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Published:

- with international search report (Art. 21(3))
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(88) Date of publication of the international search report:

24 December 2014

(54) Title: PYRIMIDO-DIAZEPINONE COMPOUNDS AND METHODS OF TREATING DISORDERS

(57) Abstract: The present invention relates to novel pyrimido-diazepinone compounds, methods of modulating protein kinases, including MPS1 (TTK), ERK5 (BMK1, MAPK7), LRKK2, EphA2, polo kinase 1,2,3, or 4, Ack1, Ack2, Ab1, DCAMKL1, ABL1, Ab1 mutants, DCAMKL2, ARK5, BRK, MKNK2, FGFR4, TNK1, PLK1, ULK2, PLK4, PRKD1, PRKD2, PRKD3, ROS1, RPS6KA6, TAOK1, TAOK3, TNK2, Bcr-Ab1, GAK, cSrc, TPR-Met, Tie2, MET, FGFR3, Aurora, Ax1, Bmx, BTK, c-kit, CHK2, Flt3, MST2, p70S6K, PDGFR, PKB, PKC, Raf, ROCK-H, Rsk1, SGK, TrkA, TrkB and TrkC, and the use of such compounds in the treatment of various diseases, disorders or conditions.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/030760**A. CLASSIFICATION OF SUBJECT MATTER****C07D 487/14(2006.01)i, C07D 487/12(2006.01)i, A61K 31/519(2006.01)i, A61K 31/505(2006.01)i, A61P 35/00(2006.01)i, A61P 29/00(2006.01)i**

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 487/14; C07D 487/12; C07D 487/04; C07D 471/18; A61K 31/519; A61K 31/505; A61P 35/00; A61P 29/00

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

Google, eKOMPASS(KIPO internal) & Keywords: pyrimido[4□,5□:2,3][1,4]diazepino[6,7,1-hi]indol-6(5H)-one, dihydropyrimido[4□,5□:2,3]zepino[6,7,1-hi]indol-6(5H)-one, pyrimido-diazepinone derivatives, protein kinase modulator, benzo[e]pyrimido-[5,4-b]diazepine-6(11H)-one, anticancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010-080712 A2 (DANA FARBER CANCER INSTITUTE) 15 July 2010 See Formula (A)	1-10, 44, 62-64
A	Chandrasekhar V. Miduturu et al, 'High-Throughput Kinase Profiling: A More Efficient Approach toward the Discovery of New Kinase Inhibitors', Chemistry & Biology, 2011, Vol. 18, No. 7, pp. 868-879 See Table 1	1-10, 44, 62-64
A	Nicholas Kwiatkowski et al, 'Selective Aurora Kinase Inhibitors Identified Using a Taxol-Induced Checkpoint Sensitivity Screen', Chemical Biology, 2012, Vol. 7, No. 1, pp. 185-196 See Table 1,2	1-10, 44, 62-64
A	Xianming Deng et al, 'Discovery of a benzo[e]pyrimido-[5,4-b][1,4]diazepin-6(11H)-one as a Potent and Selective Inhibitor of Big MAP Kinase 1', Medicinal Chemistry Letters, 2011, Vol. 2, No. 3, pp. 195-200 See Scheme 1,2, Table 2,3	1-10, 44, 62-64
A	WO 2008-113711 A1 (F. HOFFMANN-LA ROCHE AG) 25 September 2008 See Formula I	1-10, 44, 62-64

 Further documents are listed in the continuation of Box C. See patent family annex.

* 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

30 October 2014 (30.10.2014)

Date of mailing of the international search report

30 October 2014 (30.10.2014)

Name and mailing address of the ISA/KR


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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.: 45-61
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 45-61 pertain to methods for treatment of the human body by therapy and thus related to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. Claims Nos.: 61
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:
Claim 61 is unsearchable, because it is worded in reference to multiple dependent claims.
3. Claims Nos.: 60
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:

See extra page

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 an additional fees, this Authority did not invite payment of any 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.: 1-10, 44(partial), 62-64(partial)

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.

Group 1, claims 1-10, 44(partial), 62-64(partial) relate to a compound of formula I, a pharmaceutical composition comprising a compound of formula I, a kit comprising a compound of formula I, a method of synthesizing a compound of formula I, and a compound of Table 6.

Group 2, claims 11-20, 44(partial), 62-64(partial) relate to a compound of formula II, a pharmaceutical composition comprising a compound of formula II, a kit comprising a compound of formula II, a method of synthesizing a compound of formula II, and a compound of Table 6.

Group 3, claims 21-29, 44(partial), 62(partial), 63(partial) relate to a compound of formula III, a pharmaceutical composition comprising a compound of formula III, a kit comprising a compound of formula III, a method of synthesizing a compound of formula III, and a compound of Table 6.

Group 4, claims 30-38, 44(partial), 62-64(partial) relate to a compound of formula IV, a pharmaceutical composition comprising a compound of formula IV, a kit comprising a compound of formula IV, a method of synthesizing a compound of formula IV, and a compound of Table 6.

Group 5, claims 39-43, 44(partial), 62-64(partial) relate to a compound of formula V, a pharmaceutical composition comprising a compound of formula V, a kit comprising a compound of formula V, a method of synthesizing a compound of formula V, and a compound of Table 6.

Group 6, claim 64 relate to a compound of Table 6(compounds which are not belong to the formula I, II, IV, V, VI, VII, VIII, IX).

Group 7, claim 65 relate to a compound of formula VI.

Group 8, claim 66 relate to a compound of formula VII.

Group 9, claim 67 relate to a compound of formula VIII.

Group 10, claim 68 relate to a compound of formula IX.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2014/030760

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010-080712 A2	15/07/2010	CA 2748181 A1	15/07/2010
		EP 2379559 A2	26/10/2011
		EP 2379559 A4	16/05/2012
		JP 2012-514601A	28/06/2012
		US 2012-0040961 A1	16/02/2012
		WO 2010-080712 A3	11/11/2010
WO 2008-113711 A1	25/09/2008	AR065794A1	01/07/2009
		AT524472 T	15/09/2011
		AU 2008-228303 A1	25/09/2008
		AU 2008-228303 B2	19/04/2012
		BR PI0809088A2	09/09/2014
		CA 2680757 A1	25/09/2008
		CN101636399 A	27/01/2010
		CN101636399 B	18/04/2012
		CN102746175 A	24/10/2012
		CN102746175 B	15/01/2014
		DK2139892T3	12/12/2011
		EP 2139892 A1	06/01/2010
		EP 2139892 B1	14/09/2011
		ES2371832 T3	10/01/2012
		HK1139936 A1	03/02/2012
		HR20110807T1	31/12/2011
		IL200617A	27/02/2014
		IL200617D0	17/05/2010
		JP 05-087640B2	05/12/2012
		JP 2010-521514 T	24/06/2010
		JP 2010-521514A	24/06/2010
		KR 10-1157848 B1	11/07/2012
		KR20090119913A	20/11/2009
		MX2009010034 A	12/10/2009
		PE04952012A1	12/05/2012
		PT2139892E	21/11/2011
		SI2139892T1	30/12/2011
		TW I363629B	11/05/2012
		TW200843781 A	16/11/2008
		US 2008-234255 A1	25/09/2008
US 7517873 B2	14/04/2009		