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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 October 2013 (03.10.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/144977 A2

(51) International Patent Classification:
C07D 213/61 (2006.01)

(21) International Application Number:
PCT/IN2013/000187

(22) International Filing Date:
20 March 2013 (20.03.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1261/CHE/2012 30 March 2012 (30.03.2012) IN
2794/CHE/2012 10 July 2012 (10.07.2012) IN

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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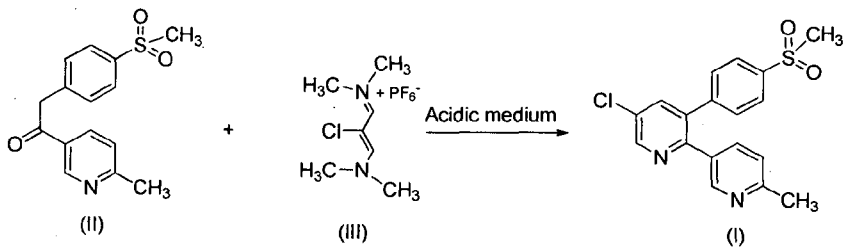
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF ETORICOXIB



(II) (III) (I)

(57) Abstract: The present invention relates to an improved process for the preparation of Etoricoxib by reacting ketosulfone of formula-II with vinamidinium salt of formula-III in the presence of an acid, followed by conversion to an acid addition salt and finally desaltifying to get Etoricoxib of formula-I.

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AN IMPROVED PROCESS FOR THE PREPARATION OF ETORICOXIB

This application claims priority to Indian patent applications numbered 1261/CHE/2012 filed on March 30, 2012 & 2794/CHE/2012 filed on July 10, 2012.

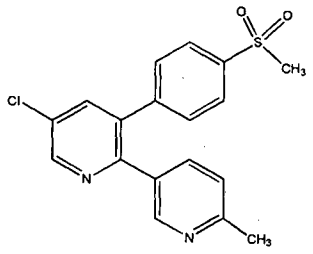
FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of Etoricoxib or its pharmaceutically acceptable salts thereof. The present invention also relates to process for the preparation of Etoricoxib polymorphic form-I.

BACK GROUND OF THE INVENTION

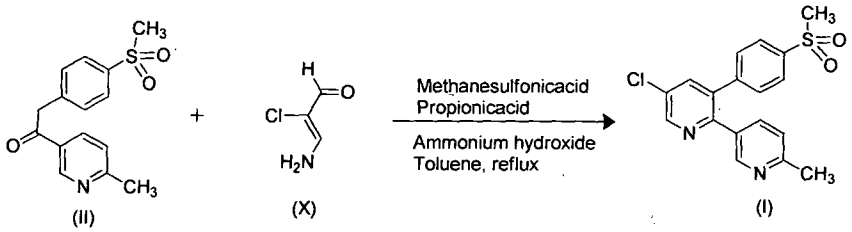
Etoricoxib is a potent and selective COX-2 inhibitor, which is effective in the management of chronic pain in rheumatoid arthritis, osteoarthritis and other COX-2 mediated disorders. Etoricoxib is sold by Merck Sharp & Dohme Limited under the brand name ARCOXIA®.

Etoricoxib is designated chemically as 5-chloro-3-[4-methylsulfonyl) phenyl]-2-(2-methyl-5-pyridinyl) pyridine and is represented by the compound of formula (I).



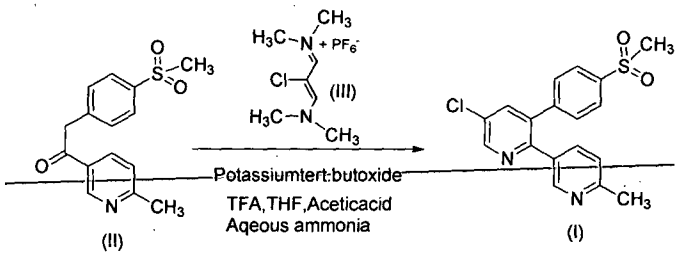
Formula- (I)

US5861419 first discloses processes for the preparation Etoricoxib and its pharmaceutically acceptable salts such as hydrochloride, pharmaceutical compositions and method of use as selective cyclooxygenase-2 (COX-2) inhibitors. US'419 patent discloses a process for preparation of etoricoxib, wherein ketosulfone (II) is reacted with the 3-amino-2-chloroacrolein(X) in the presence of an acid followed by work-up to get Etoricoxib. The step wise process is as shown in the scheme-I given below.



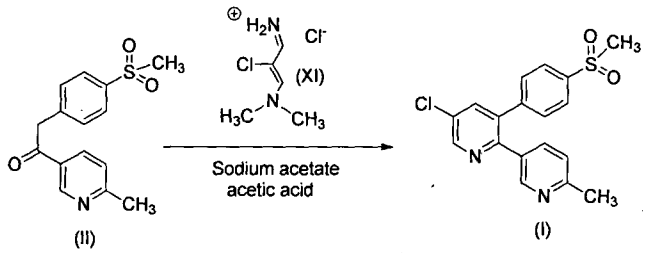
Scheme-I

US 6040319 discloses a process for preparation of Etoricoxib by reacting ketosulfone (II) with the vinamidinium hexafluorophoshate salt (III) in basic condition to obtain Etoricoxib. The step wise process is as shown in the scheme-II given below.



Scheme-II

WO 2011158250A1 discloses a process for preparation of Etoricoxib by reacting ketosulfone (II) with 2 chloro-3-(dimethylamino) prop-2-en-1-iminium chloride (XI) in acidic condition to obtain Etoricoxib. The step wise process is as shown in the scheme-III given below.



Scheme-III

US6441002 and US6858631 disclose different polymorphic forms such as hemihydrate, sesquihydrate, amorphous and four different anhydrous crystalline forms of Etoricoxib, which are designated as Forms I to IV. According to aforesaid patents, Etoricoxib is obtained by eluting

column chromatography with ethyl acetate and the obtained form is named as Form-II. Recrystallisation of Form-II in a mixture of isopropanol/ hexane produced Form-I.

US6800647 discloses Form-V of Etoricoxib, whereas Form-V is obtained by crystallizing Etoricoxib with isopropyl acetate.

WO2005085199A1 publication discloses eight different crystalline forms of Etoricoxib. Which are designated as Forms IX to XVI.

Reaction of ketosulfone with vinamidinium hexafluorophoshate salt in the presence of an acid medium is not reported in the prior art. The present invention provides an improved process for the preparation of Etoricoxib by reacting ketosulfone with vinamidinium salt in the presence of an acid.

The present invention relates to a process for the preparation of Etoricoxib polymorphic Form-I, wherein Etoricoxib is dissolved in a solvent and the resulting solution is added to pre-seeded hydrocarbon solvent to get crystalline Etoricoxib polymorphic Form-I with improved quality.

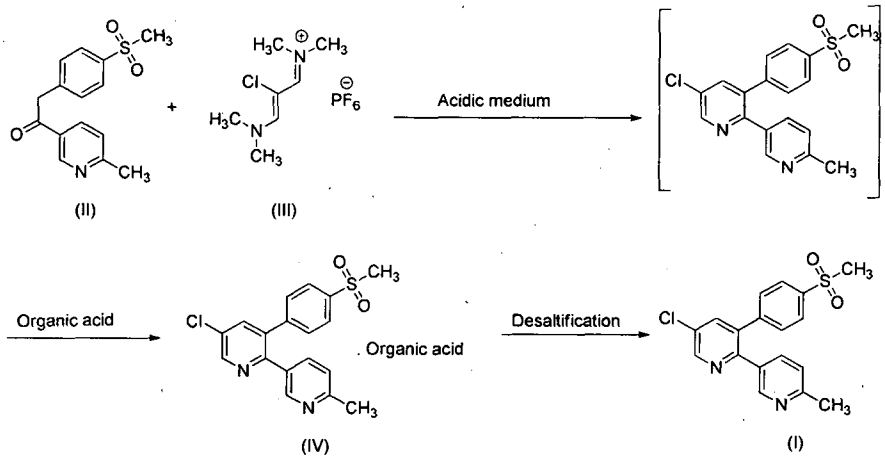
SUMMARY OF THE INVENTION

The present invention provides an improved process for the preparation of Etoricoxib or its salt thereof.

In one aspect, the present invention encompasses a process for preparation of Etoricoxib comprising the steps of;

a) reacting vinamidinium hexafluorophoshate salt of formula-III with ketosulfone of formula-II in the presence of acid to get crude Etoricoxib,
b) converting the crude etoricoxib to acid addition salt,
c) setting free of the acid addition salt, and
d) isolating Etoricoxib.

The present invention is shown in scheme-III



(II) (III) (IV) (I)

Scheme-III

Another aspect of the present invention encompasses a process for preparation of Etoricoxib polymorphic Form-I comprising the steps of;

a) dissolving Etoricoxib in a solvent,

b) adding step a) solution to an anti-solvent containing the seed of Etoricoxib Form-I, and

c) isolating pure Etoricoxib polymorphic Form-I.

Yet another aspect of the present invention encompasses a process for preparation of Etoricoxib polymorphic Form-I comprising the steps of;

a) dissolving Etoricoxib in a solvent,

b) adding step a) solution to an anti-solvent, and

c) isolating pure Etoricoxib polymorphic Form-I.

BRIEF DESCRIPTION OF THE FIGURE

FIG. 1 is a representative X-ray diffraction pattern of Etoricoxib polymorphic Form-I.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an improved process for the preparation of Etoricoxib by reacting ketosulfone with vinamidinium salt in the presence of an acid, followed by conversion to an acid addition salt and finally desaltifying to get Etoricoxib.

One embodiment of the present invention provides, an improved process for the preparation of Etoricoxib comprising the steps of;

a) reacting vinamidinium hexafluorophoshate salt of formula-III with ketosulfone of formula-II in the presence of acid to get crude Etoricoxib,
b) converting the crude etoricoxib to an acid addition salt,
c) setting free of the acid addition salt, and
d) isolating Etoricoxib.

According to the present invention vinamidinium hexafluorophosphate of formula (III) is reacted with ketosulfone of formula (II) in the presence of acid and a buffer in a solvent. After completion of the reaction, etoricoxib is isolated as residue, to this an organic acid is added to form an acid addition salt of formula (IV), desaltifying the acid addition salt with a base to get crude Etoricoxib. Crude Etoricoxib is further purified in alcoholic solvent.

According to the present invention the acid for the reaction is selected from acetic acid, propionic acid, methanesulfonic acid, trifluoroacetic acid, sulfuric acid or mixtures thereof, preferably methanesulfonic acid and propionic acid mixture in the presence of a buffer. The reaction is carried out in the presence of a buffer selected from sodium acetate, potassium acetate or ammonium acetate. Organic acid to form acid addition salt is selected from p-toluenesulfonic acid, methanesulfonic acid, benzenesulfonic acid, succinic acid, fumaric acid, benzoic acid, glutamic acid, sulfamic acid, oxalic acid, cinnamic acid or salicylic acid. The base is used for desaltification is selected from ammonia, potassium hydroxide, calcium hydroxide, sodium hydroxide, sodium carbonate, potassium carbonate, calcium carbonate, sodium bicarbonate, triethylamine or pyridine, preferably ammonia solution.

According to the present invention, the solvent is selected from the group comprising alcohols, esters, ethers, ketones, chlorinated solvent, acetonitrile, aromatic hydrocarbons, water or mixtures thereof. The alcoholic solvent is selected from methanol, ethanol, isopropanol, n-propanol or butanol; the ester solvent is selected from ethyl acetate, methyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate or isopropyl acetate; the ether solvent selected from tetrahydrofuran, diethyl ether, methyl tert-butyl ether or diisopropyl ether; the ketone solvent is selected from acetone, methylethylketone or methylisobutylketone; the chlorinated solvent is selected from methylene dichloride orethylene dichloride,; aromatic hydrocarbon solvent is selected from toluene or xylene.

According to the present invention crude Etoricoxib is purified by recrystallization in alcohol solvent selected from methanol, ethanol, isopropanol or butanol.

According to the present embodiment, the reaction is carried out at temperature in the range of about 30°C to about 120°C, preferably 60°C to about 120°C. The reaction is carried out for a period of about 12 hours to about 30 hours, preferably 16 hours to about 24 hours.

Another embodiment of the present invention provides, a process for the preparation of Etoricoxib polymorphic Form-I comprising the steps of;

a) dissolving Etoricoxib in a solvent,
b) adding step a) solution to an anti-solvent containing the seed of Etoricoxib Form-I, and
c) isolating pure Etoricoxib polymorphic Form-I.

According to the present invention Etoricoxib is dissolved in a solvent at 40° to 80°C, preferably at 65 °to 70°C. Undissloved particles are filtered to get clear solution. The resulting solution is added to a pre-seeded Form-I of hydrocarbon solvent at 10-25°C for 5-10min, solvent is removed by filtration to obtain pure crystalline polymorphic Form-I of Etoricoxib.

According to the present invention, the solvent is selected from the group comprising alcohols, esters, ethers, ketones, chlorinated solvents, nitrile solvents. The alcoholic solvent is selected from methanol, ethanol, isopropanol, n-propanol or butanol; the ester solvent is selected from ethyl acetate, methyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate or isopropyl acetate; the ether solvent selected from tetrahydrofuran, methyl tert-butyl ether or diisopropyl ether; the ketone solvent is selected from acetone, methylethylketone or methylisobutylketone; the nitrile solvent is acetonitrile.

According to the present invention, the anti-solvent is selected from pentane, hexane, heptane, cyclohexane or methylcyclohexane.

Yet another embodiment of the present invention provides, a process for the preparation of Etoricoxib polymorphic Form-I comprising the steps of;

a) dissolving Etoricoxib in a solvent,
b) adding step a) solution to an anti-solvent, and
c) isolating pure Etoricoxib polymorphic Form-I.

According to the present invention Etoricoxib is dissolved in a solvent at 40° to 80°C, preferably at 65 °to 70°C. Undissloved particles are filtered to get clear solution. The resulting solution is added to hydrocarbon solvent at 10-25°C for 5-10min, solvent is removed by filtration to obtain pure crystalline polymorphic Form-I of Etoricoxib.

According to the present invention, the solvent is selected from the group comprising alcohols, esters, ethers, ketones, chlorinated solvents, nitrile solvents. The alcoholic solvent is selected from methanol, ethanol, isopropanol, n-propanol or butanol; the ester solvent is selected from ethyl acetate, methyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate or isopropyl acetate; the ether solvent selected from tetrahydrofuran, methyl tert-butyl ether or diisopropyl ether; the ketone solvent is selected from acetone, methylethylketone or methylisobutylketone; the nitrile solvent is acetonitrile.

The following examples are provided to illustrate the process of the present invention. How ever, they are not intended to limit the scope of an invention.

Example: 1

Preparation of 5-chloro-3-[4-methylsulfonyl)phenyl]-2-(2-methy1-5-pyridinyl) pyridine (Etoricoxib).

n-Propionic acid (30 ml) and methanesulfonic acid (5.7gm) was added to 2-(4-methanesulfonyl-phenyl)-1-(6-methyl-pyridin-3-yl)-ethanone(10 gm) in toluene (100 ml) at 25 to 35°C. The resulting mixture was heated to 70-75°C to get clear solution. Vinamidinium hexaflurophophate (15.9 gm) was added, followed by ammonium acetate (18.7gm). Reaction mass was refluxed for 14-16hrs. After completion, the reaction mixture was cooled to room temperature. Ethyl acetate and water was added to the reaction mass, adjusted pH to 7.5 -8.5 with ammonia solution. Salts were removed through hyflo bed and the filtrate was washed with 30% aqueous sodium chloride solution, followed by water. Ethyl acetate layer was concentrated to residue. The residue was dissolved in isopropyl alcohol and a solution of p-toluenesulfonic acid (6.55 gm) in isopropyl alcohol was added. Stirred the solution for 3-4 hrs at room temperature, followed by reflux for 1hr. Reaction mass was slowly cooled to room temperature, the obtained solid was filtered and washed with isopropyl alcohol to gave 12.4 gm of PTSA salt of etoricoxib.

PTSA salt of Etoricoxib (12.4 gm) was taken in a mixture of ethyl acetate and water, to this mixture 18-20% of aqueous ammonia (8.0 ml) solution was added. The organic layer was separated and the ethyl acetate layer was washed with 30% sodium chloride solution. Ethyl acetate layer was concentrated to get residue, isopropyl alcohol was added and then heated to 65-70°C for 1hr. The reaction mixture was cooled 5-10°C and the obtained solid was filtered to give pure Etoricoxib.

Example : 2

Preparation of Etoricoxib polymorphic Form-I

Etoricoxib (10gm) was dissolved in isopropyl alcohol (50ml) at 65-70°C and stirred for 10-15 minutes. The resulting solution was filtered through micron filter to remove any undissolved

particles. n-Heptane (70ml) and Form-I(0.25gm) seed were taken in another RB flask at 25-30°C and cooled to10-15°C. The above isopropyl alcoholic solution of Etoricoxib was slowly added to pre-seeded n-heptane mixture at 10-25°C and it was stirred for 60 to 90 minutes at 25-35°C. The obtained solid was filtered and washed with a mixture of n-heptane (10ml)/ isopropyl alcohol (10ml) and further dried under vacuum at 45-50°C for 12 hrs. The solid obtained was identified as crystalline Etoricoxib polymorphic Form-I. (Yield: 85-95%).

We claim:

1. An improved process for the preparation of Etoricoxib comprising the steps of;
   a) reacting vinamidinium hexafluorophoshate of formula-III with ketosulfone of formula-II in the presence of acid to get crude Etoricoxib,
   b) converting the crude Etoricoxib to an acid addition salt,
   c) setting free of the acid addition salt, and
   d) isolating Etoricoxib.

2. The process according to claim 1, wherein reaction is carried out in the presence of acid such as acetic acid, propionic acid, methanesulfonic acid, trifluoroacetic acid, sulfuric acid or mixtures thereof.

3. The process according to claim 1, wherein the reaction is carried out in solvent is selected from methanol, ethanol or toluene.

4. A process according to claim 1, wherein the reaction is carried out in the presence of a buffer solution selected from sodium acetate, potassium acetate or ammonium acetate.

5. The process according to claim 1, wherein the acid addition salt is selected from p-toluenesulfonic acid salt, methanesulfonic acid salt or benzenesulfonic acid salt.

6. The process according to claim 1, wherein the setting free of acid addition salt is carried out in presence of base selected from ammonia, potassium hydroxide, sodium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, triethylamine or pyridine.

7. An improved process for the preparation of Etoricoxib polymorphic Form-I comprising the steps of;
   a. dissolving Etoricoxib in a solvent,
   b. adding step a) solution to an anti-solvent containing the seed of Etoricoxib Form-I, and
   c. isolating pure Etoricoxib polymorphic Form-I.

8. An improved process for the preparation of Etoricoxib polymorphic Form-I comprising the steps of;
   a. dissolving Etoricoxib in a solvent,
   b. adding step a) solution to an anti-solvent, and
   c. isolating pure Etoricoxib polymorphic Form-I.

9. The process according to claim 7 and 8, wherein the solvent is selected from methanol, ethanol, isopropanol, acetone, ethyl acetate, methyl acetate or acetonitrile.

10. The process according to claim 7 and 8, wherein the anti-solvent is selected from pentane, hexane, heptane, cyclohexane or methylcyclohexane.

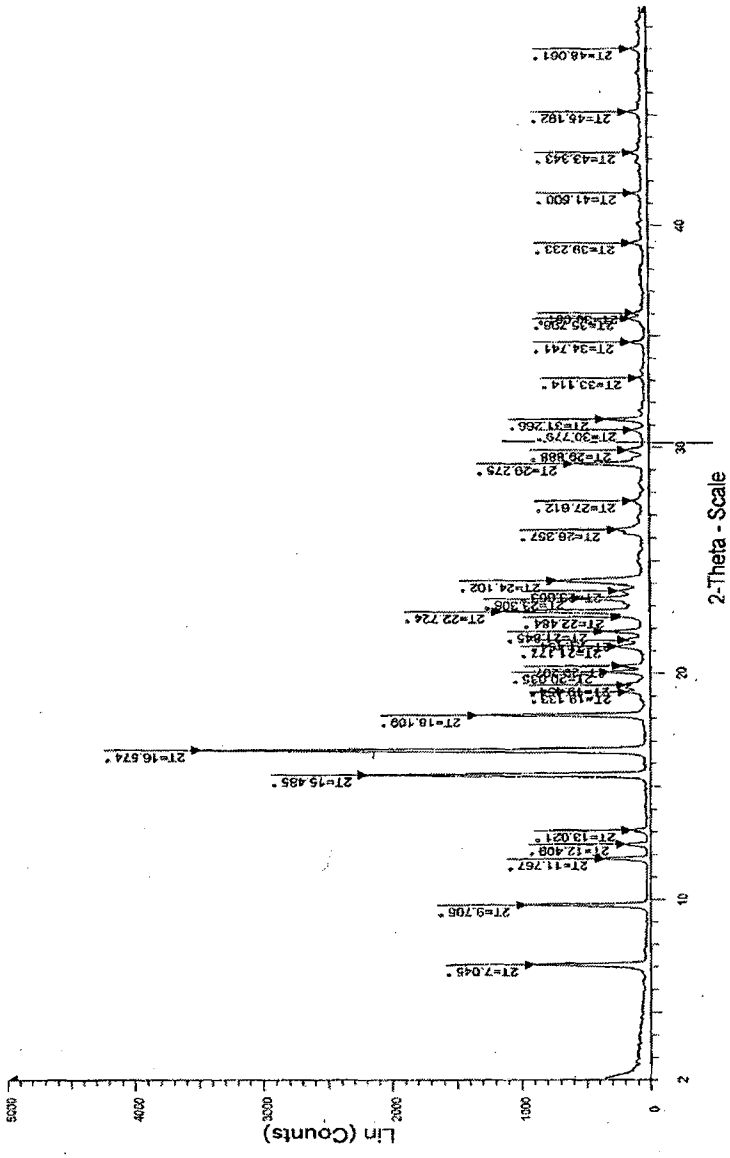

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Figure 1