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Muller et al.

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(54) **METHODS OF TREATING ARTHRITIC CONDITIONS USING (+)-2-[1-(3-ETHOXY-4-METHOXYPHENYL)-2-METHYLSULFONYLETHYL]-4-ACETYLAMINOISOINDOLINE 1,3-DIONE**

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(52) **U.S. Cl.**
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(58) **Field of Classification Search**
USPC 548/469, 478; 514/417
See application file for complete search history.

(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.
5,736,570	A	4/1998	Muller et al.
5,798,373	A	8/1998	Warrellow
5,801,195	A	9/1998	Muller et al.
5,849,770	A	12/1998	Head et al.
5,877,200	A	3/1999	Muller
5,891,896	A	4/1999	Warrellow et al.
6,011,050	A	1/2000	Muller et al.
6,020,339	A	2/2000	Perrier et al.
6,020,358	A	2/2000	Muller et al.
6,034,089	A	3/2000	Han et al.
6,046,221	A	4/2000	Muller et al.
6,069,156	A	5/2000	Oku et al.
6,162,830	A	12/2000	Connor et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP	0 347 146	6/1989
EP	0 349 239 A2	6/1989

(Continued)

OTHER PUBLICATIONS

U.S. Appl. No. 60/454,155, filed Mar. 12, 2003, Muller, G. et al.
U.S. Appl. No. 60/454,149, filed Mar. 12, 2003, Muller, G. et al.
U.S. Appl. No. 60/438,448, filed Jan. 7, 2003, Muller, G. et al.
U.S. Appl. No. 60/436,975, filed Dec. 30, 2002, Muller, G. et al.
U.S. Appl. No. 60/366,515, filed Mar. 20, 2002, Muller, G. et al.
Co 1 Akazome, M. et al., 1997, "Asymmetric recognition of 1-arylethylamines by (R)-phenylglycyl-(R)-phenylglycine and its mechanism," Tetrahedron: Asymmetry, Elsevier Scince Publishers, Amsterdam, NL, 8(14):2331-2336.

(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.

22 Claims, 2 Drawing Sheets