US007803788B2

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

(10) **Patent No.: US 7,803,788 B2**
(45) **Date of Patent: Sep. 28, 2010**

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

(75) Inventors: **Mark W. Becker**, Redwood City, 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**, Cupertino, 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**, Boulder, CO (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 197 days.

(21) Appl. No.: **12/110,829**

(22) Filed: **Apr. 28, 2008**

(65) **Prior Publication Data**

US 2008/0227754 A1 Sep. 18, 2008

**Related U.S. Application Data**

(63) Continuation of application No. 10/798,692, filed on Mar. 11, 2004, now Pat. No. 7,390,791, which is a 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.**
***A61K 31/675*** (2006.01)
***A61P 31/12*** (2006.01)

(52) **U.S. Cl.** ..... **514/81**; 514/7; 514/85; 435/4; 435/9.1

(58) **Field of Classification Search** ..... 435/4, 435/9.1; 514/7, 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. |

(Continued)

FOREIGN PATENT DOCUMENTS

| | | |
|---|---|---|
| EP | 0336364 | 10/1989 |
| EP | 0481214 | 4/1992 |
| WO | WO-9200988 | 1/1992 |
| WO | WO-9507920 | 3/1995 |
| WO | WO-9629336 | 9/1996 |
| WO | WO-9633200 | 10/1996 |
| WO | WO-9637503 | 11/1996 |
| WO | WO-9724361 | 7/1997 |
| WO | WO-9937753 | 7/1999 |
| WO | WO-0018775 | 4/2000 |
| WO | WO-0208241 | 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.

Alexander et al. (1994) "Prodrugs of Analogs of Nucleic acid components," *Collect Czech Chem Comm.* 59:2127-2165.

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

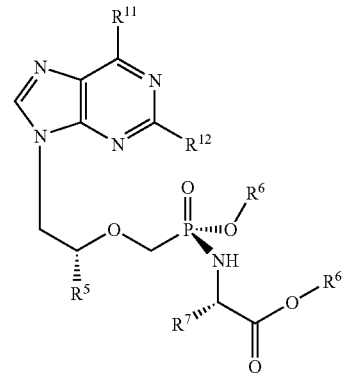
(Continued)

*Primary Examiner*—Jon P Weber
*Assistant Examiner*—Kailash C Srivastava
(74) *Attorney, Agent, or Firm*—Allan N. Kutzenco

(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.

**10 Claims, 3 Drawing Sheets**