



(51) International Patent Classification:

C07D 471/04 (2006.01) **C07D 487/04** (2006.01)
C07D 213/40 (2006.01) **A61K 31/437** (2006.01)
C07D 213/73 (2006.01) **A61K 31/44** (2006.01)
C07D 213/74 (2006.01) **A61K 31/496** (2006.01)
C07D 213/75 (2006.01) **A61K 31/4985** (2006.01)
C07D 213/84 (2006.01) **A61K 31/501** (2006.01)
C07D 213/85 (2006.01) **A61K 31/5025** (2006.01)
C07D 277/46 (2006.01) **A61K 31/506** (2006.01)
C07D 401/06 (2006.01) **A61K 31/519** (2006.01)
C07D 417/06 (2006.01) **A61P 35/00** (2006.01)

(21) International Application Number:

PCT/SG2015/050005

(22) International Filing Date:

19 January 2015 (19.01.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1400787.6 17 January 2014 (17.01.2014) GB

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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, 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, ST, 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).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

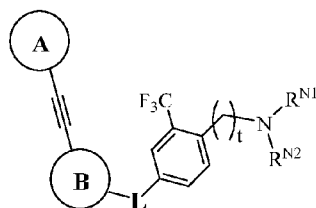
Published:

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

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

26 November 2015

(54) Title: HETEROARYL ALKYNE DERIVATIVES AND USES THEREOF



(1)

(57) Abstract: The present invention relates to certain heteroaryl alkyne compounds of Formula (I) that act as kinase inhibitors. The present invention further relates to pharmaceutical compositions comprising these compounds, and to the use of the compounds for the prevention and treatment of diseases (e.g., proliferative diseases (e.g., cancer), inflammatory diseases, autoimmune disease, metabolic diseases, neurodegenerative diseases (e.g., Alzheimer's disease), or neurodevelopmental disorders (e.g., autism)), as well as methods of treating these diseases.

A. CLASSIFICATION OF SUBJECT MATTER**[See Supplemental Sheet]**

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)

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)

Registry and CAPLUS: Structure search based on Formula (I) excluding CAS Registry Number 943319-70-8 (Ponatinib)

Pubmed: Keyword search using Ponatinib and series, structure or derivatives and like terms

Espacenet: Inventor and Applicant Search

Applicant/Inventor names searched in internal databases provided by IP Australia

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 26 August 2015	Date of mailing of the international search report 26 August 2015
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustalia.gov.au	Authorised officer Kate Bryce AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61262223682

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/SG2015/050005
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/075869 A2 (ARIAD PHARMACEUTICALS, INC.) 05 July 2007 See page 1, lines 29-35; pages 2-3, Formula I; page 10; pages 7-9, Formula III; page 12, lines 33-39; page 15, lines 14-18; page 39, lines 12-21; pages 44-49; page 72, lines 15-21; and pages 73-82.	1, 8, 9, 19-23, 25, 28, 30-37, 41, 44-47, 50-56, 59, 61, 70-77, 79-83, 84-90 & 95-97
X	HUANG, W.-S. et al. 'Discovery of 3-[2-(Imidazo[1,2-b]pyridazin-3-yl)ethynyl]-4-methyl-N-{4-[(4-methylpiperazin-1-yl)-methyl]-3-(trifluoromethyl)phenyl}benzamide (AP24534), a Potent, Orally Active Pan-Inhibitor of Breakpoint Cluster Region-Abelson (BCR-ABL) Kinase Including the T315I Gatekeeper Mutant', J. Med. Chem., 2010, Vol. 53, No. 12, pages 4701-4719. See page 4706, Table 3; page 4708, Table 4, compound 20g in particular; page 4709, Table 5; and page 4712, right col., lines 3-16 & 37-39.	1, 19-23, 33, 34, 41, 44-47, 50-55, 61, 70, 74-78, 84, 85, 87 & 96
X	WO 2013/170774 A1 (SHANGHAI PHARMACEUTICALS HOLDING CO., LTD.) 21 November 2013 See pages 17-26; page 25, lines 27-37; page 26, lines 11-13 & 17-20; page 101; and page 103.	1, 19-21, 23, 24, 26, 27, 29, 33, 34, 42-47, 50, 52, 57, 58, 60, 61, 70-77, 79-81, 84-87, 95 & 96
X	WO 2013/170770 A1 (SHANGHAI PHARMACEUTICALS HOLDING CO., LTD.) 21 November 2013 See pages 14-15; page 16, lines 25-29; page 17, lines 2-3 and 8-11; and pages 41-42.	1, 19-24, 29, 37-42, 44-47, 50-54, 60, 61, 70-77, 79-81, 84-87, 95 & 96
X	WO 2012/139027 A1 (ARIAD PHARMACEUTICALS, INC.) 11 October 2012 See page 10; page 14, lines 19-35; page 39; and pages 75-86.	1, 19-23, 33-35, 37, 41, 44-47, 50-55, 61, 70-77, 84, 91-93, 96 & 97
X	DESAI, B. et al. 'Rapid Discovery of a Novel Series of Abl Kinase Inhibitors by Application of an Integrated Microfluidic Synthesis and Screening Platform', J. Med. Chem., 2013, Vol. 56, pages 3033-3047. See page 3035, Fig.4, compound 4; left col. 2nd para & right col. 2nd para; page 3036, left col., 3rd para-right col., 1st para; page 3038, Table 1; page 3040, Table 2, alkynes 22-8, 22-16, 22-17, 22-18, 22-19, 22-20 and 22-24; page 3042, Fig. 15; and page 3044, Table 5.	1, 2, 4-7, 10-23, 33-35, 44-47, 50, 52-55, 61, 70-77, 84, 85, 87 & 96
X	THOMAS, M. et al. 'Discovery of 5-(arenethynyl) hetero-monocyclic derivatives as potent inhibitors of BCR-ABL including the T315I gatekeeper mutant', Bioorg. Med. Chem. Lett., 2011, Vol. 21, pages 3743-3748. See page 3746, Table 1	1, 4-18, 33, 34, 44-47, 50, 52, 53, 57, 60, 61, 70-77, 84, 85, 87 & 96
X	DENG, X. et al. 'Broad spectrum alkynyl inhibitors of T315I Bcr-Abl', Bioorg. Med. Chem. Lett., 2010, Vol. 20, pages 4196-4200. See page 4197, Tables 1 and 2, compounds 3-17 and 20.	1, 12-23, 29, 33, 34, 41, 44-47, 50-53, 57, 60, 61, 70 & 74-77
P,X	WO 2014/194667 A1 (SHANGHAI INSTITUTE OF MATERIA MEDICA, CHINESE ACADEMY OF SCIENCES) 11 December 2014 See pages 10-15 and page 89, claims 8-10.	1, 12-26, 29-39, 41-53, 57, 58, 60, 61, 70, 71-73, 84-87 & 96
Form PCT/ISA/210 (fifth sheet) (July 2009)		

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. PCT/SG2015/050005
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2014/082578 A1 (NANJING SANHOME PHARMACEUTICAL CO., LTD.) 05 June 2014 See abstract, pages 15-17 and page 19, 3rd para.	1, 4-7, 12-14, 16, 19-23, 33, 34, 44-47, 50, 52, 53, 56, 61, 70-77, 81, 84-86 & 96
P,X	WO 2014/040549 A1 (NANJING SANHOME PHARMACEUTICAL CO., LTD.) 20 March 2014 See page 9, 4th & 6th paras and pages 11-13.	1, 19-21, 23, 24, 29, 33, 34, 44-47, 50, 52, 56, 60, 61, 70-77, 79-82, 84-87 & 96
Form PCT/ISA/210 (fifth sheet) (July 2009)		

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:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including
2. ☒ Claims Nos.: 62-68 **69**
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:
See Supplemental Box
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:

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.:

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.

Supplemental Box**Continuation of Box II**

Claims 62-68 further define variables R^{N1} and R^{N2} but there are no such variables in claim 50 to which they are appended.

Claim 69 does not comply with Rule 6.2(a) because it relies on references to the description and/or drawings.

INTERNATIONAL SEARCH REPORT	International application No. PCT/SG2015/050005
Supplemental Box – IPC Marks	
C07D 471/04 (2006.01) C07D 213/40 (2006.01) C07D 213/73 (2006.01) C07D 213/74 (2006.01) C07D 213/75 (2006.01) C07D 213/84 (2006.01) C07D 213/85 (2006.01) C07D 277/46 (2006.01) C07D 401/06 (2006.01) C07D 417/06 (2006.01) C07D 487/04 (2006.01) A61K 31/437 (2006.01) A61K 31/44 (2006.01) A61K 31/496 (2006.01) A61K 31/4985 (2006.01) A61K 31/501 (2006.01) A61K 31/5025 (2006.01) A61K 31/506 (2006.01) A61K 31/519 (2006.01) A61P 35/00 (2006.01)	

INTERNATIONAL SEARCH REPORT		International application No.			
Information on patent family members		PCT/SG2015/050005			
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.					
Patent Document/s Cited in Search Report		Patent Family Member/s			
Publication Number	Publication Date	Publication Number	Publication Date		
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		AU 2006331673 A1	05 Jul 2007		
		AU 2006331673 B2	28 Feb 2013		
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		AU 2007249924 B2	04 Jul 2013		
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		EP 1973545 B1	30 Jan 2013		
		EP 2023933 A2	18 Feb 2009		
		EP 2024366 A2	18 Feb 2009		
		EP 2495016 A1	05 Sep 2012		
		IL 194677 A	31 Mar 2014		
		JP 2009521462 A	04 Jun 2009		
		JP 5200939 B2	05 Jun 2013		
		JP 2009536650 A	15 Oct 2009		
		JP 5273037 B2	28 Aug 2013		
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		JP 5273038 B2	28 Aug 2013		
		Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			
		Form PCT/ISA/210 (Family Annex)(July 2009)			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/SG2015/050005	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		JP 2013064004 A	11 Apr 2013
		KR 20080081191 A	08 Sep 2008
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		US 8778942 B2	15 Jul 2014
		US 2013231337 A1	05 Sep 2013
		US 9029533 B2	12 May 2015
		US 2013018046 A1	17 Jan 2013
		US 9090561 B2	28 Jul 2015
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			
Form PCT/ISA/210 (Family Annex)(July 2009)			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/SG2015/050005	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2013/170774 A1	21 November 2013	WO 2013170774 A1	21 Nov 2013
		CN 103420977 A	04 Dec 2013
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			
Form PCT/ISA/210 (Family Annex)(July 2009)			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/SG2015/050005	
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Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2014/194667 A1	11 December 2014	WO 2014194667 A1	11 Dec 2014
		CN 104211639 A	17 Dec 2014
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		AU 2013351622 A1	04 Jun 2015
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		AU 2013314839 A1	05 Feb 2015
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		EP 2896620 A1	22 Jul 2015
		KR 20150067140 A	17 Jun 2015
		US 2015152088 A1	04 Jun 2015
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