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(54) **Title**: PREPARATION OF PURE AMORPHOUS IBRUTINIB

(57) **Abstract**: The present invention refers to the preparation of the amorphous form of the Bruton's tyrosine kinase (Btk) inhibitor 1 -((*R*)-3-(4-armno-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1- yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib). In particular, the invention refers to a process for the preparation of substantially pure amorphous ibrutinib. In a further aspect, the invention refers to a process for the preparation of a salt of ibrutinib.

Preparation of Pure Amorphous Ibrutinib

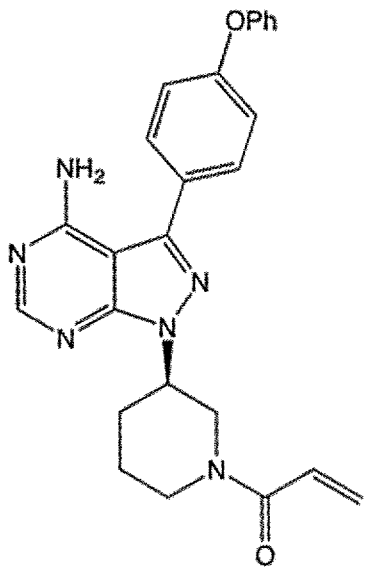
FIELD OF THE INVENTION

The present invention refers to the preparation of the amorphous form of the Bruton's tyrosine kinase (Btk) inhibitor 1-((*R*)-3-(4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib). In particular, the invention refers to a process for the preparation of substantially pure amorphous ibrutinib, which uses a salt of ibrutinib as starting material.

BACKGROUND OF THE INVENTION

Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

1-((*R*)-3-(4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is also known by its IUPAC name as 1-{(*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo [3,4-*d*]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one or 2-propen-1-one,1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinyl]-, and has been given the USAN name "*Ibrutinib*", which will be used further in the document and refers to the compound with the following structure:



Ibrutinib is a selective, irreversible inhibitor of BTK first disclosed in WO 2008/039218, which has been shown to be highly clinically efficacious in relapsed/refractory CLL and mantle cell lymphoma (see e.g. Burger et. Leukemia & Lymphoma (2013), 54(11), 2385-91).

Amorphous ibrutinib is moisture stable. It is therefore a good alternative to crystalline ibrutinib as amorphous material has a higher solubility, which is connected with better bioavailability, than corresponding crystalline forms. Thus, amorphous ibrutinib is the preferred physical form for the preparation of pharmaceutical compositions.

CN 103121999 A discloses ibrutinib of undisclosed form with an HPLC purity of 98.6% and >98% ee by crystallization from toluene.

CN 103923084 A discloses anhydrous, hydrous as well as solvate crystal forms of ibrutinib, the solvate forms of ibrutinib being solvates of oxolane and trichloromethane.

Three anhydrous polymorphs and solvates from methanol, methylisobutylketone (MIBK), and toluene of ibrutinib have been specifically disclosed in WO 2013/184572 including formulations containing them and their use. However, the toluene solvate has been reported as being unstable. Moreover, solvates with methanol and MIBK suffer from low solubility of ibrutinib in those solvents (about 1 wt% or less), thereby limiting their use for purification and subsequent preparation of amorphous ibrutinib on industrial scale as this would require very large amounts of solvent. Thus, the solvates from methanol and methylisobutylketone are not suitable for the preparation of amorphous ibrutinib for use in the manufacture of a medicament.

Furthermore, according to WO 2008/039218 amorphous ibrutinib can be obtained from material that has been purified by chromatography on silica gel using dichloromethane/alcohol mixtures. This approach bears the disadvantage that the eluent in the final purification step generally may contain unspecified amounts of silica gel leaking from the column. Because such impurities might affect chemical stability in an uncontrolled manner, such a material is not appropriate for use in a medicament. Furthermore, use of ICH class II solvents such as dichloromethane and methanol is not preferred for API synthesis. Moreover, amorphous ibrutinib material prepared by fast rotary evaporation as described in WO 2008/039218 features a solid state best described as honey-like, gum, or foam, depending on the amount of residual dichloromethane still present. Such a material is difficult or even impossible to handle and process on a large scale.

IPCOM000238881D describes the preparation of the hydrochloride salt of ibrutinib, which is obtained by reaction of tert-butyl-(*R*)-3-(4-amino-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-carboxylate with (4-phenoxyphenyl)boronic acid and treating the resulting tert-butyl-(*R*)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-carboxylate with ethanolic HCl. Further, the document discloses a preparation process for amorphous ibrutinib. Therein, ibrutinib as obtained by dissolving the starting material in acetone or 2-methyl THF and concentrating to dryness following the procedures described in US 7,514,444, in which the resulting material is purified by chromatography on silica gel, and thus the approach bears the disadvantage that the eluent in the final purification step contains unspecified amounts of silica gel leaking from the column.

Therefore, a need exists in the art for processes to prepare amorphous ibrutinib in substantially pure form. In particular, a need exists in the art for processes to prepare amorphous ibrutinib in pure form without using column chromatography. The processes should be scalable and lead to amorphous ibrutinib in high yield. Further, process-specific byproducts should be efficiently depleted.

BRIEF DESCRIPTION OF FIGURES

Figure 1 shows an X-ray powder diffraction (XRPD) spectrum of amorphous ibrutinib obtained in Example 2 by the process of the present invention.

Figure 2 shows an X-ray powder diffraction (XRPD) spectrum of amorphous ibrutinib obtained in Example 3 by the process of the present invention.

Figure 3 shows an XRPD spectrum of ibrutinib hydrochloride obtained in Example 7 by the process of the present invention.

SUMMARY OF THE INVENTION

It has surprisingly been found in the present invention that the above objects can be achieved by the provision of a process for the preparation of amorphous ibrutinib starting from a salt of ibrutinib.

Hence, in a first aspect the present invention refers to a process for the preparation of amorphous 1-((*R*)-3-(4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), comprising the steps of:

(i) providing a salt of ibrutinib,

(ii) adding an organic solvent and an alkaline component to obtain a solution of ibrutinib,

(iii) isolating amorphous ibrutinib from the reaction mixture of step (ii), or

(iii-1) isolating ibrutinib from the reaction mixture of step (ii), and

(iv) optionally adding an organic solvent to obtain a solution of ibrutinib and isolating amorphous ibrutinib from the solution.

Further, a need exists in the art for more economic and efficient processes to prepare a salt of ibrutinib, which can be used in the processes of the present invention.

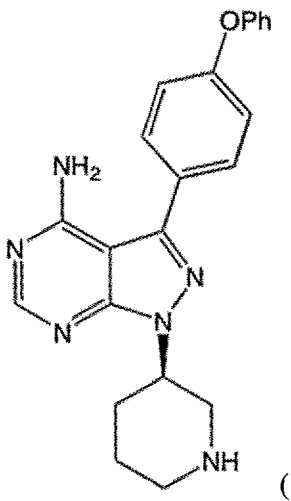
Thus, in another aspect the present invention provides a process for the preparation of a salt of ibrutinib, the process comprising the steps of:

(a) reacting a compound of formula (1) or a salt and/or solvate thereof with 2-propenoyl chloride in the presence of an organic solvent and an aqueous solution of an inorganic alkaline component to obtain the compound of formula (2),

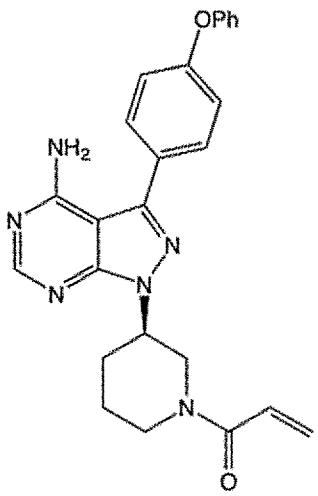
(b) optionally isolating the compound of formula (2) from the reaction mixture,

(c) subjecting the compound of formula (2) to an organic or inorganic acid, and

(d) isolating the salt of ibrutinib from the reaction mixture



(1)



(2).

DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the invention relates to a process for preparing amorphous ibrutinib. The process comprises the steps of:

(i) providing a salt of ibrutinib,

(ii) adding an organic solvent and an alkaline component to obtain a solution of ibrutinib,

(iii) isolating amorphous ibrutinib from the reaction mixture of step (ii), or

(iii-1) isolating ibrutinib from the reaction mixture of step (ii), and

(iv) optionally adding an organic solvent to obtain a solution of ibrutinib and isolating amorphous ibrutinib from the solution.

It has surprisingly been found that amorphous ibrutinib can be prepared by the process of the present invention in substantially pure form, and in particular can be prepared in pure form. The terms "*pure*" and "*substantially pure*" in the context of the present invention refer to phase-purity and chemical purity of the amorphous ibrutinib. Phase purity of amorphous ibrutinib is characterized by the absence of any peaks in the XRPD pattern. Chemical purity of the amorphous ibrutinib can for example be determined by HPLC analysis. The amorphous ibrutinib obtained by the process described herewith thus preferably has a chemical purity of 98.0 wt.% or more, preferably of 99.0 wt.% or more, more preferably of 99.5 wt.%, most preferably of 99.9 wt.%, based on the total weight of the amorphous ibrutinib.

In particular, amorphous ibrutinib can be prepared according to the process of the present invention without using column chromatography. As a consequence, any possible product contamination with silica, such as silica gel, can be avoided. The amorphous ibrutinib thus preferably has a content of silica, which is less than 1.0 wt.%, preferably is less than 0.3 wt.%, more preferably is less than 0.1 wt.%, further more preferably is less than 0.03 wt.%, most preferably is less than 0.01 wt%, based on the total weight of the amorphous ibrutinib.

Further, it is possible with the process of the present invention to prepare amorphous ibrutinib, which is substantially free from any crystal form of ibrutinib, such as crystal form A of ibrutinib. "*Substantially free*" in the context of the present invention means that no crystalline form, such as crystalline form A can be detected by XRPD measurement, i.e. no peaks of a crystalline form can be observed in an XRPD measurement. Thus, in a further embodiment, the

invention is directed to the amorphous form of ibrutinib having no noticeable peak in a powder X-ray diffraction.

In step (i) of the process of the present invention, a salt of ibrutinib is provided, such as a crystalline salt. The salt provided in step (i) is not particularly limited but is typically a pharmaceutically acceptable salt, including, but not limited to, acid addition salts formed by reacting the free base form of ibrutinib with an organic or inorganic acid, such as salts of

(1) an organic acid, comprising aliphatic and aromatic sulfonic acid, trifluoroacetic acid, pyruvic acid, oxalic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, naphthyl disulfonic acid, and formic acid, or

(2) an inorganic acid, comprising hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, and phosphorous acid.

The salt in step (i) includes solvent addition forms, hydrates, alcoholates or any other (co)crystal forms thereof, particularly solvates or polymorphs. Solvates can contain either stoichiometric or non-stoichiometric amounts of a solvent. The solvate may be any solvate of ibrutinib and an organic solvent use for cocrystallization, including ibrutinib solvates of methanol, methylisobutylketone (MIBK), toluene, anisole, dichloromethane, chlorobenzene, 1,4-dioxane, isopropanol and pyridine, preferably solvates of ibrutinib and a solvent selected from chlorobenzene, 1,4-dioxane, isopropanol and pyridine. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is an alcohol.

Preferably, the salt is in crystalline form. Further preferably, the salt is ibrutinib hydrochloride or ibrutinib nitrate, most preferably, the salt is crystalline ibrutinib hydrochloride.

Step (ii) of the process of the present invention includes adding an organic solvent and an alkaline component to obtain a solution of ibrutinib. The organic solvent is not particularly limited as long as ibrutinib can be completely dissolved therein and can subsequently be isolated from the organic solvent, such as by the addition of an anti-solvent such as water or an aqueous salt solution.

Hence, the organic solvent is preferably selected from acetone, methanol, ethyl acetate, isopropyl acetate, isopropyl alcohol, methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK), tetrahydrofuran (THF), dichloromethane (DCM), dioxane, toluene, anisole, 2-methyl tetrahydrofuran or combinations thereof. Particularly preferred solvents include acetone,

isopropanol, methanol, and 2-methyl tetrahydrofuran, most preferably the solvent is acetone or isopropanol.

The alkaline component may be an organic or inorganic alkaline component. The alkaline component is typically selected from one or more of triethylamine (TEA), sodium hydroxide (NaOH), potassium carbonate (K_2CO_3), sodium carbonate (Na_2CO_3), potassium hydroxide (KOH), sodium bicarbonate ($NaHCO_3$). Preferred alkaline components are selected from NaOH or TEA.

Step (iii) of the process of the present invention includes isolating ibrutinib from the solution obtained in step (ii). Isolating ibrutinib from the solution is not particularly limited as long as ibrutinib can be obtained in high purity.

In a first alternative embodiment of step (iii), ibrutinib is directly obtained in amorphous form. In this embodiment, amorphous ibrutinib may be obtained from the reaction mixture by the addition of a suitable anti-solvent, such as water, leading to precipitation of amorphous ibrutinib. In particular, an amorphous product may be obtained in case the solution of ibrutinib is added to the anti-solvent rapidly, i.e. typically in one portion. Further, obtaining an amorphous product is typically achieved when the solution of ibrutinib is added in a small volume to a large volume of the anti-solvent. Therefore, the ratio of the volume of the ibrutinib solution to the volume of the anti-solvent is typically between 1:5 and 1:50, preferably between 1:10 and 1:40, more preferably between 1:15 and 1:30. Further, the temperature of the anti-solvent is preferably below 30°C, more preferably about room temperature, i.e. 20°C to 25 °C. One or more of the above features will ensure a rapid precipitation of ibrutinib from the solution, thereby inhibiting formation of ibrutinib crystals. Thus, a combination of two or more of the above features, such as adding the solution of ibrutinib in one portion to the anti-solvent, wherein the ratio of ibrutinib solution to the anti-solvent is (v/v) 1:10 or less typically leads to the formation of a pure amorphous ibrutinib product. The process variables relevant for obtaining an amorphous ibrutinib product from a solution are for example described in "S.L. Morissette et al., Advanced Drug Delivery Reviews, 56 (2004) 275–300".

The amorphous ibrutinib can then be isolated by processes known in the art, such as filtration or centrifugation, preferably by filtration. Additionally, isolation of ibrutinib by optional extraction and removal of organic solvent typically leads to substantially pure amorphous ibrutinib.

Therefore, amorphous ibrutinib can be obtained in step (iii) in substantially pure form, preferably in pure form. Thus, it is typically not necessary to perform any further purification steps. In particular, further purification by column chromatography can be avoided.

In an alternative and preferred embodiment of step (iii), also designated herein as step (iii-1), ibrutinib is obtained in non-amorphous form, such as crystalline form A, form B or form C of ibrutinib, preferably in crystalline form A. Isolation of crystalline ibrutinib is typically achieved by the addition of a suitable anti-solvent, such as water and isolation of crystalline ibrutinib. In this embodiment, a crystalline product is typically achieved if the anti-solvent is added in more than one portion to the solution of ibrutinib, preferably in three or more portions, and most preferably the anti-solvent is added in multiple small portions, such as dropwise, to the ibrutinib solution. In this case addition of the anti-solvent to the ibrutinib solution is slow enough to allow the formation of ibrutinib crystals and inhibiting precipitation of amorphous ibrutinib. Further, it is preferred that the ratio of the volume of the ibrutinib solution to the volume of the anti-solvent is typically between 2:1 and 1:5, more preferably is between 1: 1 and 1:4, most preferably about 1:3. Further, the temperature of the solvent is preferably 30°C or more, more preferably 40°C or more, and most preferably 50°C or more, wherein the upper limit of the temperature of the solvent is defined by the boiling point of the anti-solvent and the organic solvent. Preferably, the anti-solvent having about room temperature, i.e. about 20 to 25°C is added to the ibrutinib solution having a temperature as described above, such as 40°C or more, most preferably about 50°C, while maintaining the temperature of the resulting mixture at a temperature corresponding to the temperature of the ibrutinib solution. One or more of the above features will ensure the formation of ibrutinib crystals, thereby inhibiting precipitation of amorphous ibrutinib. Thus, a combination of two or more of the above features, such as adding the anti-solvent slowly, such as dropwise, to the ibrutinib solution, wherein the ratio of ibrutinib solution to the anti-solvent is (v/v) about 1:3, typically leads to the formation of ibrutinib crystals, i.e. a crystalline ibrutinib product. Further, the addition of seeding crystals to the ibrutinib solution after addition of the anti-solvent is preferred for obtaining a crystalline product. The process variables relevant for obtaining a crystalline ibrutinib product from a solution are for example described in "S.L. Morissette et al., Advanced Drug Delivery Reviews, 56 (2004) 275–300". The crystalline ibrutinib can be isolated by processes known in the art, such as filtration or centrifugation, preferably by filtration.

In order to further enhance purity of the amorphous ibrutinib obtained in step (iii), for example in case the starting material is of low purity, or in case residual crystalline forms of ibrutinib

should still be present after step (iii) or (iii-1), step (iv) described in the following may optionally be performed. Further, step (iv) is essentially performed in the embodiment in which ibrutinib is obtained in step (iii-1) in crystalline form.

Step (iv) includes adding an organic solvent to obtain a solution of ibrutinib. The solvent used in step (iv) is not particularly limited as long as ibrutinib can be completely dissolved therein, and the solvent can easily be removed, for example by evaporation. Typically, the organic solvent used in step (iv) has a boiling point at ambient conditions of 1013 mbar, 25°C of 101°C or below, preferably of 80°C or below most preferably of 66°C or below. Preferably, the organic solvent used in step (iv) is selected from methanol, dichloromethane, tetrahydrofuran, acetone, dioxane or combinations thereof, most preferably methanol.

Step (iv) further includes isolating amorphous ibrutinib from the solution. Isolating amorphous ibrutinib thus requires removal of the organic solvent to obtain substantially pure amorphous ibrutinib, preferably pure amorphous ibrutinib. Isolating is typically performed by precipitation of ibrutinib by anti-solvent addition as described above, such as addition of water to the solution of ibrutinib obtained in step (iv) and isolation of the precipitate by e.g. filtration or fast evaporation of solvent, preferably by filtration. Alternatively, anti-solvent addition includes addition of a suitable organic solvent to affect precipitation of ibrutinib from the solution. Typical anti-solvents include, but are not limited to methyltertbutylether (MTBE), acetonitrile, heptane and water, preferably water.

Alternatively, isolating of ibrutinib in step (iv) may be performed by processes conventionally known in the art, such as spray drying, lyophilisation, thermal desolvation, or hot melt-extrusion. In consequence, isolating of ibrutinib in step (iv) is not limited as long as crystallization of ibrutinib from the solution is substantially inhibited.

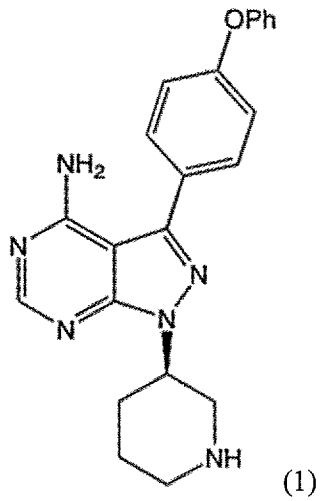
In a further embodiment, a salt of ibrutinib, such as the salt provided in step (i) of the above-described process, is obtained by a process comprising the steps of:

(a) reacting a compound of formula (1), a salt and/or solvate thereof with 2-propenoyl chloride in the presence of an organic solvent and an aqueous solution of an inorganic alkaline component to obtain the compound of formula (2),

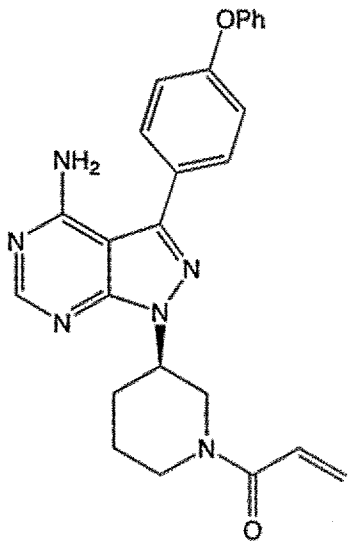
(b) optionally isolating the compound of formula (2) from the reaction mixture,

(c) subjecting the compound of formula (2) to an organic or inorganic acid, and

(d) isolating the salt of ibrutinib from the reaction mixture



(1)



(2).

The compound of formula (1) may be provided in its base form, or may alternatively be provided as salt and/or solvate thereof, including hydrates, alcoholates or any other typical (co)crystals. The salt may be any typical acid addition salt, such as those described in step (i) of the process for preparing amorphous ibrutinib. Preferably, the salt is the monohydrochloride or the dihydrochloride salt. For some embodiments, specific salts such as the monohydrochloride are preferred for the purpose of enantiomeric purification Solvates may contain either stoichiometric or non-stoichiometric amounts of a solvent. The solvate may be any solvate of compound (1) and an organic solvent use for cocrystallization, including solvates of methanol, methylisobutylketone (MIBK), toluene, anisole, dichloromethane, chlorobenzene, 1,4-dioxane, isopropanol and pyridine, preferably solvates of chlorobenzene, 1,4-dioxane, isopropanol and pyridine.

The salt obtained by the process of this embodiment is typically a salt as described above for step (i) of the process for preparing amorphous ibrutinib, and is preferably obtained in crystalline form. Hence, the preferred embodiments described above for the salt provided in step (i) of the process for preparing amorphous ibrutinib equally apply to the salt obtained by the process of this embodiment.

The inorganic alkaline component in step (a) is typically selected from one or more of sodium hydroxide (NaOH), potassium carbonate (K_2CO_3), sodium carbonate (Na_2CO_3), potassium hydroxide (KOH), sodium bicarbonate ($NaHCO_3$), preferably is selected from NaOH, Na_2CO_3, KOH and $NaHCO_3$, most preferably is NaOH. Whereas the physical attributes of the reaction (clear solution, no precipitation during the reaction) where observed to be most beneficial when

using NaOH as the alkaline component, concerning the reaction (conversion, purity) NaOH, KOH, $NaHCO_3$, Na_2CO_3 are considered to be equally preferred.

Although the inorganic alkaline component in step (a) is typically provided in form of an aqueous solution, reaction efficiency, i.e. increased yield and higher purity of the compound of formula (2), could be further increased by firstly adding an aqueous solution of the inorganic alkaline component to the compound of formula (1) and subsequently removing water before the addition of acryloyl chloride. This essentially water-free solution may then be cooled and added to the substrate, concomitant with a further addition of an aqueous solution of the inorganic alkaline component. In this embodiment, removal of water is preferably performed by azeotropic drying, such as azeotropic drying by use of a Dean-Stark trap. The water content is preferably reduced to 0.1 wt% or less, based on the amount of organic solvent.

Further, the organic solvent in step (a) is preferably selected from one or more of dichloromethane (DCM), isopropanol, isobutanol, anisole, n-butanol, t-butanol, n-propanol, tetrahydrofuran, methyl tetrahydrofuran, methyltertbutylether (MTBE), diisopropylethylether (DIPET), methylisobutylketone (MIBK), methylethylketone (MEK), and acetone (ACT), preferably is selected from isopropanol and dichloromethane.

Therefore, the reaction conditions of step (a) of the process of the present invention are conventionally designated as "*Schotten-Baumann*" reaction conditions, using an amine and an aqueous solution of an alkaline component as starting compounds for the formation of the amide. Although the skilled person could have expected that the presence of the aqueous environment would lead to a significant formation of byproducts due to hydrolysis of the resulting amide or due to potential polymerization of the compound of formula (2), thereby leading to polymeric byproducts, it could surprisingly be found by the inventors of the present invention that the process as described herein leads to the formation of the salt of ibrutinib in high yield and high purity, i.e. without the formation of byproducts in step (a). In addition, the reaction allows for an easy purification of the salt obtained in step (d) even without isolating the intermediate compound (2) from the reaction mixture.

In step (b), the compound of formula (2) may optionally be isolated from the reaction mixture. Isolating may be achieved by washing the reaction mixture with a suitable aqueous salt solution, such as a NaCl or $(NH_4)_2SO_4$ salt solution, preferably an $(NH_4)_2SO_4$ salt solution. Preferably, the organic and inorganic layers are separated and the organic layer dried by azeotropic drying, which is preferably performed by use of a Dean-Stark trap. Preferably, the residual water

content of the organic layer is reduced to 1.5 wt% water or less, based on the amount of the organic layer. In an alternative embodiment, step (c) is directly performed after step (a), thus without isolating the compound of formula (2) from the reaction mixture of step (a).

The acid used in step (c) is not particularly limited and typically includes the organic and inorganic acids described above for the formation of pharmaceutically acceptable acid addition salts provided in step (i) of the process for preparing amorphous ibrutinib. Most preferably, the acid in step (c) is hydrochloric acid.

Step (d) of isolating the salt of ibrutinib from the reaction mixture may be performed by processes known in the art, such as extraction, precipitation or addition of seed crystals, which may be followed by filtration of the solid form of ibrutinib from the reaction mixture, centrifugation, or evaporation of solvent. Moreover, in case the salt is obtained in crystalline form, the isolated crystals may optionally be dried, e.g. under reduced pressure, typically at room temperature, or heated up to a temperature between 25°C and 50°C or the crystals may directly be used in further processes, such as the preparation of amorphous ibrutinib as described above, or isolated crystals may be used as seed crystals in the processes of the present invention for the preparation of a salt of ibrutinib.

The salt of ibrutinib obtained in step (d) may optionally be further purified, such as by dissolving ibrutinib in a suitable solvent following crystallization from the solution.

In a most preferred embodiment, the process of preparing a salt of ibrutinib comprises the steps of:

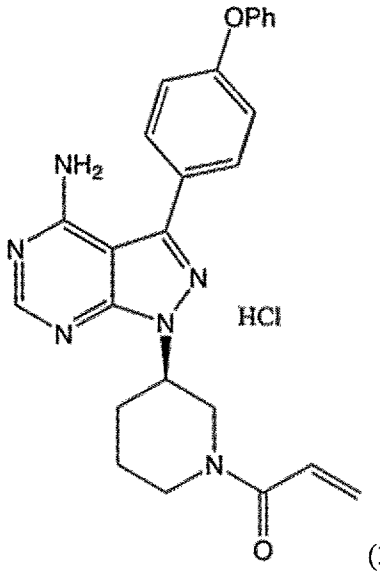
(a) reacting the compound of formula (1) with 2-propenoyl chloride in the presence of isopropanol and an aqueous solution of NaOH to obtain the compound of formula (2),

(b) washing the reaction mixture with an aqueous salt solution,

(c) removal of water from the solution of compound of formula (2) in isopropanol, preferably by azeotropic drying, and adding hydrochloric acid to the solution, and

(d) isolating the crystalline ibrutinib hydrochloride by the addition of seed crystals and separation of the precipitate from the reaction mixture.

Hence, in a preferred embodiment the invention is directed to a process for preparing the hydrochloride salt of ibrutinib, as represented by formula (3) below, and which is further preferably obtained in crystalline form.



(3)

The invention as described herein therefore allows access to amorphous ibrutinib in very high purity without the requirement of chromatography, such as silica chromatography. Moreover, the processes of the invention have the following advantages:

- Provision of a high yielding, scaleable procedure, which is suitable for bulk-scale synthesis
- Preparation of highly pure amorphous Ibrutinib
- No column chromatography required
- Product is free of SiO_2
- Process-specific byproducts can efficiently be depleted

The process of the present invention has the further advantage that the amorphous ibrutinib can be obtained in powder form, and therefore has beneficial properties making it especially suitable for use in the preparation of a medicament and preparing same on industrial scale. In particular, the amorphous ibrutinib obtained in powder form is typically free flowing, and its particle size and particle size distribution can be controlled by processes known in the art, such as by milling and/or sieving the amorphous ibrutinib in powder form.

Therefore, as the amorphous ibrutinib prepared by the processes of the present invention described above can be obtained in high purity and high yield, it can beneficially be used for the manufacture of pharmaceutical compositions. Thus, in a further embodiment, the present

invention relates to a pharmaceutical composition comprising the amorphous form of ibrutinib as described above, such as tablets or capsules, preferably for use in the treatment of cancer.

EXAMPLES

The present invention is further illustrated by way of the following non-limiting examples.

X-Ray Powder Diffraction (XRPD)

XRPD diffractograms were obtained with an X'Pert PRO diffractometer (PANalytical, Almelo, The Netherlands) equipped with a theta/theta coupled goniometer in transmission geometry, programmable XYZ stage with well plate holder, Cu-Kalpha$_{1,2}$ radiation source (wavelength 0.15419 nm) with a focusing mirror, a 0.5° divergence slit, a 0.02° soller slit collimator and a 0.5° anti-scattering slit on the incident beam side, a 2 mm anti-scattering slit, a 0.02° soller slit collimator, a Ni-filter and a solid state PIXcel detector on the diffracted beam side. The diffractogram was recorded at room temperature at a tube voltage of 40 kV, tube current of 40 mA, applying a step size of 0.013° 2-theta with 40 sec per step in the angular range of 2 ° to 40 ° 2-theta. A typical precision of the 2-theta values is in the range of ± 0.2° 2-theta. Thus, a diffraction peak that appears for example at 9.4° 2-theta can appear between 9.2 and 9.6° 2-theta on most X-ray diffractometers under standard conditions.

High Performance Liquid Chromatography (HPLC)

HPLC measurements were performed, if not indicated otherwise, with a Agilent 1100 Series (UV/Vis detector) and a reversed phase column YMC-Pack Pro C18 RS (150 x 4.60 mm, 3 µm), using the following process:

Oven Temperature:	30°C
UV wavelength:	245 nm
Injection Volume:	3 µL
Flow Rate:	1.0 mL/min
Run time:	16 minutes
Post time:	2 minutes
Mobile Phase A:	0.39 g of sulfamic acid, 996 g of H2O
Mobile Phase B:	0.39 g of sulfamic acid, 300 g of H2O, 587 g of acetonitrile
Diluent:	water:acetonitrile (1:1)

Sample preparation: 2 mg / 2.5 mL diluent

HPLC solvent gradient:

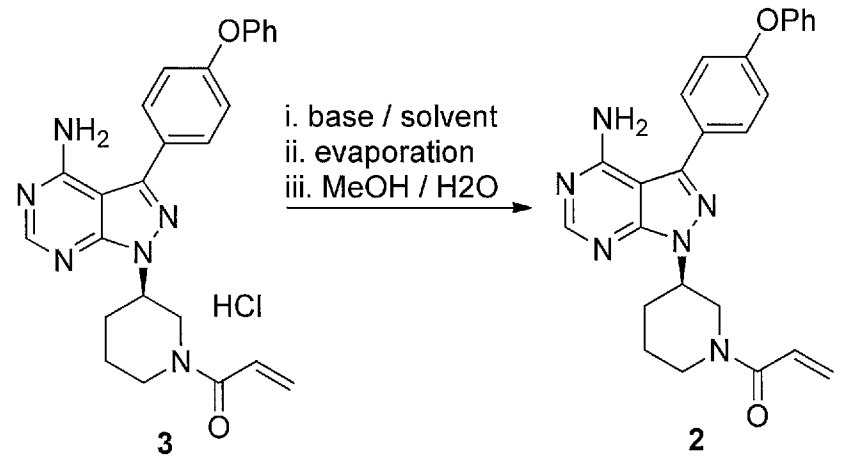
Time (minutes)	0	10	15	16
Solvent B (%)	5	100	100	5

Preparation of amorphous ibrutinib

Example 1

200 mL of dichloromethane were charged into a 1L reaction vessel, 19.9 g of crystalline ibrutinib hydrochloride (41.7 mmol, 1 eq.) (**3**) were added and the resulting suspension was treated with 6.1 mL of triethylamine (44.0 mmol, 1.05 eq.). To the resulting clear solution were added 100 mL of H_2O and the biphasic mixture stirred for 10 min. After separation of the organic layer, it was dried with Na_2SO_4 and concentrated in vacuo, yielding 20.8g amorphous ibrutinib (**2**) as a foamy solid (assay: >98 area% by HPLC).

Example 2



3 Ibrutinib*HCl (crystalline)

2 amorphous Ibrutinib

The reaction according to the above reaction scheme is carried out as follows:

Amorphous ibrutinib (13.6 g) obtained as a foamy solid by the procedure as set forth in Example 1 (steps i and ii of the above reaction scheme) was re-dissolved in 50 mL methanol

and the resulting solution was then added to 1200 mL H_2O with intense stirring. After stirring for 10 min, the product was isolated by filtration. The residue was dried in vacuo at 50°C to give 12.3 g of ibrutinib (**2**) in powder form. (~90% yield). The XRPD-analysis of the obtained ibrutinib shown in Figure 1 clearly indicates an amorphous product.

Stability of amorphous ibrutinib as obtained by the process described herewith at 40°C/75% relative humidity has been investigated over 8 weeks. Amorphous ibrutinib was stable under these conditions, as determined by the absence of XRPD peaks, in particular the absence of characteristic XRPD peaks of form A of ibrutinib after 8 weeks at 40°C / 75% RH.

Example 3

40 g of ibrutinib hydrochloride (83.8 mmol, 1 eq.) (**3**) were suspended in 600 mL acetone at ambient temperature, 51 mL NaOH (100.6 mmol, 1.2 eq, 2M) were added and the solution was stirred for 15 min. 4 g activated charcoal was added and the mixture was stirred for 30 min. The solids were filtered of and the filter was washed with 67 mL acetone. The solution was warmed to 50 °C and 800 mL water was added, upon clouding seeding crystals were added, followed by additional 1200 mL water. After 30 min the mixture was cooled to ambient temperature, stirred for an additional hour and the precipitate was isolated by filtration. Drying at 50 °C under reduced pressure gave 33.3 g Ibrutinib (form A) (assay: >98.5 area% by HPLC).

5 g of crystalline ibrutinib (form A) were dissolved in 50 mL methanol at 50°C. The clear solution was added to a vessel containing 750 mL water and the suspension was stirred for 30 min at 25°C. The white precipitate was isolated by filtration dried under vacuum at 50°C over night to give 4.53g of amorphous Ibrutinib (assay: >98.5 area% by HPLC). The XRPD-analysis of the obtained ibrutinib shown in Figure 2 clearly indicates an amorphous product.

Example 4

Crystalline ibrutinib (form A) was obtained in the same way as described in Example 3. 18 g of the crystalline ibrutinib were dissolved in 300 mL dichloromethane resulting in a turbid solution. After filtration of the solids, the solvent was removed under reduced pressure yielding amorphous ibrutinib as a foamy solid. The material was homogenized using a mortar and pestle resulting in a white powder (16.8 g, 93% yield).

Example 5

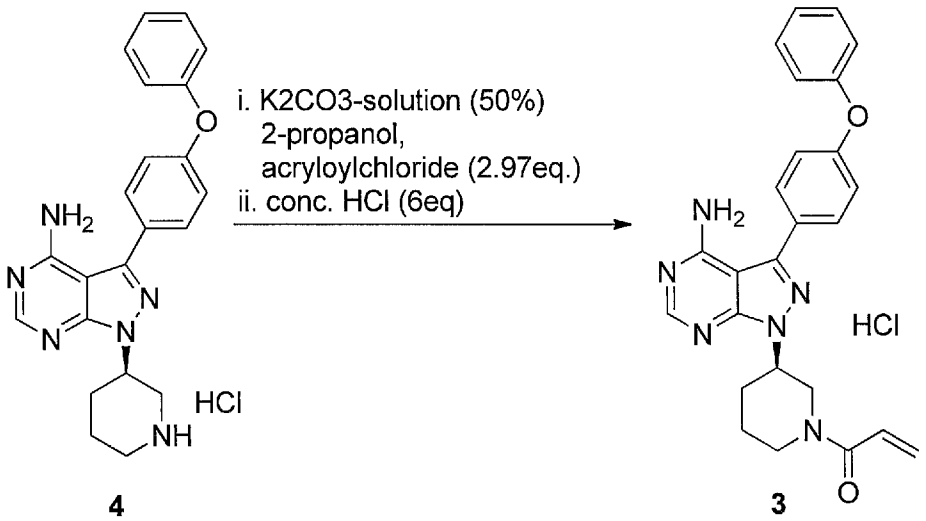
Amorphous ibrutinib was obtained in the same way as described in Example 4 except that after filtration of the solids, the ibrutinib solution was subjected to spray drying, yielding amorphous ibrutinib as a white powder.

Example 6

Amorphous ibrutinib was obtained in the same way as described in Example 4 except that after filtration of the solids, the ibrutinib solution was subjected to lyophilisation, yielding amorphous ibrutinib as a white powder.

Preparation of ibrutinib hydrochloride

Example 7



The reaction according to the above reaction scheme is carried out as follows:

Amine-hydrochloride (**4**) (1.0 g, 1 eq.) is suspended in 2-propanol (20 mL), followed by the addition of an aqueous K_2CO_3-solution (50% w/w, 2.7 g, 5 eq.). The mixture is cooled with an ice/acetone bath. Acryloyl chloride (148 µl, 0.97 eq.) is added and the mixture is stirred for 15 min. Another portion of acryloyl chloride (152 µL, 1.0 eq.) is added, followed by stirring for 35 min. The reaction mixture is quenched by the addition of a saturated aqueous sodium chloride-

solution (15 mL), then water (30 mL) and 2-propanol (10 mL) is added. The layers were separated at 50°C and the organic layer was concentrated to dryness. The residue was re-suspended in 2-propanol (25 mL) and filtered. The clear solution was concentrated to 9.87 g weight, then concentrated HCl (687 µl, 6eq.) and seeding crystals were added. After stirring overnight at ambient temperature followed by 1 h at 0° C, the precipitate was filtered off, rinsed with 2-propanol and dried, yielding ibrutinib hydrochloride (**3**) (0.59 g). An XRPD spectrum of the resulting yielding ibrutinib hydrochloride is shown in Figure 3.

The characteristic peaks in the XRPD spectrum of Figure 3 are listed in the following Table 1.

Table 1

Pos. [°2Th.]	Rel. Int. [%]
9.8±0.2	100
13.6±0.2	46.0
15.3±0.2	75.6
17.1±0.2	42.9
21.2±0.2	90.6
22.7±0.2	70.2
24.3±0.2	56.5
25.5±0.2	43.3

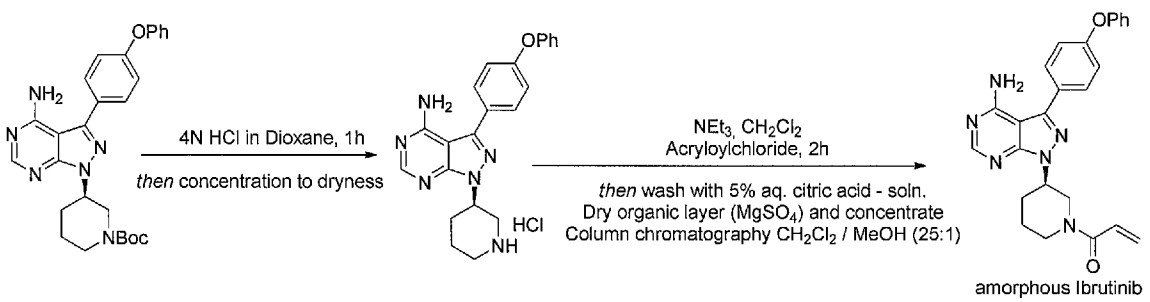
Examples 8-11

Ibrutinib hydrochloride was prepared by the procedures basically as set forth in Example 7 with the use of different alkaline components as shown below in Table 2.

Table 2

	Base	Conversion [area%]	Starting Material [area%]	Biggest Impurity [area%]	Total Impurities [area%]
Example 7	K_2CO_3	64.1	28.4	1.9	7.2
Example 8	NaOH	81.5	14.0	0.9	4.4
Example 9	$NaHCO_3$	84.2	11.4	1.0	4.3
Example 10	KOH	82.4	14.0	0.8	3.5
Example 11	Na_2CO_3	88.1	8.69	0.9	3.2

Comparative Example 1: Preparation of amorphous ibrutinib in accordance with Example 1b of US 7,514,444



Reproduction of Example 1b of US 7,514,444 according to the above reaction scheme gave amorphous ibrutinib with a purity of only ~ 60 area% (HPLC) after performing the reported chromatographic purification in silica gel. In particular, the product obtained contained high amounts of residual silicate and starting materials. Therefore, the obtained product would not be suitable for pharmaceutical applications, such as the preparation of pharmaceutical compositions.

Example 12

Amine-hydrochloride (**4**) (5 g, 1 eq.) is suspended in 2-propanol (85 mL), followed by the addition of 2M NaOH (4.9 mL, 1 eq.). Then the water is removed by azeotropic drying using a Dean-Stark trap to a limit < 0.1% H_2O in 2-propanol. Then the mixture is cooled to -5°C. In the meantime, acryloyl chloride (1,0 mL, 1.3 eq.) is dissolved in 3 mL 2-propanol cooled to -15°C and stirred for 1h at this temperature. Then this cold solution is added to the substrate,

concomitant with 2M NaOH (15.5mL, 3.2 eq.). The reaction is stirred for 20 min and the conversion is checked by HPLC. If the conversion is < 99%, further 0.2 eq. of acryloyl chloride are added, until the conversion complies.

The reaction mixture is warmed to r.t. and quenched by the addition of 42% $(NH_4)_2SO_4$-solution (15 mL), then water (30 mL) and 2-propanol (10 mL) is added. The layers were separated at 50°C and the organic layer was dried by azeotropic drying using a Dean-Stark trap to a limit < 1.5 % H_2O in 2-propanol. The resulting solution is filtered and then concentrated HCl (1.2 mL, 1.5 eq.) and seeding crystals were added. After stirring overnight at 50 °C followed by 3 h at ambient temperature, the precipitate was filtered off, rinsed with 2-propanol and dried, yielding ibrutinib hydrochloride (**3**) (4.01 g) in a purity of more than 99 area% as determined by HPLC measurement.

Example 13: Preparation of ibrutinib form A including ibrutinib hydrochloride as intermediate

Amine-hydrochloride (4) (4.0 g, 1 eq.) is suspended in 2-propanol (76 mL), followed by the addition of a 2M NaOH solution (17.7 mL) whilst stirring at ambient temperature. The solution is cooled to -1° C and acryloylchloride (810 µl, 1.3 eq.) is added, followed by stirring for 35 min. The reaction mixture is quenched by the addition of a 42% aqueous $(NH_4)_2SO_4$-solution (~ 42 mL) and the phases were separated. To the organic layer was added 2-propanol (310 mL). The mixture was concentrated to a total weight of 53.75 g followed by filtration. The solids were washed with 2-propanol (8 mL) and the resulting organic layers were again concentrated to a total weight of 48.56 g. To the solution was added concentrated HCl (2.52 mL) and seeding crystals of ibrutinib hydrochloride (0.2 g), followed by stirring at 30° C for 3h. Stirring at ambient temperature was continued overnight; the resulting crystals were filtered and washed with 2-propanol (10 mL). Drying of the cake in vacuum at 50° yields ibrutinib hydrochloride (2.93g).

Ibrutinib hydrochloride (1 g, 1 eq.) (3) was suspended in acetone (16.7 mL) at ambient temperature, 2M NaOH – solution (1.2 mL) were added and the solution was stirred for 15 min. Activated charcoal (0.2 g) was added and the mixture was stirred for 30 min at ambient temperature. The solids were filtered off, rinsed with 10 mL acetone and the solution was concentrated to a total weight of 15 g. Concentrated HCl (37%, 17 µl) was added followed by stirring for 15 minutes. The solution was warmed to 50 °C and 25 mL of water were added

dropwise. Seeding crystals were added, followed by stirring for 30 minutes upon which a white suspension is obtained. Additional 12.5 mL water were added dropwise followed by stirring at 50 °C. After 30 min the mixture was cooled to ambient temperature, stirred for further 2 h and the resulting precipitate was isolated by filtration. The crystals were washed with water (2 x 5 mL) and dried at 50 °C under reduced pressure, yielding ibrutinib form A (0.71 g, 77%). Ibrutinib form A was then converted to amorphous ibrutinib in accordance with the procedures described in Example 3.

Comparative Example 2: Preparation of ibrutinib form A not including ibrutinib hydrochloride as intermediate

Amine-hydrochloride (4) (10 g, 1 eq.) is suspended in 2-propanol (190 mL) and cooled to 0° C to 5° C. After addition of 2M NaOH – solution (38.4 mL), a clear solution was obtained. The mixture was cooled to -12° C and acryloyl chloride (1.82 mL) was added in two portions. The reaction mixture was stirred for 15 minutes upon which consumption of 4 was judged to be greater than 99% by HPLC.

Half-saturated $(NH_4)_2SO_4$-solution (100 mL) was added and the resulting mixture warmed to 25° C - 30° C. After separation of the aqueous layer, the organic layer was treated with activated charcoal (0.5g). After stirring the suspension for 15 minutes, the solids were filtered off and rinsed once with 2-propanol (10 mL). The obtained filtrate was concentrated to dryness and re-suspended in hot (65° C) 2-propanol (70 mL). After addition of filter aid (Randalite, 2g) the warm suspension was filtered over a small bed of Randalite. Subsequently, the solids were washed with 2-propanol (10 mL). To the resulting yellow solution was added further 2-propanol until a total weight of 86.6 g is obtained. The mechanically stirred solution is warmed to 40° C, heptane (70 mL) and seeding crystals (Ibrutinib-Form A) were successively added. The solution was allowed to slowly cool to ambient temperature. After 3 h, a white suspension was obtained which was stirred at ambient temperature overnight. Stirring was continued at 0° C to 2° C for further 24 h; after that time, heptane (52 mL) was added and stirring was continued at 0° C to 2° C for 5 h. The crystals were filtered, washed with a cold (0° C) 2-propanol / heptane (1:1) – mixture and dried in vacuum at 50° C. Ibrutinib form A (6.24 g, 73 %) was obtained as a coarse white powder. Ibrutinib form A was then converted to amorphous ibrutinib in accordance with the procedure described in Example 3.

HPLC – Method used for Examples 12, 13 and Comparative Example 2

Eluent A:	1.36g KH_2PO_4 + 950mL H_2O, pH adjusted to 6.8 with 5M NaOH + 50mL ACNL
Eluent B:	2.72g KH_2PO_4 + 600mL H_2O pH adjusted to 6.8 with 5M NaOH + 1400mL ACNL
Column:	YMC-Triart C18, S-1,9 µm, 100 x 3 mm (YMC order no. TA12SP9-1003PT)
Flow:	0.9 ml/min
Wavelength:	260nm
Column Temperature:	70°C
Sample:	5mg/25mL Solvent
Solvent:	0.64g NH_4HCO_2 + 1000mL H_2O pH adjusted to 3.7 with HCO_2H+ 1000mL ACNL
Injection volume:	5 µL
Stop time:	25 min
Post time:	0 min

Gradient:

Time [min]	0.0	16.0	21.0	21.1	25.0
B [%]	40.0	100	100	40.0	40.0

Table 3:

HPLC-measurements of purity of ibrutinib prepared in accordance with Example 12 and Comparative Example 2

	Example 13 (including ibrutinib hydrochloride as intermediate)	**Comparative Example 2** (NOT including ibrutinib hydrochloride as intermediate)
Purity of ibrutinib form A [area-%]	99.33	97.69
Process-impurity 1 (RT 6.7 min) [area-%]	0.05	0.36
Process-impurity 2 (RT 9.3 min) [area-%]	0.14	0.94
Process-impurity 3 (RT 14.2 min) [area-%]	0.06	0.52

CLAIMS

1. A process for the preparation of amorphous 1-((*R*)-3-(4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), comprising the steps of:

(i) providing a salt of ibrutinib,

(ii) adding an organic solvent and an alkaline component to obtain a solution of ibrutinib,

(iii) isolating amorphous ibrutinib from the reaction mixture of step (ii), or

(iii-1) isolating ibrutinib from the reaction mixture of step (ii), and

(iv) adding an organic solvent to obtain a solution of ibrutinib and isolating amorphous ibrutinib from the solution.

2. The process of claim 1, wherein the salt of ibrutinib provided in step (i) is in crystalline form.

3. The process of claim 2, wherein the crystalline salt is ibrutinib hydrochloride.

4. The process of any one of the previous claims, wherein the organic solvent in step (ii) is selected from acetone, isopropyl alcohol, methanol, 2-methyl tetrahydrofurane and combinations thereof.

5. The process of any one of the previous claims, wherein the alkaline component in step (ii) is selected from triethylamine, potassium carbonate, sodium hydroxide and combinations thereof.

6. The process of any one of the previous claims, wherein isolating in step (iii) or step (iii-1) comprises the addition of water and subsequent extraction and isolation of ibrutinib from the organic phase.

7. The process of any one of the previous claims, wherein ibrutinib is isolated in step (iii-1) as crystalline ibrutinib form A.

8. The process of any one of the previous claims, wherein the organic solvent in step (iv) is selected from methanol, dichloromethane, tetrahydrofurane, acetone, dioxane or combinations thereof.

9. The process of any one of the previous claims, wherein step (iv) comprises the precipitation of ibrutinib from the solution by anti-solvent addition, wherein the anti-solvent comprises methyltertbutylether, acetonitrile, heptane, water and combinations thereof.

10. The process of any one of the previous claims, wherein isolating in step (iv) is performed by spray drying, lyophilisation, filtration and/or evaporation of solvent.

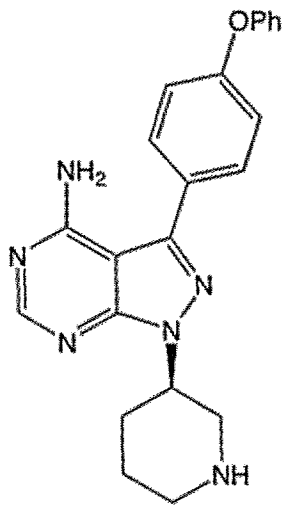
11. The process of any one of the previous claims, wherein the salt of ibrutinib is obtained by a process comprising the steps of:

(a) reacting a compound of formula (1) or a salt and/or solvate thereof with 2-propenoyl chloride in the presence of an organic solvent and an aqueous solution of an inorganic alkaline component to obtain the compound of formula (2),

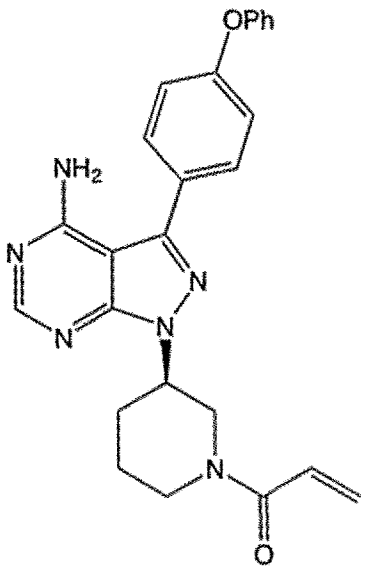
(b) optionally isolating the compound of formula (2) from the reaction mixture,

(c) subjecting the compound of formula (2) to an organic or inorganic acid, and

(d) isolating the salt of ibrutinib from the reaction mixture



(1)



(2) .

12. The process of claim 11, wherein the inorganic alkaline component comprises sodium hydroxide , potassium carbonate, sodium carbonate, potassium hydroxide, sodium bicarbonate and combinations thereof.

13. The process of claim 11 or 12, wherein in step (a) the compound of formula (1) is subjected to 2-propenoyl chloride in the presence of an aqueous solution of NaOH and isopropanol to obtain the compound of formula (2).

14. The process of any one of claims 11 to 13, wherein step (d) comprises the addition of seed crystals.

15. The process of any one of claims 11 to 14, comprising the steps of:

(a) reacting the compound of formula (1) with 2-propenoyl chloride in the presence of isopropanol and an aqueous solution of NaOH to obtain the compound of formula (2),

(b) washing the reaction mixture with an aqueous $(NH_4)_2SO_4$ solution,

(c) removal of water from the solution of compound of formula (2) in isopropanol and adding hydrochloric acid to the solution ,

(d) adding seed crystals to the solution to obtain crystalline ibrutinib hydrochloride in solid form and

(e) isolating the crystalline ibrutinib hydrochloride from the reaction mixture.

Figure 1

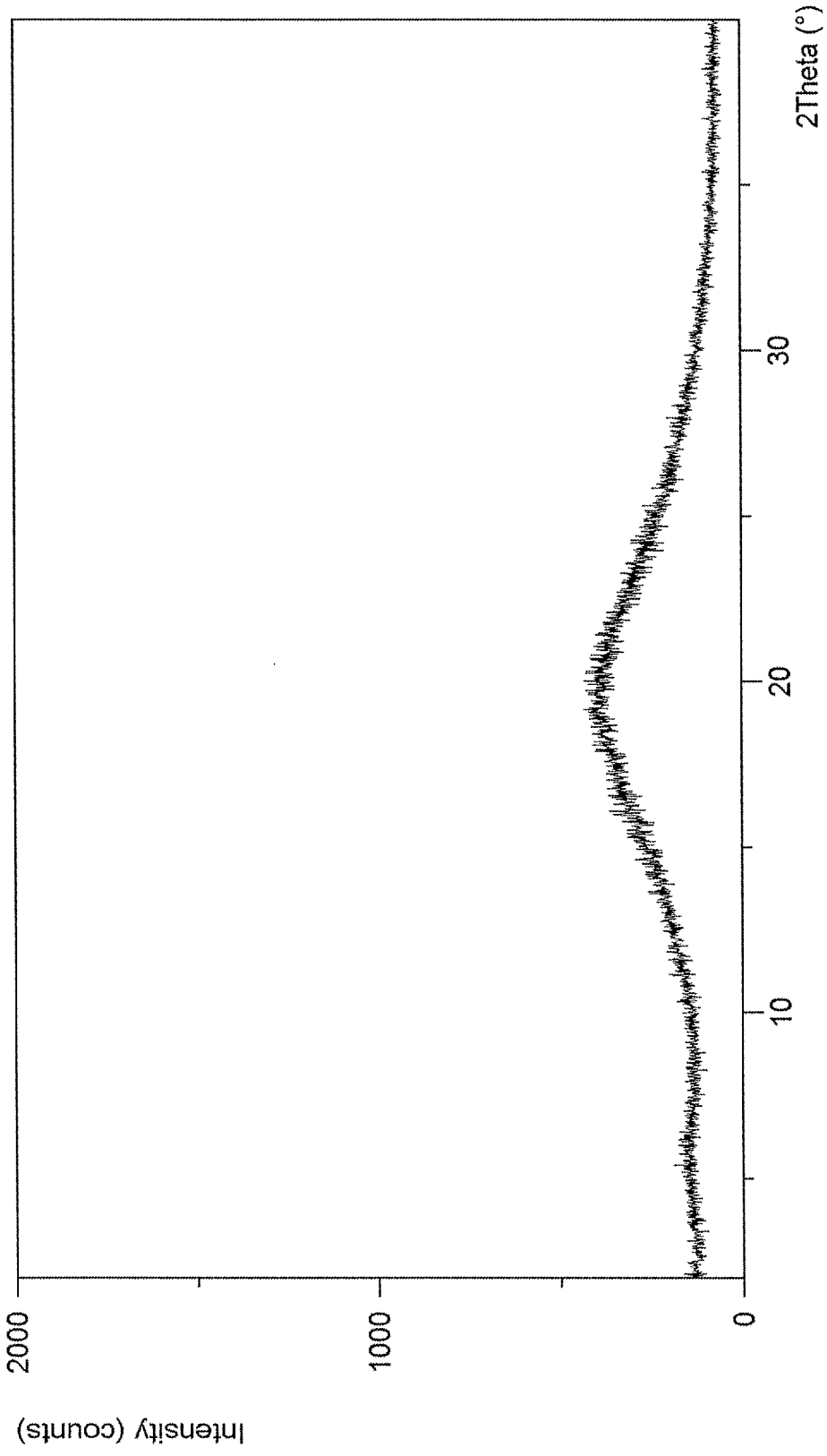


Figure 2

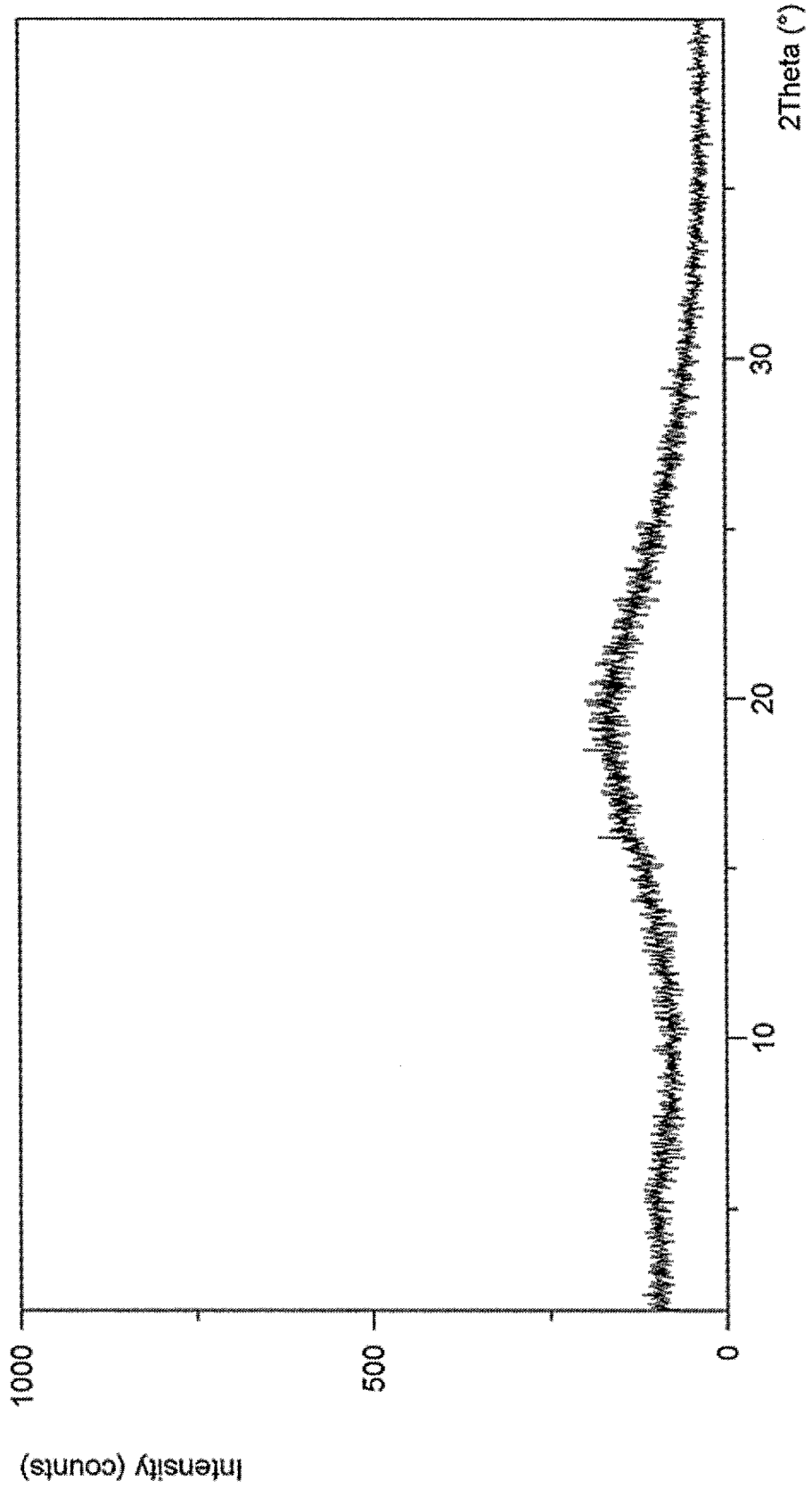
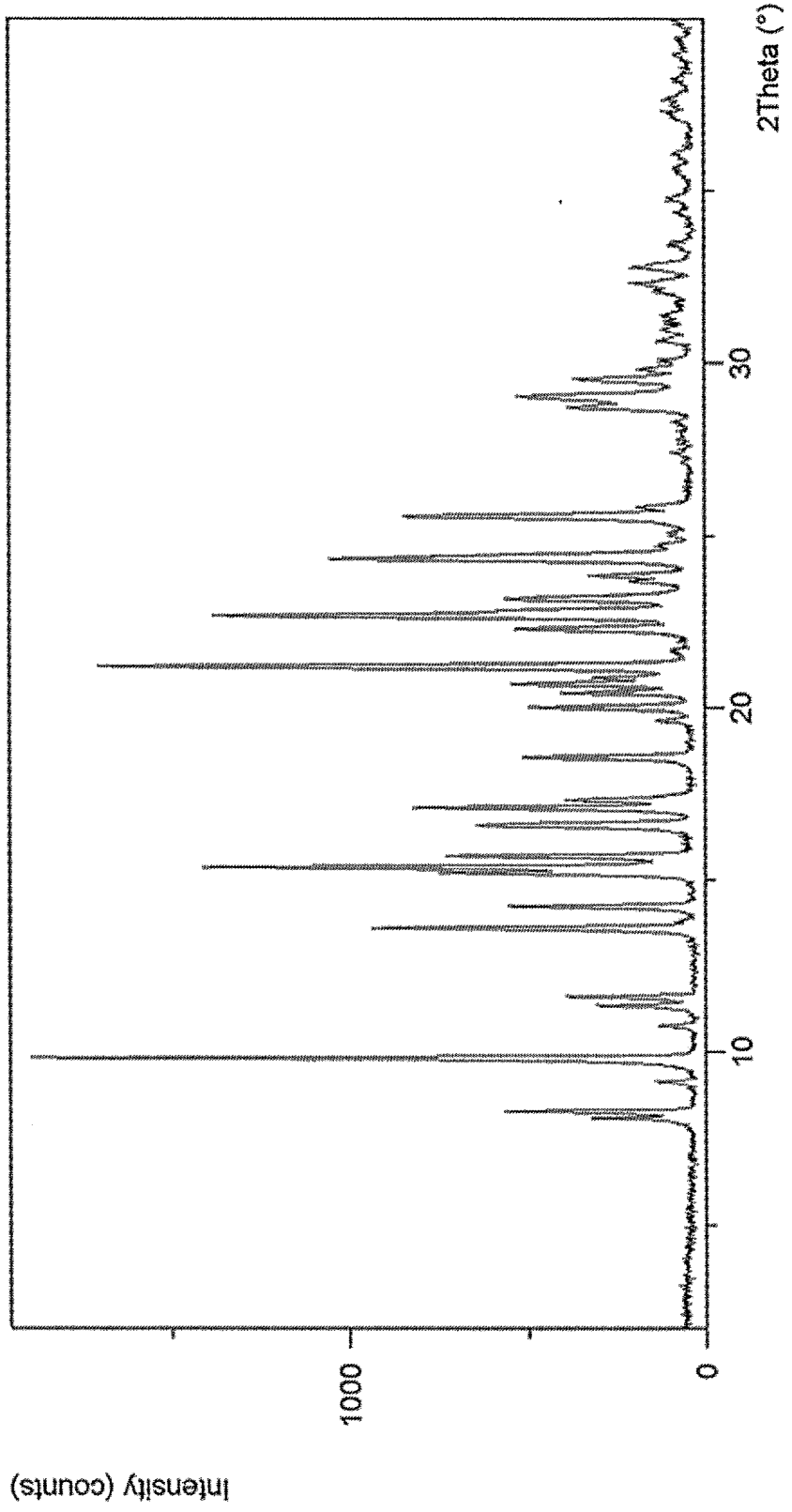


Figure 3



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/064332

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/184572 A1 (PHARMACYCLICS INC [US]; PURRO NORBERT [US]) 12 December 2013 (2013-12-12) cited in the application paragraphs [0250], [0441] -----	1-15
A	US 7 514 444 B2 (HONIGBERG LEE [US] ET AL) 7 April 2009 (2009-04-07) cited in the application example 1a -----	1-15
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
26 July 2016	03/08/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Grassi, Damian

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/064332

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"Preparation of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, its salt and intermediates thereof", IP.COM JOURNAL, IP.COM INC., WEST HENRIETTA, NY, US, 23 September 2014 (2014-09-23), XP013164909, ISSN: 1533-0001 example 3 -----	1-15
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