

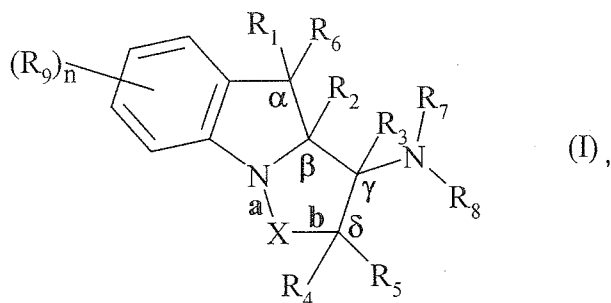
**New aminopyrrolo[1,2-*a*]indole and aminopyridazino[1,6-*a*]indole compounds,  
a process for their preparation  
and pharmaceutical compositions containing them**

The present invention relates to new aminopyrrolo[1,2-*a*]indole and aminopyridazino[1,6-*a*]indole compounds, to a process for their preparation and to pharmaceutical compositions containing them.

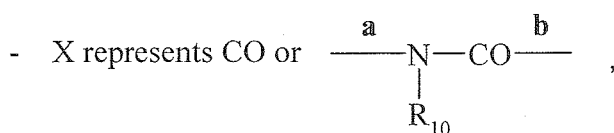
The literature provides a large number of examples of compounds having an eburnane structure. This is the case especially with the patent specification US 3 454 583 which deals with vincamine (methyl (3 $\alpha$ ,14 $\beta$ ,16 $\alpha$ )-(14,15-dihydro-14-hydroxy-eburnamenine-14-carboxylate) and its compounds for their vasodilatory properties. The patent applications FR 2 433 528 and FR 2 381 048 present new 20,21-dinoreburnamenine compounds and the application EP 0 287 468 new 17-aza-20,21-dinoreburnamenine compounds. Patent application EP 0 658 557 describes eburnane compounds modified in positions 14 and 15 of the eburnane skeleton. Patent application EP 0 563 916 describes 1*H*-indole-cyclohexanecarboxamide compounds.

In addition to the fact that they are novel, the compounds of the present invention exhibit very valuable pharmacological properties. They have been shown to be powerful inducers of tyrosine hydroxylase, both selectively and non-selectively.

The present invention relates more especially to the compounds of formula (I):



wherein:



R<sub>1</sub> represents hydrogen, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)aminoalkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)hydroxyalkyl, aryl-(C<sub>1</sub>-C<sub>6</sub>)alkyl in which the alkyl moiety may be linear or branched,

5 R<sub>2</sub> represents hydrogen, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)aminoalkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)hydroxyalkyl,

or R<sub>1</sub> and R<sub>2</sub>, together with the carbon atoms carrying them, form a carbon-carbon bond,

R<sub>3</sub> represents hydrogen, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)aminoalkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)hydroxyalkyl,

10 R<sub>4</sub> represents hydrogen, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)aminoalkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)hydroxyalkyl,

or R<sub>3</sub> and R<sub>4</sub>, together with the carbon atoms carrying them, form a carbon-carbon bond,

R<sub>5</sub> represents hydrogen, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl,

R<sub>6</sub> represents hydrogen, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl,

15 R<sub>7</sub>, R<sub>8</sub> represent a hydrogen atom, a group linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl-(C<sub>1</sub>-C<sub>6</sub>)alkyl in which the alkyl moiety may be linear or branched, linear or branched (C<sub>2</sub>-C<sub>6</sub>)alkenyl, linear or branched (C<sub>2</sub>-C<sub>6</sub>)alkynyl, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl chain substituted by one or more hydroxy, cyano, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, NR<sub>13</sub>R<sub>14</sub>, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkenyl chain substituted by the same substituents as those  
20 defined for the alkyl chain, or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkynyl chain substituted by the same substituents as those defined for the alkyl chain,

or,

either R<sub>5</sub> and R<sub>8</sub>, together with the carbon and nitrogen atoms carrying them, form a heterocycle having 5, 6 or 7 ring members, optionally substituted by a group R<sub>12</sub>,

or R<sub>6</sub> and R<sub>7</sub>, together with the carbon and nitrogen atoms carrying them, form a heterocycle having 5, 6 or 7 ring members, optionally substituted by a group R<sub>11</sub>,

it being understood that of necessity one, but only one, of the two groupings "R<sub>5</sub> and R<sub>8</sub>" or "R<sub>6</sub> and R<sub>7</sub>" together with the carbon and nitrogen atoms carrying them forms a heterocycle having 5, 6 or 7 ring members, optionally substituted by a group R<sub>11</sub>,

R<sub>9</sub> represents hydrogen, 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, cyano, nitro, linear or branched (C<sub>1</sub>-C<sub>6</sub>)polyhaloalkyl, NR<sub>15</sub>R<sub>16</sub>, or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl chain substituted by one or more halogens, one or more hydroxy, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, or NR<sub>15</sub>R<sub>16</sub>,

n represents an integer 0, 1, 2, 3 or 4,

R<sub>10</sub> represents hydrogen, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>2</sub>-C<sub>6</sub>)alkenyl, aryl-(C<sub>1</sub>-C<sub>6</sub>)alkyl in which the alkyl moiety may be linear or branched, linear or branched (C<sub>1</sub>-C<sub>6</sub>)polyhaloalkyl, or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl chain substituted by one or more halogen atoms, one or more groups hydroxy, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, or NR<sub>15</sub>R<sub>16</sub>,

R<sub>11</sub>, R<sub>12</sub>, which may be identical or different, represent a -COOT or -CH<sub>2</sub>O-U group wherein T and U, which may be identical or different, represent a hydrogen atom or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

R<sub>13</sub>, R<sub>14</sub>, which may be identical or different, represent a hydrogen atom or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group or, together with the nitrogen atom carrying them, form an optionally substituted heterocycle having from 4 to 8 ring members optionally containing a double bond in the heterocycle and optionally containing in the ring system a second hetero atom selected from an oxygen atom and a nitrogen atom,

R<sub>15</sub>, R<sub>16</sub>, which may be identical or different, represent a hydrogen atom or a group linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>2</sub>-C<sub>6</sub>)alkenyl,

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

5       wherein:

- (3a*SR*,4*SR*)-3-benzyl-4-ethyl-2,3,3a,4-tetrahydrobenzo[*b*]pyrido[2,3,4-*gh*]pyrrolizin-5(1*H*)-one,
- pyrido[3',2':4,5]pyridazino[1,6-*a*]indol-5(6*H*)-one,
- 6-methylpyrido[3',2':4,5]pyridazino[1,6-*a*]indol-5(6*H*)-one,
- 10   - 6-methyl-1,2,3,4-tetrahydropyrido[3',2':4,5]pyridazino[1,6-*a*]indol-5(6*H*)-one,
- (4a*R*,12b*R*)-6-methyl-1,2,3,4,4a,12b-hexahydropyrido[3',2':4,5]pyridazino[1,6-*a*]-indol-5(6*H*)-one,
- 1-methyl-3a,10b-dihydro[1,2,3]triazolo[4',5':3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one,
- 1-benzyl-3a,10b-dihydro[1,2,3]triazolo[4',5':3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one,
- 15   do not form part of the invention,

aryl means a phenyl or naphthyl group, both groups optionally being substituted by one or more halogen atoms, nitro, amino, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl or linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy groups,

20   a heterocycle having 5, 6 or 7 ring members means a saturated or unsaturated monocyclic group having 5, 6 or 7 sides and containing one or two hetero atoms selected from nitrogen and oxygen; pyrrolidine, piperidine, azepane and pyridine may be mentioned,

as optionally substituted heterocycle having from 4 to 8 ring members optionally containing one or more double bonds in the heterocycle and optionally containing in the ring system a second hetero atom selected from an oxygen atom and a nitrogen atom, there  
25   may be mentioned, without implying any limitation, pyrrolidine, piperidine, azepane, piperazine and morpholine, wherein those heterocycles may optionally be substituted,

including on the second nitrogen atom of piperazine, 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>)hydroxy-alkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy-(C<sub>1</sub>-C<sub>6</sub>)alkyl and linear or branched (C<sub>1</sub>-C<sub>6</sub>)amino-alkyl in which the amino moiety may optionally be substituted by one or two identical or  
5 different linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl groups,

$\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$  mean the chiral centres that may be present in the compounds of formula (I).

Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric  
10 acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, camphoric acid, etc..

Among the pharmaceutically acceptable bases there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, triethylamine, *tert*-butylamine, lysine etc..

15 An advantageous embodiment relates to compounds of formula (I) wherein R<sub>1</sub> and R<sub>4</sub>, which may be identical or different, each represent a hydrogen atom or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group.

Another advantageous embodiment relates to compounds of formula (I) wherein R<sub>2</sub> and R<sub>3</sub> each represent a hydrogen atom.

20 Another particular aspect of the invention concerns compounds of formula (I) wherein R<sub>1</sub> and R<sub>2</sub>, together with the carbon atoms carrying them, form a carbon-carbon bond.

R<sub>9</sub> advantageously represents a hydrogen atom.

n advantageously represents an integer 0.

Preferred compounds of the invention are compounds of formula (I) wherein R<sub>5</sub> and R<sub>8</sub>, together with the carbon and nitrogen atoms carrying them, form a heterocycle having 5, 6 or 7 ring members and more especially a heterocycle having 6 ring members.

Another advantageous embodiment of the invention relates to compounds of formula (I) wherein R<sub>6</sub> and R<sub>7</sub>, together with the carbon and nitrogen atoms carrying them, form a heterocycle having 5, 6 or 7 ring members and more especially a heterocycle having 6 ring members.

Even more especially, the invention relates to the following compounds of formula (I):

(4aSR,11aSR,11bRS)-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo-[1,2-*a*]indol-5-one,

(4aSR,11aRS,11bSR)-1-allyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,

(4aSR,11aSR,11bRS)-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo-[1,2-*a*]indol-5-one,

(4aSR,11aSR,11bRS)-1,2,3,4,4a,11,11a,11b-octahydro-1,6,6a-triazabenz[*a*]fluoren-5-one,

(4aSR,11aSR,11bRS)-(5-oxo-3,4,4a,11,11a,11b-hexahydro-2*H*,5*H*-pyrido[2',3':3,4]-pyrrolo[1,2-*a*]indol-1-yl)-acetonitrile,

(3aSR,6aRS,10cRS)-4-propyl-(3a,4,5,6,6a,10c-hexahydro)-3*H*-1,4,10b-triazafluoranthren-2-one,

(3aRS,6aSR,10cRS)-4-propyl-(3a,4,5,6,6a,10c-hexahydro)-3*H*-1,4,10b-triazafluoranthren-2-one,

(4aSR,11aRS,11bSR)-1-allyl-9-methoxy-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]-pyrrolo[1,2-*a*]indol-5-one,

(4aSR,11aSR,11bRS)-9-fluoro-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,

(4aSR,11aSR,11bRS)-9-chloro-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido-[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,

1,9-dimethyl-1,2,3,4-tetrahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,

(11aRS)-1,9-dimethyl-1,2,3,4,11,11a-hexahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,

(4a*S*,11a*R*,11b*S*) 1-allyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]-indol-5-one,

(4a*R*,11a*S*,11b*R*) 1-allyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]-indol-5-one,

5 (3a*RS*,10b*SR*,10c*RS*)-3-benzyl-2,3,3a,4,10b,10c-hexahydrobenzo[*b*]pyrido[2,3,4-*gh*]-pyrrolizin-5(1*H*)-one,

(4a*S*,11a*S*,11b*R*)-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,

10 (4a*SR*,11a*RS*,11b*SR*)-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,

(4a*R*,11a*R*,11b*S*)-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one.

15 The enantiomers, diastereoisomers, N-oxides, and the pharmaceutically acceptable addition salts with an acid or base, of the preferred compounds constitute an integral part of the invention.

The notation (3a*RS*,10b*SR*,10c*RS*) followed by the name of the compound signifies that the product obtained is a racemic mixture and accordingly that both configurations are possible; for example:

20 (3a*RS*,10b*SR*,10c*RS*)-3-benzyl-2,3,3a,4,10b,10c-hexahydrobenzo[*b*]pyrido[2,3,4-*gh*]-pyrrolizin-5(1*H*)-one signifies that the product obtained, the racemic mixture, contains (3a*R*,10b*S*,10c*R*)-3-benzyl-2,3,3a,4,10b,10c-hexahydrobenzo[*b*]pyrido[2,3,4-*gh*]pyrrolizin-5(1*H*)-one and (3a*S*,10b*R*,10c*S*)-3-benzyl-2,3,3a,4,10b,10c-hexahydrobenzo[*b*]pyrido[2,3,4-*gh*]pyrrolizin-5(1*H*)-one.

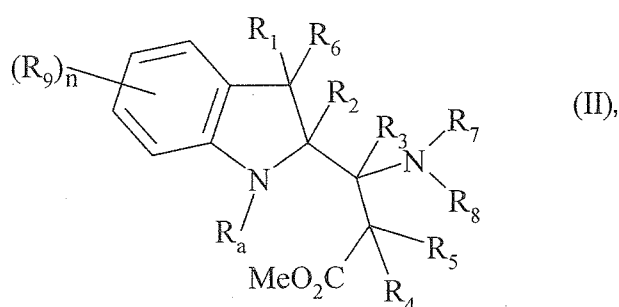
25 The notation (3a*R*,10b*S*,10c*R*) or (3a*S*,10b*R*,10c*S*) followed by the name of the compound signifies that the product obtained is an optically pure enantiomer; for example:

(3a*R*,10b*S*,10c*R*)- or (3a*S*,10b*R*,10c*S*)-3-benzyl-2,3,3a,4,10b,10c-hexahydrobenzo[*b*]pyrido[2,3,4-*gh*]pyrrolizin-5(1*H*)-one signifies that the product obtained, the optically pure enantiomer, is (3a*R*,10b*S*,10c*R*)-3-benzyl-2,3,3a,4,10b,10c-hexahydrobenzo[*b*]pyrido-

[2,3,4-*gh*]-pyrrolizin-5(1*H*)-one or (3*aS*,10*bR*,10*cS*)-3-benzyl-2,3,3*a*,4,10*b*,10*c*-hexahydro-benzo[*b*]pyrido-[2,3,4-*gh*]pyrrolizin-5(1*H*)-one.

Enantiomer  $\alpha$  and enantiomer  $\beta$  are understood to mean the optically pure enantiomers of the corresponding racemic mixtures.

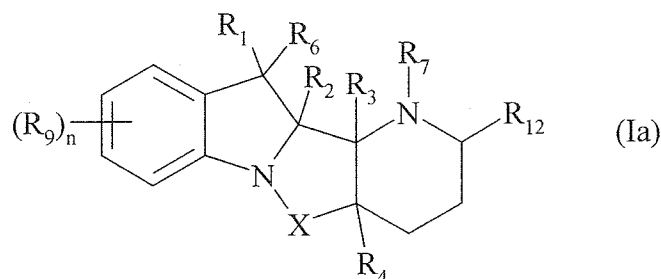
- 5 The present invention relates also to a process for the preparation of compounds of formula (I), which is characterised in that there is used as starting material a compound of formula (II):



- 10 wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_4$ ,  $R_6$ ,  $R_7$ ,  $R_8$ ,  $R_9$  and  $n$  are as defined for formula (I),  $R_a$  represents a hydrogen atom, a nitroso, amino or *tert*-butyl carboxylate group,

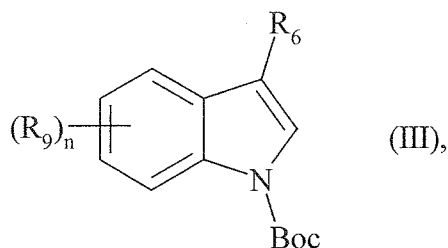
- which compound of formula (II) is subjected to a cyclisation reaction in basic medium to yield compounds of formula (I), which may be purified according to a conventional separation technique, are converted, if desired, into their additions salts with a pharmaceutically acceptable acid or base and are optionally separated into their isomers  
15 according to a conventional separation technique.

An advantageous embodiment relates to a process for the preparation of compounds of formula (I/a), a particular case of the compounds of formula (I):

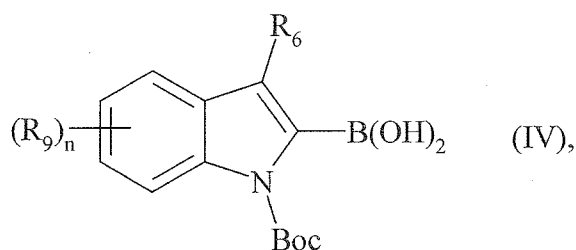


wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_6$ ,  $R_7$ ,  $R_9$ ,  $R_{12}$  and  $n$  are as defined for formula (I),

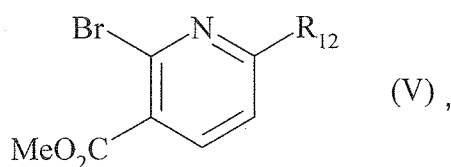
which is characterised in that there is used as starting material a compound of formula (III):



wherein R<sub>6</sub>, R<sub>9</sub> and n are as defined for formula (I) and Boc represents a *tert*-butyl carboxylate group, which is reacted with triisopropyl borate in anhydrous medium to yield a compound of formula (IV):

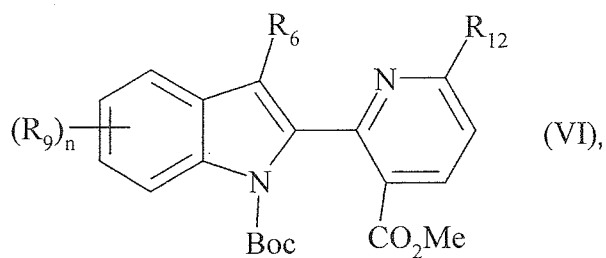


wherein R<sub>6</sub>, R<sub>9</sub>, n and Boc are as defined hereinbefore, which is reacted with a compound of formula (V):



wherein R<sub>12</sub> is as defined for formula (I),

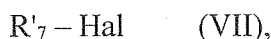
in the presence of a base and tetrakis(triphenylphosphine)palladium to yield a compound of formula (VI):



wherein  $R_6$ ,  $R_9$ ,  $R_{12}$ ,  $n$  and Boc are as defined hereinbefore,

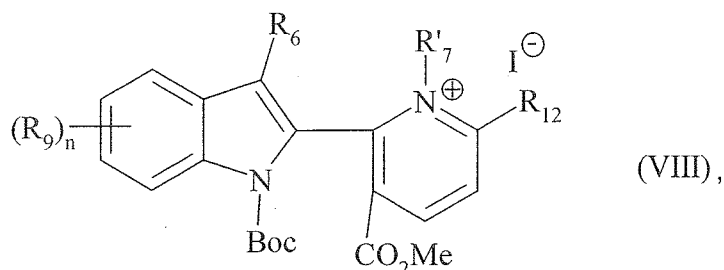
which compound of formula (VI) is subjected,

- either to an alkylation reaction with a compound of formula (VII):



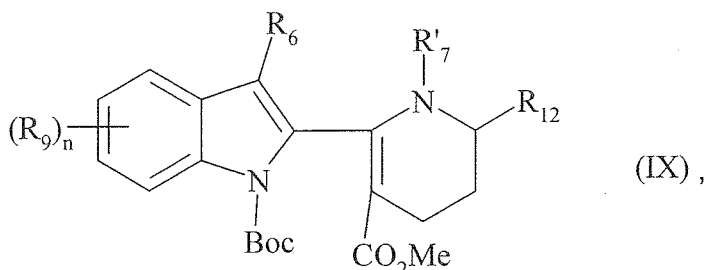
wherein  $R'_7$  has all of the meanings given for  $R_7$  as defined for formula (I) with the exception of a hydrogen atom, and Hal represents a halogen atom,

to yield a compound of formula (VIII):



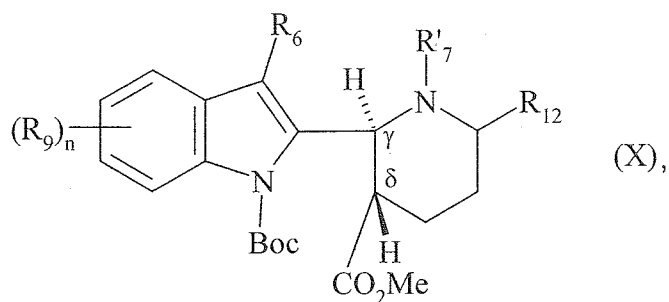
wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$ ,  $n$  and Boc are as defined hereinbefore,

which is subjected to a partial reduction reaction with hydrogen in the presence of triethylamine and platinum oxide to yield a compound of formula (IX):

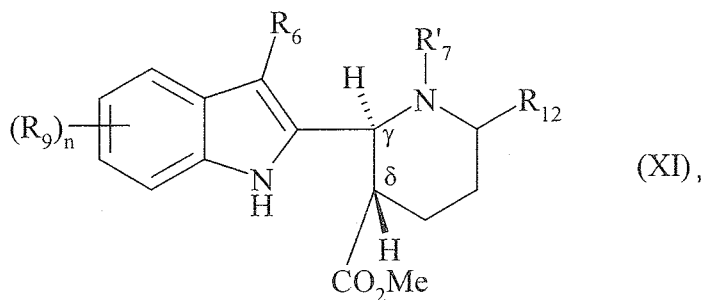


wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$ ,  $n$  and Boc are as defined hereinbefore,

which is subjected to reduction in the presence of hydrochloric acid and sodium cyanoborohydride to yield a compound of formula (X) having *trans* stereochemistry:

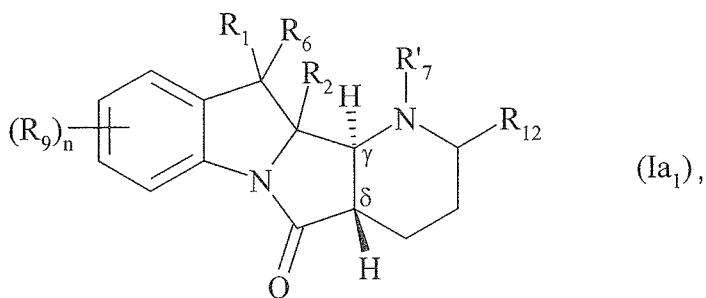


wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$ ,  $n$  and Boc are as defined hereinbefore,  $\gamma$  and  $\delta$  are as defined for formula (I) and  $H_\gamma$  and  $H_\delta$  have *trans* stereochemistry, which is subjected to a deprotection reaction in the presence of trifluoroacetic acid to yield a compound of formula (XI),



5

wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$  and  $n$  are as defined hereinbefore, which is subjected to a cyclisation reaction in the presence of a borane-THF complex and trifluoroacetic acid to yield a compound of formula (Ia<sub>1</sub>), a particular case of the compounds of formula (I):

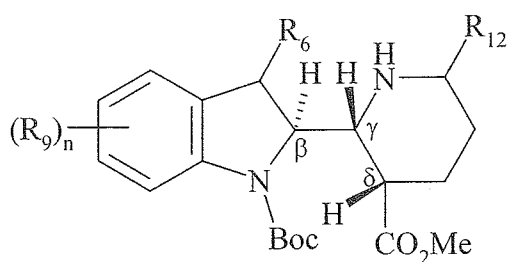


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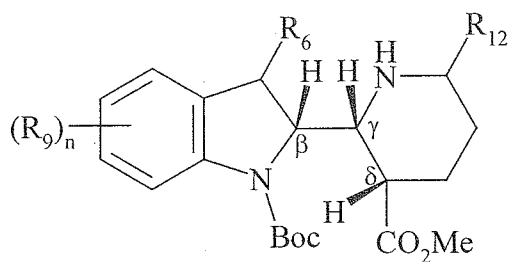
wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$  and  $n$  are as defined hereinbefore and  $R_1$  and  $R_2$  are as defined for formula (I),

- or to a reduction reaction with hydrogen in the presence of acetic acid and a rhodium catalyst to yield compounds of formulae (XIIa) and (XIIb) having (*trans*, *cis*) and (*cis*, *cis*) stereochemistry, respectively:

15



(XIIa)

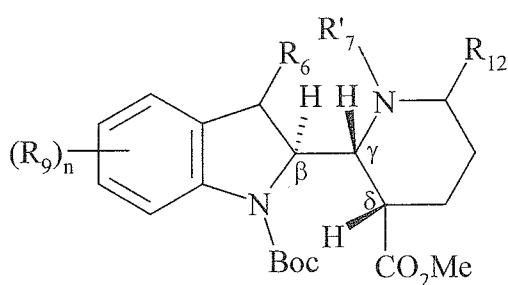


(XIIb)

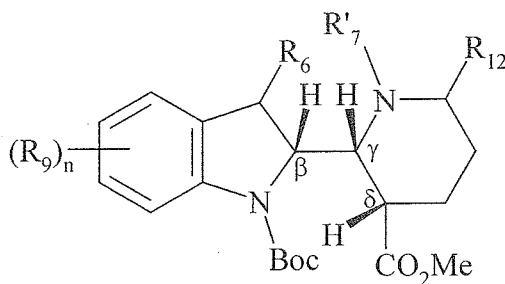
wherein  $R_6$ ,  $R_9$ ,  $R_{12}$ ,  $n$  and Boc are as defined hereinbefore,  $\beta$ ,  $\gamma$  and  $\delta$  are as defined for formula (I) and  $H_\beta$  and  $H_\gamma$  have *trans* stereochemistry in the compound of formula (XIIa) and *cis* stereochemistry in the compound of formula (XIIb) and  $H_\gamma$  and  $H_\delta$  have *cis* stereochemistry in the compounds of formulae (XIIa) and (XIIb),

which compounds of formulae (XIIa) and (XIIb) are:

● reacted with a compound of formula (VII) as defined hereinbefore, in the presence of a base, to yield compounds of formulae (XIIIa) and (XIIIb):



(XIIIa)

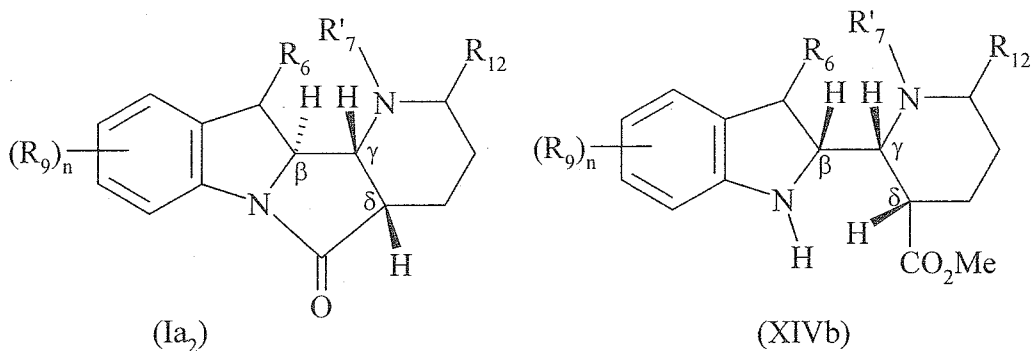


(XIIIb)

wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$ ,  $n$  and Boc are as defined hereinbefore,

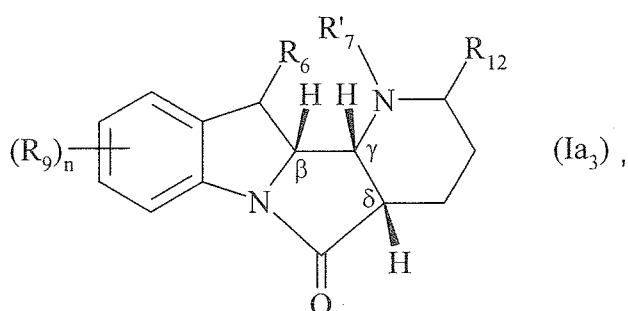
which compounds of formulae (XIIIa) and (XIIIb) are:

□ placed in the presence of trifluoroacetic acid to yield compounds of formulae (I<sub>a2</sub>) and (XIVb), compounds of formula (I<sub>a2</sub>) being a particular case of the compounds of formula (I):



wherein R<sub>6</sub>, R'<sub>7</sub>, R<sub>9</sub>, R<sub>12</sub>, and n are as defined hereinbefore,

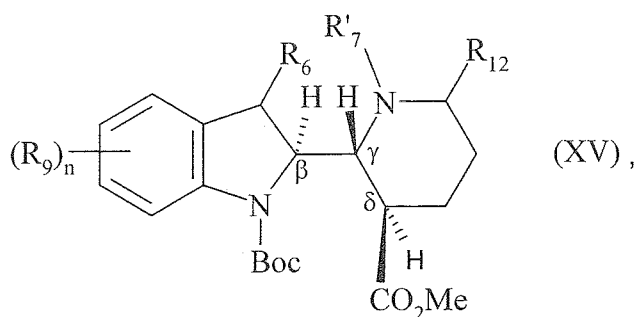
which compound of formula (XIVb) is subjected to a cyclisation reaction in the presence of sodium hydride to yield a compound of formula (Ia<sub>3</sub>), a particular case of the compounds of formula (I):



wherein R<sub>6</sub>, R'<sub>7</sub>, R<sub>9</sub>, R<sub>12</sub>, and n are as defined hereinbefore,

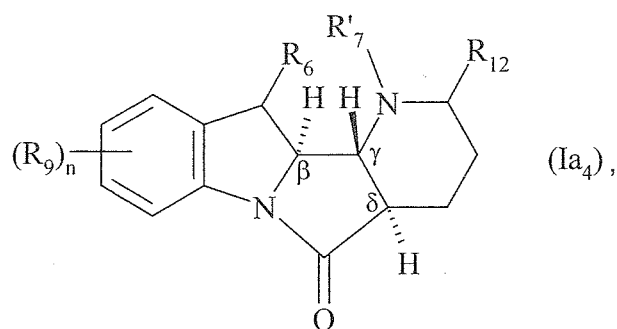
or which compound of formula (XIIIa) is:

□ alternatively placed in the presence of sodium methanolate in methanol to yield a compound of formula (XV):



wherein R<sub>6</sub>, R'<sub>7</sub>, R<sub>9</sub>, R<sub>12</sub>, n and Boc are as defined hereinbefore,

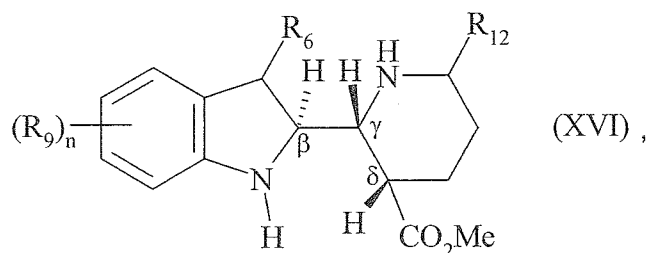
which is subjected to a cyclisation reaction in the presence of trifluoroacetic acid to yield a compound of formula (Ia<sub>4</sub>), a particular case of the compounds of formula (I):



wherein R<sub>6</sub>, R<sub>7</sub>, R<sub>9</sub>, R<sub>12</sub> and n are as defined hereinbefore,

or which compound of formula (XIIa) is:

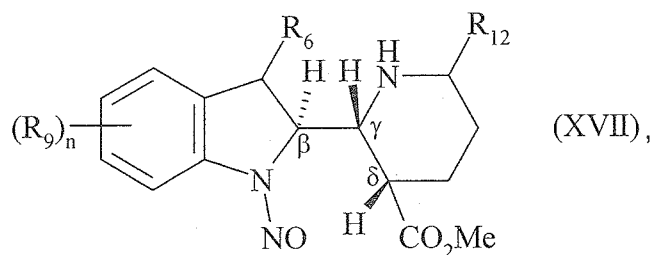
● alternatively subjected to the same conditions as the compounds of formulae (XIIIa) and (XIIIb) to yield a compound of formula (XVI):



wherein R<sub>6</sub>, R<sub>9</sub>, R<sub>12</sub> and n are as defined hereinbefore,

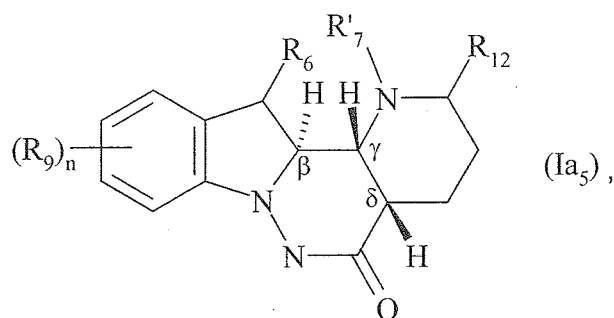
which compound of formula (XVI) is:

\* dissolved in a mixture of acetic acid and water and a sodium nitrite solution to yield a compound of formula (XVII):



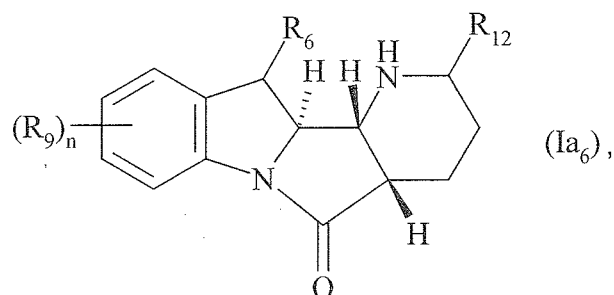
wherein R<sub>6</sub>, R<sub>9</sub>, R<sub>12</sub> and n are as defined hereinbefore,

which is reacted in succession with a compound of formula (VII) as defined hereinbefore, then zinc and ammonium carbonate to yield a compound of formula (I<sub>a5</sub>), a particular case of the compounds of formula (I):



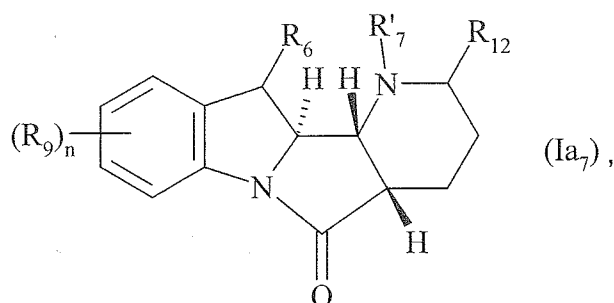
wherein R<sub>6</sub>, R'<sub>7</sub>, R<sub>9</sub>, R<sub>12</sub> and n are as defined hereinbefore,  
or which compound of formula (XVI) is:

\* alternatively subjected to a cyclisation reaction in the presence of potassium carbonate to  
yield a compound of formula (Ia<sub>6</sub>), a particular case of the compounds of formula (I):



wherein R<sub>6</sub>, R<sub>9</sub>, R<sub>12</sub> and n are as defined hereinbefore,

which is subjected to an alkylation reaction with a compound of formula (VII) as defined  
hereinbefore, in basic medium, to yield a compound of formula (Ia<sub>7</sub>), a particular case of  
the compounds of formula (I):

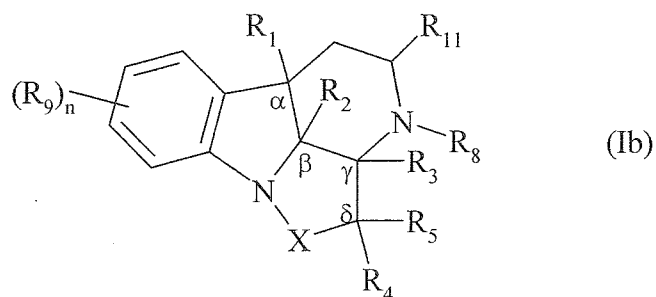


wherein R<sub>6</sub>, R'<sub>7</sub>, R<sub>9</sub>, R<sub>12</sub> and n are as defined hereinbefore,

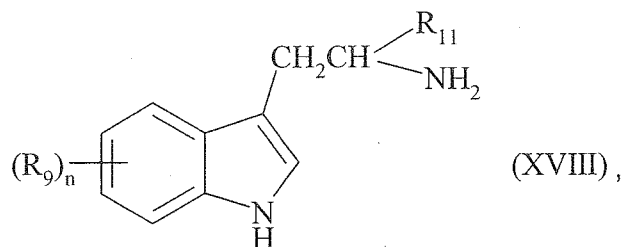
which compounds of formulae (Ia<sub>1</sub>) to (Ia<sub>7</sub>) constitute compounds of formula (Ia), which  
may be purified according to a conventional separation technique, are converted, if desired,

into their addition salts with a pharmaceutically acceptable acid or base and are optionally separated into their isomers according to a conventional separation technique.

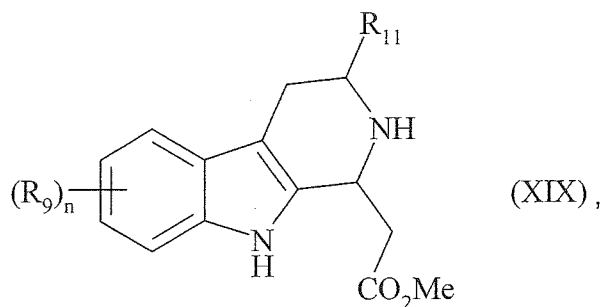
A second advantageous embodiment relates to a process for the preparation of compounds of formula (Ib), a particular case of the compounds of formula (I):



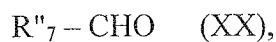
wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_8$ ,  $R_9$ ,  $R_{11}$ ,  $X$  and  $n$  are as defined for formula (I), which is characterised in that there is used as starting material a compound of formula (XVIII):



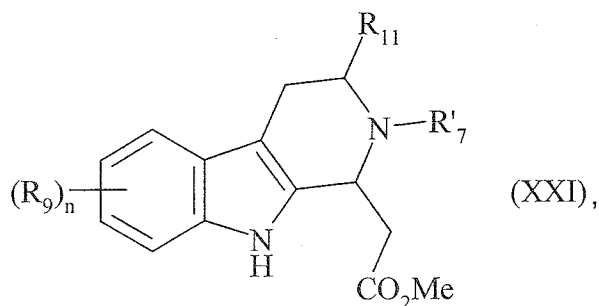
wherein  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore, which is reacted with methyl cyanoacetate in the presence of Pd/C in glacial acetic acid to yield a compound of formula (XIX):



wherein  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore, which is reacted with a compound of formula (XX):

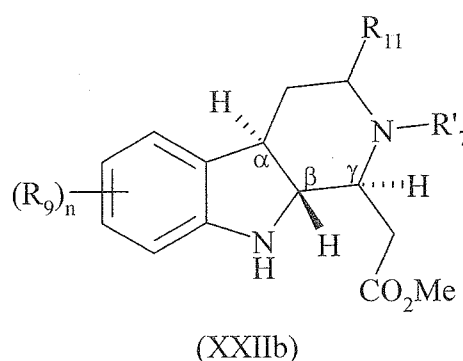
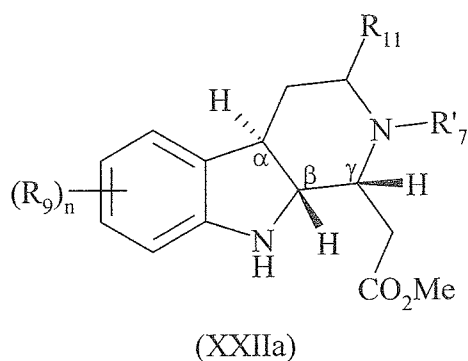


wherein  $R''_7$  has all of the meanings given for  $R_7$  as defined for formula (I) with the exception of a hydrogen atom, followed by reduction with sodium borohydride or sodium cyanoborohydride to yield a compound of formula (XXI):



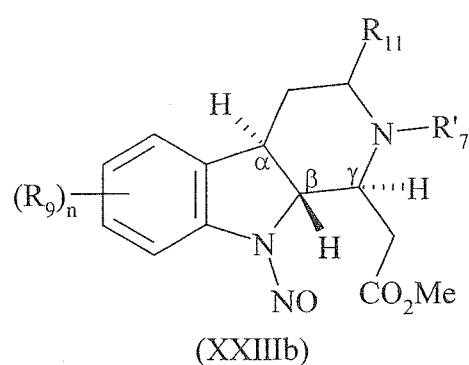
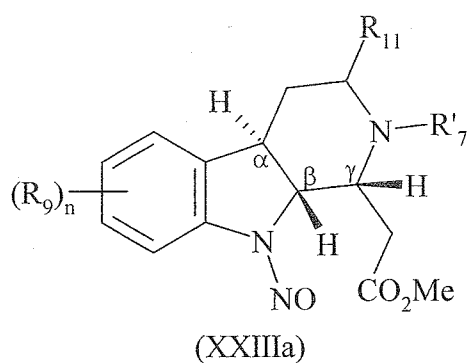
wherein  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore and  $R'_7$  has all of the meanings given for  $R_7$  as defined for formula (I) with the exception of a hydrogen atom, which compound of formula (XXI) is:

- reacted with a  $\text{BH}_3$ -THF complex in THF and then dissolved with trifluoroacetic acid to yield compounds of formulae (XXIIa) and (XXIIb) having (*trans*, *cis*) and (*trans*, *trans*) stereochemistry, respectively:



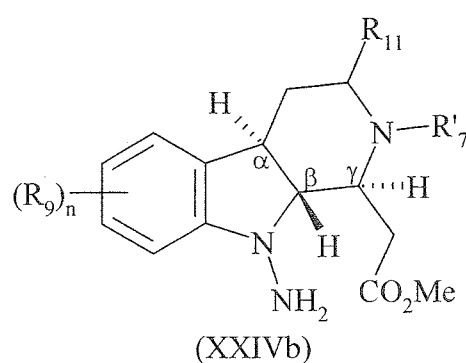
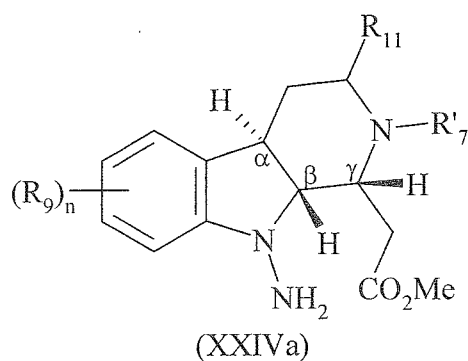
wherein  $R'_7$ ,  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore, and  $H_\alpha$  and  $H_\beta$  have *trans* stereochemistry in the compounds of formulae (XXIIa) and (XXIIb) and  $H_\beta$  and  $H_\gamma$  have *cis* stereochemistry in the compound of formula (XXIIa) and *trans* stereochemistry in the compound of formula (XXIIb),

which are dissolved in a mixture of acetic acid and water and a sodium nitrite solution to yield compounds of formulae (XXIIIa) and (XXIIIb):



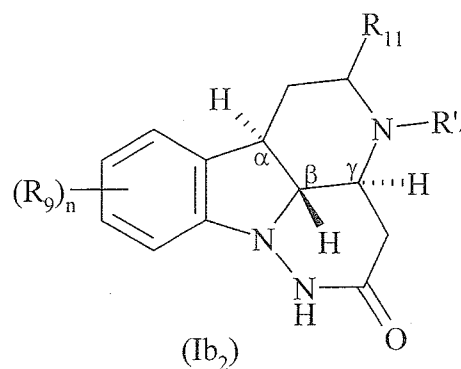
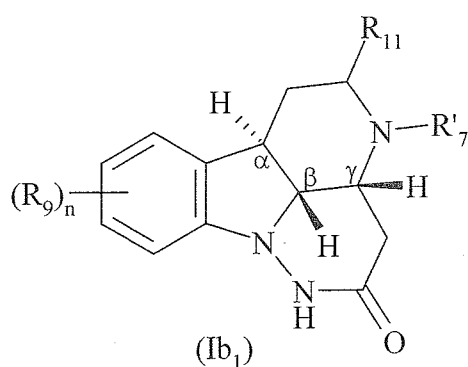
wherein  $R'_7$ ,  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore,

which are placed in the presence of ammonium carbonate and zinc to yield compounds of formulae (XXIVa) and (XXIVb):



wherein  $R'_7$ ,  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore,

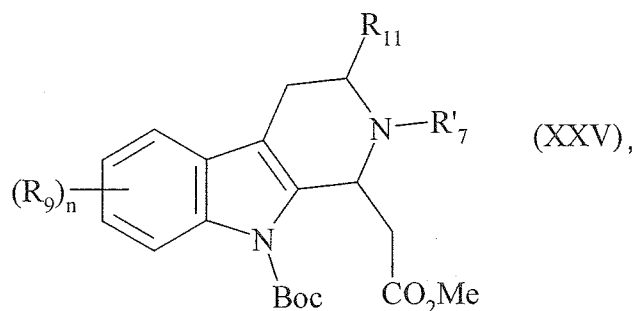
which are subjected to a cyclisation reaction in the presence of sodium hydride or trimethylaluminium dissolved in hexane to yield compounds of formulae (I<sub>b1</sub>) and (I<sub>b2</sub>), particular cases of the compounds of formula (I):



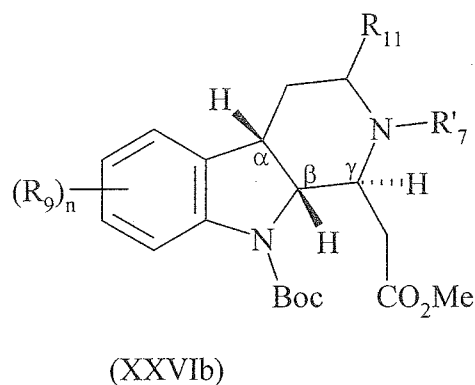
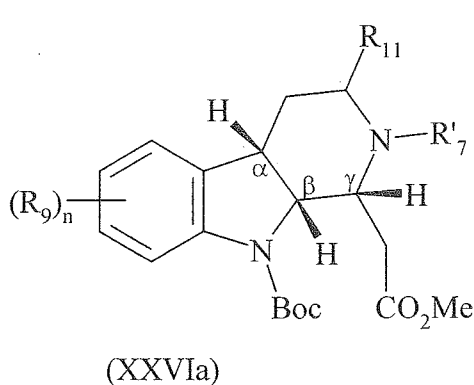
wherein  $R'_7$ ,  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore,

or which compound of formula (XXI) is:

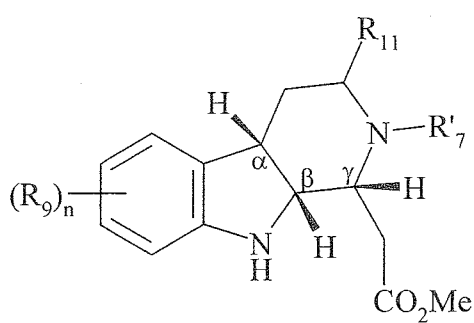
- alternatively reacted with di-*tert*-butyloxycarboxylic acid anhydride and dimethylamino-pyridine to yield a compound of formula (XXV):



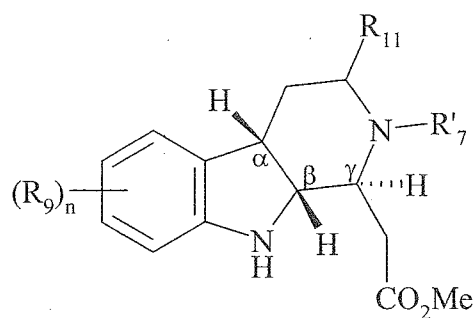
5 wherein R<sub>7</sub>, R<sub>9</sub>, R<sub>11</sub> and n are as defined hereinbefore and Boc represents a *tert*-butyl carboxylate group, which is subjected to a reduction reaction in the presence of platinum oxide and hydrogen to yield compounds of formulae (XXVIa) and (XXVIb) having (*cis*, *cis*) and (*cis*, *trans*) stereochemistry, respectively:



10 wherein R<sub>7</sub>, R<sub>9</sub>, R<sub>11</sub>, n and Boc are as defined hereinbefore,  
and H<sub>α</sub> and H<sub>β</sub> have *cis* stereochemistry in the compounds of formulae (XXVIa) and (XXVIb) and H<sub>β</sub> and H<sub>γ</sub> have *cis* stereochemistry in the compound of formula (XXVIa) and *trans* stereochemistry in the compound of formula (XXVIb),  
which are placed in the presence of trifluoroacetic acid in an anhydrous medium to yield  
15 compounds of formulae (XXVIIa) and (XXVIIb):



(XXVIIa)

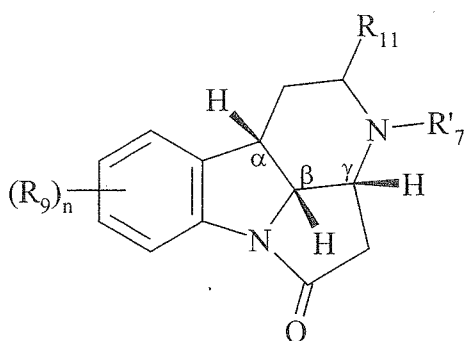


(XXVIIb)

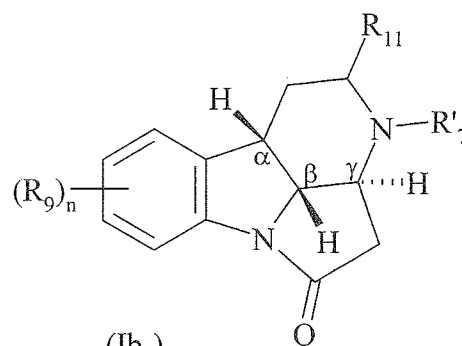
wherein  $R'_7$ ,  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore,

which are:

- either subjected to a cyclisation reaction under the same conditions as the compounds of formulae (XXIVa) and (XXIVb) to yield compounds of formulae (I<sub>b3</sub>) and (I<sub>b4</sub>), a particular case of the compounds of formula (I):



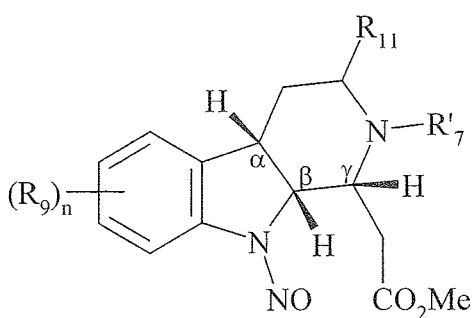
(I<sub>b3</sub>)



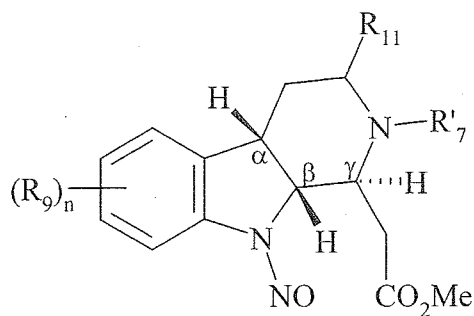
(I<sub>b4</sub>)

wherein  $R'_7$ ,  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore,

- or subjected to the same conditions as the compounds of formulae (XXIIa) and (XXIIb) to yield compounds of formula (XXVIIIa) and (XXVIIIb):



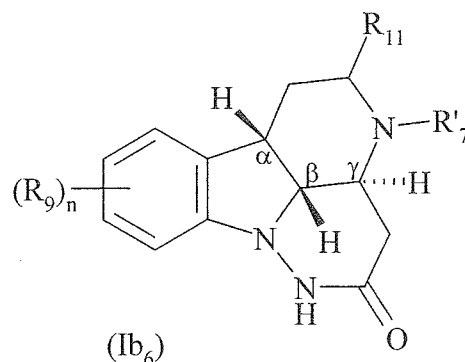
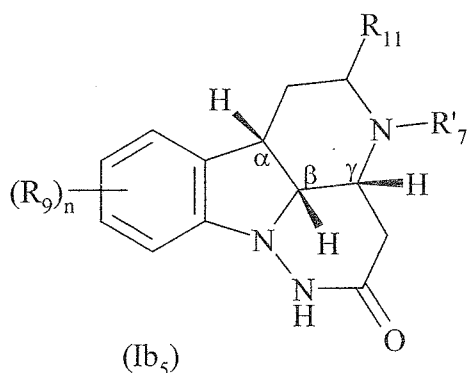
(XXVIIIa)



(XXVIIIb)

wherein R'<sub>7</sub>, R<sub>9</sub>, R<sub>11</sub> and n are as defined hereinbefore,

which are subjected to the same conditions as the compounds of formulae (XXIIIa) and (XXIIIb) to yield compounds of formulae (I<sub>b5</sub>) and (I<sub>b6</sub>), a particular case of the compounds of formula (I):



wherein R'<sub>7</sub>, R<sub>9</sub>, R<sub>11</sub> and n are as defined hereinbefore,

which compounds of formulae (I<sub>b1</sub>) to (I<sub>b6</sub>) constitute the compounds of formula (Ib), which may be purified according to a conventional separation technique, are converted, if desired, into their addition salts with a pharmaceutically acceptable acid or base and are optionally separated into their isomers according to a conventional separation technique.

Compounds of formulae (III), (V), (VII), (XVIII) and (XX) are either commercially available compounds, or are compounds obtained according to conventional methods of organic synthesis well known to the person skilled in the art.

The compounds of formula (I) have valuable pharmacological properties, especially that of being powerful tyrosine hydroxylase (TH) inducers. It is known that tyrosine hydroxylase is a rate-limiting enzyme which controls particularly the synthesis of neurotransmitters in central catecholaminergic and dopaminergic neurons. The rate of synthesis of those neurotransmitters is related especially to the appearance of tonic brain dysfunctions constituting numerous behavioural pathologies in humans, such as anxiety, psychoses, depression, stress etc..

By virtue of their ability to induce tyrosine hydroxylase, the compounds of the invention will accordingly be used therapeutically in the treatment of depression, anxiety, disorders

of memory in the course of ageing and/or neurodegenerative diseases, and in the palliative treatment of Parkinson's disease, and for adaptation to stress.

The present invention relates also to pharmaceutical compositions containing as active ingredient at least one compound of formula (I), its enantiomers, diastereoisomers, N-oxides or one of its addition salts with a pharmaceutically acceptable acid or base, alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

The pharmaceutical compositions so obtained are generally presented in dosage form. They may, for example, be in the form of tablets, dragées, capsules, suppositoires or injectable or drinkable solutions and may be administered by the oral, rectal, intramuscular or parenteral route.

Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those which are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, intravaginal, rectal, nasal, perlingual, buccal, ocular or respiratory administration.

The pharmaceutical compositions according to the invention for parenteral injections include especially sterile solutions, which may be aqueous or non-aqueous, dispersions, suspensions or emulsions and also sterile powders for the reconstitution of injectable solutions or dispersions.

The pharmaceutical compositions according to the invention for solid oral administration include especially tablets or dragées, sublingual tablets, sachets, capsules and granules, and those for liquid oral, nasal, buccal or ocular administration include especially emulsions, solutions, suspensions, drops, syrups and aerosols.

The pharmaceutical compositions for rectal or vaginal administration are preferably suppositories or ovules, and those for per- or trans-cutaneous administration include especially powders, aerosols, creams, ointments, gels and patches.

The pharmaceutical compositions mentioned above illustrate the invention but do not limit it in any way.

5     Among the pharmaceutically acceptable, inert, non-toxic excipients or carriers there may be mentioned, by way of example and without implying any limitation, diluents, solvents, preservatives, wetting agents, emulsifiers, dispersing agents, binders, swelling agents, disintegrators, retardants, lubricants, absorbents, suspending agents, colorants, flavourings etc.

10

The useful dosage varies according to the age and weight of the patient, the administration route, the pharmaceutical composition employed, the nature and severity of the disease, and the administration of any associated treatments. The dosage ranges from 0.1 mg to 100 mg in one or more administrations per day.

15     The Examples which follow illustrate the invention but do not limit it in any way.

The starting materials used are known products or products prepared according to known procedures. The various preparations result in synthesis intermediates for use in the preparation of the compounds of the invention.

20     The structures of the compounds described in the Examples and in the Preparations were determined according to customary spectrophotometric techniques (infra-red, nuclear magnetic resonance, mass spectrometry, ...).

The melting points were determined using TOTTOLI apparatus (without emergent column correction). When the compound is in salt form, the melting point corresponds to that of the salt product.

**PREPARATION 1: Methyl (2SR,3SR)-2-(1H-indol-2-yl)-1-methylpiperidine-3-carboxylate**

**Step A: 1-(tert-Butoxycarbonyl)-1H-indol-2-yl-2-boronic acid**

75 ml of a 2M solution of LDA is added dropwise, at 0°C, to a solution of 25 g of *tert*-butyl 1H-indole-1-carboxylate and 32.4 g of triisopropyl borate in 120 ml of anhydrous THF under a nitrogen atmosphere. Stirring is maintained for 40 min. before the addition of 200 ml of aqueous 2M hydrochloric acid. The pH is adjusted to pH = 7 by adding a concentrated solution of ammonium hydroxide. After separation of the phases, the aqueous phase is extracted with ethyl acetate (2 × 100 ml). The organic phases are collected, washed with saturated sodium chloride solution (100 ml), dried over sodium sulphate, filtered and concentrated under reduced pressure. Water is added to the residue and the mixture is triturated until precipitation of the boronic acid, which is filtered off and washed four times with pentane to obtain 29.27 g of the expected product.

Melting point: 96-98°C

**Step B: tert-Butyl 2-[(3-methoxycarbonyl)pyridin-2-yl]indole-1-carboxylate**

13.46 g of a solution of sodium carbonate in 50 ml of water and 4.77 g of tetrakis-(triphenylphosphine)palladium are added in succession to a degassed solution of 9.94 g of methyl 2-bromonicotinate in 170 ml of DME at 85°C. A solution of 12.96 g of the compound of the above Step A in 50 ml of ethanol is then added dropwise. Stirring is maintained for 6 h at 85°C before returning to ambient temperature and adding 200 ml of water. After separation of the phases, the aqueous phase is extracted with diethyl ether (2 × 100 ml). The organic phases are collected, washed with saturated sodium chloride solution, dried over sodium sulphate, filtered and concentrated under reduced pressure. Chromatography on a silica gel column (cyclohexane/ethyl acetate: 9/1) allows 14.11 g of the expected product to be obtained.

Melting point: 83°C

Mass spectrometry (ES +, *m/z*): 375 (*M*+Na)<sup>+</sup>; 353 (*M*+H)<sup>+</sup>

Elemental analysis:

|             | C %   | H %  | N %  |
|-------------|-------|------|------|
| Calculated: | 68.17 | 5.72 | 7.95 |
| Found:      | 68.03 | 5.85 | 7.85 |

5     Step C: 2-(1-tert-Butoxycarbonyl-1H-indol-2-yl)-3-(methoxycarbonyl)-1-methyl-pyridinium iodide

A mixture of 1.40 g of the compound of the above Step B and 5 ml of iodomethane is stirred at ambient temperature for 4 days. The reaction mixture is then concentrated under reduced pressure and the residue is taken up in diethyl ether and filtered to obtain 1.73 g of the expected product.

Melting point: degradation at 120°C

Mass spectrometry (ES +, m/z): 367 (M-I)

Elemental analysis:

|             | C %   | H %  | N %  |
|-------------|-------|------|------|
| Calculated: | 51.02 | 4.69 | 5.67 |
| Found:      | 50.79 | 4.88 | 5.71 |

15     Step D: tert-Butyl 2-[3-(methoxycarbonyl)-1-methyl-1,4,5,6-tetrahydropyridin-2-yl]-1H-indole-1-carboxylate

A mixture of 1.01 g of the compound of the above Step C, 0.63 ml of triethylamine and 100 mg of platinum oxide in 10 ml of methanol is stirred under a hydrogen atmosphere for 3 h. The reaction mixture is then filtered over Celite and the filtrate is concentrated. The residue is taken up in dichloromethane and washed with water. The organic phase is dried over sodium sulphate, filtered and concentrated under reduced pressure to yield 0.73 g of the expected compound.

25     Infrared ( $\nu_{cm^{-1}}$ ): 2943 ( $\nu_{C-H}$ ); 1730 ( $\nu_{C=O}$  ester); 1686 ( $\nu_{C=O}$  carbamate); 1597, 1581, 1545 ( $\nu_{C=C}$ ); 1365 ( $\delta_{C-H}$  tBu); 1338 ( $\nu_{C-N}$ ); 1259, 1117 ( $\delta_{C-H}$ ).

Step E: *tert*-Butyl 2-[(2*SR*,3*SR*)-3-(methoxycarbonyl)-1-methylpiperidin-2-yl]-1*H*-indole-1-carboxylate

2.0 g of sodium cyanoborohydride are added at ambient temperature, in portions of 0.5 g every 5 min., to a solution of 1.36 g of the compound of the above Step D in 22 ml of methanol and 2 ml of aqueous 37% hydrochloric acid. Stirring is maintained for 30 min. before adding saturated aqueous potassium carbonate solution. The methanol is evaporated off under reduced pressure. The aqueous phase is extracted with dichloromethane. The organic phase is dried over sodium sulphate, filtered and concentrated under reduced pressure to yield 1.21 g of the expected compound.

Mass spectrometry (ES +,  $m/z$ ): 373 ( $M+H$ )<sup>+</sup>; 317.

Infrared ( $\nu_{cm-1}$ ): 2945 and 2785 ( $\nu_{C-H}$ ); 1729 ( $\nu_{C=O}$ ); 1452 ( $\nu_{C=C}$ ); 1369 ( $\delta_{C-H}$  *t*Bu); 1322 ( $\nu_{C-N}$ ); 1157 ( $\delta_{C-H}$ ).

Step F: Methyl (2*SR*,3*SR*)-2-(1*H*-indol-2-yl)-1-methylpiperidine-3-carboxylate

15 ml of trifluoroacetic acid are added to a solution of 0.57 mg of the compound of the above Step E in 5 ml of dichloromethane. The mixture is stirred at ambient temperature for 6 h and concentrated under reduced pressure. The residue is taken up in water and dichloromethane. Potassium carbonate is added until the pH of the aqueous phase is basic. The aqueous phase is extracted twice with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and concentrated under reduced pressure. Chromatography on a silica gel column (dichloromethane/methanol: 98/2) allows 365 mg of the expected compound to be obtained.

Mass spectrometry (ES +,  $m/z$ ): 273 ( $M+H$ )<sup>+</sup>.

Infrared ( $\nu_{cm-1}$ ): 3386 ( $\nu_{N-H}$ ); 2946 and 2789 ( $\nu_{C-H}$ ); 1721 ( $\nu_{C=O}$ ); 1456 and 1435 ( $\nu_{C=C}$ ); 1162 ( $\delta_{C-H}$ ).

PREPARATION 2: *tert*-Butyl (SR)-2-[*(2RS,3SR)*-3-(methoxycarbonyl)-1-methylpiperidin-2-yl]indoline-1-carboxylate

Step A: *tert*-Butyl (SR)-2-[*(2RS,3SR)*-3-(methoxycarbonyl)piperidin-2-yl]indoline-1-carboxylate

A mixture of 6.00 g of the compound of Step B of Preparation 1 and 7.0 g of 5% rhodium on alumina in 60 ml of acetic acid is stirred at ambient temperature under 15 bars of hydrogen pressure for 20 h. The reaction mixture is then filtered through paper. The paper is then rinsed with methanol. The filtrate is concentrated under reduced pressure and the residue is taken up in dichloromethane and water. Potassium carbonate is added until the pH of the aqueous phase is basic. The phases are separated and the aqueous phase is extracted twice with dichloromethane. The organic phases are combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. Chromatography on a silica gel column (dichloromethane/methanol: 95/5) allows 3.49 g of the expected compound to be obtained.

Melting point: 79-80°C

Mass spectrometry (ES<sup>+</sup>, *m/z*): 383 (*M*+Na)<sup>+</sup>; 361 (*M*+H)<sup>+</sup>; 305.

Elemental analysis:

|             | C %   | H %  | N %  |
|-------------|-------|------|------|
| Calculated: | 66.64 | 7.83 | 7.77 |
| Found:      | 66.45 | 7.96 | 7.67 |

Step B: *tert*-Butyl (SR)-2-[*(2RS,3SR)*-3-(methoxycarbonyl)-1-methylpiperidin-2-yl]indoline-1-carboxylate

0.15 ml of aqueous 37% aldehyde solution is added at ambient temperature to a solution of 0.50 g of the compound of the above Step A in 15 ml of acetonitrile. The solution is stirred at ambient temperature for 40 min. and then 1.5 ml of acetic acid is added. After 10 minutes' stirring, 100 mg of sodium borohydride are added in small portions. After the addition of the final portion, the reaction mixture is stirred for 1 h at ambient temperature and then water and potassium carbonate are added until the pH of the solution is basic. The

solution is then extracted three times with ethyl acetate. The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure to yield 0.50 g of the expected product.

*Infrared* ( $\nu_{cm-1}$ ): 2931 ( $\nu_{C-H}$ ); 1736 ( $\nu_{C=O}$  ester); 1702 ( $\nu_{C=O}$  carbamate); 1482 ( $\nu_{C=C}$ ); 1368 ( $\delta_{C-H}$ ).

**PREPARATION 3: *tert*-Butyl (RS)-2-[(2RS,3SR)-3-(methoxycarbonyl)piperidin-2-yl]indoline-1-carboxylate**

The product is obtained during the synthesis of the compound of Step A of Preparation 2. Chromatography on a silica gel column (dichloromethane/methanol: 95/5) allows 0.43 g of the expected product to be obtained.

*Infrared* ( $\nu_{cm-1}$ ): 3335 ( $\nu_{N-H}$ ); 2934 ( $\nu_{C-H}$ ); 1725 ( $\nu_{C=O}$  ester); 1697 ( $\nu_{C=O}$  carbamate); 1483 ( $\nu_{C=C}$ ); 1391 and 1368 ( $\delta_{C-H}$ ).

**PREPARATION 4: Methyl (2RS,3SR)-2-[(SR)-1-nitrosoindolin-2-yl]piperidine-3-carboxylate**

**Step A: Methyl (2RS,3SR) 2-[(SR)-indolin-2-yl]piperidine-3-carboxylate**

15 ml of trifluoroacetic acid are added at ambient temperature to a solution of 927 mg of the compound of Step A of Preparation 2 in 15 ml of dichloromethane. The mixture is stirred at ambient temperature for 2 h and concentrated under reduced pressure. The residue is taken up in dichloromethane and water. Potassium carbonate is added until the pH of the aqueous phase is basic. The aqueous phase is extracted with dichloromethane. The organic phases are combined, dried over sodium sulphate and concentrated under reduced pressure to yield 633 mg of the expected product.

*Infrared* ( $\nu_{cm-1}$ ): 3369 ( $\nu_{N-H}$ ); 2942 and 2857 ( $\nu_{C-H}$ ); 1720 ( $\nu_{C=O}$ ); 1485 ( $\nu_{C=C}$ ); 1249, 1197 and 1165 ( $\nu_{N-C}$ ).

Step B: Methyl (2RS,3SR)-2-[(SR)-1-Nitrosoindolin-2-yl]piperidine-3-carboxylate

633 mg of the compound of the above Step A are dissolved in a mixture of 6 ml of acetic acid and 6 ml of water at 0°C and a solution of 168 mg of sodium nitrite in 4 ml of water is added dropwise. The mixture is stirred for 20 min. at 0°C before adding dichloromethane.

Potassium carbonate is added until the pH of the aqueous phase is basic. The aqueous phase is extracted twice with dichloromethane. The organic phases are collected, dried over sodium sulphate and concentrated under reduced pressure. Chromatography on a silica gel column (dichloromethane/methanol: 99/1) allows 538 mg of the expected product to be isolated.

Infrared ( $\nu_{cm-1}$ ): 3314 ( $\nu_{N-H}$ ); 2939 and 2857 ( $\nu_{C-H}$ ); 1721 ( $\nu_{C=O}$ ); 1485 and 1477 ( $\nu_{C=C}$ ); 1430 ( $\nu_{N=O}$ ); 1168 ( $\nu_{C-N}$ ).

PREPARATION 5: tert-Butyl (SR)-2-[(2RS,3SR)-3-(methoxycarbonyl)-1-allylpiperidin-2-yl]indoline-1-carboxylate

0.3 ml of allyl bromide and 800 mg of potassium carbonate are added in succession at ambient temperature to a solution of 440 mg of the compound of Step A of Preparation 2 in 10 ml of acetonitrile. The mixture is stirred at ambient temperature for 3 h and then water is added. The aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and concentrated under reduced pressure. Chromatography on a silica gel column (cyclohexane/ethyl acetate: 8/2) allows 382 mg of the expected product to be isolated.

Melting point: 119-121°C

Elemental analysis:

|             | C %   | H %  | N %  |
|-------------|-------|------|------|
| Calculated: | 68.97 | 8.05 | 6.99 |
| Found:      | 68.85 | 8.15 | 7.04 |

PREPARATION 6: *tert*-Butyl (RS)-2-[ (2SR,3SR)-3-(methoxycarbonyl)-1-allylpiperidin-2-yl]indoline-1-carboxylate

0.80 g of a solution of the compound of Preparation 5 in 10 ml of THF is added to a solution of sodium methanolate in methanol (prepared by adding 0.23 g of sodium in small portions to 10 ml of methanol at 0°C). The reaction mixture is heated for 3 hours with reflux of the solvent. After the reaction mixture has been cooled to ambient temperature, 15 ml of water are added; the methanol and THF are removed by evaporation under reduced pressure. The resulting solution is extracted twice with ethyl acetate. The organic phases are combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. Chromatography on a silica gel column (cyclohexane/diethyl ether: 9/1) allows 0.58 g of the expected product to be isolated.

Infrared ( $\nu_{cm^{-1}}$ ): 2929 ( $\nu_{C-H}$ ); 1732 ( $\nu_{C=O}$  ester); 1698 ( $\nu_{C=O}$  carbamate); 1483 ( $\nu_{C=C}$ ); 1369 ( $\delta_{C-H}$  *t*Bu).

PREPARATION 7: Methyl (2RS,3SR)-2-[ (RS)-indolin-2-yl]-1-methylpiperidine-3-carboxylate

Step A: *tert*-Butyl (RS)-2-[ (2RS,3SR)-3-(methoxycarbonyl)-1-methylpiperidin-2-yl]-indoline-1-carboxylate

0.12 ml of aqueous 37% formaldehyde solution is added at ambient temperature to a solution of 0.43 g of the compound of Preparation 3 in 10 ml of acetonitrile. The solution is stirred at ambient temperature for 40 min. and then 1.0 ml of acetic acid is added. After 10 minutes' stirring, 75 mg of sodium borohydride are added in small portions. After the addition of the final fraction, the reaction mixture is stirred for 1 h at ambient temperature and then water is added. Potassium carbonate is added until the pH of the solution is basic. The solution is extracted three times with dichloromethane. The organic phases are combined, dried over sodium sulphate, filtered and concentrated under reduced pressure to yield 0.37 g of the expected product.

Melting point: 100-104°C.

Infrared ( $\nu_{cm^{-1}}$ ): 2948 and 2773 ( $\nu_{C-H}$ ); 1736 ( $\nu_{C=O}$  ester); 1694 ( $\nu_{C=O}$  carbamate); 1485 ( $\nu_{C=C}$ ); 1390 ( $\delta_{C-H}$  *t*Bu).

Step B: Methyl (2*RS*,3*SR*)-2-[(*RS*)-Indolin-2-yl]-1-methylpiperidine-3-carboxylate

The product is obtained in accordance with the procedure of Step A of Preparation 4, with the replacement of the compound of Step A of Preparation 2 with the compound of the above Step A.

Infrared ( $\nu_{cm^{-1}}$ ): 3396 ( $\nu_{N-H}$ ); 2939 and 2858 ( $\nu_{C-H}$ ); 1727( $\nu_{C=O}$ ); 1485 ( $\nu_{C=C}$ ).

PREPARATION 8: Methyl (1*RS*,4*aRS*,9*aRS*)-(2-propyl-2,3,4,4*a*,9,9*a*-hexahydro-1*H*- $\beta$ -carbolin-1-yl)acetate

Step A: Methyl (*RS*)-(2,3,4,9-tetrahydro-1*H*- $\beta$ -carbolin-1-yl)acetate

4.4 ml of methyl cyanoacetate and then 550 mg of 10% Pd/C are added to a solution of 8 g of tryptamine in 150 ml of glacial acetic acid. After degassing under reduced pressure, the reaction mixture is placed under a hydrogen atmosphere at ambient temperature and then stirred for 72 hours. The suspension is filtered over Celite (elution: methanol). The solution is evaporated under reduced pressure and the residue is taken up in dichloromethane and in water. The aqueous phase is rendered alkaline to pH 10 by the addition of sodium carbonate. The organic phase is recovered and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and then evaporated under reduced pressure. Flash chromatography on silica gel (ethyl acetate/methanol: 95/5) allows 7.7 g of the expected product to be obtained.

Melting point: 98°C.

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 68.83 | 6.60 | 11.47 |
| Found:      | 68.69 | 6.74 | 11.34 |

**Step B: Methyl (RS)-(2-propyl-2,3,4,9-tetrahydro-1H- $\beta$ -carbolin-1-yl)acetate**

There are added to a solution of 2.1 g of the compound of the above Step A in 40 ml of a 95/5 methanol/acetic acid mixture at 0°C 1.32 ml of propionaldehyde and then 1.62 g of sodium cyanoborohydride in portions over a period of thirty minutes at 0°C. The solution is stirred for 1h 30 and diluted with dichloromethane and water; the aqueous phase is rendered alkaline by the addition of sodium carbonate. The organic phase is separated off and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered, and then evaporated under reduced pressure. Flash chromatography on silica gel (cyclohexane/ethyl acetate: 85/15 to 8/2) allows 2.2 g of the expected product to be obtained.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 3403; 3351 ( $\nu_{\text{N-H}}$ ); 3042 ( $\nu_{\text{=C-H}}$ ); 2957; 2926; 2848 ( $\nu_{\text{C-H}}$ ); 1722 ( $\nu_{\text{C=O}}$ ); 1608 ( $\nu_{\text{C=C}}$ ); 1456; 1436 ( $\delta_{\text{C-H}}$ ); 1360 ( $\nu_{\text{N-C}}$ ); 1231 ( $\nu_{\text{C-O}}$ ).

Elemental analysis:

|             | C %   | H %  | N %  |
|-------------|-------|------|------|
| Calculated: | 71.30 | 7.74 | 9.78 |
| Found:      | 71.03 | 7.95 | 9.59 |

**Step C: Methyl (1RS,4aRS,9aRS)-(2-propyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate**

5.56 ml of  $\text{BH}_3$ -THF complex (1M in THF) are added to a solution of 1.52 g of the compound of the above Step B in 40 ml of anhydrous THF which has been cooled to 0°C. The solution is stirred for 1h 30 at 0°C and is then diluted with dichloromethane and water. The aqueous phase is rendered alkaline to pH 10 and extracted twice with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and evaporated under reduced pressure. 1.6 g of amineborane is obtained. This amineborane is dissolved in 16 ml of TFA and the solution is stirred for 1h at ambient temperature. The solvent is removed by evaporation under reduced pressure and then the residue is taken up in dichloromethane and in water. The aqueous phase, rendered alkaline to pH 10 using sodium carbonate, is extracted twice with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered, and then evaporated under reduced

pressure. Flash chromatography on silica gel (cyclohexane/ethyl acetate: 85/15) allows 305 mg of the expected product to be obtained.

Melting point: 41°C.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 3261 ( $\nu_{\text{N-H}}$ ); 3033 ( $\nu_{\text{=C-H}}$ ); 2961; 2937; 2887; 2869; 2833 ( $\nu_{\text{C-H}}$ ); 1724 ( $\nu_{\text{C=O}}$ ); 1612 ( $\nu_{\text{C=C}}$ ); 1460; 1433 ( $\delta_{\text{C-H}}$ ); 1357; 1339 ( $\nu_{\text{C-N}}$ ); 1252; 1239 ( $\nu_{\text{C-O}}$ ).

Elemental analysis:

|             | C %   | H %  | N %  |
|-------------|-------|------|------|
| Calculated: | 70.80 | 8.39 | 9.71 |
| Found:      | 70.70 | 8.16 | 9.63 |

**PREPARATION 9: Methyl (1SR,4aRS,9aRS)-(9-amino-2-propyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate**

**Step A: Methyl (1SR,4aRS,9aRS)-(2-propyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate**

The product is obtained during the synthesis of the compound of Step C of Preparation 8.

Chromatography on a silica gel column (cyclohexane/ethyl acetate: 8/2) allows 760 mg of the expected product to be obtained.

Melting point: 85°C.

Mass spectrometry (ESI +, m/z): 289.2 (M + H<sup>+</sup>); 311.2 (M + Na<sup>+</sup>).

Elemental analysis:

|             | C %   | H %  | N %  |
|-------------|-------|------|------|
| Calculated: | 70.80 | 8.39 | 9.71 |
| Found:      | 70.77 | 8.52 | 9.60 |

**Step B: Methyl (1SR,4aRS,9aRS)-(9-nitroso-2-propyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate.**

A solution of 160 mg of NaNO<sub>2</sub> in 3 ml of water is added dropwise to a solution of 660 mg of the compound of the above Step A in 10 ml of a 1/1 acetic acid/water mixture at 0°C. The reaction mixture is then stirred for 30 min. at 0°C and subsequently diluted with

dichloromethane. The aqueous phase is rendered alkaline to pH 10 using sodium carbonate. The organic phase is separated and the aqueous phase is extracted twice with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and then evaporated. Flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2) allows the expected product to be obtained.

Melting point: 76°C.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 2955; 2929; 2877; 2840; 2806 ( $\nu_{\text{C-H}}$ ); 1732 ( $\nu_{\text{C=O}}$ ); 1474; 1455 ( $\delta_{\text{C-H}}$ ); 1370; 1356 ( $\nu_{\text{N-C}}$ ); 1242; 1204 ( $\nu_{\text{C-O}}$ ).

Elemental analysis:

|             |       |      |       |
|-------------|-------|------|-------|
|             | C %   | H %  | N %   |
| Calculated: | 64.33 | 7.30 | 13.24 |
| Found:      | 64.07 | 7.43 | 13.05 |

Step C: Methyl (1SR,4aRS,9aRS)-(9-amino-2-propyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate

10 ml of water, 1.89 g of ammonium carbonate and 1.28 g of zinc are added to a solution of 700 mg of the compound of the above Step B in 22 ml of ethanol at 0°C. The reaction mixture is stirred for 1h 30 at 0°C. The suspension is filtered over a frit (the insoluble material is washed with dichloromethane and with water). The organic phase is recovered and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered, and then evaporated under reduced pressure. Flash chromatography on silica gel (cyclohexane/ethyl acetate: 8/2 then 7/3) allows 250 mg of the expected product to be obtained.

Melting point: 82°C.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 3307 ( $\nu_{\text{N-H}}$ ); 2957; 2922; 2860 ( $\nu_{\text{C-H}}$ ); 1731 ( $\nu_{\text{C=O}}$ ); 1641; 1606 ( $\nu_{\text{C=C}}$ ); 1469; 1456 ( $\delta_{\text{C-H}}$ ); 1372 ( $\nu_{\text{N-C}}$ ); 1242; 1194 ( $\nu_{\text{C-O}}$ ).

Elemental analysis:

|             |       |      |       |
|-------------|-------|------|-------|
|             | C %   | H %  | N %   |
| Calculated: | 67.30 | 8.31 | 13.85 |
| Found:      | 67.29 | 8.43 | 13.79 |

PREPARATION 10: Methyl (1RS,4aSR,9aRS)-(2-propyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate

Step A: Methyl (RS)-(2-propyl-9-tert-butyloxycarbonyl-2,3,4,9-tetrahydro-1H- $\beta$ -carbolin-1-yl)acetate

425 mg of Boc<sub>2</sub>O and 16 mg of DMAP are added to a solution of 370 mg of the compound of Step B of Preparation 8 in 7 ml of anhydrous dichloromethane. The reaction mixture is stirred for three hours at ambient temperature and then evaporated under reduced pressure. Flash chromatography on silica gel (cyclohexane/ethyl acetate 85/15) allows 400 mg of the expected product to be obtained.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 2930; 2873; 2849 ( $\nu_{\text{C-H}}$ ); 1726 ( $\nu_{\text{C=O}}$ ); 1607 ( $\nu_{\text{C=C}}$ ); 1478; 1455 ( $\delta_{\text{C-H}}$ ); 1368 ( $\nu_{\text{N-C}}$ ); 1243; 1167 ( $\nu_{\text{C-O}}$ ).

Elemental analysis:

|             | C %   | H %  | N %  |
|-------------|-------|------|------|
| Calculated: | 68.37 | 7.82 | 7.37 |
| Found:      | 68.45 | 7.98 | 7.25 |

Step B: Methyl (1RS,4aSR,9aRS)-(2-propyl-9-tert-butyloxycarbonyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate

20 mg of platinum oxide are added to a solution of 200 mg of the compound of the above Step A in 4.5 ml of methanol. The system is degassed twice, placed under hydrogen pressure, and then stirred under a pressure of 4 bars for 24 hours. 20 mg of platinum oxide are again added, and the reaction mixture is stirred for an additional 24 hours. The suspension is filtered over Celite (eluant: dichloromethane) and then the solution is evaporated under reduced pressure. Flash chromatography on silica gel (cyclohexane/ethyl acetate: 9/1) allows 100 mg of the expected product to be obtained.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 2956; 2933; 2873 ( $\nu_{\text{C-H}}$ ); 1734; 1703 ( $\nu_{\text{C=O}}$ ); 1603 ( $\nu_{\text{C=C}}$ ); 1479; 1459 ( $\delta_{\text{C-H}}$ ); 1367 ( $\nu_{\text{N-C}}$ ); 1254; 1147 ( $\nu_{\text{C-O}}$ ).

Step C: Methyl (1RS,4aSR,9aRS)-(2-propyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate

1.5 ml of trifluoroacetic acid is added to a solution of 120 mg of the compound of the above Step B in 1.5 ml of anhydrous dichloromethane at 0°C. The solution is stirred for 30 minutes at 0°C and then for 30 minutes at ambient temperature. The reaction mixture is concentrated under reduced pressure and then the residue is taken up in dichloromethane and water. The aqueous phase is rendered alkaline to pH 10 using sodium carbonate. The organic phase is recovered and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered, and then evaporated under reduced pressure to yield 85 mg of the expected product.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 3366 ( $\nu_{\text{N-H}}$ ); 2932; 2872 ( $\nu_{\text{C-H}}$ ); 1731 ( $\nu_{\text{C=O}}$ ); 1610 ( $\nu_{\text{C=C}}$ ); 1543 ( $\delta_{\text{N-H}}$ ); 1484; 1464 ( $\delta_{\text{C-H}}$ ); 1371 ( $\nu_{\text{N-C}}$ ); 1250; 1200 ( $\nu_{\text{C-O}}$ ).

PREPARATION 11: Methyl (1SR,4aSR,9aRS)-(2-propyl-9-tert-butyloxycarbonyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate

The product is obtained during the synthesis of the compound of Step B of Preparation 10. Chromatography on a silica gel column (cyclohexane/ethyl acetate: 9/1) allows 30 mg of the expected product to be obtained.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 2933; 2872 ( $\nu_{\text{C-H}}$ ); 1737; 1690 ( $\nu_{\text{C=O}}$ ); 1603 ( $\nu_{\text{C=C}}$ ); 1479; 1460 ( $\delta_{\text{C-H}}$ ); 1383; 1367 ( $\nu_{\text{N-C}}$ ); 1253; 1165 ( $\nu_{\text{C-O}}$ ).

PREPARATION 12: Methyl (1RS,4aSR,9aRS)-(9-nitroso-2-propyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate

The product is obtained in accordance with the procedure of Step B of Preparation 9, with the replacement of the compound of Step A of Preparation 9 with the compound of the Step C of Preparation 10.

Flash chromatography on silica gel (cyclohexane/ethyl acetate: 85/15) allows 105 mg of the expected product to be obtained.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 2953; 2872 ( $\nu_{\text{C-H}}$ ); 1735 ( $\nu_{\text{C=O}}$ ); 1613 ( $\nu_{\text{C=C}}$ ); 1596 ( $\nu_{\text{N=O}}$ ); 1482; 1466 ( $\delta_{\text{C-H}}$ ); 1363 ( $\nu_{\text{N-C}}$ ); 1218; 1192 ( $\nu_{\text{C-O}}$ ).

**PREPARATION 13: Methyl (1RS,4aRS,9aRS)-(9-amino-2-propyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate**

5

**Step A: Methyl (1RS,4aRS,9aRS)-(9-nitroso-2-propyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate**

10

The product is obtained in accordance with the procedure of Step B of Preparation 9, with the replacement of the compound of Step A of Preparation 9 with the compound of Step C of Preparation 8.

Flash chromatography on silica gel (cyclohexane/ethyl acetate: 85/15) allows 150 mg of the expected product to be obtained.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 2955; 2932; 2872 ( $\nu_{\text{C-H}}$ ); 1737 ( $\nu_{\text{C=O}}$ ); 1612 ( $\nu_{\text{C=C}}$ ); 1435 ( $\delta_{\text{C-H}}$ ); 1367 ( $\nu_{\text{C-N}}$ ); 1270; 1236 ( $\nu_{\text{C-O}}$ ).

15

**Step B: Methyl (1RS,4aRS,9aRS)-(9-amino-2-propyl-2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate.**

The product is obtained in accordance with the procedure of Step C of Preparation 9, with the replacement of the compound of Step B of Preparation 9 with the compound of the above Step A.

20

Flash chromatography on silica gel (cyclohexane/ethyl acetate: 7/3) allows 90 mg of the expected product to be obtained.

Melting point: 57°C.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 3353 ( $\nu_{\text{N-H}}$ ); 2955; 2931; 2870; 2809 ( $\nu_{\text{C-H}}$ ); 1725 ( $\nu_{\text{C=O}}$ ); 1458; 1436 ( $\delta_{\text{C-H}}$ ); 1360 ( $\nu_{\text{C-N}}$ ); 1264; 1235 ( $\nu_{\text{C-O}}$ ).

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 67.30 | 8.31 | 13.85 |
| Found:      | 67.15 | 8.32 | 13.76 |

PREPARATION 14: *tert*-Butyl (2*SR*)-5-methoxy-2-[(2*RS*,3*SR*)-3-(methoxycarbonyl)-piperidin-2-yl]indoline-1-carboxylate

Step A: *tert*-Butyl 5-methoxy-1*H*-indole-1-carboxylate

10 15.57 g of di-*tert*-butyl carbonate and then, in small portions, 8.72 g of 4-(dimethylamino)-pyridine, are added to a solution of 7 g of 5-methoxyindole in 90 ml of THF. The solution is then stirred for two hours at ambient temperature and the reaction mixture is subsequently hydrolysed with 100 ml of water. The organic phase is then separated and extracted with diethyl ether (3 × 70 ml). The organic phases are collected, washed with 1M  
15 hydrochloric acid solution (150 ml) and then with saturated sodium chloride solution. After drying over sodium sulphate and evaporating the solvents off *in vacuo*, 11.76 g of the protected indole are obtained.

Melting point: 74-76°C.

20 Step B: [1-(*tert*-Butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl]boronic acid

26.3 ml of a 2M solution of lithium diisopropylamide is added dropwise at 0°C, under an argon atmosphere, to a solution of 10 g of *tert*-butyl 5-methoxy-1*H*-indole-1-carboxylate and 11.41 g of triisopropyl borate in 27 ml of anhydrous THF. The reaction mixture is then  
25 brought to ambient temperature, stirring being maintained for one hour. An aqueous 2M hydrochloric acid solution (70 ml) is then added to the reaction mixture and the pH of the aqueous phase is subsequently adjusted to a value of 7 using concentrated ammonium hydroxide solution. The phases are separated and the aqueous phase is extracted with ethyl acetate (3 × 70 ml). The organic phases are collected and then concentrated under reduced  
30 pressure. Water (50 ml) and pentane (50 ml) are added to the residual red oil and the round-bottomed flask is placed in an ultrasonic bath for one hour. The precipitate formed

in that manner is then filtered off and subsequently washed with pentane to obtain 10.88 g of the boronic acid in the title.

Melting point: 110-112°C.

5

Step C: *tert*-Butyl 5-methoxy-2-[3-(methoxycarbonyl)pyridin-2-yl]indole-1-carboxylate

A solution of 4.65 g of sodium carbonate in water (18 ml) and 1.65 g of tetrakis(triphenylphosphine)palladium are added in succession to a degassed solution of 3.09 g of methyl 2-bromonicotinate in 1,2-dimethoxyethane (58 ml) at 85°C. The reaction mixture is maintained at a temperature of 85°C, at which temperature a solution containing 5.00 g of the acid obtained in Step B in 18 ml of 1,2-dimethoxyethane is then added dropwise. Stirring is maintained for 6 hours at 85°C before returning to ambient temperature and adding water (60 ml). The phases are separated and the aqueous phase is extracted with diethyl ether (2 × 60 ml) and then with ethyl acetate (2 × 60 ml). The organic phases are collected, washed with saturated sodium chloride solution, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is purified by chromatography on a silica column using an ethyl acetate/cyclohexane (25/75) mixture as eluant to yield the expected coupling product in the form of an oil.

20 Infrared ( $\nu_{cm-1}$ ): 2980 ( $\nu_{C-H}$ ); 1726 ( $\nu_{C=O}$ ).

Step D: *tert*-Butyl (2SR)-5-methoxy-2-[3-(methoxycarbonyl)piperidin-2-yl]indoline-1-carboxylate

25 A mixture containing 5.40 g of *tert*-butyl 5-methoxy-2-[3-(methoxycarbonyl)pyridin-2-yl]indole-1-carboxylate and 5.90 g of 5% rhodium on alumina in glacial acetic acid (50 ml) is stirred at ambient temperature under a hydrogen pressure of 16 bars hydrogen for 16 hours. The reaction mixture is then filtered over Celite which is washed with methanol. The filtrate is then concentrated under reduced pressure and the residue is subsequently taken up in diethyl ether (60 ml) and water (100 ml). Potassium carbonate is added until a basic pH is obtained. The phases are separated and the aqueous phase is extracted with diethyl ether (60 ml) and then with ethyl acetate (2 × 60 ml). The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure.

30

The residue is subsequently purified by chromatography on a silica column, using diethyl ether as eluant, to yield 3.65 g of the title product.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 2934 ( $\nu_{\text{C-H}}$ ); 1725 ( $\nu_{\text{C=O}}$ ); 1693 ( $\nu_{\text{C=O}}$ ).

5 **PREPARATION 15: tert-Butyl (2RS)-5-methoxy-2-[(2RS,3SR)-3-(methoxycarbonyl)-piperidin-2-yl]indoline-1-carboxylate**

The product is obtained during the synthesis of the compound of Step D of Preparation 14.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 2936 ( $\nu_{\text{C-H}}$ ); 1725 ( $\nu_{\text{C=O}}$ ); 1691 ( $\nu_{\text{C=O}}$ ).

10

**PREPARATION 16: tert-Butyl (2SR)-5-fluoro-2-[(2RS,3SR)-3-(methoxycarbonyl)-piperidin-2-yl]indoline-1-carboxylate**

The product is obtained according to an analogous procedure to that described in Preparation 14 with the replacement of 5-methoxyindole with 5-fluoroindole.

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 2983 ( $\nu_{\text{C-H}}$ ); 1735 ( $\nu_{\text{C=O}}$ ).

15

**PREPARATION 17: tert-Butyl (2RS)-5-fluoro-2-[(2RS,3SR)-3-(methoxycarbonyl)-piperidin-2-yl]indoline-1-carboxylate**

The product is obtained during the synthesis of the compound of Step D of Preparation 16.

Melting point: 107-108°C.

20

**PREPARATION 18: tert-Butyl 5-chloro-2-[3-(methoxycarbonyl)pyridin-2-yl]indole-1-carboxylate**

The product is obtained in accordance with an analogous procedure to that described in Steps A, B, and C of Preparation 14 with the replacement of 5-methoxyindole with 5-chlororoindole.

Mass spectroscopy: [ES<sup>+</sup>] m/z = 409 [M+Na]<sup>+</sup>.

**PREPARATION 19: tert-Butyl 2-[3-(methoxycarbonyl)-1-methyl-1,4,5,6-tetrahydro-pyridin-2-yl]-3-methylindole-1-carboxylate**

**STEP A: tert-Butyl 3-methyl-1H-indole-1-carboxylate**

5  
50 g of di-*tert*-butyl carbonate and then 21 g of 4-(dimethylamino)pyridine are added to a solution of 15 g of 3-methylindole in 180 ml of tetrahydrofuran. The solution is stirred for 1 hour under an argon atmosphere. The reaction mixture is subsequently hydrolysed with water (300 ml), and the organic phase is separated and washed with 1M hydrochloric acid  
10 solution and then with saturated sodium chloride solution. After drying over sodium sulphate and then evaporating off the solvent *in vacuo*, the expected product is obtained.

Melting point: 106°C.

**STEP B: [1-(tert-Butyloxycarbonyl)-3-methyl-1H-indol-2-yl]boronic acid**

15  
Under an argon atmosphere, a 1.6M solution of *n*-butyllithium in 6 ml of hexane is added to a solution, cooled to -78°C, of 2.1 g of the compound obtained in the above Step in 25 ml of anhydrous tetrahydrofuran. Stirring is maintained for 30 min. before the addition of a solution of 1.87 g of triisopropyl borate in 10 ml of anhydrous tetrahydrofuran.  
20 Stirring of the mixture is maintained for 2 hours at ambient temperature before the addition of water (25 ml). After separation of the phases, the aqueous phase is extracted with diethyl ether (2 × 30 ml). The organic phases are collected, washed with 1M hydrochloric acid solution and dried over sodium sulphate. The residue obtained is suspended in a water/pentane mixture to yield the expected product after filtration and drying.

25  
<sup>1</sup>H NMR (400 MHz; DMSO-*d*<sub>6</sub>): δ (ppm) = 8.15 (sl, 2H); 8.07 (d, 1H, *J* = 8 Hz); 7.51 (d, 1H, *J* = 7 Hz); 7.28 (d, 1H, *J* = 8 Hz); 7.22 (t, 1H, *J* = 7 Hz); 2.20 (s, 3H); 1.60 (s, 9H).

**STEP C: tert-Butyl 2-[3-(methoxycarbonyl)pyridin-2-yl]-3-methylindole-1-carboxylate**

30  
The product is obtained in accordance with the same procedure as that described in Step C of Preparation 14, using a solution of the boronic acid described in the above Step.

<sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>):  $\delta$  (ppm) = 8.81 (dd, 1H,  $J$  = 1.5 4.8 Hz); 8.34 (dd, 1H,  $J$  = 1.8 8.1 Hz); 8.19 (d, 1H,  $J$  = 9.0 Hz); 7.55 (d, 1H,  $J$  = 2.1 Hz); 7.45 (dd, 1H,  $J$  = 4.8 7.8 Hz); 7.31 (dd, 1H,  $J$  = 2.1 9.0 Hz); 6.57 (s, 1H); 3.72 (s, 3H); 1.29 (s, 9H).

5 **STEP D: [2-[1-(tert-Butoxycarbonyl)-3-methyl-1H-indol-2-yl]-3-(methoxycarbonyl)-1-methyl]pyridinium iodide**

A mixture of 1.8 g of the compound obtained in Step C and 6.9 ml of iodomethane is stirred at ambient temperature for 3 days. The precipitate obtained is taken up in diethyl ether and filtered. The residue is washed twice with diethyl ether, and then a final time with pentane. The residue is dried *in vacuo* to yield the expected product.

10 <sup>1</sup>H NMR (400 MHz; DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 9.46 (d, 1H,  $J$  = 6.5 Hz); 9.08 (d, 1H,  $J$  = 8 Hz); 8.45 (dd, 1H,  $J$  = 6.5 and 8 Hz); 8.20 (d, 1H,  $J$  = 8 Hz); 7.76 (d, 1H,  $J$  = 8 Hz); 7.54 (t, 1H,  $J$  = 8 Hz); 7.40 (t, 1H,  $J$  = 8 Hz); 4.16 (s, 3H); 3.67 (s, 3H); 2.03 (s, 3H); 1.31 (s, 9H).

**STEP E: tert-Butyl 2-[3-(methoxycarbonyl)-1-methyl-1,4,5,6-tetrahydropyridin-2-yl]-3-methylindole-1-carboxylate**

15 A mixture of 2.1 g of the compound obtained in Step D, 12.8 ml of triethylamine and 187 mg of platinum oxide in 32 ml of methanol is stirred under a hydrogen atmosphere for 3 h. The mixture is then filtered over Celite and the filtrate is concentrated. The residue is taken up in diethyl ether and a white precipitate is formed, which is removed by filtration. The organic phase is dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue obtained is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (30/70) mixture to yield the expected product.

20 Melting point: 124°C.

**PREPARATION 20: tert-Butyl 2-[3-(methoxycarbonyl)-1-methyl-1,4,5,6-tetrahydropyridin-2-yl]-5-methylindole-1-carboxylate**

25

The product is obtained according to the same procedure as that described in Preparation 19, with the replacement of 5-methylindole with 3-methylindole.

<sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ (ppm) = 8.08 (d, 1H, J = 8 Hz); 7.27 (s, 1H); 7.09 (d, 1H, J = 8 Hz); 6.26 (s, 1H); 3.31 (s, 3H); 3.20-3.24 (m, 2H); 2.64-2.70 (m, 1H); 2.60 (s, 3H); 2.40 (s, 3H); 2.28-2.32 (m, 1H); 1.88-2.02 (m, 2H); 1.55 (s, 9H).

5 **PREPARATION 21: Methyl (2RS,3SR)-2-[(SR)-5-methoxy-1-nitrosoindolin-2-yl]-1-methylpiperidine-3-carboxylate**

**STEP A: Methyl (2RS,3SR)-2-[(SR)-5-methoxy-1-nitrosoindolin-2-yl]piperidine-3-carboxylate**

10 7.60 ml of trifluoroacetic acid are added to a solution of 1.92 g of the compound of Step D of Preparation 14 in 8 ml of dichloromethane. The mixture is stirred for 6 hours at ambient temperature and then concentrated under reduced pressure. The residue is taken up in diethyl ether and the salt, which has precipitated, is filtered off over a frit and then washed  
15 with diethyl ether. This solid is then dissolved in glacial acetic acid (9.5 ml) and water (9.5 ml). A solution containing 339 mg of sodium nitrite in 4.3 ml of water is then added dropwise, at 0°C, to the reaction mixture. After stirring for 30 minutes at 0°C, dichloromethane (20 ml) and water (20 ml) are added to the reaction mixture. Potassium carbonate is then added until the pH of the aqueous phase is basic. The phases are  
20 separated and the aqueous phase is extracted with dichloromethane (2 × 25 ml). The organic phases are combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The yellow solid obtained is then recrystallised from a pentane - ethanol mixture to yield the expected product.

Melting point: 152-153°C.

25 **STEP B: Methyl (2RS,3SR)-2-[(SR)-5-methoxy-1-nitrosoindolin-2-yl]-1-methylpiperidine-3-carboxylate**

30 An aqueous solution of 0.13 ml of 37% formaldehyde is added at ambient temperature to a solution containing 0.39 g of the compound of the above Step in 12 ml of acetonitrile. The solution is then stirred at ambient temperature for 40 minutes and acetic acid (1.35 ml) is subsequently added. After stirring for 10 minutes, 88 mg of sodium borohydride are added

in small portions. The mixture is then stirred at ambient temperature for one hour. Water (30 ml) is then added and the reaction mixture is rendered alkaline with potassium carbonate. The aqueous phase is extracted with ethyl acetate (3 × 20 ml) and then the organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue obtained is subsequently purified by chromatography on a silica column using an ethyl acetate/methanol (98/2) mixture as eluant to yield the expected product.

Melting point: 99-100°C.

**PREPARATION 22: Methyl (2SR,3SR)-2-[(RS)-1-aminoindolin-2-yl]-1-methyl-piperidine-3-carboxylate**

**STEP A: tert-Butyl (RS)-2-[(2SR,3SR)-3-(methoxycarbonyl)piperidin-2-yl]indoline-1-carboxylate**

0.54 g of sodium is added in small portions to 25 ml of methanol at 0°C under a nitrogen atmosphere. Once the sodium has dissolved completely, a solution of 1.68 g of the compound of Step A of Preparation 2 in 25 ml of methanol is added at ambient temperature. The mixture is then refluxed for 15 hours. The reaction mixture is subsequently brought to ambient temperature and then concentrated under reduced pressure. Water is added and the aqueous phase is extracted with ethyl acetate (3 × 20 ml). The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is purified by chromatography on silica gel using a cyclohexane/ethyl acetate (70/30) mixture as eluant to yield the expected product.

Melting point: 109°C.

**STEP B: Methyl (2SR,3SR)-2-[(RS)-indolin-2-yl]piperidine-3-carboxylate**

Trifluoroacetic acid (15 ml) is added to a solution of 0.70 g of the compound of the above Step in 15 ml of dichloromethane. The mixture is stirred at ambient temperature for one hour and then concentrated under reduced pressure. The residue is taken up in

dichloromethane (15 ml) and in water (15 ml). Potassium carbonate is added until the pH of the aqueous phase is basic. The phases are separated and the aqueous phase is extracted with dichloromethane (2 × 10 ml). The organic phases are collected, dried over sodium sulphate, filtered and concentrated *in vacuo* to yield the expected product, which is used without additional purification.

Melting point: 99-102°C.

Infrared ( $\nu_{cm^{-1}}$ ): 3353 ( $\nu_{N-H}$ ); 2948 and 2869 ( $\nu_{C-H}$ ); 1725 ( $\nu_{C=O}$ ); 1486 ( $\nu_{C=C}$ ).

**STEP C: Methyl (2SR,3SR)-2-[(RS)-1-nitrosoindolin-2-yl]piperidine-3-carboxylate**

A solution of 110 mg of sodium nitrite in 3 ml of water is added at 0°C to a solution of 0.43 g of the compound of the above Step in 8 ml of acetic acid and 8 ml of water. The mixture is stirred at that temperature for 30 minutes and then dichloromethane (20 ml) and water (10 ml) are added. Potassium carbonate is then added until the pH of the aqueous phase is basic. The phases are separated. The aqueous phase is extracted with dichloromethane (2 × 10 ml). The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is then purified by chromatography on silica gel, using an ethyl acetate/cyclohexane (60/40) mixture as eluant, to yield the expected product.

Melting point: 100-101°C.

**STEP D: Methyl (2SR, 3SR)-1-methyl-2-[(RS)-1-nitrosoindolin-2-yl]piperidine-3-carboxylate**

0.04 ml of aqueous 37% formaldehyde solution is added to a solution of 101 mg of the compound of the above Step in 2 ml of acetonitrile. The mixture is stirred at ambient temperature for 40 min. and then acetic acid (2 ml) is added. After 10 minutes, 23 mg of sodium borohydride are added, and stirring is maintained for 40 minutes before the addition thereto of water (10 ml) and then potassium carbonate until a basic pH is obtained. The aqueous phase is extracted twice with dichloromethane. The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure to yield the expected product.

Infrared ( $\nu$  cm<sup>-1</sup>): 2947 to 2792 ( $\nu_{C-H}$ ); 1730 ( $\nu_{C=O}$ ); 1485 ( $\nu_{C=C}$ ); 1428 ( $\nu_{N=O}$ ); 1154 ( $\nu_{C-N}$ ).

**STEP E: Methyl (2SR,3SR)-2-[*(RS)*-1-aminoindolin-2-yl]-1-methyl-piperidine-3-carboxylate**

5

0.19 g of zinc and 0.28 g of ammonium carbonate are added in succession, at 0°C, to a solution of 99 mg of the compound of the above Step in 4 ml of ethanol and 2 ml of water. The mixture is stirred at that temperature for 20 minutes and then filtered over Celite which is washed with water and dichloromethane. The phases of the filtrate are separated. The aqueous phase is extracted twice with dichloromethane. The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure to yield the expected product.

10

Melting point: 122-124°C.

15

**PREPARATION 23: Methyl (1RS,4aSR,9aRS)-(2-benzyl -2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate**

**STEP A: Methyl (RS)-(2-benzyl-2,3,4,9-tetrahydro-1H- $\beta$ -carbolin-1-yl)acetate**

20

The compound is obtained according to the same procedure as that used in Step B of Preparation 8, with the replacement of propionaldehyde with benzaldehyde.

**STEP B: Methyl (1RS,4aSR,9aRS)-(2-benzyl -2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carbolin-1-yl)acetate**

25

The compound is obtained according to the same procedure as that used in Preparation 10, with the replacement of the compound of Step B of Preparation 8 with that of the above Step A.

**EXAMPLE 1: (4aSR,11aSR,11bSR)-1-Methyl-1,2,3,4,4a,11,11a,11b-octahydro-1,6,6a-triazabenzofluoren-5-one**

2.3 ml of a 1M solution of borane-THF complex in THF is added dropwise under a nitrogen atmosphere to a solution of 563 mg of the compound of Preparation 1 in 20 ml of anhydrous THF at 0°C. Stirring is maintained for 30 min. at 0°C and the reaction mixture is concentrated under reduced pressure. The residue is dissolved in 20 ml of trifluoroacetic acid and the mixture is stirred for 1 hour at ambient temperature before being concentrated under reduced pressure. The residue is taken up in dichloromethane and water. Potassium carbonate is added until the pH of the aqueous phase is basic. The aqueous phase is extracted twice with dichloromethane. The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is purified by chromatography on a silica gel column (dichloromethane/methanol: 9/1) to yield a mixture containing the reduced product. This mixture is dissolved in 10 ml of acetic acid and 10 ml of water and cooled to 0°C. A solution of 0.62 g of sodium nitrite in 20 ml of water is then added dropwise. After stirring for 1 hour at 0°C, 20 ml of dichloromethane are added, followed by potassium carbonate until the pH of the aqueous phase is basic. The aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is dissolved in a mixture of 8 ml of ethanol and 4 ml of water and cooled to 0°C. 0.64 g of zinc and 0.94 g of ammonium carbonate are added in succession and the reaction mixture is stirred for 15 min. at 0°C before being filtered. The zinc is subsequently washed with water and then with dichloromethane. The phases of the filtrate are separated. The aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is taken up in 10 ml of anhydrous dichloromethane, and 1.3 ml of a 2.0M solution of trimethylaluminium in hexane is added at -20°C under a nitrogen atmosphere. Stirring is maintained for 1 h at -20°C and then the reaction mixture is refluxed for 3 h. The solution is then poured into 20 ml of aqueous 20% sodium hydroxide solution. The aqueous phase is extracted twice with dichloromethane. The organic phases are dried over sodium sulphate, filtered and concentrated under reduced pressure. Chromatography on a silica gel column (cyclohexane/ethyl acetate: 3/7) allows 176 mg of the expected product to be obtained.

Melting point: 132°C.

Mass spectrometry (ES +, m/z): 258 (M+H)<sup>+</sup>.

Elemental analysis:

|                                    | C %   | H %  | N %   |
|------------------------------------|-------|------|-------|
| 5                      Calculated: | 70.01 | 7.44 | 16.33 |
| Found:                             | 69.79 | 7.64 | 16.13 |

**EXAMPLE 2: (4aSR,11aRS,11bSR)-1-Methyl-1,2,3,4,4a,11,11a,11b-octahydro-pyrido-[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

The product is obtained during the synthesis of the compound of Example 1.

10        Chromatography on a silica gel column (cyclohexane/ethyl acetate: 3/7) then (dichloromethane/methanol: 95/5) allows 134 mg of the expected product to be obtained.

Melting point: 157-159°C

Mass spectrometry (ES +, m/z): 243 (M+H)<sup>+</sup>.

Elemental analysis:

|                                     | C %   | H %  | N %   |
|-------------------------------------|-------|------|-------|
| 15                      Calculated: | 74.35 | 7.49 | 11.56 |
| Found:                              | 74.51 | 7.67 | 11.38 |

**EXAMPLE 3: (4aSR,11aSR,11bRS)-1-Methyl-1,2,3,4,4a,11,11a,11b-octahydro-pyrido-[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

20        5 ml of trifluoroacetic acid are added at ambient temperature to a solution of 180 mg of the compound of Preparation 2 in 5 ml of dichloromethane. The reaction mixture is stirred at that temperature for 2 h before being concentrated under reduced pressure. The residue is taken up in dichloromethane and water; potassium carbonate is then added until the pH of the aqueous phase is basic. After separation of the phases, the aqueous phase is extracted  
25        with dichloromethane. The organic phases are combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. Chromatography on a silica gel column (ethyl acetate/methanol: 9/1) allows 85 mg of the expected product to be obtained.

Melting point: 125-127°C.

Mass spectrometry (ES +, m/z): 243 (M+H)<sup>+</sup>.

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 74.35 | 7.49 | 11.56 |
| Found:      | 74.09 | 7.29 | 11.49 |

**EXAMPLE 4: [(4aSR,11aSR,11bRS)-5-Oxo-3,4,4a,5,6,11,11a,11b-octahydro-2H-1,6,6a-triazabenzofluoren-1-yl]acetonitrile**

0.1 ml of bromoacetonitrile and 0.5 g of potassium carbonate are added at ambient temperature to a solution of 351 mg of the compound of Preparation 4 in 10 ml of acetonitrile. The reaction mixture is stirred at ambient temperature for 3 h before adding 20 ml of water. After separation of the phases, the aqueous phase is extracted with ethyl acetate (3 × 10 ml). The organic phases are combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is then dissolved in 10 ml of ethanol and 5 ml of water and the solution is cooled to 0°C. 0.51 g of zinc and 0.75 g of ammonium carbonate are added in succession and the reaction mixture is stirred at 0°C for 15 min. before being filtered. The solid is washed with water and then with dichloromethane. After separation of the phases, the aqueous phase is extracted with dichloromethane. The organic phases are combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. Chromatography on a silica gel column (cyclohexane/ethyl acetate: 1/1) allows 66 mg of the expected product to be isolated.

Melting point: 223°C.

Mass spectrometry (ES +, m/z): 305 (M+Na)<sup>+</sup>.

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 68.06 | 6.43 | 19.84 |
| Found:      | 67.93 | 6.38 | 19.75 |

**EXAMPLE 5: (4aSR,11aSR,11bRS)-1-Allyl-1,2,3,4,4a,11,11a,11b-octahydro-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

Trifluoroacetic acid is added at ambient temperature to a solution of 80 mg of the compound of Preparation 5 in 3 ml of dichloromethane. The mixture is stirred at ambient temperature for 6 h. The reaction mixture is concentrated under reduced pressure. The residue is taken up in dichloromethane and water. Potassium carbonate is added until the pH of the aqueous phase is basic. After separation of the phases, the aqueous phase is extracted with dichloromethane. The organic phases are collected, filtered and concentrated under reduced pressure. Chromatography on a silica gel column (cyclohexane/ethyl acetate: 1/1) allows 36 mg of the expected product to be isolated.

Melting point: 145°C.

Mass spectrometry (ES +, m/z): 291 (M+Na)<sup>+</sup>.

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 76.09 | 7.51 | 10.44 |
| Found:      | 75.84 | 7.76 | 10.33 |

**EXAMPLE 6: (4aSR,11aRS,11bSR)-1-Allyl-1,2,3,4,4a,11,11a,11b-octahydro-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

The product is obtained according to the procedure of Example 5, with the replacement of the compound of Preparation 5 with the compound of Preparation 6.

Melting point: 163°C.

Mass spectrometry (ES +, m/z): 291 (M+Na)<sup>+</sup>.

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 76.09 | 7.51 | 10.44 |
| Found:      | 76.00 | 7.61 | 10.37 |

**EXAMPLE 7: (4aSR,11aSR,11bRS)-1-Methyl-1,2,3,4,4a,11,11a,11b-octahydro-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

The product is obtained according to the procedure of Example 4, with the replacement of bromoacetonitrile with iodomethane.

- 5 Chromatography on a silica gel column (ethyl acetate/methanol: 98/2) allows 124 mg of the expected product to be obtained.

Melting point: 231°C.

Mass spectrometry (ES +, m/z): 537 (2M+Na)<sup>+</sup>; 280 (M+Na)<sup>+</sup>.

Elemental analysis:

|    |             |       |      |       |
|----|-------------|-------|------|-------|
| 10 |             | C %   | H %  | N %   |
|    | Calculated: | 70.01 | 7.44 | 16.33 |
|    | Found:      | 70.08 | 7.56 | 16.30 |

**EXAMPLE 8: (4aSR,11aSR,11bRS)-1,2,3,4,4a,11,11a,11b-Octahydro-1,6,6a-triaza-benzof[*a*]fluoren-5-one**

- 15 1.14 g of zinc and 1.67 g of ammonium carbonate are added in succession to a solution of 0.56 g of the compound of Preparation 4 in 18 ml of ethanol and 9 ml of water at 0°C. The mixture is stirred at 0°C for 20 min. and then filtered. The solid is washed with water and dichloromethane. The phases of the filtrate are separated. The aqueous phase is extracted  
20 twice with dichloromethane. The organic phases are combined, dried over sodium sulphate and concentrated under reduced pressure. The residue is purified by chromatography on a silica gel column (dichloromethane/methanol 9/1) to yield a mixture of compounds. That mixture is then dissolved in 10 ml of anhydrous dichloromethane and cooled to -20°C under a nitrogen atmosphere. 1.2 ml of 2M trimethylaluminium solution is added to that solution. The reaction mixture is stirred at -20°C for 90 min. and then refluxed for 16 h  
25 before being cooled and poured into 24 ml of aqueous 1M hydrochloric acid solution. The phases are separated. Potassium carbonate is added to the aqueous phase until a basic pH is obtained. That solution is then extracted twice with dichloromethane. The organic phase is dried over sodium sulphate, filtered and concentrated under reduced pressure.

Chromatography on a silica gel column (ethyl acetate/methanol: 9/1) allows 158 mg of the expected product to be obtained.

Melting point: 211°C.

Mass spectrometry (ES +, m/z): 266 (M+Na)<sup>+</sup>; 244 (M+H)<sup>+</sup>.

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 69.11 | 7.04 | 17.24 |
| Found:      | 68.89 | 7.21 | 17.11 |

**EXAMPLE 9: (4aSR,11aSR,11bRS)-1,2,3,4,4a,11,11a,11b-Octahydropyrido[2',3':3,4]-pyrrolo[1,2-a]indol-5-one**

A mixture of 0.99 g of the compound of Step A of Preparation 4 and 2.22 g of potassium carbonate in 25 ml of acetonitrile is refluxed for 48 h. 20 ml of water are then added and the phases are separated. The aqueous phase is extracted twice with dichloromethane. The organic phases are combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is then taken up in 20 ml of diethyl ether and filtered to yield 0.60 g of the expected product.

Melting point: 194-196°C.

Mass spectrometry (ES +, m/z): 251 (M+Na)<sup>+</sup>; 229 (M+H)<sup>+</sup>.

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 73.66 | 7.06 | 12.17 |
| Found:      | 73.41 | 7.17 | 12.19 |

**EXAMPLE 10: [(4aSR,11aSR,11bRS)-5-Oxo-3,4,4a,11,11a,11b-hexahydro-2H,5H-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-1-yl]acetonitrile**

0.08 ml of bromoacetonitrile and 0.2 g of potassium carbonate are added in succession at ambient temperature to a solution of 100 mg of the compound of Example 9 in 10 ml of acetonitrile. The reaction mixture is stirred at ambient temperature for 4 h. 10 ml of water are then added and the phases are separated. The aqueous phase is extracted with ethyl

acetate. The organic phases are combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. Chromatography on a silica gel column (ethyl acetate/cyclohexane: 6/4) allows 85 mg of the expected product to be obtained.

Melting point: 172-173°C.

5 Mass spectrometry (ES +, m/z): 290 (M+Na)<sup>+</sup>.

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 71.89 | 6.41 | 15.72 |
| Found:      | 71.79 | 6.50 | 15.66 |

10 EXAMPLE 11: (4aSR,11aRS,11bRS)-1-Methyl-1,2,3,4,4a,11,11a,11b-octahydro-pyrido-[2',3':3,4]pyrrolo[1,2-a]indol-5-one

A solution of 0.26 g of the compound of Preparation 7 in 5 ml of THF is added at ambient temperature to 76 mg of a 60% sodium hydride suspension in oil in 5 ml of THF under a nitrogen atmosphere. The mixture is stirred at ambient temperature for 1 h. Water is added.

15 After separation of the phases, the aqueous phase is extracted with ethyl acetate. The organic phases are combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is then purified by chromatography on a silica gel column (cyclohexane/ethyl acetate: 6/4) to yield 120 mg of a solid which is taken up in 4 ml of THF and 4 ml of water. 100 mg of lithium hydroxide monohydrate are added and the  
20 mixture is stirred for 18 h at ambient temperature before adding water. The solution is extracted with ethyl acetate. The organic phase is washed with saturated sodium hydrogen carbonate solution, dried over sodium sulphate, filtered and concentrated under reduced pressure to yield 90 mg of the expected product.

Melting point: 135-136°C.

25 Mass spectrometry (ES +, m/z): 265 (M+Na)<sup>+</sup>; 243 (M+H)<sup>+</sup>.

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 74.35 | 7.49 | 11.56 |
| Found:      | 74.18 | 7.61 | 11.43 |

EXAMPLE 12: (4aSR,11aSR,11bRS)-1-(2-Hydroxyethyl)-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one

The product is obtained according to the procedure of Example 10, with the replacement of bromoacetonitrile with bromoethanol.

5 Chromatography on a silica gel column (ethyl acetate/methanol: 93/7) allows 75 mg of the expected product to be obtained.

Melting point: 158-159°C.

Mass spectrometry (ES +, m/z): 295 (M+Na)<sup>+</sup>.

Elemental analysis:

|    |             |       |      |       |
|----|-------------|-------|------|-------|
| 10 |             | C %   | H %  | N %   |
|    | Calculated: | 70.56 | 7.40 | 10.29 |
|    | Found:      | 70.69 | 7.43 | 10.20 |

EXAMPLE 13: (4aSR,11aSR,11bRS)-1-Prop-2-ynyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one

15 The product is obtained according to the procedure of Example 10, with the replacement of bromoacetonitrile with propargyl bromide.

Chromatography on a silica gel column (cyclohexane/ethyl acetate: 1/1) allows 88 mg of the expected product to be obtained.

Melting point: 149°C.

20 Mass spectrometry (ES +, m/z): 289 (M+Na)<sup>+</sup>.

Elemental analysis:

|  |             |       |      |       |
|--|-------------|-------|------|-------|
|  |             | C %   | H %  | N %   |
|  | Calculated: | 76.66 | 6.81 | 10.52 |
|  | Found:      | 76.68 | 6.89 | 10.46 |

**EXAMPLE 14: (4aSR,11aSR,11bRS)-1-[2-(Piperidin-1-yl)ethyl]-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

0.16 ml of triethylamine and then 0.06 ml of mesyl chloride are added at 0°C to a solution of 154 mg of the compound of Example 12 in 5 ml of dichloromethane under a nitrogen atmosphere. The mixture is stirred for 30 min. at 0°C and then for 1 h at ambient temperature before adding 10 ml of saturated sodium hydrogen carbonate solution. After separation of the phases, the aqueous phase is extracted twice with dichloromethane. The organic phases are combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is dissolved in 5 ml of acetonitrile and 0.17 ml of piperidine is added. The reaction mixture is stirred at ambient temperature for 48 h. Water is added. After separation of the phases, the aqueous phase is extracted twice with dichloromethane. The organic phases are combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. Chromatography on a silica gel column (dichloromethane/-methanol: 93/7) to obtain 63 mg of the expected product.

Melting point: 124°C.

Mass spectrometry (ES +, m/z): 362 (M+Na)<sup>+</sup>; 340 (M+H)<sup>+</sup>; 255.

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 74.30 | 8.61 | 12.38 |
| Found:      | 74.17 | 8.65 | 12.30 |

**EXAMPLE 15: (3aSR,6aRS,10cRS)-4-Propyl-(3a,4,5,6,6a,10c-hexahydro)-3H-1,4,10b-triazafluoranthene-2-one**

60 mg of 60% sodium hydride are added to 220 mg of a solution of the compound of Preparation 9 in 5 ml of anhydrous THF at 0°C. The solution is stirred for 30 minutes at 0°C and then stirred for 3 hours at ambient temperature. The solution is diluted with water and with dichloromethane. The organic phase is recovered and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered, and then evaporated under reduced pressure. Flash chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 97/3) allows 120 mg of the expected product to be obtained.

Melting point: 187°C.

*Mass spectrometry* (ESI +, m/z): 272.2 (M + H)<sup>+</sup>.

*Elemental analysis:*

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 70.82 | 7.80 | 15.49 |
| Found:      | 70.74 | 7.89 | 15.40 |

**EXAMPLE 16: (3aRS,10bSR,10cRS)-3-Propyl-2,3,3a,4,10b,10c-hexahydro-1H-benzo-[b]pyrido[2,3,4-gh]pyrrolizin-5-one**

9 mg of 60% sodium hydride are added at 0°C to a solution of 65 mg of the compound of Preparation 10 in 2 ml of anhydrous THF. After stirring for 30 minutes at 0°C, the solution is stirred for 2 hours at ambient temperature. The suspension is diluted with water and then extracted with dichloromethane. The aqueous phase is extracted twice with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and then evaporated under reduced pressure. Flash chromatography on silica gel (cyclohexane/ethyl acetate: 6/4) allows 40 mg of the expected product to be obtained.

*Melting point:* 103°C.

*Mass spectrometry* (ESI +, m/z): 257.1 (M + H)<sup>+</sup>; 279.1 (M + Na)<sup>+</sup>.

*Elemental analysis:*

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 74.97 | 7.86 | 10.93 |
| Found:      | 74.89 | 7.96 | 10.79 |

**EXAMPLE 17: (3aRS,6aSR,10cRS)-4-Propyl-3a,4,5,6,6a,10c-hexahydro-3H-1,4,10b-triazafluoranthene-2-one**

2 ml of water, 290 mg of ammonium carbonate and 200 mg of zinc are added to a solution of 105 mg of the compound of Preparation 12 in 3.5 ml of EtOH at 0°C. The reaction mixture is stirred for 20 min. at 0°C. The suspension is filtered over a frit (the insoluble material is washed with dichloromethane and with water). The organic phase is recovered and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and evaporated under reduced pressure. Flash

chromatography on silica gel (cyclohexane/ethyl acetate: 7/3) allows 70 mg of the expected product to be obtained.

Melting point: 98°C.

Mass spectrometry (ESI +, m/z): 272.2 (M + H)<sup>+</sup>.

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 70.82 | 7.80 | 15.49 |
| Found:      | 70.73 | 7.79 | 15.23 |

**EXAMPLE 18: (3aRS,6aRS,10cRS)-4-Propyl-3a,4,5,6,6a,10c-hexahydro-3H-1,4,10b-triazafluoranthene-2-one**

365 ml of 2M trimethylaluminium solution in hexane are added to a solution of 90 mg of the compound of Preparation 13 in 3 ml of anhydrous dichloromethane at -20°C. The solution is stirred for 1h 30 without controlling the temperature and is then diluted with 2 ml of anhydrous dichloromethane. The reaction mixture is stirred for 12 h at reflux, diluted with dichloromethane again and then poured into aqueous 20% (w/v) sodium hydroxide solution. The organic phase is recovered and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and evaporated under reduced pressure. Flash chromatography on silica gel (ethyl acetate/-methanol: 97/3) allows 50 mg of the expected product to be obtained.

Melting point: 143°C.

Infrared (ν<sub>cm-1</sub>): 3254; 3133 (ν<sub>N-H</sub>); 3004 (ν<sub>C-H</sub>); 2952; 2924; 2905; 2870 (ν<sub>C-H</sub>); 1636 (ν<sub>C=O</sub>); 1607 (ν<sub>C=C</sub>); 1459; 1443 (δ<sub>C-H</sub>); 1362; 1348 (ν<sub>C-N</sub>).

Elemental analysis:

|             | C %   | H %  | N %   |
|-------------|-------|------|-------|
| Calculated: | 70.82 | 7.80 | 15.49 |
| Found:      | 70.73 | 7.91 | 15.34 |

EXAMPLE 19: (4aSR,11aRS,11bSR)-1-Allyl-9-methoxy-1,2,3,4,4a,11,11a,11b-octahydro-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one

STEP 1: tert-Butyl (2SR)-5-methoxy-2-[(2RS,3SR)-1-allyl-3-(methoxycarbonyl)-piperidin-2-yl]indoline-1-carboxylate

5

4.46 g of potassium carbonate and 1.68 ml of allyl bromide are added at ambient temperature to a solution of 2.52 g of the compound of Preparation 14 in 20 ml of acetonitrile. The mixture is stirred at ambient temperature for 12 hours and then water (30 ml) is added. The phases are separated and the aqueous phase is extracted with ethyl acetate (3 × 25 ml). The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure to yield the *N*-allyl compound in the form of an oil.

10

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 2933 ( $\nu_{\text{C-H}}$ ); 1728 ( $\nu_{\text{C=O}}$ ); 1692 ( $\nu_{\text{C=O}}$ ).

15

STEP 2: tert-Butyl (2RS)-5-methoxy-2-[(2SR,3SR)-1-allyl-3-(methoxycarbonyl)-piperidin-2-yl]indoline-1-carboxylate

20

A solution of 2.68 g of the compound obtained in the above Step in freshly distilled tetrahydrofuran (31 ml) is added at ambient temperature to a solution of sodium methanolate [prepared with 0.72 g of sodium dissolved in 31 ml of freshly distilled methanol. The reaction mixture is refluxed for 3 hours; water (30 ml) is then added and the mixture is subsequently concentrated under reduced pressure. The residue is then taken up in ethyl acetate (30 ml) and in water (50 ml); the phases are separated and the aqueous phase is extracted with ethyl acetate (2 × 30 ml). The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure to yield the isomerisation product in the form of an oil.

25

Infrared ( $\nu_{\text{cm}^{-1}}$ ): 2931 ( $\nu_{\text{C-H}}$ ); 1730 ( $\nu_{\text{C=O}}$ ); 1692 ( $\nu_{\text{C=O}}$ ).

STEP 3: (4aSR,11aRS,11bSR)-1-Allyl-9-methoxy-1,2,3,4,4a,11,11a,11b-octahydro-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one

9 ml of trifluoroacetic acid are added to a solution of 2.48 g of the compound obtained in  
5 Step 2 in 9 ml of dichloromethane. The mixture is stirred for 6 hours at ambient  
temperature and then concentrated under reduced pressure. The residue is taken up in  
dichloromethane (20 ml) and water (30 ml). Potassium carbonate is then added until a  
basic pH is obtained. The phases are separated and the aqueous phase is extracted with  
10 dichloromethane (2 × 20 ml). The organic phases are collected, dried over sodium  
sulphate, filtered and concentrated under reduced pressure. The solid obtained is filtered  
and then washed with pentane and finally recrystallised from a pentane/diethyl ether  
mixture to yield 1.52 g of the expected product.

Melting point: 198-199°C.

15 EXAMPLE 20: (4aSR,11aRS,11bSR)-9-Methoxy-1-propyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one

A catalytic amount of 10% palladium-on-carbon is added to a solution of 300 mg of the  
compound of Example 19 in 15 ml of methanol. The round-bottomed flask is then placed  
20 under atmospheric hydrogen pressure; stirring is maintained for 12 hours at ambient  
temperature. The reaction mixture is then filtered over Celite which is washed with  
methanol. After evaporating off the solvent under reduced pressure, the residue obtained is  
purified by chromatography on a silica column using as eluant an ethyl acetate/methanol  
(95/5) mixture. The expected product is obtained in the form of solid recrystallised from a  
25 pentane – dichloromethane mixture.

Melting point: 170°C.

EXAMPLE 21: (4aSR,11aRS,11bSR)-9-Methoxy-1-methyl-1,2,3,4,4a,11,11a,11b-octahydro-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one

STEP 1: Mixture of (4aSR,11aRS,11bSR)-9-methoxy-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one and (4aSR,11aSR,11bRS)-9-methoxy-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one

A round-bottomed flask containing 0.45 g of the compound of Example 19, 40 mg of 10% palladium-on-carbon, 0.2 ml of glacial acetic acid and 1.60 ml of water is refluxed for 12 hours. After cooling, the reaction mixture is filtered over Celite which is washed with dichloromethane (50 ml) and with water (80 ml). After neutralisation of the reaction mixture by means of potassium carbonate, the phases are separated and the aqueous phase is extracted with dichloromethane (2 × 50 ml). The organic phases are then collected, dried over sodium sulphate and evaporated under reduced pressure. The mixture of the two diastereoisomers (inseparable) is purified by chromatography on a silica column using a dichloromethane/methanol (95/5) mixture as eluant.

STEP 2: (4aSR,11aRS,11bSR)-9-Methoxy-1-methyl-1,2,3,4,4a,11,11a,11b-octahydro-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one

82 µl of aqueous 37% formaldehyde solution is added at ambient temperature to a solution of 190 mg of the above mixture of diastereoisomers in 8 ml of acetonitrile. The solution is then stirred at ambient temperature for 40 minutes and acetic acid (0.85 ml) is subsequently added. After stirring for 10 minutes, sodium borohydride (56 mg; 1.47 mmol) is added in small portions. The reaction mixture is then stirred at ambient temperature for one hour. Subsequently, water (30 ml) is added and the reaction mixture is rendered alkaline with potassium carbonate. The aqueous phase is extracted with ethyl acetate (3 × 20 ml) and then the organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is subsequently purified by chromatography on a silica column using an ethyl acetate/methanol (95/5) mixture as eluant to yield the expected product, which is recrystallised from a pentane – diethyl ether mixture.

Melting point: 178°C.

**EXAMPLE 22: (4aSR,11aSR,11bRS)-9-Methoxy-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

5

The compound is obtained during the synthesis of the compound of Example 21 at the end of the chromatography step on a silica column using an ethyl acetate/methanol (95/5) mixture as eluant. The expected product is then recrystallised from a pentane – diethyl ether mixture.

10

Melting point: 164°C.

**EXAMPLE 23: (4aSR,11aSR,11bRS)-9-Methoxy-1,2,3,4,4a,11,11a,11b-octahydro-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

15

15 ml of trifluoroacetic acid are added to a solution of 3.70 g of the compound of Preparation 14 in 15 ml of dichloromethane. The reaction mixture is stirred for 6 hours at ambient temperature and then concentrated under reduced pressure. The residue is taken up in dichloromethane (20 ml) and water (30 ml). Potassium carbonate is then added until a basic pH is obtained. The phases are separated and the aqueous phase is extracted with

20 dichloromethane (2 × 20 ml). The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The solid obtained is filtered off and washed with pentane and then finally recrystallised from a pentane - diethyl ether mixture to yield the expected product.

20

Melting point: 187°C.

25

**EXAMPLE 24: (4aSR,11aSR,11bRS)-9-Fluoro-1,2,3,4,4a,11,11a,11b-octahydro-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

30

4 ml of trifluoroacetic acid are added to a solution of 1 g of the compound of Preparation 16 in 4 ml of dichloromethane. The mixture is stirred for 6 hours at ambient temperature then concentrated under reduced pressure. The residue is taken up in dichloromethane (20 ml) and water (30 ml). Potassium carbonate is then added until a

basic pH is obtained. The phases are separated and the aqueous phase is extracted with dichloromethane (2 × 20 ml). The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The resulting residue is then dissolved in freshly distilled tetrahydrofuran (10 ml) and subsequently added dropwise, at ambient temperature and under an argon atmosphere, to a 60% suspension of 320 mg of sodium hydride in freshly distilled tetrahydrofuran (15 ml). The mixture is stirred at ambient temperature for 3 hours and then water (30 ml) and ethyl acetate (20 ml) are added. The phases are separated and the aqueous phase is extracted with ethyl acetate (2 × 20 ml). The organic phases are collected, dried over sodium sulphate and evaporated under reduced pressure. The residue obtained is purified by chromatography on a silica column using an ethyl acetate/methanol (95/5) mixture as eluant, and then finally recrystallised from a pentane/diethyl ether mixture to yield the expected product.

Melting point: 231°C.

**EXAMPLE 25: (4aSR,11aSR,11bRS)-9-Fluoro-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

An aqueous 37% formaldehyde solution (0.42 ml) is added at ambient temperature to a solution of 1.47 g of the compound of Preparation 16 in 40 ml of acetonitrile. The solution is stirred at ambient temperature for 40 minutes and then acetic acid (4 ml) is added. After stirring for 10 minutes, 280 mg of sodium borohydride are added in small portions. The mixture is then stirred at ambient temperature for one hour. Water (30 ml) is subsequently added and the reaction mixture is rendered alkaline with potassium carbonate. The aqueous phase is extracted with ethyl acetate (3 × 20 ml) and then the organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue obtained is subsequently dissolved in dichloromethane (6 ml) and trifluoroacetic acid (6 ml; 76.70 mmol) is added. The mixture is stirred for 6 hours at ambient temperature and then concentrated under reduced pressure. The residue is taken up in dichloromethane (20 ml) and water (30 ml). Potassium carbonate is then added until a basic pH is obtained. The phases are separated and the aqueous phase is extracted with dichloromethane (2 × 20 ml). The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is purified by chromatography on a silica

column using an ethyl acetate/methanol (95/5) mixture as eluant, and subsequently recrystallised from a pentane/diethyl ether mixture to yield the expected compound.

Melting point: 158°C.

5 **EXAMPLE 26: (4aSR,11aRS,11bRS)-9-Fluoro-1-methyl-1,2,3,4,4a,11,11a,11b-octahydro-5H-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

An aqueous 37% formaldehyde solution (0.17 ml) is added at ambient temperature to a solution containing 618 mg of the compound of Preparation 17 in 20 ml of acetonitrile.

10 The solution is stirred at ambient temperature for 40 minutes and then acetic acid (2 ml) is added. After stirring for 10 minutes, 115 mg of sodium borohydride are added in small portions. The mixture is then stirred at ambient temperature for one hour. Water (15 ml) is subsequently added and the reaction mixture is rendered alkaline with potassium carbonate. The aqueous phase is extracted with ethyl acetate (3 × 10 ml) and then the

15 organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue obtained is subsequently dissolved in dichloromethane (3 ml) and trifluoroacetic acid (3 ml; 76.70 mmol) is added. The mixture is stirred for 6 hours at ambient temperature and then concentrated under reduced pressure. The residue is taken up in dichloromethane (10 ml) and water (15 ml). Potassium carbonate is then

20 added until a basic pH is obtained. The phases are separated and the aqueous phase is extracted with dichloromethane (2 × 100 ml). The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The resulting residue is then dissolved in freshly distilled tetrahydrofuran (10 ml) and subsequently added dropwise, at ambient temperature and under an argon atmosphere, to a 60% suspension of

25 103 mg of sodium hydride in 15 ml of freshly distilled tetrahydrofuran. The mixture is stirred at ambient temperature for one hour and then water (30 ml) and ethyl acetate (20 ml) are added. The phases are separated and the aqueous phase is extracted with ethyl acetate (2 × 20 ml). The organic phases are collected, dried over sodium sulphate and evaporated under reduced pressure. The residue obtained is purified by chromatography on

30 a silica column using an ethyl acetate/methanol (95/5) mixture as eluant, and then recrystallised from a pentane – diethyl ether mixture to yield the expected product.

EXAMPLE 27: (4aSR,11aSR,11bRS)-9-Chloro-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrindo[2',3':3,4]pyrrolo[1,2-a]indol-5-one

STEP 1: tert-Butyl (2SR)-5-chloro-2-[(2RS,3SR)-3-(methoxycarbonyl)piperidin-2-yl]indoline-1-carboxylate

A mixture of 4 g of the compound obtained in Preparation 18 and 4.24 g of 5% rhodium on alumina in 40 ml of glacial acetic acid is stirred at ambient temperature under a hydrogen pressure of 16 bars for 16 h. The reaction mixture is then filtered over Celite. The filtrate is concentrated under reduced pressure and the residue is taken up in dichloromethane and water. Potassium carbonate is added until the pH of the aqueous phase is basic. The phases are separated and the aqueous phase is extracted twice with dichloromethane. The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is then purified by chromatography on silica gel with diethyl ether containing 2% of methanol to yield the expected product.

Mass spectroscopy: [ES<sup>+</sup>] m/z = 417 [M+Na]<sup>+</sup>; 395 [M+H]<sup>+</sup>

STEP 2: tert-Butyl (2SR)-5-chloro-2-((2RS,3SR)-3-(methoxycarbonyl)-1-methylpiperidin-2-yl)indoline-1-carboxylate

An aqueous 37% formaldehyde solution (0.4 ml) is added at ambient temperature to a solution of 1.34 g of the compound obtained in the above Step in 40 ml of acetonitrile. The solution is stirred at ambient temperature for 40 min. and then acetic acid (4 ml) is added. After stirring for 15 min., 245 mg of sodium borohydride are added in small portions. The mixture is then stirred for 3 h. After evaporation of the residue, the latter is taken up in water and rendered alkaline with potassium carbonate. The aqueous phase is extracted with ethyl acetate and then the organic phases are collected, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue is purified by chromatography on a silica column eluted with a dichloromethane/methanol (98/2) mixture to yield the expected product.

Mass spectroscopy: [ES<sup>+</sup>] m/z = 409 [M+H]<sup>+</sup>

STEP 3: (4aSR,11aSR,11bRS)-9-Chloro-1-methyl-1,2,3,4,4a,11,11a,11b-octahydro-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one

Trifluoroacetic acid (20 ml) is added at ambient temperature to a solution of 769 mg of the compound obtained in the above Step in 20 ml of dichloromethane. The mixture is stirred at that temperature for 18 h before being concentrated under reduced pressure. The residue is taken up in ethyl acetate and water; potassium carbonate is then added until the pH of the aqueous phase is basic. The phases are separated and the aqueous phase is then extracted with ethyl acetate. The organic phases are collected, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue is purified by chromatography on silica gel with dichloromethane containing 1% of methanol to yield the expected product.

Melting point: 272°C.

EXAMPLE 28: 9-Chloro-1-methyl-1,2,3,4-tetrahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one

STEP 1: [2-[1-(tert-Butoxycarbonyl)-5-chloro-1H-indol-2-yl]-3-(methoxycarbonyl)-1-methyl]pyridinium iodide

A mixture of 2.242 g of the compound of Preparation 18 and 9 ml of iodomethane is stirred at ambient temperature for 3 days. The mixture is then concentrated under reduced pressure. The residue is washed first with diethyl ether. The ethereal phase is separated and the residue is dried. The expected pyridinium salt is obtained in the form of a solid by precipitation from a diethyl ether/ethyl acetate mixture.

Mass spectroscopy: [ES<sup>+</sup>] m/z = 401 [M-I]<sup>+</sup>

STEP 2: tert-Butyl 5-chloro-2-[3-(methoxycarbonyl)-1-methyl-1,4,5,6-tetrahydropyridin-2-yl]indole-1-carboxylate

A mixture of 1.5 g of the compound obtained in the above Step, 0.88 ml of triethylamine and 129 mg of platinum oxide in 15 ml of methanol is stirred under a hydrogen atmosphere

for 3 h. The mixture is then filtered over Celite and the filtrate is concentrated. The residue is taken up in dichloromethane and washed with water. The organic phase is dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue obtained is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (30/70) mixture to yield the expected product.

Melting point: 109°C.

**STEP 3: Methyl 2-(5-chloro-1H-indol-2-yl)-1-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate**

Trifluoroacetic acid (7 ml) is added to a solution of 583 mg of the compound obtained in the above Step in 5 ml of dichloromethane. The mixture is stirred for 6 h at ambient temperature and then concentrated under reduced pressure. The residue is taken up in water and dichloromethane. Saturated potassium carbonate solution is added to render the aqueous phase alkaline. The latter is extracted with dichloromethane and ethyl acetate. The organic phases are collected, dried over sodium sulphate and concentrated under reduced pressure. The residue is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (30/70) mixture to yield the expected product.

Melting point: 176°C.

**STEP 4: 9-Chloro-1-methyl-1,2,3,4-tetrahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

There are added to a solution of 350 mg of the compound obtained in the above Step in 50 ml of diethyl ether, Aliquat-336 (0.029 mmol) and then 28.4% sodium hydroxide solution (20 ml) until partial precipitation of the tetracyclic compound occurs in the reaction mixture. The precipitate is redissolved in a large amount of ethyl acetate and then the phases are separated and the aqueous phase is re-extracted with ethyl acetate. The organic phases are dried over sodium sulphate and then evaporated *in vacuo*. The crude product is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (50/50) mixture to yield the expected product. The latter is recrystallised from a diethyl ether/ethyl acetate mixture.

Melting point: 176°C.

**EXAMPLE 29: (4aSR,11bRS)-9-Chloro-1-methyl-1,2,3,4,4a,11b-hexahydro-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

194 mg of sodium cyanoborohydride are added in small fractions at ambient temperature to a solution of 168 mg of the compound of Example 28 in glacial acetic acid. The solution gradually loses its colour and is stirred for thirty minutes. The acetic acid is evaporated off and the residue is taken up in water and then rendered alkaline with saturated potassium carbonate solution and, finally, the aqueous phase is extracted with ethyl acetate. The crude product is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (30/70) mixture to yield 146 mg of the expected product. The latter is recrystallised from a petroleum ether/pentane mixture.

Melting point: 118°C.

**EXAMPLE 30: (4aSR,11aRS,11bRS)-9-Chloro-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

A mixture of 780 mg of the compound of Example 29 and 936 mg of 5% rhodium on alumina in 20 ml of glacial acetic acid is stirred at ambient temperature under a hydrogen pressure of 14 bars for 16 h. The reaction mixture is then filtered through cotton-wool, the filtrate is concentrated under reduced pressure and the residue is taken up in water. Potassium carbonate is added until the pH of the aqueous phase is basic. The aqueous phase is extracted with ethyl acetate, and the organic phase is dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue obtained is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (30/70) mixture to yield the expected product.

Melting point: 164°C.

**EXAMPLE 31: 9-Chloro-1,2,3,4-tetrahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

Trifluoroacetic acid (8 ml) is added to a solution of 2 g of the compound of Preparation 18 in 8 ml of dichloromethane. The mixture is stirred for 24 h at ambient temperature and then

concentrated under reduced pressure. The residue is taken up in water. Saturated potassium carbonate solution is added to render the aqueous phase alkaline. The latter is extracted with ethyl acetate. The organic phases are collected, dried over sodium sulphate and concentrated under reduced pressure. The residue so obtained is dissolved in ethyl acetate (30 ml). Aliquat-336 (0.13 mmol) and 28.4% sodium hydroxide solution (30 ml) are then added. The mixture is stirred for 24 h at ambient temperature. The phases are separated and the aqueous phase is extracted with ethyl acetate. The organic phase is dried over magnesium sulphate and then evaporated *in vacuo*. The crude product is subsequently purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (30/70) mixture to yield the expected product. Finally, the latter is recrystallised from ethyl acetate.

Melting point: 233°C.

**EXAMPLE 32: 1-Methyl-1,2,3,4-tetrahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

Trifluoroacetic acid (4 ml) is added to a solution of 795 mg of the compound obtained in Step D of Preparation 1 in 7 ml of dichloromethane. The mixture is stirred for 20 h at ambient temperature, then concentrated under reduced pressure. The residue is taken up in water and dichloromethane. Saturated potassium carbonate solution is added to render the aqueous phase alkaline. The latter is extracted with dichloromethane and ethyl acetate. The organic phases are collected, dried over sodium sulphate and concentrated under reduced pressure. The residue so obtained is dissolved in ethyl acetate (10 ml); Aliquat-336 (0.03 mmol) is added and then 28.4% sodium hydroxide solution (20 ml) is added until partial precipitation of the tetracyclic compound is observed in the reaction mixture. The precipitate is redissolved using an adequate amount of ethyl acetate. The phases are separated and the aqueous phase is re-extracted with ethyl acetate. The organic phase is dried over sodium sulphate and then evaporated *in vacuo*. The crude product is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (30/70) mixture to yield the expected product. Finally, the latter is recrystallised from a diethyl ether/ethyl acetate mixture.

Melting point: 202°C.

**EXAMPLE 33: (4aSR,11bRS)-1-Methyl-1,2,3,4,4a,11b-hexahydropyrido[2',3':3,4]-pyrrolo[1,2-a]indol-5-one**

Sodium cyanoborohydride (390 mg ) is added in small fractions, at ambient temperature, to a solution of 296 mg of the above compound in glacial acetic acid. The solution gradually loses its colour and is stirred for 30 min. The acetic acid is evaporated off, the residue is taken up in water and then rendered alkaline with saturated potassium carbonate solution and finally the aqueous phase is extracted with ethyl acetate. The crude product is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (50/50) mixture to yield the expected product. The latter is recrystallised from a petroleum ether/pentane mixture.

Melting point: 92°C.

**EXAMPLE 34: 1,2,3,4-Tetrahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

**STEP 1: tert-Butyl 2-[3-(methoxycarbonyl)-1,4,5,6-tetrahydropyridin-2-yl]indole-1-carboxylate**

A mixture of 2 g of the compound obtained in Step D of Preparation 1 and 2 g of 5% rhodium on alumina in 70 ml of ethyl acetate is stirred under a hydrogen atmosphere for 3 days. The mixture is then filtered over Celite. The organic phase is dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue obtained is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (30/70) mixture to yield the expected product.

Melting point: 170°C.

**STEP 2: 1,2,3,4-Tetrahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

Trifluoroacetic acid (10 ml) is added to a solution of 1.4 g of the compound obtained in the above Step in 10 ml of dichloromethane. The mixture is stirred for 24 h at ambient temperature and then concentrated under reduced pressure. The residue is taken up in water. Saturated potassium carbonate solution is added to render the aqueous phase

alkaline. The latter is extracted with ethyl acetate. The organic phases are collected, dried over sodium sulphate and concentrated under reduced pressure. The residue so obtained is dissolved in 30 ml of ethyl acetate. Aliquat-336 (0.10 mmol) and then 28.4% sodium hydroxide solution (25 ml) are added thereto. The biphasic mixture is stirred for 16 h at ambient temperature. The phases are separated and the aqueous phase is extracted with ethyl acetate. The organic phase is dried over magnesium sulphate and then evaporated *in vacuo*. This is added at ambient temperature to a suspension of 53 mg of sodium hydride in 6 ml of tetrahydrofuran. The mixture is stirred for three hours and then hydrolysed, and the aqueous phase is extracted with ethyl acetate. After evaporation, the crude product is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (30/70) mixture to yield the expected product. Finally, the latter is recrystallised from ethyl acetate.

Melting point: 284°C.

**EXAMPLE 35: 1,11-Dimethyl-1,2,3,4-tetrahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

Trifluoroacetic acid (25 ml) is added to a solution of 1.2 g of the compound of Preparation 19 in 25 ml of dichloromethane. The mixture is stirred for 3 h at ambient temperature and then concentrated under reduced pressure. The residue is taken up in diethyl ether cooled in an ice bath. The precipitate formed is filtered off, washed thoroughly with cooled diethyl ether and then recovered and dried *in vacuo*. The solid obtained is subsequently suspended in ethyl acetate (80 ml) and then 28.4% sodium hydroxide solution (20 ml) is added at 0°C. After returning to ambient temperature, Aliquat-336 is added until precipitation of the tetracyclic compound occurs in the reaction mixture. The reaction mixture is stirred for 2 h. The phases are separated and the aqueous phase is extracted with ethyl acetate. The organic phase is dried over sodium sulphate and then evaporated *in vacuo*. The crude product is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (50/50) mixture to yield the expected product. Finally, the latter is recrystallised from a diethyl ether/ethyl acetate mixture.

Melting point: 182°C.

**EXAMPLE 36: (11SR,11aRS)-1,11-Dimethyl-1,2,3,4,11,11a-hexahydropyrido-[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

450 mg of 5% rhodium on alumina are added to a solution of 400 mg of the compound of Example 35 in 60 ml of ethyl acetate. The mixture is stirred at ambient temperature under normal hydrogen pressure for 22 h. The reaction mixture is then filtered over Celite and the filtrate is concentrated under reduced pressure. The residue is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (50/50) mixture to yield the expected product. Finally, the latter is recrystallised from a diethyl ether/ethyl acetate mixture.

Melting point: 188°C.

**EXAMPLE 37: (4aSR,11bRS)-1,11-Dimethyl-1,2,3,4,4a,11b-hexahydropyrido-[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

Sodium cyanoborohydride (227 mg) is added in small fractions to a solution of 130 mg of the compound of Example 35 in 40 ml of glacial acetic acid at ambient temperature. The solution gradually loses its colour and is stirred for thirty minutes. The acid is evaporated off and the residue is taken up in water and then rendered alkaline with saturated potassium carbonate solution. The aqueous phase is extracted with ethyl acetate. The crude product is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (30/70) mixture to obtain the expected product. The latter is recrystallised from a diethyl ether/pentane mixture.

Melting point: 104°C.

**EXAMPLE 38: 1,9-Dimethyl-1,2,3,4-tetrahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

The product is obtained according to the same procedure as that described in Example 35, with the replacement of the compound obtained in Preparation 19 with that obtained in Preparation 20.

Melting point: 214°C.

**EXAMPLE 39: (4aSR,11bRS)-1,9-Dimethyl-1,2,3,4,4a,11b-hexahydropyrido-[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

5 The compound is obtained according to the same procedure as that described in Example 37, with the replacement of the compound of Example 35 with the compound of Example 38.

Melting point: 132°C.

10 **EXAMPLE 40: (11aRS)-1,9-Dimethyl-1,2,3,4,11,11a-hexahydropyrido[2',3':3,4]-pyrrolo[1,2-a]indol-5-one**

The compound is obtained according to the same procedure as that described in Example 36, with the replacement of the compound of Example 35 with the compound of  
15 Example 38. The residue so obtained is purified by chromatography on a silica column eluted with an ethyl acetate/cyclohexane (50/50) mixture to yield the compound of Example 39, and then with ethyl acetate to yield the expected compound.

Melting point: 185°C.

20 **EXAMPLE 41: 9-Methoxy-1-methyl-1,2,3,4-tetrahydro-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

The compound is obtained according to the same procedure as that described in Example 28, with the replacement of the compound of Preparation 18 with the compound  
25 obtained in Step C of Preparation 14.

**EXAMPLE 42: (4aSR,11bRS)-9-Methoxy-1-methyl-1,2,3,4,4a,11b-hexahydropyrido-[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

30 The compound is obtained according to the same procedure as that described in Example 29, with the replacement of the compound of Example 28 with the compound of Example 41.

EXAMPLE 43 and EXAMPLE 44: (4aS,11aR,11bS)-1-Allyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one and (4aR,11aS,11bR)-1-allyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one

5

The compounds of Examples 43 and 44 are prepared by separation of the racemic mixture obtained in Example 6 by applying the following operating conditions:

Analytical HPLC, CHIRALPAK AD-H column (amylose tris(3,5-dimethylphenylcarbamate) 4.6 mm X 150 mm, 5µm; semi-preparative HPLC, CHIRALPAK ADH column (amylose tris(3,5-dimethylphenylcarbamate), 10 mm X 250 mm, 5µm.

Solvent: heptane/isopropanol/0.2% triethylamine.

Retention time: 9.9 minutes and 12.2 minutes.

15 EXAMPLE 45 and EXAMPLE 46: (4aS,11aS,11bR)-1-Methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one and (4aR,11aR,11bS)-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one

The compounds of Examples 45 and 46 are prepared by separating the racemic mixture obtained in Example 3 by applying the operating conditions described in Examples 43 and 44.

Retention time: 4.5 minutes ( $[\alpha]_D = +20^\circ$ ) and 6.0 minutes ( $[\alpha]_D = -20^\circ$ ).

25 EXAMPLE 47: (4aSR,11aRS,11bSR)-1,2,3,4,4a,11,11a,11b-Octahydropyrido-[2',3':3,4]pyrrolo[1,2-a]indol-5-one

134 mg of 10% Pd/C are added to a solution of 140 mg of the compound of Example 6 in 150 µl of acetic acid (2.61 mmol) and 3 ml of water. The reaction mixture is heated for 2 hours with reflux of the solvent. The mixture is filtered over Celite and the solvent is evaporated off *in vacuo*. The residue is taken up in 1M hydrochloric acid (10 ml) and is then extracted with dichloromethane (3 x 30 ml). The aqueous phase is rendered alkaline with saturated sodium carbonate solution until a pH of 10 is obtained before being

30

extracted again with dichloromethane (3 x 30 ml). The organic phase is dried over sodium sulphate, filtered and concentrated under reduced pressure to yield the expected product. The latter is recrystallised from 2 ml of ethyl acetate.

Melting point: 176°C.

5

**EXAMPLE 48: (RS)-11,11a-Dihydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

Trifluoroacetic acid (5 ml) is added to a solution of 861 mg of the compound obtained in Step 1 of Example 34 in 5 ml of dichloromethane. The mixture is stirred for 24 h at  
10 ambient temperature and then concentrated under reduced pressure. The residue is taken up in water and dichloromethane. Saturated potassium carbonate solution is added to render the aqueous phase alkaline. The latter is extracted with dichloromethane and ethyl acetate. The organic phases are collected, dried over magnesium sulphate and concentrated under reduced pressure. The crude product so obtained is dissolved in tetrahydrofuran before  
15 being added to 328 mg of a sodium hydride suspension in 10 ml of tetrahydrofuran at ambient temperature. The mixture is stirred for 4 h. Water is then added and the aqueous phase is subsequently extracted several times with ethyl acetate. The organic phase is dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue obtained is purified by chromatography on a silica column eluted with an ethyl  
20 acetate/cyclohexane (30/70) mixture to yield the compound of Example 34 and the expected product.

Melting point: 168°C.

**EXAMPLE 49: (4aSR,11aSR,11bRS)-9-Methoxy-1-methyl-1,2,3,4,4a,11,11a,11b-octahydro-1,6,6a-triazabenzofluoren-5-one**

25 591 mg of zinc and 869 mg of ammonium carbonate are added at a temperature of 0°C to a solution containing 335 mg of the compound of Preparation 21 in a mixture of ethanol (10 ml) and water (5 ml). Stirring is maintained for 30 minutes at 0°C and then the reaction mixture is filtered over Celite which is washed with water and dichloromethane. The phases are separated and the aqueous phase is extracted with dichloromethane (3 x 20 ml).  
30 The organic phases are then collected, dried over sodium sulphate, filtered and

concentrated under reduced pressure. The residue obtained is subsequently purified by chromatography on a silica column using an ethyl acetate/methanol (95/5) mixture as eluant to yield the expected product.

Melting point: 195-197°C.

5 **EXAMPLE 50: (4aSR,11aRS,11bSR)-1-Methyl-1,2,3,4,4a,11,11a,11b-octahydro-1,6,6a-triazabenzofluoren-5-one**

0.33 ml of a 2M trimethylaluminium solution in hexane is added to a solution of 80 mg of the compound of Preparation 22 in 10 ml of methylene chloride under a nitrogen atmosphere at -20°C. The mixture is stirred for one hour at -20°C and is then refluxed for 10 4 hours. After returning to ambient temperature, the reaction mixture is poured into aqueous 20% sodium hydroxide solution (10 ml). The phases are separated. The aqueous phase is extracted twice with dichloromethane. The organic phases are collected, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue is purified by chromatography on silica gel using an ethyl acetate/methanol (98/2) mixture as 15 eluant to yield the expected product.

Mass spectrometry (ESI +, m/z): 280 (M+Na, 100%); 258 (M+H, 6%); 150 (7%).

**EXAMPLE 51 and EXAMPLE 52: (4aS,11aS,11bR)-1-Methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one and (4aR,11aR,11bS)-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one**

20

The compounds of Examples 51 and 52 are prepared by separating the racemic mixture obtained in Example 7.

Melting points: 168 and 169°C.

**EXAMPLE 53: (3aRS,10bSR,10cRS)-3-Benzyl-2,3,3a,4,10b,10c-hexahydrobenzo-[b]pyrido[2,3,4-gh]pyrrolizin-5(1H)-one**

25

The compound is obtained according to a procedure analogous to that used in Example 16, with the replacement of the compound of Preparation 10 with that of Preparation 23.

Melting points: 139°C.

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

#### **EXAMPLE A : Induction of tyrosine hydroxylase**

5 An investigation is made among the compounds for the capability of bringing about an increase in the tyrosine hydroxylase (TH) protein in the locus coeruleus (LC) in the brain of the Balb/C mouse.

The animals used are male mice of the pure Balb/C strain (Charles River Laboratories) aged 7 to 8 weeks at the time of treatment.

10 The mice are given a single injection, by the intraperitoneal route, of the compound under test, dissolved in 0.04M HCl solution (corresponding control: 0.004M HCl), if the compound is sufficiently soluble, or in olive oil 90% / DMSO 10% (corresponding control : olive oil 90% / DMSO 10%) for compounds that are insoluble in an aqueous medium.

15 Three days after the injection of each compound, all the animals are sacrificed by decapitation. The brains are removed and then frozen in liquid nitrogen and stored at -80°C.

Coronal sections 8 microns thick are then taken along the posterior-anterior axis of the LC and fixed. The sections are transferred onto Immobilon-P membranes. TH is measured by  
20 immunodetection and image analysis.

#### **Results :**

The results for TH induction in the LC are given in Table I below.

**TABLE I**

**Measurement of the amount of TH in the various LC sections, numbered from 1 to 8  
in the posterior-to-anterior direction, after i.p. administration (20 mg/kg)**

*The results are expressed in %, relative to the mean value of the control group<sup>1</sup>*

| %      | 1   | 2  | 3  | 4  | 5  | 6  | 7  | 8  |
|--------|-----|----|----|----|----|----|----|----|
| Ex. 3  | 104 | 97 | 69 | 58 | 49 | 31 | 10 | 8  |
| Ex. 6  | 65  | 62 | 50 | 53 | 41 | 27 | 9  | 6  |
| Ex. 7  | 59  | 57 | 57 | 51 | 28 | 23 | 13 | 4  |
| Ex. 8  | 59  | 61 | 59 | 50 | 33 | 17 | 9  | 5  |
| Ex.10  | 58  | 50 | 49 | 47 | 34 | 26 | 18 | 1  |
| Ex. 15 | 79  | 75 | 72 | 79 | 33 | 27 | 7  | 5  |
| Ex. 17 | 73  | 72 | 56 | 38 | 34 | 36 | 13 | 3  |
| Ex. 19 | 49  | 48 | 55 | 50 | 21 | 15 | 6  | 9  |
| Ex. 24 | 51  | 71 | 63 | 55 | 44 | 33 | 6  | 3  |
| Ex. 27 | 55  | 67 | 54 | 46 | 26 | 29 | 3  | 5  |
| Ex. 38 | 64  | 99 | 76 | 62 | 27 | 14 | -3 | 5  |
| Ex. 40 | 72  | 96 | 66 | 66 | 58 | 34 | 39 | 4  |
| Ex. 43 | 69  | 88 | 87 | 60 | 36 | 34 | 9  | 4  |
| Ex. 44 | 83  | 99 | 78 | 58 | 38 | 29 | 18 | 3  |
| Ex. 52 | 69  | 86 | 79 | 77 | 40 | 22 | 12 | 1  |
| Ex. 53 | 82  | 68 | 64 | 71 | 53 | 52 | 32 | 18 |

5

<sup>1</sup>animals treated with the same carrier

**EXAMPLE B : Affinity for receptors**

The affinity for receptors is determined according to customary methods relating the specific ligand and the receptor, which may be of animal origin or a human recombinant.

10 The affinity was determined by the method of displacement of the labelled specific ligand by the compound under test and expressed by the dissociation constant  $K_i$ .

The receptor affinity was accordingly studied for 28 conventional receptors. The study shows that the TH induction observed does not proceed by way of affinity for receptors

customarily affected by psychotropic compounds, such as alpha adrenergic receptors (type  $\alpha_2$ ), 5HT receptors (type 5HT<sub>2A</sub>) or dopaminergic receptors (types D<sub>1</sub> and D<sub>2</sub>).

Some compounds exhibit an affinity for sigma ( $\sigma$ ) receptors (ligand: haloperidol) or muscarinic (M) receptors that is not insignificant.

**TABLE II**

| % inhibition<br>concentration (M) | $\alpha_2$       |                  | 5HT <sub>2A</sub> |                  | D <sub>1</sub>   |                  | D <sub>2</sub>   |                  | M                |                  | $\sigma$         |                  |
|-----------------------------------|------------------|------------------|-------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                                   | 10 <sup>-7</sup> | 10 <sup>-5</sup> | 10 <sup>-7</sup>  | 10 <sup>-5</sup> | 10 <sup>-7</sup> | 10 <sup>-5</sup> | 10 <sup>-7</sup> | 10 <sup>-5</sup> | 10 <sup>-7</sup> | 10 <sup>-5</sup> | 10 <sup>-7</sup> | 10 <sup>-5</sup> |
| Example 3                         | —                | —                | —                 | 84               | —                | 39               | —                | —                | —                | —                | —                | —                |
| Example 19                        | —                | —                | —                 | —                | —                | —                | —                | —                | —                | —                | 10               | 36               |
| Example 27                        |                  | 10               |                   | 84               |                  |                  |                  |                  |                  |                  |                  | 10               |
| Example 45                        |                  | 23               | 13                | 92               |                  | 49               |                  |                  |                  |                  |                  |                  |

**EXAMPLE C : Predicted crossing of the blood-brain barrier (BBB)**

The substances are incubated at 20 $\mu$ M in the upper compartment of a double vessel, the upper compartment being separated from the lower compartment either solely by a polycarbonate filter or by the same filter covered with confluent endothelial cells from bovine capillaries. Evaluation of the permeability kinetics is carried out by means of LC-LS-MS quantification of the unchanged substance in the lower compartment after 10, 20, 30, 40 and 60 minutes.

The compounds tested exhibit a generally high degree of crossing of the BBB, which promotes access to the neurological target. The results are given in the form of the categories : high, intermediate, low. Accordingly, Example 17 exhibits a high degree of crossing of the BBB.

**EXAMPLE D : Predicted metabolic stability**

The predicted metabolic stability is tested by incubation of the compounds at a concentration of 10<sup>-7</sup>M in the presence of mouse, rat or human hepatic microsomes (0.33 mg of prot/ml). After addition of NADPH (nicotinamide adenine dinucleotide phosphate, reduced form), samples are taken at 0, 5, 15, 30 and 60 minutes. The enzymatic

reaction is stopped using methanol (V/V). The protein is precipitated by centrifugation and the supernatant is analysed by LC-MS-MS.

Good metabolic stability of the compounds makes it possible to envisage treatment *per os*.

**TABLE III**

**% metabolic stability predicted using hepatic microsomes**

|            | Mouse | Rat | Human |
|------------|-------|-----|-------|
| Example 3  | 61    | 31  | 59    |
| Example 8  | 86    | 52  | 80    |
| Example 47 | 99    | 5   | 86    |

**EXAMPLE E : Pharmaceutical composition**

Preparation formula for 1000 tablets each containing a dose of 10 mg

Compound of Example 8..... 10 g

Hydroxypropylcellulose ..... 2 g

Wheat starch ..... 10 g

Lactose..... 100 g

Magnesium stearate ..... 3 g

Talc ..... 3g

( )

( )



( )

or R<sub>3</sub> and R<sub>4</sub>, together with the carbon atoms carrying them, form a carbon-carbon bond,

R<sub>5</sub> represents a hydrogen atom, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

R<sub>6</sub> represents a hydrogen atom, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

R<sub>7</sub>, R<sub>8</sub> represent a hydrogen atom, a group linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl-(C<sub>1</sub>-C<sub>6</sub>)alkyl in which the alkyl moiety may be linear or branched, linear or branched (C<sub>2</sub>-C<sub>6</sub>)alkenyl, linear or branched (C<sub>2</sub>-C<sub>6</sub>)alkynyl, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl chain substituted by one or more hydroxy, cyano, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, NR<sub>13</sub>R<sub>14</sub>, a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkenyl chain substituted by the same substituents as those defined for the alkyl chain, or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkynyl chain substituted by the same substituents as those defined for the alkyl chain,

10 or,

either R<sub>5</sub> and R<sub>8</sub>, together with the carbon and nitrogen atoms carrying them, form a heterocycle having 5, 6 or 7 ring members, optionally substituted by a group R<sub>12</sub>,

or R<sub>6</sub> and R<sub>7</sub>, together with the carbon and nitrogen atoms carrying them, form a heterocycle having 5, 6 or 7 ring members, optionally substituted by a group R<sub>11</sub>,

15 it being understood that of necessity one, but only one, of the two groupings "R<sub>5</sub> and R<sub>8</sub>" or "R<sub>6</sub> and R<sub>7</sub>" together with the carbon and nitrogen atoms carrying them forms a heterocycle having 5, 6 or 7 ring members, optionally substituted by a group R<sub>11</sub>,

20 R<sub>9</sub> represents hydrogen, 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, cyano, nitro, linear or branched (C<sub>1</sub>-C<sub>6</sub>)polyhaloalkyl, NR<sub>15</sub>R<sub>16</sub>, or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl chain substituted by one or more halogens, one or more hydroxy, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy, or NR<sub>15</sub>R<sub>16</sub>,

n represents an integer 0, 1, 2, 3 or 4,

R<sub>10</sub> represents hydrogen, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>2</sub>-C<sub>6</sub>)alkenyl, aryl-(C<sub>1</sub>-C<sub>6</sub>)alkyl in which the alkyl moiety may be linear or branched, linear or

branched (C<sub>1</sub>-C<sub>6</sub>)polyhaloalkyl, or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl chain substituted by one or more halogen atoms, one or more groups hydroxy, linear or branched (C<sub>1</sub>-C<sub>6</sub>)-alkoxy, or NR<sub>15</sub>R<sub>16</sub>,

R<sub>11</sub>, R<sub>12</sub>, which may be identical or different, represent a -COOT or -CH<sub>2</sub>O-U group wherein T and U, which may be identical or different, represent a hydrogen atom or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

R<sub>13</sub>, R<sub>14</sub>, which may be identical or different, represent a hydrogen atom or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group or, together with the nitrogen atom carrying them, form an optionally substituted heterocycle having from 4 to 8 ring members optionally containing a double bond in the heterocycle and optionally containing in the ring system a second hetero atom selected from an oxygen atom and a nitrogen atom,

R<sub>15</sub>, R<sub>16</sub>, which may be identical or different, represent a hydrogen atom or a group linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl, linear or branched (C<sub>2</sub>-C<sub>6</sub>)alkenyl,

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

wherein:

- (3a*SR*,4*SR*)-3-benzyl-4-ethyl-2,3,3a,4-tetrahydrobenzo[*b*]pyrido[2,3,4-*gh*]pyrrolizin-5(1*H*)-one,
  - pyrido[3',2':4,5]pyridazino[1,6-*a*]indol-5(6*H*)-one,
  - 6-methylpyrido[3',2':4,5]pyridazino[1,6-*a*]indol-5(6*H*)-one,
  - 6-methyl-1,2,3,4-tetrahydropyrido[3',2':4,5]pyridazino[1,6-*a*]indol-5(6*H*)-one,
  - (4a*R*,12b*R*)-6-methyl-1,2,3,4,4a,12b-hexahydropyrido[3',2':4,5]pyridazino[1,6-*a*]-indol-5(6*H*)-one,
  - 1-methyl-3a,10b-dihydro[1,2,3]triazolo[4',5':3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one,
  - 1-benzyl-3a,10b-dihydro[1,2,3]triazolo[4',5':3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one,
- do not form part of the invention,

aryl means a phenyl or naphthyl group, both groups optionally being substituted by one or more halogen atoms, nitro, amino, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl or linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy groups,

a heterocycle having 5, 6 or 7 ring members means a saturated or unsaturated monocyclic group having 5, 6 or 7 sides and containing one or two hetero atoms selected from nitrogen and oxygen; pyrrolidine, piperidine, azepane and pyridine may be mentioned,

as optionally substituted heterocycle having from 4 to 8 ring members optionally containing one or more double bonds in the heterocycle and optionally containing in the ring system a second hetero atom selected from an oxygen atom and a nitrogen atom, there may be mentioned, without implying any limitation, pyrrolidine, piperidine, azepane, piperazine and morpholine, wherein those heterocycles may optionally be substituted, including on the second nitrogen atom of piperazine, 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>)hydroxyalkyl, linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy-(C<sub>1</sub>-C<sub>6</sub>)alkyl and linear or branched (C<sub>1</sub>-C<sub>6</sub>)aminoalkyl in which the amino moiety may optionally be substituted by one or two identical or different linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl groups,

$\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$  mean the chiral centres that may be present in the compounds of formula (I).

their enantiomers and diastereoisomers and also addition salts thereof with a pharmaceutically acceptable acid or base.

2. Compounds of formula (I) according to claim 1, wherein X represents CO, their enantiomers and diastereoisomers and also addition salts thereof with a pharmaceutically acceptable acid or base.

3. Compounds of formula (I) according to claim 1, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> each represent a hydrogen atom, their enantiomers and diastereoisomers and also addition salts thereof with a pharmaceutically acceptable acid or base.

4. Compounds of formula (I) according to claim 1, wherein R<sub>1</sub> and R<sub>2</sub>, together with the carbon atoms carrying them, form a carbon-carbon bond, their enantiomers and diastereoisomers and also addition salts thereof with a pharmaceutically acceptable acid or base.

5

5. Compounds of formula (I) according to claim 1, wherein R<sub>3</sub> and R<sub>4</sub>, together with the carbon atoms carrying them, form a carbon-carbon bond, their enantiomers and diastereoisomers and also addition salts thereof with a pharmaceutically acceptable acid or base.

10

6. Compounds of formula (I) according to claim 1, wherein n represents an integer 1, their enantiomers and diastereoisomers and also addition salts thereof with a pharmaceutically acceptable acid or base.

15

7. Compounds of formula (I) according to claim 1, wherein R<sub>9</sub> represents a hydrogen or halogen atom, or a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl or linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxy group, their enantiomers and diastereoisomers and also addition salts thereof with a pharmaceutically acceptable acid or base.

20

8. Compounds of formula (I) according to claim 1, wherein R<sub>5</sub> and R<sub>8</sub>, together with the carbon and nitrogen atoms carrying them, form a heterocycle having 5, 6 or 7 ring members and more especially a heterocycle having 6 ring members, their enantiomers and diastereoisomers and also addition salts thereof with a pharmaceutically acceptable acid or base.

25

9. Compounds of formula (I) according to claim 1, wherein R<sub>6</sub> and R<sub>7</sub>, together with the carbon and nitrogen atoms carrying them, form a heterocycle having 5, 6 or 7 ring members and more especially a heterocycle having 6 ring members, their enantiomers and diastereoisomers and also addition salts thereof with a pharmaceutically acceptable acid or base.

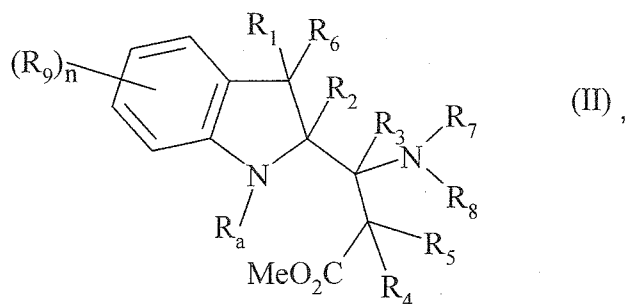
10. Compounds of formula (I) which are:

- (4a*SR*,11a*SR*,11b*RS*)-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo-[1,2-*a*]indol-5-one,
- (4a*SR*,11a*RS*,11b*SR*)-1-allyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,
- 5 (4a*SR*,11a*SR*,11b*RS*)-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo-[1,2-*a*]indol-5-one,
- (4a*SR*,11a*SR*,11b*RS*)-1,2,3,4,4a,11,11a,11b-octahydro-1,6,6a-triazabenz[*a*]fluoren-5-one,
- (4a*SR*,11a*SR*,11b*RS*)-(5-oxo-3,4,4a,11,11a,11b-hexahydro-2*H*,5*H*-pyrido[2',3':3,4]-pyrrolo[1,2-*a*]indol-1-yl)acetonitrile,
- 10 (3a*SR*,6a*RS*,10c*RS*)-4-propyl-(3a,4,5,6,6a,10c-hexahydro)-3*H*-1,4,10b-triazafluoranthene-2-one,
- (3a*RS*,6a*SR*,10c*RS*)-4-propyl-(3a,4,5,6,6a,10c-hexahydro)-3*H*-1,4,10b-triazafluoranthene-2-one,
- (4a*SR*,11a*RS*,11b*SR*)-1-allyl-9-methoxy-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]-pyrrolo[1,2-*a*]indol-5-one,
- 15 (4a*SR*,11a*SR*,11b*RS*)-9-fluoro-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,
- (4a*SR*,11a*SR*,11b*RS*)-9-chloro-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido-[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,
- 20 1,9-dimethyl-1,2,3,4-tetrahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,
- (11a*RS*)-1,9-dimethyl-1,2,3,4,11,11a-hexahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,
- (4a*S*,11a*R*,11b*S*)-1-allyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,
- (4a*R*,11a*S*,11b*R*)-1-allyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]-
- 25 indol-5-one,
- (3a*RS*,10b*SR*,10c*RS*)-3-benzyl-2,3,3a,4,10b,10c-hexahydrobenzo[*b*]pyrido[2,3,4-*gh*]-pyrrolizin-5(1*H*)-one,
- (4a*S*,11a*S*,11b*R*)-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,
- 30 (4a*SR*,11a*RS*,11b*SR*)-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,

(4a*R*,11a*R*,11b*S*)-1-methyl-1,2,3,4,4a,11,11a,11b-octahydropyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one,

their enantiomers and diastereoisomers and also addition salts thereof with a pharmaceutically acceptable acid or base.

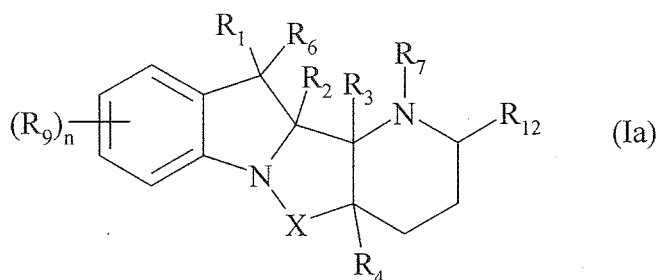
**11.** Process for the preparation of compounds of formula (I), characterised in that there is used as starting material a compound of formula (II):



wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_8$ ,  $R_9$  and  $n$  are as defined for formula (I),  $R_a$  represents a hydrogen atom, a nitroso, amino or *tert*-butyl carboxylate group,

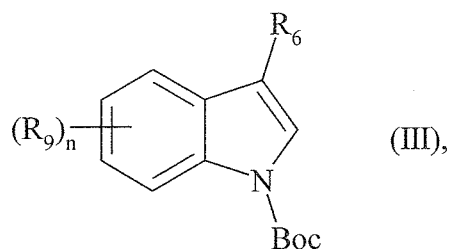
which compound of formula (II) is subjected to a cyclisation reaction in basic medium to yield compounds of formula (I), which may be purified according to a conventional separation technique, are converted, if desired, into their additions salts with a pharmaceutically acceptable acid or base and are optionally separated into their isomers according to a conventional separation technique.

**12.** Process for the preparation of compounds of formula (I/a), a particular case of the compounds of formula (I):

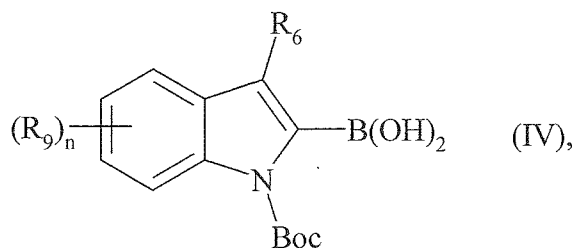


wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_8$ ,  $R_9$ ,  $R_{12}$  and  $n$  are as defined for formula (I),

characterised in that there is used as starting material a compound of formula (III):

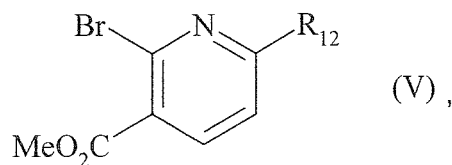


wherein  $R_6$ ,  $R_9$  and  $n$  are as defined for formula (I) and Boc represents a *tert*-butyl carboxylate group, which is reacted with triisopropyl borate in anhydrous medium to yield a compound of formula (IV):



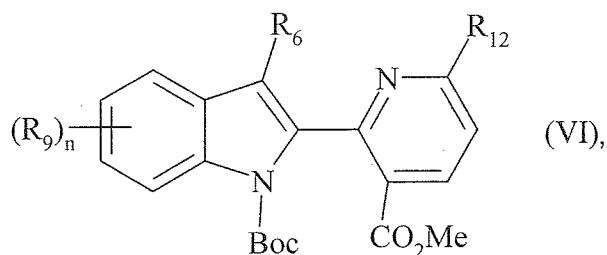
5

wherein  $R_6$ ,  $R_9$ ,  $n$  and Boc are as defined hereinbefore, which is reacted with a compound of formula (V):



10

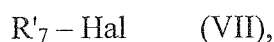
wherein  $R_{12}$  is as defined for formula (I), in the presence of a base and tetrakis(triphenylphosphine)palladium to yield a compound of formula (VI):



wherein  $R_6$ ,  $R_9$ ,  $R_{12}$ ,  $n$  and Boc are as defined hereinbefore,

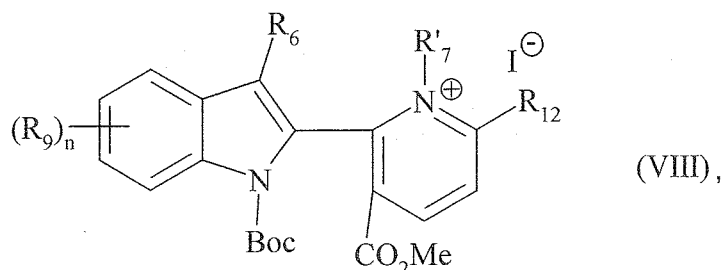
which compound of formula (VI) is subjected,

- either to an alkylation reaction with a compound of formula (VII):



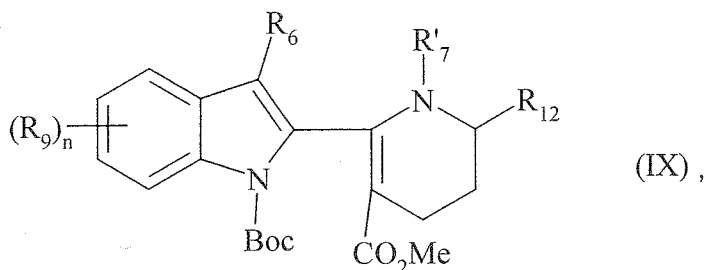
wherein  $R'_7$  has all of the meanings given for  $R_7$  as defined for formula (I) with the exception of a hydrogen atom, and Hal represents a halogen atom,

to yield a compound of formula (VIII):



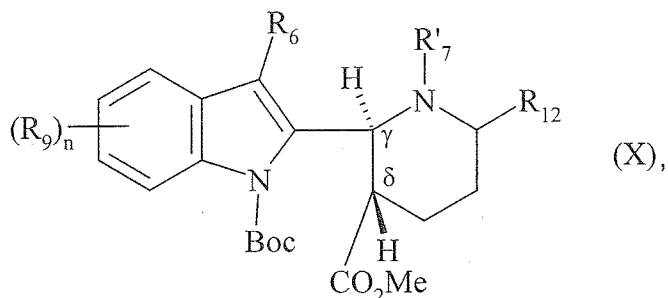
wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$ ,  $n$  and Boc are as defined hereinbefore,

which is subjected to a partial reduction reaction with hydrogen in the presence of triethylamine and platinum oxide to yield a compound of formula (IX):



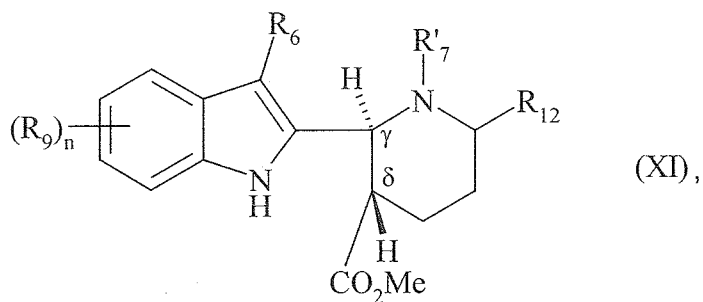
wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$ ,  $n$  and Boc are as defined hereinbefore,

which is subjected to reduction in the presence of hydrochloric acid and sodium cyanoborohydride to yield a compound of formula (X) having *trans* stereochemistry:



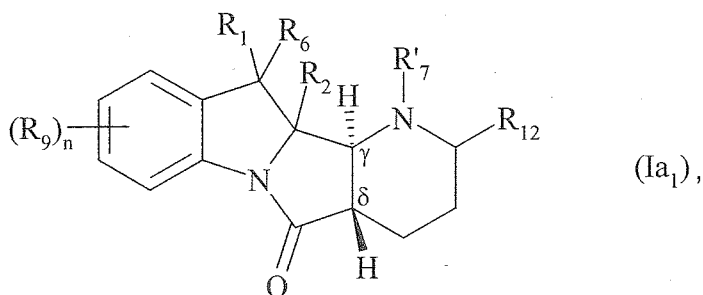
wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$ ,  $n$  and Boc are as defined hereinbefore,  $\gamma$  and  $\delta$  are as defined for formula (I) and  $H_\gamma$  and  $H_\delta$  have *trans* stereochemistry, which is subjected to a deprotection

reaction in the presence of trifluoroacetic acid to yield a compound of formula (XI),



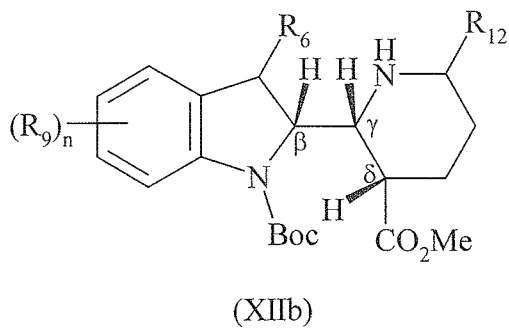
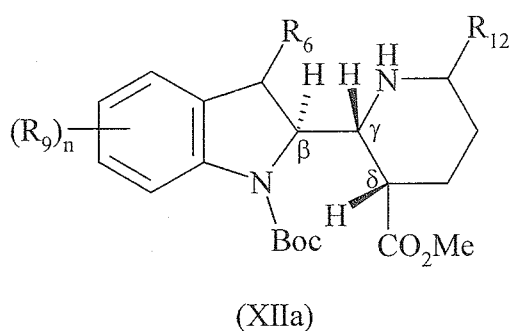
wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$  and  $n$  are as defined hereinbefore,

which is subjected to a cyclisation reaction in the presence of a borane-THF complex and trifluoroacetic acid to yield a compound of formula (Ia<sub>1</sub>), a particular case of the compounds of formula (I):



wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$  and  $n$  are as defined hereinbefore and  $R_1$  and  $R_2$  are as defined for formula (I),

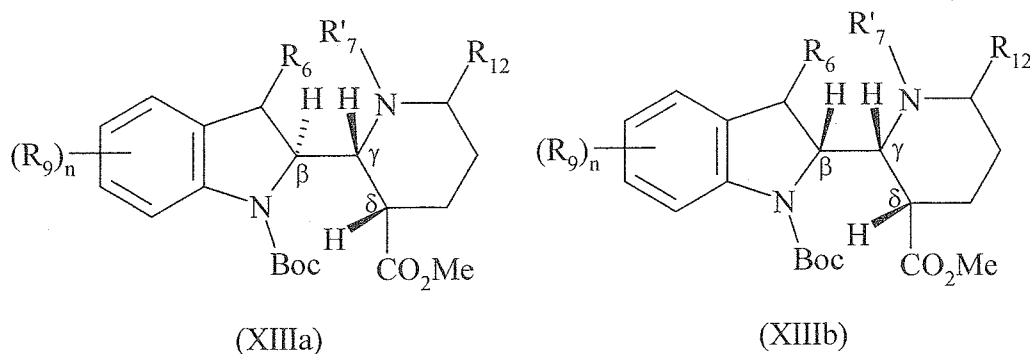
- or to a reduction reaction with hydrogen in the presence of acetic acid and a rhodium catalyst to yield compounds of formulae (XIIa) and (XIIb) having (*trans*, *cis*) and (*cis*, *cis*) stereochemistry, respectively:



wherein  $R_6$ ,  $R_9$ ,  $R_{12}$ ,  $n$  and Boc are as defined hereinbefore,  $\beta$ ,  $\gamma$  and  $\delta$  are as defined for formula (I) and  $H_\beta$  and  $H_\gamma$  have *trans* stereochemistry in the compound of formula (XIIa) and *cis* stereochemistry in the compound of formula (XIIb) and  $H_\gamma$  and  $H_\delta$  have *cis* stereochemistry in the compounds of formulae (XIIa) and (XIIb),

5 which compounds of formulae (XIIa) and (XIIb) are:

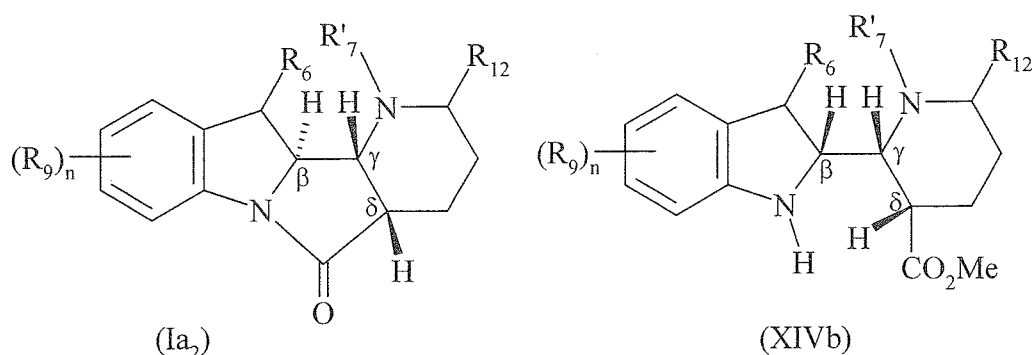
● reacted with a compound of formula (VII) as defined hereinbefore, in the presence of a base, to yield compounds of formulae (XIIIa) and (XIIIb):



wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$ ,  $n$  and Boc are as defined hereinbefore,

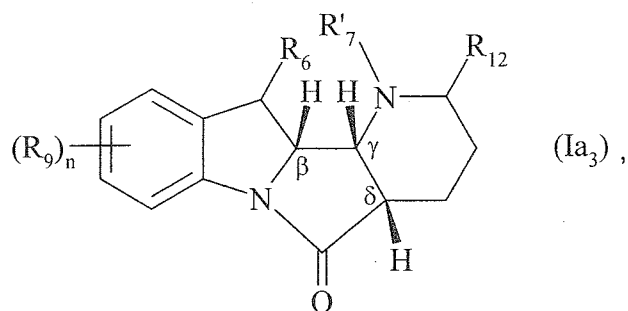
10 which compounds of formulae (XIIIa) and (XIIIb) are:

□ placed in the presence of trifluoroacetic acid to yield compounds of formulae (I<sub>a2</sub>) and (XIVb), compounds of formula (I<sub>a2</sub>) being a particular case of the compounds of formula (I):



15 wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$ , and  $n$  are as defined hereinbefore,

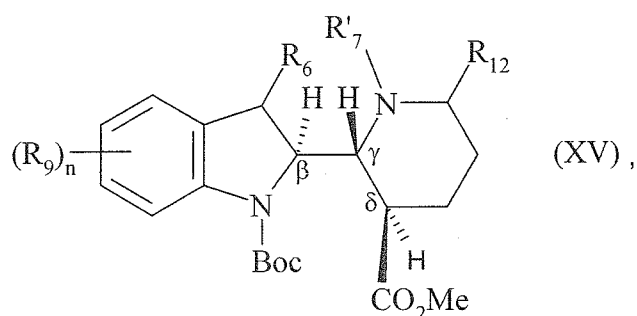
which compound of formula (XIVb) is subjected to a cyclisation reaction in the presence of sodium hydride to yield a compound of formula (I<sub>a3</sub>), a particular case of the compounds of formula (I):



wherein R<sub>6</sub>, R'<sub>7</sub>, R<sub>9</sub>, R<sub>12</sub>, and n are as defined hereinbefore,

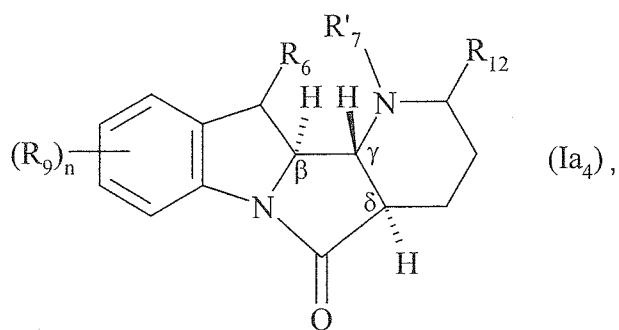
or which compound of formula (XIIIa) is:

□ alternatively placed in the presence of sodium methanolate in methanol to yield a compound of formula (XV):



wherein R<sub>6</sub>, R'<sub>7</sub>, R<sub>9</sub>, R<sub>12</sub>, n and Boc are as defined hereinbefore,

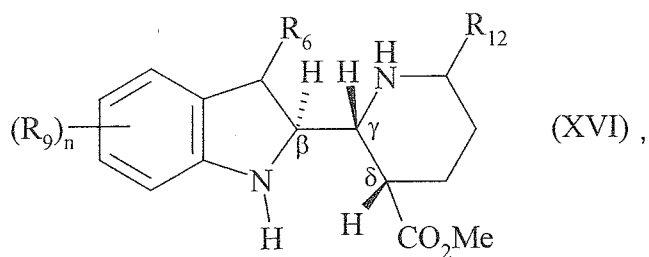
which is subjected to a cyclisation reaction in the presence of trifluoroacetic acid to yield a compound of formula (Ia<sub>4</sub>), a particular case of the compounds of formula (I):



wherein R<sub>6</sub>, R'<sub>7</sub>, R<sub>9</sub>, R<sub>12</sub> and n are as defined hereinbefore,

or which compound of formula (XIIa) is:

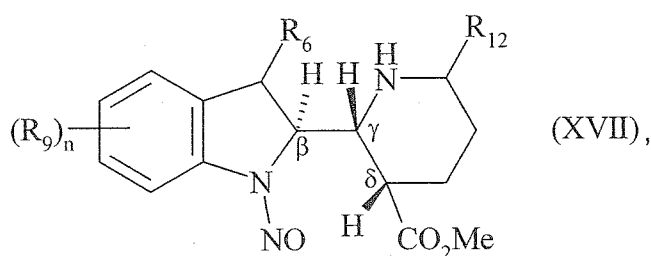
● alternatively subjected to the same conditions as the compounds of formulae (XIIIa) and (XIIIb) to yield a compound of formula (XVI):



wherein  $R_6$ ,  $R_9$ ,  $R_{12}$  and  $n$  are as defined hereinbefore,

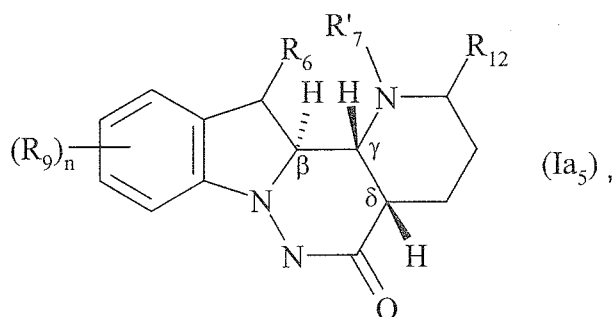
which compound of formula (XVI) is:

\* dissolved in a mixture of acetic acid and water and a sodium nitrite solution to yield a compound of formula (XVII):



wherein  $R_6$ ,  $R_9$ ,  $R_{12}$  and  $n$  are as defined hereinbefore,

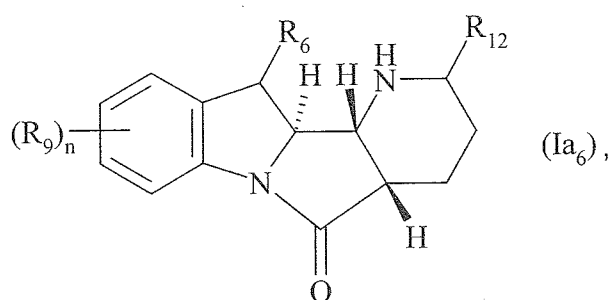
which is reacted in succession with a compound of formula (VII) as defined hereinbefore, then zinc and ammonium carbonate to yield a compound of formula ( $I_{a5}$ ), a particular case of the compounds of formula (I):



wherein  $R_6$ ,  $R'_7$ ,  $R_9$ ,  $R_{12}$  and  $n$  are as defined hereinbefore,

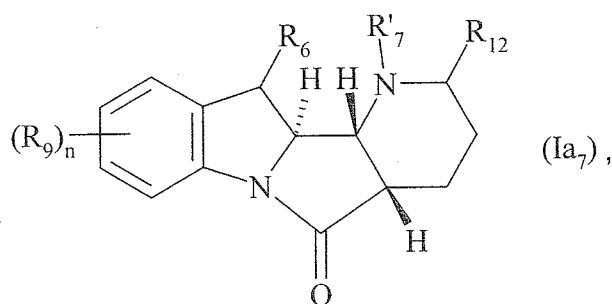
or which compound of formula (XVI) is:

\* alternatively subjected to a cyclisation reaction in the presence of potassium carbonate to yield a compound of formula ( $I_{a6}$ ), a particular case of the compounds of formula (I):



wherein R<sub>6</sub>, R<sub>9</sub>, R<sub>12</sub> and n are as defined hereinbefore,

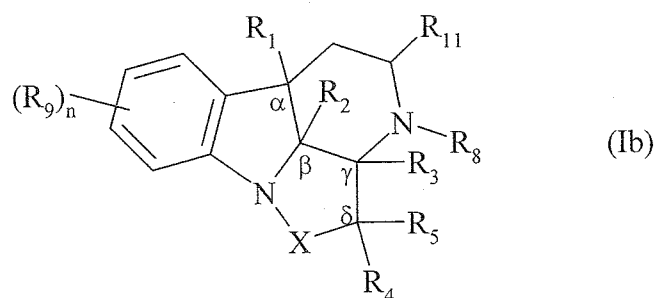
which is subjected to an alkylation reaction with a compound of formula (VII) as defined hereinbefore, in basic medium, to yield a compound of formula (Ia<sub>7</sub>), a particular case of the compounds of formula (I):



wherein R<sub>6</sub>, R'<sub>7</sub>, R<sub>9</sub>, R<sub>12</sub> and n are as defined hereinbefore,

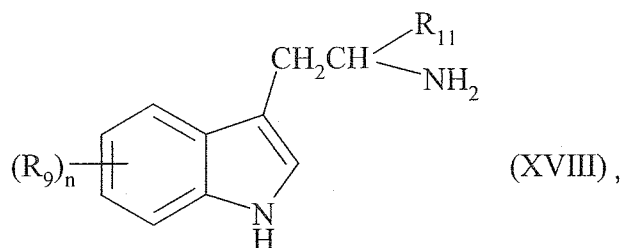
which compounds of formulae (Ia<sub>1</sub>) to (Ia<sub>7</sub>) constitute compounds of formula (Ia), which may be purified according to a conventional separation technique, are converted, if desired, into their addition salts with a pharmaceutically acceptable acid or base and are optionally separated into their isomers according to a conventional separation technique.

**13.** Process for the preparation of compounds of formula (Ib), a particular case of the compounds of formula (I):



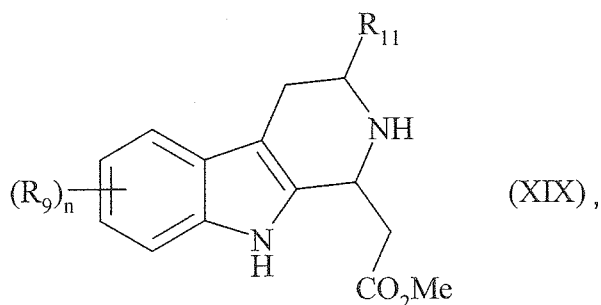
wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>11</sub>, X and n are as defined for formula (I),

characterised in that there is used as starting material a compound of formula (XVIII):



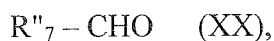
wherein  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore,

which is reacted with methyl cyanoacetate in the presence of Pd/C in glacial acetic acid to  
 5 yield a compound of formula (XIX):

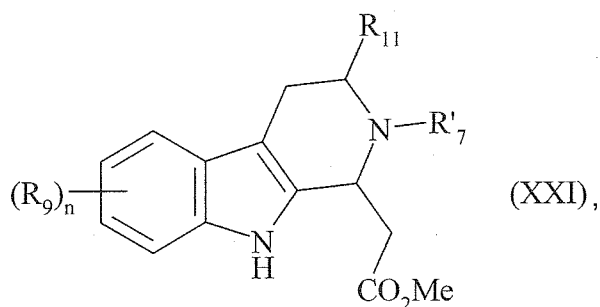


wherein  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore,

which is reacted with a compound of formula (XX):



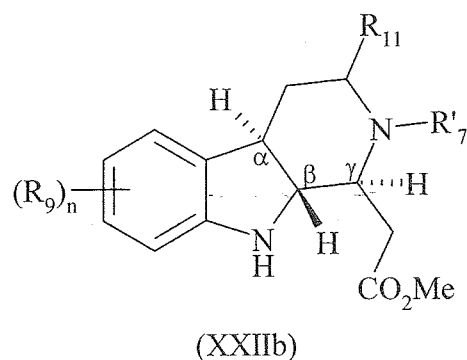
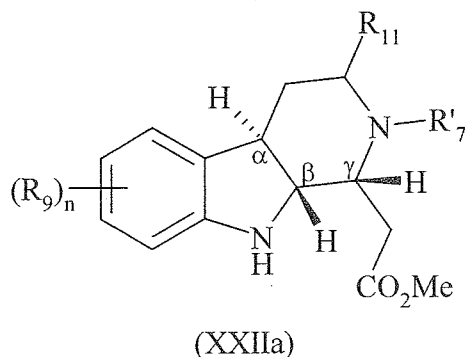
10 wherein  $R''_7$  has all of the meanings given for  $R_7$  as defined for formula (I) with the exception of a hydrogen atom, followed by reduction with sodium borohydride or sodium cyanoborohydride to yield a compound of formula (XXI):



wherein  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore and  $R'_7$  has all of the meanings given for  $R_7$  as defined for formula (I) with the exception of a hydrogen atom,

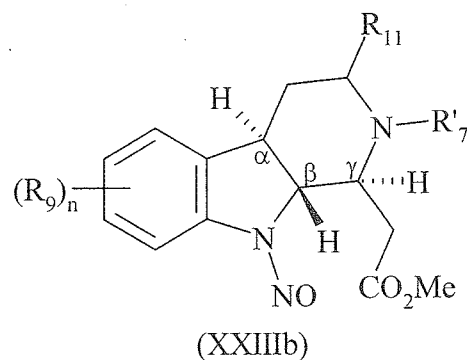
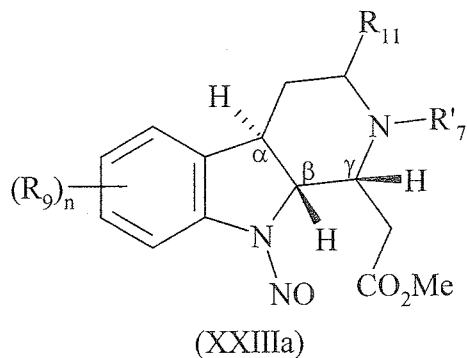
which compound of formula (XXI) is:

- reacted with a  $\text{BH}_3$ -THF complex in THF and then dissolved with trifluoroacetic acid to yield compounds of formulae (XXIIa) and (XXIIb) having (*trans*, *cis*) and (*trans*, *trans*) stereochemistry, respectively:



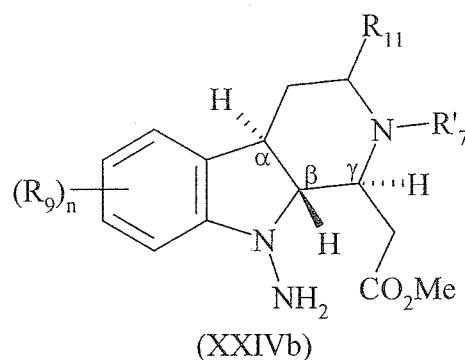
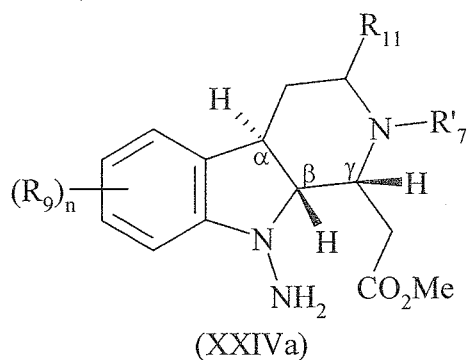
wherein  $\text{R}'_7$ ,  $\text{R}_9$ ,  $\text{R}_{11}$  and  $n$  are as defined hereinbefore, and  $\text{H}_\alpha$  and  $\text{H}_\beta$  have *trans* stereochemistry in the compounds of formulae (XXIIa) and (XXIIb) and  $\text{H}_\beta$  and  $\text{H}_\gamma$  have *cis* stereochemistry in the compound of formula (XXIIa) and *trans* stereochemistry in the compound of formula (XXIIb),

which are dissolved in a mixture of acetic acid and water and a sodium nitrite solution to yield compounds of formulae (XXIIIa) and (XXIIIb):



wherein  $\text{R}'_7$ ,  $\text{R}_9$ ,  $\text{R}_{11}$  and  $n$  are as defined hereinbefore,

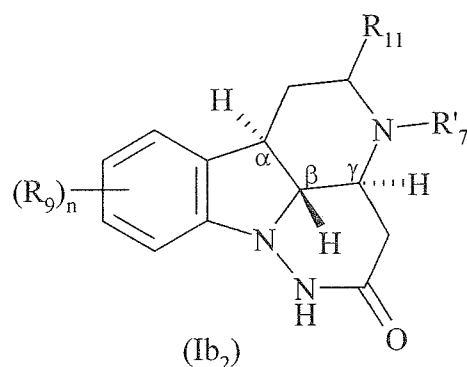
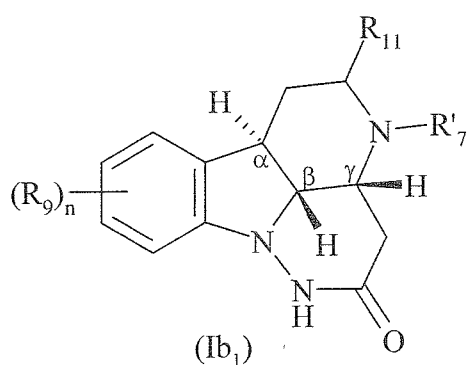
which are placed in the presence of ammonium carbonate and zinc to yield compounds of formulae (XXIVa) and (XXIVb):



wherein  $R'_7$ ,  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore,

which are subjected to a cyclisation reaction in the presence of sodium hydride or trimethylaluminium dissolved in hexane to yield compounds of formulae (I<sub>b1</sub>) and (I<sub>b2</sub>),

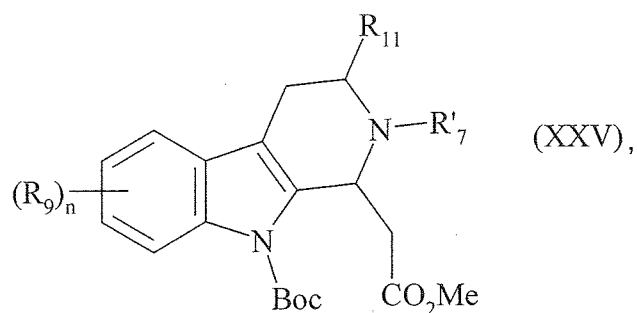
5 particular cases of the compounds of formula (I):



wherein  $R'_7$ ,  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore,

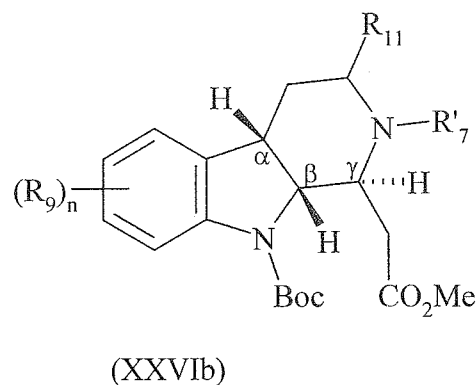
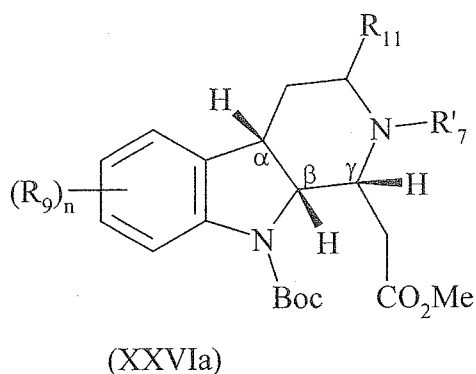
or which compound of formula (XXI) is:

- alternatively reacted with di-*tert*-butyloxycarboxylic acid anhydride and dimethylamino-  
10 pyridine to yield a compound of formula (XXV):



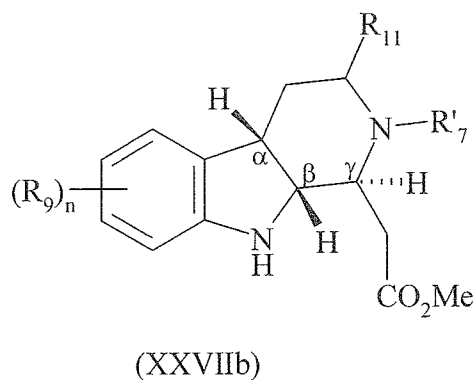
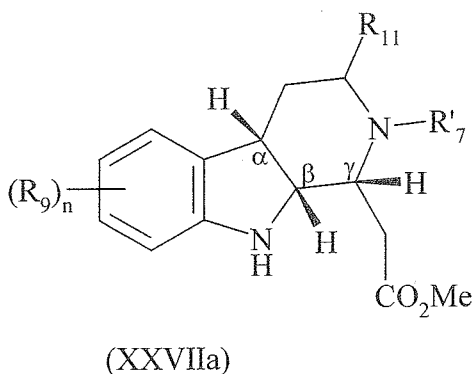
wherein  $R'_7$ ,  $R_9$ ,  $R_{11}$  and  $n$  are as defined hereinbefore and Boc represents a *tert*-butyl carboxylate group, which is subjected to a reduction reaction in the presence of platinum

oxide and hydrogen to yield compounds of formulae (XXVIa) and (XXVIb) having (*cis*, *cis*) and (*cis*, *trans*) stereochemistry, respectively:



wherein R'<sub>7</sub>, R<sub>9</sub>, R<sub>11</sub>, n and Boc are as defined hereinbefore,

- 5 and H<sub>α</sub> and H<sub>β</sub> have *cis* stereochemistry in the compounds of formulae (XXVIa) and (XXVIb) and H<sub>β</sub> and H<sub>γ</sub> have *cis* stereochemistry in the compound of formula (XXVIa) and *trans* stereochemistry in the compound of formula (XXVIb), which are placed in the presence of trifluoroacetic acid in an anhydrous medium to yield compounds of formulae (XXVIIa) and (XXVIIb):

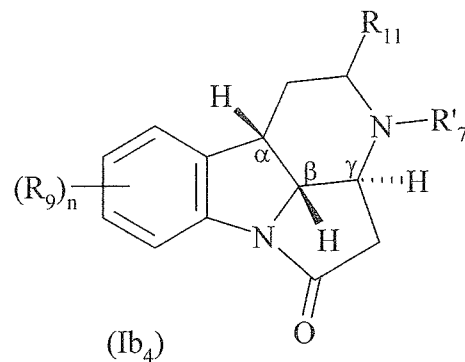
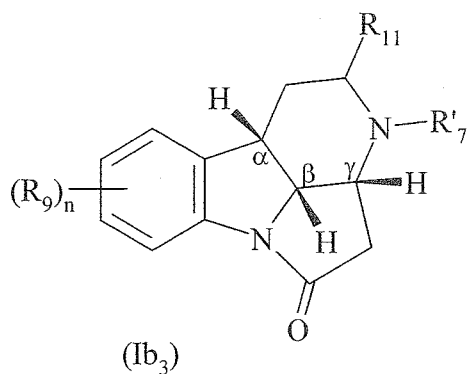


10

wherein R'<sub>7</sub>, R<sub>9</sub>, R<sub>11</sub> and n are as defined hereinbefore,

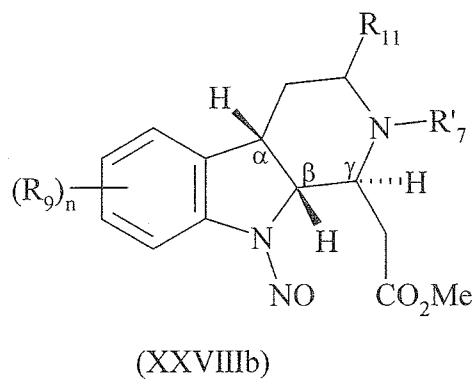
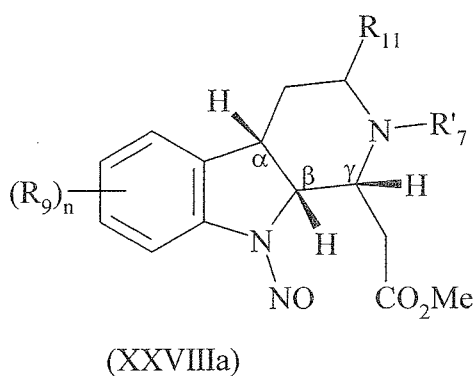
which are:

- either subjected to a cyclisation reaction under the same conditions as the compounds of formulae (XXIVa) and (XXIVb) to yield compounds of formulae (I<sub>b3</sub>) and (I<sub>b4</sub>), a
- 15 particular case of the compounds of formula (I):



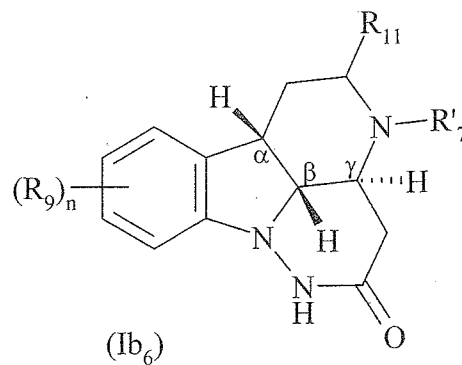
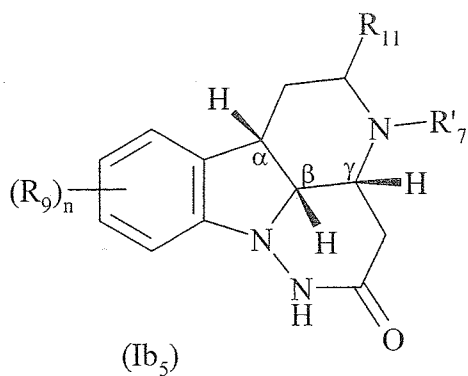
wherein R'<sub>7</sub>, R<sub>9</sub>, R<sub>11</sub> and n are as defined hereinbefore,

● or subjected to the same conditions as the compounds of formulae (XXIIa) and (XXIIb) to yield compounds of formula (XXVIIIa) and (XXVIIIb):



wherein R'<sub>7</sub>, R<sub>9</sub>, R<sub>11</sub> and n are as defined hereinbefore,

which are subjected to the same conditions as the compounds of formulae (XXIIIa) and (XXIIIb) to yield compounds of formulae (Ib<sub>5</sub>) and (Ib<sub>6</sub>), a particular case of the compounds of formula (I):



wherein R'<sub>7</sub>, R<sub>9</sub>, R<sub>11</sub> and n are as defined hereinbefore,

which compounds of formulae (I<sub>b1</sub>) to (I<sub>b6</sub>) constitute the compounds of formula (I<sub>b</sub>), which may be purified according to a conventional separation technique, are converted, if desired, into their addition salts with a pharmaceutically acceptable acid or base and are optionally separated into their isomers according to a conventional separation technique.

5     14. Pharmaceutical compositions comprising as active ingredient at least one compound according to any one of claims 1 to 10, in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

10     15. Pharmaceutical compositions according to claim 14 for use in the treatment of depression, anxiety, disorders of memory in the course of ageing and/or neurodegenerative diseases, and in the palliative treatment of Parkinson's disease, and for adaptation to stress.