(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 June 2014 (19.06.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/093230 A3

(51) International Patent Classification:
C07D 403/12 (2006.01) *C07D 403/14* (2006.01)
C07D 401/14 (2006.01) *C07D 239/34* (2006.01)
C07D 413/14 (2006.01) *C07D 239/42* (2006.01)
C07D 213/73 (2006.01) *C07D 239/47* (2006.01)
C07D 213/74 (2006.01) *C07D 239/48* (2006.01)
C07D 401/04 (2006.01) *C07D 413/12* (2006.01)
C07D 401/12 (2006.01) *C07D 495/04* (2006.01)
C07D 403/04 (2006.01)

(21) International Application Number:
PCT/US2013/073895

(22) International Filing Date:
9 December 2013 (09.12.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/735,186 10 December 2012 (10.12.2012) US

(71) Applicant: **MERCK PATENT GMBH** [DE/DE]; Frankfurter Strasse 250, 64293 Darmstadt (DE).

(72) Inventors; and
(71) Applicants : **LIU-BUJALSKI, Lesley** [CA/US]; 75 Page Road, Unit 4, Bedford, Massachusetts 01730 (US). **JOHNSON, Theresa L.** [US/US]; 63 Ocean Ave., Salem, Massachusetts 01970 (US). **GOUTOPOULOS, Andreas** [GR/US]; 73 Worcester St., Apt 5, Boston, Massachusetts 02118 (US). **QIU, Hui** [CN/US]; 20 Robinwood Road, Acton, Massachusetts 01720 (US).

(74) Agent: **KIM, Dwight**; EMD Serono Research & Development Institute, One Technology Place, Rockland, Massachusetts 02370 (US).

(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.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, 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, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
28 August 2014

(54) Title: COMPOSITIONS AND METHODS FOR THE PRODUCTION OF PYRIMIDINE AND PYRIDINE COMPOUNDS WITH BTK INHIBITORY ACTIVITY

(57) Abstract: The present invention provides novel pyrimidine and pyridine compounds which are attached to a warhead, and the manufacture and use for the treatment of hyperproliferative diseases including, but not limited to, cancer, lupus, allergic disorders, Sjogren's disease and rheumatoid arthritis. The invention also describes kinase inhibitors including, but not limited to, inhibitors of Bruton's tyrosine kinase.

WO 2014/093230 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/073895

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07D401/14 C07D413/14 C07D213/73 C07D213/74
C07D401/04 C07D401/12 C07D403/04 C07D403/14 C07D239/34
C07D239/42 C07D239/47 C07D239/48 C07D413/12 C07D495/04

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

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MI YOUNG CHA ET AL: "Synthesis and Biological Evaluation of Pyrimidine-Based Dual Inhibitors of Human Epidermal Growth Factor Receptor 1 (HER-1) and HER-2 Tyrosine Kinases", JOURNAL OF MEDICINAL CHEMISTRY, vol. 55, no. 6, 22 March 2012 (2012-03-22) , pages 2846-2857, XP055104213, ISSN: 0022-2623, DOI: 10.1021/jm201758g	1,2,7, 10-17
Y	figure 1 table 3	1-5,7, 9-17

X	WO 2011/099764 A2 (HANMI HOLDINGS CO., LTD., S. KOREA) 18 August 2011 (2011-08-18)	1,2,7, 10-17
Y	the whole document	1-5,7, 9-17

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] 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
4 June 2014	25/06/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Panday, Narendra

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/073895

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.:

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/073895

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/217417 A1 (BRUNETTE STEVEN R [US] ET AL BRUNETTE STEVEN RICHARD [US] ET AL) 28 September 2006 (2006-09-28) claim 1	1-17
Y	WO 2007/084786 A1 (NOVARTIS AG [CH]; BURGER MATTHEW [US]; NI ZHI-JIE [US]; PECCHI SABINA) 26 July 2007 (2007-07-26) page 163 - page 226; table 1	1-17
Y	WO 2010/022725 A1 (LEO PHARMA AS [DK]; FELDING JAKOB [DK]; LIANG XIFU [DK]; HORNEMAN ANNE) 4 March 2010 (2010-03-04) page 45; table 2 claims 8,9	1-17
Y	WO 2005/070934 A1 (AMGEN INC [US]; CAO GUO-QIANG [US]; CHEN JIAN J [US]; DOMINGUEZ CELIA) 4 August 2005 (2005-08-04) claim 1	1-17
Y	US 2012/208815 A1 (BURGER MATTHEW [US] ET AL) 16 August 2012 (2012-08-16) claim 27	1-17
X,P	WO 2012/170976 A2 (MERCK PATENT GMBH [DE]; HODOUS BRIAN L [US]; LIU-BUJALSKI LESLEY [US];) 13 December 2012 (2012-12-13) the whole document	1-17
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SHULTZ, MICHAEL D. ET AL: "Optimization of the in vitro cardiac safety of hydroxamate-based Histone deacetylase inhibitors", XP002720930, retrieved from STN Database accession no. 2011:776102 abstract & SHULTZ, MICHAEL D. ET AL: "Optimization of the in vitro cardiac safety of hydroxamate-based Histone deacetylase inhibitors", JOURNAL OF MEDICINAL CHEMISTRY , 54(13), 4752-4772 CODEN: JMCMAR; ISSN: 0022-2623, 2011, DOI: 10.1021/JM200388E	1,2,7

-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; NISHIKUBO, YUICHI: "Organic piezoelectric materials, ultrasonic vibrators therewith, and ultrasound probes therewith", XP002720931, retrieved from STN Database accession no. 2010:1193753 abstract & JP 2010 209277 A (KONICA MINOLTA MEDICAL & GRAPHIC, INC., JAPAN) 24 September 2010 (2010-09-24) -----	1,2,7
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PEGIADOU, S. ET AL: "The synthesis and characterization of new polymerizable pyrimidines: immobilization of the monomers onto hydrophilic graft copolymeric supports through radiation-induced copolymerization-grafting", XP002725282, retrieved from STN Database accession no. 1998:592481 abstract & PEGIADOU, S. ET AL: "The synthesis and characterization of new polymerizable pyrimidines: immobilization of the monomers onto hydrophilic graft copolymeric supports through radiation-induced copolymerization-grafting", JOURNAL OF APPLIED POLYMER SCIENCE , 70(2), 211-218 CODEN: JAPNAB; ISSN: 0021-8995, 1998, DOI: 10.1002/(SICI)1097-4628(19981010)70:2<211::AID-APP1>3.0.CO;2-X -----	1,2
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; RACK, MICHAEL ET AL: "Preparation of .alpha.-[2-(pyrimidinyloxymethyl)phenyl]acrylates as agrochemical fungicides and pesticides", XP002725285, retrieved from STN Database accession no. 1997:776155 abstract -/--	1,2

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& WO 97/44325 A1 (BASF AKTIENGESELLSCHAFT, GERMANY; RACK, MICHAEL; ROHL, FRANZ; AMMERMAN) 27 November 1997 (1997-11-27) -----	
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YAMADA, KOICHIRO ET AL: "Preparation of pyrimidine derivatives as endothelin antagonists", XP002725286, retrieved from STN Database accession no. 1997:257401 abstract & JP 9 059160 A (TANABE SEIYAKU CO, JAPAN) 4 March 1997 (1997-03-04) -----	1,2
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YAMADA, KOICHIRO ET AL: "Preparation of (N-pyrimidinyl)benzenesulfonamide endothelin antagonists", XP002725288, retrieved from STN Database accession no. 1995:890091 abstract & EP 0 658 548 A1 (TANABE SEIYAKU CO., LTD., JAPAN) 21 June 1995 (1995-06-21) -----	1,2
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CORNELL, CLIVE LEONARD ET AL: "Preparation of 2-naphthyl-3-methoxyacrylates as agrochemical fungicides and pesticides", XP002725287, retrieved from STN Database accession no. 1996:716436 abstract & WO 96/29301 A1 (AGREVO UK LIMITED, UK) 26 September 1996 (1996-09-26) -----	1,2
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DENNY, WILLIAM A. ET AL: "Potential antitumor agents. 29. Quantitative structure-activity relationships for the antileukemic bisquaternary ammonium heterocycles", XP002725283, retrieved from STN Database accession no. 1979:66509 abstract -/--	1,2

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/073895

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& DENNY, WILLIAM A. ET AL: "Potential antitumor agents. 29. Quantitative structure-activity relationships for the antileukemic bisquaternary ammonium heterocycles", JOURNAL OF MEDICINAL CHEMISTRY , 22(2), 134-50 CODEN: JMCMAR; ISSN: 0022-2623, 1979, DOI: 10.1021/JM00188A005	
Y	WO 2012/158843 A2 (UNIV CALIFORNIA [US]; PRINCIPIA BIOPHARMA INC [US]; TAUNTON JOHN WILLI) 22 November 2012 (2012-11-22) claim 1 examples	1-17
Y	WO 2011/060440 A2 (UNIV CALIFORNIA [US]; TAUNTON JACK [US]; MAGLATHLIN REBECCA [US]; SERA) 19 May 2011 (2011-05-19) claim 1 examples	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/073895

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011099764 A2	18-08-2011	KR 20110092517 A	18-08-2011
		WO 2011099764 A2	18-08-2011
US 2006217417 A1	28-09-2006	AT 432260 T	15-06-2009
		CA 2602250 A1	05-10-2006
		EP 1866286 A1	19-12-2007
		ES 2324837 T3	17-08-2009
		JP 2008534597 A	28-08-2008
		US 2006217417 A1	28-09-2006
		WO 2006105023 A1	05-10-2006
WO 2007084786 A1	26-07-2007	AR 059087 A1	12-03-2008
		AT 478064 T	15-09-2010
		AU 2007206048 A1	26-07-2007
		BR PI0707189 A2	26-04-2011
		CA 2636993 A1	26-07-2007
		CN 101389622 A	18-03-2009
		DK 1984350 T3	15-11-2010
		DK 2261223 T3	23-09-2013
		EA 200801680 A1	30-12-2008
		EC SP088630 A	29-08-2008
		EP 1984350 A1	29-10-2008
		EP 2261223 A1	15-12-2010
		ES 2351172 T3	01-02-2011
		ES 2427624 T3	31-10-2013
		GE P20115147 B	25-01-2011
		GT 200800143 A	11-06-2009
		HK 1122031 A1	31-12-2010
		HN 2008001144 A	08-04-2011
		HR P20100603 T1	31-12-2010
		HR P20130796 T1	30-09-2013
		IL 192763 A	30-04-2013
		JO 2660 B	17-06-2012
		JP 5161110 B2	13-03-2013
		JP 2009527464 A	30-07-2009
		KR 20080096776 A	03-11-2008
		MA 30208 B1	02-02-2009
		ME P3908 A	10-02-2010
		MY 144233 A	15-08-2011
		NZ 569771 A	29-07-2011
		PE 13222007 A1	27-01-2008
		PT 1984350 E	11-11-2010
		PT 2261223 E	16-09-2013
		RS 51548 B	30-06-2011
		RS 52928 B	28-02-2014
		SI 1984350 T1	31-12-2010
		SI 2261223 T1	30-10-2013
		SM AP200800048 A	13-08-2008
		SV 2008002984 A	17-08-2010
		TW 200808786 A	16-02-2008
		TW 201315723 A	16-04-2013
		US 2010249126 A1	30-09-2010
		US 2012225859 A1	06-09-2012
		WO 2007084786 A1	26-07-2007
		ZA 200806017 A	27-01-2010
WO 2010022725 A1	04-03-2010	AR 073216 A1	20-10-2010
		AU 2009287152 A1	04-03-2010

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/073895

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		CA 2734551 A1	04-03-2010
		CN 102131782 A	20-07-2011
		DK 2346827 T3	03-02-2014
		EP 2346827 A1	27-07-2011
		ES 2445517 T3	03-03-2014
		IL 211417 A	31-10-2013
		JP 2012500812 A	12-01-2012
		KR 20110045095 A	03-05-2011
		NZ 591820 A	21-12-2012
		PA 8840701 A1	21-04-2010
		PT 2346827 E	17-02-2014
		RU 2011108968 A	10-10-2012
		TW 201010702 A	16-03-2010
		US 2011190282 A1	04-08-2011
		WO 2010022725 A1	04-03-2010
WO 2005070934 A1	04-08-2005	AU 2005206524 A1	04-08-2005
		CA 2553232 A1	04-08-2005
		EP 1727821 A1	06-12-2006
		JP 2007517904 A	05-07-2007
		US 2005182072 A1	18-08-2005
		US 2009149468 A1	11-06-2009
		WO 2005070934 A1	04-08-2005
US 2012208815 A1	16-08-2012	AU 2008221263 A1	04-09-2008
		CA 2679659 A1	04-09-2008
		CN 101679266 A	24-03-2010
		EA 200901144 A1	30-04-2010
		EP 2132177 A1	16-12-2009
		ES 2431163 T3	25-11-2013
		JP 5330274 B2	30-10-2013
		JP 2010520228 A	10-06-2010
		KR 20100015331 A	12-02-2010
		US 2012208815 A1	16-08-2012
		WO 2008106692 A1	04-09-2008
WO 2012170976 A2	13-12-2012	AU 2012267491 A1	31-10-2013
		CA 2833771 A1	13-12-2012
		CN 103814016 A	21-05-2014
		EA 201301353 A1	30-05-2014
		EP 2718270 A2	16-04-2014
		KR 20140007954 A	20-01-2014
		SG 194219 A1	29-11-2013
		WO 2012170976 A2	13-12-2012
WO 2012158843 A2	22-11-2012	AU 2012255759 A1	16-01-2014
		CA 2836449 A1	22-11-2012
		CN 103717602 A	09-04-2014
		EP 2710007 A2	26-03-2014
		WO 2012158843 A2	22-11-2012
WO 2011060440 A2	19-05-2011	AU 2010319964 A1	07-06-2012
		CA 2781056 A1	19-05-2011
		CN 102711765 A	03-10-2012
		EP 2558099 A2	20-02-2013
		JP 2013510886 A	28-03-2013
		US 2013035325 A1	07-02-2013
		WO 2011060440 A2	19-05-2011

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/073895

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
----------			

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, 7, 9-17(all partially)

   A kinase inhibtor comprising a moiety of formula (I) and an electrophilic michael acceptor moiety, in which X is CH

   ---

2. claims: 6, 8(completely); 1-5, 7, 9-17(partially)

   A kinase inhibtor comprising a moiety of formula (I) and an electrophilic michael acceptor moiety, in which X is N
