

THERAPEUTICALLY ACTIVE COMPOUNDS AND THEIR METHODS OF USE

This application claims priority from U.S. Application Serial No. 61/861,884 filed August 2, 2013, International Application Serial No. PCT/CN2013/081170 filed August 9, 2013, U.S. Application Serial No. 61/939,098 filed February 12, 2014, U.S. Application Serial No. 61/975,448 filed April 4, 2014, and U.S. Application Serial No. 62/011,948 filed June 13, 2014, each of which is incorporated herein by reference in its entirety.

Isocitrate dehydrogenases (IDHs) catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate (*i.e.*, α -ketoglutarate). These enzymes belong to two distinct subclasses, one of which utilizes NAD(+) as the electron acceptor and the other NADP(+). Five isocitrate dehydrogenases have been reported: three NAD(+)-dependent isocitrate dehydrogenases, which localize to the mitochondrial matrix, and two NADP(+)-dependent isocitrate dehydrogenases, one of which is mitochondrial and the other predominantly cytosolic. Each NADP(+)-dependent isozyme is a homodimer.

IDH2 (isocitrate dehydrogenase 2 (NADP+), mitochondrial) is also known as IDH; IDP; IDHM; IDPM; ICD-M; or mNADP-IDH. The protein encoded by this gene is the NADP(+)-dependent isocitrate dehydrogenase found in the mitochondria. It plays a role in intermediary metabolism and energy production. This protein may tightly associate or interact with the pyruvate dehydrogenase complex. Human IDH2 gene encodes a protein of 452 amino acids. The nucleotide and amino acid sequences for IDH2 can be found as GenBank entries NM_002168.2 and NP_002159.2 respectively. The nucleotide and amino acid sequence for human IDH2 are also described in, *e.g.*, Huh *et al.*, Submitted (NOV-1992) to the EMBL/GenBank/DDBJ databases; and The MGC Project Team, Genome Res. 14:2121-2127(2004).

Non-mutant, *e.g.*, wild type, IDH2 catalyzes the oxidative decarboxylation of isocitrate to α -ketoglutarate (α -KG) thereby reducing NAD⁺ (NADP⁺) to NADH (NADPH), *e.g.*, in the forward reaction:



It has been discovered that mutations of IDH2 present in certain cancer cells result in a new ability of the enzyme to catalyze the NADPH-dependent reduction of α -ketoglutarate to R(-)-2-hydroxyglutarate (2-HG). 2-HG is not formed by wild-type IDH2. The production of 2-

Some embodiments of the invention are directed toward a tablet comprising at least one pharmaceutically acceptable carrier; and a mutant IDH2 inhibitor.

Some embodiments of the invention are directed toward a tablet comprising at least one pharmaceutically acceptable carrier; and compound 1. Some embodiments of the invention are directed toward a tablet comprising at least one pharmaceutically acceptable carrier; and compound 1, or a crystalline form thereof; or compound 3, or a crystalline form thereof.

Some embodiments of the invention are directed toward a tablet comprising at least one pharmaceutically acceptable carrier or diluent; and compound 1, or a crystalline form thereof; or compound 3, or a crystalline form thereof. In other embodiments, the crystalline form of compound 1 or compound 3 is at least 90% by weight of a particular crystalline form; the particular crystalline form being a form described herein. In other embodiments, the crystalline form of compound 1 or compound 3 is at least 95% by weight of a particular crystalline form; the particular crystalline form being a form described herein.

Methods of Use

The inhibitory activities of compound 1 or a crystalline form thereof; or compound 3, or a crystalline form thereof, against IDH2 mutants (e.g., IDH2R140Q and IDH2R172K) can be tested by methods described in Example 12 of PCT Publication No. WO 2013/102431 and US Publication No. US 2013/0190287 hereby incorporated by reference in their entirety, or analogous methods.

Provided is a method for inhibiting a mutant IDH2 activity, comprising contacting a subject in need thereof with a mutant IDH2 inhibitor. In one embodiment, the method for inhibiting a mutant IDH2 activity comprises contacting a subject in need thereof with compound 1. In one embodiment, the advanced hematologic malignancy described herein, such as acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, or lymphoma (e.g., T-cell lymphoma) to be treated is characterized by a mutant allele of IDH2 wherein the IDH2 mutation results in a new ability of the enzyme to catalyze the NADPH-dependent reduction of α -ketoglutarate to R(-)-2-hydroxyglutarate in a patient. In one aspect of this embodiment, the mutant IDH2 has an R140X mutation. In another aspect of this embodiment, the R140X mutation is a R140Q mutation. In another aspect of this embodiment, the R140X mutation is a R140W mutation. In

another aspect of this embodiment, the R140X mutation is a R140L mutation. In another aspect of this embodiment, the mutant IDH2 has an R172X mutation. In another aspect of this embodiment, the R172X mutation is a R172K mutation. In another aspect of this embodiment, the R172X mutation is a R172G mutation.

In another embodiment, the method for inhibiting a mutant IDH2 activity comprises contacting a subject in need thereof with compound 1, or a crystalline form thereof; or compound 3, or a crystalline form thereof. In one embodiment, the advanced hematologic malignancy described herein, such as acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, or lymphoma (e.g., T-cell lymphoma) to be treated is characterized by a mutant allele of IDH2 wherein the IDH2 mutation results in a new ability of the enzyme to catalyze the NADPH-dependent reduction of α -ketoglutarate to R(-)-2-hydroxyglutarate in a patient. In one aspect of this embodiment, the mutant IDH2 has an R140X mutation. In another aspect of this embodiment, the R140X mutation is a R140Q mutation. In another aspect of this embodiment, the R140X mutation is a R140W mutation. In another aspect of this embodiment, the R140X mutation is a R140L mutation. In another aspect of this embodiment, the mutant IDH2 has an R172X mutation. In another aspect of this embodiment, the R172X mutation is a R172K mutation. In another aspect of this embodiment, the R172X mutation is a R172G mutation. Advanced hematologic malignancies, such as acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, or lymphoma (e.g., T-cell lymphoma or B-cell lymphoma), each characterized by the presence of a mutant allele of IDH2, can be analyzed by sequencing cell samples to determine the presence and specific nature of (e.g., the changed amino acid present at) a mutation at amino acid 140 and/or 172 of IDH2.

In one embodiment, the efficacy of treatment of advanced hematologic malignancies, such as acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, or lymphoma (e.g., T-cell lymphoma), each characterized by the presence of a mutant allele of IDH2, is monitored by measuring the levels of 2HG in the subject. Typically levels of 2HG are measured prior to treatment, wherein an elevated level is indicated for the use of compound 1 to treat advanced hematologic malignancy, such as acute myelogenous leukemia (AML), myelodysplastic

CLAIMS

1. An isolated crystalline form 16 of 2-methyl-1-[(4-[6- trifluoromethyl)pyridin-2-yl]-6- {[2-(trifluoromethyl)pyridin-4-yl] amino}-1,3,5-triazin-2- yl)amino]propan-2-ol, characterized by an X-ray powder diffraction pattern having peaks at 2θ angles of 6.8, 10.6, 13.6, 14.2, and $19.2^\circ \pm 0.2^\circ$.
2. The isolated crystalline form of claim 1, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 34.
3. Use of the crystalline form of claims 1-or 2 for manufacture of a medicament for treating an advanced hematologic malignancy selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, and lymphoma, each characterized by the presence of a mutant allele of IDH2.
4. The use of claim 3, wherein the advanced hematologic malignancy is acute myelogenous leukemia (AML).
5. The use of any one of claims 3-4, wherein the advanced hematologic malignancy is relapsed or primary refractory acute myelogenous leukemia.
6. The use of any one of claims 3-5, wherein the medicament is administered as a first line, second line, third line, or fourth line treatment for acute myelogenous leukemia.
7. A pharmaceutical composition comprising the isolated crystalline form of claim 1- or 2 and a pharmaceutically acceptable carrier.