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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

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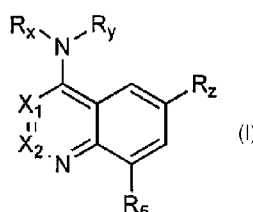
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(88) Date of publication of the international search report:

14 May 2015

(54) Title: QUINAZOLINE INHIBITORS OF PI3K



(57) Abstract: The invention is directed to compounds of formula (I): and pharmaceutically acceptable salts as well as methods of making and using the compounds to inhibit PI3K.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/025980

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D401/14 C07D413/14 C07D401/04 C07D403/04 C07D417/14 C07D471/04 C07D513/04 A61P35/00 A61K31/4709 A61K31/4725 A61K31/502											
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 A61K A61P 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, WPI Data, EMBASE, BEILSTEIN Data											
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>WO 2010/151737 A2 (AMGEN INC [US]; BROWN MATTHEW [US]; CHEN YI [US]; CUSHING TIMOTHY D [U]) 29 December 2010 (2010-12-29) claims 1, 4, 5; example 68 -----</td> <td>1-5, 10-22, 45-50</td> </tr> <tr> <td>X</td> <td>YVONNICK LOIDREAU ET AL: "Microwave-assisted thermal decomposition of formamide: a tool for coupling a pyrimidine ring with an aromatic partner", TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 67, no. 26, 3 May 2011 (2011-05-03), pages 4852-4857, XP028227650, ISSN: 0040-4020, DOI: 10.1016/J.TET.2011.05.010 [retrieved on 2011-05-17] compounds 12a, 12b ----- -/--</td> <td>1-3,18</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	WO 2010/151737 A2 (AMGEN INC [US]; BROWN MATTHEW [US]; CHEN YI [US]; CUSHING TIMOTHY D [U]) 29 December 2010 (2010-12-29) claims 1, 4, 5; example 68 -----	1-5, 10-22, 45-50	X	YVONNICK LOIDREAU ET AL: "Microwave-assisted thermal decomposition of formamide: a tool for coupling a pyrimidine ring with an aromatic partner", TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 67, no. 26, 3 May 2011 (2011-05-03), pages 4852-4857, XP028227650, ISSN: 0040-4020, DOI: 10.1016/J.TET.2011.05.010 [retrieved on 2011-05-17] compounds 12a, 12b ----- -/--	1-3,18
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X	WO 2010/151737 A2 (AMGEN INC [US]; BROWN MATTHEW [US]; CHEN YI [US]; CUSHING TIMOTHY D [U]) 29 December 2010 (2010-12-29) claims 1, 4, 5; example 68 -----	1-5, 10-22, 45-50									
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☒ 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		Date of mailing of the international search report									
23 May 2014		30/03/2015									
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Moriggi, J									

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/025980

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANDREAS SCHMIDT ET AL: "Functionalized 4-Aminoquinolines by Rearrangement of Pyrazole N-Heterocyclic Carbenes", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, vol. 49, no. 15, 12 March 2010 (2010-03-12), pages 2790-2793, XP055119383, ISSN: 1433-7851, DOI: 10.1002/anie.200905436 compounds 8f, 8g, 8k, 14 -----	1-5,18
X	GEMMA ET AL: "Microwave-assisted synthesis of 4-quinolyldiazines followed by nickel boride reduction: a convenient approach to 4-aminoquinolines and derivatives", TETRAHEDRON LETTERS, PERGAMON, GB, vol. 49, no. 13, 2 February 2008 (2008-02-02), pages 2074-2077, XP022502902, ISSN: 0040-4039, DOI: 10.1016/J.TETLET.2008.01.128 compounds 3e, 3h, 3i -----	1-3,18
X	DAVIS S E ET AL: "2,4-DIAMINO-5-BENZYLPRYIMIDINES AND ANALOGUES AS ANTIBACTERIAL AGENTS. 11. QUINOLYLMETHYL ANALOGUES WITH BASIC SUBSTITUENTS CONVEYING SPECIFICITY", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 32, 1 January 1989 (1989-01-01), pages 1936-1942, XP002273433, ISSN: 0022-2623, DOI: 10.1021/JM00128A041 compound 47 -----	1-4,18, 46,47
X	TOBE M ET AL: "A novel structural class of potent inhibitors of NF-kappaB activation: structure-activity relationship and biological effects of 6-aminoquinazoline derivatives", BIOORGANIC & MEDICINAL CHEMISTRY, PERGAMON, GB, vol. 11, no. 18, 1 January 2003 (2003-01-01), pages 3869-3878, XP003024664, ISSN: 0968-0896, DOI: 10.1016/S0968-0896(03)00438-3 compounds 4a, 10a-10e ----- -/--	1-3,46, 47

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/025980

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANDREW S ROSENTHAL ET AL: "Potent and selective small molecule inhibitors of specific isoforms of Cdc2-like kinases (Clk) and dual specificity tyrosine-phosphorylation-regulated kinases (Dyrk)", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 21, no. 10, 28 February 2011 (2011-02-28), pages 3152-3158, XP028208799, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2011.02.114 [retrieved on 2011-03-04] compounds 4, 16-29, 34, 35, 39-41, 43, 47, 48, 50-52, 54-58 -----	1-3,10, 11,13, 14,17, 46,47
X	WO 2008/009078 A2 (GILEAD SCIENCES INC [US]; GAO LING-JIE [BE]; HERDEWIJN PIET ANDRE MAUR) 24 January 2008 (2008-01-24) claims 1, 15; examples 39-47 -----	1-3,10, 11,46,47
X	SIVARAMAKRISHNAN K P ET AL: "Biquinoline Series: Part III - Synthesis of Substituted 6,6'-Biuinolines", JOURNAL OF SCIENTIFIC AND INDUSTRIAL RESEARCH. SERIE B: PHYSICALSCIENCES, COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH, NEW DEHLI, IN, vol. 20, 1 January 1961 (1961-01-01), pages 223-227, XP009178121, ISSN: 0368-4210 end product of scheme on page 224 -----	1-5
X	US 2 585 909 A (NORMAN BARTON ET AL) 19 February 1952 (1952-02-19) the last two compounds of example 4 and the last compound of example 6 -----	1-3,19
X	WO 2009/155121 A2 (AMGEN INC [US]; BO YUNXIN Y [US]; BOOKER SHON [US]; BRYAN MARIAN [US];) 23 December 2009 (2009-12-23) paragraph [0006]; claims 1, 14, 15, 18, 25, 26 -----	1-5, 10-22, 45-50
X	WO 2011/022439 A1 (INTELLIKINE INC [US]; REN PINGDA [US]; LIU YI [US]; LI LIANSHENG [US];) 24 February 2011 (2011-02-24) claims 1, 46, 52; compounds 32, 33 -----	1-5, 10-22, 45-50

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/025980

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.:

1-5, 10-22, 45-50(all 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: 1-5, 10-22, 45-50(all partially)

The compounds of formula I in which R x and Ry are not taken together with the atom to which they are attached to form a 4-6 membered ring, their compositions, uses and preparation methods

2. claims: 44(completely); 1-6, 10-22, 45-50(partially)

The compounds of formula I in which R x and Ry are taken together with the atom to which they are attached to form a 4-6 membered ring, optionally containing an additional heteroatom selected from NH and N-(C1-C6)alkyl and that is not fused, their compositions, uses and preparation methods

3. claims: 7-9, 23-43(completely); 1-6, 10-22, 45-50(partially)

The compounds of formula I in which Rx and Ry are taken together with the atom to which they are attached to form a 4-6 membered ring, optionally containing an additional heteroatom selected from NH and N-(C1-C6)alkyl and that is fused to one or more saturated, partially unsaturated or aromatic carbocyclic or heterocyclic rings, their compositions, uses and preparation methods

4. claims: 1-6, 10-22, 45-50(all partially)

The compounds of formula I in which Rx and Ry are taken together with the atom to which they are attached to form a 4-6 membered ring that contains an additional heteroatom selected from S, SO or SO₂ , their compositions, uses and preparation methods

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/025980

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010151737 A2	29-12-2010	AU 2010265971 A1 CA 2765819 A1 EP 2445902 A2 JP 2012531436 A US 2012094972 A1 WO 2010151737 A2	19-01-2012 29-12-2010 02-05-2012 10-12-2012 19-04-2012 29-12-2010
WO 2008009078 A2	24-01-2008	US 2009285782 A1 WO 2008009078 A2	19-11-2009 24-01-2008
US 2585909 A	19-02-1952	BE 492032 A DE 839641 C FR 1013708 A GB 658203 A US 2585909 A	24-03-2015 23-05-1952 04-08-1952 03-10-1951 19-02-1952
WO 2009155121 A2	23-12-2009	AU 2009260447 A1 CA 2725014 A1 EP 2307400 A2 ES 2474147 T3 JP 5599783 B2 JP 2011522806 A MX 315904 B US 2011092504 A1 WO 2009155121 A2	23-12-2009 23-12-2009 13-04-2011 08-07-2014 01-10-2014 04-08-2011 29-11-2013 21-04-2011 23-12-2009
WO 2011022439 A1	24-02-2011	AU 2010284254 A1 CA 2771532 A1 CN 102573846 A CO 6612213 A2 CR 20120110 A EA 201290103 A1 EC SP12011720 A EP 2467141 A1 JP 2013502423 A KR 20130031234 A MA 33593 B1 NZ 598220 A PE 11482012 A1 SG 178454 A1 US 2013035324 A1 WO 2011022439 A1	08-03-2012 24-02-2011 11-07-2012 01-02-2013 13-06-2012 30-09-2013 30-04-2012 27-06-2012 24-01-2013 28-03-2013 01-09-2012 28-02-2014 07-09-2012 29-03-2012 07-02-2013 24-02-2011