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(54) Titre : N-(4-HYDROXY-3-METHOXY-BENZYL)-AMIDES D'ACIDE CINNAMIQUE A SUBSTITUTION PARA-ALKYLE ET LEUR UTILISATION POUR LA FABRICATION DE MEDICAMENTS

(54) Title: PARA-ALKYL-SUBSTITUTED N-(4-HYDROXY-3-METHOXYBENZYL)-CINNAMIC ACID AMIDES AND THE USE THEREOF FOR THE PREPARATION OF MEDICINAL DRUGS

(57) Abrégé/Abstract:
The present invention relates to para-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides, to processes for the preparation thereof, to medicinal drugs containing these compounds, and to the use of these compounds for the preparation of medicinal drugs.

Abstract

The present invention relates to *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides, to processes for the preparation thereof, to medicinal drugs containing these compounds, and to the use of these compounds for the preparation of medicinal drugs.

para-Alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides and the use thereof for the preparation of medicinal drugs

The present invention relates to *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides, to processes for the preparation thereof, to medicinal drugs containing these compounds, and to the use of these compounds for the preparation of medicinal drugs.

The treatment of pain, especially of neuropathic pain, is of great importance in the field of medicine. There is a worldwide need for effective therapies for pain. The urgent need for attaining patient-friendly, target-orientated treatment of chronic and non-chronic states of pain, by which is to be understood the successful and satisfactory treatment of pain in the patient, is also documented by the large number of scientific papers which have recently appeared in the field of applied analgesics and basic research on nociception.

A suitable approach to the treatment of pain, especially pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain, preferably neuropathic pain, is the vanilloid receptor subtype 1 (VR1/TRPV1), which is frequently referred to as the capsaicin receptor. This receptor is stimulated *inter alia* by vanilloids such as, for example, capsaicin, heat, and protons and plays a central role in causing pain. Moreover, it is important for a large number of other physiological and pathophysiological processes, such as, for example, migraine; depression; neurodegenerative diseases; cognitive disorders; anxiety; epilepsy; coughing; diarrhoea; pruritus; motor neurone diseases; disorders of the cardiovascular system; disorders of food intake; medicinal drug dependency; medicinal drug abuse; and especially urinary incontinence.

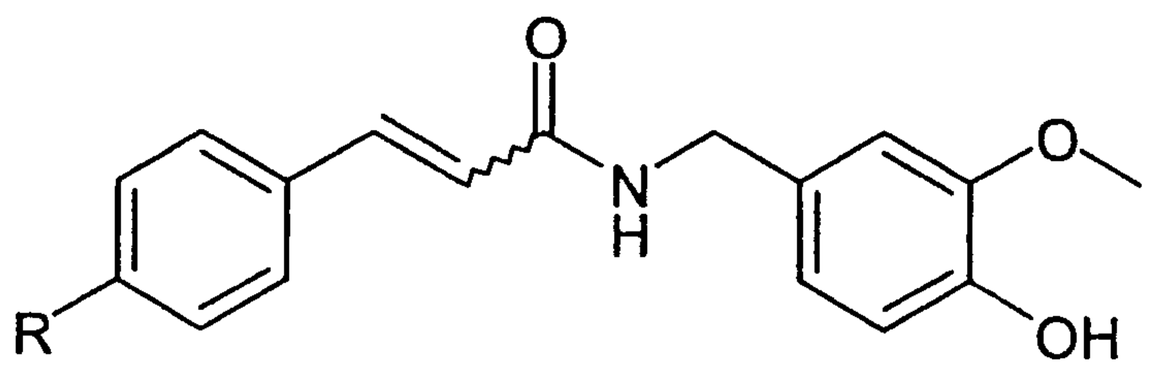
One object of the present invention is, therefore, to provide novel compounds which are particularly well-suited as pharmacologically active ingredients in medicinal drugs, especially in medicinal drugs for the treatment of disorders or diseases that are mediated at least partly by vanilloid receptors 1 (VR1/TRPV1 receptors).

Surprisingly, it has now been found that the *para*-alkyl-substituted N-(4-hydroxy-3-methoxy-benzyl)-cinnamic acid amides of the general formulas I and Ia below exhibit excellent affinity for the vanilloid receptor subtype 1 (VR1/TRPV1 receptor) and are therefore particularly well-suited for the prophylaxis and/or treatment of disorders or diseases that are mediated at least partly by vanilloid receptors 1 (VR1/TRPV1).

The compounds according to the invention are preferably suitable for the treatment and/or prophylaxis of pain, especially pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain; arthralgia; migraine; depression; nervous disorders; neurotrauma; neurodegenerative diseases, especially those selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease, and Huntington's disease; cognitive disorders, preferably cognitive deficiencies, more preferably memory disorders; anxiety; epilepsy;respiratory tract diseases, preferably selected from the group consisting of asthma and pneumonia; coughing; urinary incontinence; an overactive bladder (OAB); diarrhoea; gastric ulcers; colitis syndrome; cerebral apoplexy; irritation of the eyes; cutaneous irritation; neurotic skin diseases; inflammatory diseases, preferably inflammation of the colon; pruritus; disorders of food intake, particularly those selected from the group consisting of bulimia, cachexia, anorexia,

and obesity; medicinal drug dependency; medicinal drug abuse; withdrawal symptoms following medicinal drug dependency; development of immunity to medicinal drugs, preferably to natural or synthetic opioids; drug dependency; drug abuse; withdrawal symptoms following drug dependency; alcohol dependency; alcohol abuse; withdrawal symptoms following alcohol dependency; for diuresis; for antinatriuresis; for influencing the cardiovascular system; for increasing vigilance; for increasing libido; for modulating motor activity; or for local anaesthesia.

The present invention accordingly provides *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides of the general formula I



I

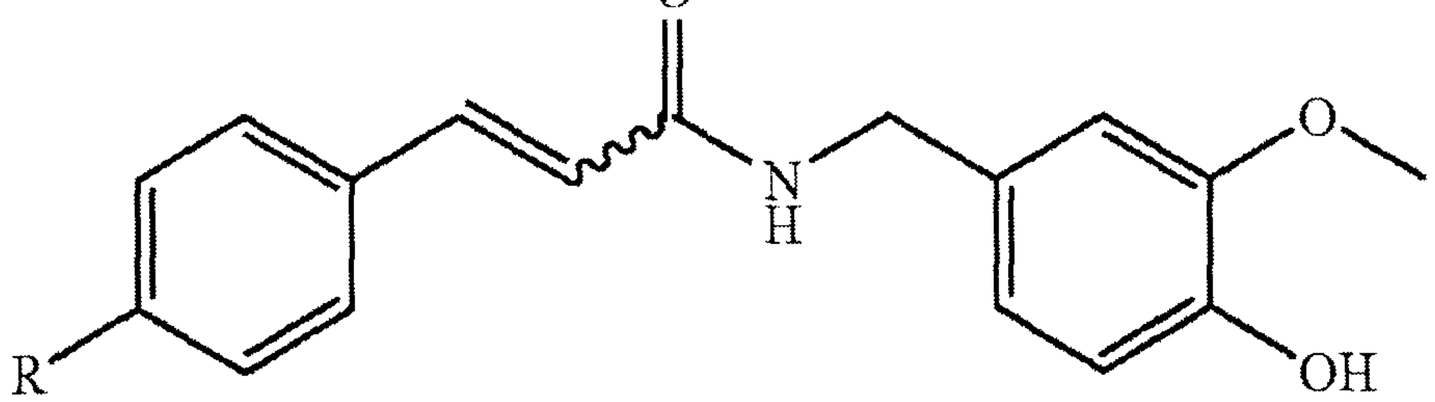
wherein

R stands for a linear or branched alkyl radical,

in each case optionally in the form of pure stereoisomers thereof, especially enantiomers or diastereoisomers thereof, in the form of their racemates or in the form of a mixture of stereoisomers, especially of the enantiomers and/or diastereoisomers, in any desired mixing ratio, or in each case in the form of appropriate salts, or in each case in the form of appropriate solvates.

In accordance with an aspect of the present invention, there is provided a para-Alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide compound corresponding to formula I:

I

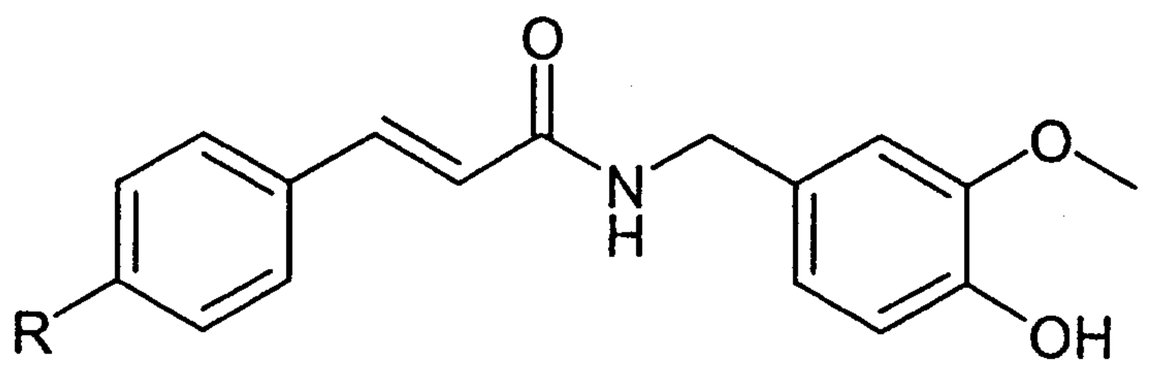


wherein R represents a linear or branched C_{1-20} alkyl group; or a pharmaceutically acceptable salt thereof;

in the form of a pure isomer or a mixture of isomers in any mixing ratio.

It will be understood by the person skilled in the art that, in the compounds of the general formula I according to the invention, the substituents on the double bond of the *para*-alkyl-substituted N-(4-hydroxy-3-methoxy-benzyl)-cinnamic acid amides that are other than hydrogen may have either the *cis* or the *trans* configuration relative to one another. The corresponding *trans* isomer is frequently also referred to as the (*E*) isomer and the *cis* isomer as the (*Z*) isomer.

Preference is given to *para*-alkyl-substituted *trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides of the general formula Ia



Ia

wherein

R stands for a linear or branched alkyl radical,

in each case optionally in the form of the pure stereoisomers thereof, especially enantiomers thereof, in the form of their racemates or in the form of a mixture of enantiomers, in any desired mixing ratio, or in each case in the form of appropriate salts, or in each case in the form of appropriate solvates.

Preference is also given to compounds of the general formulas I and Ia in which R represents a linear or branched C_{1-20} alkyl radical,

more preferably a linear or branched C_{1-10} alkyl radical,

very preferably an alkyl radical selected from the group consisting of methyl; ethyl; n-propyl; isopropyl; n-butyl; isobutyl; sec.-butyl; tert.-butyl; n-pentyl; 2-pentyl; 3-pentyl; isopentyl; neopentyl; 1,1-dimethylpropyl; 1,2-dimethylpropyl; n-hexyl; 2-hexyl; 3-hexyl; isohexyl; neohexyl; n-heptyl; 2-heptyl; 3-heptyl; 4-heptyl; isoheptyl; neoheptyl; n-octyl; 2-octyl; 3-octyl; 4-octyl; isooctyl; neooctyl; n-nonyl; 2-nonyl; 3-nonyl; 4-nonyl; 5-nonyl; isononyl; neononyl and n-decyl,

and most preferably an alkyl radical selected from the group consisting of methyl; ethyl; n-propyl; isopropyl; n-butyl; isobutyl; tert.-butyl; neopentyl; and n-octyl.

Particular preference is given to the compounds of the general formulas I and Ia selected from the group consisting of

[1] *para*-methyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide,

[2] *para*-ethyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide,

[3] *para*-isopropyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide and

[4] *para*-tert.-butyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide,

[5] *para*-propyl-*trans*-N-(hydroxy-3-methoxybenzyl)-cinnamic acid amide,

[6] *para*-isobutyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acide amide,

[7] *para*-neopentyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acide amide,

[8] *para*-butyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acide amide; and

[9] *para*-octyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acide amide;

and in each case salts thereof, in each case optionally in the form of appropriate solvates.

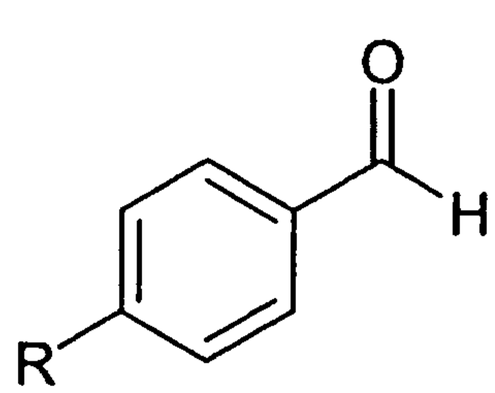
Very particular preference is given to the compound

[4] *para*-tert.-butyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide

and salts thereof, in each case optionally in the form of appropriate solvates.

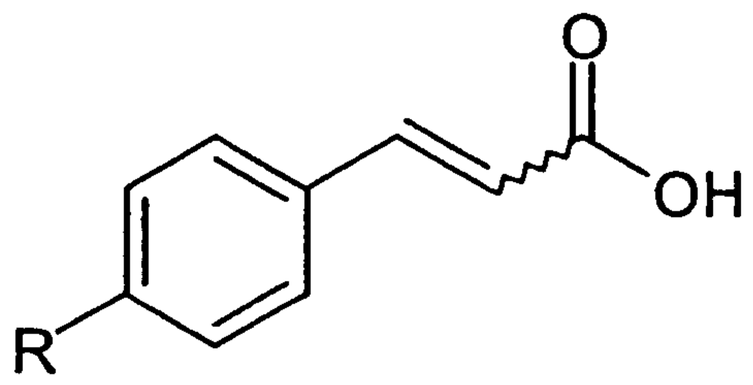
When the compounds of the general formulae I and Ia according to the invention are in the form of their salts, the salts can preferably be selected from the group consisting of the alkali metal salts, preferably the sodium or potassium salts. Also preferred are salts with cations of the general formula $[NR_xH_{4-x}]^+$, wherein R stands for a linear or optionally branched alkyl radical having from 1 to 4 carbon atoms and x stands for 0, 1, 2, 3 or 4. The above-mentioned salts may also be present in the form of appropriate solvates, preferably in the form of the hydrates.

The present invention further provides a process for the preparation of the compounds according to the invention of the above general formulas I and Ia, in which process at least one aldehyde of the general formula II



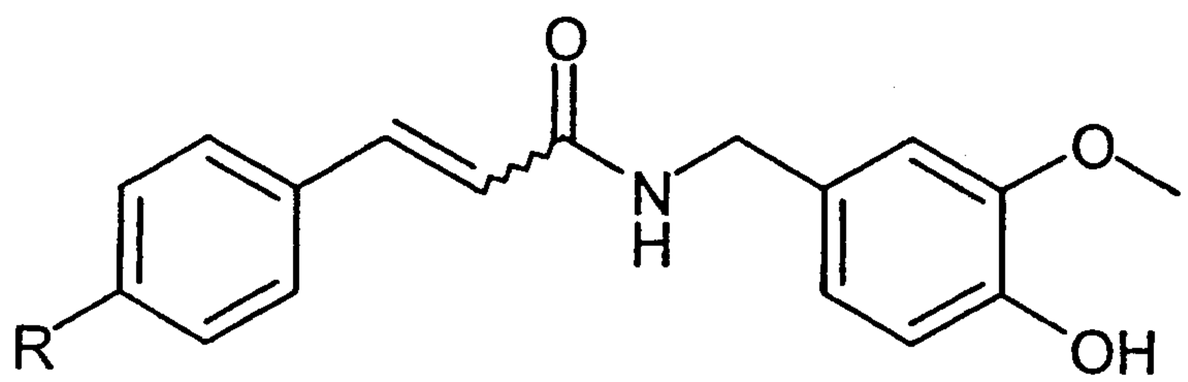
II

wherein R has the meanings stated above, is caused to react with malonic acid (OH-C(=O)-CH_2-C(=O)-OH), optionally in a reaction medium, in the presence of at least one base, the resulting *para*-alkyl-substituted cinnamic acid of the general formula III



III

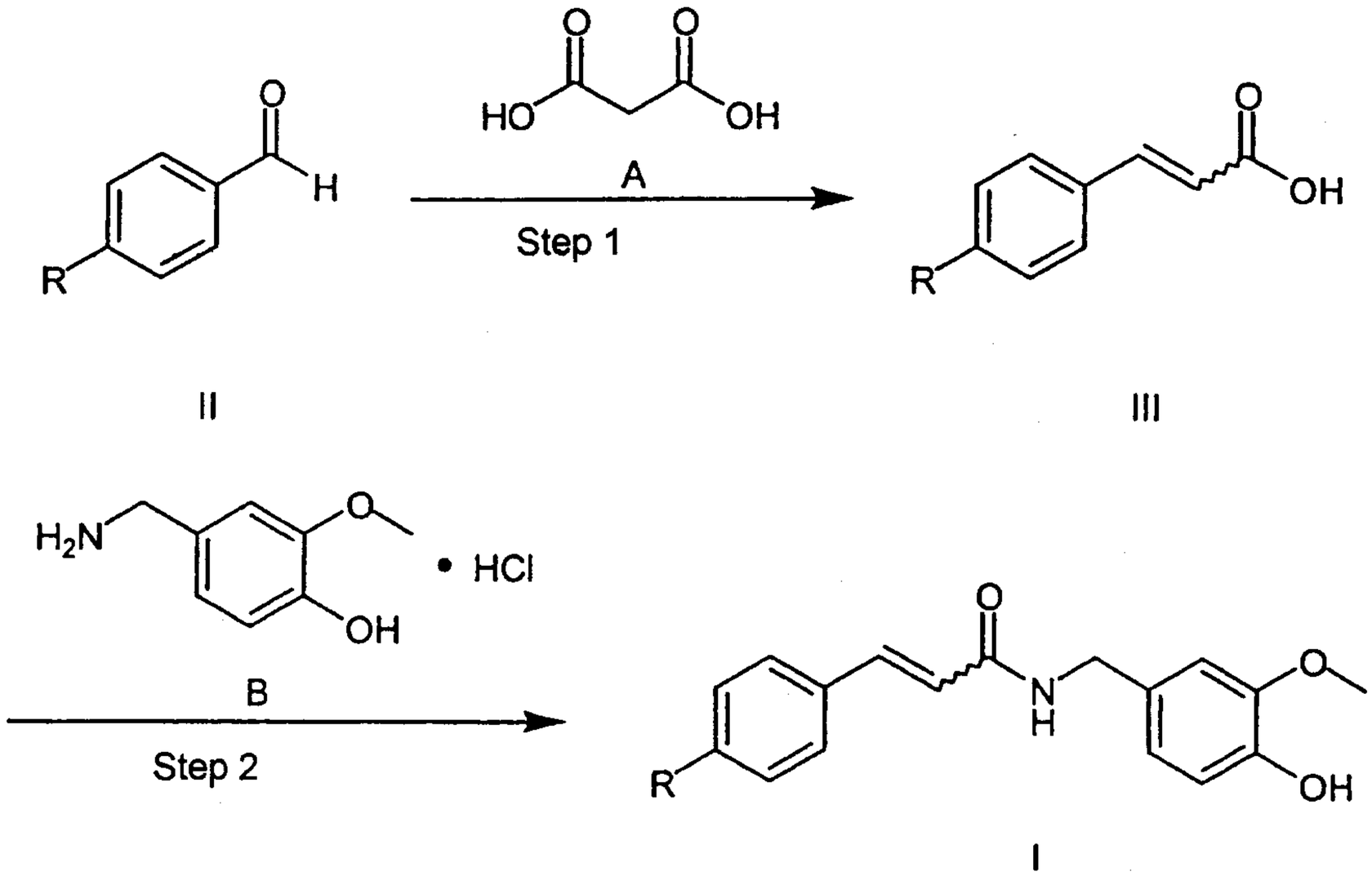
wherein R has the meaning given above, optionally in the form of an appropriate salt, is optionally isolated and optionally purified and is caused to react with 4-hydroxy-3-methoxybenzylamine, optionally in the form of an appropriate salt, preferably in the form of the hydrochloride, in a reaction medium, optionally in the presence of at least one base, optionally in the presence of at least one suitable coupling agent, to form a corresponding compound of the general formula I



I

optionally in the form of a corresponding salt, wherein R has the meanings stated above, which compound is optionally purified and optionally isolated.

The process according to the invention for the preparation of *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides is also shown in Scheme 1 below.



II III

I

Scheme 1

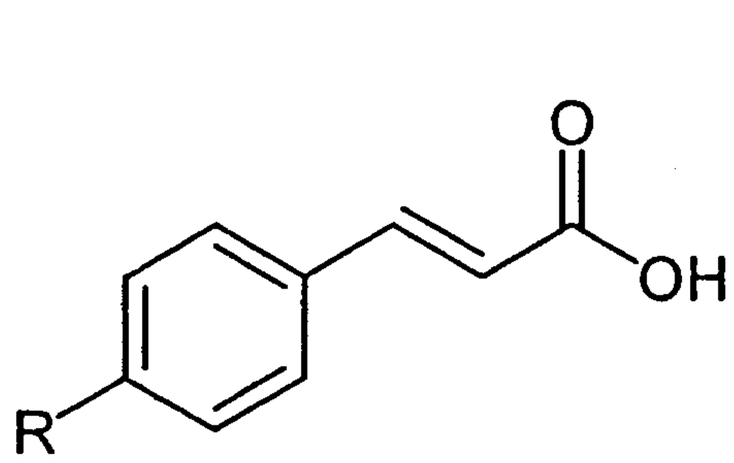
In step 1, aldehydes of the above formula II wherein R has the meanings stated above are caused to react with malonic acid (compound A), optionally in a suitable

reaction medium preferably selected from the group consisting of tetrahydrofuran, dimethylformamide, dimethylacetamide, acetonitrile, pyridine, dimethyl sulfoxide, xylene, toluene, and mixtures of at least two of the above-mentioned reaction media, optionally in the presence of at least one base, preferably in the presence of an organic base selected from the group consisting of piperidine, pyridine, dimethylaminopyridine, triethylamine, and diisopropylethylamine, preferably at temperatures ranging from 20°C to 150°C, more preferably at temperatures ranging from 60°C to 120°C, to form para-alkyl-substituted cinnamic acids of the general formula III wherein R has the meanings stated above, optionally in the form of an appropriate salt, which acids are optionally isolated and optionally purified. It is particularly preferred to carry out the reaction in pyridine in the presence of piperidine.

In step 2, compounds of the above general formula III are caused to react, preferably at temperatures ranging from -70°C to 100°C, with 4-hydroxy-3-methoxybenzylamine, optionally in the form of an appropriate salt, preferably in the form of the hydrochloride (compound B), in a reaction medium preferably selected from the group consisting of diethyl ether, tetrahydrofuran, acetonitrile, methanol, ethanol, dimethylformamide, dichloromethane, and a mixture of at least two of the above-mentioned reaction media, optionally in the presence of at least one suitable coupling agent preferably selected from the group consisting of 1-benzotriazolyl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), dicyclohexyl-carbodiimide (DCC), N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDCI), 1,1-carbonyldiimadazole (CDI), N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridino-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide (HATU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethylronium hexafluorophosphate (HBTU), O-

(benzotriazol-1-yl)-N,N,N',N'-tetramethylronium tetrafluoroborate (TBTO), and 1-hydroxy-7-azabenzotriazole (HOAt), optionally in the presence of at least one organic base preferably selected from the group consisting of triethylamine, piperidine, N-methylmorpholine, pyridine, dimethylaminopyridine, and diisopropylethylamine at temperatures ranging from -70°C to 100°C to form compounds of the general formula I, optionally in the form of an appropriate salt, preferably in the form of the corresponding hydrochloride, which compounds are optionally purified and optionally isolated.

The *para*-alkyl-substituted cinnamic acid of the general formula III obtained by the process according to the invention is usually in the form of a mixture of its *cis/trans* isomers, from which the respective diastereoisomer, especially the *trans* isomer of the general formula IIIa

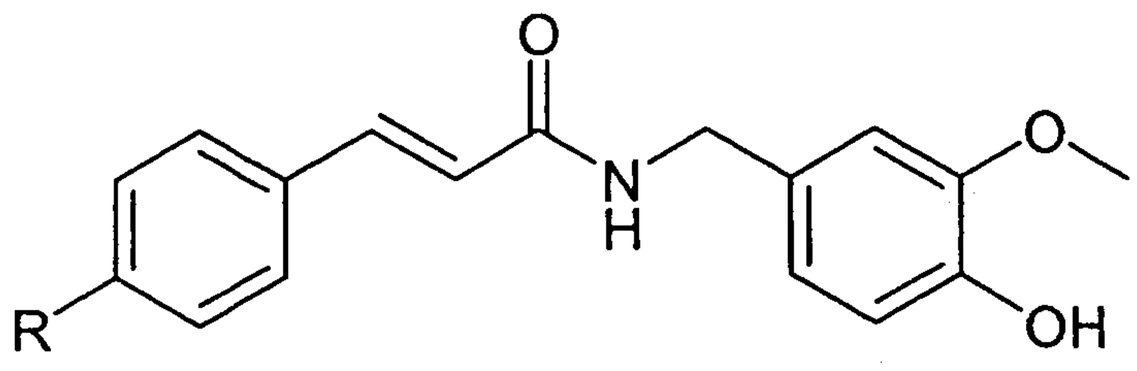


IIIa

can be isolated by conventional methods known to the person skilled in the art and can optionally be purified. Examples which may be mentioned include chromatographic separation processes, particularly liquid chromatography processes under standard pressure or under elevated pressure, preferably MPLC and HPLC processes, or recrystallisation from a suitable solvent, preferably from methanol. The *para*-alkyl-substituted cinnamic acid of the general formula IIIa can

likewise be used in step 2 of the process according to the invention according to Scheme 1.

When the *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides obtained by the process according to the invention are in the form of a mixture of their *cis/trans* isomers, the *trans* isomer of the general formula Ia



Ia,

can be isolated therefrom by conventional methods known to the person skilled in the art and can optionally be purified. Examples which may be mentioned include chromatographic separation processes, especially liquid chromatography processes under standard pressure or under elevated pressure, preferably MPLC and HPLC processes, or recrystallisation from a suitable solvent.

The compounds of formula II above and the compounds A and B are each commercially available and/or can be prepared by the conventional processes known to the person skilled in the art.

The above-described reactions can each be carried out under the conventional conditions known to the person skilled in the art, for example with regard to the pressure or the order of addition of the components. Where appropriate, the

optimal procedure for the particular conditions can be determined by the person skilled in the art by means of simple preliminary experiments.

The intermediates and end products obtained by the above-described reactions may, if desired and/or necessary, be purified and/or isolated by conventional methods known to the person skilled in the art. Suitable purification processes are, for example, extraction processes and chromatographic processes such as column chromatography or preparative chromatography.

All of the above-described process steps, and the respective purification and/or isolation of intermediates or end products may be carried out entirely or partially under an inert gas atmosphere, preferably under a blanket of nitrogen.

If, after their preparation, the *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides of the above general formulas I and Ia are obtained in the form of a mixture of their enantiomers or diastereoisomers, these can be separated by conventional processes known to the person skilled in the art and optionally isolated. Examples which may be mentioned include chromatographic separation processes on chiral phase, particularly liquid chromatography processes under standard pressure or under elevated pressure, preferably MPLC and HPLC processes.

The *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides according to the invention of the above general formulas I and Ia and, optionally, corresponding stereoisomers can be obtained in the form of appropriate salts, especially in the form of appropriate physiologically acceptable salts, by means of

conventional processes known to the person skilled in the art, while it is possible for the medicinal drug according to the invention to contain one or more salts of one or more of these compounds.

The *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides according to the invention of the above general formulas I and Ia and, optionally, corresponding stereoisomers, and in each case their physiologically acceptable salts, can alternatively be obtained in the form of their solvates, especially in the form of their hydrates, by means of conventional processes known to the person skilled in the art.

It has been found, surprisingly, that the *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides according to the invention of the above general formulas I and Ia are suitable for vanilloid receptor 1 (VR1/TRPV1) regulation, especially as agonists for vanilloid receptor 1 (VR1/TRPV1) activation, and can therefore be used, in particular, as pharmaceutically active ingredients in medicinal drugs for the prophylaxis and/or treatment of disorders or diseases associated with these receptors or processes.

The *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides according to the invention of the above general formulas I and Ia and, optionally, appropriate stereoisomers, and in each case the appropriate salts and solvates, are toxicologically harmless and are therefore suitable as pharmaceutically active ingredients in medicinal drugs.

The present invention accordingly further provides a medicinal drug comprising at least one *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide according to the invention of the above general formula I or Ia, in each case optionally in the form of one of its pure stereoisomers, particularly enantiomers or diastereoisomers, in the form of its racemates or in the form of a mixture of stereoisomers, particularly a mixture of the enantiomers and/or diastereoisomers, in any desired mixing ratio, or in each case in the form of appropriate salts, or in each case in the form of appropriate solvates, and optionally one or more pharmaceutically acceptable adjuvants.

The medicinal drug according to the invention is suitable for vanilloid receptor 1 (VR1/TRPV1) regulation, especially for vanilloid receptor 1 (VR1/TRPV1) activation. The medicinal drug according to the invention is therefore preferably suitable for the prophylaxis and/or treatment of disorders and/or diseases that are mediated at least partly by vanilloid receptors 1 (VR1/TRPV1).

The medicinal drug according to the invention is preferably suitable for the prophylaxis and/or treatment pain, especially of pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain; arthralgia; migraine; depression; nervous disorders; neurotrauma; neurodegenerative diseases, more preferably selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease, and Huntington's disease; cognitive disorders, more preferably cognitive deficiencies, very preferably memory disorders; anxiety; epilepsy; respiratory tract diseases, preferably selected from the group consisting of asthma and pneumonia; coughing; urinary incontinence; an overactive bladder (OAB); gastric ulcers; colitis syndrome;

cerebral apoplexy; irritation of the eyes; cutaneous irritation; neurotic skin diseases; inflammatory diseases, preferably inflammation of the colon; diarrhoea; pruritus; disorders of food intake, more preferably selected from the group consisting of bulimia, cachexia, anorexia and obesity; medicinal drug dependency; medicinal drug abuse; withdrawal symptoms following medicinal drug dependency; development of immunity to medicinal drugs, more preferably to natural or synthetic opioids; drug dependency; drug abuse; withdrawal symptoms following drug dependency; alcohol dependency; alcohol abuse; withdrawal symptoms following alcohol dependency; for diuresis; for antinatriuresis; for influencing the cardiovascular system; for increasing vigilance; for increasing libido; for modulating motor activity; or for local anaesthesia.

The medicinal drug according to the invention is particularly suitable for the prophylaxis and/or treatment of urinary incontinence or pain, particularly pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain.

The medicinal drug according to the invention is particularly well-suited for the prophylaxis and/or treatment of pain, particularly of pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain.

The present invention further relates to the use of at least one *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide according to the invention of the above general formula I or Ia, in each case optionally in the form of one of its pure stereoisomers, particularly its enantiomers or diastereoisomers, in the form of its racemates or in the form of a mixture of stereoisomers, particularly

of the enantiomers and/or diastereoisomers, in any desired mixing ratio, or in each case in the form of appropriate salts, or in each case in the form of appropriate solvates, and optionally one or more pharmaceutically acceptable adjuvants, in the preparation of a medicinal drug for vanilloid receptor 1 (VR1/TRPV1) regulation, particularly for vanilloid receptor 1 (VR1/TRPV1) activation.

Preference is given to the use of at least one *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide according to the invention of the above general formula I or Ia, in each case optionally in the form of one of its pure stereoisomers, particularly enantiomers or diastereoisomers, in the form of its racemates or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in any desired mixing ratio, or in each case in the form of appropriate salts, or in each case in the form of appropriate solvates, and optionally one or more pharmaceutically acceptable adjuvants, in the preparation of a medicinal drug for the prophylaxis and/or treatment of disorders and/or diseases that are mediated at least partly by vanilloid receptors 1 (VR1/TRPV1).

Particular preference is also given to the use of at least one *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide according to the invention of the above general formula I or Ia, in each case optionally in the form of one of its pure stereoisomers, particularly enantiomers or diastereoisomers, in the form of its racemates or in the form of a mixture of stereoisomers, particularly of the enantiomers and/or diastereoisomers, in any desired mixing ratio, or in each case in the form of appropriate salts, or in each case in the form of appropriate solvates, and optionally one or more pharmaceutically acceptable adjuvants, in the preparation of a medicinal drug for the prophylaxis and/or treatment of pain, more

preferably pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain; arthralgia; migraine; depression; nervous disorders; neurotrauma; neurodegenerative diseases, more preferably selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease, and Huntington's disease; cognitive disorders, more preferably cognitive deficiencies, very preferably memory disorders; anxiety; epilepsy; respiratory tract diseases, preferably selected from the group consisting of asthma and pneumonia; coughing; urinary incontinence; an overactive bladder (OAB); diarrhoea; gastric ulcers; colitis syndrome; cerebral apoplexy; irritation of the eyes; cutaneous irritation; neurotic skin diseases; inflammatory diseases, preferably inflammation of the colon; pruritus; disorders of food intake, more preferably selected from the group consisting of bulimia, cachexia, anorexia, and obesity; medicinal drug dependency; medicinal drug abuse; withdrawal symptoms following medicinal drug dependency; development of immunity to medicaments, more preferably to natural or synthetic opioids; drug dependency; drug abuse; withdrawal symptoms following drug dependency; alcohol dependency; alcohol abuse; withdrawal symptoms following alcohol dependency; for diuresis; for antinatriuresis; for influencing the cardiovascular system; for increasing vigilance; for increasing libido; for modulating motor activity; or for local anaesthesia, preferably for the prophylaxis and/or treatment of urinary incontinence or pain, particularly pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain, more preferably for the prophylaxis and/or treatment of pain, particularly pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain.

The medicinal drug according to the invention is suitable for administration to adults and children, including infants and babies.

The medicament according to the invention may exist in the form of a liquid, semi-solid, or solid medicament form, for example in the form of injection solutions, drops, juices, syrups, sprays, suspensions, tablets, patches, capsules, plasters, suppositories, ointments, creams, lotions, gels, emulsions, aerosols, or in multiparticulate form, for example in the form of pellets or granules, optionally compressed to tablets, filled into capsules or suspended in a liquid, and may also be administered as such.

In addition to at least one *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide according to the invention of the above general formula I or Ia, in each case optionally in the form of one of its pure stereoisomers, particularly enantiomers or diastereoisomers, in the form of its racemates or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in any desired mixing ratio, or in each case in the form of appropriate salts, or in each case in the form of appropriate solvates, the medicinal drug according to the invention usually comprises further physiologically acceptable pharmaceutical adjuvants which can preferably be selected from the group consisting of carriers, fillers, solvents, diluents, surface-active substances, colorants, preservatives, disintegrators, glidants, lubricants, flavorings, and binders.

The choice of physiologically acceptable adjuvants and the amounts thereof to be used are dependent on whether the medicament is to be administered orally, subcutaneously, parenterally, intravenously, intraperitoneally, intradermally,

intramuscularly, intranasally, buccally, rectally, or locally, for example on infections of the skin, the mucous membranes, or the eyes. Formulations in the form of tablets, dragées, capsules, granules, pellets, drops, juices, and syrups are preferably suitable for oral administration; whilst solutions, suspensions, readily reconstitutable dry formulations, and sprays are suitable for parenteral and topical administration and for administration by inhalation.

The *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides of the above general formulas I and Ia that are used in the medicinal drug according to the invention in a depot, in dissolved form, or in a plaster, optionally with the addition of agents which promote penetration of the skin, are suitable formulations for percutaneous administration.

Preparation forms which can be used orally or percutaneously are also capable of affording delayed release of the respective *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides of the above general formulae I and Ia.

The preparation of the medicinal drugs according to the invention is carried out by means of conventional agents, devices, methods, and processes known from the prior art, as are described, for example, in "Remington's Pharmaceutical Sciences", ed. A.R. Gennaro, 17th Edition, Mack Publishing Company, Easton, Pa., 1985, especially in Part 8, Chapters 76 to 93.

The amount of the respective *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide of the above general formula I or Ia to be

administered to the patients can vary and is dependent, for example, on the weight or age of the patient and on the mode of administration, the indication and the severity of the disease. From 0.005 to 5000 mg/kg, preferably from 0.05 to 500 mg/kg of body weight of the patient of at least one such compound are usually administered.

Pharmacological methods:

Functional study on the vanilloid receptor 1 (VR1/TRPV1 receptor)

The agonist activity or antagonist activity of the substances to be tested on the vanilloid receptor 1 (VR1/TRPV1) of the species human and rat can be determined using the following assay. According to this assay, the Ca^{2+} influx through the channel is quantified by means of a Ca^{2+}-sensitive dye (type Fluo-4, Molecular Probes Europe BV, Leiden, Netherlands) in the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices, Sunnyvale, USA).

Method:

Chinese hamster ovary cells (CHO K1 cells, European Collection of Cell Cultures (ECACC), England) are stably transfected with the human or rat vanilloid receptor 1 (VR1) gene. For functional studies, these cells are plated out in a density of 25,000 cells/well on poly-D-lysine-coated, black 96-well plates having a clear base (BD Biosciences, Heidelberg, Germany). The cells are incubated overnight at 37°C and 5 % CO_2 in culture medium (Nutrient Mixture Ham's F12, Gibco Invitrogen GmbH, Karlsruhe, Germany) with 10 % v/v of FBS (fetal bovine serum, Gibco Invitrogen GmbH, Karlsruhe, Germany) and 18 µg/ml of L-proline (Gibco Invitrogen GmbH, Karlsruhe, Germany). On the following day, the cells are charged with 2 µM of Fluo-4 and 0.01% v/v of Pluronic F127 (Molecular Probes Europe BV, Leiden, Netherlands) in HBSS buffer solution (Hank's buffered saline solution, Gibco Invitrogen GmbH, Karlsruhe, Germany) for 30 minutes at 37°C. The plates are then washed three times with HBSS buffer solution and, after incubation for a further 15

minutes at room temperature, used in the FLIPR assay for Ca^{2+} measurement. The Ca^{2+}-dependent fluorescence is measured before and after the addition of test substances (λ_{ex} = 488 nm, λ_{em} = 540 nm). Quantification is effected by measuring the highest fluorescence intensity (FC, fluorescence counts) over time.

FLIPR assay:

The FLIPR protocol consists of 2 additions of test substance. Test substances (10 μM) are first pipetted onto the cells and the Ca^{2+} influx is compared with the control (capsaicin 10 μM). This gives the percentage activation, based on the Ca^{2+} signal after the addition of 10 μM of capsaicin (CP). After 5 minutes' incubation, 100 nM of capsaicin are applied and the influx of Ca^{2+} is likewise determined.

Desensitizing agonists and antagonists lead to suppression of the Ca^{2+} influx. The percentage inhibition compared with the maximum achievable inhibition is calculated using 10 μM of capsaicin.

In order to determine the EC_{50} values, the substances are added in various concentrations. Determinations are carried out in triplicate (n = 3) and these are repeated in at least three independent experiments (N = 4).

2. Analgesic test using the writhing test on mice

The analysis of analgesic activity in the compounds of the invention of formula is carried out using the phenylquinone-induced writhing assay in mice, modified as described in the article by I. C. Hendershot and J. Forsaith (1959) in J. Pharmacol.

Exp. Ther. 125, 237-240.

For the present purpose, male NMRI mice are used having a weight of from 25 to 30 g. Groups of 10 animals per substance dose received, 10 minutes after an intravenous dose of test substances, an intraperitoneal administration of 0.3 ml/mouse of a 0.02 % strength aqueous solution of phenylquinone (phenylbenzoquinone, obtainable from Sigma, Deisenhofen; solution produced with the addition of 5 % of ethanol and storage in a water bath at 45 °C). The animals were placed individually in observation cages. Using a pushbutton counter, the number of pain-induced stretching movements (so-called writhing reactions = straightening of the body accompanied by stretching of the rear extremities) was counted over a period of from 5 to 20 minutes following the administration of phenylquinone. The control is provided by animals receiving only physiological saline. All substances were tested using the standard dosage of 10 mg/kg.

The invention is explained hereinbelow with reference to an example. These explanations are given solely by way of example and do not limit the general inventive idea.

Examples:

The yields of the compounds prepared have were optimised.

All temperatures are uncorrected.

The term "equivalent" means the equivalent weight of a substance, "RT" means room temperature, "conc." means concentrated, "min" means minutes, "h" means hours, "M" is the concentration stated in mol/l and "aq." means aqueous.

Further abbreviations:

BOP 1-benzotriazolyl-tris-(dimethylamino)-phosphonium

DCM dichloromethane

DMF N,N-dimethylformamide

DIPE diisopropyl ether

EA ethyl acetate

The chemicals and solvents used were obtained commercially from conventional suppliers (Acros, Avocado, Aldrich, Bachem, Fluka, Lancaster, Maybridge, Merck, Sigma, TCI, etc.) or were synthesised according to conventional methods known to the person skilled in the art.

Silica gel 60 (0.040 – 0.063 mm) supplied by E. Merck, Darmstadt, was employed as the stationary phase for the column chromatography.

The thin-layer chromatography analyses were carried out with HPTLC pre-coated plates, silica gel 60 F 254 supplied by

E. Merck, Darmstadt.

The mixing ratios of solvents, mobile phases or for chromatography analyses are always stated in volume/volume.

Analysis was effected by mass spectroscopy and NMR spectroscopy.

Example 4: *para*-tert.-Butyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide

a) Synthesis of *para*-tert.-butyl-*trans*-cinnamic acid

19.20 g (0.185 mol) of malonic acid were dissolved in pyridine (33 ml) and stirred for 15 minutes at RT. 25.00 g (0.154 mmol) of *para*-tert.-butylbenzaldehyde and 1.50 ml (0.020 mol) of piperidine were then added. The reaction mixture was heated for 8 hours at 100°C, with stirring. After pouring the reaction solution into a mixture of conc. hydrochloric acid and ice, stirring was continued for a further 2 h at RT. The resulting precipitate was filtered off with suction. Recrystallisation of the precipitate from methanol yielded 15.20 g (0.074 mol, 48 % of theory) of *para*-tert.-butyl-*trans*-cinnamic acid.

b) Synthesis of *para*-tert.-butyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide

400 mg (1.96 mmol) of *para*-tert.-butyl-*trans*-cinnamic acid were dissolved at 5°C in DMF (10 ml) together with 290 mg (1.94 mmol) of 4-hydroxy-3-methoxybenzyl-amine hydrochloride and 0.48 ml (6.50 mmol) of triethylamine. After the addition of a solution of 870 mg (1.97 mmol) of BOP in DCM (9 ml), stirring was continued for 16 h at RT. The reaction solution was then poured into water and extracted twice with a mixture of DIPE/EA (1:1). The combined organic phases were washed with 2M eq. hydrochloric acid and three times with 1 M eq. of sodium hydrogen carbonate solution and dried over magnesium sulfate. Follwing removal of the

solvents and recrystallisation from DIPE, 384 mg (1.13 mmol, 58 % of theory) of *para*-tert.-butyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide were obtained.

The following Examples 1 to 3 and 5 to 9 were prepared in a similar manner to that described for Example 4.

1. *para*-methyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide

2. *para*-ethyl-*trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide

3. *para*-isobutyl-*trans*-N-(4-hydroxy-3-methoxy-benzyl)-cinnamic acid amide

5. *para*-propyl-trans-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide

6. *para*-iso-butyl-trans-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide

7. *para*-neo-pentyl-trans-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide

8. *para*-butyl-trans-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide

9. *para*-octyl-trans-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide

Pharmacological data:

The agonist activity or antagonist activity was determined on human and rat vanilloid receptor 1 (VR1/TRPV1 receptor) using the above-described FLIPR assay.

The *para*-alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides according to the invention which were examined exhibit an excellent agonist activity on the vanilloid receptor 1 (VR1/TRPV1 receptor).

Table I below shows the pharmacological data for the *para*-alkyl substituted *trans*-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amides conforming to the general formular I:

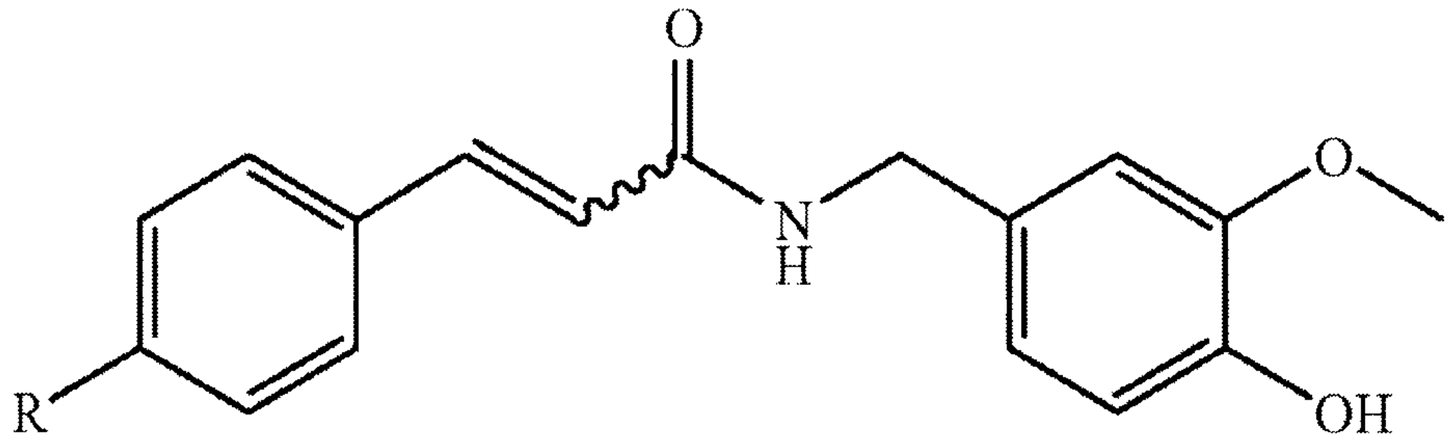
Table I.

Com-pound of Example	VR1 (Rat) (% Stimulation compared with 10 µM CP)	VR1 (Human) (% Stimulation compared with 10 µM CP)	VR1 (Rat) EC_{50} [nM]	VR1 (Human) EC_{50} [nM]
1	92	56		
2	84	71		
3	97	71		
4	106	115	0.129 ± 0,061	0.147 ± 0,043
5	119	102		
6	141	103		
7	142	102		
8	132	110		
9	126	97		

What is claimed is:

1. A para-Alkyl-substituted N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide compound corresponding to formula I:

I



wherein R represents a linear or branched C_{1-20} alkyl group; or a pharmaceutically acceptable salt thereof;

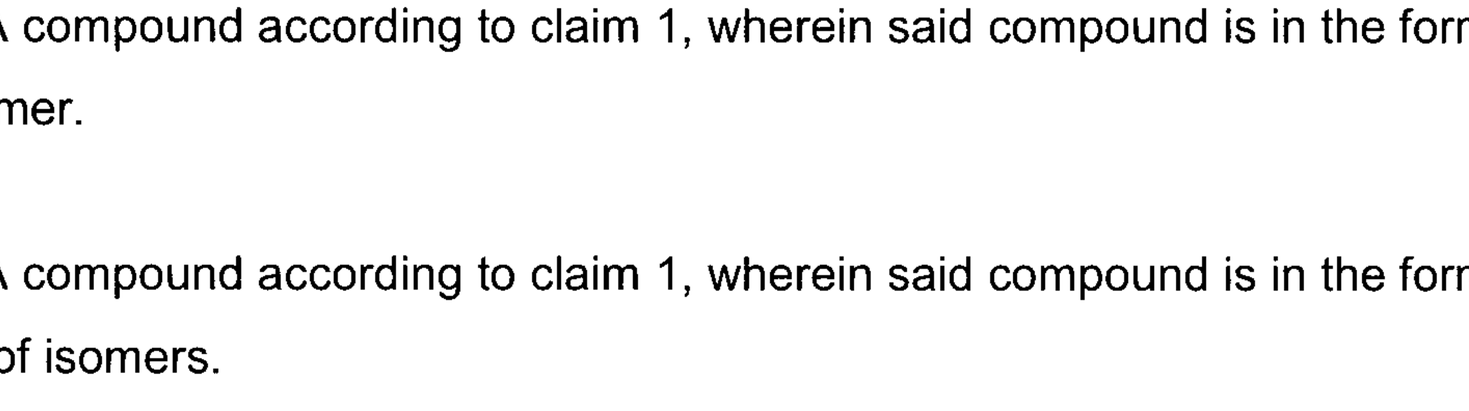
in the form of a pure isomer or a mixture of isomers in any mixing ratio.

2. A compound according to claim 1, wherein said compound is in the form of a pure isomer.

3. A compound according to claim 1, wherein said compound is in the form of a mixture of isomers.

4. A compound according to claim 1, wherein said compound is a trans isomer corresponding to formula Ia:

Ia



wherein R represents a linear or branched alkyl group; or a pharmaceutically acceptable salt thereof;

in the form of a pure isomer or a mixture of isomers in any mixing ratio.

5. A compound according to claim 1, wherein R represents a linear or branched C_{1-10} alkyl group.

6. A compound according to claim 5, wherein R represents an alkyl group selected from the group consisting of methyl; ethyl; n-propyl; isopropyl; n-butyl; isobutyl; sec.-butyl; tert.-butyl; n-pentyl; 2-pentyl; 3-pentyl; isopentyl; neopentyl; 1,1-dimethylpropyl; 1,2-dimethylpropyl; n-hexyl; 2-hexyl; 3-hexyl; isohexyl; neohexyl; n-heptyl; 2-heptyl; 3-heptyl; 4-heptyl; isoheptyl; neoheptyl; n-octyl; 2-octyl; 3-octyl; 4-octyl; isooctyl; neooctyl; n-nonyl; 2-nonyl; 3-nonyl; 4-nonyl; 5-nonyl; isononyl; neononyl, and n-decyl.

7. A compound according to claim 6, wherein R represents an alkyl group selected from the group consisting of methyl; ethyl; n-propyl; isopropyl; n-butyl; isobutyl; tert.-butyl; neopentyl, and n-octyl.

8. A compound according to any one of claims 1 to 7, selected from the group consisting of:

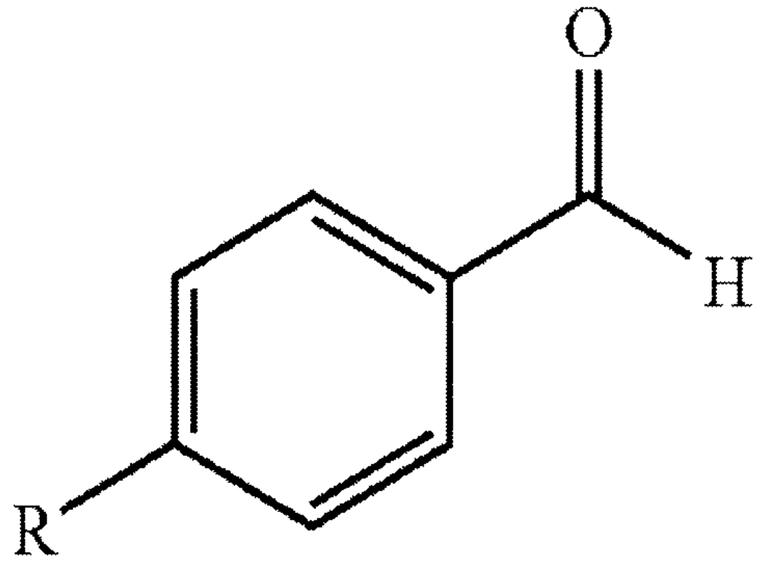
para-methyl-trans-N-(4-hydroxy-3-methoxy-benzyl)-cinnamic acid amide;
para-ethyl-trans-N-(4-hydroxy-3-methoxy-benzyl)-cinnamic acid amide;
para-isopropyl-trans-N-(4-hydroxy-3-methoxy-benzyl)-cinnamic acid amide;
para-tert.-butyl-trans-N-(4-hydroxy-3-methoxy-benzyl)-cinnamic acid amide;
para-propyl-trans-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide;
para-isobutyl-trans-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide;
para-neopentyl-trans-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide;
para-butyl-trans-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide; and
para-octyl-trans-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide;
or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 8, wherein said compound is para-tert.-butyl-trans-N-(4-hydroxy-3-methoxybenzyl)-cinnamic acid amide, or a pharmaceutically acceptable salt thereof.

10. A process for preparing a compound according to claim 1, said process comprising:

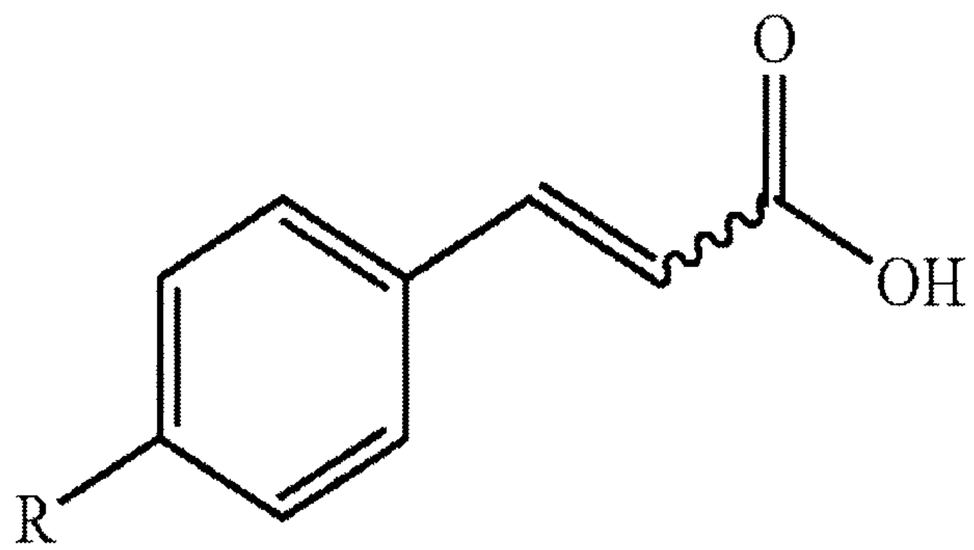
reacting an aldehyde of formula II

II



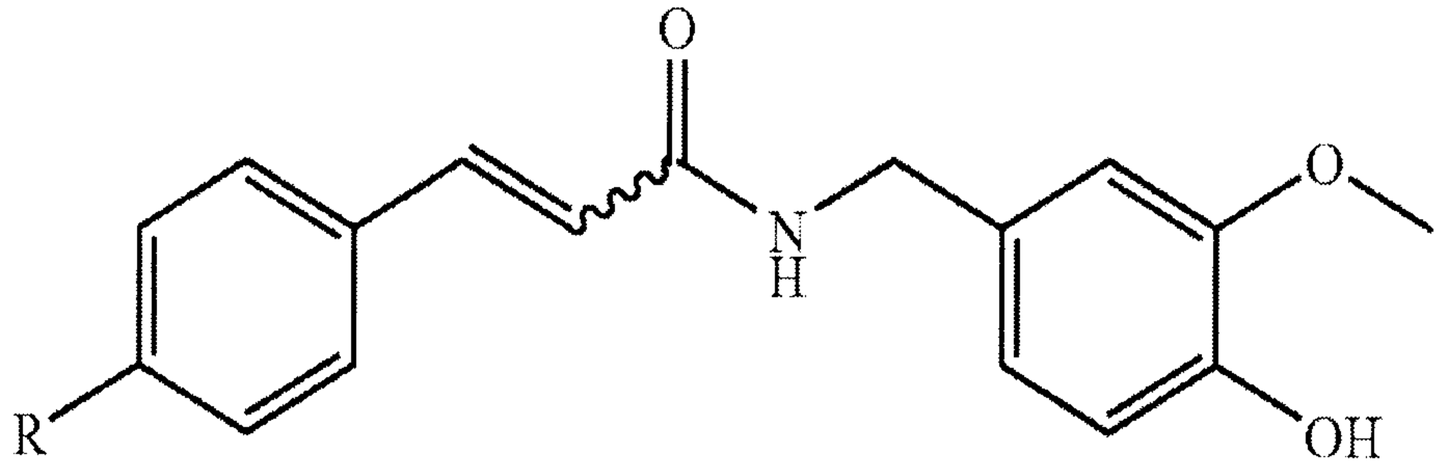
wherein R has the meaning given in claim 1, in the presence of a base with malonic acid, optionally in a reaction medium, to obtain a para-alkyl-substituted cinnamic acid of formula III

III



or salt thereof, wherein R has the meaning stated above; optionally isolating or purifying the compound of formula III or salt thereof;

then reacting the compound of formula III or salt thereof with 4-hydroxy-3-methoxybenzylamine or a salt thereof in the presence of a base in a reaction medium, and optionally in the presence of a coupling agent, to give a corresponding compound of formula I



I

or salt thereof, wherein R has the meanings stated above, and optionally purifying or isolating the compound of formula I.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9, and at least one physiologically acceptable carrier or adjuvant.

12. Use of a pharmacologically effective amount of a compound according to any one of claims 1 to 9 for treating or inhibiting pain in a patient in need thereof.

13. A medicinal drug comprising a compound according to any one of claims 1 to 9 and one or more physiologically acceptable adjuvants.

14. The medicinal drug as defined in claim 13 for the treatment and/or prophylaxis of pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain; arthralgia; migraine; depression; nervous disorders; neurotrauma; neurodegenerative diseases selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease, and Huntington's disease; cognitive disorders, cognitive deficiencies, and memory disorders; anxiety, epilepsy; respiratory tract diseases selected from the group consisting of asthma and pneumonia; coughing; urinary incontinence; an overactive bladder (OAB); gastric ulcers; colitis syndrome; cerebral apoplexy; irritation of the eyes; cutaneous irritation; neurotic skin diseases; inflammatory diseases, inflammation of the colon; diarrhoea; pruritus; disorders of food intake selected from the group consisting of bulimia, cachexia, anorexia, and obesity; medicinal drug dependency; medicinal drug abuse; withdrawal symptoms following medicinal drug dependency; development of immunity to medicaments selected from natural or synthetic opioids; drug dependency; drug abuse; withdrawal symptoms following

drug dependency; alcohol dependency; for diuresis; for antinatriuresis; for influencing the cardiovascular system; for increasing vigilance; for increasing libido; for modulating motor activity; or for local anaesthesia.