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INTELLECTUAL PROPERTY **INDIA**
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सत्यमेव जयते

बौद्धिक संपदा भारत
एकस्व| अभिकल्प| व्यापार चिह्न|
भौगोलिक उपदर्शन

भारत सरकार
GOVERNMENT OF INDIA
वाणिज्य एवं उद्योग मंत्रालय
MINISTRY OF COMMERCE & INDUSTRY
पेटेंट कार्यालय
THE PATENT OFFICE

जिस किसी से संबन्धित हो
TO WHOMSOEVER IT MAY CONCERN

मैं, अधोहस्ताक्षरी जो पेटेंट अधिनियम, 1970 की धारा 73(3) के तहत महानियंत्रक एकस्व, अभिकल्प एवं व्यापार चिह्न की ओर से प्रमाणपत्र हस्ताक्षर व जारी करने के लिए प्राधिकृत अधिकारी हूँ, एतदद्वारा यह प्रमाणित करता(ती) हूँ कि निम्नलिखित पेटेंट आवेदन के संबंध मे फाइल दस्तावेज़(जों) की सही प्रतिलिपि इसके साथ संलग्न है:

I, the undersigned, being an officer duly authorized to sign and issue the certificate on behalf of the Controller General of Patents, Designs and Trademarks in accordance with the provisions of Section 73(3) of the Patents Act, 1970, hereby certify that annexed hereto is a True Copy of the document(s) as filed in connection with the following Patent Application:

क) आवेदन संख्या / a) Application Number: **201721031453**
ख) फाइल करने की तारीख / b) Date of Filing: **05/09/2017**
ग) अनुरोधित दस्तावेज़(जों) का नाम / C) Name of the document(s) requested:

1) **Application for Grant of Patent (Form-1)**
2) **Provisional Specification filed on 05/09/2017.**

यह प्रमाणपत्र पेटेंट अधिनियम, 1970 की धारा 147(1) के अधीन मुझमे निहित शक्तियों के तहत जारी किया गया है।

This certificate is issued under the powers vested in me U/S 147(1) of The Patents Act, 1970.

दिनांक / Dated this 10th *day of* Sept. *2018*

(VIJAY T. DOYE)
सहायक नियंत्रक पेटेंट व डिजाइन / Assistant Controller of Patents and Designs
(प्राधिकृत हस्ताक्षरी/ Authorized Signatory)

FORM 1 THE PATENTS ACT, 1970 (39 of 1970) and The Patents Rules, 2003 APPLICATION FOR GRANT OF PATENT [See sections 7, 54, 135 and rule 20(1)]	(FOR OFFICE USE ONLY)	
	Application No.:	
	Filing Date:	
	Amount of Fee Paid:	
	CBR No.:	
	Signature:	

1. APPLICANT'S REFERENCE/IDENTIFICATION NO. (AS ALLOTTED BY OFFICE)	

2. TYPE OF APPLICATION [Please tick ☑ at the appropriate category]

Ordinary ☑		Convention ☒		PCT-National Phase ☒	
Divisional ☒	Patent of Addition ☒	Divisional ☒	Patent of Addition ☒	Divisional ☒	Patent of Addition ☒

3A. APPLICANT[S]

Name in full	Nationality	Country of Residence	Address of the Applicant(s)	
CADILA HEALTHCARE LIMITED	an Indian company	India	House No.	Zydus Tower
			Street	Satellite Cross Roads
			City	Ahmedabad
			State	Gujarat
			Country	India
			Pin code	380015

3B. CATEGORY OF APPLICANT [Please tick ☑ at the appropriate category]

Natural Person ☒	Other than Natural Person		
	Small Entity ☒	Startup ☒	Others ☑

4. INVENTOR[S] [Please tick ☑ at the appropriate category]

Are all the inventor[s] same as the applicant[s] named above?	Yes ☒	No ☑

If "No", furnish the details of the inventor(s):

Name in full	Nationality	Country of Residence	Address of the Inventor	
[i] SINGH, Kumar Kamlesh	Indian	India	House No.	Cadila Healthcare Limited, Zydus Tower
			Street	Satellite Cross Roads
			City	Ahmedabad
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			Country	India
			Pin code	380015
[ii] SINGH, Nikhil Amar	Indian	India	House No.	Cadila Healthcare Limited, Zydus Tower
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			State	Gujarat
			Country	India
			Pin code	380015
[iii] NARODE, Sunil Dnyaneshwar	Indian	India	House No.	Cadila Healthcare Limited, Zydus Tower
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			City	Ahmedabad
			State	Gujarat
			Country	India
			Pin code	380015
[iv] VACHHANI, Dipakkumar Dhanjibhai	Indian	India	House No.	Cadila Healthcare Limited, Zydus Tower
			Street	Satellite Cross Roads
			City	Ahmedabad
			State	Gujarat
			Country	India
			Pin code	380015
[v] PATIL, Amol Kashinath	Indian	India	House No.	Cadila Healthcare Limited, Zydus Tower
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			City	Ahmedabad
			State	Gujarat
			Country	India
			Pin code	380015

[vi] KHAIRNAR, Sandip Pundlik	Indian	India	House No.	Cadila Healthcare Limited, Zydus Tower
			Street	Satellite Cross Roads
			City	Ahmedabad
			State	Gujarat
			Country	India
			Pin code	380015

5. TITLE OF THE INVENTION

"PROCESS FOR PREPARATION OF 4-CYCLOPROPYL-5-FLUORO-6-METHYLPYRIDIN-2-AMINE"

6. AUTHORISED REGISTERED PATENT AGENT(S)	IN/PA No.	1490
	Name	AAYSU MAHLA
	Mobile No.	
7. ADDRESS FOR SERVICE OF APPLICANT IN INDIA	Name	SUBRAMANIAM & ASSOCIATES, Attorney-at-law
	Postal Address	Central Square, Suite-328, Plaza III, 20 Manoharlal Khurana Marg, Bara Hindu Rao(off Rani Jhansi Road), Delhi - 110006
	Telephone No.	+91-11-30165700
	Mobile No.	+91-7042499356/9205965311
	Fax No.	+91-11 30165798 / 30165799
	E-Mail ID	sna@sna-ip.com; sna.patent@gmail.com

8. IN CASE OF APPLICATION CLAIMING PRIORITY OF APPLICATION FILED IN CONVENTION COUNTRY,PARTICULARS OF CONVENTION APPLICATION

Country	Application Number	Filing Date	Name of the Applicant	Title of the Invention	IPC (as classified in the convention country)
N/A	N/A	N/A	N/A	N/A	N/A

9. IN CASE OF PCT NATIONAL PHASE APPLICATION, PARTICULARS OF INTERNATIONAL APPLICATION FILED UNDER PATENT CO-OPERATION TREATY (PCT)

International application Number	International filing date as allotted by the Receiving Office
Not Applicable	Not Applicable

10. IN CASE OF DIVISIONAL APPLICATION FILED UNDER SECTION 16, PARTICULARS OF ORIGINAL (FIRST) APPLICATION

Original (first) application number	Date of filing of original (first) application
Not Applicable	Not Applicable

11. IN CASE OF PATENT OF ADDITION FILED UNDER SECTION 54, PARTICULARS OF MAIN APPLICATION OR PATENT

Main application /Patent Number	Date of filing of main application
Not Applicable	Not Applicable

12. DECLARATIONS

(i) Declaration by the inventors (in case the applicant is an assignee):

We, the above-named inventors are the true and first inventors for this Invention and declare that the applicants herein are our assignees

(a) Date: 05 September 2017

(b) Signature of the inventor .....
(c) Name: **SINGH, Kumar Kamlesh**

(b) Signature of the inventor .....
(c) Name: **SINGH, Nikhil Amar**

(b) Signature of the inventor .....
(c) Name: **NARODE, Sunil Dnyaneshwar**

(b) Signature of the inventor .....
(c) Name: **VACHHANI, Dipakkumar Dhanjibhai**

(b) Signature of the inventor .....
(c) Name: **PATIL, Amol Kashinath**

(b) Signature of the inventor .....
(c) Name: **KHAIRNAR, Sandip Pundlik**

(ii) Declaration by the applicant(s) in the convention country (in case the applicant in India is different than the applicant in the convention country):

We, the applicant(s) in the convention country declare that the applicant(s) herein are our assignee or legal representative.

(iii) Declaration by the applicant(s):

We, the applicants hereby declare that:-

☑ We are in possession of the above-mentioned invention.

☑ The ~~Complete~~/Provisional specification relating to the invention is filed with this application.

☒ The invention as disclosed in the specification uses the biological material from India and the necessary permission from the competent authority shall be submitted by us before the grant of patent to us.

☑ There is no lawful ground of objection to the grant of the patent to us.

☒ We are the true and first inventors.

☑ We are the assignees of true and first inventors.

☒ The application, particulars of which are given in Paragraph-8 was the first application in convention country in respect of our invention.

☒ We claim the priority from the above-mentioned application filed in convention country and state that no application for protection in respect of the invention has been made in a convention country before that date by us or by any person from which we derive the title.

☒ Our application in India is based on International application under Patent Cooperation Treaty (PCT) as mentioned in Paragraph-9.

☒ The application is divided out of our application particulars of which are given in Paragraph-10 and pray that this application may be treated as deemed to have been filed on ..... under Section 16 of the Act.

☒ The said invention is an improvement in or modification of the invention particulars of which are given in Paragraph -11

13. FOLLOWING ARE THE ATTACHMENTS WITH THE APPLICATION

[a] Form 2

Item	Details	Fee	Remarks
~~Complete~~/Provisional specification	No. of Pages: 17	-	-
No. of Claims(s)	No. of Claims: 00; and No. of Pages: 00	-	-
Abstract	No. of Pages: 00	-	-
No. of Drawing(s)	No. of drawings: 03; and No. of pages: 03	-	-

[b] Provisional specification

[c] Drawings

[d] Statement and undertaking on Form 3

[e] General Power of Authority

Total fee ₹ **8000.00** ~~in cash/ Banker's Cheque/Bank Draft bearing No. ..... dated ..... on ..... Bank~~. [*by electronic fund transfer*]

We hereby declare that to the best of our knowledge, information and belief the facts and matters stated herein are correct and we request that a patent may be granted to us for the said invention.

Dated this 5th day of September 2017.

(AAYSU MAHLA)
[IN/PA-1490]
of SUBRAMANIAM & ASSOCIATES
ATTORNEYS FOR THE APPLICANTS

To,
The Controller of Patents
The Patent Office
At Mumbai

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)
&
The Patent Rules, 2003

PROVISIONAL SPECIFICATION

(See section 10 and rule 13)

TITLE OF THE INVENTION

"PROCESS FOR PREPARATION OF 4-CYCLOPROPYL-5-FLUORO-6-METHYLPYRIDIN-2-AMINE"

We, **CADILA HEALTHCARE LIMITED,** an Indian company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad – 380015, Gujarat, India,

The following specification describes the invention.

FIELD OF THE INVENTION

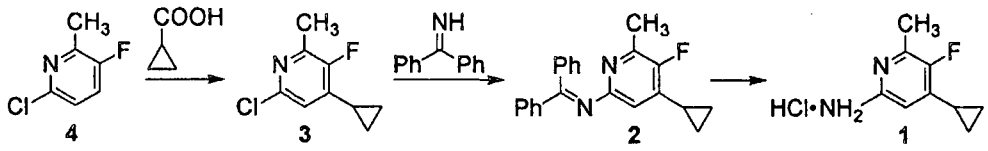
The present invention relates to process for preparation of 4-cyclopropyl-5-fluoro-6-methylpyridin-2-amine. In particular, the present invention relates to a process for preparing 4-cyclopropyl-5-fluoro-6-methylpyridin-2-amine or salts or hydrates thereof.

BACKGROUND OF THE INVENTION

The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however, reference to any prior art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

International PCT Publication No. WO 2015/165660 discloses triaminopyrimidine compounds, pharmaceutical compositions and methods for use for preventing or treating malaria.

International PCT Publication No. WO 2015/165660 discloses a process for preparation of 4-cyclopropyl-5-fluoro-6-methylpyridin-2-amine as depicted in scheme-1.



Scheme 1

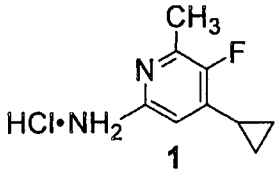
The WO '660 discloses the preparation of compound 1 as hydrochloride salt in three steps wherein isolation and/or purification of compound 3 and 2 involves preparative or flash chromatography.

In view of the above, the present invention provides a process for the preparation of intermediate compound 1 or pharmaceutically acceptable salts thereof or hydrates or solvates or polymorphs thereof, which is industrially scalable, environment friendly and efficient so as to obtain compounds of the invention in higher yields and purity. The compound 1 is useful intermediate for the preparation of various compounds used for pharmaceutical preparations.

The process for the preparation of compound 1 or intermediates thereof of the present invention, takes the advantage by using appropriate solvent systems and isolation techniques as well as purification techniques, thereby to overcome problems of lower yields, and chromatographic purifications of the prior art.

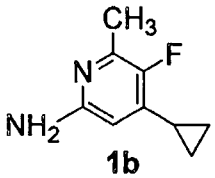
SUMMARY OF THE INVENTION

In one general aspect, there is provided a compound 1 monohydrate.



1

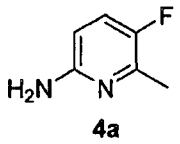
In another general aspect, there is provided a compound 1b free base.



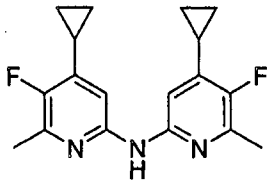
1b

In another general aspect, there is provided substantially pure compound 1 monohydrate having purity of about 99 % or more, 99.5% or more when measured by area percentage by HPLC.

In another general aspect, there is provided substantially pure compound 1 free from one or more of the following compounds:

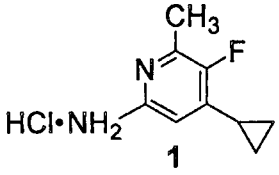


4a



4b

In another general aspect, there is provided a process for the preparation of a compound 1 monohydrate;



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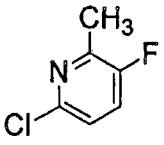
the process comprising:

(a) reacting a compound 4 with cyclopropanecarboxylic acid in one or more solvents to obtain a compound 3;



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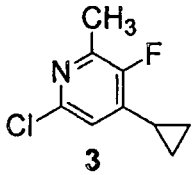
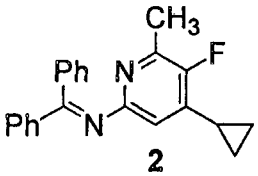


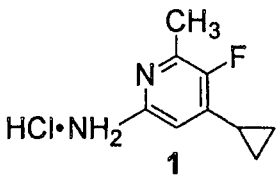
3

(b) reacting the compound 3 with diphenylmethanimine in one or more solvents to obtain a compound 2;



2

(c) reacting the compound 2 with hydrochloric acid in one or more solvents to obtain the compound 1; and



1

(d) obtaining the compound 1 monohydrate by crystallizing in one or more solvents.

In another general aspect, there is provided crystalline compound 1 monohydrate.

DETAILED DESCRIPTION OF DRAWINGS OF THE INVENTION

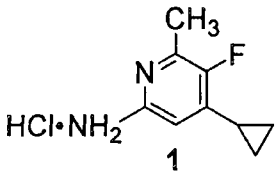
Figure-1: X-ray powder diffraction pattern of compound 1.

Figure-2: Differential Scanning Calorimetry of compound 1.

Figure-3: Thermogravimetric analysis of compound 1.

DETAILED DESCRIPTION OF THE INVENTION

The above and other objects of the present invention are achieved by the process of the present invention, which leads a process for the preparation of pure compound 1 monohydrate;



1

Optionally, the solution, prior to any solids formation, can be filtered to remove any undissolved solids or solid impurities prior to removal of the solvent. Any filtration system and filtration techniques known in the art can be used.

All ranges recited herein include the endpoints, including those that recite a range "between" two values. Term "substantially" is to be construed as modifying a term or value such that it is not an absolute. This includes, at very least, the degree of expected experimental error, technique error and instrument error for a given technique used to measure a value.

The term "substantially pure" means a compound having a purity of at least about 98% or more, by area percentage of HPLC. In particular, the compound is having a purity of at least about 99% or more, more particularly, a purity of at least about 99.5% or more, by area percentage of HPLC.

As used herein the terms, "treating", "reacting", or "condensing" have meanings as widely used by general prior art in the field of invention and can be easily understood by those skilled in the art.

As used herein the terms, "obtaining", or "getting" may include filtration, filtration under vacuum, centrifugation, and decantation for isolation of the product. The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier. The product may be preceded for further reaction with or without isolation and with or without drying in case of the product was isolated.

As used herein, the term "solution" or "reaction mixture" does not limit to a clear solution only and includes any hazy or opaque mass obtained.

The terms used throughout the description is defined herein below.

"BINAP" refers to 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

"TEA" refers to Triethylamine

"DIPEA" refers to N,N-Diisopropylethylamine

"STB" refers to Sodium-tert-butoxide

"PTB" refers to Potassium-tert-butoxide

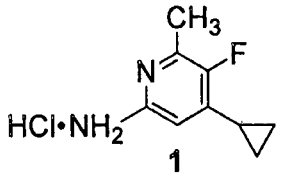
"Xantphos" refers to 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

"XPhos" refers to 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

"DBU" refers to 1,8-Diazabicyclo(5.4.0)undec-7-ene

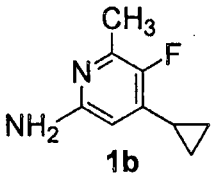
"DABCO" refers to 1,4-Diazabicyclo[2.2.0]octane

In one general aspect, there is provided a compound 1 monohydrate.



1

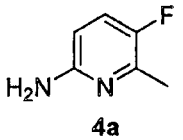
In another general aspect, there is provided a free base compound 1b.



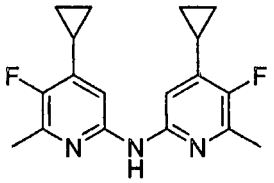
1b

In another general aspect, there is provided substantially pure compound 1 monohydrate having purity of about 99 % or more, 99.5% or more when measured by area percentage by HPLC.

In another general aspect, there is provided substantially pure compound 1 free from one or more of the following compounds:



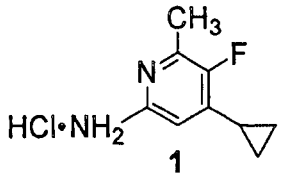
4a



4b

In general, the results of the analysis using HPLC of the compound 1 prepared by the process of the present invention has total impurities of about 0.5% or less by area percentage of HPLC and purity of about 99.5% or more, by area percentage of HPLC.

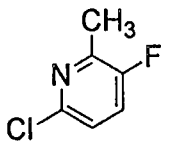
In another general aspect, there is provided a process for the preparation of a compound 1 monohydrate;



1

the process comprising:

(a) reacting a compound 4 with cyclopropanecarboxylic acid in one or more solvents to obtain a compound 3;



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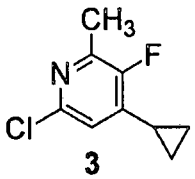
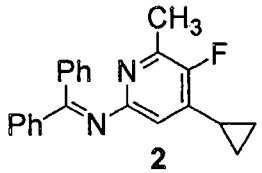


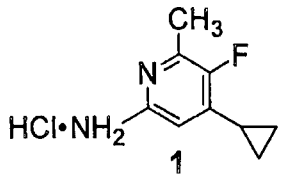
3

(b) reacting the compound 3 with diphenylmethanimine in one or more solvents to obtain a compound 2;



2

(c) reacting the compound 2 with hydrochloric acid in one or more solvents to obtain the compound 1; and



1

(d) obtaining the compound 1 monohydrate by crystallizing in one or more solvents.

In another general aspect, there is provided a process for the preparation of compound 1 monohydrate wherein the intermediate compound 3 and 2 are not isolated. The reaction of compound 4 to monohydrate compound 1 may be performed in single solvent in a one-pot process.

In general, the compound 4 is reacted with cyclopropanecarboxylic acid to obtain compound 3 in presence of acid and oxidizing agent optionally in presence of solvent.

In general, the acid comprises one or more of sulfuric acid, hydrochloric acid, hydrobromic acid, acetic acid, phosphoric acid, and trifluroacetic acid. In particular, sulfuric acid may be used.
The oxidizing agent is selected from the group consisting of mixture of ammonium persulfate and silver nitrate.

In general, the solvent comprises one or more of methanol, ethanol, isopropanol, butanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, butyl acetate, methylene dichloride, toluene, xylene, ethylbenzene, dimethylformamide, dimethylacetamide, dimethylsulfoxide, 1,4-dioxane, tetrahydrofuran, acetonitrile and water or mixture thereof. In particular, the solvent is water.

In general, the compound 3 is reacted with diphenylmethanimine to obtain compound 2 in presence of a base, a catalyst and a ligand in solvent.

In general, the base comprises one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate, barium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate, STB, PTB, pyridine, piperidine, morpholine, TEA, DIPEA, DBU, or DABCO. In particular, the STB may be used.

In general, The catalyst comprises one or more of Palladium acetate, bis(triphenylphosphine) palladium(II)chloride, Tetrakis(triphynylphosphine)palladium(0), Tris(dibenzylideneacetone) dipalladium(0), Bis(dibenzylideneacetone) dipalladium(0), Palladium(II) chloride. In particular, the Palladium acetate is used.

In general, the ligand comprises BINAP, Xantphos, Triphenylphosphine, Tributylphosphine and XPhos. In particular, BINAP is used.

In general, the solvent comprises one or more of xylene, toluene, ethylbenzene, methylene dichloride, ethylene dichloride, chloroform, carbon tetrachloride, ethyl acetate, butyl acetate, and isopropyl acetate or mixture thereof. In particular, the solvent is toluene.

In general, the compound 3 is reacted with diphenylmethanimine in presence of Di-tert-butyl dicarbonate or acetic anhydride to obtain pure compound 2. The presence of Di-tert-butyl dicarbonate or acetic anhydride resulted in reduction of impurity formation.

In general, compound 2 is reacted with hydrochloric acid to obtain compound 1 in a solvent.

In general, the solvent comprises one or more of methanol, ethanol, isopropanol, butanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, butyl acetate, methylene dichloride, toluene, xylene, ethylbenzene, dimethylformamide, dimethylacetamide, dimethylsulfoxide, 1,4-dioxane, tetrahydrofuran, acetonitrile and water or mixture thereof. In particular, the solvent is a mixture of water and toluene.

In general, the compound 1 may be extracted with one or more solvents. The compound 1 monohydrate may be obtained by removal of solvent after extraction and crystallizing the residue with one or more solvents.

The solvent for extraction is selected from methylene dichloride, toluene, ethyl acetate, methyl tert-butyl ether, 1,4-dioxane, cyclohexane, diethylether, and

tetrahydrofuran or mixture thereof. In particular, the reaction mixture is extracted with methylene dichloride.

In general, the compound 4 is reacted with cyclopropanecarboxylic acid in presence of sulphuric acid and ammonium persulfate and silver nitrate in water to obtain compound 3. The compound 3 is reacted with diphenylmethanimine in presence of BINAP, palladium acetate, STB in toluene which is further reacted with conc. HCl to obtain compound 1 and isolated as monohydrate salt of compound 1.

In another general aspect, there is provided crystalline compound 1 monohydrate.

In general, the crystalline compound 1 monohydrate is further characterized by X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 10.47°, 12.76°, 25.12°, and 25.73°±0.2 2θ.

In general, the crystalline compound 1 monohydrate is further characterized by X-ray powder diffraction pattern substantially as same as depicted in Figure-1. In general, the crystalline compound 1 monohydrate is further characterized by Differential Scanning Calorimetry (DSC) as shown in Figure-2 and crystalline compound 1 monohydrate is characterized by Thermogravimetric Analysis (TGA) curve as shown in Figure-3.

In general, wherever not specified, the reaction may be performed in presence of one or more solvents comprises of water, alcohol selected from methanol, ethanol, isopropanol, and n-butanol; ester selected from ethyl acetate, isopropyl acetate, t-butyl acetate, and isobutyl acetate; ketone selected from acetone, methyl ethyl ketone and methyl isobutyl ketone; hydrocarbon selected from toluene, xylene, ethyl benzene, heptane, hexane, and cyclohexane; halogenated hydrocarbon selected from methylene dichloride, ethylene dichloride, chlorobenzene,

chloroform, and carbon tetrachloride; nitriles selected from acetonitrile and propanenitrile.

In another general aspect, there is provided a process for crystallizing the intermediate compounds of the present invention and avoid flash chromatography techniques reported in the prior art.

The examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications.

Examples

Example-1: Preparation of 6-chloro-4-cyclopropyl-3-fluoro-2-methylpyridine

In a 250 ml 4N round bottom flask, process water (30 ml) and cyclopropanecarboxylic acid (14.19 g, 164.88 mmol) were added at 25°C to 35°C and started stirring. Sulphuric acid (4.4 ml, 82.44 mmol) was charged to the reaction mixture. Silver nitrate (4.18 g, 24.73 mmol), 6-Chloro-3-fluoro-2-methylpyridine (6 g, 41.22 mmol) were charged to the reaction mixture. Aqueous solution of ammonium persulphate (65.85 g, 288.54 mmol in 90 ml water) was added to the reaction mixture in 30 to 60 min at temperature NMT 60°C. After the completion of the reaction as monitored by HPLC, toluene (30 ml) was added to the reaction mixture and stirred for 15 min. The reaction mixture filtered, separated layers from filtrate and extracted aqueous layer using toluene (30 ml). The organic layer was washed with aqueous sodium carbonate solution (30 ml) and then by water (30 ml x 2). The organic layer was distilled completely under vacuum at 60°C to obtain 3.37 g titled compound as syrupy mass.

Example-2: Preparation of N-(4-cyclopropyl-5-fluoro-6-methylpyridin-2-yl)-1,1-diphenyl-methanimine

In a 100 ml-3N round bottom flask, 6-chloro-4-cyclopropyl-3-fluoro-2-methylpyridine (2.69 g, 14.48 mmol) and toluene (30 ml) were added at 25°C to 35°C. Diphenylmethanimine (3.15 g, 17.38 mmol) was charged to the reaction mixture and stirred for 5-10 min under nitrogen purging. Racemic BINAP (270 mg, 0.43 mmol) and palladium acetate (98 mg, 0.43mmol) were added to the reaction mixture. Sodium-*tert*-butoxide (2.78 g, 28.96 mmol) was added to the reaction mixture and heated to 100 to 110° C under nitrogen. After the completion of the reaction as monitored by HPLC, the reaction mixture was cooled to 25 to 35°C and filtered over hyflo bed and washed with toluene (12 ml). The filtrate containing titled compound was preserved for next stage of reaction.

Example-3: Preparation of N-(4-cyclopropyl-5-fluoro-6-methylpyridin-2-yl)-1,1-diphenyl-methanimine:

In a 100 ml-3N RBF, 6-chloro-4-cyclopropyl-3-fluoro-2-methylpyridine (2.69 gm, 14.48 mmol) and toluene (36 ml) were charged at 25°C to 35°C. Benzophenone imine or Diphenylmethanimine (3.15 gm, 17.38 mmol), BOC anhydride (0.79 gm, 3.62 mmol) was charged to the reaction mixture and stirred for 5-10 min under nitrogen purging. Rac BINAP (361 mg, 0.58 mmol) and Palladium acetate (130 mg, 0.58mmol) was charged to the reaction mixture. Sodium-tert-butoxide (3.48 gm, 36.20 mmol) was charged to the reaction mixture and heated to 100°C to 110°C under nitrogen. After the completion of the reaction as monitored by HPLC, the reaction mixture was cooled to 25 to 35°C. Filtered reaction mixture over hyflo bed and washed bed with toluene (18 ml). Filtrate containing titled compound submitted for next stage.

Example-4: Preparation of 4-cyclopropyl-5-fluoro-6-methylpyridin-2-amine hydrochloride monohydrate

In a 100 ml-3N round bottom flask, N-(4-cyclopropyl-5-fluoro-6-methylpyridin-2-yl)-1,1-diphenylmethanimine in toluene from example-10 was added water (25

ml) at 25 to 35° C. The conc. HCl (3 ml) was charged to the reaction mixture and heated to 40 to 50° C. After the completion of the reaction as monitored by HPLC, the reaction mixture was cooled to 25 to 35°C. Layers were separated. The aqueous layer was treated with methylene dichloride and pH was adjusted to 7.5 to 8.5 using sodium carbonate solution, stirred for 15 min and layers were separated. Aqueous layer was extracted with methylene dichloride, charcoaled and acidified to pH 3 to 4 with aqueous HCl. The solvent was distilled completely and 18 ml mixture of acetonitrile and ethyl acetate was added. The reaction mixture was stirred for 1 hour at 25 to 35° C. The product was filtered and washed with ethyl acetate. The product was dried at 50° C for 4 hours under vacuum to obtain 1.62 g title compound as monohydrate yellow crystalline solid having 99.51% HPLC purity.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Dated this 5th day of September 2017.

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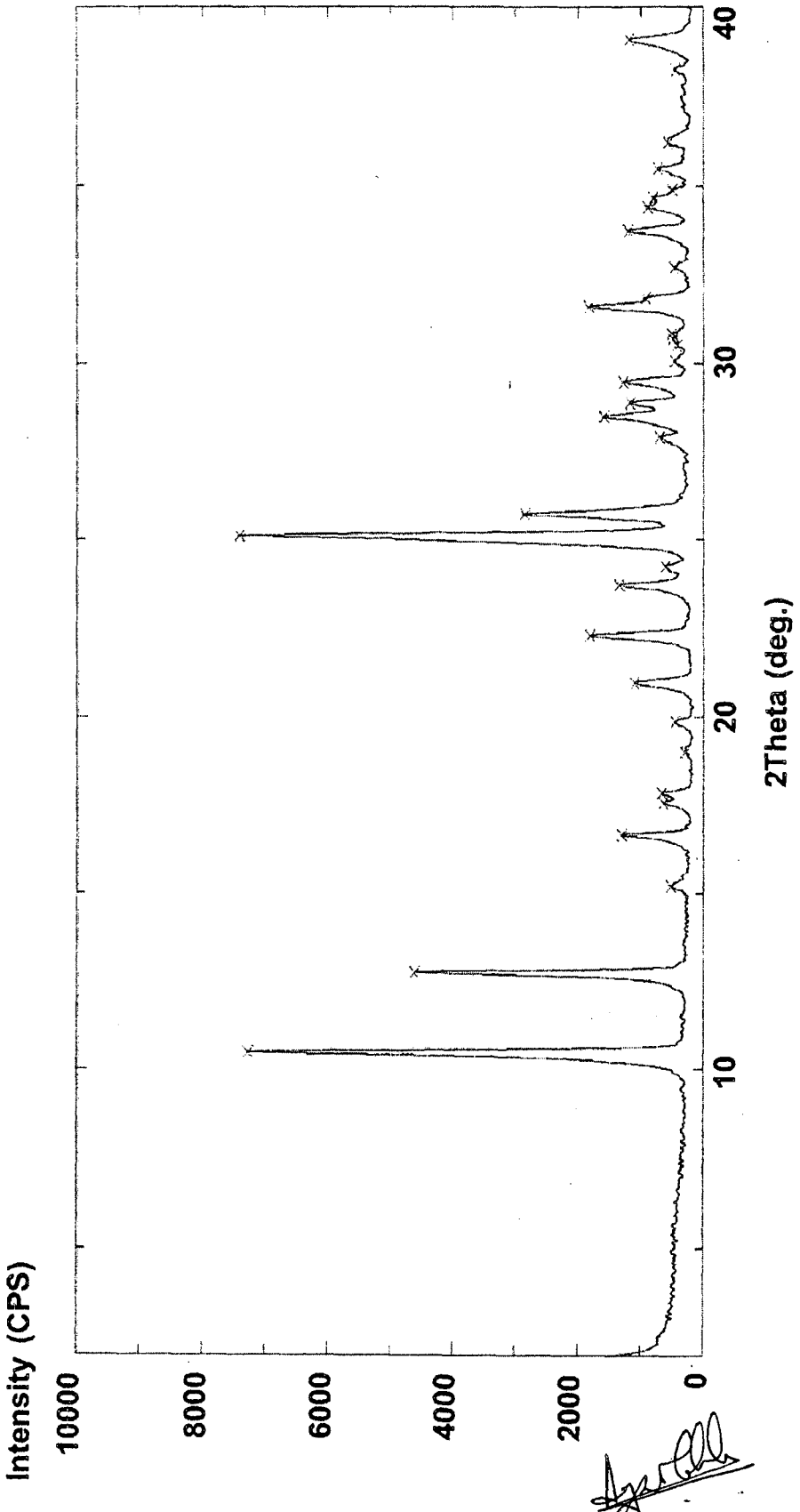
FIG.1



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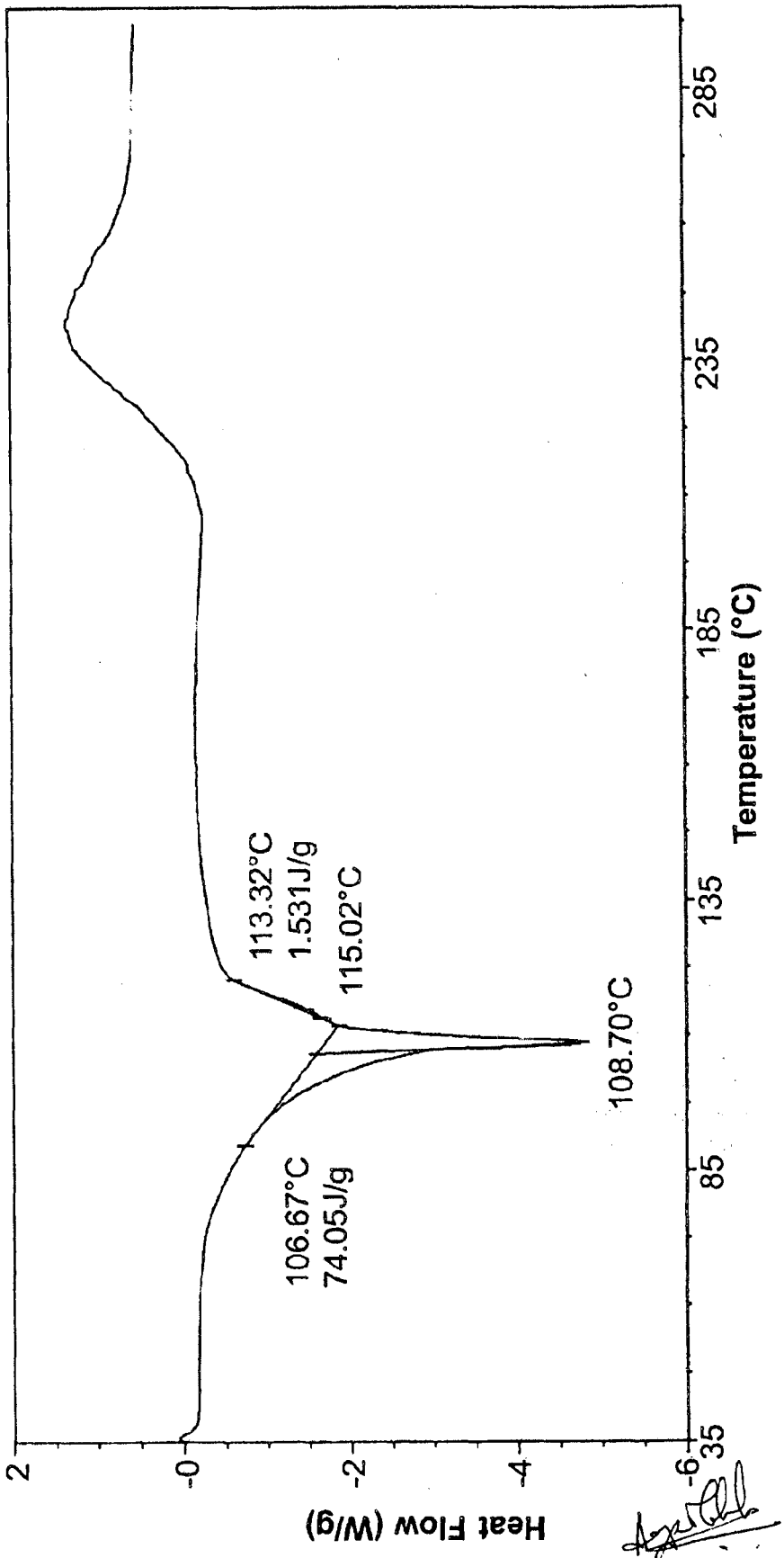

FIG.2

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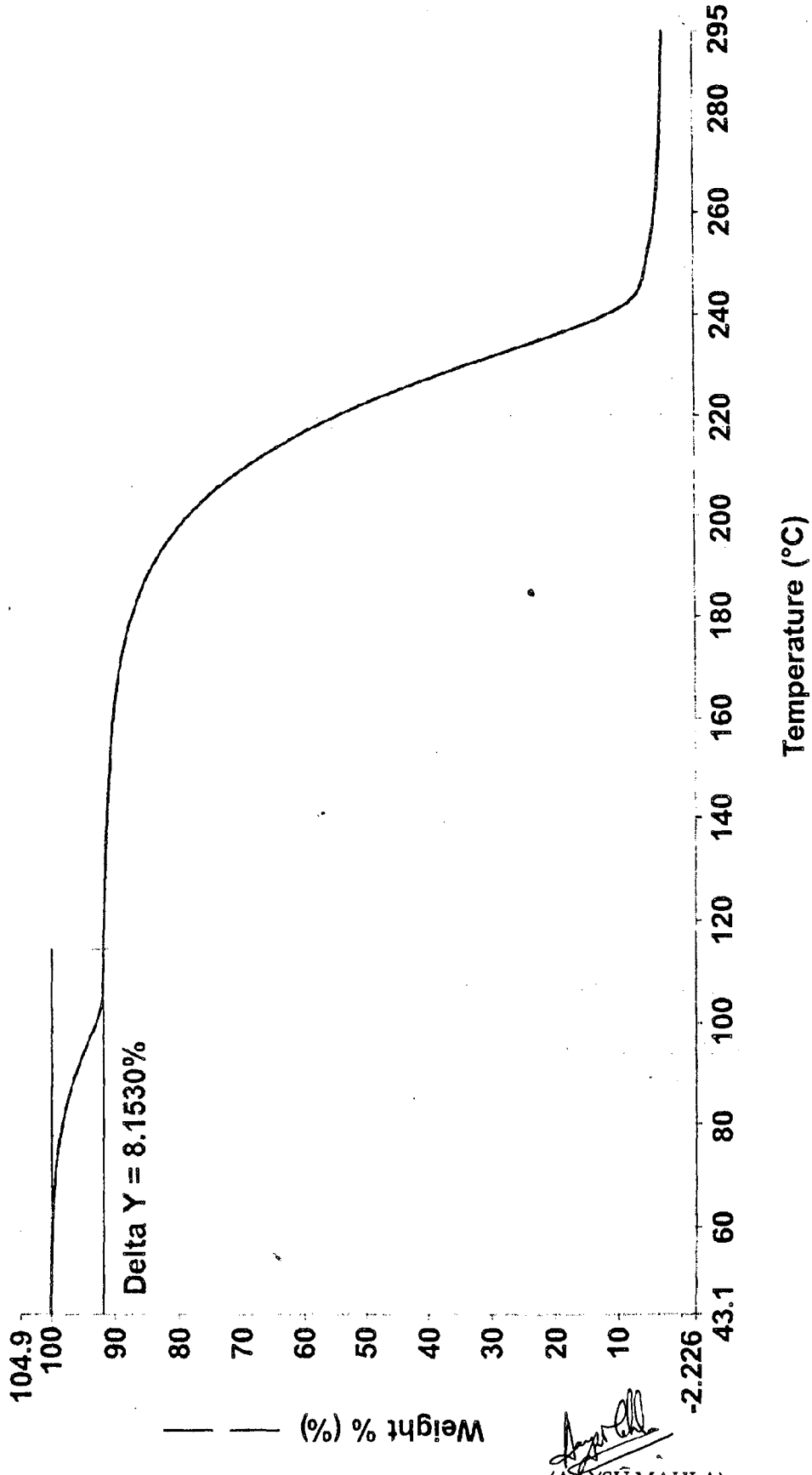
FIG.3



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