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**C07D 239/48** (2006.01)    **C07D 413/14** (2006.01)  
**C07D 401/04** (2006.01)    **C07D 495/04** (2006.01)  
**C07D 401/12** (2006.01)    **A61K 31/506** (2006.01)  
**C07D 401/14** (2006.01)    **A61K 31/513** (2006.01)  
**C07D 403/04** (2006.01)    **A61K 31/505** (2006.01)  
**C07D 403/12** (2006.01)    **A61K 31/5377** (2006.01)  
**C07D 403/14** (2006.01)    **A61K 31/4418** (2006.01)  
**C07D 413/12** (2006.01)    **A61P 35/00** (2006.01)  
**C07D 213/68** (2006.01)    **A61P 35/02** (2006.01)  
**C07D 213/73** (2006.01)

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01803 (US). **NGUYEN, Ngan** [VN/US]; 63 Marshall Street, Unit 1F, Somerville, Massachusetts 02145 (US). **QIU, Hui** [CN/US]; 20 Robinwood Road, Acton, Massachusetts 01720 (US). **GOUTOPOULOS, Andreas** [GR/US]; 73 Worcester Street, Apt. 5, Boston, Massachusetts 02118 (US). **BRUGGER, Nadia** [CH/US]; 7 Haskell Street, Cambridge, Massachusetts 02140 (US).

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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, 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, IS, JP, KE, KG, KM, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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, ML, MR, NE, SN, TD, TG).

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**(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 according to Formula (I), Formula (II), Formula (III), Formula (IV) and Formula (V) their manufacture and use for the treatment of hyperproliferative diseases including, but not limited to, cancer, lupus, allergic disorders, Sjogren's disease and rheumatoid arthritis. In preferred embodiments, the present invention describes irreversible kinase inhibitors including, but not limited to, inhibitors of Bruton's tyrosine kinase.



# INTERNATIONAL SEARCH REPORT

International application No  
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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>INV. C07D239/47 C07D239/48 C07D401/04 C07D401/12 C07D401/14<br>C07D403/04 C07D403/12 C07D403/14 C07D413/12 C07D213/68<br>C07D213/73 C07D213/74 C07D413/14 C07D495/04 A61K31/506                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>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)<br>EPO-Internal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                    | Relevant to claim No.     |
| X<br><br>A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | WO 2011/029046 A1 (BIOGEN IDEC INC [US];<br>ERLANSON DANIEL A [US]; MARCOTTE DOUG<br>[US]; KUMA) 10 March 2011 (2011-03-10)<br>paragraph [0466]; compound 290<br>paragraph [0468]; compound 292<br>IC50 values for compounds 290 and 292;<br>page 271<br>the whole document<br><div style="text-align: center; margin-top: 10px;">           -----<br/>           -/--         </div> | 1-8,<br>11-22<br><br>9,10 |
| <div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.</span> <span><input checked="" type="checkbox"/> See patent family annex.</span> </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&amp;" document member of the same patent family</p> </div> </div> |                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| Date of the actual completion of the international search                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Date of mailing of the international search report                                                                                                                                                                                                                                                                                                                                    |                           |
| 18 December 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 04/01/2013                                                                                                                                                                                                                                                                                                                                                                            |                           |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Authorized officer<br><br>Sarakinis, Georgios                                                                                                                                                                                                                                                                                                                                         |                           |

## 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                                                    | <p>TRAVERSO J J ET AL: "THE SYNTHESIS AND PHARMACOLOGICAL ACTIVITIES OF AMIDE, SULFAMIDE, AND UREA DERIVATIVES OF 4,6-DIAMINOPYRIMIDINES", JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 5, 1 July 1962 (1962-07-01), pages 808-815, XP000653960, DOI: 10.1021/JM01239A015 page 811; table 1; compound C11H11BrN4</p> <p>-----</p> | 1-8                                   |
| X                                                    | <p>KOSARY J ET AL: "preparation of pyrimidine derivatives with potential cardiotonic activity", ACTA PHARMACEUTICA HUNGARICA, HUNGARICAN PHARMACEUTICAL ASSOCIATION, BUDAPEST, HU, vol. 59, 1 January 1989 (1989-01-01), pages 241-247, XP002119936, ISSN: 0001-6659 page 243; compound 10c</p> <p>-----</p>                                                                        | 1-7                                   |
| X                                                    | <p>US 2005/171131 A1 (KOSOGOF CHRISTI [US] ET AL) 4 August 2005 (2005-08-04) example 129B</p> <p>-----</p>                                                                                                                                                                                                                                                                          | 1-7                                   |
| X                                                    | <p>O'BRIEN D E ET AL: "Pyrimidines. XI. Structural Variations of 2,4-Diamino-6-(halogenoanilino)-5-nitrosopyrimidines", JOURNAL OF MEDICINAL CHEMISTRY,, vol. 6, no. 5, 11 September 1963 (1963-09-11), pages 467-471, XP002647746, The 4th, 5th and 6th compound; page 468; table 1</p> <p>-----</p>                                                                               | 1-7                                   |
| X<br>A                                               | <p>US 5 753 668 A (MOSCHEL ROBERT C [US] ET AL) 19 May 1998 (1998-05-19) example 17 column 13 - column 18</p> <p>-----</p>                                                                                                                                                                                                                                                          | 1-7,11,<br>15-21<br>8-10,<br>12-14,22 |
| X                                                    | <p>JP 8 283246 A (NIPPON SODA CO) 29 October 1996 (1996-10-29) compounds 1, 7, 13, 16, 18, 30, 31,32,41-43 compounds 106,107,110,122,138,173,174</p> <p>-----</p>                                                                                                                                                                                                                   | 1-8                                   |
| X                                                    | <p>WO 2008/058229 A1 (SQUIBB BRISTOL MYERS CO [US]; BORZILLERI ROBERT M [US]; SCHROEDER GRET) 15 May 2008 (2008-05-15) The product of Example 1, step C (page 17)</p> <p>-----</p> <p>-/--</p>                                                                                                                                                                                      | 1-8                                   |

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                       |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                                 | Relevant to claim No. |
| X                                                    | <p>VISHWAKARMA J N ET AL: "Reactions of Polarized Keten S,N-Acetals with Guanidine: A Facile General Route to Novel 5,6-Substituted 2-Amino-4-N-alkyl/aryl/N-azacycloalkylaminopyrimidines", INDIAN JOURNAL OF CHEMISTRY. SECTION B: ORGANIC AND MEDICINAL CHEMISTRY, COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH (C S I R), IN, vol. 24, 1 January 1985 (1985-01-01), pages 466-471, XP009162452, ISSN: 0376-4699 compounds 11a, 11b, 11c, 11d</p> <p>-----</p> | 1-7                   |
| X                                                    | <p>SHISHOO C J ET AL: "Synthesis of Some 2,4-Diamino-6-substituted-amino-5-arylpyrimidines", INDIAN JOURNAL OF CHEMISTRY. SECTION B: ORGANIC AND MEDICINAL CHEMISTRY, COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH (C S I R), IN, vol. 28, no. 1-11, 1 January 1989 (1989-01-01), pages 42-47, XP009162451, ISSN: 0376-4699 compounds 5a, 5h</p> <p>-----</p>                                                                                                     | 1-7                   |
| X                                                    | <p>ACKERMANN H ET AL: "Konstitution und Reaktionsfaehigkeit von Trichlor-pyrimidylamino-Verbindungen", HELVETICA CHIMICA ACTA, VERLAG HELVETICA CHIMICA ACTA, BASEL, CH, vol. 45, no. 5, 1 January 1962 (1962-01-01), pages 1683-1698, XP009162477, ISSN: 0018-019X compound II</p> <p>-----</p>                                                                                                                                                                   | 1-7                   |
| X                                                    | <p>BIRESSI ET AL: "Su Alcune 5-Fluoro-6-Anilino-Aminopirimidine", BOLLETTINO CHIMICO FARMACEUTICO, SOCIETA EDITORIALE FARMACEUTICA, MILANO, IT, vol. 105, 1 January 1966 (1966-01-01), pages 660-665, XP009162478, ISSN: 0006-6648 compounds 3804-3809, 3814, 3830, 3847, 3862 compounds 7227, 7241, 7242, 7243, 7250, 7252, 7253</p> <p>-----</p> <p>-/--</p>                                                                                                     | 1-7                   |

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| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                             | Relevant to claim No.    |
|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| X         | WO 2009/044162 A1 (CANCER REC TECH LTD [GB]; COLLINS IAN [GB]; READER JOHN CHARLES [GB];) 9 April 2009 (2009-04-09)                                                                                                                                                                                                                                                                                            | 1-7                      |
| A         | Page 230: 167-B<br>Page 231: 167-C<br>Page 235: 169-B<br>Page 240: 171-B<br>Page 241: 171-C<br>-----                                                                                                                                                                                                                                                                                                           | 8-22                     |
| X         | EP 0 471 297 A1 (HOECHST ROUSSEL PHARMA [US]) 19 February 1992 (1992-02-19)                                                                                                                                                                                                                                                                                                                                    | 1,4-8,11                 |
| A         | The third compound in the list of six compounds on the top of page 7<br>-----                                                                                                                                                                                                                                                                                                                                  | 2,3,9,<br>10,12-22       |
| X         | EP 1 348 706 A1 (TAKEDA CHEMICAL INDUSTRIES LTD [JP]; KUSAKA MASAMI [JP] TAKEDA PHARMAC)<br>1 October 2003 (2003-10-01)                                                                                                                                                                                                                                                                                        | 1-8,11,<br>15            |
| A         | page 78, paragraph 308<br>table 10; compound 117<br>-----                                                                                                                                                                                                                                                                                                                                                      | 9,10,<br>12-14,<br>16-22 |
| X         | WO 2008/046049 A1 (XENON PHARMACEUTICALS INC [CA]; CADIEUX JEAN-JACQUES [CA]; CHOWDHURY S) 17 April 2008 (2008-04-17)<br>4-(benzyloxy)-3-bromopyridine;<br>pages 106-107<br>-----                                                                                                                                                                                                                              | 1-8                      |
| X         | WO 2007/089512 A1 (ARRAY BIOPHARMA INC [US]; AICHER THOMAS DANIEL [US]; BOYD STEVEN ARMEN) 9 August 2007 (2007-08-09)<br>4-(benzyloxy)-5-bromopyridine-2-amine;<br>paragraph [0553]<br>-----                                                                                                                                                                                                                   | 1-7                      |
| X         | CHANG SUNG HONG ET AL: "Synthesis of Aromatic Ring Fused Pyrrole Derivatives by Palladium-catalyzed Annulation of o-Iodoarylamines with Allyl Acetate", HETEROCYCLES, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL,<br>vol. 63, no. 3,<br>1 January 2004 (2004-01-01), pages 631-639, XP001526304,<br>ISSN: 0385-5414<br>Table 2, starting material of entry 5; see also page 637, synthesis of (5)<br>----- | 1-8                      |
| X         | SHIGENOBU OKUDA ET AL:<br>THE JOURNAL OF ORGANIC CHEMISTRY,<br>vol. 24, no. 7, 1 July 1959 (1959-07-01),<br>pages 1008-1011, XP55037406,<br>ISSN: 0022-3263, DOI: 10.1021/jo01089a616<br>Page 1010, right column, bottom:<br>4-benzylamino-3-bromopyridine<br>-----                                                                                                                                            | 1-8                      |
|           | -----<br>-/--                                                                                                                                                                                                                                                                                                                                                                                                  |                          |

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| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                       |                       |
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| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                    | Relevant to claim No. |
| X                                                    | IWAKI ET AL: "Novel synthetic strategy of carbolines via palladium-catalyzed amination and arylation reaction", JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY, LETCHWORTH; GB, 1 January 1999 (1999-01-01), pages 1505-1510, XP002458090, ISSN: 0300-922X, DOI: 10.1039/A901088B compounds 5c, 6c<br>----- | 1-8                   |
| X                                                    | ARTHUR P. PHILLIPS ET AL: "Syntheses of 1,3-Diazaphenothiazines.1 I.", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 28, no. 6, 1 June 1963 (1963-06-01), pages 1488-1490, XP55042306, ISSN: 0022-3263, DOI: 10.1021/jo01041a012 Compound: 2,4-Diamino-5-bromo-6-anilinopyrimidine; page 1490<br>-----                                       | 1-7                   |
| X                                                    | WO 2010/057126 A1 (AMGEN INC [US]; ALLEN JENNIFER R [US]; BISWAS KAUSTAV [US]; CHAVEZ FRA) 20 May 2010 (2010-05-20) Product of paragraph [00578] Product of paragraph [00579]<br>-----                                                                                                                                                | 1,4-7                 |
| X                                                    | US 2004/053908 A1 (FUNAHASHI YASUHIRO [JP] ET AL) 18 March 2004 (2004-03-18) 4-(3-phenylpyridin-4-yl)oxyaniline; example 125 The product of Production Example 209-1, page 105<br>-----                                                                                                                                               | 1-8                   |
| X                                                    | WO 2008/046216 A1 (METHYLGENE INC [CA]; RAEPPPEL STEPHANE [CA]; SAAVEDRA OSCAR [CA]; CLARI) 24 April 2008 (2008-04-24) page 172; compound 53<br>-----                                                                                                                                                                                 | 1-8                   |
| A                                                    |                                                                                                                                                                                                                                                                                                                                       | 9-22                  |
| X                                                    | WEN SONG YUE ET AL: "A Concise Synthesis of All Four Possible Benzo[4,5]furopyridines via Palladium-Mediated Reactions", ORGANIC LETTERS, vol. 4, no. 13, 1 June 2002 (2002-06-01), pages 2201-2203, XP55042429, ISSN: 1523-7060, DOI: 10.1021/o10260425 compound 8<br>-----<br>-/--                                                  | 1-8                   |

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| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                       |
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| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                                                                               | Relevant to claim No. |
| X                                                    | ZHANG Y M ET AL: "Synthesis of pyrimido[4,5-b]indoles and benzo[4,5]furo[2,3-d]pyrimidines via palladium-catalyzed intramolecular arylation", TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 43, no. 46, 11 November 2002 (2002-11-11), pages 8235-8239, XP027330566, ISSN: 0040-4039 [retrieved on 2002-11-11] Table 2 and Table 3: all compounds Note: in the scheme of Table 3, the generic structure 3 is wrongly a regioisomer of the actual structure; table 3; compounds 6i, 6k, 6l<br>-----          | 1-8,23                |
| X,P                                                  | WO 2011/139891 A1 (DECIPHERA PHARMACEUTICALS LLC [US]; FLYNN DANIEL L [US]; KAUFMAN MICHA) 10 November 2011 (2011-11-10) Compounds in the experimental section: 4-[(3-bromo-4-pyridinyl)oxy]-2,5-difluorobenzenamine<br>2,5-difluoro-4-[(5-iodo-4-pyrimidinyl)oxy]-benzenamine<br>4-(2,5-difluorophenoxy)-3-iodo-2-pyridinamine<br>4-(4-amino-2,5-difluorophenoxy)-3-iodo-2-pyridinamine<br>3-bromo-4-(2-chloro-5-fluorophenoxy)-pyridine<br>4-[(3-bromo-4-pyridinyl)oxy]-5-chloro-2-fluoro-benzenamine<br>----- | 1-8                   |
| A                                                    | WO 2011/029043 A1 (BIOGEN IDEC INC [US]; SUNESIS PHARMACEUTICALS INC [US]; BUI MINNA [US]) 10 March 2011 (2011-03-10) the whole document<br>-----                                                                                                                                                                                                                                                                                                                                                                | 1-22                  |
| A                                                    | WO 2010/144647 A1 (SQUIBB BRISTOL MYERS CO [US]; DELUCCA GEORGE V [US]; SHI QING [US]; LI) 16 December 2010 (2010-12-16) the whole document<br>-----                                                                                                                                                                                                                                                                                                                                                             | 1-22                  |
| X                                                    | WO 2009/158571 A1 (AVILA THERAPEUTICS AND USES TH [US]; KLUGE ARTHUR F [US]; PETTER RUSSE) 30 December 2009 (2009-12-30) the whole document<br>-----                                                                                                                                                                                                                                                                                                                                                             | 24                    |
| A                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1-22                  |
| A                                                    | WO 2009/051822 A1 (AVILA THERAPEUTICS INC [US]; TESTER RICHLAND W [US]; SINGH JUSWINDER []) 23 April 2009 (2009-04-23) the whole document<br>-----                                                                                                                                                                                                                                                                                                                                                               | 1-22                  |
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|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                    | Relevant to claim No. |
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| X                                                    | -----<br>HURST D T: "Application of the Elbs Persulfate Oxidation to the Preparation of 5-Hydroxypyrimidines",<br>AUSTRALIAN JOURNAL OF CHEMISTRY, CSIRO, AU,<br>vol. 36, 1 January 1983 (1983-01-01),<br>pages 1285-1289, XP009088310,<br>ISSN: 0004-9425<br>page 1288; compound 7j                                                                                  | 23                    |
| X                                                    | -----<br>D. J. BROWN ET AL: "120. Pyrimidine reactions. Part VII. Methylation of substituted 2,4-diaminopyrimidines",<br>JOURNAL OF THE CHEMICAL SOCIETY (RESUMED),<br>1 January 1965 (1965-01-01), page 755,<br>XP55048118,<br>ISSN: 0368-1769, DOI: 10.1039/jr9650000755<br>Page 756, directly under the chemical structures:<br>2-amino-4-dimethylamino-pyrimidine | 23                    |
| X                                                    | -----<br>ALAN C. SPIVEY ET AL: "Atropisomeric [alpha]-methyl substituted analogues of 4-(dimethylamino)pyridine: synthesis and evaluation as acyl transfer catalysts",<br>JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1,<br>no. 15, 1 January 2001 (2001-01-01), pages 1785-1794, XP55048017,<br>ISSN: 1472-7781, DOI: 10.1039/b103385a<br>compound 9        | 23                    |
| X                                                    | -----<br>SATOSHI MIZUKAMI ET AL: "The Ionization Constants of Some 4,5-Substituted 2-Methylpyrimidines",<br>THE JOURNAL OF ORGANIC CHEMISTRY,<br>vol. 31, no. 4, 1 April 1966 (1966-04-01),<br>pages 1199-1202, XP55048013,<br>ISSN: 0022-3263, DOI: 10.1021/jo01342a051<br>table 1; compound 1<br>-----<br>-/--                                                      | 23                    |

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                       |
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| X                                                    | WILLIAM W. PAUDLER ET AL: "Bromination of some pyridine and diazine N-oxides", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 48, no. 7, 1 April 1983 (1983-04-01), pages 1064-1069, XP55047990, ISSN: 0022-3263, DOI: 10.1021/jo00155a027 Tables II and III: the compounds bearing 4-amino(alkyl or dialkyl) or 4-methoxy substituents in the first column of the tables<br>-----                                                                                      | 23                    |
| X                                                    | WHITEHEAD C W & TRAVERSO J J: "Diuretics. III. 4,6-Diaminopyrimidines", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, ACS PUBLICATIONS, US, vol. 80, 5 May 1958 (1958-05-05), pages 2185-2189, XP002081959, ISSN: 0002-7863, DOI: 10.1021/JA01542A038 Many compounds in Table I<br>-----                                                                                                                                                                            | 23                    |
| X                                                    | B]TTELMANN B ET AL: "4-(3,4-DIHYDRO-1H-ISOQUINOLIN-2YL)-PYRIDINES AND 4-(3,4-DIHYDRO-1H-ISOQUINOLIN-2-YL)-QUINOLINES AS POTENT NR1/2B SUBTYPE SELECTIVE NMDA RECEPTOR ANTAGONISTS", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 13, 1 January 2003 (2003-01-01), pages 1759-1762, XP003009973, ISSN: 0960-894X, DOI: 10.1016/S0960-894X(03)00232-4 table 2; compounds 14a-14h table 4; compounds 15, 16, 17<br>-----<br>-/-- | 23                    |

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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| X         | JANG M Y ET AL: "Synthesis of novel 5-amino-thiazolo[4,5-d]pyrimidines as E. coli and S. aureus SecA inhibitors",<br>BIOORGANIC & MEDICINAL CHEMISTRY,<br>PERGAMON, GB,<br>vol. 19, no. 1,<br>1 January 2011 (2011-01-01), pages<br>702-714, XP027577807,<br>ISSN: 0968-0896<br>[retrieved on 2010-12-28]<br>compounds 1a, 1d<br>----- | 23                    |
| X         | US 6 007 798 A (BOHN MANFRED [DE] ET AL)<br>28 December 1999 (1999-12-28)<br>2,6-diamino-4-piperidinopyridine;<br>column 3, line 63<br>-----                                                                                                                                                                                           | 23                    |
| X         | ALLA BESSMERTNYKH ET AL: "Efficient Palladium-Catalyzed Synthesis of Aminopyridyl Phosphonates from Bromopyridines and Diethyl Phosphite",<br>SYNTHESIS,<br>vol. 2008, no. 10, 1 May 2008 (2008-05-01)<br>, pages 1575-1579, XP55048046,<br>ISSN: 0039-7881, DOI:<br>10.1055/s-2008-1072570<br>compound 4<br>-----                     | 23                    |
| X         | WO 99/19305 A2 (KRENITSKY PHARMACEUTICALS INC [US]; KELLEY JAMES L [US]; KRENITSKY THO) 22 April 1999 (1999-04-22)<br>Many compounds of the examples on pages<br>31-55<br>-----                                                                                                                                                        | 23                    |
| X         | WO 2006/096405 A2 (ALSGEN LLC [US]; SCOTT SEAN [US]; BENJAMIN DANIEL [US] ALSGEN INC [US]) 14 September 2006 (2006-09-14)<br>Several compounds in Figure 3<br>-----<br>-/--                                                                                                                                                            | 23                    |

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| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                                    |                       |
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| X                                                    | BONGKOCH TARNCHOMPOO ET AL: "Development of 2,4-Diaminopyrimidines as Antimalarials Based on Inhibition of the S108N and C59R+S108N Mutants of Dihydrofolate Reductase from Pyrimethamine-Resistant Plasmodium falciparum", JOURNAL OF MEDICINAL CHEMISTRY, vol. 45, no. 6, 1 March 2002 (2002-03-01), pages 1244-1252, XP55048052, ISSN: 0022-2623, DOI: 10.1021/jm010131q table 7; compounds 26, 30, 35<br>----- | 23                    |
| X                                                    | US 2009/163516 A1 (DUNKEL RALF [FR] ET AL) 25 June 2009 (2009-06-25)<br>Many different<br>5-(aryl)-4-pyrimidinylamines from the preparation examples<br>-----                                                                                                                                                                                                                                                      | 23                    |
| X                                                    | S. A. LANG ET AL:<br>"4-Amino-5-arylpyrimidines as antiinflammatory agents", JOURNAL OF MEDICINAL CHEMISTRY, vol. 18, no. 6, 1 June 1975 (1975-06-01), pages 623-625, XP55048074, ISSN: 0022-2623, DOI: 10.1021/jm00240a021<br>Several compounds from Tables I and II<br>-----                                                                                                                                     | 23                    |
| X                                                    | PEGIADOU: "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, vol. 70, no. 2, 1 January 1998 (1998-01-01), page 211, XP55048115, ISSN: 0021-8995<br>Scheme 5, the 1st tautomer of compound IV'<br>-----                     | 23                    |
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## INTERNATIONAL SEARCH REPORT

International application No

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| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                       |
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International application No.  
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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.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-8, 11-23(all partially)  
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 FURTHER INFORMATION sheet PCT/ISA/210
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.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

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

1. claims: 1-22

Pyridines and pyrimidines of formula I

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2. claim: 23

Pyridines and pyrimidines of formula II

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3. claim: 24

Pyridines and pyrimidines of formula V

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**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box II.2

Claims Nos.: 1-8, 11-23(all partially)

Due to Novelty overflow and the immense scope of independent claims 1 and 23, a complete search for claims 1-8 and 11-23 was not possible to perform. More compounds from additional documents may thus be pertinent to Novelty and Inventive step for claims 1-8 and 11-23.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2) declaration be overcome.

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Information on patent family members

International application No

PCT/US2012/041803

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