US006962940B2

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

(10) **Patent No.: US 6,962,940 B2**
(45) **Date of Patent: Nov. 8, 2005**

(54) **(+)-2-[1-(3-ETHOXY-4-METHOXYPHENYL)-2-METHYLSULFONYLETHYL]-4-ACETYLAMINOISOINDOLINE-1,3-DIONE: METHODS OF USING AND COMPOSITIONS THEREOF**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/392,195**

(22) Filed: **Mar. 19, 2003**

(65) **Prior Publication Data**

US 2003/0187052 A1 Oct. 2, 2003

Related U.S. Application Data

(60) Provisional application No. 60/366,515, filed on Mar. 20, 2002, and provisional application No. 60/438,450, filed on Jan. 7, 2003.

(51) **Int. Cl.**[7] **A61K 31/4035**; C07D 209/44

(52) **U.S. Cl.** **514/417**; 548/478; 548/469

(58) **Field of Search** 548/478, 469; 514/417

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,031,450	A	4/1962	Fischer et al.
3,322,755	A	5/1967	Roch et al.
3,920,636	A	11/1975	Takahashi et al.
4,001,237	A	1/1977	Partyka et al.
4,001,238	A	1/1977	Partyka et al.
4,047,404	A	9/1977	Hayashi
4,060,615	A	11/1977	Matier et al.
4,101,548	A	7/1978	Crenshaw et al.
4,162,316	A	7/1979	Nishimura et al.
4,209,623	A	6/1980	Juby
4,880,810	A	11/1989	Lowe, III
4,885,301	A	12/1989	Coates
5,147,875	A	9/1992	Coates et al.
5,354,571	A	10/1994	Morikawa et al.
5,401,774	A	3/1995	Pamukcu et al.
5,439,895	A	8/1995	Lee et al.
5,488,055	A	1/1996	Kumar et al.
5,608,914	A	3/1997	Keesler
5,614,530	A	3/1997	Kumar et al.
5,614,627	A	3/1997	Takase et al.
5,658,940	A	8/1997	Muller et al.
5,698,579	A	12/1997	Muller
5,703,098	A	12/1997	Muller et al.
5,710,170	A	1/1998	Guay et al.
5,728,844	A	3/1998	Muller et al.
5,728,845	A	3/1998	Muller et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP	0 347 146		6/1989
EP	0 349 239	A2	6/1989
EP	0 351 058		6/1989
EP	0 352 960	A2	7/1989
EP	0 395 328		4/1990
EP	0 428 268	A2	10/1990
EP	0 463 756	A1	6/1991
EP	0 526 004	A1	7/1992
EP	0 607 439	A1	9/1992
EP	0 722 937	A1	1/1996
EP	0 722 943	A1	1/1996
EP	0 722 944	A1	1/1996
GB	2 063 249	A	9/1980
WO	WO 93/07149		4/1993
WO	WO 93/12095		6/1993
WO	WO 94/01728		1/1994
WO	WO 94/05661		3/1994
WO	WO 94/29277		12/1994
WO	WO 95/19978		7/1995
WO	WO 96/32379		10/1996
WO	WO 97/03070		1/1997
WO	WO 97/03675		2/1997
WO	WO 97/03985		2/1997
WO	WO 97/24334		7/1997
WO	WO 98/06722		2/1998
WO	WO 98/08848		3/1998
WO	WO 98/14448		4/1998
WO	WO 98/16521		4/1998
WO	WO 98/17668		4/1998
WO	WO 98/23597		6/1998
WO	WO 98/38168		9/1998
WO	WO 99/06041		2/1999

OTHER PUBLICATIONS

U.S. Appl. No. 60/454,155, G. Muller et al., filed Mar. 12, 2003.

U.S. Appl. No. 60/454,159, G. Muller et al., filed Mar. 12, 2003.

U.S. Appl. No. 60/438,448, G. Muller et al., filed Jan. 7, 2003.

U.S. Appl. No. 60/436,975, G. Muller et al., filed Dec. 30, 2002.

U.S. Appl. No. 60/366,515, G. Muller et al., filed Mar. 20, 2002.

(Continued)

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(57) **ABSTRACT**

Stereomerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, substantially free of its (−) isomer, and prodrugs, metabolites, polymorphs, salts, solvates, hydrates, and clathrates thereof are discussed. Also discussed are methods of using and pharmaceutical compositions comprising the (+) enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione are disclosed. The methods include methods of treating and/or preventing disorders ameliorated by the reduction of levels of TNF-α or the inhibition of PDE4.

23 Claims, 2 Drawing Sheets