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(71) Applicant (for all designated States except US): **RANBAXY LABORATORIES LIMITED** [IN/IN]; Plot No. 90, Sector 32, 122001 Gurgaon, Haryana (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **KUMAR, Naresh** [IN/IN]; C-1796, Palam Vihar, 122017 Gurgaon, Haryana (IN). **NAYYAR, Sandeep** [IN/IN]; House No. 1254, Sector 15b, 160015 Chandigarh (IN). **GUPTA, Mitu** [IN/IN]; c/o Prof. M. L. Mahajan, Sunder Bagh Colony, Jail Road, Gurdaspur, Punjab 143521 (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o Deshmukh, Jay, R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

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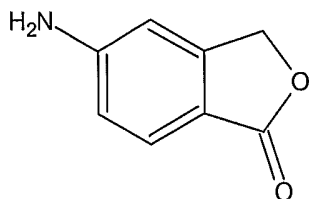
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(54) Title: PROCESSES FOR THE PREPARATION OF CITALOPRAM AND ITS INTERMEDIATE 5-AMINOPHTHALIDE



(I)

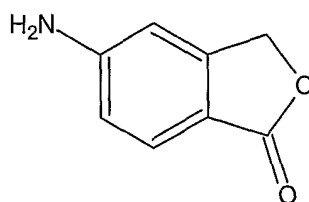
(57) Abstract: The invention relates to processes for the preparation of 5-amino-2-benzofuran-1(3H)-one of Formula (I), and to the use of this compound as an intermediate for the preparation of citalopram. The invention also relates to a process for the preparation of citalopram or a salt thereof, and pharmaceutical compositions that include the citalopram or a salt thereof.



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PROCESSES FOR THE PREPARATION OF CITALOPRAM AND ITS INTERMEDIATE
5-AMINOPHTHALIDEField of the Invention

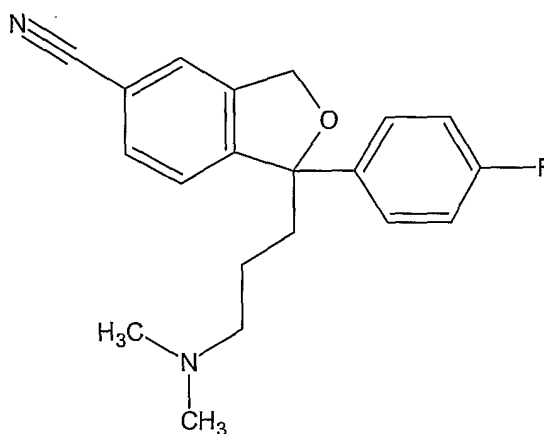
5 The field of the invention relates to processes for the preparation of 5-amino-2-benzofuran-1(3*H*)-one of Formula I,

**Formula I**

and to the use of this compound as an intermediate for the preparation of citalopram. The
10 invention also relates to a process for the preparation of citalopram or a salt thereof, and
pharmaceutical compositions that include the citalopram or a salt thereof.

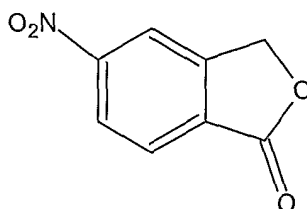
Background of the Invention

Chemically, citalopram is a racemic mixture of 1-(3-dimethylaminopropyl)-1-(4-
15 fluorophenyl)-1,3-dihydroisobenzofuran -5-carbonitrile of Formula II,

**Formula II**

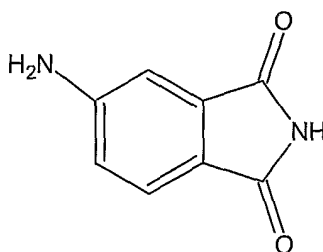
Citalopram is commercially available in the form of its hydrochloride or hydrobromide salt which is indicated for the treatment of depression. The antidepressant activity of citalopram is presumed to be linked to potentiation of serotonergic activity in the central nervous system.

5 5-amino-2-benzofuran-1(3*H*)-one is a useful intermediate in the preparation of citalopram. There are several methods known for the preparation of this intermediate for example, U.S. Patent No. 2,130,480 discloses a process for the preparation of 5-amino-2-benzofuran-1(3*H*)-one by catalytically hydrogenating 5-nitro-2-benzofuran-1(3*H*)-one of Formula III.



Formula III

Bull. Soc. Sci. Bretagne Spec., 1951, 26, 35-43 discloses a process for preparing 5-amino-2-benzofuran-1(3*H*)-one from 5-amino-1*H*-isoindole-1,3(2*H*)-dione of Formula IV,

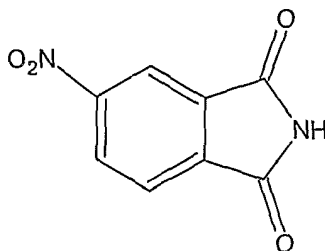


Formula IV

using zinc powder, copper sulfate in basic medium.

Ann. Pharm. France, 1958, 16, 21-26 discloses a process for the preparation of 5-amino-2-benzofuran-1(3*H*)-one by reducing 5-nitro-1*H*-isoindole-1,3(2*H*)-dione of Formula V,

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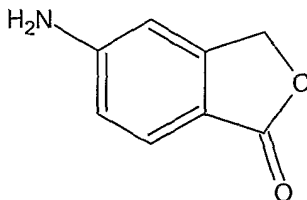
**Formula V**

with stannous chloride to get 5-amino-1H-isoindole-1,3(2H)-dione of Formula IV, followed by further reduction with zinc and sodium hydroxide.

- 5 A process reported in *Zhurnal Obshchei Khimii*, 1945, 15, 704-710 involves the conversion of 5-nitro-1H-isoindole-1,3(2H)-dione of Formula V into 5-amino-2-benzofuran-1(3H)-one by using zinc dust, 20% sodium hydroxide and copper sulfate at low temperatures, wherein the ammonia formed in the reaction is removed by steam distillation and the yield of the final product, 5-amino-2-benzofuran-1(3H)-one is reported
10 to be 44%.

Summary of the Invention

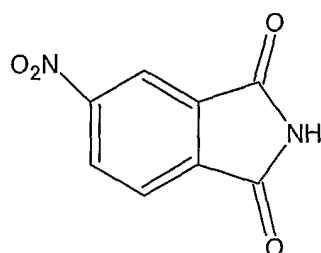
In one general aspect there is provided a process for preparing 5-amino-2-benzofuran-1(3H)-one of Formula I.

**Formula I**

The process includes:

- a) treating 5-nitro-1H-isoindole-1,3(2H)-dione of Formula V,

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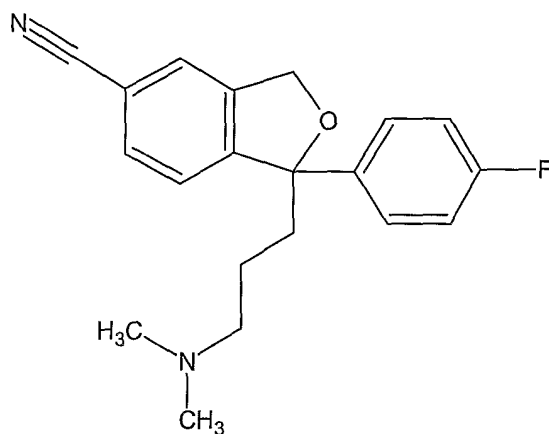
**Formula V**

with zinc in the presence of a base; and

b) isolating 5-amino-2-benzofuran-1(3*H*)-one of Formula I.

5 The process may include further drying of the product obtained. The process may include further converting the product obtained into citalopram or a salt thereof. The citalopram or a salt thereof may be made into a finished dosage form with one or more pharmaceutically acceptable excipients and administered to a patient in need of a treatment for depression

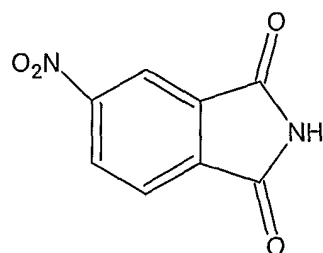
10 In another general aspect there is provided a process for the preparation of citalopram of Formula II or a salt thereof.

**Formula II**

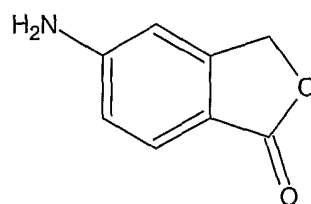
The process includes:

15 a) treating 5-nitro-1H-indole-1,3(2*H*)-dione of Formula V,

5

**Formula V**

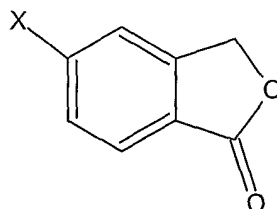
with zinc in the presence of a base to get 5-amino-2-benzofuran-1(3H)-one of Formula I;



5

Formula I

b) treating the 5-amino-2-benzofuran-1(3H)-one of Formula I with a source of halogen to get 5-halo-2-benzofuran-1(3H)-one of Formula VI,



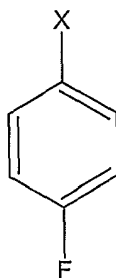
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Formula VI

wherein X is F, Br or I;

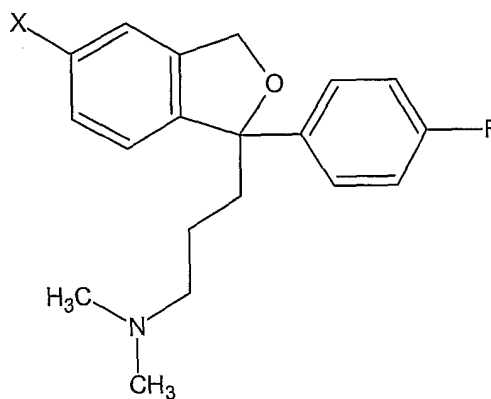
c) treating the 5-halo-2-benzofuran-1(3H)-one of Formula VI with a Grignard solution of 1-fluoro-4-halobenzene of Formula VII,

6

**Formula VII**

wherein X is Cl, Br or I,

and N,N-dimethylaminopropyl metal halide to get 3-[1-(4-fluorophenyl)-5-halo-
 5 1,3-dihydro-2-benzofuran-1-yl]-N,N-dimethylpropan-1-amine of Formula VIII,

**Formula VIII**

wherein X is Cl, Br or I;

d) treating the 3-[1-(4-fluorophenyl)-5-halo-1,3-dihydro-2-benzofuran-1-yl]-
 10 N,N-dimethylpropan-1-amine of Formula VIII with a cyanide source to get citalopram of
 Formula II; and

e) isolating the citalopram or a salt thereof.

In another general aspect there is provided a pharmaceutical composition that
 includes a therapeutically effective amount of citalopram or a salt thereof; and one or more
 15 pharmaceutically acceptable carriers, excipients or diluents. The resulting pharmaceutical
 composition or dosage form may be administered to a patient in need of a treatment for
 depression

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description and claims.

5 Detailed Description of the Invention

The inventors have developed an efficient process for the preparation of 5-amino-2-benzofuran-1(3*H*)-one of Formula I. The process involves treating 5-nitro-1*H*-isindole-1,3(2*H*)-dione of Formula V with zinc in the presence of a base, and isolating the 5-amino-2-benzofuran-1(3*H*)-one of formula I from the reaction mixture thereof.

In general, 5-nitro-1H-isoindole-1,3(2H)-dione may be added to water or an organic solvent and an alkali metal salt or an alkaline earth metal salt, or a mixture thereof, at a temperature of from about -10°C to about 25°C. The reaction mixture may be stirred at a temperature from about 0°C to about -10° C for about 0 to about 20 hours. Examples of alkali metal salts or alkaline earth metal salts which may be used include sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate, potassium bicarbonate, magnesium hydroxide, magnesium carbonate, magnesium oxide, calcium hydroxide, calcium carbonate, calcium oxide, aluminium hydroxide and ammonia.

The 5-nitro-1*H*-isoindole-1,3(2*H*)-dione may be treated with zinc containing a catalytic quantity of copper salt. Examples of copper salts include copper sulfate, copper nitrate, copper carbonate, copper acetate, copper benzoate, copper chromate, copper oxalate, copper phosphate and copper tetrafluoroborate. The temperature may be reduced below about 25°C. After the completion of the reaction, the zinc residue may be filtered off and washed with water. 5-amino-2-benzofuran-1(3*H*)-one of Formula I may be isolated from the reaction mixture after acidification and subsequent basification.

The inventors also have developed a process for the preparation of citalopram of Formula II or a salt thereof. The process involves treating 5-nitro-1H-isoindole-1,3(2H)-dione of Formula V with zinc in an alkaline medium to get 5-amino-2-benzofuran-1(3H)-one of Formula I; treating the 5-amino-2-benzofuran-1(3H)-one of Formula I with a source of halogen to get 5-halo-2-benzofuran-1(3H)-one of Formula VI; treating 5-halo-2-

benzofuran-1(3H)-one of Formula VI with a Grignard solution of 1-fluoro-4-halobenzene of Formula VII and N,N-dimethylaminopropyl metal halide to get 3-[1-(4-fluorophenyl)-5-halo-1,3-dihydro-2-benzofuran-1-yl]-N,N-dimethylpropan-1-amine of Formula VIII; treating the 3-[1-(4-fluorophenyl)-5-halo-1,3-dihydro-2-benzofuran-1-yl]-N,N-dimethylpropan-1-amine of Formula VIII with a cyanide source to get citalopram of Formula II, and isolating the citalopram or a salt thereof.

5-amino-2-benzofuran-1(3H)-one of Formula I obtained in the first aspect of the invention may be treated with a source of halogen to get 5-halo-2-benzofuran-1(3H)-one of Formula VI. 5-halo-2-benzofuran-1(3H)-one may be further treated with a Grignard solution of 1-fluoro-4-halobenzene of Formula VII and N,N-dimethylaminopropyl metal halide to get 3-[1-(4-fluorophenyl)-5-halo-1,3-dihydro-2-benzofuran-1-yl]-N,N-dimethylpropan-1-amine. N,N-dimethylaminopropyl metal halide may be N,N-dimethylaminopropyl magnesium chloride. The obtained 5-halo compound may be further treated with a cyanide source to get citalopram. The cyanide source may include one or more of cuprous cyanide, copper potassium cyanide, ferrocyanide, hydrogen cyanide, cadmium cyanide, barium cyanide, and the like. The citalopram may be treated with an acid to get an acid addition salt of citalopram.

As may be seen from the examples that follow, by using or following the processes of the present invention the 5-amino-2-benzofuran-1(3H)-one may be obtained in a yield of more than 90% by direct conversion of 5-nitro-1H-isoindole-1,3(2H)-dione of Formula V without any necessity to remove the ammonia formed in the reaction.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and should not be construed in a manner that limits the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1: Preparation of 5-amino-2-benzofuran-1(3H)-one

4-nitrophthalimide (50 g) was added into a pre-cooled mixture of zinc (200 g), copper sulfate pentahydrate (0.846 g) and sodium hydroxide (30 g) in deionised water (200 ml) at

-10° to 0°C. The mixture was stirred at 0° to -5°C for 12 h. Deionised water (150 ml) was added to the reaction mixture at 0° to -5°C, and then heated to 60°C for 8 to 10 h. The hot zinc residue was filtered off and washed with hot water. The filtrate was acidified with hydrochloric acid to a pH less than 1.0 and then heated to 90° to 95°C for 30 minutes.

- 5 After cooling to 0° to 5°C, the pH of the reaction mixture was adjusted to 8.0 to 8.5 with 25 % w/v aqueous sodium hydroxide solution. The mixture was stirred for 30 minutes at 0° to 5°C and the product was filtered, washed with water and dried to get the title compound.

Yield: 37.0 g

- 10 Purity (HPLC): 99 %

Example 2: Preparation of Citalopram Hydrobromide

a) Preparation of 5-Iodo-2-Benzofuran-1(3H)-One

- Freshly prepared sodium nitrite solution (20.4 g) in deionised water (96 ml) was added to a mixture of deionised water (120 ml), concentrated hydrochloric acid (120 ml) and 5-amino-2-benzofuran-1(3H)-one (40 g) as prepared by Example 1, at -5° to -10°C over a period of 60 minutes. A freshly prepared solution of aqueous sodium iodide (44g) in deionised water (96 ml) was added at -5° to -10°C over a period of 60 minutes. The mixture was stirred for another 2 hours at 0° to 5°C, then heated to 45° to 50°C and stirred at this temperature for 60 minutes. The mixture was cooled to 10°C and stirred for another 30 minutes at 5° to 10°C. The reaction mass obtained was filtered and washed with deionised water (80 ml). It was further washed with 5% w/v sodium thiosulfate solution. The crude product obtained was recrystallized from methanol and toluene to get the title compound.

- 25 Yield: 29 g

b) Preparation of 3-[1-(4-Fluorophenyl)-5-Iodo-1,3-Dihydro-2-Benzofuran-1-yl]-N,N-Dimethylpropan-1-Amine

To a solution of 5-iodo-2-benzofuran-1(3H)-one (50 g) as prepared by Example 2 a) in tetrahydrofuran (250 ml) was added a Grignard solution of 1-bromo-4-fluorobenzene

(prepared from p-bromofluorobenzene (77.5 g) and magnesium turnings (10.7 g) in tetrahydrofuran (250 ml)) at -35° to -20°C over a period of 60 minutes, followed by the addition of N,N- dimethylaminopropyl magnesium chloride (prepared from N,N- dimethylaminopropyl chloride (107 g) and magnesium turnings (21.49 g) in
5 tetrahydrofuran (200 ml)) at -40° to -35°C over a period of 60 minutes. The reaction mixture was stirred for another 60 minutes at -30° to -35°C and then dispersed in an aqueous saturated solution of ammonium chloride (1200 ml). The reaction mass was extracted in ethyl acetate (2 x 500 ml) followed by evaporation of the solvent under reduced pressure to get an oil. Toluene (250 ml), water (25 ml) and orthophosphoric acid
10 (144 g) were added to the oil and stirred at 65° to 70°C for 60 minutes. The reaction mixture was then dispersed in a mixture of toluene (250 ml) and water (1800 ml). The aqueous layer was washed with toluene (500 ml) followed by pH adjustment to 6.5 to 7.0 with ammonia solution. The reaction mass was extracted in toluene (2 x 500ml). The solvent was evaporated under reduced pressure to get the title compound as oil.

15 Yield: 45 g

c) Preparation of Citalopram Base

3-[1-(4-fluorophenyl)-5-iodo-1,3-dihydro-2-benzofuran-1-yl]-N,N-dimethylpropan-1-amine (7.5 g) as prepared by Example 2 b), cuprous cyanide powder (2.4 g) and pyridine (5.6 g) were added to dimethylformamide (40 ml) and the mixture obtained was heated to
20 140° to 141°C . The reaction mixture was further stirred at 141° to 145°C for about 3 hours. The reaction mixture was then cooled to 35°C , and diluted with a cooled mixture of toluene and water. The organic layer was separated, washed with ammonia solution and water. The toluene was recovered under vacuum to get the title compound as a free base in the form of oil.

25 Yield: 6.0 g

d) Preparation of Citalopram Hydrobromide

Toluene (40 ml) was added to the citalopram free base (6.0 g) as prepared by Example 2 c) and stirred to obtain a homogeneous solution. 48% w/v aqueous hydrobromide solution (3.6g) was added to this solution. The reaction mixture so obtained was stirred for about 4
30 hours at 5° to 10°C and the toluene layer was removed. Fresh toluene (40 ml) was added to

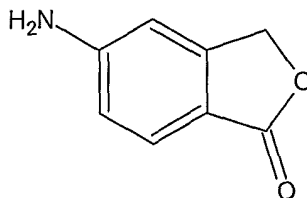
it and further stirred at 5° to 10°C. The separated solid was filtered, washed with toluene and dried to obtain the title compound as a crystalline powder.

Yield: 6.7 g

While the present invention has been described in terms of its specific
5 embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. For example, the compounds described herein can be formulated into dosage forms that are suitable for administering to patients in need of the compound for treating a medical condition for which the compound is indicated, approved, or otherwise beneficial. Specifically, the
10 citalopram or a salt thereof made according to the above processes can be formulated into a tablet, capsule, injectable solution, etc. along with one or more pharmaceutically acceptable excipients and administered to a patient in need of a treatment for depression.

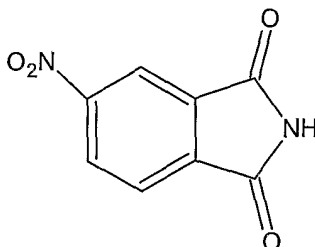
WE CLAIM:

1. A process for the preparation of 5-amino-2-benzofuran-1(3*H*)-one of Formula I,

**Formula I**

- 5 the process comprising:

- a) treating 5-nitro-1*H*-isoindole-1,3(2*H*)-dione of Formula V,

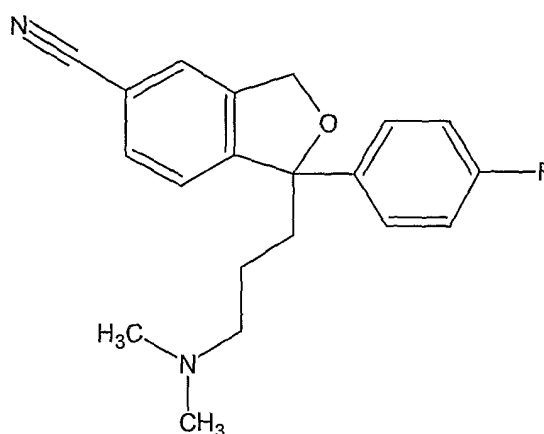
**Formula V**

with zinc in the presence of a base; and

- 10 b) isolating 5-amino-2-benzofuran-1(3*H*)-one of Formula I.

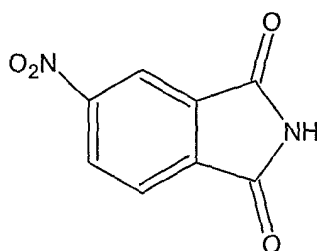
2. The process according to claim 1, wherein reaction is carried out at a temperature of from about -10° C to about 25° C.
3. The process according to claim 1, wherein the base comprises one or more of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate, potassium bicarbonate, magnesium hydroxide, magnesium carbonate, magnesium oxide, calcium hydroxide, calcium carbonate, calcium oxide, aluminium hydroxide and ammonia.
- 15 4. The process of claim 1, further comprising adding a catalytic quantity of a copper salt with zinc.

5. The process according to claim 4, wherein the copper salt comprises one or more of copper sulfate, copper nitrate, copper carbonate, copper acetate, copper benzoate, copper chromate, copper oxalate, copper phosphate and copper tetrafluoroborate.
6. The process according to claim 1, wherein the resulting 5-amino-2-benzofuran-1(3*H*)-one has a purity of 90% or more by HPLC.
7. A process for the preparation of citalopram of Formula II or a salt thereof,

**Formula II**

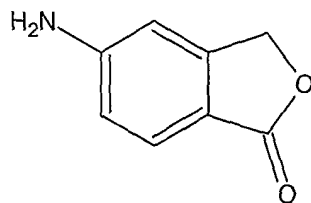
the process comprising:

- 10 a) treating 5-nitro-1*H*-isoindole-1,3(2*H*)-dione of formula V,

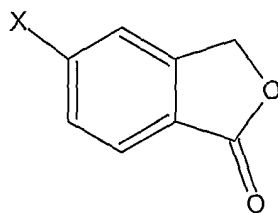
**Formula V**

with zinc in the presence of a base to get 5-amino-2-benzofuran-1(3*H*)-one of Formula I;

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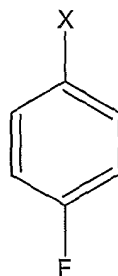
**Formula I**

b) treating the 5-amino-2-benzofuran-1(3H)-one of Formula I with a source of halogen to get 5-halo-2-benzofuran-1(3H)-one of Formula VI,

**Formula VI**

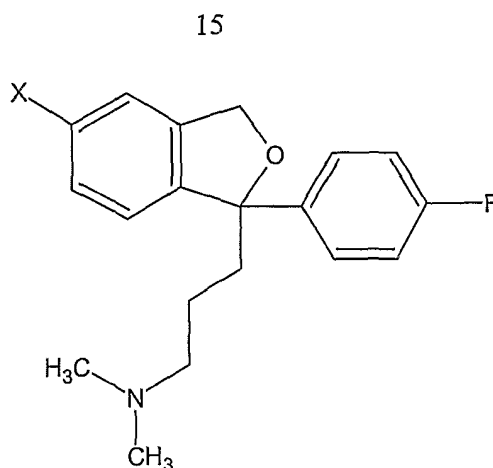
wherein X is Cl, Br or I;

c) treating the 5-halo-2-benzofuran-1(3H)-one of Formula VI with a Grignard solution of 1-fluoro-4-halobenzene of Formula VII,

**Formula VII**

wherein X is Cl, Br or I,

and N,N-dimethylaminopropyl metal halide to get 3-[1-(4-fluorophenyl)-5-halo-1,3-dihydro-2-benzofuran-1-yl]-N,N-dimethylpropan-1-amine of Formula VIII,



Formula VIII

wherein X is Cl, Br or I;

- d) treating the 3-[1-(4-fluorophenyl)-5-halo-1,3-dihydro-2-benzofuran-1-yl]-N,N-dimethylpropan-1-amine of Formula VIII with a cyanide source to get citalopram of Formula II; and
 - e) isolating the citalopram or a salt thereof.
8. The process according to claim 7, wherein the base comprises one or more of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate, potassium bicarbonate, magnesium hydroxide, magnesium carbonate, magnesium oxide, calcium hydroxide, calcium carbonate, calcium oxide, aluminium hydroxide and ammonia.
 9. The process according to claim 7, wherein the N,N-dimethylaminopropyl metal halide of step c) is N,N-dimethylaminopropyl magnesium halide.
 10. The process according to claim 7, wherein the cyanide source in step d) comprises one or more of cuprous cyanide, copper potassium cyanide, ferrocyanide, hydrogen cyanide, cadmium cyanide and barium cyanide.
 11. The process according to claim 7, further comprising adding a catalytic quantity of a copper salt with zinc.
 12. The process according to claim 11, wherein the copper salt comprises one or more of copper sulfate, copper nitrate, copper carbonate, copper acetate, copper benzoate, copper chromate, copper oxalate, copper phosphate and copper tetrafluoroborate.

13. The process according to claim 7, further comprising forming the product into a finished dosage form.
14. The process according to claim 7, further comprising administering the finished dosage form to a patient in need of a treatment for depression.
- 5 15. A pharmaceutical composition comprising a therapeutically effective amount of citalopram, or a salt thereof obtained by the process of claim 7; and one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/000752

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D307/83 C07D307/88

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)
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, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WARRENER R N ET AL: "A concise, regio and stereoselective route to fluorinated protoberberines via tandem addition-cyclisation reactions of phthalide anions with 3,4-dihydroisoquinolines" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 54, no. 26, 25 June 1998 (1998-06-25), pages 7485-7496, XP004132280 ISSN: 0040-4020 step C page 7492 ----- --/--	1-8

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

☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

29 June 2006

Date of mailing of the international search report

26/07/2006

Name and mailing address of the ISA/

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

Marzi, E

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/000752

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 665 181 A (THOMAS ET AL) 12 May 1987 (1987-05-12) step A, step B, column 7 column 6; example 8 -----	1-8
Y	WO 98/19512 A (H. LUNDBECK A/S; PETERSEN, HANS; BREGNEDAL, PETER; BOEGESOE, KLAUS, PE) 14 May 1998 (1998-05-14) the whole document -----	1-15
Y	WO 00/11926 A (H. LUNDBECK A/S; PETERSEN, HANS; ROCK, MICHAEL, HAROLD) 9 March 2000 (2000-03-09) page 1 the whole document -----	7,10-15
Y	US 4 136 193 A (BOGESO ET AL) 23 January 1979 (1979-01-23) claims 1-8,13-18 column 2, line 56 - column 4, line 5 -----	7-15
Y	"Org. Synth. Coll. Vol.2" 1943, , XP009068604 Pages 501-503 -----	1-8
Y	US 2003/153774 A1 (MALIK ASLAM A ET AL) 14 August 2003 (2003-08-14) figure 1 page 3, paragraph 43 - paragraph 45 page 5, paragraph 59 - paragraph 64 claims 1-7,24-30 -----	7,9-15
Y	SUEDKAMP B ET AL: "AMINOLYSIS OF PHTHALIDES" ARCHIV DER PHARMAZIE (WEINHEIM), vol. 318, no. 7, 1985, pages 640-648, XP009068534 ISSN: 0365-6233 page 646; example 2k -----	1-8
Y	LEVY L F ET AL: "4-AMINOPHTHALIDE AND SOME DERIVATIVES" JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL SOCIETY, LONDON, GB, vol. 99, 1931, pages 867-871, XP001038089 ISSN: 0368-1769 page 869 - page 870 -----	7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/000752

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/000752

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