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(54) **TENOFOVIR ALAFENAMIDE HEMIFUMARATE**

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(58) **Field of Classification Search**

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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,663,159	A	9/1997	Starrett, Jr. et al.	
5,798,340	A	8/1998	Bischofberger et al.	
7,390,791	B2	6/2008	Becker et al.	
7,803,788	B2	9/2010	Becker et al.	
2009/0286981	A1 *	11/2009	Vasireddy et al.	544/244

FOREIGN PATENT DOCUMENTS

WO	98/04569	2/1998
WO	02/08241	1/2002

OTHER PUBLICATIONS

Jones, et al., "Minireview: nucleotide prodrugs", Antiviral Research, vol. 27 (1995) 1-17.

McIntee, et al., "Probing the Mechanism of Action and Decomposition of Amino Acid Phosphomonoester Amidates of Antiviral Nucleoside Prodrugs", J. Med. Chem., vol. 40 (1997) 3323-31.

Chapman, et al., "Practical Synthesis, Separation, and Stereochemical Assignment of the PMPA Pro-Drug GS-7340", Nucleosides, Nucleotides & Nucleic Acids, vol. 20, No. 4-7 (2001) 621-28.

Chapman, et al., "Purification of PNPA Amidate Prodrugs by SMB Chromotagraphy and X-Ray Crystallography of the Diastereomerically Pure GS-7340", Nucleosides, Nucleotides & Nucleic Acids, vol. 20, No. 4-7 (2001) 1085-90.

Non-Final Office Action for U.S. Appl. No. 13/118,122, mailed Feb. 19, 2014, 23 pages.

Supplemental Notice of Allowance for U.S. Appl. No. 12/857,238, mailed Feb. 25, 2014, 2 pages.

Non-Final Office Action for U.S. Appl. No. 14/134,933, mailed Feb. 25, 2014, 7 pages.

Non-Final Office Action for U.S. Appl. No. 14/033,245, mailed Feb. 26, 2014, 11 pages.

Patent Owner's Request for Rehearing Under 37 C.F.R. § 41.79, in Inter Partes Npls Reexamination of U.S. Patent No. 7,714,747, Control No. 95/001,517, filed Feb. 14, 2014, 11 pages.

Statement of Opposition for Venezuelan Patent Application No. 2012-001018, filed on Aug. 15, 2012, 27 pages.

* cited by examiner

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(57) **ABSTRACT**

A hemifumarate form of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl] adenine (tenofovir alafenamide), and antiviral therapy using tenofovir alafenamide hemifumarate (e.g., anti-HIV and anti-HBV therapies).

31 Claims, 4 Drawing Sheets