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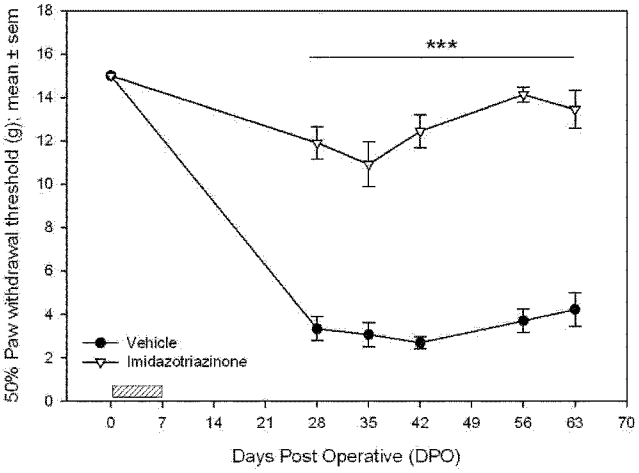
(54) **Title**: USE OF IMIDAZOTRIAZINONES IN NEUROPATHIC PAIN

FIGURE 1

The development of SCI induced pain can be prevented by imidazotriazinone treatment



(57) **Abstract**: Provided herein are compounds for use in the treatment of neuropathic pain and the neuropathic pain syndromes, in particular the use of imidazotriazinones. Pharmaceutical compositions, single unit dosage forms, and kit suitable for use for the treatment of neuropathic pain and the neuropathic pain syndromes are also disclosed.

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USE OF IMIDAZOTRIAZINONES IN NEUROPATHIC PAIN

FIELD OF THE DISCLOSURE

The technology provided herein relates to the novel use of imidazotriazinones and their derivatives in the treatment of neuropathic pain.

BACKGROUND

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.

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". Although pain is always subjective, its causes or syndromes can be classified. One of the most relevant pains is neuropathic pain which severely impairs the overall quality of life, and which is one of the most devastating forms of chronic pain.

Neuropathic pain is caused by, for example, injury or dysfunction in a peripheral or central nervous system. Disorders with neuropathic pain include, for example, disorders that exhibit hyperalgesic or allodynic symptoms, such as postherpetic neuralgia, trigeminal neuralgia, diabetic neuralgia, and persistent postoperative or posttraumatic pain.

Neuropathic pain may result from disorders of the peripheral nervous system or the central nervous system (brain and spinal cord). Thus, neuropathic pain may be divided into peripheral neuropathic pain, central neuropathic pain, or mixed (peripheral and central) neuropathic pain.

Peripheral nerve injury or dysfunction can result in peripheral neuropathic pain. Examples are mononeuropathies (eg, carpal tunnel syndrome, radiculopathy), plexopathies (typically caused by nerve compression, as by a neuroma, tumor, or herniated disk), and polyneuropathies (typically caused by various metabolic neuropathies. Under normal circumstances, pain sensations are carried by unmyelinated and thinly myelinated nerve fibers, designated C-fibers and A-delta fibers respectively. After a peripheral nervelesion, a neuroma may develop at the stump. The neurons become unusually sensitive and develop spontaneous pathological activity, abnormal excitability, and elevated sensitivity to chemical, thermal and mechanical stimuli. This phenomenon is called peripheral sensitization.

Central neuropathic pain is found in spinal cord injury, multiple sclerosis, and in some cases of stroke. In the spinal cord the spinothalamic tract (STT) constitutes the major ascending nociceptive pathway. As a consequence of ongoing spontaneous activity arising in the periphery, STT neurons in the dorsal horn develop an increased background activity, enlarged receptive field and increased responses to afferent impulses, including normally innocuous tactile stimuli. This phenomenon is called central sensitization. Central sensitization has been proposed as an important mechanism of persistent neuropathic pain. Non-neural glial cells and the immune response play a prominent role in central sensitization.

Typical symptoms of neuropathic pain are dysesthesias (spontaneous or evoked burning pain, often with a superimposed lancinating component), but pain may also be deep and aching. Other sensations like; hyperesthesia, hyperalgesia, allodynia (pain due to a nonnoxious stimulus), and hyperpathia (particularly unpleasant, exaggerated pain response) may also occur. Symptoms are long-lasting, typically persisting after resolution of the primary cause (if one was present) because the CNS has been sensitized and remodeled.

Peripheral nerve injury provokes a reaction in peripheral immune cells and glia at several different anatomical locations: macrophages and Schwann cells facilitate the wallerian degeneration of axotomized nerve fibers distal to a nerve lesion; an immune response in the dorsal root ganglia (DRGs) is driven by macrophages, lymphocytes and satellite cells; activation of spinal microglia dominates the early glial response in the CNS to peripheral nerve injury, which is followed by activation and proliferation of astrocytes. More recently, a specific role of the immune response and CNS-infiltrating T lymphocytes in nerve injury induced neuropathic pain development and maintenance has been identified (Cao and DeLeo, 2008; Costigan et al., 2009; Zenonos and Kim).

Migraine is a common head pain syndrome, often genetically determined, characterized by generally episodic but often chronic, usually throbbing pain, often unilateral in distribution and often associated with photophobia, phonophobia, osmophobia, nausea and/or vomiting. The common occurrence of throbbing head pain was wrongly interpreted earlier for the pain to arise from blood vessels; but current research points to a neural origin of the migraine pain. Several observations made over the past two decades raised the issue that there is likely to be a central pain mechanism in migraine (Afridi and Goadsby, 2003; Goadsby, 2002).

Current therapy for neuropathic pain aims only at reducing symptoms, generally by suppressing neuronal activity. Thus treatment options, e.g. NSAIDS, antidepressants, anticonvulsants, baclofen, neuromodulation modalities or opiates, predominantly alleviate symptoms via nonspecific reduction of neuronal hyperexcitability rather than targeting the specific etiologies.

Therefore, effective and improved methods and compounds that are able to treat neuropathic pain are needed.

SUMMARY OF THE DISCLOSURE

In a first aspect, embodiments of this disclosure provide compounds for the use in the treatment of neuropathic pain and/or of a neuropathic pain syndrome.

In still another aspect, embodiments of this disclosure provide pharmaceutical compositions, single unit dosage forms, and kits suitable for use in the treatment of neuropathic pain and/or a neuropathic pain syndrome which comprise compounds according to the present disclosure.

In a further aspect, embodiments of this disclosure relate to methods of treating and/or preventing neuropathic pain and/or a neuropathic pain syndrome which comprise administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of a compound according to this disclosure.

Further, embodiments of this disclosure relates to imidazotriazinones, pharmaceutically acceptable salts, solvates, hydrates, stereoisomers, clathrates, tautomers or prodrugs thereof for use in the treatment of neuropathic pain and/or a neuropathic pain syndrome.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the 50% paw withdrawal threshold (g) after contusion and oral gavage of an (7-(4-tert-butylcyclohexyl)-5-ethyl-2-phenylimidazo[5,1-f][1,2,4]triazin-4(3H)-one) or vehicle from DPO 1 till DPO 7.

FIG. 2 shows the duration (s) of reactivity to acetone applied to the plantar surface of the hindpaw.

FIG. 3 shows the 50% paw withdrawal threshold (g) after contusion and oral gavage of an (7-(4-tert-butylcyclohexyl)-5-ethyl-2-phenylimidazo[5,1-f][1,2,4]triazin-4(3H)-one) and vehicle from DPO 28 till DPO 35

FIG. 4 shows the duration (s) of reactivity to acetone applied to the plantar surface of the hindpaw.

DETAILED DESCRIPTION OF THIS DISCLOSURE

Disclosed herein is the use of imidazotriazinones, active metabolites and/or derivatives thereof for the treatment of neuropathic pain and/or neuropathic pain syndromes.

Neuropathic pain according to the present disclosure is a pain initiated or caused by a primary lesion or dysfunction in the nervous system.

For example, neuropathic pain syndromes include postherpetic neuralgia (caused by Herpes Zoster), root avulsions, painful traumatic mononeuropathy, painful polyneuropathy (particularly due to diabetes), central pain syndromes (potentially caused by virtually any lesion at any level of the nervous system), postsurgical pain syndromes (eg, postmastectomy syndrome, postthoracotomy syndrome, phantom pain), and complex regional pain syndrome (reflex sympathetic dystrophy and causalgia).

In advantageous embodiments of the present disclosure, the neuropathic pain have typical symptoms like dysesthesias (spontaneous or evoked burning pain, often with a superimposed lancinating component), but pain may also be deep and aching. Other sensations like; hyperesthesia, hyperalgesia, allodynia (pain due to a nonnoxious stimulus), and hyperpathia (particularly unpleasant, exaggerated pain response) may also occur.

Neuropathic pain according to the present disclosure could be divided into "peripheral" (originating in the peripheral nervous system) and "central" (originating in the brain or spinal cord).

In advantageous embodiments, the central neuropathic pain is of a type that has a cause that is selected from the following group of causes:

- cerebral lesions that are predominantly thalamic;
- infarction, e.g. thalamic infarction or brain stem infarction;
- cerebral tumors or abscesses compressing the thalamus or brain stem;
- multiple sclerosis;
- brain operations, e.g. thalamotomy in cases of motoric disorders;
- spinal cord lesions;
- spinal cord injuries;
- spinal cord operations, e.g. anterolateral cordotomy;
- ischemic lesions;
- anterior spinal artery syndrome;
- Wallenberg's syndrome; and
- syringomyelia.

In an advantageous embodiment according to the present disclosure the neuropathic pain is a central neuropathic pain syndrome. In some examples the central neuropathic pain syndrome is caused by spinal cord injury and/or spinal cord contusion (example 1).

In a further advantageous embodiment of the present disclosure the neuropathic pain is a head pain syndrome caused by central pain mechanisms like in migraine or migraine pain.

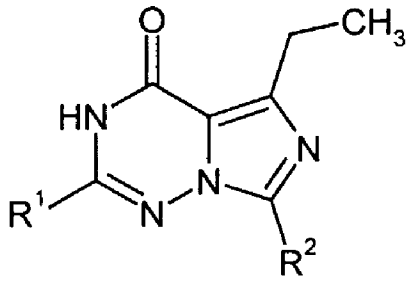
In further advantageous embodiments the neuropathic pain is a peripheral neuropathic pain. In some examples, the peripheral neuropathic pain is caused by chronic constriction injury or by ligation of the sciatic nerve.

According to the present disclosure the predominantly peripheral neuropathic pain includes a type that is selected from the following types of neuropathic pain and/or has a cause that is selected from the group of the following causes:

- systemic diseases, e.g. diabetic neuropathy;
- drug-induced lesions, e.g. neuropathy due to chemotherapy;
- traumatic syndrome and entrapment syndrome;
- lesions in nerve roots and posterior ganglia;
- neuropathies after HIV infections;
- neuralgia after Herpes infections;
- nerve root avulsions;
- cranial nerve lesions;
- cranial neuralgias, e.g., trigeminal neuralgia;
- neuropathic cancer pain;
- phantom pain;
- compression of peripheral nerves, neuroplexus and nerve roots;
- paraneoplastic peripheral neuropathy and ganglionopathy;
- complications of cancer therapies, e.g. chemotherapy, irradiation, and surgical interventions;
- complex regional pain syndrome;
- type I lesions (previously known as sympathetic reflex dystrophy); and
- type II lesions (corresponding approximately to causalgia)

In an advantageous embodiment the specific compounds of the disclosure are imidazotriazinone derivatives and metabolites described in U.S: patent no. 7,115,602 B2, which is incorporated herein by reference.

Embodiments of the compounds according to the present disclosure are Imidazotriazinones of the general formula (I)



(I)

in which R^1 denotes (C_6-C_{10})-aryl, which is optionally substituted by identical or different residues selected from the group consisting of halogen, (C_1-C_4)-alkyl, tri fluoromethyl, cyano, nitro und trifluoromethoxy, or denotes (C_1-C_8)-alkyl, which is optionally substituted by 3- to 10-membered carbocyclyl, or denotes 3-to 10-membered carbocyclyl, which is optionally substituted by identical or different (C_1-C_4)-alkyl residues, and

R^2 denotes 4-tert-butyl-cyclohex-1-yl,

Another embodiment of the disclosure relates to the use according to the present disclosure of compounds of the general formula (I), in which

R^1 denotes naphthyl, or denotes phenyl, which is optionally substituted by identical or different halogen atoms and

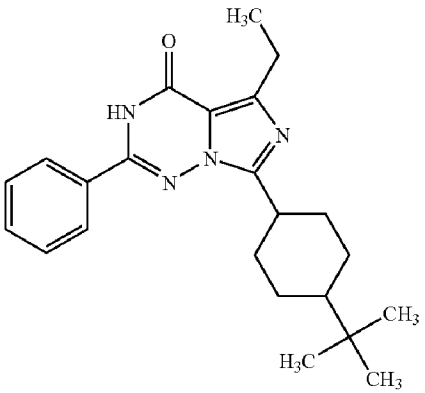
R^2 has the meaning indicated above.

Another embodiment of the disclosure relates to the use of compounds of the general formula (I), in which R^1 has the meaning indicated above, and R^2 denotes cis-4-tert-butylcyclohex-1-yl.

The compounds according to this disclosure can also be present in the form of their salts, hydrates and/or solvates.

In advantageous embodiments, the compound used for the treatment of CNS-trauma related disorders is a 7-(4-tert butyl-cyclohexyl)-imidazotriaziones.

A specific example of compounds used for the treatment of neuropathic pain disorders include, but not limited to compounds with the following structure (formula II):



In further advantageous embodiments, the compound is 7-(4-tert-butylcyclohexyl)-5-ethyl-2-phenylimidazo[5,1-f][1,2,4]triazin-4(3H)-one or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

In further advantageous embodiments, a compound according to the present disclosure is used as the only physically active compound in the treatment of neuropathic pain without a second active agent.

In yet other advantageous embodiments, the disclosure relates to pharmaceutical compositions for preventing and/or treating neuropathic pain, which comprises a therapeutically effective amount of a compound according to the present disclosure in admixture with a pharmaceutical acceptable carrier or excipient.

In advantageous embodiments, the pharmaceutical composition is used for preventing and/or treating neuropathic pain, whereby the composition comprises a therapeutically effective amount of imidazotriazinone or a physiologically functional derivative thereof in admixture with a pharmaceutical acceptable carrier or excipient. In advantageous embodiments the pharmaceutical composition comprises the imidazotriazinone 7-(4-tert-butylcyclohexyl)-5-ethyl-2-phenylimidazo[5,1-f][1,2,4]triazin-4(3H)-one or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

Compounds according to the disclosure can either be commercially purchased or prepared according to the methods described in the publications, patents or patent publications disclosed herein. Further, optically pure compositions can be asymmetrically synthesized or resolved using

known resolving agents or chiral columns as well as other standard synthetic organic chemistry techniques. Compounds used in the disclosure may include compounds that are racemic, stereomerically enriched or stereomerically pure, and pharmaceutically acceptable salts, solvates, stereoisomers, and prodrugs thereof.

As used herein and unless otherwise indicated, the term "pharmaceutically acceptable salt" encompasses non-toxic acid and base addition salts of the compound to which the term refers. Acceptable non-toxic acid addition salts include those derived from organic and inorganic acids or bases know in the art, which include, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embolic acid, enanthic acid, and the like. Compounds that are acidic in nature are capable of forming salts with various pharmaceutically acceptable bases. The bases that can be used to prepare pharmaceutically acceptable base addition salts of such acidic compounds are those that form non-toxic base addition salts, i.e., salts containing pharmacologically acceptable cations such as, but not limited to, alkali metal or alkaline earth metal salts and the calcium, magnesium, sodium or potassium salts in particular. Suitable organic bases include, but are not limited to, N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucamine), lysine, and procaine.

Examples for physiologically acceptable salts can also be salts of the compounds according to this disclosure with inorganic or organic acids. Preferred salts are those with inorganic acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonic acids such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, ethanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid. Preferred pyridinium salts are salts in combination with halogen.

As used herein, and unless otherwise specified, the term "solvate" means a compound of the present disclosure or a salt thereof that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide the compound. Examples of prodrugs include, but are not limited to,

derivatives of compounds according to the present disclosure that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of immunomodulatory compounds of the disclosure that comprise -NO, -NO2, -ONO, or -ONO2 moieties. Prodrugs can typically be prepared using well-known methods, such as those described in Burger's Medicinal Chemistry and Drug Discovery, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed. 1995), and Design of Prodrugs (H. Bundgaard ed., Elselvier, New York 1985). As used herein and unless otherwise indicated, the terms "biohydrolyzable amide," "biohydrolyzable ester," "biohydrolyzable carbamate," "biohydrolyzable carbonate," "biohydrolyzable ureide," "biohydrolyzable phosphate" mean an amide, ester, carbamate, carbonate, ureide, or phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, lower acyloxyalkyl esters (such as acetoxylmethyl, acetoxyethyl, aminocarbonyloxymethyl, pivaloyloxymethyl, and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxycarbonyl- oxymethyl, ethoxycarbonyloxyethyl and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters, and acylamino alkyl esters (such as acetamidomethyl esters). Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, [alpha]-amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, amino acids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

As used herein, and unless otherwise specified, the term "stereoisomer" encompasses all enantiomerically/stereomerically pure and enantiomerically/stereomerically enriched compounds of this disclosure. Furthermore, the term "stereoisomer" includes also tautomers which are isomers of organic compounds that readily interconvert by a chemical reaction (tautomerization).

As used herein, and unless otherwise indicated, the term "stereomerically pure" or "enantiomerically pure" means that a compound comprises one stereoisomer and is substantially free of its counter stereoisomer or enantiomer. For example, a compound is stereomerically or enantiomerically pure when the compound contains 80%, 90%, or 95% or more of one stereoisomer and 20%, 10%, or 5% or less of the counter stereoisomer, in certain cases, a

compound of the disclosure is considered optically active or stereomerically/enantiomerically pure {i.e., substantially the R-form or substantially the S- form) with respect to a chiral center when the compound is about 80% ee (enantiomeric excess) or greater, preferably, equal to or greater than 90% ee with respect to a particular chiral center, and more preferably 95% ee with respect to a particular chiral center.

As used herein, and unless otherwise indicated, the term "stereomerically enriched" or "enantiomerically enriched" encompasses racemic mixtures as well as other mixtures of stereoisomers of compounds of this disclosure {e.g., R/S = 30/70, 35/65, 40/60, 45/55, 55/45, 60/40, 65/35 and 70/30). Various inhibitor compounds of the present disclosure contain one or more chiral centers, and can exist as racemic mixtures of enantiomers or mixtures of diastereomers. This disclosure encompasses the use of stereomerically pure forms of such compounds, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular inhibitor compound of the disclosure may be used in methods and compositions of the disclosure. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. See, e.g., Jacques, J., et ah, Enantiomers, Racemates and Resolutions (Wiley-Interscience, New York, 1981); Wilen, S. H., et al, Tetrahedron 33:2725 (1977); Eliel, E. L., Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S. H., Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

The term "physiologically functional derivative" as used herein refers to compounds which are not pharmaceutically active themselves but which are transformed into their pharmaceutical active form in vivo, i. e. in the subject to which the compound is administered. Examples of physiologically functional derivatives are prodrugs such as those described below in the present application.

The term "derivative" as used herein refers to a compound that is derived from a similar compound or a compound that can be imagined to arise from another compound, if one atom is

replaced with another atom or group of atoms. The term" derivative" as used herein refers also to a compound that at least theoretically can be formed from the precursor compound (see Oxford Dictionary of Biochemistry and Molecular Biology. Oxford University Press. ISBN 0-19-850673-2.)

The disclosure is also directed to the use of compounds of the formula I or II and of their pharmacologically tolerable salts or physiologically functional derivatives for the production of a medicament for the prevention and treatment of neuropathic pain.

Methods and uses according to the present disclosure encompass methods of preventing, treating and/or managing neuropathic pain and related syndromes, but are not limited to, postherpetic neuralgia (caused by Herpes Zoster), root avulsions, painful traumatic mononeuropathy, painful polyneuropathy (particularly due to diabetes), central pain syndromes (potentially caused by virtually any lesion at any level of the nervous system), postsurgical pain syndromes (eg, postmastectomy syndrome, postthoracotomy syndrome, phantom pain), and complex regional pain syndrome (reflex sympathetic dystrophy and causalgia).

The symptoms, conditions and/or symptoms associated with neuropathic pain include, but are not limited to, dysesthesias (spontaneous or evoked burning pain, often with a superimposed lancinating component), but pain may also be deep and aching. Other sensations like; hyperesthesia, hyperalgesia, allodynia (pain due to a nonnoxious stimulus), and hyperpathia (particularly unpleasant, exaggerated pain response).

The suitability of a particular route of administration of an compound according to the present disclosure employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. An advantageous embodiment of the route of administration for a compound according to the present disclosure is orally. Further routes of administration are known to those of ordinary skill in the art.

The dosage of therapeutically effective amount of at least one compound varies from and also depends upon the age and condition of each individual patient to be treated. In an embodiment of the present disclosure, the recommended daily dose range of a compound according to the present disclosure for the conditions and disorders described herein lies within the range of from about, a daily dose of about 0.01 mg-10g/body, preferable 0.5 mg-5g/body and more preferable 0.1 mg-1g/body of the active ingredient is generally given for preventing and /or treating this disease, and an average single dose of about 0.01-1 mg, 0.5 mg, 0.1 mg, 1 mg, 5 mg,

10 mg, 50 mg, 100 mg, 250 mg, 500 mg, 1 g, 2 g and 3 g is generally administered. Daily dose for administration in humans for preventing this disease (neuropathic pain) could be in the range of about 0.01-50 mg/kg.

While the term for administering of at least one compound to prevent this disease (neuropathic pain) varies depending on species, and the nature and severity of the condition to be prevented, the compound may usually be administered to humans for a short term or a long term, i.e. for 1 week to 1 year.

Pharmaceutical compositions can be used in the preparation of individual, single unit dosage forms. The compounds of the present disclosure can be used in the form of pharmaceuticals compositions, for example, in solid, semisolid or liquid form, which contains one or more of the compounds according to the present disclosure as active ingredient associated with pharmaceutically acceptable carriers or excipient suitable for oral, parenteral such as intravenous, intramuscular, intrathecal, subcutaneous, enteral, intrarectal or intranasal administration. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions (saline for example), emulsion, suspensions (olive oil, for example), ointment and any other form suitable for use. The carriers which can be used are water, glucose, lactose gum acacia, gelatine, manitol, starch paste, magnesium trisilicate, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid or liquid form, and in addition auxiliary, stabilizing, thickening and colouring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an effective amount sufficient to prevent and/or treat the disease.

Single unit dosage forms of the disclosure are suitable for oral, mucosal (e.g., nasal, sublingual, vaginal, buccal, or rectal), parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical (e.g., eye drops or other ophthalmic preparations), transdermal or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in- water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; eye drops or other ophthalmic preparations suitable for topical administration; and sterile

solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The composition, shape, and type of dosage forms of the disclosure will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active agents it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active agents it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms encompassed by this disclosure will vary from one another will be readily apparent to those skilled in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990).

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active agents in the dosage form. For example, the decomposition of some active agents may be accelerated by some excipients such as lactose, or when exposed to water. Active agents that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, this disclosure encompasses pharmaceutical compositions and dosage forms that contain little, if any, lactose or other mono- or di-saccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

Lactose-free compositions of the disclosure can comprise excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopeia (USP) 25-NF20 (2002). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

This disclosure further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some

compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the disclosure can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprise a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g. vials), blister packs, and strip packs.

The disclosure further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

Like the amounts and types of excipients, the amounts and specific types of active agents in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the disclosure comprise a compound according to the present disclosure or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of from about 0.10 to about 150 mg. Typical dosage forms comprise a compound according to the present disclosure or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of about 0.01, 0.1, 0.5, 1, 2, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25, 50, 100, 150 or 200 mg. In a particular embodiment, a preferred dosage form comprises a compound according to the present description in an amount of about 0.01, 0.1, 0.5, 1, 2, 5, 10, or 50 mg. In a specific

embodiment, a preferred dosage form comprises a compound according to the present description in an amount of about 0.01, 0.1, 0.5, 1, 2, 5, or 25 mg.

Oral Dosage Forms of pharmaceutical compositions of the disclosure that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, Remington 's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990).

Typical oral dosage forms of the disclosure are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms {e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the disclosure include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato

starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives {e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, {e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH- 103(TM) and Starch 1500 LM. Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the disclosure is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants are used in the compositions of the disclosure to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the disclosure. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the disclosure include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the disclosure include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Piano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

A preferred solid oral dosage form of the disclosure comprises a compound of the disclosure, anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

Active ingredients of the disclosure can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein can be readily selected for use with the active ingredients of the disclosure. The disclosure thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations

can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled- release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intra-arterial. Because their administration typically bypasses patients' natural defences against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions. Suitable vehicles that can be used to provide parenteral dosage forms of the disclosure are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the disclosure. For example, cyclodextrin and its derivatives can be used to increase the solubility of a compound of the disclosure and its derivatives. See, e.g., U.S. Patent No. 5,134,127, which is incorporated herein by reference.

Topical and mucosal dosage forms of the disclosure include, but are not limited to, sprays, aerosols, solutions, emulsions, suspensions, eye drops or other ophthalmic preparations, or other forms known to one of skill in the art. See, e.g., Remington 's Pharmaceutical Sciences, 16th

and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels.

Suitable excipients {e.g., carriers and diluents) and other materials that can be used to provide topical and mucosal dosage forms encompassed by this disclosure are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-l,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form solutions, emulsions or gels, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. See, e.g., Remington's Pharmaceutical Sciences, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990).

The pH of a pharmaceutical composition or dosage form may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Typically, active ingredients of the disclosure are preferably not administered to a patient at the same time or by the same route of administration. This disclosure therefore encompasses kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a patient.

A typical kit of the disclosure comprises a dosage form of a compound of the disclosure, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof. Kits encompassed by this disclosure can further comprise additional active agents. Examples of the additional active agents include, but are not limited to, those disclosed herein (see, e.g., section 4.2). Kits of the disclosure can further comprise devices that are used to administer the

active ingredients. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers.

Kits of the disclosure can further comprise cells or blood for transplantation as well as pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water- miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

In further advantageous embodiments, the compounds according to the present disclosure, preferably the imidazotriazinone derivatives, more preferably the compounds with the formula (I) and/or formula (II) like 7-(4-tert-butylcyclohexyl)-5-ethyl-2-phenylimidazo[5,1-f][1,2,4]triazin-4(3H)-one are used in the treatment of neuropathic pain and/or neuropathic pain syndromes.

The following examples and methods are offered for illustrative purposes only, and are not intended to limit the scope of the present disclosure in any way.

Methods and Examples

A series of non-clinical pharmacology and toxicology studies have been performed to support the clinical evaluation of the compounds according to the present disclosure in human subjects. These studies were performed in accordance with internationally recognized guidelines for study design and in compliance with the requirements of Good Laboratory Practice (GLP) unless otherwise noted.

Example 1

Imidazotriazinone treatment to suppress the development of central neuropathic pain induced by severe spinal cord contusion injury in the rat.

Surgical methods

Thirteen week-old female Lewis rats (Charles River, Sulzfeld Germany) were housed under a 12:12 h dark/light regime and allowed free access to water and food. After one week of habituation the animals underwent general anesthesia with a mixture of isoflurane and air (induction: 5% isoflurane, maintenance: 2.2% isofluorane). A Th10 laminectomy was performed without rupturing the dura and a severe contusive SCI (25 gcm NYU/MASCIS II impactor) {Gruner, 1992 #3} was induced. After suturing muscle and skin, a subcutaneous (s.c.) injection of 5 ml of Ringers Lactate was given. Bladders were emptied manually 2 times a day until spontaneous voiding returned (usually within 1 week). The lesion severity was verified by the impact velocity and contusion depth of the impactor rod. Animals with an impact velocity error > 5% were excluded from further analysis. After injury, individual rats were randomly assigned into a treatment group. The following groups were used:

Group 1: SCI + vehicle (Ethanol, Solutol® and sterile water) by gavage for 7 days (from DPO 1 -7).

Group 2: SCI + 7-(4-tert-butylcyclohexyl)-5-ethyl-2-phenylimidazo[5,1-f][1,2,4]triazin-4(3H)-one in vehicle (10 mg/kg/day) by gavage for 7 days (from DPO 1 -7).

Assessment of mechanical sensitivity:

The tactile sensitivity response was measured as the direct pressure stimulus required eliciting foot withdrawal in nonrestrained conditions. All tests were conducted in the morning between 7:30 and 10:30 am and the person performing the behavioural tests was blinded to the experimental groups. Animals were habituated to the testing apparatus for at least 20 min before testing. Each animal was subjected to the stimulation of a series of von Frey filaments ranging from 0.4 to 15 g (log force 3.61, 3.84, 4.08, 4.31, 4.56, 4.74, 4.93 and 5.18) using the Up-Down paradigm according to Chaplan (Chaplan et al., 1994). The selected von Frey filament was pressed against the plantar surface of the hind paw to the point of 30° bending for 3 s. Paw withdrawal response was considered as the positive response. The 50% threshold force needed for paw withdrawal was calculated for both hind paws of each rat and the value of the most sensitive hind paw was used to represent the mechanical sensitivity of this animal.

Thermal allodynia:

A slightly modified method of De la Calle et al. {De la Calle, 2002 #918} was used to determine the reactivity to a cold chemical stimulus. At the designated post-operative time points the spinal

cord injured rats were placed in an elevated clear-plastic, wire mesh-bottomed cage. After a 10- to 15- min acclimation period, acetone was applied to the plantar surface of the hindpaw. To do this, 100 µl of acetone was sprayed onto the plantar surface of the rat's hind leg from below the grid with a 2.5ml syringe. The time spent with the leg withdrawn from the floor during the 60s following exposure to acetone was recorded. Both hind legs were tested in each animal with an interval of 5-10 min between each test and the average reaction time was used for calculating the group means. A minimal value of 0.5 s was assigned to convey a fast a brisk reaction, while 0 was assigned if there was no reaction at all.

Results:

Mechanical sensitivity

The mechanical sensitivity (indicated by the 50% threshold force for paw withdrawals) was determined by the Up-Down method using von Frey filaments. All rats were baseline tested before surgery and tested again on day 28 post surgery, because this is the first time point at which all rats can sit with the hind paws in plantar position. Before injury the threshold was 15g for all animals, as a consequence of the contusion injury the nociceptive threshold in the vehicle control animals decreased to about 3g one month after injury. However, the threshold in the imidazotriazinone treated animals did decrease on average only a few grams to values between 12 and 14 grams. The nociceptive threshold remained fairly constant over time and as a consequence statistical testing revealed a strong significant effect between the vehicle control group and the imidazotriazinone treated animals (see figure 1).

Thermal allodynia:

At DPO 28, we observed a meaningful reaction to the stimulus which lasted about 14s in the vehicle control animals. In the following weeks this reaction even increased to about 18s. In the imidazotriazinone treated animals on the contrary we observed only a modest reaction which lasted about 7s and remained constant over the experiment. As a consequence statistical testing revealed a strong significant effect between the vehicle control group and the imidazotriazinone treated animals (see figure 2).

Altogether, the data presented in this example clearly demonstrate that imidazotriazinone treatment significantly attenuate the development of mechanical and thermal allodynia associated

with spinal cord injury. This is the first evidence that imidazotriazinone can be used as treatment to prevent the development of central neuropathic pain.

Example 2

Imidazotriazinone treatment can reverse central neuropathic pain induced by severe spinal cord contusion injury in the rat.

Surgical methods

For surgical methods see example 1.

After injury, individual rats were randomly assigned into a treatment group. The following groups were used:

Group 1: SCI + vehicle (Ethanol, Solutol® and sterile water) by gavage for 7 days (from DPO 28-35).

Group 2: SCI + 7-(4-tert-butylcyclohexyl)-5-ethyl-2-phenylimidazo[5,1-f][1,2,4]triazin-4(3H)-one (10 mg/kg/day) in vehicle by gavage for 7 days (from DPO 28-35).

Assessment of mechanical sensitivity:

For the assessment of mechanical sensitivity see example 1.

The acetone test:

For the assessment of mechanical sensitivity see example 1.

Results:

Mechanical sensitivity

The mechanical sensitivity (indicated by the 50% threshold force for paw withdrawals) was determined by the Up-Down method using von Frey filaments. All rats were baseline tested before surgery and tested again on day 28 post surgery, because this is the first time point at which all rats can sit with the hind paws in plantar position. At baseline all animals reached the maximal 50% threshold force of 15 g, as consequence there were no differences between the two groups. As expected, all animals showed severe mechanical hypersensitivity at DPO 28, the withdrawal threshold dropped from 15 grams before injury to 3.6 and 3.8 grams in vehicle control animals and imidazotriazinone treated animals respectively and the treatment with either

imidazotriazinone or vehicle was started. As a consequence of this 7 days treatment the 50% threshold force increased, at DPO 35 the withdrawal threshold was significantly higher in imidazotriazinone treated animals when compared to vehicle control animals (Student T-test; $p< 0.001$, see figure 3). A comparable difference between the groups was noted at the end of the experiment at DPO 63 (Student T-test; $p< 0.001$, see figure 3). Thus, imidazotriazinone can reverse a chronic mechanical allodynia caused by spinal cord trauma.

Thermal allodynia

The acetone test was used for the determination of the reactivity to a cold chemical stimulus. The obtained results show clearly that before injury the acetone does not evoke any reaction at all when applied to the plantar surface of the hind paws. However, at DPO 28 most animals showed a clear reaction to the acetone exposure. At DPO 28 the 7 days oral treatment started with either imidazotriazinone or vehicle. As a consequence of the treatment the first significant differences between the two groups became obvious at DPO 35 (Student T-test; $p< 0.01$, see figure 4). A comparable difference between the groups was noted at the end of the experiment at DPO 63 (Student T-test; $p< 0.001$, see figure 4). Thus, imidazotriazinone treatment can reverse a cold allodynia caused by spinal cord trauma.

Altogether, the data presented in this example clearly demonstrates that imidazotriazinone treatment can reverse both mechanical- and thermal allodynia associated with spinal cord injury.

The results show that a controlled pharmacotherapy by an imidazotriazinone can be used for treating neuropathic pain and neuropathic pain syndromes.

The embodiments of the disclosure described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the disclosure.

Additional References

The following additional publications are incorporated herein by references:

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Chaplan, S. R., et al., 1994. Quantitative assessment of tactile allodynia in the rat paw. J Neurosci Methods. 53, 55-63.

Costigan, M., et al., 2009. T-cell infiltration and signaling in the adult dorsal spinal cord is a major contributor to neuropathic pain-like hypersensitivity. J Neurosci. 29, 14415-22.

Kuo, E. A., et al., 1996. Synthesis, structure-activity relationships, and pharmacokinetic properties of dihydroorotate dehydrogenase inhibitors: 2-cyano-3-cyclopropyl-3-hydroxy-N-[3'-methyl-4'-(trifluoromethyl)phenyl] propenamide and related compounds. J Med Chem. 39, 4608-21.

Zenonos, G., Kim, J. E., A T cell-orchestrated immune response in the adult dorsal spinal cord as a cause of neuropathic pain-like hypersensitivity after peripheral nerve damage: a door to novel therapies? Neurosurgery. 66, N24-5.

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Greene, S., et al., 1995. Inhibition of dihydroorotate dehydrogenase by the immunosuppressive agent leflunomide. Biochem Pharmacol. 50, 861-7.

Williamson, R. A., et al., 1995. Dihydroorotate dehydrogenase is a high affinity binding protein for A77 1726 and mediator of a range of biological effects of the immunomodulatory compound. J Biol Chem. 270, 22467-72.

Zielinski, T., et al., 1995. Leflunomide, a reversible inhibitor of pyrimidine biosynthesis? Inflamm Res. 44 Suppl 2, S207-8.

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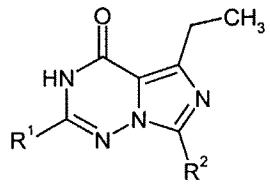
CLAIMS

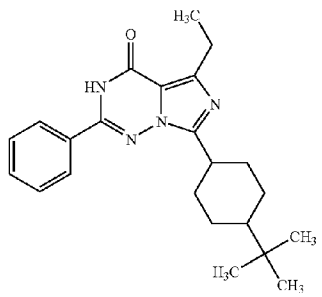
1. A compound for use in treating neuropathic pain and/or neuropathic pain syndrome, wherein the compound is an imidazotriazinone.

2. The compound for use according to claim 1, wherein the imidazotriazinone is a compound of the general formula (I)



(I)

3. The compound for use according to any one of claims 1 to 2, wherein the imidazotriazinone is a compound of the formula (II)



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

4. The compound for use according to claim 3, wherein the stereoisomer of the compound is the R or S enantiomer.

5. The compound for use according to any one of claims 1 to 4, wherein the compound is used in the treatment of peripheral and/or predominantly peripheral neuropathic pain or central and/or predominantly central neuropathic pain.

6. The compound for use according to any one of the claims 1 to 4, wherein the neuropathic pain syndrome is postherpetic neuralgia (caused by Herpes Zoster), root avulsions, painful traumatic mononeuropathy, painful polyneuropathy (particularly due to diabetes), central pain syndromes (potentially caused by virtually any lesion at any level of

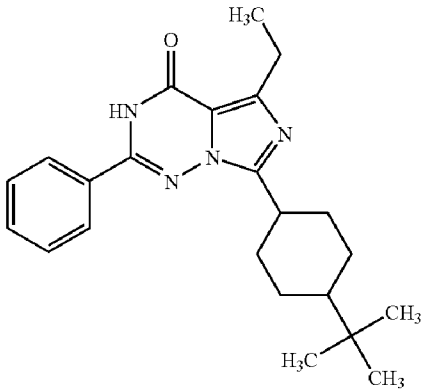
the nervous system), postsurgical pain syndromes (eg, postmastectomy syndrome, postthoracotomy syndrome, phantom pain), complex regional pain syndrome (reflex sympathetic dystrophy and causalgia), and/or migraine or migraine pain.

7. The compound for use according to any one of the claims 1 to 7, wherein the neuropathic pain is a chronic neuropathic pain.

8. The compound for use according to any one of the claims 1 to 8, wherein said compound is administered at daily dosages between 0.01 mg-10g/body, preferable 0.5 mg-5g/body and more preferable 0.1 mg-1g/body beginning after a damage of the nervous system.

9. A pharmaceutical composition for use in the treatment and/or prevention of neuropathic pain and/or neuropathic pain syndromes comprising a compound as defined in any of claims 1 to 4 in free form or in the form of a pharmaceutically acceptable salt or physiologically functional derivative, together with pharmaceutically acceptable diluents or carriers, and whereby the neuropathic pain is a neuropathic pain and/or neuropathic pain syndrome as defined in any of claims 5 to 8.

10. The pharmaceutical composition for use according to claim 10, wherein the compound has the formula



or analogs, homologues, esters, prodrugs or pharmaceutically acceptable salts, solvates, tautomers, stereoisomers or physiologically functional derivatives thereof.

11. The pharmaceutical composition for use according to any one of the claims 10 to 11, wherein said compound is administered at daily dosages between 0.01 mg-10g/body,

preferable 0.5 mg-5g/body and more preferable 0.1 mg-1g/body beginning after a damage of the nervous system.

12. A method for treating and/or preventing neuropathic pain and/or neuropathic pain syndromes in a patient, which comprises administering a therapeutically effective amount of a pharmaceutical composition according to claim 11 or 12.

13. The method according to claim 13, wherein the patient is a human.

14. The method according to any one of claims 13 to 14, wherein the neuropathic pain syndrome is postherpetic neuralgia (caused by Herpes Zoster), root avulsions, painful traumatic mononeuropathy, painful polyneuropathy (particularly due to diabetes), central pain syndromes (potentially caused by virtually any lesion at any level of the nervous system), postsurgical pain syndromes (eg, postmastectomy syndrome, postthoracotomy syndrome, phantom pain), complex regional pain syndrome (reflex sympathetic dystrophy and causalgia), and/or migraine or migraine pain.

15. The method according to any of claims 13 to 14, whereby the type of neuropathic pain is selected from those that have a cause that is selected from the group of the following causes: systemic diseases, e.g. diabetic neuropathy; drug-induced lesions, e.g. neuropathy due to chemotherapy; traumatic syndrome and entrapment syndrome; lesions in nerve roots and posterior ganglia; neuropathies after HIV infections; neuralgia after Herpes infections; nerve root avulsions; cranial nerve lesions; cranial neuralgias, e.g., tri-geminal neuralgia; neuropathic cancer pain; phantom pain; compression of peripheral nerves, neuroplexus and nerve roots; paraneoplastic peripheral neuropathy and ganglionopathy; complications of cancer therapies, e.g. chemotherapy, irradiation, and surgical interventions; complex regional pain syndrome; type I lesions (previously known as sympathetic reflex dystrophy); and type II lesions (corresponding approximately to causalgia); migraine and migraine pain; cerebral lesions that are predominantly thalamic; infarction, e.g. thalamic infarction or brain stem infarction; cerebral tumors or abscesses compressing the thalamus or brain stem; multiple sclerosis; brain operations, e.g. thalamotomy in cases of motoric disorders; spinal cord lesions; spinal cord injuries; spinal cord operations, e.g. anterolateral cordotomy; ischemic lesions; anterior spinal artery syndrome; Wallenberg's syndrome; and syringomyelia

16. The method according to any one of claims 13 to 16, wherein the neuropathic pain is a chronic neuropathic pain

17. The method according to any one of claims 13 to 17, wherein said composition is administered at daily dosages between 0.01 mg-10g/body, preferable 0.5 mg-5g/body and more preferable 0.1 mg-1g/body beginning after a damage of the nervous system.

18. A medical kit suitable for the treatment of a neuropathic pain and/or a neuropathic pain syndrome, comprising:

(a) printed instructions for administering the compound to the patient having a damage of the nervous system

(b) a compound defined in any one of claims 1 to 4, or

(c) a pharmaceutical composition according to claim 10 to 12.

FIGURE 1

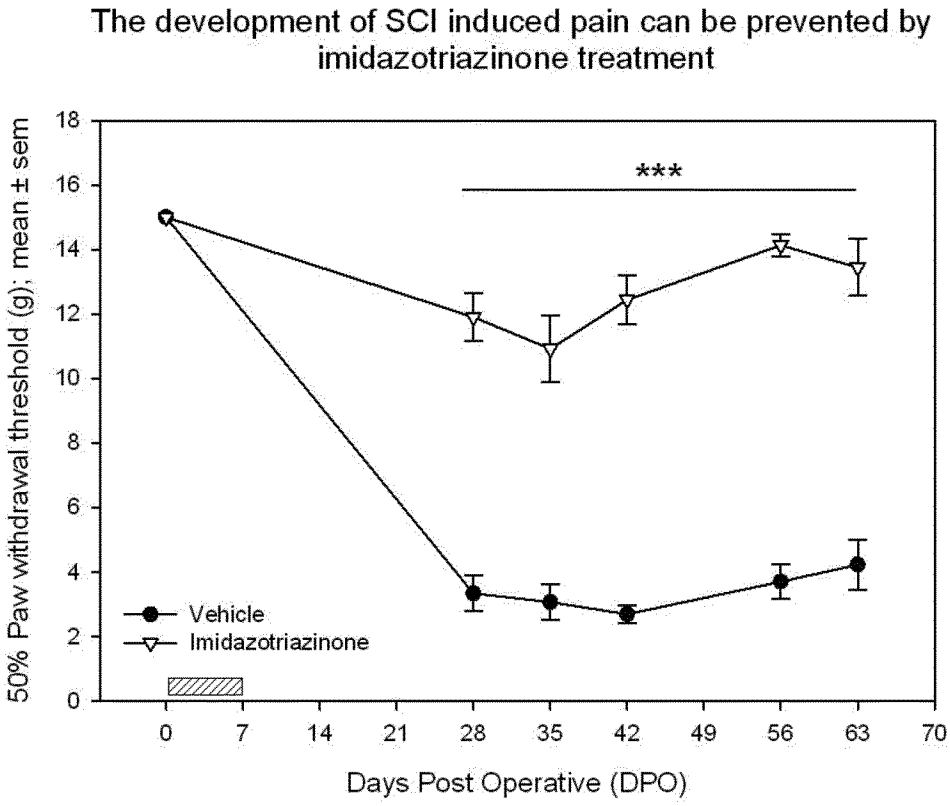
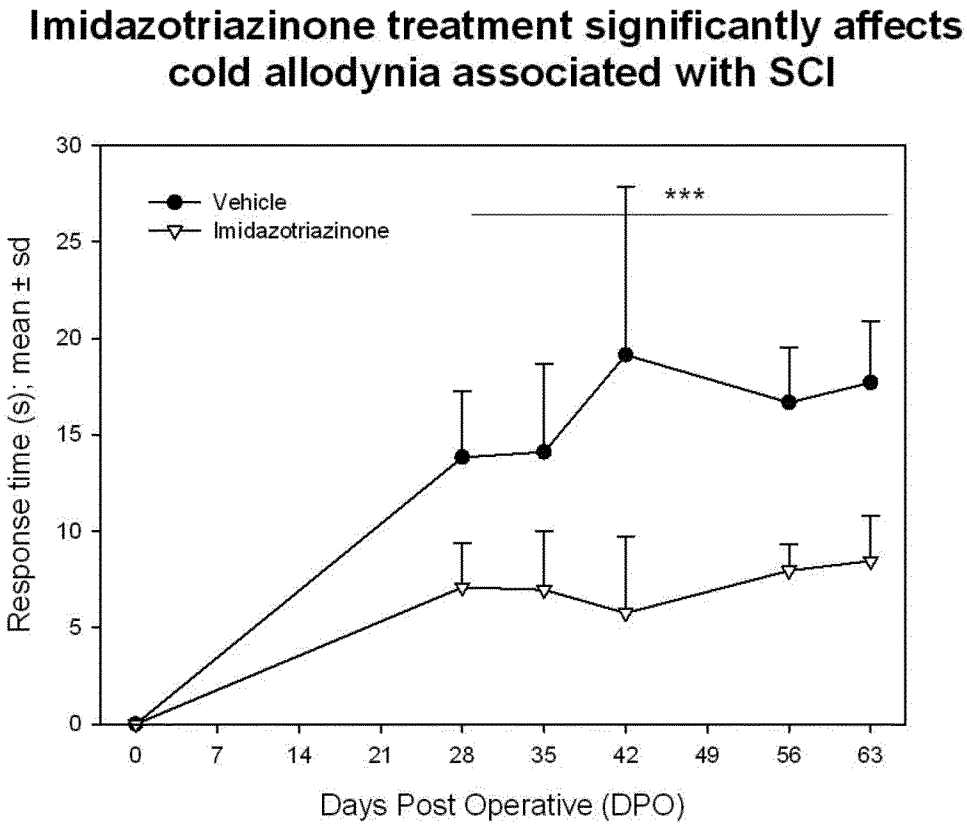

The development of SCI induced pain can be prevented by imidazotriazinone treatment
50% Paw withdrawal threshold (g); mean ± sem
Days Post Operative (DPO)
***
Vehicle
Imidazotriazinone
0
2
4
6
8
10
12
14
16
18
0
7
14
21
28
35
42
49
56
63
70

FIGURE 2


Imidazotriazinone treatment significantly affects cold allodynia associated with SCI
Vehicle
Imidazotriazinone
***
Response time (s); mean ± sd
Days Post Operative (DPO)
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30
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7
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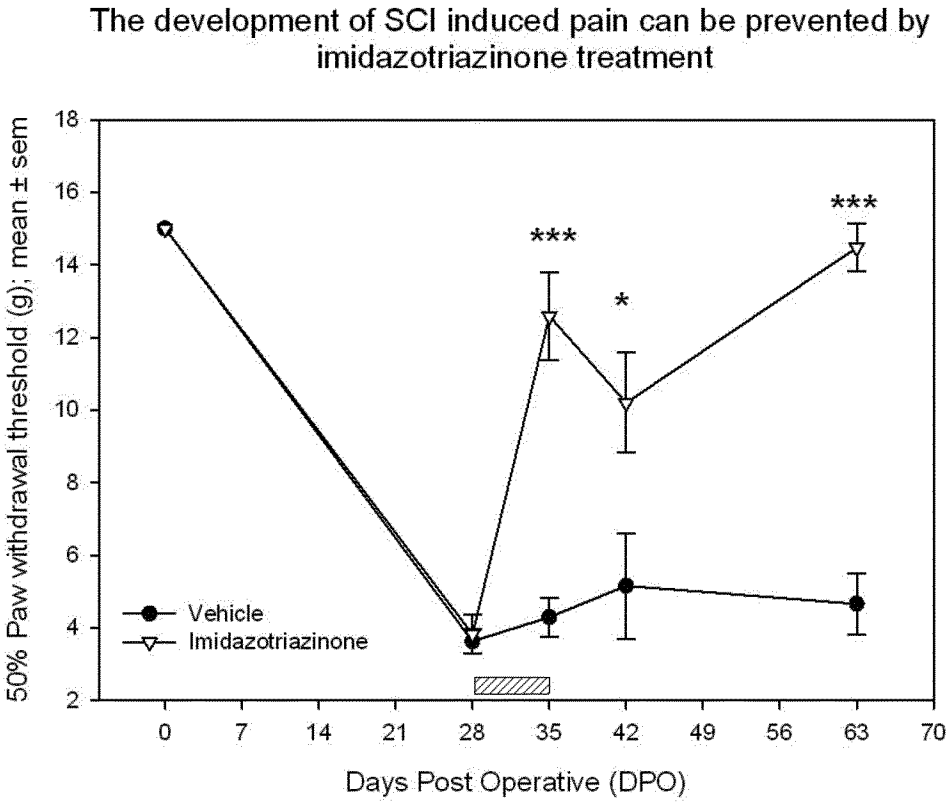
42
49
56
63

FIGURE 3


The development of SCI induced pain can be prevented by imidazotriazinone treatment
50% Paw withdrawal threshold (g); mean ± sem
18
16
14
12
10
8
6
4
2
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Vehicle
Imidazotriazinone
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56
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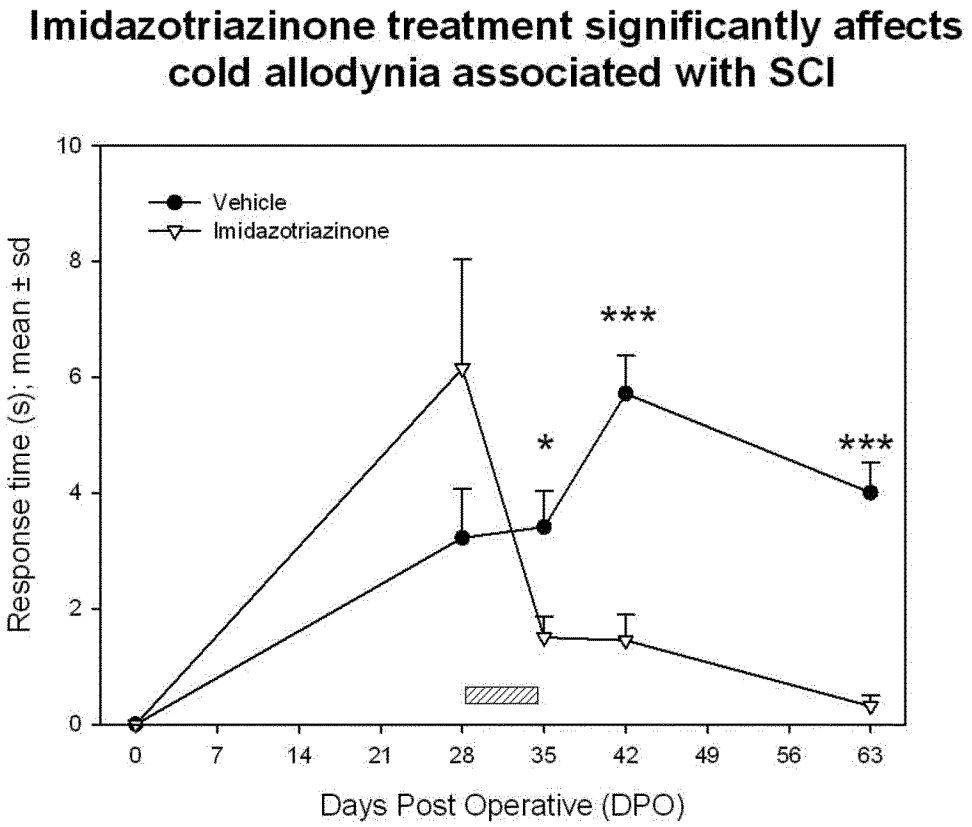
70
Days Post Operative (DPO)

FIGURE 4


Imidazotriazinone treatment significantly affects cold allodynia associated with SCI
Vehicle
Imidazotriazinone
Response time (s); mean ± sd
Days Post Operative (DPO)
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/055514

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61K31/53
ADD. A61P25/04

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

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 practicable, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/098879 A1 (BAYER AG [DE]; ALONSO-ALIJA CRISTINA [DE]; GIELEN HEIKE [DE]; HENDRIX) 12 December 2002 (2002-12-12)	18
Y	claims	1-18

X	GB 2 388 594 A (BAYER AG [DE]) 19 November 2003 (2003-11-19)	18
Y	claims	1-18

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2013	29/04/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dahse, Thomas

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/055514

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