

- [54] **CYTOTOXIC AGENTS COMPRISING MAYTANSINOIDS AND THEIR THERAPEUTIC USE**
- [75] Inventors: **Ravi J. Chari, Boston; Victor S. Goldmacher, Newton Center; John M. Lambert, Cambridge; Walter A. Blattler, Brookline, all of Mass.**
- [73] Assignee: **ImmunoGen Inc., Cambridge, Mass.**
- [21] Appl. No.: **911,380**
- [22] Filed: **Jul. 13, 1992**

Related U.S. Application Data

- [63] Continuation of Ser. No. 426,247, Oct. 25, 1989, abandoned.
- [51] Int. Cl.⁵ **A61K 39/00; A61K 31/535; A61K 49/00; A01N 57/00**
- [52] U.S. Cl. **424/85.91; 514/279.5; 540/462; 530/388.8; 530/388.15; 530/391.7; 530/388.9**
- [58] Field of Search **424/85.91; 514/229.5; 540/462; 530/390**

References Cited

U.S. PATENT DOCUMENTS

3,896,111	7/1975	Kupchan	540/462
4,137,230	1/1979	Hashimoto	540/462
4,248,870	2/1981	Miyashita	514/229.5
4,256,246	3/1981	Miyashita	514/229.5
4,260,608	4/1981	Miyashita	514/229.5
4,263,294	4/1981	Miyashita	514/229.5
4,264,596	4/1981	Miyashita	514/229.5
4,294,757	10/1981	Asai	540/462
4,307,016	12/1981	Asai	540/462
4,308,268	12/1981	Miyashita	514/229.5
4,308,269	12/1981	Miyashita	514/229.5
4,309,428	1/1982	Miyashita	514/229.5
4,313,946	2/1982	Powell	514/229.5
4,362,663	12/1982	Kida	540/462
4,364,866	12/1982	Asai	540/462
4,418,064	11/1983	Powell	514/229.5

4,424,219 1/1984 Hashimoto 514/229.5

FOREIGN PATENT DOCUMENTS

0205326 12/1986 European Pat. Off. .
0376176 7/1990 European Pat. Off. .

OTHER PUBLICATIONS

Ravi V. J. Chari et al, "Immunoconjugates Containing Novel Maytansinoids: Promising Anticancer Drugs" (Cancer Research), Cambridge, Mass., pp. 127-131, (Jan. 1, 1992).
Greenfield et al Cancer Research, 50: 6600-6607 Oct. 15, 1990.
Mueller et al, Bioconjugate Chem. 1: 325-330 (1990).
Endo et al, Cancer Research 47; 1076-1080 (Feb. 15, 1987).

Primary Examiner—Frederick E. Waddell
Assistant Examiner—Gregory Hook
Attorney, Agent, or Firm—Sughrue, Mion, Zinn, Macpeak & Seas

[57] **ABSTRACT**

A cytotoxic agent comprising one or more maytansinoids linked to a cell binding agent. A therapeutic agent for killing selected cell populations comprising: (a) a cytotoxic amount of one or more maytansinoids linked to a cell binding agent, and (b) a pharmaceutically acceptable carrier diluent or excipient. A method for killing selected cell populations comprising contacting a cell population or tissue suspected of containing cells from said selected cell population with a cytotoxic amount of a cytotoxic agent comprising one or more maytansinoids linked to a cell binding agent. An N-methyl-alanine-containing ester of maytansinol or an analogue of maytansinol, said N-methyl-alanine-containing ester comprising a linking group capable of linking an N-methyl-alanine-containing maytansinoid ester to a chemical moiety. N-methyl-cysteine-containing ester of maytansinol or an analogue of maytansinol.

18 Claims, 4 Drawing Sheets

FIG. 1 PRIOR ART

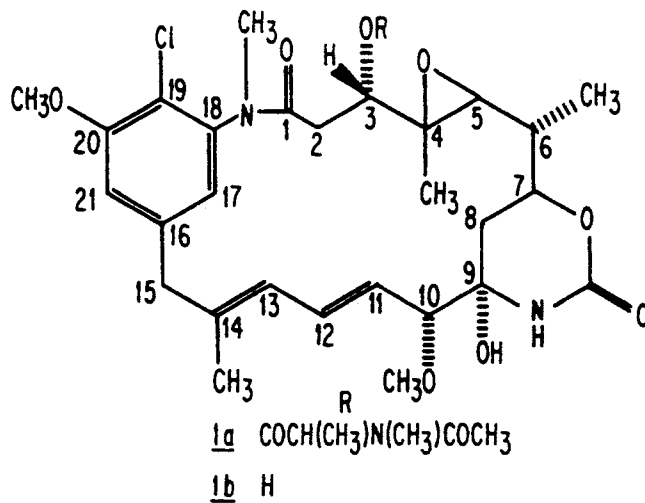
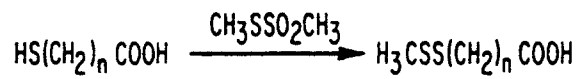
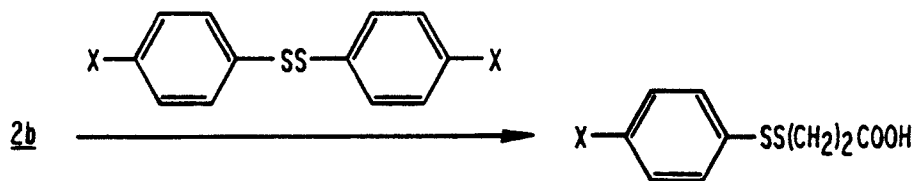


FIG. 2

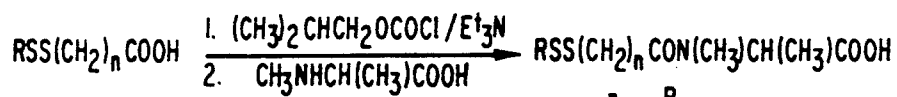


2 a n = 1
 b n = 2
 c n = 3
 d n = 4

3 a n = 1
 b n = 2
 c n = 3
 d n = 4



4 a x = H
 b x = NO₂



5 n R
 a 1 CH₃
 b 2 CH₃
 c 3 CH₃
 d 4 CH₃
 e 5 C₆H₅
 f 6 p-NO₂-C₆H₄

FIG. 3

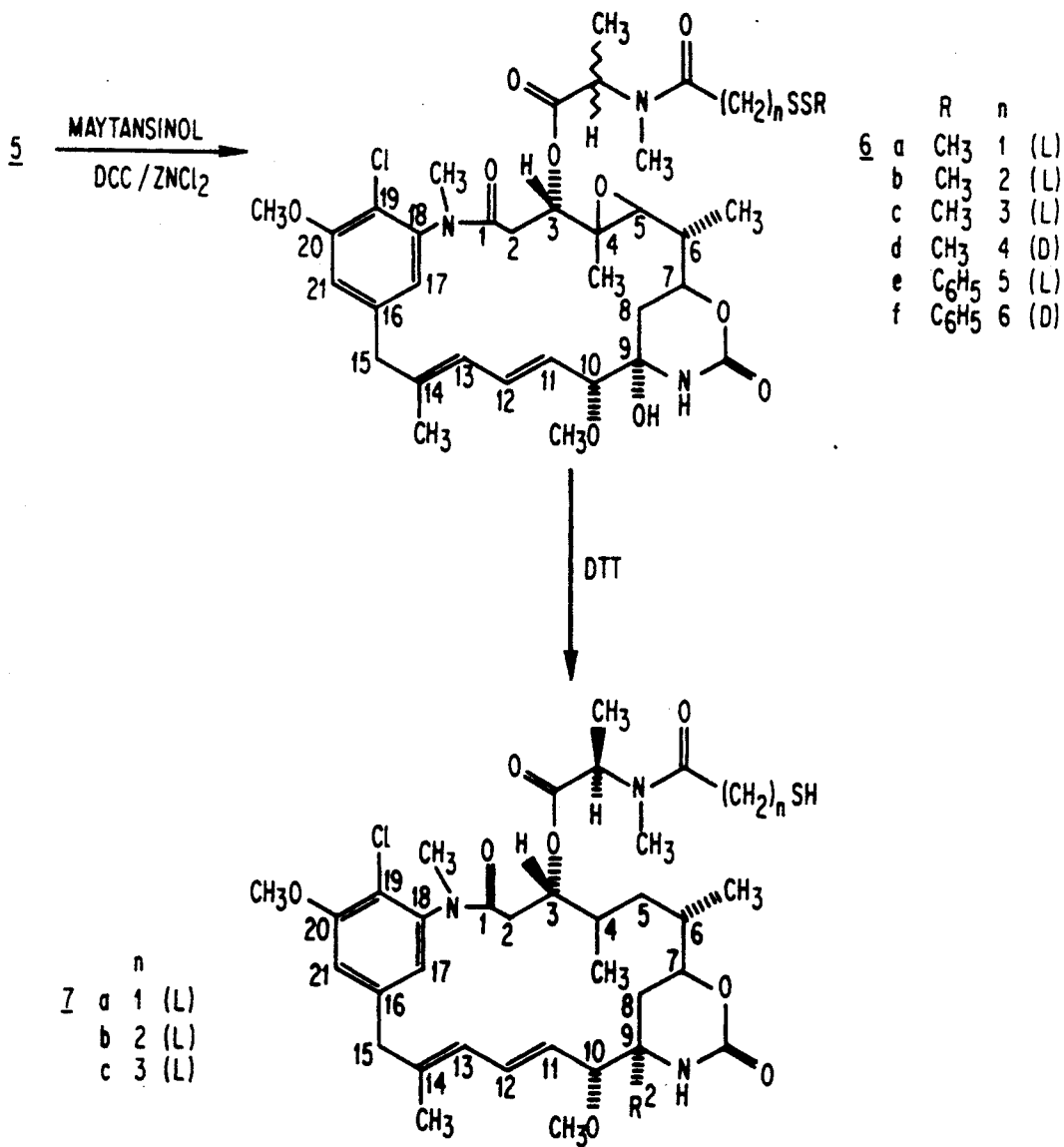


FIG. 4a

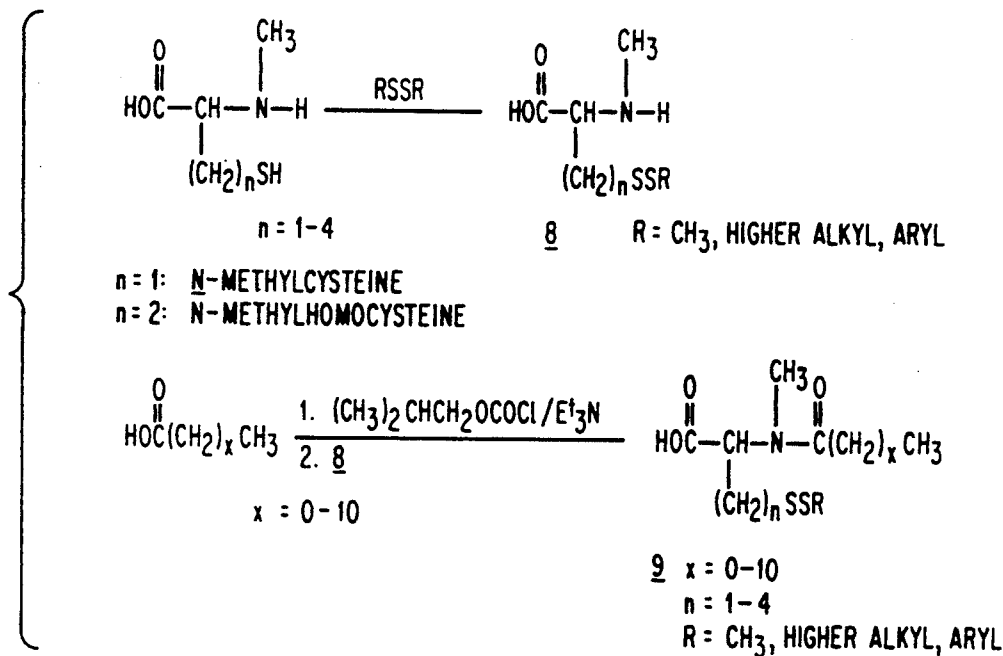
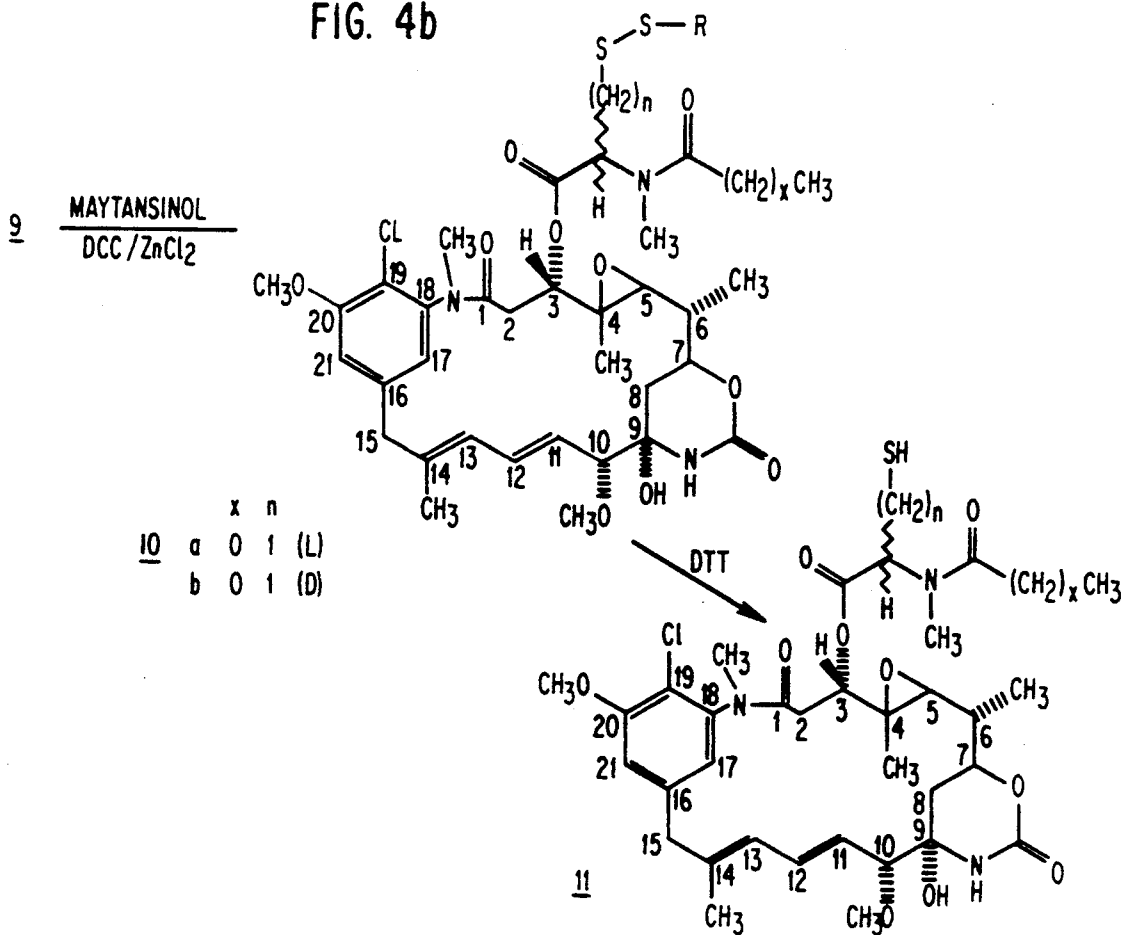


FIG. 4b



Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.