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(71) Applicant: **DR. REDDY'S LABORATORIES LIM¬ITED** [IN/IN]; 8-2-337, Road No. 3, Banjara Hills, Hyderabad 500034 (IN).

(72) Inventors: **DAHANUKAR, Vilas Hareshwar;** Plot No. 11, Lalitha Bloomfield, Near Oakridge International School, Khajaguda, Telangana., Hyderabad 500008 (IN). **ORUGANTI, Srinivas;** Flat No. 205-G, Manjeera Diamond Towers, Gopanapally, Gachibowli, Telangana, Hyderabad 500046 (IN). **RAO, Pallavi;** Flat No. 505, Fortune Kumkum Heights, Masid banda, Kondapur, Hyderabad 500081 (IN). **CHAKKA, Ramesh;** Flat No. 206, Sri Tirumala's Kasaani Residency, Survey No.: 81 to 85, Petbasheerabad, Jeedimetla Village, Telangana., Hyderabad 500067 (IN). **BAIG, Mohammed Azeezulla;** Plot no. 2 11, Street no. 22, HMT Swarnapuri colony, Miyapur, Telangana, Hyderabad 500050 (IN). **VYALA, Sunitha;** Flat No.407, Sundaram Apartments, Ramaraju nagar colony, Suchitra, Medchal road, Telangana., Hyderabad 500055 (IN). **SALADI, Venkata Narasayya;** H. No. 48-579/5/1, Ganesh Nagar, Chintal, Hyderabad 500055 (IN). **PEDDY, Vishweshwar;** Plot No. 341, Vasavi Colony, Green Hills Road No. 1, Saroornagar, Hyderabad 500035 (IN). **ELATI, Raviram Chandrasekhar;** Plot No: 531, Flat No : 202, Pragathi nagar, KPHB, Telangana., Hyderabad 500072 (IN). **MOHANARANGAM, Saravanan;** H. No: 22, Pattarai Street, Valavanur, Villapuram, Tamilnadu 605 108 (IN). **RAJ, Gopal;** Plot No 11 & 14, Srinivasa residency, Incoise road, Pragathi nagar, Kukatpally, Telangana, Hyderabad 500090 (IN). **MAMIDIPALLI, Phani;** 10-95/2, Vinayak Nagar, Balanagar, Hyderabad, Telangana., Hyderabad 500042 (IN).

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(54) Title: SOLID FORMS OF LUMACAFTOR, ITS SALTS AND PROCESSES THEREOF

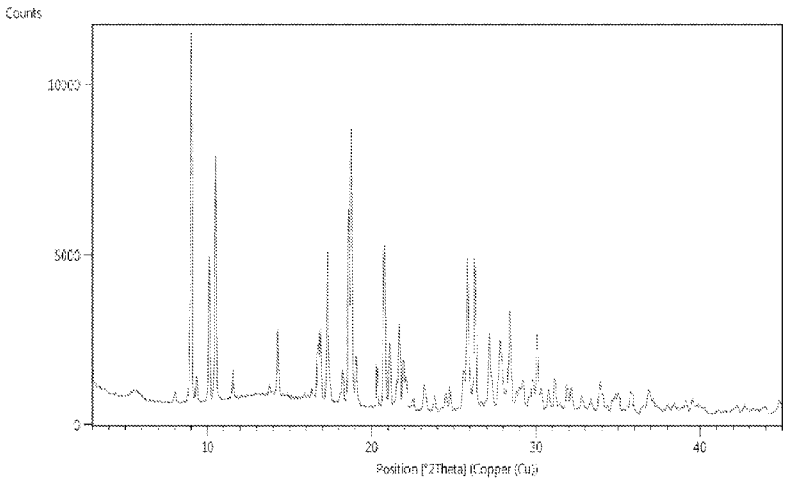

Figure 9

(57) Abstract: Aspects of the present application relate to solid forms of Lumacaftor, its salts and processes thereof. Specific aspects of the present application relate to alternate processes for the preparation of Lumacaftor and intermediates thereof. Present application further relates to the solid forms of Lumacaftor and its salts.

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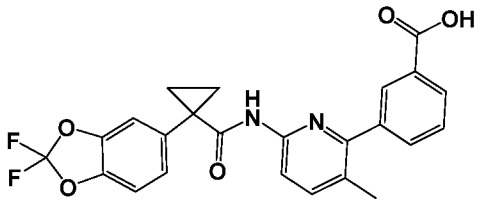
SOLID FORMS OF LUMACAFTOR, ITS SALTS AND PROCESSES THEREOF.

INTRODUCTION

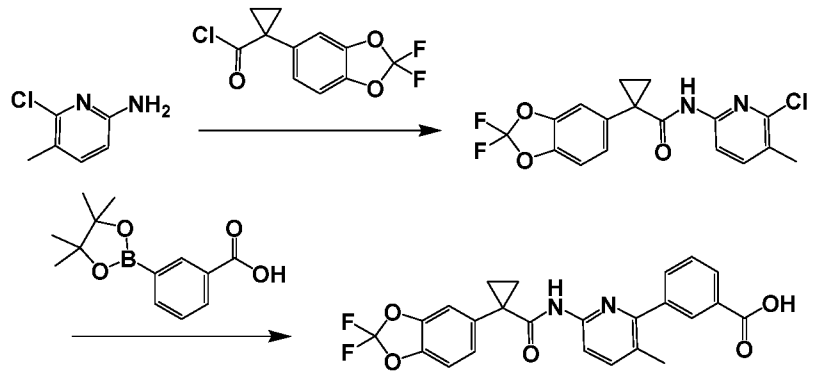
Aspects of the present application relate to solid forms of Lumacaftor, its salts and processes thereof. Specific aspects of the present application relate to alternate processes for the preparation of Lumacaftor and intermediates thereof.

The drug compound having the adopted name "Lumacaftor" has chemical name: 3-{6-{[1 -(2,2-Difluoro-1 ,3-benzodioxol-5-yl)cyclopropanecarbonyl]amino}-3-methylpyridin-2-yl}benzoic acid as below.



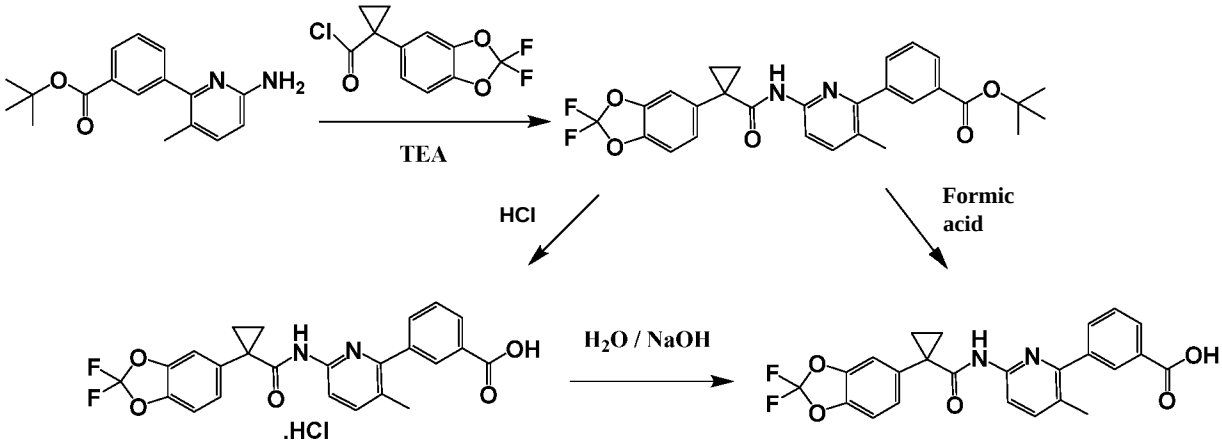
Lumacaftor partially corrects the fundamental molecular defect caused by F508del-CFTR to increase the amount of functional F508del-CFTR at the cell surface, resulting in enhanced chloride transport. The channel gating activity of F508del-CFTR delivered to the cell surface by Lumacaftor can be potentiated by Ivacaftor to further enhance chloride transport. When added to F508del/F508del-HBE, the magnitude of chloride transport observed with the combination of Lumacaftor and either acute or chronic Ivacaftor treatment was greater than that observed with Lumacaftor alone. Orkambi is approved in US and Europe as a fixed dose combination (FDC) pink immediate-release film-coated tablet for oral administration. Orkambi contains 200 mg of Lumacaftor and 125 mg of Ivacaftor as active substances. US FDA label prescribes two tablets to be taken orally every 12 hours for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

US 8993600 B2 discloses Lumacaftor as compound-396, its pharmaceutical use for the treatment of cystic fibrosis. Further, it discloses preparative methods for the preparation of compounds disclosed therein including Lumacaftor by reacting N-(6-chloro-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropanecarboxamide (which is obtained by the N-acylation of 2-chloro-3-methyl pyridine amine with (2,2-difluorobenzo[d][1 ,3] dioxol-5-yl)cyclopropane carboxylic acid chloride) with 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid as depicted in scheme-1 .



Scheme - 1

US 8124781 B2 describes a process for the preparation of Lumacaftor by reacting t-butyl-3-(6-amino-3-methylpyridin-2-yl)benzoate with 1-(2,2-difluoro-l,3-benzodioxol-5-yl)-cyclopropanecarbonylchloride in the presence of triethyl amine (TEA) to obtain t-butyl ester of Lumacaftor, which is either hydrolyzed directly to its free carboxylic acid form i.e., Lumacaftor or converted to its HCI salt and then neutralized to afford Lumacaftor as depicted in scheme-2.



Scheme - 2

US 8507534 B2 discloses a similar approach as in scheme-2 for the synthesis of Lumacaftor and discloses a crystalline Form I of Lumacaftor, which was prepared either by dispersing or dissolving a salt form, such as HCI, of Lumacaftor in an appropriate solvent for an effective amount of time (or) directly by treating t-butyl ester intermediate of Lumacaftor with an appropriate acid, such as formic acid.

US 8507687 B2 discloses the crystalline solvate Form A of Lumacaftor, which is an isostructural solvate. Solvate Form A includes, but not limited to methanol, ethanol, 2-propanol, acetone, acetonitrile, tetrahydrofuran, methyl

acetate, 2-butanone, ethyl formate, 2-methyl tetrahydrofuran and a crystalline Form A of Lumcaftor HCI salt.

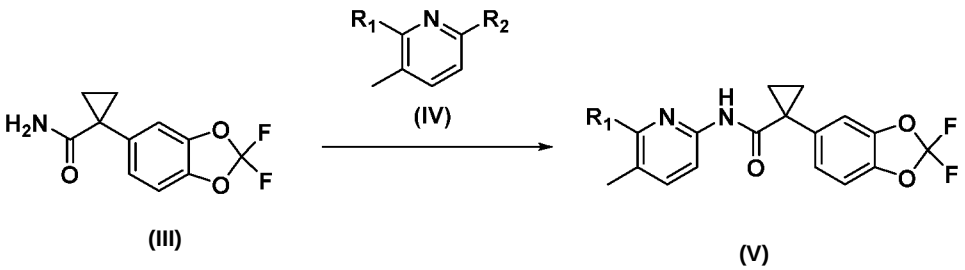
The physicochemical properties of a solid form is a critical parameter in the development of pharmaceutical dosage forms of and these properties can affect the bioavailability, stability and process ability of the active pharmaceutical ingredient. It is known that a solid active pharmaceutical ingredient can exist in amorphous and crystalline state. Crystalline solids may further exist as various polymorphs and solvates.

The discovery of new polymorphs and solvates of a pharmaceutical active compound provides an opportunity to improve the performance of a drug product in terms of its bioavailability or release profile in vivo, or it may have improved stability or advantageous handling properties. Polymorphism is an unpredictable property of any given compound. This subject has been reviewed in recent articles, including A. Goho, "Tricky Business," Science News, August 21, 2004. In general, one cannot predict whether there will be more than one form for a compound, how many forms will eventually be discovered, or how to prepare any previously unidentified form.

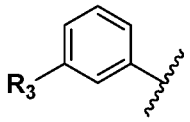
Prior art processes does not disclose an amenable synthetic process for Lumacaftor or its crystalline Forms. Hence, there remains a need for alternate process for the preparation of Lumacaftor in a more cost effective and industrially viable manner and a need for alternate solid forms, particularly, need for alternate crystalline forms of Lumacaftor or a salt thereof, which are stable, reproducible and can be prepared through an industrially viable manner.

SUMMARY

In an aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of reacting the cyclopropyl carboxamide of formula (III) with 3-methylpyridine of formula (IV) to obtain 5-methylpyridin-2-amine of formula (V).



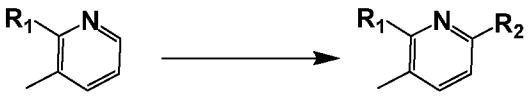
wherein R_1 is selected from hydrogen, any leaving group such as halogen or a phenyl group of formula (A);



(A)

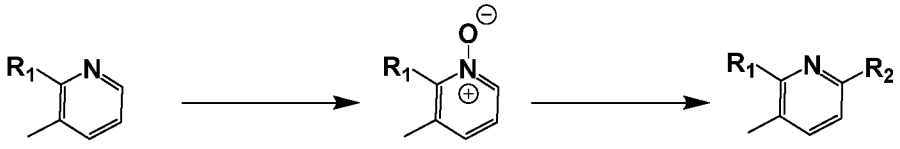
R_2 is any leaving group such as halogen and R_3 is hydrogen or a group selected from cyano, carboxylic acid or carboxylic ester.

In another aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of halogenating 3-methylpyridine of formula (VIII) to obtain 2-halo 5-methylpyridine of formula (IV), wherein R_1, R_2 and R_3 are same as defined above.



(VIII) (IV)

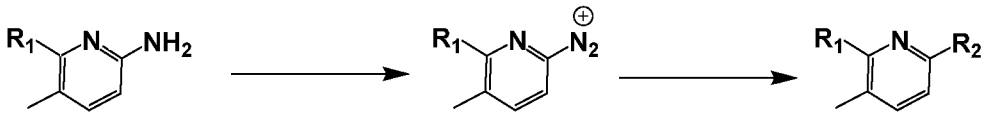
In another aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of halogenating 3-methylpyridine of formula (VIII) through N-oxide formation to obtain 2-halo 5-methylpyridine of formula (IV) as depicted below, wherein R_1, R_2 and R_3 are same as defined above.



(VIII) (IV)

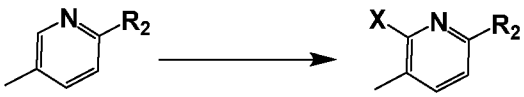
In another aspect, the present application provides a process for the

preparation of Lumacaftor, comprising the step of halogenation through diazotization of 5-methylpyridin-2-amine of formula (IX) as depicted below; wherein R_1, R_2 and R_3 are same as defined above.



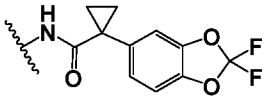
(IX) (IV)

In another aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of halogenating 3-methylpyridine of formula (IVc) to obtain 2-halo 3-methylpyridine of formula (IV), wherein X is any halogen



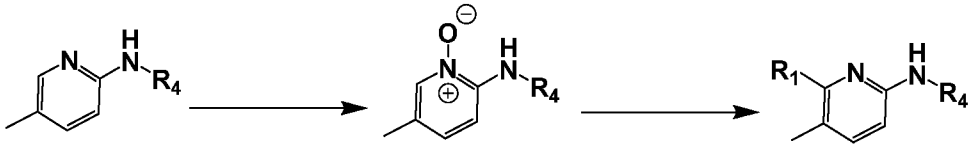
(IVc) (IV)

and R_2 may be any halogen, amino group which is optionally protected or amide group of formula (C).



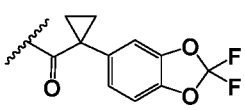
(C)

In another aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of halogenating 2-aminopyridine of formula (VI) through N-oxide formation to obtain 6-halo pyridine-2-amine of formula (VII) as depicted below, wherein R_1 is a halogen.



(VI) (VII)

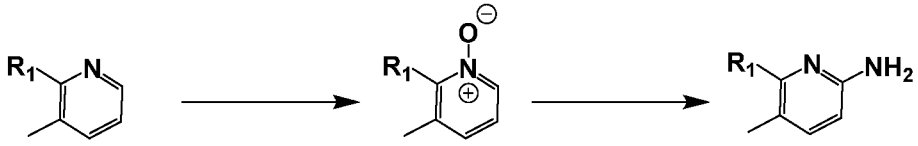
and R_4 is selected from hydrogen, a amine protecting group or a group of formula (B)



(B)

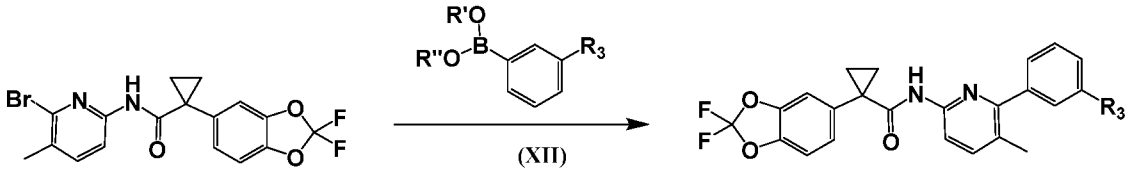
In another aspect, the present application provides a process for the

preparation of Lumacaftor, comprising the step of amination of 3-methylpyridine of formula (VIII) through N-oxide formation to obtain 5-methyl pyridine-2-amine of formula (IX) as depicted below, wherein R_1 is any leaving group such as halogen.



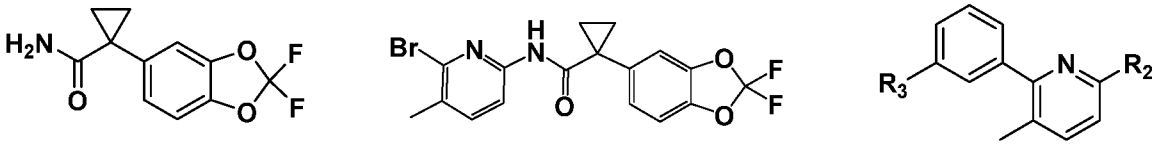
(VIII) (IX)

In another aspect, the present application provides an improved process for the preparation of Lumacaftor of formula or ester thereof, comprising the step of reacting N-(6-bromo pyridin-2-yl) cyclopropyl carboxamide of formula (XI) with borolanyl benzene of formula (XII) or its derivatives thereof; wherein **R_3** is same as defined above and **R'** and **R"** may be same or different selected from hydrogen, alkyl, aryl or both together form a ring with **C2** to C 6 aliphatic chain.



(XT) (XII)

In another aspect, the present application provides novel and alternative intermediates of formula (III), (XI) and (IVa) useful in the preparation of Lumacaftor, its esters or salts thereof, wherein **R_2** is leaving group such as halogen and **R_3** is hydrogen or a group selected from cyano, carboxylic acid or carboxylic ester.

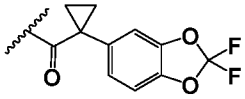


(III) (XI) (IVa)

In another aspect, the present application provides N-oxides of intermediates of formula (VI) and (VIII) useful in the preparation of Lumacaftor, its esters or salts thereof,

wherein **R_1** is any leaving group such as halogen and **R_4** is selected from

hydrogen or a group of formula (B)



(B)

In another aspect, the present application provides a hydrobromide salt of Lumacaftor.

In another aspect, the present application provides a process for the preparation of hydrobromide salt of Lumcaftor comprising the step of contacting hydrobromic acid with Lumacaftor.

In another aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of converting hydrobromide salt of Lumcaftor to its free form.

In another aspect, the present application provides a pharmaceutical composition comprising salts of Lumacaftor with hydrobromic acid.

In another aspect, the present application provides a process for the preparation of Lumacaftor or salts thereof, comprising the step of reacting 3-boronobenzoic acid or a derivative thereof with N-(6-halo-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropanecarboxamide in presence of an inert solvent selected from the group comprising of water, dimethylformamide, dimethoxyethane, 1,4-dioxane, 2-propanol, n-butanol, 2-butanol, tert. Butanol or mixtures thereof.

In another aspect, the present application provides a crystalline form SV1 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 6.52, 9.30, 10.45, 10.73, 11.88, 17.19, 19.46, 20.28 and 24.7 ±0.2° 2Θ. In an embodiment, the application provides crystalline form SV1 of Lumacaftor, characterized by a PXRD pattern having one or more additional peaks at about, 8.88, 11.10, 16.08, 16.63, 16.85, 17.82, 18.73, 19.79 and 21.54 ±0.2° 2Θ.

In another aspect, the present application provides a crystalline form SV2 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 9.67, 10.74, 11.32, 13.85, 19.25, 20.34, 26.47 and 27.25 ±0.2° 2Θ. In an embodiment, the application provides crystalline form SV2 of Lumacaftor, characterized by a PXRD pattern having one or more additional peaks at about 16.45, 17.84, 18.77, 21.64 and 22.43 ±0.2° 2Θ.

In another aspect, the present application provides a crystalline form SV3

of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 6.13, 12.19, 12.83, 17.08, 22.78, 24.20, 25.47, 26.39 and 28.02 ±0.2° 2Θ. In an embodiment, the application provides crystalline form SV3 of Lumacaftor, characterized by a PXRD pattern having one or more additional peaks at about 14.87, 15.22, 16.53, 17.85, 18.43, 19.68, 20.44, 21.56 and 22.10 ±0.2° 2Θ.

In another aspect, the present application provides a crystalline form SV4 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 9.39, 12.91, 14.23, 15.98, 23.69, 27.12 and 27.95 ±0.2° 2Θ. In an embodiment, the application provides crystalline form SV4 of Lumacaftor, characterized by a PXRD pattern having one or more additional peaks at about 7.80, 15.58, 18.71 and 21.6 ±0.2° 2Θ.

In another aspect, the present application provides a process for the preparation of crystalline form SV1 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 6.52, 9.30, 10.45, 10.73, 11.88, 17.19, 19.46, 20.28 and 24.7 ±0.2° 2Θ comprising the step of crystallizing Lumacaftor form SV1 from the solution comprising Lumacaftor and 1,4-dioxane.

In another aspect, the present application provides a process for the preparation of crystalline form SV2 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 9.67, 10.74, 11.32, 13.85, 19.25, 20.34, 26.47 and 27.25 ±0.2° 2Θ, comprising the step of drying crystalline form SV1 of Lumacaftor.

In another aspect, the present application provides a process for the preparation of crystalline form SV3 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 6.13, 12.19, 12.83, 17.08, 22.78, 24.20, 25.47, 26.39 and 28.02 ±0.2° 2Θ, comprising the step of treating Lumacaftor with solvent or solvent mixture comprising acetic acid.

In another aspect, the present application provides a process for the preparation of crystalline form SV3 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 6.13, 12.19, 12.83, 17.08, 22.78, 24.20, 25.47, 26.39 and 28.02 ±0.2° 2Θ, comprising the step of suspending Lumacaftor in a solvent selected from the group comprising of nitromethane, 1,2-dimethoxy ethane and hexane.

In another aspect, the present application provides a process for the preparation of crystalline form SV4 of Lumacaftor, characterized by a PXRD

pattern comprising the peaks at about 9.39, 12.91 , 14.23, 15.98, 23.69, 27. 12 and 27.95 ±0.2° 2Θ, comprising the step of crystallizing Lumacaftor from solvent or mixture of solvents comprising 1,2-dimethoxy ethane.

In another aspect, the present application provides a process of converting crystalline form SV1 of Lumacaftor to crystalline form SV3 of Lumacaftor.

In another aspect, the present application provides a process for the preparation of crystalline form SV1 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 6.52, 9.30, 10.45, 10.73, 11.88, 17.1 9, 19.46, 20.28 and 24.7 ±0.2° 2Θ comprising the step of treating Lumacaftor with 1,4-dioxane or a mixture thereof.

In another aspect, the present application provides a pharmaceutical composition comprising crystalline Form of Lumacaftor selected from the group comprising form SV1 , form SV2, form SV3, form SV4 or mixtures thereof together with atleast one pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is an illustrative X-ray powder diffraction pattern of crystalline Form SV1 of Lumacaftor prepared by the method of Example-31 .

Figure 2 is an illustrative X-ray powder diffraction pattern of crystalline Form SV2 of Lumacaftor prepared by the method of Example-32.

Figure 3 is an illustrative X-ray powder diffraction pattern of crystalline Form SV3 of Lumacaftor prepared by the method of Example-35.

Figure 4 is an illustrative X-ray powder diffraction pattern of crystalline Form SV4 of Lumacaftor prepared by the method of Example-37.

Figure 5 is an illustrative X-ray powder diffraction pattern of crystalline Form SV3 of Lumacaftor prepared by the method of Example-38.

Figure 6 is an illustrative X-ray powder diffraction pattern of crystalline Form SV1 of Lumacaftor prepared by the method of Example-39.

Figure 7 is an illustrative X-ray powder diffraction pattern of crystalline Form SV1 of Lumacaftor prepared by the method of Example-40.

Figure 8 is an illustrative X-ray powder diffraction pattern of crystalline Form SV2 of Lumacaftor prepared by the method of Example-41 .

Figure 9 is an illustrative PXRD pattern of hydrobromic acid salt of Lumacaftor prepared by the method of example No 30.

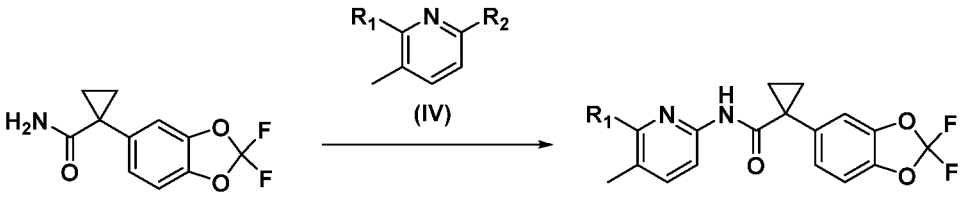
Figure 10 is an illustrative DSC thermogram of hydrobromic acid salt of Lumacaftor prepared by the method of example No 30.

Figure 11 is an illustrative PXRD pattern of Lumacaftor prepared by the method of example 20.

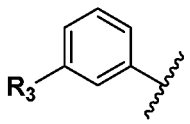
Figure 12 is an illustrative DSC thermogram of Lumacaftor prepared by the method of example No 20.

DETAILED DESCRIPTION

In an aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of reacting the cyclopropyl carboxamide of formula (III) with 3-methylpyridine of formula (IV) to obtain 5-methylpyridin-2-amine of formula (V).



wherein R_1 is selected from hydrogen, any leaving group such as halogen or a phenyl group of formula (A);



(A)

R_2 is any leaving group such as halogen and R_3 is hydrogen or a group selected from cyano, carboxylic acid or carboxylic ester.

In an embodiment, the reaction of cyclopropyl carboxamide of formula (III) with 3-methylpyridine of formula (IV) may be carried out in the presence of a catalyst. Catalyst are those which can facilitate C-N bond-forming such as palladium catalysts in the presence of a ligand and palladium catalyst may include, but not limited to Palladium acetate $[Pd(OAc)_2]$ Tris(dibenzylideneacetone) dipalladium (O)-chloroform adduct $[Pd_2(dba)_3.$ CHCl3] Dichloro-[1 ,1-bis(diphenylphosphino) ferrocene]palladium(ll) $(Pd(dppf)Cl_2)$, Allylpalladium(ll) chloride dimer $[(allyl)PdCl]_2$ or the like.

In an embodiment, the reaction of cyclopropyl carboxamide of formula (III)

with 3-methylpyridine of formula (IV) may be carried out in the presence of a ligand such as Xantphos (X-phos), BrettPhos, DavePhos or the like. In an embodiment, the reaction may be carried out according to a copper-catalyzed method such as in the presence of a combination of copper iodide and N,N'-dimethyl ethylenediamine.

In an embodiment, the reaction of cyclopropyl carboxamide of formula (III) with 3-methylpyridine of formula (IV) may be carried out under suitable coupling conditions known in the art such as Buchwald et al, (Org. Lett., 2000, 2 (8), pp 1101-1 104 and Org. Lett., 2003, 5 (20), pp 3667-3669)

In an embodiment, the reaction may be carried out between cyclopropyl carboxamide of formula (III) and 3-methylpyridine of formula (IV), wherein R_2 is a leaving group such as halogen like Chlorine, Bromine, Iodine; O-triflates; sulphonate or the like.

In an embodiment, the reaction of cyclopropyl carboxamide of formula (III) with 3-methylpyridine of formula (IV) may be carried out in a mole ratio of cyclopropyl carboxamide of formula (III) to 3-methylpyridine of formula (IV) of 1: 0.5 to 0.5: 1.

In an embodiment, the reaction of cyclopropyl carboxamide of formula (III) with 3-methylpyridine of formula (IV) may be carried out in the presence of a base. Base may include but not limited to an organic base such as organic amines, alkoxides or an inorganic base such as carbonates, bicarbonates, alkoxides and hydroxides. In an embodiment, the reaction may be carried out in the presence of Cesium carbonate, potassium carbonate or sodium tert butoxide.

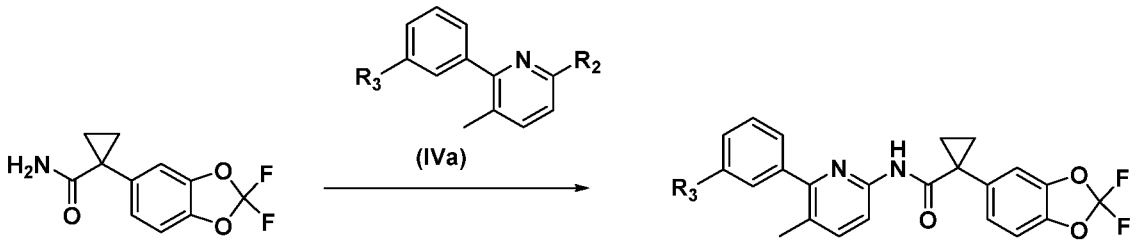
In an embodiment, the reaction of cyclopropyl carboxamide of formula (III) with 3-methylpyridine of formula (IV) may be carried out in the presence of a suitable solvent or mixture of solvents. Suitable solvents may include but not limited to tert-butanol, dioxane, tetrahydrofuran, toluene, 2-propanol, n-butanol or the like.

In an embodiment, the reaction of cyclopropyl carboxamide of formula (III) with 3-methylpyridine of formula (IV) may be carried out at suitable temperature of about 50°C and above for atleast 10 hours and more. In an embodiment, the reaction of cyclopropyl carboxamide of formula (III) with 3-methylpyridine of formula (IV) may be carried out at 80°C to 120°C for atleast 15 hours or more.

In alternate embodiments, the reaction conditions may be altered

depending on the other parameters used.

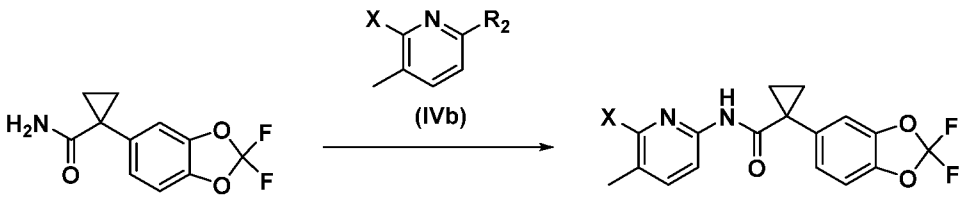
In an embodiment, when R_1 is a phenyl group of formula (A), the process for the preparation of Lumacaftor or a ester thereof, comprising the step of reacting the cyclopropyl carboxamide of formula (III) with 3-methylpyridine of formula (IVa) to afford Lumacaftor intermediate of formula (Va), wherein R_3 is selected from hydrogen or a group selected from cyano, carboxylic acid or carboxylic ester.



(III) (IVa) (Va)

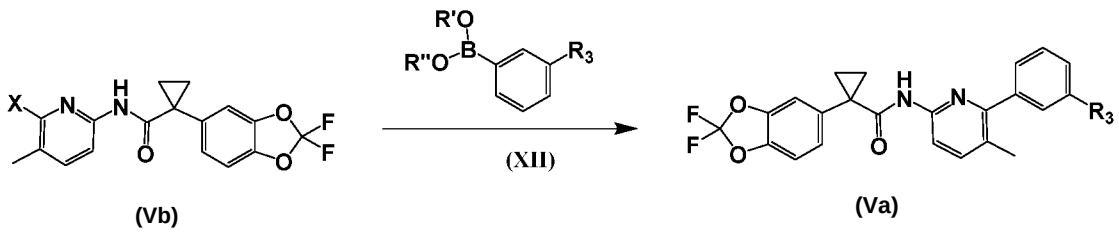
In an embodiment, when R_1 is any leaving group such as halogen, the process for the preparation of Lumacaftor comprising the steps of:

a) reacting the cyclopropyl carboxamide of formula (III) with 3-methylpyridine of formula (IVb) to afford Lumacaftor intermediate of formula (Vb), wherein X is any leaving group such as halogen;



(III) (IVb) (Vb)

b) reacting intermediate of formula (Vb) with borolanyl benzene of formula (XII) or its derivatives thereof; wherein R3 is selected from hydrogen or a group selected from cyano, carboxylic acid or carboxylic ester and R' and R" may be same or different selected from hydrogen, alkyl, aryl or both together form a ring with C2 to C6 aliphatic chain.

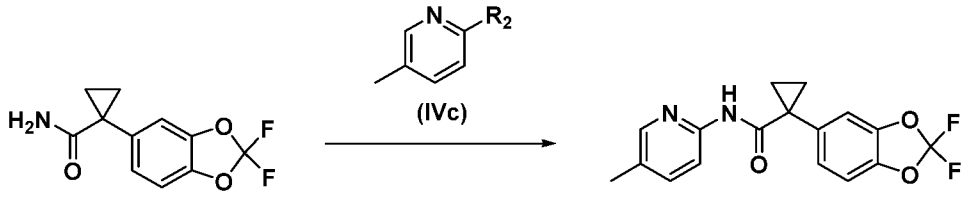


(Vb) (XII) (Va)

In an embodiment, when R_1 is hydrogen, the process for the preparation of

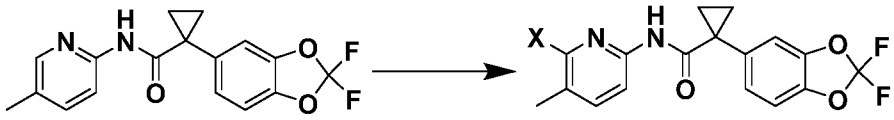
Lumacaftor comprising the steps of:

a) reacting the cyclopropyl carboxamide of formula (III) with 3-methylpyridine of formula (IVc) to afford Lumacaftor intermediate of formula (Vc);



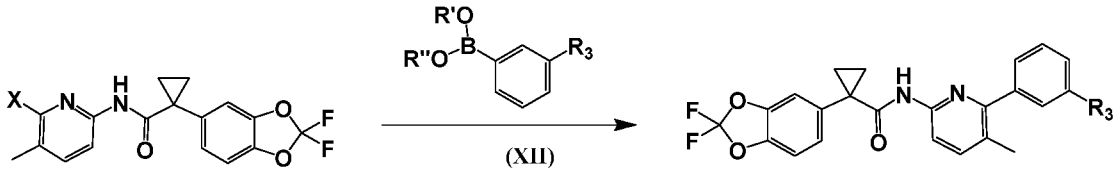
(III) (IVc) (Vc)

b) halogenating intermediate of formula (Vc) to obtain intermediate of formula (Vb)



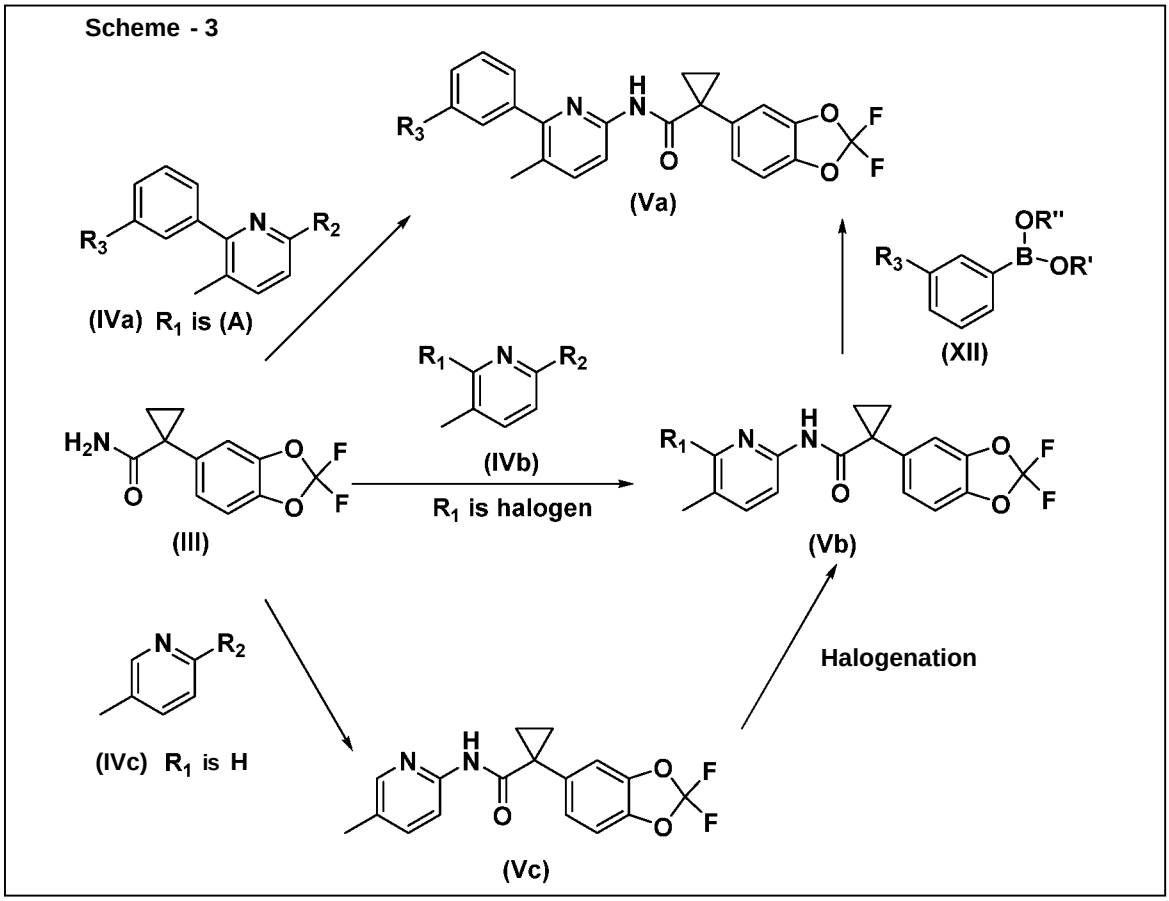
(Vc) (Vb)

c) reacting intermediate of formula (Vb) with borolanyl benzene of formula (XII) or its derivative thereof to afford compound of formula (Va); wherein R_3, R' and R" are same as defined above.



(Vb) (XII) (Va)

The process of this aspect may be schematically depicted by scheme -3 as below.



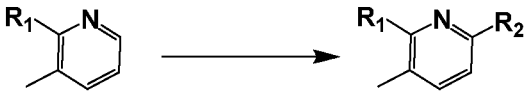
In an embodiment, when R_3 is other than carboxylic acid the process further comprises the step of converting intermediate of formula (Va) to Lumacaftor, its ester or salts thereof according to methods known in the art or procedures described or exemplified in the instant application.

In an embodiment, the esters of Lumacaftor may be hydrolyzed according to suitable conditions known in the art or according to methods or procedures described or exemplified in the instant applications. In an embodiment, ester of Lumacaftor may be hydrolyzed under acidic, neutral or basic conditions.

The starting materials of this aspect, compound of formula (III) and compound of formula (IV) may be prepared in different methods. However, certain alternative methods to prepare these starting materials will be explained in detail with reference to the following, which are provided only for purposes of illustration and should not be construed as limiting the scope of the application in any manner. Variations of the described procedures, as will be apparent to those skilled in the art, are intended to be within the scope of the present application.

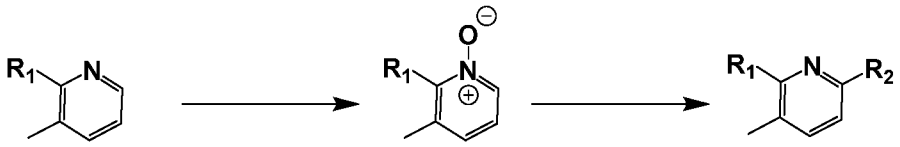
In an embodiment, 3-methylpyridine of formula (IV) may be prepared employing a process comprising the step of halogenating 3-methylpyridine of

formula (VIII) to obtain 2-halo 3-methylpyridine of formula (IV), wherein R_1, R_2 and R_3 are same as defined above.



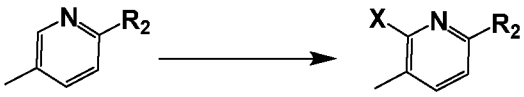
(VIM) (IV)

In an embodiment, 3-methylpyridine of formula (IV) may be prepared employing a process comprising the step of halogenating 3-methylpyridine of formula (VIII) through N-oxide formation as depicted below, wherein R_1, R_2 and R_3 are same as defined above.



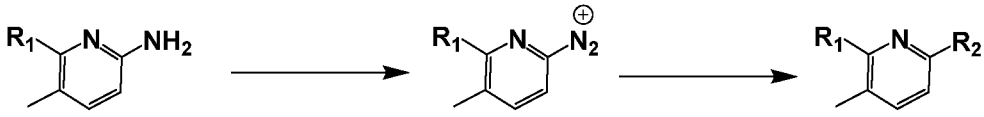
(VIM) (IV)

In an embodiment, obtain 3-methylpyridine of formula (IV) may be also prepared employing a process comprising the step of halogenating 3-methylpyridine of formula (IVc) as depicted below; wherein X is any halogen and R_2 may be any leaving group such as halogen.



(IVc) (IV)

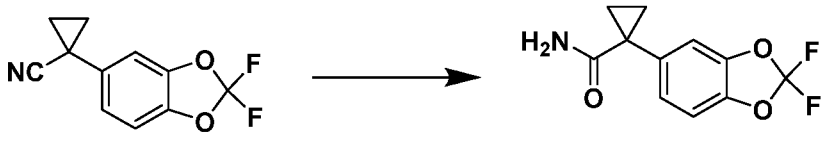
In an embodiment, 3-methylpyridine of formula (IV) may be also prepared employing a process comprising the step of halogenation through diazotization of 5-methylpyridin-2-amine of formula (IX) as depicted below; wherein R_1 and R_2 are same as defined above.



(IX) (IV)

Alternatively, 3-methylpyridine of formula (IV) may be prepared according to any method known in the art or procedures described in any aspect or exemplified in the present application.

In an embodiment, cyclopropyl carboxamide of formula (III) may be prepared employing a process comprising the step of hydrolysis of cyclopropyl nitrile of formula (XIII) to corresponding amide as depicted below.



(XIII) (III)

Inventors of the instant application have surprisingly found that the partial hydrolysis of the cyclopropyl nitrile of formula (XIII) is advantageous over prior art methods. Prior art methods are tedious, time consuming, low yielding, multi-step synthesis as against to instant single step synthesis of this amide in a short, simple and economic approach.

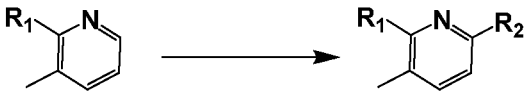
In an embodiment, cyclopropyl nitrile of formula (XIII) may be hydrolyzed to corresponding amide either in the presence of an acid or a base catalyst.

Suitable acid catalyst may include, but not limited to hydrogen halides such as HCl, HBr, HI; sulphuric acid, phosphoric acid, nitric acid or the like and a suitbale base catalyst may include, but not limited to hydroxides such as NaOH, KOH, $Mg(OH)_2$,$Ca(OH)_2$ or the like; alkoxides such as methoxides, ethoxides, t-butoxides or the like ; carbonates such as $NaC0_3$, $KC0_3$ or the like.

In an embodiment, hydrolysis of cyclopropyl nitrile of formula (XIII) may be carried out in the presence of an inert solvent which include, but not limited to alcohols such as tert-butanol or the like; ketones such as methyl tert-butyl ketone or the like and hydrocarbons such as toluene or the like.

Alternatively, cyclopropyl carboxamide of formula (III) may be prepared according to any method known in the art or procedures described in any aspect or exemplified in the present application.

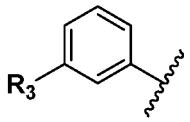
In another aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of halogenating 3-methylpyridine of formula (VIII) to obtain 2-halo 3-methylpyridine of formula (IV),



(VIM) (IV)

wherein R_1 is, hydrogen, any leaving group such as halogen or a phenyl group of

formula (A);



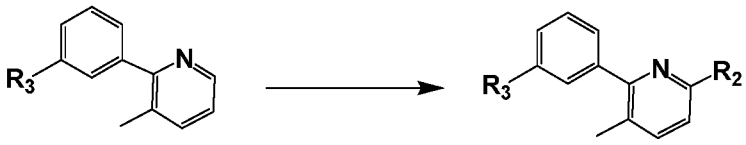
(A)

R_2 is any halogen and R_3 is hydrogen or a group selected from cyano, carboxylic acid or carboxylic ester.

In an embodiment, halogenating 3-methylpyridine of formula (VIII) may be carried out under suitable conditions known in the art. In an embodiment, halogenation may be carried out by reacting 3-methylpyridine of formula (VIII) with halogen source such as chlorine ($Cl_{2)}$, Bromine ($Br_{2)}$, Iodine (I_2) in the presence of suitable catalyst that include, but not limited to n-Bu Li / di Isopropyl amine; n-Bu Li / dimethyl amino ethanol; $PdCl_2$ /CCl_4 or the like.

In an embodiment, halogenation may be carried out by reacting 3-methylpyridine of formula (VIII) in an inert atmosphere at suitable temperature of about 0°C or below, optionally the presence of an inert solvent such as hexane or the like.

In an embodiment, when R_1 is a phenyl group of formula (A), 3-methylpyridine of formula (IVa), may be prepared following a process comprising the steps of halogenating 3-methylpyridine of formula (Villa) as depicted below.

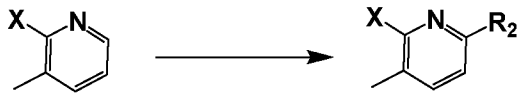


(Villa) (IVa)

In an embodiment, the process further comprises the step of converting 3-methylpyridine of formula (IVa) to Lumacaftor, salt or an ester thereof.

In an embodiment, 3-methylpyridine of formula (IVa) may be reacted with cyclopropyl carboxamide of formula (III) according to conditions or methods described at any aspect or exemplified in the instant application.

In an embodiment, when R_1 is any leaving group (X) such as halogen, 3-methylpyridine of formula (IVb), may be prepared following a process comprising the steps of halogenating 3-methylpyridine of formula (Vlllb) as depicted below.

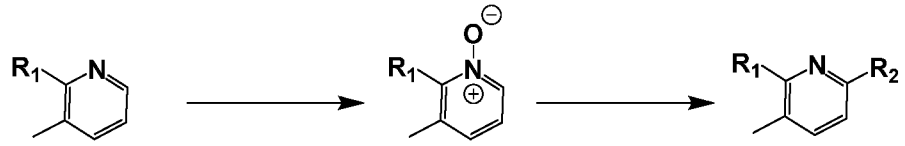


(VIIIb) (IVb)

In an embodiment, the process further comprises the step of converting 2-halo 3-methylpyridine of formula (IV) to Lumacaftor. 2-halo 3-methylpyridine of formula (IV) obtained by the process of this aspect may be isolated or taken directly to the next step for the preparation of Lumacaftor.

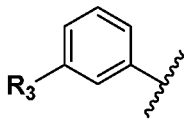
In an embodiment, 2-halo 3-methylpyridine of formula (IV) may be converted to Lumacaftor according to any of the methods known in the art or procedures described at any aspect or exemplified in the instant application.

In another aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of halogenating 3-methylpyridine of formula (VIII) through N-oxide formation to obtain 2-halo 3-methylpyridine of formula (IV),



(VIM) (IV)

wherein R_1 is any leaving group such as halogen or a phenyl group of formula (A);



(A)

R_2 is any halogen and R_3 is hydrogen or a group selected from cyano, carboxylic acid or carboxylic ester.

In an embodiment, halogenation of 3-methylpyridine of formula (VIII) may be carried out through the formation of corresponding N-oxide followed by its halogenation. In an embodiment, the N-oxide may be either isolated or continued for the halogenation directly without isolating it.

In an embodiment, formation of N-oxide of 3-methylpyridine of formula (VIII) may be carried out in the presence of an oxidation agent including, but not limited to peroxides or per acids such as hydrogen peroxide, per acetic acid

perphtalic acids (magnesium- monoperphtalate (MMPP)), performic acid, pertrifuoricacetic acid, peroxymonosulfuric acid, bromate, metal oxidants such as chromic acid and permanganate, perphosphoric acid, permaleinic acid, urea-hydrogen peroxide (UHP), urea-hydrogen peroxide / phthalic anhydride , m-chloro Perbenzoic acid (m-CPBA) or the like.

In an embodiment, N-oxide formation may be carried out in a mole ratio of 3-methylpyridine of formula (VIII) to oxidation agent of 2:1 to 1:2.

In an embodiment, N-oxide formation may be carried out at suitable temperature of about 30°C and above for sufficient time of atleast 30 minutes or more.

In an embodiment, N-oxide formation may be carried out according to conditions known in the art or methods described at any aspect or exemplified in the instant application.

N-oxide obtained according to the process of this aspect may be halogenated using suitable halogen source which may include but not limited to phosphorus oxyhalide such as POCl3, $POBr_3$; thionyl halides such as SOCl2; Oxalyl halides such as $(COCl)_2$.

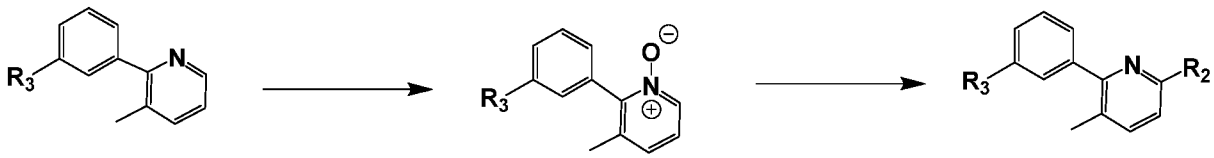
In an embodiment, halogenation of N-oxide may be carried out in a mole ratio of 3-methylpyridine of formula (VIII) to halogen source of 1:1 to 1:2.

In an embodiment, halogenation of N-oxide may be carried out in the presence of a base such as triethyl amine, diisopropyl amine, diisopropyl ethyl amine or the like.

In an embodiment, halogenation of N-oxide may be carried out in the presence of an inert solvent such as halogenated hydrocarbons such dichloromethane.

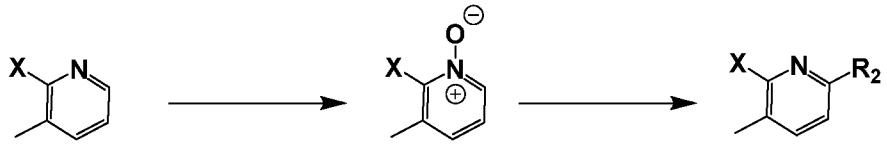
In an embodiment, halogenation of N-oxide may be carried out at suitable temperature of about 30°C and above for sufficient time of atleast 30 minutes or more.

In an embodiment, when R_1 is a phenyl group of formula (A), 3-methylpyridine of formula (IVa), may be prepared following a process comprising the steps of halogenating 3-methylpyridine of formula (Villa) as depicted below.



(VIIIa) (IVa)

In an embodiment, when R_1 is any leaving group (X) such as halogen, 3-methylpyridine of formula (IVb), may be prepared following a process comprising the steps of halogenating 3-methylpyridine of formula (VIIIb) as depicted below.

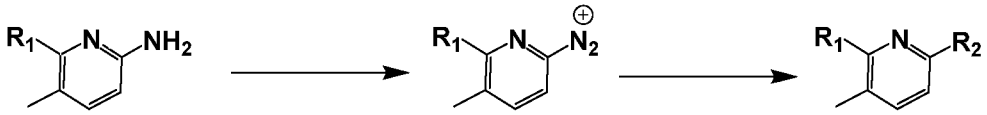


(VIIIb) (IVb)

In an embodiment, the process further comprises the step of converting 2-halo 3-methylpyridine of formula (IV) to Lumacaftor. 2-halo 3-methylpyridine of formula (IV) obtained by the process of this aspect may be isolated or taken directly to the next step for the preparation of Lumacaftor.

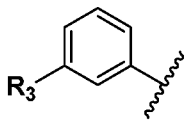
In an embodiment, 2-halo 3-methylpyridine of formula (IV) may be converted to Lumacaftor according to any of the methods known in the art or procedures described at any aspect or exemplified in the instant application.

In another aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of diazotization of 5-methylpyridin-2-amine of formula (IX) as depicted below;



(IX) (IV)

wherein R_1 is hydrogen, any leaving group such as halogen or a phenyl group of formula (A);



(A)

R_2 is any halogen and R_3 is hydrogen or a group selected from cyano, carboxylic acid or carboxylic ester.

In an embodiment, diazotization of 5-methylpyridin-2-amine of formula (IX) may be carried out using nitrites including, but not limited to sodium nitrite or other nitrites such as methyl nitrite, nitrosyl chloride or the like to obtain corresponding diazo derivative. In an embodiment, diazo derivative is prepared insitu and taken directly for the halogenation step.

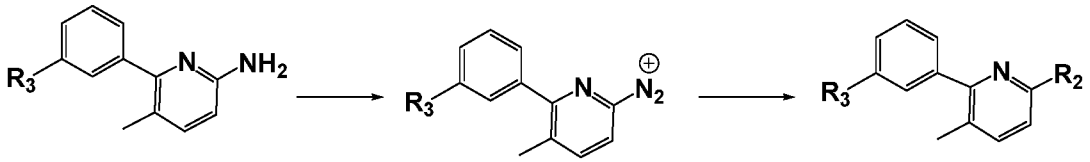
Diazotization of 5-methylpyridin-2-amine of formula (IX) may be carried out under conditions known in the art or procedures described or exemplified in the instant application. Diazotization may be carried out at suitable temperature of about 0°C or below.

The diazo derivative obtain above may be treated with the halogenating agent with its isolation. In an embodiment, the diazotization may be carried out in the presence of halogenating agent. Suitable halogenating agents may include, but not limited to Hydrogen halides such as HCl, HBr, HI; Br_2, I2, Cl_2 or the like.

In an embodiment, halogenation of diazo derivative may be carried out in the presence of an acid such as sulphuric acid or a hydrogen halide either in concentrated or diluted form.

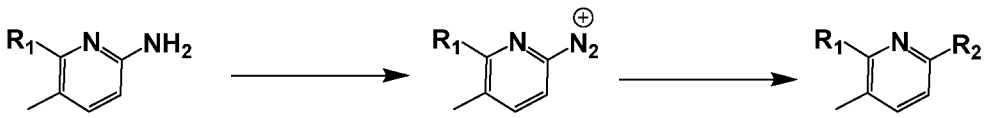
Diazotization and / or halogenation of 5-methylpyridin-2-amine of formula (IX) may be carried out under conditions known in the art or procedures described or exemplified in the instant application. In an embodiment, the process of this aspect may be carried out at suitable temperature of about 0°C or below, preferably at a temperature between -10°C and -30°C.

In an embodiment, 3-methylpyridine of formula (IVa) may be prepared employing a process comprising the step of diazotization of 5-methylpyridin-2-amine of formula (IXa) as depicted below.



(IXa) **(IVa)**

In an embodiment, 3-methylpyridine of formula (IVb) may be prepared employing a process comprising the step of diazotization of 5-methylpyridin-2-amine of formula (IXb) as depicted below.

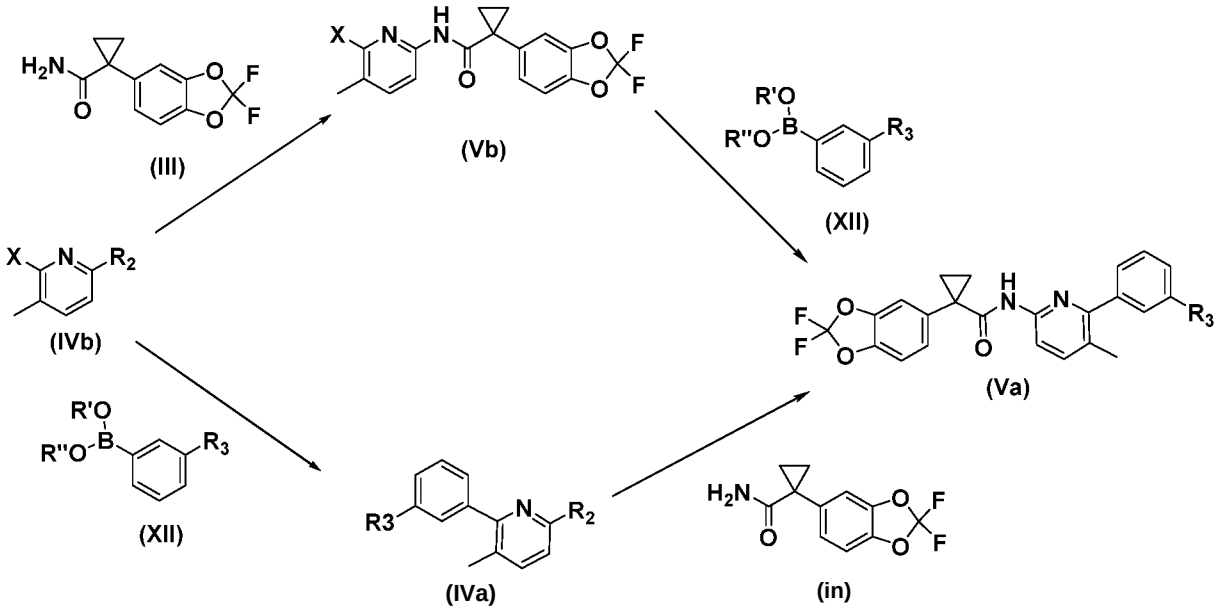


(IXb) (IVb)

In an embodiment, the process further comprises the step of converting 2-halo 3-methylpyridine of formula (IV) to Lumacaftor. 2-halo 3-methylpyridine of formula (IV) obtained by the process of this aspect may be isolated or taken directly to the next step for the preparation of Lumacaftor.

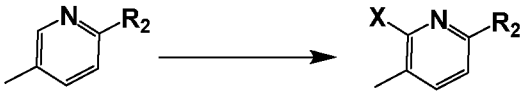
In an embodiment, the processes for the preparation of 3-methylpyridine of formula (IVa) in any of the aspects further comprises the step of converting 3-methylpyridine of formula (IVa) to Lumacaftor, salt or an ester thereof. In an embodiment, 3-methylpyridine of formula (IVa) may be reacted with cyclopropyl carboxamide of formula (III) according to conditions or methods described at any aspect or exemplified in the instant application.

In an embodiment, the processes for the preparation of 3-methylpyridine of formula (IVb) in any of the aspects further comprises the step of converting 3-methylpyridine of formula (IVb) to Lumacaftor, salt or an ester thereof. In an embodiment, 3-methylpyridine of formula (IVb) may be reacted with cyclopropyl carboxamide of formula (III) or with borolanyl benzene of formula (XII) or its derivative thereof according to methods known in the art or procedures described at any aspect or exemplified in the instant application as depicted below.



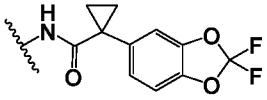
In an embodiment, 2-halo 3-methylpyridine of formula (IV) may be converted to Lumacaftor according to any of the methods known in the art or procedures described at any aspect or exemplified in the instant application.

In another aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of halogenating 3-methylpyridine of formula (IVc) to obtain 2-halo 3-methylpyridine of formula (IV),



(IVc) (IV)

wherein X is any halogen and R_2 may be any halogen, amino group which is optionally protected or amide group of formula (C).

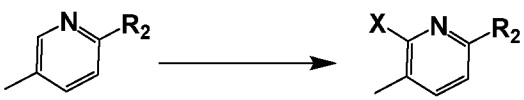


(C)

In an embodiment, halogenating 3-methylpyridine of formula (IVc) may be carried out under suitable conditions known in the art. In an embodiment, halogenation may be carried out by reacting 3-methylpyridine of formula (IVc) with halogen source such as chlorine (Cl_2), Bromine (Br_2), Iodine (I_2) in the presence of suitable catalyst that include, but not limited to n-Bu Li / di Isopropyl amine; n-Bu Li / dimethyl amino ethanol; $PdCl_2$ /CCl_4 or the like.

In an embodiment, halogenation may be carried out by reacting 3-methylpyridine of formula (IVc) in an inert atmosphere at suitable temperature of about 0°C or below, optionally the presence of an inert solvent such as hexane or the like.

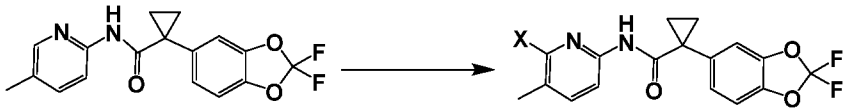
In an embodiment, when R_2 is halogen, 3-methylpyridine of formula (IVb), may be obtained following a process comprising the step of halogenating 3-methylpyridine of formula (IVc) as depicted below.



(IVc) (IVb)

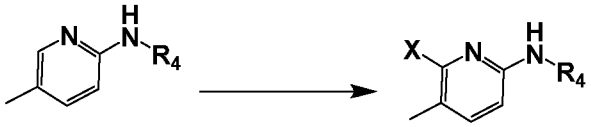
In an embodiment, when R_2 is amide group of formula (C), 3-methylpyridine of formula (Vb) may be obtained following a process comprising the step of

halogenating 3-methylpyridine of formula (Vc) as depicted below.



(Vc) (Vb)

In an embodiment, when R_2 is amino group which is optionally protected, 3-methylpyridine of formula (VIIb) may be obtained following a process comprising the step of halogenating 3-methylpyridine of formula (Vlb) as depicted below; wherein R_4 is hydrogen or amine protecting group.

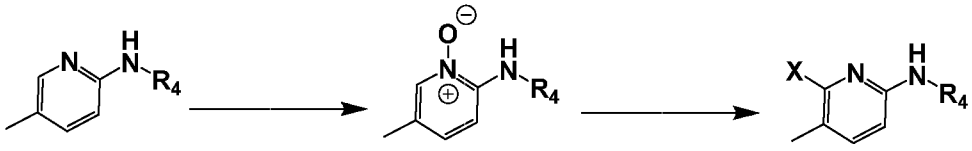


<Vlb > (VIIb)

In an embodiment, the process further comprises the step of converting 2-halo 3-methylpyridine of formula (IV) of this aspect to Lumacaftor. 2-halo 3-methylpyridine of formula (IV) obtained by the process of this aspect may be isolated or taken directly to the next step for the preparation of Lumacaftor.

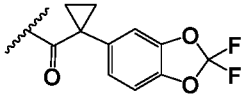
In an embodiment, 2-halo 3-methylpyridine of formula (IV) may be converted to Lumacaftor according to any of the methods known in the art or procedures described at any aspect or exemplified in the instant application.

In another aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of halogenating 2-aminopyridine of formula (VI) to obtain 6-halo pyridine-2-amine of formula (VII),



(VI) (vii)

wherein R_4 is selected from hydrogen, a amine protecting group or group B and X is a halogen.

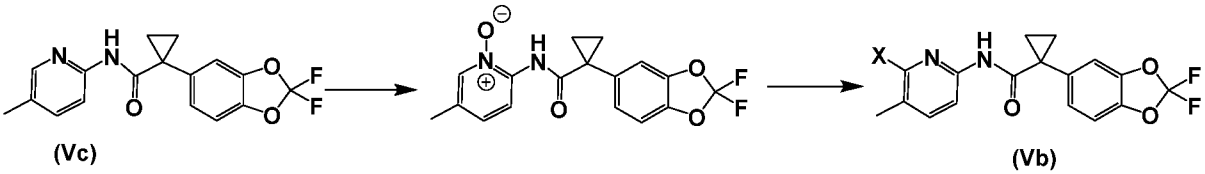


(B)

In an embodiment, halogenation of 3-methylpyridine of formula (VI) may be carried out through the formation of corresponding N-oxide followed by its halogenation. In an embodiment, the N-oxide may be either isolated or continued for the halogenation directly without isolating it.

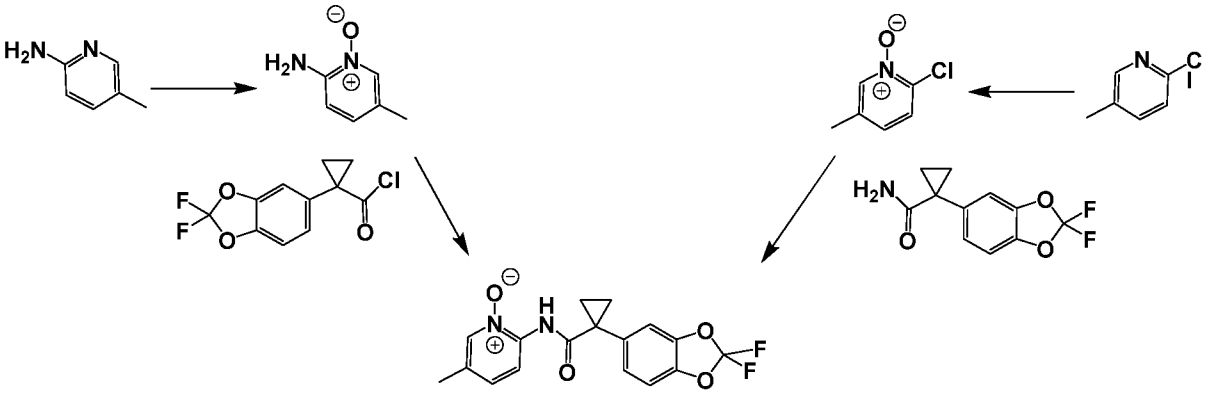
In an embodiment, the N-oxide formation and subsequent halogenation may be carried out according to previous aspects for the preparation of 3-methylpyridine of formula (IV).

In an embodiment, when R_4 is group (B), halogenation of 2-aminopyridine of formula (Vc) to obtain 6-halo pyridine-2-amine of formula (Vb), may be carried out as depicted below, wherein X is a halogen.



(Vc) (Vb)

In an alternate embodiment, the N-oxide of 2-aminopyridine of formula (Vc) may be prepared as depicted below according any methods known in the art or procedures described in any aspect or exemplified in the instant application.

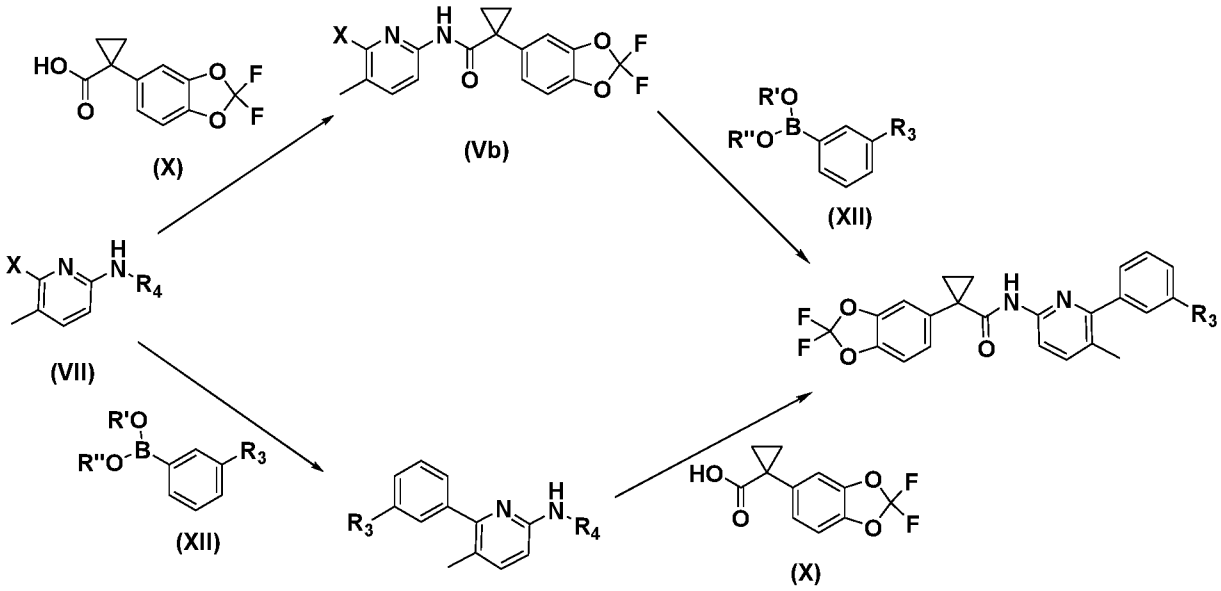


In an embodiment, when R_4 is hydrogen or an amino protecting group, halogenation of 2-aminopyridine of formula (VI) to obtain 6-halo pyridine-2-amine of formula (VII), may be carried out according to any method known in the art or procedures described in any aspect or exemplified in the present application.

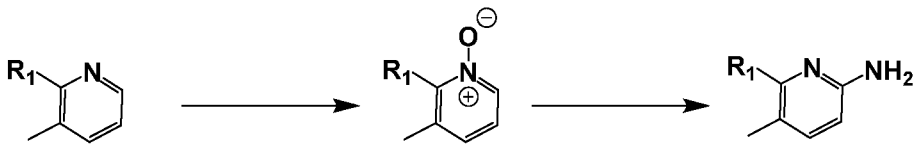
In an embodiment, the process for the preparation of 6-halo pyridines-amine of formula (VII) in any of the aspects further comprises the step of converting 6-halo pyridine-2-amine of formula (VII) to Lumacaftor, salt or ester

thereof. In an embodiment, 6-halo pyridine-2-amine of formula (VII) may be reacted with borolanyl benzene of formula (XII) or its derivative, wherein R', R'' and R_3 are same as defined in other aspects, according to any methods known in the art or procedures described at any aspect or exemplified in the instant application.

In an embodiment, 6-halo pyridine-2-amine of formula (VII) may be reacted with cyclopropyl carboxylic acid of formula (X), its derivatives or with borolanyl benzene of formula (XII) or its derivatives thereof as depicted below.



In another aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of amination of 3-methylpyridine of formula (VIII) through the formation of N-oxide to obtain 5-methyl pyridines-amine of formula (IX), wherein R_1 is any leaving group such as halogen.



(VIII) (IX)

In an embodiment, amination of 3-methylpyridine of formula (VIII) may be carried out through the formation of corresponding N-oxide followed by its amination. In an embodiment, the N-oxide may be either isolated or continued for the amination directly without isolating it.

In an embodiment, the N-oxide formation may be carried out according to

previous aspects for the preparation of 3-methylpyridine of formula (IV).

In an embodiment, amination of N-oxide of 3-methylpyridine of formula (VIII) may be carried out under suitable conditions for Chichibabin amination of pyridines known in the art such as in Lawin, Phillip B. et al (WO 9600216)

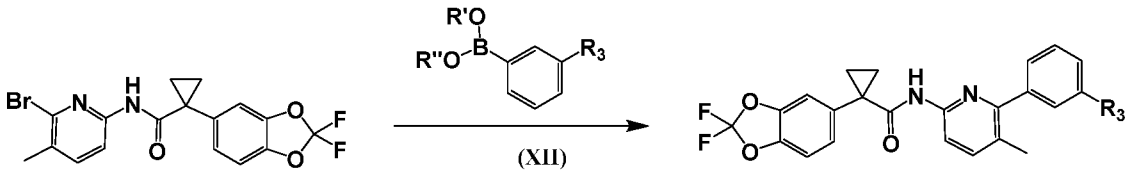
In an embodiment, amination of N-oxide may be carried out by reacting with a suitable amine compound which include, but not limited to ammonia; organic amines such as alkyl amines; such as methyl amine, ethyl amine, ethanol amine, propyl amine, propanol amine, butyl amine, butanol amine; aryl amines such as 4-tolyl amine; inorganic amines such as sodamide, potassamide or the like.

In an embodiment, the amination of N-oxide may be carried out in the presence of an inert solvent such as acetonitrile, toluene or the like.

In an embodiment, the amination of N-oxide may be carried out at suitable temperature of about 50°C and above for sufficient time for atleast 30 minutes.

In an embodiment, pyridine-2-amine of formula (IX) may be reacted with cyclopropyl carboxylic acid of formula (X), reactive derivatives thereof or with borolanyl benzene of formula (XII) or its derivative thereof according to methods known in the art or procedures described at any aspect or exemplified in the instant application.

In another aspect, the present application provides an improved process for the preparation of Lumacaftor or intermediate thereof, comprising the step of reacting N-(6-bromo pyridin-2-yl) cyclopropyl carboxamide of formula (XI) with borolanyl benzene of formula (XII) or its derivatives thereof; wherein R_3 is same as defined above and R' and R'' may be same or different selected from hydrogen, alkyl, aryl or both together form a ring with C_2 to C_6 aliphatic chain.



(XI)

N-(6-bromo 5-methyl pyridin-2-yl) cyclopropyl carboxamide of formula (XI) may be prepared according to any of the methods known in the art or procedures

described in any aspect or exemplified in the instant application. In an embodiment, the N-(6-bromo 5-methyl pyridin-2-yl) cyclopropyl carboxamide of formula (XI) may be optionally purified before using by any methods known in the art such as column chromatography, fractional distillation, recrystallization or the like, before using.

In an embodiment, the N-(6-bromo pyridin-2-yl) cyclopropyl carboxamide of formula (XI) may be reacted with borolanyl benzene of formula (XII) or its derivative thereof in the presence of suitable catalyst.

Catalyst may include but not limited to palladium catalyst such as palladium acetate ($Pd(OAc)_2$), Dichloro-[1 ,1-bis(diphenylphosphino) ferrocene]palladium(ll) ($Pd(dppf)Cl_2$), Tetrakis(triphenylphosphine)palladium (0) ($Pd(PPh_3)_4$) or the like.

In an embodiment, this coupling reaction may be carried out under Suzuki coupling conditions known in the art.

Inventors of the instant application have surprisingly found that this coupling step with bromo derivative of formula (XI) is furnished in a very fast and efficient manner without formation of undesired products and in good yield as compared to the coupling step using analogous chloro derivative as described in the art such as US 8993600 B2.

In an embodiment, mole ratio of N-(6-bromo 5-methyl pyridin-2-yl) cyclopropyl carboxamide of formula (XI) to borolanyl benzene of formula (XII) may vary from 0.5: 2 to 2:0.5

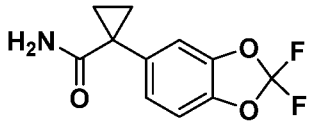
In an embodiment, the reaction may be carried out in the presence of an inert solvent including, but not limited to an aprotic solvent such as dimethyl formamide, dioxane, N-methyl pyrrolidone, dimethyl sulfoxide, toluene, acetonitrile, dimethyl acetamide, dichloromethane or the like.

In an embodiment, the reaction may be carried out at suitable temperature of about 0°C and above for sufficient time for atleast 15 minutes.

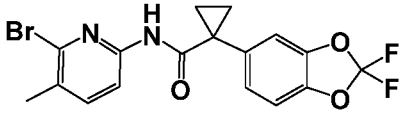
In an embodiment, when R_3 is other than carboxylic acid, the process further comprises the step converting the obtained intermediate to Lumacaftor , its esters or salt thereof under suitable condition known in the art or procedures described at any aspect or exemplified in the present application.

In another aspect, the present application provides novel and alternative intermediates of formula (III), (XI) and (IVa) useful in the preparation of

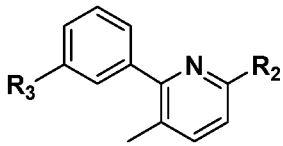
Lumacaftor, its esters or salts thereof, wherein R_2 is leaving group such as halogen and R_3 is hydrogen or a group selected from cyano, carboxylic acid or carboxylic ester.



(III)

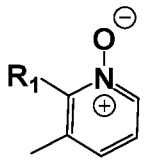


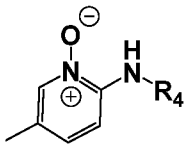
(XI)



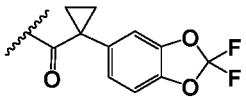
(IVa)

In another aspect, the present application provides N-oxides of intermediates of formula (VI) and (VIII) useful in the preparation of Lumacaftor, its esters or salts thereof,





wherein R_1 is any leaving group such as halogen and R_4 is selected from hydrogen or a group of formula (B)



(B)

Starting materials used in any aspect of the instant application may be obtained from either commercially available sources or prepared according to the methods known in the art. Starting materials used in any aspect of the instant application may be purified according to the methods known in the art such as recrystallization, acid - base treatment, chromatography, fractional distillation, slurrying or the like, before using.

Lumacaftor obtained according to any aspects of the instant patent application may be purified according to any of the methods known in the art recrystallization, acid - base treatment, chromatography or the like. Further, Lumacaftor may be dried under suitable drying conditions such as air drying or vacuum drying.

In an aspect, the present application provides a salt of Lumacaftor with hydrobromic acid.

In an embodiment, the salt of this aspect may contain Lumacaftor and the

hydrobromic acid in any stoichiometric ratio. In an embodiment, the salt may be in crystalline or an amorphous form. In preferred embodiment, the salt may be in crystalline form.

In another aspect, the present application provides a hydrobromic acid salt of Lumcaftor. In an embodiment, the hydrobromic acid salt is in crystalline form, characterized by a PXRD pattern of figure 9 and / or a DSC thermogram of figure 10.

In another aspect, the present application provides a process for the preparation of hydrobromic acid salt of Lumacaftor comprising the step of contacting hydrobromic acid with Lumacaftor.

In an embodiment Lumacaftor may be contacted with hydrobromic acid in a mole ratio of about 1: 0.8 to 1:1.6.

In an embodiment, Lumacaftor may be contacted with hydrobromic acid in a heterogeneous or homogenous phase. In an embodiment, Lumacaftor may be contacted with hydrobromic acid in homogeneous phase. In an embodiment, solution comprising Lumacaftor in an inert solvent may be contacted with hydrobromic acid.

In an embodiment, the hydrobromic acid may be used either in concentrated or diluted form before contacting with Lumacaftor.

In an embodiment, Lumacaftor may be contacted with hydrobromic acid at a suitable temperature at about 0°C and above for time sufficient for salt formation. In an embodiment, the reaction mixture comprising Lumacaftor and the hydrobromic acid may be stirred for sufficient time and at suitable temperature for the completion of salt formation.

In an embodiment, the reaction mixture comprising Lumacaftor and the acid may be concentrated and / or cooled to suitable temperature before isolating the salt of Lumcaftor.

In an embodiment, suitable anti-solvent may be added to the reaction mixture comprising Lumacaftor and hydrobromic acid before isolating the salt of Lumcaftor.

Isolation of salt of Lumacaftor may be carried out by any methods known in the art or procedures described in the present application. In an embodiment, salt of Lumacaftor may be isolated by employing any of the techniques, but not limited to: decantation, filtration by gravity or suction, centrifugation, adding solvent to make

slurry followed by filtration, or other techniques specific to the equipment used and the like, and optionally washing with a solvent.

In an embodiment, drying salt of Lumacaftor may be carried out at temperatures and times sufficient to achieve desired quality of product. Drying may be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to 10 hours or longer.

It is worth noting, that the option of purifying a low soluble drug substances among BCS class IV or class II like Lumacaftor, by conventional methods like recrystallization from a solvent or mixture of solvents may not be suitable due to the limited solvents. Therefore, purification of such drug substance through salt formation is a boon to a chemist. Lumacaftor may be purified through the formation of a suitable salt followed by its neutralization to free from.

Further, these salts may be optionally purified by any method known in the art including recrystallization, before neutralization, unlike the free forms. The salt forms are generally regarded as superior in terms of solubility compared to respective free forms and may be conveniently recrystallized from suitable solvents according to techniques known in the art such cooling crystallization, anti-solvent addition, or the like.

The present application provides a purification process for Lumacaftor, comprising the step of converting a salt of Lumacaftor obtained according any of the previous aspects into its free form.

In another aspect, the present application provides a process for the preparation of Lumacaftor, comprising the step of converting a salt of Lumacaftor to its free form, wherein the salt may be hydrobromide salt.

In an embodiment, the salt of Lumacaftor may be converted to Lumacaftor in free form by neutralization. In an embodiment, the salt may be neutralized in the presence of a suitable base. Base may be used directly or may diluted form in water or any inert suitable solvent, before using.

Suitable base may include, but not limited to: hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide; carbonates such sodium carbonate, potassium carbonate, ammonium carbonate; bicarbonates such as sodium bicarbonate, potassium bicarbonate, ammonium bicarbonate; an organic base like amines such as triethyl amine, diisopropyl amine, diisopropyl ethyl

amine; alkoxides such as methoxide, ethoxide, isopropoxide, tert. Butoxide; N-heterocyclic Compounds; tetraalkylammonium and phosphonium hydroxides; Amides; metal silanoates; and the like.

In another embodiment, the salt of Lumacaftor may be converted to its free form by subjecting the salt to suitable conditions which may include, but not limited to: suspending the salt of Lumacaftor in a suitable solvent optionally at elevated temperatures.

In an embodiment, the free form of Lumcaftor obtained according to the process of this aspect may be either in crystalline form or amorphous form. In an embodiment, the free form of Lumacaftor may be in crystalline form.

In another aspect, the present application provides a pharmaceutical composition comprising salt of Lumacaftor with hydrobromic acid.

Similar procedures for the preparation of any other salts of Lumcaftor described here may be useful which include, but not limited to inorganic acids such as phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as oxalic acid, maleic acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like and salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts.

In another aspect, the present application provides a process for the preparation of Lumacaftor or salts thereof, comprising the step of reacting 3-boronobenzoic acid or a derivative thereof with N-(6-halo-5-methylpyridin-2-yl)-1 -

(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclo propanecarboxamide in presence of an inert solvent selected from the group comprising of water, dimethylformamide, dimethoxyethane, 1,4-dioxane, 2-propanol, n-butanol, 2-butanol, tert. Butanol or mixtures thereof.

In an embodiment, the reaction between 3-boronobenzoic acid or a derivative thereof and N-(6-halo-5-methyl pyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropanecarboxamide may be carried out in the presence of a suitable catalyst selected from the group comprising of palladium acetate; dichloro-[1 ,1 -bis(diphenylphosphino) ferrocene]palladium(ll) ($Pd(dppf)Cl_2$); palladium acetate / triphenyl phosphine; Tetrakis(triphenylphosphine)palladium (0) ($Pd(PPh_3)_4$) or the like.

In an embodiment, the reaction between 3-boronobenzoic acid or a derivative thereof and N-(6-halo-5-methyl pyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropanecarboxamide may be carried out in the presence of a suitable base selected from the group comprising of hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide; carbonates such sodium carbonate, potassium carbonate, ammonium carbonate; bicarbonates such as sodium bicarbonate, potassium bicarbonate, ammonium bicarbonate; Potassium phosphate tribasic (K_3P0_4); an organic base like amines such as triethyl amine, diisopropyl amine, diisopropyl ethyl amine; alkoxides such as methoxide, ethoxide, isopropoxide, tert. Butoxide; N-heterocyclic Compounds; tetraalkylammonium and phosphonium hydroxides; Amides; metal silanoates; and the like.

In an embodiment, 3-boronobenzoic acid may reacted directly or its derivatives such as 3-(4,4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)benzoic acid or the like may be reacted with N-(6-halo-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropanecarboxamide.

In an embodiment, the mole ratio of 3-boronobenzoic acid or a derivative thereof to N-(6-halo-5-methyl pyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropanecarboxamide that may be used is about 1: 0.8 to 1: 1.2.

In an embodiment, the reaction between 3-boronobenzoic acid or a derivative thereof and N-(6-halo-5-methylpyridin-2-yl)-1 -(2,2-difluoro benzo[d][1 ,3]dioxol-5yl)cyclopropane carboxamide may be carried out at a suitable temperature of about 0°C to reflux temperature of the reaction mixture.

In an embodiment, the reaction between 3-boronobenzoic acid or a derivative thereof and N-(6-halo-5-methylpyridin-2-yl)-1 -(2,2-difluoro benzo[d][1 ,3]dioxol-5yl)cyclopropane carboxamide may be carried out for sufficient time to complete the formation of Lumacaftor or salts thereof for about 1 hour or more.

In embodiment, Lumacaftor that is obtained according to the process of this aspect may be purified through the formation of any salt described in the instant application.

Starting materials or Lumacaftor used in any aspect of the instant application may be purified according to the methods known in the art such as recrystallization, acid - base treatment, chromatography, fractional distillation, slurrying or the like, before using.

Starting materials used for the preparation of Lumacaftor may be obtained from either commercially available sources or prepared according to the methods known in the art.

Lumacaftor used as starting material for the preparation of any salt of the present application may be obtained according to the methods known in the art or according to the procedure described or exemplified in the present application.

Lumacaftor obtained according to any aspects of the instant patent application may be further purified according to any of the methods known in the art recrystallization, acid - base treatment, chromatography or the like. Further, Lumacaftor may be dried under suitable drying conditions such as air drying or vacuum drying.

In another aspect, the present application provides a pharmaceutical composition comprising Lumacaftor obtained according any of the previous aspects and atleast one additional pharmaceutically acceptable excipient.

In another aspect, the present application provides a pharmaceutical composition comprising Lumacaftor obtained according any of the previous aspects and atleast one additional pharmaceutically acceptable excipient.

Lumacaftor that is used as starting material for the preparation of any of the solid forms of present application may be purified before using employing any of the purification techniques known in the art such as recrystallization, slurrying

or chromatography or according to the procedures described or exemplified in the instant application.

Starting material may be either in a crystalline or amorphous state. In embodiments, crystalline form of Lumacaftor that may be used may include but not limited to crystalline form I or solvate form A of Lumacaftor or an alternate crystalline form of Lumacaftor known in the art.

In an aspect, the present application provides a crystalline form SV1 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 6.52, 9.30, 10.45, 10.73, 11.88, 17.19, 19.46, 20.28 and 24.7 ±0.2° 2Θ. In an embodiment, the application provides crystalline form SV1 of Lumacaftor, characterized by a PXRD pattern having one or more additional peaks at about, 8.88, 11.10, 16.08, 16.63, 16.85, 17.82, 18.73, 19.79 and 21.54 ±0.2° 2Θ.

In an embodiment, the present application provides crystalline form SV1 of Lumacaftor, characterized by a PXRD pattern substantially as shown in figure 1.

In another aspect, the present application provides a crystalline form SV2 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 9.67, 10.74, 11.32, 13.85, 19.25, 20.34, 26.47 and 27.25 ±0.2° 2Θ. In an embodiment, the application provides crystalline form SV2 of Lumacaftor, characterized by a PXRD pattern having one or more additional peaks at about 16.45, 17.84, 18.77, 21.64 and 22.43 ±0.2° 2Θ.

In an embodiment, the present application provides crystalline form SV2 of Lumacaftor, characterized by a PXRD pattern substantially as shown in figure 2.

In an embodiment, the present application provides crystalline form SV2 of Lumacaftor, which is stable for atleast 3 months under packed condition when stored ambient temperature. In an embodiment, crystalline form SV2 of Lumacaftor is stable for more than 3 months when stored in an amber colored bottle and stored at 25°C - 30°C.

In an aspect the present application provides a crystalline form SV2 of Lumacaftor. In an embodiment, the crystalline form SV2 is stable under humidity of about 60% RH, under both closed or packed and open conditions. In an embodiment, the crystalline form SV2 of Lumacaftor is stable for atleast a week when placed under open atmospheric conditions.

In another aspect, the present application provides a crystalline form SV3 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 6.13, 12.19, 12.83, 17.08, 22.78, 24.20, 25.47, 26.39 and 28.02 ±0.2° 2Θ. In an embodiment, the application provides crystalline form SV3 of Lumacaftor, characterized by a PXRD pattern having one or more additional peaks at about 14.87, 15.22, 16.53, 17.85, 18.43, 19.68, 20.44, 21.56 and 22.10 ±0.2° 2Θ.

In an embodiment, the present application provides crystalline form SV3 of Lumacaftor, characterized by a PXRD pattern substantially as shown in figure 3.

In another aspect, the present application provides a crystalline form SV4 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 9.39, 12.91, 14.23, 15.98, 23.69, 27.12 and 27.95 ±0.2° 2Θ. In an embodiment, the application provides crystalline form SV4 of Lumacaftor, characterized by a PXRD pattern having one or more additional peaks at about 7.80, 15.58, 18.71 and 21.6 ±0.2° 2Θ.

In an embodiment, the present application provides crystalline form SV4 of Lumacaftor, characterized by a PXRD pattern substantially as shown in figure 4.

Lumacaftor that is used as starting material for the preparation of any of the solid forms of present application may be purified before using employing any of the purification techniques known in the art such as recrystallization, slurrying or chromatography or according to the procedures described or exemplified in the instant application.

Starting material may be either in a crystalline or amorphous state. In embodiments, crystalline form of Lumacaftor that may be used may include but not limited to crystalline form I or solvate form A of Lumacaftor or an alternate crystalline form of Lumacaftor known in the art.

In another aspect, the present application provides a process for the preparation of crystalline form SV1 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 6.52, 9.30, 10.45, 10.73, 11.88, 17.19, 19.46, 20.28 and 24.7 ±0.2° 2Θ comprising the step of crystallizing Lumacaftor form SV1 from the solution comprising Lumacaftor and 1,4-dioxane.

In an embodiment, solution comprising Lumacaftor and 1,4-dioxane may obtained by dissolving Lumacaftor in a solvent or mixture of solvents comprising 1,4-dioxane, optionally by heating.

In an embodiment, dissolution of Lumacaftor may be carried out by optionally heating a mixture of Lumacaftor and a solvent or mixture of solvents comprising 1,4-dioxane at about 30°C to reflux temperature of the solvent. The solution may be made particle free by filtering the solution, optionally the solution may be treated with carbon, hydrose or any decolorizing agent before filtration.

In an embodiment, crystallization of Lumacaftor form SV1 may be carried out according to any methods known in the art for the reduction of solubility of Lumacaftor such as lowering the temperature (i.e., cooling crystallization) of the solution; adding anti-solvent to the solution; evaporating the solvent from the solution; or the combinations thereof.

In an embodiment, crystallization of Lumacaftor form SV1 may be carried out by lowering the temperature of the solution comprising Lumacaftor and 1,4-dioxane to a suitable temperature of about 25°C and below. In an embodiment, crystallization may be carried out by lowering the temperature of the solution to 0°C and below.

In an embodiment, temperature lowering may be carried out slowly or drastically. In an embodiment, drastic lowering of temperature may be effected by placing the solution in a pre-cooled bath. In further embodiments, temperature lowering may be carried out in gradually in single step or stepwise in multiple steps.

In an embodiment, after lowering the temperature, the solution comprising Lumacaftor and 1,4-dioxane may be stirred at the same temperature for time sufficient to obtain crystalline form SV1 of Lumacaftor.

Isolation of crystalline form SV1 of Lumacaftor may be carried out by any methods known in the art or procedures described in the present application. In an embodiment, crystalline form SV1 may be isolated by employing any of the techniques, but not limited to: decantation, filtration by gravity or suction, centrifugation, adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used and the like, and optionally washing with a solvent.

In another aspect, the present application provides a process for the preparation of crystalline form SV2 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 9.67, 10.74, 11.32, 13.85, 19.25, 20.34, 26.47 and 27.25 ±0.2° 2Θ, comprising the step of drying crystalline form SV1 of Lumacaftor.

In an embodiment, drying crystalline form SV1 of Lumacaftor may be carried out in suitable drying equipment such as a tray drier optionally under reduced pressure or other drying conditions known in the art such as Buchi rotavapour vacuum drying, rotatory cone vacuum drying; fluid bed drying optionally under nitrogen atmosphere, thin film drying; or the like.

In an embodiment, drying crystalline form SV1 of Lumacaftor may be carried out at suitable temperatures of about 25°C and above, optionally under reduced pressure. In an embodiment, drying may be carried out at about 100°C and above.

In an embodiment, drying crystalline form SV1 of Lumacaftor may be carried out for sufficient time to complete its conversion to crystalline form SV2 of Lumacaftor. Drying can be carried out at temperatures and times sufficient to achieve desired quality of product. Drying may be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to 10 hours or longer.

In another aspect, the present application provides a process for the preparation of crystalline form SV3 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 6.13, 12.19, 12.83, 17.08, 22.78, 24.20, 25.47, 26.39 and 28.02 ±0.2° 2Θ, comprising the step of treating Lumacaftor with solvent or solvent mixture comprising acetic acid.

In an embodiment, crystalline form SV3 of Lumacaftor may be obtained by treating Lumacaftor with solvent or solvent mixture comprising acetic acid, wherein the mixture of Lumacaftor and the solvent is either heterogeneous or homogeneous.

In an embodiment, crystalline form SV3 of Lumacaftor may be obtained by suspending Lumacaftor in a solvent or mixture of solvents comprising acetic acid for at suitable temperature and sufficient time.

In an embodiment, crystalline form SV3 of Lumacaftor may be obtained by

crystallizing it from the solution comprising Lumacaftor and solvent or mixture of solvents comprising acetic acid.

In embodiments, crystallization of Lumacaftor form SV3 may be carried out according to any method known in the art for the reduction of solubility of Lumacaftor such as lowering the temperature (i.e., cooling crystallization) of the solution; adding anti-solvent to the solution; evaporating the solvent from the solution; or the combinations thereof. Crystallization may be carried out by any method described in any aspect or according to procedures exemplified in the instant application.

In an embodiment, crystallization of Lumacaftor form SV3 may be carried out by lowering the temperature of the solution comprising Lumacaftor and solvent or mixture of solvents comprising acetic acid to a suitable temperature of about 25°C and below. In an embodiment, crystallization may be carried out by lowering the temperature of the solution to 0°C and below.

In an embodiment, temperature lowering may be carried out slowly or drastically. In an embodiment, drastic lowering of temperature may be effected by placing the solution in a pre-cooled bath. In further embodiments, temperature lowering may be carried out in gradually in single step or stepwise in multiple steps.

In an embodiment, after lowering the temperature, the solution comprising Lumacaftor and solvent or mixture of solvents comprising acetic acid may be stirred at the same temperature for time sufficient to obtain crystalline form SV3 of Lumacaftor.

Isolation of crystalline form SV3 of Lumacaftor may be carried out by any methods known in the art or procedures described in the present application. In an embodiment, crystalline form SV3 may be isolated by employing any of the techniques, but not limited to: decantation, filtration by gravity or suction, centrifugation, adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used and the like, and optionally washing with a solvent.

In an embodiment, isolated crystalline form SV3 of Lumacaftor may be optionally dried in a suitable drying equipment for times sufficient to achieve desired quality of product at suitable temperatures.

In another aspect, the present application provides a process for the preparation of crystalline form SV3 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 6.13, 12.19, 12.83, 17.08, 22.78, 24.20, 25.47, 26.39 and 28.02 ±0.2° 2Θ, comprising the step of suspending Lumacaftor in a solvent or mixture of solvents, wherein solvent is selected from the group comprising of nitromethane, ,2-dimethoxy ethane and hexane.

In embodiments, crystalline form SV3 of Lumacaftor may be obtained by suspending Lumacaftor in the solvent with suitable concentrations such that the mixture of Lumacaftor and the solvent remain heterogeneous throughout the transformation.

In embodiments, crystalline form SV3 of Lumacaftor may be obtained by suspending Lumacaftor in the solvent at suitable temperature of about 0°C and above for sufficient time to complete the formation of crystalline form SV3, for atleast 1 hour or more.

In an embodiment, crystalline form SV3 of Lumacaftor may be obtained by suspending Lumacaftor in the solvent at 25°C and above for sufficient time to complete the formation of crystalline form SV3, for more than 10 hours.

In another aspect, the present application provides a process for the preparation of crystalline form SV4 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 9.39, 12.91 , 14.23, 15.98, 23.69, 27.12 and 27.95 ±0.2° 2Θ, comprising the step of crystallizing Lumacaftor from solvent or mixture of solvents comprising 1,2-dimethoxy ethane.

In an embodiment, solution comprising Lumacaftor and solvent or mixture of solvents comprising 1,2-dimethoxy ethane may obtained by dissolving Lumacaftor in a solvent or mixture of solvents, optionally by heating.

In an embodiment, dissolution of Lumacaftor may be carried out by optionally heating a mixture of Lumacaftor and a solvent or mixture of solvents comprising 1,2-dimethoxy ethane at about 30°C to reflux temperature of the solvent. The solution may be made particle free by filtering the solution, optionally the solution may be treated with carbon, hydrose or any decolorizing agent before filtration.

In an embodiment, crystallization of Lumacaftor form SV4 may be carried out according to any methods known in the art for the reduction of solubility of Lumacaftor such as lowering the temperature (i.e., cooling crystallization) of the

solution; adding anti-solvent to the solution; evaporating the solvent from the solution; or the combinations thereof.

In an embodiment, crystallization of Lumacaftor form SV4 may be carried out by lowering the temperature of the solution comprising Lumacaftor and 1,2-dimethoxy ethane to a suitable temperature of about 25°C and below. In an embodiment, crystallization may be carried out by lowering the temperature of the solution to 0°C and below.

In an embodiment, temperature lowering may be carried out slowly or drastically. In an embodiment, drastic lowering of temperature may be effected by placing the solution in a pre-cooled bath. In further embodiments, temperature lowering may be carried out in gradually in single step or stepwise in multiple steps.

In an embodiment, after lowering the temperature, the solution comprising Lumacaftor and 1,2-dimethoxy ethane may be stirred at the same temperature for time sufficient to obtain crystalline form SV4 of Lumacaftor.

Isolation of crystalline form SV4 of Lumacaftor may be carried out by any methods known in the art or procedures described in the present application. In an embodiment, crystalline form SV4 may be isolated by employing any of the techniques, but not limited to: decantation, filtration by gravity or suction, centrifugation, adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used and the like, and optionally washing with a solvent.

In an aspect, the present application provides a process of converting crystalline form SV1 of Lumacaftor to crystalline form SV3 of Lumacaftor.

In an embodiment, the conversion of crystalline form SV1 may be carried out by holding crystalline form SV1 under closed condition at suitable temperature of about 0°C to 40°C. In an embodiment, crystalline form SV1 may be held under closed condition for sufficient time to complete the conversion for atleast 24 hours or more. In an embodiment, crystalline form SV1 may be held under suitable packing condition.

In an embodiment, the present application provides crystalline form SV3 of Lumacaftor obtained according to the process of this aspect may be, characterized by a PXRD pattern substantially as shown in figure 5.

In an aspect, the present application provides a process for the preparation of crystalline form SV1 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at about 6.52, 9.30, 10.45, 10.73, 11.88, 17.19, 19.46, 20.28 and 24.7 ±0.2° 2Θ comprising the step of treating Lumacaftor with 1,4-dioxane or a mixture thereof.

In an embodiment, treating Lumacaftor with 1,4-dioxane or a mixture thereof may be carried out by combining Lumacaftor and 1,4-dioxane or a mixture thereof.

In an embodiment, the mixture of Lumacaftor and 1,4-dioxane or a mixture thereof may form a homogeneous or heterogeneous mixture. In an embodiment, the mixture of Lumacaftor and 1,4-dioxane or a mixture thereof is a heterogeneous mixture in the form a suspension.

In an embodiment, crystalline form SV1 of Lumacaftor may be obtained by treating Lumacaftor with a mixture of 1, 4-dioxane and atleast one additional solvent. In an embodiment, additional solvent may be selected from the group comprising of water, methanol, ethanol, 2-propanol, acetone, methyl isobutyl ketone, diethyl ether, di isopropyl ether, methyl tert. butyl ether or a mixture thereof.

In an embodiment, combining Lumacaftor with 1,4-dioxane or a mixture thereof may be carried out optionally by heating a mixture of Lumacaftor and 1,4-dioxane or a mixture thereof at about 30°C to reflux temperature.

In an embodiment, the mixture of Lumacaftor and 1,4-dioxane or a mixture thereof may be stirred for sufficient time to complete the formation of form SV1 and at suitable temperature where crystalline form SV1 is stable and do not convert to any other form of Lumacaftor.

In an embodiment, optionally seeds of crystalline form SV1 of Lumacaftor may be added to the mixture of Lumacaftor and 1,4-dioxane or a mixture thereof, in case the mixture forms a homogenous solution. In an embodiment, seeds may be added at a suitable temperature and sufficient quantity such that the seeds are not dissolved.

In an embodiment, the mixture of Lumacaftor and 1,4-dioxane or a mixture thereof may be stirred for atleast one hour or more. In an embodiment, the mixture of Lumacaftor and 1,4-dioxane or a mixture thereof may be stirred at a

temperature of about 0°C to reflux temperature.

In an embodiment, optionally anti-solvent may be added to the mixture of Lumacaftor and 1,4-dioxane or a mixture thereof, in case the mixture forms a homogenous solution. The anti-solvent may be a solvent in which Lumacaftor has low solubility and which include, but not limited to water; hydrocarbons like n-pentane, n-hexane, n-heptane, cyclohexane, methyl cyclohexane; ethers like diethyl ether, di isopropyl ether or mixtures thereof.

In an embodiment, the mixture of Lumacaftor and 1,4-dioxane or a mixture may be optionally cooled to a suitable temperature before or after formation of Form SV1 .

In an optional embodiment, the mixture of Lumacaftor and 1,4-dioxane or a mixture thereof may be cooled to a relatively lower temperature. In an embodiment, after lowering the temperature, the mixture comprising Lumacaftor and 1,4-dioxane or a mixture thereof may be stirred at the same temperature for time sufficient to obtain crystalline form SV1 of Lumacaftor.

Isolation of crystalline form SV1 of Lumacaftor may be carried out by any methods known in the art or procedures described in the present application. In an embodiment, crystalline form SV1 may be isolated by employing any of the techniques, but not limited to: decantation, filtration by gravity or suction, centrifugation, adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used and the like, and optionally washing with a solvent.

In another aspect, the present application provides a pharmaceutical composition comprising crystalline Form of Lumacaftor selected from the group comprising form SV1 , form SV2, form SV3, form SV4 or mixtures thereof together with atleast one pharmaceutically acceptable excipient.

In another aspect, the present application provides Lumacaftor, its salt, crystalline forms thereof or their pharmaceutical compositions comprising Lumacaftor having a chemical purity of atleast 99% by HPLC or atleast 99.5% by HPLC or atleast 99.9% by HPLC.

In another aspect, the present application provides Lumacaftor, its salt, crystalline forms thereof or their pharmaceutical compositions, wherein particle

size (D90) of Lumacaftor may be less than 100 microns or less than 50 microns or less than 20 microns.

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the application in any manner. Variations of the described procedures, as will be apparent to those skilled in the art, are intended to be within the scope of the present application.

Definitions

The term "about" when used in the present application preceding a number and referring to it, is meant to designate any value which lies within the range of ±10%, preferably within a range of ±5%, more preferably within a range of ±2%, still more preferably within a range of ±1 % of its value. For example "about 10" should be construed as meaning within the range of 9 to 11 , preferably within the range of 9.5 to 10.5, more preferably within the range of 9.8 to 10.2, and still more preferably within the range of 9.9 to 10.1.

The term "inert solvent" when used in the present application is a solvent that does not react with the reactants or reagent s under conditions that cause the chemical reaction indicated to take place.

An "alcohol" is an organic compound containing a carbon bound to a hydroxyl group. "C1 -C6 alcohols" include, but are not limited to, methanol, ethanol, ethylene glycol, diethylene glycol, 1-propanol, 2-propanol (isopropyl alcohol), 2-methoxyethanol, 1-butanol, 2-butanol, i-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, cyclohexanol, phenol, glycerol, or the like.

An "aliphatic hydrocarbon" is a liquid hydrocarbon compound, which may be linear, branched, or cyclic and may be saturated or have as many as two double bonds. A liquid hydrocarbon compound that contains a six-carbon group having three double bonds in a ring is called "aromatic." Examples of "C5-C8aliphatic or aromatic hydrocarbons" include, but are not limited to, n-pentane, isopentane, neopentane, n-hexane, isohexane, 3-methylpentane, 2,3-dimethylbutane, neohexane, n-heptane, isoheptane, 3-methylhexane, neoheptane, 2,3-dimethylpentane, 2,4-dimethylpentane, 3,3-dimethylpentane, 3-ethylpentane, 2,2,3-trimethylbutane, n-

octane, isooctane, 3-methylheptane, neooctane, cyclohexane, methylcyclohexane, cycloheptane, benzene, toluene, ethylbenzene, m-xylene, o-xylene, p-xylene, trimethylbenzene, chlorobenzene, fluorobenzene, trifluorotoluene, anisole, or any mixtures thereof.

An "ester" is an organic compound containing a carboxyl group -(C=0)-0- bonded to two other carbon atoms. "C3-C6esters" include, but are not limited to, ethyl acetate, n-propyl acetate, n-butyl acetate, isobutyl acetate, t-butyl acetate, ethyl formate, methyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like.

An "ether" is an organic compound containing an oxygen atom -0- bonded to two other carbon atoms. "C2-C6 ethers" include, but are not limited to, diethyl ether, diisopropyl ether, methyl t-butyl ether, glyme, diglyme, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, dibutyl ether, dimethylfuran, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like.

A "halogenated hydrocarbon" is an organic compound containing a carbon bound to a halogen. Halogenated hydrocarbons include, but are not limited to, dichloromethane, 1,2-dichloroethane, trichloroethylene, perchloroethylene, 1,1,1-trichloroethane, 1,1,2-trichloroethane, chloroform, carbon tetrachloride, or the like.

A "ketone" is an organic compound containing a carbonyl group -(C=0)- bonded to two other carbon atoms. "C3-C6 ketones" include, but are not limited to, acetone, ethyl methyl ketone, diethyl ketone, methyl isobutyl ketone, ketones, or the like.

A "nitrile" is an organic compound containing a cyano -(C≡N) bonded to another carbon atom. "C2-C6Nitriles" include, but are not limited to, acetonitrile, propionitrile, butanenitrile, or the like.

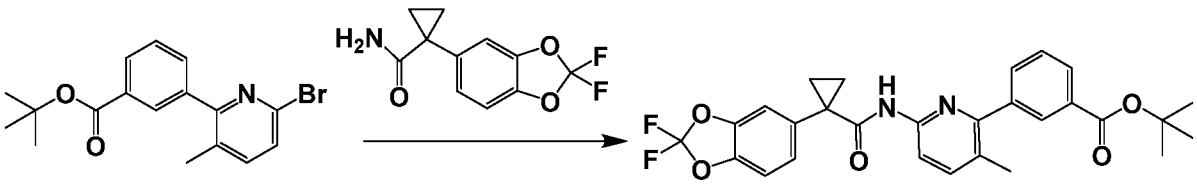
The terms "crystalline form" indicates that the Lumacaftor is present in substantially crystalline Form. "Substantially" crystalline denotes that atleast 80 %, preferably 90 % or 95 %, more preferably all of the Lumacaftor is crystalline form. In other words, "crystalline form" of Lumacaftor denotes Lumacaftor, which does not contain substantial amounts, preferably does not contain noticeable amounts, of any other crystalline portions of Lumacaftor e.g. measurable upon X-ray powder diffraction analysis.

X-ray powder diffraction patterns described herein were generated using a Bruker AXS D8 Advance powder X-ray diffractometer with a copper K-alpha radiation source. Generally, a diffraction angle (2Θ) in powder X-ray diffractometry

may have an error in the range of ±0.2°. Therefore, the aforementioned diffraction angle values should be understood as including values in the range of about ± 0.2°. Accordingly, the present invention includes not only crystals whose peak diffraction angles in powder X-ray diffractometry completely coincide with each other, but also crystals whose peak diffraction angles coincide with each other with an error of about ± 0.2°. Therefore, in the present specification, the phrase "having a diffraction peak at a diffraction angle (2Θ) ±0.2° of 6.3°" means "having a diffraction peak at a diffraction angle (2Θ) of 6.1 ° to 6.5°. Although the intensities of peaks in the x-ray powder diffraction patterns of different batches of a compound may vary slightly, the peak relationships and the peak locations are characteristic for a specific polymorphic form. The relative intensities of the PXRD peaks may vary somewhat, depending on factors such as the sample preparation technique, crystal size distribution, various filters used, the sample mounting procedure, and the particular instrument employed. Moreover, instrumental variation and other factors may slightly affect the 2-theta values. Therefore, the term "substantially" in the context of PXRD is meant to encompass that peak assignments may vary by plus or minus about 0.2°. Moreover, new peaks may be observed or existing peaks may disappear, depending on the type of the machine or the settings (for example, whether a filter is used or not).

EXAMPLES

Example-1 : Preparation of tert-butyl ester of Lumacaftor (or) tert-butyl 3-(6-(1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane-1 -carboxamido)-3-methylpyridin-2-yl)benzoate.

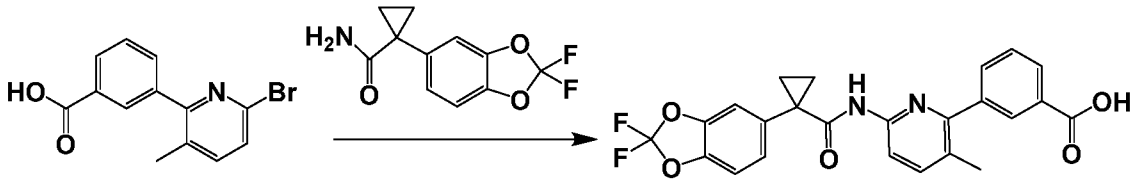


To a mixture of tert-butyl 3-(6-bromo-3-methylpyridin-2-yl)benzoate (150 mg) and 1-(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane-1 -carboxamide (124 mg) in tert-butanol (10 ml_) in a 50 ml_ seal tube, Cesium carbonate (210 mg), 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-phos) (8.2 mg) and Tris(dibenzylideneacetone) dipalladium (O)-chloroform adduct [$Pd_2(dba)_3$. CHCl3] (8.9 mg) were charged at 27°C under nitrogen atmosphere. The reaction mixture

was degassed with nitrogen for 30 minutes at 27°C. The reaction mixture was heated at 100°C for 16 hours. Reaction mixture monitored by TLC showed presence of starting material, the reaction mixture was cooled to 27°C and Cesium carbonate (210 mg), 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-phos) (8.2 mg) and Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct [$Pd_2(dba)_3$. $CHCl_3$] (8.9 mg) were added. The reaction mixture was degassed with nitrogen for 30 minutes at 27°C. The reaction mixture was heated at 100°C for 21 hours. Cooled the reaction mixture to 27° and filtered on celite bed. The celite bed was washed with tert-butanol (10 ml_). The organic filtrate was evaporated at 45°C under reduced pressure to obtain pale yellow liquid. The compound was purified by column chromatography using 60-120 silica mesh using 20% ethyl acetate / hexane as eluent to obtain title compound as brown solid.

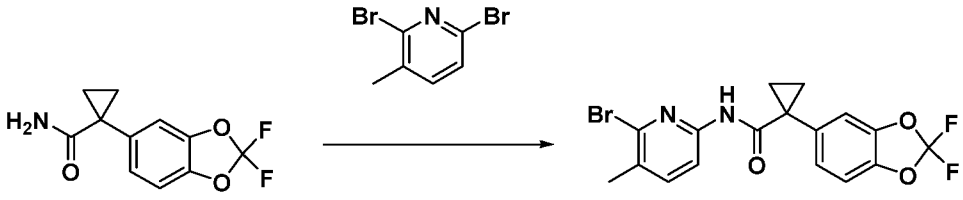
Yield: 137 mg; Purity by HPLC: 97.40%

Example-2: Preparation of Lumacaftor.



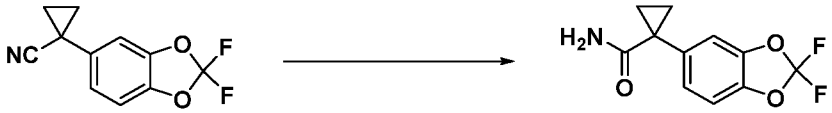
To a mixture of 3-(6-bromo-3-methylpyridin-2-yl)benzoic acid (200 mg) and 1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropane-1-carboxamide (198.1 mg) in tert-butanol (10 ml_) in a 50 ml_ seal tube at 27°C, Cesium carbonate (669 mg), 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-phos) (32.6 mg) and Tris(dibenzylideneacetone) dipalladium (O)-chloroform adduct [$Pd_2(dba)_3$. CHCl3] (35.4 mg) were charged at 27°C under nitrogen atmosphere. The reaction mixture was degassed with nitrogen for 30 minutes at 27°C. The reaction mixture was heated at 100°C for 16 hours. Cooled the reaction mixture to 27°C and filtered on celite bed. The celite bed was washed with tert-butanol (10 ml_). The organic filtrate was evaporated at 27°C under reduced pressure to obtain pale yellow liquid. The compound was dissolved in dichloromethane (3 ml_) and added n-hexane (7 ml_) to the above solution and stirred for 10 minutes at 27°C. Solid was filtered dried under vacuum to obtain title compound as pale yellow solid. Yield: 290 mg; Purity by HPLC: 89.91 %

Example-3: Preparation of N-(6-bromo-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane-1 -carboxamide



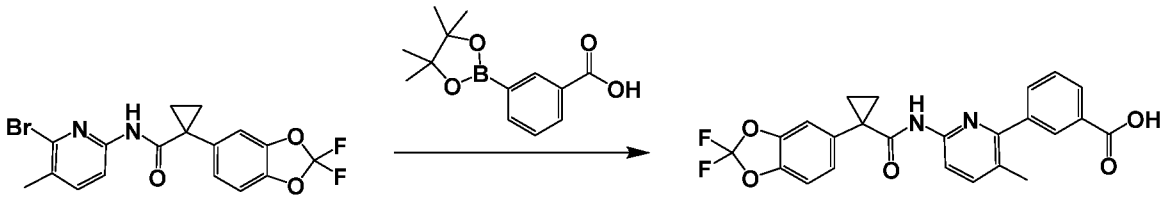
To a mixture of 2, 6-dibromo-3-methylpyridine (200 mg) and 1-(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane-1 -carboxamide (230.6 mg) in tert-butanol (10 mL) in a 50 ml_ seal tube at 30°C, Cesium carbonate (779 mg), 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-phos) (30.0 mg) and Tris(dibenzylideneacetone) dipalladium (O)-chloroform adduct [$Pd_2(dba)_3$. CHCl3] (33.0 mg) were charged at 30°C under nitrogen atmosphere. The reaction mixture was degassed with nitrogen for 30 minutes at 27°C. The reaction mixture was heated at 100°C for 22 hours. Cooled the reaction mixture to 30°C and filtered on celite bed. The celite bed was washed with tert-butanol (5 mL). The organic filtrate was evaporated at 30°C under reduced pressure to obtain title compound as pale yellow liquid.

Example-4: Preparation of 1-(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane-1 -carboxamide



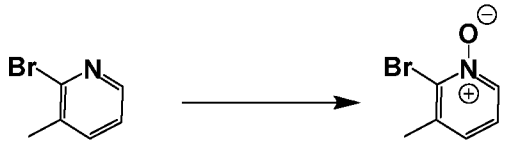
To a mixture of 1-(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane nitrile (6.5 g) in tert-butanol (65 mL), potassium hydroxide (9.8 g) was added at 30°C. The reaction mixture was heated to 95°C and stirred at the same temperature for 16 hours. Quenched the reaction mixture with water (150 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (50 mL) and dried the solution over sodium sulphate. The solution was evaporated under reduced pressure at 45 °C to obtain the title compound as white solid. Yield: 5.6 g; Purity by HPLC: 97.37%

Example-5: Preparation of Lumacaftor



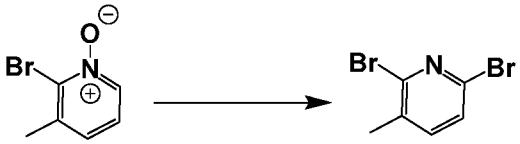
To a mixture of N-(6-bromo-5-methylpyridin-2-yl)-1 -(2,2-difluoro benzo[d][1 ,3]dioxol-5-yl)cyclopropane-1 -carboxamide (120 mg) and 3-(4, 4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)benzoic acid (217 mg) in dimethyl formamide - water (1.2 mL and 0.36 mL), potassium carbonate (201 mg) was added and degassed the reaction mixture with argon gas for 30 minutes at 30°C. Dichloro-[1,1-bis(diphenylphosphino) ferrocene]palladium(ll) ($Pd(dppf)Cl_2$) (3.5 mg) was added to the reaction mixture and heated to 100°C for 45 minutes under argon atmosphere. The reaction mixture was quenched with water (15 mL) and extracted the reaction mixture using ethyl acetate (3 x 20 mL). The organic layer was washed with water (2 x 15 mL) and dried over sodium sulphate. The organic layer was evaporated under reduced pressure to obtain crude product as brown semi solid. The crude product was purified by column chromatography using 60-120 silica mesh using 30-50 % ethyl acetate / hexane as eluent to obtain title compound as off-white solid. Yield: 0.04 g; Purity by HPLC: 97.24%

Example-6: Preparation of 2-bromo 3-methyl pyridine N-oxide



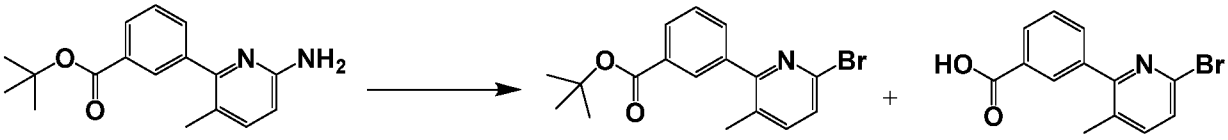
2-bromo 3-methyl pyridine (25 g) was dissolved in dichloromethane (250 mL) at 30°C and cooled to 0°C. m-chloroperbenzoic acid (65.58 g) was added to the above solution slowly portion wise in 20 minutes at 0°C. The reaction mixture was warmed to 30°C and stirred for 16 hours. The reaction mixture was quenched with saturated sodium sulfite (2 x 50 mL) and extracted with dichloromethane (200 mL). The organic layer was washed with saturated sodium bicarbonate solution (2 x 60 mL), then with brine solution (50 mL) and dried over sodium sulfate and concentrated the solution to obtain 18 g of 2-bromo 3-methyl pyridine N-oxide as brown color solid having 92. 19% purity by HPLC.

Example-7: Preparation of 2, 6-dibromo-3-methylpyridine



2-bromo 3-methyl pyridine N-oxide (1 g) was dissolved in toluene (10 mL) at 30°C. Phosphorus oxybromide (2.38 g) was added slowly portion wise to the reaction mixture at 30°C and heated at 90°C for 4 hours. The reaction mixture was cooled to 30°C and quenched with aqueous solution of potassium carbonate (10. 2 g in 50 mL of water) to adjust the pH to 8. The reaction mixture was extracted with ethyl acetate (2 x 50 mL) and the combined organic layer was washed with saturated sodium chloride solution (30 mL). The organic solution was dried over sodium sulfate and evaporated under reduced pressure at 45°C to obtain crude product. The crude product was purified by column chromatography using 60-120 silica gel mesh and 2-3% of ethyl acetate / hexane as eluent to obtain 244 mg of title compound as white solid.

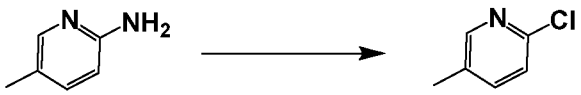
Example-8: Preparation of tert-butyl 3-(6-bromo-3-methylpyridin-2-yl)benzoate and 3-(6-bromo-3-methylpyridin-2-yl)benzoic acid



Tert-butyl 3-(6-amino-3-methylpyridin-2-yl) benzoate (3. 0 g) was added to 47% aqueous solution of hydrogen bromide (15 mL) portion wise at 27°C in 15 minutes. The reaction mixture was cooled to -20°C and bromine (1.52 mL) was added drop wise. Stirred the reaction mixture at -20°C for 90 minutes and sodium nitrite solution (1.96 g in 7.5 mL of water) was added for 20 minutes at the same temperature. Reaction mixture was warmed to 15°C and stirred for 1 hour and 45 minutes at the same temperature. Again cooled the reaction mixture to -20°C and sodium hydroxide solution (8.44 g in 30 mL of water) was added slowly. The reaction mass was extracted with ethyl acetate (3 x 50 mL) and dried over sodium sulfate. The solution was concentrated under reduced pressure to obtain crude product. The crude product was purified by column chromatography using (10% to 50%) ethyl acetate / hexane as eluent to obtain 185 mg of tert-butyl 3-(6-bromo-3-methylpyridin-2-yl)benzoate as a colorless liquid with 96.07% purity by HPLC and 1.0 g of 3-(6-bromo-3-methylpyridin-2-yl)benzoic acid as a white solid

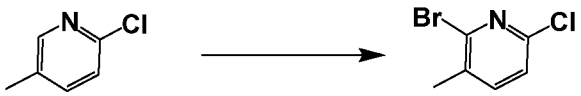
with 98.36% purity by HPLC.

Example-9: Preparation of 2-chloro 5-methyl pyridine



2-amino 5-methyl pyridine (5.0 g) was cooled to 5°C and Con. HCl (90 mL) was added. Sodium nitrite (5.16 g) was added portion wise slowly to the reaction mixture in 15 minutes. The reaction mixture was allowed to warm to 30°C and stirred for 1.5 hours at the same temperature. Cooled the reaction mixture to 5°C and 40% aqueous sodium hydroxide solution (150 mL) was added and pH adjusted to 13. Extracted the reaction mixture with ethyl acetate (3 x 50 mL) and washed the combined organic layer with brine solution (50 mL). The solution was dried over sodium sulfate and evaporated the solvent under reduced pressure to afford crude compound. The crude product was purified by column chromatography using 60-120 silica mesh and (10% to 20%) ethyl acetate / hexane as eluent to obtain title compound as colorless liquid. Yield: 2.62 g; Purity by HPLC: 99.97%

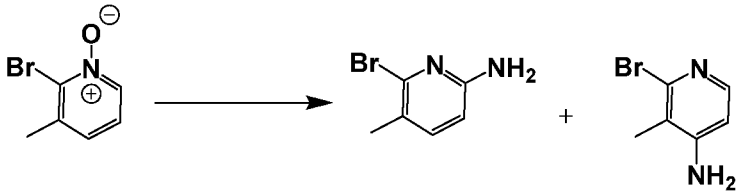
Example-10: Preparation of 2-bromo 3-methyl 6-chloro pyridine



A mixture of dimethyl amino ethanol (2.3 mL) in hexane (13 mL) was cooled to 0°C and n-butyl lithium (29.4 mL) was added drop wise in 15 minutes and stirred for 15 minutes at 0°C. 2-chloro 5-methyl Pyridine (1.0 g) was dissolved in hexane (10.5 mL) and added to the above solution at 0°C. Cooled the reaction mixture further to -78°C and tetrabromomethane solution (9.21 g in 47.5 mL of tetrahydrofuran) was added in 15 minutes at the same temperature. Stirred the reaction mixture at -78°C for 1 hour and allowed to warm to 30°C. Quenched the reaction mixture with water (30 mL) and extracted with ethyl acetate (2x 20 mL). The combined organic solution was washed with brine solution (10 mL) and dried over sodium sulfate. The organic solution was concentrated to obtain crude product. The crude product was purified by column chromatography using 60-120 mesh and 5% ethyl acetate / hexane as eluent to obtain 403 mg of title compound as brown solid.

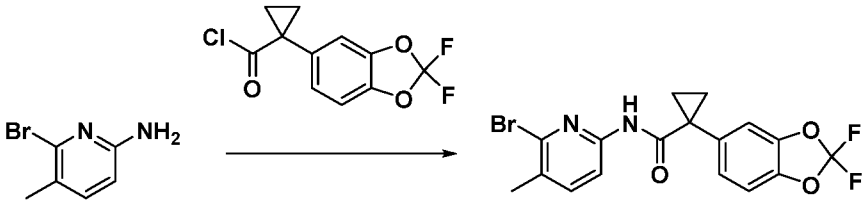
Example-11: Preparation of 6-bromo 5-methyl pyridin-2-amine and 2-bromo 3-

methyl pyridin-4-amine.



A mixture of 6-bromo 5-methyl pyridine N-oxide (1.2 g) and Pyridine (2.06 mL) in acetonitrile (4.8 mL) was heated to 70°C and a solution of methane sulfonic anhydride (1.667 g in 2.4 mL of acetonitrile) was added to it drop wise over a period of 20 minutes. The reaction mixture was stirred for 1 hour at 70°C and allowed to cool to 30°C. Ethanol amine (3.851 mL) was added drop wise over 10 minutes under nitrogen atmosphere at 30°C and stirred the reaction mixture for 15 hours at the same temperature. The reaction mixture was quenched with water (15 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic solution was dried over sodium sulfate and concentrated under reduced pressure to obtain crude product. The crude product was purified by column chromatography using 60-120 mesh and 20-30% ethyl acetate / hexane as eluent to obtain 0.32 g of 6-bromo 5-methyl pyridin-2-amine with 93.41 % purity by HPLC as a brown solid and 0.34 g of 2-bromo 3-methyl pyridin-4-amine with 97.94% purity by HPLC as a brown solid.

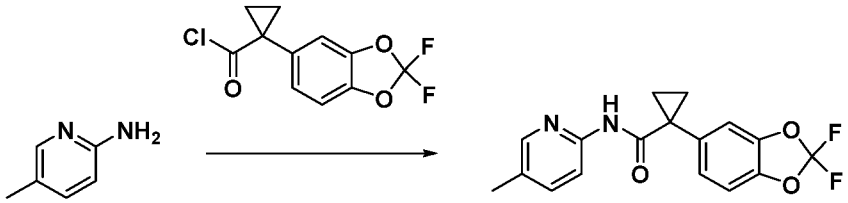
Example-12: Preparation of N-(6-bromo-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane-1 -carboxamide



6-bromo 5-methyl pyridin-2-amine (0.1 g) was dissolved in dichloromethane (1 mL) under nitrogen atmosphere. The solution was cooled to 0°C and triethyl amine (0.149 mL) was added. 1-(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane-1 -carbonyl chloride (0.209 g) in dichloromethane (0.5 mL) was added drop wise into the reaction mixture in 5 minutes. The reaction mixture was warmed to 30°C and stirred for 18 hours at the same temperature. Quenched the reaction mixture with saturated potassium hydroxide solution (30 mL) and extracted with dichloromethane (30 mL). The organic solution was dried over sodium sulphate and evaporated under reduced pressure to afford crude product.

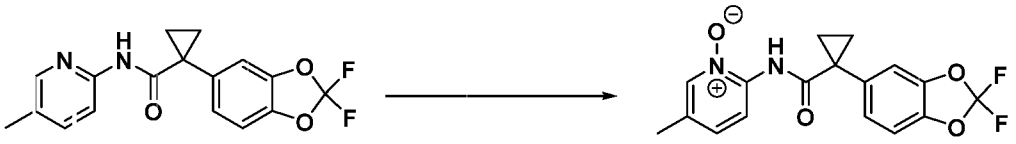
The crude product was purified by column chromatography using 60-120 mesh and 10-20% ethyl acetate / hexane as eluent to obtain the title compound as brown color solid. Yield: 0.150 g; Purity by HPLC: 96.90%

Example-13: Preparation of N-(5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropane-1-carboxamide



5-methyl pyridin-2-amine (2.0 g) was suspended in toluene (20 mL) under nitrogen atmosphere at 29°C. Triethyl amine (7.79 mL) and 4-dimethylaminopyridine (45 mg) were added to the reaction mixture and stirred for 10 minutes. 1-(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane-1 -carbonyl chloride (7.71 g) in toluene (4 mL) was added drop wise into the reaction mixture at 29°C in 15 minutes and stirred for 3 hours at the same temperature. Quenched the reaction mixture with saturated sodium bicarbonate solution (30 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with 1N HCl (2 x 20 mL) followed by brine solution (20 mL). Dried the organic solution over sodium sulphate and evaporated under reduced pressure to afford crude product. The crude product was purified by column chromatography using 60-120 mesh and 5% ethyl acetate / hexane as eluent to obtain the title compound as pale yellow liquid. Yield: 2.5 g; Purity by HPLC: 98.62%

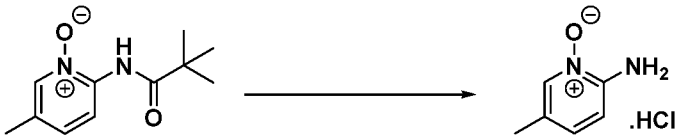
Example-14: Preparation of N-oxide of N-(5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropane-1-carboxamide



N-(5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane-1 -carboxamide (1 g) was dissolved in ethyl acetate (10 mL) and water (0.3 mL). To the reaction mixture urea - hydrogen peroxide (566 mg) was added and then phthalic anhydride (891 mg) was added portion wise in 20 minutes at 27°C. The reaction mixture was heated to 55°C and stirred at the same temperature for 16 hours. Cooled the reaction mixture to 27°C and diluted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was

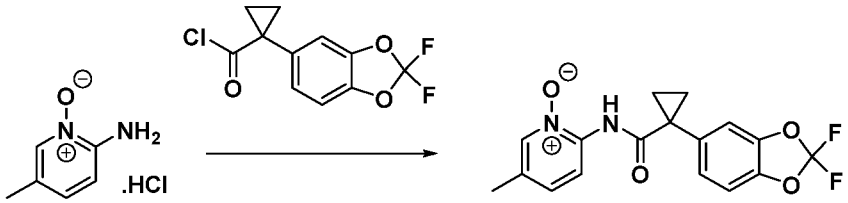
extracted with ethyl acetate (10 mL). The combined organic layer was washed with 10% sodium sulfite (10 mL), 10% sodium bicarbonate (10 mL) and brine solution (10 mL). The organic solution was dried over sodium sulfate and evaporated the solvent under reduced pressure to obtain title compound as white solid. Yield: 890 mg; Purity by HPLC: 99.80%

Example-15: Preparation of hydrochloride of 5-methyl pyridin-2-amine N-oxide



5-methyl-2-pivalamidopyridine N-oxide (500 mg) was combined with 6 N HCl (5 mL) and heated to 90°C. Stirred the reaction mixture for 6 hours at 90°C and cooled to 32°C. Evaporated HCl under reduced pressure and co-distilled the product with toluene (2 x 5 mL). The solid was dried under reduced pressure for 45 minutes to obtain title compound as white solid. Yield: 320 mg; Purity by HPLC: 99.638%

Example-16: Preparation of N-oxide of N-(5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropane-1-carboxamide



N-oxide of 5-methyl pyridin-2-amine hydrochloride (0.3 g) was dissolved in dichloromethane (6 mL) under nitrogen atmosphere. The solution was cooled to 5°C and triethyl amine (0.78 mL) was added. 1-(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane-1 -carbonyl chloride (0.486 g) in dichloromethane (3 mL) was added drop wise into the reaction mixture. The reaction mixture was warmed to 30°C and stirred for 3 hours at the same temperature. Quenched the reaction mixture with water (10 mL) and extracted with dichloromethane (2 x 5 mL). The organic solution was washed with 10% potassium hydroxide solution (10 mL), 1 N HCl (10 mL) and brine solution (5 mL). Dried the organic solution over sodium sulphate and evaporated under reduced pressure to afford crude product. The crude product was dissolved in methyl tert-butyl ether (4 mL) at 32°C and added hexane (16 mL). Stirred the mixture for 10 minutes at 32°C and the solid was filtered to obtain title compound as white solid. Yield: 0.380 g; Purity by HPLC:

99.448%

Example-17: Preparation of N-(6-chloro-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane-1 -carboxamide

N-oxide of N-(5-methylpyridin-2-yl)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropane-1 -carboxamide (200 mg) was dissolved in dichloromethane (5 mL) and cooled to 0°C. Triethylamine (0. 12 mL) and Phosphorous oxychloride (0.079 mL) were added to the reaction mixture at 0°C. Then the reaction mixture was heated to 45°C and stirred at the same temperature for 16 hours and cooled to 29°C. Quenched the reaction mixture with water (10 mL) and extracted with dichloromethane (2 x 5 mL). The combined organic solution was washed with saturated sodium bicarbonate solution (5 mL) and brine solution (5 mL). Dried the solution on sodium sulfate and evaporated the solvent under reduced pressure to obtain crude product. The crude product was purified by column chromatography using 60-120 mesh and 20% ethyl acetate / hexane as eluent to obtain the title compound as brown solid. Yield: 53 mg; Purity by HPLC: 95. 17%

Example-18: Preparation of N-(6-chloro-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo [d][1 ,3]dioxol-5-yl)cyclopropanecarboxamide

To a mixture of 1-(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropane carboxylic acid (50 g) in toluene (500 mL) at 26°C, Thionyl chloride (31 .9 g) and dimethyl formamide (0.5 mL) was added. The reaction mixture was heated to 59.6°C and stirred for 2 hours at the same temperature. The solvent was removed from the reaction mixture through evaporation at 52°C under reduced pressure and the crude product was dissolved in toluene (300 mL). A mixture of 6-chloro-5-methylpyridin-2-amine (29.4 g) in toluene (400 mL) was added to the reaction mixture at 30°C in 35 minutes and stirred for 10 minutes at the same temperature. Triethylamine (20.89 g) was added in 10 minutes at 27.3°C and stirred for 2 hours at the same temperature. Quenched the reaction mixture with water (250 mL) and separated the organic layer. The organic layer was washed with 5% HCI (2 x 50 mL), then with 3% sodium carbonate (2 x 100 mL) and then with water (50 mL). The solvent was removed completely from the organic layer through evaporation under reduced pressure at 55°C. Hexane (2 x 100 mL) was added to the crude

product and removed by evaporation at 55°C. Again hexane (130 mL) was added and stirred the mixture at 26°C for 1 hour and the solid was filtered. Washed the wet compound with hexane (50 mL) and dried under reduced pressure at 53°C for 1.5 hours to obtain the title compound. Yield: 69.4 g

Example-19: Preparation of hydrobromide salt of Lumacaftor

A solution of potassium carbonate (37.7 g) in water (125 mL) was added to a mixture of N-(6-chloro-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3] dioxol-5-yl)cyclopropanecarboxamide (25 g) and 3-boronobenzoic acid (13.57 g) in n-butanol (200 mL) at 26°C. Triphenylphosphine (2.68 g) and Palladium acetate (0.765 g) were added to the reaction mixture at 26°C and heated to 90°C. Stirred the reaction mixture at the same temperature for 1 hour and cooled to 26°C. The reaction mixture was filtered and the filtrate was concentrated by evaporating n-butanol under reduced pressure at 56°C and water (200 mL) was added. The aqueous layer was washed with toluene (200 mL) and the pH was adjusted to 2 using concentrated hydrochloric acid. The reaction mixture was extracted with ethyl acetate (500 mL) and the organic layer was washed with water (200 mL). The organic layer was washed with 5% sodium bicarbonate solution (100 mL) and then with water (200 mL). The solvent was removed from the organic layer completely by evaporation under reduced pressure at 50°C. Isopropyl alcohol (300 mL) was added to the crude product and evaporated completely at 50°C. Again Isopropyl alcohol (300 mL) was added and heated to 82.2°C to obtain clear solution and stirred for 20 minutes at the same temperature. Cooled the solution to 67.2°C and hydrobromide (6.62 g) was added slowly. Further cooled the reaction mixture to 26°C and stirred for 2 hours at the same temperature. The solid was filtered and washed with isopropyl alcohol (30 mL) to obtain the title compound. Yield: 29.5 g

Example-20: Preparation of Lumacaftor from Lumacaftor hydrobromide salt.

To a mixture of hydrobromide salt of Lumacaftor (5 g) in ethyl acetate (50 mL), a solution of sodium bicarbonate (0.788 g) in water (20 mL) at 26°C and stirred for 20 minutes at the same temperature. Separated the organic layer and removed the solvent through evaporation under reduced pressure at 26°C. The solid was dried at 45°C for 3 hours under reduced pressure to obtain the title compound. Yield: 4.1 g

Example-21 : Preparation of Lumacaftor

N-(6-bromo-5-methylpyndin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl) cyclopropanecarboxamide (20 g) and 3-(4,4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)benzoic acid (14.48 g) were added to a mixture of potassium carbonate (32.3 g) in dimethylformamide (100 ml_) and water (20 ml_) at 26°C. $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.984 g) was added to the above reaction mixture at the same temperature and heated to 70°C. The reaction mixture was stirred for 1 hour at 70°C and cooled to 26°C. The reaction mixture was quenched with water (200 ml_) and ethyl acetate (200 ml_) was added. Cooled the reaction mixture to 10°C and adjusted the pH of the reaction mixture to 2 using 36% hydrochloric acid. The reaction mixture was filtered and separated the organic layer. 10% aqueous hydrochloride (100 ml_) was added and stirred for 15 minutes at 26°C. Separated the organic layer and again 10% aqueous hydrochloride (100 ml_) was added. Stirred the reaction mixture for 15 minutes and separated the organic layer. The solvent was evaporated completely at 52°C under reduced pressure and chased with 2-propanol (50 ml_). 2-propanol (50 ml_) was added to the crude product at 26°C and stirred for 1.5 hours at the same temperature. 36% aqueous hydrochloride (5 ml_) was added at 26°C and stirred for 15 hours at same temperature. The reaction mixture was cooled to 5°C and stirred for 1 hour at this temperature. The solid was filtered and washed with 2-propanol (5 ml_). The solid was dried at 68°C for 4.5 hour under reduced pressure to obtain the title compound. Yield: 13 g; Purity by HPLC: 99.23%

Example-22: Preparation of Lumacaftor

To a mixture of N-(6-chloro-5-methylpyridin-2-yl)-1 -(2,2-difluoro benzo[d][1 ,3] dioxol-5-yl)cyclopropanecarboxamide (2 g) and 3-(4,4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)benzoic acid (1.623 g) in dioxane (40 ml_) under nitrogen atmosphere, Potassium carbonate (3.39 g) in water (12 ml_) was added at 26°C. $Pd(dppf)Cl2.CH_2Cl2$ (0.445 g) was added at the same temperature and heated to 87°C. Stirred the reaction mixture at 87°C for 14 hours and cooled to 26°C. Adjusted the pH of the reaction mixture to 2 with concentrated hydrochloric acid and extracted into ethyl acetate (60 ml_). Solvent was evaporated under reduced pressure at 26°C to obtain the title compound. Yield: 4 g (crude)

Example-23: Preparation of Lumacaftor

To a mixture of N-(6-chloro-5-methylpyridin-2-yl)-1 -(2,2-difluoro benzo[d][1 ,3] dioxol-5-yl)cyclopropanecarboxamide (2 g) and 3-(4,4,5,5-tetramethyl-1 ,3,2-

dioxaborolan-2-yl)benzoic acid (1.623 g) in dimethoxyethane (40 mL) under nitrogen atmosphere, Potassium carbonate (3.39 g) in water (12 mL) was added at 26°C. $Pd(dppf)Cl_2.CH_2Cl_2$ (0.445 g) was added at the same temperature and heated to 77°C. Stirred the reaction mixture at 77°C for 15 hours and cooled to 26°C. Adjusted the pH of the reaction mixture to 2 with concentrated hydrochloric acid and extracted into ethyl acetate (60 mL). Solvent was evaporated under reduced pressure at 26°C to obtain the title compound. Yield: 4 g (crude).

Example-24: Preparation of Lumacaftor

To a mixture of N-(6-chloro-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3] dioxol-5-yl)cyclopropanecarboxamide (2 g) and 3-boronobenzoic acid (1.086 g) in dimethylformamide (40 mL) under nitrogen atmosphere, sodium carbonate (3.01 g) in water (4.5 mL) was added at 26°C. Palladium acetate (0.122 g) and triphenylphosphine (0.429 g) was added at the same temperature and heated to 80°C. The reaction mixture was stirred for 3 hours at 80°C for the completion of the reaction.

Example-25: Preparation of Lumacaftor

To a mixture of N-(6-chloro-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3] dioxol-5-yl)cyclopropanecarboxamide (2 g) and 3-boronobenzoic acid (1.086 g) in 2-propanol (15 mL) under nitrogen atmosphere, potassium carbonate (3.01 g) in water (5 mL) was added at 26°C. Palladium acetate (0.122 g) and triphenylphosphine (0.429 g) was added at the same temperature and heated to 80°C. The reaction mixture was stirred for 5.5 hours at 80°C and the solvent was removed by evaporation at 45°C and water (20 mL) was added. Washed the aqueous layer with toluene (20 mL) and adjusted the pH of the aqueous layer to 2 with concentrated hydrochloric acid. Extracted the aqueous layer with ethyl acetate (50 mL) and the organic layer was washed with water (20 mL), 5% sodium bicarbonate solution (10 mL) and then with water (20 mL). The solvent was evaporated at 45°C under reduced pressure and hexane (10 mL) was added. The mixture was stirred for 1.5 hour at 26°C and filtered to obtain the title compound. Yield: 700 mg

Example-26: Preparation of Lumacaftor

To a mixture of N-(6-chloro-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3] dioxol-5-yl)cyclopropanecarboxamide (2 g) and 3-boronobenzoic acid (1.086 g) in dioxane (15 mL) under nitrogen atmosphere, potassium carbonate (3.01 g) in

water (5 ml_) was added at 26°C. Palladium acetate (0.122 g) and triphenylphosphine (0.429 g) was added at the same temperature and heated to 80°C. The reaction mixture was stirred for 14 hours at 80°C and the solvent was removed by evaporation at 45°C and water (20 ml_) was added. Washed the aqueous layer with toluene (20 ml_) and adjusted the pH of the aqueous layer to 2 with concentrated hydrochloric acid. Extracted the aqueous layer with ethyl acetate (50 ml_) and the organic layer was washed with water (20 ml_), 5% sodium bicarbonate solution (10 ml_) and then with water (20 ml_). The solvent was evaporated at 45°C under reduced pressure and hexane (10 ml_) was added. The mixture was filtered to obtain the title compound. Yield: 1.1 g

Example-27: Preparation of Lumacaftor

To a mixture of N-(6-chloro-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3] dioxol-5-yl)cyclopropanecarboxamide (2 g) and 3-boronobenzoic acid (1.086 g) in tert. Butanol (15 ml_) under nitrogen atmosphere, potassium carbonate (3.01 g) in water (5 ml_) was added at 26°C. Palladium acetate (0.122 g) and triphenylphosphine (0.429 g) was added at the same temperature and heated to 80°C. The reaction mixture was stirred for 7.5 hours at 80°C for the completion of the reaction.

Example-28: Preparation of Lumacaftor

To a mixture of N-(6-chloro-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3] dioxol-5-yl)cyclopropanecarboxamide (2 g) and 3-boronobenzoic acid (1.086 g) in 2-butanol (15 ml_) under nitrogen atmosphere, potassium carbonate (3.01 g) in water (10 ml_) was added at 26°C. Palladium acetate (0.061 g) and triphenylphosphine (0.215 g) was added at the same temperature and heated to 80°C. The reaction mixture was stirred for 7 hours at 81°C for the completion of the reaction.

Example-29: Preparation of Lumacaftor

To a mixture of N-(6-chloro-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3] dioxol-5-yl)cyclopropanecarboxamide (2 g) and 3-boronobenzoic acid (1.086 g) in n-butanol (10 mL) under nitrogen atmosphere, sodium carbonate (2.312 g) in water (10 mL) was added at 26°C. Palladium acetate (0.061 g) and triphenylphosphine (0.215 g) was added at the same temperature and heated to 80°C. The reaction mixture was stirred for 5 hours at 91°C for the completion of the reaction.

Example-30: Preparation of hydrobromide salt of Lumacaftor

Lumacaftor (1 g) was dissolved in isopropyl alcohol (10 ml_) at 72°C and cooled to 60°C. Hydrobromic acid (0.268 g) was added at 60°C into the above solution and cooled to 26°C. Stirred the reaction mixture for 3 hours at same temperature and the solid was filtered. The cake was washed with isopropyl alcohol (3 ml_) and dried under vacuum at 60°C for 11.5 hours to obtain the title compound. Yield: 786 mg.

Example-31 : Preparation of crystalline form SV1 of Lumacaftor.

Lumacaftor (3 g) was dissolved in 1,4-dioxane (15 mL) at 50°C and rapidly cooled to -78°C to precipitate solid. The reaction mixture was allowed to attain 25°C and solid was filtered to obtain 1.6 g of the title compound.

Example-32: Preparation of crystalline form SV2 of Lumacaftor

Crystalline form SV1 of Lumcaftor (0.8 g) obtained in example-34 was dried under vacuum at 100°C for 1 hour to obtain the title compound.

Example-33: Preparation of crystalline form SV1 of Lumacaftor.

Lumacaftor (0.5 g) was dissolved in 1,4-dioxane (2 mL) at 25°C and rapidly cooled to -78°C to precipitate solid. The precipitated solid was allowed to attain 25°C and solid was filtered to obtain title compound.

Example-34: Preparation of crystalline form SV2 of Lumacaftor

Crystalline form SV1 of Lumacaftor that was obtained in example- 37 was heated to 140°C and cooled to 25°C in a thermo gravimetric analyzer to obtain title compound.

Example-35: Preparation of crystalline form SV3 of Lumacaftor

Lumacaftor (2 g) was dissolved in acetic acid (20 mL) at 60°C and rapidly cooled to -78°C. The reaction mixture was then allowed to attain 26°C and maintained for 1 hour at the same temperature. The solid was filtered and dried under vacuum for 2 hours at 100°C to obtain title compound.

Example-36: Preparation of crystalline form SV3 of Lumacaftor

Lumacaftor (3 x 0.1 g) was stirred with 0.7 mL of each solvent (i.e., Nitromethane, 1,2-dimethoxy ethane and hexane) at 30°C for 24 hours to obtain title compound.

Example-37: Preparation of crystalline form SV4 of Lumacaftor

Lumacaftor (0.5 g) was dissolved in 1,2-dimethoxy ethane (10 mL) at 60°C and rapidly cooled to -70°C and maintained for 10 minutes at the same temperature. The solution was then allowed to evaporate the solvent under atmospheric

pressure at 26°C in an open beaker for 20 hours to obtain title compound.

Example-38: Preparation of crystalline form SV3 of Lumacaftor

Crystalline form SV1 of Lumacaftor obtained at example-34 was packed in an amber colour glass vial and stored for 12 days at 25°C to obtain the title compound.

Example-39: Preparation of crystalline form SV1 of Lumacaftor.

Lumacaftor (1 g) was dissolved in a mixture of 1,4-dioxane (5 mL) and water (1 mL) and a crystalline form SV1 seed (100 mg) at 26°C. The mixture was stirred for 5.5 hours at the same temperature and the solid was filtered to obtain the title compound.

Example-40: Preparation of crystalline form SV1 of Lumacaftor.

A suspension of Lumacaftor (1 g) in 1,4-dioxane (7 mL) was stirred at 26°C for 2 hours and the solid was filtered to obtain title compound.

Example-41 : Preparation of crystalline form SV2 of Lumacaftor

Crystalline form SV1 (100 mg) was heated to 100°C in 1 hour under reduced pressure in a tray drier to obtain the title compound.

Example-42: Preparation of crystalline form SV2 of Lumacaftor

Crystalline form SV1 (100 mg) was dried in tray drier at 70°C for 13 hours under reduced pressure to obtain the title compound.

Example-43: Preparation of crystalline form SV2 of Lumacaftor

Lumacaftor (5.02 g) was dissolved in 1,4-dioxane (25 mL) at 52°C and the solution was filtered to make it particle free. The filtrate was cooled to -78°C rapidly and stirred at the same temperature for 1 hour. Reaction mass was allowed to reach 26°C and filtered the solid under nitrogen pressure in nutsche filter to obtain crystalline form SV1 of Lumacaftor. This solid was dried under nitrogen pressure for 1 hour in the nutsche filter and dried further in a tray drier under reduced pressure at 70°C for 12 hours to obtain 2.5 g of title compound.

CLAIMS

1. Hydrobromide salt of Lumacaftor.

2. A process for the preparation of Hydrobromide salt of Lumacaftor comprising the step of contacting hydrobromic acid with Lumacaftor.

3. A crystalline form SV1 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at 6.52, 9.30, 10.45, 10.73, 11.88, 17.19, 19.46, 20.28 and 24.7 ±0.2° 2Θ.

4. A crystalline form SV2 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at 9.67, 10.74, 11.32, 13.85, 19.25, 20.34, 26.47 and 27.25 ±0.2° 2Θ.

5. A crystalline form SV4 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at 9.39, 12.91 , 14.23, 15.98, 23.69, 27. 12 and 27.95 ±0.2° 2Θ.

6. A process for the preparation of crystalline form SV1 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at 6.52, 9.30, 10.45, 10.73, 11.88, 17.19, 19.46, 20.28 and 24.7 ±0.2° 2Θ comprising the step of crystallizing Lumacaftor form SV1 from the solution comprising Lumacaftor and 1,4-dioxane.

7. A process for the preparation of crystalline form SV2 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at 9.67, 10.74, 11.32, 13.85, 19.25, 20.34, 26.47 and 27.25 ±0.2° 2Θ, comprising the step of drying crystalline form SV1 of Lumacaftor.

8. A process for the preparation of crystalline form SV3 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at 6.13, 12.1 9, 12.83, 17.08, 22.78, 24.20, 25.47, 26.39 and 28.02 ±0.2° 2Θ, comprising the step of treating Lumacaftor with solvent or solvent mixture comprising acetic acid.

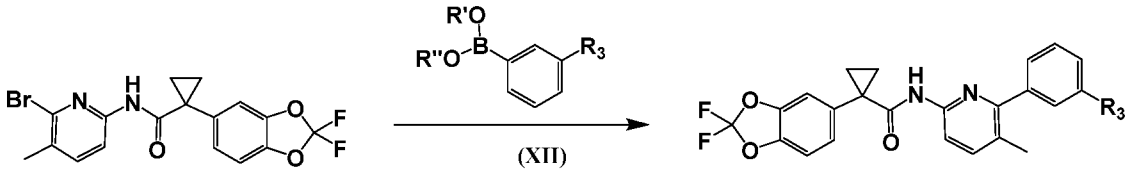
9. In another aspect, the present application provides a process for the preparation of crystalline form SV3 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at 6.13, 12.19, 12.83, 17.08, 22.78, 24.20, 25.47, 26.39 and 28.02 ±0.2° 2Θ, comprising the step of suspending Lumacaftor in a solvent selected from the group comprising of nitromethane, 1,2-dimethoxy ethane and hexane.

10. A process for the preparation of crystalline form SV4 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at 9.39, 12.91 , 14.23, 15.98, 23.69, 27. 12 and 27.95 ±0.2° 2Θ, comprising the step of crystallizing Lumacaftor from solvent or mixture of solvents comprising 1,2-dimethoxy ethane.

11. A process for the preparation of crystalline form SV1 of Lumacaftor, characterized by a PXRD pattern comprising the peaks at 6.52, 9.30, 10.45, 10.73, 11.88, 17.19, 19.46, 20.28 and 24.7 ±0.2° 2Θ comprising the step of treating Lumacaftor with 1,4-dioxane or a mixture thereof.

12. A process for the preparation of Lumacaftor or salts thereof, comprising the step of reacting 3-boronobenzoic acid or a derivative thereof with N-(6-halo-5-methylpyridin-2-yl)-1 -(2,2-difluorobenzo[d][1 ,3]dioxol-5-yl)cyclopropanecarboxamide in presence of an inert solvent selected from the group comprising of water, dimethylformamide, dimethoxyethane, 1,4-dioxane, 2-propanol, n-butanol, 2-butanol, tert. Butanol or mixtures thereof.

13. A process for the preparation of Lumacaftor of formula or ester thereof, comprising the step of reacting N-(6-bromo pyridin-2-yl) cyclopropyl carboxamide of formula (XI) with borolanyl benzene of formula (XII) or its derivatives thereof; wherein R3 is same as defined above and R' and R" may be same or different selected from hydrogen, alkyl, aryl or both together form a ring with C2 to C6 aliphatic chain.



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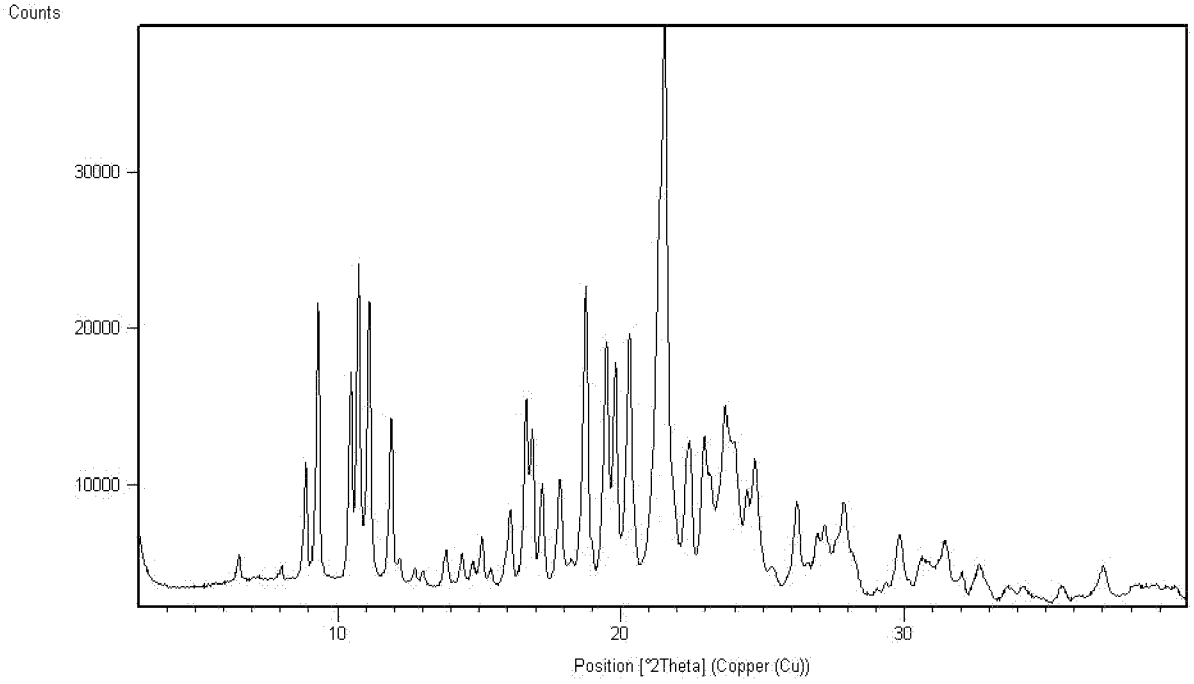


Figure 1

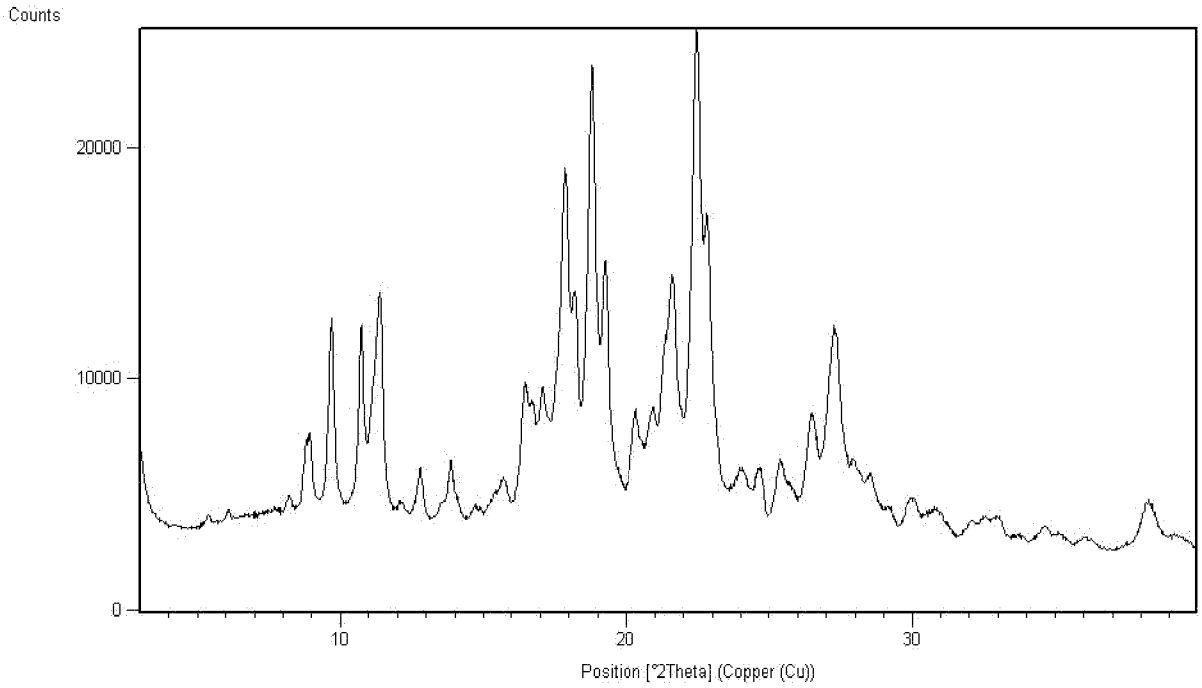


Figure 2

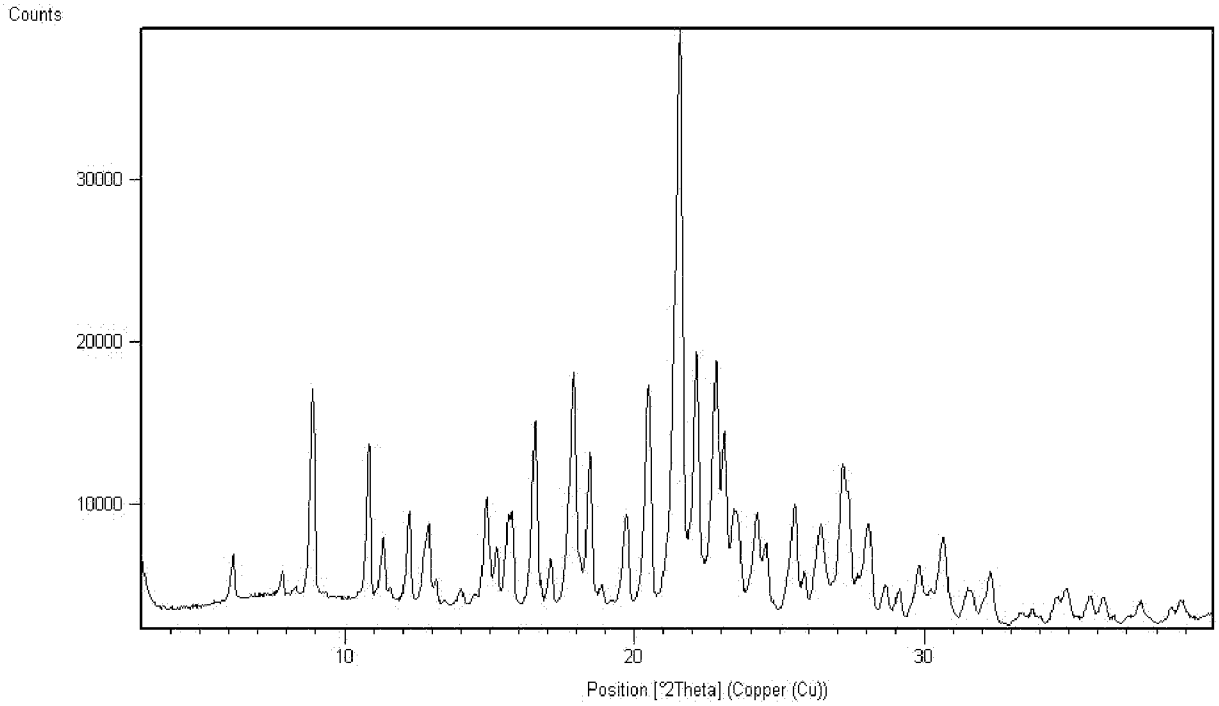


Figure 3

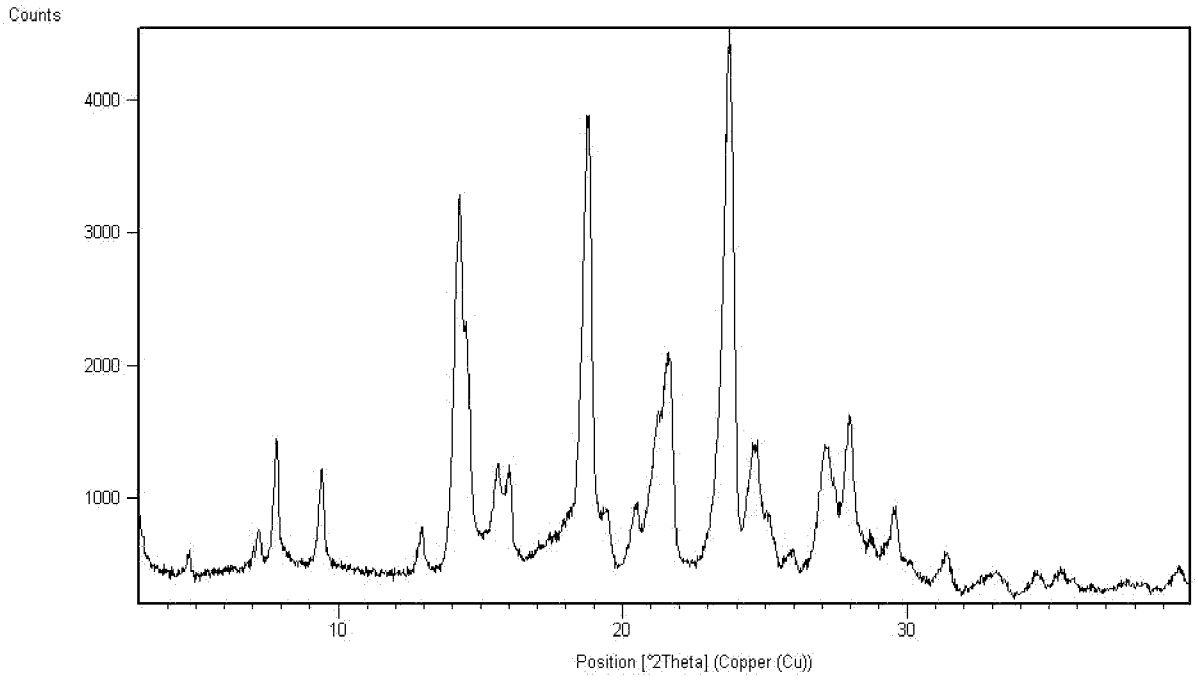
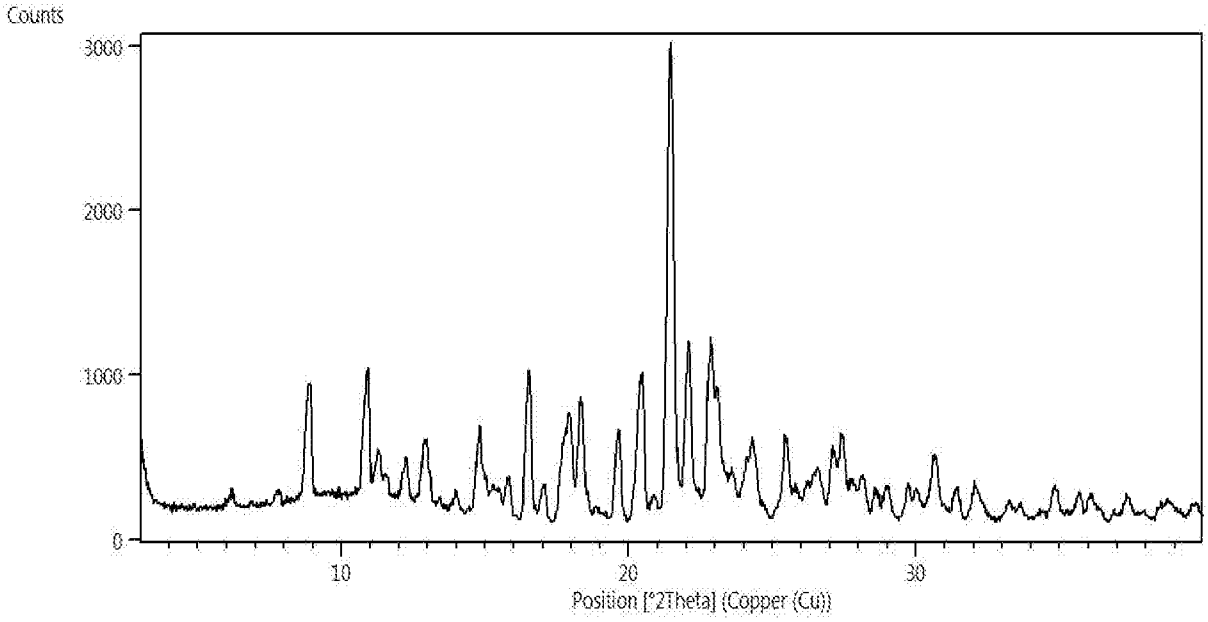


Figure 4



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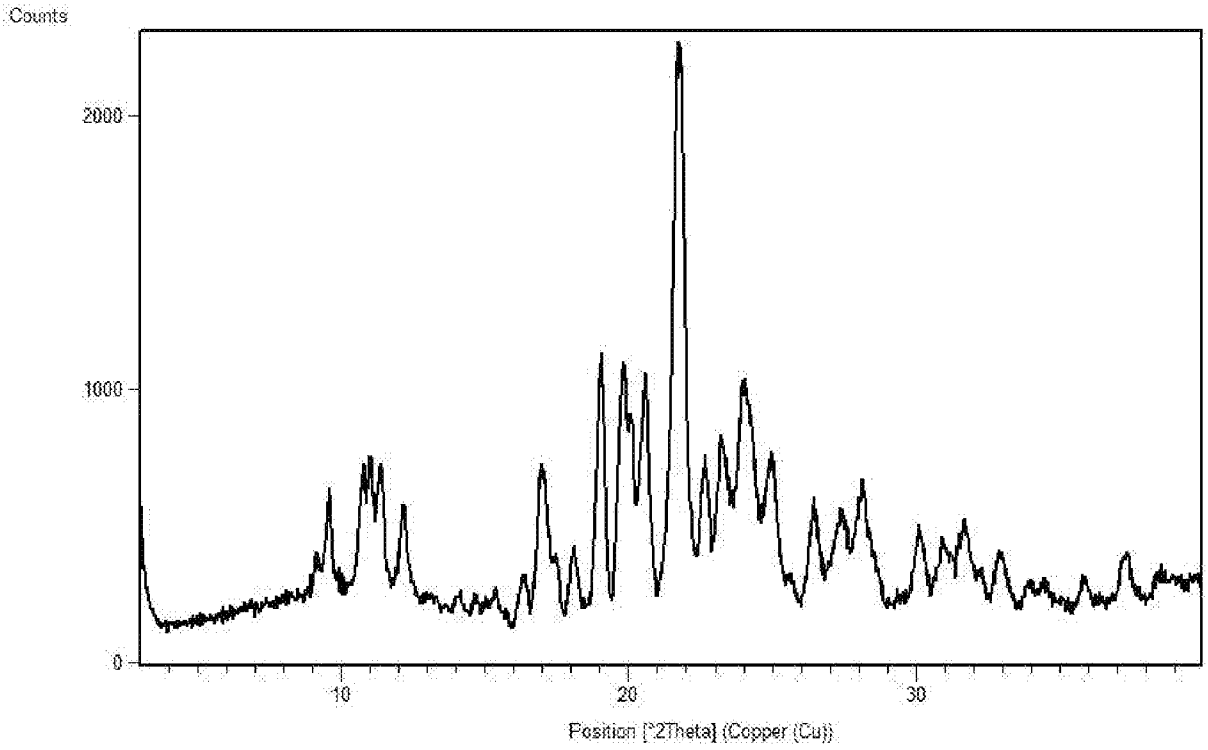

Figure 6

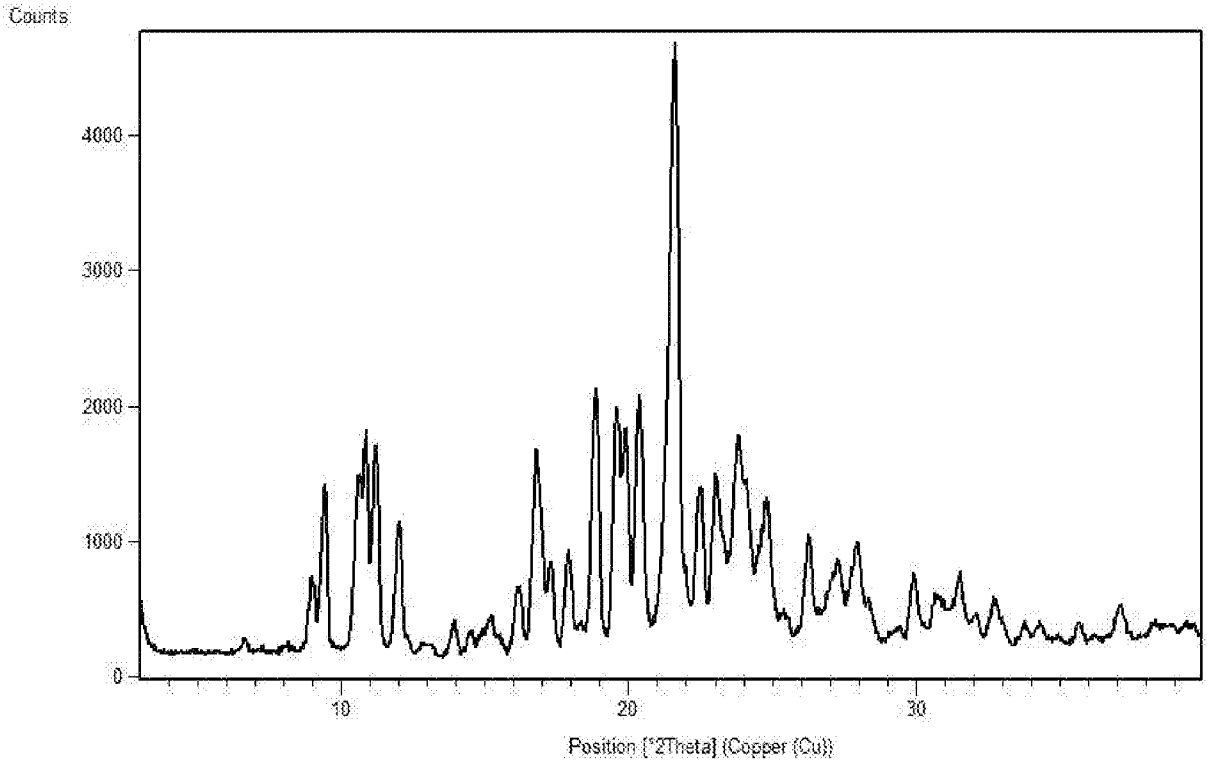

Figure 7

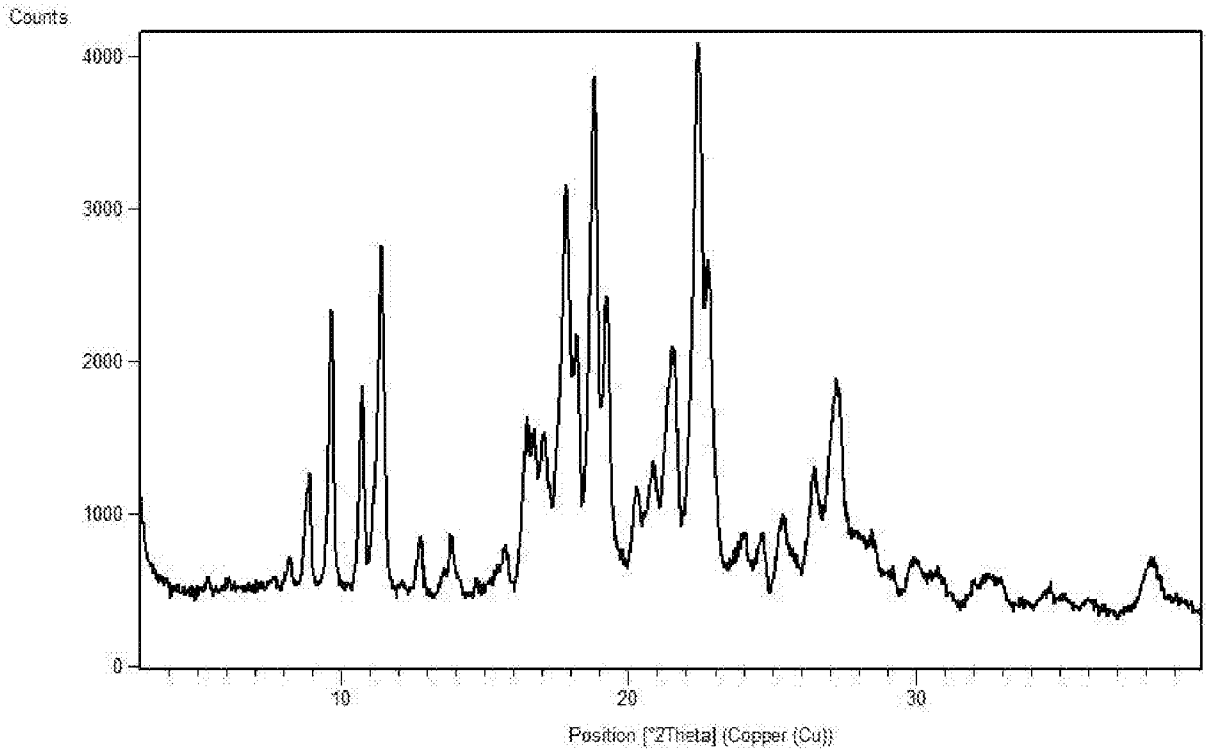

Figure 8

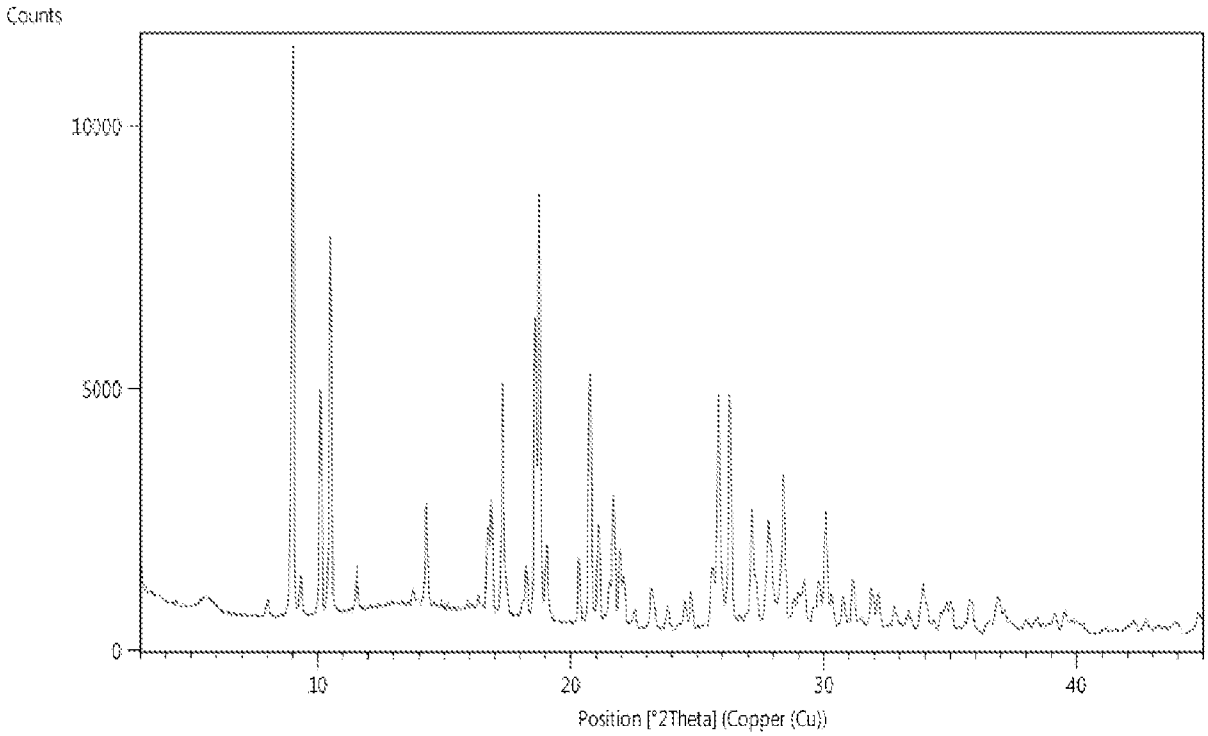

Figure 9

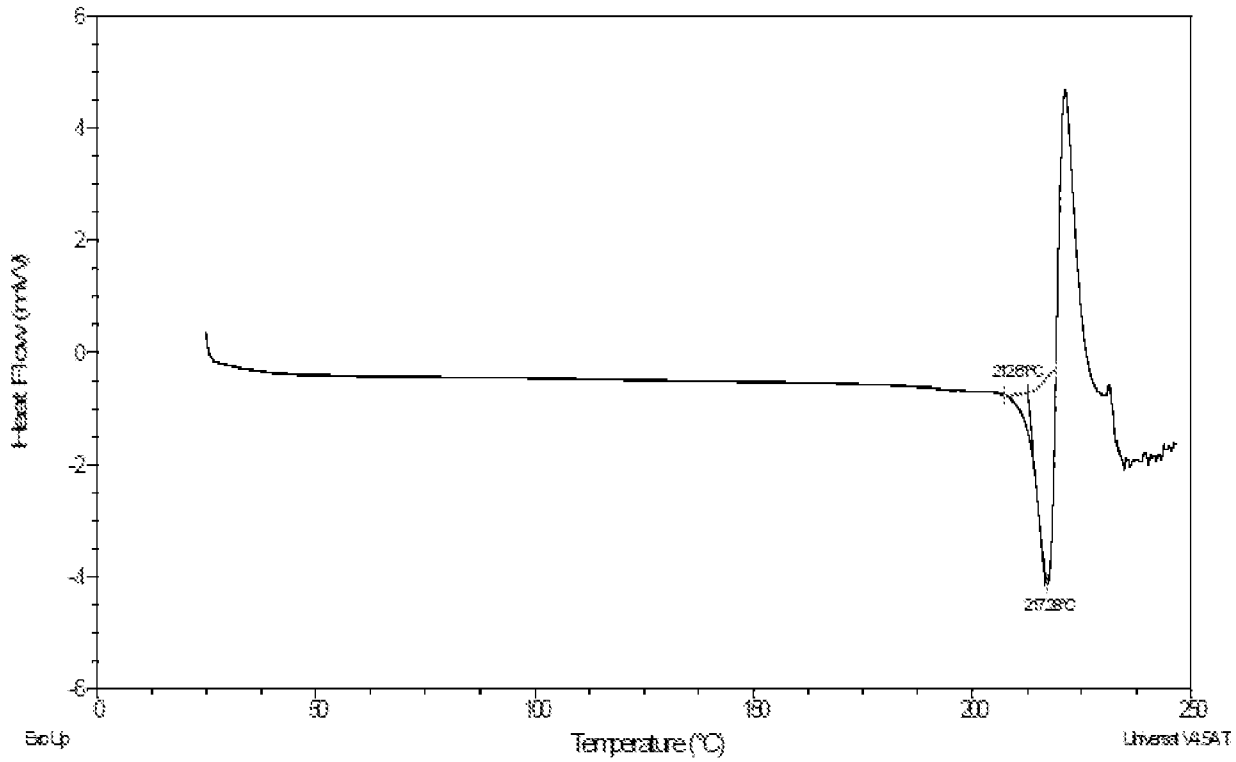

Figure 10

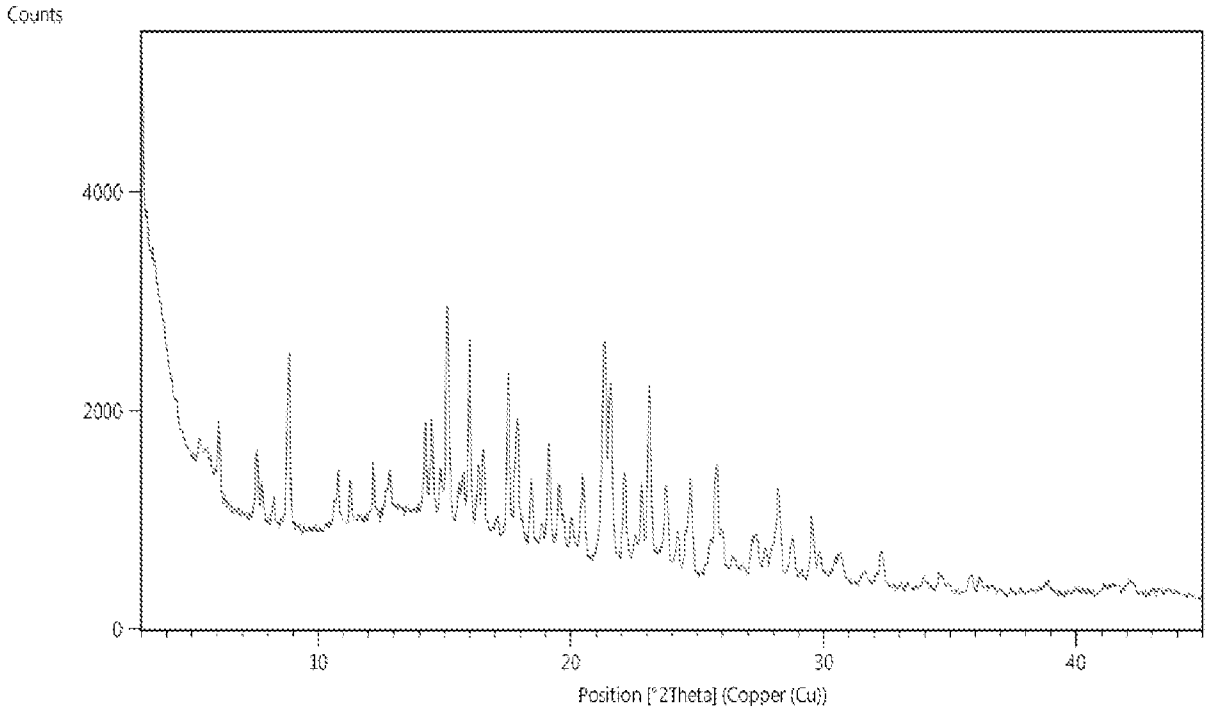

Figure 11

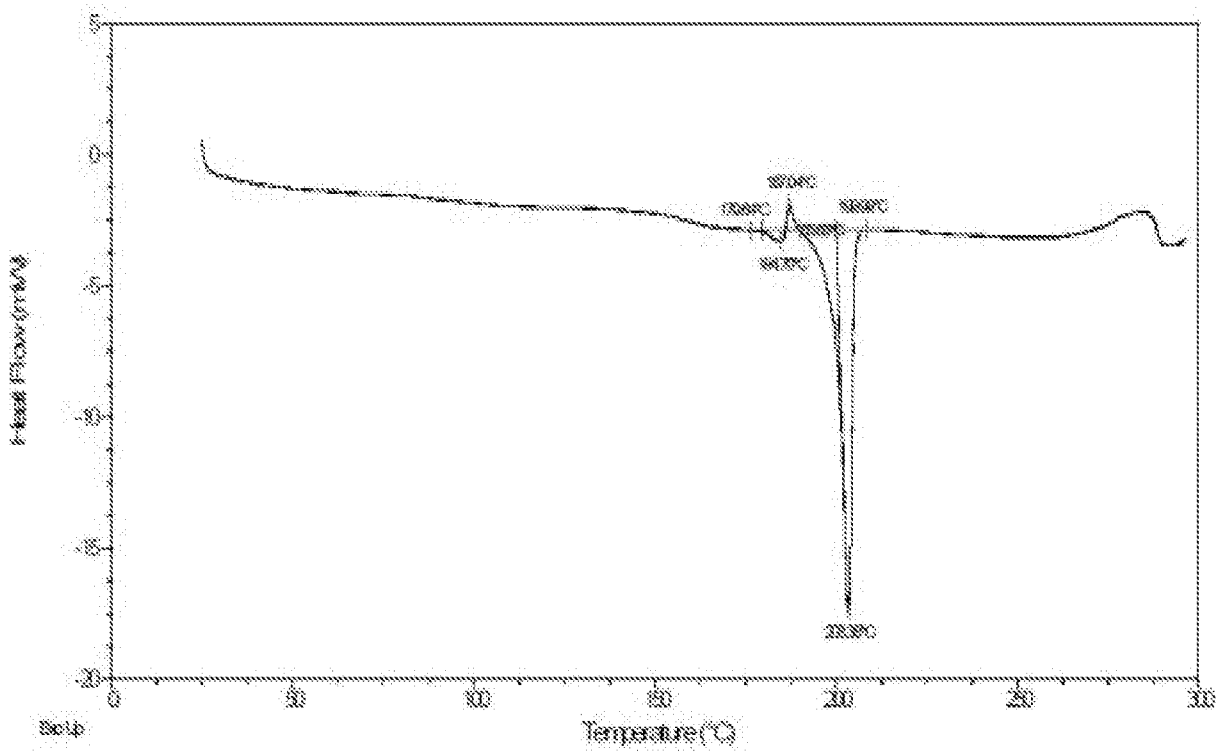

Figure 12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/051970

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/553, C07D405/14 Version=2017.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007056341 A1 (VERTEX PHARMACEUTICALS INCORPORATED [US]) 18 May 2007 abstract; paragraphs [0318], [0416], [0429], [0430]; page 94, table 1, compound 396; page 148, table 4, compound 396; claim 36	1-13

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28-06-2017	28-06-2017

Name and mailing address of the ISA/	Authorized officer
Indian Patent Office Plot No. 32, Sector 14,Dwarka, New Delhi-110075 Facsimile No.	Manvender Singh Dagur Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2017/051970

Citation	Pub.Date	Family	Pub.Date
WO 2007056341 A1	18-05-2007	EP 2774925 A1	09-09-2014
		US 9216969 B2	21-12-2015
		CA 2627358 A1	17-05-2007
		JP 2015134835 A	26-07-2015