



US005770623A

# United States Patent [19]

[11] Patent Number: **5,770,623**

Kilbourn et al.

[45] Date of Patent: **Jun. 23, 1998**

[54] **ARGININE ANTAGONISTS FOR INHIBITION OF SYSTEMIC HYPOTENSION ASSOCIATED WITH NITRIC OXIDE PRODUCTION OR ENDOTHELIAL DERIVED RELAXING FACTOR**

[75] Inventors: **Robert G. Kilbourn**, Naperville, Ill.; **Steven S. Gross**; **Roberto Levi**, both of New York, N.Y.; **Owen W. Griffith**, Milwaukee, Wis.

[73] Assignees: **Board of Regents, The University of Texas System**, Austin, Tex.; **Cornell Research Foundation, Inc.**, Ithaca, N.Y.

[21] Appl. No.: **561,717**

[22] Filed: **Nov. 22, 1995**

### Related U.S. Application Data

[63] Continuation of Ser. No. 838,814, Mar. 13, 1992, abandoned, which is a continuation-in-part of Ser. No. 406,909, Sep. 19, 1989, Pat. No. 5,028,627.

[51] **Int. Cl.<sup>6</sup>** ..... **A61K 31/195**

[52] **U.S. Cl.** ..... **514/565**; 514/12; 514/930; 424/85.1; 424/85.2; 424/85.5

[58] **Field of Search** ..... 514/565, 12, 930; 424/85.2, 85.5, 85.1

### References Cited

#### U.S. PATENT DOCUMENTS

4,282,217	8/1981	Baglioni et al.	424/240
4,477,428	10/1984	Silbering et al.	424/52
4,477,429	10/1984	Silbering et al.	424/52
4,499,067	2/1985	Silbering et al.	424/542
4,789,681	12/1988	Sportoletti et al.	514/392
5,028,627	7/1991	Kilbourn et al.	514/565
5,059,712	10/1991	Griffith	562/560

#### FOREIGN PATENT DOCUMENTS

WO 91/04024	9/1990	WIPO	.
WO 91/84023	4/1991	WIPO	..... A61K 31/195
WO 91/09574	7/1991	WIPO	.

#### OTHER PUBLICATIONS

Sakuma, I. et al., (1988) *Proc. Natl. Acad. Sci. USA*, 85:8664-8667.  
 Abstract entitled "Nitric oxide damages DNA in bacteria," *Chem. and Engineering News*, Nov. 18, 1991.  
 Wink et al., (1991) *Science*, 254:1001-1003.  
 Kilbourn et al., (1984) *J. Immunology*, 133:2577-2581.  
 Kilbourn et al., (1990) *Biochem. and Biophys. Res. Commun.*, 172:1132-1138.  
 Kilbourn, R.G., et al., (1990) *Proc. Natl. Acad. Sci. USA*, 87:3629-3632.  
 Schmidt et al., (1992) *Science*, 255:721-723.  
 Turan, A. et al., (1975) *Acta Chimica Academiae Scientiarum Hungaricae, Tomas*, 85:327-332.  
 Iyengar, R. et al., (1987) *Proc. Natl. Acad. Sci. USA*, 84:6369-6373.  
 Stuehr et al., (1987) *J. Immunology*, 139:518-525.  
 Marletta et al., (1988) *Biochemistry*, 27:8706-8711.

Palmer, R.M.J. et al., (1988) *Nature*, 333:664-666.  
 Palmer, R.M.J. et al. (1988) *Biochem. Biophys. Res. Commun.*, 153:1251-1256.  
 Schmidt et al., (1988) *European J. Pharmacology*, 154:213-216.  
 Aisaka et al., (1989) *Biochem. Biophys. Res. Commun.*, 160:881-886.  
 Rees, D.D. et al., (1989) *Proc. Natl. Acad. Sci. USA*, 86:3375-3378.  
 Stuehr, D.J., et al., (1989) *J. Exp. Med.*, 169:1011-1020.  
 Stuehr, D.J. et al., (1989) *Biochem. Biophys. Res. Commun.*, 161:420-426.  
 Piguert et al., (1989) *J. Exp. Med.*, 170:655-663.  
 Kilbourn et al., (1990) *J. Natl. Cancer Institute*, 82:772-776.  
 Gross et al. (1991) *Biochem. Biophys. Res. Commun.*, 178:823-829.  
 Moncada et al., "Nitric Oxide: Physiology, Pathophysiology, and Pharmacology," *Pharmacological Reviews*, 43(2):109-142, 1991, published in USA.  
 Moncada et al., "The L-Arginine: Nitric Oxide Pathway," *Journal of Cardiovascular Pharmacology*, 17(Suppl. 3):S1-S9, 1991, published in USA.  
 Parratt, J.R., and Stoclet, Jean-Claude, "Possible Role of Nitric Oxide in Refractory Hypotension Associated with Sepsis and Endotoxaemia and with Multiple Organ Failure," *Applied Cardiopulmonary Pathophysiology*, 4:143-149, 1991, published in USA.  
 Johnston, Jeff, "Molecular Science Sets Its Sights. On Septic Shock," *The Journal of NIH Research*, 3:61-65, 1991, published in USA.  
 Moncada, S., and Higgs, E.A., "Endogenous Nitric Oxide: Physiology, Pathology and Clinical Relevance," *European Journal of Clinical Investigation*, 21:361-374, 1991, published in Europe.  
 Palmer et al., "Nitric Oxide Release Accounts for the Biological Activity of Endothelium-Derived Relaxing Factor," *Nature*, 327:524-526, 1987, published in the United Kingdom.

(List continued on next page.)

Primary Examiner—Chhaya D. Sayala  
 Attorney, Agent, or Firm—Arnold, White & Durkee

### [57] ABSTRACT

A method for prophylaxis or treatment of an animal for systemic hypotension induced by internal nitrogen oxide production. The method involves administering a therapeutically effective amount of certain arginine derivatives to inhibit nitrogen oxide formation from arginine. Preferably N<sup>G</sup>-substituted arginine or an N<sup>G</sup>,N<sup>G</sup>-disubstituted arginine (having at least one hydrogen on a terminal guanidino amino group replaced by another atomic species) is administered to an animal possibly developing or already having such induced systemic hypotension. The arginine derivatives are preferably of the L configuration and include pharmaceutically acceptable addition salts. Prophylaxis or treatment of systemic hypotension in a patient which has been induced by chemotherapeutic treatment with biologic response modifiers such as tumor necrosis factor or interleukin-2 may be accomplished. Treatment of an animal for systemic hypotension induced by endotoxin, i.e., septic shock may also be accomplished by treatment with the arginine derivatives.