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(54) Title: PROCESS FOR THE PREPARATION OF SUBSTITUTED IMIDAZO[4,5-C]QUINOLINE COMPOUNDS, INTERMEDIATES AND POLYMORPHS THEREOF

(57) Abstract: The present invention relates to a process for preparation of substituted imidazo[4,5- c]quinoline compounds (the compounds of formula I as described) and intermediates thereof. The present invention also relates to polymorphs of a compound encompassed in the compound of formula I and their use in the treatment of proliferative disorders, particularly cancers.

PROCESS FOR THE PREPARATION OF SUBSTITUTED IMIDAZO[4,5-C]QUINOLINE COMPOUNDS, INTERMEDIATES AND POLYMORPHS THEREOF

Field of the invention

The present invention relates to a process for the preparation of substituted imidazo[4,5-c]quinoline compounds represented by formula I (as described herein) and intermediates thereof. Further the present invention relates to polymorphs of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (referred to herein as Compound A), their preparation and pharmaceutical compositions containing them. The compounds of formula I (as described herein) are useful in the treatment of proliferative diseases or disorders such as cancer.

Background of the invention

In spite of extensive research and efforts directed to provide effective treatments for cancer, it still remains one of the few diseases that are extremely difficult to treat. Treatment regimens for cancer are determined by the type and stage of the cancer, and include surgery, radiation therapy, chemotherapy, bone marrow transplantation, stem cell transplantation, hormonal therapy, immunotherapy, anti-angiogenic therapy, targeted therapy, gene therapy and others. Phosphoinositide 3-kinases (PI3Ks) and mammalian target of rapamycin (mTOR) are attractive therapeutic targets in various diseases, such as autoimmune and inflammatory disorders and cancer.

PI3K mediated signaling pathway plays a very important role in cancer cell survival, cell proliferation, angiogenesis and metastasis. Activation of PI3K results in a disturbance of control of cell growth and survival, and hence this pathway is an attractive target for the development of novel anticancer agents (Nat. Rev. Drug Discov., 2005, 4, 988-1004). Activation of PI3K results in the recruitment and activation of protein kinase B (AKT) onto the membrane, which gets phosphorylated at Serine 473 (Ser-473).

AKT is a serine/threonine protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, cell proliferation, apoptosis, transcription and cell migration. It is known to positively regulate cell growth (accumulation of cell mass) by activating the mTOR (mammalian target of rapamycin) serine threonine kinase. mTOR

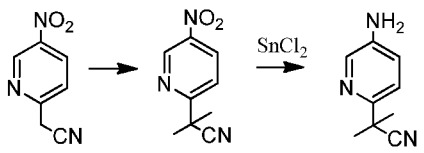
serves as a molecular sensor that regulates protein synthesis on the basis of nutrients. mTOR regulates biogenesis by phosphorylating and activating p70S6 kinase (S6K1), which in turn enhances translation of mRNAs that have polypyrimidine tracts. The phosphorylation status of S6K1 is a bonafide read-out of mTOR function. Most tumors have an aberrant PI3K pathway (Nat. Rev. Drug Discov., 2005, 4, 988-1004). Since mTOR lies immediately downstream of PI3K, these tumors also have hyperactive mTOR function. Thus, most of the cancer types will potentially benefit from molecules that target PI3K and mTOR pathways.

Certain imidazoquinoline compounds are disclosed in WO2006122806 (WO'806 patent application) as lipid kinase inhibitors that are used alone or in combination with one or more pharmaceutically active compounds for the treatment of an inflammatory or obstructive airway disease such as asthma or a proliferative disease such as cancer. The WO'806 patent application also discloses synthesis of imidazoquinoline compounds and intermediates thereof. In particular, an intermediate, 6-bromo-4-chloro-3-nitroquinoline was prepared by treating 6-bromo-3-nitroquinolin-4-ol with 4 volumes of $POCl_3$. Further, the example 1g of WO'806 patent application describes reduction of 2-(5-((6-bromo-3-nitroquinolin-4-yl)amino)pyridin-2-yl)-2-methylpropanenitrile using Raney-Ni as catalyst to obtain 2-(5-((3-amino-6-bromoquinolin-4-yl)amino)pyridin-2-yl)-2-ethylpropanenitrile.

WO2012007926 (WO'926 patent application) discloses substituted imidazo[4,5-c]quinoline compounds, which are reported to be PI3K/mTOR inhibitors. The said imidazo[4,5-c]quinoline compounds are reported to inhibit other kinases such as DNA-PK and ALK-l . WO'926 patent application also describes processes for the manufacture of the imidazo[4,5-c]quinoline compounds. Particular reference is made to example 5 wherein preparation of the compound, N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide is described. The process described in the example 5 comprises the steps of: a) methylating 2-5-nitropyridine-2-yl)acetonitrile in the presence of sodium hydride and tetrahydrofuran (THF) as the solvent to obtain 2-methyl-2-(5-nitropyridin-2-yl)propanenitrile which was purified by column chromatography; b) the resulting compound, 2-methyl-2-(5-nitropyridin-2-yl)propanenitrile was subjected to reduction using Raney-Ni to obtain 2-(5-aminopyridin-2-yl)-2-methylpropanenitrile, which was purified by column chromatography; c) 6-bromo-3-nitroquinolin-4-ol was treated with phosphorous oxy chloride ($POCl_3$) (4 volumes) at 120°C to obtain 6-bromo-4-chloro-3-nitroquinoline which was treated with 2-(5-

aminopyridin-2-yl)-2-methylpropanenitrile to obtain 2-(5-((6-bromo-3-nitroquinolin-4-yl)amino)pyridin-2-yl)-2-ethylpropanenitrile; d) the resulting compound, 2-(5-((6-bromo-3-nitroquinolin-4-yl)amino)pyridin-2-yl)-2-ethylpropanenitrile was subjected to reduction using Raney-Ni to obtain 2-(5-((6-bromo-3-aminoquinolin-4-yl)amino)pyridin-2-yl)-2-ethylpropanenitrile which was purified by column chromatography; e) 2-(5-((6-bromo-3-aminoquinolin-4-yl)amino)pyridin-2-yl)-2-ethylpropanenitrile was then cyclised using diphenyl cyanodithioimino carbonate and cesium carbonate in the presence of dimethylformamide (DMF) to obtain *N*-(8-bromo-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide which was purified by column chromatography; f) the resulting compound was subjected to methylation to obtain *N*-(8-bromo-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide which was purified by column chromatography; and g) the purified methylated compound was treated with boronic acid compound to obtain the desired N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide which was further purified by column chromatography to obtain the pure compound.

WO2012034526 (WO'526 patent application) describes heteroaryl compounds that are PI3K and/or mTOR inhibitors. WO'526 patent application also discloses process for preparation of heteroaryl compounds and its intermediates. This patent application describes a process for the preparation of an intermediate compound (I-1) represented by formula I-1 as depicted in the following Scheme I. The process comprises overnight reaction of tertiary butyl 2-cyanoacetate and iodomethane in the presence of potassium carbonate in CH_3CN at 40℃ to obtain the compound of formula I-1d (2-methyl-2-(5-nitropyridin-2-yl)propanenitrile), which was reduced using $SnCl_2$ to obtain 2-(5-aminopyridin-2-yl)-2-methylpropanenitrile. The resulting compound was purified by column chromatography.



I-1c I-1d I-1

Scheme I

The process for the preparation of intermediate compounds which are useful for preparation of the compound of formula I, as described in the afore discussed patent documents, involves purification of each intermediate using column chromatography which is time consuming and renders the process costly. Moreover, processes involving use of column chromatography are not viable at commercial scale. Further, the processes which involve usage of large volume of $POCl_3$ for chlorinating 6-bromo-3-nitroquinolin-4-ol as well as usage of Raney-Ni catalyst and $SnCl_2$ catalyst for reduction, as discussed above, are tedious and not feasible for scale-up.

Considering the fact that the substituted imidazo[4,5-c]quinoline compounds (the compounds of formula I) being potent PI3K/mTOR inhibitors, have potential for development for use in the treatment of certain proliferative disorders, particularly cancers, there is a need for improved process for the synthesis of such compounds i.e. the compounds of Formula (I). Particularly, there is a need to provides a simple, industrially scalable, efficient and cost-effective process in comparison to the process reported in the cited documents. The inventors of the present invention have made efforts in this direction to provide a process which is not only simple, cost-effective and industrially viable but also provide the compounds of formula I in good yield and enhanced purity. In fact, the process of the instant invention overcomes the drawbacks associated with the prior art processes and affords operational advantages on large scale production.

Summary of the invention

In one aspect, the present invention relates to a process for the preparation of a compound of formula I (as described herein) or a stereoisomer, a tautomer, a polymorph, a pharmaceutically acceptable salt or a solvate thereof.

In another aspect, the present invention relates to a process for the preparation of one or more intermediates used for preparing the compound of formula I or a pharmaceutically acceptable salt or solvate thereof.

In a further aspect, the present invention relates to a process for preparation of compound of formula IA (as described herein) or a stereoisomer, a tautomer, a polymorph, a pharmaceutically acceptable salt or a solvate thereof.

In a further aspect, the present invention relates to a process for the preparation of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-

yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (referred to herein as 'Compound A') or a stereoisomer, a tautomer, a polymorph, a pharmaceutically acceptable salt or a solvate thereof.

In a further aspect, the present invention relates to a process for preparing intermediates for the preparation of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene) cyanamide (Compound A) or a stereoisomer, a tautomer, a polymorph, a pharmaceutically acceptable salt or a solvate thereof.

In another aspect, the present invention relates to a process for the purification of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) or a pharmaceutically acceptable salt or a solvate thereof.

In another aspect, the present invention relates to a process for the purification of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A).

In an aspect, the present invention relates to polymorphs of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) or a pharmaceutically acceptable salt or a solvate thereof.

In an aspect, the present invention relates to polymorphs of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A).

In another aspect, the present invention relates to crystalline polymorph of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A). The said polymorph is referred to herein as Form A.

In another further aspect, the present invention relates to a process for the preparation of Form A of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A).

In another aspect, the present invention relates to crystalline polymorph of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-

imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A). The said polymorph is referred to herein as Form B.

In another aspect, the present invention relates to a process for the preparation of Form B of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A).

In another aspect the present invention relates to a mixture of crystalline and amorphous forms of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) or a pharmaceutically acceptable salt or a solvate thereof.

In another aspect the present invention relates to a mixture of crystalline and amorphous forms of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A).

In yet another aspect the present invention relates to process for the preparation of a mixture of crystalline and amorphous forms of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A).

In another aspect the present invention relates to use of Form A of the Compound A or pharmaceutically acceptable salts thereof for the treatment of cancers.

In another aspect the present invention relates to use of Form B of Compound A or pharmaceutically acceptable salts thereof for the treatment of cancers.

In another aspect the present invention relates to use of a mixture of crystalline and amorphous form of Compound A or pharmaceutically acceptable salts thereof; for the treatment of cancers.

In another aspect, the present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of at least one polymorphic form of the Compound A and at least one pharmaceutically acceptable excipient; wherein the said polymorphic form is Form A, Form B or a mixture of crystalline and amorphous form of the Compound A.

In another aspect, the present invention relates to use of pharmaceutical composition comprising a therapeutically effective amount of at least one polymorphic form of the Compound A for the manufacture of a medicament for the treatment of cancers wherein the

said polymorphic form is Form A, Form B or a mixture of crystalline and amorphous form of the Compound A.

In yet another aspect the present invention relates to a method of treating cancer comprising administrating to a subject in need thereof, a therapeutically effective amount of Form A of the Compound A or a pharmaceutical composition of the present invention.

In another further aspect the present invention relates to a method of treating cancer comprising administrating to a subject in need thereof, a therapeutically effective amount of Form A of the Compound A or a pharmaceutical composition containing the Form A in combination with a known therapeutically active agent.

These and other objectives and advantages of the present invention will be apparent to those skilled in the art from the following description.

Brief Description of the drawings

Figure 1 shows characteristic X-Ray powder diffraction (diffractogram) of crystalline Form A of the Compound A.

Figure 2 shows characteristic differential scanning calorimetric (DSC) thermogram of crystalline Form A of the Compound A.

Figure 3 shows characteristic Fourier Transform Infrared (FTIR) spectrum of crystalline Form A of the Compound A.

Figure 4 shows characteristic X-Ray powder diffraction (diffractogram) of crystalline Form B of Compound A.

Figure 5 shows characteristic differential scanning calorimetric (DSC) thermogram of crystalline Form B of the Compound A.

Figure 6 shows characteristic Fourier Transform Infrared (FTIR) spectrum of crystalline Form B of the Compound A.

Figure 7 shows characteristic X-Ray powder diffraction (diffractogram) of a mixture of crystalline and amorphous form of the Compound A.

Figure 8 shows characteristic differential scanning calorimetric (DSC) thermogram of a mixture of crystalline and amorphous form of the Compound A.

Figure 9 shows characteristic Fourier Transform Infrared (FTIR) spectrum of a mixture of crystalline and amorphous form of Compound A.

Detailed description of the invention

It should be understood that the detailed description and specific examples, while indicating embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art. One skilled in the art, based upon the definitions herein, may utilize the present invention to its fullest extent. The following specific embodiments are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Except as defined herein, all the technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention belongs.

Definitions

For the purpose of the disclosure, listed below are definitions of various terms used to describe the present invention. Unless otherwise indicated, these definitions apply to the terms as they are used throughout the specification and the appended claims, either individually or as part of a larger group. These definitions should not be interpreted in the literal sense. They are not general definitions, and are relevant only for this application.

The singular forms “a”, “an” and “the” include plural references unless the context clearly indicates otherwise. . For instance, the terms “a”, “an” and “the” refers to “one or more” when used in the subject specification, including the claims. Thus, for example, reference to “a compound” may include a plurality of such compounds.

Also, use of “(s)” as part of a term, includes reference to the term singly or in plurality, for example the term salt(s) indicates a single salt or more than one salt of the compound of formula I.

The term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

A symbol (-) is used to indicate a point of attachment to the atom, for example -COOH is attached through the carbon atom.

Unless indicated otherwise, the term “substitution” or “substituted by” or “substituted with” includes the implicit proviso that such substitution is in accordance with the permitted valence of the substituted atom and the substituent, as well as represents a stable compound, which does not readily undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, the term "halogen" refers to fluorine, chlorine, bromine or iodine atom.

As used herein, the term "(C_1-C_8)alkyl" or "alkyl" whether used alone or as part of a substituent group, refers to the radical of saturated aliphatic groups, including straight or branched-chain containing from 1 to 8 carbon atoms. Furthermore, unless stated otherwise, the term "alkyl" includes unsubstituted as well as substituted alkyl. When substituted, the alkyl group can be substituted with substituents selected from the group consisting of halogen, hydroxy, cyano, (C_1-C_8)-alkoxy, halo(C_1-C_8)alkyl and halo(C_1-C_8)alkoxy; preferably, alkyl is substituted with halogen or cyano. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, *sec*-butyl, *tert*-butyl and the like. The "alkyl" group as defined above may be interrupted by oxygen or sulfur, means, any ether and thioether groups respectively containing from 1 to 8 carbon atoms are also included in the definition of "alkyl" group.

The term "aryl" as used herein refers to a monocyclic or polycyclic hydrocarbon group having up to 10 ring carbon atoms, preferably up to 6 ring carbon atoms in which at least one carbocyclic ring is present that has a conjugated π electron system. Accordingly, the term "aryl" refers to -C_6-C_{10} aryl. Furthermore, unless stated otherwise, the term "aryl" includes unsubstituted as well as substituted aryl. Examples of aryl include but are not limited to phenyl, naphthyl and tetrahydronaphthyl. Aryl residues can be bonded via any desired position, and in substituted aryl residues, the substituents can be located in any desired position.

The term "heteroaryl" as used herein refers to an aromatic heterocyclic ring system containing 5 to 10 ring atoms, which can be monocyclic or bicyclic rings fused together or linked covalently. The "heteroaryl" is 5- to 10-membered heteroaryl. The rings can contain from 1 to 4 heteroatoms selected from N, O or S, wherein the N or S atom is optionally oxidized, or the N atom is optionally quaternized. Any suitable ring position of the heteroaryl moiety may be covalently linked to the defined chemical structure. Furthermore, unless stated otherwise, the term "heteroaryl" includes unsubstituted as well as substituted heteroaryl. When substituted, the heteroaryl group can be substituted with substituents selected from the group consisting of halogen, hydroxy, cyano, (C_1-C_8)-alkoxy, halo(C_1-C_8)alkyl and halo(C_1-C_8)alkoxy. Examples of heteroaryl include, but are not limited to, furan, thiophene, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, cinnolinyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl,

oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, benzotriazinyl, phthalazinyl, benzimidazolyl, indolyl, isoindolyl, indazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, purinyl, pteridinyl, indolizinyl, benzoisothiazolyl, benzoxazolyl, pyrrolopyridyl, furopyridinyl, purinyl, benzothiadiazolyl, benzooxadiazolyl, benzotriazolyl, benzodiazolyl, and the like.

The term "compound of formula I" as used herein encompasses the compound of formula IA and a pharmaceutically acceptable salt, a stereoisomer, a tautomer, a polymorph or a solvate, thereof.

The term “pharmaceutically acceptable” refers to a compound or a carrier or an additive or a salt that is not biologically or otherwise undesirable. In other words a pharmaceutically acceptable compound or a salt must not cause any undesirable biological effects or interact in an undesirable manner with any of the other ingredients of the pharmaceutical composition in which it is contained.

The term "pharmaceutically acceptable salt(s)" as used herein refers to organic and inorganic salts of a compound of the invention. The compounds of the present invention represented by the general formula I, which contain acidic groups, can be converted into salts with pharmaceutically acceptable bases. Such salts include, for example, alkali metal salts, like lithium, sodium and potassium salts; alkaline earth metal salts like calcium and magnesium salts, ammonium salts, for example, tris(hydroxymethyl)aminomethane, trimethylamine salts and diethylamine salts; salts with organic amino acids such as lysine, arginine, guanidine and the like.

The term "stereoisomer" as used herein refers to all isomers of individual compounds that differ only in the orientation of their atoms in space. The term stereoisomer includes mirror image isomers (enantiomers), mixtures of mirror image isomers (racemates, racemic mixtures), geometric (cis/trans or syn/anti or E/Z) isomers, and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereoisomers). The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, individual diastereoisomers, or enantiomers, or may exist as geometric isomers, with all isomeric forms of said compounds being included in the present invention.

The term "tautomer" as used herein refers to the coexistence of two (or more) compounds that differ from each other only in the position of one (or more) mobile atoms and in electron distribution, for example, keto-enol and imine-enamine tautomers.

As used herein, the term “polymorph” or “polymorphic form” or “polymorphs” refers to crystals of the same compound that differs only in the arrangement and/or conformation of the molecule in the crystal lattice.

The polymorph of ‘Compound A’ which is encompassed in the "compound of formula I" or the “compound of formula IA” are part of this invention. The presence of polymorphs can be determined by infrared (IR) spectroscopy, solid probe nuclear magnetic resonance (NMR) spectroscopy, differential scanning calorimetry (DSC), powder X-ray diffraction (XRPD) or such other techniques.

The term “pharmaceutically acceptable solvate” or “solvate(s)” as used herein refers to a compound formed by the interaction of a solute (in this invention, a compound of formula I or compound of formula IA or Compound A or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples for suitable solvates are the mono- or di-hydrates including hemihydrates or alcoholates of the compounds of formula I or the compound of formula IA or Compound A.

The compounds of formula I, which contain one or more basic groups, i.e. groups which can be protonated, can form an addition salt with an inorganic or organic acid. Examples of suitable acid addition salts include: acetates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, cinnamates, citrates, ethanesulfonates, fumarates, glucuronates, glutamates, glycolates, hydrochlorides, hydrobromides, hydrofluorides, ketoglutarates, lactates, maleates, malonates, methanesulfonates, nitrates, oxalates, palmoates, perchlorates, phosphates, picrates, salicylates, succinates, sulfamate, sulfates, tartrates, toluenesulfonates and other acid addition salts known to the person skilled in the art.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment. The term “mammal” as used herein is intended to encompass humans, as well as non-human mammals. Non-human mammals include, but are not limited to, domestic animals, such as cows, pigs, horses, dogs, cats, rabbits, rats and mice, and non-domestic animals. The term “subject” may be interchangeably used with the term “patient” in the context of the present invention.

The term “treat”, "treating" or "treatment" as used herein includes (a) preventing the disease or disorder or condition (e.g. cancer) developing in a subject that may be afflicted

with or predisposed to the state, disorder or condition or accompanying symptoms; (b) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or accompanying symptoms or (c) relieving the disease, i.e., causing regression of the state, disorder or condition or accompanying symptoms.

The term "therapeutically active agent" as used herein is intended to encompass any known therapeutically active agent or investigational new drug that will produce a therapeutically beneficial pharmacological response when administered to a subject, both human and animal, in need thereof. Suitable known therapeutically active agent include, but are not limited to analgesics, immunosuppressants, anti-inflammatories, and anti-cancer agents, which can be useful in the treatment of diseases as described herein when used in combination with the polymorph. More than one therapeutically active agent may be used, if desired, in combination with the composition specified herein.

The term "therapeutically effective amount" as used herein, refers to the amount of a compound that, when administered to a subject for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated.

The term "pharmaceutically acceptable excipient" as used herein means a non-toxic, inert solid, semi-solid, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable excipients are sugars such as lactose, glucose, and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; malt; gelatin; talc; as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents; preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator which are well known to those skilled in the art.

The term "particle size distribution (PSD)" as used herein refers to the cumulative volume size distribution of equivalent spherical diameters as determined by laser diffraction in equipment. Typically, the Particle Size Distribution (PSD) is determined by laser diffraction in Malvern master Sizer 2000 equipment.

The term "about" as used herein in reference to a peak in a XRPD diffractogram, means the peak may vary by ±0.2 degrees of determined 2-theta value. The term "about" as

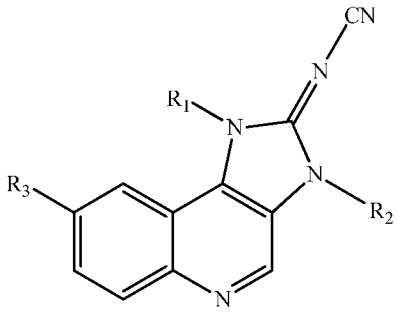
used herein in reference to a peak in a FTIR spectrum, means the peak may vary by ± 5 cm^{-1} of determined subject value.

The "solvent" as mentioned herein includes but is not limited to alcohols such as methanol, ethanol, tert-butyl alcohol, isobutyl alcohol, n-propyl alcohol, 2-propyl alcohol and the like; nitriles such as acetonitrile, propionitrile and the like; esters such as ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and the like; ketones such as methyl ethyl ketone, acetone and the like; ethers such as, methyl tert-butyl ether, dimethyl ether, diethyl ether, diisopropyl ether tetrahydrofuran and the like; halogenated solvents such as ethylene dichloride, methylene dichloride, chloroform, carbon tetrachloride and the like; hydrocarbon solvents such as, cyclohexane, isobutyl benzene, toluene, xylene, hexane and the like; aprotic polar solvents such as dimethyl sulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide and the like or water. Any solvent or mixture of solvents or their combination with water can be used in the present invention.

The term "acid" as referred to herein includes but is not limited to acetic acid, methane sulfonic acid, para-toluene sulfonic acid, sulfuric acid or hydrochloric acid.

Base is selected from the group comprising alkali metal hydroxide, alkaline earth metal carbonate or bicarbonate. The example of the base as mentioned herein is selected from the group comprising NaOH, KOH, LiOH, $NaHCO_3$, $KHCO_3$, Na_2CO_3, K_2CO_3, DIPEA or mixture thereof.

In an aspect, the present invention relates to a process for the preparation of the compound of formula I:



formula I

or a stereoisomer, a tautomer, a polymorph, a pharmaceutically acceptable salt or a solvate thereof;

wherein,

R_1 is -(C_6-C_{10})aryl or heteroaryl;

R_2 is -(C_1-C_8) alkyl, which is unsubstituted or substituted with -CN;

R_3 is -(C_6-C_{10})aryl or heteroaryl;

wherein each of -(C_6-C_{10})aryl and heteroaryl is unsubstituted or substituted with one or more of R^a;

R^a at each occurrence is independently selected from the group consisting of halogen, -CN, -OR_x, -SR_x, -NR_xR_y or -(C_1-C_8)alkyl, wherein -(C_1-C_8)alkyl is unsubstituted or substituted with one or more of R^b; wherein R^x and R^y are independently selected from group consisting of hydrogen and -(C_1-C_8)alkyl, wherein -(C_1-C_8)alkyl is unsubstituted or substituted with R^b; and R^b is halogen or -CN.

In an embodiment, the present invention encompasses a compound of formula I, wherein R_1 is selected from phenyl, pyridyl, quinolinyl and 2-morpholinoethyl, wherein each of phenyl, pyridyl, quinolinyl and 2-morpholinoethyl is unsubstituted or substituted with one or more groups R^a, wherein R^a is as defined above.

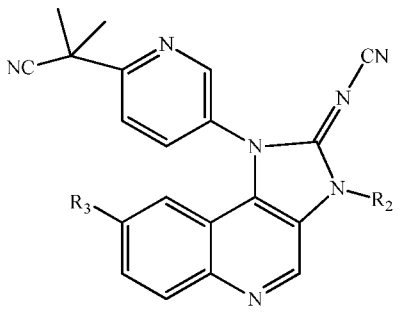
In an embodiment, the present invention encompasses a compound of formula I; R_1 is pyridyl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -CN, -O-(C_1-C_8)alkyl and -C_1-C_8)alkyl, wherein -(C_1-C_8)alkyl is substituted with halogen or -CN;

R_2 is -(C_1-C_8)alkyl;

R_3 is pyridyl which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -CN, -O-(C_1-C_8)alkyl, -NR^xR^y, and -(C_1-C_8)alkyl, wherein -(C_1-C_8)alkyl is optionally substituted with halogen; and

R^x and R^y are independently hydrogen or -(C_1-C_8)alkyl.

In an embodiment, the compound of formula I encompass the compound of formula IA as represented below;



Formula IA

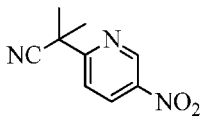
or a stereoisomer, a tautomer, a polymorph, a pharmaceutically acceptable salt or a solvate thereof;

wherein, R_2 is $-CH_3$ and R_3 is pyridyl which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -CN, -O-(C_1-C_8)alkyl, -NR_xR_y, and -(C_1-C_8)alkyl, wherein -(C_1-C_8)alkyl is optionally substituted with halogen; and R_x and R_y are independently selected from hydrogen or -(C_1-C_8)alkyl.

In an embodiment, the compound of formula IA is N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (referred to herein as the 'Compound A').

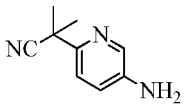
In another aspect the present invention relates to a process for preparation of compound of formula I (as described above) which involves;

a) preparation of the intermediate compound (2);



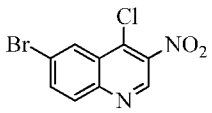
(2)

b) preparation of intermediate compound (3);



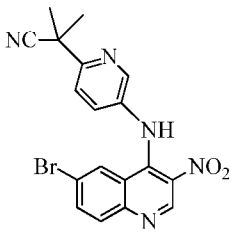
(3)

c) preparation of the intermediate compound (5);



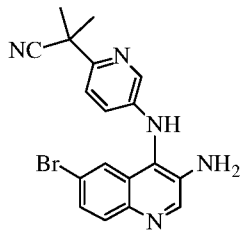
(5)

d) preparation of the intermediate compound (6);



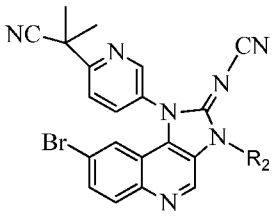
(6)

e) preparation of the intermediate compound (7);



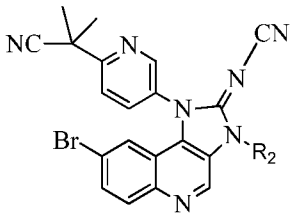
(7)

f) preparation of the compound of formula (8);



(8)

g) preparation of the compound of formula (9) and



(9) (wherein R_2 is $-CH_3$)

h) preparation of the compound of formula I.

In an aspect of the present invention the process for the preparation of the compound of formula I comprises the steps of:

a) methylating 5-nitro-2-pyridine acetonitrile (compound (1)) using methyl iodide in the presence of dimethylformamide (DMF) and sodium hydride to obtain the compound (2);

b) reducing the compound (2) using an iron catalyst to obtain the compound (3);

c) chlorinating 6-bromo-4-hydroxy-3-nitroquinoline (4) using phosphorus oxychloride($POCl_3$) in relatively lower volume in the presence of an organic solvent to obtain the compound (5);

d) reacting the compound (3) with the compound (5) in acetic acid medium to get intermediate compound (6);

e) reducing the compound (6) using iron catalyst to obtain compound (7);

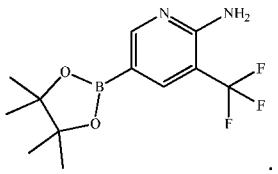
f) cyclising the compound (7) with a reagent selected from diphenylcyanocarbonoimidate or dimethyl cyanocarbonimidodithioate in the presence of a base selected from diisopropylethylamine or cesium carbonate, to obtain the compound (8);

g) methylating the compound (8) using methyl iodide to obtain the compound (9);

h) treating the compound (9) with a compound of formula, R_3-$B(OH)_3$,wherein R_3 is as defined above, to obtain the compound of formula I.

A representative compound of the formula R_3-$B(OH)_3$ is 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine, which can be procured from commercially available sources. Alternatively, the said compound can be prepared by the process described in PCT Application Publication No. WO2012/007926.

The compound 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine is represented as below:



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In an embodiment, the present invention relates to a process for the preparation of the compound of formula IA; comprising the steps of;

a) preparation of the intermediate compound (2) as described above;

b) preparation of the intermediate compound (3) as described above;

c) preparation of intermediate compound (5) as described above;

d) preparation of an intermediate compound (6) comprising reaction of the compound (3) with the compound (5) in acetic acid medium to obtain intermediate compound (6);

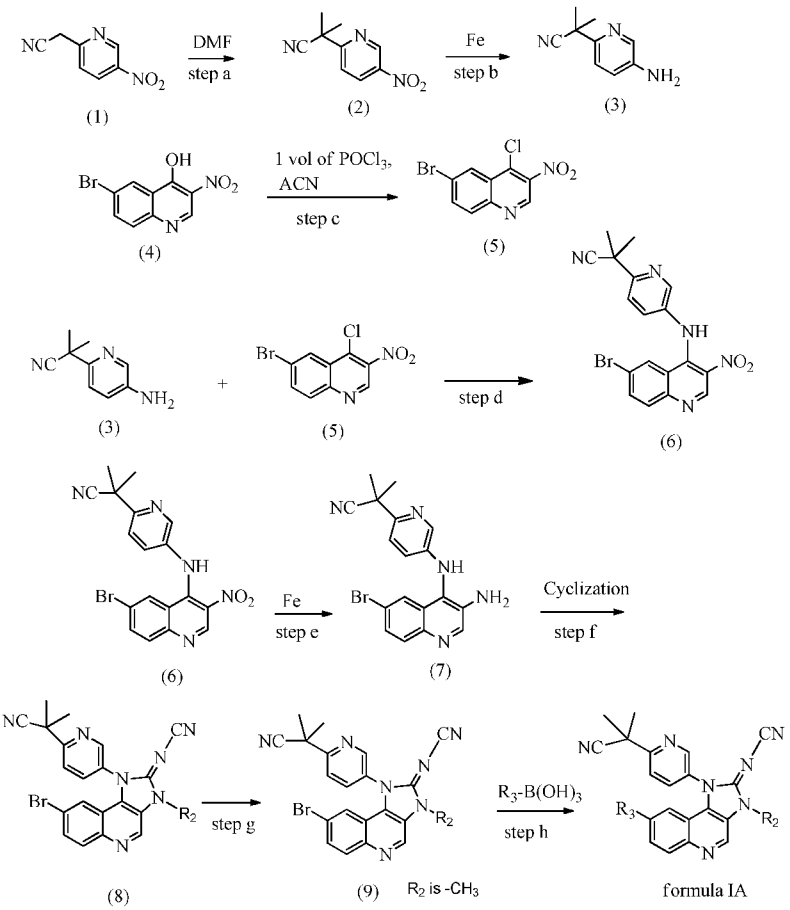
e) preparation of intermediate compound (7) comprising subjecting the compound (6) to reduction using iron catalyst to obtain the desired intermediate compound (7);

f) cyclisation of the compound (7) using diphenylcyanocarbonoimidate or dimethyl cyanocarbonimidodithioate in the presence of a base selected from diisopropylethylamine or cesium carbonate, to obtain the compound (8);

g) methylating the compound (8) using methyl iodide to obtain the compound (9);

h) treating the compound (9) with a compound of formula, R_3-$B(OH)_3$,wherein R_3 is as defined above, to obtain the compound of formula IA.

In accordance with the present invention, the process for preparation of compound of formula IA is represented in the following Scheme II; wherein for each of reference each reaction step is referred to as step(s) a, b, c, d, e, f, g and h respectively.



Scheme II

Each reaction step involved in the process for the preparation of compound of formula IA is further discussed below.

Step a: This step of the process for the preparation of the compound of formula IA involves preparation of 2-methyl-2-(5-nitropyridin-2-yl)propanenitrile (compound (2)) comprising reacting 2-(5-nitropyridin-2-yl)acetonitrile with methyl iodide in the presence of sodium hydride and DMF at a temperature ranging from -20°C to -10°C. Use of DMF is said

reaction step results in a cleaner and faster reaction. Moreover, the compound (2) can be used as such in the next step without any purification.

Step b: This step of the process for the preparation of the compound of formula IA involves preparation of 2-methyl-2-(5-aminopyridin-2-yl)propanenitrile (compound (3)) comprising subjecting the compound 2 to reduction using iron catalyst in the presence of ammonium chloride in an organic solvent selected from ethanol or tetrahydrofuran (THF) at a temperature ranging from 60℃ to 80℃ for 3 to 4 hours. After completion of reaction, the mixture was cooled to 25℃ to 30℃ and filtered. The solvent was distilled out from the reaction mixture and the compound (3) was isolated from the mixture.

Step c: This step of the process for the preparation of the compound of formula IA involves treating 6-bromo-4-hydroxy-3-nitroquinoline (compound (4)) is treated with lower volume of $POCl_3$ in the presence of a base and an organic solvent at a temperature ranging from 65℃ to 75℃ for 2 to 3 hours. In particular, the reaction is carried out using one volume of $POCl_3$ and acetonitrile as the organic solvent. After the completion of reaction, the mixture is cooled to 25℃ to 30℃ and the compound, 6-bromo-4-chloro-3-nitroquinoline (compound (5)) is isolated.

It was observed in the batch production of the compound (5) that when reaction was carried out using $POCl_3$ in higher volumes, for instance, in 4 volumes, as described in the PCT Publication No. WO2012/007926, the work up of the reaction becomes tedious and the product gets converted into the starting material. However, this problem is addressed by the process of the instant invention by which $POCl_3$ is used in relatively lower volume, for instance it is used in 1 volume only.

Step d: This step of the process for the preparation of the compound of formula IA involves preparation of 2-(5-((6-bromo-3-nitroquinolin-4-yl)amino)pyridin-2-yl)-2-ethylpropanenitrile (compound (6)) comprising reaction of 2-methyl-2-(5-aminopyridin-2-yl)propanenitrile (compound (3)) with 6-bromo-4-chloro-3-nitroquinoline (compound (5)) in acetic acid medium to obtain intermediate, compound (6).

Step e: This step of the process for the preparation of the compound of formula IA involves preparation of 2-(5-((6-bromo-3-aminoquinolin-4-yl)amino)pyridin-2-yl)-2-ethylpropanenitrile (compound (7)) comprising reduction of 2-(5-((6-bromo-3-nitroquinolin-4-yl)amino)pyridin-2-yl)-2-ethylpropanenitrile (compound (6)) using iron and ammonium chloride in an organic solvent selected from ethanol or THF at a temperature range from 60℃ to 80℃ for 2 to 3 hours to obtain the compound (7).

Step f: This step of the process for the preparation of the compound of formula IA involves reaction of compound (7) with a reagent selected from diphenylcyanocarbonoimidate or dimethyl cyanocarbonimidodithioate in the presence of a base selected from diisopropylethylamine or cesium carbonate, to obtain the compound (8). The resulting compound (8) is optionally purified with a solvent such as methanol, ethyl acetate or a mixture thereof.

Step g: This step of the process for the preparation of the compound of formula IA involves methylation of the compound (8) using methyl iodide in the presence of sodium hydride and an alcohol or DMF as solvent to obtain the compound (9).

Step h: This step of the process for the preparation of the compound of formula IA involves reaction of compound (9) in DMF with a compound of formula: R_3-$B(OH)_3$ (wherein R_3 is as defined above) in the presence of dichlorbis(triphenylphosphine)-palladium(II) and sodium carbonate at a temperature ranging from 80 to 90°C. After the completion of the reaction, the resulting reaction mixture is treated with charcoal and filtered. The filtrate is treated with silica-thiol (Si-thiol) at a temperature ranging from 75 to 80°C for 16 to 20 hours and the compound of formula IA is isolated. The advantage of treating the reaction mixture with Si-thiol is that it controls the palladium impurities in the final product which is isolated from the reaction mixture. It has been found that the level of palladium content gets reduced from about 500 ppm to about 1 ppm thereby making the process safer and commercially viable.

In an embodiment, the present invention relates to a process for the preparation of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) comprising the steps of;

a) methylating 2-(5-nitropyridin-2-yl)acetonitrile in the presence of sodium hydride and DMF to obtain 2-methyl-2-(5-nitropyridin-2-yl)propanenitrile;
b) subjecting 2-methyl-2-(5-nitropyridin-2-yl)propanenitrile to reduction using iron as reducing catalyst in presence of ammonium chloride to obtain 2-methyl-2-(5-aminopyridin-2-yl)propanenitrile;
c) treating 6-bromo-3-nitroquinoline with 1 volume of $POCl_3$ in presence of base to obtain 6-bromo-4-chloro-3-nitroquinoline;
d) subjecting 2-(5-((6-bromo-3-nitroquinolin-4-yl)amino)pyridin-2-yl)-2-ethylpropanenitrile to reduction using catalytic amount of iron as reducing catalyst in

presence of ammonium chloride to obtain 2-(5-((3-amino-6-bromoquinolin-4-yl)amino)pyridin-2-yl)-2-methylpropanenitrile;

e) treating 2-(5-((3-amino-6-bromoquinolin-4-yl)amino)pyridin-2-yl)-2-methylpropanenitrile with a reagent selected from diphenylcyanocarbonoimidate or dimethyl cyanocarbonimidodithioate in the presence of a base selected from diisopropylethylamine or cesium carbonate, to obtain N-(8-bromo-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide;

f) methylating N-(8-bromo-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide using methyl iodide in the presence of sodium hydride to obtain N-(8-bromo-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide;

g) optionally purifying N-(8-bromo-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide using an organic solvent;

h) treating N-(8-Bromo-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine at a temperature of 80-90°C for about 1 to 2 hour to obtain N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A).

In an embodiment of the present invention, N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) is optionally purified to get the desired compound in good purity.

According to an embodiment, Compound A is treated with Si-thiol prior to purification to control the metal content, preferably palladium content in the said Compound A.

The process for the preparation of the compound of formula I or formula IA or of the Compound A according to the present invention is advantageous in that none of the intermediates formed in the process as well as the final compound was purified using column chromatography. Thus, avoiding column chromatography purification renders the process provided by present invention economically viable at commercial scale.

In an embodiment, the process for the purification of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) comprising the steps of;

a) providing a slurry of the Compound A in a solvent;

b) heating the slurry obtained in step a) at a temperature ranging from 70 to 90°C;

c) cooling the hot solution of step b) to a temperature of 25 of 35°C and

d) isolating pure Compound A.

In an embodiment, the solvent used in step (a) of the process for purification of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) is selected from the group consisting of methanol, ethanol, n-propanol, isopropyl alcohol (IPA), butanol, dichloromethane, ethylene dichloride, chloroform, acetic acid, acetinitrile, carbon tetrachloride, toluene, xylene, hexane, heptanes, dimethylformamide (DMF) and water or a mixture thereof.

In an embodiment, the solvent used in step (a) of the purification process is DMF, water or IPA.

In an embodiment, the solvent used in step (a) of the purification process is dimethylformamide.

In an embodiment, the solvent used in step (a) of the purification process is water.

In an embodiment, the solvent used in step (a) of the purification process is isopropyl alcohol.

In an embodiment, the step b) is carried out at temperature of 70 to 90°C.

In an embodiment, the step b) is carried out under stirring for 2 to 4 hours.

In an embodiment, the step c) is carried out at temperature of 25 of 30°C.

In an embodiment, pure Compound A in step d) is isolated by filtering the compound obtained in step c) and washing it with suitable solvent used in step a) to get pure compound. In an embodiment, Compound A obtained in step d) can be purified with water to get the pure compound.

According to an embodiment the present invention relates to a process for purification of the Compound A which comprises isolating pure Compound A from a solution containing the Compound A and an organic solvent. The said organic solvent used for isolating pure Compound A is DMF.

According to an embodiment the present invention relates to a process for purification of the Compound A which comprises isolating pure Compound A from a solution containing the Compound A and an organic solvent. The said organic solvent used for isolating pure Compound A is water or IPA.

The process of the present invention, particularly the process for the purification according to the present invention provides N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) or pharmaceutically acceptable salt thereof, having a purity of at least 97%, preferably 98% by HPLC.

In an embodiment, the pure compound A can be converted to its pharmaceutically acceptable salts or hydrates or solvates by the processes known to the person skilled in the art.

In an embodiment, the present invention provides N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) having particle size distribution such that 90 volume percent of the particles (D_{90}) have particle size of less than about 250 microns, specifically less than about 100 microns, more specifically less than about 50 microns, still more specifically less than about 10 microns. The particles may be further micronized using conventional micronization techniques to get desired particle size.

In another embodiment, the particle size of the Compound A can be achieved by a mechanical process of reducing the size of particles which includes any one or more of cutting, crushing, milling, grinding, micronizing, spray drying or other particle size reduction methods known in the art. An appropriate mechanical process can be used to get the desired particle size range for the Compound A so as to impart on the compound good flowability, better dissolution and solubility thereby making it suitable for formulation.

Typically, the compound of formula I, particularly that of formula IA, more particularly Compound A obtained according to the process of the present invention can be micronized by jet milling method and the particle size is determined using a Malvern Mastersizer 2000 instrument, Scirocco 2000, which is commercially available from Malvern Instruments Ltd., United Kingdom.

Typically, the micronized Compound A (N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cynamide) obtained according to the process of the present invention has particle size

distribution such that D_{90} is less than about 7-10 μ, D_{50} is less than about 2-5 μ and D_{10} is less than about 0.5 - 1 μ.

It is a known fact that a chemical compound can possess multiple crystalline structures and this phenomenon is referred to as polymorphism. In drug discovery research, it has been demonstrated that certain specific polymorphs of a drug substance exhibit varying physical properties, however, obtaining proper polymorph of a drug substance is important to use the drug substance advantageously. Accordingly, a polymorph screening study was performed on the Compound A to obtain the desired polymorphs. Based on the polymorph screening study, it was found that compound A can exist in numerous polymorphic forms, however, only a few polymorphs of the said compound are found to be stable. One polymorphic form of the Compound A which is found to be the most stable form is designated herein as the Form A.

Accordingly, in an aspect, the present invention also relates to crystalline polymorphs of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) exhibiting an X-ray diffraction diagram as presented in the figures.

In another aspect, the present invention relates to a mixture of crystalline and amorphous form of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) exhibiting an X-ray diffraction diagram as presented in the figures.

According to an aspect, the present invention relates to a crystalline polymorph of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) referred to herein as Form A.

In an embodiment of the present invention, Form A of the Compound A exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2-theta values) of about 7.97, 11.38, 14.93, 15.95, 16.46, 17.40, 19.92, 20.98, 22.53, 22.84, 28.33, 29.05, 30.09 and 30.12 ± 0.2 degrees.

In an embodiment, of the present invention, Form A of the Compound A (exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2-theta values) of about 7.97, 11.38, 14.93, 15.95, 22.53 and 22.84 ± 0.2 degrees.

In another embodiment of the present invention, Form A of the Compound A exhibits at least the characteristic X-ray powder diffraction peaks shown in the following Table 1.

Table 1: X-ray powder diffraction peaks of Form A of the Compound A

2 theta values in Degrees	d spacing values in Angstrom	2 theta values in Degrees	d spacing values in Angstrom
7.97	11.07	23.91	3.71
10.47	8.43	24.74	3.59
10.95	8.07	25.50	3.48
11.38	7.76	26.28	3.38
14.46	6.11	26.69	3.33
14.93	5.92	27.2	3.27
15.38	5.75	27.36	3.25
15.95	5.55	28.33	3.14
16.46	5.37	29.04	3.07
17.40	5.09	30.12	2.96
18.07	4.90	31.01	2.88
18.83	4.70	31.34	2.85
19092	4.45	32.28	2.77
20.37	4.35	33.54	2.66
20.98	4.23	33.13	2.62
21.30	4.12	35.36	2.53
21.53	4.12	35.81	2.50
22.27	3.98	36.81	2.43
22.53	3.94	38.19	2.35
22.84	3.89	38.60	2.33

In another embodiment of the present invention, Form A of Compound A exhibits an X-ray powder diffraction pattern as shown in Figure 1.

In yet another embodiment of the present invention, Form A of the Compound A represents Differential Scanning calorimetry (DSC) onset of 295.98°C ± 2.0°C as shown in Figure 2.

In yet another embodiment of the present invention, Form A of the Compound A is characterized by an infra-red (IR) spectrum showing bands at about 3593, 3501, 3438, 3335, 3204, 2180, 1847, 1626, and 499 cm^{-1} as shown in Figure 3.

In an aspect, the present invention provides a process for the preparation of crystalline polymorph of the compound A i.e. the Form A of compound A (N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide) comprising the steps of;

a) forming a slurry of the Compound A in a solvent;

b) heating the slurry as obtained in step (a) at a temperature ranging from about 75°C to 80°C;

c) cooling the solution obtained in the above step (b) to a temperature of about 25°C to 35°C; and

d) isolating the Form A of the Compound A

Suitable solvents used for the preparation of crystalline polymorph of Compound A i.e. the Form A include, but are not limited to, an alcoholic solvent aromatic hydrocarbon solvent, water and/or mixtures thereof.

In an embodiment, an alcoholic solvent is used for the preparation of crystalline polymorph of compound A; which is selected from the group consisting of methanol, ethanol, isopropanol and butanol or a mixture thereof.

In an embodiment, an aromatic hydrocarbon is used for the preparation of crystalline polymorph of Compound A; which is selected from isobutyl benzene, toluene or xylene or a mixture thereof.

In an embodiment, Form A of the Compound A is prepared by suspending the Compound A in a solvent selected from the group consisting of water, IPA, toluene, xylene, isobutyl benzene and heating the suspension at temperature 60 to 80℃ for 2 to 3 hours. The hot solution is then cooled to 25 to 30℃ to obtain the crystalline Form A.

In an embodiment, Form A of the Compound A is prepared by suspending the Compound A in IPA and heating the suspension at temperature ranging from 60 to 80℃ for 2 to 3 hours. The hot solution is then cooled to 25 to 35℃ to obtain the crystalline Form A.

In an embodiment, Form A of the Compound A is prepared by suspending the Compound A in water and heating the suspension at temperature ranging from 60 to 80℃ for 2 to 3 hours. The hot solution is then cooled to 25 to 35℃ to obtain the crystalline Form A.

The Form A of the Compound A is a substantially crystalline Form A of the Compound A and refers to at least 80% of the crystalline Form A of the Compound A.

In an embodiment, the Form A of the Compound A is at least 90% of the crystalline Form A of the Compound A.

In an embodiment, the Form A of compound is at least 95% of the crystalline Form A of the Compound A.

In another aspect, the present invention relates to Form B of the Compound A (N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide).

In an aspect of the present invention, Form B of the Compound A is obtained in a crystalline form which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2-theta values) of about: 10.15, 14.33, 17.35, 19.26, 19.66, 21.90, 23.62, 25.91 and 26.06 ± 0.2 degrees.

In an embodiment of the present invention, Form B of the Compound A is obtained in a crystalline form which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2-theta values) of about: 19.26, 19.66, 21.90, 25.91 and 26.06 ± 0.2 degrees.

In an embodiment of the present invention, Form B of the Compound A exhibits at least the characteristic X-ray powder diffraction peaks shown in the following Table 2.

Table 2: X-ray powder diffraction peaks of Form B of the Compound A

2 theta values in Degrees	d spacing values in Angstrom	2 theta values in Degrees	d spacing values in Angstrom
7.31	12.06	25.91	3.43
10.15	8.70	26.06	3.41
10.77	8.20	26.45	3.36
14.57	6.07	26.66	3.34
11.32	7.80	26.95	3.30
12.73	6.94	27.23	3.27
13.59	6.50	27.39	3.25
14.33	6.17	27.86	3.19
14.98	5.90	28.35	3.14
16.09	5.50	28.87	3.08
16.44	5.38	29.29	3.04
16.80	5.27	29.92	2.98
17.06	5.19	30.67	2.91
17.35	5.10	30.85	2.89

17.59	5.03	31.50	2.83
19.26	4.60	32.44	2.75
19.66	4.51	32.90	2.71
19.94	4.44	33.73	2.65
20.36	4.35	33.91	2.64
21.34	4.15	34.45	2.60
21.62	4.10	34.77	2.57
21.90	4.05	35.55	2.52
22.40	3.96	36.44	2.46
22.80	3.89	37.21	2.41
23.09	3.84	38.39	2.34
23.62	3.76	38.67	2.32
24.27	3.66	39.06	2.30
25.59	3.47		

In an embodiment of the present invention, Form B of the Compound A exhibits an X-ray powder diffraction pattern as shown in the Figure 4.

In yet another embodiment of the present invention, Form B of the compound A represents Differential Scanning Calorimetry (DSC) onset of 195.48±2.0°C and 296.22±2.0°C as shown in the Figure 5.

In an embodiment of the present invention, Form B of the Compound A is characterized by an infra-red (IR) spectrum showing bands at about 3458, 3328, 3189, 2180, 1965, 1711, 1618 and 1498 cm^{-1} as shown in the Figure 6.

In an aspect, the present invention provides a process for the preparation of Form B of the Compound A (N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide) comprising the steps of;

a) forming a slurry of the Compound A in an organic solvent;
b) heating the slurry of step a) at a temperature ranging from 60°C to 80°C;
c) cooling the obtained solution to a temperature of about 25°C to 35°C and
d) isolating the crystalline Form B.

Suitable solvents include, but are not limited to, methyl ethyl ketone, acetone and/or mixtures thereof.

In an embodiment, Form B of the Compound A is prepared by suspending the Compound A in methyl ethyl ketone and heating the resulting mixture at a temperature ranging from 60 to 80℃ for 2-3 hours. The hot solution is then cooled to a temperature of about 25 to 30℃ to obtain the crystalline polymorph of Compound A i.e. the Form B.

In another embodiment, Form B of the Compound A is prepared by suspending the Compound A in acetone and heating the resulting mixture at temperature ranging from 60 to 80℃ for 2-3 hours. The hot solution is then cooled to a temperature of about 25 to 35℃ to obtain the crystalline Form B.

The Form B of the Compound A is a substantially crystalline Form B of the Compound A and refers to at least 80% of the crystalline Form B of the Compound A.

In an embodiment, the Form B of the Compound A is at least 90% of the crystalline Form B of the Compound A.

In an embodiment, the Form B of Compound A is at least 95% of the crystalline Form B of the Compound A.

In another aspect, the present invention provides a mixture of crystalline and amorphous form of the Compound A (N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide).

In an embodiment of the present invention, a mixture of crystalline and amorphous form of the Compound A exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2-theta values) of about: 5.06, 5.24, 7.72, 8.28, 10.23, 12.78, 13.43, 14.19, 14.47, 15.16, 15.95, 16.48, 17.51, 17.86, 18.37, 19.20, 19.89, 20.95, 21.52, 22.56, 23.28, 25.05, 25.55, 26.40, 26.71, 27.65, 29.06 and 30.32 ± 0.2 degrees.

In an embodiment of the present invention, a mixture of crystalline and amorphous form of the Compound A exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2-theta values) of about: 5.06, 5.24, 15.95, 17.51, 17.86, 18.37, 25.05, 25.55 and 26.40 ± 0.2 degrees.

In another embodiment of the present invention, a mixture of crystalline and amorphous form of the Compound A exhibits at least the characteristic X-ray powder diffraction peaks shown in the following Table 3.

Table 3: X-ray powder diffraction peaks of a mixture of crystalline and amorphous form of the Compound A

2 theta values in Degrees	d spacing values in Angstrom
4.63	19.06
5.06	17.43
5.24	16.82
6.83	12.91
7.72	11.43
8.28	10.66
9.13	9.67
10.23	8.63
12.21	7.23
12.78	6.91
13.43	6.58
14.19	6.23
14.47	6.11
15.16	5.83
15.95	5.55
16.48	5.37
17.51	5.05

2 theta values in Degrees	d spacing values in Angstrom
17.86	4.96
18.37	4.82
19.20	4.61
19.89	4.45
20.95	4.23
21.52	4.12
22.56	3.93
23.28	3.81
25.05	3.55
25.55	3.48
26.40	3.37
26.71	3.33
27.65	3.22
29.06	3.06
30.32	2.94
35.27	2.54
38.51	2.33

A mixture of crystalline and amorphous form of the compound A according to the present invention is characterized by an X-ray powder diffraction pattern as that shown in the Figure 7.

In another embodiment of the present invention, a mixture of crystalline and amorphous form of the compound A shows DSC onsets of 295.88°C ±2.0°C as shown in the Figure 8.

In yet another embodiment of the present invention, a mixture of crystalline and amorphous form of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide is characterized by an infra-red (IR) spectrum showing bands at about 3478, 3328, 3197, 2185, 1618 and 1499 cm^{-1} as shown in the Figure 9.

In an aspect, the present invention provides a process for the preparation of a mixture of crystalline and amorphous form of the Compound A (N-(8-(6-amino-5-

(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide) comprising the steps of;

a) providing a slurry of the Compound A in an organic solvent;

b) heating the solution obtained in step a) at temperature ranging from 60 to 80°C;

c) cooling the solution to a temperature of about 25 to 35°C and

d) isolating the mixture of crystalline and amorphous form of the Compound A.

The organic solvent used in step a) is dimethylformamide (DMF).

In an embodiment, the mixture of crystalline and amorphous form of the Compound A is prepared by suspending the Compound A in DMF and heating the suspension at temperature ranging from 60 to 80°C for 2 to 3 hours. The hot solution is then cooled to a temperature of about 25 to 30°C to obtain the mixture of crystalline and amorphous form of the Compound A.

The crystalline forms of the Compound A according to present invention can exist in both unsolvated and solvated forms. The term 'solvate' as used herein refers to a molecular complex comprising the Compound A and an amount of one or more pharmaceutically acceptable solvent selected from tetrahydrofuran, chloroform, acetone, 1,4-dioxane, 1,2-ethanediol, N-methyl-2-pyrrolidone, formamide, ethanol, dimethylsulfoxide, dichloromethane, acetonitrile or ethanol.

According to the present invention the Form A of the Compound A and/or the Form B of the Compound A and/or the mixture of the crystalline and amorphous form of the Compound A is/are referred to as polymorphic crystalline form of the Compound A.

In an aspect, the present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of the polymorphic crystalline form of the compound A and at least one pharmaceutically acceptable excipient; wherein said polymorphic crystalline form is selected from the Form A of the Compound A, the Form B of the compound A or a mixture of the crystalline and amorphous form of the Compound A.

In an embodiment, the pharmaceutical composition comprises a therapeutically effective amount of the Form A of the Compound A and at least one pharmaceutically acceptable excipient.

In another embodiment, the pharmaceutical composition comprises a therapeutically effective amount of the Form B of the Compound A and at least one pharmaceutically acceptable excipient.

In an embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a mixture of the crystalline and amorphous form of the Compound A and at least one pharmaceutically acceptable excipient.

Pharmaceutically acceptable excipient(s), carrier(s), adjuvant(s) and vehicle(s) that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers and polyethylene glycol.

The administration route of the pharmaceutical composition of the present invention is not particularly limited. In one embodiment, the active ingredients (Compound A in crystalline and/or a mixture of crystalline and amorphous form or pharmaceutically acceptable salts thereof as described herein) comprised in the composition may have to be administered by different routes either orally or parenterally depending on the dosage form. The dosage form suitable for oral administration may be a tablet or capsule, forms of parenteral administration include intravenous injection, intravenous infusion, subcutaneous injection, transdermal injection, intraperitoneal injection and so on. In the case of tablets for oral use, carriers which are commonly used include lactose, corn starch, magnesium carbonate, talc, and sugar, and lubricating agents such as magnesium stearate are commonly added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually employed, and the pH of the solutions should be suitably adjusted and buffered.

In practice, oral preparations for oral administration may be produced by adding to the active ingredients the fillers, and if necessary, binders, disintegrants, lubricants, coloring agents, flavoring agents, etc. and formulating the resultant mixture according to conventional procedures into tablets, coated tablets, granules, subtle granules, powders, capsules or the like. Resultant tablets and granules may be appropriately coated with, for example, sugar or gelatin according to necessity.

The polymorphic forms of the Compound A (as described herein) can be administered as pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to

90%) of active ingredient in combination with a pharmaceutically acceptable carrier. The ultimate dose will depend on the condition being treated, severity of symptom, the route of administration, the age, sex, body weight, condition of the patient, sensitivity difference of the patient, the mode, time, interval and duration of administration, the nature, formulation and type of the preparation, the type of the active ingredient, etc.

In one aspect, the polymorphic crystalline form of the Compound A (as described herein) is provided for use in the treatment of a disease or disorder mediated by kinases selected from a group consisting of PI3K (phosphoinositide 3-kinases), mTOR (mammalian target of rapamycin), DNA-PK (DNA-dependent protein kinase) and ALKl (activin receptor-like kinase 1) or a combination thereof; wherein said polymorphic crystalline form is selected from the Form A of the Compound A, the Form B of the Compound A or a mixture of the crystalline and amorphous form of the Compound A.

In one aspect, the invention relates to N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) in a mixture of crystalline and amorphous form for use in the treatment of diseases or disorders mediated by one or more kinases, particularly proliferative diseases or disorders such as cancer.

In an embodiment, the disease or disorder mediated by one or more kinases (as described herein) is a proliferative disease or disorder, an inflammatory disorder or an angiogenesis related disorder.

In an embodiment, the proliferative disease or disorder is cancer.

Accordingly, in an embodiment of the present invention, the polymorphic crystalline form of the Compound A is provided for use in the treatment of cancer; wherein said polymorphic crystalline form is selected from the Form A of the Compound A, the Form B of the Compound A or a mixture of the crystalline and amorphous form of the Compound A.

In another embodiment of the present invention, there is provided a method for the treatment of cancer in a subject; comprising administering to the subject a therapeutically effective amount of the polymorphic crystalline form of the Compound A selected from the Form A of the Compound A, the Form B of the Compound A or a mixture of the crystalline and amorphous form of the Compound A.

In an embodiment of the present invention, there is provided use of the polymorphic crystalline form of the Compound A for the manufacture of a medicament for use in the treatment of cancer; wherein said polymorphic crystalline form is selected from the Form A

of the Compound A, the Form B of the Compound A or a mixture of the crystalline and amorphous form of the Compound A.

In an embodiment, the cancer is selected from the group consisting of leukemia such as acute lymphocytic leukemia; acute myeloid leukemia; adult acute myeloid leukemia; acute lymphoblastic leukemia; chronic lymphocytic leukemia; chronic myeloid leukemia; hairy cell leukemia, lung cancer including non-small-cell lung cancer and small-cell lung cancer, brain tumors such as brain stem glioma; glioblastoma; astrocytoma including cerebellar astrocytoma and cerebral astrocytoma, visual pathway and hypothalamic glioma; supratentorial primitive neuroectodermal and pineal tumors; medulloblastoma, lymphoma such as primary central nervous system lymphoma; non-Hodgkin's lymphoma particularly mantle cell lymphoma, Hodgkin's disease, liver cancer such as hepatocellular carcinoma, kidney cancer such as renal cell carcinoma and Wilms' tumor, sarcoma such as Ewing's sarcoma family of tumors; osteosarcoma; rhabdomyosarcoma; soft tissue sarcomas, mesothelioma, bladder cancer, breast cancer, endometrial cancer, head and neck cancer, melanoma, cervical cancer, thyroid cancer, gastric cancer, germ cell tumor, cholangiocarcinoma, extracranial cancer, malignant fibrous histiocytoma of bone, retinoblastoma, esophageal cancer, multiple myeloma, oral cancer, pancreatic cancer, ependymoma, neuroblastoma, skin cancer, ovarian cancer, recurrent ovarian cancer, prostate cancer, testicular cancer, colorectal cancer, lymphoproliferative disease, refractory multiple myeloma, resistant multiple myeloma and myeloproliferative disorder.

In an embodiment, the present invention relates to use of the polymorphic crystalline form of the Compound A; in combination with a further therapeutically active agent, in the treatment of a disease or a condition mediated by one or more kinases (as described herein); wherein said polymorphic crystalline form is selected from the Form A of the Compound A, the Form B of the Compound A or a mixture of the crystalline and amorphous form of the Compound A. The therapeutically active agents include, but are not limited to, known analgesics, immunosuppressants, anti-inflammatory agents and anti-cancer agents.

It is understood that modifications that do not substantially affect the activity of the various embodiments of this invention are included within scope of the invention disclosed herein. Accordingly, the following examples are intended to illustrate but not to limit scope of the present invention.

General Experimental Conditions:

X-ray Powder Diffraction (XRPD):

X-ray powder diffraction pattern were obtained on Bruker D8 Advance (Bragg Brentano geometry) using Copper Kα radiation with scanning range between 3 to 40 degree 2 [theta] at scanning speed of 0.25 steps/sec.

Differential Scanning Calorimeter (DSC):

Differential Scanning Calorimetry was performed on Diamond DSC of Perkin Elmer instrument. The experiments were performed at a heating rate of 20°C/minute over a temperature range of 40°C-320°C purging with nitrogen at a flow rate of 25ml/min.

Fourier Transform Infrared (FTIR) spectra:

The FT-IR spectra were obtained on Perkin Elmer instrument in the range of 450-4000 cm^{-1} with a resolution of 4 cm^{-1}.

Unless otherwise stated all temperatures are in degree Celsius. Also, in the examples described below and throughout the specification, abbreviations have the following meanings:

Abbreviations:

ATP: Adenosine triphosphate	h: hour(s)
MeOH: Methanol	min: minutes
NaH: Sodium hydride	$POCl_3$: Phosphorus oxychloride
DCM: Dichloromethane	g: Gram
$NaHCO_3$: Sodium bicarbonate	HCl: Hydrochloric acid
NaOH: Sodium hydroxide	RT: Room Temperature (20 to 30 °C)
Na_2SO_4: Sodium sulphate	mL: Milliliter
THF: Tetrahydrofuran	mmol: Millimolar

Examples:

Example 1

Preparation of the compound A (N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide)

Step 1: Synthesis of 2-methyl-2-(5-nitropyridin-2-yl)-propanenitrile (Compound 2)

A solution of 2-(5-nitropyridin-2-yl)acetonitrile (250 g) in DMF (750 mL) was added drop wise to a mixture of sodium hydride (126.44 g) and dimethylformamide (2000 mL) and the mass was cooled to a temperature ranging from -15 to -10°C over a period of 1 h at -15 to

-10°C. Methyl iodide (656.6 g) was added to the reaction mass and stirred for 25 to 30 min. The temperature was raised to 20-25°C over a period of 1 h and the reaction mass was maintained for 2 h at the same temperature. The reaction mass was cooled to temperature of -15 to -10°C and quenched with methanol (250 mL) and followed by 20% ammonium chloride solution (1500 mL) to attain pH of reaction mixture to 6.0 to 6.5. The reaction mass was diluted with water (4750 mL). Mass was filtered and washed the bed with water (250 mL) followed by *n*-heptane (500 mL). The resulting compound was dried below 40°C to get title compound (250 g). Yield: 83% g,

Purity: 96.6%.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.43 (d, 1H, J=2.7Hz), 8.55 (dd, 1H, J=8.7Hz, 2.4Hz), 7.86 (d, 1H, J=8.7Hz), 1.82 (s, 6H).

Mass Spectrum (MS): m/z 192 (M+1)

Step 2: Synthesis of 2-(5-aminopyridin-2-yl)-2-methylpropanenitrile (Compound 3)

2-Methyl-2-(5-nitropyridin-2-yl)propanenitrile (compound 2) (280 g), iron (163.5 g) and ammonium chloride (232.1 g) were added to a mixture of ethanol (1568 mL), THF (700 mL), water (350 mL) and heated the reaction mass to a temperature ranging from 70 to 75°C for 3 to 4 h. The reaction mass was cooled to 25 to 30°C, filtered through celite bed and washed the bed with ethanol (1400 mL). The filtrate was distilled out completely below 50°C. The resulting residue after the distillation was dissolved in ethyl acetate (4200 mL) and washed with water (1400 mL). The organic layer was separated and washed with 10% sodium chloride solution (1400 mL). Organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was distilled out under vacuum until 280 mL of reaction mass volume. The residue was chased below 40°C with *n*-heptane (560 mL) and suspended in *n*-heptane (560 mL). The mass was cooled to 25-30°C, filtered and washed with *n*-heptane (280 mL). The compound was dried at 45-50°C to get title compound (140 g). Yield: 59%

Purity: 96.12%

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.89 (d, 1H, *J*=2.7Hz), 7.13 (d, 1H, *J*=8.7Hz), 6.93 (dd, 1H, *J*=2.7Hz, 8.7Hz), 5.38 (s, 2H), 1.57 (s, 6H).

MS: m/z 162 (M+1)

Step 3: Synthesis of 5-bromo-3-(trifluoromethyl)pyridin-2-amine

3-(Trifluoromethyl)-2-pyridinamine (150 g) was added to acetic acid (1500 mL) and stirred the mass for 10 to 15 min. Bromine (47.54 mL) was added to the mixture over a

period of 45-60 min at 25-30°C. The reaction mass was maintained under stirring at 25-30°C for 2-3 h. After completion of the reaction, the mass was cooled to 10 to 15°C and diluted with water (2500 mL) subsequently neutralized the mass with solid sodium carbonate (420 g). The reaction mass was filtered and bed was washed with water (300 mL) and dried at 25 to 30°C for 12 h. The dried mass was dissolved in ethyl acetate (2250 mL) and washed with 5% sodium bicarbonate solution (750 mL). The separated organic layer was washed with 10% sodium chloride solution (750 mL). Clean organic layer was distilled out completely to obtain the title compound (183 g). Yield: 82%

Purity: 99.52%

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.25 (s, 1H), 7.89 (s, 1H), 6.7 (bs, 2H).

MS: m/z 242 (M+1)

Step 4: Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine

A mixture of 5-bromo-3-(trifluoromethyl)pyridin-2-amine (180 g) and 1,4-dioxane (3600 mL) was stirred in a flask. Bis(pinacolato)diboron (284.47 g), potassium acetate (109.95 g) and 1,1-bis(diphenylphosphino)ferrocene dichloropalladium (II) DCM complex (18 g), were then added under stirring at a temperature of about 25 to 30°C. Reaction mass was heated to 95 to 100°C and maintained for 15-16 hr. After the completion of reaction, the mass was cooled to 25 to 30°C, filtered through celite bed and the bed was washed with ethyl acetate (1800 mL). The filtrate was distilled out completely under vacuum to get crude title compound (450 g).

Purification

The crude title compound was dissolved in methanol (1800 mL) in a round bottom flask. Charcoal (45 g) and silica gel (60-120 mesh size, 450 g) were added to the mass and maintained under stirring at a temperature of about 25 to 30°C for 1 h. The mass was filtered through celite bed and washed the bed with methanol (450 mL). The filtrate was added into a flask containing cold water (6750 mL) at 0-5°C, over a period of 1 h. The precipitated solid was filtered out, washed with cold water (900 mL). The wet compound was unloaded and dried at 45 to 50°C to obtain the title compound (209 g). Yield: 97.47%

Purity: 98.43%

^{1}H NMR (300 MHz, DMSO-d6): δ 8.38 (s, 1H), 7.80 (s, 1H), 6.92 (s, 2H), 1.27 (s, 12H).

MS: m/z 289.1 (M+1)

Step 5: Synthesis of 6-bromo-4-chloro-3-nitroquinoline (Compound 5)

6-Bromo-3-nitroquinolin-4-ol (50 g) and N,N-diisopropylethylamine (60 mL) were added to acetonitrile (500 mL) and stirred for 10 to 15 min under nitrogen atmosphere. The reaction mass was cooled to a temperature of about 0-5°C and phosphorusoxychloride (50 mL) was added dropwise to the cooled solution while maintaining the temperature below 10°C. The reaction mass was heated to 70 to 75°C for 2 to 3 h. After completion of the reaction, the mass was cooled to 25 to 30°C. The cooled reaction mass was added dropwise into a mixture of ice-water (1.25 Kg) and sodium chloride (50 g) maintaining the temperature below 0°C. The mixture was stirred for 15 to 30 min. The compound obtained was filtered and washed with ice-cold water (250 mL). The wet compound was dissolved in MDC (750 mL) and filtered through celite bed. The bed was washed with MDC (250 mL). The combined organic layer from the filtrate was separated and washed with ice cold water (500 mL). The separated organic layer was dried over anhydrous sodium sulphate and subjected to distillation below 35°C under vacuum to obtain the title compound (55 g). This compound was dissolved in 500 mL of acetic acid and used for the next step without isolation. Yield: 93.5%

Step 6: Synthesis of 2-(5-((6-bromo-3-nitroquinolin-4-yl)amino)pyridin-2-yl)-2-methylpropanenitrile (Compound 6)

2-(5-Aminopyridin-2-yl)-2-methylpropanenitrile (28 g) was added to a solution of 6-bromo-4-chloro-3-nitroquinoline (55 g) in acetic acid (500 mL) under stirring. The reaction mass was maintained for 12 to 16 h at a temperature of about 25 to 30°C. After the completion of reaction, the precipitated compound was filtered. The bed was washed with acetic acid (100 mL) followed by water (250 mL). The wet solid was stirred in water (250 mL) and filtered. The wet solid was then stirred again in water (250 mL) and adjusted the pH of water to 7 with 100 mL of 5% solution of sodium bicarbonate solution and filtered. The bed was washed with water (500 mL) and unloaded the compound in a tray. Compound was subjected to drying at 50 to 55 °C to obtain the title compound. Yield: 59%

Purity: 95%

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.19 (bs, 1H), 9.09 (s, 1H), 8.70 (d, 1H, *J*=1.5Hz), 8.41 (s, 1H), 8.01 (d, 1H, *J*=5.1Hz), 7.95 (d, 1H, *J*=5.1Hz), 7.50 (s, 2H), 1.68 (s, 6H).

MS: m/z 412 (M+1)

Step 7: Synthesis of 2-(5-((3-amino-6-bromoquinolin-4-yl)amino)pyridin-2-yl)-2-methylpropanenitrile (Compound 7)

Ammonium chloride (45 g), iron (56 g; 100 mesh electrolytic) and 2-(5-((6-bromo-3-nitroquinolin-4-yl)amino)pyridin-2-yl)-2-methylpropanenitrile (100 g) were added to a mixture of ethanol (560 mL), THF (280 mL), water (140 mL) and heated to a temperature of about 70 to 75°C for 2 to 3 h. The reaction mass was cooled to a temperature of about 25-30°C and filtered through celite bed. The filtrate was subjected to distillation until it reaches volume of ~300 mL inside the flask. The mixture was charged into a mixture of ice-water (1.5 Kg) maintaining the temperature below 10°C. The mass was stirred for 30 to 45 min. The solid obtained was filtered, washed with water (500 mL) and dried to obtain the title compound (87 g). Yield: 93%

Purity: 95.6%

^{1}H NMR (300 MHz, DMSO-d6): δ 8.60 (s, 1H), 8.15 (s, 1H), 8.01 (d, 1H, J=2.1Hz), 7.86 (s, 1H), 7.77 (d, 1H, J=9Hz), 7.47 (d, 1H, 8.7Hz), 7.30 (d, 1H, J=8.4Hz), 6.67 (dd, 1H, J=2.4Hz, 8.4Hz), 5.57 (s, 2H), 1.61 (s, 6H).

MS: m/z 384.1 (M+1)

Step 8: Synthesis of *N*-(8-bromo-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound 8)

2-(5-((3-amino-6-bromoquinolin-4-yl)amino)pyridin-2-yl)-2-methylpropanenitrile (163.5 g), cesium carbonate (209 g) and dimethyl cyanodithioimino carbonate (156.4 g) in DMF (820 mL) were taken in a round bottom flask and heated to 60 to 65°C for 24 to 25 h under stirring. After completion of the reaction, the mass was cooled to 25 to 30°C. The cooled reaction mass was added to a solution of ammonium chloride (30%, 3270 mL) while maintaining the temperature below 0-5°C. The pH of the reaction mass was adjusted in the range of 4 to 5 with 1N hydrochloric acid (~ 817.5 mL). The temperature of the reaction mass was raised to 25 to 30°C and stirred for 15 to 30 min. The precipitated compound was filtered and washed twice with water (816 mL) and dried at 50 to 55°C. The dried compound was added to a mixture of methanol (1400 mL) and ethyl acetate (600 mL) then the mixture was heated to 50 to 55°C for 1 to 1.15 h. The mass was then cooled to 25 to 30°C. The solid obtained was filtered, washed with a mixture of 30% methanol in ethyl acetate (200 mL) and dried at 45 to 50°C to get title compound (122 g). Yield: 74.7%

Purity: 98%

^{1}H NMR (300 MHz, DMSO-d6): δ 8.82 (s, 1H), 8.73 (d, 1H, J=2.1Hz), 8.09 (dd, 1H, J=2.4Hz, 8.4Hz), 7.88 (d, 2H, J=8.7Hz), 7.49 (dd, 1H, J=1.8Hz, 8.7Hz), 6.91 (d, 1H, J=2.1Hz), 1.80 (s, 6H).

MS: m/z 434 (M+1)

Step 9: Synthesis of *N*-(8-bromo-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound 9)

Sodium hydride (30.84 g) was added in DMF (2200 mL) and cooled the mass to a temperature of about -5 to 0°C. N-(8-bromo-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (220 g) was added to the cooled mixture at -5 to 0°C. Methyl iodide (180.57 g) was added dropwise to the reaction mass and temperature of the mixture was raised to 25 to 30°C and maintained for 2 to 3 h. After completion of the reaction, the reaction mass was cooled to -10 to -5 °C and quenched with methanol (110 mL) followed by ammonium chloride solution (20%, 440 mL). Reaction mass was diluted with water (3300 mL) and the mixture was stirred for 30 min. The precipitated compound was filtered, washed with water (440 mL) followed by *n*-heptane (440 mL). Compound was unloaded in a tray and dried at 50 to 55°C to get crude compound (250 g).

Purification 1:

The crude compound was added to MDC (5000 mL) and stirred for 60 min. The mass was filtered. The layer of the bed was suspended in MDC (5000 mL), stirred for 30 to 45 min and filtered. The combined filtrate was subjected to distillation under vacuum until residue. The obtained mass was stirred with *n*-heptane (500 mL) as slurry and stirred for 30 to 45 min. The compound obtained was filtered, washed the bed with *n*-heptane (100 mL). Compound was unloaded and dried at 45 to 50°C to get partially purified compound (150 g).

Purification 2:

The partially purified compound (150 g) was charged in a mixture of methanol (1050 mL): ethyl acetate (450 mL) and heated to 50 to 55°C for 1 to 1.15 h. The solution was cooled to a temperature of about 25 to 30°C and filtered the compound. Bed was washed with a mixture of 30% methanol in ethyl acetate (150 mL). Compound was unloaded in a tray and dried at 45 to 50°C to get the title compound (116 g). Yield: 57.7%,

Purity: 94%

^{1}H NMR (300 MHz, DMSO-d6): δ 9.27 (s, 1H), 9.03 (d, 1H, J=2.1Hz), 8.40 (dd, 1H, J=2.4Hz, 8.4Hz), 8.06 (d, 2H, J=9.3Hz), 7.78 (dd, 1H, J=1.8Hz, 9Hz), 6.70 (d, 1H, J=2.1Hz), 3.88 (s, 3H), 1.81 (s, 6H).

MS: m/z 446.1 (M+1)

Step 10

Synthesis of *N*-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A)

N-(8-Bromo-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (10g) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine (12.9 g) were added in DMF (100 mL) in a round bottom flask. The reaction mass was purged with nitrogen for 15 min and added sodium carbonate (5.9 g), purified water (5 mL) and dichlorobis(triphenylphosphine)palladium (II) (0.95 g). The reaction mixture was then heated to a temperature of about 85 to 90°C for 0.5 to 1 h. After completion of the reaction, activated charcoal (0.1 g) was added into it and stirred for 15 to 30 min. The reaction mass was filtered through celite bed and washed the bed with hot DMF (10 mL). The filtrate was treated with Si-thiol (7.5 g) at 75 to 80°C for 16 to 20 h. The solid mass was filtered through celite bed and washed bed with hot DMF (10 mL). The filtrate obtained was cooled to 0 to 5°C over a period of 2 to 3 h. The solid obtained was filtered and washed with cold DMF (10 mL).

Purification:

The wet compound (15 g) as obtained above was added to water (100 mL) and heated to a temperature of about 80 to 85°C with stirring for 2 h. The mass was cooled to a temperature of about 25 to 30°C, filtered and washed with water (30 mL) to get the solid (12 g).

The wet compound (12 g) was added to IPA (100 mL) and heated to a temperature of about 80 to 85°C for 2 h. The mass was cooled to 25 to 30°C. The solid obtained was filtered and washed with IPA (30 mL). Compound was unloaded in a tray and dried at 45 to 50°C to obtain the title compound (8 g)

Yield: 67.8%

Purity: 98%.

^{1}H NMR (300 MHz, DMSO-d6): δ 9.23 (s, 1H), 9.07 (d, 1H, J=2.1Hz), 8.50 (m, 1H), 8.19 (d, 2H, J=9Hz), 8.01 (d, 2H, J=7.8Hz), 7.75 (s, 1H), 6.90 (d, 1H, J=1.8Hz), 6.75 (s, 2H), 3.92 (s, 3H), 1.80 (s, 6H).

MS: m/z 528.2 (M+1)

Example 2

Polymorph screening for the Compound A:

The polymorph screening of Compound A involves two crystallization methods: slurry conversion and evaporative experiments.

Slurry Experiments:

The experiments were carried out by stirring a mixture of the compound (Compound A) in a solvent at a controlled temperature. The solvent can be selected from the group consisting of tetrahydrofuran (THF), chloroform, acetone, 1,4-dioxane, 1,2-ethanediol, dimethylformamide (DMF), acetonitrile, ethanol, dimethyl sulfoxide (DMSO), dichloromethane (DCM), N-methyl-2-pyrrolidone (NMP), isopropanol (IPA) and water. Following completion of the slurry experiments, the solids were separated from the solutions by centrifugation, harvested wet and dried and samples were analyzed by XRPD and digital imaging. The clear solutions were evaporated under mild vacuum. Following this, all the solids were exposed to accelerated aging conditions and reanalysed by XRPD and digital imaging.

Based on the screening of all the samples, the Form A of the Compound A is physically stable under applied accelerated stress conditions.

Polymorphs of the Compound A:

Form A of the Compound A:

Example 3

Compound A (1 g) was suspended in water (10 mL) and heated at a temperature of about 75 to 80°C. The suspension was maintained at this temperature for 2 to 3 h. The obtained hot solution was cooled to 25 to 30°C. The solid obtained was filtered, washed with water (1 mL) and dried at a temperature of about 50 to 55°C to obtain Form A of Compound A.

Yield: 90%

Purity: 98%

Example 4

Compound A (1 g) was suspended in IPA (10 ml) and heated at a temperature of about 75 to 80°C. The suspension was maintained at this temperature for 2 to 3 h. The obtained hot solution was cooled to a temperature of about 25 to 30°C. The solid obtained was filtered, washed with IPA (1 mL) and dried at a temperature of about 50 to 55°C to obtain Form A of Compound A.

Yield: 90%

Purity: 98%

Example 5

Compound A (1 g) was suspended in toluene (10 mL) and heated at a temperature of about 75 to 80°C. The suspension was maintained at this temperature for 2 to 3 h. The obtained hot solution was cooled to a temperature of about 25 to 30°C. The solid obtained was filtered, washed with toluene (1 mL) and dried at 50 to 55°C to obtain Form A of compound A.

Yield: 90%

Purity: 98%

Example 6

Compound A (1 g) was suspended in xylene (10 mL) and heated at a temperature of about 75 to 80°C. The suspension was maintained at this temperature for 2 to 3 h. The obtained hot solution was cooled to a temperature of about 25 to 30°C. The solid obtained was filtered, washed with xylene (1 mL) and dried at 50 to 55°C to obtain Form A of the Compound A.

Yield: 90%

Purity: 98%

Example 7

Compound 1 (1 g) was suspended in isobutyl benzene (10 mL) and heated at a temperature of about 75 to 80°C. The suspension was maintained at this temperature for 2 to 3 h. The obtained hot solution was cooled to a temperature of about 25 to 30°C. The solid obtained was filtered, washed with isobutyl benzene (1 mL) and dried at a temperature of about 50 to 55°C to obtain Form A of Compound A.

Yield: 90%

Purity: 98%

Form B of the Compound A:

Example 8

Compound A (1 g) was suspended in acetone (10 ml) and heated at a temperature of about 50 to 55°C. The suspension was maintained at this temperature for 2 to 3 h. The obtained hot solution was cooled to a temperature of about 25 to 30°C for 30 to 45 min. The solid obtained was filtered, washed with acetone (1 mL) and dried at 50 to 55°C to obtain Form B of the Compound A.

Yield: 70%

Purity: 98%

Example 9

Compound A (1 g) was suspended in methyl ethyl ketone (10 ml) and heated at a temperature of about 75 to 80°C. The suspension was maintained at this temperature for 2 to 3 h. The obtained hot solution was cooled to a temperature of about 25 to 30°C. The solid obtained was filtered, washed with methyl ethyl ketone (1 mL) and dried at 50 to 55°C to obtain Form B of Compound A.

Yield: 70%

Purity: 98%

Example 10

A mixture of crystalline and amorphous form of the Compound A:

Compound A (1 g) was dissolved in DMF (10 ml) at a temperature of about 75 to 80°C. The solution was maintained at this temperature for 1 to 2 h. The hot solution was cooled to 25 to 30°C. The solid obtained was filtered, washed with DMF (1 mL) and dried at 50 to 55°C to get mixture of crystalline and amorphous Form of the Compound A.

Yield: 70%, Purity: 98%

Pharmacology:

The efficacy of the compounds particularly the polymorphic forms of the Compound A (the test compounds) can be determined by a number of pharmacological assays well known in the art, such as described below. The exemplified pharmacological assays, which follow herein, are carried out with the test compounds.

Example 10: Protocol for kinase assay (PI3Ka)

P110α radioactive lipid kinase assay

The assay is designed as in the reference, Journal of Biomolecular Screening, 2002, Vol. 7, No. 5, 441 -450, the disclosure of which is incorporated by reference for the teaching of the assay.

The p110α biochemical assay is performed using a radioactive assay measuring the incorporation of ^{32}P into the p110α substrate, phosphatidylinsoitol (PI). For the generation of IC_{50} curves, the reaction is performed in a 96-well MaxiSorp plates. Plates are pre-coated with 4μg/well of a 1:1 ratio of phosphatidylinositol (PI: Avanti #840042C) and phosphatidylserine (PS: Avanti #840032C) diluted in $CHCl_3$. Equal amount of p 110α (Upstate Millipore) protein was added to each well, containing reaction buffer (50 mM MOPSO pH7.0, 100 mM NaCl, 4 mM $MgCl_2$, 0.1% (*w/v*) BSA) whereas, for negative control, only reaction buffer is added. Test compounds are dissolved in DMSO are treated at nine-point dose responses. Reactions are initiated by the addition of 25 μM ATP solution containing 50 μCi/ml[γ-^{32}P]-ATP and incubated at RT for 2 h with gentle shaking. Reactions are finally terminated by the addition of 50 mM EDTA stock solution. Plates are washed 3 times with TBS buffer. The plates are air dried, Microscint 0 (Perkin Elmer) is added to each well and the plates are sealed. The radioactivity incorporated into the immobilized PI substrate is determined with Top Count (Perkin Elmer). Inhibition is calculated using the following equation:

% inhibition = $(D_{cpm} - T_{cpm})/(D_{cpm})X100$

T_{cpm} = ^{32}P-cpm in presence of test compounds

D_{cpm} = ^{32}P-cpm in DMSO control (enzyme control deducted)

Example 11: Angiogenesis assay

Tube formation assay

Human umbilical vein endothelial cells (HUVECs) are grown in endothelial medium (Promocell), supplemented with 20% fetal bovine serum (FBS), 100 units/ml penicillin, 100μg/ml streptomycin, 3ng/ml basic fibroblast growth factor, and 5 units/ml heparin at 37°C under a humidified 95% -5% (v/v) mixture of air and CO_2.

For the assay, 250μl of growth factor-reduced Matrigel (BD Biosciences) is pipetted into a 24 well tissue culture plate and polymerized for 30 min at 37°C. HUVECs incubated in endothelial media containing 1% FBS for 6 h are harvested after trypsin treatment and suspended in endothelial medium containing 1% FBS. Cells are plated onto matrigel layer at a density of $2x10^4$ cells/well. These cells are treated with test compounds for 30 min at RT followed by the addition of 40 ng/ml VEGF. After 18 h, the cultures are photographed and inhibition is recorded.

Claims

We Claim:

1. A crystalline polymorph of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) or a pharmaceutically acceptable salt or a solvate thereof.

2. The crystalline form of Compound A according to claim 1 is Form A.

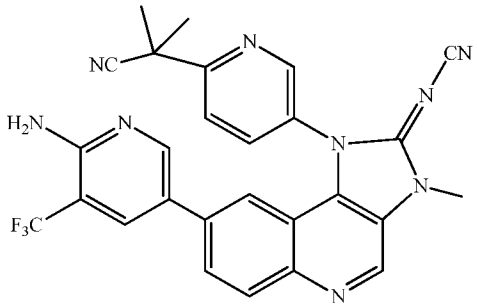
3. The crystalline form of Compound A according to claim 2, wherein said crystalline form is characterized by X-Ray diffraction peaks (expressed in degrees 2-theta values) of about 7.97, 11.38, 14.93, 15.95, 22.53 and 22.84 ± 0.2 degrees.

4. The crystalline form of Compound A according to claim 1 is Form B.

5. The crystalline form of Compound A according to claim 4, wherein said crystalline form is characterized by X-Ray diffraction peaks (expressed in degrees 2-theta values) of about: 19.26, 19.66, 21.90, 25.91 and 26.06 ± 0.2 degrees.

6. A mixture of crystalline and amorphous forms of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) or a pharmaceutically acceptable salt or a solvate thereof.

7. A process for the preparation of the compound A,

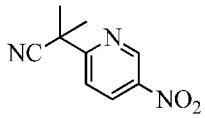


Compound A

or a stereoisomer, a tautomer, a polymorph, a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof;

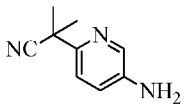
comprising the steps of:

a) methylating 5-nitro-2-pyridine acetonitrile (compound (1)) using methyl iodide in the presence of dimethylformamide (DMF) and sodium hydride to obtain the compound (2);



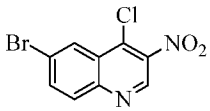
(2)

b) reducing the compound (2) using an iron catalyst in the presence of ammonium chloride in an organic solvent to obtain the compound (3);



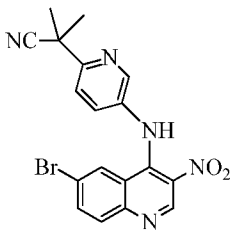
(3)

c) chlorinating 6-bromo-4-hydroxy-3-nitroquinoline (4) using phosphorus oxychloride($POCl_3$) in relatively lower volume in the presence of an organic solvent to obtain the compound (5);



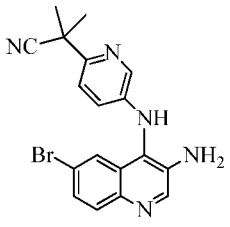
(5)

d) reacting the compound (3) with the compound (5) in acetic acid medium to get intermediate compound (6);



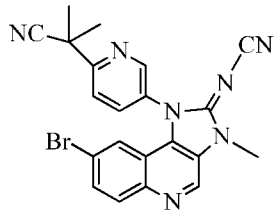
(6)

e) reducing the compound (6) using iron catalyst to obtain compound (7);



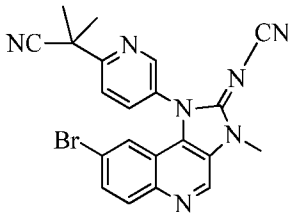
(7)

f) cyclising the compound (7) with a reagent selected from diphenylcyanocarbonoimidate or dimethyl cyanocarbonimidodithioate in the presence of a base, to obtain the compound (8);



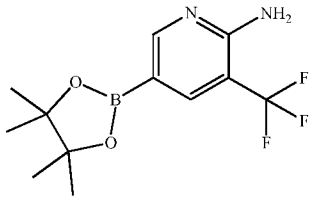
(8)

g) methylating the compound (8) using methyl iodide to obtain the compound (9);



(9)

h) treating the compound (9) with a compound (10)



(10) ,

to obtain the compound A.

8. The process according to claim 7 wherein the organic solvent used in step (b) is selected from ethanol and tetrahydrofuran (THF).

9. The process according to claim 7 wherein the solvent used in step (e) is selected from ethanol and tetrahydrofuran (THF).

10. The process according to claim 7 wherein the base used in step (f), is selected from diisopropylethylamine and cesium carbonate.

11. The process according to claim 7, wherein compound A is further treated with Si-thiol to reduce metal content.

12. A process for the purification of N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (Compound A) comprising the steps of:

a) providing a slurry of the Compound A in a solvent;

b) heating the slurry obtained in step a) at a temperature ranging from 70°C to 90°C;

c) cooling the hot solution of step b) to a temperature of 25°C of 35°C and

d) isolating pure Compound A.

13. The process according to claim 12 wherein the solvent used in step (a) is selected from methanol, ethanol, n-propanol, isopropyl alcohol (IPA), butanol, dichloromethane, ethylene dichloride, chloroform, acetic acid, acetonitrile, carbon tetrachloride, toluene, xylene, hexane, heptanes, dimethylformamide (DMF) and water or a mixture thereof.

14. The process according to claim 13 wherein the solvent used in step (a) is selected from dimethylformamide (DMF), water and isopropyl alcohol (IPA).

15. Use of Form A of the Compound A or pharmaceutically acceptable salts thereof for the treatment of cancer.

16. Use of Form B of Compound A or pharmaceutically acceptable salts thereof for the treatment of cancer.

17. Use of mixture of crystalline and amorphous form of Compound A or pharmaceutically acceptable salts thereof for the treatment of cancer.

18. A pharmaceutical composition comprising therapeutically effective amount of at least one polymorphic form of the Compound A as claimed in claim 1 and claim 6 and a pharmaceutically acceptable excipient.

19. A use of a therapeutically effective amount of at least one polymorphic form of the Compound A as claimed in claim 1, for the manufacture of a medicament for the treatment of cancers.

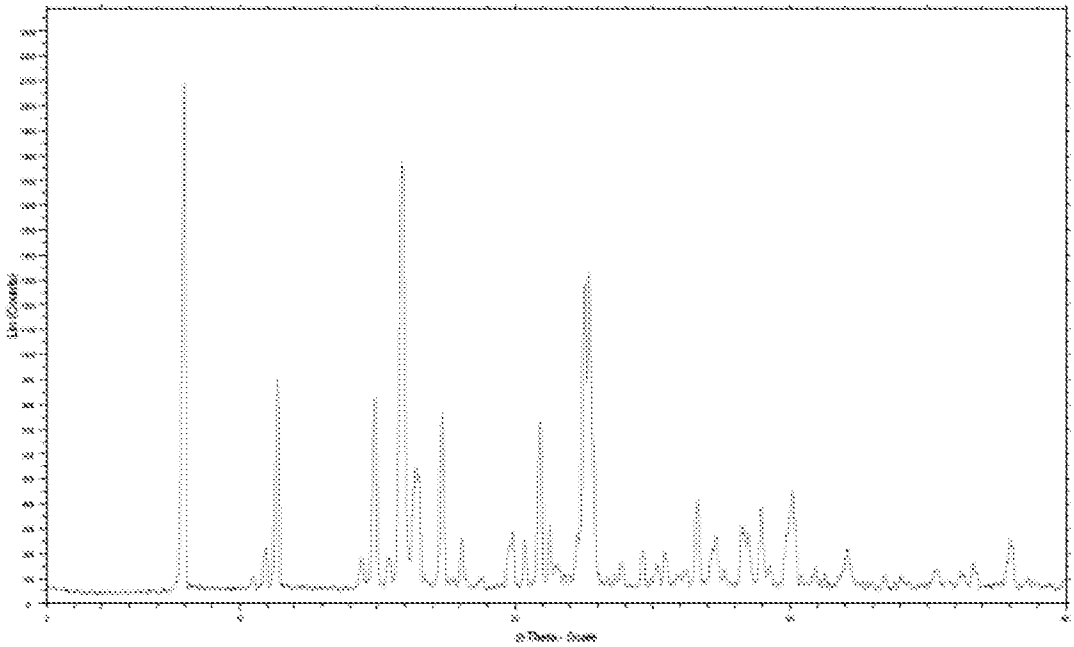


Figure 1

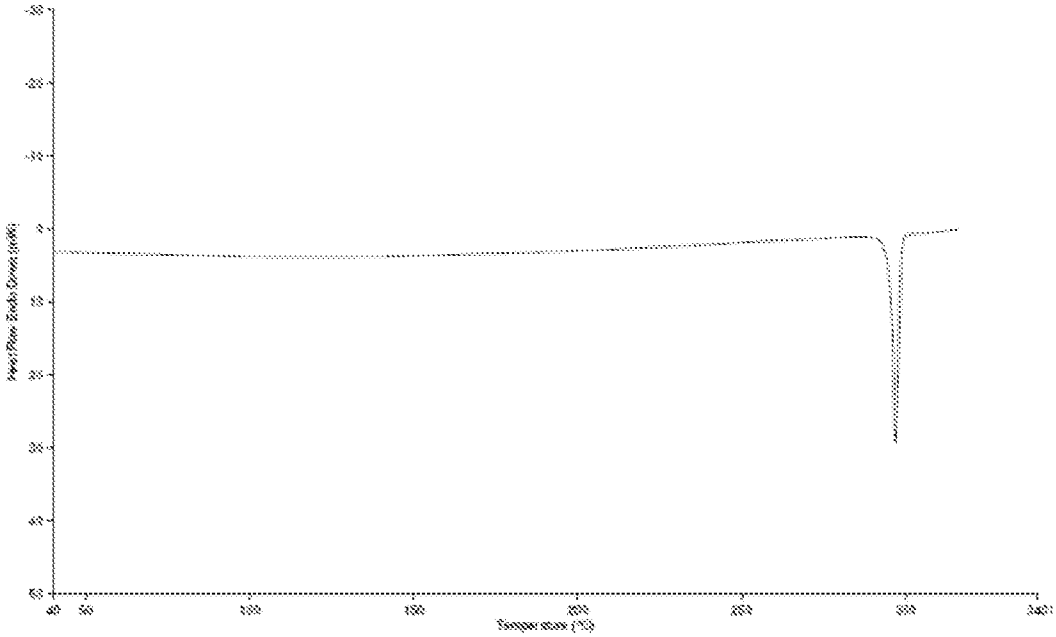


Figure 2

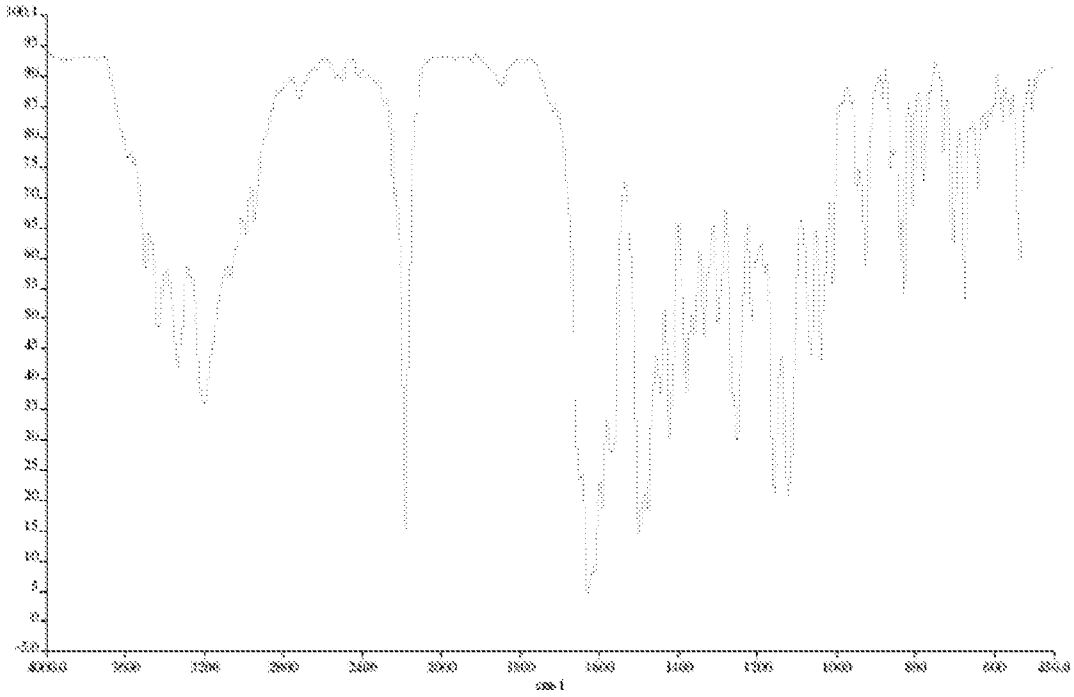


Figure 3

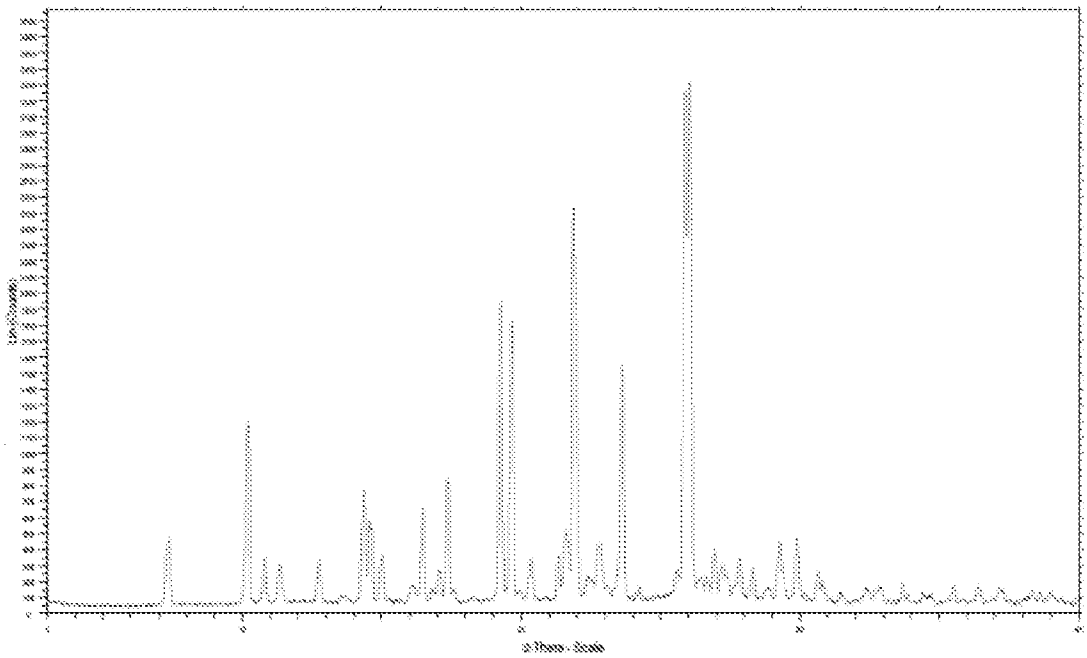


Figure 4

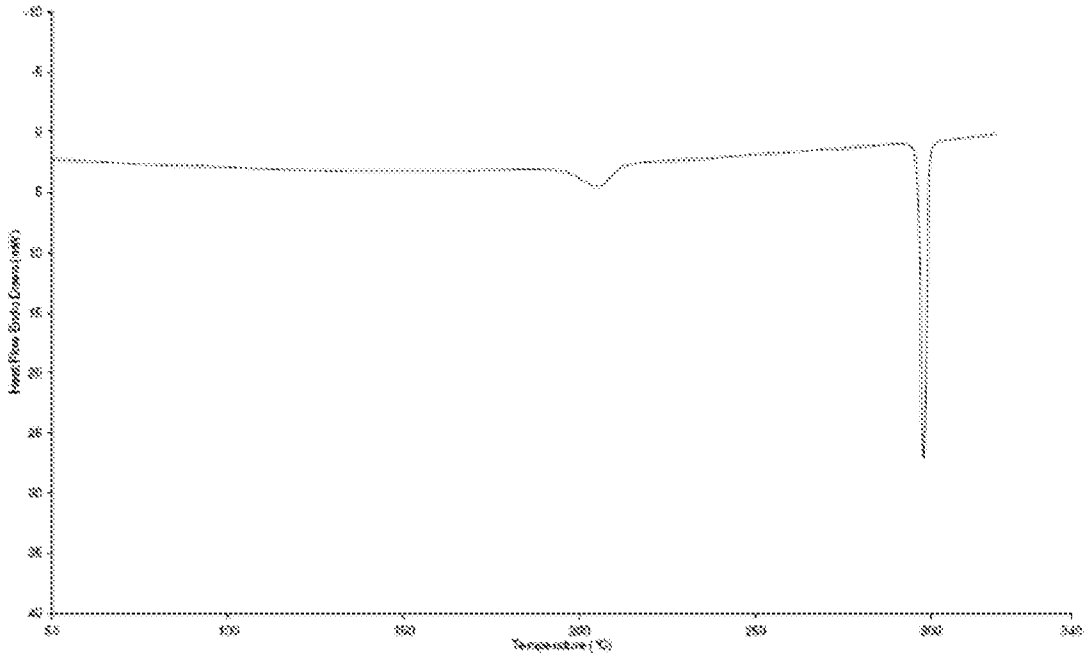


Figure 5

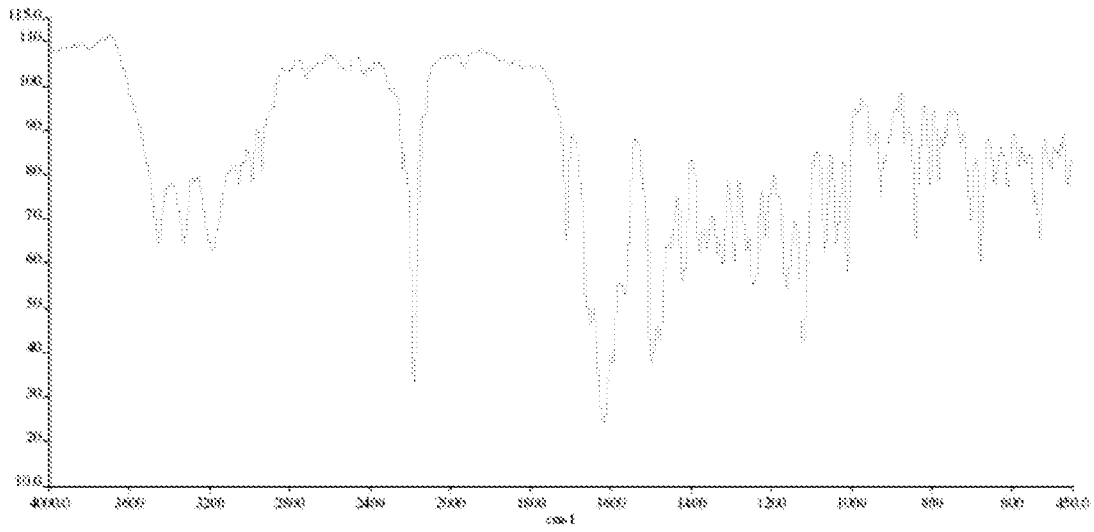


Figure 6

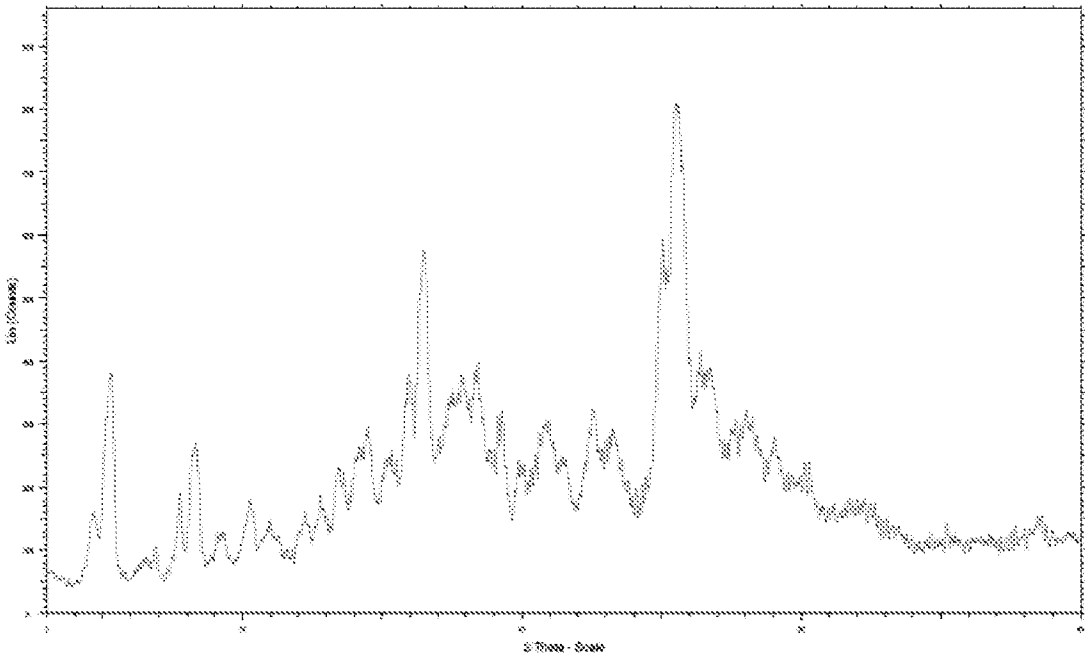


Figure 7

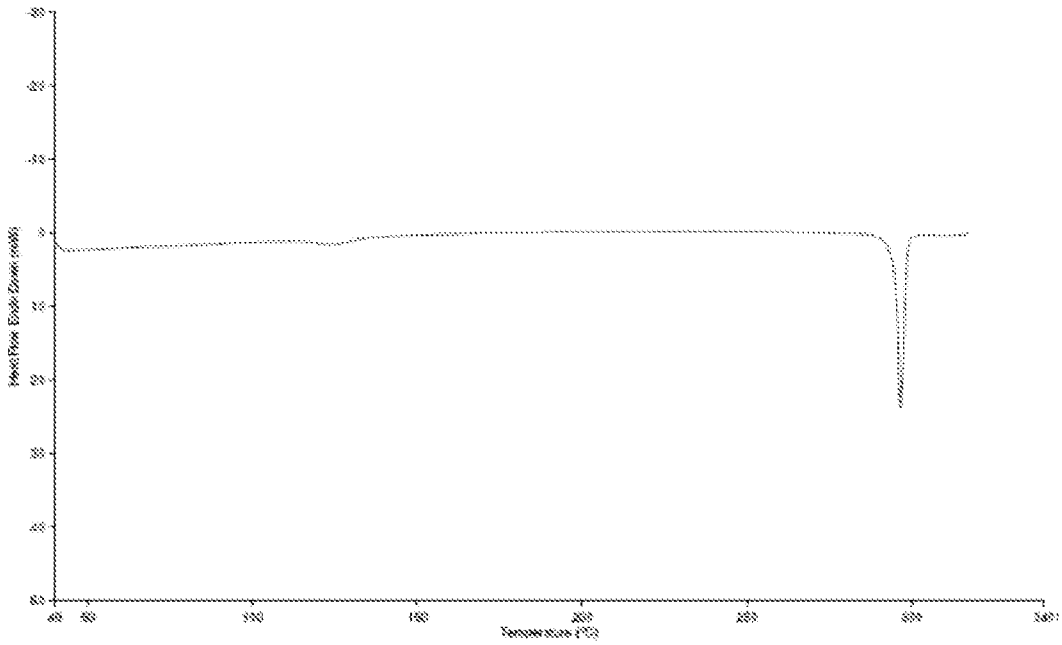


Figure 8

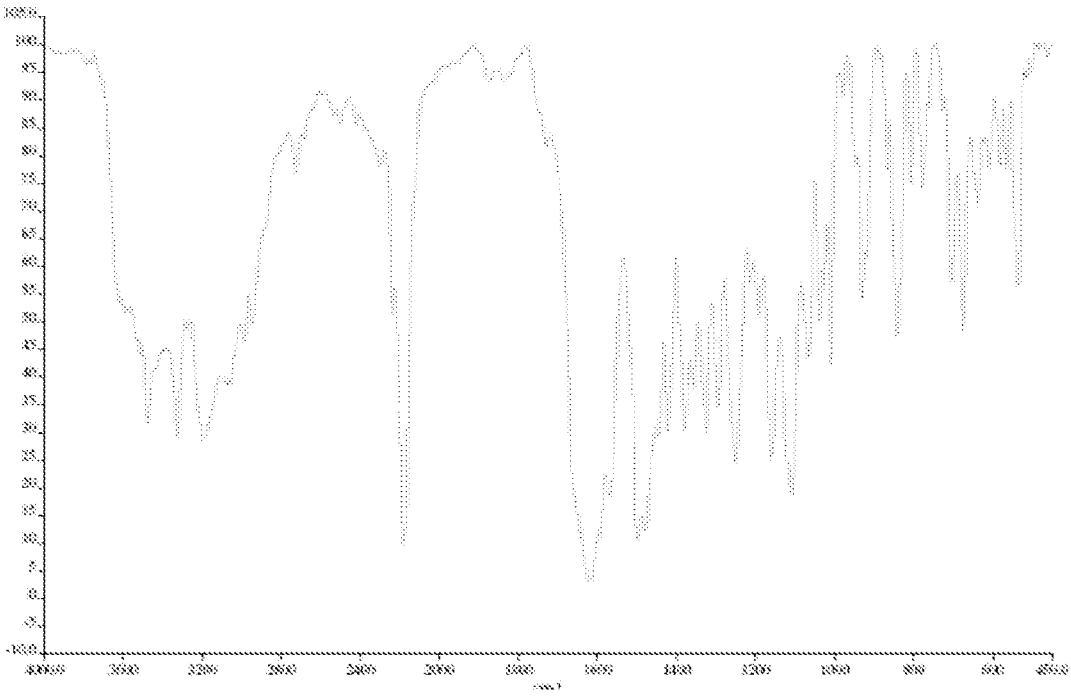


Figure 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/052194

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04 (2006.01) A61K 31/4745 (2006.01) A61P 35/00 (2006.01)

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)

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)

Invention Search- STN (Registry and CAPLUS): Based upon registry number 1356033-60-7

Applicant and Inventor search (Patentscope): Keywords- PIRAMAL ENTERPRISES LIMITED, Suneel Manohar Babu CHENNAMSETTY, Yogesh HULAWALE, Selvam PARAMASIVAN, Sivaramakrishnan HARIHARAN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2015	21 July 2015
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Will Findlay AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. (02) 62832018

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/IB2015/052194**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/007926 A1 (PIRAMAL LIFE SCIENCES LIMITED) 19 January 2012 Abstract, example 5 and claim 13	1-19
P,A	WO 2014/177915 A1 (PIRAMAL ENTERPRISES LIMITED) 06 November 2014 Abstract and page 25	1-19

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/IB2015/052194**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2012/007926 A1	19 January 2012	WO 2012007926 A1	19 Jan 2012
		AR 084706 A1	05 Jun 2013
		AU 2011277935 A1	07 Mar 2013
		AU 2011277935 B2	22 Jan 2015
		CA 2805608 A1	19 Jan 2012
		CN 103108873 A	15 May 2013
		EP 2593450 A1	22 May 2013
		JP 2013535446 A	12 Sep 2013
		KR 20130043198 A	29 Apr 2013
		MX 2013000617 A	13 Jun 2013
		NZ 607060 A	27 Feb 2015
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		TW 201204725 A	01 Feb 2012
		US 2013116248 A1	09 May 2013
		US 9062046 B2	23 Jun 2015
WO 2014/177915 A1	06 November 2014	WO 2014177915 A1	06 Nov 2014

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.