(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 August 2005 (04.08.2005)

PCT

(10) International Publication Number
WO 2005/070914 A1

(51) International Patent Classification[7]: C07D 307/87

(21) International Application Number:
PCT/IN2004/000017

(22) International Filing Date: 23 January 2004 (23.01.2004)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **JUBILANT ORGANOSYS LIMITED** [IN/IN]; 1-A, Sector 16A, Institutional Area,, Noida 201 301, Uttar Pradesh (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **NARAHARI, Babu, Ambati** [IN/IN]; K. No: 1238, 3rd Cross, Grange Road, Kuvempunagar., Mysore 570 023, Karnataka (IN). **SRINIVAS GOUD, Vuddamari** [IN/IN]; D.No: 2166, 6th Cross, K, block, Kuvempunagar, Mysore 570 023, Karnataka (IN). **GAONKAR, Santosh, Laxman** [IN/IN]; D.No:5342/1, Basavanagudi Block, Nanjangud, Mysore 571 301, Karnataka (IN). **KISHORE, Charugundla** [IN/IN]; D.No.225, 5th Cross, Navilu Road, Kuvempunagar, Mysore 570 023 (IN). **LINGABHAT, Anil, Kumar, Haribhat** [IN/IN]; Kusumanilaya, opp: JSS College, R.P. Road,, Nanjangud, 571 301, Mysor, Karnataka (IN). **DEVARAJU** [IN/IN]; Kesagodu (post), Belur (Taluk) 573215, Hassana (Dist), Karnataka (IN). **THOMAS, Saji** [IN/IN]; D. No. 622,, 3rd Main, 9th Cross, Aravind Nagar, Mysore- 571 301, Karnataka (IN). **MANJUNATHA, Sulur, G.** [IN/IN]; D. No. 491 A-B, Chitrabanu Road, Kuvempunagar, Mysore, Karnataka 570 023 (IN). **KULKARNI, Ashok, Krishna** [IN/IN]; D.No: 1447, C & D Block, Sanje Ravi Road, Kuvempu Nagar, Mysore 570 023, Karnataka (IN). **KHANNA, Jagmohan** [IN/IN]; J-1/23, DLF City, Phase-II, Gurgaon 122 022, Haryana (IN).

(74) Agents: **SUBRAMANIAM, Hariharan** et al.; Subramaniam, Nataraj & Associates, E-556, Greater Kailash-II, New Delhi 110 048, Maharashtra (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A METHOD FOR THE PREPARATION OF CITALOPRAM ACID ADDITION SALTS

(57) Abstract: The present invention discloses a simple *in situ* method for the purification of citalopram acid addition salts without isolating crystalline citalopram base as a solid, wherein citalopram base is treated with metal hydrides in solvent medium followed by acid addition, to remove structurally similar impurities by filtration to get crude citalopram acid addition salts. The resulting citalopram salts are subjected to simple purification to get pharmaceutically acceptable acid addition salts. The said citalopram base is prepared by subjecting 5-cyanophthalane to an eco-friendly and safe C-alkylation reaction with 3,N,N dimethylaminopropyl chloride in the presence of strong base in a mixture of dimethylsulfoxide and toluene.

WO 2005/070914 A1

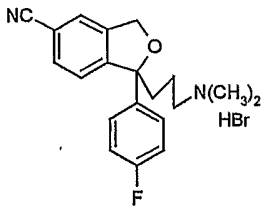
A METHOD FOR THE PREPARATION OF CITALOPRAM ACID ADDITION SALTS

FIELD OF INVENTION

The present invention relates to a simple method for the preparation of citalopram acid addition salts. In particular, present invention relates to a simple *in situ* purification of citalopram base and converting into citalopram acid addition salts without isolating crystalline citalopram base as a solid. More particularly, the present invention relates to a simple method for the preparation of citalopram acid addition salts wherein citalopram base is treated with metal hydrides in solvent medium followed by acid addition to get crude citalopram acid addition salts , which is filtered to remove structurally similar impurities. The resulting citalopram salts are subjected to simple purification to get pharmaceutically acceptable acid addition salts. In a preferred embodiment, the said citalopram base is prepared by subjecting 5-cyanophthalane to an eco-friendly and safe C-alkylation reaction with 3,N,N-dimethylaminopropylchloride in the presence of strong base in a mixture of dimethylsulfoxide and toluene.

BACKGROUND OF THE INVENTION

Citalopram and its pharmaceutically acceptable acid addition salts, such as its hydrogen bromide salt (Formula (I))



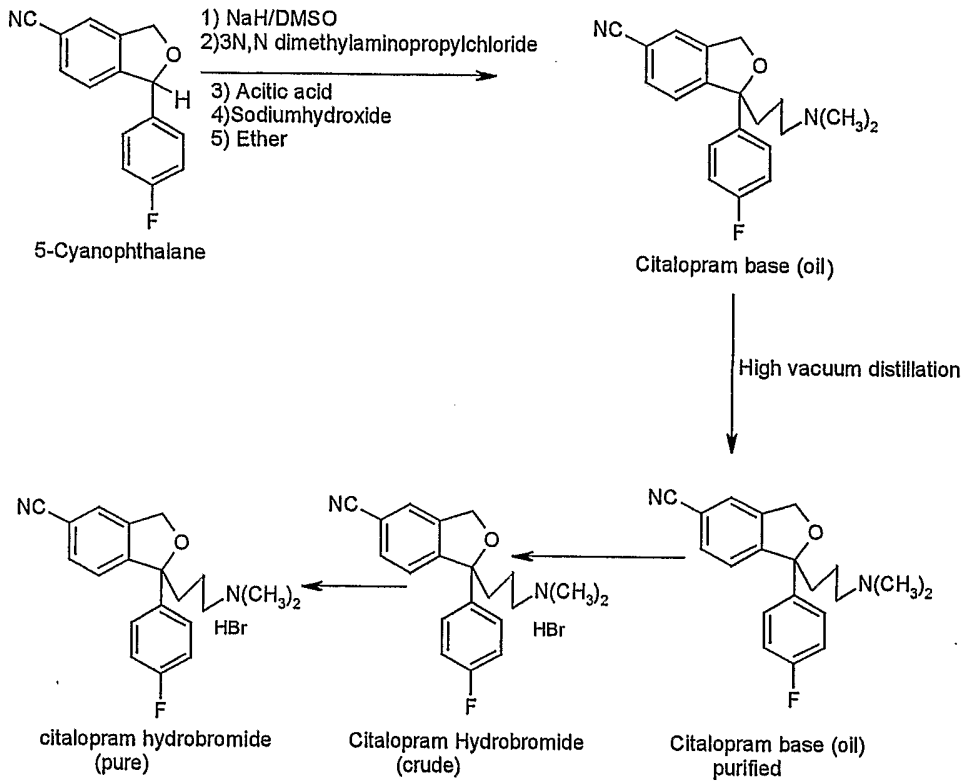
(I)

are well known. US patent specification No. 4,136,193 teaches said citalopram hydrobromide salts and its use as an anti-depressant drugs with few side effects.

Various processes for the preparation of citalopram hydrobromide have also been described in the prior art. For instance, US Patent No. 4, 136, 193 describes the C-alkylation reaction of 5-cyanophthalane with 3-N,N`dimethylaminopropylchloride, using sodium hydride as a base in a dimethyl sulphoxide (DMSO) medium, 13 volume of dimethyl sulfoxide is used in the reaction with respective to 5-cyanophthalane (Scheme - 1). After the completion of the reaction, the reaction mixture is poured into ice water and extracted with ether. Then, after standard acid-base work-up, citalopram

base is isolated as an oil. The isolated oil is purified by high vacuum distillation, (0.03mm at 175-180°C) and then converted in to acid addition salts by conventional methods. The method of this US Patent is schematically represented below:

Scheme - 1



Main drawback of the process of said US Patent No. 4, 136, 193 is the need to purify the oily citalopram base using high vacuum distillation (0.03mm) at 175-181°C. Achieving such a high vacuum at plant level is difficult and hence the process described above is not easily transferable to commercial scale. Apart from these constraints, the above process suffers from another serious drawback in that citalopram base having a cyano group at the 5th position of the bicyclic ring system may decompose during high vacuum distillation at high temperature to form citalopram carboxamide as one of the impurity, resulting in poor quality product and yield.

Another major drawback of the above process is using 13 volumes of dimethyl sufoxide as a reaction medium for generation of sodium salt of dimethyl sulfoxide (demsil ion). DMSO being a very high polar solvent may result in the formation of impurities such as 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-5-acetyl-1,3-dihydroisobenzofuran(acetyl citalopram), 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxamide(amide), 1-[3-

(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxalic acid(acid) and 1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile(desmethyl), are formed during the work up due to the degradation and decomposition of the reaction mass, resulting in poor quality of citalopram. Citalopram salts prepared by these processes require at least two to three further purification in different solvents to get pharmaceutical grade citalopram .

Another process for the preparation of citalopram is disclosed in PCT Application No. WO 02/ 066453, wherein potassium tertiary butoxide is used as a base instead of sodium hydride in dimethyl sulfoxide medium for C-alkylation reaction of 5-cyanophthalide with 3,N,N-dimethylaminopropylchloride. After completion of the reaction, the reaction mass is quenched on ice cold water. The resulting solution is subjected to acid base work up and citalopram base is isolated as crystalline solid from diisopropyl ether medium.

Again a major drawback of this process is the use of 13 volumes (large quantity) of dimethylsufoxide in reaction medium for generation of potassium salt of dimethyl sulfoxide (demsil ion). As a consequence, impurities like acetyl, amide, acid and desmethyl are formed due to degradation and decomposition of the reaction mass in large quantity of polar solvent like dimethyl sulfoxide. It results in poor quality of the citalopram, which again requires at least two to three purification steps in different solvents to get pharmaceutical grade citalopram.

In the above process 13 volumes of dimethysulfoxide is used as a reaction medium. After completion of the reaction, the reaction mass is quenched on large quantity of ice –water (minimum 13x5 volumes of ice water). Therefore, in these processes toxic aqueous effluent generation is high and this has a direct adverse effect on cost and to the environment. In addition, since citalopram is soluble in polar solvent like dimethylsulfoxide, it is not completely extracted in to non-polar solvent like toluene from a mixture of huge volumes of dimethylsulfoxide and water, resulting poor yield of the end product. Other than that DMSO being an oxidising agent, it generates structurally similar oxidized coloring impurities during the C-alkylation reaction. These oxidized and coloring impurities are very difficult to remove by normal purification methods.

OBJECTS OF THE INVENTION

Accordingly, it is an object of the present invention to provide a process for the preparation citalopram acid addition salts.

It is another object of the present invention to provide a process for the preparation of citalopram acid addition salts without isolating crystalline citalopram base as a solid.

Yet another object of the present invention to provide a process for the preparation of citalopram acid addition salts without the drawbacks of the prior art.

It is yet another object of the present invention to provide a process for the preparation of citalopram acid addition salts in high purity and yield.

The above and other objects of the present invention are achieved by fine tuning of reaction conditions, safer handling of hazard chemicals in the plant level and reduction highly toxic solvent usage, with simple *in situ* preparation of citalopram acid addition salts in the presence of metal hydrides.

SUMMARY OF THE INVENTION

The present invention is based on the surprising finding that citalopram acid addition salts in high purity and yield can be obtained by a simple *in situ* purification of citalopram base and converting into citalopram acid addition salts without isolating solid citalopram base. According to the present invention citalopram base is treated with metal hydrides such as sodiumborohydride in a solvent medium followed by acid addition to get crude citalopram acid addition salts, which is filtered to remove structurally similar impurities. The resulting citalopram acid addition salts are subjected to simple purification to get pharmaceutically acceptable acid addition salts. The said citalopram base is prepared by subjecting 5-cyanophthalane to an eco-friendly and safe C-alkylation reaction with 3,N,N-dimethylaminopropylchloride in the presence of strong base in a mixture of dimethylsulfoxide and toluene. The C-alkyaltion reaction mixture is diluted with ice cold water and the immiscible organic solvent is separated from the resulting mixture. The water immiscible organic solvent is then subjected to acid/base work up followed by the extraction of citalopram base into water-immiscible organic solvent. The water-immiscible organic solvent is dried and distilled off completely under reduced pressure to get citalopram base. The citalopram base is optionally purified and converted into acid additional salts as per the process described below.

The citalopram base is dissolved in a solvent or mixture of solvents and treated with catalytic amount of metal hydrides. The resulting solution is stirred for 2-4 hours. The solution is optionally diluted with water and cooled 5-10°C to get crystalline citalopram base. The crystalline citalopram base is then converted into acid addition salts as per the process described below.

However, the preferred method is to cool the said solution and then molar equivalent quantity of acid is added to the solution to obtain corresponding crude citalopram acid addition salts , which are filtered and comfortably purified in single solvent or mixture of solvents to get pharmaceutically acceptable citalopram salts with highest single impurity level is less than 0.1%.

DETAILED DESCRIPTION

The present invention describes a simple *in situ* purification method of citalopram base and converting into citalopram acid addition salts without isolating crystalline citalopram base as a solid. The purification process of the present invention achieves surprisingly high levels of purity not withstanding the fact that the citalopram base contains structurally similar impurities like amide, acid, desmethyl, acetyl and oxo citalopram. These impurities are removed by the process according to the present invention by dissolving said citalopram base in a solvent like methanol, ethanol, IPA, THF, ether, acetone and ethylacetate or mixtures thereof. The most preferred organic solvent is isopropyl alcohol,and the most preferred mixture of solvent is a mixture of isopropylalcohol and ethylacetate. Preferably, Citalopram base is dissolved in said solvent or mixture of solvents at 25-40°C, preferably, at 30-40°C, followed by addition of a catalytic amount of metal hydrides such as sodium cyanoborohydride and sodiumborohydride, preferably, sodiumborohydride. The solution is then maintained for 2-4hrs, at 25-40° temperature. Optionally, the solution is cooled to room temperature and added water under stirring. The resulting solution is further cooled to 5-10°C the separated solid is filtered to get crystalline citalopram base. The crystalline citalopram base is converted into acid addition salts as per process described below.

Our main invention is preparation of citalopram acid addition salts without isolation of crystalline citalopram base. Therefore, the most preferred method is the said solution is cooled to 0-5°C and 1.0-1.25 molar quantity of acids such as hydrochloric acid, hydrobromic acid, Sulphuric acid , tartaric acid and oxalic acid, is added. Preferably, the acid is selected from hydrobromic acid, hydrochloric acid and oxalic acid and molar ratio is preferably, 1.05 to 1.10. The reaction mass is stirred for about 4-6hrs at 0-5°C temperature. The said structurally similar impurities are highly soluble in water miscible organic solvent such as methanol, ethanol, isopropyl alcohol. Thereafter, the impurities are separated by filtration to get good quality of crude citalopram acid addition salts.

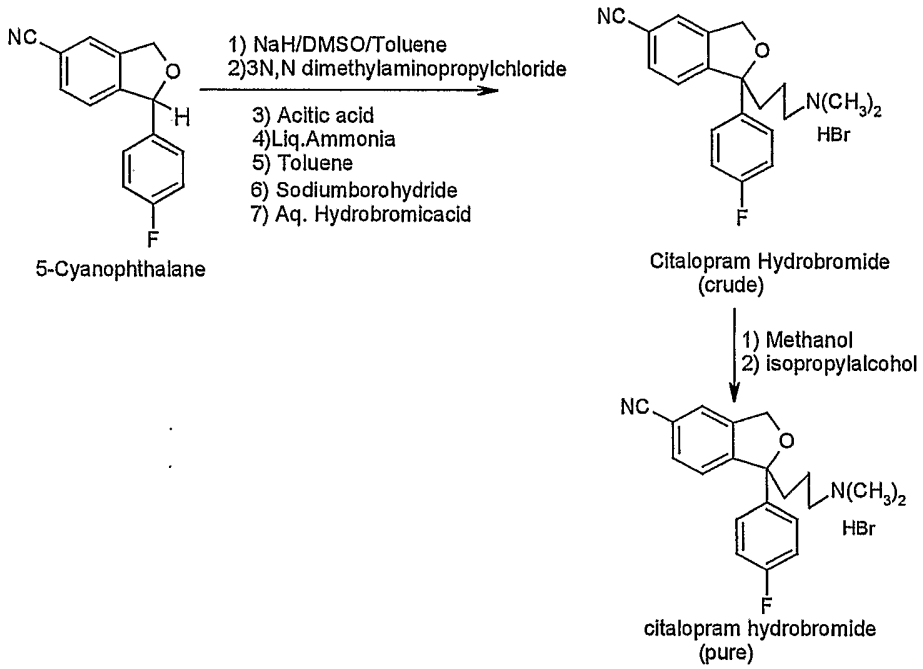
The above isolated citalopram acid addition salts are subjected to simple purification in a solvents such as methanol, ethanol, isopropyl alcohol, acetone, ethylacetate and methyl ethyl ketone and mixture or mixture thereof with water. The most preferred mixture of solvents are methanol/isopropyl alcohol and methanol/ethylacetate to get pharmaceutically acceptable acid addition salts.

Metal hydrides such as sodium borohydride, in chemical literature, is used for scavenging the oxidized aldehyde – ketonic impurities and coloured metal salts of higher oxidation state from the product and thus improving the purity and appearance of the product. In fact, it is known in the literature that sodium borohydride, in many

folds, is superior to activated carbon in removing the colour from the products. The purpose of treating the citalopram base in the present invention with sodium borohydride in a solvent medium before treating with acid is the same.

Sodiumborohydride reduces the coloured oxidized impurities and structurally related to citalopram like acetyl citalopram & oxo citalopram to form corresponding hydroxy compounds, which are highly soluble in a mixture of water and alcoholic solvents. Therefore, these impurities goes with the ML`s during the filtration thus improving the colour of the crude citalopram salts.

Scheme-2



The second part of the invention describes a process for the preparation of citalopram base by a eco-friendly and safe C-alkylation reaction of 5-cyanophthalane with 3,N,N dimethylaminopropylchloride in the presence of strong base in a mixture of dimethylsulfoxide and toluene . According to this invention, the generated demsil ion is reacted with 5-Cyanophthalane to get sodium/potassium salt of cyanophthalane. The demsil ion is prepared by dissolving 1.0 -1.7 molar equivalents of bases such as sodium hydride and potassium tertiary butoxide, pereferably, 1.2 molar equivalent of sodium hydride and 1.5 equivalents of potassiumtertiarybotoxide in a mixture of Dimethylsulfoxide and Toluene. In a preferred embodiment, the ratio of

dimethylsulfoxide : toluene is from 13:0 to 4:9 v/v, more preferably 4:6 v/v, with respect to input of 5-Cyanophthalide .

In another aspect, the present invention obviates some of the hazards encountered in the prior art with respect to the safe handling of sodium hydride in C-alkylation reaction. According to the process described in US Patent No 4,136,193 for the basic product, sodium hydride is charged in to the reaction mass for making demsil ion. Sodium hydride can ignite spontaneously in air/ moisture and posing fire hazards. The present invention is based *inter alia*, on the finding that, self dissolve polythene bag containing sodium hydride is not soluble in polar solvent like dimethyl sulfoxide. However, polythene bag containing sodium hydride is soluble in a mixture of dimethysulfoxide and toluene at 55-60°C. This method results in a safe handling of sodiumhydride without exposing it to air and moisture while charging large quantity in to the reaction mass at the plant level.

In a preferred embodiment, 3,N,N-dimethylaminopropylchloride in toluene solution is added to salt of 5-cyanophthalane between 10-35°C , more preferably at temperature in the range of 10-15°C. Alternatively, readily prepared salt of 5-cyanophthalane is added to 3N,N dimethyl aminopropyl chloride in toluene between 10-35°C, preferably, 10-15°C. By this method formation of the impurities are considerably reduced as compared to when 3,N,N-dimethylaminopropylchloride is added to a salt of 5-cyanophthalane.

After completion of the C-alkylation reaction, reaction mass is quenched on 4x5 volumes of ice-cold water preferably at a temperature in the range of 5-25°C, more preferably, at a temperature in the range 5-10°C. As per the prior art, after completion of the C-alkylation reaction, reaction mass, because of the use of large quantity of DMSO, is quenched on excess quantity of ice cold water and therefore citalopram is in direct contact with water at high basic pH. Hence, hydrolysis of cyano group leads to formation of amide, and acid citalopram as impurities. On the other hand, according to the method of present invention, C-alkylation reaction mass contains less quantity of DMSO and large quantity of toluene. After completion of the C-alkylation reaction, reaction mass is quenched on ice cold water. In this method, long contact time between citalopram and water is avoided. As soon as reaction mass is quenched on ice –cold water, citalopram is extracted into the toluene. Therefore, in this process formation of amide, and acid impurities are considerably less as compared to the process disclosed in prior art processes.

The organic layer is separated from the above resulting solution. Thereafter, the organic layer is washed with water, then organic layer is extracted into 10-20% of aqueous acids such as hydrobromic acid, hydrochloric acid, oxalic acid, formic acid,

acetic acid. The most preferred aqueous acidic acid is 15-20% aqueous acidic acid at 10-15°C. Acidic aqueous extract is optionally subjected to isolation of crystalline citalopram base as per the process disclosed in the prior art WO 03/080590 A1. Preferably acidic aqueous extract is cooled to 5-20°C, most preferred temperature being 10-15°C. then the pH of the acidic extract is adjusted to basic using bases like aqueous sodium hydroxide, aqueous potassium hydroxide , ammonia solution, etc,. The most preferred base being lq. ammonia at 10-15°C. Thereafter, citalopram base is exacted into water-immiscible organic solvents such as toluene , ethylacetate, dichloromethane, dichloroethane and the like, the most preferred water-immiscible solvent being toluene. The water –immiscible organic solvent is washed with water and dried over anhydrous sodium sulfate and distilled off completely to get citalopram base.

Majors advantageous of the process of then present invention are as follows:

1) The process of the present invention comprises a simple *in situ* purification method of citalopram acid addition salts without isolation of citalopram base as a solid as well as use of high vacuum distillation of citalopram base are avoided. The process of the present invention can be implemented in the plant level without facing any practical problems.
2) Safe handling of large quantity of sodiumhydride in self dissolving polythene bags in the commercial pant level is achieved
3) Reductions of highly toxic and polar solvent like dimethyl sulfoxide in C-alkylation reaction is achieved leading to reduction of the process effluent and raw material costs.
4) Reductions of highly toxic and polar solvent like dimethyl sulfoxide in C-alkylation reaction, leading to reduction of the formation of structurally similar impurities.

The present invention will now be described in greater detail with reference to the following non-limiting examples the purpose of which is to merely illustrate the invention and not to limit the scope of the invention.

Example 1

a)Preparation of citalopram base

25 grams sodium hydride (60% in mineral oil) in a self dissolving bag was added in to a mixture of 540 ml dimethyl sulphoxide and 810ml toluene at 20-25°C then heated to 60-65°C under nitrogen atmosphere. To the resulting solution of sodium salt of dimethylsuphoxide, 135 g of 1-(4'-fluorophenyl)-1,3-dihydro-*iso*benzofuran-5-carbonitrile, was added at 10-15°C. The mixture was then stirred for additional 10 min at 15-20°C. 152 g of 3,N,N-dimethylaminopropylchloride in 540 ml of

toluene was added quickly and the reaction mixture was then warmed to 25-30°C and maintained for 4 hours. The reaction mixture was then poured into ice-water and extracted with toluene. The toluene phase was extracted with 500ml of 20% aqueous acetic acid (100ml acetic acid and 400ml water). The aqueous acidic extract was cooled to 10-15°and the resulting solution pH was adjusted to 9.0-10 with aqueous ammonia and resulting mixture extracted into 2x300ml of toluene and washed with 100ml of water. Toluene layer was dried over anhydrous sodium sulphate and the solvent was distilled off completely under reduced pressure to get crude citalopram base (105-110gm).

b) Preparation of crude citalopram hydrobromide

The crude citalopram base (Example 1a) was dissolved in 600ml of isopropyl alcohol followed by the addition of sodiumborohydride (1gm) at 25-30°C. The reaction mixture was maintained at the same temperature for 2-hours and then cooled to 10-15°C , followed by the addition of 47% hydrobromic acid (30-35ml). The reaction mass was then stirred for 4 hours at 25-30°C and cooled to 10°C. The citalopram hydrobromide salt so precipitated was separated by filtration followed by washing with chilled Isopropyl alcohol (200ml).

Dry weight = 105-110gm

Purity by HPLC = >99 %

c) Preparation of crude citalopram hydrochloride

The crude citalopram base (Example 1a) was dissolved in 600ml of isopropyl alcohol followed by the addition of sodiumborohydride (1gm) at 30-35°C. The reaction mass was then maintained at the same temperature for 2-hours. The reaction mass was then cooled to 10-15°C, and 36% hydrochloric acid (30-35ml) was added to it. The reaction mass was then stirred for 4 hours at 25-30°C and cooled to 10° C. The citalopram hydrochloride salt so precipitated was separated by filtration followed by washing with chilled Isopropyl alcohol (200ml).

Dry weight = 95-100gm

Purity by HPLC => 99%

d) Purification of crude citalopram hydrobromide

Citalopram hydrobromide (100gm) was dissolved in methanol (200ml)at 55-60°C and then treated with activated carbon and filtered and washed with methanol (100ml) The clear filtrate was diluted with isopropyl alcohol(600ml). The resulting

solution was cooled to 5-10°C, to obtain a crystallized product. The crystallized product was filtered and washed with chilled isopropyl alcohol to get pure citalopram HBr.

Dry weight= 85 gm

Purity by HPLC => 99.5%

Any single impurity Less than 0.1%

e) Purification of crude citalopram hydrobromide

Citalopram hydrobromide (100gm) was dissolved in methanol (200ml) at 55-60°C and then treated with activated carbon and filtered and washed with methanol (100ml). The clear filtrate was diluted with ethylacetate (600ml). The resulting solution was cooled to 5-10°C, to obtain a crystallized product. The crystallized product was filtered and washed with chilled ethylacetate to get pure citalopram HBr.

Dry weight= 70gm

Purity by HPLC => 99.5%

Any single impurity Less than 0.1%

f) Purification of crude citalopram hydrobromide

Citalopram hydrobromide (100gm) was dissolved in a mixture of isopropyl alcohol (600ml) and water (100ml) at 55-60°C and then treated with activated carbon and filtered and washed with isopropyl alcohol (100ml) The clear filtrate was diluted was cooled to 5-10°C, to obtain a crystallized product. The crystallized product was filtered and washed with chilled isopropyl alcohol to get pure citalopram HBr.

Dry weight= 70gm

Purity by HPLC => 99.5%

Any single impurity Less than 0.1%

g) Purification of crude citalopram Base

The crude citalopram base (Example 1a) was dissolved in 250ml of isopropyl alcohol followed by the addition of sodiumborohydride (1gm) at 30-35°C. The reaction mass was then maintained at the same temperature for 2-hours. The reaction mass was then cooled to 10-15°C, and 250 ml of water was added to it. The reaction mass was then stirred for 4 hours at 25-30°C and cooled to 10° C. The citalopram base precipitated was separated by filtration followed by washing with chilled Isopropyl: water alcohol (50:50l).

Dry weight = 85-90gm

Purity by HPLC => 99%

h) Purification of crude citalopram Base

The crude citalopram base (Example 1a) was dissolved in 250ml of isopropyl alcohol then maintained at the same temperature for 2-hours. The resulting solution was cooled to 10-15°C, and 250 ml of water was added to it. The mass was then stirred for 4 hours at 25-30°C and cooled to 10° C. The citalopram base precipitated was separated by filtration followed by washing with chilled Isopropyl: water alcohol (50:50l).

Dry weight = 85-90gm

Purity by HPLC => 99%

Claims:

1) A process for the preparation of acid addition salt of citalopram comprising
a) dissolving citalopram base in a solvent or mixture of solvents and then treating with metal hydrides,
b) treating the resulting solution with one or more acids to get corresponding acid addition salts of citalopram base without the isolation of crystalline citalopram base;
c) and if desired, subjecting citalopram salts to purification in a solvent or mixture of solvents to get pharmaceutically acceptable acid addition salts.

2) A process claimed in claim 1, wherein said citalopram base is prepared by
a) subjecting 5-cyanophthalane to C-alkylation reaction with 3,N,N - dimethylaminopropylchloride in the presence of strong base in a mixture of dimethylsulfoxide and toluene;
b) quenching the C-alkylation reaction mass obtained in step a) on ice-cold water and subjecting it to acid/base work up to get citalopram base;
c) citalopram base is optionally subjected to purification in a mixture of water and water miscible solvents to get pure citalopram base.

3. A process as claimed in claim 2, wherein said strong base is selected from alkali metal amides such as sodamide or potassium amide, organo lithiums such as butyllithium, phenyl lithium, metal hydrides such as sodiumhydride, potassium hydride, metal alkoxides such as sodiummethoxide, potassium tertiary butoxide and metal hydroxides such as sodium hydroxide and potassium hydroxide.

4. A process as claimed in claim 3 wherein the said base is selected from metal hydride, preferably, sodium hydride.

5. A process as claimed in claim 2, wherein said dimethylsulfoxide and toluene are present in a ratio in the range of 3:7 to 6:3.

6. A process as claimed in claim 5, wherein said dimethylsulfoxide :tolune ratio is 4:6.

7. A process as claimed in claim 2, wherein the said C-alkylation reaction mass is diluted with water and the toluene layer is separated.

8. A process as claimed in claim 7, wherein the said toluene layer is subjected to acid/base work up and the citalopram base is extracted into water immiscible organic solvent selected from the group consisting of benzene, toluene, ethylacetate, dichloromethane, dichloroethane, chloroform, diethyl ether and mixtures thereof

9. A process as claimed in claim 8 or 9 wherein the said toluene layer is concentrated under reduced pressure to get citalopram base.

10. A process as claimed in claim 1 wherein said citaopram base is dissolved in a solvent or a mixture of solvents selected from the group consisting of methanol, ethanol, n-propanol, isopropyl alcohol, n-butano , ethyl acetate, tetrahydrofuran, ether, water and mixtures thereof.

11. A process as claimed in claim 1 wherein said metal hydrides are selected from sodium cyanoborohydride and sodium borohydride.

12. A process as claimed in claim 13 wherein said metal hydride is sodiumborohydride, and is used in catalytic amount.

13. A process as claimed in claim 1 wherein said citaopram base is converted *in situ* into citalopram acid addition salts by addition of acid selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid , tartaric acid and oxalic acid.

14. A process as claimed in claim 15 wherein said acid is added in a molar quantity of 1.0 to 1.25.

15. A process as claimed in claim 1 wherein said citalopram acid addition salts are subjected to purification in a solvent or mixture of solvents selected from the group consisting of methanol, ethanol, isopropyl alcohol, acetone, ethylacetate and methyl ethyl ketone and mixture or mixture thereof with water.

INTERNATIONAL SEARCH REPORT

International Application No
../IN2004/000017

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 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)
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, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 346 989 A (JUBILANT ORGANOSYS LTD) 24 September 2003 (2003-09-24) claim 12; examples 1c,4	1-15
A	EP 0 171 943 A (LUNDBECK & CO AS H) 19 February 1986 (1986-02-19) example 2	1-15

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

☒ Patent family members are listed in 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	Date of mailing of the international search report
20 September 2004	27/09/2004

Name and mailing address of the ISA	Authorized officer
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	Seelmann, I

1

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

ernational Application No
. CT/IN2004/000017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1346989 A	24-09-2003	EP 1346989 A1	24-09-2003
		WO 03080590 A1	02-10-2003
EP 0171943 A	19-02-1986	AT 38661 T	15-12-1988
		AU 574819 B2	14-07-1988
		AU 4577685 A	13-02-1986
		CA 1237147 A1	24-05-1988
		DE 3566251 D1	22-12-1988
		DK 89595 A	10-08-1995
		DK 356285 A	07-02-1986
		EP 0171943 A1	19-02-1986
		ES 8606257 A1	01-10-1986
		FI 852902 A ,B,	07-02-1986
		FI 20031369 A	23-09-2003
		GR 851894 A1	03-12-1985
		IE 57817 B1	21-04-1993
		IL 75690 A	31-10-1988
		JP 1902596 C	08-02-1995
		JP 6025099 B	06-04-1994
		JP 61087654 A	06-05-1986
		NO 853091 A ,B,	07-02-1986
		NZ 212541 A	30-05-1988
		PT 80913 A ,B	01-09-1985
		US 4650884 A	17-03-1987
		ZA 8505026 A	25-06-1986