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CONFIDENTIAL TREATMENT REQUESTED

April 29, 2004

Carboplatin

Dear Ms. Schenof:

Bristol-Myers Squibb Company ("BMS") submits this letter and the enclosed materials in response to the requests for additional information contained in your letter of April 20, 2004, and made during recent conversations with outside counsel for BMS and/or Teva Pharmaceuticals USA, Inc. ("Teva").

1. Termination.

You asked us to consider modifying the term of Teva's distributorship rights to provide that Teva's distributorship rights expire at the earlier of some period after Teva receives Food and Drug Administration ("FDA") approval of its ANDA (perhaps 30 or 60 days) or June 24, 2005.

The parties addressed this request in Article 9 of the Distribution and Supply Agreement between BMS and Teva, dated April 26, 2004, (the "Distribution and Supply Agreement") submitted to the FTC on April 27, 2004. BMS respectfully refers you to the following specific provisions of the Distribution and Supply Agreement: Sections 9.1.1, 9.5 and 9.6.1(c).

2. Carboplatin ANDA Filers.

You requested that BMS identify, by the form and dose specified in the Agreement, which companies have filed an ANDA for carboplatin.

Enclosed is a list of generic companies that, to BMS's knowledge, have filed ANDAs for carboplatin. BMS does not generally have knowledge of ANDA filings prior to tentative approval unless it receives notice that a company filed an ANDA containing a paragraph IV certification. It is therefore possible that other generic companies have filed ANDAs for carboplatin about which BMS does not have knowledge.

3. BMS's Annual Sales of Paraplatin®.

You requested that BMS identify its annual sales of carboplatin.

Enclosed is a chart that provides annual domestic net sales for Paraplatin® in lyophilized and solution form, by dose, for 2003. BMS also markets a 600 Mgs solution product. This product launched earlier this year and accordingly no net sales figures for this dosage are included.

4. Claims and Potential Claims that are Resolved by the Agreements.

You requested a copy of any counterclaims asserted by Teva that would be dismissed as part of the resolution of the litigation at issue.

Pharmachemie B.V. ("Pharmachemie") filed three answers in which it asserted counterclaims. In its most recent answer, the Amended Answer and Counterclaim to Consolidated Amended Complaint, dated October 22, 2002, Teva asserted only one counterclaim for declaratory judgment of patent invalidity. A copy of the Amended Answer and Counterclaim to Consolidated Amended Complaint is enclosed.

REDACTED

Pharmachemie has also argued that it could obtain approval of ANDA 76-162 notwithstanding BMS's pending pediatric exclusivity. BMS disagreed, and continues to disagree, with this contention.

The language in the agreements relevant to the resolution of the claims and potential claims of the parties may be found in paragraphs 2, 3 and 4 of the Settlement Agreement between BMS, Teva and Research Corporation Technologies, Inc., dated April 26, 2004, submitted to the FTC on April 27, 2004, and section 2.1.4 of the Distribution and Supply Agreement.

5. Teva's Corporate Structure.

You requested information regarding Teva's corporate structure and the relationship between Teva and Pharmachemie.

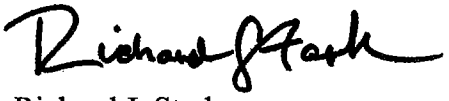
Teva and Pharmachemie are both subsidiaries of Teva Pharmaceutical Industries Ltd., an Israeli company that does not do business in the United States. Pharmachemie is a European company that does not directly distribute products in the United States and relies upon Teva and others physically to sell and distribute products in the United States.

To aid in the FTC's understanding of the corporate structure of Teva, I am enclosing a printout from Mergent Online that provides additional information concerning Teva Pharmaceutical Industries Ltd.

Confidential treatment of this letter and the enclosed materials is respectfully requested.

Thank you for your consideration and assistance. If you have any questions, please do not hesitate to call me at the number above.

Respectfully,



Richard J. Stark

Anne Schenof, Esq.
Bureau of Competition
Federal Trade Commission
601 New Jersey Avenue, N.W.
Washington, DC 20580

Encls.

FEDERAL EXPRESS

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FEDERAL EXPRESS

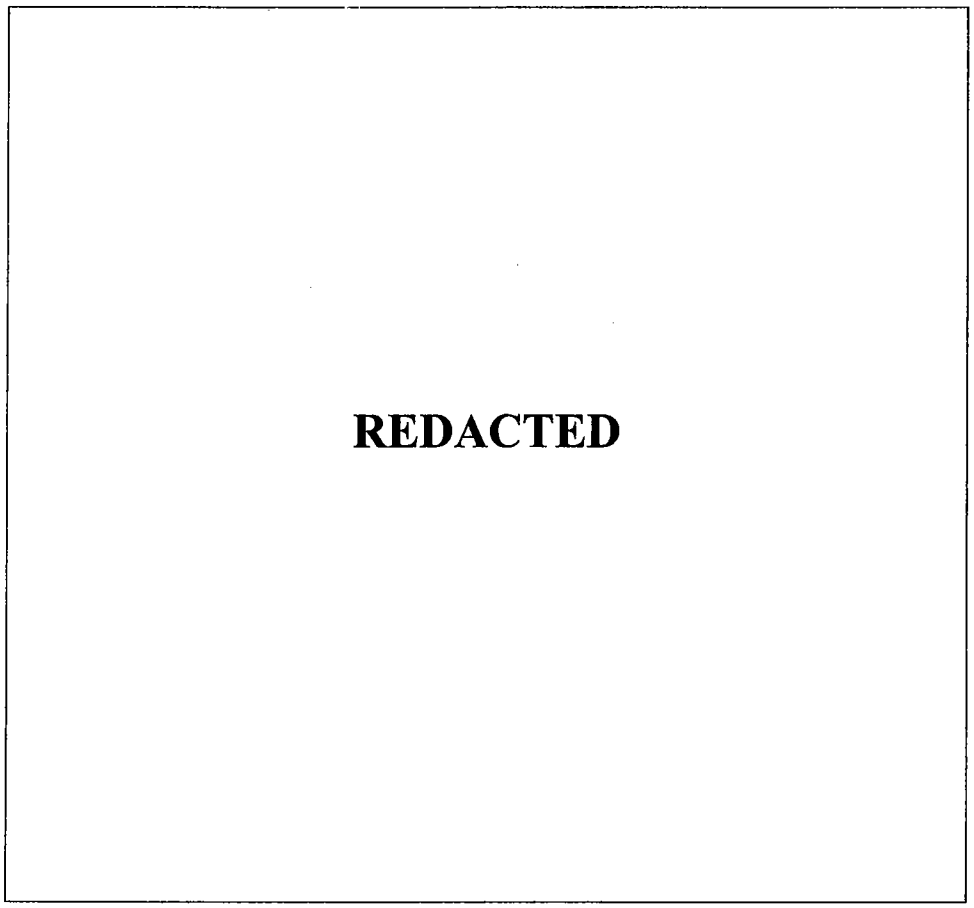
Carboplatin

Known ANDA Filers

Product Name	Company	ANDA Number	Tentative Approval Date	Lyophilized/ Solution	Source
Caboplatin Injection USP 10 mg/mL, Rx *Tentatively Approved*	Mayne Pharma	ANDA 76-517	3/30/04	Solution	FDA Website
Carboplatin Injection USP 50, 150 and 450 mg, Rx *Tentatively Approved*	Faulding Pharmaceutical	ANDA 76-473	4/16/03	Lyophilized	FDA Website
Carboplatin Injection USP 50, 150 or 450 mg, Rx *Tentatively Approved*	American Pharmaceutical Partners, Inc.	ANDA 76-235	5/22/02	Lyophilized	FDA Website
Carboplatin Injection USP 10 mg/mL, Rx *Tentatively Approved*	Gensia Sicor Pharmaceuticals, Inc.	ANDA 76-227	8/12/02	Solution	FDA Website
Carboplatin Injection USP 50, 150 or 450 mg, Rx *Tentatively Approved*	Pharmachemie B.V.	ANDA 76-162	1/14/03	Lyophilized	FDA Website
Carboplatin Injection 10 mg/mL, 5 mL, 15 mL and 45 mL vials *Status Unknown*	Pharmachemie B.V.	ANDA 76-292	N/A	Solution	Notice of Paragraph IV Certification
Carboplatin Injection USP 10 mg/mL, Rx *Tentatively Approved*	Bedford Laboratories	ANDA 76-039	6/6/03	Solution	FDA Website
Carboplatin Injection USP 50, 150 & 450 mg, Rx *Tentatively Approved*	Bedford Laboratories	ANDA 76-099	9/18/02	Lyophilized	FDA Website
Carboplatin Injection *Dosage Unknown* *Status Unknown*	Spectrum Pharmaceuticals, Inc.	Unknown	N/A	Unknown	Public Press Release

Paraplatin®

2003 Domestic Net Sales



Teva Pharmaceutical Industries Ltd. (Israel) (NMS: TEVA)

Teva Pharmaceutical Industries Ltd. (Israel)
5 Basel St.
Petach Tikva, 49131 Israel

Incorporated: 1944, Israel

Number of Employees: 10,960 (Approximate Full-Time as of 12/31/2003)

Country: Israel

Ticker: TEVA

Primary SIC: 2834 - Pharmaceutical preparations

Primary NAICS: 325412 - Pharmaceutical Preparation Manufacturing

Number of Shareholders: 1,600 (as of 01/30/2004)

Closing Stock Price: As of 4/2/2004 $64.47

PE Ratio N/A

Company Website: www.tevapharm.com

Mergent Dividend Achiever: No

Annual Meeting:

Other Search Tools
EDGAR

Business Summary

Teva Pharmaceutical Industries Limited is a global pharmaceutical company producing drugs in all major treatment categories. Co. utilizes its production and research capabilities to establish a global pharmaceutical operation focused on supplying the growing demand for generic drugs and on the opportunities for proprietary branded products for specific niche categories, such as its branded drug Copaxone®for multiple sclerosis. Co.'s active pharmaceutical ingredients (API) business provides both significant revenues and profits from sales to third party manufacturers and strategic benefits to Co.'s own pharmaceutical production through its timely delivery of significant raw materials.

Custom Report List

to Custom Reporting List

to Company Analysis List

Remove | Report

Financial Highlights (In USD as of 12/31/2003)

Total Revenue	3,276,400,000
Net Income	691,000,000
Total Assets	5,915,900,000
Current Assets	3,716,400,000
Total Liabilities	2,626,500,000
Current Liabilities	1,694,900,000
Long Term Debt	449,900,000
Stockholders' Equity	3,289,400,000

Key Executives

Eli Hurvitz - Chmn.
Israel Makov - Pres., C.E.O.

Principal Offices

5 Basel St.
Petach Tikva, 49131
Israel

Auditor

Kesselman & Kesselman

Legal Counsel

Tulchinsky - Stern & Co.;
Willkie Farr & Gallagher

Pricing Information

Ticker: TEVA Exchange: NMS

Closing Price As of 4/2/2004 $64.47

	Weeks Ending 04/03/2004	03/27/2004	03/20/2004	03/13/2004
Open Price	64.07	64.30	64.18	63.44
High Price	64.95	62.75	63.88	65.40
Low Price	61.86	61.20	62.22	61.79
Last Price	62.49	61.24	62.45	64.66
Total Volume	8,714,800	8,375,200	8,421,200	12,287,000
Average Volume for Past 30 days	62	63	64	65
52-Week Range	55.14 - 67.20			

History

Incorporated in Israel on Feb. 13, 1944. Present Co. established in 1976 upon the merger of three companies, Teva, Zori and Assia, which were originally established in Israel in the 1930's.

In Mar. and Apr. 1980, Co. acquired Ikapharm Ltd., a pharmaceutical manufacturer (merged effective Mar. 31, 1982), and Dr. N. Preminger Ltd. (now Promedico Ltd.) an importer of medicines and medical equipment.

In Feb. 1986, Co., through its U.S. joint venture company, acquired Lemmon Company, a U.S. producer and marketer of generic drugs.

On Apr. 10, 1987, Co. sold Promedico to foreign investors for US$4,000,000.

On Jan. 21, 1988, Co. purchased from Baxter–International Inc., a U.S. company, all of the issued and outstanding shares of Travenol Laboratories (Israel) Ltd. The shares of the above two companies were purchased for a total of approx. US$8,200,000.

On Mar. 29, 1988, Co. acquired the remaining outstanding shares of Migada Ltd. and Adam Ltd., Israeli companies which were previously 45% owned and 50% controlled, for approx. US$1,000,000.

On Oct. 11, 1988, Co. acquired approx. 98% of the equity of the issued and outstanding shares of Abic Ltd., an Israeli corporation which, directly and indirectly, through subsidiaries, manufactures and markets pharmaceutical and veterinary products, for approx. US$26,6000,000.

In 1989, Travenol Laboratories and Migada Ltd., subsidiaries of Co., were merged.

In Jan. 1991, Co. acquired the remaining 49.8% interest in TAG Pharmaceuticals, Inc. from W.R. Grace &Co. for US$20,000,000, plus up to US$4,000,000 payable based on the operating results of TAG until the year 2000.

In 1992, Co. acquired 100% of the share capital of Prochemia S.r.l. and is subsidiaries for a total payment of US$23,200,000.

In 1994, Co. acquired 34% of the share capital of Prographarm Laboratories for consideration of US$7,200,000 and 30% of the share capital of Portman Pharmaceuticals Inc. in consideration of US$1,500,000.

In Oct. 1995, Co. acquired Industrie Chimiche Italiane S.p.A.

In Nov. 1995, Co. acquired 78% of Biogal Pharmaceutical Works.

In 1996, Co. acquired Approved Prescription Services Ltd., a U.K. generic drug company, for US$52.2 million.

On July 1, 1998, Co. acquired full ownership and control of Pharmachemie N.V. for approx. US$83 million.

On Sept. 21, 1999, Co. acquired Copley Pharmaceutical, Inc. for US$220 million (including acquisition costs).

In Apr. 2000, Co. acquired Novopharm Ltd. In consideration, the vendor was issued 2.1 million ordinary shares of Co. and 6.3 million special shares that are exchangeable into ordinary shares of Co. at his discretion on a one–to–one ratio.

On Dec. 31, 2000, Co. acquired the shares in a subsidiary of Novopharm from the minority shareholders in this subsidiary, for a total amount of US$12 million.

In June 2002, Co. acquired full control and ownership of Honeywell Pharmaceutical Fine Chemicals S.r.l. (subsequently renamed Teva Pharmaceutical Fine Chemicals S.r.l.) in Italy and Bayer Classics S.A. (subsequently renamed Teva Classics S.A.) in France, as well as a shareholders' loan of US$34 million granted to the acquired company by the vendor. Total

consideration paid for the two acquisitions (including the shareholder's loan mentioned above and acquisition costs) was US$168 million in cash. Co. accounted for these acquisitions by the purchase method.

On Jan. 22, 2004, Co. acquired Sicor Inc. The purchase price paid by Co. amounted to approximately $3,460,000,000 in a combination of cash and Co. shares.

Joint Ventures

Subsidiaries

Company	% Owned	Country
Novopharm Ltd.	–	Canada
Plantex USA, Inc.	–	United States
Teva Neuroscience, Inc.	–	United States
Teva Pharamceuticals USA, Inc.	–	United States
Approved Prescription Services Limited	–	United Kingdom
Biogal Pharmaceutical Works Ltd.	99.30%	Hungary
Gry Pharma GmbH	–	Germany
Human Pharmaceutical Works Co. Ltd.	99.98%	Hungary
Orphahell BV	–	Netherlands
Pharmachemie Group	–	Netherlands
Prosintex Industrie Chimiche Italiane S.r.l.	–	Italy
Teva Pharmaceuticals Europe B.V.	–	Netherlands
Teva Classics S.A.	–	France
Teeva Sante SAS	–	France
Teva Pharmaceutical Fine Chemicals s.r.l.	–	Italy
Teva Pharma Italia S.r.l.	–	Italy
Abic Ltd.	–	–
Assia Chemical Industries Ltd.	–	–
Abic Biological Laboratories Teva Ltd.	–	–
Plantex Ltd.	–	–
Salomon, Levin and Elstein Ltd.	–	–
Teva Medical Ltd.	–	–
Genchem Pharma Ltd.	–	United States
Sicor Inc.	–	United States
Sicor Pharmaceuticals Sales, Inc.	–	United States
Sicor Pharmaceuticals, Inc.	–	United States
Rakepoll Holding B.V.	–	Netherlands
Sicor Biotech UAB	–	Lithuania
Sicor Europe S.A.	–	Switzerland
Sicor Societa Italiana Corticosteroidi S.p.A.	–	Italy
Tianjin Hualida Biotechnology Company Ltd	45.00%	China (Peoples Rep. Of)
Lemery S.A. de C.V.	–	Mexico
Sicor de Mexico S.A. de C.V.	–	Mexico
Sicor Latinoamerica S.A. de C.V.	–	Mexico

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Attorneys for Defendant
Pharmachemie B.V.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

BRISTOL-MYERS SQUIBB COMPANY and RESEARCH CORPORATION TECHNOLOGIES, INC. Plaintiffs, v. PHARMACHEMIE B.V. Defendant.	CIVIL ACTION No. 01-3751 (MLC) (Civil Action No. 02-1270 has been consolidated herewith)

AMENDED ANSWER AND COUNTERCLAIM TO CONSOLIDATED AMENDED COMPLAINT

Defendant Pharmachemie B.V. ("Pharmachemie") answers the correspondingly numbered paragraphs of plaintiffs' Amended Complaint for Patent Infringement as follows:

1. Pharmachemie is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 1, except that it believes that Bristol-Myers Squibb Company ("BMS") is a Delaware corporation with a principal place of business in New York, New York.

2. Pharmachemie is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 2, except that it believes that Research Corporation Technologies, Inc. ("RCT") is a Delaware corporation with a principal place of business in Tucson, Arizona.

3. Admits.

4. Admits.

5. Pharmachemie admits that it designated an agent for service of process in New Jersey in connection with the originally filed Civil Action No. 01-3751 (MLC) and further admits, for purposes of this action only, that Pharmachemie is subject to personal jurisdiction in this judicial district and that venue is proper in this Court under 28 U.S.C. §§ 1391(c) and 1400(b). Pharmachemie denies the remaining allegations of Paragraph 5.

6. Pharmachemie admits that United States Patent No. 4,657,927 (hereinafter the "'927 patent") issued on April 14, 1987, and that copies of the '927 patent and Certificates of Correction are attached to the Amended Complaint as Exhibit A. Pharmachemie is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations of Paragraph 6.

7. Pharmachemie is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 7.

8. Pharmachemie is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 8.

9. Pharmachemie admits that it filed an abbreviated new drug application ("ANDA") with the United States Food and Drug Administration ("FDA") for approval to market powder for injection products containing carboplatin as their active ingredient; that its ANDA included a certification under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the '927 patent is invalid, unenforceable, or will not be infringed; and that RCT and BMS received notice of the certification on June 26, 2001. Pharmachemie denies the remaining allegations of Paragraph 9.

10. Pharmachemie admits that it filed an ANDA with the FDA for approval to market injection products containing carboplatin as their active

ingredient (together with the powder for injection products which are the subject of ¶ 9 above referred to as "Pharmachemie Carboplatin Products"); that its ANDA included a certification under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the '927 patent is invalid, unenforceable, or will not be infringed; and that BMS received notice of the certification on February 25, 2002. Further answering, Pharmachemie states that RCT received notice of the certification on February 27, 2002. Pharmachemie denies the remaining allegations of Paragraph 10.

11. Pharmachemie admits that if the '927 patent is valid, its filing of the ANDAs referenced in ¶¶ 9 and 10 constitutes an act of infringement of at least one claim of the '927 patent pursuant to 35 U.S.C. § 271(e)(2)(A) entitling plaintiffs to an order that the effective date of the approval of both of Pharmachemie's ANDAs be a date which is not earlier than the April 14, 2004 expiration date of the '927 patent. Pharmachemie denies the remaining allegations of Paragraph 11.

FIRST AFFIRMATIVE DEFENSE

Claims 1 and 3 of the '927 patent are invalid and unenforceable against Pharmachemie by reason of obviousness-type double patenting.

COUNTERCLAIM

DECLARATORY JUDGMENT OF PATENT INVALIDITY

For its counterclaim Pharmachemie alleges the following:

1. Pharmachemie is a Netherlands corporation with a principal place of business in Haarlem, The Netherlands.

2. On information and belief, BMS is a Delaware corporation with a principal place of business in New York, New York.

3. On information and belief, RCT is a Delaware corporation with a principal place of business in Tucson, Arizona.

4. Subject matter jurisdiction exists pursuant to 28 U.S.C. § 1331 and § 1338.

5. Pharmachemie incorporates by reference the statements in paragraph 5 of its Answer establishing venue over this action in this Court.

THE RCT/BMS PATENTS

6. U.S. Patent No. 4,140,707 (the "'707 patent"), issued on February 20, 1979, identifies the inventors of that patent as Michael Cleare, James Hoeschele, Barnett Rosenberg, and Loretta VanCamp. The patent was subject to reexamination and a Reexamination Certificate issued on December 19, 1989. The term of the '707 patent was extended by 916 days under 35

U.S.C. § 156 in response to an application submitted to the United States Patent and Trademark Office by RCT based on the period of time required by FDA to review BMS' application for approval to market its carboplatin products in the United States. Copies of the '707 patent, the Reexamination Certificate and the Certificate Extending Patent Term are attached as Exhibit A.

7. The '707 patent expired on August 24, 1998.

8. Claims 1, 5, 6 and 7 of the '707 patent, after Reexamination, claim diammineplatinum(II) dicarboxylate compounds. Claim 7 is limited to carboplatin.

9. The '927 patent issued on April 14, 1987, and identifies the inventors of that patent as the same inventors identified in the '707 patent: Michael Cleare, James Hoeschele, Barnett Rosenberg, and Loretta Van Camp. Unless declared invalid or unenforceable, the '927 patent will continue in force until April 14, 2004, when it is currently scheduled to expire.

10. Claims 1 and 3 of the '927 patent generally claim compositions containing, and a method of treatment using, compounds, including those claimed in claims 1, 5, 6 and 7 of the '707 patent, to be administered parenterally. More specifically, claim 1 of the '927 patent claims a method for treating a specified malignant tumor which "comprises parenterally administering to an animal affected with said malignant tumor a solution

containing in an amount sufficient to cause regression of the tumor . . . [one of the diammineplatinum(II) dicarboxylate compounds claimed in the '707 patent and other [platinum(II) and] platinum(IV) compounds] . . . ." Claim 3 of the '927 patent claims a "composition suitable for parenteral administration to an animal affected with a . . . [specified malignant] tumor . . . comprising a pharmaceutically acceptable carrier and . . . [one of the diammineplatinum(II) dicarboxylate compounds claimed in the '707 patent and other [platinum(II) and] platinum(IV) compounds] . . . ."

THE PHARMACHEMIE CARBOPLATIN PRODUCTS

11. The Pharmachemie Carboplatin Products are 1) powder for injection products containing carboplatin as their active ingredient which, if approved for marketing in the United States, will be available in strengths of 50mg per vial, 150mg per vial and 450mg per vial; and 2) injection products containing carboplatin as their active ingredient which, if approved for marketing in the United States, will be available in 10mg/mL, 5mL, 15mL and 45mL vials.

12. On or about April 16, 2001, Pharmachemie filed with the FDA an ANDA seeking approval to market the powder for injection form of the Pharmachemie Carboplatin Products in the United States. On or about December 6, 2001, Pharmachemie filed with the FDA an ANDA seeking

approval to market the injection form of the Pharmachemie Carboplatin Products in the United States.

13. Pursuant to the Federal Food, Drug and Cosmetic Act, each ANDA contained a certification by Pharmachemie that, in its opinion, the '927 patent was invalid, unenforceable or not infringed. By letter dated June 20, 2001, notice of the certification in the April 16, 2001 ANDA submission setting forth the factual and legal basis for the opinion regarding the '927 patent was sent to RCT and BMS. By letter dated February 20, 2002, notice of the certification in the December 6, 2001 ANDA submission setting forth the factual and legal basis for the opinion regarding the '927 patent was sent to RCT and BMS.

14. BMS and RCT have asserted and are continuing to assert that the Pharmachemie Carboplatin Products will infringe claims 1 and 3 of the '927 patent.

15. Pharmachemie seeks a declaratory judgment that claims 1 and 3 of the '927 patent are invalid based on obviousness-type double patenting and, therefore, the Pharmachemie Carboplatin Products, when marketed in the United States, will not infringe those claims.

16. The only difference between the subject matter of the earlier issued claims in the '707 patent and the subject matter of the later issued claims 1 and 3 of the '927 patent, with respect to the compounds claimed in the '707 patent, is

the parenteral use of a solution containing such compounds to treat a specified malignant tumor (claim 1) and a composition that includes such compounds together with a "pharmaceutically acceptable carrier" (claim 3). The administration of such compounds to regress the tumors specified in those claims, and the manufacture or use of a composition containing such compounds in an amount sufficient to regress such tumors, would have been, to a person of ordinary skill in the relevant art and in light of the prior art, an obvious modification of the inventions claimed in the '707 patent.

17. An actual controversy exists between RCT/BMS and Pharmachemie with respect to invalidity of claims 1 and 3 of the '927 patent by reason of obviousness-type double patenting.

WHEREFORE, Pharmachemie prays for judgment against BMS and RCT:

(a) Dismissing the Amended Complaint herein;

(b) Declaring that claims 1 and 3 of the '927 patent are invalid and unenforceable based on obviousness-type double patenting; and

(c) Permanently enjoining RCT/BMS, their officers, agents, directors, servants, employees, subsidiaries and assigns, and all those acting under the authority of or in privity with them or with any of them, from asserting or otherwise seeking to enforce the '927 patent against Pharmachemie.

PHARMACHEMIE B.V.
By its attorneys,

STERNS & WEINROTH
A Professional Corporation
50 West State Street
Suite 1400
Trenton, NJ 08607

Dated: October 22, 2002

Karen A. Confoy (KC-0848)

OF COUNSEL:
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111 Huntington Avenue
Boston, MA 02199

United States Patent [19]

Cleare et al.

[11] 4,140,707

[45] Feb. 20, 1979

[54] MALONATO PLATINUM ANTI-TUMOR COMPOUNDS

[75] Inventors: Michael J. Cleare; James D. Hoeschele; Barnett Rosenberg; Loretta L. Van Camp, all of East Lansing, Mich.

[73] Assignee: Research Corporation, New York, N.Y.

[21] Appl. No.: 778,955

[22] Filed: Mar. 18, 1977

Related U.S. Application Data

[63] Continuation of Ser. No. 260,989, Jun. 8, 1972, abandoned.

[51] Int. Cl.[2] C07F 15/00

[52] U.S. Cl. ..... 260/429 R; 424/245; 424/287; 546/4

[58] Field of Search ..... 260/429 R

[56] References Cited

PUBLICATIONS

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Attorney, Agent, or Firm—Dennis P. Clarke

[57] ABSTRACT

Malonato platinum coordination compounds and a method of treating malignant tumors comprising the parenteral administration to an affected animal of a solution of the compound.

4 Claims, No Drawings

MALONATO PLATINUM ANTI-TUMOR COMPOUNDS

The invention described herein was made in the course of work under a grant or award from the Department of Health, Education and Welfare.

This is a continuation, of application Ser. No. 260,989, filed June 8, 1972, now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to novel malonato platinum coordination compounds and to their use in cancer chemotherapy.

SUMMARY OF THE INVENTION

The invention provides platinum coordination compounds having the formula:

$$[Pt(II)A_x(OOC)_2{-}CRR_1] \text{ or}$$

$$\text{cis or trans}[Pt(IV)A_x(OOC)_2{-}CRR_1)_yL_z]$$

wherein:

x = 1 or 2;

y = 1 or 2;

z = 0, 1 or 2,

provided that when y = 2, z = 0 and when y = 1, z is greater than 0;

R and R_1 are selected from the group consisting of H, lower alkyl, aryl, aralkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, OH, or are combined with the carbon atom to form a cycloalkyl or cycloalkenyl group, and substituted derivatives thereof;

when x = 1, A is $HR_2N{-}CHR_3{-}CHR_4{-}NR_5H$ and when x = 2, A is H_2NR_6 a heterocyclic amine or an amino acid, wherein R_2, R_3, R_4 and R_5 are the same or different and are selected from the group consisting of H, CH_3, C_2H_5, hydroxy and lower alkoxy provided that R_2 and R_5 may also be aryl or aralkyl, and each R_6 is the same or different and is selected from the group consisting of H, lower alkyl, aryl, aralkyl, hydroxy lower alkyl, hydroxyl and alkoxyl amines, alkoxylalkylamines wherein all of said alkyl groups are lower alkyls and heterocyclic substituents including said N as a ring member;

when z = 1, L is a bidentate anionic ligand, and

when z = 2, L is a monodentate anionic ligand.

The invention also relates to a composition and method for treating malignant tumors in animals comprising parenterally administering to an animal affected with a malignant tumor a solution containing a platinum coordination compound as defined hereinabove in an amount sufficient to cause regression of the tumor.

DETAILED DESCRIPTION OF THE INVENTION

Platinum coordination compounds and methods for their production are described by J. C. Bailar, Jr., *The Chemistry of the Coordination Compounds*, Reinhold Publishing Corp., N.Y., 1956, Chap. 2; J. Lewis et al, *Modern Coordination Chemistry: Principles and Methods*, Interscience Publishers, Inc., N.Y., 1960 and Kauffman *Inorganic Synthesis*, 7, McGraw-Hill Book Co., Inc., N.Y., 1963.

Platinum (II) forms dsp^2 coordination compounds which have a square planar arrangement in space. Platinum (IV) forms d^2sp^3 coordination compounds which have an octahedral arrangement in space.

The coordination compounds of the invention include the cis and trans isomers of platinum (II) and platinum (IV) which contain the bidentate malonato ligand which may be substituted or unsubstituted. The malonato ligand may contain substituents selected from the group consisting of lower alkyl, (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, etc.); aryl, (e.g., phenyl; lower alkyl-, lower alkenyl-, halo-, nitro-, lower alkoxy-substituted phenyl and naphthyl); aralkyl, (e.g., phenylmethyl (benzyl), 2-(1-naphthyl)methyl); alkenyl, (e.g., 4-amino-1-butene, allyl); cycloalkyl, (e.g., cyclopropyl, cyclohexyl, etc.); cycloalkenyl, (e.g., 2-cyclopenten-1-yl, 2-cyclohexen-1-yl); alkoxy, (e.g., methoxy, ethoxy, etc.), and hydroxy. Also suitable are the 1,1-cycloalkylenedicarboxylic acids, (e.g., 1,1-cyclopropanedicarobxylic acid, 1,1-cyclobutanedicarboxylic acid, etc.) and the 1,1-cycloalkenyldicarboxylic acids, (e.g., 1,1-cyclopropenedicarboxylic acid, 1,1-cyclobutenedicarboxylic acid, etc.)

The coordination compounds of the invention also contain two monodentate ammonia or primary or heterocyclic amine ligands, i.e., when x in the above formula is 2 or one bidentate amine ligand, i.e., when x is 1.

Suitable monodentate amine ligands include lower alkyl amines, (e.g., methyl-, ethyl-, n-propyl-, isopropyl-, n-butyl- amines, etc.), aryl amines, (e.g., aniline), aralkyl amines, (e.g., benzylamine), hydroxy lower alkyl amines, (e.g., ethanolamine, propanolamine; etc), hydroxylamine, lower alkoxy amines (e.g., methoxylamine, etc.), alkoxyalkylamines (e.g., methoxymethylamine, etc.), and heterocyclic amines (e.g., pyridine and aziridine). Also included are the amino acids, i.e., $R_7{-}CHNH_2{-}COOH$ wherein R_7 is H, lower alkyl (e.g., methyl, isopropyl, etc.), hydroxy lower alkyl (e.g., hydroxymethyl, hydroxyethyl, etc.), aralkyl (e.g., benzyl, etc).

It is to be understood that the coordination compounds of the invention may include two identical or different monodentate ligands.

Suitable bidentate amine ligands include the substituted and unsubstituted primary and secondary ethylenediamines. One or both of the carbon atoms of the ethylenediamine may contain substituents such as lower alkyl (e.g., methyl, ethyl), hydroxyl, alkoxy (e.g., methoxy, ethoxy, etc). Secondary ethylenediamines wherein one or more of the amine groups contains substituents such as listed above for the carbon atoms of the primary amine and aryl (e.g., phenyl) and aralkyl (, e.g. benzyl) may also be utilized.

The Pt (II) coordination compounds specified herein do not exist as geometrical isomers; however, the Pt (IV) compounds exist as cis and trans isomers. It is to be further understood that the invention is inclusive of the cis and trans isomers.

The Pt (IV) coordination compounds may also contain two monodentate or one bidentate anionic ligand where only one malonato ligand is present, i.e., where y = 1 in the above formula.

Suitable monodentate anionic ligands include chloride, bromide, iodide, nitrite, hydroxide, nitrate, sulfmate, etc. Among the bidentate anionic ligands which may be present are oxalate, pyrophosphate, dithioxalate.

It is to be understood that the invention includes those coordination compounds containing mixed monodentate anionic ligands.

The preferred compounds are those wherein R and R_1 in the above formula are H, methyl or ethyl, i.e., malonatoplatinum, methylmalonatoplatinum and ethylmalonatoplatinum coordination compounds. The most preferred Pt (II) compounds are those malonatoplatinum (II) compounds of the above formula wherein x = 1 and R_2, R_3, R_4 and R_5 are each H, i.e., malonatoethylenediamine platinum (II), methylmalonatoethylenediaminеplatinum (II) and ethylmalonatoethylenediaminеplatinum (II); and wherein x = 2 and each R_6 is H, i.e., malonatodiammineplatinum (II), methylmalonatodiammineplatinum (II) and ethylmalonatodiammineplatinum (II).

The preferred Pt (IV) compounds are those wherein x = 2, each R_6 is H and y = 2, i.e., bismalonato (or bismethylmalonato or bisethylmalonato) diammine platinum (IV).

The coordination compounds of the invention may be prepared by one of a variety of well-known methods. A general method of preparation of the Pt (II) coordination compounds is as follows: Starting compounds having the formula cis-[Pt A(Hal)$_2$] wherein Hal is I, Cl or Br and A is one bidentate or two monodentate amine ligands (prepared by the method of S. C. Dhara, Indian J. Chem., Vol 8, p. 193 (1970)) are reacted with silver nitrate to form the diaquo complex. The latter is then reacted with the malonate ion to form the coordination compounds of the invention. This method is represented by the following reaction scheme:

$$\text{cis-[Pt A Cl}_2\text{]} + 2AgNO_3 + 2H_2O \rightarrow \text{cis-[Pt A(H}_2\text{O)}_2\text{](NO}_3\text{)}_2 + 2AgCl$$

$$\text{cis-[Pt A(H}_2\text{O)}_2\text{](NO}_3\text{)}_2 + H_2C\text{-(COO)}_2 \rightarrow \text{[Pt A(OOC)}_2\text{-CH}_2\text{]} + 2NO_3^- + 2H_2O$$

wherein A is one bidentate amine ligand or two monodentate amine ligands.

The following non-limiting examples are illustrative of the methods for preparing the compounds of the invention.

EXAMPLE 1

Malonatodiammineplatinum(II)

$[Pt(NH_3)_2(C_3H_2O_4)]$

Reactions:

$$[Pt(NH_3)_2Cl_2] + 2AgNO_3 + 2H_2O \rightarrow [Pt(NH_3)_2(H_2O)_2](NO_3) + 2AgCl \quad \text{I}$$

$$[Pt(NH_3)_2(H_2O)_2](NO_3)_2 + C_3H_2O_4{}^{2-} \rightarrow [Pt(NH_3)_2(C_3H_2O_4)] + 2NO_3^- + 2H_2O. \quad \text{II}$$

Silver nitrate (22.55g — slightly less than the stoichiometric amount in order to avoid silver contamination) was dissolved in water (50 ml.) and added to $[Pt(NH_3)_2Cl_2]$ (20g) in a 250 ml. conical flask. The contents were warmed (60° C.) on a hot plate with rapid stirring until the silver chloride precipitation was complete and the mother liquor was almost colorless. The silver chloride was filtered off using a fine pore sintered glass filter and the precipitate was washed several times with hot water to give a total filtrate volume of 100–200 ml.

Malonic acid (13g — a twofold excess) was dissolved in water (30 ml.) and neutralized with a solution of KOH (~13g in 30 ml.) to pH 5–6. The resulting potassium malonate solution was added to the platinum containing filtrate and the mixture was carefully warmed (to avoid "bumping") on the hot plate until white crystals of the product started to form in great quantity. The mixture was then cooled to room temperature and the product filtered off. The filtrate was reheated for 5–10 minutes and cooled to 0° C. to collect a further crop. The crude yield at this stage was 20.5g (93%).

The product was recrystallized by dissolving in boiling or near boiling water. The above yield (20.5g) required about 3 liters of boiling water for complete dissolution. Malonic acid 1g/L was dissolved in the water to suppress any hydrolysis.* The filtered solution was cooled to 0° C. to give white fluffy needles (18.25g–83%).

*U.V./vis spectral and conductivity studies have shown that hydrolysis is negligible.

The crystals decompose between 185°–190° C. The structure of the product was verified via an i.r. spectrum. Solubility of the product is low in cold water, i.e., 20 mg/100 mls at 20° C. and 43 mg/100 mls at 37° C., but higher in near boiling water (90°–100° C.)~65g/100 ml.

The empirical composition was verified by elemental analysis:

Malonatodiammineplatinum(II) $[Pt(NH_3)_2(C_3H_2O_4)]$

Calculated for $C_3H_8N_2O_4Pt$.C.: 10.88; H: 2.43; N: 8.46: Pt 58.9; Found C: 10.67; H: 2.35; N: 8.54; Pt 58.7.

EXAMPLE 2

$[Pt\ (en)\ (C_4H_4O_4)]$ (en = $H2N(CH_2)_2NH_2$; $C_4H_4O_4{}^{2-}$ = $O_2C\ CH(CH_3)\ CO_2{}^{2-}$)

Silver nitrate (3.64g) was dissolved in 20 ml of water and added to $[Pt(NH_2)_2(CH_2)_2CL_2]$ (3.5g) suspended in water (30 mL) in a conical flask. The mixture was stirred on a warm hot plate for 5–10 minutes until all the yellow platinum complex had dissolved to give a yellow liquor plus a copious white silver chloride precipitate. The mixture was filtered through a fine pore filter and the precipitate washed twice with small volumes of hot water. The clear filtrate plus washings was added to an aqueous solution of methylmalonic acid (2g in 20mls) which had been adjusted to pH 5–6. The mixture was heated to about 80° C. for five minutes and then cooled to 0° C. The shiny white crystals which formed were filtered and washed with cold water and acetone (Yield 2.65g). The mother liquor plus aqueous washings was reduced to about half its original volume (~30 mls) to yield a second crop on cooling to 0° C. (Yield 0.85g). Total Crude yield was 3.50 gms (88%). The complex was recrystallized from a minimum volume of boiling water (around 250 mls) with filtration through a fine pore filter prior to cooling to 0° C.

Yield of shiny white leaflets 2.96g (74%).

Calculated for $C_6H_{12}N_2O_4Pt$: C:19.41 H 3.26 N:7.55; Found C:19.11 H 3.61 N:7.89.

A second crop (0.33g–8%) was obtained by reducing the bulk of the mother liquor.

EXAMPLE 3

trans-[Pt IV$(NH_3)_2$(mal)$_2$]

Silver nitrate (5.45g) was dissolved in water (30 ml) and added to trans $[Pt(NH_3)_2Cl_4]$ (3g) suspended in water (30 mls) containing concentrated nitric acid (3 ml). The contents were warmed on a hot plate (70°–80° C.) and stirred for at least one hour. The mixture was filtered through a fine pore sintered glass filter to remove the silver chloride. The precipitate was washed twice with a small volume of hot water. The clear fil-

trate plus washings was tested with a drop of 1M KCl solutions to determine if excess silver chloride was present. (If the test is positive, sufficient KCl is added dropwise to the bulk solution until no silver chloride is precipitated.) The solution was refiltered and the filtrate reduced to 20–30 mls in volume and cooled to 0° C. to yield plate yellow crystals (presumably trans $(Pt(NH_3)_2(NO_3)_4)$). These were washed with a little cold water and then acetone (Yield 1.8g). A portion of this yield (1g) was dissolved in a minimum of hot water to which sodium nitrate (0.2g) had been added. This solution was filtered into an aqueous solution of malonic acid (0.5g — a slight excess) which had been adjusted to pH 5–6 with sodium hydroxide. White nucro-crystals of the complex quickly form on cooling. These were filtered off and washed with cold water and acetone. (Yield 0.7g — 30–40%).

Calculated for $C_6H_{10}N_2O_8Pt$ C:16.63 H 2.33 N:6.47; Found C:16.60 H 2.64 N:6.80.

GENERAL STRUCTURE CONFORMATION

The malonate group is shown to be coordinated to the platinum by the observed change in the electronic spectra on going from the aquo to the malonate species. Thus, structures such as $[Pt(NH_3)_2(H_2O)_2]_2(H_2C_3O_4)]$ are ruled out confirming the analytical data. Similarly, zero-time conductivity measurements support a neutral compound. The i.r. spectra show the presence of coordinated carboxyl groups (1600–1650 cm^{-1} and 1400 cm^{-1}) with no CO_2H groups (which would show at 1700–1750 cm). Finally the carboxyl group vibrations are compatible with a chelated structure as compared to oxalate complexes of known structures.

The compounds of the invention were tested for anti-tumor activity using our standard screening tumor, solid sarcoma 180 tumor in female Swiss white mice, following standard protocols for this testing as set by the National Cancer Institute. (*Cancer Chemotherapy Rep.*, 25(1962)).

For these tests an S 180 tumor taken from a sacrificed mouse was dissected free of superfluous tissue and cut under sterile conditions into approximately 10 milligram size pieces. These tissue pieces were then implanted by trocar in the left axillary region, subcutaneously, in new mice. The mice were, on the average, approximately four weeks old and weighed 18–20 grams. Taking day 0 as the day of implant, the animals were sacrificed on day 10. The tumors were excised and weighed and the ratio of the weights of the tumors in mice in the treated animals to the control set of animals was obtained. This ratio, multiplied by 100, is given as the T/C ratio in Table I.

For the first set of tests the coordination compound was freshly dissolved in sterile distilled water and injected intraperitoneally on day 1 into each of the test mice. The volume of the injection was usually ½ ml. In some cases, in order to get an active dose into the animal where the chemical was not soluble in this amount of solvent, a fine dispersion was prepared of the dose needed for the test. Thus, some of our test results were obtained on animals where a slurry of the compound was injected. These are so noted in Table I below. In addition, for some of the compounds, there was injected about 1 ml of solution, either in one single injection, or in 2 injections given a few hours apart of ½ ml each. These injections were initially given in 4 different dose levels for each new compound with 6 mice in each dose level. The tests covered a dose range from a low ineffective dose, to an upper dose level which produced some deaths within the time period of the experiment. The results are set forth in Table I.

TABLE I

Tests of Antitumor Activity of Malonato and Substituted Malonato Coordination Complexes of Platinum.

Tumor-Sarcoma 180 Animal-Female Swiss white mice
Single injection on days noted, intraperitoneally

Coordination Complex	Day of Injection	Dose Level	T/C	No. of Deaths
Malonatodiammineplatinum (II) (slurry in H_2O)	1	10 mg/kg	76	0
		15 mg/kg	38	0
		20 mg/kg	64	0
		25 mg/kg	31	0
		30 mg/kg	7	1/6
		40 mg/kg	—	6/6
		50 mg/kg	1	5/6
		60 mg/kg	—	6/6
(solution in H_2O)	Daily for days 1–10	4 mg/kg	54	0
		5 mg/kg	56	0
		6 mg/kg	23	0
		7 mg/kg	12	0
Methylmalonatodiammine-platinum(II) (Solution in H_2O)	1	30 mg/kg	39	0
		40 mg/kg	26	0
		50 mg/kg	35	0
		60 mg/kg	6	0
		70 mg/kg	124	3/6
		80 mg/kg	—	6/6
malonatoethylenediamine-platinum (II)	1	60	80	0
		80	138	0
		100	85	0
		120	50	0
ethylmalonatoethylenediamine-platinum (II)	1	40	72	0
		60	81	0
		80	79	0
		90	47	0
		100	55	1
		110	41	0
		120	58	0
malonato-1,2 propylenediamine-platinum (II)	1	45	50	0
		60	9	1
		75	16	3
		90	—	5

-continued

Coordination Complex	Day of Injection	Dose Level	T/C	No. of Deaths
malonato-1,3 propylenediamine-platinum (II)	1	20	69	0
		40	79	0
		60	21	0
		80	35	1
methylmalonatoethylene-diamineplatinum (II) (solution in H_2O)	1	30 mg/kg	78	0
		40 mg/kg	80	0
		50 mg/kg	51	0
		60 mg/kg	26	0
		70 mg/kg	20	1
		90 mg/kg	4	1
ethylmalonatodiammine-platinum(II) (solution in H_2O)	1	30 mg/kg	57	0
		40 mg/kg	43	0
		50 mg/kg	47	0
		60 mg/kg	39	0
		70 mg/kg	17	0
		80 mg/kg	16	0
malonatoethylenediamine-platinum (II) (solution in H_2O)	1	10 mg/kg	88	0
		20 mg/kg	58	0
		40 mg/kg	18	0
		45 mg/kg	49	0
		50 mg/kg	33	0
		55 mg/kg	38	0
		60 mg/kg	15	3/6
		80 mg/kg	24	3/6
1,1-cyclobutanedicarboxylate diammineplatinum (II)	1	20 mg/kg	71	0
		40 mg/kg	60	0
		60 mg/kg	38	0
		80 mg/kg	42	0
		100 mg/kg	69	0
		120 mg/kg	18	0
		160 mg/kg	62	4
malonatobis(methylamine) platinum (II)	1	80 mg/kg	58	0
		100 mg/kg	53	0
		120 mg/kg	28	0
		140 mg/kg	25	0
		160 mg/kg	17	1
		180 mg/kg	19	1

In addition to the day 1 injections described above, in a number of cases injections were delayed until day 8 of tumor growth. In these cases the tumor was usually at least larger than ½ gm, as estimated by palpation. The animals were then injected and observed for a period of approximately 60 days. Activity was measured by the number of animals whose tumors had regressed to the vanishing point, while still allowing the animal to survive for this time period. Such test results are described in TABLE II below.

TABLE II

Tests of Large Sarcoma 180 Regressions by Malonato Coordination Complexes of Platinum.
Tumor-Sarcoma 180 Animal-Female Swiss white mice
Single injections on Day 8 intraperitoneally in H_2O solutions

Coordination Complex	Dose	Total Number of Regressions	Deaths
malonatodiammine-platinum(II)	14 mg/kg	2	4
	16 mg/kg	3	3
	18 mg/kg	4	2
	20 mg/kg	5	1
malonatoethylene-diamineplatinum(II)	40 mg/kg	3	3
	45 mg/kg	1	5
	50 mg/kg	2	4
	60 mg/kg	3	3

The results described in Tables I and II indicate that the compounds of the invention are very potent antitumor agents against the S 180 tumor in Swiss white mice.

Confirmatory tests of antitumor activity against the Walker 256 Circinosarcoma in rats, and the ADJ/PC6A tumor in mice were conducted. The initial test results are shown in Table III and confirm the potent action of the compounds of the invention against these other tumor systems.

TABLE III

Confirmatory Tests of Antitumor Activity
Malonatodiammineplatinum(II)
Tumor: Walker 256 Carcinosarcoma - Animal - Rat
Single injection Day 1 in Oil, Intraperitoneally

Dose	% Inhibition	Deaths
10 mg/kg	100	0
20 mg/kg	100	0
40 mg/kg	100	0
80 mg/kg	—	0

Malonatoethylenediammineplatinum(II)
Tumor: Walker 256 Carcinosarcoma - Animal - Rat
Single injection Day 1 in Oil, Intraperitoneally

Dose	% Inhibition	Deaths
10	1	0
20	25	0
40	100	0
80	100	0
160	—	all

Tumor: ADJ/PC6A - Animal - Mouse
Single injection Day 25 in Oil, Intraperitoneally

Dose	% Inhibition	Deaths
4	13	0
20	94	0
100	100	0
500	—	all

Samples of the malonato diammine and malonato ethylene diamino complexes of platinum(II) were submitted to the Drug Research and Development Branch of the National Cancer Institute for screening for antitumor activity against the L1210 tumor in mice. The results obtained on this tumor system are shown in Table IV. They confirm the activity of the compounds of the invention.

TABLE IV

Confirmatory Tests of Antitumor Activity at the National Cancer Institute.
Tumor: L1210 Animal - Mice
Daily injectons Days 1-9, Intraperitoneally

TABLE IV-continued

Confirmatory Tests of Antitumor Activity at the National Cancer Institute.

Coordination Complex	Dose	% Increase in Lifespan
Malonatodiammineplatinum(II)	50 mg/kg	163
	25 mg/kg	133
	12.5 mg/kg	115
Malonatoethylenediammineplatinum(II)		
	50 mg/kg	101
	25 mg/kg	160
	12.5 mg/kg	151
(repeat test)	37.5 mg/kg	121
Tumor: L1210	Animal - Mice	
Daily injections Days 1-9, Intraperitoneally		
Coordination Complex	Dose	% Increase in Lifespan
	25 mg/kg	196
	16.5 mg/kg	160
	11 mg/kg	145

The malonatoplatinum coordination compounds of the invention are preferably dissolved or suspended in water or other pharmaceutically acceptable carrier liquids. The parenterally administerable composition should preferably contain from about 0.5mg to about 10mg per ml., it being understood that the amount may vary greatly depending upon the particular compound employed and the animal to be treated.

The platinum coordination compounds of the invention are preferably administered parenterally to an animal affected with a malignant tumor. The duration of treatment and the dose level, of course, will depend in each case upon the size of the host animal, nature and size of the tumor, etc. Generally, however, a dose level of from about 20 to about 200 mg/kg of body weight per day will be sufficient. It is to be understood, however, that the platinum coordination compounds compounded with a suitable pharmaceutical carrier in the same proportions as recited above may also be administered orally at the same dosage levels.

We claim:

1. Platinum coordination compounds having the formula:

$$[Pt(II)A_x((OOC)_2{-}CRR_1)]$$

wherein:

x = 1 or 2;

R and R_1 are selected from the group consisting of H, lower alkyl, aryl, aralkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, OH, or combine with the carbon atom to form a cycloalkyl or cycloalkenyl group;

when x = 1, A is $HR_2N{-}CHR_3{-}CHR_4{-}NR_5H$ and when x = 2, A is H_2NR_6 or an amino acid, wherein R_2, R_3, R_4 and R_5 are the same or different and are selected from the group consisting of H, CH_3, C_2H_5, hydroxy and lower alkoxy, provided that R_2 and R_5 may also be aryl or aralkyl and each R_6 is the same or different and is selected from the group consisting of H, lower alkyl, aryl, aralkyl, hydroxy lower alkyl, hydroxyl- and alkoxylamines, and alkoxyl alkyl amines.

2. The compound of claim 1 having the formula:

$$[Pt(II)A_x((OOC)_2{-}CH_2)]$$

wherein:

x = 1, and

R_2, R_3, R_4 and R_5 are each H.

3. The compound of claim 1 having the formula:

$$[Pt(II)A_x((OOC)_2{-}CH_2)]$$

wherein:

x = 2, and each R_6 is H.

4. Malonato diammine platinum (II).

* * * * *

REEXAMINATION CERTIFICATE (1173rd)

United States Patent [19]

[11] B1 4,140,707

Cleare et al.

[45] Certificate Issued Dec. 19, 1989

[54] MALONATO PLATINUM ANTI-TUMOR COMPOUNDS

[75] Inventors: Michael J. Cleare; James D. Hoeschele; Barnett Rosenberg; Loretta L. Van Camp, all of East Lansing, Mich.

[73] Assignee: Research Corporation Technologies, Inc., Tucson, Ariz.

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[52] U.S. Cl. 556/137; 546/2; 556/17
[58] Field of Search 546/2; 556/17, 137

[56] References Cited

PUBLICATIONS

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Primary Examiner—A. McFarlane

[57] ABSTRACT

Malonato platinum coordination compounds and a method of treating malignant tumors comprising the parenteral administration to an affected animal of a solution of the compound.

REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims 3 and 4 are cancelled.

Claim 1 is determined to be patentable as amended.

Claim 2, dependent on an amended claim, is determined to be patentable.

New claims 5, 6, and 7 are added and determined to be patentable.

1. Platinum coordination compounds having the formula:

$$[Pt(L)_{2-x}A_x((OOC)_2—CRR_1)]$$

wherein:

$x=1$ or 2;

R and R_1 are selected from the group consisting of H, lower alkyl, aryl, aralkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, OH, or combine with the carbon atom *in* CRR_1 to form a cycloalkyl or cycloalkenyl group;

when $x=1$, A is $HR_2N—CHR_3—CHR_4—NR_5H$ and when $x=2$, A is H_2NR_6 or an amino acid, wherein R_2, R_3, R_4 and R_5 are the same or different and are selected from the group consisting of H, CH_3, C_2H_5, hydroxy and lower alkoxy, provided that R_2 and R_3 [may also be] *are also selected from the group consisting of* aryl or aralkyl and each R_6 is the same or different and is selected from the group consisting of H, lower alkyl, aryl, aralkyl, hydroxy lower alkyl, hydroxyl- and alkoxylamines, and alkoxyl alkyl amines, *provided that when* $x=2$ *and A is* H_2NR_6 *and* R_4 *is H, then R and* R_1 *are not both H.*

5. The compound of claim 1 wherein R and R_1 *taken together with the carbon to which they are attached form a cycloalkyl group.*

6. The compound of claim 5 wherein R and R_1 *taken together with the carbon atom to which they are attached form a cyclobutane.*

7. 1,1 cyclobutane dicarboxylate diammine platinum (II).

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. 156

Patent No. : 4,140,707

Dated : February 20, 1979

Inventor(s) : Michael J. Cleare et al

Patent Owner : Research Corporation Technologies, Inc.

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

916 DAYS

with all rights pertaining thereto as provided by 35 USC 156 (b).

I have caused the seal of the Patent and Trademark Office to be affixed this 25th day of January 1990.

Jeffrey M. Samuels
Acting Commissioner of
Patents and Trademarks