

(12) **United States Patent**
Robertus et al.(10) **Patent No.:** US 6,562,969 B1
(45) **Date of Patent:** May 13, 2003(54) **RICIN INHIBITORS AND METHODS FOR USE THEREOF**

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Chem. Abstr. 105: 153031.*(73) Assignee: **Research Development Foundation**, Carson City, NV (US)

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

* cited by examiner

Primary Examiner—Mary E. Ceperley(74) *Attorney, Agent, or Firm*—Benjamin Aaron Adler(21) Appl. No.: **09/535,460**(22) Filed: **Mar. 24, 2000**(57) **ABSTRACT****Related U.S. Application Data**

(63) Continuation-in-part of application No. 09/118,535, filed on Jul. 17, 1998, now Pat. No. 6,177,280, which is a continuation-in-part of application No. 08/773,398, filed on Dec. 24, 1996, now abandoned.

(51) **Int. Cl.**⁷ **C07D 487/02**; C07D 473/00(52) **U.S. Cl.** **544/280**; 544/262; 544/265(58) **Field of Search** 544/262, 280, 544/276, 320, 326, 265(56) **References Cited****U.S. PATENT DOCUMENTS**4,371,514 A * 2/1983 Nagatsu et al.
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Ricin A-chain is an N-glycosidase that attacks ribosomal RNA at a highly conserved adenine residue. Crystallographic studies show that not only adenine and formycin, but also pterin-based rings can bind in the ricin active site. For a better understanding of the recognition mode between ricin, and adenine-like rings, the interaction energies and geometries were calculated for a number of complexes. Shiga toxin, a compound essentially identical to the protein originally isolated from *Shigella dysenteriae*, has an active protein chain that is a homologue of the ricin active chain, and catalyzes the same depurination reaction. The present invention is drawn to identifying inhibitors of ricin and Shiga toxin, using methods molecular mechanics and ab initio methods and using the identified inhibitors as antidotes to ricin or Shiga toxin, or to facilitate immunotoxin treatment by controlling non-specific cytotoxicity.

1 Claim, 31 Drawing Sheets

 29	 15
IC ₅₀ 2.4 mM	IC ₅₀ 2.8 mM
 1	 25
IC ₅₀ 3.4 mM	IC ₅₀ 2.7 mM
 26	 27
IC ₅₀ 2.5 mM	IC ₅₀ 3.2 mM
 28	 14
IC ₅₀ 0.7 mM	IC ₅₀ 1.4 mM
 21	 24
IC ₅₀ 0.7 mM	IC ₅₀ 1.4 mM
 15	 6
IC ₅₀ 2.8 mM	IC ₅₀ 2.1 mM