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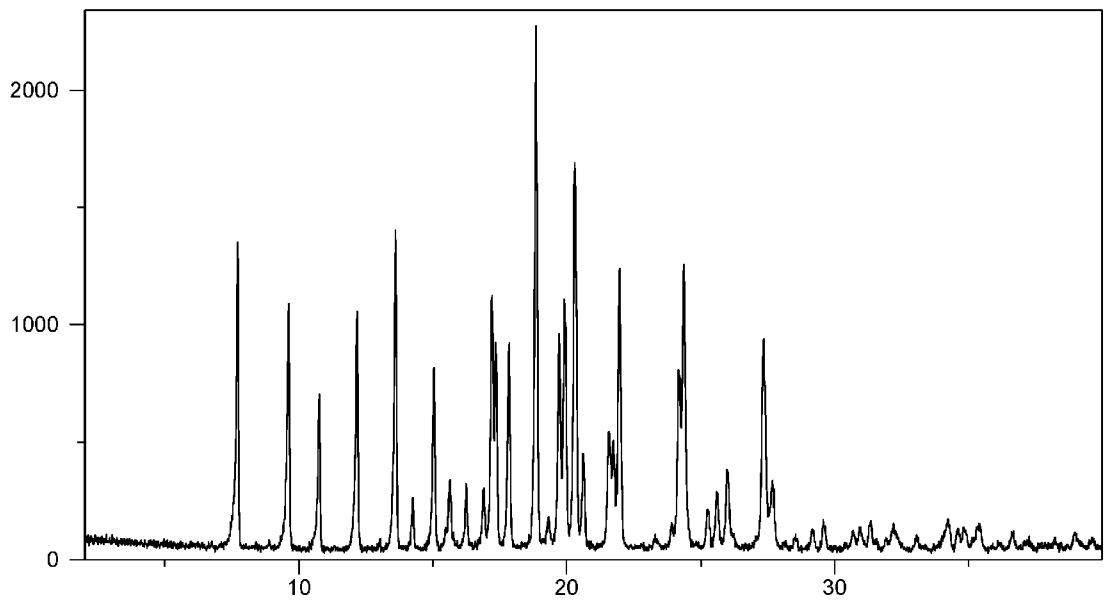
(54) Title: MULTI-COMPONENT COMPOUNDS COMPRISING ZANUBRUTINIB AND A BENZOIC ACID DERIVATIVE

Figure 1



(57) Abstract: The present invention relates to compounds, comprising (*S*)-7-(1-acryloylpiperidin-4-yl)-2-(4- phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (INN: zanubrutinib) and a benzoic acid derivative selected from 4-hydroxybenzoic acid and 3,4- dihydroxybenzoic acid and to crystalline forms thereof. Also provided are processes of producing said compounds and their crystalline forms. Furthermore, the invention relates to pharmaceutical compositions comprising the compounds of the present invention and at least one pharmaceutically acceptable excipient. The pharmaceutical compositions of the present invention can be used as medicaments, in particular for the treatment and/or prevention of B- cell proliferative diseases such as mantle cell lymphoma (MCL).

[Continued on next page]

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MULTI-COMPONENT COMPOUNDS COMPRISING ZANUBRUTINIB AND A BENZOIC ACID DERIVATIVE

FIELD OF THE INVENTION

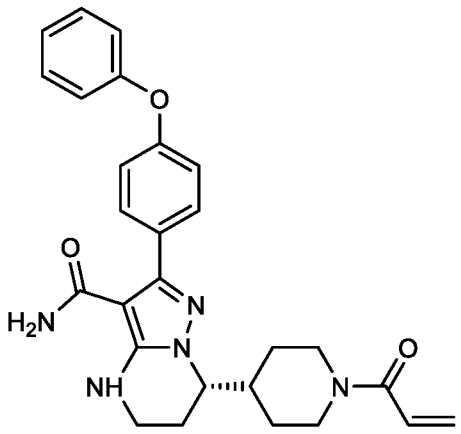
The present invention relates to compounds, comprising (*S*)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (INN: zanubrutinib) and a benzoic acid derivative selected from 4-hydroxybenzoic acid and 3,4-dihydroxybenzoic acid and to crystalline forms thereof. Also provided are processes of producing said compounds and their crystalline forms. Furthermore, the invention relates to pharmaceutical compositions comprising the compounds of the present invention and at least one pharmaceutically acceptable excipient. The pharmaceutical compositions of the present invention can be used as medicaments, in particular for the treatment and/or prevention of B-cell proliferative diseases such as mantle cell lymphoma (MCL).

BACKGROUND OF THE INVENTION

Zanubrutinib is an orally available reversible inhibitor of Bruton's Tyrosine kinase (BTK). 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. By forming a covalent bond with a cysteine residue in the BTK active site, zanubrutinb leads to inhibition of BTK activity and hence inhibits malignant B-cell proliferation and reduces tumor growth.

In 2019 zanubrutinib has been approved by the US FDA for the second-line treatment of adult patients with relapsed and refractory mantle cell lymphoma (MCL).

Chemically also designated as (*S*)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide, zanubrutinib can be represented by the chemical structure as depicted in Formula (I)



Formula (I).

Zanubrutinib and its preparation are disclosed in WO 2014/173289 A2 (Compound 27). A crystalline Form A of zanubrutinib is described in WO 2018/033853 A2. The same Form A is also mentioned in WO 2019/108795 A1 as a result of Example 1, Step 16. The marketed product BRUKINSA™ contains zanubrutinib Form A according to the quality product review published on the FDA website.

Different solid-state forms of an active pharmaceutical ingredient (API) often possess different physical and chemical properties such as but not limited to dissolution rate, solubility, chemical stability, physical stability, hygroscopicity, melting point, morphology, flowability, bulk density and compressibility. Differences in physicochemical properties of solid-state forms can play a crucial role for the improvement of pharmaceutical compositions, for example, pharmaceutical formulations with improved dissolution profile and bioavailability or with improved stability or shelf-life can become accessible due to an improved solid-state form of an API. Also processing or handling of an API during the formulation process may be improved. New solid-state forms of an API can thus have desirable processing properties. They can be easier to handle, better suited for storage, and/or allow for better purification, compared to previously known solid-state forms.

According to the quality product review of BRUKINSA™, which has been published on the FDA website, zanubrutinib Form A suffers from certain drawbacks, *e.g.* it is practically insoluble in water and consists of irregularly shaped, cohesive particles with poor flow characteristics and a tendency to agglomerate. Also, as apparent from the description of WO 2018/033853 A2, in particular from Figure 2 of the document, Form A possesses a relatively low melting point with an onset temperature of only about 139°C. Finally, according

to the teaching of WO 2018/033853 A2 Form A can only be produced from starting materials of high enantiomeric purity *e.g.* having an "ee value" of above 97%.

It is thus an objective of the present invention to provide an improved solid-state form of zanubrutinib *e.g.* a form of zanubrutinib which possesses improved physicochemical properties. In particular, it is an objective of the present invention to provide a solid-state form of zanubrutinib which is chemically and physically stable against temperature and/or moisture stress, has a low residual solvent content, possesses improved aqueous solubility and/or dissolution properties and/or possesses improved powder characteristics.

SUMMARY OF THE INVENTION

The inventors of the present invention have surprisingly found that under very specific conditions and when applying particular coformers, zanubrutinib can form multi-component compounds, which have improved properties relevant for pharmaceutical purposes. In particular, the inventors of the present invention have identified multi-component compounds comprising zanubrutinib and benzoic acid derivatives selected from 4-hydroxybenzoic acid and 3,4-dihydroxybenzoic acid.

The zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form of the present invention, possess one or more unexpected improved physicochemical properties selected from the group consisting of dissolution rate, solubility, chemical stability, physical stability, chemical purity, residual solvent content, hygroscopicity, melting point, morphology, flowability, wettability, bulk density and compressibility.

In particular, the zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form of the present invention possess high melting points with onset temperatures of about 174°C and 187°C (see Example 5, Figure 3 and Figure 8), show low residual solvent contents (see Example 6, Figure 4 and Figure 9) exhibit high crystallinity (see Example 3, Figure 1 and Figure 6), are non-hygroscopic or at maximum slightly hygroscopic and show no hysterises between their sorption and desorption curves during a gravimetric moisture sorption experiment (see Example 7, Figure 5 and Figure 10 hereinafter) and are physically stable in aqueous media and upon exposure to high temperature and humidity conditions (see Examples 9 and 10).

In addition, the zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form of the present invention exhibit improved solubilities and dissolution

rates in aqueous phosphate buffer pH 6.8, aqueous acetate buffer pH 4.5 and FaSSIF medium (see Example 11, Figure 13 – 15).

This unique combination of advantageous properties renders the zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form of the present invention the forms of choice in terms of manufacturing and stable storage of a uniform and bioavailable drug product containing zanubrutinib.

Abbreviations

PXRD	Powder X-ray diffraction
SXRD	Single crystal X-ray diffraction
DSC	Differential scanning calorimetry
TGA	Thermogravimetric analysis
GMS	Gravimetric moisture sorption
RT	Room temperature
RH	Relative humidity
w-%	Weight percent
FaSSIF	Fasted state simulated small intestinal fluid
SDS	Sodium dodecyl sulfate
MCC	Microcrystalline cellulose

Definitions

As used herein the term “room temperature” refers to a temperature in the range of from 20 to 30°C.

The term “zanubrutinib” as used herein refers to the compound having the chemical name (*S*)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide and the chemical structure as depicted in Formula (I) disclosed herein above.

The term “co-crystal” as used herein refers to crystalline materials composed of two or more different molecular and/or ionic compounds in the same crystal lattice that are associated by nonionic and noncovalent bonds, wherein at least two of the individual molecular and/or ionic compounds are solids at room temperature. Unlike salts, the components of co-crystals are in a neutral state and interact nonionically.

The term "zanubrutinib Form A" as used herein, refers to the crystalline form of zanubrutinib, which is disclosed in WO 2018/033853 A2. Form A of zanubrutinib can be characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of (5.4 ± 0.2)°, (14.8 ± 0.2)° and (21.4 ± 0.2)°, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

As used herein, the term "measured at a temperature in the range of from 20 to 30°C" refers to a measurement under standard conditions. Typically, standard conditions mean a temperature in the range of from 20 to 30°C, *i.e.* at room temperature. Standard conditions can mean a temperature of about 22°C. Typically, standard conditions can additionally mean a measurement under 20-50% relative humidity.

The term "reflection" with regard to powder X-ray diffraction as used herein, means peaks in an X-ray diffractogram, which are caused at certain diffraction angles (Bragg angles) by constructive interference from X-rays scattered by parallel planes of atoms in solid material, which are distributed in an ordered and repetitive pattern in a long-range positional order. Such a solid material is classified as crystalline material, whereas amorphous material is defined as solid material, which lacks long-range order and only displays short-range order, thus resulting in broad scattering. According to literature, long-range order e.g. extends over approximately 100 to 1000 atoms, whereas short-range order is over a few atoms only (see *"Fundamentals of Powder Diffraction and Structural Characterization of Materials" by Vitalij K. Pecharsky and Peter Y. Zavalij, Kluwer Academic Publishers, 2003*, page 3).

The term "essentially the same" with reference to powder X-ray diffraction means that variabilities in reflection positions and relative intensities of the reflections are to be taken into account. For example, a typical precision of the 2-Theta values is in the range of ± 0.2° 2-Theta, preferably in the range of ± 0.1° 2-Theta. Thus, a reflection that usually appears at 7.7° 2-Theta for example can appear between 7.5° and 7.9° 2-Theta, preferably between 7.6 and 7.8° 2-Theta on most X-ray diffractometers under standard conditions. Furthermore, one skilled in the art will appreciate that relative reflection intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, sample preparation and other factors known to those skilled in the art and should be taken as qualitative measure only.

The term "essentially the same" with reference to infrared spectrometry means that variabilities in peak positions and relative intensities of the peaks are to be taken into account. For example,

a typical precision of the wavenumber values is in the range of ± 4 cm^{-1}, preferably in the range of ± 2 cm^{-1} . Thus, a peak at 1678 cm^{-1} for example can appear between 1674 and 1682 cm^{-1}, preferably between 1676 and 1680 cm^{-1} on most infrared spectrometers under standard conditions. Peak intensities can be derived from according figures, but one skilled in the art will appreciate that differences in peak intensities due to degree of crystallinity, sample preparation, measurement method and other factors can also occur in infrared spectroscopy. Peak intensities should therefore be taken as qualitative measure only.

The term “solid-state form” as used herein refers to any crystalline and/or amorphous phase of a compound. Crystalline phases include anhydrous/non-solvated forms of a compound and their polymorphs; hydrates and solvates of a compound and their polymorphs; salts and co-crystals of a compound and their polymorphs and pseudopolymorphic forms; and any mixtures thereof.

As used herein, the term “essentially free of any other solid-state form” with reference to the composition comprising the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form of the present invention, means that the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form contains at most 20 w-%, preferably at most 10 w-%, more preferably at most 5 w-%, 4 w-%, 3 w-%, 2 w-% or 1 w-% of any other solid-state form of zanubrutinib, based on the total weight of the composition.

The zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form of the present invention may be referred to herein as being characterized by a powder X-ray diffractogram or an FTIR spectrum "as shown in" a figure. The person skilled in the art understands that factors such as variations in instrument type, response and variations in sample directionality, sample concentration, sample purity, sample history and sample preparation may lead to variations, for example relating to the exact reflection/peak positions and intensities. However, a comparison of the graphical data in the figure herein with the graphical data generated for an unknown physical form and the confirmation that two sets of graphical data relate to the same crystal form is well within the knowledge of a person skilled in the art.

As used herein, the term “mother liquor” refers to the solution remaining after crystallization of a solid from said solution.

A “predetermined amount” as used herein with regard to the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form of the present invention refers to the

initial amount of the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form used for the preparation of a pharmaceutical composition having a desired dosage strength of zanubrutinib.

As used herein, the term "effective amount" in conjunction with the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form of the present invention encompasses an amount of the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form of the present invention which causes the desired therapeutic or prophylactic effect.

As used herein, the term "about" means within a statistically meaningful range of a value. Such a range can be within an order of magnitude, typically within 10%, more typically within 5%, even more typically within 1% and most typically within 0.1% of the indicated value or range. Sometimes, such a range can lie within the experimental error, typical of standard methods used for the measurement and/or determination of a given value or range.

The term "pharmaceutically acceptable excipient" as used herein refers to substances, which do not show a significant pharmacological activity at the given dose and that are added to a pharmaceutical composition in addition to the active pharmaceutical ingredient. Excipients may take the function of vehicle, diluent, release agent, disintegrating agent, dissolution modifying agent, absorption enhancer, wetting agent, stabilizer or a manufacturing aid among others.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: illustrates a representative PXRD of the zanubrutinib 4-hydroxybenzoate form according to the present invention. The x-axis shows the scattering angle in °2-Theta, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

Figure 2: illustrates a representative FTIR spectrum of the zanubrutinib 4-hydroxybenzoate form according to the present invention. The x-axis shows the wavenumbers in cm^{-1}, the y-axis shows the relative intensity in percent transmittance.

Figure 3: illustrates a representative DSC curve of the zanubrutinib 4-hydroxybenzoate form according to the present invention. The x-axis shows the temperature in degree Celsius (°C), the y-axis shows the heat flow rate in Watt per gram (W/g) with endothermic peaks going up.

Figure 4: illustrates a representative TGA curve of the zanubrutinib 4-hydroxybenzoate form according to the present invention. The x-axis shows the temperature in degree Celsius (°C), the y-axis shows the mass (loss) of the sample in weight percent (w-%).

Figure 5: illustrates representative GMS isotherms of the zanubrutinib 4-hydroxybenzoate form according to the present invention in the range of from 0 to 90% relative humidity. The x-axis displays the relative humidity in percent (%) measured at a temperature of (25.0 ± 0.1) °C, the y-axis displays the mass changes in weight percent (w-%). The sorption cycles are marked by triangles, whereas the desorption cycles are marked by squares. The sample weight at 0% relative humidity at the end of the desorption cycle was set as reference weight.

Figure 6: illustrates a representative PXRD of the zanubrutinib 3,4-dihydroxybenzoate form according to the present invention. The x-axis shows the scattering angle in °2-Theta, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

Figure 7: illustrates a representative FTIR spectrum of the zanubrutinib 3,4-dihydroxybenzoate form according to the present invention. The x-axis shows the wavenumbers in cm^{-1}, the y-axis shows the relative intensity in percent transmittance.

Figure 8: illustrates a representative DSC curve of the zanubrutinib 3,4-dihydroxybenzoate form according to the present invention. The x-axis shows the temperature in degree Celsius (°C), the y-axis shows the heat flow rate in Watt per gram (W/g) with endothermic peaks going up.

Figure 9: illustrates a representative TGA curve of the zanubrutinib 3,4-dihydroxybenzoate form according to the present invention. The x-axis shows the temperature in degree Celsius (°C), the y-axis shows the mass (loss) of the sample in weight percent (w-%).

Figure 10: illustrates representative GMS isotherms of the zanubrutinib 3,4-dihydroxybenzoate form of the present invention in the range of from 0 to 90% relative humidity. The x-axis displays the relative humidity in percent (%) measured at a temperature of (25.0 ± 0.1) °C, the y-axis displays the the mass change in weight percent (w-%). The sorption cycles are marked by triangles, whereas the desorption cycles are marked by squares. The sample weight at 0% relative humidity at the end of the desorption cycle was set as reference weight.

Figure 11: illustrates the single crystal structure of the zanubrutinib 4-hydroxybenzoic acid co-crystal of the present invention.

Figure 12: illustrates the single crystal structure of the zanubrutinib 3,4-dihydroxybenzoic acid co-crystal of the present invention.

Figure 13: displays the dissolution curves of the zanubrutinib 4-hydroxybenzoate form of the present invention (black triangles), the zanubrutinib 3,4-dihydroxybenzoate form of the present invention (white triangles) and zanubrutinib Form A of WO 2018/033853 A2 (white squares)

in phosphate buffer pH 6.8 measured at 37°C. The x-axis shows the time in hours, the y-axis the zanubrutinib concentration of the solution in mg/mL.

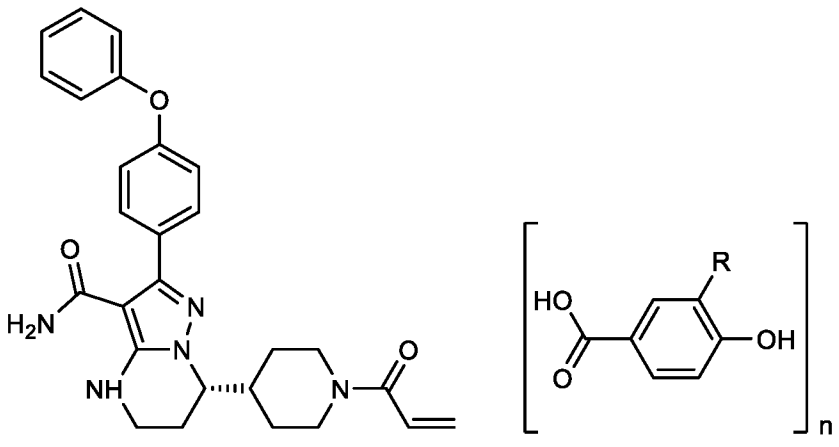
Figure 14: displays the dissolution curves of the zanubrutinib 4-hydroxybenzoate form of the present invention (black triangles), the zanubrutinib 3,4-dihydroxybenzoate form of the present invention (white triangles) and zanubrutinib Form A of WO 2018/033853 A2 (white squares) in acetate buffer pH 4.5 measured at 37°C. The x-axis shows the time in hours, the y-axis the zanubrutinib concentration of the solution in mg/mL.

Figure 15: displays the dissolution curves of the zanubrutinib 4-hydroxybenzoate form of the present invention (black triangles), the zanubrutinib 3,4-dihydroxybenzoate form of the present invention (white triangles) and zanubrutinib Form A of WO 2018/033853 A2 (white squares) in FaSSIF medium measured at 37°C. The x-axis shows the time in hours, the y-axis the zanubrutinib concentration of the solution in mg/mL.

Figure 16: displays a flowchart of the manufacturing process for hard gelatin capsules comprising the zanubrutinib 4-hydroxybenzoate form of the present invention or the zanubrutinib 3,4-dihydroxybenzoate form of the present invention

DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the present invention relates to a compound comprising zanubrutinib and a benzoic acid derivative characterized by having the chemical structure as depicted in Formula (II)



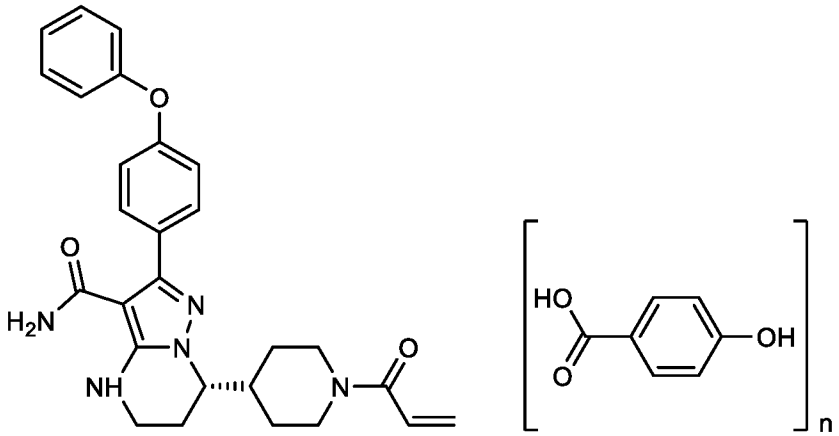
Formula (II),

wherein R is hydrogen or hydroxy and n is in the range of from 0.8 to 1.2, preferably of from 0.9 to 1.1, even more preferably of from 0.95 to 1.05 and most preferably n is 1.0.

In a preferred embodiment, the compound of the present invention as defined above is crystalline. More preferably, the compound is a co-crystal, a salt or a mixture of a co-crystal and a salt and most preferably the compound is a co-crystal.

The zanubrutinib 4-hydroxybenzoate form, compositions comprising the same and a method for its preparation

In one aspect, the invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by the chemical structure as depicted in Formula (IIa),



Formula (IIa),

wherein n is in the range of from 0.8 to 1.2, preferably of from 0.9 to 1.1, even more preferably of from 0.95 to 1.05 and most preferably n is 1.0.

Preferably, the crystalline form of the present invention as defined above is a co-crystal, a salt or a mixture of a co-crystal and a salt and most preferably the crystalline form is a co-crystal.

The zanubrutinib 4-hydroxybenzoate form of the present invention may be characterized by analytical methods well known in the field of the pharmaceutical industry for characterizing crystalline solids. Such methods comprise but are not limited to PXRD, SXRD, FTIR, DSC, TGA and GMS. The zanubrutinb 4-hydroxybenzoate form of the present invention may be characterized by one of the aforementioned analytical methods or by combining two or more of them. In particular, the zanubrutinb 4-hydroxybenzoate form of the present invention may be characterized by any one of the following embodiments or by combining two or more of the following embodiments.

In one embodiment the invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by having a PXRD comprising reflections at 2-Theta angles of:

(7.7 ± 0.2)°, (9.6 ± 0.2)° and (18.9 ± 0.2)°; or

(7.7 ± 0.2)°, (9.6 ± 0.2)°, (10.8 ± 0.2)° and (18.9 ± 0.2)°; or

(7.7 ± 0.2)°, (9.6 ± 0.2)°, (10.8 ± 0.2)°, (12.2 ± 0.2)° and (18.9 ± 0.2)°; or

(7.7 ± 0.2)°, (9.6 ± 0.2)°, (10.8 ± 0.2)°, (12.2 ± 0.2)°, (13.6 ± 0.2)° and (18.9 ± 0.2)°; or

(7.7 ± 0.2)°, (9.6 ± 0.2)°, (10.8 ± 0.2)°, (12.2 ± 0.2)°, (13.6 ± 0.2)°, (18.9 ± 0.2)° and (20.3 ± 0.2)°; or

(7.7 ± 0.2)°, (9.6 ± 0.2)°, (10.8 ± 0.2)°, (12.2 ± 0.2)°, (13.6 ± 0.2)°, (15.0 ± 0.2)°, (18.9 ± 0.2)° and (20.3 ± 0.2)°; or

(7.7 ± 0.2)°, (9.6 ± 0.2)°, (10.8 ± 0.2)°, (12.2 ± 0.2)°, (13.6 ± 0.2)°, (15.0 ± 0.2)°, (17.8 ± 0.2)°, (18.9 ± 0.2)° and (20.3 ± 0.2)°; or

(7.7 ± 0.2)°, (9.6 ± 0.2)°, (10.8 ± 0.2)°, (12.2 ± 0.2)°, (13.6 ± 0.2)°, (15.0 ± 0.2)°, (17.8 ± 0.2)°, (18.9 ± 0.2)°, (20.3 ± 0.2)° and (22.0 ± 0.2)°; or

(7.7 ± 0.2)°, (9.6 ± 0.2)°, (10.8 ± 0.2)°, (12.2 ± 0.2)°, (13.6 ± 0.2)°, (15.0 ± 0.2)°, (17.8 ± 0.2)°, (18.9 ± 0.2)°, (20.3 ± 0.2)°, (22.0 ± 0.2)° and (24.4 ± 0.2)°; or

(7.7 ± 0.2)°, (9.6 ± 0.2)°, (10.8 ± 0.2)°, (12.2 ± 0.2)°, (13.6 ± 0.2)°, (15.0 ± 0.2)°, (17.8 ± 0.2)°, (18.9 ± 0.2)°, (20.3 ± 0.2)°, (22.0 ± 0.2)°, (24.4 ± 0.2)° and (27.3 ± 0.2)°;

when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In a further embodiment the invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by having a PXRD comprising reflections at 2-Theta angles of:

(7.7 ± 0.1)°, (9.6 ± 0.1)° and (18.9 ± 0.1)°; or

(7.7 ± 0.1)°, (9.6 ± 0.1)°, (10.8 ± 0.1)° and (18.9 ± 0.1)°; or

(7.7 ± 0.1)°, (9.6 ± 0.1)°, (10.8 ± 0.1)°, (12.2 ± 0.1)° and (18.9 ± 0.1)°; or

(7.7 ± 0.1)°, (9.6 ± 0.1)°, (10.8 ± 0.1)°, (12.2 ± 0.1)°, (13.6 ± 0.1)° and (18.9 ± 0.1)°; or

(7.7 ± 0.1)°, (9.6 ± 0.1)°, (10.8 ± 0.1)°, (12.2 ± 0.1)°, (13.6 ± 0.1)°, (18.9 ± 0.1)° and (20.3 ± 0.1)°; or

(7.7 ± 0.1)°, (9.6 ± 0.1)°, (10.8 ± 0.1)°, (12.2 ± 0.1)°, (13.6 ± 0.1)°, (15.0 ± 0.1)°, (18.9 ± 0.1)° and (20.3 ± 0.1)°; or

(7.7 ± 0.1)°, (9.6 ± 0.1)°, (10.8 ± 0.1)°, (12.2 ± 0.1)°, (13.6 ± 0.1)°, (15.0 ± 0.1)°, (17.8 ± 0.1)°, (18.9 ± 0.1)° and (20.3 ± 0.1)°; or

(7.7 ± 0.1)°, (9.6 ± 0.1)°, (10.8 ± 0.1)°, (12.2 ± 0.1)°, (13.6 ± 0.1)°, (15.0 ± 0.1)°, (17.8 ± 0.1)°, (18.9 ± 0.1)°, (20.3 ± 0.1)° and (22.0 ± 0.1)°; or

(7.7 ± 0.1)°, (9.6 ± 0.1)°, (10.8 ± 0.1)°, (12.2 ± 0.1)°, (13.6 ± 0.1)°, (15.0 ± 0.1)°, (17.8 ± 0.1)°, (18.9 ± 0.1)°, (20.3 ± 0.1)°, (22.0 ± 0.1)° and (24.4 ± 0.1)°; or

(7.7 ± 0.1)°, (9.6 ± 0.1)°, (10.8 ± 0.1)°, (12.2 ± 0.1)°, (13.6 ± 0.1)°, (15.0 ± 0.1)°, (17.8 ± 0.1)°, (18.9 ± 0.1)°, (20.3 ± 0.1)°, (22.0 ± 0.1)°, (24.4 ± 0.1)° and (27.3 ± 0.1)°;

when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In another embodiment the present invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by having a PXRD comprising reflections at 2-Theta angles of (7.7 ± 0.2)°, (9.6 ± 0.2)°, (12.2 ± 0.2)°, (13.6 ± 0.2)°, (17.2 ± 0.2)°, (18.9 ± 0.2)°, (19.9 ± 0.2)°, (20.3 ± 0.2)°, (22.0 ± 0.2)° and (24.4 ± 0.2)°, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In an additional embodiment the invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by having a PXRD comprising reflections at 2-Theta angles of (7.7 ± 0.1)°, (9.6 ± 0.1)°, (12.2 ± 0.1)°, (13.6 ± 0.1)°, (17.2 ± 0.1)°, (18.9 ± 0.1)°, (19.9 ± 0.1)°, (20.3 ± 0.1)°, (22.0 ± 0.1)° and (24.4 ± 0.1)°, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In another embodiment the invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by having a PXRD essentially the same as shown in Figure 1 of the present invention, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In addition, the present invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by having an FTIR spectrum comprising peaks at wavenumbers of:

(3405 ± 4) cm^{-1}, (1678 ± 4) cm^{-1} and (1236 ± 4) cm^{-1} or;

(3405 ± 4) cm^{-1}, (3196 ± 4) cm^{-1}, (1678 ± 4) cm^{-1} and (1236 ± 4) cm^{-1}; or

(3405 ± 4) cm^{-1}, (3196 ± 4) cm^{-1}, (1678 ± 4) cm^{-1}, (1236 ± 4) cm^{-1} and (968 ± 4) cm^{-1}; or

(3405 ± 4) cm^{-1}, (3298 ± 4) cm^{-1}, (3196 ± 4) cm^{-1}, (1678 ± 4) cm^{-1}, (1236 ± 4) cm^{-1} and (968 ± 4) cm^{-1}; or

(3405 ± 4) cm^{-1}, (3298 ± 4) cm^{-1}, (3196 ± 4) cm^{-1}, (1678 ± 4) cm^{-1}, (1538 ± 4) cm^{-1}, (1236 ± 4) cm^{-1} and (968 ± 4) cm^{-1}; or

(3405 ± 4) cm^{-1}, (3298 ± 4) cm^{-1}, (3196 ± 4) cm^{-1}, (1678 ± 4) cm^{-1}, (1636 ± 4) cm^{-1}, (1538 ± 4) cm^{-1}, (1236 ± 4) cm^{-1} and (968 ± 4) cm^{-1}; or

(3405 ± 4) cm^{-1}, (3298 ± 4) cm^{-1}, (3196 ± 4) cm^{-1}, (1678 ± 4) cm^{-1}, (1636 ± 4) cm^{-1}, (1586 ± 4) cm^{-1}, (1538 ± 4) cm^{-1}, (1236 ± 4) cm^{-1} and (968 ± 4) cm^{-1}; or

(3405 ± 4) cm^{-1}, (3298 ± 4) cm^{-1}, (3196 ± 4) cm^{-1}, (1678 ± 4) cm^{-1}, (1636 ± 4) cm^{-1}, (1609 ± 4) cm^{-1}, (1586 ± 4) cm^{-1}, (1538 ± 4) cm^{-1}, (1236 ± 4) cm^{-1} and (968 ± 4) cm^{-1};

when measured at a temperature in the range of from 20 to 30°C with a diamond ATR cell.

Alternatively, the present invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by having an FTIR spectrum comprising peaks at wavenumbers of:

(3405 ± 2) cm^{-1}, (1678 ± 2) cm^{-1} and (1236 ± 2) cm^{-1} or;

(3405 ± 2) cm^{-1}, (3196 ± 2) cm^{-1}, (1678 ± 2) cm^{-1} and (1236 ± 2) cm^{-1}; or

(3405 ± 2) cm^{-1}, (3196 ± 2) cm^{-1}, (1678 ± 2) cm^{-1}, (1236 ± 2) cm^{-1} and (968 ± 2) cm^{-1}; or

(3405 ± 2) cm^{-1}, (3298 ± 2) cm^{-1}, (3196 ± 2) cm^{-1}, (1678 ± 2) cm^{-1}, (1236 ± 2) cm^{-1} and (968 ± 2) cm^{-1}; or

(3405 ± 2) cm^{-1}, (3298 ± 2) cm^{-1}, (3196 ± 2) cm^{-1}, (1678 ± 2) cm^{-1}, (1538 ± 2) cm^{-1}, (1236 ± 2) cm^{-1} and (968 ± 2) cm^{-1}; or

(3405 ± 2) cm^{-1}, (3298 ± 2) cm^{-1}, (3196 ± 2) cm^{-1}, (1678 ± 2) cm^{-1}, (1636 ± 2) cm^{-1}, (1538 ± 2) cm^{-1}, (1236 ± 2) cm^{-1} and (968 ± 2) cm^{-1}; or

(3405 ± 2) cm^{-1}, (3298 ± 2) cm^{-1}, (3196 ± 2) cm^{-1}, (1678 ± 2) cm^{-1}, (1636 ± 2) cm^{-1}, (1586 ± 2) cm^{-1}, (1538 ± 2) cm^{-1}, (1236 ± 2) cm^{-1} and (968 ± 2) cm^{-1}; or

(3405 ± 2) cm^{-1}, (3298 ± 2) cm^{-1}, (3196 ± 2) cm^{-1}, (1678 ± 2) cm^{-1}, (1636 ± 2) cm^{-1}, (1609 ± 2) cm^{-1}, (1586 ± 2) cm^{-1}, (1538 ± 2) cm^{-1}, (1236 ± 2) cm^{-1} and (968 ± 2) cm^{-1};

when measured at a temperature in the range of from 20 to 30°C with a diamond ATR cell.

Moreover, the present invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by having an FTIR spectrum essentially the same as shown in Figure 2 of the present invention, when measured at a temperature in the range of from 20 to 30°C with a diamond ATR cell.

In yet another embodiment, the present invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by having a DSC curve comprising an endothermic peak, preferably a single endothermic peak, having an onset at a temperature of (187 ± 5)°C, preferably of (187 ± 3)°C, more preferably of (187 ± 2)°C and most preferably of (187 ± 1)°C, when measured at a heating rate of 10 K/min.

In a further embodiment, the present invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by having a DSC curve comprising an endothermic peak, preferably a single endothermic peak, having a maximum at a temperature of (187 ± 5)°C, preferably of (187 ± 3)°C, more preferably of (187 ± 2)°C and most preferably of (187 ± 1)°C, when measured at a heating rate of 10 K/min.

In one embodiment, the present invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by having a TGA curve showing a mass loss of not more than 0.5 w-%, preferably of not more than 0.4 w-%, more preferably of not more than 0.3 w-% based on the weight of the crystalline form, when heated from 25 to 180°C at a rate of 10 K/min.

In one embodiment, the present invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by showing a mass change of not more than 0.5 w-%, preferably of not more than 0.4 w-%, more preferably of not more than 0.3 w-% and most preferably of not more than 0.2 w-%, based on the weight of the crystalline form, when measured with GMS at a relative humidity in the range of from 0 to 90% and a temperature of (25.0 ± 0.1)°C.

In still another embodiment, the present invention relates to a crystalline form comprising zanubrutinib and 4-hydroxybenzoic acid characterized by exhibiting an orthorhombic unit cell having space group $P2_12_12_1$. Preferably, the unit cell has the following parameters

a = 11.803 Ångstrom

b = 14.390 Ångstrom

c = 18.441 Ångstrom

alpha = 90°

beta = 90°

gamma = 90°,

when measured with single crystal X-ray diffraction at 193 K with Mo radiation having a wavelength of 0.71073 Ångstrom.

In another aspect, the present invention relates to a composition comprising the zanubrutinib 4-hydroxybenzoate form as defined in any one of the above described embodiments, characterized in that the composition is essentially free of any other solid-state form of zanubrutinib. For example, a composition comprising the zanubrutinib 4-hydroxybenzoate form of the present invention comprises at most 20 w-%, preferably at most 10 w-%, more preferably at most 5 w-%, 4 w-%, 3 w-%, 2 w-% or 1 w-% of any other solid-state form of zanubrutinib, based on the total weight of the composition. Preferably, the any other solid-state form of zanubrutinib is Form A of WO 2018/033853 A2. Form A of zanubrutinib exhibits a PXRD comprising amongst others a characteristic reflection at (5.4 ± 0.2)° 2-Theta, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm. Therefore, the absence of reflections at 2-Theta angles in the range of (5.4 ± 0.2)° in the PXRD confirms the absence of form A of zanubrutinib in the composition.

Hence, in a preferred embodiment, the present invention relates to a composition comprising the zanubrutinib 4-hydroxybenzoate form as defined in any one of the above described embodiments, characterized by having a PXRD comprising no reflections at 2-Theta angles in the range of (5.4 ± 0.2)°, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In another embodiment, the invention relates to a composition comprising at least 90 w-%, including at least 90, 91, 92, 93, 94, 95, 96, 97, 98 and 99 w-%, and also including equal to about 100 w-% of the zanubrutinib 4-hydroxybenzoate form as defined in any one of the above described embodiments, based on the total weight of the composition. The remaining material may comprise other solid-state form(s) of zanubrutinib and/or reaction impurities and/or processing impurities arising from the preparation of the composition.

In a further aspect, the present invention relates to a process for the preparation of the zanubrutinib 4-hydroxybenzoate form or the composition comprising the zanubrutinib 4-hydroxybenzoate form as defined in any one of the above described aspects and their corresponding embodiments comprising:

(a) dissolving zanubrutinib and 4-hydroxybenzoic acid in a solvent comprising ethyl acetate and ethanol, wherein the volume ratio of ethyl acetate and ethanol is about 9: 1 (volume:

volume) and the molar ratio of zanubrutinib and 4-hydroxybenzoic acid is in the range of from about 1.0: 1.0 to 1.0: 3.0 (zanubrutinib : 4-hydroxybenzoic acid);

(b) optionally filtering the solution obtained in (a) in order to remove any undissolved solid;

(c) optionally adding seed crystals comprising the zanubrutinib 4-hydroxybenzoate form of the present invention;

(d) crystallizing the zanubrutinib 4-hydroxybenzoate form of the present invention from the solution obtained in (a) or (b) or from the mixture obtained in (c);

(e) separating at least a part of the crystals obtained in (d) from the mother liquor;

(f) optionally washing the isolated crystals obtained in (e);

(g) drying the crystals obtained in any one of steps (d) to (f).

Zanubrutinib free base can for example be prepared according to the procedures provided in WO 2014/173289 A2, WO 2018/033853 A2 and WO 2019/108795 A1, all of the douments which are herewith incorporated by reference. Zanubrutinib, which is used as starting material in step (a) of the above described process, may be applied as crystalline and/or amorphous material.

In a first step of the above described process a solution comprising zanubrutinib free base, 4-hydroxybenzoic acid and a solvent mixture comprising ethyl acetate and ethanol is provided. Thereby, the volume ratio of ethyl acetate and ethanol is about 9: 1 (volume: volume) and the molar ratio of zanubrutinib and 4-hydroxybenzoic acid is in the range of from about 1.0: 1.0 to 1.0: 3.0 (zanubrutinib: 4-hydroxybenzoic acid), preferably the molar ratio is in the range of from about 1.0: 1:0 to 1.0: 1.5 (zanubrutinib: 4-hydroxybenzoic acid) and most preferably the molar ratio is about 1.0: 1.1 (zanubrutinib: 4-hydroxybenzoic acid). The applied zanubrutinib concentration in step (a) of the above described process may be in the range of from about 200 to 400 g/L, preferably of from about 200 to 350 g/L and most preferably the applied zanubrutinib free base concentration is about 300 g/L. Dissolution may be accelerated by increasing the temperature of the mixture provided in step (a) to about 40 to 70°C or by heating the mixture under reflux.

In order to initiate crystallization the solution is stirred, *e.g.* at a temperature of about 30°C or below about 30°C, preferably at a temperature in the range of from about 0 to 30°C, more preferably at RT. Optionally, seed crystals comprising the zanubrutinib 4-hydroxybenzoate form are added in order to promote crystallization and/or to control particle size distribution. The amount of seed crystals employed may be in the range of from about 1 to 20 w-%,

preferably of from about 1 to 10 w-% and most preferably of from about 1 to 5 w-%, based on the weight of applied zanubrutinib starting material. Seed crystals may be prepared according to Example 1 hereinafter.

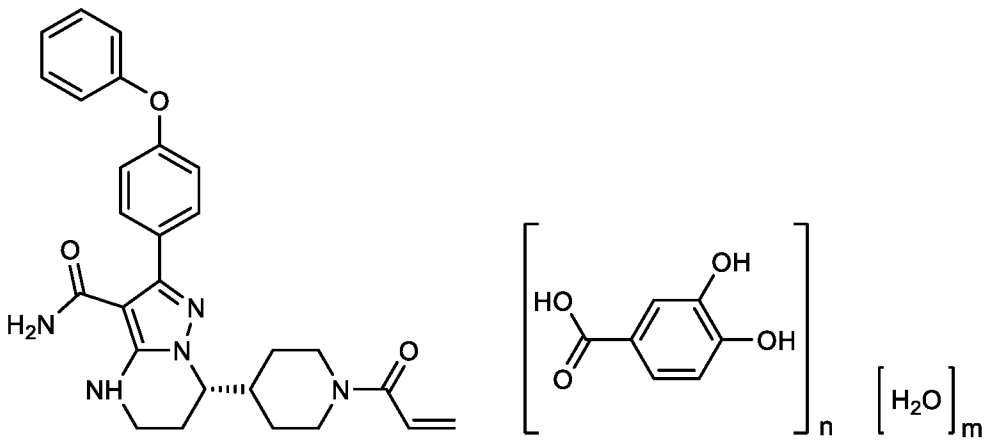
Once the zanubrutinib 4-hydroxybenzoate form is obtained or preferably obtained in essentially pure form, at least a part of the crystals, is separated from the mother liquor. Preferably, the crystals are separated from the mother liquor by any conventional method such as filtration, centrifugation, solvent evaporation or decantation, more preferably by filtration or centrifugation and most preferably by filtration.

Optionally, in a further step the isolated crystals are washed with a solvent comprising ethyl acetate and ethanol, wherein the volume ratio of ethyl acetate and ethanol is about 9:1 (volume: volume).

In a final step, the obtained crystals are dried. Drying may be performed at a temperature in the range of from about 20 to 80°C, preferably in the range of from about 20 to 60°C and most preferably drying is performed at 40 °C. Drying may be performed for a period in the range of from about 1 to 72 hours, preferably of from about 2 to 48 hours, more preferably of from about 4 to 24 hours and most preferably of from about 6 to 18 hours. Drying may be performed at ambient pressure and/ or under reduced pressure. Preferably, drying is performed at a pressure of about 100 mbar or less, more preferably of about 50 mbar or less.

The zanubrutinib 3,4-dihydroxybenzoate form, compositions comprising the same and a method for its preparation

In one aspect, the invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by the chemical structure as depicted in Formula (IIb),



Formula (IIb),

wherein n is in the range of from 0.8 to 1.2, preferably of from 0.9 to 1.1, even more preferably of from 0.95 to 1.05 and most preferably n is 1.0 and m is in the range of from 0.0 to 0.3.

Preferably, the crystalline form of the present invention as defined above is a co-crystal, a salt or a mixture of a co-crystal and a salt and most preferably the crystalline form is a co-crystal.

In another embodiment the invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by having a PXRD comprising reflections at 2-Theta angles of:

(7.6 ± 0.2)°, (10.7 ± 0.2)° and (13.8 ± 0.2)°; or

(7.6 ± 0.2)°, (10.7 ± 0.2)°, (12.4 ± 0.2)° and (13.8 ± 0.2)°; or

(7.6 ± 0.2)°, (10.7 ± 0.2)°, (11.7 ± 0.2)°, (12.4 ± 0.2)° and (13.8 ± 0.2)°; or

(7.6 ± 0.2)°, (10.7 ± 0.2)°, (11.7 ± 0.2)°, (12.4 ± 0.2)°, (13.8 ± 0.2)° and (17.2 ± 0.2)°; or

(7.6 ± 0.2)°, (10.7 ± 0.2)°, (11.7 ± 0.2)°, (12.4 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)° and (19.9 ± 0.2)°; or

(7.6 ± 0.2)°, (10.7 ± 0.2)°, (11.7 ± 0.2)°, (12.4 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (19.9 ± 0.2)° and (21.8 ± 0.2)°; or

(7.6 ± 0.2)°, (10.7 ± 0.2)°, (11.7 ± 0.2)°, (12.4 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (19.9 ± 0.2)°, (21.8± 0.2)° and (23.8 ± 0.2)°; or

(7.6 ± 0.2)°, (10.7 ± 0.2)°, (11.7 ± 0.2)°, (12.4 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (19.9 ± 0.2)°, (21.8 ± 0.2)°, (23.8 ± 0.2)° and (26.9 ± 0.2)°; or

(7.6 ± 0.2)°, (10.7± 0.2)°, (11.7 ± 0.2)°, (12.4 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (17.8 ± 0.2)°, (19.9 ± 0.2)°, (21.8 ± 0.2)°, (23.8 ± 0.2)° and (26.9 ± 0.2)°; or

(7.6 ± 0.2)°, (10.1 ± 0.2)°, (10.7 ± 0.2)°, (11.7 ± 0.2)°, (12.4 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (17.8 ± 0.2)°, (19.9 ± 0.2)°, (21.8 ± 0.2)°, (23.8 ± 0.2)° and (26.9 ± 0.2)°;

when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In a further embodiment the invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by having a PXRD comprising reflections at 2-Theta angles of:

(7.6 ± 0.1)°, (10.7 ± 0.1)° and (13.8 ± 0.1)°; or

(7.6 ± 0.1)°, (10.7 ± 0.1)°, (12.4 ± 0.1)° and (13.8 ± 0.1)°; or

(7.6 ± 0.1)°, (10.7 ± 0.1)°, (11.7 ± 0.1)°, (12.4 ± 0.1)° and (13.8 ± 0.1)°; or
(7.6 ± 0.1)°, (10.7 ± 0.1)°, (11.7 ± 0.1)°, (12.4 ± 0.1)°, (13.8 ± 0.1)° and (17.2 ± 0.1)°; or
(7.6 ± 0.1)°, (10.7 ± 0.1)°, (11.7 ± 0.1)°, (12.4 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)° and (19.9 ± 0.1)°; or
(7.6 ± 0.1)°, (10.7 ± 0.1)°, (11.7 ± 0.1)°, (12.4 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (19.9 ± 0.1)° and (21.8 ± 0.1)°; or
(7.6 ± 0.1)°, (10.7 ± 0.1)°, (11.7 ± 0.1)°, (12.4 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (19.9 ± 0.1)°, (21.8± 0.1)° and (23.8 ± 0.1)°; or
(7.6 ± 0.1)°, (10.7 ± 0.1)°, (11.7 ± 0.1)°, (12.4 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (19.9 ± 0.1)°, (21.8 ± 0.1)°, (23.8 ± 0.1)° and (26.9 ± 0.1)°; or
(7.6 ± 0.1)°, (10.7± 0.1)°, (11.7 ± 0.1)°, (12.4 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (17.8 ± 0.1)°, (19.9 ± 0.1)°, (21.8 ± 0.1)°, (23.8 ± 0.1)° and (26.9 ± 0.1)°; or
(7.6 ± 0.1)°, (10.1 ± 0.1)°, (10.7 ± 0.1)°, (11.7 ± 0.1)°, (12.4 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (17.8 ± 0.1)°, (19.9 ± 0.1)°, (21.8 ± 0.1)°, (23.8 ± 0.1)° and (26.9 ± 0.1)°;
when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In another embodiment the present invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by having a PXRD comprising reflections at 2-Theta angles of (10.7 ± 0.2)°, (12.4 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (18.7 ± 0.2)°, (19.3 ± 0.2)°, (19.9 ± 0.2)°, (21.8 ± 0.2)°, (23.8 ± 0.2)° and (26.9 ± 0.2)°, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In an additional embodiment the invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by having a PXRD comprising reflections at 2-Theta angles of (10.7 ± 0.1)°, (12.4 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (18.7 ± 0.1)°, (19.3 ± 0.1)°, (19.9 ± 0.1)°, (21.8 ± 0.1)°, (23.8 ± 0.1)° and (26.9 ± 0.1)°, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In another embodiment the invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by having a PXRD essentially the same as shown in Figure 6 of the present invention, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In addition, the present invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by having an FTIR spectrum comprising peaks at wavenumbers of:

(3526 ± 4) cm^{-1}, (3467 ± 4) cm^{-1} and (1678 ± 4) cm^{-1} or;

(3526 ± 4) cm^{-1}, (3467 ± 4) cm^{-1}, (3409 ± 4) cm^{-1} and (1678 ± 4) cm^{-1}; or

(3526 ± 4) cm^{-1}, (3467 ± 4) cm^{-1}, (3409 ± 4) cm^{-1}, (3188 ± 4) cm^{-1} and (1678 ± 4) cm^{-1}; or

(3526 ± 4) cm^{-1}, (3467 ± 4) cm^{-1}, (3409 ± 4) cm^{-1}, (3188 ± 4) cm^{-1}, (1678 ± 4) cm^{-1} and (1280 ± 4) cm^{-1}; or

(3526 ± 4) cm^{-1}, (3467 ± 4) cm^{-1}, (3409 ± 4) cm^{-1}, (3188 ± 4) cm^{-1}, (1678 ± 4) cm^{-1}, (1280 ± 4) cm^{-1} and (1237 ± 4) cm^{-1}; or

(3526 ± 4) cm^{-1}, (3467 ± 4) cm^{-1}, (3409 ± 4) cm^{-1}, (3188 ± 4) cm^{-1}, (1678 ± 4) cm^{-1}, (1280 ± 4) cm^{-1}, (1237 ± 4) cm^{-1} and (1202 ± 4) cm^{-1}; or

(3526 ± 4) cm^{-1}, (3467 ± 4) cm^{-1}, (3409 ± 4) cm^{-1}, (3298 ± 4) cm^{-1}, (3188 ± 4) cm^{-1}, (1678 ± 4) cm^{-1}, (1280 ± 4) cm^{-1}, (1237 ± 4) cm^{-1} and (1202 ± 4) cm^{-1}; or

(3526 ± 4) cm^{-1}, (3467 ± 4) cm^{-1}, (3409 ± 4) cm^{-1}, (3298 ± 4) cm^{-1}, (3188 ± 4) cm^{-1}, (1678 ± 4) cm^{-1}, (1280 ± 4) cm^{-1}, (1237 ± 4) cm^{-1}, (1202 ± 4) cm^{-1} and (967 ± 4) cm^{-1};

when measured at a temperature in the range of from 20 to 30°C with a diamond ATR cell.

Alternatively, the present invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by having an FTIR spectrum comprising peaks at wavenumbers of:

(3526 ± 2) cm^{-1}, (3467 ± 2) cm^{-1} and (1678 ± 2) cm^{-1} or;

(3526 ± 2) cm^{-1}, (3467 ± 2) cm^{-1}, (3409 ± 2) cm^{-1} and (1678 ± 2) cm^{-1}; or

(3526 ± 2) cm^{-1}, (3467 ± 2) cm^{-1}, (3409 ± 2) cm^{-1}, (3188 ± 2) cm^{-1} and (1678 ± 2) cm^{-1}; or

(3526 ± 2) cm^{-1}, (3467 ± 2) cm^{-1}, (3409 ± 2) cm^{-1}, (3188 ± 2) cm^{-1}, (1678 ± 2) cm^{-1} and (1280 ± 2) cm^{-1}; or

(3526 ± 2) cm^{-1}, (3467 ± 2) cm^{-1}, (3409 ± 2) cm^{-1}, (3188 ± 2) cm^{-1}, (1678 ± 2) cm^{-1}, (1280 ± 2) cm^{-1} and (1237 ± 2) cm^{-1}; or

(3526 ± 2) cm^{-1}, (3467 ± 2) cm^{-1}, (3409 ± 2) cm^{-1}, (3188 ± 2) cm^{-1}, (1678 ± 2) cm^{-1}, (1280 ± 2) cm^{-1}, (1237 ± 2) cm^{-1} and (1202 ± 2) cm^{-1}; or

(3526 ± 2) cm^{-1}, (3467 ± 2) cm^{-1}, (3409 ± 2) cm^{-1}, (3298 ± 2) cm^{-1}, (3188 ± 2) cm^{-1}, (1678 ± 2) cm^{-1}, (1280 ± 2) cm^{-1}, (1237 ± 2) cm^{-1} and (1202 ± 2) cm^{-1}; or

(3526 ± 2) cm^{-1}, (3467 ± 2) cm^{-1}, (3409 ± 2) cm^{-1}, (3298 ± 2) cm^{-1}, (3188 ± 2) cm^{-1}, (1678 ± 2) cm^{-1}, (1280 ± 2) cm^{-1}, (1237 ± 2) cm^{-1}, (1202 ± 2) cm^{-1} and (967 ± 2) cm^{-1};

when measured at a temperature in the range of from 20 to 30°C with a diamond ATR cell.

Moreover, the present invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by having an FTIR spectrum essentially the same as shown in Figure 7 of the present invention, when measured at a temperature in the range of from 20 to 30°C with a diamond ATR cell.

In yet another embodiment, the present invention relates a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by having a DSC curve comprising an endothermic peak, preferably a single endothermic peak, having an onset at a temperature of (174 ± 5)°C, preferably of (174 ± 3)°C, more preferably of (174 ± 2)°C and most preferably of (174 ± 1)°C, when measured at a heating rate of 10 K/min.

In a further embodiment, the present invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by having a DSC curve comprising an endothermic peak, preferably a single endothermic peak, having a maximum at a temperature of (175 ± 5)°C, preferably of (175 ± 3)°C, more preferably of (175 ± 2)°C and most preferably of (175 ± 1)°C, when measured at a heating rate of 10 K/min.

In one embodiment, the present invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by having a TGA curve showing a mass loss of not more than 0.9 w-%, preferably of not more than 0.6 w-%, more preferably of not more than 0.5 w-% and most preferably of not more than 0.4 w-%, based on the weight of the crystalline form, when heated from 25 to 170°C at a rate of 10 K/min.

In one embodiment, the present invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by showing a mass change of not more than 1.0 w-%, more preferably of not more than 0.9 w-%, based on the weight of the crystalline form, when measured with GMS at a relative humidity in the range of from 0 to 90% and a temperature of (25.0 ± 0.1)°C.

In still another embodiment, the present invention relates to a crystalline form comprising zanubrutinib and 3,4-dihydroxybenzoic acid characterized by exhibiting an orthorhombic unit cell having space group $P2_12_12_1$. Preferably, the unit cell has the following parameters

a = 12.141 Ångstrom

b = 14.730 Ångstrom

c = 17.450 Ångstrom

alpha = 90°

beta = 90°

gamma = 90°

when measured with single crystal X-ray diffraction at 193 K with Mo radiation having a wavelength of 0.71073 Ångstrom.

In another aspect, the present invention relates to a composition comprising the zanubrutinib 3,4-dihydroxybenzoate form of the present invention as defined in any one of the above described embodiments, characterized in that the composition is essentially free of any other solid-state form of zanubrutinib. For example, a composition comprising the zanubrutinib 3,4-dihydroxybenzoate form of the present invention comprises at most 20 w-%, preferably at most 10 w-%, more preferably at most 5 w-%, 4 w-%, 3 w-%, 2 w-% or 1 w-% of any other solid-state form of zanubrutinib, based on the total weight of the composition. Preferably, the any other solid-state form of zanubrutinib is Form A of WO 2018/033853 A2. Form A of zanubrutinib exhibits a PXRD comprising amongst others a characteristic reflection at (5.4 ± 0.2)° 2-Theta, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm. Therefore, the absence of reflections at 2-Theta angles in the range of (5.4 ± 0.2)° in the PXRD confirms the absence of form A of zanubrutinib in the composition.

Hence, in a preferred embodiment, the present invention relates to a composition comprising the zanubrutinib 3,4-dihydroxybenzoate form of the present invention as defined in any one of the above described embodiments, characterized by having a PXRD comprising no reflections at 2-Theta angles in the range of (5.4 ± 0.2)°, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In another embodiment, the invention relates to a composition comprising at least 90 w-%, including at least 90, 91, 92, 93, 94, 95, 96, 97, 98 and 99 w-%, and also including equal to about 100 w-% of the zanubrutinib 3,4-dihydroxybenzoate form as defined in any one of the above described embodiments, based on the total weight of the composition. The remaining material may comprise other solid-state form(s) of zanubrutinib and/or reaction impurities and/or processing impurities arising from the preparation of the composition.

In a further aspect, the present invention relates to a process for the preparation of the zanubrutinib 3,4-dihydroxybenzoate form or the composition comprising the zanubrutinib 3,4-dihydroxybenzoate form as defined in any one of the above described aspects and their corresponding embodiments comprising:

(a) dissolving zanubrutinib and 3,4-dihydroxybenzoic acid in a solvent comprising ethyl acetate and ethanol, wherein the volume ratio of ethyl acetate and ethanol is about 9: 1 (volume: volume) and the molar ratio of zanubrutinib and 3,4-dihydroxybenzoic acid is in the range of from about 1.0: 1.0 to 1.0: 3.0 (zanubrutinib: 3,4-dihydroxybenzoic acid);
(b) optionally filtering the solution obtained in (a) in order to remove any undissolved solid;
(c) optionally adding seed crystals comprising the zanubrutinib 3,4-dihydroxybenzoate form of the present invention;
(d) crystallizing the zanubrutinib 3,4-dihydroxybenzoate form of the present invention from the solution obtained in (a) or (b) or from the mixture obtained in (c);
(e) separating at least a part of the crystals obtained in (d) from the mother liquor;
(f) optionally washing the isolated crystals in (e); and
(g) drying the crystals obtained in any one of steps (d) to (f).

Zanubrutinib free base can for example be prepared according to the procedures provided in WO 2014/173289 A2, WO 2018/033853 A2 and WO 2019/108795 A1, all of the douments which are herewith incorporated by reference. Zanubrutinib, which is used as starting material in step (a) of the above described process, may be applied as crystalline and/or amorphous material.

In a first step of the above described process a solution comprising zanubrutinib free base, 3,4-dihydroxybenzoic acid and a solvent mixture comprising ethyl acetate and ethanol is provided. Thereby, the volume ratio of ethyl acetate and ethanol is about 9: 1 (volume: volume) and the molar ratio of zanubrutinib and 3,4-dihydroxybenzoic acid is in the range of from about 1.0: 1.0 to 1.0: 3.0 (zanubrutinib: 3,4-dihydroxybenzoic acid), preferably the molar ratio is in the range of from about 1.0: 1:0 to 1.0: 1.5 (zanubrutinib: 3,4-dihydroxybenzoic acid) and most preferably the molar ratio is about 1.0: 1.1 (zanubrutinib: 3,4-dihydroxybenzoic acid). The applied zanubrutinib concentration in step (a) of the above described process may be in the range of from about 200 to 400 g/L, preferably of from about 200 to 350 g/L and most preferably the applied zanubrutinib free base concentration is about 300 g/L. Dissolution may be

accelerated by increasing the temperature of the mixture provided in step (a) to about 40 to 70°C or by heating the mixture under reflux.

In order to initiate crystallization the solution is stirred, *e.g.* at a temperature of about 30°C or below about 30°C, preferably at a temperature in the range of from about 0 to 30°C, more preferably at RT. Optionally, seed crystals comprising the zanubrutinib 3,4-dihydroxybenzoate form are added in order to promote crystallization and/or to control particle size distribution. The amount of seed crystals employed may be in the range of from about 1 to 20 w-%, preferably of from about 1 to 10 w-% and most preferably of from about 1 to 5 w-%, based on the weight of applied zanubrutinib starting material. Seed crystals may be prepared according to Example 2 hereinafter.

Once the zanubrutinib 3,4-dihydroxybenzoate form is obtained or preferably obtained in essentially pure form, at least a part of the crystals is separated from the mother liquor. Preferably, the crystals are separated from their mother liquor by any conventional method such as filtration, centrifugation, solvent evaporation or decantation, more preferably by filtration or centrifugation and most preferably by filtration.

Optionally, in a further step the isolated crystals are washed with a solvent comprising ethyl acetate and ethanol, wherein the volume ratio of ethyl acetate and ethanol is about 9:1 (volume: volume).

In a final step, the obtained crystals are dried. Drying may be performed at a temperature in the range of from about 20 to 80°C, preferably in the range of from about 20 to 60°C and most preferably drying is performed at 40 °C. Drying may be performed for a period in the range of from about 1 to 72 hours, preferably of from about 2 to 48 hours, more preferably of from about 4 to 24 hours and most preferably of from about 6 to 18 hours. Drying may be performed at ambient pressure and/ or under reduced pressure. Preferably, drying is performed at a pressure of about 100 mbar or less, more preferably of about 50 mbar or less.

Pharmaceutical composition and medical use

In a further aspect the present invention relates to the use of the compound comprising zanubrutinib and 4-hydroxybenzoic acid or 3,4-dihydroxybenzoic acid, preferably the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form or the composition comprising one of the forms as defined in any one of the above described aspects and their corresponding embodiments for the preparation of a pharmaceutical composition.

In a further aspect, the present invention relates to a pharmaceutical composition comprising the compound comprising zanubrutinib and 4-hydroxybenzoic acid or 3,4-dihydroxybenzoic acid, preferably the zanubrutinib 4-hydroxybenzoate form, the zanubrutinib 3,4-dihydroxybenzoate form or the composition comprising one of the forms as defined in any one of the above described aspects and their corresponding embodiments, preferably in an effective and/or predetermined amount, and at least one pharmaceutically acceptable excipient.

Preferably, the predetermined and/or effective amount of the compound comprising zanubrutinib and 4-hydroxybenzoic acid or 3,4-dihydroxybenzoic acid, preferably of the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate or the composition comprising one of the forms as defined in any one of the above described aspects and their corresponding embodiments is in the range of from 20 to 100 mg calculated as zanubrutinib free base. For example the predetermined and/or effective amount is selected from the group consisting of 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg and 100 mg calculated as zanubrutinib free base. In a particular preferred embodiment the predetermined and/or effective amount is 25 mg or 100 mg, calculated as zanubrutinib free base. Most preferably, the predetermined and/or effective amount is 80 mg, calculated as zanubrutinib free base.

In another embodiment, the at least one pharmaceutically acceptable excipient is selected from the group consisting of filler, disintegrant, flowability aid, glidant and solubilizer. Preferably, the at least one pharmaceutically acceptable excipient is selected from the group consisting of microcrystalline cellulose, colloidal silicon dioxide, sodium dodecyl sulfate, croscarmellose sodium and magnesium stearate.

Preferably, the pharmaceutical composition of the present invention as described above is an oral solid dosage form. In a particular preferred embodiment the pharmaceutical composition of the present invention as described above is a capsule, preferably a hard gelatin capsule, more preferably a hard gelatin capsule with capsule size 0. In an alternative embodiment, the pharmaceutical composition of the present invention as described above is a tablet, preferably a film-coated tablet.

In a further aspect, the present invention relates to the compound comprising zanubrutinib and 4-hydroxybenzoic acid or 3,4-dihydroxybenzoic acid, preferably the zanubrutinib 4-hydroxybenzoate form, the zanubrutinib 3,4-dihydroxybenzoate form, the composition

comprising the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form or the pharmaceutical composition comprising the compound comprising zanubrutinib and 4-hydroxybenzoic acid or 3,4-dihydroxybenzoic acid, in particular the zanubrutinib 4-hydroxybenzoate form, the zanubrutinib 3,4-dihydroxybenzoate form or the composition comprising the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form as defined in any one of the above described aspects and their corresponding embodiments for use as a medicament.

In yet another aspect, the present invention relates to the compound comprising zanubrutinib and 4-hydroxybenzoic acid or 3,4-dihydroxybenzoic acid, preferably the zanubrutinib 4-hydroxybenzoate form, the zanubrutinib 3,4-dihydroxybenzoate form, the composition comprising the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form or the pharmaceutical composition comprising the compound comprising zanubrutinib and 4-hydroxybenzoic acid or 3,4-dihydroxybenzoic acid, in particular the zanubrutinib 4-hydroxybenzoate form, the zanubrutinib 3,4-dihydroxybenzoate form or the composition comprising the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form as defined in any one of the above described aspects and their corresponding embodiments for use in the treatment of a B-cell proliferative disease.

In an alternative embodiment, the invention concerns a method of treating a B-cell proliferative disease said method comprising administering an effective amount of the compound comprising zanubrutinib and 4-hydroxybenzoic acid or 3,4-dihydroxybenzoic acid, preferably the zanubrutinib 4-hydroxybenzoate form, the zanubrutinib 3,4-dihydroxybenzoate form, the composition comprising the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form or the pharmaceutical composition comprising the compound comprising zanubrutinib and 4-hydroxybenzoic acid or 3,4-dihydroxybenzoic acid, in particular the zanubrutinib 4-hydroxybenzoate form, the zanubrutinib 3,4-dihydroxybenzoate form or the composition comprising the zanubrutinib 4-hydroxybenzoate form or the zanubrutinib 3,4-dihydroxybenzoate form as defined in any one of the above described aspects and their corresponding embodiments to a patient in need of such a treatment.

In some embodiments, the B-cell proliferative disease is a B-cell malignancy including but not limited to lymphoma, non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenstrom macroglobulinemia

(WM), marginal zone lymphoma (MZL), Hairy cell leukemia (HCC), Burkitt's-like leukemia or a combination of two or more thereof.

In some embodiments the B-cell proliferative disease is a relapsed/refractory (R/R) B-cell malignancy including but not limited to mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenstrom macroglobulinemia (WM) or a combination of two or more thereof.

EXAMPLES

The following non-limiting examples are illustrative for the disclosure and are not to be construed as to be in any way limiting for the scope of the invention.

Example 1: Preparation of the zanubrutinib 4-hydroxybenzoate form

Zanubrutinib (1.50 g, 3.18 mmol, *e.g.* prepared according to Example 1 of WO 2019/108795 A1) and 4-hydroxybenzoic acid (0.49 g, 3.55 mmol) were dissolved in a mixture of ethyl acetate/ethanol (5 mL, 9/1 v/v) upon gentle heating. The resulting clear solution was stirred at room temperature, whereat a suspension was formed within a minute. After 140 minutes of stirring the crystals were collected by filtration, washed twice with a mixture of ethyl acetate/ethanol (2.5 mL, 9/1 v/v) and dried for 48 hours at 40°C and under reduced pressure of about 50 mbar to obtain the zanubrutinib 4-hydroxybenzoate form of the present invention.

Yield: 1.67 g (86% of theory)

Example 2: Preparation of the crystalline zanubrutinib 3,4-dihydroxybenzoate form

Zanubrutinib (1.49 g, 3.16 mmol, *e.g.* prepared according to Example 1 of WO 2019/108795 A1) and 3,4-dihydroxybenzoic acid (0.55 g, 3.57 mmol) were dissolved in a mixture of ethyl acetate/ethanol (5 mL, 9/1 v/v) upon gentle heating. The resulting clear solution was stirred at room temperature, whereat a suspension was formed within a minute. After 140 minutes of stirring the crystals were collected by filtration, washed twice with a mixture of ethyl acetate/ethanol (2.5 mL, 9/1 v/v) and dried for 48 hours at 40°C and under reduced pressure of about 50 mbar to obtain the zanubrutinib 3,4-dihydroxybenzoate form of the present invention.

Yield: 1.69 g (93% of theory)

Example 3: Powder X-ray diffraction

The zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form according to the present invention were investigated by powder X-ray diffraction, which was performed on a PANalytical Empyrean diffractometer equipped with a theta/theta coupled goniometer in transmission geometry, Cu-Kα1,2 radiation (wavelength 0.15419 nm) with a focusing mirror and a solid state PIXcel1D detector. The patterns were recorded at a tube voltage of 45 kV and a tube current of 40 mA, applying a stepsize of 0.026° 2-Theta with 50s per step in the angular range of 2° to 40° 2-Theta at ambient conditions. A typical precision of the 2-theta values is in the range of about ± 0.2° 2-Theta, preferably of about ± 0.1° 2-Theta . Thus a diffraction peak that appears for example at 7.7° 2-Theta can appear between 7.5 and 7.9° 2-Theta, preferably between 7.6 and 7.8° 2-Theta on most X-ray diffractometers under standard conditions.

A representative diffractogram of the zanubrutinib 4-hydroxybenzoate form according to the present invention is displayed in Figure 1 and the corresponding reflection list (peak list) from 2 to 30° 2-Theta is provided in Table 1 below.

Reflection position [° 2-Theta]	**Reflection position [° 2-Theta]**	**Reflection position [° 2-Theta]**	**Reflection position [° 2-Theta]**
7.7	16.9	20.6	25.6
9.6	17.2	21.6	26.0
10.8	17.4	21.7	27.3
12.2	17.8	22.0	27.7
13.6	18.9	23.3	28.5
14.3	19.3	23.9	29.2
15.0	19.7	24.2	29.6
15.6	19.9	24.4	
16.3	20.3	25.3	

Table 1: Reflection (peak) positions of the zanubrutinib 4-hydroxybenzoate form according to the present invention in the range of from 2 to 30° 2-Theta; A typical precision of the 2-Theta values is in the range of ± 0.2° 2-Theta, preferably of ± 0.1° 2-Theta.

A representative diffractogram of the zanubrutinib 3,4-dihydroxybenzoate form according to the present invention is displayed in Figure 6 and the corresponding reflection list (peak list) from 2 to 30° 2-Theta is provided in Table 2 below.

Reflection position	**Reflection position**	**Reflection position**	**Reflection position**

[° 2-Theta]	[° 2-Theta]	[° 2-Theta]	[° 2-Theta]
7.8	15.8	20.3	24.6
8.9	16.3	20.6	25.4
9.4	16.6	21.1	25.9
10.1	17.2	21.4	26.9
10.7	17.8	21.8	27.5
11.7	18.5	21.9	27.8
12.4	18.7	22.4	28.1
13.8	19.3	23.3	28.9
14.6	19.5	23.8	29.4
14.8	19.9	24.3	

Table 2: Reflection (peak) positions of the zanubrutinib 3,4-dihydroxybenzoate form according to the present invention in the range of from 2 to 30° 2-Theta; A typical precision of the 2-Theta values is in the range of ± 0.2° 2-Theta, preferably of ± 0.1° 2-Theta.

Example 4: Fourier transform infrared spectroscopy

The zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form according to the present invention were investigated by FTIR spectroscopy, which was performed on an MKII Golden Gate™ Single Reflection Diamond ATR cell with a Bruker Tensor 27 FTIR spectrometer with 4 cm^{-1} resolution at RT. To record a spectrum a spatula tip of the sample was applied to the surface of the diamond in powder form. Then the sample was pressed onto the diamond with a sapphire anvil and the spectrum was recorded. A spectrum of the clean diamond was used as background spectrum. A typical precision of the wavenumber values is in the range of ± 4 cm^{-1}, preferably of ± 2 cm^{-1}. Thus, for example the infrared peak of the zanubrutinib 4-hydroxybenzoate form according to the present invention at 1678 cm^{-1} can appear between 1674 and 1682 cm^{-1}, preferably between 1676 and 1680 cm^{-1} on most infrared spectrometers under standard conditions.

A representative FTIR spectrum of the zanubrutinib 4-hydroxybenzoate form according to the present invention is displayed in Figure 2 and the corresponding peak list is provided in Table 3 below.

Wavenumber [cm^{-1}]	Wavenumber [cm^{-1}]	Wavenumber [cm^{-1}]	Wavenumber [cm^{-1}]
3405	1609	1271	850

3298	1586	1236	776
3196	1538	1199	759
3068	1478	1160	693
2956	1446	1124	662
2925	1381	1098	628
2808	1355	1059	
1678	1332	1021	
1636	1311	968	

Table 3: FTIR peak list of the zanubrutinib 4-hydroxybenzoate form according to the present invention; a typical precision of the wavenumbers is in the range of ± 4 cm^{-1}, preferably of ± 2 cm^{-1}.

A representative FTIR spectrum of the zanubrutinib 3,4-dihydroxybenzoate form according to the present invention is displayed in Figure 7 and the corresponding peak list is provided in Table 4 below.

Wavenumber [cm^{-1}]	**Wavenumber [cm^{-1}]**	**Wavenumber [cm^{-1}]**	**Wavenumber [cm^{-1}]**
3526	1566	1202	852
3467	1537	1165	814
3409	1487	1113	771
3298	1457	1078	749
3188	1430	1061	692
2956	1382	1022	626
2325	1339	967	
1678	1280	942	
1635	1237	873	

Table 4: FTIR peak list of the zanubrutinib 3,4-dihydroxybenzoate form according to the present invention; a typical precision of the wavenumbers is in the range of ± 4 cm^{-1}, preferably of ± 2 cm^{-1}.

Example 5: Differential scanning calorimetry (DSC)

The zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form according to the present invention were investigated by DSC, which was performed on a Mettler Polymer DSC R instrument. The samples (4.28 mg zanubrutinib 4-hydroxybenzoate form and 2.30 mg zanubrutinib 3,4-dihydroxybenzoate form) were each heated in a 40 microliter aluminium pan with a pierced aluminium lid from 25 to 220°C at a rate of 10 K/min. Nitrogen (purge rate 50 mL/min) was used as purge gas.

The DSC curves of the crystalline zanubrutinib 4-hydroxybenzoate form (see Figure 3) and the 3,4-dihydroxybenzoate form (see Figure 8) of the present invention both show no thermal events until a single sharp endothermic peak appears, which is due to the melting of the samples. Compared to prior art Form A of zanubrutinib free base (see Figure 2 of WO 2018/033853 A2), the crystalline forms of the present invention display a significant higher melting point indicating their superior thermal stability. An overview of the DSC data is displayed in Table 5 below.

Zanubrutinib solid form	**Thermal event in DSC**
4-hydroxybenzoate form	endotherm: T_{onset}: 186.6°C, T_{peak}: 187.2°C, H_{Fus}: 99 J/g
3,4-dihydroxybenzoate form	endotherm: T_{onset}: 173.8°C, T_{peak}: 174.9°C, H_{Fus}: 91 J/g
Form A	endotherm: T_{onset}: 139.4°C, T_{peak}: 142.8°C, H_{Fus}: 66 J/g

Table 5: Thermal events of various zanubrutinib forms occuring in the DSC curves

Example 6: Thermogravimetric analysis

TGA was performed on a Mettler TGA/DSC 1 instrument. The samples (8.14 mg zanubrutinib 4-hydroxybenzoate form and 4.34 mg zanubrutinib 3,4-dihydroxybenzoate form) were each heated in a 100 microliter aluminium pan closed with an aluminium lid from 25 to 220°C at a rate of 10 K/min. The lid was automatically pierced at the beginning of the measurement. Nitrogen (purge rate 50 mL/min) was used as purge gas.

The TGA curves of the crystalline zanubrutinib 4-hydroxybenzoate form (see Figure 4) and the 3,4-dihydroxybenzoate form (see Figure 9) of the present invention both show almost no weight loss until they melt. For example, the zanubrutinib 4-hydroxybenzoate form shows a mass loss of only about 0.3 w-% up to a temperature of about 180°C and the zanubrutinib 3,4-dihydroxybenzoate form shows a mass loss of only about 0.0 w-% to 0.9 w-% up to a temperature of about 170°C. Compared to prior art Form A of zanubrutinib free base (see figure 3 of WO 2018/033853 A2) which loses about 1 w-% in two distinct steps up to a temperature of about 160°C, the crystalline forms of the present invention show a reduced mass loss during TGA measurements. A summary of the TGA data is displayed in Table 6 below.

Zanubrutinib solid form	**Mass loss during TGA experiment**
4-hydroxybenzoate form	0.3 w-% until 180°C
3,4-dihydroxybenzoate form	0.0 – 0.9 w-% until 170°C

Form A	1 w-% until 160°C

Table 6: Mass losses during TGA experiments of various zanubrutinib forms

Example 7: Gravimetric moisture sorption

Moisture sorption isotherms were recorded with an SPSx-1µ moisture sorption analyzer (ProUmid, Ulm). The measurement cycle was started at ambient relative humidity (RH) of 30%. RH was then decreased to 5% in 5% steps, followed by a further decrease to 3% and to 0%. Afterwards RH was increased from 0% to 90% in a sorption cycle and subsequently decreased to 0 % in a desorption cycle each in 5% steps. Finally, RH was increased to ambient relative humidity of 30% in 5% steps. The time per step was set to a minimum of 2 hours and a maximum of 6 hours. If an equilibrium condition with a constant mass of ± 0.01% within 1 hour was reached before the maximum time for all examined samples the sequential humidity step was applied before the maximum time of 6 hours. If no equilibrium was achieved the consecutive humidity step was applied after the maximum time of 6 hours. The temperature was 25 ± 0.1 °C.

As can be seen from Figures 5 and 10 of the present invention the water uptakes in the sorption cycle between 0 and 90% are only about 0.2 w-% for the zanubrutinib 4-hydroxybenzoate form and only about 0.9 w-% for the zanubrutinib 3,4-dihydroxybenzoate form, respectively. In addition, neither of the forms shows a significant hysteresis between the sorption and desorption curves, which indicates that no structural changes appear during the experiment. This assumption is strengthened by the fact that the samples still show the same PXRDs after the experiment.

On the other hand according to Figure 6 of WO 2018/033853 A2 zanubrutinib Form A shows a higher water uptake of about 1.5 w-% in the sorption cycle between 0 and 90% and a significant hysteresis between the sorption and the desorption curves. Table 7 below provides a summary of the behaviours of the various forms during GMS experiments.

Zanubrutinib solid form	**Water uptake (0-90%RH)**	**Hysteresis**
4-hydroxybenzoate form	0.2 w-%	no
3,4-dihydroxybenzoate form	0.9 w-%	no
Form A	1.5 w-%	yes

Table 7: Behaviours of various zanubrutinib forms during GMS experiments

Example 8: Single crystal X-ray diffraction

Intensity data were collected at 193 K, using Mo radiation (lambda = 0.71073 Å), on an Oxford Diffraction Gemini-R Ultra diffractometer operated by the CrysAlisPro software (Rigaku OD, 2015). The data were corrected for absorption effects by means of comparison of equivalent reflections. The structure was solved with the direct methods procedure implemented in SHELXT and refined by full-matrix least squares refinement on F^2 using SHELXL-2014. [Sheldrick, Acta Cryst. **A71** (2015), 3 – 8 and **C71** (2015), 3 – 8].

Non-hydrogen atoms were located in difference maps and refined anisotropically. The hydrogen atoms bonded to C atoms fixed in idealized positions and the thermal displacement parameters of the former were set to $1.2U_{eq}$ of the parent C atom. All other H atoms bonded to O and N atoms were located in difference maps and refined using distance restraints, O–H = 0.84(1) Å and N–H = 0.86(1) Å, and their thermal displacement parameters were refined freely.

The absolute structure of the models (chirality at C9: S) was not established from diffraction data (Mo radiation) but was assigned in accordance with the known chirality of zanubrutunib.

The investigated zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form both don't show any intermolecular proton transfers and are therefore co-crystals. The water position in the structure model of the zanubrutinib 3,4-dihydroxybenzoate form is only partially occupied.

Example 9: Physical stability at increased temperature/humidity conditions

The zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form of the present invention were stored in open vials in climate chambers at 30°C/65% RH and 40°C/75% RH respectively. For the condition RT/97% RH the samples were stored in open vials in an exsiccator with a saturated K_2SO_4 solution at the bottom. Samples were taken at predefined time points of 1 day, 1 week, 2 weeks, 4 weeks, 9 weeks, 12 weeks and 24 weeks and subjected to PXRD to determine the physical stability of the forms. No phase changes took place at any conditions proofing the physical stability of both forms.

Example 10: Physical stability in aqueous media

The zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form of the present invention were each slurried in water and aqueous HCl solution (1M), respectively. About 35 mg of the respective form was magnetically stirred at RT in 2 mL of

each media. Samples were taken at predefined timepoints of 60 min, 90 min and 6 days and investigated by powder X-ray diffraction. No phase changes took place at any conditions proofing the physical stability of both forms in the investigated media.

Example 11: Dissolution rates in phosphate buffer pH 6.8, acetate buffer pH 4.5 and FaSSIF medium

Powder dissolution experiments were carried out in phosphate buffer pH 6.8, acetate buffer pH 4.5 and FaSSIF medium at 37°C for zanubrutinib Form A of WO 2018/033853 A2, the zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form of the present invention. Particle sizes of the forms were kept as similar as possible to allow for proper comparison. The respective concentrations were determined by HPLC at a wavelengths of 241 nm (zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form) and 235 nm (Form A), respectively.

As can be seen from Table 8 and Figure 13 herein the zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form of the present invention exhibit an increased solubility (≥ 2-fold) in phosphate puffer pH 6.8 over the whole range from 15 minutes to 24 hours compared to zanubrutinib Form A of WO 2018/033853 A2.

time [h]	Zanubrutinib Form A	Zanubrutinib 4-hydroxybenzoate form	Zanubrutinb 3,4-dihydroxybenzoate form
0.25	0.04 mg/mL	0.09 mg/mL	0.09 mg/mL
0.5	0.05 mg/mL	0.10 mg/mL	0.10 mg/mL
1	0.05 mg/mL	0.14 mg/mL	0.12 mg/mL
2	0.05 mg/mL	0.15 mg/mL	0.13 mg/mL
4	0.06 mg/mL	0.15 mg/mL	0.15 mg/mL
24	0.06 mg/mL	0.19 mg/mL	0.17 mg/mL

Table 8: Dissolution profiles of various zanubrutinib forms in phosphate buffer pH 6.8

As can be seen from Table 9 and Figure 14 herein the zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form of the present invention exhibit an increased solubility in acetate buffer pH 4.5 over the whole range from 15 minutes to 24 hours compared to zanubrutinib Form A of WO 2018/033853 A2.

time	Zanubrutinib	Zanubrutinib	Zanubrutinb

[h]	Form A	4-hydroxybenzoate form	3,4-dihydroxybenzoate form
0.25	0.08 mg/mL	0.11 mg/mL	0.14 mg/mL
0.5	0.08 mg/mL	0.10 mg/mL	0.14 mg/mL
1	0.08 mg/mL	0.11 mg/mL	0.13 mg/mL
2	0.07 mg/mL	0.12 mg/mL	0.15 mg/mL
4	0.07 mg/mL	0.12 mg/mL	0.17 mg/mL
24	0.07 mg/mL	0.13 mg/mL	0.21 mg/mL

Table 9: Dissolution profiles of various zanubrutinib forms in acetate buffer pH 4.5

As can be seen from Table 10 and Figure 15 herein the zanubrutinib 4-hydroxybenzoate form and the zanubrutinib 3,4-dihydroxybenzoate form of the present invention exhibit an increased solubility in FaSSIF medium over the whole range from 15 minutes to 24 hours compared to zanubrutinib Form A of WO 2018/033853 A2.

time [h]	Zanubrutinib Form A	Zanubrutinib 4-hydroxybenzoate form	Zanubrutinb 3,4-dihydroxybenzoate form
0.25	0.03 mg/mL	0.22 mg/mL	0.16 mg/mL
0.5	0.04 mg/mL	0.26 mg/mL	0.19 mg/mL
1	0.04 mg/mL	0.28 mg/mL	0.22 mg/mL
2	0.03 mg/mL	0.29 mg/mL	0.20 mg/mL
4	0.04 mg/mL	0.32 mg/mL	0.23 mg/mL
24	0.03 mg/mL	0.37 mg/mL	0.29 mg/mL

Table 10: Dissolution profiles of various zanubrutinib forms in FaSSIF medium

Example 12: Hard gelatin capsule formulations comprising the crystalline zanubrutinib 4-hydroxybenzoate form or the crystalline zanubrutinib 3,4-dihydroxybenzoate form

The capsules were manufactured according to the procedure displayed in the flowchart of figure 16 using the compositions of tables 11 and 12 below.

Component	Amount per HGC [mg]	Amount per HGC [%]	Function
Zanubrutinib 4-hydroxybenzoate form	103.4	27.7	API
Microcrystalline cellulose	224.9	60.3	Filler
Croscarmellose sodium	35.4	9.5	Disintegrant

Colloidal silicon dioxide	3.7	1.0	Flowability aid
Sodium dodecyl sulfate	1.9	0.5	Solubilizer
Magnesium stearate	3.7	1.0	Glidant
Capsule fill mass	373		
Gelatin capsule size 0	94		Capsule shell
Total mass	467		

Table 11: Hard gelatin capsule comprising the zanubrutinib 4-hydroxybenzoate form

Component	**Amount per HGC [mg]**	**Amount per HGC [%]**	**Function**
Zanubrutinib 3,4-dihydroxybenzoate form	106.1	27.7	API
Microcrystalline cellulose	222.2	60.3	Filler
Croscarmellose sodium	35.4	9.5	Disintegrant
Colloidal silicon dioxide	3.7	1.0	Flowability aid
Sodium dodecyl sulfate	1.9	0.5	Solubilizer
Magnesium stearate	3.7	1.0	Glidant
Capsule fill mass	373		
Gelatin capsule size 0	94		Capsule shell
Total mass	467		

Table 12: Hard gelatin capsule formulation comprising the zanubrutinib 3,4-dihydroxybenzoate form

Example 13: Stress stability testing of hard gelatin capsule comprising the zanubrutinib 4-hydroxybenzoate form

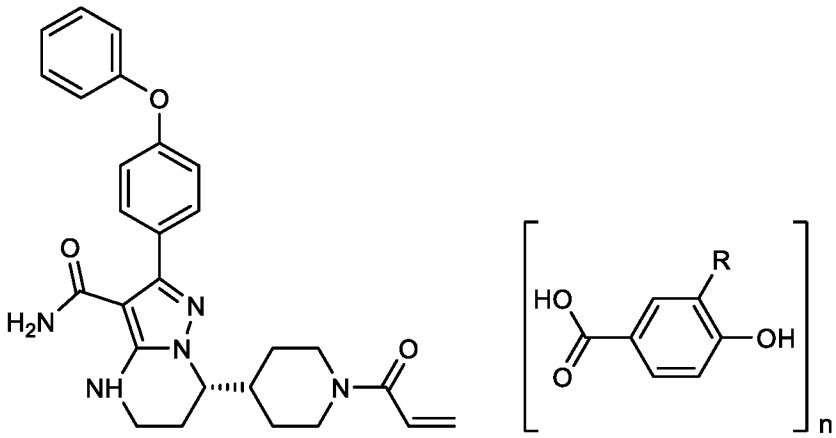
Capsules prepared according to example 12 comprising the zanubrutinib 4-hydroxybenzoate form were subjected to stress conditions at 25°C/60%RH and 30°C/65%RH respectively. Samples were taken at predefined timepoints of 1 month, 2 months and 3.5 months. The chemical stability was determined by HPLC at a wavelength of 241 nm while the physical stability was investigated by powder X-ray diffraction. As can be seen from the results summarized in table 13 below, the the zanubrutinib 4-hydroxybenzoate form was stable at all conditions.

25°C/60% RH	**0 month**	**1 month**	**2 months**	**3.5 months**
Total impurities	0.39%	0.53%	0.45%	0.52%
PXRD	complies	complies	complies	complies
30°C/65% RH	**0 month**	**1 month**	**2 months**	**3.5 months**
Total impurities	0.39%	0.53%	0.49%	0.43%
PXRD	complies	complies	complies	complies

Table 13: Results from stress stability studies with capsules comprising the zanubrutinib 4-hydroxybenzoate form

CLAIMS

1) A compound comprising zanubrutinib and a benzoic acid derivative characterized by having the chemical structure as depicted in Formula (II)



Formula (II),

wherein R is hydrogen or hydroxy and n is in the range of from 0.8 to 1.2.

2) The compound of claim 1, characterized in that the compound is crystalline.

3) The compound of claim 1 or 2, characterized in that the compound is a co-crystal, a salt or a mixture of a co-crystal and a salt.

4) The compound as defined in any one of the preceding claims, characterized in that the compound is a co-crystal.

5) A crystalline form of the compound as defined in any one of the preceding claims, wherein the benzoic acid derivative is 4-hydroxybenzoic acid and the crystalline form is characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of (7.7 ± 0.2)°, (9.6 ± 0.2)° and (18.9 ± 0.2)°, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

6) The crystalline form according to claim 5 characterized by having a powder X-ray diffractogram comprising additional reflections at 2-Theta angles of (10.8 ± 0.2)° and/or (12.2 ± 0.2)°, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

7) The crystalline form according to claim 5 or 6 characterized by having a Fourier transform infrared spectrum comprising peaks at wavenumbers of (3526 ± 4) cm^{-1},

(3467 ± 4) cm^{-1}, (3409 ± 4) cm^{-1}, (3188 ± 4) cm^{-1} and (1678 ± 4) cm^{-1}, when measured at a temperature in the range of from 20 to 30°C with a diamond ATR cell.

8) The crystalline form as defined in any one of claims 5 to 7 characterized by having a DSC curve comprising an endothermic peak having an onset at a temperature of (187 ± 5)°C, when measured at a heating rate of 10 K/min.

9) A crystalline form of the compound as defined in any one of claims 1 to 4, wherein the benzoic acid derivative is 3,4-dihydroxybenzoic acid and the crystalline form is characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of (7.6 ± 0.2)°, (10.7 ± 0.2)° and (13.8 ± 0.2)°, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

10) The crystalline form according to claim 9 characterized by having a powder X-ray diffractogram comprising additional reflections at 2-Theta angles of (11.7 ± 0.2)° and/or (12.4 ± 0.2)°, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

11) The crystalline form according to claim 9 or 10 characterized by having a Fourier transform infrared spectrum comprising peaks at wavenumbers of (3526 ± 4) cm^{-1}, (3467 ± 4) cm^{-1}, (3409 ± 4) cm^{-1}, (3188 ± 4) cm^{-1} and (1678 ± 4) cm^{-1}, when measured at a temperature in the range of from 20 to 30°C with a diamond ATR cell.

12) The crystalline form as defined in any one of claims 9 to 11 characterized by having a DSC curve comprising an endothermic peak having an onset at a temperature of (174 ± 5)°C, when measured at a heating rate of 10 K/min.

13) A composition comprising the compound as defined in any one of claims 1 to 4 or the crystalline form as defined in any one of claims 5 to 8 or the crystalline form as defined in any one of claims 9 to 12 characterized by having a powder X-ray diffractogram comprising no reflections at 2-Theta angles in the range of (5.4 ± 0.2)°, when measured at a temperature in the range of from 20 to 30°C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

14) Use of the compound as defined in any one of claims 1 to 4 or the crystalline form as defined in any one of claims 5 to 8 or the crystalline form as defined in any one of claims 9 to 12 or the composition as defined in claim 13 for the preparation of a pharmaceutical composition.

15) A pharmaceutical composition comprising the compound as defined in any one of claims 1 to 4 or the crystalline form as defined in any one of claims 5 to 8 or the crystalline form as defined in any one of claims 9 to 12 or the composition as defined in claim 13 and at least one pharmaceutically acceptable excipient.

16) The pharmaceutical composition according to claim 15, wherein the pharmaceutical composition is an oral solid dosage form.

17) The pharmaceutical composition of claim 16, wherein the oral solid dosage form is a capsule or a tablet.

18) The compound as defined in any one of claims 1 to 4 or the crystalline form as defined in any one of claims 5 to 8 or the crystalline form as defined in any one of claims 9 to 12 or the composition as defined in claim 13 or the pharmaceutical composition according to any one of claims 15 to 17 for use in the treatment of a B-cell proliferative disease.

19) The use according to claim 18, wherein the B-cell proliferative disease is selected from the group consisting of lymphoma, non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenstrom macroglobulinemia (WM), marginal zone lymphoma (MZL), Hairy cell leukemia (HCC), Burkitt's-like leukemia or a combination of two or more thereof.

Figure 1

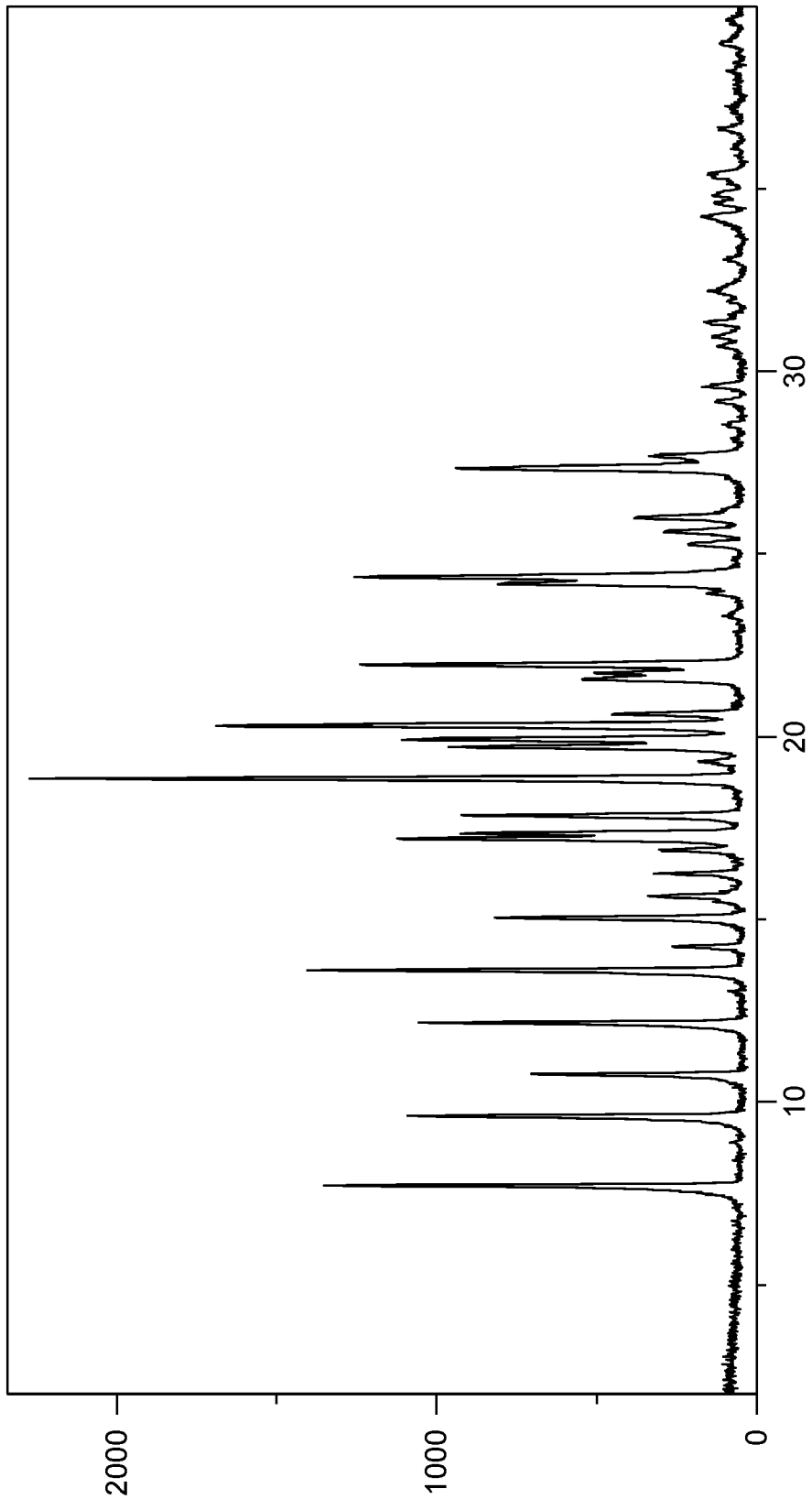
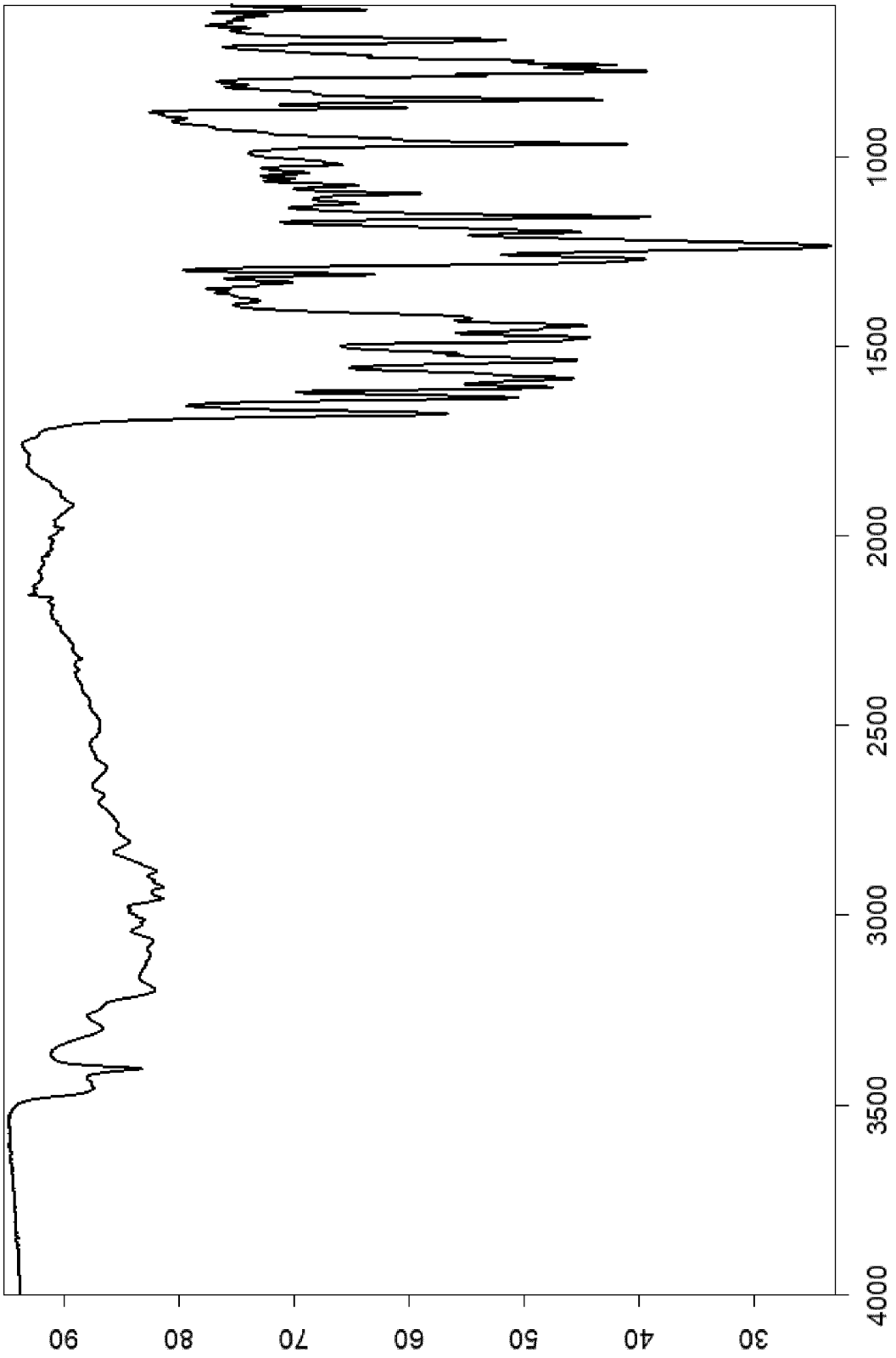


Figure 2



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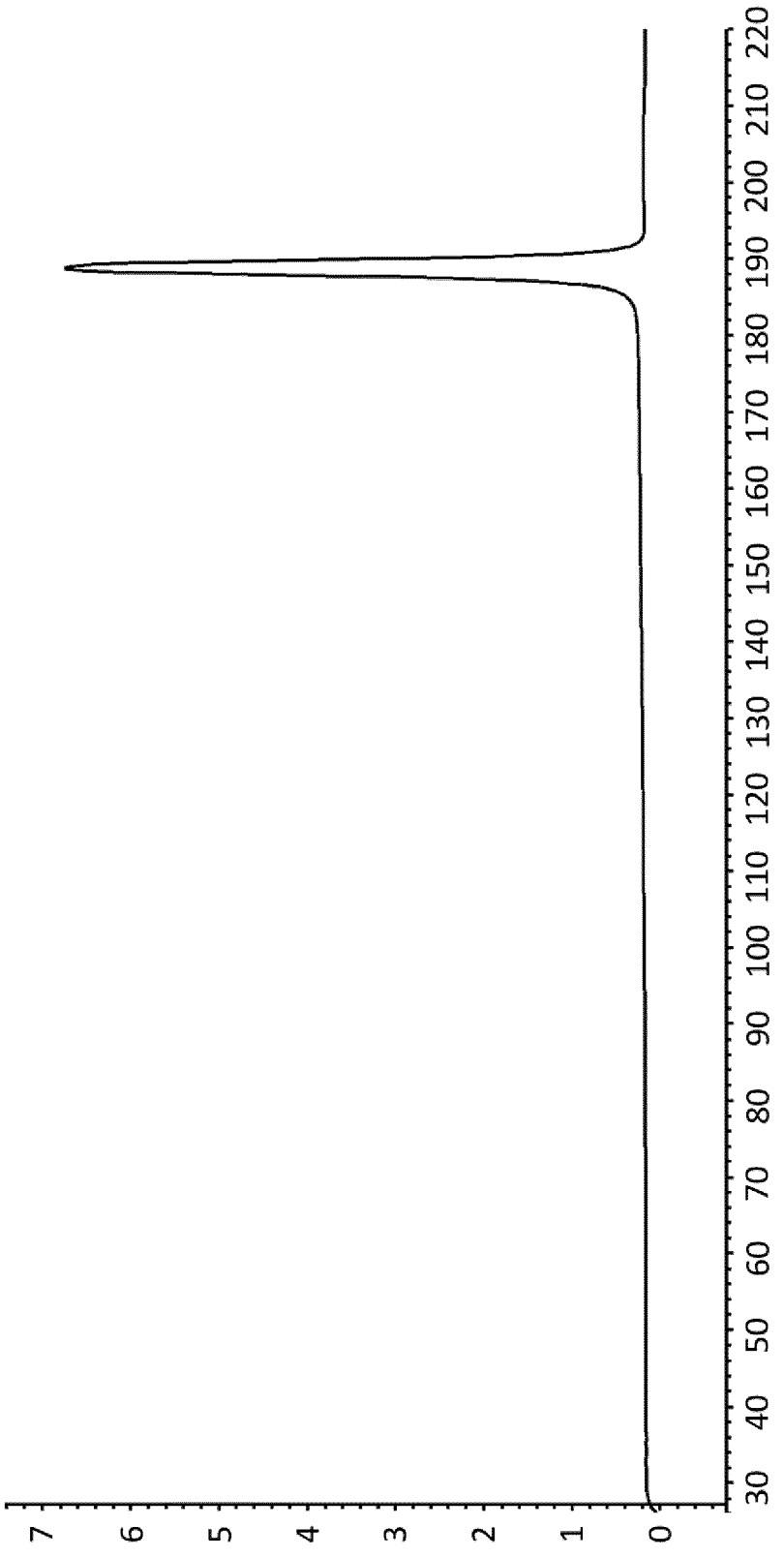
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Figure 4

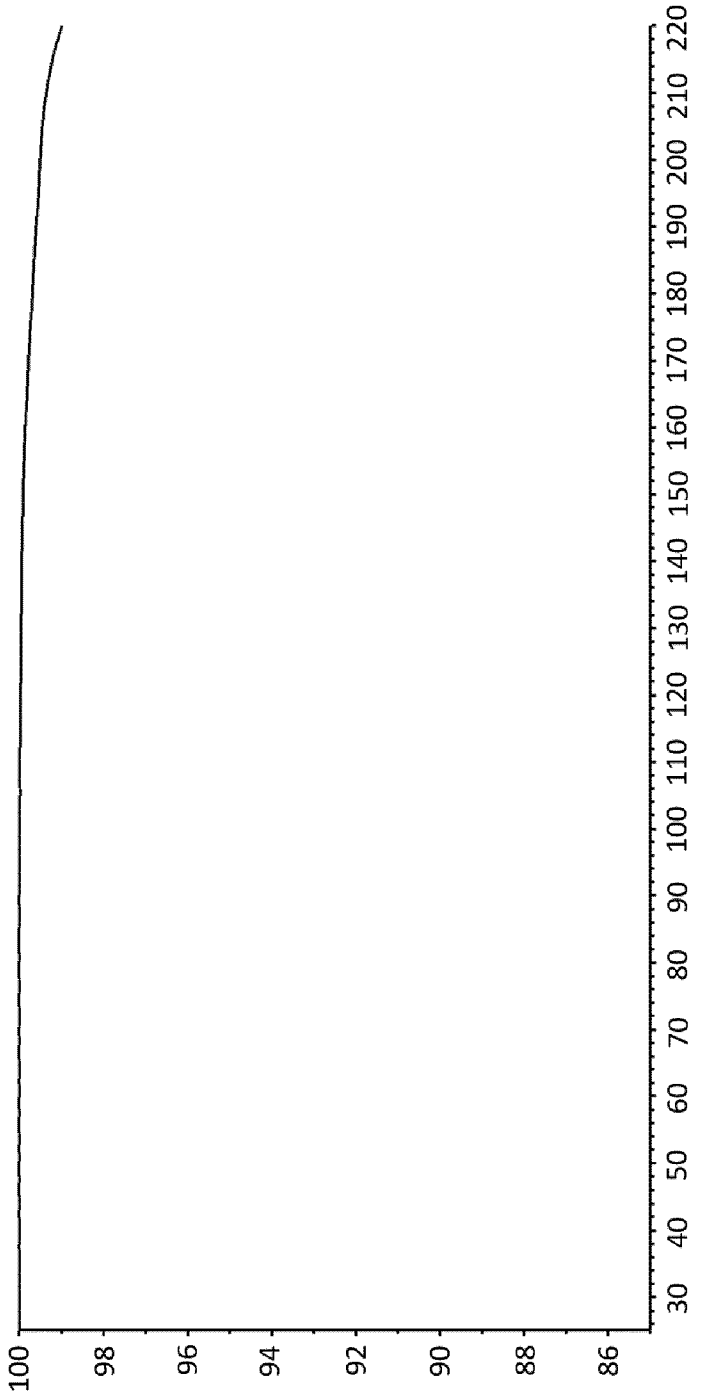
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Figure 5

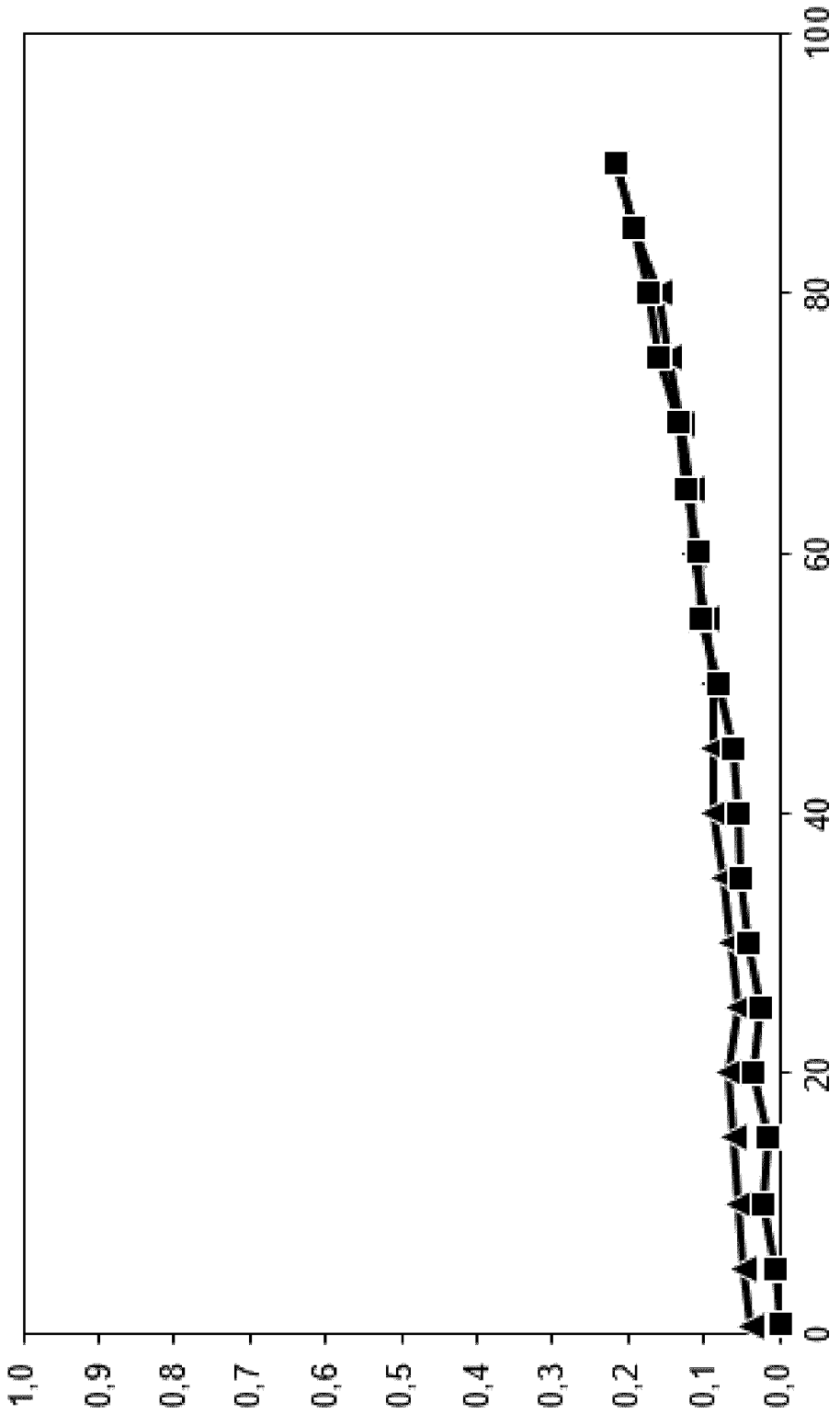

Figure 6

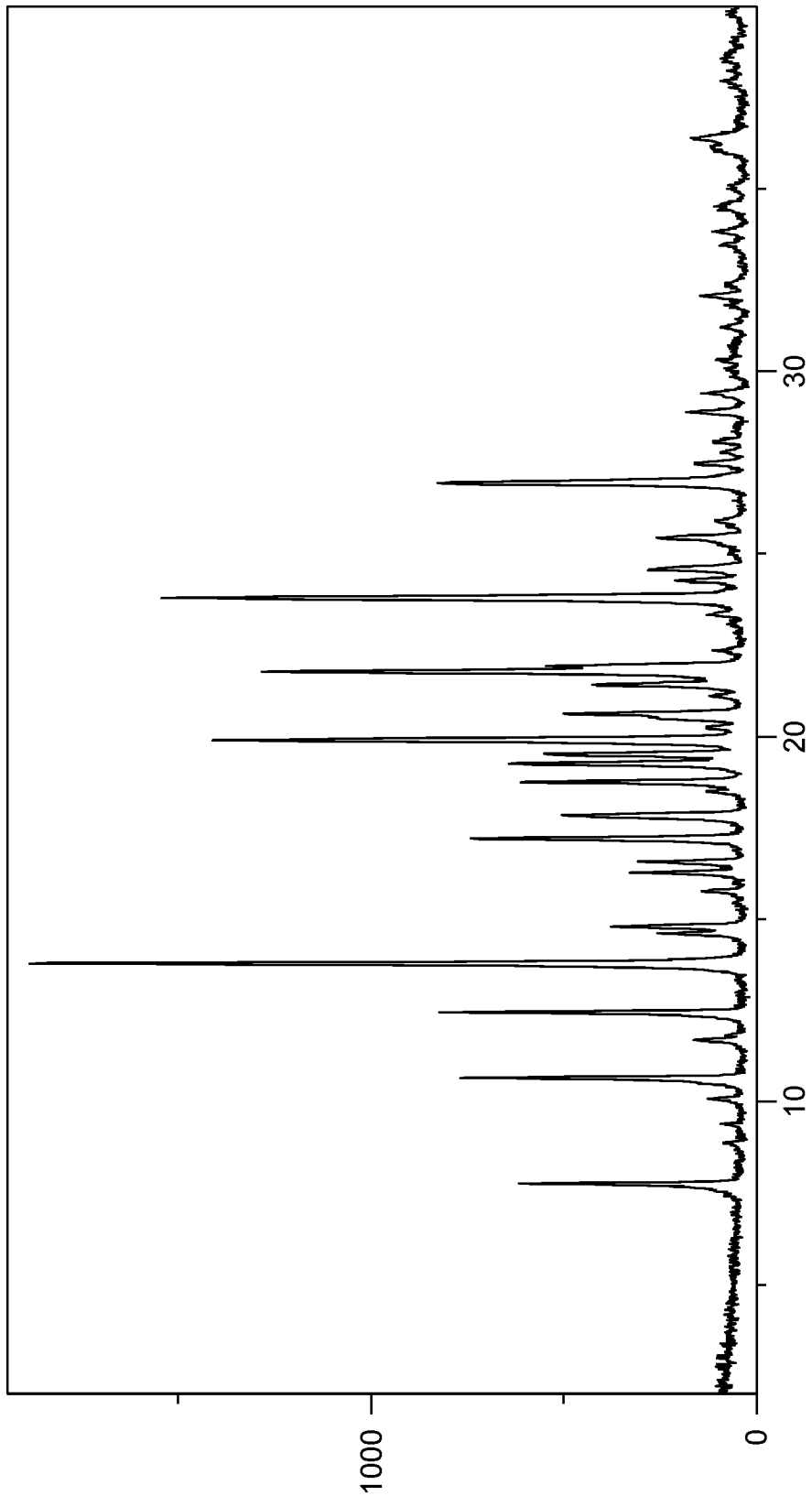

Figure 7

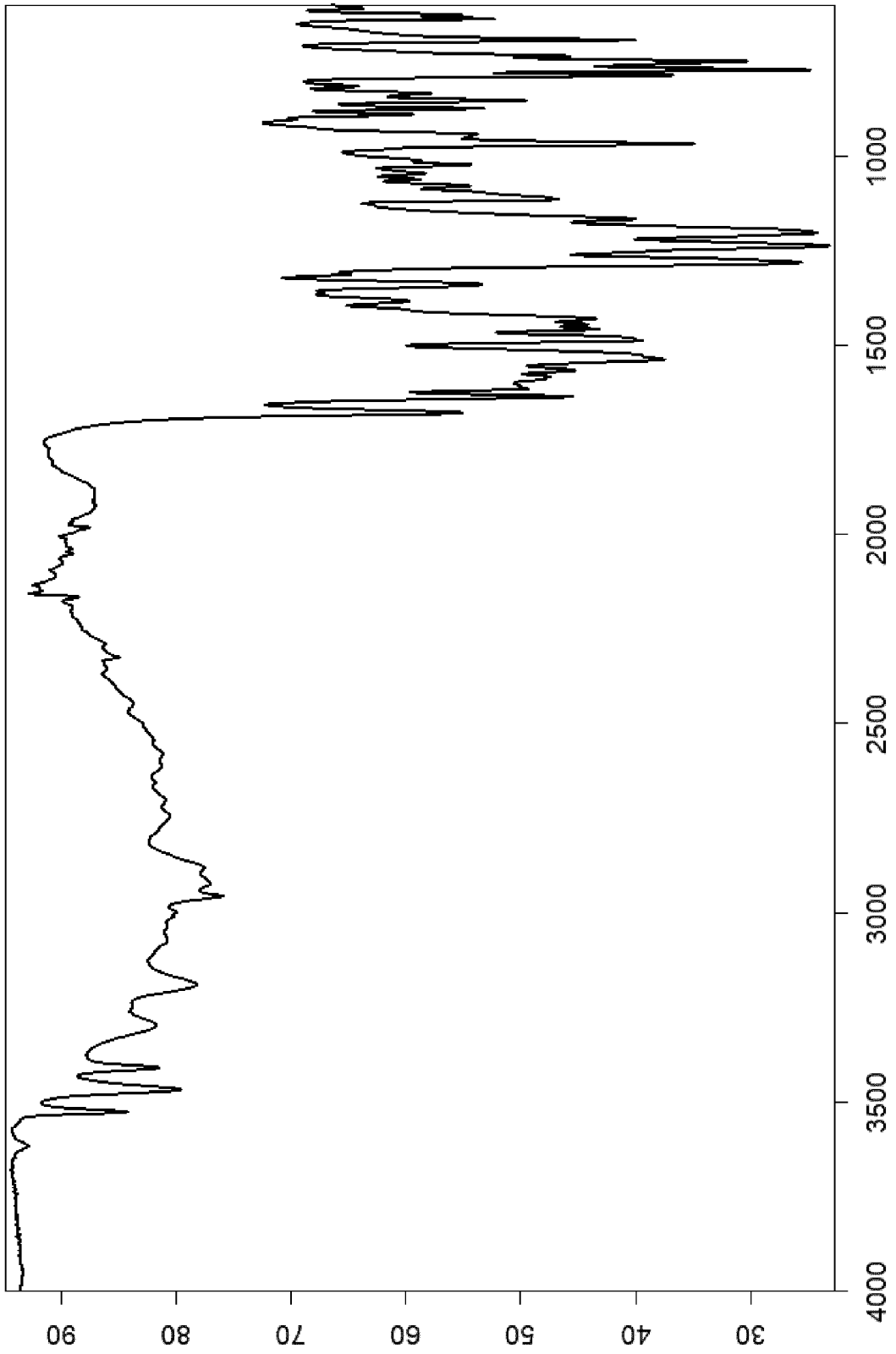

Figure 8

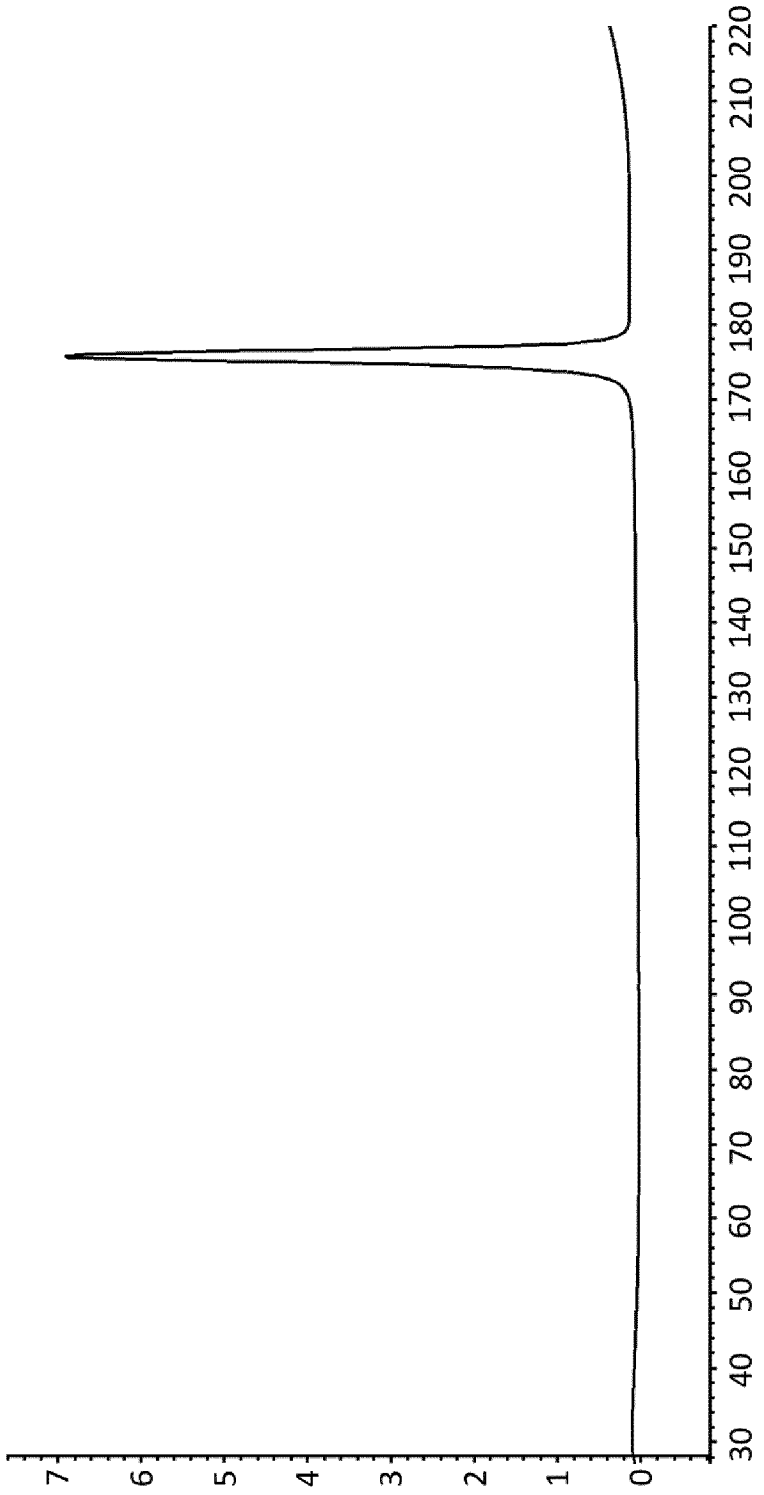
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Figure 9

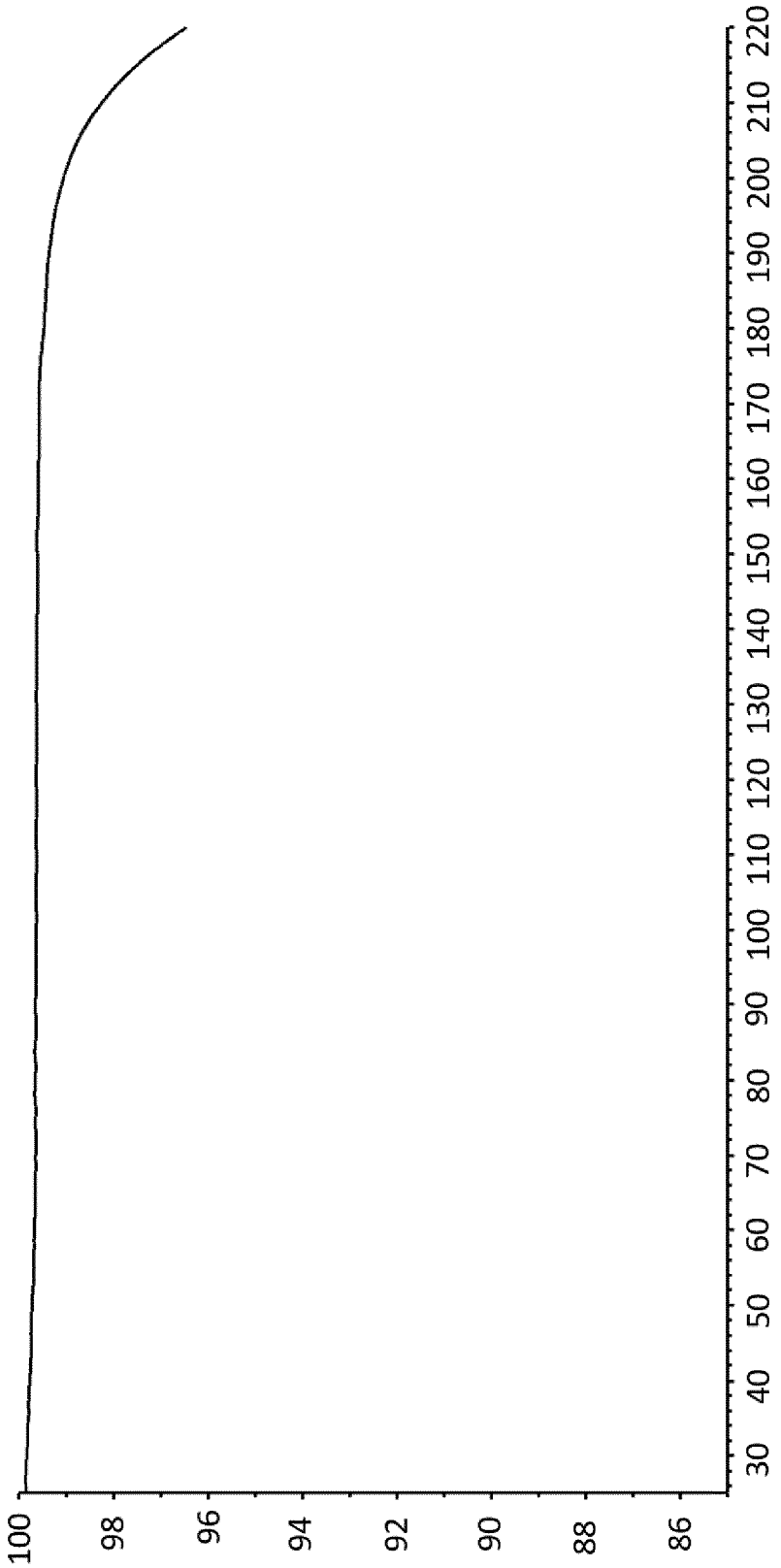
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Figure 10

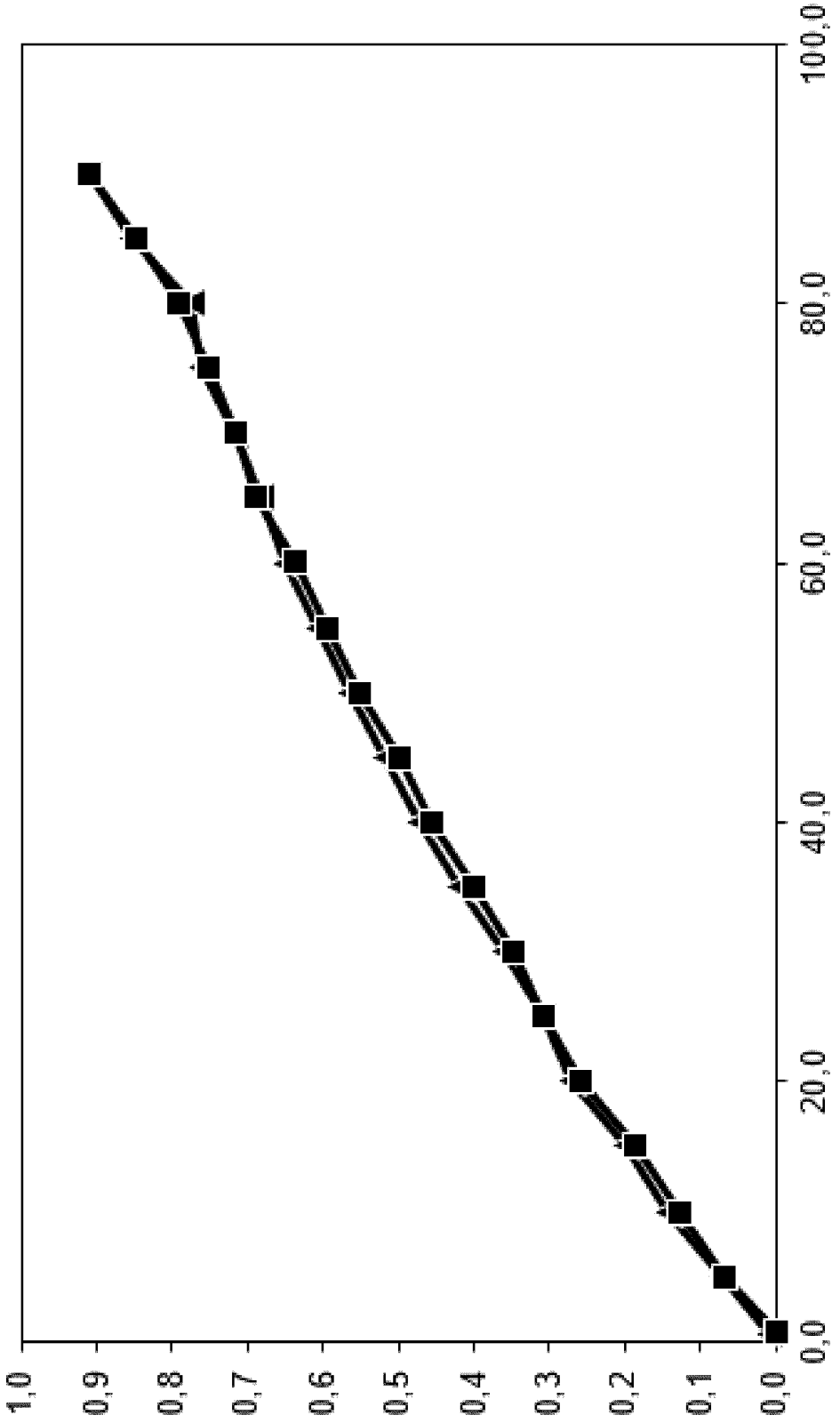


Figure 11

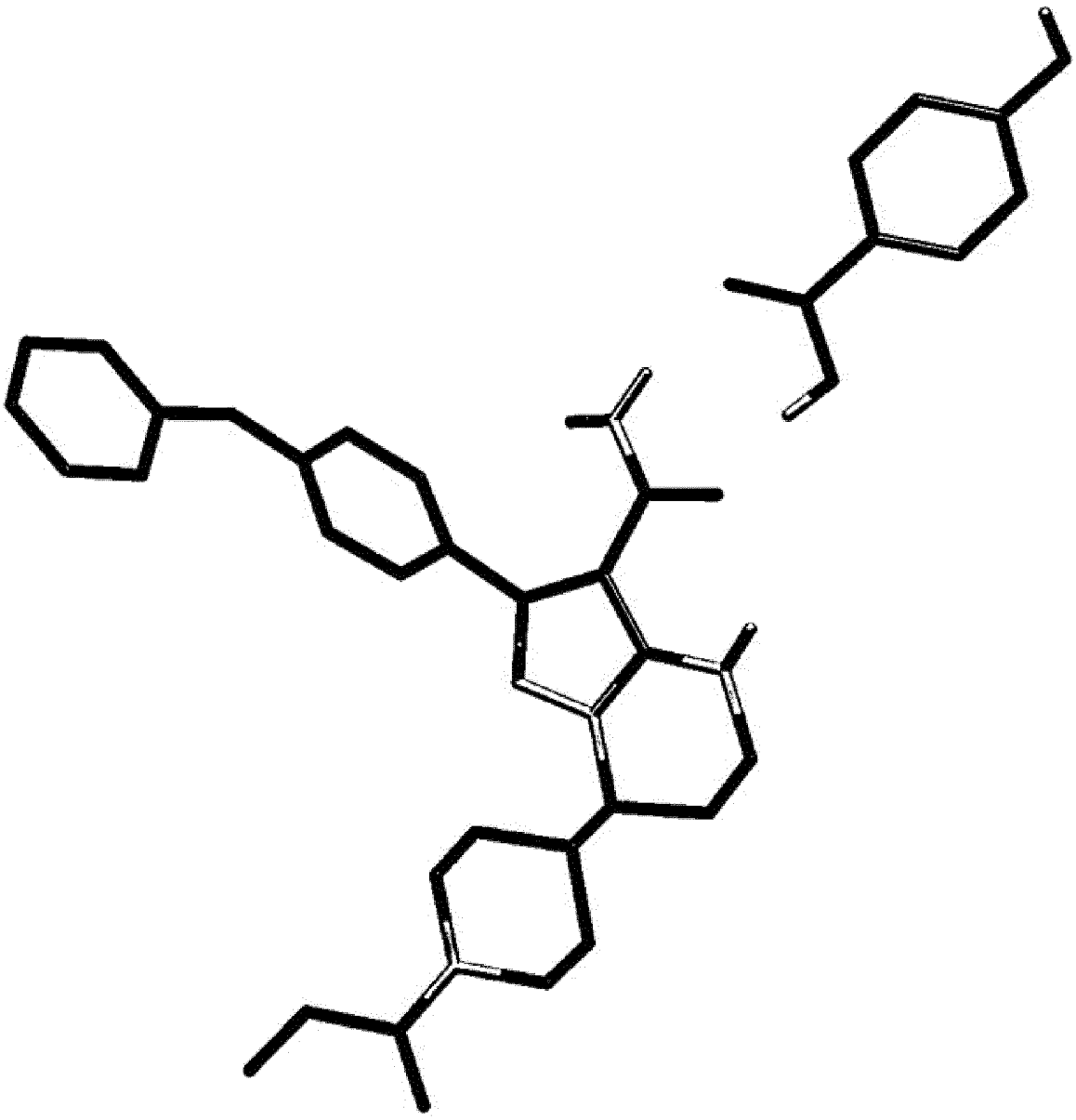


Figure 12

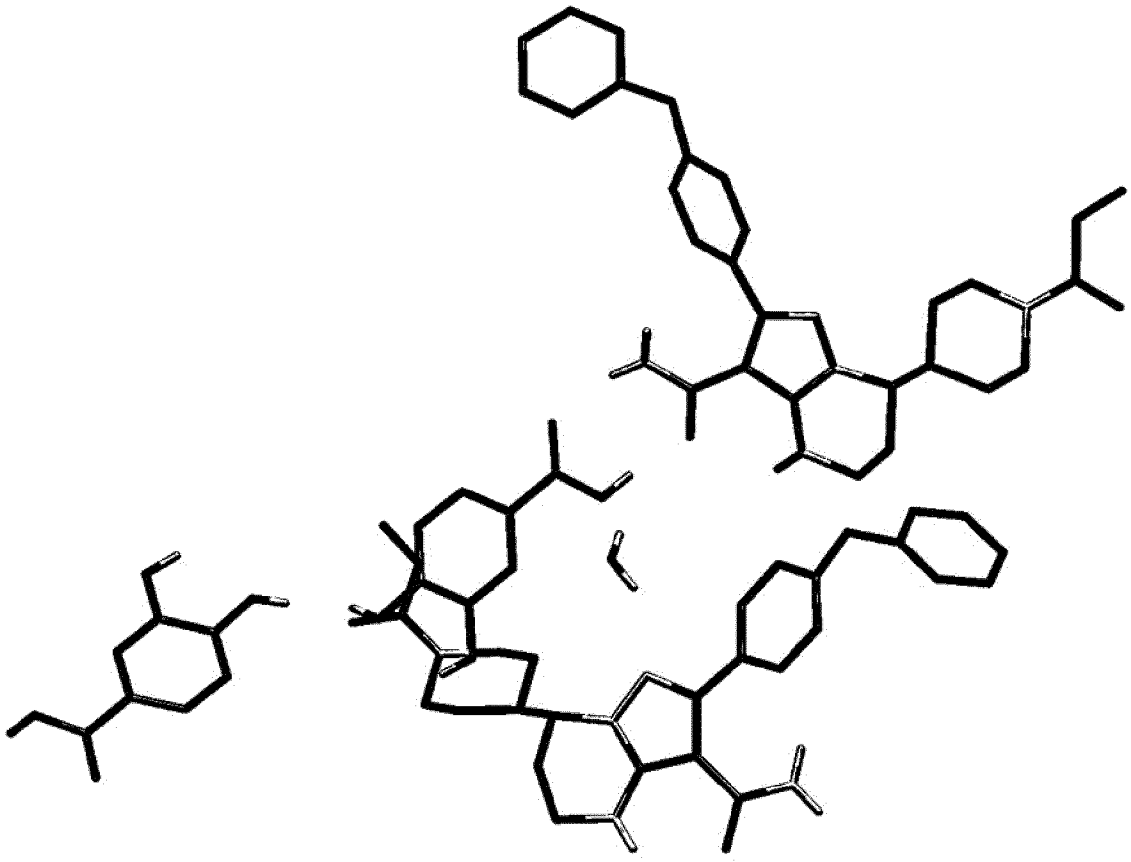


Figure 13

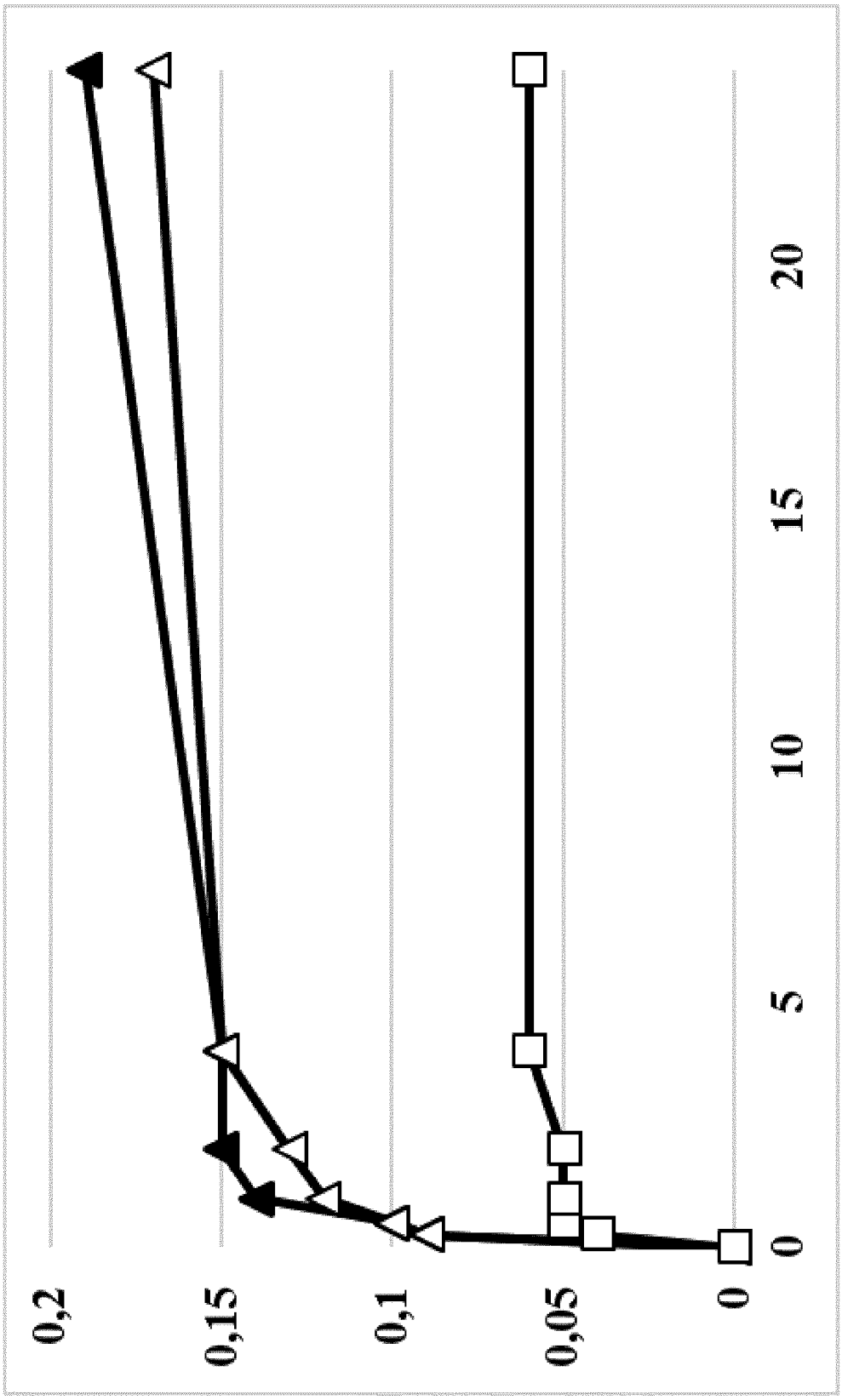


Figure 14

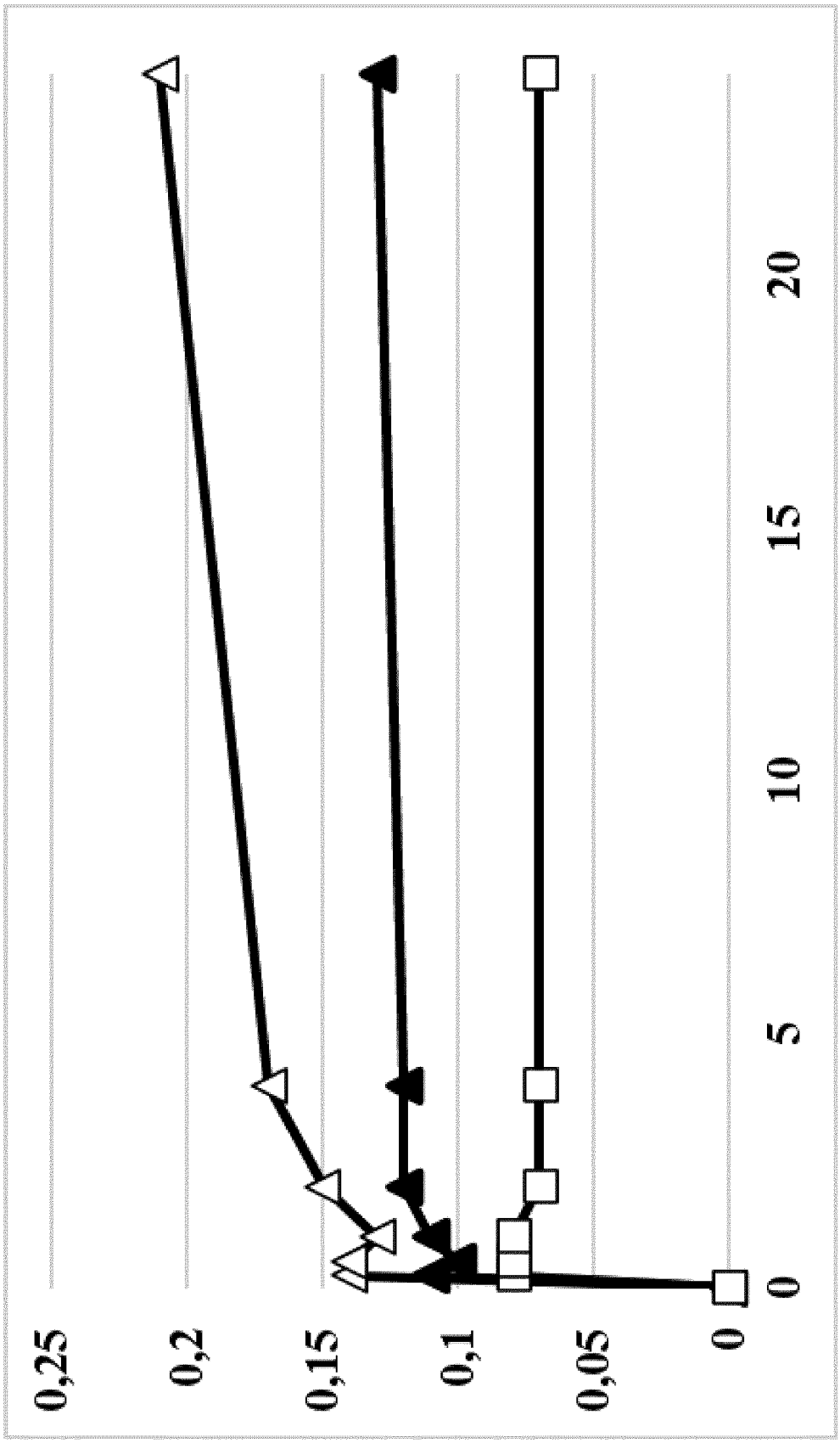


Figure 15

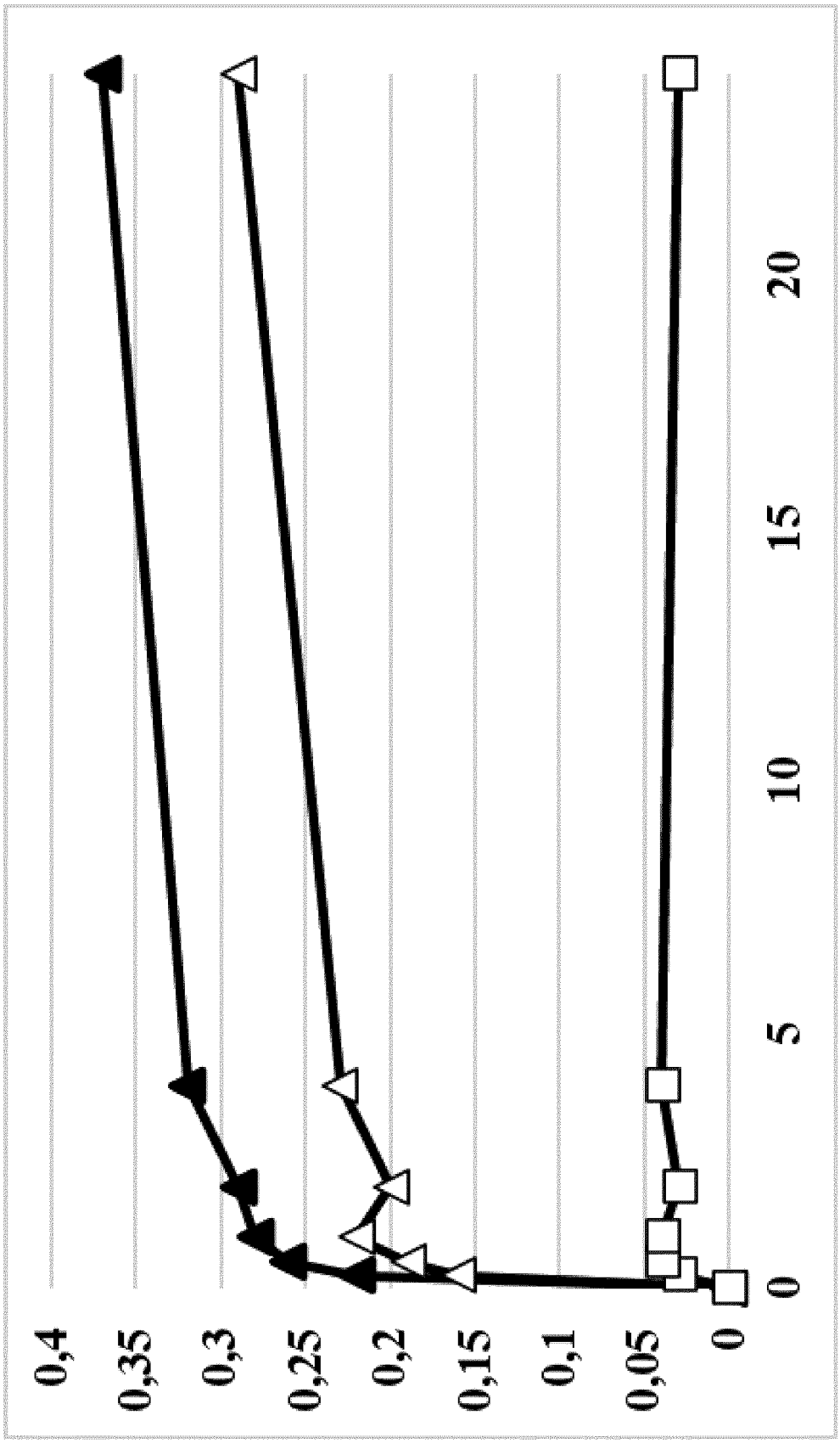
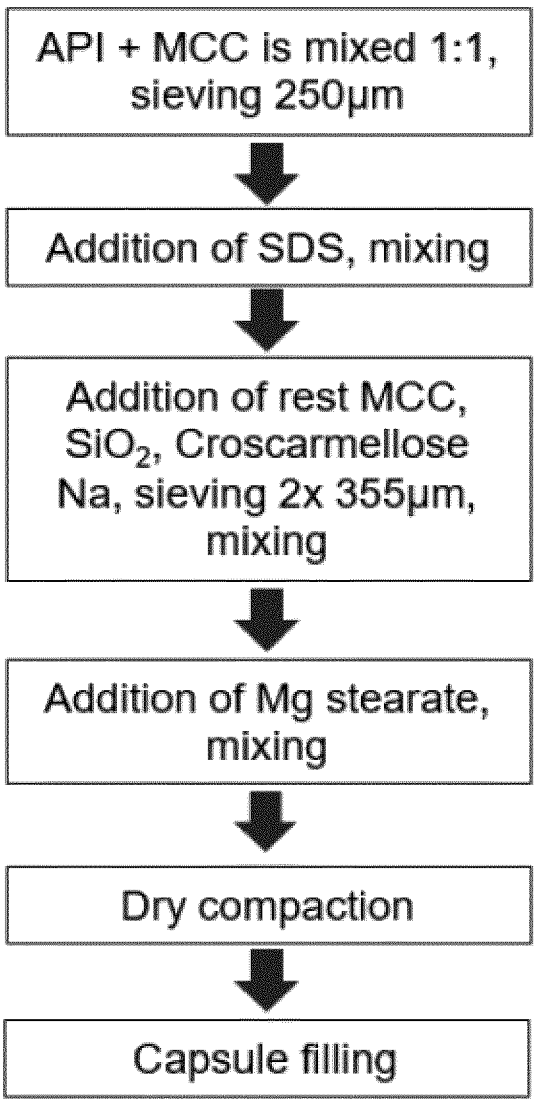


Figure 16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Addition of SDS, mixing
Addition of rest MCC, SiO_2, Croscarmellose Na, sieving 2x 355µm, mixing
Addition of Mg stearate, mixing
Dry compaction
Capsule filling

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/066261

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5517 A61P35/00
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/173289 A1 (GUO YUNHANG [CN]; BEIGENE LTD [GB]) 30 October 2014 (2014-10-30) cited in the application paragraphs [0044], [0083]; example 27 -----	1-19
X	WO 2018/033135 A1 (BEIGENE LTD; HU NAN [CN]) 22 February 2018 (2018-02-22) paragraph [0056]; compound 1 -----	1-19
A	WO 2018/033853 A2 (BEIGENE LTD; WANG ZHIWEI [CN]; GUO YUNHANG [CN]) 22 February 2018 (2018-02-22) cited in the application claim 1 -----	1-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2021	07/09/2021

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	Baston, Eckhard

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2021/066261

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