



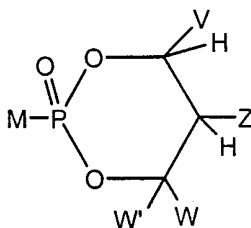
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07H 19/20, 19/10, 19/207, C07F 9/6571, 9/6574, A61K 31/70	A3	(11) International Publication Number: WO 99/45016 (43) International Publication Date: 10 September 1999 (10.09.99)
<p>(21) International Application Number: PCT/US99/04908</p> <p>(22) International Filing Date: 5 March 1999 (05.03.99)</p> <p>(30) Priority Data: 60/077,164 6 March 1998 (06.03.98) US 60/077,165 6 March 1998 (06.03.98) US</p> <p>(71) Applicant: METABASIS THERAPEUTICS, INC. [US/US]; 9390 Towne Centre Drive, San Diego, CA 92121 (US).</p> <p>(72) Inventors: ERION, Mark, D.; 13455 Mango Drive, Del Mar, CA 92014 (US). REDDY, K., Raja; 4146 Federman Lane, San Diego, CA 92130 (US). ROBINSON, Edward, D.; 3567 Tony Drive, San Diego, CA 92122 (US).</p> <p>(74) Agents: WOLFF, Jessica, R. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 15 June 2000 (15.06.00)</p>	

(54) Title: NOVEL PRODRUGS FOR PHOSPHORUS-CONTAINING COMPOUNDS

(57) Abstract

Prodrugs of formula (I), their uses, their intermediates, and their method of manufacture are described, wherein V is selected from the group consisting of -H, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or together V and Z are connected via 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, or aryloxy, attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or together V and Z are connected via 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the



(I)

beta and gamma position to the oxygen attached to the phosphorus; or together V and W are connected via 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, alkoxy, or aryloxy, attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; W and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³, -CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR², -CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²)OH, -CH(C=CR²)OH, -R², -NR², -OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl, -(CH₂)_p-OR², and -(CH₂)_p-SR²; R² is an R³ or -H; R³ is selected from the group consisting of alkyl, aryl, aralkyl, and alicyclic; and R⁹ is selected from the group consisting of alkyl, aralkyl, and alicyclic; p is an integer from 2 to 3; with the provisos that a) V, Z, W, and W' are not all -H; and b) when z is -R², then at least one of V and W is not -H, or -R⁹; and M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, or P₃O₉⁴⁻ is biologically active *in vivo*, and that is attached to the phosphorus in formula (I) via a carbon, oxygen, or nitrogen atom; and pharmaceutically acceptable prodrugs and salts thereof.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/04908

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07H19/20 C07H19/10 C07H19/207 C07F9/6571 C07F9/6574 A61K31/70				
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 6 C07H C07F 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)				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	EP 0 481 214 A (SQUIBB BRISTOL MYERS CO) 22 April 1992 (1992-04-22) page 2, line 1 - line 8 page 9, line 25 - line 45 page 5, line 4 - line 5 page 6, line 21 - line 45 --- -/--	1,135, 136,140, 142,143, 152,154, 156, 177-183, 188-191, 211,212, 215,219, 220,243, 248,263		
<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 :				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> *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 </td> <td style="width: 50%; border: none; vertical-align: top;"> *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 </td> </tr> </table>			*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
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 <p style="text-align: center; font-size: 1.2em;">2 March 2000</p>	Date of mailing of the international search report <p style="text-align: center; font-size: 1.2em;">05. 04. 2000</p>			
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 <p style="text-align: center; font-size: 1.2em;">Held, P</p>			

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US 99/04908

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 353 692 A (NISSAN CHEMICAL IND LTD) 7 February 1990 (1990-02-07) page 3 -page 4 table 1 (see pages 12, 15, 16, 18-20, 22-32) ---	73,76, 77,95, 97,102, 105,135
X	WO 97 03679 A (CEPHALON INC) 6 February 1997 (1997-02-06) page 4 -page 5 claim 1 ---	1,135, 142,143, 215
X	PREDVODITELEV D. A. ET AL: "Glycero-2-hydroxymethylene phosphates" JOURNAL OF ORGANIC CHEMISTRY OF THE USSR (ENGLISH TRANSLATION), vol. 13, 1977, pages 1489-1492, XP002112973 page 1489 page 1491, paragraph 3 ---	132
X	PREDVODITELEV D. A. ET AL.: "Synthesis of lipids and their models on the basis of glycerol alkylene phosphites. V. Cyclic phosphatidylglycerol and phosphatidylhydroxyhomocholine" JOURNAL OF ORGANIC CHEMISTRY OF THE USSR (ENGLISH TRANSLATION), vol. 17, 1981, pages 1156-1165, XP002112974 pages 1160 and 1164, compound XVI ---	132
X	US 3 018 302 A (BIELEFELD H. A. ET AL.) 23 January 1962 (1962-01-23) example 8 ---	133
X	EP 0 180 276 A (OCE ANDENO BV) 7 May 1986 (1986-05-07) table 1 claim 1 ---	135
A	EP 0 338 372 A (AMERICAN CYANAMID CO) 25 October 1989 (1989-10-25) page 2 -page 3 page 43; examples 45,46 --- -/--	1-264

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/04908

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FARQUHAR D. ET AL.: "5'-4-(Pivaloyloxy)-1,3,2-dioxaphosphorin an-2-yl-2'-deoxy-5-fluorouridine: a membrane-permeating prodrug of 5-fluoro-2'-deoxyuridylic acid (FdUMP)" JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, 1995, pages 488-495, XP002112975 page 488 - page 489: introduction page 489, see scheme 2 ---	1-264
X	WO 96 01267 A (SOHDA TAKASHI ;ODA TSUNEO (JP); TAKEDA CHEMICAL INDUSTRIES LTD (JP) 18 January 1996 (1996-01-18) page 2, line 18 -page 3, line 19 pages 74-76, tables 8-10, examples 50, 51, 60, 64, 67, 71 and 75 ---	1,135
A	CHEMICAL ABSTRACTS, vol. 89, no. 17, 23 October 1978 (1978-10-23) Columbus, Ohio, US; abstract no. 146864, HILLERS, S. ET AL: "Analog of pyrimidinemono- and polynucleotides. VI. Phosphates of 1-(1,4-dihydroxy-2-pentyl)thymine and 1-(1,3-dihydroxy-2-propyl)uracil" XP002132078 abstract & KHIM. GETEROTSIKL. SOEDIN. (1978), (5), 678-83 , ---	1-264
A	EP 0 161 955 A (MERCK & CO INC) 21 November 1985 (1985-11-21) --- page 1 -page 2 examples 14,15 ---	1,107, 121,135, 143,215, 248
A	NIFANTYEV, E. E. ET AL: "Synthesis and structure of some stable phospholane-phospholanes" PHOSPHORUS, SULFUR SILICON RELAT. ELEM. (1996), 113(1-4), 1-13 , XP000884616 schemes 6 and 7 ---	121,132, 133,135
A	NEIDLEIN, RICHARD ET AL: "Mild preparation of '1-(benzyloxy)iminoalkylphosphonic dichlorides: application to the synthesis of cyclic phosphonic diesters and cyclic monoester amides" HETEROCYCLES (1993), 35(2), 1185-203 , XP002132077 schemes 1-3 ---	121,135

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/04908

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	<p>WO 98 39343 A (METABASIS THERAPEUTICS INC) 11 September 1998 (1998-09-11)</p> <p>page 15, line 6 -page 16, line 29 claims 1,43 page 5, line 20 -page 6, line 10 ---</p>	<p>1, 10, 13-15, 18-21, 24-27, 29, 30, 42-45, 55, 57, 59, 68, 73, 79, 89, 95, 116, 121, 134, 135, 142, 143, 155, 184, 215, 221, 230, 236, 257, 262, 263</p>
P, X	<p>WO 98 39344 A (METABASIS THERAPEUTICS INC) 11 September 1998 (1998-09-11)</p> <p>page 15, line 17 -page 17, line 10 claim 1 -----</p>	<p>1, 10, 13-15, 18-21, 24-27, 29, 30, 42-45, 55, 57, 59, 67, 73, 79, 89, 95, 116, 121, 134, 135, 142, 143, 154, 184, 209, 215, 221, 230, 236, 257, 262, 263</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/04908

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.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-120, 134, 142 and 211-261 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.:
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 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:

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.:
1-25 (partially), 26-30, 35-43 (partially), 44-49, 51-54 (partially), 55-59, 60-167 (partially), 168-172, 177-185 (partially), 186-191, 193-196 (partially), 197-201, 202-264 (partially)
- 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

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

1. Claims: 1-23 (partially), 35 (partially),
38-41 (partially), 46-49, 69-165 (partially),
177-183 (partially), 188-191, 211-264 (partially).

Cyclic pro-drugs of formula (I) when V is hydrogen.

2. Claims: 1-23 (partially), 35-41 (partially),
69-165 (partially), 177-183 (partially),
211-264 (partially).

Cyclic pro-drugs of formula (I) when V is alkyl, aralkyl,
1-alkenyl or 1-alkynyl.

3. Claims: 1-23 (partially), 35-41 (partially),
69-165 (partially), 177-183 (partially),
211-264 (partially).

Cyclic pro-drugs of formula (I) when V is alicyclic.

4. Claims: 1-25 (partially), 26-30, 35-43 (partially), 44, 45,
51-54 (partially), 55-59, 60-167 (partially),
168-172, 177-185 (partially), 186, 187,
193-196 (partially), 197-201, 202-264 (partially).

Cyclic pro-drugs of formula (I) when V is (substituted) aryl
or (substituted) heteroaryl.

5. Claims: 1-24 (partially), 31, 32, 35-41 (partially),
69-166 (partially), 173, 174, 177-183 (partially),
211-264 (partially).

Cyclic pro-drugs of formula (I) when together V and Z are
connected via 3-5 atoms to form a cyclic group, optionally
containing 1 heteroatom, substituted with hydroxy, acyloxy,
alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a
carbon that is three atoms from an oxygen attached to the
phosphorus OR V and Z are connected via 3-5 atoms to form a
cyclic group, optionally containing 1 heteroatom, that is
fused to an aryl group at the beta and gamma position to the
oxygen attached to the phosphorus.

6. Claims: 1-24 (partially), 33, 34, 35-41 (partially), 50,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

69-166 (partially), 175, 176, 177-183 (partially),
192, 211-264 (partially).

Cyclic pro-drugs of formula (I) when together V and W are connected via 3-5 atoms to form an optionally cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy-carbonyloxy, alkylthiocarbonyloxy, and aryloxy-carbonyloxy, attached to a carbon that is three atoms from an oxygen attached to the phosphorus.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/04908

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0481214 A	22-04-1992	AT 167679 T	15-07-1998
		CA 2051239 A	15-03-1992
		DE 69129650 D	30-07-1998
		DE 69129650 T	25-03-1999
		ES 2118069 T	16-09-1998
		HK 1010053 A	11-06-1999
		JP 4230694 A	19-08-1992
		US 5663159 A	02-09-1997
		US 5792756 A	11-08-1998
		EP 0353692 A	07-02-1990
CA 1334752 A	14-03-1995		
DE 68924456 D	09-11-1995		
DE 68924456 T	30-05-1996		
EP 0655455 A	31-05-1995		
US 5304550 A	19-04-1994		
US 5508403 A	16-04-1996		
US 5130303 A	14-07-1992		
JP 2138221 A	28-05-1990		
JP 2850376 B	27-01-1999		
WO 9703679 A	06-02-1997	US 5639732 A	17-06-1997
		AU 6458396 A	18-02-1997
		CA 2226414 A	06-02-1997
		EP 0871454 A	21-10-1998
		JP 11509231 T	17-08-1999
US 3018302 A	23-01-1962	BE 554888 A	
		BE 563332 A	
		CH 361279 A	
		CH 369451 A	
		CH 370406 A	
		DE 1054997 B	
		DE 1057119 B	
		DE 1116672 B	
		FR 75178 E	08-09-1961
		FR 75308 E	11-10-1961
		FR 1246708 A	10-02-1961
		GB 812651 A	
		GB 853044 A	
		NL 99649 C	
		NL 99688 C	
		NL 222157 A	
		US 3074992 A	22-01-1963
EP 0180276 A	07-05-1986	NL 8403224 A	16-05-1986
		ES 548135 A	16-11-1986
		ES 554328 A	01-04-1987
		JP 1931268 C	12-05-1995
		JP 6062652 B	17-08-1994
		JP 61103886 A	22-05-1986
		US 4814477 A	21-03-1989
EP 0338372 A	25-10-1989	JP 1311091 A	15-12-1989
		US 5212291 A	18-05-1993
WO 9601267 A	18-01-1996	AU 2808495 A	25-01-1996
		CA 2191980 A	18-01-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No PCT/US 99/04908

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9601267 A		CN 1151744 A EP 0769015 A JP 8073476 A US 5716944 A	11-06-1997 23-04-1997 19-03-1996 10-02-1998
EP 0161955 A	21-11-1985	US 4579849 A JP 60228480 A	01-04-1986 13-11-1985
WO 9839343 A	11-09-1998	AU 6691498 A EP 0970095 A	22-09-1998 12-01-2000
WO 9839344 A	11-09-1998	AU 6452098 A	22-09-1998