(12) PATENT APPLICATION PUBLICATION
(19) INDIA
(22) Date of filing of Application :14/10/2016

(21) Application No.201621035182 A
(43) Publication Date : 25/10/2019

(54) Title of the invention : PROCESS FOR THE PREPARATION OF ISAVUCONAZONIUM SULFATE

(51) International classification :A61L21/11
(31) Priority Document No :NA
(32) Priority Date :NA
(33) Name of priority country :NA
(86) International Application No :NA
Filing Date :NA
(87) International Publication No : NA
(61) Patent of Addition to Application Number :NA
Filing Date :NA
(62) Divisional to Application Number :NA
Filing Date :NA

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(57) Abstract :
Abstract The present invention provides process for the preparation of isavuconazonium sulfate. The invention further discloses process for the preparation of isavuconazole. To, The Controller of Patents The Patent Office Branch



No. of Pages : 30 No. of Claims : 10

THE PATENTS ACT 1970

(Act 39 of 1970)

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THE PATENTS RULE 2003

(SECTION 10 and rule 13)

PROVISIONAL SPECIFICATION

"PROCESS FOR THE PREPARATION OF ISAVUCONAZONIUM SULFATE"

Glenmark Pharmaceuticals Limited
an Indian Company, registered under the Indian company's Act 1957 and having its registered office at
Glenmark House,
HDO – Corporate Bldg, Wing -A,
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Andheri (East), Mumbai – 400 099

The following specification describes the nature of the invention:

FIELD OF THE INVENTION

The present invention relates to process for preparation of isavuconazonium sulfate.

BACKGROUND OF THE INVENTION

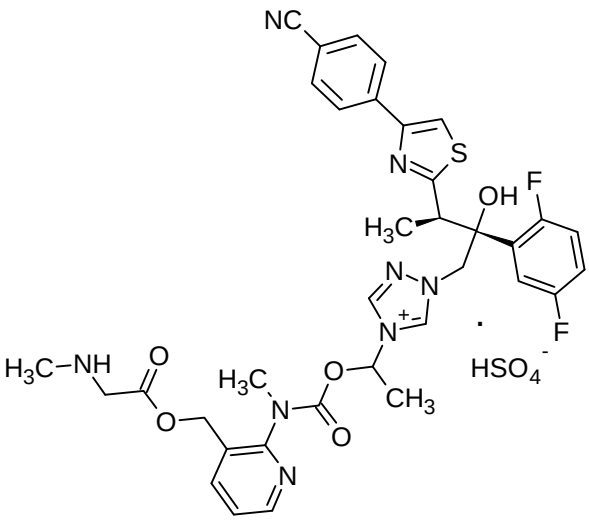
Isavuconazonium sulfate is chemically known as Glycine, N-methyl-, [2-[[[1-[1-[(2R, 3R)-3-[4-(4-cyanophenyl)-2-thiazolyl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4H-1, 2, 4-triazolium-4-yl]ethoxy]carbonyl]methylamino]-3-pyridinyl]methyl ester, sulfate (1:1).

Isavuconazonium sulfate marketed as CRESEMBA® is a capsule for oral administration. Isavuconazonium sulfate is also marketed as CRESEMBA® for injection for intravenous administration.

The present invention provides novel process for preparation of isavuconazonium sulfate which provides better a purity profile and which can be easily performed on industrial scale.

SUMMARY OF THE INVENTION

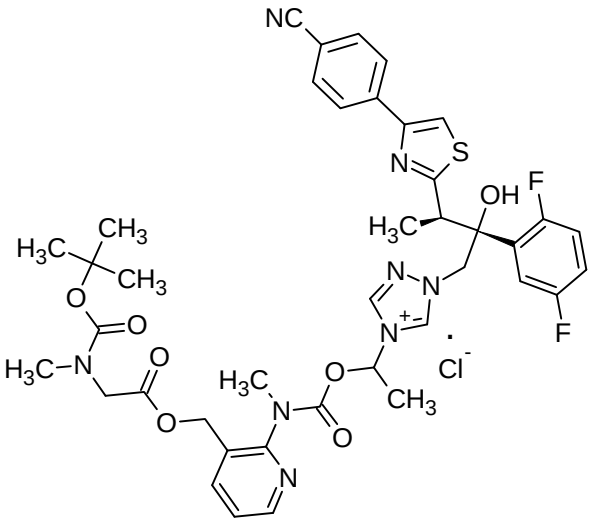
In one embodiment, the present invention provides a process for the preparation of isavuconazonium sulfate, a compound of formula I



I

comprising:

a) reacting N-boc isavuconazonium chloride, a compound of formula VI with hydrochloric acid to generate isavuconazonium chloride hydrochloride;

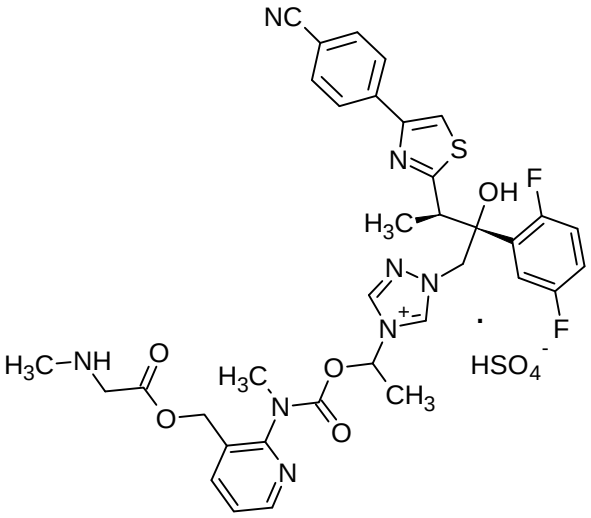


VI

b) contacting isavuconazonium chloride hydrochloride with anion exchange resin to obtain isavuconazonium sulfate; and

c) isolating isavuconazonium sulfate.

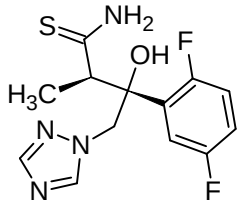
In one embodiment, the present invention provides a process for the preparation of isavuconazoium sulfate, a compound of formula I



I

comprising:

a) reacting a compound of formula II, with a compound of formula III in the presence of a non-alcoholic solvent to obtain isavuconazole, a compound of formula IV;



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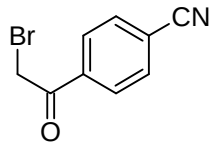
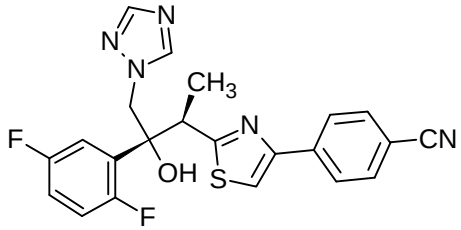
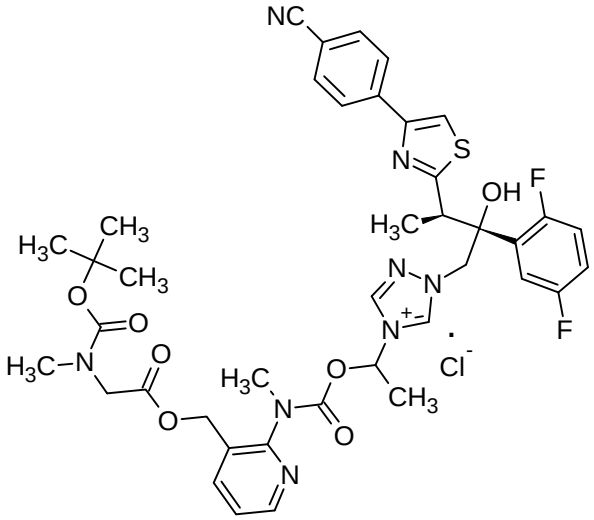


III



IV

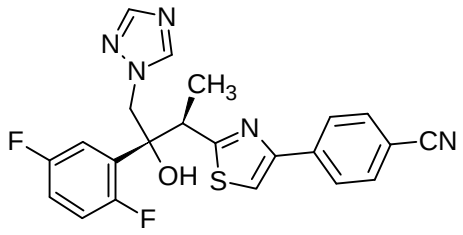
b) converting isavuconazole, a compound of formula IV to N-boc isavuconazonium chloride, a compound of formula VI ; and



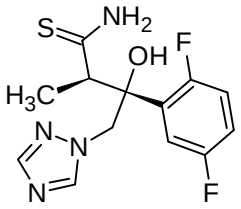
VI

c) converting N-boc isavuconazonium chloride, a compound of formula VI to isavuconazonium sulfate.

In one embodiment, the present invention provides a process for the preparation of isavuconazole, a compound of formula IV comprising reacting a compound of formula II,



IV



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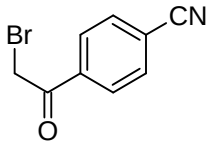


III

with a compound of formula III, in the presence of a non-alcoholic solvent to obtain isavuconazole, a compound of formula IV.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1: XRD pattern of isavuconazole according to example 1.

Fig. 2: DSC pattern of isavuconazole according to example 1.

Fig. 3: XRD pattern of N-boc isavuconazonium chloride according to example 2.

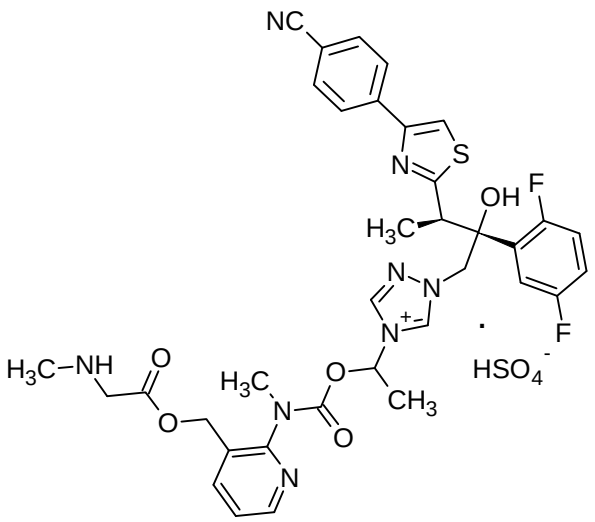
Fig. 4: DSC pattern of N-boc isavuconazonium chloride according to example 2.

Fig 5: XRD pattern of isavuconazonium sulphate according to example 3.

Fig 6: DSC pattern of isavuconazonium sulphate according to example 3.

DETAILED DESCRIPTION OF THE INVENTION

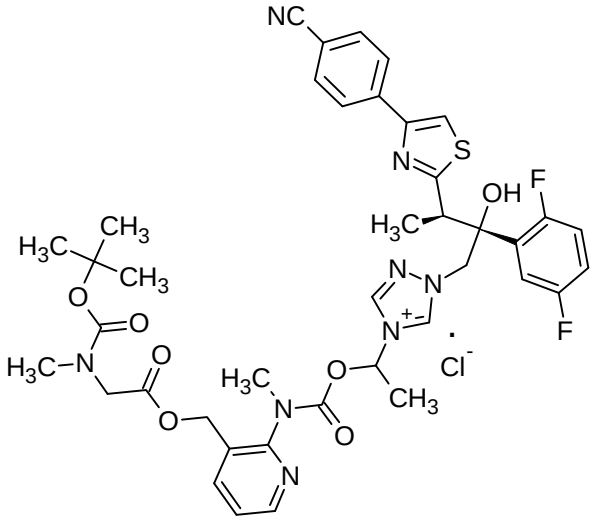
In one embodiment, the present invention provides a process for the preparation of isavuconazonium sulfate, a compound of formula I



I

comprising :

a) reacting N-boc isavuconazonium chloride, a compound of formula VI with hydrochloric acid to generate isavuconazonium chloride hydrochloride;



VI

b) contacting isavuconazonium chloride hydrochloride with anion exchange resin to obtain isavuconazonium sulfate; and

c) isolating isavuconazonium sulfate.

In one embodiment, in step 'a' of the above process N-boc isavuconazonium chloride, a compound of formula VI is reacted with hydrochloric acid to generate isavuconazonium chloride hydrochloride.

The above reaction is carried out in a suitable solvent selected from the group consisting of C_1-C_5 alcohol, ketone, hydrocarbon, halogenated hydrocarbon, amides, sulfoxides, ether, ester, nitriles, water or mixtures thereof.

In one embodiment, the alcohol solvent may be selected from the group consisting of methanol, ethanol, propanol, isopropanol, n-butanol, tert-butanol, cyclohexanol and the like; ketone solvent may be selected from the group consisting of acetone, methyl ethyl ketone, isopropyl ketone, methyl tert-butyl ketone and the like; hydrocarbon solvent may be selected from the group consisting of toluene, xylene, cyclohexane, n-heptane, hexane and the like; halogenated hydrocarbon solvent may be selected from the group consisting of methylene dichloride, ethylene dichloride, chloroform and the like; amide solvent may be selected from the group consisting of dimethyl formamide, dimethyl acetamide, formamide and the like; sulfoxides such as dimethyl sulfoxide and the like; an ether solvent may be selected from the group consisting of diethyl ether, di-isopropyl ether, methyl tert-butyl ether, tetrahydrofuran and the like; esters may be selected from the group consisting of ethyl acetate, butyl acetate, isopropyl acetate and the like; nitriles may be selected from the group consisting of acetonitrile, propionitrile and the like.

In one embodiment, the hydrochloric acid used may be commercially available hydrochloric acid or can be passed as a hydrochloride gas or hydrochloride gas in any organic solvent.

In one embodiment, N-boc isavuconazonium chloride in ethyl acetate is reacted with hydrochloric acid in ethyl acetate to obtain isavuconazonium chloride hydrochloride.

In one embodiment, isavuconazonium chloride hydrochloride is generated *in situ* on reaction of N-boc isavuconazonium chloride, a compound of formula VI with hydrochloric acid.

In one embodiment, the generated isavuconazonium chloride hydrochloride is contacted *in situ* with sulfate containing anion exchange resin to obtain isavuconazonium sulfate.

In one embodiment, isavuconazonium chloride hydrochloride is not isolated on completion of reaction of N-boc isavuconazonium chloride, a compound of formula VI with hydrochloric acid.

In one embodiment, the generated isavuconazonium chloride hydrochloride is contacted *in situ* with sulfate containing anion exchange resin i.e isavuconazonium chloride hydrochloride is not isolated as a solid from the reaction mixture and contacted with sulfate containing anion exchange resin to obtain isavuconazonium sulfate.

In one embodiment, N-boc isavuconazonium chloride, a compound of formula VI is reacted with hydrochloric acid in an organic solvent to generate isavuconazonium chloride hydrochloride which is not isolated and after work up isavuconazonium chloride hydrochloride is converted to isavuconazonium sulfate without isolating N-boc isavuconazonium chloride hydrochloride.

In one embodiment, step 'b' of the above process involves contacting isavuconazonium chloride hydrochloride with sulfate containing anion exchange resin to obtain isavuconazonium sulfate.

In one embodiment, isavuconazonium chloride hydrochloride in a suitable solvent or a mixture of solvents is contacted with a sulfate containing anion exchange resin to obtain isavuconazonium sulfate.

In one embodiment, the solvent may be selected from the group consisting of C_1-C_5 alcohol, ketone, hydrocarbon, halogenated hydrocarbon, amides, sulfoxides, ether, ester, nitriles, water or mixtures thereof.

In one embodiment, isavuconazonium chloride hydrochloride in a mixture of water and methanol is passed through a sulphate containing anion exchange resin to obtain isavuconazonium sulfate.

In one embodiment, isavuconazonium chloride hydrochloride is converted to isavuconazonium sulfate using a sulphate containing reagent. The reagent may be selected from the group consisting of sulfuric acid, sodium hydrogen sulphate and the like.

In one embodiment, isavuconazonium chloride hydrochloride is converted to isavuconazonium base and then treated with a sulfate containing reagent to obtain isavuconazonium sulfate.

In one embodiment, the steps 'a' and 'b' are carried out in one pot.

In one embodiment, the present invention provides a process of reacting N-boc isavuconazonium chloride, a compound of formula VI with ethyl acetate hydrochloric acid to generate isavuconazonium chloride hydrochloride *in situ*, the *in situ* generated isavuconazonium chloride hydrochloride is extracted with water and the aqueous layer is passed through a sulfate containing anion exchange resin to obtain isavuconazonium sulfate.

In one embodiment, the process of preparation of isavuconazonium sulfate from N-boc isavuconazonium chloride is a one pot process.

In one embodiment, the "one-pot" refers to the process wherein the intermediates formed are not isolated as a solid.

In one embodiment, the "one-pot" refers to the process wherein the intermediates formed are not isolated as solid and are extracted from reaction mixture and the solution containing the intermediate is subjected to further conversion to obtain desired product.

In one embodiment, the "one-pot" refers to the process wherein the intermediates formed are not isolated as a solid or extracted from reaction mixture and desired product is isolated from a single reaction pot by converting intermediates *in situ* to desired product.

In one embodiment, the isavuconazonium sulfate is in amorphous form.

In one embodiment, the isavuconazonium sulfate obtained from the above described process is in amorphous form.

In one embodiment, the present invention provides a process of preparation of amorphous isavuconazonium sulfate comprising reacting N-boc isavuconazonium chloride, a compound of formula VI with ethyl acetate hydrochloric acid to generate isavuconazonium chloride hydrochloride *in situ*, the *in situ* generated isavuconazonium chloride hydrochloride is extracted with water and the aqueous layer is passed through a sulfate containing anion exchange resin to obtain isavuconazonium sulfate which in a

solvent or a mixture of solvent is subjected to lyophilisation to obtain amorphous isavuconazonium sulfate.

In one embodiment, the amorphous isavuconazonium sulfate is isolated by a process comprising:

a) obtaining a solution containing isavuconazonium sulfate in a solvent or a mixture of solvents;

b) optionally adding a second solvent to the solution; and

c) removing the solvent to obtain amorphous isavuconazonium sulfate.

In one embodiment, step ‘a’ of the above process involves obtaining a solution of isavuconazonium sulfate by dissolving isavuconazonium sulfate in a solvent or a mixture of solvents.

In one embodiment, step ‘a’ of the above process involves obtaining an alcoholic solution of isavuconazonium sulfate.

In one embodiment, in step ‘a’ of the above process the solvent may be an ester selected from the group consisting of ethyl acetate, isopropyl acetate and the like; halogenated hydrocarbon selected from the group consisting of methylene dichloride, chloroform and the like;hydrocarbons selected from the group consisting of hexane, heptane, cyclohexane, xylene and the like; ketones selected from the group consisting of acetone, ethyl methyl ketone, methyl isobutyl ketone, alcohol selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, tert-butanol and the like; and water or mixtures thereof.

In one embodiment, step ’a’ of the above process involve obtaining an aqueous butanol solution of isavuconazonium sulfate.

In one embodiment, step ‘b’ of the above process involves adding a second solvent to the solution obtained in step’a’.

In one embodiment, in step ‘b’ the second solvent is selected from the group consisting of water, alcohol and ketone.

In one embodiment, step ‘c’ of the above process involves removing the solvent from step ‘a’ or step ‘b’ to obtain amorphous isavuconazonium sulfate.

In one embodiment, in step ‘c’ the removal of solvent is carried out by rotavapour, spray drying, fluid bed drying, lyophilization, flash drying, spin flash drying, freez drying or thin-film drying techniques.

In one embodiment, the present invention provides a process for preparation of amorphous isavuconazonium sulfate comprising subjecting a mixture of water and methanol to lyophilsation.

In one embodiment, the present invention provides a process for preparation of amorphous isavuconazonium sulfate comprising subjecting a mixture of water and methanol to rotavapor distillation.

In one embodiment, the present invention provides a process for preparation of amorphous isavuconazonium sulfate comprising subjecting a mixture of water and n-butanol to lyophilsation.

In one embodiment, the present invention provides a process for preparation of amorphous isavuconazonium sulfate comprising subjecting a mixture of water and butanol to rotavapor distillation.

In one embodiment, the present invention provides isavuconazonium sulfate characterized by X-ray Diffraction (XRD) spectrum as depicted in Fig. 5.

In one embodiment, the present invention provides isavuconazonium sulfate characterized by Differential Scanning Calorimetric (DSC) thermogram having endothermic peak at about $63.90\pm1^{o}C$ and $136.22\pm1^{o}C$.

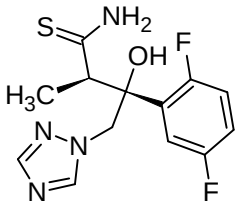
In one embodiment, the present invention provides isavuconazonium sulfate characterized by Differential Scanning Calorimetry (DSC) spectrum as depicted in Fig. 6.

In one embodiment, the isavuconazonium sulfate obtained by the present invention has a chemical purity of about 99.9%.

In one embodiment, the isavuconazonium sulfate obtained by the present invention has a chiral purity of about 99.9%.

In one embodiment, the N-boc isavuconazonium chloride, a compound of formula VI is prepared by a process comprising:

a) reacting, a compound of formula II, with a compound of formula III in the presence of a non-alcoholic solvent to obtain isavuconazole, a compound of formula IV;



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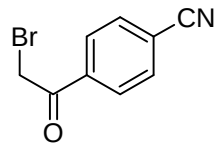
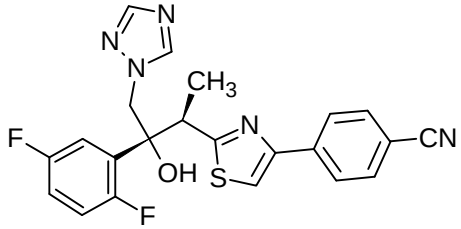
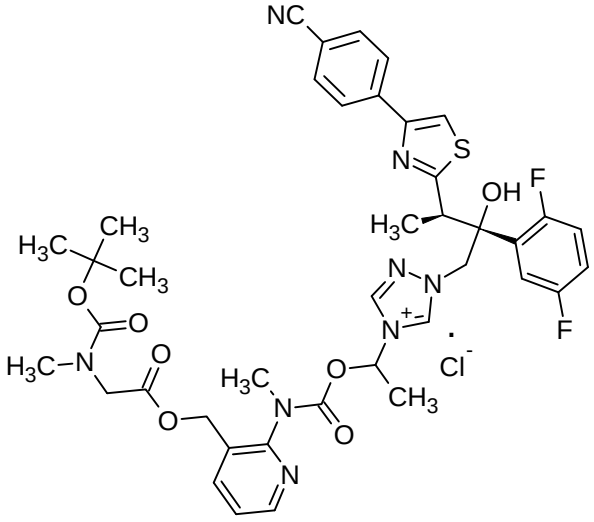


III



IV

b) converting isavuconazole, a compound of formula IV to N-boc isavuconazonium chloride, a compound of formula VI .



VI

In one embodiment, step ‘a’ of the above process involves reacting, a compound of formula II, with a compound of formula III in the presence of a non-alcoholic solvent to obtain isavuconazole, a compound of formula IV.

In one embodiment, in step ‘a’ the non-alcoholic solvent is selected from the group consisting of ketone, hydrocarbon, halogenated hydrocarbon, amide, sulfoxide, ester, ether, water, nitrile or mixtures thereof.

In one embodiment, a ketone solvent may be selected from the group consisting of acetone, methyl ethyl ketone, isopropyl ketone, methyl tert-butyl ketone and the like; a hydrocarbon solvent may be selected from the group consisting of toluene, xylene, cyclohexane, n-heptane, hexane and the like; a halogenated hydrocarbon solvent may be selected from the group consisting of methylene dichloride, ethylene dichloride, chloroform and the like; amide solvent may be selected from the group consisting of dimethyl formamide, dimethyl acetamide, formamide and the like; sulfoxides such as dimethyl sulfoxide and the like; an ether solvent may be selected from the group consisting of diethyl ether, di-isopropyl ether, methyl tert-butyl ether, tetrahydrofuran and the like; esters such as ethyl acetate, butyl acetate, isopropyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like.

In one embodiment, a compound of formula II is reacted with a compound of formula III in dimethylformamide to obtain isavuconazole, a compound of formula IV.

The reaction is carried at a temperature of about 20°C to reflux temperature of the solvent. Preferably the reaction is carried out at a temperature of about 45°C to 70°C.

In one embodiment, isavuconazole is recrystallized from a solvent selected from the group consisting of esters, nitriles, ethers, C_1-C_5 alcohols and the like.

In one embodiment, the esters may be selected from the group consisting of esters such as ethyl acetate, butyl acetate, isopropyl acetate and the like, nitriles may be selected from the group consisting of acetonitrile, propionitrile and the like; ethers may be selected from the group consisting of diethyl ether, diisopropyl ether and the like, C_1-C_5 alcohols may be selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, water or mixtures thereof.,

In one embodiment, isavuconazole, the compound of formula IV is recrystallized from aqueous methanol.

In one embodiment, the present invention provides crystalline isavuconazole characterized by X-ray diffraction (XRD) spectrum having peak reflections at about 10.02, 17.62, 18.06, 21.04 and 22.14±0.2 degrees 2 theta.

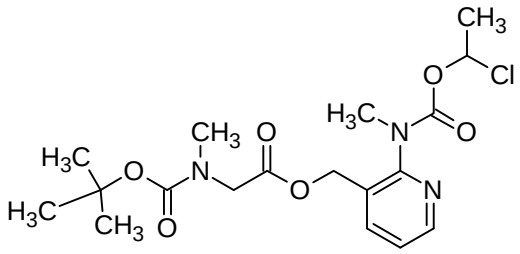
In one embodiment, the present invention provides isavuconazole characterized by Differential Scanning Calorimetric (DSC) thermogram having endothermic peak at about 118.52±1°C .

In one embodiment, the present invention provides isavuconazole characterized by X-ray Diffraction (XRD) spectrum as depicted in Fig. 1.

In one embodiment, the present invention provides isavuconazole characterized by Differential scanning calorimetry (DSC) spectrum as depicted in Fig. 2.

In one embodiment, step 'b' of the above process involves converting isavuconazole, a compound of formula IV to N-boc isavuconazonium chloride, a compound of formula VI.

In one embodiment, isavuconazole, a compound of formula IV is reacted with an



V

ester of formula V to obtain N-boc isavuconazonium chloride compound of formula VI.

In one embodiment, the reaction may be carried out in presence of a catalyst.

The catalyst may be selected from the group consisting of lithium bromide, magnesium bromide, lithium chloride, magnesium chloride, magnesium iodide, lithium iodide, lithium chloride, zinc chloride, tetra-n-butylammonium bromide, tetra-n-butylammonium chloride, or any mixture thereof.

In one embodiment, the reaction may be carried out in presence of a suitable iodide source selected from the group consisting of trimethylsilyl iodide, hydrogen iodide, sodium iodide or potassium iodide.

In one embodiment, the reaction may be carried out in presence of a suitable solvent.

The solvent may be selected from the group consisting of a ketone solvent selected from the group consisting of acetone, methyl ethyl ketone, isopropyl ketone, methyl tert-butyl ketone and the like; a hydrocarbon solvent selected from the group consisting of toluene, xylene, cyclohexane, n-heptane, hexane and the like; a halogenated hydrocarbon solvent selected from the group consisting of methylene dichloride, ethylene dichloride, chloroform and the like; amide solvent selected from the group consisting of dimethyl formamide, dimethyl acetamide, formamide and the like; sulfoxides such as dimethyl sulfoxide and the like; an ether solvent selected from the group consisting of diethyl ether, di-isopropyl ether, methyl tert-butyl ether, tetrahydrofuran and the like; esters solvent selected from the group consisting ofethyl acetate, butyl acetate, isopropyl acetate and the like; nitriles such as acetonitrile, propionitrile, C_1-C_5 alcohol selected from the group consisting of methanol, ethanol, propanol, butanol, isopropanol and the like.

In one embodiment, isavuconazole, a compound of formula IV is reacted with an ester of formula V in the presence of sodium iodide in acetonitrile to obtain an intermediate compound N-boc isavuconazonium iodide.

In one embodiment, the reaction is carried out at a temperature of about 0°C to about reflux temperature of the solvent.

In one embodiment, the reaction is carried out at a temperature of about 45-55°C.

In one embodiment, the N-boc isavuconazonium iodide obtained is dissolved in a solvent and contacted with a chloride containing anion exchange resin to obtain N-boc isavuconazonium chloride.

In one embodiment, N-boc isavuconazonium chloride is not isolated by column chromatography.

In one embodiment, the N-boc isavuconazonium chloride may be isolated from the solution containing N-boc isavuconazonium chloride by rotavapour, distillation or evaporation techniques.

In one embodiment, the N-boc isavuconazonium chloride is purified by a process comprising:

a) dissolving in a first organic solvent;

b) removing undesired particles; and

c) isolating from a second organic solvent.

In one embodiment, in step ‘a’ of the above process N-boc isavuconazonium chloride is dissolved in suitable solvent selected from the group consisting of esters such as ethyl acetate, isopropyl acetate; chlorinated hydrocarbon such as methylene dichloride, chloroform and the like.

In one embodiment, in step ‘b’ of the above process, the solution containing N-boc isavuconazonium chloride is treated with water to remove any undesired particles.

In one embodiment, in step ‘c’ of the above process N-boc isavuconazonium chloride from step ‘b’ is extracted into a second solvent and isolated by methods such as centrifugation, filtration and the like.

In one embodiment , the N-boc isavuconazonium chloride, the compound of formula VI is isolated by crystallization or precipitation method.

In one embodiment, the N-boc isavuconazonium chloride obtained by the present invention has a chemical purity of at least 99%.

In one embodiment, the N-boc isavuconazonium chloride obtained by the present invention has a chiral purity of at least 99%.

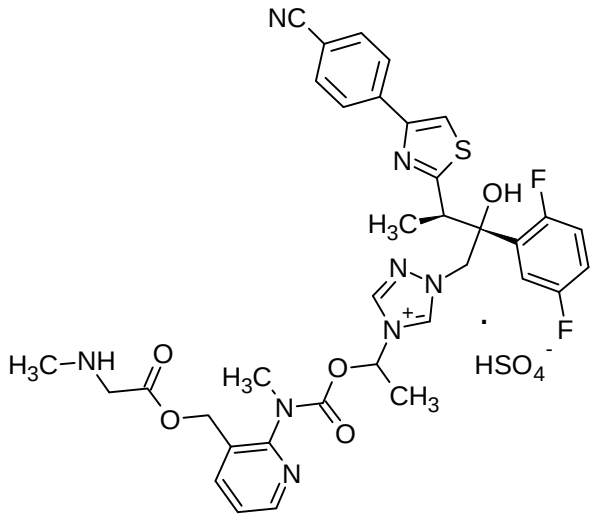
In one embodiment, the N-boc isavuconazonium chloride compound of formula VI is further converted to isavuconazonium sulfate in one pot.

In one embodiment, the present invention provides N-boc isavuconazonium chloride characterized by X-ray Diffraction (XRD) spectrum as depicted in Fig. 3.

In one embodiment, the present invention provides N-boc isavuconazonium chloride characterised by Differential Scanning Calorimetric (DSC) thermogram having endothermic peak at about and 60.57±1°C , 152.35±1°C and 201.65±1°C .

In one embodiment, the present invention provides N-boc isavuconazonium chloride characterized by Differential scanning calorimetry (DSC) spectrum as depicted in Fig. 4.

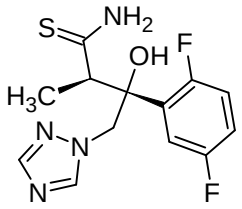
In one embodiment, the present invention provides a process for the preparation of isavuconazoium sulfate, a compound of formula I



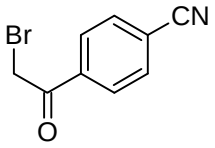
I

comprising :

a) reacting, a compound of formula II, with a compound of formula III in the presence of a non-alcoholic solvent to obtain isavuconazole, a compound of formula IV;



II



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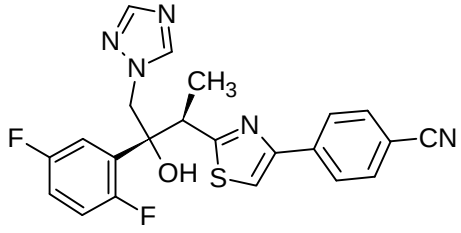
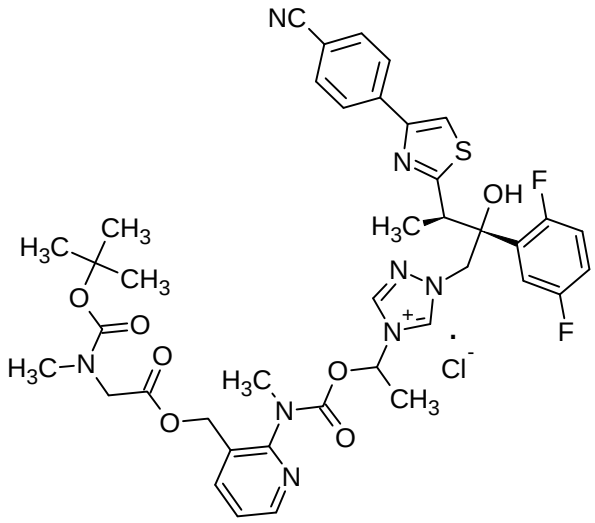


IV

b) converting isavuconazole, a compound of formula IV to N-boc isavuconazonium chloride compound of formula VI ; and



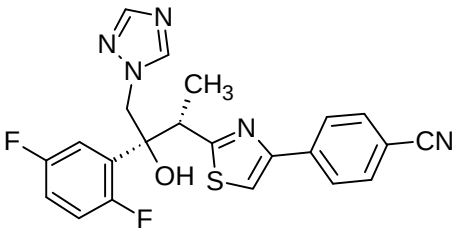
VI

c) converting N-boc isavuconazonium chloride compound of formula VI to isavuconazonium sulfate.

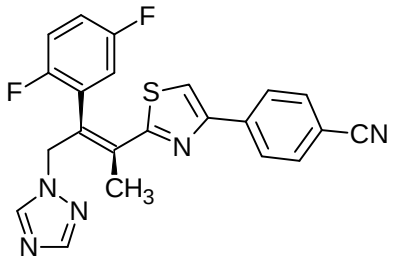
In one embodiment the steps ‘a, ‘b’ and ‘c’ are carried out by methods as disclosed above.

In one embodiment, the present invention provides a process for the preparation of isavuconazole, a compound of formula IV comprising reacting, a compound of formula II, with a compound of formula III in the presence of a non-alcoholic solvent to obtain isavuconazole, a compound of formula IV.

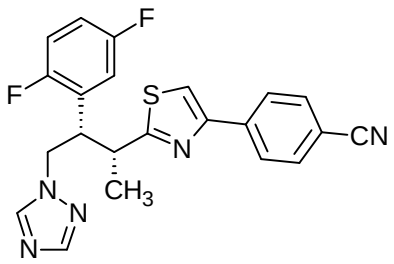
In one embodiment, the present invention provides substantially pure isavuconazonium sulfate having a purity of at least 99% and having less than 0.1% of any of the below compounds:



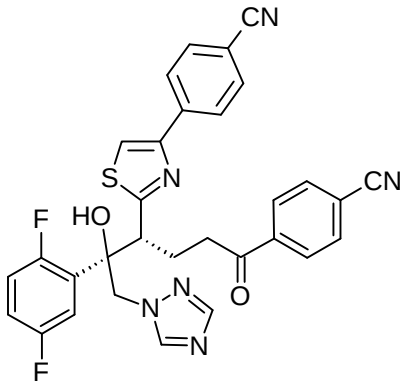
VII



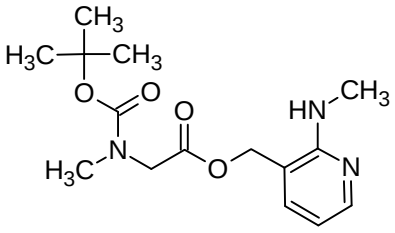
VIII



IX



X



XI

In one embodiment, the present invention provides pharmaceutical compositions comprising isavuconazonium sulfate or salt thereof obtained by the processes herein described, having a D_{90} particle size of less than about 150 microns, D_{50} particle size of less than about 100 microns, preferably D_{90} particle size less than about 100 microns, more preferably D_{90} particle size less than about 50 microns, still more preferably D_{90} particle size less than about 20 microns, still more preferably D_{90} particle size less than about 15 microns and most preferably D_{90} particle size less than about 10 microns. The particle size disclosed here can be obtained by, for example, any milling, grinding, micronizing or other particle size reduction method known in the art to bring the solid state isavuconazonium sulfate into any of the foregoing desired particle size range.

The examples that follow are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the features and advantages.

Examples

Example 1: Preparation of 4-{2-[(2*R*,3*R*)-3-(2,5-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]-1,3-thiazol-4-yl}benzonitrile:

(2*R*,3*R*)-3-(2,5-difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-ylthiobutyramide (10gm) was suspended in DMF (20ml). The reaction mass was heated to about 55°C, and to this a solution of 4-cyano-2'-bromoacetophenone (7.8 gm) in dimethylforamide (20ml) was charged over a period of 15-20 minutes. The reaction mass was stirred for 5 hrs. The reaction mass was cooled and to this water and ethyl acetate were added. The layers were separated and organic layer was washed with sodium bicarbonate solution. The ethyl acetate layer was distilled to obtain an oily mass. The product was crystallized from the aqueous methanol solution. The product was dried to obtain 11 g of title product. Purity > 95%.

XRD of Isavuconazole.

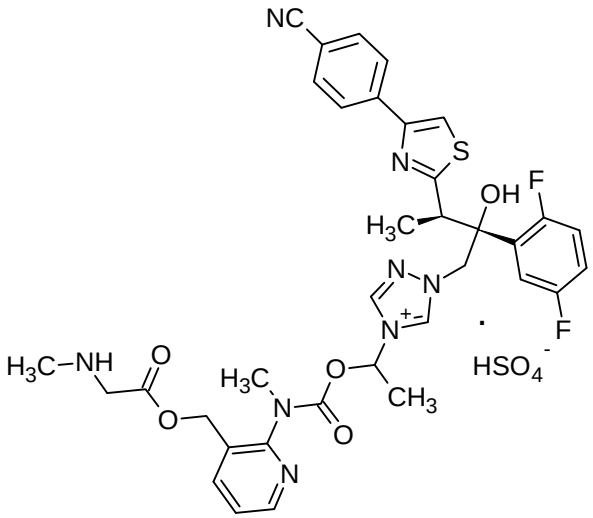
Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]	Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]	Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
9.06	9.75	10.92	19.44	4.56	10.05	25.22	3.53	27.05
10.02	8.82	49.67	20.13	4.4	6.49	25.52	3.48	11.72
10.36	8.53	23.76	21.04	4.22	71.44	26.23	3.39	6.02
13.54	6.53	44.22	21.32	4.16	8.53	26.88	3.31	5.79
14.98	5.91	5.47	22.14	4.01	70.41	27.46	3.24	38.89
15.8	5.6	16.01	22.51	3.94	19.66	29.53	3.02	25.78
17.36	5.1	35.01	22.84	3.89	34.23	30.22	2.95	15.75
17.62	5.03	100	23.75	3.74	16.93	31.49	2.84	19.94
18.06	4.91	66.81	23.91	3.72	10	32.69	2.73	2.24
19.1	4.64	8.43	24.49	3.63	11.68			

Example 2: Preparation of (2-{[(1-{1-[(2R,3R)-3-[4-(4-cyanophenyl)-1,3-thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-1H-1,2,4-triazol-4-ium-4-yl}ethoxy)carbonyl](methyl)amino}pyridin-3-yl)methyl-N-(tert-butoxycarbonyl)-N-methylglycinate chloride: 4-{2-[(2*R*,3*R*)-3-(2,5-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]-1,3-thiazol-4-yl}benzonitrile(10gm) was suspended in acetonitrile (70ml). A solution of (2-{[(1-chloroethoxy)carbonyl](methyl)amino}pyridin-3-yl)methyl-N-(tert-butoxycarbonyl)-N-methylglycinate(12.36gm) in acetonitrile (30ml) and sodium iodide(4.56gm) was added to the above suspension. The reaction mass was heated to 50-55°C for about 15 hours. The reaction mass was filtered and distilled completely under vacuum. The obtained residue was dissolved in aqueous methanol filtered through celite and the filtrate was passed through resin SA10A(chloride). The obtained solution containing product was distilled under vacuum. The residue was dissolved in ethyl acetate and washed with water. The ethyl acetate layer was distilled under vacuum. The residue was slurried in n-hexane. The precipitated product was filtered and dried at 45-50°C under vacuum to obtain 14 gm of title product. Purity > 85%.

Example 3: Preparation of (2-{[(1-{1-[(2*R*,3*R*)-3-[4-(4-cyanophenyl)-1,3-thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-1*H*-1,2,4-triazol-4-ium-4-yl}ethoxy) carbonyl](methyl)amino}pyridin-3-yl)methyl-N-methylglycinate Sulfonium salt: 4*H*-1,2,4-triazolium,1-[(2*R*,3*R*)-3-[4-(4-cyanophenyl)-2-thiazolyl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[1-[[[[3-[[[2-[[(1,1-dimethylethoxy)carbonyl]methylamino]acetyl] oxy]methyl]-2-pyridinyl]methylamino]carbonyl]oxy]ethyl]chloride (10gm) was suspended in ethyl acetate(160ml). The reaction mass was cooled to 0 to 5°C and to this ethyl acetate hydrochloric acid (12 % w/w) was added. The reaction mass was warmed to 25 to 30°C and after completion of reaction water was added. The aqueous layer was washed with methylene chloride followed by n-heptane. The aqueous layer was passed through sulfate containing anion exchange resin and the obtained aqueous layer was extracted with n-butanol. The butanol solution was partially concentrated and the residual mass was diluted with water. The resultant solution was lyophilized to obtain 7gm of the title product. Purity>99.8%.

Features and Advantages

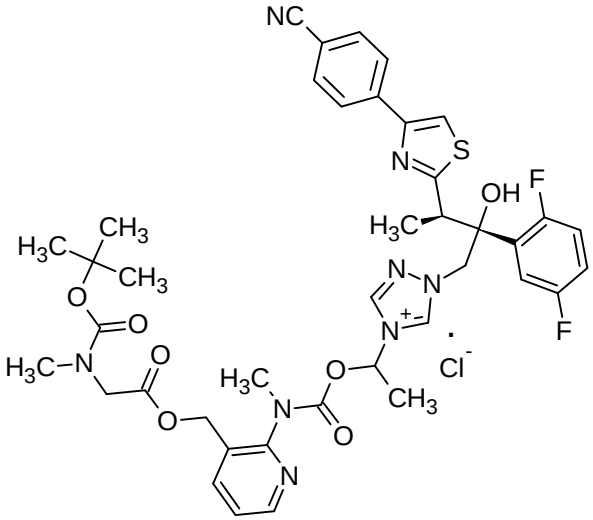
A] A process for the preparation of isavuconazonium sulfate, a compound of formula I,



I

comprising :

a) reacting N-boc isavuconazonium chloride, a compound of formula VI with hydrochloric acid to generate isavuconazonium chloride hydrochloride;



VI

b) contacting isavuconazonium chloride hydrochloride with anion exchange resin to obtain isavuconazonium sulfate; and

c) isolating isavuconazonium sulfate.

B] The process as defined in 'A' wherein isavuconazonium chloride hydrochloride is generated *in situ* on reaction of N-boc isavuconazonium chloride, a compound of formula VI with hydrochloric acid.

C] The process as defined in 'A' wherein the steps 'a' and 'b' are carried out in one pot.

D] The process as defined in 'A' wherein the isavuconazonium sulfate is in amorphous form.

E] The process as defined in 'D' wherein the amorphous isavuconazonium sulfate is isolated by a process comprising:

a) obtaining a solution containing isavuconazonium sulfate in a solvent or a mixture of solvents;

b) optionally adding a second solvent to the solution; and

c) removing the solution to obtain amorphous isavuconazonium sulfate.

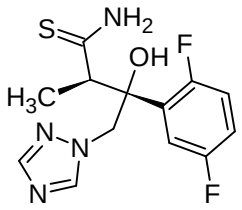
F] The process as defined in 'E' wherein in step 'a' the solvent is selected from the group comprising ester, halogenated hydrocarbon, hydrocarbon, ketone, alcohol and water.

G] The process as defined in 'E' wherein in step 'b' the second solvent is selected from the group comprising water, alcohol and ketone.

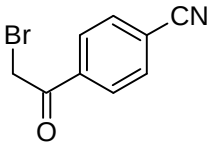
H] The process as defined in 'E' wherein in step 'c' removal of solvent is carried out by rotavapour, spray drying, fluid bed drying, lyophilization, flash drying, spin flash drying, freez drying or thin-film drying techniques.

I] The process as defined in 'A' wherein N-boc isavuconazonium chloride, a compound of formula VI is prepared by a process comprising:

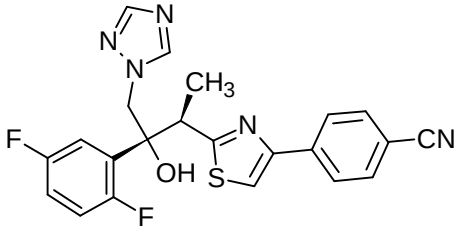
a) reacting, a compound of formula II, with a compound of formula III in the presence of a non-alcoholic solvent to obtain isavuconazole, a compound of formula IV; and



II

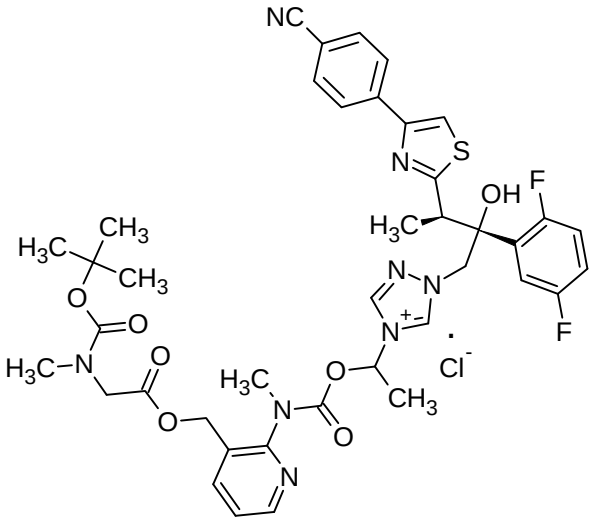


III



IV

b) converting isavuconazole, a compound of formula IV to N-boc isavuconazonium chloride, a compound of formula VI.



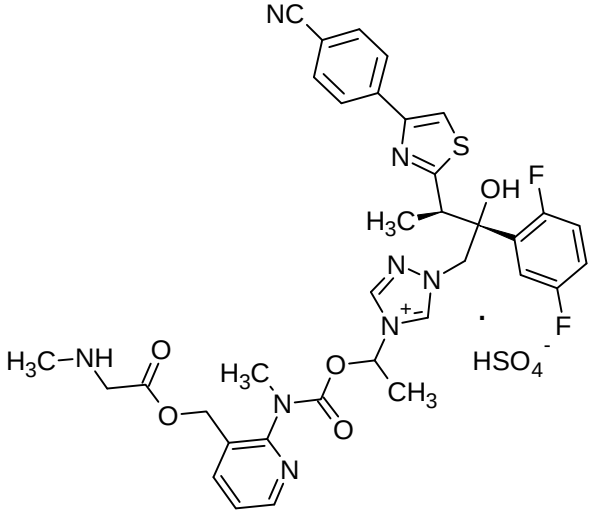
VI

J] The process as defined in 'I' wherein in step 'a' the non-alcoholic solvent is selected from the group consisting of ketone, hydrocarbon, halogenated hydrocarbon, amide, sulfoxide, ester, ether, water, nitrile or mixtures thereof.

K] The process as defined in 'I' wherein in step 'b' the N-boc isavuconazonium chloride, the compound of formula VI is isolated by crystallization or precipitation method.

L] The process as defined in 'I' the N-boc isavuconazonium chloride, the compound of formula VI is further converted to isavuconazonium sulfate in one pot.

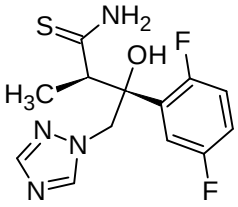
M] A process for the preparation of isavuconazoium sulfate, a compound of formula I



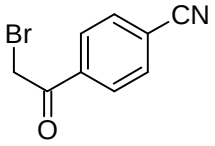
I

comprising :

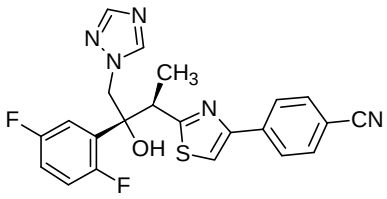
a) reacting, a compound of formula II, with a compound of formula III in the presence of a non-alcoholic solvent to obtain isavuconazole, a compound of formula IV;



II

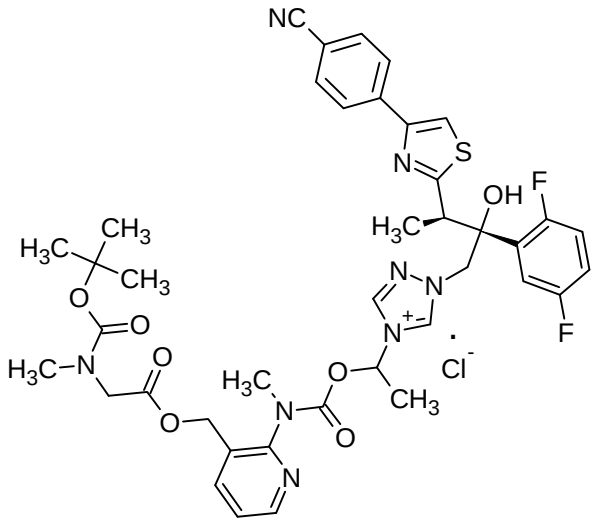


III



IV

b) converting isavuconazole, a compound of formula IV to N-boc isavuconazonium chloride, a compound of formula VI ; and



VI

c) converting N-boc isavuconazonium chloride, a compound of formula VI to isavuconazonium sulfate.

N] A process for the preparation of isavuconazole, a compound of formula IV comprising reacting a compound of formula II, with a compound of formula III in the presence of a non-alcoholic solvent to obtain isavuconazole, a compound of formula IV.

Dated this 14th day of October, 2016

(Signed) _____

Dr. Madhavi Karnik
General Manager-IPM
Glenmark Pharmaceuticals Limited

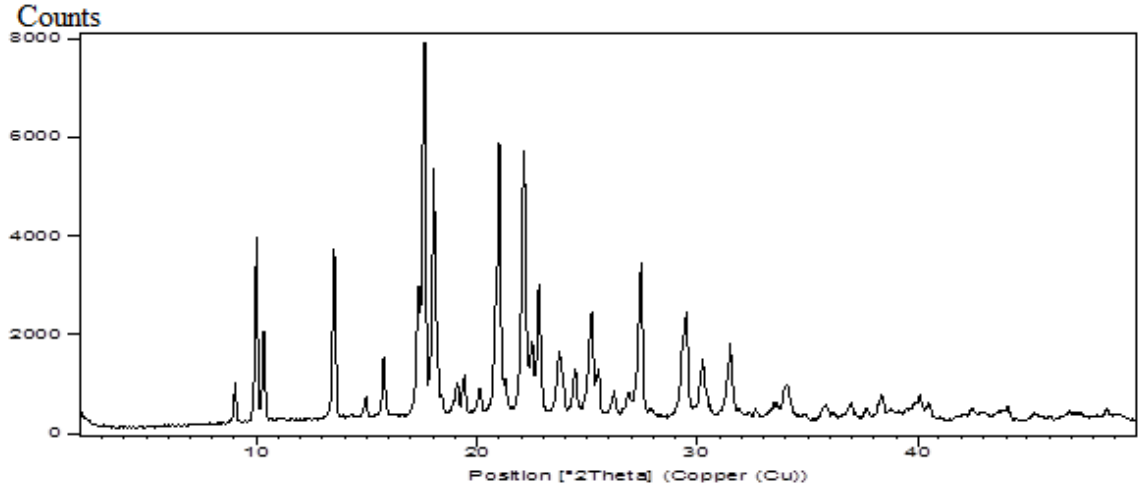


Fig. 1

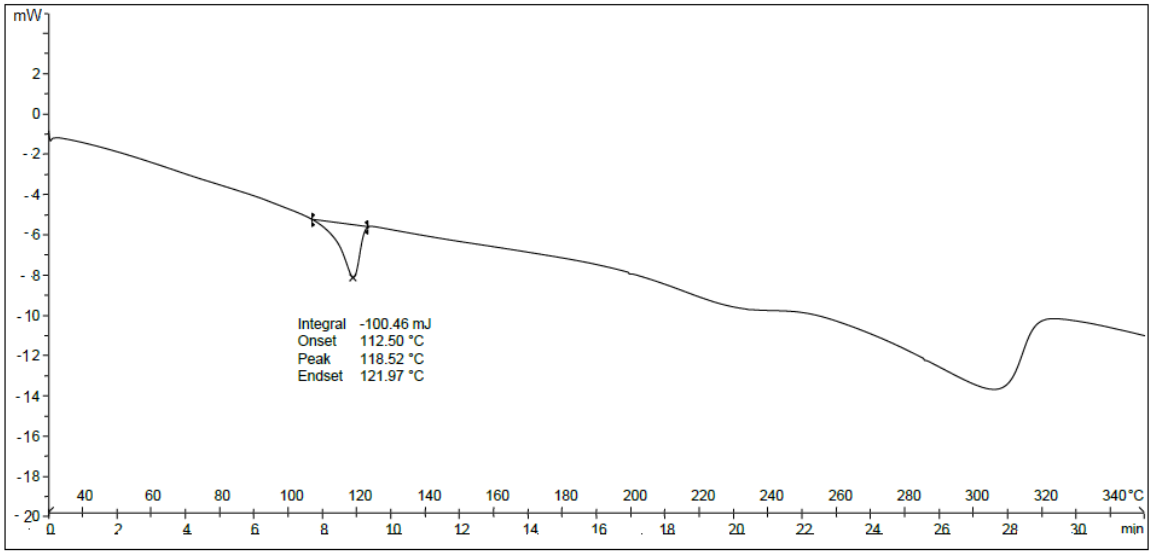


Fig. 2

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Dr. Madhavi Karnik
General Manager-IPM
Glenmark Pharmaceuticals Limited

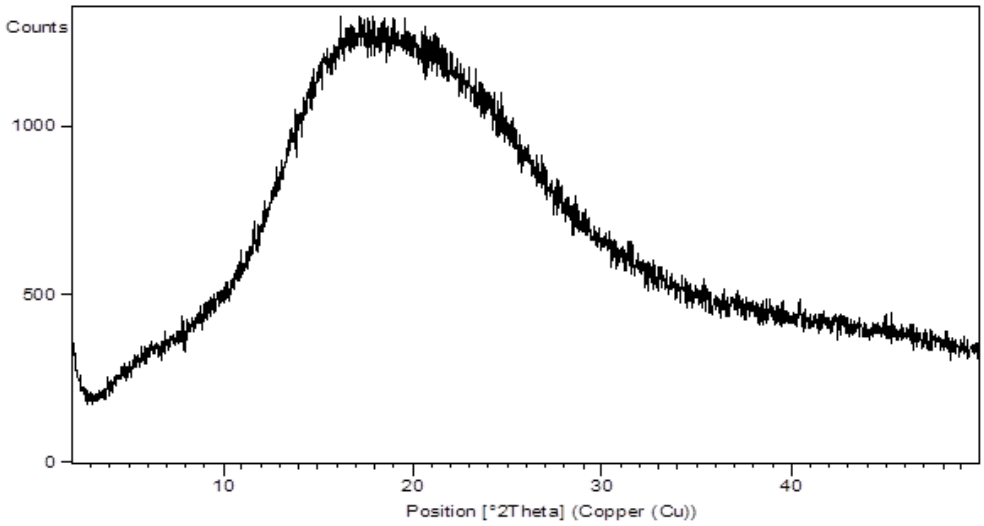

Fig. 2

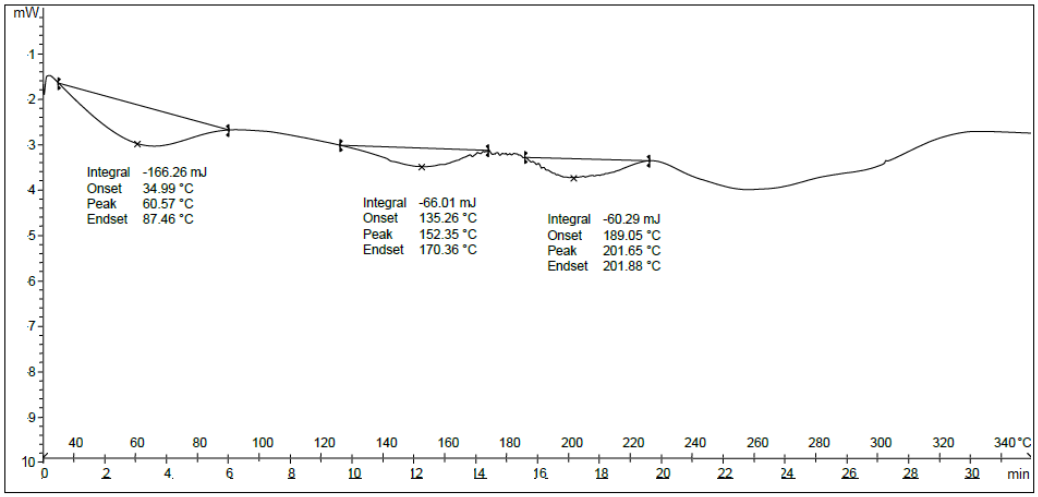

Fig 3

Dated this 14th day of October, 2016

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Dr. Madhavi Karnik
General Manager-IPM
Glenmark Pharmaceuticals Limited

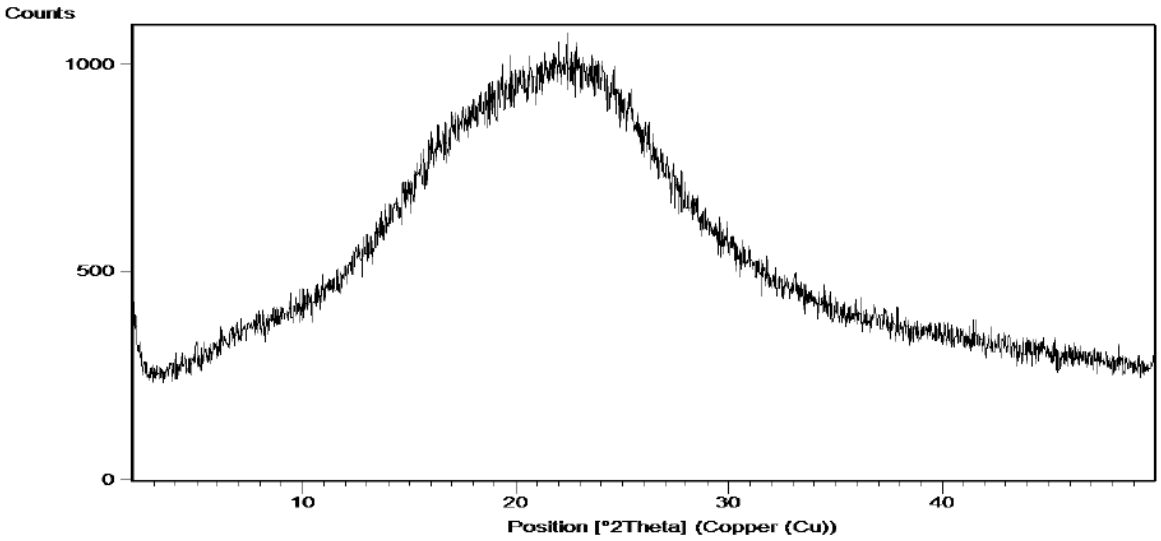

Fig. 5

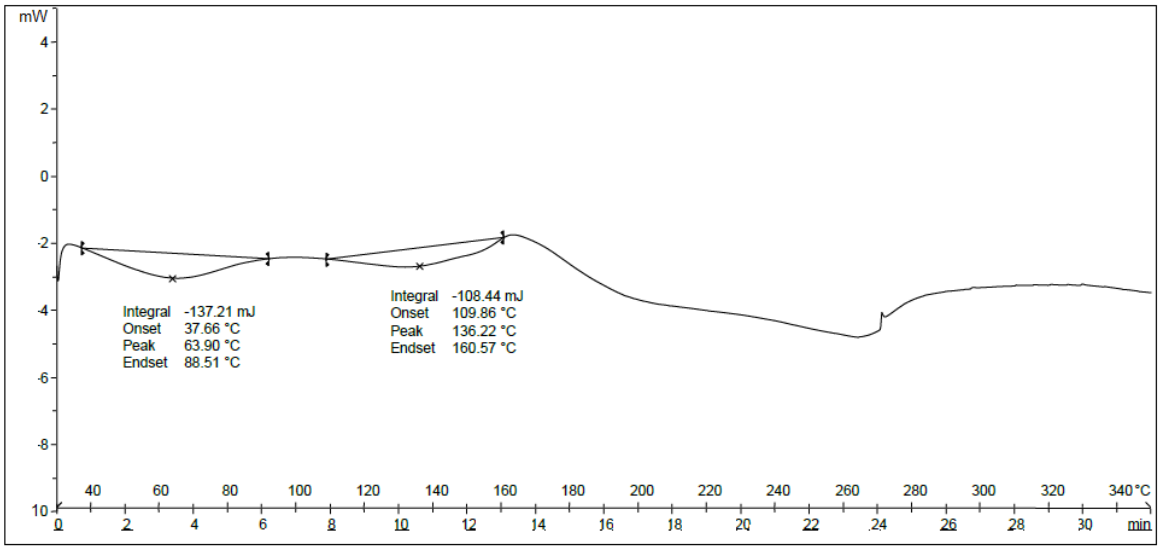

Fig. 6

Dated this 14th day of October, 2016

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Dr. Madhavi Karnik
General Manager-IPM
Glenmark Pharmaceuticals Limited

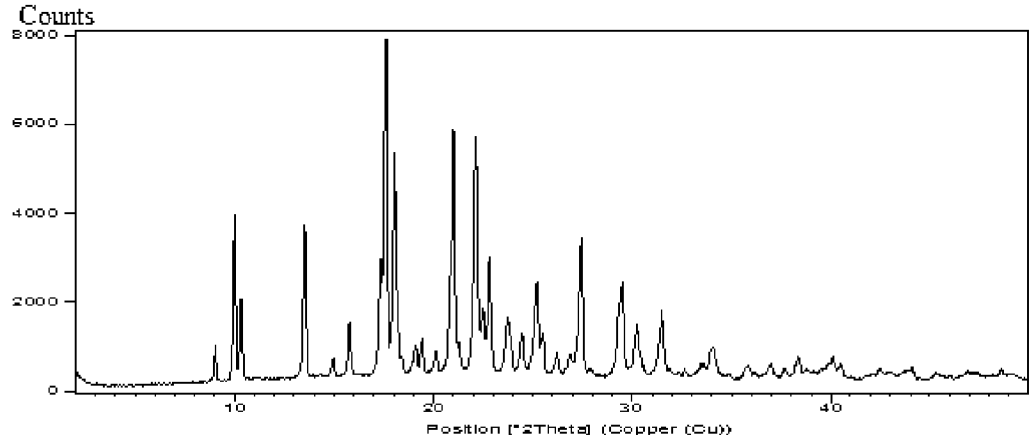

Fig. 1

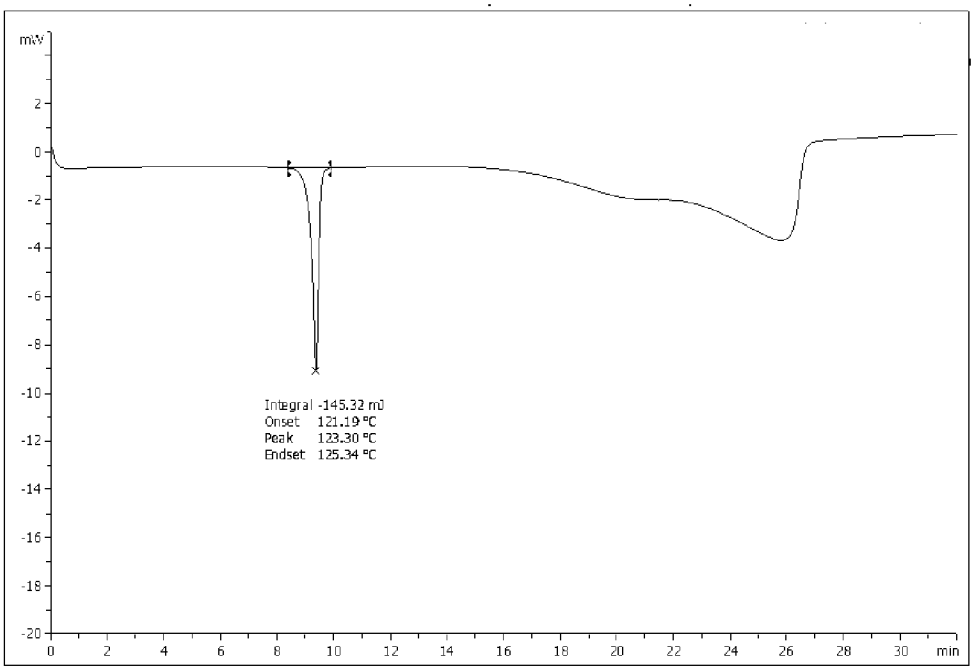

Fig. 2

Dated this 11th day of October, 2017

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Dr. Madhavi Karnik

Senior General Manager-IPM

Glenmark Pharmaceuticals Limited

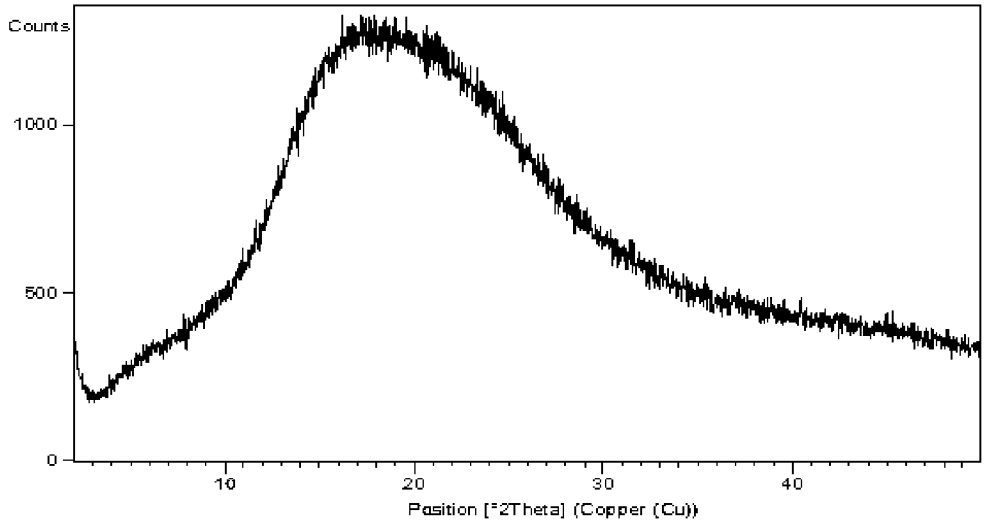

Fig. 3

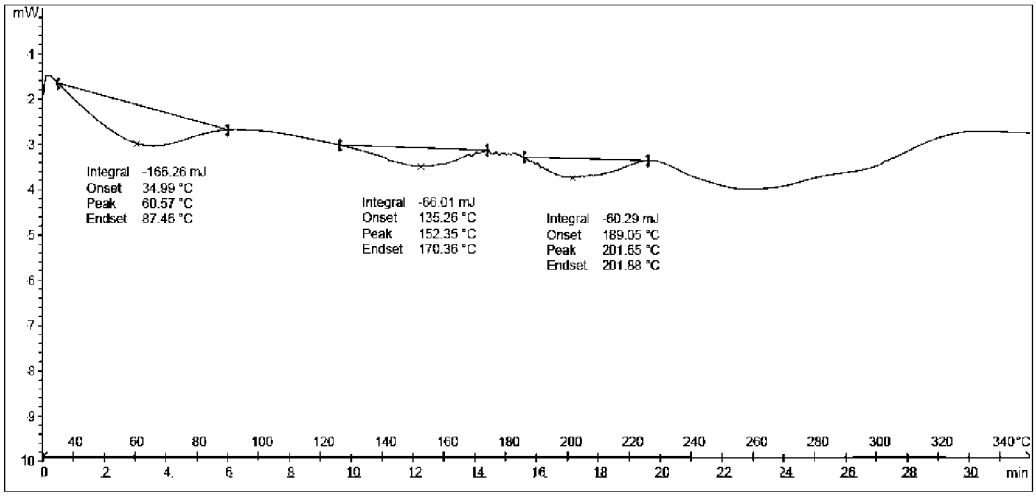

Fig 4

Dated this 11th day of October, 2017

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Dr. Madhavi Karnik

Senior General Manager-IPM

Glenmark Pharmaceuticals Limited

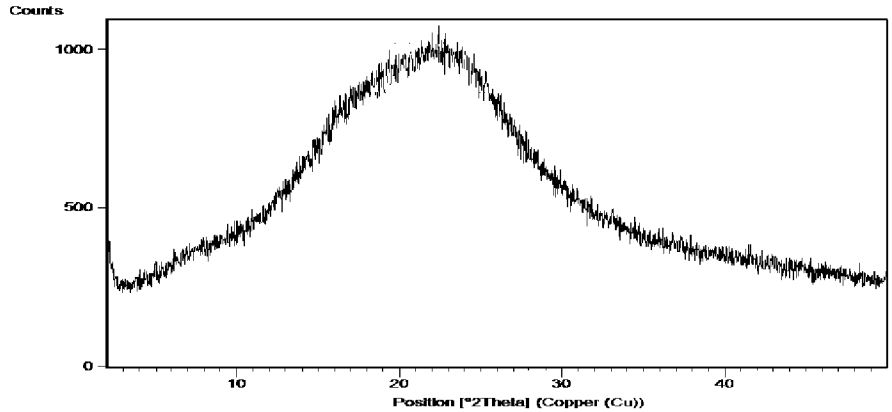

Fig. 5

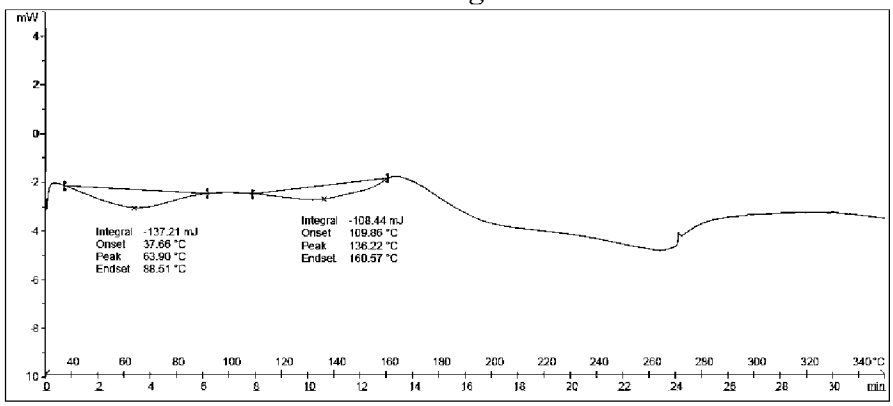

Fig. 6

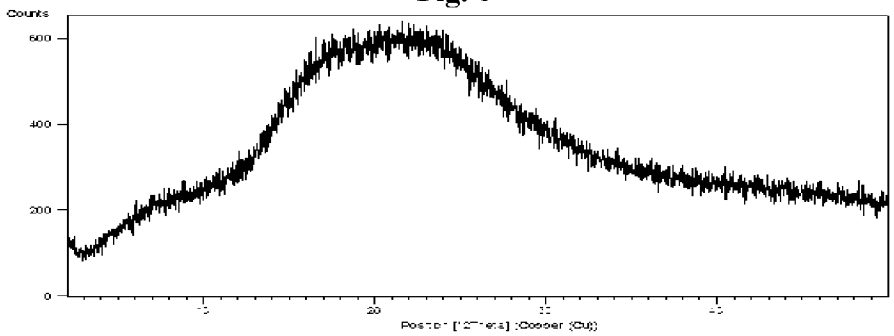

Fig. 7

Dated this 11th day of October, 2017

(Signed)

Dr. Madhavi Karnik
Senior General Manager-IPM
Glenmark Pharmaceuticals Limited