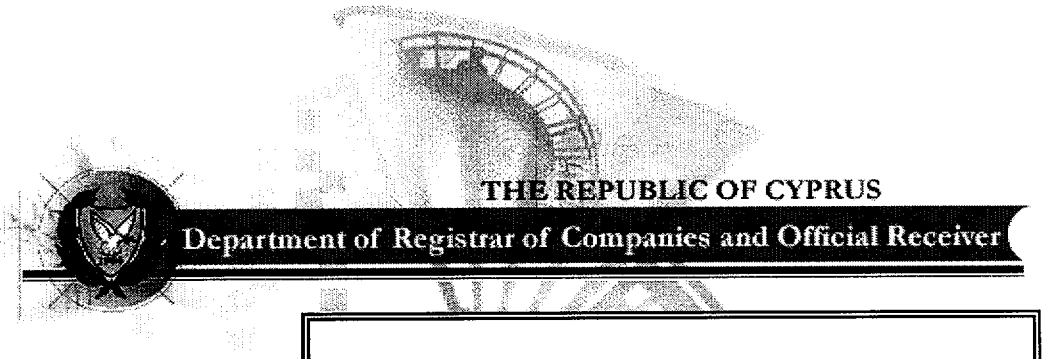

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

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(54) **Substituted 1-pyridyloxy-3-indolylalkylamino-2-propanols, preparation, and use thereof**

(57) 1-(Pyridinyloxy)-3-(indolylalkylamino)-2-propanols, novel cardiovascular agents having vasodilator activity and a range of adrenergic *beta*-receptor blocking action, are prepared by any one of three routes that comprise a novel general process. The general process comprises coupling a hydroxyl- or halogen-substituted pyridine with a suitable halogen- or hydroxyl-substituted propanol or incipient propanol intermediate; and the products of these couplings are also novel. In the preferred of the three coupling routes, product 1-(pyridinyloxy)-3-(indolylalkylamino)-2-propanols are formed directly; in the other two coupling routes further processing of the coupling products is required to form the 1-(pyridinyloxy)-3-(indolylalkylamino)-2-propanols. Preferred compounds bear an amide or cyano substituent in the 3-position of the pyridine ring.

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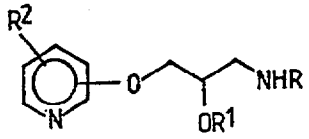
SPECIFICATION

Substituted 1-pyridyloxy-3-indolylalkylamino-2-propanols, preparation, and use thereof

The present invention is concerned with heterocylic carbon compounds of the indole series having an amino substituent, and with drug bio-affecting and body-treating processes employing these compounds.

A rather large body of prior art exists relating to compounds of 3-(aryloxy)-2-hydroxypropylamine series which have *beta*-adrenergic receptor blocking activity and/or vasodilating properties and are useful in treatment of cardiovascular diseases. Much of this prior are concerns the *beta*-adrenergic blocking agent class of these series of compounds. The prototype for these structures is propranolol; chemically, 1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol. Propranolol and some related naphthyloxy propanolamines are the subject of U.S. Patent No. 3,337,628 issued August 22, 1967. Numerous subsequent patents have been granted covering carbocyclic ethers in which other aromatic rings or heterocyclic systems replaced the naphthyloxy group of propranolol.

A series of patents has been granted to J. J. Baldwin disclosing the employment of the pyridinyloxy group in this fashion. These compounds and their salts are disclosed and claimed as useful antihypertensive agents. These patents, which are listed below, generally disclose the following generic structure (1)



(1)

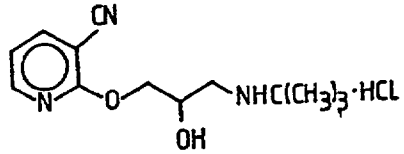
wherein R is alkyl, phenalkyl, phenoxyalkyl; R^1 is H,

with L being alkyl or aryl; R^2 is H, CN, CF_3, OH,

Cl, NO_2, F, pyrrolyl, oxadiazolyl.

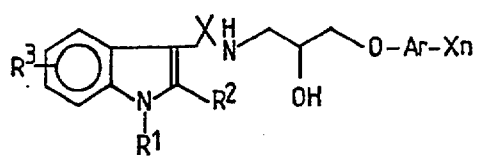
The series of Baldwin patents, assigned to Merck & Co., Inc., comprise the following: 4,000,282, December 28, 1976; 4,060,601, November 29, 1977; 4,091,104, May 23, 1978; 4,092,419, May 30, 1978; 4,144,343, March 13, 1979; 4,145,425, March 20, 1979; 4,151,284, April 24, 1979; 4,210,653, July 1, 1980; 4,259,327, March 31, 1981; 4,263,307, April 21, 1981; 4,279,913, July 21, 1981; and 4,329,351, May 11, 1982.

A preferred compound of this series, 2-[3-(*tert.*-butylamino)-2-hydroxypropoxy]-3-cyanopyridine, also known as MK-761, has undergone considerable further study as described in: Sweet, *et al., The Journal of Pharmacology and Experimental Therapeutics*, 211/1, 195—296 (1979); Sweet, *et al., Clinical and Experimental Hypertension*, 1(4), 449—471 (1979) and Vickers, *et al., Drug Metabolism and Disposition*, 8/3, 163—167 (1980). Acute studies in man were terminated, however, when MK-761 was found to be teratogenic in rabbits after chronic administration at high doses (cf: *Journal of Medicinal Chemistry*, 22/11, 1284—1290 (1979)).

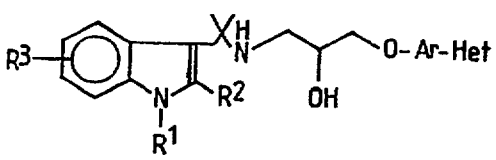


MK-761

A series of indol-3-yl-*tert*. butylaminopropanols (2,3) with antihypertensive properties was described in: Kreighbaum, *et al.*, U.S. Patent No. 4,234,595 patented November 18, 1980; U.S. Patent No. 4,314,943 patented February 9, 1982; and *Journal of Medicinal Chemistry*, 23:3, 285—289 (1980).



(2)



(3)

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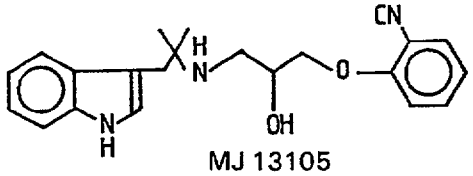
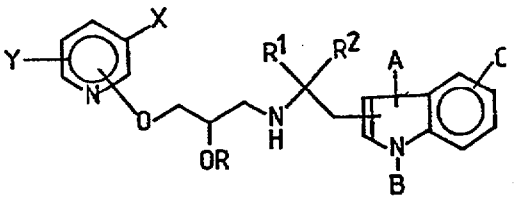
A preferred compound of the series represented by structure (2) is designated MJ 13105, also known as bucindolol, and is currently undergoing evaluation clinically as an antihypertensive agent.



MJ 13105

This invention concerns a series of vasodilating agents having a range of *beta*-adrenergic blocking potency and possessing the general formula I and the pharmaceutically acceptable acid addition salts thereof:

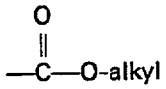


(I)

In the foregoing structural formula, X is CHO, CH_2OH, CN, CF_3, $CONR^aR^b$ or CO_2R^c with R^a and R^b being independently chosen from hydrogen or R^c, and R^c being lower alkyl, aryl, or arylalkyl; Y is hydrogen, halogen, acyloxy, alkoxy, aralkyloxy, aryloxy, or hydroxyl; R is hydrogen or

with L being selected from alkyl, aryl, substituted aryl, or arylalkyl; R^1, R^2, A and B are independently selected from hydrogen or alkyl; and C can be halogen, hydrogen, hydroxy, alkyl or alkoxy. Preferred compounds have X in the 3-position of the pyridine ring and the indolylalkylaminopropoxy side chain is attached to the 2-position of the pyridine nucleus.

The invention includes compounds having the foregoing structural formula (I) and the acid addition salts thereof. In structural Formula I, X can be —CHO, —CN, —CF_3, —$CONR^aR^b$, or —CO_2R^c. R^a and R^b are independently chosen from hydrogen or R^c which can be lower alkyl (C_1 to C_4); aryl; or aryl-lower alkyl, aryl being preferably phenyl. It is also preferred that X be attached to the 3-position in the pyridine ring system. Y represents a second substituent on the pyridine ring and may be hydrogen, halogen, lower (C_1—C_4)alkoxy, aryl-lower alkoxy hydroxy, or



wherein alkyl is C_1—C_6 alkyl. The entire pyridinyl group is coupled to the indolylalkylaminopropoxy side chain at the pyridine 2-position. R is hydrogen or

with L being selected from C_1—C_{10} alkyl, phenyl, substituted phenyl, or phenalkyl. R^1, R^2, A, and B are independently chosen from hydrogen or lower alkyl. C represents a substituent in the benzo ring of indole and is selected from hydrogen, halogen, lower alkyl, lower alkoxy, or hydroxy. The indole moiety itself is preferably coupled to the main side chain through its 3-position.

For medicinal use, the pharmaceutically acceptable acid addition salts, those salts in which the anion does not contribute significantly to toxicity or pharmacological activity of the organic cation, are preferred. The acid addition salts are obtained either by reaction of an organic base of structure I with an organic or inorganic acid, preferably by contact in solution, or by any of the standard methods detailed in the literature and available to any practitioner skilled in the art. Examples of useful organic acids are carboxylic acids such as maleic acid, acetic acid, tartaric acid, propionic acid, fumaric acid, isethionic acid, succinic acid, pamoic acid, cyclamic acid, pivalic acid, and the like useful inorganic acids are hydrohalide acids such as HCl, HBr, HI; sulfuric acid; phosphoric acid; and the like.

It is also to be understood that the compounds of the present invention include all the optical isomer forms, that is, mixtures of enantiomers, e.g., racemic modifications as well as the individual enantiomers. These individual enantiomers are commonly designated according to the optical rotation they effect, by (+) and (—), (l) and (d), or combinations of these symbols. The symbols (L) and (D) and

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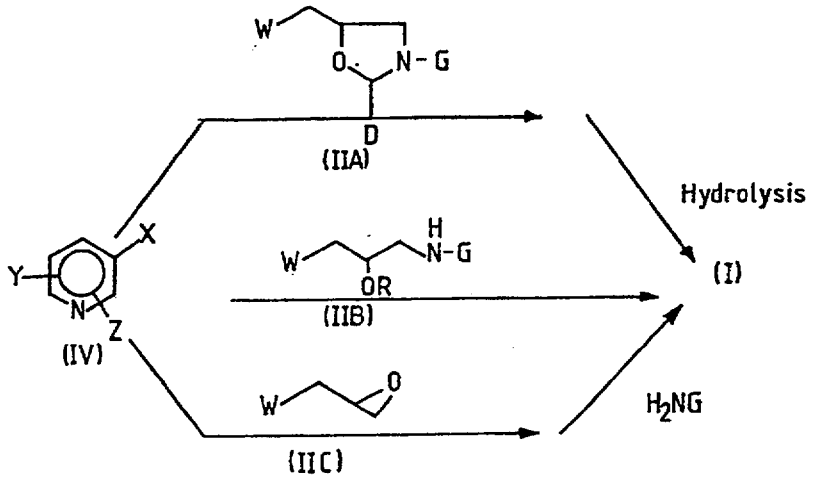
the symbols (S) and (R), which stand for sinister and rectus respectively, designate an absolute spatial configuration of the enantiomer. Where no isomer designation is given for a compound, the compound is the racemic modification.

Biological testing of the subject compounds of Formula I in animals demonstrates that they possess potent vasodilating properties along with varying degrees of adrenergic *beta*receptor blocking properties and intrinsic sympathomimetic activity. Preferred members have a particularly desirable combination of the foreging actions, and ancillary pharmacological effects, or a lack thereof, which particularly suits them for specific cardiovascular indications, e.g. use as antihypertensives. The utility of the compounds of Formula I can be demonstrated in various animal models including antagonism of isoproterenol in the anesthetized dog treated intravenously (adrenergic *beta*receptor action), the spontaneous hypertensive and DOCA salt hypertensive rat (antihypertensive action), angiotensin-maintained ganglion-blocked rat model (vasodilator action), and in various other animal and laboratory models (cf: Deitchman, *et al.*, *Journal Pharmacological Methods*, *3*, 311321, (1980)). No evidence of teratogenicity or mutagenicity has been found to be associated with the compounds of Formula I.

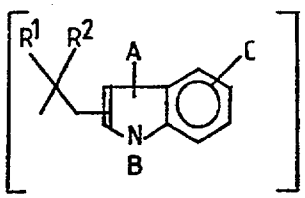
For use as antihypertensives, vasodilators, and/or *beta*-adrenergic blocking agents, therapeutic processes of this invention comprise systemic administration, by both oral and parenteral routes, of an effective, nontoxic amount of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof. An effective amount is construed to mean a dose which exerts the desired pharmacological activity, such as those stated hereinabove, without undue toxic side effects when administered to a mammal in need of such treatment. Dosage will vary, according to the subject and route of administration selected, with an expected range of about 0.1 mcg to 100 mg/kg body weight of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof generally providing the desired therapeutic effect.

The compounds of the present invention can be prepared by a convenient general process. This process involves the coupling of a Z-substituted pyridine (IV) with a suitable W-substituted propanol or incipient propanol intermediate (II).

General process



In the foregoing general process, D is hydrogen, or preferably, phenol; G is the radical



Z is hydroxyl or halogen, preferably chloride; W is halogen, preferably chloride, when Z is hydroxyl and is hydroxyl when Z is halogen. Generally, the hydroxyl-bearing reactant is initially converted to the oxide anion with a strong base prior to reaction with the halogen-bearing intermediate.

This process employs methods known in the prior art for the preparation of 1-(substituted amino)-3-(hetaryloxy)-2-propanols as represented by the patents and publications cited in "Background of the Invention". The process involves reaction of the appropriately substituted pyridine with either 1) a [3-(indolylalkyl)oxazolidin-5-yl]methanol (or methyl halide) of Formula IIA, or 2) an indolylalkylaminopropanediol (or halopropanol) of Formula IIB, or 3) glycidol of Formula IIC.

The intermediate from reaction of IV and IIa is converted to the product I by hydrolysis under acidic conditions. This hydrolysis is accomplished with dilute mineral acid of from 0.1N to 1N concentration at temperatures of from about 20—100°C. The product of Formula I can be recovered

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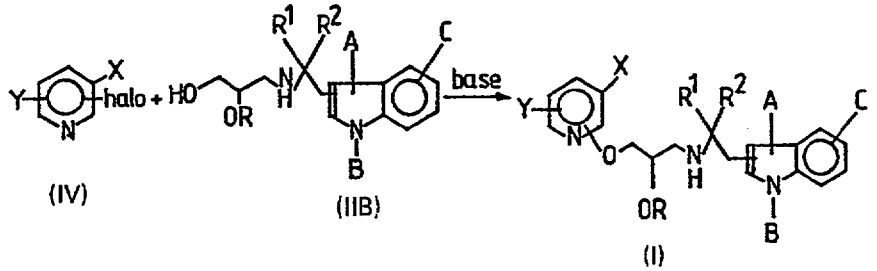
as the free base by neutralization of the hydrolysis mixture and collecting the precipitate. Acid addition salts may be obtained by evaporating the hydrolysis mixture or by reaction of the free base with acid. Purification is accomplished by conventional means such as recrystallization.

The conversion of the epoxide intermediate resulting from the reaction of IV with IIC into the product of Formula I is carried out simply by heating the epoxy ether either neat or in the presence of a reaction inert organic solvent with an amine of the formula H_2NG as shown. No catalyst or condensation agent is required. Suitable solvents include 95% ethanol but other reaction-inert organic liquids in which the reactants are soluble may be employed. These include but are not limited to benzene, tetrahydrofuran, dibutylether, butanol, hexanol, methanol, dimethoxyethane, ethylene glycol, etc. Suitable reaction temperatures are from about 60—200°C.

The single step process pathway involves the reaction of IV with IIB and this is the preferred pathway for synthesis of the products of this invention.

This process is illustrated by the following specific reaction equation which shows the preferred synthetic method of the above as Reaction 1.

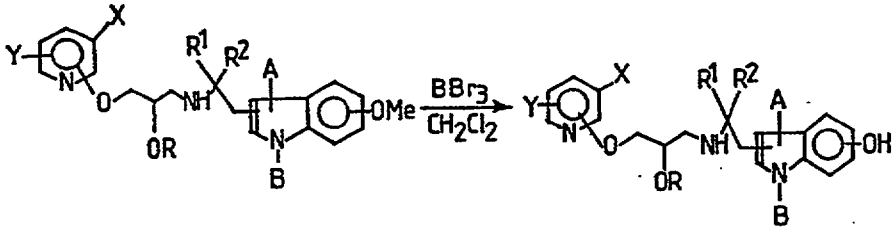
Reaction 1



In the foregoing scheme, X, Y, R, R^1, R^2, A, B, and C are as defined in Formula I. Essentially this process involves heating the selected substituted halopyridine with the appropriate indolylalkylaminopropanol intermediate (IIB) in the presence of a base, all in an inert organic liquid under mild conditions. Standard strong bases such as potassium *t*-butoxide, potassium hydroxide, or sodium hydride may be employed but the sodium hydride is preferred. Similarly, any of a number of inert organic liquids may be chosen as the reaction medium or the cyanopyridine and indolylalkylaminopropanol may be reacted neat in the presence of the base. Suitable solvents include but are not limited to benzene, toluene, tetrahydrofuran, dibutylether, dimethoxyethane, etc. Suitable reaction temperatures are from about 20—80°C. Addition of a suitable crown ether, such as 18-crown-6 ether, aids the reaction process.

Formula I products in which Y and/or C are hydroxy, are prepared by cleavage of the corresponding methoxy precursor as shown in Reaction 2:

Reaction 2



Other synthetic methods resulting in conversion to hydroxylated products, e.g. such as hydrogenolysis of benzyloxy precursors, are well known to the chemical practitioner and may also be applied in these cases.

Requisite halopyridines are available commercially or may be prepared using standard methods for their preparation reported in the literature. Preparation of related trisubstituted pyridines is disclosed in U.S. 4,329,351, issued May 11, 1982 to Baldwin, *et al.*, and which is hereby incorporated by reference in its entirety.

The intermediate indolylalkylaminopropanols (IIB; R=H), preferred synthetic intermediates, are conveniently prepared by reacting an appropriately substituted indolylalkylamine (III) with 3-chloro-1,2-propanediol in refluxing alcohol containing sodium carbonate. This process is illustrated by reaction equation 3.

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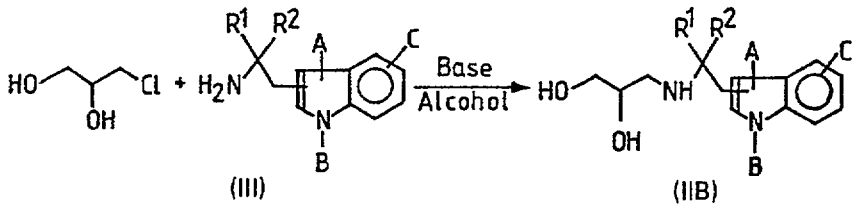
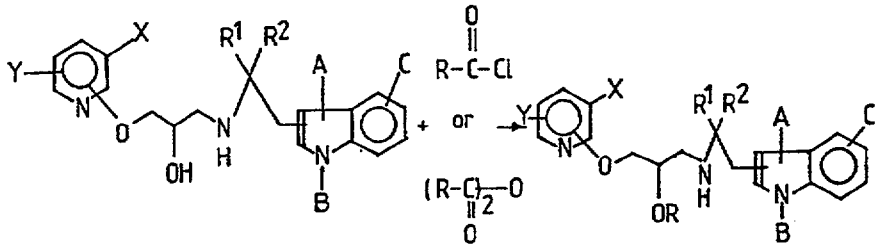
Reaction 3



In reaction scheme 3, R^1, R^2, A, B, and C are as defined in Formula I.

Formula I products of the present invention wherein R is other than hydrogen are conveniently prepared by treating the corresponding Formula I product wherein R is hydrogen with an appropriate acylating agent such as an acyl halide, e.g. undecanoyl chloride, pivaloyl chloride, benzoyl chloride, para-methoxybenzoyl chloride, or anhydride, e.g. acetic anhydride, and the like. The reaction is illustrated by the following equation shown below as Reaction 4:

Reaction 4



The indolylalkylamines (III) are described in the aforementioned Kreighbaum, *et al.* patents and *Journal of Medicinal Chemistry* article, which are hereby incorporated by reference, as well as certain references cited therein. Although these referenced procedures are applicable to the preparation of other indolylalkylamine intermediates not specifically disclosed therein but which are required as intermediates for the present invention, representative syntheses of Formula III compounds are given hereinbelow for further exemplification.

The compounds of the present invention can be formulated according to conventional pharmaceutical practice to provide pharmaceutical compositions of unit dosage form comprising, for example, tablets, capsules, powders, granules, emulsions, suspensions, and the like. The solid preparations contain the active ingredient in admixture with non-toxic pharmaceutical excipients such as inert diluents, for example, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize, starch, or alginic acid, binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques so as to defy disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

Liquid preparations suitable for parenteral administration include solutions, suspensions, or emulsions of the compounds of Formula I. The aqueous suspensions of the pharmaceutical dosage forms of the compounds of Formula I contain the active ingredient in admixture with one or more non-toxic pharmaceutical excipients known to be suitable in manufacture of aqueous suspensions. Suitable excipients are, for example, suspending agents such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinyl pyrrolidone, gum tragecanth, and gum acacia. Suitable disbursing or wetting agents are naturally occurring phosphatides, for example, lecithin, polyoxyethylene stearate.

Non-aqueous suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, olive oil, sesame oil, or coconut oil, or in a mineral oil, for example, liquid paraffin. The suspensions may contain a thickening agent such as beeswax, hard paraffin, or cetyl alcohol. Sweetening and flavoring agents generally used in pharmaceutical compositions may also be included such as saccharin, sodium cyclamate, sugar and caramel to provide a palatable oral preparation. The compositions may also contain other absorbing agents, stabilizing agents, wetting agents and buffers.

The compounds which constitute this invention, their methods of preparation and their biologic actions will appear more fully from a consideration of the following examples and appended claims which are given for the purpose of illustration only and are not to 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 resonance (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

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(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.

Synthesis of intermediates
A. Intermediates of formula III

Example 1
3-(2-Amino-2-methylpropyl)-6-methoxyindole (R^1=R^2=Me, A and B=H, C=6-MeO)

To 15.2 mL of a chilled 25% aqueous solution of dimethylamine the following were added sequentially with stirring and continued cooling: 16.9 mL of acetic acid, 7.2 mL of 37% formaldehyde, 27 mL of 95% ethanol. The resulting stirred solution was kept at 0° to —5° with a cooling bath while 6-methoxyindole (10.0 g, 0.07 mole) was added in portions. This mixture was stirred and gradually warmed to 30° over a period of one-half hour and then held at 30° with stirring for 3 hrs. The reaction mixture was then chilled to 10—15° and acidified with 170 mL of 2N HCl. This acidic mixture was decolorized (Darco G-60), filtered and the filtrate made basic using 245 mL of 20% NaOH while being cooled and stirred. A resulting brown oily precipitate was ether extracted, and the extracts were water-washed, dried ($MgSO_4$) and concentrated to a brown oily residue (14 g). The residue was recrystallized from isopropylether and hexane to yield 9 g (65%) of 6-methoxygramine as a tan solid, m.p. 88—90°.

A mixture comprised of the 6-methoxygramine (7.7 g, 0.04 mole), 2-nitropropane (26.5 g, 0.3 mole), and NaOH (1.7 g pellets, 0.04 mole) was refluxed under a nitrogen atmosphere for 3—5 hrs. The reaction mixture was cooled to room temperature, acidified with 10% acetic acid and extracted with ether. The ether extracts were water-washed, dried $MgSO_4$), and concentrated *in vacuo* to a residue. Recrystallization of the residue from isopropyl alcohol-water gave 7.6 g (80%) of 3-(2-methyl-2-nitropropyl)-6-methoxyindole as a tan solid, m.p. 98—100°.

The nitropropylindole compound and activated Raney nickel (4.2 g) were combined in 80 mL 95% ethanol and heated to reflux. Heating was halted as a solution comprised of 85% hydrazine hydrate (7.8 g) in 8 mL 95% ethanol was added dropwise. The reaction mixture was then heated at reflux for 2 hrs, cooled to room temperature and filtered. The filtrate was concentrated to a residual oil which slowly solidified and the recrystallized from ethyl acetate-isopropyl ether to give 4.2 g of product, m.p. 125—128°.

Example 2
2-(2-Amino-2-methylpropyl)indole (R^1=R^2=Me, A, B, and C=H)

A solution comprising indole-2-carboxylic acid (10.0 g, 0.06 mole) and thionyl chloride (20.0 g, 0.17 mole) in 130 mL of dry Et_2O was stirred for 12—18 hrs at room temperature under a nitrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated to an oily residue which was taken up in 150 mL of dry Et_2O. This ether solution was treated wtih 80 mL of dimethylamine in 90 mL of Et_2O. The ethereal reaction mixture was concentrated to dryness and the residue crystallized in isopropyl alcohol. The solid was isolated by filtration to give 4.0 g (34%) of the 2-indolylamide product, m.p. 181—183°.

The amide was dissolved in 100 mL THF and this solution was added dropwise to a stirred suspension comprised of 3 g lithium aluminum hydride in 50 mL of THF under a nitrogen atmosphere. After heat at reflux for 2 hr, the reaction mixture was cooled and decomposed with a small amount of water and dilute NaOH solution. This mixture was filtered and the filtrate concentrated to a residual oil which was taken up in absolute ethanol and treated with a slight excess of dimethyl sulfate. The resulting alcoholic solution was stirred at room temperature for 4 hrs and then concentrated *in vacuo* to dryness giving as residue the trimethylamine quaternary salt.

The crude quaternary salt product (3.0 g, 0.01 mole) was combined with NaOH (2.0 g pellets, 0.05 mole) and 2-nitropropane (15 mL) and the mixture was heated at reflux under a nitrogen atmosphere for 1 hr. The resultant dark thick mixture was cooled, diluted with water, acidified with acetic acid to a pH of approximately 6 and then extracted with Et_2O. These Et_2O extracts were combined, washed with water, dried ($NgSO_4$) and concentrated to a dark residue which was chromatographed on a silica column and diluted with methylene chloride. Removal of the methylene chloride and recrystallization of the crude material from isopropyl alcohol-water gave 0.4 g of 2-(2-methyl-2-nitropropyl)indole as a cream colored solid, m.p. 102—103°.

Reduction of this nitro product with Raney nickel and hydrazine according to the procedure used in Example 1 above yields the desired indolalkylamine as a white solid, m.p. 130—133°.

Additional examples of indolealkylamines are displayed in Table 1.

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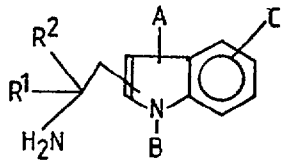
Table 1
Indolealkylamines



(III)

Example	R^1	R^2	A	B	C
3	Me	H	3-H	Me	H
4	Me	Me	2-Me	H	H
5	Me	Me	2-H	H	5-Br
6	Me	Me	2-H	H	5-OMe
7	H	Me	2-H	H	H
8	H	Me	2-Me	Me	5-OPr
9	H	Me	3-Me	Me	5-Br
10	Me	Me	2-H	H	6-OMe
11	Me	H	2-Et	H	4-Cl
12	Me	H	2-H	H	7-OMe

B. Intermediates of Formula II

Example 13

3-[[2-(3-Indolyl)-1,1-dimethylethyl]amino]-1,2-propanediol hydrate (IIB)

A mixture of α,α-dimethyl-β-(3-indolyl)ethanamine (10.0 g, 0.05 mole), Na_2CO_3 (11.3 g, 0.11 mole), 3-chloro-1,2-propanediol (7.0 g, 0.06 mole) and EtOH (250 mL) was stirred overnight at reflux. After cooling, the mixture was filtered and concentrated *in vacuo*. The residue was dissolved in EtOAc, decolorized (Darco G-60), and evaporated to a volume of 100 mL. The solution deposited a white solid which was recrystallized from EtOAc to give 7.7 g (55%), m.p. 112—114°C. The material crystallized with one-fifth mole of water.

Using other intermediates of Formula III in this or a similar procedure readily gives a variety of Formula IIB intermediates.

Synthesis of products

Example 14

2-[2-Hydroxy-3-[[2-(1H-indol-3-yl)-)-1-dimethylethyl]amino]propoxy]-3-pyridinecarbonitrile hydrochloride (Y=H, X=CN, R=H, R^1 and R^2=Me, A, B, and C=H)

3-[[2-(3-Indolyl)-1,1-dimethylethyl]amino]-1,2-propanediol (47.3 g, 0.18 mole) and sodium hydride (7.6 g of 57% dispersion in oil, 0.18 mole) were stirred in 2.5 liters of toluene and heated at 70° for 3 hrs under a nitrogen atmosphere. The mixture was then allowed to cool to room temperature while being stirred and 18-crown-6-ether (0.5 g), anhyd. powdered K_2CO_3 (62.1 g of powder, 0.45 mole) and 2-chloro-3-cyanopyridine (25.0 g, 0.18 mole) were added sequentially to the stirring mixture and then the whole was stirred for an additional 42 hrs. Concentration to dryness gave a residue which was partitioned between hot H_2O and EtOAc. After cooling to room temperature, the aqueous layer was separated, washed with additional EtOAc and this wash combined with the original EtOAc layer. The EtOAc was dried ($MgSO_4$) and concentrated hot to about half volume. Upon cooling, a solid precipitated and was isolated by filtration to give approximately 41 g (62%) of the crude product base.

Conversion of the base into the hydrochloride salt is accomplished by treating an isopropyl alcohol solution of the base with ethanolic HCl. Recrystallization of the crude hydrochloride salt from absolute ethanol gives a white solid, m.p. 181—183°.

Anal. Calcd. for $C_{21}H_{24}N_4O_2 \cdot HCl$: C, 62.92; H, 6.29; N, 13.98. Found: C, 62.85; H, 6.29; N, 14.04.

NMR (DMSO-d_6): 1.30 (6, s); 3.20 (4, m); 3.99 (3, m); 6.02 (1, d [4.0 Hz]); 7.30 (6, m); 8.31 (1, dd [2.0, 7.6 Hz]); 8.51 (1, dd [2.0, 5.6 Hz]); 8.82 (1, bs); 9.32 (1, bs); 11.27 (1, bs).

IR (KBr):750, 1110, 1310, 1440, 1460, 1580, 1588, 2230, 2790, 2980, and 3400 cm^{-1}.

Preparation of the cyclamate salt

The cyclamate salt may be prepared by treating the crude base synthesized above (2 g crude base) with cyclamic acid (1 g) in 50 mL methanol. The methanol solution was warmed, filtered and the filtrate concentrated *in vacuo* to give a residue which was crystallized in 10 mL acetonitrile. Recrystallization of the crude salt from methanol-acetonitrile gave 2.0 g of white solid, m.p. 172—174°.

Anal. Calcd. for $C_{21}H_{24}N_4O_2 \cdot C_6H_{13}NO_3S$: C, 59.65; H, 6.87; N, 12.89. Found: C, 59.74; H, 6.77; N, 12.82.

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Example 15

4-[2-Hydroxy-3-[[2-(1H-indol-3-yl)-1, 1-dimethylethyl]amino]propoxy]-3-pyridinecarbonitrile

Using the procedure of Example 14 and utilizing 3-[[2-(3-indolyl)-1,1-dimethylethyl]amino]-1,2-propanediol (10.4 g, 0.04 mole); sodium hydride (1.7 g, 0.04 mole), 550 mL toluene, 4-chloro-3-cyanopyridine (5.5 g, 0.04 mole), Cf: Wieland and Biener, *Chem. Berichte., 96*, pages 268—274 (1963)); 18-crown-6 ether (0.11 g) and anhydrous powdered K_2CO_3 (13.7 g, 0.1 mole), a gummy material (15 g) was obtained. The gum was chromatographed on a silica column eluting with methylene chloride (90 parts), methanol (10 parts) and ammonium hydroxide (1 part) to give 2 fractions. The second fraction to be eluted gave 6.8 g of gum which was crystallized in ethyl acetate to give 5 g of solid, m.p. 124—126°. Recrystallization of this material from ethyl acetate gave 4.2 g of white solid, m.p. 126—128°.

Anal. Calcd. for $C_{21}H_{24}N_4O_2$: C, 69.21; H, 6.64; N, 15.38. Found: C, 69.42; H, 6.75; N, 15.65.

NMR (DMSO-d_6): 1.00 (6, s); 1.55 (1, bs); 2.75 (4, m); 3.90 (1, m); 4.27 (2, m); 5.10 (1, bs); 7.25 (6, m); 8.64 (1, d [6.0 Hz]); 8.78 (1, s); 10.82 (1, bs).

IR (KBr): 745, 1010, 1190, 1290, 1315, 1455, 1495, 1520, 1590, 2225, 2970, and 3400 cm^{-1}.

Example 16

2-[2-Hydroxy-3-[[2-(1H-indol-3-yl)- 1,1-dimethylethyl]amino]propoxy]-3-pyridinecarboxamide

Using a procedure similar to that outlined in Example 4 above, 3-[[2-(3-indolyl)-1,1-dimethylethyl]amino]-1,2-propanediol (10.5 g, 0.04 mole), sodium hydride (1.7 g, 0.04 mole), 400 mL toluene, 2-chloronicotinamide (5.6 g, 0.04 mole), 18-crown-6 ether (0.11 g) and anhydrous powdered K_2CO_3 (13.8 g, 0.1 mole) were reacted to give 17 g of residual gum. The gum was chromatographed on a silica column eluting with methylene chloride (90 parts), methanol (10 parts) and ammonium hydroxide (1 part). The product-containing fractions were combined and concentrated to a residue which was crystallized in ethyl acetate to give 5.2 g of material, m.p. 68—72°. Recrystallization from ethyl acetate and drying in a vacuum oven afforded 4 g of white solid, m.p. 131—133°.

Anal. Calcd. for $C_{21}H_{26}N_4O_3$: C, 65.95; H, 6.86; N, 14.65. Found: C, 65.80; H, 6.85; N, 14.31.

NMR (DMSO-d_6): 1.03 (6, s); 2.77 (4, m); 3.95 (1, m); 4.46 (2, m); 7.20 (6, m); 7.81 (2, bs); 8.30 (2, d [6.1 Hz]); 10.85 (1, bs).

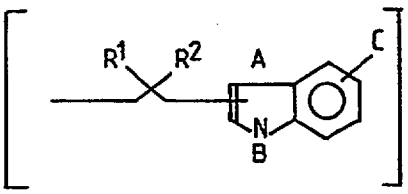
IR (KBr): 740, 780, 1100, 1235, 1430, 1460, 1585, 1670, 2970, 3330, and 3470 cm^{-1}.

Example 17

Conversion of methoxy products to hydroxy products—general procedure

Dissolve the methoxy product in methylene chloride and stir under a nitrogen atmosphere while keeping chilled with an ice bath. Add dropwise 3 equivalents of boron tribromide in methylene chloride solution. Following addition, remove the ice bath and allow the reaction mixture to stir at room temperature for 6—8 hrs. Again, chill the reaction mixture with an ice bath and decompose excess reagent by adding excess H_2O dropwise, causing a gummy mateial to precipitate. The supernatant is decanted from the gummy material which is rinsed with two portions of water. The gum is dissolved in hot water, treated with activated charcoal (Darco), filtered, the filtrate chilled and made basic with ammonium hydroxide to a pH of approximately 8. The resultant precipitate is filtered, washed with water, dried and further purified by column chromatography on silica gel, eluting with $CHCl_3$ (90 parts)—methanol (10 parts)—NH_4OH (1 part). Concentration of product-containing fractions gives a residue which is recrystallized from ethanol-water to give pure hydroxy product.

Starting with the appropriate pyridine and indolylalkylamine, additional examples of Formula I products may be synthesized using substantially the same procedures as outlined hereinabove. Some additional products of Formula I which may be synthesized are shown in Table 2. G in the formulae represents the



group as determined by the intermediate III selected (cf: examples 1—12).

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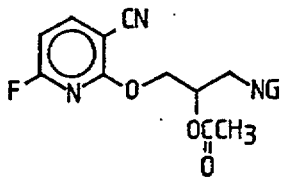
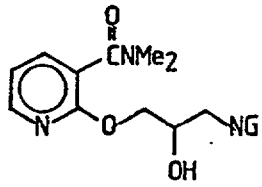
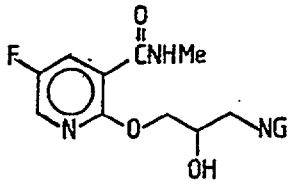
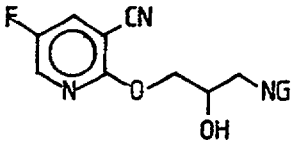
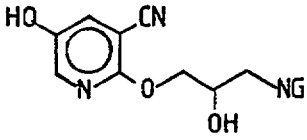
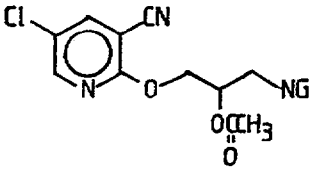
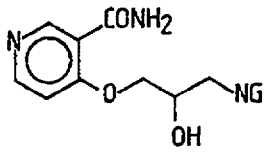
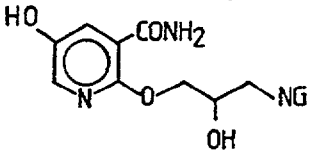
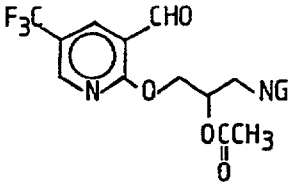
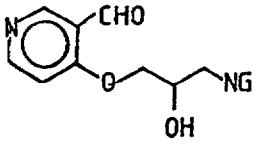
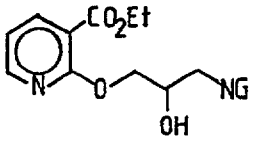
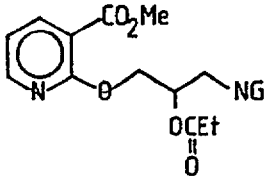
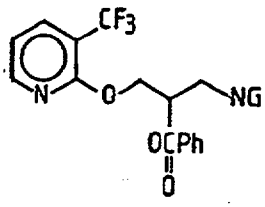
Table 2

Example	*Formula*	*Example*	*Formula*
18		25	
19		26	
20		27	
21		28	
22		29	
23		30	
24			

Biological evaluation

These biological tests were used to gauge the cardiovascular profile of a number of the compounds of Formula I as vasodilators with a range of *beta*-adrenergic blocking activity.

Example 31

The efficacy of antihypertensive agents other than adrenergic *beta*-receptor blocking agents is commonly estimated in the spontaneous hypertensive rat. Blood pressure values are determined for test animals prior to and 24 hours after oral doses of 50 mg/kg of test compounds; the observed percentage change in heart rate is noted as well. A fall in blood pressure in the range of 19—24 mmHg is considered "questionable". "Active" and "inactive" designations are decreases greater and less than that range.

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Example 32

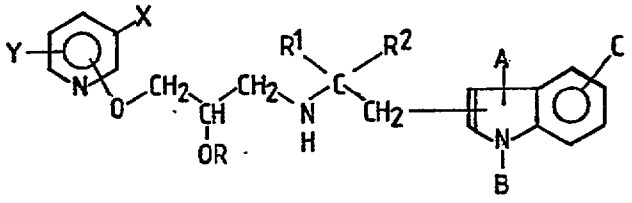
The angiotensin-maintained ganglion-blocked rat model is utilized as a screening test for estimation of the vasodilator component of activity. Percentage changes in blood pressure in anesthetized rats 30 minutes after intravenous dosing are determined. The intravenous dosing is done with test compound at 3 mg/kg. Borderline activity is defined as a 15—20% decrease in blood pressure measured 30 minutes after dosing. "Active" and "inactive" designations are increases greater and less than that range.

Example 33

Diastolic blood pressure and heart rate response to a fixed challenge dose of isoproterenol are obtained before and 15-minutes after graded doses of test compound administered intravenously over a 3-min interval to anesthetized dogs. A branch of a femoral artery and vein are cannulated to record blood pressure and to administer the drugs which are dissolved in saline. The vagi were sectioned bilaterally in the mid-cervical region of the neck and the dogs are ventilated mechanically (Harvard respirator) with room air at a rate of 20/minute and a stroke volume of 20 mL/kg. Heart rate is monitored with a cardiotachometer triggered by the pressure pulse. All measurements are recorded on a Beckman R-612 recorder. The drug effect is expressed in terms of a cumulative dose (microgram/kg) causing 50% inhibition of isoproterenol response.

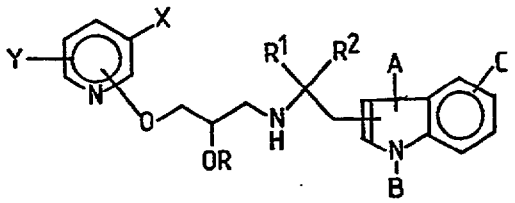
The following abbreviations used herein have the following meanings: Ph stands for a phenyl group, Pr stands for a propyl group, Me stands for methyl group, and Et stands for an ethyl group.

Additionally, an accepted convention in modern organic chemistry has been used throughout. For alkyl structures, in a shorthand form, joined line segments substitute for explicit notation of C and H groups. Thus, for example, formula I can also be written:



Claims

1. A compound having the formula



(I)

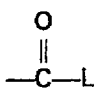
and the acid addition salts thereof, wherein

X is selected from the group consisting of —CHO, —CN, —CF_3, —$CONR^aR^b$, or —CO_2R^c with R^a and R^b being independently chosen from hydrogen or R^c and wherein R^c can be lower alkyl (C_1 to C_4), aryl, or aryl-lower alkyl,

Y represents a second substitutent on the pyridine ring and is hydrogen, halogen, lower (C_1 to C_4) alkoxy, aryl-lower alkoxy, hydroxy, or —C—O-alkyl wherein alkyl is C_1—C_6 alkyl;

the indolylalkylaminopropoxy side chain is coupled at the pyridine 2- or 4-position;

R is hydrogen or



with L being selected from C_1 to C_{10} alkyl, phenyl, or phenalkyl;

R^1, R^2, A and B are independently chosen from hydrogen at lower alkyl;

C represents a substituent in the benzo ring of indole and is selected from hydrogen, halogen, lower alkyl, lower alkoxy, or hydroxy; and

the indolyl system is attached by its 2- or 3-position.

2. A compound of claim 1 wherein the indolylalkylaminopropoxy side chain is coupled to the pyridine 2-position.

3. A compound of claim 1 wherein the indolyl ring is attached at its 3-position.

4. A compound of claim 2 or claim 3 wherein X is cyano or amido; Y is hydrogen; R is hydrogen; R^1 and R^2 are lower alkyl; A and B are hydrogen; and C is halogen, hydrogen, hydroxy, alkyl, or alkoxy.

5. A compound of claim 1, which is 2-[2-hydroxy-3-[[2-(1*H*-indol-3-yl)-1,1-

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dimethylethyl]amino]propoxy]-3-pyridinecarbonitrile or a pharmaceutically acceptable acid addition salt thereof.

6. The cyclamic acid addition salt of the compound of claim 5.

7. The HCl acid addition salt of the /compound of Claim 5.

8. A compound of claim 1, which is 4-[2-hydroxy-3-[[2-(1*H*-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]-3-pyridinecarbonitrile or a pharmaceutically acceptable acid addition salt thereof.

9. A compound of claim 1, which is 2-[2-hydroxy-3-[[2-(1*H*-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]-3-pyridinecarboxamide or a pharmaceutically acceptable acid addition salt thereof.

10. A method of exerting a vasodilating effect in a mammalian host, wherein said method comprises administering to a mammal having a condition in which therapeutic benefit is derived from vasodilation a non-toxic effective vasodilating dose of a compound as claimed in claim 1.

11. A method of treating hypertension, said method comprising administering to a mammalian host having hypertension a non-toxic antihypertensive effective dose of a compound claimed in claim 1.

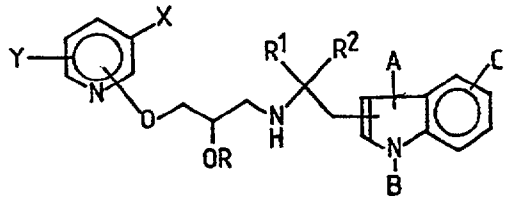
12. A pharmaceutical composition in dosage unit form suitable for systemic administration to a mammalian host, said composition comprising a pharmaceutical carrier and an amount of a Formula I compound according to claim 1 to provide an effective non-toxic dose of from 0.1 mcg to 100 mg/kg body weight of said host.

13. A pharmaceutical composition of claim 12 wherein the Formula I compound of 2-[2-hydroxy-3[[2-(1*H*-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]-3-pyridinecarbonitrile or a pharmaceutically acceptable acid addition salt thereof.

14. A pharmaceutical composition of claim 12 wherein the Formula I compound is 4-[2-hydroxy-3-[[2-(1*H*-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]-3-pyridinecarbonitrile or a pharmaceutically acceptable acid addition salt thereof.

15. A pharmaceutical composition of claim 12 wherein the Formula I compound is 2-[2-hydroxy-3-[[2-(1*H*-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]-3-pyridinecarboxamide or a pharmaceutically acceptable acid addition salt thereof.

16. A process for preparing a compound having the formula

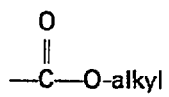


(I)

and the acid addition salts thereof, wherein

X is selected from the group consisting of —CHO, —CN, —CF_3, —$CONR^aR^b$, or —CO_2R^c, with R^a and R^b being independently chosen from hydrogen or R^c and wherein R^c can be lower alkyl (C_1 to C_4), aryl, or aryl-lower alkyl;

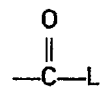
Y represents a second substitutent on the pyridine ring and is hydrogen, halogen, lower (C_1 to C_4) alkoxy, aryl-lower alkoxy, hydroxy, or



wherein alkyl is C_1—C_6 alkyl;

the indolylalkylaminopropoxy side chain is coupled at the pyridine 2- or 4-position;

R is hydrogen or



with L being selected from C_1 to C_{10} alkyl, phenyl, or phenalkyl;

R^1, R^2, A and B are independently chosen from hydrogen or lower alkyl;

C represents a substituent in the benzo ring of indols and is selected from hydrogen, halogen, lower alkyl, lower alkoxy, or hydroxy; and

the indolyl system is attached by its 2- or 3-position, said process comprising:

(a) coupling a Z-substituted pyridine of formula IV

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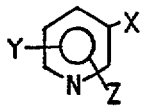
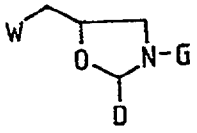
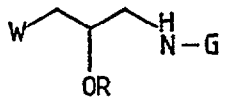


(IV)

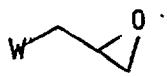
halogen, with a W-substituted propanol or incipient propanol intermediate II selected from the group consisting of IIA, IIB, and IIC:



IIA

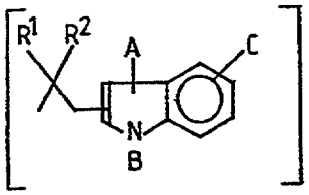


IIB



IIC

wherein D is hydrogen or phenyl and preferably phenyl; wherein G is the radical



wherein R^1, R^2, A, B, and C are as defined above; wherein W is halogen and preferably cloride when Z is hydroxyl and wherein W is hydroxyl when Z is halogen; and

(b) i) when compound IIA is reacted with compound IV, then converting the product thereof by hydrolysis under acidic conditions to said compound I;

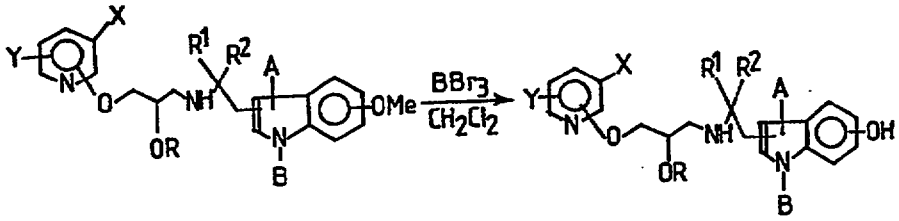
ii) when compound IIC is reacted with compound IV, an epoxy ether is formed and including a further step of heating said epoxy ether either neat or in the presence of a reaction inert organic solvent with an amine of the formula H_2NG, wherein G is as defined above, so as to form said compound I.

17. A process according to Claim 16, wherein said compound IIB is used, wherein W is hydroxyl, wherein Z is halogen, and said coupling in step (a) comprises heating compound IV with compound IIB in the presence of a base, all in an inert organic liquid under mild conditions.

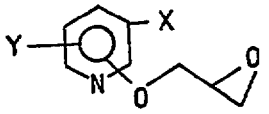
18. A process according to Claim 16, wherein said hydrolysis under acidic conditions employs dilute mineral acid of from 0.1N to 1N concentration and temperatures within the range from about 20—100°C and including also the step of recovering either (a) the product of Formula I as the free base of neutralization of the hydrolysis mixture and collecting the precipitate or (b) the acid addition salts thereof by evaporating the hydrolysis mixture or by reacting the free base with acid.

19. A process according to Claim 16, wherein said Y and/or C in said Formula I products are/is hydroxy, said process comprising the process according to Claim 16 wherein said compound IIB is used and including also the step of cleaving the corresponding methoxy precursor by the reaction as shown in Reaction 2:

Reaction 2



20. A compound having the formula:



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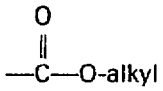
and the acid addition salts thereof, wherein

X is selected from the group consisting of —CHO, —CN, —CF_3, —$CONR^aR^b$, or —CO_2R^c, with R^a and R^b being independently chosen from hydrogen or R^c and wherein R^c can be lower alkyl (C_1 to C_4), aryl, or aryl-lower alkyl;

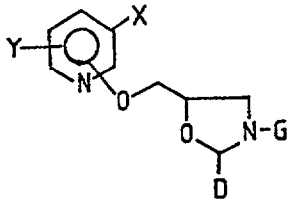
Y represents a second substituent on the pyridine ring and is hydrogen, halogen, lower (C_1 to C_4) alkoxy, aryl-lower alkoxy; hydroxy, or



wherein alkyl is C_1—C_6 alkyl; and

the indolylalkylaminopropoxy side chain is coupled at the pyridine 2- or 4-position.

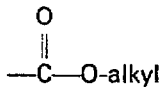
21. A compound having the formula:



and the acid addition salts thereof, wherein

X is selected from the group consisting of —CHO, —CN, —CF_3, —$CONR^aR^b$, or —CO_2R^c, with R^a and R^b being independently chosen from hydrogen or R^c and wherein R^c can be lower alkyl (C_1 to C_4), aryl, or aryl-lower alkyl;

Y represents a second substituent on the pyridine ring and is hydrogen, halogen, lower (C_1 to C_4) alkoxy, aryl-lower alkoxy, hydroxy, or

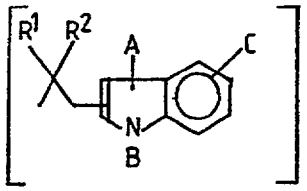


wherein alkyl is C_1—C_6 alkyl;

the indolylalkylaminopropoxy side chain is coupled at the pyridine 2- or 4-position:

D is hydrogen or phenyl and preferably is phenyl;

G is the radical



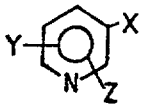
wherein R^1, R^2, A and B are independently chosen from hydrogen or lower alkyl;

C represents a substituent in the benzo ring of indol and is selected from hydrogen, halogen, lower alkyl, lower alkoxy, or hydroxy; and

the indolyl system is attached by its 2- or 3-position.

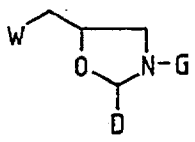
22. A process for preparing the compound of Claim 21, said process comprising:

coupling a Z-substituted pyridine of formula IV



(IV)

wherein X and Y are as defined in claim 21 and wherein Z is hydroxyl or halogen, with a W-substituted propanol or incipient propanol intermediate of formula IIA



IIA

wherein D is hydrogen or phenyl and preferably phenyl; wherein G is the radical

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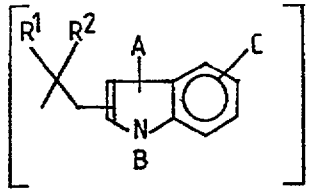
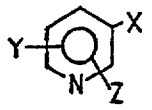


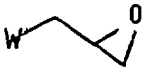
wherein R^1, R^2, A and B are independently chosen from hydrogen or lower alkyl;
C represents a substituent in the benzo ring of indole and is selected from hydrogen, halogen, lower alkyl, lower alkoxy, or hydroxy; and
wherein W is halogen and preferably chloride when Z is hydroxyl and wherein W is hydroxyl when Z is halogen.

23. A process for preparing the compound of claim 20, said process comprising:
coupling a Z-substituted pyridine of formula IV



(IV)

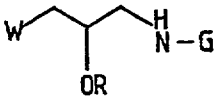
wherein X and Y are as defined in Claim 20 and wherein Z is hydroxyl or halogen, with a W-substituted propanol or incipient propanol intermediate of formula IIC



IIC

wherein W is halogen and preferably chloride when Z is hydroxyl and wherein W is hydroxyl when Z is halogen.

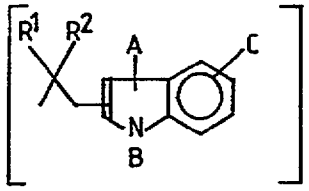
24. A compound having the formula IIB



IIB

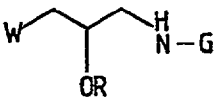
wherein W is a halogen or hydroxyl group; wherein R is hydrogen or

with L being selected from C_1—C_{10} alkyl, phenyl, substituted phenyl, or phenalkyl; and wherein G is the radical



with R^1, R^2, A, and B being independently chosen from hydrogen or lower alkyl and with C representing a substituent in the benzo ring of indole and being selected from hydrogen, halogen, lower alkyl, lower alkoxy, or hydroxy.

25. A process for preparing a compound having the formula IIB



wherein W is a halogen or hydroxyl group; wherein R is hydrogen or

with L being selected from C_1—C_{10} alkyl, phenyl, substituted phenyl, or phenalkyl; and wherein G is the radical

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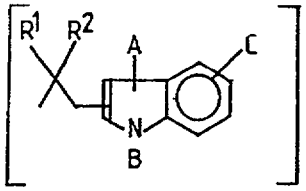
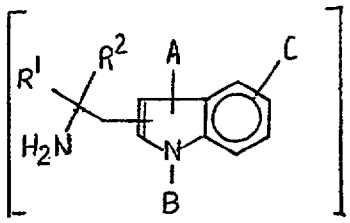


with R^1, R^2 A, and B being independently chosen from hydrogen or lower alkyl and with C representing a substituent in the benzo ring of indole and being selected from hydrogen, halogen, lower alkyl, lower alkoxy, or hydroxy; said process comprising:

reacting a compound of formula III



wherein A, B, R^1, R^2, and C are as defined above, with 3-chloro-1,2-propanediol in refluxing alcohol and a base which is preferably sodium carbonate.

26. A process as claimed in Claim 16, substantially as indicated in respect of any of Examples 14—16 and 18—30.

27. A compound of the formula "(I)" specified in Claim 16, prepared by a process as claimed in Claims 16, 17, 18, 19 or 26.

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