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(54) Title: A PROCESS FOR THE PREPARATION OF SUBSTANTIALLY PURE 4-AMINO-1-ISOBUTYL-1H-IMIDAZO[4,5-C]-QUINOLINE (IMIQUIMOD)

(57) Abstract: A process for preparation of Imiquimod comprising oxidation of 1-Isobutyl-1H-imidazo-[4,5-c]-quinoline (II) afforded 1-Isobutyl-1H- imidazo-[4,5-c]-quinoline-5-N-oxide(III) which is isolated in pure form as its hydrochloride salt (IV) followed by conversion to 4-chloro derivative(V) and conversion to corresponding 4-iodo derivative (VI) which is a novel intermediate. This novel intermediate is converted to imiquimod (VIII) and purified via its organic salt. The invention also relates to crystalline polymorphic forms of Imiquimod Maleate, Fumarate and Oxalate.

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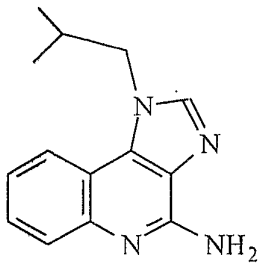
A process for the preparation of substantially pure 4-Amino-1-isobutyl-1H-imidazo[4,5-c]-quinoline (Imiquimod)

Field of the invention

The present invention relates to a process for synthesis of substantially pure 4-Amino-1-isobutyl-1H-imidazo [4,5-c]-quinoline. The invention also relates to a novel purification method via novel organic salts.

Background of the invention

Imiquimod, 4-Amino-1-isobutyl-1H- imidazo-[4,5-c]-quinoline (VIII) is an immune response modifier, useful for treating viral infections such as genital warts. Imiquimod is disclosed in US patents 4,689,338 and 5,238,944 and has the structure (VIII).



(VIII)

Several methods are known in the prior art for making Imiquimod (VIII).

Reported prior art describe various methods for the preparation of 4-Amino-1-isobutyl-1H-imidazo [4,5-c] quinoline (VIII) i.e. Imiquimod wherein the introduction of amino function in the 4-position is described in three ways. Nucleophilic substitution of a leaving group e.g. Cl or triflate with ammonia, dibenzylamine or an azido group is the first method. The second, is by reacting 1-Isobutyl- 1H-imidazo-[4,5-c]-quinoline-5-N-oxide (III) with ammonium hydroxide or its salts in presence of tosyl chloride at 0 – 5°C. The third reported method is by reacting 1-Isobutyl-1H-imidazo-[4,5-c]-quinoline-5-N-oxide with benzoyl isocyanate.

WO Publications WO2004009593, WO9206093; US patents 5,395,937; 5,756,747; 4,988,815; 5,602256; 5,578,727; 4,698,348; 4,689,388; European patents EP 145340, EP 0385630, EP 310950 and JP 04193866 and examples therein, describe nucleophillic substitution reactions.

In WO9748704 the amino group is introduced by reaction of a 4-Chloro derivative with sodium azide to obtain a tetrazole moiety. Treatment of the tetrazole moiety with triphenyl phosphine gives the 4-amino derivative.

In US patent 5,395,937 a 4-triflate derivative reacts with dibenzylamine to give 4-dibenzylamino derivative. Subsequent catalytic reduction gives the desired amino function in 4-position.

U.S. patent 5,756,747 discloses the nucleophilic substitution with ammonia on the corresponding 4-chloro derivative, which is prepared by isomerization of 1-Isobutyl-1H- imidazo-[4,5-c]-quinoline-5-N-oxide (III) via the 4-hydroxy derivative followed by reaction with $POCl_3$. Several patents disclose nucleophilic substitution of 4-Chloro-1-isobutyl-1H- imidazo-[4,5-c]-quinoline (V) with ammonia at high temperature and high pressure. These include US 4,988,815; US 5,602,256; US 5,578,727; US 4,698,348; US 4,689,388; EP 145340; EP 0385630; EP 310950 and JP 04193866.

The process of converting 1-Isobutyl-1H- imidazo-[4,5-c]-quinoline (II) to 1-Isobutyl-1H- imidazo-[4,5-c]-quinoline-5-N-oxide (III) has been disclosed in WO2004/0011462 A1, WO 2004/009593 A1 using peracetic acid in toluene as a solvent. This conversion is also reported in WO9215581, WO9206093 and US 5175296 using a combination of formic acid and peracetic acid. However, since the yields are poor and reaction is incomplete, there is a need to develop an oxidation process with milder conditions.

The patents WO 2004/009593, US2004138459, disclose a process for the preparation of 4-Amino-1-isobutyl-1H- imidazo-[4,5-c]-quinoline (VIII) (i.e. Imiquimod) by introducing an amino group in the 4-position via 1-Isobutyl-1H-imidazo-[4,5-c]-quinoline-4-phthalimide intermediate (i.e. phthalimido protecting group).

WO 9206093 discloses reaction of 1-Isobutyl-1H-imidazo-[4,5-c]-quinoline-5-N-oxide (III) with ammonium hydroxide or ammonium salts in the presence of tosyl chloride at 0 - 5°C to give Imiquimod.

WO 9215581 relates to reaction of 1-Isobutyl-1H-imidazo-[4,5-c]-quinoline-5-N-oxide (III) with benzoyl isocyanate which on subsequent hydrolysis yields Imiquimod (VIII).

Purification of Imiquimod has been described via formation of pharmaceutical salts in WO 2004009593, US 4,689,338 i.e. using HCl, H_2SO_4, H_3PO_4, HNO_3 and methane sulfonic acid. There is still a need for preparation of 4-Amino-1-isobutyl-1H-imidazo-[4,5-c]-quinoline (VIII) namely Imiquimod in high yield and purity. The use of organic acid in place of inorganic acid gives corresponding organic salt with better yield and thus improves the yield of pure imiquimod.

Objects of the invention

An object of the present invention is to develop a simple process for the preparation of Imiquimod.

Another object of the present invention is to provide a purification process, which is simple and implemented on a large scale.

A further object of the present invention is to produce Imiquimod (VIII) of substantial high purity.

Another object of the present invention is to provide a process for the preparation of Imiquimod Maleate crystals, Imiquimod Fumarate crystals and Imiquimod oxalate crystals.

Yet another object of the present invention is to provide polymorphic forms of Imiquimod maleate, Imiquimod fumarate and Imiquimod oxalate salts.

Summary of the Invention

Accordingly the present invention provides a process for the preparation of substantially pure 4-Amino-1-isobutyl-1H-imidazo-[4,5-c]-quinoline (VIII) comprising:

i. treating 3-Amino-4-(isobutylamino)-quinoline (I) with formic acid to obtain 1-isobutyl-1H-imidazo-[4,5-c]-quinoline (II);

ii. reacting 1-Isobutyl-1H-imidazo-[4,5-c]-quinoline (II) with per acid preferably meta-chloro perbenzoic acid in organic solvent to yield 1-Isobutyl-1H-imidazo-[4,5-c]-quinoline-5-N-oxide (III). This is further converted to its hydrochloride salt (IV);

iii. converting 5-N-oxide hydrochloride (IV) to 4-Chloro-1H- imidazo-[4,5-c]-quinoline (V) by treating with phosphorous oxychloride;

iv. reacting compound 4-Chloro-1H- imidazo-[4,5-c]-quinoline (V) with an alkali halide preferably sodium iodide to produce the corresponding 4-iodo derivative (VI) which is treated with ammonia to obtain crude (VIII);

v. treating the crude (VIII) to obtain a pharmaceutically acceptable salt of an organic acid selected from a group consisting of Imiquimod Maleate (VIIa), Fumarate (VIIb) and Oxalate (VIIc); and

vi. finally converting the pharmaceutically acceptable salt of above step to highly pure Imiquimod (VIII) in methanolic ammonia.

These and other aspects of the present invention are described in more detail with reference to the following detailed description of the invention.

Detailed Description of Figures

Fig. 1 shows X Ray Powder diffraction pattern of pure Imiquimod.
Fig. 2 shows X Ray Powder diffraction pattern of Imiquimod Maleate Form I
Fig. 3 shows FT-IR spectrum of Imiquimod Maleate Form I
Fig. 4 shows X Ray Powder diffraction pattern of Imiquimod Fumarate Form I
Fig. 5 shows FT-IR spectrum of Imiquimod Fumarate Form I
Fig. 6 shows X Ray Powder diffraction pattern of Imiquimod Fumarate Form II
Fig. 7 shows FT-IR spectrum of Imiquimod Fumarate Form II
Fig. 8 shows X Ray Powder diffraction pattern of Imiquimod Fumarate Form III
Fig. 9 shows FT-IR spectrum of Imiquimod Fumarate Form III
Fig. 10 shows X Ray Powder diffraction pattern of Imiquimod Oxalate Form I
Fig. 11 shows FT-IR spectrum of Imiquimod Oxalate Form I
Fig. 12 shows X Ray Powder diffraction pattern of Imiquimod Oxalate Form II
Fig. 13 shows FT-IR spectrum of Imiquimod Oxalate Form II
Fig. 14 shows X Ray Powder diffraction pattern of Imiquimod Oxalate III
Fig. 15 shows FT-IR spectrum of Imiquimod Oxalate Form III

X-ray powder diffraction pattern has been obtained on PANalytical X'PertPRO diffractometer equipped with accelerator detector using Copper Kα (λ = 1.5406 Å) radiation with scanning range between 2-50 θ at scanning speed of 2°/min.

The Fourier-transform infrared (FT-IR) spectrum of Form I was obtained on a FT-IR 8300 Shimadzu instrument, in the range of 400-4000 cm^{-1} with a resolution of 4 cm^{-1}.

Detailed description of invention

The present invention relates to a process for preparing Imiquimod, 4-Amino-1-isobutyl-1H- imidazo-[4,5-c]-quinoline of formula (VIII). However, the inventive process can be used to prepare any compound within the scope of formula (VIII) and its derivative including those disclosed in US patents 5,756,747; 5,395,937; 4,689,338; EP 385630, WO 9748704; WO 9206093 and WO 9215581 all of which are incorporated by reference in their entirety.

The cyclisation of 3-Amino-4-(isobutylamino)-quinoline (I) is accomplished by treating it with formic acid to obtain 1-isobutyl-1H- imidazo-[4,5-c]-quinoline (II). Satisfactory yield by any method known in the art including those disclosed in patents WO 92 06093 and US 5,175,296 all of which are incorporated by reference in their entirety.

The 1-Isobutyl-1H- imidazo-[4,5-c]-quinoline-5-N-oxide of formula (III) can be obtained by any method known in the art including those in U.S. patent 5,756,747; WO 9206093 and WO 9215581 all of which are incorporated by reference in their entirety. In the present invention it has been achieved using meta-chloroperbenzoic acid. A preferred solvent is an aliphatic alkyl ester where in carbon chain may be preferably C_1-C_4. Preferably Ethyl acetate is used as solvent. The reaction is preferably carried out at a temperature of between 20 - 80°C more preferably between 40 - 80°C. The meta-chloroperbenzoic acid is preferably added over a period of about 1 to 3 h more preferably from about 1 - 2 h. The reaction is complete when no 1-Isobutyl-1H-imidazo-[4,5-c]-quinoline (II) is detected by TLC. When the reaction is complete this excess of m-chloro benzoic acid is filtered, washed with ethyl acetate and the organic layer containing the 1H- Imidazo-[4,5-c]-quinoline-5-N-oxide (III) compound is further concentrated. This is more efficient with respect to yield and purity in comparison to reported reference disclosed in patent WO 2004/011462, WO 2004/009593, WO 9215581, WO 9206093, US 5175296.

The 1-Isobutyl-1H-imidazo-[4,5-c]-quinoline-5-N-oxide (III) is purified by preparing its hydrochloride salt (IV) in 8 % alcoholic hydrochloride solution. A preferred alcohol is from C1-C4 aliphatic alcohol. The hydrochloride formation is carried out at a temperature between 5 - 20 °C, more preferably between 10 - 20°C. When the hydrochloride formation is complete the product (IV) is filtered and washed with ethyl alcohol.

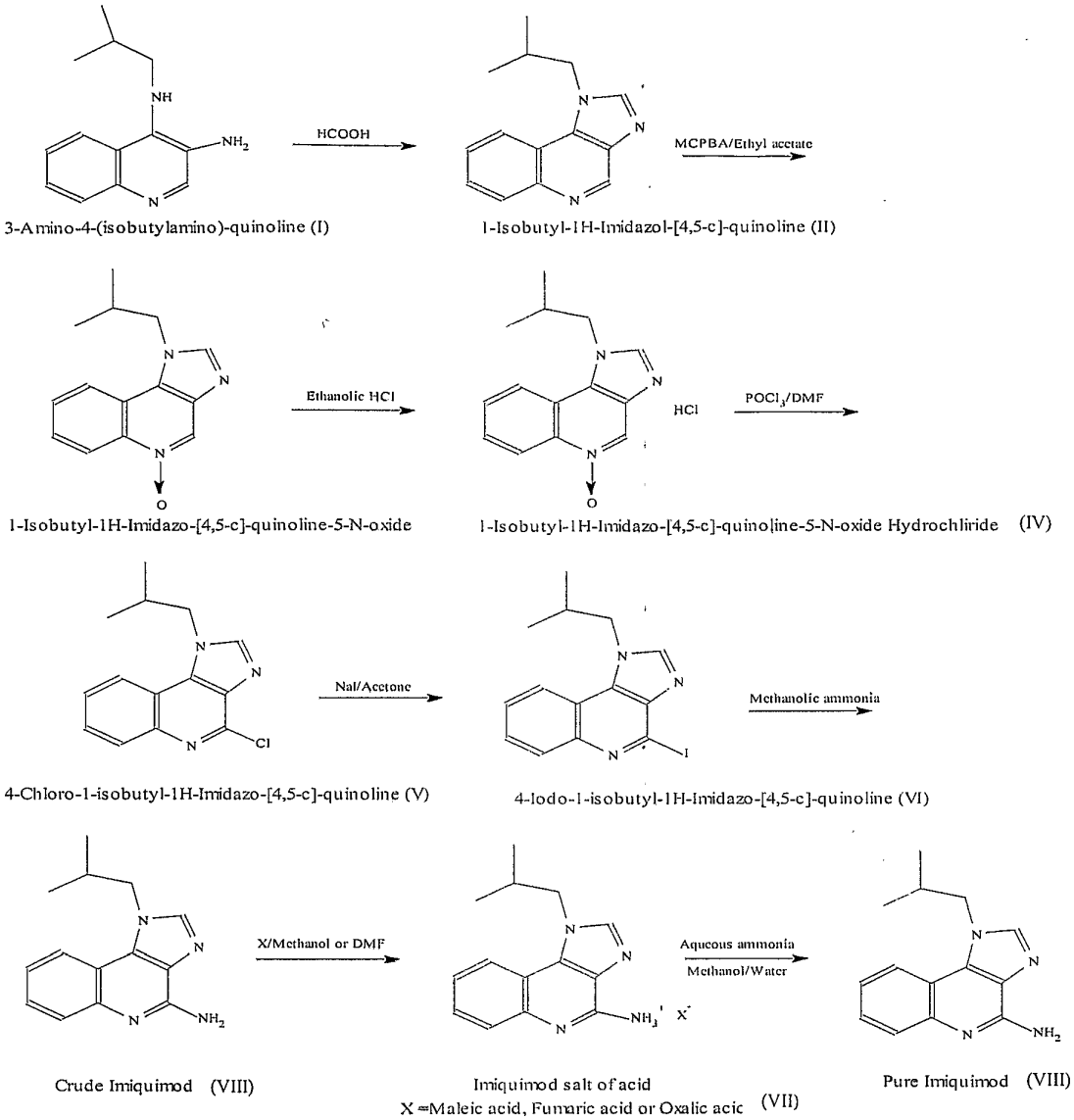
The 4-Chloro-1H- imidazo-[4,5-c]-quinoline an intermediate of formula (V) is obtained by reaction of 1H- imidazo-[4,5-c]-quinoline-5-N-oxide hydrochloride of formula (IV) with phosphorous oxychloride in an aprotic solvent i.e. dimethylformamide by any method known in the art including those disclosed in US patent US 4,689,338 all of which are incorporated by reference in their entirety herein.

The 4-Iodo-1H- imidazo-[4,5-c]-quinoline (VI), a novel intermediate is prepared by reacting 4-Chloro-1H- imidazo-[4,5-c]-quinoline- (V) in an aliphatic ketone preferably with alkali halide via the halogen exchange reaction. The reaction is preferably carried out in the presence of sodium iodide. The reaction is achieved in acetone as a solvent. The reaction is preferably carried out at temperatures between 25 - 35 °C over a period of about 8 – 10 h. This novel compound is characterized by its M.P., ^{1}HNMR and mass spectroscopy.

In the penultimate stage, 4-Iodo-1H- imidazo-[4,5-c]-quinoline (VI) is converted to Imiquimod (Crude) by ammonolysis in a lower aliphatic alcohol. The reaction is carried out in the presence of ammonium hydroxide or ammonium carbonate or ammonia, preferably ammonia.

Imiquimod (Crude) is subsequently converted to its pharmaceutically acceptable organic salt (VII) in aqueous alcohol or in dipolar aprotic solvents. The reaction is carried out in aliphatic alcohol and most preferably in methanol. The proportion of alcohol: water is 2:1. The salt formation is preferably done at 60 - 90°C, more preferably about 50 – 80 °C in alcohol or at 150 - 180 °C, more preferably about 150-160 °C in dipolar aprotic solvents.

Scheme I



3-Amino-4-(isobutylamino)-quinoline (I)

1-Isobutyl-1H-Imidazol-[4,5-c]-quinoline (II)

1-Isobutyl-1H-Imidazo-[4,5-c]-quinoline-5-N-oxide

1-Isobutyl-1H-Imidazo-[4,5-c]-quinoline-5-N-oxide Hydrochliride (IV)

4-Chloro-1-isobutyl-1H-Imidazo-[4,5-c]-quinoline (V)

4-Iodo-1-isobutyl-1H-Imidazo-[4,5-c]-quinoline (VI)

Crude Imiquimod (VIII)

Imiquimod salt of acid
X =Maleic acid, Fumaric acid or Oxalic acic (VII)

Pure Imiquimod (VIII)

Salt formation is completed in 2 -3 h and then reaction mass is cooled slowly to 25-35 °C, when Imiquimod salt (VII) crystallizes out. The product is isolated by filtration. Imiquimod salt (VII) is obtained in good yield (~90 %) and purity (99 % by HPLC). Imiquimod salt (VII) is taken preferably in a mixture of water, methanol and liquor ammonia. The reaction mass is preferably heated to 60 - 80 °C more preferably at 70 °C for neutralization of salt. At an alkaline pH ~9–11 pale white pure Imiquimod (VIII) precipitates out. The reaction mass is cooled initially to 25-30 °C and finally cooled to 8 -10 °C wherein pure Imiquimod precipitates out. The purity of product is enhanced from 99 to >99.5 % by HPLC.

The pure Imiquimod thus prepared shows characteristic peaks in the XRPD at 2θ values: 10.81, 11.26, 11.3963, 15.38, 19.16, 20.22, 21.56, 22.13, 24.48, 26.42, 30.25, and 31.86 **(Fig. 1).**

Another embodiment of the present invention relates to the process of preparation of Imiquimod maleate (VIIa) Form I crystals. Imiquimod maleate (VIIa) prepared by the process described in the experimental session result in to polymorphic crystalline Form I. Imiquimod maleate Form I is also prepared by using polar aprotic solvents like acetone, acetonitrile, DMF and 1,4-Dioxane as dissolving solvents and polar protic solvents like water, C_1-C_4 alcohols, chlorinated hydrocarbons like chloroform and MDC as antisolvents.

The Imiquimod maleate Form I thus prepared shows characteristic peaks in the XRPD at 2θ value 9.50, 9.95, 17.13, 19.15, 19.93, 21.63, 24.37, 24.71, 27.09 **(Fig. 2).**

The Imiquimod maleate Form I thus prepared shows characteristic absorption peaks in FT-IR spectrum at 3298, 3129.3, 3089.8, 1676, 1608.5, 1494.1 1467, 1448, 1407, 1361.7, 1213.1, 1083.9, 948.9, 867.9, 776.3, 754.1, 692.4, 673.1, 661.5, 640.3, 590.2, 563.2 cm^{-1} **(Fig. 3).**

One more embodiment of the present invention provides a process for preparation of Imiquimod fumarate (VIIb) and its three polymorphic crystalline forms viz. Form I, Form II and Form III.

Imiquimod fumarate Form I is prepared by using polar aprotic solvents like 1,4-Dioxane and DMF as dissolving solvents and polar protic solvents like water, C_1-C_4 alcohols or aromatic hydrocarbon like toluene, chlorinated hydrocarbons like

chloroform, MDC or aliphatic ethers like diethyl ether, diisopropyl ether as antisolvents.

The Imiquimod fumarate Form I thus prepared shows characteristic peaks in the XRPD at 2θ value 6.86, 8.87, 10.74, 13.57, 14.63, 18.34, 20.30, 20.87, 21.51, 22.33, 22.85, 22.98, 25.48, 26.43, 27.03, 27.85, 29.71, 30.08, 31.21, 33.91, 35.28 **(Fig. 4).**

The Imiquimod fumarate Form I thus prepared shows characteristic absorption peaks in FT-IR spectrum at 3489.0, 3093.6, 2970.21695.3, 1527.5, 1379, 1124.4, 1103.2, 985, 754.1, 682.8, 563.2 cm^{-1} **(Fig. 5).**

Imiquimod fumarate Form II is prepared by crystallizing it from polar aprotic solvents like 1,4-Dioxane or by using polar aprotic solvents like DMF and DMSO solvents as dissolving solvent and polar protic solvents like C_1-C_4 alcohols or aromatic hydrocarbons like toluene or aliphatic ethers like diethyl ether, diisopropyl ether or acetone or acetonitrile as antisolvents.

The Imiquimod fumarate Form II thus prepared shows characteristic peaks in the XRPD at 2θ value 10.87, 11.44, 12.43, 14.36, 15.46, 18.39, 19.25, 21.62, 22.03, 22.18, 24.55, 31.91 **(Fig. 6).**

The Imiquimod fumarate Form II thus prepared shows characteristic absorption peaks in FT-IR spectrum at 3311.5, 3178, 2958.6, 1645.2, 1614.3, 1527.5, 1469.7, 1396.4, 1371.3, 1251.7, 1097.4, 991.3, 873.7, 848.6, 821.6, 759.9, 640.3, 607.5 cm^{-1} **(Fig. 7).**

Imiquimod fumarate Form III is prepared by crystallizing it from polar protic solvents like C_1-C_4 alcohols preferably methanol, isopropyl alcohol.

The Imiquimod fumarate Form III thus prepared shows characteristic peaks in the XRPD at 2θ value 9.10, 11.47, 16.48, 17.34, 18.00, 19.24, 19.60.21.38, 22.80, 23.50, 24.98, 25.99, 26.79, 27.32, 28.69, 29.51, 30.76, 37.36 **(Fig. 8).**

The Imiquimod fumarate Form III thus prepared shows characteristic absorption peaks in FT-IR spectrum at 3477, 3234.4, 3093.6, 2758, 2362.6, 1693, 1606.6, 1531.4, 1375.2, 756.0, 684.7, 569 cm^{-1} **(Fig. 9).**

Another embodiment of the present invention further provides a process for preparation of Imiquimod oxalate (VIIc) and its three crystalline polymorphic forms viz. Form I, Form II and Form III.

Imiquimod oxalate Form I is prepared by crystallizing it from polar protic solvents like water or by using polar aprotic like 1,4-Dioxane and protic solvents like C_1-C_4 alcohols as dissolving solvents and polar protic solvents like water, methanol or chlorinated hydrocarbons like chloroform, MDC or C_1-C_4 aliphatic ethers as antisolvents.

The Imiquimod oxalate Form I thus prepared shows characteristic peaks in the XRPD at 2θ value 10.83, 11.43, 14.39, 15.44, 18.36, 19.10, 19.24, 21.63, 22.17, 24.56, 31.88 **(Fig. 10).**

The Imiquimod oxalate Form I thus prepared shows characteristic absorption peaks in FT-IR spectrum at 3419.6, 3217, 3062.7, 2962.5, 2360.7, 1701, 1541 1309, 756, 769,715,688, 669, 567 cm^{-1} **(Fig. 11).**

Imiquimod oxalate Form II is prepared by crystallizing it from polar aprotic solvents like DMF and DMSO.

The Imiquimod oxalate Form II thus prepared shows characteristic peaks in the XRPD at 2θ value 7.92, 15.56, 15.91, 16.60, 16.76, 17.74, 18.03, 23.25, 25.01, 27.92, 31.48 **(Fig. 12).**

The Imiquimod oxalate Form II thus prepared shows characteristic absorption peaks in FT-IR spectrum at 3315, 3182, 2958,1647,1614, 1529, 1583, 1465, 1475, 1253, 1095, 873, 848, 761, 665 cm^{-1} **(Fig. 13).**

Imiquimod oxalate Form III is prepared by suspending under stirring Form I or Form II in a mixture of polar protic solvent like C_1-C_4 alcohols preferably methanol and chlorinated hydrocarbon solvent like Chloroform, MDC

The Imiquimod oxalate Form III thus prepared shows characteristic peaks in the XRPD at 2θ value 6.96, 7.42, 9.99, 10.31, 10.45, 12.41, 13.31, 13.79, 16.16, 19.21, 21.12, 23.74, 24.90, 25.62, 25.94, 26.60 **(Fig. 14).**

The Imiquimod oxalate Form III thus prepared shows characteristic absorption at in FT-IR spectrum and they are at 3101, 2962, 1685, 1218, 1099, 948, 748,713, 690, 657, 632, 590 cm^{-1} **(Fig. 15).**

Experimental data

Example No. (i)

Preparation of 1-Isobutyl-1H- imidazo-[4,5-c]-quinoline (II)

Dissolve 3-Amino-4-isobutyl amino quinoline (215 gm, 1.0 mole) in formic acid (1.0 L) and reflux the reaction mass to 110–115 °C. Maintain refluxing for 8–10 h. On completion of reaction remove excess formic acid under reduced pressure and add 3.5 L of water to the concentrated mass. Basify this diluted mass with 30 % NaOH to pH 10-11 at 20 °C. Cool the reaction mass to 10 °C and stir for further 3 h to obtain solid product. Filter the solid, wash with water and dry to get the title compound as a white solid.

M.P. 91 to 94°C
MS – (m/z) M^+ 226
^{1}HNMR (200 MHz, DMSO D_6)
Yield: 221 gm, 98 %

δ values	Proton
0.95	(6H, d, CH_3 x 2)
2.1-2.2	(1H, m, -CH_2)
4.5	(2H, d, CH_2)
7.7	(2H, m, Ar)
8.2-8.3	(2H, m, Ar)
8.4	(1H, s, >N-CH=N-)
9.25	(1H, s, -N-CH=N-)

Example No. (ii)

Preparation of 1-Isobutyl-1H- imidazo-[4,5-c]-quinoline-5-N-oxide.HCl (IV)

Add compound from Example (i) (220 gm, 0.97 mole) to ethyl acetate (1.7 L). Heat the reaction mass to 60 to 65 °C for dissolution. Add meta-chloroperbenzoic acid (485 gm, 70 %, 1.37 mole) in lots at 60–65 °C over a period of 2–3 h and maintain the temperature for 6–8 h. On completion of reaction, separate the upper aqueous layer.

Concentrate the lower organic layer under vacuum. To this concentrated mass, add 8 % ethanolic hydrochloride (450 ml) at 10–15 °C. Filter the precipitated hydrochloride salt, wash with ethyl acetate and dry to obtain the title product

M.P. 200 to 204 °C
MS – (m/z) M^+ 241
^{1}HNMR (200 MHz, DMSO D_6)
Yield: 255 gm, 94 %

δ values	Proton
0.95	(6H, d, CH_3 x 2)
2.2-2.5	(1H, m, -CH)
4.6	(2H, d, CH_2)
8.0-8.1	(2H, m, Ar)
8.5-8.7	(2H, m, Ar)
8.85	(1H, s, -CH=N-)
10.0	(1H, s, -CH=N-) O

Example No. (iii)

Preparation of 4-Chloro-1-isobutyl-1H- imidazo-[4,5-c]-quinoline (V)

Take the compound from Example (ii) (100 gm, 0.36 mole) and phosphorous oxychloride (157 gm) in N,N-Dimethylformamide (600 ml) at 20 °C. Stir the resulting solution for 30 minutes at 20 °C and subsequently heat to 80 °C for 2 h. Drown the resulting suspension in 3.0 L cold water and basify to pH 9-10 with 30 % sodium hydroxide solution. Filter the precipitated solid, wash with water and dry to obtain the title product.

M.P. 134 to 136°C
MS – (m/z) M^+ 261
^{1}HNMR (200 MHz, DMSO D_6)
Yield: 70 gm, 74 %

δ values	Proton
0.95	(6H, d, CH_3 x 2)
2.17-2.2	(1H, m, -CH)
4.5	(2H, d, CH_2)
7.7-7.8	(2H, m, Ar)

8.0-8.3	(2H, m, Ar)
8.5	(1H, s, -CH=N-)

Example No. (iv)

Preparation of 4-Iodo-1-isobutyl-1H- Imidazo-[4,5-c]-quinoline (VI)

Add the compound from Example (iii) (50 gm, 0.19 mole) to acetone (200 ml). Then add dropwise separately prepared solution of sodium iodide in acetone (i.e. 28 gm in 200 ml acetone) to the reaction mass and maintain at 25 – 30 °C for 8 h. Filter the precipitated sodium chloride and concentrate the acetone under vacuum to obtain the title product.

M.P. 125 to 127°C
MS – (m/z) M^+ 351
^{1}HNMR (200 MHz, DMSO D_6)
Yield: 55 gm, 82 %

δ values	Proton
0.93	(6H, d, CH_3 x 2)
2.1-2.7	(1H, m, -CH)
4.53-4.57	(2H, d, NCH_2)
7.75-7.8	(2H, m, Ar)
8.08-8.11	(1H, m, Ar)
8.33-8.38	(1H, m, Ar)
8.5	(1H, s, -CH=N-)

Example No. (v)

Preparation of Imiquimod (Crude)

Add the compound from Example (iv) (67 gm, 0.19 mole) to 750 ml of 15 % methanolic ammonia solution in a pressure reactor (i.e. autoclave) and heat to 150 – 155 °C (~ 20 Kg pressure). Maintain the reaction mass at this temperature, till the product precipitates out. Filter the precipitated solid, wash with 50 ml methanol. Dry at 55 to 60 °C for 8 h to obtain the title product. Yield: 40 gm, 86 %, Purity: 95 %.

Example No: (v-a)

Part A

Preparation of 4-Amino-1-isobutyl-1H- Imidazo-[4,5-c]-quinoline maleate salt (VIIa)

Add the compound from Example (v) (35 gm, 0.14 mole) to a mixture of 350 ml of methanol and 175 ml water. Subsequently, add 35 gm (0.30 mole) maleic acid in one lot and heat the reaction mass to reflux temperature of 74 °C. Charcoalise and maintain the reaction mass for 0.5 hr, wash the hyflo bed with 20 ml hot methanol and filter the hot reaction mass through hyflo. The filtrate is then slowly cooled to RT and then to 8–10 °C in 1 hr. Filter the precipitated product, wash with 20 ml methanol. Dry at 55–60 °C. Yield: 47.2 gm, 91 %; Purity: 99.9 %.

M.P.	190 to 192°C
MS – (m/z)	M^+ 241
^{1}HNMR (200 MHz, DMSO D_6)	

δ values	Proton
0.93	(6H, d, CH_3 x 2)
2.1-2.3	(1H, m, -CH)
4.5	(2H, d, NCH_2)
6.09	(2H, s, =C-H of maleic acid)
7.5-7.8	(3H, m, Ar)
8.1	(1H, d, Ar)
8.5	(1H, s, -CH=N-)
8.8	(2H, brs, -NH_2) D_2O exchangeable

Part B

Preparation of 4-Amino-1-isobutyl-1H- Imidazo-[4,5-c]-quinoline (VIII)

Add 4-Amino-1-isobutyl-1H- Imidazo-[4,5-c]-quinoline maleate salt (VIIa) (47.2 gm, 0.13 mole) to a mixture of 350 ml methanol and 175 ml water. Heat the reaction mass to 75 °C and further add 3.5 gm charcoal, maintaining the reaction for 0.5 hr. Filter the hot reaction mass through hyflo and subsequently add 25 % ammonia solution (40 ml) till alkaline pH. Filter the precipitated product, wash with water. Dry to obtain the title product. Yield: 31.4 gm, 89.7 %; Purity: 99.9 %.

M.P.	292 to 294°C
MS – (m/z)	M^+ 241

^{1}HNMR (200 MHz, DMSO D_6)

δ values	Proton
0.97	(6H, d, CH_3 x 2)
2.1-2.25	(1H, m, -CH)
4.5	(2H, d, CH_2)
7.5-7.72	(2H, m, Ar)
7.8-7.9	(2H, m, Ar)
8.5	(1H, s, -CH=N-)
8.8	(1H, s, $-NH_2$) D_2O exchangeable

Example No: (v-b)

Part A

Preparation of 4-Amino-1-isobutyl-1H- Imidazo-[4,5-c]-quinoline fumarate salt (VIIb)

Add the compound from Example (v) (50 gm, 0.20 mole) to a mixture of 350 ml of DMF and 175 ml water. Subsequently, add 48 gm (0.41 mole) fumaric acid in one lot and reflux the reaction mass temperature of 160 °C. Charcoalise and maintain the reaction mass for 0.5 hr, wash the hyflo bed with 20 ml hot water and filter the hot reaction mass through hyflo. Cool the filtrate slowly to RT and then to 8 – 10 °C in 1 hr. Filter the precipitated product, wash with 20 ml of water. Dry the product at 55 – 60 °C. Yield: 66.4 gm, 89 %; Purity: 99.9 %.

Part B

Preparation of 4-Amino-1-isobutyl-1H- Imidazo-[4,5-c]-quinoline (VIII)

Add 4-Amino-1-isobutyl-1H- Imidazo-[4,5-c]-quinoline fumarate salt (VIIb) (66.49 gm, 0.18 mole) to a mixture of 350 ml methanol and 175 ml water. Heat the reaction mass to 75 °C and further add 3.5 gm of charcoal, maintaining the reaction for 0.5 hr. Filter the hot reaction mass through hyflo and subsequently add 25 % ammonia solution (40 ml) till alkaline pH. Filter the precipitated product, wash with water. Dry to obtain the title product. Yield: 40.9 gm, 90 %; Purity: 99.92 %.

Example No: (v-c)

Part A

Preparation of 4-Amino-1-isobutyl-1H- Imidazo-[4,5-c]-quinoline oxalate salt (VIIc)

Add the compound from Example v (50 gm, 0.20 mole) to a mixture of 350 ml of DMF and 175 ml water. Subsequently, add 49 gm (0.41 mole) oxalic acid in one lot and reflux the reaction mass at a temperature of 160 °C. Charcoalise and maintain the reaction mass for 0.5 hr, wash the hyflo bed with 20 ml hot water and filter the hot reaction mass through hyflo. Slowly cool the filtrate to RT and then to 8 – 10 °C in 1 hr. Filter the precipitated product, wash with 20 ml of water. Dry the product at 55 – 60 °C. Yield: 61.8 gm, 90 %; Purity: 99.9 %.

Part B

Preparation of 4-Amino-1-isobutyl-1H- Imidazo-[4,5-c]-quinoline (VIII)

Add 4-Amino-1-isobutyl-1H- Imidazo-[4,5-c]-quinoline oxalate salt (VIIc) (61.8 gm, 0.18 mole) to a mixture of 350 ml methanol and 175 ml water. Heat the reaction mass to 75 °C and further add 3.5 gm of charcoal, maintaining the reaction for 0.5 hr. Filter the hot reaction mass through hyflo and subsequently add 25 % ammonia solution (40 ml) till alkaline pH. Filter the precipitated product, wash with water. Dry to obtain the title product. Yield: 38.4 gm, 88 %; Purity: 99.91 %.

PROCESS OF OBTAINING IMIQUIMOD MALEATE (VIIa) CRYSTALS

Example 1

Dissolve 0.5 g of Imiquimod maleate in 25 ml of acetonirile at 60 °C. Allow the hot solution to cool to 25 °C following it by addition of 25 ml water. Maintain the solution at 25 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 2

Dissolve 0.5 g of Imiquimod maleate in 25 ml of acetone at 60 °C. Allow the hot solution to cool to 25 °C following it by addition of 25 ml water. Further cool the solution to 5 °C and maintain for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 3

Dissolve 0.5 g of Imiquimod maleate in 75 ml of methylene dichloride at 60 °C. Allow the hot solution to cool to 25 °C following it by addition of 25 ml hexane. Further cool the solution to 5 °C and maintain for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 4

Dissolve 0.5 g of Imiquimod maleate in 75 ml of water at 100 °C. Allow the hot solution to cool to 25 °C. Further cool the solution to 5 °C and maintain for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals

Example 5

Dissolve 0.5 g of Imiquimod maleate in 15 ml of DMF at 60 °C. Allow the hot solution to cool to 25 °C following it by addition of 25 ml of IPA. Maintain the solution at 25 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals

Example 6

Disperse 1 g of Imiquimod Maleate in 50 ml IPA at 30 °C. Maintain the solution at 30°C under stirring for 16 h. Filter the dispersed solid and dry at 55 °C to get Form I crystals

Example 7

Dissolve 0.5 g of Imiquimod maleate in 15 ml of DMF at 60 °C. Allow the hot solution to cool to 25 °C following it by addition of 25 ml of MDC. Further cool the solution and maintain at 5 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals

Example 8

Dissolve 0.5 g of Imiquimod maleate in 15 ml of DMF at 60 °C. Allow the hot solution to cool to 25 °C for 1 hr, Filter the separated solid and dry at 55 °C to get Form I crystals

Example 9

Dissolve 0.5 g of Imiquimod maleate in 15 ml of DMF at 60 °C. Allow the hot solution to cool to 25 °C following it by addition of 25 ml of DIPE. Maintain the solution at 25 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals

Example 10

Dissolve 0.5 g of Imiquimod maleate in 15 ml of DMF at 60 °C. Allow the hot solution to cool to 25 °C following it by addition of 25 ml of acetone. Maintain the solution at 25 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals

Example 11

Dissolve 0.5 g of Imiquimod maleate in 5 ml of acetonirile at 60 °C. Allow the hot solution to cool to 25 °C following it by addition of 25 ml of ethyl acetate. Maintain the solution at 25 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals

Example 12

Dissolve 0.5 g of Imiquimod Maleate in 40 ml of 1, 4-Dioxane at 60 °C. Allow the hot solution to cool to 25 °C following it by addition of 25 ml water. Maintain the solution at 25 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals

Example 13

Dissolve 0.5 g of Imiquimod Maleate in 25 ml of methanol at 60 °C. Allow the hot solution to cool to 25 °C following it by addition of 25 ml of DIPE and 5 ml water. Maintain the solution at 25 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

PROCESS OF PREPARING IMIQUIMOD FUMARATE (VIIb) CRYSTALS

A) Imiquimod Fumarate Form I

Example 14

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of 1,4-Dioxane at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of toluene. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals

Example 15

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of 1,4-Dioxane at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml water. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 16

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of 1,4-Dioxane at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of diisopropyl ether. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 17

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMF at 160 °C. Allow the hot solution to cool to 30 °C, further cooling it to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 18

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMF at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of chloroform. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 19

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMF at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of toluene. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 20

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMF at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of water. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 21

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMF at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of methanol. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 22

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMF at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of ethanol. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 23

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMF at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of isopropyl alcohol. Cool

the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

B) Imiquimod Fumarate Form II

Example 24

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMSO at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of diisopropyl ether. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form II crystals.

Example 25

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMSO at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of methanol. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form II crystals.

Example 26

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMSO at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of toluene. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form II crystals.

Example 27

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMSO at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of isopropyl alcohol. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form II crystals.

Example 28

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMF at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of acetone. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form II crystals.

Example 29

Dissolve 0.5 g of Imiquimod fumarate in 20 ml of DMF at 105 °C. Allow the hot solution to cool to 70 °C following it by addition of 40 ml of acetonitrile. Cool the hot solution to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form II crystals.

C) Imiquimod Fumarate Form III

Example 30

Dissolve 0.5 g of Imiquimod Fumarate in 20 ml of methanol at 70 °C. Allow the hot solution to cool to 30 °C, further cooling to 10 °C for one hour. Filter the separated solid and dry at 55 °C to get Form III crystals.

PROCESS OF PREPARING IMIQUIMOD OXALATE (VIIc) CRYSTALS

A) Imiquimod oxalate Form I

Example 31

Dissolve 0.5 g of Imiquimod oxalate in 40 ml of water at 100 °C. Allow the hot solution to cool to 30 °C, further cooling to 5 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 32

Dissolve 0.5 g of Imiquimod oxalate in 10 ml of methanol at 60 °C. Allow the hot solution to cool to 30 °C following it by addition of 40 ml chloroform. Cool the solution to 5 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 33

Dissolve 0.5 g of Imiquimod oxalate in 10 ml of dioxane at 60 °C. Allow the hot solution to cool to 30 °C following it by addition of 20 ml methanol. Cool the solution to 5 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 34

Dissolve 0.5 g of Imiquimod oxalate in 20 ml of methanol at 60 °C. Allow the hot solution to cool to 30 °C following it by addition of 40 ml water. Cool the solution to 5 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 35

Dissolve 0.5 g of Imiquimod oxalate in 20 ml of methanol at 60 °C. Allow the hot solution to cool to 30 °C following it by addition of 40 ml diisopropyl ether. Cool the solution to 5 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

Example 36

Dissolve 0.5 g of Imiquimod oxalate in 10 ml of isopropyl alcohol at 60 °C. Allow the hot solution to cool to 30 °C following it by addition of 20 ml water. Cool the solution to 5 °C for one hour. Filter the separated solid and dry at 55 °C to get Form I crystals.

B) Imiquimod oxalate Form II

Example 37

Dissolve 0.5 g of Imiquimod oxalate in 20 ml of DMF at 160 °C. Allow the hot solution to cool to 30 °C following it by cooling the solution to 5 °C for one hour. Filter the separated solid and dry at 55 °C to get Form II crystals.

Example 38

Dissolve 0.5 g of Imiquimod oxalate in 10 ml of DMSO at 170 °C. Allow the hot solution to cool to 30 °C, further cooling the solution to 5°C for one hour. Filter the separated solid and dry at 55 °C to get Form II crystals.

C) Imiquimod oxalate Form III

Example 39

Suspend 0.5 g of Imiquimod oxalate Form I crystals in 20 ml methanol and 40 ml chloroform. Stir the resultant suspension at 25 °C for 12 h. Filter the solid and dry at 55 °C to get Form III

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

ADVANTAGES OF THE PRESENT INVENTION

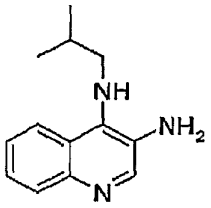
The present invention provides Imiquimod in substantially pure form. The product is having purity greater than 99 %.

The present invention provides Imiquimod with 88% yield.

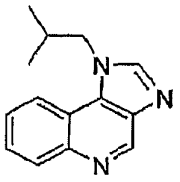
Received by the International Bureau on 04 december 2006
(04.12.2006)

1. A process for preparation of substantially pure 4-amino-1-isobutyl-1H- imidazo-[4,5-c]-quinoline (VIII), said process comprising of:

a. cyclizing 3-amino-4-(isobutylamino)-quinoline (I) with formic acid to obtain 1-isobutyl-1H- imidazo-[4,5-c]-quinoline (II);

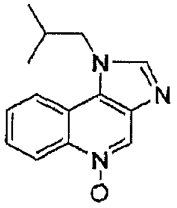


I



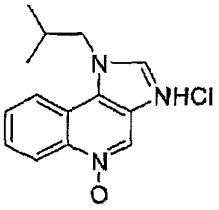
II

b. oxidizing 1-isobutyl-1H-imidazo-[4,5-c]-quinoline (II) with peracid in an organic solvent affording 1-isobutyl-1H- imidazo-[4,5-c]-quinoline-5-N-oxide (III);



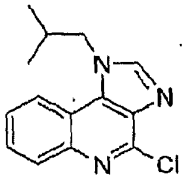
III

c. treating 1-isobutyl-1H-imidazo-[4,5-c]-quinoline-5-N-oxide (III) with alcoholic hydrochloric acid to form its hydrochloric salt (IV);



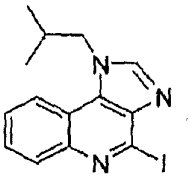
IV

d. reacting hydrochloride salt (IV) with a chlorinating agent to form its 4–chloro-1H-imidazo-[4,5-c]-quinoline (V);



V

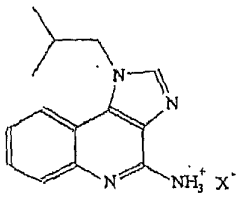
e. reacting 4-chloro-1H- imidazo-[4,5-c]-quinoline (V) with an alkali halide in a dipolar aprotic solvent medium to obtain the corresponding 4-iodo derivative (VI);



VI

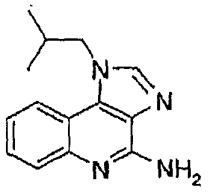
f. ammonolysing said 4-iodo derivative (VI) to obtain crude product imiquimod (VIII) in ammonia solution;

g. converting the crude product imiquimod (VIII) into a pharmaceutically acceptable organic acid salt (VII) by reacting the crude (VIII) with an aliphatic dicarboxylic acid, in a suitable solvent medium; and



VII

h. obtaining pure imiquimod (VIII) from imiquimod salt (VII) by treating it with ammonia.



VIII

2. The process as claimed in claim 1, wherein in step (b) the peracid is meta-chloroperbenzoic acid.
3. The process as claimed in claim 1, wherein in step (b) the organic solvent used in oxidation is ethyl acetate.
4. The process as claimed in claim 1, wherein in step (b) oxidation is performed at about 60 to 70°C.
5. The process as claimed in claim 1, wherein in step (b) the oxidation reaction is completed in about 6 to10 hrs.
6. The process as claimed in claim 1, wherein in step (c) the alcoholic hydrochloric acid is ethanolic hydrochloric acid.
7. The process as claimed in claim 1, wherein in step (d) the chlorinating agent used to convert 5-N-oxide hydrochloride (IV) to 4–chloro derivative (V) is phosphorous oxychloride.
8. The process as claimed in claim1, wherein in step (e) the alkali halide is sodium iodide.
9. The process as claimed in claim 1, wherein in step (e) the dipolar aprotic solvent is acetone.
10. The process as claimed in claim 1, wherein in step (f) the ammonia solution is methanolic ammonia.
11. The process as claimed in claim 1, wherein in step (f) the ammonolysis is performed at about 140 to 155 °C temperature and at 15 to 20 Kg pressure.
12. The process as claimed in claims 10 and 11, wherein in step (f) the product is dried for about 8 hrs.
13. The process as claimed in claim 1, wherein in step (g) ~~in~~ the acid used to prepare the organic salts is an aliphatic dicarboxylic acid.

14. The process as claimed in claim 1, wherein in step (g) the aliphatic dicarboxylic acids is selected from a group consisting of maleic acid, fumaric acid and oxalic acid.

15. The process as claimed in claim 1, wherein in step (g), the solvent used is selected from a group consisting of water, methanol and DMF, or mixture thereof.

16. The process as claimed in claim 1, wherein in step (g) the preparation of 4-amino-1-isobutyl-1H-imidazo[4,5-c] quinoline maleate (VIIa) is achieved in aqueous methanol at a temperature in the range of about 70 to 80°C.

17. The process as claimed in claim 1, wherein in step (g) the preparation of 4-amino-1-isobutyl-1H-imidazo[4,5-c] quinoline fumarate (VIIb) is achieved in DMF at a temperature in the range of about 150 to 170°C

18. The process as claimed in claim 1, wherein in step (g) the preparation of 4-amino-1-isobutyl-1H-imidazo[4,5-c] quinoline oxalate (VIIc) is achieved in DMF at a temperature in the range of about 150 to 170°C

19. The process as claimed in claim 1, wherein in step (g) the product (VII) is isolated at 8 to 10°C for about 1 hour.

20. The process as claimed in claim 1, wherein in step (g) the product obtained is having purity greater than 99 %.

21. The process as claimed in claim 1, wherein in step (h) the conversion of 4-amino-1-isobutyl-1H-imidazo[4,5-c] quinoline maleate (VIIa) to 4-amino-1-isobutyl-1H-imidazo-[4,5-c]-quinoline (VIII) pure, is performed in aqueous methanol.

22. The process as claimed in claim 1, wherein in step (h) the product obtained is having purity greater than 99.5 %.

23. The process according to claim 1, wherein in step (h) the product shows peaks in XRPD at 2θ values, 10.81,11.26, 11.3963, 15.38, 19.16, 20.22, 21.56, 22.13, 24.48, 26.42,30.25, 31.86.

24. The process as claimed in claim 1, wherein in step (h) the said compound pure imiquimod (VIII) formation is carried out in mixture of water and polar protic or aprotic solvent.

25. The process as claimed in claim 24, wherein in step (h) the ratio of water to solvent is in the ratio of 1: 2.

26. The process as claimed in claim 24, wherein the polar protic solvent is selected from C_1-C_4 alcohols.

27. The process as claimed in claim 24, wherein the polar protic solvent used is methanol.

28. The process as claimed in claim 24, where in the polar aprotic solvent used is either Dimethyl formamide or Dimethyl sulfoxide.

29. The process as claimed in claim 24, wherein the polar aprotic solvent is N,N-dimethyl formamide.

30. A process for preparing crystalline polymorphic form I of imiquimod maleate, said process comprising dissolving imiquimod maleate in suitable polar aprotic solvent and optionally adding polar protic solvent as antisolvent.

31. The process as claimed in claim 30, wherein the polar aprotic solvent is selected from acetone, acetonitrile, DMF and 1,4-Dioxane.

32. The process as claimed in claim 30, wherein the polar protic solvent is selected from water, C_1-C_4 alcohols, and chlorinated hydrocarbons.

33. The process as claimed in claim30, wherein the polar protic solvent is selected from isopropyl alcohol (IPA), chloroform, and methylene dichloride (MDC).

34. A process to prepare crystalline polymorphic form of imiquimod fumarate *viz.* Form I or Form II or Form III, said process comprising dissolving the imiquimod fumarate in an solvent and optionally adding an anti solvent.

35. The process for preparation of imiquimod fumarate form I crystals as claimed in claim 34 comprises dissolving the imiquimod fumarate in polar aprotic solvent and optionally adding an antisolvent selected from a group consisting of polar protic solvent, polar aprotic solvent, aromatic hydrocarbon, chlorinated hydrocarbon and aliphatic ether to crystallize.

36. The process as claimed in claim 35, wherein the polar aprotic solvent is either 1,4-Dioxane or DMF.

37. The process as claimed in claim 35, wherein the antisolvent is selected from a group consisting of water, C_1-C_4 alcohol, toluene, chloroform, methylene dichloride and diisopropyl ether.

38. The process for preparation of imiquimod fumarate Form II crystals as claimed in claim 34 comprises dissolving imiquimod fumarate in polar aprotic solvent and adding an antisolvent selected from a group consisting of polar protic solvent, polar aprotic solvent, aromatic hydrocarbon and aliphatic ether.

39. The process as claimed in claim 38, wherein the polar aprotic solvent used to dissolve imiquimod fumarate is either DMF or DMSO.

40. The process as claimed in claim 38, wherein the antisolvent used is selected from, polar protic solvent selected from C_1-C_4 alcohols such as methanol and IPA, polar aprotic solvent such as acetone and acetonitrile, aromatic hydrocarbon solvent such as toluene, and ethers selected from C_1-C_4 aliphatic ether such as diisopropyl ether.

41. The process as claimed in claim 38, when DMF is the solvent, the antisolvent is either acetone or acetonitrile.

42. The process as claimed in claim 38, when DMSO is the solvent, the antisolvent is selected from methanol, IPA, toluene and diisopropyl ether.

43. The process for the preparation of imiquimod fumarate Form III crystals as claimed in claim 34 comprises dissolving imiquimod fumarate in a polar protic solvent selected from C_1-C_4 alcohols.

44. The process as claimed in claim 43, wherein the polar protic solvent is either methanol or isopropyl alcohol.

45. A process to prepare crystalline polymorphic forms of imiquimod oxalate *viz.* Form I or Form II, said process comprising dissolving the imiquimod oxalate in an solvent and optionally adding an anti solvent.

46. The process for preparation of imiquimod oxalate Form I crystals as claimed in claim 45 comprises dissolving imiquimod oxalate in a solvent selected from polar protic solvent and aprotic solvent, and optionally adding an antisolvent which is selected from polar protic solvent, chlorinated hydrocarbon and aliphatic ether.

47. The process as claimed in claim 46, wherein the polar protic solvent is water.

48. The process as claimed in claim 46, wherein the solvent for dissolving imiquimod oxalate is selected from a group consisting of methanol, isopropyl alcohol and 1,4-dioxane.

49. The process as claimed in claim 46, wherein the antisolvent is selected from a group consisting of water, methanol, chloroform, MDC, and diisopropyl ether.

50. The process for preparation of imiquimod oxalate Form II crystals as claimed in claim 45 comprises dissolving imiquimod oxalate in a polar aprotic solvent.

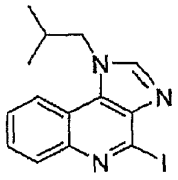
51. The process as claimed in claim 50, wherein the polar aprotic solvent is either DMF or DMSO.

52. A process for preparation of imiquimod oxalate Form III crystals comprises suspending imiquimod oxalate Form I or imiquimod oxalate Form II in a mixture of polar protic solvent and chlorinated hydrocarbon solvent.

53. The process as claimed in claim 52, wherein the polar protic solvent is selected from a group of C_1-C_4 alcohol and chlorinated hydrocarbon.

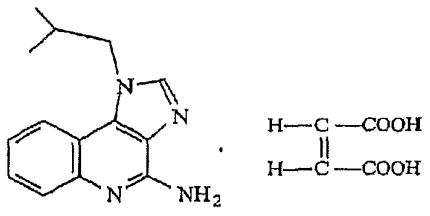
54. The process as claimed in claim 52, wherein the polar protic solvent is selected from methanol, chloroform and MDC.

55. A compound 4-iodo-1-isobutyl-1H- Imidazo-[4,5-c]-quinoline (VI).



VI

56. A compound 4-amino-1-isobutyl-1H-imidazo[4,5-c] quinoline maleate(VIIa) and its polymorphic forms thereof.

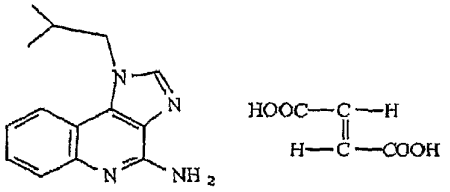


VIIa

57. A substantially pure 4-amino-1-isobutyl-1H-imidazo[4,5-c] quinoline maleate (VIIa) polymorph form I, being characterized by peaks at below shown diffraction angles in XRPD and absorption peaks in FTIR spectrum:

Form I : Characteristic peaks in XRPD at 2θ values 9.50, 9.95, 17.13, 19.15, 19.93, 21.63, 24.37, 24.71, 27.09 and wave numbers (cm^{-1}) in FT-IR spectrum at 3298, 3129.3, 3089.8, 1676, 1608.5, 1494.1 1467, 1448, 1407, 1361.7, 1213.1,1083.9, 948.9, 867.9, 776.3, 754.1, 692.4, 673.1, 661.5, 640.3, 590.2, 563.2.

58. A compound 4-amino-1-isobutyl-1H-imidazo[4,5-c] quinoline fumarate(VIIb).



VIIb

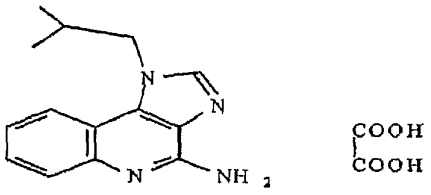
59. A substantially pure 4-amino-1-isobutyl-1H-imidazo[4,5-c] quinoline fumarate (VIIb) in the form of crystalline polymorphs selected from a group consisting of I, II and III, each polymorph being characterized by peaks at below shown diffraction angles in XRPD and absorption peaks in FTIR spectra:

a. **Form I**: Characteristic peaks in XRPD at 2θ values 6.86, 8.87, 10.74, 13.57, 14.63, 18.34, 20.30, 20.87, 21.51, 22.33, 22.85, 22.98, 25.48, 26.43, 27.03, 27.85, 29.71, 30.08, 31.21, 33.91, 35.28 and wave numbers (cm^{-1}) in the FT-IR spectrum 3489.0, 3093.6, 2970.21695.3, 1527.5, 1379, 1124.4, 1103.2, 985, 754.1, 682.8, 563.2.

b. **Form II**: Characteristic peaks in XRPD at 2θ values 10.87, 11.44, 12.43, 14.36, 15.46, 18.39, 19.25, 21.62, 22.03, 22.18, 24.55, 31.91 and wave numbers (cm^{-1}) in the FT-IR spectrum 3311.5, 3178, 2958.6, 1645.2, 1614.3, 1527.5, 1469.7, 1396.4, 1371.3, 1251.7, 1097.4, 991.3, 873.7, 848.6, 821.6, 759.9,640.3, 607.5.

c. **Form III**: Characteristic peaks in XRPD at 2θ values 9.10, 11.47, 16.48, 17.34, 18.00, 19.24, 19.60.21.38, 22.80, 23.50, 24.98, 25.99, 26.79, 27.32, 28.69, 29.51, 30.76, 37.36 and wave numbers (cm^{-1}) in the FT-IR spectrum 3477, 3234.4, 3093.6, 2758, 2362.6, 1693, 1606.6, 1531.4, 1375.2, 756.0, 684.7, 569.

60. A compound 4-amino-1-isobutyl-1H-imidazo[4,5-c] quinoline oxalate(VIIc).



VIIc

61. A substantially pure 4-amino-1-isobutyl-1H-imidazo[4,5-c] quinoline oxalate (VIIc) in the form of crystalline polymorphs selected from a group consisting of I, II and III, each polymorph being characterized by peaks at below shown diffraction angles in XRPD and absorption peaks in FTIR spectra:

a. **Form I**: Characteristic peaks in XRPD at 2θ values 10.83, 11.43, 14.39, 15.44, 18.36, 19.10, 19.24, 21.63, 22.17, 24.56, 31.88 and wave numbers (cm^{-1}) in the FT-IR spectrum 3419.6, 3217, 3062.7, 2962.5, 2360.7, 1701, 1541 1309, 756, 769,715,688, 669, 567.

b. **Form II**: Characteristic peaks in XRPD at 2θ values 7.92, 15.56, 15.91, 16.60, 16.76, 17.74, 18.03, 23.25, 25.01, 27.92, 31.48 and wave numbers (cm^{-1}) in the FT-IR spectrum 3315, 3182, 2958,1647,1614, 1529, 1583, 1465, 1475, 1253, 1095, 873, 848, 761, 665.

c. **Form III**: Characteristic peaks in XRPD at 2θ values 6.96, 7.42, 9.99, 10.31, 10.45, 12.41, 13.31, 13.79, 16.16, 19.21, 21.12, 23.74, 24.90, 25.62, 25.94, 26.60 and wave numbers (cm^{-1}) in the FT-IR spectrum 3101, 2962, 1685, 1218, 1099, 948, 748,713, 690, 657, 632, 590.

STATEMENT UNDER ARTICLE 19 (1)

The present invention relates to a process for synthesis of substantially pure 4-amino-1-isobutyl-1H-imidazo [4, 5-c]-quinoline. It also relates to a novel purification method via novel organic salts and its polymorphic forms thereof.

Applicant has gone through the written opinion of International Search Report (ISR) and observes that:

a) Novelty and Industrial Applicability of claims 1 – 58 are acknowledged.

b) Claims 28 – 51 and 53 – 58 lacks inventive step.

ISR refers to five prior art documents D1, D2, D3, D4 & D5. Examiner, commented in the written opinion that the present invention could be arrived at from the cited prior arts D1, D4 and D5 which are the closest prior arts and hence, the claims 28 – 51 and 53 – 58 lack inventive step.

D1 discloses imiquimod as a compound and a process for the preparation. The written opinion of the ISA acknowledges that imiquimod maleate, imiquimod fumarate, and imiquimod oxalate, which were not mentioned in **D1**.

D4 discloses certain class of compounds 1H-imidazo[4,5-c] quinoline derivatives in the treatment of protein kinase dependent diseases. There is no teaching in D4 to arrive at pure maleate, fumarate, and oxalate salts of imiquimod. In addition, there is no teaching in D4 to obtain pure base by directly preparing a salt and reconverting into its base.

Therefore, by combining D1 and D4 a skilled person will not be prompted to prepare pure imiquimod and/or salts. There is no motivation in combining the above documents in order to arrive at the pure form of compounds of the present invention.

D5 claims strong acids used to deprotect N-benzyl group, and the strong acid salts are isolated after deprotection. The yield is in the range of 70-80% [Page 29, lines 10-12] and purity is not mentioned. The salts thus obtained are without purification converted to free base imiquimod. Also, in this patent there is no mention of purification of imiquimod via salt formation. This document does not teach use of weak acid for purification and the weak acid does not play any role in deprotection.

Applicant does not use strong acids which are corrosive. The salts are obtained in above 90% yield with above 99% purity. Also, the strong acids disclosed encompass acids having a Ka (25°C) of at least about 1.

The Applicant's process does not involve production of imiquimod salt of strong acid. Applicant uses maleic acid (at 25°C, $Ka_1 = 1.47 \times 10^{-2}$ and $Ka_2 = 8.51 \times 10^{-7}$), fumaric acid (at 18°C, $Ka_1 = 9.33 \times 10^{-4}$ and $Ka_2 = 3.63 \times 10^{-5}$) and oxalic acid (at 25°C, $Ka_1 = 5.88 \times 10^{-2}$ and $Ka_2 = 6.45 \times 10^{-5}$) having Ka less than 1.

Also **D5** was published after the priority date of the current application but before the international filing date. Therefore, it should not be considered as prior art to the current application.

The inventive step of the present invention is to obtain **pure** salts in **high yields** including the **polymorphs** which are not known and the **processes** of producing them. Applicant wishes to invite the attention of the Examiner that many pharmaceutically acceptable addition salts are known in literature. However, the patent application discloses imiquimod salts of maleic acid, fumaric acid and oxalic acid and their polymorphs only.

The present application provides substantially pure polymorphs in high yields which are not derivable by a person skilled in the art after considering the prior arts as a whole.

In addition, applicant has amended the claims to rectify obvious errors. Applicant believes that no new subject matter has been added.

FIGURE 1

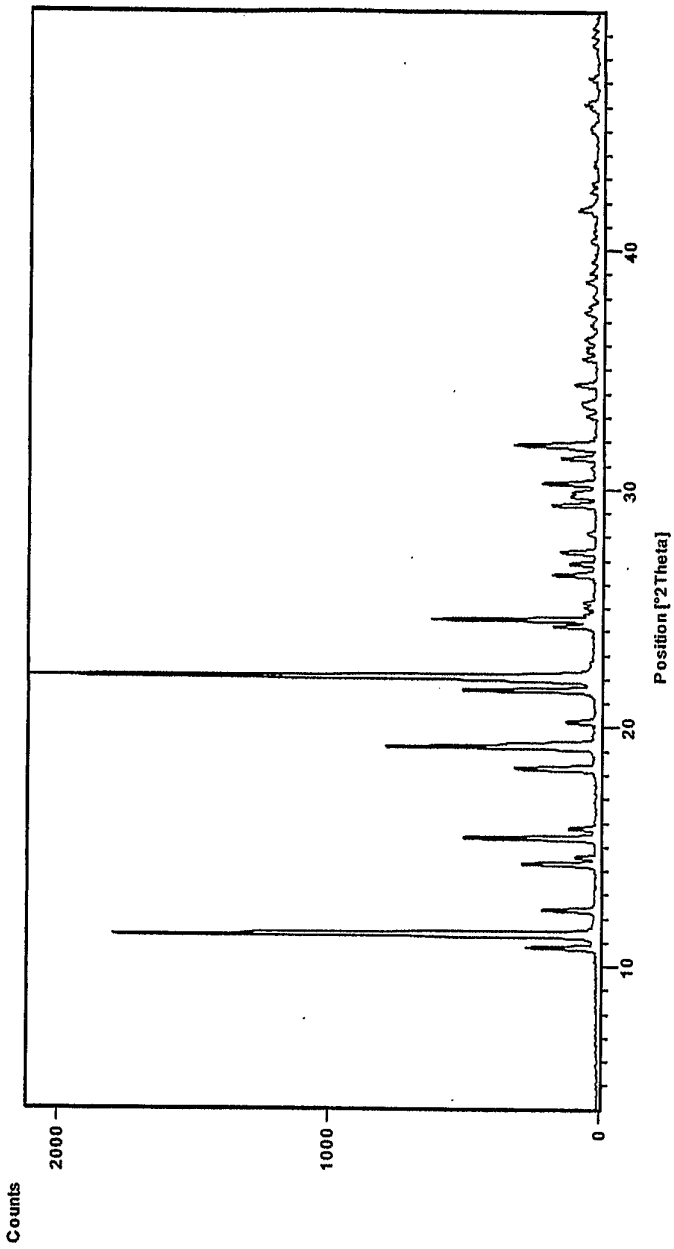


FIGURE 2

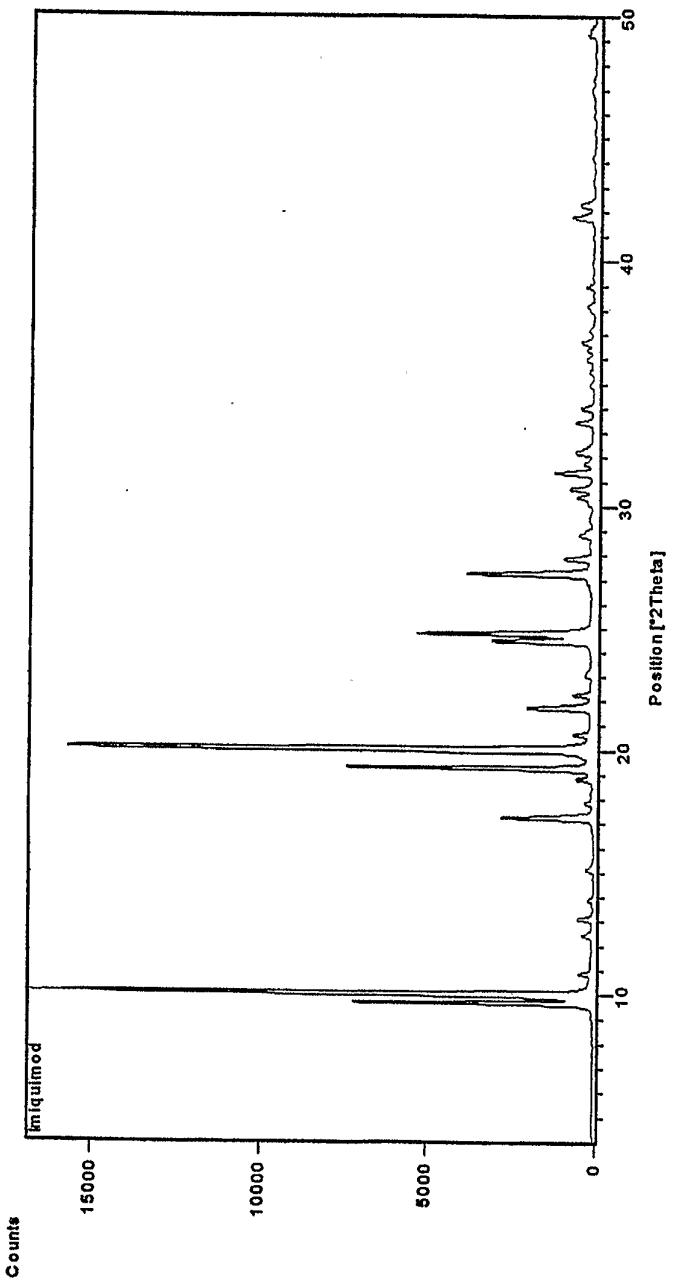

imiquimod
Counts
15000
10000
5000
0
10
20
30
40
50
Position [°2Theta]

FIGURE 3

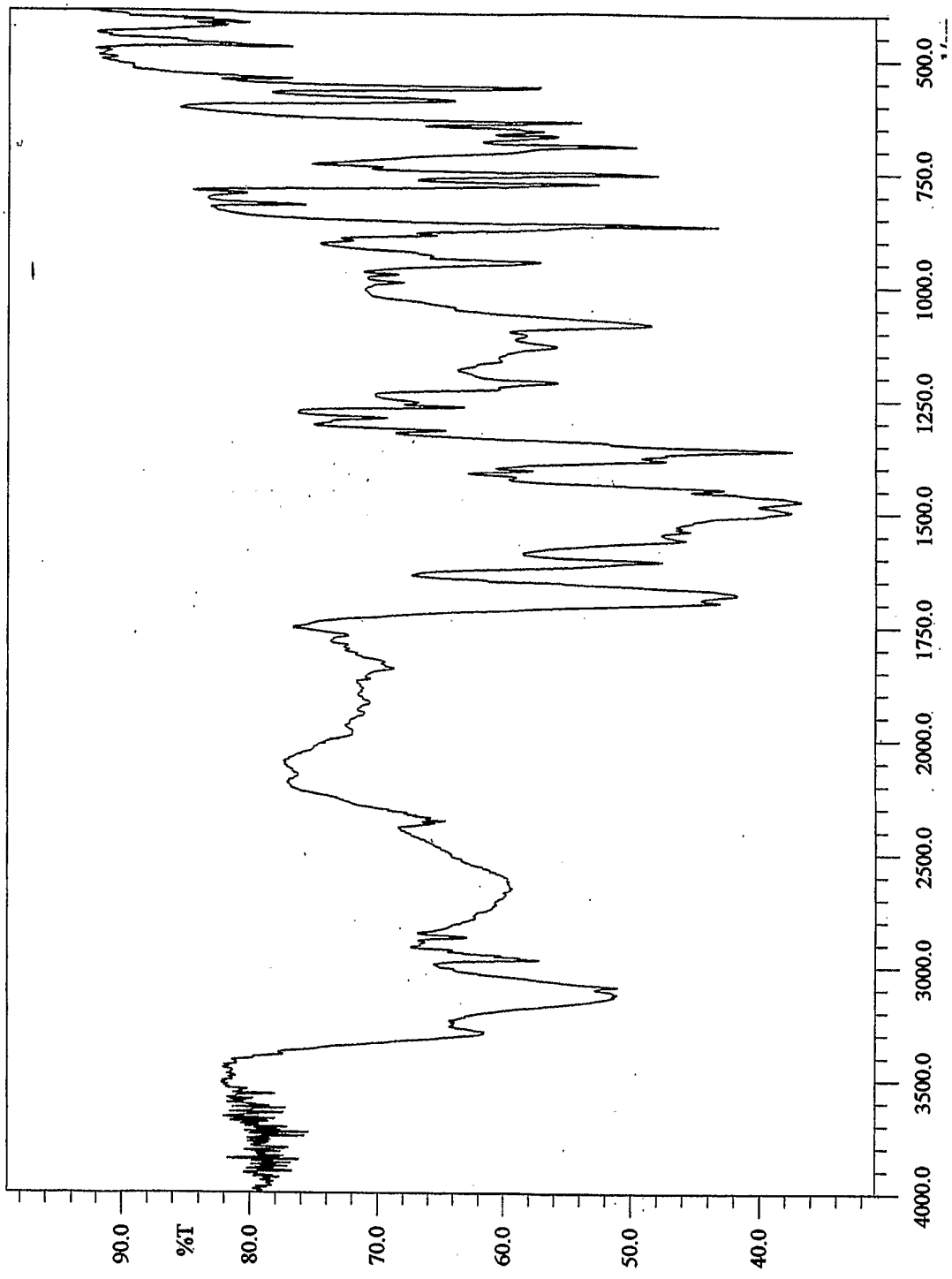

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750.0
500.0

FIGURE 4

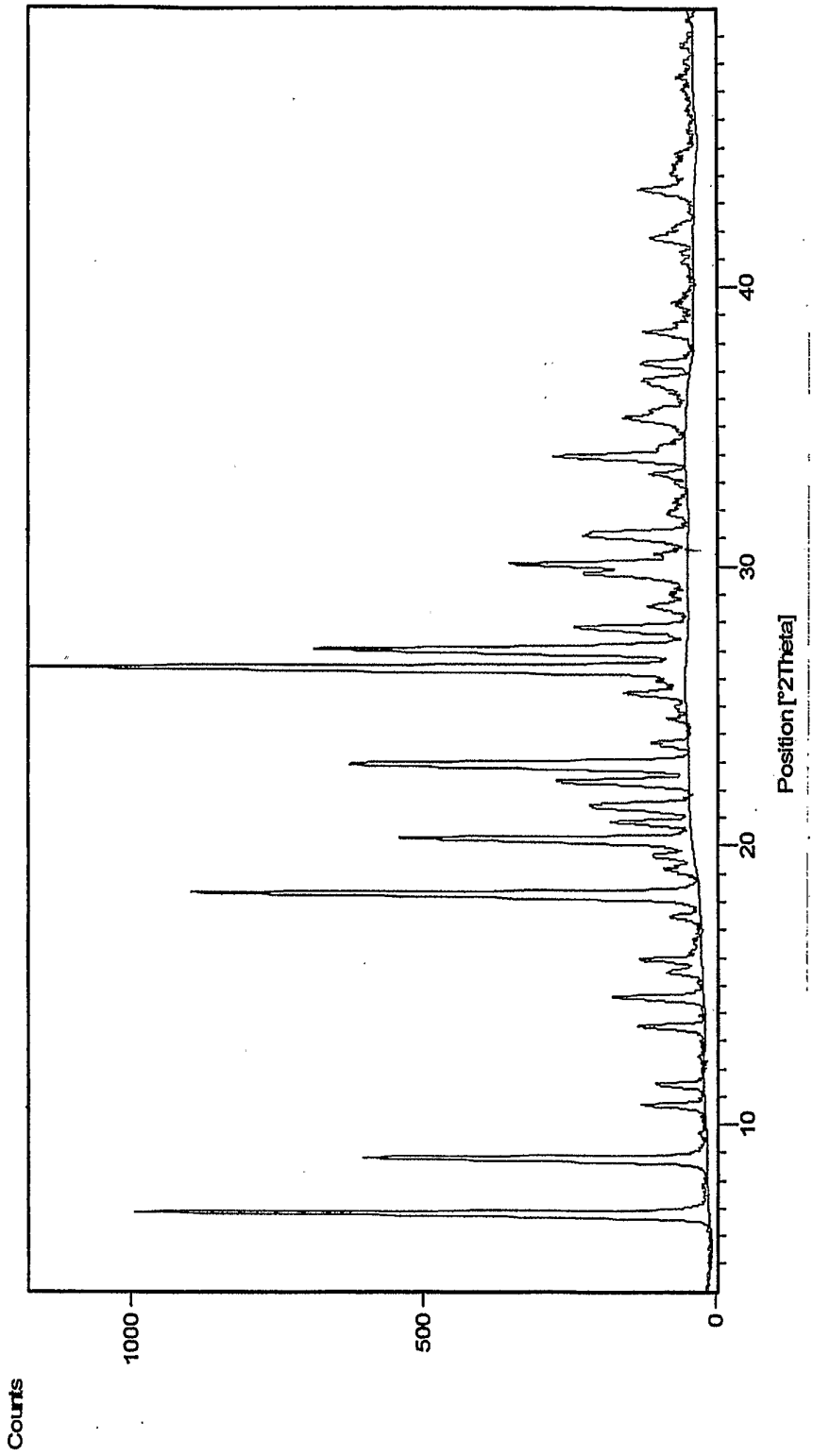


FIGURE 5

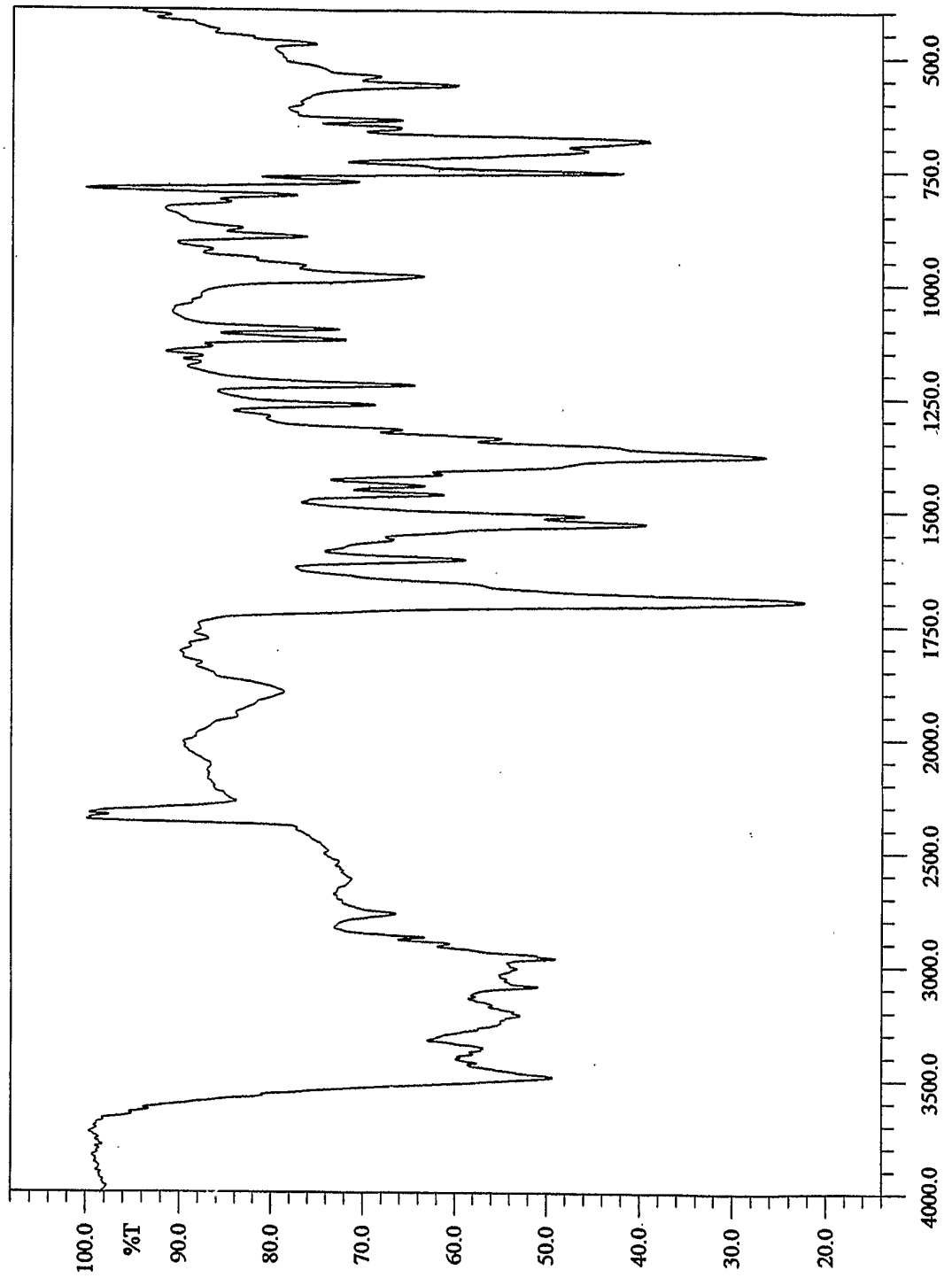

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750.0
500.0

FIGURE 6

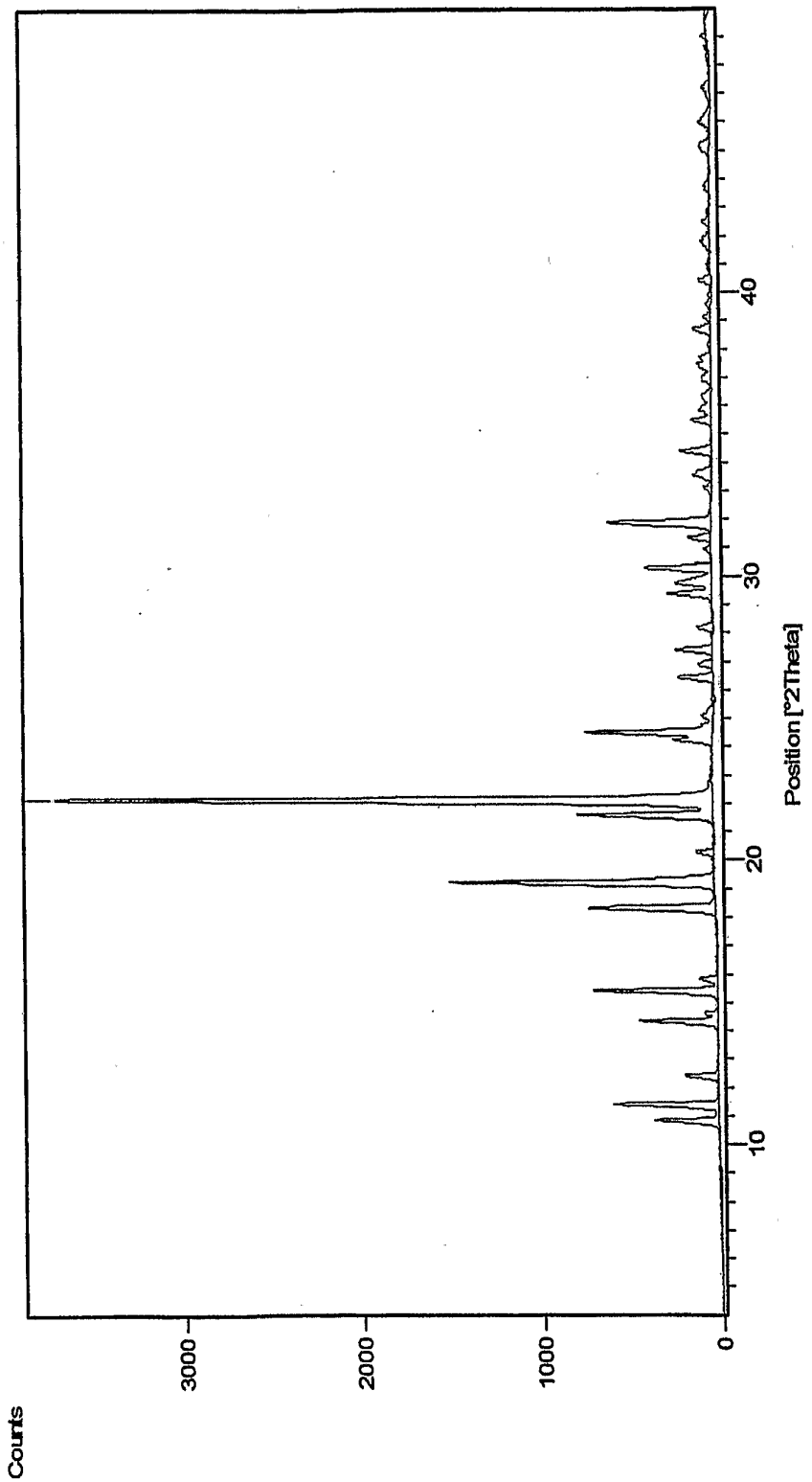


FIGURE 7

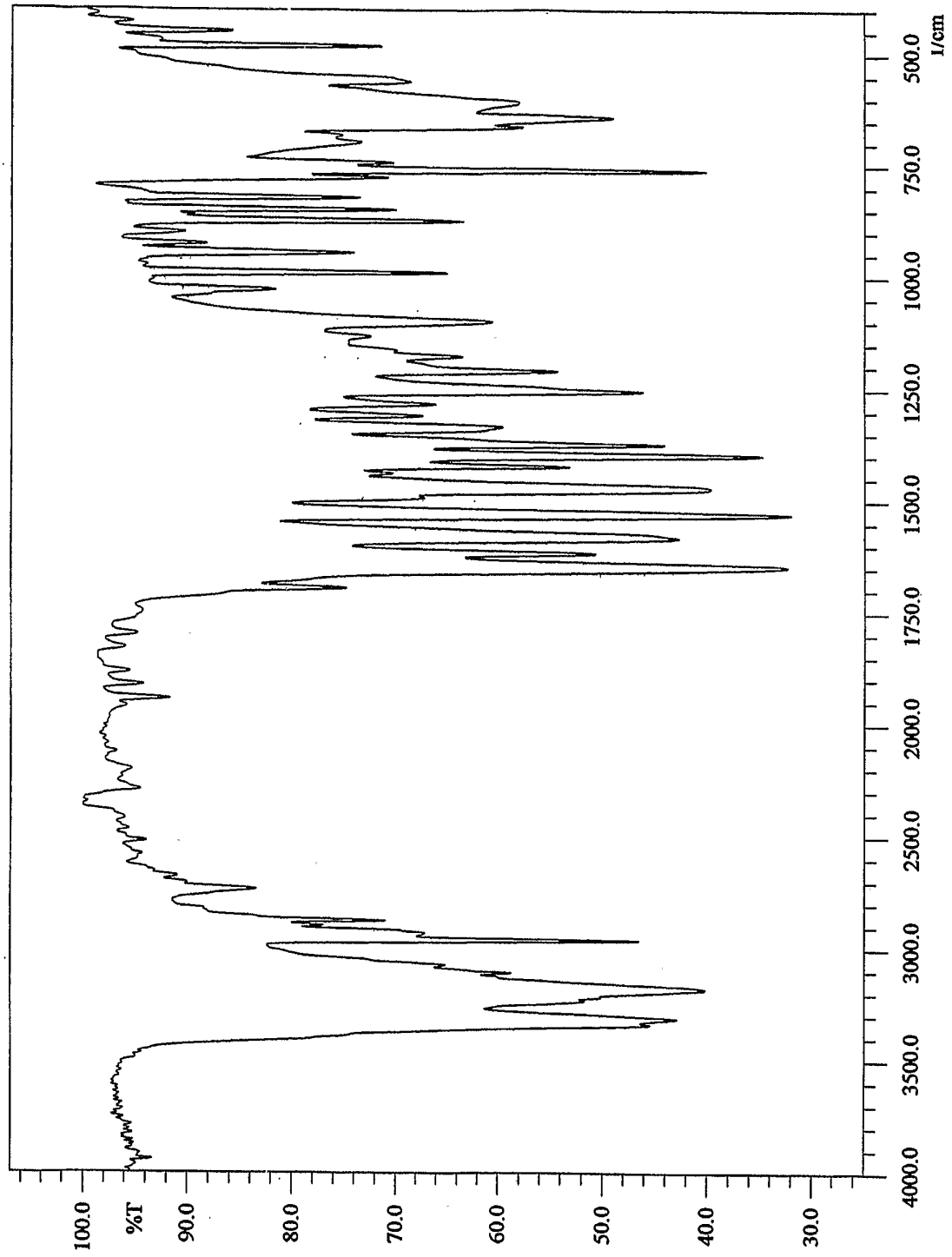

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500.0
1/cm

FIGURE 8

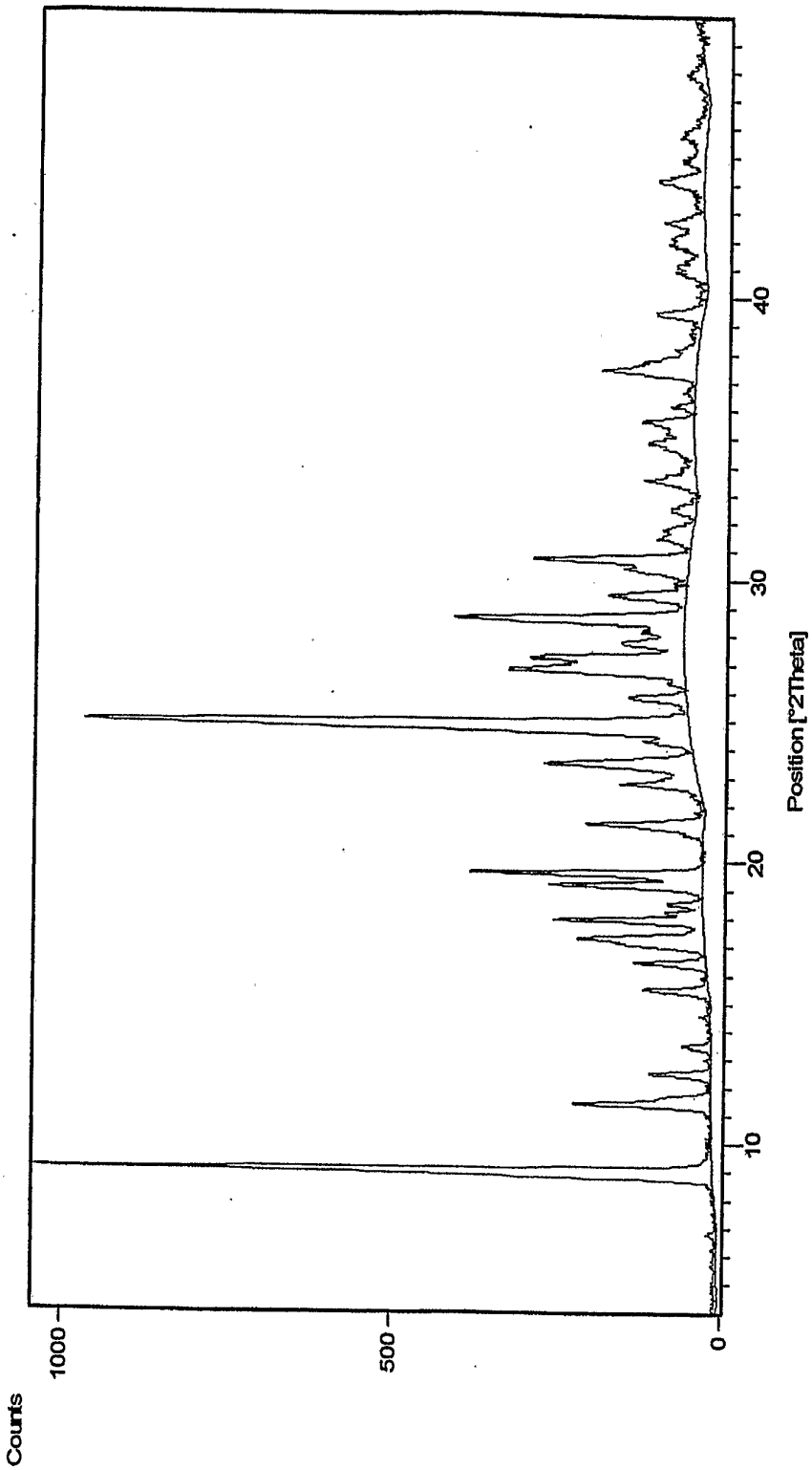


FIGURE 9

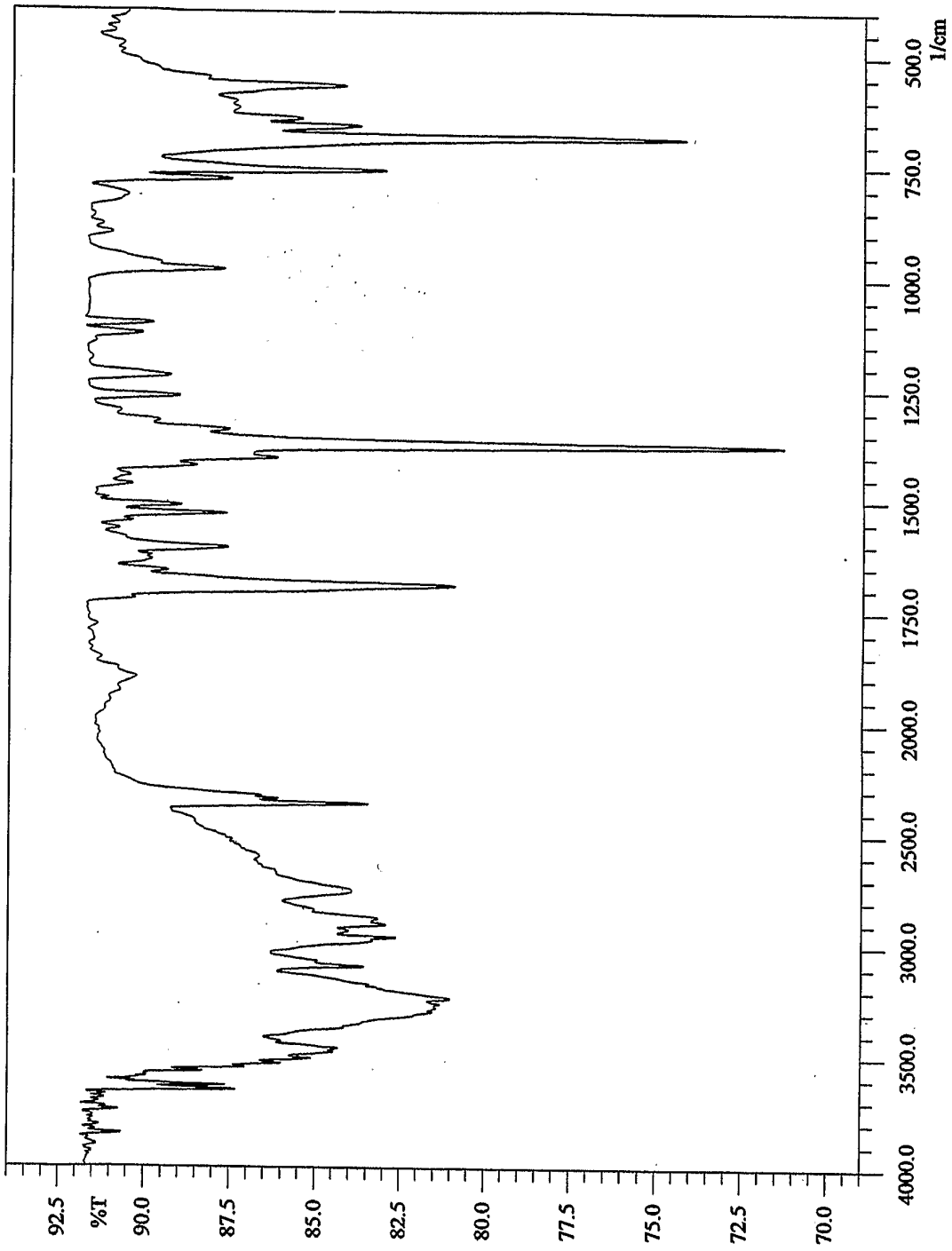

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4000.0
3500.0
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500.0
1/cm

FIGURE 10

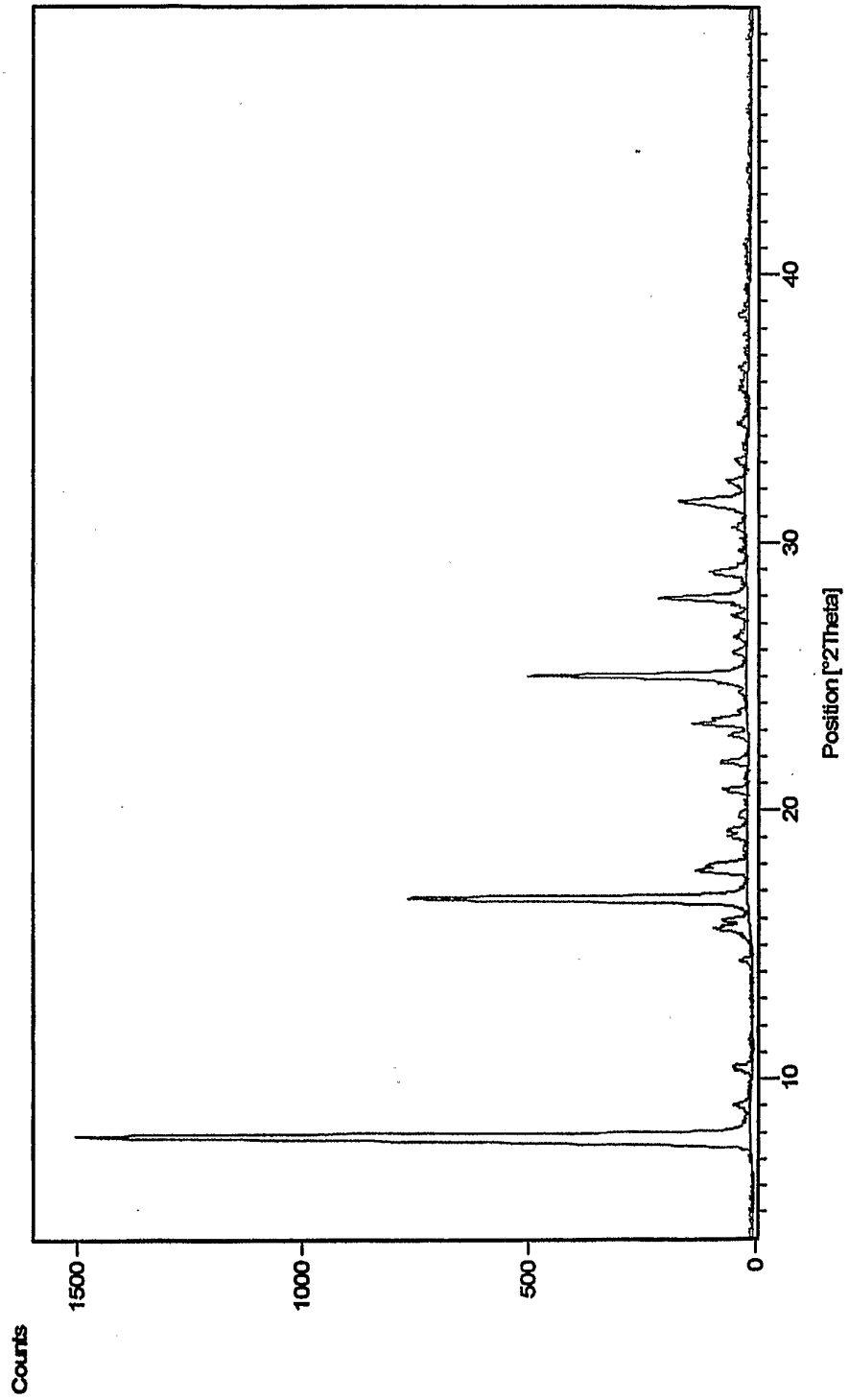


FIGURE 11

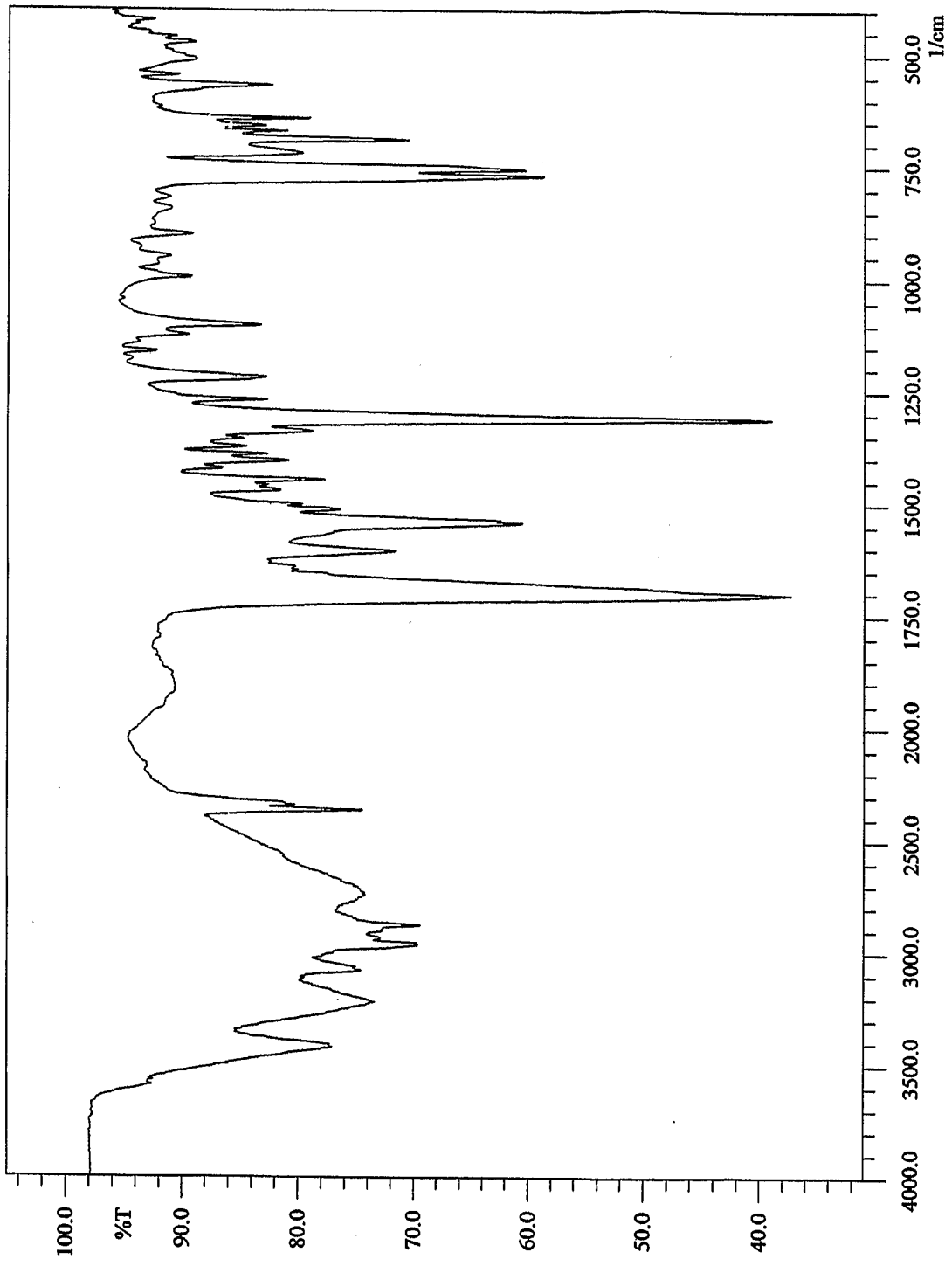

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4000.0
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1500.0
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750.0
500.0
1/cm

FIGURE 12

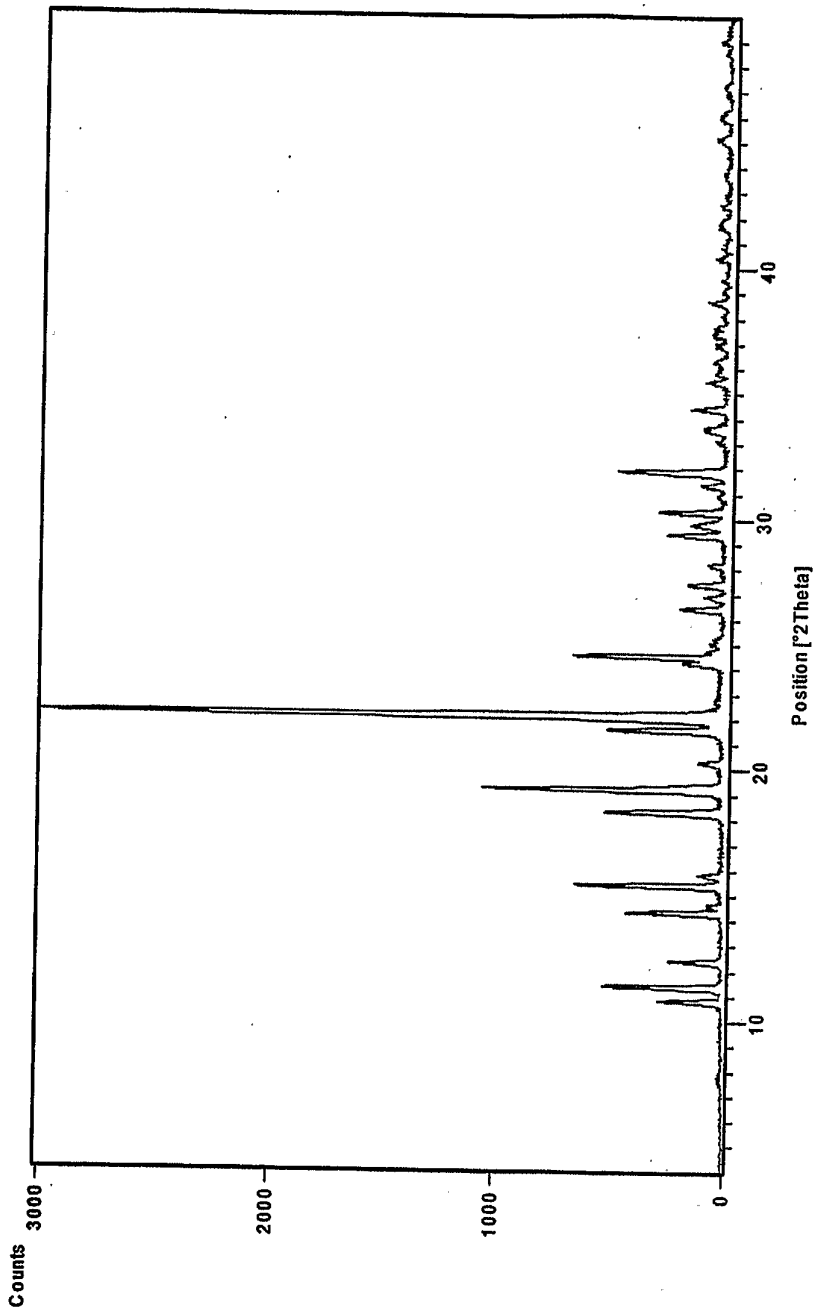


FIGURE 13

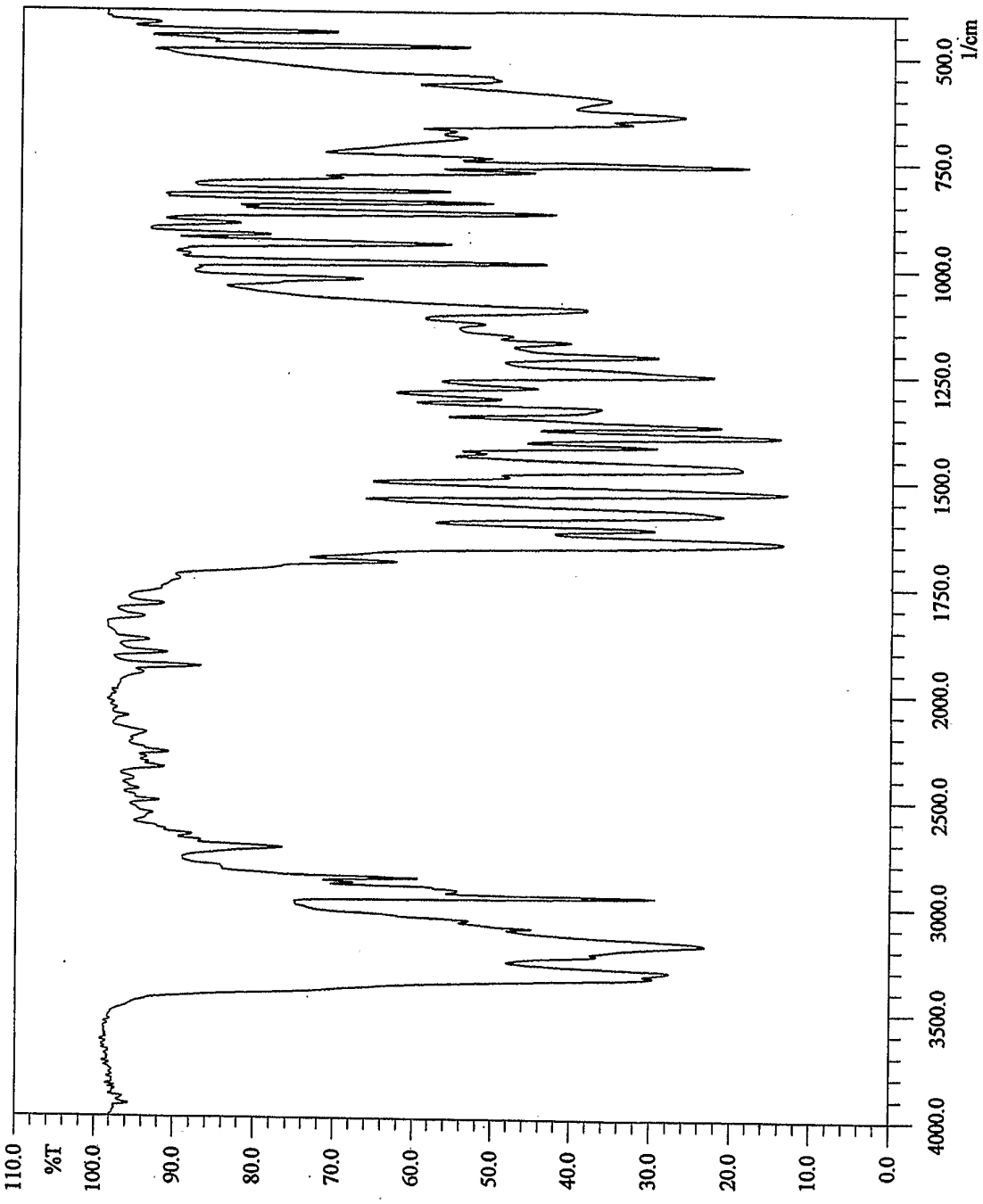

%T
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1/cm

FIGURE 14

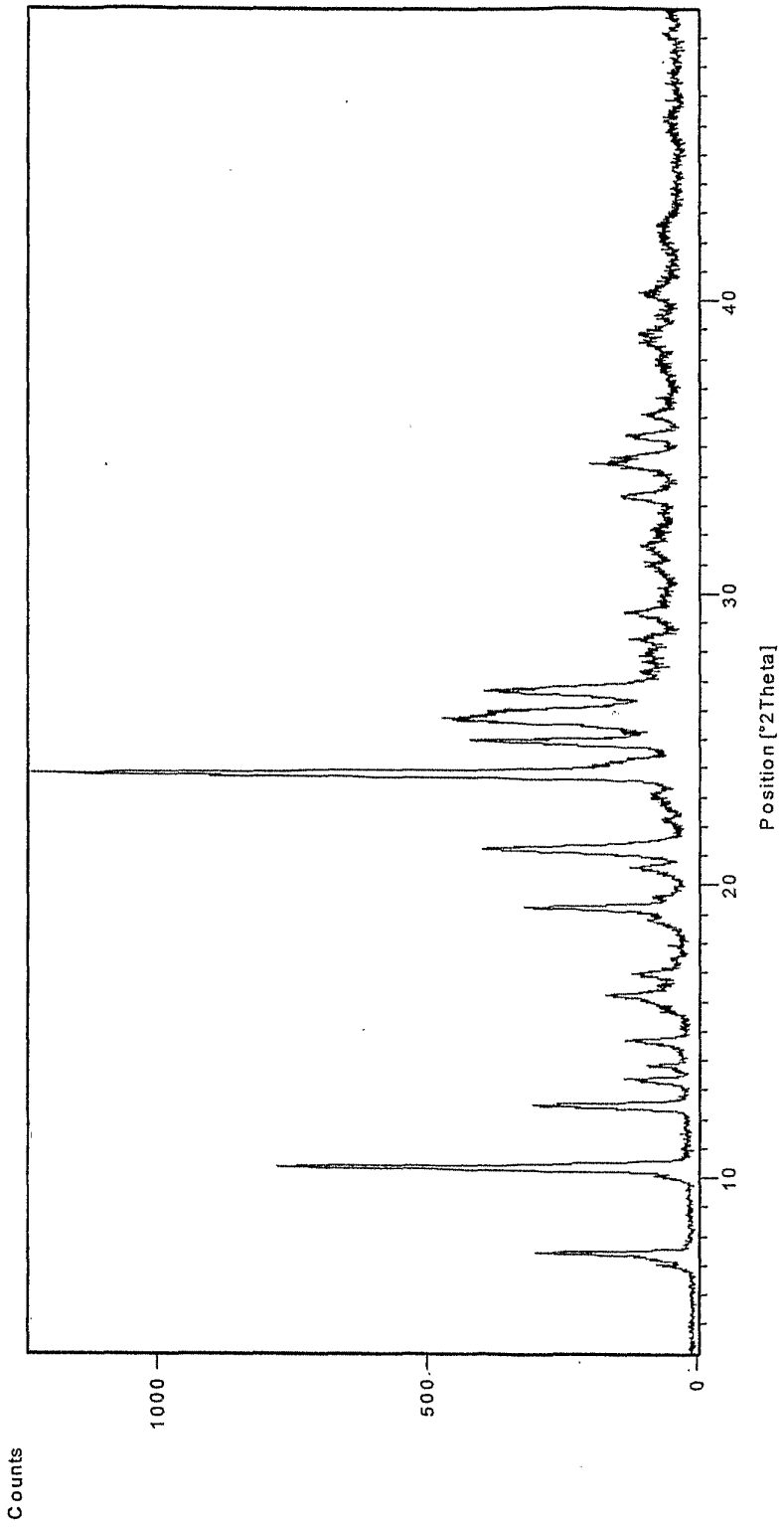
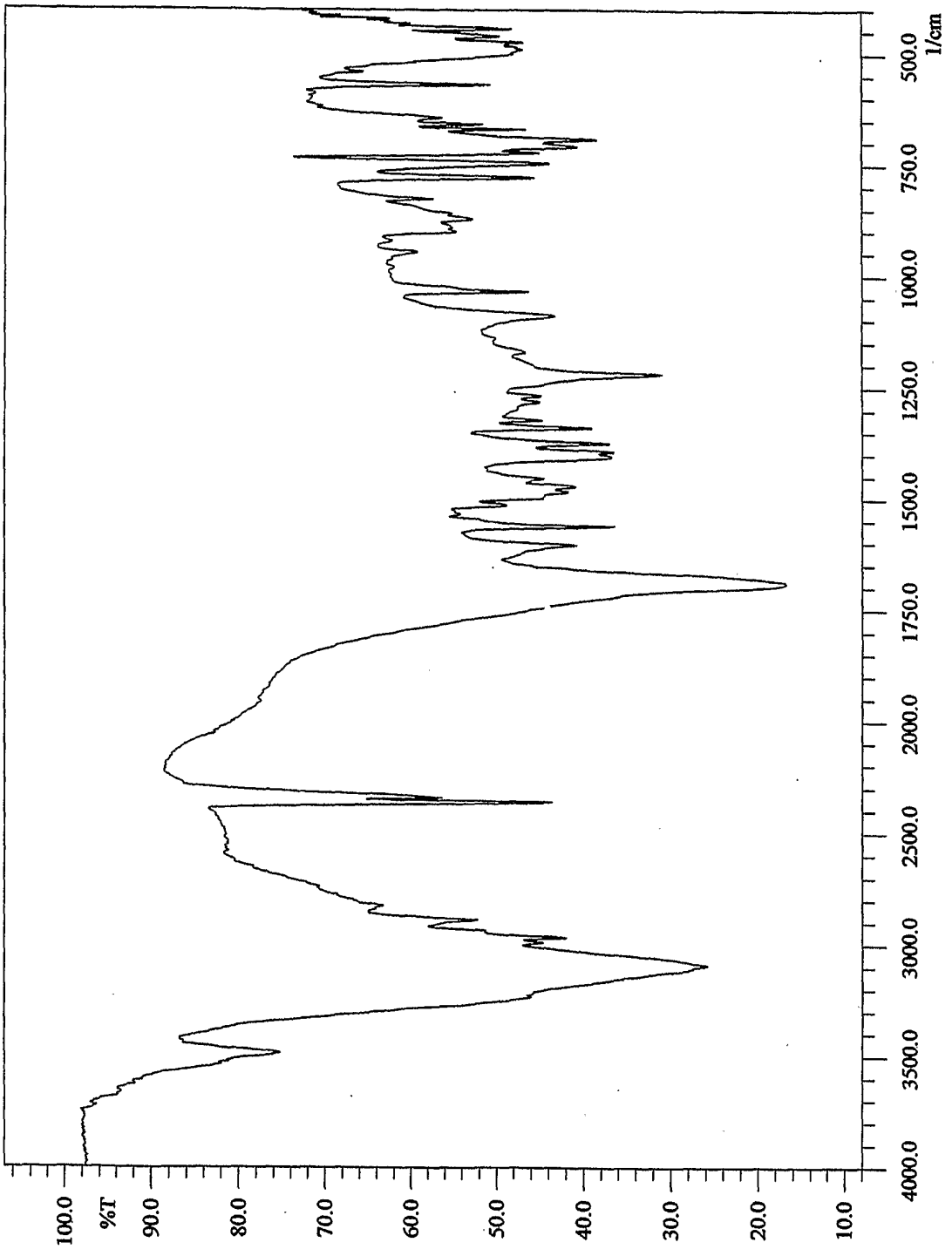


FIGURE 15


%T
100.0
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70.0
60.0
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30.0
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10.0
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm