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C07H 19/06 (2006.01) **A61P 31/14** (2006.01)

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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, 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, 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.

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Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

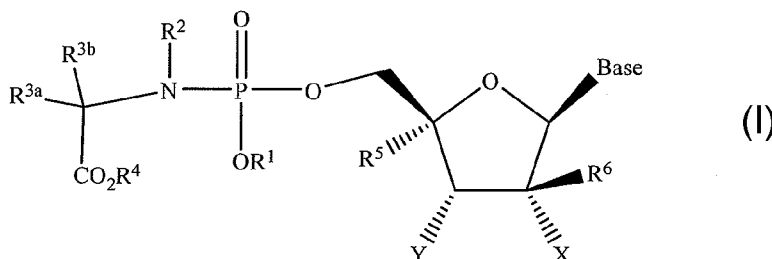
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(88) **Date of publication of the international search report:**
20 May 2010

(54) Title: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS



(57) Abstract: Disclosed herein are phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections in mammals, which is a compound, its stereoisomer, salt (acid or basic addition salt), hydrate, solvate, or crystalline form thereof, represented by the following structure: Also disclosed are methods of treatment, uses, and processes for preparing each of which utilize the compound represented by formula (I).

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/058183

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07H19/10 C07H19/20 C07H19/04 C07H19/06 A61K31/7064
A61K31/7076 A61K31/706 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)

C07H 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 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) cited in the application claims 2-16	1,2,4,6, 8,10,12
X	WO 2006/065335 A (MERCK & CO INC [US]; MACCOSS MALCOLM [US]; OLSEN DAVID B [US]; LEONE J) 22 June 2006 (2006-06-22) cited in the application claims 3-6 page 8, lines 6-17 ----- -/--	1,2,4,6, 8,10,12

☒ 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

"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

11 February 2010

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31/03/2010

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/058183

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>GUNIC ET AL: "6-Hydrazinopurine 2'-methyl ribonucleosides and their 5'-monophosphate prodrugs as potent hepatitis C virus inhibitors"</p> <p>BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 17, no. 9, 14 February 2007 (2007-02-14), pages 2456-2458, XP022015324</p> <p>Online</p> <p>ISSN: 0960-894X</p> <p>compounds 34A-41A</p> <p>compounds 34B-42B</p> <p>abstract</p>	1,2,4,6, 8,10,12
X	<p>US 6 475 985 B1 (WAGNER CARSTON R [US] ET AL) 5 November 2002 (2002-11-05)</p> <p>* Compound of formula V *</p> <p>figures 5,8</p>	1,2,4,6, 8,10,12
X	<p>WO 03/000713 A (GLAXO GROUP LTD [GB]; HOWES PETER DAVID [GB]; SLATER MARTIN JOHN [GB]) 3 January 2003 (2003-01-03)</p> <p>* Compound of formula (I) *</p> <p>page 3</p> <p>page 7, lines 34-42</p>	1,2,4,6, 8,10,12
X	<p>WO 2005/012327 A (UNIV CARDIFF [GB]; MCGUIGAN CHRISTOPHER [GB])</p> <p>10 February 2005 (2005-02-10)</p> <p>cited in the application</p> <p>claims 1,7,17</p> <p>page 4, lines 20-23</p>	1,2,4,6, 8,10,12
X	<p>WO 2007/020193 A (HOFFMANN LA ROCHE [CH]; KLUMPP KLAUS [US]; MARTIN JOSEPH ARMSTRONG [GB]) 22 February 2007 (2007-02-22)</p> <p>claims</p>	1,2,4,6, 8,10,12
Y	<p>US 2006/241064 A1 (ROBERTS CHRISTOPHER D [US] ET AL ROBERTS CHRISTOPHER D [US] ET AL) 26 October 2006 (2006-10-26)</p> <p>cited in the application</p> <p>claims 19-37</p> <p>claim 42; page 69</p> <p>pages 60-62; examples 6,11-15</p> <p>page 45, paragraphs 160,161</p>	1,2,4,6, 8,10,12
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/058183

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/003147 A (PHARMASSET LTD [US]; CLARK JEREMY [US]) 13 January 2005 (2005-01-13) claims 6-8,4-15,21-23,25-,26,28-30,36-38 claims 40,41,43-45,51-53,55-60,66-68 claims 1-71,73-75,81-83,85,86,88-90,96,97 claims 100,101,103-106,108-110,112-114 claims 116-118, 120-121, 126-127, 129 -----	1,2,4,6, 8,10,12
P,X	WO 2007/095269 A (MERCK & CO INC [US]; ANGELETTI P IST RICHERCHE BIO [IT]; MACCOSS MALCO) 23 August 2007 (2007-08-23) cited in the application claims -----	1,2,4,6, 8,10,12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/058183

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.:

see annex

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, 2, 4, 6, 8, 10, 12

directed to compounds of formula (I) wherein R6 is CH3, X is F, R5 is H and the specific 2'-deoxy-2'-fluoro-2'-C-methyl-nucleoside phosphoramidate derivatives according to claim 2 except compound 9, pharmaceutical compositions comprising them, the use thereof in a manufacture of a medicament, method of treatment comprising their administration and the process for their preparation.

2. claims: 1, 3, 5, 7, 9, 11

directed to compounds of formula (I) wherein R6 is F, X is F and R5 is H, pharmaceutical compositions comprising them, the use thereof in a manufacture of a medicament, method of treatment comprising their administration and the process for their preparation.

3. claims: 1, 3, 5, 7, 9, 11

directed to compounds of formula (I) wherein R6 is H, X is OH and R5 is H, pharmaceutical compositions comprising them, the use thereof in a manufacture of a medicament, method of treatment comprising their administration and the process for their preparation.

4. claims: 1, 3, 5, 7, 9, 11

directed to compounds of formula (I) wherein R5 is other than H, pharmaceutical compositions comprising them, the use thereof in a manufacture of a medicament, method of treatment comprising their administration and the process for their preparation.

5. claims: 2, 4, 6, 8, 10, 12

Claims 2, 4, 6, 8, 10 and 12 directed to compound 9 N4-(N,N-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methyl cytidine, pharmaceutical compositions comprising it, the use thereof in a manufacture of a medicament, method of treatment comprising its administration and the process for its preparation.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/058183

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2006012078	A	02-02-2006	AU 2005267421 A1 CA 2571079 A1 EP 1773355 A2 JP 2008504265 T US 2007265222 A1	02-02-2006 02-02-2006 18-04-2007 14-02-2008 15-11-2007
WO 2006065335	A	22-06-2006	AU 2005317081 A1 CA 2584367 A1 EP 1804812 A2 JP 2008517912 T US 2008280842 A1	22-06-2006 22-06-2006 11-07-2007 29-05-2008 13-11-2008
US 6475985	B1	05-11-2002	NONE	
WO 03000713	A	03-01-2003	EP 1404694 A1 JP 2004534830 T US 2005009775 A1	07-04-2004 18-11-2004 13-01-2005
WO 2005012327	A	10-02-2005	AU 2004261455 A1 CA 2518115 A1 EP 1646639 A2 JP 2006528162 T MX PA05012606 A NZ 541974 A US 2006142238 A1	10-02-2005 10-02-2005 19-04-2006 14-12-2006 08-02-2006 31-03-2009 29-06-2006
WO 2007020193	A	22-02-2007	CA 2618335 A1 CN 101287472 A EP 1928475 A2 JP 2009504704 T	22-02-2007 15-10-2008 11-06-2008 05-02-2009
US 2006241064	A1	26-10-2006	NONE	
WO 2005003147	A	13-01-2005	AU 2004253860 A1 BR PI0410846 A CA 2527657 A1 CN 1816558 A EP 1633766 A2 JP 2006526629 T KR 20060020649 A MX PA05012788 A NZ 543867 A RU 2358979 C2 ZA 200509521 A	13-01-2005 27-06-2006 13-01-2005 09-08-2006 15-03-2006 24-11-2006 06-03-2006 22-02-2006 31-05-2009 20-06-2009 25-10-2006
WO 2007095269	A	23-08-2007	AU 2007215114 A1 CA 2637879 A1 EP 1987050 A2 JP 2009526850 T	23-08-2007 23-08-2007 05-11-2008 23-07-2009