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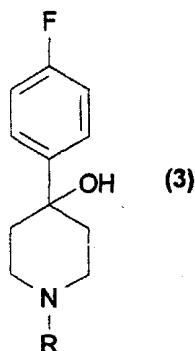
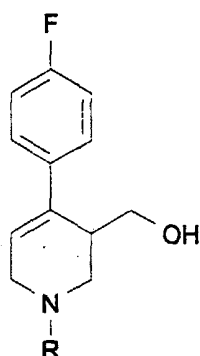
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- (71) Applicant (for all designated States except US):  
SMITHKLINE BEECHAM P.L.C. [GB/GB]; New  
Horizons Court, Brentford, Middlesex TW8 9EP (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): CROWE, David  
[GB/GB]; SmithKline Beecham Pharmaceuticals, Old  
Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN  
(GB). WARD, Neal [GB/GB]; SmithKline Beecham Phar-  
maceuticals, Old Powder Mills, Near Leigh, Tonbridge,  
Kent TN11 9AN (GB).
- (74) Agent: WEST, Vivien; SmithKline Beecham, Corporate  
Intellectual Property, Two New Horizons Court, Brentford,  
Middlesex TW8 9EP (GB).
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(54) Title: PROCESS FOR THE PREPARATION OF PAROXETIN INTERMEDIATE

WO 01/25201 A1



(57) Abstract: Compounds of formula (1) where R is an optionally substituted benzyl group, are valuable intermediate in the preparation of paroxetine, and are prepared by reacting a compound of formula (3), where R is as defined for formula (1) with formaldehyde in an acidic medium at elevated temperature.

## PROCESS FOR THE PREPARATION OF PAROXETIN INTERMEDIATE

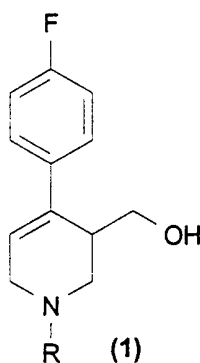
The present invention relates to a new process for the manufacture of intermediates to pharmaceutically active compounds, in particular for the preparation of paroxetine.

- 5    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-phenoxy-methyl)-piperidine. This compound is used in therapy as the hydrochloride salt to treat *inter alia* depression, obsessive compulsive disorder  
10    (OCD) and panic.

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

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This invention has been developed on the basis that compounds of structure (1) below, where R is an optionally substituted benzyl group, are valuable chemical intermediates useful *inter alia* for the manufacture of paroxetine hydrochloride.

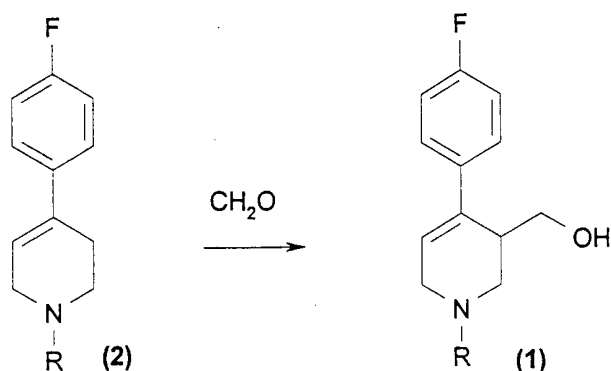


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The use of a compound of structure (1) where R is an unsubstituted benzyl group, that is 1-benzyl-4-(4'-fluorophenyl)-3-hydroxymethyl-1,2,3,6-tetrahydropyridine, for the preparation of paroxetine is described in WO 98/01424 (Gedeon Richter).

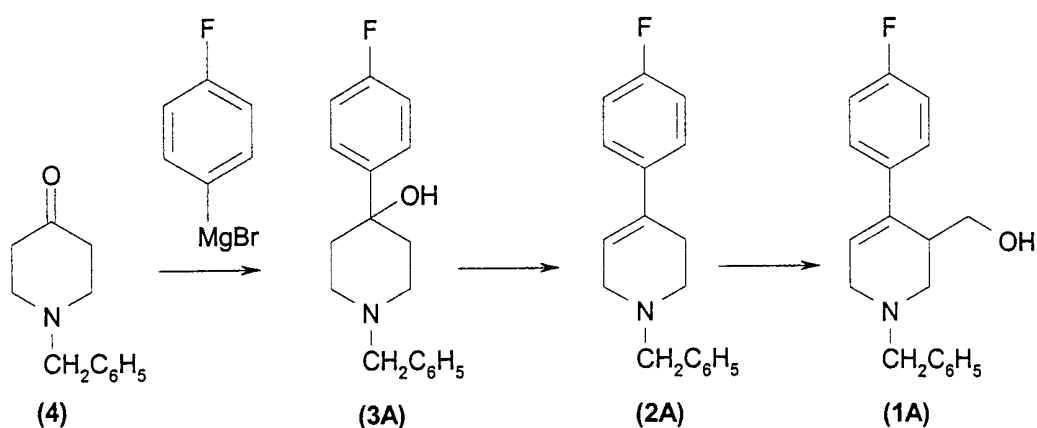
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All known processes for the preparation of compounds of structure (1) involve the isolation of a compound of structure (2), followed by reaction with formaldehyde:



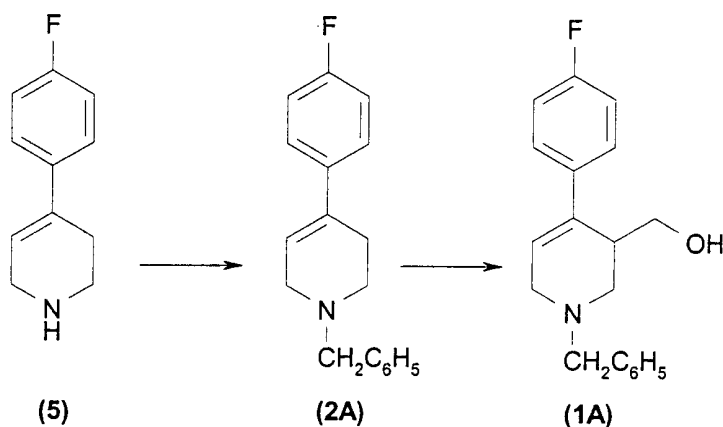
The preparation of a compound of structure (1), where R is an unsubstituted benzyl group, compound (1A) below, is described in WO 98/01424 and WO 97/09311 (Hoffmann-La Roche).

Example 2 of WO 98/01424 describes the preparation of compound (1A) by the reaction of 1-benzyl-4-(4'-fluorophenyl)-1,2,3,6-tetrahydropyridine (2A) with formaldehyde. Compound (2A) is prepared from 1-benzyl-4-(4'-fluorophenyl)-4-hydroxypiperidine (3A) which is in turn prepared by the reaction of 1-benzyl-4-piperidinone (4) and 4-fluorophenylmagnesium bromide.



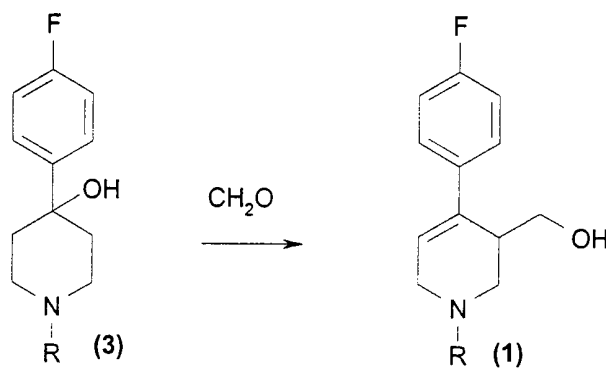
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Example 74 (a) of WO 97/09311 describes the preparation of 1-benzyl-4-(4'-fluorophenyl)-1,2,3,6-tetrahydropyridine (2A) by benzylation of 4-(4'-fluorophenyl)-1,2,3,6-tetrahydropyridine (5), and Example 74 (b) describes the preparation of compound (1A) by reaction of 1-benzyl-4-(4'-fluorophenyl)-1,2,3,6-tetrahydropyridine (2A) with paraformaldehyde.



In order to carry out any of the processes described in the prior art, a compound of  
 5 general structure (2) must be prepared and isolated. This is a highly undesirable and  
 hazardous operation, particularly on a manufacturing scale, as compounds of structure  
 (2) are structurally very similar to known potent neurotoxins (*Drug Metabolism  
 Reviews* (1990) volume 22 pages 291-332). No process has been described for the  
 preparation of a compound of structure (1) other than by the isolation of a compound  
 10 of structure (2).

We have surprisingly found that it is possible, indeed advantageous, to prepare a  
 compound of structure (1) directly from a compound structure (3) by reaction with  
 formaldehyde in an acidic medium. Although some compound (2) may be formed in  
 15 the reaction solution, the hazards involved with the isolation and handling of  
 compound (2) are avoided, and the process is suited to large scale manufacture.



In the process of this invention, a compound of structure (3) is reacted with formaldehyde in an acidic medium at elevated temperature, preferably in the range 50 to 100°C, more preferably at about 80°C. The acid medium may be an aqueous mineral acid, such as hydrochloric or sulphuric acid, or a mixture thereof, or a strong  
5 organic acid such as 4-toluene sulphonic acid or trifluoroacetic acid.

The formaldehyde may be added in the form of a solution, for example in water, or preferably as solid paraformaldehyde. It may be present at the start of the reaction, or may be added in one or more portions during the reaction.

10

In a preferred embodiment of the invention, the desired product is isolated in substantially pure form as a salt of an acid, preferably a sulphonic acid such as 4-toluene sulphonic acid.

15 Compounds of formula (3) used as starting materials in the process of this invention may be prepared as described in WO 98/01424 cited above, or by the procedure described in the Journal of Medicinal Chemistry (1995) volume 38 pages 1998 to 2008.

20 Compounds of formula (1) prepared in accordance with this invention may be converted to the pharmaceutical products described in US-A-3912743 and US-A-4007196 using analogous procedures to those described in EP 0374 674 A2 for the preparation of paroxetine. Thus, for the preparation of paroxetine, the compound of formula (1) is reduced to obtain the corresponding piperidine, and coupled with  
25 sesamol, followed by removal of the N-benzyl protecting group. Since paroxetine is the (-) *trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-phenoxy-methyl)-piperidine, the synthetic procedure will include selection of the appropriate isomers from racemic mixtures of *cis* and *trans* compounds produced in the various steps of the reaction scheme, and/or epimerisation or resolution steps where necessary.

30

Included in the scope of this invention is paroxetine as the free base and as pharmaceutically acceptable salts and polymorphs thereof obtainable from compounds of formula (1) prepared in accordance with this invention. Suitable salts

include the methanesulphonate and hydrochloride, especially the hemihydrate and anhydrate forms of the latter.

Paroxetine and its salts obtained using this invention may be formulated for therapy in the dosage forms described in EP-A-0223403 or WO 96/24595, either as solid formulations or as solutions for oral or parenteral use.

Therapeutic uses of paroxetine, especially paroxetine mesylate or 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".

Most suitably the paroxetine products obtainable by the present invention is applied to the treatment of depression, OCD and panic.

Compositions containing paroxetine products 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 utilised in conventional manner, for example in a manner similar to that already used for marketed anti-depressant agents.

Specific examples of pharmaceutical compositions include those described EP-B-0223403, and US 4,007,196 in which the anhydrate product of the present invention may be used as the active ingredient.

10

Accordingly, the present invention also provides:

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

15 the use of paroxetine or paroxetine hydrochloride obtained using the process of this invention to manufacture a medicament 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 mesylate or paroxetine hydrochloride obtained using the process of this invention to a person suffering from one or more of the Disorders.

20

This invention is illustrated by the following Example.

## 25 **Example**

Preparation of ( $\pm$ ) 1-benzyl-4-(4'-fluorophenyl)-3-hydroxymethyl-1,2,3,6-tetrahydropyridine 4-toluene sulphonate salt.

30 Concentrated sulphuric acid (14 ml) was added cautiously to water (16 ml) with stirring and cooling, then concentrated hydrochloric acid (4 ml) and 1-benzyl-4-(4-fluorophenyl)-4-hydroxypiperidine (5.8 g) were added at ambient temperature. The mixture was stirred at ca. 80°C for 30 minutes then allowed to cool to ca. 60°C, when

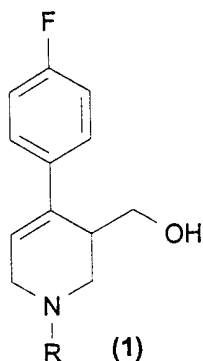
paraformaldehyde (0.8 g) was added. The mixture was stirred at 80°C for a further 45 minutes, cooled to ambient temperature, then water (40 ml) and dichloromethane (40 ml) were added.

- 5 The mixture was made alkaline by the cautious addition of a solution of sodium hydroxide (24 g) in water (50 ml) at a temperature not higher than 40°C, then cooled to 30°C. The phases were separated and the aqueous layer extracted with dichloromethane (2 x 20 ml). The combined organic phases were dried over anhydrous magnesium sulphate, filtered and the filtrate evaporated to dryness under  
10 reduced pressure. The remaining yellow oil was dissolved in acetone (10 ml), 4-toluene sulphonic acid monohydrate (3 g) was added and the mixture stirred at 0 to +5°C. The product precipitated within a few minutes and the suspension was stirred in the cold for 30 minutes then stored in the refrigerator for 16 hours. Finally, the crystals were filtered, washed with cold acetone and dried under vacuum, to give the  
15 title compound in substantially pure form.

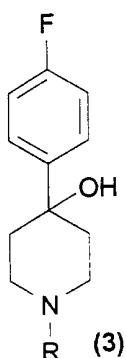
Yield 5.02 g

# Claims

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



- 5 where R is an optionally substituted benzyl group,  
which comprises reacting a compound of formula (3),



where R is as defined for formula (1) with formaldehyde in an acidic medium at elevated temperature.

10

2. A process according to claim 1 in which the compound of formula (1) is isolated as an acid salt.
3. A process according to claim 2 in which the acid salt is a salt of a sulphonic acid.
4. A process according to any preceding claim in which the process is carried out in the presence of hydrochloric, sulphuric acid, toluene sulphonic acid or trifluoroacetic acid.

20

5. A process according to any preceding claim in which the process is carried out at a temperature of 50 - 100°C.
6. A process according to any preceding claim in which the formaldehyde is added as solid paraformaldehyde.
7. A process according to any preceding claim in which the compound of formula (3) is prepared by reaction of an N-optionally substituted benzyl piperidinone and 4-fluorophenylmagnesium bromide.
8. A process according to any preceding claim in which the compound of formula (1) is reduced to the corresponding piperidine, coupled with sesamol, and the group R is removed, to obtain paroxetine.
9. A process according to claim 8 in which the paroxetine is isolated as the free base or as a salt of a pharmaceutically acceptable acid.
10. A method of treating the Disorders which comprises administering an effective or prophylactic amount of paroxetine or paroxetine mesylate or paroxetine hydrochloride obtained by a process as claimed in claim 8 or 9 to a person suffering from one or more of the Disorders.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/03797

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/70

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 007 196 A (CHRISTENSEN JORGEN ANDERS ET AL) 8 February 1977 (1977-02-08) the whole document	10
X	US 5 371 092 A (JOHNSON ANTHONY M) 6 December 1994 (1994-12-06) the whole document	10
Y	WO 98 01424 A (BORZA ISTVAN ;CZIBULA LASZLO (HU); DOBAY LASZLO (HU); HARSANYI KAL) 15 January 1998 (1998-01-15) page 2, line 5 - line 10 -/--	1-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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25 January 2001

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European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Diederer, J

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 00/03797

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>ZIERING ET AL.: "Piperidine Derivatives. Part III. 4-Arylpiperidines" J. ORG. CHEM., vol. 12, 1947, pages 894-903, XP002158497 page 894, line 22 - line 25 figure 1 Prep. of 1-Methyl-4-(m-hydroxyphenyl)-1,2,5,6-tetra hydropyridine page 901</p> <p>-----</p>	1-9

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 00/03797

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