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**New heterocyclic compounds, a process for their preparation and pharmaceutical compositions containing them**

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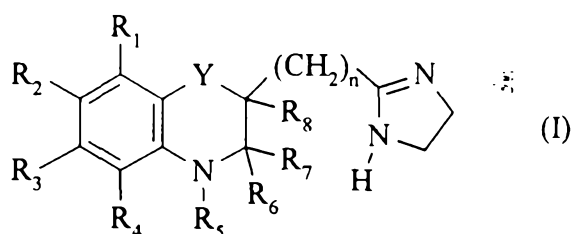
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## ABSTRACT

**NEW HETEROCYCLIC COMPOUNDS,  
A PROCESS FOR THEIR PREPARATION  
AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

Compound of formula (I) :



wherein :

Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> and n are as defined in the description.

Medicaments.

AUSTRALIA

Patents Act 1990

**ORIGINAL**  
**COMPLETE SPECIFICATION**  
**STANDARD PATENT**

Application Number:

Lodged:

Invention Title:

NEW HETEROCYCLIC COMPOUNDS, A PROCESS FOR THEIR  
PREAPRATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING  
THEM

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

The invention relates to new heterocyclic compounds, to a process for their preparation and to pharmaceutical compositions containing them.

The new compounds are characterised structurally by the presence of an imidazoline nucleus substituted by a heterocyclic structure. Some compounds of that type have been described in the literature for their  $\alpha_2$ -antagonist properties and for their usefulness in the treatment of depression (R.C.M. Butler *et al.*, J. Heterocyclic Chem., 1985, 22, 177 ; EP 92328 ; EP 58006 ; EP 74711).

The compounds of the present invention, on the other hand, have a very great affinity for imidazoline receptors, which is particularly valuable for the development of new pharmacologically active substances.

There have recently been found in the central nervous system specific binding sites for compounds having an imidazoline structure (P. Bousquet *et al.*, Biochem. Pharmacol., 1983, 32, 1459 ; J. Pharmacol. Exp. Ther., 1984, 230, 232), different from histamine receptors (P. Emsberger *et al.* Soc. Neurosci. Abstr., 1986, 12, 1334). Those receptors have been characterised at the level of the *nucleus reticularis lateralis*, in the rostroventral portion of the medulla oblongata (G. Brica *et al.*, Eur. J. Pharmacol., 1989, 162, 1), are distributed heterogeneously in the brain (P. Emsberger *et al.*, J. Pharmacol. Exp. Ther., 1990, 253, 408), and are also present at the peripheral level (P. Emsberger *et al.*, Am. J. Hypertens., 1990, 3, 90 ; J. E. Piletz *et al.*, Biochem. Pharmacol., 1991, 42, 346). Two receptor sub-types, I<sub>1</sub> and I<sub>2</sub>, have been identified (M.C. Michel *et al.*, Trends Pharmacol. Sci., 1992, 13, 369) according to their ability to bind clonidine (sub-type I<sub>1</sub>) and idazoxan (sub-type I<sub>2</sub>).

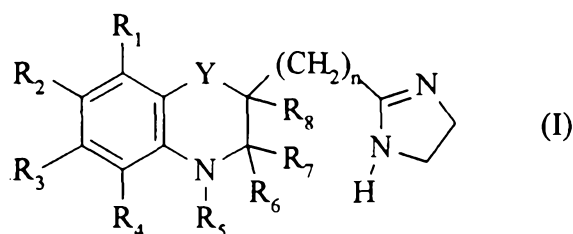
Those receptors appear to be strongly implicated, together with  $\alpha_2$ -adrenoreceptors, in the vasodepressive and anti-hypertensive action of certain compounds such as clonidine and rilmenidine (G. Brica *et al.* Eur. J. Pharmacol., 1989, 162, 1 ; R.E. Gomez *et al.* Eur. J. Pharmacol., 1991, 195, 181). Their role in stimulating the release of insulin by the  $\beta$  cells

of the pancreas has also been demonstrated (Schutz *et al.*, Naunyn-Schniedeberg's Arch. Pharmacol., 1989, 340, (6/712). It has also been shown that imidazoline receptor ligands can be especially valuable in the treatment of psychiatric and neurological disorders (D.S. Nutt *et al.*, Annals New York Academy of Sciences, 1995, 125).

The compounds of the invention have a novel structure which surprisingly provides them with very great affinity for imidazoline receptors. They are thus able to be used in the treatment of pathologies associated with disturbances in the functioning of those receptors, such as cardio-vascular diseases and arterial hypertension, diabetes, obesity, and psychiatric and neurological disorders, such as depression, Parkinson's disease, anorexia, Alzheimer's disease, etc..

The compounds of the invention are especially useful in the treatment of cardiovascular diseases and arterial hypertension.

More specifically, the present invention relates to compounds of formula (I) :



wherein :

- n is 0 or 1,
- Y represents an oxygen or sulphur atom or a CH<sub>2</sub> group,
- R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub>, which may be identical or different, each represent a hydrogen or halogen atom or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy, linear or branched (C<sub>1</sub>-C<sub>6</sub>) hydroxyalkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)trihaloalkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl-carbonyl, formyl, cyano, carboxy, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy-carbonyl, nitro or optionally substituted amino group, or, (R<sub>1</sub>-R<sub>2</sub>) or (R<sub>2</sub>-R<sub>3</sub>) or (R<sub>3</sub>-R<sub>4</sub>) form with the carbon atoms bearing them an optionally substituted saturated or unsaturated 5- or 6-membered ring,
- R<sub>5</sub> represents a hydrogen atom, a (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl group or a linear or branched (C<sub>1</sub>-

C<sub>6</sub>)alkyl group optionally substituted by a group selected from (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl and optionally substituted phenyl,

or, with R<sub>4</sub>, forms a saturated or unsaturated 5-, 6- or 7-membered ring optionally substituted by one or more identical or different groups selected from : linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy, oxo, and optionally substituted amino,

- R<sub>6</sub> and R<sub>7</sub> each represent a hydrogen atom or together form an oxo group,
- R<sub>x</sub> represents a halogen or hydrogen atom or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkenyl, hydroxy, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy (optionally substituted by an amino, pyrrolyl or piperidinyl group), (C<sub>3</sub>-C<sub>7</sub>)cycloalkyloxy, optionally substituted phenyloxy or optionally substituted benzyloxy group; or, with R<sub>7</sub>, forms a bond.

with the proviso that :

- when n is 0, Y represents an oxygen atom and each of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>x</sub> represents a hydrogen atom, then R<sub>5</sub> is other than a hydrogen atom or a methyl, ethyl or benzyl group,
- when n is 0, Y represents a sulphur atom and each of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>x</sub> represents a hydrogen atom, then R<sub>5</sub> is other than a hydrogen atom,

their N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

"Optionally substituted amino group" is understood to mean an amino group substituted by one or two groups, which may be identical or different, selected from linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, optionally substituted phenyl and optionally substituted benzyl.

The term "optionally substituted", applied to the groups phenyloxy, benzyloxy, phenyl and benzyl and also to the term "5- or 6-membered ring", means that those groups may be substituted by one or more substituents, identical or different, selected from halogen, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy and linear or branched (C<sub>1</sub>-C<sub>6</sub>)trihaloalkyl.

Amongst the pharmaceutically acceptable acids, there may be mentioned by way of non-limiting example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, methanesulphonic acid, camphoric acid, oxalic acid, etc..

Amongst the pharmaceutically acceptable bases, there may be mentioned by way of non-limiting example sodium hydroxide, potassium hydroxide, triethylamine, *tert*-butylamine, etc..

The invention relates especially to compounds of formula (I) wherein n is 0.

The preferred compounds of the invention are those wherein Y represents an oxygen atom. Other preferred compounds of the invention are those wherein Y represents a sulphur atom.

In the compounds of formula (I), preferably each of R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> represents a hydrogen atom.

In the compounds of formula (I), preferably three of the groups R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are identical and each of the three represents a hydrogen atom, the remaining group being as defined in formula (I).

Other preferred compounds of formula (I) are those wherein (R<sub>1</sub>-R<sub>2</sub>) or (R<sub>2</sub>-R<sub>3</sub>) or (R<sub>3</sub>-R<sub>4</sub>) form with the carbon atoms bearing them an optionally substituted saturated or unsaturated 5- or 6-membered ring, for example a phenyl or cyclohexyl ring.

In the compounds of formula (I), a preferred group for R<sub>8</sub> is a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group.

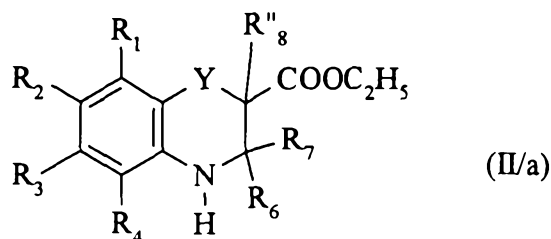
In the compounds of formula (I), a preferred group for R<sub>5</sub> is a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group.

In the compounds of formula (I), especially,  $R_4$  and  $R_5$  together form an optionally substituted saturated or unsaturated 5-, 6- or 7-membered ring.

More especially, the invention relates to compounds of formula (I) wherein Y represents an oxygen atom, n is 0, each of  $R_6$ ,  $R_7$  and  $R_8$  represents a hydrogen atom, each of  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$ , which may be identical or different, represents a hydrogen or halogen atom or a linear or branched  $(C_1-C_6)$ alkyl,  $(C_3-C_7)$ cycloalkyl, linear or branched  $(C_1-C_6)$ alkoxy, hydroxy, linear or branched  $(C_1-C_6)$  hydroxyalkyl, linear or branched  $(C_1-C_6)$ trihaloalkyl, linear or branched  $(C_1-C_6)$ alkyl-carbonyl, formyl, cyano, carboxy, linear or branched  $(C_1-C_6)$ alkoxy-carbonyl, nitro or optionally substituted amino group, or,  $(R_1-R_2)$  or  $(R_2-R_3)$  or  $(R_3-R_4)$  form with the carbon atoms bearing them an optionally substituted saturated or unsaturated 5- or 6-membered ring, whilst  $R_5$  represents a linear or branched  $(C_1-C_6)$ alkyl group or, with  $R_4$ , forms a saturated or unsaturated 5-, 6- or 7-membered ring.

The invention relates also to a process for the preparation of compounds of formula (I), characterised in that:

- when, in the desired compound of formula (I),  $R_4$  and  $R_5$  do not together form a ring, there is used as starting material a compound of formula (II/a) :



wherein  $R''_8$  represents a hydrogen atom or, with  $R_7$ , forms a bond and Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,

$R_6$  and  $R_7$  are as defined for formula (I),

which is treated with either:

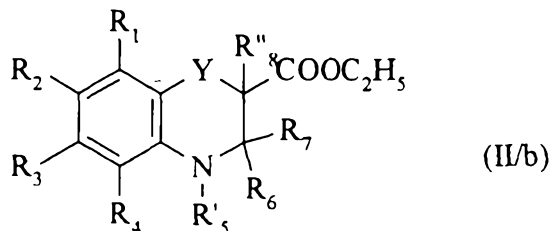
↳ a compound of formula (III) :





wherein X represents a halogen atom and R'<sub>5</sub> represents a (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl group or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group optionally substituted by a (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl or optionally substituted phenyl group,

to yield a compound of formula (II/b) :



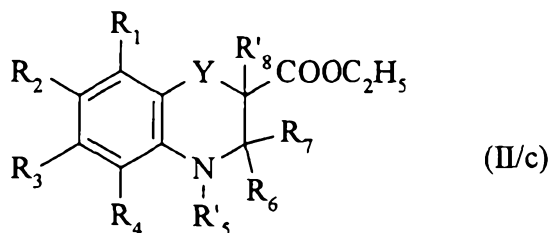
wherein Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R'<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R''<sub>8</sub> are as defined above,

which may, when R''<sub>8</sub> represents a hydrogen atom, be subjected to the action of a halogenating agent, or to the action of a strong base followed by treatment with a compound of formula (IV) :



wherein X represents a halogen atom and R'<sub>8</sub>, which is other than a hydrogen atom, has the same meaning as R<sub>8</sub> for formula (I),

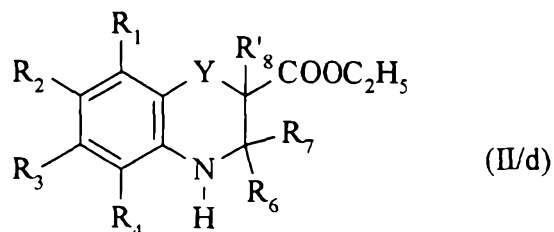
to yield a compound of formula (II/c) :



wherein Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R'<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R'<sub>8</sub> are as defined above,

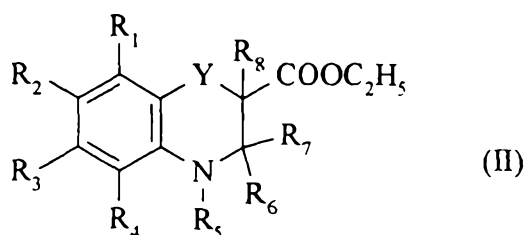
or, when, in the compound of formula (II/a) used, R''<sub>8</sub> represents a hydrogen atom, with a compound of formula (IV) as defined above, after treatment with a strong base,

to yield a compound of formula (II/d) :



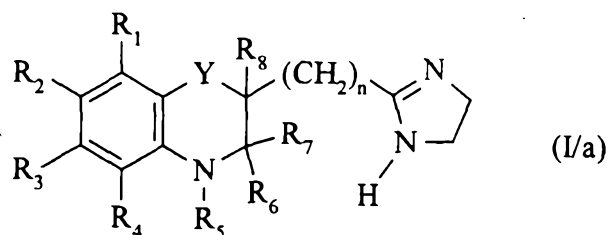
wherein Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub> and R'<sub>8</sub> are as defined above,

which compounds (II/a), (II/b), (II/c) and (II/d) constitute the totality of the compounds of formula (II) :



wherein Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are as defined above,

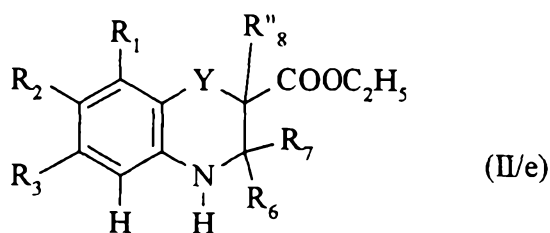
which are treated, optionally after homologization of the chain that carries the ester function, with ethylenediamine to yield a compound of formula (I/a) :



which is a particular case of the compounds of formula I wherein Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> and n have the same meanings as for formula (I), it being understood that R<sub>4</sub> and R<sub>5</sub> do not together form a ring,

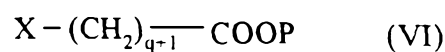
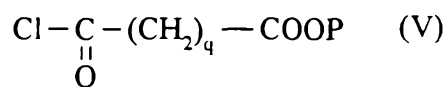
or,

- when, in the desired compound of formula (I), R<sub>4</sub> and R<sub>5</sub> together form a ring, there is used as starting material a compound of formula (II/e) :



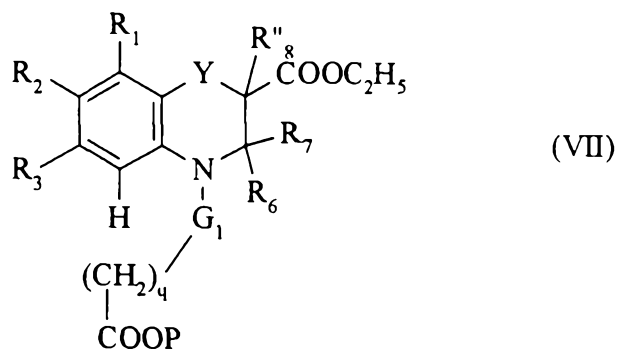
wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_6$ ,  $R_7$  and  $R''_8$  are as defined above,

which is treated with a compound of formula (V) or (VI) :



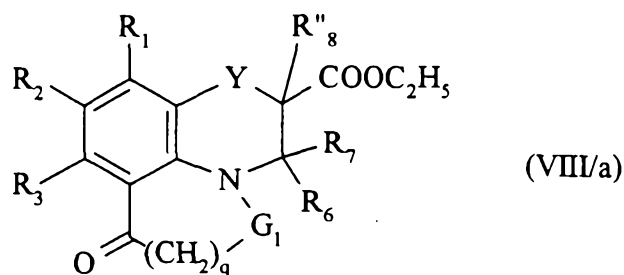
5 wherein X represents a halogen atom or a leaving group, P represents a group that masks the acid function, and q is an integer 0, 1 or 2,

to yield a compound of formula (VII) :



wherein  $G_1$  represents a  $\text{CH}_2$  or  $\text{CO}$  group, and q, P, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_6$ ,  $R_7$  and  $R''_8$  have the same meanings as above,

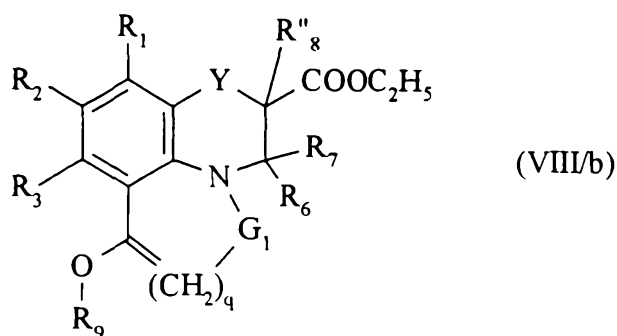
10 which, after freeing of the acid function and cyclisation, yields a compound of formula (VIII/a) :



wherein Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_6$ ,  $R_7$ ,  $R''_8$ ,  $G_1$  and q have the same meanings as above,

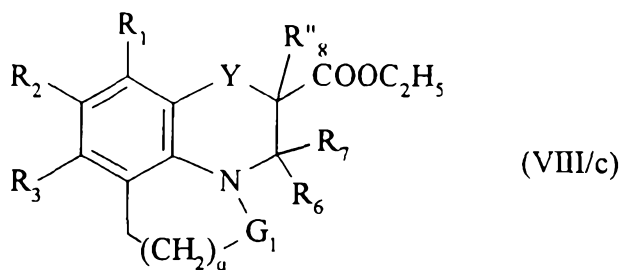
15 which compound (VIII/a),

- can be converted, after treatment with an alkyl halide, to a compound of formula (VIII/b)



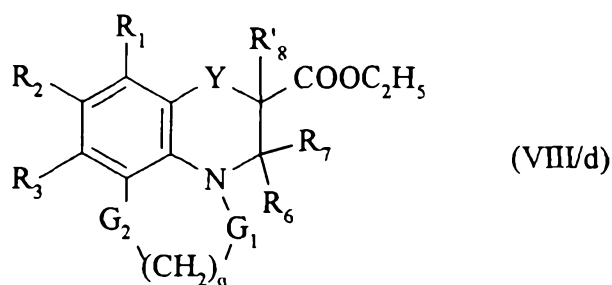
wherein  $R_9$  represents a linear or branched ( $C_1$ - $C_6$ )alkyl group, and  $Y$ ,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_6$ ,  $R_7$ ,  $R''_8$ ,  $G_1$  and  $q$  have the same meanings as above,

5 - or can be reduced to yield a compound of formula (VIII/c) :



wherein  $Y$ ,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_6$ ,  $R_7$ ,  $R''_8$ ,  $G_1$  and  $q$  are as defined above,

10 it being possible for each of the compounds (VIII/a), (VIII/b) and (VIII/c) to be treated, when that is compatible with the substituents present on the molecule, with a strong base and then with a compound of formula (IV) as defined above to yield a compound of formula (VIII/d) :

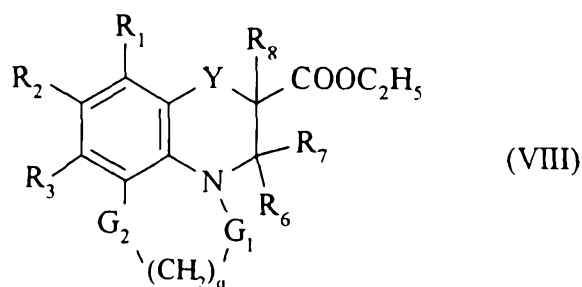


wherein  $G_2$  represents a  $CH_2$  or  $CO$  group or, with the carbon atom of the adjacent methylene, forms a group



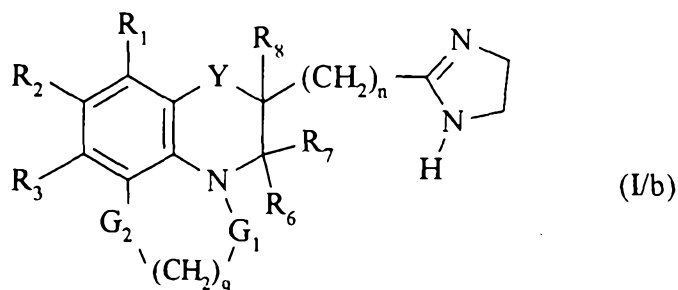
and Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, R'<sub>8</sub>, R<sub>9</sub>, G<sub>1</sub> and q are as defined above,

which compounds (VIII/a), (VIII/b), (VIII/c) and (VIII/d) constitute the totality of the compounds of formula (VIII) :



5 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, G<sub>1</sub>, G<sub>2</sub> and q are as defined above,

and which are treated, optionally after homologization of the chain that carries the ester function, with ethylenediamine to yield a compound of formula (I/b) :



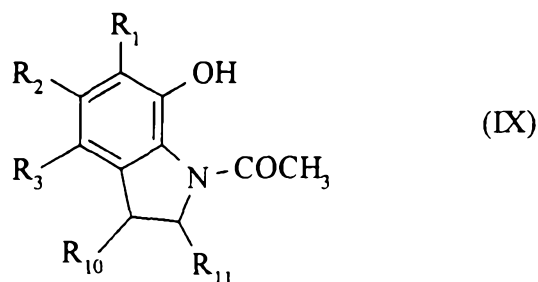
10 which is a particular case of the compounds of formula (I) wherein Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, G<sub>1</sub>, G<sub>2</sub>, n and q are as defined above,

which compounds (I/a) and (I/b) :

- are optionally purified in accordance with a conventional purification technique,
- optionally separated into their isomers in accordance with a conventional separation technique, and
- 15 - converted, where appropriate, into their N-oxides or into addition salts thereof with a pharmaceutically acceptable acid or base.

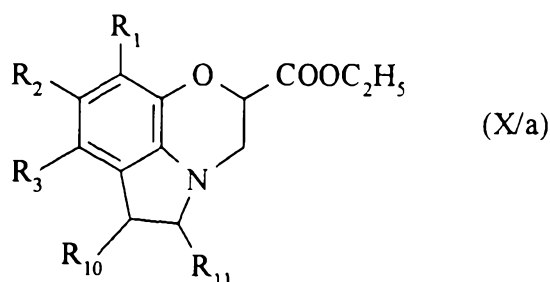
In order to achieve a synthesis that is more appropriate to certain desired compounds of formula (I), it is possible to use a number of variants of the process indicated above.

One of those variants consists of using as starting material a compound of formula (IX) :



wherein  $R_{10}$  and  $R_{11}$  simultaneously represent a hydrogen atom or together form a bond, and  $R_1$ ,  $R_2$  and  $R_3$  have the same meanings as for formula (I) ,

- 5 which, after deprotection of the indole nitrogen atom, is treated with ethyl 2,3-dibromopropionate in a basic medium to yield a compound of formula (X/a) :



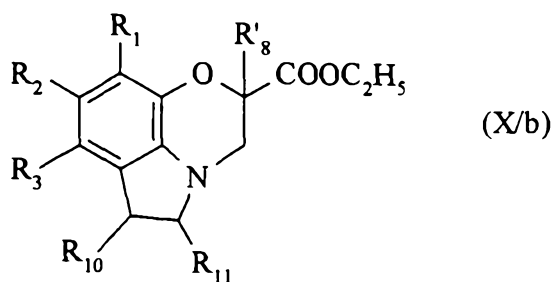
wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{10}$  and  $R_{11}$  are as defined above,

which can be reacted with a strong base and with a compound of formula (IV) :



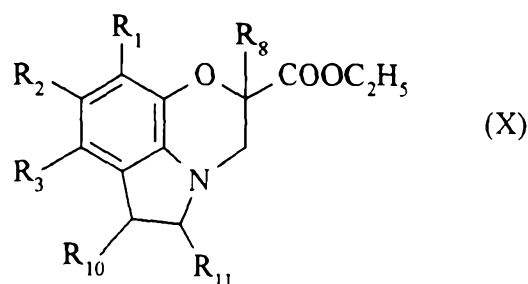
wherein X represents a halogen atom and  $R'_8$ , which is other than a hydrogen atom, has the same meaning as  $R_8$  for formula (I),

to yield a compound of formula (X/b) :



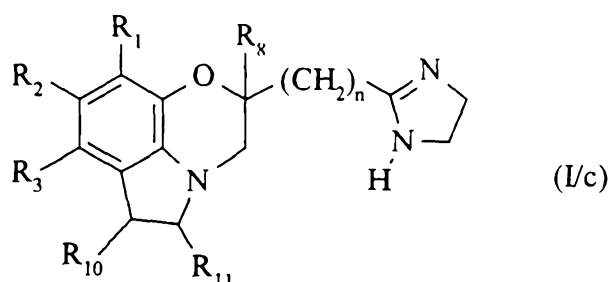
wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R'_8$ ,  $R_{10}$  and  $R_{11}$  are as defined above,

which compounds (X/a) and (X/b) constitute the totality of the compounds of formula (X):



wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_8$ ,  $R_{10}$  and  $R_{11}$  are as defined above,

which are treated, after optional homologization of the chain that carries the ester function,  
5 with ethylenediamine to yield a compound of formula (I/c) :



which is a particular case of the compounds of formula (I) wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_8$ ,  $R_{10}$ ,  $R_{11}$  and  $n$  are as defined above,

which compound (I/c) :

- 10
- is optionally purified in accordance with a conventional purification technique,
  - optionally separated into its isomers in accordance with a conventional separation technique, and
  - converted, where appropriate, into its N-oxide or into an addition salt thereof with a pharmaceutically acceptable acid or base,
- 15
- it being understood that when  $R_{10}$  and  $R_{11}$  each represent a hydrogen atom, they can be converted into a bond using a conventional technique of aromatization, at any stage of the process.

The invention relates also to pharmaceutical compositions comprising as active ingredient

at least one compound of formula (I) on its own or in combination with one or more inert non-toxic excipients or carriers.

Amongst the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, etc..

The useful dosage varies according to the age and weight of the patient, the nature and severity of the affection and the mode of administration, which may be nasal, rectal, parenteral or oral. The unit dose generally ranges from 1 to 500 mg for treatment in from 1 to 3 administrations per 24 hours.

The following Preparations (Preparations A-D) yield synthesis intermediates for use in the preparation of the compounds of the invention.

**Preparation A : 2-Ethoxycarbonyl-6-fluoro-2,3-dihydro-2H-1,4-benzoxazine**

**Step a : 4-Fluoro-2-aminophenol**

47.7 mmol (10.8 g) of  $\text{SnCl}_2 \cdot \text{H}_2\text{O}$  are added to a solution of 7.96 mmol (1.26 g) of 4-fluoro-2-nitrophenol in 20 ml of ethanol. The solution is stirred at reflux for 2 hours. After cooling, the reaction mixture is hydrolysed over ice and rendered alkaline with a 30% sodium hydroxide solution. The mixture is extracted 4 times with ethyl acetate, and the combined organic phases are washed with an aqueous saturated sodium chloride solution and then dried over magnesium sulphate and concentrated to yield the expected product.

**Step b : 2-Ethoxycarbonyl-6-fluoro-2,3-dihydro-2H-1,4-benzoxazine**

The expected product is obtained in accordance with the process described in J. Heterocyclic Chem., 1985, 22, 177, starting from the compound described in the preceding Step.



**Preparation B : 2-Ethoxycarbonyl-6-trifluoromethyl-3,4-dihydro-2H-1,4-benzoxazine**

The expected product is obtained in accordance with the process described in Preparation A using 4-trifluoromethyl-2-nitrophenol as starting material.

**Preparation C : 2-Ethoxycarbonyl-8-trifluoromethyl-3,4-dihydro-2H-1,4-benzoxazine**

5 The expected product is obtained in accordance with the process described in Preparation A using 6-trifluoromethyl-2-nitrophenol as starting material.

**Preparation D : 2-Ethoxycarbonyl-7-methoxy-3,4-dihydro-2H-1,4-benzoxazine**

The expected product is obtained in accordance with the process described in Preparation A using 4-methoxy-2-nitrophenol as starting material.

10 The following Examples illustrate the invention but do not limit it in any way. The structures of the compounds described have been confirmed by the customary spectroscopic techniques.

**EXAMPLE 1 : 2-(4,5-Dihydro-1H-2-imidazolyl)-4-propyl-3,4-dihydro-2H-1,4-benzoxazine oxalate****Step a : 2-Ethoxycarbonyl-4-propyl-2,3-dihydro-2H-1,4-benzoxazine**

27.8 mmol (3.84 g) of potassium carbonate and 18.5 mmol (1.8 ml) of iodopropane are added to 9.2 mmol (1.92 g) of 2-ethoxycarbonyl-3,4-dihydro-2H-1,4-benzoxazine (described in J. Heterocyclic Chem., 1985, 22, 177) in 20 ml of acetonitrile and 2 ml of hexamethylphosphoramide. The reaction mixture is refluxed for 18 hours. After cooling and filtration, the filtrate is evaporated, taken up in a water/ethyl acetate mixture and extracted. The organic phase is dried, concentrated and purified by chromatography on silica gel using an ethyl acetate/petroleum ether mixture (1/9) as eluant to yield the expected compound.

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-4-propyl-3,4-dihydro-2H-1,4-benzoxazine**

A solution of 18.8 mmol (1.13 g) of ethylenediamine in 50 ml of toluene is added to 18.8 mmol (9.4 ml) of 2M trimethylaluminium in toluene whilst maintaining the temperature at below 10°C. A solution of 11 mmol of the compound described in Step a in 10 ml of toluene is added, and the reaction mixture is refluxed for 3 hours. After cooling, a water/methanol/dichloromethane mixture (1/1/1) is added, and the mixture is then refluxed for a further 15 minutes. After cooling and filtration over Celite, the filtrate is concentrated. The residue is taken up in a water/dichloromethane mixture and extracted. The organic phase is dried, concentrated and purified by chromatography on silica gel using a dichloromethane/methanol/triethylamine mixture (98/2/1) as eluant to yield the title compound.

The corresponding oxalate is obtained by the action of a titrated solution of oxalic acid in ethanol.

Melting point (base) : 138-140°C

Elemental microanalysis :

|              | C     | H    | N     |
|--------------|-------|------|-------|
| % calculated | 57.29 | 6.32 | 12.53 |
| % found      | 57.39 | 6.33 | 12.39 |

**EXAMPLE 2 : 2-(4,5-Dihydro-1H-2-imidazolyl)-4,6-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

**Step a : 2-Ethoxycarbonyl-4,6-dimethyl-3,4-dihydro-2H-1,4-benzoxazine**

The expected product is obtained in accordance with the process described in Example 1, Step a, replacing iodopropane by iodomethane and using 2-ethoxycarbonyl-6-methyl-3,4-dihydro-2H-1,4-benzoxazine (prepared in accordance with the process described in J. Heterocyclic Chem., 1985, 22, 177, starting from 2-hydroxy-5-methylaniline) as starting material.

**Step b :** *2-(4,5-Dihydro-1H-2-imidazolyl)-4,6-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate*

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

**Elemental microanalysis :**

|              | C     | H    | N     |
|--------------|-------|------|-------|
| % calculated | 56.07 | 5.96 | 13.08 |
| % found      | 55.86 | 5.89 | 12.80 |

**EXAMPLE 3 :** *2-(4,5-Dihydro-1H-2-imidazolyl)-4,5-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate*

**Step a :** *4,5-Dimethyl-2-ethoxycarbonyl-3,4-dihydro-2H-1,4-benzoxazine*

The expected product is obtained in accordance with the process described in Example 1, Step a, replacing iodopropane by iodomethane and using 2-ethoxycarbonyl-5-methyl-3,4-dihydro-2H-1,4-benzoxazine (prepared in accordance with the process described in J. Heterocyclic Chem., 1985, 22, 177, starting from 2-hydroxy-4-methylaniline) as starting material.

**Step b :** *2-(4,5-Dihydro-1H-2-imidazolyl)-4,5-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate*

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

**Melting point (base) :** 132-134°C

**Elemental microanalysis :**

|              | C     | H    | N     |
|--------------|-------|------|-------|
| % calculated | 56.07 | 5.96 | 13.08 |
| % found      | 56.07 | 5.98 | 12.98 |

**EXAMPLE 4: 6-Chloro-2-(4,5-dihydro-1H-2-imidazolyl)-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

**Step a : 6-Chloro-2-ethoxycarbonyl-4-methyl-2H-1,4-benzoxazine**

The expected product is obtained in accordance with the process described in Example 1, Step a, replacing iodopropane by iodomethane and using 6-chloro-2-ethoxycarbonyl-3,4-dihydro-2H-1,4-benzoxazine (prepared in accordance with the process described in J. Heterocyclic Chem., 1985, 22, 177, starting from 2-hydroxy-4-chloroaniline) as starting material.

**Step b : 6-Chloro-2-(4,5-dihydro-1H-2-imidazolyl)-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

Melting point (base) : 170-172°C

Elemental microanalysis :

|              | C     | H    | N     |
|--------------|-------|------|-------|
| % calculated | 49.20 | 4.72 | 12.30 |
| % found      | 49.17 | 4.70 | 12.27 |

**EXAMPLE 5 : 2-(4,5-Dihydro-1H-2-imidazolyl)-2,4-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

**Step a : 2,4-Dimethyl-2-methoxycarbonyl-3,4-dihydro-2H-1,4-benzoxazine**

20 ml of 5% KOH are added to 11.3 mmol (2.5 g) of 2-ethoxycarbonyl-4-methyl-3,4-dihydro-2H-1,4-benzoxazine (described in J. Heterocyclic Chem., 1985, 22, 177) in 10 ml of ethanol and 10 ml of tetrahydrofuran. The reaction mixture is stirred at room temperature for 1 hour. The solvent is evaporated off, and the resulting residue is taken up

in an ethyl acetate/water mixture, at acidic pH, and extracted. The organic phase is dried and concentrated. The residue is then dissolved in 90 ml of tetrahydrofuran and the temperature is reduced to -50°C before the addition of 45.2 mmol (22.6 ml) of lithium diisopropylamide as a 2M solution in tetrahydrofuran. The reaction mixture is stirred for 2 hours at -50°C, and then 45.2 mmol (2.7 ml) of iodomethane are added and the temperature is brought back up to 25°C in the course of 2 hours. After hydrolysis, the mixture is acidified to pH = 4 and extracted with ethyl acetate. The organic phase is dried and concentrated. The residue is then dissolved in 150 ml of methanol in the presence of *para*-toluenesulphonic acid. The reaction mixture is heated at reflux for 18 hours. The solvent is evaporated off, and the mixture is taken up in an ethyl acetate/water mixture and extracted. The organic phase is dried, concentrated and purified by chromatography on silica gel using an ethyl acetate/petroleum ether mixture (3/7) as eluant to yield the expected compound.

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-2,4-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

Elemental microanalysis :

|              | C     | H    | N     |
|--------------|-------|------|-------|
| % calculated | 56.07 | 5.96 | 13.08 |
| % found      | 56.40 | 6.10 | 12.55 |

**EXAMPLE 6 : 2-(4,5-Dihydro-1H-2-imidazolyl)-4-methyl-2-propyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

**Step a : 2-Methoxycarbonyl-4-methyl-2-propyl-3,4-dihydro-2H-1,4-benzoxazine**

The expected product is obtained in accordance with the process described in Example 5, Step a, replacing iodomethane by 1-iodopropane.

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-4-methyl-2-propyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound obtained in the preceding Step.

5 **Elemental microanalysis :**

|              | C     | H    | N     |
|--------------|-------|------|-------|
| % calculated | 58.44 | 6.63 | 12.03 |
| % found      | 58.67 | 6.79 | 12.01 |

10 **EXAMPLE 7 : 2-(4,5-Dihydro-1H-2-imidazolyl)-2,4-dimethyl-3,4-dihydro-2H-1,4-benzoxazin-3-one**

**Step a : 2,4-Dimethyl-2-ethoxycarbonyl-3,4-dihydro-2H-1,4-benzoxazin-3-one**

15 5.5 mmol (1.2 g) of 2-ethoxycarbonyl-3,4-dihydro-2H-1,4-benzoxazin-3-one (described in C.R. Acad. Sci. Paris Series C, 1969, 269, 154) in 5 ml of dimethylformamide are added at 0 °C to a suspension of 11 mmol (0.44 g) of 60% sodium hydride in 5 ml of dimethylformamide. The reaction mixture is stirred at 0 °C for 30 minutes. 22.2 mmol (1.38 ml) of iodomethane are then added, and the reaction mixture is stirred at room temperature for 1 hour. After hydrolysis and extraction with ethyl acetate, the organic phase is dried, concentrated and purified by chromatography on silica gel using an ethyl acetate/petroleum ether mixture (3/7) as eluant to yield the expected compound.

20 **Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-2,4-dimethyl-3,4-dihydro-2H-1,4-benzoxazin-3-one**

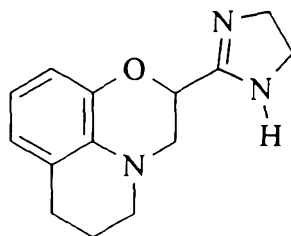
25 The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound obtained in the preceding Step, and stopping at the stage of the free base.

**Melting point : 152-154°C**

Elemental microanalysis :

|              | C     | H    | N     |
|--------------|-------|------|-------|
| % calculated | 63.65 | 6.18 | 17.13 |
| % found      | 63.55 | 6.20 | 17.51 |

5 **EXAMPLE 8 :** 2-(4,5-Dihydro-1*H*-2-imidazolyl)-2,3,6,7-tetrahydro-5*H*[1,4]oxazino[2,3,4-*i,j*]quinoline oxalate



Step a : 4-[2-(Benzyloxycarbonyl)-ethyl]-2-ethoxycarbonyl-3,4-dihydro-2*H*-1,4-benzoxazine

10 2.3 mmol (0.9 ml) of 40% Triton B in water are added at 0°C to 22.6 mmol (5 g) of 2-ethoxycarbonyl-3,4-dihydro-2*H*-1,4-benzoxazine (described in J. Heterocyclic Chem., 1985, 22, 177) and 79 mmol (12.8 g) of benzyl acrylate in 17 ml of toluene. The reaction mixture is refluxed overnight, the solvent is evaporated off and the reaction mixture is heated again for 24 hours. After cooling, hydrolysis and extraction with ethyl acetate, the organic phase is concentrated and purified by chromatography on silica gel using an ethyl acetate/petroleum ether mixture (3/7) as eluant to yield the expected compound.

Step b : 2-Ethoxycarbonyl-7-oxo-2,3,6,7-tetrahydro-5*H*[1,4]oxazino[2,3,4-*i,j*]-quinoline

0.15 g of 10% palladium-on-carbon is added to 4 mmol (1.5 g) of the compound obtained in the preceding Step in 20 ml of ethanol. The reaction mixture is stirred under a hydrogen atmosphere for 4 hours, the catalyst is then filtered off and the filtrate is concentrated. Trifluoroacetic anhydride (8 mmol) is added at 0 °C to the resulting residue dissolved in 10 ml of dichloromethane. The reaction mixture is stirred at room temperature for 5 hours and then hydrolysed. The reaction mixture is adjusted to basic pH using 5*N* sodium hydroxide

solution, and the mixture is extracted with ethyl acetate. The organic phase is concentrated and purified by chromatography on silica gel using dichloromethane as eluant to yield the expected compound.

**Step c : 2-Ethoxycarbonyl-2,3,6,7-tetrahydro-5H[1,4]oxazino[2,3,4-i,j]quinoline**

5 50 mg of 10% palladium-on-carbon are added to 0.76 mmol (0.2 g) of the compound described in the preceding Step in 20 ml of ethanol. The reaction mixture is stirred under a hydrogen atmosphere for 48 hours. The catalyst is filtered off, and the filtrate is concentrated and purified by chromatography on silica gel using dichloromethane as eluant to yield the expected compound.

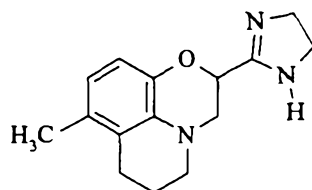
10 **Step d : 2-(4,5-Dihydro-1H-2-imidazolyl)-2,3,6,7-tetrahydro-5H[1,4]oxazino[2,3,4-i,j]quinoline oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

**Elemental microanalysis :**

|              | C     | H    | N     |
|--------------|-------|------|-------|
| % calculated | 57.65 | 5.74 | 12.61 |
| % found      | 57.10 | 5.77 | 12.28 |

**EXAMPLE 9 : 2-(4,5-Dihydro-1H-2-imidazolyl)-8-methyl-2,3,6,7-tetrahydro-5H[1,4]-oxazino[2,3,4-i,j]quinoline oxalate**



**Step a : 4-[2-(Benzyloxycarbonyl)-ethyl]-2-ethoxycarbonyl-6-methyl-3,4-dihydro-2H-1,4-benzoxazine**

The expected product is obtained in accordance with the process described in Example 8,



Step a, starting from 2-ethoxycarbonyl-6-methyl-3,4-dihydro-2H-1,4-benzoxazine.

**Step b :** *2-Ethoxycarbonyl-8-methyl-7-oxo-2,3,6,7-tetrahydro-5H[1,4]oxazino[2,3,4-i,j]quinoline*

The expected product is obtained in accordance with the process described in Example 8,

5 Step b, starting from the compound described in the preceding Step.

**Step c :** *2-(4,5-Dihydro-1H-2-imidazolyl)-8-methyl-2,3,6,7-tetrahydro-5H[1,4]-oxazino[2,3,4-i,j]quinoline oxalate*

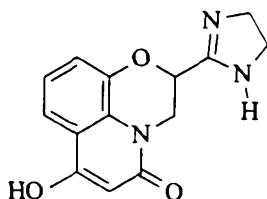
The expected product is obtained in accordance with the process described in Example 1,

Step b, starting from the compound described in the preceding Step.

10 Elemental microanalysis :

|              | C     | H    | N     |
|--------------|-------|------|-------|
| % calculated | 58.78 | 6.09 | 12.10 |
| % found      | 58.50 | 6.11 | 11.92 |

**EXAMPLE 10 :** *2-(4,5-Dihydro-1H-2-imidazolyl)-7-hydroxy-2,3-dihydro-5H[1,4]oxazino-[2,3,4-i,j]quinolin-5-one*



**Step a :** *4-[2-(Benzyloxycarbonyl)-acetyl]-2-ethoxycarbonyl-3,4-dihydro-2H-1,4-benzoxazine*

54.6 mmol (7.6 ml) of triethylamine and 35.9 mmol (7.64 g) of benzyl 3-chloro-3-oxopropanoate are added to 17.1 mmol (3.53 g) of 2-ethoxycarbonyl-3,4-dihydro-2H-1,4-benzoxazine (described in J. Heterocyclic Chem., 1985, 22, 177) in 35 ml of dichloromethane. The reaction mixture is stirred at room temperature for 1 hour. After hydrolysis and extraction with dichloromethane, the organic phase is concentrated and purified by chromatography on silica gel using an ethyl acetate/petroleum ether mixture

(2/8) as eluant to yield the expected compound.

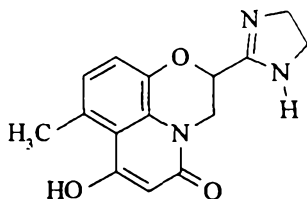
**Step b :** *2-Ethoxycarbonyl-7-hydroxy-2,3-dihydro-5H[1,4]oxazino[2,3,4-i,j]-quinolin-5-one*

The expected product is obtained in accordance with the process described in Example 8, Step b, starting from the compound described in the preceding Step.

**Step c :** *2-(4,5-Dihydro-1H-2-imidazolyl)-7-hydroxy-2,3-dihydro-5H[1,4]oxazino-[2,3,4-i,j]quinolin-5-one*

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step, stopping at the stage of the free base.

**EXAMPLE 11 :** *2-(4,5-Dihydro-1H-2-imidazolyl)-7-hydroxy-8-methyl-2,3-dihydro-5H-[1,4]oxazino[2,3,4-i,j]quinolin-5-one*



**Step a :** *4-[2-(Benzyloxycarbonyl)-acetyl]-2-ethoxycarbonyl-6-methyl-3,4-dihydro-2H-1,4-benzoxazine*

The expected product is obtained in accordance with the process described in Example 10, Step a, using 2-ethoxycarbonyl-6-methyl-3,4-dihydro-2H-1,4-benzoxazine as starting material.

**Step b :** *2-Ethoxycarbonyl-7-hydroxy-8-methyl-2,3-dihydro-5H[1,4]oxazino[2,3,4-i,j]quinolin-5-one*

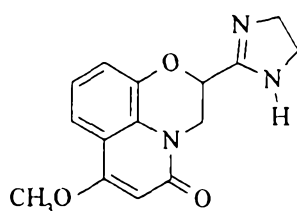
The expected product is obtained in accordance with the process described in Example 8,

Step b, starting from the compound described in the preceding Step.

**Step c :** 2-(4,5-Dihydro-1H-2-imidazolyl)-7-hydroxy-8-methyl-2,3-dihydro-5H[1,4]-oxazino[2,3,4-i,j]quinolin-5-one

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step, stopping at the stage of the free base.

**EXAMPLE 12 :** 2-(4,5-Dihydro-1H-2-imidazolyl)-7-methoxy-2,3-dihydro-5H[1,4]oxazino-[2,3,4-i,j]quinolin-5-one



**Step a :** 2-Ethoxycarbonyl-7-methoxy-2,3-dihydro-5H[1,4]oxazino[2,3,4-i,j]-quinolin-5-one

7.3 mmol (1 g) of potassium carbonate and 5.4 mmol (1 g) of methyl tosylate are added to 3.6 mmol (1 g) of the compound described in Example 10, Step b, in 10 ml of dimethylformamide. The reaction mixture is heated at 50 °C for 1 hour and then hydrolysed and extracted with ethyl acetate. The organic phase is concentrated and purified by chromatography on silica gel using dichloromethane as eluant to yield the expected compound.

**Step b :** 2-(4,5-Dihydro-1H-2-imidazolyl)-7-methoxy-2,3-dihydro-5H[1,4]oxazino-[2,3,4-i,j]quinolin-5-one

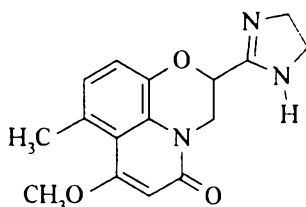
The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step, stopping at the stage of the free base.

**Melting point :** 228-230°C

Elemental microanalysis :

|              | C     | H    | N     |
|--------------|-------|------|-------|
| % calculated | 63.15 | 5.30 | 14.73 |
| % found      | 62.49 | 5.39 | 14.07 |

5 **EXAMPLE 13 : 2-(4,5-Dihydro-1H-2-imidazolyl)-7-methoxy-8-methyl-2,3-dihydro-5H-[1,4]oxazino[2,3,4-*i,j*]quinolin-5-one**



**Step a : 2-Ethoxycarbonyl-7-methoxy-8-methyl-2,3-dihydro-5H[1,4]oxazino[2,3,4-*i,j*]quinolin-5-one**

- 10 The expected product is obtained in accordance with the process described in Example 12, Step a, starting from the compound described in Example 11, Step b.

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-7-methoxy-8-methyl-2,3-dihydro-5H[1,4]-oxazino[2,3,4-*i,j*]quinolin-5-one**

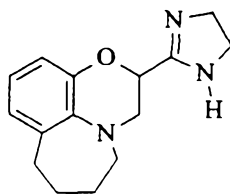
The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step, stopping at the stage of the free base.

Melting point : 222-224°C

Elemental microanalysis :

|              | C     | H    | N     |
|--------------|-------|------|-------|
| % calculated | 64.20 | 5.72 | 14.04 |
| % found      | 64.02 | 5.87 | 13.36 |

**EXAMPLE 14 : 2-(4,5-Dihydro-1H-2-imidazolyl)-1,2,7,8,9,10-hexahydro-10a-aza-3-oxa-cyclohepta[*d,e*]naphthalene oxalate**



***Step a : 4-[3-(Benzyloxycarbonyl)-propionyl]-2-ethoxycarbonyl-3,4-dihydro-2H-1,4-benzoxazine***

The expected product is obtained in accordance with the process described in Example 10, Step a, replacing benzyl 3-chloro-3-oxopropanoate by benzyl 4-chloro-4-oxobutanoate.

***Step b : 4-[3-(Benzyloxycarbonyl)-propyl]-2-ethoxycarbonyl-3,4-dihydro-2H-1,4-benzoxazine***

32.5 mmol (32.5 ml) of  $\text{BH}_3$ .THF (1M solution in tetrahydrofuran) are added to 10.8 mmol (4.3 g) of the compound described in Step a in 20 ml of tetrahydrofuran. The reaction mixture is heated at reflux for 4 hours. After cooling and removal of the solvent by evaporation, the residue is taken up in a water/ethyl acetate mixture and extracted. The organic phase is dried, concentrated and purified by chromatography on silica gel using an ethyl acetate/petroleum ether mixture (3/7) as eluant to yield the expected compound.

***Step c : 2-Ethoxycarbonyl-7-oxo-1,2,7,8,9,10-hexahydro-3-oxa-10a-azacyclohepta[d,e]-naphthalene***

The expected product is obtained in accordance with the process described in Example 8, Step b, starting from the compound described in the preceding Step.

***Step d : 2-Ethoxycarbonyl-1,2,7,8,9,10-hexahydro-3-oxa-10a-azacyclohepta[d,e]-naphthalene***

The expected product is obtained in accordance with the process described in Example 8, Step c, starting from the compound described in the preceding Step.

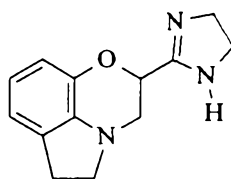
**Step e : 2-(4,5-Dihydro-1H-2-imidazolyl)-1,2,7,8,9,10-hexahydro-3-oxa-10a-azacyclohepta[d,e]naphthalene oxalate.**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

5 **Elemental microanalysis :**

|              | C     | H    | N     |
|--------------|-------|------|-------|
| % calculated | 58.77 | 6.11 | 12.10 |
| % found      | 58.67 | 6.12 | 11.87 |

10 **EXAMPLE 15 : 2-(4,5-Dihydro-1H-2-imidazolyl)-2,3,5,6-tetrahydro  
[1,4]oxazino[2,3,4-h,i]indole oxalate**



**Step a : 7-Hydroxyindoline**

The expected product was obtained in accordance with the process described in J.Chem. Soc. (c), 1966, 344.

15 **Step b : 2-Ethoxycarbonyl-2,3,5,6-tetrahydro[1,4]oxazino[2,3,4-h,i]indole**

0.85 mmol (0.12 ml) of ethyl 2,3-dibromopropionate is added to a solution of 0.8 mmol (0.1 g) of the compound described in the preceding Step, in 2 ml of acetone, in the presence of 2.1 mmol (0.3 g) of potassium carbonate. The reaction medium is heated at reflux for 18 hours. After cooling and filtration, the solvent is evaporated off. The residue is taken up in a water/ethyl acetate mixture and extracted. The organic phase is dried and purified by chromatography on silica gel using an ethyl acetate/petroleum ether mixture (1/9) as eluant to yield the expected compound.

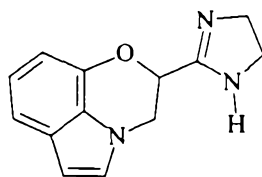
20 **Step c : 2-(4,5-Dihydro-1H-2-imidazolyl)-2,3,5,6-tetrahydro[1,4]oxazino[2,3,4-h,i]-indole oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

Elemental microanalysis :

|   |              | C     | H    | N     |
|---|--------------|-------|------|-------|
| 5 | % calculated | 56.42 | 5.37 | 13.16 |
|   | % found      | 56.24 | 5.42 | 12.96 |

**EXAMPLE 16 : 2-(4,5-Dihydro-1H-2-imidazolyl)-2,3-dihydro[1,4]oxazino[2,3,4-h,i]indole oxalate**



**Step a : 2-Ethoxycarbonyl-2,3-dihydro[1,4]oxazino[2,3,4-h,i]indole**

0.90 mmol (0.204 g) of DDQ is added at 0°C to a solution of 0.86 mmol (0.2 g) of the compound described in Example 15, Step b, in 6 ml of toluene. The reaction mixture is stirred at that temperature for 30 minutes before being hydrolysed. After neutralisation with a 5% sodium hydroxide solution and extraction with ethyl acetate, the combined organic phases are dried over magnesium sulphate and concentrated. Purification by chromatography on silica gel using an ethyl acetate/petroleum ether mixture (1/9) as eluant enables the expected product to be isolated.

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-2,3-dihydro[1,4]oxazino[2,3,4-h,i]indole oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

Melting point : 190-192°C

**EXAMPLE 17 : 2-(4,5-Dihydro-1H-2-imidazolyl)-4,7-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

**Step a : 2-Ethoxycarbonyl-4,7-dimethyl-3,4-dihydro-2H-1,4-benzoxazine**

The expected product is obtained in accordance with the process described in Example 1, Step a, replacing iodopropane by iodomethane and using 2-ethoxycarbonyl-7-methyl-3,4-dihydro-2H-1,4-benzoxazine (prepared in accordance with the method described in J. Heterocyclic Chem., 1985, 22, 177, starting from 2-amino-5-methylphenol) as starting material.

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-4,7-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, using the compound described in the preceding Step as starting material.

Melting point (base) : 106-108°C

**EXAMPLE 18 : 2-(4,5-Dihydro-1H-2-imidazolyl)-4,8-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate****Step a : 2-Ethoxycarbonyl-4,8-dimethyl-3,4-dihydro-2H-1,4-benzoxazine**

The expected product is obtained in accordance with the process described in Example 1, Step a, replacing iodopropane by iodomethane and using as starting material 2-ethoxycarbonyl-8-methyl-2,3-dihydro-2H-1,4-benzoxazine, prepared in accordance with the method described in J. Heterocyclic Chem., 1985, 22, 177, starting from 2-amino-6-methylphenol (described in J. Org. Chem., 1996, 3289).

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-4,8-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

Melting point : 216-218°C



**EXAMPLE 19 : 2-(4,5-Dihydro-1H-2-imidazolyl)-6-methoxy-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

**Step a : 2-Ethoxycarbonyl-6-methoxy-4-methyl-3,4-dihydro-2H-1,4-benzoxazine**

The expected product is obtained in accordance with the process described in Example 1, Step a, replacing iodopropane by iodomethane and using as starting material 2-ethoxycarbonyl-6-methoxy-2,3-dihydro-2H-1,4-benzoxazine, prepared in accordance with the method described in J. Heterocyclic Chem., 1985, 22, 177, starting from 2-amino-4-methoxyphenol (described in J. Org. Chem., 1996, 3289).

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-6-methoxy-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

Melting point : 202-204°C

**EXAMPLE 20 : 2-(4,5-Dihydro-1H-2-imidazolyl)-6-fluoro-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

**Step a : 2-Ethoxycarbonyl-6-fluoro-4-methyl-3,4-dihydro-2H-1,4-benzoxazine**

The expected product is obtained in accordance with the process described in Example 1, Step a, replacing iodopropane by iodomethane and using as starting material the 2-ethoxycarbonyl-6-fluoro-2,3-dihydro-2H-1,4-benzoxazine described in Preparation A.

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-6-fluoro-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1,

Step b, starting from the compound described in the preceding Step.

Melting point : 198-200°C

**EXAMPLE 21 : 2-(4,5-Dihydro-1H-2-imidazolyl)-6-hydroxy-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

1.14 mmol (0.11 ml) of boron tribromide are added to a solution of 0.57 mmol (140 mg) of the compound described in Example 19 in 5 ml of dichloromethane at -10°C. The reaction mixture is heated at reflux for 1 hour. The reaction mixture is hydrolysed and rendered alkaline by a 10% sodium hydroxide solution. After extraction with dichloromethane, the organic phases are combined, dried over magnesium sulphate and concentrated. Purification by chromatography on silica gel using a dichloromethane/triethylamine mixture (100/1) as eluant enables the expected product to be obtained. The corresponding oxalate is obtained by the action of a titrated solution of oxalic acid in ethanol.

**EXAMPLE 22 : 2-(4,5-Dihydro-1H-2-imidazolyl)-4-methyl-6-trifluoromethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

Step a : 2-Ethoxycarbonyl-4-methyl-6-trifluoromethyl-3,4-dihydro-2H-1,4-benzoxazine

The expected product is obtained in accordance with the process described in Example 1, Step a, replacing iodopropane by iodomethane and using as starting material the 2-ethoxycarbonyl-6-trifluoromethyl-3,4-dihydro-2H-1,4-benzoxazine described in Preparation B.

Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-4-methyl-6-trifluoromethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

**EXAMPLE 23 : 2-(4,5-Dihydro-1H-2-imidazolyl)-4-methyl-8-trifluoromethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

**Step a : 2-Ethoxycarbonyl-4-methyl-8-trifluoromethyl-3,4-dihydro-2H-1,4-benzoxazine**

- 5 The expected product is obtained in accordance with the process described in Example 1, Step a, replacing iodopropane by iodomethane and using as starting material 2-ethoxycarbonyl-8-trifluoromethyl-3,4-dihydro-2H-1,4-benzoxazine described in Preparation C.

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-4-methyl-8-trifluoromethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

- 10 The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

**EXAMPLE 24 : 6-Acetyl-2-(4,5-dihydro-1H-2-imidazolyl)-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

**Step a : 6-Acetyl-2-ethoxycarbonyl-4-methyl-3,4-dihydro-2H-1,4-benzoxazine**

- 15 1.6 mmol (0.1 ml) of acetyl chloride and 4 mmol (545 mg) of aluminium chloride are added to a solution of 1.6 mmol (355 mg) of 2-ethoxycarbonyl-4-methyl-3,4-dihydro-2H-1,4-benzoxazine (described in J. Heterocyclic Chem., 1985, 22, 177) in 18 ml of dichloromethane at -10°C. The reaction mixture is stirred at room temperature for 1 hour before being hydrolysed by a cooled aqueous solution of 2M hydrochloric acid. The mixture is extracted with dichloromethane and the organic phase is washed with a saturated solution of NaHCO<sub>3</sub>, dried over magnesium sulphate, concentrated and purified by chromatography on silica gel using a petroleum ether/ethyl acetate mixture (7/3) as eluant to yield the expected product.
- 20

- 25 **Note** : the compound 7-acetyl-2-ethoxycarbonyl-4-methyl-3,4-dihydro-2H-benzoxazine is also isolated.

**Step b : 6-Acetyl-2-(4,5-dihydro-1H-2-imidazolyl)-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

**5      EXAMPLE 25 : 7-Acetyl-2-(4,5-dihydro-1H-2-imidazolyl)-4-methyl-3,4-dihydro-2H-1,4- benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, using as starting material the 7-acetyl-2-ethoxycarbonyl-4-methyl-3,4-dihydro-2H-1,4-benzoxazine isolated in Step a of Example 24.

**10      EXAMPLE 26 : 2-(4,5-Dihydro-1H-2-imidazolyl)-6-formyl-4-methyl-3,4-dihydro-2H-1,4- benzoxazine oxalate**

**Step a : 2-Ethoxycarbonyl-6-formyl-4-methyl-3,4-dihydro-2H-1,4-benzoxazine**

6.5 mmol (0.6 ml) of dichloromethyl methyl ether and 6.5 mmol (0.7 ml) of titanium tetrachloride are added to a solution of 4.3 mmol (950 mg) of 2-ethoxycarbonyl-4-methyl-3,4-dihydro-2H-1,4-benzoxazine (described in J. Heterocyclic Chem., 1985, 22, 177) in 30 ml of dichloromethane at -10°C. Stirring is maintained at from -10°C to 0°C for 2 hours. The reaction mixture is hydrolysed using a water/ice mixture, and extracted with dichloromethane. The organic phase is dried over magnesium sulphate, concentrated and purified by chromatography on silica gel using a petroleum ether/ethyl acetate mixture (7/3) as eluant to yield the title product.

**Note** : the compound 2-ethoxycarbonyl-7-formyl-4-methyl-3,4-dihydro-2H-1,4-benzoxazine is also isolated.

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-6-formyl-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

**EXAMPLE 27 : 2-(4,5-Dihydro-1H-2-imidazolyl)-7-formyl-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

- 5 The expected product is obtained in accordance with the process described in Example 1, Step b, using as starting material the 2-ethoxycarbonyl-7-formyl-4-methyl-3,4-dihydro-2H-1,4-benzoxazine isolated in Step a of Example 26.

**EXAMPLE 28 : 2-(4,5-Dihydro-1H-2-imidazolyl)-7-methoxy-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

- 10 Step a : 2-Ethoxycarbonyl-7-methoxy-4-methyl-3,4-dihydro-2H-1,4-benzoxazine

The expected product is obtained in accordance with the process described in Example 1, Step a, replacing iodopropane by iodomethane and using as starting material the 2-ethoxycarbonyl-7-methoxy-3,4-dihydro-2H-1,4-benzoxazine described in Preparation D.

15 Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-7-methoxy-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

**EXAMPLE 29 : 7-Chloro-2-(4,5-dihydro-1H-2-imidazolyl)-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

- 20 Step a : 7-Chloro-2-ethoxycarbonyl-4-methyl-3,4-dihydro-2H-1,4-benzoxazine

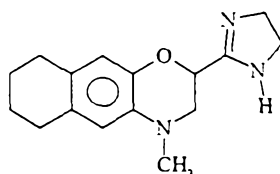
The expected product is obtained in accordance with the process described in Example 1,

Step a, replacing iodopropane by iodomethane and using as starting material 7-chloro-2-ethoxycarbonyl-3,4-dihydro-2H-1,4-benzoxazine (obtained in accordance with the process described in J. Heterocyclic Chem., 1985, 22, 177, starting from 5-chloro-2-hydroxyaniline).

**Step b : 7-Chloro-2-(4,5-dihydro-1H-2-imidazolyl)-4-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

**EXAMPLE 30 : 2-(4,5-Dihydro-1H-2-imidazolyl)-4-methyl-3,4,6,7,8,9-hexahydro-2H-naphtho[2,3-b][1,4]oxazine oxalate**



**Step a : 2-Ethoxycarbonyl-4-methyl-3,4,6,7,8,9-hexahydro-2H-naphtho[2,3-b][1,4]oxazine**

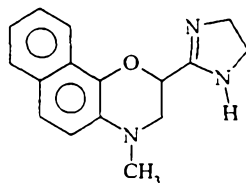
The expected product is obtained in accordance with the process described in Example 1, Step a, replacing iodopropane by iodomethane and using as starting material 2-ethoxycarbonyl-3,4,6,7,8,9-hexahydro-2H-naphtho[2,3-b][1,4]oxazine, prepared in accordance with the process described in J. Heterocyclic Chem., 1985, 22, 177, starting from 3-amino-5,6,7,8-tetrahydro-2-naphthol (described in Chem. Pharm. Bull., 1991, 39, 2896).

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-4-methyl-3,4,6,7,8,9-hexahydro-2H-naphtho[2,3-b][1,4]oxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

Melting point (base) : 120-122°C

**EXAMPLE 31 : 2-(4,5-Dihydro-1H-2-imidazolyl)-4-methyl-3,4-dihydro-2H-naphtho-[1,2-b][1,4]oxazine oxalate**



***Step a : 2-Ethoxycarbonyl-4-methyl-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine***

- 5 The expected product is obtained in accordance with the process described in Example 1, Step a, replacing iodopropane by iodomethane and using as starting material 2-ethoxycarbonyl-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine, prepared in accordance with the process described in J. Heterocyclic Chem., 1985, 22, 177, starting from 2-amino-1-naphthol.

***Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-4-methyl-3,4-dihydro-2H-naphtho-[1,2-b][1,4]oxazine oxalate***

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

Melting point : > 260°C

**EXAMPLE 32 : 4-Cyclobutyl-2-(4,5-dihydro-1H-2-imidazolyl)-6-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 2, replacing iodopropane by cyclobutyl chloride in Step a.

**EXAMPLE 33 : 4-Cyclopropylmethyl-2-(4,5-dihydro-1H-2-imidazolyl)-6-methyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 2,

replacing iodopropane by bromomethylcyclopropane in Step a.

**EXAMPLE 34 : 4-Benzyl-2-(4,5-dihydro-1*H*-2-imidazolyl)-6-methyl-3,4-dihydro-2*H*-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 2, replacing iodopropane by benzyl bromide in Step a.

**EXAMPLE 35 : 2-Allyl-2-(4,5-dihydro-1*H*-2-imidazolyl)-4,6-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 5, replacing iodomethane by allyl bromide in Step a.

**EXAMPLE 36 : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-4,6-dimethyl-2-propyl-3,4-dihydro-2*H*-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 5, replacing iodomethane by iodopropane in Step a.

**EXAMPLE 37 : 2-Bromo-2-(4,5-dihydro-1*H*-2-imidazolyl)-4,6-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine oxalate**

***Step a : 2-Bromo-2-ethoxycarbonyl-4,6-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine***

3.1 mmol (570 mg) of N-bromosuccinimide and 50 mg of benzoyl peroxide are added to a solution of 3.1 mmol (730 mg) of the compound described in Step a of Example 2 in 15 ml of carbon tetrachloride. The reaction mixture is heated at reflux for 5 hours. After cooling, the precipitate is filtered off, and the filtrate is concentrated and purified by chromatography on silica gel to yield the expected compound.



**Step b : 2-Bromo-2-(4,5-dihydro-1H-2-imidazolyl)-4,6-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

**5      EXAMPLE 38 : 2-(4,5-Dihydro-1H-2-imidazolyl)-2-methoxy-4,6-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

**Step a : 2-Ethoxycarbonyl-2-methoxy-4-methyl-3,4-dihydro-2H-1,4-benzoxazine**

2.5 mmol of ethylenediamine are added to a solution of 2.1 mmol of the compound described in Step a of Example 37 in 8 ml of methanol at 0°C. The reaction mixture is stirred for 18 hours at room temperature and then hydrolysed by a saturated NaHCO<sub>3</sub> solution. After extraction with dichloromethane, the combined organic phases are dried over magnesium sulphate and concentrated. The resulting residue is purified by chromatography on silica gel using dichloromethane as eluant to yield the expected compound.

**Step b : 2-(4,5-Dihydro-1H-2-imidazolyl)-2-methoxy-4,6-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

**EXAMPLE 39 : 2-Benzyloxy-2-(4,5-dihydro-1H-2-imidazolyl)-4,6-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 38, replacing methanol by benzyl alcohol in Step a.

**EXAMPLE 40 : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-4,6-dimethyl-4*H*-1,4-benzoxazine oxalate**

**Step a : 4,6-Dimethyl-2-ethoxycarbonyl-4*H*-1,4-benzoxazine**

The expected product is obtained in accordance with the process described in Tetrahedron Lett., 1978, 1059, using the compound described in Example 2, Step a, as starting material.

**Step b : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-4,6-dimethyl-4*H*-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

The compounds of Examples 41 to 44 are obtained in accordance with the process described in Example 40, using as starting material the 3,4-dihydro-2*H*-1,4-benzoxazines described in the preceding Examples.

**EXAMPLE 41 : 6-Chloro-2-(4,5-dihydro-1*H*-2-imidazolyl)-4-methyl-4*H*-1,4-benzoxazine oxalate**

**EXAMPLE 42 : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-4,7-dimethyl-4*H*-1,4-benzoxazine oxalate**

**EXAMPLE 43 : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-5,6-dihydro[1,4]oxazino[2,3,4-*h,i*]indole oxalate**

**EXAMPLE 44 : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-4-methyl-6-trifluoromethyl-4*H*-1,4-benzoxazine oxalate**

The compounds of Examples 45 to 60 are obtained using processes identical to those described in the preceding Examples, starting from substrates having a 2-ethoxycarbonyl-

3,4-dihydro-2*H*-1,4-benzothiazine structure (J. Heterocyclic Chem., 1985, 177, 22 ; *ibid.*, 1980, 17, 377).

**EXAMPLE 45** : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-4,6-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

5 **EXAMPLE 46** : 6-Chloro-2-(4,5-dihydro-1*H*-2-imidazolyl)-4-methyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

**EXAMPLE 47** : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-4-methyl-6-trifluoromethyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

10 **EXAMPLE 48** : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-6-methoxy-4-methyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

**EXAMPLE 49** : 6-Acetyl-(4,5-Dihydro-1*H*-2-imidazolyl)-4-methyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

**EXAMPLE 50** : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-4,7-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

15 **EXAMPLE 51** : 7-Chloro-2-(4,5-dihydro-1*H*-2-imidazolyl)-4-methyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

**EXAMPLE 52** : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-4-methyl-8-trifluoromethyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

20 **EXAMPLE 53** : 4-Cyclopropylmethyl-2-(4,5-dihydro-1*H*-2-imidazolyl)-6-methyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

**EXAMPLE 54** : 4-Benzyl-2-(4,5-dihydro-1*H*-2-imidazolyl)-6-methyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

**EXAMPLE 55** : 6-Chloro-2-(4,5-dihydro-1*H*-2-imidazolyl)-2,4-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

**EXAMPLE 56** : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-4,6-dimethyl-2-propyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

5 **EXAMPLE 57** : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-2,3,5,6-tetrahydro[1,4]thiazino-[2,3,4-*h,i*]indole oxalate

**EXAMPLE 58** : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-2,3,6,7-tetrahydro-5*H*[1,6]thiazino-[2,3,4-*i,j*]quinoline oxalate

10 **EXAMPLE 59** : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-4,6-dimethyl-4*H*-1,4-benzothiazine oxalate

**EXAMPLE 60** : 2-(4,5-Dihydro-1*H*-2-imidazolyl)-4,7-dimethyl-4*H*-1,4-benzothiazine oxalate

The compounds of Examples 61 to 66 are obtained using processes identical to those described in Examples 1 to 44, starting from substrates having a 2-ethoxycarbonyl-1,2,3,4-tetrahydroquinoline structure (Khim. Geterotsikl. Soedin., 1988, (1), 77).

15 **EXAMPLE 61** : 3-(4,5-Dihydro-1*H*-2-imidazolyl)-1-methyl-1,2,3,4-tetrahydroquinoline oxalate

**EXAMPLE 62** : 3-(4,5-Dihydro-1*H*-2-imidazolyl)-1-propyl-1,2,3,4-tetrahydroquinoline oxalate

20 **EXAMPLE 63** : 1-Cyclopropylmethyl-3-(4,5-dihydro-1*H*-2-imidazolyl)-1,2,3,4-tetrahydroquinoline oxalate

**EXAMPLE 64 : 3-(4,5-Dihydro-1*H*-2-imidazolyl)-1-methyl-3-propyl-1,2,3,4-tetrahydro-quinoline oxalate**

**EXAMPLE 65 : 7-Chloro-3-(4,5-dihydro-1*H*-2-imidazolyl-1-methyl-1,2,3,4-tetrahydro-quinoline oxalate**

5 **EXAMPLE 66 : 3-(4,5-Dihydro-1*H*-2-imidazolyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydro-quinoline oxalate**

**EXAMPLE 67 : 2-(4,5-Dihydro-1*H*-2-imidazolylmethyl)-4,6-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine oxalate**

*Step a : 4,6-Dimethyl-2-hydroxymethyl-3,4-dihydro-2*H*-1,4-benzoxazine*

10 20 mmol of the compound described in Step a of Example 2 in 15 ml of tetrahydrofuran are added dropwise to a suspension of 40 mmol of lithium aluminium hydride in 100 ml of tetrahydrofuran at 0°C. The reaction is stirred at room temperature for 1 hour. After hydrolysis, the solution is filtered over Celite and the filtrate is concentrated. The residue is taken up in water and extracted with dichloromethane. The organic phase is dried over magnesium sulphate, concentrated and purified by chromatography on silica gel using a dichloromethane/methanol mixture (98/2) as eluant to yield the expected product.

*Step b : 4,6-Dimethyl-2-iodomethyl-3,4-dihydro-2*H*-1,4-benzoxazine*

13.4 mmol of triphenylphosphine and 27.4 mmol of imidazole are added to a solution of 6.1 mmol of the compound described in the preceding Step in 20 ml of toluene and 10 ml of acetonitrile. The mixture is brought to reflux and then 12.8 mmol of iodine are added. The reaction mixture is stirred at reflux for 1 hour. After cooling, the solvent is evaporated off, and the residue is hydrolysed and then extracted with dichloromethane. The organic phase is dried over magnesium sulphate, concentrated and purified by chromatography on silica gel using a petroleum ether/dichloromethane mixture (5/5) as eluant to yield the expected compound.

**Step c : (4,6-Dimethyl-3,4-dihydro-2H-1,4-benzoxazin-2-yl)acetonitrile**

28 mmol of potassium cyanide are added to a solution of 4 mmol of the compound described in the preceding Step in 6 ml of DMSO. The reaction mixture is stirred at room temperature for 36 hours. The mixture is then diluted with dichloromethane and washed 10 times with water. The organic phase is dried over magnesium sulphate, concentrated and purified by chromatography on silica gel using a dichloromethane/petroleum ether mixture (5/5) as eluant to yield the expected compound.

**Step d : Ethyl 2-(4,6-dimethyl-3,4-dihydro-2H-1,4-benzoxazin-2-yl)acetate**

The compound described in the preceding Step dissolved in a 10% sodium hydroxide solution is heated at reflux for 50 minutes. After cooling, the mixture is acidified by a 2N hydrochloric acid solution and extracted with dichloromethane. The organic phase is dried over magnesium sulphate and concentrated. The residue is dissolved in ethanol in the presence of a catalytic quantity of *para*-toluenesulphonic acid. The reaction mixture is heated at reflux for 18 hours. After cooling, the solvent is evaporated off, and the residue is taken up in an ethyl acetate/water mixture and extracted. The organic phase is dried, concentrated and purified by chromatography on silica gel using a petroleum ether/ethyl acetate mixture (7/8) as eluant to yield the expected product.

**Step e : 2-(4,5-Dihydro-1H-2-imidazolylmethyl)-4,6-dimethyl-3,4-dihydro-2H-1,4-benzoxazine oxalate**

The expected product is obtained in accordance with the process described in Example 1, Step b, starting from the compound described in the preceding Step.

The compounds of Examples 68 to 75 are obtained in accordance with a process identical to that described in Example 67 using as substrate the appropriate compounds described in Examples 1 to 66.

**EXAMPLE 68** : 2-(4,5-Dihydro-1*H*-2-imidazolylmethyl)-2,4-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine oxalate

**EXAMPLE 69** : 2-(4,5-Dihydro-1*H*-2-imidazolylmethyl)-4-methyl-6-trifluoromethyl-3,4-dihydro-2*H*-1,4-benzoxazine oxalate

**EXAMPLE 70** : 4-Cyclopropylmethyl-2-(4,5-dihydro-1*H*-2-imidazolylmethyl)-6-methyl-3,4-dihydro-2*H*-1,4-benzoxazine oxalate

**EXAMPLE 71** : 2-(4,5-Dihydro-1*H*-2-imidazolylmethyl)-4,6-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

**EXAMPLE 72** : 2-(4,5-Dihydro-1*H*-2-imidazolylmethyl)-6-methoxy-4-methyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

**EXAMPLE 73** : 2-(4,5-Dihydro-1*H*-2-imidazolylmethyl)-4,6-dimethyl-2-propyl-3,4-dihydro-2*H*-1,4-benzothiazine oxalate

**EXAMPLE 74** : 3-(4,5-Dihydro-1*H*-2-imidazolylmethyl)-1-methyl-1,2,3,4-tetrahydroquinoline oxalate

**EXAMPLE 75** : 3-(4,5-Dihydro-1*H*-2-imidazolylmethyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline oxalate

## **PHARMACOLOGICAL STUDY OF THE COMPOUNDS OF THE INVENTION**

### **EXAMPLE A** : Measurement of *in vitro* affinity for the I<sub>1</sub> and I<sub>2</sub> receptors

The profile of binding to the imidazoline I<sub>1</sub> and I<sub>2</sub> receptors was determined for the compounds of the invention by evaluating the ability of those compounds to displace specific radioligands of the receptors in question.

The following Table indicates the radioligand used to label each receptor, the compound and the concentration selected to determine the non-specific fraction, and the tissue selected.

| <i>Receptor or site</i> | <i>Radioligand</i>                                           | <i>Non-specific</i>          | <i>Tissue</i>                         |
|-------------------------|--------------------------------------------------------------|------------------------------|---------------------------------------|
| I <sub>1</sub>          | [ <sup>3</sup> H] clonidine<br>+ 10 $\mu$ M<br>noradrenaline | 10 <sup>-5</sup> M clonidine | bovine lateral<br>reticulated nucleus |
| I <sub>2</sub>          | [ <sup>3</sup> H] idazoxan<br>+ 10 $\mu$ M<br>noradrenaline  | 10 <sup>-5</sup> M idazoxan  | renal cortex of rabbit                |

## 5 Results :

The results obtained show the compounds of the invention to have a very high affinity for the I<sub>1</sub> and I<sub>2</sub> receptors, ranging from a few nanomoles to several tens of nanomoles.

By way of example, the compound of Example 2 has K<sub>i</sub> values of 2.2x10<sup>-8</sup>M and 2.0x10<sup>-9</sup>M for the I<sub>1</sub> and I<sub>2</sub> receptors, respectively.

## 10 EXAMPLE B : Demonstration of antihypertensive activity in anaesthetised rats

The tests were carried out in 18-week-old male SHR rats. The rats are anaesthetised with pentobarbital (50 mg/kg i.p.). A catheter is introduced into the left carotid artery so as to record the systolic and diastolic arterial pressure and the heart rate. Only animals whose arterial pressure is higher than or equal to 170 mmHg are included in the study.

15 The parameters to be measured are allowed to stabilise for a period of at least 30 minutes. The test compound, or carrier, is administered intraperitoneally at a dose of 25 mg/kg (the compound is suspended in distilled water containing 0.5 % carboxymethylcellulose, the volume injected being 0.25 ml / 100 g); the control animals are given only the carrier.

20 The measurements taken are expressed in mmHg for the arterial pressure and in bpm for the heart rate, and are compared with the base values.

A compound is considered to be active if the effect recorded on the arterial pressure or on the heart rate is greater than 25 mmHg or 50 bpm, respectively.

## Results

The compounds of the invention appear to be able to lower the arterial pressure and the



heart rate significantly.

**EXAMPLE C : Demonstration of hypotensive activity in anaesthetised rabbits**  
**having normal blood pressure**

The tests were carried out in male rabbits having normal blood pressure. The rabbits are  
 5 anaesthetised with pentobarbital (40 mg/kg; i.v.), artificially ventilated and then curarised.  
 The arterial pressure and the heart rate are measured using a catheter introduced into the  
 right femoral artery.

Before each test, an equal volume of carrier is administered, and the parameters to be  
 measured are allowed to stabilise. The test compound or the carrier is then administered,  
 10 either intracisternally or intravenously, in increasing and cumulative doses of from 1 to 300  
 µg/kg.

The measurements of the instantaneous systolic and diastolic arterial pressure and of the  
 heart rate are carried out from 5 to 10 minutes after the injections.

Results : The results are expressed as a variation percentage relative to the base values.

15 The compounds of the invention appear to lower the arterial pressure and heart rate  
 significantly with a dose-dependent effect.

By way of example, the compound of Example 2 induces a drop of from 19 to 30% in the  
 arterial pressure and of from 9 to 22% in the heart rate.

**EXAMPLE D : Demonstration of antihypertensive activity in conscious rats**

20 The tests were carried out in SHR rats. The animals are anaesthetised. A heparinised  
 catheter is introduced into the left carotid artery and connected to a recording apparatus so  
 as to measure the systolic and diastolic arterial pressure and the heart rate. The animals are  
 returned to their cage and the tests are carried out after 24 hours.

25 The parameters to be measured stabilise during a period of at least 30 minutes, during  
 which a maximum of 1.5 ml of saline solution is injected in such a manner as to optimise  
 the measurements. Only animals whose arterial pressure is higher than or equal to 170  
 mmHg are included in the study.

The test compounds or the carrier are administered orally and the measurements are carried out before the treatment and every ten minutes after treatment, for 4 hours, and then 8 and 24 hours after treatment.

## 5 Results:

The compounds of the invention appear to be able to lower the arterial pressure and the heart rate significantly.

By way of example, the compound of Example 2 given at a dose of 15 mg/kg allowed the  
10 arterial pressure to be normalized.

### EXAMPLE E : Acute toxicity

Acute toxicity was evaluated after oral administration of a dose of 650 mg.kg<sup>-1</sup> to groups each comprising 8 mice (26 ± 2 grammes). The animals were observed at regular  
15 intervals during the course of the first day and daily for the two weeks following treatment. Most of the compounds of the invention appear to be totally atoxic. Most of them bring about no deaths after administration of a dose of 650 mg/kg<sup>-1</sup> and, generally, no disorders are observed after administration of that dose.

### 20 EXAMPLE F : Pharmaceutical composition

Formulation for the preparation of 1000 tablets each containing 10 mg of active ingredient.

|                               |       |
|-------------------------------|-------|
| Compound of Example 2 .....   | 10 g  |
| Hydroxypropyl cellulose ..... | 2 g   |
| 25 Wheat starch .....         | 10 g  |
| Corn starch .....             | 10 g  |
| Lactose .....                 | 100 g |
| Magnesium stearate .....      | 3 g   |
| Talc .....                    | 3 g   |

30

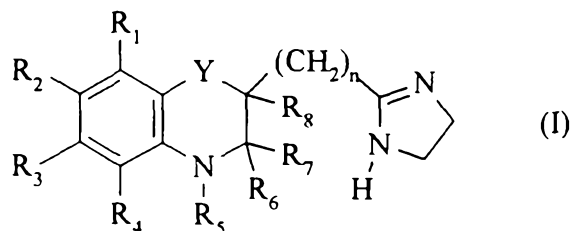
"Comprises/comprising" when used in this specification is taken to specify the presence of stated features, integers, steps or components but does not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.



~~CLAIMS~~xx

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Compounds of formula (I) :



wherein :

- n is 0 or 1,
- Y represents an oxygen or sulphur atom or a CH<sub>2</sub> group,
- R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub>, which may be identical or different, each represent a hydrogen or halogen atom or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy, linear or branched (C<sub>1</sub>-C<sub>6</sub>) hydroxyalkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)trihaloalkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl-carbonyl, formyl, cyano, carboxy, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy-carbonyl, nitro or optionally substituted amino group, or, (R<sub>1</sub>-R<sub>2</sub>) or (R<sub>2</sub>-R<sub>3</sub>) or (R<sub>3</sub>-R<sub>4</sub>) form with the carbon atoms bearing them an optionally substituted saturated or unsaturated 5- or 6-membered ring,
- R<sub>5</sub> represents a hydrogen atom, a (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl group or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group optionally substituted by a group selected from (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl and optionally substituted phenyl, or, with R<sub>4</sub>, forms a saturated or unsaturated 5-, 6- or 7-membered ring optionally substituted by one or more identical or different groups selected from : linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy, oxo, and optionally substituted amino,
- R<sub>6</sub> and R<sub>7</sub> each represent a hydrogen atom or together form an oxo group,
- R<sub>8</sub> represents a halogen or hydrogen atom or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkenyl, hydroxy, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy (optionally substituted by an amino, pyrrolyl or piperidinyl group), (C<sub>3</sub>-C<sub>7</sub>)cycloalkyloxy, optionally substituted phenyloxy or optionally substituted benzyloxy group;

or, with R<sub>7</sub>, forms a bond,

with the proviso that :

- when n is 0, Y represents an oxygen atom and each of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> represents a hydrogen atom, then R<sub>5</sub> is other than a hydrogen atom or a methyl, ethyl or benzyl group,
- when n is 0, Y represents a sulphur atom and each of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> represents a hydrogen atom, then R<sub>5</sub> is other than a hydrogen atom,

their N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

2. Compounds of formula (I) according to claim 1 wherein n is 0, their N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.
3. Compounds of formula (I) according to claim 1 wherein Y represents an oxygen atom, their N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.
4. Compounds of formula (I) according to claim 1 wherein Y represents a sulphur atom, their N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.
5. Compounds of formula (I) according to claim 1 wherein each of R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> represents a hydrogen atom, their N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid.
6. Compounds of formula (I) according to claim 1 wherein R<sub>5</sub> represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group, their N-oxides, their enantiomers and diastereoisomers, and

addition salts thereof with a pharmaceutically acceptable acid.

7. Compounds of formula (I) according to claim 1 wherein three of the groups  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are identical and each of the three represents a hydrogen atom, the remaining group being as defined in formula (I), their N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid.
8. Compounds of formula (I) according to claim 1 wherein  $(R_1-R_2)$  or  $(R_2-R_3)$  or  $(R_3-R_4)$  form with the carbon atoms bearing them an optionally substituted saturated or unsaturated 5- or 6-membered ring, their N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid.
9. Compounds of formula (I) according to claim 1 wherein  $R_4$  and  $R_5$  together form a saturated or unsaturated 5-, 6- or 7-membered ring optionally substituted by one or more of the following groups: linear or branched  $(C_1-C_6)$ alkyl, linear or branched  $(C_1-C_6)$ alkoxy, hydroxy, oxo, optionally substituted amino, their N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.
10. Compounds of formula (I) according to claim 1 wherein Y represents an oxygen atom, n is 0, each of  $R_6$ ,  $R_7$  and  $R_8$  represents a hydrogen atom, each of  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$ , which may be identical or different, represents a hydrogen or halogen atom or a linear or branched  $(C_1-C_6)$ alkyl,  $(C_3-C_7)$ cycloalkyl, linear or branched  $(C_1-C_6)$ alkoxy, hydroxy, linear or branched  $(C_1-C_6)$  hydroxyalkyl, linear or branched  $(C_1-C_6)$ trihaloalkyl, linear or branched  $(C_1-C_6)$ alkyl-carbonyl, formyl, cyano, carboxy, linear or branched  $(C_1-C_6)$ alkoxy-carbonyl, nitro or optionally substituted amino group, or  $(R_1-R_2)$  or  $(R_2-R_3)$  or  $(R_3-R_4)$  form with the carbon atoms bearing them an optionally substituted saturated or unsaturated 5- or 6-membered ring, whilst  $R_5$  represents a linear or branched  $(C_1-C_6)$ alkyl group or, with  $R_4$ , forms a saturated or unsaturated 5-, 6- or 7-membered ring; their N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

11. Compounds of formula (I) according to claim 1 which are :

- 2-(4,5-dihydro-1*H*-2-imidazolyl)-4,6-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine,
  - 2-(4,5-dihydro-1*H*-2-imidazolyl)-4,7-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine,
  - 2-(4,5-dihydro-1*H*-2-imidazolyl)-4,8-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine,
- their N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid.

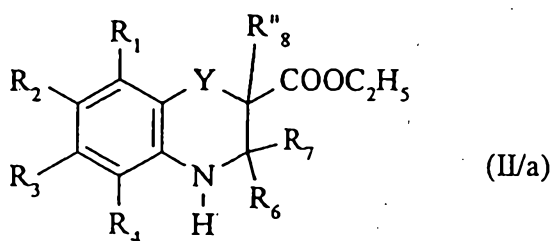
12. Compound of formula (I) according to claim 1 which is 6-chloro-2-(4,5-dihydro-1*H*-2-imidazolyl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine, its N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid.

13- Compounds of formula (I) according to claim 1 which are :

- 2-(4,5-dihydro-1*H*-2-imidazolyl)-2,3,5,6-tetrahydro[1,4]oxazino[2,3,4-*h,i*]indole,
  - 2-(4,5-dihydro-1*H*-2-imidazolyl)-2,3-dihydro[1,4]oxazino[2,3,4-*h,i*]indole,
- their N-oxides, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid.

14. Process for the preparation of compounds of formula (I) according to claim 1 characterised in that:

- when, in the desired compound of formula (I),  $R_4$  and  $R_5$  do not together form a ring, there is used as starting material a compound of formula (II/a):



wherein  $R''_8$  represents a hydrogen atom or, with  $R_7$ , forms a bond and Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_6$  and  $R_7$  are as defined for formula (I),

which is treated with either:

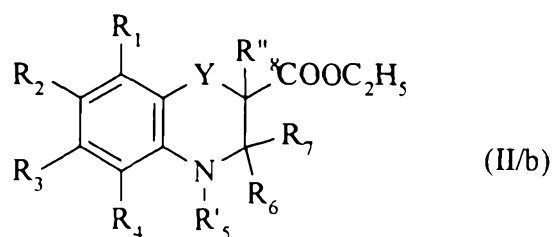


↳ a compound of formula (III) :



wherein X represents a halogen atom and  $R'_5$  represents a (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl group or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group optionally substituted by a (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl or optionally substituted phenyl group,

to yield a compound of formula (II/b) :



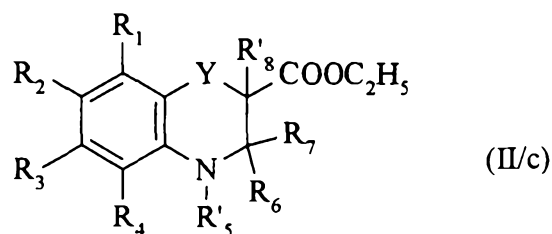
wherein Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R'_5$ ,  $R_6$ ,  $R_7$  and  $R''_8$  are as defined above,

which may, when  $R''_8$  represents a hydrogen atom, be subjected to the action of a halogenating agent, or to the action of a strong base followed by treatment with a compound of formula (IV) :



wherein X represents a halogen atom and  $R'_8$ , which is other than a hydrogen atom, has the same meaning as  $R_8$  for formula (I),

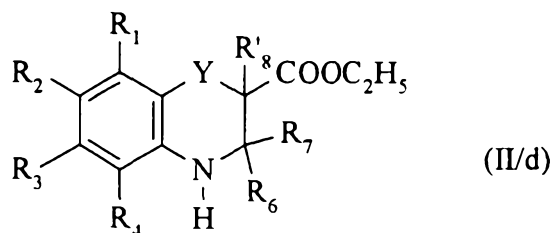
to yield a compound of formula (II/c) :



wherein Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R'_5$ ,  $R_6$ ,  $R_7$  and  $R'_8$  are as defined above,

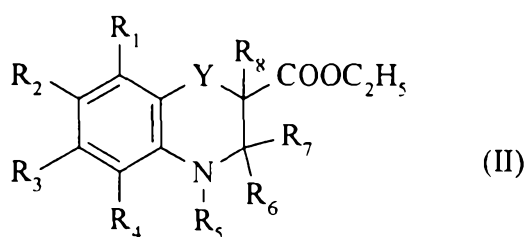
↳ or, when, in the compound of formula (II/a) used,  $R''_8$  represents a hydrogen atom, with a compound of formula (IV) as defined above, after treatment with a strong base,

to yield a compound of formula (II/d) :



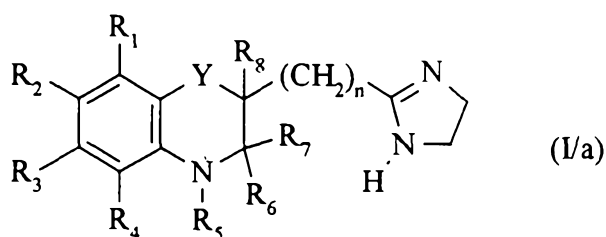
wherein Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub> and R'<sub>8</sub> are as defined above,

which compounds (II/a), (II/b), (II/c) and (II/d) constitute the totality of the compounds of formula (II) :



wherein Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are as defined above,

which is treated, optionally after homologization of the chain that carries the ester function, with ethylenediamine to yield a compound of formula (I/a) :

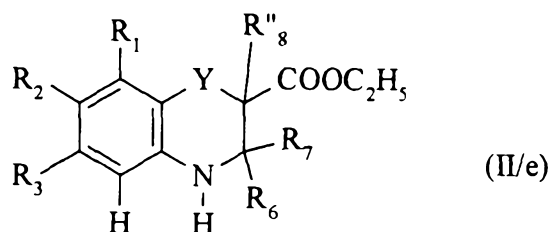


which is a particular case of the compounds of formula I wherein Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> and n have the same meanings as for formula (I), it being understood that R<sub>4</sub> and R<sub>5</sub> do not together form a ring,

or,

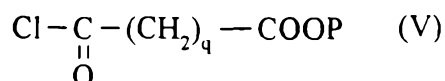
- when, in the desired compound of formula (I), R<sub>4</sub> and R<sub>5</sub> together form a ring, there is used as starting material a compound of formula (II/e) :





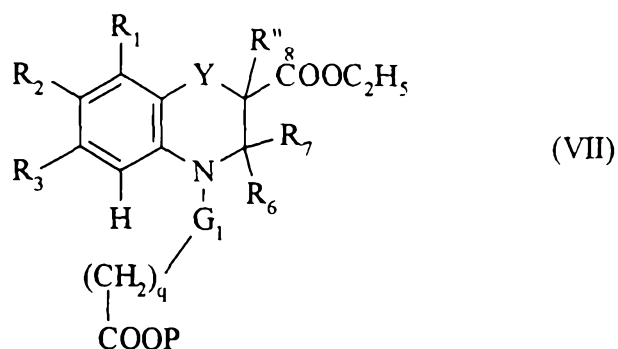
wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_6$ ,  $R_7$  and  $R''_8$  are as defined above,

which is treated with a compound of formula (V) or (VI) :



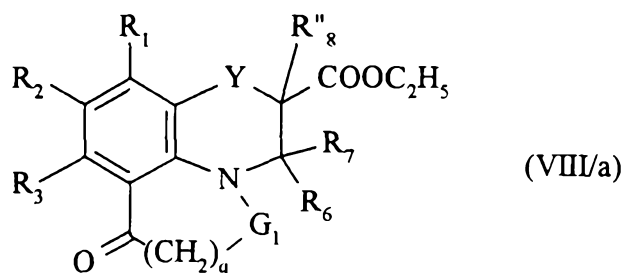
wherein X represents a halogen atom or a leaving group, P represents a group that masks the acid function, and q is an integer 0, 1 or 2,

to yield a compound of formula (VII) :



wherein  $G_1$  represents a  $\text{CH}_2$  or CO group, and q, P, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_6$ ,  $R_7$  and  $R''_8$  have the same meanings as above,

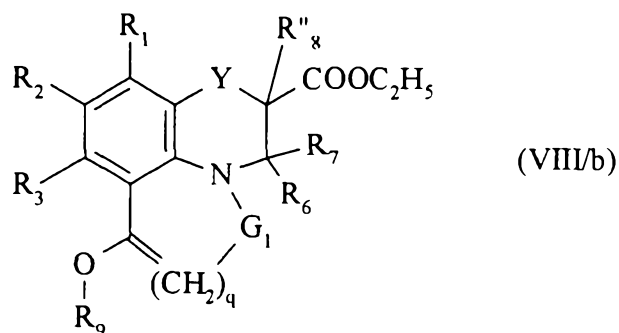
which, after freeing of the acid function and cyclisation, yields a compound of formula (VIII/a) :



wherein Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_6$ ,  $R_7$ ,  $R''_8$ ,  $G_1$  and q have the same meanings as above,

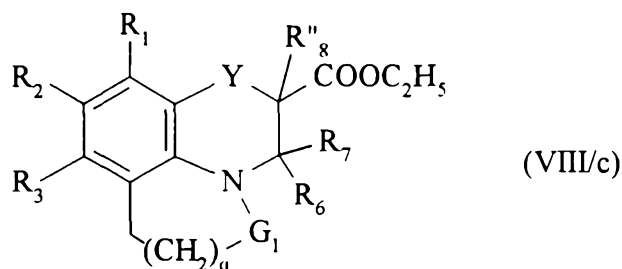
which compound (VIII/a),

- can be converted, after treatment with an alkyl halide, to a compound of formula (VIII/b)



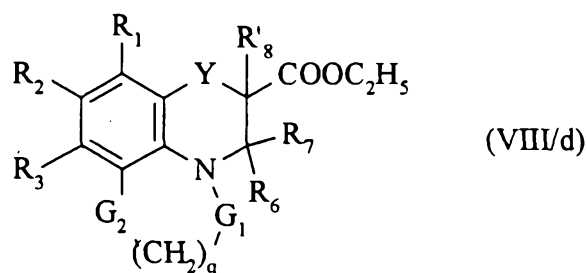
wherein R<sub>9</sub> represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group, and Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>', G<sub>1</sub> and q have the same meanings as above,

- or can be reduced to yield a compound of formula (VIII/c) :



wherein Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>', G<sub>1</sub> and q are as defined above,

it being possible for each of the compounds (VIII/a), (VIII/b) and (VIII/c) to be treated, when that is compatible with the substituents present on the molecule, with a strong base and then with a compound of formula (IV) as defined above to yield a compound of formula (VIII/d) :



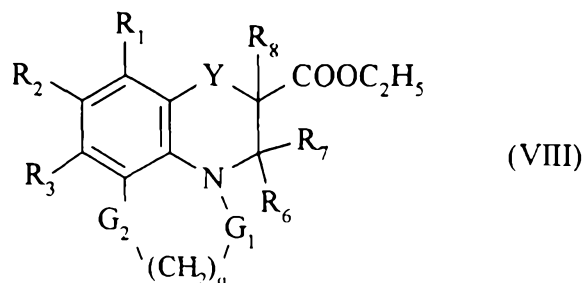
wherein G<sub>2</sub> represents a CH<sub>2</sub> or CO group, or, with the carbon atom of the

adjacent methylene, forms a group



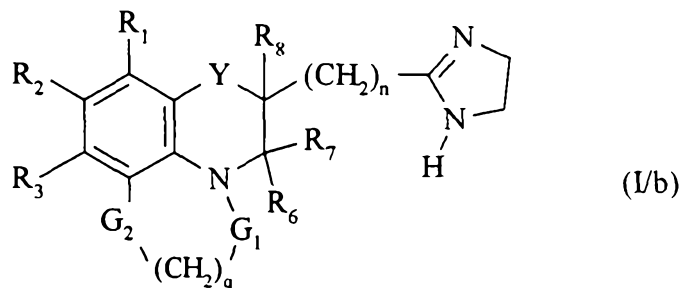
and Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, R'<sub>8</sub>, R<sub>9</sub>, G<sub>1</sub> and q are as defined above,

which compounds (VIII/a), (VIII/b), (VIII/c) and (VIII/d) constitute the totality of the compounds of formula (VIII) :



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, G<sub>1</sub>, G<sub>2</sub> and q are as defined above,

and which are treated, optionally after homologization of the chain that carries the ester function, with ethylenediamine to yield a compound of formula (I/b) :

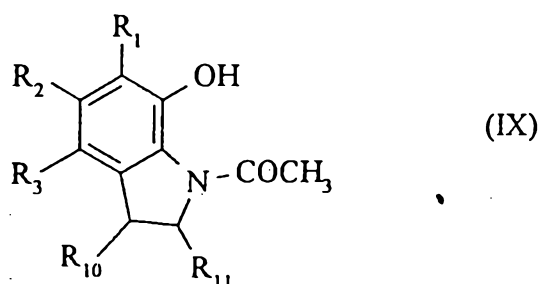


which is a particular case of the compounds of formula (I) wherein Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, G<sub>1</sub>, G<sub>2</sub>, n and q are as defined above,

which compounds (I/a) and (I/b) :

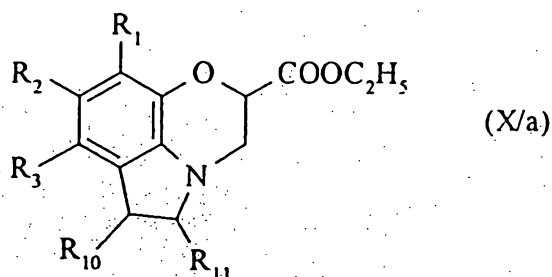
- are optionally purified in accordance with a conventional purification technique,
- optionally separated into their isomers in accordance with a conventional separation technique, and
- converted, where appropriate, into their N-oxides or into addition salts thereof with a pharmaceutically acceptable acid or base.

15. Process for the preparation of compounds of formula (I) according to claim 1, characterised in that there is used as starting material a compound of formula (IX):



wherein  $R_{10}$  and  $R_{11}$  simultaneously represent a hydrogen atom or together form a bond, and  $R_1$ ,  $R_2$  and  $R_3$  have the same meanings as for formula (I),

which, after deprotection of the indole nitrogen atom, is treated with ethyl 2,3-dibromopropionate in a basic medium to yield a compound of formula (X/a):



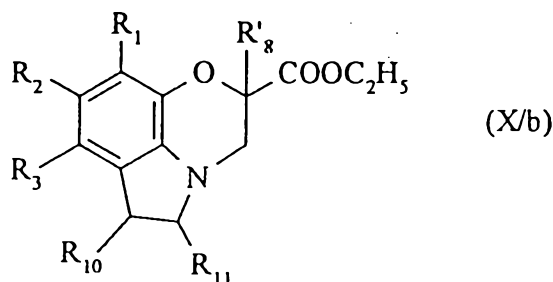
wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{10}$  and  $R_{11}$  are as defined above,

which can be reacted with a strong base and a compound of formula (IV):



wherein X represents a halogen atom and  $R'_8$ , which is other than a hydrogen atom, has the same meaning as  $R_8$  for formula (I),

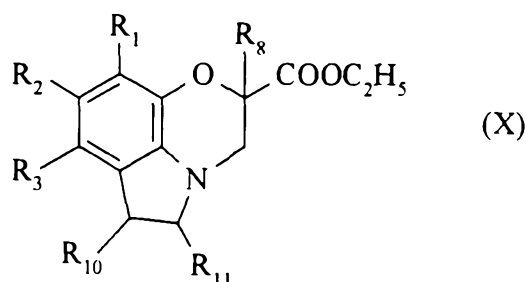
to yield a compound of formula (X/b):



wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R'_8$ ,  $R_{10}$ ,  $R_{11}$  are as defined above,

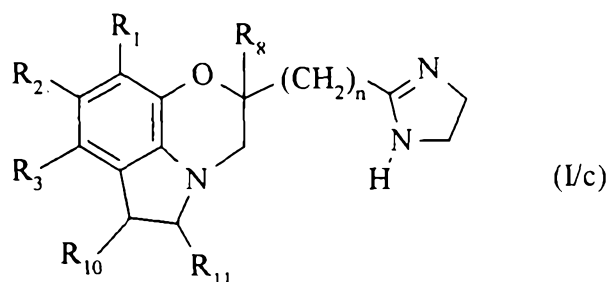


which compounds (X/a) and (X/b) constitute the totality of the compounds of formula (X):



wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_8$ ,  $R_{10}$  and  $R_{11}$  are as defined above,

which are treated, after optional homologization of the chain that carries the ester function, with ethylenediamine to yield a compound of formula (I/c) :



which is a particular case of the compounds of formula (I) wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_8$ ,  $R_{10}$ ,  $R_{11}$  and  $n$  are as defined above,

which compound (I/c) :

- is optionally purified in accordance with a conventional purification technique,
- optionally separated into its isomers in accordance with a conventional separation technique, and
- converted, where appropriate, into its N-oxide or into an addition salt thereof with a pharmaceutically acceptable acid or base,

it being understood that when  $R_{10}$  and  $R_{11}$  each represent a hydrogen atom, they can be converted into a bond using a conventional technique of aromatization, at any stage of the process.

16. Pharmaceutical compositions comprising as active ingredient at least one compound

according to any one of claims 1 to 13, on its own or in combination with one or more inert, non-toxic pharmaceutically acceptable excipients or carriers.

5 17. Pharmaceutical compositions according to claim 16 comprising at least one active ingredient according to any one of claims 1 to 8 for use in the treatment of diseases associated with disturbances in the functioning of the imidazoline receptors, such as cardiovascular diseases and arterial hypertension, diabetes, obesity, and psychiatric or neurological disorders, such as depression, Parkinson's disease, anorexia or Alzheimer's disease.

10 18. Pharmaceutical compositions according to claim 16 comprising an active ingredient according to any one of claims 1 to 13 for use in the treatment of cardiovascular diseases and arterial hypertension.

DATED this 30th day of July 1998.

ADIR ET COMPAGNIE

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