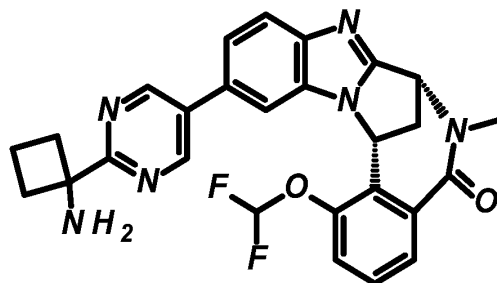


CRYSTALLINE FORM

Disclosed herein is a crystalline form of a compound of Formula (I):



i.e. (7R,14R)-11-[2-(1-aminocyclobutyl)pyrimidin-5-yl]-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-b][2,5]benzodiazocin-5(14H)-one. A pharmaceutical composition comprising this crystalline form, and medical uses of the crystalline form and pharmaceutical composition are also described.

Background

(7R,14R)-11-[2-(1-aminocyclobutyl)pyrimidin-5-yl]-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-b][2,5]benzodiazocin-5(14H)-one (the compound of Formula (I)) is a pharmacologically active substituted fused pentacyclic benzimidazole derivative which shows pharmacological activity on TNF α signalling.

TNF α is the prototypical member of the Tumour Necrosis Factor (TNF) superfamily of proteins that share a primary function of regulating cell survival and cell death. One structural feature common to all known members of the TNF superfamily is the formation of trimeric complexes that bind to, and activate, specific TNF superfamily receptors. By way of example, TNF α exists in soluble and transmembrane forms and signals through two receptors, known as TNFR1 and TNFR2, with distinct functional endpoints.

Various products capable of modulating TNF α activity are already commercially available. All are approved for the treatment of inflammatory and autoimmune disorders such as rheumatoid arthritis and Crohn's disease. All currently approved products are macromolecular and act by inhibiting the binding of human TNF α to its receptor. Typical macromolecular TNF α inhibitors include anti-TNF α antibodies and soluble TNF α receptor fusion proteins. Examples of commercially available anti-TNF α antibodies include fully human antibodies such as adalimumab (Humira®) and golimumab (Simponi®), chimeric

antibodies such as infliximab (Remicade®), and pegylated Fab' fragments such as certolizumab pegol (Cimzia®). An example of a commercially available soluble TNF α receptor fusion protein is etanercept (Enbrel®).

The compound of Formula (I) is a potent modulator of human TNF α activity and is therefore beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders, neurological and neurodegenerative disorders, pain and nociceptive disorders, cardiovascular disorders, metabolic disorders, ocular disorders, and oncological disorders.

The compound of Formula (I) is known in the art in its amorphous form (see Example 6 of WO 2018/197503). However, no crystalline or polymorphic forms of the compound of Formula (I) are known in the art.

In general, there is a desire to produce solid forms of pharmacologically active substances with advantageous physical properties, for example in terms of optimal chemical and physical stability, acceptable solubility, better handling properties, etc. From a chemistry point of view, generating a crystalline form of an active ingredient allows access to purification processes, which permits easier control of the final impurity profile of the compound. Typically, amorphous forms (such as known in the art for Formula (I)) are not desirable, for example due to having sub-optimal stability profiles and/or handling properties. Amorphous compounds often exhibit a high propensity to absorb water.

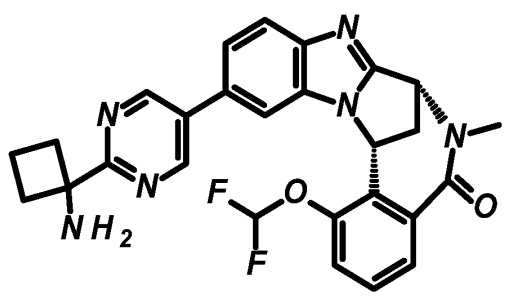
Thus, there is a need to develop solid forms of the compound of Formula (I) with advantageous properties.

Polymorphism refers to the existence of multiple crystalline forms of the same substance. Particular polymorphic or crystalline forms of a drug may have advantageous characteristics versus other polymorphic, crystalline, or amorphous forms, including, for example, increased stability, increased solubility, better handling properties, lack of associated toxic solvents, and increased purity. Thus, the polymorphic behaviour of drugs can be of crucial importance in pharmacy and pharmacology. However, the existence of polymorphic or different crystalline forms, and the properties associated with each particular form, is highly unpredictable.

Summary

The present disclosure is based on the unexpected finding that: a) several crystalline forms of (7R,14R)-11-[2-(1-aminocyclobutyl)pyrimidin-5-yl]-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-b][2,5]benzodiazocin-5(14H)-one (the compound of Formula (I)) exist; and b) that one particular crystalline form (referred to herein as Form A) has significantly improved properties compared to the other crystalline forms that have been identified.

Herein is therefore provided a specific crystalline form of a compound of Formula (I):



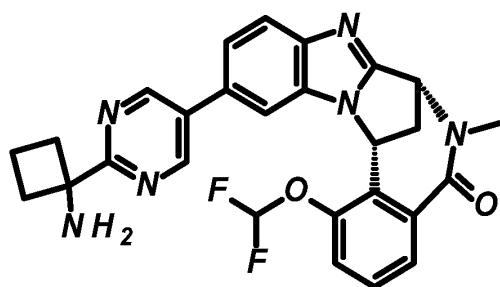
wherein the crystalline form is Form A, having an X-ray powder diffraction pattern comprising characteristic peaks at $4.0^\circ \pm 0.2^\circ$ 2θ , $10.5^\circ \pm 0.2^\circ$ 2θ , and $12.0^\circ \pm 0.2^\circ$ 2θ .

Herein is also provided a pharmaceutical composition comprising crystalline Form A as described above.

Herein is also provided crystalline Form A as defined above, or a pharmaceutical composition as defined herein, for use in therapy, for example in the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder.

Herein is also provided a process of manufacturing crystalline Form A as defined above, wherein the process comprises:

a) combining compound of Formula (I):



with a solvent to form a mixture;

b) heating the mixture to a temperature of about 50 °C or greater;

c) cooling the mixture to ambient temperature or lower.

Brief Description of the Figures

Fig. 1 shows a differential scanning calorimetry (DSC) plot of crystalline Form A.

Fig. 2 shows an X-ray powder diffraction pattern of crystalline Form A.

Fig. 3a and 3b show dynamic vapor sorption (DVS) plots of crystalline Form A, obtained on two samples.

Fig. 4 shows a TGA plot of crystalline Form A.

Fig. 5 shows an X-ray powder diffraction (XRPD) pattern of crystalline Form B.

Fig. 6 shows an XRPD comparison between crystalline Forms B (upper graph) and A (lower graph).

Fig. 7a shows an XRPD comparison between crystalline Form B (wet, upper graph) and isopropyl alcohol solvate dried form (lower graph).

Fig. 7b shows the molecular representation of the single crystal structure of crystalline Form B.

Fig. 8 shows an XRPD comparison between crystalline Form C (wet, upper graph) and compound of Formula (I) butanol-2 solvate dry (lower graph).

Fig. 9 shows DSC and TGA plots of crystalline Form C.

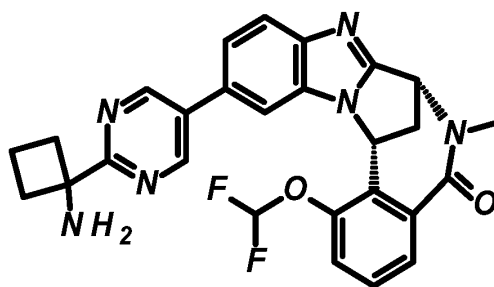
Fig. 10 shows an XRPD comparison between crystalline Forms B (upper graph) and F (lower graph).

Fig. 11 shows DSC and TGA plots of crystalline Form F.

Fig. 12 shows a comparison of the DSC patterns of crystalline Forms F (upper graph) and Form A (lower graph).

Detailed Description

Herein is disclosed a specific crystalline form of a compound of Formula (I):



i.e. (7R,14R)-11-[2-(1-aminocyclobutyl)pyrimidin-5-yl]-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-b][2,5]benzodiazocin-5(14H)-one, which is referred to herein as Form A.

Crystalline Form A may be characterised by powder X-ray diffraction. Crystalline Form A may have an X-ray powder diffraction pattern comprising characteristic peaks at $4.0^\circ \pm 0.2^\circ 2\theta$, $10.5^\circ \pm 0.2^\circ 2\theta$, and $12.0^\circ \pm 0.2^\circ 2\theta$. The X-ray powder diffraction pattern may further comprise a peak at $12.6^\circ \pm 0.2^\circ 2\theta$. The X-ray powder diffraction pattern may further comprise a peak at $16.1^\circ \pm 0.2^\circ 2\theta$. The X-ray powder diffraction pattern may further comprise a peak at $18.0^\circ \pm 0.2^\circ 2\theta$. Thus, the X-ray powder diffraction pattern may comprise 3, 4, 5, 6, or more characteristic peaks.

The X-ray powder diffraction pattern of crystalline Form A may comprise peaks at 4.0, 10.5, 12.0, 12.6, 15.5, 16.1, and 18.0, with each peak measured to $\pm 0.2^\circ 2\theta$.

The X-ray powder diffraction pattern of crystalline Form A may comprise peak positions corresponding to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or all of the peak positions listed in Table 1 below, which is generated from experimental powder diffraction data:

Angle (2-theta °) (± 0.2)	Relative Intensity (%)
3.9868	98.06
10.4515	37.66
12.0165	33.51
12.5481	18.11
15.5144	7
16.1037	5.66
17.0345	4.25
17.9941	100
18.8573	12.02
19.3668	28.55
20.5324	14.62
21.5995	10.23
22.8452	13.32
24.1724	15.64
24.6379	13.86
24.9435	18.49
25.9258	11.16
27.4774	7.41
31.9646	3.77

Table 1

The X-ray powder diffraction pattern of crystalline Form A may be substantially as illustrated in Fig. 2.

Crystalline Form A may be characterised by DSC or by TGA. A DSC thermogram of crystalline Form A may have a single endothermic peak at about $222\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$. The enthalpy change of the endothermic peak may be about -50 J/g.

Crystalline Form A is only slightly hygroscopic (defined as presenting an increase in mass of less than 2% according to European Pharmacopeia Ed. 11.0, section 5-11). In particular, crystalline Form A is only slightly hygroscopic (defined as presenting an increase in mass of less than 2% between 0 and 80 % RH at 25 °C, according to European Pharmacopeia Ed. 11.0, section 5-11). Specifically, crystalline Form A demonstrates an increase in mass of at most 0.5% between 0 to 90% HR (relative humidity). In particular, crystalline Form A demonstrates an increase in mass of at most 0.5% between 0 to 90% HR (relative humidity) at 25°C. This low hygroscopicity provides significant advantages in terms of storage (shelf stability) and physical stability behaviour. Crystalline Form A is also thermally stable: this is evident from the DSC of Fig. 1 which shows that crystalline Form A

has only a single, clean melting/decomposition peak at about 222 °C (± 2 °C). TGA analysis also shows the crystalline Form A is chemically stable until close to its melting temperature, as shown in Fig. 4.

Herein is also provided a pharmaceutical composition comprising crystalline Form A as defined above. For example, the pharmaceutical composition may comprise crystalline Form A and one or more pharmaceutically acceptable excipients, carriers, or diluents.

In various embodiments, the pharmaceutical composition comprises at least about 20 wt% of crystalline Form A, optionally about 30 wt% of crystalline Form A, optionally about 40 wt% of crystalline Form A, optionally about 50 wt% of crystalline Form A, optionally about 60 wt% of crystalline Form A, optionally about 70 wt% of crystalline Form A, optionally about 80 wt% of crystalline Form A, optionally about 90 wt% of crystalline Form A, optionally about 95 wt% of crystalline Form A.

At least about 50 mol% of the compound of Formula (I) in the composition may be in the form of crystalline Form A. For example, at least about 60 mol%, or 70 mol%, or 80 mol%, or 90 mol%, or 95 mol% of the compound of Formula (I) in the composition may be in the form of crystalline Form A. Substantially all of the compound of Formula (I) in the composition may be in the form of crystalline Form A.

The crystalline form and pharmaceutical composition described herein are beneficial in the treatment and/or prevention of various indications, including those that occur in humans. These include autoimmune and inflammatory disorders, neurological and neurodegenerative disorders, pain and nociceptive disorders, cardiovascular disorders, metabolic disorders, ocular disorders, and oncological disorders.

Thus, herein is provided a crystalline form or a pharmaceutical composition as defined above for use in the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder.

Herein is also provided a method for the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder, which comprises administering to a patient in need of such treatment an effective amount of a crystalline form or a pharmaceutical composition as defined herein.

Herein is also provided the use of a crystalline form or a pharmaceutical composition as defined above for the manufacture of a medicament for the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder.

Inflammatory and autoimmune disorders include systemic autoimmune disorders, autoimmune endocrine disorders, and organ-specific autoimmune disorders. Systemic autoimmune disorders include systemic lupus erythematosus (SLE), psoriasis, psoriatic arthropathy, vasculitis, inflammatory myopathy (including polymyositis, dermatomyositis, and inclusion body myositis), scleroderma, multiple sclerosis, systemic sclerosis, ankylosing spondylitis, rheumatoid arthritis, non-specific inflammatory arthritis, juvenile inflammatory arthritis, juvenile idiopathic arthritis (including oligoarticular and polyarticular forms thereof), anaemia of chronic disease (ACD), Still's disease (juvenile and/or adult onset), Behçet's disease, and Sjögren's syndrome. Autoimmune endocrine disorders include thyroiditis. Organ-specific autoimmune disorders include Addison's disease, haemolytic or pernicious anaemia, acute kidney injury (AKI; including cisplatin-induced AKI), diabetic nephropathy (DN), obstructive uropathy (including cisplatin-induced obstructive uropathy), glomerulonephritis (including Goodpasture's syndrome, immune complex-mediated glomerulonephritis, and antineutrophil cytoplasmic antibodies (ANCA)-associated glomerulonephritis), lupus nephritis (LN), minimal change disease, Graves' disease, idiopathic thrombocytopenic purpura, inflammatory bowel disease (including Crohn's disease, ulcerative colitis, indeterminate colitis, and pouchitis), pemphigus, atopic dermatitis, autoimmune hepatitis, primary biliary cirrhosis, autoimmune pneumonitis, autoimmune carditis, myasthenia gravis, spontaneous infertility, osteoporosis, osteopenia, erosive bone disease, chondritis, cartilage degeneration and/or destruction, fibrosing disorders (including various forms of hepatic and pulmonary fibrosis), asthma, rhinitis, chronic obstructive pulmonary disease (COPD), respiratory distress syndrome, sepsis, fever, muscular dystrophy (including Duchenne muscular dystrophy), organ transplant rejection (including kidney allograft rejection), scleritis (including giant cell arteritis scleritis), Takayasu arteritis, hidradenitis suppurativa, pyoderma gangrenosum, sarcoidosis, polymyalgia rheumatic, and axial spondyloarthritis.

Neurological and neurodegenerative disorders include Alzheimer's disease, Parkinson's disease, Huntington's disease, ischaemia, stroke, amyotrophic lateral sclerosis, spinal cord injury, head trauma, seizures, and epilepsy.

Cardiovascular disorders include thrombosis, cardiac hypertrophy, hypertension, irregular contractility of the heart (e.g. during heart failure), and sexual disorders (including erectile dysfunction and female sexual dysfunction). Modulators of TNF α function may also be of use in the treatment and/or prevention of myocardial infarction.

Metabolic disorders include diabetes (including insulin-dependent diabetes mellitus and juvenile diabetes), dyslipidemia, and metabolic syndrome.

Ocular disorders include retinopathy (including diabetic retinopathy, proliferative retinopathy, non-proliferative retinopathy, and retinopathy of prematurity), macular oedema (including diabetic macular oedema), age-related macular degeneration (ARMD), vascularisation (including corneal vascularisation and neovascularisation), retinal vein occlusion, and various forms of uveitis (including iritis) and keratitis.

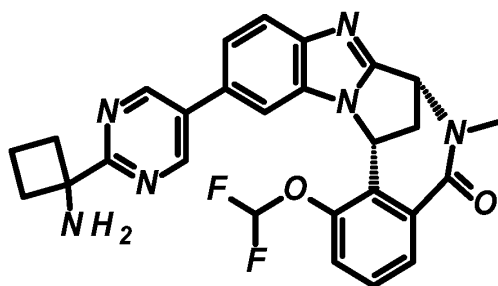
Oncological disorders, which may be acute or chronic, include proliferative disorders, especially cancer, and cancer-associated complications (including skeletal complications, cachexia, and anaemia). Particular categories of cancer include haematological malignancy (including leukaemia and lymphoma) and non-haematological malignancy (including solid tumour cancer, sarcoma, meningioma, glioblastoma multiforme, neuroblastoma, melanoma, gastric carcinoma, and renal cell carcinoma). Chronic leukaemia may be myeloid or lymphoid. Varieties of leukaemia include lymphoblastic T cell leukaemia, chronic myelogenous leukaemia (CML), chronic lymphocytic/lymphoid leukaemia (CLL), hairy-cell leukaemia, acute lymphoblastic leukaemia (ALL), acute myelogenous leukaemia (AML), myelodysplastic syndrome, chronic neutrophilic leukaemia, acute lymphoblastic T cell leukaemia, plasmacytoma, immunoblastic large cell leukaemia, mantle cell leukaemia, multiple myeloma, acute megakaryoblastic leukaemia, acute megakaryocytic leukaemia, promyelocytic leukaemia, and erythroleukaemia. Varieties of lymphoma include malignant lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, MALT1 lymphoma, and marginal zone lymphoma. Varieties of non-haematological malignancy include cancer of the prostate, lung, breast, rectum, colon, lymph node, bladder, kidney, pancreas, liver, ovary, uterus,

cervix, brain, skin, bone, stomach, and muscle. Modulators of TNF α function may also be used to increase the safety of the potent anticancer effect of TNF.

Herein is also provided a process for manufacturing crystalline Form A as defined above.

In an embodiment, the process comprises:

- a) combining compound of Formula (I):



with a solvent to form a mixture;

- b) heating the mixture to a temperature of about 50 °C or greater;
c) cooling the mixture to ambient temperature or lower.

As used herein, the term “ambient temperature” refers to the temperature of the room in which the mixture is cooled. Typically, ambient temperature is from about 18 °C to about 25 °C.

In step a) the solvent may be selected from acetonitrile, ethyl acetate, and propyl acetate, and is optionally selected from acetonitrile.

The mixture may be stirred during step a).

The compound of Formula (I) may be provided in any form. For example, solid compound of Formula (I) may be added to the solvent to form a mixture. Alternatively, a solution of compound of Formula (I) may be added to another solvent to form a mixture in step a). For example, a solution of compound of Formula (I) dissolved in 2-methyltetrahydrofuran may be added to another solvent to form a mixture in step a).

The mixture may be heated to a temperature of about 50°C or greater in step b), optionally from about 60 °C to about 90 °C, for example to a temperature of from about 75 °C to about 90 °C.

After step b), a seed crystal of crystalline Form A may be added to the mixture to promote nucleation. For example, a seed crystal of crystalline Form A may be added when the temperature of the mixture is in the range of about 50 °C to about 65 °C. After seeding, the mixture may be cooled to 0-10 °C, for example applying a linear cooling ramp rate of about -10 °C/h.

In step c) the mixture may be cooled at a linear cooling ramp, for example at a rate of about -10°C/h. The mixture may be cooled for about 4 h or greater.

In an embodiment, the mixture may be cooled in one, two, or more phases. For example, the mixture may be cooled in an initial cooling phase from 75 °C-85 °C to about 65 °C, after which the mixture is cooled to about 0°C. The mixture may also be cooled in an initial cooling phase from about 90 °C to about 56 °C, followed by a cooling to about 50°C, after which the mixture is cooled to about 10 °C.

Following the cooling step c), the mixture may be stirred for between 5 and 25 h, optionally at a temperature below ambient temperature, for example at about 0-10 °C. The mixture may be washed with one or more solvents that crystalline Form A is not soluble in, for example with tert-butyl methyl ether. The resulting wet cake may be dried under vacuum to produce dry, crystalline Form A.

EXAMPLES

Having been generally described herein, the follow non-limiting examples are provided to further illustrate the disclosure.

Unless otherwise specified, parameters disclosed herein are measured as set out in the Examples below.

Synthesis of amorphous (7R,14R)-11-[2-(1-aminocyclobutyl)pyrimidin-5-yl]-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-b][2,5]benzodiazocin-5(14H)-one

Amorphous (7R,14R)-11-[2-(1-aminocyclobutyl)pyrimidin-5-yl]-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-b][2,5]benzodiazocin-5(14H)-one (the compound of Formula (I)) was synthesised as is disclosed in WO 2018/197503.

Analytical methods

I. DIFFERENTIAL SCANNING CALORIMETRY (DSC)

DSC analyses were carried out on a DSC821 or on a DSC 2 Star System (Mettler Toledo Instruments). The samples are prepared in Aluminum 40 μ l crucibles with perforated lids crimped not tightly and analyses under a nitrogen sweep of 50 ml/min. Analyses were carried out, with a scanning rate of 2 °C/min up to 250 °C.

II. THERMOGRAVIMETRIC ANALYSIS (TGA)

TG analyses were carried out on a TGA 1 Star System (Mettler Toledo Instruments). Sample masses of few mg were deposited in aluminum 100 μ l crucibles without pin and analyzed under a nitrogen sweep of 20 ml/min. Analyses were carried out, with a scanning rate of 2 °C/min (Fig. 9 and 11) or 10 °C/min (Fig. 4) up to 250 °C.

III. X-RAY POWDER DIFFRACTION (XRPD)

Analyses were carried out at room temperature on a Panalytical diffractometer controlled by X'Pert Pro software, in Bragg-Brentano assembly with a sealed copper anode X-ray tube (λ CuK α average = 1.54178 Å) (45kV and 40mA). A counting time of few seconds per step in an angular range from few 2-Theta degrees to 40°degrees with a 0.016° step size in 2 θ was used for each sample analysis. For each experiment, the powder (or the suspension) was deposited onto the surface of a monocrystalline silicon sample holder.

IV. DYNAMIC VAPOR SORPTION (DVS)

Approximately 10 mg of sample was placed into pan and loaded into a DVS Intrinsic Vapour Measurement Systems or TA Instrument Q2000. The sample was first equilibrated at 40 %RH and 25 °C then subjected to a ramping profile from 40 %RH to 90 %RH then from 90 %RH to 0%RH, and finally from 0%RH to 40 %RH or 90 %RH, at 10% increments. At each step, the sample was maintained until a stable weight had been achieved or for a maximum step length of 360 minutes. The weight change during the sorption/desorption cycles were plotted, allowing for the hygroscopic nature of the sample to be determined.

Example 1 – Crystalline Form A of the compound of Formula (I) (anhydrate)**Obtaining seed crystals of Form A in acetonitrile:**

A solution at 300 g/l of amorphous form of the compound of Formula (I) in acetonitrile was prepared at 50 °C. Natural cooling at ambient temperature led to obtention of crystalline Form A by spontaneous nucleation.

Obtaining Form A crystals in Et₂O/hexane:

A solution of 17.987 g (29.85 mmol) of tert-butyl (1-{5-[(7R,14R)-1-(difluoromethoxy)-6-methyl-5-oxo-5,6,7,14-tetrahydro-7,14-methanobenzimidazo[1,2-b][2,5]benzodiazocin-11-yl]pyrimidin-2-yl}cyclobutyl)-carbamate (Intermediate 17 in patent application WO 2018/197503, which is the N-1 intermediate for the compound of formula (I)) was prepared in 25 mL of 1,4-dioxane (25 mL). 40 mL of 4M HCl in dioxane were added, in one portion. The resulting mixture was stirred at room temperature for 1 hour before it was concentrated in vacuo. The residue was taken up in water (500 mL) and washed with EtOAc (2x300 mL). The aqueous layer was then basified to pH 9 with 2 N NaOH, which resulted in ready and visible product precipitation. EtOAc (500 mL) was added and the mixture was stirred until all solids dissolved before it was partitioned. The aqueous layer was further extracted with EtOAc (500 mL). The combined organic layers were dried over Na₂SO₄, filtered, concentrated in vacuo and dried overnight under high vacuum. The foamy product was then suspended in a 1:1 mixture of Et₂O and hexane, stirred and shaken vigorously, and concentrated in vacuo to afford 11.76 g of the compound of Formula (I) as white solid, later analyzed as corresponding to crystalline Form A.

Preparing crystalline Form A using seed crystals:

Solutions of amorphous form of the compound of Formula (I) were prepared at 50 °C using ethyl acetate or propyl acetate. The solutions were seeded using seed crystals obtained as described above. Crystals of Form A of the compound of Formula (I) were obtained.

Scale-up 1:

Into a 5-mL double-jacketed vessel was placed crude compound of Formula (I) (1.024 g, 2.03 mmol) and 3.409 ml acetonitrile. The resulting suspension was stirred with an impeller (8 mm diameter) at 1250 rpm during the heating ramp to dissolution. Total dissolution was observed at 90°C. A linear cooling ramp was applied to the solution at -

20 °C/h to 56 °C. A suspension of seed was introduced at 56 °C, leading to nucleation, followed by a cooling to 50 °C. Two hours isotherm at 50 °C was maintained, and the suspension was finally cooled with a linear cooling ramp of -10 °C/h to 10 °C. After 25 hours of isotherm at 10 °C, the suspension was filtered on sintered glass filter, porosity 4, followed by two hours of solvent expurgation under vacuum. The powder was then dried in a static oven under vacuum at 50 °C. This process led to a white powder of 99.6% purity with a weight Loss corrected yield of 74%. The dry solid was analysed by XRPD, DSC, and TGA and identified as Form A.

Scale-up 2:

A solution of compound of Formula (I) in 2-methyltetrahydrofuran (4.1% w/w; 26.2 kg net, 52.14 mol) was charged through 0.22 µm cartridge in a double jacketed vessel. The clear solution was concentrated to 2-3 volumes at 50 °C under vacuum, then 3 volumes of acetonitrile was added. The operation was repeated 5 times to reach a 2-methyltetrahydrofuran residual content < 0.10% and a water content < 0.50%. The suspension was heated at 75-85 °C for 0.5 to 2h. The clear solution obtained was cooled to 65 °C, and seed of compound of Formula (I) was added. A linear cooling ramp was applied down to 0 °C. The suspension was stirred for 5-24h at 0 °C and then filtered. After washing with 4 volumes of tert-butyl methyl ether, the cake was dried under vacuum at 60 °C. 20.8 kg of an off-white powder was obtained with 80% yield. The crystalline Form A was confirmed by XRPD.

Differential scanning calorimetry (DSC):

Differential scanning calorimetry was performed on crystalline Form A as described herein. The results are shown in Fig. 1. Form A exhibits a clean melting/decomposition peak at about 222 °C (± 2 °C) with an enthalpy of -50 J/g.

X-ray powder diffraction:

X-ray powder diffraction was performed on crystalline Form A as described herein. The results are shown in Fig. 2 and are summarised in Table 2:

Angle (2-theta °) (± 0.2)	Relative Intensity (%)
3.9868	98.06
10.4515	37.66
12.0165	33.51
12.5481	18.11
15.5144	7
16.1037	5.66
17.0345	4.25
17.9941	100
18.8573	12.02
19.3668	28.55
20.5324	14.62
21.5995	10.23
22.8452	13.32
24.1724	15.64
24.6379	13.86
24.9435	18.49
25.9258	11.16
27.4774	7.41
31.9646	3.77

Table 2

DVS (Dynamic Vapor Sorption) and TGA (thermogravimetric analysis)

DVS of crystalline Form A was performed as described herein. The results are shown in Fig. 3a and 3b, showing DVS plots performed on two samples of Form A. Crystalline Form A demonstrated an increase in mass of 0.5% (Fig. 3a) or about 0.3% (Fig. 3b) between 0 to 90% HR (relative humidity). Form A is therefore considered to be only slightly hygroscopic.

TGA of crystalline Form A was performed as described herein, at 10 °C/min. The results are shown in Fig. 4. The results show the anhydrate nature of the crystalline form, with nearly no loss of weight until the decomposition temperature.

Example 2 – Crystalline Form B of compound of Formula (I) (isopropyl alcohol solvate)**Obtaining crystals:**

Crystals of Form B of compound of Formula (I) (isopropyl alcohol solvate, also named IPA solvate) were obtained by adding, to 0.035 g of amorphous crude compound of Formula (I), 350 μ l of isopropyl alcohol (10 vol) at ambient temperature. Crystallization was apparent from transformation of the suspension (visual observation).

Scale-up:

Compound of Formula (I) (6.947 g, 13.8 mmol) was placed into a 100-mL double-jacketed vessel, with 10 V isopropanol (corresponding to 70 ml). The resulting suspension was stirred with an impeller (120 W/m³) at 468 rpm during the heating ramp to dissolution. Total dissolution was observed at 69 °C. A fast cooling ramp was applied to the solution to 25 °C, followed by a 16 hours isothermal step. The suspension was then filtered, washed, and analyzed wet showing an XRPD pattern corresponding to the isopropanol solvated form. After drying in an oven at 50°C under vacuum, the XRPD pattern changed to another pattern.

X-ray powder diffraction:

X-ray powder diffraction was performed on crystalline Form B as described herein. The results are shown in Fig. 5 and are summarised in Table 3:

Angle (2-theta °) ($\pm$ 0.2)	Relative Intensity (%)
5.92	100
10.27	0.99
10.78	1.04
11.84	1.02
12.92	0.71
13.66	0.8
15.84	1.66
16.66	1.41
17.95	0.61
18.53	0.97
20.63	4.13
21.44	1.63
22.30	0.49

Table 3

Fig. 6 shows an XRPD comparison between crystalline Form B (upper graph) and the anhydrate Form A (lower graph).

Comparison of wet form (crystal Form B of compound of Formula (I) isopropyl alcohol solvate) and dry form:

Fig. 7a shows an XRPD comparison between crystalline Form B (wet, upper graph) and isopropyl alcohol solvate dried form (lower graph). It shows that drying has an impact on the XRPD pattern, which indicates lack of stability of this solvate form upon drying. Thus, crystalline Form B is not an industrially developable form.

Single crystal structure:

A single crystal structure determination was performed to assess the solvated aspect of Form B. Examination of the structure showed that the asymmetric unit in the crystal contain one compound of Formula (I) crystallized with one IPA molecule, therefore, the stoichiometry ratio in Form B is 1:1, as shown in Fig. 7b, which shows an ORTEP representation of the structure of compound of Formula (I) crystallized with IPA in the crystal (Form B).

Example 3 – Crystalline Form C of compound of Formula (I) (butanol-2 solvate)

Obtaining crystals:

Crystals of Form C were obtained by recrystallizing Form A of compound of Formula (I) in butan-2-ol with 100 g/l of solvent.

Crystals of Form C were also obtained by adding 100 g/l of butan-2-ol to amorphous compound of Formula (I), heating to 50 °C, and then cooling.

X-ray powder diffraction:

The results of X-ray powder diffraction performed on crystalline Form C are summarised in Table 4:

Angle (2-theta °) (± 0.2)	Relative Intensity (%)
5.888	100
10.1543	0.55
10.4876	1.36
11.7595	3.17
12.8079	0.51
13.3794	1.18
15.3931	1.77
16.2101	1.65
16.6421	0.29
17.516	0.58
18.144	1.25
18.3755	2.85
18.8303	0.64
19.7031	0.25
20.3617	6.11
21.2531	4
22.1505	1.11
22.7504	0.45
23.6146	1.02
24.1597	0.52
25.7672	0.66
26.4165	0.45
27.1373	0.24
28.5435	0.48
29.6415	1.23
30.1096	0.24
30.7797	0.28
37.2348	0.14

Table 4

Comparison of wet form (crystal Form C of compound of Formula (I) butanol-2 solvate) and dry form:

Fig. 8 shows an XRPD comparison between crystalline Form C (wet, upper graph) and compound of Formula (I) butanol-2 solvate dry (lower graph). The graphs demonstrate that drying has an impact on the XRPD pattern, indicating a lack of stability of this solvate form upon drying. Thus, crystalline Form C is not an industrially developable form.

Differential scanning calorimetry (DSC) / thermogravimetric analysis (TGA):

DSC and TGA were performed on crystalline Form C. The results are shown in Fig. 9.

Example 4 – Crystalline Form F of compound of Formula (I) (anhydrate)**Obtaining crystals:**

Crystals of Form F of compound of Formula (I) were obtained by desolvation of crystals of Form B (the isopropyl alcohol crystal form described above), followed by hydration and then dehydration.

Crystals of Form B (compound of Formula (I) isopropyl alcohol form) were first obtained as described above, then dried 12 h at 60 °C and desolvated in the oven. The solid was then rehydrated by leaving at ambient temperature, then dehydrated to produce anhydrous Form F.

X-ray powder diffraction:

Fig. 10 shows an XRPD comparison between compound of Formula (I) isopropyl alcohol Form B (upper graph) and anhydrous Form F (lower graph).

The results of X-ray powder diffraction performed on crystalline Form F are summarised in Table 5:

Angle (2-theta °) (± 0.2)	Relative Intensity (%)
6.1058	38.37
7.0284	100
8.6158	14.43
12.2032	74.6
14.0663	31.03
15.3942	19.39
16.5292	33.68
17.0042	15.5
17.6955	49.54
18.3094	48.22
19.0822	18.86
19.4418	19.35

Angle (2-theta °) (± 0.2)	Relative Intensity (%)
20.2548	27.24
21.1979	12.88
22.1422	65.87
23.288	15.23
25.883	26.72
26.8223	14.05

Table 5

Differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and Dynamic Vapor Sorption (DVS):

DSC/TGA were performed on crystalline Form F. The results are shown in Fig. 11.

Comparison of crystalline Form A and crystalline Form F:

Fig. 12 shows a comparison of the DSC patterns of crystalline Form F (upper graph) and crystalline Form A (lower graph).

DVS was performed on crystalline Forms A and F as described herein. The results are shown in Tables 6 and 7, showing a 0.3% increase in mass for Form A *versus* about 11% for Form F. In other experiments, the maximum increase in mass observed for Form A was 0.5%.

HR in %	Weight change in %: Absorption		
	Form A	Form A Values aligned at 0	Form F
0	-0.027	0	0
10	-0.01	0.02	0.304
20	0.029	0.06	0.81
30	0.066	0.09	3.37
40	0.11	0.14	4.04
50	0.14	0.17	4.14
60	0.17	0.20	5.8
70	0.21	0.24	7.25
80	0.24	0.27	8.78
90	0.27	0.3	11.55

Table 6

	Weight change in %: Desorption		
HR in %	Form A	Form A Values aligned at 0	Form F
0	-0.027	0	0
10	0.006	0.03	0.99
20	0.05	0.08	1.46
30	0.1	0.13	3.8
40	0.15	0.18	4.28
50	0.19	0.22	5.05
60	0.22	0.25	6.67
70	0.24	0.27	7.83
80	0.26	0.29	9.21
90	0.27	0.3	11.53

Table 7

These results confirm that crystalline Form A is significantly less hygroscopic than crystalline Form F.

Table 8 provides a comparison of the two anhydrate crystalline Forms A and F, and shows that the more stable form is Form A. Specifically, Form A has a higher melting temperature, and higher enthalpy of fusion. Weight loss was measured by TGA.

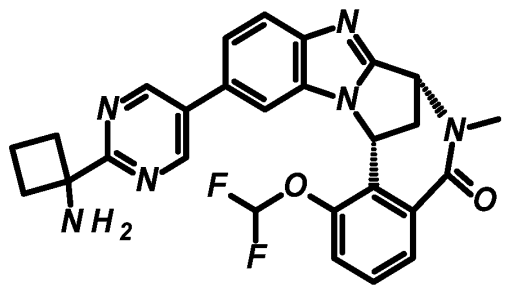
	FORM A	FORM F
Peak temperature (°C)	222	215
ΔH (J/g)	-50.02 (Fig. 1) -50.89 (Fig. 12)	-23.28 (Fig. 11) -23.38 (Fig. 12)
Weight loss	-0.14% * (between 30 and 210°C)	-0.55% * (between 170 and 210°C)

*Low figures (-0.14%, -0.55%), confirming that both forms are anhydrous

Table 8

CLAIMS

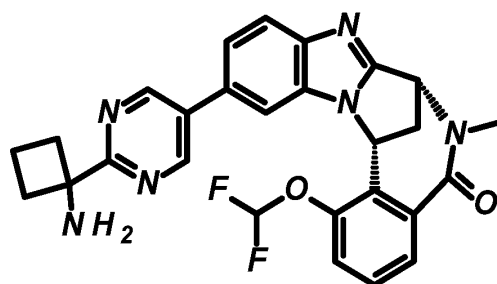
1. A crystalline form of a compound of Formula (I):



wherein the crystalline form is of Form A, having an X-ray powder diffraction pattern comprising characteristic peaks at $4.0^\circ \pm 0.2^\circ 2\theta$, $10.5^\circ \pm 0.2^\circ 2\theta$, and $12.0^\circ \pm 0.2^\circ 2\theta$.

2. The crystalline form according to claim 1, wherein the X-ray powder diffraction pattern further comprises a peak at $12.6^\circ \pm 0.2^\circ 2\theta$.
3. The crystalline form according to claim 1 or claim 2, wherein the X-ray powder diffraction pattern further comprises a peak at $16.1^\circ \pm 0.2^\circ 2\theta$.
4. The crystalline form according to any one of claims 1 to 3, wherein the X-ray powder diffraction pattern further comprises a peak at $18.0^\circ \pm 0.2^\circ 2\theta$.
5. The crystalline form according to any one of claims 1 to 4, wherein the X-ray powder diffraction pattern comprises peaks at 4.0, 10.5, 12.0, 12.6, 15.5, 16.1, and 18.0° , with each peak measured to $\pm 0.2^\circ 2\theta$.
6. The crystalline form according to any one of claims 1 to 5, wherein the X-ray powder diffraction pattern is substantially as illustrated in Fig. 2.
7. The crystalline form according to any one of claims 1 to 6, wherein the DSC thermogram of crystalline Form A has a single endothermic peak at about $222^\circ\text{C} \pm 2^\circ\text{C}$.
8. The crystalline form according to any one of claims 1 to 7, wherein the crystalline form is an anhydrate.
9. A pharmaceutical composition comprising: a) crystalline Form A as defined in any one of claims 1 to 8; and b) one or more pharmaceutically acceptable excipients, carriers, or diluents.

10. The pharmaceutical composition according to claim 9, wherein the pharmaceutical composition comprises at least about 50 wt% of crystalline Form A as defined in any one of claims 1 to 8.
11. The pharmaceutical composition according to claim 9 or claim 10, wherein at least about 80 mol% of the compound of Formula (I) in the composition is crystalline Form A as defined in any one of claims 1 to 8.
12. A crystalline form as defined in any one of claims 1 to 8, or a pharmaceutical composition as defined in any one of claims 9 to 11, for use in therapy.
13. A crystalline form as defined in any one of claims 1 to 8, or a pharmaceutical composition as defined in any one of claims 9 to 11, for use in the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder.
14. A process of manufacturing a crystalline form as defined in any one of claims 1 to 8, wherein the process comprises:
- a) combining compound of Formula (I):



with a solvent to form a mixture;

b) heating the mixture to a temperature of about 50 °C or greater;

c) cooling the mixture to ambient temperature or lower.

15. The process of claim 14, wherein the solvent is selected from acetonitrile, ethyl acetate and propyl acetate, and is optionally acetonitrile.

16. The process according to claim 14 or 15, wherein in step b) the mixture is cooled for greater than about 4 h.

17. The process according to any one of claims 14 to 16, wherein in step b) the mixture is heated to a temperature of about 50 °C or greater, optionally from about 60 °C to about 90 °C.
18. The process according to any one of claims 14 to 17, wherein the process further comprises adding a seed crystal to the mixture, wherein the seed crystal is a crystal of Form A as defined in any one of claims 1 to 8.