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INDOLE DERIVATIVES AS 5-HT1A AND/OR 5-HT2 LIGANDS

The present invention relates to novel pharmacologically active indole derivatives and acid addition salts thereof, to processes for their preparation and to pharmaceutical compositions containing them. The new compounds possess central serotonergic activity and are useful in the treatment of central nervous system (CNS) disorders.

It is known that 1 A and 2 serotonergic receptors ($5\text{-}HT_{1A}$ and $5\text{-}HT_2$) seem to be important for many functions in the animal body. For instance, altered function of these receptors is involved in the genesis and/or treatment of anxiety, depression, psychoses, abnormality of sleep and feeding, organic mental diseases and alteration of blood pressure. In spite of the clear involvement of $5\text{-}HT_{1A}$ receptors in such a huge amount of pathological events, it is not clear why, for example, some compounds acting upon $5\text{-}HT_{1A}$ receptors exert in humans a preferential anxiolytic effects, while others exert a preferential hypotensive action. The same holds for $5\text{-}HT_2$ antagonists. This is probably due to heterogeneous characteristics, so far unknown, of $5\text{-}HT_{1A}$ and $5\text{-}HT_2$ receptors. Therefore, there is the possibility that compounds acting on $5\text{-}HT_{1A}$ and/or $5\text{-}HT_2$ receptors may exert a wide range of therapeutic effects in humans.

WO Patent 9206973 refers to 5-substituted 3(N-methyl-pyrrolidin-2-yl-methyl) indoles. The compounds are said to be useful for the treatment of depression, anxiety, migraine. WO Patent 9213856 refer to 5-hete-

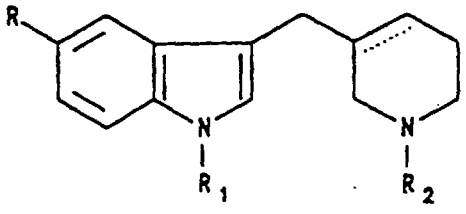
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royl indoles. The compounds are said to be useful in treating migraine.

European Patent Application Number 429341 refer to 5-substituted to heterocyclic derivatives, including among the others, the compound named 3[N(isothiazole-dioxyde-ethyl)-1,2,3,6-tetrahydropyridin-4-ylmethyl]-indole. Such compounds are said to be 5-HT reuptake inhibitors, useful in the treatment of depression.

We have now synthetized, and this is the object of the present invention, a novel class of structurally distinct compounds showing affinity for the $5\text{-}HT_{1A}$ and/or $5\text{-}HT_2$ receptors. These new compounds may be useful in the treatment of CNS diseases such as affective disorders, (for example depression and bipolar disorders), anxiety, sleep and sexual disorders, psychosis, schizophrenia, personality disorders, mental organic disorders and mental disorders in childhood, aggressiveness, age associated memory impairment, cerebral ictus, motion sickness. Moreover they may be used for cardiovascular disorders such as hypertension and thrombosis.

The present invention has for object compounds of general formula (I)



wherein:

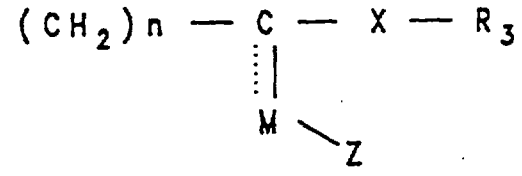
R represents H, C_{1-6} alkyl, lower alkoxy, aralkoxy,

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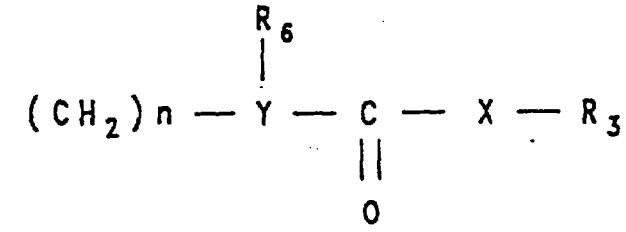
halogen, hydroxy, cyano or C_{1-6} acyl;

R_1 represents H, C_{1-6} alkyl, optionally substituted aryl, C_{3-6} cycloalkyl C_{1-2} alkyl or lower alkyl bearing an optionally substituted phenyl;

R_2 represents H, C_{1-6} alkyl, lower alkyl bearing a phenyl, phenoxy or anilino, each group being optionally substituted by one or more substituents selected from lower alkyl, lower alkoxy, amino, halogen or trifluoromethyl; or R_2 is a group selected from



(a)



(b)

where n is an integer from 1 to 3;

R_3 represents an aryl or heteroaryl group, each group being optionally substituted by one or more substituents selected from lower alkyl, halogen or trifluoromethyl; C_{1-6} alkyl or C_4-C_{10} cycloalkyl;

M represents oxygen or nitrogen, or when the bond C-M is single, represents NH;

Z is absent when M is oxygen or it represents H, C_{1-6} acyl or OR_4 where R_4 is hydrogen, lower alkyl, lower alkyl bearing a phenyl being optionally substituted by one or more substituents selected from lower alkyl, lower alkoxy, halogen, trifluoro-

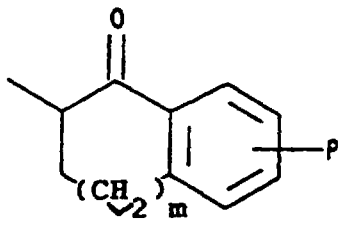
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methyl;

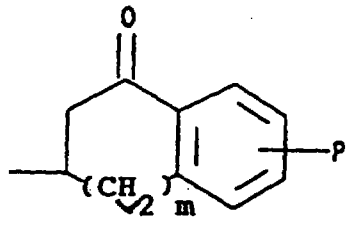
X is absent or it represents CH_2 or NR_5 where R_5 is H or lower alkyl;

Y represents CH or nitrogen atom;

R_6 represents hydrogen, lower alkyl, aryl or R_3 and R_6 together with the carbonyl group to which they are bound constitute benzocondensed cycloalkanones of formula



(c)



(d)

m is an integer from 0 to 2;

P represents H, lower alkyl, halogen or trifluoromethyl;

and acid addition salts thereof.

For pharmaceutical use the compounds of general formula (I) may be used as such or in the form of tautomers or of physiologically acceptable acid addition salts thereof. The term "acid addition salts" includes salts either with inorganic or organic acids. Physiologically acceptable organic acids which may be used in salt formation include, for example, maleic, citric, tartaric, fumaric, methanesulphonic, acetic, benzoic, succinic, gluconic, isethionic, glycinic, lactic, malic, mucoic, glutamic, sulphamic and ascorbic acid; suitable inorganic acids include hydrochloric, hydrobromic, nitric, sulfuric or phosphoric acid.

Some of the compounds of formula (I) according to

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the present invention contain chiral or prochiral centres and thus may exist in different stereoisomeric forms including enantiomers of (+) and (-) type or mixtures of them. The present invention includes in its scope both the individual isomers and the mixtures thereof.

It has to be understood that, when mixtures of optical isomers are present, they may be separated according to the classic resolution methods based on their physico-chemical properties, e.g. by fractional crystallization of their acid addition salts with a suitable optically active acid or by the chromatographic separation with a suitable mixture of solvents.

In the present specification, the term C_{1-6} alkyl denotes a straight or branched chain. Typical groups of that kind include methyl, ethyl, n-propyl, i-propyl, n-butyl, n-hexyl, 2-methyl-pentyl and the like. The term lower alkyl group denotes a straight alkyl group having 1 to 3 carbon atoms such as methyl, ethyl, propyl. The term lower alkoxy refers to a straight alkoxy group containing 1 to 3 carbon atoms such as methoxy, ethoxy, propoxy. The term halogen means fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine, chlorine and bromine.

When R represents an aralkoxy group, it may, for example, be benzyloxy.

When R_1 represents a C_{3-6} cycloalkyl C_{1-2} alkyl group, it may, for example, be a cyclopropylmethyl, cyclopentylmethyl.

When R represents a C_{1-6} acyl group, it may, for example, be a acetyl, propionyl, butyryl, pentoyl,

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hexoyl.

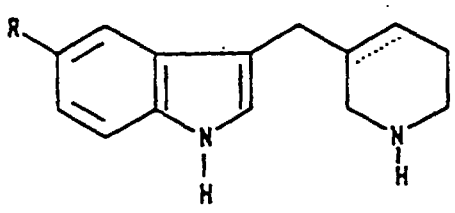
When R_1 is a lower alkyl bearing an optionally substituted phenyl, it may, for example, be benzyl.

When R_1 is optionally substituted aryl, it may, for example, be phenyl, fluorophenyl.

When R_3 and R_6 together with the carbonyl group to which they are bound form benzocondensed cycloalkanones (formula c, d) they may, for example, be indalones, tetralones.

When R_3 is aryl, it may, for example, be phenyl, mono-or difluorophenyl, trifluoromethylphenyl. When R_3 is heteroaryl, it may, for example, be thienyl. When R_3 is a C_{4-10} cycloalkyl, it may, for example, be an adamantyl group.

The compounds of formula I wherein R_1 is hydrogen may be prepared by reacting compounds of the formula (II)



II

wherein R is defined above, with a compound of formula (III)

$$R_2 - X \qquad \text{III}$$

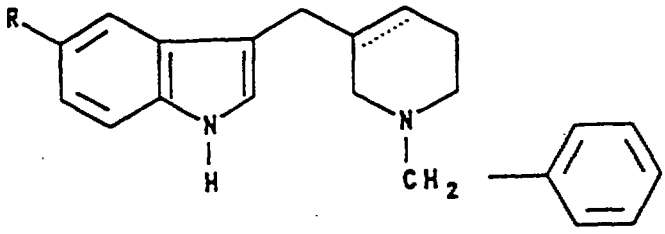
wherein R_2 is as defined above and X is a halogen atom in the presence of a base such as sodium carbonate or potassium carbonate. The reaction is carried out in an inert polar solvent such as diethyl ether, tetrahydrofuran or dimethylformamide, preferably dimethylfor-

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mamide at a temperature ranging from 50° to 80°C.

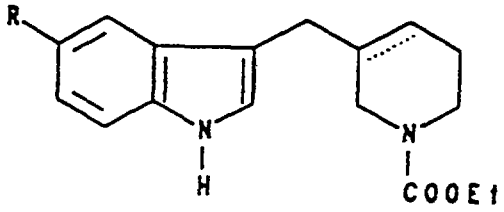
The compounds of formula III are either commercially available or may be conveniently prepared by conventional methods.

The compounds of formula II, used as starting material in the above described process, may be prepared from compounds of formula IV



IV

wherein R is as defined before, by debenzylation with ethyl chloroformate, followed by hydrolysis of the intermediate carbamate of formula (V)



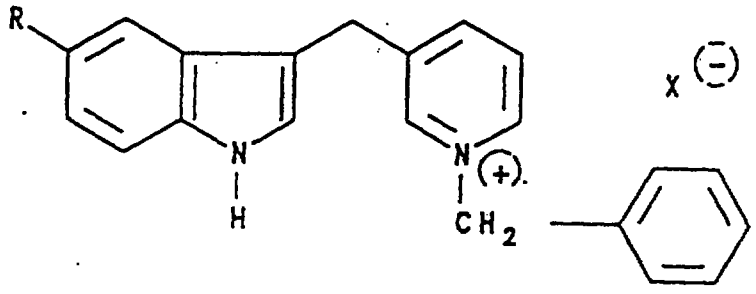
V

The carbamate formation is carried out in an inert solvent such as benzene or toluene, preferably toluene, at a temperature ranging from about 20°C to about 80°C. The subsequent hydrolysis of the carbamate of formula V is carried out in basic conditions. Suitable bases are inorganic base preferably potassium hydro-

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xide. A polar solvent should be used such as an alcohol, preferably ethanol, at a temperature of about 80°C.

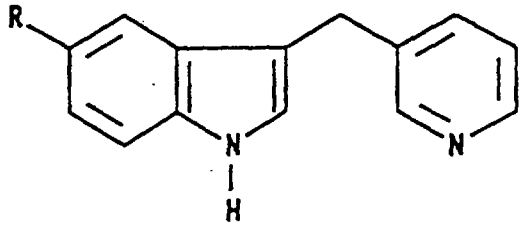
The compounds of formula IV may be, in turn, prepared by hydride reduction of the quaternized salts of formula VI



VI

wherein R is as defined above and X is a halogen atom. Suitable hydride reducing agents include, lithium borohydride and sodium borohydride, preferably sodium borohydride. The reaction is carried out in the presence of a polar solvent such as an alcohol like ethanol, isopropanol or methanol, preferably methanol, at a temperature ranging from about -10°C to about 10°C.

The quaternized salts of formula VI may be formed, in turn, by quaternarization of compounds of formula VII

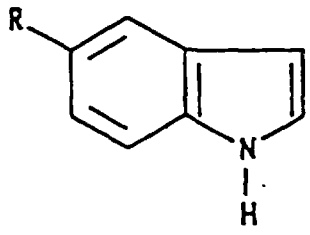


VII

wherein R is as defined above, with a benzyl halide in the presence of suitable solvents such as ketones, for

example methyl-ethyl-ketone, dimethyl-ketone preferably methyl-ethyl-ketone at a temperature ranging from 60°C to about 90°C, preferably the reflux temperature of the solvent.

The compounds of formula VII may be, in turn, prepared by reacting a magnesium salt of an indole derivative of the formula VIII



VIII

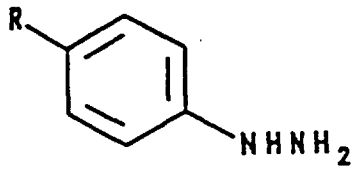
wherein R is as defined above, with the 3-chloromethylpyridine. The indole magnesium salt is first prepared from the reaction of the indole of formula VIII with an alkyl or aryl magnesium halide preferably ethylmagnesium bromide. [De Gran J.J. et al., J. Heterocyclic Chem., 3, 67 (1966)]. The reaction is generally conducted in an inert solvent at a temperature between about -30°C and 65°C, preferably at about 25°C.

Suitable solvents include diethyl ether, tetrahydrofuran, and other alkyl ethers, preferably diethyl ether.

Preferably, a solution of the commercial 3-chloromethylpyridine in an inert solvent (e.g. diethyl ether, tetrahydrofuran or toluene) is added slowly to the solution of the magnesium salt of an indole of formula VIII at a temperature ranging from about 0°C to about 50°C, preferably at about 25°C.

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The compounds of formula VII may be, in turn, also prepared by the typical Fischer indole synthesis between an apropriate phenyl hydrazine of formula IX



IX

wherein R is as defined above, and the 3-pyridinpropionaldehyde. The Fischer reaction is usually carried out under acidic conditions in a polar solvent. Suitable acids for the use in the reaction include acetic acid, hydrobromic acid or hydrochloric acid, preferably hydrochloric acid. A suitable polar solvent may be an alcohol, preferably ethanol. The reaction is performed at a temperature between 60°C and about 90°C, preferably the reflux temperature of the solvent. The 3-pyridinpropionaldehyde is prepared according to a conventional oxidation of the relative alcohol. [D. Swern et al., Tetrahedron, 34, 1651 (1978)].

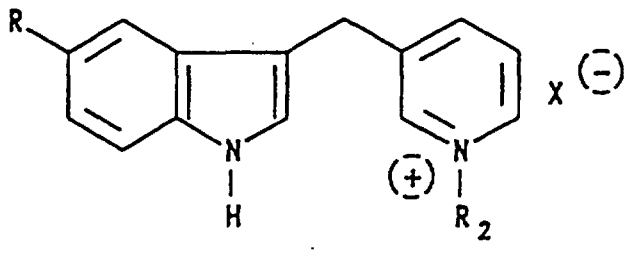
The compounds of formula I, wherein R_1 is any meaning as defined above except hydrogen may be prepared by reacting compounds of formula I, wherein R_1 = H, with a base such as sodium hydride, potassium hydroxide, potassium terbutylate, preferably sodium hydride. This is followed by the addition of compounds of the formula X

$$R_1 - X \qquad X$$

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wherein R_1 is any meaning as defined above except hydrogen and X is halogen atom, in a stoichiometric amount. The reaction is carried out in an inert polar solvent such as diethyl ether, tetrahydrofuran or dimethylformamide, preferably dimethylformamide, at a temperature ranging from 0° to room temperature.

The compounds of formula I, wherein R_1 is hydrogen, may also be prepared by hydride reduction of the quaternized salts of formula



XI

wherein R and R_2 are as defined above, and X is a halogen atom. Suitable hydride reducing agents include lithium borohydride and sodium borohydride, preferably sodium borohydride. The reaction is carried out in the presence of a polar solvent as an alcohol like ethanol, isopropanol or methanol, preferably methanol at a temperature ranging from -10°C to about 10°C.

When the compounds of formula I with the 3-pyridine ring completely saturated are desired, the reduction of the quaternized salts of formula XI is carried out catalytically, under hydrogen atmosphere, preferably at a pressure of about 1 atmosphere. Suitable catalysts include Raney nickel, platinum oxide, preferably platinum oxide. The reaction is carried out in the presence of a polar solvent such as an alcohol like

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ethanol or methanol, preferably methanol at a temperature ranging from about 0°C to 40°C, preferably at about 25°C.

The quaternized salts of formula XI, used as starting material in the above process, may be prepared by reacting compounds of formula VI with compounds of formula III, both already defined above.

It has to be understood that compounds of general formula (I) containing an R, R_1, R_2, R_3, R_4, R_5 and R_6, group which may give rise to another R, R_1, R_2, R_3, R_4, R_5 and R_6 group, are useful novel intermediates. Some of these transformations may also occurr in the intermediates for compounds of general formula (I).

Some examples of such conversions, which obviously are not exhaustive of all possibilities, are:

1) a nitro group may be transformed into an amino group by reduction
2) an amino group may be transformed into a C_{1-6} acylamino group by acylation with a suitable carboxylic acid derivative
3) an amino group may be transformed into a lower alkyl N-mono or di-substituted group by alkylation
4) an amino group may be transformed into a lower alkoxy carbonyl amino group by reaction with a suitable reactive lower alkyl carbonic acid monoester derivative
5) a carboxyl group may be transformed into a lower alkoxy carbonyl group, or into a carbamoyl group optionally lower alkyl N-mono or di-substituted by reaction of a suitable reactive carboxylic acid derivative with appropriate alkohols and amines

6) a carbamoyl group may be transformed into a cyano group by dehydration

7) a C_{1-6} alkyl thio or a C_{1-6} alkyl sulphinyl group may be transformed into a C_{1-6} alkyl sulphinyl or a C_{1-6} alkylsulphonyl group by oxidation

8) an aromatic hydrogen may be transformed into a nitro group by nitration

9) a hydrogen group may be transformed into a halogen group by halogenation

10) a product of general formula I where R_1 is H obtained according to the above described process, may be transformed in a product of formula I, where R_1 is C_{1-6} alkyl, by alkylation with a suitable alkyl halide in the presence of a strong base such as sdium or potassium hydroxide, sodium or potassium hydride, potassium t-butylate in an aprotic solvent such as dimethylformamide or tetrahydrofuran at a temperature between 20°C and 100°C. When aqueous concentrated solutions of sodium or potassium hydroxide are used, the reaction may be conveniently carried out in the presence of an unsoluble organic solvent, such as methylene chloride in the presence of phase transfer catalyst such as a suitable ammonium quaternary salt at a temperature between 20°C and 50°C

11) a tertiary amino group may be transformed into a quaternary ammonium derivative by reaction with a suitable alkylating agent such as methyl bromide or methyl iodide.

These transformations are well known to any expert of the branch.

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The compounds of the general formula (I) prepared according to the above methods may optionally be converted by inorganic or organic acids into non-toxic, physiologically acceptable acid addition salts, for example by conventional methods such as by reacting the compounds as bases with a solution of the corresponding acid in a suitable solvent. Example of non-toxic physiologically acceptable acid addition salts are those formed with hydrochloric, nitric sulfuric, maleic, fumaric, citric, tartaric, methanesulphonic, acetic, benzoic, succinic, gluconic, lactic, glycinic, malic, mucoic, glutamic, isethionic, phosphoric, ascorbic or sulphamic acid. Particularly preferred acids are hydrochloric, maleic and fumaric acid.

Particularly preferred compounds according to the present invention are:

5-methoxy-3-(N-methyl-1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole (Compound 1)

5-methoxy-3-[N-(2-(4-amino-phenyl)-ethyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole (Compound 13)

5-methoxy-3-[N-(4'-fluoro-phenoxy-ethyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole (Compound 2)

5-methoxy-3-[N-(4-(4-fluoro-phenyl)-4-oxo-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole (Compound 9)

5-methoxy-3-[N-(3-(4-fluoro-phenyl)-3-oxo-propyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole (Compound 11)

5-methoxy-3-[N-(4-(4-fluoro-phenyl)-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole (Compound 14)

5-methoxy-3-[N-2(4-fluoro-benzamide)ethyl)-1,2,5,6-te-

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trahydro-pyridin-3-ylmethyl]-1H-indole (Compound 16)
5-methoxy-3-[N-(3-(4-fluoro-phenyl)-propyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole (Compound 15)
5-methoxy-3-[N-(4-(2--thienyl)-4-oxo-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole (Compound 32)

As already mentioned hereinbefore, the new compounds of formula (I), according to the present invention, show interesting pharmacological properties owing to their activity on CNS serotonergic receptors, particularly 5-HT_{1A} and/or 5-HT_2 receptor subtypes. Therefore the new compounds are commercially useful in the prevention and in the treatment of disorders wherein the alterated functionality of 5-HT_{1A} and/or 5-HT_2 receptors, as above mentioned, is involved.

The biochemical and pharmacological profile of the compounds object of the present invention was assessed by evaluating their affinity for 5-HT_{1A} and 5-HT_2 receptors and their efficacy was established: a) in inducing the well-known behavioural syndrome due to the stimulation of 5-HT_{1A} receptors and b) by evaluating the antagonism towards the behavioural syndrome induced by quipazine stimulating the 5-HT_2 receptors.

RECEPTOR BINDING STUDIES

Receptor binding studies on 5-HT_{1A} and 5-HT_2 receptors were carried out to determine the affinity of the test compounds.

5-HT_{1A} Receptors

- Tissue preparation

Rats (male Sprague Dawley, 200-250 g) were used. The Hippocampi of these animals were homogeneized in 10 volumes of ice cold TRIS buffer (pH 7.4). The homoge-

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nate was diluted 1:400 (w:v) in the same buffer to have a final protein concentration of about 200 µg/mL, filtered and incubated at 37°C for 10 min, before use.

- Binding assay

Displacement experiments were performed by incubating the homogenate (980 µL) in the presence of [^{3}H]-8OH-DPAT (1.0-1.5 nM) (10 µL) and of different concentrations of the test compounds dissolved in the test buffer (10 µL), at 30°C for 15 min (final volume: 1 mL).

Non specific binding was determined in the presence of 100 µM 5-HT (10 µL). The separation of [^{3}H]-8-OH-DPAT, free from that bound to the receptor, was carried out by the filtration technique (GF/B filters, Whatman). The radioactivity present was counted by liquid scintillation spectrometry.

- Data analysis

The affinity values (Ki) for the compounds were obtained by a non linear least squares regression analysis on the basis of a one binding site model. The values were corrected on the basis of the radioligand occupancy on the receptors according to the equation: $Ki = IC_{50}/(1 + [C]/K_D)$, where [C] and K_D represent the concentration and the dissociation constant, respectively, of the radioligand used ([^{3}H]-8-OH-DPAT).

5-HT$_2$ Receptors

- Tissue preparation

Rats (male Sprague Dawley, 200-250 g) were used. Cerebral cortices were homogenized in 10 volumes of ice cold 0.32 M sucrose. After the centrifugation of the homogenate (1,000 x g for 10 min) the supernatant was

then recentrifuged at 48,000 x g for 15 min. The resulting pellet was resuspended in 10 volumes of 50 mM TRIS buffer (pH 7.4), incubated at 37°C for 10 min and recentrifuged at 48,000 x g for 15 min. The residue was then resuspended in 10 volumes of 50 mM TRIS buffer (pH 7.4).

- Binding assay

The tissue was diluted 1:100 (w:v) in 50 mM TRIS buffer (pH 7.4) to have a final protein concentration of about 200 µg/mL.

Displacement experiments were performed by incubating the homogenate (980 µL) in the presence of [^{3}H]-Ketanserine (0.5-1.0 nM) (10 µL) and of different concentrations of the test compounds dissolved in the assay buffer (10 µL), at 37°C for 10 min (final volume: 1 mL).

Non specific binding was determined in the presence of 100 µM Methysergide (10 µL). The separation of [^{3}]-Ketanserine free from that bound to the receptor was carried by the filtration technique (GF/B filters, Whatman). The radioactivity present was counted by liquid scintillation spectrometry.

- Data analysis

The affinity values (Ki) for the compounds were obtained by non linear least squares regression analysis on the basis of a one binding site model. These values were corrected on the basis of the radioligand occupancy on the receptors according to the equation: $Ki = IC_{50}/(1 + [C]/K_D)$, where [C] and K_D represent the concentration and the dissociation constant, respectively, of the radioligand used ([^{3}H]-Ketanserine).

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The results of some of the compounds of the present invention on the affinity to the 5-HT_{1A} and 5-HT_2 receptors are reported in Tables 1 and 2.

TABLE 1 - AFFINITY FOR 5-HT_{1A} RECEPTORS

Compound	Ki (nM)
1	35
2	10
9	30
11	30
13	100
14	80
16	1
17	1
15	10
32	30

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TABLE 2 - AFFINITY FOR 5-HT_2 RECEPTORS

Compound	Ki (nM)
2	50
9	15
11	20
13	50
14	100
15	10
32	10

According to a further feature of the present invention there are provided pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), as hereinbefore defined, or a physiologically acceptable acid addition salt thereof in association with one or more pharmaceutical carriers, diluents or excipients. For pharmaceutical administration the compounds of general formula (I) and their physiologically acceptable acid addition salts may be incorporated into the conventional pharmaceutical preparations in solid, liquid or spray form. The compositions may, for example, be presented in a form suitable for oral, rectal, parenteral administration or for nasal inhalation. Preferred forms include, for example, capsules, tablets, coated tablets, ampoules, suppositories and nasal spray.

The active ingredient may be incorporated in excipients or carriers conventionally used in pharmaceutical compositions such as, for example, talc, arabic gum, lactose, gelatine, magnesium stearate, corn

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starch, aqueous or non-aqueous vehicles, polyvinylpirrolidone, semisynthetic glicerides of fatty acids, benzalcon chloride, sodium phosphate, EDTA, polysorbate 80.

In order to increase the solubility of the compounds of general formula (1) or their physiological acceptable salts, surfactants, non-ionic surfactants such as PEG 400, cyclodextrins, metastable polymorphs, inert absorbents such as bentonite may be incorporate. Furthermore some techniques may be employed by preparing for example eutetic mixtures and/or solid dispersions by using mannitol, sorbitol, saccharose, succinic acid, or physical modified forms by using hydrosoluble polymers, PVP, PEG 4000-20000.

The compositions are advantageously formulated in dosage units, each dosage unit being adapted to supply a single dose of the active ingredient. Each dosage unit may conveniently contain from 0,01 mg to 100 mg and preferably from 0,1 mg to 50 mg.

The following examples illustrate the preparation of some new compounds according to the present invention and will enable other skilled in the art to understand it more completely. It should be understood, however, that the invention is not limited solely to the particular examples given below.

Description 1

5-methoxy-3-(pyridin-3-ylmethyl)-1H-indole

The above mentioned compound was prepared analogously to the procedure described in J. Het. Chem. 3, 67 (1966) from 5-methoxy-indolyl-magnesium bromide and 3-chloromethylpyridine. After purification by Flash

Chromatography on silica gel using as eluent methylene chloride/methanol/ammonia (98:2:0,1), the desired compound was obtained.

Mp 112°C

Analogously were prepared:

5-Fluoro-3-(pyridin-3-ylmethyl)-1H-indole

Mp 108°C

5-methyl-3-(pyridin-3-ylmethyl)-1H-indole

Mp 110°C

Description 2

5-benzyloxy-3-(pyridin-3-ylmethyl)-1H-indole

The above mentioned compound was prepared similarly to the procedure described in Arch. Pharm. 308, 209 (1975) from 5-benzyloxy-indolyl-magnesium bromide and 3-chloromethyl-pyridine. After recrystallization from acetonitrile, the desired compound was obtained.

Mp 148°C

Description 3

5-bromo-3-(pyridin-3-ylmethyl)-1H-indole

i) 3-Pyridin-propionaldehyde

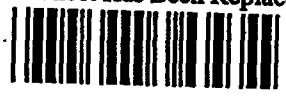
The above mentioned compound was prepared analogously to the procedure described in Tetrahedron 34, 1651 (1978).

The compound was used as such without further purification.

ii) 5-Bromo-3-(pyridin-3-ylmethyl)-1H-indole

A mixture of 3-pyridin-propionaldehyde (1 g; 0.0074 mol) and of 4-bromophenylhydrazin hydrochloride (1.8 g; 0.0074 mol) with acetic acid (4.44 ml) in absolute ethanol (50 ml) was refluxed for 3 hours. The reaction was then quenched with a

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saturated solution of aqueous sodium carbonate and the product was extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated under vacuum. After purification by Flash Chromatography on silica gel using as eluent methylene chloride/methanol (98/2), the desired compound was obtained.

Mp 122°C

Following the above described process and using the appropriate substituted phenylhydrazine the following compounds were prepared:

5-chloro-3-(pyridin-3-ylmethyl)-1H-indole

Mp 125°C

5-fluoro-3-(pyridin-3-ylmethyl)-1H-indole

Mp 109°C

5-methoxy-3-(pyridin-3-ylmethyl)-1H-indole

Mp 112°C

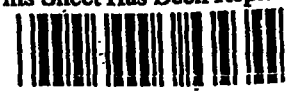
Description 4

5-Cyano-3-(pyridin-3-ylmethyl)-1H-indole

A mixture of compound of Description 3 [5-Bromo-3-(pyridin-3-ylmethyl)-1H-indole] (1.1 g; 0.0038 mol) and copper cyanide (0.86 g; 0.0096 mol) in dimethylformamide (35 ml) was treated at 140°C for 8 hours. The reaction mixture was poured into an ice ammonium hydroxide solution and the product was extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated under vacuum. After purification by Flash Chromatography on silica gel using as eluent methylene chloride/methanol (97/3), the desired compound was obtained.

Mp 125°C

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Description 5

5-methoxy-3-(1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole

i) 3[(5-methoxy-1H-indol-3-yl)methyl]-1-benzyl-pyridinium bromide

Benzyl bromide (8.7 ml; 0.073 mol) was added to a stirring mixture of compound of Description 1 [5-methoxy-3-(pyridin-3-ylmethyl)-1H-indole] (3.5 g; 0.0146 mol) in methyl ethyl ketone (70 ml). The reaction mixture was refluxed for 3 hours. The product precipitated as a yellow solid was filtered and washed with diethyl ether and dried under vacuum. The compound was used as such without further purification.

ii) 5-Methoxy-3-(N-benzyl-1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole

Sodium borohydride in pellets (1.5 g; 0.0396 mol) was added to a cold (0°C) stirring mixture of 3[(5-methoxy-1H-indol-3-yl)methyl]-1-benzyl-pyridinium bromide (5.8 g; 0,0141 mol) in methanol (130 ml). The reaction mixture was stirred at 0°C for 2 hours. The product precipitated as a white-pink solid was filtered and washed with cold methanol and dried under vacuum.

iii) 5-Methoxy-3-(N-ethoxycarbonyl-1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole

Ethyl chloroformate (5.74 ml; 0.060 mol) was added to a mixture of 5-methoxy-3-(N-benzyl-1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole (4 g; 0.012 mol) in toluene (430 ml). The reaction mixture was heated at 75°C for 3 hours. The reaction mixture

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was then cooled and the desired compound was obtained after evaporation of the solvent. The compound was used as such without further purification.

iiii) 5-Methoxy-3-(1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole

A mixture of 5-methoxy-3-(N-ethoxycarbonyl-1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole (3.8 g; 0.012 mol) with a saturated (45%) aqueous solution of potassium hydroxide (208 ml) in absolute ethanol (313 ml) was refluxed for 12 hours. The reaction mixture was then cooled and the ethanol was evaporated under vacuum. The residual alkaline aqueous solution was diluted with water. Then the product was extracted several times with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated under wacuum. The desired compound was obtained after trituration of the solid residue with diethyl ether.

Mp 139-145°C

Following the above described process and using the appropriate indole derivative already described in Description 1 and Description 3, the following compound was prepared:

5-Bromo-3-(1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole

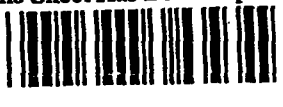
Mp 140-145°C

Description 6

<u>5-methoxy-3-(Piperidin-3-ylmethyl)-1H-indole</u>

i) 5-methoxy-3-(pyridin-3-ylmethyl)-1H-indole hydrochloride

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A solution of compound of Description 1 [5-methoxy-3-(pyridin-3-ylmethyl)-1H-indole] (3 g) in diethyl ether was saturated with gaseous hydrogen chloride. A solid was precipitated. The title compound was collected by filtration washed with diethyl ether and dried under vacuum. The compound was used as such without further purification.

ii) 5-methoxy-3-(piperidin-3-ylmethyl)-1H-indole

The above mentioned compound was prepared analogously to the procedure described in Arch. Pharm. 308, 209 (1975) from 5-methoxy-3-(pyridin-3-ylmethyl)-1H-indole hydrochloride.

Mp 150-160°C

Description 7

3-[(5-methoxy-1H-indol-3-yl)methyl]-1-methyl-pyridinium iodide

Methyl iodide (10.4 ml; 0.167 mol) was added to a stirring mixture of compound of Description 1 [5-methoxy-3-(pyridin-3-ylmethyl)-1H-indole] (5.3 g; 0.022 mol) in acetone (150 ml). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated under vacuum. The residual solid was washed with diethyl ether giving the desired compound (7.5 g).

Following the above described process and using the appropriate halide and the appropriate indole derivative already described in Description 1 the following compounds can be prepared:

3-[(5-methoxy-1H-indol-3-yl)methyl]-1-[2-(4-nitrophenyl)-ethyl)]-pyridinium bromide

3-[(5-methoxy-1H-indol-3-yl)methyl]-1-[(4'-fluoro-phe-

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noxy)-ethyl)]-pyridinium bromide

3-[(5-methoxy-1H-indol-3-yl)methyl]-1-propyl-pyridinium bromide

3-[(5-bromo-1H-indol-3-yl)methyl]-1-methyl-pyridinium bromide

3-[(5-bromo-1H-indol-3-yl)methyl]-1-ethyl-pyridinium bromide

3-[(5-cyano-1H-indol-3-yl)methyl]-1-methyl-pyridinium bromide

3-[(5-cyano-1H-indol-3-yl)methyl]-1-ethyl-pyridinium bromide

3-[(5-methyl-1H-indol-3-yl)methyl]-1-ethyl-pyridinium bromide

All the above mentioned compounds were used as such without further purification.

Example 1

5-methoxy-3-(N-methyl-1,2,5,6-tetrahydro-pyridin-3-yl-methyl)-1H-indole

(Compound 1)

Sodium borohydride in pellets (5.71 g; 0.0396 mol) was added to a cold (~ 0°C) stirring mixture of compound of Description 7 [3-[(5-methoxy-1H-indol-3-yl)methyl]-1-methyl-pyridinium iodide] (7.45 g; 0.0196 mol) in methanol (150 ml). The reaction mixture was stirred at 0°C for 2 hours. The reaction was then quenched with a saturated solution of aqueous sodium carbonate and the solvent (methanol) was evaporated under vacuum. The product was extracted with methylene chloride from the residual alkaline aqueous solution. The organic extract was dried ($MgSO_4$) and evaporated under vacuum. Purification by Flash Chromatography of the

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crude product using silica gel and elution with methylene chloride/methanol/ammonia (90/10/1) yielded the desired compound. A solution of the desired compound in diethyl ether was saturated with gaseous hydrogen chloride. A white solid was precipitated. The title compound hydrochloride was collected by filtration, washed with diethyl ether and dried under vacuum (3.5 g).

Mp 192°C

Analysis

$C_{16}H_{20}N_2O$. HCl

	C	H	N	Cl
Found%	64.71	7.29	9.36	12.00
Calc.%	65.63	7.23	9.50	12.11

^1H NMR (DMSO + $CDCl_3$) δ - 10.9-10.3 (b, 2H), 7.23 (d, 1H), 7.12 (d, 1H), 6.94 (d, 1H), 6.70 (m, 1H), 5.75 (b, 1H), 3.77 (s, 3H), 3.8-2.2 (8H), 2.76 (d, 3H).

MS (C.I.): $[M + H]^+$ 257 m/z

Following the above described process and using the appropriate pyridinium salt, the following compounds can be prepared:

<u>5-methoxy-3-[N-(4'-fluoro-phenoxy-ethyl)-1,2,5,6-tetrahydro-pyridin-3-yl-methyl]-1H-indole</u>

(Compound 2)

Mp 60°C

Analysis

$C_{23}H_{25}FN_2O_2$. HCl

	C	H	N
Found%	64.96	6.52	6.65
Calc.%	66.26	6.29	6.72

^1H NMR (DMSO + $CDCl_3$) δ - 12.43 (b, 1H), 8.68 (b, 1H), 7.29 (d, 1H), 7.0-6.6 (7H), 5.84 (b, 1H), 4.35 (b, 2H),

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3.82 (s, 3H), 3.9-1.8 (10 H).

MS (C.I.): $(M+H)^+$ 381 m/z

5-methoxy-3-[N-propyl-1,2,5,6-tetrahydro-pyridin-3-yl-methyl]-1H-indole

(Compound 3)

Mp 80-85°C

Analysis

$C_{18}H_{24}N_2O$

	C	H	N
Found%	74.10	8.57	9.30
Calc.%	76.02	8.55	9.15

^1H NMR (DMSO + $CDCl_3$) δ = 10.59 (b, 1H), 7.21 (d, 1H), 7.03 (1d, 1H), 6.95 (1d, 1H), 6.70 (dd, 1H), 5.52 (b, 1H), 3.73 (s, 3H), 3.30 (b, 2H), 2.81 (b, 2H), 2.6-1.9 (6H), 1.34 (m, 2H), 0.80 (t, 3H).

MS (C.I.): $[M + H]^+$ 285 m/z

5-bromo-3-[N-methyl-1,2,5,6-tetrahydro-pyridin-3yl-methyl]-1H-indole

(Compound 4)

Mp 131-133°C

Analysis

$C_{15}H_{17}N_2Br$

	C	H	N
Found%	58.98	5.64	9.10
Calc.%	59.03	5.61	9.18

^1H NMR (DMSO + $CDCl_3$) δ = 11.19 (b, 1H), 10.81 (b, 1H), 7.64 (d, 1H), 7.35 (d, 1H), 7.26 (d, 1H), 7.13 (m, 1H), 5.72 (b, 1H), 3.6-3.2 (6H), 2.76 (s, 3H), 2.48 (b, 2H).

MS (C.I.): $[M + H]^+$ 306 m/z

5-bromo-3-[N-ethyl-1,2,5,6-tetrahydro-pyridin-3-yl-methyl]-1H-indole

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(Compound 5)

Mp 132-134°C

Analysis

$C_{16}H_{19}N_2Br$

	C	H	N
Found%	59.91	6.04	8.66
Calc.%	60.20	6.00	8.77

^1H NMR ($CDCl_3$) δ = 9.25 (b, 1H), 7.69 (d, 1H), 7.3-7.1 (2H), 6.90 (d, 1H), 5.56 (b, 1H), 3.35 (s, 2H), 2.92 (s, 2H), 2.58 (t, 2H), 2.49 (q, 2H), 2.24 (b, 2H), 1.08. (t, 3H).

MS (C.I.): $[M + H]^+$ 320 m/z

5-cyano-3-[N-methyl-1,2,5,6-tetrahydro-pyridin-3yl-methyl]-1H-indole

(Compound 6)

Mp 166-167°C

Analysis

$C_{16}H_{17}N_3$

	C	H	N
Found%	75.8	6.95	16.3
Calc.%	76.46	6.82	16.72

^1H NMR ($CDCl_3$) δ = 9.46 (b, 1H), 7.91 (s, 1H), 7.4-7.2 (2H), 7.04 (d, 1H), 5.03 (b, 1H), 3.40 (b, 2H), 2.87 (d, 2H), 2.57 (m, 2H), 2.35 (s, 3H), 2.5-2.2 (2H).

MS (C.I.): $[M + H]^+$ 252 m/z

5-cyano-3-[N-ethyl-1,2,5,6-tetrahydro-pyridin-3-yl-methyl]-1H-indole

(Compound 7)

Mp 105-107°C

Analysis

$C_{17}H_{19}N_3$

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	C	H	N
Found%	76.86	7.35	16.02
Calc.%	76.95	7.22	15.84

^{1}H NMR ($CDCl_3$) δ - 10.10 (b, 1H), 7.93 (d, 1H), 7.5-7.3 (2H), 6.99 (d, 1H), 5.62 (b, 1H), 3.40 (s, 2H), 2.93 (s, 2H), 2.62 (t, 2H), 2.52 (q, 2H), 2.27 (b, 2H), 1.08 (t, 3H).

MS (C.I.): $[M + H]^+$ 266 m/z

5-methyl-3-[N-methyl-1,2,5,6-tetrahydro-pyridin-3-yl-methyl]-1H-indole

(Compound 8)

Mp 96-105°C

Analysis

$C_{16}H_{20}N_2.HCl$

	C	H	N
Found%	69.1	7.35	9.8
Calc.%	69.42	7.65	10.12

^{1}H NMR ($CDCl_3$) δ = 12.56 (b, 1H), 8.29 (b, 1H), 7.3-7.2 (2H), 7.1-7.0 (2H), 5.87 (b, 1H), 3.76 (gem, 1H), 3.8-3.5 (3H), 3.13 (m, 1H), 3.0-2.7 (2H), 2.66 (d, 3H), 2.33 (m, 1H), 2.45 (s, 3H).

MS (C.I.): $[M + H]^+$ 241 m/z

Example 2

5-methoxy-3-[N-(4-(4-fluoro-phenyl)-4-oxo-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 9)

A mixture of compound of Description 5 [5-methoxy-3-(1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole] (1.5 g; 0.0062 mol), potassium carbonate (4.3 g; 0.031 mol), KI (0.06 g; 0.0004 mol) and 2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane (1.3 ml; 0.0064 mol) in

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dry dimethylformamide (30 ml) was heated at 80°C for 6 hours. The reaction mixture was cool down to room temperature, quenched with water and then extracted with diethyl ether. The organic extract was dried ($MgSO_4$) and evaporated under vacuum. The residue was taken up in a solution of hydrochloric acid (37%; 6 ml) in methanol (30 ml). The resulting mixture was stirred for 2 hours at room temperature. The reaction was then quenched with a saturated solution of aqueous sodium carbonate and the solvent (methanol) was evaporated under vacuum. The residual alkaline aqueous solution was extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and evaporated under vacuum. After purification by Flash Chromatography on silica gel using as eluent methylene chloride/methanol/ammonia (95/5/0,5), the desired compound was obtained (1,72 g). A solution of the compound in ethanol was saturated with gaseous hydrogen chloride. A white solid was precipitated. The title compound hydrochloride was collected by filtration, washed with ethanol and dried under vacuum.

Mp 95-97°C

Analysis

$C_{25}H_{27}FN_2O_2 \cdot HCl$

	C	H	N
Found%	66.24	6.58	6.11
Calc.%	67.79	6.37	6.32

^1H NMR (DMSO + $CDCl_3$) δ = 12.18 (b, 1H), 8.59 (s, 1H), 7.88 (m, 2H), 7.3-6.7 (6H), 5.84 (b, 1H), 3.81 (s, 3H), 4.1-1.9 (14H).

MS (C.I.): $[M + H]^+$ 407 m/z

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Following the above described process and using the appropriate indole derivative already described in Description 5, the following compound was prepared:

5-bromo-3-[N-(4-(4-fluoro-phenyl)-4-oxo-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 10) Mp 237°C

Analysis: $C_{24}H_{24}BrFN_2O \cdot HCl$

	C	H	N
Found%	58.23	5.18	5.63
Calc.%	58.61	5.12	5.70

^1H NMR (DMSO) δ = 11.25 (s, 1H), 10.64 (b, 1H), 8.06 (m, 2H), 7.69 (d, 1H), 7.4-7.3 (4H), 7.17 (m, 1H), 5.71 (b, 1H), 3.77 (gem, 1H), 3.7-3.4 (4H), 3.3-3.0 (5H), 2.7-2.4 (1H), 2.26 (gem, 1H), 2.01 (m, 2H)

MS (C.I.): $[M + H]^+$ 456 m/z

3-[N-(4-(4-fluoro-fenil)-4-oxo-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole (Compound 40)

Example 3

5-methoxy-3-[N-(3-(4-fluoro-phenyl)-3-oxo-propyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 11)

Triethylamine (0.9 ml; 0.0063 mol) was added to a solution of 3-chloro-4'-fluoropropiophenone (1.2 g; 0.0063 mol) in diethyl ether (10 ml). The resulting mixture was stirred for 3 hours at room temperature. Then the mixture was filtered and the filtrate was concentrated under vacuum. The residue was taken up with a mixture of compound of Description 5 [5-methoxy-3-(1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole] (0.79 g; 0.0028 mol), triethylamine (0.8 ml; 0.0057 mol) in methylene chloride (20 ml). The reaction mix-

ture was refluxed for 4 hours. Then the reaction was concentrated under vacuum and the residue was triturated with 1N hydrochloric acid. The aqueous phase was decanted, and the guming solid was twice washed with water and triturated with diethyl ether. The title compound hydrochloride was collected by filtration, washed with diethyl ether and recrystallized with a mixture (1/2) of ethyl acetate/acetone. 0.86 g of the desired compound were obtained.

Mp 186-188°C

Analysis

$C_{24}H_{25}FN_2O_2 \cdot HCl$

	C	H	N
Found%	66.83	6.29	6.42
Calc.%	67.20	6.11	6.53

^1H NMR (DMSO + $CDCl_3$) δ - 10.79 (b, 1H), 10.45 (b, 1H), 8.08 (m, 2H), 7.40 (m, 2H), 7.23 (d, 1H), 7.18 (d, 1H), 6.98 (d, 1H), 6.72 (m, 1H), 5.80 (b, 1H).

MS (C.I.): $[M + H]^+$ 393 m/z

Following the above described process and using the appropriate halide, the following compound was prepared:

<u>5-methoxy-3-[N-(3-(2,4-difluoro-phenyl)-3-oxo-propyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole</u>

(Compound 12)

Mp 185°C

Analysis

$C_{24}H_{24}F_2N_2O_2$

	C	H	N
Found%	69.15	5.97	6.63
Calc.%	70.33	5.89	6.82

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Description 8

5-methoxy-3-[N-(2-(4-nitro-phenyl)-ethyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

Sodium borohydride in pellets (0.8 g; 0.0211 mol) was added to a cold (~ 0°C) stirring mixture of compound of Description 7 [3-[(5-methoxy-1H-indol-3-yl)-methyl]-1-(2-(4-nitro-phenyl)-ethyl)-pyridinium bromide] (1.75 g; 0.0038 mol) in methanol (50 ml). The reaction mixture was stirred at 0°C for 2 hours. The reaction was then quenched with a saturated solution of aqueous sodium carbonate and the solvent (methanol) was evaporated under vacuum. The product was extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and evaporated under vacuum giving the desired compound (1.38 g). The compound was used as such without further purification.

Example 4

5-methoxy-3-[N-(2-(4-amino-phenyl)-ethyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 13)

Iron powder (0.97 g; 0.0174) was added to a suspension of the compound of Description 8 [5-methoxy-3-[N-(2-(4-nitro-phenyl)-ethyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole] (1.36 g; 0.0035 mol) in 10% aqueous hydrochloric acid (70 ml). The reaction mixture was refluxed for 3 hours. The reaction mixture was then cool down to room temperature and quenched with a saturated solution of aqueous sodium carbonate. The resulting mixture was filtered through diatomaceous earth (Celite$^{(R)}$), washed with water and extracted with methylene chloride. The organic extract was dried

($MgSO_4$) and evaporated under vacuum. After purification by Flash Chromatography on silica gel using as eluent methylene chloride/methanol/ammonia (95/5/0.5), the title compound was obtained as a yellow solid (0.2 g).

Mp 76-79°C

Analysis

$C_{23}H_{27}N_3O$

	C	H	N
Found%	74.53	7.71	11.31
Calc.%	76.42	7.53	11.62

^1H NMR ($CDCl_3$) δ = 8.15 (b, 1H), 7.3-6.4 (6H), 6.57 (d, 2H), 5.58 (b, 1H), 3.83 (s, 3H), 3.38 (b, 4H), 3.2-2.5 (8H), 2.22 (b, 2H).

MS (C.I.): $[M + H]^+$ 262 m/z

Description 9

1-(4-chloro-butyl)-4-fluoro-benzene

Triethylsilane (22.5 ml; 0.141 mol) was added dropwise to a cold (~ 0°C) stirring mixture of 4-chloro-4'-fluoro-butyrophenone (10 ml; 0.0613 mol) in trifluoroacetic acid (47 ml). The reaction mixture was stirred at room temperature under nitrogen for 6 hours. The reaction was quenched with brine and extracted with diethyl ether. The organic extract was dried ($MgSO_4$) and evaporated under vacuum giving the desired compound as an oil.

Following the above described process and using the appropriate acyl halide the following compound can be prepared:

1-(3-chloro-propyl)-4-fluoro-benzene.

All the above mentioned compounds were used as such without further purification

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Example 5

5-methoxy-3-[N-(4-(4-fluoro-phenyl)-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 14)

A mixture of compound of Description 5 [5-methoxy-3-(1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole] (1.4 g; 0.0058 mol), potassium carbonate (4 g; 0.0029 mol), a catalytic amount of potassium iodide (0.030 g) and compound of Description 9 [1-(4-chloro-butyl)-4-fluoro-benzene] (5.4 g; 0.029 mol) in dimethylformamide (40 ml) was heated at 80°C for 6 hours. The reaction mixture was cool down to room temperature. quenched with water and then extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated under vacuum. After purification by Flash Chromatography on silica gel using as eluent methylene chloride/methanol/ammonia (95/5/0,5), the desired compound was obtained as an oil. A solution of this oil in methanol was saturated with gaseous hydrogen chloride. A solid was precipitated. The title compound hydrochloride was collected by filtration, washed with hexane and dried under vacuum (0.66 g).

Mp 65-70°C

Analysis

$C_{25}H_{29}FN_2O.$ HCl

	C	H	N
Found%	68.43	7.21	6.39
Calc.%	70.00	7.05	6.53

^1H NMR (DMSO + $CDCl_3$) δ - 12.42 (b, 1H), 8.28 (b, 1H), 7.3-6.8 (8H), 5.87 (b, 1H), 3.82 (s, 3H), 3.7-2.3 (12 H), 1.8-1.2 (4H).

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MS (C.I.): $[M + H]^+$ 393 m/z

Following the above described process and using the appropriate halide synthesized according to Description 5, the following compound was prepared

5-methoxy-3-[N-(3-(4-fluoro-phenyl)-propyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 15)

Mp 114-116°C

Analysis

$C_{24}H_{27}N_2OF$

	C	H	N
Found%	76.16	7.20	7.40
Calc.%	76.16	7.19	7.40

^1H NMR ($CDCl_3$) δ = 8.23 (b, 1H), 7.22 (d, 1H), 7.2-6.9 (6H), 6.84 (m, 1H), 5.56 (b, 1H), 3.84 (s, 3H), 3.37 (s, 2H), 2.90 (b, 2H), 2.55 (t, 2H), 2.52 (t, 2H), 2.39 (m, 2H), 2.18 (b, 2H), 1.79 (m, 2H).

MS (C.I.): $[M + H]^+$ 379 m/z

Description 10

N-(2-bromo-ethyl)-4-fluoro-benzamide

4-fluoro-benzoyl chloride (3 ml; 0.026 mol) was added dropwise to a cold (~ 0°C). Stirring mixture of 2-bromo-ethyl-amine hydrobromide (5 g; 0.0236 mol) and 10% aqueous sodium hydroxide (21 ml; 0.052 mol). Crystalline product started to precipitate out of the reaction mixture almost immediately. After 15 minutes of stirring, the product was collected by filtration, triturated with diethyl ether and dried under vacuum giving the desired compound as a white solid (4 g).

Following the above described process and using the appropriate acyl halide the following compounds can

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be prepared:

N-(2-bromo-ethyl)-2-thiophene-carboxamide

N-(2-bromo-ethyl)-1-adamantane-carboxamide

All the above mentioned compounds were used as such without further purification.

Example 6

5-methoxy-3-[N-(2-(4-fluoro-benzamide)-ethyl-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 16).

A mixture of compound of Description 5 [5-methoxy-3-(1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole] (1.5 g; 0.0062 mol) and compound of Description 10 [N-(2-bromo-ethyl)-4-fluoro-benzamide (1.68 g; 0.0068 mol) in dry acetonitrile. The reaction mixture was refluxed for 8 hours. The reaction was then concentrated under vacuum. Purification by Flash Chromatography of the crude product using silica gel and elution with methylene chloride/methanol/ammonia (95/5/0,5) yielded the desired compound. A solution of the desired compound in ethanol was saturated with gaseous hydrogen chloride. A solid was precipitated. The title compound hydrochloride was collected by filtration, washed with diethyl ether and dried under vacuum (0.3 g).

Analysis

$C_{24}H_{26}N_3O_2F$. HCl

	C	H	N
Found%	63.87	6.27	9.13
Calc.%	64.93	6.13	9.47

^1H NMR ($CDCl_3$) δ = 11.91 (b, 1H), 8.79 (b, 1H), 8.05 (m, 3H), 7.4-6.7 (6H), 5.87 (b, 1H), 4.4-3.1 (10H), 3.83 (s, 3H), 2.55 (m, 2H).

This Sheet Has Been Replaced



MS (C.I.): $[M + H]^+$ 408 m/z

Following the above described process and using the appropriate 2-halo-ethyl-amide, the following compounds were prepared:

5-methoxy-3-[N-(2-(2-thiophene-carboxamide)-ethyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 17)

Mp 185-190°C

Analysis

$C_{22}H_{25}N_3O_2S$. HCl

	C	H	N
Found%	59.94	6.18	9.46
Calc.%	61.17	6.07	9.79

^1H NMR (DMSO) δ - 10.78 (b, 1H), 10.27 (b, 1H), 8.96 (t, 1H), 7.9-7.7 (2H), 7.23 (d, 1H), 7.3-7.1 (2H), 6.98 (d, 1H), 6.71 (m, 1H), 5.73 (b, 1H), 3.74 (s, 3H), 4.0-3.0 (10H), 2.33 (m, 2H).

MS (C.I.): $[M + H]^+$ 396 m/z

5-methoxy-3-[N-(2-(1-adamantane-carboxamide)-ethyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 18)

Mp 128°C

Analysis

$C_{28}H_{37}N_3O_2$

	C	H	N
Found%	75.18	8.30	9.40
Calc.%	75.13	8.33	9.39

^1H NMR ($CDCl_3$) δ = 7.99 (b, 1H), 7.24 (d, 1H), 7.03 (d, 1H), 6.97 (d, 1H), 6.84 (m, 1H), 6.25 (b, 1H), 5.62 (b, 1H), 3.85 (s, 3H), 3.39 (s, 2H), 3.30 (m, 2H), 2.85 (m, 2H), 2.54 (t, 2H), 2.51 (t, 2H), 2.17 (b, 2H), 2.01 (b,

This Sheet Has Been Replaced



3H), 1.9-1.6 (12H).

MS (C.I.): $[M + H]^+$ 448 m/z

Example 7

5-Methoxy-3-(N-methyl-1,2,5,6-tetrahydro-pyridin-3-yl-methyl)-1-pentyl-indole

(Compound 19)

To a suspension of sodium hydride (80% dispersion in mineral oil; 0.22 g; 0.0072 mol) in dry dimethylformamide (30 ml), compound 1 of Example 1 (5-Methoxy-3-(N-methyl-1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole) (1.54 g; 0.006 mol) was added portionwise at room temperature. After 30 minutes, a solution of 1-bromopentane (0.820 ml; 0.0066 mol) in dry dimethylformamide (5 ml) was added. The resultant mixture was stirred under nitrogen for 8 hours at room temperature. The reation mixture was quenched with a saturated solution of aqueous sodium carbonate and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated under vacuum. After purification by Flash Chromatography on silica gel using as eluent methylene chloride/methanol/ammonia (95/5/0.5), the desired compound was obtained (0.77 g). A solution of the compound in ethanol was saturated with gaseous hydrogen chloride. A white solid was precipitated. The title compound hydrochloride was collected by filtration, washed with ethanol and dried under vacuum (0.84 g).

Mp 135°C

Analysis

$C_{21}H_{30}N_2O$. HCl

This Sheet Has Been Replaced



	C	H	N
Found%	67.79	8.77	7.5
Calc.%	69.5	8.61	7.72

^{1}H NMR ($CDCl_3$) δ = 12.7 (b, 1H), 7.3-6.8 (4H), 5.85 (b, 1H), 4.03 (t, 2H), 3.84 (s, 3H), 3.47 (b, 4H), 3.23 (m, 2H), 2.74 (b, 3H), 2.40 (b, 2H), 1.80 (m, 2H), 1.5-1 (4H), 0.87 (t, 3H).

MS (C.I.): $[M + H]^+$ 327 m/z

Following the above described process and using the appropriate halide, the following compounds were prepared:

5-methoxy-3-(N-methyl-1,2,5,6-tetrahydro-pyridin-3-yl-methyl)-1-(cyclo-propyl-methyl)-indole

(Compound 20)

Mp 95-98°C

Analysis

$C_{20}H_{26}N_2O \cdot C_4H_6O_6$

	C	H	N
Found%	62.68	7.03	6.15
Calc.%	62.59	7.0	6.08

^{1}H NMR (DMSO + $CDCl_3$) δ - 7.31 (d, 1H), 7.15 (s, 1H), 6.95 (d, 1H), 6.75 (m, 1H), 5.66 (b, 5H), 4.11 (s, 2H), 3.94 (d, 2H), 3.75 (s, 3H), 3.35 (b, 2H), 3.23 (b, 2H), 2.82 (m, 2H), 2.53 (s, 3H), 2.25 (b, 2H), 1.18 (m, 1H), 0.6-0.2 (4H).

MS (C.I.): $[M + H]^+$ 285 m/z

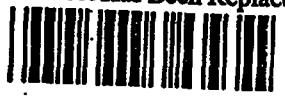
5-methoxy-3-[N-methyl-1,2,5,6-tetrahydro-pyridin-3-yl-methyl]-1-methyl-indole

(Compound 21)

Mp 126°C

Analysis

This Sheet Has Been Replaced



$C_{17}H_{22}N_2O$. HCl

	C	H	N
Found%	65.65	7.42	9.08
Calc.%	66.55	7.56	9.13

^1H NMR ($CDCl_3$) δ = 12.6 (b, 1H), 7.3-6.7 (4H), 5.87 (b, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 4.0-2.7 (11H).

MS (C.I.): $[M + H]^+$ 271 m/z

Example 8

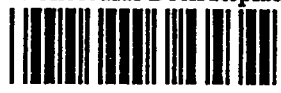
5-Methoxy-3-[N-[4-(4-fluoro-phenyl)-4-(hydroxy-imino)-butyl]-1,2,5,6-tetrahydro-pyridin-3ylmethyl]-1H-indole (Compound 22)

A mixture of Compound 8 of Example 2 (5-methoxy-3-[N-(4-(4-fluoro-phenyl)-4-oxo-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole) (0.9 g; 0.0022 mol) and hydroxylamine hydrochloride (0.61 g; 0.0044 mol) in methanol (70 ml) was refluxed for 4 hours. The solvent (methanol) was concentrated under vacuum. The residue was taken up with 30% aqueous ammonia and then extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated under vacuum. Purification by Flash Chromatography of the crude product using silica gel and elution with methylene chloride/methanol (93/7) yielded the desired compound as a light yellow solid (0.6 g).

Mp 129-130°C

Analysis

This Sheet Has Been Replaced



$C_{25}H_{28}N_3FO_2$

	C	H	N
Found%	70.35	6.73	9.81
Calc.%	71.24	6.70	9.97

^1H NMR (DMSO) δ - 11.17 (s, 1H), 10.64 (s, 1H), 7.65

(m, 2H), 7.19 (m, 2H), 7.13 (d, 1H), 7.05 (d, 1H), 6.95 (d, 1H), 6.70 (m, 1H), 5.51 (b, 1H), 3.72 (s, 3H), 3.29 (s, 2H), 2.76 (s, 2H), 2.68 (t, 2H), 2.37 (t, 2H), 2.31 (t, 2H), 2.05 (b, 2H), 1.57 (m, 2H).

MS (C.I.): $[M + H]^+$ 422 m/z

Following the above described process and using the appropriate hydroxylamine derivative, the following compounds were prepared:

5-Methoxy-3-[N-[4-(4-fluoro-phenyl)-4-(benzyl-oxy-imino)-butyl]-1,2,5,6-tetrahydro-pyridin-3ylmethyl]-1H-indole

(Compound 23)

Mp 61-63°C

Analysis

$C_{32}H_{34}N_3FO_2$. HCl

	C	H	N
Found%	68.85	6.71	6.11
Calc.%	70.12	6.44	6.47

^1H NMR ($CDCl_3$) δ = 12.19 (b, 1H), 8.41 (b, 1H), 7.56 (m, 2H), 7.4-6.8 (11H), 5.75 (b, 1H), 3.83 (s, 3H), 3.8-1.2 (16H).

MS (C.I.): $[M + H]^+$ 512 m/z

[E] 5-Methoxy-3-[N-[4-(4-fluoro-phenyl)-4-(methoxy-imino)-butyl]-1,2,5,6-tetrahydro-pyridin-3ylmethyl]-1H-indole

(Compound 24)

Mp 86-90°C

Analysis

$C_{26}H_{30}N_3FO_2$. $C_4H_6O_6$

This Sheet Has Been Replaced



	C	H	N
Found%	59.21	6.41	6.90
Calc.%	61.53	6.20	7.18

^{1}H NMR (DMSO) δ - 10.70 (s, 1H), 7.44 (m, 2H), 7.30-7.15 (3H), 7.09 (d, 1H), 6.95 (d, 1H), 6.70 (m, 1H), 5.62 (b, 1H), 4.13 (s, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.5 (b, 4H), 3.33 (s, 2H), 3.13 (b, 2H), 2.8-2.4 (6H), 2.16 (b, 2H), 1.6 (m, 2H).

MS (C.I.): $[M + H]^+$ 436m/z

[Z] 5-Methoxy-3-[N-[4-(4-fluoro-phenyl)-4-(methoxy-imino)-butyl]-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 25)

Mp 176-181

This Sheet Has Been Replaced



Analysis

$C_{26}H_{30}N_3FO_2 \cdot C_4H_6O_6$

	C	H	N
Found%	60.01	6.38	6.97
Calc.%	61.53	6.20	7.18

^{1}H NMR ($CDCl_3$) δ = 8.31 (b, 1H), 7.57 (m, 2H), 7.21 (d, 1H), 7.1-6.9 (4H), 6.83 (m, 1H), 5.57 (b, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.36 (s, 2H), 2.91 (b, 2H), 2.70 (t, 2H), 2.53 (t, 2H), 2.44 (t, 2H), 2.19 (b, 2H), 1.73 (m, 2H).

MS (C.I.): $[M + H]^+$ 436 m/z

Example 9

5-Methoxy-3-[N-(4-(4-fluoro-phenyl)-4-hydroxy-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 26)

Sodium borohydride (0.2 g; 0,0053 mol) was added to a cool (~ 5°C) stirring mixture of compound 8 of

Example 2 (5-methoxy-3-[N-(4-(4-fluoro-phenyl)-4-oxo-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole) (1.08 g; 0.0027 mol) in isopropanol (20 ml). The reaction mixture was stirred at 5°C for 4 hours. The reaction was then quenched with a saturated solution of aqueous sodium carbonate and the solvent (isopropanol) was evaporated under vacuum. The product was extracted with diethyl ether from the residual alkaline aqueous solution. The organic extract was dried ($MgSO_4$) and evaporated under vacuum giving the desired compound (0.8 g). A solution of the desired compound in diethyl ether was saturated with gaseous hydrogen chloride. The obtained precipitate which consists of the title compound hydrochloride, was collected by filtration, washed with diethyl ether and dried under vacuum (0.75 g).

Mp 160-170°C

Analysis

$C_{25}H_{29}FN_2O_2 \cdot HCl$

	C	H	N
Found%	65.28	6.92	5.6
Calc.%	67.48	6.8	6.3

^1H NMR (DMSO) δ = 10.83 (s, 1H), 10.46 (b, 1H), 7.4-7.1 (6H), 6.97 (d, 1H) 6.72 (m, 1H), 5.73 (b, 1H), 4.52 (t, 1H), 3.75 (s, 3H), 3.8-3.3 (5H), 3.2-2.9 (3H), 2.53 (m, 1H), 2.23 (m, 1H), 1.9-1.5 (2H), 1.55 (m, 2H).

MS (C.I.): $[M + H]^+$ 409 m/z

Following the above described process the following compound was prepared:

5-methoxy-3-[N-(3-(4-fluoro-phenyl)-3-hydroxy-propyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

This Sheet Has Been Replaced



(Compound 27)

Mp 70°C

Analysis

$C_{24}H_{27}N_2OF \cdot HCl.H_2O$

	C	H	N
Found%	64.34	6.84	6.10
Calc.%	64.21	6.74	6.24

^1H NMR (DMSO) δ - 10.81 (s, 1H), 10.59 (b, 1H), 7.4-7.1 (6H), 6.97 (d, 1H), 6.71 (m, 1H), 5.71 (b, 1H), 4.62 (m, 1H), 3.74 (s, 3H), 3.9-3.7 (1H), 3.6-2.9 (7H), 2.51-2.25 (m, 2H), 1.98 (m, 2H).

MS (C.I.): $[M + H]^+$ 395 m/z

Description 11

3-(2-chloro-ethyl)-benzofurane

i) 4-chloro-butyraldehyde-O-phenyl-oxime

A mixture of 2-(3-chloro-propyl)-[1,3]-dioxolane (5.7 g; 0.038 mol), THF (50 ml) and aqueous acid chloride (1/1) was stirred at room temperature for 24 hours. O-phenyl-hydroxylamine hydrochloride (5 g; 0.034 mol) was then added and the resulting mixture was stirred at room temperature for 48 hours. The reaction mixture was concentrated under vacuum. Then the product was extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and evaporated under vacuum. After purification by Flash Chromatography on silica gel using as eluent hexane/ethyl acetate (95/5), the desired compound was obtained.

ii) 3-(2-chloroethyl)-benzofurane

A mixture of 4-chloro-butyraldehyde-O-phenyl-oxime (2.5 g; 0.0126 mol), acetic acid (50 ml) and boron

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trifluoride etherate (1.45 ml; 0.0115 mol) was heated at 100°C for 1.5 hour. The reaction was then quenched with water and the product was extracted with diethyl ether. The organic extract was dried (Mg SO_4) and evaporated under vacuum. After purification by Flash Chromatography on silica gel using as eluent methylene chloride, the desired compound was obtained

Example 10

5-methoxy-3-[N-(2-benzofuran-3-yl)-ethyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 28)

The title compound was prepared according to the procedure described in Example 5, using compound of Description 5 [5-methoxy-3-(1,2,5,6-tetraydro-pyridin-3-ylmethyl)-1H-indole]and compound of Description 11 [3-(2-chloro-ethyl)-benzofurane]

Mp 96-99°C

Analysis

$C_{25}H_{26}N_2O_2$. HCl

	C	H	N
Found%	69.4	6.70	6.33
Calc.%	70.99	6.43	6.62

^1H NMR ($CDCl_3$) δ - 12.63 (b, 1H), 8.54 (s, 1H), 7.6-6.8 (9H), 5.87 (b, 1H), 3.3-2.1 (15H)

MS (C.I.): $[M + H]^+$ 387 m/z

This Sheet Has Been Replaced



Description 12

3-trifluoromethyl-N-(2-chloroethylcarbonyl)-aniline

The title compound was prepared according to the known Schotten-Baumann procedure using 3-(trifluoromethyl)-aniline and 3-chloro-propionyl chlo-

ride.

The above mentioned compound was used as such without further purification.

Example 11

5-methoxy-3-[N-(3-(3'-trifluoromethyl-phenyl-amino)-3-oxo-propyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 29)

The title compound was prepared according to the procedure described in Example 5, using compound of Description 5 [5-methoxy-3-(1,2,5,6-tetrahydro-pyridin--3-ylmethyl)-1H-indole] and compound of Description 12 [3-trifluoromethyl-N-(2-chloroethyl-carbonyl)-aniline]

Mp 172°C

Analysis

$C_{25}H_{26}N_3O_2F_3 \cdot HCl$

	C	H	N
Found%	59.9	5.56	8.50
Calc.%	60.59	5.51	8.51

^1H NMR ($CDCl_3$) δ - 11.39 (b, 1H), 10.28 (s, 1H), 8.27 (s, 1H), 8.08 (s, 1H), 7.76 (m, 1H), 7.4-7.2 (m, 3H), 7.01 (s, 1H), 6.91 (d, 1H), 6.81 (m, 1H), 5.81 (b, 1H), 3.81 (s, 3H), 3.9-3.8 (1H), 3.5-2.9 (9H), 2.77-2.31 (m, 2H)

MS (C.I.): $[M + H]^+$ 458 m/z

Example 12

5-methoxy-3-[N-(3-(3'-trifluoromethyl-phenyl-amino)-propyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 30)

To a stirred solution of Compound 29 of Example 11

This Sheet Has Been Replaced

[5-methoxy-3-[N(3-(3'-trifluoromethyl-phenyl-amino)-3-oxo-propyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole] (1.7 g; 0.0037 mol) in anhydrous tetrahydrofuran (50 ml) at room temperature under nitrogen was carefully added lithium aluminium hydride (0.3 g; 0.0078 ml) and the resulting mixture was refluxed for 16 hours. The reaction was then quenched with successive additions of water, aqueous sodium hydroxide and then additional water and the resulting mixture filtered through diatomaceous earth [Celite$^{(R)}$].

The solids were then washed with ethyl acetate. The combined filtrate was then washed with water, dried (Mg SO_4), and evaporated under vacuum.

After purification by Flash Chromatography on silica gel using as eluent methylene chloride/methanol/ammonia (95/5/0.5), the desired compound was obtained. A solution of the compound in ethanol was saturated with gaseous hydrogen chloride. A solid was precipitated. The title compound hydrochloride was collected by filtration, washed with hexane and dried under vacuum

Mp 132°C

Analysis

$C_{25}H_{28}N_3OF_3$. HCl

	C	H	N
Found%	62.26	6.07	8.70
Calc.%	62.56	6.09	8.75

^{1}H NMR (DMSO) δ = 10.71 (b, 1H), 10.5 (b, 1H), 7.4-6.6 (8H), 5.77 (b, 1H), 3.75 (s, 3H), 3.9-1.9 (14H).

MS (C.I.): $[M + H]^+$ 444 m/z

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Description 13

5-methoxy-3-[N-(4-(4-fluoro-phenyl)-4-amino-butyl)]-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

To a stirred solution of Compound 22 of Example 8 [5-methoxy-3-[N-[4-(4-fluoro-phenyl)-4-(hydroxy-imino)-butyl]-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole] (1 g; 0.0023 mol) in anhydrous tetrahydro furan (80 ml) at room temperature under nitrogen was carefully added lithium aluminium hydride (0.45 g; 0.0118 mol) and the resulting mixture was heated at reflux for 8 hours. The reaction was then quenched with successive additions of water, aqueous sodium hydroxide and then additional water and the resulting mixture filtered through diatomaceous earth (Celite$^{(R)}$). The solids were then washed with ethyl acetate. The combined filtrate was then washed with water, dried (Mg SO_4), and evaporated under vacuum. After purification by Flash Chromatography on silica gel using as eluent methylene chloride/methanol/ammonia (92/8/0.8), the desired compound was obtained (0.330 g)

Example 13

5-methoxy-3-[N-(4-fluoro-phenyl)-4-(acetyl-amino)butyl]-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

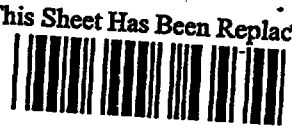
(Compound 31)

A mixture of compound of Description 13 [5-methoxy-3-[N-(4-(4-fluoro-phenyl)-4-amino-butyl)]-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole] (0.330 g; 0.00081 mol) in methylene chloride (40 ml) and acetic anhydride (3 ml) was stirred at room temperature for 4 hours. The reaction mixture was quenched

with aqueous sodium bicarbonate and the product was extracted with methylene chloride. The organic extract was dried (Mg SO_4) and evaporated under vacuum. After purification by Flash Chromatography on silica gel using as eluent methylene chloride/methanol/ammonia (94/6/0.6). A solution of the compound in ethanol was treated with the stechiometric amount of oxalic acid in ethanol. A solid was precipitated. The title compound oxalate was collected by filtration, washed with ethyl acetate and dried under vacuum

Mp 92°C

This Sheet Has Been Replaced



Analysis

$C_{27}H_{32}N_3O_2F \cdot C_2H_2O_4$

	C	H	N
Found%	63.2	6.70	7.2
Calc.%	64.55	6.35	7.79

^1H NMR (DMSO) δ - 10.81 (s, 1H), 8.35 (d, 1H), 7.4-7.1 (6H), 6.96 (d, 1H), 6.71 (m, 1H), 5.71 (b, 1H), 4.75 (m, 1H), 3.74 (s, 3H), 3.52 (b, 2H), 3.39 (s, 2H), 3.14 (b, 2H), 3.00 (b, 2H), 2.30 (b, 2H), 1.83 (s, 3H), 1.8-1.4 (4H)

MS (C.I.): $[M + H]^+$ 450 m/z

Example 14

5-methoxy-3-[N-(4-(2-thienyl)-4-oxo-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 32)

The title compound was prepared according to the procedure described in Example 5, using compound of Description 5 [5-methoxy-3-(1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole) and the commercial halide 4-chloro-2'-butyrothienone

Mp 140-150°C

Analysis

$C_{23}H_{26}N_2O_2S$. HCl

	C	H	N
Found%	63.9	6.1	6.0
Calc.%	64.1	6.31	6.5

^1H NMR (DMSO) δ - 10.79 (s, 1H), 10.28 (b, 1H), 8.02 (m, 1H), 7.93 (m, 1H) 7.3-7.1 (3H), 6.98 (d, 1H), 6.71 (m, 1H), 5.75 (b, 1H), 3.78 (gem, 1H), 3.75 (s, 3H), 3.6-2.9 (9H), 2.6-2.2 (2H), 1.99 (m, 2H)

MS (C.I.): $[M + H]^+$ 395 m/z

Following the above mentioned procedure and using the appropriate commercial halide, the following compounds were prepared:

5-methoxy-3-[N-(4-(4-methoxy-phenyl)-4-oxo-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 33)

Mp 140-147°C

Analysis

$C_{20}H_{26}N_2O_2$. HCl

	C	H	N
Found%	68.4	6.45	6.0
Calc.%	68.63	6.87	6.16

^1H NMR (DMSO) δ - 10.79 (b, 1H), 8.36 (b, 1H), 7.83 (d, 2H), 7.26 (d, 1H) 7.10 (d, 1H), 6.92 (d, 2H), 7.0-6.9 (1H), 6.82 (m, 1H), 5.86 (b, 1H), 3.87 (s, 3H), 3.9-3.7 (1H), 3.6-2.5 (10H), 2.38 (m, 1H), 2.17 (m, 2H)

MS (C.I.): $[M + H]^+$ 419 m/z

5-methoxy-3-[N-(3-ethyl-3-oxo-propyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 34)

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Mp 156-160°C

$C_{20}H_{26}N_2O_2$. HCl

	C	H	N
Found%	66.03	7.2	7.1
Calc.%	66.19	7.5	7.72

^1H NMR (DMSO) δ - 10.80 (s, 1H), 10.49 (b, 1H), 7.21 (d, 1H), 7.17 (d, 1H) 6.97 (d, 1H), 6.72 (m, 1H), 5.72 (b, 1H), 3.75 (s, 3H), 3.70 (gem, 1H), 3.6-3.2 (6H), 3.1-2.9 (3H), 2.45 (q, 2H), 2.26-2.2 (2H), 0.92 (t, 3H)

MS (C.I.): $[M + H]^+$ 327 m/z

5-methoxy-3-[N-(4-(4-methyl-phenyl)-4-oxo-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl-1H-indole

(Compound 35)

Mp 86-93°C

Analysis

$C_{26}H_{30}N_2O_2$. HCl

	C	H	N
Found%	71.0	6.9	6.1
Calc.%	71.14	7.12	6.38

^1H NMR ($CDCl_3$) δ - 12.22 (b, 1H), 8.35 (s, 1H), 7.80 (d, 2H), 7.3-7.2 (3H) 7.11 (s, 1H), 6.93 (d, 1H) 6.82 (m, 1H), 5.87 (b, 1H), 3.86 (gem, 1H), 3.82 (s, 3H) 3.8-2.7 (10H), 2.41 (s, 3H), 2.5-2.2 (1H), 2.18 (m, 2H)

MS (C.I.): $[M + H]^+$ 403 m/z

Example 15

5-methoxy-3-[N-methyl-1,2,5,6-tetrahydro-pyridin-3-yl-methyl]-1-(4-fluoro-phenyl)-indole

(Compound 36)

A mixture of compound 1 of Example 1 [5-methoxy-3-(N-methyl-1,2,5,6-tetrahydro-pyridin-3-yl-methyl)-1H-indole] (1 g; 0.0039 mol), 1-fluoro-4-iodobenzene (0.6

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ml; 0.0058 mol), finally powdered anhydrous K_2CO_3 (0.7 g; 0.0051 mol), copper bromide (0.3 g; 0.0023 mol) and copper bronze (0.002 g) in 1-methyl-2-pyrrolidone (20 ml) was heated at 180°C under nitrogen for 4 hours. After cooling (below 100°C) the mixture was poured into diluted hydrochloric acid. After the mixture was stirred, the precipitated material was filtered off, washed with water, and subsequently dried in vacuo.

Purification was performed by dissolving in methylene chloride, treating the solution with activated carbon, and finally by Flash chromatography on silica gel using as eluent methylene chloride/methanol/ammonia (95/5/0.5). A solution of the desired compound in diethyl ether was saturated with gaseous hydrogen chloride. The title compound hydrochloride was collected by filtration, washed with diethyl ether and dried under vacuum

Mp 200°C

Analysis

$C_{22}H_{23}N_2OF_3 \cdot HCl$

	C	H	N
Found%	67.9	6.2	7.01
Calc.%	68.3	6.5	7.24

^1H NMR (DMSO) δ = 10.43 (b, 1H), 7.7-7.3 (6H), 7.11 (d, 1H), 6.84 (m, 1H), 5.85 (b, 1H), 3.80 (s, 3H), 3.75 (gem, 1H), 3.6-3.4 (4H), 3.05 (m, 1H), 2.78 (d, 3H), 2.50 (m, 1H), 2.30 (m, 1H).

MS (C.I.): $[M + H]^+$ 351 m/z

Example 16

5-methoxy-3-(N-methyl-piperidin-3-ylmethyl)-1H-indole

(Compound 37)

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To a stirred solution of compound of Description 6 [5-methoxy-3-(piperidin-3-ylmethyl)-1H-indole] (2g, 0.0082 mol) in methanol (50 ml) was added dropwise aqueous formaldehyde (40%) (5.63 ml; 0.082 mol). The mixture was heated at reflux for 2 hours. The reaction mixture was cooled at 10°C and then sodium borohydride (0.93 g; 0.025 mol) was added. The resulting mixture was stirred at room temperature for 1.5 hours. The reaction was then quenched with water and the solvent (methanol) was evaporated under vacuum. The product was extracted with ethyl acetate, the organic extract was dried (Mg SO_4) and evaporated under vacuum, then the compound was triturated with diethyl ether and dried under vacuum giving the title compound as a solid (1.8 g)

Mp 112-114°C

Analysis

$C_{16}H_{22}N_2O$

	C	H	N
Found%	74.3	8.84	10.73
Calc.%	74.38	8.58	10.84

^1H NMR ($CDCl_3$) δ = 8.15 (b, 1H), 7.3-6.7 (4H), 3.85 (s, 3H), 2.80 (m, 2H), 2.61 (d, 2H), 2.23 (s, 3H), 2.4-0.7 (7H)

MS (C.I.): $[M + H]^+$ 259 m/z

Example 17

5-methoxy-3-[N-(α-tetralon-2-ylmethyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

(Compound 38)

The title compound was prepared according to a known Mannich procedure, using compound of Description

[5-methoxy-3-(1,2,5,6-tetrahydro-pyridin-3-ylmethyl)-1H-indole] and the commercial compound α-tetralone

Mp 154-156°C

Analysis

$C_{26}H_{28}N_2O_2$. HCl

	C	H	N
Found%	70.89	6.71	6.32
Calc.%	71.46	6.69	6.41

^1H NMR (DMSO) δ = 10.80 (s, 1H), 10.26 (b, 1H), 7.88 (d, 1H), 7.57 (m, 1H), 7.4-7.3 (2H) 7.23 (m, 1H), 7.17 (s, 1H) 6.98 (d, 1H), 6.71 (d, 1H), 3.76 (m, 1H), 3.9-2.8 (11H), 3.76 (s, 3H), 2.6-2.2 (3H), 1.88 (m, 1H)

MS (C.I.): $[M + H]^+$ 401 m/z

Example 18

5-methoxy-3-[N-(4-(4-fluoro-phenyl)-4-oxo-butyl)piperidin-3-ylmethyl]-1-H-indole

(Compound 39)

A mixture of compound of Description 6 [5-methoxy-3-(piperidin-3-ylmethyl)-1H-indole] (2 g; 0.0082 mol), sodium bicarbonate (0.68 g; 0.0082 mol), KI (0.087 g; 0.00053 mol) and 2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane [2.2 g (1,8 ml); 0.009 mol] in dry dimethylformamide (25 ml) and tetrahydrofuran (25 ml), was heated under reflux for 5 hours. After evaporation under vacuum, the residue was flash chromatographed on silica gel using as eluent methylene chloride/methanol/ammonia (95/5/0.5) and the desired compound was obtained. A solution of the compound in ethanol was saturated with gaseous hydrogen chloride, a solid was precipitated. The title compound hydrochloride was collected by filtration.

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The following not limitative examples of pharmaceutical compositions according to the invention are given:

Example 19

Tablets

- active ingredient	10 mg
- lactose	187 mg
- corn starch	50 mg
- magnesium stearate	3 mg

Method of preparation: the active ingredient, lactose and corn starch were mixed and homogeneously moistened with water. After screening of the moist mass and drying in a tray drier, the mixture was again passed through a screen and magnesium stearate was added. Then the mixture was pressed into tablets weighing 250 mg each. Each tablet contains 10 mg of active ingredient.

Example 20

Capsules

- active ingredient	10 mg
- lactose	188 mg
- magnesium stearate	2 mg

Method of preparation: the active ingredient was mixed with the auxiliary products, and the mixture was passed through a screen and mixed homogeneously in a suitable device. The resulting mixture was filled into hard gelatine capsules (200 mg per capsule); each capsule contains 10 mg of active ingredient.

Example 21

Ampoules

- active ingredient	2 mg

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- sodium chloride 9 mg

Method of preparation: the active ingredient and sodium chloride were dissolved in an apropriate amount of water for injection. The resulting solution was filtered and filled into vials under sterile conditions.

Example 22

Suppositories

- active ingredient 25 mg
- semisynthetic glicerides of fatty acids 1175 mg

Method of preparation: the semisynthetic glicerides of fatty acids were melted and the active ingredient was added while stirring homogeneously. After cooling at a proper temperature the mass was poured into preformed moulds for suppositories weighing 1200 mg each. Each suppository contains 25 mg of active ingredient.

Example 23

Nasal spray

- active ingredient 80 mg
- benzalconchloride 0,1 mg
- sodium chloride 8 mg
- EDTA 1 mg
- sodium phosphate (buffer pH 6,5) 10 mg
- polysorbate 80 10 mg
- bidistilled water q.s. to 2 ml

Method of preparation: the single components were added in the suitable volume of bidistilled water by stirring until a complete dissolution before an further addition. After taking to volume, the solution was fil-

tered upon sterilising filter, introduced in suitable bottles and blocked up by the opportune dosage system.

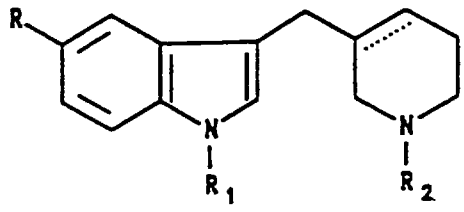
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CLAIMS

1. Compounds of general formula (I)

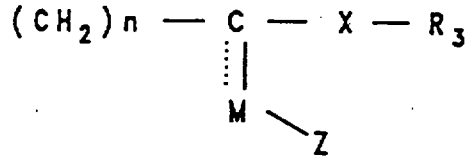


wherein:

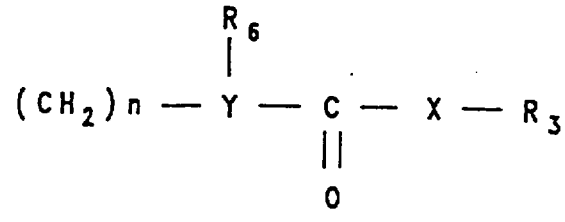
R represents H, C_{1-6} alkyl, lower alkoxy, aralkoxy, halogen, hydroxy, cyano or C_{1-6} acyl;

R_1 represents H, C_{1-6} alkyl, optionally substituted aryl, C_{3-6} cycloalkyl C_{1-2} alkyl or lower alkyl bearing an optionally substituted phenyl;

R_2 represents H, C_{1-6} alkyl, lower alkyl bearing a phenyl, phenoxy, or anilino, each group being optionally substituted by one or more substituents selected from lower alkyl, lower alkoxy, amino, halogen or trifluoromethyl; or R_2 is a group selected from



(a)



(b)

where n is an integer from 1 to 3;

* C L M S *

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R_3 represents an aryl or heteroaryl group, each group being optionally substituted by one or more substituents selected from lower alkyl, halogen or trifluoromethyl; C_{1-6} alkyl, or C_4-C_{10} cycloalkyl;

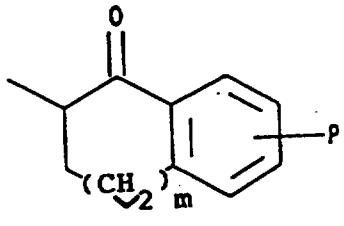
M represents oxygen or nitrogen, or when the bond C-M is single - represents NH;

Z is absent when M is oxygen or it represents H. C_{1-6} acyl or OR_4 where R_4 is hydrogen, lower alkyl, lower alkyl bearing a phenyl being optionally substituted by one or more substituents selected from lower alkyl, lower alkoxy, halogen, trifluoromethyl;

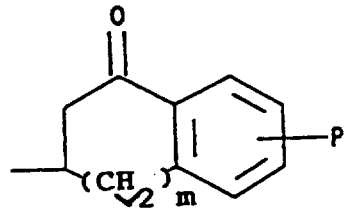
X is absent or it represents CH_2 or NR_5 where R_5 is H or lower alkyl;

Y represents CH or nitrogen atom;

R_6 represents hydrogen, lower alkyl, aryl or R_3 and R_6 together with the carbonyl group to which they are bound constitute benzocondensed cycloalkanones of formula



(c)



(d)

m is an integer from 0 to 2;

P represents H, lower alkyl, halogen or trifluoromethyl;

and acid addition salts therof.

2. Compounds of formula I selected from:

5-methoxy-3-(N-methyl-1,2,5,6-tetrahydro-pyridin-

* C L M S *

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3-ylmethyl)-1H-indole

5-methoxy-3-[N-(2-(4-amino-phenyl)-ethyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole)

5-methoxy-3-[N-(4'-fluoro-phenoxy-ethyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

5-methoxy-3-[N-(4-(4-fluoro-phenyl)-4-oxo-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

5-methoxy-3-[N-(3-(4-fluoro-phenyl)-3-oxo-propyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

5-methoxy-3-[N-(4-(4-fluoro-phenyl)-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

5-methoxy-3-[N-2(4-fluoro-benzamide)ethyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

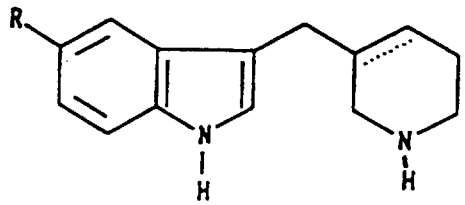
5-methoxy-3-[N-(3-(4-fluoro-phenyl)-propyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

5-methoxy-3-[N-(4-(2-thienyl)-4-oxo-butyl)-1,2,5,6-tetrahydro-pyridin-3-ylmethyl]-1H-indole

3. Physiologically acceptable acid addition salts of compounds of general formula (I) according to claim 1-2.

4. Salts according to claim 3, characterized in that the physiologically acceptable acids are hydrochloric, maleic or fumaric acid.

5. Process for the preparation of compounds of general formula I, according to claim 1, in which R_1 is hydrogen, characterized in that a compound of formula II



II

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wherein R is as defined in claim 1 is reacted with a compound of formula III

$$R_2 - X \qquad (III)$$

wherein R_2 is as defined in claim 1 and X is a halogen atom in the preference of a base and in an inert polar solvent at a temperature ranging from 50° to 80°C.

6. Process for the preparation of compounds of general formula I according to claim 1, in which R_1 represents any meaning as defined in claim 1 except hydrogen, characterized in that a compound of formula I, wherein R_1 is hydrogen, is reacted with a base and then with a compound of formula (X)

$$R_1 - X \qquad (X)$$

in which R_1 represents any meaning as defined in claim 1 except hydrogen and X is a halogen atom in an inert polar solvent at a temperature ranging from 0° to room temperature.

7. Process according to claim 6, characterized in that the base is selected from sodium hydride, potassium hydroxide or potassium ter-butylate.

8. Pharmaceutical compositions comprising as active ingredient an effective amount of a compound of general formula (I), as defined in claim 1, or physiologically acceptable acid addition salts thereof, in association with pharmaceutically acceptable carriers, diluents or excipients.

9. Pharmaceutical compositions according to claim 8 for the use in the treatment of patients suffering from central nervous system disorders, in particular in affective disorders (e.g. depression, bipolar disorders), anxiety, sleep and sexual disorders, psychosis, schi-

* C L M S *

zophrenia, personality disorders, mental organic disorders, mental disorders in chilhood, aggressiveness, age associated memory impairment, cerebral ictus and motion sickness.

10. Pharmaceutical compositions according to claim 8 for the use in the treatment of patients suffering from cardiovascular disorders, e.g. hypertension and thrombosis.

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