



(11) **EP 2 207 776 B9**

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

(15) Correction information:

Corrected version no 1 (W1 B1)
Corrections, see
Claims EN 5

(51) Int Cl.:

C07D 401/12 ^(2006.01) **C07D 401/14** ^(2006.01)
A61K 31/4545 ^(2006.01) **A61P 29/00** ^(2006.01)

(48) Corrigendum issued on:

21.12.2016 Bulletin 2016/51

(86) International application number:

PCT/EP2008/065081

(45) Date of publication and mention
of the grant of the patent:

17.08.2016 Bulletin 2016/33

(87) International publication number:

WO 2009/062883 (22.05.2009 Gazette 2009/21)

(21) Application number: **08850378.4**

(22) Date of filing: **06.11.2008**

(54) **DRUG ACTIVE IN NEUROPATHIC PAIN**

GEGEN NEUROPATHISCHEN SCHMERZEN WIRKSAMES ARZNEIMITTEL

MÉDICAMENT ACTIF CONTRE LA DOULEUR NEUROPATHIQUE

(84) Designated Contracting States:

**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HR HU IE IS IT LI LT LU LV MC MT NL NO PL PT
RO SE SI SK TR**

- **FURLOTTI, Guido**
I-00151 Roma (IT)
- **GUGLIELMOTTI, Angelo**
I-00149 Roma (IT)
- **POLENZANI, Lorenzo**
I-00046 Grottaferrata (IT)

(30) Priority: **12.11.2007 EP 07425709**

(43) Date of publication of application:
21.07.2010 Bulletin 2010/29

(74) Representative: **Allaix, Roberto et al**
Marchi & Partners S.r.l.
Via Vittor Pisani, 13
20124 Milano (IT)

(73) Proprietor: **Aziende Chimiche Riunite Angelini**
Francesco A.C.R.A.F. S.p.A.
00181 Roma (IT)

(56) References cited:

EP-A- 1 182 193 WO-A-98/46589
WO-A-2004/101548 WO-A-2005/013989

(72) Inventors:

- **ALISI, Maria Alessandra**
I-00199 Roma (IT)
- **CAZZOLLA, Nicola**
I-00041 Albano Laziale (IT)

- **C.G. WERMUTH: "THE PRACTICE OF MEDICINAL
CHEMISTRY, pages 203-237" 1996, ACADEMIC
PRESS LTD , LONDON UK , XP002190259 page
216, table 13.8**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 2 207 776 B9

Description

FIELD OF THE INVENTION

[0001] The present invention relates to a novel indazole, to a process for preparing it and to a pharmaceutical composition comprising it. The invention also relates to the use of an indazole for preparing a pharmaceutical composition that is active in the treatment of neuropathic pain.

PRIOR ART

[0002] Chronic pain represents a series of pathologies from which, on average, about 10-20% of the adult population suffers. Chronic pain is generally associated with clinical conditions characterized by chronic and/or degenerative lesions.

[0003] Chronic pain differs from acute pain mainly by the duration. Acute pain has a duration of a few days or weeks, correlated with recovery from the event that caused the pain (trauma, burns, intense efforts, surgical or dental interventions, and the like). On the other hand, chronic pain persists for months and even years, causing muscular tension, limited mobility, fatigue, loss of appetite and apathy.

[0004] Typical examples of pathologies characterized by chronic pain are rheumatoid arthritis, osteoarthritis, fibromyalgia, neuropathies, etc. [Ashbum MA, Staats PS. Management of chronic pain. Lancet 1999; 353: 1865-69].

[0005] Chronic pain, and in particular neuropathic pain, is often debilitating and is a cause of loss of working capacity and of poor quality of life. Economic and social damage thus also follow.

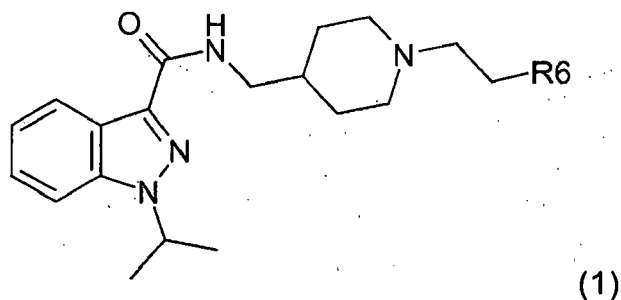
[0006] The analgesic drugs currently used in the treatment of neuropathic pain include non-steroidal anti-inflammatory drugs (NSAID), antidepressants, opioid analgesics, and anticonvulsants [Woolf CJ, Mannion RJ, Neuropathic pain: aetiology, symptoms, mechanism, and management. Lancet 1999; 353: 1959-1964].

[0007] However, chronic pain, and in particular neuropathic pain, is notoriously difficult to treat with the drugs currently available. Consequently, the development of novel drugs has always been one of the main objectives of the pharmaceutical industry.

[0008] In addition, despite the numerous research efforts directed towards identifying a suitable analgesic compound, there is a significant number of patients whose pain condition still lacks a suitable treatment [Scholz J, Woolf CJ. Can we conquer pain? Nat Neurosci. 2002; 5: 1062-76].

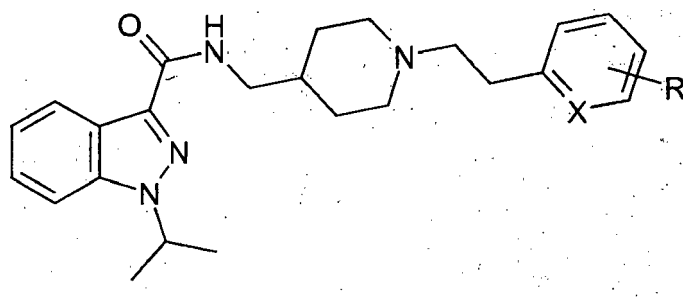
[0009] Certain drugs active on the serotonergic system were considered capable of controlling chronic pain and in particular neuropathic pain.

[0010] Patent applications EP-A-0 975 623 and WO 98/46589 relate to numerous compounds of formula 1:



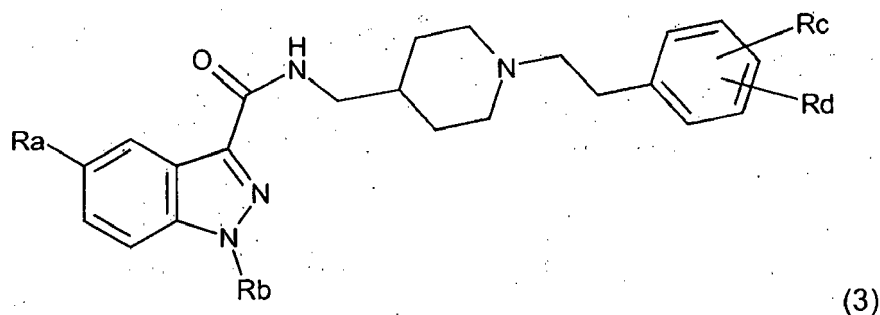
included those where R6 is represented by an aryl, possibly substituted with a hydroxyl or halogen group. According to the abovementioned documents, the compounds of formula (A) have affinity towards the 5HT₄ receptors and act as partial agonist or antagonist of the serotonin, and it has been suggested to use them in the treatment of gastrointestinal motility disorders, urinary incontinence, cardiac arrhythmia and central nervous system disorders such as memory disorders and anxiety.

[0011] Patent applications WO 2005/013989 and EP 1 646 387 relate to the use of indazole derivatives for preparing a pharmaceutical composition that is active in the treatment of neuropathic pain, these indazole derivatives being represented by formula 2 below:



in which X may be N or CH, and, when X is N, R is hydrogen, and when X is CH, R is a hydrogen atom, a hydroxyl group, an alkyl with a linear or branched chain containing from 1 to 3 carbon atoms, an alkoxy with a linear or branched chain containing from 1 to 3 carbon atoms, or a halogen atom.

[0012] Patent application WO2004/101548 relates to the use of certain indazole derivatives for preparing a pharmaceutical composition that is active in the treatment of chronic pain. Some of the indazole derivatives disclosed in WO2004/101548 are represented by formula 3 below:



where R_a is H, $\text{NH}_2\text{C(O)}$, $\text{CH}_3\text{C(O)NH}$, CH_3SO_2 , $\text{CH}_3\text{SO}_2\text{NH}$, linear or branched $\text{C}_1\text{-C}_3$ alkyl, linear or branched $\text{C}_1\text{-C}_3$ alkoxy, or halogen; R_b is H, linear or branched $\text{C}_1\text{-C}_6$ alkyl; aryl- $(\text{C}_1\text{-C}_3)$ alkyl optionally substituted with 1 or 2 halogen atoms, with a $\text{C}_1\text{-C}_3$ alkyl group or a $\text{C}_1\text{-C}_3$ alkoxy group; R_c is hydroxy, amino, di- $(\text{C}_1\text{-C}_3)$ alkyl-amino, tri- $(\text{C}_1\text{-C}_3)$ alkyl-ammoniomethyl, nitro, trifluoromethyl, nitrile, $\text{CH}_3\text{C(O)NH}$, $\text{CH}_3\text{SO}_2\text{NH}$, CH_3SO_2 , $\text{R}'\text{R}''\text{NSO}_2$, where R' and R'' are H, or a linear or branched $\text{C}_1\text{-C}_6$ alkyl, R_d is H, hydroxy, amino, di- $(\text{C}_1\text{-C}_3)$ alkyl-amino, tri- $(\text{C}_1\text{-C}_3)$ alkyl-ammoniomethyl, nitro, trifluoromethyl, nitrile, $\text{CH}_3\text{C(O)NH}$, $\text{CH}_3\text{SO}_2\text{NH}$, CH_3SO_2 , $\text{R}'\text{R}''\text{NSO}_2$, where R' and R'' have the meanings stated above, with the proviso that when R_a and R_d are both H, and R_b is isopropyl, then R_c is not hydroxy.

[0013] Unfortunately, the drugs active on the serotonergic system that are currently used have side and adverse effects which are due to the low selectivity towards other serotonergic receptors, which often oblige stoppage of the treatment or avoidance of treatment in the case of particular types of patients who, besides the presence of chronic pain, present concomitant pathological conditions on specific systems, such as the cardiovascular system.

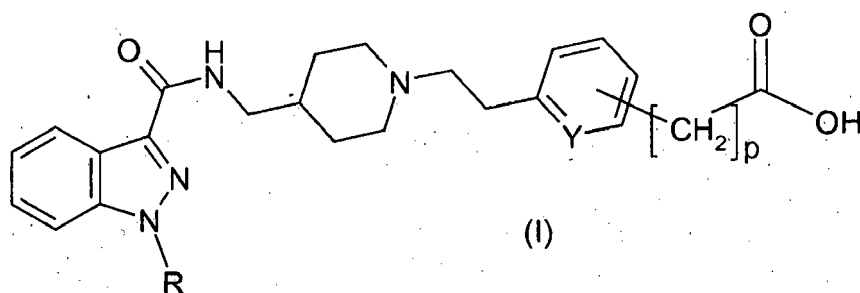
[0014] In point of fact, interaction with the serotonergic system, and even more particularly with specific subreceptors such as $5\text{HT}_{1\text{B}}$ or $5\text{HT}_{2\text{A}}$, may give rise to adverse effects on the cardiovascular system, inducing effects on the heart rhythm.

[0015] In addition, interactions with the hERG ion channel have been observed, which may be responsible for adverse side effects in the cardiovascular system.

DESCRIPTION OF THE INVENTION

[0016] It has now been found, surprisingly, that when the group R of formula 2 is represented by a carboxylic or alkenylcarboxylic group, the compounds of formula (B) maintain their action in neuropathic pain, with increased affinity towards the 5HT_4 serotonergic receptor and increased selectivity with respect to the other serotonergic receptors and towards the hERG channel.

[0017] Thus, the present invention relates to a compound of formula (I):



in which:

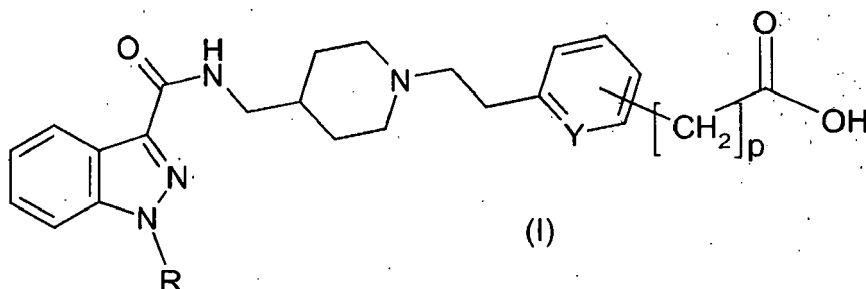
R is a linear or branched alkyl group containing between 1 and 3 carbon atoms,

Y is CH or N, and

p is an integer between 0 and 3 and preferably 0 and 1,

and salts thereof, either acid-addition salts with a pharmaceutically acceptable organic or mineral acid, or base-addition salts with a pharmaceutically acceptable organic or mineral base.

[0018] In a second aspect, the present invention relates to a pharmaceutical formulation comprising an effective amount of a compound of formula (I):



in which:

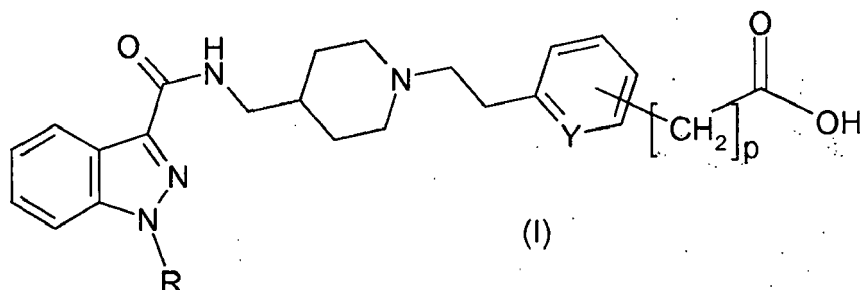
R is a linear or branched alkyl group containing between 1 and 3 carbon atoms,

Y is CH or N, and

p is an integer between 0 and 3, preferably 0 and 1,

and salts thereof, either acid-addition salts with a Pharmaceutically acceptable organic or mineral acid, or base-addition salts with a pharmaceutically acceptable organic or mineral base, and at least one pharmaceutically acceptable excipient.

[0019] In a third aspect, the present invention relates to a process for preparing a compound of formula (I):



in which

R is a linear or branched alkyl group containing between 1 and 3 carbon atoms,

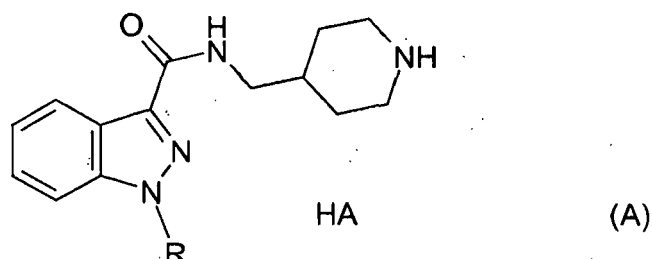
Y is CH or N, and

p is an integer between 0 and 3, preferably 0 and 1,

and salts thereof, either acid-addition salts with a pharmaceutically acceptable organic or mineral acid, or base-addition salts with a pharmaceutically acceptable organic or mineral base,

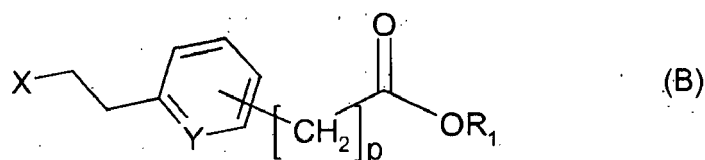
characterized in that it comprises

(1) the reaction between the compound of formula A:



in which:

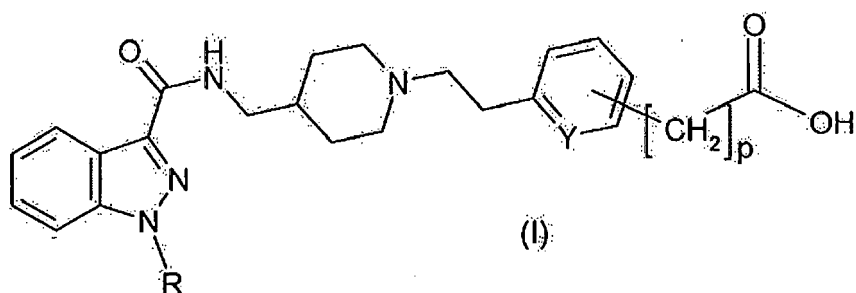
R has the meaning described above, and A represents an anionic residue of a mineral or organic acid, and the compound of formula B:



in which Y and p have the meaning described above, R₁ represents a linear or branched alkyl, aryl, arylalkyl or alkylaryl group containing between 1 and 10 carbon atoms, and X represents a halogen atom, and

(2) the subsequent hydrolysis of the ester obtained from reaction (1).

[0020] In a fourth aspect, the present invention relates to the use of a compound of formula (I)



in which:

R is a linear or branched alkyl group containing between 1 and 3 carbon atoms,

Y is CH or N, and

p is an integer between 0 and 3, preferably 0 and 1,

and salts thereof, either acid-addition salts with a pharmaceutically acceptable organic or mineral acid, or base-addition salts with a pharmaceutically acceptable organic or mineral base, for the preparation of a pharmaceutical composition that is active in the treatment of neuropathic pain.

[0021] Typical examples of compounds represented by the abovementioned formula (I) are illustrated in the following Table 1. The "Position" column indicates the position of the carboxylic or alkenylcarboxylic group on the aryl relative to the carbon bonded to the N-ethylpiperidino group.

Table 1

Compound	R	Y	p	Position
1	Isopropyl	CH	0	Para
2	Isopropyl	CH	1	Para
3	Isopropyl	CH	2	Para
4	Isopropyl	CH	3	Para
5	Ethyl	CH	0	Para
6	Methyl	CH	0	Para
7	Isopropyl	N	0	Para
8	Isopropyl	N	1	Para
9	Isopropyl	N	3	Para
10	Ethyl	N	0	Para
11	Methyl	N	0	Para
12	Ethyl	N	1	Para
13	Isopropyl	CH	0	Meta
14	Isopropyl	CH	0	Ortho

[0022] Typical examples of pharmaceutically acceptable organic and mineral acids are: oxalic acid, maleic acid, methanesulfonic acid, para-toluenesulfonic acid, succinic acid, citric acid, tartaric acid, lactic acid, hydrochloric acid, phosphoric acid, sulfuric acid. Amino acids such as aspartic acid and glutamic acid may also be used as organic acids.

[0023] Typical examples of pharmaceutically acceptable organic and mineral bases are: mono-, di- and trialkylamines, for instance methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, propylamine, dipropylamine, tripropylamine, ethylenediamine, mono-, di- and trialkanolamines, for instance monoethanolamine, diethanolamine and triethanolamine; guanidine, morpholine, piperidine, pyrrolidine, piperazine, 1-butylpiperidine, 1-ethyl-2-methyl-piperidine, N-methylpiperazine, 1,4-dimethylpiperazine, N-benzylphenyl-ethylamine, N-methylglucosamine, tris(hydroxymethyl)aminomethane, ammonia, sodium hydroxide, calcium hydroxide, potassium hydroxide, aluminium hydroxide, iron hydroxide, magnesium hydroxide and zinc hydroxide. Amino acids such as arginine and lysine may also be used as organic bases.

[0024] Typical examples of pathologies characterized by neuropathic pain are diabetes, cancer, immunodeficiency, trauma, ischemia, multiple sclerosis, sciatica, trigeminal neuralgia and post-herpetic syndrome.

[0025] Preferably, the pharmaceutical compositions of the present invention are prepared in the form of suitable dosage forms including an effective dose of at least one compound (I) or a salt thereof, either an acid-addition salt with a pharmaceutically acceptable organic or mineral acid, or a base-addition salt with pharmaceutically acceptable organic and mineral bases, and at least one pharmaceutically acceptable excipient.

[0026] The term "pharmaceutically acceptable excipient" is intended to mean, without any particular limitations, a material that is suitable for preparing a pharmaceutical composition to be administered to a living being.

[0027] These materials, known in the art, are, for example, release agents, binders, disintegrants, fillers, diluents, dyes, fluidizers, glidants, lubricants, preserving agents, stabilizers, humectants, absorbents, surfactants, buffers, salts for regulating the osmotic pressure, emulsifiers, flavourings and sweeteners.

[0028] Useful examples of pharmaceutically acceptable excipients are sugars, such as lactose, glucose or sucrose, starches, such as corn starch and potato starch, cellulose and derivatives thereof, such as sodium carboxymethylcellulose, ethylcellulose and cellulose acetate, gum tragacanth, malt, gelatin, talc, cocoa butter, waxes, oils, such as groundnut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil, glycols, such as propylene glycol, polyols, such as glycerol, sorbitol, mannitol and polyethylene glycol, esters, such as ethyl oleate and ethyl laurate, agar, buffers, such as magnesium hydroxide and aluminium hydroxide, alginic acid, water, isotonic solutions, ethanol, buffer solutions, polyesters, polycarbonates, polyanhydrides, and the like.

[0029] Examples of suitable dosage forms are tablets, capsules, coated tablets, granules, solutions and syrups for oral administration; antiseptic plasters, solutions, pastes, creams and ointments for transdermal administration; suppositories for rectal administration and sterile solutions for injection or aerosol administration.

[0030] Other suitable dosage forms are sustained-release forms or liposome-based forms, for either the oral or injection route.

[0031] When required for particular therapies, the pharmaceutical composition of the present invention may contain other pharmacologically active ingredients whose simultaneous administration is useful.

[0032] The amount of compound (I) or acid-addition salt or base-addition salt thereof in the pharmaceutical composition of the present invention may vary within a wide range as a function of known factors, for instance the type of pathology with which the neuropathic pain to be treated is associated, the severity of the affliction, the weight of the patient, the dosage form, the selected route of administration, the number of daily administrations and the efficacy of the selected compound of formula (I). However, the optimum amount may be readily and routinely determined by a person skilled in the art.

[0033] Typically, the amount of compound (I) or acid-addition salt or base-addition salt thereof in the pharmaceutical composition of the present invention will be such that it ensures a level of administration of between 0.001 and 100 mg/kg/day of compound (I), expressed as base. Preferably, the level of administration will be between 0.05 and 50 mg/kg/day and even more preferably between 0.1 and 10 mg/kg/day.

[0034] The dosage forms of the pharmaceutical composition of the present invention may be prepared according to techniques well known to pharmaceutical chemists, including mixing, granulation, compression, dissolution, sterilization and the like.

[0035] In the production process of the present invention, the residue A is preferably represented by halide (such as chloride, bromide or iodide), phosphate (such as pyrophosphate, monophosphate, diphosphate or triphosphate), sulfate, nitrate, or an organic carboxylate (such as acetate, benzoate, lactate and the like). The residue A is more preferably represented by halide, in particular chloride.

[0036] In the production process of the present invention, the residue X is preferably represented by halide, more preferably by chloride, bromide or iodide. The preferred residue X is bromide.

[0037] In the production process of the present invention, the group represented by R_1 is preferably a linear or branched alkyl containing 1-6 carbon atoms, an aryl, an arylalkyl or an alkylaryl containing 7-8 carbon atoms. The group R_1 may also comprise conventional organic substituents, such as halide, nitro, hydroxy, and the like. The group R_1 is preferably selected from methyl, ethyl, isopropyl, phenyl and benzyl.

[0038] Reaction (1) of the production process of the present invention is preferably performed in an organic solvent. Typical examples of organic solvents that are useful in the production process of the present invention are preferably polar aprotic solvents, such as ketones (for example acetone or methyl ethyl ketone), tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, dioxane, acetonitrile and the like.

[0039] Reaction (1) of the production process of the present invention is performed under hot conditions, preferably at the boiling point of the reaction solution.

[0040] Reaction (1) of the production process of the present invention is preferably performed in the presence of a basic organic or mineral compound. Useful examples of basic organic substances are aliphatic or aromatic amines, such as mono-, di- or trialkylamines, mono-, di- or trialkanolamines, benzylamine, N-methylbenzylamine and the like. Useful examples of mineral bases are strong bases such as NaOH or KOH, or weak bases such as NH_4OH , Na_2CO_3 and the like.

[0041] Reaction (1) of the production process of the present invention is preferably performed in the presence of an activating agent, for instance potassium iodide, caesium iodide, tetrabutylammonium iodide or trimethylphenylammonium iodide.

[0042] The hydrolysis (2) of the ester obtained from reaction (1) of the production process of the present invention is performed by methods known in the art. Preferably, the hydrolysis is performed in polar protic organic solvents, for instance methanol, ethanol, propanol, isopropanol, butanol and the like or aprotic organic solvents such as methyl ethyl ketone, tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, dioxane, acetonitrile and the like, and in the presence of a base such as NaOH or KOH.

[0043] The preparation of the compounds of formula (A) may be performed according to the process described in patent EP 0 975 623 B1.

[0044] The preparation of the compounds of formula (B) may be performed as described in the Journal of the American Chemical Society (1940), 62 1435-8.

[0045] The analgesic activity of compound (I) was demonstrated by means of an experimental model in rats represented by the allodynia induced by ligature of the sciatic nerve.

[0046] As is known to those skilled in the art, the abovementioned experimental model may be considered as predictive of activity in man.

[0047] The experimental model of ligature of the sciatic nerve in rats represents a neuropathy that reproduces a series

of responses similar to those observed in man in numerous traumatic and pathological conditions associated with neuropathic pain. The reason for this is that ligature of the sciatic nerve is capable of inducing a syndrome associated with the activation of specific circuits dedicated to controlling the perception of pain and characterized by the appearance of allodynia, hyperalgesia and spontaneous pain. This model is well known to constitute a valid instrument for studying drugs to be used in the treatment of neuropathic pain in man, and in particular in controlling conditions such as allodynia and hyperalgesia.

[0048] Typical examples of human pathologies characterized by the dysfunctions described in the abovementioned experimental model and characterized by the presence of neuropathic pain are diabetes, cancer, immunodeficiency, trauma, ischemia, multiple sclerosis, sciatica, trigeminal neuralgia and post-herpetic syndrome.

[0049] Confirmation of the binding to the serotonergic receptors was performed by means of the biochemical test on purified membranes from recombinant human cells that stably express the specific receptors or from animal tissues selected as described in particular for each type of serotonergic receptor, in: Martin G.R. and Humphrey P.P.A. *Neuropharmacol.* 1994, 33:261; Hoyer D. *Eur. J. Pharmacol.* 1985, 118:1; Bonhaus DW et al. *Br. J. Pharmacol.* 1995, 115:622; Wolf WA et al. *J. Neurochem.* 1997, 69:1449; Boess FG et al. *Neuropharmacol.* 1997, 36:637; Mialet J et al. *Br. J. Pharmacol.* 2000, 129:771; Rees S et al. *FEBS Lett.* 1994, 355:242; Monsma F.J. et al. *Mol. Pharmacol.* 1993, 43:320; Roth BL et al. *J. Pharmacol. Exp. Ther.* 1994, 268:1403; and Shearman LP et al. *Am. J. Physiol.* 1998, 275: C1621.

[0050] As is known to those skilled in the art, this test constitutes a predictive model of molecular interaction and of selectivity with the selected receptors.

[0051] Confirmation of interaction with the potassium channels was made by means of a functional cell test (patch clamp) that uses HEK-293 recombinant human cells that stably express the hERG ion channel, as described in Zhou Z. et al. *Biophys. J.* 1998; 74:230.

[0052] As is known to those skilled in the art, this test constitutes a predictive model of induction of changes in heart functionality and in particular of effects on the heart rhythm following changes in the Qt time.

TESTS

1. Allodynia induced by ligature of the sciatic nerve in rats

[0053] Male CD rats weighing 200-250 g on arrival were used.

[0054] The allodynia was induced by ligature under anaesthesia of the sciatic nerve of the left hindleg [Seltzer Z, Dubner R, Shir Y. A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury. *Pain* 1990; 43: 205-218; Bennet GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain* 1988; 33: 87-107]. At least two weeks after ligature of the sciatic nerve, rats who showed a reduction of at least 50% in the response threshold recorded before the intervention were selected. The pain threshold was measured with a von Frey machine, which makes it possible, by applying a gradual increase in pressure to the paw of the left hindleg of the rat, to record the nociceptive response, expressed in grams, corresponding to the moment at which the animal withdraws the leg.

[0055] At 30 minutes, 1, 2 and 4 hours of treatment, the pain threshold measured in control animals was compared with that measured in animals treated with the test product (compound 1 of Table 1).

[0056] The control animals were treated with the same vehicle (methylcellulose) used to administer the test product. The results are illustrated in Figure 1.

2. Blinding to the serotonergic receptors

[0057] Confirmation of the binding to the serotonergic receptors was made using purified membranes from selected animal tissues or from recombinant human cells that stably express the specific receptors, as described in: Martin G.R. and Humphrey P.P.A. *Neuropharmacol.* 1994, 33:261; Hoyer D. *Eur. J. Pharmacol.* 1985, 118:1; Bonhaus DW et al. *Br. J. Pharmacol.* 1995, 115:622; Wolf WA et al. *J. Neurochem.* 1997, 69:1449; Boess FG et al. *Neuropharmacol.* 1997, 36:637; Mialet J et al. *Br. J. Pharmacol.* 2000, 129:771; Rees S et al. *FEBS Lett.* 1994, 355:242; Monsma F.J. et al. *Mol. Pharmacol.* 1993, 43:320; Roth BL et al. *J. Pharmacol. Exp. Ther.* 1994, 268: 1403; and Shearman LP et al. *Am. J. Physiol.* 1998, 275: C1621.

[0058] Under the experimental conditions used, compound 1 of Table 1 showed selective inhibition of binding to the 5-HT₄ receptor. The results obtained are given in Table 2.

Table 2

Receptor	IC ₅₀ (nM)
5-HT _{1A}	>10 000

(continued)

Receptor	IC50 (nM)
5-HT _{1B}	>10 000
5-HT _{2A}	>10 000
5-HT _{2B}	>10 000
5-HT _{2c}	>10 000
5-HT ₃	>10 000
5-HT ₄	0.8
5-HT _{5A}	>10 000
5-HT ₆	>10 000
5-HT ₇	>10 000
5-HT transporter - SERT	>10 000

3. Interaction with potassium channels (hERG)

[0059] Confirmation of interaction with the potassium channels was made by means of the patch clamp test described in Zhou Z. et al. Biophys. J. 1998; 74:230 using the recombinant human cell line HEK-293, which stably expresses the hERG ion channel.

[0060] Under the experimental conditions used, compound 1 of Table 1 showed an IC₅₀ >50 μ M. The results obtained are given in Table 3.

Table 3

μ M	% inhibition
0.01	0.0
0.10	0.0
1.00	0.9
10.00	6.5
50.00	18.8

Examples

Example 1

Preparation of compound 1 of Table 1 4-{2-[4-({[(1-Isopropyl-1H-indazol-3-yl)carbonyl]amino}methyl)-piperidin-1-yl]ethyl}benzoic acid

1a) 1-[4-(2-Bromoethyl)phenyl]ethanone

[0061] A solution containing acetyl chloride (85 ml; 0.85 mol) and bromo-ethylbenzene (82 ml; 0.60 mol) was added, at 0°C, to a mixture containing anhydrous aluminium trichloride (72 g; 0.54 mol), dichloromethane (300 ml) and acetyl chloride (42.5 ml; 0.6 mol). The mixture was stirred under cold conditions for 3 hours and then added to a cold solution of 6N HCl (600 ml). The resulting mixture was stirred at room temperature overnight.

[0062] The two phases formed after leaving to stand at room temperature for a few minutes were separated. The acidic phase was extracted twice with 300 ml of dichloromethane. The combined organic phases were washed three times with 100 ml of water and once with 100 ml of saturated NaCl solution, and then dried with anhydrous Na₂SO₄. The solvent was then evaporated off under reduced pressure, to give 138 g of crude product, which product was subsequently purified by fractional distillation under reduced pressure. 79.0 g (0.35 mol) of 1-[4-(2-bromo-ethyl)phenyl]ethanone were thus obtained (T = 120°C; P = 7 mmHg).

¹H NMR (δ ppm, CDCl₃, 300 MHz): 2.59 (s, 3 H) 3.23 (t, J = 7.31 Hz, 2 H) 3.59 (t, J = 7.31 Hz, 2 H) 7.31 (d, J = 7.89

Hz, 2 H) 7.92 (d, J = 8.18 Hz, 2 H).

2a) 4-(2-Bromoethyl)benzoic acid

5 **[0063]** A solution containing 1-[4-(2-bromoethyl)phenyl]ethanone (38.2 g; 0.17 mol) in dioxane (100 ml) was added slowly to a solution containing bromine (80.6 g; 0.50 mol), sodium hydroxide (55.4 g; 1.39 mol), water (470 ml) and dioxane (340 ml) stirred at 0°C. The mixture was stirred at the same temperature for 3 hours, followed by addition, while still cold, of 120 ml of concentrated HCl. The resulting mixture was stirred at room temperature overnight.

10 **[0064]** The solid obtained from the mixture was filtered off and washed on the filter with 1 N HCl (200 ml). 20.3 g of 4-(2-bromoethyl)benzoic acid (0.09 mol) were thus obtained, and were used for the following reaction without further purification.

¹H NMR (δ ppm, 300 MHz, DMSO-d₆): 3.21 (t, J = 6.95 Hz, 2 H) 3.77 (t, J = 7.14 Hz, 2 H) 7.40 (d, J = 8.42 Hz, 2 H) 7.89 (d, J = 8.05 Hz, 2 H) 12.83 (s, 1 H).

15 3a) Ethyl 4-(2-bromoethyl)benzoate

[0065] A mixture containing 4-(2-bromoethyl)benzoic acid (10 g; 43.7 mmol), 9.5 N hydrochloric ethanol (50 ml; 475 mmol) and absolute ethanol (50 ml) was stirred at reflux for 4 hours.

20 **[0066]** The mixture was then cooled to room temperature and the solvent was evaporated off under reduced pressure. The residue was taken up in saturated Na₂CO₃ solution (100 ml) and then extracted with ethyl acetate (3 × 100 ml).

[0067] The combined organic phases were washed first with water (50 ml) and then with saturated NaCl solution (30 ml). The solution was then dried with anhydrous Na₂SO₄. Finally, the solvent was evaporated off under reduced pressure, thus giving 10.8 g of ethyl 4-(2-bromoethyl)-benzoate (42 mmol), which was used in the following reaction without further purification.

25 ¹H NMR (δ ppm, 300 MHz, CDCl₃) 1.39 (t, J = 6.87 Hz, 3 H) 3.22 (t, J = 7.45 Hz, 2 H) 3.58 (t, J = 7.45 Hz, 2 H) 4.37 (q, J = 6.90 Hz, 2 H) 7.28 (d, J = 8.15 Hz, 2 H) 8.00 (d, J = 8.18 Hz, 2 H)

4a) Ethyl 4-{2-[4-({[(1-isopropyl-1 H-indazol-3-yl)carbonyl]amino)methyl}piperidin-1-yl]ethyl}benzoate

30 **[0068]** A mixture containing 1-isopropyl-N-(piperidin-4-ylmethyl)-1H-indazol-3-carboxamide hydrochloride (45.9 g, 136 mmol), prepared as described in EP 0 975 623, ethyl 4-(2-bromoethyl)benzoate (37 g; 144 mmol), 2-butanone (1600 ml) and triethylamine (18.9 ml; 136 mmol) was stirred at reflux. After reaction for 1.5 hours, a second aliquot of triethylamine (9.5 ml; 68 mmol) was added, while maintaining the reflux. After reaction for a further 1.5 hours, a third aliquot of triethylamine (9.5 ml; 68 mmol) was added, while maintaining the reflux. After a further 1.5 hours, potassium iodide (6.2 g; 37.3 mmol) was added to the reaction mixture, while still at reflux. Finally, the mixture was then stirred at reflux overnight.

35 **[0069]** The resulting mixture was then cooled to room temperature and poured into water (2 L). The two phases were separated and the aqueous phase was extracted with 2-butanone (2 × 400 ml). The combined organic phases were then washed with water (50 ml) and with saturated NaCl solution (50 ml). The solution was dried with anhydrous Na₂SO₄ and the solvent was then evaporated off under reduced pressure. 58.9 g of crude product were obtained, which product was purified by gravity chromatography on neutral alumina (1400 g), using an 8/2 mixture of chloroform and hexane as eluent.

40 **[0070]** 14.2 g of ethyl 4-{2-[4-({[(1-isopropyl-1 H-indazol-3-yl)carbonyl]amino)methyl}piperidin-1-yl]ethyl}benzoate (29.8 mmol) were thus obtained.

45 ¹H NMR (δ ppm, 300 MHz, CDCl₃): 1.32-1.51 (m, 2 H) 1.38 (t, J = 7.16 Hz, 3 H) 1.61 (d, J = 6.72 Hz, 6 H) 1.64-1.91 (m, 3 H) 2.05 (td, J = 11.55, 2.34 Hz, 2 H) 2.54-2.66 (m, 2 H) 2.81-2.91 (m, 2 H) 3.02 (d, J = 11.69 Hz, 2 H) 3.42 (t, J = 6.43 Hz, 2 H) 4.36 (q, 2 H) 4.87 (spt, 1 H) 7.15 (t, J = 6.28 Hz, 1 H) 7.22-7.31 (m, 3 H) 7.35-7.49 (m, 2 H) 7.96 (d, 2 H) 8.39 (dt, J = 8.18, 1.02 Hz, 1 H).

50 5a) 4-{2-[4-({[(1-isopropyl-1 H-indazol-3-yl)carbonyl]amino)methyl}piperidin-1-yl]ethyl}benzoic acid

[0071] The solution containing ethyl 4-{2-[4-({[(1-isopropyl-1H-indazol-3-yl)-carbonyl]amino)methyl}piperidin-1-yl]ethyl}benzoate (6.2 g; 13 mmol), tetrahydrofuran (30 ml), absolute ethanol (30 ml) and 1 N sodium hydroxide (28.5 ml; 28.5 mmol) was stirred at room temperature for 3 days. The resulting mixture was neutralized to pH 7 by adding glacial acetic acid (about 1.7 ml) and was then stirred at room temperature overnight.

55 **[0072]** The solid thus formed was filtered off while cold and was then washed on the filter with a 1/1 mixture of tetrahydrofuran and absolute ethanol. The solid was crystallized several times from a 4/3 mixture of ethyl acetate and ethanol. 3.7 g of 4-{2-[4-({[(1-isopropyl-1H-indazol-3-yl)carbonyl]amino)methyl}piperidin-1-yl]ethyl}benzoic acid (8.3

EP 2 207 776 B9

mmol) were thus obtained.

¹H NMR (δ ppm, 300 MHz, DMSO-d₆) 1.23 (d, J = 11.34 Hz, 2 H) 1.53 (d, J = 6.59 Hz, 6 H) 1.57-1.77 (m, 3 H) 2.01 (t, J = 10.79 Hz, 2 H) 2.57 (t, J = 8.00 Hz, 2 H) 2.81 (t, J = 7.68 Hz, 2 H) 2.96 (d, J = 10.98 Hz, 2 H) 3.21 (t, J = 6.22 Hz, 2 H) 5.06 (spt, J = 6.62 Hz, 1 H) 7.21-7.28 (m, 1 H) 7.31 (d, J = 8.05 Hz, 2 H) 7.42 (ddd, J = 8.51, 7.04, 1.28 Hz, 1 H) 7.76 (d, J = 8.42 Hz, 1 H) 7.84 (d, J = 8.05 Hz, 2 H) 8.12-8.24 (m, 2 H) 10.78 (br. s., 1 H).
m.p. = 179-181 °C; MS showed 449 (MH⁺) base peak;

Elemental analysis for C₂₆H₃₂N₄O₃

	C	H	N
% found	69.37	7.23	12.25
% calculated	69.62	7.19	12.49

Example 2

[0073] A tablet containing, as active principle, Compound 1 of the present invention, has the following composition:

Active principle	50 mg
Lactose monohydrate	161 mg
Dibasic calcium phosphate dehydrate	161 mg
Microcrystalline cellulose	95 mg
Corn starch	30 mg
Sodium carboxymethylstarch	24 mg
Povidone	11 mg
Magnesium stearate	3 mg

Example 3

[0074] A vial containing, as active principle, Compound 1 of the present invention, has the following composition:

Active principle	25 mg
Sorbitol	qs iso-osmotic solution
Water	qs 100 ml

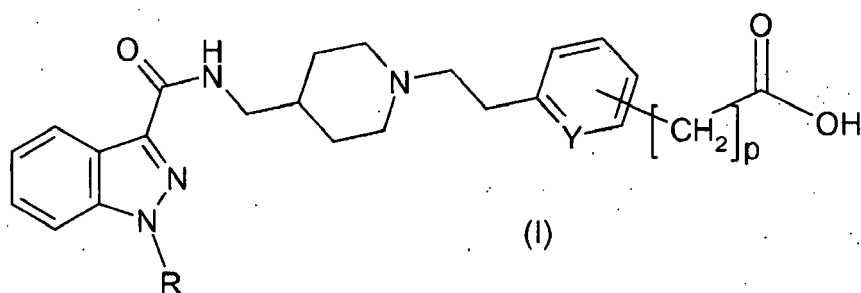
Example 4

[0075] A pharmaceutical composition in the form of granules containing, as active principle, Compound 1 of the present invention, has the following composition:

Active principle	50 mg
Maltitol	1300 mg
Mannitol	2700 mg
Sucrose	1000 mg
Citric acid	20 mg
Aspartame	20 mg
Flavourings	200 mg

Claims

1. Compound of formula (I):



in which:

R is a linear or branched alkyl group containing between 1 and 3 carbon atoms,

Y is CH or N, and

p is an integer between 0 and 3,

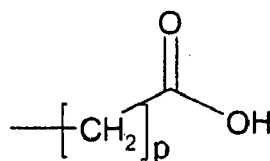
and salts thereof, either acid-addition salts with a pharmaceutically acceptable organic or mineral acid, or base-addition salts with a pharmaceutically acceptable organic or mineral base.

2. Compound according to Claim 1, in which R is a linear or branched alkyl group containing from 2 to 3 carbon atoms.

3. Compound according to Claim 1, in which Y is CH.

4. Compound according to Claim 1, in which p is an integer from 0 to 1.

5. Compound according to Claim 1, in which R, Y, p and the position of the group



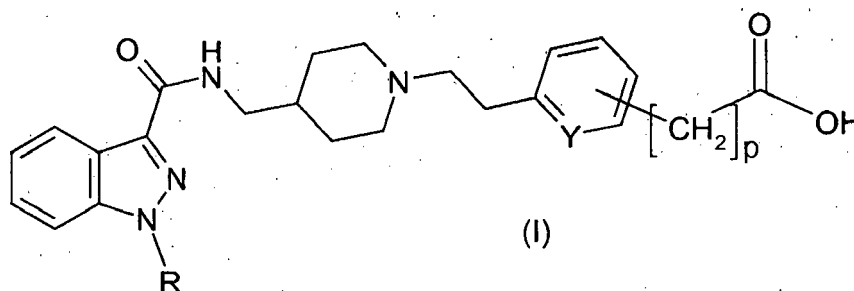
are represented in the following table:

Compound	R	Y	p	Position
1	Isopropyl	CH	0	Para
2	Isopropyl	CH	1	Para
3	Isopropyl	CH	2	Para
4	Isopropyl	CH	3	Para
5	Ethyl	CH	0	Para
6	Methyl	CH	0	Para
7	Isopropyl	N	0	Para
8	Isopropyl	N	1	Para
9	Isopropyl	N	3	Para
10	Ethyl	N	0	Para
11	Methyl	N	0	Para
13	Ethyl	N	1	Para
13	Isopropyl	CH	0	Meta

(continued)

Compound	R	Y	p	Position
14	Isopropyl	CH	0	Ortho

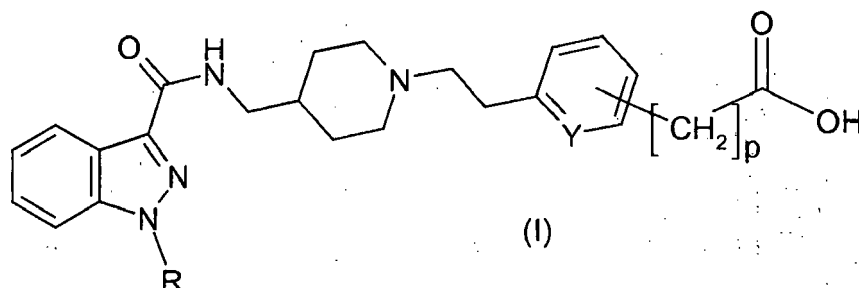
6. Compound according to any one of the preceding claims, in which the said pharmaceutically acceptable organic or mineral acid is chosen from the group comprising oxalic acid, maleic acid, methanesulfonic acid, para-toluenesulfonic acid, succinic acid, citric acid, tartaric acid, lactic acid, hydrochloric acid, phosphoric acid, sulfuric acid, aspartic acid and glutamic acid.
7. Compound according to any one of Claims 1 to 5, in which the said pharmaceutically acceptable organic or mineral base is chosen from the group comprising methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, propylamine, dipropylamine, tripropylamine, ethylenediamine, monoethanolamine, diethanolamine, triethanolamine, guanidine, morpholine, piperidine, pyrrolidine, piperazine, 1-butylpiperidine, 1-ethyl-2-methylpiperidine, N-methyl-piperazine, 1,4-dimethylpiperazine, N-benzylphenylethylamine, N-methylglucosamine, tris(hydroxymethyl)aminomethane, arginine, lysine, ammonia, sodium hydroxide, calcium hydroxide, potassium hydroxide, aluminium hydroxide, iron hydroxide, magnesium hydroxide and zinc hydroxide.
8. Pharmaceutical formulation comprising an effective amount of a compound of formula (I):



in which:

- R is a linear or branched alkyl group containing between 1 and 3 carbon atoms,
 Y is CH or N, and
 p is an integer between 0 and 3,
 and salts thereof, either acid-addition salts with a pharmaceutically acceptable organic or mineral acid, or base-addition salts with a pharmaceutically acceptable organic or mineral base, and
 at least one pharmaceutically acceptable excipient.
9. Pharmaceutical formulation according to Claim 8, in which the said at least one pharmaceutically acceptable excipient is chosen from the group comprising release agents, binders, disintegrants, fillers, diluents, dyes, fluidizers, glidants, lubricants, preserving agents, stabilizers, humectants, absorbents, surfactants, buffers, salts for regulating the osmotic pressure, emulsifiers, flavourings and sweeteners.
10. Pharmaceutical formulation according to Claim 8, in which the compound of formula (I) is defined according to any one of Claims 1 to 7.
11. Pharmaceutical formulation according to any one of Claims 8 to 10, in which the pharmaceutical formulation is chosen from the group comprising tablets, capsules, coated tablets, granules, solutions and syrups for oral administration, antiseptic plasters, solutions, pastes, creams and ointments for transdermal administration, suppositories for rectal administration, sterile solutions for injection or aerosol administration, in either immediate-release or sustained-release form.
12. Pharmaceutical formulation according to any one of Claims 8 to 11, in which the said pharmaceutical formulation comprises an amount of compound of formula (I) or an acid-addition salt or base-addition salt thereof to ensure a level of administration of between 0.001 and 100 mg/kg/day of compound of formula (I), expressed in free form.

13. Pharmaceutical formulation according to Claim 12, in which the said amount will ensure a level of administration of between 0.05 and 50 mg/kg/day.
14. Pharmaceutical formulation according to Claim 12, in which the said amount will ensure a level of administration of between 0.1 and 10 mg/kg/day.
15. Process for preparing a compound of formula (I):



in which

R is a linear or branched alkyl group containing between 1 and 3 carbon atoms,

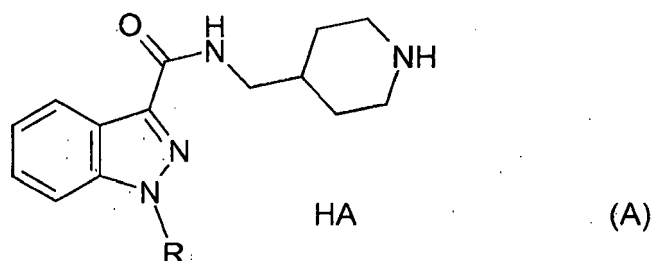
Y is CH or N, and

p is an integer between 0 and 3,

and salts thereof, either acid-addition salts with a pharmaceutically acceptable organic or mineral acid, or base-addition salts with a pharmaceutically acceptable organic or mineral base,

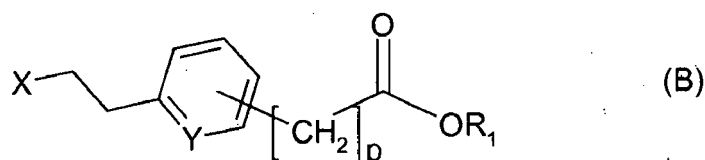
characterized in that it comprises

(1) the reaction between the compound of formula A:



in which:

R has the meaning described above, and A represents an anionic residue of a mineral or organic acid, and the compound of formula B:

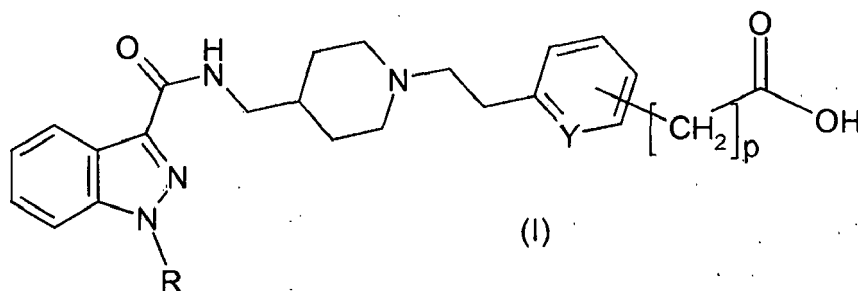


in which Y and p have the meaning described above, R₁ represents a linear or branched alkyl, aryl, arylalkyl or alkylaryl group containing between 1 and 10 carbon atoms, and X represents a halogen atom, and (2) the subsequent hydrolysis of the ester obtained from reaction (1).

16. Preparation process according to Claim 15, in which the said residue A is chosen from the group comprising halide,

phosphate, sulfate, nitrate and organic carboxylate.

17. Preparation process according to Claim 16, in which the said residue A is chosen from the group comprising chloride, bromide and iodide.
18. Preparation process according to Claim 15, in which the said residue X is chosen from the group comprising chloride, bromide and iodide.
19. Preparation process according to Claim 15, in which the said group R₁ is chosen from the group comprising a linear or branched alkyl containing 1-6 carbon atoms, an aryl, an arylalkyl and an alkylaryl containing 7-8 carbon atoms.
20. Preparation process according to any one of Claims 15 to 19, in which the said reaction (1) is performed in an organic solvent chosen from the group comprising polar aprotic solvents.
21. Preparation process according to Claim 20, in which the said organic solvent is chosen from the group comprising acetone, methyl ethyl ketone, tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, dioxane and acetonitrile.
22. Preparation process according to any one of Claims 15 to 21, in which the said reaction (1) is performed in the presence of a basic organic or mineral compound.
23. Preparation process according to any one of Claims 15 to 22, in which the said reaction (1) is performed in the presence of an activating agent chosen from the group comprising potassium iodide, caesium iodide, tetrabutylammonium iodide and trimethylphenylammonium iodide.
24. Use of a compound of formula (I):



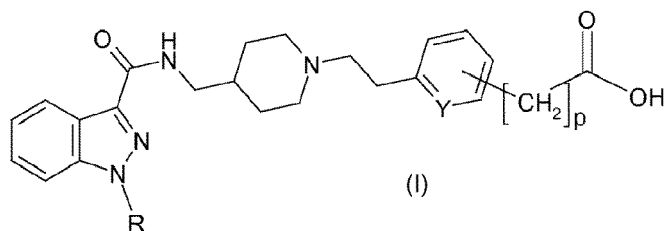
in which:

R is a linear or branched alkyl group containing between 1 and 3 carbon atoms,
Y is CH or N, and
p is an integer between 0 and 3,
and salts thereof, either acid-addition salts with a pharmaceutically acceptable organic or mineral acid, or base-addition salts with a pharmaceutically acceptable organic or mineral base, for the preparation of a pharmaceutical composition for treating of neuropathic pain.

25. Use of a compound according to Claim 24, for preparing a pharmaceutical composition for treating neuropathic pain caused by diabetes, cancer, immunodeficiency, trauma, ischemia, multiple sclerosis, sciatica, trigeminal neuralgia and post-herpetic syndrome.

Patentansprüche

1. Verbindung der Formel (I):



worin:

R für eine lineare oder verzweigte Alkylgruppe mit 1 bis 3 Kohlenstoffatomen steht,

Y für CH oder N steht, und

p für eine ganze Zahl von 0 bis 3 steht,

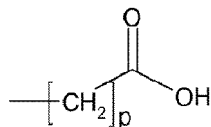
und Salze davon, entweder Säureadditionssalze mit einer pharmazeutisch akzeptablen organischen oder mineralischen Säure, oder Basenadditionssalze mit einer pharmazeutisch akzeptablen organischen oder mineralischen Base.

2. Verbindung nach Anspruch 1, worin R für eine lineare oder verzweigte Alkylgruppe mit 2 bis 3 Kohlenstoffatomen steht.

3. Verbindung nach Anspruch 1, worin Y für CH steht.

4. Verbindung nach Anspruch 1, worin p für eine ganze Zahl von 0 bis 1 steht.

5. Verbindung nach Anspruch 1, worin R, Y, p und die Position der Gruppe



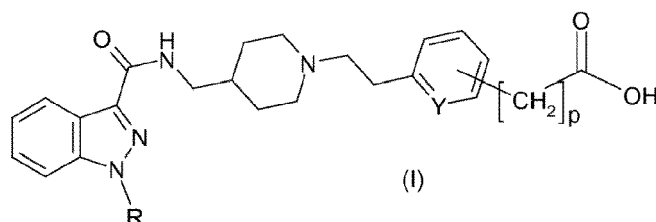
wie in der folgenden Tabelle dargestellt sind:

Verbindung	R	Y	p	Position
1	Isopropyl	CH	0	para
2	Isopropyl	CH	1	para
3	Isopropyl	CH	2	para
4	Isopropyl	CH	3	para
5	Ethyl	CH	0	para
6	Methyl	CH	0	para
7	Isopropyl	N	0	para
8	Isopropyl	N	1	para
9	Isopropyl	N	3	para
10	Ethyl	N	0	para
11	Methyl	N	0	para
12	Ethyl	N	1	para
13	Isopropyl	CH	0	meta
14	Isopropyl	CH	0	ortho

6. Verbindung nach einem der vorhergehenden Ansprüche, worin die pharmazeutisch akzeptable organische oder mineralische Säure ausgewählt ist unter Oxalsäure, Maleinsäure, Methansulfonsäure, para-Toluolsulfonsäure, Bernsteinsäure, Citronensäure, Weinsäure, Milchsäure, Salzsäure, Phosphorsäure, Schwefelsäure, Asparaginsäure und Glutaminsäure.

7. Verbindung nach einem der Ansprüche 1 bis 5, worin die pharmazeutisch akzeptable organische oder mineralische Base ausgewählt ist unter Methylamin, Dimethylamin, Trimethylamin, Ethylamin, Diethylamin, Triethylamin, Propylamin, Dipropylamin, Tripropylamin, Ethylendiamin, Monoethanolamin, Diethanolamin, Triethanolamin, Guanidin, Morpholin, Piperidin, Pyrrolidin, Piperazin, 1-Butylpiperidin, 1-Ethyl-2-methylpiperidin, N-Methylpiperazin, 1,4-Dimethylpiperazin, N-Benzylphenylethylamin, N-Methylglucosamin, Tris(hydroxymethyl)aminomethan, Arginin, Lysin, Ammoniak, Natriumhydroxid, Calciumhydroxid, Kaliumhydroxid, Aluminiumhydroxid, Eisenhydroxid, Magnesiumhydroxid und Zinkhydroxid.

8. Pharmazeutische Formulierung umfassend eine wirksame Menge einer Verbindung der Formel (I):



worin:

R für eine lineare oder verzweigte Alkylgruppe mit 1 bis 3 Kohlenstoffatomen steht,

Y für CH oder N steht, und

p für eine ganze Zahl von 0 bis 3 steht,

und Salze davon, entweder Säureadditionssalze mit einer pharmazeutisch akzeptablen organischen oder mineralischen Säure, oder Basenadditionssalze mit einer pharmazeutisch akzeptablen organischen oder mineralischen Base, und

zumindest einen pharmazeutisch akzeptablen Träger.

9. Pharmazeutische Formulierung nach Anspruch 8, worin der zumindest eine pharmazeutisch akzeptable Träger ausgewählt ist unter Trennmitteln, Bindemitteln, Desintegrationsmitteln, Füllstoffen, Verdünnern, Farbstoffen, Fluidisierungsmitteln, Fließregulierungsmitteln, Schmiermitteln, Konservierungsstoffen, Stabilisatoren, Befeuchtungsmitteln, Absorptionsmitteln, Tensiden, Puffern, Salzen zur Regulierung des osmotischen Drucks, Emulgatoren, Aromastoffen und Süßstoffen.

10. Pharmazeutische Formulierung nach Anspruch 8, worin die Verbindung der Formel (I) wie nach einem der Ansprüche 1 bis 7 definiert ist.

11. Pharmazeutische Formulierung nach einem der Ansprüche 8 bis 10, worin die pharmazeutische Formulierung ausgewählt ist unter Tabletten, Kapseln, Filmtabletten, Granalien, Lösungen und Sirupen zur oralen Verabreichung, antiseptischen Pflastern, Lösungen, Pasten, Cremes und Salben zur transdermalen Verabreichung, Zäpfchen zur rektalen Verabreichung, sterilen Lösungen für Injektions- oder Aerosol-Verabreichung, in nicht retardierter oder Retard-Form.

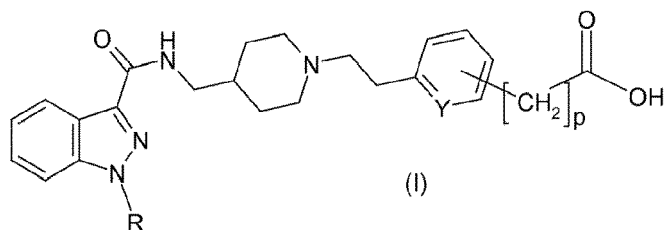
12. Pharmazeutische Formulierung nach einem der Ansprüche 8 bis 11, worin die pharmazeutische Formulierung eine Menge der Verbindung der Formel (I) oder ein Säureadditionssalz oder Basenadditionssalz davon enthält, um eine Verabreichungsmenge von 0,001 bis 100 mg/kg/Tag der Verbindung der Formel (I), ausgedrückt in freier Form, zu gewährleisten.

13. Pharmazeutische Formulierung nach Anspruch 12, worin die Menge eine Verabreichungsmenge von 0,05 bis 50 mg/kg/Tag gewährleistet.

14. Pharmazeutische Formulierung nach Anspruch 12, worin die Menge eine Verabreichungsmenge von 0,1 bis 10

mg/kg/Tag gewährleistet.

15. Verfahren zur Herstellung einer Verbindung der Formel (I):



worin:

R für eine lineare oder verzweigte Alkylgruppe mit 1 bis 3 Kohlenstoffatomen steht,

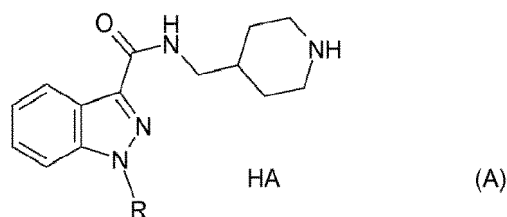
Y für CH oder N steht, und

p für eine ganze Zahl von 0 bis 3 steht,

und Salze davon, entweder Säureadditionssalze mit einer pharmazeutisch akzeptablen organischen oder mineralischen Säure, oder Basenadditionssalze mit einer pharmazeutisch akzeptablen organischen oder mineralischen Base,

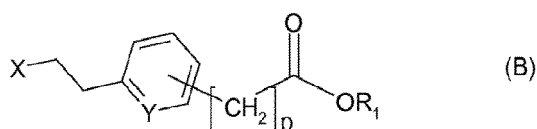
dadurch gekennzeichnet, dass es umfasst:

(1) die Umsetzung der Verbindung der Formel A:



worin:

R die oben angegebene Bedeutung aufweist, und A für einen anionischen Rest einer mineralischen oder organischen Säure steht,
mit der Verbindung der Formel B:



worin Y und p die oben angegebenen Bedeutungen aufweisen, R₁ für eine lineare oder verzweigte Alkyl-, Aryl-, Arylalkyl- oder Alkylaryl-Gruppe mit 1 bis 10 Kohlenstoffatomen steht, und X für ein Halogenatom steht, und

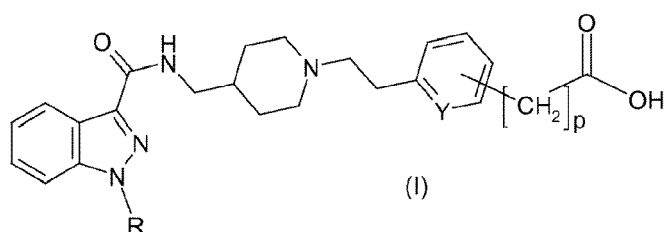
(2) die anschließende Hydrolyse des aus der Umsetzung (1) erhaltenen Esters.

16. Herstellungsverfahren nach Anspruch 15, worin der Rest A ausgewählt ist unter Halogenid, Phosphat, Sulfat, Nitrat und organischem Carboxylat.

17. Herstellungsverfahren nach Anspruch 16, worin der Rest A ausgewählt ist unter Chlorid, Bromid und Iodid.

18. Herstellungsverfahren nach Anspruch 15, worin der Rest X ausgewählt ist unter Chlorid, Bromid und Iodid.

19. Herstellungsverfahren nach Anspruch 15, worin die Gruppe R_1 ausgewählt ist unter einem linearen oder verzweigten Alkyl mit 1 bis 6 Kohlenstoffatomen, einem Aryl, einem Arylalkyl und einem Alkylaryl mit 7 bis 8 Kohlenstoffatomen.
20. Herstellungsverfahren nach einem der Ansprüche 15 bis 19, worin die Umsetzung (1) in einem unter polar aprotischen Lösungsmitteln ausgewählten organischen Lösungsmittel durchgeführt wird.
21. Herstellungsverfahren nach Anspruch 20, worin das organische Lösungsmittel ausgewählt ist unter Aceton, Methyl-ethylketon, Tetrahydrofuran, Dimethylformamid, Dimethylsulfoxid, Dioxan und Acetonitril.
22. Herstellungsverfahren nach einem der Ansprüche 15 bis 21, worin die Umsetzung (1) in Gegenwart einer basischen organischen oder mineralischen Verbindung durchgeführt wird.
23. Herstellungsverfahren nach einem der Ansprüche 15 bis 22, worin die Umsetzung (1) in Gegenwart eines Aktivierungsmittels durchgeführt wird, das unter Kaliumiodid, Caesiumiodid, Tetrabutylammoniumiodid und Trimethylphenylammoniumiodid ausgewählt ist.
24. Verwendung einer Verbindung der Formel (I):

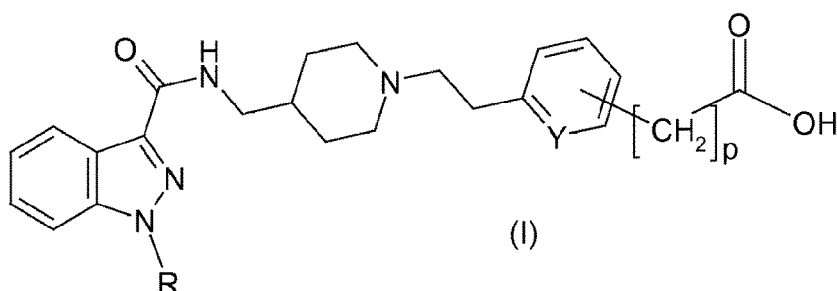


worin:

- R für eine lineare oder verzweigte Alkylgruppe mit 1 bis 3 Kohlenstoffatomen steht,
 Y für CH oder N steht, und
 p für eine ganze Zahl von 0 bis 3 steht,
 und Salze davon, entweder Säureadditionssalze mit einer pharmazeutisch akzeptablen organischen oder mineralischen Säure, oder Basenadditionssalze mit einer pharmazeutisch akzeptablen organischen oder mineralischen Base, zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung neuropathischer Schmerzen.
25. Verwendung einer Verbindung nach Anspruch 24 zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung neuropathischer Schmerzen verursacht durch Diabetes, Krebs, Immuninsuffizienz, Trauma, Ischämie, multiple Sklerose, Ischialgie, Trigeminusneuralgie und post-herpetisches Syndrom.

Revendications

1. Composé de formule (I) :



dans laquelle :

EP 2 207 776 B9

R est un groupe alkyle linéaire ou ramifié contenant entre 1 et 3 atomes de carbone,

Y est CH ou N, et

p est un entier compris entre 0 et 3,

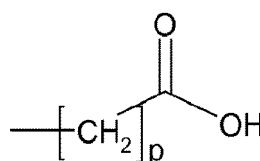
et ses sels, qui sont soit des sels d'addition d'acide avec un acide organique ou minéral pharmaceutiquement acceptable, soit des sels d'addition de base avec une base organique ou minérale pharmaceutiquement acceptable.

2. Composé selon la revendication 1, dans lequel R est un groupe alkyle linéaire ou ramifié contenant 2 à 3 atomes de carbone.

3. Composé selon la revendication 1, dans lequel Y est CH.

4. Composé selon la revendication 1, dans lequel p est un entier de 0 à 1.

5. Composé selon la revendication 1, dans lequel R, Y, p et la position du groupe



sont représentés dans le tableau suivant :

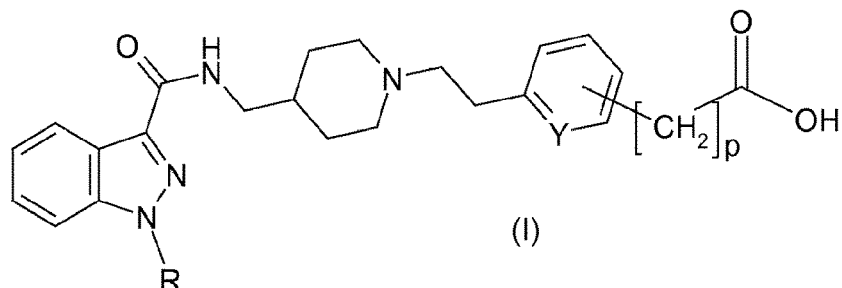
Composé	R	Y	p	Position
1	isopropyle	CH	0	para
2	isopropyle	CH	1	para
3	isopropyle	CH	2	para
4	isopropyle	CH	3	para
5	éthyle	CH	0	para
6	méthyle	CH	0	para
7	isopropyle	N	0	para
8	isopropyle	N	1	para
9	isopropyle	N	3	para
10	éthyle	N	0	para
11	méthyle	N	0	para
12	éthyle	N	1	para
13	isopropyle	CH	0	méta
14	isopropyle	CH	0	ortho

6. Composé selon l'une quelconque des revendications précédentes, dans lequel ledit acide organique ou minéral pharmaceutiquement acceptable est choisi dans le groupe comprenant l'acide oxalique, l'acide maléique, l'acide méthanesulfonique, l'acide paratoluènesulfonique, l'acide succinique, l'acide citrique, l'acide tartrique, l'acide lactique, l'acide chlorhydrique, l'acide phosphorique, l'acide sulfurique, l'acide aspartique et l'acide glutamique.

7. Composé selon l'une quelconque des revendications 1 à 5, dans lequel ladite base organique ou minérale pharmaceutiquement acceptable est choisie dans le groupe comprenant la méthylamine, la diméthylamine, la triméthylamine, l'éthylamine, la diéthylamine, la triéthylamine, la propylamine, la dipropylamine, la tripropylamine, l'éthylènediamine, la monoéthanolamine, la diéthanolamine, la triéthanolamine, la guanidine, la morpholine, la pipéridine,

la pyrrolidine, la pipérazine, la 1-butylpipéridine, la 1-éthyl-2-méthylpipéridine, la N-méthylpipérazine, la 1,4-diméthylpipérazine, la N-benzylphényléthylamine, la N-méthylglucosamine, le tris(hydroxyméthyl)aminométhane, l'arginine, la lysine, l'ammoniac, l'hydroxyde de sodium, l'hydroxyde de calcium, l'hydroxyde de potassium, l'hydroxyde d'aluminium, l'hydroxyde de fer, l'hydroxyde de magnésium et l'hydroxyde de zinc.

8. Formulation pharmaceutique comprenant une quantité efficace d'un composé de formule (I) :



dans laquelle :

R est un groupe alkyle linéaire ou ramifié contenant entre 1 et 3 atomes de carbone,

Y est CH ou N, et

p est un entier compris entre 0 et 3,

et ses sels, qui sont soit des sels d'addition d'acide avec un acide organique ou minéral pharmaceutiquement acceptable, soit des sels d'addition de base avec une base organique ou minérale pharmaceutiquement acceptable, et

au moins un excipient pharmaceutiquement acceptable.

9. Formulation pharmaceutique selon la revendication 8, dans laquelle ledit au moins un excipient pharmaceutiquement acceptable est choisi dans le groupe comprenant les agents de démoulage, les liants, les délitants, les charges, les diluants, les colorants, les fluidifiants, les agents de glissement, les lubrifiants, les agents conservateurs, les stabilisants, les humectants, les absorbants, les tensioactifs, les tampons, les sels pour réguler la pression osmotique, les émulsionnants, les aromatisants et les édulcorants.

10. Formulation pharmaceutique selon la revendication 8, dans laquelle le composé de formule (I) est défini conformément à l'une quelconque des revendications 1 à 7.

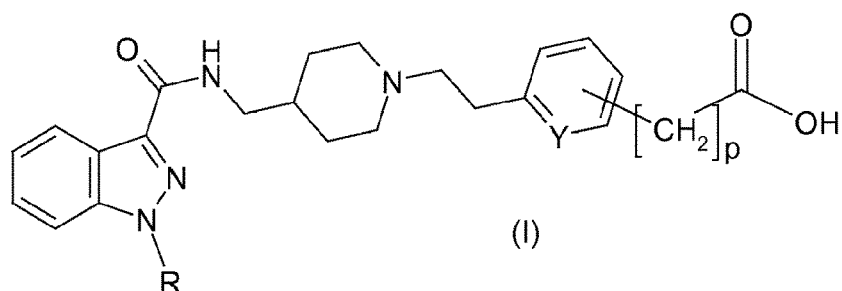
11. Formulation pharmaceutique selon l'une quelconque des revendications 8 à 10, laquelle formulation pharmaceutique est choisie dans le groupe comprenant les comprimés, les capsules, les comprimés enrobés, les granules, les solutions et sirops pour administration par voie orale, les emplâtres antiseptiques, les solutions, les pâtes, les crèmes et les pommades pour administration par voie transdermique, les suppositoires pour administration par voie rectale, les solutions stériles pour administration par injection ou par aérosol, sous forme soit à libération immédiate soit à libération prolongée.

12. Formulation pharmaceutique selon l'une quelconque des revendications 8 à 11, laquelle formulation pharmaceutique comprend une quantité de composé de formule (I) ou d'un sel d'addition d'acide ou d'un sel d'addition de base de celui-ci assurant un niveau d'administration compris entre 0,001 et 100 mg/kg/jour de composé de formule (I), exprimé sous forme libre.

13. Formulation pharmaceutique selon la revendication 12, dans laquelle ladite quantité va assurer un niveau d'administration compris entre 0,05 et 50 mg/kg/jour.

14. Formulation pharmaceutique selon la revendication 12, dans laquelle ladite quantité va assurer un niveau d'administration compris entre 0,1 et 10 mg/kg/jour.

15. Procédé pour préparer un composé de formule (I) :



dans laquelle :

R est un groupe alkyle linéaire ou ramifié contenant entre 1 et 3 atomes de carbone,

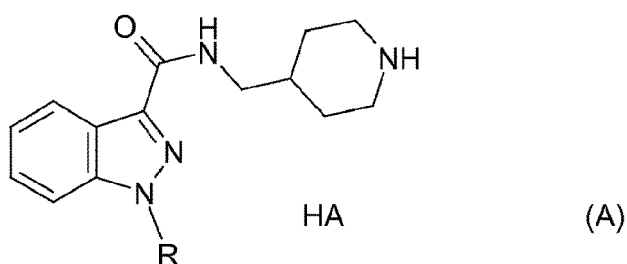
Y est CH ou N, et

p est un entier compris entre 0 et 3,

et ses sels, qui sont soit des sels d'addition d'acide avec un acide organique ou minéral pharmaceutiquement acceptable, soit des sels d'addition de base avec une base organique ou minérale pharmaceutiquement acceptable,

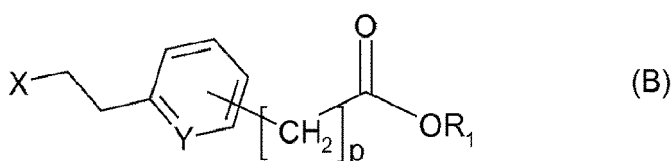
caractérisé en ce qu'il comprend :

(1) la réaction entre le composé de formule A :



dans laquelle :

R a la signification décrite ci-dessus, et A représente un résidu anionique d'un acide minéral ou organique, et le composé de formule B :



dans laquelle Y et p ont la signification décrite ci-dessus, R₁ représente un groupe alkyle, aryle, arylalkyle ou alkylaryle linéaire ou ramifié contenant entre 1 et 10 atomes de carbone, et X représente un atome d'halogène, et

(2) l'hydrolyse subséquente de l'ester obtenu par la réaction (1).

16. Procédé de préparation selon la revendication 15, dans lequel ledit résidu A est choisi dans le groupe comprenant les halogénures, le phosphate, le sulfate, le nitrate et les carboxylates organiques.

17. Procédé de préparation selon la revendication 16, dans lequel ledit résidu A est choisi dans le groupe comprenant le chlorure, le bromure et l'iodure.

18. Procédé de préparation selon la revendication 15, dans lequel ledit résidu X est choisi dans le groupe comprenant le chlorure, le bromure et l'iodure.

19. Procédé de préparation selon la revendication 15, dans lequel ledit groupe R_1 est choisi dans le groupe comprenant un alkyle linéaire ou ramifié contenant 1 à 6 atomes de carbone, un aryle, un arylalkyle et un alkylaryle contenant 7 ou 8 atomes de carbone.

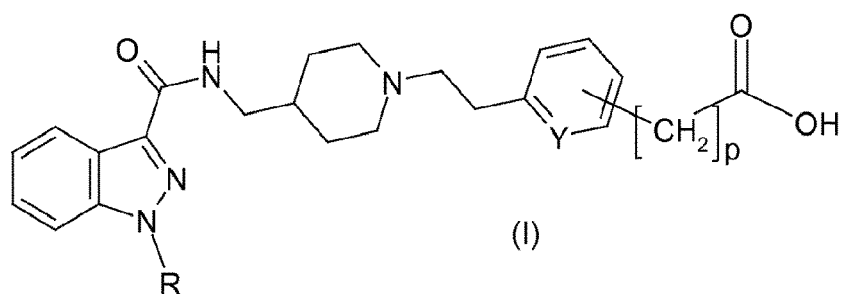
20. Procédé de préparation selon l'une quelconque des revendications 15 à 19, dans lequel ladite réaction (1) est effectuée dans un solvant organique choisi dans le groupe comprenant les solvants aprotiques polaires.

21. Procédé de préparation selon la revendication 20, dans lequel ledit solvant organique est choisi dans le groupe comprenant l'acétone, la méthyléthylcétone, le tétrahydrofurane, le diméthylformamide, le diméthylsulfoxyde, le dioxane et l'acétonitrile.

22. Procédé de préparation selon l'une quelconque des revendications 15 à 21, dans lequel ladite réaction (1) est effectuée en présence d'un composé organique ou minéral basique.

23. Procédé de préparation selon l'une quelconque des revendications 15 à 22, dans lequel ladite réaction (1) est effectuée en présence d'un agent d'activation choisi dans le groupe comprenant l'iodure de potassium, l'iodure de césium, l'iodure de tétrabutylammonium et l'iodure de triméthylphénylammonium.

24. Utilisation d'un composé de formule (I) :



dans laquelle :

R est un groupe alkyle linéaire ou ramifié contenant entre 1 et 3 atomes de carbone,

Y est CH ou N, et

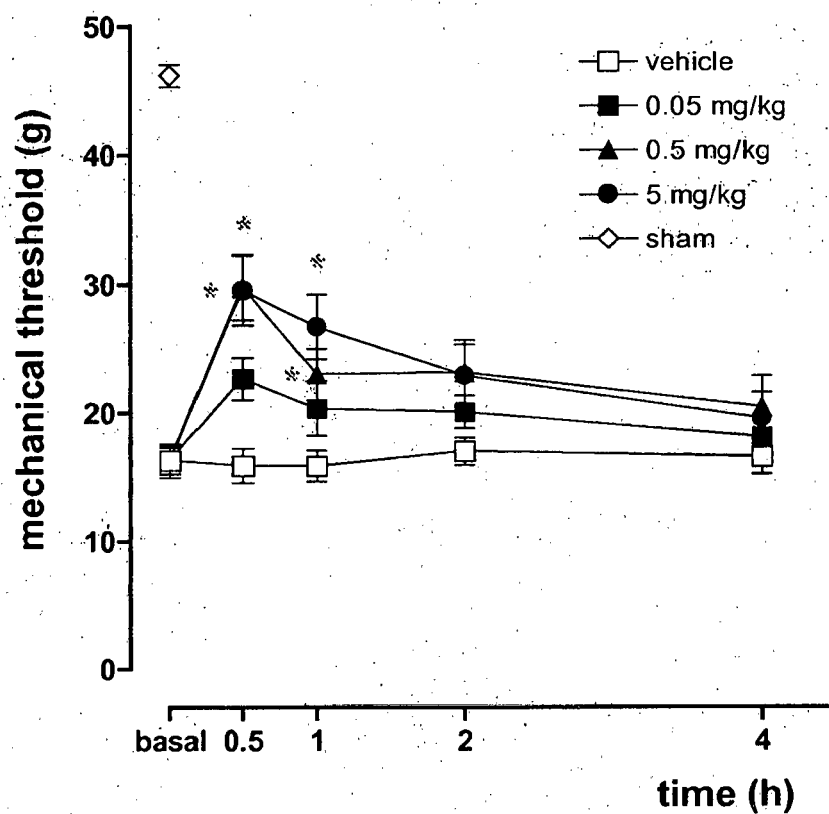
p est un entier compris entre 0 et 3,

et de ses sels, qui sont soit des sels d'addition d'acide avec un acide organique ou minéral pharmaceutiquement acceptable, soit des sels d'addition de base avec une base organique ou minérale pharmaceutiquement acceptable,

pour la préparation d'une composition pharmaceutique destinée au traitement d'une douleur neuropathique.

25. Utilisation d'un composé selon la revendication 24, pour la préparation d'une composition pharmaceutique destinée au traitement d'une douleur neuropathique provoquée par un diabète, un cancer, une immunodéficience, un traumatisme, une ischémie, une sclérose en plaques, une sciatique, une névralgie du trijumeau et un syndrome post-herpétique.

TABLE I



11 rats per group were used; media $\pm$ SEM; * p <0.05 vs vehicle treated group by ANOVA followed Dunnett's test

Pain threshold of normal animals having same weight/age = 42.2 $\pm$ 2.88 g

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- EP 0975623 A [0010] [0068]
- WO 9846589 A [0010]
- WO 2005013989 A [0011]
- EP 1646387 A [0011]
- WO 2004101548 A [0012]
- EP 0975623 B1 [0043]

Non-patent literature cited in the description

- **ASHBUM MA ; STAATS PS.** Management of chronic pain. *Lancet*, 1999, vol. 353, 1865-69 [0004]
- **WOOLF CJ ; MANNION RJ.** Neuropathic pain: aetiology, symptoms, mechanism, and management. *Lancet*, 1999, vol. 353, 1959-1964 [0006]
- **SCHOLZ J ; WOOLF CJ.** Can we conquer pain?. *Nat Neosci.*, 2002, vol. 5, 1062-76 [0008]
- *Journal of the American Chemical Society*, 1940, vol. 62, 1435-8 [0044]
- **MARTIN G.R. ; HUMPHREY P.P.A.** *Neuropharmacol.*, 1994, vol. 33, 261 [0049]
- **HOYER D.** *Eur. J. Pharmacol.*, 1985, vol. 118, 1 [0049] [0057]
- **BONBAUS DW et al.** *Br. J. Pharmacol.*, 1995, vol. 115, 622 [0049]
- **WOLF WA et al.** *J. Neurochem.*, 1997, vol. 69, 1449 [0049] [0057]
- **BOESS FG et al.** *Neuropharmacol.*, 1997, vol. 36, 637 [0049] [0057]
- **MIALET J et al.** *Br. J. Pharmacol.*, 2000, vol. 1129, 771 [0049]
- **REES S et al.** *FEBS Lett.*, 1994, vol. 355, 242 [0049] [0057]
- **MONSMA F.J. et al.** *Mol. Pharmacol.*, 1993, vol. 43, 320 [0049] [0057]
- **ROTH BL et al.** *J. Pharmacol. Exp. Ther.*, 1994, vol. 268, 1403 [0049] [0057]
- **SHEARMAN LP et al.** *Am. J. Physiol.*, 1998, vol. 275, C1621 [0049] [0057]
- **ZHOU Z. et al.** *Biophys. J.*, 1998, vol. 74, 230 [0051] [0059]
- **SELTZER Z ; DUBNER R ; SHIR Y. A.** novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury. *Pain*, 1990, vol. 43, 205-218 [0054]
- **BENNET GJ ; XIE YK.** A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain*, 1988, vol. 33, 87-107 [0054]
- **MARTIN G.R. ; HUMPHREY P.P.A.** *Neuropharmacol.*, 1994, vol. 33, 261 [0057]
- **BONHAUS DW et al.** *Br. J. Pharmacol.*, 1995, vol. 115, 622 [0057]
- **MIALET J et al.** *Br. J. Pharmacol.*, 2000, vol. 129, 771 [0057]