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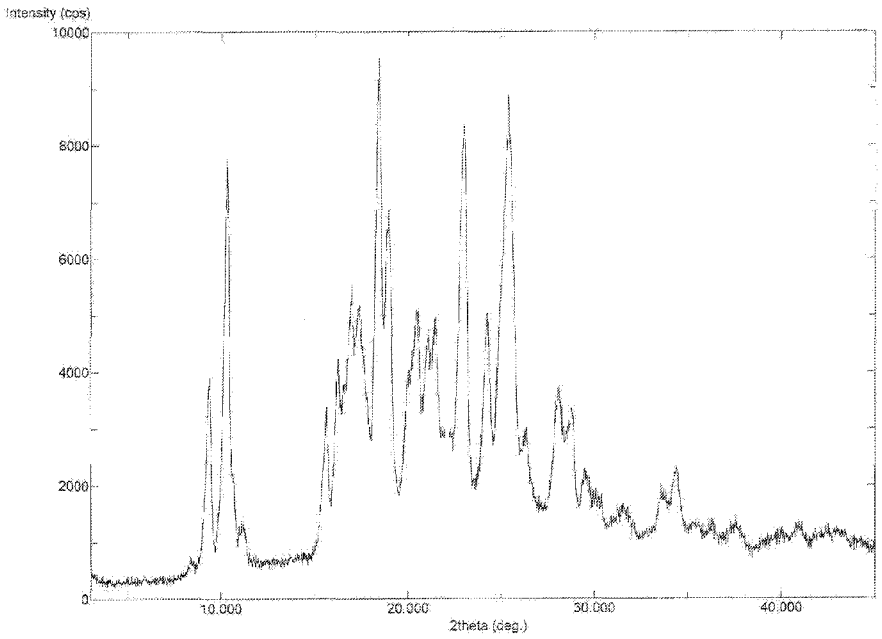
(54) Title: NOVEL PROCESS FOR PREPARATION OF IDELALISIB



(57) Abstract: The present invention provides the process for preparation of idelalisib or a pharmaceutically acceptable salt thereof using novel intermediates. The present invention 0 also provides polymorphic forms of the novel intermediates.

WO 2017/191608 A1

[Continued on next page]

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"Novel process for preparation of Idelalisib"

PRIORITY

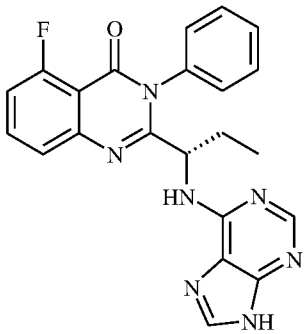
This application claims the benefit under Indian Provisional Application No.(s) 201641015654 filed on 05 May, 2016 entitled "Novel process for preparation of Idelalisib" and 201641027120 filed on 09 Aug, 2016 entitled "Novel process for preparation of Idelalisib", the contents of each of which are incorporated by reference herein.

FIELD OF THE INVENTION

The present invention generally relates to a process for preparation of idelalisib or pharmaceutically acceptable salts thereof using novel intermediates.

BACKGROUND OF THE INVENTION

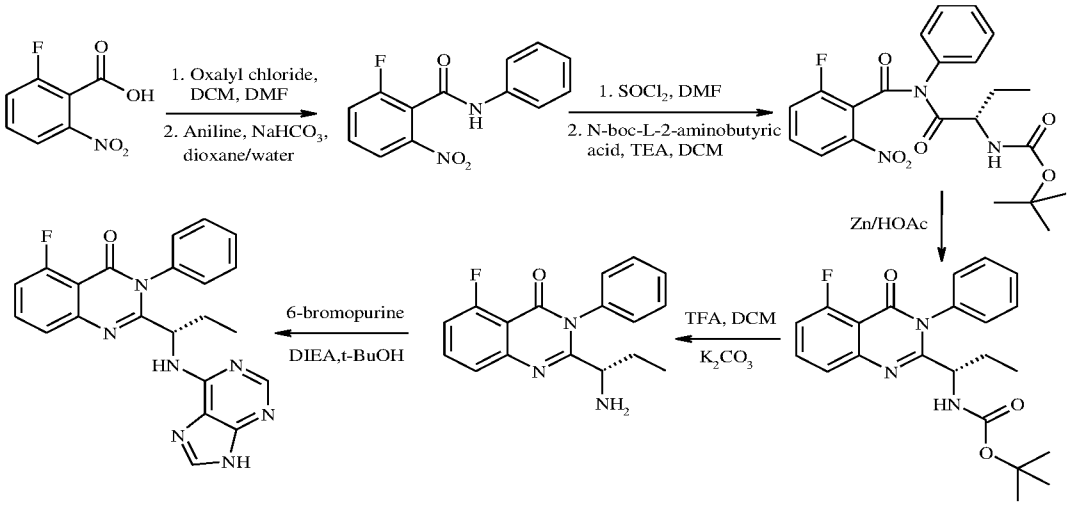
Idelalisib, also known as 5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino) propyl] quinazolin-4(3H)-one (GS-1101 or CAL-101) of Formula I:



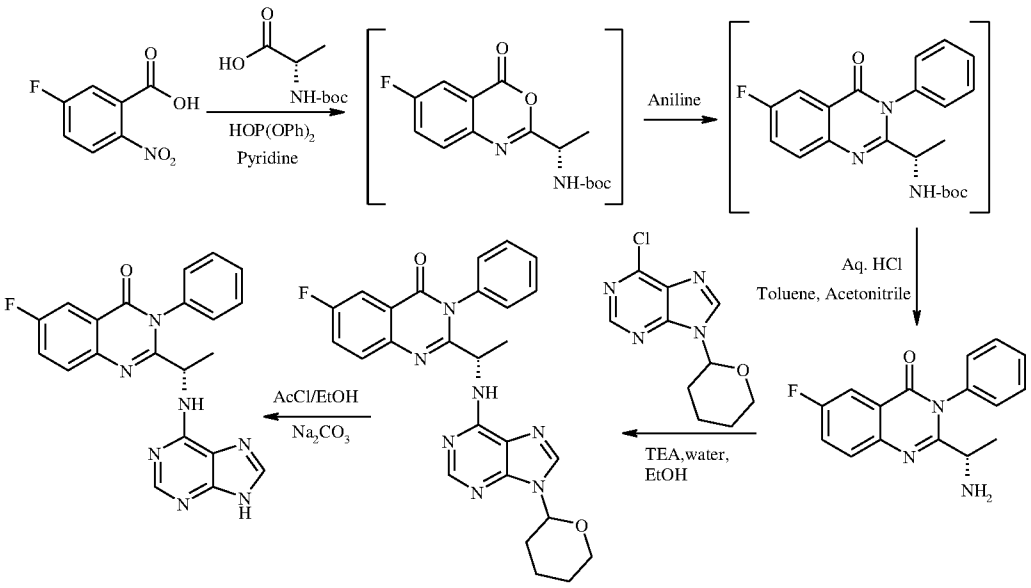
Formula I

Idelalisib is marketed by Gilead Sciences under the trade name Zydelig® for the treatment of relapsed chronic lymphocytic leukemia (CLL), relapsed follicular B-cell non-hodgkin lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL). The substance acts as a phosphoinositide 3-kinase inhibitor; more specifically, it blocks P110δ, the delta isoform of the enzyme phosphoinositide 3-kinase.

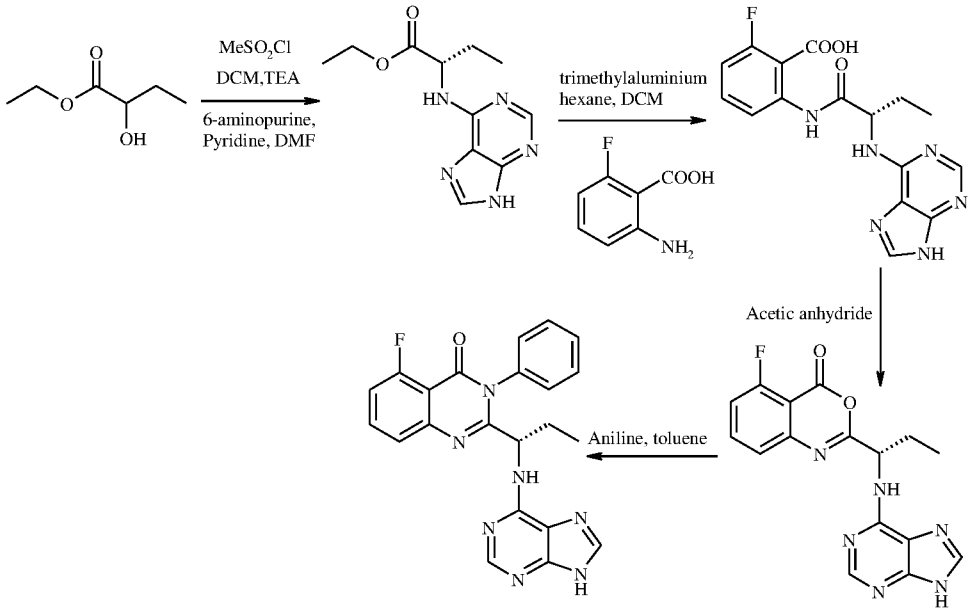
U.S. Patent No. RE44638 ("the '638 patent") discloses a variety of quinazolinone derivatives such as idelalisib and process for preparation thereof. The process disclosed in the '638 patent is schematically represented as follows:



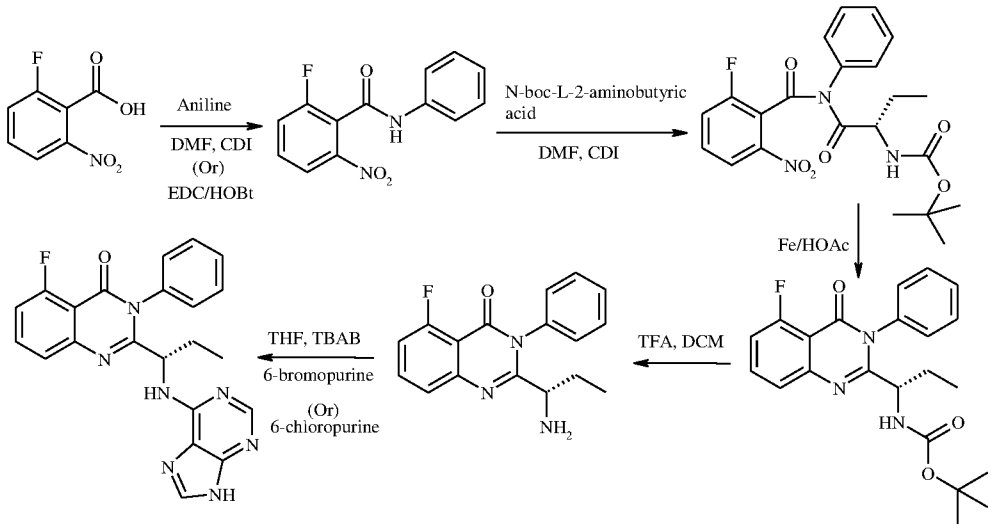
PCT Publication No. 2015/095601 ("the '601 publication") discloses a process for the preparation of idelalisib and its analogous. However, the '601 publication specifically exemplifies methyl analogue of idelalisib. The process disclosed in the '601 publication is schematically represented as follows:



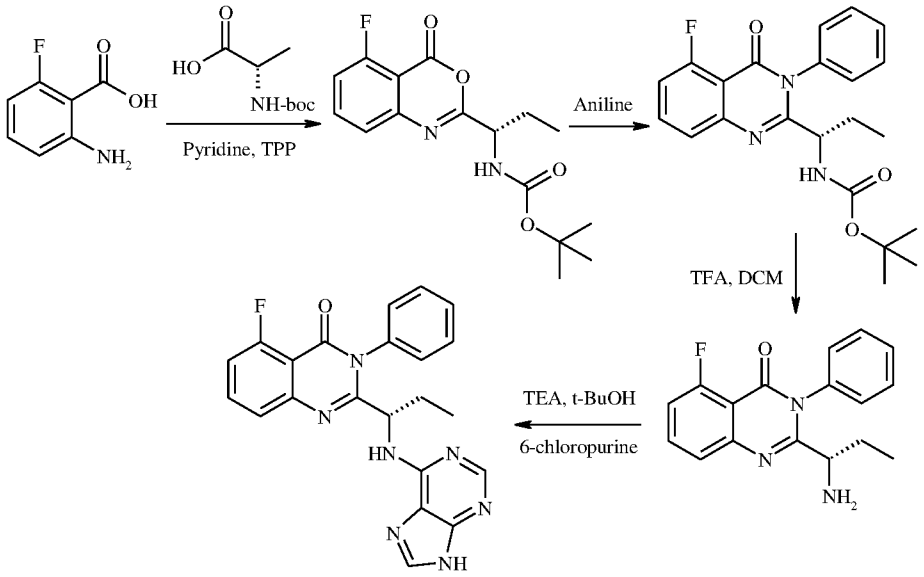
PCT Publication No. 2016/026380 ("the '380 publication) discloses a process for the preparation of idelalisib. The process disclosed in the '380 publication is schematically represented as follows:



CN Patent No. 104130261B ("the '261 patent) discloses an improved process for the preparation of idelalisib. The process disclosed in the '261 patent is schematically represented as follows:

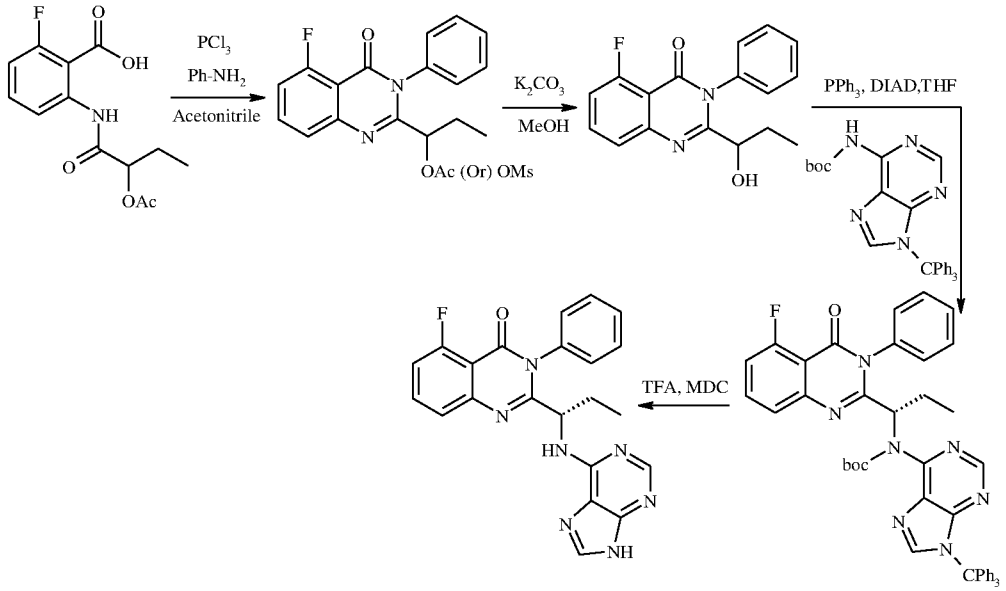


CN Patent Publication No. 104876931A ("the '931 publication) discloses an improved process for the preparation of idelalisib. The process disclosed in the '931 publication is schematically represented as follows:

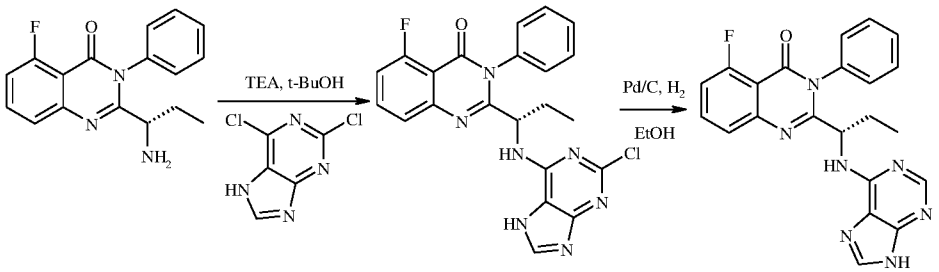


PCT Publication No. 2016/108206 ("the '206 publication) discloses a process for the preparation of idelalisib. The process disclosed in the '206 publication is schematically represented as follows:

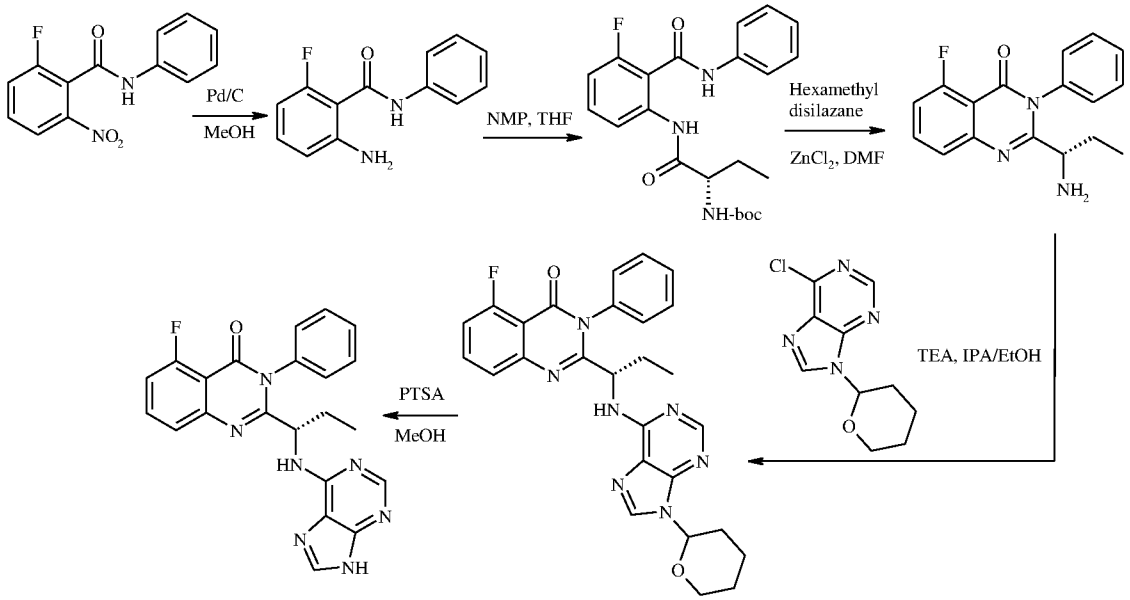
Scheme-1:



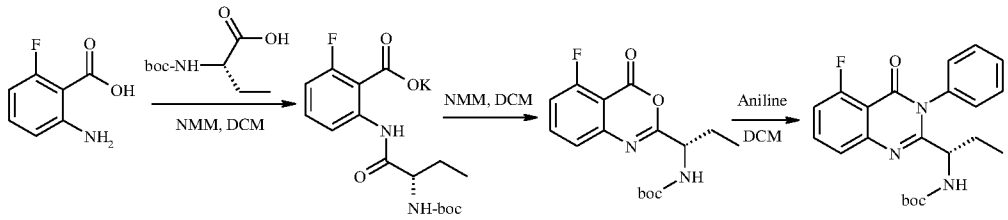
Scheme-2:



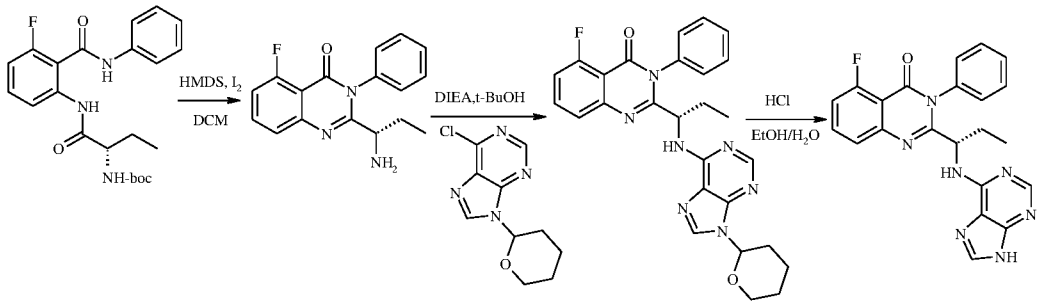
CN Patent Publication No.(S) 106146502A ("the '502 publication) and 106146503A ("the '503 publication) discloses an improved process for the preparation of idelalisib. The process disclosed in these publications is schematically represented as follows:



CN Patent Publication No. 106146505A ("the '505 publication) discloses an improved process for the preparation of idelalisib intermediate. The process disclosed in the '505 publication is schematically represented as follows:



CN Patent Publication No. 106279171A ("the '171 publication) discloses an improved process for the preparation of idelalisib. The process disclosed in the '171 publication is schematically represented as follows:



PCT Publication No. 2016/156240 ("the '240 publication) discloses a process for the preparation of hydrochloride salt of idelalisib intermediate idelalisamine.

PCT Publication No. 2017/009333 ("the '333 publication) discloses a process for purification of idelalisib by formation of idelalisib hydrochloride salt or nitrate salts.

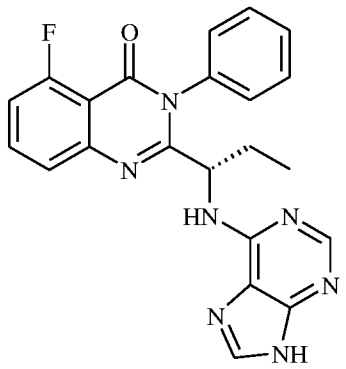
There is a need in the art to develop a novel process for the preparation of idelalisib, which is readily amenable to large scale production.

Hence, present inventors focused alternative process for the preparation of idelalisib with greater yield, and higher purity by using novel intermediates.

SUMMARY OF THE INVENTION

The present invention provides processes for the preparation of idelalisib using novel intermediates.

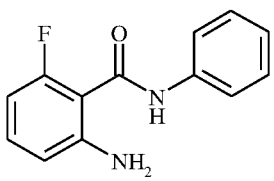
In accordance with one embodiment, the present invention provides processes for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof:



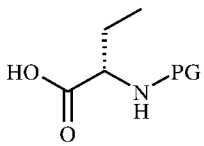
Formula I

comprising:

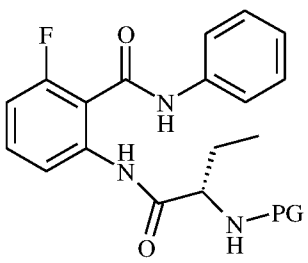
a) reacting a compound of Formula IV or a salt thereof with aminobutyric acid or a reactive derivative of Formula V to obtain a compound of Formula VI, wherein 'PG' represents a suitable amine protecting group,



Formula IV

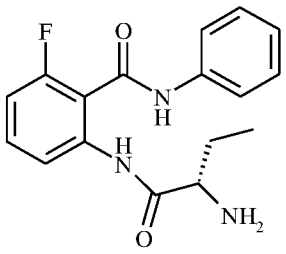


Formula V



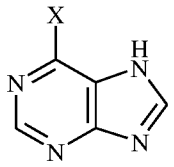
Formula VI

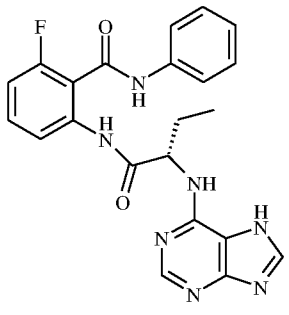
b) deprotecting the compound of Formula VI in presence of a suitable deprotecting agent to obtain a compound of Formula VII or a salt thereof,



Formula VII

c) reacting the compound of Formula VII or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula IX or a salt thereof, wherein 'X' represents a suitable leaving group, and





Formula VIII Formula IX

d) cyclizing the compound of Formula IX or a salt thereof to obtain the compound of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising: cyclizing a compound of Formula IX or a salt thereof to obtain the compound of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a compound of Formula VII or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula IX or a salt thereof, wherein 'x' represents a suitable leaving group, and

b) cyclizing the compound of Formula IX or a salt thereof to obtain the compound of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a compound of Formula VI with a suitable deprotecting agent to obtain a compound of Formula VII or a salt thereof,

b) reacting the compound of Formula VII or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula IX or a salt thereof, wherein 'X' represents a suitable leaving group, and
c) cyclizing the compound of Formula IX or a salt thereof to obtain the compound of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a compound of Formula IV or a salt thereof with aminobutyric acid or a reactive derivative of Formula V to obtain a compound of Formula VI, wherein 'PG' represents a suitable amine protecting group,
b) deprotecting the compound of Formula VI in presence of a suitable deprotecting agent to obtain a compound of Formula VII or a salt thereof,
c) reacting the compound of Formula VII or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula IX or a salt thereof, wherein 'X' represents a suitable leaving group, and
d) converting the compound of Formula IX or a salt thereof in to compound of Formula I.

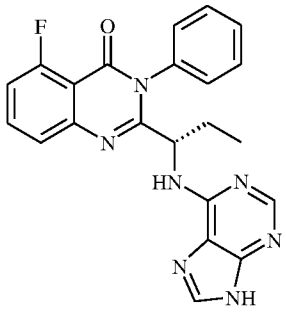
In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a compound of Formula IV or a salt thereof with aminobutyric acid or a reactive derivative of Formula V to obtain a compound of Formula VI, wherein 'PG' represents a suitable amine protecting group,
b) deprotecting the compound of Formula VI in presence of a suitable deprotecting agent to obtain a compound of Formula VII or a salt thereof, and
c) converting the compound of Formula VII or a salt thereof in to compound of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a compound of Formula IV or a salt thereof with aminobutyric acid or a reactive derivative of Formula V to obtain a compound of Formula VI, wherein 'PG' represents a suitable amine protecting group, and
b) converting the compound of Formula VI in to compound of Formula I.

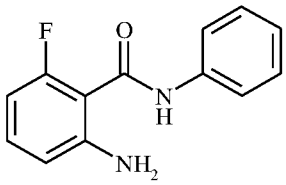
In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof:



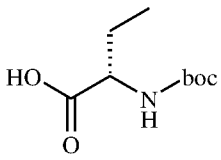
Formula I

comprising:

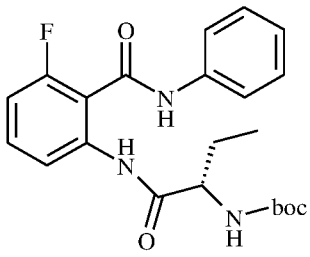
a) reacting a compound of Formula IV or a salt thereof with aminobutyric acid or a reactive derivative of Formula Va to obtain a compound of Formula VIa,



Formula IV

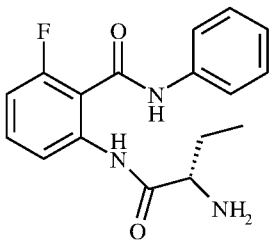


Formula Va



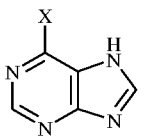
Formula VIa

b) deprotecting the compound of Formula VIa in presence of a suitable deprotecting agent to obtain a compound of Formula VII or a salt thereof,

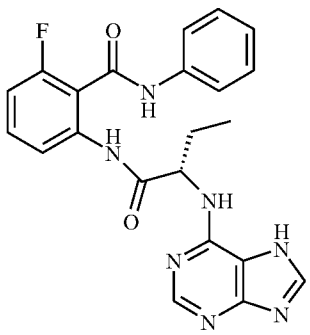


Formula VII

c) reacting the compound of Formula VII or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula IX or a salt thereof, wherein 'X' represents a suitable leaving group, and



Formula VIII

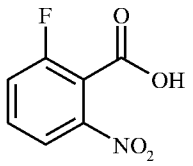


Formula IX

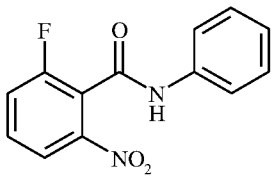
d) cyclizing the compound of Formula IX or a salt thereof to obtain the compound of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof substantially free of desfluoro impurity of Formula C; comprising:

i) reacting 2-fluoro-6-nitrobenzoic acid or a reactive derivative of Formula II with aniline to obtain a compound of Formula III,

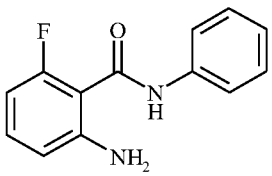


Formula II



Formula III

ii) reducing the compound of Formula III in presence of a suitable reducing agent and a suitable hydrogen source to obtain a compound of Formula IV or a salt thereof,



Formula IV

iii) purifying the compound of Formula IV with a suitable hydrocarbon solvent to obtain the compound of Formula IV substantially free of corresponding desfluoro impurity of Formula A, and

iv) converting the compound of Formula IV or a salt thereof into compound of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof; comprising:

a) reacting a compound of Formula IV or a salt thereof with aminobutyric acid or a reactive derivative of Formula Va to obtain a compound of Formula VIa,

b) deprotecting the compound of Formula VIa in presence of a suitable deprotecting agent to obtain a compound of Formula VII or a salt thereof,

c) reacting the compound of Formula VII or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula IX, wherein 'X' represents a suitable leaving group,

d) isolating the compound of Formula IX as an organic acid salt,

e) neutralizing the organic acid salt of compound of Formula IX with a suitable base to obtain pure compound of Formula IX,

f) cyclizing the compound of Formula IX to obtain idelalisib of Formula I,
g) isolating the idelalisib of Formula I as an organic acid salt, and
h) neutralizing the organic acid salt of idelalisib with a suitable base to obtain pure idelalisib.

In accordance with another embodiment, the present invention provides a process for purification of compound of Formula IX, comprising:
a) providing a solution of compound of Formula IX in one or more organic solvents,
b) adding an organic acid to the step a) solution,
c) isolating the compound of Formula IX as an organic acid salt,
d) neutralizing the organic acid salt of compound of Formula IX with a suitable base, and
e) isolating the compound of Formula IX.

In accordance with another embodiment, the present invention provides a process for purification of compound of Formula IX, comprising:
a) providing a solution of compound of Formula IX in one or more organic solvents,
b) adding trifluoroacetic acid to the step a) solution,
c) isolating the trifluoroacetate salt of compound of Formula IX,
d) neutralizing the trifluoroacetate salt of compound of Formula IX with a suitable base, and
e) isolating the compound of Formula IX.

In accordance with another embodiment, the present invention provides a process for preparation of trifluoroacetic acid salt of compound of Formula IX, comprising:
a) providing a solution of compound of Formula IX in one or more organic solvents,
b) adding trifluoroacetic acid to the step a) solution, and
c) isolating the trifluoroacetate salt of compound of Formula IX.

In accordance with another embodiment, the present invention provides a process for purification of idelalisib, comprising:
a) providing a solution of idelalisib in one or more organic solvents,
b) adding an organic acid to the step a) solution,
c) isolating the idelalisib organic acid salt,
d) optionally drying the idelalisib organic acid salt,
e) neutralizing the idelalisib organic acid salt in a water and water immiscible organic solvent using a suitable base, and
f) isolating the idelalisib from the water immiscible organic solvent.

In accordance with another embodiment, the present invention provides a process for purification of idelalisib, comprising:
a) providing a solution of idelalisib in one or more organic solvents,

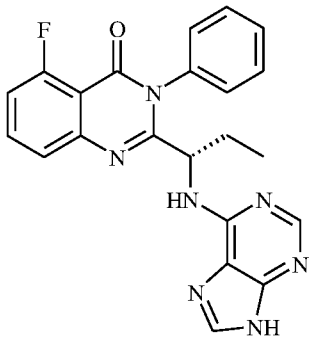
b) adding trifluoroacetic acid to the step a) solution,
c) isolating the idelalisib trifluoroacetate salt,
d) optionally drying the idelalisib trifluoroacetate salt,
e) neutralizing the idelalisib trifluoroacetate salt in a water and water immiscible organic solvent using a suitable base, and
f) isolating the idelalisib from the water immiscible organic solvent.

In accordance with another embodiment, the present invention provides a process for preparation of idelalisib trifluoroacetic acid salt, comprising:
a) providing a solution of idelalisib in one or more organic solvents,
b) adding trifluoroacetic acid to the step a) solution, and
c) isolating the idelalisib trifluoroacetate salt.

In accordance with another embodiment, the present invention provides a process for preparation of amorphous Form of idelalisib, comprising:
a) providing a solution or suspension of idelalisib organic acid salt in a water and water immiscible organic solvent,
b) neutralizing the step a) solution with a suitable base,
c) concentrating the water immiscible organic solvent to obtain a residue,
d) dissolving the residue in one or more organic solvents,
e) optionally, concentrating the step c) solution,
f) adding a suitable anti-solvent to the step d) or step e) (or) vice-versa, and
g) isolating the idelalisib amorphous form.

In accordance with another embodiment, the present invention provides a process for preparation of amorphous Form of idelalisib, comprising:
a) providing a solution or suspension of idelalisib trifluoroacetate salt in a water and water immiscible organic solvent,
b) neutralizing the step a) solution with a suitable base,
c) concentrating the water immiscible organic solvent to obtain a residue,
d) dissolving the residue in one or more organic solvents,
e) optionally, concentrating the step c) solution,
f) adding a suitable anti-solvent to the step d) or step e) (or) vice-versa, and
g) isolating the idelalisib amorphous form;
wherein the one or more organic solvents are selected from the group comprising of diols, ketones, sulfoxides, esters, nitriles and the like and mixtures thereof; wherein the suitable anti-solvent is selected from the group comprising of water, ethers, aliphatic hydrocarbons, alicyclic hydrocarbons and the like and mixtures thereof.

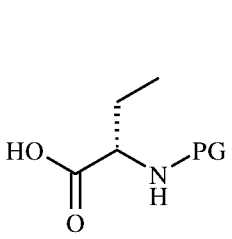
In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof:



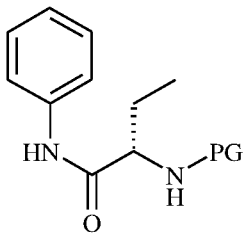
Formula I

comprising:

a1) reacting aminobutyric acid or a reactive derivative of Formula V with aniline to obtain a compound of Formula X, wherein 'PG' represents a suitable amine protecting group,

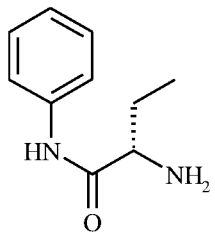


Formula V



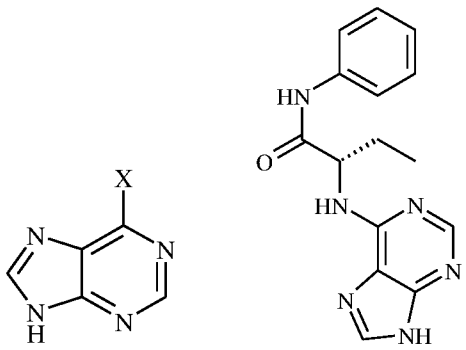
Formula X

b1) deprotecting the compound of Formula X in presence of a suitable deprotecting agent to obtain a compound of Formula XI or a salt thereof,



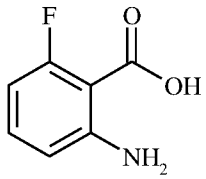
Formula XI

c1) reacting the compound of Formula XI or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula XII or a salt thereof, wherein 'X' represents a suitable leaving group, and



Formula VIII Formula XII

d1) reacting the compound of Formula XII or a salt thereof with a compound of Formula XIII or a salt thereof to obtain the compound of Formula I.



Formula XIII

In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising: reacting a compound of Formula XII or a salt thereof with a compound of Formula XIII or a salt thereof to obtain the compound of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a1) reacting a compound of Formula XI or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula XII or a salt thereof, wherein 'X' represents a suitable leaving group, and

b1) reacting the compound of Formula XII or a salt thereof with a compound of Formula XIII or a salt thereof to obtain the compound of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a1) deprotecting a compound of Formula X in presence of a suitable deprotecting agent to obtain a compound of Formula XI or a salt thereof,

b1) reacting the compound of Formula XI or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula XII or a salt thereof, wherein 'X' represents a suitable leaving group, and

c1) reacting the compound of Formula XII or a salt thereof with a compound of Formula XIII or a salt thereof to obtain the compound of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a1) reacting aminobutyric acid or a reactive derivative of Formula V with aniline to obtain a compound of Formula X, wherein 'PG' represents a suitable amine protecting group,

b1) deprotecting the compound of Formula X in presence of a suitable deprotecting agent to obtain a compound of Formula XI or a salt thereof,

c1) reacting the compound of Formula XI or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula XII or a salt thereof, wherein 'X' represents a suitable leaving group, and

d1) converting the compound of Formula XII or a salt thereof in to compound of Formula I.

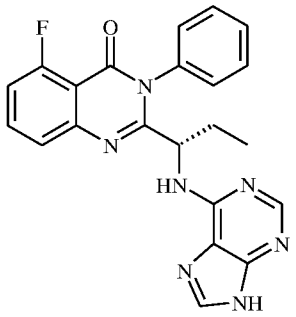
In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a1) reacting aminobutyric acid or a reactive derivative of Formula V with aniline to obtain a compound of Formula X, wherein 'PG' represents a suitable amine protecting group,

b1) deprotecting the compound of Formula X in presence of a suitable deprotecting agent to obtain a compound of Formula XI or a salt thereof, and

c1) converting the compound of Formula XI or a salt thereof in to compound of Formula I.

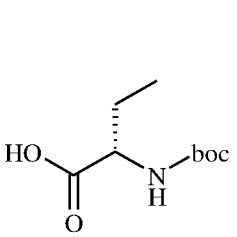
In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof:



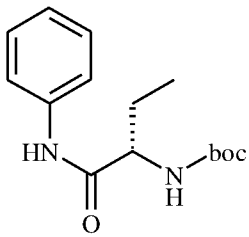
Formula I

comprising:

a1) reacting aminobutyric acid or a reactive derivative of Formula Va with aniline to obtain a compound of Formula Xa,

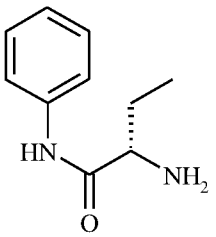


Formula Va



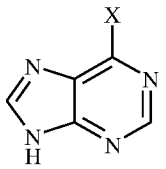
Formula Xa

b1) deprotecting the compound of Formula Xa in presence of a suitable deprotecting agent to obtain a compound of Formula XI or a salt thereof,

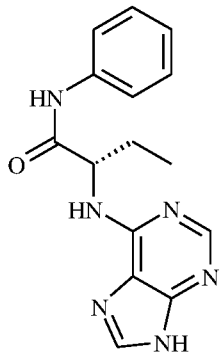


Formula XI

c1) reacting the compound of Formula XI or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula XII or a salt thereof, wherein 'X' represents a suitable leaving group, and

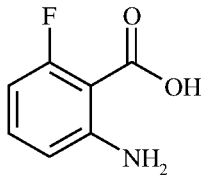


Formula VIII



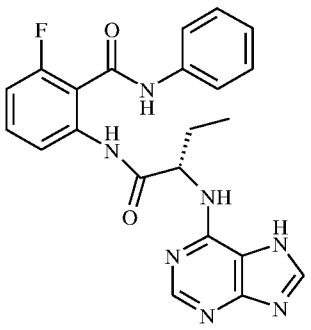
Formula XII

d1) reacting the compound of Formula XII or a salt thereof with a compound of Formula XIII or a salt thereof to obtain the compound of Formula I.



Formula XIII

In accordance with another embodiment, the present invention provides a compound of Formula IX or a salt thereof.



Formula IX

In accordance with another embodiment, the present invention provides crystalline compound of Formula IX.

In accordance with another embodiment, the present invention provides crystalline compound of Formula IX characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 1.

In accordance with another embodiment, the present invention provides trifluoroacetate salt of compound of Formula IX.

In accordance with another embodiment, the present invention provides crystalline trifluoroacetate salt of compound of Formula IX.

In accordance with another embodiment, the present invention provides crystalline trifluoroacetate salt of compound of Formula IX characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 2.

In accordance with another embodiment, the present invention provides idelalisib trifluoroacetate salt.

In accordance with another embodiment, the present invention provides crystalline idelalisib trifluoroacetate salt.

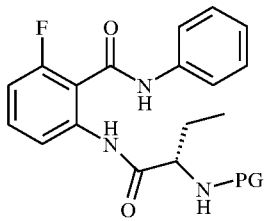
In accordance with another embodiment, the present invention provides crystalline idelalisib trifluoroacetate salt characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 3.

In accordance with another embodiment, the present invention provides crystalline idelalisib trifluoroacetate salt characterized by a differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure 4.

In accordance with another embodiment, the present invention provides crystalline idelalisib trifluoroacetate salt characterized by a thermo gravimetric analysis (TGA) substantially in accordance with Figure 5.

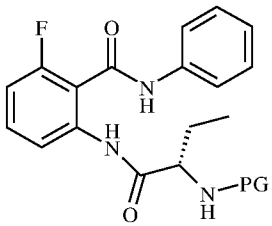
In accordance with another embodiment, the present invention provides crystalline idelalisib trifluoroacetate salt characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 3, a differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure 4 and/or a thermo gravimetric analysis (TGA) substantially in accordance with Figure 5.

In accordance with another embodiment, the present invention provides a compound of Formula VI, wherein 'PG' represents a suitable amine protecting group.



Formula VI

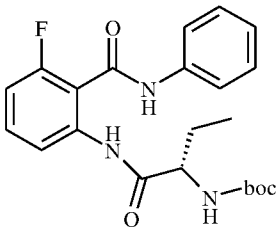
In accordance with another embodiment, the present invention provides a compound of Formula VI,



Formula VI

wherein the "PG" is selected from the group comprising carbobenzyloxy (Cbz), p-methoxybenzyl carbonyl, tert-butyloxycarbonyl (boc), 9-fluorenylmethyloxycarbonyl (FMOC), acetyl, pivaloyl, benzoyl (Bz), benzyl (Bn), p-methoxybenzyl (PMB), p-methoxybenzoyl, 3,4-dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP), p-nitro benzoyl (PNB), p-nitro benzyl, p-phenyl benzyl (PPB), p-phenyl benzoyl, trimethylsilyl (TMS), triethylsilyl (TES), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS), succinimide, tosyl (Ts), and other sulfonamides such as Nosyl.

In accordance with another embodiment, the present invention provides a compound of Formula VIa.

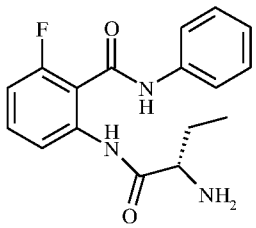


Formula VIa

In accordance with another embodiment, the present invention provides crystalline compound of Formula VIa.

In accordance with another embodiment, the present invention provides crystalline compound of Formula VIa characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 6.

In accordance with another embodiment, the present invention provides a compound of Formula VII or a salt thereof.



Formula VII

In accordance with another embodiment, the present invention provides crystalline compound of Formula VII.

In accordance with another embodiment, the present invention provides crystalline compound of Formula VII characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 7.

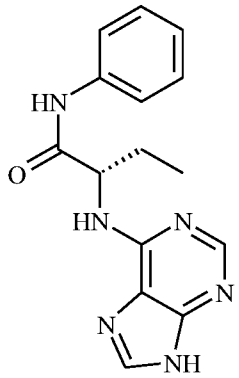
In accordance with another embodiment, the present invention provides crystalline compound of Formula III.

In accordance with another embodiment, the present invention provides crystalline compound of Formula III characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 8.

In accordance with another embodiment, the present invention provides crystalline compound of Formula IV.

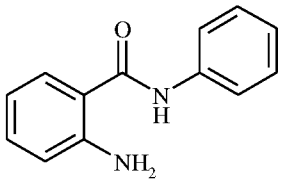
In accordance with another embodiment, the present invention provides crystalline compound of Formula IV characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 9.

In accordance with another embodiment, the present invention provides a compound of Formula XII or a salt thereof.



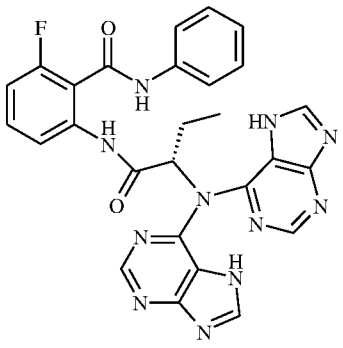
Formula XII

In accordance with another embodiment, the present invention provides a compound of Formula IV substantially free of desfluoro impurity of Formula A:



Formula A

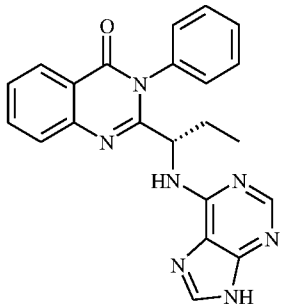
In accordance with another embodiment, the present invention provides a compound of Formula IX substantially free of dimer impurity of Formula B:



Formula B

In accordance with another embodiment, the present invention provides a compound of Formula B.

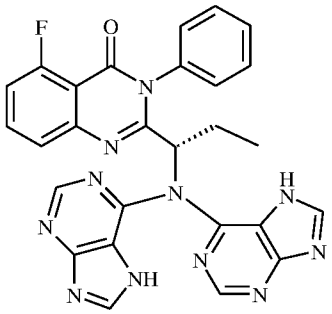
In accordance with another embodiment, the present invention provides desfluoro idelalisib of Formula C.



Formula C

In accordance with another embodiment, the present invention provides idelalisib of Formula I substantially free of desfluoro impurity of Formula C.

In accordance with another embodiment, the present invention provides a compound of Formula D.



Formula D

In accordance with another embodiment, the present invention provides idelalisib of Formula I substantially free of dimer impurity of Formula D.

In accordance with another embodiment, the present invention provides a pharmaceutical composition comprising idelalisib or a pharmaceutically acceptable salt thereof prepared by the processes of the present invention and at least one pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

Figure 1 is the characteristic powder X-ray diffraction (XRD) pattern of crystalline compound of Formula IX.

Figure 2 is the characteristic powder X-ray diffraction (XRD) pattern of crystalline trifluoroacetate salt of Formula IX.

Figure 3 is the characteristic powder X-ray diffraction (XRD) pattern of crystalline idelalisib trifluoroacetate salt.

Figure 4 is the characteristic differential scanning calorimetric (DSC) thermogram of crystalline idelalisib trifluoroacetate salt.

Figure 5 is the characteristic thermo gravimetric analysis (TGA) of crystalline idelalisib trifluoroacetate salt.

Figure 6 is the characteristic powder X-ray diffraction (XRD) pattern of crystalline compound of Formula VIa.

Figure 7 is the characteristic powder X-ray diffraction (XRD) pattern of crystalline compound of Formula VII.

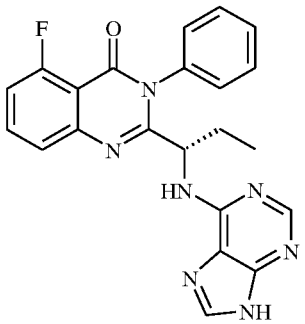
Figure 8 is the characteristic powder X-ray diffraction (XRD) pattern of crystalline compound of Formula III.

Figure 9 is the characteristic powder X-ray diffraction (XRD) pattern of crystalline compound of Formula IV.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides processes for the preparation of idelalisib using novel intermediates.

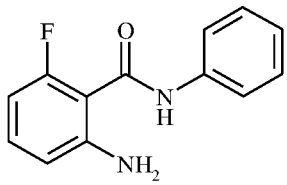
In accordance with one embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof:



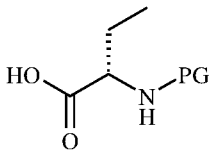
Formula I

comprising:

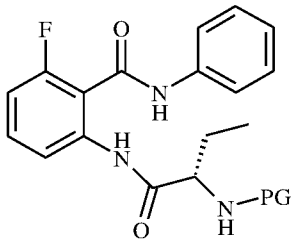
a) reacting a compound of Formula IV or a salt thereof with aminobutyric acid or a reactive derivative of Formula V to obtain a compound of Formula VI, wherein 'PG' represents a suitable amine protecting group,



Formula IV

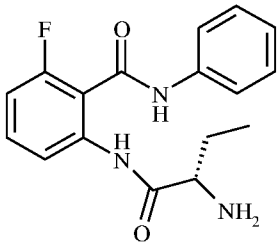


Formula V



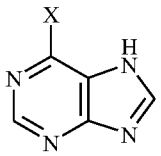
Formula VI

b) deprotecting the compound of Formula VI in presence of a suitable deprotecting agent to obtain a compound of Formula VII or a salt thereof,

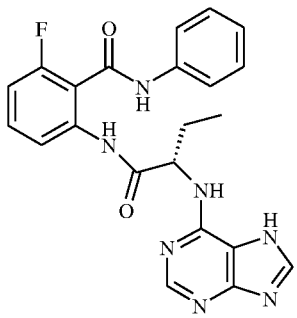


Formula VII

c) reacting the compound of Formula VII or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula IX or a salt thereof, wherein 'X' represents a suitable leaving group, and



Formula VIII



Formula IX

d) cyclizing the compound of Formula IX or a salt thereof to obtain the compound of Formula I.

Unless otherwise specified the term 'PG' represents a "suitable amino protecting group" refers to a moiety that can be selectively attached to and removed from a nitrogen atom to prevent it from participating in undesired chemical reactions, without unacceptably adverse effects on desired reactions. Examples of amino protecting groups include carbamates, such as tert-butyloxycarbonyl (boc), carbobenzyloxy (Cbz), 9-fluorenylmethyloxycarbonyl (Fmoc), alloc, methyl and ethyl carbamates, among others; cyclic imide derivatives, such as phthalimide; amides, such as formyl, (un)substituted acetyl, and (un)substituted

benzoyl; and trialkyl silyl groups, such as t-butyldimethylsilyl and triisopropylsilyl; toluene sulfonyl, Pmc (2,2,5,7,8-pentamenthyl chroman-6-sulfonyl), Pbf (2,2,4,6,7-pentamethyl dihydrobenzofuran-5-sulfonyl), Mtr (4-methoxy-2,3,6-trimethylbenzenesulfonyl). Other amino protecting groups are well known in the art and are described in detail in Protecting Groups in Organic Synthesis, Theodora W. Greene and Peter G. M. Wuts, 3rd Edition, 1999, published by John Wiley and Son, Inc.

Unless otherwise specified the term 'x' used herein the specification represents a halo group such as chloro, bromo, iodo, fluoro; triflate, tosylate, mesylate, nosyl and the like; preferably chloro or bromo.

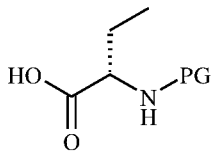
The starting Formula V, particularly boc-protected formula V is known in the art and is available commercially from various sources. Further, another starting compound of Formula IV or a salt thereof is known in the art and can be prepared by the processes known in the art, for example: USRE44638, WO2015/042077, CN102838600 and CN102838601 or may be prepared by the process described in the following embodiment.

Step a):

The step a) of the aforementioned process involves reaction of a compound of Formula IV or a salt thereof with a protected aminobutyric acid or a reactive derivative of Formula V to obtain a compound of Formula VI, wherein 'PG' represents a suitable amine protecting group.

In a preferred embodiment, the compound of Formula V is used as free base and is obtained according to the process described just as above and the protected aminobutyric acid is used as its free acid.

In another embodiment, the protected aminobutyric acid used herein is represented as follows:



Formula V

wherein the "PG" is selected from the group comprising carbobenzyloxy (Cbz), p-methoxybenzyl carbonyl, tert-butyloxycarbonyl (boc), 9-fluorenylmethyloxycarbonyl (FMOC), acetyl, pivaloyl, benzoyl (Bz), benzyl (Bn), p-methoxybenzyl (PMB), p-methoxybenzoyl, 3,4-dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP), p-nitro benzoyl (PNB), p-nitro benzyl, p-phenyl benzyl (PPB), p-phenyl benzoyl, trimethylsilyl (TMS), triethylsilyl (TES), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl

(TBS/TBDMS), triisopropylsilyl (TIPS), succinimide, tosyl (Ts), and other sulfonamides such as Nosyl.

In another preferred embodiment, the protected aminobutyric acid used herein is a boc-protected aminobutyric acid.

The reaction of compound of Formula IV and the boc-protected aminobutyric acid of Formula Va is carried out in presence of a suitable coupling agent optionally in presence of an additive in a suitable organic solvent at a temperature of about -20°C to about 85°C.

The suitable coupling agent used herein is selected from 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), carbonyldiimidazole (CDI), diisopropylcarbodiimide (DCI), N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide (EDC), dicyclohexyl carbodiimide (DCC), propanephosphonic acid cyclic anhydride (PPA), benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate (PyBOP), bromo- tripyrrolidino- phosphonium hexafluorophosphate (PyBrOP), benzotriazol-1-yloxy-tris (dimethylamino)-phosphonium hexafluorophosphate (BOP), Propylphosphonic anhydride (T3P), 2-(7-Aza-1H-benzotriazol-1-yl)- N,N,N',N'-tetramethylaminium hexafluorophosphate) (HATU), (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexa fluorophosphate (COMU), N,N,N′,N′-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluoro phosphate (HBTU) and 2-(1H-Benzotriazol-1-yl) - N,N,N',N'- tetramethylaminium tetrafluoroborate (TBTU) and the like and mixture thereof; preferably carbonyldiimidazole (CDI), benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate (PyBOP) or -(3-dimethylaminopropyl)-N'-ethyl carbodiimide (EDC) and mixture thereof; more preferably carbonyldiimidazole (CDI).

The additive used herein include, but is not limited to hydroxy benzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), 6-halo-1-hydroxy-1H-benzotriazole (halo-HOBt), hydroxy pyridines (HOPy), imidazole or its salts, 1,8-diazabicyclo[5.4.0] undec-7-en (DBU), N-methylmorpholine, 4-dimethylaminopyridine, pyridine, dimethylaniline, tertiary amines or its salts and the like.

The suitable organic solvent used herein for step a) include, but is not limited to alcohols, amides, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, n-propanol, t-butanol and the like; amides include, but are not limited to dimethyl formamide, dimethyl acetamide and the like; nitriles include, but are not limited to acetonitrile, propionitrile, benzonitrile and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not

limited to toluene, xylene and the like and mixtures thereof; preferably toluene, methanol or methylene chloride and mixture thereof; more preferably toluene.

The step a) reaction is advantageously carried out at a temperature of about -20°C to about 85°C; preferably the compound of Formula IV, Formula V, coupling agent and the reaction solvent are mixed at about -5°C to 20°C followed by stirring the contents at about 20°C to about 45°C for a period of about 30 minutes to about 16 hours.

After completion of the reaction, the resultant compound of formula VI can be isolated as solid by methods known in the art. For example, the compound of Formula VI may be isolated from the reaction mass by filtration followed by optional drying of the wet material.

Optionally, the compound of Formula VI, preferably boc-protected compound of Formula VIa may be purified using a suitable solvent to remove unwanted by-products or unwanted impurities if any formed during the coupling reaction. The suitable solvent used herein for purification include, but is not limited to alcohols, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and the like and mixture thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, n-propanol, t-butanol and the like; nitriles include, but are not limited to acetonitrile, propionitrile, benzonitrile and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like and mixtures thereof; preferably acetonitrile.

The purification of compound of Formula VI may be carried out by either slurry method or by recrystallization method. The purification may be carried out at a temperature of about 25°C to about reflux temperature of the solvent used. The pure compound of Formula IV may be isolated by methods known in the art, for example filtration. The isolation step further includes, optional step of cooling the reaction mass to less than 25°C for better precipitation of the product.

The present invention provides a compound of Formula VI, preferably boc-protected compound of Formula VIa prepared by the process described as above having a chemical purity of at least about 99%, as measured by HPLC, preferably at least about 99.5% as measured by HPLC.

The compound of Formula VI, preferably boc-protected compound of Formula VIa obtained by the processes described above can be used as an intermediate or as a starting material in the preparation of idelalisib of Formula I.

Step b):

The step b) of the aforementioned process involves deprotection of the compound of Formula VI; wherein 'PG' is defined as above, in presence of a suitable deprotecting agent to obtain a compound of Formula VII or a salt thereof.

The suitable deprotecting agent used herein for the deprotection of compound of Formula VI is known in the art. Specific deprotecting agents include, but are not limited to metal catalyzed deprotecting agents such as palladium on carbon, palladium hydroxide and the like in presence of a hydrogen source such as hydrogen gas, ammonium formate, ammonium acetate and the like; base catalyzed deprotecting agents such as potassium carbonate, sodium carbonate, diethyl amine, diisopropyl amine, piperidine, N-methyl morpholine (NMM), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and the like and mixtures thereof; acid catalyzed deprotecting agents such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoro acetic acid, trichloro acetic acid, methane sulfonic acid and the like and mixtures thereof; preferably hydrochloric acid or trifluoro acetic acid; more preferably trifluoro acetic acid.

The deprotection of compound of Formula VI is carried out in a suitable organic solvent at a temperature of about 0°C to reflux temperature. The suitable organic solvent includes, but is not limited to alcohols, ketones, nitriles, ethers, halogenated hydrocarbons and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol and the like; ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like and mixture thereof; preferably methanol, 1,4-dioxane or methylene chloride and mixture thereof; more preferably methylene chloride.

After completion of reaction, the resultant compound of formula VII can be isolated as solid or insituly reaction mass containing compound of Formula VII is converted in to further processing steps by methods known in the art. For instance, the compound of Formula VII is isolated from the reaction mass by precipitating the product from the reaction mass by adjusting pH to neutral or basic with a suitable base followed by filtration and optional drying of the wet material.

The suitable base for neutralizing the reaction mass include, but is not limited to sodium hydroxide, potassium hydroxide, ammonium hydroxide, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate and the like and mixtures thereof; preferably sodium bicarbonate.

The present invention provides a compound of Formula VII prepared by the process described as above having a chemical purity of at least about 99%, as measured by HPLC, preferably at least about 99.5% as measured by HPLC.

In another embodiment, the compound of Formula VII prepared by the process described above is recovered in the form of crystalline form.

The compound of Formula VII obtained by the processes described above can be used as an intermediate or as a starting material in the preparation of idelalisib of Formula I.

Step c):

The step c) of the aforementioned process involves reaction of the compound of Formula VII or a salt thereof with a compound of Formula VIII or a salt thereof, wherein 'X' represents a suitable leaving group selected from chloro, bromo, iodo or fluoro; in presence of a suitable base in a suitable solvent at a temperature of about 25°C to reflux temperature to obtain a compound of Formula IX or a salt thereof.

The suitable base used herein for the step c) reaction include but is not limited to inorganic bases selected from alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; organic bases selected from the group comprising of triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine and the like; guanidine bases such as 1,1,3,3-tetramethylguanidine and the like and mixtures thereof; preferably sodium tert-butoxide, potassium carbonate, diisopropyl ethylamine or triethylamine and mixture thereof; more preferably triethylamine.

The suitable solvent used herein for step c) includes but is not limited to alcohols, amides, sulfoxides, ketones, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons, water and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, butanol and the like; amides include, but are not limited to dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidinone and the like; sulfoxides include, but are not limited to dimethylsulfoxide, diethyl sulfoxide and the like; ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like; water and mixtures thereof;

preferably butanol, dimethyl formamide, acetonitrile or water and mixture thereof; more preferably water.

After completion of reaction, the resultant compound of Formula IX can be isolated as solid compound by methods known in the art. For example, the compound of Formula IX may be isolated by optional step of cooling the reaction mass to less than 30°C and filtering the precipitated product.

The present invention provides a compound of Formula IX prepared by the process described as above having chemical purity of at least about 97%, as measured by HPLC, preferably at least about 98% as measured by HPLC, and more preferably at least about 99.0%, as measured by HPLC; and content of dimer impurity of Formula B is less than about 3%, as measured by HPLC, preferably less than about 2% as measured by HPLC, and more preferably less than about 1%, as measured by HPLC.

Optionally, the compound of Formula IX may be purified using a suitable solvent to remove unwanted by-products or unwanted impurities if any formed during the step c) reaction and hereinafter described as an embodiment for the purification.

The compound of Formula IX obtained by the processes described above can be used as an intermediate or as a starting material in the preparation of idelalisib of Formula I.

Step d):

In another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising: cyclizing a compound of Formula IX or a salt thereof to obtain the compound of Formula I.

The cyclization of the compound of Formula IX or a salt thereof is carried out with a suitable dehydrating agent optionally in presence of a suitable catalyst in a suitable organic solvent.

The suitable dehydrating agent includes, but is not limited to hexamethyldisilazane (HMDS), bis(trimethylsilyl)acetamide (BSA), bis-trimethylsilylurea (BSU), trimethylsilylphosphate, phosphorous oxychloride ($POCl_3$), thionyl chloride ($SOCl_2$), cyanuric chloride, aluminium chloride, aluminum bromide, zinc chloride, zinc bromide, boron trichloride, iron chloride, iron bromide, tinchloride, titanium chloride, sulfuric acid, phosphorous pentoxide, trifluoroacetic anhydride, acetic anhydride, dicyclohexylcarbodiimide, p-toluene sulfonic acid, methane sulfonic acid and calcium hydride; preferably hexamethyldisilazane and the suitable catalyst used along with dehydrating agent is Iodine.

The suitable organic solvent used herein for cyclization of the compound of Formula IX includes, but is not limited to ketones, esters, amides, sulfoxides, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. The ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; esters include, but are not limited to ethylacetate, isopropyl acetate, butyl acetate and the like; amides include, but are not limited to dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidinone and the like; sulfoxides include, but are not limited to dimethylsulfoxide, diethyl sulfoxide and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, 2-methyltetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like mixtures thereof; preferably dimethyl formamide, acetonitrile or tetrahydrofuran and mixture thereof; more preferably acetonitrile.

The cyclization reaction of step d) is advantageously carried out at a temperature of about 25°C to reflux temperature; preferably at about reflux temperature.

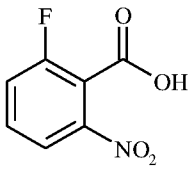
After completion of the reaction, the obtained idelalisib can be recovered by any conventional techniques known in the art, for example filtration or by subjecting the reaction mass to evaporation under vacuum.

The present invention provides idelalisib prepared by the process described as above having a purity of at least about 98%, as measured by HPLC, preferably at least about 99% as measured by HPLC.

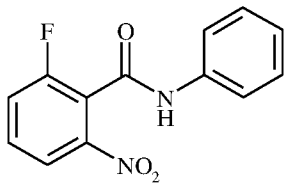
In another embodiment, the present invention provides a process for the preparation of idelalisib of formula I having substantially low levels of desfluoro impurity of Formula C, comprising: use of compound of Formula IV having substantially low levels of desfluoro impurity of Formula A obtained by the process described as below as an intermediate or as a starting material in the preparation of idelalisib of Formula I according to the above mentioned embodiment of the invention.

In another embodiment, the present invention provides a process for the preparation of compound of Formula IV or a salt thereof, comprising:

i) reacting 2-fluoro-6-nitrobenzoic acid or a reactive derivative of Formula II with aniline to obtain a compound of Formula III,

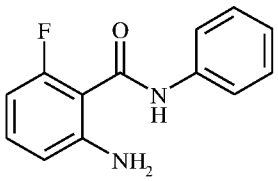


Formula II



Formula III

ii) reducing the compound of Formula III in presence of a suitable reducing agent and a suitable hydrogen source to obtain a compound of Formula IV or a salt thereof,



Formula IV

iii) purifying the compound of Formula IV with a suitable hydrocarbon solvent to obtain the compound of Formula IV substantially free of corresponding desfluoro impurity of Formula A, and

iv) converting the compound of Formula IV or a salt thereof into compound of Formula I.

The starting material of Formula II or a reactive derivative, preferably chloro derivative is known in the art and can be prepared by any known method, for example USRE44638.

The reaction of 2-fluoro-6-nitrobenzoic acid or a reactive derivative of Formula II, preferably its chloro derivative with aniline is carried out in presence of a suitable base and in a suitable solvent to obtain a compound of Formula III. The suitable base herein used includes, but is not limited to sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate, triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine and the like and mixtures thereof. The suitable solvent used herein, includes but is not limited to ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. The ethers include, but are not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like and mixture thereof; preferably the base is sodium bicarbonate and the solvent is 1,4-dioxane.

The reaction of Formula II and aniline is carried out at a temperature of about 25°C to about reflux for a period of about 30 min to about 10 hours; preferably at about 25°C to 50°C for a period of about 1 hour to 3 hours.

The resultant compound of Formula III is isolated by quenching the reaction mass in to water to precipitate out as solid. The precipitated compound of Formula III may be separated by methods known in the art, for example filtration. The resultant product may optionally slurred with a non-polar organic solvent at ambient temperature to about reflux to obtain Formula III as a crystalline compound. The suitable non-polar organic solvent include, but is not limited to ether solvent such as diethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; aliphatic hydrocarbons such as hexane, heptane, propane and the like; alicyclic hydrocarbons such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, methyl cyclohexane, cycloheptane, cyclooctane and the like; and mixtures thereof; preferably diisopropyl ether.

The reduction step of compound of Formula III is carried out using a suitable reducing agent and a suitable hydrogen source in a suitable solvent at a temperature of about 25°C to about reflux. The suitable reducing agent herein used include, but is not limited to raney nickel, platinum oxide, sodium hydrosulfite, sodium dithionate, zinc, Iron powder, tin chloride and the like. The reducing agent used along with suitable hydrogen source is selected from hydrogen gas, ammonium acetate, ammonium formate, ammonium chloride and the like and mixtures thereof; preferably reduction step is carried out using zinc and ammonium formate.

The suitable solvent for reduction includes, but is not limited to alcohols, halogenated hydrocarbons, aromatic hydrocarbons, water and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, propanol, isopropanol and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like; water and mixtures thereof; preferably a mixture of methanol and methylene chloride.

The resultant compound of Formula IV after the nitro reduction is isolated by first separating the unreacted reduction catalyst by filtration followed by concentrating the resultant reaction mass. Then, the resultant compound of Formula IV may optionally be purified to remove unwanted impurities if any, formed during the reduction, for example desfluoro impurity of Formula A. The purification may be carried out by first suspending the compound of Formula IV in a suitable hydrocarbon solvent at a temperature of ambient to about reflux, at which time the compound of Formula IV may be completely in solution. Then, the resultant reaction solution may optionally be cooled to less than room temperature for product precipitation followed by isolating the pure compound of Formula IV by techniques known in the art, for example, filtration.

The suitable hydrocarbon solvent used herein for the purification of compound of Formula IV, include, but is not limited to, alcohols, nitriles, esters, halogenated hydrocarbons,

aromatic hydrocarbons and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, n-propanol, t-butanol and the like; nitriles include, but are not limited to acetonitrile, propionitrile, benzonitrile and the like; esters include, but are not limited to ethyl acetate, methyl acetate, isopropyl acetate and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like and mixtures thereof; preferably toluene.

The compound of Formula IV recovered using the process described just as above is having substantially low levels of desfluoro impurity of Formula A.

The present invention provides a compound of Formula IV prepared by the process described as above having chemical purity of at least about 99.5%, as measured by HPLC and containing less than 0.1% of desfluoro impurity of Formula A as measured by HPLC; preferably containing less than 0.05% of desfluoro impurity of Formula A as measured by HPLC.

The compound of Formula IV having substantially low levels of desfluoro impurity of Formula A obtained by the process described above can be used as intermediate in the preparation of idelalisib of Formula I with low levels of corresponding desfluoro impurity of Formula C.

In another embodiment, the compounds of Formula III and Formula IV prepared by the process described above are recovered as crystalline form.

In another embodiment, the present invention provides crystalline compound of Formula III characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 8.

In another embodiment, the present invention provides crystalline compound of Formula IV characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 9.

In another embodiment, the present invention provides a process for preparation of pure idelalisib of Formula I, comprising: purification of compound of Formula IX by forming an organic acid salt of compound of Formula IX as an intermediate, neutralization of the salt and converting the pure compound of Formula IX in to idelalisib of Formula I.

In another embodiment, the present invention provides a process for purification of compound of Formula IX, comprising:

a) providing a solution of compound of Formula IX in one or more organic solvents,
b) adding an organic acid to the step a) solution,

c) isolating the compound of Formula IX as an organic acid salt,
d) neutralizing the organic acid salt of compound of Formula IX with a suitable base, and
e) isolating the compound of Formula IX.

The one or more organic solvents for providing a solution of compound of Formula IX include, but are not limited to alcohols, ketones, esters, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, butanol and the like; ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; esters include, but are not limited to ethylacetate, isopropyl acetate, butyl acetate and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like and mixtures thereof; preferably acetonitrile, tetrahydrofuran or 1,4-dioxane and mixture thereof; more preferably acetonitrile.

The suitable temperature for providing a solution of compound of Formula IX may be carried out at a temperature of about 25°C to reflux temperature; preferably at 25°C to about 45°C.

The organic acid used herein are selected from the group comprising of trifluoro acetic acid, methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, 4-bromo benzenesulfonic acid, p-toluenesulfonic acid, oxalic acid, phosphoric acid, tartaric acid, dibenzoyl tartaric acid, maleic acid, mandelic acid, malonic acid, succinic acid, camphorsulfonic acid and the like; preferably trifluoro acetic acid.

The compound of Formula IX as organic acid salt can be isolated by any conventional techniques known in the art, for example filtration. If necessary, cooling step may be involved for better precipitation of the product prior to filtration. The wet compound may be optionally dried at ambient temperature.

The compound of Formula IX as organic acid salt recovered by the purification process described as above is trifluoroacetate salt of compound of Formula IX. Preferably the trifluoroacetate salt of compound of Formula IX is isolated as a crystalline form.

The step of neutralizing the organic acid salt of compound of Formula IX involves treating the resultant organic acid salt of compound of Formula IX with a suitable base such as sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, ammonium hydroxide and the like and mixture thereof in water; preferably base is sodium

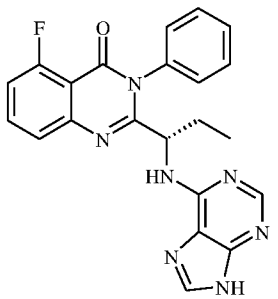
bicarbonate. The neutralization step may be carried out in water at a temperature of about 0°C to about 50°C. Then, the resultant precipitated compound of Formula IX can be isolated by any conventional techniques known in the art, for example filtration.

The compound of Formula IX obtained by the purification process described above has a chemical purity of at least about 99.5%, as measured by HPLC and less than about 0.5% of dimer impurity of Formula B, preferably less than about 0.1% as measured by HPLC.

The pure compound of Formula IX obtained by the purification process described above can be used as an intermediate in the preparation of pure idelalisib having substantially free of dimer impurity of Formula B. The process of conversion of compound of Formula IX in to idelalisib of Formula I can be carried out according to the process described hereinbefore.

In another embodiment, idelalisib obtained according to processes described as above may be purified to get pure product. The purification step includes forming idelalisib organic acid salt as an intermediate and followed by neutralizing the organic acid salt with a suitable neutralizing agent to obtain a pure idelalisib which is having chemical purity of at least about 99.5% and substantially free of des fluoro impurity of Formula C and dimer impurity of Formula B as measured by HPLC.

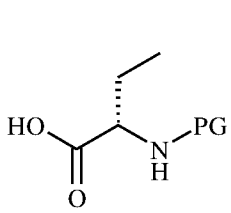
In accordance with another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof:



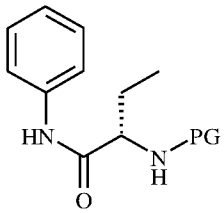
Formula I

comprising:

a1) reacting aminobutyric acid or a reactive derivative of Formula V with aniline to obtain a compound of Formula X, wherein 'PG' represents a suitable amine protecting group,

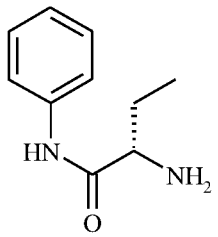


Formula V



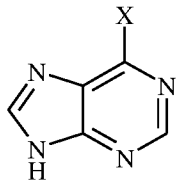
Formula X

b1) deprotecting the compound of Formula X in presence of a suitable deprotecting agent to obtain a compound of Formula XI or a salt thereof,

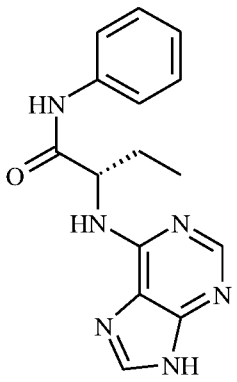


Formula XI

c1) reacting the compound of Formula XI or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula XII or a salt thereof, wherein 'X' represents a suitable leaving group, and

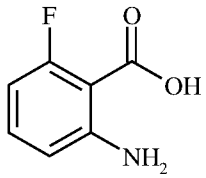


Formula VIII



Formula XII

d1) reacting the compound of Formula XII or a salt thereof with a compound of Formula XIII or a salt thereof to obtain the compound of Formula I.



Formula XIII

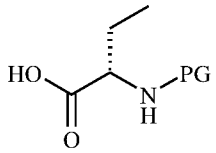
The terms 'PG' represents a "suitable amino protecting group" and 'X' represents a suitable leaving group specified same as above in the present specification.

The compound of Formula V or a reactive derivative, Formula VIII and Formula XIII are known in the art and are may be available from commercial source.

Step a1):

The step a1) of the aforementioned process involves reaction of aminobutyric acid or a reactive derivative of Formula V with aniline to obtain a compound of Formula X, wherein 'PG' represents a suitable amine protecting group.

In another embodiment, the protected aminobutyric acid used herein is represented as follows:



Formula V

wherein the "PG" is selected from the group comprising carbobenzyloxy (Cbz), p-methoxybenzyl carbonyl, tert-butyloxycarbonyl (boc), 9-fluorenylmethyloxycarbonyl (FMOC), acetyl, pivaloyl, benzoyl (Bz), benzyl (Bn), p-methoxybenzyl (PMB), p-methoxybenzoyl, 3,4-dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP), p-nitro benzoyl (PNB), p-nitro benzyl, p-phenyl benzyl (PPB), p-phenyl benzoyl, trimethylsilyl (TMS), triethylsilyl (TES), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS), succinimide, tosyl (Ts), and other sulfonamides such as Nosyl.

In another preferred embodiment, the protected aminobutyric acid used herein is a boc-protected aminobutyric acid of Formula Va and is used as its free acid.

The reaction of boc-protected aminobutyric acid of Formula Va with aniline is carried out in presence of a suitable coupling agent optionally in presence of an additive in a suitable organic solvent at a temperature of about -20°C to about 85°C.

The suitable coupling agent used herein is selected from 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), carbonyldiimidazole (CDI), diisopropylcarbodiimide (DCI), N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide (EDC), dicyclohexyl carbodiimide (DCC), propanephosphonic acid cyclic anhydride (PPA), benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate (PyBOP), bromo- tripyrrolidino- phosphonium hexafluorophosphate (PyBrOP), benzotriazol-1-yloxy-tris (dimethylamino)-phosphonium hexafluorophosphate (BOP), Propylphosphonic anhydride (T3P), 2-(7-Aza-1H-benzotriazol-1-yl)- N,N,N',N'-tetramethylaminium hexafluorophosphate) (HATU), (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexa fluorophosphate (COMU), N,N,N′,N′-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluoro phosphate (HBTU) and 2-(1H-Benzotriazol-1-yl) - N,N,N',N'- tetramethylaminium tetrafluoroborate (TBTU) and the like; preferably carbonyldiimidazole (CDI), benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate (PyBOP) or -(3-dimethylaminopropyl)-N'-ethyl carbodiimide (EDC) and mixture thereof; more preferably carbonyldiimidazole (CDI).

The additive used herein include, but is not limited to hydroxy benzotriazole, 1-hydroxy-7-azabenzotriazole, 6-halo-1-hydroxy-1H-benzotriazole, hydroxy pyridines, imidazole or its salts, 1,8-diazabicyclo[5.4.0] undec-7-en, N-methylmorpholine, 4-dimethylaminopyridine, pyridine, dimethylaniline, tertiary amines or its salts and the like.

The suitable organic solvent used herein for step a1) includes, but is not limited to alcohols, amides, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, n-propanol, t-butanol and the like; amides include, but are not limited to dimethyl formamide, dimethyl acetamide and the like; nitriles include, but are not limited to acetonitrile, propionitrile, benzonitrile and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like and mixtures thereof; preferably toluene, methanol or methylene chloride and mixture thereof; more preferably toluene.

The step a1) reaction is advantageously carried out at a temperature of about -20°C to about 85°C; preferably at about 20°C to about 45°C.

Step b1):

The step b1) of the aforementioned process involves deprotection of the compound of Formula X; wherein 'PG' is defined as above, in presence of a suitable deprotecting agent to obtain a compound of Formula XI or a salt thereof.

The suitable deprotecting agent used herein for the deprotection of compound of Formula X is known in the art. Specific deprotecting agents include, but are not limited to metal catalyzed deprotecting agents such as palladium on carbon, palladium hydroxide and the like in presence of a hydrogen source such as hydrogen gas, ammonium formate, ammonium acetate and the like; base catalyzed deprotecting agents such as potassium carbonate, sodium carbonate, diethyl amine, diisopropyl amine, piperidine, N-methyl morpholine , 1,8-diazabicyclo[5.4.0]undec-7-ene and the like and mixtures thereof; acid catalyzed deprotecting agents such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoro acetic acid, trichloro acetic acid, methane sulfonic acid and the like and mixtures thereof; preferably hydrochloric acid or trifluoro acetic acid; more preferably trifluoro acetic acid.

The deprotection of compound of Formula X is carried out in a suitable organic solvent. The suitable organic solvent includes, but is not limited to alcohols, ketones, nitriles, ethers, halogenated hydrocarbons and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol and the like; ketones include, but are not limited

to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like and mixture thereof; preferably methanol, 1,4-dioxane or methylene chloride and mixture thereof; more preferably methylene chloride.

The deprotection reaction is advantageously carried out at a temperature of about 0°C to reflux temperature; preferably at about 15°C to about 45°C.

Step c1):

The step c1) of the aforementioned process involves reaction of the compound of Formula XI or a salt thereof with a compound of Formula VIII or a salt thereof, wherein 'X' represents a suitable leaving group selected from chloro, bromo, iodo or fluoro; in presence of a suitable base in a suitable solvent.

The suitable base used herein for the step c1) reaction include but is not limited to inorganic bases selected from alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; organic bases selected from the group consisting of triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine and the like; guanidine bases such as 1,1,3,3-tetramethylguanidine and the like and mixtures thereof; preferably sodium tert-butoxide, potassium carbonate, triethylamine or diisopropyl ethylamine and mixture thereof; more preferably diisopropyl ethylamine.

The suitable solvent used herein for step c1) includes but is not limited to alcohols, amides, sulfoxides, ketones, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons, water and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, butanol and the like; amides include, but are not limited to dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidinone and the like; sulfoxides include, but are not limited to dimethylsulfoxide, diethyl sulfoxide and the like; ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like; water and mixtures thereof;

preferably butanol, dimethyl formamide, acetonitrile or water and mixture thereof; more preferably acetonitrile.

The reaction of compound of Formula XI or a salt with a compound of Formula VIII or a salt thereof is advantageously carried out at a temperature of about 25°C to reflux temperature; preferably at about 50°C to about 100°C.

Step d1):

In another embodiment, the present invention provides a process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof, comprising: reaction of a compound of Formula XII or a salt thereof with a compound of Formula XIII or a salt thereof to obtain the compound of Formula I.

The reaction of the compound of Formula XII or a salt thereof with a compound of Formula XIII or a salt thereof is carried out in presence of a suitable dehydrating agent optionally in presence of a suitable catalyst in a suitable organic solvent.

The suitable dehydrating agent includes, but is not limited to hexamethyldisilazane, bis(trimethylsilyl)acetamide, bis-trimethylsilylurea, trimethylsilylphosphate, phosphorous oxychloride, thionyl chloride, cyanuric chloride, aluminum chloride, aluminum bromide, zinc chloride, zinc bromide, boron trichloride, iron chloride, iron bromide, tinchloride, titanium chloride, sulfuric acid, phosphorous pentoxide, trifluoroacetic anhydride, acetic anhydride, dicyclohexylcarbodiimide, p-toluene sulfonic acid, methane sulfonic acid and calcium hydride; preferably hexamethyldisilazane and zinc chloride. The suitable catalyst used along with dehydrating agent is Iodine.

The suitable organic solvent used herein for reaction of the compound of Formula XII or a salt thereof with a compound of Formula XIII or a salt thereof includes, but is not limited to ketones, esters, amides, sulfoxides, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. The ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; esters include, but are not limited to ethylacetate, isopropyl acetate, butyl acetate and the like; amides include, but are not dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidinone and the like; sulfoxides include, but are not limited to dimethylsulfoxide, diethyl sulfoxide and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, 2-methyltetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like mixtures thereof; preferably dimethyl formamide, acetonitrile or tetrahydrofuran and mixture thereof; more preferably acetonitrile.

The reaction of reaction of the compound of Formula XII or a salt thereof with a compound of Formula XIII or a salt thereof is advantageously carried out at a temperature of about 25°C to reflux temperature; preferably at about reflux temperature.

In another embodiment, the present invention provides a process for purification of idelalisib, comprising:

a) providing a solution of idelalisib in one or more organic solvents,
b) adding an organic acid to the step a) solution,
c) isolating the idelalisib organic acid salt,
d) optionally drying the idelalisib organic acid salt,
e) neutralizing the idelalisib organic acid salt in a water and water immiscible organic solvent using a suitable base, and
f) isolating the idelalisib from the water immiscible organic solvent.

The one or more organic solvents for providing a solution of idelalisib include, but are not limited to alcohols, ketones, esters, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, butanol and the like; ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; esters include, but are not limited to ethylacetate, isopropyl acetate, butyl acetate and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like mixtures thereof; preferably methanol, methyl isobutyl ketone or acetonitrile and mixture thereof; more preferably methanol.

The suitable temperature for providing a solution of idelalisib may be carried out at a temperature of about 25°C to reflux temperature; preferably at about 25°C to about 45°C.

The step b) of aforementioned process involves adding an organic acid to the solution of idelalisib of step a). The suitable organic acid includes, but is not limited to trifluoro acetic acid, methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, 4-bromo benzenesulfonic acid, p-toluenesulfonic acid, oxalic acid, phosphoric acid, tartaric acid, dibenzoyl tartaric acid, maleic acid, mandelic acid, malonic acid, succinic acid, camphorsulfonic acid and the like. The organic acid may be added at a temperature of about 25°C to reflux temperature; preferably trifluoro acetic acid, camphorsulfonic acid, tartaric acid or maleic acid; more preferably trifluoro acetic acid or camphorsulfonic acid.

After completion of salt formation reaction, the idelalisib organic acid salt can be isolated by any conventional techniques known in the art, for example filtration. Typically, if stirring is involved, the temperature during stirring can range from about 25°C to about

35°C and the resultant product may optionally be further dried. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven and the like. The drying can be carried out at a temperature ranging from about 40°C to about 60°C.

The organic acid salt of idelalisib recovered by the purification process described as above is trifluoroacetate salt of idelalisib. Preferably the trifluoroacetate salt of idelalisib is isolated as a crystalline form.

The step of neutralizing the idelalisib organic acid salt, preferably trifluoroacetate salt involves treating the idelalisib organic acid salt with a suitable base such as sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, ammonium hydroxide and the like and mixture thereof; preferably sodium bicarbonate, in a water and water immiscible organic solvent. The water immiscible organic solvent include, but are not limited to ethyl acetate, isopropyl acetate, butyl acetate, methylene chloride, ethylene chloride, chloroform, toluene, xylene and the like and mixtures thereof; preferably a mixture of methylene chloride and water. The neutralization step may be carried out at a temperature of about 0°C to 50°C; preferably at about 10°C to about 25°C.

Pure Idelalisib may be isolated from the reaction mass by methods known in the art, for instance, the product containing organic layer may be separated followed by concentrating the organic layer under vacuum to obtain idelalisib.

In another embodiment, the present invention provides a process for preparation of amorphous Form of idelalisib, comprising:

a) providing a solution or suspension of idelalisib organic acid salt in a water and water immiscible organic solvent,
b) neutralizing the step a) solution with a suitable base,
c) concentrating the water immiscible organic solvent to obtain a residue,
d) dissolving the residue in one or more organic solvents,
e) optionally, concentrating the step c) solution,
f) adding a suitable anti-solvent to the step d) or step e) (or) vice-versa, and
g) isolating the idelalisib amorphous form.

Any form of idelalisib organic acid salt or a solution of idelalisib organic acid salt obtained from previous processing steps can be used as starting material in the process of making the amorphous idelalisib of the present invention.

The idelalisib organic acid salt used to prepare idelalisib amorphous form is any organic acid salt of idelalisib; preferably trifluoroacetate salt of idelalisib.

The step of providing a solution of idelalisib organic acid salt, preferably trifluoroacetate salt in water and water immiscible organic solvent is carried out at a temperature of about 25°C to reflux temperature; preferably at about 25°C to about 45°C.

The water immiscible organic solvents of step a) include, but are not limited to esters, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. The esters include, but are not limited to ethylacetate, isopropyl acetate, butyl acetate and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like and mixtures thereof; preferably methylene chloride.

The suitable base used herein for step b) include, but are not limited to sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, ammonia, ammonium hydroxide, triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine and the like and mixtures thereof; preferably sodium bicarbonate.

Then the water immiscible organic layer may be separated and followed by concentrating the water immiscible organic layer under vacuum at a temperature of about 25°C to about 50°C to obtain idelalisib as a residue.

The residue so obtained is dissolved in one or more organic solvents to obtain a solution at a suitable temperature. Typically, the solution is heated at a temperature of at least about 30°C to about reflux. Optionally, the solution obtained above may be filtered to remove any insoluble particles. The insoluble particles may be removed suitably by filtration, centrifugation, decantation, or any other suitable techniques.

The one or more organic solvents used herein for step d) include, but are not limited to diols, ketones, sulfoxides, esters, nitriles and the like and mixtures thereof. The diols include, but are not limited to ethylene glycol, propylene glycol, 2-methyl-1,2-propane-diol, 1,2-butanediol, 2,3-butanediol, 1,4-butanediol, 1,5-pentanediol, 1,6-hexanediol, 1,7-heptandiol and the like; ketones include, but are not limited to acetone, methylisobutylketone, methylethylketone and the like; sulfoxides include, but are not limited to dimethyl sulfoxide, diethyl sulfoxide and the like; esters include, but are not limited to methyl acetate, ethyl acetate, isopropyl acetate and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like and mixture thereof; preferably acetone, 1,2-butanediol, 2,3-butanediol, propylene glycol or diethyl sulfoxide and mixture thereof; more preferably acetone.

Optionally, the reaction solution may be concentrated by removal of the solvent from the solution by evaporation prior to precipitating the product. Solvent concentration can be achieved by a distillation, rotational drying (such as with the Buchi Rotavapor), fluid bed

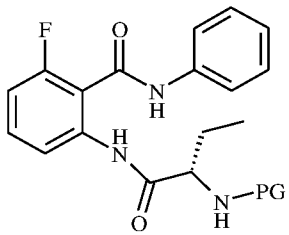
drying, flash drying, spin flash drying, agitated thin-film drying and the like. Preferably, the solvent may be evaporated partially by distillation under vacuum at a temperature of about 25°C to about 90°C; preferably at about 45°C to about 60°C.

The step f) of aforementioned process involves precipitation of amorphous form of idelalisib by either addition of suitable antisolvent to the idelalisib solution obtained as above, (or) addition of idelalisib solution obtained as above into a suitable antisolvent at a temperature of less than about 25°C, preferably, less than about 15°C. The suitable antisolvent include, but are not limited to water, ethers, aliphatic hydrocarbons, alicyclic hydrocarbons and the like and mixtures thereof. The ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; aliphatic hydrocarbons include, but are not limited to hexane, heptane, propane and the like; alicyclic hydrocarbons include, but are not limited to cyclopropane, cyclobutane, cyclopentane, cyclohexane, methyl cyclohexane, cycloheptane, cyclooctane and the like; water and mixture thereof; preferably water.

The resultant amorphous Form of idelalisib can be recovered by any conventional techniques known in the art, for example filtration. Typically, if stirring is involved, the temperature during stirring can range from about -10°C to about 10°C, preferably at about -5°C to 5°C. The amorphous Form of idelalisib obtained by the above process may be dried in, for example, Vacuum Tray Dryer, Rotocon Vacuum Dryer, Vacuum Paddle Dryer or pilot plant Rota vapor.

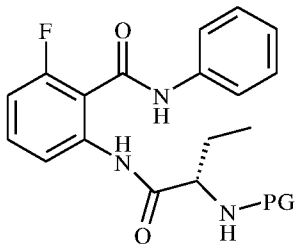
Amorphous idelalisib prepared by the process described as above having chemical purity of at least about 99%, as measured by HPLC, preferably at least about 99.5%, as measured by HPLC; and contains less than 0.05% of des fluoro impurity of Formula C and dimer impurity of Formula D, as measured by HPLC; preferably less than 0.01% of desfluoro impurity of Formula C and dimer impurity of Formula D, as measured by HPLC.

In another embodiment, the present invention provides a compound of Formula VI, wherein 'PG' represents a suitable amine protecting group.



Formula VI

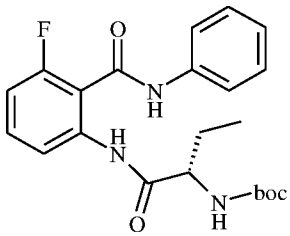
In another embodiment, the present invention provides a compound of Formula VI,



Formula VI

wherein the "PG" is selected from the group comprising carbobenzyloxy (Cbz), p-methoxybenzyl carbonyl, tert-butyloxycarbonyl (boc), 9-fluorenylmethyloxycarbonyl (FMOC), acetyl, pivaloyl, benzoyl (Bz), benzyl (Bn), p-methoxybenzyl (PMB), p-methoxybenzoyl, 3,4-dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP), p-nitro benzoyl (PNB), p-nitro benzyl, p-phenyl benzyl (PPB), p-phenyl benzoyl, trimethylsilyl (TMS), triethylsilyl (TES), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS), succinimide, tosyl (Ts), and other sulfonamides such as Nosyl.

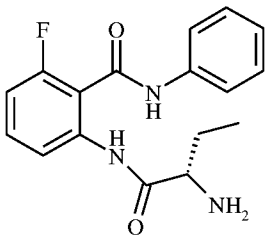
In another embodiment, the present invention provides a compound of Formula VIa.



Formula VIa

In another embodiment, the present invention provides crystalline compound of Formula VIa characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 6.

In another embodiment, the present invention provides a compound of Formula VII or a salt thereof.

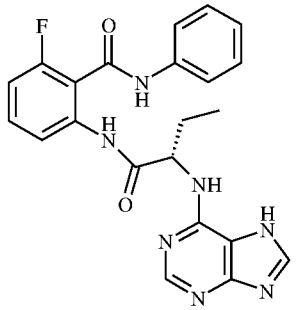


Formula VII

In another embodiment, the present invention provides crystalline compound of Formula VII.

In another embodiment, the present invention provides crystalline compound of Formula VII characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 7.

In another embodiment, the present invention provides a compound of Formula IX or a salt thereof.



Formula IX

In another embodiment, the present invention provides crystalline compound of Formula IX.

In another embodiment, the present invention provides crystalline compound of Formula IX characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 1.

In another embodiment, the present invention provides trifluoroacetate salt of compound of Formula IX.

In another embodiment, the present invention provides crystalline trifluoroacetate salt of compound of Formula IX.

In another embodiment, the present invention provides crystalline trifluoroacetate salt of Formula IX characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 2.

In another embodiment, the present invention provides idelalisib trifluoroacetate salt.

In another embodiment, the present invention provides crystalline idelalisib trifluoroacetate salt.

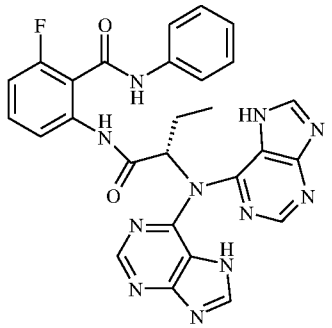
In another embodiment, the present invention provides crystalline idelalisib trifluoroacetate salt characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 3.

In another embodiment, the present invention provides crystalline idelalisib trifluoroacetate salt characterized by a differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure 4.

In another embodiment, the present invention provides crystalline idelalisib trifluoroacetate salt characterized by a thermo gravimetric analysis (TGA) substantially in accordance with Figure 5.

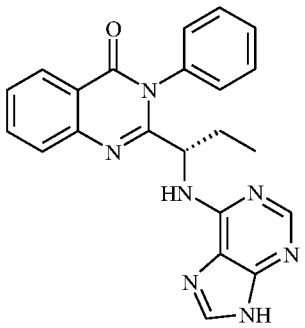
In another embodiment, the present invention provides crystalline idelalisib trifluoroacetate salt characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 3, a differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure 4 and/or a thermo gravimetric analysis (TGA) substantially in accordance with Figure 5.

In another embodiment, the present invention provides a compound of Formula IX substantially free of dimer impurity of Formula B.



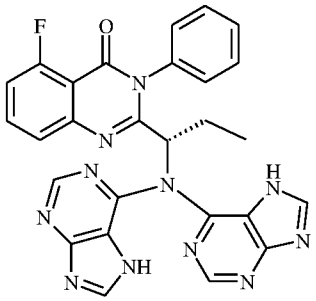
Formula B

In another embodiment, the present invention provides idelalisib of Formula I substantially free of desfluoro impurity of Formula C.



Formula C

In another embodiment, the present invention provides idelalisib of Formula I substantially free of dimer impurity of Formula D.



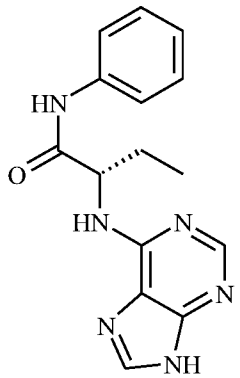
Formula D

In another embodiment, the present invention provides a compound of Formula B.

In another embodiment, the present invention provides desfluoro idelalisib of Formula C.

In another embodiment, the present invention provides a compound of Formula D.

In another embodiment, the present invention provides a compound of Formula XII or a salt thereof.



Formula XII

Idelalisib prepared by the process described as above having chemical purity of at least about 99%, as measured by HPLC, preferably at least about 99.5%, as measured by HPLC; and substantially free of des-fluoro impurity of Formula C and dimer impurity of Formula D; wherein the word substantially free refers to compound of Formula C or Formula D in Idelalisib are less than 0.1% as measured by HPLC; preferably less than 0.05% as measured by HPLC and more preferably less than 0.02% as measured by HPLC.

The present invention provides a idelalisib or a pharmaceutically acceptable salt thereof obtained by the process described herein, having chemical purity of at least about 97%, as measured by HPLC, preferably at least about 98% as measured by HPLC, and more preferably at least about 99.5%, as measured by HPLC.

The present invention provides a idelalisib or a pharmaceutically acceptable salt thereof obtained by the process described herein, having chiral purity of at least about 99%, as measured by HPLC, preferably at least about 99.5% as measured by HPLC, and more preferably at least about 99.9%, as measured by HPLC.

In another embodiment, the present invention provides a pharmaceutical composition, comprising idelalisib or a pharmaceutically acceptable salt thereof prepared by the processes of the present invention and at least one pharmaceutically acceptable excipient. Such pharmaceutical composition may be administered to a mammalian patient in any dosage form, e.g., solid, liquid, powder, injectable solution, etc.

EXAMPLES

The following non limiting examples illustrate specific embodiments of the present invention. They are not intended to be limiting the scope of the present invention in any way.

EXAMPLE-1:

Preparation of 2-fluoro-6-nitro-phenylbenzamide of Formula III

Methylene chloride (600 mL), 2-fluoro-5-nitro benzoic acid (100 g) and dimethyl formamide (5 mL) were charged in a reaction flask at 25-35°C. To the reaction mass oxalyl chloride (102.8 mL dissolved in 410 mL methylene chloride) was added at 25-35°C and stirred for 2-3 hrs at same temperature. After completion of the reaction, the reaction mass was distilled completely under vacuum at less than 35°C and the resultant residue was dissolved in 1,4-dioxane (80 mL). In another reaction flask 1,4-dioxane (250 mL), aniline (50.3 g) and sodium bicarbonate (90 g) were charged at 25-35°C and allowed to cool to 0-5°C. To the reaction mass, the above 1,4-dioxane solution was added at 0-5°C and the reaction mass was heated to 25-35°C and stirred for 1 hr at same temperature. After completion of the reaction, the reaction mass was quenched in to water (1.5 lit) at 25-35°C and the solid obtained was filtered, washed with water (500 mL). To the obtained wet solid diisopropylether (600 mL) was charged and heated to reflux and stirred for 2 hrs at same temperature. Reaction mass was allowed to cool to 25-35°C and the precipitated solid was filtered and washed with diisopropylether and dried at 50-55°C under vacuum to get the title compound. Yield: 120 g; HPLC Purity: 99%; PXRD: Fig. 8; DSC: endothermic peak at 167.86°C.

EXAMPLE-2:

Preparation of 2-fluoro-6-amino-phenylbenzamide of Formula IV

2-fluoro-6-nitro-phenylbenzamide (100 g), Zinc (140 g) methanol (500 mL) and methylene chloride (500 mL) were charged in a reaction flask at 25-35°C. To the reaction mass ammonium formate solution (170 g dissolved in 300 mL water) was added at 25-35°C and stirred for 2 hrs at same temperature. The reaction mass was filtered and concentrated under vacuum at below 35°C to obtain a residue. To the residue, water (1 lit) was added at 25-35°C and stirred for 3 hrs at same temperature. Filtered the solid and the wet product was dissolved in toluene (500 mL) at reflux temperature. Reaction mass was allowed to cool to 25-35°C and stirred for 3 hrs at same temperature. Precipitated solid was filtered and washed with heptane and dried at 50-55°C under vacuum to get the title compound. Yield: 60 g; HPLC Purity: 99%; PXRD: Fig. 9; DSC: endothermic peak at 112.56°C.

EXAMPLE-3:

Preparation of compound of Formula VIa

Toluene (500 mL) was charged in a reaction flask and N-boc-L-2-amino butyric acid (50 g) and carbonyldiimidazole (140.8 g) were added at 0-5°C and stirred for 1 hr at same temperature. To the reaction mass, 2-fluoro-6-amino-phenylbenzamide (100 g) was added at 0-5°C, heated to 25-35°C and stirred for 12 hrs at same temperature. After completion of the reaction, precipitated solid was filtered and washed with toluene (100 mL) and dried at 60-65°C under vacuum. Then the dried solid was dissolved in acetonitrile (300 mL) at 75-80°C and stirred for 2 hrs at same temperature. Reaction mass was allowed to cool to 25-35°C and stirred for 3 hrs at same temperature. Precipitated solid was filtered and washed with acetonitrile (100 mL) and dried at 60-65°C under vacuum to get the title compound. Yield: 120 g; HPLC Purity: 99.1%; PXRD: Fig. 6; DSC: endothermic peak at 167.48°C;^{1}HNMR(DMSO-d6):δ0.84-0.89 (t,3H),1.3-1.74 (m,9H),1.76 (m,1H),1.78 (t,1H),3.82-3.93 (m,1H),7.02-7.08 (m,2H),7.11-7.15 (m,3H),7.22 (m,1H),7.3-7.9 (m,2H),8.0 (d,1H),10.4 (s,1H),10.61 (s,1H); MS (ESI)[M+H]:-415.47.

EXAMPLE-4:

Preparation of compound of Formula VII

Formula VIa (100 g), methylene chloride (200 mL) and trifluoroacetic acid (200 mL) were charged in a reaction flask at 25-35°C and stirred for 4 hrs at same temperature. After completion of the reaction, reaction mass pH was adjusted to 7-8 with sodium bicarbonate solution at 25-35°C and stirred for 2 hrs a same temperature. Precipitated solid was filtered and washed with water (300 mL) and dried to obtain compound of Formula VII. Yield: 82.0g; HPLC Purity: 98%; PXRD: Fig. 7; DSC: endothermic peak at 89.5°C and 195.46°C; ^{1}HNMR (DMSO-d6): δ 0.84-0.95 (m,3H),1.7-1.79 (m,2H),3.94-3.98 (t,1H),7.08-7.12 (t,1H),7.19-7.21 (t,1H),7.24-7.36 (q,2H),7.46-7.47 (d,2H),7.49-7.6 (m,2H),7.7-8.13 (dd,3H),10.63 (s,1H); MS (ESI)[M+H]:315.

EXAMPLE-5:

Preparation of compound of Formula IX Trifluoroacetate salt.

Compound of Formula VII (82g), water (500 mL), 6-chloropurine (39 g) and triethylamine (36.5 g) were charged in a reaction flask at 25-35°C. Reaction mass was heated to 90-105°C and stirred for 24 hrs at same temperature. After completion of the reaction, the reaction mixture was allowed to cool to 25-35°C and stirred for 3 hrs at same temperature. Precipitated solid was filtered and washed with water (100mL) and dried at 55-60°C under vacuum to obtain a solid (65 gms). To the obtained solid, acetonitrile (400 mL) and trifluoroacetic acid (240 mL) was charged at 25-35°C and stirred for 3 hrs at same temperature. Precipitated solid compound was filtered and washed with acetonitrile (50mL) to obtain trifluoroacetate salt of Formula IX. Yield: 55g; HPLC Purity: 99.1%; PXRD: Fig. 2; DSC: endothermic peak at 141.36°C and 167°C; ^{1}HNMR(DMSO-d6): δ 0.92-0.97 (m,3H),1.95-2.00 (m,2H),4.7 (s,1H),7.06-7.09 (m,2H),7.11-7.12 (m,2H),7.43-7.50 (m,3H),7.51-7.60 (m,2H),7.9-8.1 (s,2H),10.11 (s,1H),10.47 (s,1H)12.22-12.96 (Broad,1H); MS (ESI)[M+H]:434.

EXAMPLE-6:

Preparation of compound of Formula IX

Trifluoroacetate salt of Formula IX (55gms) and water (100mL) were charged in a reaction flask at 25-35°C and reaction mass pH was adjusted to 7-8 with sodium bicarbonate solution at 25-35°C and stirred for 2 hrs at same temperature. Precipitated solid was filtered and washed with water (300 mL) and dried at 40-45°C under vacuum. Then the dried solid was dissolved in tetrahydrofuran (200 mL) at 60-65°C and stirred for 2 hrs at same temperature. Reaction mass was allowed to cool to 25-35°C and stirred for 2 hrs at same temperature. Precipitated solid was filtered and washed with tetrahydrofuran (50 mL) and dried at 40-45°C under vacuum to get the title compound. Yield: 50 g; HPLC Purity: 99%; PXRD: Fig. 1; DSC: endothermic peak at 265.77°C.

EXAMPLE-7:

Preparation of Idelalisib Trifluoroacetate salt

Formula IX (50 g), acetonitrile (250 mL), hexamethyldisilazane (55.8 g) and iodine (20.5 g) were charged in a reaction flask at 25-35°C and stirred for 2 hrs at same temperature. Reaction mass was heated to 75-80°C and stirred for 12 hrs at same temperature. After completion of the reaction, the reaction mass was distilled completely under vacuum at less than 45°C and the obtained residue was dissolved in methylene chloride (5.5 lit) at 25-35°C and the solution was washed with sodium sulphite solution and the organic layer and

aqueous layers were separated. Then the organic layer was passed through silycycleM60 column and the column was eluted with a mixture of methanol and methylene chloride. Then the product containing solvent fractions was distilled under vacuum at below 40°C to obtain a residue. The obtained residue was dissolved in methanol (100 mL) at 25-35°C and trifluoroacetic acid (50 mL) was added and stirred for 3 hrs at same temperature. Precipitated solid compound was filtered and washed with methanol (25 mL) and dried to obtain idelalisib trifluoroacetate salt. Yield: 40g; HPLC Purity: 99.4%; PXRD: Fig. 3; DSC: Fig. 4; TGA: Fig. 5; 1HNMR(DMSO-d6): δ 0.75 (s,3H),1.93 (s,2H),4.7 (s,1H),7.3 (d,1H),7.45-7.78 (m,6H),7.8 (t,2H), 8.1 (s,2H),12.96 (s,1H); MS (ESI)[M+H]:414.

EXAMPLE-8:

Preparation of Idelalisib

Idelalisib trifluoroacetate salt (40g) was dissolved in a mixture of methylene chloride (200mL) and water (200mL) and pH was adjusted to 7-8 with sodium bicarbonate solution at 15-20°C. Then the organic and aqueous layers were separated and to the organic layer methanol (200mL) was added and distilled completely under vacuum at below 45°C to obtain a residue. The obtained residue was dissolved in acetone (400 mL) and heated to 50-55°C. The reaction mass was concentrated up to 125 mL solvent remains in the flask at below 50-55°C. The reaction solution was added to precooled water (1250 mL) at 5-10°C and stirred for 30 min at same temperature. Precipitated solid was filtered and washed with water (500 mL) and dried at 60-65°C under vacuum for 12 hrs to obtain idelalisib amorphous form. Yield: 30 g; HPLC Purity: 99.8%; des fluoro impurity of Formula C by HPLC: Not detected; dimer impurity of Formula D by HPLC: Not detected.

EXAMPLE-9:

Preparation of compound of Formula Xa

N-boc-L-2-amino butyric acid (100 g), toluene (500 mL), carbonyldiimidazole (159.6 g) and aniline (93 g) were charged in a reaction flask at 0-5°C and stirred for 1 hr at same temperature. Then the reaction mass was heated to 25-35°C and stirred for 12 hrs at same temperature. After completion of the reaction, precipitated solid was filtered and washed with toluene (100 mL) and dried at 60-65°C under vacuum to get the title compound. Yield: 120 g.

EXAMPLE-10:

Preparation of compound of Formula XI

Formula Xa (100 g), methylene chloride (200 mL) and trifluoroacetic acid (200 mL) were charged in a reaction flask at 25-35°C and stirred for 4 hrs at same temperature. After completion of the reaction, reaction mass pH was adjusted to 7-8 with sodium bicarbonate solution at 25-35°C and stirred for 2 hrs a same temperature. Precipitated solid was filtered and washed with water (300 mL) and dried to get the title compound. Yield: 60 g.

EXAMPLE-11:

Preparation of compound of Formula XII

Compound of Formula XI (60 g), acetonitrile (300 mL), 6-chloropurine (58.2 g), zinc chloride (146.8 g) and diisopropyl ethylamine (69.6 g) were charged in a reaction flask at 25-35°C. Reaction mass was heated to 70-80°C and stirred for 4 hrs at same temperature. After completion of the reaction, the reaction mixture was allowed to cool to 25-35°C. Reaction mass was quenched in to water (2.5 lit) at 25-35°C and stirred for 3 hrs at same temperature. Precipitated solid was filtered and washed with water (1.5 L) and dried at 55-60°C under vacuum to get the title compound. Yield: 50 g.

EXAMPLE-12:

Preparation of Idelalisib camphor sulfonate salt.

Compound of Formula XII (50 g), acetonitrile (250 mL) and 2-amino-6-fluoro-benzoic acid (28.8 g) were charged in a reaction flask at 25-35°C. To the reaction mass hexamethyldisilazane (5.4 g) and zinc chloride (68.9 g) were charged at 25-35°C and stirred for 2 hrs at same temperature. Reaction mass was heated to 70-80°C and stirred for 4 hrs at same temperature. After completion of the reaction, the reaction mass was allowed to cool to 25-35°C and quenched in to water (1.25 lit). Precipitated solid was filtered and the obtained solid was dissolved in a mixture of methylene chloride (3 lit) and trifluoro acetic acid (50 mL) at 25-35°C. To the reaction mass water (250 lit) was added at 25-35°C and pH was adjusted to 7-7.5 with sodium bicarbonate solution at same temperature. Then the organic and aqueous layers were separated distilled completely under vacuum at below 40°C to obtain a residue. The obtained residue was dissolved in acetonitrile (100 mL) at 25-35°C and R (-)-camphor sulfonic acid (43 g) was added and stirred for 3 hrs at same temperature. Precipitated solid compound was filtered and washed with acetonitrile (25 mL) and dried to obtain idelalisib camphor sulfonate salt. Yield: 40g.

EXAMPLE-13:

Preparation of Idelalisib.

Idelalisib camphor sulfonate salt (30 g) was dissolved in a mixture of methylene chloride (450 mL) and water (150 mL) and pH was adjusted to 7-7.5 with sodium bicarbonate

solution at 25-35°C. Then the organic and aqueous layers were separated and to the organic layer methylene chloride (450 mL) was added and distilled completely under vacuum at below 40°C to obtain a residue. The obtained residue was dissolved in acetone (2.4 lit) and heated to 50-55°C. The reaction mass was concentrated up to 90 mL solvent remains in the flask at below 50-55°C. The reaction solution was added to precooled water (750 mL) at 5-10°C. Reaction mass was heated to 25-35°C and stirred for 14 hrs at same temperature. Precipitated solid was filtered and washed with water (500 mL) and dried at 50-60°C under vacuum for 12 hrs to obtain idelalisib amorphous form. Yield: 15 g.

EXAMPLE-14:

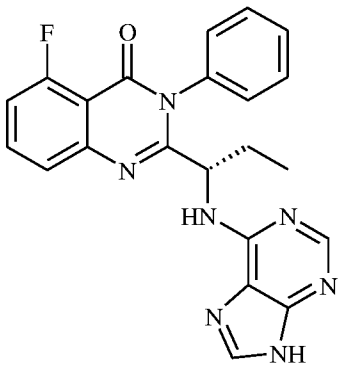
Characterization of compound of Formula C and Formula D are as follows:

Formula C MS (ESI)[M+H]: 397 and Formula D MS (ESI)[M+H]: 535

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be constructed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of the specification appended hereto.

WE CLAIM:

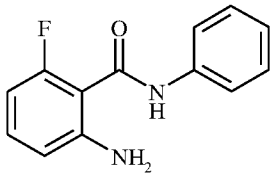
Claim 1: A process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof:



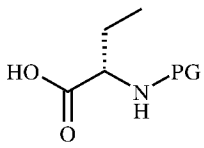
Formula I

comprising:

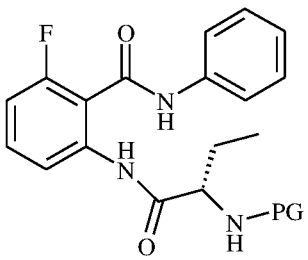
a) reacting a compound of Formula IV or a salt thereof with aminobutyric acid or a reactive derivative of Formula V to obtain a compound of Formula VI, wherein 'PG' represents a suitable amine protecting group,



Formula IV

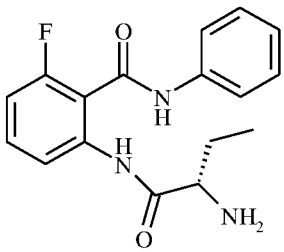


Formula V



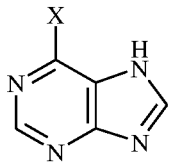
Formula VI

b) deprotecting the compound of Formula VI in presence of a suitable deprotecting agent to obtain a compound of Formula VII or a salt thereof,

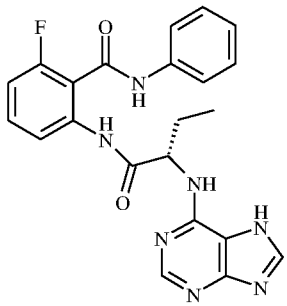


Formula VII

c) reacting the compound of Formula VII or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula IX or a salt thereof, wherein 'X' represents a suitable leaving group, and



Formula VIII



Formula IX

d) cyclizing the compound of Formula IX or a salt thereof to obtain the compound of Formula I.

Claim 2: The process of claim 1, wherein the suitable amine protecting group is selected from the group comprising carbobenzyloxy, p-methoxybenzyl carbonyl, tert-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, acetyl, pivaloyl, benzoyl, benzyl, p-methoxybenzyl, p-methoxybenzoyl, 3,4-dimethoxybenzyl, p-methoxyphenyl, p-nitro benzoyl, p-nitro benzyl, p-phenyl benzyl, p-phenyl benzoyl, trimethylsilyl, triethylsilyl, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, triisopropylsilyl, succinimide, tosyl or Nosyl.

Claim 3: The process of claim 2, wherein the suitable amine protecting group is tert-butyloxycarbonyl.

Claim 4: The process of claim 1, wherein the step a) reaction is carried out in presence of a suitable coupling agent and in a suitable organic solvent.

Claim 5: The process of claim 4, wherein the suitable coupling agent is selected from the group comprising 2-chloro-4,6-dimethoxy-1,3,5-triazine, carbonyldiimidazole, diisopropylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide, dicyclohexyl carbodiimide, propanephosphonic acid cyclic anhydride, benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate, bromo-tripyrrolidino- phosphonium hexafluorophosphate, benzotriazol-1-yloxy-tris (dimethylamino)-phosphonium hexafluorophosphate, Propylphosphonic anhydride, 2-(7-Aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate), (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbeniumhexa fluoro phosphate, N,N,N′,N′-Tetramethyl-O-(1H-benzotriazol-1-yl)uroniumhexafluoro phosphat, O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluoro phosphate, 2-(1H-Benzotriazol-1-yl)- N,N,N',N'-tetramethylaminium tetrafluoroborate and mixture thereof.

Claim 6: The process of claim 4, wherein the suitable organic solvent is selected from the group comprising alcohols selected from methanol, ethanol, isopropanol, n-propanol, or t-butanol; amides selected from dimethyl formamide or dimethyl acetamide;

nitriles selected from acetonitrile, propionitrile or benzonitrile; ethers selected from tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether or 1,4-dioxane; halogenated hydrocarbons selected from methylene chloride, ethylene chloride, or chloroform; aromatic hydrocarbons selected from toluene, xylene and mixtures thereof.

Claim 7: The process of claim 4, wherein the suitable coupling agent is carbonyldiimidazole and the suitable organic solvent is toluene.

Claim 8: The process of claim 1, wherein the step a) is carried out at a temperature of about 20°C to about 45°C.

Claim 9: The process of claim 1, wherein the suitable deprotecting agent is selected from the group comprising metal catalyzed deprotecting agents selected from palladium on carbon, palladium hydroxide in presence of a hydrogen source selected from hydrogen gas, ammonium formate or ammonium acetate; base catalyzed deprotecting agents selected from potassium carbonate, sodium carbonate, diethyl amine, diisopropyl amine, piperidine, N-methyl morpholine or 1,8-Diazabicyclo[5.4.0]undec-7-ene; acid catalyzed deprotecting agents selected from hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoro acetic acid or trichloro acetic acid or methane sulfonic acid and mixtures thereof.

Claim 10: The process of claim 9, wherein the suitable deprotecting agent is trifluoro acetic acid.

Claim 11: The process of claim 1, wherein the step b) is carried out at a temperature of about 0°C to reflux temperature.

Claim 12: The process of claim 1, wherein the suitable leaving group is selected from the group comprising chloro, bromo, iodo or fluoro.

Claim 13: The process of claim 12, wherein the suitable leaving group is chloro.

Claim 14: The process of claim 1, wherein the step c) reaction is carried out in presence of a suitable base and in a suitable solvent.

Claim 15: The process of claim 14, wherein the suitable base is selected from the group comprising alkali metal hydroxides selected from lithium hydroxide, sodium hydroxide or potassium hydroxide; alkali metal alkoxides selected from sodium methoxide, sodium ethoxide, sodium tert-butoxide or potassium tert-butoxide; alkali metal carbonates selected from sodium carbonate, potassium carbonate or cesium carbonate; alkali metal bicarbonates selected from sodium bicarbonate or potassium bicarbonate; organic bases selected from triethylamine, isopropyl ethylamine, diisopropyl amine,

diisopropyl ethylamine, N-methyl morpholine, piperidine or pyridine; 1,1,3,3-tetramethylguanidine and mixtures thereof.

Claim 16: The process of claim 14, wherein the suitable solvent is selected from the group comprising alcohols selected from methanol, ethanol, isopropanol or butanol; amides selected from dimethyl formamide, dimethyl acetamide or N-methyl pyrrolidinone; sulfoxides selected from dimethylsulfoxide or diethyl sulfoxide; ketones selected from acetone, methyl isobutyl ketone or methyl ethyl ketone; nitriles selected from acetonitrile or propionitrile; ethers selected from tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether or 1,4-dioxane; halogenated hydrocarbons selected from methylene chloride, ethylene chloride or chloroform; aromatic hydrocarbons selected from toluene or xylene; water and mixtures thereof.

Claim 17: The process of claim 14, wherein the suitable base is triethylamine and the suitable solvent is water.

Claim 18: The process of claim 1, wherein the step c) is carried out at a temperature of about 25°C to reflux temperature.

Claim 19: The process of claim 1, wherein the cyclization step is carried out with a suitable dehydrating agent, optionally in presence of a suitable catalyst in a suitable organic solvent.

Claim 20: The process of claim 19, wherein the dehydrating agent is selected from the group comprising hexamethyldisilazane, bis(trimethylsilyl)acetamide, bis-trimethylsilylurea, trimethylsilylphosphate, phosphorous oxychloride, thionyl chloride, cyanuric chloride, aluminium chloride, aluminum bromide, zinc chloride, zinc bromide, boron trichloride, iron chloride, iron bromide, tinchloride, titanium chloride, sulfuric acid, phosphorous pentoxide, trifluoroacetic anhydride, acetic anhydride, dicyclohexylcarbodiimide, p-toluene sulfonic acid, methane sulfonic acid or calcium hydride.

Claim 21: The process of claim 19, wherein the suitable organic solvent is selected from the group comprising ketones selected from acetone, methyl isobutyl ketone or methyl ethyl ketone; esters selected from ethylacetate, isopropyl acetate or butyl acetate; amides selected from dimethyl formamide, dimethyl acetamide or N-methyl pyrrolidinone; sulfoxides selected from dimethylsulfoxide or diethyl sulfoxide; nitriles selected from acetonitrile or propionitrile; ethers selected from tetrahydrofuran, 2-methyltetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether or 1,4-dioxane; halogenated hydrocarbons selected from methylene chloride, ethylene chloride or chloroform; aromatic hydrocarbons selected from toluene or xylene; and mixtures thereof.

Claim 22: The process of claim 19, wherein the suitable dehydrating agent is hexamethyldisilazane; suitable catalyst is Iodine and the suitable organic solvent is acetonitrile.

Claim 24: The process of claim 1, wherein the step d) is carried out at a temperature of about 25°C to reflux temperature.

Claim 25: The process of claim 1, wherein the step c) further comprises the steps of:

a) providing a solution of compound of Formula IX in one or more organic solvents,
b) adding an organic acid to the step a) solution,
c) isolating the compound of Formula IX as an organic acid salt,
d) neutralizing the organic acid salt of compound of Formula IX with a suitable base, and
e) isolating the compound of Formula IX.

Claim 26: The process of claim 25, wherein the organic solvent is selected from the group comprising alcohols selected from methanol, ethanol, isopropanol or butanol; ketones selected from acetone, methyl isobutyl ketone or methyl ethyl ketone; esters selected from ethylacetate, isopropyl acetate or butyl acetate; nitriles selected from acetonitrile or propionitrile; ethers selected from tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether or 1,4-dioxane; halogenated hydrocarbons selected from methylene chloride, ethylene chloride or chloroform; aromatic hydrocarbons selected from limited to toluene or xylene and mixtures thereof.

Claim 27: The process of claim 26, wherein the organic solvent is acetonitrile.

Claim 28: The process of claim 25, wherein the step a) is carried out at a temperature of about 25°C to about 45°C.

Claim 29: The process of claim 25, wherein the organic acid is selected from the group comprising trifluoro acetic acid, methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, 4-bromo benzenesulfonic acid, p-toluenesulfonic acid, oxalic acid, phosphoric acid, tartaric acid, dibenzoyl tartaric acid, maleic acid, mandelic acid, malonic acid, succinic acid or camphorsulfonic acid.

Claim 30: The process of claim 29, wherein the organic acid is trifluoro acetic acid.

Claim 31: The process of claim 25, wherein the suitable base is selected from the group comprising sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, ammonium hydroxide and mixture thereof.

Claim 32: The process of claim 31, wherein the suitable base is sodium bicarbonate.

Claim 33: The process of claim 25, wherein the neutralization step is carried out at a temperature of about 0°C to about 50°C.

Claim 34: A process for purification of idelalisib, comprising:

a) providing a solution of idelalisib in one or more organic solvents,
b) adding an organic acid to the step a) solution,
c) isolating the idelalisib organic acid salt,
d) optionally drying the idelalisib organic acid salt,
e) neutralizing the idelalisib organic acid salt in a water and water immiscible organic solvent using a suitable base, and
f) isolating the idelalisib.

Claim 35: The process of claim 34, wherein the organic solvent is selected from the group comprising alcohols selected from methanol, ethanol, isopropanol or butanol; ketones selected from acetone, methyl isobutyl ketone or methyl ethyl ketone; esters selected from ethyl acetate, isopropyl acetate or butyl acetate; nitriles selected from acetonitrile or propionitrile; ethers selected from tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether or 1,4-dioxane; halogenated hydrocarbons selected from methylene chloride, ethylene chloride or chloroform; aromatic hydrocarbons selected from toluene or xylene and mixtures thereof.

Claim 36: The process of claim 34, wherein the organic acid is selected from the group comprising trifluoro acetic acid, methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, 4-bromo benzenesulfonic acid, p-toluenesulfonic acid, phosphoric acid, tartaric acid, mandelic acid, malonic acid, succinic acid or camphorsulfonic acid.

Claim 37: The process of claim 34, wherein the organic solvent is methanol and the organic acid is trifluoro acetic acid or camphorsulfonic acid.

Claim 38: The process of claim 34, wherein the step a) is carried out at a temperature of about 25°C to about 45°C.

Claim 39: The process of claim 34, wherein the water immiscible organic solvent is selected from the group comprising ethyl acetate, isopropyl acetate, butyl acetate, methylene chloride, ethylene chloride, chloroform, toluene, xylene and mixtures thereof.

Claim 40: The process of claim 34, wherein the suitable base is selected from the group comprising sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, ammonium hydroxide and mixture thereof.

Claim 41: The process of claim 34, wherein the water immiscible organic solvent is methylene chloride and the suitable base is sodium bicarbonate.

Claim 42: The process of claim 34, wherein the step b) is carried out at a temperature of about 10°C to about 25°C.

Claim 43: A process for preparation of amorphous Form of idelalisib, comprising:

a) providing a solution or suspension of idelalisib organic acid salt in water and a water immiscible organic solvent,
b) neutralizing the step a) solution with a suitable base,
c) concentrating the water immiscible organic solvent to obtain a residue at a temperature of about 25°C to about 50°C,
d) dissolving the residue in one or more organic solvents,
e) optionally, concentrating the step c) solution at a temperature of 45°C to about 60°C,
f) adding a suitable anti-solvent to the step d) or step e) (or) vice-versa, and
g) isolating the idelalisib amorphous form.

Claim 44: The process of claim 43, wherein the organic acid salt of idelalisib is selected from the group comprising trifluoro acetic acid, methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, 4-bromo benzenesulfonic acid, p-toluenesulfonic acid, phosphoric acid, tartaric acid, mandelic acid, malonic acid, succinic acid or camphorsulfonic acid.

Claim 45: The process of claim 43, wherein the water immiscible organic solvent is selected from the group comprising esters selected from ethylacetate, isopropyl acetate or butyl acetate; halogenated hydrocarbons selected from methylene chloride, ethylene chloride or chloroform; aromatic hydrocarbons selected from toluene or xylene; and mixtures thereof.

Claim 46: The process of claim 43, wherein the organic acid salt of idelalisib is idelalisib trifluoro acetic acid salt or idelalisib camphorsulfonic acid salt and the water immiscible organic solvent is methylene chloride.

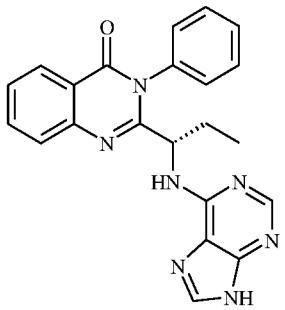
Claim 47: The process of claim 43, wherein the step a) is carried out at a temperature of about 25°C to about 45°C.

Claim 48: The process of claim 43, wherein the organic solvent is selected from the group comprising diols selected from ethylene glycol, propylene glycol, 2-methyl-1,2-propane-diol, 1,2-butanediol, 2,3-butanediol, 1,4-butanediol, 1,5-pentanediol, 1,6-hexanediol or 1,7-heptandiol; ketones selected from acetone, methylisobutylketone or methylethylketone; sulfoxides selected from dimethyl sulfoxide or diethyl sulfoxide; esters selected from methyl acetate, ethyl acetate or isopropyl acetate; nitriles selected from acetonitrile or propionitrile and mixture thereof.

Claim 49: The process of claim 43, wherein the suitable anti-solvent is selected from the group comprising ethers selected from tetrahydrofuran, dimethyl ether, diethyl ether, diisopropyl ether, methyl tertiary butyl ether or 1,4-dioxane; aliphatic hydrocarbons selected from hexane, heptane or propane; alicyclic hydrocarbons selected from cyclopropane, cyclobutane, cyclopentane, cyclohexane, methyl cyclohexane, cycloheptane or cyclooctane; water and mixture thereof.

Claim 50: The process of claim 43, wherein the organic solvent is acetone and the anti-solvent is water.

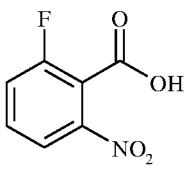
Claim 51: A process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof substantially free of desfluoro impurity of Formula C:



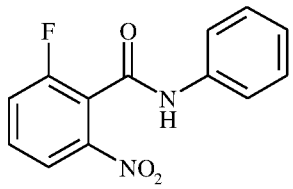
Formula C

comprising:

i) reacting 2-fluoro-6-nitrobenzoic acid or a reactive derivative of Formula II with aniline to obtain a compound of Formula III,

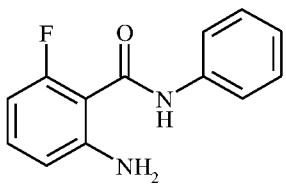


Formula II



Formula III

ii) reducing the compound of Formula III in presence of a suitable reducing agent and a suitable hydrogen source in a suitable solvent to obtain a compound of Formula IV or a salt thereof,



Formula IV

iii) purifying the compound of Formula IV with a suitable hydrocarbon solvent to obtain the compound of Formula IV substantially free of corresponding desfluoro impurity of Formula A, and

iv) converting the compound of Formula IV or a salt thereof into compound of Formula I.

Claim 52: The process of claim 51, wherein the compound of Formula II is used as its chloro derivative.

Claim 53: The process of claim 51, wherein the step i) is carried out in presence of a suitable base and in a suitable solvent.

Claim 54: The process of claim 53, wherein the suitable base is selected from the group comprising sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate, triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine and mixtures thereof.

Claim 55: The process of claim 53, wherein the suitable solvent is selected from the group comprising ethers selected from tetrahydrofuran, 2-methyl tetrahydrofuran, methyl tertiary butyl ether or 1,4-dioxane; halogenated hydrocarbons selected from methylene chloride, ethylene chloride or chloroform; aromatic hydrocarbons selected from toluene or xylene and mixture thereof.

Claim 56: The process of claim 53, wherein the suitable base is sodium bicarbonate and the suitable solvent is 1,4-dioxane.

Claim 57: The process of claim 51, wherein the step i) is carried out at a temperature of about 25°C to about 50°C.

Claim 58: The process of claim 51, wherein the suitable reducing agent is selected from the group comprising raney nickel, platinum oxide, sodium hydrosulfite, sodium dithionate, zinc, Iron powder or tin chloride and mixtures thereof.

Claim 59: The process of claim 51, wherein the suitable hydrogen source is selected from the group comprising hydrogen gas, ammonium acetate, ammonium formate, ammonium chloride and mixtures thereof.

Claim 60: The process of claim 51, wherein the suitable solvent is selected from the group comprising alcohols selected from methanol, ethanol, propanol or isopropanol; halogenated hydrocarbons selected from methylene chloride, ethylene chloride or

chloroform; aromatic hydrocarbons selected from toluene or xylene; water and mixtures thereof.

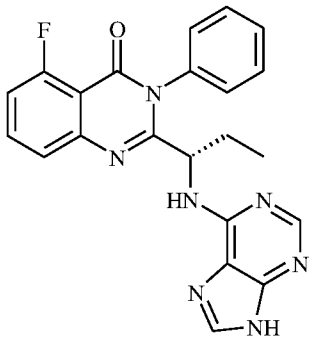
Claim 61: The process of claim 51, wherein the reducing agent is zinc, hydrogen source is ammonium formate and the suitable solvent is methylene chloride.

Claim 62: The process of claim 51, wherein the step ii) is carried out at a temperature of about 25°C to reflux temperature.

Claim 63: The process of claim 51, wherein the suitable hydrocarbon solvent is selected from the group comprising alcohols selected from methanol, ethanol, isopropanol, n-propanol or t-butanol; nitriles selected from acetonitrile, propionitrile or benzonitrile; esters selected from ethyl acetate, methyl acetate or isopropyl acetate; halogenated hydrocarbons selected from methylene chloride, ethylene chloride or chloroform; aromatic hydrocarbons selected from toluene or xylene and mixtures thereof.

Claim 64: The process of claim 63, wherein the suitable hydrocarbon solvent is toluene.

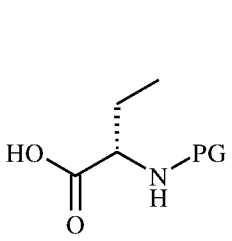
Claim 65: A process for the preparation of idelalisib of Formula I or a pharmaceutically acceptable salt thereof:



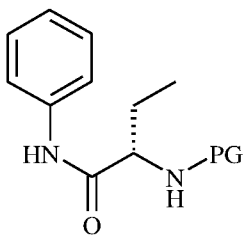
Formula I

comprising:

a1) reacting aminobutyric acid or a reactive derivative of Formula V with aniline to obtain a compound of Formula X, wherein 'PG' represents a suitable amine protecting group,

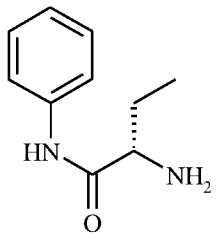


Formula V



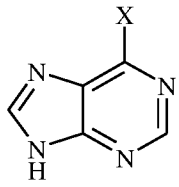
Formula X

b1) deprotecting the compound of Formula X in presence of a suitable deprotecting agent to obtain a compound of Formula XI or a salt thereof,

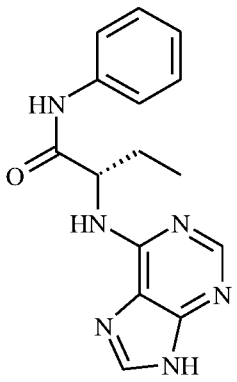


Formula XI

c1) reacting the compound of Formula XI or a salt thereof with a compound of Formula VIII or a salt thereof to obtain a compound of Formula XII or a salt thereof, wherein 'X' represents a suitable leaving group, and

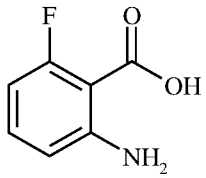


Formula VIII



Formula XII

d1) reacting the compound of Formula XII or a salt thereof with a compound of Formula XIII or a salt thereof to obtain the compound of Formula I.



Formula XIII

Claim 66: The process of claim 65, wherein the suitable amine protecting group selected from the group comprising carbobenzyloxy, p-methoxybenzyl carbonyl, tert-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, acetyl, pivaloyl, benzoyl, benzyl, p-methoxybenzyl, p-methoxybenzoyl, 3,4-dimethoxybenzyl, p-methoxyphenyl, p-nitro benzoyl, p-nitro benzyl, p-phenyl benzyl, p-phenyl benzoyl, trimethylsilyl, triethylsilyl, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, triisopropylsilyl, succinimide, tosyl or Nosyl.

Claim 67: The process of claim 65, wherein the suitable amine protecting group is tert-butyloxycarbonyl.

Claim 68: The process of claim 65, wherein the step a1) reaction is carried out in presence of a suitable coupling agent and in a suitable organic solvent.

Claim 69: The process of claim 65, wherein the suitable coupling agent is selected from the group comprising 2-chloro-4,6-dimethoxy-1,3,5-triazine, carbonyldiimidazole, diisopropylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide, dicyclohexyl carbodiimide, propanephosphonic acid cyclic anhydride, benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate, bromo- tripyrrolidino- phosphonium hexafluorophosphate, benzotriazol-1-yloxy-tris (dimethylamino)-phosphonium hexafluorophosphate, Propylphosphonic anhydride, 2-(7-Aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate), (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluoro phosphate, N,N,N′,N′-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluoro phosphate, O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluoro phosphate, 2-(1H-Benzotriazol-1-yl) -N,N,N',N'- tetramethylaminium tetrafluoroborate and mixture thereof.

Claim 70: The process of claim 65, wherein the suitable organic solvent is selected from the group comprising alcohols selected from methanol, ethanol, isopropanol, n-propanol or t-butanol; amides selected from dimethyl formamide or dimethyl acetamide; nitriles selected from acetonitrile, propionitrile or benzonitrile; ethers selected from tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether or 1,4-dioxane; halogenated hydrocarbons selected from methylene chloride, ethylene chloride or chloroform; aromatic hydrocarbons selected from toluene or xylene and mixtures thereof.

Claim 71: The process of claim 65, wherein the suitable coupling agent is carbonyldiimidazole and the suitable organic solvent is toluene.

Claim 72: The process of claim 65, wherein the step a1) is carried out at a temperature of about 20°C to about 45°C.

Claim 73: The process of claim 65, wherein the suitable deprotecting agent is selected from the group comprising metal catalyzed deprotecting agents selected from palladium on carbon, palladium hydroxide in presence of a hydrogen source selected from hydrogen gas, ammonium formate or ammonium acetate; base catalyzed deprotecting agents selected from potassium carbonate, sodium carbonate, diethyl amine, diisopropyl amine, piperidine, N-methyl morpholine or 1,8-Diazabicyclo[5.4.0]undec-7-ene; acid catalyzed deprotecting agents selected from hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoro acetic acid, trichloro acetic acid or methane sulfonic acid; and mixtures thereof.

Claim 74: The process of claim 73, wherein the suitable deprotecting agent is trifluoro acetic acid.

Claim 75: The process of claim 65, wherein the step b1) is carried out at a temperature of about 0°C to reflux temperature.

Claim 76: The process of claim 65, wherein the suitable leaving group selected from the group comprising chloro, bromo, iodo or fluoro.

Claim 77: The process of claim 76, wherein the suitable leaving group is chloro.

Claim 78: The process of claim 65, wherein the step c1) reaction is carried out in presence of a suitable base and in a suitable solvent.

Claim 79: The process of claim 78, wherein the suitable base is selected from the group comprising alkali metal hydroxides selected from lithium hydroxide, sodium hydroxide or potassium hydroxide; alkali metal alkoxides selected from sodium methoxide, sodium ethoxide, sodium tert-butoxide or potassium tert-butoxide; alkali metal carbonates selected from sodium carbonate, potassium carbonate or cesium carbonate; alkali metal bicarbonates selected from sodium bicarbonate or potassium bicarbonate; organic bases selected from triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine or pyridine; 1,1,3,3-tetramethylguanidine, and mixtures thereof.

Claim 80: The process of claim 78, wherein the suitable solvent is selected from the group comprising alcohols selected from methanol, ethanol, isopropanol or butanol; amides selected from dimethyl formamide, dimethyl acetamide or N-methyl pyrrolidinone; sulfoxides selected from dimethylsulfoxide or diethyl sulfoxide; ketones selected from acetone, methyl isobutyl ketone or methyl ethyl ketone; nitriles selected from acetonitrile or propionitrile; ethers selected from tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether or 1,4-dioxane; halogenated hydrocarbons selected from methylene chloride, ethylene chloride or chloroform; aromatic hydrocarbons selected from toluene or xylene; water and mixtures thereof.

Claim 81: The process of claim 78, wherein the suitable base is diisopropyl ethylamine and the suitable solvent is acetonitrile.

Claim 82: The process of claim 65, wherein the step c1) is carried out at a temperature of about 25°C to reflux temperature.

Claim 83: The process of claim 65, wherein the step d1) is carried out with a suitable dehydrating agent optionally in presence of a suitable catalyst in a suitable organic solvent.

Claim 84: The process of claim 83, wherein the dehydrating agent is selected from the group comprising hexamethyldisilazane, bis(trimethylsilyl)acetamide, bis-

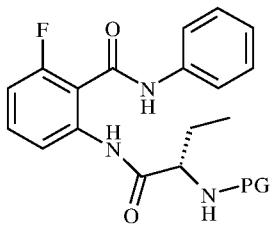
trimethylsilylurea, trimethylsilylphosphate, phosphorous oxychloride, thionyl chloride, cyanuric chloride, aluminium chloride, aluminum bromide, zinc chloride, zinc bromide, boron trichloride, iron chloride, iron bromide, tinchloride, titanium chloride, sulfuric acid, phosphorous pentoxide, trifluoroacetic anhydride, acetic anhydride, dicyclohexylcarbodiimide, p-toluene sulfonic acid, methane sulfonic acid or calcium hydride.

Claim 85: The process of claim 83, wherein the suitable organic solvent is selected from the group comprising ketones selected from acetone, methyl isobutyl ketone or methyl ethyl ketone; esters selected from ethylacetate, isopropyl acetate or butyl acetate; amides selected from dimethyl formamide, dimethyl acetamide or N-methyl pyrrolidinone; sulfoxides selected from dimethylsulfoxide or diethyl sulfoxide; nitriles selected from acetonitrile or propionitrile; ethers selected from tetrahydrofuran, 2-methyltetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether or 1,4-dioxane; halogenated hydrocarbons selected from methylene chloride, ethylene chloride or chloroform; aromatic hydrocarbons selected from toluene or xylene and mixtures thereof.

Claim 86: The process of claim 83, wherein the suitable dehydrating agent is hexamethyldisilazane; the suitable catalyst is Iodine and the suitable organic solvent is acetonitrile.

Claim 87: The process of claim 65, wherein the step d1) is carried out at a temperature of about 25°C to reflux temperature.

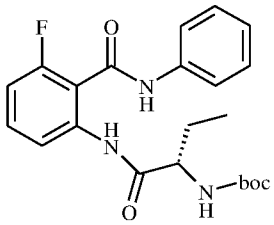
Claim 88: A compound of Formula VI,



Formula VI

wherein the "PG" is selected from the group comprising carbobenzyloxy, p-methoxybenzyl carbonyl, tert-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, acetyl, pivaloyl, benzoyl, benzyl, p-methoxybenzyl, p-methoxybenzoyl, 3,4-dimethoxybenzyl, p-methoxyphenyl, p-nitro benzoyl, p-nitro benzyl, p-phenyl benzyl, p-phenyl benzoyl, trimethylsilyl, triethylsilyl, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, triisopropylsilyl, succinimide, tosyl or Nosyl.

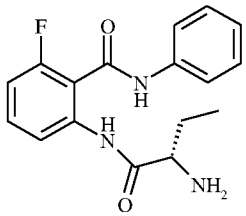
Claim 89: A compound of Formula VIa.



Formula VIa

Claim 90: Crystalline compound of Formula VIa characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 6.

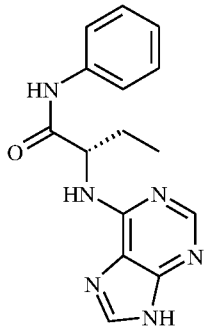
Claim 91: A compound of Formula VII or a salt thereof.



Formula VII

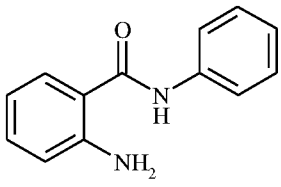
Claim 92: Crystalline compound of Formula VII characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 7.

Claim 93: A compound of Formula XII or a salt thereof.



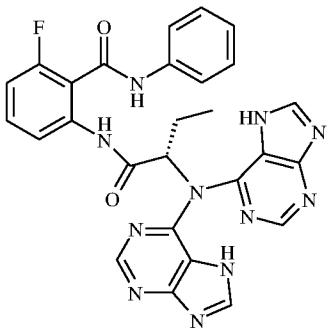
Formula XII

Claim 94: A compound of Formula IV substantially free of desfluoro impurity of Formula A:



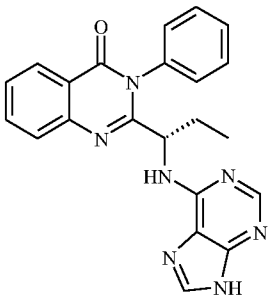
Formula A

Claim 95: A compound of Formula IX substantially free of dimer impurity of Formula B:



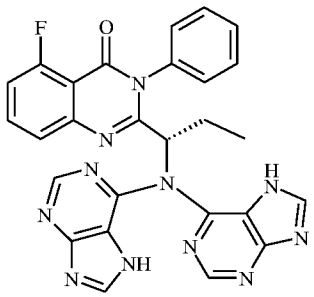
Formula B

Claim 96: Desfluoro idelalisib of Formula C:



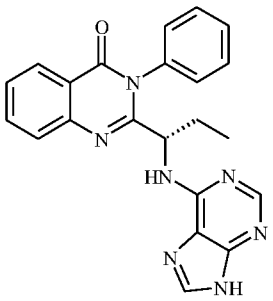
Formula C

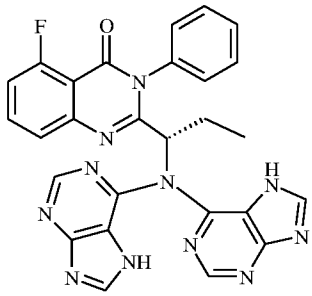
Claim 97: A compound of Formula D:



Formula D

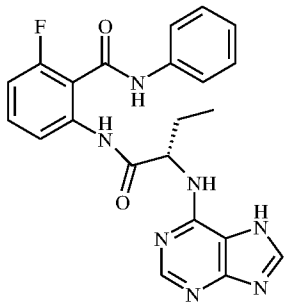
Claim 98: Idelalisib of Formula I substantially free of desfluoro impurity of Formula C and/or dimer impurity of Formula D.





Formula C Formula D

Claim 99: Crystalline compound of Formula IX characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 1.



Formula IX

Claim 100: Crystalline trifluoroacetate salt of compound of Formula IX characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 2.

Claim 101: Crystalline idelalisib trifluoroacetate salt characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 3.

Claim 102: Crystalline idelalisib trifluoroacetate salt characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 3, characterized by a differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure 4 and thermo gravimetric analysis (TGA) substantially in accordance with Figure 5.

Claim 103: Crystalline compound of Formula III characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 8.

Claim 104: Crystalline compound of Formula IV characterized by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 9.

Claim 105: A pharmaceutical composition comprising Idelalisib according to claim 1-104 and at least one pharmaceutically acceptable excipient.

Figure 1

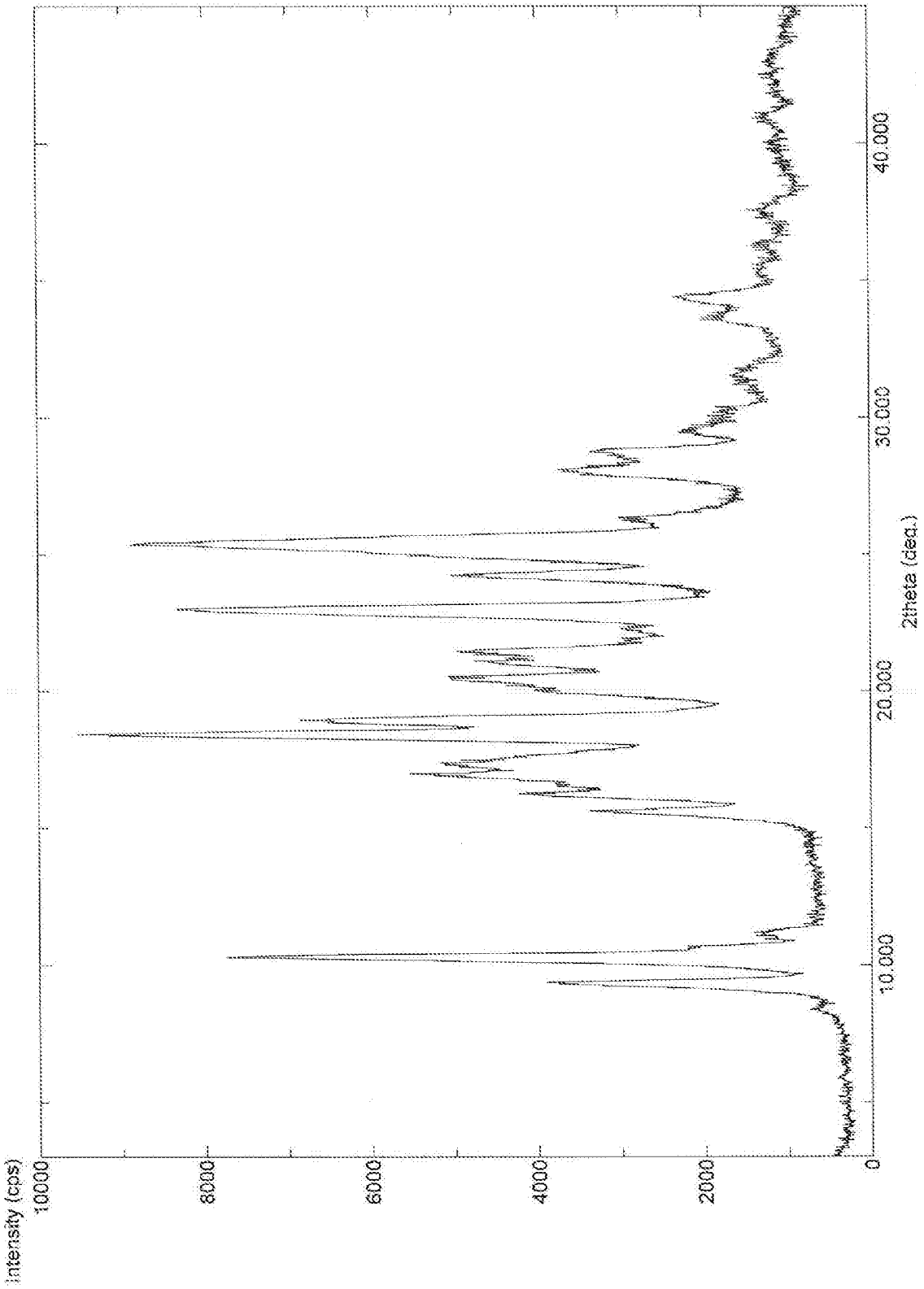

Intensity (cps)
10000
8000
6000
4000
2000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Figure 2

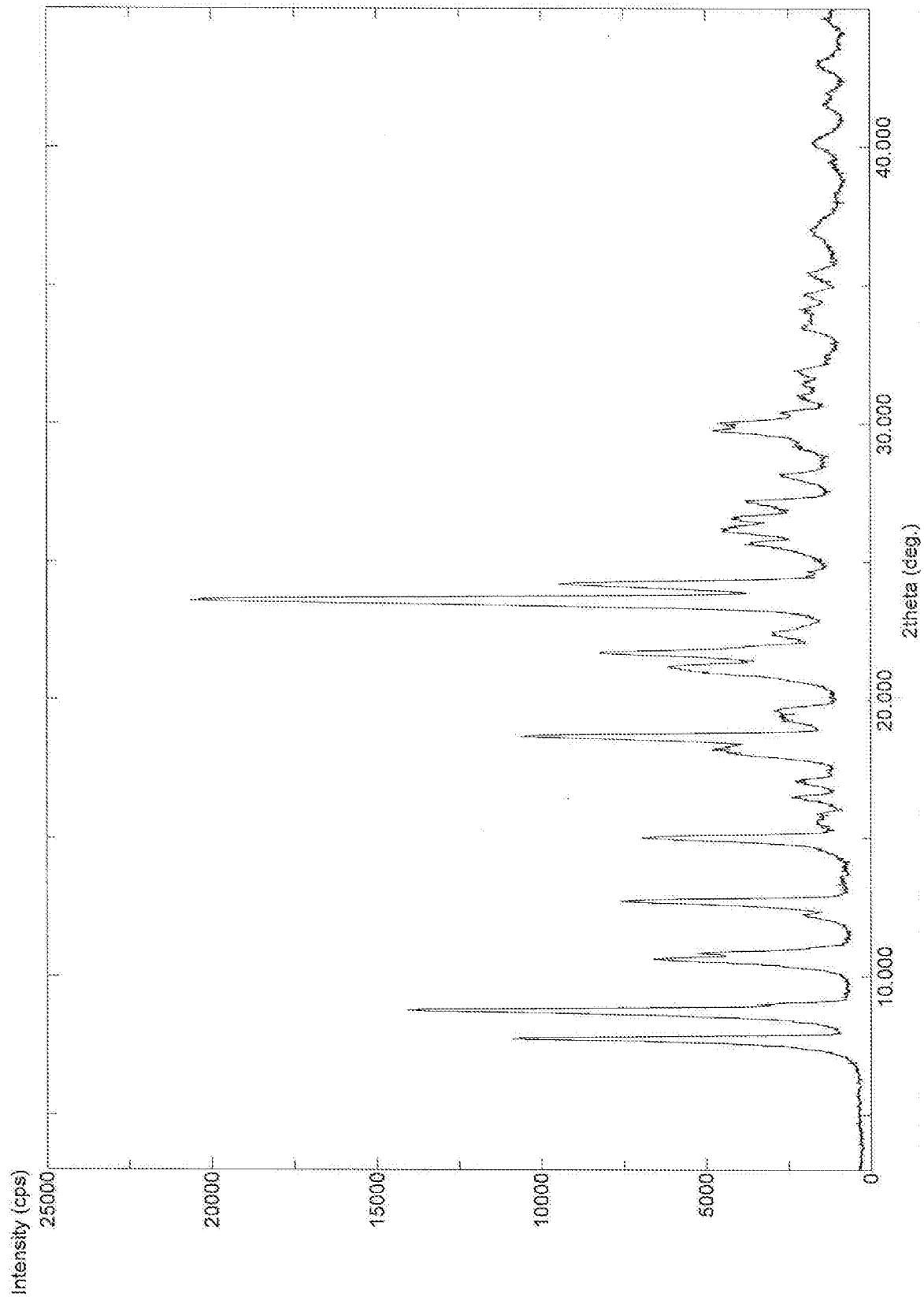

Intensity (cps)
25000
20000
15000
10000
5000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Figure 3

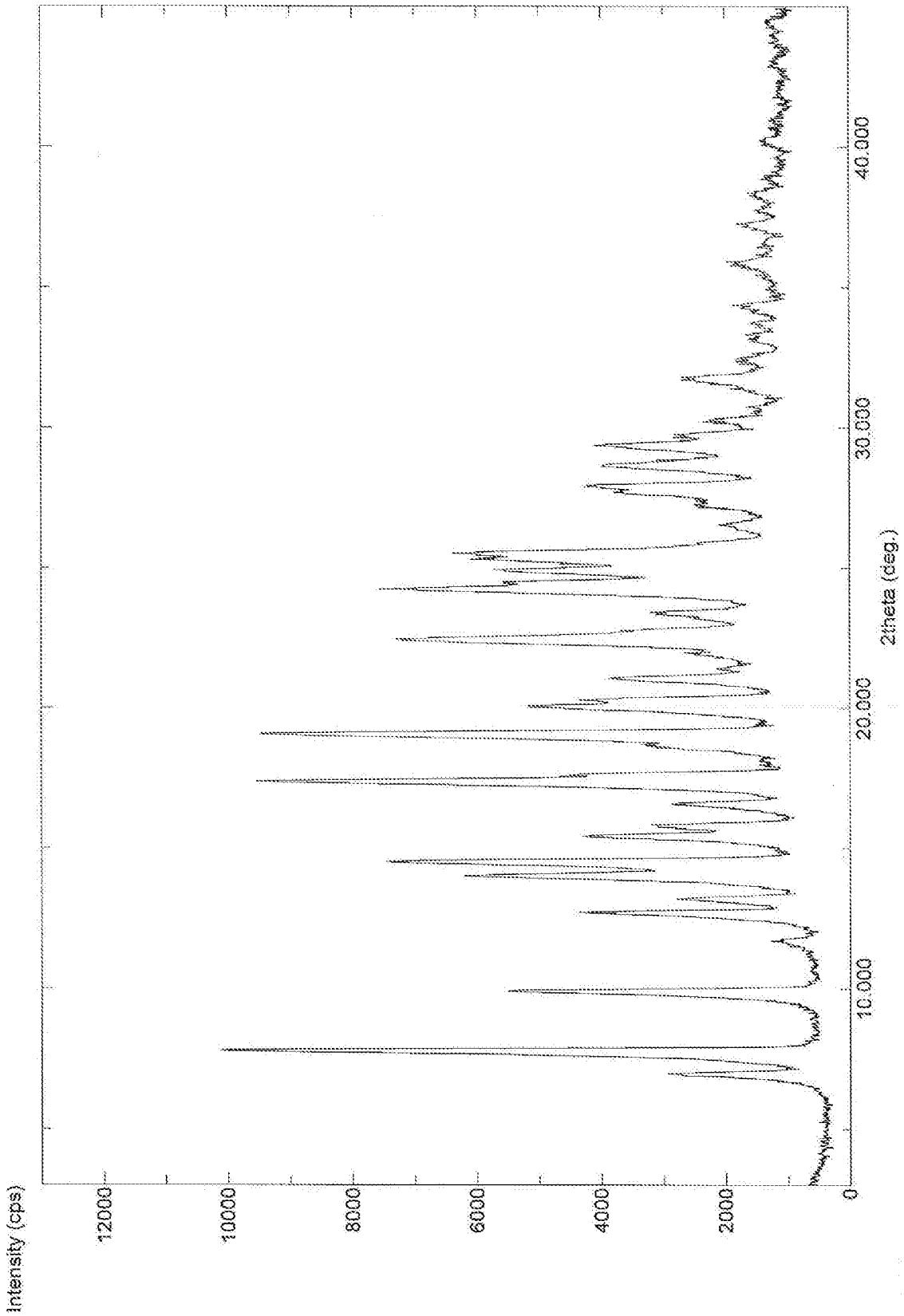

Intensity (cps)
12000
10000
8000
6000
4000
2000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Figure 4

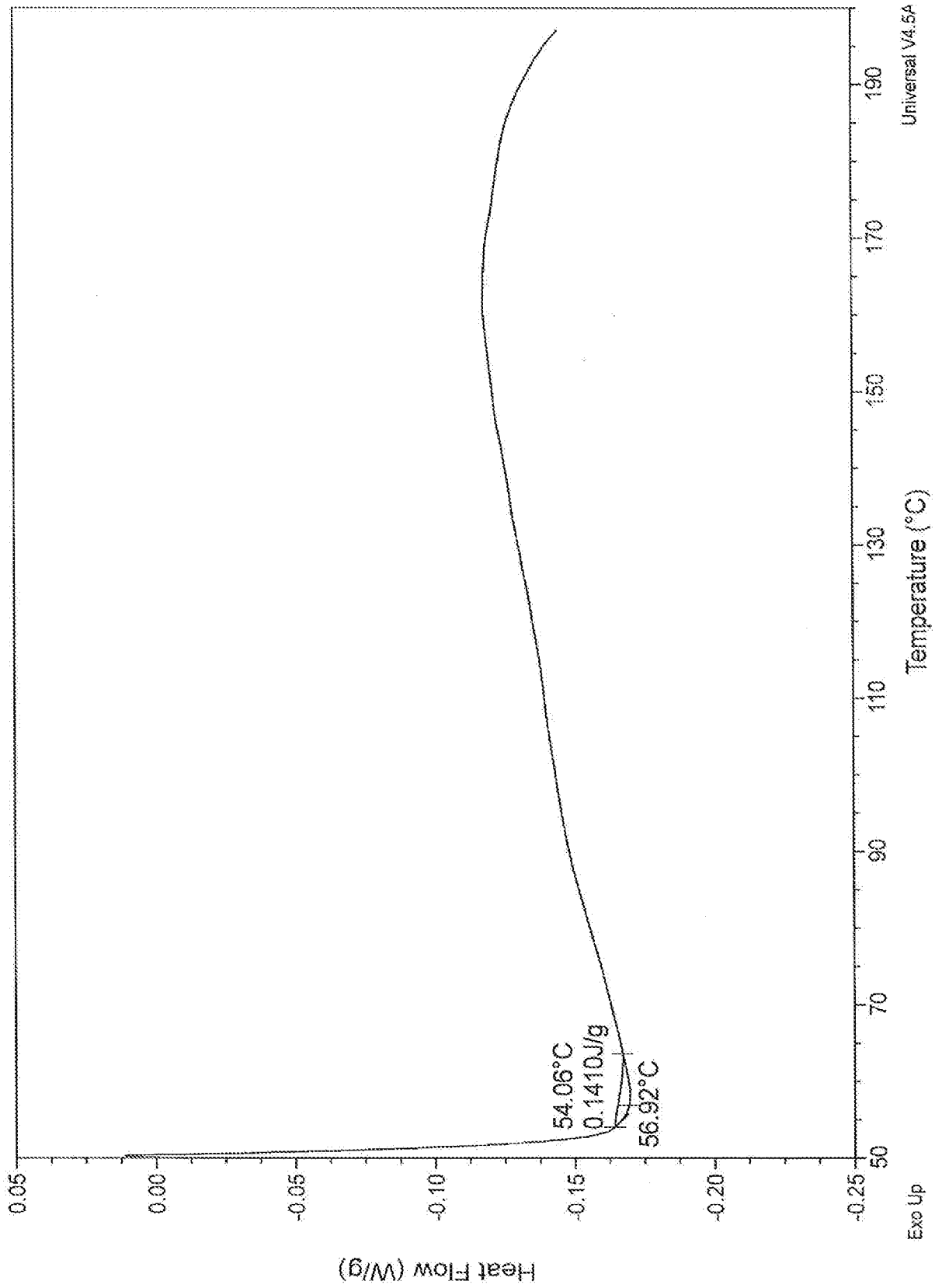

Heat Flow (W/g)
0.05
0.00
-0.05
-0.10
-0.15
-0.20
-0.25
Exo Up
Temperature (°C)
50
70
90
110
130
150
170
190
Universal V4.5A
54.06°C
0.1410J/g
56.92°C

Figure 5

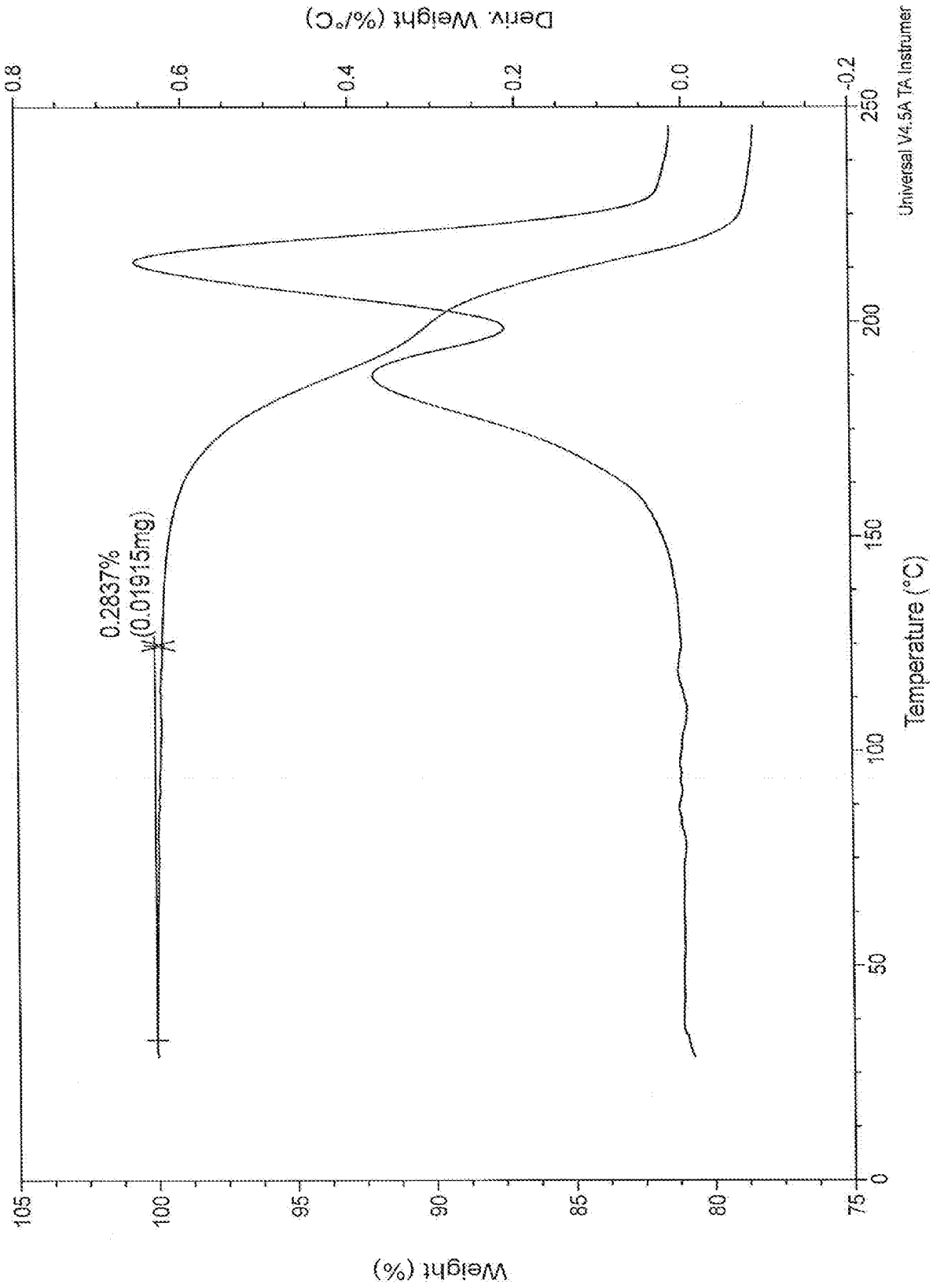

Deriv. Weight (%/°C)
0.8
0.6
0.4
0.2
0.0
-0.2
Universal V4.5A TA Instrumer
0.2837%
(0.01915mg)
Weight (%)
105
100
95
90
85
80
75
0
50
100
150
200
250
Temperature (°C)

Figure 6

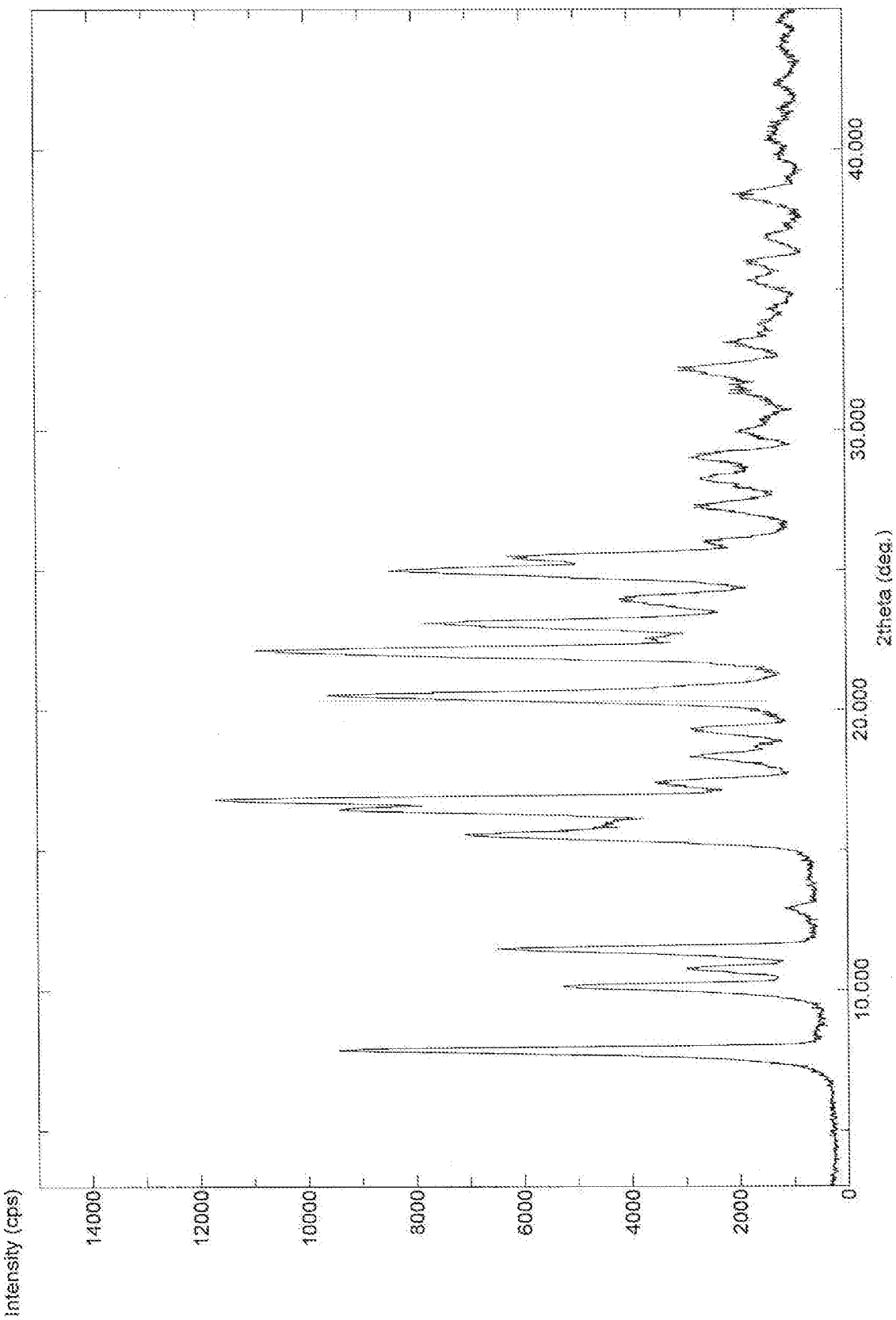

Intensity (cps)
14000
12000
10000
8000
6000
4000
2000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Figure 7

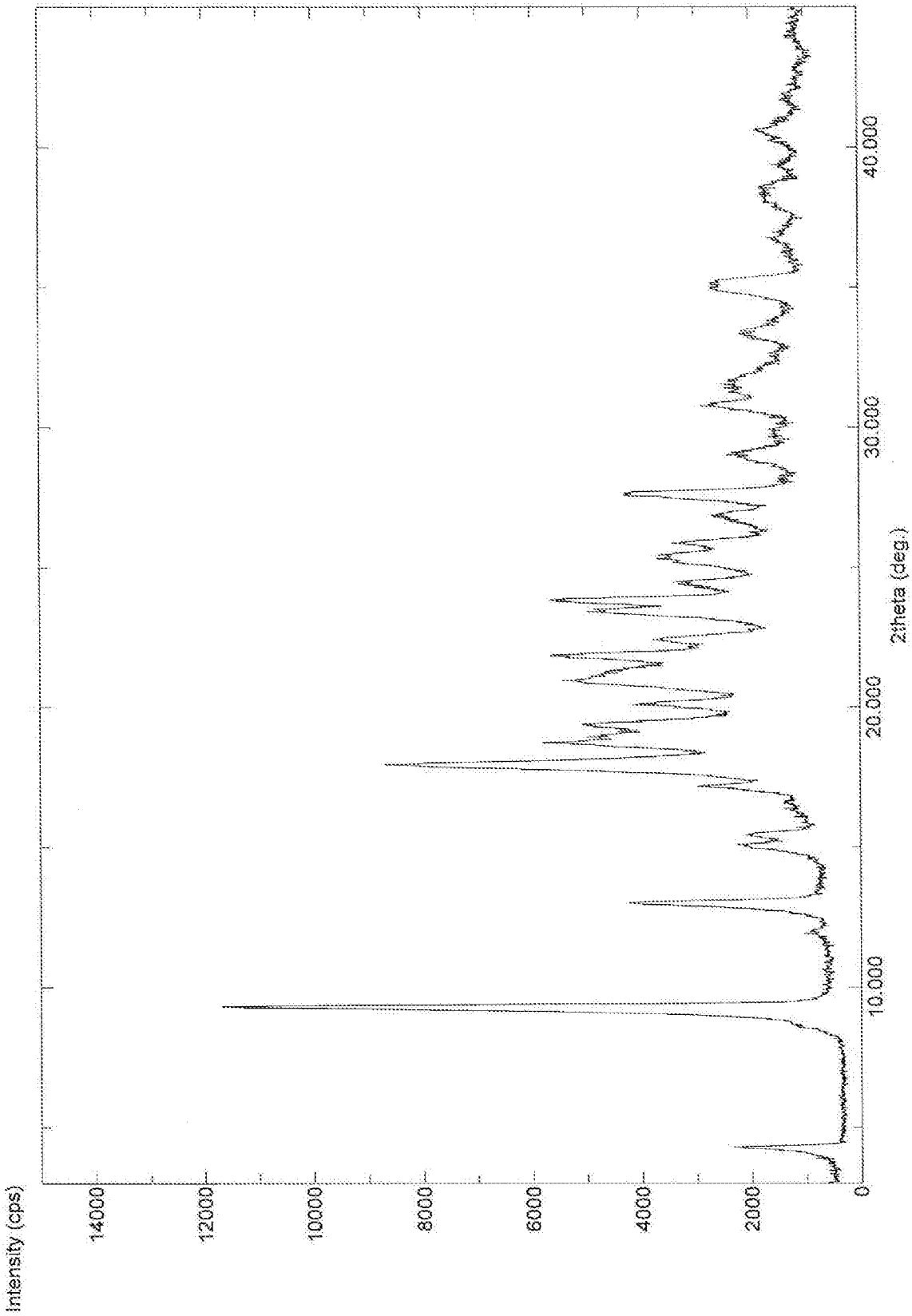

Intensity (cps)
14000
12000
10000
8000
6000
4000
2000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Figure 8

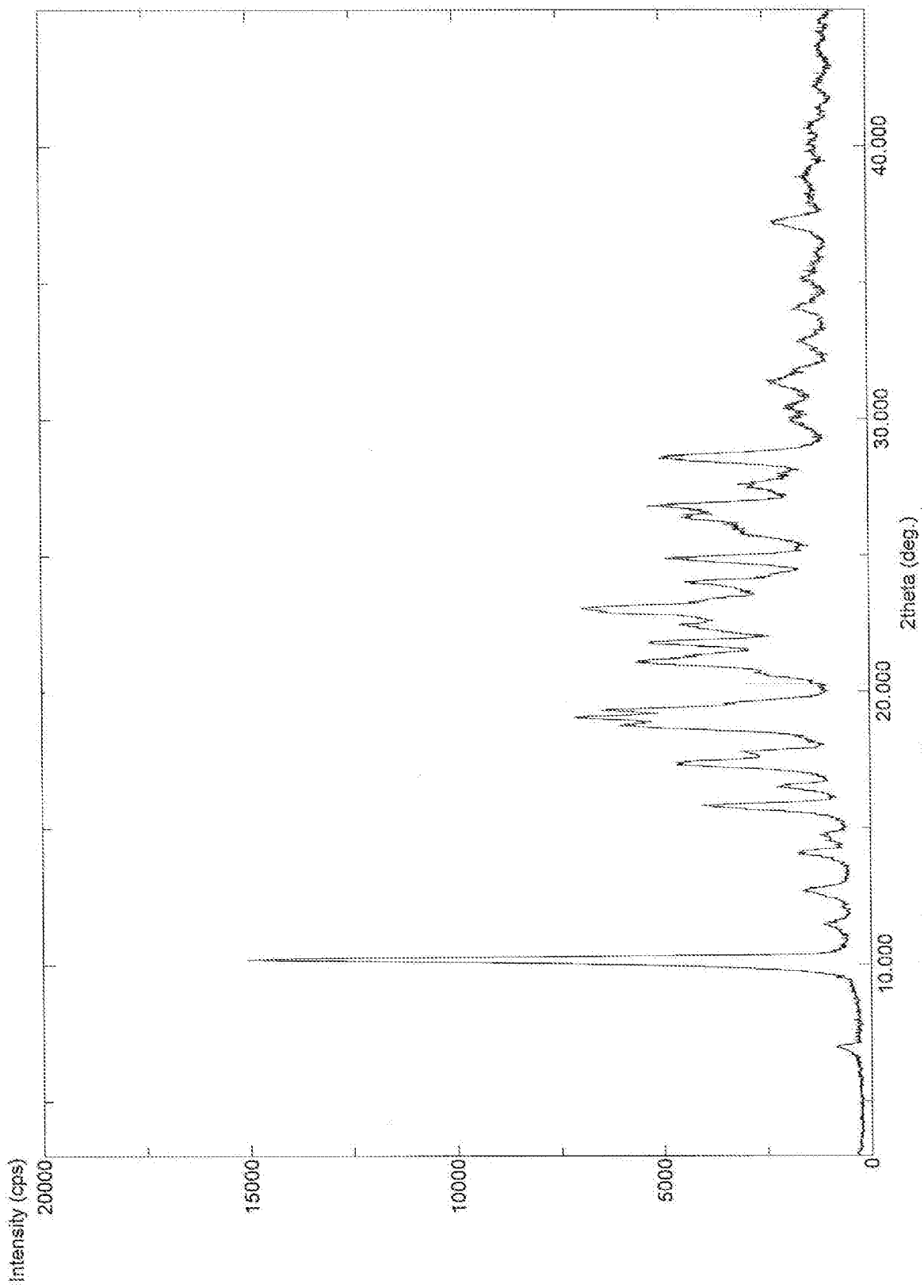
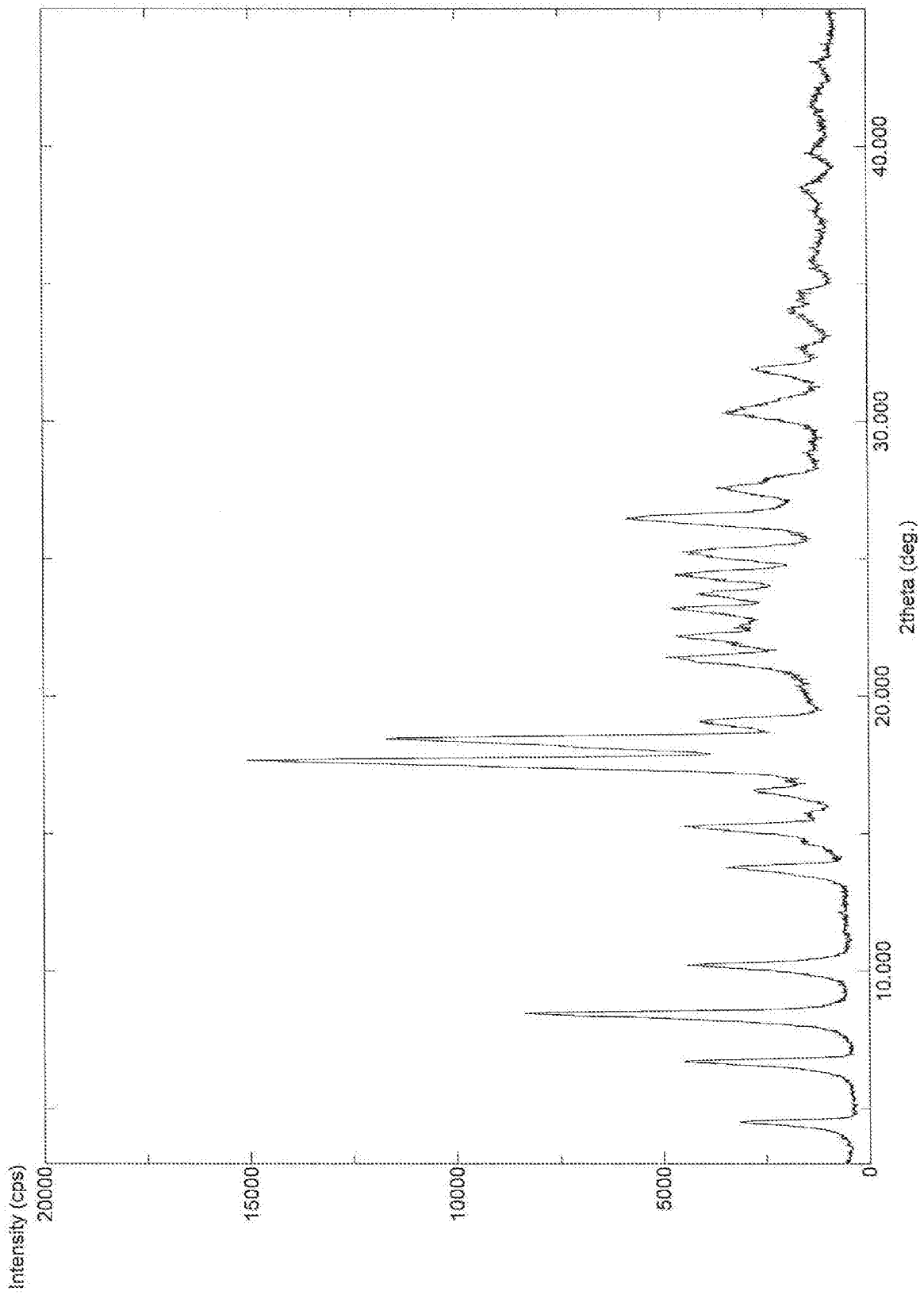

Intensity (cps)
20000
15000
10000
5000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Figure 9


Intensity (cps)
20000
15000
10000
5000
0
10.000
20.000
30.000
40.000
2theta (deg.)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/052628

A. CLASSIFICATION OF SUBJECT MATTER
C07D487/04,A61K31/00 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.
X	WO2015042077A1 (CALITOR SCIENCES LLC[US]; SUNSHINE LAKE PHARMA CO LTD[CN]), 26-03-2015 (26 March 2015); See the step 3) of Example 39 at paragraph [497]	88, 89
Y	WO2015042077A1 (CALITOR SCIENCES LLC[US]; SUNSHINE LAKE PHARMA CO LTD[CN]), 26-03-2015 (26 March 2015); See the paragraphs [347], [348], [388] and [495]-[500]	1-87, 90-105
Y	CN104262344 A ((XU XUENONG,; SUZHOU MIRACPHARMA TECHNOLOGY CO., LTD), 07-01-2015 (7 January 2015); See the reaction sequence at paragraph [0012] and examples at paragraph [0027] to [0039]	1-105
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:	1-105

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
12-09-2017	12-09-2017
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Krishna G Telephone No. +91-1125300200

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 the page 3243, scheme 1; Page 3244, Table 1, entries 1-11, particularly entry 4	
Y	CN104892612 A (SHANGHAI FANGNAN BIOTECHNOLOGY CO., LTD), 09-09-2015 (9 September 2015); See the claims 3-6; examples 1-7	1-105
E	WO2017134607 A1 (Lupin Limited), 10-08-2017 (10 August 2017); See the claims	1-24, 91

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2017/052628

Citation	Pub.Date	Family	Pub.Date
WO 2015042077 A1	26-03-2015	AU 2014321419 A1	28-01-2016
		AU 2014321420 A1	28-01-2016
		CA 2918938 A1	26-03-2015
		CA 2920059 A1	26-03-2015
		EP 3046563 A1	27-07-2016
		JP 2016530338 A	29-09-2016
		KR 20160058889 A	25-05-2016
		MX 2016003456 A	25-05-2017
		SG 11201600028Y A	26-02-2016
		US 2015087658 A1	26-03-2015
		US 2015087663 A1	26-03-2015
		WO 2015042078 A2	26-03-2015
		WO 2015042497 A2	26-03-2015
CN 104262344 A	07-01-2015	CN 104262344 B	04-11-2015
		KR 20170075713 A	03-07-2017
		WO 2016026380 A1	25-02-2016
CN 104892612 A	09-09-2015	WO 2016165618 A1	20-10-2016