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— of inventorship (Rule 4.17(iv)) for US only

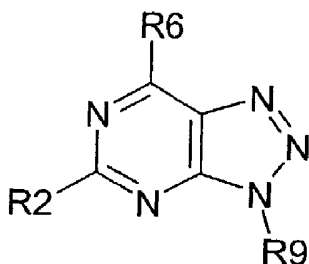
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(54) Title: AZAPURINE DERIVATIVES



(I)

(57) Abstract: The present invention relates to a compound of formula (I), or a pharmaceutically acceptable acid salt thereof. The invention further relates to the use of said compounds in the treatment of hyperproliferative skin disorders, viral infections, cancer, rheumatoid arthritis, lupus, type I diabetes, multiple sclerosis, restenosis, polycystic kidney disease, graft rejection, graft versus host disease and gout, or for psoriasis, parasitoses such as those caused by fungi or protists, or Alzheimer's disease. Further aspects of the invention relate to the use of such compounds in the inhibition of cell proliferation, in the induction of apoptosis, to modulate the activity of adrenergic and/or purinergic receptors or to suppress immunostimulation. The invention also relates to the use of 2,6,9-trisubstituted 8-azapurines in maintaining mammalian oocytes at the germinal vesicle stage.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/505 C07D487/04 A61P3/10 A61P9/00 A61P25/00 A61P31/12 A61P35/00		
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) IPC 7 A61K A61P C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, PAJ, WPI Data, CHEM ABS 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 97/20842 A (CENTRE NAT RECH SCIENT ; MEIJER LAURENT (FR); BISAGNI EMILE (FR); LEGR) 12 June 1997 (1997-06-12) olomoucine; claims and examples -----	1-47
X	US 5 866 702 A (LUM ROBERT T ET AL) 2 February 1999 (1999-02-02) claims and examples; table 3 (see certificate of correction) -----	1-47
X	EP 1 142 893 A (PENN STATE RES FOUNDATION INC ; ARCH DEV CORP (US); US OF AMERICA (US)) 10 October 2001 (2001-10-10) cpds. 8a-b claims 4-6 ----- -/--	1-12
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in 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. *Z* document member of the same patent family		
Date of the actual completion of the international search 1 March 2004		Date of mailing of the international search report 12/03/2004
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 Stroeter, T

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PCT/IB 03/04188

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 107 301 A (ALDRICH PAUL EDWARD ET AL) 22 August 2000 (2000-08-22) tables 16, 19 and 21, e.g. cpds. 592, 637, 638, 640, 1120 claims 4-7 -----	1-12
X	WO 99/41254 A (ASTRA PHARMA PROD ; BROWN ROGER (GB); WILLIS PAUL (GB); THOM STEPHEN ()) 19 August 1999 (1999-08-19) examples, e.g. ex. 90, 91; claims -----	1-12
X	WO 99/05143 A (ASTRA PHARMA PROD ; GUILLE SIMON (GB); WILLIS PAUL (GB); INGALL ANTHONY) 4 February 1999 (1999-02-04) claims, various examples, e.g. ex. 82 or 102ff (page 113) -----	1-12
X	PATENT ABSTRACTS OF JAPAN vol. 0081, no. 62 (C-235), 26 July 1984 (1984-07-26) & JP 59 062595 A (ESUESU SEIYAKU KK), 10 April 1984 (1984-04-10) formulae (I), (I-3), (I-4), (I-5), (II) and (VII) abstract -----	1-12
X	WO 98/28300 A (ASTRA PHARMA PROD ; BONNERT ROGER (GB); WILLIS PAUL (GB); INGALL ANTHO) 2 July 1998 (1998-07-02) claims; examples, e.g. ex. 3, 4 or 7 -----	1-12
X	WO 97/35846 A (DU PONT MERCK PHARMA) 2 October 1997 (1997-10-02) citations on: page 11, line 15 - page 12, line 15 -----	1-12
X	WO 97/35539 A (ARVANITIS ARGYRIOS GEORGIOS ; BAKTHAVATCHALAM RAJAGOPAL (US); CHORVAT) 2 October 1997 (1997-10-02) claims; examples in tables 1,5,6 e.g. ex. 264 -----	1-12
X	SHEALY Y F ET AL: "v-Triazolo'4,5-d!pyrimidines. 3. N-(3-alkyl-5-amino-3H-v-triazolo'4,5 d!pyrimidin-7-yl)-amino acids." JOURNAL OF MEDICINAL CHEMISTRY. MAY 1966, vol. 9, no. 3, May 1966 (1966-05), pages 417-419, XP002271920 ISSN: 0022-2623 cpds. III and IV ----- -/--	1-12

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	SHEALY Y. F. ET AL: "v-Triazolo'4,5-d!pyrimidines. I." JOURNAL OF ORGANIC CHEMISTRY, vol. 26, 1961, pages 4433-4440, XP002271921 cpds. of tab. 1, e.g. VIa - XII, XV - XVII -----	1-12
X	ASHTON ET AL: "Synthesis and antiherpetic activity of (+-)-9-''(Z)-2-(hydroxymethyl) cyclopropyl!methyl!guanine and related compounds" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 31, no. 12, 1988, pages 2304-2315, XP002235539 ISSN: 0022-2623 cpd. 11 -----	1-12
X	CHORVAT R J ET AL: "SYNTHESIS, CORTICOTROPIN-RELEASING FACTOR RECEPTOR BINDING AFFINITY AND PHARMACOKINETIC PROPERTIES OF TRIAZOLO-, IMIDAZO- AND PYRROLOPYRIMIDINES AND -PYRIDINES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, no. 5, 11 March 1999 (1999-03-11), pages 833-848, XP001093941 ISSN: 0022-2623 cpds. 3, 4s, 4an (tab. 3) -----	1-12
X	BEAUCHAMP L M ET AL: "MODIFICATIONS ON THE HETEROCYCLIC BASE OF ACYCLOVIR: SYNTHESIS AND ANTIVIRAL PROPERTIES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 28, no. 8, 1 August 1985 (1985-08-01), pages 982-987, XP000614317 ISSN: 0022-2623 cpd. 28; page 984, last two paragraphs of the left column the whole document -----	1,2,45

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/04188

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 1,2
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 14-24 are directed to 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.: 1,2
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 II Observations where unity of invention is lacking (Continuation of item 2 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 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.:

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

Continuation of Box I.1

Although claims 14-24 are directed to 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.

Continuation of Box I.2

Claims Nos.: 1,2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for claims 1 and 2. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to those compounds of claims 1 (or 2) wherein R6 is as defined in claim 3 (R6 = X-R6' = N(substituted arylalkyl)-R6') or in claim 4 (R6 = X-R6' = X-aryl). All further claims are consequently based on the compounds of formula I so defined.

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, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/IB 03/04188

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9720842	A	12-06-1997	FR 2741881 A1	06-06-1997
			AT 234838 T	15-04-2003
			CA 2238843 A1	12-06-1997
			DE 69626855 D1	24-04-2003
			DE 69626855 T2	24-12-2003
			DK 874847 T3	14-07-2003
			EP 1308447 A1	07-05-2003
			EP 0874847 A1	04-11-1998
			ES 2195027 T3	01-12-2003
			WO 9720842 A1	12-06-1997
			JP 2000501408 T	08-02-2000
			US 6316456 B1	13-11-2001
			US 2003186999 A1	02-10-2003
			US 2002049218 A1	25-04-2002
US 5866702	A	02-02-1999	AU 731778 B2	05-04-2001
			AU 3900097 A	25-02-1998
			BR 9710801 A	27-11-2001
			CA 2262454 A1	12-02-1998
			CN 1231611 A	13-10-1999
			EP 1021186 A1	26-07-2000
			HU 9902414 A2	28-04-2001
			IL 128323 A	25-11-2001
			JP 2000515550 T	21-11-2000
			KR 2000029781 A	25-05-2000
			NO 990466 A	25-03-1999
			NZ 334061 A	25-08-2000
			PL 331408 A1	19-07-1999
			TR 9900683 T2	21-01-2002
			WO 9805335 A1	12-02-1998
			US 2002032327 A1	14-03-2002
			US 2002035252 A1	21-03-2002
EP 1142893	A	10-10-2001	US 5525606 A	11-06-1996
			EP 1142893 A1	10-10-2001
			AT 207490 T	15-11-2001
			AU 702711 B2	04-03-1999
			AU 3207995 A	04-03-1996
			CA 2195856 A1	15-02-1996
			DE 69523462 D1	29-11-2001
			DE 69523462 T2	11-07-2002
			DK 775142 T3	18-02-2002
			EP 0775142 A1	28-05-1997
			ES 2167451 T3	16-05-2002
			JP 10508288 T	18-08-1998
			PT 775142 T	29-04-2002
			WO 9604281 A1	15-02-1996
			US 6172070 B1	09-01-2001
			US 6333331 B1	25-12-2001
			US 6303604 B1	16-10-2001
			US 5753668 A	19-05-1998
			US 5958932 A	28-09-1999
			US 5916894 A	29-06-1999
			US 2002013299 A1	31-01-2002
US 6107301	A	22-08-2000	AU 692484 B2	11-06-1998
			AU 8012294 A	04-05-1995
			BR 9407799 A	06-05-1997

INTERNATIONAL SEARCH REPORT

International Search No
PCT/IB 03/04188

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6107301 A		CA 2174080 A1	20-04-1995
		CZ 9601014 A3	13-11-1996
		EP 0723533 A1	31-07-1996
		HR 940664 A1	31-12-1996
		HU 74464 A2	30-12-1996
		NO 961425 A	12-06-1996
		NZ 274978 A	27-04-1998
		PL 313973 A1	05-08-1996
		SK 47096 A3	01-10-1996
		US 6342503 B1	29-01-2002
		CN 1142817 A	12-02-1997
		FI 961599 A	07-06-1996
		JP 9504520 T	06-05-1997
		JP 3398152 B2	21-04-2003
		RU 2153494 C2	27-07-2000
		WO 9510506 A1	20-04-1995
		ZA 9407921 A	11-04-1996
WO 9941254 A	19-08-1999	AT 232866 T	15-03-2003
		AU 2650099 A	30-08-1999
		BR 9907934 A	24-10-2000
		CA 2316264 A1	19-08-1999
		CN 1291193 T	11-04-2001
		DE 69905451 D1	27-03-2003
		DE 69905451 T2	20-11-2003
		EP 1056749 A1	06-12-2000
		HU 0100328 A2	28-09-2001
		ID 27127 A	01-03-2001
		JP 2002503663 T	05-02-2002
		NO 20004089 A	16-10-2000
		NZ 505250 A	25-10-2002
		PL 342430 A1	04-06-2001
		WO 9941254 A1	19-08-1999
		SK 12242000 A3	12-03-2001
		TR 200002380 T2	21-03-2001
		US 6369064 B1	09-04-2002
		ZA 9900942 A	17-08-1999
WO 9905143 A	04-02-1999	AT 251161 T	15-10-2003
		AU 745381 B2	21-03-2002
		AU 8370698 A	16-02-1999
		BR 9810802 A	12-09-2000
		CN 1270590 T	18-10-2000
		DE 69818668 D1	06-11-2003
		DK 996621 T3	02-02-2004
		EE 200000044 A	16-10-2000
		EP 0996621 A1	03-05-2000
		HU 0004333 A2	28-04-2001
		JP 2001510842 T	07-08-2001
		NO 20000312 A	21-03-2000
		NZ 502381 A	21-12-2001
		PL 338516 A1	06-11-2000
		WO 9905143 A1	04-02-1999
		SK 188199 A3	09-10-2000
		TR 200000197 T2	21-06-2000
		TW 530058 B	01-05-2003
		US 6251910 B1	26-06-2001
		ZA 9806050 A	06-04-1999

INTERNATIONAL SEARCH REPORT

 International Publication No
 PCT/IB 03/04188

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
JP 59062595	A	10-04-1984	JP 1697203 C	28-09-1992
			JP 3066310 B	16-10-1991
WO 9828300	A	02-07-1998	AT 213245 T	15-02-2002
			AU 5501598 A	17-07-1998
			DE 69710490 D1	21-03-2002
			DE 69710490 T2	24-10-2002
			EP 0946561 A1	06-10-1999
			JP 2001507023 T	29-05-2001
			WO 9828300 A1	02-07-1998
			US 6297232 B1	02-10-2001
WO 9735846	A	02-10-1997	AU 725254 B2	12-10-2000
			AU 2545397 A	17-10-1997
			CA 2249598 A1	02-10-1997
			EP 0901476 A1	17-03-1999
			JP 2000507552 T	20-06-2000
			NZ 331647 A	27-03-2000
			WO 9735846 A1	02-10-1997
			US 6258809 B1	10-07-2001
			US 6124300 A	26-09-2000
			ZA 9701896 A	07-09-1998
WO 9735539	A	02-10-1997	AU 2545897 A	17-10-1997
			BR 9708261 A	04-12-2001
			CA 2250241 A1	02-10-1997
			CN 1230184 A	29-09-1999
			CZ 9803040 A3	17-02-1999
			EE 9800329 A	15-06-1999
			EP 0935601 A2	18-08-1999
			HR 970173 A1	31-08-1999
			HU 9902340 A2	29-11-1999
			JP 2002515032 T	21-05-2002
			KR 2000005037 A	25-01-2000
			LT 98133 A , B	26-04-1999
			LV 12262 A	20-04-1999
			LV 12262 B	20-10-1999
			NO 984418 A	03-11-1998
			NZ 331874 A	27-03-2000
			PL 335258 A1	10-04-2000
			SI 9720026 A	30-04-1999
			SK 131798 A3	16-05-2000
			WO 9735539 A2	02-10-1997
			US 6448261 B1	10-09-2002
			US 6107300 A	22-08-2000
			ZA 9702497 A	25-09-1998