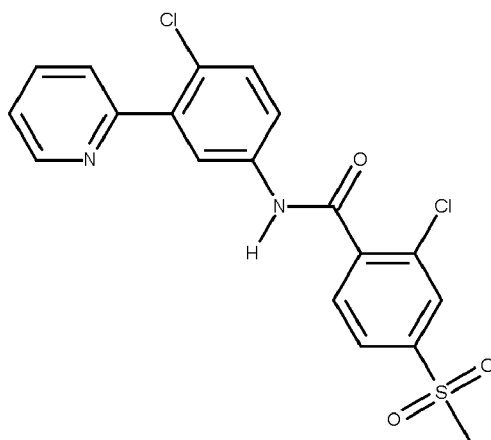




(43) International Publication Date
11 February 2016 (11.02.2016)

- (51) International Patent Classification:
C07D 213/40 (2006.01)
- (21) International Application Number:
PCT/EP2015/067822
- (22) International Filing Date:
3 August 2015 (03.08.2015)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
14180255.3 7 August 2014 (07.08.2014) EP
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- (81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report (Art. 21(3))

(54) Title: MULTI-COMPONENT CRYSTALS OF VISMODEGIB AND SELECTED CO-CRYSTAL FORMERS OR SOLVENTS



formula 1

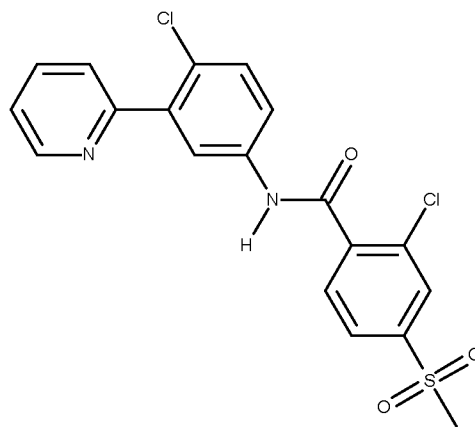
(57) Abstract: The present invention primarily relates to multi-component crystals comprising a compound of formula 1 and a second compound selected from the group consisting of co-crystal formers and solvents. The invention is further related to pharmaceutical compositions comprising such multi-component crystals. Furthermore, the invention relates to processes for preparing said multi-component crystals. The invention also relates to several aspects of using said multi-component crystals or pharmaceutical compositions to treat a disease.

Multi-component Crystals of Vismodegib and selected co-crystal formers or solvents

Description

Vismodegib was first disclosed in WO Patent Publication No. 06/028959. Vismodegib, chemically 2-Chloro-N-(4-chloro-3-pyridin-2-ylphenyl)-4-methylsulfonylbenzamide, is

5 represented by the following structure:



formula 1

Vismodegib is an active pharmaceutical ingredient produced by Genentech (Roche) and sold under the trade name Erivedge® (which contains crystalline Vismodegib as the active ingredient). Erivedge® is an oral Hedgehog signaling pathway inhibitor approved for the treatment of basal-cell carcinoma (BCC).

The present invention primarily relates to multi-component crystals comprising a compound of formula 1 (cf. above) and a second compound selected from the group consisting of co-crystal formers and solvents.

The invention is further related to pharmaceutical compositions comprising said multi-component crystals. Furthermore, the invention also relates to processes for preparing said multi-component crystals. The invention also relates to several aspects of using

said multi-component crystals or pharmaceutical compositions to treat a disease. Further details as well as further aspects of the present invention will be described herein below.

- 5 Vismodegib is a BCS class II compound with a high permeability but a low solubility where enhanced solubility or dissolution rates can lead to a significant advantage in respect to bio-availability.

Vismodegib is known to exist as crystalline free base. Salts of Vismodegib are mentioned in US 7,888,364 B2 but not specified. In particular, the HCl salt is mentioned as
10 intermediate but not characterized. Co-crystals or solvates are not reported at all.

The solubility of Vismodegib is reported to be 0.1 µg/mL at pH 7 and 0.99 mg/mL at pH 1 for Erivedge®. The absolute bio-availability after single dose is reported to be 31.8 %
15 and the ex-posure is not linear at single doses higher than 270 mg. Erivedge® capsules do not have a food label. The estimated elimination half-life (t_{1/2}) after continuous once-daily dosing is 4 days and 12 days after a single dose treatment (Highlights of Prescribing Information: ERIVEDGE® (vismodegib) capsule for oral use; Revised: 01/2012).

20

The discovery and preparation of new co-crystals or solvates offer an opportunity to improve the performance profile of a pharmaceutical product. It widens the reservoir of techniques/materials that a formulation scientist can use for designing a new dosage form of an active pharmaceutical ingredient (API) with improved characteristics. One of

the most important characteristics of an API such as Vismodegib is the bio-availability which is often determined by the aqueous solubility.

A compound like Vismodegib may give rise to a variety of crystalline forms having distinct crystal structures and physical characteristics like melting point, X-ray diffraction pattern, infrared spectrum, Raman spectrum and solid state NMR spectrum. One crystalline form may give rise to thermal behavior different from that of another crystalline form. Thermal behavior can be measured in the laboratory by such techniques as capillary melting point, thermogravimetry (TG), and differential scanning calorimetry (DSC) as well as content of solvent in the crystalline form, which have been used to distinguish polymorphic forms.

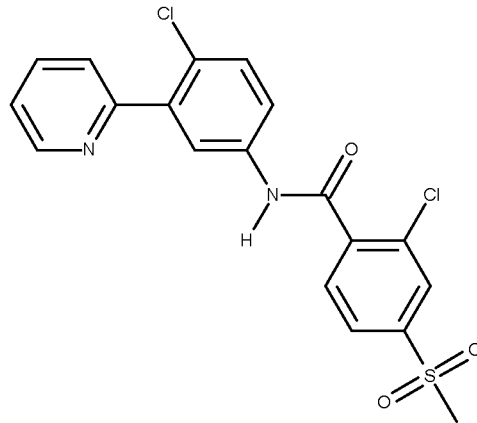
Multi-component crystals comprising Vismodegib and selected co-crystal formers or solvents may improve the dissolution kinetic profile and allow to control the hygroscopicity of Vismodegib.

Therefore, there is a need for multi-component crystals comprising Vismodegib that avoid the above disadvantages. In particular, it is an object of the present invention to provide multi-component crystals of Vismodegib with optimized manufacture, formulation, stability and/or biological efficacy.

Summary of the Invention

The invention provides novel multi-component crystals comprising a compound of formula 1 (INN: Vismodegib)

4



formula 1

and

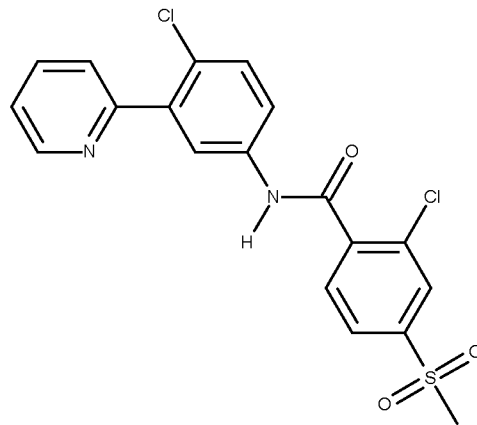
a second compound selected from the group consisting of co-crystal formers and sol-
5 vents.

Novel pharmaceutical compositions containing these multi-component crystals and
processes for manufacture of such multi-component crystals as well as aspects of us-
ing said multi-component crystals or compositions to treat a disease are also described
10 herein.

Detailed Description of the Invention

The present invention is directed to multi-component crystals comprising a compound
15 of formula 1 (INN: Vismodegib)

5



formula 1

and

a second compound selected from the group consisting of co-crystal formers and sol-
5 vents.

The herein disclosed solid forms (multi-component crystals comprising Vismodegib and selected co-crystal formers or solvents) give rise to advantages in comparison to Vismodegib with respect to solubility, dissolution rate, hygroscopicity, storage stability,
10 bioavailability, purity, purification etc. This means the new solid forms have higher solubility, higher dissolution rate, lower hygroscopicity, better storage stability, higher bioavailability, bioavailability with less variability, higher purity or better purification properties.

15 In the meaning of the present invention a co-crystal former is any compound in the solid state that forms a co-crystal with the compound of formula 1. Accordingly, in the meaning of the present invention a solvent is any compound in the liquid state.

Preferably, the co-crystal former is selected from the group consisting of maleic acid, N-cyclohexyl-sulfamic acid, sorbitol and xylitol. Preferably, the solvent is selected from the group consisting of benzylamine and triethanolamine.

- 5 Preferably, the multi-component crystals are characterized in that the molar ratio of Vismodegib to the second compound is in the range of from 3 : 1 to 1 : 3.

In a preferred embodiment, the second compound is maleic acid and a single multi-component crystal has a PXRD pattern with at least one, preferably more or all characteristic peak(s) (expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ (CuK α radiation)) selected from the follow-
10 teristic peak(s) located at 6.7, 10.7, 13.1, 15.8, 18.0, 19.5, 20.1, 20.4, 21.8, 22.3, 25.4, 26.1, 27.0, 27.4, 27.9, 28.3, 29.0, 29.3.

In another preferred embodiment, the second compound is N-cyclohexyl-sulfamic acid
15 and a single multi-component crystal has a PXRD pattern with at least one, preferably more or all characteristic peak(s) (expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ (CuK α radiation)) selected from the following peaks located at 7.9, 11.3, 12.1, 13.4, 15.8, 16.0, 16.8, 17.6, 18.6, 19.0, 19.9, 21.3, 21.7, 22.0, 24.6, 24.8, 26.1, 26.7 or selected from the following peaks located at 6.4, 12.8, 18.5, 19.2, 21.6, 26.0.

20

In another preferred embodiment, the second compound is sorbitol and a single multi-component crystal has a PXRD pattern with at least one, preferably more or all characteristic peak(s) (expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ (CuK α radiation)) selected from the follow-
ing peaks located at 9.8, 11.4, 12.1, 13.4, 16.0, 16.9, 17.4, 17.7, 18.1, 19.1, 19.5, 20.0,
25 21.5, 22.0, 24.7, 24.9, 26.1, 26.7.

In another further preferred embodiment, the second compound is xylitol and a single multi-component crystal has a PXRD pattern with at least one, preferably more or all characteristic peak(s) (expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ (CuK α radiation)) selected from the following peaks located at 9.7, 11.4, 12.1, 13.4, 16.0, 16.8, 17.4, 17.6, 18.0, 19.0, 19.8,
5 21.5, 22.0, 22.5, 23.7, 24.6, 24.8, 26.1, 26.7, 27.0, 31.5, 32.9.

In another preferred embodiment, the second compound is benzylamine and a single multi-component crystal has a PXRD pattern with at least one, preferably more or all characteristic peak(s) (expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ (CuK α radiation)) selected from the
10 following peaks located at 9.8, 11.3, 12.0, 13.5, 16.0, 16.7, 17.3, 17.6, 17.9, 18.9, 20.7, 21.5, 21.9, 22.7, 24.3, 24.7, 26.1, 26.8, 27.1, 28.3, 28.6.

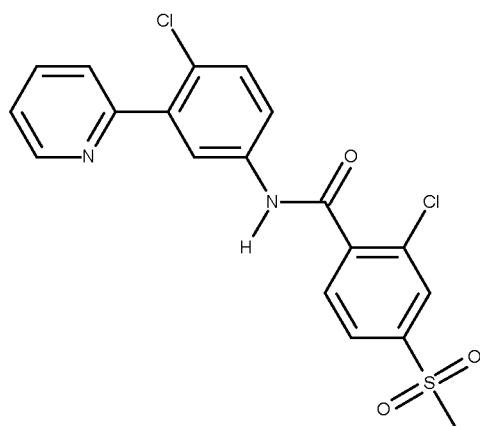
In yet another preferred embodiment, the second compound is triethanolamine and a single multi-component crystal has a PXRD pattern with at least one, preferably more
15 or all characteristic peak(s) (expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ (CuK α radiation)) selected from the following peaks located at 9.4, 10.7, 11.5, 12.1, 13.7, 14.3, 15.7, 16.0, 16.6, 17.3, 18.0, 18.9, 21.4, 22.2, 23.1, 23.9, 24.4, 25.6, 25.9, 27.3, 27.7, 28.4.

In a preferred embodiment of the present invention, the single multi-component crystal
20 is selected from those characterized above, with a PXRD pattern showing all characteristic peaks listed above for the specific crystal.

Another object of the invention is a process for obtaining multi-component crystals according to the invention (as described herein) comprising the steps of:

25 a) providing a compound of formula 1 (INN: Vismodegib)

8



formula 1

as a solid or in solution;

- b) adding maleic acid, N-cyclohexyl-sulfamic acid, sorbitol, xylitol, benzylamine or
5 triethanolamine to the compound/composition of step a);
- c) optionally concentrating the composition of step b) or adding an antisolvent to the
composition of step b);
- d) crystallizing;
- e) optionally evaporating to dryness or equilibrating the obtained suspension of step
10 d); and
- f) isolating the obtained precipitate.

In the meaning of the present invention, an antisolvent is a solvent that causes precipi-
tation when added to a solution in another solvent.

15

The multi-component crystals of the present invention are generally obtained as a fine
powder with typical particle size distributions with the median size between 0.1 and 100
 μm , preferably between 1 and 50 μm , preferably between 1 to 10 μm . This particle size

range ensures a fast dissolution profile, while retaining the favorable handling properties in the formulation process.

The multi-component crystals of the present invention may be used in pharmaceutical
5 compositions in the same way as other forms of Vismodegib previously known. Additionally, the present multi-component crystals may be employed as intermediates or starting materials to produce the pure active ingredient.

A further aspect of the present invention is a pharmaceutical composition comprising,
10 as active ingredient, multi-component crystals according to the present invention, preferably multi-component crystals as described herein above as being preferred, and preferably further comprising one, two, three, or more pharmaceutically acceptable carriers, and/or diluents, and/or further ingredients, in particular one, two, three, or more pharmaceutical excipients.

15

The amount of the multi-component crystals in the composition depends on the type of formulation and the desired dosage regimen during administration time periods. The Vismodegib amount in the multi-component crystals in each oral formulation may be from 0.1 to 500 mg, preferably from 20 to 250 mg, in particular from 50 to 200 mg.

20

Oral formulations (as preferred pharmaceutical compositions according to the present invention) may be solid formulations such as capsules, tablets, pills and troches, or a liquid suspension formulation.

The multi-component crystals according to the invention may be used directly in the form of powders, granules, suspensions, or they may be combined together with other pharmaceutically acceptable ingredients in admixing the components and optionally finely divide them, and then filling capsules, composed for example from hard or soft gelatin, compressing tablets, pills or troches, or suspend in suspensions. Coatings may be applied after compression to form pills.

Pharmaceutically acceptable ingredients are well known for the various types of formulation and may be for example binders such as natural or synthetic polymers, excipients, disintegrants, lubricants, surfactants, sweetening and other flavouring agents, coating materials, preservatives, dyes, thickeners, adjuvants, antimicrobial agents and carriers for the various formulation types.

Examples for binders are gum tragacanth, acacia, starch, gelatin, and biological degradable polymers such as homo- or co-polyesters of dicarboxylic acids, alkylene glycols, polyalkylene glycols and/or aliphatic hydroxyl carboxylic acids; homo- or copolyamides of dicarboxylic acids, alkylene diamines, and/or aliphatic amino carboxylic acids; corresponding polyester-polyamide-co-polymers, polyanhydrides, polyorthoesters, polyphosphazene and polycarbonates. The biological degradable polymers may be linear, branched or crosslinked. Specific examples are poly-glycolic acid, poly-lactic acid, and poly-d,l-lactide/glycolide. Other examples for polymers are water-soluble polymers such as polyoxaalkylenes (polyoxaethylene, polyoxapropylene and mixed polymers thereof, poly-acrylamides and hydroxylalkylated polyacrylamides, poly-maleic acid and esters or -amides thereof, poly-acrylic acid and esters or -amides thereof,

poly-vinylalcohol und esters or -ethers thereof, polyvinylimidazole, poly-vinylpyrrolidon, und natural polymers like chitosan, carragenan or hyaluronic acid.

Examples for excipients are phosphates such as dicalcium phosphate.

5

Examples for disintegrants are croscarmellose sodium, crospovidone, low-substituted hydroxypropyl cellulose, sodium starch glycolate or alginic acid.

Surfactants may be anionic, cationic, amphoteric or neutral. Examples for surfactants
10 are lecithin, phospholipids, octyl sulfate, decyl sulfate, dodecyl sulfate, tetradecyl sulfate, hexadecyl sulfate and octadecyl sulfate, Na oleate or Na caprate, 1-acylaminoethane-2-sulfonic acids, such as 1-octanoylaminoethane-2-sulfonic acid, 1-decanoylaminoethane-2-sulfonic acid, 1-dodecanoylaminoethane-2-sulfonic acid, 1-tetradecanoylaminoethane-2-sulfonic acid, 1-hexadecanoylaminoethane-2-sulfonic
15 acid, and 1-octadecanoylaminoethane-2-sulfonic acid, and taurocholic acid and taurodeoxycholic acid, bile acids and their salts, such as cholic acid, deoxycholic acid and sodium glycocholates, sodium caprate or sodium laurate, sodium oleate, sodium lauryl sulphate, sodium cetyl sulphate, sulfated castor oil and sodium dioctylsulfosuccinate, cocamidopropylbetaine and laurylbetaine, fatty alcohols, cholesterol, glycerol mono-
20 or -distearate, glycerol mono- or -dioleate and glycerol mono- or -dipalmitate, and polyoxyethylene stearate.

Examples for sweetening agents are sucrose, fructose, lactose or aspartam.

Examples for flavouring agents are peppermint, oil of wintergreen or fruit flavours like cherry or orange flavour.

5 Examples for coating materials are gelatin, wax, shellac, sugar or biological degradable polymers.

Examples for preservatives are methyl or propylparabens, sorbic acid, chlorobutanol, phenol and thimerosal.

10 Examples for adjuvants are fragrances.

Examples for thickeners are synthetic polymers, fatty acids and fatty acid salts and esters and fatty alcohols.

15 Examples for solid carriers are talc, clay, microcrystalline cellulose, lactose monohydrate, silica, alumina and the like.

The formulation according to the invention may also contain isotonic agents, such as sugars, buffers or sodium chloride.

20

The multi-component crystals of the present invention may also be formulated as effervescent tablet or powder, which can disintegrate in an aqueous environment to provide a drinking solution.

The most preferred route is oral administration. The dosages may be conveniently presented in a unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

5 Capsule dosages, of course, will contain the solid composition within a capsule which may be made of gelatin or other conventional encapsulating material. Tablets and powders may be coated. Tablets and powders may be coated with an enteric coating. The enteric coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl-cellulose phthalate, polyvinyl alcohol phthalate, carbox-
10 ymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

15

The multi-component crystals of the present invention and its formulations, respectively, can also be administered in combination with other therapeutic agents being effective to treat a given condition and/or to provide a combination therapy.

20 The multi-component crystals of the present invention and the respective pharmaceutical compositions are useful in the treatment of basal-cell carcinoma (BCC).

The multi-component crystals of the present invention may be used as single component or as mixtures with other solid forms, which may be crystalline or amorphous.

In view of the above, the present invention also relates to multi-component crystals of the present invention and pharmaceutical compositions according to the invention for use as a medicament, preferably for use in the treatment of cancer, in particular for use in the treatment of basal-cell carcinoma (BCC).

5

In the following, the present invention will be described more closely by way of selected examples illustrating the invention.

Wherever noted, in the following, room temperature depicts a temperature from the
10 range 22-25 °C, ambient temperature is defined as 25±10 °C and percentages are given by weight, if not indicated otherwise.

Abbreviations:

	DMSO	dimethyl sulfoxide
15	NMR	nuclear magnetic resonance (H-NMR denoting to proton NMR)
	TG	thermogravimetry
	r.h.	relative humidity (air, if not indicated otherwise)
	v/v	volume by volume
	PXRD	powder X-ray diffraction
20	DSC	differential scanning calorimetry

Instrumental:Powder X-ray diffraction:

The measurements were carried out with a Panalytical X'Pert Pro diffractometer (man-
5 ufacturer: Panalytical) using Cu K α radiation in the Bragg-Brentano reflection geome-
try. Generally, the 2θ values are accurate within an error of $\pm 0.1-0.2^\circ$. The relative peak
intensities can vary considerably for different samples of the same crystalline form be-
cause of different preferred orientations of the crystals. The samples were prepared
without any special treatment other than the application of slight pressure to get a flat
10 surface. Generally, silicon single crystal sample holders of 0.1 – 1.0 mm depth were
used. The tube voltage and current were 45 kV and 40 mA, respectively. Diffraction
patterns were recorded in the range from $2\theta=3^\circ-35^\circ$ with increments of 0.0167° . The
samples were rotated during the measurement.

15 Thermogravimetry:

Thermogravimetry is a well known method that allows monitoring the mass loss of a
given sample upon heating. Thermogravimetry was performed on a Seico TG/DTA
7200. The measurements were carried out with platinum crucibles under a nitrogen
atmosphere and at a heating rate of $10^\circ\text{C}/\text{min}$ over the range $30-410^\circ\text{C}$ or below.

Differential scanning calorimetry (DSC):

DSC was performed on a Mettler Toledo DSC 823e module. The sample was placed in crimped but vented aluminium pans. The heating rate was 10 °C per minute and the samples were exposed to a nitrogen stream of 150 mL/min.

5

¹H-NMR:

The ¹H-NMR spectra were recorded on a Bruker DRX 500 spectrometer using deuterated solvents.

10 Solvents: For all experiments, standard grade solvents are used.

Examples:**Vismodegib Maleic Acid Co-Crystal 1:2**

15

The Vismodegib maleic acid co-crystal 1:2 is prepared from Vismodegib and maleic acid. The PXRD pattern is displayed in Figure 1. Characteristic PXRD peaks (expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$; Cu K α radiation) are observed at 6.7, 13.1, 15.8, 19.5, 27.0, especially at 6.7, 10.7, 13.1, 15.8, 18.0, 19.5, 20.1, 20.4, 21.8, 22.3, 25.4, 26.1, 27.0, 27.4, 27.9, 28.3, 29.0, 29.3. The PXRD pattern complies with the result of the single crystal structure (Table 1). The co-crystal crystallizes in the monoclinic space group *P2*₁. The stoichiometry of the co-crystal can be proven by the crystal structure. The crystal structure also shows that no protonation/deprotonation is present. Unit cell dimensions are shown in Table 1.

25 Table 1: Crystallographic data for Vismodegib maleic acid co-crystal 1:2.

crystal system	monoclinic
space group	$P2_1$
a (Å)	5.05640(10)
b (Å)	26.1914(6)
c (Å)	10.7941(3)
α (°)	90.00
β (°)	102.1710(10)
γ (°)	90.00
V (Å ³)	1397.38(6)
Z	2
T (K)	100(2)
ρ_{calc} (g/cm ³)	1.553
μ (mm ⁻¹)	3.375
λ (Å)	1.54178
reflections collected	9031
θ range (°)	3.37 – 58.97
unique reflns	3384
largest diff peak and hole (eÅ ⁻³)	0.364 / -0.255

Example 1:

314 mg Vismodegib and 86 mg maleic acid are suspended in toluene saturated with
5 maleic acid for 2 d, filtered and dried.

TG data shows a mass loss of about 2.3 wt % between 100 and 118 °C which is attributed to rest solvent. DSC data shows a single endothermal peak with an onset of about 115 °C (99 J/g).

- 5 H-NMR spectroscopy indicates a molar ratio of Vismodegib to maleic acid of about 1:1.3. However single crystal X-ray data confirms a ratio of 1:2 (Table 1).

Example 2:

- 10 200 mg Vismodegib and 110 mg maleic acid are suspended in 3 mL ethyl acetate, stirred, heated to 75 °C and kept at this temperature for 1 h. The temperature is decreased by about 10 °C/min. The solid is filtered and dried.

Yield: about 170 mg (about 55 %).

TG data shows no mass loss up to 120 °C where decomposition starts.

15

Example 3:

- 500 mg Vismodegib and 275 mg maleic acid are suspended in 3 mL ethyl acetate, stirred, heated to 75 °C and kept at this temperature for 1 h. The temperature is decreased by about 10 °C/min. The solid is filtered and dried.

20

Yield: about 552 mg (about 55 %).

H-NMR spectroscopy indicates a molar ratio of Vismodegib to maleic acid of about 1:2.

TG data shows no mass loss up to 120 °C where decomposition starts. DSC data shows a first endothermal peak with an onset of about 126 °C (138 J/g).

25

Vismodegib N-Cyclohexyl-sulfamic Acid Co-Crystals

Two forms of Vismodegib N-cyclohexyl-sulfamic acid co-crystals can be prepared.

a) Vismodegib N-Cyclohexyl-sulfamic Acid Co-Crystal Form A

5

The Vismodegib N-cyclohexyl-sulfamic acid co-crystal form A, ratio 1:1 is prepared from Vismodegib and N-cyclohexyl-sulfamic acid.

The PXRD pattern is displayed in Figure 2. Characteristic PXRD peaks (expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$; Cu K α radiation) are observed at 13.4, 16.8, 22.0, 24.8, 26.1 especially
10 at 7.9, 11.3, 12.1, 13.4, 15.8, 16.0, 16.8, 17.6, 18.6, 19.0, 19.9, 21.3, 21.7, 22.0, 24.6, 24.8, 26.1, 26.7.

Single crystals of Vismodegib N-cyclohexyl-sulfamic acid co-crystal form A are obtained. The stoichiometry of the co-crystal can be proven by the crystal structure.

15 Example 4:

281 mg VIS and 219 mg N-cyclohexyl-sulfamic acid are suspended in saturated N-cyclohexyl-sulfamic acid solution in toluene for 2 d, filtered and dried.

H-NMR spectroscopy indicates a molar ratio of Vismodegib to N-cyclohexyl-sulfamic
20 acid of about 1:1.

TG data shows a mass loss of about 3.3 wt % between room temperature and 130 °C.

DSC data shows a first endothermal event with an onset of about 123 °C (95 J/g).

b) Vismodegib N-Cyclohexyl-sulfamic Acid Co-Crystal Form B

25

The Vismodegib N-cyclohexyl-sulfamic acid co-crystal form B is prepared from Vismodegib and N-cyclohexyl-sulfamic acid.

The PXRD pattern is displayed in Figure 3. Characteristic PXRD peaks (expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$; Cu K α radiation) are observed at 6.4, 12.8, 18.5, 19.2, 21.6, 26.0.

- 5 Single crystals of Vismodegib N-cyclohexyl-sulfamic acid co-crystal form B are obtained. The stoichiometry of the co-crystal can be proven by the crystal structure.

Example 5:

- 10 200 mg Vismodegib and 170 mg N-cyclohexyl-sulfamic acid are suspended in 3 mL ethyl acetate and stirred at 75 °C for 24 h. The temperature is decreased by about 10 °C/min. The solid is filtered and dried.

Yield: about 212 mg

15

Vismodegib Sorbitol Co-Crystal 1:1

The Vismodegib sorbitol co-crystal 1:1 is prepared from Vismodegib and sorbitol.

- 20 The PXRD pattern is displayed in Figure 4. Characteristic PXRD peaks (expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$; Cu K α radiation) are observed at 13.4, 16.0, 16.9, 21.5, 22.0, especially at 9.8, 11.4, 12.1, 13.4, 16.0, 16.9, 17.4, 17.7, 18.1, 19.1, 19.5, 20.0, 21.5, 22.0, 24.7, 24.9, 26.1, 26.7. Single crystals of Vismodegib sorbitol co-crystal 1:1 are obtained. The stoichiometry of the co-crystal can be proven by the crystal structure.

25

Example 6:

280 mg VIS and 120 mg sorbitol are suspended in toluene for 2 d, filtered and dried.

H-NMR spectroscopy indicates a molar ratio of Vismodegib to sorbitol of about 1:1.

- 5 TG data shows a mass loss of about 7 wt % (0.5 mol toluene) between 100 and 160 °C. DSC data shows a first endothermal peak with an onset of about 96 °C (49 J/g) and further endothermal peaks at onset points of 156 °C (35 J/g) and 181 °C (58 J/g).

Vismodegib Xylitol Co-Crystal 1:1

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The Vismodegib xylitol co-crystal 1:1 is prepared from Vismodegib and xylitol.

The PXRD pattern is displayed in Figure 5. Characteristic PXRD peaks (expressed in $2\theta \pm 0.2^\circ 2\theta$; Cu K α radiation) are observed at 9.7, 13.4, 16.0, 21.5, 24.6, especially at

- 15 9.7, 11.4, 12.1, 13.4, 16.0, 16.8, 17.4, 17.6, 18.0, 19.0, 19.8, 21.5, 22.0, 22.5, 23.7,

24.6, 24.8, 26.1, 26.7, 27.0, 31.5, 32.9.

Single crystals of Vismodegib xylitol co-crystal 1:1 are obtained. The stoichiometry of the co-crystal can be proven by the crystal structure.

Example 7:

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294 mg VIS and 106 mg xylitol are suspended in toluene for 2 d, filtered and dried.

H-NMR spectroscopy indicates a molar ratio of Vismodegib to xylitol of about 1:1.

TG data shows a mass loss of about 7 wt % (0.5 mol toluene) between 100 and 150 °C. DSC data shows a first endothermal peak with an onset of about 92 °C (52 J/g) and further endothermal peaks at onset points of 155 °C (31 J/g) and 178 °C (55 J/g).

5 Vismodegib Benzylamine Solvate 2:1

The Vismodegib benzylamine solvate 2:1 is prepared from suspension of Vismodegib in benzylamine.

The PXRD pattern is displayed in Figure 6. Characteristic PXRD peaks (expressed in $2\theta \pm 0.2^\circ 2\theta$; Cu K α radiation) are observed at 9.8, 13.5, 16.0, 18.9, 21.9, 24.7, especially at 9.8, 11.3, 12.0, 13.5, 16.0, 16.7, 17.3, 17.6, 17.9, 18.9, 20.7, 21.5, 21.9, 22.7, 24.3, 24.7, 26.1, 26.8, 27.1, 28.3, 28.6. The PXRD pattern complies with the result of the single crystal structure (Table 2).

Single crystals of Vismodegib benzylamine solvate 2:1 are obtained. The co-crystal crystallizes in the monoclinic space group $P2_1$. Unit cell dimensions are shown in Table 2. The stoichiometry of the solvate can be proven by the crystal structure.

Table 2: Crystallographic data for Vismodegib benzylamine solvate 2:1.

crystal system	monoclinic
space group	$P2_1$
a (Å)	11.5307(14)
b (Å)	10.1979(13)
c (Å)	18.314(2)
α (°)	90.00

β (°)	101.670(4)
γ (°)	90.00
V (Å ³)	2109.0(4)
Z	4
T (K)	100(2)
ρ_{calc} (g/cm ³)	1.554
μ (mm ⁻¹)	3.976
λ (Å)	1.54178
reflns collected	12354
θ range (°)	3.91 – 63.42
unique reflns	2865
largest diff peak and hole (eÅ ⁻³)	-0.672 / -0.500

Example 8:

- 200 mg Vismodegib are suspended in 0.25 mL benzylamine and stirred for 3 days at
- 5 room temperature, filtered and dried in vacuum.
- H-NMR spectroscopy indicates a molar ratio of Vismodegib to benzylamine of about
- 2:1.
- TG data shows a mass loss of about 11.4 % between 100 and 170 °C (theoretical ben-
- zylamine content 11.3 %). DSC data in a closed sample pan shows a first endothermal
- 10 peak with an onset of about 151 °C (72 J/g).

Example 9:

200 mg Vismodegib are suspended in 255 mg benzylamine and 1 mL heptane and stirred at 50 °C for 28 h. The temperature is decreased by about 10 °C/min. The solid
5 is filtered and dried.

TG data shows a mass loss of about 10.8 % between 100 and 170 °C (theoretical benzylamine content 11.3 %). DSC data in a closed sample pan shows a first endothermal peak with an onset of about 150 °C (96 J/g).

10 Example 10:

260 mg Vismodegib are suspended in 434 mg benzylamine and 2 mL heptane and stirred at 50°C for 24 h, temperature cycled between 25 and 50 °C for 5 days, filtered and dried in vacuum.

15

Vismodegib Triethanolamine Solvate

The Vismodegib triethanolamine solvate can be prepared from Vismodegib and triethanolamine.

20 The PXRD pattern is displayed in Figure 7. Characteristic PXRD peaks (expressed in $2\theta \pm 0.2^\circ 2\theta$; Cu K α radiation) are observed at 9.4, 11.5, 21.4, 23.9, 25.9, especially at 9.4, 10.7, 11.5, 12.1, 13.7, 14.3, 15.7, 16.0, 16.6, 17.3, 18.0, 18.9, 21.4, 22.2, 23.1, 23.9, 24.4, 25.6, 25.9, 27.3, 27.7, 28.4.

Single crystals of Vismodegib triethanolamine solvate are obtained. The stoichiometry
25 of the solvate can be proven by the crystal structure.

Example 11:

300 mg Vismodegib are suspended in 730 mg triethanolamine and 1 mL acetone and stirred at room temperature for 14 days, filtered and dried.

- 5 H-NMR spectroscopy indicates a molar ratio of Vismodegib to triethanolamine of about 1:0.9.

TG data shows a mass loss of about 2.1 % between room temperature and 100 °C and no further significant weight loss up to 150°C. DSC data in a closed sample pan shows a first endothermic peak with an onset of about 135 °C (77 J/g).

Brief description of Figures:

Figure 1: PXRD pattern of Vismodegib maleic acid co-crystal 1:2; Cu K α radiation.

- 5 Figure 2: PXRD pattern of Vismodegib N-cyclohexyl-sulfamic acid co-crystal form A;
Cu K α radiation.

Figure 3: PXRD pattern of Vismodegib N-cyclohexyl-sulfamic acid co-crystal form B;
Cu K α radiation.

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Figure 4: PXRD pattern of Vismodegib sorbitol co-crystal 1:1; Cu K α radiation.

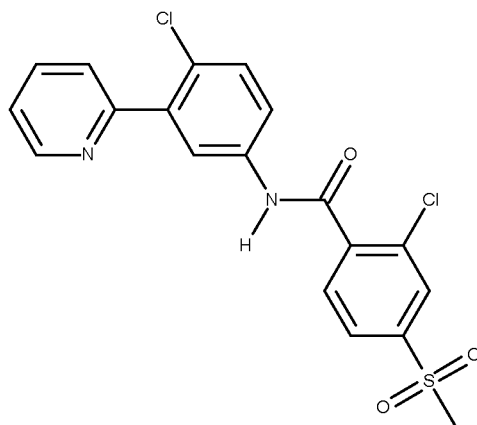
Figure 5: PXRD pattern of Vismodegib xylitol co-crystal 1:1; Cu K α radiation.

- 15 Figure 6: PXRD pattern of Vismodegib benzylamine co-crystal 2:1; Cu K α radiation.

Figure 7: PXRD pattern of Vismodegib triethanolamine co-crystal; Cu K α radiation.

Claims

1. Multi-component crystals comprising a compound of formula 1, also known as Vismodegib,



formula 1

5 and

a second compound selected from the group consisting of co-crystal formers and solvents.

10 2. Multi-component crystals according to claim 1, characterized in that the co-crystal former is selected from the group consisting of maleic acid, N-cyclohexyl-sulfamic acid, sorbitol and xylitol.

3. Multi-component crystals according to claim 1, characterized in that the solvent is
15 selected from the group consisting of benzylamine and triethanolamine.

4. Multi-component crystals according to any of claims 1 to 3, characterized in that the molar ratio of Vismodegib to the second compound is in the range of from 3 : 1 to 1 : 3.

5. Multi-component crystals according to any of claims 1, 2 or 4, characterized in that the second compound is maleic acid and the multi-component crystal has a PXRD pattern with at least one characteristic peak, expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ using $\text{CuK}\alpha$ radiation, selected from the following peaks located at 6.7, 10.7, 13.1, 15.8, 18.0, 19.5, 20.1, 20.4, 21.8, 22.3, 25.4, 26.1, 27.0, 27.4, 27.9, 28.3, 29.0, 29.3.
6. Multi-component crystals according to any of claims 1, 2 or 4, characterized in that the second compound is N-cyclohexyl-sulfamic acid and the multi-component crystal has a PXRD pattern with at least one characteristic peak, expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ using $\text{CuK}\alpha$ radiation, selected from the following peaks located at 7.9, 11.3, 12.1, 13.4, 15.8, 16.0, 16.8, 17.6, 18.6, 19.0, 19.9, 21.3, 21.7, 22.0, 24.6, 24.8, 26.1, 26.7.
7. Multi-component crystals according to any of claims 1, 2 or 4, characterized in that the second compound is N-cyclohexyl-sulfamic acid and the multi-component crystal has a PXRD pattern with at least one characteristic peak, expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ using $\text{CuK}\alpha$ radiation, selected from the following peaks located 6.4, 12.8, 18.5, 19.2, 21.6, 26.0.
8. Multi-component crystals according to any of claims 1, 2 or 4, characterized in that the second compound is sorbitol and the multi-component crystal has a PXRD pattern with at least one characteristic peak, expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ using $\text{CuK}\alpha$ radiation, selected from the following peaks located at 9.8, 11.4, 12.1, 13.4, 16.0, 16.9, 17.4, 17.7, 18.1, 19.1, 19.5, 20.0, 21.5, 22.0, 24.7, 24.9, 26.1, 26.7.

9. Multi-component crystals according to any of claims 1, 2 or 4, characterized in that the second compound is xylitol and the multi-component crystal has a PXRD pattern with at least one characteristic peak, expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ using $\text{CuK}\alpha$ radiation, selected from the following peaks located at 9.7, 11.4, 12.1, 13.4, 16.0, 16.8, 17.4,
5 17.6, 18.0, 19.0, 19.8, 21.5, 22.0, 22.5, 23.7, 24.6, 24.8, 26.1, 26.7, 27.0, 31.5, 32.9.

10. Multi-component crystals according to any of claims 1, 3 or 4, characterized in that the second compound is benzylamine and the multi-component crystal has a PXRD pattern with at least one characteristic peak, expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ using
10 $\text{CuK}\alpha$ radiation, selected from the following peaks located at 9.8, 11.3, 12.0, 13.5, 16.0, 16.7, 17.3, 17.6, 17.9, 18.9, 20.7, 21.5, 21.9, 22.7, 24.3, 24.7, 26.1, 26.8, 27.1, 28.3, 28.6.

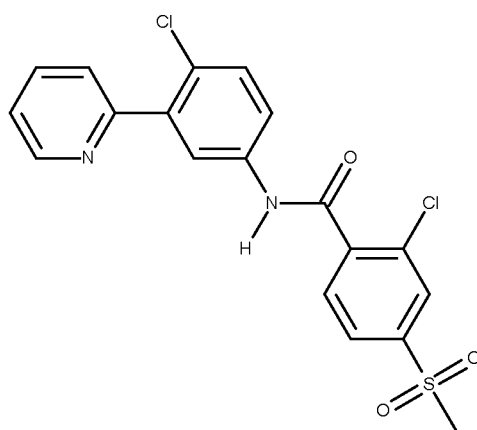
11. Multi-component crystals according to any of claims 1, 3 or 4, characterized in
15 that the second compound is triethanolamine and the multi-component crystal has a PXRD pattern with at least one characteristic peak, expressed in $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ using $\text{CuK}\alpha$ radiation, selected from the following peaks located at 9.4, 10.7, 11.5, 12.1, 13.7, 14.3, 15.7, 16.0, 16.6, 17.3, 18.0, 18.9, 21.4, 22.2, 23.1, 23.9, 24.4, 25.6, 25.9, 27.3, 27.7, 28.4.

20

12. Pharmaceutical composition comprising, as active ingredient, multi-component crystals according to any of claims 1 to 11, and preferably further comprising one, two, three, or more pharmaceutically acceptable carriers, and/or diluents, and/or further ingredients, in particular one, two, three, or more pharmaceutical excipients.

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13. Pharmaceutical composition according to claim 12, wherein the total amount of Vismodegib in the multi-component crystals in the composition is in the range from 0.1 to 500 mg, preferably from 20 to 250 mg, in particular from 50 to 200 mg.
- 5 14. Multi-component crystals according to any of claims 1 to 11, or pharmaceutical composition according to any of claims 12 to 13, for use as a medicament, preferably for use in the treatment of cancer, in particular for use in the treatment of basal-cell carcinoma.
- 10 15. A process for obtaining multi-component crystals according to at least one of claims 1 to 11 comprising the steps of:
- a) providing a compound of formula 1, also known as Vismodegib,



formula 1

- 15 as a solid or in solution;
- b) adding maleic acid, N-cyclohexyl-sulfamic acid, sorbitol, xylitol, benzylamine or triethanolamine to the compound/composition of step a);
- c) optionally concentrating the composition of step b) or adding an antisolvent to the composition of step b);

- d) crystallizing;
- e) optionally evaporating to dryness or equilibrating the obtained suspension of step d); and
- f) isolating the obtained precipitate.

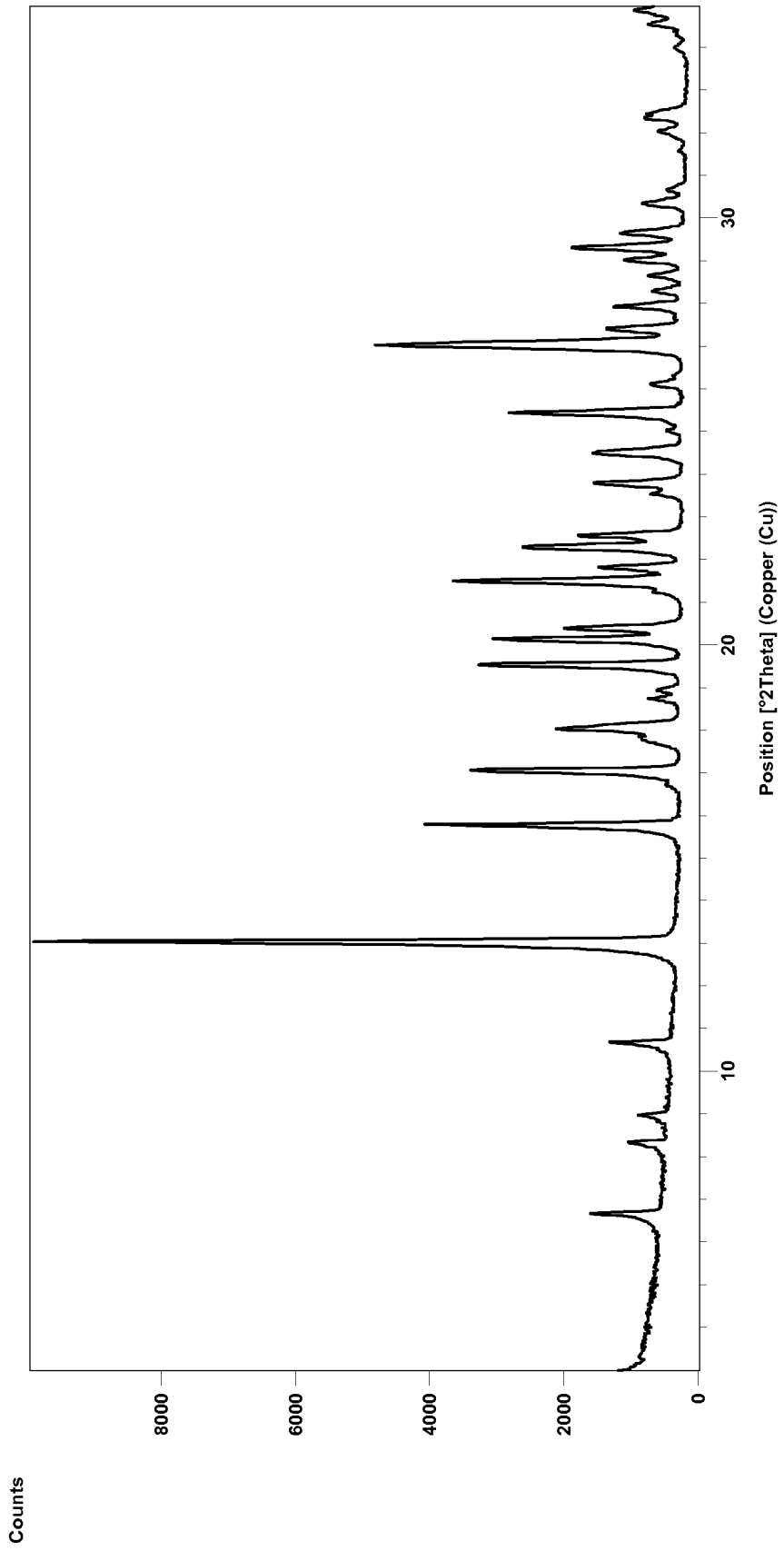


Fig. 1

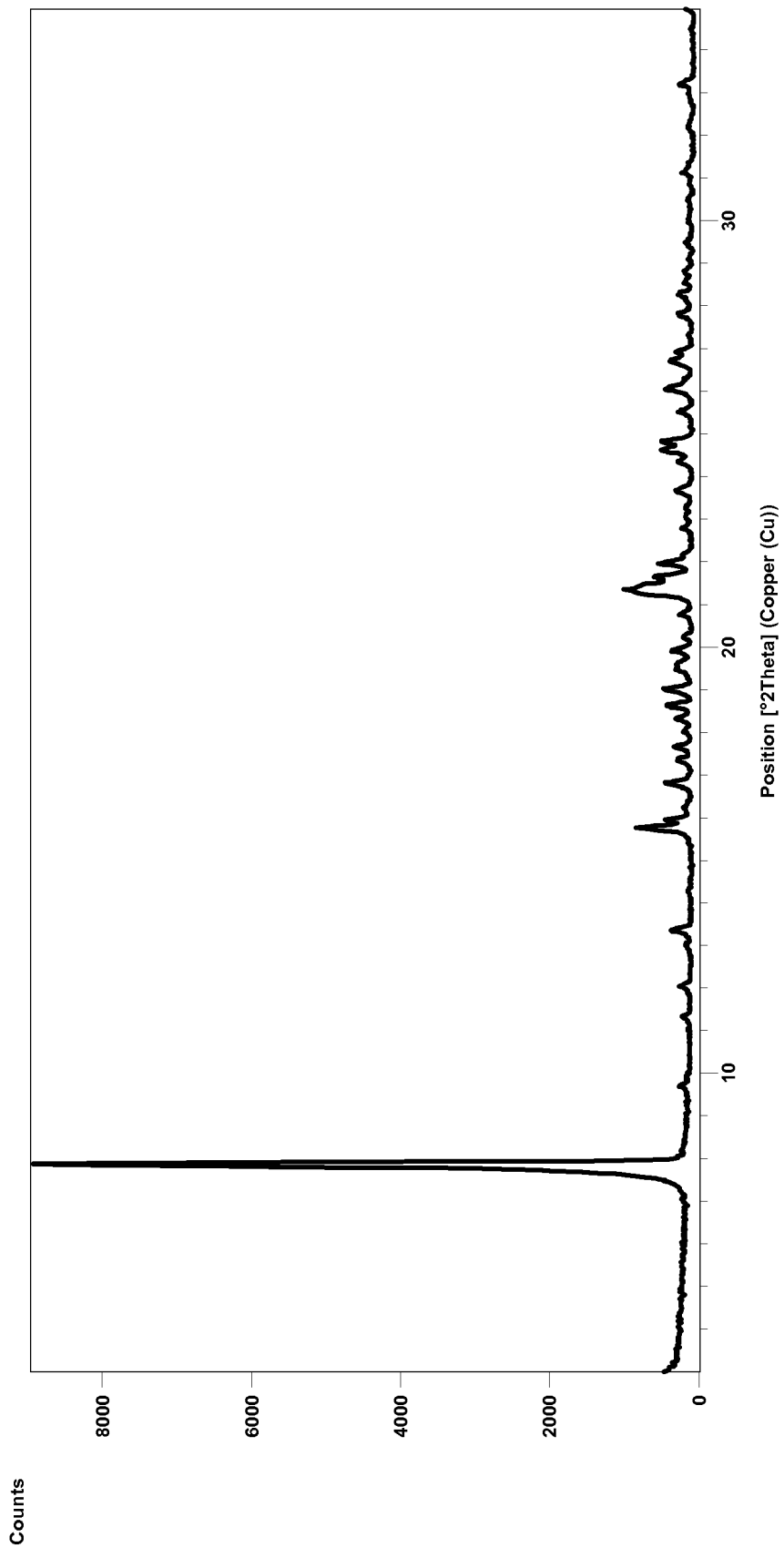


Fig. 2

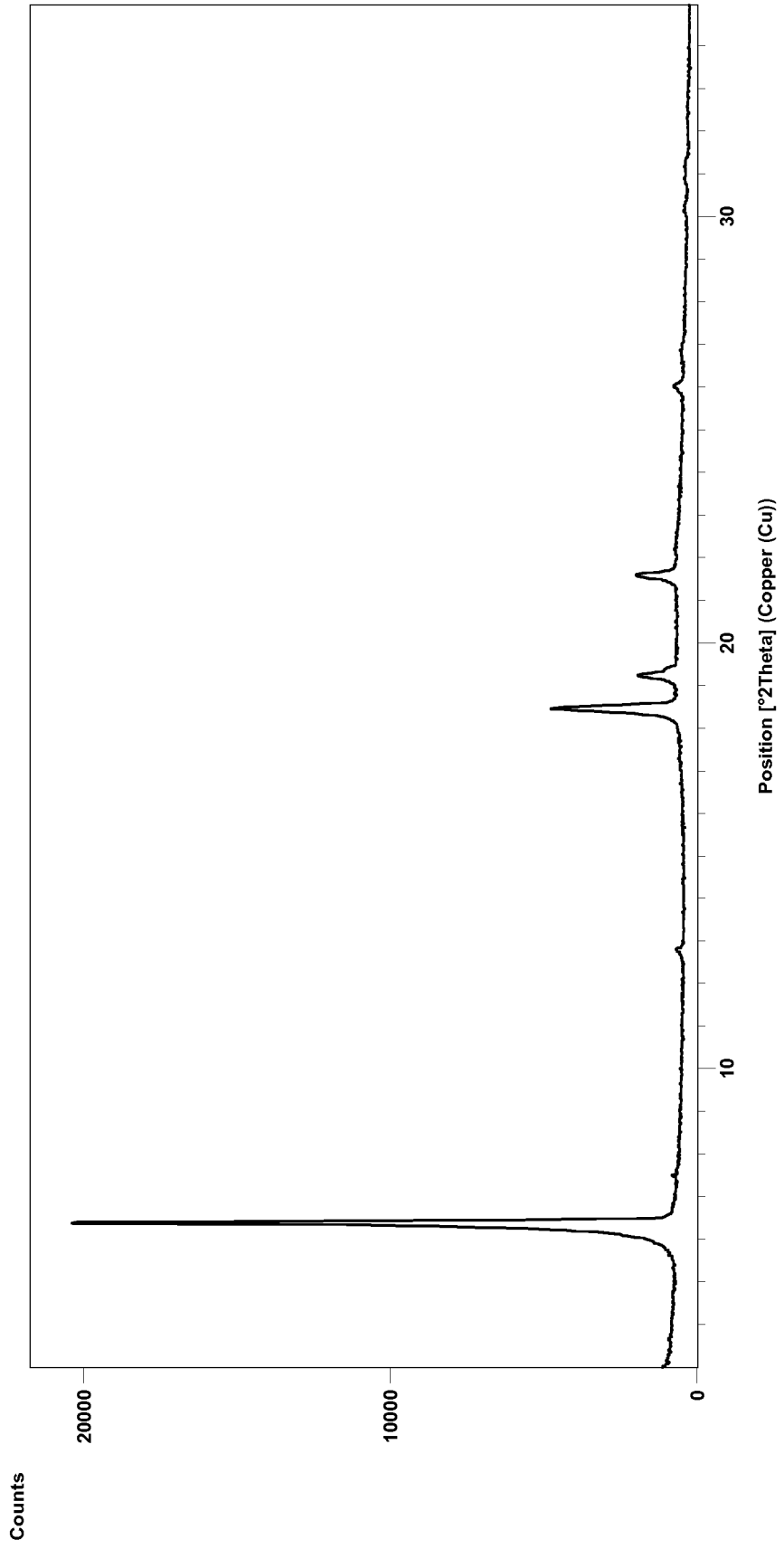


Fig. 3

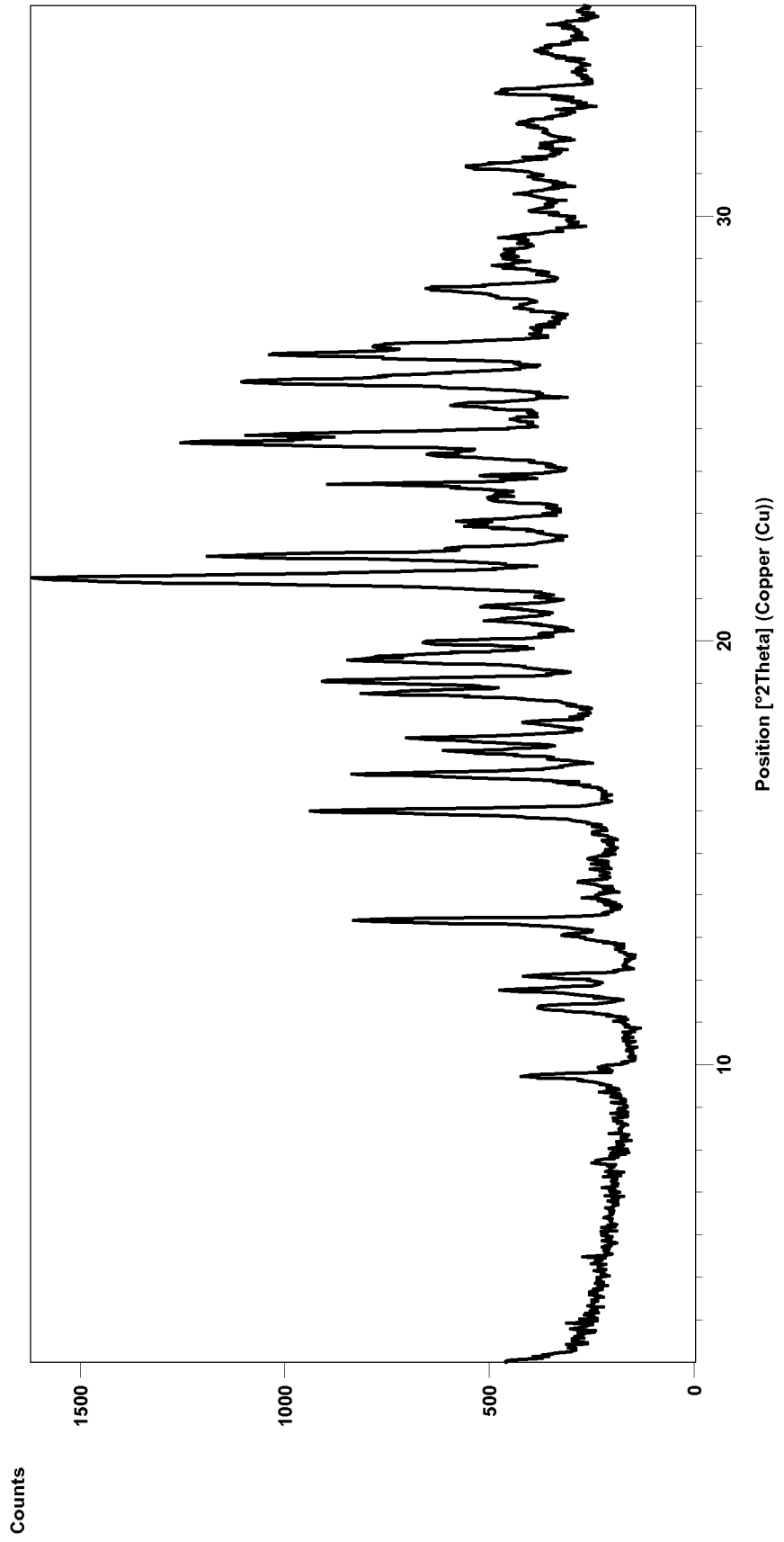


Fig. 4

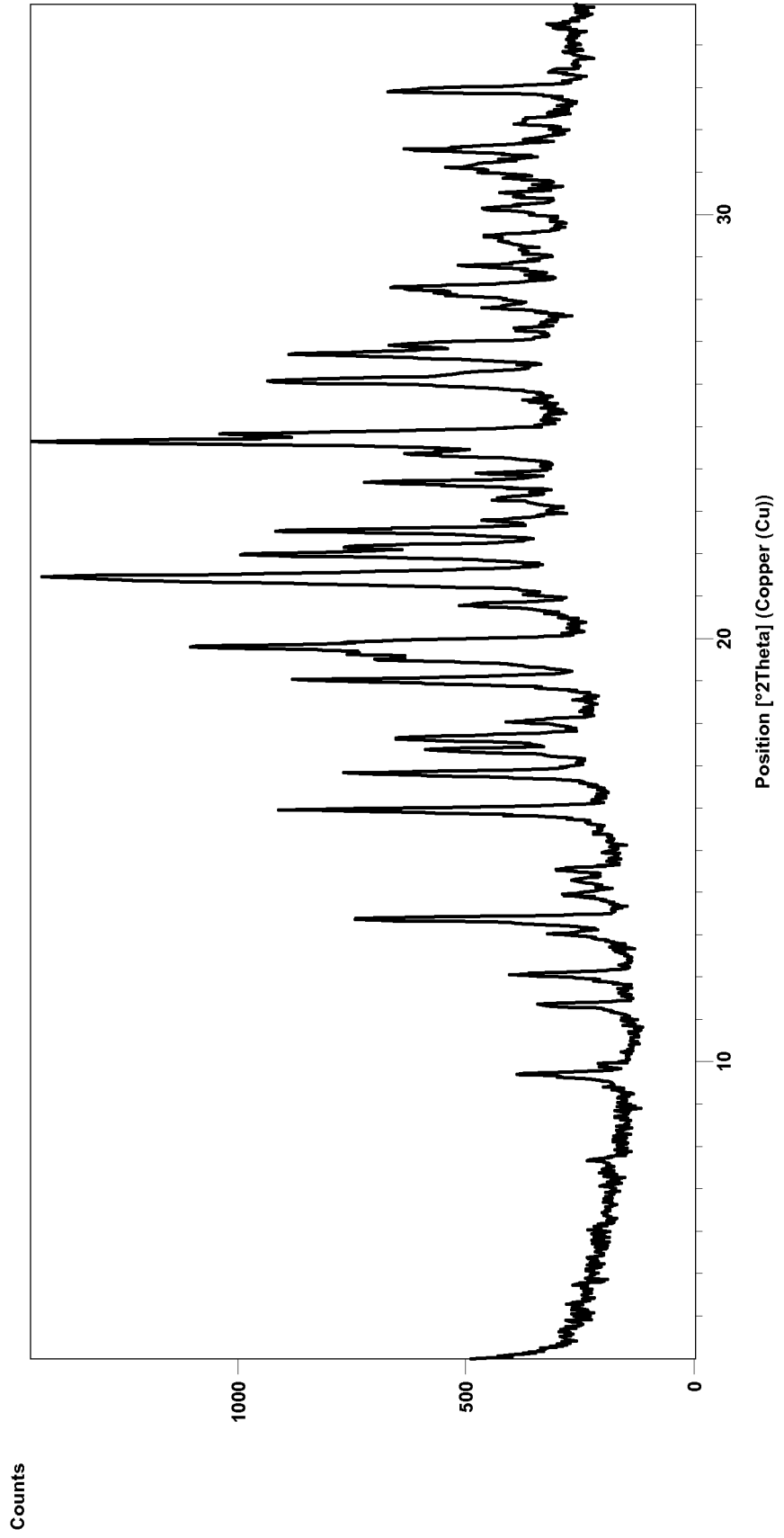


Fig. 5

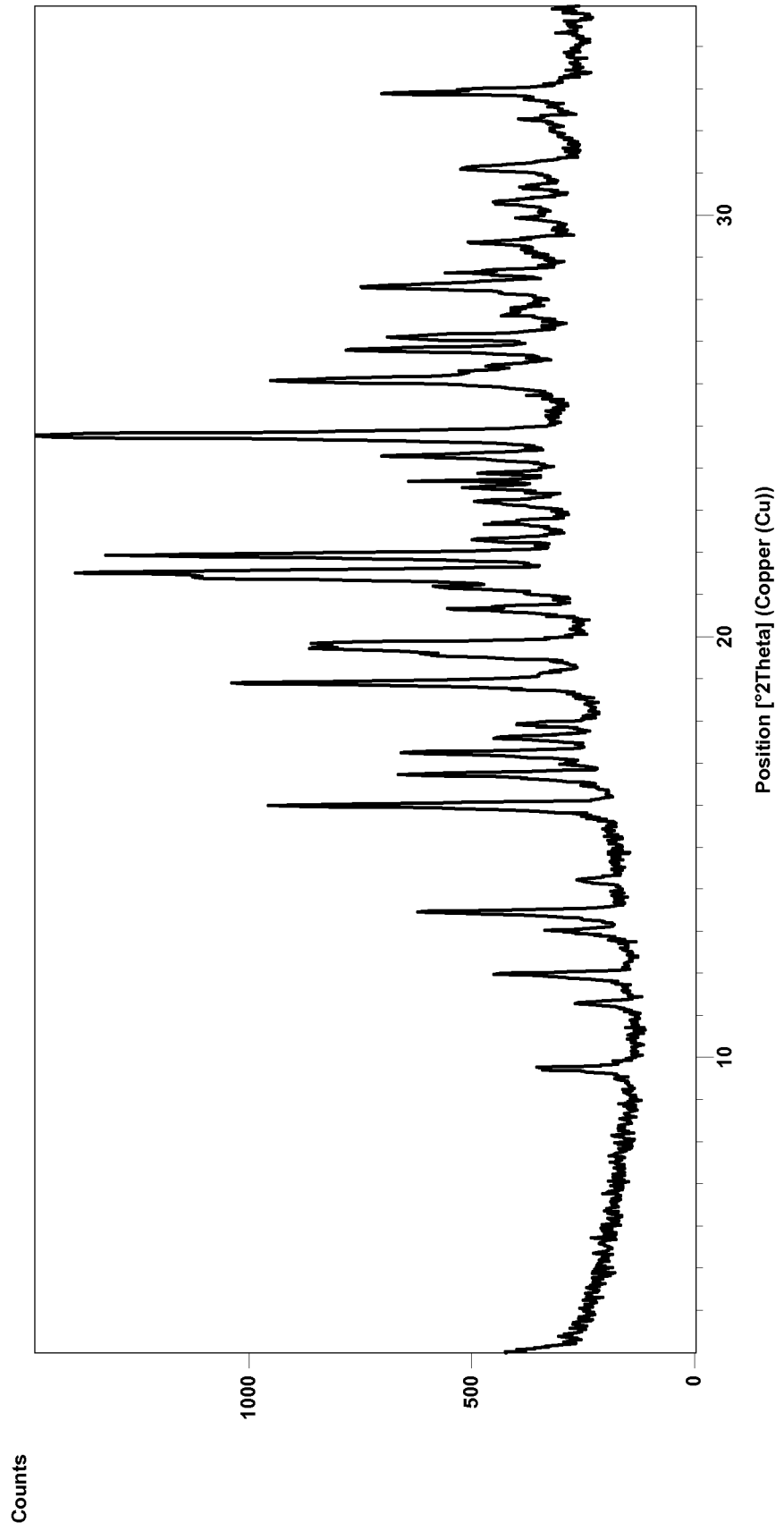


Fig. 6

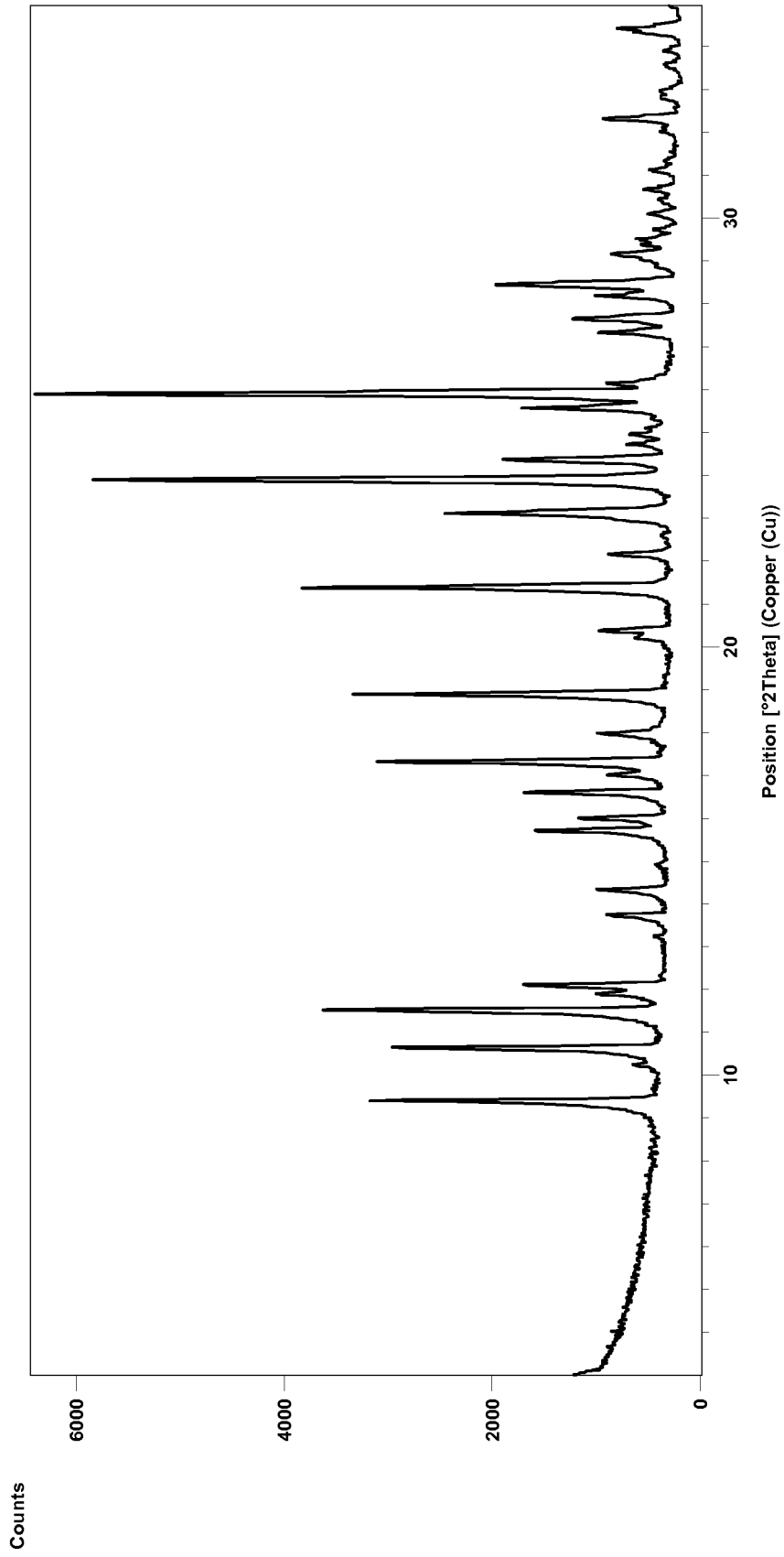


Fig. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/067822

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/40
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 2006/028958 A2 (GENENTECH INC [US]; CURIS INC [US]; GUNZNER JANET [US]; SUTHERLIN DANI) 16 March 2006 (2006-03-16) claim 1; example 37	1-15
A	AITIPAMULA, S. ET AL.: "Polymorphs, Salts, and Cocrystals: What's in a Name ?", CRYST. GROWTH DES., vol. 12, 2012, pages 2147-2152, XP002733448, the whole document	1-15

Further documents are listed in the continuation of Box C.

See patent family annex.

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Date of the actual completion of the international search 18 September 2015	Date of mailing of the international search report 30/09/2015
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Baston, Eckhard
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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