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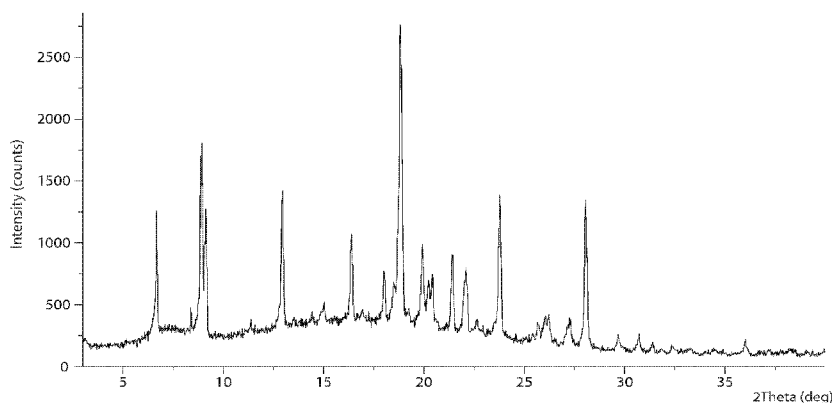
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- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI,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

(54) **Title:** THERAPEUTICALLY ACTIVE COMPOUNDS AND THEIR METHODS OF USE



XRPD pattern of Form 1

Fig. 1

(57) **Abstract:** Provided are isocitrate dehydrogenase 2 (IDH2) inhibitor compounds useful for treating cancer and methods of treating cancer, comprising administering to a subject in need thereof a compound described herein. Also provided are polymorphic forms of the IDH2 inhibitor compounds characterized by X Ray powder diffraction patterns, having improved physicochemical properties that influence in vivo dissolution rate for formulation purposes.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/49469

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/5377, A61K 31/53, C07D 401/12 (2014.01)

CPC - C07D251/18, C07D413/14, A61K31/53, C07D401/12, A61K31/5377, C07D251/26

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC - A61K 31/5377, A61K 31/53, C07D 401/12 (2014.01)

CPC - C07D251/18, C07D413/14, A61K31/53, C07D401/12, A61K31/5377, C07D251/26

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

USPC: 514/210.2, 544/209, 514/236.2, 514/245, 544/208.5

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

Minesoft Patbase, Google Scholar, PubChem: Triazin*, power diffraction, X-ray, 28 angles, 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,

C1(=NC(=NC(=N1)N(CC(C)O[H])([H])N([H])C2=CC(=NC=C2)C)C3=CC=CC(=N3)C

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/0129350 A1 (Zacharie et al.) 27 May 2010 (27.05.2010) para [0002], [0041]	1-6, 15-20
A	US 2012/0238576 A1 (Tao et al.) 20 September 2012 (20.09.2012) para [0027], [0071], [0075], [0076], [0218]	1-6, 15-20
A	US 2013/0190287 A1 (Cianchetta et al.) 25 July 2013 (25.07.2013) para [0148], [0163], Table 1, pg 36, Compound No. 409	1-6, 15-20

 Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

06 January 2015 (06.01.2015)

Date of mailing of the international search report

22 JAN 2015

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

international application no.
PCT/US 14/49469

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

- 2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- 3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
--Please see attached sheet--

- 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
- 2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
- 3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
- 4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-6 and 15-20

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - No protest accompanied the payment of additional search fees.

Attachment to Box.No.III:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-6 and 15-20 directed to isolated crystalline forms of compound 3, characterized by X-ray powder diffraction patterns.

Group II: Claims 7-14 directed to isolated crystalline forms of compound 1, characterized by X-ray powder diffraction patterns.

Group III: Claims 21-48 directed to methods of treating an advanced hematologic malignancy characterized by the presence of a mutant allele of IDH2, comprising administering to a subject in need thereof, a therapeutically effective amount of compound 3 or its salt form (compound 1).

The inventions listed as Group I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special technical features:

Group I includes the technical feature of an isolated crystalline form of compound 3, not shared by Groups II-III.

Group II includes the technical feature of an isolated crystalline form of compound 1, not shared by Groups I and III.

Group III includes the technical feature of a method of treating an advanced hematologic malignancy characterized by the presence of a mutant allele of IDH2, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound, not shared by Groups I-II.

Common technical features:

Groups I and III share the technical feature of a compound 3.

Groups II and III share the technical feature of compound 1.

Groups I and II share the technical feature of a compound having the core structure of compound 3 [compound 1 being the methanesulfonate salt form of compound 3 - see Applicant's specification - pg 11, para 3; pg 40, para 3].

These shared technical features, however, does not provide a contribution over the prior art as being anticipated by US 2013/0190287 A1 to Cianchetta et al. [published on 25 July 2013] (hereinafter 'Cianchetta'), which discloses compound 3, namely, 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 (para [0148], Table 1, pg 36, Compound No. 409).

Cianchetta further discloses compound 1, namely, 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 methanesulfonate (para [0148], Table 1, pg 36, Compound No. 409; para [0163], Mesylates of each compound of Table 1 are explicitly included herein).

As said compounds were known in the art at the time of the invention these cannot be considered special technical features that would otherwise unify Group I-III.

Groups I-III, thus lack unity under PCT Rule 13.2, because they do not share a same or corresponding special technical feature providing a contribution over the prior art.