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(12) **United States Patent**  
**Okamura et al.**(10) **Patent No.: US 6,288,067 B1**  
(45) **Date of Patent: \*Sep. 11, 2001**(54) **PROPHYLACTIC OR THERAPEUTIC AGENTS FOR DRUG-INDUCED RENAL INJURY**(75) Inventors: **Mikio Okamura; Yoshiharu Kanayama**, both of Osaka; **Junichi Yoshikawa**, Hyogo-ken; **Haruo Shintaku**, Osaka, all of (JP)(73) Assignee: **Suntory Limited**, Osaka (JP)

(\*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(51) **Int. Cl.<sup>7</sup>** ..... **A61K 31/50**; A61K 31/495(52) **U.S. Cl.** ..... **514/252.16**; 514/258(58) **Field of Search** ..... 514/252.16, 258(56) **References Cited****U.S. PATENT DOCUMENTS**

4,920,122 \* 4/1990 Naruse et al. .... 514/254

**FOREIGN PATENT DOCUMENTS**0 908 182 4/1999 (EP) .  
59-25323 2/1984 (JP) .  
59-76086 4/1984 (JP) .  
61-277618 12/1986 (JP) .  
002157755 3/1994 (JP) .  
63-267781 11/1998 (JP) .  
WO 92/07566 5/1992 (WO) .**OTHER PUBLICATIONS**Fukushima, et al. "Analysis of Reduced Forms of Biopterin in Biological Tissues and Fluids", *Analytical Biochemistry* 102, (1980) pp., 176-188.R.M.J. Palmer, et al. "Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor", *Nature* 327, (1987) pp. 524-526.Kwon, et al., "Reduced Biopterin as a Cofactor in the Generation of Nitrogen Oxides by Murine Macrophages", *J. Biol. Chem.*, (1989) 264(34) pp. 20496-20501.Bobadilla, et al. "Role of nitric oxide in renal hemodynamic abnormalities of cyclosporin nephrotoxicity", *Kidney Int.* 46, (1994) pp. 773-779.

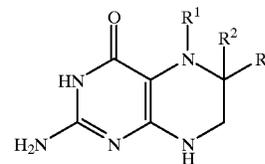
Medical Practice, vol. 14, No. 8, (1997) pgsz 1273-1275. "ZINZOUGAKU" Approach from renal pathophysiology, ed. Kurokawa, K. Nankoudou, (1995) pp. 419-428.

Bune, et al., Inhibition of Tetrahydrobiopterin Synthesis Reduces Nitric Oxide Production by Isolated Glomeruli in Immune Complex Glomerulonephritis, *Experimental Nephrology*, 1996, vol. 4, pp. 43-47.Gardner et al., Clinically Relevant Doses and Blood Levels Produce Experimental Cyclosporine Nephrotoxicity When Combined with Nitric Oxide Inhibition, *Transplantation*, 1996, vol. 61, pp. 1506-1512.Bune et al., Inhibition of Tetrahydrobiopterin Synthesis Reduces in Vivo Nitric Oxide Production in Experimental Endotoxic Shock, *Biochemical and Biophysical Research Communications*, 1996, vol. 220, pp. 13-19.

\* cited by examiner

*Primary Examiner*—Frederick Krass(74) *Attorney, Agent, or Firm*—Pillsbury Winthrop LLP(57) **ABSTRACT**

It is an object of the present invention to provide a pharmaceutical composition for effectively preventing or improving drug-induced renal injury. The present invention provides pharmaceutical composition for preventing or treating drug-induced renal injury, comprising as an active ingredient a compound of the formula (I):

wherein R<sup>1</sup> and R<sup>2</sup> each represents a hydrogen atom or taken together with each other represent a single bond, while R<sup>3</sup> represents —CH(OH)CH(OH)CH<sub>3</sub>, —CH(OCOCH<sub>3</sub>)CH(OCOCH<sub>3</sub>)CH<sub>3</sub>, —CH<sub>3</sub>, —CH<sub>2</sub>OH or a phenyl group when R<sup>1</sup> and R<sup>2</sup> each represents a hydrogen atom, or —COCH(OH)CH<sub>3</sub> when R<sup>1</sup> and R<sup>2</sup> together represent a single bond, or a pharmaceutically acceptable salt thereof.**6 Claims, No Drawings**