

(12) **United States Patent**  
Naicker et al.

(10) **Patent No.:** US 6,613,739 B1  
(45) **Date of Patent:** Sep. 2, 2003

(54) **DEUTERATED CYCLOSPORINE ANALOGS  
AND THEIR USE AS  
IMMUNOMODULATING AGENTS**

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(\* ) Notice: 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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(21) Appl. No.: **09/634,945**

(22) Filed: **Aug. 7, 2000**

**Related U.S. Application Data**

(63) Continuation of application No. 09/184,109, filed on Nov. 2, 1998.

(51) **Int. Cl.<sup>7</sup>** ..... **A61K 38/00**

(52) **U.S. Cl.** ..... **514/11; 530/321; 530/350;**  
**530/363; 530/806; 530/807**

(58) **Field of Search** ..... 514/11; 530/321,  
530/350, 363, 806, 807

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(57) **ABSTRACT**

Cyclosporine derivatives are disclosed which possess enhanced efficacy and reduced toxicity over naturally occurring and other presently known cyclosporins and cyclosporine derivatives. The cyclosporine derivatives of the present invention are produced by chemical and isotopic substitution of the cyclosporine A (CsA) molecule by: (1) Chemical substitution and optionally deuterium substitution of amino acid 1; and (2) deuterium substitution at key sites of metabolism of the cyclosporine A molecule such as amino acids 1, 4, 9. Also disclosed are methods of producing immunosuppression with reduced toxicity with the disclosed cyclosporine derivatives.

**16 Claims, 4 Drawing Sheets**

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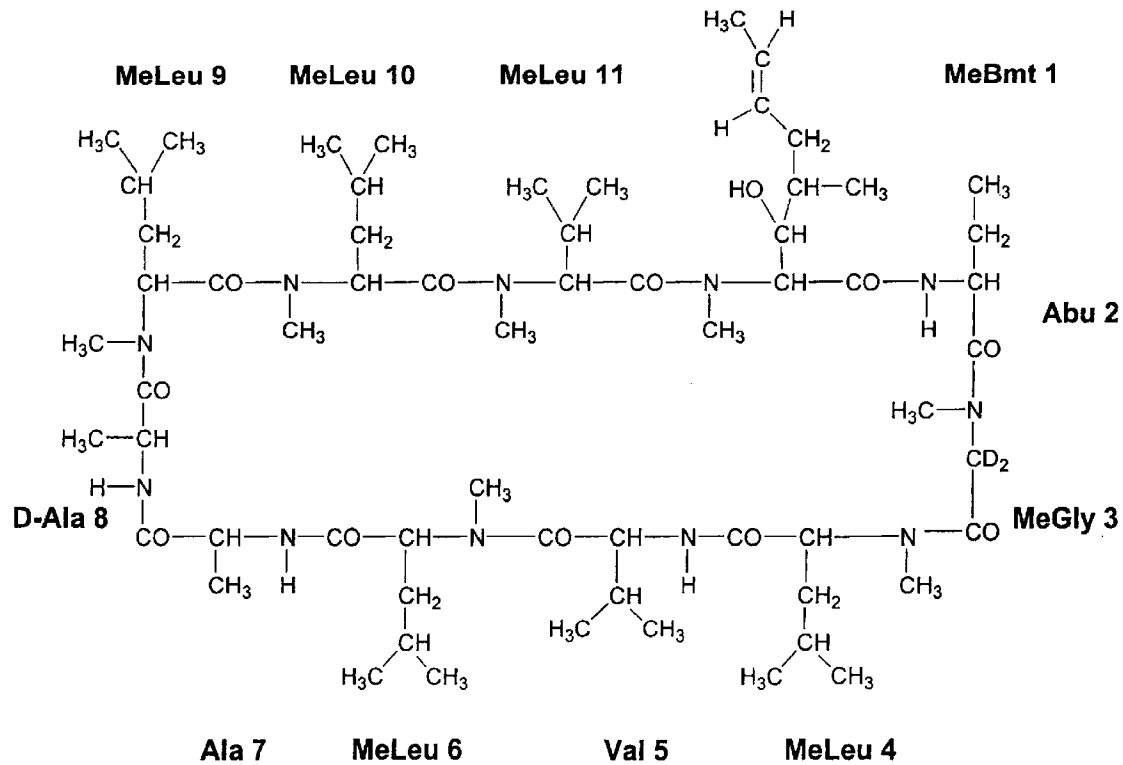


Fig. 1

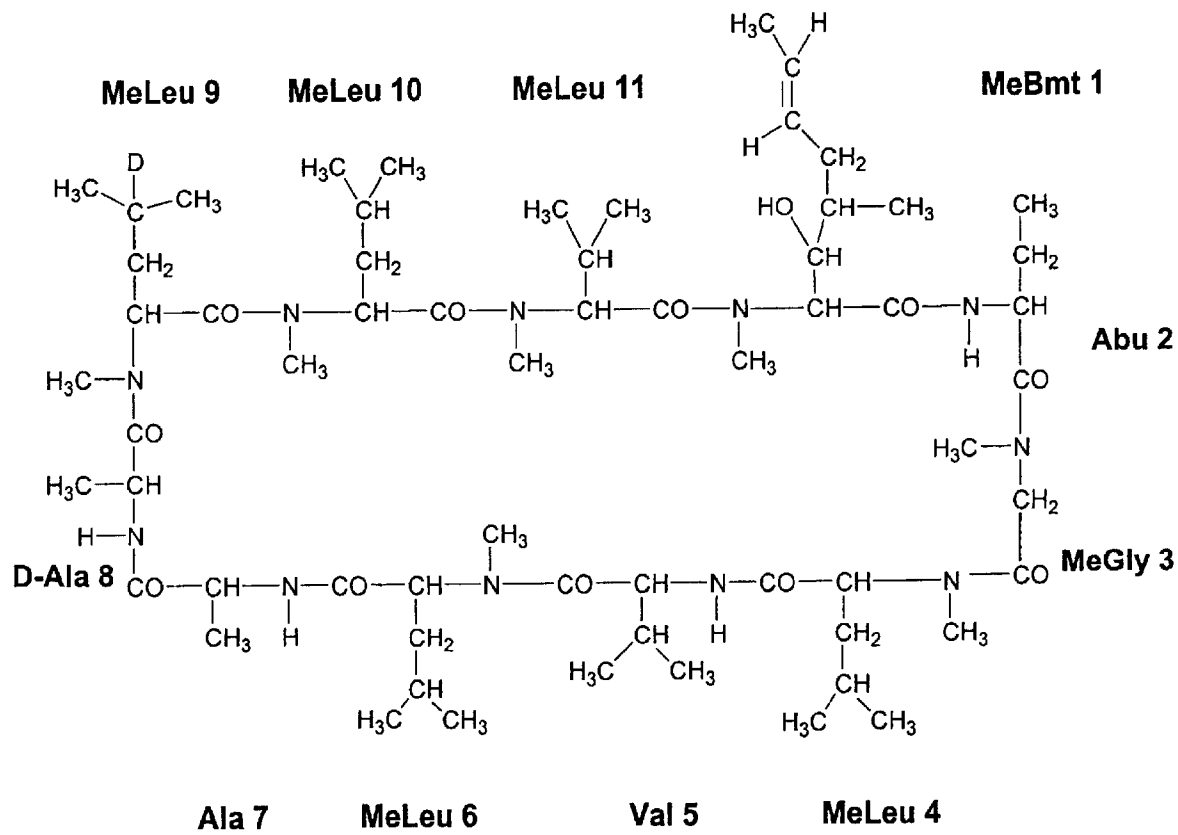


Fig. 2

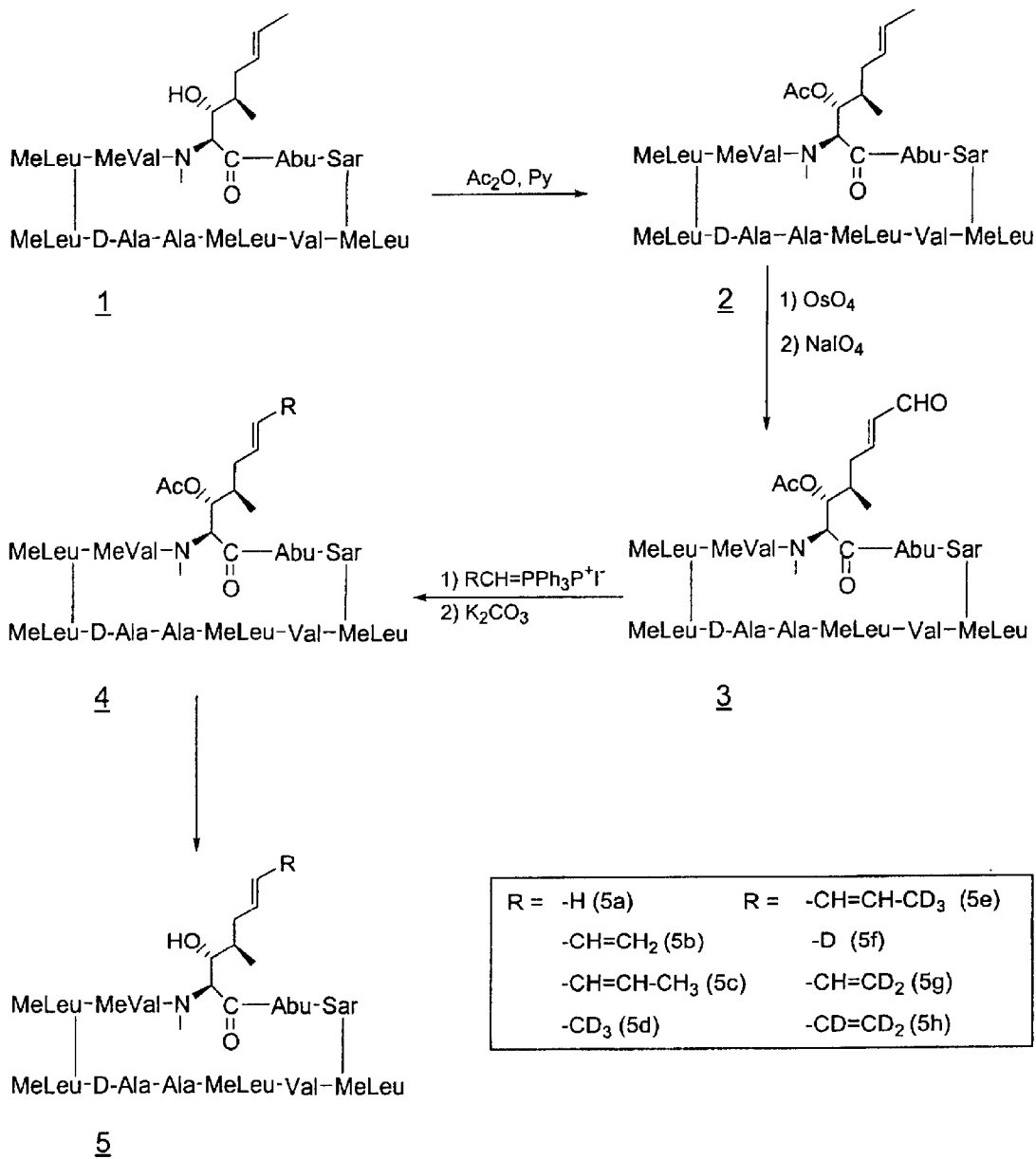


Fig. 3

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