

AUSTRALIA

615171

Patents Act 1952-1973

CONVENTION APPLICATION FOR A PATENT

We, ROUSSEL-UCLAF

of 35, Boulevard des Invalides, 75007, Paris, France

hereby apply for the grant of a Patent

for an invention entitled

"NEW INDANE DERIVATIVES, THE PROCESS FOR
PREPARING THEM AND THE NEW INTERMEDIATES
THEREBY OBTAINED, THEIR APPLICATION AS
MEDICINAL PRODUCTS AND THE COMPOSITIONS
CONTAINING THEM"

This application is a Convention application and is based on
the application numbered 86-18026 for a patent or similar
protection made in France on 23rd December, 1986.

Our address for service is: CALLINANS, Patent Attorneys, of
48 Bridge Road, Richmond, 3121, Victoria, Australia.

D A T E D this 22nd day of December 1987.

ROUSSEL-UCLAF

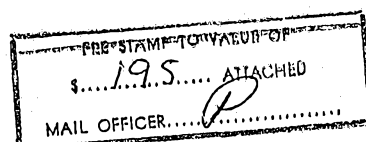
By its Patent Attorneys:

CALLINANS

LODGED AT SUB-OFFICE

22 DEC 1987

To: The Commissioner of Patents



Colin Macaulay

AUSTRALIA
Patents Act 1952-1973

Regulation 11 (1)
Regulation 11 (2)

Declaration in Support of
(a) A Convention Application
(b) An Application
for a Patent or Patent of Addition

In support of the ~~Application~~/Convention Application made by
(c) ROUSSEL-UCLAF hereinafter termed ("the said Company")

for a patent/~~patent of addition~~ for an invention entitled:

(d) THE NEW INDANE DERIVATIVES, THE PROCESS FOR PREPARING THEM AND
AS MEDICINAL PRODUCTS AND THE COMPOSITIONS CONTAINING THEM

I/~~We~~ (e) HUBERT FRITEL

of (f) 35 Boulevard des Invalides, 75007 PARIS, FRANCE

do solemnly and sincerely declare as follows:—

1. (g) ~~I am/we are the applicant(s) for the patent/patent of addition~~
~~or~~

(h) I am/~~we are~~ authorised by the said Company, the nominated
person and
the applicant for the patent/~~patent of addition~~ to make this declaration on its behalf.

2. (i) The basic application(s) as defined by Section 141 of the Act was/~~were~~ made
in France on the 23 day of December 1986
by the said Company.

3. (j) ~~I am/we are the actual inventor(s) of the invention~~
~~or~~

(k) ~~I am/we are the actual inventor(s) of the invention referred to in the basic application.~~
~~or~~

FRANCOIS CLEMENCE, of 2 rue Turgot, 75009 PARIS, FRANCE
ODILE LE MARTRET, of 42 Avenue de Versailles, 75016
PARIS, FRANCE

MICHEL FORTIN, of 12 passage Cottin, 75018 PARIS, FRANCE
FRANCOISE DELEVALLEE, of 48-50 avenue de la Dame Blanche,
94120, FONTENAY-SOUS-BOIS, FRANCE

(l) ~~I am/we are~~ the actual inventor(s) of the invention and the facts upon which
~~I am/we are~~ the said Company is entitled to make the application are as follows:

The said Company would, if a patent were to be granted
upon an application made by the said actual inventors
(m) be entitled to have the patent assigned to it; the
said Company is the nominated person.

4. The basic application referred to in paragraph 2 of this Declaration was the first
application made in a Convention country in respect of the invention the subject of the
application.

(n) Declared at Paris, France this 14 day of Dec 1987

SIGN

X

[Signature]

ADHESIF APPOSE PAR
ROUSSEL UCLAF
Société Anonyme au Capital de

(12) PATENT ABRIDGMENT (11) Document No. **AU-B-82958/87**
 (19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. **615171**

(54) Title
INDANE DERIVATIVES

International Patent Classification(s)
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C07C 091/23

C07C 103/82

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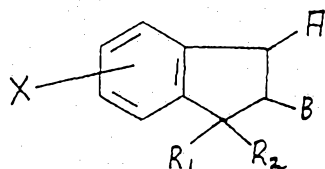
(71) Applicant(s)
ROUSSEL-UCLAF

(72) Inventor(s)
FRANCOIS CLEMENCE; ODILE LE MARTRET; MICHEL FORTIN; FRANCOISE DELEVALLEE

(74) Attorney or Agent
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(56) Prior Art Documents
AU 77254/87 C07D 295/12

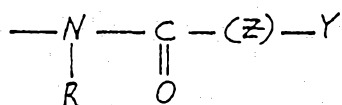
(57) Claim
 1. Compounds of formula (I):



(I)

in which X denotes a hydrogen atom, a halogen atom, an alkyl radical containing from 1 to 5 carbon atoms or an alkoxy radical containing from 1 to 5 carbon atoms, R_1 and R_2 , which may be identical or different, denote a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms and A and B are such that one of the substituents A or B is chosen from:

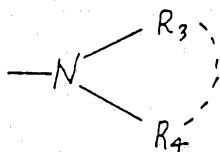
- the group of formula:



R being a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms and Z a linear alkylene chain $\text{---}(\text{CH}_2)_n\text{---}$, n being an integer which can vary between

0 and 5, or a branched alkylene chain containing from 1 to 8 carbon atoms, and Y denoting a naphthyl or indenyl radical, a 5- or 6-membered heteromonocyclic radical containing one or more heteroatoms selected from oxygen, nitrogen and sulphur, or a heterobicyclic radical containing one or more heteroatoms selected from oxygen, nitrogen and sulphur, all the radicals mentioned above optionally being substituted with one or more radicals chosen from alkyl or alkoxy radicals containing from 1 to 5 carbon atoms, halogen, hydroxyl, trifluoromethyl, nitro, amino, monoalkyl- or dialkylamino or phenyl which is itself optionally substituted with one or more radicals chosen from alkyl or alkoxy radicals containing from 1 to 4 carbon atoms and halogen, and the other of the substituents A or B is chosen from

- the group of formula:



R₃ and R₄, which may be identical or different, denoting a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms, or R₃ and R₄ form, together with the nitrogen atom to which they are attached, a 5- or 6-membered heterocycle optionally containing another hetero atom such as oxygen, nitrogen or sulphur, it being possible for the said compounds of formula (I) to be in all the possible enantiomeric and diastereoisomeric forms and in the form of addition salts with acids.

14. A method of treatment of a subject suffering from dental pain, migraine, shingles, intense pain unresponsive to peripheral analgesics, pancreatitis, nephritic or biliarycolic, or post-operative or post-traumatic pain,

(11) AU-B-82958/87

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wherein is administered to said subject an effective amount of a compound of formula I as defined in any one of Claims 1 to 4.

10. By way of intermediate products, the products of formulae (IV), (VI), (VII), (IX) and (XI) in which X does not denote a hydrogen atom.

Australia

6 1 5 1 7 1

PATENTS ACT 1952

Form 10

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Short Title:

Int. Cl:

Application Number:
Lodged:

Complete Specification—Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: ROUSSEL-UCLAF

Address of Applicant: 35, Boulevard des Invalides, 75007, Paris, France

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Françoise DELEVALLEE

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48-50 Bridge Road, Richmond, State of Victoria, Australia.

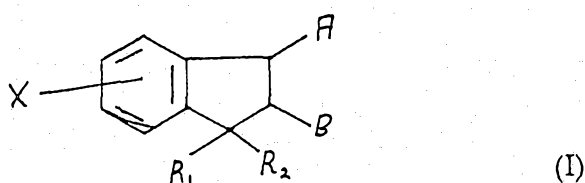
Complete Specification for the invention entitled: "NEW INDANE DERIVATIVES, THE PROCESS FOR PREPARING THEM AND THE NEW INTERMEDIATES THEREBY OBTAINED, THEIR APPLICATION AS MEDICINAL PRODUCTS AND THE COMPOSITIONS CONTAINING THEM"

The following statement is a full description of this invention, including the best method of performing it known to me:—

* Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 160 mm in width, on tough white paper of good quality and it is to be inserted inside this form.

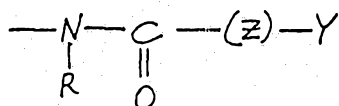
The invention relates to new indane derivatives, the process for preparing them and the new intermediates thereby obtained, their application by way of medicinal products and the pharmaceutical compositions containing them.

5 The subject of the invention is the compounds of formula (I):



10 in which X denotes a hydrogen atom, a halogen atom, an alkyl radical containing from 1 to 5 carbon atoms or an alkoxy radical containing from 1 to 5 carbon atoms, R₁ and R₂, which may be identical or different, denote a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms and A and B are such that one of the substituents A or B is chosen from:

- the group of formula:

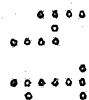
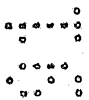
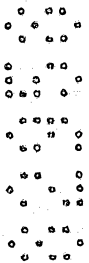


15 R being a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms and Z a linear alkylene chain $-(\text{CH}_2)_n-$, n being an integer which can vary between 0 and 5, or a branched alkylene chain containing from 2 to 8 carbon atoms, and
20 Y denoting a naphthyl or indenyl radical, a 5- or 6-membered heteromonocyclic radical containing one or more heteroatoms selected from oxygen, nitrogen and sulphur, or a heterobicyclic radical containing one or more heteroatoms selected



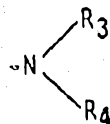
- 1b -

from oxygen, nitrogen and sulphur, all the radicals mentioned above optionally
being substituted with one or more radicals chosen



from alkyl or alkoxy radicals containing from 1 to 5 carbon atoms, halogen, hydroxyl, trifluoromethyl, nitro, amino, monoalkyl- or dialkylamino or phenyl which is itself optionally substituted with one or more radicals chosen from alkyl or alkoxy radicals containing from 1 to 4 carbon atoms and halogen, and the other of the substituents A or B is chosen from

5 - the group of formula:



10 R₃ and R₄, which may be identical or different, denoting a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms, or R₃ and R₄ form, together with the nitrogen atom to which they are attached, a 5- or 6-membered heterocycle optionally containing another hetero atom

15 such as oxygen, nitrogen or sulphur, it being possible for the said compounds of formula (I) to be in all the possible enantiomeric and diastereoisomeric forms and in the form of addition salts with acids.

20 When X, R₁, R₂, R, R₃ and R₄ denote an alkyl radical, the radicals are preferably methyl, ethyl, n-propyl or isopropyl radicals, but these substituents can also denote an n-butyl, isobutyl or n-pentyl radical.

25 When X is a halogen atom, it is preferably a chlorine atom, but X can also denote a fluorine, bromine or iodine atom.

When X is an alkoxy radical, it is preferably a methoxy or ethoxy radical, but X can also denote a propoxy, isopropoxy or linear, secondary or tertiary butoxy radical.

30 When Z denotes a group - (CH₂)_n-, n is preferably equal to 0 or 1.

When Z is a branched alkylene chain, it is preferably a chain substituted with one or more methyl or ethyl radicals. Examples of this are the following chains:

1,1-ethanediyl; 1-methyl-1,2-ethanediyl; 1- or 2-methyl-1,2-propanediyl; 1-ethyl-1,2-ethanediyl.

35

When Y denotes a 5- or 6-membered heteromonocyclic

radical, it is preferably a thiazolyl, pyridyl, oxazolyl, isoxazolyl, imidazolyl or thienyl radical.

When Y denotes a heterobicyclic radical, it is, for example, indolyl, quinolyl, benzofuranyl, benzo[b]thienyl, benzimidazolyl, benzoxazolyl or benzothiazolyl radical.

When Y denotes a substituted naphthyl, indenyl, heteromonocyclic or heterobicyclic radical, it is preferably such a radical substituted with one or two radicals chosen from methyl or ethyl, methoxy or ethoxy radicals, a chlorine, bromine or fluorine atom, trifluoromethyl, nitro or phenyl.

When the substituents are monoalkyl- or dialkyl-amino radicals, they are preferably monoalkyl- or dialkyl-amino radicals in which the alkyl radicals are methyl or ethyl radicals.

The phenyl radical is itself optionally substituted with one or two radicals chosen from methyl, ethyl, methoxy and ethoxy radicals and one or more chlorine, bromine or fluorine atoms.

R₃ and R₄ preferably form, with the nitrogen to which they are attached, a pyrrolidinyl, piperazinyl, piperidyl or morpholinyl radical.

The addition salts with inorganic or organic acids can be, for example, the salts formed with hydrochloric, hydrobromic, nitric, sulphuric, phosphoric, acetic, propionic, formic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic and aspartic acids, alkanesulphonic acids such as methanesulphonic acid and arylsulphonic acids such as benzenesulphonic acid.

The invention relates, in particular, to the compounds of formula (I) which are characterized in that the groups A and B are in the trans configuration, as well as their addition salts with acids.

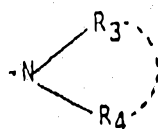
The invention relates, more especially, to the compounds of formula (I) which are characterized in that, in the group -N-C-(Z)-Y , R denotes a hydrogen atom or a

methyl or ethyl radical, Z denotes a $\text{-CH}_2\text{-}$ or -CH- group,



and Y denotes a naphthyl, indenyl, benzo[b]thienyl, indolyl, benzofuranyl, quinolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl or thienyl radical optionally substituted with a phenyl radical, as well as their addition salts with acids.

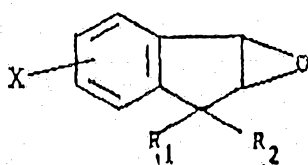
Its subject is more especially compounds of formula (I) which are characterized in that X, R₁ and R₂ denote a hydrogen atom and in that, in the group:



R₃ and R₄ form a pyrrolidine heterocycle with the nitrogen atom to which they are attached, as well as their addition salts with acids, and more especially:

- trans-(+)-N-[2,3-dihydro-2-(1-pyrrolidinyl)-1H-inden-1-yl]-N-methyl-4-benzo[b]thiopheneacetamide and its salts with acids, and trans-(±)-N-[2,3-dihydro-2-(1-pyrrolidinyl)-1H-inden-1-yl]-N-methyl-1-naphthaleneacetamide and its salts with acids.

The invention relates also to a process for preparing the products of formula (I) in which the groups A and B are in the trans configuration, characterized in that the product of formula (II):



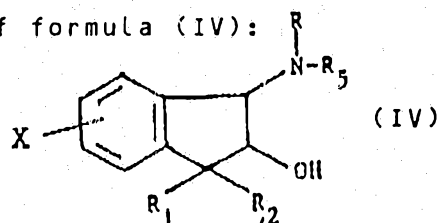
(II)

X, R₁ and R₂ having the meanings given above, is condensed - either with an amine of formula (III):



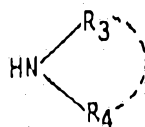
(III)

R having the meaning given above and R₅ being a group protecting the amine function, and in particular a benzyl group, to obtain a product of formula (IV):



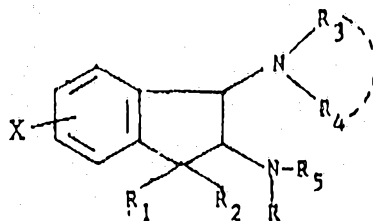
(IV)

in which the hydroxyl group is activated and which is condensed with an amine of formula (V):



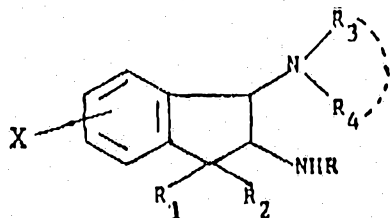
(V)

5 in which R₃ and R₄ have the meanings stated above, to obtain a product of formula (VI):



(VI)

from which the group R₅ protecting the amine function is removed to obtain a product of formula (VII):



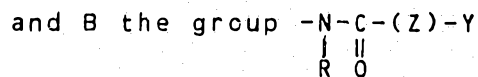
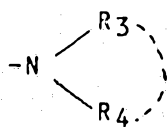
(VII)

10 which is treated with an acid of formula (VIII) or a functional derivative of this acid:

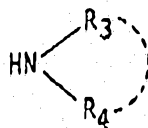


in which Y and Z have the above meanings, to obtain a product of formula (I) in which A denotes a group

15

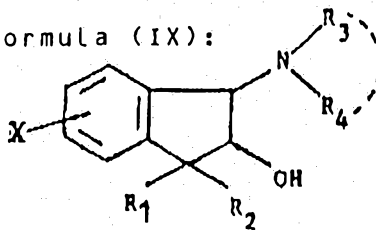


- or with an amine of formula (V):



(V)

20 to obtain a product of formula (IX):

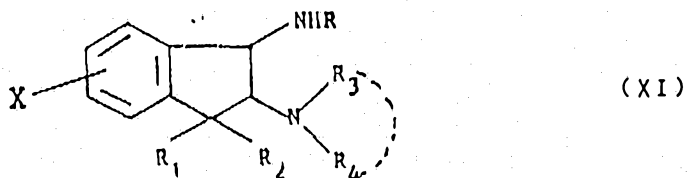


(IX)

in which the hydroxyl is activated and which is treated with an amine of formula (X):



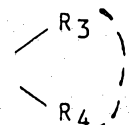
in which R has the above meaning, to obtain a product of formula (XI):



which is condensed with an acid of formula (VIII) or a functional derivative of this acid:



in which Z and Y have the above meanings, to obtain a product of formula I in which A denotes a group -N-C(Z)-Y

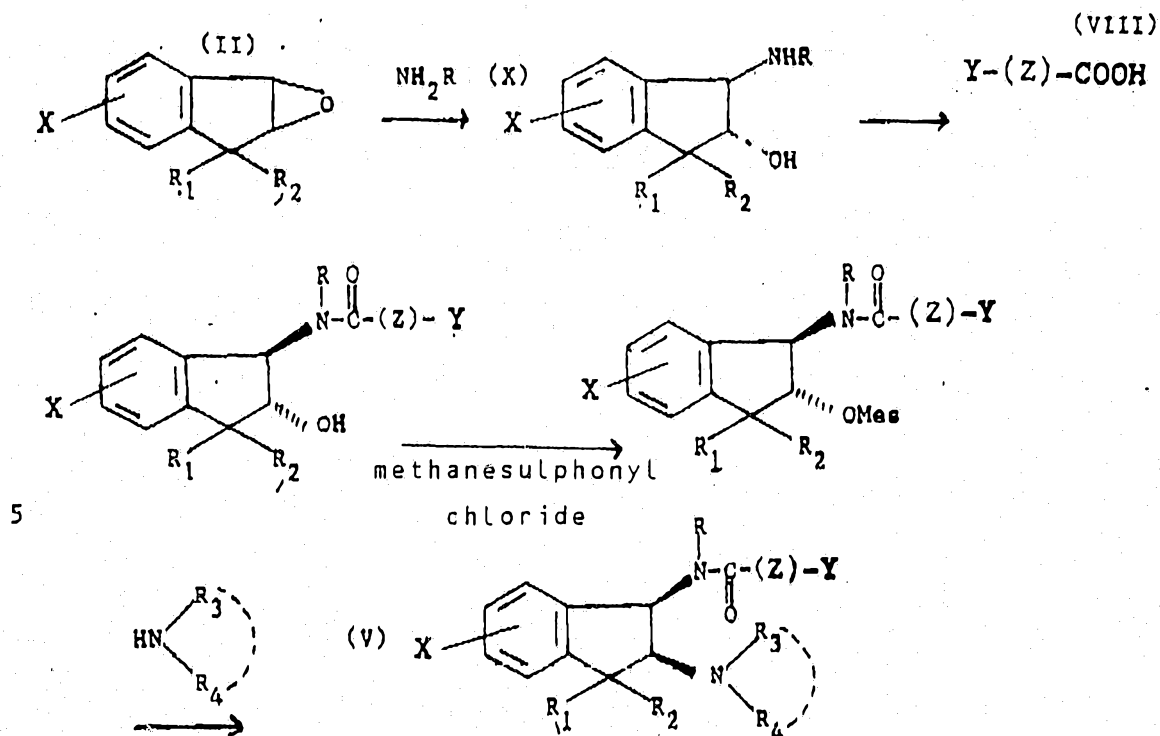
and B a group -N , it being possible for the

said compounds of formula (I) to be resolved to obtain the optically active forms, and in that the latter are treated, if desired, with an inorganic or organic acid to obtain a salt.

Under the preferred conditions of the process of the invention:

- Methanesulphonyl chloride is used to activate the hydroxyl group of the products of formula (IV) and the products of formula (IX);
- In the products of formula (VI), the protective group R_5 is a benzyl radical which may be removed by catalytic hydrogenation. The catalyst used is preferably palladium;
- The activation of the hydroxyl group of the compounds of the formula (VIII) in order to carry out the condensation with the compound of formula (VII) or (XI) is performed in the presence of carbonyldiimidazole. It is also possible to activate the acids of formula (VIII) in the form of an acid chloride or mixed anhydride;
- The products of formula (I) may be resolved by the usual methods.

The products of formula (I) for which the groups A and B are in the cis configuration may be prepared, in particular, according to the following scheme:



The compounds of formula (I) as defined above, as well as their addition salts with acids, possess interesting pharmacological properties. They possess, in particular, a strong affinity for opiate receptors and, in particular, for the κ receptors, and are endowed with central analgesic properties. The products possess, in addition, diuretic activity and antiarrhythmic, cerebral anti-ischaemic and hypotensive properties.

These properties justify the use of the indane derivatives as well as their pharmaceutically acceptable salts by way of medicinal products.

The subject of the present invention is thus also the application of the indane derivatives of formula (I), as well as their addition salts with pharmaceutically acceptable acids, by way of medicinal products.

Among the medicinal products that are the subject of the invention, the medicinal products preferably selected are those which are characterized in that they consist of the compounds of formula (I) in which the groups A and B are in the trans configuration, as well as their addition salts with pharmaceutically acceptable acids.

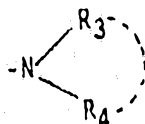
Among these compounds, there are selected, in particular, those corresponding to the formula (I) containing a $-N-C(Z)-Y$ group, in which R denotes a hydrogen atom



or a methyl or ethyl radical, Z denotes a group $-CH_2-$ or $-CH-$, and Y denotes a naphthyl, indenyl, benzo[b]thienyl, CH_3

indolyl, benzofuranyl, quinolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl or thienyl radical optionally substituted with a phenyl radical, as well as their addition salts with pharmaceutically acceptable acids.

Among these compounds, there are selected especially those corresponding to the formula (I) in which X, R₁ and R₂ denote a hydrogen atom and in which, in the group:



R₃ and R₄ form a pyrrolidine heterocycle with the nitrogen atom to which they are attached, as well as their addition salts with pharmaceutically acceptable acids.

Among the latter, the following are selected more especially:

- trans-(+)-N-[2,3-dihydro-2-(1-pyrrolidinyl)-1H-inden-1-yl]-N-methyl-4-benzo[b]thiopheneacetamide,
- trans-(+)-N-[2,3-dihydro-2-(1-pyrrolidinyl)-1H-inden-1-yl]-N-methyl-1-naphthaleneacetamide and their salts with pharmaceutically acceptable acids.

The medicinal products which are the subject of the invention enable, in particular, pain to be relieved irrespective of its origin, for example pain of a muscular, articular or nervous nature.

They can also be used in the treatment of dental

pain, migraine, shingles; in the treatment of intense pain, especially pains that are unresponsive to peripheral analgesics, for example during neoplastic processes, in the treatment of pancreatitis and nephritic or biliary colic, and in the treatment of post-operative and post-traumatic pain.

The dosage varies, in particular, according to the administration route, the condition being treated and the subject in question.

For example, in adults, it can vary between 20 and 400 mg of active principle per day administered orally, and between 5 and 100 mg per day administered parenterally.

The medicinal products which are the subject of the invention also find application in the treatment of arrhythmias.

In this treatment, the usual dose, which varies according to the derivative used, the subject and the condition in question, can be, for example, from 50 mg to 1 g per day.

Orally, the active principle can be administered at a daily dose of 200 mg to 800 mg, for example for the treatment of ventricular, supraventricular and junctional arrhythmias, equivalent to approximately 3 mg to 12 mg per kilogramme of body weight.

The medicinal products which are the subject of the invention can also be used in the treatment of oedematous syndromes, cardiac insufficiency, certain types of obesity, cirrhosis, in the treatment of severe and refractory oedema, especially those caused by congestive cardiac insufficiency, and in the long-term treatment of arterial hypertension.

The daily dose of active principle is variable. It can be, for example, from 60 to 100 mg/day administered orally.

The invention encompasses the pharmaceutical compositions containing as active principle the medicinal products defined above.

These pharmaceutical compositions can be administered orally, rectally, parenterally or locally as a topical application on the skin and mucosae.

These compositions can be solid or liquid, and can be presented in the pharmaceutical forms commonly used in human medicine such as, for example, simple or sugar-coated tablets, gelatin capsules, granules, suppositories, injectable preparations, ointments, creams, gels and aerosol preparations; they are prepared according to the usual methods. The active principle can be incorporated therein with excipients customarily employed in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fats of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersant or emulsifying agents and preservatives.

The dosage varies, in particular, according to the administration route, the condition being treated and the subject in question.

Furthermore, the starting substances of formula (II) for which R_1 and R_2 are hydrogen atoms or alkyl radicals containing from 1 to 5 carbon atoms are prepared by oxidation of the corresponding indene.

The compounds of formulae (IV), (VI), (VII), (IX) and (XI), in which X does not denote a hydrogen atom, are new chemical products.

The subject of the invention is hence these products by way of new industrial products, in particular by way of intermediate products required for carrying out the process of the invention.

The examples given below illustrate the invention without, however, limiting it.

Example 1: Trans-(+)-N-[2,3-dihydro-2-(1-pyrrolidinyl)-1H-inden-1-yl]-N-methyl-4-benzo[b]thiopheneacetamide and its hydrochloride.

Stage A: Trans-(+)-2,3-dihydro-1-(1-pyrrolidinyl)-1H-inden-2-ol.

10.8 cm³ of pyrrolidine are added slowly to 6.75 g of 2,3-epoxyindane (described by Mousseron et al., Bulletin de la Société Chimique de France, 1946, p. 629-630) in 10.8 cm³ of demineralized water. The temperature rises to 65°C and the solution is stirred for 1 hour

30 minutes at this temperature. 20 cm³ of demineralized water are added at the end of the reaction, the excess pyrrolidine is distilled off under reduced pressure, an oily phase and an aqueous phase are obtained, the mixture is saturated with sodium chloride at 20°C, 1 cm³ of 32% strength sodium hydroxide solution is added and the mixture is extracted with ether. The extract is dried and concentrated by distillation under reduced pressure, the oil obtained is purified by chromatography on silica (eluent: ethyl acetate containing 5% of triethylamine) and 8.81 g of expected product are obtained.

Stage B: Trans-(±)-2,3-dihydro-N-methyl-2-(1-pyrrolidinyl)-1H-inden-1-amine.

A mixture containing 8.71 g of product obtained in stage A, 87 cm³ of methylene chloride and 13.8 cm³ of triethylamine is cooled to -20°C and a solution containing 6.6 cm³ of methanesulphonyl chloride and 8.7 cm³ of methylene chloride is added to it at this temperature. The mixture is stirred for 20 minutes at -20°C, allowed to return to 0°C and washed with ice-cold water, and the washings are extracted with methylene chloride. The organic phases are dried and concentrated to dryness under reduced pressure, and 13.36 g of a resin corresponding to (±)-2,3-dihydro-1-(1-pyrrolidinyl)-1H-inden-2-ol methanesulphonate is obtained. The residue is treated in an autoclave with an 35-40% strength aqueous solution of monomethylamine. The mixture is heated to 80°C for 20 hours (pressure stabilized at 3 bars). The mixture is cooled to 20°C, taken up with 100 cm³ of ether and saturated with sodium chloride, settling is allowed to occur and the organic phase and washed with saturated aqueous saline solution. The organic phase is dried, treated with active charcoal, filtered, rinsed and concentrated to dryness under reduced pressure. 6.98 g of a resin are obtained, which are purified by chromatography on silica (eluent: ethyl acetate/methanol/triethylamine 85:10:5). 3.71 g of expected product are obtained.

Stage C: Trans-(±)-N-[2,3-dihydro-2-(1-pyrrolidinyl)-1H-inden-1-yl]-N-methyl-4-benzo[b]thiopheneacetamide and

its hydrochloride.

0.5 g of 4-thionaphtheneacetic acid, 0.422 g of carbonyldiimidazole and 20 cm³ of tetrahydrofuran are stirred for 1 hour, and a solution of 0.432 g of product obtained in stage B in 5 cm³ of tetrahydrofuran is then added slowly. The mixture is stirred for 3 hours 30 minutes, the tetrahydrofuran distilled off under reduced pressure, the residue taken up with 100 cm³ of ether, the mixture washed with saturated sodium bicarbonate solution and then with saturated aqueous saline solution, dried and concentrated to dryness under reduced pressure, and 0.61 g of expected (oil) obtained in the form of the base.

0.405 g of the product obtained above is dissolved in 4 cm³ of ethanol (99° alcoholic strength), and 0.5 cm³ of anhydrous ethanolic hydrochloric acid solution (titre = 5.75 N) is added hot. The mixture is immediately filtered hot and rinsed with ethanol at 50°C, crystallization is primed at 30°C and the product left to crystallize undisturbed at 20°C for 2 hours. The product is drained, rinsed with ethanol and ether and dried under reduced pressure, and 0.150 g of the expected hydrochloride is obtained.

M.p. 192°C.

Example 2: Trans-(+)-N-[2,3-dihydro-2-(1-pyrrolidinyl)-1H-inden-1-yl]-N-methyl-5-phenyl-2-thiopheneacetamide and its hydrochloride.

The procedure is as in stage C of Example 1, starting with 0.432 g of product prepared as in stage B, 0.567 g of 5-phenyl-2-thiopheneacetic acid and 0.422 g of carbonyldiimidazole. 0.571 g of base and 0.457 g of expected hydrochloride are obtained. M.p. = 249°C.

Analysis: C₂₆H₂₈N₂O₂S. HCl: 453.05

Calculated: C% 68.93 H% 6.45 N% 6.18 S% 7.08 Cl% 7.82

Found: 69.2 6.5 6.2 7.0 8.1

Example 3: Trans-(+)-N-[2,3-dihydro-2-(1-pyrrolidinyl)-1H-inden-1-yl]-N-methyl-1-naphthaleneacetamide and its hydrochloride.

The procedure is as in stage C of Example 1, starting with 0.432 g of product prepared as in stage B,

0.484 g of 1-naphthylacetic acid and 0.422 g of carbonyl-diimidazole. 0.718 g of base (m.p. $\approx 127^{\circ}\text{C}$) and then 0.533 g of expected hydrochloride are obtained from 0.655 g of base. M.p. $\approx 240^{\circ}\text{C}$.

5 Analysis: $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}$. HCl : 420.986
Calculated: C% 74.18 H% 6.94 N% 6.65 Cl% 8.42
Found: 74.2 7.1 6.8 8.3

Example 4: Trans-(+)-N-[2,3-dihydro-2-(1-pyrrolidinyl)-1H-inden-1-yl]-N-methyl-2-naphthaleneacetamide and its
10 hydrochloride.

Using the same working quantities as in Example 3, but starting with 2-naphthylacetic acid, the base and then 0.805 g of expected hydrochloride are obtained. M.p. $\approx 255^{\circ}\text{C}$ after recrystallization in isopropanol.

15 Analysis: $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}$. HCl : 420.986
Calculated: C% 74.18 H% 6.94 N% 6.65 Cl% 8.42
Found: 74.4 7.0 6.5 8.6

In a manner similar to that described in the above examples, the following product was also prepared:

20 - trans-(+)-N-[2,3-dihydro-2-(1-pyrrolidinyl)-1H-inden-1-yl]-N-methyl-1H-indole-4-acetamide maleate. M.p. 202°C - 204°C .

Example 5:

Tablets corresponding to the following formula
25 were prepared:

- Product of Example 1 200 mg
- Excipient q.s. 800 mg
(detail of the excipient: lactose, talc, starch, magnesium stearate).

30 Example 6:

An injectable solution (for intramuscular administration) corresponding to the following formula was prepared:

35 - Product of Example 1 50 mg
- Sterile solvent 5 cm^3

PHARMACOLOGICAL STUDY

1) Binding to the κ opiate receptor in vitro

Membrane pellets stored at -30°C for approximately 30 days and prepared from guinea pig cerebella are used.

These pellets are resuspended in Tris buffer pH 7.7. 2-ml fractions are distributed in haemolysis tubes and 1nM [9-³H]ethylketocyclazocine and the test product are added. [The product is first tested at a concentration of 5 x 10⁻⁶M (in triplicate). When the test product displaces by more than 50% the radioactivity specifically bound to the receptor, it is again tested according to a series of 7 doses in order to determine the dose which inhibits by 50% the radioactivity specifically bound to the receptor. The 50% inhibitory concentration is thereby determined].

The non-specific binding is determined by adding the product known under the name U-50488 H (Lahti et al. 1982, Life Sci. 31, 2257) at a concentration of 10⁻⁵M (in triplicate). The suspensions are incubated at 25°C for 40 minutes, brought back to a water bath at 0°C for 5 minutes, filtered under vacuum and rinsed with Tris buffer pH 7.7, and the radioactivity is counted in the presence of Triton scintillant.

The result is expressed directly as the 50% inhibitory concentration IC₅₀ (that is to say, the concentration of test product, expressed in nM, required for displacing 50% of the specific radioactivity bound to the receptor in question).

Result:

The IC₅₀ found for the product of Example 1 is 1.8 nanomolar, and 4.9 nanomolar for the product of Example 3.

2) Analgesic activity in vivo

- Hot-plate test

Female mice weighing 22 to 24 g are placed individually on a copper plate maintained at 56°C: the reaction to pain is manifested by the animal licking its fore-paws; the time taken for this reaction is noted and only the mice reacting in less than 8 seconds are included.

The animals are distributed in homogeneous groups and treated with the test product administered subcutaneously, one group receiving only the vehicle. The time for reaction to the pain is again measured 30 to 60 minutes

after the treatment. The active dose or AD₁₀₀ is the dose which increases the reaction time by 100% 30 minutes after the treatment, taking into account the variations in the reaction time of the control animals.

5 For the product of Example 1, the AD₁₀₀ is 8 mg/kg.

3) Antiarrhythmic action in rats

Male rats weighing 300-350 g, anaesthetized intraperitoneally by means of 1.20 g/kg of urethane, are tracheotomized and subjected to artificial respiration (40-50
10 3-ml insufflations/minute).

Needles are implanted subcutaneously so as to record the electrocardiogram of the rats on the basis of the signal from the DII lead.

Test products are administered intravenously.

15 Five minutes after the administration of the product, the jugular vein of the rats is perfused with 10 µg/min, in a volume of 0.2 ml, of a solution of aconitine, and the time taken for onset of the disorders of cardiac rhythm is noted.

20 The results are expressed as a percentage prolongation of the time taken for onset of the disorders of cardiac rhythm compared with the controls and in terms of the dose of the test product.

25 The results recorded in the table below show that some of the products of the present application are endowed with good antiarrhythmic properties.

30

Product of Example	Dose mg/kg	Percentage prolongation of the time
1	10	+65%

4) Measurement of diuretic activity

Male Sprague-Dawley strain rats weighing 180-200 g are fasted for 17 hours before the trial while receiving
35 water ad libitum.

Batches of 8 animals are formed per dose tested. The rats receive the test product or its vehicle orally.

The urinary volume is measured every hour during the 2 hours following the administration of the product.

At the end of this period, the urine is collected and the activity of the product is expressed as a percentage change calculated on the urinary volume corresponding to the period $t_{1h}-t_{2h}$.

5

10

Product of Example	Dose mg/kg	Percentage change
1	1	+ 131
3		+ 267

5) Study of acute toxicity

The lethal doses LD_0 of the different test compounds was measured after oral administration in mice.

15

LD_0 denotes the maximum dose not causing any mortality in 8 days.

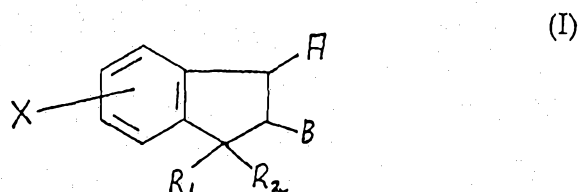
Results:

20

Product of Example	LD_0
1	100 mg/kg
3	100 mg/kg
4	200 mg/kg

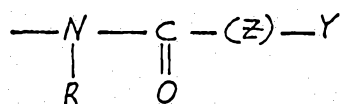
The claims defining the invention are as follows:

1. Compounds of formula (I):



in which X denotes a hydrogen atom, a halogen atom, an alkyl radical containing from 1 to 5 carbon atoms or an alkoxy radical containing from 1 to 5 carbon atoms, R_1 and R_2 , which may be identical or different, denote a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms and A and B are such that one of the substituents A or B is chosen from:

- the group of formula:



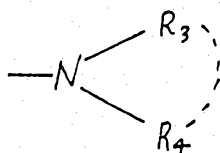
R being a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms and Z a linear alkylene chain $-(CH_2)_n-$, n being an integer which can vary between 0 and 5, or a branched alkylene chain containing from 2 to 8 carbon atoms, and Y denoting a naphthyl or indenyl radical, a 5- or 6-membered heteromonocyclic radical containing one or more heteroatoms selected from oxygen, nitrogen and sulphur, or a heterobicyclic radical containing one or more heteroatoms selected from oxygen, nitrogen and sulphur, all the radicals mentioned above optionally being substituted with one or more radicals chosen from alkyl or alkoxy radicals containing from 1 to 5 carbon atoms, halogen, hydroxyl, trifluoromethyl, nitro,



- 17a -

amino, monoalkyl- or dialkylamino or phenyl which is itself optionally substituted with one or more radicals chosen from alkyl or alkoxy radicals containing from 1 to 4 carbon atoms and halogen, and the other of the substituents A or B is chosen from

5 - the group of formula:



R₃ and R₄, which may be identical or different, denoting a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms, or R₃ and R₄ form, together with the nitrogen atom to which they are attached, a 5- or 6-membered heterocycle optionally containing another hetero atom such as oxygen, nitrogen or sulphur, it being possible for the said compounds of formula (I) to be in all the possible enantiomeric and diastereoisomeric forms and in the form of addition salts with acids.

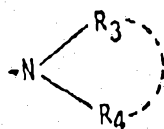
2. Compounds of formula (I) as defined in Claims 1, characterized in that the groups A and B are in the trans configuration, as well as their addition salts with acids.

3. Compounds of formula (I) as defined in Claim 1 or 2, characterized in that, in the group $\begin{array}{c} \text{-N-C-(Z)-Y} \\ | \quad || \\ \text{R} \quad \text{O} \end{array}$, R denotes

a hydrogen atom or methyl or ethyl radical, Z denotes a -CH₂- or $\begin{array}{c} \text{-CH-} \\ | \\ \text{CH}_3 \end{array}$ group, and Y denotes a naphthyl, indenyl,

benzo[b]thienyl, indolyl, benzofuranyl, quinolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl or thienyl radical optionally substituted with a phenyl radical, as well as their addition salts with acids.

4. Compounds of formula (I) as defined in any one of Claims 1 to 3, characterized in that X, R₁ and R₂ denote a hydrogen atom and in that, in the group:

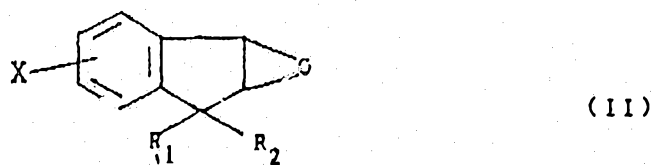


R₃ and R₄ form a pyrrolidine heterocycle with the nitrogen atom to which they are attached, as well as their addition salts with acids.

5. Trans-(+)-N-[2,3-dihydro-2-(1-pyrrolidinyl)-1H-inden-1-yl]-N-methyl-4-benzo[b]thiopheneacetamide and its salts with acids, and trans-(+)-N-[2,3-dihydro-2-(1-pyrrolidinyl)-1H-inden-1-yl]-N-methyl-1-naphthaleneacetamide and its addition salts with acids.

6. Process for preparing the products of formula (I)

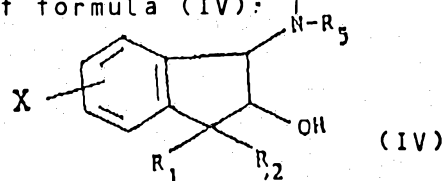
in which the groups A and B are in the trans configuration, characterized in that the product of formula (II):



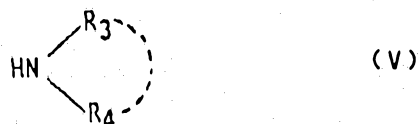
5 X, R₁ and R₂ having the meanings given above, is condensed - either with an amine of formula (III):



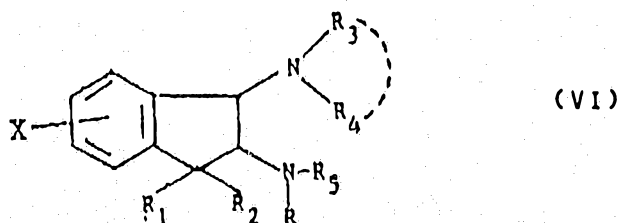
R having the meaning given above and R₅ being a group protecting the amine function, and in particular a benzyl group, to obtain a product of formula (IV):



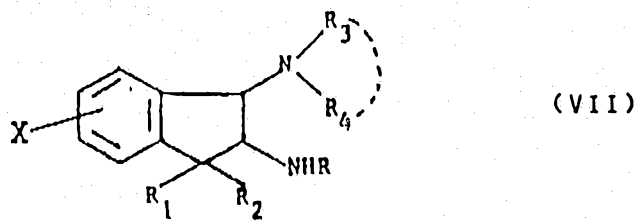
10 in which the hydroxyl group is activated and which is condensed with an amine of formula (V):



15 in which R₃ and R₄ have the meanings stated above, to obtain a product of formula (VI):



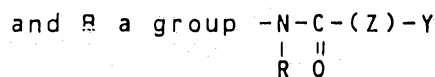
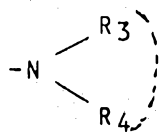
from which the group R₅ protecting the amine function is removed to obtain a product of formula (VII):



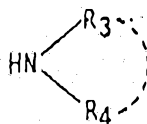
which is treated with an acid of formula (VIII) or a functional derivative of this acid:



in which Y and Z have the above meanings, to obtain a product of formula (I) in which A denotes a group

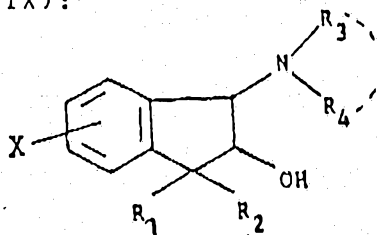


- or with an amine of formula (V):



(V)

in which R₃ and R₄ have the above meaning to obtain a product of formula (IX):

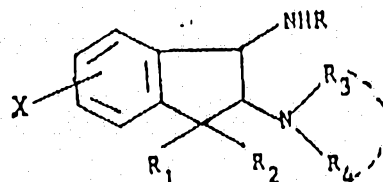


(IX)

in which the hydroxyl is activated and which is treated with an amine of formula (X):



in which R has the above meaning, to obtain a product of formula (XI):



(XI)

which is condensed with an acid of formula (VIII) or a functional derivative of this acid:



in which Z and Y have the above meanings, to obtain a product of formula I in which A denotes a group $\begin{array}{c} -N-C-(Z)-Y \\ | \quad || \\ R \quad O \end{array}$

and B a group $\text{-N} \begin{array}{l} \text{---} \text{R}_3 \\ \text{---} \text{R}_4 \end{array}$, it being possible for the said compounds of formula

(I) to be resolved to obtain the optically active forms, and in that the latter are treated, if desired, with an inorganic or organic acid to obtain a salt.

5 7. ~~By way of medicinal products, the products~~ ^{The compounds} of formula (I) as defined in any one of Claims 1 to 4, as well as their additions salts with pharmaceutically acceptable acids.

8. ~~By way of a medicinal product, the product~~ ^{The compound} of Claim 5 as well as its addition salts with pharmaceutically acceptable acids.

9. The pharmaceutical compositions containing, by way of active principle, at least one of the medicinal products as defined by Claim 7 or 8 in association with a pharmaceutically acceptable excipient.

10. By way of intermediate products, the products of formulae (IV), (VI), (VII), (IX) and (XI) in which X does not denote a hydrogen atom.

11. A compound of formula I as claimed in any one of Claims 1 to 5 substantially as hereinbefore described with reference to any one of Examples 1 to 4.

12. A process as claimed in Claim 6 substantially as hereinbefore described with reference to any one of Examples 1 to 4.

13. A pharmaceutical composition as claimed in Claim 9 substantially as hereinbefore described with reference to either of Example 5 or Example 6.

14. A method of treatment of a subject suffering from dental pain,



migraine, shingles, intense pain unresponsive to peripheral analgesics, pancreatitis, nephritic or biliarycolic, or post-operative or post-traumatic pain, wherein is administered to said subject an effective amount of a compound of formula I as defined in any one of Claims 1 to 4.

5

DATED this 22 day of May 1991.

ROUSSEL-UCLAF

By its Patent Attorneys

CALLINAN LAWRIE

