

CRYSTALLINE FORMS OF 3-[[3-FLUORO-2-(METHYLSULFAMOYLAMINO)-4-PYRIDYL]METHYL]-7-[(3-FLUORO-2-PYRIDYL)OXY]-4-METHYL-CHROMEN-2-ONE

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to International Patent Application No. PCT/CN2023/126940, filed October 26, 2023, the entire contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Cancer is among the most common causes of death in the United States. In the United States, cancer has accounted for approximately one of every four deaths. The 5-year relative survival rate for cancer patients diagnosed in 1996-2003 is approximately two-thirds, up from about one half in 1975-1977 (Cancer Facts & Figures, American Cancer Society: Atlanta, Ga. (2008)). The rate of new cancer cases decreased by an average 0.6% per year among men between 2000 and 2009, but stayed the same for women. From 2000 through 2009, death rates from all cancers combined decreased on average 1.8% per year among men and 1.4% per year among women. This improvement in survival reflects progress in diagnosing at an earlier stage as well as improvements in treatment, for which there remains a need. Discovering highly effective anticancer agents with low toxicity is a primary goal of cancer research.

Mitogen-activated protein kinase (MEK) is a critical signaling intermediate in the MAPK/ERK pathway, which is inappropriately activated across a broad spectrum of human tumors, including those derived from lung, pancreas, ovary, skin and colon. While several MEK inhibitors have achieved regulatory approval to date, these MEK inhibitors have yet to deliver against clinical efficacy expectations, and combinations of these MEK inhibitors with RAF inhibitors are required to achieve more durable responses. Novel small molecules which act as dual inhibitors of MEK and extra cellular signal-regulated kinases (ERK) are described in PCT/US2023/019588. Of these compounds, 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one, shows great therapeutic potential for treating a variety of conditions associated with the inhibition of MEK and/or ERK as it not only displays excellent potency, but it also has good CNS penetration and is effective against impeding the growth of multiple cancer cell lines. The

development of alternative forms of this compound is therefore needed in an effort to e.g., facilitate isolation, manufacturing, and formulation development, as well as to maximize storage stability.

SUMMARY OF THE INVENTION

Provided herein are crystalline forms of 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one, hereinafter referred to as Compound **1**. Pharmaceutical compositions comprising one or more crystalline forms of Compound **1** are also provided. Further provided are methods of preparing crystalline forms of Compound **1** and the use of one or more crystalline forms Compound **1** (or a composition comprising one or more crystalline forms of Compound **1**) for treating conditions responsive to inhibition of MEK or ERK, or both, e.g., in a subject. Compound **1** is disclosed in International Application Serial No. PCT/US2023/019588, filed April 24, 2023, and entitled HETEROCYCLIC DERIVATIVES AS MITOGEN-ACTIVATED PROTEIN KINASE (MEK) INHIBITORS. The entire teachings of International Application Serial No. PCT/US2023/019588 are incorporated herein by reference. Compound **1** is disclosed in this application to inhibit MEK and ERK.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 depicts an X-ray powder diffraction pattern (XRPD) for crystalline Form I of 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one.

FIG. 2 depicts a differential scanning calorimetry (DSC) thermogram for crystalline Form I of 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one.

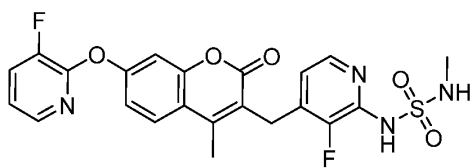
FIG. 3 depicts an X-ray powder diffraction pattern (XRPD) for crystalline Form II of 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one.

FIG. 4 depicts a differential scanning calorimetry (DSC) thermogram for crystalline Form II of 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one.

DETAILED DESCRIPTION

In one embodiment, provided is crystalline Form I of 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one. In another embodiment, provided is crystalline Form II of 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one.

Compound **1** and 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one are used interchangeably and each refer to the compound having the following chemical structure:



As used herein, “crystalline” refers to a solid form of a compound wherein there exists long-range atomic order in the positions of the atoms. The crystalline nature of a solid can be confirmed, for example, by examination of the X-ray powder diffraction pattern.

When used alone, the terms “Form I” and “crystalline Form I”, and “Form II” and “crystalline Form II”, refer to the crystalline salt Form I and the crystalline salt Form II of Compound **1**, respectively, as described herein.

In one embodiment, crystalline Form I and Form II are each single crystalline forms. A “single crystalline form” means that the recited compound, i.e., Compound **1**, is present as a single crystal or a plurality of crystals in which each crystal has the same crystal form (e.g., Form I or Form II). Percent by weight of a particular crystal form is determined by the weight of the particular crystal form divided by the sum weight of the particular crystal, plus the weight of the other crystal form(s) present plus the weight of amorphous form, if present, multiplied by 100%. In some instances, crystalline Form I or crystalline Form II as described herein are at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% a single crystalline form. “Pure single crystalline form” means that Compound **1** is present as a single crystal or a plurality of crystals in which each crystal has the same crystal form with no other detectable amounts of other crystal forms present and/or amorphous forms.

The term “amorphous” refers to a solid that is present in a non-crystalline state or form. Amorphous solids are disordered arrangements of molecules and therefore possess no distinguishable crystal lattice or unit cell and consequently have no definable long range

ordering. Solid state ordering of solids may be determined by standard techniques known in the art, e.g., by X-ray powder diffraction (XRPD) or differential scanning calorimetry (DSC).

The term “anhydrous” and “anhydrate” are used interchangeably and mean that the referenced crystalline form has substantially no water in the crystal lattice, e.g., less than 1% by weight as determined by Karl Fisher analysis

The 2-theta values of the X-ray powder diffraction patterns for the crystalline forms described herein may vary slightly from one instrument to another and also depending on variations in sample preparation and batch to batch variation due to factors such as temperature variation, sample displacement, and the presence or absence of an internal standard. Therefore, unless otherwise defined, the XRPD patterns / assignments recited herein are not to be construed as absolute and can vary ± 0.2 degrees. It is well known in the art that this variability will account for the above factors without hindering the unequivocal identification of a crystal form. Unless otherwise specified, the 2-theta values provided herein were obtained using Cu K α 1 radiation.

“Substantially the same XRPD pattern” or “an X-ray powder diffraction pattern substantially similar to” a defined figure means that for comparison purposes, at least 90% of the peaks shown are present. It is to be further understood that for comparison purposes some variability in peak intensities from those shown are allowed, such as $\pm 5\%$ of the intensity of the most intense peak.

Temperature values, e.g., for DSC peaks herein may vary slightly from one instrument to another and also depending on variations in sample preparation, batch to batch variation, and environmental factors. Therefore, unless otherwise defined, temperature values recited herein are not to be construed as absolute and can vary ± 5 degrees or ± 2 degrees.

In one embodiment, crystalline Form I is characterized by at least three, at least four, at least five, at least six, or at least seven x-ray powder diffraction peaks at 2Θ angles selected from 13.15°, 17.76°, 19.57°, 21.16°, 25.00°, 26.32°, 26.83°, and 29.99°. In another embodiment, crystalline Form I is characterized by at least three x-ray powder diffraction peaks at 2Θ angles selected from 13.15°, 17.76°, 19.57°, 21.16°, 25.00°, 26.32°, 26.83°, and 29.99°. In another embodiment, crystalline Form I is characterized by at least four x-ray powder diffraction peaks at 2Θ angles selected from 13.15°, 17.76°, 19.57°, 21.16°, 25.00°, 26.32°, 26.83°, and 29.99°. In another embodiment, crystalline Form I is characterized by at least five x-ray powder diffraction peaks at 2Θ angles selected from 13.15°, 17.76°, 19.57°, 21.16°, 25.00°, 26.32°, 26.83°, and 29.99°. In another embodiment, crystalline Form I is

characterized by at least six x-ray powder diffraction peaks at 2Θ angles selected from 13.15° , 17.76° , 19.57° , 21.16° , 25.00° , 26.32° , 26.83° , and 29.99° . In another embodiment, crystalline Form I is characterized by at least seven x-ray powder diffraction peaks at 2Θ angles selected from 13.15° , 17.76° , 19.57° , 21.16° , 25.00° , 26.32° , 26.83° , and 29.99° . In another embodiment, crystalline Form I is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 17.76° , 26.32° , and 29.99° . In another embodiment, crystalline Form I is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 17.76° , 26.32° , and 29.99° , and at least one additional peak selected from 13.15° , 21.16° , 26.32° , and 26.83° . In another embodiment, crystalline Form I is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 17.76° , 26.32° , 26.83° , and 29.99° . In another embodiment, crystalline Form I characterized by x-ray powder diffraction peaks at 2Θ angles selected from 17.76° , 26.32° , 26.83° , and 29.99° , and at least one or at least two additional peaks selected from 13.15° , 17.76° , and 21.16° . In another embodiment, crystalline Form I characterized by x-ray powder diffraction peaks at 2Θ angles selected from 17.76° , 19.57° , 26.32° , 26.83° , and 29.99° . In another embodiment, crystalline Form I characterized by x-ray powder diffraction peaks at 2Θ angles selected from 17.76° , 19.57° , 21.16° , 26.32° , 26.83° , and 29.99° . In another embodiment, crystalline Form I characterized by x-ray powder diffraction peaks at 2Θ angles selected from 13.15° , 17.76° , 19.57° , 21.16° , 26.32° , 26.83° , and 29.99° . In another embodiment, crystalline Form I characterized by one or more, or all, of the x-ray powder diffraction peaks at 2Θ angles provided in **Table 1**. In another embodiment, crystalline Form I characterized by an x-ray powder diffraction substantially similar to **FIG. 1**.

In one embodiment, crystalline Form II is characterized by at least three, at least four, at least five, at least six, at least seven, or at least eight x-ray powder diffraction peaks at 2Θ angles selected from 8.85° , 13.33° , 14.69° , 17.28° , 17.70° , 18.25° , 22.17° , 25.24° , and 26.77° . In another embodiment, crystalline Form II is characterized by at least three x-ray powder diffraction peaks at 2Θ angles selected from 8.85° , 13.33° , 14.69° , 17.28° , 17.70° , 18.25° , 22.17° , 25.24° , and 26.77° . In another embodiment, crystalline Form II is characterized by at least four x-ray powder diffraction peaks at 2Θ angles selected from 8.85° , 13.33° , 14.69° , 17.28° , 17.70° , 18.25° , 22.17° , 25.24° , and 26.77° . In another embodiment, crystalline Form II is characterized by at least five x-ray powder diffraction peaks at 2Θ angles selected from 8.85° , 13.33° , 14.69° , 17.28° , 17.70° , 18.25° , 22.17° , 25.24° , and 26.77° . In another embodiment, crystalline Form II is characterized by at least six x-ray powder diffraction

peaks at 2Θ angles selected from 8.85° , 13.33° , 14.69° , 17.28° , 17.70° , 18.25° , 22.17° , 25.24° , and 26.77° . In another embodiment, crystalline Form II is characterized by at least seven x-ray powder diffraction peaks at 2Θ angles selected from 8.85° , 13.33° , 14.69° , 17.28° , 17.70° , 18.25° , 22.17° , 25.24° , and 26.77° . In another embodiment, crystalline Form II is characterized by at least eight x-ray powder diffraction peaks at 2Θ angles selected from 8.85° , 13.33° , 14.69° , 17.28° , 17.70° , 18.25° , 22.17° , 25.24° , and 26.77° . In another embodiment, crystalline Form II is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 14.69° , 17.70° , and 22.17° . In another embodiment, crystalline Form II is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 14.69° , 17.70° , and 22.17° , and at least one, at least two, at least three, or at least four additional peaks selected from 8.85° , 13.33° , 17.28° , 18.25° , and 25.24° . In another embodiment, crystalline Form II is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 8.85° , 13.33° , 14.69° , 17.28° , 17.70° , 18.25° , 22.17° , and 25.24° . In another embodiment, crystalline Form II is characterized by one or more, or all, of the x-ray powder diffraction peaks at 2Θ angles provided in **Table 2**. In another embodiment, crystalline Form II is characterized by an x-ray powder diffraction substantially similar to **FIG. 3**.

In one embodiment, crystalline Form I or crystalline Form II as described herein is anhydrous.

Also provided herein are pharmaceutical compositions comprising crystalline Form I or crystalline Form II. In one embodiment, the pharmaceutical composition comprises a pharmaceutically acceptable carrier and crystalline Form I or II as described herein. In one embodiment, the pharmaceutical composition comprises at least one solid pharmaceutically acceptable carrier and crystalline Form I or II as described herein.

“Pharmaceutically acceptable carrier” refers to a substance that aids the formulation and/or administration of an active agent to and/or absorption by a subject and can be included in the compositions of the present disclosure without causing a significant adverse toxicological effect on the subject. Non-limiting examples of pharmaceutically acceptable carriers include water, NaCl, normal saline solutions, lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer’s solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, hydroxymethylcellulose, fatty acid esters, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for

influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with or interfere with the activity of the compounds provided herein. One of ordinary skill in the art will recognize that other pharmaceutical carriers are suitable for use with disclosed compounds. As used herein, a “solid pharmaceutically acceptable carrier” refers to carriers which are not in liquid form at room temperature. Thus, a “solid pharmaceutically acceptable carrier” excludes water and organic solvents such as acetonitrile.

The pharmaceutical compositions described herein optionally include one or more pharmaceutically acceptable carriers such as lactose, starch, cellulose and dextrose. Other excipients, such as flavoring agents, sweeteners, and preservatives, such as methyl, ethyl, propyl and butyl parabens, can also be included. More complete listings of suitable excipients can be found in the Handbook of Pharmaceutical Excipients (5th Ed., Pharmaceutical Press (2005)). A person skilled in the art would know how to prepare formulations suitable for various types of administration routes. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003 - 20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999. The carriers, diluents and/or excipients are “acceptable” in the sense of being compatible with the other ingredients of the pharmaceutical composition and not deleterious to the recipient thereof.

In one embodiment, provided are methods for inhibiting mitogen-activated protein kinase (MEK) or extra cellular signal-regulated kinases (ERK) in a subject in need thereof, comprising: administering to the subject an effective amount of crystalline Form I or crystalline Form II, or an effective amount of a pharmaceutical composition thereof.

A “subject” is a mammal in need of treatment. The mammal can be a veterinary animal (e.g., dog or cat, and the like), farm animal (e.g., horse, cow, sheep or goat and the like) or laboratory animal (e.g., mouse, rat or guinea pig and the like). Most commonly, the subject is a human.

A “subject in need of treatment” is a subject with a disease in which medical treatment is desirable. In some embodiments, the disease is cancer. In some embodiments, the cancer is selected from breast cancer, prostate cancer, esophageal cancer, colon cancer, endometrial cancer, blood cancer, brain cancer, glioma, head and neck cancer, thyroid cancer, gallbladder cancer, bladder cancer, skin cancer, malignant melanoma, cancer of the uterus,

cancer of the ovary, lung cancer, pancreatic cancer, liver cancer, renal cancer, testicular cancer, renal pelvic and ureteral cancer, prostate cancer, gastric cancer, stomach cancer, and hematological cancer.

In some embodiments, the lung cancer is selected from non-small cell lung cancer, small cell lung cancer, and lung carcinoid tumor. In some embodiments, the head and neck cancer is selected from pharyngeal cancer, laryngeal cancer, tongue cancer, and the like. In some embodiments, the hematological cancer is selected from leukemia, lymphoma, and multiple myeloma.

In some embodiments, the hematological cancer is acute myeloblastic leukemia, chronic myeloid leukemia, B cell lymphoma, chronic lymphocytic leukemia (CLL), Non-Hodgkins lymphoma, hairy cell leukemia, Mantle cell lymphoma, Burkitt lymphoma, small lymphocytic lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, extranodal marginal zone lymphoma, activated B-cell like (ABC) diffuse large B cell lymphoma, or germinal center B cell (GCB) diffuse large B cell lymphoma.

In some embodiments, the leukemia is selected from acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML), acute myelocytic leukemia, acute lymphocytic leukemia, chronic myeloid leukemia (CML), chronic myelocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, T-cell prolymphocytic leukemia, juvenile myelomonocytic leukemia, myelodysplastic syndrome, and follicular lymphoma.

In some embodiments, the lymphoma is Hodgkin's lymphoma or non-Hodgkin's lymphoma (NHL).

In some embodiments, the non-Hodgkin lymphoma (NHL) is selected from relapsed NHL, refractory NHL, and recurrent follicular NHL.

In one embodiment, the cancer is characterized by an NRAS mutation. In another embodiment, the cancer is characterized by an NRAS mutation at position 61 (i.e., Q61X, where X is a naturally occurring amino acid). In another embodiment, the cancer is characterized by an NRAS Q61R, NRAS Q61L, NRAS Q61K, NRAS Q61P or NRAS Q61H mutation. In another embodiment, the cancer is characterized by an NRAS Q61R, NRAS Q61L, NRAS Q61K, NRAS Q61P or NRAS Q61H mutation and is a cancer of the bladder/urinary tract, lung, skin, liver, myeloid, lymphoid, ovarian/fallopian tube, peripheral nervous system, soft tissue or vulva/vagina. In another embodiment, the cancer is of the bladder/urinary tract, lung or skin, each characterized by an NRAS Q61R mutation; cancer of

the liver, myeloid, skin, lymphoid or bladder/urinary tract, each characterized by an NRAS Q61L mutation; cancer of the lung, lymphoid, ovarian/fallopian tube, peripheral nervous system, soft tissue, vulva/vagina, liver or skin, each characterized by an NRAS Q61K mutation; cancer of the myeloid characterized by an NRAS Q61P mutation; or cancer of the soft tissue characterized by an NRAS Q61H mutation. In another embodiment, the cancer is characterized by an NRAS Q61R, NRAS Q61L, NRAS Q61K, NRAS Q61P or NRAS Q61H and is bladder urothelial carcinoma, non-small cell lung cancer, melanoma, hepatoblastoma, acute myeloid leukemia, non-hodgkin lymphoma, ovarian epithelial tumor, neuroblastoma, fibrosarcoma, mucosal melanoma of the vulva/vagina, hepatocellular carcinoma or rhabdomyosarcoma. In another embodiment, the cancer is characterized by an NRAS Q61R mutation, and is bladder urothelial carcinoma, non-small cell lung cancer or melanoma. In another embodiment, the cancer is characterized by an NRAS Q61L mutation, and is hepatoblastoma, acute myeloid leukemia, melanoma, non-hodgkin lymphoma or bladder urothelial carcinoma. In another embodiment, the cancer is characterized by an NRAS Q61K mutation, and is non-small cell lung cancer, non-hodgkin lymphoma, ovarian epithelial tumor, neuroblastoma, melanoma, fibrosarcoma, mucosal melanoma of the vulva/vagina or hepatocellular carcinoma. In another embodiment, the cancer is characterized by an NRAS Q61P mutation, and is acute myeloid leukemia. In another embodiment, the cancer is characterized by an NRAS Q61H mutation, and is rhabdomyosarcoma.

In another embodiment, the cancer is characterized by an NRAS A91V or E132K mutation. In another embodiment, the cancer is characterized by an NRAS A91V or E132K mutation and is from the bowel, e.g., the cancer is colorectal adenocarcinoma.

In another embodiment, the cancer is characterized by an NRAS T20 frame shift deletion. In another embodiment, the cancer is characterized by an NRAS T20 frame shift deletion and is from the lung, e.g., the cancer is lung neuroendocrine tumor.

In another embodiment, the cancer is characterized by an NRAS G12C, G12V, G12D, G12A, G12S or G12R mutation. In another embodiment, the cancer is characterized by an NRAS G12C, G12V, G12D, G12A, G12S or G12R mutation and is a cancer from myeloid, skin, lymphoid or ovary/fallopian tubes. In another embodiment, the cancer is characterized by an NRAS G12C mutation and is from myeloid. In another embodiment, the cancer is characterized by an NRAS G12V mutation and is from skin. In another embodiment, the cancer is characterized by an NRAS G12D mutation and is from lymphoid, myeloid and ovaries/fallopian tubes. In another embodiment, the cancer is characterized by an NRAS

G12R mutation and is from myeloid. In another embodiment, the cancer is characterized by an NRAS G12C, G12V, G12D, G12A, G12S or G12R mutation and is acute myeloid leukemia, non-hodgkins lymphoma, melanoma or ovarian epithelial tumor. In another embodiment, the cancer is characterized by an NRAS G12C mutation and is acute myeloid leukemia. In another embodiment, the cancer is characterized by an NRAS G12V mutation and is melanoma. In another embodiment, the cancer is characterized by an NRAS G12D mutation and is acute myeloid leukemia, non-hodgkins lymphoma or ovarian epithelial tumor. In another embodiment, the cancer is characterized by an NRAS G12R mutation and is acute myeloid leukemia.

In another embodiment, the cancer is characterized by an NRAS G13D or NRAS G13R mutation. In another embodiment, the cancer is characterized by an NRAS G13D or NRAS G13R mutation and is a cancer of the myeloid, lymphoid or skin. In another embodiment, the cancer is characterized by an NRAS G13D mutation and is a cancer from lymphoid (e.g., non-hodgkin lymphoma). In another embodiment, the cancer is characterized by an NRAS G13R mutation and is a cancer from myeloid (e.g., acute myeloid leukemia) or skin (e.g., melanoma).

In one embodiment, the cancer is characterized by a KRAS mutation. In another embodiment, the cancer is characterized by an KRAS mutation at position 13 (i.e., G13X, where X is a naturally occurring amino acid). In another embodiment, the cancer is characterized by a KRAS G13D, KRAS G13C or KRAS G13V mutation. In another embodiment, the cancer is characterized by a KRAS G13D, KRAS G13C or KRAS G13V mutation and is a cancer of the bowel, lung, breast. In another embodiment, the cancer is characterized by a KRAS G13D mutation and is of the bowel, lung or breast; or by a KRAS G13C mutation and is of the lung. In another embodiment, the cancer is characterized by a KRAS G13D or KRAS G13C mutation and is colorectal carcinoma, non-small lung cell cancer or invasive breast carcinoma.

In another embodiment, the cancer is characterized by a KRAS mutation at V14L, V9I, I187V, A59T, P140H, A146T, L19F, A18D, A146V, K117N, P121H, A59G, V160A. In another embodiment, the cancer is lymphoid characterized by a KRAS mutation at V14L or V9I. In another embodiment, the cancer is bone characterized by a KRAS mutation at I187V or A59T. In another embodiment, the cancer is bowel characterized by a KRAS mutation at P140H or A146T. In another embodiment, the cancer is lung characterized by a KRAS mutation at L19F. In another embodiment, the cancer is myeloid characterized by a KRAS

mutation at A18D, A146V or K117N. In another embodiment, the cancer is ovary/fallopian tube characterized by a KRAS mutation at P121H or A59G. In another embodiment, the cancer is uterus characterized by a KRAS mutation at V160A. In another embodiment, the cancer is characterized by a KRAS mutation at V14L and is B-lymphoblastic leukemia/lymphoma. In another embodiment, the cancer is characterized by a KRAS mutation at V9I and is non-hodgkin lymphoma. In another embodiment, the cancer is characterized by a KRAS mutation at I187V or A59T and is osteosarcoma. In another embodiment, the cancer is characterized by a KRAS mutation at P140H or A146T and is colorectal adenocarcinoma. In another embodiment, the cancer is characterized by a KRAS mutation at L19F and is non-small cell lung cancer. In another embodiment, the cancer is characterized by a KRAS mutation at A18D, A146V or K117N and is acute myeloid leukemia. In another embodiment, the cancer is characterized by a KRAS mutation at P121H or A59G and is ovarian epithelial tumor. In another embodiment, the cancer is characterized by a KRAS mutation at V160A and is endometrial carcinoma.

In another embodiment, the cancer is characterized by an KRAS mutation at position 12 (i.e., G12X, where X is a naturally occurring amino acid). In another embodiment, the cancer is characterized by a KRAS G12D, G12V, G12A, G12R, G12S or G12C mutation. In another embodiment, the cancer is characterized by a KRAS G12D, G12V, G12A, G12R, G12S or G12C mutation and is a cancer of the bowel, esophagus/stomach, ovary/fallopian tube, pancreas, uterus, lung, soft tissue, biliary tract, breast, lymphoid, thyroid or cervix. In another embodiment, the cancer is characterized by a KRAS G12D mutation and is a cancer of the bowel, esophagus/stomach, ovary/fallopian tube, pancreas, uterus or lung. In another embodiment, the cancer is characterized by a KRAS G12V mutation and is a cancer of the bowel, lung, pancreas, uterus, soft tissue, biliary tract or breast. In another embodiment, the cancer is characterized by a KRAS G12A mutation and is a cancer of the lymphoid, lung or bowel. In another embodiment, the cancer is characterized by a KRAS G12R mutation and is a cancer of the thyroid or pancreas. In another embodiment, the cancer is characterized by a KRAS G12S mutation and is a cancer of the lungs or bowel. In another embodiment, the cancer is characterized by a KRAS G12C mutation and is a cancer of the bowel, lung, cervix, esophagus/stomach or pancreas.

In another embodiment, the cancer is characterized by a KRAS G12D, G12V, G12A, G12R, G12S or G12C mutation and is colorectal adenocarcinoma, esophagogastric adenocarcinoma, ovarian epithelial tumor, pancreatic adenocarcinoma, endometrial

carcinoma, non-small cell lung cancer, lung neuroendocrine tumor, leiomyosarcoma, intraductal papillary neoplasm of the bile duct, invasive breast carcinoma, non-hodgkin lymphoma, anaplastic thyroid cancer, cervical squamous cell carcinoma or esophageal squamous cell carcinoma. In another embodiment, the cancer is characterized by a KRAS G12D and is colorectal adenocarcinoma, esophagogastric adenocarcinoma, ovarian epithelial tumor, pancreatic adenocarcinoma, endometrial carcinoma or non-small cell lung cancer. In another embodiment, the cancer is characterized by a KRAS G12V mutation and is colorectal adenocarcinoma, non-small cell lung cancer, lung neuroendocrine tumor, pancreatic adenocarcinoma, endometrial carcinoma, leiomyosarcoma, intraductal papillary neoplasm of the bile duct or invasive breast carcinoma. In another embodiment, the cancer is characterized by a KRAS G12A mutation and is colorectal adenocarcinoma, non-hodgkin lymphoma or non-small cell lung cancer. In another embodiment, the cancer is characterized by a KRAS G12R mutation and is anaplastic thyroid cancer or pancreatic adenocarcinoma. In another embodiment, the cancer is characterized by a KRAS G12S mutation and is non-small cell lung cancer or colorectal adenocarcinoma.

In another embodiment, the cancer is characterized by an KRAS mutation at position 61 (i.e., Q61X, where X is a naturally occurring amino acid). In another embodiment, the cancer is characterized by a KRAS Q61H, Q61L, Q61K, Q61R, Q61P or G61E mutation. In another embodiment, the cancer is characterized by a KRAS Q61H, Q61L, Q61K, Q61R, Q61P or G61E mutation and are cancers of the bowel, pancreas or lung. In another embodiment, the cancer is characterized by a Q61H KRAS mutation and is a cancer of the bowel or pancreas. In another embodiment, the cancer is characterized by a KRAS Q61L mutation and is a cancer of the bowel. In another embodiment, the cancer is characterized by a KRAS Q61K and is a cancer of the lung. In another embodiment, the cancer is characterized by a KRAS Q61R and is a cancer of the lung.

In another embodiment, the cancer is characterized by a KRAS Q61H, Q61L, Q61K, Q61R, Q61P or G61E mutation and is colorectal adenocarcinoma, pancreatic adenocarcinoma or non-small cell lung cancer. In another embodiment, the cancer is characterized by a KRAS Q61R and is non-small cell lung cancer. In another embodiment, the cancer is characterized by a KRAS Q61H mutation and is colorectal adenocarcinoma or pancreatic adenocarcinoma. In another embodiment, the cancer is characterized by a KRAS Q61L mutation and is colorectal adenocarcinoma. In another embodiment, the cancer is characterized by a KRAS Q61K mutation and is non-small cell lung cancer.

A subject with one of the aforementioned cancers may be treated by administering to the subject an effective amount of crystalline Form I or Form II as described herein, or a pharmaceutical composition thereof.

In some embodiments, the methods comprise administering an effective amount of a crystalline Form I or Form II as described herein, or a pharmaceutical composition thereof, in combination with an effective amount of an anticancer agent, wherein the amounts of the combination and the chemotherapeutic are together effective in treating a subject with cancer. Many chemotherapeutics are presently known in the art and can be used in combination. In some embodiments, the chemotherapeutic is selected from mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti- androgens. Also described are methods for treating a subject with cancer comprising administering to the mammal an amount of a MEK protein kinase inhibitor and/or Raf protein kinase inhibitor in combination with radiation therapy, wherein the amounts of the MEK protein kinase inhibitor and/or Raf protein kinase inhibitor in combination with the radiation therapy effective in treating a subject with cancer. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein.

In some embodiments, the disclosure also relates to a method of inhibiting abnormal cell growth in a mammal which may comprise crystalline Form I or Form II as described herein, or a pharmaceutical composition thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents. Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with a compound of the present invention and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREXTM (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European

Patent Publication 606,046 (published July 13,1994), European Patent Publication 931, 788 (published July 28,1999), WO 90/05719 (published May 31,1990), WO 99/52910 (published October 21,1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17,1999), PCT International Application No. PCT/IB98/01113 (filed July 21,1991), European Patent Application No. 99302232.1 (filed March 25,1999), Great Britain Patent Application No. 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12,1999), United States Patent 5,863, 949 (issued January 26,1999), United States Patent 5,861, 510 (issued January 19,1999), and European Patent Publication 780,386 (published June 25, 1997). Some MMP-2 and MMP-9 inhibitors have little or no activity inhibiting MMP-1, while some selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (L e., MAP-1, NEMP-3, MMP-4, M7vIP-5, MMP-6, MMP- 7, MMP-8, MMP-10, MMP-11, and MMP-13). Some specific examples of MlvIP inhibitors useful in the present invention are AG-3340, RU 32-3555, and RS 13-0830.

In some embodiments, crystalline Form I or Form II as described herein, or a pharmaceutical composition thereof, is administered with at least one additional therapeutic agent. In some embodiments, the therapeutic agent is a taxol, bortezomib or both. In further or additional embodiments, the therapeutic agent is selected from cytotoxic agents, anti-angiogenesis agents and antineoplastic agents. In further or additional embodiments, the anti-neoplastic agents selected from the group of consisting of alkylating agents, anti-metabolites, epicyclotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazine, mitoxantrone, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors.

Many chemotherapeutics are presently known in the art and can be used in combination with crystalline Form I or Form II as described herein, or a pharmaceutical composition thereof. In some embodiments, the chemotherapeutic is selected from mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

In some embodiments, the combination is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy, surgery or any combination thereof. In further or additional embodiments, the combination is administered in combination with at least one additional therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from

the group of cytotoxic agents, anti-angiogenesis agents and antineoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors.

In some embodiments, the second therapeutic is an agent for co-regulating MEK or RAF pathways. In some embodiments, the second therapeutic agent is a MEK or RAF inhibitor. In some embodiments, the RAF inhibitor is vemurafenib, dabrafenib, XL-281, LGX-818, CEP-32496, ARQ-736, MEK-162, refametinib, E-620L, pimasertib, WX-554, GDC-0973 or LXH254.

In some embodiments, the second therapeutic is an agent for co-regulating MAPK pathway. In some embodiments, the agent for co-regulating MAPK pathway is KRAS G12C mutant selective inhibitors including but not limited to sotorasib, adagrasib, ARS-1620, ARS-3248, LY3499446, AMG-510, and MRTX849; KRAS G12D mutant selective inhibitors; Son of Sevenless 1 (SOS1) inhibitors (e.g., BI1701963, BI-3406 and RMC-023); SHP2 inhibitors (e.g., TNO155, BBP-398 and ICP-189); EGFR inhibitors including but not limited to gefitinib, erlotinib, afatinib, lazertinib, aumolertinib (formerly almonertinib), olmutinib, dacomitinib, nazartinib and osimertinib.

In some embodiments, the second therapeutic is an agent for mutant p53 reactivators (PC14586, APR-246 and COTI-2).

In some embodiments, the second therapeutic agent is selected from aspirin; diflunisal; salsalate; acetaminophen; ibuprofen; dexibuprofen; naproxen; fenoprofen; ketoprofen; dexketoprofen; flurbiprofen; oxaprozin; loxoprofen; indomethacin; tolmetin; sulindac; etodolac; ketorolac; diclofenac; aceclofenac; nabumetone; enolic acid; piroxicam; meloxicam; tenoxicam; droxicam; lomoxicam; isoxicam; mefenamic acid; meclofenamic acid; flufenamic acid; tolfenamic acid; sulfonanilides; clonixin; licofelone; dexamethasone; and prednisone.

In some embodiments, the second therapeutic agent is selected from mechlorethamine; cyclophosphamide; melphalan; chlorambucil; ifosfamide; busulfan; N-nitroso-N-methylurea (MNU); carmustine (BCNU); lomustine (CCNU); semustine (MeCCNU); fotemustine; streptozotocin; dacarbazine; mitozolomide; temozolomide; thiotepa; mytomycin; diaziquone (AZQ); cisplatin; carboplatin; and oxaliplatin.

In some embodiments, the second therapeutic agent is selected from vincristine; vinblastine; vinorelbine; vindesine; vinflunine; paclitaxel; docetaxel; etoposide; teniposide; tofacitinib; ixabepilone; irinotecan; topotecan; camptothecin; doxorubicin; mitoxantrone; and teniposide.

In some embodiments, the second therapeutic agent is selected from actinomycin; bleomycin; plicamycin; mitomycin; daunombicin; epimbicin; idarubicin; pirarubicin; aclarubicin; mitoxantrone; cyclophosphamide; methotrexate; 5-fluorouracil; prednisolone; folinic acid; methotrexate; melphalan; capecitabine; mechlorethamine; uramustine; melphalan; chlorambucil; ifosfamide; bendamustine; 6-mercaptopurine; and procarbazine.

In some embodiments, the second therapeutic agent is selected from cladribine; pemetrexed; fludarabine; gemcitabine; hydroxyurea; nelarabine; cladribine; clofarabine; ytarabine; decitabine; cytarabine; cytarabine liposomal; pralatrexate; floxuridine; fludarabine; colchicine; thioguanine; cabazitaxel; larotaxel; ortataxel; tesetaxel; aminopterin; pemetrexed; pralatrexate; raltitrexed; pemetrexed; carmofur; and floxuridine.

In some embodiments, the second therapeutic agent is selected from azacitidine; decitabine; hydroxycarbamide; topotecan; irinotecan; belotecan; teniposide; aclarubicin; epimbicin; idarubicin; amrubicin; pirarubicin; valrubicin; zombicin; mitoxantrone; pixantrone; mechlorethamine; chlorambucil; prednimu stine; uramustine; estramustine; carmustine; lomustine; fotemustine; nimustine; ranimustine; carboquone; thioTEPA; triaziquone; and triethylenemelamine.

In some embodiments, the second therapeutic agent is selected from nedaplatin; satraplatin; procarbazine; dacarbazine; temozolomide; altretamine; mitobronitol; pipobroman; actinomycin; bleomycin; plicamycin; aminolevulinic acid; methyl aminolevulinate; efaproxiral; talaporfin; temoporfin; verteporfin; alvocidib; seliciclib; palbociclib; bortezomib; carfilzomib; anagrelide; masoprocol; olaparib; belinostat; panobinostat; romidepsin; vorinosta; idelalisib; atrasentan; bexarotene; testolactone; amsacrine; trabectedin; alitretinoin; tretinoin; demecolcine; elsamitrucin; etoglucid; lonidamine; lucanthone; mitoguazone; mitotane; oblimersen; omacetaxine mepesuccinate; and eribulin.

In some embodiments, the second therapeutic agent is selected from azathioprine; Mycophenolic acid; leflunomide; teriflunomide; tacrolimus; cyclosporin; pimecrolimus; abetimus; gusperimus; lenalidomide; pomalidomide; thalidomide; anakinra; sirolimus; everolimus; ridaforolimus; temsirolimus; umirolimus; zotarolimus; eculizumab; adalimumab; afelimomab; certolizumab pegol; golimumab; infliximab; nerelimomab; mepolizumab;

omalizumab; faralimomab; elsilimomab; lebrikizumab; ustekinumab; etanercept; orelizumab; teplizumab; visilizumab; clenoliximab; keliximab; zanolimumab; efalizumab; erlizumab; obinutuzumab; rituximab; and ocrelizumab.

In some embodiments, the second therapeutic agent is selected from pascolizumab; gomiliximab; lumiliximab; teneliximab; toralizumab; aselizumab; galiximab; gavilimomab; ruplizumab; belimumab; blisibimod; ipilimumab; tremelimumab; bertilimumab; lerdelimumab; metelimumab; natalizumab; tocilizumab; odulimomab; basiliximab; daclizumab; inolimomab; zolimoma; atorolimumab; cedelizumab; fontolizumab; maslimomab; morolimumab; pexelizumab; reslizumab; rovelizumab; sipilizumab; talizumab; telimomab; vapaliximab; vepalimomab; abatacept; belatacept; pegsunercept; aflibercept; alefacept; and rilonacept.

In some embodiments, the second therapeutics is an immune checkpoint inhibitor such as a PD-1 inhibitor or a PD-L1 inhibitor. In some embodiments, the immune checkpoint inhibitor is an anti PD-1 antibody selected from balstilimab, camrelizumab, cemiplimab, dostarlimab, geptanolimab, nivolumab, pembrolizumab, penpulimab, pidilizumab, prolgolimab, retifanlimab, sasanlimab, serplulimab, serplulimab, sintilimab, spartalizumab, sulituzumab, tebotelimab, teripalimab, tislelizumab, toripalimab, toripalimab, zimberelimab, AMP -224 (MedImmunne), AMP-514 (MedImmunne), AT-16201 (AIMM Therapeutics BV), AVI-102 (Ab Vision Inc), BAT-1308 (Bio-Thera Solutions Ltd), BH-2950 (Beijing Hanmi Pharmaceutical Co Ltd), BSI-050K01 (Biosion Inc), CB-201 (Crescendo Biologies Ltd), CYTO-101 (Cytocom Inc), DB-004 (DotBio Pte Ltd), EX- 105 (Excelmab Inc), EX- 108 (Excelmab Inc), GNR-051 (Generium), HAB-21 (Suzhou Stainwei Biotech Inc), IBI-319 (Innovent Biologies Inc), IBI-321 (Innovent Biologies Inc), IKT-202 (Icell Kealex Therapeutics LLC), IMU-201 (Imugene Ltd), JS-201 (Shanghai Junshi Bioscience Co Ltd), LBL-006 (Leads Biolabs Inc), LBL-024 (Leads Biolabs Inc), LD-01 (Leidos Health Holdings LLC), LQ-005 (Shanghai Novamab Biopharmaceuticals Co Ltd), LQ-008 (Shanghai Novamab Biopharmaceuticals Co Ltd), MD-402 (MD Biosciences GmbH), OT-2 (OncoTrap Inc), PE-0105 (Shanghai Yunyi Health Technology Development Co Ltd), PF-07209960 (Pfizer Inc), PH-762 (Phio Pharmaceuticals Corp), REGN-PD-1/XX (Regeneron), R07121661 (Genentech), SAUG-1 (Juvenescence UK Ltd), SCT-HIOA (Sinocelltech), SG-001 (CSPC Pharmaceutical Group Ltd), SI-B003 (SysImmune), SL-279137 (Shattuck Labs), SSI-361 (Lyvgen Biopharma Ltd), STI-A1110 (Servier), STM-418 (Stcube Inc), Sym-021 (Symphogen A/S), TSR-075 (GlaxoSmithKline Pic), TY101 (Tayu Huaxia Biotech), Twist-

PD-1 (Twist Bioscience), XmAb-TGFpR2 (Xencor), XmAb-YYCD28 (Xencor), XmAb20717 (Xencor), XmAb23104 (Xencor), YBL-006 (Y Biologies), YBL-019 (Y Biologies), and mDX-400 (Merck & Co Inc)..

In one embodiment, the anti-cancer agent and crystalline Form I or Form II as described herein, or a pharmaceutical composition thereof, are administered contemporaneously. When administered contemporaneously, the anti-cancer agent and the crystalline Form I or Form II can be administered in the same formulation or in different formulations. Alternatively, crystalline Form I or Form II as described herein and the additional anti-cancer agent are administered separately. Alternatively, crystalline Form I or Form II as described herein, and the additional anti-cancer agent can be administered sequentially, as separate compositions, within an appropriate time frame (e.g., a cancer treatment session/interval (e.g., about 1.5 to about 5 hours to about 10 hours to about 15 hours to about 20 hours; about 1 day to about 2 days to about 5 days to about 10 days to about 14 days)) as determined by the skilled clinician (e.g., a time sufficient to allow an overlap of the pharmaceutical effects of the therapies). Crystalline Form I or Form II as described herein and the additional anti-cancer agent can be administered in a single dose or multiple doses in an order and on a schedule suitable to achieve a desired therapeutic effect (e.g., inhibition of tumor growth).

As used herein, the term "treating" or "treatment" refers to obtaining a desired pharmacological and/or physiological effect. The effect can be therapeutic, which includes achieving, partially or substantially, one or more of the following results: partially or totally reducing the extent of the disease, disorder or syndrome; ameliorating or improving a clinical symptom or indicator associated with the disorder; or delaying, inhibiting or decreasing the likelihood of the progression of the disease, disorder or syndrome.

The precise amount of crystalline Form I or Form II administered to provide an "effective amount" to the subject will depend on the mode of administration, the type, and severity of the disease or condition, and on the characteristics of the subject, such as general health, age, sex, body weight, and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. When administered in combination with other therapeutic agents, e.g., when administered in combination with an anti-cancer agent, an "effective amount" of any additional therapeutic agent(s) will depend on the type of drug used. Suitable dosages are known for approved therapeutic agents and can be adjusted by the skilled artisan according to the condition of the subject, the type of

condition(s) being treated and the amount of a compound of the invention being used by following, for example, dosages reported in the literature and recommended in the *Physician's Desk Reference* (57th Ed., 2003).

The term "effective amount" means an amount when administered to the subject which results in beneficial or desired results, including clinical results, *e.g.*, inhibits, suppresses or reduces the symptoms of the condition being treated in the subject as compared to a control. For example, a therapeutically effective amount can be given in unit dosage form (*e.g.*, 0.1 mg to about 50 g per day).

The terms "administer", "administering", "administration", and the like, as used herein, refer to methods that may be used to enable delivery of compositions to the desired site of biological action. These methods include, but are not limited to, intraarticular (in the joints), intravenous, intramuscular, intratumoral, intradermal, intraperitoneal, subcutaneous, orally, topically, intrathecally, inhalationally, transdermally, rectally, and the like. Administration techniques that can be employed with the agents and methods described herein are found in *e.g.*, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current ed.; Pergamon; and Remington's, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa.

The particular mode of administration and the dosage regimen will be selected by the attending clinician, taking into account the particulars of the case (*e.g.* the subject, the disease, the disease state involved, the particular treatment). Treatment can involve daily or multi-daily or less than daily (such as weekly or monthly etc.) doses over a period of a few days to months, or even years. However, a person of ordinary skill in the art would immediately recognize appropriate and/or equivalent doses looking at dosages of approved compositions for treating a disease using the disclosed MEK inhibitors for guidance.

Crystalline Form I or Form II as described herein, or a pharmaceutical composition thereof, can be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the present teachings may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal and topical modes of administration. Parenteral administration can be by continuous infusion over a selected period of time.

The pharmaceutical composition described herein is formulated to be compatible with its intended route of administration. In an embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal, or topical administration to human beings. In preferred embodiments, the pharmaceutical composition is formulated for intravenous administration.

Typically, for oral therapeutic administration, a compound of the present teachings may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

Typically for parenteral administration, solutions of a compound of the present teachings can generally be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Typically, for injectable use, sterile aqueous solutions or dispersion of, and sterile powders of, a compound described herein for the extemporaneous preparation of sterile injectable solutions or dispersions are appropriate.

The following Examples are offered to illustrate exemplary embodiments of the invention and do not define or limit its scope.

EXEMPLIFICATION

General Methods

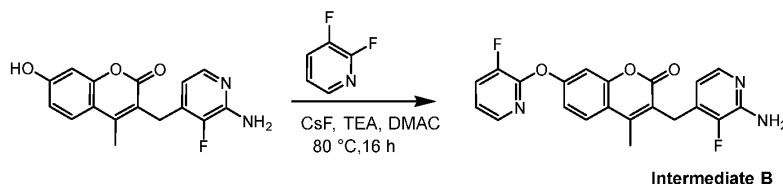
XRPD analysis was performed using Bruker D8 Advance X-ray powder diffractometer using Cu K α 1 radiation.

Differential Scanning Calorimetry (DSC) analysis was performed using TA DSC 250 Analysis System with the following instrument parameters:

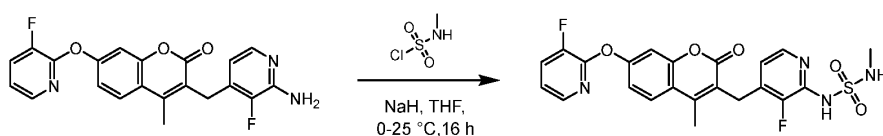
Gas (flow)	50 mL/min N2	Initial Temperature (°C)	30
Pan Type	TA Tzero Low-Mass Pan (aluminum)	Initial Temperature (°C)	300
Data Acquisition	1.00 s/pt	Ramp (heating) rate (°C/min)	10
Lid Type	Tzero Lid (aluminum)		

Preparation of 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one

The title compound can be prepared following the procedures for Example 35 in PCT/US2023/019588, reproduced below.



To a solution of 3-[(2-amino-3-fluoro-4-pyridyl)methyl]-7-hydroxy-4-methyl-chromen-2-one (synthesis described in WO 2013/035754) (3 g, 9.99 mmol) in DMAc (30 mL) were added TEA (3.03 g, 29.97 mmol), CsF (2.28 g, 14.99 mmol) and 2,3-difluoropyridine (2.30 g, 19.98 mmol). The mixture was stirred at 80 °C for 16 h. The reaction mixture was quenched with H₂O (10 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with water (30 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (MeOH in DCM = 0% - 5%) to give the 3-[(2-amino-3-fluoro-4-pyridyl)methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one (1.6 g, 4.1 mmol, 40.5% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.00-7.97 (m, 1H), 7.95-7.86 (m, 2H), 7.58 (d, J = 5.2 Hz, 1H), 7.32-7.24 (m, 2H), 7.24-7.19 (m, 1H), 6.30-6.25 (m, 1H), 6.11 (s, 2H), 3.93 (s, 2H), 2.45 (s, 3H).



To a solution of 3-[(2-amino-3-fluoro-4-pyridyl)methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one (100 mg, 252.9 μmol) in THF (2 mL) was added NaH (50.6 mg, 1.3 mmol, 60% purity in oil) at 0 °C. The mixture was stirred at 0 °C for 1 h. Then N-methylsulfamoyl chloride (36.1 mg, 278.2 μmol) was added to the above mixture. The mixture was stirred at 25 °C for 16 h. The mixture was quenched with water (20 mL). The mixture was extracted with EtOAc (20 mL x 2). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was purified by flash column chromatography on silica gel (EtOAc in Dichloromethane = 0-40%) and prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5μm; mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN]; B%: 35%-65%,

7min) to give 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one (6 mg, 12.3 μ mol, 4.9% yield) as white solid. ^1H NMR (400 MHz, CD_3CN) δ = 8.29 (br s, 1H), 7.98-7.95 (d, J = 4.8 Hz, 1H), 7.93-7.90 (m, 1H), 7.87-7.83 (m, 1H), 7.74-7.67 (m, 1H), 7.25-7.17 (m, 3H), 6.88-6.83 (m, 1H), 5.85 (br s, 1H), 4.07 (s, 2H), 2.61 (s, 3H), 2.48 (s, 3H). ^{19}F NMR (376.5 MHz, CDCl_3) δ = -136.38, -141.72 ppm. LCMS R_t = 0.865 min, in 1.5 min chromatography, 5-95AB, ESI calcd. for $\text{C}_{22}\text{H}_{19}\text{N}_4\text{F}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$ 489.1, found 489.1.

Preparation of Crystalline Form I

N-methylsulfamoyl chloride (about 2.8 eq.) was added dropwise to a solution of dimethylformamide (about 10 vol.), acetonitrile (about 10 vol.), and pyridine (about 3 eq.) at a temperature of about 0°C to about 10°C. About 1 eq. of 3-[(2-amino-3-fluoro-4-pyridyl)methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one, prepared according to the procedures described in PCT/US2023/019588 reproduced above, was added and the reaction was aged for about 2 hours. The reaction was then warmed to about 20 °C to about 30 °C and about 20 vol. of water was added, and the mixture was aged for about 0.5 hours. The solid was filtered and dried at about 40 °C to about 50°C to afford the crude product. The product was stirred in a mixture of dimethyl sulfoxide/acetonitrile (about 1 vol. / about 10 vol.) at about 20 °C to about 30 °C for about 2 hours. The mixture was filtered and the cake was dried for about 2 hours at about 40 °C to about 50 °C to afford crystalline Form I of 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one.

Alternatively, Form I of 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one can also be obtained following the procedures described above and utilizing seeding to facilitate Form I isolation.

An XRPD of Form I is shown in FIG. 1 and a DSC is shown in FIG. 2. A listing of XRPD is provided below in Table 1.

Table 1

Position 2 Θ	Rel. Intensity (%)	Position 2 Θ	Rel. Intensity (%)
7.13	0.5	25.90	6.2
8.71	11.5	26.32	40.8
13.15	14.9	26.83	32.0

13.45	3.4
14.22	2.7
14.54	2.6
15.23	2.9
15.8	11.9
16.99	1.9
17.26	4.2
17.52	11.5
17.76	100
18.42	1.7
19.39	4.0
19.57	16.6
20.27	7.4
20.90	8.1
21.16	17.5
21.43	8.3
22.67	1.9
22.83	1.0
23.43	4.7
24.36	10.0
25.00	13.8

27.77	5.6
28.38	4.4
28.59	4.5
28.85	5.9
29.32	3.3
29.49	1.6
30.00	35.8
30.68	3.9
32.28	2.2
32.66	2.2
33.03	4.8
33.78	1.3
34.77	3.1
35.39	1.6
35.91	1.7
36.02	3.2
36.65	1.4
36.95	0.7
38.17	1.7
38.36	2.0
38.97	0.7

Preparation of Crystalline Form II

N-methylsulfamoyl chloride (about 1.8 eq.) was added dropwise to a solution of dimethylformamide (about 10 vol.), acetonitrile (about 10 vol.), and pyridine (about 2.2 eq.), with molecular sieve (about 1 eq.). About 1 eq. of 3-[(2-amino-3-fluoro-4-pyridyl)methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one, prepared according to the procedures described in PCT/US2023/019588, was added and the reaction was aged for about 1 hour. The reaction was filtered and the filtrate was warmed to about 20 °C to about 30 °C. About 25 vol. of water was added, and the mixture was aged for about 0.5 hours. The solid was filtered and slurried in acetonitrile (about 6 vol.) at about 20 °C to about 30 °C for about 35 hours.

The mixture was filtered and the cake was dried for about 15 hours at about 40 °C to about 50 °C to afford crystalline Form II of 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one. An XRPD is shown in **FIG. 3** and a DSC is shown in **FIG. 4**. A listing of XRPD is provided below in **Table 2**.

Table 2

Position 2 θ	Rel. Intensity (%)	Position 2 θ	Rel. Intensity (%)
4.49	1.8	25.24	27.8
7.69	7.0	25.62	4.0
8.85	22.4	26.00	9.3
12.57	2.7	26.77	18.9
13.33	21.3	27.24	11.7
14.67	29.3	28.64	1.2
15.38	1.7	29.64	3.8
15.77	1.0	29.94	3.9
17.28	26.3	31.20	5.9
17.70	54.0	31.86	7.1
18.25	24.7	32.25	3.6
19.40	2.5	32.89	1.8
20.18	4.3	34.17	1.5
20.88	6.0	35.10	1.4
21.16	1.1	35.78	6.4
22.17	100	36.26	3.9
23.33	5.5	37.47	4.4
23.83	6.0	38.63	3.0
24.68	3.7	39.20	1.3

Equilibration with solvents at 25 °C

Based on approximate solubility results, about 50 mg of crystalline Form I as prepared above was equilibrated in 0.4 mL of solvents at 25 °C for 2 weeks with a stirring bar on a magnetic stirring plate at a rate of 400 rpm. About 400 mg of crystalline Form I as prepared above, was ground with a pestle and a motor to obtain a low crystalline form for equilibration. About 50 mg of crystalline Form I post grinding was equilibrated in 0.4 mL of

solvents at 25 °C for 1 week with a stirring bar on a magnetic stirring plate at a rate of 400 rpm. Obtained suspensions were filtered through a 0.45 µm nylon membrane filter by centrifugation at 14,000 rpm. Solid parts (wet cakes) were investigated by XRPD. For samples with different XRPD patterns, additional analysis including HPLC was performed. The results are shown in **Table 3**.

Table 3

Solvents	XRPD
Water	Form I
Methanol	Form I
Acetone	Form I
Ethyl acetate	Form I
Acetonitrile	Form I
Dichloromethane	Form I
Tetrahydrofuran	Form I
1,4-Dioxane	Form I
Ethanol/water (1:1, v:v)	Form I + one peak at 2 θ : 11.6°
Isopropanol/water (1:1, v:v)	Form I
Acetone/water (1:1, v:v)	Form I + peaks at 2 θ : 11.6° and 12.4°
Methyl ethyl ketone/water (1:1, v:v)	Form I + one peak at 2 θ : 11.6°
Acetonitrile/water (1:1, v:v)	Form I + one peak at 2 θ : 11.6°
Tetrahydrofuran/water (1:1, v:v)	Form I + one peak at 2 θ : 11.6°
Ethanol/water (1:1, v:v)	Form I
Acetone/water (1:1, v:v)	Form I
Acetonitrile/water (1:1, v:v)	Form I
Tetrahydrofuran/water (1:1, v:v)	Form I

Equilibration with solvents at 50 °C

Based on approximate solubility results, about 50 mg of crystalline Form I as prepared above was equilibrated in 0.4 mL of solvents at 50 °C for 1 week with a stirring bar on a magnetic stirring plate at a rate of 400 rpm. About 400 mg of crystalline Form I was ground with a pestle and a mortar to obtain a low crystalline form for equilibration. About 50 mg of crystalline Form I post grinding was equilibrated in 0.4 mL of solvents at 50 °C for 1 week with a stirring bar on a magnetic stirring plate at a rate of 400 rpm. Obtained suspensions were filtered through a 0.45 µm nylon membrane filter by centrifugation at 14,000 rpm. Solid parts (wet cakes) were investigated by XRPD. For samples with different

XRPD patterns, additional analysis including DSC, ¹H-NMR, HPLC and LC-MS were performed. Results are shown in **Table 4**.

Table 4

Solvents	XRPD
Water	Form I
Methanol	Form I
Acetone	Form I
Ethyl acetate	Form I
Acetonitrile	Form I
Tetrahydrofuran	Form I
1,4-Dioxane	Form I
Ethanol/water (1:1, v:v)	Form I + one peak at 2 θ : 11.6°
Isopropanol/water (1:1, v:v)	Form I + one peak at 2 θ : 22.3°
Acetone/water (1:1, v:v)	Form I + peaks at 2 θ : 5.2°, 11.6°, 12.4°, 22.2° and 29.1°
Methyl ethyl ketone/water (1:1, v:v)	Form I + one peak at 2 θ : 11.6°
Acetonitrile/water (1:1, v:v)	Form I + peaks at 2 θ : 5.2° and 22.3°
Tetrahydrofuran/water (1:1, v:v)	Type 1
Ethanol/water (1:1, v:v)	Form I + one peak at 2 θ : 12.4°
Acetone/water (1:1, v:v)	Form I
Acetonitrile/water (1:1, v:v)	Form I + peaks at 2 θ : 5.2° and 12.4°
Tetrahydrofuran/water (1:1, v:v)	Form I + peaks at 2 θ : 4.2°, 5.2°, 16.9° and 25.4°

Equilibration under a temperature cycle

Based on approximate solubility results, about 50 mg of crystalline Form I as prepared above was equilibrated in 0.4 mL of solvents under a temperature cycle between 5 °C to 50 °C at a heating/cooling rate of 0.1 °C/min for 10 cycles. The equilibration was executed with a stirring bar on a magnetic stirring plate at a rate of 400 rpm. Obtained suspensions were filtered through a 0.45 μ m nylon membrane filter by centrifugation at 14,000 rpm. Solid parts (wet cakes) were investigated by XRPD. Results are shown in **Table 5**.

Table 5

Solvents	XRPD
Water	Form I
Methanol	Form I
Acetone	Form I
Ethyl acetate	Form I
Acetonitrile	Form I
Tetrahydrofuran	Form I
1,4-Dioxane	Form I
Ethanol/water (1:1, v:v)	Form I
Isopropanol/water (1:1, v:v)	Form I
Acetone/water (1:1, v:v)	Form I
Methyl ethyl ketone/water (1:1, v:v)	Form I
Acetonitrile/water (1:1, v:v)	Form I
Tetrahydrofuran/water (1:1, v:v)	Form I

Crystallization at room temperature by slow evaporation

Based on approximate solubility results, about 30 mg of crystalline Form I as prepared above was dissolved in 0.4 mL of solvents. Obtained solutions were filtered through a 0.45 µm syringe nylon membrane filter. The clear solutions were slowly evaporated in ambient condition (about 24-26 °C, 60-80% RH). Solid residues were investigated by XRPD. Results are shown in **Table 6**.

Table 6

Solvents	XRPD
Acetone	Form I
Dichloromethane	Form I
Tetrahydrofuran	Form I
1,4-Dioxane	Form I

Crystallization by addition of anti-solvent

Based on approximate solubility results, about 50 mg of crystalline Form I as prepared above was dissolved in the minimal amount of selected good solvents at ambient temperature (about 24-26 °C). Obtained solutions were filtered through a 0.45 µm syringe membrane filter. 1 fold of anti-solvent was added into the clear solutions slowly until a large amount of solids precipitated out. Precipitates were collected by centrifugation filtration

through a 0.45 μm nylon membrane filter at 14,000 rpm. Solid parts (wet cakes) were investigated by XRPD. Results are shown in **Table 7**.

Table 7

Solvents (mL)	Anti-solvent (mL)	XRPD
Tetrahydrofuran (3.5)	Water (3.5)	Form I
1,4-Dioxane (3.5)	Water (3.5)	Form I

While a number of embodiments have been described, the scope of this disclosure is to be defined by the appended claims, and not by the specific embodiments that have been represented by way of example. The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

What is claimed is:

1. Crystalline Form I or II of the compound 3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-7-[(3-fluoro-2-pyridyl)oxy]-4-methyl-chromen-2-one.
2. The crystalline form of Claim 1, wherein the crystalline form is crystalline Form I.
3. The crystalline Form I of Claim 1 or 2, wherein the crystalline form is characterized by at least three, at least four, at least five, at least six, or at least seven x-ray powder diffraction peaks at 2Θ angles selected from 13.15° , 17.76° , 19.57° , 21.16° , 25.00° , 26.32° , 26.83° , and 29.99° .
4. The crystalline Form I of any one of Claims 1 to 3, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 17.76° , 26.32° , and 29.99° .
5. The crystalline Form I of any one of Claims 1 to 4, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 17.76° , 26.32° , and 29.99° , and at least one additional peak selected from 13.15° , 21.16° , 26.32° , and 26.83° .
6. The crystalline Form I of any one of Claims 1 to 5, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 17.76° , 26.32° , 26.83° , and 29.99° .
7. The crystalline Form I of any one of Claims 1 to 6, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 17.76° , 26.32° , 26.83° , and 29.99° , and at least one additional peak selected from 13.15° , 17.76° , and 21.16° .
8. The crystalline Form I of any one of Claims 1 to 7, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 17.76° , 19.57° , 26.32° , 26.83° , and 29.99° .
9. The crystalline Form I of any one of Claims 1 to 8, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 17.76° , 19.57° , 21.16° , 26.32° , 26.83° , and 29.99° .

10. The crystalline Form I of any one of Claims 1 to 9, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 13.15° , 17.76° , 19.57° , 21.16° , 26.32° , 26.83° , and 29.99° .
11. The crystalline Form I of any one of Claims 1 to 9, wherein the crystalline form is characterized by an x-ray powder diffraction substantially similar to **FIG. 1**.
12. The crystalline form of Claim 1, wherein the crystalline form is crystalline Form II.
13. The crystalline Form II of Claim 1 or 12, wherein the crystalline form is characterized by at least three, at least four, at least five, at least six, at least seven, or at least eight x-ray powder diffraction peaks at 2Θ angles selected from 8.85° , 13.33° , 14.69° , 17.28° , 17.70° , 18.25° , 22.17° , 25.24° , and 26.77° .
14. The crystalline Form II of any one of Claims 1, 12, and 13, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 14.69° , 17.70° , and 22.17° .
15. The crystalline Form II of any one of Claims 1 and 12 to 14, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 14.69° , 17.70° , and 22.17° , and at least one, at least two, at least three, or at least four additional peaks selected from 8.85° , 13.33° , 17.28° , 18.25° , and 25.24° .
16. The crystalline Form II of any one of Claims 1 and 12 to 15, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 8.85° , 13.33° , 14.69° , 17.28° , 17.70° , 18.25° , 22.17° , and 25.24° .
17. The crystalline Form II of any one of Claims 1 and 12 to 16, wherein the crystalline form is characterized by an x-ray powder diffraction substantially similar to **FIG. 3**.
18. The crystalline Form I or Form II of any one of Claims 1 to 17, wherein the crystalline form is anhydrous.
19. The crystalline Form I or Form II of any one of Claims 1 to 17, wherein the crystalline form is at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% a single crystalline form.

20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the crystalline Form I or II of any one of claims 1 to 19.
21. A pharmaceutical composition comprising at least one solid pharmaceutically acceptable carrier and the crystalline Form I or II of any one of claims 1 to 19.
22. The pharmaceutical composition of Claim 20 or 21, wherein the pharmaceutical composition is in solid form.
23. The pharmaceutical composition of any one of Claims 20 to 22, wherein the pharmaceutical composition is a tablet or capsule.
24. A method of inhibiting mitogen-activated protein kinase (MEK) in a subject in need thereof, comprising administering an effective amount of: i) the crystalline Form I or II of any one of Claims 1 to 19; or ii) the pharmaceutical composition of any one of Claims 20 to 23.
25. A method of treating a subject with cancer, comprising administering an effective amount of: i) the crystalline Form I or II of any one of Claims 1 to 19; or ii) the pharmaceutical composition of any one of Claims 20 to 23.