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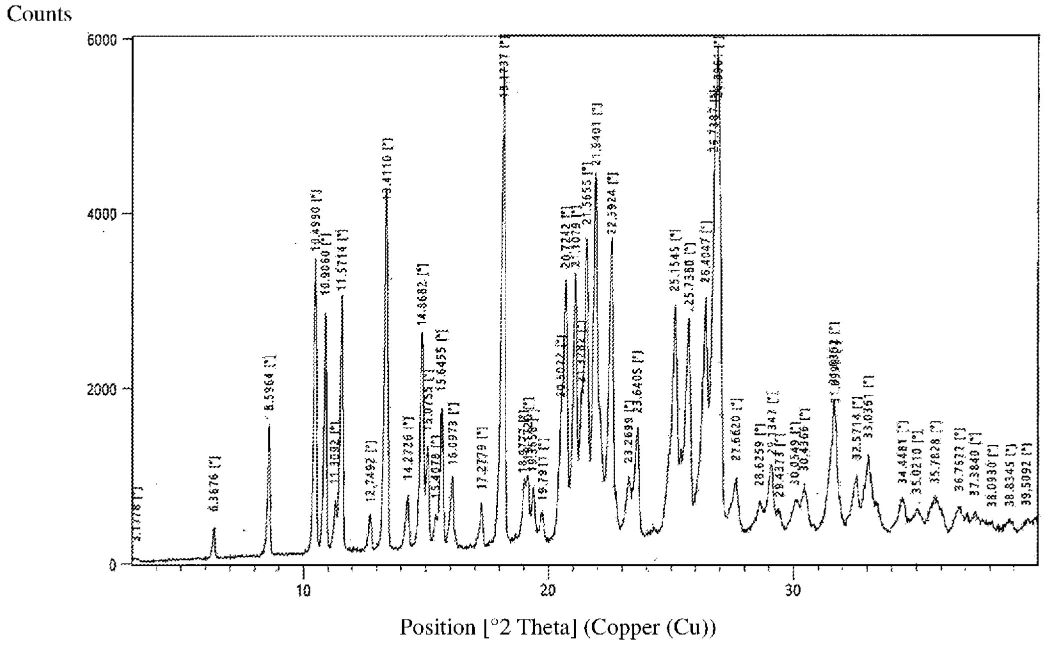

Fig. 1

(57) **Abstract:** The present invention provides an improved and industrially viable process for the preparation of Acalabrutinib and its intermediates in high yield and eliminating the use of time-consuming purification process. The present invention also relates to the purification of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl) benzamide, a key intermediate for the preparation of Acalabrutinib. Further present invention relates to new polymorphic form of Acalabrutinib.

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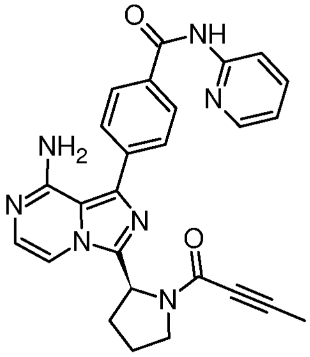
PROCESS FOR THE PREPARATION OF ACALABRUTINIB AND ITS INTERMEDIATES

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of Acalabrutinib and its intermediates. The present invention relates to the purification of 4-(8-amino-3-(pyrrolidin-2-yl)imidazol[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, a key intermediate for Acalabrutinib. Also, the present application relates to a new polymorphic form of Acalabrutinib.

BACKGROUND OF THE INVENTION

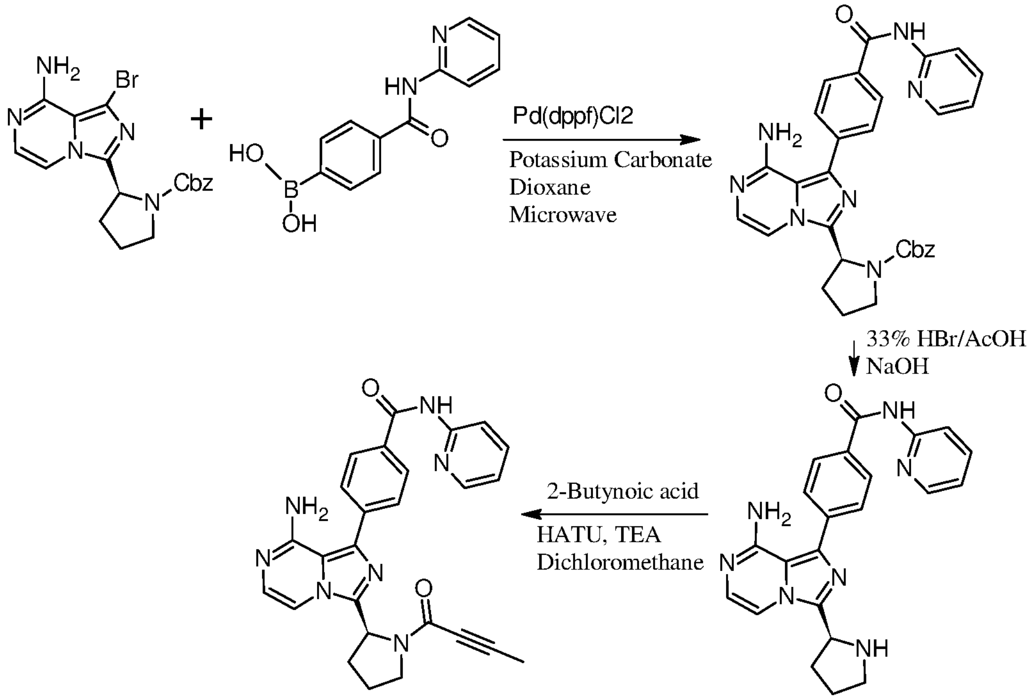
Acalabrutinib, chemically known as 4-{8-amino-3-[(2S)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl)}-N-(pyridine-2-yl)benzamide, is represented by the Formula (I):



Formula I

Acalabrutinib (marketed under the trade name **CALQUENCE®**, Acerta Pharma) is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. It was approved by U.S. Food and Drug Administration (FDA) on 30 Oct. 2017 for the treatment of patients suffering from Mantle cell lymphoma (MCL) who have received at least one prior therapy.

Acalabrutinib, as represented by the formula (I), is described in WO2013/010868. Example 6 of this PCT application describes the preparation of Acalabrutinib in accordance with scheme I:



SCHEME - I

In the above process, reaction of (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5]pyrazin-3-yl)pyrrolidin-1-carboxylate with 4-(pyridin-2-yl-aminocarbonyl)bezeneboronic acid in the presence of potassium carbonate and palladium catalyst (Pd(dppf)Cl_2) in Microwave gives benzyl protected intermediate, which is purified using silica gel chromatography. The resulting intermediate is treated with an acid to remove the benzyl protection followed by reaction with 2-butynoic acid in the presence of triethylamine and HATU to give Acalabrutinib, which is purified by preparative HPLC.

The above-mentioned process has several disadvantages like use of microwave for the reaction, use of basic conditions (HATU and TEA) for the final coupling and chromatographic techniques for purification of intermediate as well as final API.

Use of microwave for the reaction is not suitable for commercial manufacturing and has safety concern. Also, the yield of Acalabrutinib as obtained by the process described above is very low. Further, the last reaction step involves use of basic reaction conditions, which results in the formation of by-products which are difficult to remove, rendering the above process unsuitable for industrial production.

From the foregoing, it is apparent that the methods for the preparation of Acalabrutinib and its intermediates reported so far suffer from one or more drawbacks, such as the extensive use of column chromatography, low yield and the use of basic reaction conditions in last stage, the later resulting in the formation of impurities.

Thus, there is still a need to formulate an efficient, simple, and industrially viable synthetic process, which can overcome the drawbacks of the prior art and which provides Acalabrutinib and its intermediates in high yield and high purity.

Further, problem also lies with the solubility of Acalabrutinib as it has pH-dependent solubility (BCS Class II compound), solubility decreases with increasing pH.

There are various routine techniques available in the art to enhance the solubility of such drugs such as physical and chemical modifications of the drug e.g. particle size reduction, solid dispersion, use of surfactant and complexation. Selection of a solubility improving method depends on drug property, site of absorption and required dosage form characteristics. Polymorphic forms of drugs can prove interesting for drug developers because their thermodynamic and physicochemical properties, such as energy, melting point, density, stability and in particular solubility, may offer an improvement over the original form. Crystalline polymorphs have the same chemical composition, but different internal crystal structures and therefore possess different physicochemical properties because of their different lattice structures and/or different molecular conformations.

Acalabrutinib shows polymorphism and exists in different polymorphic forms.

WO2017/002095 discloses eight polymorphic forms of Acalabrutinib including amorphous and anhydrous form I. Other polymorphic forms are trihydrate Form II and metastable forms, Form III (dihydrate), Form IV, Form V, Form VI (Methanol solvate), VII (methanolate-hydrate), Form VIII (acetic acid solvate).

WO2017/002095 discloses that out of 100 different solvent systems only 5 solvent system result in Form I of Acalabrutinib. WO2017/002095 also discloses that, when solids are obtained, the amorphous is obtained from most of solvents, and that Form I is difficult to crystallize. The solvent systems which results Form I of Acalabrutinib in particular, are certain mixtures with n-heptane.

WO2018/064797 discloses four polymorphic forms of Acalabrutinib, namely Form 1, Form 2, Form 3, and Form 4. Form 1 of Acalabrutinib as disclosed in this publication is dihydrate.

In view of above, the polymorphic forms of Acalabrutinib known in the prior art may be unstable, are difficult to crystallise, and/or are difficult to purify. Thus, there is a need in the art to develop an improved process for Form I of Acalabrutinib and to develop a new polymorphic form of Acalabrutinib with enhanced properties to meet the stringent requirements of regulatory agencies, such as morphology, purity and stability of the active substance.

To overcome the problems associated with the prior art and to fulfill the need of the art, the inventors of the present invention have developed a process which provides Acalabrutinib in high yield and eliminating expensive and time-consuming column chromatography. Also, the present invention provides novel polymorphic form of Acalabrutinib that have advantageous properties.

OBJECTS OF THE INVENTION

It is an objective of the present invention to overcome the drawbacks of the prior art as described above.

It is another objective of the present invention to provide an improved and industrially viable process for the synthesis of Acalabrutinib.

It is yet another objective of the present invention to provide an improved and industrially viable process for the synthesis of Acalabrutinib without using chromatographic techniques.

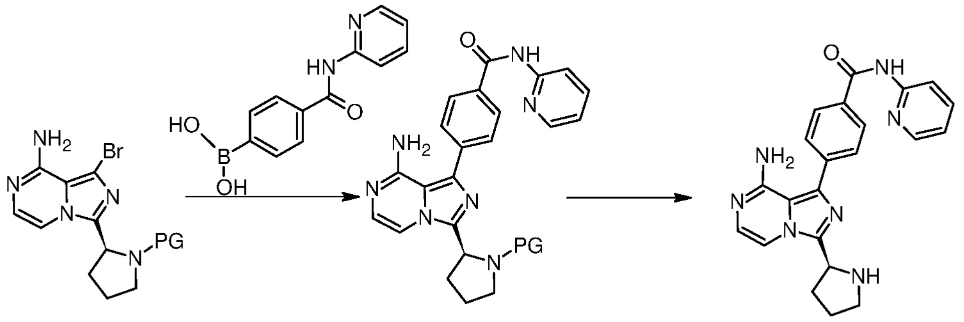
It is a further objective of the present invention to provide a purification process for (S)-4-(8-amino-3-(pyrrolidin-2-yl)imidazol[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, a key intermediate of Acalabrutinib.

It is another objective of the present invention to provide a process for the preparation of Form I of Acalabrutinib.

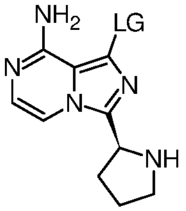
It is yet another objective of the present invention to provide novel polymorphic form of Acalabrutinib.

SUMMARY OF THE INVENTION

The inventors have surprisingly found that the drawbacks of the prior art may be overcome by conducting the following reaction, without protecting the pyrrolidine moiety with an amine protecting group.



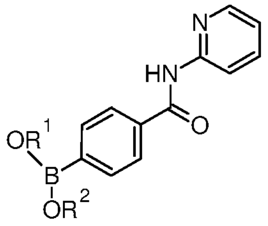
Reacting the compound of formula II, wherein the pyrrolidine moiety is unprotected,



Formula II

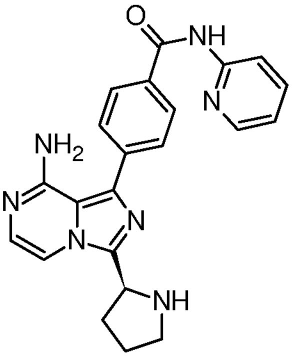
and wherein LG is a leaving group

with a compound of formula III,



Formula III

surprisingly yielded a compound of formula IV,

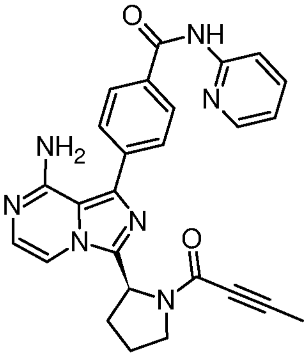


Formula IV

in high yield. The compound of formula II, with unprotected pyrrolidine moiety, can be easily purified by industrially viable purification methods to remove non-volatile impurities, rendering the tedious chromatographic purification superfluous. Thus, the use of compound of formula II, with unprotected pyrrolidine moiety, results in a reduced amount of nonvolatile impurities and yields the compound of formula IV in high yield.

Thus the present invention provides an improved, industrially viable process for the preparation of Acalabrutinib and its intermediates. The process of the present invention provides products with high yield and high purity.

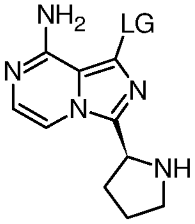
In a first aspect, the present invention provides a process for the preparation of Acalabrutinib (formula I),



Formula I

comprising the steps of:

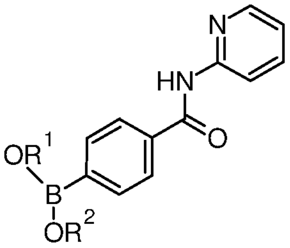
a) reacting a compound of formula II or a salt thereof,



Formula II

wherein LG is a leaving group

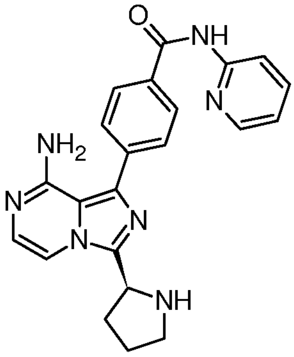
with a compound of formula III,



Formula III

wherein R^1 and R^2 are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl; or wherein R^1 and R^2 jointly form a substituted or unsubstituted cycloalkyl ring,

to form a compound of formula IV or a salt thereof,

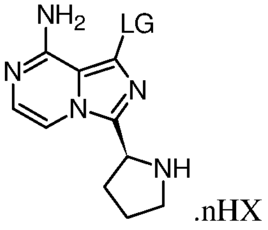


Formula IV

b) optionally purifying the compound of formula IV, and

c) converting the compound of formula IV into Acalabrutinib.

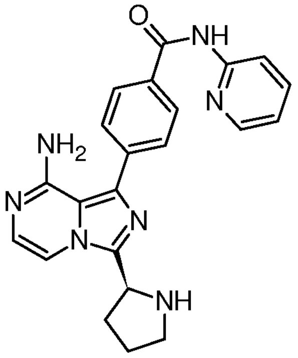
In a second aspect, the present invention provides an acid addition salt of formula IIa,



Formula IIa

wherein LG is a leaving group, n is selected from 1 or 2, and HX is an inorganic acid or an organic acid.

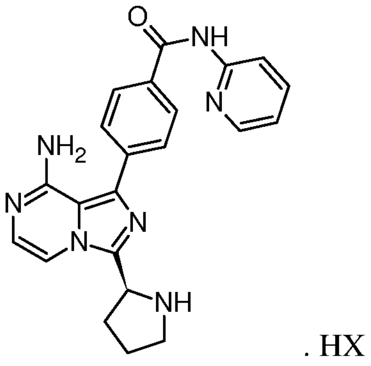
In a third aspect, the present invention provides a process for the purification of the compound of formula IV,



Formula IV

comprising the steps of:

a) treating the compound of formula IV with an inorganic acid or an organic acid to form an acid addition salt of formula IVa,



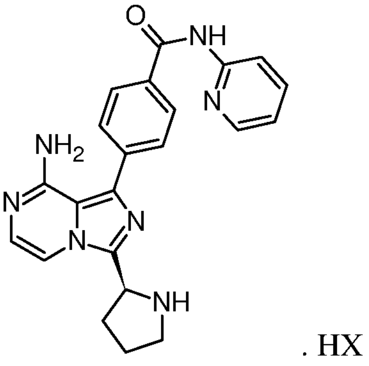
Formula IVa

wherein HX is an inorganic acid or an organic acid

b) neutralising the acid addition salt of formula IVa with a base, and

c) isolating the purified compound of formula IV.

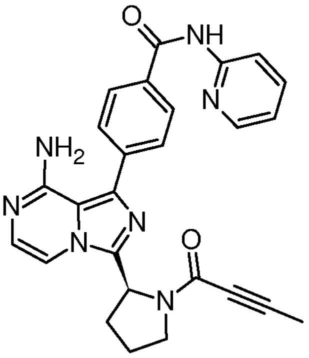
In a fourth aspect, present invention provides an acid addition salt of formula IVa,



Formula IVa

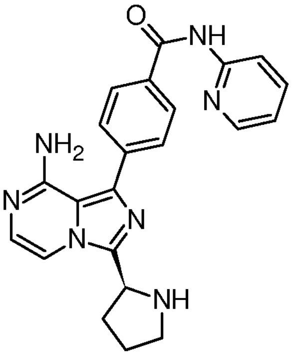
wherein HX is an inorganic acid or an organic acid.

In a fifth aspect, the present invention provides a process for the preparation of Acalabrutinib (formula I),



Formula I

comprising reacting a compound of formula IV or a salt thereof,



Formula IV

with 2-butynoic acid in the presence of a carbodiimide reagent.

In a sixth aspect, the present invention provides a process for preparing the crystalline form I of Acalabrutinib, comprising the steps of:

a) dissolving Acalabrutinib in a first solvent,

b) adding a second solvent to the resulting solution, and

c) isolating crystalline form I of Acalabrutinib.

wherein first solvent is selected from acetone and methanol; second solvent is selected from water, methylisobutyl ketone, isopropanol, and methylethyl ketone.

In a seventh aspect, the present invention provides crystalline form IX of Acalabrutinib characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at about 8.5, 10.1, and 12.0 ±0.2° 2θ.

In an eighth aspect, the present invention provides a process for preparing the crystalline form IX of Acalabrutinib, comprising the steps of:

a) contacting Acalabrutinib with methanol and water; and

b) isolating crystalline form IX of Acalabrutinib.

In a ninth aspect, the present invention provides a pharmaceutical composition comprising Acalabrutinib prepared by the process of the present invention and at least one pharmaceutically acceptable excipient.

In a tenth aspect, the present invention provides a pharmaceutical composition comprising

crystalline form IX of Acalabrutinib and at least one pharmaceutically acceptable excipient.

In an eleventh aspect, the present invention provides a method of treating cancer, comprising administering a therapeutically effective amount of Acalabrutinib prepared by the process of the present invention.

In a twelfth aspect, the present invention provides a method of treating cancer, comprising administering a therapeutically effective amount of crystalline form IX of Acalabrutinib.

In a thirteen aspect, the present invention provides a method of preparing a pharmaceutical composition, comprising a step of admixing crystalline form IX of Acalabrutinib with one or more pharmaceutically acceptable excipients.

DEFINITIONS

The following definitions are used in connection with the present application unless it is indicated otherwise.

The term “leaving group” as used herein refers to moieties which are readily displaced in a given reaction. Suitable leaving groups include, but are not limited to, halogens like chlorine, bromine, and iodine; and triflate.

As used herein the term “protecting group” refers to an amino protecting group, a moiety that can be selectively attached to and removed from a nitrogen atom to prevent it from participating in undesired chemical reactions, without having unacceptable adverse effects on the desired reactions. Examples of amino protecting groups include alkoxycarbonyl groups such as butoxycarbonyl, fluorenylmethyloxycarbonyl; aryloxycarbonyl groups such as benzyloxycarbonyl; acyl groups such as acetyl, trifluroacetyl and benzoyl; sulfonyl groups such as methanesulfonyl and toluenesulfonyl.

The term “ambient temperature” refers to a temperature ranging from about 15 °C to 35 °C, preferably to a temperature ranging from about 20 °C to 30 °C, more preferably to a temperature of about 25 °C.

The terms "comprising" and "comprises" mean the elements recited, or their equivalents in structure or function, plus any other element or elements which are not recited.

The terms "having" and "including" are also to be construed as open ended. All ranges recited herein include the endpoints, including those that recite a range between two values. Whether so indicated or not, all values recited herein are approximate as defined by the circumstances, including the degree of expected experimental error, technique error, and instrument error for a given technique used to measure a value.

The term "optional"/ "optionally" is taken to mean that the event or circumstance described in the specification may or may not occur, and that the description includes instances where the event occurs and instances where it does not.

As used herein, the term "contacting" includes mixing, adding, slurring, stirring or a combination thereof.

As used herein, the terms “about” are to be construed as modifying a term or value such that it is not an absolute. Such terms will be defined by the circumstances. This includes, at the very least, the degree of expected experimental error, technique error and instrument error for a given technique used to measure a value.

The term "substantially the same" with reference to analytical characterization such as X-ray powder diffraction (XRPD) peak positions means that typical peak position and intensity variability are taken in to consideration. For example, one skilled in the art will appreciate that the peak positions (2 theta) will show some inter-apparatus variability, typically as much as 0.2°. Further, one skilled in the art will appreciate that relative peak intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, prepared sample surface, and other factors known to those skilled in the art and should be taken as qualitative measure only.

ABBREVIATIONS

XRPD	X-ray powder diffraction
TGA	Thermal gravimetric analysis
^{1}H-NMR	Proton nuclear magnetic resonance
HPLC	High Performance Liquid Chromatography

BRIEF DESCRIPTION OF FIGURES

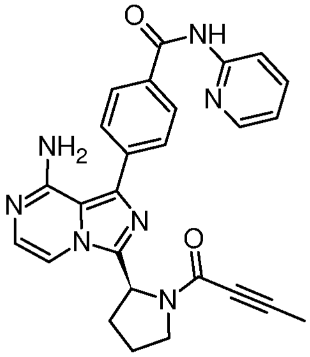
Fig. 1; represents an X-ray powder diffraction (XRPD) pattern of the crystalline form I of Acalabrutinib

Fig. 2; represents an X-ray powder diffraction (XRPD) pattern of the crystalline form IX of Acalabrutinib of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an improved and industrially viable process for preparing Acalabrutinib and its intermediates. Further, the present invention provides novel polymorphic form of Acalabrutinib.

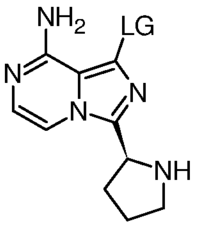
In a first aspect, a process for the preparation Acalabrutinib of formula (I),



Formula I

comprising the steps of:

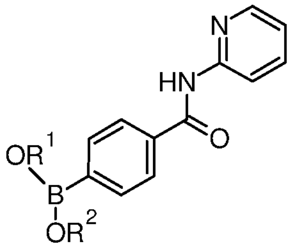
a) reacting a compound of formula II or a salt thereof,



Formula II

wherein LG is a leaving group

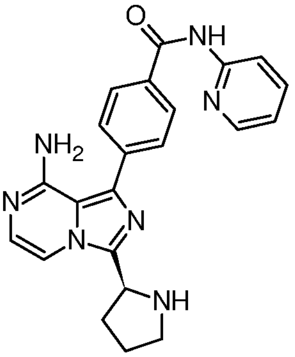
with a compound of formula III,



Formula III

wherein R^1 and R^2 are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl; or wherein R^1 and R^2 jointly form a substituted or unsubstituted cycloalkyl ring,

to form a compound of formula IV or a salt thereof,



Formula IV

b) optionally, purifying the compound of formula IV, and

c) converting the compound of formula IV into Acalabrutinib.

The reaction of step a) may be carried out utilizing a compound of formula II as starting material in form of the free base or in form of a salt thereof.

The reaction step a) is carried out in the presence of a base and a palladium catalyst.

In some embodiments, the palladium catalyst is selected from the group consisting of palladium(II) chloride, palladium(II) acetate, bis(triphenylphosphine)palladium(II) dichloride, tetrakis(triphenylphosphine) palladium(0), bis(dibenzylideneacetone)palladium(0) (Pd(dba)2), bis(acetonitrile)dichloropalladium(II), [1,1′-[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Pd(dppf)Cl_2), and [1,1′-[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Pd(dppf)Cl_2) complex with dichloromethane. Preferably the reaction is carried out in the presence of bis(triphenylphosphine)palladium(II) dichloride, [1,1'-bis(diphenylphosphino) ferrocene]palladium(II) dichloride, or [1,1′-[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Pd(dppf)Cl_2) complex with dichloromethane.

The base used is an inorganic or an organic base. In some embodiments, the inorganic base is selected from the group consisting of alkali or alkaline earth metal carbonates, bicarbonates, acetates, phosphates, hydroxides thereof such as sodium carbonate, potassium carbonate, potassium phosphate, cesium carbonate and mixtures thereof. In some embodiments, the organic base is an amine selected from the group consisting of triethylamine, diisopropylethylamine, and tetramethylguanidine. Preferably the reaction is carried out in the presence of sodium carbonate, potassium carbonate, potassium phosphate, cesium carbonate, tetramethylguanidine or triethylamine.

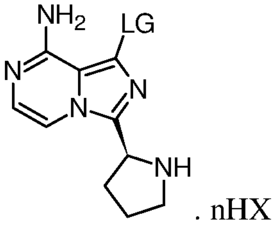
The reaction of step a) may optionally be carried in the presence of a solvent.

In some embodiments, the solvent is selected from the group consisting of water, alcohols such as methanol, ethanol, propanol, isopropanol, or butanol, ethers such as tetrahydrofuran or 1,4-dioxane, esters such as methylacetate, ethylacetate, or isopropylacetate, nitriles such as acetonitrile, propionitrile, amide solvents such as dimethylformamide, dimethylacetamide and hydrocarbon solvents such as heptane, hexane, toluene or mixtures thereof. Preferably the solvent is methanol, ethanol, isopropanol, tetrahydrofuran, 1,4-dioxane, toluene, mixtures thereof or a mixture of one or more of these with water. Most preferably, the solvent is tetrahydrofuran, 1,4-dioxane, a mixture of water and tetrahydrofuran or a mixture of water and 1,4-dioxane.

A phase transfer catalyst can be added to the reaction mixture, particularly in case water immiscible solvents are used. The phase transfer catalyst can be a quaternary ammonium salt, e.g. tetrabutylammonium halide or a benzyl triethylammonium halide.

The compound of formula IV, (S)-4-(8-amino-3-(pyrrolidin-2-yl)imidazol[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, is a key intermediate for the synthesis of Acalabrutinib. The compound of formula IV as obtained by the process of the present invention can optionally be purified and converted to Acalabrutinib using methods known in the art.

In a second aspect, the present invention provides an acid addition salt of formula IIa,



Formula IIa

wherein LG is a leaving group, n is selected from 1 or 2, and HX is an inorganic acid or an organic acid.

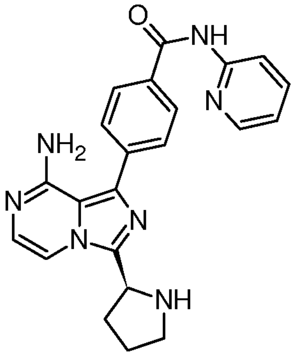
In some embodiments, the inorganic acid is hydrochloric acid or hydrobromic acid. In some embodiments, the organic acid is a carboxylic acid selected from the group consisting of succinic acid, formic acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, tartaric acid, oxalic acid, malic acid, maleic acid, citric acid, benzoic acid, and substituted benzoic acid; or a sulfonic acid, such as p-toluenesulfonic acid or methanesulfonic acid. Preferably, the acid addition salt of formula IIa exist as hydrochloride, hydrobromide, acetate, trifluoroacetate, tartrate, oxalate, p-toluenesulfonate, or methanesulfonate; or, more preferably, the hydrochloride or hydrobromide salt.

The acid addition salt of formula IIa can be prepared by treating compound of formula II with a suitable acid, such as an inorganic acid or an organic acid as described above.

The salt formation reaction may be carried out in the presence of a polar or non-polar solvent selected from the group consisting of alcohols such as methanol, ethanol, or isopropanol, ketones such as acetone, diisopropyl ketone, or methylisobutyl ketone, halogenated solvents such as dichloromethane, or dichloroethane, and ethers such as tetrahydrofuran, 1,4-dioxane, or mixtures thereof.

Preferably, the process employs a dihydrochloride or dihydrobromide salt of formula IIa.

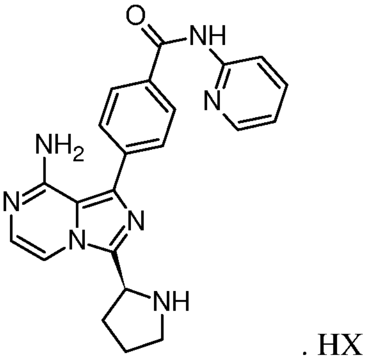
In a third aspect, the present invention provides a process for the purification of the compound of formula IV,



Formula IV

comprising the steps of:

a) treating the compound of formula IV with an inorganic acid or an organic acid to form an acid addition salt of formula IVa,



Formula IVa

wherein HX is an inorganic acid or an organic acid

b) neutralising the acid addition salt of formula IVa with a base, and

c) isolating the purified compound of formula IV.

Inorganic acid used in the step a) may be selected from hydrochloric acid or hydrobromic acid. Organic acid used in the step a) may be selected from carboxylic acid such as succinic acid, formic acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, tartaric acid, oxalic acid, malic acid, maleic acid, citric acid, benzoic acid, substituted benzoic acid or a sulfonic acid such as p-toluenesulfonic acid or methanesulfonic acid. Preferably the acid used in the step a) is hydrochloric acid, hydrobromic acid, acetic acid, trifluoroacetic acid, tartaric, succinic acid, oxalic acid, citric acid, p-toluenesulfonic acid or methanesulfonic acid, most preferably hydrochloric acid, hydrobromic acid, succinic acid, tartaric acid, oxalic acid or citric acid.

The salt formation reaction may optionally be carried out in a polar or non-polar solvent selected from the group consisting of water, alcohols such as methanol, ethanol, isopropanol, or butanol; ketones such as acetone, diisopropyl ketone, or methylisobutyl ketone; halogenated solvents such as dichloromethane, or dichloroethane; hydrocarbon solvents such as toluene, xylene, heptane, or hexane; esters such as ethylacetate, or isopropylacetate; amides such as dimethylformamide, or dimethylacetamide and ethers such as tetrahydrofuran or 1,4-dioxane; or mixtures thereof. Preferably, the salt formation reaction is carried out in water, methanol, ethanol, isopropanol, dichloromethane, dichloroethane, ethylacetate, tetrahydrofuran or 1,4-dioxane or mixture thereof. More preferably, the salt formation reaction is carried out in water, methanol, ethanol, isopropanol, tetrahydrofuran, acetone, 1,4-dioxane or mixture thereof. Most preferably, the salt formation reaction is carried out in water, acetone, methanol, isopropanol or mixture thereof.

The acid addition salt of formula IVa may be isolated using conventional methods such as filtration, centrifugation and the like.

The base used in step b) may be an inorganic base selected from the group consisting of alkali or alkaline earth metal hydroxides, alkoxides, carbonates or bicarbonates such as sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, magnesium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, calcium carbonate, magnesium carbonate, sodium methoxide, sodium ethoxide, and potassium methoxide or an organic base such as an amine selected from the group consisting of triethylamine and diisopropylamine. Preferably, the base is sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, or triethylamine. Most preferably the base is sodium hydroxide or potassium hydroxide.

The neutralisation reaction may optionally be carried out in the presence of a polar or non-polar solvent selected from the group consisting of water, alcohols such as methanol, ethanol, isopropanol or butanol; ketones such as acetone, diisopropyl ketone or methylisobutyl ketone; halogenated solvents such as dichloromethane or dichloroethane; hydrocarbon solvents such as toluene, xylene, heptane or hexane; esters such as ethylacetate or isopropylacetate; amides such as dimethylformamide or dimethylacetamide and ethers such as tetrahydrofuran or 1,4-dioxane; or mixtures thereof. Preferably, the neutralisation reaction is carried out in water, methanol, ethanol, isopropanol, dichloromethane, dichloroethane, ethylacetate, tetrahydrofuran, 1,4-dioxane, acetone, diisopropylketone or mixtures thereof. More preferably, the neutralisation reaction is carried out in water, methanol, ethanol, isopropanol, acetone, tetrahydrofuran, 1,4-dioxane or mixtures thereof. Most preferably, the neutralisation reaction is carried out in water, methanol, isopropanol, acetone, tetrahydrofuran or mixtures thereof.

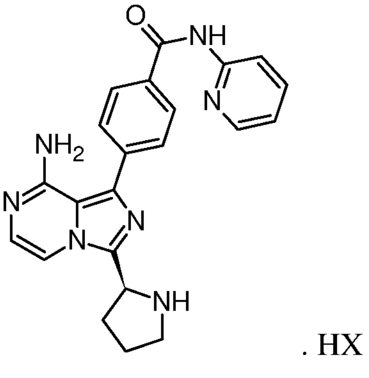
The purified compound of formula IV can be isolated from the reaction mixture using conventional methods such as filtration, centrifugation and the like.

The inventors of the present invention have found that the process of the present invention provides the compound of formula IV in higher yield as compared to processes known in the art. The method for the preparation of compound of formula IV reported in WO2013/010868 involves the use of tedious purification techniques such as silica gel or preparative column chromatography. The product is obtained with an overall yield of approximately 27.9%, which is too low to be commercially attractive.

The process of the present invention provides the compound of formula IV in an overall yield of more than 40%, preferably more than 50%, or more preferably more than 60%, or even more preferably more than 70%. In some embodiments, the compound of formula IV is provided in an overall yield of 40%-70%, 40%-60%, 40%-50%, 50%-70%, 50%-60%, or 60%-70%.

The purification of compound of formula IV according to the process of present invention has the further advantage of reducing colored impurities. The compound of formula IV obtained by the process of the present invention has a high overall yield. Also, the process of present invention avoids the use of tedious purification e.g. by silica gel/preparative column chromatography.

In a fourth aspect, present invention provides an acid addition salt of formula IVa,

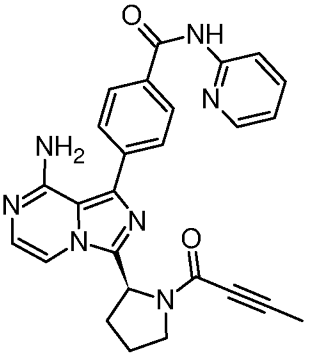


Formula IVa

wherein HX is an inorganic acid or an organic acid

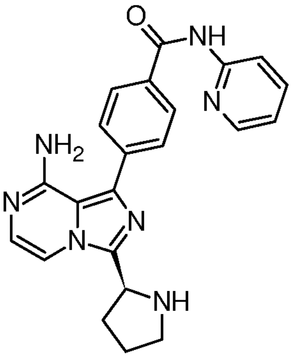
In some embodiments, the inorganic acid is hydrochloric acid or hydrobromic acid. In some embodiments, the organic acid is a carboxylic acid selected from the group consisting of succinic acid, formic acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, tartaric acid, oxalic acid, malic acid, maleic acid, citric acid, benzoic acid, and substituted benzoic acid; or a sulfonic acid, such as p-toluenesulfonic acid or methanesulfonic acid. Preferably, the acid addition salt of formula IVa is the hydrochloride, hydrobromide, acetate, trifluoroacetate, succinate, citrate, tartrate, oxalate, p-toluenesulfonate, methanesulfonate; more preferably the hydrochloride, hydrobromide, succinate, tartrate, oxalate, or citrate salt. The salt of formula IVa is prepared by reacting compound of formula IV with the appropriate acid as described above.

In a fifth aspect, present invention provides a process for the preparation of Acalabrutinib (formula I),



Formula I

comprising reacting a compound of formula IV or a salt thereof,



Formula IV

with 2-butynoic acid in the presence of a carbodiimide reagent.

In some embodiments, the carbodiimide reagent is selected from the group consisting of N,N'-dicyclohexylcarbodiimide, N,N'-diisopropylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

In certain preferred embodiments, the reaction is carried out in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

The reaction may optionally be carried out in the presence of an aprotic solvent. In some embodiments, the aprotic solvent is selected from the group consisting of halogenated solvents such as dichloromethane, or dichloroethane; hydrocarbon solvents such as xylene, toluene or heptane; ketones such as acetone, or diisopropyl ketone; amide solvents such as dimethylformamide, or dimethylacetamide; ethers such as tetrahydrofuran or 1,4-dioxane and mixtures thereof. Preferably the reaction is carried out in the presence of dichloromethane, toluene, acetone, dimethylformamide, tetrahydrofuran or mixtures thereof.

Acalabrutinib may be isolated from the reaction mixture by conventional methods such as, but not limited to, filtration and/or centrifugation.

In some embodiments, Acalabrutinib obtained by the process of present invention may optionally further be purified by treating Acalabrutinib with a clay such as Montmorillonite, Fuller`s earth, SiliaMet, modified silica or activated charcoal to reduce the level of palladium in the final API. Preferably, Acalabrutinib is purified with modified silica such as SiliaMet S Thiol. The purification of Acalabrutinib may be repeated using the same or different clay or silica. The removal of palladium from the final product, Acalabrutinib, also results in the improvement of color of the product.

The process of the present invention yields Acalabrutinib with reduced level of palladium content and avoids the use of tedious purification processes such as column/flash chromatography thereby drastically reducing the time for commercial manufacturing

In a sixth aspect, the present invention provides a process for preparing the crystalline form I of Acalabrutinib, comprising the steps of:

a) dissolving Acalabrutinib in a first solvent,

b) adding a second solvent to the resulting solution, and

c) isolating crystalline form I of Acalabrutinib.

The mixture of the Acalabrutinib in first solvent may be stirred at ambient temperature or be heated to 35 °C to 70 °C for 20 minutes to 8 hours until dissolution has occurred; preferably at ambient temperature for 20 minutes to 5 hours. The first solvent may be selected from acetone and methanol, preferably acetone. It will be appreciated that small quantities of insoluble material may be removed by filtration of the mixture. The solution obtained after step a) may optionally be treated with clay and/or activated carbon at 60-75°C followed by cooling. The activated carbon may be removed by method such as filtration through hyflow.

The resulting solution after step a), with or without clay and/or activated carbon treatment, is mixed with second solvent to precipitate the product from the solution. The second solvent may be selected from water, methylisobutyl ketone, isopropanol, and methylethyl ketone, preferably water. The reaction mixture may be stirred at 40 to 70 °C for 1 to 12 hours, preferably at 50 to 55°C for 1 to 5 hours to give form I of Acalabrutinib.

Form I of Acalabrutinib may be isolated by methods such cooling, filtration, centrifugation or combination thereof followed by optional washing it with the solvent or a mixture of solvents used during the process.

Thus obtained Form I of Acalabrutinib is optionally dried by the methods such as vacuum drying, heat drying, spray drying, freeze drying, supercritical drying or natural air drying.

The Form I of Acalabrutinib is characterized by X-ray powder diffraction (XRPD) pattern as depicted in Fig. 1.

The process described above may be varied, for example in terms of the quantity of the starting Acalabrutinib that is treated, the volume of the solvent, the temperature of the treatment, cooling phases and/or drying conditions.

The inventors of present invention found that Acalabrutinib exists in different polymorphic forms when prepared using different solvent. Accordingly, the present invention also provides novel polymorphic form of Acalabrutinib, which may be characterized using various techniques. Examples of characterization methods include, but are not limited to, single crystal X-ray diffraction, X-ray powder diffraction (XRPD), simulated powder X-ray patterns, solid state ^{13}C-NMR, Raman spectroscopy, infrared spectroscopy (IR), moisture sorption isotherms, thermal gravimetric analysis (TGA), differential scanning calorimetric (DSC) and hot stage techniques etc.

In a seventh aspect, the present invention provides crystalline form IX of Acalabrutinib.

The crystalline Form IX of Acalabrutinib is characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at about 8.5, 10.1, and 12.0 ±0.2° 2θ. The crystalline form IX of Acalabrutinib may be characterized by an X-ray powder diffraction (XRPD) pattern further comprising peaks at about 15.9, 20.1, 22.0 and 26.0 ±0.2° 2θ. The crystalline Form IX of Acalabrutinib may be characterized by an X-ray powder diffraction (XRPD) pattern substantially the same as depicted in Fig. 2.

The crystalline form IX of Acalabrutinib contains about 7 % by weight of water.

In an eighth aspect, the present invention provides a process for preparing the crystalline form IX of Acalabrutinib, comprising the steps of:

a) contacting Acalabrutinib with methanol and water; and

b) isolating crystalline form IX of Acalabrutinib.

Step a) may be carried out at 40-70°C for 10 minutes to 12 hours; preferably reaction is carried out at 55 to 65 °C for 20 minutes to 4 hours. The solution obtained after step a) may optionally be treated with clay and/or activated carbon at 60-75°C followed by cooling. The activated carbon may be removed by method such as filtration through hyflow.

The resulting solution after step a), with or without clay and/or activated carbon treatment, is mixed with water to precipitate the product from the solution. The mixture can be stirred for a period of 30 minutes to 20 hours, preferably for 5 to 18 hours, at a suitable temperature, preferably ambient temperature for the preparation of crystalline form IX of Acalabrutinib.

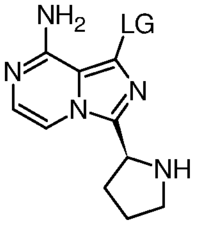
The crystalline form IX of Acalabrutinib may be isolated by methods such as cooling, filtration, centrifugation or combination thereof followed by optional washing with the solvent or a mixture of solvents used during the process.

Thus obtained Acalabrutinib, crystalline form IX of Acalabrutinib may be optionally dried by the methods such as vacuum drying, heat drying, supercritical drying or natural air drying.

Preferably, the crystalline form I or IX of Acalabrutinib is dried by vacuum drying method. As will be recognized, the drying time will be dependent upon, amongst other things, the amount of material to be dried, and the particular drying method used. Generally, a drying time of 30 minutes to 20 hours, preferably 3 to 16 hours is sufficient. Conveniently the drying is performed under vacuum and optionally under inert atmosphere, for example by passing a stream of warm inert gas such as nitrogen over or through the material. The process described above may be varied, for example in terms of the quantity of the starting Acalabrutinib that is treated, the volume of the methanol or water, the temperature of the treatment, cooling phases and/or drying conditions.

The starting material, the compound of formula II, used in the process of present invention, may be obtained by methods known in the art, preferably by the process described below.

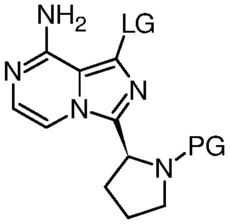
The present invention provides a process for preparing the compound of formula II,



Formula II

wherein LG is a leaving group, preferably halogen or triflate,

comprising the step of reacting a compound of formula V,



Formula V

wherein LG is a leaving group, preferably halogen or triflate; and PG is a protecting group with a suitable deprotecting reagent.

The deprotecting reagent can be an acid or base depending on the nature of the protecting group. In some embodiments, the acid is an inorganic acid such as hydrochloric acid, hydrobromic acid or an organic acid such as trifluoroacetic acid. In some embodiments, the base is an alkali or alkaline earth metal hydroxide, alkoxide, carbonate or bicarbonate thereof e.g. sodium hydroxide, sodium carbonate, potassium carbonate or an organic base such as piperidine.

The compound of formula II can be used in form of the free base or in form of an acid addition salt for the further reaction with compound of formula III.

The compound of formula II or salts thereof obtained by the process of present invention, with or without purification, is optionally dried by the methods such as vacuum drying, heat drying, supercritical drying or natural air drying. Preferably the compound of formula II or salts thereof is dried by vacuum drying method. As will be recognized, the drying time will be dependent upon, amongst other things, the amount of material to be dried, and the particular drying method used. Generally, a drying time of 30 minutes to 20 hours, preferably 2 to 14 hours is sufficient. Conveniently the drying is performed under vacuum and optionally under inert atmosphere, for example by passing a stream of warm inert gas such as nitrogen over or through the material.

The process described above may be varied, for example in terms of the quantity of the starting compound that is treated, the volume of the solvent or a mixture of solvents, the temperature of the treatment, cooling phases and/or drying conditions.

In a ninth aspect, the present invention provides a pharmaceutical composition comprising Acalabrutinib prepared by the process of the present invention and at least one pharmaceutically acceptable excipient.

In a tenth aspect, the present invention provides a pharmaceutical composition comprising crystalline form IX of Acalabrutinib and at least one pharmaceutically acceptable excipient.

The pharmaceutical composition can be intended for any route of administration, such as oral, buccal, sublingual, nasal, intravenous, intramuscular, intradermal, and subcutaneous. The pharmaceutical composition can be in any suitable dosage form, such as tablet, capsule, powder, film, solution, suspension, or emulsion. In certain embodiments, the pharmaceutical composition is a capsule for oral administration.

In an eleventh aspect, the present invention provides a method of treating cancer, comprising administering a therapeutically effective amount of Acalabrutinib prepared by the process of the present invention. In some embodiments, the cancer is blood cancer, such as leukemia, lymphoma, or myeloma. In certain embodiments, the cancer is mantle cell lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, or lymphoplasmacytic lymphoma.

In a twelfth aspect, the present invention provides a method of treating cancer, comprising administering a therapeutically effective amount of crystalline form IX of Acalabrutinib.

In a thirteen aspect, the present invention provides a method of preparing a pharmaceutical composition, comprising a step of admixing crystalline form IX of Acalabrutinib with one or more pharmaceutically acceptable excipients.

The major advantage of the present invention is to provide compound of formula IV in high yield, which noticeably enhances the yield of the obtained final product i.e. Acalabrutinib and the high purity of the final pharmaceutical active ingredient which is highly important for the pharmaceutical industry. Also, the present invention provides a simple process for the synthesis of Acalabrutinib resulting in high yield, high purity and avoids chromatographic purification. Additionally, the present invention provides a new crystalline form of Acalabrutinib.

Instrument

XRPD: X-ray diffraction data is obtained using a Bruker AXS D8 advance powder X-ray diffractometer, CuKα radiation, wavelength 1.54 Å.

EXAMPLES

Detailed experimental parameters suitable for the preparation of Acalabrutinib according to the present invention are provided by the following examples, which are intended to be illustrative and not limiting.

Reference Example 1: Preparation of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide according to process of WO2013010868 (intermediate 2)

Step I: Preparation of (S)-benzyl 2-(8-amino-1-(4-(pyridin- 2-ylcarbamoyl)phenyl)imidazo[1 ,5-a]pyrazin-3-yl)pyrrolidine-1 -carboxylate

(S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (20g, 0.0480 moles) and 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid (12.79 g, 0.0528 moles) were suspended in a mixture of 2N aqueous potassium carbonate solution (255 ml) and dioxane (550 mL). Nitrogen was bubbled through the mixture, followed by the addition of [1,1′-[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (9.81 g, 0.0120 moles). The reaction mixture was heated for 2 hours at 120-130°C. Water (200 mL) was added to the reaction mixture, followed by an extraction with ethyl acetate (150 mL). The combined organic layer was washed with brine and dried over sodium sulfate. The organic layer was filtered through celite bed, concentrated and purified using column chromatography using dichloromethane/methanol = 9/1 v/v% as eluent to afford 17.80 g (69.42%) of (S)-benzyl 2-(8-amino-1-(4-(pyridin- 2-ylcarbamoyl)phenyl)imidazo[1 ,5-a]pyrazin-3-yl)pyrrolidine-1 -carboxylate

Step II: (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide

To (S)-benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1 ,5-a]pyrazin-3-yl)pyrrolidine-1- carboxylate (15g, 0.0281 moles) was added a 33% hydrobromic acid/acetic acid solution (394 ml, 2.1671 moles) and the mixture was left at room temperature for 1 hour. The mixture was diluted with water (300 mL) and extracted with dichloromethane (300 mL). The aqueous phase was neutralized using 2N sodium hydroxide solution, and then extracted with dichloromethane (300 mL). The organic layer was dried over sodium sulfate, filtered, and distilled to give 4.52g of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N- (pyridin-2-yl)benzamide (40.25%).

Overall yield of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide: **27.9%**

Reference Example 2: Preparation of Acalabrutinib, according to example 6 of WO2013010868

To a solution of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (3 g, 0.0075 moles), triethylamine (0.42g, 0.0041 moles) and 2-butynoic acid (0.63g, 0.0075 moles) in dichloromethane (300 mL) was added HATU (2.86g, 0.0075 moles). The mixture was stirred for 30 minutes at room temperature. The mixture was washed with water (150 mL), resultant organic layer was dried over magnesium sulfate and distilled. The residue was purified using column chromatography to give 700 mg of Acalabrutinib with purity of 78.09% by HPLC (Amorphous).

Example 1: Preparation of dihydrobromide salt of 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine

A mixture of (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (5 g) and concentrated hydrobromic acid (10 mL) was stirred for one hour at ambient temperature for 24 hours and then heated to 50-55 °C for 5 hours. Isopropanol (50 mL) and methanol (10 mL) was added to the reaction mass and stirred for 30 minutes. The reaction mixture was cooled to ambient temperature, then to 0-5°C and stirred for 3 hours. The resulting product was filtered, washed with isopropanol (15 mL) and dried at to give 4.16 g (78%) of dihydrobromide salt of 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine.

M/z (ESI$^+$) 284.1 [M+H]$^+$

^{1}H NMR (400 MHz, DMSO-d6, ppm) 2.009-2.270 (m, 3H),2.400-2.469 (m, 1H), 3.3505 (t(br), 2H), 5.169-5.208 (t, 1H), 7.242-7.256 (d, 1H), 8.015-8.030 (d, 1H), 8.746, 9.312, 9.720 (s(br), 4H)

Example 2: Preparation of dihydrochloride salt of 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine

A mixture of (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (300 g) and concentrated hydrochloric acid (600 mL) was stirred at 50-55°C for 18-20 hours. Water (300 mL) was added to the reaction mixture and extracted using dichloromethane (750 mL). The resulting aqueous layer was treated with sodium hydroxide (259.5 g in 900 mL water), extracted with dichloromethane (3000 mL) and combined organic layer was concentrated. Methanol (900 mL) and concentrated hydrochloric acid (150. 2 g) was added to resulting residue and stirred for 30 minutes at 40-45°C. Isopropanol (900 mL) was added to the reaction mixture and stirred for 30 to 40 minutes at 20-30°C followed by 2 - 3 hours at 0-5°C. Solid was filtered, washed with isopropanol and dried to give 201 g (78.6%) of dihydrochloride salt of 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine.

IR (KBR, cm^{-1}) 1667.85, 1650.25 (-C=N Stretching); 1592.13 (-C=C-C- Stretching, aromatic)

M/z (ESI$^+$) 282.1, 284.1 [M+H]$^+$

^{1}H NMR (400 MHz, DMSO-d6, ppm) 1.984-2.036, 2.126-2.158 (m, 2H), 2.332-2.417 (m, 2H), 3.310 (t(br), 2H), 5.244-5.281 (t, 1H), 7.291-7.306 (d, 1H), 8.140-8.155 (d, 1H), 8.962, 9.617, 10.823 (s(br), 4H)

Example 3: Preparation of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide

Method A: A mixture of water (600 mL), potassium carbonate (233.5 g), tetrahydrofuran (1000 mL), dihydrochloride salt of 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine (100 g) and 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid (81.80g) was stirred for 10-15 minutes and Pd(dppf)$Cl_2CH_2Cl_2$ (11.5 g) was added to resulting mixture under N_2 atmosphere. The reaction mixture was stirred at 64-67°C for 22-24 hours and then cooled at ambient temperature. Aqueous hydrochloric acid (411 g HCl in 300 mL water) was added to the reaction mixture and stirred at ambient temperature for 10-15 minutes followed by washing of aqueous layer using Tetrahydrofuran (500 mL). Methanol (300 mL), Montmorillonite K10 (15.0 g) and activated carbon were added to combined aqueous layer followed by stirring and filtration. Combined filtrate was neutralized using aqueous sodium hydroxide solution (67.6 g in 300 mL water) and stirred for 6-7 hours at ambient temperature. The product was filtered, washed with water, and dried u/v at 60-65°C for 16-18 hours to give 89 g (79.1%) of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide.

Method B: A mixture of water (600 mL), potassium carbonate (233.5 g), tetrahydrofuran (1000 mL), dihydrochloride salt of 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine (100 g) and 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid pinacol ester (109.31 g) was stirred for 10-15 minutes and Pd(dppf)$Cl_2CH_2Cl_2$ (11.5 g) was added to resulting mixture under N_2 atmosphere. The reaction mixture was stirred at 64-67°C for 22-24 hours and then cooled at ambient temperature. Aqueous hydrochloric acid (411 g HCl in 300 mL water) was added and stirred at ambient temperature for 10-15 minutes followed by washing of aqueous layer using Tetrahydrofuran (500 mL). Methanol (300 mL), Montmorillonite K10 (15.0 g) and activated carbon were added to combined aqueous layer followed by stirring and filtration. Combined filtrate was neutralized using aqueous sodium hydroxide solution (67.6 g in 300 mL water) and stirred for 6-7 hours at ambient temperature. The product was filtered, washed with water (500 mL) and dried u/v at 55-

60°C for 16-18 hours to give 88 g (78.2%) of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide.

Method C: A mixture of water (70 mL), potassium carbonate (24.49 g), tetrahydrofuran (90 mL), 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine (10 g) and 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid (10.29 g) was stirred for 10-15 minutes and Pd(dppf)$Cl_2CH_2Cl_2$ (1.45 g) was added to resulting mixture under N_2 atmosphere. The reaction mixture was stirred at 65-70°C for 46 hours and then cooled at ambient temperature. Aqueous hydrochloric acid (40.66 g HCl in 50 mL water) was added and stirred at ambient temperature for 10-15 minutes followed by washing of aqueous layer using Tetrahydrofuran (50 mL) followed by Toluene (50 mL). Methanol (50 mL) was added to the combined aqueous layer, neutralized using aqueous sodium hydroxide solution (5.67 g in 20 mL water) and stirred for one hour at ambient temperature. The product was filtered, washed with water (50 mL) and dried u/v at 45-50°C for 16 hours to give 10.8 g (76.8%) of (S)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide.

Overall yield of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide (starting from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate as in Example 1 or 2): more than 60%

Example 4: Purification of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide

Step I: Preparation of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide citrate

To a mixture of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide (88 g, purity: 97 % by HPLC) in methanol (500 mL) at 45-55°C, citric acid solution (74.7 g in 300 mL methanol) was added and stirred for one hour at 50-55°C. The reaction mixture was cooled to 20-25°C, then to 0-5°C and stirred for 2-3 hours. The resulting product was filtered, washed with methanol (100 mL) and dried to give (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide citrate.

IR (KBR, cm^{-1}) 1666.71, 1656.27 (>C=O Stretching amide); 1607.34, 1576.08 (-C=C-C- Stretching aromatic)

M/z (ESI$^+$) 400.3 [M+H]$^+$

^{1}H NMR (400 MHz, DMSO-d6, ppm) 2.031-2.072 (m, 2H), 2.163-2.327 (m, 2H), 2.505 (m, 1H), 2.571 (m, 1H), 2.859-2.892 (t, 2H), 5.212-5.279 (t, 1H), 6.337 (s (br), 2H), 7.055-7.067 (d, 1H), 7.145-7.174 (t, 1H), 7.716-7.135 (d, 2H), 7.753-7.765 (d, 1H), 7.819-7.855 (t, IH), 8.177-8.197 (d, 2H), 8.208-8.229 (d, 1H), 8.403-8.415 (d, 1H), 10.826 (s, 1H)

Step II: Preparation of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide

To a mixture of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide citrate, water (100 mL) and tetrahydrofuran (50 mL), aqueous sodium hydroxide (45 g in 300 mL water) was added and mixture was stirred at ambient temperature for 2-3 hours. The reaction mixture was cooled to 0-5°C and stirred for 1-2 hour. The resulting product was filtered, washed with mixture of water: methanol: tetrahydrofuran (300 mL: 20 mL: 10 mL) and dried to give 70 g of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide with purity of 99.49% by HPLC.

Example 5: Preparation of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide oxalate

A mixture of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide (1 g, purity: 97 % by HPLC), methanol (30 mL) and oxalic acid (0.67 g) was stirred for one hour at ambient temperature. Acetone (20 mL) was added to the reaction mass and stirred for 1 hour. The resulting product was filtered, washed with acetone (10 mL) and dried to give 0.66 g of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide oxalate.

M/z (ESI$^+$) 400.2 [M+H]$^+$

^{1}H NMR (400 MHz, DMSO-d6, ppm) 2.084-2.193 (m, 2H), 2.326-2.393 (m, 2H), 3.390 (t, 2H), 5.244 (t, 1H), 6.418 (s(br), 2H), 7.171-7.185 (d, 1H), 7.189-7.247 (t, 1H), 7.774 -7.794 (d, 2H), 7.841-7.862 (d, 1H), 7.880-7.884 (d, 1H), 8.181-8.226 (m, 3H), 8.403-8.413 (d, 1H), 10.820 (s, 1H)

Example 6: Preparation of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide succinate

A mixture of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide (1 g, purity: 97% by HPLC), methanol (10 mL), isopropanol (10 mL) and succinic acid (0.88 g) was stirred for 30 minutes at 40-45 °C. Thereafter, reaction mixture was stirred for 18 hours at ambient temperature. The resulting product was filtered, washed with methanol: isopropanol (5:5 mL) and dried to give 1.3 g of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide succinate.

M/z (ESI$^+$) 400.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d6, ppm) 1.882-2.069 (m, 2H), 2.278-2.314 (m, 2H), 2.349-2.499 (m, 2H), 3.121-3.135 (t, 2 H), 4.873-4.909 (t, 1 H), 6.134 (s(br), 2 H), 7.121-7.133 (d, 1 H), 7.176-7.194 (t, 1 H), 7.745-7.765 (d 2 H), 7.789-7.801 (d 1 H), 7.834-7.855 (t, 1 H), 8.152-8.173 (d 2 H), 8.205-8.225 (d 1 H), 8.399-8.408 (d 1 H), 10.795 (s, 1 H)

Example 7: Preparation of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide tartrate

A mixture of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide (1 g, purity: 97% by HPLC), methanol (50 mL) and tartaric acid solution (5.63 g in 50 mL methanol) was stirred for 2.5 hours at 50-55 °C. Thereafter, reaction mixture was stirred for 30 minutes at ambient temperature. The solid was filtered, washed with methanol (20 mL) and the stirred in water (50 mL) for 2 hours. The product was filtered, washed with water (20 mL) and dried to give 4.8 g of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide tartrate.

M/z (ESI$^+$) 400.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d6, ppm) 1.997-2.121 (m, 2H), 2.390-2.504 (m, 2H), 3.169-3.250 (t, 2H), 4.052 (br(s) 1H), 5.108 (t, 1H), 6.232 (s (br), 2H), 7.168-7.181 (d, 1H), 7.187-7.199 (t, 1H), 7.762-7.783 (d, 2H), 7.753-7.765 (d, 1H), 7.819-7.838 (d, 1H), 8.169-8.189 (d, 2H), 8.206-8.226 (d, 1H), 8.403-8.411 (d, 1H), 10.804 (s, 1H),

Salt of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide prepared in examples 5, 6 and 7 were neutralized using the procedure same as given in example 4, step II to give (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide with purity of more than 99 % by HPLC.

Example 8: Preparation of Acalabrutinib

To a mixture of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide (30 g), 2-butynoic acid (7.6 g), dichloromethane (600 mL), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (18.7 g) was added and reaction mixture stirred at ambient temperature for 4 – 5 hours. 5% Aq. hydrochloric acid (300 mL) was added to reaction mixture and stirred for 5-10 min at ambient temperature followed by layer separation. Organic layer was treated with 5% aq. hydrochloric acid (300 mL). Potassium carbonate (300 mL) was added to combined aqueous layer and stirred at 10-20°C for 1-2 hours and then at ambient temperature for 1-2 hours. The precipitated product was filtered, washed with water (150 mL) and dried to give 28.1 g of Acalabrutinib with purity of 99.4% by HPLC.

Example 9: Preparation of Acalabrutinib

To a mixture of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide (300 g), 2-butynoic acid (82.1 g), dichloromethane (6000 mL), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (201.5 g) was added and reaction mixture was stirred at ambient temperature for 4 – 5 hours. Water (3000 mL) and isopropanol (1500 mL) was added to reaction mixture and stirred for 10-15 minutes at ambient temperature followed by layer separation. Lower organic layer was concentrated followed by addition of methanol (450 mL) and concentrated. Resulting residue was stirred in water (525 mL) and methanol (2250 mL) at 60-65 °C for 30-40 minutes, treated with activated carbon and filtered. Water (625 mL) was added to combined filtrate and stirred at ambient temperature for 15-16 hours. The reaction mixture was cooled at 0-5 °C and stirred for 1-2 hours. The resulting product was filtered, washed with methanol: water (1:1, 300 mL) and dried to give 219 g of Acalabrutinib with purity of 99.5% by HPLC.

Example 10: Preparation of Crystalline form IX of Acalabrutinib

A mixture of Acalabrutinib (28.1 g) in methanol: water mixture (3:1, 330 mL) was stirred at 50-60°C for 50-60 minutes. Water (40 mL) was added to resulting solution and stirred at ambient temperature for 3-4 hours. The mixture was cooled to 0-5°C and stirred for 3-4 hours. The resulting product was filtered, washed with methanol: water mixture (1:1, 30 mL) and dried u/v at 60-65°C for 16-18 hours to give 27.3 g of crystalline form IX of Acalabrutinib.

Example 11: Preparation of Crystalline form IX of Acalabrutinib

A mixture of Acalabrutinib (27.3 g) in methanol: water mixture (3:1, 275 mL) was stirred at 50-60°C for 50-60 minutes. SiliaMetS Thiol (2.5 g) and charcoal (2.5 g) was added to resulting solution and stirred at 50-60°C for 2-3 hours. The mixture was filtered through celite bed and bed was washed with methanol: water mixture (1:1, 50 mL). Water (40 mL) was added to the resulting filtrate at 50-60°C and stirred at 20-30°C for 3-4 hours. The solid was filtered, washed with methanol: water mixture (1:1, 25 mL) and dried u/v at 60-65°C for 16-18 hours to give 22.7 g of crystalline form IX of Acalabrutinib.

Example 12: Preparation of Crystalline form IX of Acalabrutinib

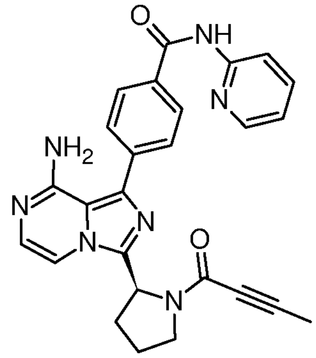
A mixture of Acalabrutinib (219 g) in methanol (1800 mL) and water (300 mL) was stirred at 60-65°C for 30-40 minutes. SiliaMetS Thiol (30 g) was added to the resulting solution at 40-50 °C and stirred for 3-4 hours at 60 – 65°C. The mixture was filtered through celite bed and bed was washed with methanol (300 mL): water mixture (100 mL). Water (650 mL) was added to the resulting filtrate and stirred at ambient temperature for 15-16 hours. The reaction mixture was cooled to 0-5°C and stirred for 1-2 hours. The solid was filtered, washed with methanol: water mixture (1:1, 300 mL) and dried u/v at 55-60 °C for 16-18 hours to give 205 g of crystalline form IX of Acalabrutinib.

Example 13: Preparation of Crystalline form I of Acalabrutinib

Acalabrutinib (200 g) was stirred in Acetone (800 mL) at ambient temperature for 30-40 minutes. Water (30 mL) was added to resulting solution and stirred at 50-55°C for 3-4 hours. Thereafter, mixture was stirred at ambient temperature for 1-2 hours and then at 0-5°C for 2-3 hours. The resulting product was filtered, washed with pre cooled Acetone (200 mL) and dried u/v at 60-65°C for 16-18 hours to give 166 g of crystalline form I of Acalabrutinib.

Claims:

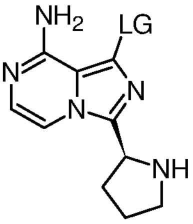
1. A process for the preparation of Acalabrutinib of formula I,



Formula I

comprising the steps of:

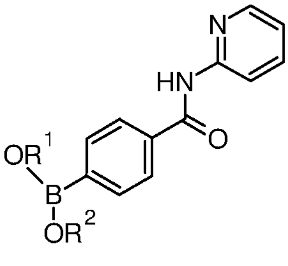
a) reacting a compound of formula II or a salt thereof,



Formula II

wherein LG is a leaving group

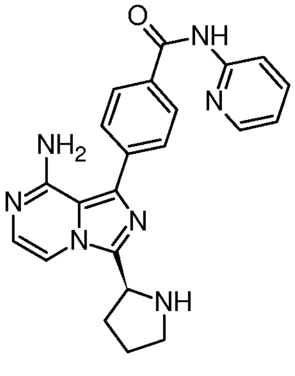
with a compound of formula III,



Formula III

wherein R^1 and R^2 are independently selected from hydrogen, substituted or unsubstituted alkyl, and substituted or unsubstituted aryl; or wherein R^1 and R^2 jointly form a substituted or unsubstituted cycloalkyl ring,

to form a compound of formula IV or a salt thereof,



Formula IV

b) optionally purifying the compound of formula IV, and

c) converting the compound of formula IV into Acalabrutinib.

2. The process according to claim 1, wherein step a) is carried out in the presence of a base and a palladium catalyst.

3. The process according to claim 2, wherein the base is an inorganic base selected from the group consisting of alkali or alkaline earth metal carbonates, bicarbonates, acetates, phosphates, and hydroxides, or the base is an organic base.

4. The process according to claim 3, wherein the base is sodium bicarbonate, potassium carbonate, potassium phosphate, cesium carbonate, tetramethylguanidine or triethylamine.

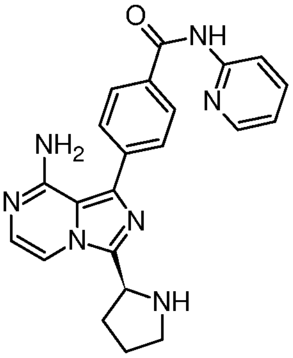
5. The process according to claim 2-4, wherein the palladium catalyst is selected from the group consisting of palladium(II) chloride, palladium(II) acetate, bis(triphenylphosphine)palladium(II) dichloride, tetrakis(triphenylphosphine) palladium(0), bis(dibenzylideneacetone)palladium(0) (Pd(dba)$_2$), Bis(acetonitrile)dichloropalladium(II), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (Pd(dppf)Cl$_2$), and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane (Pd(dppf)Cl$_2$) .

6. The process according to claim 5, wherein the palladium catalyst is bis(triphenylphosphine)palladium(II) dichloride, [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (Pd(dppf)Cl$_2$), or [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane (Pd(dppf)Cl$_2$).

7. The process according to claim 1-6, wherein step a) is carried out in the presence of a solvent selected from the group consisting of water, alcohols, esters, ethers, nitriles, amide solvents, hydrocarbon solvents, halogenated solvents and mixtures thereof.

8. The process according to claim 7, wherein the solvent is methanol, ethanol, isopropanol, tetrahydrofuran, 1,4-dioxane, toluene, dichloromethane, dimethylformamide, acetonitrile, propionitrile, dimethylacetamide, mixtures thereof or a mixture of one or more of the foregoing with water.

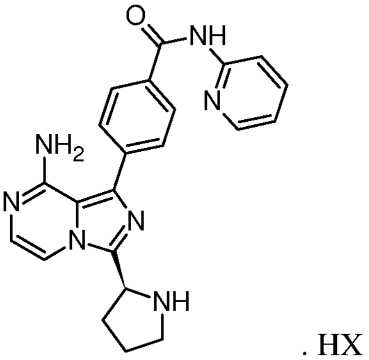
9. A process for the purification of the compound of formula IV,



Formula IV

comprising the steps of:

a) treating the compound of formula IV with an inorganic acid or an organic acid to form an acid addition salt of formula IVa,



Formula IVa

wherein HX is the inorganic acid or the organic acid,

b) neutralising the acid addition salt of formula IVa with a base, and

c) isolating the purified compound of formula IV.

10. The process according to claim 9, wherein the inorganic acid is selected from hydrochloric acid and hydrobromic acid; and the organic acid is a carboxylic acid selected from the group consisting of succinic acid, formic acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, tartaric acid, oxalic acid, malic acid, maleic acid, citric acid, benzoic acid, substituted benzoic acid, p-toluenesulfonic acid, and methanesulfonic acid.

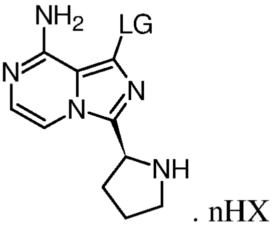
11. The process according to claim 9, wherein the organic acid is selected from the group consisting of acetic acid, tartaric acid, oxalic acid, succinic acid, p-toluenesulfonic acid, methanesulfonic acid, and citric acid.

12. The process according to claim 9-11, wherein the base is selected from an alkali or alkaline earth metal hydroxide, alkoxide, carbonate, bicarbonate, and an amine.

13. The process according to claim 9, wherein the base is sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, or triethylamine.

14. The process according to claim 9-13, wherein the reaction is carried out in the presence of a polar or non-polar solvent selected from the group consisting of water, alcohols, ketones, halogenated solvents, hydrocarbon solvents, esters, amide solvents, ethers, and mixtures thereof.

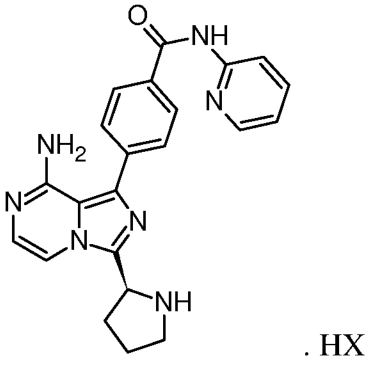
15. An acid addition salt of formula IIa,



Formula IIa

wherein LG is a leaving group, n is selected from 1 or 2, and HX is an inorganic acid or an organic acid.

16. An acid addition salt of formula IVa,



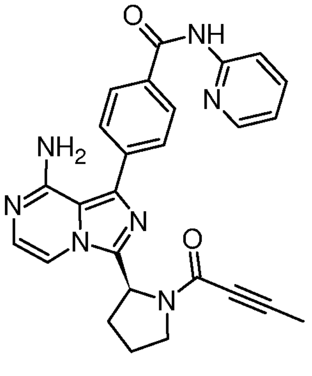
Formula IVa

wherein HX is an inorganic acid or an organic acid.

17. The acid addition salt according to claim 15 or 16, wherein the inorganic acid is selected from hydrochloric acid and hydrobromic acid.

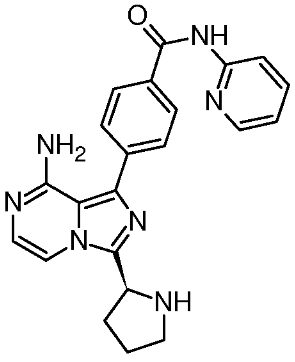
18. The acid addition salt according to claim 15 or 16, wherein the organic acid is a carboxylic acid selected from the group consisting of succinic acid, formic acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, tartaric acid, oxalic acid, malic acid, maleic acid, citric acid, benzoic acid, substituted benzoic acid, p-toluenesulfonic acid, and methanesulfonic acid.

19. A process for the preparation of Acalabrutinib of formula I,



Formula I

comprising reacting a compound of formula IV or a salt thereof,



Formula IV

with 2-butynoic acid in the presence of a carbodiimide reagent.

20. The process according to claim 19, wherein the carbodiimide reagent is selected from the group consisting of N,N'-dicyclohexylcarbodiimide, N,N'-diisopropylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride.

21. The process according to claim 19 or 20, wherein the reaction is carried out in the presence of an aprotic solvent selected from the group consisting of halogenated solvents, hydrocarbon solvents, ketones, amide solvents, ethers and mixtures thereof.

22. The process according to claim 21, wherein the solvent is selected from the group consisting of dichloromethane, toluene, acetone, dimethylformamide, tetrahydrofuran and mixtures thereof.

23. A process for preparing crystalline form I of Acalabrutinib, comprising the steps of:

a) dissolving Acalabrutinib in a first solvent,

b) adding a second solvent to the resulting solution, and

c) isolating crystalline form I of Acalabrutinib

wherein the first solvent is selected from acetone and methanol and the second solvent is selected from water, methylisobutyl ketone, isopropanol, and methylethyl ketone.

24. The process according to claim 23, wherein step a) is carried out at 35 °C to 70 °C for 20 minutes to 8 hours.

25. Crystalline form IX of Acalabrutinib characterized by X-ray powder diffraction (XRPD) pattern comprising peaks at about 8.5, 10.1, and 12.0 ±0.2° 2θ.

26. The crystalline form IX of Acalabrutinib according to claim 25, characterized by X-ray powder diffraction (XRPD) pattern further comprising peaks at about 15.9, 20.1, 22.0 and 26.0 ±0.2° 2θ.

27. A process for preparing crystalline form IX of Acalabrutinib, comprising the steps of:

a) contacting Acalabrutinib with methanol and water; and

b) isolating crystalline form IX of Acalabrutinib.

28. The process according to claim 27, wherein step a) is carried out at 40-70°C for 10 minutes to 12 hours**.**

29. The process according to claim 27 or 28, wherein after step a), the resulting solution is mixed with water to precipitate crystalline form IX of Acalabrutinib.

30. A pharmaceutical composition comprising Acalabrutinib prepared by the process according to claim 1-8 or 19-29 and at least one pharmaceutically acceptable excipient.

31. A method of treating cancer, comprising administering a therapeutically effective amount of Acalabrutinib prepared by the process according to claim 1-8 or 19-29.

32. A pharmaceutical composition comprising crystalline form IX of Acalabrutinib and at least one pharmaceutically acceptable excipient.

33. A method of treating cancer, comprising administering a therapeutically effective amount of crystalline form IX of Acalabrutinib.

34. A method of preparing a pharmaceutical composition, comprising a step of admixing crystalline form IX of Acalabrutinib with one or more pharmaceutically acceptable excipients.

35. Acalabrutinib prepared by the process according to claim 1-8 or 19-29 for use in the treatment of cancer.

36. Crystalline form IX of Acalabrutinib for use in the treatment of cancer.

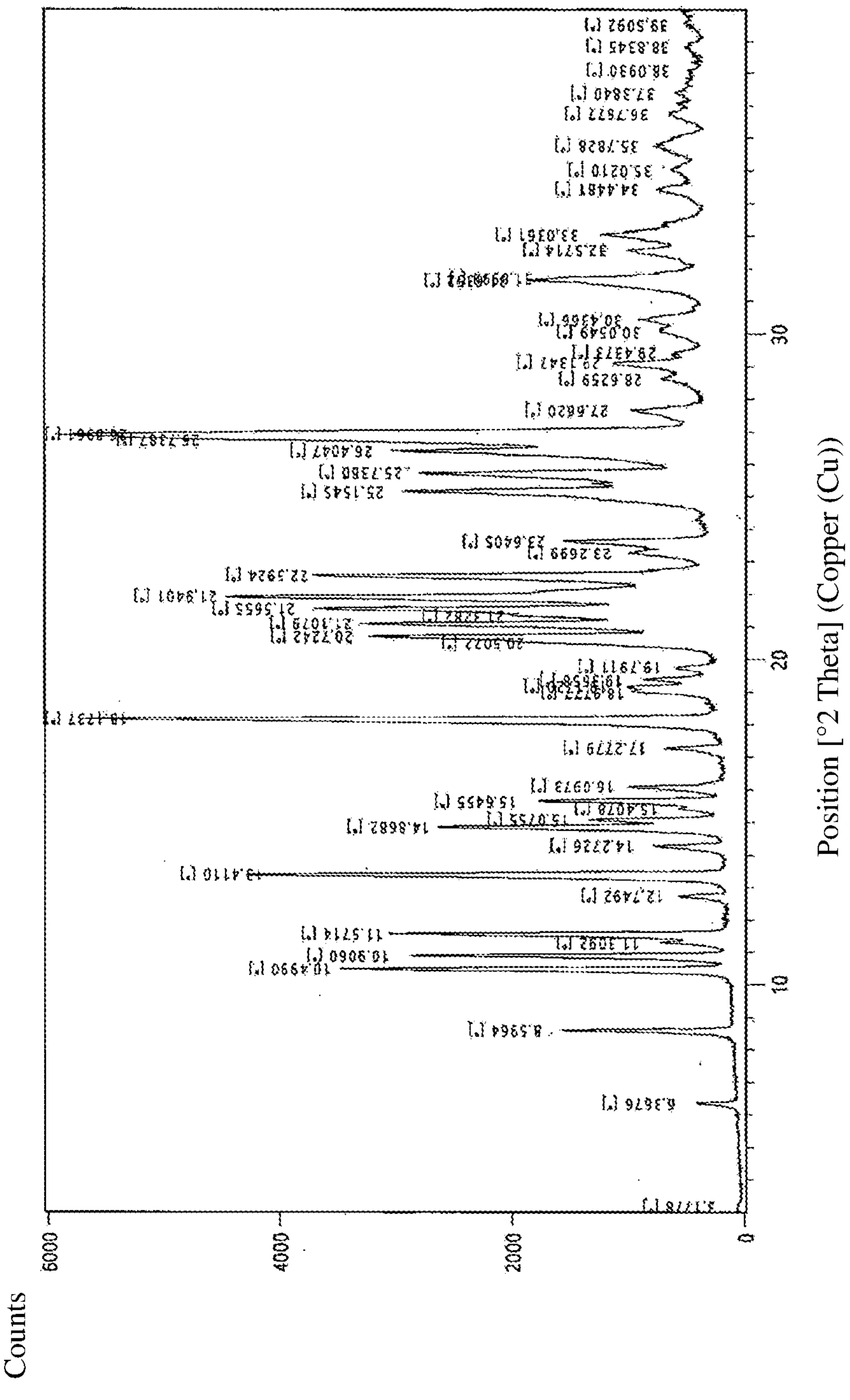

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Fig. 1

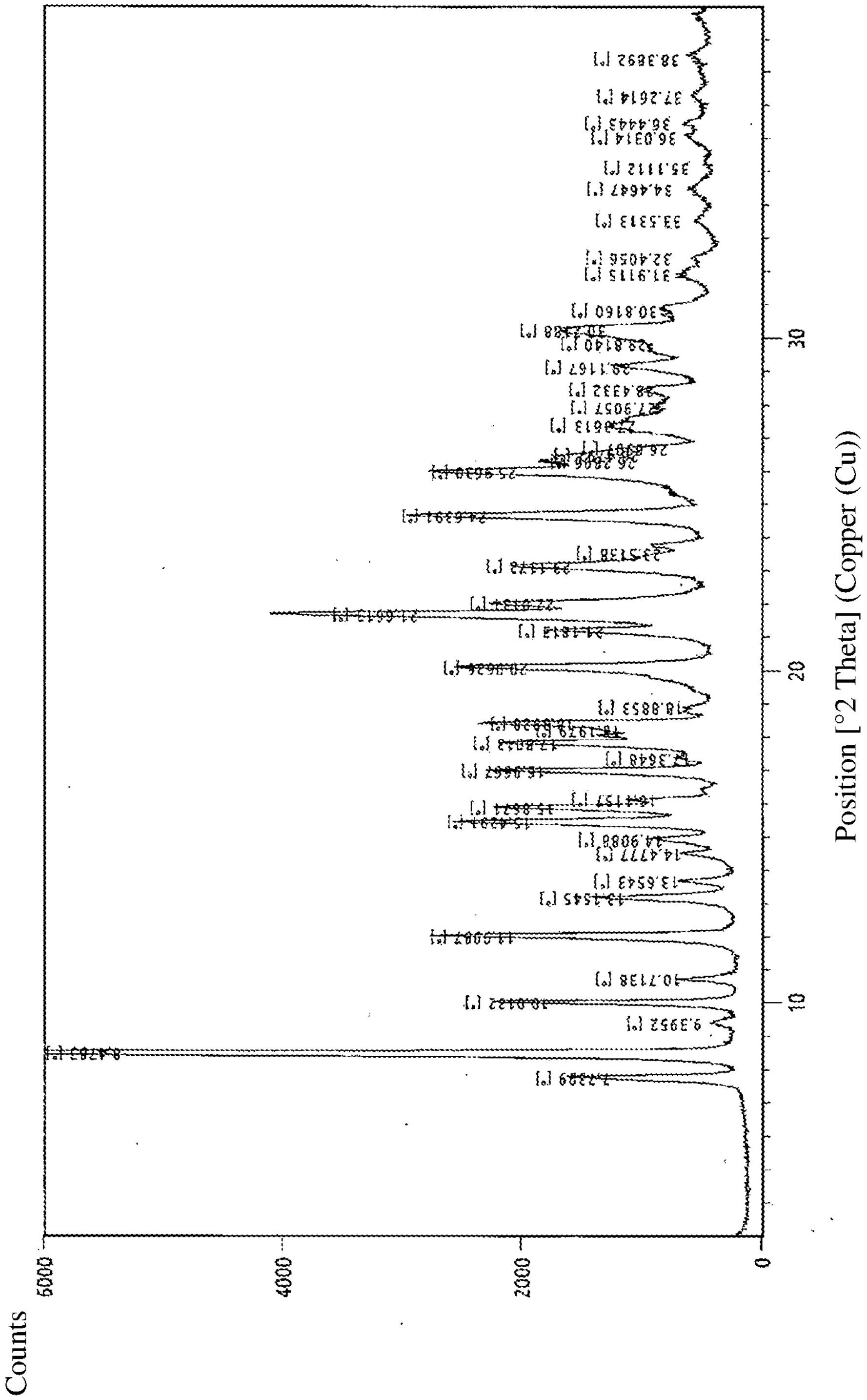
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Fig. 2