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[54] **INHIBITION OF NITRIC OXIDE-MEDIATED HYPOTENSION AND SEPTIC SHOCK WITH IRON-CONTAINING HEMOPROTEIN**

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[52] U.S. Cl. **514/6**

[58] Field of Search **514/6**

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,061,736	12/1977	Morris et al.	424/177
4,584,130	4/1986	Bucci et al.	260/112
4,598,064	7/1986	Walder	514/6
4,751,068	6/1988	Bickar et al.	423/437
5,028,627	7/1991	Kilbourn et al.	514/12
5,082,642	1/1992	Bickar et al.	423/402

FOREIGN PATENT DOCUMENTS

US90/02654	7/1990	PCT Int'l Appl.	.
US90/05199	9/1990	PCT Int'l Appl.	.
WO91/04023	4/1991	PCT Int'l Appl.	.
WO91/04024	4/1991	PCT Int'l Appl.	.
WO91/84023	4/1991	PCT Int'l Appl.	.
WO93/00893	1/1993	PCT Int'l Appl.	.

OTHER PUBLICATIONS

Wang et al., Nitric oxide hemoglobin in mice and rats in endotoxic shock, *Chemical Abstracts*, vol. 115, No. 15, issued 1991, Oct. 14, p. 659m, col. 1, the abstract-No. 156 199a, Life Sci. 1991, 49(11), PL55-PL60.

Westenberger et al., Formation of free radicals and nitric oxide derivative of hemoglobin in rats during shock syndrome, *Chemical Abstracts*, vol. 114, No. 21, issued 1991, May 27, p. 597, col. 2-p. 598, col. 1, the

abstract-No. 204 845m, Free Radical Res. Commun. 1990, 11(1-3), 167-178.

Wang et al., "Nitric Oxide Hemoglobin in Mice and Rats in Endotoxic Shock", *Lifesciences*, 49, p155-p160, 1991.

Westenberger et al., "Formation of Free Radicals and Nitric Oxide Derivative of Hemoglobin in Rats During Shock Syndrome", *Free Radical Res. Commun.*, 11, 167-178, 1990.

Kosaka et al., "Detection of Nitric Oxide Production in Lipopoyasaccharide-Treated Rats by ESR Using Carbon Monoxide Hemoglobin", *Biochem. and Biophys. Res. Commun.*, 1119-1124, Apr. 30. 1992.

Stamler et al., "Biochemistry of Nitric Oxide and Its Redox-Activated Forms", *Science*, 258, 1898-1902, 1992.

Koshland, Jr., "Editorial-The Molecule of the Year", (*Science*, 258, 1861) 1992.

Culotta et al., "No News Is Good News", *Science*, 258, 1862-1865, 1992.

Bickar et al., "Carbon Monoxide-Driven Reduction of Ferric Heme and Heme Proteins," *Journal of Biological Chemistry*, 259(17): 10777-10783, 1984, published in USA.

Martin et al., "Selective Blockade of Endothelium-Dependent and Glyceryl Trinitrate-Induced Relaxation by Hemoglobin and by Methylene Blue in the Rabbit Aorta," *The Journal of Pharmacology and Experimental Therapeutics*, 232(3):708-716, 1985, published in USA.

(List continued on next page.)

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[57] **ABSTRACT**

The invention is directed to a method for the prophylaxis or treatment of an animal for deleterious physiological effects such as systemic hypotension caused by nitric oxide production induced by a biological response modifier. Examples of such biological response modifiers include but are not limited to a cytokine and an endotoxin. The invention is also directed to a method for the treatment of septic shock.

15 Claims, 1 Drawing Sheet