Description

Background of the Invention

This invention generally pertains to heterocyclic carbon compounds having drug and bio-affecting properties and to their preparation and use. In particular the invention is concerned with 1,4-disubstituted piperazine derivatives wherein one substituent is indol-3-yl-alkyl and the other is a substituted pyridin-2-yl moiety. These compounds possess a unique serotonergic profile that should make them useful in treatment of depression.

Archer disclosed a large series of CNS-depressant indolylalkylpiperazines in U.S. 3,188,313 which issued June 8, 1965. Among the large number of moieties listed for possible substituent selection on the 4-nitrogen atom of the piperazine ring was pyridyl (unsubstituted). In U.S. 3,562,278, issued February 9, 1971, Archer claimed a series of 1-(indol-3-ylethyl)-4-substituted-piperazines having psychomotor depressant activity. Among the possible 4-substituents listed was pyridyl, again unsubstituted.

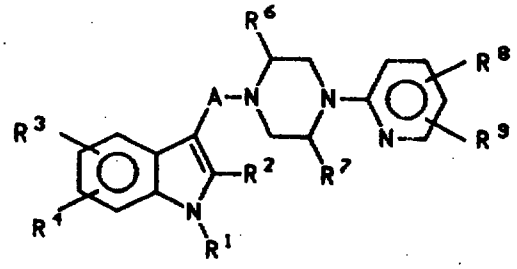
Of less relevance is U.S. 3,472,855, issued October 1969 to Archer, which discloses extension of the series to benz[g]indolyl moieties as replacements for indolyl.

Similarly less relevant is U.S. 4,302,589, issued November 1981 to Fanshawe, et al., which discloses a series of related compounds wherein indoline has replaced the indole moiety. These compounds were disclosed as having antipsychotic properties.

None of the aforementioned references disclose or suggest the 1-indolylalkyl-4-(substituted-pyridinyl)-piperazine derivatives and their antidepressant utility of the present invention.

Summary and Detailed Description of the Invention

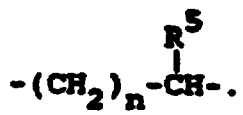
In its broadest aspect, the present invention is concerned with piperazinyl derivatives having useful antidepressant properties characterized by a compound of Formula I.



(I)

In Formula I; R^1 and R^2 are independently selected from hydrogen or lower alkyl. The descriptive term "lower" is used herein to denote an organic radical containing from 1 to 4 carbon atoms. The symbols R^3, R^4, R^8 and R^9 refer to moieties which are independently selected from among hydrogen, lower alkyl, lower alkoxy, carboxamide, halogen, trifluoromethyl, and thio-lower alkyl; with the proviso that both R^8 and R^9 cannot be hydrogen at the same time.

The symbol A represents a cycloalkanyl or cycloalkenyl ring comprised of from 5 to 7 carbon atoms. These bridging rings may be 1,2-; 1,3-; or 1,4-disubstituted bridging cycloalkanes or cycloalkenes. In the cycloalkenyl ring the double bond is adjacent to the point of attachment of the 3-indolyl ring. The symbol A can also be the structural fragment:



In this fragment linking the indole and piperazine rings, n is an integer from 1 to 3 and R^5 can be either hydrogen or lower alkyl. The carbon atom to which R^5 is attached is adjacent to the piperazine ring.

Lastly, R^6 and R^7 are independently selected from hydrogen or methyl, or R^6 and R^7 can be taken together as a methylene bridge. Subclasses of compounds envisioned would be: A is cyclic or linear in structure; the piperazine ring is bridged or unbridged. Preferred classes of compounds are those wherein the indolyl and piperazinyl rings are connected by a 2 or 3 carbon linking chain and wherein R^9 is other than hydrogen and is attached to the 6-position of the 2-pyridinyl ring.

Additionally compounds of Formula I also encompass all pharmaceutically acceptable acid addition salts and/or solvates thereof. The present invention is also considered to include stereoisomers as well as optical isomers, e.g. mixtures of enantiomers as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds of the instant series. Separation of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

It is to be understood that, as used herein, halogen denotes fluorine, chlorine, bromine and iodine; with the term "lower alkyl" referring to both straight and branched chain carbon radicals of from 1 to 4 carbon atoms inclusive. Illustrative of these radicals are carbon chains which can be methyl, ethyl, propyl, isopropyl, 1-butyl, 1-methylpropyl and 2-methylpropyl. Carboxamide intends a

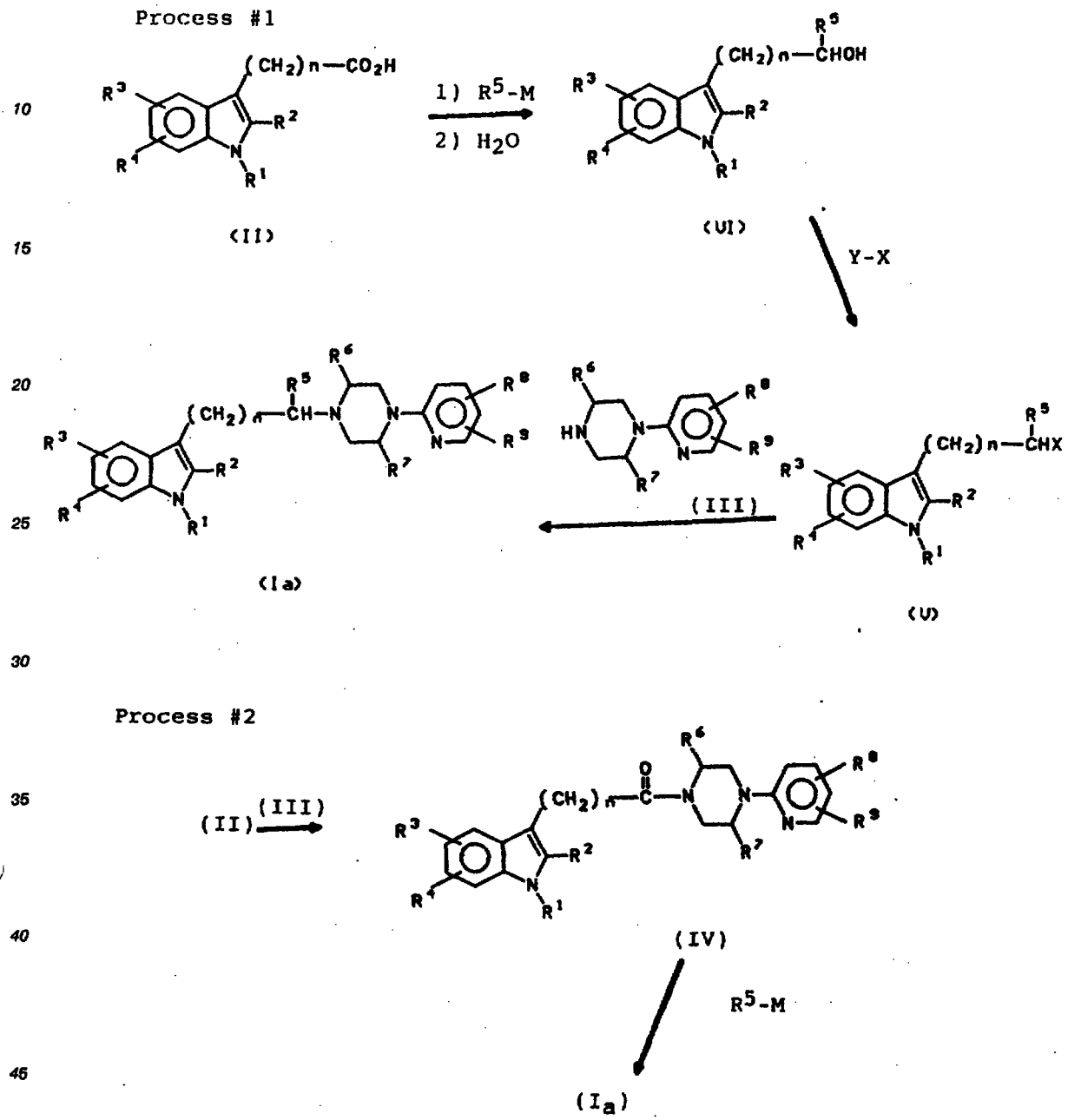


radical.

The pharmaceutically acceptable acid addition salts of the invention are those in which the counter-ion does not contribute significantly to the toxicity or pharmacological activity of the salt and, as such, they are the pharmacological equivalents of the bases of Formula I. They are generally preferred for medical usage. In some instances, they have physical properties which makes them more desirable for pharmaceutical formulation such as solubility, lack of hygroscopicity, compressibility with respect to tablet formation and compatibility with other ingredients with which the substance may be used for pharmaceutical purposes. The salts are routinely made by admixture of a Formula I base with the selected acid preferably by contact in solution employing an excess of commonly used inert solvents such as water, ether, benzene, methanol, ethanol, ethyl acetate and acetonitrile. They may also be made by metathesis or treatment with an ion exchange resin under conditions in which the anion of one salt of the substance of the Formula I is replaced by another anion under conditions which allow for separation of the desired species such so by precipitation from solution or extraction into a solvent, or elution from or retention on an ion exchange resin. Pharmaceutically acceptable acids for the purposes of salt formation of the substances of Formula I include sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, citric, acetic, benzoic, cinnamic, mandelic, phosphoric, nitric, mucic, isethionic, palmitic, heptanoic, and others.

The compounds of Formula I can be prepared by means of the processes shown in Scheme 1.

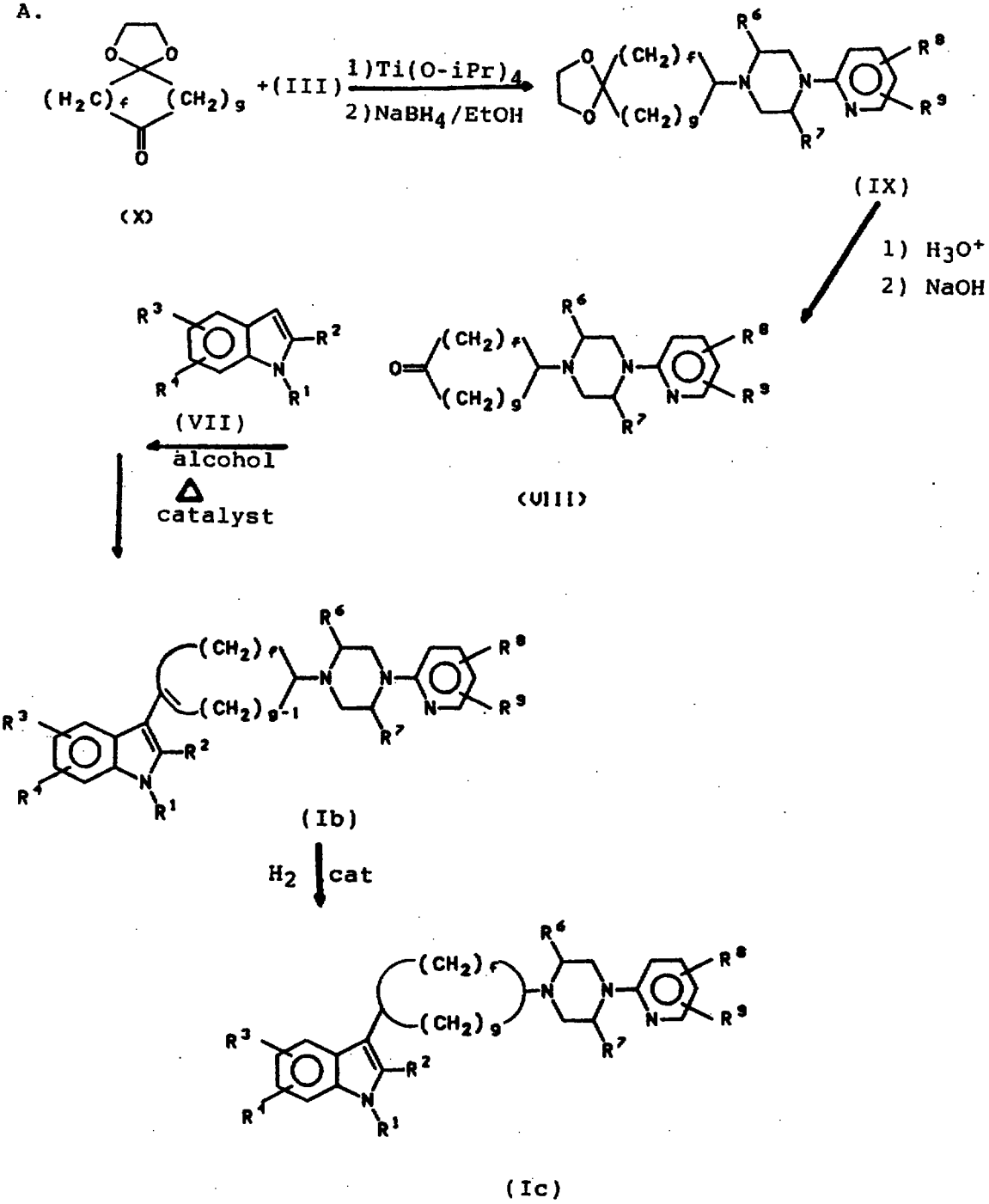
Scheme 1



Scheme 1 (continued)

Process #3

A.

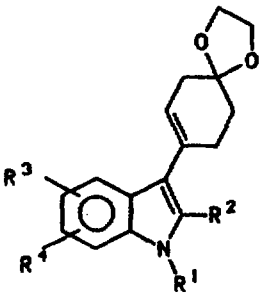


Scheme 1 (continued)

Process #3

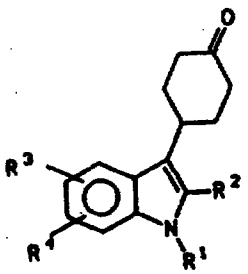
B.

(VII) + (X) → (XII) [catalyst, alcohol, Δ]



(XII)

↓ 1) 10 % Pd/C; H_2; alcohol
2) p-TsOH
acetone/H_2O



(XI)

(XI) → (Ic) [(III), 1) $Ti(O\text{-}iPr)_4$, 2) EtOH/cyanoborohydride]

For the three processes depicted in Scheme 1; R^1 through R^9, and n are as defined hereinabove. Additional symbols appearing in Scheme 1 are f, g, M, X and Y. The symbols f and g are integers from 0 to 5 with the proviso that f+g must be equal to 3, 4 or 5. M represents a metalloid species such as magnesium, lithioaluminum, and the like; which, taken with R^5 are either hydride-type reducing agents such as lithium aluminum hyrides, diborane complexes, etc.; or organometallic alkylating agents such as Grignard reagents, etc. The reagent Y-X represents an organic leaving group reagent wherein X is the leaving group fragment such as tosyl, mesyl, halide, sulfate, phosphate and so forth; and Y is either a proton or a counter ion: e.g. XY can be HBr or tosyl chloride and the like. These reagents, symbolized by R^5-M and Y-X, as well as other reagent acronyms, are familiar to the practitioner skilled in organic synthesis and their structure and usage would be readily understood.

Process #1 in Scheme 1 comprises the following steps:

1) Treatment of an indole carboxylic acid II with R^5-M, which is either a hyride reducing agent or alkylating agent depending on the selection of R^5 (hydrogen or lower alkyl). This results in generation of the indolylalkanol VI which is a secondary alcohol when R^5 is lower alkyl and a primary alcohol when R^5 is hydrogen.

2) Conversion of the alcohol VI to an organic leaving group (also referred to as a nucleofuge in synthetic organic reaction terminology) by use of an appropriate Y-X reagent such as HBr or tosyl chloride to give intermediate V.

3) Displacement of the leaving group anion by the nucleophilic pyridinylpiperazine III to provide the desired product of formula Ia.

Process #2 in Scheme 1 comprises a two-step reaction sequence:

1) Condensation of the indolylcarboxylic acid II with the pyridinylpiperazine III, using standard condensation agents such as acid chlorides, acid anhydrides, dicyclohexylcarbodiimide, and the like, to afford the amide intermediate IV.

2) Treatment of the amide IV with R^5-M to reductively alkylate or reduce to the desired formula Ia product.

Process #3 in Scheme 1 comprises the following sequence of steps:

A.

1) The pyridinylpiperazine III is reductively alkylated with a cycloalkanedione mono-ethylene ketal X to give the ketal intermediate IX.

2) Deprotecting the ketal IX to produce the cycloalkanone intermediate VIII.

3) Condensing the cycloalkanone VIII with indole VII to yield the cycloalkenyl product Ib which can be catalytically reduced to the cycloalkanyl product Ic if desired.

B.

1) The indole VII, cycloalkanedione mono-ethylene ketal X, and an acid or base catalyst (e.g. pyrrolidine) are refluxed in alcohol to give the condensation product XII.

2) Intermediate XII is catalytically reduced to the saturated cycloalkane ketal which is deketalized to the cycloalkanone intermediate XI.

3) Cycloalkanone XI is condensed with the pyridinylpiperazine III using conditions as shown to yield product Ic.

Reagents, solvents, and reaction conditions for the above described steps of the three processes would be known to one skilled in organic synthesis as all the steps comprise standard organic reactions, the details of which are readily available in the chemical literature. These processes may be adapted to variation in order to produce other compounds embraced by this invention but not specifically disclosed. Variations of the methods to produce the same compounds in somewhat different fashion will also be evident to one skilled in the art. As example of this, VI intermediate compounds wherein n is 1 are conveniently prepared by treating various substituted 3-indoleglyoxylic acid esters with $LiAlH_4$.

To provide greater descriptive detail, representative synthetic examples are provided hereinbelow in the "Description of Specific Embodiments" section. Similarly, preparations of starting intermediate compounds such as II and III, while readily available in the chemical literature, are also described using specific examples in that section of the patent specification.

The compounds comprising the present invention inhibit the re-uptake of endogenous serotonin. Selective inhibitors of serotonin uptake are effective for the treatment of mental depression and have been reported to be useful for treating chronic pain (see: R.W. Fuller. "Pharmocologic Modification of Serotonergic Function: Drugs for the Study and Treatment of Psychiatric and Other Disorders", J. Clin. Psychiatry 47:4 (Suppl.) April 1986, pp. 4-8). Compounds of the present invention are also envisioned to be useful in the following disorders: obsessive-compulsive disorder, feeding disorders, anxiety disorders and panic disorders.

Additionally, selected compounds of the invention potently inhibit norepinephrine re-uptake and blockade of endogenous norepinephrine re-uptake is also a mechanism through which it is believed that various antidepressant agents exert their therapeutic effect (see: "Antidepressants: Neurochemical, Behavioral, and Clinical Perspectives", edited by S.J. Enna, J.B. Malick and E. Richardson, (1981), Raven Press, New York, pp. 1-12).

Determination of endogenous monoaminergic re-uptake inhibition values both for serotonin and norepinephrine was accomplished using test methods described by P. Skolnick, et al., Br. J. Pharmacology (1985), 86, pp. 637-644; with only minor modifications. In vitro IC_{50} (nM) test values were determined for representative compounds of Formula I based on their inhibition of synaptosomal reuptake of tritiated serotonin. Test data IC_{50} values lower than 500nM are considered to reflect activity as an inhibitor of serotonin reuptake. Compounds with IC_{50} values lower than 100nM comprise preferred compounds.

Another aspect of the instant invention provides a method for treating a mammal afflicted with depression or chronic pain which comprises administering systemically to said mammal a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof.

The administration and dosage regimen of compounds of Formula I is considered to be done in the same manner as for the reference compound fluoxetine, cf: Schatzberg, et al., J. Clin. Psychopharmacology 7/6 Suppl. (1987) pp. 445-495, and references therein. Although the dosage and dosage regimen must in each case be carefully adjusted, utilizing sound professional judgment and considering the age, weight and condition of the recipient, the route of administration and the nature and gravity of the illness, generally the daily dose will be from about 0.05 to about 10 mg/kg, preferably 0.1 to 2 mg/kg, when administered

parenterally and from about 1 to about 50 mg/kg, preferably about 5 to 20 mg/kg, when administered orally. In some instances, a sufficient therapeutic effect can be obtained at lower doses while in others, larger doses will be required. Systemic administration refers to oral, rectal and parenteral (i.e. intramuscular, intravenous and subcutaneous). Generally, it will be found that when a compound of the present invention is administered orally, a larger quantity of the active agent is required to produce the same effect as a similar quantity given parenterally. In accordance with good clinical practice, it is preferred to administer the instant compounds at a concentration level that will produce effective antidepressant effects without causing any harmful or untoward side effects.

The compounds of the present invention may be administered for antidepressant purposes either as individual therapeutic agents or as mixtures with other therapeutic agents. Therapeutically, they are generally given as pharmaceutical compositions comprised of an antidepressant amount of a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Pharmaceutical compositions which provide from about 1 to 500 mg of the active ingredient per unit dose are preferred and are conventionally prepared as tablets, lozenges, capsules, powders, aqueous or oily suspensions, syrups, elixirs, and aqueous solutions.

The nature of the pharmaceutical composition employed will, of course, depend on the desired route of administration. For example, oral compositions may be in the form of tablets or capsules and may contain conventional excipients such as binding agents (e.g. starch) and wetting agents (e.g. sodium lauryl sulfate). Solutions or suspensions of a Formula I compound with conventional pharmaceutical vehicles are employed for parenteral compositions such as an aqueous solution for intravenous injection or an oily suspension for intramuscular injection.

Description of Specific Embodiments

The compounds which constitute this invention, their methods of preparation and their biologic actions will appear more fully from consideration of the following examples, which are given for the purpose of illustration only and are not be construed as limiting the invention in sphere or scope. In the following examples, used to illustrate the foregoing synthetic processes, temperatures are expressed in degrees Celsius and melting points are uncorrected. The nuclear magnetic resonances (NMR) spectral characteristics refer to chemical shifts (δ) expressed as parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the H NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m) or doublet (d). Abbreviations employed are DMSO-d_6 (deuterodimethylsulfoxide), $CDCl_3$ (deuterochloroform) and are otherwise conventional The infrared (IR) spectral descriptions include only absorption wave numbers (cm^{-1}) having functional group identification value. The IR determinations were employed using potassium bromide (KBr) as diluent. The elemental analyses are reported as percent by weight and are given in Table 3.

The following examples describe in detail the preparation of compounds of Formula I, as well as synthetic intermediates in each process. It will be apparent to those skilled in the art that modifications, both of materials and methods, will allow preparation of other compounds disclosed herein. From the foregoing description and the following examples it is believed that one skilled in the art is able to use the invention to the fullest extent.

A. Preparation of Intermediate Compounds

Some representative procedures for preparation of synthetic intermediate compounds utilized in the three processes of Scheme 1 are given hereinbelow. Most starting materials and certain intermediates (e.g. Formula II and VII compounds), are either commercially available or procedures for their synthesis are readily available in the chemical literature allowing their full utilization by one skilled in the art of organic synthetic chemistry.

Compounds of Formula III

Example 1

1-(3-Methoxy-2-pyridinyl)piperazine

To a stirred mixture of 2-bromo-3-pyridinol (71.0 g) and pulverized KOH (77.8 g) in DMSO (500 mL) at 55-60 °C and under N_2 atmosphere was added dropwise a solution of CH_3I (72.4 g) in DMSO (100 mL). After the addition was complete, the reaction was maintained at 55-60 °C for ½ h. The mixture was then poured into ice water (800 g) and the precipitate filtered. The precipitate was triturated with Et_2O (3 x 500 mL) and the combined extracts treated in turn with 1 N NaOH (500 mL), water (500 mL), 1 N HCl (3 x 250 mL), and sat. NaCl solution (500 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford 2-bromo-3-methoxypyridine (52.3 g; 68%).

Anhydrous piperazine (45.6 g) and 2-bromo-3-methoxypyridine (10.0 g) were heated neat in an autoclave at 100 °C for 20 h. Upon cooling, the mixture was treated with 5% $NaCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The extracts were dried using anhydrous K_2CO_3, filtered, and concentrated under reduced pressure to yield 1-(3-methoxy-2-pyridinyl)piperazine (III; 8.43 g; 82%) after silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH; 93:7:0.7).

Example 2

1-(3-Trifluoromethyl-2-pyridinyl)piperazine

A mixture of 2-chloro-3-trifluoromethyl pyridine (5.0 g), anhydrous piperazine (7.22 g), and micropulverized anhydrous K_2CO_3 (7.73 g) in acetonitrile (50 mL) was heated at reflux with stirring while under N_2 atmosphere for 20 h. The excess acetonitrile was removed under reduced pressure and water (15 mL) added to the concentrate. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined CH_2Cl_2 extracts were washed with sat. NaCl solution, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH; 94:6:0.6) of the residue yielded 1-(3-trifluoromethyl-2-pyridinyl)piperazine (III; 5.50 g; 85%).

Example 3

1-(6-Methoxy-2-pyridinyl)piperazine

A mixture of 1-(6-chloro-2-pyridinyl)piperazine (6.0 g) and NaOMe (16.42 g) in DMF (25 mL) was heated at 100 °C under nitrogen atmosphere for 20 h. The excess DMF was then removed under reduced pressure. Water (5 mL) was added to the residue and the mixture extracted with CH_2Cl_2. The combined organic layers were washed with sat. NaCl solution, dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH; 98:2) of the concentrate yielded the 4-(6-methoxy-2-pyridinyl)-1-piperazinecarboxaldehyde (5.13 g; 81%).

A mixture of the formamide intermediate, prepared above, (3.55 g) in 6 N HCl (30 mL) was heated it reflux for ½ h. The reaction was cooled to 0 °C, made basic with 10 N NaOH, and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with sat. NaCl solution, dried with anhydrous K_2CO_3, filtered, and concentrated under reduced pressure to afford 1-(6-methoxy-2-pyridinyl)piperazine (2.72 g; 83%).

Example 4

1-(6-Chloro-2-pyridinyl)piperazine

A mixture of 2,6-dichloropyridine (4.0 g), anhydrous piperazine (6.97 g), and micropulverized anhydrous K_2CO_3 (7.45 g) in acetonitrile (50 ml) was heated it reflux with stirring while under N_2 atmosphere for 20 h. The excess acetonitrile was removed under reduced pressure and water (15 mL) added to the concentrate The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined CH_2Cl_2 extracts were washed with sat. NaCl solution, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH; 94:6:0.6) of the residue yielded 1-(6-chloro-2-pyridinyl)piperazine (4.80 g; 90%).

Example 5

2-(3-Methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptane

A. Preparation of (1S,4S)-N-Benzyl-2,5-diazabicyclo[2.2.1]heptane
(cf: J. Org. Chem. (1966), 31, 1059-1062)

1) N-Tosylhydroxy-L-proline

To a solution of hydroxy-L-proline (80 g) in 2N NaOH (800 mL) was added tosyl chloride (136.1 g) in Et_2O (700 mL). The reaction mixture was stirred at 0 °C for 1½ h and continued for an additional 3½ h at 23 °C. The aqueous layer was separated, acidified with concentrated HCl to pH 1 and allowed to stand at -10 °C for 12 h. The precipitate was filtered, washed with cold water, and concentrated in vacuo to a volume of 300 mL. The precipitate obtained was combined with the previous precipitate. The combined solids were recrystallized from ethyl acetate. Drying in vacuo at 50 °C for 24 h afforded trans-4-hydroxy-1-(4-toluenesulfonyl)-L-proline (107.38 g, 62%).

2) Potassium salt of trans-4-hydroxy-1-(4-toluenesulfonyl)-L-proline

To a solution of trans-4-hydroxy-1-(4-toluenesulfonyl)-L-proline (107.38 g) in acetone (450 mL) was added potassium 2-ethyl hexanoate in BuOH (1.91 N; 189.5 mL). After standing at 23 °C for 20 min, the insoluble material was filtered and the resulting solution was concentrated to 320 mL. Et_2O (1000 mL) was added to the concentrate and the solvents removed under reduced pressure yielding a solid (122.90 g). The hygroscopic product was used in the next step without further purification.

3) N-Tosylhydroxy-L-proline methyl ester

To a solution of potassium trans-4-hydroxy-1-(4-toluenesulfonyl)-L-proline (122.90 g) in 250 mL of N,N-dimethylacetamide was added methyl iodide (24.5 mL) while under nitrogen atmosphere. The light protected mixture was stirred 16 h. The mixture was poured onto ice water and extracted with CH_2Cl_2 (3 x 400 mL). The combined organic extracts were washed with 2% $NaHCO_3$ (400 mL), H_2O (4 x 1.5 L), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to leave a viscous oil. The crude oil was triturated within petroleum ether to give N-tosylhydroxy-L-proline methyl ester as a pale yellow solid (63.20 g, 56.2%) which was used in the next step without further purification.

4) (2S,4R)-1-(4-toluenesulfonyl)-2-hydroxymethyl-4-hydroxy pyrrolidine

To a solution of N-tosylhydroxy-L-proline methyl ester (62.20 g) in THF (600 mL) at 0 °C for 1 h and allowed to stand at 23 °C for 18 h. The reaction mixture was cooled to -20 °C, made neutral with 6N HCl, and concentrated under reduced pressure. The residue was treated with water (550 mL) and extracted with EtOAc (4 x 300 mL). The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give N-tosylhydroxy-L-prolinol as a white solid (50.56 g, 88.8%) which was used in the next step without further purification.

5) (2S,4R)-1-(4-toluenesulfonyl)-2-(4-toluenesulfonyloxymethyl)-4-(4-toluenesulfonyloxy)-pyrrolidine

To a solution of p-toluenesulfonyl chloride (155 g) in pyridine (330 mL) at 0 °C was added N-tosylhydroxy-L-prolinol (104.40 g). The reaction mixture was kept at 6 °C for 72 h and then poured into cold 2N HCl (2.5 L). The aqueous layer was extracted with CH_2Cl_2 (3 x 1000 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an oil. The oil was triturated with EtOH and the solid that formed was collected by filtration. The crude product was recrystallized from EtOH (3.5 L) to give tritosylhydroxy-L-prolinol (99.87 g, 44.2%, m.p. 130-132 °C, $[\alpha]_D^{24} = -57.1$, c = 1.2, acetone).

6) (1S,4S)-2-(4-toluenesulfonyl)-5-phenylmethyl-2,5-diazabicyclo[2.2.1]heptane

To a suspension of tritosylhydroxy-L-prolinol (98.87 g) in toluene (350 mL) was added benzylamine (54.83 g). The resulting mixture was heated at reflux for 18 h and allowed to cool to 23 °C. The reaction

mixture was filtered and the solvent removed under reduced pressure. The residue was triturated with ethanol and the solid that formed was collected by filtration to give (1S,4S)-2-(4-toluenesulfonyl)-5-phenylmethyl-2,5-diazabicycloheptane (54.18 g, 93.2%) which was used in the next step without further purification.

7) (1S,4S)-N-benzyl-2,5-diazabicyclo[2.2.1]heptane dihydrobromide

A mixture of (1S,4S)-2-(4-toluenesulfonyl)-5-phenylmethyl-2,5-diazabicyclo[2.2.1]heptane (54.0 g) in acetic acid (830 mL) containing hydrobromic acid (30% wt) was heated at 70 °C for 18 h. The reaction mixture was allowed to cool and concentrated under reduced pressure to a final volumen of ca. 300 mL. The precipitate that formed was filtered and washed with acetone to give (1S,4S)-N-benzyl-2,5-diazabicyclo-[2.2.1]heptane (50.30 g 91.3%, m.p. 272-275 °C).

By adjusting the starting materials and using the foregoing synthetic scheme the other isomer, (1R,4R)-N-benzyl-2,5-diazabicyclo[2.2.1]heptane can be obtained (cf: J. Org. Chem. (1981), 46 2954-2960).

B. 2-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane

1) 2-(3-methoxy-2-pyridinyl)-5-phenylmethyl-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane

A mixture of 2-bromo-3-methoxy pyridine (9.9 g) and (1S,4S)-N-benzyl-2,5-diazabicyclo[2.2.1]-heptane (10.9 g) was heated at 100 °C in a Parr bomb for 67 h. The reaction mixture was cooled to 23 °C, dissolved in CH_2Cl_2, extracted with 5% $NaHCO_3$, and finally with H_2O. The organic layer was dried over K_2CO_3, filtered, and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (CH_2Cl_2:MeOH; 96:4) to give the desired product (7.93 g, 51%).

2) 2-(3-methoxy-2-pyridinyl)-5-phenylmethyl-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane (7.88 g) in EtOH (250 mL) was acidified to a pH of 1 with ethanolic HCl. The reaction mixture was treated with 5% palladium-on-carbon (2.05 g) and hydrogenated at 50 psi at 60 °C for 6 h. After this time, the heating was discontinued and the reaction mixture was allowed to cool to room temperature and the hydrogenation continued for 16 h. The reaction mixture was filtered through celite. The filtrate was concentrated under reduced pressure and the residue was made alkaline by the addition of 5N NaOH. The solution was extracted with CH_2Cl_2 (4 x 250 mL) and combined CH_2Cl_2 extracts were dried over K_2CO_3, filtered, and concentrated under reduced pressure to give 2-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1]-heptane (4.67 g; 85.2%).

Compounds of Formula IV

Example 6

1-[4-(1H-indol-3-yl)-1-oxobutyl]-4-(3-methoxy-2-pyridinyl)piperazine

To a mixture of 1-(3-methoxy-2-pyridinyl)piperazine (III; 1.28 g), 3-indolebutyric acid (1.08 g), and triethylamino (1.02 g) in CH_2Cl_2 (50 mL) was added 1-methyl-2-chloropyridinium iodide (1.62 g). The reaction was heated at reflux with stirring and under N_2 atmosphere for 4 h. After cooling to ambient temperature, the solution was extracted with aqueous 5% HCl followed by aqueous 5% $NaHCO_3$. The organic phase was dried with anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH; 98:2) of the concentrate afforded the amide product (IV; 1.00 g; 50%).

Compounds of Formula V

Example 7

3-(3-bromopropyl)-1H-indole

Phosphorus tribromide (17.4 g) in Et_2O (30 mL) was added dropwise to a Et_2O solution (100 mL) containing 3-(3-hydroxypropyl)indole (VI; 7.5 g) at 0 °C with stirring and under N_2 atmosphere. After the addition was complete, the reaction was allowed to warm to 23 °C and continuously stirred for 16 h. At the end of this time, the reaction was cooled to 0 °C and ice (ca. 25 mL) added portionwise and stirred an additional 2 h. The organic phase was separated from the aqueous phase and the aqueous layer extracted with Et_2O. The combined organic phases were washed with sat. NaCl solution, dried with $MgSO_4$, filtered,

and concentrated under reduced pressure to afford 3-(3-bromopropyl)indole (V; 1.51 g; 15%).

Example 8

5-Fluoro-3-(2-bromoethyl)indole

To a solution of 5-fluoro-3-(2-hydroxyethyl)indole (10.3 g, 0.056 mol) and CBr_4 (24.8 g, 0.073 mol) in 100 mL of dry acetonitrile at 0 °C under Ar was added a solution of triphenylphosphine (19.6 g, 0.073 mol) in 200 mL of dry acetonitrile. The mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. The resulting mixture was evaporated and the residue was chromatographed (SiO_2/ethyl acetate-hexane = 1:4) to give the product (8.50 g, 61%) as a brown solid;

IR (neat) 3440 cm^{-1};

^{1}Hnmr (80 MHz, $CDCl_3$)

δ: 7.75 (br s, 1H), 7.15-6.57 (m, 4H), 3.53-3.32 (m, 2H), 3.17-2.94 (m,2H).

Compounds of Formula VI

Example 9

3-(3-hydroxypropyl)-1H-indole

To a stirred suspension of $LiAlH_4$ (4.02 g) in THF (200 mL) at 0 °C and under N_2 atmosphere was added dropwise a THF solution (100 mL) containing indole-3-propanoic acid (20.0 g). After the addition was complete, the reaction was heated at reflux for 16 h, after which time the mixture was cooled to 0 °C and water (4 mL) added, followed by 15% NaOH (4 mL), and finally additional water (12 mL). The reaction was filtered and the THF filtrate extracted with 5% NaOH (4 mL), and finally additional water (12 mL). The reaction was filtered and the THF filtrate extracted with 5% $NaHCO_3$ followed by a sat. NaCl solution The organic phase was dried with anhydrous K_2CO_3, filtered, and concentrated under reduced pressure to yield 3-(3-hydroxypropyl)indole (VI; 7.5 g; 41%).

Example 10

3-(2-hydroxyethyl)-1H-indole

To a stirred suspension of $LiAlH_4$ (3.24 g) in THF (200 mL) at 0 °C and under N_2 atmosphere was added dropwise a THF solution (50 mL) containing indole-3-acetic acid (10.0 g). After the addition was complete, the reaction was heated at reflux for 3 h, after which time the mixture was cooled to 0 °C and water (3.3 mL) added, followed by 15% NaOH (3.3 mL), and finally additional water (9.9 mL). The reaction was filtered and the filter cake washed with Et_2O. The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield 3-(2-hydroxyethyl)indole (VI; 7.4 g; 80%).

Example 11

5-Floro-3-(2-hydroxyethyl)indole

To a suspension of $LiAlH_4$ (8.60 g, 0.23 mol) in 400 mL of dry THF was added 5-fluoro-3-indoleglyoxylic acid ethyl ester (13.50 g, 0.057 mol) portionwise at room temperature. Preparation of this ester intermediate is given hereinbelow. The mixture was heated to reflux under Ar for 1 h and was then cooled at 0 °C and quenched according to the method of Fieser (Fieser and Fieser, "Reagents for Organic Synthesis", Vol. 1, pg. 584). The resulting slurry was filtered and the filter cake was washed with THF. The filtrate was dried (Na_2SO_4) and evaporated to give the product (10.00 g, 100%) as a yellow oil. It was used as such without further purification;

IR (neat) 3420 cm^{-1}

^{1}Hnmr (80 MHz, $CDCl_3$)

δ: 7.73 (br s, 1H), 7.1-6.4 (m, 4H), 3.57 (t, J = 8 Hz, 2H), 2.66 (t, J = 8 Hz, 2H), 1.20 (br s, 1H).

5-Fluoro-3-indoleglyoxylic acid ethyl ester

To a solution of 5-fluoroindole (7.35 g, 0.054 mol) in 75 mL of anhydrous ether was added oxalyl chloride (5.60 mL, 0.064 mol) dropwise at 0 °C under Ar.

The yellow suspension was stirred at 0 °C for 1½ h and then the solid was collected by filtration and dried in vacuo to give 5-fluoro-3-indoleglyoxylyl chloride (12.0 g, 100%) as a yellow solid; IR (neat) 1765, 1627 cm^{-1}.

This solid was taken up in 160 mL of absolute ethanol and was then treated with triethylamine (8.1 mL, 0.058 mol) dropwise at 0 °C under Ar. The mixture was refluxed for 4½ h and was then allowed to cool to room temperature. The resulting precipitate was filtered and then dried in vacuo to give the product (10.8 g, 87%) as a yellow solid which was used without further purification.

Compounds of Formula VIII

Example 12

4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-cyclohexan-1-one

A solution of 4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]cyclohexan-1-one ethylene ketal (IX, Example 11: 7.56 g, 22 mmole) in 10% aqueous HCl (200 mL) was refluxed for 16 h. The solution was cooled and then neutralized with 30% aqueous NaOH solution. The mixture was then extracted with ethyl acetate (3 x 75 mL) and the extracts were dried over Na_2CO_3. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel using ethyl acetate as the eluent to give the desired ketone product (VIII) as an oil (5.70 g, 92%).

Compounds of Formula IX

Example 13

4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-cyclohexan-1-one ethylene ketal

A solution of 1-(6-chloro-2-pyridinyl)-piperazine (8.00 g, 40 mmole), 1,4-cyclohexanedione mono-ethylene ketal (6.25 g, 40 mmole), and titanium(IV) isopropoxide (15 mL, 14.21 g, 50 mmole) was heated to 80 °C for 30 min. The mixture was cooled and diluted with absolute ethanol (40 mL). Sodium borohydride (ten 0.4 g tablets, 0.1 mole) was added and the mixture was stirred for 4 h. Water (10 mL) was added to the solution with stirring and the solid titanium dioxide was filtered off. The filtrate was concentrated in vacuo and the residue was dissolved in CH_2Cl_2 (75 mL). The solution was again filtered and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel using ethyl acetate as the eluent to give the desired ketal product (IX) as an oil (7.56 g, 56%).

B. Preparation of Formula I Products

By Process 1 (Ia Products)

Example 14

4-[6-Chloro-2-pyridinyl]-1-[2-(1H-indol-3-yl)-ethyl]piperazine hydrochloride

A mixture of 3-(2-bromoethyl)indole (2.05 g), 1-(6-chloro-2-pyridinyl)piperazine (3.61 g), micropulverized K_2CO_3 (2.52 g) and tetrabutylammonium hydrogen sulfate (0.16 g) in acetonitrile (25 mL) was heated at reflux under N_2 atmosphere for 2½ h. The excess acetonitrile was removed under reduced pressure and water (15 mL) added to the concentrate. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined CH_2Cl_2 extracts were washed with sat. NaCl solution, dried with anhydrous K_2CO_3, and concentrated under reduced pressure. Silica gel chromatography (EtOAc/Hexanes; 70:30) of the residue yielded the free base (3.10 g; 99%) which was treated with ethanolic HCl to provide the desired Ia product (2.63 g; 77%).

Anal. Calcd. for $C_{19}H_{21}N_4Cl \cdot HCl$:			
found:	C, 60.49; C, 60.27;	H, 5.88; H, 5.88;	H, 14.85 N, 14.66

NMR (DMSO-d_6): 3.24 (8H, m); 3.72 (2H, m); 4.40 (2H, m); 6.81 (1, d, 7.4 Hz); 7.02 (3H, m); 7.25 (1H, d, 1.0 Hz); 7.39 (1H, m); 7.64 (2H, m); 10.85 (1H, bs); 10.98 (1H, bs).

IR (KBr): 750, 770, 960, 1140, 1270, 1420, 1460, 1550, 1600, 2440 and 3240 cm^{-1}.

Example 15

1-[2-(1H-indol-3-yl)-ethyl]-4-[6-trifluoromethyl-2-pyridinyl]piperazine hydrochloride

A mixture of 3-(1-bromoethyl)indole (1.12 g), 1-(6-trifluoromethyl-2-pyridinyl)piperazine (2.31 g), micropulverized K_2CO_3 (1.38 g) and tetrabutylammonium hydrogen sulfate (0.08 g) in acetonitrile (50 mL) was heated at reflux under N_2 atmosphere for 2½ h. The excess acetonitrile was removed under reduced pressure and water (10 mL) added to the concentrate. The aqueous phase was extracted with CH_2Cl_2 (3x 50 mL). The combined CH_2Cl_2 extracts were washed with sat. NaCl solution, dried with anhydrous K_2CO_3, and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH; 98:2) of the residue yielded the free base (1.56 g; 83%) which was treated with ethanolic HCl to yield the hydrochloride salt of the desired Ia product (1.17 g; 68%).

Anal. Calcd. for $C_{20}H_{21}N_4F_3 \cdot HCl$:			
Found:	C, 58.47; C, 58.37;	H, 5.40; H, 5.38;	N, 13.64 N, 13.56.

NMR (DMSO-d_6): 3.25 (8H, m); 3.72 (2H, d, 13.4 Hz); 4.48 (2H, d, 13.4 Hz); 7.10 (5H, m); 7.34 (1H, d, 7.0 Hz); 7.61 (1H, d, 7.0 Hz); 7.83 (1H, m); 10.60 (1H, bs); 10.95 (1H, bs).

IR (KBr): 740, 800, 960, 1120, 1130, 1340, 1490, 1610, 2600, 2925 and 3250 cm^{-1}.

Example 16

1-[2-(1H-indol-3-yl)-ethyl]-4-[6-methoxy-2-pyridinyl]piperazine hydrate

A mixture of 3-(2-bromoethyl)indole (1.66 g), 1-(6-methoxy-2-pyridinyl)piperazine (2.86 g), micropulverized K_2CO_3 (2.04 g) and tetrabutylammonium hydrogen sulfate (0.13 g) in acetonitrile (50 mL) was heated at reflux under N_2 atmosphere for 2 h. The excess acetonitrile was removed under reduced pressure and water (10 mL) added to the concentrate. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined CH_2Cl_2 extracts were washed with sat. NaCl solution, dried with anhydrous K_2CO_3, and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH; 96:4) of the residue yielded the free base of the desired Ia product (2.20 g; 89%).

Anal. Calcd. for $C_{20}H_{24}N_4O \cdot 0.5\ C_2H_6O \cdot 0.5\ H_2O$:				
Found:	C, 68.46; C, 68.24;	H, 7.66; H, 7.59;	N, 15.21; N, 15.35;	H_2O, 2.45 H_2O, 2.30.

NMR ($CDCl_3$): 2.70 (6H, m); 3.08 (2H, m); 3.61 (4H, m); 3.90 (3H, s); 6.11 (1H, d, 9.5 Hz); 6.20 (1H, d, 9.0 Hz); 7.12 (3H, m); 7.40 (2H, m); 7.68 (1H, m); 8.00 (1H, bs).

IR (KBr): 745, 790, 985, 1250, 1450, 1460, 1590, 2840, 3180 and 3550 cm^{-1}.

Example 17

1-[2-(1H-indol-3-yl)-ethyl]-4-[3-trifluoromethyl-2-pyridinyl]piperazine hydrochloride

A mixture of 3-(2-bromoethyl)indole (1.79 g), 1-(3-trifluoromethyl-2-pyridinyl)piperazine (1.85 g), micropulverized K_2CO_3 (2.21 g) and tetrabutylammonium hydrogen sulfate (.014 g) in acetonitrile (50 mL) was heated at reflux under N_2 atmosphere for 3 h. The excess acetonitrile was removed under reduced pressure and water (10 mL) added to the concentrate. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined CH_2Cl_2 extracts were washed with sat. NaCl solution, dried with anhydrous K_2CO_3,and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH; 97:3) of the residue yielded the free base (1.66 g; 56%) which was treated with ethanolic HCl to yield the hydrochloride salt of the desired Ia product (1.45 g; 80%).

Anal. Calcd. for $C_{20}H_{21}N_4F_3 \cdot HCl$:			
Found:	C, 58.47; C, 58 60;	H, 5.40; H, 5.43;	N, 13.64 N, 13.66.

NMR (DMSO-d_6): 3.30 (10H, m); 3.72 (2H, m); 7.08 (2H, m); 7.22 (1H, d, 4.9 Hz); 7.35 (2H, m); 7.66 (1H, m); 8.12 (1H, m); 8.60 (1H, m).

IR (KBr): 750, 1040, 1130, 1320, 1450, 1580, 1595, 2460, 2580 and 3230 cm^{-1}.

Example 18

1-[2-(1H-indol-3-yl)-ethyl]-4-[3-methoxy-2-pyridinyl]piperazine

A mixture of 3-(2-bromoethyl)indole (2.00 g), 1-(3-methoxy-2-pyridinyl)piperazine (1.72 g), micropulverized K_2CO_3 (2.46 g) and tetrabutylammonium hydrogen sulfate (0.15 g), in acetonitrile (50 mL) was heated at reflux under N_2 atmosphere for 5 h. The excess acetonitrile was removed under reduced pressure and water (10 mL) was added to the concentrate. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined CH_2Cl_2 extracts were washed with sat. NaCl solution, dried with anhydrous K_2CO_3, and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH; 96:4) of the residue yielded the free base of the desired Ia product (1.32 g; 44%).

Anal. Calcd. for $C_{20}H_{24}N_4O$:			
Found:	C, 71.41; C, 71.34;	H, 7.20; H, 7.23;	N, 16.66 N, 16.55.

NMR ($CDCl_3$): 2.80 (6H, m); 3.04 (2H, m); 3.55 (4H, m); 3.90 (3H, s); 6.86 (1H, dd, 4.8, 7.6 Hz); 7.14 (4H, m); 7.36 (1H, m); 7.66 (1H, m); 7.92 (1H, dd, 1.4, 4.8 Hz); 8.14 (1H, bs).

IR (film): 740, 1210, 1240, 1440, 1450, 1470, 1590, 2840, 2940, 3200 and 3450 cm^{-1}.

Example 19

1-(6-Chloro-2-pyridinyl)-4-[3-(1H-indol-3-yl)propyl]piperazine hydrochloride

An acetonitrile solution (25 mL) containing 3-(3-bromopropyl)indole (V; 1.51 g), 1-(6-chloro-2-pyridinyl)-piperazine (III; 2.50 g), micropulverized K_2CO_3 (1.75 g), and tetrabutylammonium hydrogen sulfate was heated at reflux with stirring and under N_2 atmosphere for 1 h. Excess acetonitrile was removed under reduced pressure and the remaining mixture was extracted with CH_2Cl_2. The solid residue was dissolved in water (10 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried with anhydrous K_2CO_3, filtered, and concentrated under reduced pressure to afford a viscous material. Silica gel chromatography (EtOAc/CH_2Cl_2; 4:1) yielded the free base (1.67 g; 74%) which was treated with ethanolic HCl to provide the hydrochloride salt of the desired Ia product (1.6 g; 87%).

Anal. Calcd. for $C_{20}H_{23}ClN_4 \cdot HCl$:			
Found:	C, 61.39; C, 61.49,	H, 6.19; H, 6.24;	N, 14.32 N, 14.35.

NMR (DMSO-d_6): 2.14 (2H, m); 2.80 (2H, t, 6.9 Hz); 3.18 (4H, m); 3.55 (4H, m); 4.36 (2H, d, 13.6 Hz); 6.82 (1H, d, 8.1 Hz); 6.91 (1H, d, 8.1 Hz); 7.05 (3H, m); 7.40 (1H, d, 9.2 Hz); 7.62 (2H, m); 11.00 (1H, bs); 11.55 (1H, bs).

IR (KBr): 740, 785, 950, 1130, 1260, 1440, 1590, 2600, 2920 and 3150 cm^{-1}.

Example 20

1-[3-(1H-indol-3-yl)-propyl]-4-[3-methoxy-2-pyridinyl]-piperazine dihydrochloride hydrate

A mixture of 3-(3-bromopropyl)indole (1.55 g), 1-(3-methoxy-2-pyridinyl)piperazine (2.51 g), micropulverized K_2CO_3 (1.79 g) and tetrabutylammonium hydrogen sulfate (0.11 g) in acetonitrile (100 mL) was heated at reflux under N_2 atmosphere for 3 h. The excess acetonitrile was removed under reduced pressure and water (15 mL) added to the concentrate. The aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL). The combined CH_2Cl_2 extracts were washed with sat. NaCl solution, dried with anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH; 95:5) of the residue yielded the free base which was treated with ethanolic HCl to yield the dihydrochloride salt of the desired Ia product (1.30 g; 45 %).

Anal. Calcd. for $C_{21}H_{26}N_4O \cdot 2\ HCl \cdot 0.95\ H_2O$:				
Found:	C, 57.27; C, 57.67;	H, 6.85; H, 6.82;	N, 12.72; N, 12.67;	H_2O, 3.89 H_2O, 4.18.

NMR (DMSO-d_6): 2.16 (2H, m); 2.78 (2H, t, 6.7 Hz); 3.20 (6H, m) 3.57 (2H, d, 12.5 Hz); 3.85 (3H, S); 4.08 (2H, d, 12.5 Hz); 4.80 (3H, bs); 7.02 (4H, m); 7.39 (2H, m); 7.56 (1H, d, 7.8 Hz); 7.81 (1H, dd, 5.8, 0.8 Hz); 10.85 (2H, bs).

IR (KBr): 760, 770, 1010, 1255, 1430, 1470, 1555, 1610, 2450, 2910 and 3210 cm^{-1}.

By Process 2. (Ia Products)

Example 21

1-[4-(1H-indol-3-yl)butyl]-4-(3-methoxy-2-pyridinyl)piperazine dihydrochloride

Borane-methyl sulfide complex (3.3 mL; 2.0 M THF soln.) was added dropwise to a THF (9 mL) solution containing 1-[4-(indol-3-yl)-1-oxobutyl]-4-(3-methoxy-2-pyridinyl)piperazine (IV; 1.0 g) at 0 °C while under N_2 atmosphere. After the addition was complete, the reaction was heated it reflux for 3 h. Upon cooling to 0 °C, MeOH (5 mL) was added and the reaction allowed to stand 20 h at 22 °C. The reaction was cooled to 0 °C and HCl gas introduced until a pH<2 was attained, after which the solution was gently refluxed for 1 h. The reaction was cooled, MeOH (10 mL) added, and, concentrated under reduced pressure. The residue was heated at reflux in 4 N acetic acid for 5 h. After cooling, the reaction was made basic with 10 N NaOH (pH>10) and extracted with Et_2O. The combined Et_2O extracts were dried with anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. Silica gel chromatography (EtOAc/MeOH; 97:3) afforded the free base which was treated with ethanolic HCl to provide the dihydrochloride of the desired Ia product (83 mg; 8%).

Anal. Calcd. for $C_{22}H_{28}N_4O \cdot 2\ HCl$:			
Found:	C, 60.42; C, 60.15;	H, 6.92; H, 6.78;	N, 12.81 N, 12.67.

NMR (DMSO-d_6): 1.73 (4H, m); 2.74 (2H, t, 6.6 Hz); 3.18 (4H, m); 3.33 (2H, m); 3.53 (2H, d, 12.0 Hz); 4.00 (v, m, bs: CH_2, H^+, H_2O); 3.85 (3H, s); 7.04 (3H, m); 7.16 (1H, d, 2.2 Hz); 7.34 (1H, d, 7.6 Hz); 7.42 (1H, dd, 8.0, 1.2 Hz); 7.52 (1H, d, 7.2 Hz), 7.83 (1H, dd, 5.2, 1.2 Hz).

IR (KBr): 740, 805, 1000, 1270, 1460, 1550, 1560, 1600, 2570, 2930 and 3250 cm^{-1}.

Example 22

4-[6-Chloro-2-pyridinyl]-1-[2-(1H-indol-3-yl)-propyl]piperazine

To a mixture of 1-(6-chloro-2-pyridyl)piperazine (1.418 g, 7.2 mmol), triethylamine hydrochloride (994 mg, 7.2 mmol) and $NaCNBH_3$ (1.512 g, 24 mmol) in 12 mL of dry tetrahydrofuran was added a solution of 3-(2-oxopropyl)indole (416 mg, 2.4 mmol) in 5 ml of tetrahydrofuran. The reaction mixture was vigorously stirred at room temperature under Ar for 17 h and then it was poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (x3). The organic phase was washed with H_2O (x2) and 0.1N HCl (25 mL) and then it was dried (Na_2SO_4) and evaporated to give a gum. Chromatography (SiO_2/CH_2Cl_2-acetonitrile = 1:1) of this gum gave the product (714 mg, 84%) as a white foam.

NMR ($CDCl_3$)

δ: 7.98 (br s, 1H), 7.64-7.59 (m, 1H), 7.43-7.343 (m, 2H), 7.24-7.08 (m, 2H), 7.06 (d, J = 2.3 Hz, 1H), 6.59 (d, J = 7.3 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 3.62-3.57 (m, 4H), 3.18-3.09 (m, 1H), 3.06-2.93 (m, 1H), 2.79-2.74 (m, 4H), 2.65 (dd, J = 13.5, 9.1 Hz, 1.03 (d, J = 6.5 Hz, 3H).

The hydrochloride was prepared by treating an ethereal solution of the product with anhydrous HCl. The resulting white fluffy solid was crystallized from ethanol-ether to give the hydrochloride salt (660 mg, 85%) as a white, micro-crystalline solid: m.p. 242-244 °C (dec).

By Process 3 (Ib and Ic Products)

Example 23

3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-methoxy-1H-indole

A solution of 5-methoxyindole (0.26 g, 1.8 mmole), 4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-cyclohexan-1-one (VIII; 0.50 g, 1.7 mmole), and pyrrolidine (0.5 mL) in ethanol (10 mL) was refluxed for 18 h. The solution was concentrated in vacuo and the residue chromatographed on silica gel using ethyl acetate as the eluent to give the desired product of formula Ib (0.59 g, 82%, m.p. 210-213 °C).

Anal. Calcd. for $C_{27}H_{27}ClN_4O$:			
Found:	C, 68.16; C, 68.00;	H, 6.44; H, 6.57;	N, 13.25 N, 12.97

NMR(DMSO-d_6): 1.52 (1H, m); 2.04 (1H, m), 2.22 (1H, m); 2.40 (2H, m); 2.64 (6H, m); 3.48 (4H, m); 3.75 (3H, s); 8.07 (1H, m); 6.63 (1H, d, 7.4 Hz); 6.75 (2H, m); 7.26 (3H, m); 7.53 (1H, dd, 7.9, 8.1 Hz); 10.91 (1H, bs).

IR (KBr): 780,800, 980, 1140, 1260, 1450, 1480, 1550, 1600, 2840 and 2920 cm^{-1}.

Example 24

3-[4-[4-(Substituted-2-pyridinyl)-1-piperazinyl]-1-cyclohexan-1-yl]-1H-indole

4-(1H-indol-3-yl)cyclohex-3-enone, ethylene ketal, XII

Indole (1.17 g, 10 mmol), 1.4-cyclohexanedione monoethylene ketal (1.95 g, 12.5 mmol), and pyrrolidine (1.77 g, 25 mmol, 2.1 mL) were refluxed in ethanol (50 mL) for 3 days. The solution was concentrated in vacuo. The residue was washed with ethyl acetate (30 mL) and the solid product was collected and dried (yield: 2.05 g, 80%). The product was recrystallized from methanol (20 mL) to give compound XII as a white powder (1.75 g).

4-(1H-indol-3-yl)cyclohexanone, XI

Compound XII (1.75 g, 6.9 mmol) was hydrogenated for 18 h at 60 psi using 10% Pd/C (0.15 g). The mixture was filtered and the filtrate concentrated in vacuo. The residue was refluxed for 18 h in acetone (150 mL) with water (10 mL) and p-toluene sulfonic acid (0.10 g). Sodium carbonate (5.0 g) was added and the mixture refluxed for 30 min. The mixture was cooled and filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel using ethyl acetate as the eluent to give the XI desired product (1.29 g, 88%).

3-[4-(4-(Substituted-2-pyridinyl)-1-piperazinyl)-1-cyclohexyl]-1H-indole, Ic

A mixture of compound II (10 mmol), the desired substituted-pyridinyl piperazine (III; 10 mmol), and titanium(IV) isopropoxide (3.72 mL, 12.5 mmol) would be remaining ketone band (gentle heating may be required). The viscous solution would then be diluted with ethanol (10-20 mL) and sodium cyanoborohydride (0.42 g, 6.7 mmol) added. After stirring for 20 hr, water (2 mL) would be added and the resulting inorganic precipitate filtered and washed with ethanol. The filtrate could then be concentrated in vacuo and the crude product purified by chromatography on silica gel. Alternately, cyclohexenyl products of Formula Ib may be hydrogenated to yield products of Formula Ic in cases where other substituents on the precursor molecule are stable to the hydrogenation process.

Compound preparation data for these and other Formula I compounds, prepared in a manner similar to the above procedures, is shown in Table 1. Selection of appropriate starting materials and intermediates as well as adjustments of the procedures would be well within the skill of one skilled in the art.

Table 1

Formula I Compounds

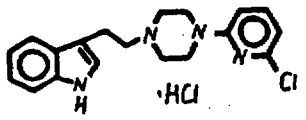
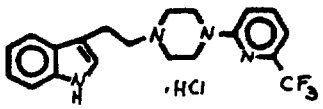
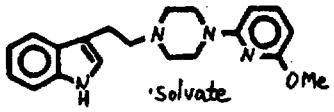
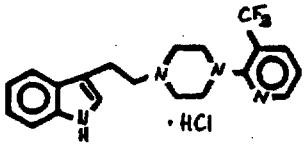
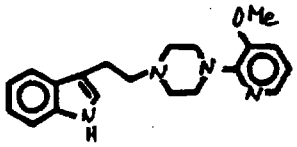
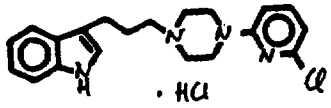
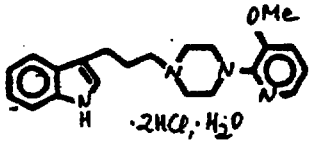
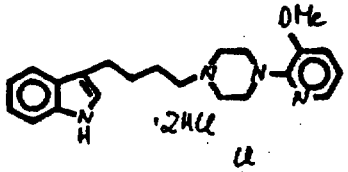
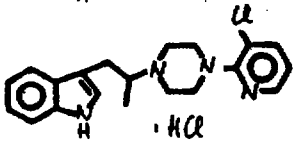
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14		77	250-252	EtOH
15		68	206-208	EtOH
16		89	60-85	EtOH
17		80	242-243	EtOH
18		44	138-140	EtOH
19		87	221-222	EtOH
20		45	216-219	EtOH
21		23	228-230	EtOH
22				

Table 1 (continued)

Formula I Compounds

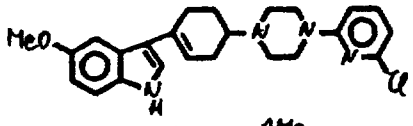
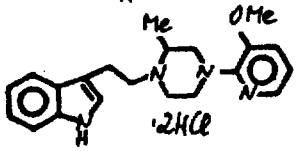
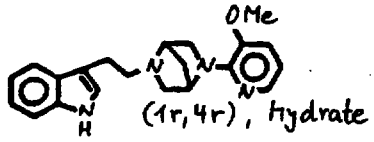
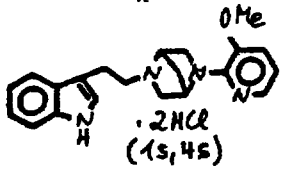
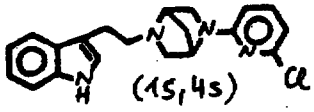
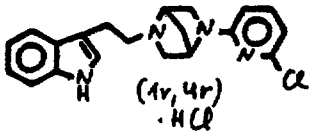
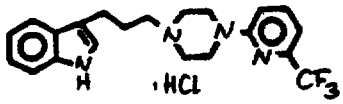
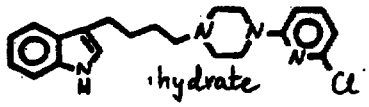
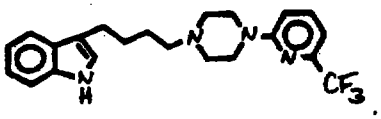
Ex. No.	Structure	%Yield	MP(°C)	Cryst. Sol.
23		82	210-213	EtOAc
25		11	155-194	EtOH
26		4	55-60	EtOH
27		43	234-236	iPrOH/EtOH/ THF
28		67	239-241	iPrOH/EtOH
29		53	239-242	iPrOH/EtOH
30		14	212-214	Hex/CH_2Cl_2
31		-1	99-101	EtOH
32		50	83-86	Hex/CH_2Cl_2

Table 1 (continued)

Formula I Compounds

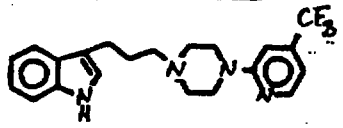
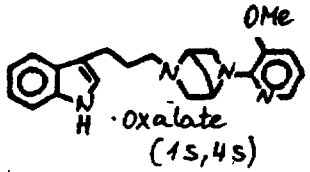
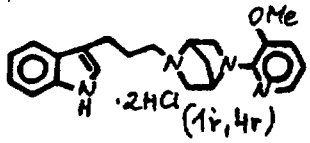
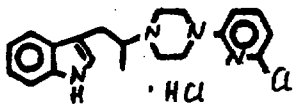
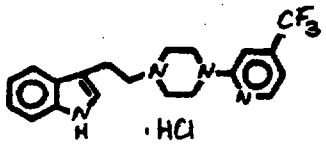
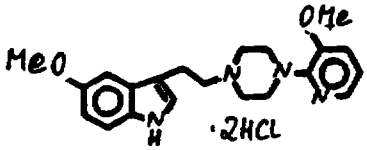
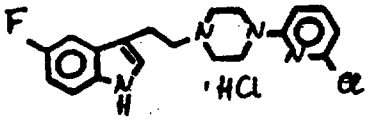
Ex. No.	Structure	%Yield	MP(°C)	Cryst. Sol.
33		28	90-93	EtOH
34		22	103-125	MeOH
35		64	155-186	EtOH
36		85	242-244	Et_2O/CH_3CN/ EtOH
37		21	150-225	EtOH
38		35	182-185	MeOH/EtOAc
39		36	140-142	EtOAc
40		19	195-196	$MeOH/Et_2O$
41		23	205-208	MeOH/EtOAc

Table 1 (continued)

Formula I Compounds

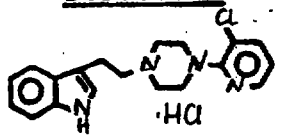
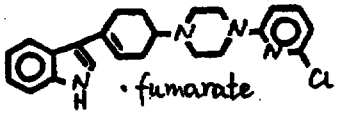
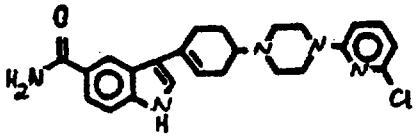
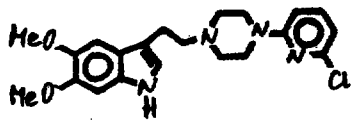
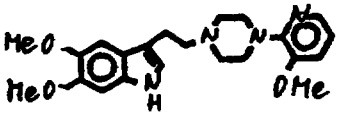
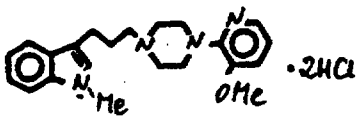
Ex. No.	Structure	%Yield	MP(°C)	Cryst. Sol.
42		42	213-216	EtOH
43		43	115-116	Ethyl acetate/ hexane
44		31	140-142	Ethyl acetate/ hexane
45		66	226-230	MeOH
46		63	225-230	10%MeOH/ EtOAc
47		46	125-127	Ethyl acetate
48		45	137-139	Ethyl acetate
49		42	160-163	Ethyl acetate
50		92	187-189	EtOH

Table 1 (continued)

Formula I Compounds

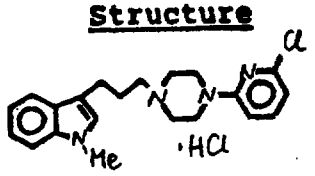
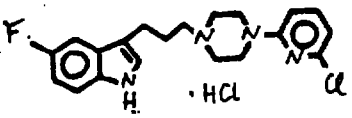
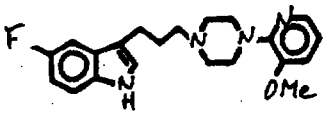
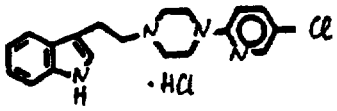
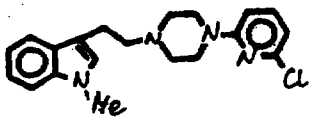
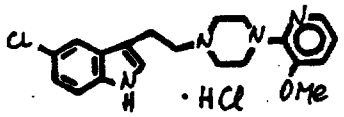
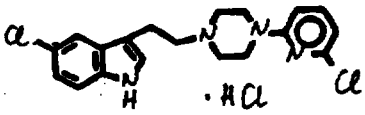
Ex. No.	Structure	%Yield	MP(°C)	Cryst. Sol.
51		83	200-203	EtOH
52		81	210-212	EtOH
53		72	127	CH_2Cl_2/Et_2O/ hexane
54		38	253-255	EtOH
55		72	115-116	Ethyl acetate
56		41	205-207	Ethyl acetate
57		40	238-242	MeOH/Et_2O

Table 2

Biological Activities of Formula I Compounds: Inhibition of Serotonin Uptake (in vitro)			
Ex. No.	IC_{50}(nM)	Ex. No.	IC_{50}(nM)
14	74	36	75
15	73	37	386
16	88	38	11
17	37	39	0.2
18	13	40	177
19	98	41	2.8
20	1.1	42	520
21	58	43	73
23	99	44	560
25	8.6	45	100
26	106	46	27
27	12.5	47	24
28	77	48	127
29	106	50	3.7
30	192	51	86
31	27	54	30
32	259	55	126
33	105		
34	5.6		
35	152		

Additional Detailed Description of the Invention

Some additional compounds of Formula I have been made, tested and found to have useful CNS properties, particularly antidepressant properties. The additional compounds were prepared by employing the synthetic processes described hereinabove, using alterations which would be apparent to a skilled chemist in order to produce the desired product compound. Some additional examples are given here for further guidance.

Additional Intermediate Compounds.

Compounds of Formula III

Example 58

1-(6-Chloro-2-pyridinyl)-2-methylpiperazine

A mixture of 2-methylpiperazine (21.31 g), 2,6-dichloropyridine (10.0 g) and micropulverized K_2CO_3 - (27.99 g) in CH_3CN (200 mL) gas heated at reflux under nitrogen atmosphere for 24 h. The reaction was filtered and the filtrate concentrated under reduced pressure. The concentrate was dissolved in CH_2Cl_2 and extracted with 5% $NaHCO_3$ and water. The organic phase was dried with K_2CO_3, filtered and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH; 96:4:0.4) of the residue yielded product, (13.34 g, 93%).

Example 59

1-(3-Methoxy-2-pyridinyl)-2-methylpiperazine

A mixture of 2-methylpiperazine (6.66 g) and 2-bromo-3-methoxypyridine (2.5 g) was heated in an autoclave at 100 C for 24 h. The reaction mixture was dissolved in CH_2Cl_2 and extracted with 5% $NaHCO_3$ and water. The organic phase was dried with K_2CO_3, filtered, and concentrated under reduced pressure.

Silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH; 92:8:0.8) of the residue yielded the product (2.28 g, 83 %).

Example 60

1-(5-Chloro-3-methoxy-2-pyridinyl)piperazine

a) 2-bromo-5-chloro-3-pyridinol

A solution of bromine (12.35 g) in 10% NaOH (70 ml) was added dropwise with stirring to a solution of 5-chloro-3-pyridinol (10.00 g) in 10% NaOH (70 ml). After the addition was complete, the reaction was stirred at 22 °C for 20 h. The reaction was cooled to 0 °C and acidified to pH 5.3 with concentrated HCl (aq). The precipitate was filtered and dried under vacuum for 60 h to afford a) (15.66 g, 97 %).

b) 2-bromo-5-chloro-3-methoxypyridine

To a stirred mixture of 2-bromo-5-chloro-3-pyridinol (15.66 g) and pulverized KOH (16.79 g) in DMSO (100 ml) at 55 - 60 °C was added dropwise a solution of CH_3I (13.27 g) in DMSO (35 ml) while under nitrogen atmosphere. After the addition was complete, the reaction was maintained at 55 - 60 °C for 1 h. The reaction was extracted with Et_2O (3 x 150 ml) and the combined Et_2O extracts were treated in turn with 1N NaOH (150 ml), water (150 ml), 1N HCl (150 ml), water (150 ml) and a saturated NaCl solution (150 ml). The organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to yield a solid material. Recrystallization of the solid from hexane afforded b) (3.52 g, 21 %).

c) 1-(5-chloro-3-methoxy-2-pyridinyl)piperazine

Anhydrous piperazine (13.41 g) and 2-bromo-5-chloro-3-methoxypridine (3.50 g) were heated in an autoclave at 100 C for 20 h. The mixture was dissolved in water (10 mL) and extracted with CH_2Cl_2 (3 X 100 mL). The combined organic extracts were washed with a saturated NaCl solution, dried with K_2CO_3, filtered, and concentrated under reduced pressure. Silica gel chromatography (CH_2Cl_2/MeOH; 90:10) of the residue yielded product (1.17 g, 33%).

Compounds of Formula V

Example 61

3-(2-Bromoethyl)-1-methylindole

a) Methyl 1-methylindole-3-acetate

A dispersion of 35% KH in oil (21.0 g, 0.18 mol) was washed free of oil with dry pentane under an Ar atmosphere. To a suspension of the resulting solid in 100 ml of dry dimethylformamide was added a solution of indole-3-acetic acid (10.5 g, 0.060 mol) in 60 ml of dimethylformamide, dropwise at -20 °C under Ar. The mixture was stirred at the same temperature for 2 h and then CH_3I (12.0 ml, 0.19 mol) was added dropwise. Stirring was continued at -20 ° to 10 °C for 2 1/2 h and then the mixture was stored at 5 °C for 16 h. Ether was then added and the mixture was washed (H_20, brine), dried (Na_2SO_4) and evaporated to give an orange oil. Flash chromatography (SiO_2/10-20% ethyl acetate-hexane x 2) of this oil afforded the product (5.25 g, 43%) as an oil: IR (neat) 1745 cm^{-1}; ^{1}Hnmr (80 MHz, $CDCl_3$) δ 7.75-7.55 (m, 1H), 7.40-7.07 (m, 4H), 3.83 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H).

b) 3-(2-Hydroxyethyl)-1-methylindole

To a suspension of $LiAlH_4$ (2.0 g, 0.052 mol) in 50 mL of dry tetrahydrofuran was added dropwise a solution of methyl 1-methylindole-3-acetate (5.25 g, 0.026 mol) in 70 mL of dry tetrahydrofuran at -10 °C under Ar. The mixture was refluxed for 1 h and then it was cooled at 0 °C and quenched by the sequential addition of 2 mL of H_2O, 2 mL of 15% aqueous NaOH and finally 6 mL of H_2O. The resulting slurry was filtered and the filter cake was washed with additional tetrahydrofuran. Evaporation of the filtrate gave the product (4.0 g, 89%) as an oil which was used without further purification.

c) 3-(2-Bromoethyl)-1-methylindole

To a solution of 1-methyl-3-(2-hydroxyethyl)indole (4.00 g, 0.023 mol) in 50 mL of acetonitrile at -20 °C under Ar was added a solution of CBr_4 (10.16 g, 0.031 mol) in 25 mL of acetonitrile, followed by a solution of triphenylphosphine (8.00 g, 0.031 mol) in 125 mL of acetonitrile. The mixture was stirred and allowed to warm to 0 °C over 2 h. The resulting mixture was evaporated and the residue was chromatographed (SiO_2/hexane, then ethyl acetate-hexane = 1:4) to give the product (4.00 g, 74%) as a brown oil: IR (neat) 2940, 1617, 1552 cm^{-1}; ^{1}Hnmr (200 MHz, $CDCl_3$) δ 7.58 (d, J = 7.6 Hz, 1H), 7.33-7.09 (m, 3H), 6.95 (s, 1H), 3.77 (s, 3H), 3.62 (t, J = 7.9 Hz, 2H), 3.32 (t, J = 7.7 Hz, 2H).

Example 62

3-[1-Methyl-3-(p-toluenesulfonyloxy)propyl]indole

To a suspension of $LiAlH_4$ (1.50 g, 39 mmol) in 100 mL of dry THF at -10 °C under Ar was added a solution of ethyl 3-(3-indolyl)-3-methylpropionate[1] (7.00 g, 30 mmol) in 50 mL of THF. The mixture was stirred at room temperature for 3 h and then it was quenched at 0 °C with 2 mL of H_2O. The resulting slurry was filtered and the filter cake was washed with THF. The filtrate was then dried (Na_2SO_4) and evaporated to give the intermediate VI product, 3-(1-methyl-3-hydroxypropyl)indole (5.05 g, 88%) as an oil: IR (neat) 3420, 3300 cm^{-1}.

To an ice cold solution of 3-(1-methyl-3-hydroxypropyl)indole (5.00 g, 0.026 mol) in 100 mL of CH_2Cl_2 was added triethylamine (4.1 mL, 0.03 mol), p-toluenesulfonyl chloride (5.50 g, 0.029 mol) and 4-N,N-dimethylaminopyridine (DMAP) (0.6 g). The mixture was stirred at room temperature under Ar for 18 h and then it was evaporated and the residue was chromatographed (SiO_2/ethyl acetate-hexane = 1:9, then ethyl acetate) to give the product (7.75 g, 86%) as a light brown gum: IR (neat) 3420, 1357, 1175 cm^{-1}.

1. Oikawa, et. al., Tetrahedron Lett., 1759 (1978).

Additional Formula I Compounds.

Example 36 - Alternate Preparation

3-[2-[4-(6-chloro-2-pyridyl)-1-piperazinyl]propyl]-indole

To a mixture of 1-(6-chloro-2-pyridyl)piperazine (1.418 g, 7.2 mmol), triethylamine hydrochloride (994 mg, 7.2 mmol) and $NaCNCH_3$ (1.512 g, 24 mmol) in 12 mL of dry tetrahydrofuran was added a solution of 3-(2-oxopropyl)indole (416 mg, 2.4 mmol) in 5 mL of tetrahydrofuran. The reaction mixture was vigorously stirred at room temperature under Ar for 17 h and then it was poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (x3). The organic phase was washed with H_2O (x2) and 0.1 N HCL (25 mL) and then it was dried (Na_2SO_4) and evaporated to give a gum. Chromatography (SiO_2/CH_2Cl_2-acetonitrile = 1:1) of this gum gave the product (714 mg, 84%) as a white foam: ^{1}Hnmr (200 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.64-7.59 (m, 1H), 7.43-7.343 (m, 2H), 7.24-7.08 (m, 2H), 7.06 (d, J = 2.3 Hz, 1H), 6.59 (d, J = 7.3 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 3.62-3.57 (m, 4H), 3.18-3.09 (m, 1H), 3.06-2.93 (m, 1H), 2.79-2.74 (m, 4H), 2.65 (dd, J = 13.5, 9.1 Hz, 1H), 1.03 (d, J = 6.5 Hz, 3H). The hydrochloride salt was prepared by treating an ethereal solution of the product with anhydrous HCl. The resulting white fluffy solid was crystallized from ethanol-ether to give the hydrochloride salt (660 mg, 85%) as a white, micro-crystalline solid: m.p. 242-244 °C (dec); IR (KBr) 3430, 3190, 1590 cm^{-1}.

Additional Formula I compounds which have been prepared by appropriate modifications of the reaction schemes and procedures given hereinabove, are displayed in Table 1A.

Table 1A

Additional Formula I Compounds

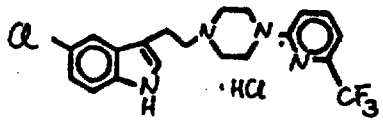
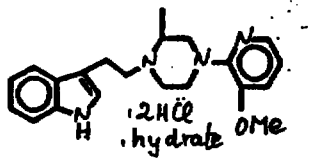
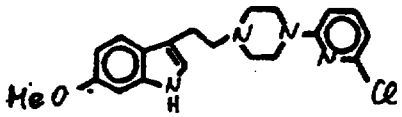
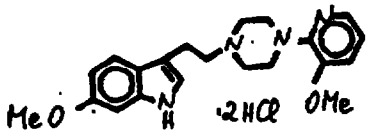
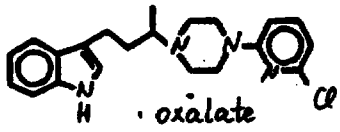
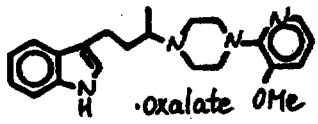
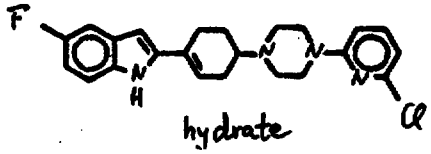
Ex. No.	Structure	% Yield	MP(°C)	Cryst. Sol.
63		49	158-62	Me_2CO-Et_2O
64		53	174-85	EtOH-ET_2O
65		69	103-05	EtOAc
66		41	218	MeOH-Et_2O
67		44	110-115	MeOH-THF
68		30	55	Et_2O
69		43	122-25	EtOAc
70		15	168-170	EtOAc

Table 1A (cont.)
Additional Formula I Compounds

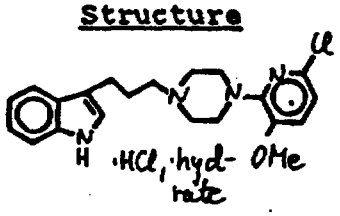
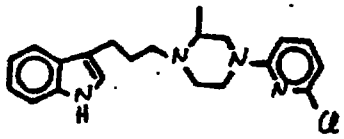
Ex. No.	Structure	% Yield	MP(°C)	Cryst. Sol.
71		65	194-98	EtOH
72		65	132-35	EtOH

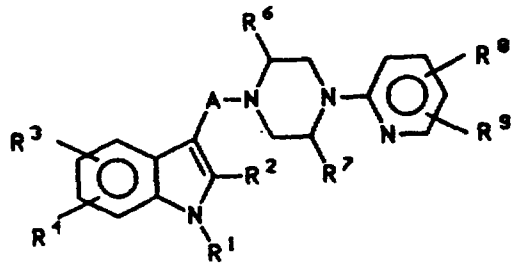
Table 2A

Biological Activities of Some Additional Formula I Compounds Inhibition of Serotonin Uptake (in vitro)			
Ex. No.	$1C_{50}$(nM)	Ex. No.	$1C_{50}$(nM)
56	<1	67	142
57	166	68	36.7
63	437	69	479
64	<1	70	141
65	134	71	4.9
66	35.9	72	18.7

Claims

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

1. A compound of Formula I and the pharmaceutically acceptable acid addition salts thereof,



(I)

wherein

R^1 and R^2 are independently selected from C_{1-4} alkyl or hydrogen;

R^3, R^4, R^8 and R^9 are independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, carbamide, halogen, trifluoromethyl and thio-C_{1-4} alkyl, with the proviso that R^8 and R^9 cannot both be hydrogen at the same time;

A is a C_{5-7} cycloalkanyl or cycloalkenyl ring, or

A is

Table 1A (cont.)

Additional Formula I Compounds

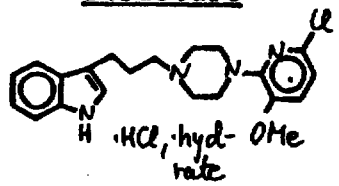
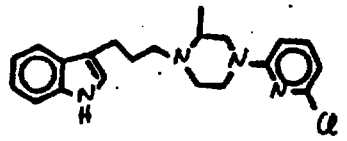
Ex. No.	Structure	% Yield	MP(°C)	Cryst. Sol.
71		65	194-98	EtOH
72		65	132-35	EtOH

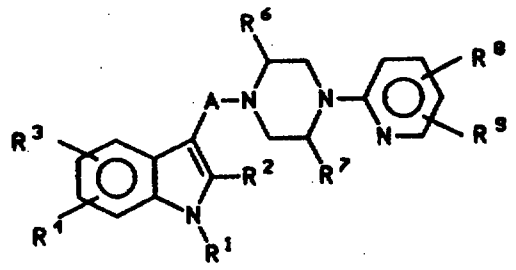
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Ex. No.	$1C_{50}$(nM)	Ex. No.	$1C_{50}$(nM)
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1. A compound of Formula I and the pharmaceutically acceptable acid addition salts thereof,



(I)

wherein

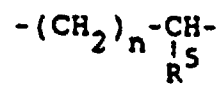
R^1 and R^2 are independently selected from C_{1-4} alkyl or hydrogen;

R^3, R^4, R^8 and R^9 are independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, carbamide, halogen, trifluoromethyl and thio-C_{1-4} alkyl, with the proviso that R^8 and R^9 cannot both be hydrogen at the same time;

A is a C_{5-7} cycloalkanyl or cycloalkenyl ring, or

A is

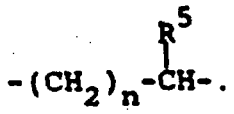




wherein n is an integer from 1 to 3 and R^5 is the same as R^1; and
R^6 and R^7 are independently selected from hydrogen, methyl or R^6 and R^7 can be taken together as a methylene bridge.

2. The compound of claim 1 wherein A is a C_{5-7} cycloalkanyl or cycloalkenyl ring.

3. The compound of claim 1 wherein A is



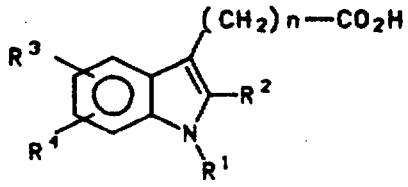
4. The compound of claim 1 wherein R^6 and R^7 are selected from hydrogen or methyl.

5. The compound of claim 1 wherein R^6 and R^7 are taken together as a methylene bridge.

6. The compounds of claim 1: 1-[2-(1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;
1-[2-(1H-indol-3-yl)ethyl]-4-(3-trifluoromethyl-2-pyridinyl)piperazine ;
1-[2-(1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)-2-methylpiperazine ;
1-[2-(1H-indol-3-yl)ethyl]-5-(3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptane ;
1-[2-(1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazine ;
1-[2-(1H-indol-3-yl)ethyl]-4-(6-methoxy-2-pyridinyl)piperazine ;
1-[2-(1H-indol-3-yl)ethyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazobicyclo[2.2.1] heptane ;
1-[2-(1H-indol-3-yl)propyl]-4-(3-methoxy-2-pyridinyl)piperazine ;
1-[3-(1H-indol-3-yl)propyl]-4-(6-chloro-2-pyridinyl)piperazine ;
1-[4-(1H-indol-3-yl)butyl]-4-(3-methoxy-2-pyridinyl)piperazine ;
1-[2-(1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;
2-[2-(1H-indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1S,4S)-2,5-diazobicyclo[2.2.1] heptane ;
2-[2-(1H-indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptane ;
1-[3-(1H-indol-3-yl)propyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;
1-[4-(1H-indol-3-yl)butyl]-4-(6-chloro-2-pyridinyl)piperazine ;
1-[4-(1H-indol-3-yl)butyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;
1-[3-(1H-indol-3-yl)propyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazine ;
2-[3-(1H-indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptane ;
2-[3-(1H-indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazobicyclo[2.2.1] heptane ;
1-[2-(1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)-2-methylpiperazine ;
1-[2-(1H-indol-3-yl)ethyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazine ;
1-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;
1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;
1-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazine ;
1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazine ;
1-[2-(1H-indol-3-yl)-ethyl]-4-(3-chloro-2-pyridinyl)piperazine ;
1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;
1-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-methoxyindole ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indole;
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indole-5-carboxamide ;
1-[2-(N-methyl-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;
1-[2-(5,6-dimethoxy-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;
1-[2-(5,6-dimethoxy-1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazine ;
1-[3-(N-methyl-1H-indol-3-yl)-propyl]-4-(3-methoxy-2-pyridinyl)piperazine ;

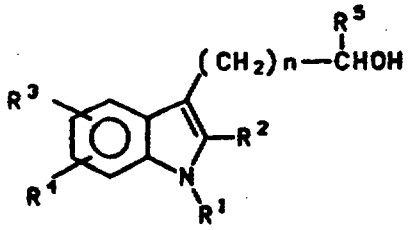
1-[3-(N-methyl-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)piperazine ;
1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)piperazine ;
1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(3-methoxy-2-pyridinyl)piperazine ;
1-[2-(1H-indol-3-yl)ethyl]-4-(5-chloro-2-pyridinyl)piperazine ;
1-[2-[N-methyl-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazine ;
1-[2-(5-chloro-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;
1-[2-(5-chloro-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazine ;
1-[2-(5-chloro-1H-indol-3-yl) ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;
1-[2-(1H-indol-3-yl)ethyl] -4-(3-methoxy-2-pyridinyl)-2-methyl-piperazine ;
4-(6-chloro-2-pyridinyl)-1-[2-(6-methoxy-1H-indol-3-yl)ethyl]-piperazine ;
1-[2-6-methoxy-1H-indol-3-yl) ethyl]-4-(3-methoxy-2-pyridinyl)-piperazine ;
1-[3-(1H-indol-3-yl)-3-methylpropyl]-4-(6-chloro-2-pyridinyl)-piperazine ;
1-[3-(1H-indol-3-yl)-3-methylpropyl]-4-(3-methoxy-2-pyridinyl)-piperazine ;
1-[2-(5,6-dimethoxy-1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-fluoro-1H-indole ;
4-(5-chloro-3-methoxy-2-pyridinyl) -1-[3-(1H-indol-3-yl)propyl]-piperazine hydrochloride ;
4-(6-chloro-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]-2-methyl-piperazine ;

7. A process for preparing the compounds of claims 1 to 6 characterized in that
A) a compound of the general formula II:



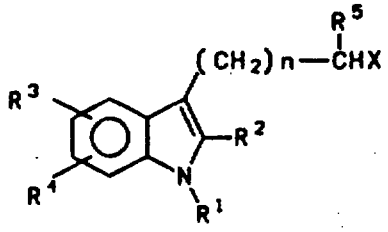
(II)

is reacted with a compound of the general formula R^5-M, wherein M represents a metalloid species, to obtain a compound of the general formula VI:



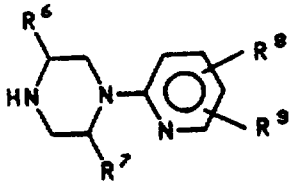
(VI)

a compound of the general formula VI is reacted with a reagent Y-X, wherein X is a leaving group and Y is a hydrogen atom or a counter ion, to obtain a compound of the general formula V:



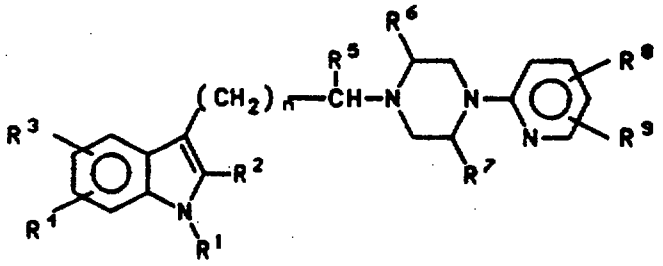
(V)

a compound of the general formula V is reacted with a compound of the general formula III:



(III)

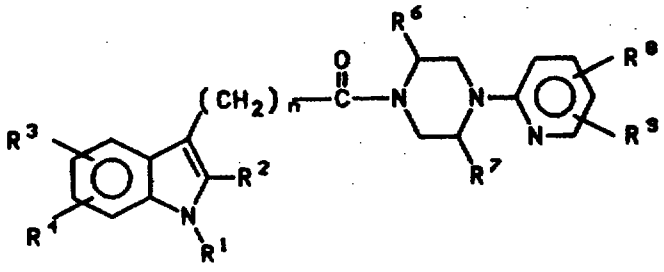
to obtain a compound of the general formula Ia



(Ia)

or

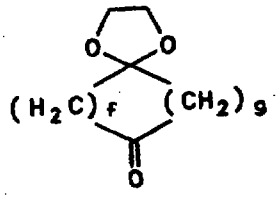
B) a compound of the general formula II or an active equivalent thereof is reacted with a compound of the general formula III to obtain a compound of the general formula IV:



(IV)

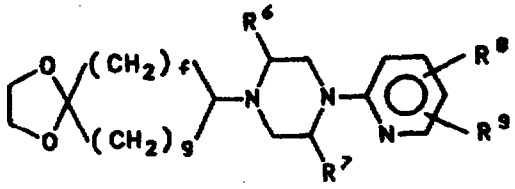
a compound of the general formula IV is reacted with R^5-M, wherein R^5 is defined as above, to obtain a compound of the general formula Ia, or

C) a compound of the general formula III is reductively alkylated with a compound of the general formula X



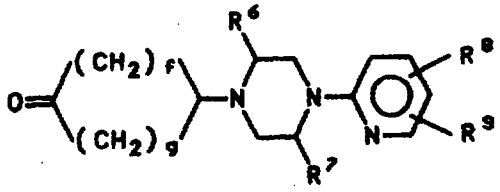
(X)

wherein f and g are integers from 0 to 5 with the proviso that f + g must be equal to 3, 4 or 5, to give a compound of the general formula IX:



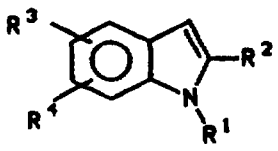
(IX)

a compound of the general formula IX is deprotected to produce a compound of the general formula VIII



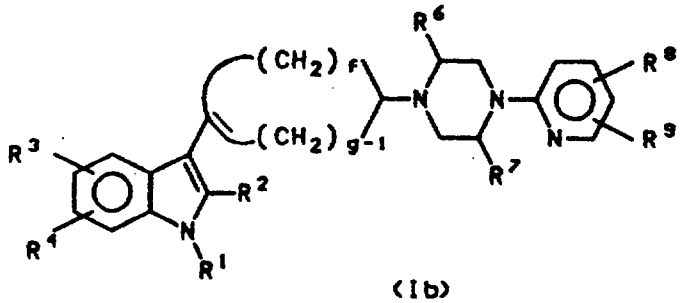
(VIII)

a compound of the general formula VIII is condensed with a compound of the general formula VII



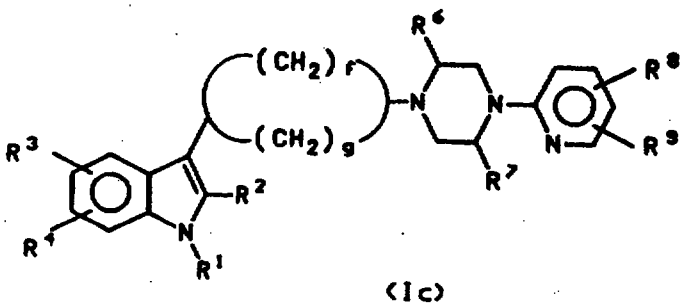
(VII)

to give a compound of the general formula Ib



(Ib)

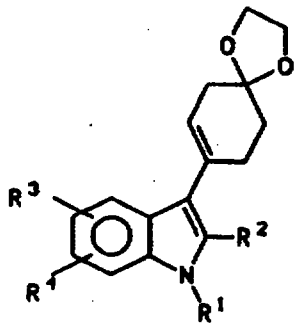
and , if desired, a compound of the general formula Ib is reduced to a compound of the general formula Ic:



(Ic)

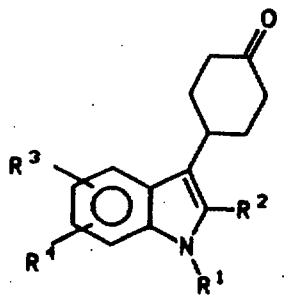
or

D) a compound of the general formula VIII is condensed with a compound of the general formula X to give a compound of the general formula XII



(XII)

a compound of the general formula XII is reduced and deketalized to a compound of the general formula XI:



(XI)

a compound of the general formula XI is condensed with a compound of the general formula III to give a compound of the general formula Ic,
the symbols R^1 through R^9 and n being defined as in claim 1, and
if desired, a so obtained compound of formula I is converted to a pharmaceutically acceptable acid addition salt thereof.

8. A pharmaceutical composition comprising at least one compound of claims 1 to 6, optionally together with a pharmaceutical carrier and/or adjuvant.

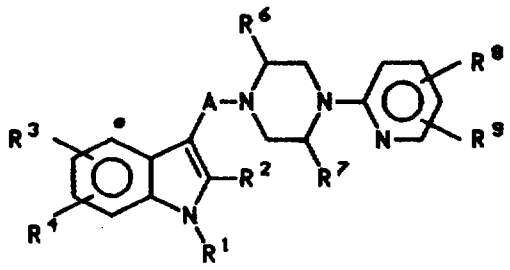
9. A pharmaceutical composition of claim 8 in dosage unit form suitable for systemic administration to a mammalian host comprising a pharmaceutical carrier and from about 1 to 500 mg of at least one compound of claims 1 to 6.

10. A process for preparing the pharmaceutical compositions of claims 8 or 9 which comprises providing at least one compound of claims 1 to 6 in a form suitable for systemic administration, preferably in dosage unit form, and optionally incorporated into a pharmaceutical carrier.

11. The use of at least one compound of claims 1 to 6 for preparing a pharmaceutical composition for ameliorating an undesirable state of depression in a mammal.

Claims for the following Contracting State : ES

1. A process for preparing a compound of formula I and the pharmaceutically acceptable acid addition salts thereof,



(I)

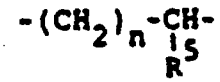
wherein

R^1 and R^2 are independently selected from C_{1-4} alkyl or hydrogen;

R^3, R^4, R^8 and R^9 are independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, carbamide, halogen, trifluoromethyl and thio-C_{1-4} alkyl, with the proviso that R^8 and R^9 cannot both be hydrogen at the same time;

A is a C_{5-7} cycloalkanyl or cycloalkenyl ring, or

A is

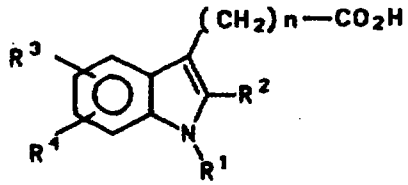


wherein n is an integer from 1 to 3 and R^5 is the same as R^1; and

R^6 and R^7 are independently selected from hydrogen, methyl or R^6 and R^7 can be taken together as a methylene bridge,

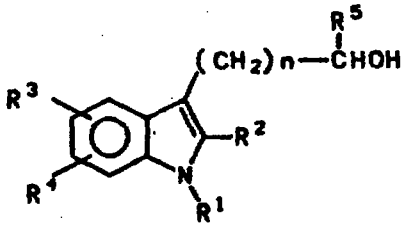
characterized in that

A) a compound of the general formula II:



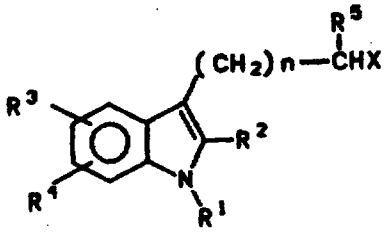
(II)

is reacted with a compound of the general formula R^5-M, wherein M represents a metalloid species, to obtain a compound of the general formula VI:



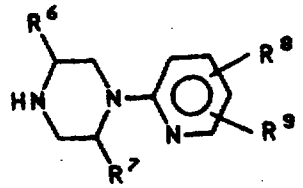
(VI)

a compound of the general formula VI is reacted with a reagent Y-X, wherein X is a leaving group and Y is a hydrogen atom or a counter ion, to obtain a compound of the general formula V:



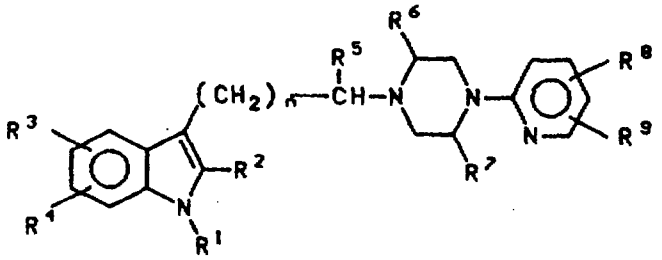
(V)

a compound of the general formula V is reacted with a compound of the general formula III:



(III)

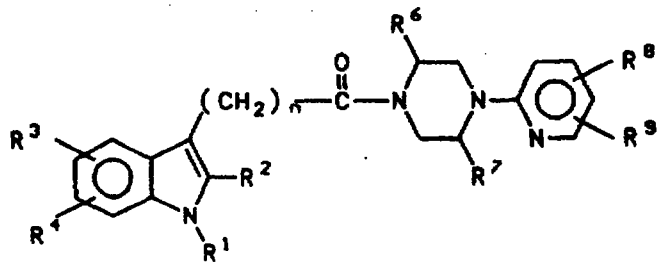
to obtain a compound of the general formula Ia



(Ia)

or

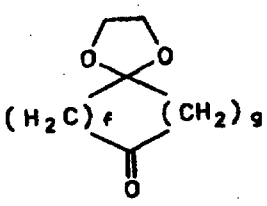
B) a compound of the general formula II or an active equivalent thereof is reacted with a compound of the general formula III to obtain a compound of the general formula IV:



(IV)

a compound of the general formula IV is reacted with R^5-M, wherein R^5 is defined as above, to obtain a compound of the general formula Ia, or

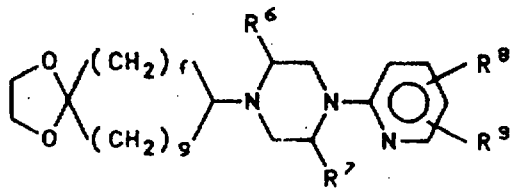
C) a compound of the general formula III is reductively alkylated with a compound of the general formula X



(X)

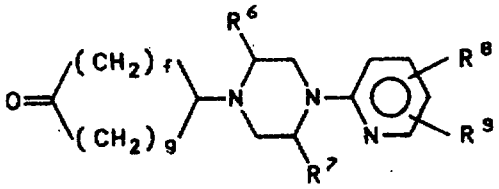
wherein f and g are integers from 0 to 5 with the proviso that f + g must be equal to 3, 4 or 5, to

give a compound of the general formula IX:



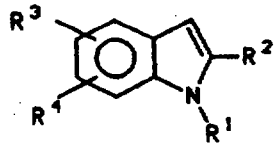
(IX)

a compound of the general formula IX is deprotected to produce a compound of the general formula VIII



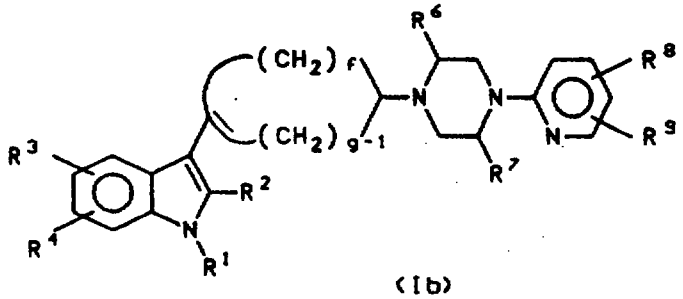
(VIII)

a compound of the general formula VIII is condensed with a compound of the general formula VII



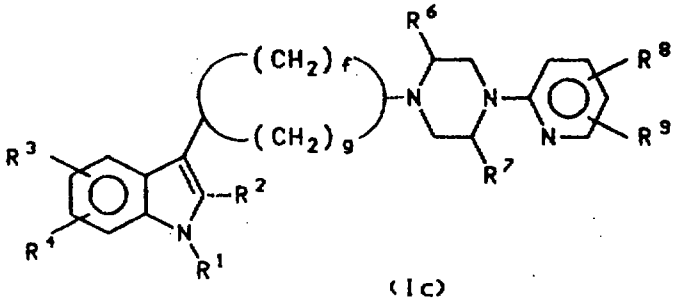
(VII)

to give a compound of the general formula Ib



(Ib)

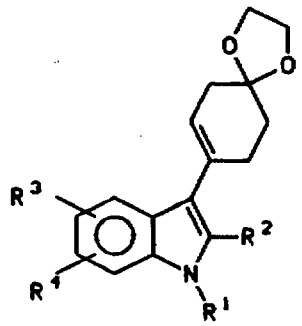
and, if desired, a compound of the general formula Ib is reduced to a compound of the general formula Ic:



(Ic)

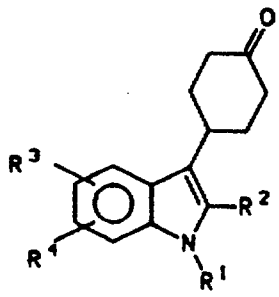
or

D) a compound of the general formula VIII is condensed with a compound of the general formula X to give a compound of the general formula XII



(XII)

a compound of the general formula XII is reduced and deketalized to a compound of the general formula XI:



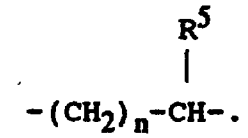
(XI)

a compound of the general formula XI is condensed with a compound of the general formula III to give a compound of the general formula Ic,
the symbols R^1 through R^9 and n being defined as in claim 1, and,
if desired, a so obtained compound of formula I is converted to a pharmaceutically aceptable acid addition salt thereof.

2. A process as claimed in claim 1 wherein A is a C_{5-7} cycloalkanyl or cycloalkenyl ring.

* C L M S *

3. A process as claimed in claim 1 wherein A is



4. A process as claimed in claim 1 wherein R^6 and R^7 are selected from hydrogen or methyl.

5. A process as claimed in claim 1 wherein R^6 and R^7 are taken together as a methylene bridge.

6. A process as claimed in claim 1 for the preparation of:
1-[2-(1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl) piperazine;
1-[2-(1H-indol-3-yl)ethyl]-4-(3-trifluoromethyl-2-pyridinyl)piperazine;
1-[2-(1H-indol-3-yl)ethyl]-4- (3-methoxy-2-pyridinyl)-2-methylpiperazine;
1-[2-(1H-indol-3-yl)ethyl]-5- (3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1]heptane;
1-[2-(1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl) piperazine;
1-[2-(1H-indol-3-yl)ethyl]-4-(6-methoxy-2-pyridinyl) piperazine;
1-[2-(1H-indol-3-yl)ethyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane;
1-[3-(1H-indol-3-yl)propyl]-4-(3-methoxy-2-pyridinyl) piperazine;
1-[3-(1H-indol-3-yl)propyl]-4-(6-chloro-2-pyridinyl) piperazine;
1-[4-(1H-indol-3-yl)butyl]-4-(3-methoxy-2-pyridinyl) piperazine;
1-[2-(1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;
2-[2-(1H-indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane;
2-[2-(1H-indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1]heptane;
1-[3-(1H-indol-3-yl)propyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;
1-[4-(1H-indol-3-yl)butyl]-4-(6-chloro-2-pyridinyl) piperazine;
1-[4-(1H-indol-3-yl)butyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;
1-[3-(1H-indol-3-yl)propyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazine;
2-[3-(1H-indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane;
2-[3-(1H-indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1]heptane;
1-[2-(1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)-2-methylpiperazine;
1-[2-(1H-indol-3-yl)ethyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazine;
1-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[2-(1H-indol-3-yl)-ethyl]-4-(3-chloro-2-pyridinyl) piperazine;
1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl -2-pyridinyl)piperazine;
1-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-methoxyindole;
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indole;
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indole-5-carboxamide;
1-[2-(N-methyl-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(5,6-dimethoxy-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(5,6-dimethoxy-1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[3-(N-methyl-1H-indol-3-yl)-propyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[3-(N-methyl-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(1H-indol-3-yl)ethyl]-4-(5-chloro-2-pyridinyl)piperazine;
1-[2-[N-methyl-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[2-(5-chloro-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(5-chloro-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[2-(5-chloro-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;

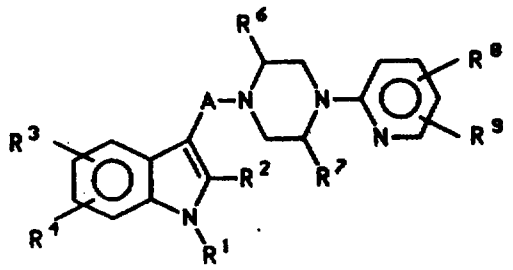
1-[2-(1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)-2-methyl-piperazine;
4-(6-chloro-2-pyridinyl)-1-[2-(6-methoxy-1H-indol-3-yl) ethyl]-piperazine;
1-[2-6-methoxy-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)-piperazine;
1-[3-(1H-indol-3-yl)-3-methyl-propyl]-4-(6-chloro-2-pyridinyl)-piperazine;
1-[3-(1H-indol-3-yl)-3-methyl-propyl]-4-(3-methoxy-2-pyridinyl)-piperazine;
1-[2-(5,6-dimethoxy-1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-fluoro-1H-indole;
4-(5-chloro-3-methoxy-2-pyridinyl)-1-[3-(1H-indol-3-yl) propyl]-piperazine hydrochloride;
4-(6-chloro-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]-2-methyl-piperazine;

7. A process for preparing a pharmaceutical composition which comprises providing at least one compound of claims 1 to 6 in a form suitable for administration optionally incorporated into a pharmaceutical carrier, and/or adjuvant.

8. A process for preparing a pharmaceutical composition of claim 7 in dosage unit form suitable for systemic administration to a mammalian host which comprises admixing a pharmaceutical carrier with from about 1 to 500 mg of at least one compound of claims 1 to 6.

Claims for the following Contracting State : GR

1. A compound of formula I and the pharmaceutically acceptable acid addition salts thereof,



(I)

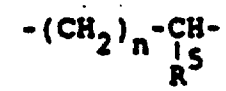
wherein

R^1 and R^2 are independently selected from C_{1-4} alkyl or hydrogen;

R^3, R^4, R^8 and R^9 are independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, carbamide, halogen, trifluoromethyl and thio-C_{1-4} alkyl, with the proviso that R^8 and R^9 cannot both be hydrogen at the same time;

A is a C_{5-7} cycloalkanyl or cycloalkenyl ring, or

A is



wherein n is an integer from 1 to 3 and R^5 is the same as R^1; and

R^6 and R^7 are independently selected from hydrogen, methyl or R^6 and R^7 can be taken together as a methylene bridge.

2. The compound of claim 1 wherein A is a C_{5-7} cycloalkanyl or cycloalkenyl ring.

* C L M S *

3. The compound of claim 1 wherein A is



4. The compound of claim 1 wherein R^6 and R^7 are selected from hydrogen or methyl.

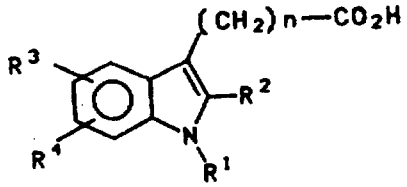
5. The compound of claim 1 wherein R^6 and R^7 are taken together as a methylene bridge.

6. The compounds of claim 1: 1-[2-(1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(1H-indol-3-yl)ethyl]-4-(3-trifluoromethyl-2-pyridinyl)piperazine;
1-[2-(1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)-2-methylpiperazine;
1-[2-(1H-indol-3-yl)ethyl]-5-(3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptane;
1-[2-(1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[2-(1H-indol-3-yl)ethyl]-4-(6-methoxy-2-pyridinyl)piperazine;
1-[2-(1H-indol-3-yl)ethyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptane;
1-[3-(1H-indol-3-yl)propyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[3-(1H-indol-3-yl)propyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[4-(1H-indol-3-yl)butyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;
2-[2-(1H-indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptane;
2-[2-(1H-indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptane;
1-[3-(1H-indol-3-yl)propyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;
1-[4-(1H-indol-3-yl)butyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[4-(1H-indol-3-yl)butyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;
1-[3-(1H-indol-3-yl)propyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazine;
2-[3-(1H-indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptane;
2-[3-(1H-indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptane;
1-[2-(1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)-2-methylpiperazine;
1-[2-(1H-indol-3-yl)ethyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazine;
1-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[2-(1H-indol-3-yl)-ethyl]-4-(3-chloro-2-pyridinyl)piperazine;
1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;
1-[2-(5-methoxy-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-methoxyindole;
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indole;
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indole-5-carboxamide;
1-[2-(N-methyl-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(5,6-dimethoxy-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(5,6-dimethoxy-1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[3-(N-methyl-1H-indol-3-yl)-propyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[3-(N-methyl-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(1H-indol-3-yl)ethyl]-4-(5-chloro-2-pyridinyl)piperazine;
1-[2-[N-methyl-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[2-(5-chloro-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazine;
1-[2-(5-chloro-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazine;
1-[2-(5-chloro-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;
1-[2-(1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)-2-methyl-piperazine;
4-(6-chloro-2-pyridinyl)-1-[2-(6-methoxy-1H-indol-3-yl)ethyl]-piperazine;
1-[2-6-methoxy-1H-indol-3-yl) ethyl]-4-(3-methoxy-2-pyridinyl)-piperazine;

* C L M S *

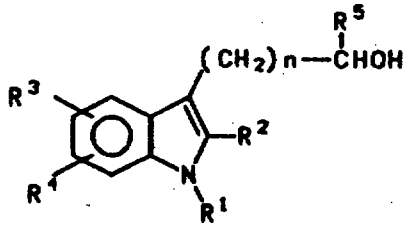
1-[3-(1H-indol-3-yl)-3-methylpropyl]-4-(6-chloro-2-pyridinyl)-piperazine;
1-[3-(1H-indol-3-yl)-3-methylpropyl]-4-(3-methoxy-2-pyridinyl)-piperazine;
1-[2-(5,6-dimethoxy-1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine;
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-fluoro-1H-indole;
4-(5-chloro-3-methoxy-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]-piperazine hydrochloride;
4-(6-chloro-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]-2-methyl-piperazine;

7. A process for preparing the compounds of claims 1 to 6 characterized in that
A) a compound of the general formula II:



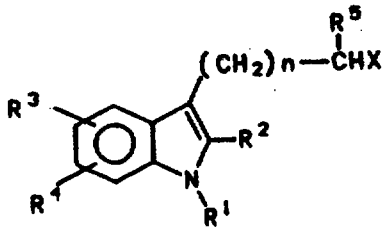
(II)

is reacted with a compound of the general formula R^5-M, wherein M represents a metalloid species, to obtain a compound of the general formula VI:



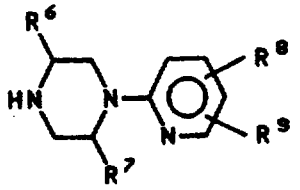
(VI)

a compound of the general formula VI is reacted with a reagent Y-X, wherein X is a leaving group and Y is a hydrogen atom or a counter ion, to obtain a compound of the general formula V:



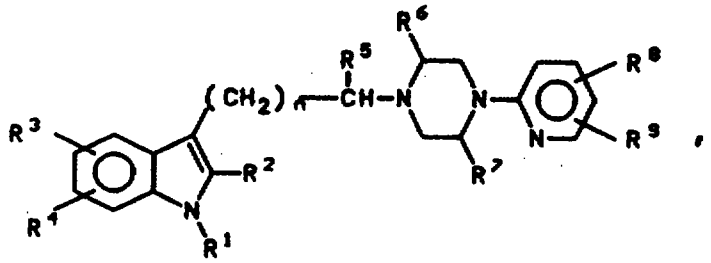
(V)

a compound of the general formula V is reacted with a compound of the general formula III:



(III)

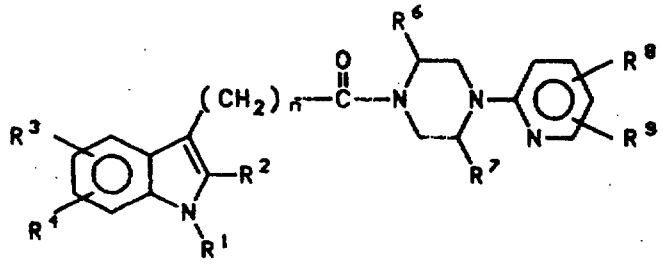
to obtain a compound of the general formula Ia



(Ia)

or

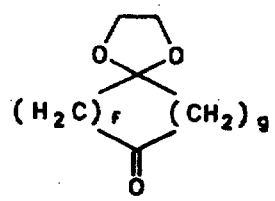
B) a compound of the general formula II or an active equivalent thereof is reacted with a compound of the general formula III to obtain a compound of the general formula IV:



(IV)

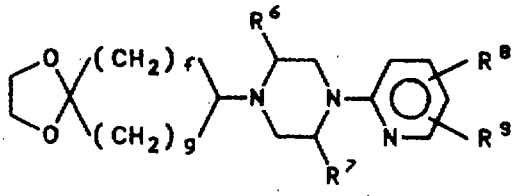
a compound of the general formula IV is reacted with R^5-M, wherein R^5 is defined as above, to obtain a compound of the general formula Ia, or

C) a compound of the general formula III is reductively alkylated with a compound of the general formula X



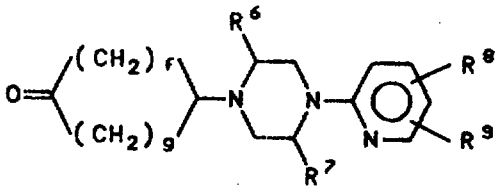
(X)

wherein f and g are integers from 0 to 5 with the proviso that f + g must be equal to 3, 4 or 5, to give a compound of the general formula IX:



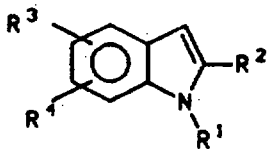
(IX)

a compound of the general formula IX is deprotected to produce a compound of the general formula VIII



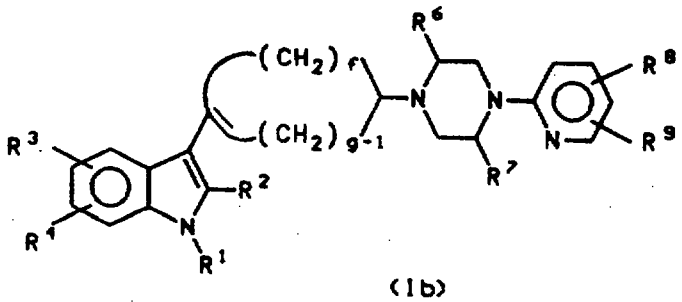
(VIII)

a compound of the general formula VIII is condensed with a compound of the general formula VII



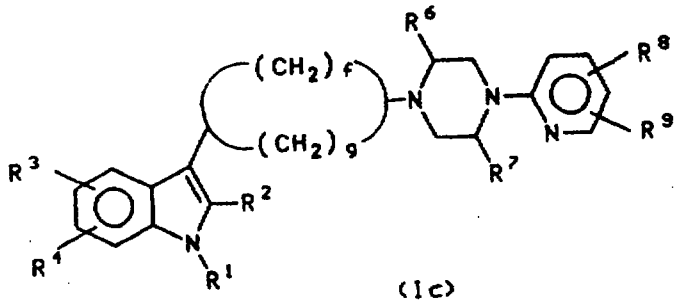
(VII)

to give a compound of the general formula Ib



(Ib)

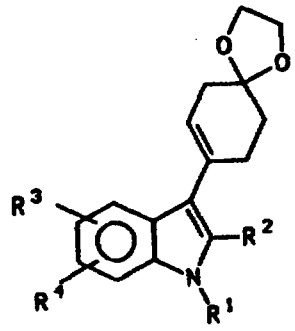
and, if desired, a compound of the general formula Ib is reduced to a compound of the general formula Ic:



(Ic)

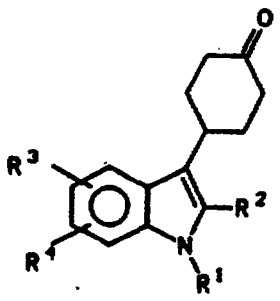
or

D) a compound of the general formula VIII is condensed with a compound of the general formula X to give a compound of the general formula XII



(XII)

a compound of the general formula XII is reduced and deketalized to a compound of the general formula XI:



(XI)

a compound of the general formula XI is condensed with a compound of the general formula III to give a compound of the general formula Ic,
the symbols R^1 through R^9 and n being defined as in claim 1, and,
if desired, a so obtained compound of formula I is converted to a pharmaceutically aceptable acid addition salt thereof.

8. A process for preparing a pharmaceutical composition which comprises providing at least one compound of claims 1 to 6 in a form suitable for administration optionally incorporated into a pharmaceutical carrier, and/or adjuvant.

* C L M S *

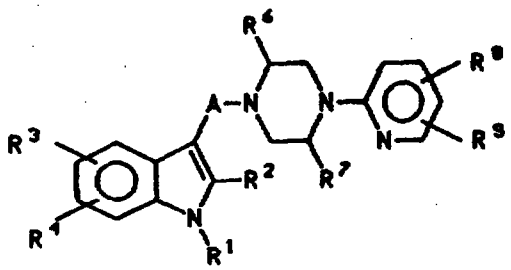
9. A process for preparing a pharmaceutical composition of claim 8 in dosage unit form suitable for systemic administration to a mammalian host which comprises admixing a pharmaceutical carrier with from about 1 to 500 mg of at least one compound of claims 1 to 6.

10. The use of at least one compound of claims 1 to 6 for preparing a pharmaceutical composition for ameliorating an undesirable state of depression in a mammal.

Patentansprüche

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

1. Verbindung der Formel I und pharmazeutisch akzeptable Säureadditionssalze davon,

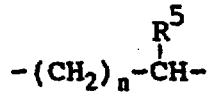


(I)

worin
R^1 und R^2 unabhängig voneinander ausgewählt sind unter C_{1-4}-Alkyl oder Wasserstoff;
R^3, R^4, R^8 und R^9 unabhängig voneinander ausgewählt sind unter Wasserstoff, C_{1-4}-Alkyl, C_{1-4}-Alkoxy, Carbamid, Halogen, Trifluormethyl und Thio-C_{1-4}-alkyl, mit der Maßgabe, daß R^8 und R^9 nicht gleichzeitig für Wasserstoff stehen können;
A für einen C_{5-7}-Cycloalkanyl- oder -Cycloalkenyl-Ring steht, oder
A für $(CH_2)_n$-CH- steht,
worin n eine ganze Zahl von 1 bis 3 und R^5 das gleiche wie R^1 bedeuten; und
R^6 und R^7 unabhängig voneinander ausgewählt sind unter Wasserstoff oder Methyl, oder R^6 und R^7 zusammen für eine Methylenbrücke stehen können.

2. Verbindung nach Anspruch 1, worin A für einen C_{5-7}-Cycloalkanyl- oder - Cycloalkenyl-Ring steht.

3. Verbindung nach Anspruch 1, worin A für



steht.

4. Verbindung nach Anspruch 1, worin R^6 und R^7 ausgewählt sind unter Wasserstoff oder Methyl.

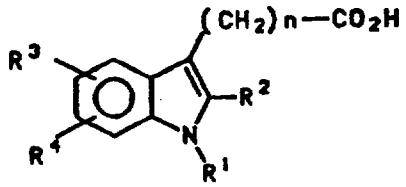
5. Verbindung nach Anspruch 1, worin R^6 und R^7 zusammen für eine Methylenbrücke stehen.

6. Verbindungen nach Anspruch 1: 1-[2-(1H-Indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(3-trifluoromethyl-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)-2-methylpiperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-5 (3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptan ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(6-chlor -2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(6-methoxy-2-pyridinyl)piperazin ;

1-[2-(1H-Indol-3-yl)ethyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptan ;
1-[3-(1H-Indol-3-yl)propyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[3-(1H-Indol-3-yl)propyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[4-(1H-Indol-3-yl)butyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
2-[2-(1H-Indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptan ;
2-[2-(1H-Indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptan ;
1-[3-(1H-Indol-3-yl)propyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
1-[4-(1H-Indol-3-yl)butyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[4-(1H-Indol-3-yl)butyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
1-[3-(1H-Indol-3-yl)propyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazin ;
2-[3-(1H-Indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptan ;
2-[3-(1H-Indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptan ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)-2-methylpiperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazin ;
1-[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5-Fluoro-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[2-(5-Fluoro-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)-ethyl]-4-(3-chloro-2-pyridinyl)piperazin ;
1-[2-(5-Fluoro-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
1-[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-methoxyindol ;
3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indol ;
3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexan-1-yl]-1H-indole-5-carboxamid ;
1-[2-(N-Methyl-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5,6-Dimethoxy-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5,6-Dimethoxy-1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[3-(N-Methyl-1H-indol-3-yl)propyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[3-(N-Methyl-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[3-(5-Fluoro-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[3-(5-Fluoro-1H-indol-3-yl)-propyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(5-chloro-2-pyridinyl)piperazin ;
1-[2-[N-Methyl-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[2-(5-Chloro-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5-Chloro-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[2-(5-Chloro-1H-indol-3-yl) ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl] -4-(3-methoxy-2-pyridinyl)-2-methyl-piperazin ;
4-(6-chloro-2-pyridinyl)-1-[2-(6-methoxy-1H-indol-3-yl)ethyl]-piperazin ;
1-[2-6-Methoxy-1H-indol-3-yl) ethyl]-4-(3-methoxy-2-pyridinyl)-piperazin ;
1-[3-(1H-Indol-3-yl)-3-methylpropyl]-4-(6-chloro-2-pyridinyl)-piperazin ;
1-[3-(1H-Indol-3-yl)-3-methylpropyl]-4-(3-methoxy-2-pyridinyl)-piperazin ;
1-[2-(5,6-Dimethoxy-1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-fluoro-1H-indol ;
4-(5-Chloro-3-methoxy-2-pyridinyl) -1-[3-(1H-indol-3-yl)propyl]-piperazine-hydrochlorid ;
4-(6-Chloro-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]-2-methyl-piperazin ;

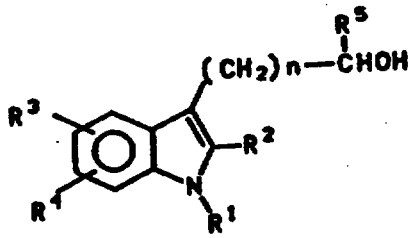
7. Verfahren zur Herstellung der Verbindungen nach den Ansprüchen 1 bis 6, dadurch gekennzeichnet, daß man

A) eine Verbindung der allgemeinen Formel II:



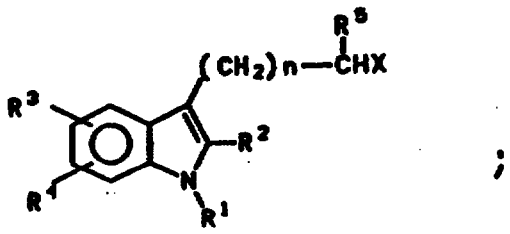
(II)

reagieren läßt mit einer Verbindung der allgemeinen Formel R^5-M, worin M ein Metalloid bedeutet, um eine Verbindung der allgemeinen Formel VI zu erhalten:



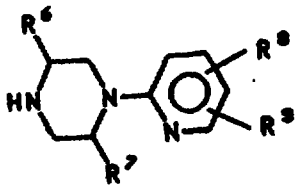
(VI)

eine Verbindung der allgemeinen Formel VI mit einem Reagens Y-X reagieren läßt, worin X für eine Abgangsgruppe und Y für ein Wasserstoffatom oder ein Gegenion steht, um eine Verbindung der allgemeinen Formel V zu erhalten:



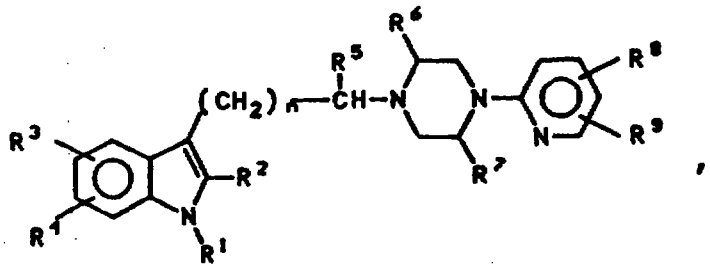
(V)

eine Verbindung der allgemeinen Formel V mit einer Verbindung der allgemeinen Formel III reagieren läßt:



(III)

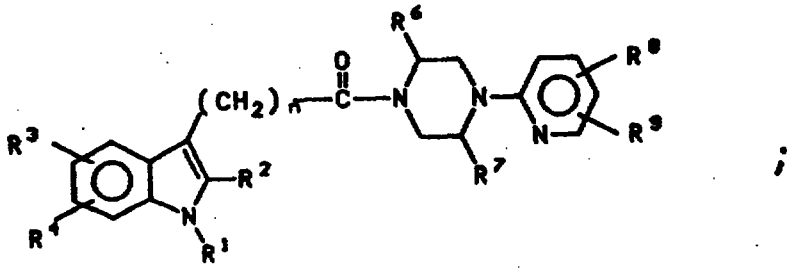
um eine Verbindung der allgemeinen Formel Ia zu erhalten



(Ia)

oder

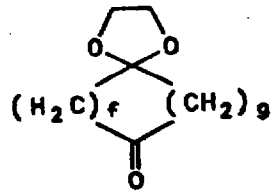
B) eine Verbindung der allgemeinen Formel II oder ein aktives Äquivalent davon mit einer Verbindung der allgemeinen Formel III reagieren läßt, um eine Verbindung der allgemeinen Formel IV zu erhalten:



(IV)

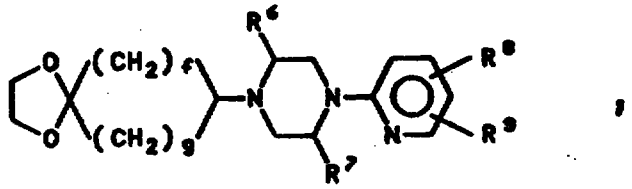
eine Verbindung der allgemeinen Formel IV mit R^5-M reagieren läßt, worin R^5 wie oben definiert ist, um eine Verbindung der allgemeinen Formel Ia zu erhalten, oder

C) eine Verbindung der allgemeinen Formel III reduktiv alkyliert mit einer Verbindung der allgemeinen Formel X



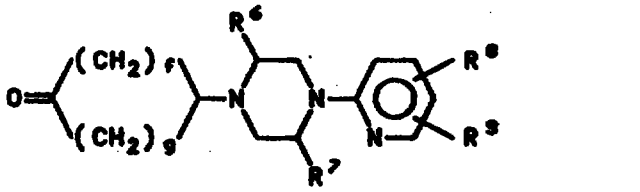
(X)

worin f und g für Zahlen von 0 bis 5 stehen, mit der Maßgabe, daß f + g 3, 4 oder 5 ergeben muß, um eine Verbindung der allgemeinen Formel IX zu erhalten:



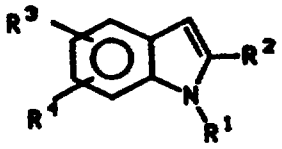
(IX)

eine Verbindung der allgemeinen Formel IX entschützt, um eine Verbindung der allgemeinen Formel VIII zu erhalten



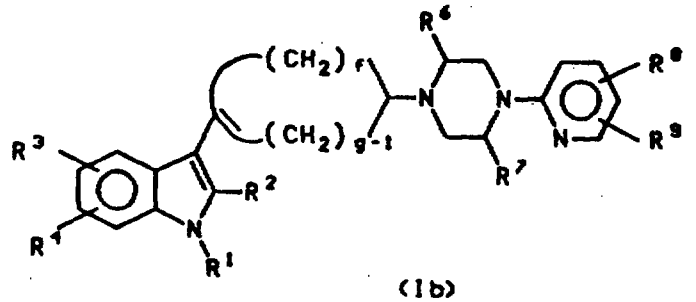
(VIII)

eine Verbindung der allgemeinen Formel VIII mit einer Verbindung der allgemeinen Formel VII kondensiert



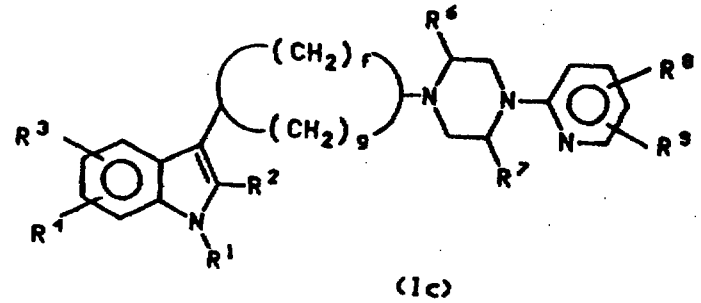
(VII)

um eine Verbindung der allgemeinen Formel Ib zu erhalten



(Ib)

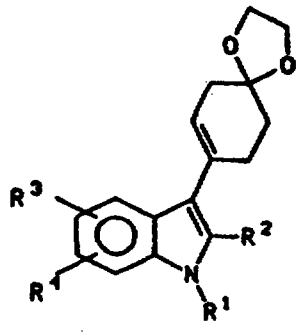
und, falls gewünscht, eine Verbindung der allgemeinen Formel Ib zu einer Verbindung der allgemeinen Formel Ic reduziert:



(Ic)

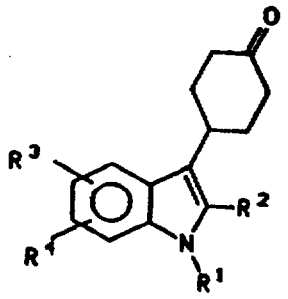
oder

D) eine Verbindung der allgemeinen Formel VIII mit einer Verbindung der allgemeinen Formel X kondensiert, um eine Verbindung der allgemeinen Formel XII zu erhalten



(XII)

eine Verbindung der allgemeinen Formel XII reduziert und deketalisiert, um eine Verbindung der allgemeinen Formel XI zu erhalten:



(XI)

eine Verbindung der allgemeinen Formel XI mit einer Verbindung der allgemeinen Formel III kondensiert, um eine Verbindung der allgemeinen Formel Ic zu erhalten, wobei die Symbole R^1 bis R^9 und n wie in Anspruch 1 definiert sind, und,
falls gewünscht, eine so erhaltene Verbindung der Formel I in ein pharmazeutisch akzeptables Säureadditionssalz davon überführt wird.

8. Pharmazeutisches Mittel, umfassend wenigstens eine Verbindung der Ansprüche 1 bis 6, gegebenenfalls zusammen mit einem pharmazeutischen Träger und/oder Adjuvans.

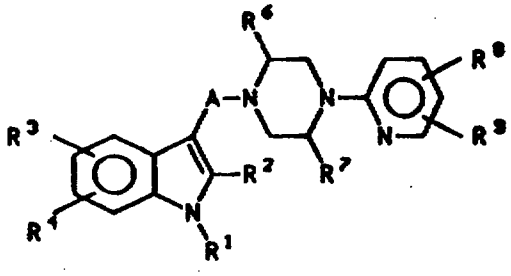
9. Pharmazeutisches Mittel nach Anspruch 8 in Dosiseinheitsform, geeignet zur systemischen Verabreichung an einen Säugerwirt, umfassend einen pharmazeutischen Träger und etwa 1 bis 500 mg wenigstens einer Verbindung der Ansprüche 1 bis 6.

10. Verfahren zur Herstellung der pharmazeutischen Mittel nach den Ansprüchen 8 oder 9, wobei man wenigstens eine Verbindung der Ansprüche 1 bis 6 in einer zur systemischen Verabreichung geeigneten Form, vorzugsweise in Dosiseinheitsform, bereitstellt, und gegebenenfalls in einem pharmazeutischen Träger aufnimmt.

11. Verwendung von wenigstens einer Verbindung der Ansprüche 1 bis 6 zur Herstellung eines pharmazeutischen Mittels zur Verbesserung eines unerwünschten Depressions-Zustandes bei einem Säuger

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Verbindung der Formel I und pharmazeutisch akzeptabler Säureadditionssalze davon,

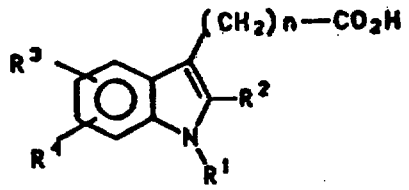


(I)

worin
R^1 und R^2 unabhängig voneinander ausgewählt sind unter C_{1-4}-Alkyl oder Wasserstoff;
R^3, R^4, R^8 und R^9 unabhängig voneinander ausgewählt sind unter Wasserstoff, C_{1-4}-Alkyl, C_{1-4}-Alkoxy, Carbamid, Halogen, Trifluormethyl und Thio-C_{1-4}-alkyl, mit der Maßgabe, daß R^8 und R^9 nicht gleichzeitig für Wasserstoff stehen können;

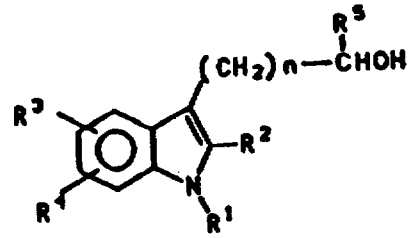
A für einen C_{5-7}-Cycloalkanyl- oder -Cycloalkenyl-Ring steht, oder
A für $(CH_2)_n$-CH- steht,
worin n eine ganze Zahl von 1 bis 3 und R^5 das gleiche wie R^1 bedeuten; und
R^6 und R^7 unabhängig voneinander ausgewählt sind unter Wasserstoff oder Methyl, oder R^6 und R^7 zusammen für eine Methylenbrücke stehen können.
dadurch gekennzeichnet, daß man

A) eine Verbindung der allgemeinen Formel II:



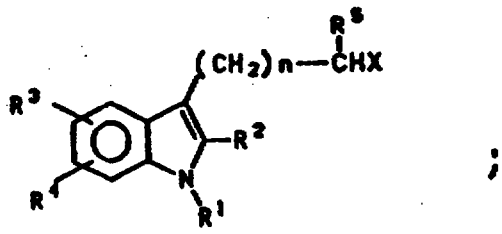
(II)

reagieren läßt mit einer Verbindung der allgemeinen Formel R^5-M, worin M ein Metalloid bedeutet, um eine Verbindung der allgemeinen Formel VI zu erhalten:



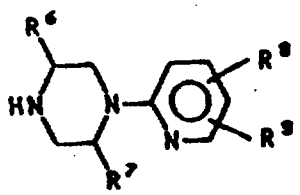
(VI)

eine Verbindung der allgemeinen Formel VI mit einem Reagens Y-X reagieren läßt, worin X für eine Abgangsgruppe und Y für ein Wasserstoffatom oder ein Gegenion steht, um eine Verbindung der allgemeinen Formel V zu erhalten:



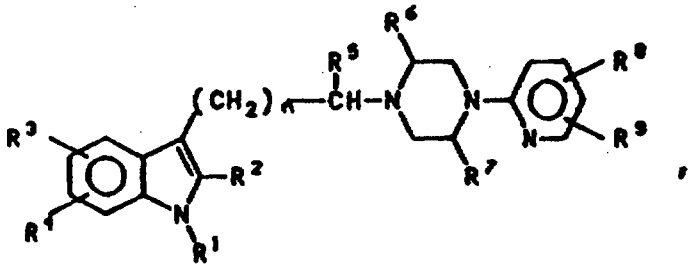
(V)

eine Verbindung der allgemeinen Formel V mit einer Verbindung der allgemeinen Formel III reagieren läßt:



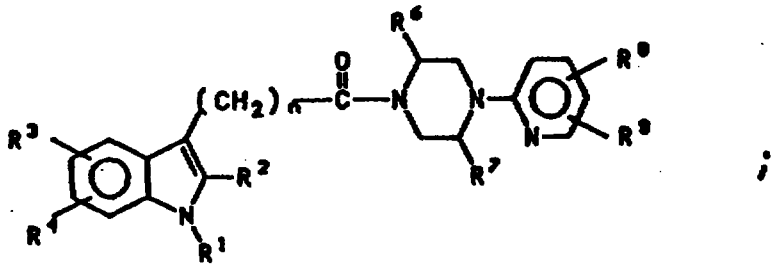
(III)

um eine Verbindung der allgemeinen Formel Ia zu erhalten



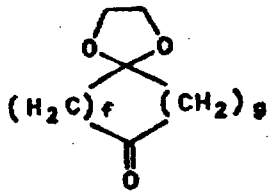
(Ia)

oder
B) eine Verbindung der allgemeinen Formel II oder ein aktives Äquivalent davon mit einer Verbindung der allgemeinen Formel III reagieren läßt, um eine Verbindung der allgemeinen Formel IV zu erhalten:



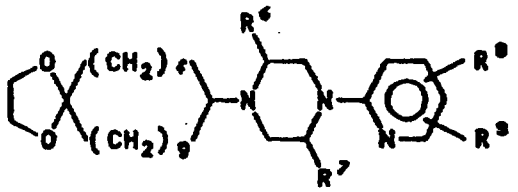
(IV)

eine Verbindung der allgemeinen Formel IV mit R^5-M reagieren läßt, worin R^5 wie oben definiert ist, um eine Verbindung der allgemeinen Formel Ia zu erhalten, oder
C) eine Verbindung der allgemeinen Formel III reduktiv alkyliert mit einer Verbindung der allgemeinen Formel X



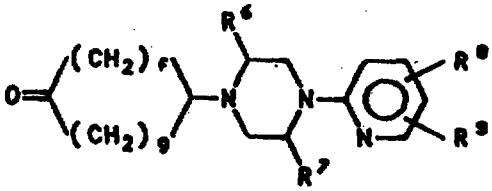
(X)

worin f und g für Zahlen von 0 bis 5 stehen, mit der Maßgabe, daß f + g 3, 4 oder 5 ergeben muß, um eine Verbindung der allgemeinen Formel IX zu erhalten:



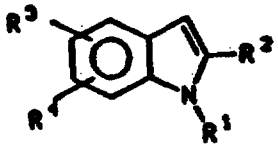
(IX)

eine Verbindung der allgemeinen Formel IX entschützt, um eine Verbindung der allgemeinen Formel VIII zu erhalten



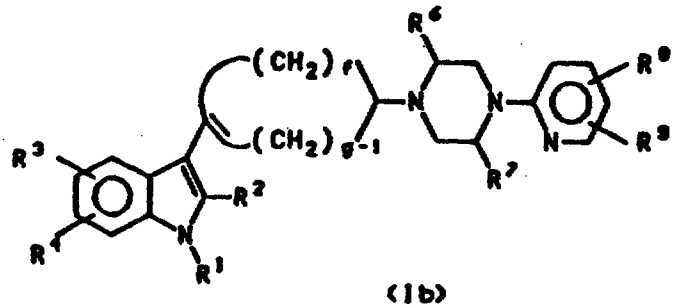
(VIII)

eine Verbindung der allgemeinen Formel VIII mit einer Verbindung der allgemeinen Formel VII kondensiert



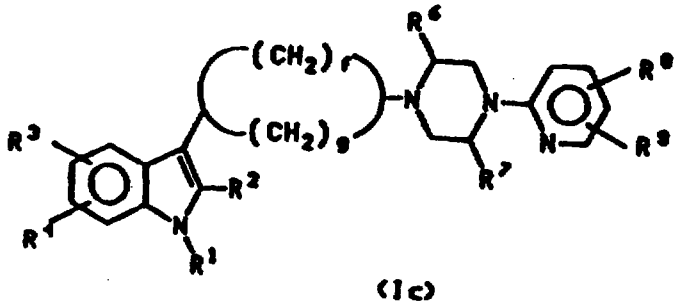
(VII)

um eine Verbindung der allgemeinen Formel Ib zu erhalten



(Ib)

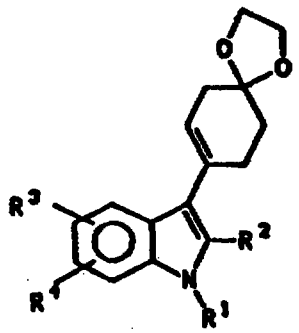
und, falls gewünscht, eine Verbindung der allgemeinen Formel Ib zu einer Verbindung der allgemeinen Formel Ic reduziert:



(Ic)

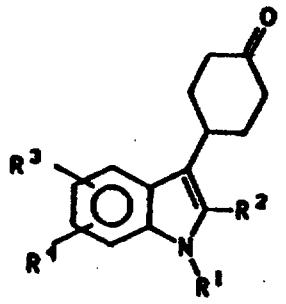
oder

D) eine Verbindung der allgemeinen Formel VIII mit einer Verbindung der allgemeinen Formel X kondensiert, um eine Verbindung der allgemeinen Formel XII zu erhalten



(XII)

eine Verbindung der allgemeinen Formel XII reduziert und deketalisiert, um eine Verbindung der allgemeinen Formel XI zu erhalten:

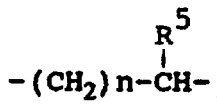


(XI)

eine Verbindung der allgemeinen Formel XI mit einer Verbindung der allgemeinen Formel III kondensiert, um eine Verbindung der allgemeinen Formel Ic zu erhalten, wobei die Symbole R^1 bis R^9 und n wie in Anspruch 1 definiert sind, und,
falls gewünscht, eine so erhaltene Verbindung der Formel I in ein pharmazeutisch akzeptables Säureadditionssalz davon überführt wird.

2. Verfahren gemäß Anspruch 1, wobei A für einen C_{5-7}-Cycloalkanyl- oder - Cycloalkenyl-Ring steht.

3. Verfahren gemäß Anspruch 1, wobei A für



steht.

4. Verfahren gemäß Anspruch 1, wobei R^6 und R^7 ausgewählt sind unter Wasserstoff oder Methyl.

5. Verfahren gemäß Anspruch 1, wobei R^6 und R^7 zusammen für eine Methylenbrücke stehen.

6. Verfahren gemäß Anspruch 1 zur Herstellung von:
1-[2-(1H-Indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(3-trifluoromethyl-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)-2-methylpiperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-5-(3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptan ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(6-chlor -2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(6-methoxy-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptan ;
1-[3-(1H-Indol-3-yl)propyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[3-(1H-Indol-3-yl)propyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[4-(1H-Indol-3-yl)butyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
2-[2-(1H-Indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptan ;
2-[2-(1H-Indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptan ;
1-[3-(1H-Indol-3-yl)propyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
1-[4-(1H-Indol-3-yl)butyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[4-(1H-Indol-3-yl)butyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
1-[3-(1H-Indol-3-yl)propyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazin ;
2-[3-(1H-Indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptan ;
2-[3-(1H-Indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptan ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)-2-methylpiperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazin ;
1-[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;

* C L M S *

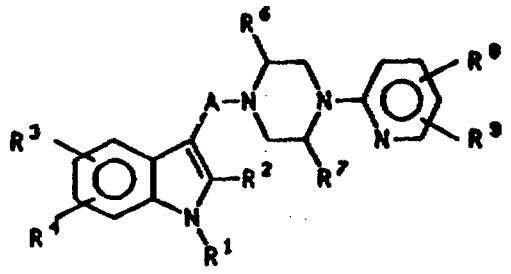
1-[2-(5-Fluoro-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[2-(5-Fluoro-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)-ethyl]-4-(3-chloro-2-pyridinyl)piperazin ;
1-[2-(5-Fluoro-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
1-[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-methoxyindol ;
3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indol ;
3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indole-5-carboxamid ;
1-[2-(N-Methyl-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5,6-Dimethoxy-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5,6-Dimethoxy-1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[3-(N-Methyl-1H-indol-3-yl)-propyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[3-(N-Methyl-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[3-(5-Fluoro-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[3-(5-Fluoro-1H-indol-3-yl)-propyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(5-chloro-2-pyridinyl)piperazin ;
1-[2-[N-Methyl-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[2-(5-Chloro-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5-Chloro-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[2-(5-Chloro-1H-indol-3-yl) ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl] -4-(3-methoxy-2-pyridinyl)-2-methyl-piperazin ;
4-(6-Chloro-2-pyridinyl)-1-[2-(6-methoxy-1H-indol-3-yl)ethyl]-piperazin ;
1-[2-6-Methoxy-1H-indol-3-yl) ethyl]-4-(3-methoxy-2-pyridinyl)-piperazin ;
1-[3-(1H-Indol-3-yl)-3-methylpropyl]-4-(6-chloro-2-pyridinyl)-piperazin ;
1-[3-(1H-Indol-3-yl)-3-methylpropyl]-4-(3-methoxy-2-pyridinyl)-piperazin ;
1-[2-(5,6-Dimethoxy-1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-fluoro-1H-indol ;
4-(5-Chloro-3-methoxy-2-pyridinyl) -1-[3-(1H-indol-3-yl)propyl]-piperazine-hydrochlorid ;
4-(6-Chloro-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]-2-methyl-piperazin ;

7. Verfahren zur Herstellung eines pharmazeutischen Mittels, wobei man wenigstens eine Verbindung gemäß den Ansprüchen 1 bis 6 in einer zur Verabreichung geeigneten Form bereitstellt, gegebenenfalls aufgenommen in einen pharmazeutischen Träger und/oder Adjuvans.

8. Verfahren zur Herstellung eines pharmazeutischen Mittels nach Anspruch 7 in Dosiseinheitsform, geeignet zur systemischen Verabreichung an einen Säugerwirt, wobei man einen pharmazeutischen Träger mit etwa 1 bis 500 mg von wenigstens einer Verbindung gemäß den Ansprüchen 1 bis 6 vermischt.

Patentansprüche für folgenden Vertragsstaat : GR

1. Verbindung der Formel I und pharmazeutisch akzeptable Säureadditionssalze davon,



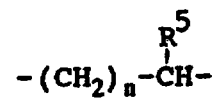
(I)

worin

R^1 und R^2 unabhängig voneinander ausgewählt sind unter C_{1-4}-Alkyl oder Wasserstoff;
R^3, R^4, R^8 und R^9 unabhängig voneinander ausgewählt sind unter Wasserstoff, C_{1-4}-Alkyl, C_{1-4}-Alkoxy, Carbamid, Halogen, Trifluormethyl und Thio-C_{1-4}-alkyl, mit der Maßgabe, daß R^8 und R^9 nicht gleichzeitig für Wasserstoff stehen können;
A für einen C_{5-7}-Cycloalkanyl- oder -Cycloalkenyl-Ring steht, oder
A für $(CH_2)_n$-CH- steht,
worin n eine ganze Zahl von 1 bis 3 und R^5 das gleiche wie R^1 bedeuten; und
R^6 und R^7 unabhängig voneinander ausgewählt sind unter Wasserstoff oder Methyl, oder R^6 und R^7 zusammen für eine Methylenbrücke stehen können.

2. Verbindung nach Anspruch 1, worin A für einen C_{5-7}-Cycloalkanyl- oder - Cycloalkenyl-Ring steht.

3. Verbindung nach Anspruch 1, worin A für



steht.

4. Verbindung nach Anspruch 1, worin R^6 und R^7 ausgewählt sind unter Wasserstoff oder Methyl.

5. Verbindung nach Anspruch 1, worin R^6 und R^7 zusammen für eine Methylenbrücke stehen.

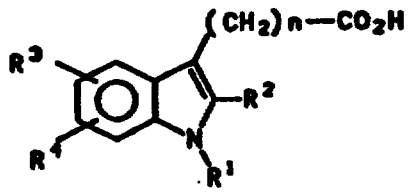
6. Verbindungen nach Anspruch 1: 1-[2-(1H-Indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(3-trifluoromethyl-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)-2-methylpiperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-5-(3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptan ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(6-chlor -2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(6-methoxy-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptan ;
1-[3-(1H-Indol-3-yl)propyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[3-(1H-Indol-3-yl)propyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[4-(1H-Indol-3-yl)butyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
2-[2-(1H-Indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptan ;
2-[2-(1H-Indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptan ;
1-[3-(1H-Indol-3-yl)propyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
1-[4-(1H-Indol-3-yl)butyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[4-(1H-Indol-3-yl)butyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
1-[3-(1H-Indol-3-yl)propyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazin ;
2-[3-(1H-Indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptan ;
2-[3-(1H-Indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptan ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)-2-methylpiperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazin ;
1-[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5-Fluoro-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[2-(5-Fluoro-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperizin ;
1-[2-(1H-Indol-3-yl)-ethyl]-4-(3-chloro-2-pyridinyl)piperazin ;
1-[2-(5-Fluoro-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
1-[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-methoxyindol ;
3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indol ;
3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indole-5-carboxamid ;
1-[2-(N)-Methyl-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5,6-Dimethoxy-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;

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1-[2-(5,6-Dimethoxy-1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[3-(N-Methyl-1H-indol-3-yl)-propyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[3-(N-Methyl-1H-Indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[3-(5-Fluoro-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[3-(5-Fluoro-1H-indol-3-yl)-propyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl]-4-(5-chloro-2-pyridinyl)piperazin ;
1-[2-[N-Methyl-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[2-(5-Chloro-1H-indol-3-yl)-ethyl]-4-(3-methoxy-2-pyridinyl)piperazin ;
1-[2-(5-Chloro-1H-indol-3-yl)-ethyl]-4-(6-chloro-2-pyridinyl)piperazin ;
1-[2-(5-Chloro-1H-indol-3-yl) ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
1-[2-(1H-Indol-3-yl)ethyl] -4-(3-methoxy-2-pyridinyl)-2-methyl-piperazin ;
4-(6-Chloro-2-pyridinyl)-1-[2-(6-methoxy-1H-indol-3-yl)ethyl]-piperazin ;
1-[2-6-Methoxy-1H-indol-3-yl) ethyl]-4-(3-methoxy-2-pyridinyl)-piperazin ;
1-[3-(1H-Indol-3-yl)-3-methylpropyl]-4-(6-chloro-2-pyridinyl)-piperazin ;
1-[3-(1H-Indol-3-yl)-3-methylpropyl]-4-(3-methoxy-2-pyridinyl)-piperazin ;
1-[2-(5,6-Dimethoxy-1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazin ;
3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-fluoro-1H-indol ;
4-(5-Chloro-3-methoxy-2-pyridinyl) -1-[3-(1H-indol-3-yl)propyl]-piperazine-hydrochlorid ;
4-(6-Chloro-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]-2-methyl-piperazin ;

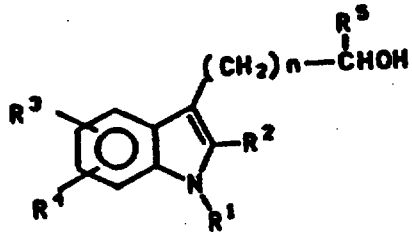
7. Verfahren zur Herstellung der Verbindungen nach den Ansprüchen 1 bis 6, dadurch gekennzeichnet, daß man

A) eine Verbindung der allgemeinen Formel II:



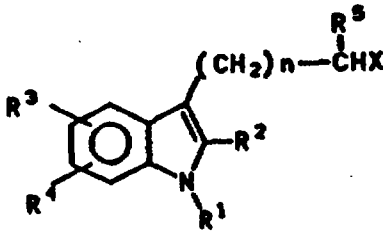
(II)

reagieren läßt mit einer Verbindung der allgemeinen Formel R^5-M, worin M ein Metalloid bedeutet, um eine Verbindung der allgemeinen Formel VI zu erhalten:



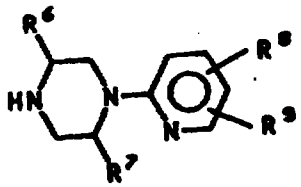
(VI)

eine Verbindung der allgemeinen Formel VI mit einem Reagens Y-X reagieren läßt, worin X für eine Abgangsgruppe und Y für ein Wasserstoffatom oder ein Gegenion steht, um eine Verbindung der allgemeinen Formel V zu erhalten:



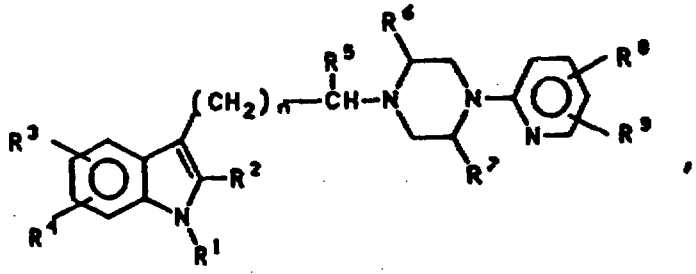
(V)

eine Verbindung der allgemeinen Formel V mit einer Verbindung der allgemeinen Formel III reagieren läßt:



(III)

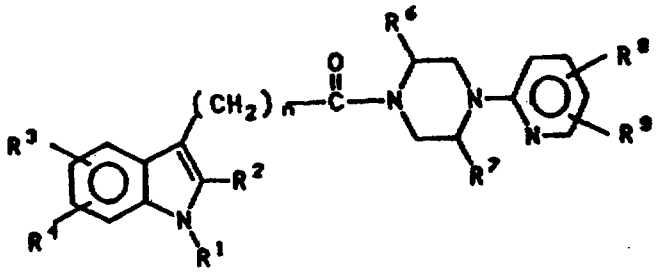
um eine Verbindung der allgemeinen Formel Ia zu erhalten



(Ia)

oder

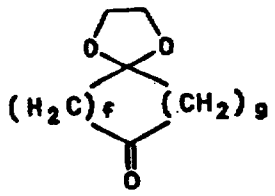
B) eine Verbindung der allgemeinen Formel II oder ein aktives Äquivalent davon mit einer Verbindung der allgemeinen Formel III reagieren läßt, um eine Verbindung der allgemeinen Formel IV zu erhalten:



(IV)

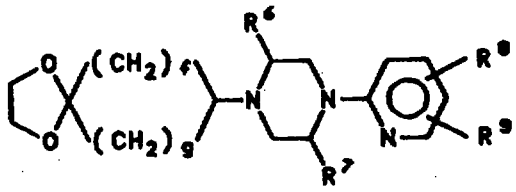
eine Verbindung der allgemeinen Formel IV mit R^5-M reagieren läßt, worin R^5 wie oben definiert ist, um eine Verbindung der allgemeinen Formel Ia zu erhalten, oder

C) eine Verbindung der allgemeinen Formel III reduktiv alkyliert mit einer Verbindung der allgemeinen Formel X



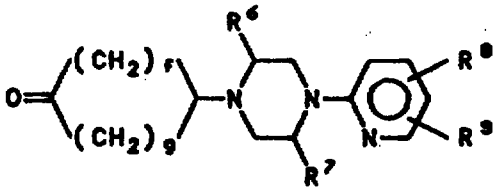
(X)

worin f und g für Zahlen von 0 bis 5 stehen, mit der Maßgabe, daß f + g 3, 4 oder 5 ergeben muß, um eine Verbindung der allgemeinen Formel IX zu erhalten:



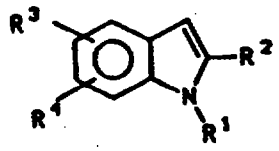
(IX)

eine Verbindung der allgemeinen Formel IX entschützt, um eine Verbindung der allgemeinen Formel VIII zu erhalten



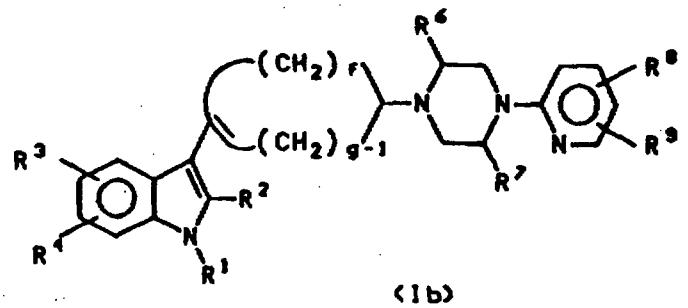
(VIII)

eine Verbindung der allgemeinen Formel VIII mit einer Verbindung der allgemeinen Formel VII kondensiert



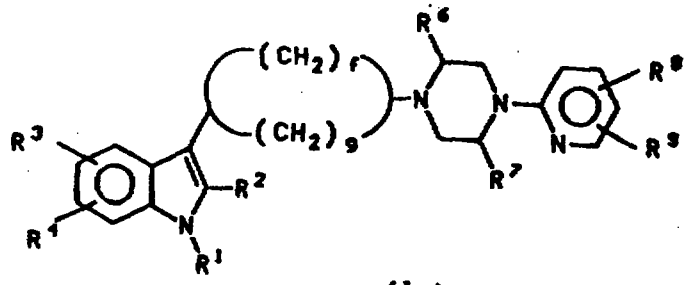
(VII)

um eine Verbindung der allgemeinen Formel Ib zu erhalten



(Ib)

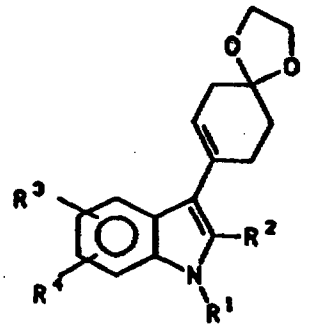
und, falls gewünscht, eine Verbindung der allgemeinen Formel Ib zu einer Verbindung der allgemeinen Formel Ic reduziert:



(Ic)

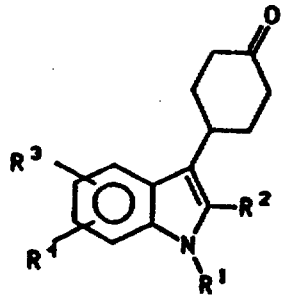
oder

D) eine Verbindung der allgemeinen Formel VIII mit einer Verbindung der allgemeinen Formel X kondensiert, um eine Verbindung der allgemeinen Formel XII zu erhalten



(XII)

eine Verbindung der allgemeinen Formel XII reduziert und deketalisiert, um eine Verbindung der allgemeinen Formel XI zu erhalten:



(XI)

eine Verbindung der allgemeinen Formel XI mit einer Verbindung der allgemeinen Formel III kondensiert, um eine Verbindung der allgemeinen Formel Ic zu erhalten, wobei die Symbole R^1 bis R^9 und n wie in Anspruch 1 definiert sind, und,
falls gewünscht, eine so erhaltene Verbindung der Formel I in ein pharmazeutisch akzeptables Säureadditionssalz davon überführt wird.

8. Verfahren zur Herstellung eines pharmazeutischen Mittels, wobei man wenigstens eine Verbindung der Ansprüche 1 bis 6 in einer zur Verabreichung geeigneten Form bereitstellt, gegebenenfalls aufgenommen in einen pharmazeutischen Träger und/oder Adjuvans.

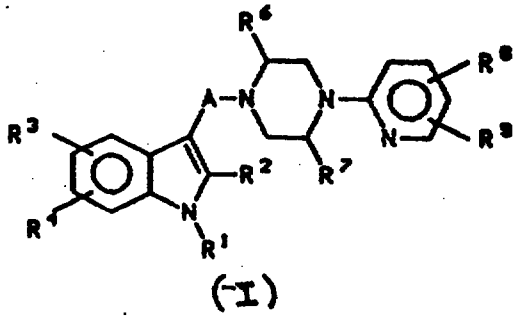
9. Verfahren zur Herstellung eines pharmazeutischen Mittels nach Anspruch 8 in Dosiseinheitsform, geeignet zur systemischen Verabreichung an einen Säugerwirt, wobei man einen pharmazeutischen Träger mit etwa 1 bis 500 mg von wenigstens einer Verbindung der Ansprüche 1 bis 6 vermischt.

10. Verwendung von wenigstens einer Verbindung der Ansprüche 1 bis 6 zur Herstellung eines pharmazeutischen Mittels zur Verbesserung eines unerwünschten Depressions-Zustandes bei einem Säuger.

Revendications

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

1. Composé de formule I et les sels d'addition d'un acide pharmaceutiquement acceptables de celui-ci.



(I)

où

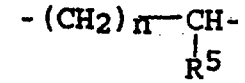
R^1 et R^2 sont indépendamment choisis parmi un alkyle en C_{1-4} ou un hydrogène ;

R^3, R^4, R^8 et R^9 sont indépendamment choisis parmi un hydrogène, un alkyle en C_{1-4}, un alcoxy en C_{1-4}, un carbamide, un halogène, un trifluorométhyle et un thio-alkyle en C_{1-4}, avec la condition que R^8 et R^9 ne peuvent pas être tous les deux un hydrogène en même temps;

A est un cycle cycloalcényle, ou cycloalcanyle en C_{5-7}, ou

A est



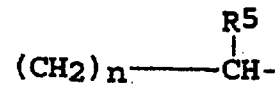


où n est un entier de 1 à 3 et R^5 est identique à R^1; et

R^6 et R^7 sont indépendamment choisis parmi un hydrogène, un méthyle ou R^6 et R^7 peuvent être pris ensemble comme un pont méthylène.

2. Composé selon la revendication 1, où A est un cycle cycloalcényle ou cycloalcanyle en C_{5-7}

3. Composé selon la revendication 1, où A est



4. Composé selon la revendication 1, où R^6 et R^7 sont choisis parmi un hydrogène ou un méthyle.

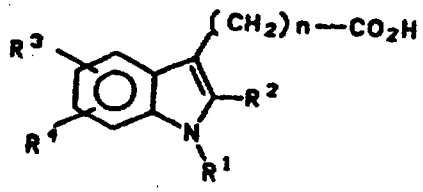
5. Composé selon la revendication 1, où R^6 et R^7 sont pris ensemble comme un pont méthylène.

6. Composés selon la revendication 1 : 1-[2-(1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine;
1-[2-(1H-indol-3-yl)éthyl]-4-(3-trifluorométhyl-2-pyridinyl)pipérazine;
1-[2-(1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)-2-méthylpipérazine;
1-[2-(1H-indol-3-yl)éthyl]-5-(3-méthoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1]heptane;
1-[2-(1H-indol-3-yl)éthyl]-4-(6-chloro-2-pyridinyl)-pipérazine;
1-[2-(1H-indol-3-yl)éthyl]-4-(6-méthoxy-2-pyridinyl)-pipérazine;
1-[2-(1H-indol-3-yl)éthyl]-5-(3-méthoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptane;
1-[3-(1H-indol-3-yl)propyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[3-(1H-indol-3-yl)propyl]-4-(6-chloro-2-pyridinyl)pipérazine;
1-[4-(1H-indol-3-yl)butyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(1H-indol-3-yl)éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
2-[2-(1H-indol-3-yl)éthyl]-5-(6-chloro-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane;
2-[2-(1H-indol-3-yl)éthyl]-5-(6-chloro-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1]heptane;
1-[3-(1H-indol-3-yl)propyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[4-(1H-indol-3-yl)butyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[4-(1H-indol-3-yl)butyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[3-(1H-indol-3-yl)propyl]-4-(4-trifluorométhyl-2-pyridinyl)pipérazine ;
2-[3-(1H-indol-3-yl)propyl]-5-(3-méthoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptane ;
2-[3-(1H-indol-3-yl)propyl]-5-(3-méthoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptane ;
1-[2-(1H-indol-3-yl)éthyl]-4-(6-chloro-2-pyridinyl)-2-méthylpipérazine ;
1-[2-(1H-indol-3-yl)éthyl]-4-(4-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[2-(5-méthoxy-1H-indol-3-yl)-éthyl-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5-fluoro-1H-indol-3-yl)-éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5-méthoxy-1H-indol-3-yl)-éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[2-(5-fluoro-1H-indol-3-yl)-éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[2-(1H-indol-3-yl)-éthyl]-4-(3-chloro-2-pyridinyl)pipérazine ;
1-[2-(5-fluoro-1H-indol-3-yl)-éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[2-(5-méthoxy-1H-indol-3-yl)-éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-pipérazinyl]-1-cyclohexen-1-yl]-5-méthoxyindole ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-pipérazinyl]-1-cyclohexèn-1-yl]-1H-indole ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-pipérazinyl]-1-cyclohexèn-1-yl]-1H-indole-5-carboxamide ;
1-[2-(N-méthyl-1H-indol-3-yl)-éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5,6-diméthoxy-1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5,6-diméthoxy-1H-indol-3-yl)éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[3-(N-méthyl-1H-indol-3-yl)-propyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[3-(N-méthyl-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)pipérazine ;

* C L M S *

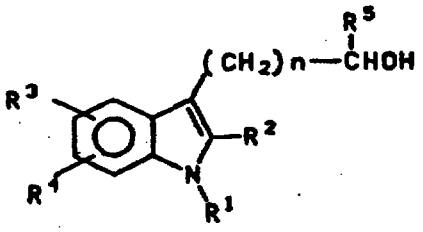
1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(1H-indol-3-yl)éthyl]-4-(5-chloro-2-pyridinyl)pipérazine ;
1-[2-[N-méthyl-1H-indol-3-yl)-éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[2-(5-chloro-1H-indol-3-yl)-éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5-chloro-1H-indol-3-yl)-éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[2-(5-chloro-1H-indol-3-yl)éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[2-(1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)-2-méthyl-pipérazine ;
4-(6-chloro-2-pyridinyl)-1-[2-(6-méthoxy-1H-indol-3-yl)éthyl]-pipérazine ;
1-[2-6-méthoxy-1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[3-(1H-indol-3-yl)-3-méthyl-propyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[3-(1H-indol-3-yl)-3-méthyl-propyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5,6-diméthoxy-1H-indol-3-yl)éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-pipérazinyl]-1-cyclohexèn-1-yl]-5-fluoro-1H-indole ;
4-(5-chloro-3-méthoxy-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]pipérazine hydrochlorure ;
4-(6-chloro-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]-2-méthyl-pipérazine ;

7. Procédé pour préparer les composés des revendications 1 à 6, caractérisé en ce que
A) un composé de formule générale II:



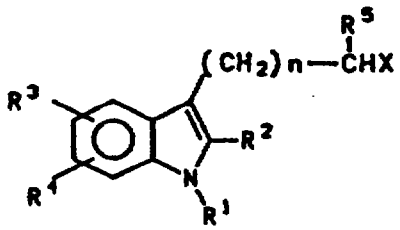
(II)

est mis à réagir avec un composé de formule générale R^5-M, où M représente une espèce métalloide, pour obtenir un composé de formule générale VI:



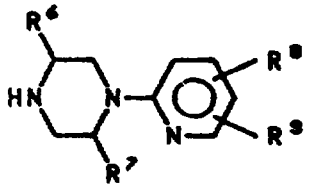
(VI)

un composé de formule générale VI est mis à réagir avec un réactif Y-X, où X est un groupe partant et Y est un atome d'hydrogène ou un contre-ion, pour obtenir un composé de formule générale V :



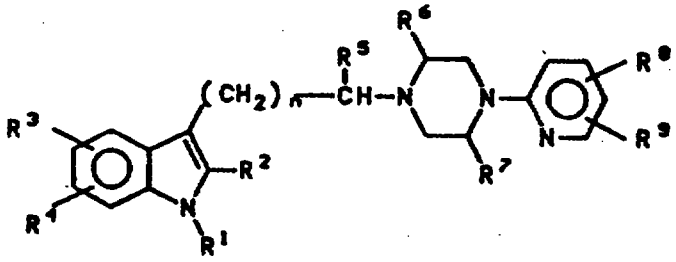
(V)

un composé de formule générale V est mis à réagir avec un composé de formule générale III :



(III)

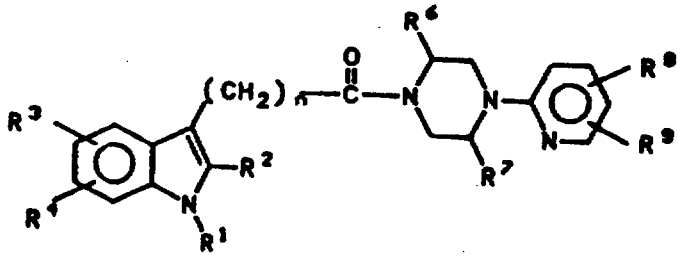
pour obtenir un composé de formule générale Ia.



(Ia)

ou

B) un composé de formule générale II ou un équivalent actif de celui-ci est mis à réagir avec un composé de formule générale III pour obtenir un composé de formule générale IV:

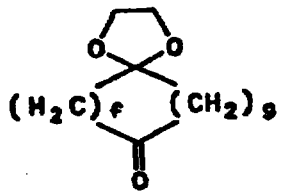


(IV)

un composé de formule générale IV est mis à réagir avec R^5-M, où R^5 est défini comme ci-dessus, pour obtenir un composé de formule générale Ia, ou

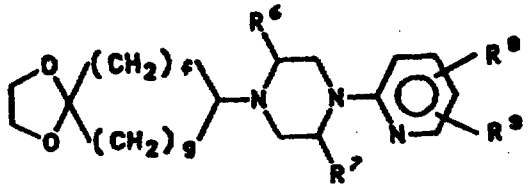
* C L M S *

C) un composé de formule générale III est alkylaté de façon réductrice avec un composé de formule générale X



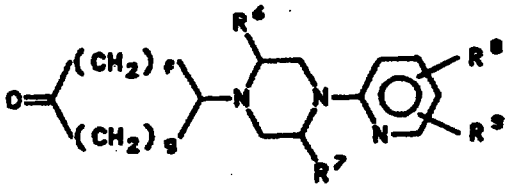
(X)

où f et g sont des entiers de 0 à 5 avec la condition que f + g doit être égal à 3, 4 ou 5, pour donner un composé de formule générale IX :



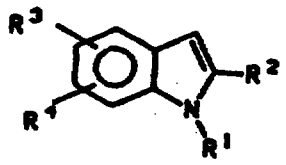
(IX)

un composé de formule générale IX est déprotégé pour produire un composé de formule générale VIII



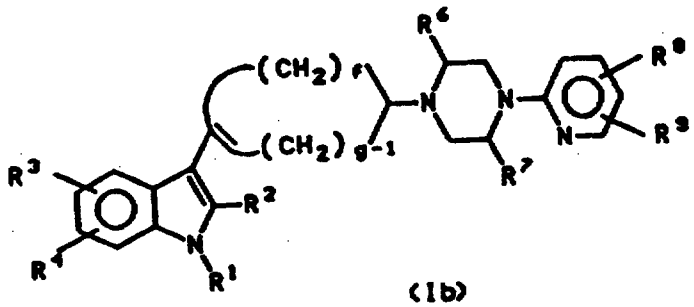
(VIII)

un composé de formule générale VIII est condensé avec un composé de formule générale VII



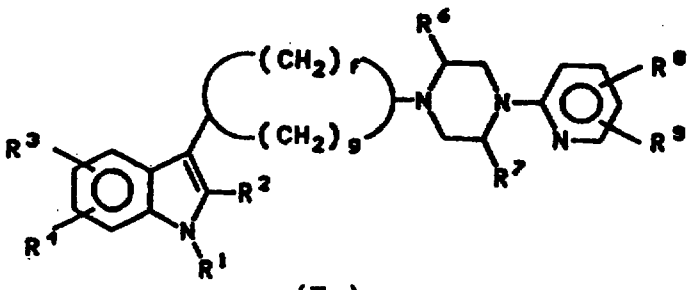
(VII)

pour donner un composé de formule générale Ib



(Ib)

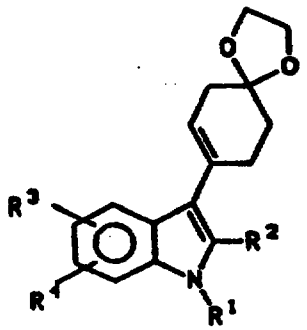
et, si souhaité, un composé de formule générale Ib est réduit en un composé de la formule générale IC:



(Ic)

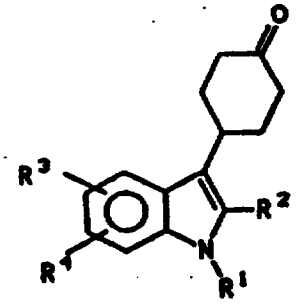
ou

D) un composé de formule générale VIII est condensé avec un composé de formule générale X pour donner un composé de formule générale XII



(XII)

un composé de formule générale XII est réduit et décétalisé en un composé de formule générale XI :



(XI)

un composé de formule générale XI est condensé avec un composé de formule générale III pour donner un composé de formule générale Ic,
les symboles R^1 à R^9 et n étant définis comme en revendication 1, et
si souhaité, un composé ainsi obtenu de formule I est converti en un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci.

8. Composition pharmaceutique comprenant au moins un composé des revendications 1 à 6, optionnellement ensemble avec un porteur et/ou un adjuvant pharmaceutique.

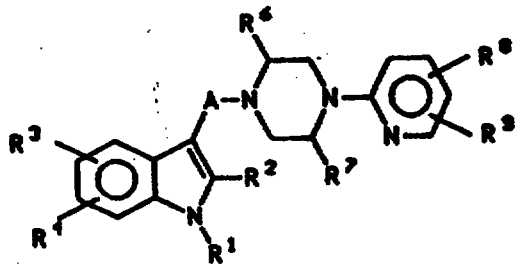
9. Composition pharmaceutique selon la revendication 8, sous forme de dosage unitaire approprié pour une administration systémique à un hôte mammalien comprenant un porteur pharmaceutique et d'environ 1 à 500 mg d'au moins un composé selon les revendications 1 à 6.

10. Procédé pour préparer les compositions pharmaceutiques des revendications 8 ou 9, qui comprend la fourniture d'au moins un composé des revendications 1 à 6, sous une forme appropriée pour administration systémique, de préférence sous forme de dosage unitaire, et optionnellement incorporée dans un porteur pharmaceutique.

11. Utilisation d'au moins un composé des revendications 1 à 6 pour préparer une composition pharmaceutique pour améliorer un état indésirable de dépression chez un mammifère.

Revendications pour l'Etat contractant suivant : ES

1. Procédé pour préparer un composé de formule I et les sels d'addition d'un acide pharmaceutiquement acceptables de celui-ci.



(I)

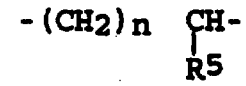
où

R^1 et R^2 sont indépendamment choisis parmi un alkyle en C_{1-4} ou un hydrogène ;

R^3, R^4, R^8 et R^9 sont indépendamment choisis parmi un hydrogène, un alkyle en C_{1-4}, un alcoxy en C_{1-4}, un carbamide, un halogène, un trifluorométhyle et un thio-alkyle en C_{1-4}, avec la condition que R^8 et R^9 ne peuvent pas être tous les deux un hydrogène en même temps;

A est un cycle cycloalcényle ou cycloalcanyle en C_{5-7}, ou

A est

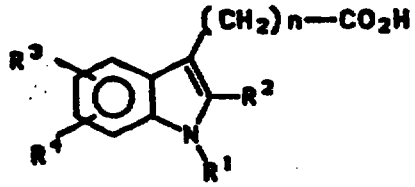


où n est un entier de 1 à 3 et R^5 est identique à R^1; et

R^6 et R^7 sont indépendamment choisis parmi un hydrogène, un méthyle ou R^6 et R^7 peuvent être pris ensemble comme un pont méthylène,

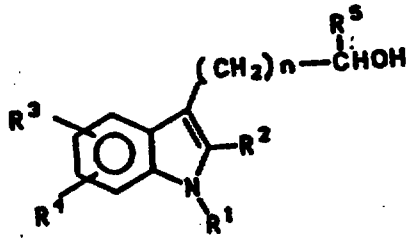
caractérisé en ce que

A) un composé de formule générale II :



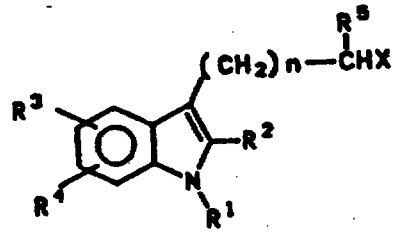
(II)

est mis à réagir avec un composé de formule générale R^5-M, où M représente une espèce métalloïde, pour obtenir un composé de formule générale VI :



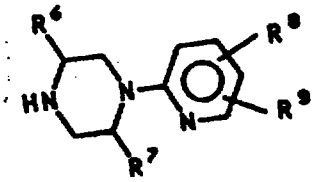
(VI)

un composé de formule générale VI est mis à réagir avec un réactif Y-X, où X est un groupe partant et Y est un atome d'hydrogène ou un contre-ion pour obtenir un composé de formule générale V :



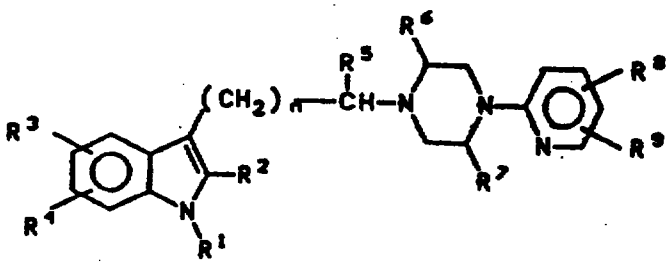
(V)

un composé de formule générale V est mis à réagir avec un composé de formule générale III :



(III)

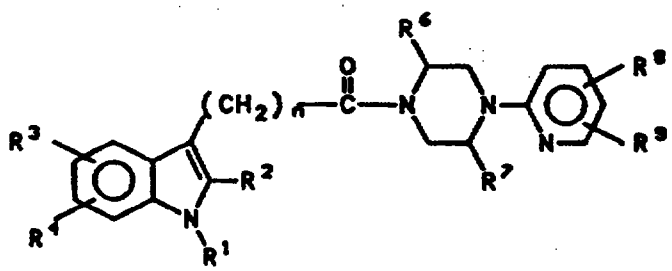
pour obtenir un composé de formule générale Ia



(Ia)

ou

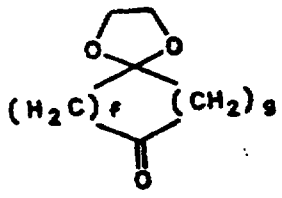
B) un composé de formule générale II ou un équivalent actif de celui-ci est mis à réagir avec un composé de formule générale III pour obtenir un composé de formule générale IV :



(IV)

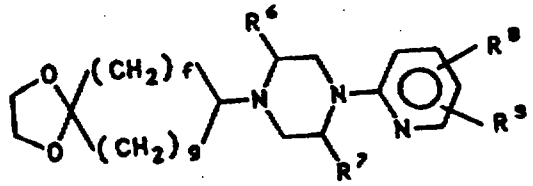
un composé de formule générale IV est mis à réagir avec R^5-M, où R^5 est défini comme ci-dessus, pour obtenir un composé de formule générale Ia, ou

C) un composé de formule générale III est alkylaté de façon réductrice avec un composé de formule générale X:



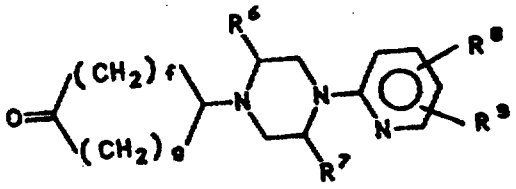
(X)

où f et g sont des entiers de 0 à 5 avec la condition que f + g doit être égal à 3, 4 ou 5, pour donner un composé de formule générale IX :



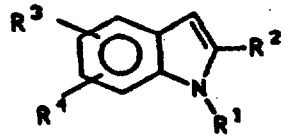
(IX)

un composé de formule générale IX est déprotégé pour produire un composé de formule générale VIII



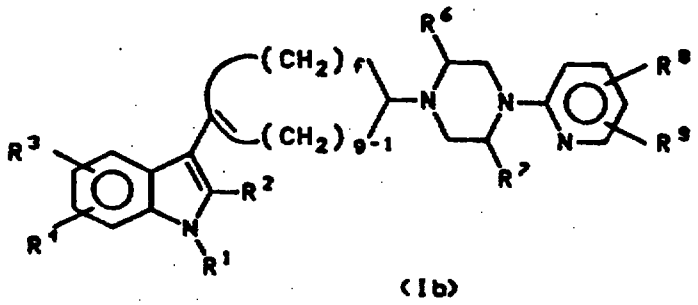
(VIII)

un composé de formule générale VIII est condensé avec un composé de formule générale VII



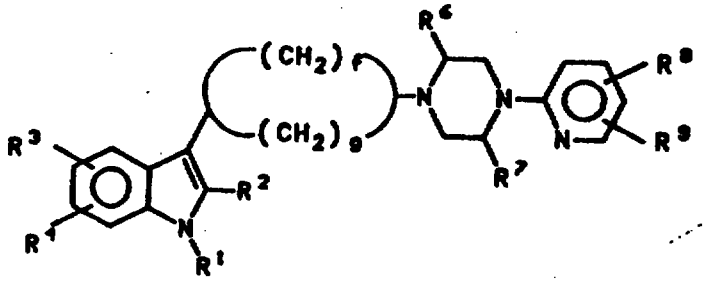
(VII)

pour donner un composé de formule générale Ib



(Ib)

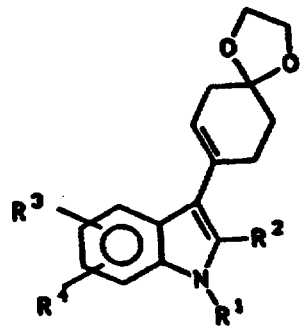
et, si désiré, un composé de formule générale Ib est réduit en un composé de formule générale Ic :



(Ic)

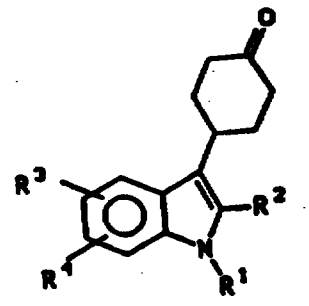
ou

D) un composé de formule générale VIII est condensé avec un composé de formule générale X pour donner un composé de formule générale XII



(XII)

un composé de formule générale XII est réduit et décétalisé en un composé de formule générale XI :



(XI)

un composé de formule générale XI est condensé avec un composé de formule générale III pour obtenir un composé de formule Ic,
les symboles R^1 à R^9 et n étant définis comme dans la revendication 1, et,
si désiré, un composé ainsi obtenu de formule I est converti en un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci.

2. Procédé selon la revendication 1 où A est un cycle cycloalcényle ou cycloalkanyle en C_{5-7}.

3. Procédé selon la revendication 1, où A est



4. Procédé selon la revendication 1, où R^6 et R^7 sont choisis parmi un hydrogène ou un méthyle.

5. Procédé selon la revendication 1, où R^6 et R^7 sont pris ensemble comme un pont méthylène.

6. Procédé selon la revendication 1 pour la préparation de :
1-[2-(1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine;
1-[2-(1H-indol-3-yl)éthyl]-4-(3-trifluorométhyl-2-pyridinyl)pipérazine;
1-[2-(1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)-2-méthylpipérazine;
1-[2-(1H-indol-3-yl)éthyl]-5-(3-méthoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1]heptane ;
1-[2-(1H-indol-3-yl)éthyl]-4-(6-chloro-2-pyridinyl)-pipérazine;
1-[2-(1H-indol-3-yl)éthyl]-4-(6-méthoxy-2-pyridinyl)-pipérazine;
1-[2-(1H-indol-3-yl)éthyl]-5-(3-méthoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptane;
1-[3-(1H-indol-3-yl)propyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[3-(1H-indol-3-yl)propyl]-4-(6-chloro-2-pyridinyl)pipérazine;
1-[4-(1H-indol-3-yl)butyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(1H-indol-3-yl)éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
2-[2-(1H-indol-3-yl)éthyl]-5-(6-chloro-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane;
2-[2-(1H-indol-3-yl)éthyl]-5-(6-chloro-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1]heptane;
1-[3-(1H-indol-3-yl)propyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[4-(1H-indol-3-yl)butyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[4-(1H-indol-3-yl)butyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[3-(1H-indol-3-yl)propyl]-4-(4-trifluorométhyl-2-pyridinyl)pipérazine ;
2-[3-(1H-indol-3-yl)propyl]-5-(3-méthoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptane ;
2-[3-(1H-indol-3-yl)propyl]-5-(3-méthoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptane ;
1-[2-(1H-indol-3-yl)éthyl]-4-(6-chloro-2-pyridinyl)-2-méthylpipérazine ;
1-[2-(1H-indol-3-yl)éthyl]-4-(4-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[2-(5-méthoxy-1H-indol-3-yl)-éthyl-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5-fluoro-1H-indol-3-yl)-éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5-méthoxy-1H-indol-3-yl)-éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[2-(5-fluoro-1H-indol-3-yl)-éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[2-(1H-indol-3-yl)-éthyl]-4-(3-chloro-2-pyridinyl)pipérazine ;
1-[2-(5-fluoro-1H-indol-3-yl)-éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[2-(5-méthoxy-1H-indol-3-yl)-éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-pipérazinyl]-1-cyclohexen-1-yl]-5-méthoxyindole ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-pipérazinyl]-1-cyclohexèn-1-yl]-1H-indole ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-pipérazinyl]-1-cyclohexèn-1-yl]-1H-indole-5-carboxamide ;
1-[2-(N-méthyl-1H-indol-3-yl)-éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5,6-diméthoxy-1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5,6-diméthoxy-1H-indol-3-yl)éthyl]-4-(6-chloro-(2-pyridinyl)pipérazine ;
1-[3-(N-méthyl-1H-indol-3-yl)-propyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[3-(N-méthyl-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(1H-indol-3-yl)éthyl]-4-(5-chloro-2-pyridinyl)pipérazine ;
1-[2-[N-méthyl-1H-indol-3-yl)-éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[2-(5-chloro-1H-indol-3-yl)-éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5-chloro-1H-indol-3-yl)-éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[2-(5-chloro-1H-indol-3-yl)éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[2-(1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)-2-méthyl-pipérazine ;
4-(6-chloro-2-pyridinyl)-1-[2-(6-méthoxy-1H-indol-3-yl)éthyl]-pipérazine ;

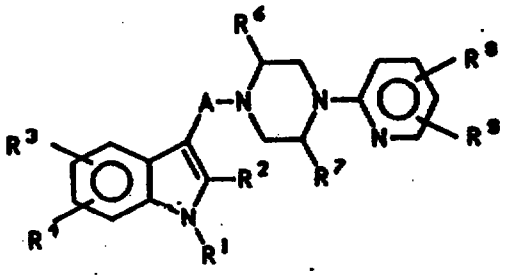
1-[2-6-méthoxy-1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[3-(1H-indol-3-yl)-3-méthyl-propyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[3-(1H-indol-3-yl)-3-méthyl-propyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5,6-diméthoxy-1H-indol-3-yl)éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-pipérazinyl]-1-cyclohexèn-1-yl]-5-fluoro-1H-indole ;
4-(5-chloro-2-méthoxy-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]pipérazine hydrochlorure ;
4-(6-chloro-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]-2-méthyl-pipérazine.

7. Procédé pour préparer une composition pharmaceutique qui comprend la fourniture d'au moins un composé selon l'une des revendications 1 à 6 sous une forme appropriée pour administration optionnellement incorporée dans un porteur pharmaceutique, et/ou un adjuvant.

8. Procédé pour préparer une composition pharmaceutique selon la revendication 7, sous forme de dosage unitaire approprié pour l'administration systémique à un hôte mammalien qui comprend le mélange d'un porteur pharmaceutique avec d'environ 1 à 500 mg d'au moins un composé selon les revendications 1 à 6.

Revendications pour l'Etat contractant suivant : GR

1. Composé de formule I et les sels d'addition d'un acide pharmaceutiquement acceptables de celui-ci.



(I)

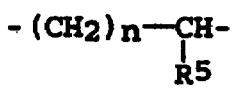
où

R^1 et R^2 sont indépendamment choisis parmi un alkyle en C_{1-4} ou un hydrogène ;

R^3, R^4, R^8 et R^9 sont indépendamment choisis parmi un hydrogène, un alkyle en C_{1-4}, un alcoxy en C_{1-4}, un carbamide, un halogène, un trifluorométhyle et un thio-alkyle en C_{1-4}, avec la condition que R^8 et R^9 ne peuvent pas être tous les deux un hydrogène en même temps;

A est un cycle cycloalcényle ou cycloalcanyle en C_{5-7}, ou

A est

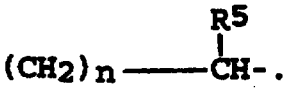


où n est un entier de 1 à 3 et R^5 est identique à R^1; et

R^6 et R^7 sont indépendamment choisis parmi un hydrogène, un méthyle ou R^6 et R^7 peuvent être pris ensemble comme un pont méthylène.

2. Composé selon la revendication 1, où A est un cycle cycloalcényle ou cycloalcanyle en C_{5-7}.

3. Composé selon la revendication 1, où A est

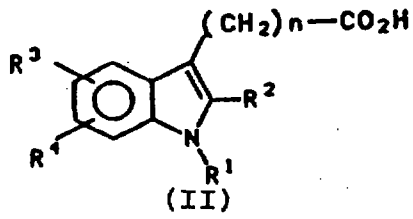


4. Composé selon la revendication 1, où R^6 et R^7 sont choisis parmi un hydrogène ou un méthyle.

5. Composé selon la revendication 1, où R^6 et R^7 sont pris ensemble comme un pont méthylène.

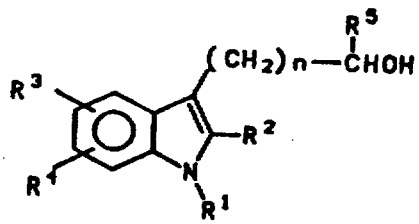
6. Composés selon la revendication 1 :
1-[2-(1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine;
1-[2-(1H-indol-3-yl)éthyl]-4-(3-trifluorométhyl-2-pyridinyl)pipérazine;
1-[2-(1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)-2-méthylpipérazine;
1-[2-(1H-indol-3-yl)éthyl]-5-(3-méthoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1]heptane ;
1-[2-(1H-indol-3-yl)éthyl]-4-(6-chloro-2-pyridinyl)-pipérazine;
1-[2-(1H-indol-3-yl)éthyl]-4-(6-méthoxy-2-pyridinyl)-pipérazine;
1-[2-(1H-indol-3-yl)éthyl]-5-(3-méthoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptane;
1-[3-(1H-indol-3-yl)propyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[3-(1H-indol-3-yl)propyl]-4-(6-chloro-2-pyridinyl)pipérazine;
1-[4-(1H-indol-3-yl)butyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(1H-indol-3-yl)éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
2-[2-(1H-indol-3-yl)éthyl]-5-(6-chloro-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane;
2-[2-(1H-indol-3-yl)éthyl]-5-(6-chloro-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1]heptane;
1-[3-(1H-indol-3-yl)propyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[4-(1H-indol-3-yl)butyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[4-(1H-indol-3-yl)butyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[3-(1H-indol-3-yl)propyl]-4-(4-trifluorométhyl-2-pyridinyl)pipérazine ;
2-[3-(1H-indol-3-yl)propyl]-5-(3-méthoxy-2-pyridinyl)(1S,4S)-2,5-diazabicyclo[2.2.1] heptane ;
2-[3-(1H-indol-3-yl)propyl]-5-(3-méthoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptane ;
1-[2-(1H-indol-3-yl)éthyl]-4-(6-chloro-2-pyridinyl)-2-méthylpipérazine ;
1-[2-(1H-indol-3-yl)éthyl]-4-(4-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[2-(5-méthoxy-1H-indol-3-yl)-éthyl-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5-fluoro-1H-indol-3-yl)-éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5-méthoxy-1H-indol-3-yl)-éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[2-(5-fluoro-1H-indol-3-yl)-éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[2-(1H-indol-3-yl)-éthyl]-4-(3-chloro-2-pyridinyl)pipérazine ;
1-[2-(5-fluoro-1H-indol-3-yl)-éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[2-(5-méthoxy-1H-indol-3-yl)-éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-pipérazinyl]-1-cyclohexen-1-yl]-5-méthoxyindole ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-pipérazinyl]-1-cyclohexèn-1-yl]-1H-indole ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-pipérazinyl]-1-cyclohexèn-1-yl]-1H-indole-5-carboxamide ;
1-[2-(N-méthyl-1H-indol-3-yl)-éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5,6-diméthoxy-1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5,6-diméthoxy-1H-indol-3-yl)éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[3-(N-méthyl-1H-indol-3-yl)-propyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[3-(N-méthyl-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[3-(5-fluoro-1H-indol-3-yl)-propyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(1H-indol-3-yl)éthyl]-4-(5-chloro-2-pyridinyl)pipérazine ;
1-[2-[N-méthyl-1H-indol-3-yl)-éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[2-(5-chloro-1H-indol-3-yl)-éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5-chloro-1H-indol-3-yl)-éthyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[2-(5-chloro-1H-indol-3-yl)éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
1-[2-(1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)-2-méthyl-pipérazine ;
4-(6-chloro-2-pyridinyl)-1-[2-(6-méthoxy-1H-indol-3-yl)éthyl]-pipérazine ;
1-[2-6-méthoxy-1H-indol-3-yl)éthyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[3-(1H-indol-3-yl)-3-méthyl-propyl]-4-(6-chloro-2-pyridinyl)pipérazine ;
1-[3-(1H-indol-3-yl)-3-méthyl-propyl]-4-(3-méthoxy-2-pyridinyl)pipérazine ;
1-[2-(5,6-diméthoxy-1H-indol-3-yl)éthyl]-4-(6-trifluorométhyl-2-pyridinyl)pipérazine ;
3-[4-[4-(6-chloro-2-pyridinyl)-1-pipérazinyl]-1-cyclohexèn-1-yl]-5-fluoro-1H-indole ;
4-(5-chloro-3-méthoxy-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]pipérazine hydrochlorure ;
4-(6-chloro-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]-2-méthyl-pipérazine.

7. Procédé pour préparer les composés des revendications 1 à 6, caractérisé en ce que
A) un composé de formule générale II:



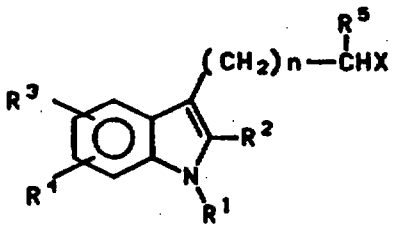
(II)

est mis à réagir avec un composé de formule générale R^5-M, où M représente une espèce métalloide, pour obtenir un composé de formule générale VI:



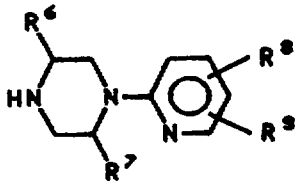
(VI)

un composé de formule générale VI est mis à réagir avec un réactif Y-X, où X est un groupe partant et Y est un atome d'hydrogène ou un contre-ion, pour obtenir un composé de formule générale V :



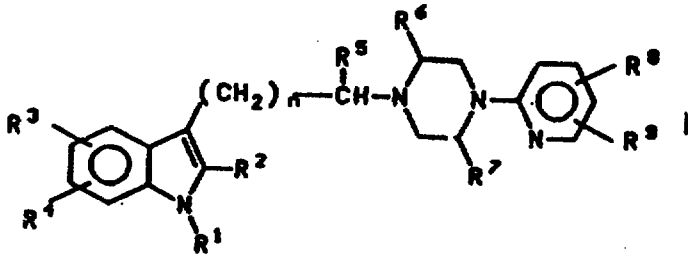
(V)

un composé de formule générale V est mis à réagir avec un composé de formule générale III :



(III)

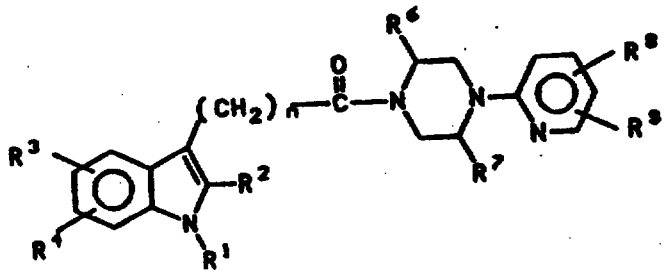
pour obtenir un composé de formule générale Ia.



(Ia)

ou

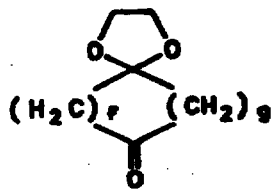
B) un composé de formule générale II ou un équivalent actif de celui-ci est mis à réagir avec un composé de formule générale III pour obtenir un composé de formule générale IV:



(IV)

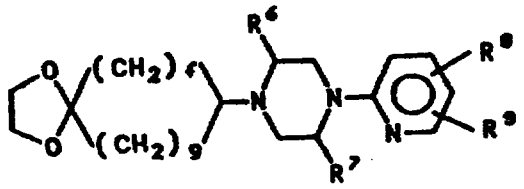
un composé de formule générale IV est mis à réagir avec R^5-M, où R^5 est défini comme ci-dessus, pour obtenir un composé de formule générale Ia, ou

C) un composé de formule générale III est alkylaté de façon réductrice avec un composé de formule générale X



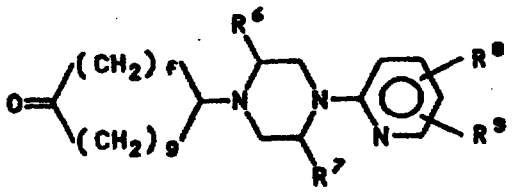
(X)

où f et g sont des entiers de 0 à 5 avec la condition que f + g doit être égal à 3, 4 ou 5, pour donner un composé de formule générale IX :



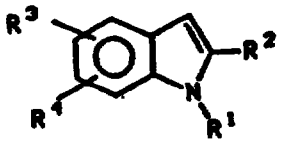
(IX)

un composé de formule générale IX est déprotégé pour produire un composé de formule générale VIII



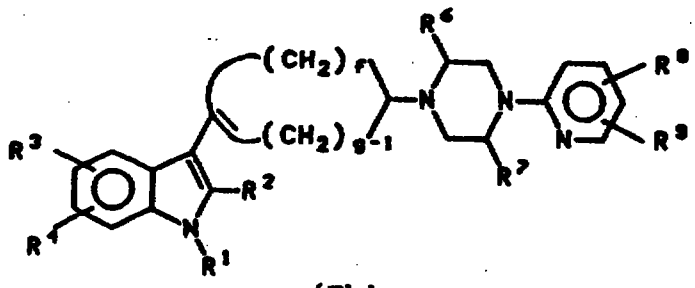
(VIII)

un composé de formule générale VIII est condensé avec un composé de formule générale VII



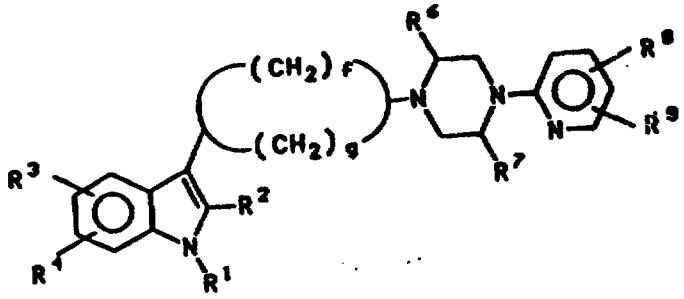
(VII)

pour donner un composé de formule générale Ib



(Ib)

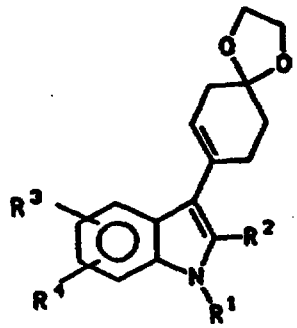
et, si souhaité, un composé de formule générale Ib est réduit en un composé de la formule générale IC:



(Ic)

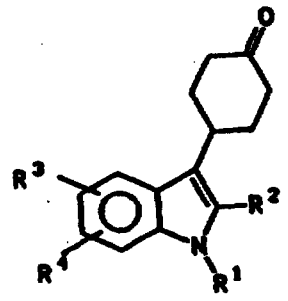
ou

D) un composé de formule générale VIII est condensé avec un composé de formule générale X pour donner un composé de formule générale XII



(XII)

un composé de formule générale XII est réduit et décétalisé en un composé de formule générale XI :



(XI)

un composé de formule générale XI est condensé avec un composé de formule générale III pour donner un composé de formule générale Ic,
les symboles R^1 à R^9 et n étant définis comme en revendication 1, et
si souhaité, un composé ainsi obtenu de formule I est converti en un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci.

8. Procédé pour préparer une composition pharmaceutique qui comprend la fourniture d'au moins un composé des revendications 1 à 6, sous une forme appropriée pour administration optionnellement

* C L M S *

incorporée dans un porteur et/ou un adjuvant pharmaceutique.

9. Procédé pour préparer une composition pharmaceutique selon la revendication 8, sous forme de dosage unitaire approprié pour une administration systémique à un hôte mammalien qui comprend le mélange d' un porteur pharmaceutique avec d'environ 1 à 500 mg d'au moins un composé selon les revendications 1 à 6.

10. Utilisation d'au moins un composé selon les revendications 1 à 6 pour préparer une composition pharmaceutique pour améliorer un état indésirable de dépression chez un mammifère.