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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 August 2021 (19.08.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/162647 A1

(51) International Patent Classification:
A61K 31/505 (2006.01) *C07D 403/02* (2006.01)
A61K 31/506 (2006.01) *C07D 403/12* (2006.01)
A61P 35/00 (2006.01)

(21) International Application Number:
PCT/TR2020/050088

(22) International Filing Date:
10 February 2020 (10.02.2020)

(25) Filing Language: English

(26) Publication Language: English

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

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

(54) Title: A NOVEL PROCESS FOR PREPARATION OF PAZOPANIB HYDROCHLORIDE

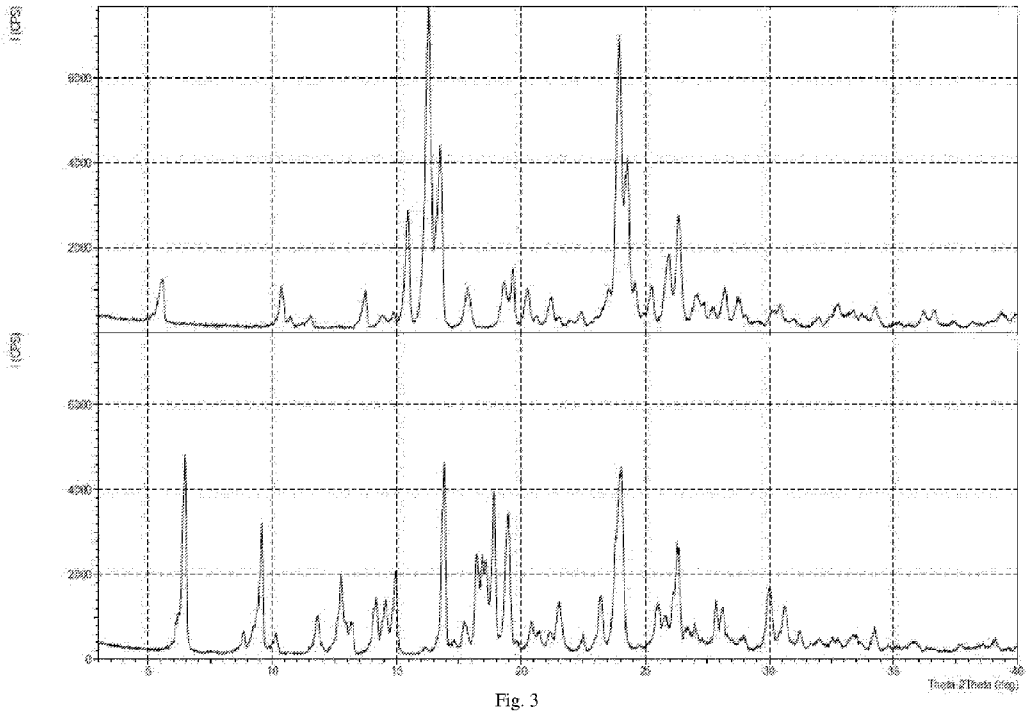

Fig. 3

(57) Abstract: The present invention relates to a new process for the preparation of a key intermediate compound and its use in a synthetic process for the preparation of pazopanib hydrochloride. The method has advantages of a simple operation, high yield and low costs. The present invention also relates to a novel polymorph of pazopanib hydrochloride.

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[Continued on next page]

Published:

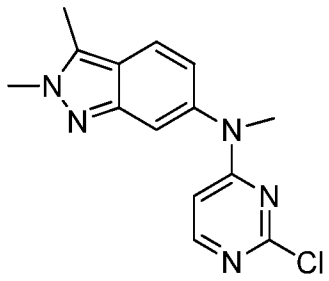
— *with international search report (Art. 21(3))*

— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

A NOVEL PROCESS FOR PREPARATION OF PAZOPANIB HYDROCHLORIDE

Technical Field

The present invention relates to an alternative and improved method for the synthesis of an intermediate which is useful for the preparation of pazopanib or pharmaceutically acceptable salts thereof. The structure of intermediate is represented by formula 4.



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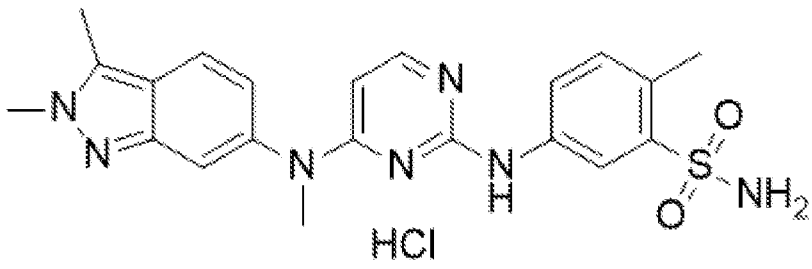
The present invention further provides a novel crystalline polymorph of pazopanib hydrochloride and its use for manufacturing crystalline forms of pazopanib hydrochloride, especially Form I.

Background Art

Pazopanib hydrochloride is chemically designated as 5-((4-((2,3-dimethyl-2*H*-indazol-6-yl)(methyl)amino)pyrimidin-2-yl)amino)-2-methylbenzenesulfonamide hydrochloride and structurally represented as below.



Pazopanib is a potent and selective multi-targeted receptor tyrosine kinase inhibitor.

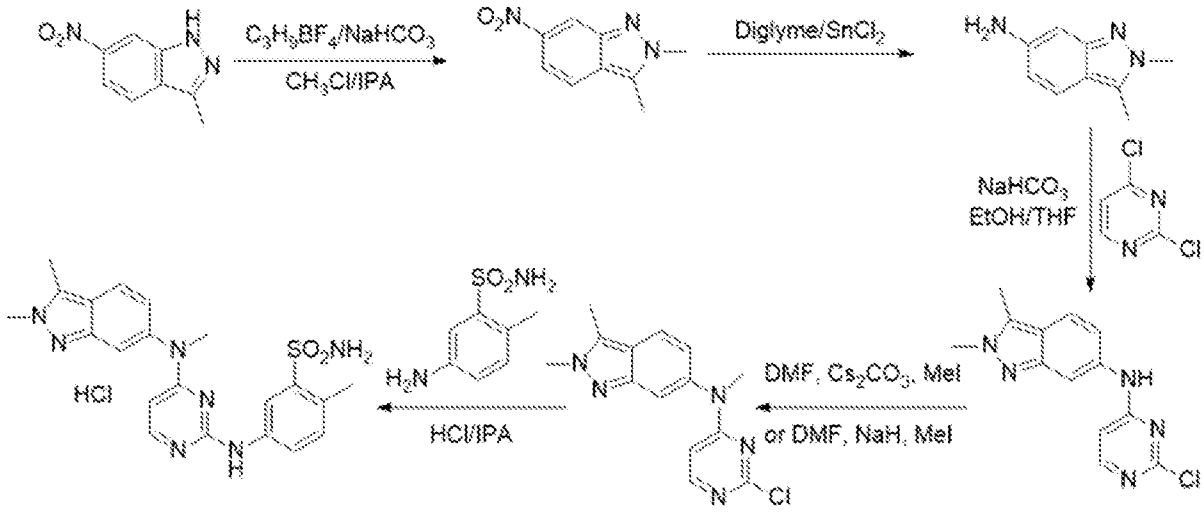
Pazopanib is marketed as its hydrochloride salt by GlaxoSmithKline in Europe and by Novartis in United States under the trade name Votrient. Votrient is indicated for the treatment of advanced Renal Cell Carcinoma (RCC) and advanced Soft-Tissue Sarcoma (STS) who have received prior chemotherapy.

The commercial tablet formulation of pazopanib hydrochloride, Votrient, contains crystalline Form I.

European Medicines Agency (EMA) public assessment report disclosed that pazopanib hydrochloride is a white to slightly yellow, non-hygroscopic, crystalline substance and the manufacturing process consistently gives pazopanib hydrochloride Form I. However, EMEA does not describe any particular characterization data for the disclosed polymorphic form.

WO 2015068175 discloses crystalline forms of pazopanib hydrochloride. A process for preparation of Form I and the characteristic powder X-ray diffraction (XRD) pattern of Form I are also disclosed in the said patent application.

Various synthetic processes for the preparation of pazopanib hydrochloride are known in the art. A method for synthesis of pazopanib hydrochloride was first disclosed and claimed in EP 1343782B1 as depicted in Scheme 1.

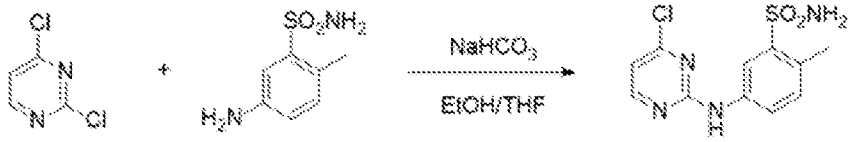


Scheme 1

According to this method, 3-methyl-6-nitro-1*H*-indazole, 2,4-dichloropyrimidine and 5-amino-2-methylbenzenesulfonamide were used as raw materials.

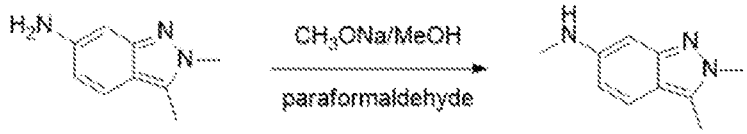
In addition, another method for synthesis of pazopanib hydrochloride was disclosed in EP 2646431B1 published on November 11, 2011. According to this method, in the first step, 5-amino-2-methylbenzenesulfonamide was reacted with 2,4-dichloropyrimidine to give 5-((4-chloropyrimidin-2-yl)amino)-2-methylbenzenesulfonamide.

First Step



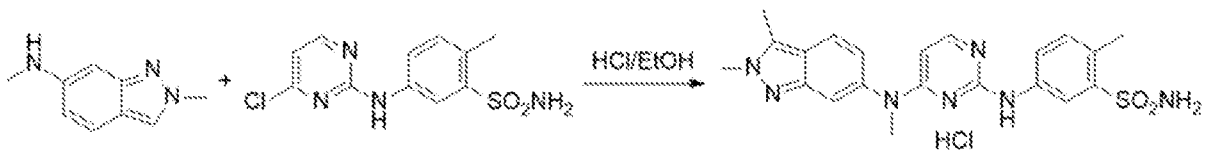
In the second step, 2,3-dimethyl-2*H*-indazol-6-amine was reacted with sodium methoxide and paraformaldehyde to obtain *N*,2,3-trimethyl-2*H*-indazol-6-amine.

Second Step



In the final step, first and second step products were reacted by using concentrated hydrochloric acid and pazopanib hydrochloride was obtained as a result.

Final Step



High yields, high purity and cost-effectiveness were claimed for both of these processes but they did not fulfill these requirements well. Since, expensive chemicals such as cesium carbonate, iodomethane, etc. were used in the first process; and starting from 2,3-dimethyl-2*H*-indazol-6-amine, yields were 89%, 83% and 42% (yield was not disclosed for pazopanib

and yield of reference example 1 is used), corresponding to 31% overall yield. In the second process, first step, second step, and final step yields were 48.3%, 70.8% and 69.1%, respectively, corresponding to 23.6% overall yield.

The increase of cost effective alternative preparation methods for intermediates of pazopanib will also affect the cost of pazopanib finished medicinal products. Thus, present invention providing cheap and high quality pazopanib intermediate would be also helpful for patients to get access to affordable and cheap pazopanib drug products.

Therefore, there is a need to develop a novel process for preparing pazopanib hydrochloride and its intermediates; in particular this novel process should be simple, cost-effective and feasible on an industrial scale production.

Summary of the invention

This invention provides an economically preferable process for the preparation of *N*-(2-chloropyrimidin-4-yl)-*N*,2,3-trimethyl-2*H*-indazol-6-amine as a key intermediate in the synthesis of pazopanib or its pharmaceutically acceptable salts thereof. The present invention provides excellent yields and purity.

Technical Problem

Active pharmaceutical ingredients (APIs) are individual components or mixture of components that are used as a part of a finished pharmaceutical drug or medicinal product, where they provide the pharmacological activity.

Research and development projects in the pharmaceutical industry mainly aim to investigate different possible synthetic routes, key intermediates, reaction steps, impurity profile, particle size, particle shape and polymorphism to produce these APIs with higher efficiency and less initial investments.

Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, may give rise to a variety of crystalline forms having distinct crystal structures and physical properties. The difference in the physical properties of different crystalline forms results from the orientation and intermolecular interactions of adjacent molecules or complexes in the bulk solid.

The relationship between polymorphic forms of pharmaceutically active substance and pharmaceutical product is well known in the pharmaceutical industry. Pharmaceutical formulation is affected by polymorphic form of the pharmaceutically active substance.

The discovery of new polymorphic forms and solvates of an active pharmaceutical ingredient provides a new opportunity to improve the performance characteristics of pharmaceutical finished product, the development of new polymorphic forms is always encouraged.

Therefore, there is a need to develop novel polymorphs of pazopanib hydrochloride having advantageous properties which are useful and well suitable for the preparation of various pharmaceutical compositions.

Most APIs can be synthesized using any of several alternative pathways.

Technical challenges involve a multitude of issues designed to improve yield, purity, stereo-selectivity, process conditions (i.e., temperature and pressure), scalability, and production economics.

By using various synthetic pathways, it is possible to lower the production costs and simplify the process; therefore, it has paramount importance to choose the right one for the general efficiency and success of the operation.

Besides the existing routes of synthesis for the preparation of pazopanib and its intermediates thereof, there remains a need for providing novel processes that would decrease the consumption of expensive chemicals that would allow cost-effective manufacturing.

Solution to Problem

For deficiencies in the prior art synthesis, our inventors developed an advanced process for the synthesis of intermediate compound to be used in the preparation of pazopanib or pharmaceutically acceptable salts thereof.

Our inventors have now discovered a method for preparation of *N*-(2-chloropyrimidin-4-yl)-*N*,2,3-trimethyl-2*H*-indazol-6-amine as intermediate in the pazopanib synthesis. Compared with the processes in the prior art this new method involves the use of cheap chemicals, mild conditions resulting in a process which substantially reduces the production cost of corresponding intermediate compound.

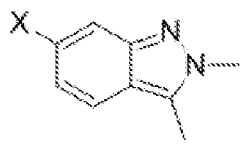
The new synthesis of intermediate shown as compound of formula 4 provides a significant economic benefit compared to the available alternative synthetic pathways of the other intermediates in the pazopanib synthesis.

A first aspect of the present invention relates to a process for preparing the compound of formula 2, wherein the process comprises of reacting 6-halo-2,3-dimethyl-2*H*-indazole (compound of formula 1) with a methylamine in presence of solvent, catalyst and a base to obtain *N*,2,3-trimethyl-2*H*-indazol-6-amine (compound of formula 2)

A second aspect of the present invention relates to a process for preparing of the compound of formula 4, wherein the compound of formula 2 reacted with 2,4-dichloropyrimidine (compound of formula 3) to prepare the compound of formula 4.

The present invention process for the synthesis of compound of formula 4 comprises the step of;

(i) reacting the 6-halo-2,3-dimethyl-2*H*-indazole



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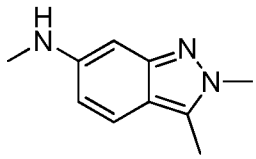
with a methylamine to obtain of compound of formula 2 in presence of a base, catalyst and a suitable solvent,



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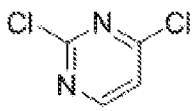
In the step (i), X is a halogen (eg: Cl, Br, I).

(ii) condensing the compound of formula 2 with the compound of formula 3



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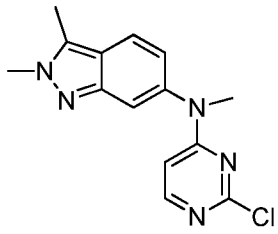
in presence of a base and a suitable solvent to obtain the key intermediate compound of formula 4.



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The base employed in the step (i) and step (ii) is selected from the group of organic base or inorganic base, wherein organic base is selected from cyclic or acyclic amines, while bases diethylamine, triethylamine and diisopropylethylamine, the reaction may be operated in alcoholic solvents. Inorganic base may be selected from the groups of alkali metal hydroxide like sodium hydroxide, calcium hydroxide, potassium hydroxide or alkali metal carbonate like sodium carbonate, potassium carbonate, sodium bicarbonate, while base is alkali metal salt, the reaction may be operated in aqueous solvent systems.

Preferably, the base employed in the step (ii) is an inorganic base such as sodium carbonate or potassium carbonate or sodium bicarbonate.

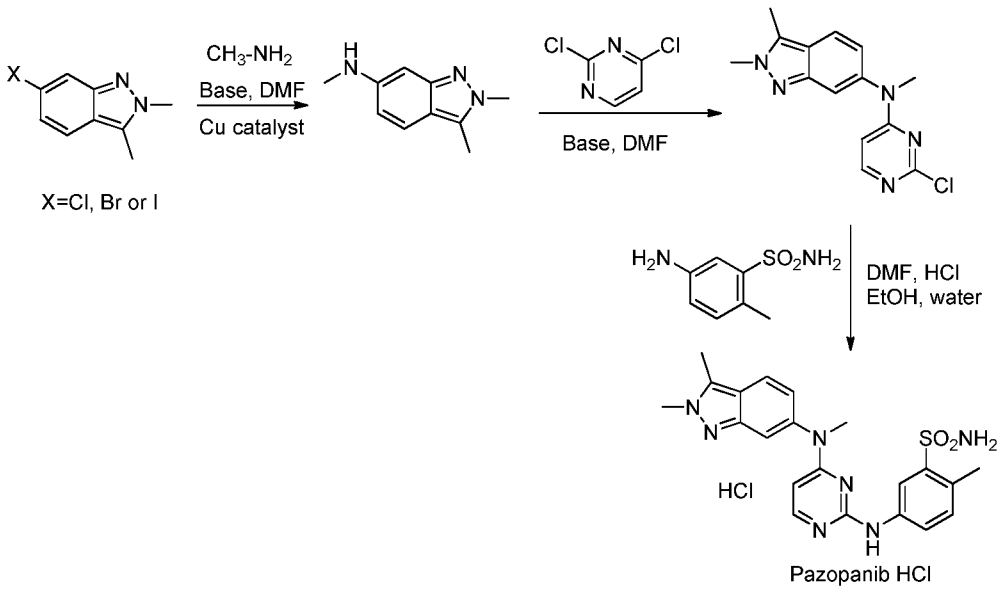
The process of the invention conducted in a suitable solvent. The suitable solvent employed in step (i) and step (ii) is selected from the group of alcohols such as methanol, ethanol, 1-propanol, 2-propanol or organic solvents such as THF, DMF, NMP, EtOAc, etc. Preferably, the solvent used in step (i) and step (ii) is DMF.

The catalyst employed in the step (i) is selected from copper halides or copper oxide like CuI, CuBr, CuCl, Cu_2O, Cu powder, $Cu(OAc)_2.H_2O$, Cu(acac), etc. Preferably, the catalyst employed in the step (i) is copper halides like CuI.

The process of the invention carried out at a suitable temperature. A temperature range for performing reaction in step (i) is 60 – 100 °C. The reaction may preferably be carried out at temperatures in the range from about 70 – 90 °C, more preferably at about 65 – 80 °C. A temperature range for performing reaction in step (ii) is 50 – 100 °C, more preferable is 60 – 90 °C.

A third aspect of the present invention relates to a process for preparing pazopanib hydrochloride, wherein the process comprises of reacting compound of formula 4 with 5-amino-2-methylbenzenesulfonamide. The method is simple, cost effective and suitable for industrial scale manufacturing.

The process according to the invention claimed in the present application and involving the key intermediate compound of formula 4 is outlined in Scheme 2.



Scheme 2

A fourth aspect of the present invention relates to a novel polymorphic solvate form of pazopanib hydrochloride. This new solvate form is dimethylformamide (DMF) solvate form, herein after designated as Form D. Form D is characterized by an XRPD pattern having characteristic peaks at 6.59 ± 0.2, 9.64 ± 0.2, 12.83 ±0.2, 15.00 ±0.2, 16.94 ±0.2, 18.95 ±0.2 and 23.99 ±0.2 degree 2-theta. Furthermore, Form D can be characterized by an XRPD pattern with characteristic peaks at 14.59 ± 0.2, 18.28± 0.2, 18.64± 0.2, 21.57 ± 0.2, 23.77 ± 0.2, 26.31 ±0.2, 27.88 ± 0.2, 30.02 ±0.2 and 30.64±0.2 degree 2-theta.

The XRPD of Form D is shown in figure 1.

A fifth aspect of the present invention relates to a novel process for preparing polymorph of pazopanib hydrochloride.

In still another aspect, the present invention relates to a process of applying Form D in the synthesis of anhydrous crystalline Form I of pazopanib hydrochloride.

The crystalline Form I according to the present invention may be obtained by:

a) dissolving or suspending Form D in a mixture of water and C1-C3 alcohol, preferably ethanol,

b) heating and stirring the solution at reflux temperature,

c) cooling the solution to room temperature,

d) isolating the obtained solid, e.g. by filtration,

e) optionally washing the obtained solid and with C1-C3 alcohol, preferably with ethanol

f) drying the solid.

Brief description of the drawings:

Fig. 1 shows a powder X-ray diffraction pattern of pazopanib hydrochloride designated as Form D obtained in example 5

Fig. 2 shows a powder X-ray diffraction pattern of pazopanib hydrochloride designated as Form I obtained in example 6

Fig.3 shows a powder X-ray diffraction pattern of Form D(Bottom one) versus a powder X-ray diffraction pattern of Form I (Upper one)

Instrumental parameters:

PXRD Method of Analysis

XRPD samples were analyzed on a Shimadzu 6100 X-Ray Diffractometer.

The measurement conditions were as follows:

Radiation:	CuKal (1.5406 A)
Kα1 ratio:	50%
Voltage:	40.0 kV
Current:	30.0 mA
Auto slit:	not used
Divergence slit:	1.0°
Scatter slit:	1.0°
Receiving slit:	0.30 mm with a Graphite monochromator
Drive axis:	Theta-2Theta
Scan range:	2.00 – 40.00°
Scan mode:	Continuous scan
Scan speed:	2.0°/min
Sampling pitch:	0.02°
Preset time:	0.60 s

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

Examples

Example 1

Preparation of *N*,2,3-trimethyl-2*H*-indazol-6-amine (Formula 2)

Procedure 1

A flask was charged with 6-bromo-2,3-dimethyl-2*H*-indazole (1 eq.), methylamine (2 eq.), Cu_2O (5 mol%) and N,N-dimethylformamide. The reaction mixture was stirred at 100 °C until completion of the reaction. Then, the reaction mixture was cooled to room temperature and water was added. The mixture was extracted with dichloromethane. Organic layer was separated and dried with anhydrous sodium sulfate. The solvent was removed in *vacuo* to obtain oily residue. Diethyl ether was added onto the oily residue and stirred for 2 h for crystallization. Product crystals were collected by filtration, washed with diethyl ether and dried to afford a brownish powder (Yield: 97%; LC-purity: 99%).

Procedure 2

A flask was charged with 6-bromo-2,3-dimethyl-2*H*-indazole (1 eq.), methylamine (2 eq.), copper powder (5 mol%) and N,N-dimethylformamide/water mixture. The reaction mixture was stirred at 100 °C until completion of the reaction. Then, the reaction mixture was cooled to room temperature and filtered to remove copper powder. Afterwards, water was added to the filtrate and extracted with dichloromethane. Organic layer was separated, dried with anhydrous sodium sulfate and solvent was removed in *vacuo* to obtain oily residue. Diethyl ether was added onto the oily residue and stirred for 2 h for crystallization. Product crystals were collected by filtration, washed with diethyl ether and dried to afford a brownish powder (Yield: 98%; LC-purity: 99%).

Procedure 3

A flask was charged with 6-bromo-2,3-dimethyl-2*H*-indazole (1 eq.), methylamine (2 eq.), CuI (5 mol%), potassium carbonate (2 eq.) and N,N-dimethylformamide. The reaction mixture was stirred at 100 °C until completion of the reaction. Then, the reaction mixture was cooled to room temperature and water was added. The mixture was extracted with dichloromethane. Organic layer was separated, dried with anhydrous sodium sulfate and solvent was removed in *vacuo* to obtain oily residue. Diethyl ether was added onto the oily residue and stirred for 2 h for crystallization. Product crystals were collected by filtration, washed with diethyl ether and dried to afford a brownish powder (Yield: 97%; LC-purity: 99%).

Example 2

Preparation of *N*-(2-chloropyrimidin-4-yl)-*N*,2,3-trimethyl-2*H*-indazol-6-amine (Formula 4)

A flask was charged with *N*,2,3-trimethyl-2*H*-indazol-6-amine (1 eq.), 2,4-dichloropyrimidine (1.5 eq.), sodium bicarbonate (2 eq.) and N,N-dimethylformamide. The reaction mixture was stirred at 85 °C until completion of the reaction. Then, water was added and stirred for 3 h. Product crystals were collected by filtration, washed with water and then dried to get title compound as off-white/beige powder (Yield: 97%; LC-purity: 98.5%).

Example 3

One pot preparation of *N*-(2-chloropyrimidin-4-yl)-*N*,2,3-trimethyl-2*H*-indazol-6-amine (Formula 4)

Procedure 1

A flask was charged with 6-bromo-2,3-dimethyl-2*H*-indazole (1 eq.), methylamine (2 eq.), copper powder (5 mol%) and N,N-dimethylformamide/water mixture. The reaction mixture was stirred at 100 °C until completion of the reaction. Then, the reaction mixture was cooled to room temperature and filtered to remove copper powder. Afterwards, 2,4-dichloropyrimidine (1.5 eq.) and sodium bicarbonate (2 eq.) were added to the filtrate. The mixture was heated to 85 °C and stirred at this temperature until completion of the reaction. Afterwards, water was added and stirred for 3 h. Product crystals were collected by filtration, washed with water and dried to afford an off-white/beige powder (Yield: 82%; LC-purity: 98.2%).

Procedure 2

A flask was charged with 6-bromo-2,3-dimethyl-2*H*-indazole (1 eq.), methylamine (2 eq.), CuI (5 mol%), potassium carbonate (2 eq.) and N,N-dimethylformamide. The reaction mixture was stirred at 100 °C until completion of the reaction. Afterwards, the mixture was cooled to room temperature, 2,4-dichloropryrimidine (1.5 eq) was added. The mixture was heated to 85 °C and stirred at this temperature until completion of the reaction. Afterwards, water was added and stirred for 3 h. Product crystals were collected by filtration, washed with water and dried to afford an off-white/beige powder (Yield: 86%; LC-purity: 97.5%).

Example 4

Synthesis of pazopanib hydrochloride

A flask was charged with intermediate synthesized in example 2 (*N*-(2-chloropyrimidin-4-yl)-*N*,2,3-trimethyl-2*H*-indazol-6-amine) (1 eq.), 5-amino-2-methylbenzenesulfonamide (1.05 eq.) and ethanol. Concentrated hydrochloric acid (3-4 drops) was added and the reaction mixture heated and stirred at reflux temperature until completion of the reaction which was monitored by thin layer chromatography (TLC). After completion of the reaction, product crystals were collected by filtration, washed with ethanol and dried to afford pazopanib hydrochloride as an off-white powder (Yield: 85%; LC-purity: 98.4%).

Example 5

Synthesis of DMF-solvate of pazopanib hydrochloride (Form D)

A flask was charged with intermediate synthesized in example 2 (*N*-(2-chloropyrimidin-4-yl)-*N*,2,3-trimethyl-2*H*-indazol-6-amine) (1 eq.), 5-amino-2-methylbenzenesulfonamide (1.05 eq.) and N,N-dimethylformamide. Concentrated hydrochloric acid (3-4 drops) was added. The reaction mixture heated to 95 °C and stirred at this temperature until completion of the reaction which was monitored by thin layer chromatography (TLC). After completion of the reaction, product crystals were collected by filtration, washed with ethanol and then dried to afford DMF-solvate of pazopanib hydrochloride as an off-white powder (Yield: 95%; LC-purity: 99.6%).

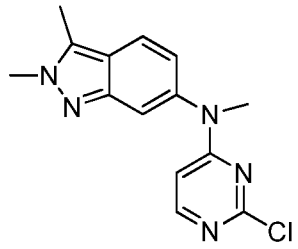
Example 6

Preparation of anhydrous crystalline Form I from pazopanib hydrochloride DMF-solvate

A flask was charged with pazopanib hydrochloride DMF-solvate synthesized in example 5 and ethanol/water mixture. The reaction mixture was heated and stirred for 2 h at reflux temperature, and then cooled to room temperature. The suspension was filtered, and then washed with ethanol. After drying, the product pazopanib hydrochloride was obtained as an off-white powder (Yield: 92%; LC-purity: 99.95%).

CLAIMS

1. A process to prepare a compound of formula 4, which is a key intermediate in the synthesis of pazopanib;



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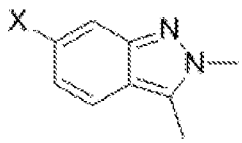
comprises the step of,

(i) reacting the 6-halo-2,3-dimethyl-2*H*-indazole (Formula 1)



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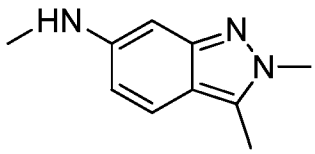
with a methylamine to obtain a compound of formula 2 in presence of a base, catalyst and a suitable solvent,



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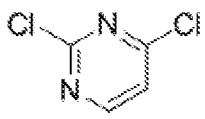
in the step (i), X is a halogen (eg: Cl, Br, I).

(ii) condensing the compound of formula 2 with the compound of formula 3



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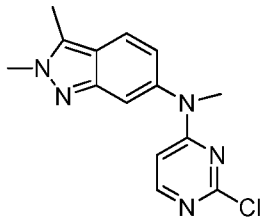
in presence of a base and a suitable solvent to obtain a compound of formula 4



4

2. The process according to claim 1, wherein the base employed in the step (i) and step (ii) is selected from the group of organic base or inorganic base. Preferably, the organic base is selected from diethylamine, triethylamine and diisopropylethylamine.
3. The process according to claim 1, wherein the base employed in the step (i) and step (ii) is selected from the group of inorganic base, wherein inorganic base may be selected from the groups of alkali metal hydroxide like sodium hydroxide, calcium hydroxide, potassium hydroxide or alkali metal carbonate like sodium carbonate, potassium carbonate, sodium bicarbonate. Preferably, the inorganic base in the step (ii) is sodium carbonate or potassium carbonate or sodium bicarbonate.
4. The process according to claim 1, wherein the suitable solvent employed in step (i) and step (ii) is selected from the group of alcohols such as methanol, ethanol isopropyl alcohol or organic solvents such as THF, DMF, NMP, EtOAc, etc. Preferably, the solvent used in step (i) and step (ii) is DMF.
5. The process according to claim 1, wherein the catalyst employed in the step (i) is selected from copper halides or copper oxide like CuI, CuBr, CuCl, Cu_2O, Cu powder, $Cu(OAc)_2.H_2O$, Cu(acac), etc. Preferably, the catalyst employed in the step (i) is copper halides like CuI.
6. The process according to claim 1, the reaction is carried out a temperature range for performing reaction in step:
   (i) 60 – 100 °C, more preferably at about 65 – 80 °C
   (ii) 50 – 100 °C, more preferable is 60 – 90 °C.
7. A process to according to claim 1, the compound of formula 4 reacts with 5-amino-2-methylbenzenesulfonamide to prepare pazopanib or its salts.
8. Crystalline polymorph Form D, characterized by its PXRD pattern having peaks at 6.59, 9.64, 12.83, 14.59, 15.00, 16.94, 18.28, 18.64, 18.95, 21.57, 23.77, 23.99, 26.31, 27.88, 30.02 and 30.64 ±0.2 degree 2-theta.
9. The crystalline polymorph Form D according to claim 8, which is further characterized by its PXRD pattern as illustrated in Fig. 1.

10. Use of the crystalline polymorph Form D according to claims 8 and 9 for the preparation of the crystalline polymorph Form I, comprising:

a) dissolving or suspending Form D in a mixture of water and C1-C3 alcohol, preferably ethanol

b) heating and stirring the solution at reflux temperature,

c) cooling the solution to room temperature,

d) isolating the obtained solid, e.g. by filtration,

e) optionally washing the obtained solid with C1-C3 alcohol, preferably with ethanol, and

f) drying the solid.

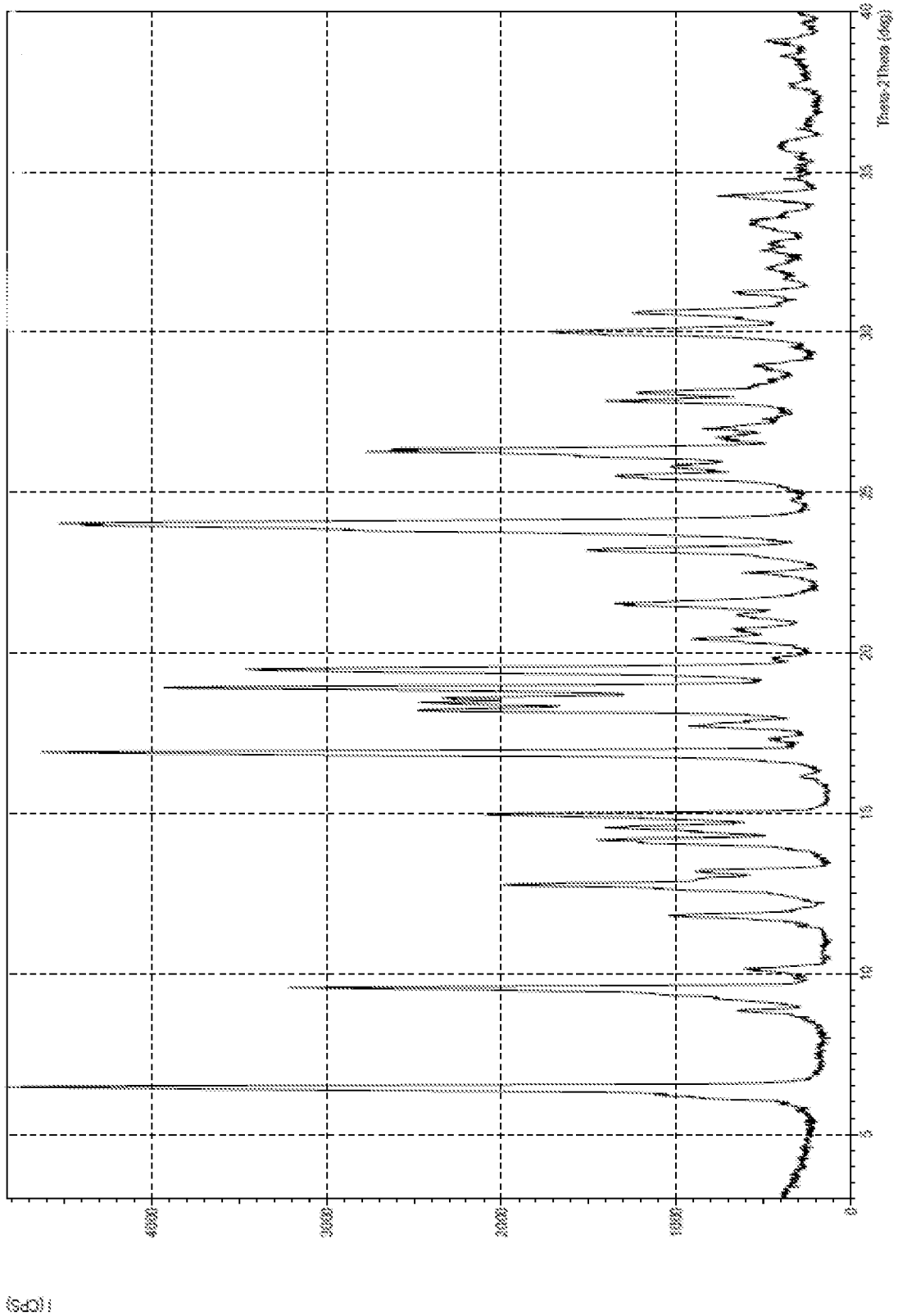


Fig. 1

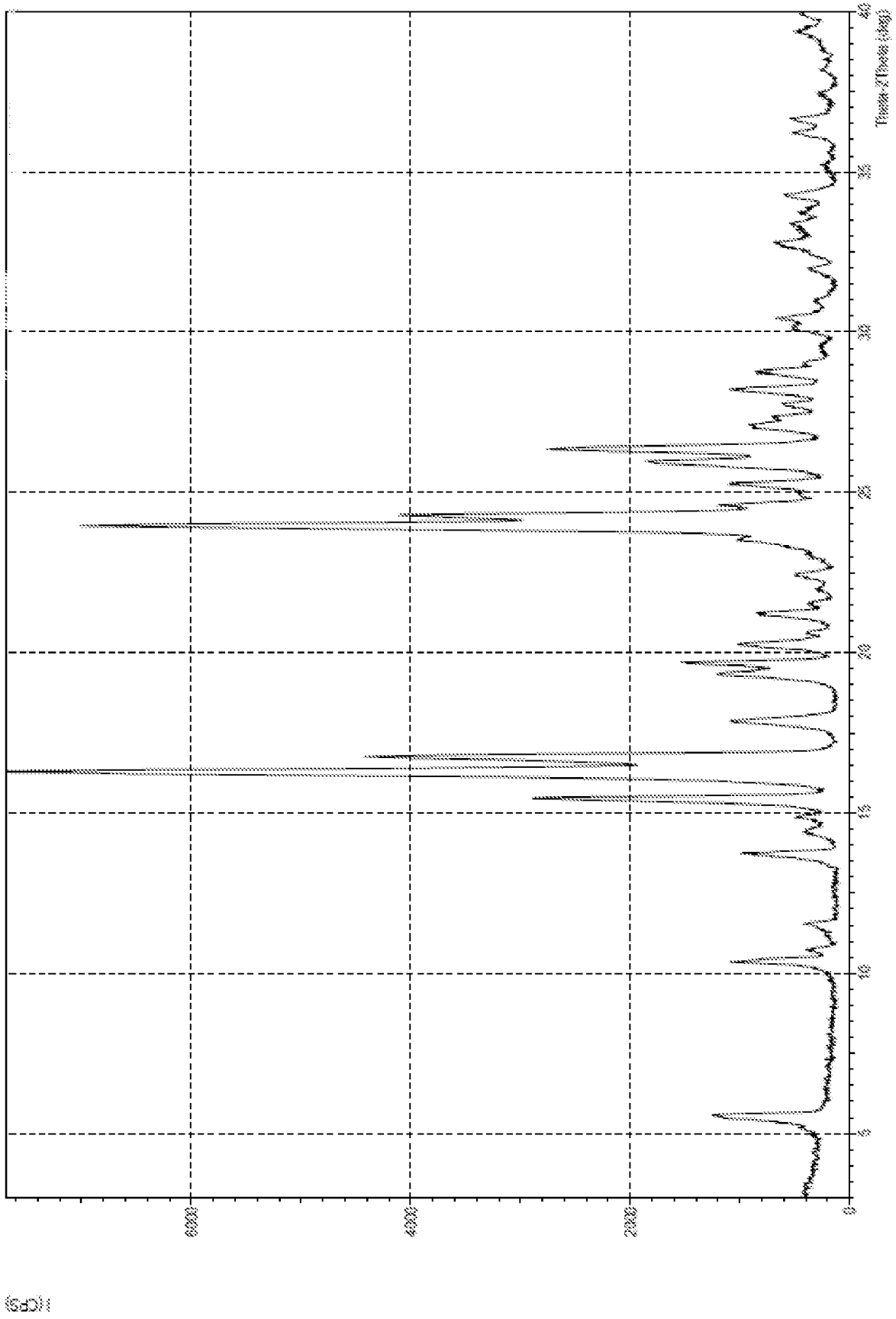


Fig. 2

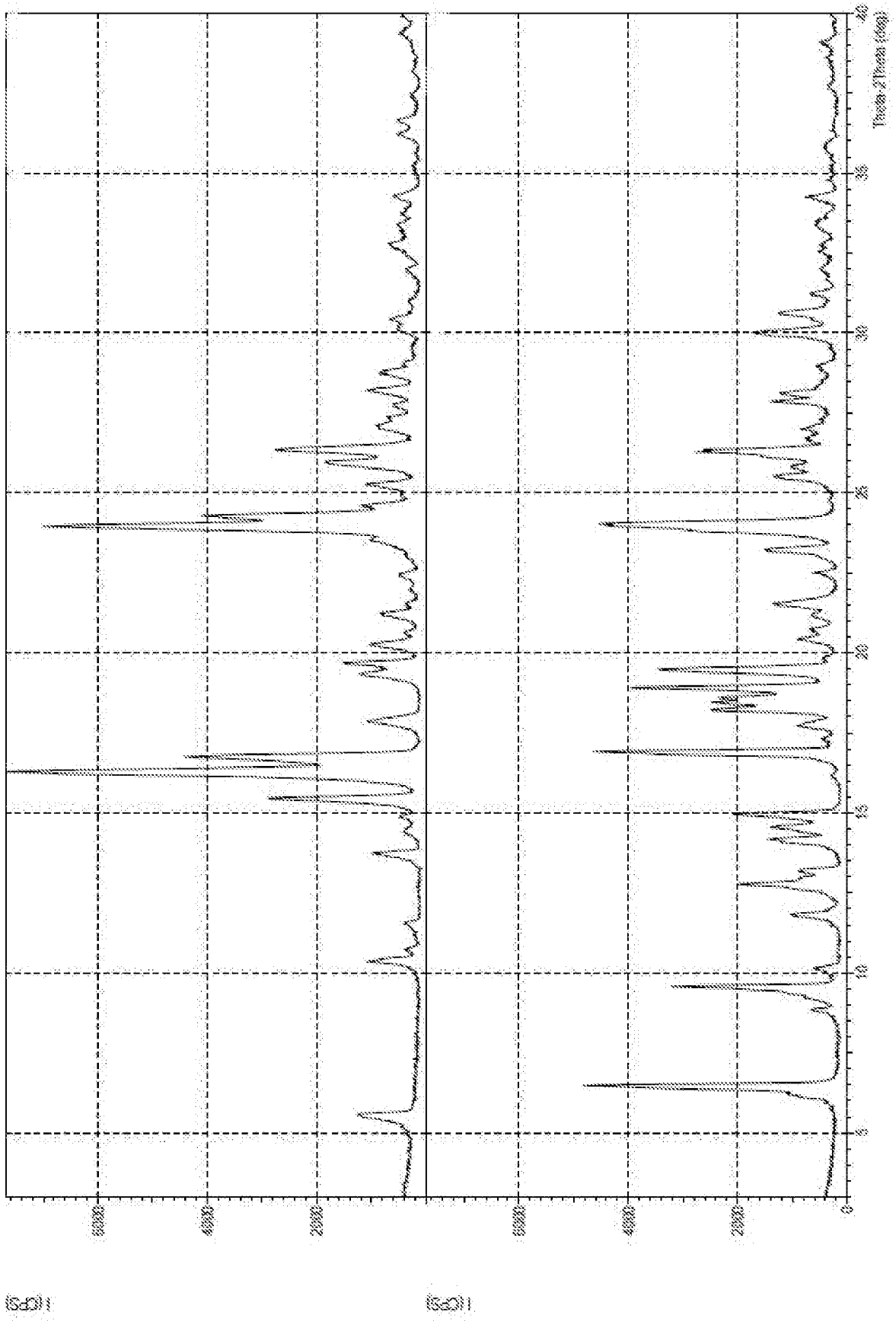


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2020/050088

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/505 (2006.01)i; A61K 31/506 (2006.01)i; A61P 35/00 (2006.01)i; C07D 403/02 (2006.01)i; C07D 403/12 (2006.01)i

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CN 107721989 A (SOUTHEAST PHARMACEUTICALS CO LTD) 23 February 2018 (2018-02-23) Paragraphs 2-8	1-10
Y,D	WO 2015068175 A2 (LAURUS LABS PRIVATE LTD) 14 May 2015 (2015-05-14) Page 2, lines 8-10	1-10
Y	Matier, C. D., Schwaben, J., Peters, J. C., & Fu, G. C. (2017). Copper-catalyzed alkylation of aliphatic amines induced by visible light. Journal of the American Chemical Society, 139(49), 17707-17710.	1-10

☐ 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
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"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
04 November 2020	**04 November 2020**

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/TR2020/050088

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
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				US	2016280689	A1	09 December 2015
				IN	326326	B	02 November 2018
				US	10730859	B2	08 December 2019
				US	2020262820	A1	08 December 2019
				US	2020262821	A1	08 December 2019
				IN	345935	B	09 December 2019