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80335 Munich (DE).(81) Designated States (unless otherwise indicated, for every
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EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
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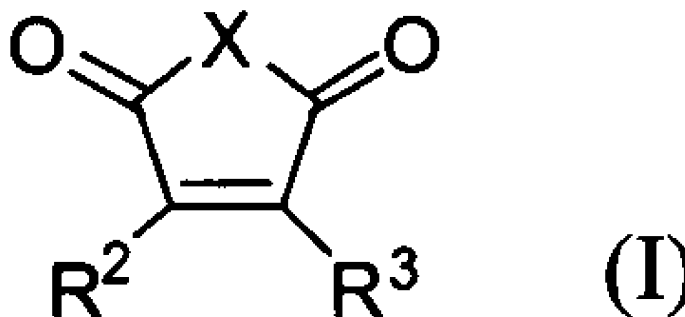
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14 August 2014

(54) Title: USE OF MALEIMIDE DERIVATIVES FOR PREVENTING AND TREATING CANCER



(57) Abstract: The present invention is related to a compound of formula (I) a pharmaceutically acceptable salt thereof, a hydrate thereof, a solvate thereof, a metabolite thereof or a prodrug thereof; for use in a method for the treatment and/or prevention of cancer, wherein X is selected from the group consisting of N-R¹, O and S; R¹ is selected from the group consisting of alkyl, cycloalkyl, aryl, arylalkyl and hydrogen; R² is selected from the group consisting of indolyl, substituted indolyl, azaindolyl and substituted azaindolyl; and R³ is selected from the group consisting of aryl, substituted aryl, unsubstituted heteroaryl, heterocyclyl and substituted heterocyclyl.



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INTERNATIONAL SEARCH REPORT

International application No

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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/404 C07D403/04 A61P35/00
ADD.

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)

A61K C07D

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

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

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>ANAHIT PEWS-DAVTYAN ET AL: "Efficient palladium-catalyzed synthesis of 3-aryl-4-indolylmaleimides", ORGANIC & BIOMOLECULAR CHEMISTRY, vol. 6, no. 6, 1 January 2008 (2008-01-01), page 992, XP055099882, ISSN: 1477-0520, DOI: 10.1039/b719160j the whole document page 992, left-hand column tables 1,2</p> <p>-----</p> <p>-/--</p>	<p>37-41, 43-56, 59-71,99</p>

☒ 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

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01/07/2014

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HEIDEL FLORIAN H ET AL: "3,4-Diarylmalesimides-a novel class of kinase inhibitors-effectively induce apoptosis in FLT3-ITD-dependent cells.", ANNALS OF HEMATOLOGY MAR 2012, vol. 91, no. 3, March 2012 (2012-03), pages 331-344, XP002720122, ISSN: 1432-0584	1-5, 7-11,15, 25-29, 37-41, 43-47, 51, 61-65, 73,95, 96, 99-102
Y	the whole document figure 1a page 337, left-hand column, paragraph 2 page 342, right-hand column, paragraph 1 -----	1-5, 7-34, 36-41, 43-102
X	GANSER CHRISTOPHER ET AL: "Novel 3-Azaindolyl-4-arylmalesimides exhibiting potent antiangiogenic efficacy, protein kinase inhibition, and antiproliferative activity.", JOURNAL OF MEDICINAL CHEMISTRY 26 NOV 2012, vol. 55, no. 22, 26 November 2012 (2012-11-26), pages 9531-9540, XP002720123, ISSN: 1520-4804	1-5, 7-11,15, 25-29, 37-41, 43-47, 51, 61-65, 73,74, 78,81, 95, 99-102
Y	the whole document Chart 1 tables 1, 4,5,6,9	1-5, 7-34, 36-41, 43-102
X	HILLIARD TYVETTE S ET AL: "Glycogen synthase kinase 3[beta] inhibitors induce apoptosis in ovarian cancer cells and inhibit in-vivo tumor growth.", ANTI-CANCER DRUGS NOV 2011, vol. 22, no. 10, November 2011 (2011-11), pages 978-985, XP002720124, ISSN: 1473-5741	1-5, 7-12, 25-30, 37-41, 43-48, 51, 61-65, 74,80, 85,99, 102
Y	the whole document table 1 ----- -/--	1-5, 7-34, 36-41, 43-102

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/003730

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PEIFER C ET AL: "Design, Synthesis, and Biological Evaluation of Novel 3-Aryl-4-(1H-indolo-3yl)-1,5-dihydro-2H-pyrrole-2-ones as Vascular Endothelial Growth Factor Receptor (VEGF-R) Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 51, 1 January 2008 (2008-01-01), pages 3814-3824, XP002501318, ISSN: 0022-2623, DOI: 10.1021/JM8001185 [retrieved on 2008-06-05]	1-5, 7-12,15, 25-29, 37-41, 43-48, 51, 61-65, 74-76, 78,81, 83,86, 89,100, 102
Y	the whole document compound 1 table 2 page 3814, left-hand column	1-5, 7-34, 36-41, 43-102
X,P	----- CHRISTIAN EISENLÖFFEL ET AL: "Interference of a novel indolylmaleimide with microtubules induces mitotic arrest and apoptosis in human progenitor and cancer cells", BIOCHEMICAL PHARMACOLOGY, vol. 85, no. 6, 1 March 2013 (2013-03-01), pages 763-771, XP055098467, ISSN: 0006-2952, DOI: 10.1016/j.bcp.2012.12.013 the whole document	7-41, 43-72, 74,76, 90,99, 100,102
X	----- WO 2006/061212 A1 (UNIV MAINZ JOHANNES GUTENBERG [DE]; DANNHARDT GERD [DE]; PEIFER CHRIST) 15 June 2006 (2006-06-15) the whole document example 5	1-5, 7-11, 15-20, 23-30, 37-41, 43-47, 52-56, 59-66, 99,100, 102
X	----- WO 2009/071620 A1 (UNIV MAINZ JOHANNES GUTENBERG [DE]; DANNHARDT GERD [DE]; FISCHER THOMA) 11 June 2009 (2009-06-11) the whole document	1-5, 7-12, 15-30, 37-41, 43-48, 51-66, 73,95, 96, 99-102

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2013/003730

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:

see additional 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 an 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.:
4, 5, 13, 14, 31-33, 35, 36, 40, 41, 49, 50, 67-69, 71, 72(completely); 1-3
7-12, 15-30, 34, 37-39, 43-48, 51-66, 70, 73-102(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 4, 5, 13, 14, 31-33, 35, 36, 40, 41, 49, 50, 67-69, 71, 72(completely); 1-3, 7-12, 15-30, 34, 37-39, 43-48, 51-66, 70, 73-102(partially)

Compounds in which X is N-R1

2. claims: 6, 42(completely); 1-3, 7-12, 15-30, 34, 37-39, 43-48, 51-66, 70, 73-102(partially)

Compounds in which X is S or O

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006061212 A1	15-06-2006	AU 2005313485 A1	15-06-2006
		CA 2589127 A1	15-06-2006
		EP 1819697 A1	22-08-2007
		JP 5289769 B2	11-09-2013
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		JP 2011506288 A	03-03-2011
		US 2011028415 A1	03-02-2011
		WO 2009071620 A1	11-06-2009
