

NOVEL CRYSTALLINE COMPOUNDS**FIELD OF THE INVENTION**

The present invention relates to a novel crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide. The compound
5 is an inhibitor of general control nonderepressible 2 (GCN2) and as such may be useful for the treatment or prevention of a variety of conditions, and particularly for use in the treatment of diseases, such as cancer. The invention also relates to pharmaceutical compositions comprising the crystalline form, and to methods of using the crystalline form
10 to treat diseases, such as cancer.

BACKGROUND

The kinase general control nonderepressible 2 (GCN2), encoded by EIF2AK4, is a pivotal regulator of cellular adaptations to amino acid shortages (Castilho, B. A., et al (2014)
15 Biochim Biophys Acta 1843, 1948-1968). GCN2 is activated when uncharged tRNAs accumulate as a consequence of low amino acid levels (Romano, P. R., et al (1998) AutMol Cell Biol 18, 2282-2297; and Wek, S. A., et al (1995) Mol Cell Biol 15, 4497-4506). Activated GCN2 phosphorylates its only known target, the translation initiation factor eIF2 α , resulting in attenuation of global protein synthesis. GCN2 also regulates Sestrin2-mediated
20 repression of mTORC1 and induces autophagy (Talloczy, Z., et al (2002) Proc Natl Acad Sci U S A 99, 190-195; Wengrod, J., et al (2015) Sci Signal 8, ra27; BChir, W., et al (2013) Nucleic Acids Res 41, 7683-7699; Ye, J., et al (2015) Genes Dev 29, 2331-2336; and Ravindran, R., et al (2016) Nature 531, 523-527). Together, these GCN2 effects promote the recovery of cells from amino acid shortages.

25 In solid tumours, GCN2 signalling is critical for cancer cell survival under conditions of nutrient deprivation (Wang, Y., et al (2013) Neoplasia 15, 989-997; Ye, J., et al (2010) EMBO J 29, 2082-2096; and Parzych, K., et al (2019) Oncogene 38, 3216-3231). GCN2 has also been shown to have a key role in MYC-driven tumour progression, by adapting protein
30 synthesis to ensure that translation rates are compatible with the bioenergetic capacity and survival of cancer cells (Tameire, F., et al (2019) Nat Cell Biol 21, 889-899; and Schmidt, S., et al. (2019) Nat Cell Biol 21, 1413-1424). Moreover, some tumours may depend on myeloid

GCN2 signals for protection from anti-cancer immune attacks (Halaby, M. J., et al (2019). *Sci Immunol* 4(42), eaax8189). GCN2 depletion enhances the anti-tumour effects of asparaginase treatment (Ye, J., et al (2010) *EMBO J* 29, 2082-2096; and Bunpo, P., et al (2009) *J Biol Chem* 284, 32742-32749). Importantly, mice deficient in GCN2 do not show gross pathologies unless they receive diets that lack essential amino acids (Anthony, T. G., et al (2004) *J Biol Chem* 279, 36553-36561; and Zhang, P., et al (2002) *Mol Cell Biol* 22, 6681-6688). Taken together, these data suggest that GCN2 inhibition may be an effective cancer therapy in a diverse range of cancers.

- 10 It has also been shown that proteasome inhibitors trigger intracellular amino acid shortage, and that this effect may be the main cause of multiple myeloma cell death upon proteasome inhibitor treatment (Parzych, K., et al (2015) *Cell death & disease* 6, e2031; Suraweera, A., et al (2012) *Mol Cell* 48, 242-253; and Vabulas, R. M., and Hartl, F. U. (2005) *Science* 310, 1960-1963). GCN2 inhibition is therefore predicted to be particularly effective
- 15 in combination with proteasome inhibitors in the treatment of multiple myeloma.

- There is a need in the art for further GCN2 inhibitor compounds, in particular GCN2 inhibitor compounds that have high potency, and GCN2 inhibitor compounds that have good pharmacokinetic properties, such as good solubility, and therefore can be used as
- 20 medicaments for the treatment of, for example, cancer. In WO 2021/250399 (IP2IPO Innovations Limited), there are disclosed compounds with potent GCN2 inhibitory properties and excellent pharmacokinetic properties.

SUMMARY OF THE INVENTION

- 25 This invention provides a crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide characterized by a powder X-ray diffractogram (XRPD) having characteristic peaks at $2\theta = 8.6 \pm 0.2^\circ$, $13.5 \pm 0.2^\circ$, $22.6 \pm 0.2^\circ$ and $24.7 \pm 0.2^\circ$.
- 30 The invention also provides a pharmaceutical composition comprising the crystalline form of the invention and at least one pharmaceutically acceptable carrier or excipient.

The invention further provides such a pharmaceutical composition wherein said composition further comprises at least one further therapeutic agent.

5 The invention further provides the crystalline form of the invention for use as a medicament.

The invention further provides the crystalline form of the invention or a pharmaceutical composition comprising the crystalline form of the invention for use in the treatment or prophylaxis of a disease or disorder in which the inhibition of GCN2 provides a therapeutic
10 effect.

The invention further provides the crystalline form of the invention or a pharmaceutical composition comprising the crystalline form of the invention for use in the treatment of a disease or disorder selected from the group consisting of: cancer (for example solid cancers
15 and hematological cancers) diabetic retinopathy, myocardial ischemia, diabetic cardiomyopathy, allergic airway inflammation, doxorubicin-induced cardiotoxicity and nonalcoholic fatty liver disease (NAFLD).

The invention further provides a method for the treatment or prophylaxis of a disease or
20 disorder in which the inhibition of GCN2 provides a therapeutic effect in a mammal (for example the treatment or prophylaxis of cancer in a mammal), which comprises administering to the mammal a therapeutically effective amount of the crystalline form of the invention or a pharmaceutical composition comprising the crystalline form of the invention.

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The invention further provides the use of the crystalline form of the invention for the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder in which the inhibition of GCN2 provides a therapeutic effect (for example the treatment or prophylaxis of cancer).

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Further advantageous features of various embodiments of the invention are defined in the dependent claims and within the detailed description below.

BRIEF DESCRIPTION OF THE FIGURES

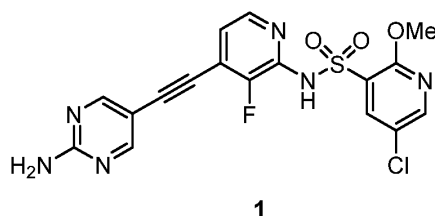
Figure 1 shows a Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) thermogram for the crystalline form A of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide.

Figure 2 shows an X-ray Powder Diffraction (XRPD) diffractogram for the crystalline form A of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide.

DETAILED DESCRIPTION

The invention provides a crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide characterized by a powder X-ray diffractogram (XRPD) having characteristic peaks at $2\theta = 8.6 \pm 0.2^\circ$, $13.5 \pm 0.2^\circ$, $22.6 \pm 0.2^\circ$ and $24.7 \pm 0.2^\circ$.

N-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide has the structure (1) below:



The compound is disclosed in WO 2021/250399 where it is described as Example compound 1. It was shown to have strong potency in the inhibition of GCN2 activity and have good kinase selectivity for GCN2. It was further shown to exhibit excellent pharmacokinetic properties, including good solubility in aqueous media and good bioavailability.

The crystalline form of the invention (referred to herein as 'Crystalline Form A') has been shown to have particularly good long term stability. The current inventors and their co-

workers have identified over half a dozen polymorphic forms of the *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide compound. Whereas other crystalline forms of the compound that have been identified convert over time into other forms, the crystalline form of the invention remains stable in the same form, Crystalline Form A. This is an important property for any compound that is to be used as a pharmaceutical as integrity of the compound during storage is critical for the controlled supply of the drug compound to patients.

As shown in the data presented in the Examples section below, the current inventors have demonstrated that the crystalline form of the invention remained intact and in the same crystalline polymorphic form when placed under accelerated storage conditions of 25°C±2°C / 60%±5% Relative Humidity or 40°C±2°C / 75%±5% Relative Humidity for an extended period.

As set out above, the present invention provides a crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide characterized by a powder X-ray diffractogram (XRPD) having characteristic peaks at $2\theta = 8.6\pm0.2^\circ$, $13.5\pm0.2^\circ$, $22.6\pm0.2^\circ$ and $24.7\pm0.2^\circ$.

Preferably, the crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide has a powder X-ray diffractogram that is further characterised by comprising additional one or more peaks, such as one additional peak, two additional peaks or three additional peaks at 2θ angles selected from the group selected from $9.1\pm0.2^\circ$, $12.7\pm0.2^\circ$ and $18.6\pm0.2^\circ$. For example, it is further characterised by an additional peak at a 2θ angle of $9.1\pm0.2^\circ$. Alternatively or additionally, it is further characterised by an additional peak at a 2θ angle of $18.6\pm0.2^\circ$. Alternatively or additionally, it is further characterised by an additional peak at a 2θ angle of $12.7\pm0.2^\circ$.

Preferably, the crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide has a powder X-ray diffractogram that is further characterised by comprising additional one or more peaks, such as one additional peak, two additional peaks or three additional peaks at 2θ angles selected from the group

selected from $19.2^{\circ} \pm 0.2^{\circ}$, $24.3^{\circ} \pm 0.2^{\circ}$ and $26.8^{\circ} \pm 0.2^{\circ}$. For example, it is further characterised by an additional peak at a 2θ angle of $24.3^{\circ} \pm 0.2^{\circ}$. Alternatively or additionally, it is further characterised by an additional peak at a 2θ angle of $19.2^{\circ} \pm 0.2^{\circ}$. Alternatively or additionally, it is further characterised by an additional peak at a 2θ angle of $26.8^{\circ} \pm 0.2^{\circ}$.

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The invention provides a crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide characterized by a powder X-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in Figure 2. The main peaks in the powder X-ray
10 diffractogram (XRPD) shown in Figure 2 are listed in Table 2 in the Examples section below.

The term “substantially in accordance with” with reference to XRPD means that usual variability in peak positions and relative intensities of the peaks are to be taken into account. For example, a typical precision of the 2θ values is in the range of $\pm 0.2^{\circ} 2\theta$. Thus,
15 a diffraction peak that usually appears at $26.8^{\circ} 2\theta$, for example, can appear between 26.6° and $27.0^{\circ} 2\theta$ on most X-ray diffractometers under standard conditions. Furthermore, one skilled in the art will appreciate that relative peak intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, sample preparation and other factors known to those skilled in the art and should be taken as
20 qualitative measure only. Typically, XRPD measurements are carried out at a temperature of 20°C .

One of ordinary skill in the art will appreciate that an X-ray diffraction pattern may be obtained with a measurement error that is dependent upon the measurement conditions
25 employed. In particular, it is generally known that intensities in an X-ray diffraction pattern may fluctuate depending upon measurement conditions employed. It should be further understood that relative intensities may also vary depending upon experimental conditions and, accordingly, the exact order of intensities should not be relied on. Additionally, a measurement error of diffraction angle for a conventional X-ray diffraction pattern is
30 typically about 5% or less, and such degree of measurement error should be taken into account as pertaining to the mentioned diffraction angles. Consequently, it is to be understood that the crystal forms of the present invention are not limited to the crystal

forms that provide X-ray diffraction patterns completely identical to the X-ray diffraction patterns depicted in the accompanying Figure 2. Rather, any crystal forms that provide X-ray diffraction patterns substantially identical to those disclosed in the accompanying Figure fall within the scope of the present invention. The ability to ascertain substantial accordance
5 of X-ray diffraction patterns is within the purview of one of ordinary skill in the art.

In certain embodiments the crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide is characterized by a differential scanning calorimetry trace substantially in accordance with that shown in Figure
10 1. As is the case for XRPD traces, the skilled person is aware that DSC traces can vary depending on the experimental conditions. The ability to ascertain substantial accordance of DSC traces is within the purview of one of ordinary skill in the art.

Both XRPD and DSC may be used in isolation or in combination with other analytical
15 techniques to characterize the crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide. In one embodiment, DSC is used in combination with XRPD to characterize the crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide. In a preferred embodiment, the crystalline form of *N*-{4-[2-(2-aminopyrimidin-
20 5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide is characterized by an XRPD having characteristic peaks at $2\theta = 8.6 \pm 0.2^\circ$, $13.5 \pm 0.2^\circ$, $22.6 \pm 0.2^\circ$ and $24.7 \pm 0.2^\circ$ and a DSC trace substantially in accordance with that shown in Figure 1. In a preferred embodiment, the XRPD trace is as further described in more detail herein. In a further preferred embodiment, the crystalline form is characterized by a powder X-ray
25 diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in Figure 2, and and a DSC trace substantially in accordance with that shown in Figure 1.

Additionally, the crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-
30 2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide can be characterized as being an anhydrous crystalline form and more preferably a non-solvated and anhydrous crystalline form.

The crystalline form of the invention may be prepared by methods described in the Examples section herein. For example, the crystalline form may be prepared from a slurry of the compound in 2-butanone at a raised temperature (for example 50 °C) for a time (for example 3 hours) followed by cooling. It may also, for example, be prepared by crystallisation of a crude reaction mixture containing the compound from methanol, water, DMF and acidic solution (for example, aqueous HCl) by stirring at a raised temperature (for example 60 °C) for a time (for example 1-1.5 hours) followed by cooling. It may also be prepared by crystallisation of the compound from methanol, DMSO, triethylamine and acidic solution (for example, HCl in IPA) by stirring, for example at room temperature, for a time (for example 1-1.5 hours). As is conventional, whilst not being necessary, the use of seed crystals can assist with the efficiency of the crystallisation in some preparation methods.

Preferably, the crystalline form of N-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide of the invention is provided in substantially pure form.

As used herein, the term “substantially pure” with reference to a particular polymorphic form of a compound means that the polymorphic form includes less than 10%, preferably less than 5%, more preferably less than 3%, most preferably less than 1% by weight of any other physical form of the compound.

Preferably, the crystalline form of N-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide of the invention has substantially pure phase homogeneity as indicated by less than 10%, preferably less than 5 %, and more preferably less than 2 % of the total peak area in the experimentally measured XRPD pattern arising from any extra peaks from other crystalline forms. Most preferred is the crystalline form of N-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide of the invention having substantially pure phase homogeneity with less than 1% of the total peak area in the experimentally measured XRPD pattern arising from any extra peaks from other crystalline forms. In the

present context the term “extra peaks” refers to XRPD peaks that do not belong or are not assigned to the crystalline form of N-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide of the invention.

5 Uses of the compound in the crystalline form of the invention:

As mentioned above, N-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide has activity as an inhibitor for GCN2. As such, the invention also provides the crystalline form of the invention for use as a medicament, or for use in therapy. The invention also provides a composition comprising the crystalline form of the invention, together with a pharmaceutically acceptable carrier, for use as a
10 medicament, or for use in therapy.

For the avoidance of doubt, as used herein the terms “therapy”, “treatment” and “treating” include both preventative and curative treatment of a condition, disease or disorder. It also
15 includes slowing, interrupting, controlling or stopping the progression of a condition, disease or disorder. It also includes preventing, curing, slowing, interrupting, controlling or stopping the symptoms of a condition, disease or disorder. For example, it includes preventing the metastasis of cancer wherein the disease or disorder is cancer.

20 The crystalline form of the invention, or a composition comprising the crystalline form of the invention, may be used in the treatment of a disease or disorder in which the inhibition of GCN2 provides a therapeutic effect. As such, they may be used in the treatment or prophylaxis of diseases or disorders for which inhibitors of GCN2 are indicated.

25 The crystalline form of the invention finds particular application in the treatment or prophylaxis of a disease or disorder in which the inhibition of GCN2 provides a therapeutic effect, for example a disease or disorder selected from the group consisting of: cancer (for example solid cancers and hematological cancers).

30 The invention also provides a method of treating a subject suffering from a medical disorder or disease. The method comprises administering to the subject a therapeutically effective amount of the crystalline form of the invention or a composition as described herein, to

treat the disorder or disease. As mentioned above, a number of diseases or disorders in which the inhibition of GCN2 provides a therapeutic effect can be treated using the crystalline form of the invention. For example, the crystalline form of the invention can be used to treat cancer (for example solid cancers and hematological cancers).

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When the crystalline form of the invention, or a composition comprising the crystalline form of the invention, is used in therapy as a medicament for the treatment or prophylaxis of a disease or disorder, for example in the therapeutic uses and methods described herein, the use or method may comprise the step of administering, to a mammal, including a human, in
10 need of such treatment or prophylaxis, a therapeutically effective amount of the crystalline form of the invention.

The crystalline form of the invention finds particular application in the treatment or prophylaxis of cancer. In certain embodiments, the cancer is a solid tumor or a
15 hematological cancer (for example leukemia or multiple myeloma). In certain embodiments, the cancer is a cancer with a MYC mutation.

Examples of cancers that the crystalline form of the invention finds particular application in the treatment or prophylaxis of include, but are not limited to: colorectal cancer (e.g.,
20 colorectal cancer, rectal cancer, anal cancer, familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma), mesothelioma, pancreatic cancer (e.g., pancreatic duct cancer, pancreatic endocrine tumor), pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric cancer (e.g., papillary adenocarcinoma,
25 mucinous adenocarcinoma, adenosquamous carcinoma), duodenal cancer, small intestinal cancer, breast cancer (e.g., invasive ductal carcinoma, ductal carcinoma in situ, inflammatory breast cancer), ovarian cancer (e.g., ovarian epithelial carcinoma, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor), testis tumor, prostate cancer (e.g., hormone-dependent prostate cancer, non-
30 hormone dependent prostate cancer, castration-resistant prostate cancer), liver cancer (e.g., hepatoma, primary liver cancer, extrahepatic bile duct cancer), thyroid cancer (e.g., medullary thyroid carcinoma), renal cancer (e.g., renal cell carcinoma (e.g., clear cell renal

- cell carcinoma), transitional cell carcinoma of renal pelvis and ureter), uterine cancer (e.g., cervixcancer, uterine body cancer, uterus sarcoma), gestational choriocarcinoma, brain tumor (e.g., medulloblastoma, glioma, glioblastoma, pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, hypophyseal adenoma), retina
- 5 blastoma, skin cancer (e.g., basal cell carcinoma, malignant melanoma (melanoma)), sarcoma (e.g., rhabdomyosarcoma, leiomyosarcoma, soft tissue sarcoma, spindle cell sarcoma, osteosarcoma, squamous cell carcinoma, fibrosarcoma), head and neck cancer, malignant bone tumor, urinary bladder cancer, and hematologic cancer (e.g., multiple myeloma, smouldering myeloma, plasmacytoma, leukemia (e.g., acute myeloid leukemia,
- 10 acute lymphocytic leukemia (including blast crisis of chronic leukemia), chronic myeloid leukemia, hairy cell leukemia, chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, large granular lymphocytic leukemia, B-cell prolymphocytic leukemia, T-cell prolymphocytic leukemia), non-Hodgkin's lymphoma, malignant lymphoma, Hodgkin's disease, myelodysplastic syndrome, myeloproliferative neoplasm, chronic
- 15 myeloproliferative disease, lymphoplasmacytic lymphoma, B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, T-cell lymphoma, erythroleukemia, histocytic lymphoma, waldenstrom macroglobulinemia), and cancer of unknown primary nucleus.
- 20 The crystalline form of the invention also finds application as a cancer growth inhibitor, cancer metastasis inhibitor, apoptosis promoter, and for the prophylaxis or treatment of precancerous lesions (e.g., bone marrow myelodysplastic syndrome, monoclonal gammopathy of undetermined significance).
- 25 In one embodiment, the crystalline form of the invention finds particular application in the treatment or prophylaxis of osteosarcoma, acute myeloid leukemia, acute lymphocytic leukemia, multiple myeloma, pancreatic cancer, colorectal cancer, melanoma, and malignant lymphoma.
- 30 Examples of solid cancers that the crystalline form of the invention finds particular application in the treatment or prophylaxis of include, but are not limited to: colorectal cancer (e.g., colorectal cancer, rectal cancer, anal cancer, familial colorectal cancer,

hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma), mesothelioma, pancreatic cancer (e.g., pancreatic duct cancer, pancreatic endocrine tumor), pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric cancer (e.g., papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous carcinoma),
 5 duodenal cancer, small intestinal cancer, breast cancer (e.g., invasive ductal carcinoma, ductal carcinoma in situ, inflammatory breast cancer), ovarian cancer (e.g., ovarian epithelial carcinoma, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor), testis tumor, prostate cancer (e.g., hormone-dependent
 10 prostate cancer, non-hormone dependent prostate cancer, castration-resistant prostate cancer), liver cancer (e.g., hepatoma, primary liver cancer, extrahepatic bile duct cancer), thyroid cancer (e.g., medullary thyroid carcinoma), renal cancer (e.g., renal cell carcinoma (e.g., clear cell renal cell carcinoma), transitional cell carcinoma of renal pelvis and ureter), uterine cancer (e.g., cervixcancer, uterine body cancer, uterus sarcoma), gestational
 15 choriocarcinoma, brain tumor (e.g., medulloblastoma, glioma, glioblastoma, pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, hypophyseal adenoma), retina blastoma, skin cancer (e.g., basal cell carcinoma, malignant melanoma (melanoma)), sarcoma (e.g., rhabdomyosarcoma, leiomyosarcoma, soft tissue sarcoma, spindle cell sarcoma, osteosarcoma), malignant bone tumor, giant cell carcinoma,
 20 sweat gland carcinoma, sebaceous gland carcinoma, mouth cancer, chest cancer, lymph node cancer, eye cancer, an acoustic neuroma, oligodendroglioma, meningioma, and urinary bladder cancer.

Examples of hematological cancers that the crystalline form of the invention finds particular
 25 application in the treatment or prophylaxis of include, but are not limited to: multiple myeloma, smouldering myeloma, plasmacytoma, leukemia (e.g., acute myeloid leukemia, acute lymphocytic leukemia (including blast crisis of chronic leukemia)), non-Hodgkin's lymphoma, malignant lymphoma, Hodgkin's disease, and chronic myeloproliferative disease. For example the hematological cancer may be one that is resistant to Venetoclax.

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In one embodiment, the crystalline form of the invention finds particular application in the treatment or prophylaxis of a cancer with high levels of MYC (i.e. a cancer in which the MYC

gene or protein are expressed at high levels). Examples of cancers having a MYC mutation that the crystalline form of the invention finds particular application in the treatment or prophylaxis of include, but are not limited to: prostate cancer, breast cancer (for example triple negative breast cancer), lung cancer (for example small cell lung cancer), ovarian
5 cancer, neuroblastomas (including pediatric neuroblastoma) and leukemia (for example acute lymphoblastic leukemia and mixed-lineage leukemia).

The crystalline form of the invention also finds application in conditions selected from: diabetic retinopathy, myocardial ischemia, diabetic cardiomyopathy, allergic airway
10 inflammation, doxorubicin-induced cardiotoxicity and nonalcoholic fatty liver disease (NAFLD).

The invention also provides a method for the treatment or prophylaxis of a disease or disorder in which the inhibition of GCN2 provides a therapeutic effect in a mammal, which
15 comprises administering to the mammal a therapeutically effective amount of the crystalline form according to the invention, or a composition comprising the crystalline form according to the invention. Diseases and disorders that may be treated by this method of the invention are preferably those described above.

20 The invention also provides the use of the crystalline form according to the invention, for the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder in which the inhibition of GCN2 provides a therapeutic effect. Diseases and disorders that may be treated by this use of the invention are preferably those described above.

25 The amount of active ingredient which is required to achieve a therapeutic effect will, of course, vary with the route of administration, the subject under treatment, including the type, species, age, weight, sex, and medical condition of the subject and the renal and hepatic function of the subject, and the particular disorder or disease being treated, as well as its severity. An ordinarily skilled physician, veterinarian or clinician can readily determine
30 and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 mg per kg of body weight per day (mg/kg/day) to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day, for adult humans. For oral administration, the compositions are preferably provided in the form of tablets or other forms of presentation provided in discrete units containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, the crystalline form of the invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, the crystalline form of the invention can be administered in intranasal form *via* topical use of suitable intranasal vehicles, or *via* transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

20 Pharmaceutical Compositions:

While it is possible for the active ingredient to be administered alone, it is preferable for it to be present in a pharmaceutical formulation or composition. Accordingly, the invention provides a pharmaceutical formulation or composition comprising the crystalline form according to the invention, and a pharmaceutically acceptable diluent, excipient or carrier (collectively referred to herein as “carrier” materials). Pharmaceutical compositions and formulations of the invention may take the form of a pharmaceutical composition or formulation as described below.

Pharmaceutical compositions according to the invention include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous [bolus or infusion], and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurized aerosols), nebulizers or

insufflators, rectal, intraperitoneal and topical (including dermal, buccal, sublingual, and intraocular) administration, although the most suitable route may depend upon, for example, the condition and disorder of the recipient.

- 5 The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided
10 solid carriers or both and then, if necessary, shaping the product into the desired composition.

- Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, pills or tablets each containing a predetermined
15 amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, for example as elixirs, tinctures, suspensions or syrups; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

- 20 A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered
25 compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so to provide slow or controlled release of the active ingredient therein. The crystalline form of the invention can, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release can be achieved by the use of suitable pharmaceutical compositions
30 comprising the crystalline form of the present invention, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps.

Exemplary compositions for oral administration include suspensions which can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which can contain, for

5 example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate, calcium sulfate, sorbitol, glucose and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate,

10 carboxymethylcellulose, polyethylene glycol, waxes and the like. Disintegrators include without limitation starch, methylcellulose, agar, bentonite, xanthan gum and the like. The crystalline form of the invention can also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those

15 formulating the present compound with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such compositions may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such compositions can also include an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose

20 (SCMC), maleic anhydride copolymer (e.g. Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. For oral administration in liquid

25 form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like.

The crystalline form of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and

30 multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, 1,2-dipalmitoylphosphatidylcholine, phosphatidyl ethanolamine (cephaline), or phosphatidylcholine (lecithin).

Compositions for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and
5 non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and
10 suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Exemplary compositions for parenteral administration include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and
15 suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor®.

Exemplary compositions for nasal, aerosol or inhalation administration include solutions in saline, which can contain, for example, benzyl alcohol or other suitable preservatives,
20 absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Compositions for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, synthetic glyceride esters or polyethylene glycol. Such carriers
25 are typically solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

Compositions for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and
30 acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerine or sucrose and acacia. Exemplary compositions for topical administration include a topical carrier such as Plastibase® (mineral oil gelled with polyethylene).

Preferred unit dosage compositions are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

5 It should be understood that in addition to the ingredients particularly mentioned above, the compositions of this invention may include other agents conventional in the art having regard to the type of composition in question, for example, those suitable for oral administration may include flavouring agents.

10 Whilst the crystalline form of the invention may be used as the sole active ingredient in a medicament, it is also possible for the compound to be used in combination with one or more further therapeutic agents. Thus, the invention also provides the crystalline form according to the invention together with a further therapeutic agent, for simultaneous, sequential or separate administration. Such further therapeutic agents may be different
15 therapeutic agents, for example another GCN2 inhibitor. The further therapeutic agent may also be a therapeutic agent for use in the treatment or prophylaxis of a disease or disorder in which the inhibition of GCN2 provides a therapeutic effect, for example a disease or disorder selected from the group consisting of cancer (for example solid cancers and hematological cancers), and autoimmune diseases, and in particular cancer.

20

Therefore, in one embodiment, the further therapeutic agent may be a different therapeutic agent for use in the treatment or prophylaxis of cancer, for example it may be a chemotherapeutic agent selected from the group consisting of L-asparaginase (ASNase), a proteasome inhibitor (for example bortezomib, carfilzomib, ixazomib, or marizomib),
25 immunomodulatory drugs (for example, thalidomide, lenalidomide and pomalidomide), SINE compounds (for example selinexor), monoclonal antibodies (for example, such as rituximab, daratumumab, isatuximab, herceptin and avastin), alkylating agents, alkyl sulfonates, aziridines, ethylenimines and methylamelamines, acetogenins, a camptothecin, bryostatin, callistatin, CC-1065, cryptophycins, dolastatin, duocarmycin, eleutherobin,
30 pancratistatin, a sarcodictyin, spongistatin, nitrogen mustards, antibiotics, enediyne antibiotics, dynemicin, bisphosphonates, esperamicin, chromoprotein enediyne antibiotic chromophores, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins,

cactinomycin, carabycin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, 5 tubercidin, ubenimex, zinostatin, zorubicin, antimetabolites, erlotinib, vemurafenib, crizotinib, sorafenib, ibrutinib, enzalutamide, folic acid analogues, purine analogs, androgens, anti-adrenals, folic acid replenisher such as folinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elfornithine, elliptinium 10 acetate, an epothilone, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansinoids, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid 2-ethylhydrazide, procarbazine, PSK® polysaccharide complex (JHS Natural Products, Eugene, OR), razoxane, rhizoxin, sizofiran, spirogermanium, tenuazonic acid, triaziquone; 2,2',2''-trichlorotriethylamine, 15 trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine), urethan, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), cyclophosphamide, thiotepa, taxoids, chloranbucil, gemcitabine, 6-thioguanine, mercaptopurine, methotrexate, platinum analogs, vinblastine, platinum, etoposide (VP-16), ifosfamide, mitoxantrone, vincristine, vinorelbine, novantrone, 20 teniposide, edatrexate, daunomycin, aminopterin, xeloda, ibandronate, irinotecan (Camptosar, CPT-11), topoisomerase inhibitor RFS 2000, difluoromethylornithine, asparaginase, retinoids, capecitabine, combretastatin, leucovorin, oxaliplatin, inhibitors of PKC-alpha, Raf, H-Ras, EGFR and VEGF-A that reduce cell proliferation, and pharmaceutically acceptable salts, acids or derivatives thereof, and combinations thereof.

25

In another embodiment, the further therapeutic agent may be a checkpoint inhibitor, for example an agent or antibody that inhibits one or more of CTLA4, PD-1, PD-L1, LAG-3, B7-H3, B7-H4, TIM3, VISTA and KIR.

30 In certain embodiments the crystalline form of the invention is administered in combination with L-asparaginase (ASNase). Such a combination treatment may be used for the treatment of cancer, and in particular for the treatment of a acute lymphocytic leukemia (including

blast crisis of chronic leukemia) and non-Hodgkin's lymphoma. Such a combination treatment may also be used for the treatment of cancer tumor resistant or tolerant to asparaginase, for example a cancer selected from the group consisting of acute lymphocytic leukemia (including blast crisis of chronic leukemia) and non-Hodgkin's lymphoma.

5

In certain embodiments the crystalline form of the invention is administered in combination with a proteasome inhibitor, for example bortezomib, carfilizomib, ixazomib, marozomib or oprozomib. Such a combination treatment may be used for the treatment of cancer, and in particular for the treatment of a hematological cancer, for example Hodgkin's lymphoma, multiple myeloma, smouldering myeloma, and the premalignant condition, monoclonal gammopathy of undetermined significance.

In embodiments where the crystalline form of the invention is used in combination with other agent(s) for use in the treatment or prophylaxis of a disease or disorder in which the inhibition of GCN2 provides a therapeutic effect, the individual components of such combinations can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of this invention with other agents for use in the treatment or prophylaxis of a disease or disorder in which the inhibition of GCN2 provides a therapeutic effect includes in principle any combination with any pharmaceutical composition useful for treating a disease or disorder in which the inhibition of GCN2 provides a therapeutic effect.

25

The above other therapeutic agents, when employed in combination with the crystalline form of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

30

The crystalline form of the invention as described above can also find use in combination with radiation therapy for the treatment of cancer.

Furthermore, the crystalline form of the present invention may be used in combination with a non-drug therapy. Specifically, the crystalline form of the present invention or the combination agent of the present invention can be used in combination with, for example, a non-drug therapy such as (1) operation, (2) hypertensive chemical therapy using angiotensin II and the like, (3) gene therapy, (4) hyperthermic therapy, (5) cryotherapy, (6) laser ablation method, (7) radiation therapy, (8) diet therapy (e.g., amino acid restriction diet) and the like.

For example, by using the crystalline form of the present invention or the combination agent of the present invention before or after the aforementioned surgery and the like, or before or after the treatment of two or three kinds of these in combination, effects such as inhibition of expression of resistance, prolongation of disease-free survival, suppression of cancer metastasis or recurrence, prolongation of life and the like can be achieved.

In addition, the treatment with the crystalline form of the present invention or the combination agent of the present invention can be combined with a supporting therapy, for example (i) administration of antibiotics (for example, P-lactam system such as pamporin and the like, macrolide system such as clarithromycin and the like) for complications of various infectious diseases, (ii) administration of intravenous hyperalimentation, amino acid preparation, multiple vitamin preparation for improving malnutrition, (iii) morphine administration for pain relief, (iv) administration of medicament for improving side effects such as nausea, vomiting, anorexia, diarrhea, leucopenia, thrombocytopenia, hemoglobin concentration reduction, hair loss, hepatopathy, renopathy, DIC, fever and the like and (v) administration of medicament for suppressing multiple drug resistance of cancer and the like.

The crystalline form of the invention as described above also finds use, optionally in labelled form, as a diagnostic agent for the diagnosis of conditions associated with a disease or disorder in which the inhibition of GCN2 provides a therapeutic effect. For example, such a compound may be radioactively labelled.

In addition to its use in therapeutic medicine, the crystalline form according to the invention may also be useful as a pharmacological tool in the development and standardization of *in vitro* and *in vivo* test systems for the evaluation of other compounds with similar activity. Furthermore, the crystalline form of the invention may be used as a molecular probe to

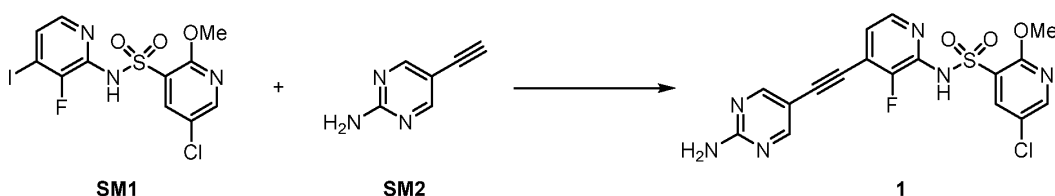
5 identify and/or locate the target of action, such as a target within the airways, as well as employed as a diagnostic tool for diagnosis of a disease or condition *in vivo*, *ex vivo* or *in vitro*, or as synthetic precursors to such probes. Molecular probes of the invention may include labeled (i.e. wherein one or several of the composing atoms have been enriched

10 with a radioactive or by other means detectable isotope) atoms as is well known to the one skilled in the art.

EXAMPLES

Example 1: Synthesis and crystallisation of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide (Compound 1) in Crystal Form A

5

Starting Materials

5-chloro-*N*-(3-fluoro-4-iodopyridin-2-yl)-2-methoxypyridine-3-sulfonamide (**SM1**), may be
 10 synthesised according to the procedure described in WO 2021/250399. 5-ethynylpyrimidin-
 2-amine (**SM2**), is commercially available (CAS: 857265-74-8).

General Synthetic Overview

The inventors have established several ways to prepare the crystalline form of the present
 15 invention, herein referred to as Crystal Form A. Three synthetic procedures are presented
 below.

Method 1: Synthesis followed by crystallisation**Synthesis**

20 To a solution of **SM1** (160 g, 324 mmol) and **SM2** (69.4 g, 454 mmol) in DMF (1200 mL) was
 added triethylamine (225 mL, 1.62 mol) and CuI (12.3 g, 64.9 mmol) followed by Pd₂(dba)₃
 (30.2 g, 33.0 mmol) at 20 °C under N₂. The reaction was stirred at 80 °C under N₂ for 2 hrs.
 The reaction mixture was cooled, diluted with MBTE (300 mL) and washed with sat. Na₂CO₃
 25 3). The aqueous phase was then further extracted with MBTE (400 mL x
 3). The aqueous phase was then adjusted to pH = 4~5 with 1N HCl solution and filtered. The
 filter cake was washed with water (300 mL x 3) and dried under vacuum. The crude product
 was dissolved in MeOH (4 L) and added to sulfhydryl silica gel (206 g). The mixture was
 stirred at 20 °C for 12 hrs, filtered and concentrated in vacuo. The resulting solid was

trituated with EtOAc (3 V) at 20 °C for 2 hrs. The mixture was filtered, the filter cake was washed with EtOAc (200 mL) and dried. The resulting solid was resuspended in a mixture of EtOAc:H₂O (1:1, 5 V) and stirred at 80 °C for 48 hrs. The mixture was filtered and the filter cake was washed with EtOAc (50 mL x 3). The resulting solid was dried to afford Compound 1 (87 g, 217 mmol, 55.7% yield) as a yellow solid.

The solid was combined with a second batch of Compound 1 and suspended in water (250 mL) with stirring at room temperature for 20 minutes. The suspension was filtered and the resulting solid was dried to afford a larger batch of Compound 1 (150 g, 343 mmol, 99.5% purity) as a yellow solid.

10 Crystallisation

Compound 1 (78.78 g) was slurried in 10 volumes (800 mL) of 2-butanone at 50 °C for 3 hours. The mixture was cooled, filtered under vacuum and dried to afford Compound 1 as a crystalline solid.

15 It was established by analysis of the characterisation data that this crystal form is the same material produced as described for Method 3 below and for which extensive characterisation data is shown in Example 2.

Method 2: All in one synthesis and crystallisation

20 A mixture of **SM1** (2000 mg, 4.47 mmol) and **SM2** (645 mg, 5.37 mmol) in DMF (14.25 mL) was evacuated and backfilled with nitrogen twice. Triethylamine was added (2.5 mL, 17.94 mmol) followed by CuI (8.56 mg, 0.045 mmol), Pd₂(dba)₃ (5 mg, 0.022 mmol) and PPh₃ (14.23 mg, 0.054 mmol) at 20 °C. The reaction was evacuated and backfilled with nitrogen twice and then heated to 60 °C under N₂ for approximately 2 hrs. Activated charcoal (100
25 mg, 8.33 mmol) was added into the reaction mixture and the reaction continued stirring at 60 °C for 30 minutes. The reaction was cooled to room temperature, diluted with MeOH (10 mL) and filtered through celite, washing through with MeOH (5 mL). Water (5 mL) was added to the filtrate dropwise with stirring followed by 2M HCl (aq) (4.2 mL) and the mixture was then heated to 60 °C for 1 h. Further 2M HCl (aq) (0.9 mL) was added with
30 further stirring at 60 °C for 20 minutes. The mixture was then cooled and filtered, washing

with MeOH (2 x 5 mL). The resulting solid was dried under vacuum to afford Compound 1 as a crystalline solid.

- It was established by analysis of the characterisation data that this crystal form is the same material produced as described for Method 3 below and for which extensive characterisation data is shown in Example 2.

Method 3: Synthesis and crystallisation of Compound 1 using seeding

Synthesis

- 10 A mixture of **SM1** (400 g, 855 mmol) and **SM2** (128 g, 1065 mmol) in DMSO (2600 mL) was purged with nitrogen before the addition of triphenylphosphine (2.79 g, 10.64 mmol), Pd(OAc)₂ (0.993 g, 4.42 mmol) and copper (I) iodide (1.685 g, 8.85 mmol). Triethylamine (493 mL, 3537 mmol) and the reaction was evacuated and backfilled with nitrogen before heating to 60 °C for 30 minutes. The reaction was cooled to room temperature and water (1000 mL) was added followed by N-acetyl-L-cysteine (2.89 g, 17.71 mmol) with stirring for 30 minutes. Activated carbon (20 g, 855 mmol, 5 wt%) was then added with further stirring for 30 minutes. The resulting suspension was filtered through celite and washed with MeOH (400 mL). The filtrate was cooled to 16 °C and treated with 2M HCl (aq) (1120 mL) dropwise over 1 hour. The reaction was seeded with Crystal Form A of Compound 1 (0.5 g, derived from Method 2) after the addition of 620 mL MeOH and heated to 60 °C for 1 hour. The reaction was cooled, filtered and dried at 60 °C for 9 hours to afford crude Compound 1 as a beige solid (295 g, 648 mmol, 76% yield).

Crystallisation

- 25 To a stirred mixture of two batches of crude Compound 1 (578.2 g, 1265 mmol) in MeOH (4700 mL) was added DMSO (650 mL). Triethylamine (311 mL, 2238 mmol) was added and the reaction stirred at room temperature for 20 minutes. Activated carbon (14.5 g, 1265 mmol) was added and the mixture stirred for 30 minutes before filtration through celite. The filtrate was collected and treated with 1M HCl in IPA (2074 mL, 2074 mmol) over 1.5 hours. The solution was seeded with Crystal Form A of Compound 1 (0.75 g, derived from Method 1) after 825 mL (40%) of the 1M HCl in IPA solution had been added. The resulting suspension was stirred at room temperature for 30 minutes and then filtered, washing with

MeOH (700 mL). The resulting solid was dried at 60 °C to afford Crystal Form A of Compound 1 (505 g, 89% yield).

Characterisation data of Compound 1 in Crystal Form A, obtained via Method 3, is provided below.

Example 2: Characterisation of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide in Crystal Form A

Characterisation data is provided for Compound 1 in Crystal Form A, obtained via Method 3.

(a) Ref standard Solution NMR

A sample of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide was dissolved in d₆-DMSO and analysed by ¹H NMR, ¹³C

NMR and ¹⁹F NMR:

¹H NMR (d₆-DMSO) δ ppm: 11.87 (br s, 1H), 8.50 (s, 2H), 8.48 (d, 1H), 8.24 (d, 1H), 7.93 (d, 1H), 7.39 (s, 2H), 7.15 (s, 1H), 3.88 (s, 3H).

¹³C NMR (d₆-DMSO) δ ppm: 162.3, 160.9, 157.8, 149.1, 138.3, 125.3, 122.8, 120.1, 104.0, 96.4, 82.9, 54.4.

¹⁹F NMR (d₆-DMSO) δ ppm: 129.1, 124.9.

(b) Differential Scanning Calorimetry (DSC)

The DSC studies are performed using a Mettler Toledo DSC1/DSC3+ STARe System. The samples are made using Al crucibles (40 µl; pierced). Typically, 1 - 8 mg of sample is loaded onto a pre-weighed Al crucible and is kept at 20 °C for 5 minutes, after which it is heated at 10 °C/min from 20 °C to 350 °C and kept at 350 °C for 1 minute. A nitrogen purge of 40 ml/min is maintained over the sample. The software used for data collection and evaluation is STARe Software v15.00 build 8668. No corrections are applied to the thermogram. As

system suitability check indium and zinc are measured. For calibration indium, lead and zinc are used as references.

A DSC thermogram for *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide in the crystalline form prepared as described in Example 1, Method 3 is shown in Figure 1.

The numerical findings of the DSC events were:

Event	T _{peak} of DSC event
Melting event	244.7 °C
Decomposition event	257.2 °C

Table 1. Numerical findings of the DSC Experiment.

10

(c) X-ray Powder Diffraction analysis (XRPD)

The X-ray powder diffraction studies are performed using a Bruker AXS D8 Advance in Bragg-Brentano configuration, equipment #3300. A scan range of 4-45° 2Theta was applied. The X-ray source is a Cu anode at 40 kV, 40 mA. The slits that are used are a primary axial Soller slit 2.5° a fixed divergence slit 0.6mm (=0.34°), an 8.0 mm detector slit and a secondary axial Soller slit 2.5°. For monochromatisation, a Kβ-filter (0.5% Ni) is used. The detector is a linear detector LYNXEYE with a receiving slit 3° detector opening. All measuring conditions are logged in the instrument control file. The software used for data collection is Diffrac.Commander v2.6.1 or newer. Data analysis is performed using Diffrac.Eva V7.5.2.0 or newer. Kα2 signals are removed by the software. No background correction or smoothing is applied to the patterns. As system suitability, corundum sample (NIST standard) is checked for peak position, peak shape, intensity and linearity.

The sample in the crystalline form prepared as described in Example 1, Method 3 was confirmed by XRPD to be crystalline. The XRPD trace is shown in Figure 2.

The peaks in the XRPD trace were as follows:

Index	Angle	d Value	Intensity	Rel. Intensity	Index	Angle	d Value	Intensity	Rel. Intensity
1	6.307	14.00324	763.829	2.4%	35	27.623	3.22663	755.545	2.3%
2	8.571	10.30844	32350.200	100.0%	36	28.028	3.18093	5468.930	16.9%
3	9.061	9.75157	16776.100	51.9%	37	28.860	3.09108	4452.560	13.8%
4	9.743	9.07048	260.503	0.8%	38	29.268	3.04897	2692.050	8.3%
5	10.600	8.33936	382.861	1.2%	39	29.925	2.98347	725.682	2.2%
6	12.291	7.19546	7313.590	22.6%	40	30.414	2.93665	412.688	1.3%
7	12.734	6.94592	13490.700	41.7%	41	30.617	2.91758	352.292	1.1%
8	13.543	6.53287	19832.300	61.3%	42	31.143	2.86957	797.643	2.5%
9	13.820	6.40281	1434.400	4.4%	43	31.533	2.83490	364.299	1.1%
10	14.163	6.24838	3158.990	9.8%	44	31.799	2.81184	1385.180	4.3%
11	14.387	6.15162	639.173	2.0%	45	32.619	2.74296	696.876	2.2%
12	15.140	5.84740	646.894	2.0%	46	33.056	2.70772	937.149	2.9%
13	15.686	5.64500	661.192	2.0%	47	33.391	2.68127	1727.640	5.3%
14	16.547	5.35293	3217.960	9.9%	48	34.087	2.62814	786.944	2.4%
15	17.266	5.13173	1901.170	5.9%	49	34.667	2.58544	192.503	0.6%
16	18.586	4.77015	15665.300	48.4%	50	35.118	2.55328	125.805	0.4%
17	19.221	4.61386	9933.170	30.7%	51	35.715	2.51196	1474.800	4.6%
18	19.778	4.48526	5642.670	17.4%	52	36.378	2.46770	146.920	0.5%
19	19.915	4.45463	3339.340	10.3%	53	36.999	2.42770	827.021	2.6%
20	20.289	4.37349	1288.950	4.0%	54	37.406	2.40223	1298.800	4.0%
21	20.505	4.32793	2110.690	6.5%	55	37.896	2.37229	1436.470	4.4%
22	20.779	4.27145	2922.170	9.0%	56	38.274	2.34972	582.044	1.8%
23	21.120	4.20319	564.812	1.7%	57	39.002	2.30753	583.582	1.8%
24	21.415	4.14600	1263.180	3.9%	58	39.330	2.28904	1656.370	5.1%
25	21.838	4.06662	2237.900	6.9%	59	39.666	2.27039	1144.300	3.5%
26	22.564	3.93735	22201.500	68.6%	60	40.436	2.22894	160.228	0.5%
27	23.165	3.83648	871.487	2.7%	61	41.238	2.18740	398.360	1.2%
28	23.498	3.78287	1615.620	5.0%	62	42.139	2.14269	301.254	0.9%
29	23.783	3.73830	3783.520	11.7%	63	42.589	2.12108	524.454	1.6%
30	24.324	3.65632	10345.600	32.0%	64	43.438	2.08158	260.389	0.8%
31	24.734	3.59665	22329.400	69.0%	65	43.828	2.06398	489.385	1.5%
32	25.413	3.50208	4699.210	14.5%	66	44.342	2.04121	440.036	1.4%
33	26.093	3.41232	2257.030	7.0%	67	44.890	2.01757	244.572	0.8%
34	26.783	3.32599	9748.190	30.1%					

Table 2. XRPD Peaks.

Example 3: Thermodynamic Stability of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide in an alternative crystalline form, Crystal Form B

The inventors have found that an alternative crystalline form, referred to herein as Crystal Form B, can be formed under certain conditions. The Form B crystalline compound was found to convert to other forms after a relatively short time upon moderate heating. Form

B was thus seen to be a relatively unstable polymorph, making it an unsuitable crystalline form for use in pharmaceutical compositions and formulations.

Example 4: Long-term stability studies of *N*-(4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl)-5-chloro-2-methoxypyridine-3-sulfonamide in Crystal Form A

The long-term stability of the crystalline form of the invention was investigated as follows:

Appearance

A visual inspection method was employed to determine the colour and physical state of the substance.

Polymorph by XRPD

A sample of the substance was analysed and the powder diffractogram compared to that of a reference diffractogram for confirmation of solid-state form.

Water Content

The water content of the sample was determined by Karl Fischer (KF) titration. This method is consistent with USP general method <921c>.

Assay/Content by High-performance liquid chromatography (HPLC)

The content of a sample was determined using a gradient HPLC reversed-phase method with UV detection and external standardization. The HPLC conditions are presented in Table 3 below.

Column	Kinetex XB-C18, 150 mm x 3 mm x 2.6 µm
Column Temperature	40°C
Mobile Phase A	Water + 0.1% Formic acid
Mobile Phase B	Acetonitrile
Detection	UV at 313 nm
Flow Rate	0.6 mL/min
Injection Volume	2.0 µL

Diluent/Blank	Acetonitrile/DMF (1:1)		
Sample concentration	0.8 mg/mL		
Run Time	60 min		
Elution mode - gradient	Time (min)	%A	%B
	0.0	95	5
	40.0	60	40
	50.0	10	90
	55.5	95	5
	60.0	95	5

Table 3. HPLC Chromatographic Conditions

Long term storage

- Samples of the test compound in the crystalline form preparable as described in Example 1
- 5 were kept under the Storage Conditions as below and they were analysed at t=0, 1 month, 3 months and 6 months:

1: 25 °C ± 2 °C / 60% ± 5% Relative Humidity, and

2: 40 °C ± 2 °C / 75% ± 5% Relative Humidity

- 10 The outcome of the long-term stability experiments are shown in Table 4 below:

<i>Storage Conditions: 25 °C ± 2 °C / 60% ± 5% Relative Humidity</i>				
Time in months	0	1	3	6
Appearance	Yellow crystalline solid	Yellow crystalline solid	Yellow crystalline solid	Yellow crystalline solid
Polymorphic form (XRPD)	Crystal Form A	Crystal Form A	Crystal Form A	Crystal Form A
Water Content (% w/w)	0.19	0.50	0.50	0.50
HPLC Assay (% w/w)	98.1	99.1	97.9	98.5

HPLC Purity (% a/a)	97.2	97.1	96.9	97.1
Total Impurities (% a/a)	2.8	2.9	3.1	3.0
<i>Storage Conditions: 40 °C ± 2 °C / 75% ± 5% Relative Humidity</i>				
Time in months	0	1	3	6
Appearance	Yellow crystalline solid	Yellow crystalline solid	Yellow crystalline solid	Yellow crystalline solid
Polymorphic form (XRPD)	Crystal Form A	Crystal Form A	Crystal Form A	Crystal Form A
Water Content (% w/w)	0.19	0.61	0.59	0.59
HPLC Assay (% w/w)	98.1	98.5	96.6	98.2
HPLC Purity (% a/a)	97.2	97.1	97.1	97.1
Total Impurities (% a/a)	2.8	2.9	2.9	2.9

Table 4. Stability of Crystal Form A after 6 months at 25 °C and 40 °C.

The results show that Crystal Form A of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide is very thermally stable, with
 5 no notable degradation to other crystal forms or other impurities over 6 months at 25 °C and 40 °C. Furthermore, the long-term storage experiments indicate that Crystal Form A of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide is suitably non-hygroscopic for use in a pharmaceutical composition, with less than 1% w/w water content detected in relatively humid conditions.

CLAIMS

1. A crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide characterized by a powder X-ray diffractogram (XRPD) having characteristic peaks at $2\theta = 8.6 \pm 0.2^\circ$, $13.5 \pm 0.2^\circ$,
5 $22.6 \pm 0.2^\circ$ and $24.7 \pm 0.2^\circ$.
2. The crystalline form as claimed in claim 1 wherein the powder X-ray diffractogram is further characterised by comprising additional one or more peaks, such as one additional peak, two additional peaks or three additional peaks at 2θ angles selected
10 from the group selected from $9.1^\circ \pm 0.2^\circ$, $12.7^\circ \pm 0.2^\circ$ and $18.6^\circ \pm 0.2^\circ$.
3. The crystalline form as claimed in claim 1 or claims 2 wherein the powder X-ray diffractogram is further characterised by comprising additional one or more peaks, such as one additional peak, two additional peaks or three additional peaks at 2θ
15 angles selected from the group selected from $19.2^\circ \pm 0.2^\circ$, $24.3^\circ \pm 0.2^\circ$ and $26.8^\circ \pm 0.2^\circ$.
4. The crystalline form as claimed in any one of claims 1 to 3 wherein the crystalline form is characterized by a powder X-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in Figure 2.
20
5. A crystalline form of *N*-{4-[2-(2-aminopyrimidin-5-yl)ethynyl]-3-fluoropyridin-2-yl}-5-chloro-2-methoxypyridine-3-sulfonamide characterized by a differential scanning calorimetry trace substantially in accordance with that shown in Figure 1.
- 25 6. A crystalline form as claimed in any one of claims 1 to 5 for use as a medicament.
7. A pharmaceutical composition comprising a crystalline form as claimed in any one of claims 1 to 5 and at least one pharmaceutically acceptable carrier or excipient.
- 30 8. The pharmaceutical composition as claimed in claim 7 further comprising one or more further therapeutic agents.

9. The pharmaceutical composition as claimed in claim 8, wherein the further therapeutic agent is an l-asparaginase or a proteasome inhibitor.
10. A crystalline form as claimed in any one of claims 1 to 6, or a composition as claimed
5 in any one of claims 7 to 9, for use in the treatment or prophylaxis of a disease or disorder in which the inhibition of GCN2 provides a therapeutic effect.
11. A crystalline form as claimed in any one of claims 1 to 6, or a composition as claimed
10 in any one of claims 7 to 9, for use in the treatment or prophylaxis of a disease or disorder selected from the group consisting of: cancer (for example solid cancers and haematological cancers), diabetic retinopathy, myocardial ischemia, diabetic cardiomyopathy, allergic airway inflammation, doxorubicin-induced cardiotoxicity and nonalcoholic fatty liver disease (NAFLD).
12. A crystalline form or a composition for use as claimed in claim 11, wherein the disease
15 or disorder is a cancer, and the cancer is selected from the group consisting of colorectal cancer (e.g., colorectal cancer, rectal cancer, anal cancer, familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant
20 mesothelioma), mesothelioma, pancreatic cancer (e.g., pancreatic duct cancer, pancreatic endocrine tumor), pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric cancer (e.g., papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous carcinoma), duodenal cancer, small intestinal cancer, breast cancer (e.g., invasive ductal carcinoma, ductal carcinoma in situ, inflammatory breast cancer),
25 ovarian cancer (e.g., ovarian epithelial carcinoma, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor), testis tumor, prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer, castration-resistant prostate cancer), liver cancer (e.g., hepatoma, primary liver cancer, extrahepatic bile duct cancer), thyroid cancer (e.g., medullary
30 thyroid carcinoma), renal cancer (e.g., renal cell carcinoma (e.g., clear cell renal cell carcinoma), transitional cell carcinoma of renal pelvis and ureter), uterine cancer (e.g., cervixcancer, uterine body cancer, uterus sarcoma), gestational choriocarcinoma,

brain tumor (e.g., medulloblastoma, glioma, glioblastoma, pineal astrocytoma,
 pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, hypophyseal
 adenoma), retina blastoma, skin cancer (e.g., basal cell carcinoma, malignant
 melanoma (melanoma)), sarcoma (e.g., rhabdomyosarcoma, leiomyosarcoma, soft
 5 tissue sarcoma, spindle cell sarcoma, osteosarcoma, squamous cell carcinoma,
 fibrosarcoma), head and neck cancer, malignant bone tumor, giant cell carcinoma,
 sweat gland carcinoma, sebaceous gland carcinoma, mouth cancer, chest cancer,
 lymph node cancer, eye cancer, an acoustic neuroma, oligodendroglioma,
 meningioma, urinary bladder cancer, and hematologic cancer (e.g., multiple myeloma,
 10 smouldering myeloma, plasmacytoma, leukemia (e.g., acute myeloid leukemia, acute
 lymphocytic leukemia (including blast crisis of chronic leukemia), chronic myeloid
 leukemia, hairy cell leukemia, chronic myelomonocytic leukemia, juvenile
 myelomonocytic leukemia, large granular lymphocytic leukemia, B-cell prolymphocytic
 leukemia, T-cell prolymphocytic leukemia), non-Hodgkin's lymphoma, malignant
 15 lymphoma, Hodgkin's disease, myelodysplastic syndrome, myeloproliferative
 neoplasm, chronic myeloproliferative disease, lymphoplasmacytic lymphoma, B-cell
 lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma,
 T-cell lymphoma, erythroleukemia, histocytic lymphoma, waldenstrom
 macroglobulinemia), and cancer of unknown primary nucleus); and/or
 20 wherein the disease or disorder is a cancer having a MYC mutation (i.e. a cancer in
 which there is a mutation in the MYC gene).

13. A method for the treatment or prophylaxis of a disease or disorder in which the
 inhibition of GCN2 provides a therapeutic effect in a mammal, which comprises
 25 administering to the mammal a therapeutically effective amount of a crystalline form
 as claimed in any one of claims 1 to 6, or a composition as claimed in any one of
 claims 7 to 9, for example a disease or disorder selected from the group consisting of:
 cancer (for example solid cancers and haematological cancers), diabetic retinopathy,
 myocardial ischemia, diabetic cardiomyopathy, allergic airway inflammation,
 30 doxorubicin-induced cardiotoxicity and nonalcoholic fatty liver disease (NAFLD).

14. The use of a crystalline form as claimed in any one of claims 1 to 6 for the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder in which the inhibition of GCN2 provides a therapeutic effect, for example a disease or disorder selected from the group consisting of: cancer (for example solid cancers and haematological cancers), diabetic retinopathy, myocardial ischemia, diabetic cardiomyopathy, allergic airway inflammation, doxorubicin-induced cardiotoxicity and nonalcoholic fatty liver disease (NAFLD).
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