Title: A PROCESS FOR THE PREPARATION OF ESCITALOPRAM

Abstract: The present invention relates to an improved process for the preparation of escitalopram of the formula-(I) which consists of a sequential double Grignard reaction on S-iodophthalide to get the dihydroxy compound of formula-(XVI), its resolution using a chiral acid, cyclization of resolved compound of the formula-(XVII), and cyamation of compound of the formula-(XVIII) using DMF and copper(I) cyanide. The present process utilizes the facile displacement of iodo group with cyanogroup in the final step of escitalopram. Escitalopram is a widely used anti-depressant.
A PROCESS FOR THE PREPARATION OF ESCITALOPRAM

FIELD OF INVENTION

The present invention relates to an improved process for the preparation of escitalopram oxalate. Escitalopram ((S)-1-[3(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile) is the S-enantiomer ((+)isomer) of the well-known antidepressant drug citalopram, having the formula-I given below. Escitalopram was found to be more active than the dl-citalopram or the R-citalopram.

\[
\begin{align*}
\text{NC} & \quad \text{O} & \quad \text{N} \\
\text{F} & \quad 1
\end{align*}
\]

BACKGROUND OF THE INVENTION

Citalopram, which has been disclosed in DE Patent no. 2,657,013 (1977) corresponding to US Patent no. 4,136,193 (1979) is a well-known antidepressant drug available in the market for some years. It is a selective, centrally acting serotonin (5-HT) reuptake inhibitor, is accordingly having the antidepressant activity. The antidepressant activity of citalopram has been reported in several publications, e.g. J. Hyttel, Prog. Neuro-Psychopharmacol. & Biol. Psychiat., 1982, 6, 277-295 and A. Gravem, Acta Psychiatr. Scand., 1987, 75, 478-486. Recently, Escitalopram is found to be more active than the dl-citalopram.

Process for the preparation of escitalopram is disclosed in U. S. Pat. No. 4,943,590. According to this patent, attempts to crystallize the diastereomeric salts of citalopram enantiomers have failed. In this patent a process for the preparation of escitalopram was described by resolving the intermediate (compound of the formula-XI) of citalopram and
ring closure of the resolved intermediate in a stereospecific manner to get the escitalopram (Shown in the Scheme-I).

\[
\begin{align*}
\text{NC} & \quad \text{O} \quad \text{MgBr} \quad \text{OH} \quad \text{N} \\
\text{II} & \quad \text{F} \\
\text{III} & \quad \text{F} \\
\text{IV} & \\
\text{V} & \\
\text{VI} & \\
\text{I} &
\end{align*}
\]

Scheme-I

The main drawback in this process is the purity of the intermediate compound of the formula-XI obtained in the Grignard reaction, which is of 80-90% only. The crude compound of the formula-XI needs extensive purification before proceeding for resolution. The purification technique given in the above patent process involves repeated charcoal and silica gel treatment to the compound of the formula-XI or its HBr salt. Also, during the HBr salt formation of compound of the formula-XI, the amount of HBr used in the process should be less than the molar quantity to avoid additional impurities formation. As the impurities present in the intermediate compound of the formula-XI have closely related properties such a purification technique is not viable on a commercial scale to make this intermediate and also the escitalopram. Also, the overall yield of escitalopram given in this patent is only 8.8% starting from 5-cyanophthalide of
the formula-IX. Therefore such a low yielding process needs to be improved for commercial production of escitalopram.

Recently a process for the preparation of escitalopram is disclosed in WO 03/0006449. According to the method given in this patent intermediates (such as compound of formula-IV, bromo citalopram) of dl-citalopram were separated into the individual enantiomers by chromatographic method and converted to escitalopram.

The main drawback in this process is the non-availability of chiral stationary phase on bulk scale and its implementation on a commercialization. Output from such a process will also be low.

Keeping in view of the difficulties in commercialization of the above-mentioned process for the preparation of escitalopram, we aimed to develop a simple and economical process for commercial production of escitalopram.

DESCRIPTION OF PRESENT INVENTION

We observed that a promising approach for a process for the preparation of escitalopram would be to (a) avoid the usage of 5-cyanophthalide as starting material (b) avoid the purification of intermediates involved in making escitalopram thereby making the process commercially viable and economical and (c) develop an efficient method for the conversion of intermediates into escitalopram.

Focusing on these points we developed an improved process for the preparation of escitalopram and filed a patent recently which is pending and having the number 052 / MAS / 2003 and dated 17/01/2003.

According to the process disclosed in the said patent application, 5-bromophthalide is subjected to double Grignard reaction and the resulting dimagnesium salt of formula-XIV is isolated by filtration. By doing so we could remove all the related impurities present in the reaction mass and get the required compound of the formula-IV in more than 98%
purity after neutralization of salt. The dihydroxy intermediate thus obtained was resolved into its isomers by treating with a resolving agent. The resolved intermediate of the formula-XVI was cyclized to the bromo derivative of the formula-XVII and finally this bromo intermediate was converted to escitalopram base by treating it with copper cyanide. The quality of escitalopram obtained by this procedure is more than 97%. The process is shown in the reaction Scheme-II.
The main drawback in this process is the conversion of bromo group present in compound of formula-XIII into cyano group present in escitalopram. Conversion is a slow process (more than 18 hr at 145-150°C) and removal of starting bromo compound present in escitalopram is difficult due to liquid nature of escitalopram and also similar solubility properties of salts derived from both the bromo impurity and escitalopram.

During our sustained research to overcome this problem we found that introduction of copper (I) iodide in the above-mentioned bromo displacement reaction increased the yield and the rate of cyanation. Introduction of copper (I) iodide converts the bromo group present in compound of formula-XIII into iodo group, which is more reactive than the bromo group during cyanation with copper (I) cyanide.

Keeping this in mind we aimed to prepare iodo analogue of compound of the formula-XIII and use the same in synthesizing escitalopram of the formula-I. Accordingly, iodo analogue of compound of the formula-XIII can be prepared from 5-iodophthalide by following the same process as that of bromo compound, This process is shown in the reaction scheme III.
Scheme-III

A process for the preparation of iodo compound of the formula-XVIII is disclosed in WO00/13648. 5-Iodophthalide of the formula-XIV is sequentially reacted with p-fluorophenylmagnesium bromide and 3-dimethylaminopropylmagnesium chloride to get the dihydroxy compound of the formula-XVI. This dihydroxy compound is subjected to acid catalyzed cyclization to get the iodo phthalane derivative of the formula-XVIII as dl-mixture. The dihydroxy compound of the formula-XVI is not isolated and characterized in the above patent process. Also, the process for isolation of compound of the formula-XVIII (dl-mixture) requires column chromatography and the overall yield is only 8%. Maintaining high purity for the compound of the formula-XVI is very essential to get optimum yield and chiral purity of compound of formula-XVII in the resolution process.
As the procedures for preparation of high purity compound of the formula-XVI are not available in the literature there is a need to develop such process for commercialization of the process for escitalopram.

During the process development of citalopram hydrobromide we observed that the Grignard reaction on 5-bromophthalide is very much temperature dependant and the best yields are possible only if the reaction is done below –10C. Similar temperature condition is anticipated for a Grignard reaction on 5-iodophthalide to get maximum yield and purity of the compound of the formula-XVI.

Accordingly, the main objective of the present invention is to provide an improved process for the preparation of escitalopram from the iodo compound of the formula-XVI, which is commercially applicable.

Yet another objective of the present invention is to provide an improved process for the preparation of escitalopram by improving the yield and quality of the dihydroxy compound of the formula-XVI.

Still another objective of the present invention is to provide an improved process for the preparation of escitalopram which involves the resolution of the dihydroxy compound of the formula-XVI into its enantiomers by making a diastereomeric salt using a chiral acid.

Another objective of the present invention is to provide an improved process for the preparation of escitalopram, which involves the cyclization of the chiral dihydroxy compound of the formula-XVII in a stereospecific manner via nucleophilic displacement technique.

Accordingly the present invention provides an improved process for the preparation of escitalopram of the formula-I,
which comprises:

(i) reacting 5-iodophthalide of the formula-XIV,

![Formula XIV](image)

with p-fluorophenylmagnesium bromide in an ether medium to get the benzophenone derivative of the formula-XV,

![Formula XV](image)

(ii) reacting the benzophenone derivative of the formula-XV with 3-(dimethylamino)propylmagnesium chloride to get the dihydroxy compound of the formula-XVI,
(iii) resolving the compound of the formula-XVI with (+)-di-p-toluoyltartaric acid by preferential crystallization in a solvent medium to get its (-)-enatiomer salt with (+)-di-p-toluoyltartaric acid

(iv) neutralizing the diastereomeric salt and isolating the liberated chiral dihydroxy compound of the formula-XVII,

(v) cyclizing the dihydroxy compound of the formula-XVII using methanesulfonyl chloride in basic medium to get the cyclic compound of the formula-XVIII,
(vi) reacting the compound of the formula-XVIII with copper cyanide in dipolar aprotic solvent medium at elevated temperature (80-160°C) to get escitalopram base of formula-I,

and if desired (vii) converting the compound of the formula-I into its pharmaceutically acceptable salt, like oxalate, etc by conventional methods.

The ether medium used in step (i) can be selected from a group of solvents such as diethyl ether, diisopropyl ether, 1,4-dioxane, 2-methyl tetrahydrofuran, terahydrufuran, preferably tetrahydrofuran or diethyl ether. The Grignard reaction in steps (i) and (ii) can be effected at a temperature in the range of -25°C to 0°C preferably, at a temperature in the range of -20°C to -10°C. The solvent used in resolution step can be methanol, ethanol, isopropanol, ethyl acetate, acetone, acetonitrile, or a mixture thereof. The solvent used in cyclization step can be methylene chloride, toluene, cyclohexane, tetrahydrofuran, isopropyl ether, ether, acetonitrile, etc. The cyanation step may be done in N, N-dimethylformamide, N,N-dimethylacetamide, pyridine, N-methyl-2-pyrrolidone, etc. Temperature of reaction during cyanation is between 80-180°C, preferably between
100-150°C, more preferably between 120-140°C. The amount of copper (I) cyanide used in the reaction can be in the range of 1.0-2.5 moles per mole of iodo compound, preferably 1.5-2.0 moles per mole of iodo compound.

The pharmaceutically acceptable oxalate salt formation can be done in solvents like, methanol, ethanol, isopropanol, water, acetone, acetonitrile, or a mixture thereof.

Escitalopram prepared according to the process disclosed in this application has high yield (>75%) and high purity (>99%) with no bromo impurity. Doing cyanation on the iodo compound of formula-XVII is novel and applied for the first time in making escitalopram. Cyanation on the iodo compound of formula-XVII has improved the quality of escitalopram and the yields are high.

The details of the process of the invention are provided in the Examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

**Example 1**

**Preparation of escitalopram:**

(i) Preparation of dihydroxy compound of formula-XVI:

The Grignard solution prepared from 90g of 4-fluorobromobenzene and 13g magnesium turnings in 450ml of THF was added drop wise to a suspension of 5-iodophthalide (100g) in THF (400ml) at -15 to -10°C under nitrogen atmosphere. After the addition was completed, the reaction mixture was stirred at same temperature for another 3h. The second Grignard reagent prepared from 68g of 3-(dimethylamino) propyl chloride and 16g of magnesium turnings in THF (300ml) and toluene (300ml) was added to the above reaction mixture at -15 to 0°C over a period of 2-3h and maintained for additional 2h. TLC of the reaction mixture showed the absence of starting material.
The reaction mass was quenched into 1L water containing 150ml of acetic acid. Toluene (1L) was added to the reaction mass and stirred for 1h. Layers were separated and the water layer extracted with 500ml of toluene. Combined toluene layer was washed with water, dried and distilled to get 140g of crude dihydroxy compound of the formula-XVI as syrup.

The above crude of the formula-XVI was dissolved in 300ml of toluene. Water (200ml) was added to the reaction mass and acidified with 45g of aqueous hydrobromic acid. The reaction was stirred for 15h at RT and cooled to 10°C. The reaction mass maintained at 10°C for 1h before filtration. The wet solid was washed with 50ml of chilled water.

Drying of the product yielded 120g of hydrobromide salt of the compound of the formula-XVI as white solid. M. P is 192.9°C. Purity by HPLC is 99.18%. IR (KBr): 3279, 2958, 2700, 1601, 1505, 1475, 1410, 1387, 1211, 1182, 1158, 1084, 1014, 964, 913, 846, 818, 554, 577, and 525cm⁻¹.

The above HBr salt (100g) was taken into a flask and diluted with water (1L). Sodium hydroxide flakes (19g) were added to the reaction mass and stirred for 1hr. The compound was extracted into toluene (2 x 500ml). Combined toluene layer was washed with water, dried and distilled under vacuum to get 88g of the dihydroxy compound of formula-XVI as an oily compound.

(ii) Resolution of dihydroxy compound of formula-XVI:

The dihydroxy compound of formula-XVI (100g) obtained as described above was dissolved in 200ml of isopropyl alcohol at 40-45°C. Solid (+)-di-p-toluoyltartaric acid monohydrate (52g) was added to the reaction mixture and kept under stirring for overnight at 20-25°C. The crystals formed in the reaction mixture were filtered and washed with 50ml of isopropyl alcohol to get 55g (74%) of (-)-4-iodo-α¹-(4-fluorophenyl)-α¹-[3-(dimethylamino) propyl]-1,2-benzenedimethanol, hemi (+)-di-p-toluoyltartaric acid salt. Melting point: 139°C. Optical rotation 8.45 (c = 1, MeOH). IR (KBr): 3350, 3288, 2959, 1729, 1613, 1507, 1383, 1288, 1220, 1154, 1109, 1036, 838, 816, 755, and 578cm⁻¹. Chiral purity by HPLC is 99.2%.
(iii) Cyclization of resolved dihydroxy compound of formula-XVII:

To 50g of (-)-4-iodo-α<sup>1</sup>-(4-fluorophenyl)-α<sup>1</sup>-[3-(dimethylamino) propyl]-1,2-benzenedimethanol, hemi (+)-di-p-toluoyltartaric acid salt prepared as described above in 500ml of water was added a solution of 8g of sodium hydroxide in 100ml of water. After stirring for 1h at 25-30°C product was extracted into toluene (2 x 500ml) and the toluene layer distilled off below 60°C to get 30g of the (-)-isomer of dihydroxy compound as oil. [α]<sub>19</sub> = -46.2 (c = 1, methanol).

To a solution of the above base in toluene (500ml) was added triethylamine (15g) and cooled to -5°C. Methanesulfonyl chloride (10.0g) was slowly added to the reaction mixture at -5 to 0°C over a period of 3hrs. After maintaining for 1h at same temperature reaction was found to complete by TLC. The reaction mixture was poured into water (300ml) and separated toluene layer. Aqueous layer was extracted with toluene (2 x 50ml) and the combined toluene layer washed with 200ml of water. Toluene was distilled off from the reaction mixture below 60°C to get 28g of the iodo compound of formula-XVIII. [α]<sub>19</sub> = 1.47° (c = 1, methanol). Chiral purity by HPLC: 99.2%.

A small sample (5.0g) was converted to its oxalate salt in acetone medium. Melting point: 163.9°C. Chiral purity by HPLC: 99.5%.

(iv) Cyanation of iodo compound of formula-XVIII:

To a solution of iodo compound (30g) of the formula-XVIII in DMF (300ml) was added copper(I) cyanide (13g) and the reaction mixture heated under nitrogen atmosphere at 120°C. After maintaining the reaction mixture at this temperature for 8h, reaction mixture was cooled to 25-30°C and poured into water (1000ml). After stirring for 1h, ethylenediamine (30ml) was slowly added to the reaction mixture and maintained for 3h under stirring. Toluene (200ml) was added to the reaction mixture and stirred for 30min. Inorganic copper salts were filtered off from the reaction mixture with the aid of hiflow. The hiflow bed was washed with 100ml of toluene. Filtrate was taken into a separating funnel and the toluene layer separated. The aqueous layer was extracted with toluene (100ml). The combined organic layer was washed with water. The organic layer was
extracted with 10% aqueous acetic acid (2 x 100ml). The combined acetic acid layer was treated with charcoal (10g) and filtered. Aqueous ammonia was added to the filtrate to get a pH of 8.5-9.0. The product was extracted into isopropyl ether (2 x 200ml) and the solvent distilled off to get 18g (80%) of crude escitalopram base as oil. Purity by HPLC was found to be 99.2%. Iodo compound of the formula-XVIII was found to be nil in the escitalopram. Chiral purity by HPLC is 99.0%.

**Advantages of the present invention:**

1. Escitalopram of the formula-I can be prepared in a simple and easy to adopt manner without involving any tedious purification steps.
2. Escitalopram of formula-I can be prepared in >25% yield, which is better than the earlier known process.
3. An improved process for the preparation of the intermediate compound of the formula-XVI.
4. The present process produces pure (>99.8%) enantiomeric forms of the intermediates of the formulae-XVII and XVIII or its salts.
5. The present utilizes mild cyanation conditions on the iodo compound of formula-XVIII thereby making the process simpler, efficient and impurity free.
We Claim:

1. An improved process for the preparation of escitalopram of formula-I,

which comprises:

   (i) reacting 5-iodophthalide of the formula-XIV,

   (ii) reacting the benzophenone derivative of the formula-XV with 3-(dimethylamino)propylmagnesium chloride to get the dihydroxy compound of the formula-XVI,
(iii) resolving the compound of the formula-XVI with (+)-di-p-toluoyltartaric acid
by preferential crystallization in a solvent medium to get its (-)-enantiomer salt
with (+)-di-p-toluoyltartaric acid

(iv) neutralizing the diastereomeric salt and isolating the liberated chiral
dihydroxy compound of formula-XVII,

(v) cyclizing the dihydroxy compound of formula-XVII using methanesulfonyl
chloride in basic medium to get the cyclic compound of the formula-XVIII,
(vi) reacting the compound of the formula-XVIII with copper cyanide in dipolar aprotic solvent medium at elevated temperature to get escitalopram base of formula-I,

(vii) converting the compound of the formula-I into its pharmaceutically acceptable salt, like oxalate, etc by conventional methods.

2. An improved process as claimed in claim 1 wherein the ether solvent used in step (i) is selected from a group of solvents such as diethyl ether, diisopropyl ether, 1,4-dioxane, 2-methyl tetrahydrofuran, terahydrofuran, preferably tetrahydrofuran or diethyl ether.

3. An improved process as claimed in claims 1 and 2 wherein the temperature of reaction in step (i) and (ii) is in the range of -25°C to 0°C, preferably, at a temperature in the range of -20°C to -10°C.

4. An improved process as claimed in claims 1-3 wherein the solvent used in resolution step (iii) is selected from methanol, ethanol, isopropanol, ethyl acetate, acetone, acetonitrile, or a mixture thereof.

5. An improved process as claimed in claims 1-4 wherein the neutralization reagent used in step (iv) is selected from sodium or potassium hydroxide, carbonate, bicarbonate, ammonia, preferably sodium or potassium hydroxide.
6. An improved process as claimed in claims 1-5 wherein the solvent used in cyclization step (v) is selected from methylene chloride, toluene, cyclohexane, tetrahydrofuran, isopropyl ether, ether, acetonitrile, preferably toluene or methylene chloride.

7. An improved process as claimed in claims 1-6 wherein the solvent used in cyanation step (vi) N,N-dimethylformamide, N,N-dimethylacetamide, pyridine, N-methyl-2-pyrrolidone, preferably N,N-dimethylformamide.

8. An improved process as claimed in claims 1-7 wherein the temperature of the reaction during cyanation is between 80-180°C, preferably between 100-150°C, more preferably between 120-140°C.

9. An improved process as claimed in claims 1-9 wherein the amount of copper (I) cyanide used in the reaction can be in the range of 1.0-2.5 moles per mole of iodo compound, preferably 1.5-2.0 moles per mole of iodo compound.

10. An improved process for the preparation of escitaslopram of the formula-I and its pharmaceutically acceptable salts substantially as described herein with reference to the Example.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

C07D307/87

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

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<tr>
<td>Y</td>
<td>WO 2004/065375 A (NATCO PHARMA LIMITED; NANNAPANENI, VENKAIAH, CHOWDARY; MUDDASANI, PULL) 5 August 2004 (2004-08-05) claim 1</td>
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Patent family members are listed in annex.

* Special categories of cited documents:
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Date of the actual completion of the international search

9 December 2005

Date of mailing of the international search report

20/12/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 MV Rijswijk
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<td>Y</td>
<td>WO 03/087081 A (TORGAN CHEMICAL LTD; TSE, HOI, LUN, ALLAN) &lt;br&gt; 23 October 2003 (2003-10-23) &lt;br&gt; abstract</td>
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<td>A</td>
<td>US 4 943 590 A (BOGESOE ET AL) &lt;br&gt; 24 July 1990 (1990-07-24) &lt;br&gt; cited in the application &lt;br&gt; claims 3,4</td>
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