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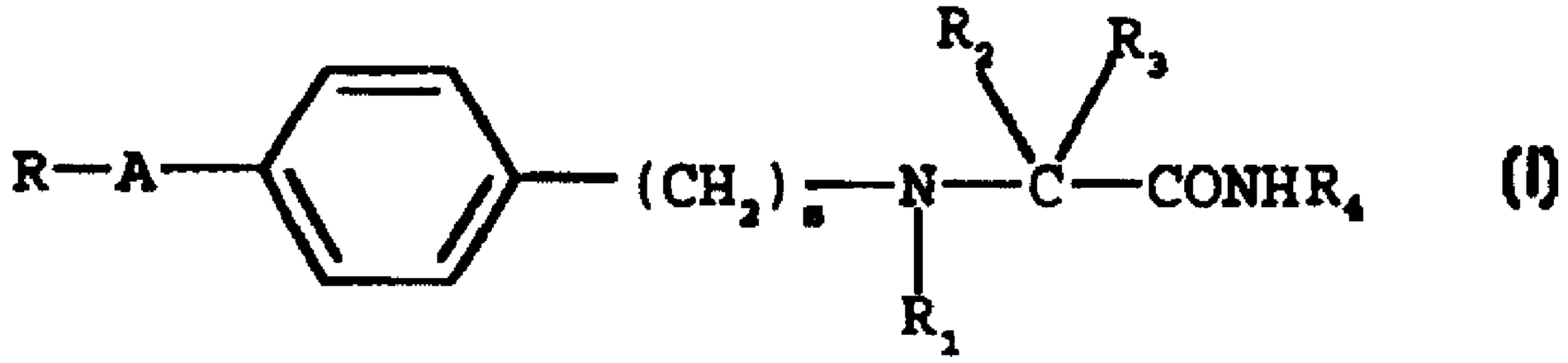
(54) Titre : DERIVES ALPHA-AMINOAMIDES UTILES EN TANT QU'AGENTS ANALGESIQUES
(54) Title: ALPHA-AMINOAMIDE DERIVATIVES USEFUL AS ANALGESIC AGENTS



(I)

(57) Abrégé/Abstract:
The use, in the manufacture of a medicament for use as an analgesic, of a compound which is an alpha-aminoamide of formula (I) wherein: A is a $-(CH_2)_m-$, $-(CH_2)_n-X-$ or $-(CH_2)_v-O-$ group wherein m is an integer of 1 to 4, n is zero or an integer of 1 to 4, X is -S- or -NH-, and v is zero or an integer of 1 to 5; s is 1 or 2; R is a furyl, thienyl, or pyridyl ring of a phenyl ring; R_1 is hydrogen or C_1-C_4 alkyl; one of R_2 and R_3 is hydrogen and the other is hydrogen or C_1-C_4 alkyl optionally substituted by hydroxy or phenyl; or R_2 and R_3 taken together with the carbon atom to which they are linked form a C_3-C_6 cycloalkyl ring; or R_2 and R_3 are both methyl; R_4 is hydrogen or C_1-C_4 alkyl ring; or a pharmaceutically acceptable salt thereof.

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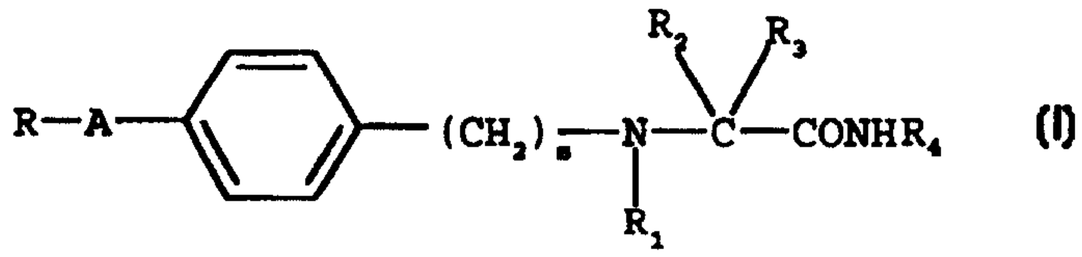


(I)

(57) Abstract

The use, in the manufacture of a medicament for use as an analgesic, of a compound which is an alpha–aminoamide of formula (I) wherein: A is a $-(CH_2)_m-$, $-(CH_2)_n-X-$ or $-(CH_2)_v-O-$ group wherein m is an integer of 1 to 4, n is zero or an integer of 1 to 4, X is –S– or –NH–, and v is zero or an integer of 1 to 5; s is 1 or 2; R is a furyl, thienyl, or pyridyl ring of a phenyl ring; R_1 is hydrogen or C_1–C_4 alkyl; one of R_2 and R_3 is hydrogen and the other is hydrogen or C_1–C_4 alkyl optionally substituted by hydroxy or phenyl; or R_2 and R_3 taken together with the carbon atom to which they are linked form a C_3–C_6 cycloalkyl ring; or R_2 and R_3 are both methyl; R_4 is hydrogen or C_1–C_4 alkyl ring; or a pharmaceutically acceptable salt thereof.

ALPHA-AMINOAMIDE DERIVATIVES USEFUL AS ANALGESIC AGENTS

The present invention relates to novel and known alpha-aminoamide compounds, to a process for their preparation, to pharmaceutical composition containing them and to their use as therapeutic agents.

In particular, the compounds of the present invention are endowed with analgesic properties and are particularly useful for the treatment and alleviation of chronic and neuropathic pain.

Chronic and neuropathic pain are associated with prolonged tissue damage or injuries to the peripheral or central nervous system and result from a number of complex changes in nociceptive pathways.

Clinical manifestations of chronic pain include a sensation of burning or electric shock, feelings of bodily distortion, allodynia and hyperpathia.

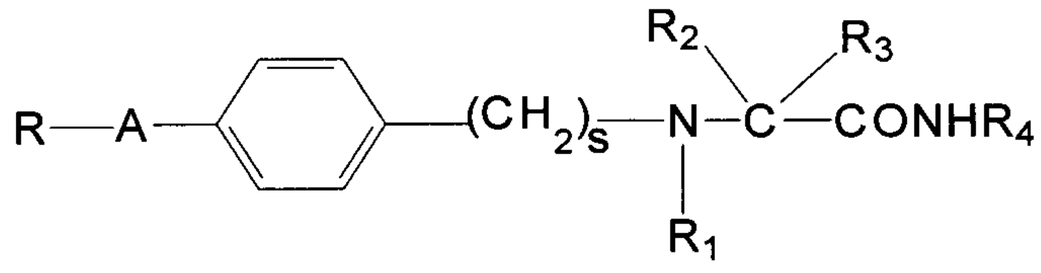
Despite the large number of available analgesics, their use is limited by severe side effects and modest activity in some pain conditions. Therefore there is still a clear need to develop new compounds.

International applications WO 90/14334, WO 94/22808, WO 97/05102 and WO 97/05111 disclose substituted benzylaminopropionamide compounds active on the central nervous system and useful as anti-epileptic, anti-Parkinson, neuroprotective, antidepressant, antispastic and hypnotic agents.

The present invention is based on the finding that compounds known from the above-cited international applications and new ones, closely related thereto, have

analgesic properties in mammals, including humans.

Accordingly, the present invention provides the use of a compound of formula (I)



(I)

wherein:

A is a $-(CH_2)_m-$, $-(CH_2)_n-X-$ or $-(CH_2)_v-O-$ group wherein m is an integer of 1 to 4, n is zero or an integer of 1 to 4, X is -S- or -NH-, and v is zero or an integer of 1 to 5;

s is 1 or 2;

R is a furyl, thienyl, or pyridyl ring or a phenyl ring optionally substituted by one or two substituents independently chosen from halogen, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy and trifluoromethyl;

R_1 is hydrogen or C_1-C_4 alkyl;

one of R_2 and R_3 is hydrogen and the other is hydrogen or C_1-C_4 alkyl optionally substituted by hydroxy or phenyl;

or R_2 and R_3 taken together with the carbon atom to which they are linked form a C_3-C_6 cycloalkyl ring; or R_2 and R_3 are both methyl;

R_4 is hydrogen or C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof; and wherein

when A is a $-(CH_2)_5-O-$ group then s is 1, R is a phenyl group optionally substituted by one or two substitutents selected independently from halogen, trifluoromethyl and C_1-C_4 alkoxy, R_1 is hydrogen and one of R_2 and R_3 is hydrogen and the other is hydrogen or C_1-C_4 alkyl

optionally substituted by hydroxy;

and wherein

when R_2 and R_3 are both methyl then R is other than furyl, thienyl or pyridyl ring, in the manufacture of a medicament for use as analgesic, in particular for the treatment and alleviation of chronic and neuropathic pain.

A $-(CH_2)_m-$, $-(CH_2)_n-$ or $-(CH_2)_v-$ chain may be a branched or straight chain.

Alkyl and alkoxy groups may be branched or straight groups. Representative examples of C_1-C_4 alkyl groups include methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl.

Representative examples of C_1-C_4 alkoxy groups include methoxy and ethoxy.

A C_3-C_6 cycloalkyl group is for instance cyclopropyl, cyclopentyl or cyclohexyl, in particular cyclopentyl or cyclohexyl.

A halogen atom is fluorine, bromine, chlorine or iodine, in particular, chlorine or fluorine.

Pharmaceutically acceptable salts of the compounds of the invention include acid addition salts with inorganic, e.g. nitric, hydrochloric, hydrobromic, sulphuric, perchloric and phosphoric acids or organic, e.g. acetic, trifluoroacetic, propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic and salicylic acids.

The compounds of formula (I) have asymmetric carbon atoms and therefore they can exist either as racemic mixtures or

as individual optical isomers (enantiomers).

Accordingly, the present invention also include within its scope all the possible isomers and their mixtures and both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

Preferred compounds of formula (I) are those wherein

A is a group chosen from $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$ and $-(CH_2)_v-O-$ in which v is an integer of 1 to 5;

s is 1 or 2;

R is a phenyl ring optionally substituted by one or two substitutents independently chosen from halogen and cyano or a thienyl ring;

R_1 is hydrogen or C_1-C_4 alkyl;

one of R_2 and R_3 is hydrogen and the other is C_1-C_4 alkyl optionally substituted by hydroxy or phenyl; or R_2 and R_3 are both methyl;

R_4 is hydrogen or C_1-C_4 alkyl; and the pharmaceutically acceptable salts thereof.

Examples of specific compounds of formula (I) are:

2-[4-(3-fluorobenzyloxy)benzylamino]-2-methylpropanamide;

2-[4-(3-fluorobenzyloxy)benzylamino]propanamide;

2-(4-benzyloxybenzylamino)propanamide;

2-[4-(2-fluorobenzyloxy)benzylamino]propanamide;

2-[4-(4-fluorobenzyloxy)benzylamino]propanamide;

2-[4-(2-chlorobenzyloxy)benzylamino]propanamide;

2-[4-(3-chlorobenzyloxy)benzylamino]propanamide;

2-[4-(3-fluorobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-[4-(2-fluorobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-[4-(2-chlorobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-[4-(3-cyanobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-[4-(3-chlorobenzyloxy)phenylethylamino]propanamide;

2-(4-benzyloxybenzylamino)-3-hydroxy-N-methylpropanamide;

2-(4-(2-thenyloxy)benzylamino)propanamide;

2-[4-(3-fluorobenzyloxy)benzylamino]-N-methylpropanamide;

2-[4-(3-fluorobenzyloxy)benzylamino]-3-hydroxypropanamide;

2-[4-(2-(3-fluorophenyl)ethyloxy)benzylamino]propanamide;

2-[4-(2-(3-fluorophenyl)ethyl)benzylamino]propanamide;

2-[N-(4-benzyloxybenzyl)-N-methyl-amino]propanamide;

2-[2-(4-(3-chlorobenzyloxy)phenylethyl)amino]propanamide;

2-(4-benzylthiobenzylamino)propanamide;

2-[4-(3-phenylpropyloxy)benzylamino]propanamide;

2-[4-(4-phenylbutyloxy)benzylamino]propanamide;

2-[4-(5-phenylpentyloxy)benzylamino]propanamide;

2-(4-benzyloxybenzylamino)-3-phenyl-N-methylpropanamide;

2-(4-benzyloxybenzylamino)-3-methyl-N-methylbutanamide,

if the case either as a single isomer or as a mixture thereof, and the pharmaceutically acceptable salts thereof.

An aspect of this invention relates to a pharmaceutically composition having analgesic activity, in particular against chronic and neuropathic pain, comprising a compound of formula (I), as herein defined, as an active agent and a pharmaceutically acceptable salt thereof.

A further aspect of this invention relates to a method of treating a mammal, including humans, in need of an analgesic agent, said method comprising administering thereto an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Neuropathic and chronic pain conditions in a mammal can thus be alleviated and treated. Examples of pain conditions that can be treated by a compound of formula (I) include:

- peripheral neuropathies, such as trigeminal neuralgia, postherapeutic neuralgia, diabetic neuropathy, glossopharyngeal neuralgia, radiculopathy, and neuropathy secondary to metastatic infiltration, adiposis dolorosa and burn pain; and
- central pain conditions following stroke, thalamic lesions and multiple sclerosis.

"Treatment" as used herein covers any treatment of a condition in a mammal, particularly a human, and includes:

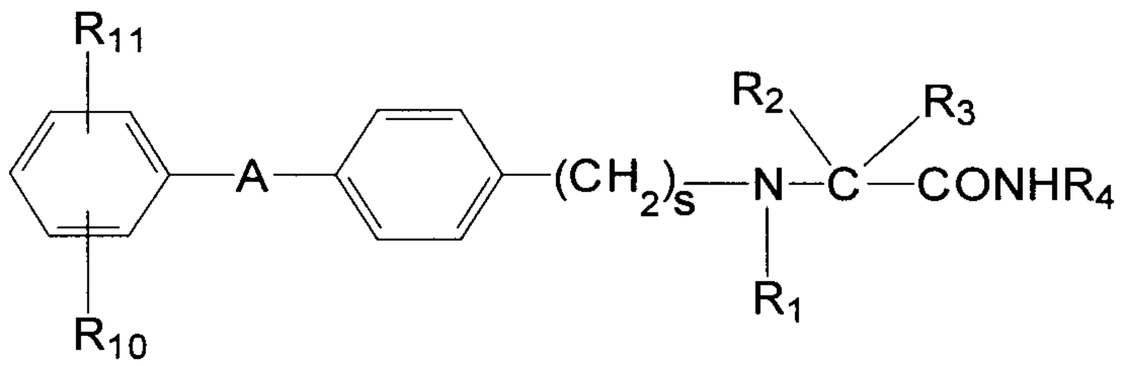
(i) preventing the disease from occurring in a subject which may be predisposed to the disease, but has not yet been diagnosed as having it;

(ii) inhibiting the condition, i.e., arresting its development; or

(iii) relieving the condition, i.e., causing

regression of the disease.

The present invention also provides the novel compounds of formula (IA)



(IA)

wherein:

A is a $-(CH_2)_m-$ or $-(CH_2)_n-E-$ group wherein m is an integer of 1 to 4, n is zero or an integer of 1 to 4 and E is

-O-, -S- or -NH-;

s is 1 or 2;

one of R_{10} and R_{11} is cyano and the other is independently selected from hydrogen, halogen, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy and trifluoromethyl;

R_1 is hydrogen or C_1-C_4 alkyl;

one of R_2 and R_3 is hydrogen and the other is hydrogen or C_1-C_4 alkyl optionally substituted by hydroxy or phenyl; or R_2 and R_3 taken together with the carbon atom to which they are linked form a C_3-C_6 cycloalkyl ring; or R_2 and R_3 are both methyl;

R_4 is hydrogen or C_1-C_4 alkyl; and the pharmaceutically acceptable salts.

The compounds of formula (IA) fall within the scope of the compound of formula (I), as herein defined. Therefore all the definitions and biological properties stated above as to a compound of formula (I) apply also to a compound of formula (IA).

In particular, preferred compounds of formula (IA) are those wherein

A is a group $-CH_2-O-$ or $-CH_2-CH_2-O-$,

s is 1;

one of R_{10} and R_{11} is cyano and the other is hydrogen, cyano or halogen; and

one of R_2 and R_3 is hydrogen and the other is C_1-C_4 alkyl optionally substituted by hydroxy; or R_2 and R_3 are both methyl and the pharmaceutically acceptable salts thereof.

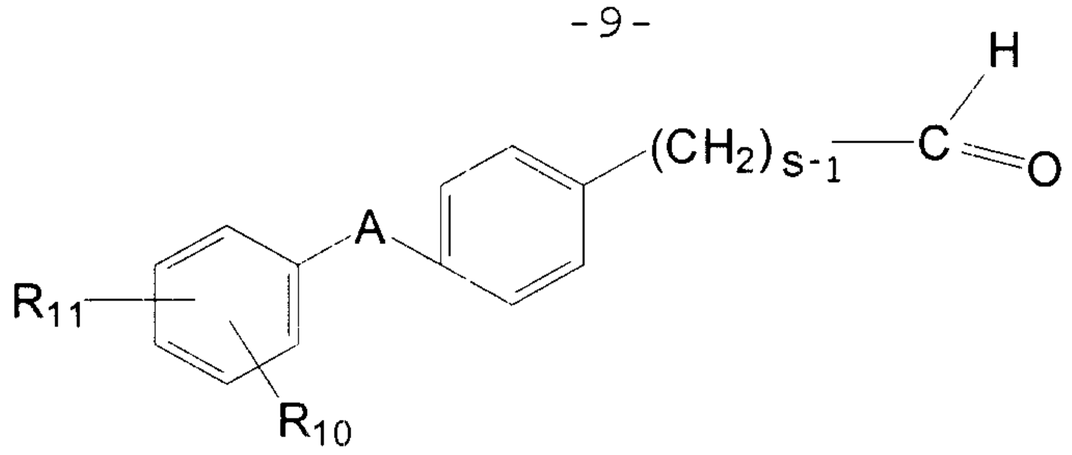
Specific examples of compounds of formula (IA) are:

2-[4-(3-cyanobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-[N-[4-(3-cyanobenzyloxy)benzyl]-N-methylamino]-3-hydroxy-N-methylpropanamide, if the case either as a single isomer or as a mixture thereof, and the pharmaceutically acceptable salts thereof.

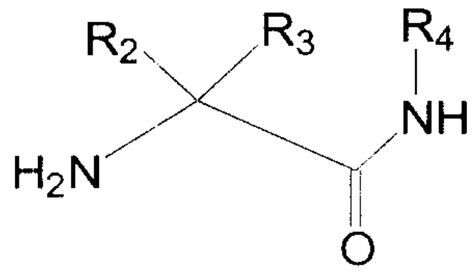
The compounds of formula (I) and (IA) and the pharmaceutically acceptable salts thereof can be obtained by well known processes as described in the above cited international applications. In particular, a compound of formula (IA) and the salts thereof can be obtained by a process comprising:

a) reacting a compound of formula (II)



(II)

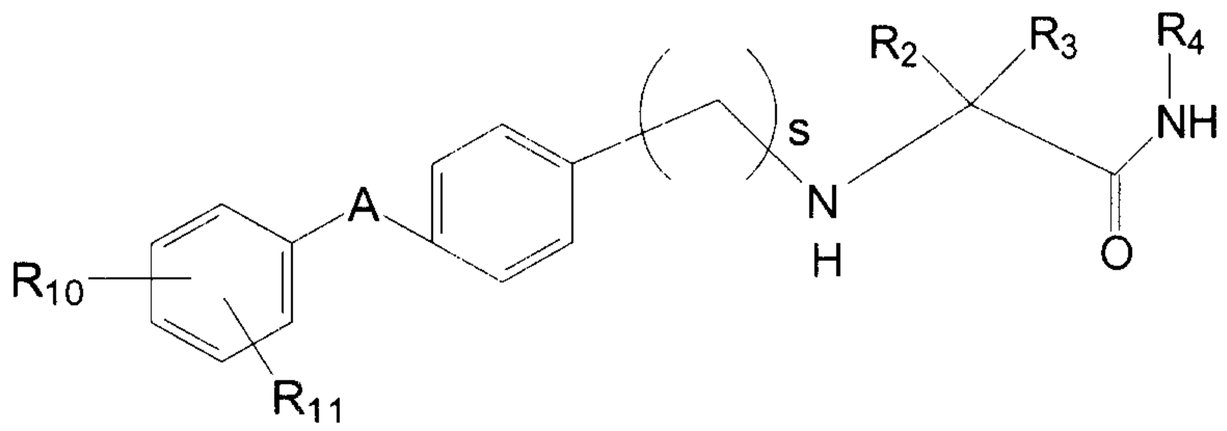
wherein R_{10}, R_{11}, A and s are as defined above, with a compound of formula (III)



(III)

wherein R_2, R_3 and R_4 are as defined above, in the presence of a reducing agent thus obtaining a compound of formula (IA) in which R_1 is hydrogen; or

(b) reacting a compound of formula (IV)



(IV)

wherein R_2, R_3, R_4, R_{10}, R_{11}, A and s are as defined above, with a compound of formula (V) or (VI) in this latter case in the presence of a reducing agent,

R'_5W (V) R''_5CHO (VI)

wherein W is a halogen atom; R'_5 is C_1-C_4 alkyl and R''_5 is hydrogen or C_1-C_3 alkyl, thus obtaining a compound of formula (IA) in which R_1 is C_1-C_4 alkyl; and, if desired, converting a compound of formula (IA) into another compound of formula (IA) and/or, if desired, converting a compound of formula (IA) into a pharmaceutically acceptable salt

and/or, if desired, converting a salt into a free compound.

All the processes described hereabove are analogy processes and can be carried out according to well known methods in organic chemistry.

A compound of formula (IV) is a compound of formula (IA) in which R_1 is hydrogen.

The reaction of a compound of formula (II) with a compound of formula (III) to give a compound of formula (IA) or (IV) is a reductive amination reaction which can be carried out according to well known methods. According to a preferred embodiment of the invention it may be performed under nitrogen atmosphere, in a suitable organic solvent, such as an alcohol, e.g. a lower alkanol, in particular methanol, or in acetonitrile, at a temperature ranging from about 0°C to about 40°C, in the presence of a reducing agent, the most appropriate being sodium cyanoborohydride.

Occasionally molecular sieves can be added to the reaction mixture for facilitating the reaction.

In a compound of formula (V) the halogen W is preferably iodine. The alkylation reaction of a compound of formula (IV) with a compound of formula (V) can be carried out in a suitable organic solvent, such as an alcohol, e.g. methanol, ethanol or isopropanol, in particular in ethanol, at a temperature ranging from about 0°C to about 50°C.

The alkylation reaction of a compound of formula (IV) with an aldehyde of formula (VI) can be carried out in a suitable organic solvent, such as an alcohol, e.g. methanol, ethanol or acetonitrile in the presence of a suitable reducing agent, such as sodium cyanoborohydride,

at a temperature ranging from about 0°C to about 30°C.

A compound of formula (IA) can be converted, as stated above, into another compound of formula (IA) by known methods. Process-variant b) above may be regarded as an example of optional conversion of a compound of formula (IA) into another compound of formula (IA).

Also the optional salification of a compound of formula (IA) as well as the conversion of a salt into the free compound may be carried out by conventional methods.

The compounds of formula (II) and (III), (V) and (VI) are known compounds or can be obtained by known methods.

When in the compounds of the present invention and in the intermediate-products thereof, groups are present, which need to be protected before submitting them to the hereabove illustrated reactions, they may be protected before being reacted and then deprotected according to methods well known in organic chemistry.

The compounds of formula (I), (IA) and the pharmaceutically acceptable salts thereof are hereinafter defined as "the compounds of the invention" or "the active agents of the invention".

PHARMACOLOGY

As stated above, the compounds of the invention are active as analgesic agents, as proven for instance by the fact that they have been found to be active in the formalin test.

Formalin test is a useful tool for obtaining neurogenic inflammation and continuous pain (Shibata et al, Pain, 38: 347-352, 1989).

Formalin produces a distinct biphasic response. The earl phase seems to be caused predominantly by C-fibre activatio due to peripheral stimulus, while the late phase appears t be dependent on the combination of an inflammatory reactio in the peripheral tissue and functional changes in th dorsal horn of the spinal cord. This functional changes see to be initiated by the C-fibre barrage during the earl phase (Tjolsen et al. Pain, 51: 5-17, 1992). Substance P an bradykinin participate in the early phase, while histamine serotonin, prostaglandins and bradykinin are involved in th late phase.

Formalin test

Male NMRI mice (22-25 g) were injected with 20 ml of 2.7 solution of formalin into the right hindpaw and place immediately into observation chambers. The cumulativ licking time of the injected paw was recorded in the acut phase (0-5 min) and in the chronic phase (30-40 min) of th nociceptive response of formalin.

The two representative compounds of the invention (S)-2-[4-(3-fluorobenzyloxy)benzylamino]propanamide, methanesulfonate (internal code PNU 151774E) and (S)-2-[4-(3-fluorobenzyloxy)benzylamino]-2-methylpropanamide (internal code PNU 156654E) were administered 60 min befor formalin injection at the doses of 7.5, 15.0, 30.0 and 60. mg/kg; po. Morphine (5 mg/kg; sc) was used as a positiv standard. The activities data analysed by Dunnett's t-test.

Locomotor activity and Rotarod

The effects of these compounds on locomotor activity and rotarod (a test for evaluating motor co-ordination) were studied in order to exclude changes in these parameters as confounding factors in the evaluation of the formalin response. The locomotor activity test lasted 15 min. Five minutes after testing locomotor activity, the mice were put on the rotarod for 2 min and the number of mice falling within this time were counted.

Compounds PNU 151774E and PNU 156654E were tested at the doses of 7.5, 15.0, 30.0 and 60.0 mg/kg; po. The compounds were administered 60 min before locomotor activity test.

Results

Compounds PNU 151774E and PNU 156654E dose-dependently reduced cumulative licking time in both phases of the formalin test (Table 1) demonstrating analgesic activity without any effect on locomotor or rotarod activity (Table 2).

Table 1

Effects of PNU 151774E and PNU 156654E in the formalin nociception test in mice

Compound	Dose (mg/kg; po)	Licking time (sec) Acute phase	Chronic phase
vehicle	0.0	160.2 ± 2.6	74.8 ± 3.7
PNU 151774E	7.5	137.9 ± 2.4 [a]	72.4 ± 2.4
	15.0	87.9 ± 3.3 [a]	64.3 ± 2.8 [b]
	30.0	79.4 ± 3.0 [a]	56.9 ± 2.6 [a]
	60.0	63.1 ± 2.6 [a]	38.1 ± 3.6 [a]
vehicle	0.0	119.4 ± 5.2	73.1 ± 6.0
PNU 156654E	7.5	108.4 ± 4.2	62.4 ± 3.6
	15.0	79.7 ± 3.7 [a]	42.1 ± 6.2 [a]
	30.0	60.0 ± 2.3 [a]	37.7 ± 6.9 [a]
	60.0	44.4 ± 4.2 [a]	17.3 ± 6.6 [a]

[a] = $p < 0.01$; [b] = $p < 0.05$

Table 2

Effects of PNU 151774E and PNU 156654E on locomotor activity and rotarod			
Compound	Dose (mg/kg; po)	Locomotor activity counts (mean ± sem)	Rotarod co-ordination (mice fallen/ total mice)
vehicle	0	2653 ± 163	0/10
PNU 151774E	7.5	2908 ± 234	0/10
	15	2795 ± 255	0/10
	30	2347 ± 203	0/10
	60	2240 ± 195	0/10
vehicle	0	1976 ± 232	0/10
PNU 156654E	7.5	1966 ± 188	0/10
	15	2110 ± 256	0/10
	30	2272 ± 317	0/10
	60	2119 ± 310	0/10

In view of their biological activity, the compounds of the invention are useful in mammals, including humans, as analgesic agents. In particular they are useful in treating pain associated with damage or permanent alteration of the peripheral or central nervous system, for example peripheral neuropathies, such as trigeminal neuralgia, postherapeutic neuralgia, diabetic neuropathy, radiculopathy, glossopharyngeal neuralgia, and neuropathy secondary to metastatic infiltration, adiposis dolorosa,

and burn pain; and central pain conditions following stroke, thalamic lesions and multiple sclerosis.

The conditions of a patient in need of an analgesic agent may thus be improved.

The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous injection or infusion.

The dosage depends on the age, weight, conditions of the patient and on the administration route; for example, the dosage adopted for oral administration to adult humans e.g. for the representative compounds of the invention

(S)-2-[4-(3-fluorobenzyloxy)benzylamino]propanamide, methanesulfonate,

(S)-2-[4-(3-fluorobenzyloxy)benzylamino]-2-methylpropanamide, and

(S)-2-[4-(3-cyanobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide may range from about 1 to about 500 mg pro dose, from 1 to 5 times daily.

The invention includes pharmaceutical compositions comprising a compound of formula (IA), as an active principle, in association with a pharmaceutically acceptable excipient (which can be a carrier or a diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together

with the active compound, diluents, e.g. lactose, destrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersion for oral administration may be e.g. syrups, emulsions and suspension.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

The suspension and the emulsion may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or

infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The invention also provides for the uses of the known or novel compounds or compositions of the invention for (i) the preparation of a medicament for use as an analgesic or (ii) for use as an analgesic, e.g., for the treatment or allevation of chronic or neuropathic pain.

The invention also provides a commercial package comprising the known or novel compounds or compositions of the invention and instructions for the use thereof as an analgesic, e.g., for the treatment or allevation of chronic or neuropathic pain.

The following examples illustrate but do not limit the invention.

Example 1

(S)-2-[4-(3-cyanobenzyloxy)benzylamino]-3-hydroxy-N-methyl-propanamide

To a solution of N-methylserinamide hydrochloride (2 g; 0.0129 mol), in methanol (40 ml), 2 g of powdered 3A molecular sieves are added; after stirring 15' at room temperature, 0.65 g (0.0102 mol) of sodium cyanoborohydride are added in a single portion followed by 2.85 g (0.012 mol) of
4-(3-cyanobenzyloxy)benzaldehyde. The mixture is stirred for 2 hours at room temperature, then filtered and the

residue after evaporation is separated by flash-chromatography on silica gel (eluant: chloroform 98: methanol 2: 30% NH_4OH 0.2). 2.6 g (63%) of pure titled compound (m.p. 130-134 °C) are obtained.

$[\alpha]^{20}_D$: $+12.8^0$ (c = 1.25 AcOH)

Example 2

(S)-2-[N-(4-(3-cyanobenzyloxy)benzyl)-N-methylamino]-3-hydroxy-N-methylpropanamide

(S)-2-[4-(3-cyanobenzyloxy)benzylamino]-3-hydroxy-N-methyl-propanamide (2 g; 0.0059 mol) is dissolved in methanol (30 ml) and 1.8 g (0.013 mol) of anhydrous potassium carbonate are added to the solution. Methyl iodide (1.5 ml; 0.025 mol) is dropped into the mixture which is stirred for 2 hours at room temperature and then evaporated to dryness. The crude residue is chromatographed on silica gel (eluant: chloroform/methanol; 95/5). 1.88 g (90%) of (S)-2-[N-(4-(3-cyanobenzyloxy)benzyl)-N-methylamino]-3-hydroxy-N-methylpropanamide are obtained.

Elemental Analysis:

Atom	Calc.	Found
C	67.97	67.69
H	6.56	6.48
N	11.89	11.98

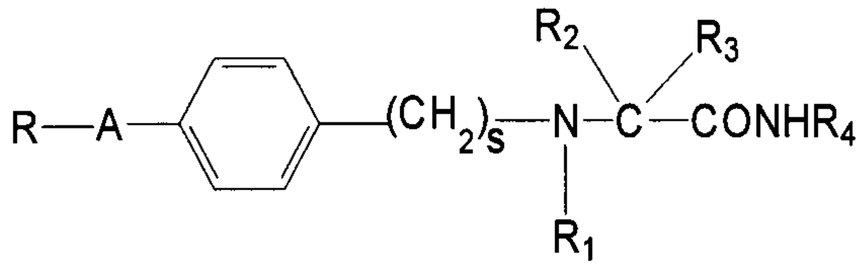
Example 3

With the usual methods of pharmaceutical technique, preparation can be made of capsules having the following composition:

(S)-2-[4-(3-cyanobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide	50 mg
Talc	2 mg
Corn starch	2 mg
Microcristalline cellulose	6 mg
Magnesium stearate	1 mg

CLAIMS:

1. Use, in the manufacture of a medicament for use as an analgesic, of a compound which is an alpha-aminoamide of formula (I)



(I)

wherein:

A is a $-(CH_2)_m-$, $-(CH_2)_n-X-$ or $-(CH_2)_v-O-$ group wherein m is an integer of 1 to 4, n is zero or an integer of 1 to 4, X is -S- or -NH-, and v is zero or an integer of 1 to 5;

s is 1 or 2;

R is a furyl, thienyl, or pyridyl ring or a phenyl ring optionally substituted by one or two substitutents independently chosen from halogen, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy and trifluoromethyl;

R_1 is hydrogen or C_1-C_4 alkyl;

one of R_2 and R_3 is hydrogen and the other is hydrogen or C_1-C_4 alkyl optionally substituted by hydroxy or phenyl;

or R_2 and R_3 taken together with the carbon atom to which they are linked form a C_3-C_6 cycloalkyl ring; or R_2 and R_3 are both methyl;

R_4 is hydrogen or C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof;

with the provisos that, when A is a $-(CH_2)_5-O-$ group then s is 1, R is a phenyl group optionally substituted by one or two substitutents selected independently from halogen, trifluoromethyl and C_1-C_4 alkoxy, R_1 is hydrogen and one of R_2 and R_3 is hydrogen and the other is hydrogen or C_1-C_4 alkyl optionally substituted by hydroxy;

and

when R_2 and R_3 are both methyl then R is other than a furyl, thienyl or pyridyl ring.

2. Use according to claim 1, wherein the medicament is for the treatment or alleviation of chronic or neuropathic pain.

3. Use according to claim 1 or 2, wherein, in formula (I)

A is a group chosen from $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$ and $-(CH_2)_v-O-$ in which v is an integer of 1 to 5;

s is 1 or 2;

R is a phenyl ring optionally substituted by one or two substituents independently chosen from halogen and cyano or a thienyl ring;

R_1 is hydrogen or C_1-C_4 alkyl;

one of R_2 and R_3 is hydrogen and the other is C_1-C_4 alkyl optionally substituted by hydroxy or phenyl; or R_2 and R_3 are both methyl; and

R_4 is hydrogen or C_1-C_4 alkyl.

4. Use according to claim 1 or 2, wherein the compound is selected from:

2-[4-(3-fluorobenzyloxy)benzylamino]-2-methylpropanamide;

2-[4-(3-fluorobenzyloxy)benzylamino]propanamide;

2-(4-benzyloxybenzylamino)propanamide;

2-[4-(2-fluorobenzyloxy)benzylamino]propanamide;

2-[4-(4-fluorobenzyloxy)benzylamino]propanamide;

2-[4-(2-chlorobenzyloxy)benzylamino]propanamide;

2-[4-(3-chlorobenzyloxy)benzylamino]propanamide;

2-[4-(3-fluorobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-[4-(2-fluorobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-[4-(2-chlorobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-[4-(3-cyanobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-[4-(3-chlorobenzyloxy)phenylethylamino]propanamide;

2-(4-benzyloxybenzylamino)-3-hydroxy-N-methylpropanamide;

2-[4-(2-thenyloxy)benzylamino]propanamide;

2-[4-(3-fluorobenzyloxy)benzylamino]-N-methylpropanamide;

2-[4-(3-fluorobenzyloxy)benzylamino]-3-hydroxypropanamide;

2-[4-(2-(3-fluorophenyl)ethyloxy)benzylamino]propanamide;

2-[4-(2-(3-fluorophenyl)ethyl)benzylamino]propanamide;

2-[N-4-(benzyloxybenzyl)-N-methylamino]propanamide;

2-[2-(4-(3-chlorobenzyloxy)phenylethyl)amino]propanamide;

2-(4-benzylthiobenzylamino)propanamide;

2-[4-(3-phenylpropyloxy)benzylamino]propanamide;

2-[4-(4-phenylbutyloxy)benzylamino]propanamide;

2-[4-(5-phenylpentyloxy)benzylamino]propanamide;

2-(4-benzyloxybenzylamino)-3-phenyl-N-methylpropanamide;

2-(4-benzyloxybenzylamino)-3-methyl-N-methylbutanamide,

if the case either as a single isomer or as a mixture thereof, or a pharmaceutically acceptable salt thereof.

5. Use according to claim 4, wherein the compound is (S)-2-[4-(3-fluorobenzyloxy)benzylamino]propanamide or a pharmaceutically acceptable salt thereof.

6. Use according to claim 5, wherein the salt is the methanesulfonic acid salt.

7. Use according to claim 4, wherein the compound is (S)-2-[4-(2-fluorobenzyloxy)benzylamino]propanamide or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound as defined in any one of claims 1, 3 and 4 to 7 for use as an analgesic.

9. A pharmaceutical composition according to claim 8 for use in the treatment or alleviation of chronic or neuropathic pain.

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10. Use of a compound as defined in any one of claims 1, 3 and 4 to 7, or a pharmaceutical composition as defined in claim 8, as an analgesic.

11. Use according to claim 10 for the treatment or alleviation of chronic or neuropathic pain.

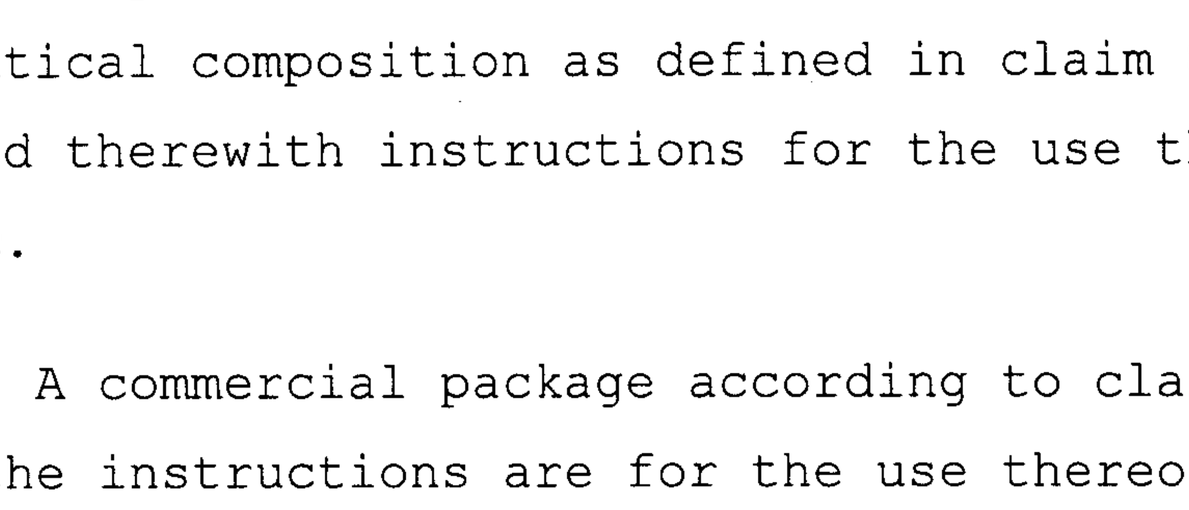
12. Use of a pharmaceutical composition according to claim 8 for preparing a medicament for use as an analgesic.

13. Use according to claim 12, wherein the medicament is for the treatment or alleviation of chronic or neuropathic pain.

14. A commercial package comprising a compound as defined in any one of claims 1, 3 and 4 to 7, or a pharmaceutical composition as defined in claim 8, and associated therewith instructions for the use thereof as an analgesic.

15. A commercial package according to claim 14, wherein the instructions are for the use thereof in the treatment or alleviation of chronic or neuropathic pain.

16. A compound which is an alpha-aminoamide of formula (IA)



(IA)

wherein:

A is a $-(CH_2)_m-$ or $-(CH_2)_n-E-$ group wherein m is an integer of 1 to 4, n is zero or an integer of 1 to 4 and E is -O-, -S- or -NH-;

s is 1 or 2;

one of R_{10} and R_{11} is cyano and the other is independently selected from hydrogen, halogen, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy and trifluoromethyl;

R_1 is hydrogen or C_1-C_4 alkyl;

one of R_2 and R_3 is hydrogen and the other is hydrogen or C_1-C_4 alkyl optionally substituted by hydroxy or phenyl;

or R_2 and R_3 taken together with the carbon atom to which they are linked form a C_3-C_6 cycloalkyl ring; or R_2 and R_3 are both methyl;

R_4 is hydrogen or C_1-C_4 alkyl; or a pharmaceutically acceptable salt thereof.

17. A compound according to claim 16, wherein:

A is a group $-CH_2-O-$ or $-CH_2-CH_2-O-$;

s is 1;

one of R_{10} and R_{11} is cyano and the other is hydrogen, cyano or halogen; and

one of R_2 and R_3 is hydrogen and the other is C_1-C_4 alkyl optionally substituted by hydroxy; or R_2 and R_3 are both methyl.

18. A compound selected from:

2-[4-(3-cyanobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide; and

2-[N-(4-(3-cyanobenzyloxy)benzyl)-N-methylamino]-3-hydroxy-N-methylpropanamide, if the case either as a single isomer or as a mixture thereof, and the pharmaceutically acceptable salts thereof.

19. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound as defined in any one of claims 16 to 18, or a pharmaceutically acceptable salt thereof.

20. Use of a compound as defined in any one of claims 16 to 18, or a pharmaceutically acceptable salt thereof, or a composition as defined in claim 19, as an analgesic.

21. Use according to claim 20 for the treatment or alleviation of chronic or neuropathic pain.

22. Use of a compound as defined in any one of claims 16 to 18, or a pharmaceutically acceptable salt thereof, or a composition as defined in claim 19, for preparing a medicament for use as an analgesic.

23. Use according to claim 22, wherein the medicament is for the treatment or alleviation of chronic or neuropathic pain.

24. A commercial package comprising a compound as defined in any one of claims 16 to 18, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined in claim 19, and associated therewith instructions for the use thereof as an analgesic.

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25. A commercial package according to claim 24, wherein the instructions are for the use thereof in the treatment or alleviation of chronic or neuropathic pain.

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