



US005389675A

# United States Patent [19]

[11] Patent Number: **5,389,675**

Christodoulou et al.

[45] Date of Patent: **Feb. 14, 1995**

- [54] **MIXED LIGAND METAL COMPLEXES OF NITRIC OXIDE-NUCLEOPHILE ADDUCTS USEFUL AS CARDIOVASCULAR AGENTS**
- [75] Inventors: **Danae D. Christodoulou**, Frederick; **David A. Wink, Jr.**, Hagerstown; **Larry K. Keefer**, Bethesda, all of Md.
- [73] Assignee: **The United States of America as represented by the Department of Health and Human Services**, Washington, D.C.
- [21] Appl. No.: **858,885**
- [22] Filed: **Mar. 27, 1992**
- [51] Int. Cl.<sup>6</sup> ..... **A61K 31/28; C07F 13/00**
- [52] U.S. Cl. .... **514/492; 514/494; 514/499; 514/906; 514/929; 556/45; 556/113; 556/130**
- [58] Field of Search ..... **556/45, 113, 130; 514/494, 499, 492, 906, 929**

[56]

### References Cited

#### U.S. PATENT DOCUMENTS

3,153,094	10/1964	Reilly	.....	260/576
4,954,526	9/1990	Keefer	.....	514/611
5,039,705	8/1991	Keefer et al.	.....	514/611

#### OTHER PUBLICATIONS

1991, Article by Maragos, et al., Complexes of .NO with Nucleophiles as Agents for the Controlled Biological Release of Nitric Oxide. Vasorelaxant Effects, Journal of Medicinal Chemistry, vol. 34, No. 11.

May 10, 1990, Article by Myers, et al., Vasorelaxant Properties of the Endothelium-Derived Relaxing Factor More Closely Resemble S-Nitrosocysteine than Nitric Oxide, Nature, vol. 345.

Jan. 1989, Article by Louis J. Ignarro, Endothelium-derived Nitric Oxide: Actions and Properties, The FASEB Journal, vol. 3.

1988, Article by Francis V. DeFeudis, Endothelium-Dependent Vasorelaxation—A New Basis For Developing Cardiovascular Drugs, Drugs of Today, vol. 24, No. 2, pp. 103-115.

Jun. 11, 1987, Article by Palmer, et al., Nitric Oxide

Release Accounts for the Biological Activity of Endothelium-Derived Relaxing Factor, Nature, vol. 327.

1987, Article by Kruszyna, et al., Red Blood Cells Generate Nitric Oxide from Directly Acting, Nitrogenous Vasodilators, Toxicology and Applied Pharmacology 91, 429-438.

1986, Article by Lawrence A. Trissel, Intravenous Infusion Solutions, Handbook on Injectable Drugs, Fourth Addition.

1984, Article by Robert F. Furchgott, The Role of Endothelium in the Responses of Vascular Smooth Muscle to Drugs, Ann. Rev. PHARMACOL TOXICOL, 24:175-97.

1982, Article by DeLuca, et al., Parenteral Drug-Delivery Systems, Pharmaceutics and Pharmacy Practice.

1982, Article by Hansen, et al., N-Nitrosation of Secondary Amines by Nitric Oxide Via the 'Drago Complex,' ARC Sci., Publ., pp. 21-29.

1981, Article by Ignarro, et al., Mechanism of Vascular Smooth Muscle Relaxation by Organic Nitrates, Nitrites, Nitroprusside and Nitric Oxide: Evidence for the Involvement of S-Nitrosothiols as Active Intermedi-  
(List continued on next page.)

Primary Examiner—José G. Dees

Assistant Examiner—Porfirio Nazario

Attorney, Agent, or Firm—Leydig, Voit & Mayer, Ltd.

[57]

### ABSTRACT

Mixed ligand metal complexes of nitric oxide-nucleophile adducts, useful as cardiovascular agents of the formula KA, wherein A is



K is a pharmaceutically acceptable counterion present in the composition when the overall charge of A is not zero, counterion K being present only in an amount to neutralize A. Methods of treating mammals with such compounds are provided. Pharmaceutical compositions containing such compounds are also provided.

41 Claims, 1 Drawing Sheet