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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 June 2016 (09.06.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/088094 A1

(51) International Patent Classification:
C07D 487/04 (2006.01)

(21) International Application Number:
PCT/IB2015/059364

(22) International Filing Date:
4 December 2015 (04.12.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
3554/DEL/2014 5 December 2014 (05.12.2014) IN

(71) Applicant: **SUN PHARMACEUTICAL INDUSTRIES LIMITED** [IN/IN]; Sun House, Plot No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai, Maharashtra 400 063 (IN).

(72) Inventors: **AZAD, Md Abul Kalam**; s/o Md Mokodos Ali, Village - Sheralipur, Post - Lamajour, Karimgang, Assam 788701 (IN). **PANDEY, Gyanendra**; C-4/605, SRS Residency, Sector - 88, Faridabad, Haryana 121001 (IN). **SINGH, Kaptan**; House No. 3202, DLF Phase - IV, Chandralok, Gurgaon, Haryana 122015 (IN). **PRASAD, Mohan**; H.No.P-3/3, Phase-II, DLF Qutab Enclave, Gurgaon, Haryana 122001 (IN).

(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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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).

Published:

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

WO 2016/088094 A1

(54) Title: PROCESS FOR THE PREPARATION OF BARICITINIB AND AN INTERMEDIATE THEREOF

(57) Abstract: The present invention provides a process for the preparation of baricitinib and an intermediate thereof. The present invention provides a convenient, economical, and industrially advantageous two-step process for the preparation of [4-(IH-pyrazol-4-yl)-7Hpyrrolo[2,3-d] pyrimidin-7-yl]methyl pivalate of Formula (II). The process of the present invention involves the use of an alkali or alkaline earth metal hydroxide, carbonate, or bicarbonate as a base for reacting 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula (III) with chloromethyl pivalate of Formula (IV), and the use of an unprotected pyrazole borolane of Formula (VIII) for the conversion of (4-chloro-7H-pyrrolo[2,3-d] pynmidin-7- yl)methyl 2,2-dimethylpropanoate of Formula V into [4-(1 H-pyrazol-4-yl)-7Hpyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula (II). The process of the present invention provides [4-(1 H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula (I) in high yield.

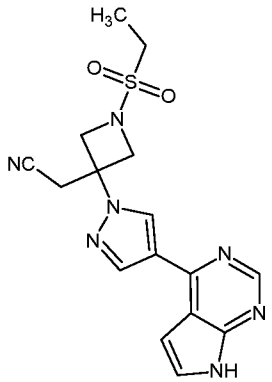
PROCESS FOR THE PREPARATION OF BARICITINIB AND AN INTERMEDIATE THEREOF

Field of the Invention

The present invention provides a process for the preparation of baricitinib and an intermediate thereof.

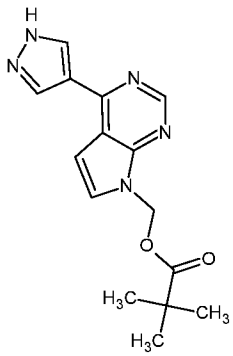
Background of the Invention

Baricitinib is a Janus kinase (JAK) inhibitor. It is chemically designated as {1-(ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile, having the structure as depicted in Formula I.



Formula I

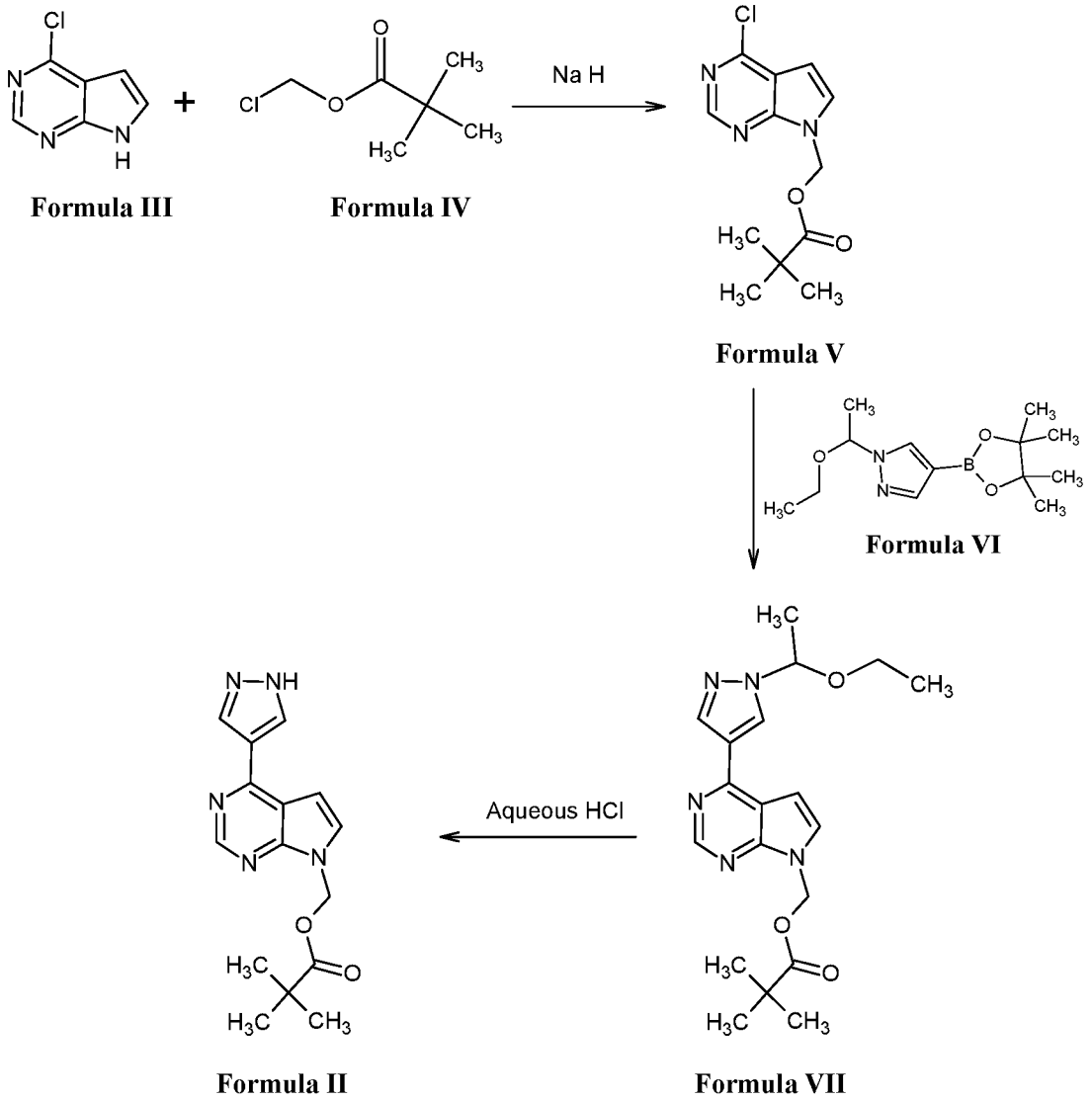
U.S. Patent No. 8,158,616 discloses processes for the preparation of baricitinib of Formula I and [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II.



Formula II

U.S. Patent No. 8,158,616 involves a three-step process for the preparation of [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II as depicted in Scheme 1 below:

Scheme 1



Formula III **Formula IV** **Formula V** **Formula VI** **Formula II** **Formula VII**

The process disclosed in U.S. Patent No. 8,158,616 involves the use of sodium hydride as a base for reacting 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula III with chloromethyl pivalate of Formula IV, and the use of a protected pyrazole borolane derivative of Formula VI for the conversion of (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V into [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II.

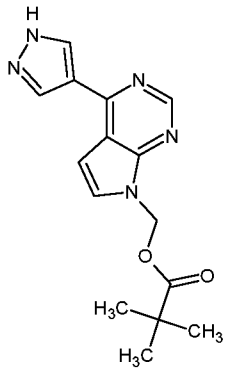
The use of sodium hydride is not suitable on an industrial scale due to its inflammable and hazardous nature. The use of a protected pyrazole borolane derivative of Formula VI increases the cost of the manufacturing process, as an additional deprotection step is required for obtaining [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II.

Thus, there exists a need for the development of an economical and industrially advantageous process for the preparation of [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II that avoids the use of sodium hydride and involves a lesser number of steps.

Summary of the Invention

The present invention provides a convenient, economical, and industrially advantageous two-step process for the preparation of [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II. The process of the present invention involves the use of an alkali or alkaline earth metal hydroxide, carbonate, or bicarbonate as a base for reacting 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula III with chloromethyl pivalate of Formula IV, and the use of an unprotected pyrazole borolane of Formula VIII for the conversion of (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V into [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II. The process of the present invention provides [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II in high yield.

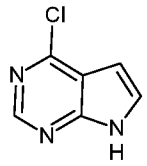
A first aspect of the present invention provides a process for the preparation of [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II,



Formula II

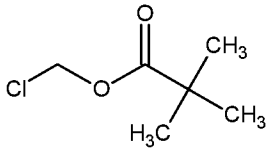
comprising the steps of:

i) reacting 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula III



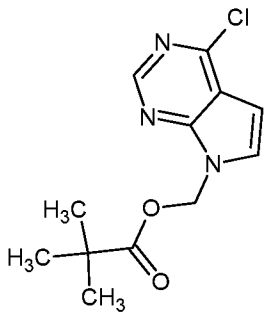
Formula III

with chloromethyl pivalate of Formula IV



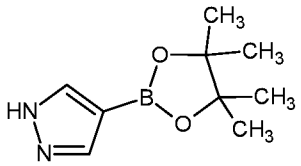
Formula IV

in the presence of an alkali or alkaline earth metal hydroxide, carbonate, or bicarbonate as a base to obtain (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V; and



Formula V

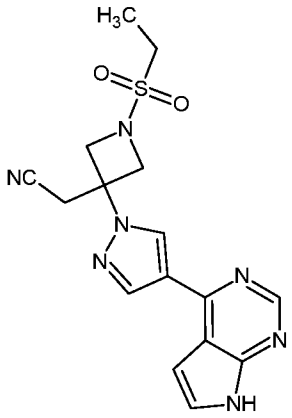
ii) reacting the (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole of Formula VIII



Formula VIII

to obtain the [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II.

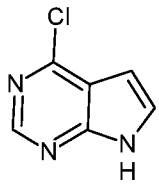
A second aspect of the present invention provides a process for the preparation of baricitinib of Formula I,



Formula I

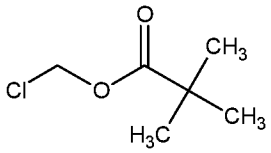
comprising the steps of:

i) reacting 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula III



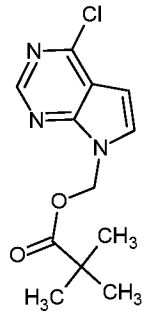
Formula III

with chloromethyl pivalate of Formula IV



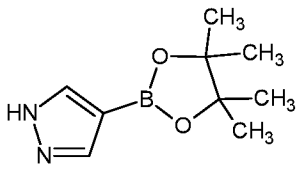
Formula IV

in the presence of an alkali or alkaline earth metal hydroxide, carbonate, or bicarbonate base to obtain (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V;



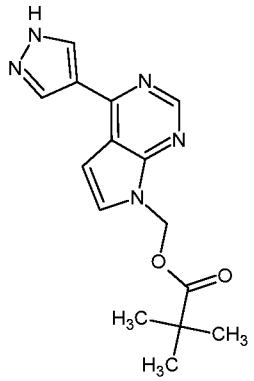
Formula V

ii) reacting the (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole of Formula VIII



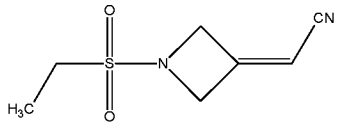
Formula VIII

to obtain [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II; and



Formula II

iii) reacting the [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II with [1-(ethylsulfonyl)azetidin-3-ylidene]acetonitrile of Formula IX



Formula IX

to obtain baricitinib of Formula I.

Detailed Description of the Invention

Various embodiments and variants of the present invention are described hereinafter.

The term "about," as used herein, refers to any value which lies within the range defined by a number up to ±10% of the value.

The term "ambient temperature," as used herein, refers to a temperature in the range of about 20°C to about 35°C.

The reaction of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula III with chloromethyl pivalate of Formula IV is carried out in the presence of an alkali or alkaline earth metal hydroxide, carbonate, or bicarbonate as a base. Examples of alkali and alkaline earth metal hydroxides include lithium hydroxide, sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, and barium hydroxide. Examples of alkali and alkaline earth metal carbonates include sodium carbonate, potassium carbonate, calcium carbonate, and magnesium carbonate. Examples of alkali metal bicarbonates include sodium bicarbonate and potassium bicarbonate. In an embodiment of the present invention, the reaction of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula III with chloromethyl pivalate of Formula IV is carried out in the presence of potassium carbonate.

The reaction of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula III with chloromethyl pivalate of Formula IV is carried out at ambient temperature in the presence of a solvent. Examples of solvents include hydrocarbons, ethers, chlorinated hydrocarbons, ketones, amides, sulphoxides, water, and mixtures thereof. Examples of hydrocarbons include benzene, toluene, and xylene. Examples of ethers include diethyl ether, ethyl methyl ether, di-isopropyl ether, tetrahydrofuran, and 1,4-dioxane. Examples of chlorinated hydrocarbons include dichloromethane and chloroform. Examples of ketones include acetone, dimethyl ketone, ethyl methyl ketone, and methyl iso-butyl

ketone. Examples of amides include N,N-dimethylformamide and N,N-dimethylacetamide. Examples of sulphoxides include dimethyl sulphoxide and diethyl sulphoxide. In an embodiment of the present invention, the solvent used is N,N-dimethylformamide.

The reaction of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula III with chloromethyl pivalate of Formula IV is carried out in about 4 hours to about 24 hours. In an embodiment of the present invention, the reaction is carried out in about 14 hours to about 18 hours.

The reaction of (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole of Formula VIII is carried out in the presence of a base in a solvent. The base may be selected from the group consisting of inorganic and organic bases. Examples of inorganic bases include alkali and alkaline earth metal hydroxides, carbonates, and bicarbonates. Examples of alkali and alkaline earth metal hydroxides include lithium hydroxide, sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, and barium hydroxide. Examples of alkali and alkaline earth metal carbonates include sodium carbonate, potassium carbonate, calcium carbonate, and magnesium carbonate. Examples of alkali metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of organic bases include N,N-diisopropylethylamine, triethylamine, triisopropylamine, N,N-2-trimethyl-2-propanamine, N-methylmorpholine, 4-dimethylaminopyridine, 2,6-di-tert-butyl-4-dimethylaminopyridine, 1,4-diazabicyclo[2.2.2]octane, and 1,8-diazabicyclo[5.4.0]undec-7-ene. In an embodiment of the present invention, potassium carbonate is used as the base. Examples of solvents include hydrocarbons, ethers, chlorinated hydrocarbons, ketones, amides, sulphoxides, water, and mixtures thereof. Examples of hydrocarbons include benzene, toluene, and xylene. Examples of ethers include diethyl ether, ethyl methyl ether, di-isopropyl ether, tetrahydrofuran, and 1,4-dioxane. Examples of chlorinated hydrocarbons include dichloromethane and chloroform. Examples of ketones include acetone, dimethyl ketone, ethyl methyl ketone, and methyl iso-butyl ketone. Examples of amides include N,N-dimethylformamide and N,N-dimethylacetamide. Examples of sulphoxides include dimethyl sulphoxide and diethyl sulphoxide. In an embodiment of the present invention, the reaction of (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate

of Formula V with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole of Formula VIII is carried out in the presence of water and 1,4-dioxane.

The reaction of (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole of Formula VIII is initiated by adding a palladium catalyst. Examples of palladium catalysts include tetrakis(triphenylphosphine)palladium(0) and tetrakis(tri(o-tolyl)phosphine)palladium(0). In an embodiment of the present invention, the catalyst used is tetrakis(triphenylphosphine)palladium(0).

The reaction of (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole of Formula VIII is carried out at ambient temperature to the reflux temperature of the solvent. In an embodiment of the present invention, the reaction is carried out at a temperature of about 65°C to about 90°C.

The reaction of (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole of Formula VIII is carried out in about 4 hours to about 24 hours. In an embodiment of the present invention, the reaction is carried out in about 14 hours to about 18 hours.

The isolation of [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II and (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V is carried out by concentration, precipitation, cooling, filtration, centrifugation, or a combination thereof, followed by drying. Drying is carried out under reduced pressure at a temperature of about 35°C to about 60°C for about 5 hours to about 24 hours.

The reaction of [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II with 2-(1-ethylsufonyl)azetidin-3-ylidene)acetonitrile of Formula IX to obtain baricitinib of Formula I may be carried out by the process disclosed in U.S. Patent No. 8,158,616, which is incorporated herein by reference.

While the present invention has been described in terms of its specific aspects and 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.

The following examples are for illustrative purposes only and should not be construed as limiting the scope of the invention in any way.

EXAMPLES

Example 1: Preparation of (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate (Formula V)

4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (25 g; Formula III), potassium carbonate (27 g), and chloromethyl pivalate (27 g; Formula IV) were added to a reaction vessel containing N,N-dimethylformamide (100 mL) at ambient temperature. The reaction mixture was stirred for 14 hours. The progress of the reaction was monitored by thin layer chromatography. Water (250 mL) was added to the reaction mixture, and then the mixture was stirred for 2 hours. The reaction mixture was filtered, then washed with water (50 mL), and then dried under reduced pressure at 40°C to 45°C for 12 hours to obtain (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate.

Yield: 98.85%

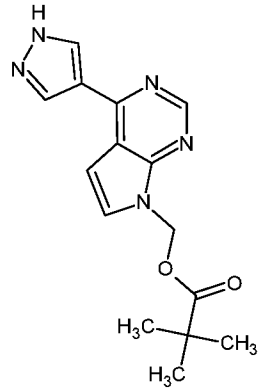
Example 2: Preparation of [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate (Formula II)

(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate (10 g; Formula V), water (50 mL), and potassium carbonate (15.5 g) were added into a reaction vessel at ambient temperature. 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (8.7 g; Formula VIII), 1,4-dioxane (100 mL), and tetrakis(triphenylphosphine)palladium(0) (0.08 g) were added to the reaction mixture. The reaction mixture was heated to a temperature of 80°C to 85°C, and then stirred at the same temperature for 14 hours. The progress of the reaction was monitored by thin layer chromatography. On completion, ethyl acetate (100 mL) was added to the reaction mixture. The contents were stirred for 1 hour, then filtered through a Hyflo®, and then washed with ethyl acetate (40 mL). The organic layer was separated, and then concentrated under reduced pressure to obtain [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate.

Yield: 82.27%

We claim:

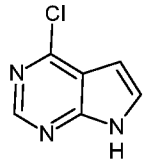
1. A process for the preparation of [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II,



Formula II

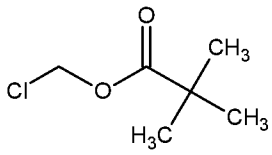
comprising the steps of:

i) reacting 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula III



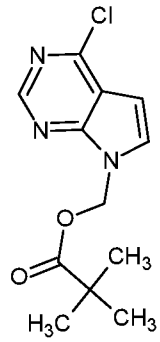
Formula III

with chloromethyl pivalate of Formula IV



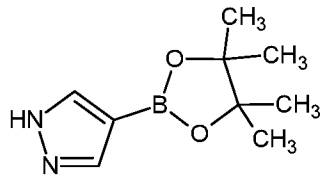
Formula IV

in the presence of an alkali or alkaline earth metal hydroxide, carbonate, or bicarbonate base to obtain (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V; and



Formula V

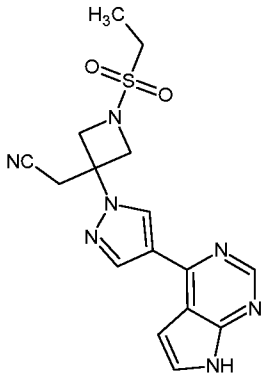
ii) reacting the (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole of Formula VIII



Formula VIII

to obtain the [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II.

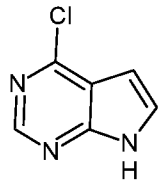
2. A process for the preparation of baricitinib of Formula I,



Formula I

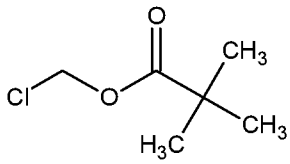
comprising the steps of:

i) reacting 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula III



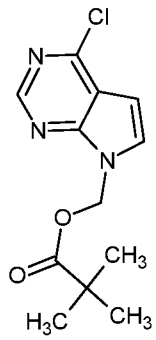
Formula III

with chloromethyl pivalate of Formula IV



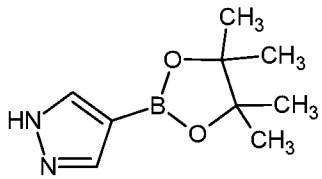
Formula IV

in the presence of an alkali or alkaline earth metal hydroxide, carbonate, or bicarbonate base to obtain (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V;



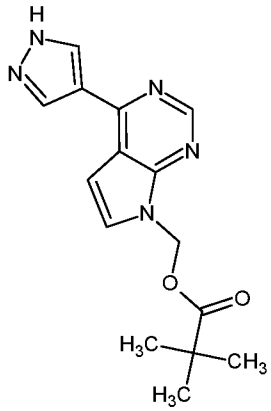
Formula V

ii) reacting the (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole of Formula VIII



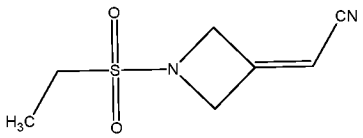
Formula VIII

to obtain [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II; and



Formula II

iii) reacting the [4-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl pivalate of Formula II with [1-(ethylsulfonyl)azetidin-3-ylidene]acetonitrile of Formula IX



Formula IX

to obtain baricitinib of Formula I.

3. The process according to claim 1 or 2, wherein the alkali or alkaline earth metal hydroxide is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, and barium hydroxide.

4. The process according to claim 1 or 2, wherein the alkali or alkaline earth metal carbonate is selected from the group consisting of sodium carbonate, potassium carbonate, calcium carbonate, and magnesium carbonate.

5. The process according to claim 1 or 2, wherein the alkali metal bicarbonate is selected from sodium bicarbonate and potassium bicarbonate.

6. The process according to claim 1 or 2, wherein the reaction of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula III with chloromethyl pivalate of Formula IV is carried out at ambient temperature.

7. The process according to claim 1 or 2, wherein the reaction of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine of Formula III with chloromethyl pivalate of Formula IV is carried out in the presence of a solvent selected from the group consisting of hydrocarbons, ethers, chlorinated hydrocarbons, ketones, amides, sulphoxides, water, and mixtures thereof.

8. The process according to claim 1 or 2, wherein the reaction of (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl 2,2-dimethylpropanoate of Formula V with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole of Formula VIII is carried out in the presence of an organic or inorganic base.

9. The process according to claim 7, wherein the solvent is selected from the group consisting of hydrocarbons, ethers, chlorinated hydrocarbons, ketones, amides, sulphoxides, water, and mixtures thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/059364

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 487/04 (2016.01)
CPC - Y02P 20/55 (2016.02)
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)
IPC(8) - C07D 231/38, 401/14, 487/04 (2016.01)
CPC - C07D 231/38, 401/14, 487/04; Y02P 20/55 (2016.02)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/210.21, 265.1; 544/229, 280; IPC(8) - C07D 231/38, 401/14, 487/04; CPC - C07D 231/38, 401/14, 487/04; Y02P 20/55 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google; STN; PubChem; SureChem
Search terms used: baricitinib, dioxaborolane, chloromethyl pivalate.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2013/0253190 A1 (INCYTE CORPORATION) 26 September 2013 (26.09.2013) entire document	1-9
A	US 2013/0225556 A1 (INCYTE CORPORATION) 29 August 2013 (29.08.2013) entire document	1-9
A	WO 2010/083283 A2 (INCYTE CORPORATION) 22 July 2010 (22.07.2010) entire document	1-9
A	US 2014/0228348 A1 (MERCK SHARP & DOHME CORP) 14 August 2014 (14.08.2014) entire document	1-9

☐ 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
25 February 2016	11 MAR 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774