FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

&

The Patents Rules, 2003

COMPLETE SPECIFICATION

(See section 10 and rule 13)

PROCESS FOR PREPARATION OF IDELALISIB AND INTERMEDIATES THEREOF

Dr. Reddy's Laboratories Limited
An Indian company having its registered office at
8-2-337, Road No. 3, Banjara hills,
Hyderabad – 500034,
Telangana,
India

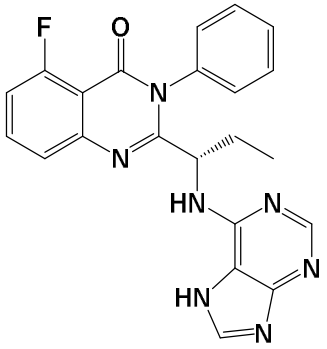
The following specification particularly describes the invention and the manner in which it is to be performed:

FIELD OF THE INVENTION

The present application relates to novel processes for preparation of Idelalisib and intermediates thereof.

BACKGROUND OF THE INVENTION

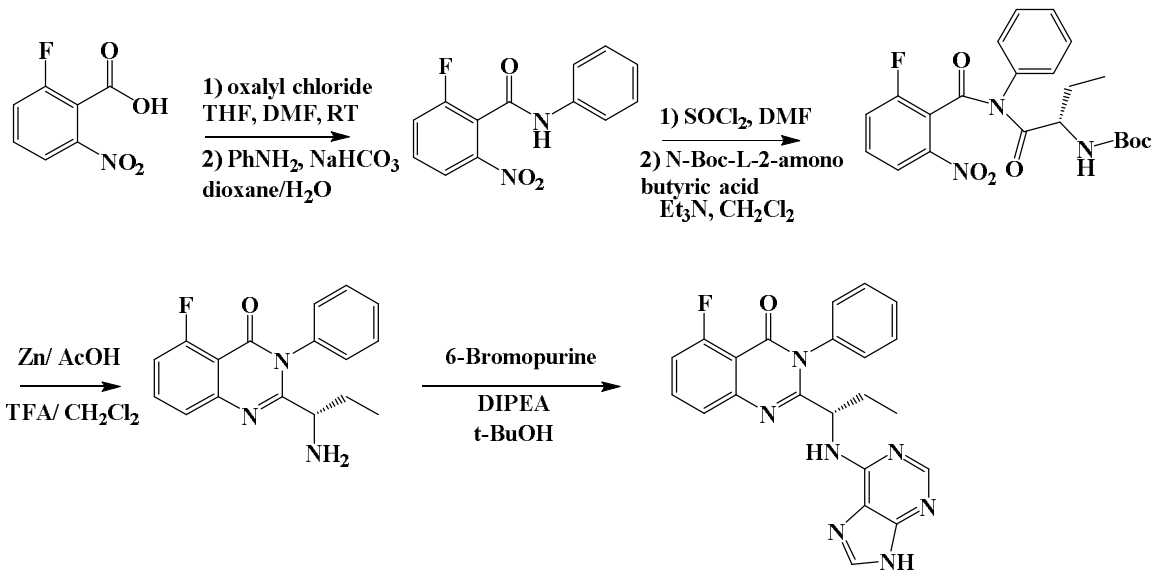
The drug compound having the adopted name Idelalisib (GS-1101, CAL-101) has a chemical name (S)-2-(1-(9H-purin-ylamino)propyl)-5-fluoro-3-phenylquinazolin-4(3H)-one and is represented by structure of formula I.



Formula I

Idelalisib is an oral inhibitor of phosphatidylinositol 3-kinase-δ and is indicated for the treatment of relapsed chronic lymphocytic leukemia (CLL), relapsed follicular B-cell non-Hodgkin lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL).

US Patent No. US 7932260 B2 (US ‘260) discloses Idelalisib, related compounds, and their pharmaceutical compositions. Further, it describes a process for the preparation of Idelalisib, in which2-fluoro-6-nitrobenzoic acid was reacted with oxalyl chloride in presence of catalytic amount of DMF, and the obtained acid chloride was reacted with aniline to form 2-fluoro-6-nitro-N-phenylbenzamide, the phenylbenzamide was reacted with N-Boc-L-2-aminobutyric acid in presence of thionyl chloride to form tert-butyl (S)-(1-(2-fluoro-6-nitro-N-phenylbenzamido)-1-oxobutan-2-yl)carbamate then the nitro carbamate was reduced using Zinc and acetic acid and the intermediate amino compound was cyclized and deprotected to yield (S)-2-(1-aminopropyl)-5-fluoro-3-phenylquinazolin-4(3H)-one, finally the quinazolinone was reacted with 6-bromopurine to form idelalisib. The synthetic process disclosed in US ‘260 is schematically represented below.



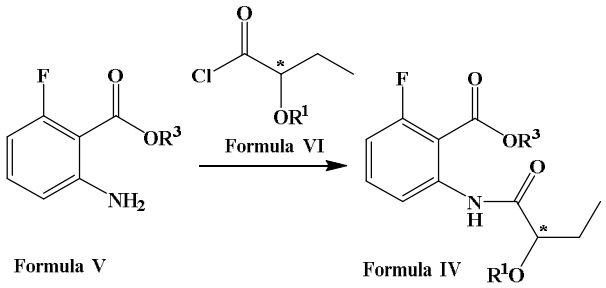
The process disclosed in US ‘260involves use of Bromopurine for synthesis of idelalisib and use of chromatography for purification of idelalisib and intermediate compounds, and the process is not desirable for large-scale manufacturing. In addition, the process disclosed in US ‘260 ends up with low yield, less purity.

It is therefore essential to develop simplified and viable process for preparation of pure idelalisib that alleviates the deficits of prior art process.

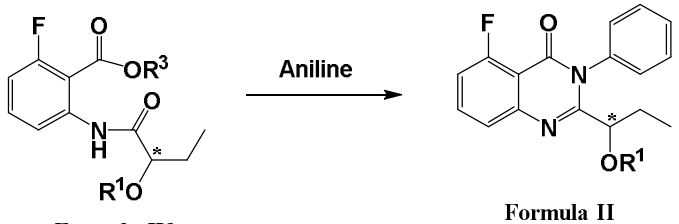
SUMMARY OF THE INVENTION

In one embodiment, the present application provides a process for preparation of idelalisib, comprising:

(a) reacting a compound of formula V with a compound of formula VI to form a compound of formula IV



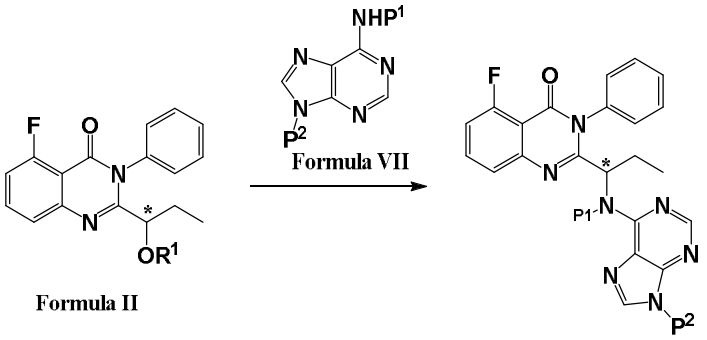
(b) reacting the compound of formula IV with aniline in presence of a dehydrating agent to form a compound of formula II



Formula IV

Formula II

(c) reacting the compound of formula II with a compound of Formula VII to get compound of formula I-A



Formula VII

Formula II

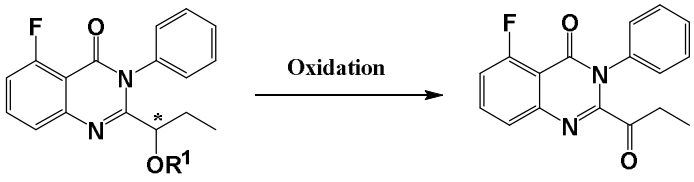
Formula I-A

(d) optionally deprotecting the compound of formula I-A to form idelalisib.

wherein, $R^1$is selected from the group comprising hydrogen, C_1-C_5alkyl, alkenyl, alkynyl, aryl, aralkyland each of which may optionally be substituted, -COR^2 and SO_2R^2; $R^2$is selected from the group comprising C_1-C_5 alkyl, optionally substituted phenyl and tolyl; P^1 and P^2each independently represent a hydrogen atom or a protective group for the amino group.

In another embodiment, the present application provides a process for preparation of Idelalisib, comprising:

(a) oxidizing a compound of formula II to get a compound of formula II-A

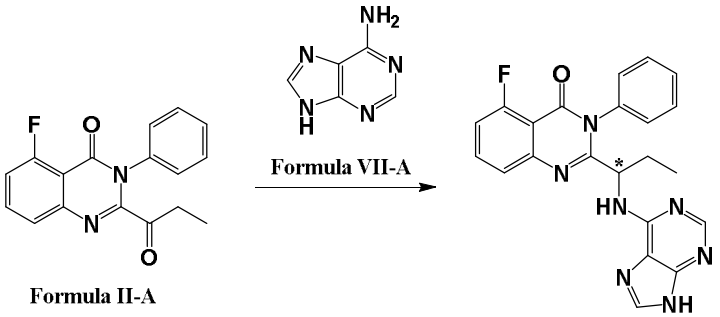


Formula II

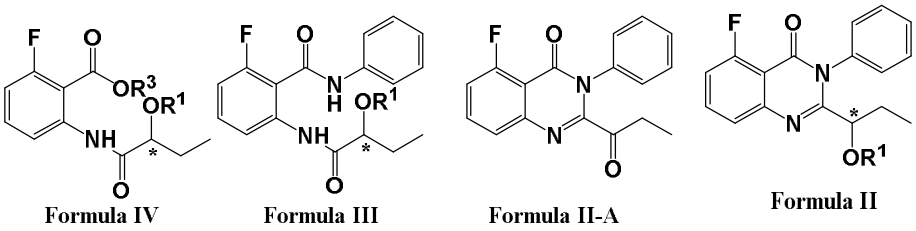
Formula II-A

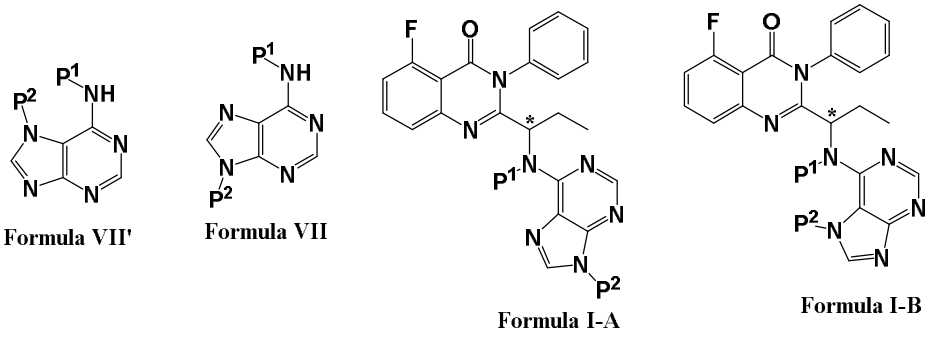
wherein R^1 is hydrogen.

(b) reactingthe compound of formula II-A with a compound of Formula VII-A to form idelalisib.



In another embodiment, the present application provides novel intermediates of the compounds of formula I-A, I-B, II, II-A, III, IV, VII and formula VII'.





wherein, R^1 is selected from the group comprising hydrogen, C_1-C_5 alkyl, alkenyl, alkynyl, aryl, aralkyl and each of which may optionally be substituted, -COR^2 and SO_2R^2; R^2 is selected from the group comprising C_1-C_5 alkyl, optionally substituted phenyl and tolyl; P^1 and P^2 each independently represent a hydrogen atom or a protective group for the amino group.

In another embodiment, the present application provides use of the compounds of formula I-A, II, II-A, III, IV and formula VII in the synthesis of idelalisib.

In another embodiment, the present application provides use of Idelalisib prepared by the processes disclosed above in the preparation of a pharmaceutical composition for the treatment of cancer.

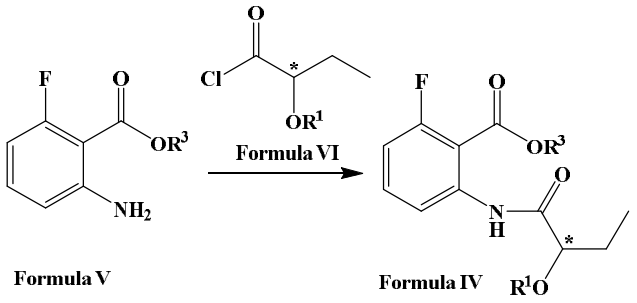
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is powder X-ray power diffraction pattern of an amorphous form of idelalisib prepared according to Example 23.

DETAILED DESCRITPION OF THE INVENTION

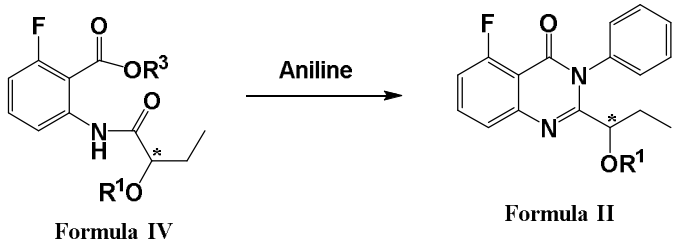
In another embodiment, the present application provides a process for preparation of idelalisib, comprising:

(a) reacting a compound of formula V with a compound of formula VI to form a compound of formula IV



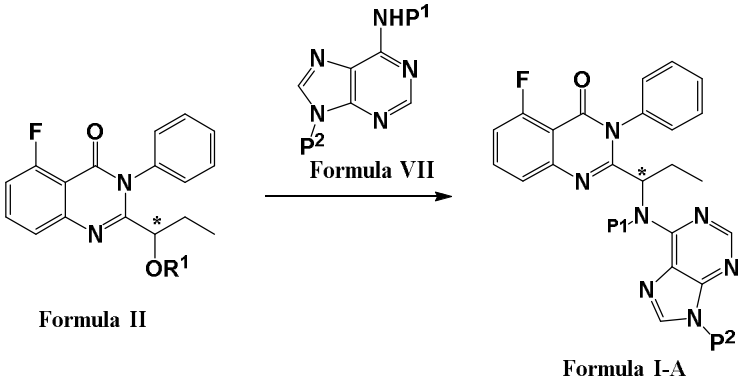
Formula V Formula IV

(b) reacting the compound of formula IV with anilinein presence of a dehydrating agent to form a compound of formula II



Formula IV Formula II

(c) reacting the compound of formula II with a compound of Formula VII to get compound of formula I-A



Formula II Formula I-A

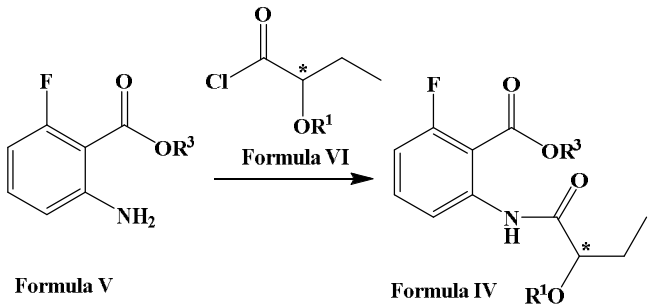
(d) optionally deprotecting the compound of formula I-A to form idelalisib.

wherein, $R^1$is selected from the group comprising hydrogen, C_1-C_5 alkyl, alkenyl, alkynyl, aryl, aralkyl and each of which may optionally be substituted, -COR^2 and SO_2R^2; $R^2$is selected from the group comprising C_1-C_5 alkyl, optionally substituted phenyl and tolyl; P^1 and P^2each independently represent a hydrogen atom or a protective group for the amino group.

The protective group for the amino group is a group for protecting an amino group. As the groups to be generally used, the protective groups described in PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 4th Ed. (published by JOHN WILEY & SONS in 2006) can be used. The preferred protective groups in the above general formula I-A and formula VII- are not specifically limited, but include, for example, carbamate-type protective groups such as methyloxy carbonyl group, an ethyloxy carbonyl group, a benzyloxy carbonyl group, and a tert-butyloxy carbonyl group; acyl groups such as an acetyl group, a trifluoroacetyl group, a phthaloyl group, and a benzoyl group; alkyl groups such as a benzyl group, a trityl group, and a dibenzoyl group; sulfonyl groups such as tosyl group and a mesyl group; and silyl groups such as a trimethylsilyl group. Preferred are carbamate-type protective groups. Among them a tert-butyloxy carbonyl group, a benzyloxy carbonyl group and a trityl group are preferably used.

The absolute configuration of the carbon which is marked with * in the compounds of general formula (I-A) to (VI) is not specifically limited, but an optically active compound having an asymmetric carbon is preferable. Especially, a compound having an absolute configuration (R) is preferable as the compounds of formula II, formula IV and formula to VI; and a compound having an absolute configuration (S) is preferable as the compounds of formula I-A.

The step (a) of the process involves reaction of compound of formula V with compound of formula VI in presence of suitable base and solvent to form compound of formula IV. In one embodiment R^1 of compound of formula VI is 'acetyl' and the compound is 1-chloro-1-oxobutan-2-yl acetate. In another embodiment, the R^3 of compound of formula V is hydrogen and the compound is 2-amino-6-fluorobenzoic acid.



Formula V Formula IV

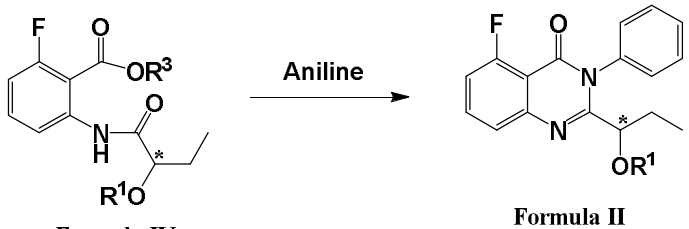
Compounds of formula V and formula VI may be obtained by any process including processes described in the art, or by a process described in this application.

The reaction is effected in the presence of suitable solvent. The solvent that can be used, include, but or not limited to, hydrocarbon solvents such as n-hexane, n-heptane, cyclohexane, toluene, or the like;a halogenated hydrocarbon solvent such as dichloromethane, ethylene dichloride, chloroform, or the like; ether solvents such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, or the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), dimethylacetamide (DMA), acetonitrile or the like; or mixtures thereof.

Optionally, the reaction is carried out in presence of a base. The base that can be used, include, but or not limited to methylamine, ethylamine, dimethylamine, diethylamine, triethylamine, diisopropylethylamine, dimethylaminopyridine, sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, or the like; or mixtures thereof.

The reaction may be carried out at a temperature about -10°C to about 80°C, preferably at about 10°C to about 40°C. After completion of the reaction, the reaction mass may be acidified with acids such as aqueous hydrochloric acid, aqueous sulfuric acid, or aqueous acetic acid. The product is isolated by filtrationof the mass, or the reaction mass containing product is extracted with an organic solvent. The product may be isolated by removing solvent from the resulting organic solvent extractionor may be used directly in the next step.

Step (b) of the process involves reaction of the compound of formula IV with aniline in presence of a suitable dehydrating agent to form a compound of formula II. In one embodiment R^1 of compound of formula IV is 'acetyl' and the compound is 2-(2-acetoxybutanamido)-6-fluorobenzoic acid. In another embodiment, the R^3 of compound of formula II is hydrogen and the compound is 1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl acetate.



Formula IV **Formula II**

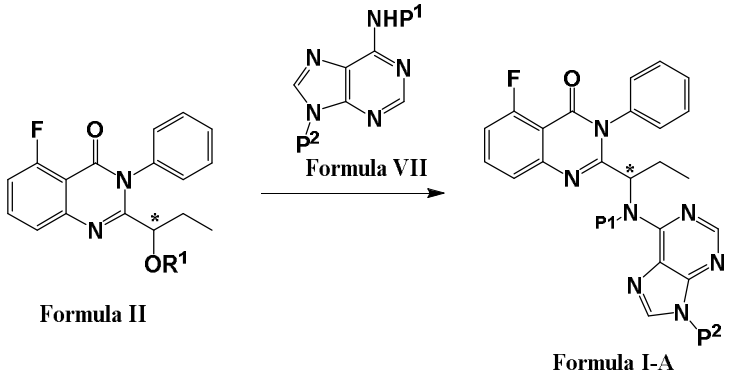
The reaction is carried in the presence of suitable solvent. The solvent that can be used, include, but or not limited to, hydrocarbon solvents such as n-hexane, n-heptane, cyclohexane,

toluene, or the like; a nitrile solvent such as acetonitrile, propionitrile, or the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), dimethylacetamide (DMA), or the like; or mixtures thereof.

The dehydrating agent that can be used is selected form the group comprising thionyl chloride, oxalyl chloride, phosphorous trichloride and phosphorous pentachloride. In one embodiment, the dehydrating agent is phosphorous trichloride.

The reaction is carried out at ambient temperature. The higher limit is not specifically limited, but is generally 100°C., preferably 50°C. After completion of the reaction, the reaction mass may be quenched with acids such as aqueous hydrochloric acid, aqueous sulfuric acid, or aqueous acetic acid. The product is isolated by filtration of the mass, or the reaction mass containing product is extracted with an organic solvent. The product may be isolated by removing solvent from the resulting organic solvent extraction or may be used directly in the next step.

Step (c) of the process involves reaction of the compound of formula II with a compound of formula VII to form compound of formula I-A. In one embodiment R^1 of compound of formula II is 'acetyl' and the compound is 1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl acetate.



The 6-Amino purine of compound of formula VII can also exist as compound of formula VII'or a mixture of compound of formula VII and VII'

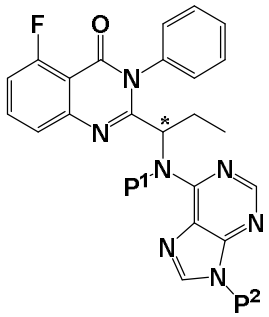
In another embodiment, before reacting with compound of formula VII, the compound of formula II may be hydrolyzed. In one embodiment, 1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl acetate is hydrolyzed to get 5-fluoro-2-(1-hydroxypropyl)-3-phenylquinolin-4(3H)-one.

In another embodiment, the P^1 of compound of formula VII is tert.-butyloxycarbonyl and P^2 is triphenylmethyl, and the compound of formula VII is tert-butyl-(9-trityl-9H-purin-6-yl)carbamate; and the compound of formula VII' is tert-butyl (7-trityl-7H-purin-6-yl)carbamate.

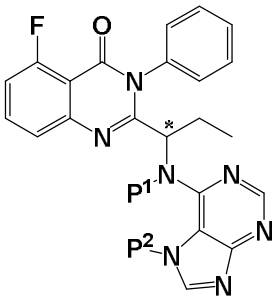
The compound of formula II is reacted with compound of formula VII using a suitable nucleophilic displacement reaction such as 'Mitsunobu reaction'. The reaction is carried out in a suitable solvent. The solvent that can be usedinclude,but or not limited to, hydrocarbon solvents such as n-hexane, n-heptane, cyclohexane, toluene, or the like; a halogenated hydrocarbon solvent such as dichloromethane, ethylene dichloride, chloroform, or the like; ether solvents such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, or the like; a nitrile solvent such as acetonitrile, propionitrile, or the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), dimethylacetamide (DMA), or the like; or mixtures thereof.

The reaction is carried out at ambient temperature or at elevated temperature. The higher limit is not specifically limited, but is generally 130°C., preferably 80°C.After completion of the reaction, the reaction mass may be concentrated and the inorganic salts are separated to get compound of formula I-A.

The compound of formula I-A can also exist as compound of formula I-B, or a mixture of compound of formula I-A and I-B.



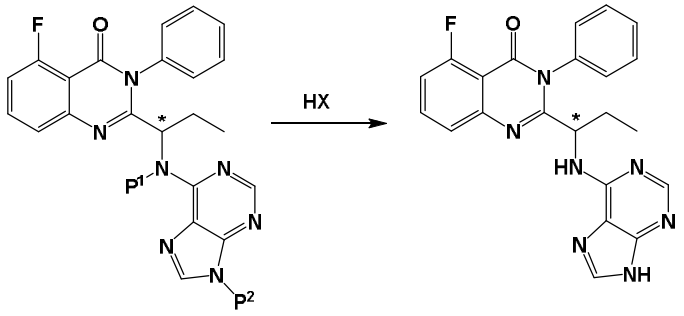
Formula I-A



Formula I-B

The application further provides a process for converting compound of formula I-A into idelalisib of formula I. For the conversion, a suitable method may be selected depending on the

type of P^1 and P^2 which represent the N-protective group. For example when P^1 and P^2 are a protective group capable of being deprotected with an acid such as tert-butoxycarbonyl, benzyloxycarbonyl, triphenylmethyl, the reaction of the process may be attained by acid treatment as shown below.



The acid to be used includes, for example, a mineral acid, a sulfonic acid, and a carboxylic acid. The mineral acid is not specifically limited, but includes hydrogen halides such as hydrogen chloride, and hydrogen bromide; sulfuric acid; phosphoric acid. The sulfonic acid is not specifically limited, but includes, for example, methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, and 1-phenylethanesulfonic acid. The carboxylic acid is not specifically limited, but includes, for example, formic acid, acetic acid and trifluoroacetic acid.

The amount of acid to be used may be at least a theoretical amount; but the use thereof in a large amount is not economical. Therefore the lower limit of the amount is generally not less than 1 mol equivalent, and the higher limit is generally not more than 10 mol equivalents, preferably not more than 3 mol equivalents, more preferably not more than 2 molequivalentsrelative to the compound of the formula (I).

The acid may be added directly as it is, or the aqueous solution or the solution in which the acid is previously dissolved in a solvent mentioned below may be used. The concentration of the acid to be added is not specifically limited, but the lower limit is generally 0.1% by weight, preferably 1% by weight, more preferably 5% by weight and the higher limit is 100% by weight.

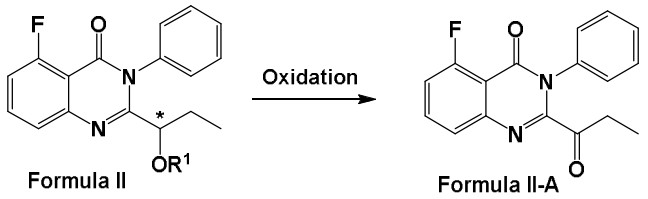
The reaction is generally carried out in a solvent. The solvent is not specifically limited, but includes alcohols such as methanol, ethanol, isopropanol, n-propanol, tert-butanol; ethers such as tetrahydrofuran, diethyl ether, methyl tert-butyl ether, 1,3-dioxolan, 1,2-dimethoxy ethane, diethylene glycol dimethyl ether; and halogenated hydrocarbons such as dichloromethane, 1,2-dichloethane.

Among the above mentioned solvents alcohols are preferable from the view point of the high reactivity and the stability to acid.

In case where P^1 and P^2 are protective groups that could not be deprotected by acid, the compound is appropriately deprotected according to the type of the protective group to obtain idelalisib.

In another embodiment, the present application provides a process for preparation of Idelalisib, comprising:

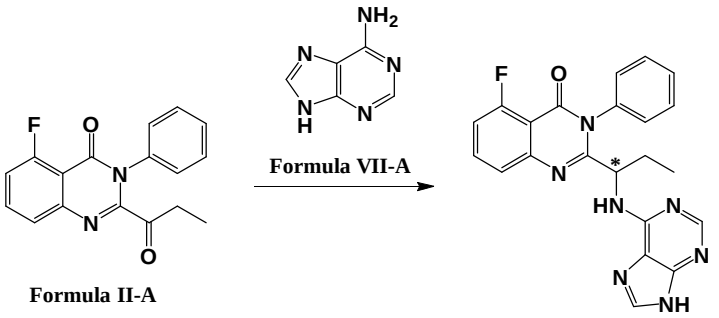
(a) oxidizing a compound of formula II to get a compound of formula II-A



Formula II Formula II-A

wherein R^1 is hydrogen.

(b) reacting a compound of formula II-A with a compound of Formula VII-A to form idelalisib.



Formula II-A Formula VII-A Idelalisib

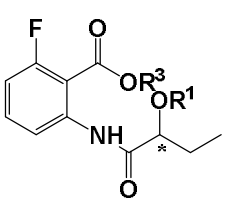
Step (a) of the process involves oxidation of the compound of formula II to form compound of formula II-B. Typical reagents/methods that may be employed for this purpose include (but are not limited to) Swern oxidation, Oppenauer oxidation, sodium hypochlorite, manganese (IV) oxide, pyridinium chlorochromate, pyridinium dichromate, Jones reagent, 2-iodoxybenzoic acid and Dess-Martin periodinane (1,1- dihydro-1,1,1-triacetoxy-1,2-benzoiodooxol-3(1H)-one). The oxidation is typically carried out in the presence of a solvent. The solvents that can be used include, but are not limited to, ethers such as diethyl ether, tetrahydrofuran (THF) and the like; halogenated solvent such as dichloromethane, ethylene dichloride, chloroform and the like; aprotic polar solvents such as N,N-dimethylformamide

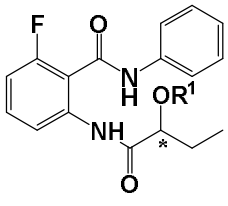
(DMF), dimethylsulfoxide (DMSO), dimethylacetamide (DMA), acetonitrile and the like; hydrocarbon solvents such as n-hexane, n-heptane, cyclohexane, toluene and the like and mixtures thereof. With Dess-Martin periodinane as the oxidizing agent, the solvent is preferably dichloromethane and the oxidation is carried out at a temperature from about -20°C to about 60°C (preferably from about 0°C to about 40°C).

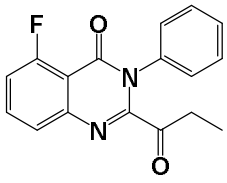
After completion of the reaction the reaction mass may be diluted and washed with water. The reaction mass containing product is extracted with an organic solvent.

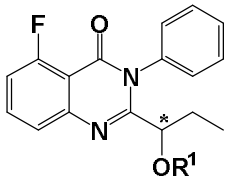
Step (b) of the process involves reaction of compound of formula II-B with a compound of formula VII-A to form idelalisib. The reaction may be carried out in presence of a chiral agent.

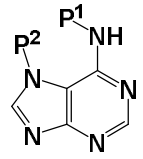
In another embodiment, the present application provides novel intermediates of the compounds of formula I-A, I-B, II, II-A, III, IV, VII and formula VII'.

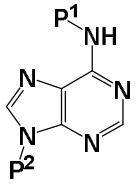

Formula IV

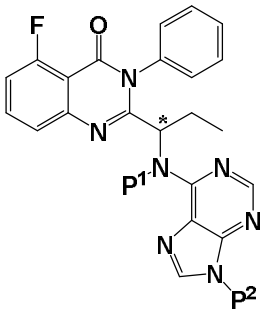

Formula III

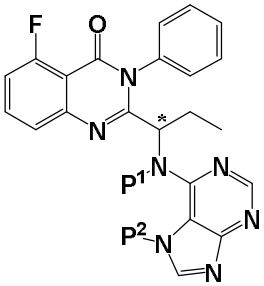

Formula II-A


Formula II


Formula VII'


Formula VII


Formula I-A


Formula I-B

wherein, R^1 is selected from the group comprising hydrogen, C_1-C_5 alkyl, alkenyl, alkynyl, aryl, aralkyl and each of which may optionally be substituted, -COR^2 and SO_2R^2; R^2 is selected from the group comprising C_1-C_5 alkyl, optionally substituted phenyl and tolyl; P^1 and P^2 each independently represent a hydrogen atom or a protective group for the amino group.

In another embodiment, the present application provides use of the compounds of formula I-A, II, II-B, III, IV and formula VII in the synthesis of idelalisib.

In another embodiment, the present application provides use of Idelalisib prepared by the process disclosed above in the preparation of a pharmaceutical composition for the treatment of cancer.

Idelalisib or the intermediates obtained according to the aspects of present application may be in either crystalline or amorphous state.

In another aspect, the present application provides, Idelalisib obtained according to the processes of the present application may be milled or micronized by any of the processes known in the art, such as ball milling, jet milling, wet milling and the like, to produce desired particle sizes and particle size distributions.

In another embodiment, the present application provides use of Idelalisib prepared by the process disclosed above in the preparation of a pharmaceutical composition for the treatment of cancer.

In another aspect, the present application provides a pharmaceutical composition comprising idelalisib prepared by the processes described herein.

Definitions

The following definitions are used in connection with the present application unless the context indicates otherwise. Polymorphs are different solids sharing the same molecular formula, yet having distinct physical properties when compared to other polymorphs of the same formula. The abbreviation “MC” mean moisture content. Moisture content can be conveniently measured, for example, by the Karl Fischer method.

The term "about" when used in the present invention preceding a number and referring to it, is meant to designate any value which lies within the range of ±10%,preferably within a range of ±5%, more preferably within a range of ±2%, still more preferably within a range of ±1 % of its value. For example "about 10" should be construed as meaning within the range of 9 to 1 1 , preferably within the range of 9.5to 10.5, more preferably within the range of 9.8 to 10.2, and still more preferably within the range of 9.9 to 10.1 .

All percentages and ratios used herein are by weight of the total composition, unless the context indicates otherwise. All temperatures are in degrees Celsius unless specified otherwise and all measurements are made at 25^{o}C and normal pressure unless otherwise designated. The

present disclosure can comprise the components discussed in the present disclosure as well as other ingredients or elements described herein.

As used herein, "comprising" means the elements recited, or their equivalents in structure or function, plus any other element or elements which are not recited. The terms "having" and "including" are also to be construed as open ended unless the context suggests otherwise.

Terms such as "about," "generally," "substantially," or the like are to be construed as modifying a term or value such that it is not an absolute. Such terms will be defined by the circumstances and the terms that they modify, as those terms are understood by those of skill in the art. This includes, at very least, the degree of expected experimental error, technique error and instrument error for a given technique used to measure a value.

When a molecule or other material is identified herein as "pure", it generally means, unless specified otherwise, that the material is 99% pure or more, as determined by methods conventional in art such as high performance liquid chromatography (HPLC) or optical methods. In general, this refers to purity with regard to unwanted residual solvents, reaction byproducts, impurities, and unreacted starting materials. In the case of stereoisomers, "pure" also means 99% of one enantiomer or diastereomer, as appropriate. "Substantially" pure means, the same as "pure except that the lower limit is about 98% pure or more and likewise, "essentially" pure means the same as "pure" except that the lower limit is about 95% pure.

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the application in any manner. Variations of the described procedures, as will be apparent to those skilled in the art, are intended to be within the scope of the present application.

The invention is further defined by reference to the following examples describing in detail the processes of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

Idelalisib and its intermediates can be analyzed using HPLC equipped with variable wavelength UV-detector and the parameters described below:

Column	Symmetry C-18 (75 x 4.6mm, 3.5µm)
Detector Wavelength	210 or 220 or 230

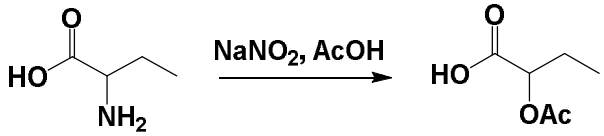
Flow rate	1.0mL/min
Buffer Preparation	Add 1mL of Trifluoroacetic acid in 1000mL of water and filter this solution through 0.45µm membrane filter and sonicate to degas.

Mobile Phase A : 0.1% Trifluoroacetic acid in Water
Mobile Phase B : Acetonitrile
Gradient Program:

Time(min)	0.0	2.0	10.0	20.0	22.0	25.0
% of Mobile Phase A	90	90	5	5	90	90
% of Mobile Phase B	10	10	95	95	10	10

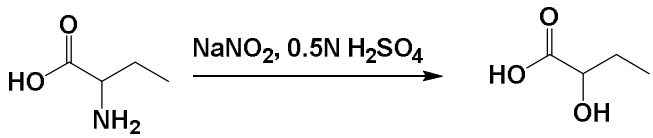
EXAMPLES

Example 1: Preparation of DL-2-acetoxybutanoic acid



DL-2-aminobutyric acid (11 gm, 0.106 mol) and acetic acid (330 mL) were charged into 500 mL round bottom flask. The obtained white suspension was cooled to 15°C and sodium nitrite (14.7 gm, 0.213 mol) was added slowly. The resultant mixture was stirred for 30 minutes at 15°C. Then the reaction mixture was heated to 25°C and stirred for 4 hours. The reaction mixture was concentrated completely under vacuum at 50°C to get crude. Toluene (50 mL) was added the crude and concentrated completely under vacuum at 50°C. The resultant crude was dissolved in water (100 mL) and the solution was extracted with diethyl ether (3 x 70 mL). The combined organic layer was washed with water (3 x 50 mL) and brine (50 mL). The organic layer was dried with sodium sulphate and evaporated under reduced pressure to obtain 5.8 gm of title product as a pale yellow liquid.

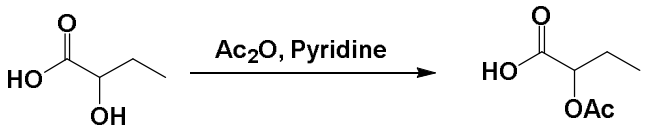
Example 2: Preparation of DL-2-hydroxybutanoic acid



DL-2-aminobutyric acid (50 gm, 0.484 mol) and 0.5 N sulfuric acid (95 gm in 1937 mL of water) were charged into 1000 mL round bottom flask and the resulted solution was heated to

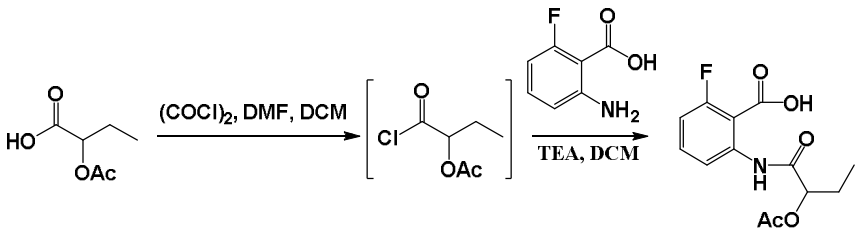
60°C. Sodium nitrite (200.5 gm, 2.906 mol) was added slowly over a period of one hour and the resultant mixture was stirred for 4 hours at 60°C. The reaction mixture was allowed to cool to 25°C and stirred for 16 hours at 25°C. Sodium sulphate (400 gm) was added to the reaction mixture and stirred for 10 minutes. The mixture was extracted with ethylacetate (5 x 600 mL). The combined organic layer was dried with sodium sulphate and concentrated completely under reduced pressure. The resultant crude was triturated with hexane (100 mL) at 0°C to obtain 34.2 gm of title compound as an off-white solid.

Example 3: Preparation of DL-2-acetoxybutanoic acid



DL-2-hydroxybutanoic acid (33 gm, 0.316 mol) and Pyridine (165 mL) were charged into 500 mL round bottom flask and the resulted solution was cooled to 0°C. Acetic anhydride (44.85 mL, 0.474 mol) was added slowly over a period of 20 minutes and the resulted reaction mixture was stirred for 30 minutes at 0°C. The reaction mixture was heated to 25°C and stirred for 16 hours. The reaction mixture was concentrated completely under reduced pressure at 50°C. The crude was dissolved in water (150 mL) and the solution was extracted with ethylacetate (4 x 250 mL). The combined organic layer was washed with water (500 mL) and brine (300 mL). The organic layer was dried with sodium sulphate and concentrated completely under reduced pressure to obtain 42 gm of title compound as pale yellow liquid.

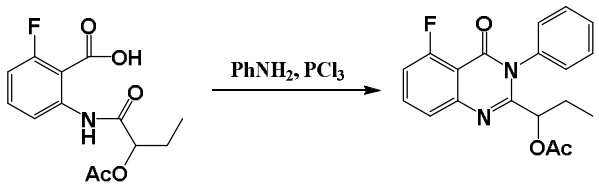
Example 4: Preparation of2-(2-acetoxybutanamido)-6-fluorobenzoic acid



DL-2-acetoxybutanoic acid (2.7 gm, 0.0174 mol) and dichloromethane (30 mL) were charged into 100 mL round bottom flask. The resulted solution was cooled to 0°C then oxalyl chloride (3.36 mL, 0.039 mol) was added slowly over a period of 10 minutes. The resultant mixture was stirred at 0°C for 30 minutes and heated to 25°C and stirred for 2 hours. The reaction mass was concentrated completely under reduced pressure. The crude acid chloride was dissolved in dichloromethane (20 mL). 2-Amino-6-fluorobenzoic acid (2.7 gm, 0.0174 mol) and

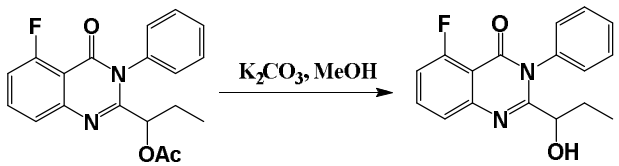
dichloromethane (30 mL) were charged into another 100 mL round bottom flask and the resulted suspension was cooled to 0°C. Triethylamine (9.42 mL, 0.068 mol) was added then the solution of acid chloride in dichloromethane was added slowly over a period of 15 minutes. The reaction mixture was stirred for 16 hours at 25°C. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with 1N hydrochloric acid (20 mL), water (2 x 15 mL) and brine (2 x 15 mL). The organic layer was dried with sodium sulphate and concentrated completely under reduced pressure. The resulted crude was dissolved in ethyl acetate (200 mL) and activated charcoal (1 gm) was added and the resulting suspension was heated to 50°C. The hot suspension was filtered and the filtrate was concentrated completely under reduced pressure. The crude product was triturated with 10% ethylacetate-hexane (100 mL) to obtain 3.25 gm of the title product as pale yellow solid.

Example 5: Preparation of 1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl acetate



2-(2-acetoxybutanamido)-6-fluorobenzoic acid (2.5 gm, 8.833 mmol) and acetonitrile (25 mL) were charged into 100 mL round bottom flask. Aniline (1.1 gm, 11.749 mmol) was added then PCl_3 (1.54 mL, 17.666 mmol) was added slowly over a period of 10 minutes. The resultant suspension was heated to 50°C and stirred for 3 hours. The reaction mixture was allowed to cool to 25°C and stirred for 16 hours. The reaction mixture was diluted with ethyl acetate (100 mL) and quenched with 1N hydrochloric acid. Organic layer was separated and aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (20 mL) and brine (2 x 20 mL). The organic layer was dried with sodium sulphate and concentrated completely under reduced pressure to obtain 3.012 gm of the title product as pale yellow solid. Purity: 98.42% by HPLC

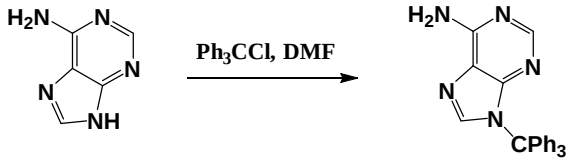
Example 6: Preparation of5-fluoro-2-(1-hydroxypropyl)-3-phenylquinazolin-4(3H)-one



1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl acetate (3 gm, 8.823 mmol) and methanol (30 mL) were charged into 100 mL round bottom flask. Potassium carbonate (1.52 gm, 11.029 mmol) was added and the resultant mixture was stirred at 25°C for 3 hours. The reaction mixture was diluted with water (70 mL) and stirred at 25°C for 30 minutes. The precipitated product was filtered and washed with water (3 x 20 mL) and dried under vacuum for 1 hour to obtain 2 gm of the title compound.

Purity: 99.87% by HPLC.

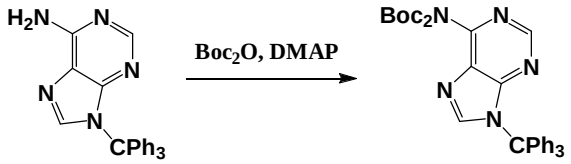
Example 7: Preparation of 9-trityl-9H-purin-6-amine



Adenine (3 gm, 0.022 mol) and 1:3 DMF-pyridine (88 mL) were charged under nitrogen atmosphere into a 250 mL round bottom flask. Trityl chloride (6.18 gm, 0.022 mol) was added. The reaction mixture was stirred at 25°C for 16 hours. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (200 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL). Then the combined organic layers were washed with water (4 x 100 mL) and brine (100 mL). The organic layer was dried with sodium sulphate and concentrated completely under reduced pressure. The crude was triturated with 10% ethylacetate-hexane (100 mL) to obtain 3.97 gm of the title product as off-white solid.

Purity: 98.82 by HPLC.

Example 8: Preparation of di-tert-butyl (9-trityl-9H-purin-6-yl)-di-carbamate

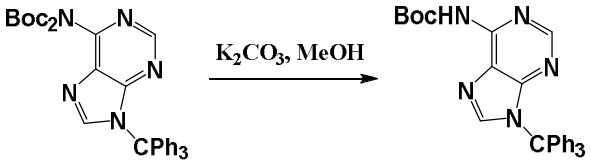


9-trityl-9H-purin-6-amine (3.97 gm, 10.344 mmol) and THF (60 mL) were charged into a 250 mL round bottom flask. DMAP (126 mg, 1.034 mmol) and Boc_2O (11.27 gm, 51.724 mmol) were added to the mixture. The resulted mixture was stirred for one hour at 25°C. The reaction mixture was heated to 50°C and stirred for 16 hours at the same temperature. The reaction mixture was cooled to 25°C and evaporated completely under reduced pressure at 40°C. The resultant residue was diluted with ethylacetate (200 mL) and solution was washed with water (20 mL), 0.5 N hydrochloric acid (20 mL) and brine (20 mL). The organic layer was dried with

sodium sulphate and concentrated completely under reduced pressure. The crude was triturated with hexane (100 mL) and the solid was dried under vacuum for one hour to obtain 5.1 gm of the title product as pale yellow solid.

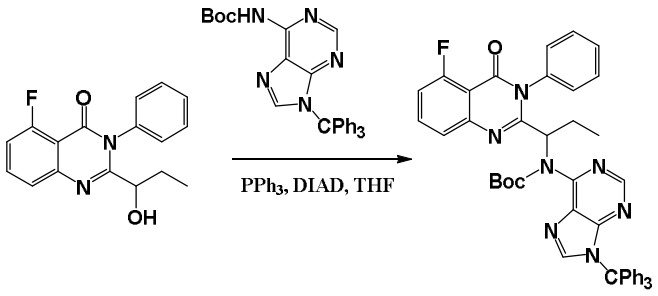
Purity: 91.52% by HPLC.

Example 9: Preparation of tert-butyl (9-trityl-9H-purin-6-yl)carbamate



The Di-Boc compound of example 8 (5 gm, 8.665 mmol) and methanol (80 mL) were charged into a 250 mL round bottom flask. Potassium carbonate (3.58 gm, 25.986 mmol) was added and the resulted mixture was heated to 50°C and stirred for six hours. The reaction mixture was cooled to 25°C and evaporated completely under reduced pressure at 40°C. The resultant residue was diluted with ethylacetate (200 mL) and the solution was washed with water (2^{x} 50 mL) and brine (50 mL). The organic layer was dried with sodium sulphate and concentrated completely under reduced pressure. The crude was triturated with 10% ethylacetate-hexane (100 mL) to obtain 2.2 gm of the title mono-Boc product as off-white solid.

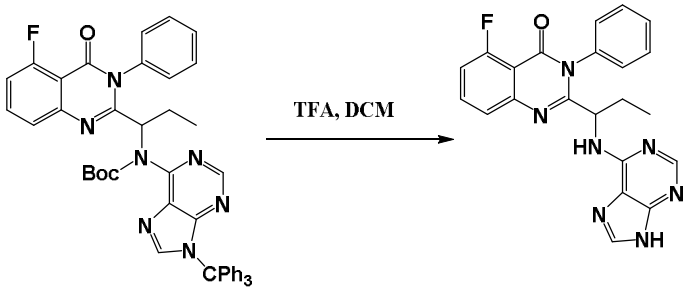
Example 10: Preparation of(±)-tert-butyl (1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydro quinazolin-2-yl)propyl)(9-trityl-9H-purin-6-yl)carbamate



tert-butyl (9-trityl-9H-purin-6-yl)carbamate (2 gm, 4.192 mmol), (±)-5-fluoro-2-(1-hydroxypropyl)-3-phenylquinazolin-4(3H)-one (1.87 gm, 6.287 mmol), triphenyl phosphine (1.64 gm, 6.287 mmol) and THF (100 mL) were charged into a 250 mL round bottom flask. The resultant solution was heated to 45°C and Diisopropylazodicarboxylate (DIAD, 1.24 mL, 6.287 mmol) was added. The resultant reaction mixture was stirred for five hours at 45°C. The reaction mixture was cooled to 25°C and stirred for 16 hours at 25°C. The reaction mixture was cooled to 25°C and evaporated completely under reduced pressure at 40°C. Inorganic solids were removed

from the crude mixture by column chromatography using silica gel (100-200 mesh, 1:1 ethylacetate-hexane to give 5 gm of the title compound as colorless thick liquid.

Example 11: Preparation of (±)-Idelalisib



5 gm of the compound prepared in example 10 and DCM (30 mL) were charged into a 250 mL round bottom flask. The contents of the flask were cooled to 0°C and trifluoro acetic acid (30 mL) was added. The resultant reaction mixture was stirred at 0°C for 15 minutes. The reaction mixture was heated to 25°C and stirred for 3 hours. The reaction mixture was evaporated completely under reduced pressure at 40°C. The resultant residue was diluted with ethylacetate (150 mL) and the solution was washed with saturated $NaHCO_3$ solution (50 mL). The organic layer was filtered through a celite pad and the pad was washed with ethylacetate (50 mL). The combined filtrates were washed with water (50 mL) and brine (50 mL) and dried over sodium sulphate and concentrated completely under reduced pressure to yield 1.1 gm of racemic idelalisib as an off-white solid.

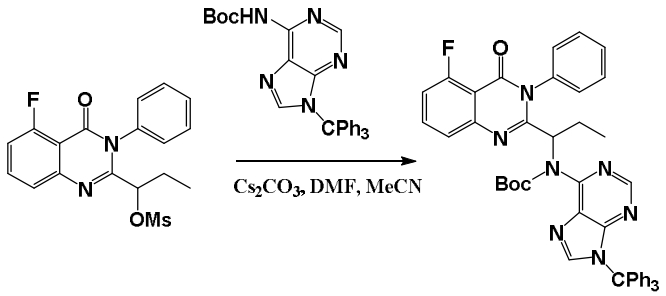
Example 12: Preparation of (±)-1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl methanesulfonate

(±)-5-fluoro-2-(1-hydroxypropyl)-3-phenylquinazolin-4(3H)-one (200 mg, 0.671 mmol) and DCM (8 mL) were charged into a 50 mL round bottom flask. The contents of the flask were cooled to 0°C. Triethylamine (0.18 mL, 1.342 mmol) and Mesyl chloride (78 µL, 1.006 mmol) were added. The reaction mixture was stirred at 0°C for 20 minutes. The reaction mixture was heated to 25°C and stirred for 4 hours. The reaction mixture was diluted with DCM (20 mL) and the solution was washed with water (5 mL) and with brine (5 mL) and dried over sodium

sulphate and concentrated completely under reduced pressure. The crude product was triturated with hexane (10 mL) to obtain 200 mg of the title product as off-white solid.

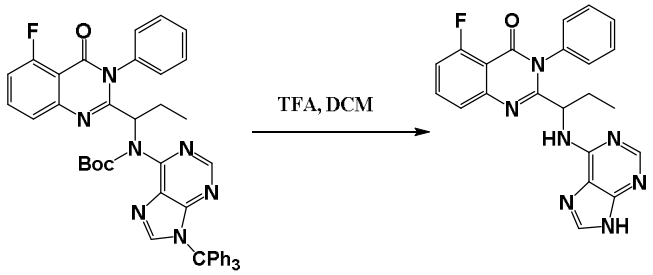
Purity: 99.14% by HPLC.

Example 13: Preparation of (±)-tert-butyl (1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydro quinazolin-2-yl)propyl)(9-trityl-9H-purin-6-yl)carbamate



tert-butyl (9-trityl-9H-purin-6-yl)carbamate (100 mg, 0.209 mmol), (±)-1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propylmethanesulfonate (95 mg, 0.251 mmol) and 1:1 DMF-MeCN (5 mL) were charged into a 50 mL round bottom flask. Cesium carbonate (170 mg, 0.522 mmol) was added to the resultant mixture. The reaction mixture was heated to 80°C and stirred for 6 hours. The reaction mixture was cooled to 25°C and stirred for 16 hours. The reaction mixture was evaporated completely under reduced pressure at 40°C. The resultant residue was diluted with ethylacetate (20 mL) and the solution was washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried with sodium sulphate and concentrated completely under reduced pressure to yield 170 mg of title compound as thick mass.

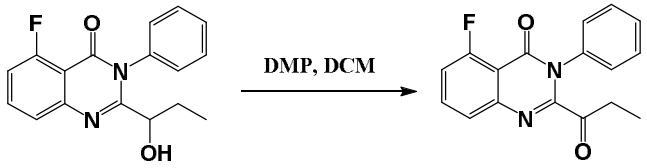
Example 14: Preparation of2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-phenyl quinazolin-4(3H)-one ((±)-Idelalisib)



170 mg of the compound prepared in example 13 and DCM (1 mL) were charged into a 25 mL round bottom flask. The contents of the flask were cooled to 0°C and trifluoro acetic acid (1 mL) was added. The resultant reaction mixture was stirred at 0°C for 15 minutes. The reaction mixture was heated to 25°C and stirred for 2 hours. The reaction mixture was evaporated

completely under reduced pressure at 40°C. The resultant residue was diluted with ethylacetate (20 mL) and the solution was washed with saturated $NaHCO_3$ solution (5 mL). The organic layer was filtered through a celite pad and the pad was washed with ethylacetate (2 mL). The combined filtrates were washed with water (2^x 5 mL) and brine (5 mL) and dried over sodium sulphate and concentrated completely under reduced pressure to yield 33 mg of racemic idelalisib as an off-white solid. Purity: 98.99% by HPLC.

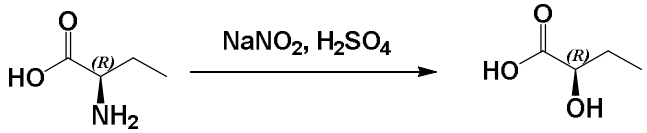
Example 15: Preparation of5-fluoro-3-phenyl-2-propionylquinazolin-4(3H)-one



(±)-5-fluoro-2-(1-hydroxypropyl)-3-phenylquinazolin-4(3H)-one (1.4 gm, 4.105 mmol) and DCM (25 mL) were charged into a 100 mL round bottom flask. Dess-Martin Periodinane (DMP, 4.35 gm, 10.263 mmol) is added. The resultant mixture was stirred at 25°C for 3 hours. The reaction mixture was diluted with DCM (100 mL), quenched with saturated $NaHCO_3$ solution (20 mL) and stirred for another 15 minutes. The mixture was filtered through a thin celite pad and the pad was washed with DCM (10 mL). The combined filtrates were washed with saturated $NaHCO_3$ solution (10 mL), saturated $Na_2S_2O_3$ solution (20 mL), water (20 mL) and brine (20 mL). The organic layer was dried over sodium sulphate and concentrated completely under reduced pressure. The resultant crude product was purified by column chromatography using silica gel (100-200 mesh; eluent: 40%ethylacetate-hexane). The isolated product was triturated with hexane (20 mL) to obtain 1.1 gm of the title product as off-white solid.

Purity: 96.92% by HPLC.

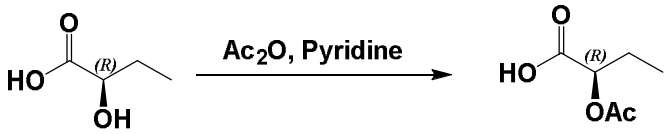
Example 16: Preparation of (R)-2-hydroxybutanoic acid



D-2-aminobutyric acid (10 gm, 0.096 mol) and aqueous sulfuric acid (5.15 mL in 300 mL of water) were charged into 1000 mL round bottom flask and the resulted solution was heated to 60°C. Sodium nitrite (40.1 gm, 0.581 mol) was added slowly over a period of one hour and the resultant mixture was stirred for 30 minutes at 60°C. The reaction mixture was allowed to cool to 25°C and stirred for 16 hours at 25°C. Sodium sulphate (50 gm) was added to the reaction

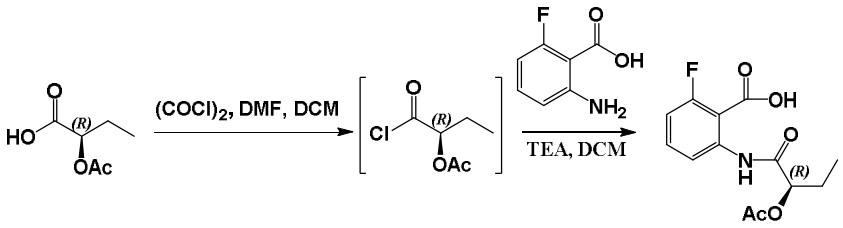
mixture and stirred for 10 minutes. The mixture was extracted with ethylacetate (4 x 150 mL). The combined organic layer was dried with sodium sulphate and concentrated completely under reduced pressure. The resultant crude was triturated with hexane (15 mL) at 0°C to obtain 5.5 gm of title compound as an off-white solid.

Example 17: Preparation of (R)-2-acetoxybutanoic acid



(R)-2-hydroxybutanoic acid (4.2 gm, 0.040 mol) and Pyridine (21 mL) were charged into 500 mL round bottom flask and the resulted solution was cooled to 0°C. Acetic anhydride (5.71 mL, 0.060 mol) was added slowly over a period of 10 minutes and the resulted reaction mixture was stirred for 30 minutes at 0°C. The reaction mixture was heated to 25°C and stirred for 16 hours. The reaction mixture was concentrated completely under reduced pressure at 50°C. The crude was added to a mixture of water (60 mL) and 1N aqueous HCl; and the solution was extracted with ethylacetate (3 x 40 mL). The combined organic layer was washed with water (20 mL) and brine (20 mL). The organic layer was dried with sodium sulphate and concentrated completely under reduced pressure to obtain 5.5 gm of title compound as pale yellow liquid.

Example 18: Preparation of (R)-2-(2-acetoxybutanamido)-6-fluorobenzoic acid

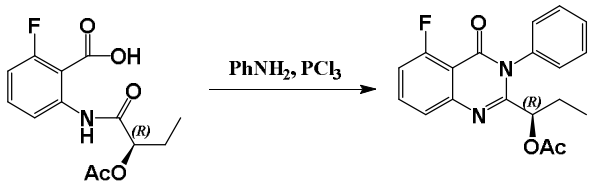


(R)-2-acetoxybutanoic acid (5.5 gm, 0.032 mol) and dichloromethane (44 mL) were charged into 250 mL round bottom flask and the resulted solution was cooled to 0°C.Oxalyl chloride (4.19 mL, 0.048 mol) was added slowly over a period of 10 minutes. The resultant mixture was stirred at 0°C for 30 minutes and heated to 25°C and stirred for 2 hours. The reaction mass was concentrated completely under reduced pressure. The crude acid chloride was dissolved in dichloromethane (22 mL). 2-Amino-6-fluorobenzoic acid (5.02 gm, 0.032 mol) and DMF (11 mL) were charged into another 100 mL round bottom flask and the resulted suspension was cooled to 0°C. The solution of acid chloride in dichloromethane was added slowly over a period of 15 minutes. The reaction mixture was stirred for 2 hours at 25°C. The reaction mixture

was concentrated under reduced pressure to remove dichloromethane. 1N HCl (22 mL) and water (100 mL) were added to the crude and the resulted heterogeneous mixture was stirred vigorously for 30 minutes. The resulted solution was seeded with (R)-2-(2-acetoxybutanamido)-6-fluorobenzoic acid (20 mg) and stirred for 30 minutes. The suspension was filtered and the wet material was washed with water (50 mL) to obtain 6.3 gm of the title product as pale yellow solid.

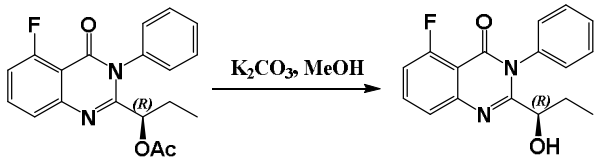
Purity: 95.27% by HPLC.

Example 19: Preparation of (R)-1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl acetate



(R)-2-(2-acetoxybutanamido)-6-fluorobenzoic acid (6 gm, 0.021 mol) and acetonitrile (60 mL) were charged into 250 mL round bottom flask. Aniline (2.62 gm, 0.028 mol) was added then PCl_3 (3.74 mL, 0.042 mol) was added slowly over a period of 10 minutes. The resultant suspension was heated to 50°C and stirred for 3 hours. The reaction mixture was allowed to cool to 25°C and stirred for 5 hours. The reaction mixture was quenched with water (20 mL) and concentrated completely under reduced pressure. The crude was diluted with ethylacetate (200 mL) and washed with 1N HCl (50 mL), water (2 x 25 mL), sat. $NaHCO_3$ (50 mL) and brine (2 x 25 mL). The organic layer was dried with sodium sulphate and concentrated completely under reduced pressure to obtain 7.2 gm of the title product as pale yellow sticky liquid. Purity: 72.36% by HPLC.

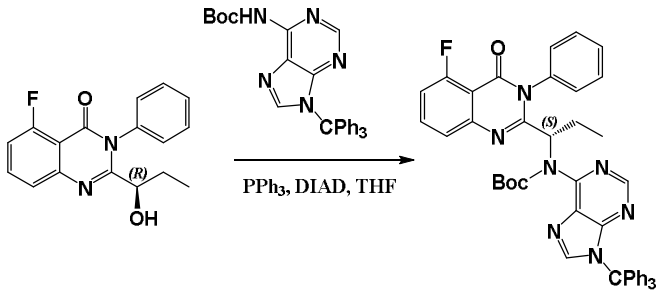
Example 20: Preparation of (R)-5-fluoro-2-(1-hydroxypropyl)-3-phenylquinazolin-4(3H)-one



(R)-1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl acetate (7.2 gm, 0.0211 mol) and methanol (36 mL) were charged into 100 mL round bottom flask. Potassium carbonate (3.79 gm, 0.0275 mol) was added and the resultant mixture was stirred at 25°C for 30

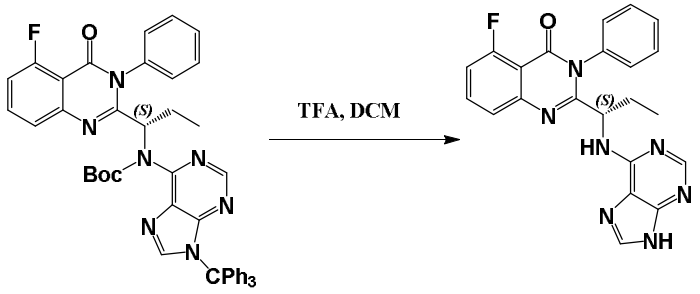
minutes. The reaction mixture was diluted with water (150 mL) and stirred at 25°C for 30 minutes. The precipitated product was filtered and washed with water (50 mL) and dried under vacuum for 1 hour to obtain 4.5 gm of the title compound. Purity: 99.21% by HPLC.

Example 21: Preparation of (S)-tert-butyl (1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydro quinazolin-2-yl)propyl)(9-trityl-9H-purin-6-yl)carbamate



tert-butyl (9-trityl-9H-purin-6-yl)carbamate (1 gm, 2.096 mmol), (R)-5-fluoro-2-(1-hydroxypropyl)-3-phenylquinazolin-4(3H)-one (0.937 gm, 3.144 mmol), triphenyl phosphine (0.824 gm, 3.144 mmol) and THF (100 mL) were charged into a 250 mL round bottom flask. The resultant solution was heated to 45°C and Diisopropylazodicarboxylate (DIAD, 0.62 mL, 3.144 mmol) was added. The resultant reaction mixture was stirred for five hours at 45°C. The reaction mixture was cooled to 25°C and stirred for 16 hours. The reaction mixture was evaporated completely under reduced pressure at 40°C. Inorganic salts were removed from the crude mixture by column chromatography using silica gel (100-200 mesh, 1:1ethylacetate-hexane to give 2 gm of the title compound as pale yellow thick liquid.

Example 22: Preparation of Idelalisib



2 gm of the compound prepared in example 21 and DCM (10 mL) were charged into a 100 mL round bottom flask. The contents of the flask were cooled to 0°C and trifluoroacetic acid (10 mL) was added. The resultant reaction mixture was stirred at 0°C for 15 minutes. The reaction mixture was heated to 25°C and stirred for 2 hours. The reaction mixture was evaporated completely under reduced pressure at 40°C. The resultant residue was diluted with

ethylacetate (50 mL) and the solution was washed with saturated $NaHCO_3$ solution (20 mL). The organic layer was filtered through a celite pad and the pad was washed with ethylacetate (10 mL). The combined filtrates were washed with water (2^x 10 mL) and brine (20 mL) and dried over sodium sulphate and concentrated completely under reduced pressure to yield 525 mg of idelalisib as pale yellow solid. Purity: 96.87% by HPLC

Example 23: Preparation of idelalisib according to the process described in WO2005092877A1

Idelalisib (0.8 gm) and ethanol (25 mL) were charged into a 50 mL round bottom flask and the mixture was stirred for 10 minutes, clear solution formed. The solution was concentrated completely under vacuum. The solid was dried under vacuum at 60°C for 3 hours to obtain 0.65 gm of amorphous idelalisib. PXRD pattern is shown in Figure 1.

Example 24: Preparation of idelalisib according to the process described in WO2005092877A1

Idelalisib (0.8 gm) and ethanol (25 mL) were charged into a 50 mL round bottom flask and the mixture was stirred for 15 minutes. The clear solution was concentrated completely under vacuum. The solid was dried under vacuum at 60°C for 3 hours to obtain 0.65 gm of amorphous idelalisib. PXRD pattern is same as Figure 1.

Purity: 99.26% by HPLC; Moisture content: 5.2%; GC (ethanol): 12265 ppm; TGA: 6.87%.

Example 25: Preparation of idelalisib according to the process described in WO2005092877A1

Idelalisib (0.8 gm) and ethanol (25 mL) were charged into a 50 mL round bottom flask and the mixture was stirred for 15 minutes. The clear solution was concentrated completely under vacuum. The solid was dried under vacuum at 58°C for 2 hours to obtain 0.61 gm of amorphous idelalisib. PXRD pattern is same as Figure 1.

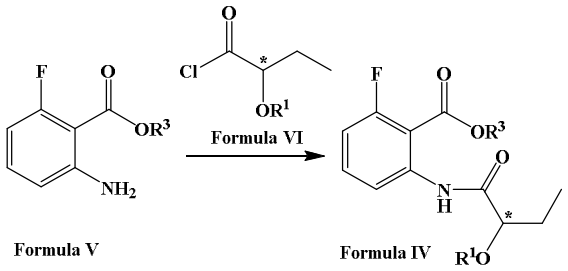
Purity: 99.15% by HPLC; Moisture content: 5.45%; GC (ethanol): 60769 ppm.

CLAIMS

We claim:

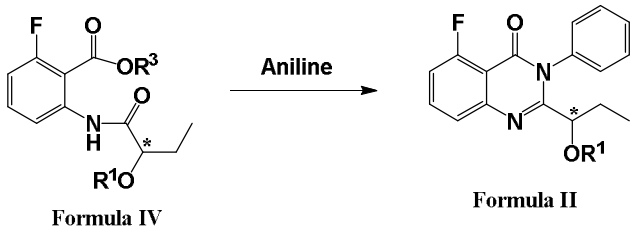
1. A process for preparation of idelalisib, comprising:

(a) reacting a compound of formula V with a compound of formula VI to form a compound of formula IV



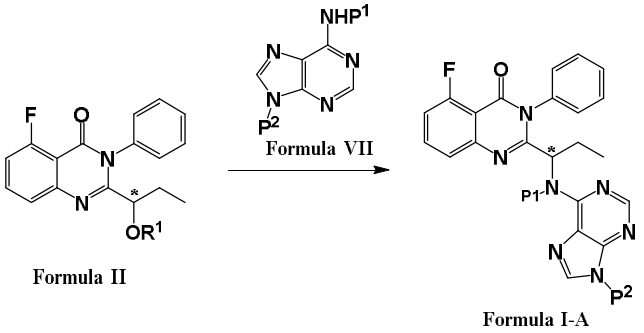
Formula V Formula IV

(b) reacting the compound of formula IV with aniline in presence of a dehydrating agent to form a compound of formula II



Formula IV Formula II

(c) reacting the compound of formula II with a compound of Formula VII to get compound of formula I-A



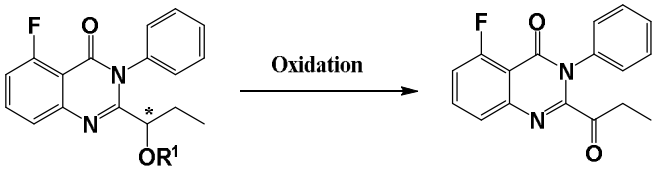
Formula II Formula I-A

(d) optionally deprotecting the compound of formula I-A to form idelalisib.

wherein, $R^1$is selected from the group comprising hydrogen, C_1-C_5alkyl, alkenyl, alkynyl, aryl, aralkyl and each of which may optionally be substituted, -COR^2 and SO_2R^2; $R^2$is selected from the group comprising C_1-C_5 alkyl, optionally substituted phenyl and tolyl; P^1 and P^2each independently represent a hydrogen atom or a protective group for the amino group.

2. A process for preparation of Idelalisib, comprising:

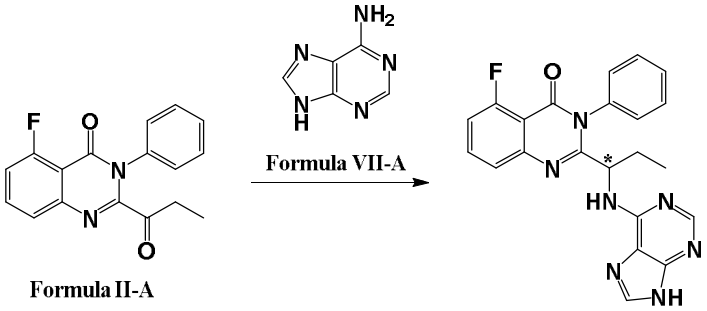
(a) oxidizing a compound of formula II to get a compound of formula II-A



Formula II Formula II-A

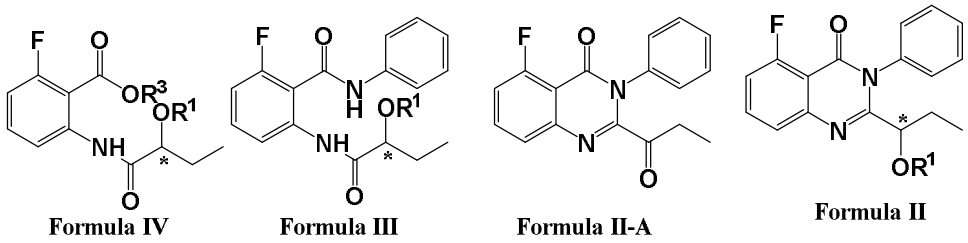
wherein R^1 is hydrogen.

(b) reacting the compound of formula II-A with a compound of Formula VII-A to form idelalisib.

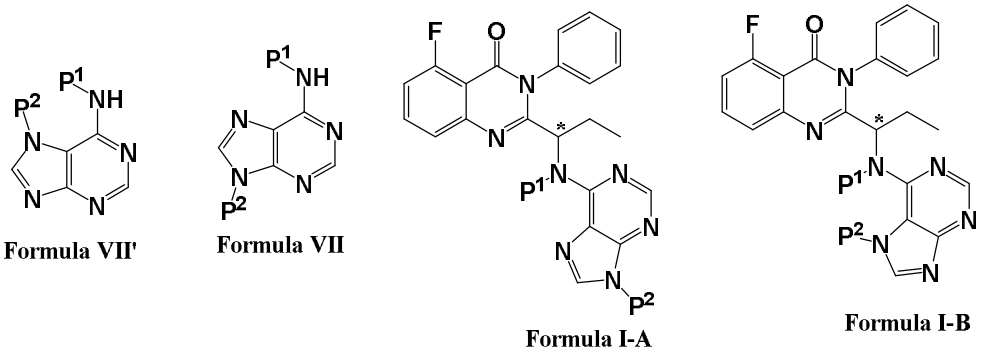


Formula II-A Idelalisib

3. The compounds of formula I-A, I-B, II, II-A, III, IV, VII and formula VII'.



Formula IV Formula III Formula II-A Formula II



Formula VII' Formula VII Formula I-A Formula I-B

wherein, R^1 is selected from the group comprising hydrogen, C_1-C_5 alkyl, alkenyl, alkynyl, aryl, aralkyl and each of which may optionally be substituted, -COR^2 and SO_2R^2; R^2 is selected from the group comprising C_1-C_5 alkyl, optionally substituted phenyl and tolyl; P^1 and P^2 each independently represent a hydrogen atom or a protective group for the amino group.

4. Use of the compounds of claim 3 in the preparation of idelalisib.

5. Use of Idelalisib prepared by the process of claim 1 or claim 2 in the preparation of a pharmaceutical composition for the treatment of cancer.

6. Use of idelalisib prepared by using the compounds according to claims 3 in the preparation of a pharmaceutical composition for the treatment of cancer.

Dated this 31st December 2015 Signature: _____

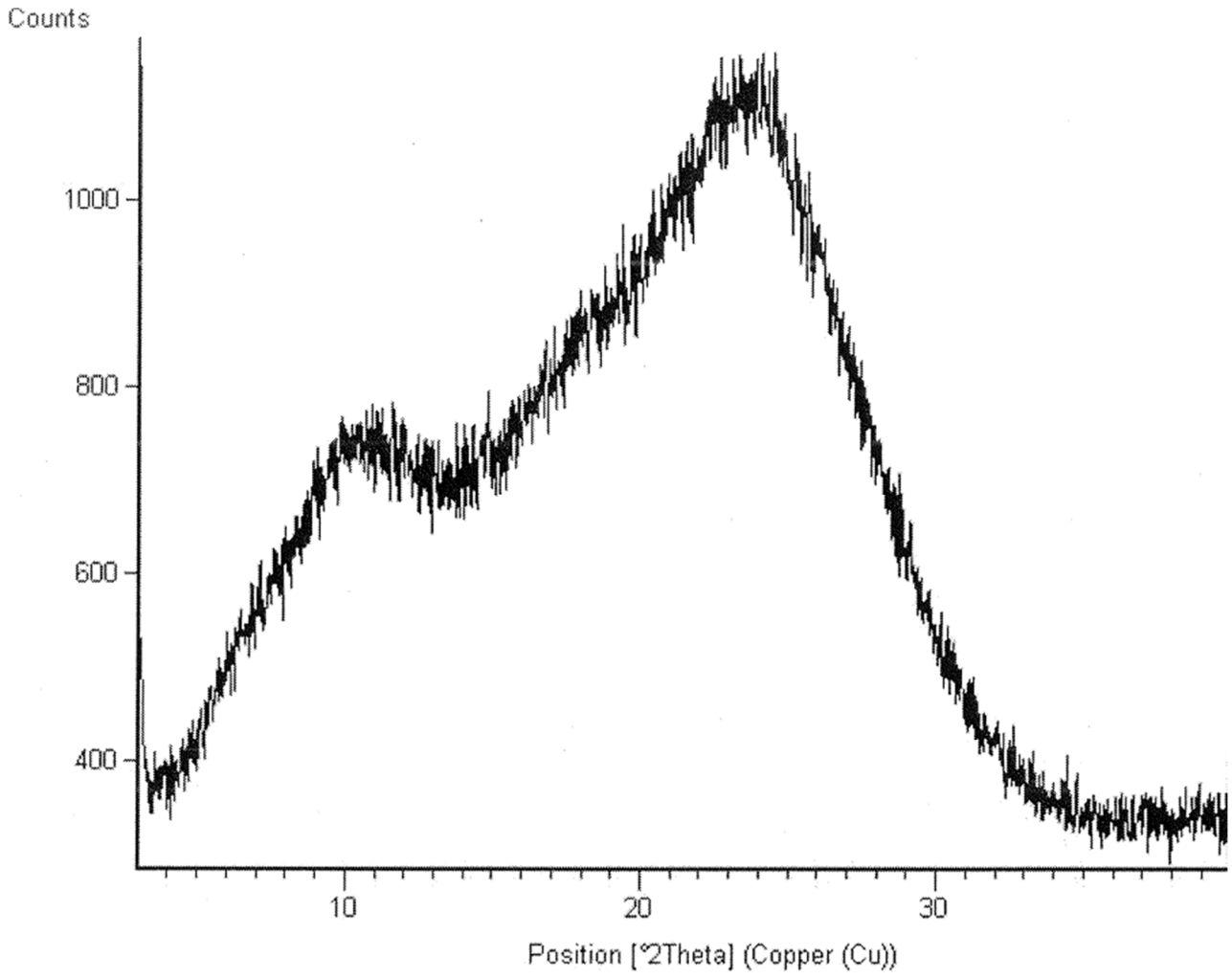
Dr. Poonam Raghuvanshi

ABSTRACT

The present application provides novel processes for preparation of Idelalisib and intermediates thereof.

Dr. Reddys Laboratories Limited Figure 1of 1

Application No: 6844/CHE/2014



Signature: _____

Dr. Poonam Raghuvanshi