

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
8 November 2007 (08.11.2007)

PCT

(10) International Publication Number
WO 2007/125321 A3

(51) International Patent Classification:

A61K 31/52 (2006.01) A61P 25/00 (2006.01)
 A61K 31/522 (2006.01) A61P 37/00 (2006.01)
 A61K 31/4523 (2006.01) C07D 471/04 (2006.01)
 A61K 31/519 (2006.01) C07D 473/34 (2006.01)
 A61P 29/00 (2006.01) C07D 487/04 (2006.01)
 A61P 35/00 (2006.01)

(21) International Application Number:

PCT/GB2007/001518

(22) International Filing Date: 25 April 2007 (25.04.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0608176.4 25 April 2006 (25.04.2006) GB
 0608179.8 25 April 2006 (25.04.2006) GB

(71) Applicants (for all designated States except US): **ASTEX THERAPEUTICS LIMITED** [GB/GB]; 436 Cambridge Science Park, Milton Road, Cambridge CB4 0QA (GB). **THE INSTITUTE OF CANCER RESEARCH: ROYAL CANCER HOSPITAL** [GB/GB]; 123 Old Brompton Road, London SW7 3RP (GB). **CANCER RESEARCH TECHNOLOGY LIMITED** [GB/GB]; Sardinia House, Sardinia Street, London WC2A 3NL (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DAVIES, Thomas, Glanmor** [GB/GB]; 436 Cambridge Science Park, Milton Road, Cambridge CB4 0QA (GB). **GARRETT, Michelle, Dawn** [GB/GB]; Cancer Research UK, 15 Cotswold Road, Sutton SM2 5NG (GB). **BOYLE, Robert, George** [GB/GB]; 30 Catharine Street, Cambridge CB1 3AW (GB). **COLLINS, Ian** [GB/GB]; Cancer Research UK, 15 Cotswold Road, Sutton SM2 5NG (GB).

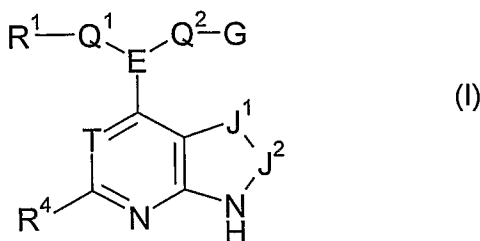
(74) Agent: **HUTCHINS, Michael, Richard**; M.R. Hutchins & Co., 23 Mount Sion, Tunbridge Wells, Kent TN11 1TZ (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, 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, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),

[Continued on next page]

(54) Title: PURINE AND DEAZAPURINE DERIVATIVES AS PHARMACEUTICAL COMPOUNDS



(57) Abstract: The invention provides a compound of the formula (I) or salts, solvates, tautomers or N-oxides thereof, wherein T is N or CR⁵; J¹-J² is N=C(R⁶), (R⁷)C=N, (R⁸)N-C(O), (R⁸)₂C-C(O), N=N or (R⁷)C=C(R⁶); E is a monocyclic carbocyclic or heterocyclic group of 5 or 6 ring members, the heterocyclic group containing up to 3 heteroatoms selected from O, N and S; Q¹ is a bond or a saturated C₁₋₃ hydrocarbon linker group, one of the carbon atoms in the linker group being optionally replaced by an oxygen or nitrogen atom, or an adjacent pair of carbon atoms may be replaced by CONR⁹ or NR⁹CO where R⁹ is hydrogen or methyl, or R⁹ is a C₁₋₄ alkylene chain linked to R¹ or a carbon atom of Q¹ to form a cyclic moiety; and wherein the carbon atoms of the linker group Q¹ may optionally bear one or more substituents selected from fluorine and hydroxy; Q² is a bond or a saturated hydrocarbon linker group containing from 1 to 3 carbon atoms, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group may optionally bear one or more substituents selected from fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the G group; and provided that when E is aryl or heteroaryl, then Q² is other than a bond; G is hydrogen, NR²R³, OH or SH provided that when E is aryl or heteroaryl and Q² is a bond, then G is hydrogen; R¹ is hydrogen or an aryl or heteroaryl group, with the proviso that when R¹ is hydrogen and G is NR²R³, then Q² is a bond; and R², R³, R⁴, R⁶ and R⁸ are as defined in the claims, wherein the compound is for use in: (a) the treatment or prophylaxis of a disease or condition in which the modulation (e.g. inhibition) of ROCK kinase or protein kinase P70S6K is indicated; and/or (b) the treatment of a subject or patient population in which the modulation (e.g. inhibition) of ROCK kinase or protein kinase P70S6K is indicated.

WO 2007/125321 A3



European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(88) Date of publication of the international search report:
27 December 2007

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/001518

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D471/04 C07D473/34 C07D487/04 A61K31/4523 A61K31/519 A61K31/52 A61K31/522 A61P35/00 A61P25/00 A61P37/00 A61P29/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K 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 practical, search terms used) EPO-Internal, WPI Data, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/117909 A (EXELIXIS INC [US]; ANAND NEEL K [US]; BLAZEY CHARLES M EXELIXIS INC [U] 15 December 2005 (2005-12-15) paragraphs [0020], [0227]; middle column on page 40; claims 60-65	1-56, 58-113
X	WO 01/46196 A (SUGEN INC [US]; LIANG CONGXIN [US]; SUN LI [US]; WEI CHUNG CHEN [US];) 28 June 2001 (2001-06-28) page 6, line 20 - page 9, line 16; claims 1-5,9,10,25-28,31-35; example 45; compound 48	1-56, 58-113
A	EP 1 444 982 A (MERCKLE GMBH [DE]) 11 August 2004 (2004-08-11) claims	1-56, 58-113
	----- -/--	
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> 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 document 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 27 July 2007		Date of mailing of the international search report 11/10/2007
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Hanisch, Inken

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/001518

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/65909 A (PFIZER PROD INC [US]; BLUMENKOPF TODD ANDREW [US]; FLANAGAN MARK EDWAR) 23 December 1999 (1999-12-23) page 1, line 7 - line 13; claims; examples 6-8,32-35,46,47,60,61,78	1-56, 58-94, 98-113
X	WO 2005/026149 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BREEZE ALEXANDER LOUIS []) 24 March 2005 (2005-03-24) claims 1,3,9,20,21,24; example 72	1-56, 58-80, 95,96, 98, 103-105, 111-113
P,X	WO 2006/046023 A (ASTEX THERAPEUTICS LTD [GB]; PITAL THE INST OF CANCER RES R [GB]; CANC) 4 May 2006 (2006-05-04) page 91, line 8 - page 94, line 3; claims 1,34-60; examples 11-15,17-21,242-6,29,32	1-56, 58-113
P,X	WO 2006/046024 A (ASTEX THERAPEUTICS LTD [GB]; INST OF CANCER RES ROYAL CANCER [GB]; CANC) 4 May 2006 (2006-05-04) page 97, line 1 - page 99, line 26; claims; examples	1-56, 58-113
P,X	WO 2006/071819 A (EXELIXIS INC [US]; RICE KEN [US]; CO ERICK WANG [US]; KIM MOON HWAN [U]) 6 July 2006 (2006-07-06) paragraph [0022]; claims 1,48-57; example 1; compounds 1,22,40,59,101,103	1-56, 58-113
P,X	WO 2006/075095 A (AVENTIS PHARMA SA [FR]; MAILLIET PATRICK [FR]; CARREZ CHANTAL [FR]; FA) 20 July 2006 (2006-07-20) page 1, line 8 - line 11; claims 1,7; example 9	1-56, 58-84, 98,99, 101-109, 111-113
P,X	WO 2006/075094 A (AVENTIS PHARMA SA [FR]; CARREZ CHANTAL [FR]; FASSY FLORENCE [FR]; MAIL) 20 July 2006 (2006-07-20) claims 1,17,20-22; examples 5,8,16,17	1-56, 58-84, 98,99, 101-109, 111-113
P,X	WO 2006/091450 A (LEXICON GENETICS INC [US]; RAWLINS DAVID BRENT [US]; VORONKOV MICHAEL) 31 August 2006 (2006-08-31) claims 1,6,7,30-32; examples	1-56, 58-84, 89-91, 98,99, 101-109, 111-113

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/001518

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2007/007919 A (ASTELLAS PHARMA INC [JP]; INOUE TAKAYUKI [JP]; TOJO TAKASHI [JP]; MORI) 18 January 2007 (2007-01-18) page 31, line 4 - page 33, line 18; claims 1,12-19; examples 8,223	1-56, 58-94, 98-113
P, X	WO 2007/025090 A (KALYPSYS INC [US]; PINKERTON ANTHONY B [US]; DAVIS ROBERT L [US]; GAHM) 1 March 2007 (2007-03-01) page 56, line 4 - page 59; claims 12,21,22,25,27; compound 6	1-56, 58-94, 98-113
X	QUINTELA J M ET AL: "Pyrazolopyrimidines: synthesis, effect on histamine release from rat peritoneal mast cells and cytotoxic activity" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 36, no. 4, May 2001 (2001-05), pages 321-332, XP004255694 ISSN: 0223-5234 column 1, "introduction"; compound 5c in figure 2, table 1 and on page 330	1-80,87, 88,94, 103,104

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2007/001518

Box 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.: 57
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-56, 58-69, 75, 79-102, 104-113 are directed to a second medical use of known pharmaceutically active compounds or a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 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 fee, this Authority did not invite payment of any additional fee.
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.:

see annex

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims:

1-5(part), 6-9, 10-45(part), 46-54,
55(part), 56(part), 58(part), 59(part)
, 60-79, 80-99(part), 100, 101-113(part)

The compounds of formula (I) in which "E" stands for a
monocyclic non-aromatic heterocycle of 5 or 6 ring members

2. claims:

1-5(part), 10-45(part), 55(part), 56(part),
58(part), 80-99(part), 101-11
3(part)

The compounds of formula (I) in which "E" stands for a
monocyclic non-aromatic carbocycle of 5 or 6 ring members

3. claims: 1-5(part), 10-45(part), 57(part), 80-99(part), 101-113(part)

The compounds of formula (I) in which "E" stands for a
monocyclic aromatic heterocycle of 5 or 6 ring members

4. claims: 1-5(part), 10-45(part), 57(part), 80-99(part), 101-113(part)

The compounds of formula (I) in which "E" stands for a
monocyclic aromatic carbocycle of (5 or) 6 ring members

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2007/001518

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005117909 A	15-12-2005	AU 2005249380 A1	15-12-2005
		CA 2563699 A1	15-12-2005
		EP 1750727 A2	14-02-2007
WO 0146196 A	28-06-2001	AR 029423 A1	25-06-2003
		AT 299881 T	15-08-2005
		AU 2728201 A	03-07-2001
		CA 2395520 A1	28-06-2001
		DE 60021423 D1	25-08-2005
		DE 60021423 T2	13-04-2006
		EP 1244672 A1	02-10-2002
		ES 2245955 T3	01-02-2006
		JP 2003518123 T	03-06-2003
		EP 1444982 A	11-08-2004
WO 9965909 A	23-12-1999	AP 1157 A	30-06-2003
		AT 270673 T	15-07-2004
		AU 758427 B2	20-03-2003
		AU 4054599 A	05-01-2000
		BG 65063 B1	31-01-2007
		BG 105122 A	31-10-2001
		BR 9912171 A	10-04-2001
		CA 2335186 A1	23-12-1999
		CN 1305479 A	25-07-2001
		CZ 20004726 A3	13-03-2002
		DE 69918552 D1	12-08-2004
		DE 69918552 T2	04-11-2004
		DK 1087971 T3	11-10-2004
		EP 1087971 A1	04-04-2001
		ES 2223172 T3	16-02-2005
		HK 1036800 A1	27-02-2004
		HR 20000886 A2	31-10-2001
		HU 0103472 A2	28-02-2002
		ID 27595 A	12-04-2001
		IS 5721 A	21-11-2000
		IS 5722 A	21-11-2000
		JP 3497823 B2	16-02-2004
		JP 2002518394 T	25-06-2002
		MA 26653 A1	20-12-2004
		NO 20006454 A	15-02-2001
		NZ 508034 A	28-11-2003
		OA 11571 A	01-07-2004
		PL 345118 A1	03-12-2001
		PT 1087971 T	29-10-2004
		SK 18992000 A3	06-08-2002
TR 200003720 T2	21-03-2001		
TW 542834 B	21-07-2003		
UA 63013 C2	15-03-2001		
ZA 9904003 A	18-12-2000		
WO 2005026149 A	24-03-2005	AU 2004272338 A1	24-03-2005
		BR PI0414330 A	07-11-2006
		CA 2538552 A1	24-03-2005
		EP 1664025 A1	07-06-2006
		IS 8403 A	07-04-2006
		JP 2007505092 T	08-03-2007
		KR 20070026318 A	08-03-2007

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2007/001518

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2005026149	A		MX PA06002847 A US 2006223801 A1	14-06-2006 05-10-2006
WO 2006046023	A	04-05-2006	AR 051403 A1 EP 1812003 A1	10-01-2007 01-08-2007
WO 2006046024	A	04-05-2006	AR 051342 A1 EP 1812004 A1	03-01-2007 01-08-2007
WO 2006071819	A	06-07-2006	AU 2005322085 A1 CA 2590961 A1	06-07-2006 06-07-2006
WO 2006075095	A	20-07-2006	EP 1838322 A2 FR 2880540 A1	03-10-2007 14-07-2006
WO 2006075094	A	20-07-2006	AR 052454 A1 FR 2880626 A1	21-03-2007 14-07-2006
WO 2006091450	A	31-08-2006	NONE	
WO 2007007919	A	18-01-2007	NONE	
WO 2007025090	A	01-03-2007	NONE	