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Benzodioxinopyrroles

This invention relates to heterocyclic amino compounds. More specifically this invention relates to benzodioxinopyrrole derivatives, to processes for the preparation thereof, to pharmaceutical preparations containing them, and to their use in medicine.

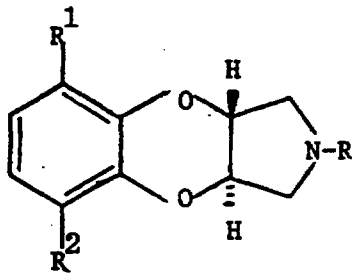
The alpha (α)-adrenoreceptors of the sympathetic nervous system are classified pharmacologically into two sub-groups, namely α_1 and α_2. The α_2- type are situated predominantly on the presynaptic terminals of noradrenergic neurones and are activated by the released neurotransmitter. Such activation results in a diminished release of noradrenaline on subsequent stimulation of the neurones, the α_2-adrenoreceptors thus forming part of an autoinhibitory feedback mechanism for regulating the synaptic concentration of the neurotransmitter. A selective α_2-adrenoreceptor antagonist would be expected to produce an increase in the synaptic concentrations of noradrenaline by blocking the autoinhibitory feedback mechanism and would thus be of potential value in human medicine for the treatment of disorders such as depression which are associated with a deficiency of noradrenaline at postsynaptic adrenoreceptors.

α_2-Adrenoreceptors also occur at non-neuronal sites such as on blood-platelets, in pancreatic islet cells, on adipocytes and in the proximal tubules of the kidney. Activation of α_2-adrenoreceptors at these sites leads to platelet aggregation, inhibition of insulin release, inhibition of lipolysis and retention of sodium respectively.

A selective α_2-adrenoreceptor antagonist thus has a potential therapeutic use as an antidepressant either alone or in a complimentary combination with an established antidepressant, and in either treating or preventing conditions such as migraine, thrombosis, diabetes, obesity, hypertension, constipation, paralytic ileus and senile dementia.

We have now found that the compounds of formula (I) below and their physiologically acceptable salts have a selective α_2-adrenoreceptor antagonist action.

The invention thus provides compounds of general formula (I)



(I)

wherein

R is a hydrogen atom or a group selected from C_{1-6} alkyl (optionally substituted by C_{3-7} cycloalkyl), C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl, aralkyl (in which the alkyl moiety contains 1-5 carbon atoms) and -CHO;

R^1 is a halogen atom or a group selected from C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, cyano, nitro and $-NR^3R^4$ where R^3 and R^4 is each a hydrogen atom or a C_{1-4} alkyl group; and

R^2 is a hydrogen atom, a halogen atom or is a group as defined above for R^1;

and the physiologically acceptable salts and hydrates thereof.

In general formula (I), the alkyl, alkenyl and alkynyl groups represented by R, R^1 and R^2 may be straight or branched chain groups.

When R contains a -C=C- or -C≡C- linkage this is not directly attached to the nitrogen atom. When R is alkyl it may be, for example, methyl, ethyl or propyl, methyl being preferred. When R is an alkyl group substituted by a C_{3-7} cycloalkyl group it may be, for example, cyclopropyl C_{1-3} alkyl such as cyclopropylmethyl. When R is alkenyl it may be, for example, allyl and when R is alkynyl it may be, for example, propynyl. When R is cycloalkyl it may be, for example, cyclopropyl. When R is an aralkyl group it may be, for example phenC_{1-5}alkyl, such as benzyl.

The halogen atoms represented by R^1 and R^2 may be fluorine, chlorine, bromine or iodine atoms. Examples of alkyl and alkoxy groups represented by R^1 and R^2 are methyl, ethyl, methoxy and ethoxy

groups. The group $-NR^3R^4$ may be, for example, an amino, methylamino, ethylamino, dimethylamino or diethylamino group.

Suitable physiologically acceptable salts are the acid addition salts formed with inorganic acids, for example hydrochlorides, hydrobromides, phosphates and sulphates, and with organic acids, for example citrates, tartrates, acetates, maleates and succinates. The hydrochlorides are particularly useful.

It will be appreciated that each compound of general formula (I) is a trans isomer and exists as two enantiomers. The structural formulae herein are to be understood to depict either enantiomer of each compound as well as mixtures of the enantiomers, including racemates, even though the precise structure as set out only relates to one enantiomer.

A preferred group of compounds of general formula (I) is that wherein R is a hydrogen atom. Another preferred group of compounds of general formula (I) is that wherein R is a C_{1-3} alkyl group, particularly a methyl or ethyl group.

In a further preferred group of compounds of formula (I) R^1 is a halogen atom or a C_{1-4} alkyl or C_{1-4} alkoxy group, in particular a chlorine or fluorine atom or a methyl or methoxy group.

A further preferred group of compounds of formula (I) is that in which R^2 is a hydrogen or fluorine atom, particularly a hydrogen atom.

Particularly important compounds of formula (I) are those in which R is a hydrogen atom or a methyl or ethyl group, particularly a hydrogen atom; R^1 is a chlorine or fluorine atom or a methyl or methoxy group, particularly a chlorine or fluorine atom and especially a fluorine atom; and R^2 is a hydrogen or fluorine atom, especially a hydrogen atom.

Important compounds are (±)-trans-2,3,3a,9a-tetrahydro-5-methyl-1H-[1,4]benzodioxino[2,3-c]pyrrole, and its 3aS- and 3aR-isomers; (±)-trans-5-chloro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]-pyrrole, and its 3aS- and 3aR-isomers; (±)-trans-5,8-difluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole and its 3aS- and 3aR-isomers; and their physiologically acceptable salts and hydrates, particularly the hydrochlorides.

Particularly important compounds, by virtue of their especially useful biological profiles, are (±)-trans-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole and its 3aS- and 3aR-isomers and their physiologically acceptable salts and hydrates, particularly the hydrochlorides.

The compounds of the invention have selective α_2-adrenoreceptor antagonist action. The test for determining the α_2-adrenoreceptor antagonist action is based on the ability to prevent the action of the selective α_2-adrenoreceptor agonist such as clonidine or 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine, [R-(R*R*)]-2,3-dihydroxybutanedioate (UK 14304-18) on the rat field stimulated vas deferens preparation.

Clonidine and UK 14304-18 inhibit the twitch response of the rat isolated vas deferens to low frequency motor nerve stimulation. This inhibition is a consequence of activation of presynaptic adrenoreceptors of the α_2- type. Antagonism of the effect of clonidine or UK 14304-18 is quantified by measuring the parallel shift to the right of the inhibitory α_2-adrenoreceptor agonist $\log_{10}$ (concentration)/response curve in the presence of increasing concentrations of the antagonist. Potency and competitiveness of antagonism are determined by the method of Arunlakshana & Schild (Br. J.Pharmac. 1959, 14 48-58).

The α-adrenoreceptor-type selectivity of the compounds of general formula (I) is similarly assessed by measuring the ability to produce a parallel shift to the right of the $\log_{10}$ (concentration)/response curve for the α_1-adrenoreceptor agonist phenylephrine. The α_1-adrenoreceptor-mediated responses of phenylephrine measured were contractions of the rat isolated anococcygeus muscle (Leighton, Butz & Parameter, Eur.J.Pharmac., 1979, 58 27-38).

The compounds of the invention are thus of interest in the treatment or prevention of migraine, thrombosis, diabetes, obesity, hypertension, constipation, paralytic ileus and senile dementia, and in particular for the treatment of depression.

According to a further aspect, the invention provides compounds of general formula (I) and their physiologically acceptable salts for use in the therapy or prophylaxis of migraine, thrombosis, diabetes, obesity, hypertension, constipation, paralytic ileus and senile

dementia and in particular depression. The compounds of the invention may be used either alone or with an additional active ingredient. Thus, for example, in the treatment of depression, the compound of the invention may be used alone, or may be co-administered with an established antidepressant (e.g. desmethylimipramine, imipramine or amitriptyline) either in a single formulation or in separate formulations. The established antidepressant can be used in accordance with conventional practice.

The compounds according to the invention may be formulated in a conventional manner, optionally together with one or more other active ingredients, for administration by any convenient route for example for oral, rectal, intravenous or intramuscular administration. Oral administration is preferred.

Thus according to another aspect, the invention provides a pharmaceutical composition comprising a compound of general formula (I) and/or a physiologically acceptable salt thereof together with a physiologically acceptable carrier or excipient. The composition may optionally contain an additional active ingredient, for example an antidepressant such as desmethylimipramine, imipramine or amitriptyline.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, syrups or suspensions prepared by conventional means with physiologically acceptable excipients.

Compositions for rectal administration may be in the form of suppositories using a conventional suppository excipient.

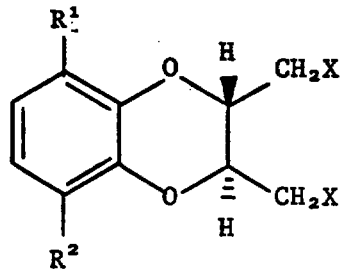
The compounds may be formulated for intravenous or intramuscular administration in dry form for reconstitution before use, or as a sterile solution or suspension.

A proposed daily dose for administration to man is 0.01 to 10mg/kg, for example 0.05 to 3mg/kg, which may be conveniently administered in 1 to 3 doses per day. The precise dose administered will of course depend on the age and condition of the patient. The daily dosage may conveniently be administered in the form of dosage units, each unit containing for example 0.01 to 3 mg/kg of active ingredient.

The compounds according to the invention may be prepared by a number of processes. In the following description the groups R, R^1 and R^2 are as previously defined for general formula (I) except where otherwise indicated.

It will be appreciated that certain of the reactions described below are capable of affecting other groups in the starting material (e.g. nitro, cyano) which are desired in the end product; care must therefore be taken in accordance with conventional practice, either to use reaction conditions under which such groups remain substantially inert, or to perform the reaction as part of a sequence which avoids its use when such groups are present in the starting material.

According to a first example (A), a compound of general formula (I) may be prepared by amination of a compound of general formula (II).



(II)

[where X is a leaving group such as a halogen atom, (e.g. chlorine, bromine or iodine), or a hydrocarbylsulphonyloxy group (e.g. methylsulphonyloxy)] with ammonia, aqueous ammonia or an amine of formula RNH_2 where R is as previously defined except that R is not a hydrogen atom or the group -CHO.

In a particular embodiment of this process, following the amination reaction, the resulting compound of general formula (I) or a salt thereof, may be converted into another compound of general formula (I). Thus, for example, when R is arylmethyl, the amination reaction may optionally be followed by removal of the arylmethyl group to yield a compound of formula (I) where R is a hydrogen atom.

The amination reaction is conveniently effected at an elevated temperature e.g. under reflux or in a sealed tube at e.g. 110°C, preferably in the presence of a suitable base e.g. sodium hydride or an alkali metal hydroxide such as sodium hydroxide, or in the presence of an excess of the amine RNH_2 optionally in the presence of a solvent

(13)

such as a chlorinated hydrocarbon e.g. chloroform or an ether e.g. dioxan, or an alcohol eg ethanol. Optional removal of an arylmethyl group may be carried out, for example, by hydrogenolysis or, where appropriate, under acidic conditions, as described below.

According to another example (B), a compound of general formula (I) where R represents a hydrogen atom may be prepared by deprotection of a corresponding compound where R represents a protecting group. Suitable protecting groups include, for example, arylmethyl and acyl groups. Conventional deprotection procedures may be used. For example, where appropriate an arylmethyl group (e.g. benzyl) may be removed by hydrogenolysis using, for example, hydrogen in the presence of a catalyst, such as platinum or palladium on a support (e.g. charcoal), in a solvent such as an alcohol e.g. methanol. Alternatively, where appropriate, an arylmethyl group (e.g. trityl or bis (4-methoxyphenyl) methyl) may be removed under acidic conditions, using for example an acid such as trifluoroacetic acid, formic acid, hydrochloric acid or hydrobromic acid. Acyl groups may be removed by hydrolysis using an acid such as a mineral acid or a base such as an alkali metal hydroxide as appropriate. The protected starting materials for this process may be prepared using standard methods for the protection of amines, for example as described by McOmie (see below).

According to a further example (C), a compound of general formula (I) where R represents an alkyl group may be prepared by reduction of the corresponding compound in which R is an acyl group using a reducing agent such as lithium aluminium hydride or diborane in a suitable solvent such as ether or tetrahydrofuran at an elevated temperature e.g. reflux. Suitable acyl groups are, for example, formyl, acetyl, or carbonyloxyalkyl e.g. carbonyloxymethyl. The intermediate starting materials for this reaction may be prepared by acylation using conventional methods, for example by reaction of the compound of formula (I) in which R represents a hydrogen atom, with an acid chloride, acid anhydride, or ester.

Compounds of formula (I) in which R_1 and/or R_2 is cyano may be prepared by heating the corresponding carboxamide with a dehydrating agent such as phosphorus pentoxide (P_2O_5). The carboxamide may be

prepared by methods analogous to those described herein for the preparation of a compound of formula (I).

The product of any of the processes (A), (B) and (C) described above may be subjected to one or two further reactions comprising:

(D)(i) converting the resulting compound of general formula (I) or a salt thereof into another compound of general formula (I); and/or

(D)(ii) converting a compound of general formula (I) or a salt thereof into a physiologically acceptable salt thereof.

Thus, it is also possible to prepare a compound of general formula (I) by a process comprising interconversion of another compound of general formula (I).

For example, a compound of general formula (I) in which R is a hydrogen atom may be converted by alkylation to a compound of general formula (I) in which R is an alkyl, substituted alkyl, alkenyl, alkynyl or aralkyl group. Conventional alkylation procedures may be used, for example reductive alkylation using an appropriate aldehyde with a complex metal hydride such as sodium or potassium borohydride or sodium cyanoborohydride in a suitable solvent such as an alcohol e.g. methanol. Methylation may be achieved using a formic acid/formaldehyde reagent system. Alternatively, the alkylation may be performed with an alkylating agent RX (where R is an alkyl, substituted alkyl, alkenyl, alkynyl or aralkyl group and X is a leaving group such as a halogen atom e.g. chlorine or bromine, or a hydrocarbylsulphonyloxy group e.g. p-toluenesulphonyloxy) preferably in the presence of a base, such as potassium carbonate, optionally in a solvent such as an alcohol, e.g. ethanol.

Another example of this embodiment is the preparation of a compound of general formula (I) where R is a group -CHO, which may be prepared by formylation of a corresponding compound of formula (I) in which R is a hydrogen atom using an appropriate formylating agent such as a formyl ester, e.g. an alkyl formate such as methyl formate.

In a further example, a compound of formula (I) in which R^1 and/or R^2 is an amino group may be prepared by reduction of a corresponding compound of formula (I) in which R^1 and/or R^2 is a nitro group. Suitable reducing agents include lithium aluminium hydride, in

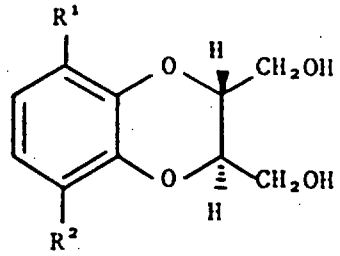
a solvent such as ether or tetrahydrofuran at elevated temperature, or hydrogen in the presence of a catalyst such as platinum or palladium on a support (e.g. charcoal) in a solvent such as an alcohol e.g. methanol.

In yet another example, a compound of formula (I) in which R^1 and/or R^2 is hydroxyl may be prepared by O-dealkylation of a corresponding compound of formula (I) in which R^1 and/or R^2 is an alkoxy group. For example, O-demethylation may be effected using an appropriate thiol e.g. methyl, ethyl or propyl mercaptan in the presence of a strong alkali metal base such as sodium hydride. The reaction is conveniently carried out in a refluxing solvent (e.g. dimethylacetamide, dimethylsulphoxide or dimethylformamide). Alternatively, the O-dealkylation reaction may be carried out using a Lewis acid such as boron tribromide or boron trichloride in a halohydrocarbon solvent (e.g. dichloromethane) or using pyridinium hydrochloride or hydrobromide as a melt, or aqueous hydrogen bromide.

Physiologically acceptable salts of the compounds of general formula (I) may be prepared by reacting the free base of formula (I) or a salt thereof with an appropriate acid, such as hydrogen chloride in the presence of a suitable solvent e.g. ethyl acetate, ether or CH_2Cl_2 or hydrochloric acid in a solvent such as methanol, to obtain the desired physiologically acceptable salt.

It may be desirable to protect various reactive substituents in the starting materials for a particular reaction or sequence of reactions and subsequently to remove the protecting group after completion of the reaction or sequence. Such protection and subsequent deprotection may be particularly pertinent when R_1 and/or when R_2 is a hydroxy or amino substituent. Conventional protection and deprotection procedures can be employed cf. "Protective Groups in Organic Chemistry" Ed. by J F W McOmie (Plenum Press, 1973). Thus, for example, a primary amine may be protected by formation of a phthalimide group which may subsequently be cleaved by treatment with a hydrazine, e.g. hydrazine hydrate or a primary amine, for example methylamine, and a phenolic hydroxyl group may be protected as an ether e.g. a 2-tetrahydropyranyl or methyl ether, which may subsequently be cleaved by a Lewis acid such as boron tribromide or aqueous hydrogen bromide.

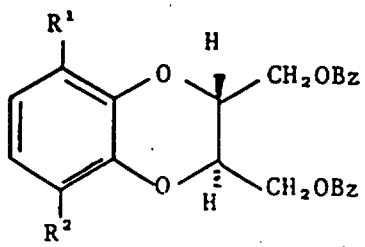
The intermediate compounds of general formula (II) may be prepared by reaction of a corresponding diol of formula (III)



(III)

with a halide of formula X_1A (where X_1 is a hydrocarbylsulphonyl group e.g. methylsulphonyl and A is a halogen atom e.g. a chlorine atom) in the presence of a base e.g. triethylamine in a solvent such as dichloromethane; or with a halogenating agent such as thionyl chloride, phosphorous tribromide or hydrogen iodide.

Diols of formula (III) are described and claimed in co-pending Divisonal Application No. 8802949 and may be prepared by reduction of a corresponding dibenzyl ether of formula (IV):

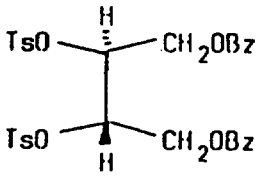


(IV)

(where Bz represents benzyl) using hydrogen and palladium on charcoal with a solvent e.g. ethanol.

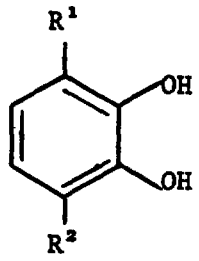
Alternatively, an ether of formula (IV) may be treated with a Lewis acid, such as aluminium chloride, in a solvent such as toluene to yield a diol of formula (III).

A compound of formula (IV) may be prepared by heating the bis-tosylate (V):



(V)

(where Ts represents CH_3-C$_6$H$_4$-SO_2-) with a catechol of formula (VI)

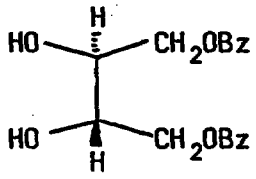


(VI)

in acetonitrile or dimethylformamide containing cesium fluoride or cesium carbonate.

The intermediates of formula (VI) are known compounds and may be prepared by standard methods of benzene ring substitution (cf. for example Barton, Linnell & Senior, Quat.J.Pharmacy & Pharmac., 1945, 18, 41-47 and Ladd & Weinstock, J.Org.Chem. 1981, 46, 203-206).

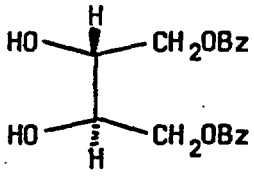
The bis-tosylate of formula (V) may be prepared by reaction of the known dibenzyl threitol of formula (VII)



(VII)

with 4-toluenesulphonyl chloride in pyridine.

To obtain a specific enantiomer of formula (I), a diol of formula (III) having the required chirality should be used in the above processes. The enantiomeric diol starting material can be prepared from the appropriate dibenzyl threitol of formula (VII) or (VIII)



(VIII)

as described above.

A specific enantiomer of general formula (I) may also be prepared by resolution of a mixture of enantiomers of formula (I) by conventional methods, e.g. by salt formation with an optically active acid followed by separation of the resulting diastereoisomeric salts,

e.g. by fractional crystallisation. Alternatively, resolution may be effected at any suitable intermediate stage.

The following examples illustrate the invention. All temperatures are in ^{0}C. In the following, ER represents ether, IMS represents industrial methylated spirits, MeOH represents methanol, EtOH represents ethanol and "light petroleum" refers to the fraction boiling at 60-80^0. "Dried" refers to drying over magnesium sulphate unless otherwise stated.

Intermediate 1

(±)-(trans)-5-Fluoro-2,3-dihydro-2,3-bis[(phenylmethoxy)methyl]-1,4-benzodioxin

A mixture of 3-fluorobenzene-1,2-diol (5.12g) and (R*,R*)-(±)-1,4-bis(phenylmethoxy)-2,3-butanediol, bis(4-methylbenzenesulphonate) (24.4g) was stirred with dimethylformamide (D.M.F.) (160ml) under a nitrogen stream for 45 min. Anhydrous cesium carbonate (13.0g) was added and the mixture was heated to 150^0 under reflux for 18 hours. The dark brown mixture was cooled to 30^0 and diluted with di-isopropyl ether (370ml) and water (320ml). The layers were separated and the aqueous layer was re-extracted with di-isopropyl ether (150ml then 100ml). The extracts were sequentially washed with M hydrochloric acid (300ml), 30% aqueous sodium chloride (100ml) and were combined and evaporated *in vacuo* to a dark brown oil (12.6g) which was dissolved in light petroleum-dichloromethane (3:1) (40ml) and chromatographed over Sorbsil (Trade Mark) (126g) using light petroleum-dichloromethane mixtures of gradually increasing polarity. Combination of appropriate fractions and evaporation of the solvents gave the title compound as a yellow oil (7.0g), NMR τ ($CDCl_3$) 2.6-2.8 (10H, m, Ph), 3.18-3.38 (3H, m, 6-H, 7-H, 8-H), 5.32-5.58 (4H, m, CH_2 Ph), 5.64 (2H, m, 2-H, 3-H), 6.06-6.32 (4H, m, CH_2O).

Intermediates 2-8 (shown in Table 1) were prepared in a similar manner from the appropriate catechol and (R*,R*)-(±)-1,4-bis(phenylmethoxy)-2,3-butanediol, bis(4-methylbenzenesulphonate).

TABLE 1

R^1	R^2	Reaction Solvent	NMR τ ($CDCl_3$)						
			Ph	Ph $\underline{CH_2}$	OCH_2	2-H,3-H	Aromatic	Me	OMe
CH_3 (2)	H	CH_3CN	2.68	5.41	6.21	5.6-5.8	3.29	7.78	-
CH_3O (3)	H	CH_3CN	2.7	5.2-5.8	5.8-6.5	5.2-5.8	3.0-3.6	-	6.13
Cl (4)	H	CH_3CN	2.66	5.3-5.55	6.0-6.3	5.55-5.7	3.0-3.3	-	-
NO_2 (5)	H	D.M.F.	2.6-2.8	5.3-5.54	6.05-6.27	5.6	2.51,2.85 3.12	-	-
CH_3 (6)	CH_3	CH_3CN	2.6-2.8	5.38-5.44	6.1-6.3	5.67	3.39	7.82	-
Cl (7)	Cl	CH_3CN	2.73	5.43	6.18	5.6	3.17	-	-
F (8)	F	D.M.F.	2.5-2.8	5.37,5.48	6.1,6.2	5.58	3.39	-	-

Intermediate 9

(±)-(trans)-5-Chloro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol

A solution of (trans)-(±)-5-chloro-2,3-bis[(phenylmethoxy)methyl]-2,3-dihydro-1,4-benzodioxin (2.2g) in trifluoroacetic acid (T.F.A.) (50mls) was hydrogenated over 10% palladium on carbon (0.22g). The solid was filtered off, washed with chloroform and the solution was evaporated to dryness to give the diol as a colourless liquid 1.2g, NMR τ ($CDCl_3$) 2.9-3.3 (3H, m, aromatic), 7.72 (2H, s, OH), 5.7-6.2 (6H, m, 2-H, 3-H, CH_2O).

Intermediate 11-15 (shown in Table 2) were prepared in a similar manner

Intermediate 11 from Intermediate 2
Intermediate 12 from Intermediate 3
Intermediate 13 from Intermediate 6
Intermediate 14 from Intermediate 7
Intermediate 15 from Intermediate 8

Intermediate 10

(±)-(trans)-5-Fluoro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol

Intermediate 1 (7.0g) was dissolved in a mixture of toluene (70ml) and anisole (7.8ml) and the solution was stirred and cooled to -5^0 under a gentle stream of nitrogen. Anhydrous aluminium chloride (2.4g) was added and the temperature was maintained at $0-5^0$ for 20 min. More anhydrous aluminium chloride (2.4g) was added and after 20 min. at $0-5^0$ the mixture was allowed to warm to 20^0 with continued stirring. After 20 min. at 20^0, it was cooled back to 0^0, water (25ml) was added and after 5 min. stirring at 20^0, the mixture was diluted with ethyl acetate (75ml) and the layers were separated. The aqueous (lower) layer was re-extracted with ethyl acetate (2x50ml) and the organic solutions were washed with 30% aqueous sodium chloride (25ml) and were combined and concentrated in vacuo to 36g, giving a thick slurry of slightly purple crystals. After 30 min. at 20^0, the crystals were harvested, washed with toluene (10ml), light petroleum (20ml) and di-isopropyl ether (20ml) and dried to give the title compound (2.93g) m.p. $122-124^0$. Concentration of the mother liquor gave a crude second crop of title compound (0.32g) which after chromatographic

purification afforded a further quantity of pure title compound (0.24g) m.p. 121-123°. NMR τ (DMSO-d_6) 3.1-3.3 (3H, m, aromatic), 4.85-5.0 (2H, m, OH)- 5.8-5.9 (2H, m, 2-H,3H) 6.1-6.4 (4H, m, $\underline{CH_2}O$).

Intermediate 16 (shown in table 2) was prepared in a similar manner from intermediate 5.

TABLE 2

R^1	R^2	Reaction Solvent	NMR (τ)						M.pt
			Solvent	Aromatic	CH_2OH	2-H,3-H	OH	Me	
CH_3 (11)	H	EtOH	$CDCl_3$	3.3	5.8-6.1	5.8-6.1	7.59	7.8	-
CH_3O (12)	H	EtOH	compound unstable, used without characterisation						
CH_3 (13)	CH_3	MeOH	DMSO-d_6	3.42	6.3	5.9	5.04	7.89	77-9°
Cl (14)	Cl	TFA	DMSO-d_6	3.02	6.0-6.4	5.75	4.8-5.5	-	172-5°
F (15)	F	EtOH	DMSO-d_6	3.2	6.08-6.32	5.8	4.89	-	128-130°
NO_2 (16)	H	Toluene	used without characterisation						

Intermediate 17

(±)-(trans)-5-Fluoro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol, bis methanesulphonate

A solution of Intermediate 10 (3.10g) in dichloromethane (30ml) and triethylamine (6.4ml) was stirred for 10 min, with ice-bath cooling. A solution of methanesulphonyl chloride (3.2ml) in dichloromethane (10ml) was added during 10 min. and the resultant suspension was stirred for 30 min. Water (25ml) was added and the mixture was stirred for 20 min, the layers were then separated and the aqueous layer was re-extracted with dichloromethane (25ml). The organic solutions were washed with water (25ml), and were combined and evaporated to an oil which was chromatographed over Sorbsil (Trade Mark) (40g), eluting with 9:1 dichloro methane-ethyl acetate. Appropriate fractions were combined and evapor ted to a pale yellow oil (5.9g) which crystallised slowly from ethyl acetate - di-isopropyl ether to afford the title compound as prisms (4.15g) m.p. 65.5-67.5°. NMR τ ($CDCl_3$) 3.1-3.35 (3H, m, aromatic), 5.3-5.5 (4H, m, CH_2O) 5.5-5.65 (2H, m, 2-H,3-H) 6.89, 6.91 (6H, singlets, CH_3SO_3).

Intermediates 18-24 (shown in Table 3) were prepared in a similar manner

Intermediate 18 from Intermediate 11
Intermediate 19 from Intermediate 12
Intermediate 20 from Intermediate 9
Intermediate 21 from Intermediate 16
Intermediate 22 from Intermediate 13
Intermediate 23 from Intermediate 14
Intermediate 24 from Intermediate 15

TABLE 3

R^1	R^2	NMR τ							M.pt
		Solvent	Aromatic	CH_2O	2-H,3-H	$MeSO_3$	Me	OMe	
CH_3 (18)	H	DMSO-d_6	3.19	5.2-5.7	5.2-5.7	6.69	7.8	-	-
CH_3O (19)	H	$CDCl_3$	3.0-3.6	5.3-5.7	5.3-5.7	6.82	-	6.1	-
Cl (20)	H	$CDCl_3$	2.92-3.2	5.3-5.5	5.5-5.7	6.87,6.91	-	-	-
NO_2 (21)	H	DMSO-d_6	2.35, 2.58, 2.87	5.1-5.6	5.1-5.6	6.7	-	-	140-1°
CH_3 (22)	CH_3	$CDCl_3$	3.34	5.46	5.6	6.93	7.85	-	121-3°
Cl (23)	Cl	$CDCl_3$ + DMSO-d_6	3.1	5.3-5.5	5.3-5.5	6.81	-	-	142-4°
F (24)	F	$CDCl_3$	3.33	5.38	5.54	6.89	-	-	106-7°

Example 1

(±)-(trans)-5-Fluoro-2,3,3a,9a-tetrahydro-2-(phenylmethyl)-1H-[1,4]benzodioxino[2,3-c]pyrrole

A homogenised mixture of phenylmethanamine (8ml) and Intermediate 17 (5.3g) was heated to 130° for 15 min. then cooled to 25°. The partly crystalline mixture was partitioned between di-isopropyl ether (80ml) and water (80ml). The aqueous layer was re-extracted with di-isopropyl ether (100ml) and the organic solutions were sequentially washed with 2.5% aqueous acetic acid (2x50ml) and 15% aqueous sodium chloride (100ml) containing sodium hydrogen carbonate (5g). They were then combined and evaporated in vacuo to an orange-brown oil (3.8g) which crystallised spontaneously. This was recrystallised from di-isopropyl ether - light petroleum (1:1) to give pink crystals of the title compound as two crops; (1) 1.5g m.p. 79-81° and (2) 1.4g m.p. 79.5-81°. Chromatography of the mother liquor gave a third crop (0.6g). A recrystallised sample, m.p. 80-81° had the following analysis:

Found: C,71.7; H,5.65; N,4.95; F,6.8

$C_{17}H_{16}FNO_2$ requires: C,71.6; H,5.65; N,4.9; F,6.65%

NMR τ ($CDCl_3$) 2.6-2.8 (5H, broad singlet, Ph), 3.1-3.35 (3H, m, aromatics), 5.6-5.8 (2H, m, 3a-H, 9a-H), 6.09 and 6.19 (2H, ABq, Ph CH_2), 6.65-6.85 and 6.9-7.1 (4H, multiplets, 1-H_2, 3-H_2).

The compounds of Examples 2-7 were prepared in a similar manner to the compound of Example 1.

Example 2 from Intermediate 18

Example 3 from Intermediate 19

Example 4 from Intermediate 20

Example 5 from Intermediate 22

Example 6 from Intermediate 23

Example 7 from Intermediate 24

TABLE 4

R^1	R^2	Salt or free base	NMR τ									M.pt
			Solvent	Aromatic	Ph	Ph $\underline{CH_2}$	3a-H, 9a-H	1-H_2, 3-H_2	NH^+	Me	OMe	
CH_3 (2)	H	HCl	TFA	3.17	2.47	5.34	5.2-6.7	5.2-6.7	0.75	7.79	-	-
CH_3O (3)	H	HCl	TFA	2.7-3.4	2.43	5.31	5.2-5.7	5.7-6.7	0.75	-	6.0	-
Cl (4)	H	HCl	TFA	2.8-3.2	2.3-2.6	5.2,5.5	5.4-6.1 6.3-6.5	5.4-6.1 6.3-6.5	-	-	-	215-222°
CH_3 (5)	CH_3	Free base	$CDCl_3$	3.36	2.6-2.8	6.07, 6.19	5.78	6.73, 7.02	-	7.83	-	83°
Cl (6)	Cl	HCl	TFA	2.94	2.39	5.0-6.6			-	-	-	25 257°
F (7)	F	Free base	$CDCl_3$	3.34	2.5-2.8	6.07, 6.17	5.67	6.69, 6.96	-	-	-	86°

Example 8

(±)-(trans)-5-Fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride

A solution of the compound of Example 1 (2.3g) in IMS (110ml) was stirred under hydrogen at ca. 25° with 5% palladium on charcoal (1.15g) until uptake ceased (270ml). The catalyst was filtered off using a kieselguhr pad, the filter was washed through with IMS (3x20ml) and the combined filtrates were evaporated in vacuo to a pale pink oil (1.6g). This was re-dissolved in IMS (10ml) and 10M hydrochloric acid (1ml) was added. After 30 min. at 20°, the resultant white crystals were harvested, washed with IMS (3ml), 1:1 IMS -di-isopropyl ether (4ml) and di-isopropyl ether (2x5ml) to afford the title compound as a hemihydrate, (1.09g) m.p. ca. 245° (sublimes above 210°) NMR τ (DMSO-d_6) -0.25 (2H, broad s, NH_2^+), 2.9-3.2 (3H, m, 6-H, 7-H and 8-H), 5.4-5.65 (2H, m, 3a-H, 9a-H), 6.0-6.3, 6.6-6.8 (4H, ABq, 1-H_2, 3-H_2).

The compounds of Examples 9-14 were prepared in a similar manner to the compound of Example 8 from the compounds of Examples 2-7.

of the dye, a solution of the hydroxybenzoates and lastly the flavour. Adjust almost to volume with water and stir. Check the pH and adjust to 4.5 with citric acid if necessary. Make up to volume with water.

3. Oral Tablet

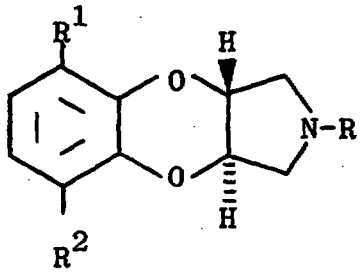
	per tablet
Active Ingredient	50 mg
Polyvinylpyrrolidone	4.0 mg
Sodium starch glycollate	10.0 mg
Magnesium stearate	2.0 mg
Lactose to tablet core weight to	200 mg

Blend the active ingredient with the lactose. Add a sufficient quantity of polyvinylpyrrolidone solution to produce a damp mass suitable for granulation. Prepare the granules and dry using a tray or fluid bed dryer. Pass through a sieve, blend with the remaining ingredients and compress into 8mm diameter tablets on a tablet machine.

Film coat the tablet cores with hydroxypropyl methyl cellulose or similar film forming material, using either an aqueous or non-aqueous solvent system. A plasticizer and suitable colour may be included in the film coating solution.

CLAIMS:

1. A compound of general formula (I):



(I)

wherein

R is a hydrogen atom or a group selected from C_{1-6} alkyl (optionally substituted by C_{3-7} cycloalkyl), C_{3-6} alkenyl and C_{3-6} alkynyl (wherein the -C=C- or -C≡C- linkage is not directly attached to the N-atom), C_{3-7} cycloalkyl, aralkyl (in which the alkyl moiety contains 1-5 carbon atoms) and -CHO;

R^1 is a halogen atom or a group selected from C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, cyano, nitro and $-NR^3R^4$ where R^3 and R^4 is each a hydrogen atom or a C_{1-4} alkyl group; and

R^2 is a hydrogen atom, a halogen atom or is a group as defined above for R^1;

and the physiologically acceptable salts and hydrates thereof.

2. A compound according to claim 1, wherein, in the general formula (I), R is a hydrogen atom.

3. A compound according to claim 1, wherein, in the general formula (I), R is a C_{1-3} alkyl group.

4. A compound according to claim 1, wherein, in the general formula (I), R^1 is a halogen atom or a C_{1-4} alkyl or C_{1-4} alkoxy group.

5. A compound according to claim 1, wherein, in the general formula (I), R^2 is a hydrogen or fluorine atom.

6. A compound according to claim 1, wherein, in the general formula (I), R is a hydrogen atom or a methyl or

ethyl group; R^1 is a chlorine or fluorine atom or a methyl or methoxy group; and R^2 is a hydrogen or fluorine atom.

7. A compound selected from (±)-trans-2,3,3a,9a-tetrahydro-5-methyl-1H-[1,4]benzodioxino[2,3-c]pyrrole, and its 3aS- and 3aR-isomers; (±)-trans-5-chloro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]-pyrrole, and its 3aS- and 3aR-isomers; (±)-trans-5,8-difluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole and its 3aS- and 3aR-isomers; and their physiologically acceptable salts.

8. A compound selected from (±)-trans-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole and its 3aS- and 3aR-isomers and their physiologically acceptable salts.

9. (±)-trans-5-Fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride and its 3aS- and 3aR-isomers.

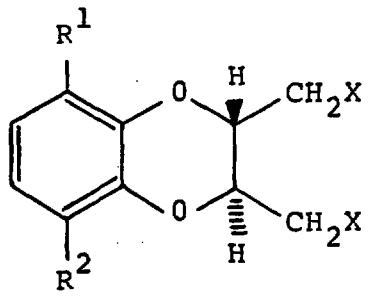
10. A pharmaceutical composition comprising a compound of general formula (I) and/or a physiologically acceptable salt thereof according to any of claims 1 to 9, together with a physiologically acceptable carrier or excipient.

11. A pharmaceutical composition according to claim 10 which also comprises an established antidepressant.

12. A compound of general formula (I) or a physiologically acceptable salt thereof according to any of claims 1 to 9, for use in the therapy or prophylaxis of depression, migraine, thrombosis, diabetes, obesity, hypertension, constipation, paralytic ileus or senile dementia.

13. A process for the preparation of a compound of general formula (I) as defined in claim 1 or a physiologically acceptable salt thereof which comprises:

(A) aminating a compound of general formula (II):



(II)

where R^1 and R^2 are as defined for general formula (I) and X is a leaving group

with ammonia, aqueous ammonia or an amine of formula RNH_2 where R is as defined for general formula (I) except that R is not a hydrogen atom or the group -CHO; or

(B) in order to prepare a compound of general formula (I) where R represents a hydrogen atom, deprotecting a corresponding compound where R represents a protecting group; or

(C) in order to prepare a compound of general formula (I) where R represents an alkyl group, reducing the corresponding compound where R represents an acyl group; and,if desired, subjecting the compound thus obtained to one or two further reactions comprising:

(D) (i) converting the resulting compound of general formula (I) or a salt thereof into another compound of general formula (I) and/or

(D) (ii) converting a compound of general formula (I) or a salt thereof into a physiologically acceptable salt thereof.