

AUSTRALIA
Patents Act 1990

PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

I/We, being the person(s) identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow.

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Address: 1 RUE CARLE HEBERT, 92415 COURBEVOIE CEDEX, FRANCE

[54] Invention Title: NEW BENZODIOXANE COMPOUNDS, PROCESS FOR THEIR PREPARATION AND THE PHARMACEUTICAL COMPOSITIONS WHICH CONTAIN THEM

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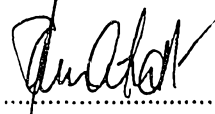
BASIC CONVENTION APPLICATION(S) DETAILS

[31] Application Number	[33] Country	Country Code	[32] Date of Application
94.02161	FRANCE	FR	25 FEBRUARY 1994

Basic Applicant(s): ADIR ET COMPAGNIE

Drawing number recommended to accompany the abstract

By my/our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS


.....

IAN SCOTT

Registered Patent Attorney

DATED this 23rd day of February 1995.

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P/00/008b 12/11/91
Section 29 (1)
Regulation 3.1 (2)

AUSTRALIA

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NOTICE OF ENTITLEMENT
(To be filed before acceptance)

We, **ADIR ET COMPAGNIE** of, 1 RUE CARLE HEBERT, 92415 COURBEVOIE CEDEX, FRANCE being the applicant in respect of Application No. 13448/95 state the following:-

The Person nominated for the grant of the patent has entitlement from the actual inventors by virtue of employment of the inventors.

••••• The person nominated for the grant of the patent is the applicant of the basic application listed on the patent request form.

••••• The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

••••• **ADIR ET COMPAGNIE**

••••• By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

Shahnaz Irani
.....
Shahnaz Irani

18 June 1997
.....

Registered Patent Attorney

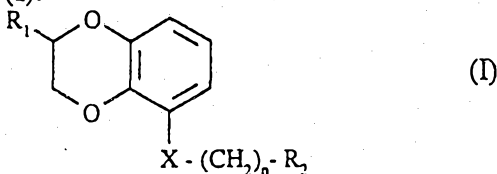


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(12) PATENT ABRIDGMENT (11) Document No. AU-B-13448/95
 (19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 681740

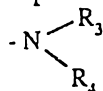
- (54) Title
 NEW BENZODIOXANE COMPOUNDS, PROCESS FOR THEIR PREPARATION AND THE PHARMACEUTICAL COMPOSITIONS WHICH CONTAIN THEM
- (51)⁶ International Patent Classification(s)
 C07D 405/12 A61K 031/40 C07D 319/18 C07D 319/20
 C07D 405/14 C07D 413/14 A61K 031/335
- (21) Application No. : 13448/95 (22) Application Date : 23.02.95
- (30) Priority Data
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- (43) Publication Date : 07.09.95
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- (74) Attorney or Agent
 WATERMARK PATENT & TRADEMARK ATTORNEYS , Locked Bag 5, HAWTHORN VIC 3122
- (56) Prior Art Documents
 FR 1343644
- (57) Claim

1. A compound of formula (I):



in which:

- X represents an oxygen atom or a methylene group,
 n represents 1, 2 or 3,
 R₁ represents a hydrogen atom, an aminocarbonyl group or a hydroxymethyl group,
 R₂ represents a group:



in which:

- either R₃ represents a hydrogen atom or a linear or branched (C₁-C₆) alkyl group,
 and R₄ represents:
 * a linear or branched (C₁-C₄) alkyl group
 - which is unsubstituted or substituted with a phenyl group (which may or may not be substituted with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, trihalomethyl groups or hydroxyl groups), on condition that, in these cases, R₁ is other than a hydrogen atom,

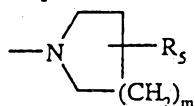
(11) AU-B-13448/95
(10) 681740

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- or which is substituted with a benzoylamino group (which may or may not be substituted on the phenyl ring with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, trihalomethyl groups or hydroxyl groups),

* or a benzoyl group (which may or may not be substituted with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, trihalomethyl groups or hydroxyl groups).

or R₃ and R₄ form, together with the nitrogen atom to which they are attached, a group:



in which:

m represents 1, 2 or 3,

R₅ represents a benzoyl (which may or may not be substituted with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, hydroxyl groups or trihalomethyl groups),

benzoylmethyl (which may or may not be substituted on the phenyl ring with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, hydroxyl groups or trihalomethyl groups),

2-oxo-(3H)-benzimidazol-1-yl,

1H-indazol-3-ylmethyl (which may or may not be substituted on the phenyl ring with a halogen atom),

or 1,2-benzisoxazol-3-ylmethyl group (which may or may not be substituted on the phenyl ring with a halogen atom),

an enantiomer, diastereoisomer or epimer thereof, or an addition salt thereof with a pharmaceutically acceptable acid or base.

11. A method of treating Schizophrenia comprising the administration of a pharmaceutical composition as claimed in claim 10 containing at least one active principle as claimed in one of claims 1 to 6 to a patient in need thereof.

AUSTRALIA

Patents Act 1990

**ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT**

Application Number:

Lodged:

Invention Title: NEW BENZODIOXANE COMPOUNDS, PROCESS FOR THEIR
PREPARATION AND THE PHARMACEUTICAL COMPOSITIONS WHICH
CONTAIN THEM

The following statement is a full description of this invention, including the
best method of performing it known to us :-

The present invention relates to new benzodioxane compounds, to a process for their preparation and to the pharmaceutical compositions which contain them.

A certain number of 1,4-benzodioxane derivatives have been described in the literature. This is more particularly the case for the compounds described in Patents EP 307,970, EP 210,581
5 or FR 2,449,088, which exhibit a vasodilatory activity or alternatively for the compounds described in Patent EP 446,921, which possess anxiolytic properties.

Besides the fact that they are novel, the compounds of the present invention exhibit particularly advantageous pharmacological properties. Indeed, one of the challenges in psychopharmacology today is to find novel medicaments which allow better control of
10 schizophrenia, the treatment of which is currently unsatisfactory. Conventional neuroleptic agents, such as haloperidol, provide quite good care for the productive symptoms (such as fabulation and hallucinations) but their effectiveness with regard to deficiency symptoms (such as social withdrawal) is very poor. Furthermore, they induce an extrapyramidal syndrome of Parkinson type, as has been indicated by A.Y. Deutch et al. (Schizophrenia
15 Research, 4, 121-151, 1991) and H.Y. Meltzer et al. (Pharmacol. Rev., 43, 587-604, 1991).

Unlike haloperidol, clozapine is more effective in treating the deficiency symptoms, and it is even effective in patients who are resistant to haloperidol. Moreover, it appears not to bring about an extrapyramidal syndrom, as has been indicated by Coward et al. (Psychopharmacology, 99, s6-s12, 1989). This difference is apparently due to the receptor
20 profile of clozapine, which differs from that of haloperidol: for example, its low relative activity on the D₂ receptors and its relatively high affinity for the adrenergic (α_1) and serotin-ergic (5-HT_{2A}; 5-HT_{2C}) receptors. These results have been indicated by H.Canton et al. (Eur. J. Pharmacol., 191, 93-96, 1990) as well as by A.Y. Deutch and H.Y. Meltzer, cited above.

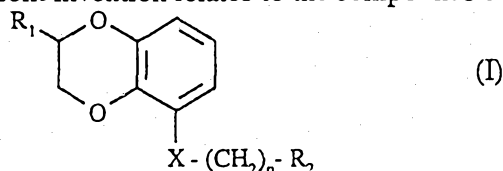
Moreover, unlike haloperidol, clozapine shows a certain affinity for the 5-HT_{1A} receptors, the
25 activation of which is associated with anxiolytic, antidepressant and possibly even antipsychotic effects, as has been indicated by S. Ahlenius (Pharmacol. & Toxicol., 64, 3-5, 1989), J.E. Barrett et al. (in "5-HT_{1A} agonists, 5-HT₃ antagonists and benzodiazepines: their comparative behavioural pharmacology" Ed. R.J. Rogers and S.J. Cooper, Wiley & Sons Ltd.,
30 Chichester, pp. 59-105, 1991), M.J. Millan et al. (Drug News & Perspectives, 5, 397-466, 1992), J.M.A. Sitsen (Drug News & Perspectives, 4, 414-418, 1991).

However, on account of its toxicity, clozapine cannot be envisaged in the general treatment of schizophrenic states. It was thus particularly advantageous to find products sharing the

mechanism of clozapine but devoid of its toxic effects, which are directly associated with its specific chemical structure.

The compounds described in this patent correspond to the desired profile. Indeed, they exhibit (in vitro and in vivo) a very similar biochemical and functional profile to that of clozapine and, in addition, have higher affinities for the 5-HT_{1A} receptors. They thus possess an original profile which appears to be well suited to a better treatment of schizophrenia, in comparison with that which may currently be obtained with the products available.

More specifically, the present invention relates to the compounds of formula (I):



10 in which:

X represents an oxygen atom or a methylene group,

n represents 1, 2 or 3,

R₁ represents a hydrogen atom, an aminocarbonyl group or a hydroxymethyl group,

R₂ represents a group:



15

in which:

either R₃ represents a hydrogen atom or a linear or branched (C₁-C₆) alkyl group,

and R₄ represents:

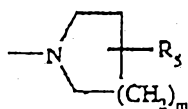
* a linear or branched (C₁-C₄) alkyl group

- which is unsubstituted or substituted with a phenyl group (which may or may not be substituted with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, trihalomethyl groups or hydroxyl groups), on condition that, in these cases, R₁ is other than a hydrogen atom,

- or which is substituted with a benzoylamino group (which may or may not be substituted on the phenyl ring with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, trihalomethyl groups or hydroxyl groups),

* or a benzoyl group (which may or may not be substituted with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, trihalomethyl groups or hydroxyl groups).

or R₃ and R₄ form, together with the nitrogen atom to which they are attached, a group:



in which:

m represents 1, 2 or 3,

R₅ represents a benzoyl (which may or may not be substituted with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, hydroxyl groups or trihalomethyl groups),

benzoylmethyl (which may or may not be substituted on the phenyl ring with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, hydroxyl groups or trihalomethyl groups),

2-oxo-(3H)-benzimidazol-1-yl,

1H-indazol-3-ylmethyl (which may or may not be substituted on the phenyl ring with a halogen atom),

or 1,2-benzisoxazol-3-ylmethyl group (which may or may not be substituted on the phenyl ring with a halogen atom),

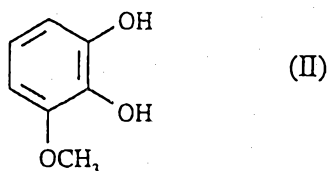
the enantiomers, diastereoisomers and epimers thereof, and the addition salts thereof with a pharmaceutically acceptable acid or base.

Among the pharmaceutically acceptable acids which may be mentioned, without any limitation being implied, are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulfonic acid, camphoric acid, etc.

Among the pharmaceutically acceptable bases which may be mentioned, without any limitation being implied, are sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine, etc.

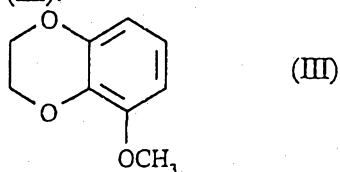
The invention also covers the process for the preparation of the compounds of formula (I).

The process for the preparation of the compounds of formula (I), such that X represents an oxygen atom and R₁ represents a hydrogen atom, comprises a compound of formula (II) being used as starting material:

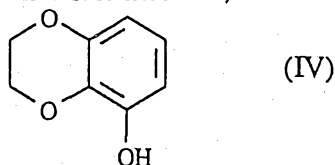


which compound is reacted with 1,2-dibromoethane in the presence of potassium carbonate and copper powder in an alcoholic medium,

to give the compound of formula (III):

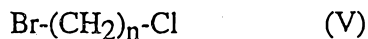


which compound is converted, in an acidic medium, into the compound of formula (IV):



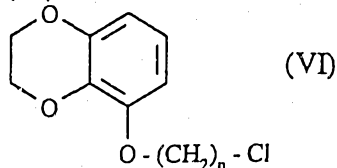
which compound of formula (IV) is condensed:

either with a compound of formula (V), after reacting with sodium ethoxide:



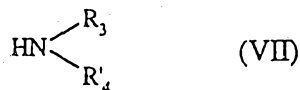
in which n has the same meaning as in the formula (I),

to give the compound of formula (VI):



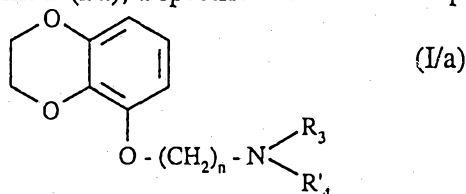
in which n has the same meaning as in the formula (I),

which compound is then reacted with an amine of formula (VII), the isomers of which have optionally been separated:



in which R'₄ has the same meaning as R₄ except for the case where R₄ represents a substituted or unsubstituted benzoyl group,

to give the compound of formula (I/a), a specific case of the compounds of formula (I):

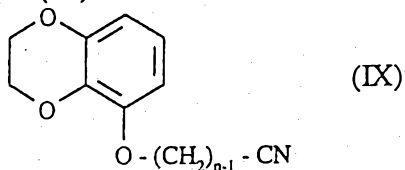


in which n, R₃ and R'₄ have the same meaning as above,

or with a nitrile of formula (VIII), in a basic medium,

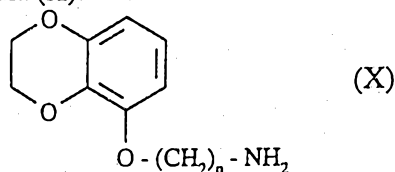


in which n has the same meaning as in the formula (I),
to give the compound of formula (IX):



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in which n has the same meaning as in the formula (I),
which compound is reduced using lithium aluminum hydride,
to give the compound of formula (X):

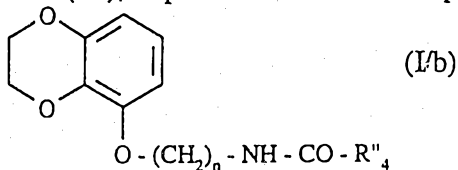


10 in which n has the same meaning as in the formula (I),
which compound is reacted with an acid chloride of formula (XI):



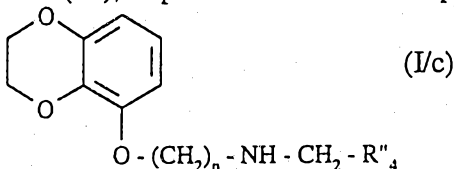
in which R''₄ represents a phenyl group (which may or may not be substituted with one or
more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄)
15 alkoxy groups, trihalomethyl groups or hydroxyl groups),

to give the compound of formula (I/b), a specific case of the compounds of formula (I):



in which n and R''₄ have the same meaning as above,
which compound of formula (I/b) may, if so desired, undergo a reduction in the presence of
tetrabutylammonium borohydride,

to give the compound of formula (I/c), a specific case of the compounds of formula (I):



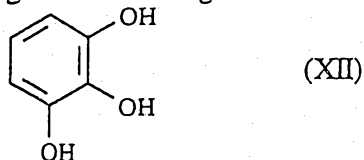
in which n and R''₄ have the same meaning as above,

which compound of formula (I/a), (I/b) or (I/c):

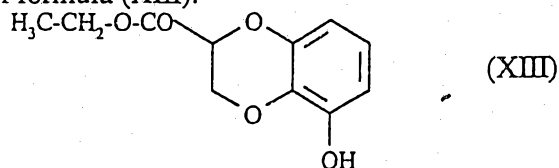
25 - may be purified, if required, according to a standard purification technique, and

- the isomers of which are, if required, separated according to a standard separation technique, and
- which is converted, if so desired, into the addition salts thereof with a pharmaceutically acceptable base.

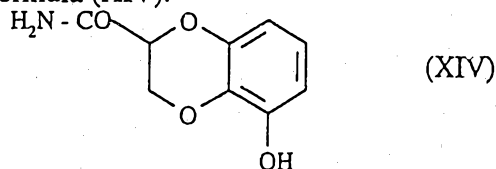
5 The process for the preparation of the compounds of formula (I), such that X represents an oxygen atom and R₁ represents an aminocarbonyl or hydroxymethyl group, comprises a compound of formula (XII) being used as starting material:



10 which compound is reacted with ethyl 2,3-dibromopropionate, in a basic medium, to give the compound of formula (XIII):

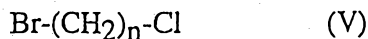


which compound is reacted, if so desired, in an ammoniacal solution, to give the compound of formula (XIV):



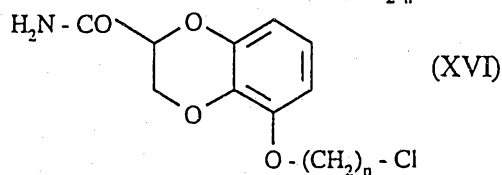
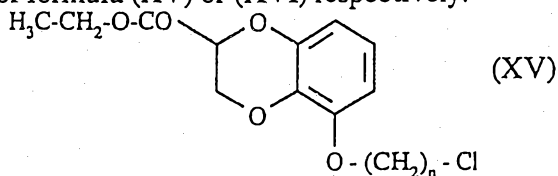
15 which compound of formula (XIII) or (XIV) is condensed:

either with a compound of formula (V):



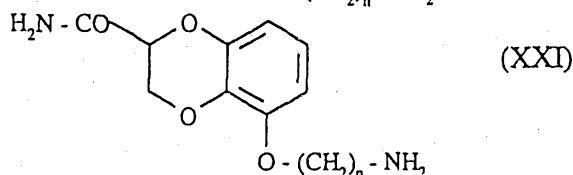
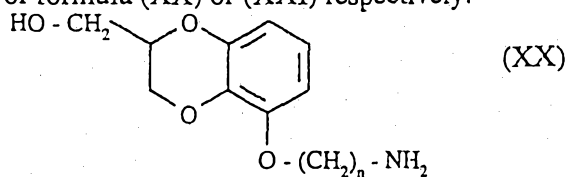
in which n has the same meaning as in the formula (I),

to give the compounds of formula (XV) or (XVI) respectively:



in which n has the same meaning as in the formula (I),

to give the compounds of formula (XX) or (XXI) respectively:



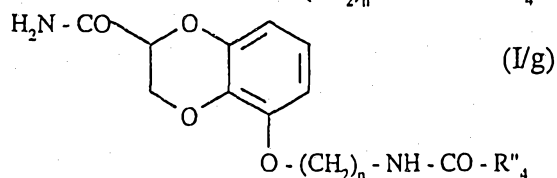
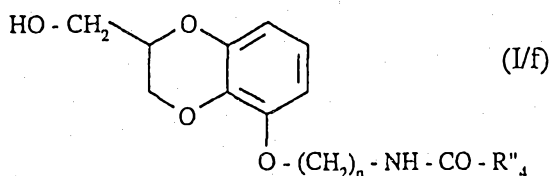
in which n has the same meaning as in the formula (I),

5 which compounds are reacted, respectively, with an acid chloride of formula (XI):



in which R''_4 represents a phenyl group (which may or may not be substituted with one or more halogen atoms or linear or branched (C_1 - C_4) alkyl groups, linear or branched (C_1 - C_4) alkoxy groups, trihalomethyl groups or hydroxyl groups),

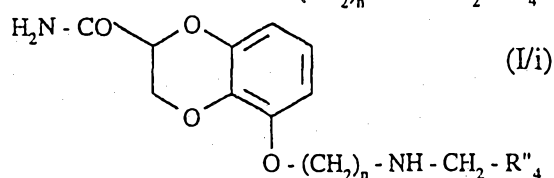
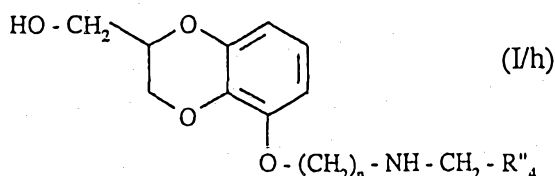
10 to give the compounds of formula (I/f) or (I/g) respectively, specific cases of the compounds of formula (I):



in which n and R''_4 have the same meaning as above,

15 which compounds of formula (I/f) or (I/g) may, if so desired, undergo a reduction in the presence of tetrabutylammonium borohydride,

to give the compounds of formula (I/h) or (I/i) respectively, specific cases of the compounds of formula (I):



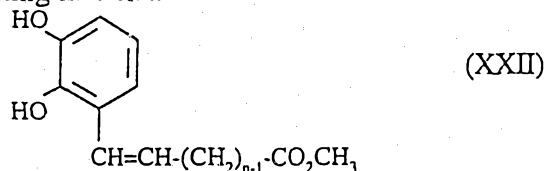
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in which n and R''_4 have the same meaning as above,

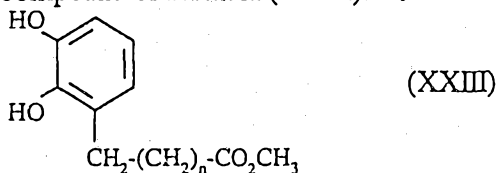
which compound of formula (I/d), (I/e), (I/f), (I/g), (I/h) or (I/i):

- may be purified, if required, according to a standard purification technique, and
- the isomers of which are, if required, separated according to a standard separation technique, and
- which is converted, if so desired, into the salts thereof with a pharmaceutically acceptable base.

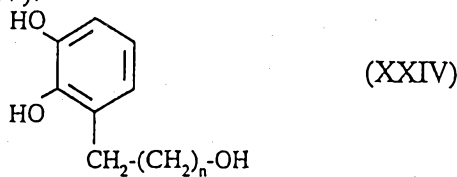
The process for the preparation of the compounds of formula (I), such that X represents a methylene group, comprises a compound of formula (XXII) (obtained from 2,3-dihydroxybenzaldehyde according to the process described in J. Med. Chem., 26, 193, 1989) being used as starting material:



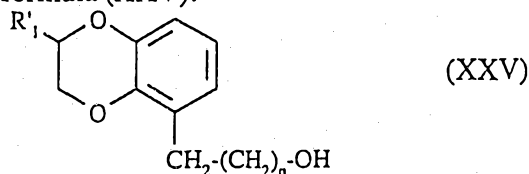
in which n has the same meaning as in the formula (I), which undergoes a catalytic hydrogenation to give the compound of formula (XXIII):



in which n has the same meaning as in the formula (I), which compound is reduced in the presence of lithium aluminum hydride, to give the compound of formula (XXIV):

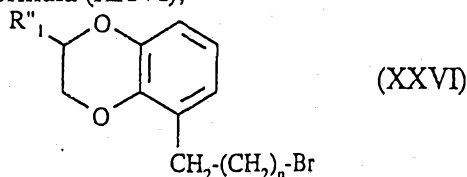


in which n has the same meaning as in the formula (I), which compound is reacted with 1,2-dibromoethane or with ethyl 2,3-dibromopropionate, depending on the derivative of formula (I) which it is desired to obtain, to give the compound of formula (XXV):



in which R'₁ represents a hydrogen atom or an ethoxycarbonyl group, which compound of formula (XXV) (which, when R'₁ represents an ethoxycarbonyl group, may, if so desired, be subjected to the action of an ammoniacal solution, to give the corresponding amide),

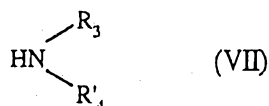
is then reacted with carbon tetrabromide in the presence of triphenylphosphine, to give the compound of formula (XXVI),



in which n has the same meaning as in the formula (I), and R''1 represents a hydrogen atom or an ethoxycarbonyl or aminocarbonyl group,

5

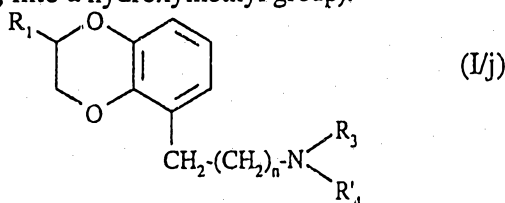
which compound is then reacted with an amine of formula (VII), the isomers of which have optionally been separated:



in which R'4 has the same meaning as R4, except for the case where R4 represents a substituted or unsubstituted benzoyl group,

10

to give the compound of formula (I/j), a specific case of the compounds of formula (I) (after conversion, in the presence of lithium aluminum hydride, of the group R''1, when it represents an ethoxycarbonyl group, into a hydroxymethyl group):



in which R1, n, R3 and R'4 have the same meaning as above, which compound of formula (I/j):

- may, if required, be purified according to a standard purification technique, and
- the isomers of which are separated, if required, according to a standard separation technique, and
- which is converted, if so desired, into the addition salts thereof with a pharmaceutically acceptable base.

The subject of the present invention is also the pharmaceutical compositions containing, as active principle, at least one compound of formula (I), alone or in combination with one or more inert, non-toxic vehicles or excipients.

25 Among the pharmaceutical compositions according to the invention, there may more particularly be mentioned those which are suitable for oral, parenteral or nasal administration, simple or coated tablets, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, etc.

The useful dosage varies depending on the age and weight of the patient, the nature and severity of the complaint, and the route of administration. The latter may be oral, nasal, rectal or parenteral. Generally speaking, the unit dosage ranges between 20 µg and 2 mg for a treatment dose taken 1 to 3 times per 24 hours.

- 5 The examples which follow illustrate the invention and in no way imply a limitation thereof.

The starting materials used are known products or are prepared according to known procedures.

Preparations A, B and C do not lead to the compounds of the invention, but to synthesis intermediates which are useful in the preparation of the compounds of formula (I).

10 **Preparation A : N-Propyl-N-[2-(4-fluorobenzoylamino)ethyl]amine**

Stage A: N-(2-Bromoethyl)-4-fluorobenzamide

To a suspension containing 0.23 mol of 2-bromoethylamine hydrobromide in 200 ml of chloroform, stirred at 5°C, is added dropwise a solution containing 0.21 mol of 4-fluorobenzoyl chloride in 50 ml of chloroform, followed by a solution containing 0.46 mol of triethylamine in 100 ml of chloroform. The mixture is then stirred at room temperature for 1 hour and then at reflux for 4 hours. After cooling and evaporation of the solvent, the residue is taken up in 200 ml of ether. After filtration of the salts and concentration of the solvent, the expected product is obtained by purification of the residue by chromatography on a column of silica, using a dichloromethane/acetone (98/2) mixture as eluent.

20 **Stage B**: N-Propyl-N-[2-(4-fluorobenzoylamino)ethyl]amine

The product obtained in the preceding stage, dissolved in 40 ml of propylamine, is maintained at reflux for 4 hours. After cooling and distillation of the excess propylamine, the expected product is obtained after purification by chromatography on a column of silica, using a dichloromethane/methanol/aqueous ammonia (90/10/1) mixture as eluent.

25 **Preparation B : 3-[(6-Fluoro-1,2-benzisoxazol-3-yl)methyl]pyrrolidine**

Stage A : 1-Benzyl-3-[2-(2,4-difluorophenyl)-2-hydroxyethyl]pyrrolidine

A solution containing 0.38 mol of 1-benzyl-3-chloromethylpyrrolidine in 200 ml of tetrahydrofuran (THF) is added, at 65°C, to a suspension containing 9.3 g of magnesium in 100 ml of THF. The mixture is maintained at reflux and, after disappearance of the metal, followed by cooling, this solution is added to a solution containing 0.38 mol of
5 2,4-difluorobenzaldehyde in 300 ml of THF. The mixture is maintained at room temperature for 12 hours and is then hydrolyzed with 220 ml of saturated ammonium chloride solution. After extraction with dichloromethane and then evaporation, the residual oil is purified by chromatography on a column of silica, using a dichloromethane/methanol/aqueous ammonia (98/2/0.2) mixture as eluent, and gives the expected product.

10 Stage B : 1-Benzyl-3-(2,4-difluorobenzoylmethyl)pyrrolidine

67 g of chromium trioxide are added, with stirring and at 0°C, to 700 ml of pyridine, followed, 15 minutes later, by 0.214 mol of the compound described in the preceding stage, dissolved in 150 ml of pyridine. The mixture is maintained at room temperature for 12 hours, evaporated and the residue is taken up in 500 ml of water and 500 ml of dichloromethane. The
15 precipitate formed is filtered off and washed with dichloromethane. The organic phases are combined, washed with 1N sodium hydroxide, with saturated sodium chloride solution and then dried and evaporated. The residual oil is purified by chromatography on a column of silica, using a dichloromethane/methanol/aqueous ammonia (98/2/0.2) mixture as eluent, and gives the expected product.

20 Stage C : 1-Benzyl-3-[6-fluoro-1,2-benzisoxazol-3-yl)methyl]pyrrolidine

0.19 mol of the product obtained in the preceding stage and 0.95 mol of hydroxylamine hydrochloride in 600 ml of pyridine are maintained at reflux for 24 hours. After concentration of the solvent, the residue is taken up in dichloromethane. The organic phase is then washed with water and evaporated. The residue is taken up in 100 ml of dimethylformamide (DMF)
25 and is added to a suspension containing 4.3 g of sodium hydride in 50 ml of DMF. After stirring for one hour, the reaction mixture is hydrolyzed and then extracted with dichloromethane. After washing the organic phase with water and evaporation of the solvent, the residual oil is purified by chromatography on a column of silica, using a dichloromethane/methanol (97/3) mixture as eluent, and gives the expected product.

30 Stage D : 1-Ethoxycarbonyl-3-[6-fluoro-1,2-benzisoxazol-3-yl)methyl]pyrrolidine

A mixture containing 80 mmol of the compound obtained in the preceding stage and 160 mmol of ethyl chloroformate in 350 ml of toluene is maintained at reflux for 24 hours. After

cooling, washing of the toluene phase with 1N hydrochloric acid, then with 1N sodium hydroxide and evaporation, the expected product is obtained.

Stage E : 3-[(6-Fluoro-1,2-benzisoxazol-3-yl)methyl]pyrrolidine

5 58 mmol of the compound obtained in the preceding stage and 250 ml of 48% hydrobromic acid are heated at 90°C for 1 hour. After concentration, the expected product is obtained by release from the residue using 5N sodium hydroxide.

Preparation C : 3-[(6-Fluoro-1H-indazol-3-yl)methyl]pyrrolidine

Stage A : 1-Benzyl-[(6-Fluoro-1H-indazol-3-yl)methyl]pyrrolidine

10 64 mmol of the compound obtained in Stage B of Preparation B and 64 mmol of hydrazine hydrate in 200 ml of 1-butanol are maintained at reflux for 72 hours. After cooling and evaporation, the residue is taken up in dichloromethane. The organic phase is washed with water and evaporated. The residual oil is purified by chromatography on a column of silica, using a dichloromethane/methanol/aqueous ammonia (96/4/0.4) mixture as eluent.

Stage B : 3-[(6-Fluoro-1H-indazol-3-yl)methyl]pyrrolidine

15 The product obtained in the preceding stage undergoes a catalytic debenylation in ethanol, at 45°C, using 10% palladium on charcoal as catalyst.

EXAMPLE 1 : 5-{2-[4-(4-Fluorobenzoyl)piperidino]ethoxy}-1,4-benzodioxane hydrochloride

Stage A : 5-Methoxy-1,4-benzodioxane

20 A heterogeneous mixture containing 1.42 mol of 3-methoxycatechol, 1.57 mol of 1,2-dibromoethane, 1.42 mol of potassium carbonate and 4 g of copper powder in 150 ml of glycerol is heated at 110°C for 15 hours. After cooling, the mixture is poured into 1 l of water. The aqueous phase is extracted with ethyl ether. The ether phases are then washed with 1N sodium hydroxide, dried and evaporated, and give the expected product.

25 Stage B : 5-Hydroxy-1,4-benzodioxane

The compound obtained in the preceding stage is maintained at reflux in 500 ml of 48% hydrobromic acid and 800 ml of glacial acetic acid. After cooling and concentration, the residue is taken up in 1 l of water and the aqueous phase is extracted with ethyl ether. The ether phases are combined and evaporated. The expected product is obtained after purification by chromatography on a column of silica, using dichloromethane as eluent.

Stage C: 5-(2-Chloroethoxy)-1,4-benzodioxane

To 500 ml of 1N sodium ethoxide solution is added dropwise a solution containing 500 mmol of the compound obtained in the preceding stage in 150 ml of ethanol. The mixture is stirred for 1 hour, and a solution containing 500 mmol of 1-bromo-2-chloroethane in 150 ml of ethanol is added to the above mixture. The mixture is then maintained at reflux for 24 hours. After cooling, filtration of the salts and evaporation, the residue is taken up in isopropyl ether and the expected product which precipitates is filtered off.

Melting point: 73°C

Stage D: 5-{2-[4-(4-Fluorobenzoyl)piperidino]ethoxy}-1,4-benzodioxane hydrochloride

A mixture containing 21 mmol of the product obtained in the preceding stage, 17 mmol of 4-(4-fluorobenzyl)piperidine, 21 mmol of potassium carbonate and a few mg of potassium iodide in 50 ml of 4-methyl-2-pentanone is maintained at reflux for 18 hours. After cooling, 50 ml of water are added to the reaction medium and the aqueous phase is extracted with dichloromethane. The organic phases are combined, washed, dried and evaporated. The expected product, in the form of the base, is obtained after purification of the residue by chromatography on a column of silica, using a dichloromethane/ethanol (98/2) mixture as eluent. It is converted into the corresponding hydrochloride by dilution in ethyl ether and dropwise addition of the stoichiometric amount of 10N hydrochloric ethanol. The hydrochloride is then filtered off, washed with ether and dried.

Melting point: 152°C

Elemental microanalysis:

	C%	H%	N%	Cl%
calculated	62.63	5.97	3.32	8.40
found	62.49	5.95	3.18	8.47

The products of Examples 2 to 8 were prepared according to the process described in Example 1, using the corresponding starting materials.

EXAMPLE 2: 5-{2-[3-(4-Fluorobenzoylmethyl)pyrrolidin-1-yl]-1,4-benzodioxane hydrochloride

Stages A, B, C : identical to Stages A, B and C of Example 1.

Stage D : Replace 4-(4-fluorobenzoyl)piperidine with 3-(4-fluorobenzylmethyl)pyrrolidine.

Melting point: 134°C

Elemental microanalysis:

	C%	H%	N%	Cl%
5 calculated	62.63	5.97	3.32	8.40
found	62.64	6.06	3.16	8.52

**EXAMPLE 3 : 5-{2-[4-(2-Oxo-(3H)-benzimidazol-1-yl)
piperidino]ethoxy}-1,4-benzodioxane hydrochloride**

10 Stages A, B, C : identical to Stages A, B and C of Example 1.

Stage D : Replace 4-(4-fluorobenzoyl)piperidine with
1-(piperidin-4-yl)-2-(3H)-benzimidazolone.

Melting point: 155°C

Elemental microanalysis:

	C%	H%	N%	Cl%
15 calculated	61.18	6.07	9.73	8.21
found	61.07	6.1	9.71	8.14

**EXAMPLE 4 : 5-{2-[N-propyl-N-[2-(4-Fluorobenzoylamino)
ethyl]amino]ethoxy}-1,4-benzodioxane hydrochloride**

20 Stages A, B, C : identical to stages A, B and C of Example 1.

Stage D : Replace 4-(4-fluorobenzoyl)piperidine with the amine described in Preparation A.

Melting point: 147°C

Elemental microanalysis:

	C%	H%	N%	Cl%
25 calculated	60.20	6.43	6.38	8.08
found	59.71	6.53	6.33	8.27

**EXAMPLE 5 : 5-{2-[3-(4-Fluorobenzoylmethyl)pyrrolidin-1-yl]
ethoxy}-1,4-benzodioxane hydrochloride, (+) isomer**

Stages A, B, C : identical to Stages A, B and C of Example 1.

Stage D: Replace 4-(4-fluorobenzoyl)piperidine with the (+) isomer of 3-(4-fluorobenzoylmethyl)pyrrolidine obtained according to the process described in Patent EP 389,352.

The hydrochloride is obtained by salification of the base in an acetone/ethyl ether (50/50) mixture with one equivalent of hydrochloric acid in ethanol.

Melting point: 120-122°C

Optical rotation: $[\alpha]_D^{21} = +4.15^\circ$ (c = 1%, methanol)

Elemental microanalysis:

	C%	H%	N%	Cl%
10 calculated	62.63	5.97	3.32	8.40
found	62.65	5.89	3.31	8.41

EXAMPLE 6 : 5-{2-[3-(4-Fluorobenzoylmethyl)pyrrolidin-1-yl]ethoxy}-1,4-benzodioxane hydrochloride, (-) isomer

Stages A, B, C : identical to Stages A, B and C of Example 1.

15 Stage D: Replace 4-(4-fluorobenzoyl)piperidine with the (-) isomer of 3-(4-fluorobenzoylmethyl)pyrrolidine obtained according to the process described in Patent EP 389,352.

The hydrochloride is obtained as described in Example 5.

Melting point: 120-122°C

20 Optical rotation: $[\alpha]_D^{21} = -4.75^\circ$ (c = 1%, methanol)

Elemental microanalysis:

	C%	H%	N%	Cl%
calculated	62.63	5.97	3.32	8.40
found	62.59	5.86	3.37	8.28

25 **EXAMPLE 7 : 5-{2-[3-[(6-Fluoro-1H-indazol-3-yl)methyl]pyrrolidin-1-yl]ethoxy}-1,4-benzodioxane hydrochloride**

Stages A, B, C : identical to Stages A, B and C of Example 1.

Stage D: Replace 4-(4-fluorobenzoyl)piperidine with 3-[(6-fluoro-1H-indazol-3-yl)methyl]pyrrolidine described in Preparation C.

Purification of the expected product, in base form, is performed by chromatography on a column of silica, using a dichloromethane/methanol/aqueous ammonia (95/5/0.5) mixture as eluent.

Elemental microanalysis:

	C%	H%	N%	Cl%
5 calculated	61.26	5.78	9.75	7.40
found	61.33	6.05	9.14	7.35

EXAMPLE 8 : 5-{2-[3-[(6-Fluoro-1,2-benzisoxazol-3-yl)methyl]pyrrolidin-1-yl]ethoxy}-1,4-benzodioxane hydrochloride

10 Stages A, B, C : identical to Stages A, B and C of Example 1.

Stage D : Replace 4-(4-fluorobenzoyl)piperidine with 3-[(6-fluoro-1,2-benzisoxazol-3-yl)methyl]pyrrolidine described in Preparation B.

Purification of the product obtained, in base form, is performed by chromatography on a column of silica, using a dichloromethane/methanol (97/3) mixture as eluent.

15 Elemental microanalysis:

	C%	H%	N%
calculated	60.76	5.56	6.44
found	61.21	5.54	6.49

EXAMPLE 9: 5-{2-(4-(4-Fluorobenzoyl)piperidino)ethoxy}-1,4-benzodioxane-2-carboxamide hydrochloride

Stage A : Ethyl ester of 5-hydroxy-1,4-benzodioxane-2-carboxylic acid

To a solution containing 0.8 mol of pyrogallol in 1 l of acetate are added 2.4 mol of potassium carbonate, followed by dropwise addition of 2.4 mol of ethyl 2,3-dibromopropionate. The mixture is then maintained at reflux for 15 hours. After cooling, filtration of the precipitate and washing of the latter with acetone, the filtrate is recovered and concentrated. The residue is taken up in ether and, after filtration of the ether phase, the latter is evaporated and gives the expected product.

Stage B : 5-Hydroxy-1,4-benzodioxane-2-carboxamide

30 A mixture containing 350 mmol of the product obtained in the preceding stage in 1.3 l of a 28% ammoniacal solution is stirred at room temperature for 18 hours. After concentration of the reaction medium, the residue is taken up in 300 ml of ether. The expected product is obtained after filtration of the precipitate formed and is dried.

Stage C : 5-(2-Chloroethoxy)-1,4-benzodioxane-2-carboxamide

The expected product is obtained according to the process described in Stage C of Example 1, from the compound obtained in the above stage.

Stage D : 5-{2-(4-(4-Fluorobenzoyl)piperidino)ethoxy}-1,4-benzodioxane-2-carboxamide
5 hydrochloride

The expected product is obtained according to the process described in Stage D of Example 1, from the compound described in the above stage.

Melting point: 215°C

Elemental microanalysis:

	C%	H%	N%	Cl%
10 calculated	59.42	5.64	6.03	7.63
found	59.39	5.80	5.83	7.59

EXAMPLE 10: 2-Hydroxymethyl-5-[2-(N,N-dipropylamino)ethoxy]-1,4-benzodioxane oxalate

Stage A : Ethyl ester of 5-(2-chloroethyl)-1,4-benzodioxane-2-carboxylic acid

The expected product is obtained from the compound described in Stage A of Example 9, according to the process described in Stage C of Example 1.

Stage B : Ethyl ester of 5-[2-(N,N-dipropylaminoethoxy)-1,4-benzodioxane-2-carboxylic acid

50 mmol of the compound obtained in the preceding stage in 50 ml of dipropylamine are maintained at 150°C for 10 hours. After cooling, the medium is concentrated under vacuum and the expected product is obtained after purification of the residue by chromatography on a column of silica, using a dichloromethane/ethanol/aqueous ammonia (90/10/1) mixture as eluent.

Stage C : 2-Hydroxymethyl-5-[2-(N,N-dipropylamino)ethoxy]-1,4-benzodioxane oxalate

To a suspension containing 13.7 mmol of lithium aluminum hydride in 100 ml of ether, stirred at room temperature under a nitrogen atmosphere, is added dropwise a solution containing 12 mmol of the product obtained in the above stage in 50 ml of ether. The mixture is kept stirring for 1 hour and is hydrolyzed with saturated ammonium chloride solution. The organic phase is

recovered, washed with water, dried and evaporated, and gives the expected product in the form of the base. To the latter, diluted in 50 ml of ethanol, is added 1 equivalent of oxalic acid, followed, after stirring for 5 minutes, by 50 ml of isopropyl ether. The oxalate is obtained by filtration and is dried.

5 *Melting point : 148°C*

EXAMPLE 11: 5-[2-(2,3,4-Trimethoxybenzoylamino)ethoxy]-1,4-benzodioxane

Stage A : 5-Cyanomethoxy-1,4-benzodioxane

10 To a stirred suspension containing 0.38 mol of the compound obtained in Stage B of Example 1 and 1.14 mol of potassium carbonate in 500 ml of acetone is added dropwise a solution containing 0.76 mol of bromoacetonitrile in 100 ml of acetone. The medium is then kept stirring for 18 hours. After filtration of the salts and evaporation, the expected product is obtained.

Stage B : 5-(2-Aminoethoxy)-1,4-benzodioxane

15 The expected product is obtained according to the process described in Stage C of Example 10, from the product described in the above stage.

Stage C : 5-[2-(2,3,4-Trimethoxybenzoylamino)ethoxy]-1,4-benzodioxane

20 To a stirred solution, at room temperature, containing 4.7 mmol of the product obtained in the preceding stage in 20 ml of dichloromethane is added dropwise a solution containing 10.5 mmol of 3,4,5-trimethoxybenzoyl chloride in 20 ml of dichloromethane, followed by 10.5 mmol of triethylamine in 20 ml of dichloromethane. The mixture is then stirred at room temperature for 2 hours. After filtration of the salts and washing of the medium with water, the organic phase is dried and evaporated. The residue is taken up in ether and gives the expected product which precipitates and which is recrystallized in ethanol.

25 *Melting point: 128°C*

Elemental microanalysis:

	C%	H%	N%
calculated	61.69	5.95	3.60
found	61.26	5.89	3.70

EXAMPLE 12: 2-Hydroxymethyl-5-[2-(4-fluorobenzoylamino)ethoxy]-1,4-benzodioxane

30

Stage A : Ethyl ester of 5-cyanomethyl-1,4-benzodioxane-2-carboxylic acid

The expected product was obtained according to the process described in Stage A of Example 11, from the compound described in Stage A of Example 9 and bromoacetonitrile.

Stage B : 2-Hydroxymethyl-5-(2-aminoethoxy)-1,4-benzodioxane

- 5 The expected product was obtained according to the process described in Stage C of Example 10, from the compound described in the above stage, using 2 equivalents of lithium aluminum hydride.

Stage C : 2-Hydroxymethyl-5-[2-(4-fluorobenzoylamino)ethoxy]-1,4-benzodioxane

- 10 The expected product was obtained according to the process described in Stage C of Example 11, from the compound described in the above stage and 4-fluorobenzoyl chloride.

Melting point: 124°C

Elemental microanalysis:

	C%	H%	N%
<i>calculated</i>	62.24	5.22	4.03
<i>found</i>	62.13	5.30	3.88

EXAMPLE 13: 5-[2-(3,4,5-Trimethoxybenzylamino)ethoxy]-1,4-benzodioxane hydrochloride

6.3 mmol of the compound obtained in Stage C of Example 11 and 19 mmol of tetrabutylammonium borohydride are maintained at reflux in 100 ml of dichloromethane for 24 hours. After evaporation of the solvent, the reaction medium is hydrolyzed with 50 ml of 10% hydrochloric acid at room temperature. The mixture is then maintained at reflux for one hour. After extraction with dichloromethane, the organic phase is washed with sodium hydroxide, dried and concentrated under vacuum. The expected product, in the form of the base, is then obtained after purification of the residue by chromatography on a column of silica, using a dichloromethane/methanol (97/3) mixture as eluent. After dilution in ether and stoichiometric addition of 6N hydrochloric ether, the corresponding hydrochloride is obtained.

Melting point: 149°C

Elemental microanalysis:

	C%	H%	N%	Cl%
30 <i>calculated</i>	58.32	6.36	3.40	8.61
<i>found</i>	58.02	6.35	3.45	8.44

**EXAMPLE 14: 5-{3-[3-(4-Fluorobenzoylmethyl)pyrrolidin-1-yl]propyl}-
1,4-benzodioxane hydrochloride**

Stage A : Methyl ester of 3-(2,3-dihydroxyphenyl)propionic acid

The expected product is obtained by catalytic hydrogenation in methanol, at room temperature and pressure, in the presence of 10% palladium on charcoal as catalyst, of the methyl ester of (2,3-dihydroxy-phenyl)cinnamic acid (obtained from 2,3-dihydroxybenzaldehyde according to the procedure described in J. Het. Chem., 26, 193, 1989).

Stage B : 3-(2,3-Dihydroxyphenyl)propanol

The expected product is obtained according to the process described in Stage C of Example 10, from the compound obtained in the above stage.

Stage C : 5-(3-Hydroxypropyl)-1,4-benzodioxane

The expected product is obtained according to the process described in Stage A of Example 1, from the compound obtained in the above stage.

Stage D : 5-(3-Bromopropyl)-1,4-benzodioxane

To a stirred solution, at 8°C, containing 36 mmol of the compound obtained in the preceding stage and 58.4 mmol of carbon tetrabromide in 150 ml of dimethylformamide are added portionwise 58.4 mmol of triphenylphosphine. The mixture is stirred at 8°C for 2 hours and is then poured into 300 ml of ice-water. The medium is extracted with ether and the ether phase is dried and evaporated. The expected product is then obtained by purification of the residue by chromatography on a column of silica, using dichloromethane as eluent.

Stage E : 5-{3-[3-(4-Fluorobenzoylmethyl)pyrrolidin-1-yl]propyl}-1,4-benzodioxane
hydrochloride

The expected product is obtained according to the process described in Stage D of Example 1, from the compound obtained in the above stage and 3-(4-fluorobenzoylmethyl)pyrrolidine.

Elemental microanalysis:

	C%	H%	N%	Cl%
calculated	65.79	6.48	3.34	8.44
found	65.11	6.11	4.03	8.32

EXAMPLE 15: 5-{2-[4-(4-Fluorobenzoyl)perhydroazepin-1-yl]ethoxy}-1,4-benzodioxane hydrochloride

A mixture of 5 g of 5-(2-chloroethoxy)-1,4-benzodioxane, 7.8 g of 4-(4-fluorobenzoyl) perhydroazepine hydrobromide (described in Patent EP 389,352), 1 g of potassium iodide and 6.5 g of potassium carbonate in 100 ml of diethyl ketone is maintained at 100C for 24 hours. The inorganic salts are then filtered off and the filtrate is concentrated under vacuum. The residue is purified by chromatography on a column of silica, with a dichloromethane/methanol/aqueous ammonia (97/3/0.3) eluent mixture. The base obtained is salified with hydrochloric methanol in an acetone/ether mixture.

Melting point: 106-107°C

Elemental microanalysis:

	C%	H%	N%	Cl%
calculated	63.37	6.24	3.21	8.13
found	63.01	6.13	2.98	7.94

Pharmacological study of the compounds of the invention

EXAMPLE 16: Receptor profile of the compounds of the invention

The interaction of these compounds with various receptors was determined using standard binding studies as described by M.J. Millan et al. (J. Pharmacol. Exp. Ther., 268, 337-352, 1994 and Drug News & Perspectives, 5, 397-406, 1992). The receptor profile of the compounds of the invention is presented in the table below. The affinities of the compounds are expressed as pKi.

Receptor Profile (pKi)

Examples	D ₁	D ₂	5-HT _{1A}	5-HT _{2A}	5-HT _{2C}	α ₁
ex. 2	6.60	7.36	8.31	8.40	8.10	8.61
ex. 5	6.56	7.33	8.32	8.48	8.03	8.19
ex. 6	6.69	7.27	8.44	8.62	8.18	8.93
ex. 7	NT	7.27	8.77	7.66	7.03	NT
ex. 8	NT	6.59	8.41	7.88	7.02	NT
Halopéridol	7.39	8.73	5.55	7.08	5.24	8.01
Clozapine	6.74	6.65	6.53	7.63	8.06	8.22

NT = not tested

EXAMPLE 17: Antipsychotic properties

Two well-established tests were used in order to determine the antipsychotic properties of the compounds of the invention, in which tests all of the antipsychotic agents are clinically active, as has been shown by A.Y. Deutch et al. (Schizophrenia Research, 4, 121-156, 1991) and A.A. Mengens et al. (J. Pharmacol. Exp. Ther., 260, 160-167, 1992):

- verticalization inhibition induced by a dopaminergic agonist: apomorphine (according to the procedure described by P. Protais et al., Psychopharmacol., 50, 1-6, 1976),
- motor activity inhibition induced by amphetamine (which increases the release of catecholamines) according to the procedure described by A.A. Mengens, cited above.

- 10 An activity in these tests appears to reflect blocking of the mesolimbic dopaminergic pathways, which are believed to be hyperactive in schizophrenics, as described by P.C. Waldmeier et al. (Eur. J. Pharmacol., 55, 363-373, 1979) and A.Y. Deutch, cited above. The activities of the compounds of the invention were compared with those of haloperidol and of clozapine.

Verticalization test using apomorphine in mice

The experiment was performed on male CF (Charles River) mice of average weight 25 g. thirty minutes before the start of the test, each mouse was placed in a cylindrical cage (Ø12 cm 14 cm), with vertical metal bars and a smooth plastic lid, after having received a subcutaneous injection of solvent or of product. At T₀, a solution of apomorphine (0.75 mg/kg) or of physiological saline was administered subcutaneously to the animal, which was returned to the barred cage. At T₁₀ (10 minutes) and at T₂₀ (20 minutes), a score was attributed to each animal after observation for approximately one minute:

- score 0 (4 feet on the floor);
- score 1 (animal raised on hind legs, forefeet on the vertical bars);
- score 2 (animal gripping on to the bars with all 4 feet).

The total score of the 2 measurements then represents the verticalization value of the animal, which is used for the statistical analysis.

Test of the motor activity induced by amphetamine

Male Wistar rats (200-220 g) were placed in transparent polycarbonate individual cages the night before the test. The locomotor activity was recorded using photoelectric cells (Système Labline, Coulbourn) connected via an interface to a microcomputer. There are two transverse

banks of photoelectric cells per cage. The test takes place under artificial light, starting from 1.00 p.m., during daylight hours. The product or solvent was administered to the animal subcutaneously, 30 minutes before the start of the test. At T₀, the animal received an intraperitoneal injection of physiological saline or of D-amphetamine (2.5 mg/kg): the motor activity of the animal (small and large movements) was recorded continuously for 1 hour, from T₀ to T₆₀.

The results of these two tests are presented in the table below:

Examples	Verticalization (Apomorphine)		Locomotion (Amphetamine)	
	DI ₅₀ (mg/kg)	(95 % L.C.) (mg/kg)	DI ₅₀ (mg/kg)	(95 % L.C.) (mg/kg)
Ex. 2	0.28	(0.17-0.47)	2.17	(1.44-3.28)
Ex. 5	0.26	(0.12-0.57)	2.80	(1.51-5.18)
Ex. 6	0.25	(0.15-0.41)	1.94	(1.05-3.60)
Ex. 7	0.41	(0.04-3.99)	NT	
Ex. 8 (*)	= 0.63		NT	
Haloperidol	0.013	(0.008-0.022)	0.043	(0.03-0.06)
Clozapine	2.22	(1.70-2.90)	12.85	(9.25-17.86)

ID₅₀ (95% C.L.) = Inhibitory Dose₅₀ (95% Confidence Limits)

NT = not tested

(*) The precise value could not be determined

EXAMPLE 18: Catalepsy in rats

In order to determine the potential of the compounds of the invention to generate a syndrome of extrapyramidal type, the capacity to induce a catalepsy in rats was examined. This phenomenon is due to an antagonism of the nigrostriatal dopaminergic transmission. The activities of the compounds were compared with those of haloperidol and clozapine.

Procedure:

Male Wistar rats (220-240 g) were placed in individual cages and food was withheld the night before the test.

The test used to evaluate the cataleptogenic properties of a product consists in placing each of the animal's hind feet on the forefoot located on the same side and in measuring the time in seconds for which the animal kept this "crossed feet" position, up to 30 seconds, as described by P.C. Waldmeier et al. (Eur. J. Pharmacol., 55, 363-373, 1979).

Each animal underwent three tests, at intervals of one minute; the average value of the three tests then represents the catalepsy time of the animal, which is used for the statistical analysis. The product to be tested was administered to the animal subcutaneously, 30 minutes before the test.

5 The results of the induction of catalepsy in rats are presented in the table below.

The effective cataleptogenic dose ED₅₀ is that which induces catalepsy for an average duration of 15 seconds, that is to say for 50% of the maximum duration of the test (30 seconds).

Examples	Induction of the catalepsy	
	DE ₅₀ (mg/kg)	(95 % C.L.) (mg/kg)
Ex. 2	> 40.0	
Ex. 5	> 40.0	
Ex. 6	> 40.0	
Haloperidol	0.156	(0.05-0.38)
Clozapine	> 40.0	

ED₅₀ (95% L.C.) = Effective Dose₅₀ (95% Confidence Limits)

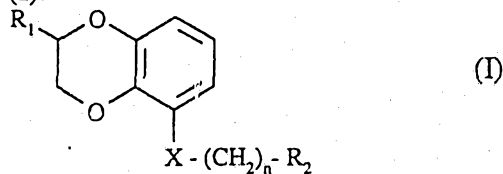
EXAMPLE 19: Pharmaceutical composition

Preparation formula for 1000 tablets containing a 0.1 mg dose

Compound of Example 2	100 mg
Hydroxypropylcellulose	2 g
Wheat starch	10 g
Lactose	100 g
Magnesium stearate	3 g
Talc	3 g

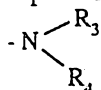
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS :

1. A compound of formula (I):



in which:

- 5 X represents an oxygen atom or a methylene group,
 n represents 1, 2 or 3,
 R₁ represents a hydrogen atom, an aminocarbonyl group or a hydroxymethyl group,
 R₂ represents a group:



10 in which:

either R₃ represents a hydrogen atom or a linear or branched (C₁-C₆) alkyl group,
 and R₄ represents:

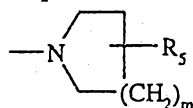
* a linear or branched (C₁-C₄) alkyl group

- which is unsubstituted or substituted with a phenyl group (which may or may not be substituted with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, trihalomethyl groups or hydroxyl groups), on condition that, in these cases, R₁ is other than a hydrogen atom,

- or which is substituted with a benzoylamino group (which may or may not be substituted on the phenyl ring with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, trihalomethyl groups or hydroxyl groups),

* or a benzoyl group (which may or may not be substituted with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, trihalomethyl groups or hydroxyl groups).

or R₃ and R₄ form, together with the nitrogen atom to which they are attached, a group:



in which:

m represents 1, 2 or 3,

- 30 R₅ represents a benzoyl (which may or may not be substituted with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear

or branched (C₁-C₄) alkoxy groups, hydroxyl groups or trihalomethyl groups),

benzoylmethyl (which may or may not be substituted on the phenyl ring with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, hydroxyl groups or trihalomethyl groups),

2-oxo-(3H)-benzimidazol-1-yl,

1H-indazol-3-ylmethyl (which may or may not be substituted on the phenyl ring with a halogen atom),

or 1,2-benzisoxazol-3-ylmethyl group (which may or may not be substituted on the phenyl ring with a halogen atom),

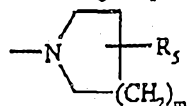
an enantiomer, diastereoisomer or epimer thereof, or an addition salt thereof with a pharmaceutically acceptable acid or base.

2.A compound of formula (I) as claimed in claim 1, in which X represents an oxygen atom, an enantiomer, diastereoisomer or epimer thereof, or an addition salt thereof with a pharmaceutically acceptable acid or base.

3.A compound of formula (I) as claimed in claim 1, in which X represents a methylene group, an enantiomer, diastereoisomer or epimer thereof, or an addition salt thereof with a pharmaceutically acceptable acid or base.

4.A compound of formula (I) as claimed in claim 1, in which X represents an oxygen atom and R₁ represents a hydrogen atom, an enantiomer, diastereoisomer or epimer thereof, or an addition salt thereof with a pharmaceutically acceptable acid or base.

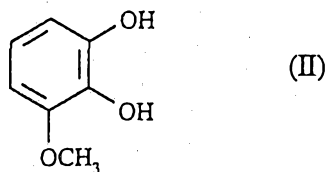
5.A compound of formula (I) as claimed in claim 1, in which R₃ and R₄ form, together with the nitrogen atom to which they are attached, a group:



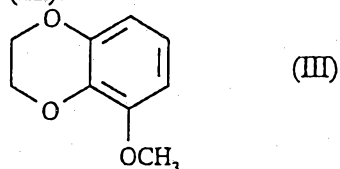
in which m and R₅ are as defined in claim 1, an enantiomer, diastereoisomer or epimer thereof, or an addition salt thereof with a pharmaceutically acceptable acid or base.

6.The compound of formula (I) as claimed in claim 1 which is 5-{2-[3-(4-fluorobenzoylmethyl)pyrrolidin-1-yl]ethoxy}-1,4-benzodioxane, an enantiomer thereof or an addition salt thereof with a pharmaceutically acceptable acid.

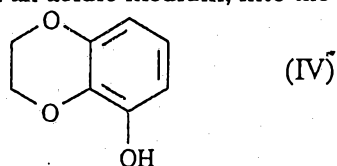
7. A process for the preparation of compounds of formula (I), such that X represents an oxygen atom and R₁ represents a hydrogen atom, wherein a compound of formula (II) is used as starting material:



5 which compound is reacted with 1,2-dibromoethane in the presence of potassium carbonate and copper powder in an alcoholic medium, to give the compound of formula (III):

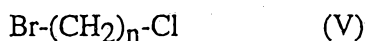


which compound is converted, in an acidic medium, into the compound of formula (IV):



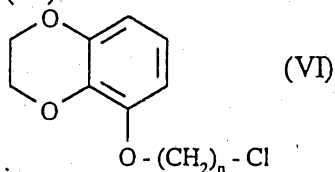
which compound of formula (IV) is condensed:

either with a compound of formula (V), after reacting with sodium ethoxide:



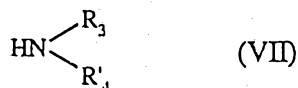
in which n has the same meaning as in the formula (I),

to give the compound of formula (VI):



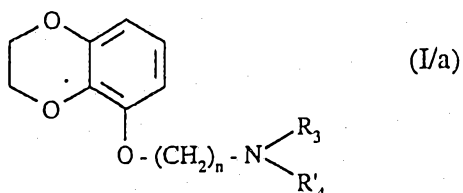
in which n has the same meaning as in the formula (I),

which compound is then reacted with an amine of formula (VII), the isomers of which have optionally been separated:



in which R'₄ has the same meaning as R₄ except for the case where R₄ represents a substituted or unsubstituted benzoyl group,

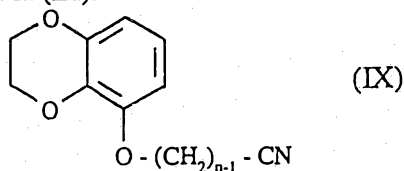
to give the compound of formula (I/a), a specific case of the compounds of formula (I):



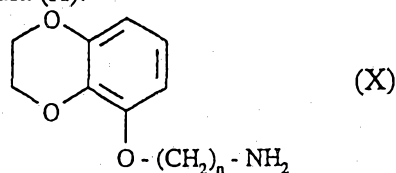
in which n, R₃ and R'₄ have the same meaning as above,
or with a nitrile of formula (VIII), in a basic medium,



- 5 in which n has the same meaning as in the formula (I),
 to give the compound of formula (IX):



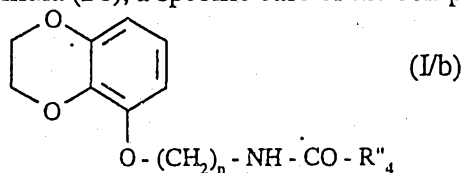
in which n has the same meaning as in the formula (I),
 which compound is reduced using lithium aluminum hydride,
 10 to give the compound of formula (X):



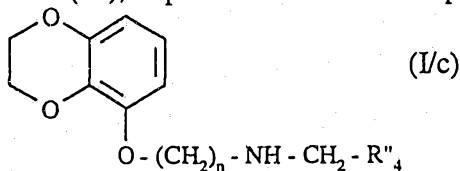
in which n has the same meaning as in the formula (I),
 which compound is reacted with an acid chloride of formula (XI):



in which R''₄ represents a phenyl group (which may or may not be substituted with one or
 more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄)
 alkoxy groups, trihalomethyl groups or hydroxyl groups),
 to give the compound of formula (I/b), a specific case of the compounds of formula (I):



- 20 in which n and R''₄ have the same meaning as above,
 which compound of formula (I/b) may, if so desired, undergo a reduction in the presence of
 tetrabutylammonium borohydride,
 to give the compound of formula (I/c), a specific case of the compounds of formula (I):

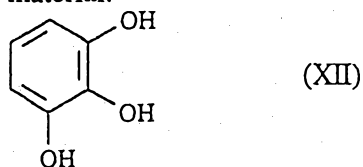


in which n and R₄ have the same meaning as above,

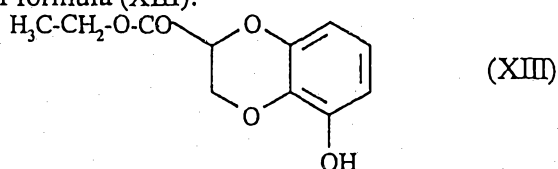
which compound of formula (I/a), (I/b) or (I/c):

- may be purified, if required, according to a standard purification technique, and
- the isomers of which are, if required, separated according to a standard separation technique,
- 5 and
- which is converted, if so desired, into the addition salts thereof with a pharmaceutically acceptable base.

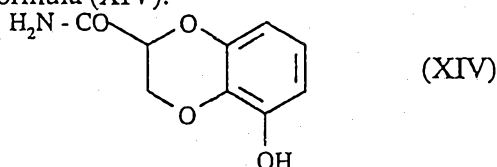
8. A process for the preparation of compounds of formula (I), such that X represents an oxygen atom and R₁ represents an aminocarbonyl or hydroxymethyl group, wherein a compound of formula (XII) is used as starting material:



which compound is reacted with ethyl 2,3-dibromopropionate, in a basic medium, to give the compound of formula (XIII):

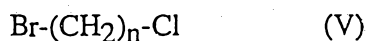


which compound is reacted, if so desired, in an ammoniacal solution, to give the compound of formula (XIV):



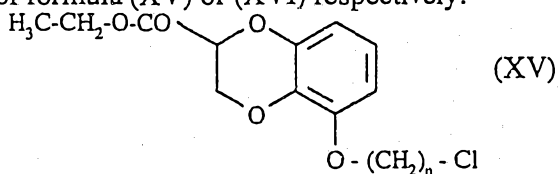
which compound of formula (XIII) or (XIV) is condensed:

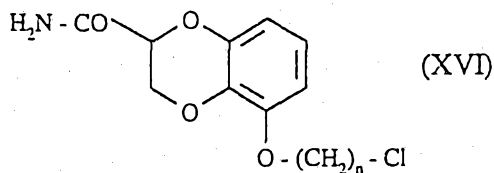
either with a compound of formula (V):



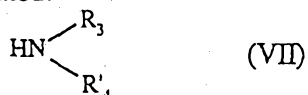
in which n has the same meaning as in the formula (I),

to give the compounds of formula (XV) or (XVI) respectively:



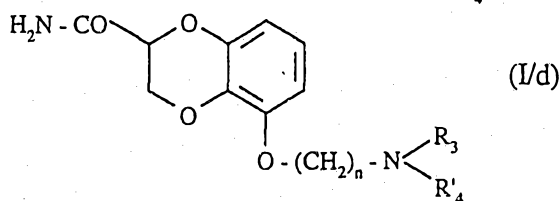
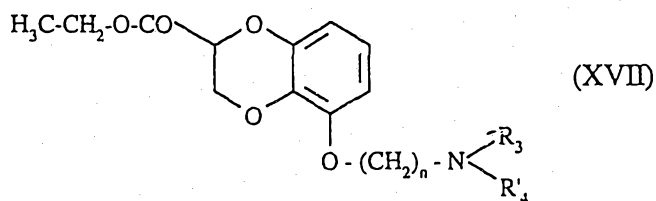


in which n has the same meaning as in the formula (I),
 which compounds are reacted respectively with an amine of formula (VII), the isomers of
 which have optionally been separated:

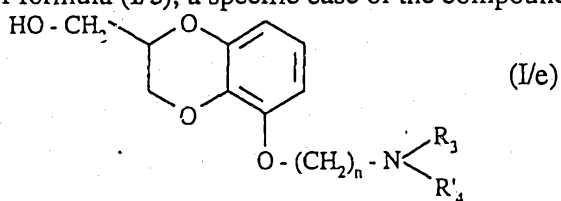


5

in which R'4 has the same meaning as R4, except for the case where R4 represents a
 substituted or unsubstituted benzoyl group,
 to give the compounds of formula (XVII) or (I/d), a specific case of the compounds of formula
 (I):



in which n, R3 and R'4 have the same meaning as above,
 which compound of formula (XVII) is reduced in the presence of lithium aluminum hydride,
 to give the compound of formula (I/e), a specific case of the compounds of formula (I):

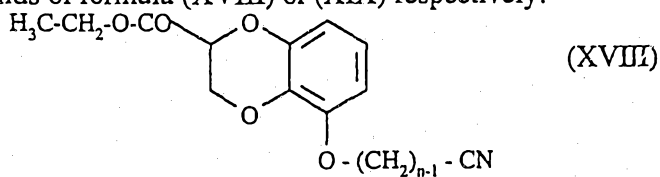


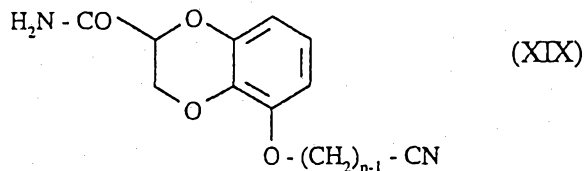
in which n, R3 and R'4 have the same meaning as in the formula (I),
or with a nitrile of formula (VIII), in a basic medium,



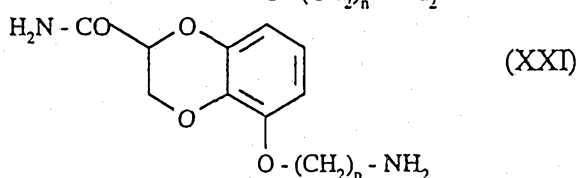
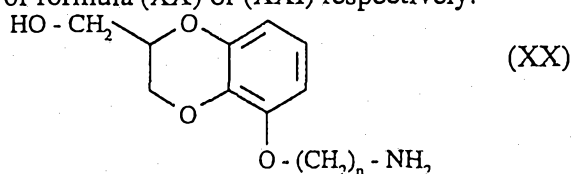
in which n has the same meaning as in the formula (I),
 to give the compounds of formula (XVIII) or (XIX) respectively:

20





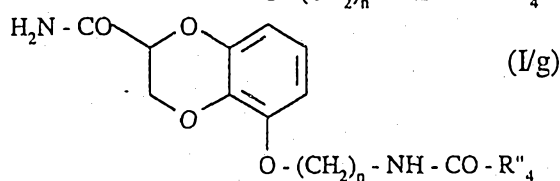
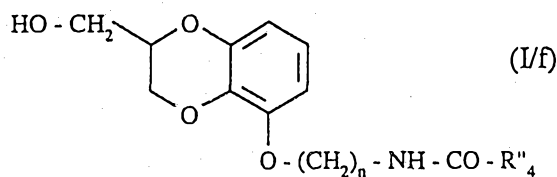
in which n has the same meaning as in the formula (I),
 which compound is reduced using lithium aluminum hydride,
 to give the compounds of formula (XX) or (XXI) respectively:



in which n has the same meaning as in the formula (I),
 which compounds are reacted, respectively, with an acid chloride of formula (XI):

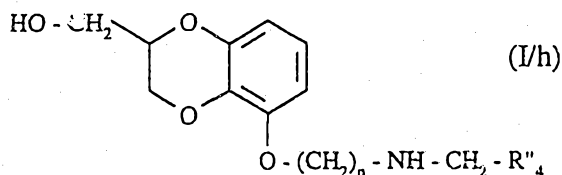


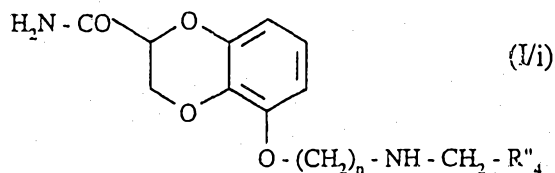
in which R"₄ represents a phenyl group (which may or may not be substituted with one or more halogen atoms or linear or branched (C₁-C₄) alkyl groups, linear or branched (C₁-C₄) alkoxy groups, trihalomethyl groups or hydroxyl groups),
 to give the compounds of formula (I/f) or (I/g) respectively, specific cases of the compounds of formula (I):



in which n and R"₄ have the same meaning as above,
 which compounds of formula (I/f) or (I/g) may, if so desired, undergo a reduction in the presence of tetrabutylammonium borohydride,

to give the compounds of formula (I/h) or (I/i) respectively, specific cases of the compounds of formula (I):





in which n and R''₄ have the same meaning as above,

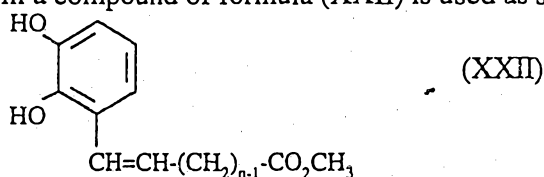
which compound of formula (I/d), (I/e), (I/f), (I/h) or (I/i):

- may be purified, if required, according to a standard purification technique, and

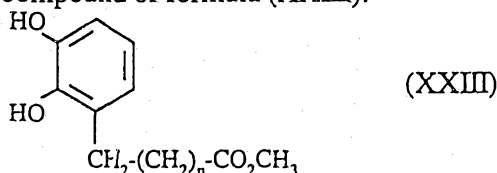
5 - the isomers of which are, if required, separated according to a standard separation technique, and

- which is converted, if so desired, into the salts thereof with a pharmaceutically acceptable base.

9.A process for the preparation of compounds of formula (I), such that X represents a methylene group, wherein a compound of formula (XXII) is used as starting material:

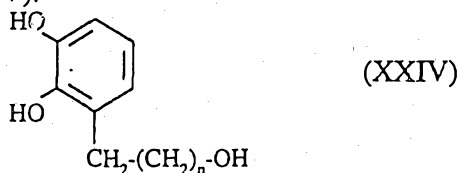


in which n has the same meaning as in the formula (I), which undergoes a catalytic hydrogenation to give the compound of formula (XXIII):



in which n has the same meaning as in the formula (I),

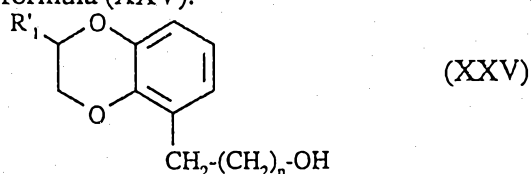
which compound is reduced in the presence of lithium aluminum hydride, to give the compound of formula (XXIV):



in which n has the same meaning as in the formula (I),

20 which compound is reacted with 1,2-dibromoethane or with ethyl 2,3-dibromopropionate, depending on the derivative of formula (I) which it is desired to obtain,

to give the compound of formula (XXV):

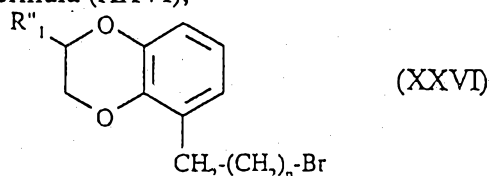


in which R'₁ represents a hydrogen atom or an ethoxycarbonyl group,

which compound of formula (XXV) (which, when R[']₁ represents an ethoxycarbonyl group, may, if so desired, be subjected to the action of an ammoniacal solution, to give the corresponding amide),

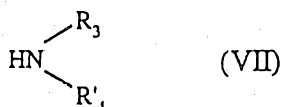
is then reacted with carbon tetrabromide in the presence of triphenylphosphine,

5 to give the compound of formula (XXVI),



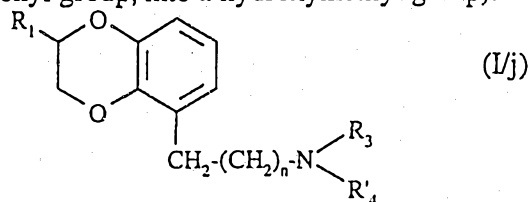
in which n has the same meaning as in the formula (I), and R[']₁ represents a hydrogen atom or an ethoxycarbonyl or aminocarbonyl group,

10 which compound is then reacted with an amine of formula (VII), the isomers of which have optionally been separated:



in which R'₄ has the same meaning as R₄, except for the case where R₄ represents a substituted or unsubstituted benzoyl group,

to give the compound of formula (Ij), a specific case of the compounds of formula (I) (after conversion, in the presence of lithium aluminium hydride, of the group R[']₁, when it represents an ethoxycarbonyl group, into a hydroxymethyl group):



in which R₁, n, R₃ and R'₄ have the same meaning as above, which compound of formula (Ij):

- may, if required, be purified according to a standard purification technique, and
- the isomers of which are separated, if required, according to a standard separation technique, and
- which is converted, if so desired, into the addition salts thereof with a pharmaceutically acceptable base.

10. A pharmaceutical composition containing, as active principle, at least one compound as claimed in any one of claims 1 to 6, alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic vehicles.

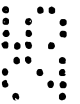
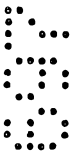
11. A method of treating Schizophrenia comprising the administration of a pharmaceutical composition as claimed in claim 10 containing at least one active principle as claimed in one of claims 1 to 6 to a patient in need thereof.

DATED this 18th day of June, 1997

ADIR ET COMPAGNIE

WATERMARK PATENT & TRADEMARK ATTORNEYS
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HAWTHORN VICTORIA 3122
AUSTRALIA

LCG:SI:KR DOC 14 AU1344895.WPC



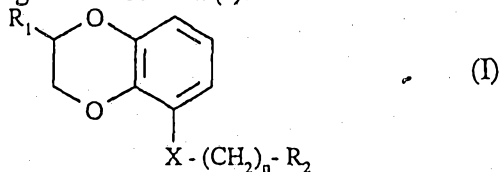
ABSTRACT

NEW BENZODIOXANE COMPOUNDS,
PROCESS FOR THEIR PREPARATION
AND THE PHARMACEUTICAL COMPOSITIONS WHICH CONTAIN THEM

5

ADIR ET COMPAGNIE
1 rue Carle Hébert
92415 COURBEVOIE Cedex

Compounds of general formula (I):



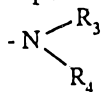
10 in which:

X represents an oxygen atom or a methylene group,

n represents 1, 2 or 3,

R_1 represents a hydrogen atom, an aminocarbonyl group or a hydroxymethyl group,

R_2 represents a group:



15 in which R_3 and R_4 are as defined in the description,

the isomers thereof and the addition salts thereof with a pharmaceutically acceptable acid or base.

Medicaments.