US007390791B2

(12) **United States Patent**
Becker et al.

(10) **Patent No.: US 7,390,791 B2**
(45) **Date of Patent: Jun. 24, 2008**

(54) **PRODRUGS OF PHOSPHONATE NUCLEOTIDE ANALOGUES**

(75) Inventors: **Mark W. Becker**, Belmont, CA (US); **Harlan H. Chapman**, La Honda, CA (US); **Tomas Cihlar**, Foster City, CA (US); **Eugene J. Eisenberg**, San Carlos, CA (US); **Gong-Xin He**, Fremont, CA (US); **Michael R. Kernan**, Pacifica, CA (US); **William A. Lee**, Los Altos, CA (US); **Ernest J. Prisbe**, Los Altos, CA (US); **John C. Rohloff**, Mountain View, CA (US); **Mark L. Sparacino**, Morgan Hill, CA (US)

(73) Assignee: **Gilead Sciences, Inc.**, Foster City, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 291 days.

(21) Appl. No.: **10/798,692**

(22) Filed: **Mar. 11, 2004**

(65) **Prior Publication Data**

US 2005/0009043 A1 Jan. 13, 2005

Related U.S. Application Data

(63) Continuation of application No. 10/354,207, filed on Jan. 28, 2003, now abandoned, which is a continuation of application No. 09/909,560, filed on Jul. 20, 2001, now abandoned.

(60) Provisional application No. 60/220,021, filed on Jul. 21, 2000.

(51) **Int. Cl.**
A01N 43/48 (2006.01)
A61K 3/1675 (2006.01)
C07F 9/6512 (2006.01)

(52) **U.S. Cl.** **514/44**; 514/7; 514/81

(58) **Field of Classification Search** 435/4, 435/7.1, 9.1; 514/44, 7, 81, 85
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,053,215	A	10/1991	Rand et al.
5,413,996	A	5/1995	Bodor
5,591,851	A	1/1997	Alexander
5,624,894	A	4/1997	Bodor
5,627,165	A	5/1997	Glazier
5,656,745	A	8/1997	Bischofberger et al.
5,663,159	A	9/1997	Starrett, Jr. et al.
5,717,095	A	2/1998	Arimilli et al.
5,756,486	A	5/1998	Alexander et al.
5,792,756	A	8/1998	Starrett, Jr. et al.
5,798,340	A	8/1998	Bischofberger et al.
5,886,179	A	3/1999	Arimilli et al.
5,977,061	A	11/1999	Holy et al.
5,977,089	A	11/1999	Arimilli et al.
6,169,078	B1	1/2001	Hughes et al.
6,225,460	B1	5/2001	Bischofberger et al.
6,245,750	B1	6/2001	Shepard
6,339,151	B1	1/2002	Shepard et al.
6,348,185	B1	2/2002	Piwnica-Worms
6,355,629	B2	3/2002	Kozak
6,436,437	B1	8/2002	Yatvin et al.
2001/0031873	A1	10/2001	Greenwald et al.
2001/0034440	A1	10/2001	Shepard et al.
2002/0120100	A1	8/2002	Bonny

FOREIGN PATENT DOCUMENTS

EP	0 336 364 A2	10/1989
EP	0 481 214 A1 *	4/1992
WO	WO 95/07920	3/1995
WO	WO 96/29336	9/1996
WO	WO 96/33200	10/1996
WO	WO 96/37503	11/1996
WO	WO 97/24361	7/1997
WO	WO 99/37753	7/1999
WO	WO 00/18775	4/2000
WO	WO 0208241 A2 *	1/2002

OTHER PUBLICATIONS

Aarons et al., "Pharmacokinetic Evaluation of Site-Specific Drug Delivery Systems", 12:121-126, Novel Drug Delivery and Its Therapeutic Application (John Wiley & Sons), 1989.

Banerjee et al., "Design of Prodrugs Based on Enzyme-Substrate Specificity", Chapter 2, pp. 118-121, Design of Prodrugs, 1985.

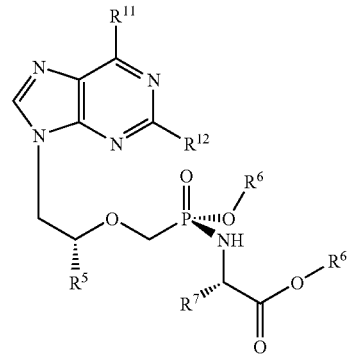
(Continued)

Primary Examiner—Jon Weber
Assistant Examiner—Kailash Srivastava
(74) *Attorney, Agent, or Firm*—Max D. Hensley

(57) **ABSTRACT**

A novel method has led to the identification of novel mixed ester-amidates of PMPA for retroviral or hepadnaviral therapy, including compounds of structure (5a)

(5a)



having substituent groups as defined herein. Compositions of these novel compounds in pharmaceutically acceptable excipients and their use in therapy and prophylaxis are provided.

13 Claims, 3 Drawing Sheets