preferably, at least one chemotherapeutic agent used in chemotherapy is carboplatin.

Preferably, at least one chemotherapeutic agent used in chemotherapy is oxaliplatin.

Preferably, at least one chemotherapeutic agent used in chemotherapy is vincristine.

Preferably, at least one chemotherapeutic agent used in chemotherapy is vinblastine.

Preferably, at least one chemotherapeutic agent used in chemotherapy is vinorelbine.

5 Preferably, at least one chemotherapeutic agent used in chemotherapy is vindesine.

Preferably, at least one chemotherapeutic agent used in chemotherapy is paclitaxel.

Preferably, at least one chemotherapeutic agent used in chemotherapy is docetaxel.

Preferably, at least one chemotherapeutic agent used in chemotherapy is bortezomib.

10 Preferably, at least one chemotherapeutic agent used in chemotherapy is thalidomide.

Preferably, at least one chemotherapeutic agent used in chemotherapy is lenolidamide.

15 This invention also includes methods for the treatment of a patient or a mammal, including human, suffering from neuropathic pain developing as a consequence of chemotherapy that involve using a compound binding to the sigma receptor, optionally in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable ratio; in neutral form, in the form of an acid or base or
20 in the form of a salt, especially a physiologically acceptable salt, or in the form of a solvate, especially a hydrate. A preferred method of treatment according to the present invention comprises the application of compound binding to the sigma receptor selected from Tables 1 or 2 or otherwise mentioned herein to a patient or mammal undergoing or about to undergo chemotherapy. It is also preferred if the
25 method of treatment comprises applying at least one chemotherapeutic agent

- selected from a platin-derivative, a vinca alkaloid or a taxane; especially if at least one chemotherapeutic agent is selected from the group consisting of cisplatin, carboplatin and oxaliplatin; vincristine, vinblastine, vinorelbine and vindesine; and paclitaxel and docetaxel. It is preferred as well if the method of treatment comprises
- 5 applying at least one chemotherapeutic agent selected from a platin-derivative, a vinca alkaloid, a taxane, bortezomib, thalidomide or its derivatives; especially if at least one chemotherapeutic agent is selected from the group consisting of cisplatin, carboplatin and oxaliplatin; vincristine, vinblastine, vinorelbine and vindesine; paclitaxel and docetaxel; bortezomib; thalidomide and lenolidamide.
- 10 The method of treatment according to the present invention includes also the co-administration of a chemotherapeutic drug or drugs jointly or in combination with a compound binding to the sigma receptor during chemotherapy. The co-administration may be performed before, during or after chemotherapy. The co-administration could also be periodic or uninterrupted.
- 15 Another highly preferred embodiment of the invention is the treatment or prevention of pain developing as a consequence of chemotherapy, wherein the compound binding to the sigma receptor is combined with at least one chemotherapeutic drug (B) forming a fixed-dose active substance combination. Preferably, the chemotherapeutic drug (B) in this active substance combination is selected from a
- 20 platin-derivative, a vinca alkaloid or a taxane, especially if chemotherapeutic drug (B) is selected from cisplatin, carboplatin and oxaliplatin; vincristine, vinblastine, vinorelbine and vindesine; or paclitaxel and docetaxel. It is also preferable if the chemotherapeutic drug (B) in this active substance combination is selected from a platin-derivative, a vinca alkaloid, a taxane, bortezomib, thalidomide or its derivatives;
- 25 especially if the chemotherapeutic drug (B) from is selected from cisplatin, carboplatin and oxaliplatin; vincristine, vinblastine, vinorelbine and vindesine; paclitaxel and docetaxel; bortezomib; or thalidomide and lenolidamide.

Another alternative embodiment of the present invention refers to a kit comprising a compound binding to the sigma receptor, optionally in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of

30 stereoisomers, especially enantiomers or diastereomers; preferably in any suitable

ratio; in neutral form, in the form of an acid or base or in the form of a salt, especially a physiologically acceptable salt, or in the form of a solvate, especially a hydrate.

5 The orofacial region, the face and mouth, represent sites of some of the most common pains in the body. Epidemiological studies have revealed the high prevalence of several orofacial pain conditions such as temporomandibular disorders (TMD), burning mouth syndrome, and toothaches, (Dworkin, 2001; Feinman and Newton-John, 2004; LeResche, 2001; Lipton et al., 2001). Many of the difficulties experienced by clinicians with the management of acute and chronic orofacial pain conditions stem from a lack of recognition and understanding of their complex factors and interactions, from uncertainties of the aetiology or pathogenesis of many of the conditions, as well as the lack of information of the comparative effectiveness of the analgesic drugs on orofacial pain.

15 Thus, a preferred aspect of the invention is the use of a compound binding to the sigma receptor, optionally in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable mixing ratio; in neutral form, in the form of an acid or base or in the form of a salt, especially a physiologically acceptable salt, or in the form of a solvate, especially a hydrate for the treatment of orofacial pain, preferably, in the form of neuropathic pain, hyperalgesia or allodynia, more preferably, in the form of neuropathic pain, hyperalgesia or allodynia, developing as a consequence of chemotherapy.

All publications mentioned hereinabove are hereby incorporated in their entirety by reference.

25 While the foregoing invention has been described in some detail for purposes of clarity and understanding, it will be appreciated by one skilled in the art from a reading of this disclosure that various changes in form and detail can be made without departing from the true scope of the invention and appended claims.

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

Pharmacological Experiments

Recently, models of paclitaxel-induced painful neuropathy have been developed in mice and rats. These models demonstrated that repeated administration of paclitaxel produced mechanical hyperalgesia and allodynia (Authier et al., 2000; Polomano et al., 2001; Dina et al., 2001 y 2004; Smith et al., 2004; Flatters y Bennett, 2004), cold allodynia (Polomano et al., 2001; Smith et al., 2004; Flatters y Bennett, 2004) and in some studies a thermal (warm) hyperalgesia (Polomano et al., 2001; Dina et al., 2001; Flatters y Bennett, 2004); however, other studies did not find this thermal hyperalgesia (Authier et al., 2000; Smith et al., 2004). Nevertheless, paclitaxel-induced painful neuropathy in rodents represents an interesting model to test the effects of drugs in chemotherapy-induced neuropathic pain.

FIGURES:

Fig. 1: Time-course of paclitaxel induced cold-allodynia in mice. Animals were treated once daily from days 1 to 5 with paclitaxel (2 mg/kg) or its vehicle via i.p. The duration of hind paw licking/biting in the acetone test was recorded 3 days before (PRE) and at several days after the first injection of paclitaxel or its vehicle. Each animal was tested only in one nociceptive model. Each point and vertical line represents the mean \pm S.E.M. of the values obtained in at least 12 mice. Statistically significant differences between the values of paclitaxel- and vehicle-treated groups: * $p < 0.05$; ** $p < 0.01$; and between the values on pre-treatment day and the days after treatment: # $p < 0.05$; ## $p < 0.01$ (two-way repeated measures ANOVA followed by Newman-Keuls test).

Fig. 2: Time-course of the effect of co-administration of paclitaxel + BD-1063 (32 mg/kg) or paclitaxel + saline on duration of hind paw licking/biting in the acetone test. Mice were treated once daily from days 1 to 5 with an s.c. injection of BD-1063 (32 mg/kg) or saline, 30 min before each i.p. injection of paclitaxel (2 mg/kg). The response evaluated was recorded in each animal 3 days before (PRE) and at several days after the first injection of paclitaxel + BD-1063 or paclitaxel + saline. Each point

and vertical line represents the mean \pm S.E.M. of the values obtained in at least 16 animals. Statistically significant differences in comparison to paclitaxel + saline: * $p < 0.05$, ** $p < 0.01$; and between the values on pre-treatment day and the days after treatment: # $p < 0.05$, ## $p < 0.01$ (two-way repeated measures ANOVA followed by Newman-Keuls test).

Fig. 3: Effect of a single treatment with several doses of BD-1063 or saline on the duration of hind paw licking/biting (acetone test) on day 10 (a day of maximum effect) in mice pre-treated with paclitaxel. Animals were treated once daily from days 1 to 5 with paclitaxel or its vehicle via i.p. and the day 10 received a single injection of BD-1063 (8, 16, 32 or 64 mg/kg) or saline. The duration of hind paw licking/biting was recorded in each animal 3 days before (PRE) and 10 days after the first injection of paclitaxel or its vehicle. This day, duration of hind paw licking/biting was recorded immediately before (time 0) and at several times (60, 120 and 180 min) after the injection of BD-1063 or saline. Each animal received either saline or one dose of BD-1063. Each point and vertical line represents the mean \pm S.E.M. of the values obtained in at least 12 animals. Statistically significant differences between the BD-1063- and saline-treated groups on the same day after treatment: * $p < 0.05$; ** $p < 0.01$; and between the values obtained in the pretreatment day and in day 10 at different times after drug or saline administration: # $p < 0.05$; ## $p < 0.01$ (two-way repeated measures ANOVA followed by Newman-Keuls test).

Fig. 4: Time-course of paclitaxel induced cold-allodynia in to groups of mice, one being sigma-1-receptor knock-out mice and the other wild-type mice. Animals were treated once daily from days 1 to 5 with paclitaxel (2 mg/kg) or its vehicle via i.p. The duration of hind paw licking/biting in the acetone test was recorded 3 days before (PRE) and at several days after the first injection of paclitaxel or its vehicle. Each animal was tested only in one nociceptive model. It turned out that only wild-type animals treated with paclitaxel showed increased duration of hind paw licking/biting in the acetone test. Each point and vertical line represents the mean \pm S.E.M. of the values obtained in at least 12 mice. Statistically significant differences between the values of paclitaxel- and vehicle-treated groups: * $p < 0.05$; ** $p < 0.01$; and between

the values on pre-treatment day and the days after treatment: # $p < 0.05$; ## $p < 0.01$ (two-way repeated measures ANOVA followed by Newman-Keuls test).

Fig. 5: Time-course of paclitaxel induced mechanical allodynia in mice. Animals were treated once daily from days 1 to 5 with paclitaxel (2 mg/kg) or its vehicle via i.p. The threshold force in the Von-Frey-test was recorded 3 days before (PRE) and at several days after the first injection of paclitaxel or its vehicle. Each animal was tested only in one nociceptive model. Each point and vertical line represents the mean \pm S.E.M. of the values obtained in at least 12 mice. Statistically significant differences between the values of paclitaxel- and vehicle-treated groups: * $p < 0.05$; ** $p < 0.01$; and between the values on pre-treatment day and the days after treatment: # $p < 0.05$; ## $p < 0.01$ (two-way repeated measures ANOVA followed by Newman-Keuls test).

Fig. 6: Effect of a single treatment with several doses of BD-1063 or saline on the threshold force (von-Frey test) to induce hind paw withdrawal on day 10 (a day of maximum effect) in mice pre-treated with paclitaxel. Animals were treated once daily from days 1 to 5 with paclitaxel or its vehicle via i.p. and the day 10 received a single injection of BD-1063 (8, 16, 32 or 64 mg/kg) or saline. The threshold force was recorded in each animal 3 days before (PRE) and 10 days after the first injection of paclitaxel or its vehicle. This day, threshold force was recorded immediately before (time 0) and at several times (60, 120 and 180 min) after the injection of BD-1063 or saline. Each animal received either saline or one dose of BD-1063. Each point and vertical line represents the mean \pm S.E.M. of the values obtained in at least 12 animals. Statistically significant differences among the BD-1063- and saline-treated groups at the same time after treatment: ** $p < 0.01$; and between the values obtained in the pretreatment day and in day 10 at different times after drug or saline administration: # $p < 0.05$; ## $p < 0.01$ (two-way repeated measures ANOVA followed by Newman-Keuls test).

Fig. 7: Time-course of paclitaxel induced mechanical-allodynia in two groups of mice, one being sigma-1-receptor knock-out mice and the other wild-type mice. Animals were treated once daily from days 1 to 5 with paclitaxel (2 mg/kg) or its vehicle via i.p.

The threshold force in the von-Frey-test was recorded 3 days before (PRE) and at several days after the first injection of paclitaxel or its vehicle. Each animal was tested only in one nociceptive model. It turned out that only wild-type animals treated with paclitaxel showed decreased threshold strength in the von-Frey test. Each point and vertical line represents the mean \pm S.E.M. of the values obtained in at least 12 mice. Statistically significant differences between the values of paclitaxel- and vehicle-treated groups: * $p < 0.05$; ** $p < 0.01$; and between the values on pre-treatment day and the days after treatment: # $p < 0.05$; ## $p < 0.01$ (two-way repeated measures ANOVA followed by Newman-Keuls test).

METHODS:

In general:

Experiments were performed in CD-1 mice (Charles River, U.S.A.) with at least $n = 10$ /experimental group. Paclitaxel-induced painful peripheral neuropathy was produced by i.p. administration of paclitaxel once daily during 5 days. Control animals received the same volume of solvent (a mixture of ethanol and cremophor EL)

Mechanical allodynia was evaluated with an electronically driven Von Frey filament (Dynamic Plantar Aesthesiometer, Ugo Basile, Varese, Italy) as previously described (Nieto et al., 2008), and cold allodynia was evaluated using the acetone drop method (Polomano et al., 2001; Smith et al., 2004).

A well-known sigma receptor antagonist, BD-1063, was injected s.c. either immediately before each paclitaxel injection to test whether a sigma-antagonist affects the development of the painful peripheral neuropathy or at day 10 (when paclitaxel injections have ended and the neuropathy is fully developed) to test whether BD-1063 interferes with the expression of the different signs of paclitaxel-induced neuropathic pain. In addition, in order to study the influence of the sigma 1 receptor in this process the difference in development of allodynia was determined using wild-type mice and sigma 1-receptor knock-out-mice.

Specific description:

Mice weighing 25-30 g were used. The animals were housed in colony cages with free access to food and water prior to the experiments. They were maintained in temperature- and light-controlled rooms (22 ± 1 °C, lights on at 08.00 h and off at 20.00 h, air replacement every 20 min). Testing took place during the light phase (from 9.00 h to 15.00 h).

Paclitaxel was dissolved in a solution made up of 50% Cremophor EL and 50% absolute ethanol to obtain a concentration of 6 mg/ml. This paclitaxel solution was conserved at -20 °C during a maximum of 14 days and was diluted in normal saline (NaCl 0.9%), just before administration, to a final concentration of 2 mg/10 ml. The vehicle of paclitaxel was diluted at the time of injection with saline (NaCl 0.9%) in the same proportion as the paclitaxel solution.

Paclitaxel (2 mg/kg) was administered intraperitoneously (i.p.), in a volume of 10 ml/kg, once per day for five consecutive days. Therefore, the cumulative dose was 10 mg/kg per mouse. In the control group the vehicle of paclitaxel was administered following the same schedule. The same schedules of paclitaxel injection also applied when testing groups of sigma-1-knock-out mice against groups of wild-type mice.

BD-1063 was dissolved in normal saline just before administration and applied at doses of 8, 16, 32 or 64 mg/kg subcutaneously.

The effects of BD-1063 on paclitaxel-induced neuropathic pain were examined in two different ways. To evaluate the effect of the sigma receptor antagonist BD-1063 on the development of paclitaxel-induced pain, the animals received an s.c. injection of BD-1063 30 min before each i.p. injection of paclitaxel for five consecutive days. The response of the animals to the different nociceptive stimuli was tested subsequently during 2-4 weeks, depending on the test (see below), without any additional treatment. Each animal was tested only in one nociceptive model. To test the effect of BD-1063 on the *expression* of paclitaxel-induced pain, a single BD-1063 injection was performed on day 10, a day of maximum expression of mechanical allodynia or cold allodynia (see

figures for details). Each animal received only one dose of BD-1063 and was tested in only one nociceptive model.

Procedure for assessment of cold allodynia. Cold allodynia was tested as previously described by Smith et al., 2004, by gently touching the plantar skin of the hind paws with an acetone bubble formed with a syringe connected to a thin polyethylene tube. The mice were housed and habituated for 30 min in transparent plastic boxes (7 x 7 x 13 cm) with a floor made of wire mesh. After the adaptation period, acetone was applied alternately three times to each paw at intervals of 30 s, and the duration and frequency of licking or biting were recorded. A small mirror was placed behind the chambers to allow clear observation of the paws. The time spent licking or biting the paw was recorded by a stopwatch and represented as the cumulative time of licking/biting in the six measurements. Since licking persisting more than 10 s in the experiments was very unusual, a cut-off time of 10 s was used for each trial.

To elucidate the time-course of paclitaxel-induced cold allodynia in control mice, the animals were tested previously to the paclitaxel administration (pretreatment value, 3 days before first paclitaxel-treatment) and on different days (days 7, 10, 14, 17, 21 and 24) after the first paclitaxel or vehicle injection.

The same procedure was followed to compare sigma-1-knock-out mice to wild type mice, thus elucidating the time-course of paclitaxel-induced cold allodynia in control mice. Accordingly, the animals (two equal groups of knock-out and wild-type mice) were tested previously to paclitaxel administration (pretreatment value, 3 days before first paclitaxel-treatment) and on different days (days 7, 10, 14, 17, 21 and 24) after the first paclitaxel or vehicle injection.

The same procedure was followed to test the effect of BD-1063 on the development of cold allodynia, but in this case, BD-1063 or its vehicle was injected s.c. 30 min before each of the 5 paclitaxel i.p. injections. Once more the animals were tested previously to the paclitaxel/BD-1063 administration (pretreatment value, 3 days before first paclitaxel/BD-1063-treatment) and on different days (days 7, 10, 14, 17, 21 and 24) after the first paclitaxel/BD-1063 or vehicle injection. The effect of BD-

1063 on the expression of paclitaxel-induced cold allodynia was evaluated on day 10, because the maximum allodynic effect was observed on that day. Therefore, the day 10, after the habituation period to the apparatus, baseline latencies were recorded, 30 min later BD-1063 or saline was injected s.c. and paw withdrawal latencies were
5 assessed again 30, 60, 90, 120 and 180 minutes after the injection. Around 33 % of the control animals treated with paclitaxel did not show cold allodynia; therefore, it was differentiated between 'responders' and 'non-responders' mice in this test. The 'non-responders' mice were easily identified because they spent less than 2 s licking/biting the paw stimulated with acetone on days 7 and 10 after paclitaxel
10 administration. The 'non-responder' animals were not used to test the effect of BD-1063 on the expression of cold allodynia since they do not express enough cold allodynia.

Procedure for assessment of mechanical allodynia. To assess mechanical allodynia, paw withdrawal thresholds were measured using a Dynamic Plantar
15 Aesthesiometer (Ugo Basile, Italy). The electronic Von Frey device employs a single nonflexible filament which applies a progressively increasing force (from 0 to 10 g) against the plantar surface of the hind paw over a 20 s period. The nocifensive withdrawal reflex automatically turns off the stimulus and the mechanical threshold value is showed in a screen. The day of the experiment, mice were placed
20 individually in test compartments (9 x 9 x 14 cm) with a wire mesh bottom and allowed to acclimatize to them for 2 h. After habituation, each mouse was tested three times alternately in each hind paw.

To elucidate the time-course of paclitaxel-induced mechanical allodynia in control mice, the animals were tested previously to the paclitaxel administration
25 (pretreatment value; day 3 before paclitaxel-treatment) and on different days (days 7, 10, 14 and 17) after the first paclitaxel or vehicle injection.

The same procedure was followed to compare sigma-1-knock-out mice to wild type mice, thus elucidating the time-course of paclitaxel-induced mechanical allodynia in control mice. Accordingly, the animals (two equal groups of knock-out and wild-type
30 mice were tested previously to the paclitaxel administration (pretreatment value, 3

days before first paclitaxel-treatment) and on different days (days 7, 10, 14, 17, 21 and 24) after the first paclitaxel or vehicle injection.

The same procedure was followed to test the effect of BD-1063, a well-know sigma-receptor antagonist, on the development of paclitaxel-induced mechanical allodynia. In this case, BD-1063 or its vehicle was injected s.c. 30 min before each of the 5 paclitaxel i.p. injections. Once more the animals were tested previously to the paclitaxel/BD-1063 administration (pretreatment value, 3 days before first paclitaxel/BD-1063-treatment) and on different days (days 7, 10, 14, 17, 21 and 24) after the first paclitaxel/BD-1063 or vehicle injection. The effect of BD-1063 on the expression of paclitaxel-induced mechanical allodynia was evaluated on day 10, because the maximum change of the mechanical threshold was observed on that day. Therefore, the day 10, after the habituation period to the apparatus, baseline latencies were recorded, 30 min later BD-1063 or saline was injected s.c. and paw withdrawal latencies were assessed again 30, 60, 90, 120 and 180 minutes after the injection. Most animals (96 %) treated with paclitaxel showed a reduction of the mechanical threshold; those animals that did not show mechanical allodynia were not used to test the effect of BD-1063 on the expression of paclitaxel-induced mechanical allodynia.

Results

A) Time-course of paclitaxel-induced cold- and mechanical-allodynia in control mice. The values obtained on the pre-treatment day in paclitaxel- and vehicle-treated animals were not significantly different in the acetone test and Von Frey test. Administration during 5 days of paclitaxel-vehicle did not significantly modify the response of the animals in any test at any post-treatment day in comparison to the pre-treatment value.

In the acetone test (Fig. 1), administration of paclitaxel (2 mg/kg, i.p.) once daily during 5 days allowed to distinguish between two groups of animals depending on their response. Most animals (67%) treated with paclitaxel increased significantly ($p < 0.01$) the time spent licking/biting the paw stimulated (Fig. 1) and the frequency of paw licking/biting at all the post-treatment days, in comparison to the pre-treatment day value. These animals constitute the paclitaxel-responder animals. On the other

hand, a 33% of paclitaxel-treated animals did not show cold allodynia, and their response to acetone was indistinguishable from that of animals treated with the paclitaxel-vehicle in both duration (Fig. 1) and frequency of licking/biting. When the values of these two variables among the different groups obtained on the same day of evaluation were compared, statistically significant differences between paclitaxel-responder and the other two groups (paclitaxel-non-responder or paclitaxel-vehicle) were observed for each day of evaluation after treatment (Fig. 1). Paclitaxel-induced cold allodynia was maximal 10-14 days after the first injection of the antineoplastic for both variables recorded (Fig. 1); therefore, the effect of BD-1063 on the expression of cold allodynia was evaluated on day 10.

Administration of paclitaxel (2 mg/kg, i.p., during 5 days) induced mechanical allodynia in mice, since it significantly reduced the threshold force for paw withdrawal in the Von Frey test on day 10, in comparison with both the pre-treatment day value and the value obtained the same day in the paclitaxel-vehicle treated animals (Fig. 5). Therefore, the effect of BD-1063 on the expression of mechanical allodynia was tested on day 10.

B) Effect of BD-1063 on the development of paclitaxel-induced cold- and mechanical-allodynia. The pre-treatment values were similar in the two experimental groups (paclitaxel + saline and paclitaxel + BD-1063) in the acetone test.

The group of animals in which paclitaxel (i.p.) and saline (s.c.) were co-administered during days 1 to 5 showed a significant increase on duration of paw licking/biting (Fig. 2) in the acetone test, which began on day 7 and became maximum on days 10-14 after the first injection, as in the experiments were only paclitaxel was injected (Fig. 1). On the other hand, in the animals which received an i.p. co-injection of BD-1063 in a dose of 32 mg/kg together with paclitaxel during days 1 to 5, the duration of paw licking/biting (throughout the 24 days after co-administration) were statistically significantly different between the values obtained in both groups (paclitaxel + saline and paclitaxel + BD-1063 (32 mg/kg)) from day 7 onwards, when duration of licking/biting was analysed. Therefore, the co-administration of paclitaxel i.p. and BD-1063 (32 mg/kg) inhibited the development of cold allodynia induced by paclitaxel.

C) Effect of BD-1063 on the expression of paclitaxel-induced cold allodynia.

The duration and the frequency of paw licking/biting on day 10, before the treatment with BD-1063 or saline, were significantly different from their values on pre-treatment day in all groups of animals treated. As expected, paclitaxel induced a cold allodynia 10 days after its first injection. A single s.c. injection of saline on day 10 did not significantly modify the expression of paclitaxel-induced cold allodynia. The acute treatment with various amounts of BD-1063 (8, 16, 32 or 64 mg/kg) inhibited the expression of paclitaxel-induced cold allodynia. This effect of BD-1063 was dose-dependently, significantly different from that of saline (Fig.3).

D) Effect of BD-1063 on the expression of paclitaxel-induced mechanical allodynia.

The threshold forces of paw withdrawal on day 10, before the treatment with BD-1063 or saline, were significantly different from their values on pre-treatment day in all groups of animals treated. As expected, paclitaxel induced mechanical allodynia 10 days after its first injection. A single s.c. injection of saline on day 10 did not significantly modify the expression of paclitaxel-induced mechanical allodynia. The acute treatment with various amounts of BD-1063 (32 or 64 mg/kg) inhibited the expression of paclitaxel-induced mechanical allodynia. This effect of BD-1063 was dose-dependently, significantly different from that of saline (Fig.6).

E) Time-course of paclitaxel-induced cold-allodynia in a comparison between

wild-type mice and sigma-1-receptor knockout mice. In the acetone test (Fig. 4), administration of paclitaxel (2 mg/kg, i.p.) once daily during 5 days resulted in two groups of animals showing different effects. In wild-type animals, paclitaxel induced cold allodynia was maximal 10 days after the first injection of the antineoplastic (Fig. 4). In contrast, in sigma-1-receptor knockout animals, paclitaxel-induced cold allodynia was not significantly expressed (Fig. 4). Therefore, paclitaxel-induced cold allodynia is an effect related to the sigma-1 receptor.

F) Time-course of paclitaxel-induced mechanical-allodynia in a comparison between wild-type mice and sigma-1-receptor knockout mice.

In the von-Frey test (Fig. 7), administration of paclitaxel (2 mg/kg, i.p.) once daily during 5 days resulted in the two groups of animals showing different effects. In wild-type animals, paclitaxel induced mechanical allodynia was maximal 10 days after the first injection

of the antineoplastic (Fig. 7). In sigma-1-receptor knockout animals, paclitaxel-induced mechanical allodynia was not significantly expressed (Fig. 7). Therefore, paclitaxel-induced mechanical allodynia is an effect related to the sigma-1 receptor.

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10 Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C. Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. Eur J Cancer 2008; 44(11):1507-15.

CLAIMS:

1. Use of a compound binding to the sigma receptor for the treatment or prevention of pain developing as a consequence of chemotherapy.
- 5 2. Use, according to claim 1, in which the compound binding to the sigma receptor is used for the prevention of the development of pain developing as a consequence of chemotherapy.
3. Use, according to claim 1, in which the compound binding to the sigma receptor is used for the treatment of pain developing as a consequence of chemotherapy.
- 10 4. Use, according to claim 3, in which the pain is neuropathic pain, allodynia or hyperalgesia.
5. Use, according to claim 4, in which the neuropathic pain is selected from peripheral neuropathic pain, allodynia, causalgia, hyperalgesia, hyperesthesia, hyperpathia, neuralgia, neuritis or neuropathy.
- 15 6. Use, according to claim 1, characterized in that the compound may be in neutral form, in the form of a base or acid, in the form of a salt, preferably a physiologically acceptable salt, in the form of a solvate or of a polymorph and/or in the form of in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable mixing ratio.
- 20 7. Use, according to claim 1, characterized in that said compound binding to the sigma receptor has an IC₅₀ value of ≤ 5000 nM, preferably in that said compound binding to the sigma receptor has an IC₅₀ value of ≤ 1000 nM, more preferably in that said compound binding to the sigma receptor has an IC₅₀ value of ≤ 500 nM, most preferably in that said compound binding to the sigma receptor has an IC₅₀ value of ≤ 250 nM.
- 25

8. Use, according to claim 1, characterized in that said compound binding to the sigma receptor has an IC₅₀ value of ≤ 100 nM, most preferably in that said compound binding to the sigma receptor has an IC₅₀ value of ≤ 50 nM.
- 5 9. Use, according to any of claims 1 to 6, characterized in that said compound binding to the sigma receptor used is binding to the sigma receptor as an antagonist, a partial antagonist or an inverse agonist.
10. Use, according to any of claims 1 to 9, characterized in that said compound binding to the sigma receptor is binding to the sigma-1 receptor subtype.
- 10 11. Use, according to claim 1, characterized in that said compound binding to the sigma receptor is selected from the group consisting of:

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
(+)-HIMBACINE	(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin- 1-Yl)-Ethyl Ester
(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)- Carbamic Acid 1-(3-Methoxy-2-Nitro- Benzyl)-Piperidin-3-Ylmethyl Ester	(S)-Methamphetamine HCl
[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)- Pyrrolidin-3-Yl]-Carbamic Acid 1-(3- Benzyloxy-4-Methoxy-Benzyl)-Piperidin- 3-Ylmethyl Ester	[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)- Pyrrolidin-3-Yl]-Carbamic Acid 2-(Tert- Butoxycarbonyl-Naphthalen-1- Ylmethyl-Amino)-Ethyl Ester
[4-(4-Ethyl-3,5-Dimethyl-Pyrazol-1-Yl)- Phenyl]-[4-(3-Phenyl-Allyl)-Piperazin-1- Yl]-Methanone	1-(1,2-Diphenylethyl)Piperidine Maleate, (+/-)

1-(1-Naphthyl)Piperazine HCl	1-(3-Chlorophenyl)Piperazine HCl
1-(4-Bromo-Benzenesulfonyl)-4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine	2-(2-[[1-(3-Chloro-Benzyl)-Pyrrolidin-3-Yl]-Methyl-Carbamoyl]-2-Methyl-Propyl)-4,6-Dimethyl-Benzoic Acid
2-Chloro-11-(4-Methylpiperazino)Dibenz[B,F]Oxepin Maleate	3,3'-Diethylthiacarbocyanine Iodide
3-Mercapto-2-Methylpropanoic Acid 1,2-Diphenylethylamine Salt	3-Quinuclidinyl Benzilate
3-Tropanyl-3,5-Dichlorobenzoate	3-Tropanyl-Indole-3-Carboxylate HCl
4-(1H-Indol-4-Yl)-Piperazine-1-Carboxylic Acid 2-(5-Bromo-2-Ethoxy-Phenylamino)-Cyclohexylmethyl Ester	4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine-1-Carboxylic Acid 2-Thiophen-2-Yl-Ethyl Ester
4-(3,5-Dimethoxy-Phenyl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-Benzyl)-Piperidin-2-Ylmethyl Ester	4-(3-Nitro-5-Sulfamoyl-Thiophen-2-Yl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-5-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	4-(5-Trifluoromethyl-Pyridin-2-Yl)-Piperazine-1-Carboxylic Acid Pent-2-Ynyl Ester
4,4'-Bis[4-(P-Chlorophenyl)-4-Hydroxypiperidino]Butyrophenone	4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl)-2-hydroxy-4-oxobut-2-enoic acid
4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-2-	4'-Chloro-3-Alpha-

Trifluoromethoxy-Benzenesulfonamide	(Diphenylmethoxy)Tropane HCl
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-10-Yl)-Propyl]-Piperazin-1-Yl}-Ethyl Ester	4-Methoxy-N-[1-(7-Methoxy-Benzo[1,3]Dioxol-5-Ylmethyl)-Pyrrolidin-3-Yl]-Benzenesulfonamide
5-(N-Ethyl-N-Isopropyl)-Amiloride	7-Hydroxy-DPAT HBr, (±)-
8-Hydroxy-DPAT HBr, (R)-(+)-	8-Hydroxy-DPAT HBr, S(-)-
9-[4-({[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl}amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide	Acepromazine Maleate
Acetophenazine Maleate	Acrinol
Ajmaline	Alaproclate HCl
Aloe-Emodin	Alprenolol D-Tartrate Salt Hydrate
Alprenolol HCl	AMI-193
Aminobenzotropine	Amiodarone HCl
Amodiaquine HCl	Amorolfine HCl
Amoxapine	Anileridine HCl
Anisotropine Methylbromide	Anpirtoline
ARC 239 DiHCl	Astemizole

Auramine O HCl	Azaperone
Azatadine Maleate	Azelastine HCl
Bamethan sulfate	BD 1008 DiHBr
BD-1047	BD-1063
Benextramine TetraHCl	Benfluorex HCl
Benidipine HCl	Benoxathian HCl
Benoxinate HCl	Benperidol
Benproperine Phosphate	Benzododecinium bromide
Benzphetamine HCl	Benztropine Mesylate
Benzydamine HCl	Bephenium Hydroxynaphthoate
Bepidil HCl	Berberine chloride
Betaxolol HCl	Bifemelane
BMY 7378 DiHCl	Bopindolol Malonate
BP 554 Maleate	Bromhexine HCl
Bromodiphenhydramine HCl	Bromperidol
Brompheniramine Maleate	BTCP HCl
Bucizine HCl	Buflomedil HCl

Bupropion HCl	Buspirone HCl
Butacaine Sulfate	Butaclamol HCl, (±)-
Butenafine HCl	Butoconazole Nitrate
BW 723C86 HCl	Carbetapentane Citrate
Carbinoxamine Maleate	Carpipramine DiHCl DiH ₂ O
Carvedilol	Cephapirin Benzathine
CGS-12066A Maleate	Chloroprocaine HCl
Chloroquine Phosphate	Chlorpheniramine Maleate
Chlorphenoxamine HCl	Chlorpromazine HCl
Chlorprothixene	Cinanserin HCl
Cinnarizine	Cirazoline HCl
Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidiny)Cyclohexamine DiHBr	Cis(Z)-Flupentixol DiHCl
Cisapride Hydrate	Citalopram HBr
Clebopride Maleate Salt	Clemastine Fumarate
Clemizole HCl	Clenbuterol HCl
Clidinium Bromide	Clobenpropit 2HBr

Clofazimine	Clofilium Tosylate
Clomiphene Citrate	Clomiphene Related Compound A
Clomipramine	Cloperastine HCl
Clorgyline HCl	Clozapine
CONESSINE	Cyclizine
Cyclobenzaprine HCl	Cycloheximide
Cyproheptadine HCl	Darrow Red HCl
Demecarium Bromide	Denatonium Benzoate
Deptropine Citrate	Desloratadine
Dexbrompheniramine Maleate	Dexchlorpheniramine Maleate
Dexfenfluramine HCl	Dibucaine HCl
Dicyclomine HCl	Diethylpropion HCl
Dimethisoquin HCl	Dimetindene Maleate
Diphepanil Methylsulfate	Diphenidol HCl
Diphenoxylate HCl	Diphenylpyraline HCl
Dipropyldopamine HBr	Dobutamine HCl
Donepezil HCl	Doxepin HCl

Droperidol	Duloxetine
Dyclonine HCl	Ebastine
Econazole Nitrate	Epinastine HCl
Ethaverine HCl	Ethopropazine HCl
Eticlopride HCl, S(-)-	Etofenamate
Etonitazenyl Isothiocyanate	Femoxetine HCl
Fenfluramine HCl	Fentanyl Citrate
Fenticonazole Nitrate	Fipexide HCl
Flavoxate HCl	Flunarizine diHCl
Fluoxetine Related Compound B	Fluperlapine
Fluphenazine Decanoate DiHCl	Fluphenazine Enanthate DiHCl
Fluphenazine HCl	Fluphenazine N-Mustard DiHCl
Flurazepam Related Compound C	Fluspirilene
Fluvoxamine Maleate	GBR 12783 DiHCl
GBR 12909 DiHCl	GBR 13069 DiHCl
GBR-12935 DiHCl	GR 89696 Fumarate
Guanabenz Acetate	Guanadrel Sulfate

Guanethidine Sulfate	Halofantrine HCl
Haloperidol	HEAT HCl
Hexylcaine HCl	Hycanthone
Hydroxychloroquine Sulfate	Hydroxyzine HCl
Hyoscyamine Sulfate	IBZM, S(-)-
ICI-199,441 HCl	Ifenprodil Tartrate
Imipramine HCl	Indatraline HCl
Iofetamine HCl	Irinotecan HCl
Isamoltane Hemifumarate	Isopromethazine HCl
Isoxsuprine HCl	Ketanserin L-Tartrate
Ketoconazole	Ketotifen Fumarate Salt
L-693,403 Maleate	L-741,626
L-741,742 HCl	L-745,870 TriHCl
Labetalol HCl	Levetimide HCl, R(-)
Levobunolol HCl	Lidoflazine
Lisuride Hydrogen Maleate, R(+)-	Lobeline HCl
Iomerizine diHCl	Loperamide HCl

Loxapine Succinate	LY-53,857 Maleate
Maprotiline HCl	Mazindol
MDL 12,330A HCl	Mebhydroline 1,5-naphthalendisulfonate Salt
Meclizine HCl	Mefloquine HCl
Meprylcaine HCl	Mesoridazine Besylate
Metaphit Methanesulfonate	Metergoline
Methantheline Bromide	Methdilazine
Methiothepin Mesylate	Methixene HCl
Methoctramine	Methotrimeprazine Maleate
Methylene Violet 3Rax HCl	Metipranolol
Mexiletine HCl	Mianserin HCl
Miconazole	ML-9 HCl
Morantel Hydrogen L-Tartrate	MR 16728 HCl
N-(2-Chloroethyl)-N-Ethyl-2-Bromobenzylamine HCl	N'-[2-(Benzo[1,2,5]Thiadiazole-4-Sulfonylamino)-Acetyl]-Hydrazinecarboxylic Acid 2-(2-{4-[(4-Chloro-Phenyl)-Phenyl-Methyl]-Piperazin-1-Yl}-Ethoxy)-Ethyl Ester

Nafronyl Oxalate Salt	Naftifine
Naftopidil diHCl	Naltriben Mesylate
NAN-190 HBr	NE-100
Nefazodone	Nefopam HCl
Nicardipine HCl	Nicergoline
Niguldipine HCl, (+/-)-	Nisoxetine HCl
Nortriptyline HCl	Nylidrin HCl
OctoclothePIN Maleate, (±)-	Orphenadrine Citrate
Oxamniquine	Oxamniquine Related Compound A
Oxamniquine Related Compound B	Oxatomide
Oxiconazole Nitrate	Oxybutynin HCl
Panaxatriol	PAPP
Paroxetine	Paxilline
p-Chlorobenzhydrylpiperazine	Penbutolol Sulfate
Pentamidine Isethionate	Pentazocine, (±)-
Pergolide Methanesulfonate	Perhexiline Maleate Salt
Perospirone	Perphenazine

Perphenazine Sulfoxide	Phenamil Methanesulfonate
Phencyclidine HCl	Phenosafranin HCl
Phenoxybenzamine HCl	Phenyltoloxamine Citrate Salt
Piboserod	Pimozide
Pinacyanol Chloride	Pindobind, (+/-)-
Piperacetazine	Piperazine-1,4-Dicarboxylic Acid Benzyl Ester 2-[4-(4-Dimethylamino- Benzyl)-Piperazin-1-Yl]-Ethyl Ester
Piperidolate HCl	Pirenperone
PPHT HCl, (±)-	Pramoxine HCl
Prenylamine Lactate Salt	Pridinol Methanesulfonate Salt
Prochlorperazine Maleate	Procyclidine HCl
Proflavine Hemisulfate Salt	Progesterone
Promazine HCl	Promethazine HCl
Propafenone HCl	Proparacaine HCl
Propericyazine	Propiomazine
Propranolol HCl	Protokylol
Protriptyline HCl	Pyrilamine Maleate

Pyrimethamine	Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-2-Ylmethyl] Ester 2-Benzyl Ester
Pyrvinium Pamoate	Quetiapine Fumarate
Quinacrine HCl	Quinaldine Red
Quipazine Dimaleate	Quipazine, 6-Nitro-, Maleate
Raloxifene	Reduced Haloperidol
Rimantadine HCl	
Risperidone	Ritanserlin
Ritodrine HCl	RS 23597-190 HCl
RS 67333 HCl	RS 67506 HCl
Safranin O HCl	Salmeterol
SB203186	SCH-23390 HCl, R(+)-
Sertaconazole Nitrate	Sertindole
Sertraline	Sibutramine HCl
SKF-525A HCl	SKF-96365 HCl
SNC 121	Spiperone HCl
Sufentanil	T-226296

Tamoxifen Citrate	Tamsulosin HCl
Tegaserod Maleate	Terbinafine HCl
Terconazole	Terfenadine
Terfenadine Related Compound A	Tetracaine HCl
Tetrindole Mesylate	Thiethylperazine Malate
Thioperamide Maleate	Thiopropazine
Thioridazine	Thiothixene
Thiothixene, (E)-	Thonzonium Bromide
Tioconazole Related Compound A	TMB-8 HCl
Tolterodine L-Tartrate	Toremifene Citrate
Tramazoline HCl	Trans-U-50488 Methanesulfonate, (±)-
Trazodone HCl	Tridihexethyl Chloride
Trifluoperazine HCl	Trifluoperidol HCl
Triflupromazine HCl	Trihexyphenidyl HCl
Trimebutine	Trimeprazine Hemi-L-Tartrate
Trimipramine Maleate	Tripelennamine HCl
Tripolidine HCl	Tripolidine HCl Z Isomer

Tropanyl 3,5-Dimethylbenzoate	Tropine 2-(4-Chlorophenoxy)Butanoate, Maleate
U-50488 HCl, (-)-	U-62066
UH 232 Maleate, (+)-	Vecuronium Bromide
Verapamil HCl	Verapamil Related Compound B
Vesamicol HCl	Vinpocetine
W-7 HCl	WB-4101 HCl
Xylazine	Xylometazoline HCl

12. Use, according to claim 11, characterized in that said compound binding to the sigma receptor is selected from the group consisting of:

(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin-1-Yl)-Ethyl Ester	(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)-Carbamic Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl)-2-hydroxy-4-oxobut-2-enoic acid
4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-2-Trifluoromethoxy-Benzenesulfonamide	4'-Chloro-3-Alpha-(Diphenylmethoxy)Tropane HCl
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-10-Yl)-	Acetophenazine Maleate

Propyl]-Piperazin-1-Yl)-Ethyl Ester	
Aminobenzotropine	Amiodarone HCl
Amodiaquine HCl	Amorolfine HCl
Anileridine HCl	Astemizole
Azaperone	Azelastine HCl
BD 1008 DiHBr	BD-1047
BD-1063	Benextramine TetraHCl
Benfluorex HCl	Benoxathian HCl
Benperidol	Benproperine Phosphate
Benzododecinium bromide	Benztropine Mesylate
Bepriidil HCl	Berberine chloride
Bifemelane	BP 554 Maleate
Bromhexine HCl	Bromodiphenhydramine HCl
Bromperidol	Buflomedil HCl
Butacaine Sulfate	Butaclamol HCl, (±)-
Butenafine HCl	Carbetapentane Citrate
Carpipramine DiHCl DiH ₂ O	Cinnarizine

Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidinyl)Cyclohexamine DiHBr	Cis(Z)-Flupentixol DiHCl
Cisapride Hydrate	Clofilium Tosylate
Clomiphene Citrate	Clomiphene Related Compound A
Clomipramine	Cloperastine HCl
Clorgyline HCl	Cyclobenzaprine HCl
Cyproheptadine HCl	Demecarium Bromide
Deptropine Citrate	Dibucaine HCl
Dicyclomine HCl	Diphenylpyraline HCl
Donepezil HCl	Doxepin HCl
Dyclonine HCl	Femoxetine HCl
Flunarizine diHCl	Fluphenazine Decanoate DiHCl
Fluphenazine Enanthate DiHCl	Fluphenazine HCl
Fluphenazine N-Mustard DiHCl	GBR 12783 DiHCl
GBR 12909 DiHCl	GBR 13069 DiHCl
GBR-12935 DiHCl	Haloperidol
HEAT HCl	Hexylcaine HCl

Hydroxyzine HCl	Ifenprodil Tartrate
Isopromethazine HCl	Isoxsuprine HCl
L-693,403 Maleate	L-741,626
L-741,742 HCl	L-745,870 TriHCl
Lidoflazine	Lobeline HCl
Iomerizine diHCl	Loperamide HCl
LY-53,857 Maleate	Metergoline
Methdilazine	Methixene HCl
Metipranolol	ML-9 HCl
MR 16728 HCl	Naftifine
Naftopidil diHCl	NAN-190 HBr
Nicardipine HCl	Nylidrin HCl
Octoclotheptin Maleate, (±)-	Oxamniquine Related Compound A
Oxybutynin HCl	PAPP
Penbutolol Sulfate	Pentazocine, (±)-
Perphenazine	Phenoxybenzamine HCl
Pimozide	Piperidolate HCl

PPHT HCl, (±)-	Prenylamine Lactate Salt
Prochlorperazine Maleate	Promazine HCl
Proparacaine HCl	Protriptyline HCl
Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-2-Ylmethyl] Ester 2-Benzyl Ester	Pyrvinium Pamoate
Raloxifene	Reduced Haloperidol
Ritanserlin	
RS 67333 HCl	RS 67506 HCl
Salmeterol	Sertindole
Sertraline	SKF-525A HCl
Tamoxifen Citrate	Tegaserod Maleate
Terbinafine HCl	Terconazole
Thioridazine	Toremifene Citrate
TMB-8 HCl	Trifluoperidol HCl
Trifluoperazine HCl	Trimeprazine Hemi-L-Tartrate
Triflupromazine HCl	Tripelennamine HCl
Trimipramine Maleate	Verapamil HCl

U-50488 HCl, (-)-	Xylazine
WB-4101 HCl	

- 5 13. Use, according to any of claims 1 to 12, characterized in that at least one chemotherapeutic agent used in the chemotherapy is selected from a platin-derivative, a vinca alkaloid or a taxane, bortezomib or thalidomide and its derivatives.
14. Use, according to claim 13 characterized in that at least one chemotherapeutic agent used in the chemotherapy is selected from the group consisting of cisplatin, carboplatin and oxaliplatin; vincristine, vinblastine, vinorelbine and vindesine; paclitaxel and docetaxel, bortezomib, thalidomide and lenolidamide.
- 10 15. Use, according to claim 1 for the treatment or prevention of pain developing as a consequence of chemotherapy, wherein the compound binding to the sigma receptor is combined with at least one chemotherapeutic drug (B) forming a fixed-dose active substance combination.
- 15 16. Use, according to claim 15, wherein the chemotherapeutic drug (B) is selected from a platin-derivative, a vinca alkaloid or a taxane, bortezomib or thalidomide and its derivatives,
- especially the chemotherapeutic drug (B) is selected from cisplatin, carboplatin and oxaliplatin; vincristine, vinblastine, vinorelbine and vindesine; paclitaxel and docetaxel, bortezomib, thalidomide and lenolidamide.

Fig. 1)

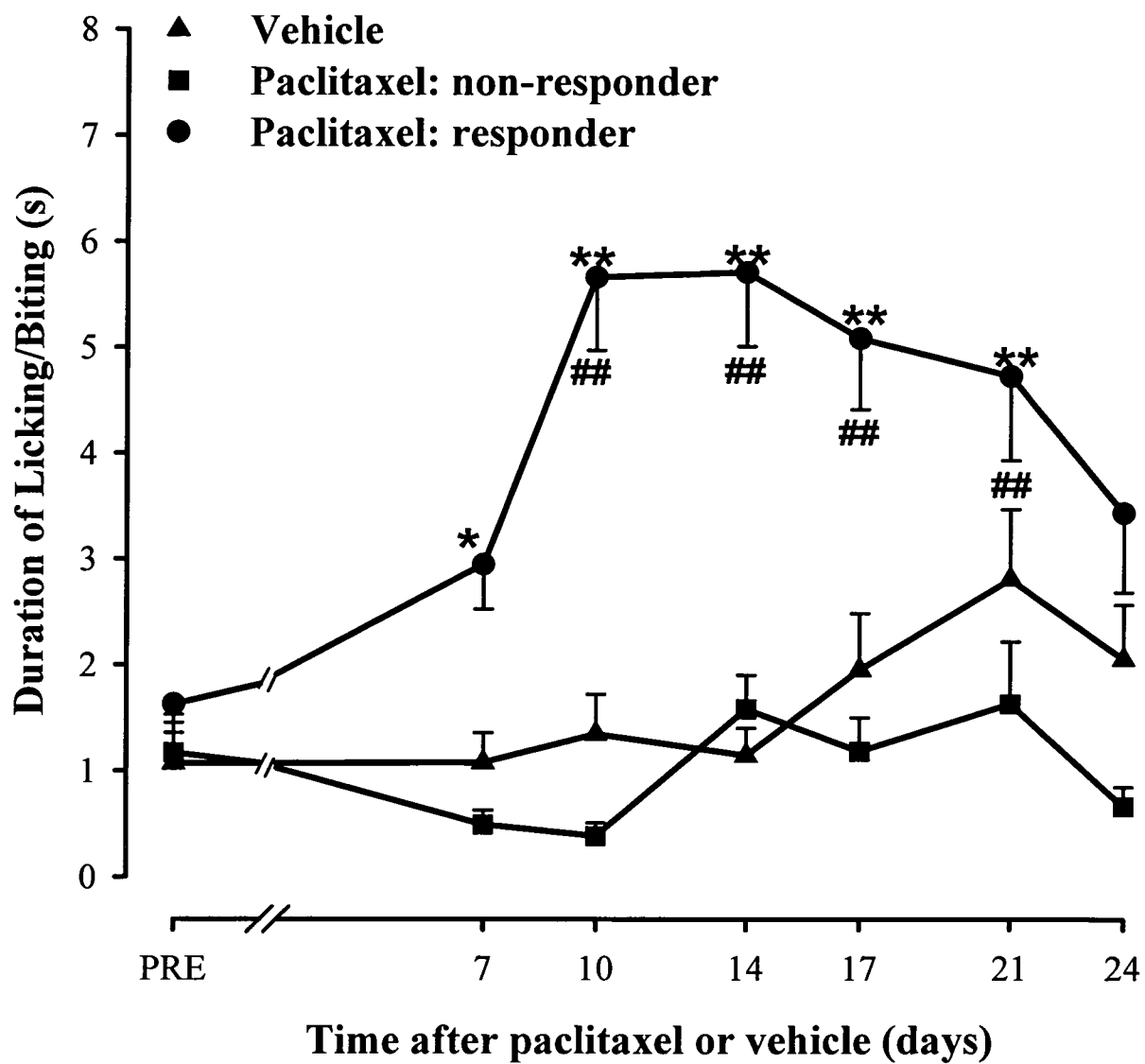


Fig. 2)

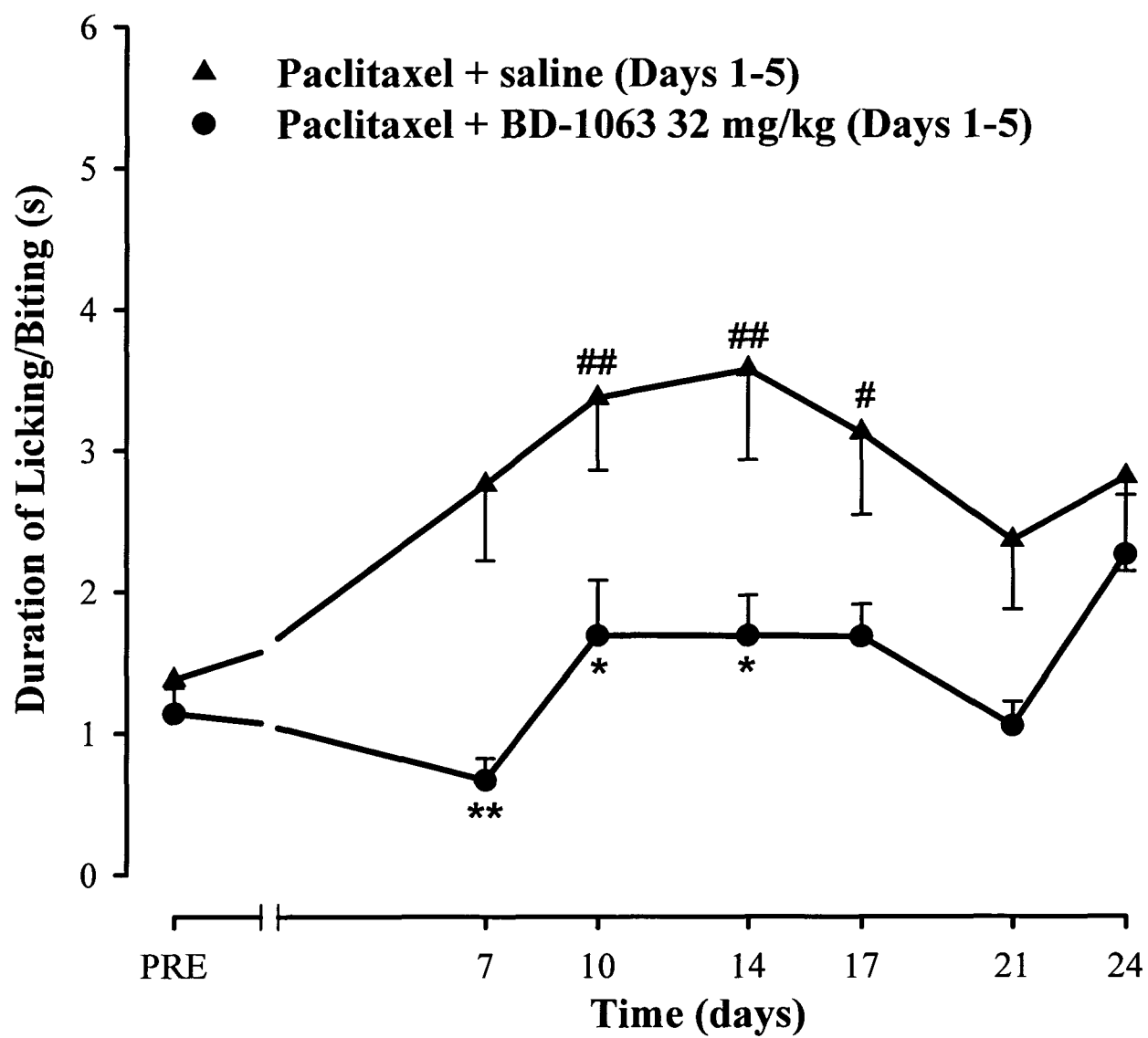


Fig. 3)

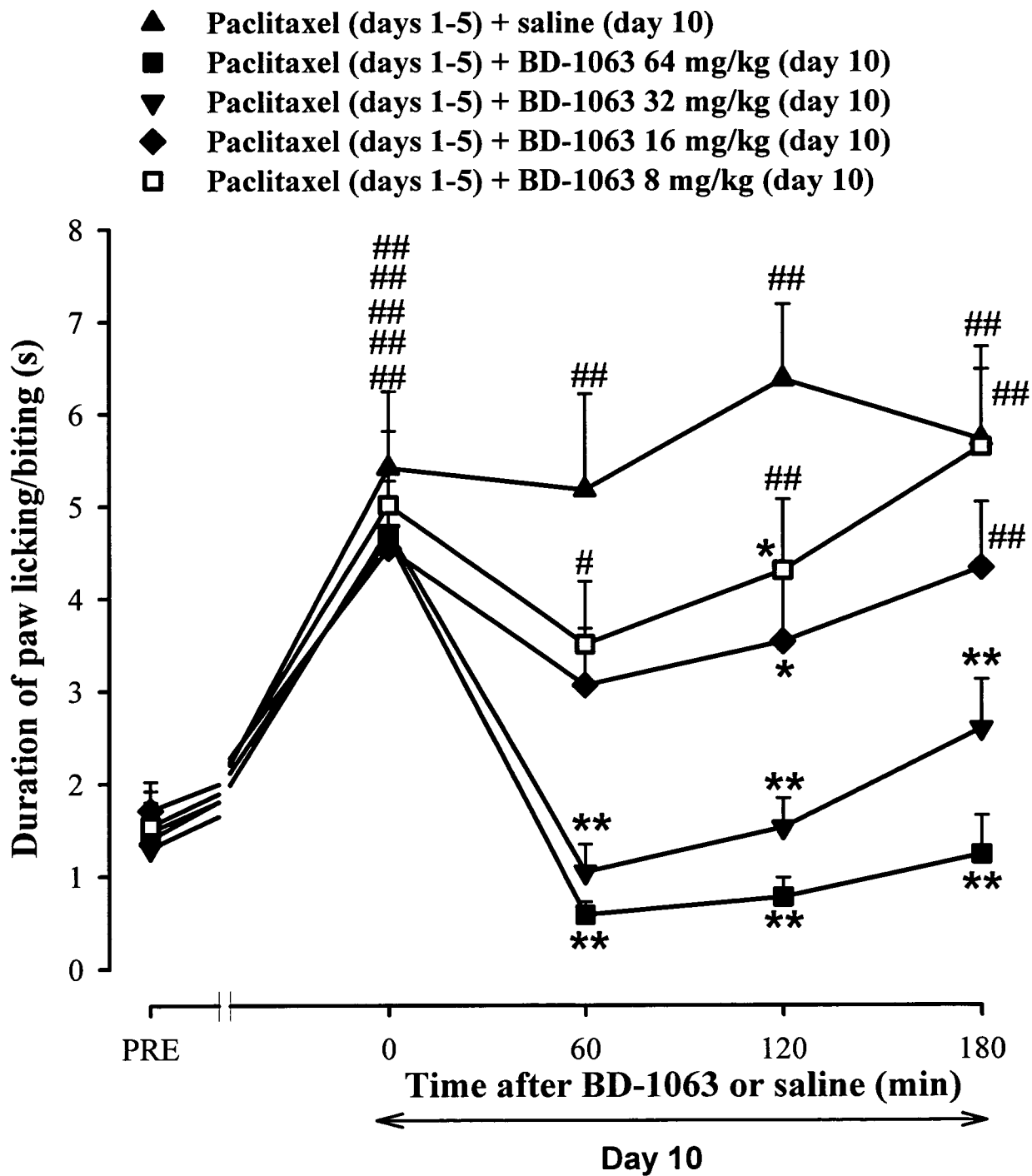


Fig. 4)

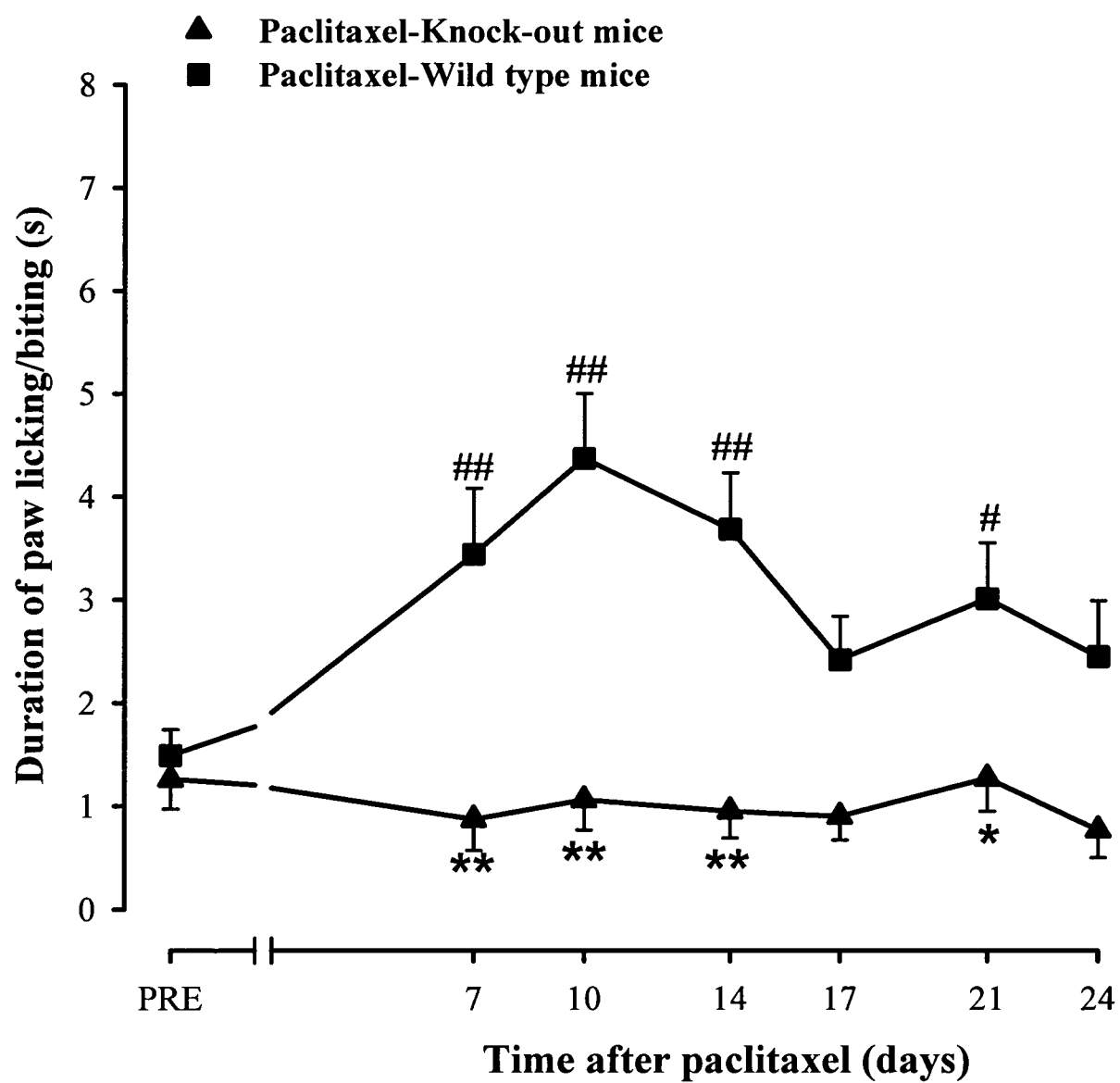


Fig. 5)

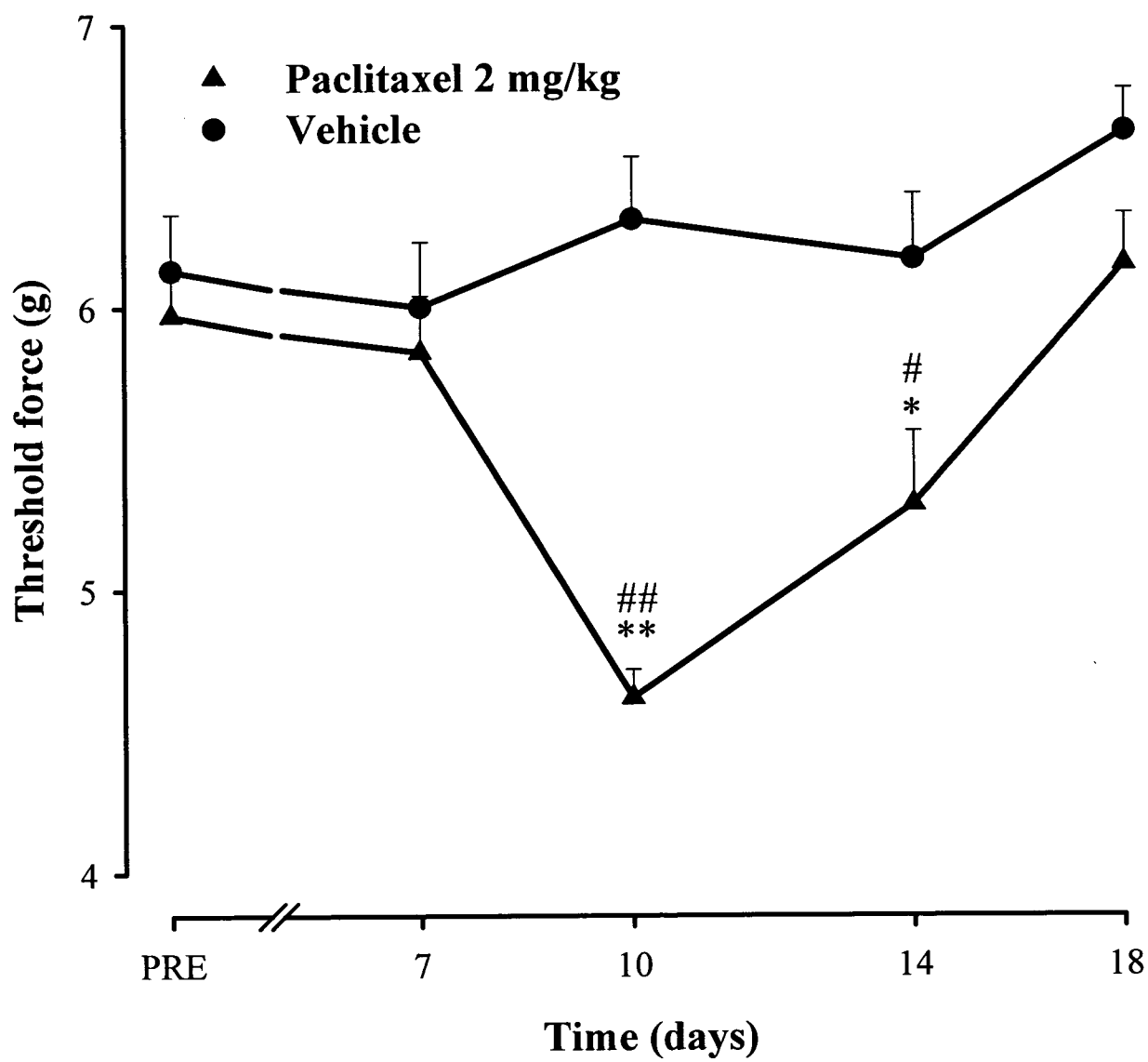


Fig. 6)

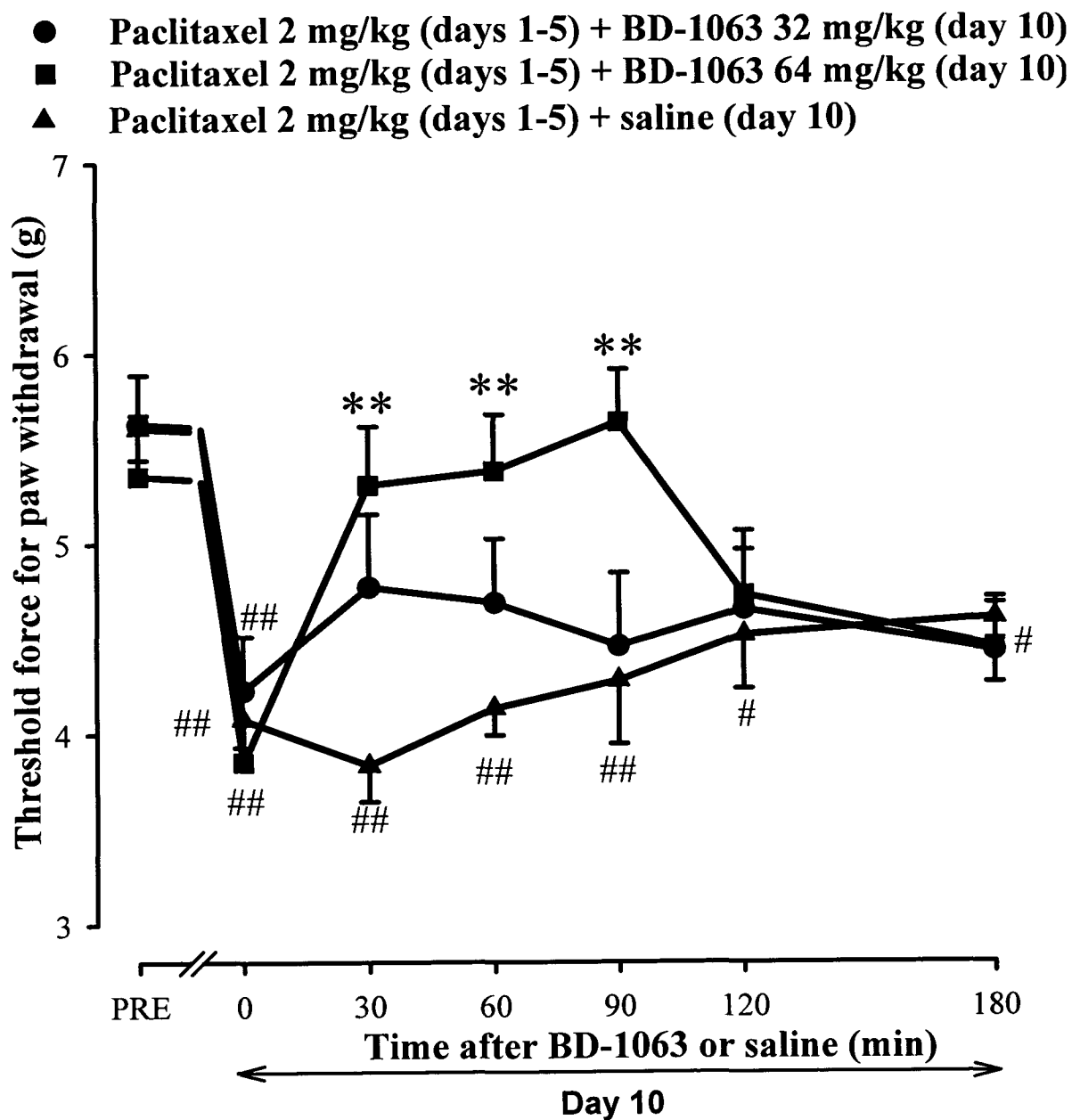
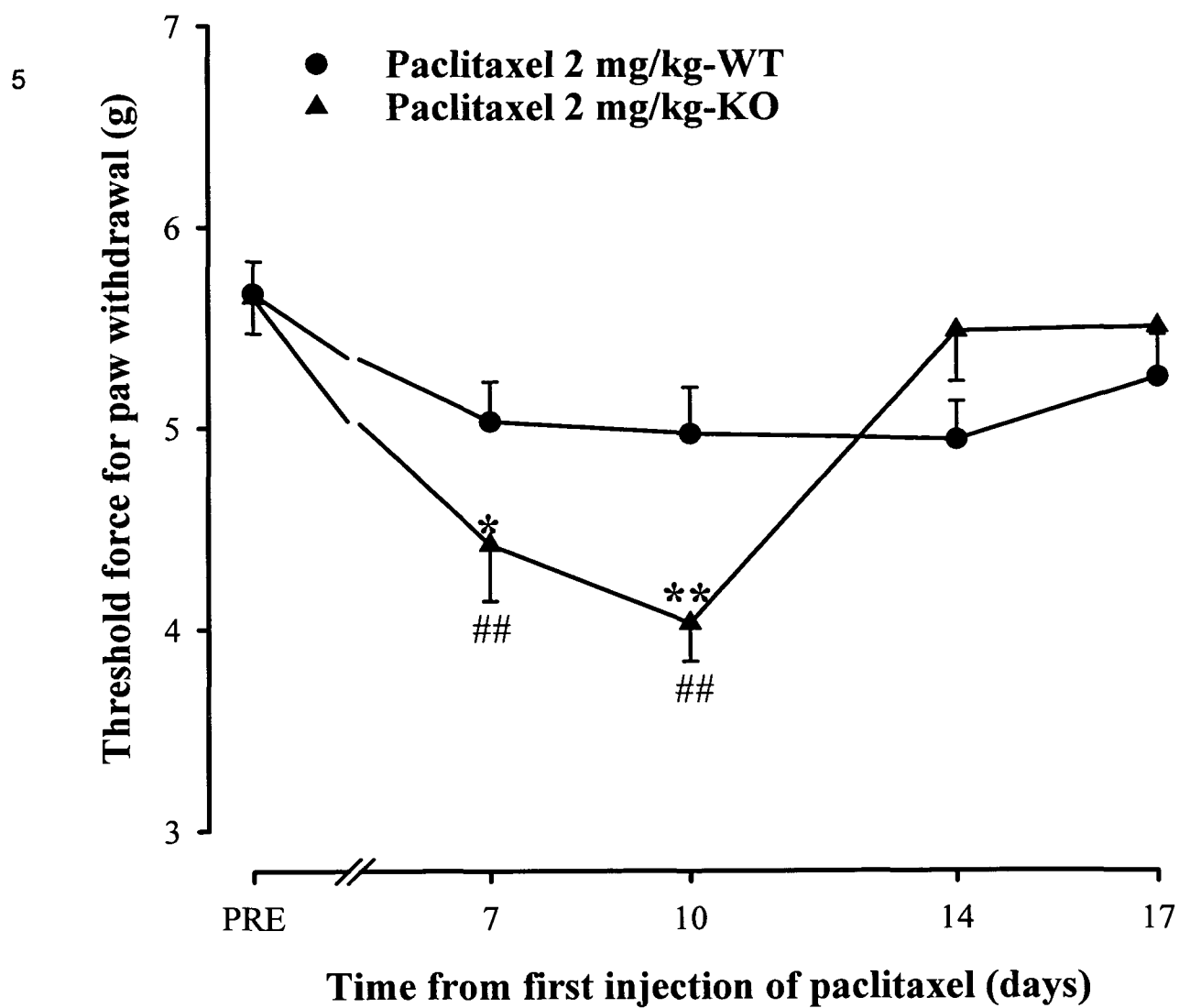


Fig. 7)



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/001109

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/495 A61P25/02 A61P29/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/025613 A (ESTEVE LABOR DR [ES]; BUSCHMANN HELMUT H [ES]) 8 March 2007 (2007-03-08) page 4 - page 12 page 16, line 3 - line 8 page 16, line 25	1-16
X	WO 2006/010587 A (ESTEVE LABOR DR [ES]; BAEYENS CABRERA JOSE MANUEL [ES]) 2 February 2006 (2006-02-02) page 4 - page 9	1-16

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

30 June 2009

Date of mailing of the international search report

07/07/2009

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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