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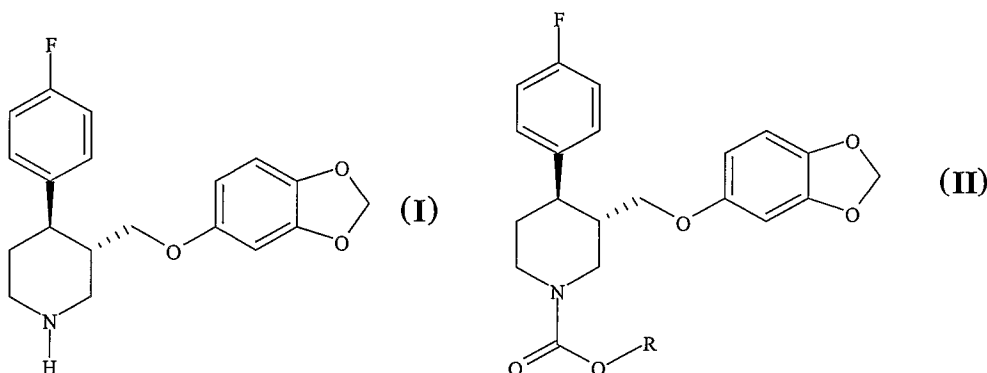
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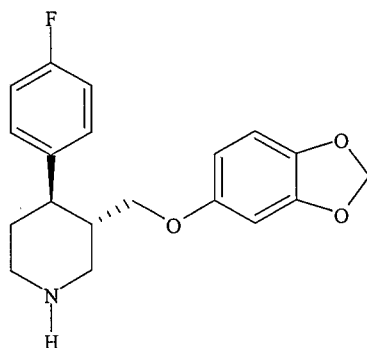
(54) Title: A PROCESS FOR THE PREPARATION OF (-)-TRANS-4-(P-FLUOROPHENYL)-3-[[3,4-(METHYLENEDIOXY)PHENOXY]METHYL]PIPERIDINE



(57) **Abstract:** A process for preparing (-)-trans-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine, a compound of formula (I) or pharmaceutically acceptable salts thereof, said process comprising hydrolyzing a compound of formula (II), wherein R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, alkylaryl, arylalkyl, by treatment with a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent wherein the polar aprotic water miscible solvent is selected from a sulfoxide solvent, an amide solvent or mixture thereof.

A PROCESS FOR THE PREPARATION OF (-)-TRANS-4-(4-FLUOROPHENYL)-3-[[3,4-(METHYLENEDIOXY)PHENOXY]METHYL]PIPERIDINE

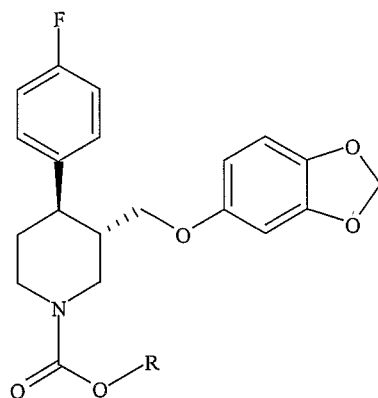
The present invention relates to a process for the preparation of (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of formula I, and its pharmaceutically acceptable salts. The compound of formula 1, commonly known as paroxetine, is used in the treatment of depression, obsessive compulsive disorder (OCD) and panic.



Formula I

BACKGROUND OF THE INVENTION

United States Patent No. 4007196 discloses hydrolysis of compound of formula II, wherein R is phenyl, with solid potassium hydroxide in methylcellosolve (2-methoxyethanol). The use of 2-methoxyethanol produces the corresponding undesired transesterified carbamate impurity which is difficult to hydrolyze and remove from the reaction mixture.

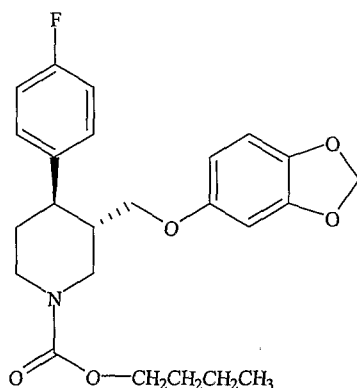


Formula II

United States Patent No. 4721723 prepares compound of formula I, by basic hydrolysis of compound of formula II, wherein R is phenyl, in large volumes of toluene. This process is not commercially viable as this method results in formation of an insoluble complex mass resulting in incomplete conversion, besides requiring large volumes of solvent (>14 volumes with respect to the compound of formula III).

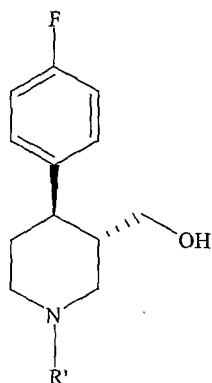
United States Patent No. 6433179 teaches hydrolysis of alkoxypiperidine compounds of formula II, wherein R is a lower alkyl, a lower cycloalkyl, an aralkyl or perfluoroalkyl group under alkaline conditions in ethanol or mixture of ethanol/toluene solvent system. However, the reaction is reported to take two/three days for completion, rendering it commercially unviable.

In **United States Patent No. 6686473** the hydrolysis of compound of formula II, wherein R is phenyl, is carried out with potassium hydroxide in 1-butanol/toluene solvent system to yield compound of formula I. However, besides formation of compound of formula I this process also generates the corresponding undesired transesterified carbamate impurity viz. the n-butyl carbamate derivative, (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine-1-carboxylic acid n-butyl ester, compound of formula IIA(compound of formula II, wherein R is n-butyl) which is difficult to remove.

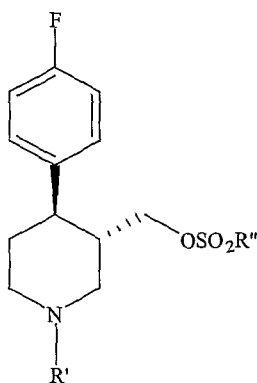


Formula IIA

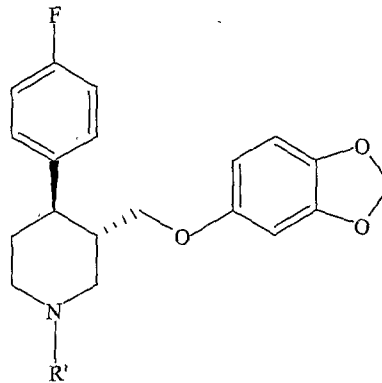
United States Patent Publication No. 2003/0187269 discloses process for the preparation of compound of formula V, by making a sulfonate derivative a compound of formula IV from a compound of formula III and coupling the compound of formula IV with sesamol in *N,N*-dimethylformamide solvent to obtain compound of formula V,



Formula III



Formula IV



Formula V

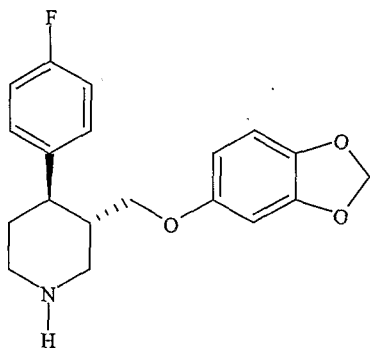
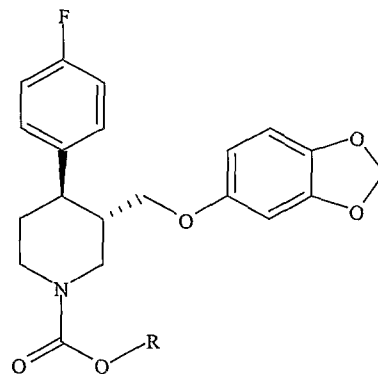
wherein, R' and R'' may be selected from halo substituted or unsubstituted linear or branched alkyl, alkylaryl, arylalkyl.

OBJECT OF THE INVENTION

The object of the present invention is to provide a commercially viable process for the preparation of (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine, compound of formula I, without the formation of unwanted impurities.

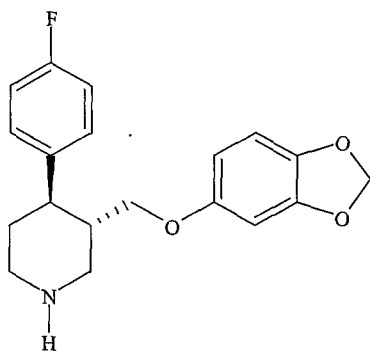
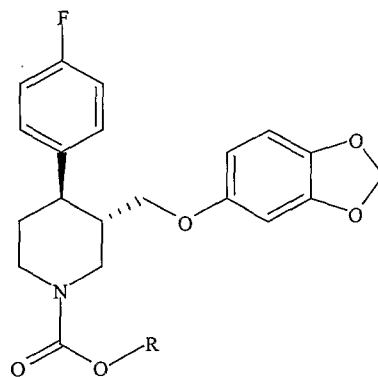
SUMMARY OF THE INVENTION

The present invention provides a process for preparing (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of formula I or pharmaceutically acceptable salts thereof, said process comprising

**Formula I****Formula II**

hydrolyzing a compound of formula II, wherein R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl, by treatment
 5 with a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent, wherein the polar aprotic water miscible solvent is selected from a sulfoxide solvent, an amide solvent, a nitrile solvent, sulfolane or mixture thereof.

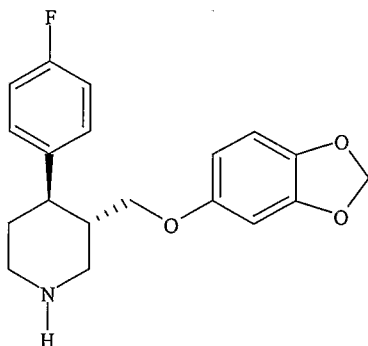
The present invention in one aspect provides a process for preparation of (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of
 10 formula I or pharmaceutically acceptable salts thereof, said process comprising

**Formula I****Formula II**

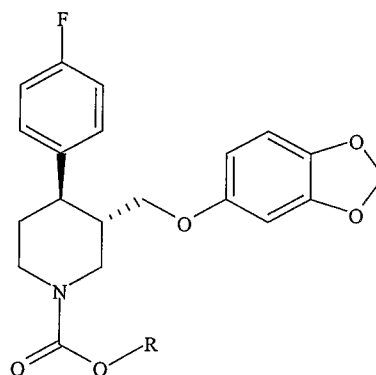
hydrolyzing a compound of formula II, wherein R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl, by treatment
 15 with a base in a solvent system comprising a polar aprotic water miscible solvent and a

hydrocarbon solvent wherein the polar aprotic water miscible solvent is selected from a sulfoxide solvent, an amide solvent, sulfolane or mixture thereof.

The present invention in one aspect provides a process for preparation of (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of
 5 formula I or pharmaceutically acceptable salts thereof, said process comprising



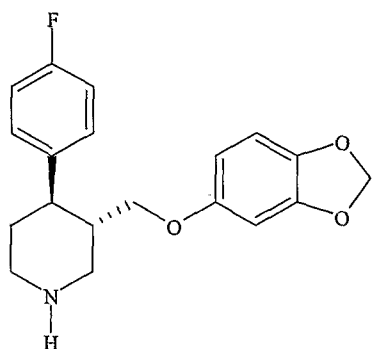
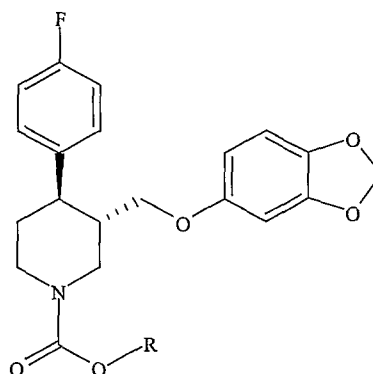
Formula I



Formula II

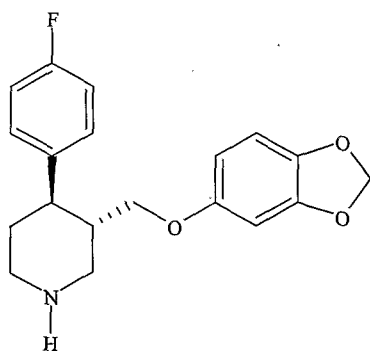
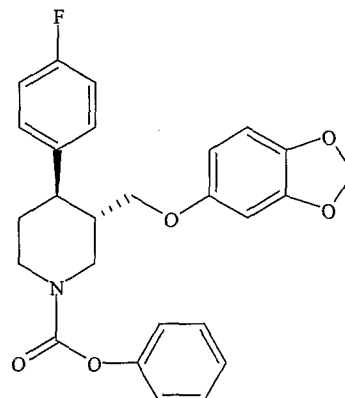
hydrolyzing a compound of formula II, wherein R may be selected from halo substituted
 10 or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl, by treatment with a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent, wherein the polar aprotic water miscible solvent is dimethyl sulfoxide.

The present invention in one aspect provides a process for preparation of (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of
 15 formula I or pharmaceutically acceptable salts thereof, said process comprising

**Formula I****Formula II**

hydrolyzing a compound of formula II, wherein R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl, by treatment
5 with a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent, wherein the polar aprotic water miscible solvent is dimethyl sulfoxide and the hydrocarbon solvent is toluene.

The present invention in one aspect provides a process for preparation of (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of
10 formula I or pharmaceutically acceptable salts thereof, said process comprising

**Formula I****Formula IIB**

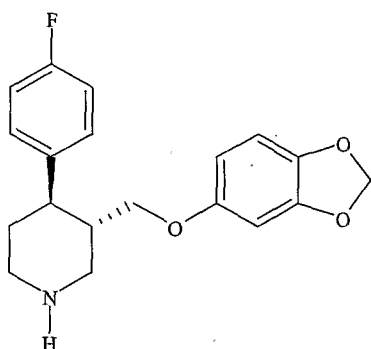
hydrolyzing a compound of formula IIB, by treatment with a base in a solvent system
15 comprising a polar aprotic water miscible solvent and a hydrocarbon solvent, wherein the

polar aprotic water miscible solvent is dimethyl sulfoxide and the hydrocarbon solvent is toluene.

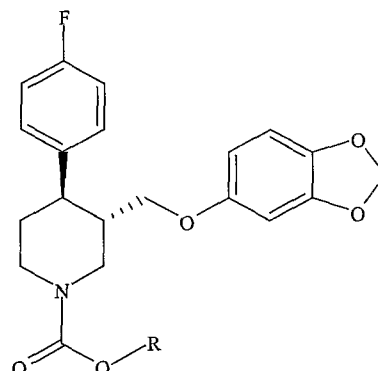
5 DESCRIPTION OF THE INVENTION

It is our endeavor to synthesize the compound of formula I in high yield, by a commercially viable process that would avoid the formation of undesired side products, including transesterified carbamate impurities.

- 10 According to one embodiment the present invention provides a process for preparing (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of formula I or pharmaceutically acceptable salts thereof, said process comprising



15 **Formula I**



Formula II

hydrolyzing a compound of formula II, wherein R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl, by treatment with a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent

20 The substituent R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl.

Alkyl group refers to a saturated aliphatic hydrocarbon radical including straight chain branched chain, and cyclic groups of 1-7 carbon atoms such as methyl, ethyl, 2-propyl, 2-butyl, cyclopropyl, cyclopentyl etc. If the alkyl group lacks substituent then it is called unsubstituted alkyl group. The term halo means a fluorine atom, chlorine atom, bromine atom or iodine atom. The term halo substituted alkyl group means an alkyl group with one or more same or different halo atoms for eg. $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{CF}_3$, $-\text{CF}_3$ and the like.

Aryl group refers to an all carbon monocyclic or fused ring polycyclic groups of 1 to 12 carbon atoms having a completely conjugated pi-electron system for eg phenyl, naphthalenyl, and anthracenyl.

Arylalkyl refers to a lower alkyl, which is substituted with an aryl group. Lower alkyl refers to a saturated aliphatic hydrocarbon radical including straight chain and branched chain groups of 1-6 carbon atoms. The definition of aryl is as described above. Examples of arylalkyl are CH_2 -phenyl, $(\text{CH}_2)_2$ -phenyl, $(\text{CH}_2)_3$ -phenyl and the like.

Alkylaryl refers to an aryl group which is substituted with an alkyl group the definitions of aryl and alkyl being same as above. Examples of alkylaryl are tolyl, phenethyl and the like.

Polar aprotic water miscible solvents are solvents which possess large dielectric constants and sizeable dipole moments. These solvents do not act as hydrogen bond donors since their hydrogen bonds are not strongly enough polarized but are good electron pair donors. Advantageously the polar aprotic water miscible solvent maybe selected from sulfoxides, amides, nitriles, sulfolane or mixtures thereof.

The sulfoxide solvent may be selected from dimethyl sulfoxide, diethyl sulfoxide ethylmethyl sulfoxide and the like.

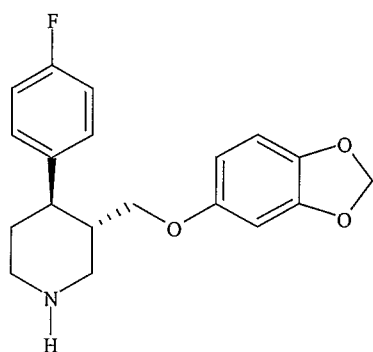
The amide solvent may be selected from *N,N*-dimethylacetamide, *N,N*-dimethylformamide, *N*-methylpyrrolidine-2-one, tetramethylurea, *N,N'*-dimethylpropyl urea (DMPU) and the like.

- 5 The nitrile solvent may be selected from acetonitrile, propionitrile and the like.

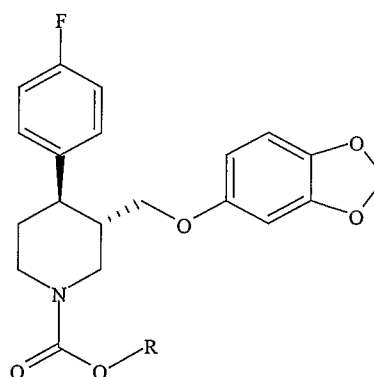
The hydrocarbon solvent may be selected from alkyl or aryl hydrocarbon such as hexane, heptane, cyclohexane, methylcyclohexane, isooctane, toluene, xylene and the like.

- 10 The base may be selected from an organic or inorganic base. Organic base may be selected from quaternary ammonium hydroxides, such as Triton B, tetrabutylammonium hydroxide, cetyltrimethylammonium hydroxide and the like. Inorganic base may be selected from hydroxides of sodium, potassium or lithium, preferably potassium hydroxide.

- 15 In one embodiment the present invention provides a process for preparation of (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of formula I or pharmaceutically acceptable salts thereof, said process comprising



20 **Formula I**

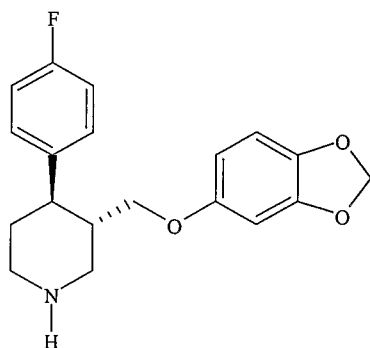


Formula II

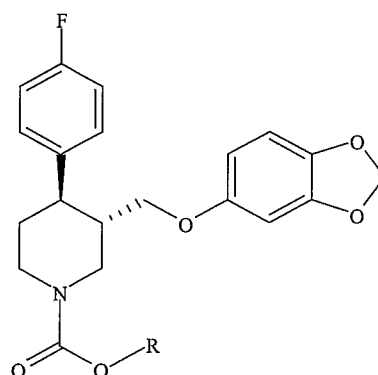
hydrolyzing a compound of formula II, wherein R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl, by treatment

with a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent, wherein the polar aprotic water miscible solvent is selected from a sulfoxide solvent, an amide solvent, sulfolane or mixture thereof.

- 5 In one embodiment the present invention provides a process for preparing (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of formula I or pharmaceutically acceptable salts thereof, said process comprising



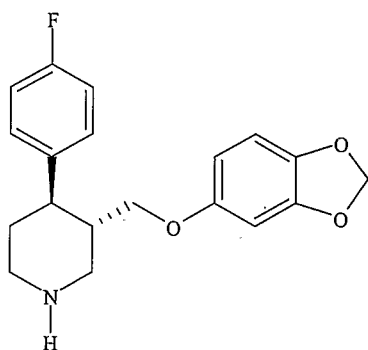
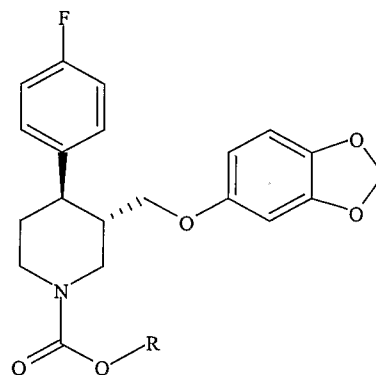
Formula I



Formula II

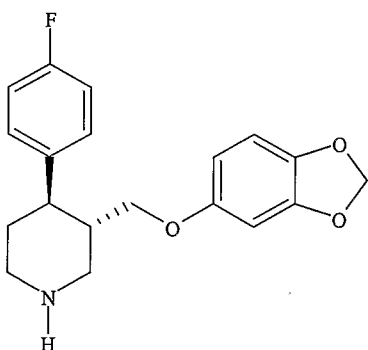
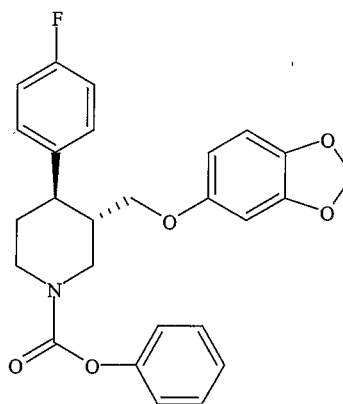
- 10 hydrolyzing a compound of formula II, wherein R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl, by treatment with a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent, wherein the polar aprotic water miscible solvent is dimethyl sulfoxide.

- 15 In one embodiment (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of formula I or pharmaceutically acceptable salts thereof, can be prepared by hydrolyzing

**Formula I****Formula II**

a compound of formula II, wherein R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl, by treatment with
 5 a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent, wherein the polar aprotic water miscible solvent is dimethyl sulfoxide and the hydrocarbon solvent is toluene.

In one embodiment *(-)-trans-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine*, a compound of formula I or
 10 pharmaceutically acceptable salts thereof, can be prepared by hydrolyzing

**Formula I****Formula IIB**

a compound of formula IIB, by treatment with a base in a solvent system comprising a
 15 polar aprotic water miscible solvent and a hydrocarbon solvent wherein the polar aprotic water miscible solvent is dimethyl sulfoxide and the hydrocarbon solvent is toluene.

In one embodiment (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of formula I or pharmaceutically acceptable salts thereof, can be prepared by hydrolyzing a compound of formula IIB, by treatment with a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent wherein the polar aprotic water miscible solvent is sulfolane and the hydrocarbon solvent is toluene.

The solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent may be in volume ratios ranging from about 1:99 to 99:1 advantageously in the volume ratio 1:10 to 1:1.

In one embodiment, the solvent system is dimethyl sulfoxide-toluene mixture in volume ratios ranging from about 1:99 to 99:1 preferably in the ratio 1:10 to 1:1, more preferably in the ratio 1:5.

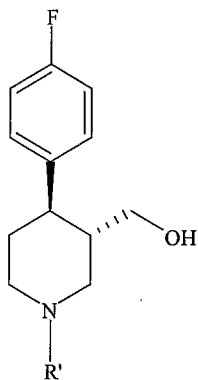
In the process of the present invention the hydrolysis of compound of formula II may be carried out at a suitable temperature, depending on the solvent system selected and the nature of R in the formula II. In general the reaction may be carried out at a temperature greater than 50°C, below the reflux temperature of any of the solvent component in the solvent system. For example, when R in formula II is phenyl, and the solvent system for the reaction is dimethyl sulfoxide and toluene in the volume ratio 1:5, the preferred temperature for the hydrolysis is 80-85°C.

The compound of formula I obtained by following the process of the present invention may be converted to a pharmaceutically acceptable salt thereof. The pharmaceutically acceptable salt of compound of formula I may be selected from hydrochloride, hydrobromide, sulfate, nitrate, acetate, fumarate, maleate, citrate and the like.

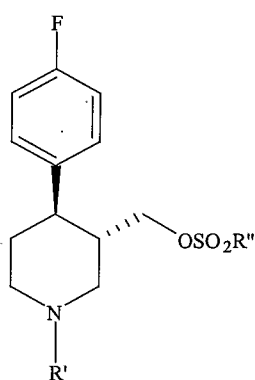
In a typical work up, after completion of reaction the mixture is quenched by addition of water, the product enriched organic layer is separated and treated with an acid to obtain a salt of compound of formula I, for example, with aqueous hydrochloric acid to obtain the hydrochloride salt of compound of formula I. The isolated salt of compound of formula I if desired, can be recrystallized from a suitable solvent(s).

According to another aspect of the process of the present invention the compound of formula II is prepared by

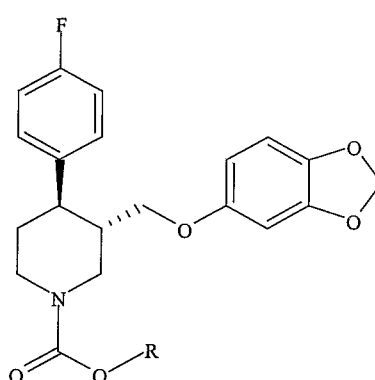
- (a) reacting a compound of formula III with $R''SO_2Cl$ or $(R''SO_2)_2O$ to give compound of formula IV, wherein R' may be selected from a methyl, an arylmethyl such as benzyl group, or an allyl group; R'' may be selected from substituted or unsubstituted linear, branched or cyclic alkyl or an aryl group wherein the substituent may be selected from halogen or alkyl group.
- (b) converting a compound of formula IV to a compound of formula II,



Formula III



Formula IV



Formula II

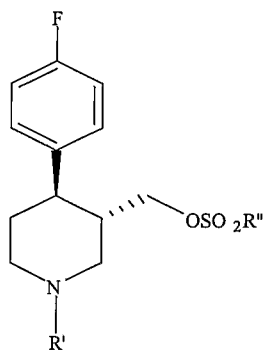
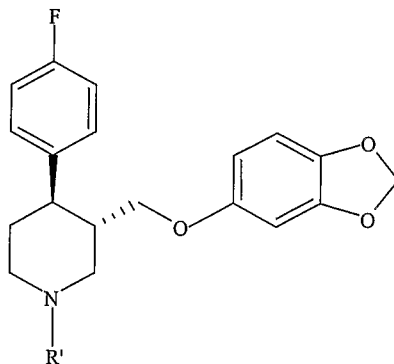
wherein R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl.

followed by isolation of compound of formula IV. The acid(s) may be selected from inorganic or an organic acid, preferably an organic acid.

The inorganic acid may be selected from hydrochloric acid, sulfuric acid, nitric acid and the like. The organic acid may be selected from an alkyl or arylcarboxylic acid such as acetic acid, citric acid, succinic acid, maleic acid, fumaric acid, oxalic acid, benzoic acid and the like, or an alkyl or arylsulfonic acid such as methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid and the like, preferably methanesulfonic acid.

For instance, compound of formula IV may be prepared by reacting a compound of formula III with $R''SO_2Cl$ for example with *p*-toluenesulfonyl chloride in an organic solvent, in presence of a base, followed by adding acid(s) to the reaction mixture after completion of reaction. The treatment of the reaction mixture with an acid after the reaction, prior to processing, protonates the nitrogen centre in formula IV and prevents possible intramolecular or intermolecular nucleophilic attack of the basic nitrogen at the electrophilic carbon bearing the tosyl group in the piperidnyl system. Thus the possibility of isomerization or quaternization of the product of formula IV is averted, and the product is isolated with high purity and yield.

The compound of formula IV may be then converted to compound of formula II by using prior known methods such as reacting compound of formula IV with sesamol to give compound of formula V wherein, R' is same as defined for a compound of formula IV,

**Formula IV****Formula V**

followed by treating the compound of formula V with a haloformate ROCOX, wherein R is selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl and arylalkyl & X is halo, in a manner similar to United States Patent No. 4007196 to give compound of formula II.

The patents and patent applications described in this application are herein incorporated by reference.

The invention is illustrated but not restricted by the description in the following examples.

Examples

Example 1:

Preparation of compound of formula IV

- 5 To a stirred solution of *trans*-(-)-paroxol (100g), compound of formula III, (wherein R' is methyl) in dichloromethane (500ml) was added triethylamine (75ml), and cooled to -5 to -15°C. *p*-Toluenesulfonyl chloride (120g) was slowly added and stirred for 1hr at -5 to -15°C. Methanesulfonic acid (44ml) was then added gradually and the mixture concentrated at about 50°C at atmospheric pressure. The residue was taken up in toluene, 10 water was added, stirred for 30min. and the top toluene layer was separated. The pH of the aqueous layer was then adjusted to 9.0 to 9.5 with saturated NaHCO₃ solution, the product was filtered, washed with water and dried to yield compound of formula IV (138.0g), as white to off-white solid, purity >99.0% by HPLC.

15 Example 2:

Preparation of *N*-methylparoxetine, compound of formula V (wherein R' is methyl).

- To a stirred solution of sesamol (27.5g) in *N,N*-dimethylacetamide (150ml) was added potassium tertiary butoxide (18.5g), followed by compound of formula IV (wherein R' is methyl and R'' is *p*-tolyl) (50g). The mixture was heated for 2hrs under stirring at 55 to 20 60°C, cooled to 10-15°C, and quenched with aqueous sodium hydroxide. The product was filtered, washed with water and dried till constant weight to obtain *N*-methylparoxetine as a white solid, purity >99.0% by HPLC.

Example 3:

- 25 Preparation of (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine-1-carboxylic acid phenyl ester, compound of formula II, wherein R is phenyl.

To a stirred solution of *N*-methylparoxetine (formula V, R'=CH₃) (50g) in toluene (250ml) was slowly introduced phenyl chloroformate (37ml) at reflux temperature and stirring continued under reflux for 3hrs. Diisopropylethylamine (5ml) was then added to the mixture and reflux continued for an additional hour. The mixture was then cooled to 25-30°C and quenched by addition of water. The upper toluene layer was separated, washed with water and concentrated. The resulting solid is recrystallized from 2-propanol, filtered and dried till constant weight, to obtain compound of formula II as white solid, purity >99.0% by HPLC.

10 Example 4

Preparation of (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, compound of formula I

A mixture of compound of formula II (50g), toluene (250ml), dimethyl sulfoxide (50ml) and potassium hydroxide (30g) is heated to 80-85°C for 4hrs, cooled to 30-35°C and then quenched by addition of water (150ml) at 30-35°C. The upper toluene layer was separated and the aqueous layer extracted once with toluene (100ml). The combined toluene layers were washed successively with water and saturated aqueous sodium chloride solution, charcoalized and acidified with conc. hydrochloric acid. After stirring at 20-25°C for 2hrs the product was filtered and washed with toluene followed by water.

The crude product was recrystallized from 2-propanol and dried until water content was within the range of 2.3 to 2.7%, to yield paroxetine hydrochloride hemihydrate, as white crystalline solid, 38.44 g (92.1% yield) purity >99.5% by HPLC.

Example 5:

Preparation of (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, compound of formula I

A mixture of compound of formula II (5g), toluene (25ml), *N,N*-dimethylacetamide (5ml) and potassium hydroxide (3g) was heated to 80-85°C for 4hrs, cooled to 30-35°C and quenched by addition of water (15ml) at 30-35°C. The upper toluene layer was separated

and the aqueous layer was extracted once with toluene. The combined toluene layer was washed successively with water and saturated aqueous sodium chloride solution, charcoalized and acidified with conc. hydrochloric acid. After stirring at 20-25°C for 2hrs the product was filtered, washed with toluene followed by water. The crude product was recrystallized from 2-propanol, filtered and dried until water content is within the range of 2.3 to 2.7%, to yield paroxetine hydrochloride, as white crystalline solid, purity >99.5% by HPLC.

Example 6:

Preparation of (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, compound of formula I

A mixture of compound of formula II (10g), toluene (50ml), sulfolane (10ml) and potassium hydroxide (6g) is heated to 80-85°C for 4hrs, cooled to 30-35°C and then quenched by addition of water (30ml) at 30-35°C. The upper toluene layer was separated and the aqueous layer extracted with toluene (20ml). The combined toluene layer were washed successively with water and saturated aqueous sodium chloride solution, charcoalized and acidified with conc. hydrochloric acid. After stirring at 20-25°C for 2hrs the product was filtered and washed with toluene followed by water. The product was dried to constant weight to yield paroxetine hydrochloride hemihydrate, as a white crystalline solid, 8.1g (97% yield), purity 99.87% by HPLC.

Comparative Example (as per United States Patent No. 6686473)

To a pre-heated mixture of potassium hydroxide (3.7g) in 1-butanol (14ml) at 80°C, was added a solution of (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine-1-carboxylic acid phenyl ester (compound of formula II, wherein R is phenyl), (5g) in toluene (8.5ml) and 1-butanol (10ml) under stirring. Exothermic reaction was observed upon addition. The mixture was stirred under reflux for 2hrs, cooled to 90-95°C and then quenched by addition of water (14ml). After stirring for 30min the upper toluene layer was separated and washed sequentially with 30% aqueous NaOH solution (6ml) and 16% aqueous NaCl solution (6ml), charcoalised and evaporated at reduced pressure at 50-60°C to give paroxetine free base as a pale yellow

syrupe base. Analysis by HPLC showed purity of paroxetine free base to be 95.66%, with (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine-1-carboxylic acid n-butyl ester, a compound of formula IIA (wherein R is n-butyl) as a major impurity (3.64%), characterized by LC-MS (mol. ion. at 430.3 [M+1]⁺).

5

Examples 4, 5 & 6 exemplify hydrolysis of compound of formula IIB using toluene-dimethyl sulfoxide, toluene-*N,N*-dimethylacetamide and toluene-sulfolane solvent systems, respectively, and KOH as a base. Since the process of the present invention, as exemplified in these examples, does not use alcoholic solvent the, (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine-1-carboxylic acid n-butyl ester, compound of formula II (wherein R is n-butyl) impurity is not formed, and the purity by HPLC of the hydrochloride of compound of formula I obtained is > 99.5%.

Comparative example discloses hydrolysis of compound of formula IIB using toluene butanol solvent system and KOH as base. HPLC analysis shows 3.64% of the (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine-1-carboxylic acid n-butyl ester, compound of formula IIA (wherein R is n-butyl).

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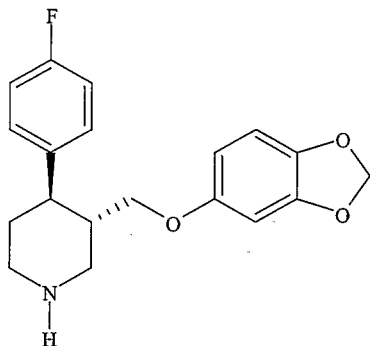
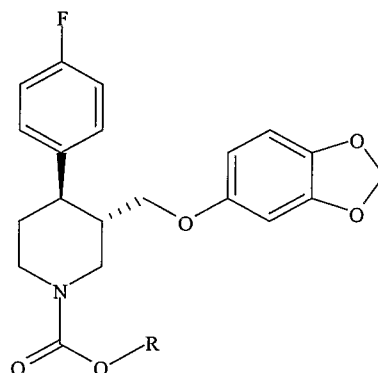
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We Claim:

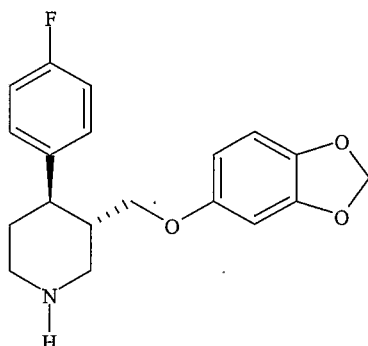
1. A process for preparation of (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of formula I or pharmaceutically acceptable salts thereof, said process comprising

**Formula I****Formula II**

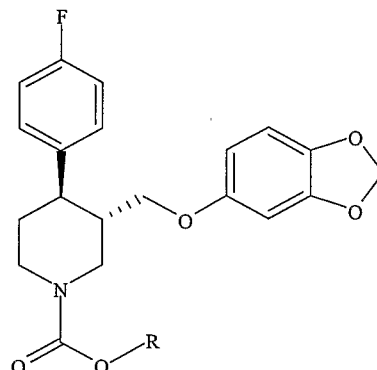
hydrolyzing a compound of formula II, wherein R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl, by treatment with a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent wherein the polar aprotic water miscible solvent is selected from a sulfoxide solvent, an amide solvent, sulfolane or mixture thereof.

2. A process as claimed in claim 1 wherein the sulfoxide solvent is dimethyl sulfoxide.
3. A process as claimed in claim 1 wherein the amide solvent is *N,N*-dimethylacetamide.
4. A process as claimed in claim 1 wherein the hydrocarbon is selected from the group consisting of benzene, toluene, xylene and mixtures thereof.

5. A process for preparing (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of formula I or pharmaceutically acceptable salts thereof, said process comprising



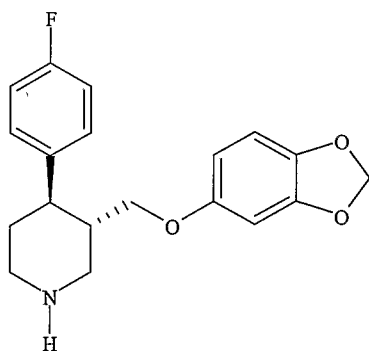
Formula I



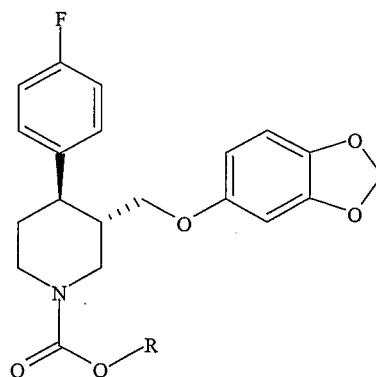
Formula II

hydrolyzing a compound of formula II, wherein R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl, by treatment with a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent wherein the polar aprotic water miscible solvent is dimethyl sulfoxide.

6. A process for preparing (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of formula I or pharmaceutically acceptable salts thereof, said process comprising



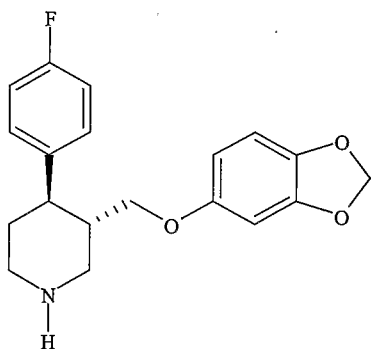
Formula I



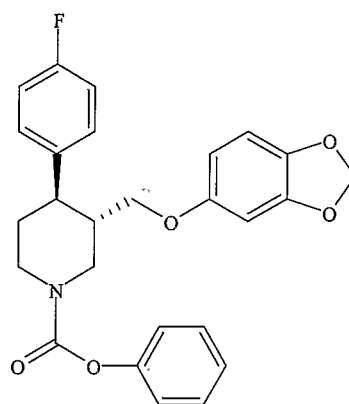
Formula II

hydrolyzing a compound of formula II, wherein R may be selected from halo substituted or unsubstituted linear, branched or cyclic alkyl, aryl, alkylaryl, arylalkyl, by treatment with a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent wherein the polar aprotic water miscible solvent is dimethyl sulfoxide and the hydrocarbon solvent is toluene.

7. A process for preparing (-)-*trans*-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, a compound of formula I or pharmaceutically acceptable salts thereof, said process comprising



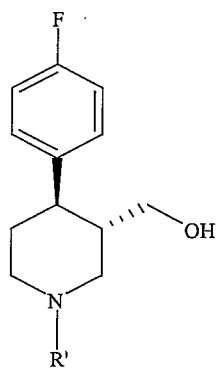
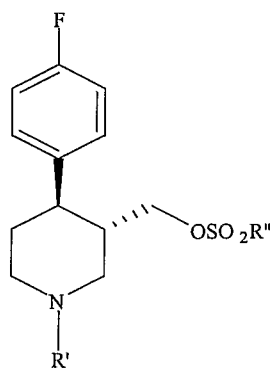
Formula I



Formula IIB

hydrolyzing a compound of formula IIB, by treatment with a base in a solvent system comprising a polar aprotic water miscible solvent and a hydrocarbon solvent wherein the polar aprotic water miscible solvent is dimethyl sulfoxide and the hydrocarbon solvent is toluene.

8. A process as claimed in claim 1 wherein the compound of formula II is prepared by
- reacting a compound of formula III with *p*-toluenesulfonyl chloride to give a compound of formula IV; and

**Formula III****Formula IV**

b. converting the compound of formula IV to the compound of formula II.

9. A process as claimed in claim 8 wherein the reaction mixture of step (a) is treated with an acid and compound of formula IV isolated.

10. A process as claimed in claim 9 wherein the acid is methanesulfonic acid.