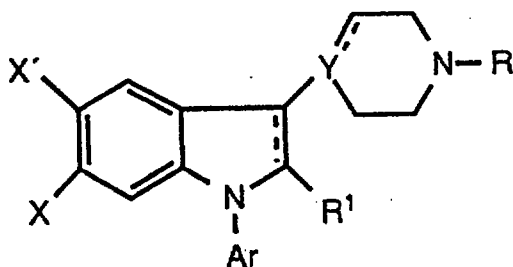


Description

The present invention relates to novel 6-substituted and/or 2-alkyl substituted indole and 2,3-dihydroindole derivatives and their acid addition salts with pronounced and long lasting central serotonin (5-Hydroxytryptamine; 5 HT) activity with specific binding to 5-HT₂ receptors, to the beneficial use of these derivatives in the treatment of CNS disorders such as anxiety, depression, sleep disturbances, migraine, schizophrenia (treatment of the negative symptoms), and Parkinson's disease with a low degree of undesired side effects and to methods for their preparation.

The novel indole and 2,3-dihydroindole derivatives of the present invention are represented by the following formula :



I.

where Ar is phenyl optionally substituted with one or more substituents selected from halogen, lower alkyl, lower alkoxy, hydroxy, trifluoromethyl, and cyano, or a hetero aromatic group preferably 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-oxazolyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

the dotted line in the indole ring indicates an optional bond;

X is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy, lower alkylthio, lower alkylsulfonyl, lower alkyl- or dialkylamino, cyano, trifluoromethyl, or trifluoromethylthio;

X' is a substituent taken from the X-substituents above; or

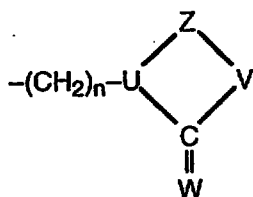
X and X' are linked to constitute a 5-7 membered carbocyclic ring;

R¹ is hydrogen or lower alkyl optionally substituted with one or two hydroxy groups, provided that when X is hydrogen or fluoro, R¹ cannot be hydrogen;

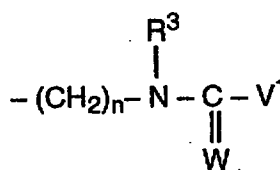
Y is N, C or CH;

when Y is C, the dotted line emanating from Y indicates a bond;

R is hydrogen, or lower alkyl, lower alkenyl, cycloalkyl, or cycloalkylmethyl, optionally substituted with one or two hydroxy groups, any hydroxy group present being optionally esterified with an aliphatic carboxylic acid having from two to twentyfour carbon atoms inclusive, or R is a group taken from structures 1a and 1b



1a.



1b.

wherein n is an integer from 2 - 6;

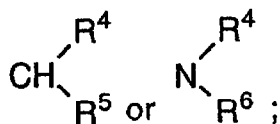
W is oxygen or sulfur;

U is N or CH;

Z is $-(CH_2)_m-$, m being 2 or 3, or Z is $-CH=CH-$, Z is $-COCH_2-$ or $-CSCH_2-$, or 1,2-phenylene optionally substituted with halogen or trifluoromethyl;

V is oxygen, sulfur, CH₂, or NR², wherein R² is hydrogen, lower alkyl or alkenyl optionally substituted with one or two hydroxy groups, or R² is a cycloalkyl or cycloalkylmethyl group;

V¹ is O-R⁴, S-R⁴,



R^3 is hydrogen, lower alkyl or alkenyl optionally substituted with one or two hydroxy groups, or a cycloalkyl group;

- 10 R^4 and R^5 are independently selected from the R^3 -substituents; and
 R^6 is as defined for R^2 above

Also the stereoisomers and prodrugs of the 6-substituted or 2-alkyl substituted 2,3-dihydroindole derivatives of formula I are embraced by this invention.

- 15 The terms lower alkyl, lower alkoxy, lower alkylthio and lower alkylsulfonyl designate such straight chained or branched groups having from one to four carbon atoms inclusive. Exemplary of such groups are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2-methyl-1-propyl, methoxy, ethoxy, 1-propoxy, 2-propoxy, methylthio, ethylthio, 1-propylthio, 2-propylthio, methylsulfonyl, ethylsulphonyl, or the like.

Cycloalkyl is such a group comprising 3-8 carbon atoms.

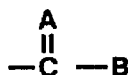
- 20 Halogen means fluoro, chloro, bromo or iodo.

The acid addition salts of the invention are pharmaceutically acceptable salts of the compounds of Formula I formed with non-toxic acids.

- 25 Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, embonic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromo-theophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

- 30 Prodrugs of the present invention may be conventional esters with available hydroxy groups, or in particular if the compound is a compound of the general formula I wherein W is oxygen and V is $>\text{NR}^2$, R^2 being hydrogen, the prodrug may be formed by acylating the nitrogen atom of the V group and being accordingly represented by the formula I wherein W is oxygen and V is $>\text{N-R}^{2'}$ wherein $\text{R}^{2'}$ designates a group

35



- 40 wherein A is O, S or NR^a with R^a being hydrogen, lower alkyl, or phenyl optionally substituted with one or more substituents selected from the group comprising halogen, trifluoromethyl, lower alkyl, lower alkoxy, lower alkylthio and cyano;

- B is a group R^b which is alkyl or alkenyl containing up to twentyfour carbon atoms inclusive, or cycloalkyl, optionally substituted with one or two hydroxy groups, phenyl optionally substituted with one or more substituents selected from the group comprising halogen, trifluoromethyl, lower alkyl, lower alkoxy, lower alkylthio, or cyano; or

45 B is QR^b , wherein Q is O or S and R^b is one of the substituents defined for R^b above; or

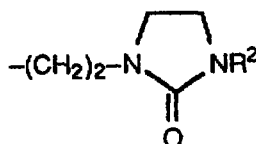
B is NR^cR^d , wherein R^c and R^d independently are either hydrogen or one of the substituents defined for R^b above.

- 50 Although the latter prodrugs are not esters, they have been found to decompose properly in order to release the compound of the invention over a desired prolonged period of time when administered parenterally as a depot formulation in an appropriate oil, such as peanut oil, sesame oil, cotton seed oil, corn oil, soy bean oil, olive oil, etc. or synthetic esters of fatty acids and glycerol or propylenglycol, e.g. viscolec®.

Preferred embodiments of the invention are those indole derivatives wherein:

- 55 Ar is phenyl substituted with halogen, most preferably 4-fluorophenyl;

R is a group



5

wherein R² is defined above, R² most preferably being hydrogen or isopropyl;

X is selected from -Cl, -Br, -CF₃, and -CH₃; and/or X' is H or Cl.

10 In another aspect the present invention provides a pharmaceutical preparation comprising at least one compound of the Formula I or a pharmaceutically acceptable acid addition salt or prodrug thereof as an active ingredient together with a pharmaceutically acceptable carrier or diluent.

In a further aspect the present invention provides the use of a compound of Formula I or a pharmaceutically acceptable acid addition salt or prodrug thereof for the manufacturing of a pharmaceutical preparation for the treatment of CNS disorders such as anxiety, depression, sleep disturbances, migraine,
15 negative symptoms of schizophrenia, and Parkinson's disease (Parkinsonian syndrome).

Finally, the present invention provides a method for the preparation of a derivative having the general Formula I, which method is described in the following.

Compounds, similar in structure to the derivatives of the present invention, are disclosed in our US patent No 4,710,500 (corresponding to EP patent No 0200322) which discloses a general formula covering
20 the corresponding 1-arylindoles optionally substituted in the benzo moiety of the indole ring system. Said compounds are stated to have potent and long lasting dopamine antagonistic and/or 5-HT₂ antagonistic activities.

However, though the 6-substituted 1-aryl indoles of the invention are included in the general formula of said US patent, no compounds substituted in the 6-position have been specifically disclosed. 2-Alkylated 1-aryl indoles are not covered by the general formula of said US patent.

Surprisingly it has now been found that by introduction of certain substituents in the 6-position of the indole ring or by introduction of lower alkyl groups in the 2-position of the indole ring, dopaminergic (D-2) and noradrenergic (α₁) blockade are practically absent, while these derivatives still are very potent and long lasting centrally acting 5-HT₂ antagonists. Even with a substituent left in the 5-position the indoles of the
30 present invention have proven to be selective for the serotonergic system. Only a few compounds with this pharmacologically unique profile are known from the literature. Such compounds include ritanserin, seganserin, ICI 169369, ICI 170809, sergolexole and MDL 11939. These compounds belong to very different chemical structural classes. Ritanserin and seganserin are 4,4-diphenyl-methylene-1-heteroarylethyl substituted piperidines. The MDL compound is similarly a 4-phenylmethyl-1-phenylethyl piperidine derivative. The
35 ICI compounds are 3-phenylquinoline derivatives whereas sergolexole belongs to the ergoline class of compounds. The indole and 2,3-dihydroindole derivatives of the present invention are very different in chemical structure from these known 5-HT₂ antagonist compounds.

Previously evidence of various clinical effects of 5-HT₂ antagonists have been presented. For example reference may be made to the following:

40 The selective 5-HT₂ antagonist ritanserin has been shown to be an antidepressant and to improve depressive symptoms of schizophrenia (E. Klierer, W. H. Strauss; Pharmacopsychiat. 21 (1988), pp. 391-393) and it has been demonstrated to exert effects in an animal test reminiscent of anxiolytic drug activity (F.C. Colpart et al.; Psychopharmacology (1985) 86; 303-305). Furthermore ritanserin has been shown to improve the quality of sleep (P. A. J. Janssen; Pharmacopsychiat. 21 (1988), 33-37).

45 Furthermore it is known that 5-HT is involved in migraine attacks. The links between 5-HT and migraine attacks are several and they suggest a number of mechanisms whereby 5-HT may be involved (Scrip Report; "Migraine - Current trends in research and treatment"; PJB Publications Ltd.; May 1991). Various 5-HT₂ antagonists are in clinical trials as anti-migraine agents, such as sergolexole (c.f. for example Pharma Projects, May 1991, 1359-1365).

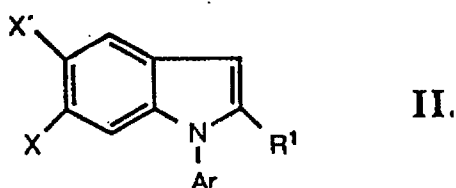
50 Studies of the serotonin and moderate dopamine receptor antagonist setoperone indicate that blockade of 5-HT₂ receptors may be related to improvement of negative symptoms of schizophrenia (Ceulemans et al., Psychopharmacology (1985) 85, 329-332).

Finally, ritanserin has been found to relieve neuroleptic-induced parkinsonism (Bersani et al.; Clinical Neuropharmacology, 13, No. 6 (1990), 500-506).

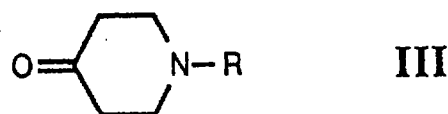
55 Accordingly the potent and selective 5-HT₂ antagonists of the present invention are useful in the treatment of anxiety, depression, sleep disturbances, migraine, schizophrenia (treatment of the negative symptoms), and Parkinson's disease (Parkinsonian syndrome) substantially without causing neurological side effects.

The invention moreover relates to a method for the preparation of the novel 6-substituted or 2-alkylated indoles and 2,3-dihydroindoles of Formula I, which comprises

a) reacting an indole derivative of the following formula :

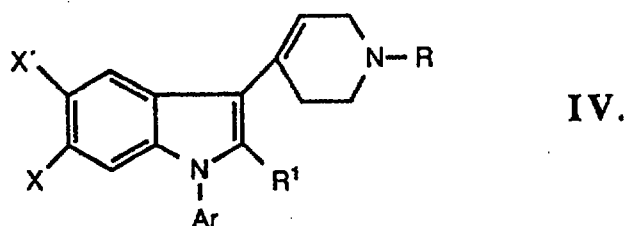


wherein R', X, X' and Ar are as defined above, with a 4-piperidone of the formula:



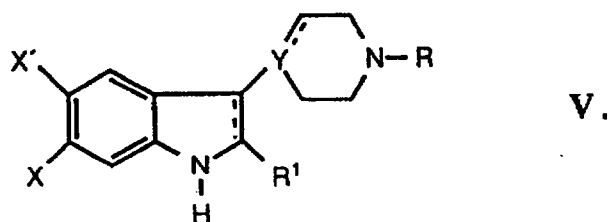
wherein R is as defined above, or

b) reducing the double bond in the tetrahydropyridyl ring of a compound of the formula:



wherein R', X, X', Ar and R are as defined above, or

c) reacting a compound of the following formula :

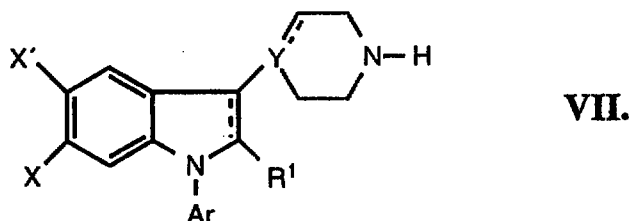


wherein R', X, X', Y, R and the dotted lines are as defined above, with a compound of the formula:



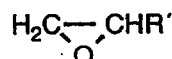
wherein Ar is as defined above and "hal" is halogen (Cl, Br or I) in the presence of a metal catalyst, or

d) alkylating a compound of the following formula :



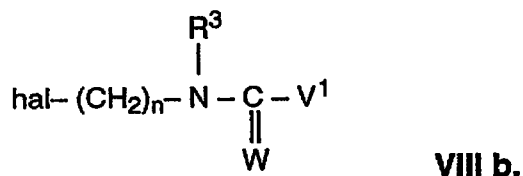
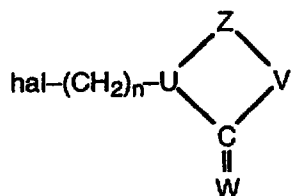
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wherein R¹, X, X', Y, Ar and the dotted lines are as defined above with a lower alkyl halide, alkyl mesylate or tosylate, an epoxide of formula



20

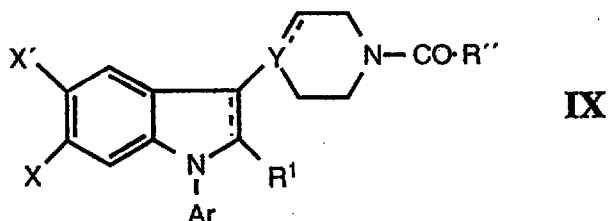
wherein R' is hydrogen, methyl or ethyl, or with a halide of the general formula :



30

wherein U, Z, V, V¹, W, R³ and n are as previously defined and "hal" is chloro, bromo or iodo, or

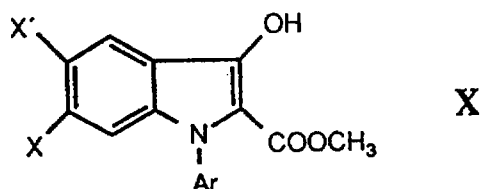
e) reducing the carbonyl group in a compound of the following formula :



40

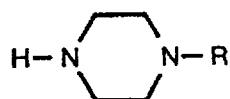
wherein R¹, X, X', Y, Ar and the dotted lines are as previously defined and R'' is hydrogen, lower alkyl or lower alkoxy, or

f) heating an indoxylester of the following formula :



50

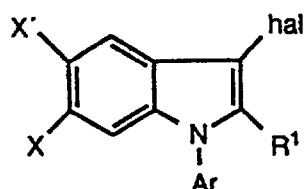
wherein X, X' and Ar are as defined above, in the presence of an inorganic salt catalyst followed by continued heating in the presence of a piperazine derivative of formula :



XI

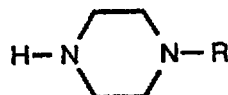
wherein R is as defined above, or

g) reacting a 3-halogen substituted indole derivative of the formula XII with a piperazine derivative of the formula XIII :



XII

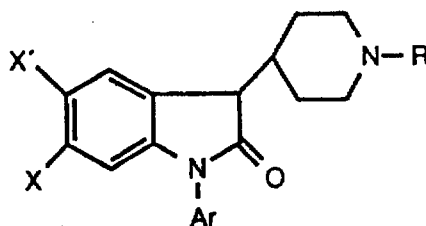
+



XIII

wherein R¹, X, X', Ar and R are as defined above and "hal" means chloro, bromo, or iodo, or

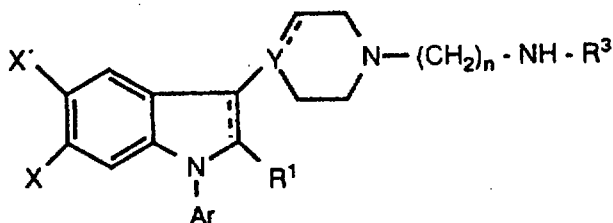
h) reducing a 2-oxindole derivative of the following formula :



XIV

wherein X, X', Ar and R are as defined above, or

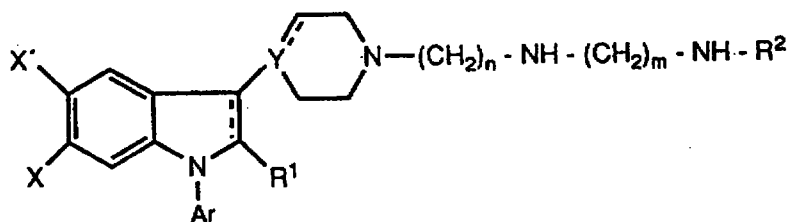
i) acylating an aminoalkyl derivative of the following formula :



XV

wherein R¹, X, X', Y, Ar, n, R³ and the dotted lines are as defined above using a carboxylic acid halogenide, anhydride or mixed anhydride, a carbamyl or thiocarbamyl chloride, isocyanate, isothiocyanates or substituted chloroformate as acylating agent, or

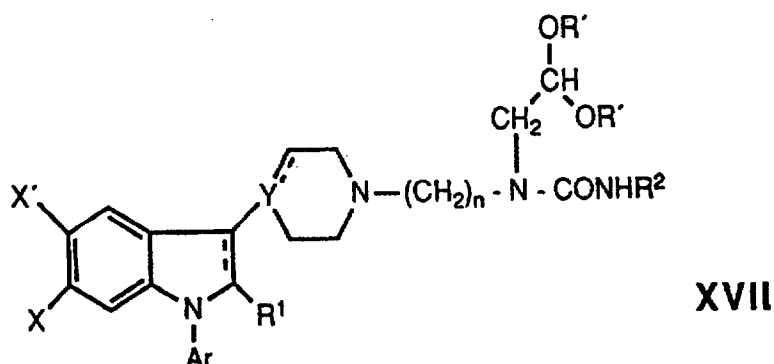
j) ringclosure reaction of an intermediate derivative of the following formula :



XVI

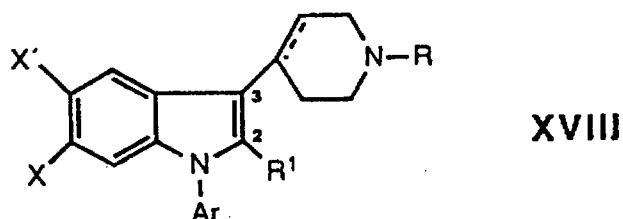
wherein R^1 , X, X' , Y, Ar, n, R^2 , m and the dotted lines are as defined above, using urea, phosgene, thiophosgene or carbondisulfide to incorporate a carbonyl or thiocarbonyl group in the heterocyclic ring of structure 1a, or

k) ringclosure reaction of an intermediate derivative of the following formula :



wherein R^1 , X, X' , Y, Ar, n, R^2 and the dotted lines are as defined above and R^1 is lower alkyl or alkenyl or constitute a ring by forming an ethylene or propylene bridge, or

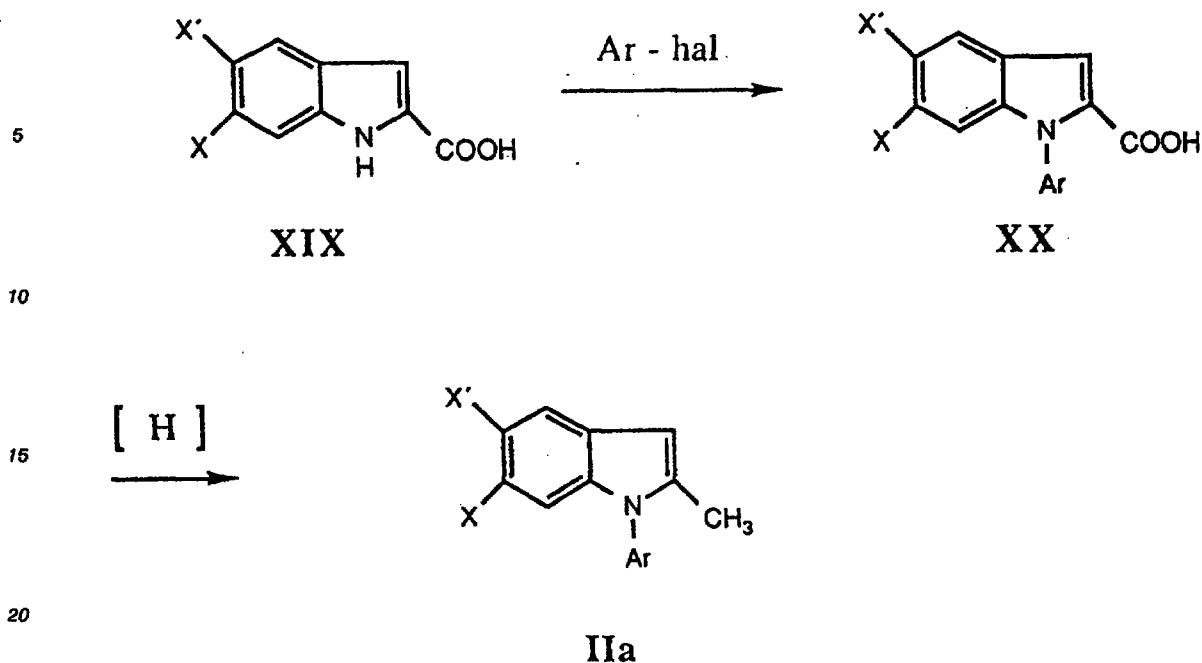
l) reducing the 2,3-double bond of a 3-piperidylindole of the following formula :



wherein R^1 , X, X' , Ar, R and the dotted line are as defined above, and then optionally converting the compound of formula I obtained into a pharmaceutically acceptable acid addition salt or prodrug thereof.

Preparation of the 2-unsubstituted intermediates and reaction conditions used in the methods a), b), c), d), e), f), and h) are described in detail in US patent No 4,710,500 and references cited therein for analogous compounds.

The 2-Alkyl substituted 1-arylindoles (i.e. compounds having the structure II in which R^1 is not hydrogen) are readily available from the corresponding 2-carboxy-1-arylindoles XX which are prepared by Ullmann arylation of 2-carboxyindoles XIX (commercially available or prepared by the Japp-Klingemann procedure). 2-Methyl substituted indoles (IIa) were prepared as outlined in the following reaction scheme:



The Ullmann reaction procedure is reported in our US pat. No 4,710,500. Reduction of the 2-carboxylic acid is conveniently performed in a two step sequence : 1) reduction with LiAlH_4 to the corresponding hydroxymethyl derivative, 2) catalytic hydrogenation to the methyl derivative IIa.

1-Aryl-3-haloindoles used in method g) are conveniently prepared from the corresponding 3-unsubstituted 1-arylindoles using N-chloro- or N-bromosuccinimide at room temperature preferably in a chlorinated solvent as e.g. dichloromethane, tetrachloromethane or 1,1,1-trichloroethane. This method is adapted from R.P. Mays et al., J.Heterocyclic Chem. 17, 1663-1664 (1980) and R.Sarges et al., J. Med. Chem. 32, 437-444 (1989). The substitution reaction with 1-alkylpiperazines of formula XIII is preferably performed at elevated temperatures (120-200 °C) in aprotic polar solvents as e.g. N,N-dimethylformamide, hexamethylphosphoric triamide or N-methyl-2-pyrrolidone with K_2CO_3 as base and optionally copper or a copper (I) salt as Ullmann catalyst.

Aminoalkyl derivatives of the formula XV used in method i) as intermediates are conveniently prepared by alkylating the appropriate piperidyl-, 1,2,3,6-tetrahydropyridyl- or piperazinyllindole derivative with an ω -halonitrile of the following formula : $\text{hal}-(\text{CH}_2)_{n-1}\text{CN}$ in the presence of a free base (e.g. K_2CO_3 or triethylamine) in an inert solvent as acetone, methyl isobutyl ketone or toluene at elevated temperatures (30-100 °C). The cyano group may be reduced according to standard methods using e.g. AlH_3 , LiAlH_4 , B_2H_6 or a BH_3 complex. The R^3 substituent is introduced by direct alkylation or by an acylation/reduction procedure which is obvious to the chemist skilled in the art. Acylation of the thus obtained aminoderivatives is accomplished by addition of an acylating agent at low temperatures (-20 - 30 °C) preferably in chlorinated solvents (dichloromethane, chloroform, 1,1,1-trichloroethane) and if needed to neutralize any acidic reaction products formed, in the presence of a base.

Ethylenediamines or propylenediamines having formula XVI used as intermediates for the ringclosure reaction in method j) are prepared by repeating with appropriate reagents the procedure described for the preparation of aminoalkyl derivatives in method i) using said aminoalkyl derivatives as starting materials. Generally heating (80-150 °C) is required to effect ringclosure reactions with the appropriate carbonyl- or thiocarbonyl precursor compounds (phosgene, thiophosgene, carbondisulfide, urea or thiourea).

Compounds XVII used in method k) as intermediates are prepared from structures XV wherein R^3 is H by monoalkylation with properly protected (ketalized) 2-haloacetaldehydes followed by addition of isocyanates to the secondary amine in an inert, chlorinated solvent as e.g. dichloromethane, chloroform or 1,1,1-trichloroethane at room temperature or slightly above.

The ringclosure of compounds XVII in method k) is effected by deprotection of the aldehyde under acidic reaction conditions at 0 - 80 °C. Potassium isocyanate serves as precursor for cyanuric acid under acidic conditions (trifluoroacetic or hydrochloric acid) for the preparation of 3-unsubstituted imidazol-2-on precursors.

Reduction of the 2,3-double bond of the indoles of structure XVIII in method I) is conveniently performed by catalytic hydrogenation at exhaustive reaction conditions, i.e. prolonged reaction times or high pressure, or by diborane reduction at elevated temperatures in inert solvents such as dioxane or THF, or by reduction with NaBH_4 or NaCNBH_3 under suitable acidic reaction conditions (acetic acid, hydrochloric acid or trifluoroacetic acid). Instead of 3-(4-piperidyl)-substituted indoles the corresponding 3-[4-(1,2,3,6-tetrahydro)pyridyl] substituted indoles may be intermediates for the 2,3-dihydroindole derivatives.

The ω -haloalkyl-2-imidazolidinone alkylating reagents (substructure of structure VIIIa) used in method d) were prepared according to modified literature procedures (see e.g. Johnston, T.P.; McCaleb, G.S.; Montgomery, J.A. The Synthesis of Antineoplastic Agents. XXXII. N-Nitrosureas. *J. Med. Chem.* 1963, 6, 669-681; Ebetino, F.F. *Belg. Patent* 853421, 1965; *Chem. Abstr.* 1966, 64, 12684; Costeli, J.; Züst, A. *Ger. Offen* 2035370, 1971; *Chem. Abstr.* 1971, 74, 87985z). Other sidechains of structure VIIIa were prepared as stated in the literature.

When R^2 is a hydroxyalkyl substituent the hydroxy group may be introduced by deprotection of a labile ether derivative e.g. by acid induced decomposition, by hydrogenolysis or by other methods obvious to the chemist skilled in the art.

6-Alkylthio substituted indoles or 2,3-dihydroindoles may also conveniently be prepared from the corresponding 6-alkylsulfone or 6-alkylsulfoxide substituted indoles or 2,3-dihydroindoles by reduction with proper reduction reagents such as LiAlH_4 and AlH_3 at reflux temperatures in inert high boiling solvents such as e.g. dioxan, dipropyl ether, dibutyl ether or diglyme.

The acid addition salts of the compounds of the invention are easily prepared by methods well known in the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling, or with an excess of the acid in an aqueous immiscible solvent such as ethyl ether or chloroform with the desired salt separating directly. Of course, these salts may also be prepared by the classical method of double decomposition of appropriate salts. The compounds of Formula I and the pharmaceutically acceptable acid addition salts thereof may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection.

When the compound of Formula I exists as a prodrug thereof, it is suitably formulated as an injectable depot formulation in an appropriate pharmaceutically acceptable oil, such as peanut oil, sesame oil, cotton seed oil, corn oil, soy bean oil, olive oil, etc. or synthetic esters of fatty acids and glycerol or propylene-glycol, e.g. viscolear®.

Suitable pharmaceutical preparations may be prepared by methods well known in the art. Conveniently, the compounds of the invention are administered in unit dosage form containing said compound in an amount of about 0.10 - 100 mg, preferably about 1 - 50 mg. The total daily dose usually ranges from about 1.0 to 500 mg of the active compound of the invention.

In the following the invention is further illustrated by way of examples, which in no way may be construed as limiting for the invention.

Example 1 (method a)

6-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, hydrochloride, 1a

6-chloro-1-(4-fluorophenyl)-1H-indole (19 g) was dissolved in 150 ml of pre-heated acetic acid and added dropwise during 1/2 h to a solution of 4-piperidone hydrate hydrochloride (30 g) in a mixture of trifluoroacetic acid (200 ml) and acetic acid (100 ml) at gentle reflux. The mixture was heated for another 2 hours. After cooling to 50 °C and slow addition of 400 ml of acetone the hydrochloride salt of the title compound 1a precipitated. The salt was filtered off yielding 15.6 g. Mp 294-295 °C.

In a corresponding manner the following 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles were prepared :

1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-6-trifluoromethyl-1H-indole, 1b, (oil)

1-(4-fluorophenyl)-6-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 1c, Mp: 262 °C

1-(4-fluorophenyl)-6-(2-propyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 1d, (oil)

6-bromo-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 1e, Mp: 188-191 °C

5,6-dichloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 1f, Mp: 196-200 °C

6-cyano-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 1g, Mp: 139-142 °C

1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1,5,6,7-tetrahydrocyclopent[*f*]-1H-indole, 1h (oil)

1-(4-fluorophenyl)-6-methoxy-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 1i

1-(4-fluorophenyl)-6-methylsulfonyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 1j

Example 2 (method d)

6-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole, hydrobromide, **2a**

5

A mixture of compound **1a** (10 g), 1-(2-chloroethyl)-3-(2-propyl)-2-imidazolidinon (6 g) (prepared according to the method of Ger.Offen. No 2035370), potassium carbonate (10 g) and a KI crystal in methyl isobutyl ketone (200 ml) was refluxed overnight. The mixture was cooled to room temperature and water (500 ml) and ethyl acetate (200 ml) were added. The organic phase was separated, washed with brine (100 ml), dried (anh. MgSO_4) and finally the organic solvents were evaporated leaving the title compound **2a** as an oil. A hydrobromide salt crystallized from acetone. Yield 4.8 g. Mp 243-245 °C

10

In a corresponding manner the following N-alkylated 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles were prepared :

1-(4-fluorophenyl)-6-methyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole, **2b**, Mp: 144 °C

15

5,6-dichloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole, **2c**, Mp: 108 °C

5,6-dichloro-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole, **2d**, Mp: 145-148 °C

20

1-(4-fluorophenyl)-6-(2-propyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole, **2e** (oil)

1-(4-fluorophenyl)-6-(2-propyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole, **2f** (oil)

25

6-bromo-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole, **2g** (oil)

6-cyano-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole, **2h**, Mp: 137 °C

30

6-cyano-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole, **2i**, Mp: 146-148 °C

1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1,5,6,7-tetrahydrocyclopent[*f*]-1H-indole, **2j** (oil)

35

1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1,5,6,7-tetrahydrocyclopent[*f*]-1H-indole, **2k** (oil)

1-(4-fluorophenyl)-6-methylthio-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole, **2l**, MP: 148-151 °C

40

Example 3 (method b)

6-chloro-1-(4-fluorophenyl)-3-(4-piperidyl)-1H-indole, hydrochloride, **3a**

45

Compound **1a** (10 g) was added to 100 ml of NaOH solution and the base was subsequently extracted with dichloromethane (2 x 50 ml). The organic phase was dried (anh. MgSO_4) and the solvent evaporated. The remaining oil was dissolved in 100 ml of acetic acid and PtO_2 (300 mg) was added. The mixture was hydrogenated in a Parr apparatus for 5 hrs at 3 atm. The catalyst was then filtered off, and the acetic acid was evaporated. Dil. NaOH solution (200 ml) and ethyl acetate (200 ml) were added to the remaining oil. The organic phase was separated, dried (anh. MgSO_4) and ethyl acetate was evaporated leaving the crude title compound **3a** as an oil. The hydrochloride salt crystallized from ethanol. Mp 268 °C

50

In a corresponding manner the following 3-(4-piperidyl)-1H-indoles were prepared:

6-bromo-1-(4-fluorophenyl)-3-(4-piperidyl)-1H-indole, **3b**, Mp : 156-158 °C

55

1-(4-fluorophenyl)-3-(4-piperidyl)-6-trifluoromethyl-1H-indole, hydrochloride, **3c** Mp: 288-291 °C

1-(4-fluorophenyl)-6-methyl-3-(4-piperidyl)-1H-indole, **3d** (oil)

1-(4-fluorophenyl)-(6-methylsulfonyl)-3-(4-piperidyl)-1H-indole, **3e** (oil)

55

Example 4 (method d)

6-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, **4a**

5 Compound **3a** (60 g) was converted into the free base by extraction with dichloromethane (2x200 ml) from dil. NaOH solution (500 ml). The organic phase was dried (anh. MgSO_4), filtered and the solvent evaporated leaving the free base as an oil. The oil thus obtained was dissolved in methyl isobutyl ketone (800 ml) and 1-(2-chloroethyl)-3-(2-propyl)-2-imidazolidinon (35 g), potassium carbonate (50 g) and a KI crystal were added. After refluxing overnight the mixture was filtered while still hot, methyl isobutyl ketone
10 was evaporated and diethyl ether (400 ml) added. After stirring for 1/2 hour the precipitated product was filtered off. Finally recrystallization from ethanol yielded 56 g of pure title compound **4a**. Mp: 134 °C.

In a corresponding manner the following N-alkylated 3-(4-piperidyl)-1H-indoles were prepared :

6-chloro-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, **4b**, Mp: 182 °C
1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-6-trifluoromethyl-1H-indole,
15 oxalate, **4c**, Mp: 139-141 °C
1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-6-trifluoromethyl-1H-indole, **4d**, Mp: 187-188 °C
1-(4-fluorophenyl)-3-[1-[2-(2-pyrrolidinon-1-yl)ethyl]-4-piperidyl]-6-trifluoromethyl-1H-indole, fumarate, **4e**,
Mp: 168-169 °C
20 6-chloro-1-(4-fluorophenyl)-3-[1-(2-hydroxyethyl)-4-piperidyl]-1H-indole, hydrochloride, **4f**, Mp: 245-249 °C
1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-6-methyl-1H-indole, **4g**, Mp: 186-188 °C
6-bromo-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, **4h**, Mp: 178-180 °C
1-(4-fluorophenyl)-6-methoxy-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, oxalate,
4i, Mp: 105-107 °C
25 1-(4-fluorophenyl)-6-methoxy-3-[1-[2-(2-oxazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, oxalate, **4j**, Mp: 108-110 °C
1-(4-fluorophenyl)-6-methylsulfonyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole,
oxalate, **4k**, Mp: 132-136 °C
3-[1-[2-[3-(2-Benzoyloxyethyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-6-chloro-1-(4-fluorophenyl)-1H-indole
30 **4l**, oil.

Example 5 (method b)

1-(4-fluorophenyl)-6-methyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, **5a**

35 The 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole derivative **2b** (40 g) was dissolved in acetic acid (500 ml) and PtO_2 (2.4 g) was added. The mixture was hydrogenated in a Parr apparatus for 20 hrs at 3 atm. The catalyst was filtered off and ethyl acetate (500 ml) and ice (2 kg) were added. By addition of dil. NH_4OH pH was adjusted to >9. The organic phase was separated, dried (anh. MgSO_4), filtered and finally
40 ethyl acetate was evaporated leaving 40 g of crude product. This product was dissolved in boiling acetone. By slowly cooling the title compound **5a** crystallized yielding 19 g. Mp: 124 °C.

In a corresponding manner the following N-alkylated 3-(4-piperidyl)-1H-indoles were prepared by catalytic reduction :

6-bromo-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, **5b** , Mp:
45 119 °C
1-(4-fluorophenyl)-6-(2-propyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, oxalate, **5c**, Mp: 179-180 °C
1-(4-fluorophenyl)-6-(2-propyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, **5d**, Mp: 175-177 °C
50 5,6-dichloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, **5e**, Mp: 141-142 °C
5,6-dichloro-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, **5f**, Mp: 182-183 °C
1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1,5,6,7-tetrahydrocyclopent[f]-
55 1H-indole, oxalate, **5g**, Mp: 197 °C
1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1,5,6,7-tetrahydrocyclopent[f]-1H-indole, **5h**, Mp: 225-228 °C
6-cyano-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, **5i**, Mp:

178 °C

6-cyano-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, **5j**, Mp: 175 °C**Example 6 (method f)**6-chloro-1-(4-fluorophenyl)-3-[4-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-1-piperazinyl]-1H-indole, **6a**

To 6-chloro-2-methoxycarbonyl-1-(4-fluorophenyl)-3-indolinon (7.5 g) in NMP (75 ml) was added $MgCl_2 \cdot 6H_2O$ (9 g). The mixture was heated at 130 °C under N_2 for one hour and finally the temperature was raised to 190 °C while H_2O vapours were carried away by a gentle stream of N_2 . 1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-piperazine (12 g) in NMP (30 ml) were added and the temperature kept at 190-200 °C for another hour. After cooling to room temperature the reaction mixture was poured into ethyl acetate (200 ml) and a saturated NH_4Cl solution (500 ml) added. The organic phase was separated, dried (anh. $MgSO_4$), filtered and the solvent evaporated. The remaining oil was purified by column chromatography on silica gel (eluent ethyl acetate/ethanol/triethylamine 90/10/4) yielding 5.7 g of pure title compound **6a**. Mp: 176-177 °C

In a corresponding manner the following 3-(1-piperazinyl)-1H-indole derivatives were prepared :

1-(4-fluorophenyl)-6-methyl-3-[4-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-1-piperazinyl]-1H-indole, dihydrochloride, **6b**, Mp: 228 °C6-chloro-1-(4-fluorophenyl)-3-[4-(2-hydroxyethyl)-1-piperazinyl]-1H-indole, **6c**, Mp: 164-165 °C**Example 7 (intermediates for method i)**3-[1-(2-aminoethyl)-4-piperidyl]-1-(4-fluorophenyl)-6-methyl-1H-indole, **7a**

To a solution of the piperidyl compound **3d** (16 g) in acetone (160 ml) were added triethylamine (4 ml) and chloroacetonitrile (4 ml). The mixture was refluxed for one hour and triethylamine (4 ml) and chloroacetonitrile (4 ml) were added once again. The mixture was then refluxed overnight, filtered and acetone was evaporated. The remaining oil was dissolved in ethyl acetate and filtered through silica gel (eluted with ethyl acetate). The compound with Rf value ~0.9 was collected yielding 6 g of 3-(1-cyanomethyl-4-piperidyl)-1-(4-fluorophenyl)-6-methyl-1H-indole. $LiAlH_4$ (2 g) was suspended in dry diethyl ether (60 ml) and the cyanomethyl derivative from above was dissolved in dry THF (100 ml) and added dropwise during 15 min. at 10-15 °C. The reaction mixture was then refluxed for 1.5 hours, cooled in an ice bath and excess $LiAlH_4$ was destroyed by cautious addition of a conc. NaOH solution (5 ml). Inorganic salts were filtered off and the solvents subsequently evaporated. The remaining oil was dissolved in dichloromethane, dried (anh. $MgSO_4$), filtered and dichloromethane was evaporated. The title compound **7a** crystallized from diisopropyl ether. Mp: 101-103 °C

In a corresponding manner the following 2-aminoethyl derivatives were prepared :

3-[1-(2-aminoethyl)-4-piperidyl]-6-chloro-1-(4-fluorophenyl)-1H-indole, **7b** (oil)**Example 8 (intermediates for method i)**6-chloro-3-[1-(N-ethyl-2-aminoethyl)-4-piperidyl]-1-(4-fluorophenyl)-1H-indole, **8a** (oil)

Compound **7b** (31 g) was dissolved in dichloromethane (400 ml) and triethylamine (10 g) was added. Chloroacetyl chloride (9 g) dissolved in dichloromethane (100 ml) was added dropwise during 30 min. at 10-15 °C. The mixture was stirred for another hour at room temperature. Cold H_2O was added, the organic phase separated, dried (anh. $MgSO_4$), filtered and the solvent evaporated yielding 35 g of the crude chloroacetamide which was subsequently reduced by $LiAlH_4$ according to the method in Example 7 yielding 28 g of the title ethylamino compound **8a** as an oil which was used in further synthesis without purification.

In a corresponding manner the following N-alkyl-2-aminoethyl derivatives were prepared :

6-chloro-1-(4-fluorophenyl)-3-[1-(N-methyl-2-aminoethyl)-4-piperidyl]-1H-indole , **8b** (oil)

Example 9 (method i)

1-(4-fluorophenyl)-3-[1-[2-(3-(2-propyl)-1-ureido)-1-ethyl]-4-piperidyl]-6-methyl-1H-indol, 9a

5 The aminoethyl derivative 7a (3 g) was dissolved in dichloromethane (40 ml) and a solution of 2-propylisocyanate (1 ml) in dichloromethane (10 ml) was added dropwise at 30 °C during 15 min. The mixture was stirred for another hour. Dichloromethane was evaporated and the remaining oil was dissolved in diethyl ether. After 1/2 hour the precipitated title compound 9a was filtered off. Yield 1.8 g. Mp: 173-174 °C

10 In a corresponding manner with intermediates from Examples 7 and 8 the following derivatives were prepared :

3-[1-[2-(3,3-dimethyl-1-ureido)-1-ethyl]-4-piperidyl]-1-(4-fluorophenyl)-6-methyl-1H-indole, oxalate, 9b, Mp: 161 °C

6-chloro-1-(4-fluorophenyl)-3-[1-[2-(3-methyl-1-thioureido)-1-ethyl]-4-piperidyl]-1H-indole, oxalate, 9c, Mp: 167-170 °C

15 6-chloro-1-(4-fluorophenyl)-3-[1-[2-[1-ethyl-3-(2-propyl)-1-ureido]-1-ethyl]-4-piperidyl]-1H-indole, oxalate, 9d, Mp: 175-176 °C

6-chloro-3-[1-[2-(3,3-dimethyl-1-ethyl-1-ureido)-1-ethyl]-4-piperidyl]-1-(4-fluorophenyl)-1H-indole, oxalate, 9e, Mp: 136-138 °C

20 6-chloro-3-[1-[2-(3,3-dimethyl-1-thioureido)-1-ethyl]-4-piperidyl]-1-(4-fluorophenyl)-1H-indole, 9f, Mp: 129-131 °C

6-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-methyl-3-(2-propyl)-1-ureido]-1-ethyl]-4-piperidyl]-1H-indole, 9g, Mp: 118-120 °C

6-chloro-1-(4-fluorophenyl)-3-[1-[2-(1,3-dimethyl-1-ureido)-1-ethyl]-4-piperidyl]-1H-indole, 9h, Mp: 106 °C

25 6-chloro-1-(4-fluorophenyl)-3-[1-[2-(1-methyl-3-(2-propyl)-1-ureido)-1-ethyl]-4-piperidyl]-1H-indole, 9i, Mp: 127 °C

3-[2-(2-acetyl-amino-1-ethyl)-4-piperidyl]-6-chloro-1-(4-fluorophenyl)-1H-indole, 9j, Mp: 150-152 °C

6-chloro-3-[2-(2-ethyloxycarbonylamino-1-ethyl)-4-piperidyl]-1-(4-fluorophenyl)-1H-indole, 9k, Mp: 101-103 °C

30 6-chloro-3-[1-[2-(3,3-dimethyl-1-ureido)-1-ethyl]-4-piperidyl]-1-(4-fluorophenyl)-1H-indole, hydrochloride, hemihydrate, 9l, Mp: 115-116 °C

Example 10 (intermediate for method j)

6-chloro-1-(4-fluorophenyl)-3-[1-[N-(2-(2-propyl)aminoethyl)-2-aminoethyl]-4-piperidyl]-1H-indole, 10a

35 To a solution in 1,1,1-trichloroethane (500 ml) of the intermediate chloroacetamide derivative (25 g) prepared as in Example 8 was added 2-propylamine (20 ml). The mixture was refluxed for 5 hrs. After cooling to room temperature, H₂O (1 L) was added, the organic phase separated, dried (anh. MgSO₄), filtered and volatile materials evaporated. The remaining oil was dissolved in dry THF and LiAlH₄ pellets (5 g) were added. The mixture was refluxed for 1.5 hours. After cooling in an ice bath H₂O/THF was added to destroy excess LiAlH₄. Inorganic salts were filtered off and THF evaporated leaving a crude product as an oil. The title compound 10a was purified by column chromatography on silica gel (eluted with methanol/ethyl acetate 1:1). Yield 15 g as an oil.

Example 11 (intermediate for method j)

3-[1-[N-(2-aminoethyl)-2-aminoethyl]-4-piperidyl]-6-chloro-1-(4-fluorophenyl)-1H-indole, 11a

50 Compound 7b (10 g), triethylamine (3.5 g) and chloroacetonitrile (3 g) were heated at 50-60 °C in 1,1,1-trichloroethane (100 ml) for 4 hrs. After cooling, dil. NH₄OH solution (200 ml) and ethyl acetate (100 ml) were added. The organic phase was separated, dried (anh. MgSO₄), filtered and the solvents were evaporated leaving 8.5 g of the crude aminoacetonitrile derivative as an oil. This crude product was added to a cooled solution of LiAlH₄ (3 g) and AlCl₃ (3 g) in dry diethyl ether (150 ml). The reaction mixture was refluxed for one hour. After cooling with an ice bath, a conc. NaOH solution (2-3 ml) was added cautiously.

55 Inorganic salts were filtered off and subsequently extracted thoroughly by refluxing twice with dichloromethane. The combined organic phases were evaporated leaving the title compound 11a which was used without further purification. Yield 4.5 g

Example 12 (method j)

6-chloro-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinthion-1-yl)ethyl]-4-piperidyl]-1H-indole, **12a**

- 5 To a solution of compound **11a** (4.5 g) in dichloromethane/methanol 1:1 (100 ml) was added 5 ml of carbondisulfide. The mixture was left at room temperature for one hour. Then the solvents were evaporated and finally the remaining viscous oil was heated at 130-140 °C in solution in 1-pentanol. When the evolution of H₂S had ceased the solvents were evaporated. The resulting oil was purified by column chromatography on silica gel (eluted with ethyl acetate/methanol 1:1) yielding 2 g of the title compound **12a** as a crystalline
10 base. Mp: 184-186 °C

Example 13 (method j)

- 15 6-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinthion-1-yl]ethyl]-4-piperidyl]-1H-indole, oxalate, **13a**

- To a solution of compound **10a** (2.2 g) and triethylamine (0.7 g) in 1,1,1-trichloroethane (50 ml) was added thiophosgene (0.6 g). The reaction mixture was slowly heated to reflux temperature. After gently refluxing for one hour the mixture was poured on ice and the organic phase was separated, dried (anh. MgSO₄), filtered and the solvent evaporated. The remaining oil was purified by column chromatography on silica gel (eluted with ethyl acetate/methanol 1:1) yielding the free base as an oil. The oxalate salt **13a** crystallized from acetone. Yield 0.6 g. Mp: 154-157 °C.

Example 14 (intermediates for method c)

- 25 3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-6-methyl-1H-indole, **14a**

- To a solution of potassium hydroxide (16 g) in methanol were added at 5 °C 4-piperidone hydrate hydrochloride (30 g) and a solution of 6-methyl-1H-indole (10 g) in methanol (50 ml). The mixture was
30 refluxed for 16 hours. After cooling precipitated inorganic salts were filtered off. Methanol was evaporated and the remaining oil was dissolved in ethyl acetate (200 ml) and subsequently washed with brine (2 x 100 ml). After drying (anh. MgSO₄) the solvent was evaporated leaving 15 g of crude 6-methyl-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole, which was used without further purification. The pure tetrahydropyridyl derivative crystallized from diethyl ether. Mp : 150-152 °C. To a solution of 1-(2-chloroethyl)-3-(2-propyl)-2-imidazolidinon (32 g) in MIBK (500 ml) were added 6-methyl-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole (15
35 g), potassium carbonate (16 g) and potassium iodide (5 g). The mixture was refluxed for 19 hours and finally filtered while still hot. MIBK was evaporated and the resulting oil was dissolved in ethyl acetate (500 ml) and washed with brine (2 x 100 ml). After drying (anh. Na₂SO₄) ethyl acetate was evaporated. The remaining oil was stirred with diethyl ether (200 ml) and the precipitated, crystalline 3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-1,2,3,6-tetrahydro-4-pyridyl]-6-methyl-1H-indole was filtered off. Yield : 14.5 g. Mp : 170-174 °C. To a solution of the thus prepared imidazolidinon derivative (14 g) in acetic acid (300 ml) was added PtO₂ (600 mg). This mixture was hydrogenated in a Parr apparatus at 3 ato. for 72 hours. The catalyst was filtered off and most of the acetic acid was evaporated *in vacuo*. The remaining oil was
40 dissolved in H₂O and pH was adjusted to 9-10 by addition of dil. NaOH solution. The title compound **14a** was extracted with dichloromethane (2 x 200 ml) and isolated as above. The crude product was purified by eluting (eluent : ethyl acetate / dichloromethane / ethanol / triethylamine 40 : 40 : 20 : 5) through silica gel. Yield : 4.5 g. Mp : 185 °C.

In a corresponding manner were prepared :

- 3-[1-[2-[2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-6-methyl-1H-indole, **14b** Mp : 168-170 °C
50 6-chloro-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, **14c** (used without purification)
6-chloro-3-[1-[2-[2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, **14d** (used without purification)

Example 15 (method c)

3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-6-methyl-1-phenyl-1H-indole, **15a**

- 5 To a solution of 3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-6-methyl-1H-indole **14a** (3.7 g) in NMP (30 ml) was added iodobenzene (4 g), potassium carbonate (3.2 g), CuI (0.5 g) and ZnO (0.16 g). The mixture were heated under N₂ at 160 °C for 4.5 hours. After cooling to room temperature the mixture was poured into ethyl acetate (100 ml) and brine (100 ml). The organic phase was separated, dried (anh. MgSO₄) and ethyl acetate evaporated. The remaining oil (7 g) was purified by column chromatography (eluted with ethyl acetate / triethyl amine 100 : 4 on silica gel). The thus purified title compound **15a** crystallized from diisopropyl ether. Yield : 2.0 g. Mp : 93 °C

In a corresponding manner were prepared the following derivatives by Ullmann arylation :

- 6-methyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1-(2-thienyl)-1H-indole, oxalate, **15b**, Mp : 145 °C
- 15 6-methyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1-(3-thienyl)-1H-indole, oxalate, **15c**, Mp : 134-135 °C
- 1-(3-furanyl)-6-methyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, oxalate, **15d**, Mp : 83-84 °C
- 6-methyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1-(4-pyridyl)-1H-indole, **15e**, Mp : 144 °C
- 20 1-(2-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-6-methyl-1H-indole, oxalate, **15f**, Mp : 150-152 °C
- 1-(3-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-6-methyl-1H-indole, oxalate, **15g**, Mp : 133-135 °C
- 25 1-(4-chlorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-6-methyl-1H-indole, oxalate, **15h**, Mp : 178 °C
- 3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-6-methyl-1-(3-trifluoromethylphenyl)-1H-indole, oxalate, **15i**, Mp : 97 °C
- 6-chloro-1-(2-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, **15j**, oxalate, **15j**, Mp : 106-109 °C
- 30 6-chloro-1-phenyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, **15k**, Mp : 100 °C
- 3-[1-[2-[2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-6-methyl-1-(4-pyridyl)-1H-indole, **15l**, Mp : 141-143 °C
- 6-chloro-3-[1-[2-[2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1-phenyl-1H-indole, **15m**, Mp : 168 °C

35 **Example 16 (intermediate for method k)**

6-chloro-1-(4-fluorophenyl)-3-[1-[2-[1-(1,1-dimethoxy-2-ethyl)-3-(2-propyl)-1-ureido]-1-ethyl]-4-piperidyl]-1H-indole, **16a**

- 40 To a solution of 3-[1-(2-aminoethyl)-4-piperidyl]-6-chloro-1-(4-fluorophenyl)-1H-indole **7b** (11 g) in dioxan (100 ml) were added 2-bromo-1,1-dimethoxyethane (5.6 g), potassium carbonate (5 g) and a potassium iodide crystal. The mixture was refluxed for 16 hours. After cooling inorganic salts were filtered off and dioxan evaporated leaving crude 6-chloro-3-[1-[N-(1,1-dimethoxyethyl)-aminoethyl]-4-piperidyl]-1-(4-fluorophenyl)-1H-indole as an oil. The crude product was purified by column chromatography on silica gel (eluted with ethyl acetate / methanol 1 : 1). Yield : 6 g as an oil. The thus obtained alkylated aminoderivative (6 g) was dissolved in dichloromethane (100 ml) and 2-propylisocyanate (1.1 g) was added. After refluxing for 2 hours dichloromethane was evaporated and the title compound **16a** was purified by column chromatography on silica gel (eluted with ethyl acetate / methanol 1 : 1). Yield : 4.9 g as an oil.

50 **Example 17 (method k)**

6-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)imidazol-2-on-1-yl]ethyl]-4-piperidyl]-1H-indole, hydrochloride, **17a**

- 55 To a solution of 6-chloro-1-(4-fluorophenyl)-3-[1-[2-[1-(1,1-dimethoxy-2-ethyl)-3-(2-propyl)-1-ureido]-1-ethyl]-4-piperidyl]-1H-indole **16a** (4.9 g) in ethanol (50 ml) was added 3 M aqueous hydrochloric acid (3 ml). The mixture was left for 3 days at room temperature and the solvents were subsequently evaporated. The title compound **17a** crystallized as the hydrochloride from acetone. Yield : 1.3 g. Mp : 216-218 °C.

Example 18 (method d variant)

6-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-hydroxyethyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, fumarate **18a**

5

A solution of **4I** (4.3 g) in 6 M hydrochloric acid (80 ml) was refluxed for 45 minutes. The solution was cooled and made alkaline with sodium hydroxide solution, and was extracted with dichloromethane. Conventional work-up of the organic phase yielded 3.3 g of the title compound as an oil which crystallized with fumaric acid from ethanol. Mp : 128-130 °C

10

Example 19

1-(4-fluorophenyl)-6-methylthio-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, oxalate, **19a**

15

To a solution of 1-(4-fluorophenyl)-(6-methylsulfonyl)-3-[4-piperidyl]-1H-indole **3e** (11 g) in a mixture of di-(n-butyl)ether (500 ml) and THF (100 ml) was added lithium aluminum hydride (5.6 g). The mixture was refluxed for 24 h and after cooling to room temperature THF (1000 ml) was added. Finally a 10 % solution of water in THF (500 ml) was added with ice cooling. The solid was filtered off and the solvents were evaporated. Solution of the remaining oil in dichloromethane followed by drying and evaporation of the solvent afforded an oil (9.4 g) which contained 1-(4-fluorophenyl)-(6-methylthio)-3-(4-piperidyl)-1H-indole. A mixture of the thus obtained crude reduction product (9.4 g), 1-(2-chloroethyl)-3-(2-propyl)-2-imidazolidinon (7.6 g), potassium carbonate (7.6 g), a KI crystal and methyl isobutyl ketone (500 ml) was refluxed overnight. The reaction mixture was then cooled, poured into water (500 ml) and extracted with ethyl acetate (2 X 200 ml). The combined organic phases were washed with brine and dried (Na₂SO₄) and the solvents were evaporated *in vacuo*. The remaining oil was purified by column chromatography on silica gel (eluted with ethyl acetate/heptane 3:1 containing 4 % triethyl amine). The title compound **19a** was finally precipitated as its oxalate salt from ethanol. Yield: 0.09 g Mp: 105-110 °C.

Example 20 (method I)

1-(4-fluorophenyl)-6-methyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-2,3-dihydro-1H-indole, dioxalate, **20a**

35

The remaining oil (19 g) after crystallization of 1-(4-fluorophenyl)-6-methyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, **5a** in example 5 was purified by preparative HPLC chromatography (eluted with ethyl acetate / triethylamine 100 : 4) yielding 3.5 g of the title compound as an oil. The dioxalate salt **20a** crystallized from acetone. Yield : 2.8 g. Mp : 85-89 °C.

Example 21 (method I)

6-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-2,3-dihydro-1H-indole, oxalate **21a**

45

To a solution of 6-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole **4a** (2 g) in trifluoroacetic acid (15 ml) was added sodiumcyanoborohydride (1 g). After 2 h reaction at room temperature the solvent was evaporated *in vacuo* and ethyl acetate (50 ml) was added. The solution was washed twice with aqueous 2 N sodium hydroxide (50 ml), dried (anh. Na₂SO₄) and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (eluted with ethyl acetate/heptane 3:1 containing 4 % triethyl amine). The title compound was finally precipitated as its oxalate salt from acetone. Yield: 0.5 g Mp: 91-100 °C.

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Example 22 (intermediate for compound 4I)

1-(2-Benzyloxyethyl)-3-(2-chloroethyl)-2-imidazolidinon, **22a**

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To 3-benzyloxypropionic acid (129.6 g) in ether (310 ml) and N,N-dimethylformamide (4ml) was added thionyl chloride (155 ml). The solution was refluxed for 2 hours, and solvents and excess thionyl chloride

were removed by evaporation *in vacuo*. Yield 132 g of 3-Benzoyloxypropionic acid chloride as an oil. To an ice cooled solution of the thus prepared acid chloride (132 g) in acetone (450 ml) was added a cold solution of sodium azide (48.5g) in water (200 ml) at 5 °C. After additional stirring at 5 °C for 30 minutes, the mixture was poured into water and toluene, and the aqueous phase was extracted twice with toluene. The combined organic phases were washed with brine. After drying (magnesium sulfate) the solution was heated slowly to 85 °C on a steam bath until evolution of nitrogen ceased. The solvent was removed *in vacuo* leaving 108.4 g of 2-benzyloxyethylisocyanate as an oil. A mixture of 2-benzyloxy-ethylisocyanate (10 g) and diethanolamine (5.72 g) in dichloromethane (60 ml) was refluxed for 2.5 hours. After cooling to room temperature, the solution was washed with brine. Drying (magnesium sulfate) and evaporation of the solvent yielded 11.4 g of N-(2-benzyloxyethyl)-N',N'-di-(2-hydroxyethyl)-urea as an oil. A solution of the urea derivative (11.4 g) in dichloromethane (55 ml) was cooled to 5 °C, and thionyl chloride (8.3 ml) was added at a temperature below 10 °C. After the addition the mixture was refluxed for 1 hour and then left over night at room temperature. The solution was washed with cold sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over magnesium sulfate and evaporated *in vacuo*. The residue was dissolved in 1,1,1-trichloroethane and refluxed for 3 hours. After cooling the solution was washed with sodium hydrogen carbonate solution, dried over magnesium sulfate and evaporated *in vacuo*, yielding 6.6 g of the title compound **22a** as an oil.

Example 23 (intermediate for method a, 2-alkylated 1-arylindoles)

1-(4-fluorophenyl)-2-methyl-1H-indole, **23a**

To a solution of 2-carboxy-1H-indole (50 g) in DMF (600 ml) were added potassium hydroxide (40 g) and 4-fluoriodobenzene (90 g). Reflux in an inert N₂ stream for 6 hours. H₂O/DMF was distilled off to obtain a constant boiling point of 148 °C. After cooling to room temperature ether (500 ml) was added. The precipitated material was filtered off and water (500 ml) was added. Undissolved material was filtered off. To the alkaline water phase was added ethyl acetate (500 ml) and pH was adjusted to 2 by addition of dil. aqueous HCl. The organic phase was worked up as yielding 2-carboxy-1-(4-fluorophenyl)-1H-indole (41 g) which melted at 213 °C. The thus obtained carboxyindole (38 g) was added cautiously to a suspension of LiAlH₄ (7.5 g) in dry THF (350 ml) at such a rate that the temperature was kept below 50 °C. The mixture was finally stirred at 50 °C for 1.5 h. After cooling 5 M NaOH solution was added under vigorous stirring. Precipitated inorganic material was filtered off and washed thoroughly with dichloromethane. After evaporation of the combined organic phases 1-(4-fluorophenyl)-2-hydroxymethyl-1H-indole (35 g) was isolated as a crystalline product. Mp : 65-66 °C. The hydroxymethyl derivative (35 g) was dissolved in ethanol (600 ml). The solution was hydrogenated in a Parr apparatus with 15 % Pd/C as catalyst at 3 ato. for 20 h. The catalyst was filtered off and ethanol evaporated leaving the crude title compound **23a** as an oil. Purification by elution (dichloromethane/heptane 1:1 as eluent) through silica gel afforded the pure 1-(4-fluorophenyl)-2-methyl-1H-indole (18 g) as a crystalline product. Mp : 43 °C

Example 24

From compound **23a** was prepared the following 2-methylindoles by methods a), b) and d) :
 1-(4-fluorophenyl)-2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, **24a**, oil
 1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-2-methyl-1H-indole, **24b**, Mp: 172-177 °C
 1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-2-methyl-1H-indole, **24c**, Mp: 182 °C

PHARMACOLOGICAL TESTS

The compounds of the invention were tested in well recognized and reliable methods. The tests were as follows and the results are given in the following Tables I and II.

QUIPAZINE INHIBITION

Quipazine is a 5-HT₂ agonist, which induces head twitches in rats. The test is a test for 5-HT₂-antagonistic effect testing the ability to inhibit head twitches. The method and test results for some reference substances are published by Arnt et al. (*Drug Development Research*, 16, 59-70, 1989).

Procedure

Test substance is injected *s.c.* 2 hrs before or *p.o.* 24 hrs before quipazine administration (6.8 mg/kg, *s.c.*, dimaleate). Four rats, male Wistar (Mol:Wist) SPF rats weighing 170-240 g, are used at each dose level. A control group is included each test day. By repeated testing (2, 24 hrs) the control group is the same, however. After quipazine administration the rats are individually placed in the observation cages and head twitches are counted in an observation period of 30-40 min. after injection of quipazine. Total number of head twitches in each group is calculated and the result for each dose is expressed as per cent of the response in the control group. ED₅₀ values are calculated by log-probit analysis. The test must be repeated if the average number of head twitches is lower than 9 in the control group.

ANTAGONISM OF PERGOLIDE-INDUCED CIRCLING BEHAVIOUR IN RATS WITH UNILATERAL 6-OHDA LESIONS

Dopamine (DA) D-2 agonists induce contralateral circling behaviour in rats with 6-OHDA lesions. Pergolide-induced circling is antagonized by DA D-2 antagonists. (Arnt, J. and J. Hyttel, *Eur. J. Pharmacol.* 102, 349-354, 1984; Arnt, J. and J. Hyttel, *J. Neural. Transm.* 67, 225-240, 1986).

Procedure

Male Wistar rats (Mol:Wist) weighing about 200 g at the time of operation are used. Unilateral lesions are made in pentobarbital anaesthetized rats by injection of 6-OHDA·HCl 9.7 µg/µl (equivalent to 8 µg free base) per 4 min. into the rostral tip of the substantia nigra. The saline solution contains ascorbic acid 0.2 mg/ml, is bubbled with N₂ and is kept ice-cold. The experiments are done when stable contralateral circling responses to pergolide (0.05 µmol/kg, *s.c.*) are obtained. The circling response is measured in rotometer bowls. Only rats showing more than 400 complete turns in 2 hrs control session are used. Dose-response curves are obtained by alternating test and control sessions on a weekly basis. The antagonists are injected *s.c.* 2 hrs before the agonist. The effect of individual doses of test drugs is calculated as per cent of the mean effect of control sessions one week before and one week after the test session for each rat. ED₅₀ values are calculated by log-probit analysis. Four to eight rats are used at each dosage.

INHIBITION OF ³H-PRazosin BINDING TO α₁ ADRENOCEPTORS IN RAT BRAIN IN VITRO

By this method the inhibition of the binding of ³H-Prazosin (0.25 nM) to α₁ adrenoceptors in membranes from rat brain is determined *in vitro*. Method and results in Hyttel & Larsen, *J. Neurochem.* 44, 1615-1622, 1985; Skarsfeldt & Hyttel, *Eur. J. Pharmacol.* 125, 323-340, 1986.

Procedure

Male Wistar (Mol:Wist) rats (125-200 g) are sacrificed and brain tissue is dissected and weighed. The tissue is homogenized (Ultra Turrax, 10 sec.) in 10 ml of ice-cold 50 mM Tris buffer pH 7.7 (at 25 °C). The homogenate is centrifuged twice at 20,000 g for 10 min. at 4 °C with rehomogenization of the pellet in 10 ml ice-cold buffer. The final pellet is homogenized in 400 vol (w/v) ice-cold buffer.

Incubation tubes kept on ice in triplicate receive 100 µl of drug solution in water (or water for total binding) and 400 µl of tissue suspension (final tissue content corresponds to 10 mg original tissue). The binding experiment is initiated by addition of 100 µl of ³H-Prazosin (final concentration 0.25 nM) and by placing the tubes in a 25 °C water bath. After incubation for 20 min. the samples are filtered under vacuum (0-50 mBar) through Whatman GF/F filters (25 mm). The tubes are rinsed with 5 ml ice-cold buffer which then are poured on the filters. Thereafter, the filters are washed with 5 ml of buffer. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor™ 15) are added. After shaking for 1 h and storage 2 hrs in the dark the content of radioactivity is determined by liquid scintillation counting. Specific binding is obtained by subtracting the nonspecific binding in the presence of 1 µM of Prazosin.

For determination of the inhibition of binding five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper and the best fitting S-shaped curve is drawn. The IC₅₀ value is determined as the concentration at which the binding is 50% of the total binding in control samples minus the nonspecific binding in the presence of 1 µM of Prazosin. ³H-Prazosin = [furoyl-5-³H]-Prazosin from New England Nuclear, specific activity approximately 20 Ci/mmol.

INHIBITION OF ³H-KETANSERIN BINDING TO SEROTONIN S₂ (5-HT₂) RECEPTORS IN RAT CORTEX *IN VITRO*

By this method the inhibition by drugs of the binding of ³H-Ketanserin (0,5 nM) to Serotonin S₂ (5-HT₂) receptors in membranes from rat is determined *in vitro*. Method in Hyttel, *Pharmacology & Toxicology*, 61, 126-129. 1987.

Procedure

Male Wistar (Mol:Wist) rats (125-250 g) are sacrificed and cortical tissue is dissected and weighed. The tissue is homogenized (Ultra Turrax, 10 sec.) in 10 ml of ice-cold 50 mM tris buffer pH 7.7 (at 25 °C). The centrifuge glassware used in this step has been rinsed by sonication for 10 min. in ethanol. The homogenate is centrifuged twice at 20,000 g for 10 min. at 4 °C with rehomogenization of the pellet in 10 ml ice-cold buffer. The final pellet is homogenized in 500 vol (w/v) ice-cold buffer.

Incubation tubes kept on ice in triplicate receive 100 µl of drug solution in water (or water for total binding) and 2000 µl of tissue suspension (final tissue content corresponds to 4 mg original tissue). The binding experiment is initiated by addition of 100 µl of ³H-Ketanserin (final concentration 0.5 nM) and by placing the tubes in a 37 °C water bath. After incubation for 30 min. the samples are filtered under vacuum (0-50 mBar) through Whatman GF/F filters (25 mm). The tubes are rinsed with 5 ml ice-cold buffer which are then poured on the filters. Thereafter, the filters are washed with 2 x 5 ml of buffer. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor TM 15) are added. After shaking for 1 h and storage 2 hrs in the dark the content of radioactivity is determined by liquid scintillation counting. Specific binding is obtained by subtracting the nonspecific binding in the presence of 1 µM mianserin.

For determination of the inhibition of binding five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper and the best fitting S-shaped curve is drawn. The IC₅₀ value is determined as the concentration at which the binding is 50% of the total binding in control samples minus the nonspecific binding in the presence of 1 µM mianserin.

³H-Ketanserin = [ethylene-³H]-ketanserin hydrochloride from New England Nuclear, specific activity 60-80 Ci/mmol).

INHIBITION OF ³H-SPIPERONE BINDING TO DOPAMINE D-2 RECEPTORS IN RAT CORPUS STRIATUM *IN VITRO*

By this method the inhibition by drugs of the binding of ³H-spiperone (0.5 nM) to dopamine D-2 receptors in membranes from rat corpus striatum is determined *in vitro*. Method and results in Hyttel & Larsen, *J. Neurochem*, 44, 1615-1622, 1985).

Procedure

Male Wistar (Mol:Wistar) rats (125-250 g) are sacrificed and striatal tissue is dissected and weighed. The tissue is homogenized (Ultra Turrax, 10 sec.) in 10 ml of ice-cold 50 mM K-phosphate buffer pH 7.4 (at 25 °C). The homogenate is centrifuged twice at 20,000 g for 10 min. at 4 °C with rehomogenization of the pellet in 10 ml ice-cold buffer. The final pellet is homogenized in 1300 vol (w/v) ice-cold buffer.

Incubation tubes kept on ice in triplicate receive 100 µl of drug solution in water (or water for total binding) and 4000 µl of tissue suspension (final tissue content corresponds to 3.08 mg original tissue). The binding experimental is initiated by addition of 100 µl of ³H-spiperone (final concentration 0.5 nM) and by placing the tubes in a 37 °C water bath. After incubation for 10 min. the samples are filtered under vacuum (0-50 mBar) through Whatman GF/F filters (25 mm). The tubes are rinsed with 5 ml ice-cold buffer which are then poured on the filters. Thereafter, the filters are washed with 2 x 5 ml of buffer. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor TM 15) are added. After shaking for 1 h and storage 2 hrs in the dark the content of radioactivity is determined by liquid scintillation counting. Specific binding is obtained by subtracting the nonspecific binding in the presence of 10 µM of 6,7-ADTN.

For determination of the inhibition of binding five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper and the best fitting S-shaped curve is drawn. The IC₅₀ value is determined as the concentration at which the binding is 50% of the total binding in control samples minus the nonspecific binding in the presence of 10 µM of 6,7-ADTN.

³H-Spiperone = [phenyl-4-³H]-spiperone from Amersham International plc. England, specific activity 15-25 Ci/mmol.

TABLE I Pharmacological activity of 6-substituted or 2-alkyl substituted 1-arylindoles and 1-aryl-2,3-dihydroindoles *in vitro*.

Compound No.	Binding (IC ₅₀ nM)		
	³ H Ket.	³ H Spi.	³ H Praz.
2a	3.5	66	55
2b	1.9	67	
4a	1.5	130	70
4b	1.4		
4c	2.9	280	91
4d	1.7		
4e	2.8	300	49
4f	11		
4g	0.8	270	24
4h	1.8		
4i	7.1	710	140
4j	40	1100	
4k	9.0	600	
5a	1.6	190	85
5b	2.0		
5c	16	2000	730
5d	18		
5e	3.4		
5f	3.5		
5g	3.2		
5h	1.2		
5i	8.6	1100	
5j	13	1500	
6a	2.7	81	
6b	2.7	180	76
9a	1.8	300	76
9b	2.6		
9c	12		
9d	1.9	150	
9e	6.4		
9f	2.5		
9g	6.2		
9h	1.6		

TABLE 1 (continued)

5	Compound No.	Binding (IC ₅₀ nM)		
		³ H Ket.	³ H Spi.	³ H Praz.
	9i	2.2		
	9j	11		
10	9k	4.0		
	9l	1.3		
	12a	6.2		
	13a	4.4	270	110
15	15a	2.0	500	120
	15b	6.7	2500	
	15c	2.6	1000	330
	15d	9.3	4500	
	15e	7.6	3500	
20	15f	2.5	730	370
	15g	11	3200	670
	15h	6.0	620	450
	15l	150	3200	
25	15j	3.7	300	120
	15k	4.5		
	15m	4.4	410	
	17a	4.6		
	18a	2.5		
30	19a	3.2		
	20a	5.3	180	
	21a	9.6		
	24b	1.0		
	24c	0.69	380	61
35	-----			
	ritanserin	0.40	12	47
	ICI 169369	15	490	300
	sertindole (Lu 23-174)	0.72	4.1	3.4
40	Lu 21-152	1.4	2.6	7.6

TABLE II

Pharmacological activity of 6-substituted or 2-alkyl substituted 1-arylindoles and 1-aryl-2,3-dihydroindoles <i>In vivo</i>			
Compound No.	Quipazine inhibition		Pergolide rot. inhibition
	ED ₅₀ (μmol/kg)		
	2h (sc)	24h (po)	2h (sc)
4a	0.11	0.06	>17
4b	0.06		>23
4g	0.02	0.04	>24
5a	0.04	0.11	>18
5f	0.12	0.04	>42
6b	0.04		
9b	0.12	<0.14	
15a	0.01		
15j	0.08		
20a	0.49		
ritanserin	0.08	0.98(sc)	>21
ICI 169369	>3.6	nt	nt
sertindole (Lu 23-174)	0.04	0.04	7.2
Lu 21-152	0.02	0.15(sc)	0.02
nt: Not tested.			

From the *in vitro* data in Table I it is evident that the novel indole and 2,3-dihydroindole derivatives in general potentially bind to 5-HT₂ receptors with nanomolar affinities. The corresponding 5-substituted indoles as disclosed by US patent no. 4,710,500 also have high affinities for 5-HT₂ receptors. Lu 21-152 (1-(4-fluorophenyl)-3-[4-(2-hydroxyethyl)-1-piperazinyl]-5-trifluoromethyl-1H-indole) and sertindole (Lu 23-174 (5-chloro-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon -1-yl)-ethyl]-4-piperidyl]-1H-indole)) are shown as examples of such 5-substituted derivatives. By introducing suitable substituents into the 6-position or suitable alkyl substituents into the 2-position of the indole or 2,3-dihydroindole ring it appears from Table I that the *in vitro* affinity for central dopamine D-2 and central noradrenergic α₁ receptors is strongly attenuated. Selectivity ratios of D-2/5-HT₂ receptor affinities better than about 20 and ratios of α₁/5-HT₂ receptor affinities better than about 20 and even for most compounds better than 100 and 50 respectively, are obtained, which is at least as good as ratios obtained for the standard 5-HT₂ antagonists ritanserin and ICI 169369. From the data presented in Table II (quipazine inhibition) it is evident that the novel indole compounds have potent central 5-HT₂ antagonism with good oral bioavailability and long duration of action. However, contrary to the 5-substituted indoles disclosed by US patent no. 4,710,500, which were also potent central 5-HT₂ antagonists *in vivo*, the novel 6-substituted derivatives of this invention show no central antidopaminergic activity *in vivo* as measured by the inhibition of pergolide induced rotations in rats with unilateral 6-OHDA lesions (Table II), which test is a extremely sensitive test for dopamine D-2 antagonistic activity *in vivo* (Arnt, J. and J. Hyttel, *J. Neural. Transm.* 67, 225-240, 1986).

FORMULATION EXAMPLES

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tableting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients. Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilization of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Typical examples of recipes for the formulation of the invention are as follows:

1) Tablets containing 5 milligrams of Compound 5a calculated as the free base:

Comp. 5a	5 mg
Lactose	18 mg
Potato starch	27 mg
Sucrose	58 mg
Sorbitol	3 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg

2) Tablets containing 50 milligrams of Compound 4a calculated as the free base:

Comp. 4a	50 mg
Lactose	16 mg
Potato starch	45 mg
Sucrose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg

3) Syrup containing per milliliter:

Comp. 5a	10 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water	ad 1 ml

4) Solution for injection containing per milliliter:

Comp. 4a	50 mg
Acetic acid	17.9 mg
Sterile water	ad 1 ml

5) Solution for injection containing per milliliter:

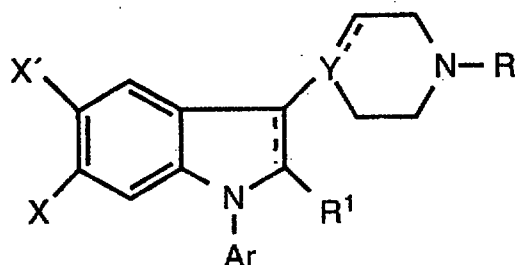
Comp. 5a	10 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water	ad 1 ml



Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A 6-substituted or 2-alkyl substituted indole or 2,3-dihydroindole derivative having the general formula I:



I.

where Ar is phenyl optionally substituted with one or more substituents selected from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, trifluoromethyl, and cyano, or a hetero aromatic group preferably 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-oxazolyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

the dotted line in the indole ring indicates an optional bond;

X is hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, cyano, trifluoromethyl, or trifluoromethylthio;

X' is a substituent taken from the X-substituents above; or

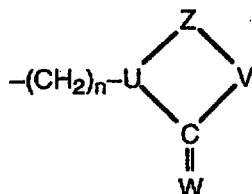
X and X' are linked to constitute a 5-7 membered carbocyclic ring;

R¹ is hydrogen or C₁-C₄ alkyl optionally substituted with one or two hydroxy groups, provided that when X is hydrogen or fluoro, R¹ cannot be hydrogen;

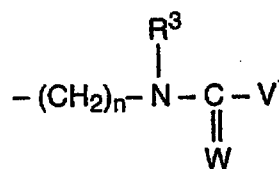
Y is N, C or CH;

when Y is C, the dotted line emanating from Y indicates a bond;

R is hydrogen, or C₁-C₄ alkyl, lower alkenyl, cycloalkyl, or cycloalkylmethyl, optionally substituted with one or two hydroxy groups, any hydroxy group present being optionally esterified with an aliphatic carboxylic acid having from two to twenty four carbon atoms inclusive, or R is a group taken from structures 1a and 1b :



1a.



1b.

wherein n is an integer from 2 - 6;

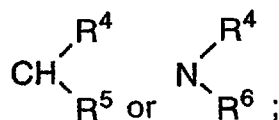
W is oxygen or sulfur;

U is N or CH;

Z is -(CH₂)_m-, m being 2 or 3, or Z is -CH=CH-, Z is -COCH₂- or -CSCH₂-, or 1,2-phenylene optionally substituted with halogen or trifluoromethyl;

V is oxygen, sulfur, CH₂, or NR², wherein R² is hydrogen, C₁-C₄ alkyl or lower alkenyl optionally substituted with one or two hydroxy groups, or R² is a cycloalkyl or cycloalkylmethyl group;

V¹ is O-R⁴, S-R⁴,

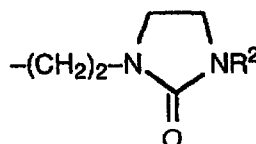


R³ is hydrogen, C₁-C₄ alkyl or lower alkenyl optionally substituted with one or two hydroxy groups, or a cycloalkyl group;



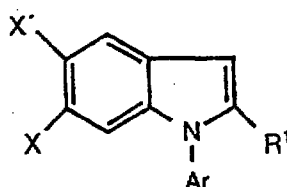
R⁴ and R⁵ are independently selected from the R³-substituents; and
 R⁶ is as defined for R² above
 and pharmaceutically acceptable acid addition salts and prodrugs thereof.

2. A derivative according to claim 1, **characterized in that** Ar is phenyl optionally substituted with halogen, preferably 4-fluorophenyl.
3. A derivative of claim 1 or 2, **characterized in that** Y is -CH-.
4. A derivative according to any of claims 1-3 **characterized in that** R is a group of the formula



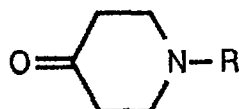
wherein R² is as defined in claim 1, R² preferably being hydrogen or isopropyl.

5. A derivative according to any of the claims 1-4, **characterized in that** X is -Cl, -Br, -CF₃, or -CH₃ and/or that X' is hydrogen or -Cl.
6. A derivative of claims 2, 3, 4 and 5, **characterized in that** it is 6-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole or 1-(4-fluorophenyl)-6-methyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole.
7. A pharmaceutical preparation **characterized in that** it comprises a compound of any of the claims 1 - 6 or a pharmaceutical acceptable acid addition salt or a prodrug thereof as an active ingredient together with a pharmaceutically acceptable carrier or diluent.
8. A pharmaceutical preparation according to claim 7, **characterized in that** it is an injectable depot preparation comprising a prodrug of a compound of any of claims 1 - 6 in a suitable pharmaceutically acceptable oil, preferably peanut oil, sesame oil, cotton seed oil, corn oil, soy bean oil, olive oil, etc. or synthetic esters of fatty acids and glycerol or propyenglycol.
9. Use of a derivative of any of claims 1 - 7 for the manufacture of a medicament for the therapeutical treatment of CNS disorders, preferably for the treatment of anxiety, depression, sleep disturbances, migraine, negative symptoms of schizophrenia, and Parkinson's disease .
10. A method for the preparation of a derivative of claim 1 comprising
 a) reacting an indole derivative of the following formula :



II.

wherein R¹, X, X' and Ar are as defined above, with a 4-piperidone of the formula:

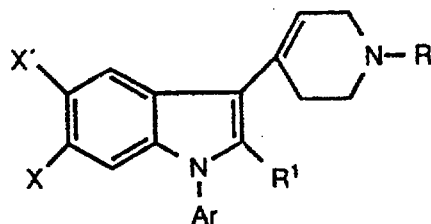


III



wherein R is as defined above, or

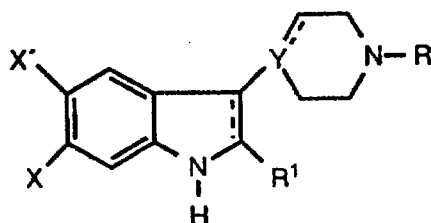
b) reducing the double bond in the tetrahydropyridyl ring of a compound of the formula :



IV.

wherein R¹, X, X', Ar and R are as defined above, or

c) reacting a compound of the following formula :



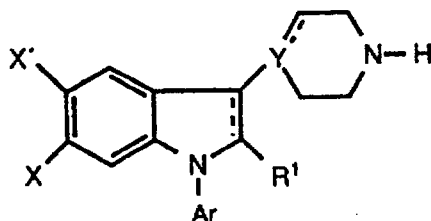
V.

wherein R¹, X, X', Y, R and the dotted lines are as defined above, with a compound of the formula :

Ar - hal VI

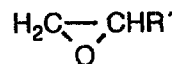
wherein Ar is as defined above and "hal" is halogen (Cl, Br or I) in the presence of a metal catalyst, or

d) alkylating a compound of the following formula :

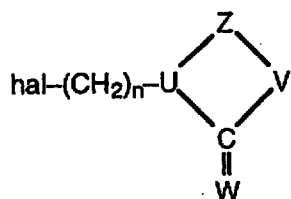


VII.

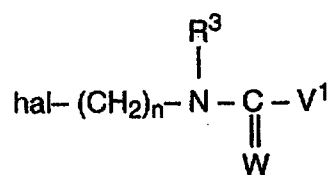
wherein R¹, X, X', Y, Ar and the dotted lines are as defined above with a C₁-C₄ alkyl halide, alkyl mesylate or tosylate, an epoxide of formula



wherein R' is hydrogen, methyl or ethyl, or with a halide of the general formula :

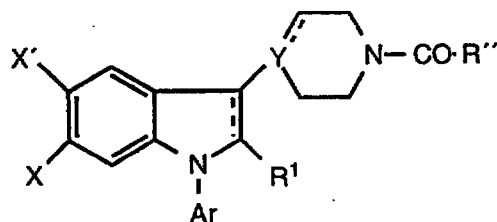


VIII a



VIII b.

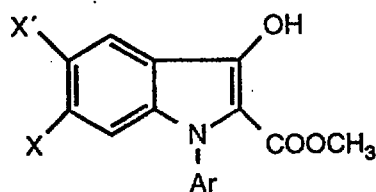
wherein U, Z, V, V¹, W, R³ and n are as previously defined and "hal" is chloro, bromo or iodo, or
e) reducing the carbonyl group in a compound of the following formula :



IX

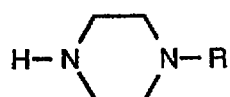
wherein R¹, X, X', Y, Ar and the dotted lines are as previously defined and R'' is hydrogen, C₁-C₄ alkyl or C₁-C₄ alkoxy, or

f) heating an indoxylester of the following formula :



X.

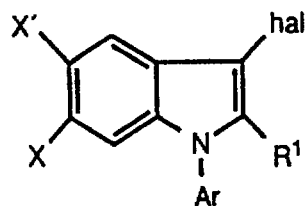
wherein X, X' and Ar are as defined above, in the presence of an inorganic salt catalyst followed by continued heating in the presence of a piperazine derivative of formula :



XI

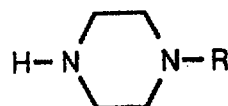
wherein R is as defined above, or

g) reacting a 3-halogen substituted indole derivative of the formula XII with a piperazine derivative of the formula XIII :



XII

+

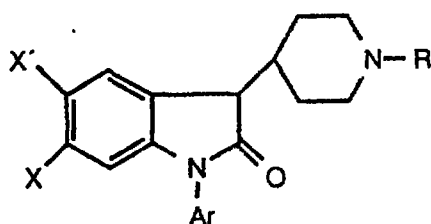


XIII

wherein R¹, X, X', Ar and R are as defined above and "hal" means chloro, bromo, or iodo, or



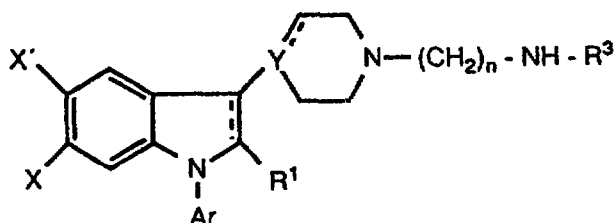
h) reducing a 2-oxindole derivative of the following formula :



XIV

wherein X, X', Ar and R are as defined above, or

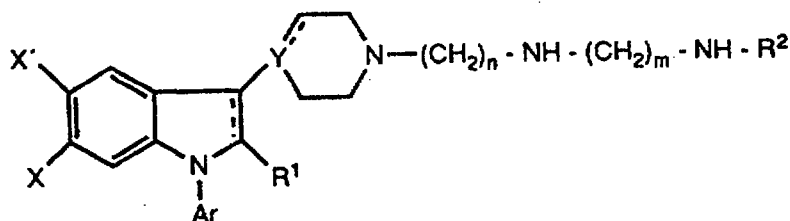
i) acylating an aminoalkyl derivative of the following formula :



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wherein R¹, X, X', Y, Ar, n, R³ and the dotted lines are as defined above using a carboxylic acid halogenide, anhydride or mixed anhydride, a carbamyl or thiocarbamyl chloride, isocyanate, isothiocyanates or substituted chloroformate as acylating agent, or

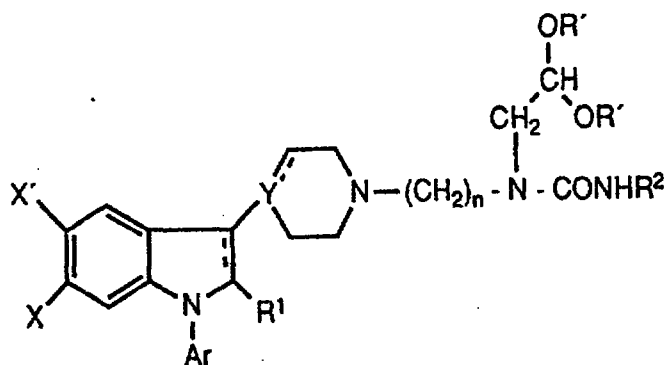
j) ringclosure reaction of an intermediate derivative of the following formula :



XVI

wherein R¹, X, X', Y, Ar, n, R², m and the dotted lines are as defined above, using urea, phosgene, thiophosgene or carbondisulfide to incorporate a carbonyl or thiocarbonyl group in the heterocyclic ring of structure 1a, or

k) ringclosure reaction of an intermediate derivative of the following formula :

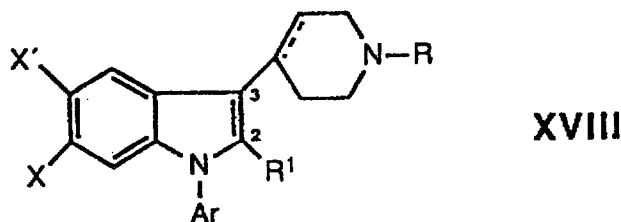


XVII

wherein R¹, X, X', Y, Ar, n, R² and the dotted lines are as defined above and R' is C₁-C₄ alkyl or lower alkenyl or constitute a ring by forming an ethylene or propylene bridge, or



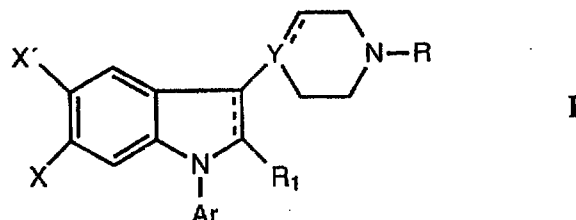
l) reducing the 2,3-double bond of an 3-piperidylindole of the following formula :



wherein R¹, X, X', Ar, R and the dotted line are as defined above,
and then optionally converting the compound of formula I obtained into a pharmaceutically acceptable acid addition salt or prodrug thereof.

Claims for the following Contracting States : ES, GR

1. A method for the preparation of a 6-substituted or 2-alkyl substituted indole or 2,3-dihydroindole derivative having the general formula I :



where Ar is phenyl optionally substituted with one or more substituents selected from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, trifluoromethyl, and cyano, or a hetero aromatic group preferably 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-oxazolyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;
the dotted line in the indole ring indicates an optional bond;

X is hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, cyano, trifluoromethyl, or trifluoromethylthio;

X' is a substituent taken from the X-substituents above; or

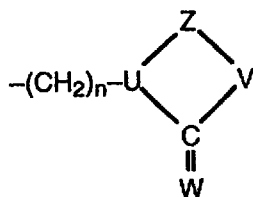
X and X' are linked to constitute a 5-7 membered carbocyclic ring;

R¹ is hydrogen or C₁-C₄ alkyl optionally substituted with one or two hydroxy groups, provided that when X is hydrogen or fluoro, R¹ cannot be hydrogen;

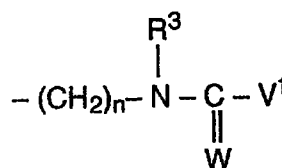
Y is N, C or CH;

when Y is C, the dotted line emanating from Y indicates a bond;

R is hydrogen, or C₁-C₄ alkyl, lower alkenyl, cycloalkyl, or cycloalkylmethyl, optionally substituted with one or two hydroxy groups, any hydroxy group present being optionally esterified with an aliphatic carboxylic acid having from two to twenty four carbon atoms inclusive, or R is a group taken from structures 1a and 1b :



1a.



1b.

wherein n is an integer from 2 - 6;
W is oxygen or sulfur;

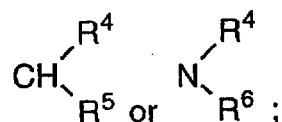


U is N or CH;

Z is $-(CH_2)_m-$, m being 2 or 3, or Z is $-CH=CH-$, Z is $-COCH_2-$ or $-CSCH_2-$, or 1,2-phenylene optionally substituted with halogen or trifluoromethyl;

V is oxygen, sulfur, CH_2 , or NR^2 , wherein R^2 is hydrogen, C_1 - C_4 alkyl or lower alkenyl optionally substituted with one or two hydroxy groups, or R^2 is or a cycloalkyl or cycloalkylmethyl group;

V' is $O-R^4$, $S-R^4$,



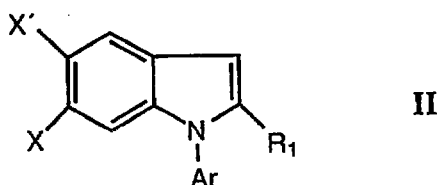
R^3 is hydrogen, C_1 - C_4 alkyl or lower alkenyl optionally substituted with one or two hydroxy groups, or a cycloalkyl group;

R^4 and R^5 are independently selected from the R^3 -substituents; and

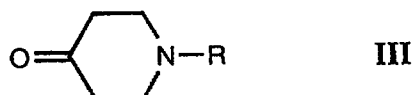
R^6 is as defined for R^2 above

and pharmaceutically acceptable acid addition salts and prodrugs thereof, comprising

a) reacting an indole derivative of the following formula :

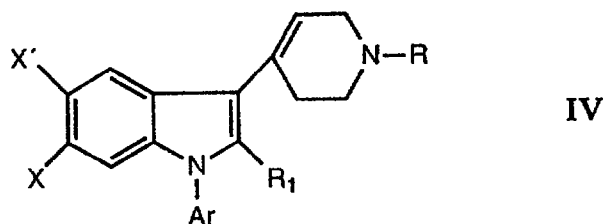


wherein R^1 , X, X' and Ar are as defined above, with a 4-piperidone of the formula:



wherein R is as defined above, or

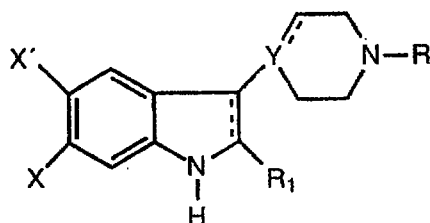
b) reducing the double bond in the tetrahydropyridyl ring of a compound of the formula :



wherein R^1 , X, X' , Ar and R are as defined above, or



c) reacting a compound of the following formula :



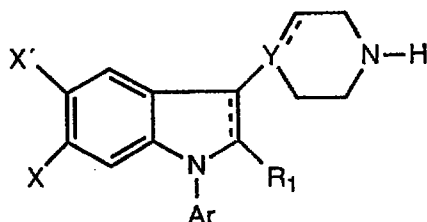
V

wherein R^1 , X, X' , Y, R and the dotted lines are as defined above, with a compound of the formula :

Ar - hal VI.

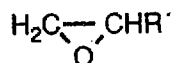
wherein Ar is as defined above and "hal" is halogen (Cl, Br or I) in the presence of a metal catalyst, or

d) alkylating a compound of the following formula :

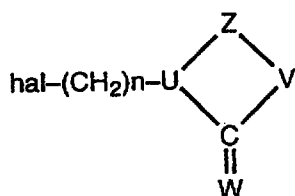


VII

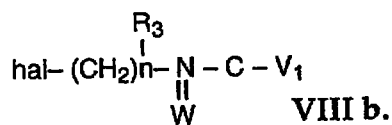
wherein R^1 , X, X' , Y, Ar and the dotted lines are as defined above with a C_1 - C_4 alkyl halide, alkyl mesylate or tosylate, an epoxide of formula



wherein R' is hydrogen, methyl or ethyl, or with a halide of the general formula :



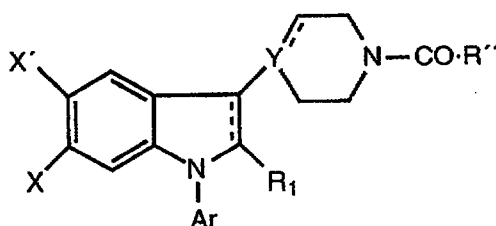
VIII a.



VIII b.

wherein U, Z, V, V^1 , W, R^3 and n are as previously defined and "hal" is chloro, bromo or iodo, or

e) reducing the carbonyl group in a compound of the following formula :

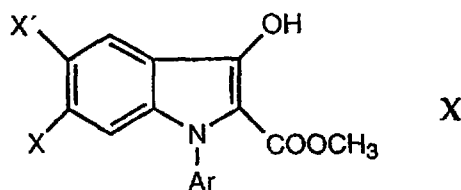


IX

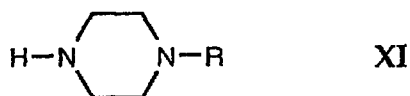


wherein R', X, X', Y, Ar and the dotted lines are as previously defined and R'' is hydrogen, C₁-C₄ alkyl or C₁-C₄ alkoxy, or

f) heating an indoxylester of the following formula :

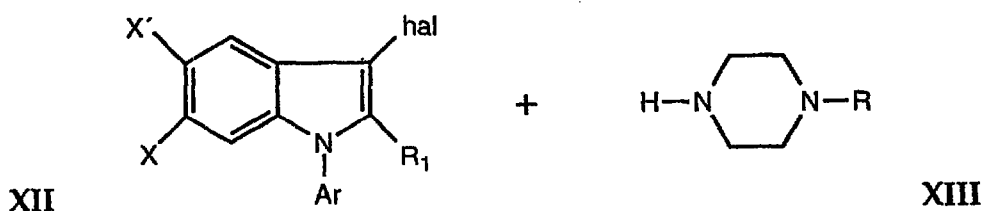


wherein X, X' and Ar are as defined above, in the presence of an inorganic salt catalyst followed by continued heating in the presence of a piperazine derivative of formula :



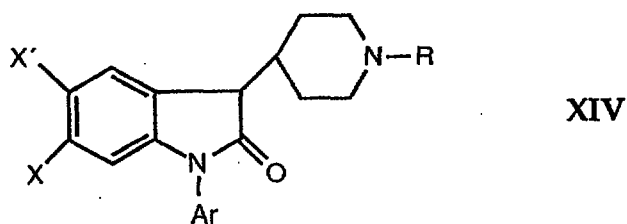
wherein R is as defined above, or

g) reacting a 3-halogen substituted indole derivative of the formula XII with a piperazine derivative of the formula XIII :



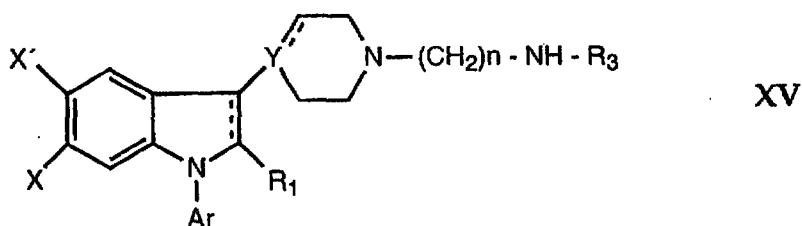
wherein R', X, X', Ar and R are as defined above and "hal" means chloro, bromo, or iodo, or

h) reducing a 2-oxindole derivative of the following formula :



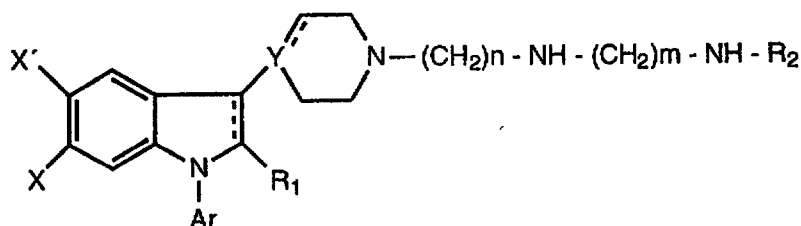
wherein X, X', Ar and R are as defined above, or

i) acylating an aminoalkyl derivative of the following formula :



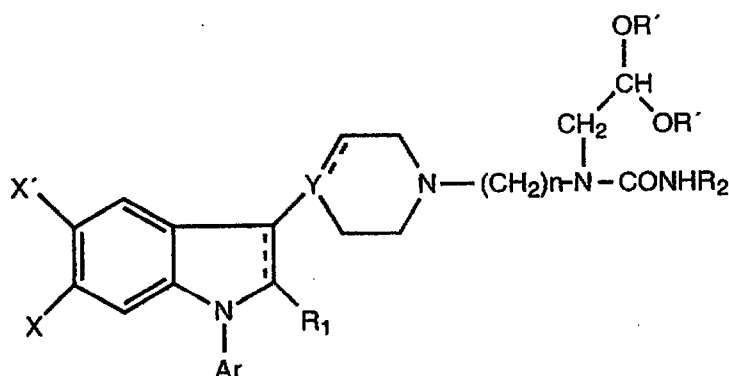


wherein R^1 , X , X' , Y , Ar , n , R^3 and the dotted lines are as defined above using a carboxylic acid halogenide, anhydride or mixed anhydride, a carbamyl or thiocarbamyl chloride, isocyanate, isothiocyanates or substituted chloroformate as acylating agent, or
j) ringclosure reaction of an intermediate derivative of the following formula :



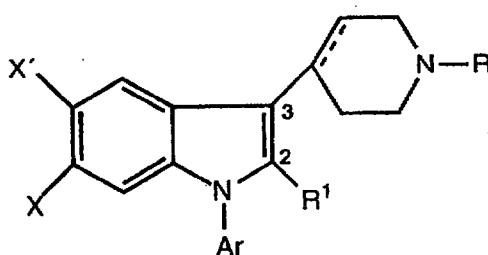
XVI

wherein R^1 , X , X' , Y , Ar , n , R^2 , m and the dotted lines are as defined above, using urea, phosgene, thiophosgene or carbondisulfide to incorporate a carbonyl or thiocarbonyl group in the heterocyclic ring of structure 1a, or
k) ringclosure reaction of an intermediate derivative of the following formula :



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wherein R^1 , X , X' , Y , Ar , n , R^2 and the dotted lines are as defined above and R' is C_1 - C_4 alkyl or lower alkenyl or constitute a ring by forming an ethylene or propylene bridge, or
l) reducing the 2,3-double bond of an 3-piperidylindole of the following formula :



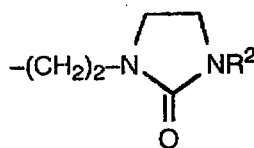
XVIII

wherein R^1 , X , X' , Ar , R and the dotted line are as defined above,
and then optionally converting the compound of formula I obtained into a pharmaceutically acceptable acid addition salt or prodrug thereof.

2. A method according to claim 1, characterized in that Ar is phenyl optionally substituted with halogen, preferably 4-fluorophenyl.
3. A method of claim 1 or 2, characterized in that Y is $-CH-$.



4. A method of any of claims 1-3 characterized in that R is a group of the formula



wherein R^2 is as defined in claim 1, R^2 preferably being hydrogen or isopropyl.

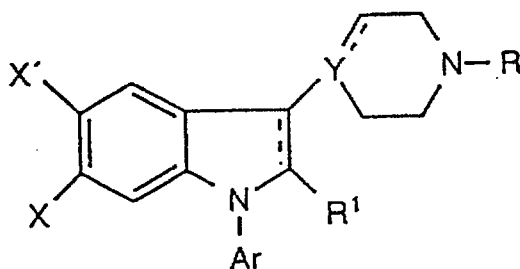
5. A method according to any of the claims 1-4, characterized in that X is -Cl, -Br, -CF₃, or -CH₃ and/or that X' is hydrogen or -Cl.

6. A method of claims 2, 3, 4 and 5, characterized in that the compound obtained is 6-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole or 1-(4-fluorophenyl)-6-methyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. 6-substituiertes oder 2-Alkyl-substituiertes Indol oder 2,3-Dihydroindol-Derivat mit der allgemeinen Formel I:



I.

wobei Ar ein Phenylrest, gegebenenfalls substituiert mit einem oder mehreren Substituenten, ausgewählt aus Halogen, C₁ - C₄-Alkyl-Gruppen, C₁ - C₄-Alkoxy-Gruppen, Hydroxy-Gruppe, Trifluormethyl-Gruppe und Cyano-Gruppe, oder eine heteroaromatische Gruppe, vorzugsweise die 2-Thienyl-, die 3-Thienyl-, die 2-Furanyl-, die 3-Furanyl-, die 2-Oxazolyl-, die 2-Imidazolyl-, die 2-Pyridyl-, die 3-Pyridyl- oder die 4-Pyridyl-Gruppe, ist;

wobei die gepunktete Linie in dem Indolring eine mögliche Bindung anzeigt;

wobei X Wasserstoff, ein Halogen, eine C₁ - C₄-Alkyl-Gruppe, eine C₁ - C₄-Alkoxy-Gruppe, eine Hydroxy-Gruppe, eine C₁ - C₄-Alkylthio-Gruppe, eine C₁ - C₄-Alkylsulfonyl-Gruppe, eine C₁ - C₄-Alkylamino-Gruppe, eine Di(C₁ - C₄-alkyl)amino-Gruppe, eine Cyano-Gruppe, eine Trifluormethyl-Gruppe oder eine Trifluormethylthio-Gruppe ist;

wobei X' ein Substituent ist, wie er unter den X-Substituenten oben definiert ist; oder

wobei X und X' unter Bildung eines 5 - 7-gliedrigen carbocyclischen Ringes miteinander verbunden sind;

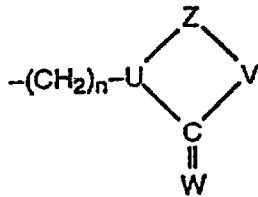
wobei R¹ Wasserstoff oder eine C₁ - C₄-Alkyl-Gruppe ist, die gegebenenfalls mit einer oder zwei Hydroxy-Gruppen substituiert ist, unter der Voraussetzung, daß R¹ nicht Wasserstoff ist, wenn X Wasserstoff oder Fluor ist;

wobei Y N, C oder CH ist,

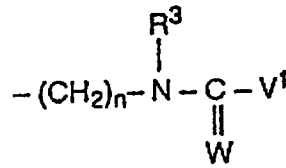
wobei die gepunktete Linie, die von Y ausgeht, eine Bindung anzeigt, wenn Y C ist;

wobei R Wasserstoff, eine C₁ - C₄-Alkyl-Gruppe, eine niedere Alkenyl-Gruppe, eine Cycloalkyl-Gruppe oder eine Cycloalkylmethyl-Gruppe ist, die gegebenenfalls mit ein oder zwei Hydroxy-Gruppen substituiert ist, wobei vorliegende Hydroxy-Gruppen gegebenenfalls mit einer aliphatischen Carbonsäure mit insgesamt zwei bis vierundzwanzig Kohlenstoff-Atomen verestert ist, oder

wobei R eine der beiden Gruppen mit den Strukturen 1a und 1b ist:



1a.



1b.

wobei n eine ganze Zahl von 2 - 6 ist;

wobei W Sauerstoff oder Schwefel ist;

wobei U N oder CH ist;

wobei Z $-(CH_2)_m-$ mit $m = 2$ oder 3 , $-CH=CH-$, $-COCH_2-$, $-CS-CH_2-$ oder 1,2-Phenylen, gegebenenfalls substituiert mit einem Halogen oder einer Trifluormethyl-Gruppe, ist;

wobei V Sauerstoff, Schwefel, CH_2 oder NR^2 ist, wobei R^2 Wasserstoff, eine $C_1 - C_4$ -Alkyl- oder eine niedere Alkenyl-Gruppe, gegebenenfalls substituiert mit einer oder mit zwei Hydroxy-Gruppen, oder eine Cycloalkyl- oder Cycloalkylmethyl-Gruppe ist;

wobei V^1 OR^4 , SR^4 , CHR^4R^5 oder NR^4R^6 ist;

wobei R^3 Wasserstoff, eine $C_1 - C_4$ -Alkyl- oder eine niedere Alkenyl-Gruppe, gegebenenfalls substituiert mit einer oder mit zwei Hydroxy-Gruppen, oder eine Cycloalkyl-Gruppe ist;

wobei R^4 und R^5 unabhängig voneinander aus den R^3 -Substituenten ausgewählt sind; und

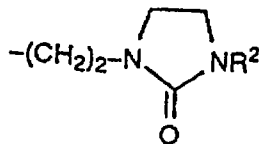
wobei R^6 wie oben für R^2 definiert ist;

und ihre pharmazeutisch verträglichen Säure-Additionssalze und deren Vorstufen von Wirkstoffen.

2. Das Derivat nach Anspruch 1, dadurch gekennzeichnet, daß Ar Phenyl, gegebenenfalls substituiert mit einem Halogen, vorzugsweise 4-Fluorphenyl, ist.

3. Das Derivat nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß Y -CH- ist.

4. Das Derivat nach einem der Ansprüche 1 - 3, dadurch gekennzeichnet, daß R eine Gruppe der Formel



ist, wobei R^2 wie in Anspruch 1 definiert ist, und wobei R^2 vorzugsweise Wasserstoff oder eine Isopropyl-Gruppe ist.

5. Das Derivat nach einem der Ansprüche 1 - 4, dadurch gekennzeichnet, daß X -Cl, -Br, $-CF_3$ oder $-CH_3$ ist, und/oder daß X' Wasserstoff oder -Cl ist.

6. Das Derivat nach den Ansprüchen 2, 3, 4 und 5, dadurch gekennzeichnet, daß es 6-Chlor-1-(4-fluorphenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indol oder 1-(4-Fluorphenyl)-6-methyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indol ist.

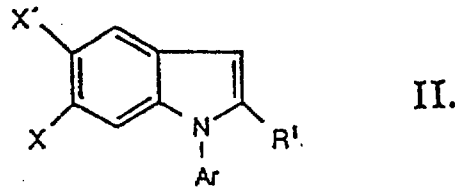
7. Pharmazeutische Zubereitung, dadurch gekennzeichnet, daß sie eine Verbindung nach einem der Ansprüche 1 - 6 oder eines ihrer pharmazeutisch verträglichen Säure-Additionssalze oder eine der Vorstufen ihrer Wirkstoffe als aktiven Bestandteil zusammen mit einem pharmazeutisch verträglichen Träger oder Verdünner enthält.

8. Die pharmazeutische Zubereitung nach Anspruch 7, dadurch gekennzeichnet, daß sie eine injizierbare Depot-Zubereitung ist, die die Vorstufe eines Wirkstoffes einer Verbindung nach einem der Ansprüche 1 - 6 in einem geeigneten, pharmazeutisch verträglichen Öl, vorzugsweise Erdnußöl, Sesamöl, Baumwollsaamenöl, Maisöl, Sojabohnenöl, Olivenöl, etc. oder in synthetischen Estern von Fettsäuren und Glycerin oder Propylenglycol, enthält.

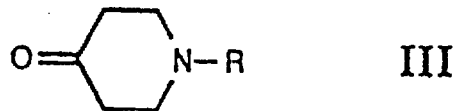


9. Verwendung eines Derivates nach einem der Ansprüche 1 - 7 für die Herstellung eines Medikamentes zur therapeutischen Behandlung von Störungen des zentralen Nervensystems, vorzugsweise für die Behandlung von Angstzuständen, Depressionen, Schlafstörungen, Migräne, negativen Symptomen der Schizophrenie und der Parkinson-Krankheit.

10. Verfahren zur Herstellung eines Derivates nach Anspruch 1, umfassend
a) ein Indol-Derivat der folgenden Formel:

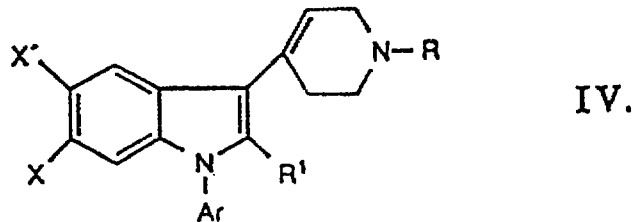


wobei R¹, X, X' und Ar wie oben definiert sind, mit einem 4-Piperidon der Formel:

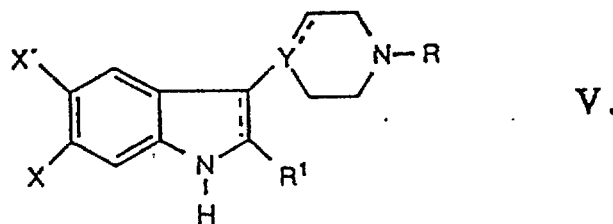


wobei R wie oben definiert ist, umzusetzen, oder

- b) die Doppelbindung in dem Tetrahydropyridyl-Ring einer Verbindung der folgenden Formel:



wobei R¹, X, X', Ar und R wie oben definiert sind, zu reduzieren, oder
c) eine Verbindung der folgenden Formel:



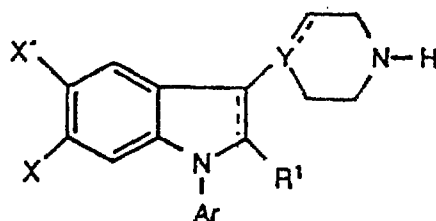
wobei R¹, X, X', Y, R und die gepunkteten Linien wie oben definiert sind, mit einer Verbindung der Formel:

Ar - hal VI

wobei Ar wie oben definiert ist, und wobei "hal" ein Halogen (Cl, Br oder I) ist, in Gegenwart eines Metall-Katalysators umzusetzen, oder

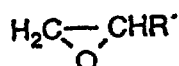


d) eine Verbindung der folgenden Formel:

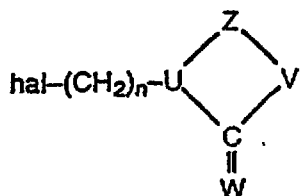


VII.

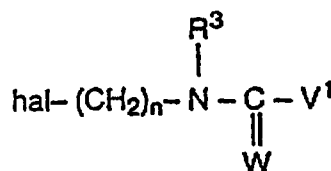
wobei R¹, X, X', Y, Ar und die gepunkteten Linien wie oben definiert sind, mit einem C₁ - C₄-Alkylhalogenid, Alkylmesylat oder -tosylat, einem Epoxid der Formel



wobei R' Wasserstoff, eine Methyl- oder Ethyl-Gruppe ist, oder mit einem Halogenid der allgemeinen Formel:



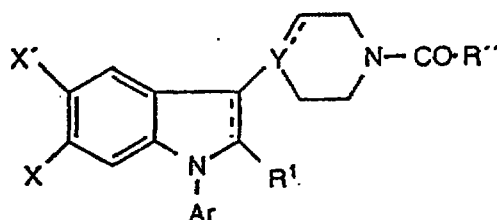
VIII a



VIII b.

wobei U, Z, V, V¹, W, R³ und n wie zuvor definiert sind, und wobei "hal" Chlor, Brom oder Iod ist, zu alkylieren, oder

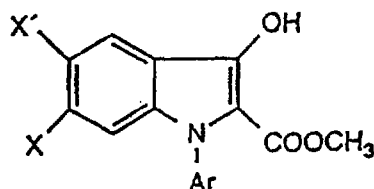
e) die Carbonyl-Gruppe in einer Verbindung der folgenden Formel:



IX

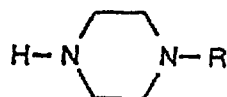
wobei R¹, X, X', Y, Ar und die gepunkteten Linien wie zuvor definiert sind, und wobei R'' Wasserstoff, eine C₁ - C₄-Alkyl- oder eine C₁ - C₄-Alkoxy-Gruppe ist, zu reduzieren, oder

f) einen Indoxylester der folgenden Formel:



X.

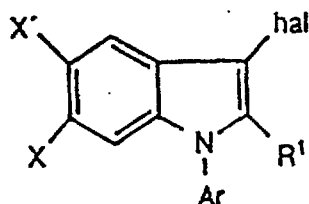
wobei X, X' und Ar wie oben definiert sind, in Gegenwart eines anorganischen Salzes als Katalysator zu erhitzen, anschließend das Erhitzen in Gegenwart eines Piperazin-Derivats der Formel:



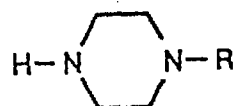
XI

wobei R wie oben definiert ist, fortzusetzen, oder

g) ein 3-Halogen-substituiertes Indol-Derivat der Formel XII mit einem Piperazin-Derivat der Formel XIII:



+

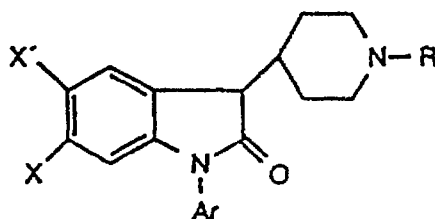


XII

XIII

wobei R¹, X, X', Ar und R wie oben definiert sind, und wobei "hal" Chlor, Brom oder Iod ist, umzusetzen, oder

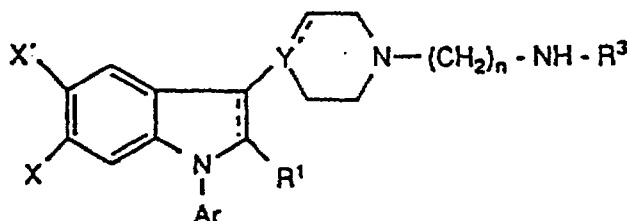
h) ein 2-Oxindol-Derivat der folgenden Formel:



XIV

wobei X, X', Ar und R wie oben definiert sind, zu reduzieren, oder

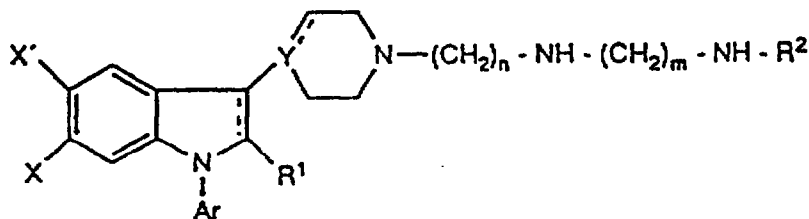
i) ein Aminoalkyl-Derivat der folgenden Formel:



XV

wobei R¹, X, X', Y, Ar, n, R³ und die gepunkteten Linien wie oben definiert sind, unter Verwendung eines Carbonsäurehalogenids, -anhydrids oder eines gemischtem Anhydrids, eines Carbamyl- oder Thiocarbamyl-Chlorids, eines Isocyanats, eines Isothiocyanats oder eines substituierten Chlorformiats als Acylierungsmittel zu acylieren, oder

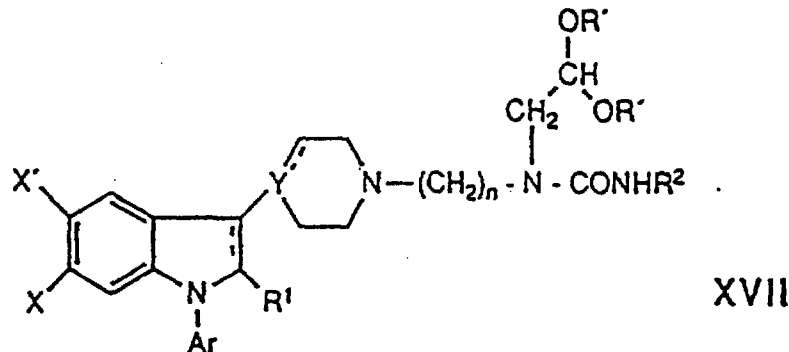
j) eine Ringschluß-Reaktion eines Zwischenstufen-Derivats der folgenden Formel:



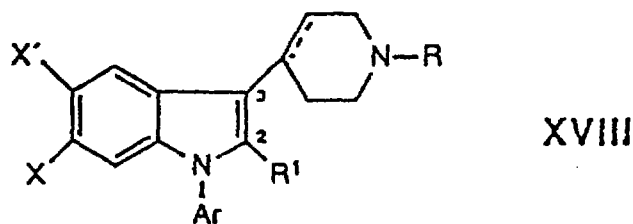
XVI



wobei R^1 , X , X' , Y , Ar , n , R^2 , m und die gepunkteten Linien wie oben definiert sind, unter Verwendung von Harnstoff, Phosgen, Thiophosgen oder Kohlenstoffdisulfid, um eine Carbonyl- oder Thiocarbonyl-Gruppe in den heterocyclischen Ring der Struktur 1a einzubauen, oder
k) eine Ringschluß-Reaktion eines Zwischenstufen-Derivats der folgenden Formel:



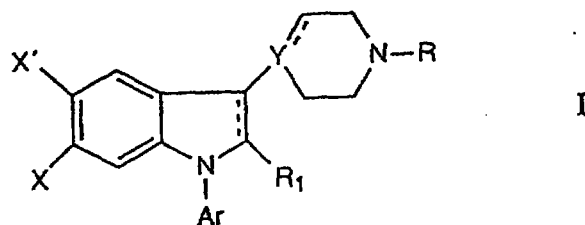
wobei R^1 , X , X' , Y , Ar , n , R^2 und die gepunkteten Linien wie oben definiert sind und wobei R' eine C_1 - C_4 -Alkyl- oder eine niedere Alkenyl-Gruppe ist, oder wobei die beiden R' gemeinsam unter Bildung einer Ethylen- oder Propylen-Brücke einen Ring bilden, oder
l) die 2,3-Doppelbindung eines 3-Piperidylindols der folgenden Formel:



wobei R^1 , X , X' , Ar , R und die gepunkteten Linien wie oben definiert sind, zu reduzieren und dann gegebenenfalls die erhaltene Verbindung der Formel I in eines ihrer pharmazeutisch verträglichen Säure-Additionssalze oder die Vorstufe eines ihrer Wirkstoffe umzuwandeln.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung von 6-substituiertem oder 2-Alkyl-substituiertem Indol oder 2,3-Dihydroindol-Derivaten mit der allgemeinen Formel I:



wobei Ar ein Phenylrest, gegebenenfalls substituiert mit einem oder mehreren Substituenten, ausgewählt aus Halogen, C_1 - C_4 -Alkyl-Gruppen, C_1 - C_4 -Alkoxy-Gruppen, Hydroxy-Gruppe, Trifluormethyl-Gruppe und Cyano-Gruppe, oder eine heteroaromatische Gruppe, vorzugsweise die 2-Thienyl-, die 3-Thienyl-, die 2-Furanyl-, die 3-Furanyl-, die 2-Oxazolyl-, die 2-Imidazolyl-, die 2-Pyridyl-, die 3-Pyridyl- oder die 4-Pyridyl-Gruppe, ist;

wobei die gepunktete Linie in dem Indolring eine mögliche Bindung anzeigt;

wobei X Wasserstoff, ein Halogen, eine C_1 - C_4 -Alkyl-Gruppe, eine C_1 - C_4 -Alkoxy-Gruppe, eine



Hydroxy-Gruppe, eine C₁ - C₄-Alkylthio-Gruppe, eine C₁ - C₄-Alkylsulfonyl-Gruppe, eine C₁ - C₄-Alkylamino-Gruppe, eine Di(C₁ - C₄-alkyl)amino-Gruppe, eine Cyano-Gruppe, eine Trifluormethyl-Gruppe oder eine Trifluormethylthio-Gruppe ist;

wobei X' ein Substituent ist, wie er unter den X-Substituenten oben definiert ist; oder

wobei X und X' unter Bildung eines 5 - 7-gliedrigen carbocyclischen Ringes miteinander verbunden sind;

wobei R¹ Wasserstoff oder eine C₁ - C₄-Alkyl-Gruppe ist, die gegebenenfalls mit einer oder zwei Hydroxy-Gruppen substituiert ist, unter der Voraussetzung, daß R¹ nicht Wasserstoff ist, wenn X Wasserstoff oder Fluor ist;

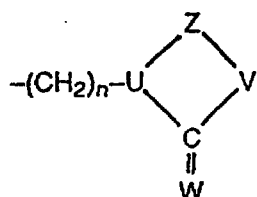
wobei Y N, C oder CH ist;

wobei die gepunktete Linie, die von Y ausgeht, eine Bindung anzeigt, wenn Y C ist;

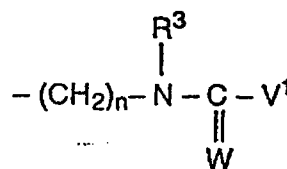
wobei R Wasserstoff, eine C₁ - C₄-Alkyl-Gruppe, eine niedere Alkenyl-Gruppe, eine Cycloalkyl-Gruppe oder eine Cycloalkylmethyl-Gruppe ist, die gegebenenfalls mit ein oder zwei Hydroxy-Gruppen substituiert ist, wobei vorliegende Hydroxy-Gruppen gegebenenfalls mit einer aliphatischen Carbonsäure mit

insgesamt zwei bis vierundzwanzig Kohlenstoff-Atomen verestert ist, oder

wobei R eine der beiden Gruppen mit den Strukturen 1a und 1b ist:



1a.



1b.

wobei n eine ganze Zahl von 2 - 6 ist;

wobei W Sauerstoff oder Schwefel ist;

wobei U N oder CH ist;

wobei Z -(CH₂)_m- mit m = 2 oder 3, -CH=CH-, -COCH₂-, -CS-CH₂- oder 1,2-Phenylen, gegebenenfalls substituiert mit einem Halogen oder einer Trifluormethyl-Gruppe, ist;

wobei V Sauerstoff, Schwefel, CH₂ oder NR² ist, wobei R² Wasserstoff, eine C₁ - C₄-Alkyl- oder eine niedere Alkenyl-Gruppe, gegebenenfalls substituiert mit einer oder mit zwei Hydroxy-Gruppen, oder eine Cycloalkyl- oder Cycloalkylmethyl-Gruppe ist;

wobei V¹ OR⁴, SR⁴, CHR⁴R⁵ oder NR⁴R⁵ ist;

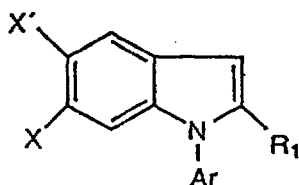
wobei R³ Wasserstoff, eine C₁ - C₄-Alkyl- oder eine niedere Alkenyl-Gruppe, gegebenenfalls substituiert mit einer oder mit zwei Hydroxy-Gruppen, oder eine Cycloalkyl-Gruppe ist;

wobei R⁴ und R⁵ unabhängig voneinander aus den R³-Substituenten ausgewählt sind; und

wobei R⁶ wie oben für R² definiert ist;

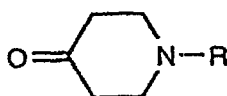
und ihre pharmazeutisch verträglichen Säure-Additionssalze und deren Vorstufen von Wirkstoffen, umfassend

a) ein Indol-Derivat der folgenden Formel:



II

wobei R¹, X, X' und Ar wie oben definiert sind, mit einem 4-Piperidon der Formel:

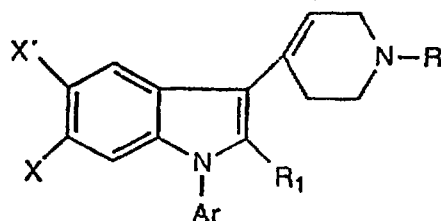


III

wobei R wie oben definiert ist, umzusetzen, oder

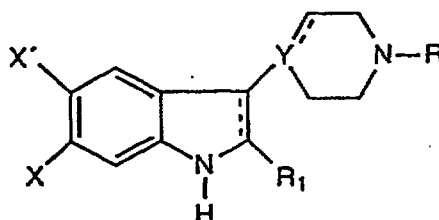


b) die Doppelbindung in dem Tetrahydropyridyl-Ring einer Verbindung der folgenden Formel:



IV

wobei R_1 , X, X' , Ar und R wie oben definiert sind, zu reduzieren, oder
c) eine Verbindung der folgenden Formel:

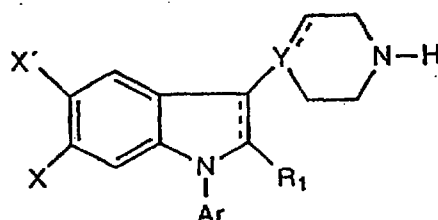


V

wobei R_1 , X, X' , Y, R und die gepunkteten Linien wie oben definiert sind, mit einer Verbindung der Formel:

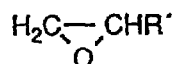
Ar - hal VI

wobei Ar wie oben definiert ist, und wobei "hal" ein Halogen (Cl, Br oder I) ist, in Gegenwart eines Metall-Katalysators umzusetzen, oder
d) eine Verbindung der folgenden Formel:

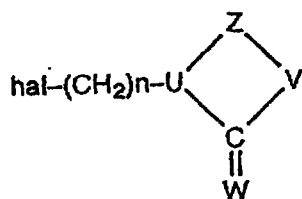


VII

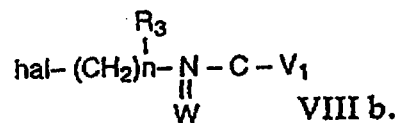
wobei R_1 , X, X' , Y, Ar und die gepunkteten Linien wie oben definiert sind, mit einem C_1 - C_4 -Alkylhalogenid, Alkylmesylat oder -tosylat, einem Epoxid der Formel



wobei R' Wasserstoff, eine Methyl- oder Ethyl-Gruppe ist, oder mit einem Halogenid der allgemeinen Formel:



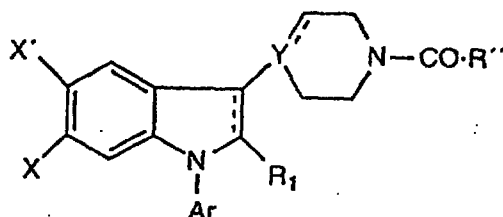
VIII a.



VIII b.

wobei U, Z, V, V', W, R³ und n wie zuvor definiert sind, und wobei "hal" Chlor, Brom oder Iod ist, zu alkylieren, oder

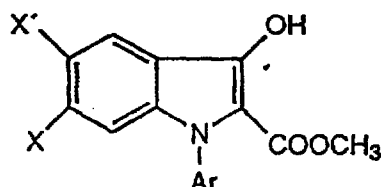
e) die Carbonyl-Gruppe in einer Verbindung der folgenden Formel:



IX

wobei R', X, X', Y, Ar und die gepunkteten Linien wie zuvor definiert sind, und wobei R'' Wasserstoff, eine C₁-C₄-Alkyl- oder eine C₁-C₄-Alkoxy-Gruppe ist, zu reduzieren, oder

f) einen Indoxylester der folgenden Formel:



X

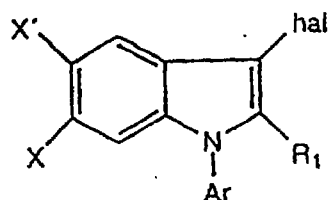
wobei X, X' und Ar wie oben definiert sind, in Gegenwart eines anorganischen Salzes als Katalysator zu erhitzen, anschließend das Erhitzen in Gegenwart eines Piperazin-Derivats der Formel:



XI

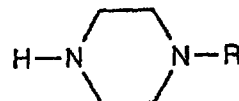
wobei R wie oben definiert ist, fortzusetzen, oder

g) ein 3-Halogen-substituiertes Indol-Derivat der Formel XII mit einem Piperazin-Derivat der Formel XIII:



XII

+

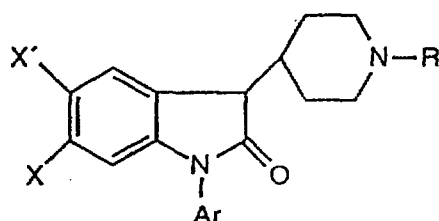


XIII

wobei R', X, X', Ar und R wie oben definiert sind, und wobei "hal" Chlor, Brom oder Iod ist, umzusetzen, oder

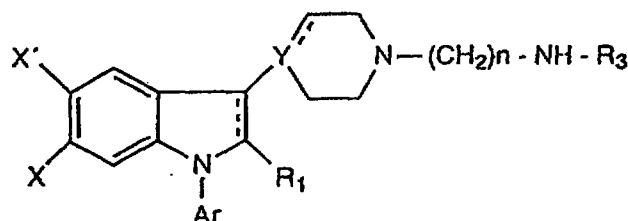


h) ein 2-Oxindol-Derivat der folgenden Formel:



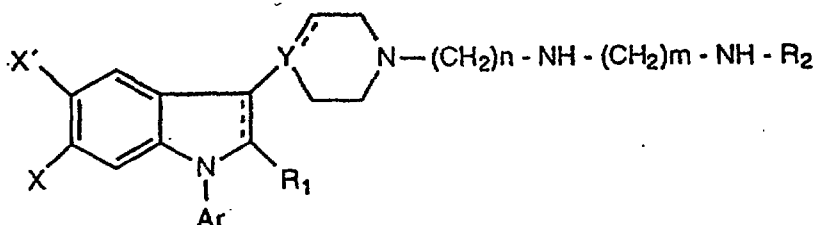
XIV

wobei X, X', Ar und R wie oben definiert sind, zu reduzieren, oder
i) ein Aminoalkyl-Derivat der folgenden Formel:



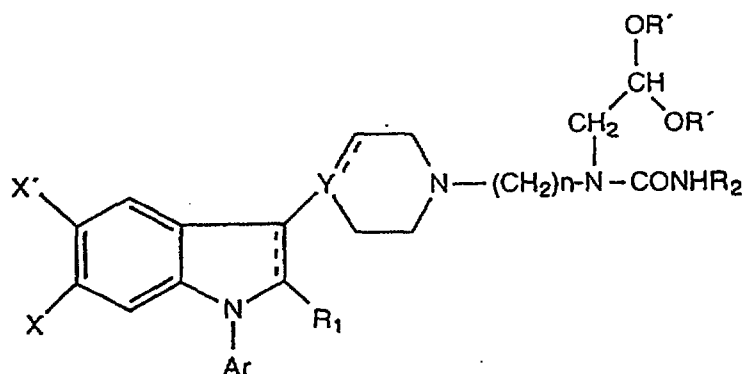
XV

wobei R¹, X, X', Y, Ar, n, R³ und die gepunkteten Linien wie oben definiert sind, unter Verwendung eines Carbonsäurehalogenids, -anhydrids oder eines gemischtem Anhydrids, eines Carbamyl- oder Thiocarbamyl-Chlorids, eines Isocyanats, eines Isothiocyanats oder eines substituierten Chlorformats als Acylierungsmittel zu acylieren, oder
j) eine Ringschluß-Reaktion eines Zwischenstufen-Derivats der folgenden Formel:



XVI

wobei R¹, X, X', Y, Ar, n, R², m und die gepunkteten Linien wie oben definiert sind, unter Verwendung von Harnstoff, Phosgen, Thiophosgen oder Kohlenstoffdisulfid, um eine Carbonyl- oder Thiocarbonyl-Gruppe in den heterocyclischen Ring der Struktur 1a einzubauen, oder
k) eine Ringschluß-Reaktion eines Zwischenstufen-Derivats der folgenden Formel:

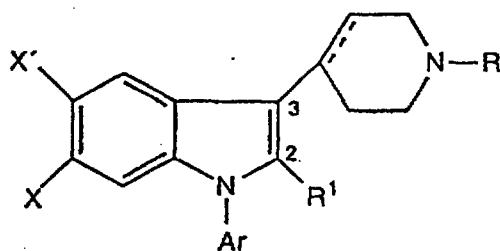


XVII

wobei R¹, X, X', Y, Ar, n, R² und die gepunkteten Linien wie oben definiert sind und wobei R' eine C₁



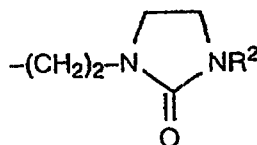
- C₄-Alkyl- oder eine niedere Alkenyl-Gruppe ist, oder wobei die beiden R' gemeinsam unter Bildung einer Ethylen- oder Propylen-Brücke einen Ring bilden, oder
l) die 2,3-Doppelbindung eines 3-Piperidylindols der folgenden Formel:



XVIII

wobei R¹, X, X', Ar, R und die gepunkteten Linien wie oben definiert sind, zu reduzieren und dann gegebenenfalls die erhaltene Verbindung der Formel I in eines ihrer pharmazeutisch verträglichen Säure-Additionssalze oder die Vorstufe eines ihrer Wirkstoffe umzuwandeln.

2. Das Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß Ar Phenyl, gegebenenfalls substituiert mit einem Halogen, vorzugsweise 4-Fluorphenyl, ist.
3. Das Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß Y -CH- ist.
4. Das Verfahren nach einem der Ansprüche 1 - 3, dadurch gekennzeichnet, daß R eine Gruppe der Formel



ist, wobei R² wie in Anspruch 1 definiert ist, und wobei R² vorzugsweise Wasserstoff oder eine Isopropyl-Gruppe ist.

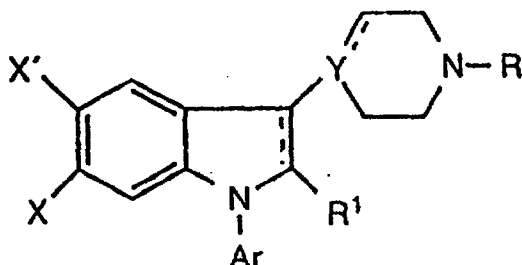
5. Das Verfahren nach einem der Ansprüche 1 - 4, dadurch gekennzeichnet, daß X -Cl, -Br, -CF₃ oder -CH₃ ist, und/oder daß X' Wasserstoff oder -Cl ist.
6. Das Verfahren nach den Ansprüchen 2, 3, 4 und 5, dadurch gekennzeichnet, daß die erhaltene Verbindung 6-Chlor-1-(4-fluorphenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indol oder 1-(4-Fluorphenyl)-6-methyl-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indol ist.



Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Indole 6-substitué ou 2-alkyle substitué ou dérivé de 2,3-dihydroindole ayant la formule générale I :



I.

où Ar est phényle facultativement substitué avec un ou plusieurs substituants choisis parmi halogène, alkyle C₁-C₄, alcoxy C₁-C₄, hydroxy, trifluorométhyle et cyano, ou un groupe hétéroaromatique, de préférence 2-thiényle, 3-thiényle, 2-furanyle, 3-furanyle, 2-oxazolyle, 2-imidazolyle, 2-pyridyle, 3-pyridyle ou 4-pyridyle ;

la ligne en tirets dans le cycle indole désigne une liaison facultative ;

X est hydrogène, halogène, alkyle C₁-C₄, alcoxy C₁-C₄, hydroxy, alkylthio C₁-C₄, alkylsulfonyl C₁-C₄, alkylamino C₁-C₄, di(C₁-C₄ alkyl)amino, cyano, trifluorométhyle ou trifluorométhylthio ;

X' est un substituant pris à partir des substituants X ci-dessus ; ou

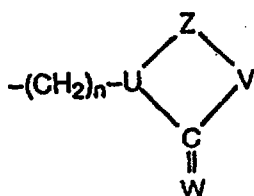
X et X' sont liés pour constituer un système carbocyclique à 5-7 éléments ;

R¹ est hydrogène ou C₁-C₄ alkyle facultativement substitué par un ou deux groupes hydroxy, dans la mesure où X est hydrogène ou fluoro, R¹ ne peut être hydrogène,

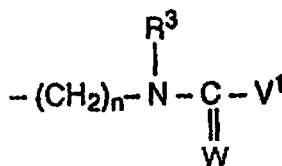
Y est N, C ou CH,

lorsque Y est C, la ligne en tirets provenant d'Y désigne une liaison.

R est l'hydrogène, ou un C₁-C₄ alkyle, alcényle, cycloalkyle ou cycloalkylméthyle, facultativement substitué par un ou deux groupes hydroxy, tout groupe hydroxy présent étant facultativement estérifié avec un acide carboxylique aliphatique ayant de 2 à 24 atomes de carbone inclus où R est un groupe pris à partir des structures 1a et 1b :



1a.



1b.

où n est un nombre entier de 2 à 6 ;

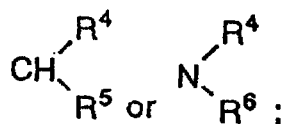
W est l'oxygène ou le soufre ;

U est N ou CH ;

Z est -(CH₂)_m-, m étant 2 ou 3, ou Z est -CH=CH-, Z est -COCH₂- ou -CSCH₂-, ou 1,2-phénylène facultativement substitué par l'halogène ou trifluorométhyle ;

V est l'oxygène, le soufre, CH₂ ou NR², où R² est l'hydrogène, C₁-C₄ alkyle ou alcényle inférieur facultativement substitué par 1 ou 2 groupes hydroxy, où R² est un groupe cycloalkyle ou cycloalkylméthyle ;

V¹ est O-R⁴, S-R⁴,



5

10

R³ est hydrogène, alkyle C₁₋₄ C4 ou alcényle inférieur facultativement substitué par un ou deux groupes hydroxy ou un groupe cycloalkyle ;

R⁴ et R⁵ sont choisis indépendamment des substituants R³ et R⁶ est tel que défini pour R² ci-dessus ; et leurs sels d'addition d'acide pharmaceutiquement acceptables et leurs produits.

15

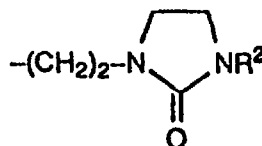
2. Dérivé selon la revendication 1, caractérisé en ce que Ar est phényle facultativement substitué par halogène de préférence 4-fluorophényle.

20

3. Dérivé selon la revendication 1 ou 2, caractérisé en ce que Y est -CH-.

4. Dérivé selon l'une quelconque des revendications 1 à 3, caractérisé en ce que R est un groupe de la formule

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où R² est tel que défini dans la revendication 1, R² étant de préférence hydrogène ou isopropyle.

30

5. Dérivé selon l'une quelconque des revendications 1 à 4, caractérisé en ce que X est -Cl, -Br, -CF₃, ou -CH₃ et/ou que X' est hydrogène ou -Cl.

35

6. Dérivé selon les revendications 2, 3, 4 et 5, caractérisé en ce qu'il s'agit de 6-chloro-1-(4-fluorophényl)-3-[1-[2-[3-(2-propyle)-2-imidazolidinon-1-yl]éthyle]-4-pipéridyle]-1H-indole ou 1-(4-fluorophényl)-6-méthyle-3-[1-[2-[3-(2-propyle)-2-imidazolinon-1-yl]éthyle]-4-pipéridyle]-1H-indole.

40

7. Préparation pharmaceutique, caractérisée en ce qu'elle comprend un composé selon l'une quelconque des revendications 1-6, ou son sel d'addition d'acide acceptable pharmaceutiquement ou un produit de celui-ci en tant que principe actif ainsi qu'un véhicule pharmaceutiquement acceptable ou un diluant.

45

8. Préparation pharmaceutique selon la revendication 7, caractérisé en ce qu'il s'agit d'une préparation injectable comprenant un produit médicamenteux d'un composé selon l'une quelconque des revendications 1-6 dans une huile appropriée pharmaceutiquement acceptable, de préférence de l'huile d'arachide, de l'huile de sésame, de l'huile de coton, de l'huile de maïs, de l'huile de soja, de l'huile d'olive, etc. ou les esters synthétiques des acides gras et glycérol ou propylèneglycol.

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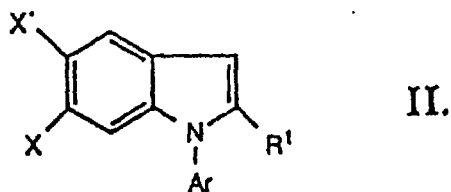
9. Utilisation d'un dérivé selon l'une quelconque des revendications 1-7 pour la fabrication d'un médicament destiné au traitement de troubles du système nerveux central, de préférence pour le traitement de l'anxiété, de la dépression, des troubles du sommeil, des migraines, des symptômes négatifs de la schizophrénie, et de la maladie de Parkinson.

10. Procédé pour la préparation d'un dérivé selon la revendication 1, comprenant :

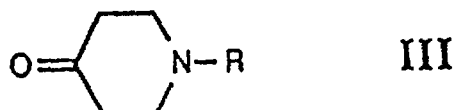
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a) Mise en réaction d'un dérivé d'indole de la formule générale :

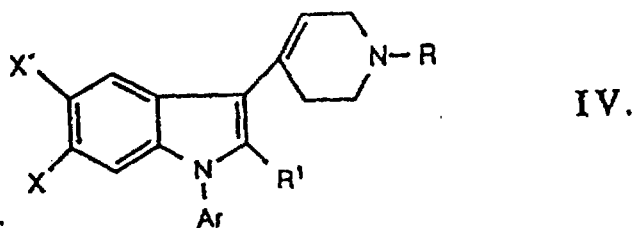


dans laquelle R^1 , X, X' et Ar sont tels que définis ci-dessus, avec une 4-piperidone de la formule :



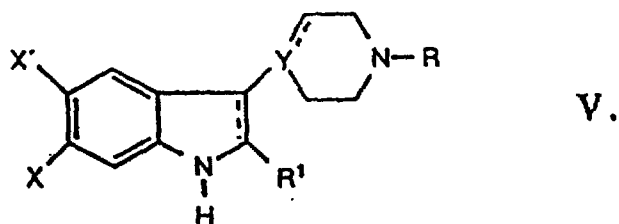
dans laquelle R est tel que défini ci-dessus, ou

b) réduction de la double liaison du cycle tétrahydropyridyle d'un composé de la formule :



dans laquelle, R^1 , X, X' , Ar et R sont tels que définis ci-dessus, ou

c) mise en réaction d'un composé de la formule suivante :



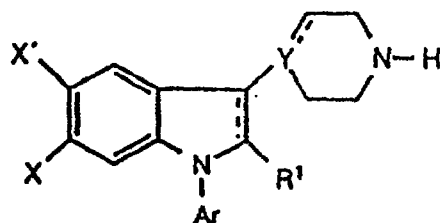
dans laquelle R^1 , X, X' , Y, R et les lignes en tirets sont tels que définis ci-dessus avec un composé de la formule :

Ar - hal VI

dans laquelle Ar est tel que défini ci-dessus et "hal" est halogène (Cl, Br ou I) en présence d'un catalyseur métallique, ou

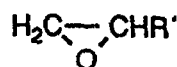


d) alcoylation d'un composé de la formule générale

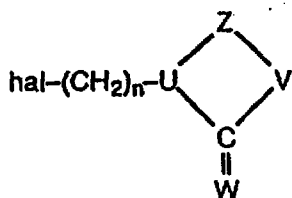


VII.

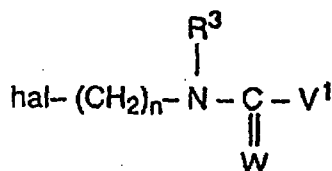
dans laquelle R^1 , X, X' , Y, Ar et les lignes en tirets sont telles que définies ci-dessus avec alkyle halogénure C_1-C_4 , mésylate ou tosylate d'alkyle, un époxyde de formule



dans laquelle R' est hydrogène, méthyle ou éthyle, ou avec un halogénure de la formule générale :



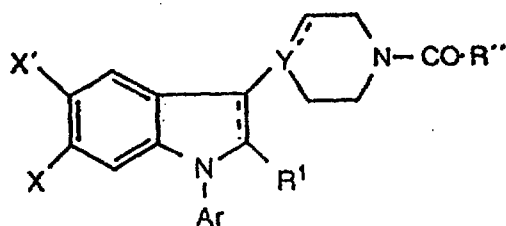
VIII a



VIII b.

dans laquelle U, Z, V, V^1 , W, R^3 et n sont tels que définis ci-dessus, et "hal" est chloro, bromo, iodo, ou

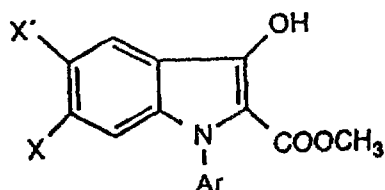
e) réduction du groupe carbonyle dans un composé de la formule générale :



IX

dans laquelle R^1 , X, X' , Ar et les lignes en tirets sont tels que préalablement définis et R'' est hydrogène, alkylé C_1-C_4 ou alcoxy C_1-C_4 , ou

f) chauffer un indoxylester de la formule générale :

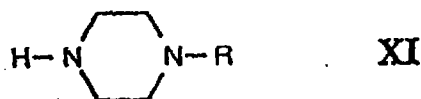


X.

dans laquelle X, X' et Ar sont tels que définis ci-dessus en présence d'un catalyseur de sel minéral

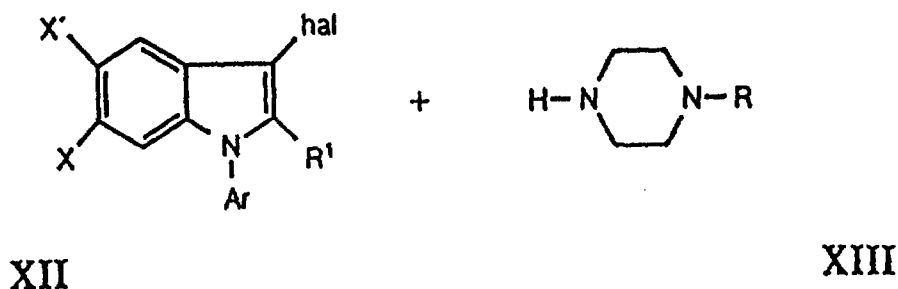


sulvi du chauffage continu en présence d'un dérivé de pipérazine de formule :



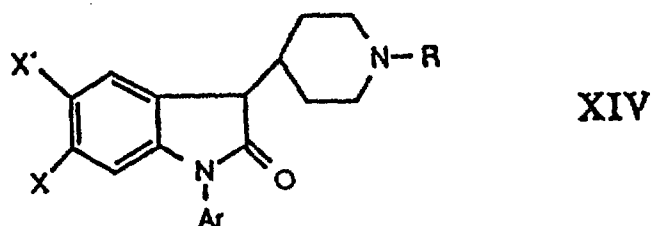
dans laquelle R est tel que défini ci-dessus, ou

g) mise en réaction d'un dérivé d'indole substitué 3-halogène de la formule XII, avec un dérivé de pipérazine de la formule XIII :



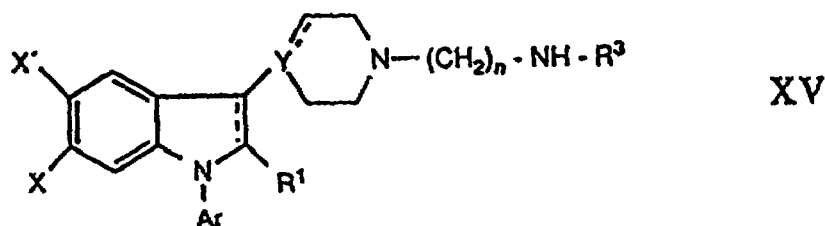
dans laquelle R¹, X, X', Ar et R sont tels que définis ci-dessus et "hal" signifie chloro, bromo, ou iodo, ou

h) réduction d'un dérivé 2-oxindole de formule suivante :



dans laquelle X, X', Ar et R sont tels que définis ci-dessus, ou

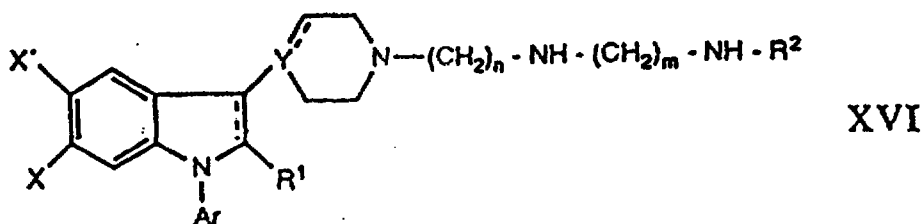
i) acylation d'un dérivé aminoalkyle de la formule suivante:



dans laquelle R¹, X, X', Y, Ar, n, R³ et les lignes en tirets sont tels que définis ci-dessus en utilisant un halogénure de l'acide carboxylique, un anhydride, ou un anhydride mixte, un chlorure carbamyle ou thiocarbamyle, isocyanate, isothiocyanate ou un chloroformate substitué en tant qu'agent d'acylation, ou



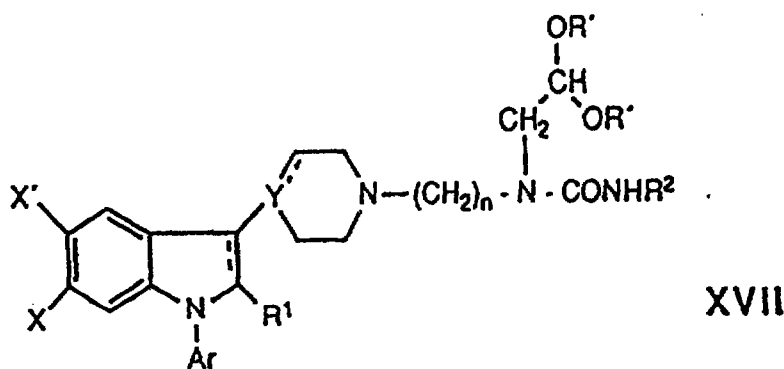
j) réaction de cyclisation d'un dérivé intermédiaire de la formule suivante :



15

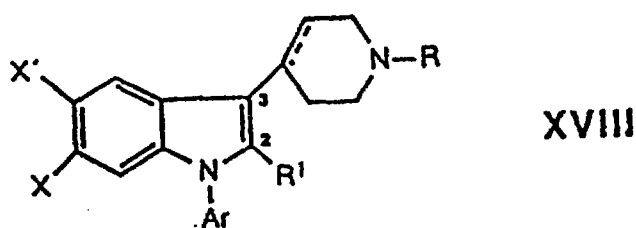
dans laquelle R^1 , X, X' , Y, Ar, n, R^2 , m et les lignes en tirets sont tels que définis ci-dessus, en utilisant l'urée, le phosgène, le thiophosgène ou un disulfure de carbone pour incorporer un groupe carbonyle ou thiocarbonyle dans le système hétérocyclique de la structure 1a, ou

k) réaction de cyclisation d'un dérivé intermédiaire de la formule suivante :



dans laquelle R^1 , X, X' , Y, R^2 et les lignes en tirets sont tels que définis ci-dessus, et R' est un alkyle C_1 - C_4 ou un alcényle inférieur ou constitue un cycle en formant un pont éthylène ou propylène, ou

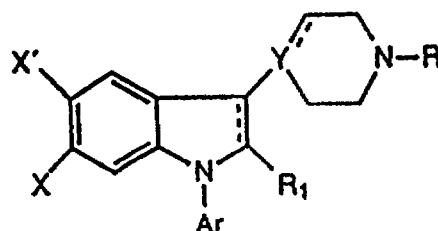
l) réduction de la liaison double 2,3 d'un 3-pipéridylindole de la formule suivante :



dans laquelle R^1 , X, X' , Ar, R et la ligne pointillée sont tels que définis ci-dessus, puis convertir facultativement le composé de la formule I obtenu en un sel d'addition d'acide pharmaceutiquement acceptable, ou son produit.

50 Revendications pour les Etats contractants suivants : ES, GR

- 55 1. Procédé pour la préparation d'un indole-6 substitué ou 2-alkyle substitué ou d'un dérivé de 2,3-dihydroindole ayant la formule générale I :



I

dans laquelle Ar est phényle facultativement substitué par un ou plusieurs substituants choisis parmi halogène, alkyle C₁-C₄, alcoxy C₁-C₄, hydroxy, trifluorométhyle et cyano, ou un groupe hétéro aromatique, de préférence 2-thiényle, 3-thiényle, 2-furanyle, 3-furanyle, 2-oxazolyle, 2-imidazolyle, 2-pyridyle, 3-pyridyle ou 4-pyridyle ;

la ligne en tirets dans le cycle indole désigne une liaison facultative ;

X est hydrogène, halogène, alkyle C₁-C₄, alcoxy C₁-C₄, hydroxy, alkylthio C₁-C₄, alkylsulfonyl C₁-C₄, alkylamino C₁-C₄, di(C₁-C₄ alkyl)amino, cyano, trifluorométhyle ou trifluorométhylthio ;

X' est un substituant pris à partir des substituants X ci-dessus ; ou

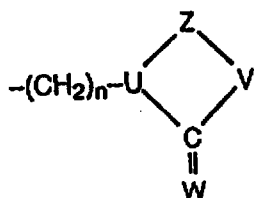
X et X' sont liés pour constituer un système carbocyclique à 5-7 éléments ;

R¹ est hydrogène ou C₁-C₄ alkyle facultativement substitué par un ou deux groupes hydroxy, dans la mesure où X est hydrogène ou fluoro, R¹ ne peut être hydrogène,

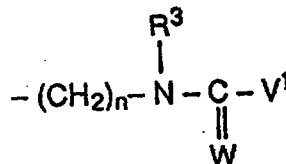
Y est N, C ou CH,

lorsque Y est C, la ligne en tirets provenant d'Y désigne une liaison.

R est l'hydrogène, ou un C₁-C₄ alkyle, alcényle, cycloalkyle ou cycloalkylméthyle, facultativement substitué avec un ou deux groupes hydroxy, tout groupe hydroxy présent étant facultativement estérifié avec un acide carboxylique aliphatique ayant de 2 à 24 atomes de carbone inclus où R est un groupe pris à partir des structures 1a et 1b :



1a.



1b.

où n est un nombre entier de 2 à 6 ;

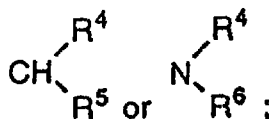
W est l'oxygène ou le soufre ;

U est N ou CH ;

Z est -(CH₂)_m-, m étant 2 ou 3, ou Z est -CH=CH-, Z est -COCH₂- ou -CSCH₂-, ou 1,2-phénylène facultativement substitué par l'halogène ou trifluorométhyle ;

V est l'oxygène, le soufre, CH₂ ou NR², où R² est l'hydrogène, C₁-C₄ alkyle ou alcényle inférieur facultativement substitué par 1 ou 2 groupes hydroxy, où R² est un groupe cycloalkyle ou cycloalkylméthyle ;

V¹ is O-R⁴, S-R⁴,

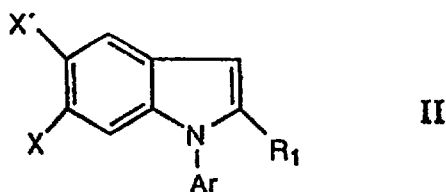


R³ est hydrogène, alkyle C₁-C₄ ou alcényle inférieur facultativement substitué par un ou deux groupes hydroxy ou un groupe cycloalkyle ;

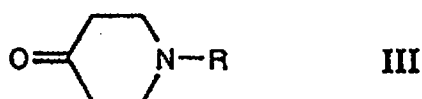
R⁴ et R⁵ sont choisis indépendamment des substituants R³ et R⁶ est tel que défini pour R² ci-dessus ; et leurs sels d'addition d'acide pharmaceutiquement acceptables et leurs produits, comprenant :



a) Mise en réaction d'un dérivé d'indole de la formule générale :

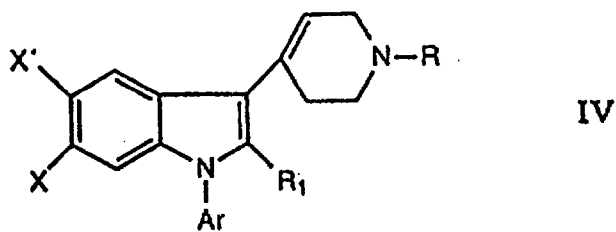


10 dans laquelle R¹, X, X' et Ar sont tels que définis ci-dessus, avec une 4-piperidone de la formule :



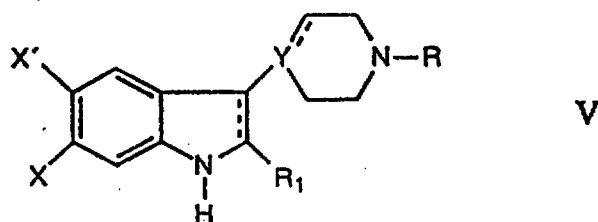
20 dans laquelle R est tel que défini ci-dessus, ou

b) réduction de la double liaison du cycle tétrahydropyridyle d'un composé de la formule :



30 dans laquelle, R¹, X, X', Ar et R sont tels que définis ci-dessus, ou

c) mise en réaction d'un composé de la formule suivante :



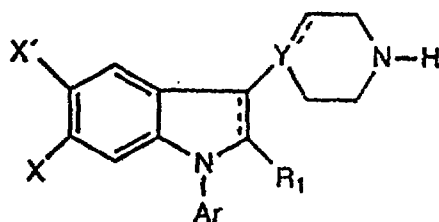
40 dans laquelle R¹, X, X', Y, R et les lignes en tirets sont tels que définis ci-dessus avec un composé de la formule :

45 Ar - hal VI

50 dans laquelle Ar est tel que défini ci-dessus et "hal" est halogène (Cl, Br ou I) en présence d'un catalyseur métallique, ou

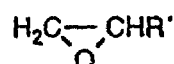


d) alcoylation d'un composé de la formule générale

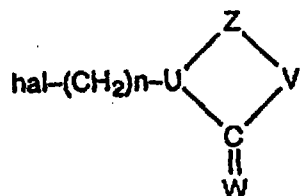


VII

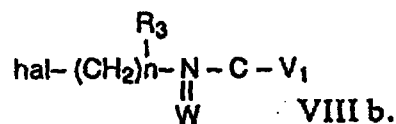
dans laquelle R^1 , X, X' , Y, Ar et les lignes en tirets sont telles que définies ci-dessus avec alkyle halogénure C_1-C_4 , mésylate ou tosylate d'alkyle, un époxyde de formule



dans laquelle R' est hydrogène, méthyle ou éthyle, ou avec un halogénure de la formule générale :



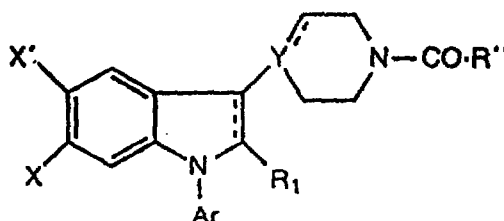
VIII a.



VIII b.

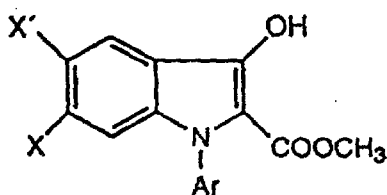
dans laquelle U, Z, V, V^1 , W, R^3 et n sont tels que définis ci-dessus, et "hal" est chloro, bromo, iodo, ou

e) réduction du groupe carbonyle dans un composé de la formule générale :



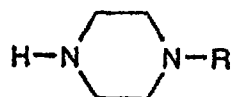
dans laquelle R^1 , X, X' , Ar et les lignes en tirets sont tels que préalablement définis et R'' est hydrogène, alkyle C_1-C_4 ou alcoxy C_1-C_4 , ou

f) chauffer un indoxylester de la formule générale :



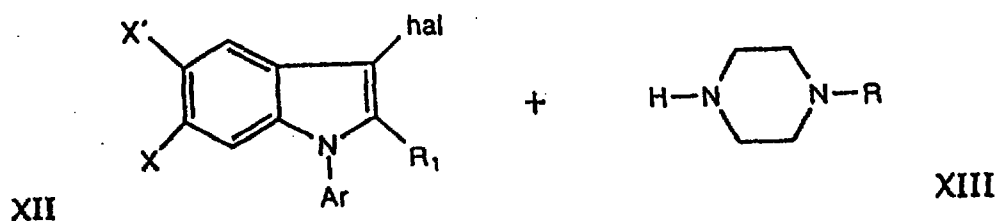
X

dans laquelle X, X' et Ar sont tels que définis ci-dessus en présence d'un catalyseur de sel minéral suivi du chauffage continu en présence d'un dérivé de pipérazine de formule :



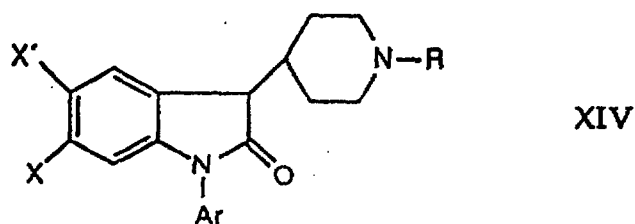
XI

dans laquelle R est tel que défini ci-dessus, ou
g) mise en réaction d'un dérivé d'indole substitué 3-halogène de la formule XII, avec un dérivé de pipérazine de la formule XIII :



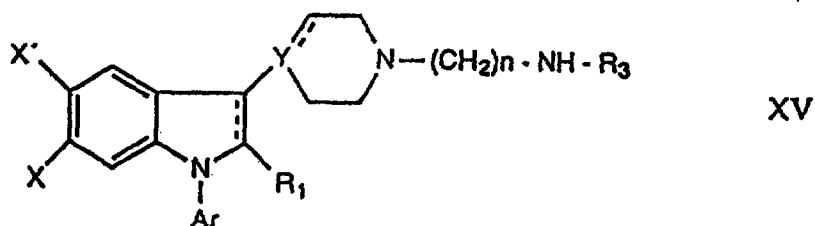
dans laquelle R', X, X', Ar et R sont tels que définis ci-dessus et "hal" signifie chloro, bromo, ou iodo, ou

h) réduction d'un dérivé 2-oxindole de formule suivante :



dans laquelle X, X', Ar et A sont tels que définis ci-dessus, ou

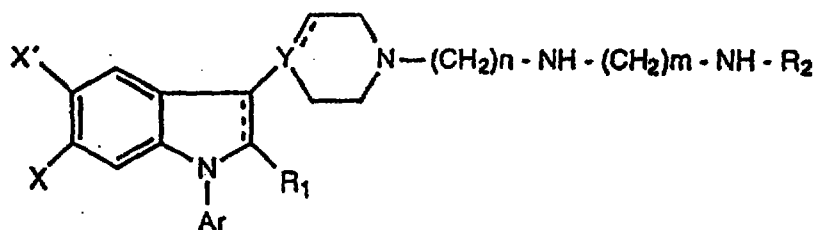
i) acylation d'un dérivé aminoalkyle de la formule suivante:



dans laquelle R', X, X', Y, Ar, n, R³ et les lignes en tirets sont tels que définis ci-dessus en utilisant un halogénure de l'acide carboxylique, un anhydride, ou un anhydride mixte, un chlorure carbamyle ou thiocarbamyle, isocyanate, isothiocyanate ou un chloroformate substitué en tant qu'agent d'acylation, ou



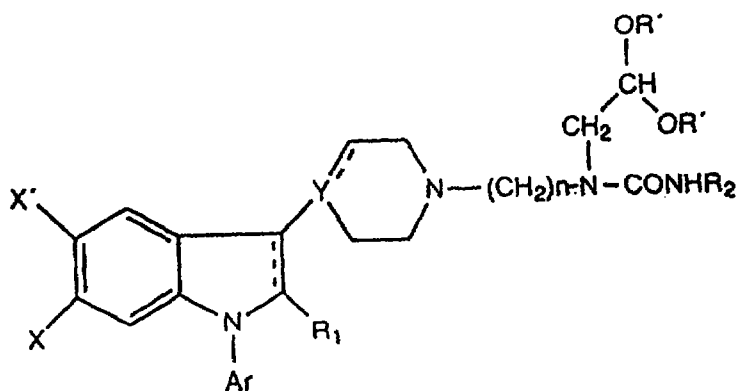
j) réaction de cyclisation d'un dérivé intermédiaire de la formule suivante :



XVI

dans laquelle R^1 , X , X' , Y , Ar , n , R^2 , m et les lignes en tirets sont tels que définis ci-dessus, en utilisant l'urée, le phosgène, le thiophosgène ou un disulfure de carbone pour incorporer un groupe carbonyle ou thiocarbonyle dans le système hétérocyclique de la structure 1a, ou

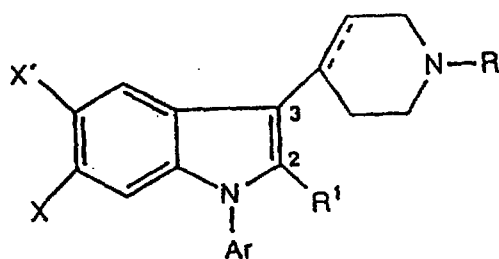
k) réaction de cyclisation d'un dérivé intermédiaire de la formule suivante :



XVII

dans laquelle R^1 , X , X' , Y , R^2 et les lignes en tirets sont tels que définis ci-dessus, et R' est un alkyle C_1-C_4 ou un alcényle inférieur ou constitue un cycle en formant un pont éthylène ou propylène, ou

l) réduction de la liaison double 2,3 d'un 3-pipéridylindole de la formule suivante :



XVIII

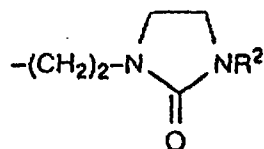
dans laquelle R^1 , X , X' , Ar , R et la ligne pointillée sont tels que définis ci-dessus,

puis convertir facultativement le composé de la formule I obtenu en un sel d'addition d'acide pharmaceutiquement acceptable, ou son produit

2. Dérivé selon la revendication 1, caractérisé en ce que Ar est phényle facultativement substitué par halogène de préférence 4-fluorophényle.

3. Dérivé selon la revendication 1 ou 2, caractérisé en ce que Y est $-CH-$.

4. Dérivé selon l'une quelconque des revendications 1 à 3, caractérisé en ce que R est un groupe de la formule



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où R^2 est tel que défini dans la revendication 1, R^2 étant de préférence hydrogène ou isopropyle.

- 10 5. Dérivé selon l'une quelconque des revendications 1 à 4, caractérisé en ce que X est -Cl, -Br, -CF₃, ou -CH₃ et/ou que X' est hydrogène ou -Cl.
- 15 6. Dérivé selon les revendications 2, 3, 4 et 5, caractérisé en ce qu'il s'agit de 6-chloro-1-(4-fluorophényl)-3-[1-[2-[3-(2-propyle)-2-imidazolidinon-1-yl]éthyle]-4-pipéridyle]-1H-indole ou 1-(4-fluorophényl)-6-méthyle-3-[1-[2-[3-(2-propyle)-2-imidazolinon-1-yl]éthyle]-4-pipéridyle]-1H-indole

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