

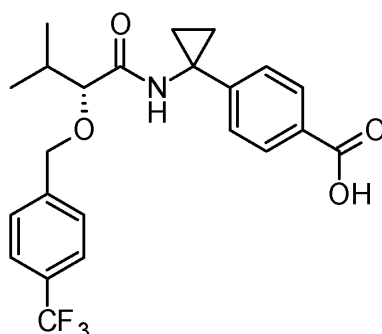
CRYSTALLINE FORM OF AN EP4 ANTAGONIST

FIELD OF THE INVENTION

The present invention relates to a crystalline form of (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl)benzoic acid and methods of preparation thereof. The invention also relates to compositions comprising the crystalline form of (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl)benzoic acid, such as pharmaceutical compositions, and therapeutic uses of the crystalline form.

BACKGROUND

WO2021/069927 discloses the compound of Formula (1) below, (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl)benzoic acid, as an antagonist of the prostaglandin E₂ receptor 4 (EP₄).



(1)

Prostaglandins (PG) are small-molecule (~400 Da) products produced by cyclooxygenases (COX; constitutively active COX1 and inducible COX2) and PG synthases, with a minor contribution from the isoprostane pathway, acting on arachidonic acid (AA). Prostaglandin E₂ (PGE₂) is the main COX product in myeloid and stromal cells whose levels are determined by the balance between synthesis and 15-hydroxyprostaglandin dehydrogenase (15-PGDH)-mediated degradation. PGE₂ has 4 receptors (EP₁–EP₄) which are present on multiple cell

types including macrophages, monocytes, platelets, sensory neurons, gastrointestinal tract, kidney, thymus, heart, lung, and uterus and drives a broad pharmacology mediating nociception, aspects of neuronal signalling, haematopoiesis, regulation of blood flow, renal filtration and blood pressure, regulation of mucosal integrity, vascular permeability, smooth muscle function and both pro-inflammatory (vasodilation, recruitment and activation of mast cells, macrophages and neutrophils) and immunosuppressive immune function. Functional PGE₂ antagonism has therapeutic potential in a wide variety of disease settings.

10 Different crystalline forms of a compound can possess different properties, such as solubility, dissolution rate, filterability, hygroscopicity, flow, and stability.

It has been discovered that (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl)benzoic acid can exist in a number of crystalline forms as well as an amorphous form. Many of these forms are undesirable from the point of view of producing pharmaceutically acceptable compositions.

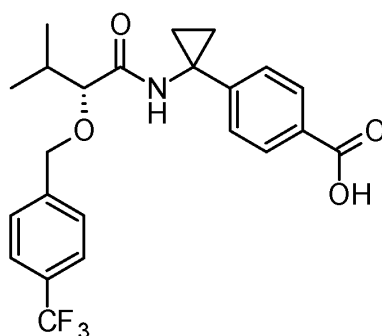
There is therefore an unmet need to provide a desirable crystalline form of (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl)benzoic acid.

20 There is also a need to provide processes for producing the selected crystalline form over other crystalline and amorphous forms. In particular, it is desirable to obtain the selected crystalline form in high purity and/or in high yield. It is also desirable to provide processes for producing the selected crystalline form that are suitable for the commercial scale, for example with respect to safety requirements and processability.

SUMMARY OF INVENTION

In one aspect the invention provides a crystalline form of the compound of Formula (1):

3



(1);

wherein said crystalline form has an X-ray powder diffraction pattern comprising peaks at 2θ of $10.0 \pm 0.1^\circ$ and $15.0 \pm 0.1^\circ$.

- 5 In another aspect, the invention provides a crystalline form of the compound of Formula (1), wherein said crystalline form has a differential scanning calorimetry (DSC) thermogram comprising an endothermic event with an onset temperature at $171 \pm 2^\circ\text{C}$.

- 10 In a particular embodiment, the crystalline form of the compound of Formula (1) has an X-ray powder diffraction pattern comprising peaks at 2θ of $10.0 \pm 0.1^\circ$ and $15.0 \pm 0.1^\circ$ and a DSC thermogram comprising an endothermic event with an onset temperature at $171 \pm 2^\circ\text{C}$.

- 15 The specific crystalline form of the invention has a number of unexpected properties that make it a desirable form. The crystalline form of the invention has been demonstrated to possess excellent physical stability, polymorphic stability, and stability towards racemisation under various test conditions. The crystalline form of the invention has also been shown to be non-hygroscopic.

In another aspect, the invention provides a composition comprising the crystalline form of the invention.

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

In another aspect, the invention provides the crystalline form of the invention for
5 use in medicine, such as for use in the treatment of cancer.

In another aspect, the invention provides a method for preparing the crystalline form of the invention. The method is safe to be conducted on large scale. The method also delivers the crystalline form of the invention in high yield and purity.

BRIEF DESCRIPTION OF DRAWINGS

10 Figure 1. XRPD spectrum of the crystalline form of the invention.

Figure 2. TGA and DSC plots for the crystalline form of the invention.

Figure 3. FT-IR spectrum of the crystalline form of the invention.

Figure 4. NMR spectrum of the crystalline form of the invention.

Figure 5. DVS sorption and de-sorption plot of the crystalline form of the invention.

15 Figure 6. DVS isothermal plot of the crystalline form of the invention.

Figure 7. XRPD spectrum of a comparative crystalline form.

Figure 8. TGA and DSC plots for a comparative crystalline form.

DETAILED DESCRIPTION

The compound of Formula (1) is also referred to herein as (R)-4-(1-(3-methyl-2-
20 ((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl)benzoic acid.

The crystalline form of the invention may exhibit an X-ray powder diffraction pattern comprising peaks at 2θ of $10.0 \pm 0.1^\circ$ and $15.0 \pm 0.1^\circ$.

The X-ray powder diffraction pattern may be measured using Cu K α radiation.

The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $18.7 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $20.9 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $14.6 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $10.7 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $17.9 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $17.7 \pm 0.09^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $19.8 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $20.1 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $15.2 \pm 0.09^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $3.5 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $4.9 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $10.4 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $11.4 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $11.9 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $12.4 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $14.2 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $15.5 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $16.8 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $18.4 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $19.0 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $20.6 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $21.5 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $21.8 \pm 0.1^\circ$. The crystalline

- form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $22.3 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $22.9 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $23.8 \pm 0.1^\circ$. The crystalline
- 5 form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $24.4 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $25.0 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $25.4 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of 26.4
- 10 $\pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $26.7 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $27.1 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $27.7 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern
- 15 comprising a peak at 2θ of $28.3 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $29.1 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $29.6 \pm 0.1^\circ$. The crystalline form may have an X-ray powder diffraction pattern comprising a peak at 2θ of $30.2 \pm 0.1^\circ$.

- 20 The crystalline form may have an X-ray powder diffraction pattern comprising peaks at 2θ of $10.0 \pm 0.1^\circ$, $14.6 \pm 0.1^\circ$, $15.0 \pm 0.1^\circ$, $18.7 \pm 0.1^\circ$, and $20.9 \pm 0.1^\circ$.

The crystalline form may have an X-ray powder diffraction pattern comprising peaks at 2θ of $10.0 \pm 0.1^\circ$, $10.7 \pm 0.1^\circ$, $14.6 \pm 0.1^\circ$, $15.0 \pm 0.1^\circ$, $17.7 \pm 0.09^\circ$, $17.9 \pm 0.1^\circ$, $18.7 \pm 0.1^\circ$, and $20.9 \pm 0.1^\circ$.

- 25 The crystalline form may have an X-ray powder diffraction pattern comprising peaks at 2θ of $10.0 \pm 0.1^\circ$, $10.7 \pm 0.1^\circ$, $14.6 \pm 0.1^\circ$, $15.0 \pm 0.1^\circ$, $15.2 \pm 0.09^\circ$, $17.7 \pm 0.09^\circ$, $17.9 \pm 0.1^\circ$, $18.7 \pm 0.1^\circ$, $19.8 \pm 0.1^\circ$, $20.1 \pm 0.1^\circ$, and $20.9 \pm 0.1^\circ$.

The crystalline form may have an X-ray powder diffraction pattern comprising peaks at 2θ of $3.5 \pm 0.1^\circ$, $4.9 \pm 0.1^\circ$, $10.0 \pm 0.1^\circ$, $10.7 \pm 0.1^\circ$, $14.6 \pm 0.1^\circ$, $15.0 \pm$

0.1°, 15.2 ± 0.09°, 17.7 ± 0.09°, 17.9 ± 0.1°, 18.7 ± 0.1°, 19.0 ± 0.1°, 19.8 ± 0.1°, 20.1 ± 0.1°, 20.6 ± 0.1°, 20.9 ± 0.1°, and 21.5 ± 0.1°.

The crystalline form may have an X-ray powder diffraction pattern comprising peaks at 2θ of 3.5 ± 0.1°, 4.9 ± 0.1°, 10.0 ± 0.1°, 10.4 ± 0.1°, 10.7 ± 0.1°, 11.9 ± 0.1°, 14.6 ± 0.1°, 15.0 ± 0.1°, 15.2 ± 0.09°, 15.5 ± 0.1°, 16.8 ± 0.1°, 17.7 ± 0.09°, 17.9 ± 0.1°, 18.4 ± 0.1°, 18.7 ± 0.1°, 19.0 ± 0.1°, 19.8 ± 0.1°, 20.1 ± 0.1°, 20.6 ± 0.1°, 20.9 ± 0.1°, 21.5 ± 0.1°, 23.8 ± 0.1°, 25.0 ± 0.1°, and 30.2 ± 0.1°.

The crystalline form may have an X-ray powder diffraction pattern comprising peaks at 2θ of 3.5 ± 0.1°, 4.9 ± 0.1°, 10.0 ± 0.1°, 10.4 ± 0.1°, 10.7 ± 0.1°, 11.9 ± 0.1°, 14.2 ± 0.1°, 14.6 ± 0.1°, 15.0 ± 0.1°, 15.2 ± 0.09°, 15.5 ± 0.1°, 16.8 ± 0.1°, 17.7 ± 0.09°, 17.9 ± 0.1°, 18.4 ± 0.1°, 18.7 ± 0.1°, 19.0 ± 0.1°, 19.8 ± 0.1°, 20.1 ± 0.1°, 20.6 ± 0.1°, 20.9 ± 0.1°, 21.5 ± 0.1°, 21.8 ± 0.1°, 22.9 ± 0.1°, 23.8 ± 0.1°, 24.4 ± 0.1°, 25.0 ± 0.1°, 25.4 ± 0.1°, 26.4 ± 0.1°, 26.7 ± 0.1°, 27.1 ± 0.1°, 27.7 ± 0.1°, 28.3 ± 0.1°, 29.1 ± 0.1°, 29.6 ± 0.1°, and 30.2 ± 0.1°.

The crystalline form may have an X-ray powder diffraction pattern comprising peaks at 2θ of 3.5 ± 0.1°, 4.9 ± 0.1°, 10.0 ± 0.1°, 10.4 ± 0.1°, 10.7 ± 0.1°, 11.4 ± 0.1°, 11.9 ± 0.1°, 12.4 ± 0.1°, 14.2 ± 0.1°, 14.6 ± 0.1°, 15.0 ± 0.1°, 15.2 ± 0.09°, 15.5 ± 0.1°, 16.8 ± 0.1°, 17.7 ± 0.09°, 17.9 ± 0.1°, 18.4 ± 0.1°, 18.7 ± 0.1°, 19.0 ± 0.1°, 19.8 ± 0.1°, 20.1 ± 0.1°, 20.6 ± 0.1°, 20.9 ± 0.1°, 21.5 ± 0.1°, 21.8 ± 0.1°, 22.3 ± 0.1°, 22.9 ± 0.1°, 23.8 ± 0.1°, 24.4 ± 0.1°, 25.0 ± 0.1°, 25.4 ± 0.1°, 26.4 ± 0.1°, 26.7 ± 0.1°, 27.1 ± 0.1°, 27.7 ± 0.1°, 28.3 ± 0.1°, 29.1 ± 0.1°, 29.6 ± 0.1°, and 30.2 ± 0.1°.

The crystalline form may have an X-ray powder diffraction pattern having peaks and substantially similar intensities as shown in Table 1:

Table 1

Angle (° 2θ)	Intensity (%)
3.5 ± 0.1	30 to 50, preferably 37.5
4.9 ± 0.1	30 to 50, preferably 35.1
10.0 ± 0.1	80 to 100, preferably 100

10.4 ± 0.1	10 to 30, preferably 21.4
10.7 ± 0.1	50 to 70, preferably 58.7
11.4 ± 0.1	1 to 20, preferably 7.5
11.9 ± 0.1	15 to 35, preferably 24.3
12.4 ± 0.1	1 to 20, preferably 6.3
14.2 ± 0.1	5 to 25, preferably 14
14.6 ± 0.1	50 to 70, preferably 60.7
15.0 ± 0.1	80 to 100, preferably 89.3
15.2 ± 0.09	35 to 55, preferably 44.1
15.5 ± 0.1	10 to 30, preferably 22.3
16.8 ± 0.1	15 to 35, preferably 25.5
17.7 ± 0.09	40 to 60, preferably 50.8
17.9 ± 0.1	45 to 65, preferably 53.6
18.4 ± 0.1	10 to 30, preferably 22.6
18.7 ± 0.1	65 to 85, preferably 76.1
19.0 ± 0.1	20 to 40, preferably 30.9
19.8 ± 0.1	40 to 60, preferably 49.8
20.1 ± 0.1	40 to 60, preferably 49.8
20.6 ± 0.1	25 to 45, preferably 33.9
20.9 ± 0.1	60 to 80, preferably 69.6
21.5 ± 0.1	25 to 45, preferably 33.8
21.8 ± 0.1	5 to 25, preferably 17.4
22.3 ± 0.1	1 to 20, preferably 9.8
22.9 ± 0.1	10 to 30, preferably 19.6
23.8 ± 0.1	10 to 30, preferably 21
24.4 ± 0.1	5 to 25, preferably 15.1
25.0 ± 0.1	15 to 35, preferably 25.9
25.4 ± 0.1	10 to 30, preferably 19.2
26.4 ± 0.1	5 to 25, preferably 16.7
26.7 ± 0.1	5 to 25, preferably 14.5
27.1 ± 0.1	10 to 30, preferably 18.3
27.7 ± 0.1	5 to 25, preferably 12.7
28.3 ± 0.1	5 to 25, preferably 15.2
29.1 ± 0.1	5 to 25, preferably 15.5
29.6 ± 0.1	10 to 30, preferably 17.9
30.2 ± 0.1	15 to 35, preferably 26.2

The crystalline form may have an X-ray powder diffraction pattern substantially as shown in Figure 1.

The crystalline form may have a differential scanning calorimetry (DSC) thermogram comprising an endothermic event with an onset temperature at 171
5 ± 2 °C. The DSC thermogram may be measured using a heating rate of 10 °C/min.

The crystalline form may have an infrared spectrum comprising at least one or all of the following peaks: 3273 ± 2 cm⁻¹, 2960 ± 2 cm⁻¹, 2870 ± 2 cm⁻¹, 1686 ± 2 cm⁻¹, 1657 ± 2 cm⁻¹, 1328 ± 2 cm⁻¹, and 1068 ± 2 cm⁻¹. The crystalline form may have an infrared spectrum comprising the following peaks: 3273 ± 2 cm⁻¹, $1686 \pm$
10 2 cm⁻¹, and 1657 ± 2 cm⁻¹. The infrared spectrum may be measured using Fourier Transform Infrared Spectroscopy (FT-IR).

The crystalline form may be a substantially pure crystalline form. Substantially pure crystalline form means that the crystalline form includes at least 95% by weight of the crystalline form of the invention by total weight of the compound of
15 Formula (1). The crystalline form may comprise at least 96%, or at least 97%, or at least 98%, or at least 99%, or at least 99.5%, or at least 99.9% by weight of the crystalline form of the invention by total weight of the compound of Formula (1).

The crystalline form may have a purity (as measured by HPLC % area) of at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or at least
20 99.5%, or at least 99.9%.

The crystalline form may have a chiral purity (as measured by HPLC % area) of at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or at least 99.5%, or at least 99.9%.

In one aspect the invention provides a composition, such as a pharmaceutical
25 composition (or formulation), comprising the crystalline form of the invention.

The pharmaceutical composition may comprise at least one pharmaceutically acceptable excipient.

The pharmaceutically acceptable excipient(s) can be selected from, for example, carriers (e.g. a solid, liquid or semi-solid carrier), adjuvants, diluents (e.g. solid diluents such as fillers or bulking agents; and liquid diluents such as solvents and co-solvents), granulating agents, binders, flow aids, coating agents, release-controlling agents (e.g. release retarding or delaying polymers or waxes), binding agents, disintegrants, lubricants, preservatives, anti-fungal agents, antibacterial agents, antioxidants, buffering agents, tonicity-adjusting agents, thickening agents, flavouring agents, sweeteners, pigments, plasticizers, taste masking agents, stabilisers, vehicles, wetting agents, emulsifying agents, suspending agents, perfuming agents, dispersing agents, or any other excipients conventionally used in pharmaceutical compositions.

Pharmaceutical compositions can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

The pharmaceutical composition may be in a form suitable for oral, parenteral, topical, intranasal, intrabronchial, sublingual, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration.

The pharmaceutical composition may take the form, for example, of tablets, dragées, powders, elixirs, syrups, liquid preparations including suspensions, sprays, inhalants, tablets, lozenges, emulsions, solutions, cachets, granules, capsules, and suppositories, as well as liquid preparations for injections, including liposome preparations.

Pharmaceutical dosage forms suitable for oral administration include tablets (coated or uncoated), capsules (hard or soft shell), caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches such as buccal patches.

The pharmaceutical composition may be a tablet composition. The pharmaceutical composition may be a capsule composition.

Tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, e.g.; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as microcrystalline cellulose (MCC), methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Tablets may be designed to release the drug either upon contact with stomach fluids (immediate release tablets) or to release in a controlled manner (controlled release tablets) over a prolonged period of time or with a specific region of the GI tract.

The pharmaceutical compositions typically comprise from approximately 1% (w/w) to approximately 95%, preferably 5% (w/w) active ingredient and from 99% (w/w) to 5% (w/w) of a pharmaceutically acceptable excipient (for example as defined above) or combination of such excipients. Preferably, the pharmaceutical compositions comprise from approximately 20% (w/w) to approximately 90% (w/w) active ingredient and from 80% (w/w) to 10% of a pharmaceutically excipient or combination of excipients. The pharmaceutical compositions may comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, pre-filled syringes, dragées, powders, tablets or capsules.

Tablets and capsules may contain, for example, 0-20% disintegrants, 0-5% lubricants, 0-5% flow aids and/or 0-99% (w/w) fillers/ or bulking agents (depending on drug dose). They may also contain 0-10% (w/w) polymer binders, 0-5% (w/w)

antioxidants, 0-5% (w/w) pigments. Slow release tablets would in addition typically contain 0-99% (w/w) release-controlling (e.g. delaying) polymers (depending on dose). The film coats of the tablet or capsule typically contain 0-10% (w/w) polymers, 0-3% (w/w) pigments, and/or 0-2% (w/w) plasticizers.

- 5 Parenteral formulations typically contain 0-20% (w/w) buffers, 0-50% (w/w) cosolvents, and/or 0-99% (w/w) water for injection (WFI) (depending on dose and if freeze dried). Formulations for intramuscular depots may also contain 0-99% (w/w) oils.

- The pharmaceutical compositions may be presented to a patient in "patient packs"
10 containing an entire course of treatment in a single package, usually a blister pack.

- The active compounds will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active
15 ingredient. Within these ranges, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to 20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

- 20 For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 milligrams to 1 gram, of active compound.

- The active compounds will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired
25 therapeutic effect (effective amount). The precise amounts of each compound administered may be determined by a supervising physician in accordance with standard procedures.

In the compositions or pharmaceutical compositions described herein the compound of Formula (1) may be from 50% to 100% crystalline. In the

compositions or pharmaceutical compositions described herein the compound of Formula (1) may be at least 50% crystalline, or at least 60% crystalline, or at least 70% crystalline, or at least 80% crystalline, or at least 90% crystalline, or at least 95% crystalline, or at least 98% crystalline, or at least 99% crystalline, or at least 5 99.5% crystalline, or at least 99.9% crystalline, for example 100% crystalline.

The composition or pharmaceutical composition may comprise a mixture of crystalline forms of the compound of Formula (1), or it may comprise a substantially pure crystalline form of the invention. The composition or pharmaceutical composition may comprise at least 5%, or at least 50%, or at least 10 90% by weight of the crystalline form of the invention by total weight of the compound of Formula (1). The composition or pharmaceutical composition may comprise at least 95% by weight of the crystalline form of the invention by total weight of the compound of Formula (1). The composition or pharmaceutical composition may comprise at least 96%, or at least 97%, or at least 98%, or at 15 least 99%, or at least 99.5%, or at least 99.9% by weight of the crystalline form of the invention by total weight of the compound of Formula (1).

In one aspect the invention provides a combination product comprising a crystalline form of the invention, or a pharmaceutical composition comprising a crystalline form of the invention, and at least one immune checkpoint inhibitor.

20 In one aspect the invention provides a kit comprising a crystalline form of the invention, or a pharmaceutical composition comprising a crystalline form of the invention, and at least one immune checkpoint inhibitor.

In the combination products and kits of the invention, the immune checkpoint inhibitor may be any immune checkpoint inhibitor. The immune checkpoint 25 inhibitor may be an antibody. The immune checkpoint inhibitor may be in the form of an injectable antibody.

A combination of immune checkpoint inhibitors may be used in the combination products and kits of the invention. The at least one immune checkpoint inhibitor may comprise or be an inhibitor of PD-1, PD-L1, CTLA4, LAG-3, TIM-3, NKG2A,

PVRIG, CEACAM1, CEACAM5/6, LIF, CD47 or CSF-1. The at least one immune checkpoint inhibitor may comprise or be a PD-1 inhibitor, a PD-L1 inhibitor or a CTLA4 inhibitor. The at least one immune checkpoint inhibitor may comprise or be an anti-CTLA4 antibody, an anti-PD-1 antibody or an anti-PD-L1 antibody.

- 5 The at least one immune checkpoint inhibitor may comprise or be an anti-PD-1 antibody selected from: nivolumab (Opdivo), Pembrolizumab (Keytruda), cemiplimab (Libtayo), Dostarlimab (Jemperli), toripalimab (Tuoyi), sintilimab (Tyvyt), Camrelizumab (AiRuiKa), Sasanlimab and Retifanlimab.

- The at least one immune checkpoint inhibitor may comprise or be an anti-PD-L1
10 antibody selected from: Atezolizumab (Tecentriq), Avelumab (Bavencio) and Durvalumab (Imfinzi).

The at least one immune checkpoint inhibitor may comprise or be ipilimumab (Yervoy).

- The crystalline form, pharmaceutical composition, combination product or kit of
15 the invention may be for use in medicine.

The crystalline form, pharmaceutical composition, combination product or kit of the invention may be for use in treating, preventing, ameliorating, controlling or reducing the risk of diseases or disorders in which EP4 receptors are involved.

- The crystalline form or pharmaceutical composition of the invention may be for
20 use in the manufacture of a medicament for treating, preventing, ameliorating, controlling or reducing the risk of diseases or disorders in which EP4 receptors are involved.

- The crystalline form or pharmaceutical composition of the invention may be for
25 use in the treatment of Abdominal aortic aneurysm (AAA), Ankylosing spondylitis (AS), Alzheimer's disease (AD), Atherosclerosis, Cancer including epithelial cancers (GBD neoplasm categories of colon and rectum, lip and oral cavity, nasopharynx, other pharynx, gallbladder and biliary tract, pancreatic, non-melanoma skin, ovarian, testicular, kidney, bladder, thyroid, mesothelioma,

esophageal, stomach, liver, larynx, tracheal, bronchus and lung, breast, cervical, uterine, prostate), Diabetic nephropathy, Endometriosis, Inflammatory bowel disease, Migraine, Multiple sclerosis (MS), Osteoarthritis (OA) and Rheumatoid arthritis.

- 5 The crystalline form, pharmaceutical composition, combination product or kit of the invention may be for use in the treatment of cancer. The invention therefore includes a method of treating cancer, the method comprising administering to a subject in need thereof a therapeutically effective amount of the crystalline form or pharmaceutical composition of the invention. The invention also provides a
- 10 method of treating cancer in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of the crystalline form of the invention and a therapeutically effective amount of an immune checkpoint inhibitor.

- The cancer may be an epithelial cancer. The cancer may be a carcinoma. The
- 15 cancer may be a sarcoma. The cancer may be a lymphoma.

- The cancer may be selected from: lung cancer including Non-Small Cell Lung Cancer Small Cell Lung Cancer (SCLC) and squamous cell lung carcinoma, renal cancer including Renal Cell Carcinoma and Urothelial Carcinoma, Hodgkin Lymphoma including Classical Hodgkin Lymphoma, head and neck cancer
- 20 including Head Neck Squamous Cell Carcinoma (HNSCC) lip cancer oral cavity cancer nasopharynx cancer and other pharynx cancer, colon cancer, rectum cancer, Colorectal Cancer (CRC) including microsatellite instability-high colorectal cancer (MSI-H CRC) mismatch repair deficient colorectal cancer (dMMR CRC) and microsatellite stable colorectal cancer (MSS CRC), liver cancer including
- 25 Hepatocellular Carcinoma, Gastric Cancer, Gastro-oesophageal cancer including oesophageal squamous cell carcinoma and gastro oesophageal junction cancer, Oesophageal cancer, Cervical cancer, breast cancer including Triple-Negative Breast Cancer, Melanoma, non-melanoma skin cancer including Merkel Cell Carcinoma and Cutaneous squamous cell carcinoma, Pancreatic cancer, Prostate
- 30 cancer including castration-resistant prostate cancer and metastatic castration-resistant prostate cancer (mCRPC), Endometrial Cancer, gallbladder cancer,

biliary tract cancer, ovarian cancer, testicular cancer, thyroid cancer, larynx cancer, tracheal cancer, bronchus cancer, mesothelioma, bladder cancer, sarcoma, or pheochromocytoma.

The cancer may be selected from: Melanoma, Non-Small Cell Lung Cancer, Small
 5 Cell Lung Cancer (SCLC), Renal Cell Carcinoma, Classical Hodgkin Lymphoma, Head Neck Squamous Cell Carcinoma, Urothelial Carcinoma, Colorectal Cancer (CRC), microsatellite instability-high colorectal cancer (MSI-H CRC), mismatch repair deficient colorectal cancer (dMMR CRC), Hepatocellular Carcinoma, Gastric Cancer, Cervical cancer, Merkel Cell Carcinoma, Cutaneous squamous
 10 cell carcinoma, Triple-Negative Breast Cancer, Gastro-oesophageal cancer, Pancreatic cancer, Prostate cancer, Oesophageal cancer, Endometrial Cancer, colon cancer, rectum cancer, colorectal cancer, lip cancer, oral cavity cancer, nasopharynx cancer, other pharynx cancer, gallbladder cancer, biliary tract cancer, non-melanoma skin cancer, ovarian cancer, testicular cancer, thyroid
 15 cancer, liver cancer, larynx cancer, tracheal cancer, bronchus cancer, breast cancer, oesophageal squamous cell carcinoma, squamous cell lung carcinoma, renal cancer, mesothelioma, lung cancer, bladder cancer, microsatellite stable colorectal cancer (MSS CRC), castration-resistant prostate cancer, metastatic castration-resistant prostate cancer (mCRPC), sarcoma, pheochromocytoma,
 20 head and neck cancer, gastro oesophageal junction cancer, or Hodgkin Lymphoma.

The cancer may be selected from: Melanoma, Non-Small Cell Lung Cancer, Small
 Cell Lung Cancer (SCLC), Renal Cell Carcinoma, Classical Hodgkin Lymphoma, Head Neck Squamous Cell Carcinoma, Urothelial Carcinoma, Colorectal Cancer
 25 (CRC) (MSI-H or dMMR), Hepatocellular Carcinoma, Gastric Cancer, Cervical cancer, Merkel Cell Carcinoma, Cutaneous squamous cell carcinoma, Triple-Negative Breast Cancer, Gastro-oesophageal cancer, Pancreatic cancer, Prostate cancer, Oesophageal cancer or Endometrial Cancer.

The cancer may be an epithelial cancer (GBD neoplasm categories of colon and
 30 rectum, lip and oral cavity, nasopharynx, other pharynx, gallbladder and biliary tract, pancreatic, non-melanoma skin, ovarian, testicular, kidney, bladder, thyroid,

mesothelioma, esophageal, stomach, liver, larynx, tracheal, bronchus and lung, breast, cervical, uterine, prostate).

The cancer may be selected from: colorectal cancer, microsatellite stable colorectal cancer (MSS CRC), gastro-oesophageal cancer, head neck squamous cell carcinoma (HNSCC), prostate cancer, castration-resistant prostate cancer, metastatic castration-resistant prostate cancer (mCRPC), pancreatic cancer, lung cancer, bladder cancer, mesothelioma, cervical cancer, renal cancer, sarcoma or phaeochromocytoma.

The cancer may be selected from: microsatellite stable colorectal cancer (MSS CRC), gastro oesophageal junction cancer, castration-resistant prostate cancer, metastatic castration-resistant prostate cancer (mCRPC), sarcoma, phaeochromocytoma, melanoma, renal cell carcinoma, Hodgkin Lymphoma, classical Hodgkin Lymphoma, urothelial carcinoma, microsatellite instability-high (MSI-H) colorectal cancer, mismatch repair deficient (dMMR) colorectal cancer, hepatocellular carcinoma and Merkel cell carcinoma.

The cancer may be selected from: microsatellite stable colorectal cancer (MSS CRC), gastro oesophageal junction cancer, head and neck squamous cell carcinoma (HNSCC), castration-resistant prostate cancer, metastatic castration-resistant prostate cancer (mCRPC), sarcoma and phaeochromocytoma.

The cancer may be selected from: microsatellite stable colorectal cancer (MSS CRC), gastro oesophageal junction cancer, castration-resistant prostate cancer, metastatic castration-resistant prostate cancer (mCRPC), sarcoma and phaeochromocytoma.

The cancer may be a solid tumour. A solid tumour is any type of cancer other than those of the blood or lymphatic system, e.g., leukaemia or lymphoma. The cancer may be an advanced solid tumour. An advanced solid tumour is a solid tumour that is refractory to treatment, or has continued to grow despite treatment, or has recurred after treatment, or that has spread from its origin to another part of the body.

The crystalline form of the invention and the immune checkpoint inhibitor may be administered by any feasible route of administration. In some embodiments the crystalline form of the invention may be administered orally and the immune checkpoint inhibitor may be administered intravenously. The crystalline form of the invention and the immune checkpoint inhibitor may be administered simultaneously sequentially or separately.

Therapeutic dosages may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compounds being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with the smaller dosages which are less than the optimum dose of the compound. Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

In general, the daily dose range may be from about 10 µg to about 30 mg per kg body weight of a human and non-human animal, preferably from about 50 µg to about 30 mg per kg of body weight of a human and non-human animal, for example from about 50 µg to about 10 mg per kg of body weight of a human and non-human animal, for example from about 100 µg to about 30 mg per kg of body weight of a human and non-human animal, for example from about 100 µg to about 10 mg per kg of body weight of a human and non-human animal and most preferably from about 100 µg to about 1 mg per kg of body weight of a human and non-human animal.

In one aspect the invention provides a method for preparing the crystalline form of the invention. The method comprises:

(a) providing a solution comprising the compound of Formula (1) in a polar organic solvent at a temperature of from 60 to 90 °C; and

(b) adding water to the solution to induce crystallisation of the crystalline form and obtain a suspension.

The solution in step (a) may comprise the polar organic solvent and water in a volume ratio of from 1:3 to 3:1, or from 1:3 to 2:1, or from 1:3 to 1:1, or from 1:2 to 1:1.

- 5 The solution in step (a) may have a pH of 3.5 or less. The solution in step (a) may have a pH of from 1 to 3.5, or from 2 to 3.5, or from 3 to 3.5. Preferably the solution in step (a) has a pH of about 3.5.

- Polar organic solvents include alcohols, ketones, esters, ethers and polyethers. The polar organic solvent may be selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, pentanol, hexanol, heptanol, octanol, acetone, cyclohexanone, toluene cyclohexanone, methyl butanone, methyl isobutyl ketone, methyl acetate, ethyl acetate, propyl acetate, tetrahydrofuran (THF), diethyl ether, propylene oxide, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, ethylene glycol monobutyl ether, and mixtures thereof. The polar organic solvent may be selected from the group consisting of methanol, tetrahydrofuran and isopropanol.
- 10
15

The polar organic solvent may be a protic solvent.

Preferably the polar organic solvent is isopropanol.

The solution in step (a) may be provided at a temperature of from 75 to 85 °C, or about 80 °C.

- 20 Step (b) may comprise maintaining the solution at a temperature of from 60 to 90 °C, or from 75 to 85 °C, or about 80 °C during the addition of water. Step (b) may comprise adding water to the solution over a period of 30 to 90 min.

- The volume ratio of polar organic solvent to water after step (b) may be from 1:1.5 to 1:10, or from 1:1.5 to 1:9, or from 1:1.5 to 1:8, or from 1:1.5 to 1:7, or from 1:1.5 to 1:6, or from 1:1.5 to 1:5, or from 1:1.5 to 1:4.
- 25

The method may further comprise the following step:

(c) stirring the suspension for at least 16 hours, and preferably not more than 36 hours, at a temperature of from 60 to 90 °C, or from 75 to 85 °C, or about 80 °C.

The method may further comprise the following step:

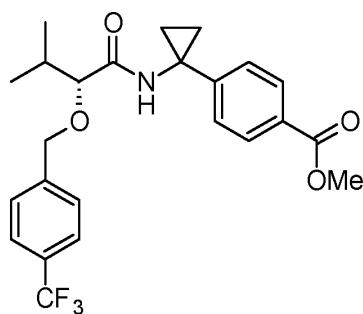
- 5 (d) adjusting the temperature of the suspension to from 15 to 25 °C, or about 20 °C. Adjusting the temperature of the suspension may be carried out over a period of 2 to 4 hours. The suspension may be stirred at 15 to 25 °C for 30 to 90 min.

10 The method may further comprise filtering the suspension to obtain a filter cake comprising the crystalline form. The filter cake may be rinsed with water at least once, for example three times.

The method may further comprise drying the filter cake to obtain the crystalline form.

Step (a) may comprise:

- 15 (a)(i) hydrolysing the ester of the compound of Formula (2) in the presence of the polar organic solvent



(2).

20 The compound of Formula (2) is also referred to herein as methyl (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl) benzoate.

The hydrolysis proceeds at a quicker rate in the presence of a polar organic solvent.

The hydrolysis may be acid-catalysed or base-catalysed. Preferably, the ester of the compound of Formula (2) is hydrolysed using an aqueous base.

- 5 Suitable bases include any base that is soluble in water and forms hydroxide ions. The base may be an alkali metal hydroxide or an alkaline earth metal hydroxide. The base may be selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonia, and mixtures thereof. Preferably the base is sodium hydroxide.
- 10 The reaction mixture in step (a)(i) may be stirred at a temperature of from 55 to 65 °C, or about 60 °C. The reaction mixture in step (a)(i) may be stirred at a temperature of from 55 to 65 °C, or about 60 °C, for 4 hours or more, such as from 4 to 8 hours. A reaction temperature of from 55 to 65 °C provides a good balance between reaction rate and purity profile.
- 15 Step (a) may further comprise:
- (a)(ii) adjusting the pH of the reaction mixture to a pH of 3.5 or less, such as about 3.5. This may provide a solution comprising the compound of Formula (1) in a polar organic solvent and water.

- The pH of the reaction mixture may be adjusted using any suitable method, for example by addition of an acid. The pH of the reaction mixture may be adjusted using any suitable acid, such as hydrochloric acid or citric acid. Preferably the pH of the reaction mixture is adjusted using citric acid.
- 20

- Step (a)(ii) may comprise maintaining the reaction mixture at a temperature of from 60 to 90 °C, or 60 to 70 °C, while adjusting the pH of the reaction mixture to a pH of 3.5 or less, such as about 3.5. This is preferred when the pH of the reaction mixture is adjusted using citric acid as maintaining the temperature above 60 °C prevents precipitation of citric acid.
- 25

The reaction mixture may be stirred at 60 to 90 °C, or 60 to 70 °C, for 10 to 30 min, or about 20 min, after adjusting the pH to 3.5 or less.

The temperature of the solution may be adjusted to from 60 to 90 °C, or from 75 to 85 °C, or about 80 °C, after adjusting the pH to 3.5 or less to provide a solution
5 comprising the compound of Formula (1) in a polar organic solvent and water.

The method may comprise:

(a) providing a solution comprising the compound of Formula (1) in a polar organic solvent at a temperature of from 60 to 90 °C, optionally in a polar organic solvent and water in a volume ratio of from 1:3 to 3:1, and/or optionally
10 wherein the solution has a pH of 3.5 or less;

(b) adding water to the solution to induce crystallisation of the crystalline form and obtain a suspension, optionally maintaining the solution at a temperature of from 60 to 90 °C, or from 75 to 85 °C, or about 80 °C, during the addition of water, and/or optionally wherein a volume ratio of the polar organic
15 solvent to water after the addition of water is from 1:1.5 to 1:10, or from 1:1.5 to 1:9, or from 1:1.5 to 1:8, or from 1:1.5 to 1:7, or from 1:1.5 to 1:6, or from 1:1.5 to 1:5, or from 1:1.5 to 1:4;

(c) stirring the suspension for at least 16 hours, and preferably not more than 36 hours, at a temperature of from 60 to 90 °C, or from 75 to 85 °C, or
20 about 80 °C;

(d) adjusting the temperature of the suspension to from 15 to 25 °C, or about 20 °C;

filtering the suspension to obtain a filter cake comprising the crystalline form; and

25 drying the filter cake to obtain the crystalline form.

The method may comprise:

(a)(i) hydrolysing the ester of the compound of Formula (2) in the presence of the polar organic solvent, optionally using an aqueous base,

and optionally stirring the reaction mixture at a temperature of from 55 to 65 °C, or about 60 °C;

- 5 (a)(ii) adjusting the pH of the reaction mixture to a pH of 3.5 or less (or about 3.5), optionally maintaining the reaction mixture at a temperature of from 60 to 90 °C, or from 60 to 70 °C, while adjusting the pH of the reaction mixture to a pH of 3.5 or less, to provide a solution comprising the compound of Formula (1) in a polar organic solvent and water, optionally wherein the volume ratio of polar
10 organic solvent to water is from 1:3 to 3:1, or from 1:3 to 2:1, or from 1:3 to 1:1, or from 1:2 to 1:1,

optionally adjusting the temperature of the solution to from 60 to 90 °C, or from 75 to 85 °C, or about 80 °C to provide a solution comprising the compound of Formula (1) in a polar organic solvent and water;

- 15 (b) adding water to the solution to induce crystallisation of the crystalline form and obtain a suspension, optionally maintaining the solution at a temperature of from 60 to 90 °C, or from 75 to 85 °C, or about 80 °C, during the addition of water, and/or optionally wherein a volume ratio of the polar organic solvent to water after the addition of water is from 1:1.5 to 1:10, or from 1:1.5 to
20 1:9, or from 1:1.5 to 1:8, or from 1:1.5 to 1:7, or from 1:1.5 to 1:6, or from 1:1.5 to 1:5, or from 1:1.5 to 1:4;

(c) stirring the suspension for at least 16 hours, and preferably not more than 36 hours, at a temperature of from 60 to 90 °C, or from 75 to 85 °C, or about 80 °C;

- 25 (d) adjusting the temperature of the suspension to from 15 to 25 °C, or about 20 °C;

filtering the suspension to obtain a filter cake comprising the crystalline form; and

drying the filter cake to obtain the crystalline form.

Definitions

In this application, the following definitions apply, unless indicated otherwise.

5 The term “pharmaceutically acceptable” as used herein means compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. a human subject) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each excipient must also be “acceptable” in the sense of being compatible with
10 the other ingredients of the formulation.

The term “treatment”, in relation to the compounds described herein is used to describe any form of intervention where a compound is administered to a subject suffering from, or at risk of suffering from, or potentially at risk of suffering from the disease or disorder in question. Thus, the term “treatment” covers both
15 preventative (prophylactic) treatment and treatment where measurable or detectable symptoms of the disease or disorder are being displayed.

The terms “effective amount” and “therapeutically effective amount” as used herein (for example in relation to methods of treatment of a disease or condition) refers to an amount of the compound which is effective to produce a desired
20 therapeutic effect. For example, if the condition is pain, then the effective therapeutic amount is an amount sufficient to provide a desired level of pain relief. The desired level of pain relief may be, for example, complete removal of the pain or a reduction in the severity of the pain.

Chemical terms are all used in their conventional sense (e.g. as defined in the
25 IUPAC Gold Book), unless indicated otherwise.

As used herein, the terms “administration” or “administering” mean a route of administration for a compound disclosed herein. Exemplary routes of administration include, but are not limited to, oral, intravenous, intraperitoneal,

intraarterial, and intramuscular. The preferred route of administration can vary depending on various factors, e.g. the components of the pharmaceutical composition comprising a compound disclosed herein, site of the potential or actual disease and severity of disease.

- 5 The terms "subject" and "patient" are used herein interchangeably. They refer to a human or another mammal (e.g., mouse, rat, rabbit, dog, cat, cattle, swine, sheep, horse or primate) that can be afflicted with or is susceptible to a disease or disorder but may or may not have the disease or disorder. It is preferred that the subject is human.
- 10 Compounds of the invention may be disclosed by the name or chemical structure. If a discrepancy exists between the name of a compound and its associated chemical structure, then the chemical structure prevails.

EXAMPLES

The invention will now be illustrated, but not limited, by reference to examples.

- 15 Biological data relating to the compound of Formula (1), (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl)benzoic acid, are provided in WO2021/069927.

Instruments and methodologies

Nuclear Magnetic Resonance (NMR)

- 20 ¹H NMR spectra may be collected on a Bruker 400 MHz instrument equipped with an auto-sampler and controlled by a DRX400 console. Samples were prepared in DMSO-*d*₆ solvent, unless otherwise stated. Automated experiments were acquired using ICON-NMR configuration within Topspin software, using standard Bruker-loaded experiments (¹H). Off-line analysis was performed using ACD
- 25 Spectrus Processor.

Fourier Transform Infrared Spectroscopy (FT-IR)

Data may be collected on a Perkin-Elmer Spectrum One fitted with a universal ATR sampling accessory using a 1 Bounce Diamond/ZnSe crystal. Spectra were collected 4000 – 650 cm^{-1} over 16 scans. The data were collected using Spectrum software and processed using ACD Spectrus Processor.

*X-ray Powder Diffraction (XRPD)**Bruker AXS D8 Advance*

- XRPD diffractograms may be collected on a Bruker D8 diffractometer using Cu K α radiation (40 kV, 40 mA) and a θ -2 θ goniometer fitted with a Ge monochromator.
- 10 The incident beam passes through a 2.0 mm divergence slit followed by a 0.2 mm anti-scatter slit and knife edge. The diffracted beam passes through an 8.0 mm receiving slit with 2.5° Soller slits followed by the Lynxeye Detector. The software used for data collection and analysis was Diffrac Plus XRD Commander and Diffrac Plus EVA respectively.
- 15 Samples were run under ambient conditions as flat plate specimens using powder as received. The sample was prepared on a polished, zero-background (510) silicon wafer by gently pressing onto the flat surface or packed into a cut cavity. The sample was rotated in its own plane.

The details of the data collection method are:

- 20
- Angular range: 2 to 42° 2 θ
 - Step size: 0.05° 2 θ
 - Collection time: 0.5 s/step (total collection time: 6.40 min)

Capillary XRPD

- 25 XRPD diffractograms may be collected on a PANalytical Empyrean diffractometer using Cu K α radiation (45 kV, 40 mA) in transmission geometry. A 0.5° slit and

0.04 rad Soller slits with a focusing mirror were used on the incident beam. The sample was prepared in a 0.7 mm borosilicate glass capillary with a knife edge placed immediately above the sample. A PIXcel^{3D} detector, placed on the diffracted beam, was fitted with a receiving slit and 0.04 rad Soller slits.

5 Samples were prepared by packing the solid into the capillary and analysed with the method details below:

- Angular range: 2.5 to 42.0° 2 θ
- Step size: 0.013° 2 θ
- Collection time: 95.6 s/step (total collection time: 20 min 26 sec)

10 The software used for data collection was X'Pert Data Collector and the data analysed and presented using Diffrac Plus EVA.

Variable temperature XRPD (VT-XRPD)

XRPD diffractograms were collected on a PANalytical Empyrean diffractometer using Cu K α radiation (45 kV, 40 mA) in reflection geometry. The instrument is fitted with an Anton Paar CHC plus+ stage fitted with graphite/Kapton windows and equipped with air cooling coupled with a proUmid MHG32 Modular Humidity Generator A programmable divergence slit (in automatic mode), with a 10 mm fixed incident beam mask, Ni filter and 0.04 rad Soller slits were used on the incident beam. A PIXcel^{3D} detector, placed on the diffracted beam, was fitted with a programmable anti-scatter slit (in automatic mode) and 0.04 rad Soller slits.

The software used for data collection was X'Pert Data Collector and the data analysed and presented using Diffrac Plus EVA or Highscore Plus.

For variable temperature (VT-XRPD) experiments the samples were prepared and analysed in an Anton Paar chromed sample holder with silicon wafer insert. A heating/cooling rate of 10 °C/min was used with a 2 min isothermal hold before the measurement started. The measurement parameters are:

- Angular range: 2.5 to 32.0° 2 θ
- Step size: 0.0130° 2 θ
- Collection time: 12.75 s/step (total collection time of 2.07 min)

Measurements were taken at various temperatures.

5 *Differential Scanning Calorimetry (DSC)*

DSC data may be collected on a TA Instruments Q2000 equipped with a 50-position auto-sampler. Typically, 0.5 - 3 mg of each sample, in a pin-holed aluminium pan, was heated at 10 °C/min from 25 °C to 275 °C. A purge of dry nitrogen at 50 ml/min was maintained over the sample.

- 10 The instrument control software was Advantage for Q Series and Thermal Advantage and the data were analysed using Universal Analysis or TRIOS.

Thermo-Gravimetric Analysis (TGA)

- 15 TGA data may be collected on a TA Instruments Q500 TGA, equipped with a 16 position auto-sampler. Typically, 5 - 10 mg of each sample was loaded onto a pre-tared aluminium DSC pan and heated at 10 °C/min from ambient temperature to 350 °C. A nitrogen purge at 60 ml/min was maintained over the sample.

The instrument control software was Advantage for Q Series and Thermal Advantage and the data were analysed using Universal Analysis or TRIOS.

Dynamic Vapour Sorption (DVS)

- 20 DVS studies may be performed using a Surface Measurement Systems Ltd. DVS Resolution with video module, equipment #3441. The software used for data collection is DVS Control Software for 21 CFR Part 11 v1.0.3.0. Data analysis is performed using DVS Standard Analysis Suite v7.2.0.9 (Standard).

- The hygroscopicity was measured according to USP <1241>. The sample was allowed to equilibrate at 0% relative humidity (RH) for six hours. Subsequently, the %RH was increased by steps of 10% until 95% RH was reached, one hour per step. The relative humidity was decreased to 0%RH using the same rate. This cycle was repeated once.

Appearance

A sample of the drug substance is examined for physical form and colour. A qualitative statement about the visual appearance of the drug substance is made. The acceptance criteria was set as white to off-white powder.

10 *Polymorphic form*

The crystalline nature of the drug substance is monitored by XRPD. The diffractogram of the drug substance is recorded and compared with that of Figure 1.

Assay and related substances

- 15 The method for the % w/w assay and the % area related substances determination is a reverse phase gradient HPLC method using a Waters Xselect CSH C18 150 mm x 4.6 mm x 3.5 µm column or equivalent. Column temperature 40 °C. Flow rate 1.0 mL/min. Mobile Phase A = 95/5/0.1 water/acetonitrile/trifluoroacetic acid. Mobile Phase B = 5/95/0.1 water/acetonitrile/trifluoroacetic acid. Gradient
- 20 [time(min)/Mobile Phase A(% v/v)/Mobile Phase B(% v/v)]: 0.0/100/0, 19.0/0/100, 25.0/0/100, 25.1/100/0, 30.0/100/0. Injection volume 5 µL. UV detection at 248 nm. The sample and standard solutions are prepared at a concentration of 0.4 mg/mL in 50/50 acetonitrile/water.

- (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl)
- 25 benzoic acid is quantified as a % w/w assay against an appropriate reference standard and related substances are quantified on a % area basis against the total peak area for all the peaks greater than 0.05 % in the sample chromatogram.

For assay, the HPLC method is used for determining the (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl)benzoic acid content of the drug substance. The acceptance criteria for the assay have been set at 97.0 to 103.0 % w/w on an anhydrous and solvent free basis.

- 5 For related substances, the HPLC method is used for determining the related substances content of the drug substance. The acceptance criterion for the chemical purity is ≥ 97.0 % area.

Total impurities are controlled to a limit of ≤ 3.0 % area.

Chiral purity

- 10 The method for chiral purity determination is a normal phase gradient HPLC method using a Phenomenex Lux Amylase-2 250 mm x 4.6 mm x 3 μ m column or equivalent. Column temperature 40 °C. Flow rate 1.0 mL/min. Mobile phase 15/85/0.1 ethanol/n-heptane/trifluoroacetic acid. Injection volume 5 μ L. UV detection at 248 nm. The sample solution is prepared at a concentration of 1.0
- 15 mg/mL in 15/85 ethanol/n-heptane.

(R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl)benzoic acid chiral purity is quantified on a % area basis calculated as the % of the peak area due to the desired enantiomer versus the total of the peak areas of both the desired and undesired enantiomers.

- 20 The level of the undesired (S) enantiomer in the drug substance is quantified as % area and a chiral purity value determined. The acceptance criterion for chiral purity was set at not less than 98.0 % area.

Water content

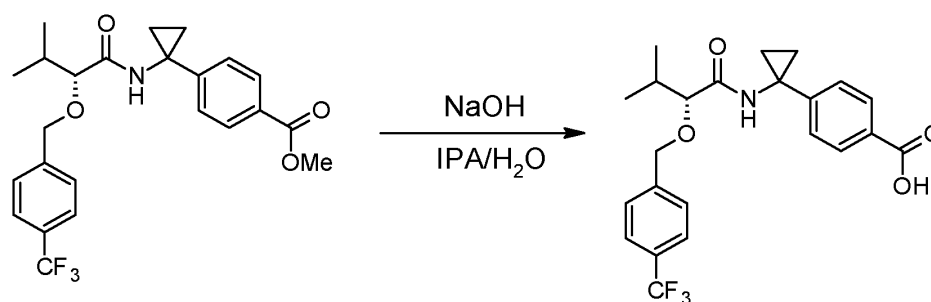
- The water content of the drug substance is determined by Karl-Fischer analysis
- 25 as per USP<921>/PH. Eur 2.5.12. The acceptance criteria was set at not more than 2.0 % w/w.

DSC $T_{(onset)}$

The crystalline nature of the drug substance is monitored by DSC. The thermogram of the drug substance is recorded and compared with that of Figure 2.

5 Example 1

The crystalline form of the invention may be prepared from methyl (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl) benzoate in accordance with the following method:



- 10 Methods for preparing methyl (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl) benzoate are disclosed in WO2021/069927.

Saponification

- 15 A 5 L jacketed reactor equipped with mechanical stirrer, thermometer, dropping funnel and reflux divider with condenser was charged with methyl (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl) benzoate (145.2 g; 0.32 mol; 1.0 eq) in isopropanol (300 mL; 2.0 rel. vol.) and aqueous sodium hydroxide 33% (58.1 g; 0.48 mol; 1.5 eq) was charged via the dosing funnel. Purified water (300 mL; 2 rel. vol.) was added and the solution was
- 20 warmed to 60 ± 5 °C. The solution was stirred at 60 ± 5 °C for 4 h.

The reaction proceeded very slowly without an organic solvent and 24 hours were needed to reach full conversion in water. The reaction worked well in mixtures of water with methanol, tetrahydrofuran or isopropanol.

- 5 The temperature of the reaction was investigated in a screening experiment. The reaction was run at 20, 40 and 60 °C. Full conversion was observed within 1 to 2 hours at 60 °C and within 4.5 hours at 40 °C but took several days at 20 °C. The *in situ* purity profile at the end of the reaction was similar for all temperatures. It is therefore preferable to use a reaction temperature of from 55 to 65 °C, or about 60 °C in this step.

10 *Isolation*

A 1N citric acid solution was prepared by dissolving 198.8 g citric acid in 510 mL purified water and 510 mL isopropanol. The reaction mixture was brought to pH 3.5 by addition of 1105 g of this 1N citric acid solution. The mixture was post-stirred at 60 °C for 20 min and a thick suspension was obtained.

- 15 The mixture was then warmed to 80 °C to dissolve everything and purified water (1750 mL; 12.0 rel. vol.) was dosed within 1 h. Crystallisation occurred after one third of the water was added. The suspension was post-stirred at 80 °C for 16 h and then cooled down to 20 °C over 3.5 h. The suspension was filtered after 1 h post-stirring at 20 °C. The cake was rinsed three times with purified water (3 x 200 mL; 3 x 2.0 rel. vol.) and dried in air to afford the crystalline form of the invention as a white powder (125.5 g; 96%). HPLC purity 99.9 % area.

Isolation of the crystalline form of the invention was optimised.

Acidification was first performed using aqueous hydrochloric acid; however, this was replaced by aqueous citric acid to prevent the formation of isopropyl chloride.

- 25 It is therefore preferable to perform acidification using citric acid.

It is preferable to maintain the reaction mixture at a temperature of from 60 to 70 °C during the acidification step to prevent crystallisation of the compound of Formula (1) during the acidification.

After acidification of the reaction mixture in isopropanol / water, addition of water led to precipitation of the compound of Formula (1).

If addition of water is carried out significantly below 80°C, there is a risk of the compound of Formula (1) precipitating too fast, leading to suspensions that cannot be stirred or gum balls. It is therefore preferable to provide the solution at a temperature of from 75 to 85 °C (about 80 °C). It is also preferable to maintain the solution at a temperature of from 75 to 85 °C, or about 80 °C, during the addition of water.

This optimised procedure delivered the crystalline form of the invention in high purity directly from the reaction mixture.

Characterisation

The XRPD peak listing for the crystalline form is provided in Table 2. The XRPD spectrum for the crystalline form is shown in Figure 1. TGA and DSC plots for the crystalline form are shown in Figure 2. The FT-IR spectrum of the crystalline form is shown in Figure 3. The NMR spectrum of the crystalline form is shown in Figure 4.

The TGA thermogram of the crystalline form indicated no loss of mass prior to degradation at about 280 °C. The ¹H-NMR spectrum was consistent with the proposed structure and no residual solvents were observed. As no solvent was detected by ¹H-NMR and no weight loss observed by TGA, the crystalline form is believed to be an anhydrous form.

Table 2.

Angle (° 2θ)	Intensity (%)
3.5	37.5
4.9	35.1
10.0	100
10.4	21.4
10.7	58.7

11.4	7.5
11.9	24.3
12.4	6.3
14.2	14
14.6	60.7
15.0	89.3
15.2	44.1
15.5	22.3
16.8	25.5
17.7	50.8
17.9	53.6
18.4	22.6
18.7	76.1
19.0	30.9
19.8	49.8
20.1	49.8
20.6	33.9
20.9	69.6
21.5	33.8
21.8	17.4
22.3	9.8
22.9	19.6
23.8	21
24.4	15.1
25.0	25.9
25.4	19.2
26.4	16.7
26.7	14.5
27.1	18.3
27.7	12.7
28.3	15.2
29.1	15.5
29.6	17.9
30.2	26.2

Example 2

The reaction as described in Example 1 was performed in a reaction calorimeter reactor (RC-1) on 28 g scale with respect to the methyl (R)-4-(1-(3-methyl-2-((4-(trifluoromethyl)benzyl)oxy)butanamido)cyclopropyl) benzoate starting material.

5 The addition of sodium hydroxide followed by the reaction at 60 °C released 100.3 kJ / mol heat, corresponding to an adiabatic temperature rise of 8.4 K. The acidification at 60 °C with the citric acid solution led to a heat release of 65.0 kJ / mol, corresponding to an adiabatic temperature rise of 2.2 K. The crystallisation occurred during addition of water at 80 °C and released 222.2 kJ / mol heat,

10 corresponding to an adiabatic temperature rise of 3.8 K. This process is safe to be conducted on large scale.

Example 3

The crystalline form is packaged in double lined anti-static LDPE bags, secured with cable ties, and placed in a sealed HDPE drum.

15 The stability of the crystalline form of the invention was evaluated at the long-term condition of 25 °C/60% relative humidity (RH) for 18 months and an accelerated condition of 40 °C/75% RH for 6 months.

The stability data for the crystalline form are detailed in Table 3 (40 °C/75% RH) and Table 4 (25 °C/60% RH).

20 Table 3

Stability Test	Acceptance Criteria	Time point			
		Initial	1 Month	3 Months	6 Months
Appearance	White to off-white powder	Complies	Complies	Complies	Complies

Polymorphic form (XRPD)	Report result	Consistent with Figure 1	Consistent with Figure 1	Consistent with Figure 1	Consistent with Figure 1
Assay (% w/w)	97.0 – 103.0	99.7	99.6	99.6	100.9
Related Substances (area %)	Purity ≥97.0	99.9	99.9	99.9	99.9
	Total Impurities ≤3.0	0.13 (1)	0.12 (1)	0.13 (1)	0.12 (1)
Chiral Purity (area %)	≥98.0	>99.9	>99.9	>99.9	>99.9
Water content (% w/w)	≤2.0	<0.1	<0.05	<0.05	<0.05
DSC T _(onset) (°C)	Report result	170.9	170.2	170.5	171.4

Table 4

Stability Test	Acceptance Criteria	Time point			
		Initial	6 Months	12 Months	18 Months
Appearance	White to off-white powder	Complies	Complies	Complies	Complies
Polymorphic form (XRPD)	Report result	Consistent with Figure 1	Consistent with Figure 1	Consistent with Figure 1	Consistent with Figure 1

Assay (% w/w)	97.0 – 103.0	99.7	100.1	100.1	100.2
Related Substances (area %)	Purity ≥97.0	99.9	99.9	99.9	99.9
	Total Impurities ≤3.0	0.13 (1)	0.12 (1)	0.13 (1)	0.12 (1)
Chiral Purity (area %)	≥98.0	>99.9	>99.9	>99.9	>99.9
Water content (% w/w)	≤2.0	<0.1	<0.05	<0.05	<0.05
DSC T _(onset) (°C)	Report result	170.9	171.4	172.3	171.0

Example 4

DVS analysis was performed on the crystalline form of the invention. The DVS sorption and de-sorption plot is displayed in Figure 5. The DVS isothermal plot is displayed in Figure 6.

Upon drying in DVS at 0% RH, 0.03 wt% mass loss was observed. Then, a constant uptake was observed with an increasing RH to 0.06 wt% at 70% RH. Above 70% RH the uptake showed a steeper slope and increased to 0.16 wt% at a RH of 95%. The total mass uptake was less than 0.2 wt% and, therefore, the crystalline form of the invention is not hygroscopic according to European pharmacopoeia. The second sorption and desorption showed a similar behaviour. Consequently, the cycle is reversible and reproducible.

XRPD was performed on the sample after DVS analysis and the sample was confirmed to be the crystalline form of the invention.

Comparative Example

A comparative crystalline form of the compound of Formula (1) was prepared in accordance with the following method.

The compound of Formula (1) (500 mg) was treated with dimethyl sulfoxide (DMSO) (3 Vol) at room temperature to give a clear solution. To this was added water (3 Vol). The resulting suspension was vigorously stirred at room temperature for 2 h. A precipitate formed. This material was isolated via Buchner filtration, washed with excess water and allowed to suction dry for 1 h. The sample was then placed into a vacuum oven (RT) for 2 h to further dry.

The XRPD peak listing for the comparative crystalline form is provided in Table 5. The XRPD spectrum for the comparative crystalline form is shown in Figure 7. TGA and DSC plots for the comparative crystalline form are shown in Figure 8. The ¹H-NMR spectrum was consistent with the proposed structure and residual DMSO was observed.

The comparative form is a crystalline, DMSO solvated form. The stability of the comparative form was evaluated at an accelerated condition of 40 °C/75% RH and was found to be unstable following static storage for 7 days. VT-XRPD analysis showed that the comparative crystalline form is also unstable above 100 °C. The comparative crystalline form is slightly hygroscopic.

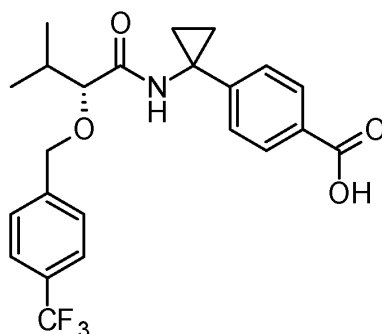
Table 5

Angle (° 2θ)	Intensity (%)
4.4	15.1
8.3	6.6
9.5	5.4
11.4	13.9
13.7	7.3

Angle (° 2 θ)	Intensity (%)
14.0	21.8
14.7	20.2
14.9	11.4
16.6	19.8
16.9	16.5
17.6	44.9
18.1	48.8
18.4	15.7
18.9	91.9
19.3	28.7
19.6	21.8
20.2	39.6
20.5	100
21.0	33.7
21.7	23
22.3	29.5
22.6	43.4
23.4	12.7
24.4	10.1
24.7	12.9
24.9	14
25.4	11.8
25.7	19.2
26.3	13.8
26.6	13.8
26.9	8.9
27.6	41.8
28.3	14.9
29.1	10.1
29.7	11.7
30.1	14.7
30.3	14.7
30.7	12.1

NUMBERED EMBODIMENTS

1. A crystalline form of the compound of Formula (1):



(1);

- 5 wherein:

(i) said crystalline form has an X-ray powder diffraction pattern comprising peaks at 2θ of $10.0 \pm 0.1^\circ$ and $15.0 \pm 0.1^\circ$; and/or

(ii) said crystalline form has a differential scanning calorimetry (DSC) thermogram comprising an endothermic event with an onset temperature at $171 \pm 2^\circ\text{C}$.

2. The crystalline form according to embodiment 1, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $18.7 \pm 0.1^\circ$.

3. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $20.9 \pm 0.1^\circ$.

4. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $14.6 \pm 0.1^\circ$.

5. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $10.7 \pm 0.1^\circ$.
6. The crystalline form according to any preceding embodiment, wherein
5 said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $17.9 \pm 0.1^\circ$.
7. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $17.7 \pm 0.09^\circ$.
- 10 8. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $19.8 \pm 0.1^\circ$.
9. The crystalline form according to any preceding embodiment, wherein
15 said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $20.1 \pm 0.1^\circ$.
10. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $15.2 \pm 0.09^\circ$.
11. The crystalline form according to any preceding embodiment, wherein
20 said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $3.5 \pm 0.1^\circ$.
12. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $4.9 \pm 0.1^\circ$.
- 25 13. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $10.4 \pm 0.1^\circ$.

14. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $11.4 \pm 0.1^\circ$.
15. The crystalline form according to any preceding embodiment, wherein
5 said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $11.9 \pm 0.1^\circ$.
16. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $12.4 \pm 0.1^\circ$.
- 10 17. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $14.2 \pm 0.1^\circ$.
18. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at
15 2θ of $15.5 \pm 0.1^\circ$.
19. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $16.8 \pm 0.1^\circ$.
20. The crystalline form according to any preceding embodiment, wherein
20 said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $18.4 \pm 0.1^\circ$.
21. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $19.0 \pm 0.1^\circ$.
- 25 22. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $20.6 \pm 0.1^\circ$.

23. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $21.5 \pm 0.1^\circ$.
24. The crystalline form according to any preceding embodiment, wherein
5 said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $21.8 \pm 0.1^\circ$.
25. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $22.3 \pm 0.1^\circ$.
- 10 26. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $22.9 \pm 0.1^\circ$.
27. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at
15 2θ of $23.8 \pm 0.1^\circ$.
28. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $24.4 \pm 0.1^\circ$.
29. The crystalline form according to any preceding embodiment, wherein
20 said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $25.0 \pm 0.1^\circ$.
30. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $25.4 \pm 0.1^\circ$.
- 25 31. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $26.4 \pm 0.1^\circ$.

32. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $26.7 \pm 0.1^\circ$.
33. The crystalline form according to any preceding embodiment, wherein
5 said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $27.1 \pm 0.1^\circ$.
34. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $27.7 \pm 0.1^\circ$.
- 10 35. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $28.3 \pm 0.1^\circ$.
36. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at
15 2θ of $29.1 \pm 0.1^\circ$.
37. The crystalline form according to any preceding embodiment, wherein said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $29.6 \pm 0.1^\circ$.
38. The crystalline form according to any preceding embodiment, wherein
20 said crystalline form has an X-ray powder diffraction pattern comprising a peak at 2θ of $30.2 \pm 0.1^\circ$.
39. The crystalline form according to any preceding embodiment, wherein the crystalline form has an X-ray powder diffraction pattern having peaks and substantially similar intensities as shown in the table below:

Angle ($^\circ 2\theta$)	Intensity (%)
3.5 ± 0.1	30 to 50, preferably 37.5
4.9 ± 0.1	30 to 50, preferably 35.1

10.0 ± 0.1	80 to 100, preferably 100
10.4 ± 0.1	10 to 30, preferably 21.4
10.7 ± 0.1	50 to 70, preferably 58.7
11.4 ± 0.1	1 to 20, preferably 7.5
11.9 ± 0.1	15 to 35, preferably 24.3
12.4 ± 0.1	1 to 20, preferably 6.3
14.2 ± 0.1	5 to 25, preferably 14
14.6 ± 0.1	50 to 70, preferably 60.7
15.0 ± 0.1	80 to 100, preferably 89.3
15.2 ± 0.09	35 to 55, preferably 44.1
15.5 ± 0.1	10 to 30, preferably 22.3
16.8 ± 0.1	15 to 35, preferably 25.5
17.7 ± 0.09	40 to 60, preferably 50.8
17.9 ± 0.1	45 to 65, preferably 53.6
18.4 ± 0.1	10 to 30, preferably 22.6
18.7 ± 0.1	65 to 85, preferably 76.1
19.0 ± 0.1	20 to 40, preferably 30.9
19.8 ± 0.1	40 to 60, preferably 49.8
20.1 ± 0.1	40 to 60, preferably 49.8
20.6 ± 0.1	25 to 45, preferably 33.9
20.9 ± 0.1	60 to 80, preferably 69.6
21.5 ± 0.1	25 to 45, preferably 33.8
21.8 ± 0.1	5 to 25, preferably 17.4
22.3 ± 0.1	1 to 20, preferably 9.8
22.9 ± 0.1	10 to 30, preferably 19.6
23.8 ± 0.1	10 to 30, preferably 21
24.4 ± 0.1	5 to 25, preferably 15.1
25.0 ± 0.1	15 to 35, preferably 25.9
25.4 ± 0.1	10 to 30, preferably 19.2
26.4 ± 0.1	5 to 25, preferably 16.7
26.7 ± 0.1	5 to 25, preferably 14.5
27.1 ± 0.1	10 to 30, preferably 18.3

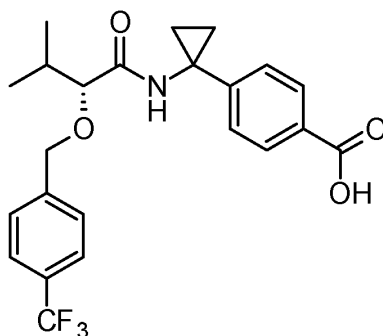
27.7 ± 0.1	5 to 25, preferably 12.7
28.3 ± 0.1	5 to 25, preferably 15.2
29.1 ± 0.1	5 to 25, preferably 15.5
29.6 ± 0.1	10 to 30, preferably 17.9
30.2 ± 0.1	15 to 35, preferably 26.2

40. The crystalline form according to any preceding embodiment, wherein the crystalline form has an X-ray powder diffraction pattern substantially as shown in Figure 1.
- 5 41. The crystalline form according to any preceding embodiment, wherein the crystalline form has an infrared spectrum comprising at least one or all of the following peaks: 3273 ± 2 cm⁻¹, 2960 ± 2 cm⁻¹, 2870 ± 2 cm⁻¹, 1686 ± 2 cm⁻¹, 1657 ± 2 cm⁻¹, 1328 ± 2 cm⁻¹, and 1068 ± 2 cm⁻¹.
42. A composition comprising the crystalline form according to any preceding
10 embodiment.
43. A pharmaceutical composition comprising the crystalline form according to any one of embodiments 1 to 41 and at least one pharmaceutically acceptable excipient.
44. The crystalline form according to any one of embodiments 1 to 41 for use
15 in medicine.
45. The crystalline form for use according to embodiment 44 for use in the treatment of cancer.
46. The crystalline form for use according to embodiment 45, where the cancer is selected from: lung cancer including Non-Small Cell Lung Cancer Small
20 Cell Lung Cancer (SCLC) and squamous cell lung carcinoma, renal cancer including Renal Cell Carcinoma and Urothelial Carcinoma, Hodgkin Lymphoma including Classical Hodgkin Lymphoma, head and neck cancer including Head Neck Squamous Cell Carcinoma (HNSCC) lip cancer oral cavity cancer

nasopharynx cancer and other pharynx cancer, colon cancer, rectum cancer, Colorectal Cancer (CRC) including microsatellite instability-high colorectal cancer (MSI-H CRC) mismatch repair deficient colorectal cancer (dMMR CRC) and microsatellite stable colorectal cancer (MSS CRC), liver cancer including Hepatocellular Carcinoma, Gastric Cancer, Gastro-oesophageal cancer including oesophageal squamous cell carcinoma and gastro oesophageal junction cancer, Oesophageal cancer, Cervical cancer, breast cancer including Triple-Negative Breast Cancer, Melanoma, non-melanoma skin cancer including Merkel Cell Carcinoma and Cutaneous squamous cell carcinoma, Pancreatic cancer, Prostate cancer including castration-resistant prostate cancer and metastatic castration-resistant prostate cancer (mCRPC), Endometrial Cancer, gallbladder cancer, biliary tract cancer, ovarian cancer, testicular cancer, thyroid cancer, larynx cancer, tracheal cancer, bronchus cancer, mesothelioma, bladder cancer, sarcoma, or pheochromocytoma.

15 47. A method for preparing the crystalline form according to any one of
embodiments 1 to 41, the method comprising:

(a) providing a solution comprising the compound of Formula (1)



(1)

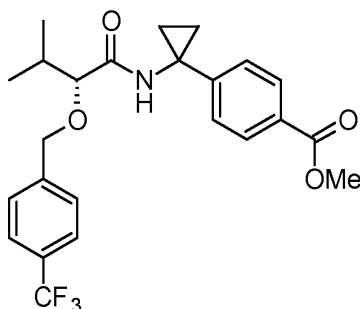
20 in a polar organic solvent at a temperature of from 60 to 90 °C; and

(b) adding water to the solution to induce crystallisation of the crystalline form and obtain a suspension.

48. The method according to embodiment 47, wherein the solution in step (a) comprises the polar organic solvent and water in a volume ratio of from 1:3 to 3:1, or from 1:3 to 2:1, or from 1:3 to 1:1, or from 1:2 to 1:1.
49. The method according to embodiment 47 or 48, wherein the solution in
5 step (a) has a pH of 3.5 or less.
50. The method according to any one of embodiments 47 to 49, wherein the polar organic solvent is isopropanol.
51. The method according to any one of embodiments 47 to 50, wherein the
10 solution in step (a) is provided at a temperature of from 75 to 85 °C, or about 80 °C.
52. The method according to any one of embodiments 47 to 51, wherein step (b) comprises maintaining the solution at a temperature of from 60 to 90 °C, or from 75 to 85 °C, or about 80 °C, during the addition of water.
53. The method according to any one of embodiments 47 to 52, further
15 comprising the following step:
- (c) stirring the suspension for at least 16 hours, and preferably not more than 36 hours, at a temperature of from 75 to 85 °C, or about 80 °C.
54. The method according to any one of embodiments 47 to 53, further comprising the following step:
- 20 (d) adjusting the temperature of the suspension to from 15 to 25 °C, or about 20 °C.
55. The method according to any one of embodiments 47 to 54, further comprising filtering the suspension to obtain a filter cake comprising the crystalline form.
- 25 56. The method according to embodiment 55, further comprising drying the filter cake to obtain the crystalline form.

57. The method according to any one of embodiments 47 to 56, wherein step (a) comprises:

(a)(i) hydrolysing the ester of the compound of Formula (2) in the presence of the polar organic solvent



5

(2).

58. The method according to embodiment 57, wherein the ester of the compound of Formula (2) is hydrolysed using an aqueous base.

59. The method according to embodiment 58, wherein the base is sodium hydroxide.

60. The method according to any one of embodiments 57 to 59, wherein the reaction mixture in step (a)(i) is stirred at a temperature of from 55 to 65 °C, or about 60 °C.

61. The method according to any one of embodiments 57 to 60, further comprising the step of:

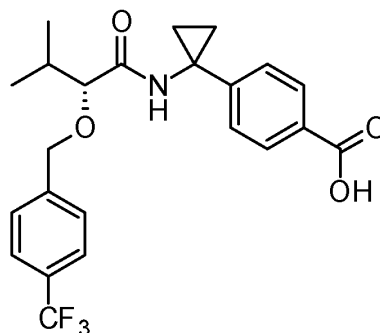
(a)(ii) adjusting the pH of the reaction mixture to a pH of 3.5 or less.

62. The method according to embodiment 61, wherein the pH of the reaction mixture is adjusted using citric acid.

63. The method according to embodiment 61 or 62, wherein step (a)(ii) comprises maintaining the reaction mixture at a temperature of from 60 to 70 °C while adjusting the pH of the reaction mixture to a pH of 3.5 or less.

CLAIMS

1. A crystalline form of the compound of Formula (1):



(1);

- 5 wherein:

(i) said crystalline form has an X-ray powder diffraction pattern comprising peaks at 2θ of $10.0 \pm 0.1^\circ$ and $15.0 \pm 0.1^\circ$; and/or

- (ii) said crystalline form has a differential scanning calorimetry (DSC) thermogram comprising an endothermic event with an onset temperature
10 at $171 \pm 2^\circ\text{C}$.

2. The crystalline form according to claim 1, wherein said crystalline form has an X-ray powder diffraction pattern comprising at least one peak at 2θ selected from the group consisting of $18.7 \pm 0.1^\circ$; $20.9 \pm 0.1^\circ$; $14.6 \pm 0.1^\circ$; $10.7 \pm 0.1^\circ$; $17.9 \pm 0.1^\circ$; $17.7 \pm 0.09^\circ$; $19.8 \pm 0.1^\circ$; $20.1 \pm 0.1^\circ$; $15.2 \pm 0.09^\circ$; $3.5 \pm 0.1^\circ$;
15 $4.9 \pm 0.1^\circ$; $10.4 \pm 0.1^\circ$; $11.4 \pm 0.1^\circ$; $11.9 \pm 0.1^\circ$; $12.4 \pm 0.1^\circ$; $14.2 \pm 0.1^\circ$; $15.5 \pm 0.1^\circ$; $16.8 \pm 0.1^\circ$; $18.4 \pm 0.1^\circ$; $19.0 \pm 0.1^\circ$; $20.6 \pm 0.1^\circ$; $21.5 \pm 0.1^\circ$; $21.8 \pm 0.1^\circ$; $22.3 \pm 0.1^\circ$; $22.9 \pm 0.1^\circ$; $23.8 \pm 0.1^\circ$; $24.4 \pm 0.1^\circ$; $25.0 \pm 0.1^\circ$; $25.4 \pm 0.1^\circ$; $26.4 \pm 0.1^\circ$; $26.7 \pm 0.1^\circ$; $27.1 \pm 0.1^\circ$; $27.7 \pm 0.1^\circ$; $28.3 \pm 0.1^\circ$; $29.1 \pm 0.1^\circ$; $29.6 \pm 0.1^\circ$; and/or $30.2 \pm 0.1^\circ$.

- 20 3. The crystalline form according to any preceding claim, wherein the crystalline form has an X-ray powder diffraction pattern having peaks and substantially similar intensities as shown in the table below:

Angle ($^\circ 2\theta$)	Intensity (%)
3.5 ± 0.1	30 to 50, preferably 37.5

4.9 ± 0.1	30 to 50, preferably 35.1
10.0 ± 0.1	80 to 100, preferably 100
10.4 ± 0.1	10 to 30, preferably 21.4
10.7 ± 0.1	50 to 70, preferably 58.7
11.4 ± 0.1	1 to 20, preferably 7.5
11.9 ± 0.1	15 to 35, preferably 24.3
12.4 ± 0.1	1 to 20, preferably 6.3
14.2 ± 0.1	5 to 25, preferably 14
14.6 ± 0.1	50 to 70, preferably 60.7
15.0 ± 0.1	80 to 100, preferably 89.3
15.2 ± 0.09	35 to 55, preferably 44.1
15.5 ± 0.1	10 to 30, preferably 22.3
16.8 ± 0.1	15 to 35, preferably 25.5
17.7 ± 0.09	40 to 60, preferably 50.8
17.9 ± 0.1	45 to 65, preferably 53.6
18.4 ± 0.1	10 to 30, preferably 22.6
18.7 ± 0.1	65 to 85, preferably 76.1
19.0 ± 0.1	20 to 40, preferably 30.9
19.8 ± 0.1	40 to 60, preferably 49.8
20.1 ± 0.1	40 to 60, preferably 49.8
20.6 ± 0.1	25 to 45, preferably 33.9
20.9 ± 0.1	60 to 80, preferably 69.6
21.5 ± 0.1	25 to 45, preferably 33.8
21.8 ± 0.1	5 to 25, preferably 17.4
22.3 ± 0.1	1 to 20, preferably 9.8
22.9 ± 0.1	10 to 30, preferably 19.6
23.8 ± 0.1	10 to 30, preferably 21
24.4 ± 0.1	5 to 25, preferably 15.1
25.0 ± 0.1	15 to 35, preferably 25.9
25.4 ± 0.1	10 to 30, preferably 19.2
26.4 ± 0.1	5 to 25, preferably 16.7
26.7 ± 0.1	5 to 25, preferably 14.5

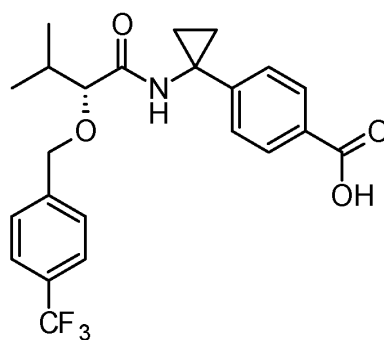
27.1 ± 0.1	10 to 30, preferably 18.3
27.7 ± 0.1	5 to 25, preferably 12.7
28.3 ± 0.1	5 to 25, preferably 15.2
29.1 ± 0.1	5 to 25, preferably 15.5
29.6 ± 0.1	10 to 30, preferably 17.9
30.2 ± 0.1	15 to 35, preferably 26.2

4. The crystalline form according to any preceding claim, wherein the crystalline form has an X-ray powder diffraction pattern substantially as shown in Figure 1.
- 5 5. The crystalline form according to any preceding claim, wherein the crystalline form has an infrared spectrum comprising at least one or all of the following peaks: 3273 ± 2 cm⁻¹, 2960 ± 2 cm⁻¹, 2870 ± 2 cm⁻¹, 1686 ± 2 cm⁻¹, 1657 ± 2 cm⁻¹, 1328 ± 2 cm⁻¹, and 1068 ± 2 cm⁻¹.
6. A composition comprising the crystalline form according to any preceding claim.
- 10 7. A pharmaceutical composition comprising the crystalline form according to any one of claims 1 to 5 and at least one pharmaceutically acceptable excipient.
8. The crystalline form according to any one of claims 1 to 5 for use in medicine; preferably for use in the treatment of cancer; and optionally wherein the cancer is selected from: lung cancer including Non-Small Cell Lung Cancer Small Cell Lung Cancer (SCLC) and squamous cell lung carcinoma, renal cancer including Renal Cell Carcinoma and Urothelial Carcinoma, Hodgkin Lymphoma including Classical Hodgkin Lymphoma, head and neck cancer including Head Neck Squamous Cell Carcinoma (HNSCC) lip cancer oral cavity cancer
- 15 nasopharynx cancer and other pharynx cancer, colon cancer, rectum cancer, Colorectal Cancer (CRC) including microsatellite instability-high colorectal cancer (MSI-H CRC) mismatch repair deficient colorectal cancer (dMMR CRC) and microsatellite stable colorectal cancer (MSS CRC), liver cancer including Hepatocellular Carcinoma, Gastric Cancer, Gastro-oesophageal cancer including
- 20

oesophageal squamous cell carcinoma and gastro oesophageal junction cancer, Oesophageal cancer, Cervical cancer, breast cancer including Triple-Negative Breast Cancer, Melanoma, non-melanoma skin cancer including Merkel Cell Carcinoma and Cutaneous squamous cell carcinoma, Pancreatic cancer, Prostate cancer including castration-resistant prostate cancer and metastatic castration-resistant prostate cancer (mCRPC), Endometrial Cancer, gallbladder cancer, biliary tract cancer, ovarian cancer, testicular cancer, thyroid cancer, larynx cancer, tracheal cancer, bronchus cancer, mesothelioma, bladder cancer, sarcoma, or pheochromocytoma.

10 9. A method for preparing the crystalline form according to any one of claims 1 to 5, the method comprising:

(a) providing a solution comprising the compound of Formula (1)



(1)

15 in a polar organic solvent at a temperature of from 60 to 90 °C; and

(b) adding water to the solution to induce crystallisation of the crystalline form and obtain a suspension.

10. The method according to claim 9, wherein:

(i) the solution in step (a) comprises the polar organic solvent and water
20 in a volume ratio of from 1:3 to 3:1, or from 1:3 to 2:1, or from 1:3 to 1:1, or from 1:2 to 1:1; and/or

(ii) the solution in step (a) has a pH of 3.5 or less; and/or

(iii) the polar organic solvent is isopropanol; and/or

(iv) the solution in step (a) is provided at a temperature of from 75 to 85
25 °C, or about 80 °C; and/or

(v) step (b) comprises maintaining the solution at a temperature of from 60 to 90 °C, or from 75 to 85 °C, or about 80 °C, during the addition of water.

11. The method according to any one of claims 9 to 10, further comprising the following step:

5 (c) stirring the suspension for at least 16 hours, and preferably not more than 36 hours, at a temperature of from 75 to 85 °C, or about 80 °C.

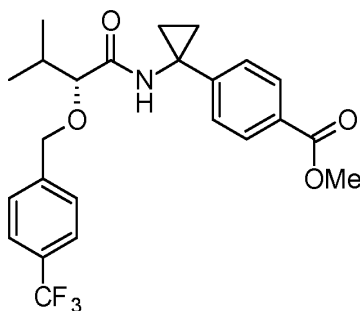
12. The method according to any one of claims 9 to 11, further comprising the following step:

10 (d) adjusting the temperature of the suspension to from 15 to 25 °C, or about 20 °C.

13. The method according to any one of claims 9 to 12, further comprising filtering the suspension to obtain a filter cake comprising the crystalline form; and optionally drying the filter cake to obtain the crystalline form.

14. The method according to any one of claims 9 to 13, wherein step (a) comprises:

15 (a)(i) hydrolysing the ester of the compound of Formula (2) in the presence of the polar organic solvent



(2);

20 preferably wherein the ester of the compound of Formula (2) is hydrolysed using an aqueous base; and optionally wherein the base is sodium hydroxide; and/or wherein the reaction mixture in step (a)(i) is stirred at a temperature of from 55 to 65 °C, or about 60 °C.

15. The method according to claim 14, further comprising the step of:
(a)(ii) adjusting the pH of the reaction mixture to a pH of 3.5 or less;
preferably wherein the pH of the reaction mixture is adjusted using citric acid; and/or
- 5 preferably wherein step (a)(ii) comprises maintaining the reaction mixture at a temperature of from 60 to 70 °C while adjusting the pH of the reaction mixture to a pH of 3.5 or less.