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(54) **IMIDAZOLES USEFUL AS NITRIC OXIDE SYNTHASE INHIBITORS**

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(58) **Field of Search** 548/319.5, 349.1; 514/40, 386

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,049,582	A	8/1936	Ziegler
3,109,848	A	11/1963	Bortnick et al.
3,121,093	A	2/1964	Bortnick et al.
3,132,151	A	5/1964	Bortnick et al.
3,501,487	A	3/1970	Poos
3,563,994	A	2/1971	Wollweber et al.
3,694,432	A	9/1972	Hershenson
3,725,435	A	4/1973	Poos
3,816,457	A	6/1974	Grisar et al.
4,046,909	A	9/1977	Rasmussen et al.
4,061,746	A	12/1977	Blohm et al.
4,126,613	A	11/1978	Grisar et al.
4,126,621	A	11/1978	Grisar et al.
4,153,235	A	5/1979	Grisar et al.
4,443,468	A	4/1984	Maillard et al.
4,523,020	A	6/1985	Moormann et al.
4,525,476	A	6/1985	Butler et al.
4,533,739	A	8/1985	Pitzele et al.
4,556,674	A	12/1985	Maillard et al.
4,579,951	A	4/1986	Pitzele et al.
4,699,918	A	10/1987	Maillard et al.
4,855,444	A	8/1989	Wambach
4,962,204	A	10/1990	Wambach
5,015,633	A	5/1991	Sudilovsky
5,028,627	A	7/1991	Kilbourn et al.
5,051,444	A	9/1991	Tamoto et al.
5,059,712	A	10/1991	Griffith
5,081,148	A	1/1992	Braquet et al.
5,132,453	A	7/1992	Griffith
5,196,439	A	3/1993	Sugimoto et al.
5,216,025	A	6/1993	Gross et al.
5,246,971	A	9/1993	Williamson et al.
5,266,594	A	11/1993	Dawson et al.
5,273,875	A	12/1993	Griffith
5,621,004	A	4/1997	Dunn et al.
5,629,322	A	5/1997	Guthikonda et al.

FOREIGN PATENT DOCUMENTS

CZ	191584	10/1978
EP	0370320	5/1990
EP	0446699	9/1991
EP	0462948	12/1991
EP	0676196	10/1995
EP	0713704	5/1996
EP	0713876	5/1996
EP	0717040	6/1996
GB	1180876	2/1970
GB	1367598	9/1974
GB	2240041	7/1991
WO	91/04023	4/1991
WO	91/04024	4/1991
WO	93/13055	7/1993
WO	93/16721	9/1993
WO	93/24126	12/1993
WO	94/12163	6/1994
WO	94/12165	6/1994
WO	94/14780	7/1994
WO	94/16729	8/1994
WO	95/05363	2/1995
WO	95/11231	4/1995
WO	95/31987	11/1995
WO	95/32203	11/1995
WO	96/14842	5/1996
WO	96/14844	5/1996
WO	96/18616	6/1996
WO	97/16430	5/1997
WO	WO 9525717 A	7/1997

OTHER PUBLICATIONS

Perrin et al., "Absence of Stereoelectronic Control in Hydrolysis of Cyclic Amidines", *J. Am. Chem. Soc.*, vol. 108, No. 19, pp. 5997–6003, 1986.

Huber et al., "Saturated Heterocycles, Part 88. Synthesis of a New Ring System: Dipyrido–[1.2–a:4,3–d] pyrimidin–11–one Derivatives", *J. Chem. Soc. Perkin Trans. 1*, pp. 909–912, 1987.

Kökösi et al., "Nitrogen Bridgehead Compounds. Part 19(1). Synthesis of Polymethylenepyrimidin–4–ones", *J. Heterocyclic Chem.*, vol. 19, pp. 909–912, 1982.

Brown et al., Hydropyrimidines, Part II, pp. 4041–4045, 1962.

Adcock et al., 2–Amino–2–imidazolines 2–Amino–2–oxazolines, Part II, pp. 474–479, 1965.

(List continued on next page.)

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(57) **ABSTRACT**

1,3-diazolino and 1,3-diazolidino heterocycle derivatives useful as nitric oxide synthase inhibitors.

22 Claims, No Drawings