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(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM P.L.C.** [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **WARD, Neal** [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills Near Leigh, Tonbridge, Kent TN11 9AN (GB).

(74) Agents: **WEST, Vivien** et al.; Smithkline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

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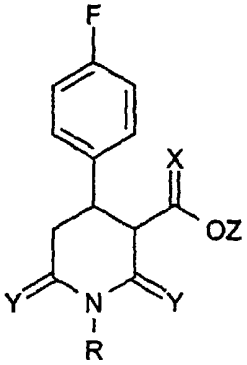
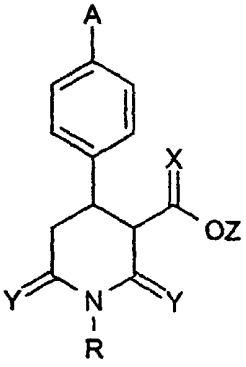


(1)



(2)

(57) Abstract: Formula (1) is prepared by reacting Formula (2) with a fluorinating agent.

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NOVEL PROCESS

The present invention relates to a new process for preparing pharmaceutically active compounds and intermediates therefor.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-) *trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-phenoxymethyl)-piperidine. This compound is used in therapy as the hydrochloride salt to treat *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

This invention aims to overcome disadvantages in the existing processes for preparation of such compounds and so to provide alternative processes for their manufacture.

This invention has been developed on the basis that compounds of structure (1) below are either valuable chemical intermediates useful for the manufacture of important medicinal products, for example paroxetine hydrochloride, or are themselves active compounds, such as disclosed in US-A-4007196.

By reference to Example 4 of US 4007196, paroxetine may be prepared from a compound of structure (1) below in which R is methyl, X and Y are each two hydrogen atoms and Z is also hydrogen, that is 4-(4'-fluorophenyl)-3-hydroxymethyl-l-methylpiperidine, by reaction with 3,4-methylenedioxyphenol followed by demethylation. In the same Example, 4-(4'-fluorophenyl)-3-hydroxymethyl-1-methyl piperidine is prepared by reduction of 4-(4'-fluorophenyl)-3-hydroxymethyl-1-methyl -1,2,3,6-tetrahydropyridine which is in turn prepared from 4-(4'-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine by reaction with formaldehyde. US 4007196 also describes the preparation of 4-(4'-fluorophenyl)-3-hydroxymethyl-l-methylpiperidine, by reduction of a compound of structure (1) in which R is methyl, X is oxygen, Y represents two hydrogen atoms and Z is a methyl group, that is 4-(4'-fluorophenyl)-3-methoxycarbonyl-l-methylpiperidine.

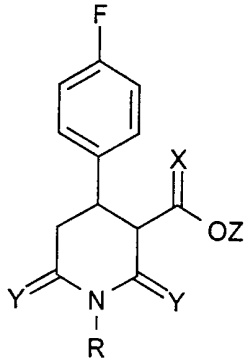
Alternative processes for the preparation of 4-(4'-fluorophenyl)-3-hydroxymethyl-l-methylpiperidine are given in EP-A-0223334 by reduction of a compound of structure (1) where R is a methyl group, X and Y are oxygen atoms and Z is a methyl or ethyl group.

The above described processes produce compounds of structure (1) as a mixture of enantiomers. Therefore conversion of compounds of structure (1) to useful pharmaceuticals, such as paroxetine i.e. the (-) *trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-phenoxymethyl)-piperidine, will normally require a resolution stage, as described in EP-A-0223334.

The structure of paroxetine incorporates a fluorine atom in the 4-position of a phenyl ring, and it is well known that fluorine containing starting materials are more expensive than those containing other common substituents such as chlorine. In all known processes for the preparation of paroxetine, the 4-fluoro substituent is introduced at a very early stage, so that a significant proportion of the fluorine introduced at the beginning of the synthesis is lost during subsequent processing as by-products or unwanted isomers.

This invention provides a more efficient process for the preparation of 4-(4'-fluorophenyl) piperidines of structure (1).

According to the present invention, there is provided a process for the preparation of a compound of structure (1)



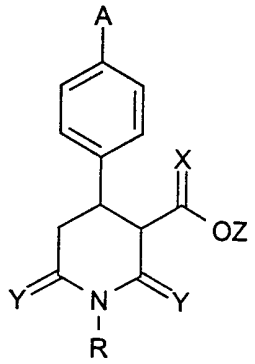
(1)

in which R is hydrogen or an alkyl, aralkyl, aryl, acyl, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl group or other conventional nitrogen protecting group,

X and Y independently represent an oxygen atom or two hydrogen atoms, and

Z is hydrogen or a substituted or unsubstituted alkyl, aralkyl or aryl group,

which comprises reacting a compound of structure (2)



(2)

where A is a group capable of being replaced by fluorine, and

R, X, Y and Z are as defined above,

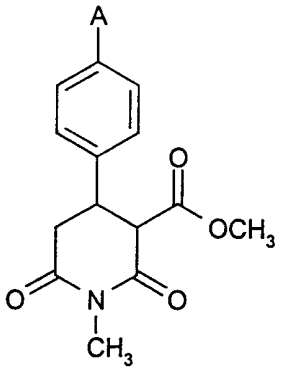
with a fluorinating agent.

When Z is an aryl or alkaryl group, the aryl moiety, for example phenyl, may be optionally substituted by one or more groups such as halogen or alkyl or alkoxy, or by two substituents linked to form a fused ring. For example, an especially suitable substituent Z is 3,4-

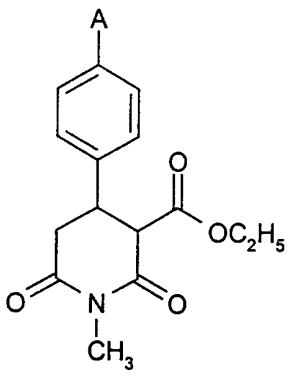
methylenedioxyphenyl, as found in paroxetine. Alkyl groups, including alkyl groups that are part of other moieties such as alkoxy or acyl, are typically C_{1-6}, especially C_{1-4} groups, such as methyl and ethyl.

Suitable groups A include amino, protected amino (such as acetylamino or benzoylamino) hydrogen, nitro, chlorine, bromine, iodine or trimethylsilyl. Especially preferred compounds of structure (2) are those where R is a hydrogen atom or a methyl or ethyl group.

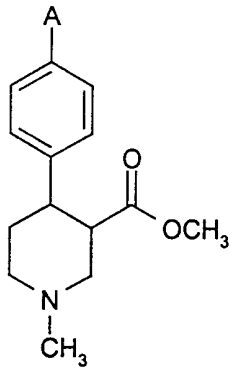
Most preferred compounds of structure (2) are represented by structures (2a) to (2g):



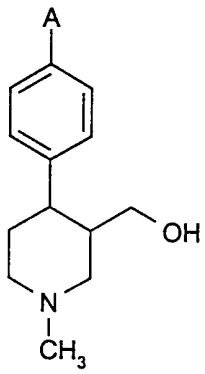
(2a)



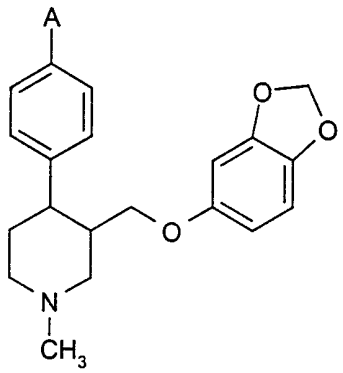
(2b)



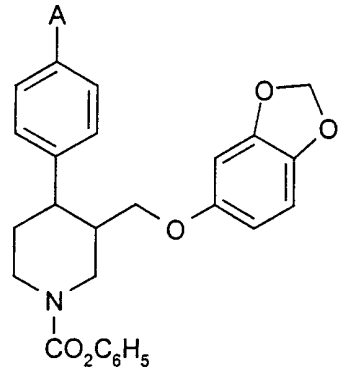
(2c)



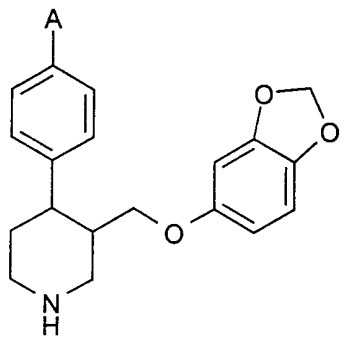
(2d)



(2e)



(2f)



(2g)

Where A is amino or protected amino, the fluorination reaction is conveniently carried out via a diazonium salt intermediate using a reagent such as sodium nitrite and HF in pyridine at ambient or below ambient temperature using procedures analogous to those described in the Journal of Fluorine Chemistry (1991) volume 51 page 299, and Tetrahedron (1996) volume 52 page 23.

Where A represents groups such as hydrogen, nitro, chlorine, bromine, iodine or trimethylsilyl, the introduction of fluorine may be carried out by direct reaction with a fluorinating agent such as potassium fluoride, rubidium fluoride, tetramethylammonium fluoride or tetrabutylammonium fluoride at ambient or elevated temperature in a suitable solvent such as dimethyl sulphoxide, sulpholane, dimethyl formamide or tetrahydrofuran, using procedures analogous to those described in the Journal of Chemical Research, Synopses (1994) volume 12 page 478.

The resulting compounds of structure (1) are either valuable chemical intermediates useful for the manufacture of important medicinal products, for example paroxetine hydrochloride, or are themselves active compounds, such as disclosed in US-A-3912743 and US-A-4007196.

Compounds of structure (2a) and (2b) and similar compounds may be prepared by the reaction of an ester of a suitably substituted cinnamic acid with a substituted malonic acid derivative using procedures analogous to those set out in EP-A-0223334. For example, the reaction of

ethyl-4-bromophenyl cinnamate with ethyl-N-methylamidomalonate gives N-methyl-3-ethoxycarbonyl-4-bromophenyl)-piperidine-2,6-dione, compound (2b), A=Br.

Compounds of structure (2c) and similar compounds may be prepared by the reaction of arecoline or analogues with other nitogen substituents with a suitably substituted Grignard reagent, following procedures analogous to those described in the Journal of Organic Chemistry (1957) volume 22 page 261. For example the reaction of phenyl magnesium bromide with arecoline gives a compound of structure (2c) where A is hydrogen. Compounds of structure (2c) may also be prepared by reduction of the corresponding pyridinium esters using methods analogous to those described in EP 0219934.

Compounds of structure (2d) may be prepared by reduction of compounds of structure (2a), (2b) or (2c) using a metal hydride such as lithium aluminium hydride as described in EP-A-0223334 or US-A-4007196.

Compounds of structure (2e) may be prepared by the reaction of compounds of structure (2d) with sesamol, as described in US-A-4007196.

Compounds of structure (2f) and similar compounds with other substituents on the ring nitrogen may be prepared by the reaction of compounds of structure (2e) with a chloroformic ester, for example phenyl chloroformate, chloroethyl chloroformate or vinyl chloroformate as described in US-A-4007196 and EP 0223403.

Compounds of structure (2g) may be prepared by hydrolysis of compounds of structure (2f) using, for example, potassium hydroxide in methyl Cellusolve as described in US-A-4007196.

Where intermediate compounds in the process of this invention are novel, such intermediates form another aspect of this invention.

Compounds of structure (1) are active compounds, such as disclosed in US-A-4007196, or are valuable chemical intermediates useful for the manufacture of such compounds. Thus in a

further aspect of the invention, a compound of structure (1) obtained by a process of this invention is converted to paroxetine using the procedures disclosed in US-A-3912743, US-A-4007196 or EP-A-0223334, typically by selecting one or more of the steps of reduction, condensation with 3,4-methylenedioxyphenol, and removal of a group R that is other than hydrogen.

As mentioned above a resolution step may be required during these procedures.

Paroxetine is preferably obtained as the hydrochloride salt and most preferably as the hemihydrate of that salt, as described in EP-A-0223403. The present invention includes within its scope the compound paroxetine, particularly paroxetine hydrochloride, especially as the hemihydrate, when obtained via any aspect of this invention, and any novel intermediates resulting from the described procedures.

Paroxetine obtained using this invention may be formulated for therapy in the dosage forms described in EP-A-0223403 or WO96/24595, either as solid formulations or as solutions for oral or parenteral use.

Therapeutic uses of paroxetine, especially paroxetine hydrochloride, obtained using this invention include treatment of: alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the disorders".

The compositions prepared in accordance with this invention are usually adapted for oral administration, but formulations for dissolution for parental administration are also within the scope of this invention.

The composition is usually presented as a unit dose composition containing from 1 to 200mg of active ingredient calculated on a free base basis, more usually from 5 to 100 mg, for example 10 to 50 mg such as 10, 12.5, 15, 20, 25, 30 or 40 mg by a human patient. Most

preferably unit doses contain 20 mg of active ingredient calculated on a free base basis. Such a composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 5 to 400 mg of active ingredient calculated on a free base basis. Most preferably the unit dose is taken once a day.

Preferred unit dosage forms include tablets or capsules, including formulations adapted for controlled or delayed release.

The compositions of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing. Suitable carriers for use in this invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or preservative. These agents may be utilized in conventional manner, for example in a manner similar to that already used for marketed anti-depressant agents.

Accordingly, the present invention also provides:

a pharmaceutical composition for treatment or prophylaxis of the disorders comprising paroxetine or paroxetine hydrochloride obtained using the process of this invention and a pharmaceutically acceptable carrier,

the use of paroxetine or paroxetine hydrochloride obtained using the process of this invention to manufacture a medicament in solid or liquid form for the treatment or prophylaxis of the disorders; and

a method of treating the disorders which comprises administering an effective or prophylactic amount of paroxetine or paroxetine hydrochloride obtained using the process of this invention to a person suffering from one or more of the disorders.

The invention is illustrated by the following Examples.

Example 1

Preparation of ethyl 4-nitrocinnamate

Absolute ethanol (0.5 ml) was slowly added to a mixture of sodium powder (3.6 g, 0.156 mol) and 60 ml ethyl acetate. The resulting mixture was cooled to 0°C and 4-nitrobenzaldehyde (17.0 g, 0.112 mol) was added, keeping the temperature below 5°C. Maintaining the same temperature, the mixture was stirred for 1 hour and glacial acetic acid (13 ml) was added slowly, followed by water (100 ml). The ethyl acetate phase was separated, washed with water (50 ml), dried with magnesium sulphate, filtered and evaporated. Crystallization from hexane afforded 6.2 g of ethyl 4-nitrocinnamate.

Example 2

Synthesis of diethyl 2-cyano-3-(4-nitrophenyl)glutarate.

A mixture of ethyl cyanoacetate (3.0 g, 0.026 mol) and ethyl 4-nitrocinnamate (2.2 g, 0.01 mol) was added at 5°C to a solution of potassium tert-butoxide (2.4 g, 20 mmol) in 12 ml tetrahydrofuran. The mixture was heated under reflux for 4 hours then cooled to 5°C. Glacial acetic acid (1.5 ml), then water (10 ml) were added slowly to the reaction mixture, keeping the temperature below 5°C. The mixture was extracted with dichloromethane (3 x 30 ml) and the combined organic phases dried with anhydrous sodium sulfate, filtered and evaporated to give a solidifying oil. Chromatography (silica gel SG-60; gradient hexane-ethyl acetate) gave 2.84 g of the title compound.

Example 3

Synthesis of ethyl 4-(4-aminophenyl)-6-oxopiperidine-3-carboxylate.

Adams catalyst (0.1 g) and a 4 *M* solution of hydrogen chloride in dioxane was added to a solution of diethyl 2-cyano-3-(4-nitrophenyl)glutarate (0.7 g, 1.8 mmol) in dioxane (10 ml). The mixture were stirred in a Buchi Miniclave glass apparatus under hydrogen (7 p.s.i) at 35-40°C for 4 hours and at 25°C overnight. The reaction mixture was then diluted with water (50 ml), filtered and evaporated. The resulting residue was dissolved in water (5 ml), made alkaline with 10% sodium hydroxide solution and extracted with dichloromethane (3 x 20 ml).

Removal of the solvent at reduced pressure gave the title compound as a mixture of trans- and cis-isomers (1:1). Yield 80%.

Part of the product was purified by column chromatography (silica gel; eluent hexane-ethyl acetate-methanol gradient). M/z = 262.

Example 4

Synthesis of ethyl 4-(4-nitrophenyl)-2,6-dioxopiperidine-3-carboxylate.

A solution of ethyl malonamide (2.62 g, 20 mmol) in tetrahydrofuran (10 ml) was added, at 5°C, to a solution of potassium tert-butoxide (3.5 g, 29 mmol) in tetrahydrofuran (20 ml). Ethyl 4-nitrocinnamate (1.8 g, 8.1 mmol) was then added as a solid, and the mixture stirred and heated under reflux for 3 hours. After cooling to 5°C the mixture was treated with glacial acetic acid (2 ml), and then water (25 ml) was added slowly, keeping the temperature below 5°C. The mixture was extracted with dichloromethane (3 x 30 ml), and the combined organic phases were dried with anhydrous sodium sulphate, filtered and evaporated to a solidifying oil. Chromatography (silica gel SG-60; hexane-ethyl acetate gradient) gave 1.23 g of the title compound (m/z 306), m.pt 179-181°C.

Example 5

Reduction of ethyl 4-(4'-nitrophenyl)-2,6-dioxopiperidine-3-carboxylate to 3-hydroxymethyl-4-(4'-aminophenyl)piperidine

A solution of lithium aluminum hydride in tetrahydrofuran (20 ml, 16 mmol) was added to a solution of ethyl 4-(4'-nitrophenyl)-2,6-dioxopiperidine-3-carboxylate (0.52 mmol) in tetrahydrofuran (9 ml) under an argon atmosphere. The mixture was stirred for 19 hours at 20°C, heated for 76 hours at 60°C and quenched with water (2 ml), then 15% NaOH solution (1 ml), followed by water (5 ml). The reaction mixture was stirred for 0.5 hours to ripen the precipitate and extracted with chloroform (230 ml) and ethyl acetate (30 ml). The filtrates

were combined and evaporated *in vacuo* to afford 0.127 g of the product, 3-hydroxymethyl-4-(4'-aminophenyl)piperidine. Yield 47%.

Example 6

Reduction of ethyl 4-(4'-aminophenyl)-6-oxopiperidine-3-carboxylate to 3-hydroxymethyl-4-(4'-aminophenyl)piperidine

A solution of lithium aluminum hydride in tetrahydrofuran (1.8 ml, 1.45 mmol) was added to a solution of ethyl 4-(4'-aminophenyl)-6-oxopiperidine-3-carboxylate (34 mg, 0.127 mmol) in tetrahydrofuran (5 ml) under an argon atmosphere. The mixture was heated for 24 hours at 60°C and treated with further lithium aluminum hydride solution (1.8 ml, 1.45 mmol). After additional heating for 20 hours the reaction mixture was cooled to 5°C and quenched with water (0.32 ml), then 15% NaOH solution (0.16 ml), followed by water (0.8 ml). The reaction mixture was stirred for 0.75 hour to ripen the precipitate and extracted with chloroform (220 ml). The filtrates were combined and evaporated *in vacuo* to afford 3-hydroxymethyl-4-(4'-aminophenyl)piperidine.

Example 7

Preparation of ethyl 1-methyl-4-(4'-nitrophenyl)-2,6-dioxopiperidine-3-carboxylate

A solution of methyl N-methylmalonamide (80% purity, 1.0 g, 6.89 mmol) in tetrahydrofuran (3 ml) was added to a solution of potassium tert-butoxide (1.3 g, 10.7 mmol) in tetrahydrofuran (20 ml) under an argon atmosphere, followed by ethyl p-nitrocinnamate (1.0 g, 4 mmol). The mixture was heated with stirring for 1 hour at 65°C and quenched with a solution of acetic acid (0.7 ml) in water (10 ml). The reaction products were extracted with dichloromethane (225 ml). After washing with water (10 ml), drying with anhydrous sodium sulfate, filtering and evaporation, 1.3 g of the crude product was obtained. The residue was adsorbed with 5 cc of silica gel SG-60 (60-230 mm) in dichloromethane and, after removal the solvent, was placed at the top of the column ID 10 mm, packed with 20 cc of the silica gel. Eluting with a ethyl acetate-hexane mixture (40:60) afforded 0.88 g of ethyl 1-methyl-4-(4'-nitrophenyl)-2,6-dioxopiperidine-3-carboxylate.

Yield 60%.

Example 8

Reduction of ethyl 1-methyl-4-(4'-nitrophenyl)-2,6-dioxopiperidine-3-carboxylate to ethyl 1-methyl-4-(4'-aminophenyl)-2,6-dioxopiperidine-3-carboxylate with iron powder

A suspension of iron powder (4.41 g, 78 mmol) and ferrous sulfate (0.44 g) in water (44 ml) was treated with 32% hydrochloric acid (0.9 ml), followed by ethyl 1-methyl-4-(4'-nitrophenyl)-2,6-dioxopiperidine-3-carboxylate (1.27 g, 3.9 mmol). The reaction mixture was heated for 16 hours at 90°C in tetrahydrofuran (30 ml, 24 mmol), allowed to cool to room temperature, diluted with ethanol (175 ml), and the solvent was syphoned off. The residue was washed with ethanol (50 ml). The filtrates were combined and evaporated, the residue of water was removed as an azeotrope with toluene, affording 1.38 g of the desired ethyl 1-methyl-4-(4'-aminophenyl)-2,6-dioxopiperidine-3-carboxylate.

Example 9

Reduction of ethyl 1-methyl-4-(4'-aminophenyl)-2,6-dioxopiperidine-3-carboxylate to 1-methyl-3-hydroxymethyl-4-(4'-aminophenyl)piperidine

A ca. 1M solution of lithium aluminum hydride in tetrahydrofuran (85 ml, 60 mmol) was added to a solution of the crude ethyl 1-methyl-4-(4'-aminophenyl)-2,6-dioxopiperidine-3-carboxylate (1.3 g, 3.56 mmol) in tetrahydrofuran (30 ml) under an argon atmosphere. The mixture was heated for 4 hours at 60°C and quenched with water (7 ml), then 15% NaOH solution (15 ml), followed by water (33 ml). The reaction mixture was stirred for 0.5 hour for completion of the precipitation and extracted with chloroform (250 ml). The extracts were combined and evaporated *in vacuo* to afford 0.53 g of the crude product as a slightly colored oil.

The reaction product was placed on top of a column packed with silica gel. Eluting with a ethyl acetate-methanol gradient furnished 0.2g of 1-methyl-3-hydroxymethyl-4-(4'-aminophenyl)piperidine.

Example 10

Preparation of 3-hydroxymethyl-4-(4'-aminophenyl)piperidine by the reduction of ethyl 1-methyl-4-(4'-aminophenyl)-2,6-dioxopiperidine-3-carboxylate

A 1M solution of lithium aluminum hydride in tetrahydrofuran (3.8 ml, 3.8 mmol) was added to a solution of ethyl 1-methyl-4-(4'-aminophenyl)-2,6-dioxopyridine-3-carboxylate (0.23 g) in tetrahydrofuran (2 ml) at 20°C under an argon atmosphere. The mixture was stirred for 2.5 hours at 20°C and quenched with water (0.29 ml), then 15% NaOH solution (0.15 ml), followed by water (0.74 ml), keeping the temperature below 40°C. The reaction mixture was stirred for 0.5 hour for completion of the precipitation, then extracted with chloroform (310 ml). The extracts were combined and evaporated under reduced pressure to afford the crude product as a slightly colored oil. The product was purified by column chromatography (neutral alumina, an ethyl acetate-methanol-gradient). Yield 35%.

Example 11

Reduction of methyl 1-methyl-4-(4'-aminophenyl)-2,6-dioxopiperidine-3-carboxylate to 1-methyl-3-hydroxymethyl-4-(4'-aminophenyl)piperidine

A 1 *M* solution of lithium aluminum hydride in tetrahydrofuran (46 ml, 45.1 mmol) was added gradually to a solution of methyl 1-methyl-4-(4'-aminophenyl)-2,6-dioxopiperidine-3-carboxylate (1.0 g, 3.26 mmol) in tetrahydrofuran (25 ml) under argon, keeping the temperature bellow 35°C. The reaction mixture was heated for 7 hours at 65°C with stirring, allowed to cool to 25°C, and quenched with water (3.6 ml), followed by 15% sodium hydroxide solution (1.8 ml), and again water (9 ml). The mixture was stirred for 1 hour to complete the decomposition of the reaction complex and diluted with chloroform (200 ml). The solid was filtered and washed with chloroform (75 ml). The filtrates were combined, dried with anhydrous magnesium sulfate, filtered and evaporated to give 0.78 g of a crude product,

containing 45% of the desired alcohol. After purification by column chromatography on alumina (neutral, eluent - a ethyl acetate-methanol gradient) 0.40 g of the product with purity >90% was obtained. Yield 57%.

Example 12

Transformation of 1-methyl-3-hydroxymethyl-4-(4'-aminophenyl)piperidine to 1-methyl-3-hydroxymethyl-4-(4'-fluorophenyl)piperidine

A solid sodium nitrite (70 mg, 1.0 mmol) was added in several portions for 5 minutes to a solution of 1-methyl-3-hydroxymethyl-4-(4'-aminophenyl)pyridine in 15% hydrochloric acid (0.8 ml), cooled to 0°C, followed by a cool solution of ammonium tetrafluoroborate (0.3 g, 2.8 mmol) in water (0.9 ml) with vigorous stirring. The reaction mixture stirred overnight at 0°C and water was removed by lyophilization. The residue was covered by toluene (2 ml) and heated in a bath at 110°C. After the cessation of the gas evolution (~30 minutes), the reaction mixture was cooled to 20°C and partitioned between a 5% sodium hydroxide solution (2.5 ml) and ethyl acetate (10 ml). The organic phase was separated, washed with water (5 ml), dried with brine and anhydrous sodium sulfate, filtered and evaporated to afford the crude reaction product,1-methyl-3-hydroxymethyl-4-(4'-fluorophenyl)piperidine. Yield 20%.
High resolution mass spectrometric study (positive ion technique) gave a mass for the product as 224.144920 compared with 224.145068 calculated mass for the desired product.

Example 13

Preparation of 1-methyl-3-hydroxymethyl-4-(4'-pyrrolophenyl)piperidine by protection of the amino group in 1-methyl-3-hydroxymethyl-4-(4'-aminophenyl)piperidine

A solution of 1-methyl-3-hydroxymethyl-4-(4'-aminophenyl)piperidine (0.22 g, 0.88 mmol), acetonylacetone (0.21 g,0.22 ml, 1.82 mmol), and glacial acetic acid (0.032 g, 0.52 mmol) in toluene (3 ml) was heated for 8.5 hours under reflux with a Dean-Stark adapter for the removal of water. After evaporation of the solvent and column chromatography on alumina

(neutral, eluent - hexane-ethyl acetate gradient) 0.24 g of 1-methyl-3-hydroxymethyl-4-(4'-pyrrolophenyl)piperidine with purity >98% was obtained. Yield 91%.

Example 14

Preparation of 1-methyl-3-[(3,4-methylenedioxyphenoxy)methyl]-4-(4'-pyrrolophenyl)piperidine by coupling of 1-methyl-3-hydroxymethyl-4-(4'-pyrrolophenyl)piperidine with sesamol

A solution of benzenesulfonyl chloride (0.203 g, 0.101 ml, 0.67 mmol) in chloroform (1.5 ml) was added gradually to a solution of 1-methyl-3-hydroxymethyl-4-(4'-pyrrolophenyl)piperidine (0.203 g, 0.667 mmol) and dimethylethylamine (0.14 g, 0.104 ml, 1.9 mmol) in chloroform (3 ml), keeping the temperature below 5°C. The reaction mixture was allowed to warm to 20°C and stirred for 4 hours. More of the benzenesulfonyl chloride (0.052 ml, total 1.0 mmol) and dimethylethylamine (0.50 ml, 2.85 mmol) were introduced into the reaction vessel to complete conversion of the substrate. The reaction mixture was stirred for 1 hour at 20°C, and the solvent was removed under reduced pressure. The residue was partitioned between water (10 ml) and diethyl ether (20 ml). The aqueous phase was extracted with an additional amount of diethyl ether (20 ml), followed by dichloromethane (20 + 20 ml). The etheric extracts were discarded. The dichloromethane extracts were combined, dried with anhydrous magnesium sulfate, filtered and evaporated to afford 0.183 g of the crude benzenesulfonate.

A solution of the sulfonate in N,N-dimethylformamide (2 ml) was added to a freshly prepared solution of sodium sesamate [from sesamol (0.1 g, 0.71 mmol) and sodium hydride (60% dispersion in mineral oil, 0.029 g, 0.73 mmol)] in N,N-dimethylformamide (2 ml). The reaction mixture was heated for 1.5 hours at 65°C, cooled to 25°C and partitioned between water (10 ml) and diethyl ether (20 ml). The aqueous phase was extracted with an additional amount of diethyl ether (20 ml) and discarded. The organic extracts were combined, washed with 15% sodium hydroxide solution (20 ml), twice with water (20 ml), and brine, dried with anhydrous magnesium sulfate, filtered and evaporated to give 0.137 g of the crude product, 1-methyl-3-[(3,4-methylenedioxyphenoxy)methyl]-4-(4'-pyrrolophenyl)piperidine. Column

chromatography on alumina (neutral, eluent - a hexane-ethyl acetate-gradient, then methanol) afforded 52 mg of the desired ether.

Example 15

Preparation of 1-methyl-3-[(3,4-methylenedioxyphenoxy)methyl]-4-(4'-aminophenyl)piperidine by deprotection of 1-methyl-3-[(3,4-methylenedioxyphenoxy)methyl]-4-(4'-pyrrolophenyl)piperidine

A solution of hydroxylamine hydrochloride (69.3 mg, 0.99 mmol) in a mixture of water (0.2 ml) and ethanol (0.2 ml) was added to a solution of 1-methyl-3-[(3,4-methylenedioxyphenoxy)methyl]-4-(4'-pyrrolophenyl) piperidine (0.051g, 0.12 mmol) in ethanol (0.4 ml). The reaction mixture was heated under reflux for 42 hours at 65°C and treated with 10% hydrochloric acid (0.2 ml). The mixture was extracted twice with dichloromethane (2 ml) and made alkaline with 15% sodium hydroxide solution. The reaction products were extracted with dichloromethane (2 + 2 ml), the extracts were washed with water (2 and 2 ml), and brine (2 ml), dried with anhydrous sodium sulfate and evaporated to give 27 mg of the desired 1-methyl-3-[(3,4-methylenedioxy-phenoxy)methyl]-4-(4'-aminophenyl)piperidine with 95% purity. Yield 68%.

Example 16

Preparation of 1-methyl-3-[(3,4-methylenedioxyphenoxy)methyl]-4-(4'-fluorophenyl)piperidine by diazotization-fluorination of 1-methyl-3-[(3,4-methylenedioxyphenoxy)-methyl]-4-(4'-aminophenyl)piperidine

Solid sodium nitrite (5 mg, 0.072 mmol) was added in two portions to a solution of 1-methyl-3-[(3,4-methylenedioxyphenoxy)-methyl]-4-(4'-aminophenyl)piperidine (20 mg, 0.058 mmol) in 32% hydrochloric acid (0.025 ml), cooled to 0°C, followed by a cool solution of ammonium tetrafluoroborate (17 mg, 0.157 mmol) in water (0.075 ml) with vigorous stirring. The reaction mixture was stirred overnight at 0°C and water was removed by lyophilization. The residue was covered with toluene (2 ml) and heated in a bath at 110°C. After cessation of gas

evolution (~30 minutes), the reaction mixture was cooled to 20°C and partitioned between a 15% sodium hydroxide solution (0.5 ml) and ethyl acetate (2 ml). The organic phase was separated, washed with water (0.5 ml), dried with brine and anhydrous sodium sulfate, filtered and evaporated to afford the desired product.

High resolution mass spectrometry (positive ion technique) gave the expected mass value for the product, 343.158644 compared with 343.158372 calculated for C20H22NO3F.

Example 17

Preparation of paroxetine hydrochloride by the resolution of (±) trans 4-(4'-fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl) piperidine.

i) (±) trans 4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxymethyl) piperidine (1.0 g) was dissolved in methanol (10 ml) and added to a solution of L(-)-di-p-toluoyl tartaric acid (1.25g) in methanol (10 ml). The mixture was seeded and allowed to stand at room temperature and the crystalline product examined by chiral HPLC, using the following system: Column:Chiralpak AD (Diacel Chemical Industries)Dimensions / particle size:250 x 4.6mm , 10umEluent: Hexane/Ethanol/Trifluoroacetic acid
88 : 12 : 0.06Eluent flow rate:1 ml/minuteDetection:UV at 295 nmColumn temperature:25°CInjection volume:20 microlitreConditions: IsocraticSample preparation:0.3 mg/ml in hexane/ethanol/methanol
80 : 10 : 10

Chiral HPLC analysis confirmed that substantially pure (-) trans L(-)-di-p-toluoyl tartrate salt had been isolated. The salt may be further purified by recrystallisation from methanol.

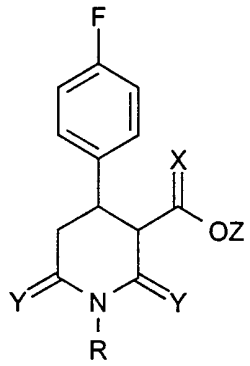
ii) (±) trans 4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxymethyl) piperidine (0.50 g) was dissolved in acetonitrile (10 ml) and added to a solution of L (-)-dibenzoyl tartaric acid (0.65g) in acetonitrile (10 ml). The mixture was seeded and stirred at room temperature. The

crystalline product was shown by chiral HPLC to be significantly enriched with the (-) trans dibenzoyl tartrate salt.

iii) Paroxetine free base is liberated from the (-) trans 4-(4'-fluoro-phenyl)-3-(3'4'-methylenedioxyphenoxymethyl) piperidine di-p-toluoyl or dibenzoyl tartrate salt by stirring in a mixture of toluene and dilute aqueous sodium hydroxide. The phases are separated and the toluene phase washed with water and dried by azeotropic distillation. Methanesulphonic acid is then added and the crystalline precipitate collected by filtration and dried.

CLAIMS

1. A process for the preparation of a compound of structure (1)



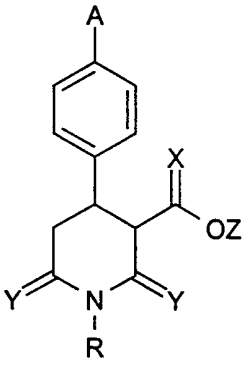
(1)

in which R is hydrogen or an alkyl, aralkyl, aryl, acyl, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl group or other conventional nitrogen protecting group,

X and Y independently represent an oxygen atom or two hydrogen atoms, and

Z is hydrogen or an optionally substituted alkyl, aralkyl or aryl group,

which comprises reacting a compound of structure (2)



(2)

where A is a group capable of being replaced by fluorine, and

R, X, Y and Z are as defined above,

with a fluorinating agent.

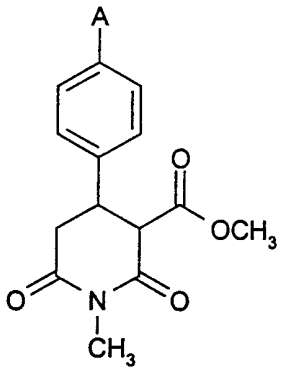
2. A process according to claim 1 in which both X and Y are two hydrogen atoms and Z is hydrogen or 3,4-methylenedioxyphenyl.

3. A process according to claim 1 in which X and Y are oxygen and Z is methyl or ethyl.

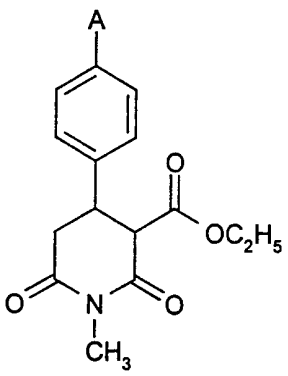
4. A process according to claim 1 in which X is oxygen, Y is two hydrogen atoms and Z is methyl or ethyl.

5. A process according to any one of claims 1 to 4 in which R is hydrogen or methyl.

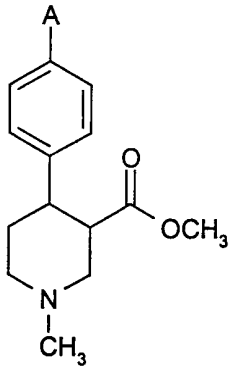
6. A process according to claim 1 in which the compound of structure (2) is one of:



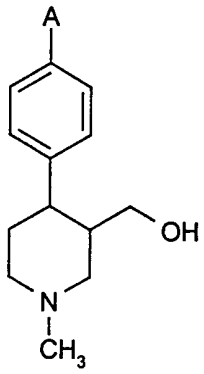
(2a)



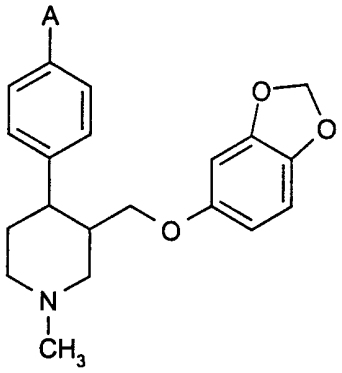
(2b)



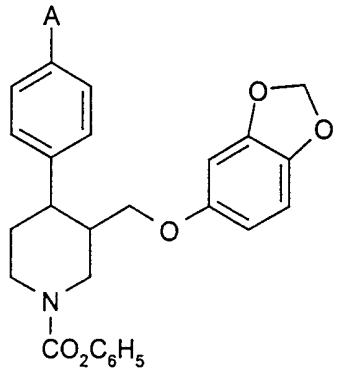
(2c)



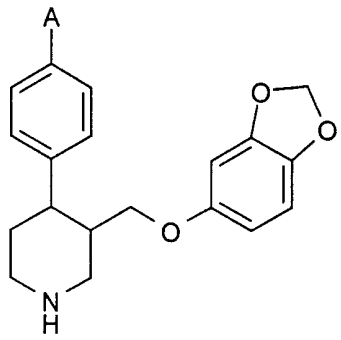
(2d)



(2e)



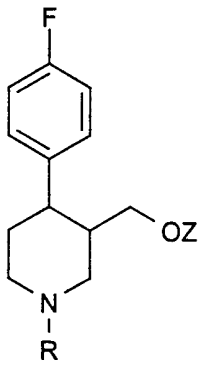
(2f)



(2g)

7. A process according to any one of claims 1 to 6 in which A is amino, protected amino, hydrogen, nitro, chlorine, bromine, iodine or trimethylsilyl.

8. A process according to any one of claims 1 to 7, further comprising treating a compound of structure (1) by reducing groups X and Y that are other than hydrogen to obtain a compound of structure (3)



(3)

in which Z is hydrogen or 3,4-methylenedioxyphenyl, and when Z is hydrogen condensing said compound with 3,4-dioxymethylenephenol, and where necessary removing a group R that is other than hydrogen, so as to obtain a compound of structure (3) in which R is hydrogen and Z is 3,4-methylenedioxyphenyl.

9. A compound of structure (3) where R is hydrogen and Z is 3,4-methylenedioxyphenyl whenever obtained by a process according to claim 8.

10. A compound according to claim 9, in the form of a hydrochloride salt.

11. A pharmaceutical composition for treatment or prophylaxis of the disorders comprising a compound as claimed in claim 9 or 10 and a pharmaceutically acceptable carrier.

12. The use of a compound as claimed in claim 9 or 10 to manufacture a medicament for the treatment or prophylaxis of the disorders.

13. A method of treating the disorders which comprises administering an effective or prophylactic amount of a compound as claimed in claim 9 or 10 to a person suffering from one or more of the disorders.