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(54) Title: IMPROVED PROCESS FOR THE MANUFACTURE OF CITALOPRAM HYDROBROMIDE

(57) Abstract: The present invention describes an improved process for the preparation of extremely pure 1-(4'-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-phthalanecarbonitrile and its bromide salt (citalopram hydrobromide), which is a well known antidepressant. Other aspect of the invention are isolation of crystalline (4-Bromo-2-hydroxymethyl)phenyl-(4-fluorophenyl)-3-(dimethylaminopropyl)methanol (Bromodiol) and conversion of desmethylcitalopram which is formed during the cyanide exchange reaction, to Citalopram by heating with a mixture of formaldhyde and formic acid in chloroform. The resulting citalopram is conventionally purified using extraction methodology.

IMPROVED PROCESS OR THE MANUFACTURE OF CITALOPRAM HYDROBROMIDE

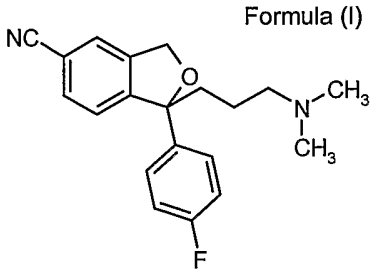
FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of extremely pure 1-(4'-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-phthalanecarbonitrile and its bromide salt (citalopram hydrobromide), which is a well known antidepressant. Other aspect of the invention are isolation of crystalline (4-Bromo-2-hydroxymethyl)phenyl-(4-fluorophenyl)-3-(dimethylaminopropyl)methanol (Bromodiol) and conversion of desmethylcitalopram to Citalopram generated in trace during the reaction by treatment with formaldehyde and formic acid in chloroform. The resulting citalopram product is optionally further worked up, purified and isolated in the form of a base or a pharmaceutically acceptable salts.

BACKGROUND OF THE INVENTION

Citalopram is a selective centrally acting serotonin (5-hydroxytryptamine; 5HT) reuptake inhibitor having antidepressant activity. The activity of citalopram is described in J. Hyttel, Prog. Neuro-Psychopharmacol. & Biol. Phychiat, 1982, 6, 277-295. Its effectiveness in the treatment of dementia and cardiovascular disorder has been disclosed in EP-A 474 580. The structure of Citalopram is shown in Formula (I):

Formula (I)



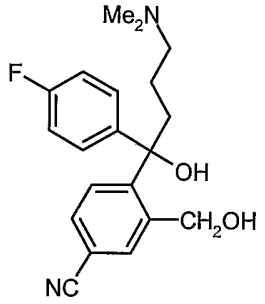
Citalopram was first discussed in DE 2,657,013, corresponding to US patent No. 4,136,193. So far several different processes for the preparation and purification of this active drug have been reported.

US Patent 4,136,193 describes preparation of Citalopram from 5-Bromophthalide using double Grignard reactions, namely with 4-Fluorobromobenzene and N,N-Dimethyl-aminopropyl

chloride. The bromo function of 1-(4'-Fluorophenyl)-1-(3-dimethylamino-propyl)-5-bromophthalan thus obtained is substituted by cyano group using copper cyanide in a suitable solvent to get the citalopram base. Small amount (1-2 %, even up to 10 % in some cases) of desmethylcitalopram is also found in this method which is formed during the high temperature substitution reaction.

WO 2000/011926 and WO/2000 013648 disclose the use of transition metals like Nickel or Palladium as catalyst for the substitution of halide group by a cyano such as KCN, NaCN or $(R'_4N)CN$, where R'_4 indicates four groups which may be same or different and are selected from hydrogen and straight chain or branched C_{1-6} alkane. Halide group discussed are bromo, iodo, and $CF_3-(CF_2)_n-SO_2-$ wherein n is an integer from the range of 0 to 8, preferably CF_3-SO_2-

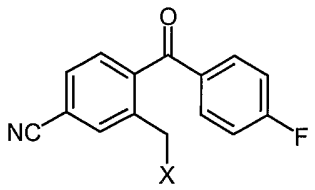
On the other hand US Patent 4,650,884 uses 5-Cyanophthalide as the starting material for the preparation of Citalopram. In that process the ring closure of the dihydroxy compound of formula



is achieved by dehydration with strong sulfuric acid at 80 °C. The dihydroxy compound is prepared from 5-cyanophthalide by two consecutive Grignard reactions. A combination of various solvents is also discussed in this patent for the re-crystallization to obtain the pure citalopram.

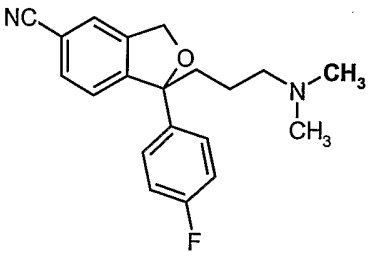
Conversion of various functional groups like hydroxyl, aldehyde, hydroxymethyl, nitromethyl, carboxy or methyl, etc. into cyano function for the preparation of Citalopram is described in patents like WO 2001/068632; WO 2001/ 066536; WO 1999/30548; EP 1,125,907; US 2001/056194, JP 2001/106681 and JP 2001/114773.

Apart from these US patent 6,579,993 describes a different production method of citalopram comprising the reaction of a compound of formula

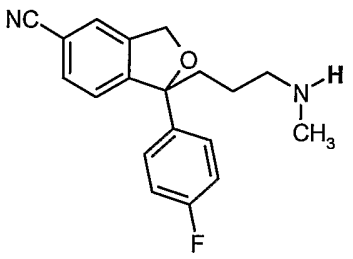


wherein X is a halogen, with organometallic dimethylaminopropyl halide.

Impurity profile of Citalopram is discussed in WO 2001/ 47877 where thin film distillation process is described for purification. It is well known that synthesis of citalopram in desired quality is very difficult. The manufacturing processes of citalopram described in the US patent 4,136,193; WO 2000/11926, WO 2000/13648 and DE 2,657,013 comprises the exchange of 5-halogen with cyano group. It has been found that along with citalopram unacceptable amount of desmethylcitalopram is also formed during the substitution of halogen group. The removal of desmethylcitalopram is very difficult by usual work up procedure, which leads to extensive and expensive purification processes. The chemical structure of citalopram and desmethylcitalopram is shown below:

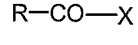


Citalopram

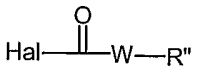


Desmethyl-citalopram

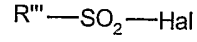
Similarly, WO 2001/045483 discloses the different purification method of citalopram. The purification method described in this patent application teaches the removal of desmethyl-citalopram formed during the cyanide exchange reaction. The crude citalopram obtained in this process after usual purification is subjected to treatment with an amide or an amide like group forming agent from the agents of formulae (a), (b) or (c):



(a)



(b)



(c)

where X is halogen or a group –O-CO-R', Hal is halogen, Y is O or S, W is O, N, or S and R', R" and R"" are each selected from the group consisting of hydrogen, alkyl and optionally substituted aryl or aralkyl.

Thus it is important to remove impurities formed during the cyanide exchange reaction in order to obtain a commercially attractive citalopram.

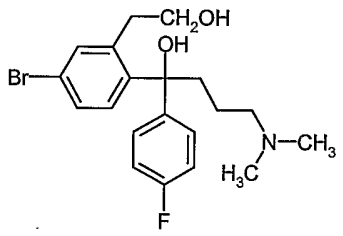
It is therefore an object of the present invention to provide an economical and industrially advantageous manufacture method of citalopram, which affords production of extremely pure citalopram in high yield.

SUMMARY OF THE INVENTION

According to the present invention a process is provided for the manufacture of highly pure 1-(4'-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-phthalanecarbonitrile and its bromide salt (Citalaopram hydrobromide).

In a first embodiment, crystalline (4-Bromo-2-(hydroxymethyl)phenyl)-(4'-fluoro-phenyl)-3-dimethylaminopropyl)methanol (Bromodiol)

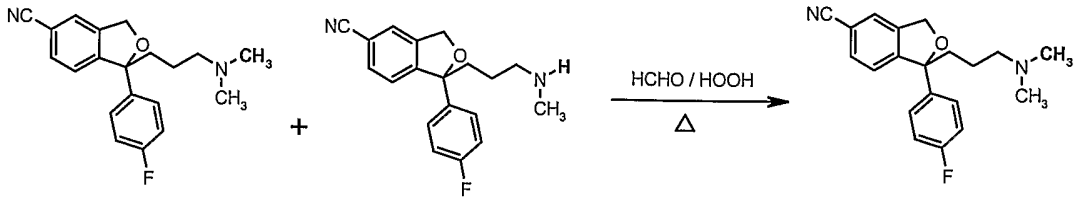
Formula (V)



Crystalline Bromodiol

is isolated. The bromodiol is synthesized from 5-Bromophthalide by two successive Grignard reactions, namely with 4-Fluorobromobenzene and N,N-Dimethylaminopropyl chloride.

In a second embodiment, the unwanted desmethylcitalopram formed during the cyanide exchange reaction is reconverted to citalopram by refluxing the crude citalopram with formaldehyde and formic acid in chloroform for 8 hours. The pictorial process is outlined below:



Crude Citalopram Desmethyl-citalopram Citalopram

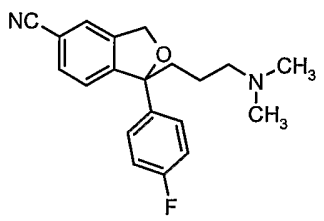
The crude citolaopram thus obtained is worked up and distilled under vacuum to get thick oily residue. HPLC purity of the obtained citalopram is found in the range of 90-94 %. Citalopram is conventionally converted to citalopram hydrobromide using 48 % hydrobromic acid in isopropyl alcohol followed by recrystallization in aqueous isopropanol. HPLC analysis showed 99.60 % purity of the crystalline citalopram hydrobromide obtained using the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Citalopram being an important and active anti-depressant therapeutic agent, a systematic study for its large scale manufacture of very high purity product and having well control over process impurities is under taken. This resulted in a robust manufacturing process, incorporating a step for re-conversion of desmethylcitalopram (the undesired product produced during the manufacture of Citalopram) into Citalopram by treatment with formic acid and formaldehyde.

The present invention is directed towards the novel manufacturing process of 1-(4'-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-phthalanecarbonitrile and its bromide salt (Citalaopram hydrobromide) of formula (I):

Formula (I)

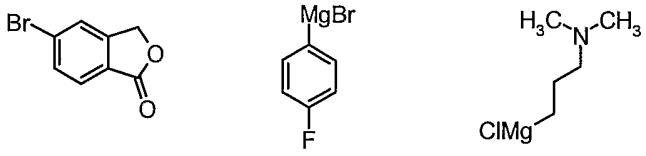


According to one embodiment the present invention, 1-(4'-Fluorophenyl)-1-(3-dimethyl-aminopropyl)-5-phthalanecarbonitrile is prepared according to the following synthetic reaction scheme:

(a) Reaction of 5-Bromophthalide with Magnesium halides of N,N-Dimethylaminopropyl chloride and 4-Fluorobromobenzene (Double Grignard Reaction)

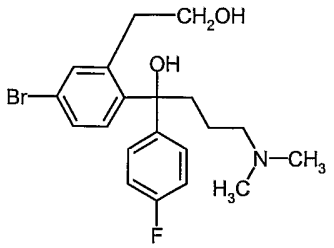
5-Bromophthalide (Formula II) is reacted with magnesium halides of 4-Fluorobromo benzene (Formula III) and N,N-Dimethylaminopropyl chloride (Formula IV)

Formula (II) Formula (III) Formula (IV)



in tetrahydrofuran to form (4-Bromo-2-hydroxymethyl)phenyl-(4-fluorophenyl)-3-(dimethylaminopropyl)methanol, (Bromodiol, Formula V)

Formula (V)



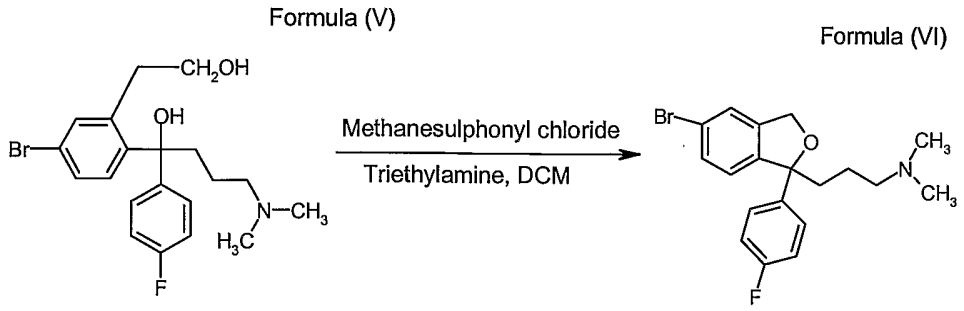
The compound having formula III is added to a cold solution of 5-Bromopthalide (Formula II) slowly over 4-6 hours followed by addition of compound having formula IV at -5 to –6 °C. The resultant mixture is stirred at –5 to –10 °C for 2 hours and additionally 3 hours at room temperature. The molar excess of magnesium halides of 4-Fluorobromo benzene and N,N-Dimethylaminopropyl chloride used in this reaction stage is typically between about 1 and about 2 fold preferably about 1.5 fold, relative to the 5-bromophthalide. Tetrahydrofuran used in the present reaction is between about 1 to 5 times, more particularly 1 to 2 times of 5-bromophthalide, which provides optimum yield and acceptable purity of Bromodiol.

Low temperature employed in the present reaction yields the lesser side products. After the desired time, organic solvent used in the reaction is distilled under industrial vacuum between 55 to 65 °C. Acetic acid is added to the residue to make it neutral to slightly basic. The reaction mass thus obtained is extracted with ethyl acetate and basified to a pH between 8.0 to 9.0 using concentrate ammonia solution. Finally, ethyl acetate extracted bromodiol is crystallized by cooling the solution at 0 °C. It is filtered and dried in the oven at 60 °C for 4 hours. HPLC Purity = 99.20%, Melting Point = 155 to 160 °C, Moisture Content = 2.30 %.

The bromodiol prepared in the present study is well crystalline solid, which is so far poorly described in the literature. Preparation of bromodiol in solid crystalline form increases its purity and this is extremely important for getting high purity of the final product.

(b) Cyclisation of Bromodiol (Bromocitalopram)

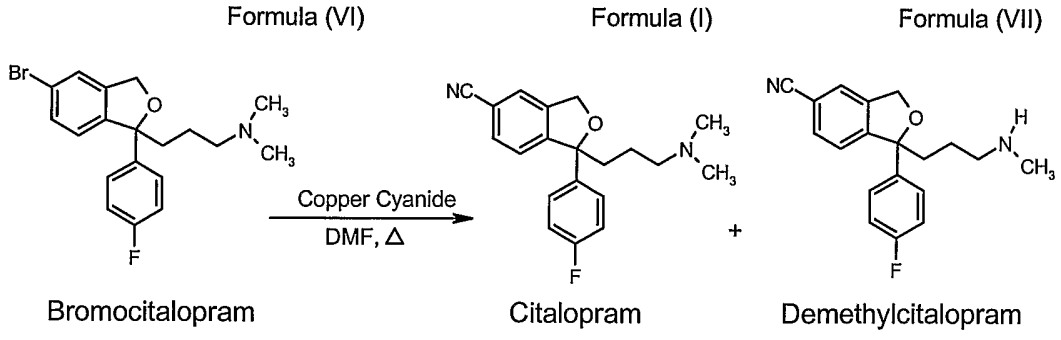
The Bromodiol (Formula V) is cyclised under very mild conditions using methane-sulphonyl chloride and triethylamine to form bromocitalopram (Formula VI):



Bromodiol is charged in aliphatic halide solvent more particularly in dichloromethane followed by addition of triethylamine. The reaction mixture is cool down to –5 °C and to it a solution of methanesulfonyl chloride in dichloromethane is added. The reaction mixture is warmed to room temperature and stirred for 1-2 hour till the reactant (Bromodiol) disappears. After usual work up crude bromocitalopram is dissolved in petroleum ether and filtered to remove insoluble impurities. This process provides more than 97 % HPLC pure Bromocitalopram.

(c) Preparation of Citalopram

1-(4'-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalan (Formula VI) is reacted with copper cyanide in a polar solvent to generate Citalopram (Formula I):



Suitable polar solvent for this reaction include dimethylformamide. The molar ratio of cyanide source is between about 1 to 5 more preferably about 2 to 3 times of Bromocitalopram. Copper cyanide reacts with Bromocitalopram under rather drastic condition of high temperature

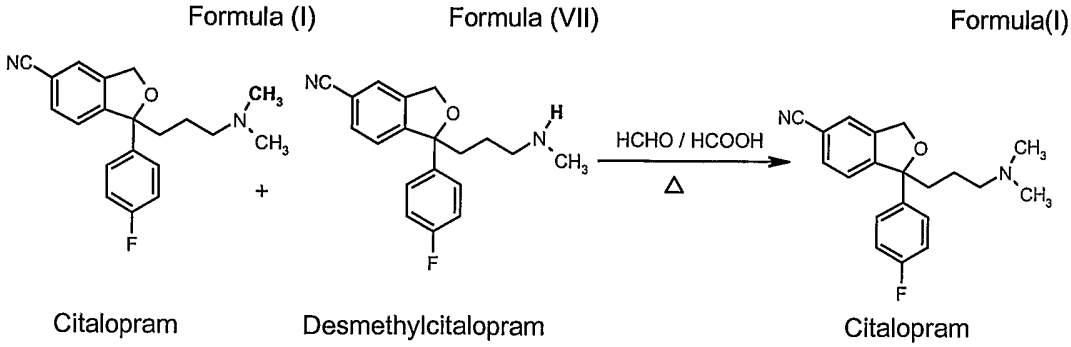
preferably around 160 °C. Molar ratio of copper cyanide is critical for this reaction. Copper cyanide about 2-3 times more particularly 2.5 times of Bromocitalopram favors the maximum conversion of bromo function into cyano.

It is observed that exchange reaction should be continued until the formation of citalopram occurs, as unreacted bromocitalopram is very difficult to remove from the final product. We have simplified the work-up procedure of this reaction. As the reaction is over, it is poured into a mixture of aqueous ethylenediamine and chloroform, stirred and filtered to remove metallic and other impurities in form of a filterable solid. Citalopram gets extracted in chloroform. This simplified work-up procedure avoids use of sodium cyanide for the removal of copper impurities as described in US Patent 4,136,193. The crude citalopram obtained after extraction consists of approximately 5-10 % of desmethylcitalopram.

Due to the structural similarity between desmethylcitalopram and Citalopram, it is very difficult to remove desmethylcitalopram from Citalopram, by simple re-crystallization operation, once it is formed. The WO 2001/045483 teaches about the purification of Citalopram, especially removal of desmethylcitalopram. This method is such that it only removes desmethylcitalopram.

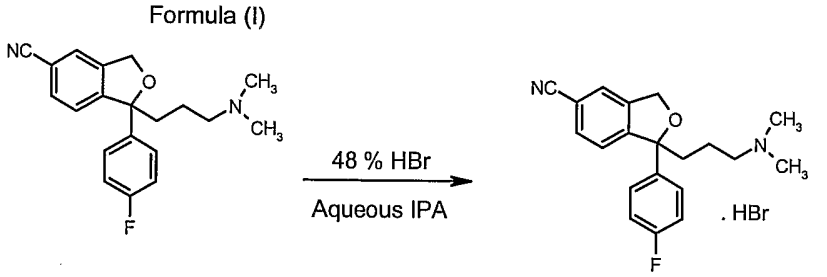
However, in the present invention desmethylcitalopram is reconverted into Citalopram. This process not only removes the impurity but increases the yield of Citalopram. The crude Citalopram is isolated by chloroform extraction from the reaction mixture and purified by treatment with acetic acid and ammonia.

An interesting and important feature of the present invention is that crude chloroform solution containing citalopram along with desmethylcitalopram is treated with formic acid and formaldehyde as shown below:



(d) Preparation of Citalopram hydrobromide

Citalopram synthesized in the above step is treated with 48 % aqueous hydrobromic acid in a mixture of water and isopropyl alcohol at room temperature to afford crude crystalline citalopram bromide salt:



Citalopram Citalpram hydrobromide

The resultant crystalline Citalopram hydrobromide is stirred for 8 to 10 hours. It is observed that for getting the right quality Hydrobromide, it is necessary to control the temperature between 30 to 35°C during its formation. Increase of temperature during hydrobromide formation leads to degradation of Citalopram. Finally, Citalopram Hydrobromide thus obtained is re-crystallized from aqueous isopropyl alcohol to get highly pure Citalopram Hydrobromide.

The following examples illustrate the invention, but is not limiting thereof.

EXAMPLE 1

(4-Bromo-2-hydroxymethyl)phenyl-(4-fluorophenyl)-3-(dimethylaminopropyl)methanol, (Bromodiol)

1.0 Ltr N,N-Dimethylaminopropyl chloride hydrochloride (in form of 60% aqueous solution) is cooled to 0 °C and 0.40 Kg 50 % caustic lye is added to it under constant stirring. The solution is allowed to warm to room temperature and layer is separated. Upper organic layer is dried over Sodium Hydroxide flakes and distilled under vacuum, fractions boiling between 50 to 55 °C at 60 mm of Hg is collected to get 425 gm of pure dry N,N-Dimethyl-aminopropyl chloride.

In a 10 Ltr three necked round bottom flask carrying stirrer thermowell and nitrogen inlet is charged magnesium turnings (104 gm), 200 ml tetrahydrofuran and a crystal of iodine. To this a solution of 4-Fluorobromobenzene (0.624 Kg) in tetrahydrofuran (800 ml) is added slowly over 2 hours to get Grignard reagent. In a separate set 10 Ltr three necked round bottom flask,

magnesium turnings (104 gm), 200 ml tetrahydrofuran and a crystal of iodine is taken. To this a solution of N,N-Dimethylaminopropyl chloride (410 gm) in 500 ml tetrahydrofuran is added over 2 hours to get the second Grignard reagent.

In a 20 Ltr round bottom flask is charged 5-Bromophthalide (532 gm), tetrahydrofuran (800 ml) and cooled to -5 to –10 °C. To this a solution of 4-Fluorophenylmagnesium bromide in tetrahydrofuran is added slowly over 4 to 6 Hours; followed by addition of N,N-Dimethylamino-propylmagnesium chloride in tetrahydrofuran in 4 to 6 hours at -5 to –6 °C. The reaction mixture is stirred at -5 to –10 °C for 2 hours and then allowed to warm to room temperature and is stirred for further 3 hours. After the reaction is completed it is cooled to 0 to –5 °C, water (10 Ltr) is added and distilled under industrial vacuum at 60 to 65 °C to recover tetrahydrofuran, acetic acid (500 ml) is added to get pH in the range of 7.0 to 8.0. The reaction mass is extracted with ethyl acetate (3 X 2.5 Ltr). Combined ethyl acetate layer is re-extracted with 20% acetic acid in water (3 X 2.5 Ltr). Acetic acid extract is basified with concentrated ammonia (1.90 Ltr) to pH 8.0 to 9.0. The bromodiol is extracted with fresh ethyl acetate (3 X 3.0 Ltr). Combined ethyl acetate extract is cooled to 0 °C and stirred for 3 hours which results in complete crystallization of bromodiol. It is filtered and dried in oven at 60 °C for 4 hours. Yield of bromodiol = 556 gm, HPLC Purity = 99.20%, Melting Point = 155 to 160 °C, Moisture Content = 2.30 %.

EXAMPLE 2

1-(4'-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalan (Bromocitalopram)

In a 20 Ltr round bottom flask carrying stirrer, thermowell and addition funnel is charged Bromodiol (550 gm), dichloromethane (9.70 Ltr) and triethylamine (571 ml). The resultant mixture is cooled to –5 °C and a solution of methanesulfonyl chloride (139.5 ml) in dichloromethane (550 ml) is added to it over 1 hour. It is then warmed to room temperature and stirred for about 1 to 2 hours till starting material disappears. Reaction mass is then washed with aqueous Sodium Hydroxide solution (0.1 N, 2 X 5.50 Ltr) followed by water (2 X 5.0 Ltr), dried over sodium sulfate and concentrated to get a thick syrupy crude Bromocitalopram. Yield of Crude Bromocitalopram = 390 gm. HPLC Purity = 90%.

Crude Bromocitalopram is refluxed with petroleum ether (60- 80 °C, 8.0 Ltr) to dissolved and is filtered while hot to remove insoluble impurities. It is then concentrated to get purified Bromocitalopram. Yield of Bromocitalopram = 350 gm, HPLC Purity = 97.6%.

EXAMPLE 3

1-(4'-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-phthalanecarbonitrile (Citalopram)

In a 2.0 Ltr three necked round bottom flask carrying stirrer, nitrogen inlet, thermowell and reflux condenser is charged dimethylformamide (240 ml) and Copper Cyanide (207 gm) and heated under stirring at 150 °C (gentle reflux). To this a solution of Bromocitalopram (350 gm) in dimethylformamide (70 ml) is added. About 70 ml of dimethylformamide is distilled out at atmospheric pressure from this reaction mass. This process raises reaction temperature to 163 to 165 °C and is maintained under stirring for 6 to 8 hours. It is allowed to cool up to 60 °C and is added into a mixture of ethylenediamine (380 ml) and water (1.80 Ltr) under nitrogen stirring. The reaction mass thus obtained is allowed to cool up to 40 °C and chloroform (1.40 Ltr) is added to it. The mixture is stirred for half an hour and filtered to remove metallic impurities. Filtrate is allowed to separate in two layers. Lower organic layer is separated followed by re-extraction of aqueous layer with chloroform (2 X 0.80 Ltr). Combined chloroform layer is washed with water (0.50 Ltr).

To this chloroform layer is added formic acid (0.31 Ltr) and formaldehyde (0.29 Ltr) and refluxed for 8 hours. It is then cooled to room temperature and basified to pH 8.0 to 9.0 using ammonia solution. Chloroform layer is separated, washed with water (0.80 Ltr), dried over sodium sulfate and concentrated to thick residue (308 gm). Residue is dissolved in toluene (1.80 Ltr) and toluene solution is extracted using 20% aqueous acetic acid (3 X 1.20 Ltr). Combined aqueous layer is basified to pH 8.0 to 9.0 using Sodium Hydroxide solution (0.75 Ltr). Citalopram thus obtained is extracted using isopropyl ether (3 X 1.20 Ltr), combined extract is washed with water, dried over sodium sulfate and concentrated under industrial vacuum to get Citalopram free base as to thick oily residue. Yield of Citalopram = 180 gm, HPLC Purity = 90 to 94%.

EXAMPLE 4

1-(4'-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-phthalanecarbonitrile hydrobromide (Citalopram hydrobromide)

In 1.0 Ltr three necked round bottom flask carrying stirrer and thermowell is charged a mixture of water (160 ml) and isopropyl alcohol (40 ml) followed by Citalopram free base (180 gm). The mixture is stirred at room temperature followed by addition of 48 % hydrobromic acid

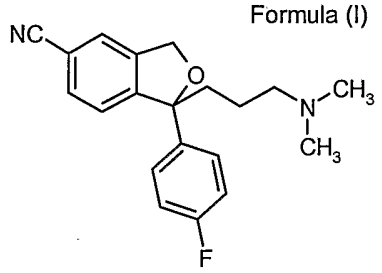
(35 ml) which forms a clear solution. It is then cooled to 0 °C to get crystalline Citalopram Hydrobromide. Stirring is continued at 0 °C for 8 to 10 hours and filtered to obtain wet stuff. Yield of wet Citalopram Hydrobromide = 150 gm.

Wet Citalopram Hydrobromide is dissolved in a mixture of water (160 ml) and isopropyl alcohol (40 ml) at 35 to 40 °C, charcoalized using 5 gm charcoal and filtered through hyflow bed. Filtrate is allowed to stir at 0 °C to get crystalline Citalopram Hydrobromide. It is stirred at 0 °C for further 4 to 5 hours and filtered. Crystalline solid is dried in vacuum oven at 60 °C for 4 to 5 hours to get re-crystallized Citalopram Hydrobromide. Yield of Citalopram Hydrobromide = 85 gm, HPLC Purity = 99.60 %. The re-crystallization procedure is repeated till a desired purity level of Citalopram is obtained.

We claim:

1 A process for the manufacturing a compound of Formula (1)

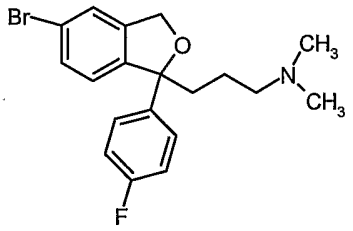
Formula (I)



and its salts, said method comprising:

(a) subjecting a compound of the Formula (VI)

Formula (VI)



to cyanide exchange reaction till the bromo group is substituted completely.

(b) resultant crude citalopram is optionally subjected to initial purification.

(c) partially purified citalopram is subsequently heated in a mixture of aldehyde and acid to convert desmethylcitalopram into citalopram base and contacting pure citalopram base with aqueous hydrogen halide and isolate the pure product.

2 The process of claim 1, wherein step (a) is carried out in an organic solvent.

3 The process of claim 2, wherein the organic solvent is N,N-Dimethylformamide.

4 The process of claim 1, wherein 5-Bromocitalopram is added to a pre heated copper cyanide in N,N-Dimethylformamide.

5 The process of claim 4, wherein 5-Bromocitalopram in N,N-Dimethylformamide solution is added.

6 The process of claim 1, wherein the reaction temperature is between about 150 to 170 °C.

7 The process of claim 1, wherein the completed reaction in step (b) is cooled to about 60 °C and poured into a basic solution.

8 The process of claim 7, wherein the basic solution comprises ethylenediamine and water in the ratio between about 1.0 : 1.0 to about 1.0 : 5.0.

9 The process of claim 1, wherein aliphatic halide solvent in step (b), is added to the reaction mass.

10 The process of claim 9, wherein said aliphatic halide is chloroform.

11 The process of claim 1, wherein said acid in step (c) is an aliphatic acid.

12 The process of claim 11, wherein said aliphatic acid is formic acid.

13 The process of claim 1, wherein said aldehyde in step (c) is an aliphatic aldehyde.

14 The process of claim 13, wherein said aldehyde is formaldehyde.

15 The process of claim 1, wherein molar ratio of formic acid and formaldehyde, in step (c), is between about 0.50 to about 3.0.

16 The process of claim 1, wherein reaction mixture in step 1 (c) is heated to reflux temperature.

17 The process of claim 1, wherein the heating time of reaction mixture, in step (c), is between about 1 to about 20 hours.

18 The process of claim 17, wherein reaction mixture is cooled to room temperature and basified.

19 The process of claim 18, wherein said basic source is concentrated ammonia.

20 The process of claim 19, wherein pH of the said crude solution is in between about 7.0 to about 10.0.

21 The process of claim 20, wherein chloroform layer is separated, washed with water and concentrated to get crude citalopram.

22 The process of claim 21, wherein said product is dissolved in aromatic hydrocarbon.

23 The process of claim 22, wherein said aromatic hydrocarbon is toluene.

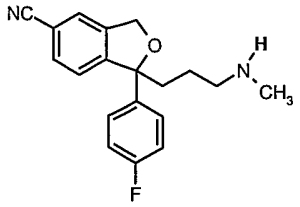
24 The process of claim 23, wherein said solution is extracted with aqueous acid.

25 The process of claim 24, wherein said acid is 20 % acetic acid in water.

26 The process of claim 25, wherein aqueous layer is basified by a metallic hydroxide.

27 The process of claim 26, wherein pH of the said solution is between about 6.5 to about 11.0.

28 The process of converting, desmethylcitalopram having the formula



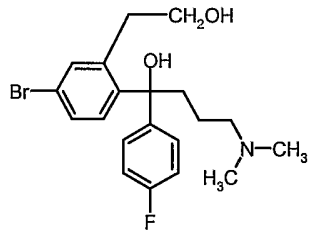
to citalopram.

29 The process of claim1, wherein citalopram is converted to citalopram hydrobromide in step (c) by using aqueous hydrogen bromide.

30 The process of claim 29, wherein reaction is carried out in aqueous alcohol.

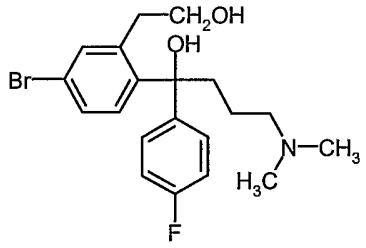
31 The process of claim 30, wherein said alcohol is isporopanol.

32 A crystalline compound having the Formula

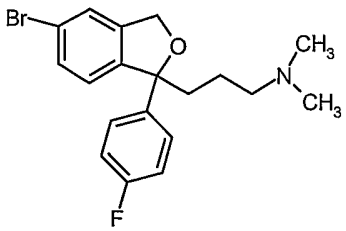


in substantially pure form.

33 A process for cyclisation of the compound having formula



into a compound having formula



in an organic solvent in the presence of a sulphonyl halide and a base.

34 The process of claim 33, wherein said organic solvent is aliphatic halide.

35 The process of claim 34, wherein said halide is sulphonyl halide.

36 The process of claim 35, wherein said sulphonyl halide is methanesulphonyl chloride.

37 The process of claim 33, wherein said base is aliphatic amine.

38 The process of claim 37, wherein more particularly aliphatic amine is triethylamine.

39 The process of claim 33, wherein solution is stirred at room temperature for about 1 to about 2 hours.

40 The process of claim 1, wherein less than 0.06 % desmethylcitalopram remains in step (C) after acid-aldehyde treatment.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB03/04757

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07C 255/00; C07D 307/78, 307/87
US CL : 549/467; 558/422

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)
U.S. : 549/467; 558/422

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 practicable, search terms used)
East, West, STN: Registry, Chemical Abstracts, Marpat

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,650,884 A (BOGESO) 17 March 1987 (17.03.1987), abstract and claims.	1-40
Y	US 6,579,993 A (HILDEN et al) 17 July 2003 (17.07.2003), columns 2-6.	1-40
Y	US 6,660,873 A (PETERSEN et al) 09 December 2003 (09.12.2003), columns 1-6.	1-40

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* *Special categories of cited documents:*

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"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

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