US008106183B2

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

(10) **Patent No.: US 8,106,183 B2**
(45) **Date of Patent: *Jan. 31, 2012**

(54) **PROCESS FOR PREPARING AN A_{2A}-ADENOSINE RECEPTOR AGONIST AND ITS POLYMORPHS**

(75) Inventors: **Jeff Zablocki**, Mountain View, CA (US); **Elfaith Elzein**, Fremont, 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 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/765,623**

(22) Filed: **Apr. 22, 2010**

(65) **Prior Publication Data**

US 2010/0267953 A1 Oct. 21, 2010

Related U.S. Application Data

(63) Continuation of application No. 11/701,699, filed on Feb. 2, 2007, now Pat. No. 7,732,595.

(60) Provisional application No. 60/801,857, filed on May 18, 2006, provisional application No. 60/765,114, filed on Feb. 3, 2006.

(51) **Int. Cl.**
C07H 19/167 (2006.01)

(52) **U.S. Cl.** **536/27.11**; 536/27.61

(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,845,770	A	11/1974	Theeuwes et al.	
4,089,959	A	5/1978	Diamond	
4,120,947	A	10/1978	Diamond	
4,325,956	A	4/1982	Kjellin et al.	
4,326,525	A	4/1982	Swanson et al.	
4,593,095	A	6/1986	Snyder et al.	
4,696,932	A	9/1987	Jacobson et al.	
4,804,664	A	2/1989	Kjellin et al.	
4,902,514	A	2/1990	Barclay et al.	
4,956,345	A	9/1990	Miyasaka et al.	
4,968,697	A *	11/1990	Hutchison	514/46
4,992,445	A	2/1991	Lawter et al.	
5,001,139	A	3/1991	Lawter et al.	
5,032,252	A	7/1991	Owen et al.	
5,070,877	A	12/1991	Mohiuddin et al.	
5,189,027	A	2/1993	Miyasita et al.	
5,270,304	A	12/1993	Kogi et al.	
5,459,254	A	10/1995	Yamaguchi et al.	
5,516,894	A	5/1996	Reppert	
5,593,975	A	1/1997	Cristalli	
5,616,345	A	4/1997	Geoghegan et al.	
5,641,784	A	6/1997	Kufner-Muhl et al.	
5,646,156	A	7/1997	Jacobsen et al.	
5,670,498	A	9/1997	Suzuki et al.	
5,703,085	A	12/1997	Suzuki et al.	
5,704,491	A	1/1998	Graves	
5,705,491	A	1/1998	Yamada	
5,770,716	A	6/1998	Khan et al.	
5,776,960	A	7/1998	Oppong et al.	
5,780,481	A	7/1998	Jacobson et al.	
5,854,081	A	12/1998	Linden et al.	
5,877,180	A	3/1999	Linden et al.	
5,939,543	A	8/1999	Morozumi et al.	
6,026,317	A	2/2000	Verani	
6,117,878	A	9/2000	Linden	
6,214,807	B1	4/2001	Zablocki et al.	
6,294,522	B1	9/2001	Zablocki et al.	
6,322,771	B1	11/2001	Linden et al.	
6,368,573	B1	4/2002	Leung	
6,387,913	B1	5/2002	Mustafa	
6,403,567	B1 *	6/2002	Zablocki et al.	514/46
6,448,235	B1	9/2002	Linden	
6,514,949	B1	2/2003	Linden et al.	
6,552,023	B2	4/2003	Zablocki et al.	
6,599,283	B1	7/2003	Marzilli et al.	
6,605,597	B1	8/2003	Zablocki et al.	
6,642,210	B1 *	11/2003	Zablocki et al.	514/46
6,670,334	B2	12/2003	Linden et al.	
6,677,336	B2	1/2004	Zablocki et al.	
6,770,634	B1	8/2004	Zablocki et al.	
6,825,349	B2	11/2004	Kalla et al.	
6,855,818	B2	2/2005	Zablocki et al.	
6,916,804	B2	7/2005	Castelhano et al.	
6,977,300	B2	12/2005	Kalla et al.	
6,995,148	B2	2/2006	Jones et al.	
7,109,180	B2	9/2006	Zablocki et al.	
7,109,203	B2	9/2006	Hart et al.	
7,125,993	B2	10/2006	Elzein et al.	

(Continued)

FOREIGN PATENT DOCUMENTS

CA	965411	4/1975

(Continued)

OTHER PUBLICATIONS

Bergmann et al., "Oxidation of Hypoxanthines, Bearing 8-Aryl or 8-Pyridyl Substituents, by Bovine Milk Xanthine Oxidase,", Biochimica et Biophysica Acta, vol. 484, No. 2, pp. 275-289 (1977).

Birdsall et al., "Purine N-Oxides-XL The 3-Acyloxypurine 8-Substitution Reaction: Scope: Syntheses of 8-Substituted Xanthines and Guanines," Tetrahedron, vol. 27, pp. 5969-5978 (1971).

Blackburn et al., "Adenosine Mediates IL-13-Induced Inflammation and Remodeling in the Lung and interacts in an IL13-Adenosine Amplification Pathway," J. Clin. Invest. vol. 112, No. 3, pp. 332-344 (2003).

Bruns, "Adenosine Antagonism by Purines, Pteridines and Benzopteridines in Human Fibroblasts," Biochemical Pharmacology, vol. 30, No. 4, pp. 325-333 (1981).

Buckle et al., "Inhibition of Cyclic Nucleotide Phosphodiesterase by Derivatives of 1,3-Bis(cyclopropylmethyl)xanthine," J. Med. Chem., vol. 37, pp. 476-485 (1994).

(Continued)

Primary Examiner — Lawrence E Crane
(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(57) **ABSTRACT**

Disclosed is a synthesis suitable for large scale manufacture of an A_{2A}-adenosine receptor agonist, and also relates to polymorphs of that compound, and to methods of isolating a specific polymorph.

9 Claims, 5 Drawing Sheets