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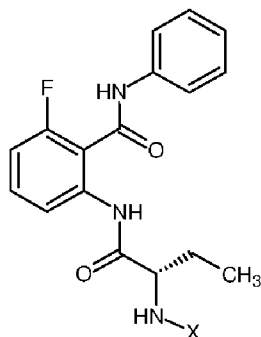
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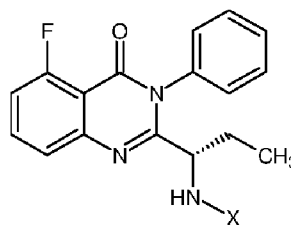
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(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF IDELALISIB



formula II



formula III

(57) Abstract: The present invention provides an improved process for the preparation of compound of formula III by cyclizing compound of formula II in presence of hexamethyldisilazane and a base in a solvent. The compound of formula III is further converted to Idelalisib. Wherein X is an amino protecting group.

IMPROVED PROCESS FOR THE PREPARATION OF IDELALISIB

RELATED APPLICATIONS

- 5 This application claims the benefit of Indian Patent Application no. IN 201621003350 filed on January 29, 2016 and IN 201621013517 filed on April 18, 2016; which is hereby incorporated by reference.

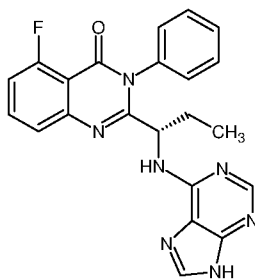
FIELD OF THE INVENTION

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The present invention provides an improved process for the preparation of Idelalisib.

BACKGROUND OF THE 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 as shown below, represented by a compound of formula I:

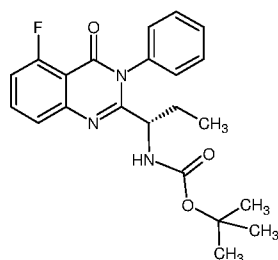


formula I

- 20 Idelalisib is marketed in the United States under the brand name Zydelig[®] as oral tablets and 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. USRE44638 (the '638 patent) discloses Idelalisib and process for its preparation, but the preparation method is relatively cumbersome, the yield is low, in particular for synthesis of intermediate compound of formula IIIa.

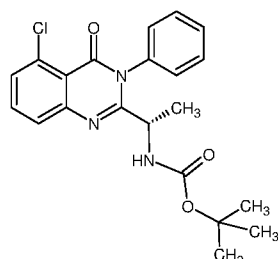


formula IIIa

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The '638 patent discloses the preparation of intermediate compound of formula IIIa, wherein it is isolated by purification with silica gel column chromatography in low yield.

- 10 The WIPO patent application WO2013116562A1 discloses preparation of related chloro analogue of intermediate compound of formula IIIa, as shown below:



- 15 by cyclizing (S)-tert-butyl 1-(3-chloro-2-(phenylcarbamoyl)phenylamino)-1-oxopropan-2-ylcarbamate using chlorotrimethylsilane, but the reaction being carried out in a sealed condition and for longer reaction time, makes it not suitable for industrial scale.

- 20 The WIPO patent application WO2015042077A1 discloses preparation of intermediate compound of formula IIIa, by cyclizing (S)-tert-butyl(1-((3-fluoro-2-(phenylcarbamoyl)phenyl)amino)-1-oxobutan-2-yl)carbamate using expensive N,O-bis(trimethylsilyl)acetamide reagent. In addition it required purification by silica gel column chromatography and the yield is low.

Various processes for the preparation of Idelalisib and its intermediates are disclosed in CN104130261A, CN104876931A, WO2015095601A1.

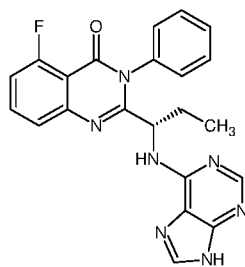
The processes reported for the preparation of Idelalisib, in particular to synthesis of intermediate compound of formula IIIa or its analogues, suffer from one or more drawbacks such as involving use of expensive reagents like *N,O*-bis(trimethylsilyl)acetamide; fuming reagents like chlorotrimethylsilane, harsh reaction conditions such as reaction in sealed condition, longer reaction time, low yield and often required purification by column chromatography which makes it difficult to prepare intermediate compound of formula IIIa on commercial scale.

There is therefore a need for a simple and efficient process for the preparation of Idelalisib.

The present invention provides a simple, scalable and economical process for the preparation of Idelalisib with desired chiral purity.

SUMMARY OF THE INVENTION

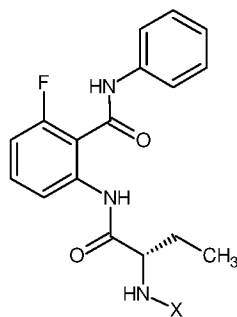
The present invention provides a process for the preparation of Idelalisib, a compound of formula I



formula I

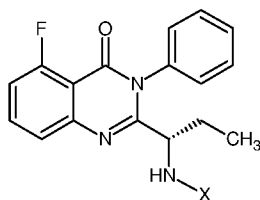
comprising:

(a) cyclizing a compound of formula II,



formula II

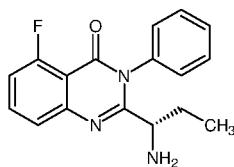
wherein X is an amino protecting group,
in presence of hexamethyldisilazane (HMDS) and a base in a solvent to obtain a
compound of formula III,



formula III

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wherein X is an amino protecting group,
(b) deprotecting the compound of formula III, to obtain a compound of formula IV

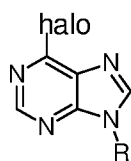


formula IV

and,

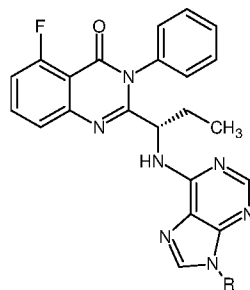
(c) reacting the compound of formula IV either with 6-halopurine to obtain the compound of
Formula I or with a compound of formula V

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formula V

wherein R is an amino protecting group and halo is halogen, to obtain a compound of
formula VI

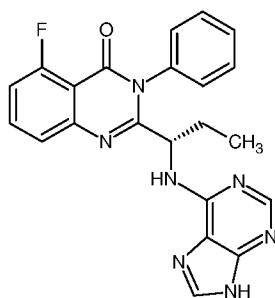


formula VI

wherein R is an amino protecting group, followed by deprotecting the compound of VI to obtain the compound of formula I.

5 DETAILED DESCRIPTION OF THE INVENTION

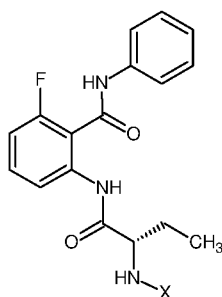
In one aspect, the present invention provides a process for the preparation of Idelalisib, a compound of formula I



formula I

10 comprising:

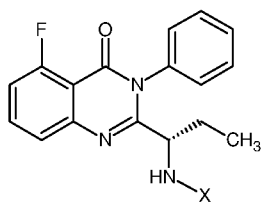
(a) cyclizing a compound of formula II,



formula II

wherein X is an amino protecting group,

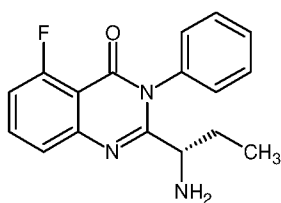
in presence of hexamethyldisilazane (HMDS) and a base in a solvent to obtain a compound of formula III,



formula III

wherein X is an amino protecting group,

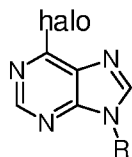
- 5 (b) deprotecting the compound of formula III, to obtain a compound of formula IV



formula IV

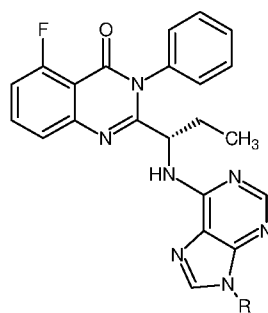
and,

- (c) reacting the compound of formula IV either with 6-halopurine to obtain the compound of Formula I or with a compound of formula V



formula V

- 10 wherein R is an amino protecting group and halo is halogen, to obtain a compound of formula VI



formula VI

wherein R is an amino protecting group, followed by deprotecting the compound of VI to obtain the compound of formula I.

In one embodiment, in step a) of above process, base may be selected from any organic or inorganic bases suitable for the reaction. Organic bases may be selected from but should not be restricted to triethylamine, trimethylamine, di-isopropylamine, *N,N*-diisopropylethylamine, pyridine, imidazole, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicycloundec-7-ene (DBU), 4-dimethylaminopyridine. The most preferred base is triethylamine. The base may be used in a molar equivalent of about 1 to 50 with respect to compound of formula II, preferably about 10 to 30 equivalent, more preferably about 15 to 20 equivalent.

In another embodiment, in step a) of above process, solvent may be selected from any suitable solvent for the reaction such as acetonitrile, dimethyl sulfoxide, dimethylacetamide or mixtures thereof. The most preferred solvent is acetonitrile.

In another embodiment, in step a) of above process, hexamethyldisilazane (HMDS) may be used in molar equivalent of about 1 to 20 with respect to compound of formula II. Preferably, HMDS may be used in molar equivalent of about 5 to 10; more preferably in molar equivalent of about 5 to 7.5.

In another embodiment, in step a) of above process, X in the compound of formula II and compound of formula III is an amino protecting group such as *tert*-butoxycarbonyl (Boc), carbobenzyloxy (Cbz), benzyl, *p*-methoxybenzyl, 9-fluorenylmethyloxycarbonyl (Fmoc) and the like. The preferred amino protecting group is Boc.

In another embodiment, step a) of above process, may be carried out at a temperature ranging from room temperature to reflux temperature of solvent; preferably reaction may be carried out at reflux temperature of solvent; more preferably at a temperature of 70 °C to 80 °C. Reaction may be carried out for a period of 10 to 30 hours; more preferably for 10-12 hours.

The present inventors found that when the cyclization of compound of formula II (wherein X is Boc) was carried out using chlorotrimethylsilane to yield compound of formula III, a dark brown color reaction mass was obtained, which made the work up procedure more tedious

due to difficulties like in organic/aqueous layer separation and requirement of number of water washes. Moreover, the product was isolated as brown oil which was found to be only 80 % pure. The yield of the product was less than 75 %. The failure of chlorotrimethylsilane led the inventors to search for the alternatives. Inventors surprisingly found that use of HMDs afforded a clean reaction and the crude product isolated from it was found to be having more than 95 % purity by ¹H NMR. The yield of the reaction also improved substantially to more than 99 %. Moreover, the obtained product of compound of formula III was found to have 99.9 % chiral purity.

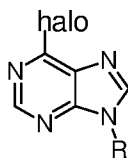
The compound of formula III may be isolated or directly subjected to deprotection without isolation as per step (b). The compound of formula III may be isolated by any process known to a person skilled in the art, for instance by concentrating the reaction mass or by extracting with a suitable solvent & concentrating under reduced pressure to obtain the compound of Formula III.

The step a) of the present invention provides compound of formula III in greater than 99 % chiral purity. In one embodiment, the chiral purity of obtained compound of formula III is greater than 99 %. In another embodiment, the chiral purity of obtained compound of formula III is greater than 99.5 %. In a preferred embodiment, the chiral purity of obtained compound of formula III is greater than 99.9 %.

Step b) of above process involves deprotection of compound of formula III to obtain a compound of formula IV. Deprotection of compound of formula III may be carried out by any process known for deprotection 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.

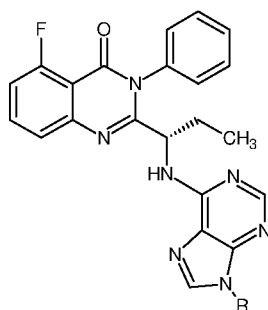
In another embodiment, in step c) of above process, the compound of formula IV is reacted with 6-halopurine to obtain Idelalisib. The 6-halopurine may be selected from 6-bromopurine, 6-chloropurine or 6-iodopurine; more preferably 6-chloropurine. The compound of formula IV may be reacted with 6-halopurine in presence or absence of base in a suitable solvent. For example, compound of formula IV may be reacted with 6-halopurine as disclosed in the United States patent No. USRE44638.

In another embodiment, in step c) of above process, the compound of formula IV is reacted with a compound of formula V (*N*-protected 6-halopurine)



formula V

wherein R is an amino protecting group and halo is halogen, to obtain a compound of formula VI



formula VI

wherein R is an amino protecting group; and the compound of formula VI is deprotected to obtain the compound of formula I.

In an embodiment, R in the compound of formula V and compound of formula VI is an amino protecting group selected from a group consisting of (C₁-C₄)alkoxymethyl, benzyloxymethyl and pivaloyloxymethyl. In a preferred embodiment, R in the compound of formula V and compound of formula VI is methoxymethyl (MOM). In another embodiment, halo in the compound of formula V is selected from chloro, bromo or iodo; preferably chloro.

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

The reaction of compound of formula IV with the compound of formula V is carried out in presence of a base in a suitable solvent to obtain the compound of formula VI. A suitable base for the reaction may be selected from organic bases such as triethylamine, trimethylamine, di-isopropylamine, *N,N*-diisopropylethylamine, pyridine, piperidine,

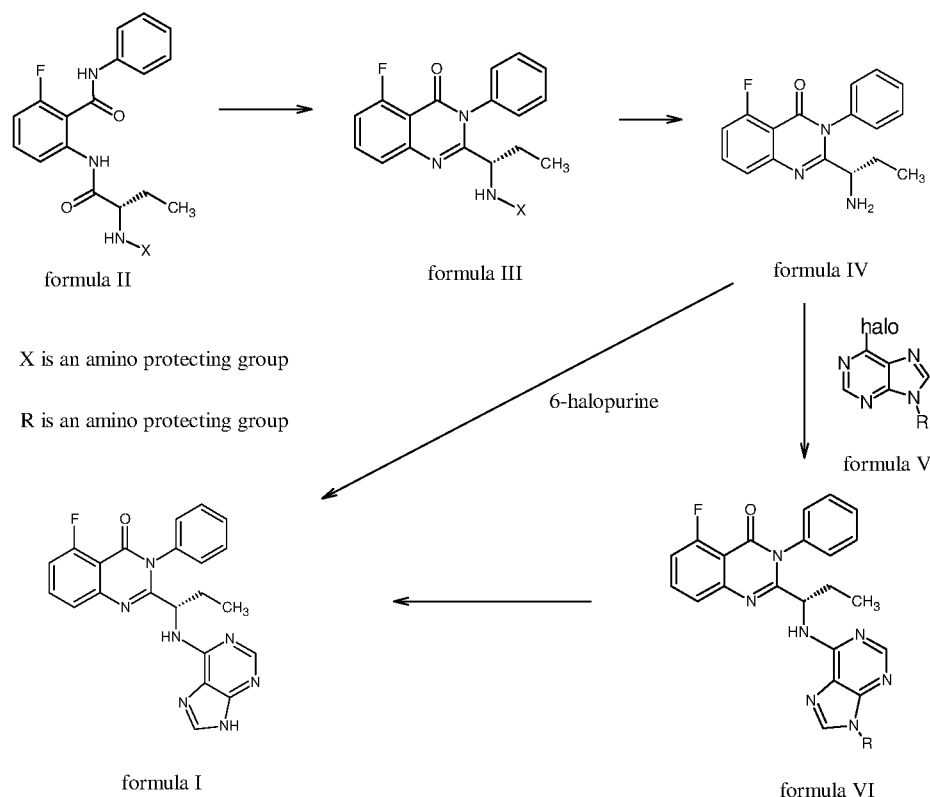
imidazole, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicycloundec-7-ene (DBU), 4-dimethylaminopyridine or a mixture thereof; or inorganic bases such as potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide or a mixture thereof. The most preferred base is triethylamine. A suitable solvent for the reaction may be selected from a group consisting of water, ethanol, methanol, n-butanol, *tert*-butanol, isopropyl alcohol, *N,N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), *N*-methylpyrrolidine, acetonitrile, acetone, methylisobutyl ketone or a mixture thereof. The most preferred solvent is a mixture of ethanol and water. Reaction may be carried out at a temperature ranging from room temperature to reflux temperature of the solvent; more preferably at a temperature of 70 °C to 80 °C and for a time suitable for the completion of reaction.

The compound of formula VI may be isolated or directly subjected to deprotection without isolation. The compound of formula VI may be isolated by any process known to a person skilled in the art, for instance by concentrating the reaction mass or by extracting with a suitable solvent & concentrating under reduced pressure to obtain the compound of Formula VI.

The deprotection of compound of formula VI may be carried out by treating the compound of formula VI with any reagent used for the deprotection of an amino protecting group such as acids or by catalytic hydrogenolysis. For instance, the methoxymethyl (MOM) deprotection can be carried out by using hydrochloric acid. The hydrochloric acid can be generated in-situ. For example, acetyl chloride and ethanol can be used in generating hydrochloric acid in-situ.

The compound of formula II used in step a) of above process, may be prepared as disclosed in prior art such as WO2015042077A1.

The process of the present invention can be depicted as in following scheme:



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.

5

EXAMPLES:

Example 1: (S)-[1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydro-quinazolin-2-yl)-propyl]-carbamic acid *tert*-butyl ester

- 10 To a solution of (S)-*tert*-butyl-1-[3-fluoro-2-(phenylcabamoyl)phenylamino]-1-oxobutan-2-ylcarbamate (10 g, 1 equivalent) in acetonitrile (300 mL) was added triethyl amine (114.1 g, 47 equivalent), followed by the drop wise addition of hexamethyldisilazane (58.1 g, 15 equivalent). The reaction mixture was stirred at reflux temperature for 10-12 hours. After completion of reaction, the reaction mass was concentrated under reduced pressure.
- 15 Dichloromethane (200 mL) was added to the residue and washed with water followed by brine wash. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield off-white solid of title compound (9.5 g, yield: 99.6 %; Purity > 95 %).

Example 2: (S)-[1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydro-quinazolin-2-yl)-propyl]-carbamic acid *tert*-butyl ester

To a solution of (S)-*tert*-butyl-1-[3-fluoro-2-(phenylcabamoyl)phenylamino]-1-oxobutan-2-ylcarbamate (100 g, 1 equivalent) in acetonitrile (2000 mL) was added triethyl amine (377.52 g, 15.5 equivalent), followed by the drop wise addition of hexamethyldisilazane (194.24 g, 5 equivalent). The reaction mixture was stirred at reflux temperature for 24 hours. After completion of reaction, the reaction mass was concentrated under reduced pressure. Dichloromethane (1000 mL) was added to the residue and washed with water followed by brine wash. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product which was further purified by slurring with cyclohexane. Yield: 80 g, 84 %; Chiral Purity: 99.9%.

Example 3: 2-[(1S)-1-Aminopropyl]-5-fluoro-3-phenyl-quinazoline-4-one

A mixture of *tert*-butyl N-[(1S)-1-(5-fluoro-4-oxo-3-phenyl-quinazoline-2-yl)propyl]carbamate (100 g, 0.251 moles) was dissolved in acetonitrile (600 mL) and treated with concentrated hydrochloric acid (125 mL) at 25-30 °C. The reaction mixture was stirred for 5-6 hours at 25-30 °C. After completion of reaction, the reaction mass was concentrated under reduced pressure and washed with toluene. The aqueous layer was basified with liquor ammonia and filtered to provide the title product as an off white solid (71.06 g).

Example 4: 6-Chloro-9-(methoxymethyl)-9H-purine

A mixture of 6-chloro-9H-purine (50 g, 0.323 moles) and triethylamine (98.20 g, 0.97 moles) in dry tetrahydrofuran (600 mL) was stirred at 0-5 °C. Chloromethoxymethane (52.1 g, 0.646 moles) was added drop wise into the reaction mixture by maintaining 0-5 °C temperature. Then the reaction mass was allowed to attain 25-30 °C temperature and stirred for 2 hours. After 2 hours, triethylamine hydrochloride salt was filtered out and washed with tetrahydrofuran. The filtrate was concentrated under reduced pressure and the crude product was crystallized in tetrahydrofuran to obtain the title product (50g, 77.8 %).

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

A mixture of 2-[(1S)-aminopropyl]-5-fluoro-3-phenyl-quinazolin-4-one (30 g, 0.100 moles), 6-chloro-9-(methoxymethyl)-9H-purine (22.02 g, 0.11 moles) and triethyl amine (15.3 g, 0.15

moles) in ethanol (150 mL) and water (75 mL) was stirred together at 75-80 °C until completion of reaction. After completion of reaction, the reaction mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was again washed with water and concentrated under reduced pressure to provide crude solid title compound (46.2 g).

Example 6: Idelalisib

A mixture of crude product from above example 5 in ethanol (400 mL) was stirred at 25-30 °C. Acetyl chloride (18.30 g, 0.233 moles) was slowly added into the reaction mass and the reaction mass was stirred at 40 °C until completion of reaction. 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 aqueous ammonia and filtered to provide the title product (25 g).

Example 7: Idelalisib

A mixture of 5-fluoro-2-[(1*S*)-1-[[9-(methoxymethyl)purin-6-yl]amino] propyl]-3-phenyl-quinazolin-4-one (100 g, 0.217 moles) in methanol (1000 mL) was stirred at 25-30 °C. Acetyl chloride (68.33 g, 0.8705 moles) was slowly added into the reaction mass and the reaction mass was stirred at 40 °C for 5 hours. After completion of reaction, the reaction mass was concentrated to afford the crude residue which was crystallized in ethanol to afford HCl salt of Idelalisib. The HCl salt of Idelalisib was basified with aqueous ammonia and filtered to afford Idelalisib. Yield: 72 g, 80 %, Purity: 99.84 % by HPLC, Chiral Purity: 99.92 %.

Example 8: 5-Fluoro-2-[(1*S*)-1-[[9-(methoxymethyl)purin-6-yl]amino]propyl]-3-phenyl-quinazolin-4-one

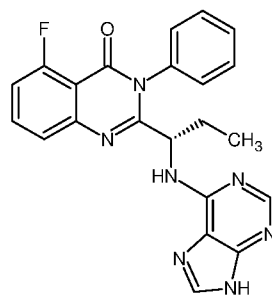
A mixture of hydrochloride salt of 2-[(1*S*)-aminopropyl]-5-fluoro-3-phenyl-quinazolin-4-one (30g, 0.0901 moles), 6-chloro-9-(methoxymethyl)-9*H*-purine (19.68 g, 0.0991 moles) and triethyl amine (22.8 g, 0.225 moles) in ethanol (150 mL) and water (75 mL) was stirred together at 75-80 °C until completion of reaction. After completion of reaction, reaction mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was again washed with water and concentrated under reduced pressure to provide crude solid product (41.2 g).

Example 9: Idelalisib

A mixture of hydrochloride salt of 2-[(1*S*)-aminopropyl]-5-fluoro-3-phenyl-quinazoli-4-one (30 g, 0.0901 moles), 6-chloro-9-(methoxymethyl)-9*H*-purine (19.68 g, 0.0991 moles) and triethyl amine (22.8 g, 0.225 moles) in ethanol (150 mL) and water (75 mL) were stirred together at 75-80 °C until completion of reaction. After completion of reaction, the reaction mixture was concentrated. The concentrated mass was dissolved in ethanol (300 mL). Acetyl chloride (18.30 g, 0.233 moles) was slowly added into the reaction mass and stirred at 40 °C for 6-8 hours. After completion of reaction, the reaction mixture was concentrated and stirred in acetone (100 mL). The solid was filtered off to provide HCl salt of Idelalisib (29.87 g, 80 %). HCl salt of Idelalisib was converted into free base by treating it with aqueous ammonia followed by filtration.

Claims:

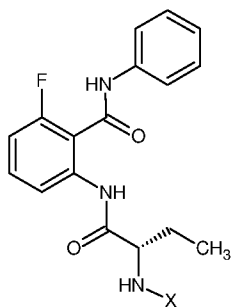
1. A process for the preparation of Idelalisib, a compound of formula I



formula I

comprising:

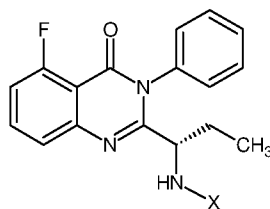
- 5 (a) cyclizing a compound of formula II,



formula II

wherein X is an amino protecting group,

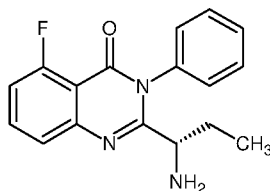
in presence of hexamethyldisilazane and a base in a solvent to obtain a compound of
10 formula III,



formula III

wherein X is an amino protecting group,

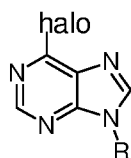
- (b) deprotecting the compound of formula III, to obtain a compound of formula IV



formula IV

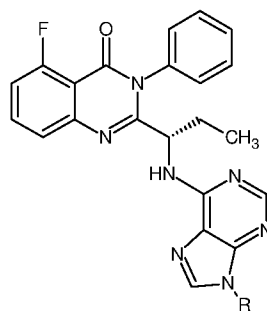
and,

- (c) reacting the compound of formula IV either with 6-halopurine to obtain the compound of Formula I or with a compound of formula V



formula V

- 5 wherein R is an amino protecting group and halo is halogen, to obtain a compound of formula VI



formula VI

wherein R is an amino protecting group, followed by deprotecting the compound of VI to obtain the compound of formula I.

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2. The process as in claim 1, wherein in step a, X in the compound of formula II and compound of formula III is *tert*-butoxycarbonyl (Boc).
3. The process as in claim 1, wherein in step a, the base is selected from a group consisting of triethylamine, trimethylamine, di-isopropylamine, *N,N*-diisopropylethylamine, pyridine, imidazole, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-Diazabicycloundec-7-ene (DBU) and 4-dimethylaminopyridine.

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4. The process as in claim 3, wherein the base is triethylamine.
5. The process as in claim 1, wherein in step a, the solvent is selected from a group consisting of acetonitrile, dimethyl sulfoxide, dimethylacetamide or mixtures thereof.
- 5 6. The process as in claim 5, wherein the solvent is acetonitrile.
7. The process as in claim 1, wherein R in the compound of formula V and compound of formula VI is methoxymethyl.
- 10 8. The process as in claim 1, wherein halo in the compound of formula V is chloro.
9. The process as in claim 1, wherein in step c, the 6-halopurine is 6-chloropurine.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/050038

A. CLASSIFICATION OF SUBJECT MATTER
C07D239/91 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	WO2015042077A1 (CALITOR SCIENCES LLC[US]; SUNSHINE LAKE PHARMA CO LTD[CN]), 26-03-2015 (26 March 2015), cited in application; See paragraphs [498]-[500]; and paragraph [388]	1-9
Y	USRE44638 E (KERRY W. FOWLER ET AL.), 10-12-2013 (10 December 2013), cited in application; See example at column 87, line 30 to column 91, line 34; compound 107, 108, 109, 110 and 111; See intermediate compound 13 at column 42, compound 18 at column 45, compound 21 at column 46, compound 25 at column 48, compound 31 at column 50, compound 34 at column 52, compound 44 at column 57	1-9
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:	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

07-06-2017

Date of mailing of the international search report

07-06-2017

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2017/050038

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	10.1016/j.tetlet.2007.03.032); See page 3243, scheme 1; Table 1, entries 1-11 at Page 3244, particularly entry 4	

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2017/050038

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