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(54) Title: PROCESS FOR THE PREPARATION OF IDELALISIB

(57) Abstract: The present invention relates to a process for the preparation of idelalisib or a pharmaceutically acceptable salt thereof, via a novel intermediate namely, 2-fluoro-6-[[[(2S)- 2-[[[9-(methoxymethyl)purin-6-yl]amino]butanoyl]amino]-N-phenyl-benzamide.



WO 2017/221272 A1

PROCESS FOR THE PREPARATION OF IDELALISIB

RELATED APPLICATIONS

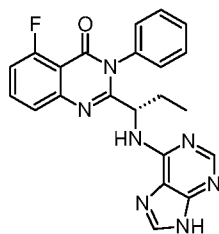
- 5 This application claims the benefit of Indian Patent Application no. IN 201621021583 filed on June 23, 2016; which is hereby incorporated by reference.

FIELD OF INVENTION

- 10 The present invention relates to a process for the preparation of idelalisib or a pharmaceutically acceptable salt thereof and intermediates thereof.

BACKGROUND OF INVENTION

- 15 Idelalisib is an inhibitor of phosphatidylinositol 3-kinase, PI3K δ ; chemically known as 5-fluoro-3-phenyl-2-[(1*S*)-1-(9*H*-purin-6-ylamino)propyl]quinazolin-4(3*H*)-one. The chemical structure of idelalisib is represented by Formula I:



Formula I

- Idelalisib is marketed in the United States under the brand name Zydelig[®] as oral tablets and
20 indicated for the treatment of patients with:

- Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received
25 at least two prior systemic therapies.
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

The United states Patent No. RE44638 (the '638 patent) discloses idelalisib and process for its preparation. The '638 patent prepares idelalisib by cyclizing (S)-[1-(2-fluoro-6-nitro-benzoyl)-phenyl-aminocarbonyl]-propyl-carbamic acid *tert*-butyl ester using Zn/acetic acid to give (S)-[1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-propyl]-carbamic acid *tert*-butyl ester followed by *tert*-butoxycarbonyl (Boc)-deprotection using trifluoroacetic acid and then reaction with 6-bromopurine. The process involves purification by column chromatography and afford idelalisib in 19.8 % overall yield.

The WIPO application WO2015095601A1 discloses preparation of idelalisib by deprotecting tetrahydropyran (THP) protected idelalisib. The THP protected idelalisib was prepared by reacting (S)-[1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-propyl]-carbamic acid *tert*-butyl ester with an acid followed by treatment with THP protected 6-chloropurine. Further (S)-[1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-propyl]-carbamic acid *tert*-butyl ester was prepared by reacting 2-amino-6-fluoro-benzoic acid with (2S)-2-(*tert*-butoxycarbonylamino)butanoic acid, followed by treatment with aniline.

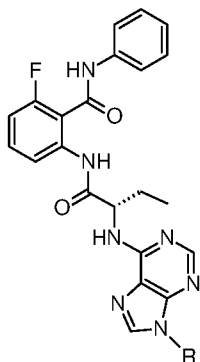
Various other processes for the preparation of idelalisib and its intermediates are disclosed in the literature for example, Chinese patent applications CN104130261A and CN104876931A.

The present invention provides a simple, scalable and economical process for the preparation of idelalisib or a pharmaceutical acceptable salt thereof.

SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of idelalisib or a pharmaceutically acceptable salt thereof, comprising:

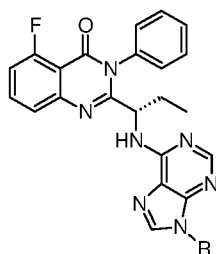
a) cyclizing a compound of Formula III



Formula III

or a salt thereof,

wherein R is an amino protecting group; to obtain a compound of Formula II



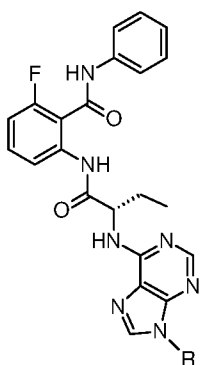
Formula II

or a salt thereof;

wherein R is an amino protecting group;

- 5 b) deprotecting the compound of Formula II or a salt thereof to obtain idelalisib and
- c) optionally converting idelalisib to a pharmaceutically acceptable salt thereof.

The present invention also provides a novel compound of Formula III



Formula III

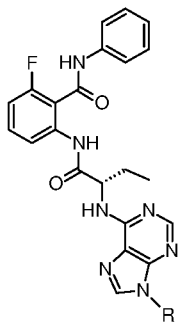
or a salt thereof;

- 10 wherein R is an amino protecting group; as an intermediate for the preparation of idelalisib.

DESCRIPTION OF THE INVENTION

In one aspect the present invention provides a process for the preparation of idelalisib or a pharmaceutically acceptable salt thereof, comprising:

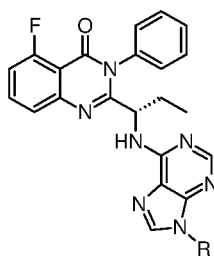
a) cyclizing a compound of Formula III



Formula III

or a salt thereof,

wherein R is an amino protecting group; to obtain a compound of Formula II



Formula II

or a salt thereof; wherein R is an amino protecting group;

b) deprotecting the compound of Formula II or a salt thereof to obtain idelalisib and

c) optionally converting idelalisib to a pharmaceutically acceptable salt thereof.

In one embodiment, R in the compound of Formula II and Formula III is an amino protecting group selected from a group consisting of (C₁-C₄)alkoxymethyl, benzyloxymethyl, pivaloxymethyl and tetrahydropyranyl; preferably R is methoxymethyl.

The term “(C₁-C₄)alkoxymethyl” as used herein refers to an alkyl group straight or branched having 1 to 4 carbon atoms, attached to methyl group via oxygen atom. Non limiting examples of (C₁-C₄)alkoxymethyl includes methoxymethyl, ethoxymethyl and the like.

In another embodiment, in step a of the above process, cyclization of compound of Formula III or a salt thereof is carried out in presence of hexamethyldisilazane (HMDS). The

cyclization can be performed in presence of a base in a suitable solvent. The base for the cyclization reaction may be selected from, but should not be restricted to, triethylamine, trimethylamine, diisopropylamine, *N,N*-diisopropylethylamine (DIPEA), pyridine, imidazole, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4-dimethylaminopyridine or a mixture thereof. The preferred base is triethylamine.

The suitable solvent for the cyclization reaction may be selected from a group consisting of acetonitrile, dimethylsulfoxide, *N,N*-dimethylformamide, *N,N*-dimethylacetamide or a mixture thereof. The preferred solvent is acetonitrile.

The cyclization of the compound of the Formula III or a salt thereof may be carried out at a temperature ranging from room temperature to reflux temperature of the solvent; preferably, the reaction may be carried out at reflux temperature of the solvent. Reaction may be carried out for a time sufficient for the completion of reaction. For example, reaction may be carried out for a time of 10 to 20 hours.

The salt of the compound of Formula II can be prepared by treating the compound of Formula II with an appropriate acid such as hydrochloric acid in a suitable solvent. For example, the hydrochloride salt can be prepared by treating the compound of Formula II with hydrochloric acid in an ethereal solvent such as diethyl ether, dioxane or tetrahydrofuran.

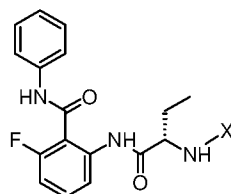
In step b of the above process, deprotection of the compound of Formula II or a salt thereof may be carried out by reacting the compound of the Formula II or a salt thereof with a reagent suitable for the removal of amino protecting group. For example, the protecting group methoxymethyl can be removed by using an acid such as hydrochloric acid. The deprotection reaction may be carried out in a suitable solvent such as alcoholic solvent selected from methanol, ethanol, 2-propanol, 1-propanol, amyl alcohol and the like. The reaction may be carried out at a temperature ranging from 20 °C to 70 °C; more preferably at a temperature of 30 °C to 50 °C.

Idelalisib obtained in step b may be isolated by the techniques known in the art and converted into a pharmaceutically acceptable salt thereof. Pharmaceutical acceptable salts of idelalisib includes acid addition salts such as those formed from hydrochloric acid, hydrobromic acid, oxalic acid, maleic acid, methanesulfonic acid, benzenesulfonic acid, sulfuric acid and the like. The idelalisib can be converted to pharmaceutically acceptable salts thereof by treating

the idelalisib with appropriate acid in a suitable solvent. For example, the hydrochloric acid salt of idelalisib can be prepared by treating the idelalisib with hydrochloric acid in an alcoholic solvent like ethanol or isopropanol.

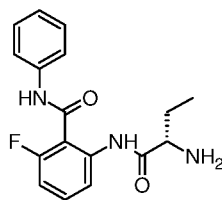
- 5 In another embodiment, the compound of Formula III or a salt thereof is prepared by a process comprising:

a) deprotecting a compound of Formula VI



Formula VI

wherein X is an amino protecting group; to obtain a compound of Formula V

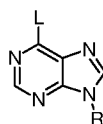


Formula V

10

or a salt thereof;

- b) reacting the compound of Formula V or a salt thereof with a compound of Formula IV



Formula IV

wherein L is a leaving group and R is an amino protecting group as defined earlier in the specification; to obtain the compound of Formula III and

15

- c) optionally converting the compound of Formula III to a salt thereof.

In one embodiment, X in the compound of Formula VI is an amino protecting group selected from, but not restricted to, *tert*-butoxycarbonyl (Boc), carbobenzyloxy (Cbz), benzyl, *p*-methoxybenzyl, 9-fluorenylmethoxycarbonyl (Fmoc) and the like; preferably X is Boc.

20

In another embodiment, L in the compound of Formula IV is a leaving group selected from, but not restricted to, halogen, mesylate, tosylate, brosylate, nosylate, triflate and the like. In one embodiment L is halogen, preferably chloro.

5 The deprotection of the compound of Formula VI may be carried out by a process known for the removal of amino protecting group, such as by using acids or by hydrogenolysis. For example, Boc-deprotection may be carried out by using reagents such as hydrochloric acid, trifluoroacetic acid, and the like.

10 The salt of the compound of Formula V includes acid addition salt such as hydrochloric acid, hydrobromic acid and the like. The salt of the compound of Formula V can be prepared by treating the compound of Formula V with an appropriate acid in a suitable solvent.

The reaction of the compound of Formula V or a salt thereof with the compound of Formula
15 IV may be carried out in presence of a base in a suitable solvent. The base for the reaction may be selected from organic or inorganic bases. The organic base for the reaction may be selected from a group consisting of triethylamine, diisopropylamine, *N,N*-diisopropylethylamine (DIPEA), pyridine, imidazole, 4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4-dimethylaminopyridine, piperidine or a mixture
20 thereof. The inorganic base for the reaction may be selected from a group consisting of potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide or a mixture thereof. Preferably, the base is triethylamine.

The suitable solvent for the reaction may be selected from a group consisting of water,
25 methanol, ethanol, 2-propanol, 1-propanol, *n*-butanol, *t*-butanol, acetonitrile, acetone, methylisobutyl ketone, *N,N*-dimethylformamide (DMF), dimethylsulfoxide, *N*-methylpyrrolidine (NMP) or a mixture thereof; preferably the solvent is a mixture of water and 2-propanol.

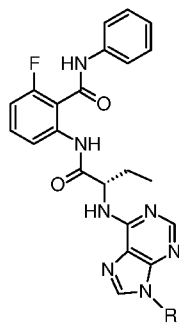
30 The reaction may be carried out at a temperature ranging from room temperature to reflux temperature of the solvent. Reaction may be carried out for a time sufficient for the completion of reaction for example, for 10 to 25 hours.

The step a and the step b of the above process can be carried out in a single pot without isolating the compound of Formula V.

The compound of Formula III may be isolated and converted into a salt thereof. The salt of the compound of Formula III can be prepared by treating the compound of Formula III with an appropriate acid such as hydrochloric acid in a suitable solvent. For example, the hydrochloride salt can be prepared by treating the compound of Formula III with hydrochloric acid in an ethereal solvent such as diethyl ether, dioxane or tetrahydrofuran.

The compound of Formula VI used in the above process, may be prepared as disclosed in prior art such as WO2015042077.

In another aspect, the present invention provides a compound of Formula III

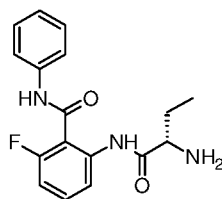


Formula III

or a salt thereof; wherein, R is an amino protecting group.

In one embodiment, R is selected from a group consisting of (C₁-C₄)alkoxymethyl, benzyloxymethyl, pivaloxymethyl and tetrahydropyranyl. In another embodiment R is (C₁-C₄)alkoxymethyl. In a preferred embodiment, R is methoxymethyl.

In another aspect, the present invention provides a compound of Formula V



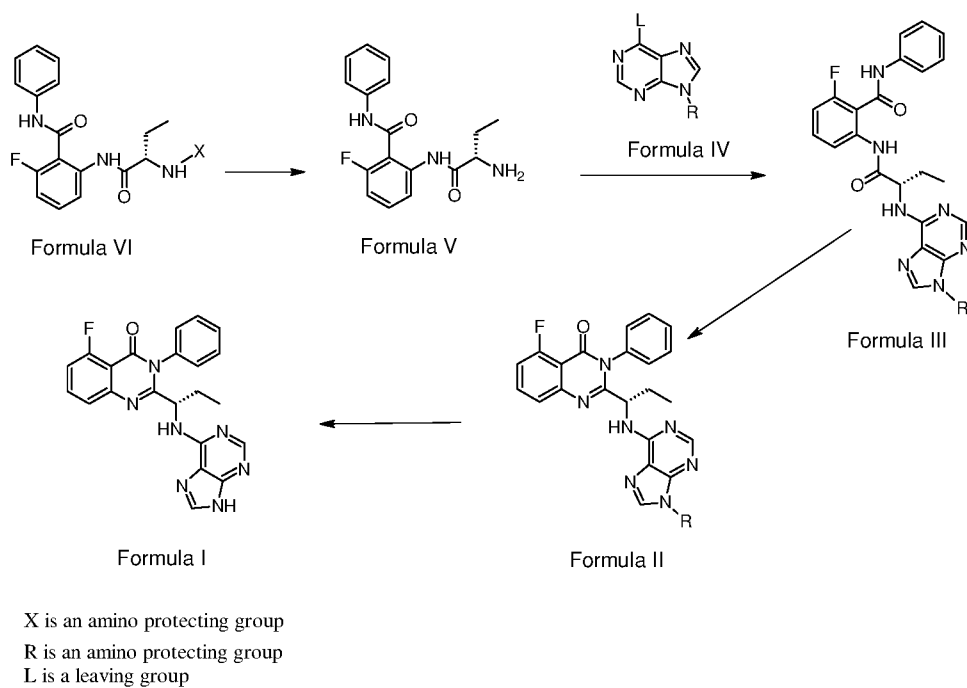
Formula V

or a salt thereof.

In another embodiment, the present invention provides idelalisib or its pharmaceutically acceptable salt prepared by the process as described in the specification.

- 5 In another embodiment, the present invention provides idelalisib or its pharmaceutically acceptable salt having impurity of compound of Formula III.

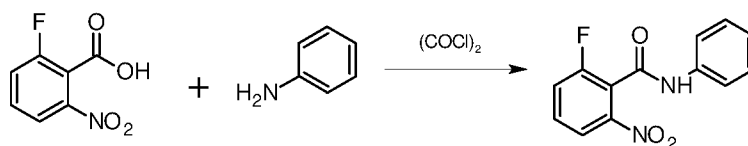
The complete process for the preparation idelalisib of the present invention can be depicted by the scheme below:



The present invention is further illustrated in detail with reference to the following examples. It is desired that the examples be considered in all respect as illustrative and are not intended to limit the scope of the claimed invention.

EXAMPLES:

Example 1: Preparation of 2-fluoro-6-nitro-N-phenylbenzamide



A mixture of 2-fluoro-6-nitrobenzoic acid and *N,N*-dimethylformamide (5 mL) in dichloromethane (600 mL) was treated drop wise with oxalyl chloride over 1 hour. After stirring for 2 hour at 25-30 °C temperature, the reaction mass was concentrated up to dryness.

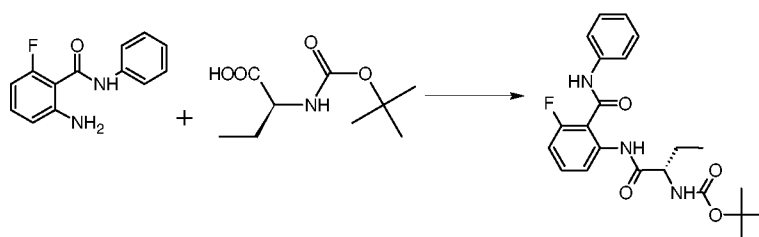
The concentrated mass was dissolved in dry 1,4-dioxane (100 mL) and slowly added to a suspension of aniline and sodium bicarbonate in a mixture of 1,4-dioxane (250 mL) and water (250 mL) at 0-5 °C temperature. After 1 hour, the reaction mixture was treated with water and stirred for 3 hours. The product was filtered, washed with water and dried in vacuum oven at below 55 °C for 12-15 hours.

Example 2: Preparation of 2-amino-6-fluoro-*N*-phenylbenzamide



A mixture of 2-fluoro-6-nitro-*N*-phenylbenzamide and 5 % palladium on carbon (50 % w/w) in methanol (3 liters) was hydrogenated at 3 kg/cm² hydrogen pressure in an autoclave for 4-5 hours. The reaction mixture was filtered through hyflow bed. The filtrate was concentrated to provide product as an off white solid.

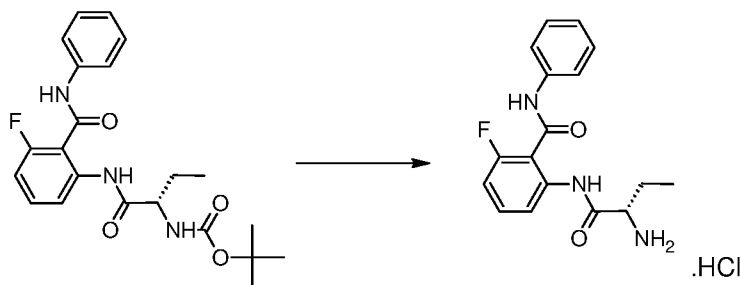
Example 3: Preparation of *tert*-butyl *N*-[(1*S*)-1-[[3-fluoro-2-(phenyl carbamoyl)phenyl]carbamoyl]propyl]carbamate



A mixture of (2*S*)-2-[(*tert*-butoxycarbonyl)amino]butanoic acid and *N*-methyl morpholine in dry tetrahydrofuran (300 mL) were stirred and cooled at -20 °C temperature. A solution of isobutyl chloroformate in dry tetrahydrofuran (200 mL) was drop wise added into the reaction mass at -20 °C temperature. The reaction mass was stirred for half an hour at -20 °C temperature. Then a solution of 2-amino-6-fluoro-*N*-phenylbenzamide in dry tetrahydrofuran

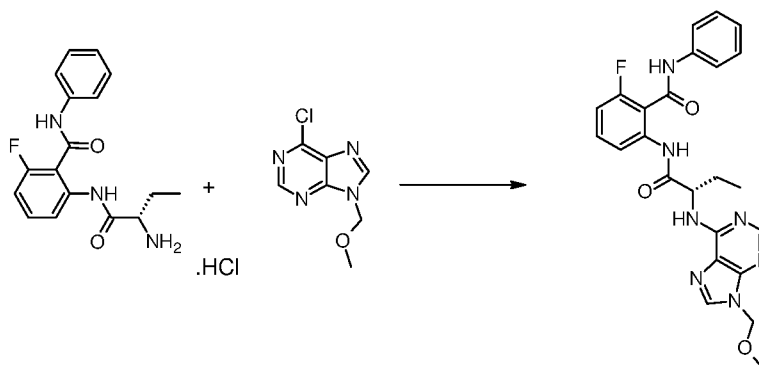
(300 mL) was added to it dropwise. After addition, the reaction mixture temperature was slowly increased up to 60 °C and stirred for 6 hours. The reaction mixture was then concentrated and partitioned between dichloromethane and water. The organic layer was again washed with water and concentrated up to dryness to provide solid product. The solid product was treated with hexane and filtered to get an off white solid of the title compound.

Example 4: Preparation of 2-[[[(2S)-2-aminobutanoyl]amino]-6-fluoro-N-phenyl-benzamide HCl salt



tert-Butyl-*N*-[(1*S*)-1-[[3-fluoro-2-(phenylcarbamoyl)phenyl]carbamoyl]propyl]carbamate was added portion wise to hydrogen chloride–2-propanol solution (6 %) at a temperature of 10-15 °C. The resultant solution was stirred at the same temperature for 4 hours. After completion of reaction, product was filtered, washed with 2-propanol and dried in hot air oven to afford the title compound. ¹H NMR (400 MHz, DMSO) δ 10.7 (s, 1H), 10.5 (s, 1H), 8.5 (d, 2H), 7.8 (d, 2H), 7.6 (m, 1H), 7.5 (d, m), 7.4 (t, 2H), 7.25 (t, 1H), 7.1 (t, 1H), 4.1 (m, 1H), 1.8 (m, 2H), 0.9 (t, 3H).

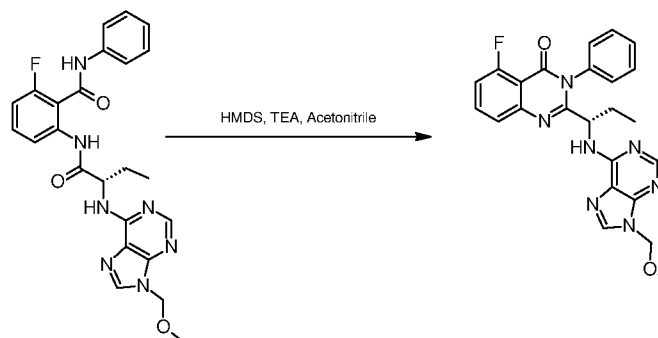
Example 5: Preparation of 2-fluoro-6-[[[(2S)-2-[[9-(methoxymethyl)purin-6-yl]amino]butanoyl]amino]-N-phenyl-benzamide



Triethylamine was added to a stirred solution of 2-[[[(2S)-2-aminobutanoyl]amino]-6-fluoro-*N*-phenyl-benzamide HCl salt in a mixture of 2-propanol and water at room temperature. The

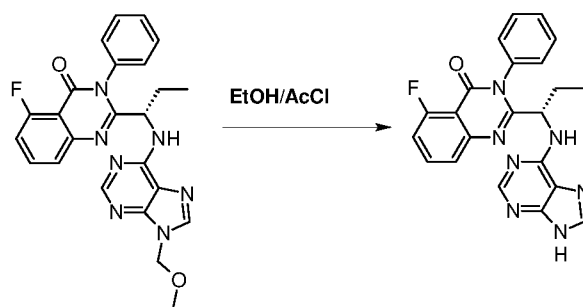
resultant reaction mass was stirred for 10 min. Then 6-chloro-9-(methoxymethyl)-9*H*-purine was added and the resultant reaction mass was heated at 75 °C to 80 °C for 16 hours. After completion of reaction, reaction mixture was concentrated and partitioned between ethylacetate and water. The organic layer was again washed with aq. sodium bicarbonate solution and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the title product. ¹H NMR (400 MHz, DMSO) δ 10.4 (s, 1H), 10.0 (s, 1H), 8.3 (brs, 1H), 8.2 (s, 1H), 8.0 (brs 1H), 7.9 (d, 1H), 7.4 (m, 3H), 7.2 (t, 2H), 7.1 (m, 2H), 5.4 (m, 2H), 4.6 (m, 1H), 3.3 (s, 3H), 2.0 (m, 2H), 0.9 (t, 3H).

Example 6: Preparation of 5-fluoro-2-[(1*S*)-1-[[9-(methoxymethyl)purin-6-yl]amino]propyl]-3-phenyl-quinazolin-4-one



A mixture of 2-fluoro-6-[[[(2*S*)-2-[[9-(methoxymethyl)purin-6-yl]amino]butanoyl]amino]-*N*-phenyl-benzamide, triethylamine (TEA), acetonitrile and hexamethyldisilazane were stirred at reflux temperature of the solvent until completion of reaction. The reaction mass was then concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated under reduce pressure to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 8.3 (s, 1H), 7.91 (brs, 1H), 7.69-7.64 (m, 1H), 7.62-7.50 (m, 4H), 7.45-7.44 (m, 1H), 7.35-7.33 (m, 1H), 7.12-7.07 (m, 1H), 6.58-6.56 (m, 1H), 5.52 (s, 2H), 5.20 (m, 1H), 3.38 (s, 3H), 2.04-1.72 (m, 2H), 0.87-0.84 (t, 3H).

Example 7: Preparation of idelalisib



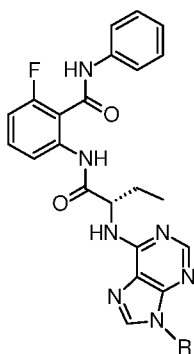
A mixture of 5-fluoro-2-[(1S)-1-[[9-(methoxymethyl)purin-6-yl]amino]propyl]-3-phenylquinazolin-4-one in ethanol was stirred at 25-30 °C. Acetyl chloride was slowly added into the reaction mass and the reaction mass was stirred at 40 °C until completion of reaction.

- 5 After completion of reaction, the reaction mass was concentrated and water was added to it. Aqueous layer was washed with di-isopropyl ether. Aqueous layer was basified with liquor ammonia and filtered to provide the title product.

Claims:

1. A process for the preparation of idelalisib or a pharmaceutically acceptable salt thereof, comprising:

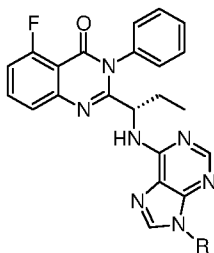
5 a) cyclizing a compound of Formula III



Formula III

or a salt thereof,

wherein R is an amino protecting group; to obtain a compound of Formula II



Formula II

or a salt thereof;

wherein R is an amino protecting group;

- 10 b) deprotecting the compound of Formula II or a salt thereof to obtain idelalisib and
c) optionally converting idelalisib to a pharmaceutically acceptable salt thereof.

2. The process as in claim 1, wherein R is selected from a group consisting of (C₁-C₄)alkoxymethyl, benzyloxymethyl, pivaloxymethyl and tetrahydropyranyl.

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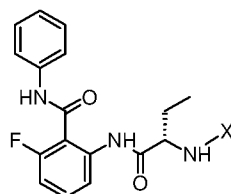
3. The process as in claim 2, wherein R is methoxymethyl.

4. The process as in claim 1, wherein in step a) the cyclization is carried out in presence of hexamethyldisilazane.

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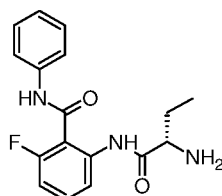
5. The process as in claim 1, wherein the compound of Formula III or a salt thereof is obtained by a process comprising:

a) deprotecting a compound of Formula VI



Formula VI

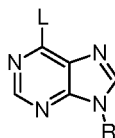
- 5 wherein X is an amino protecting group; to obtain a compound of Formula V



Formula V

or a salt thereof;

b) reacting the compound of Formula V or a salt thereof with a compound of Formula IV



Formula IV

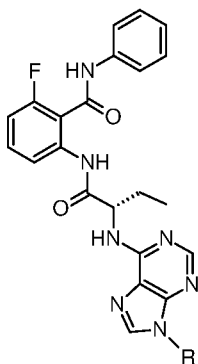
- 10 wherein L is a leaving group and R is an amino protecting group; to obtain the compound of Formula III and

c) optionally converting the compound of Formula III to a salt thereof.

6. The process as in claim 5, wherein L is chloro and R is methoxymethyl.

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7. A compound of Formula III



Formula III

or a salt thereof; wherein, R is an amino protecting group.

8. The compound as in claim 7, wherein R is methoxymethyl.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/050255

A. CLASSIFICATION OF SUBJECT MATTER
C07D473/34 Version=2017.01

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CN104262344 A (XU XUENONG; SUZHOU MIRACPHARMA TECHNOLOGY CO LTD) 07 JANUARY 2015 (07/01/2015); Reaction scheme, paragraph [0012]; Examples 1-6	1-8
Y	UA Kshirsagar et al., "Hexamethyldisilazane-iodine induced intramolecular dehydrative cyclization of diamides: a general access to natural and unnatural quinazolinones", Tetrahedron Letters, 48, pages 3243-3246, available online 12-03-2007 (12 March 2007) (DOI: 10.1016/j.tetlet.2007.03.032); Page 3243, scheme 1; Page 3244, Table 1, entries 1-11, particularly entry 4	1-4
Y	WO2015095601 A1 (GILEAD CALISTOGA LLC) 25 JUNE 2015 (25/06/2015); cited in the application; Claim 3, Examples 2-4	1-8
Y	USRE44638 E1 (ICOS CORP) 10 DECEMBER 2013 (10/12/2013); cited in the application; Compound 107, Steps D-E	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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"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

12-09-2017

Date of mailing of the international search report

12-09-2017

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/050255

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	----- WO2017134607 A1 (LUPIN LTD) 10 AUGUST 2017 (10/08/2017); claims	1-8

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2017/050255

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