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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

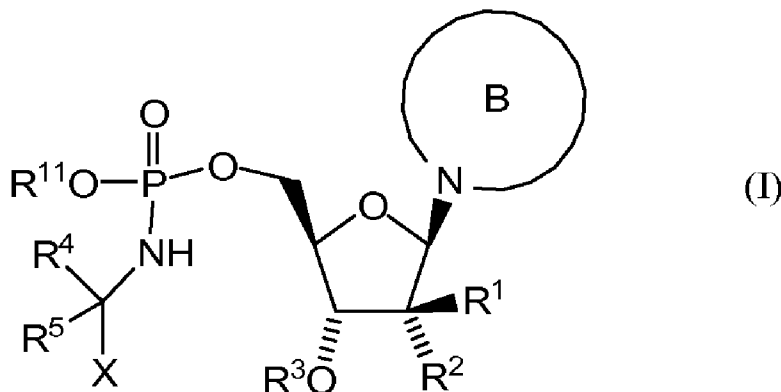
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(57) Abstract: A compound of formula (I) and pharmaceutically acceptable salts thereof; compositions containing it and its use in medicine, particularly for the treatment or inhibition of HCV infections, and processes for making it are disclosed.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/056128

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07H19/10 C07H19/20 C07H19/04 A61K31/706 A61K31/7064
 A61K31/7076 A61P31/14

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)
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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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/012078 A (MERCK & CO INC [US]; MACCOSS MALCOLM [US]; OLSEN DAVID B [US]) 2 February 2006 (2006-02-02) claims	1-15
Y	WO 2004/002422 A (IDENIX CAYMAN LTD; UNIV CAGLIARI [IT]; SOMMADOSSI JEAN-PIERRE [US]; LA) 8 January 2004 (2004-01-08) claims	1-15
X	WO 2006/065335 A (MERCK & CO INC [US]; MACCOSS MALCOLM [US]; OLSEN DAVID B [US]; LEONE J) 22 June 2006 (2006-06-22) claims page 8, lines 6-17	1-15

Further documents are listed in the continuation of Box C. 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	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 12 February 2010	Date of mailing of the international search report 18/02/2010
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Gohlke, Pascale
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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	WO 2005/012327 A (UNIV CARDIFF [GB]; MCGUIGAN CHRISTOPHER [GB]) 10 February 2005 (2005-02-10) claims; examples page 4, lines 20-23 -----	1-15
X	WO 2007/021610 A (MERCK & CO INC [US]; BUTORA GABOR [US]; KOEPLINGER KENNETH ALAN [US];) 22 February 2007 (2007-02-22) claims -----	1-15
X	GUNIC ET AL: "6-Hydrazinopurine 2'-methyl ribonucleosides and their 5'-monophosphate prodrugs as potent hepatitis C virus inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 17, no. 9, 3 April 2007 (2007-04-03), pages 2456-2458, XP022015324 ISSN: 0960-894X table 1 Schema 2 and 3 -----	1-15
Y	WO 2005/003147 A (PHARMASSET LTD [US]; CLARK JEREMY [US]) 13 January 2005 (2005-01-13) claims -----	1-15
X	EGRON D ET AL: "Anti-HIV pronucleotides: Decomposition pathways and correlation with biological activities" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 8, no. 9, 1 May 1998 (1998-05-01), pages 1045-1050, XP004137017 ISSN: 0960-894X the whole document In particular compounds 6, 9 and 12 -----	1-15
X	EGRON D ET AL: "S-Acyl-2-thioethyl Phosphoramidate Diester Derivatives as Mononucleotide Prodrugs" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 46, no. 21, 1 January 2003 (2003-01-01), pages 4564-4571, XP002519414 ISSN: 0022-2623 [retrieved on 2003-09-13] page 4565; figure 1 Scheme 1 -----	1-15
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/056128

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 2007/095269 A (MERCK & CO INC [US]; ANGELETTI P IST RICHERCHE BIO [IT]; MACCOSS MALCO) 23 August 2007 (2007-08-23) claims pages 44-49; tables 1,2 -----	9
E	WO 2008/085508 A (MERCK & CO INC [US]; ANGELETTI P IST RICHERCHE BIO [IT]; NARJES FRANK) 17 July 2008 (2008-07-17) the whole document -----	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/056128

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-15

directed to compounds of formula (I) wherein the amino group is substituted by $-C(R_4)(R_5)-C(O)-O-R_6$, pharmaceutical compositions comprising them, said compounds for use in therapy, the combination thereof with an inhibitor of HCV NS3 serine protease, the use thereof in a manufacture of a medicament and method of treatment comprising their administration.

1.1. claims: 1-15

directed to compounds of formula (I) wherein the amino group is substituted by $-C(R_4)(R_5)-C(R_{13})(R_{14})-O-C(O)-R_{12}$, pharmaceutical compositions comprising them, said compounds for use in therapy, the combination thereof with an inhibitor of HCV NS3 serine protease, the use thereof in a manufacture of a medicament and method of treatment comprising their administration.

1.2. claims: 9-15

directed to the specific compounds of formula (I) wherein the amino group is substituted by 1-(5-(1-propylbutyl)-oxadiazol-2-yl)-ethyl, pharmaceutical compositions comprising them, said compounds for use in therapy, the combination thereof with an inhibitor of HCV NS3 serine protease, the use thereof in a manufacture of a medicament and method of treatment comprising their administration.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/056128

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2006012078	A	02-02-2006	AU 2005267421	A1 02-02-2006
			CA 2571079	A1 02-02-2006
			EP 1773355	A2 18-04-2007
			JP 2008504265	T 14-02-2008
			US 2007265222	A1 15-11-2007
WO 2004002422	A	08-01-2004	AU 2003248748	A1 19-01-2004
			BR 0312278	A 19-06-2007
			CA 2489552	A1 08-01-2004
			CN 1678326	A 05-10-2005
			EP 1536804	A2 08-06-2005
			JP 2005533824	T 10-11-2005
			KR 20050035194	A 15-04-2005
			MA 27374	A1 01-06-2005
			MX PA04012802	A 19-04-2005
WO 2006065335	A	22-06-2006	AU 2005317081	A1 22-06-2006
			CA 2584367	A1 22-06-2006
			EP 1804812	A2 11-07-2007
			JP 2008517912	T 29-05-2008
			US 2008280842	A1 13-11-2008
WO 2005012327	A	10-02-2005	AU 2004261455	A1 10-02-2005
			CA 2518115	A1 10-02-2005
			EP 1646639	A2 19-04-2006
			JP 2006528162	T 14-12-2006
			MX PA05012606	A 08-02-2006
			NZ 541974	A 31-03-2009
			US 2006142238	A1 29-06-2006
WO 2007021610	A	22-02-2007	AU 2006280175	A1 22-02-2007
			CA 2618560	A1 22-02-2007
			EP 1915054	A2 30-04-2008
			JP 2009513564	T 02-04-2009
			US 2009099126	A1 16-04-2009
WO 2005003147	A	13-01-2005	AU 2004253860	A1 13-01-2005
			BR PI0410846	A 27-06-2006
			CA 2527657	A1 13-01-2005
			CN 1816558	A 09-08-2006
			EP 1633766	A2 15-03-2006
			JP 2006526629	T 24-11-2006
			KR 20060020649	A 06-03-2006
			MX PA05012788	A 22-02-2006
			NZ 543867	A 31-05-2009
			RU 2358979	C2 20-06-2009
			ZA 200509521	A 25-10-2006
WO 2007095269	A	23-08-2007	AU 2007215114	A1 23-08-2007
			CA 2637879	A1 23-08-2007
			EP 1987050	A2 05-11-2008
			JP 2009526850	T 23-07-2009
WO 2008085508	A	17-07-2008	AU 2007342367	A1 17-07-2008
			CA 2673649	A1 17-07-2008
			EP 2124555	A2 02-12-2009