(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 February 2025 (13.02.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/032190 A1

(51) International Patent Classification:
C07D 401/04 (2006.01) *A61P 37/00* (2006.01)
A61P 29/00 (2006.01) *A61K 31/435* (2006.01)

(21) International Application Number:
PCT/EP2024/072504

(22) International Filing Date:
08 August 2024 (08.08.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
23190662.9 09 August 2023 (09.08.2023) EP

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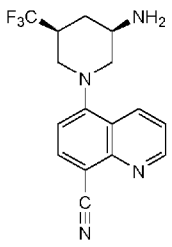
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) Title: CRYSTALLINE FORM A1 OF 5-((3R,55)-3-AMINO-5- TRIFLUOROMETHYL-PIPERIDIN-1-YL)-QUINOLINE-8-CARBONITRILE HCL



(57) **Abstract:** A crystalline anhydrous polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile HCl is provided herein. Processes for preparing the polymorph and pharmaceutical composition comprising the polymorph are also disclosed.

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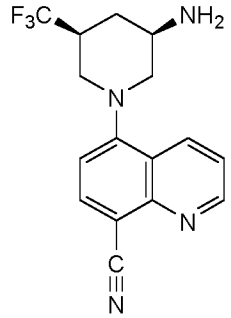
CRYSTALLINE FORM A1 OF 5-((3R,55)-3-AMINO-5- TRIFLUOROMETHYL-PIPERIDIN-1-YL)-QUINOLINE-8-CARBONITRILE HCL

FIELD

[0001] A crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile HCl is provided herein. Processes for preparing the polymorph and pharmaceutical composition comprising the polymorph are also disclosed.

BACKGROUND

[0002] 5-((3R,5S)-3-Amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile, also named Enpatoran, is a compound having the following structure:



[0003] Enpatoran is a potent and selective dual toll-like receptor (TLR) 7/8 inhibitor in clinical development, including for the treatment of cutaneous and systemic lupus erythematosus (CLE/SLE). The compound may be prepared according to the methods provided in WO 2017/106607.

[0004] Polymorphism refers to the occurrence of different crystalline forms of a compound. A single compound may give rise to a variety of polymorphic forms, each having different solid-state physical properties, such as different solubility, melting point, stability, dissolution rates and/or different X-ray diffraction peaks. Due to the possibility of variable solubility and/or stability of different polymorph, identifying the existence of polymorphs of pharmaceutical compounds is important for providing pharmaceutical products having predictable solubility profiles. It may be desirable to investigate solid state forms of a drug, including polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Unfortunately, the existence of particular polymorphic forms and their physical properties is unpredictable.

[0005] When used for treating humans, it is important that a crystalline form of a therapeutic agent, like 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile, or a salt thereof, retains appropriate polymorphic and chemical stability,

solubility, and other physicochemical properties over time and among various manufactured batches of the agent. If the physical or chemical properties vary with time and/or among batches, the administration of a therapeutically effective dose may become problematic and may lead to inconsistent dosages or to ineffective therapy. Therefore, it is important to choose a polymorphic form of the agent that is stable, is manufactured reproducibly, and has physicochemical properties favorable for its use as a therapeutic agent.

[0006] However, the art remains unable to predict which crystalline form of an agent will have a combination of the desired properties and will be suitable for human administration, and how to make the agent in such a crystalline form.

SUMMARY

[0007] In one aspect, the disclosure provides a crystalline anhydrous polymorphic form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile, termed herein Form HCl A1. The polymorphic form described herein is useful in the treatment of immune disorders, including TLR7/8-related diseases, such as cutaneous and systemic lupus erythematosus (CLE/SLE).

[0008] In another aspect, the disclosure provides a composition comprising 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1. An embodiment provides a pharmaceutical composition comprising Form HCl A1 described herein, and one or more pharmaceutically acceptable carriers or excipients.

[0009] In another aspect, the disclosure provides methods of treating diseases responsive to the administration of a dual toll-like receptor (TLR) 7/8 inhibitor by the administration of a pharmaceutical dosage form comprising 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1.

[0010] Another aspect provides methods of treating a disease or disorder modulated by TLR 7/8, comprising administering to a mammal in need of such treatment an effective amount of a composition comprising 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1. The method may comprise the administration of a composition(s) comprising Form HCl A1 alone or in combination with one or more additional polymorphs or compounds having inhibitory properties for TLR 7/8.

[0011] Another aspect provides the use of 5-((3R,5S)-3-amino-5-(trifluoromethyl)-piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 in the manufacture of a medicament for the treatment of an immune disorder.

BRIEF DESCRIPTION OF THE FIGURES

[0012] Figure 1 shows the Powder X-ray diffractogram of HCl salt Form A1.

[0013] Figure 2 shows the single crystal structure of HCl salt Form A1.

[0014] Figure 3 shows the DSC scan of HCl salt Form A1 (5 K/min).

[0015] Figure 4 shows the TGA scan of HCl salt Form A1 form (5 K/min).

[0016] Figure 5 shows the Water Vapor Sorption Isotherm (25 °C) of HCl salt Form A1.

DETAILED DESCRIPTION

[0017] As used herein, the term "polymorph" or "polymorphic form" refer to a crystallographically distinct form of a substance. The practical physical characteristics of a polymorphic form are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular polymorphic form of a substance. Different polymorphs of the same compound may have different physical, chemical, biological and/or spectroscopic properties. For example, and without limitation, different polymorphic forms may have different stability properties. A particular polymorphic form may be more sensitive to relative humidity, heat and/or light. In some cases, differences in stability result from changes in chemical reactivity, such as and without limitation, differential oxidation. Such properties may provide for more suitable product qualities such as a dosage form that is more resistant to discoloration when comprised of a particular polymorph.

[0018] Alternatively or additionally, a particular polymorphic form may have a different dissolution rate thereby providing, for example, a more desirable bioavailability. Alternatively or additionally, a particular polymorphic form may provide different compressibility and/or density properties, thereby providing more desirable characteristics for formulation and/or product manufacturing. Mechanical characteristics may differ between polymorphs also. For example and without limitation, tablets having a higher ratio of a particular polymorph may be more resistant to crumbling on storage. Also, the different physical properties of polymorphs may affect their processing. For example, a particular polymorph may be more or less likely to form solvates or may be more difficult to filter and/or wash.

[0019] Polymorphs can be detected, identified, classified and characterized using well-known techniques such as, but not limited to, powder X-ray diffractometry (PXRD), single crystal X-ray diffractometry, differential scanning calorimetry (DSC), thermogravimetry (TGA), vibrational spectroscopy, solution calorimetry, solid state nuclear magnetic resonance

(NMR), infrared (IR) spectroscopy, Raman spectroscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography, quantitative analysis, solubility, and rate of dissolution.

[0020] As used herein when referring to a spectrum and/or to data presented in a graph, the term "peak" refers a feature that one skilled in the art would recognize as not attributable to background noise.

[0021] In embodiments, the invention provides a crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 characterized by one or more peaks from the powder X-ray diffraction (PXRD) (Cu-Kα_1 radiation), presented in degrees 2θ ±0.2°, wherein the peaks comprise 8.1, 11.9, 14.4, 17.0, 17.4, 18.0, 18.9, 19.8, 20.3, 20.8, 22.5, 23.6, 24.4, 25.4, 26.2 and 29.8

[0022] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 may be characterized by two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more or ten or more, or eleven or more, twelve or more, thirteen or more, fourteen or more, fifteen or more or each of the PXRD peaks 8.1, 11.9, 14.4, 17.0, 17.4, 18.0, 18.9, 19.8, 20.3, 20.8, 22.5, 23.6, 24.4, 25.4, 26.2 and 29.8. All PXRD peaks provided herein are measured with Cu-Kα_1 radiation in degrees 2θ and include ±0.2 degrees.

[0023] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 may be characterized by PXRD peaks comprising a peak at 22.5.

[0024] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 may be characterized by PXRD peaks comprising peaks at 14.4 and 22.5.

[0025] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 may be characterized by PXRD peaks comprising peaks at 14.4, 17.0 and 22.5.

[0026] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 may be characterized by PXRD peaks comprising peaks at 8.1, 14.4, 17.0 and 22.5.

[0027] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 may be characterized by PXRD peaks comprising peaks at 8.1, 11.9, 14.4, 17.0 and 22.5.

[0028] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 may be characterized by PXRD peaks comprising peaks at 8.1, 11.9, 14.4, 17.0, 17.4 and 22.5.

[0029] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 may be characterized by PXRD peaks comprising peaks at 8.1, 11.9, 14.4, 17.0, 17.4, 22.5, and 29.8.

[0030] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 may additionally or alternatively be characterized by single crystal X-Ray diffraction. Form HCl A1 crystallizes in the monoclinic space group $P2_1$ with the lattice parameters $a = 5.20215 \pm 0.1$ Å, $b = 14.6970 \pm 0.1$ Å, $c = 10.8135 \pm 0.1$ Å, and $\beta = 90.261°$ (with $\alpha = \gamma = 90°$).

[0031] In aspects, this disclosure provides compositions comprising 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1. The composition comprising Form HCl A1, may compromise Form HCl A1 alone or in combination with one or more additional polymorphs or compounds having inhibitory properties for TLR 7/8.

[0032] Enpatoran compositions comprising crystalline polymorph Form HCl A1 may comprise Form HCl A1 in any quantity. Compositions may comprise less than about 1 % Form HCl A1. Compositions may comprise 1 % to 100% of Form HCl A1. Compositions may comprise 50 % to 100% of Form HCl A1. Compositions may comprise 80 % to 100% of Form HCl A1. Compositions may comprise 90 % to 100% of Form HCl A1. Compositions may comprise 5% to 99% of Form HCl A1. Compositions may comprise 10% to 95% Form HCl A1. Compositions may comprise 15% to 95% Form HCl A1. Compositions may comprise 1 % to 80% Form HCl A1. Compositions may comprise 1% to 75% Form HCl A1. Compositions may comprise 1 % to 70% Form HCl A1. Compositions may comprise 1% to 65% Form HCl A1. Compositions may comprise 1% to 60% Form HCl A1. Compositions may comprise 1 % to 55% Form HCl A1. Compositions may comprise 1 % to 50% Form HCl A1. Compositions may comprise 1 % to 25% Form HCl A1. Compositions may comprise 1 % to 20% Form HCl A1. Compositions may comprise 1 % to 15% Form HCl A1. Compositions may comprise 1 % to 10% Form HCl A1. Compositions may comprise 1% to 5% Form HCl A1.

[0033] Further aspects provide a pharmaceutical composition comprising Form HCl A1 described herein, and one or more pharmaceutically acceptable carriers or excipients. The term “pharmaceutically acceptable carrier or excipient” refers to a non-toxic carrier, adjuvant, excipient or vehicle that does not interfere with the pharmacological activity of the compound

with which it is formulated. Pharmaceutically acceptable carriers or excipients that may be used in the pharmaceutical compositions of Form HCl A1 include any such excipients known in the art.

[0034] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form. Exemplary oral dosage forms are capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient may be combined with emulsifying and suspending agents. If desired, sweetening, flavoring or coloring agents are optionally also added.

[0035] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound comprising Form HCl A1 may be mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form also optionally comprises buffering agents.

[0036] Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type are also employed as

fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0037] In another aspect, the disclosure provides methods of treating diseases responsive to the administration of a dual toll-like receptor (TLR) 7/8 inhibitor by the administration to a patient in need thereof a pharmaceutical dosage form comprising 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1. The term "patient" or "subject" as used herein, means an animal, preferably a mammal, and most preferably a human.

[0038] Another aspect provides methods of treating a disease or disorder modulated by TLR 7/8, comprising administering to a mammal in need of such treatment an effective amount of a composition comprising 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1. The method may comprise the administration of a composition(s) comprising Form HCl A1 alone or in combination with one or more additional polymorphs or compounds having inhibitory properties for TLR 7/8.

[0039] The present disclosure furthermore relates to a method for treating or preventing a disease or disorder in a subject, such as a TLR7/8 related disorder, comprising administering to said subject an effective amount of a composition(s) comprising Form HCl A1.

[0040] The disease or disorder to be treated or prevented by administering a composition comprising 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 may be an autoimmune disease, for instance, one characterized by joint pain, antinuclear antibody positivity, malar rash, or discoid rash. In some aspects, the autoimmune disease is associated with the skin, muscle tissue, and/or connective tissue. In some embodiments, the autoimmune disease is not evidenced in the individual by skin, muscle tissue, and/or connective tissue symptoms. In some embodiments, the autoimmune disease is systemic. Autoimmune diseases that may be treated or prevented by administering a composition comprising 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Form HCl A1 include, without limitation, rheumatoid arthritis (RA), autoimmune pancreatitis (AIP), lupus, such as systemic lupus erythematosus (SLE) or cutaneous lupus erythematosus (CLE), type I diabetes mellitus, multiple sclerosis (MS), antiphospholipid syndrome (APS), sclerosing cholangitis, systemic onset arthritis, irritable bowel disease (IBD), scleroderma, Sjogren's disease, vitiligo, myositis, such as dermatomyositis or polymyositis, pemphigus vulgaris, pemphigus foliaceus, inflammatory bowel disease including Crohn's disease and ulcerative colitis, autoimmune hepatitis, hypopituitarism, graft-versus-host disease (GvHD), autoimmune skin diseases, uveitis, pernicious anemia, and

hypoparathyroidism. The autoimmune disease may also be, without limitation, polyangiitis overlap syndrome, Kawasaki's disease, sarcoidosis, glomerulonephritis, and cryopathies.

[0041] In some aspects, the autoimmune disease is selected from the group consisting of arthritis, pancreatitis, mixed connective tissue disease (MCTD), lupus, antiphospholipid syndrome (APS), systemic onset arthritis, and irritable bowel syndrome.

[0042] In other aspects, the autoimmune disease is selected from the group consisting of pancreatitis, glomerulonephritis, pyelitis, sclerosing cholangitis, and type I diabetes. In some aspects, the autoimmune disease is rheumatoid arthritis. In some aspects, the autoimmune disease is autoimmune pancreatitis (AIP). In some aspects, the autoimmune disease is glomerulonephritis. In some aspects, the autoimmune disease is pyelitis. In some aspects, the autoimmune disease is sclerosing cholangitis. In some aspects the autoimmune disorder is psoriasis. In some aspects, the autoimmune disease is a rheumatoid disease or disorder.

[0043] In other aspects, the autoimmune disease is selected from the group consisting of systemic lupus erythematosus (SLE), rheumatoid arthritis, autoimmune skin disease, and multiple sclerosis. The autoimmune disease may be cutaneous and systemic lupus erythematosus (CLE/SLE). In some aspects, any of the above-mentioned autoimmune diseases is a TLR7/8-related autoimmune disease.

EXAMPLES

Example 1: Preparation of HCl Salt Form A1

[0044] Approx. 1.1 g of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile prepared according to the method of WO 2017/106607 (compound 73) were dissolved in 7 mL ethanol at 50 °C. 312 µL of HCl were diluted in 0.5 mL of ethanol. Both solutions were combined at 50 °C. A yellow precipitation was observed. The turbid solution was cooled down to 4 °C in 7.5 hours and filtrated. The solid was dried at ambient conditions under N_2-flux.

Example 2: NMR data for HCl salt Form A1

[0045] NMR data for HCl salt Form A1: ^{1}H NMR (500 MHz, DMSO) δ 9.08 (dd, J = 4.2, 1.6 Hz, 1H), 8.57 (dd, J = 8.6, 1.6 Hz, 1H), 8.51 (s, 3H), 8.29 (d, J = 8.0 Hz, 1H), 7.73 (dd, J = 8.6, 4.2 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 3.78 – 3.72 (m, 1H), 3.72 – 3.65 (m, 1H),

3.61 – 3.53 (m, 1H), 3.28 – 3.17 (m, 1H), 2.97 (t, J = 11.6 Hz, 1H), 2.89 (t, J = 11.0 Hz, 1H), 2.43 (d, J = 11.9 Hz, 1H), 1.67 (q, J = 12.1 Hz, 1H).

Example 3: Crystallographic studies of HCl salt Form A1

[0046] A Powder X-Ray Diffraction pattern was obtained by standard techniques as described in the European Pharmacopeia 6th Edition chapter 2.9.33, and is characterized by the X-ray powder diffractogram of Figure 1 (monochromatic Cu-Kα_1 radiation, λ = 1.5406 Å, Stoe StadiP 611 KL transmission diffractometer) and having the following peaks:

No.	°2θ (Cu-Kα_1 radiation) ± 0.2°
1	8.1
2	11.9
3	14.4
4	17
5	17.4
6	18
7	18.9
8	19.8
9	20.3
10	20.8
11	22.5
12	23.6
13	24.4
14	25.4
15	26.2
16	29.8

[0047] Single crystal X-Ray structure data were obtained on HCl salt Form A1 form (Oxford Diffraction Supernova Single Crystal X-ray Diffractometer with Graphite monochromator and CCD Detector) at 298 K. HCl salt Form A1 crystallizes in the

monoclinic space group $P2_1$ with the lattice parameters a = 5.20215 ± 0.1 Å, b = 14.6970 ± 0.1 Å, c = 10.8135 ± 0.1 Å, and β = 90.261° (with $\alpha = \gamma = 90°$). As can be seen from the single crystal structure, HCl salt Form A1 represents an anhydrous form.

Example 4: Physical Properties of HCl salt Form A1

[0048] HCl salt Form A1 is characterised by the following physical properties. Thermal behaviour shows no significant enthalpic events <300 °C. TGA shows weight loss of ~1.1 % (w/w) up to 160 °C prior start of decomposition. DSC and TGA profiles are displayed in Figures 3 and 4, respectively. The DSC scan of HCl salt Form A1 was acquired on a Mettler-Toledo DSC1 with a heating rate of 5 K/min, using nitrogen purge gas at 50 mL/min. The TGA scan of HCl salt Form A1 was acquired on a Mettler-Toledo TGA 851 with a heating rate of 5 K/min, using nitrogen purge gas at 50 mL/min.

[0049] Water Vapour Sorption behaviour reveals water uptake levels ~1 % (w/w) in the full relative humidity (RH) range 0-98% RH. HCl salt Form A1 can be classified as non-hygroscopic to slightly hygroscopic according to Ph. Eur. criteria (section 5.11.). The Water Vapour Sorption isotherm (25 °C) is displayed in Figure 5. The Water Vapour Sorption isotherm was acquired on a DVS Intrinsic system from SMS.

We Claim:

1. A crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile characterized by one or more peaks from the powder X-ray diffraction (PXRD), wherein the peaks, expressed in degrees 2θ ±0.2°, comprise 8.1, 11.9, 14.4, 17.0, 17.4, 18.0, 18.9, 19.8, 20.3, 20.8, 22.5, 23.6, 24.4, 25.4, 26.2 and 29.8.
2. The crystalline polymorph of claim 1, wherein characterized by two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more or ten or more, or eleven or more, twelve or more, thirteen or more, fourteen or more, fifteen or more or each of the PXRD peaks, expressed in degrees 2θ ±0.2°, 8.1, 11.9, 14.4, 17.0, 17.4, 18.0, 18.9, 19.8, 20.3, 20.8, 22.5, 23.6, 24.4, 25.4, 26.2 and 29.8.
3. The crystalline polymorph of claim 1, characterized by PXRD peaks, expressed in degrees 2θ ±0.2°, comprising a peak at 22.5.
4. The crystalline polymorph of claim 1, characterized by PXRD peaks, expressed in degrees 2θ ±0.2°, comprising peaks at 14.4 and 22.5.
5. The crystalline polymorph of claim 1, characterized by PXRD peaks, expressed in degrees 2θ ±0.2°, comprising peaks at 14.4, 17.0 and 22.5.
6. The crystalline polymorph of claim 1, characterized by PXRD peaks, expressed in degrees 2θ ±0.2°, comprising peaks at 8.1, 14.4, 17.0 and 22.5.
7. The crystalline polymorph of claim 1, characterized by PXRD peaks, expressed in degrees 2θ ±0.2°, comprising peaks at 8.1, 11.9, 14.4, 17.0 and 22.5.
8. The crystalline polymorph of claim 1, characterized by PXRD peaks, expressed in degrees 2θ ±0.2°, comprising peaks at 8.1, 11.9, 14.4, 17.0, 17.4, 22.5, and 29.8.
9. A crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile characterized by a monoclinic space group $P2_1$ with the lattice parameters a = 5.20215 ± 0.1 Å, b = 14.6970 ± 0.1 Å, c = 10.8135 ± 0.1 Å, and β = 90.261° (with $\alpha = \gamma = 90°$).
10. A pharmaceutical composition comprising a crystalline polymorph according to any one of claims 1 to 9 and one or more pharmaceutically acceptable carriers.
11. A pharmaceutical composition for use in a method of treating or preventing a TLR7/8-related autoimmune disease, the composition comprising a crystalline

polymorph according to any one of claims 1 to 9 and one or more pharmaceutically acceptable carriers.

12. The pharmaceutical composition for use in a method according to claim 11, wherein the TLR7/8-related autoimmune disease is selected from the group consisting of rheumatoid arthritis, autoimmune pancreatitis, lupus, systemic lupus erythematosus, cutaneous lupus erythematosus, type I diabetes mellitus, multiple sclerosis, antiphospholipid syndrome, sclerosing cholangitis, systemic onset arthritis, irritable bowel disease, scleroderma, Sjogren's disease, vitiligo, myositis, dermatomyositis, polymyositis, pemphigus vulgaris, pemphigus foliaceus, inflammatory bowel disease, Crohn's disease, ulcerative colitis, autoimmune hepatitis, hypopituitarism, graft-versus-host disease, autoimmune skin diseases, uveitis, pernicious anemia, and hypoparathyroidism.

FIGURE 1

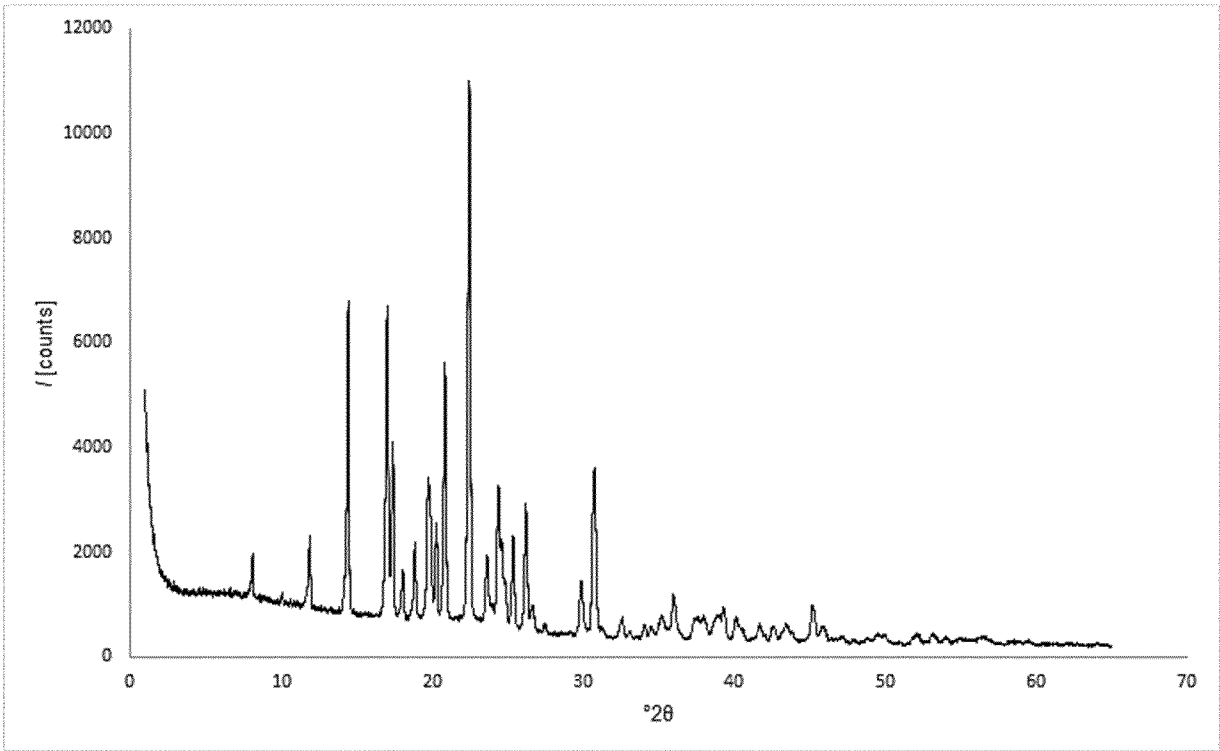


FIGURE 2

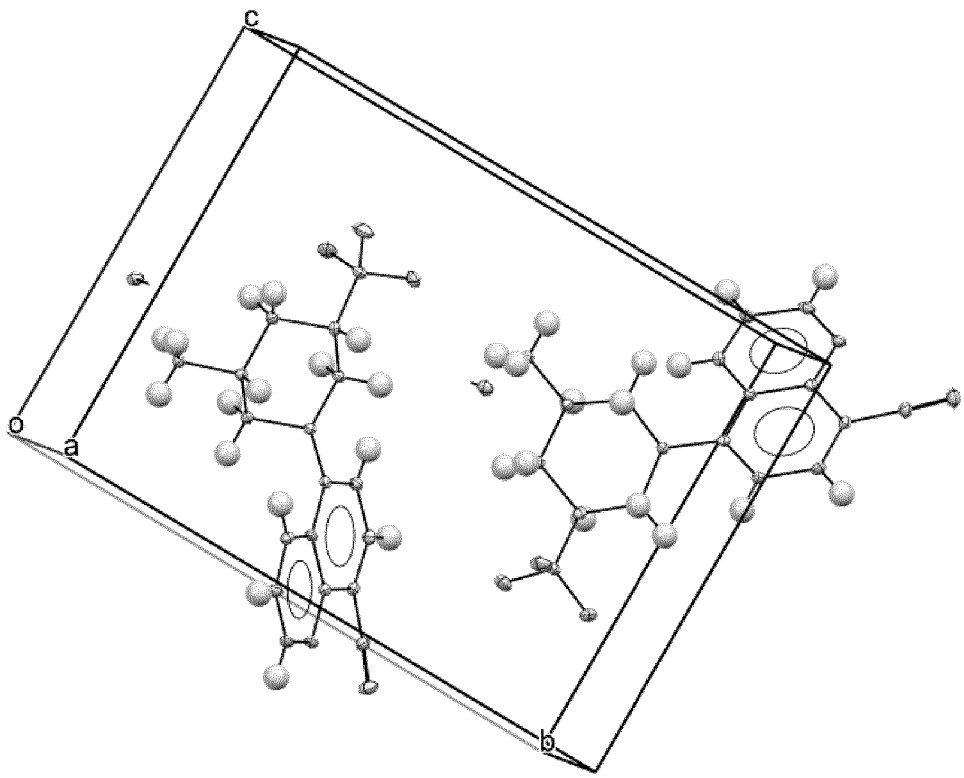


FIGURE 3

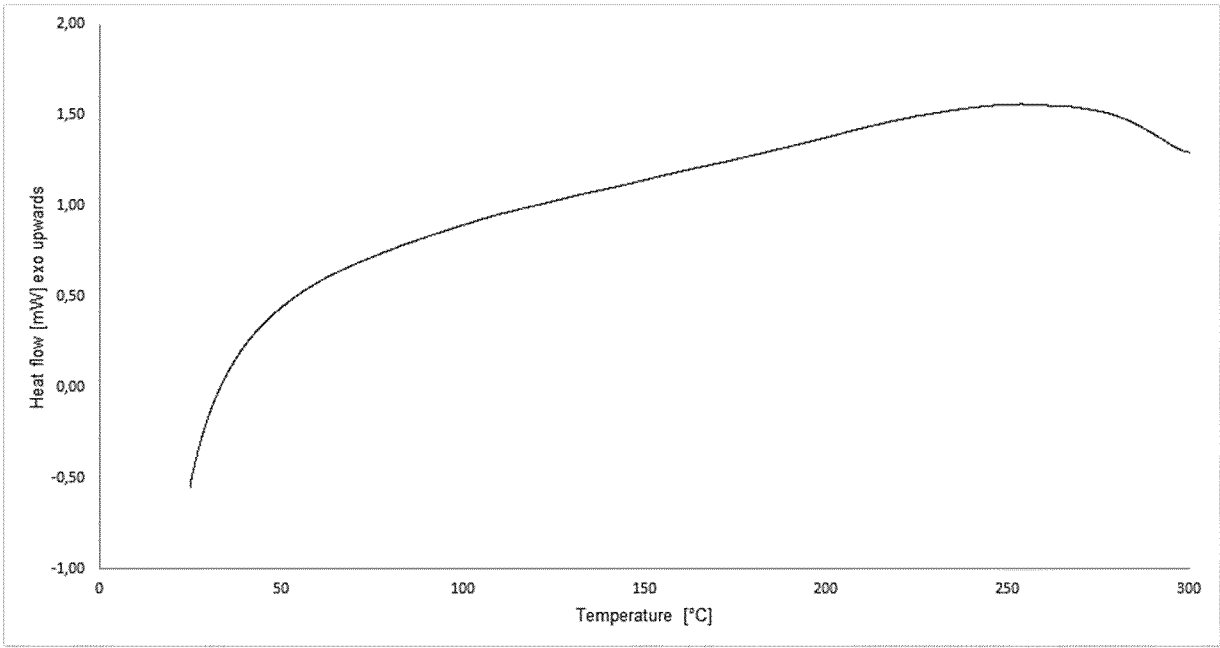


FIGURE 4

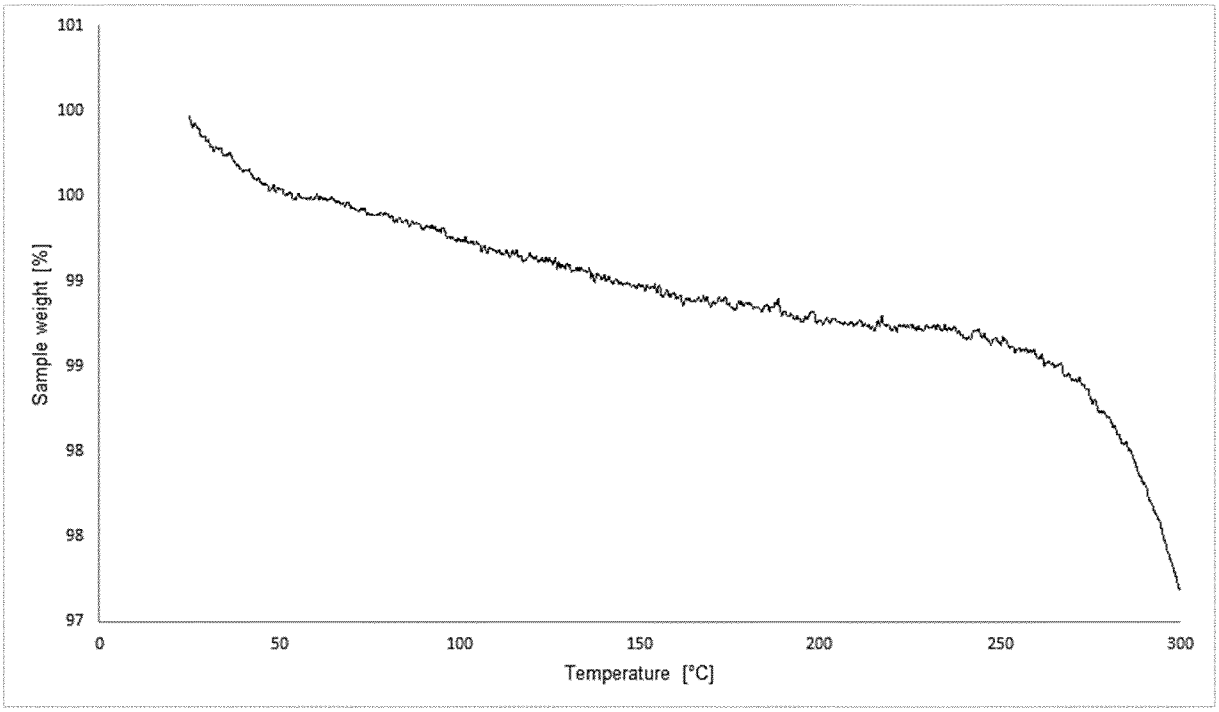
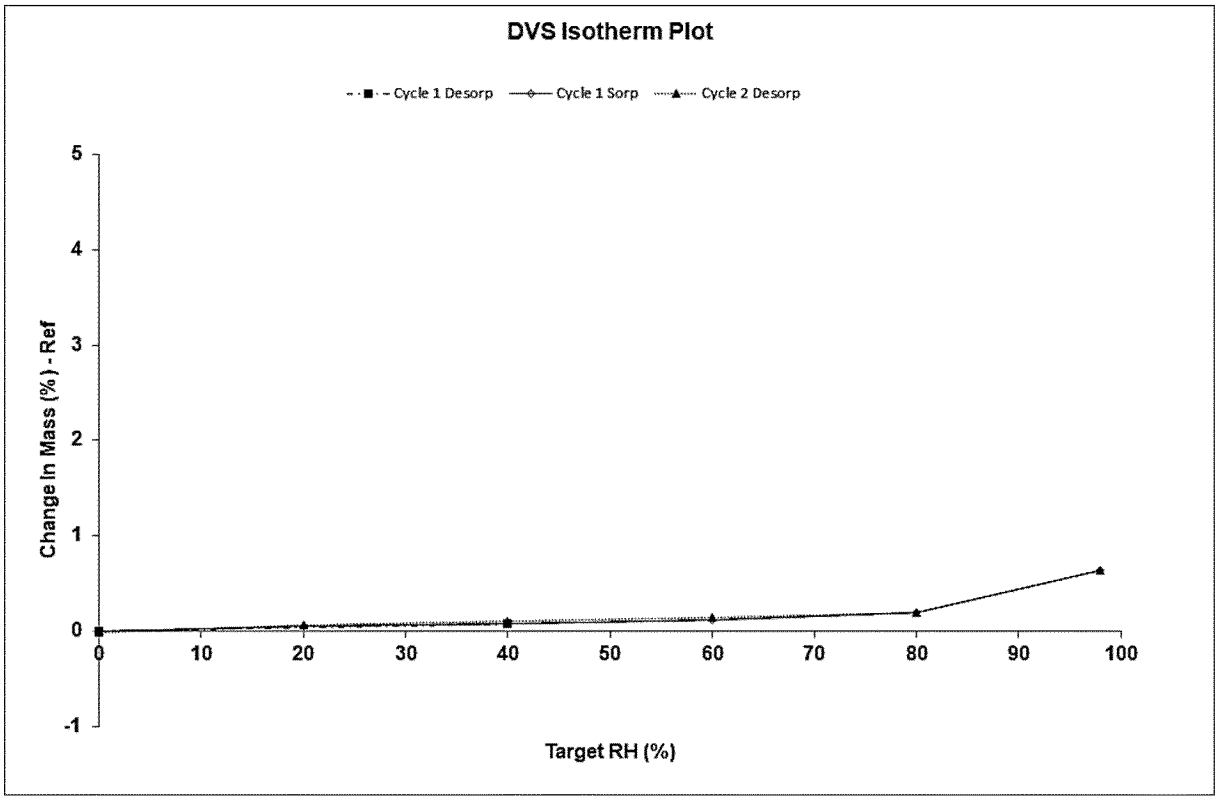


FIGURE 5


DVS Isotherm Plot
Cycle 1 Desorp
Cycle 1 Sorp
Cycle 2 Desorp
Change In Mass (%) - Ref
5
4
3
2
1
0
-1
0
10
20
30
40
50
60
70
80
90
100
Target RH (%)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/072504

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/04 A61P29/00 A61P37/00 A61K31/435
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/106607 A1 (MERCK PATENT GMBH [DE]; SHERER BRIAN A [US]; BRUGGER NADIA [US]) 22 June 2017 (2017-06-22) cited in the application example 31; compound 72 -----	1-12

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

☒ See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2024	26/11/2024

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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/072504

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017106607 A1	22-06-2017	AU 2016371014 A1	31-05-2018
		AU 2021218041 A1	07-10-2021
		AU 2023285714 A1	18-01-2024
		BR 112018011556 A2	27-11-2018
		CA 3005766 A1	22-06-2017
		CL 2018001624 A1	21-09-2018
		CN 108699032 A	23-10-2018
		CN 113603675 A	05-11-2021
		DK 3889145 T3	18-03-2024
		EP 3390389 A1	24-10-2018
		EP 3889145 A1	06-10-2021
		EP 3889146 A1	06-10-2021
		ES 2883285 T3	07-12-2021
		ES 2981114 T3	07-10-2024
		FI 3889145 T3	14-05-2024
		HR P20240355 T1	07-06-2024
		HU E066591 T2	28-08-2024
		IL 259751 A	31-07-2018
		IL 279751 A	31-01-2021
		IL 279752 A	31-01-2021
		JP 6882299 B2	02-06-2021
		JP 7317878 B2	31-07-2023
		JP 2018537501 A	20-12-2018
		JP 2021098703 A	01-07-2021
		JP 2023126574 A	07-09-2023
		KR 20180094939 A	24-08-2018
		LT 3889145 T	10-04-2024
		MY 196319 A	24-03-2023
		NZ 742476 A	30-09-2022
		PH 12018501068 A1	21-01-2019
		PL 3889145 T3	01-07-2024
		PT 3889145 T	02-04-2024
		RS 65319 B1	30-04-2024
		RU 2018123698 A	17-01-2020
		SG 10202001146P A	30-03-2020
		SG 11201804170R A	28-06-2018
		SI 3889145 T1	31-05-2024
		TW 201730175 A	01-09-2017
		TW 202229253 A	01-08-2022
		TW 202332674 A	16-08-2023
		UA 124802 C2	24-11-2021
		US 10947213 B1	16-03-2021
		US 2017174653 A1	22-06-2017
		US 2019330183 A1	31-10-2019
		US 2020095222 A1	26-03-2020
		US 2021115013 A1	22-04-2021
		US 2023303514 A1	28-09-2023
		WO 2017106607 A1	22-06-2017
		ZA 201803367 B	25-08-2021