IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

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SANOFI-AVENTIS and DEBIOPHARM S.A.

SANOFI-AVENTIS U.S. LLC, SANOFI-AVENTIS, DEBIOPHARM S.A., Plaintiffs, v. PHARMACHEMIE B.V. TEVA PARENTERAL MEDICINES, INC., TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., and SICOR DE MEXICO, S.A. DE C.V. Defendants.	CIVIL ACTION NO.:

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Sanofi-Aventis U.S. LLC, Sanofi-Aventis, and Debiopharm S.A. (hereinafter "Plaintiffs"), by way of Complaint against Pharmachemie B.V., Teva Parenteral Medicines, Inc., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., and Sicor de Mexico, S.A. DE C.V. allege as follows:

THE PARTIES

1. Sanofi-Aventis is a corporation organized and existing under the laws of France, having its principal place of business at 174 avenue de France, Paris, France. Sanofi-Aventis is a global innovator healthcare company whose core therapeutic areas are oncology, diseases of the central nervous system, cardiovascular disease, and internal medicine.

2. Sanofi-Aventis U.S. LLC is a U.S. subsidiary of Sanofi-Aventis and is a company organized under the laws of the state of Delaware, having commercial headquarters at 55 Corporate Drive, Bridgewater, New Jersey 08807.

3. Debiopharm S.A. ("Debiopharm") is a corporation, existing under the laws of Switzerland, having its principal place of business at Forum "après-demain" Chemin Messidor 5-7, Case postale 5911, CH - 1002 Lausanne, Switzerland. Debiopharm develops innovative and life-saving pharmaceuticals.

4. On information and belief, Pharmachemie B.V. is a corporation, existing under the laws of The Netherlands, having its principal place of business at Swensweg 5, 2031 GA Haarlem, The Netherlands.

5. On information and belief, Teva Parenteral Medicines, Inc. ("Teva Parenteral") is incorporated under the laws of the State of Delaware, having an office and conducting business at 2050 Springdale Rd., Cherry Hill, NJ 08003.

6. On information and belief, Teva Pharmaceuticals USA, Inc. ("Teva USA") is a corporation incorporated under the laws of the State of Delaware, conducting business from facilities at 18-01 River Road, Fair Lawn, New Jersey 07041, and having its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454.

7. On information and belief, Teva Pharmaceutical Industries, Ltd. ("Teva Israel") is a corporation organized and existing under the laws of Israel, having its corporate headquarters at 5 Basel Street, P.O.B. 3190, Petach Tikva 49131, Israel.

8. On information and belief, Sicor de Mexico, S.A. de C.V. ("Sicor") is a corporation organized and existing under the laws of Mexico, having its corporate headquarters at Av. San Rafael No. 35 Parque Industrial Lerma, Lerma 52000, Mexico.

9. On information and belief, Teva Parenteral is a wholly owned subsidiary of Teva USA. On information and belief, Teva USA is a wholly owned subsidiary of Teva Israel.

10. On information and belief, Pharmachemie BV is a subsidiary, affiliate or division of Teva Israel.

11. On information and belief, Teva Parenteral is an affiliate and agent of Pharmachemie B.V.

12. On information and belief, Sicor holds a Drug Master File ("DMF") for oxaliplatin and manufactures and sells oxaliplatin to Pharmachemie B.V., Teva Parenteral, Teva USA, and/or Teva Israel for use in oxaliplatin drug products.

13. On information and belief, Pharmachemie B.V. is in the business of developing and manufacturing generic pharmaceutical products, which are copies of products invented and developed by innovator pharmaceutical companies.

14. On information and belief, Pharmachemie B.V. assembled and caused to be filed with the United States Food and Drug Administration, pursuant to 21 U.S.C. § 355(j), Abbreviated New Drug Application ("ANDA") No. 78-820 concerning proposed drug products, Oxaliplatin Injection 5mg/mL in both 10 mL and 20 mL doses and an amendment to ANDA No. 78-820, concerning a proposed drug product, Oxaliplatin Injection, 5mg/mL in a 40 mL dose.

15. On information and belief, Teva USA, Teva Parenteral, and Teva Israel, acting alone or in concert, caused, actively encouraged, and/or directed Pharmachemie B.V. to file ANDA No. 78-820 and an amendment to ANDA No. 78-820 with the FDA, and/or participated in the work related to the submission of ANDA No. 78-820 and an amendment to ANDA No. 78-820.

16. Pharmachemie B.V., Teva Parenteral, Teva USA, and Teva Israel are referred to hereinafter, collectively, as "Pharmachemie."

JURISDICTION AND VENUE

17. This action arises under the patent laws of the United States of America. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a). Further, this Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 2201 and 2202.

18. Pharmachemie B.V. is subject to jurisdiction in New Jersey because it manufactures pharmaceuticals and pharmaceutical products that are sold and used, throughout the United States, including within New Jersey and has acted in concert with Teva Parenteral and Teva USA, which have offices and conduct business in this district.

19. Teva Parenteral and Teva USA are subject to personal jurisdiction in New Jersey because they regularly and systematically conduct business within New Jersey and have offices within New Jersey.

20. Teva Israel is subject to personal jurisdiction in New Jersey because it manufactures pharmaceuticals and pharmaceutical products that are sold and used, including by Teva USA, throughout the United States, including with New Jersey.

21. Sicor is subject to personal jurisdiction in New Jersey because, *inter alia*, it conducts business within New Jersey and manufactures and sells oxaliplatin drug substance to Pharmachemie with the knowledge that such drug substance will be sold and marketed throughout the United States, including within New Jersey.

22. In the alternative, Sicor is subject to jurisdiction in the United States under principles of general jurisdiction, and specifically in New Jersey pursuant to Fed. R. Civ. P. 4(k)(2). Sicor has contacts with the United States by, *inter alia*, its having filed a DMF with the FDA and its sale of pharmaceutical substances to Pharmachemie.

23. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391(b), (c), (d) and 28 U.S.C. § 1400(b).

COUNT 1:
INFRINGEMENT OF U.S. PATENT NO. 5,338,874

24. Plaintiffs repeat and reallege paragraphs 1-23 above as if fully set forth herein.

25. Sanofi-Aventis U.S. LLC holds approved new drug applications ("NDA") 21-492 and 21-759 for Eloxatin®, the active ingredient of which is oxaliplatin. Eloxatin® is approved for the treatment of colorectal cancer. There are no generic oxaliplatin products approved by the FDA for sale in the United States.

26. Debiopharm is the owner of United States Patent No. 5,338,874 ("the '874 patent") (attached as "Exhibit A"). Sanofi-Aventis is the exclusive licensee of the '874 patent.

27. On information and belief, Pharmachemie submitted to the FDA ANDA No. 78-820 and an amendment to ANDA No. 78-820 under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use and sale of Oxaliplatin Injection, 5 mg/mL (50mg/10ml, 100mg/20ml, and 200mg/40ml) formulations.

28. On information and belief, Pharmachemie submitted ANDA No. 78-820 and an amendment to ANDA No. 78-820 to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of its generic oxaliplatin formulations before the expiration of the '874 patent.

29. On information and belief, Pharmachemie made, and included in ANDA No. 78-820 and an amendment to ANDA No. 78-820, certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that, in its opinion and to the best of its knowledge, the '874 patent is invalid and not infringed. On May 24, 2007, Pharmachemie sent Plaintiffs notice of those certifications pursuant to 21 U.S.C. § 355(j)(2)(B).

30. On July 6, 2007, Plaintiffs filed suit against Pharmachemie for patent infringement in the United States District Court for the District of New Jersey (docket no. 3:07-cv-03144-FLW-JJH).

31. On information and belief, on September 27, 2007, Pharmachemie filed with the FDA an amendment to ANDA No. 78-820 for the new dosage strength of 5mg/ml – 40ml, included with that amendment new "Paragraph IV" certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), and sent Plaintiffs notice of the certification pursuant to 21 U.S.C. § 355(j)(2)(B).

32. By filing its ANDA No. 78-820 and an amendment to ANDA No. 78-820 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of its proposed drug products before the expiration of the '874 patent, Pharmachemie committed acts of infringement under 35 U.S.C. § 271(e)(2).

33. Further, the commercial manufacture, use, offer for sale, sale and/or importation of the generic oxaliplatin products for which Pharmachemie seeks approval in its ANDA No. 78-820 as originally filed or as amended will infringe one or more claims of the '874 patent under 35 U.S.C. § 271.

34. Further, the supply of oxaliplatin or the commercial manufacture, use, offer for sale, sale and/or importation of oxaliplatin by Sicor will directly infringe the '874 patent and will induce or otherwise contribute to acts of infringement of the '874 patent by Pharmachemie.

35. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of any approval of ANDA No. 78-820 relating to Pharmachemie's generic oxaliplatin products be a date which is not earlier than the expiration date of the '874 patent plus any other regulatory exclusivity to which Plaintiffs are or become entitled.

COUNT 2:
INFRINGEMENT OF U.S. PATENT NO. 5,420,319

36. Plaintiffs repeat and reallege paragraphs 1-35 above as if fully set forth herein.

37. Debiopharm is the owner of United States Patent No. 5,420,319 ("the '319 patent") (attached as "Exhibit B"). Sanofi-Aventis is the exclusive licensee of the '319 patent.

38. On information and belief, Pharmachemie submitted to the FDA ANDA No. 78-820 and an amendment to ANDA No. 78-820 under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use and sale of Oxaliplatin Injection, 5 mg/mL (50mg/10ml, 100mg/20ml, and 200mg/40ml) formulations.

39. On information and belief, Pharmachemie submitted ANDA No. 78-820 and an amendment to ANDA No. 78-820 to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of its generic oxaliplatin formulations before the expiration of the '319 patent.

40. On information and belief, Pharmachemie made, and included in ANDA No. 78-820 and an amendment to ANDA No. 78-820, certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that, in its opinion and to the best of its knowledge, the '319 patent is invalid and not infringed. On May 24, 2007, Pharmachemie sent Plaintiffs notice of those certifications pursuant to 21 U.S.C. § 355(j)(2)(B).

41. On July 6, 2007, Plaintiffs filed suit against Pharmachemie for patent infringement in the United States District Court for the District of New Jersey (docket no. 3:07-cv-03144-FLW-JJH).

42. On information and belief, on September 27, 2007, Pharmachemie filed with the FDA an amendment to ANDA No. 78-820 for the new dosage strength of 5mg/ml – 40ml, included with that amendment new "Paragraph IV" certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), and sent Plaintiffs notice of the certifications pursuant to 21 U.S.C. § 355(j)(2)(B).

43. By filing its ANDA No. 78-820 and an amendment to ANDA No. 78-820 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial

manufacture, use or sale of its proposed drug products before the expiration of the '319 patent, Pharmachemie committed acts of infringement under 35 U.S.C. § 271(e)(2).

44. Further, the commercial manufacture, use, offer for sale, sale and/or importation of the generic oxaliplatin products for which Pharmachemie seeks approval in its ANDA No. 78-820 as originally filed or as amended will infringe one or more claims of the '319 patent under 35 U.S.C. § 271.

45. Further, the supply of oxaliplatin or the commercial manufacture, use, offer for sale, sale and/or importation of oxaliplatin by Sicor will directly infringe the '319 patent and will induce or otherwise contribute to acts of infringement of the '319 patent by Pharmachemie.

46. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of any approval of ANDA No. 78-820 relating to Pharmachemie's generic oxaliplatin products be a date which is not earlier than the expiration date of the '319 patent plus any other regulatory exclusivity to which Plaintiffs are or become entitled.

COUNT 3:
INFRINGEMENT OF U.S. PATENT NO. 5,290,961

47. Plaintiffs repeat and reallege paragraphs 1-46 above as if fully set forth herein.

48. Debiopharm is the owner of United States Patent No. 5,290,961 ("the '961 patent") (attached as "Exhibit C"). Sanofi-Aventis is the exclusive licensee of the '961 patent.

49. On information and belief, Pharmachemie submitted to the FDA ANDA No. 78-820 and an amendment to ANDA No. 78-820 under the provisions of 21 U.S.C. § 355(j),

seeking approval to engage in the commercial manufacture, use and sale of Oxaliplatin Injection, 5 mg/mL (50mg/10ml, 100mg/20ml, and 200mg/40ml) formulations.

50. On information and belief, Pharmachemie submitted ANDA No. 78-820 and an amendment to ANDA No. 78-820 to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of its generic oxaliplatin formulations before the expiration of the '961 patent.

51. On information and belief, Pharmachemie made, and included in ANDA No. 78-820 and an amendment to ANDA No. 78-820, certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that, in its opinion and to the best of its knowledge, the '961 patent is invalid and not infringed. On May 24, 2007, Pharmachemie sent Plaintiffs notice of those certifications pursuant to 21 U.S.C. § 355(j)(2)(B).

52. On July 6, 2007, Plaintiffs filed suit against Pharmachemie for patent infringement in the United States District Court for the District of New Jersey (docket no. 3:07-cv-03144-FLW-JJH).

53. On information and belief, on September 27, 2007, Pharmachemie filed with the FDA an amendment to ANDA No. 78-820 for the new dosage strength of 5mg/ml – 40ml, included with that amendment new "Paragraph IV" certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), and sent Plaintiffs notice of the certifications pursuant to 21 U.S.C. § 355(j)(2)(B).

54. By filing its ANDA No. 78-820 and an amendment to ANDA No. 78-820 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of its proposed drug products before the expiration of the '961 patent, Pharmachemie committed acts of infringement under 35 U.S.C. § 271(e)(2).

55. Further, the commercial manufacture, use, offer for sale, sale and/or importation of the generic oxaliplatin products for which Pharmachemie seeks approval in its ANDA No. 78-820 as originally filed or as amended will infringe one or more claims of the '961 patent under 35 U.S.C. § 271.

56. Further, the supply of oxaliplatin or the commercial manufacture, use, offer for sale, sale and/or importation of oxaliplatin by Sicor will directly infringe the '961 patent and will induce or otherwise contribute to acts of infringement of the '961 patent by Pharmachemie.

57. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of any approval of ANDA No. 78-820 relating to Pharmachemie's generic oxaliplatin products be a date which is not earlier than the expiration date of the '961 patent plus any other regulatory exclusivity to which Plaintiffs are or become entitled.

COUNT 4:
DECLARATORY JUDGMENT OF INFRINGEMENT
OF U.S. PATENT NO. 5,290,961

58. Plaintiffs repeat and reallege paragraphs 1-57 above as if fully set forth herein.

59. The commercial manufacture, use, offer for sale, sale and/or importation of the generic oxaliplatin products for which Pharmachemie seeks approval in its ANDA No. 78-820 as originally filed or as amended will infringe one or more claims of the '961 patent under 35 U.S.C. § 271.

60. Further, the supply of oxaliplatin or the commercial manufacture, use, offer for sale, sale and/or importation of oxaliplatin by Sicor will directly infringe the '961 patent and will induce or otherwise contribute to acts of infringement of the '961 patent by Pharmachemie.

61. Plaintiffs are entitled to a declaration of infringement against Pharmachemie and Sicor and an order of this Court that Pharmachemie and Sicor are enjoined from engaging in the commercial manufacturing, use, offer for sale, sale, and importation of generic oxaliplatin products before the expiration of the '961 patent.

COUNT 5:
DECLARATORY JUDGMENT OF INFRINGEMENT
OF U.S. PATENT NO. 5,959,133

62. Plaintiffs repeat and reallege paragraphs 1-61 above as if fully set forth herein.

63. Debiopharm is the owner of United States Patent No. 5,959,133 ("the '133 patent") (attached as "Exhibit D"). Sanofi-Aventis is the exclusive licensee of the '133 patent.

64. The commercial manufacture, use, offer for sale, sale and/or importation of the generic oxaliplatin products for which Pharmachemie seeks approval in its ANDA No. 78-820 as originally filed or as amended will infringe one or more claims of the '133 patent under 35 U.S.C. § 271.

65. Further, the supply of oxaliplatin or the commercial manufacture, use, offer for sale, sale and/or importation of oxaliplatin by Sicor will directly infringe the '133 patent and will induce or otherwise contribute to acts of infringement of the '133 patent by Pharmachemie.

66. Plaintiffs are entitled to a declaration of infringement against Pharmachemie and Sicor and an order of this Court that Pharmachemie and Sicor are enjoined from engaging in the commercial manufacturing, use, offer for sale, sale, or importation of generic oxaliplatin products before the expiration of the '133 patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request:

A. Judgment that Pharmachemie B.V., Teva Pharmaceuticals USA, Inc., Teva Parenteral Medicines, Inc., and Teva Pharmaceutical Industries, Ltd. have infringed one or more claims of the '874, '961, and '319 patents by filing ANDA No. 78-820 and the amendment to ANDA No. 78-820 relating to Pharmachemie's generic oxaliplatin products;

B. Judgment that Pharmachemie B.V., Teva Pharmaceuticals USA, Inc., Teva Parenteral Medicines, Inc., Teva Pharmaceutical Industries, Ltd., and Sicor de Mexico, S.A. de. C.V. will infringe one of more claims of the '874, '961, '319, and '133 patents by engaging in the commercial manufacture, use, offer for sale, sale, or importation of generic oxaliplatin products before the expiration of those patents.

C. A permanent injunction restraining and enjoining Pharmachemie B.V., Teva Pharmaceuticals USA, Inc., Teva Parenteral Medicines, Inc., Teva Pharmaceutical Industries, Ltd., and Sicor de Mexico, S.A. de C.V. and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of generic oxaliplatin products as claimed in the '874, '961, '319 patents or made by the processes as claimed in the '961 and '133 patents;

D. A declaration that the effective date of any approval of ANDA Nos. 78-820 relating to Pharmachemie's generic oxaliplatin formulations be a date which is not earlier than the expiration date of the '874, '961, or '319 patents plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

E. A declaration that this case is exceptional within the meaning of 35 U.S.C. § 285 and an award of reasonable attorney fees, expenses, and disbursements of this action; and

F. Such other and further relief as the Court may deem just and proper.

Dated: November 8, 2007

Respectfully submitted,

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EXHIBIT A

US005338874A

United States Patent [19]

Nakanishi et al.

[11] **Patent Number: 5,338,874**

[45] **Date of Patent: Aug. 16, 1994**

[54] **CIS OXALATO (TRANS 1-1,2-CYCLOHEXANEDIAMINE) PT(II) HAVING OPTICALLY HIGH PURITY**

[75] Inventors: **Chihiro Nakanishi; Yuko Ohnishi; Junji Ohnishi; Junichi Taniuchi; Koji Okamoto; Takeshi Tozawa,** all of Kanagawa, Japan

[73] Assignee: **Tanaka Kikinzoku Kogyo K.K.,** Japan

[21] Appl. No.: **43,901**

[22] Filed: **Apr. 7, 1993**

[30] **Foreign Application Priority Data**

Jan. 12, 1993 [JP] Japan 5-019508

[51] **Int. Cl.**[5] **C07F 15/00**

[52] **U.S. Cl.** **556/137**

[58] **Field of Search** 556/137

[56] **References Cited**

PUBLICATIONS

Kidani et al., J. Med. Chem., vol. 21, No. 12, pp. 1315–1318 (1978).

Primary Examiner—JoseACU G. Dees
Assistant Examiner—Porfirio Nazario-Gonzalez
Attorney, Agent, or Firm—Klauber & Jackson

[57] **ABSTRACT**

Disclosed herein is cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) optically high purity. Because of its complete optical purity, the compound is effective as raw material of such a medicine as a carcinostatic agent. The complete optical purity of the above compound may be proved by comparing the respective melting points of the cis-oxalato (trans-1-1,2-cyclohexanediamine).

2 Claims, 1 Drawing Sheet

FIG. 1

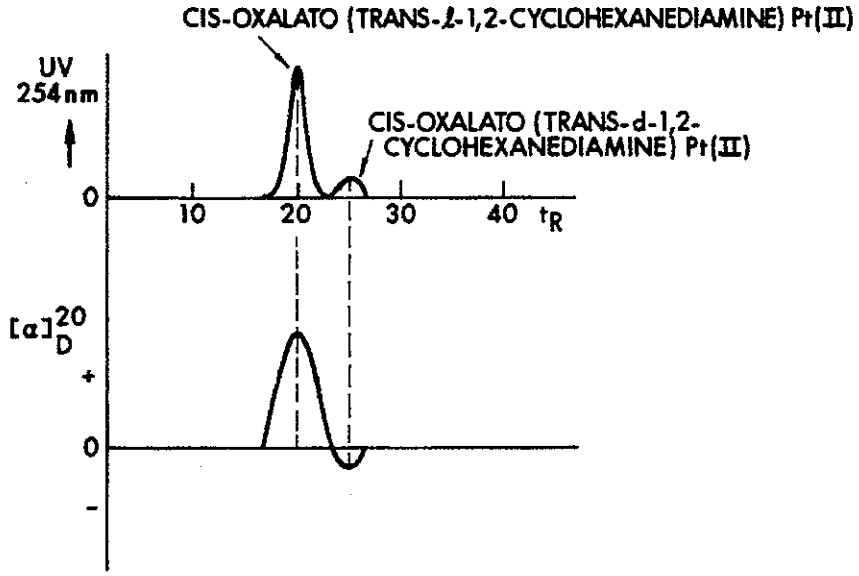
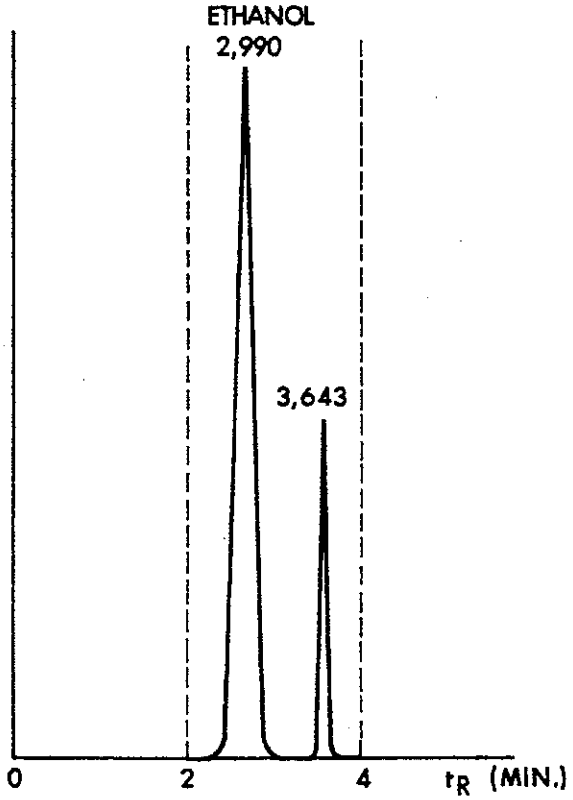


FIG. 2



GAS CHROMATOGRAM TRANS-dℓ-1,2-CYCLOHEXANEDIAMINE

CIS OXALATO (TRANS 1-1,2--CYCLOHEXANEDIAMINE) PT(II) HAVING OPTICALLY HIGH PURITY

BACKGROUND OF THE INVENTION

The present invention relates to cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) of optically high purity which can be employed as raw material of a carcinostatic agent.

While a platinum (II) complex of 1,2-cyclohexanediamine as a platinum (II) complex exhibiting a carcinostatic activity is known, the complex is a mixture of isomers synthesized from a mixture of isomers (cis, trans-d and trans-l) existing in 1,2-cyclohexanediamine the starting material thereof.

The trans and cis isomers of the 1,2 cyclohexanediamine may be optically resoluted by means of a metal complex utilizing the difference of solubilities between the two isomers. For example, in Japanese patent publication No. 60-41077, while the cis-isomer is precipitated by adding a nickel (II) salt to such a nonaqueous solvent such pure methanol containing the two isomers, the trans-isomer is precipitated by adding the nickel salt and hydrochloric acid and aqueous sodium hydroxide. Since the trans-isomer of the nickel complex is slightly soluble in water and easily soluble in an organic solvent and the cis-isomer is slightly soluble in an organic solvent and easily soluble in water, the optical resolution can be conducted.

Although cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) was synthetically obtained through a reaction between the trans-1-1,2-cyclohexanediamine obtained in accordance with the above method and K_2PtCl_1 (Japanese patent publication No. 60-41077). This was also found to be the mixture with cis-oxalato (trans-d-1,2-cyclohexanediamine) Pt(II). No data are presented in the Japanese patent publication No. 60-41077 which confirm the optical purity of the cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) and relate to circular duchroism (CD) exhibiting its steric configuration and to an angle of rotation ($[\alpha]_D$) exhibiting its optical activity. No differences can be distinguished between their respective elemental analysis values, infrared spectra and electron spectra of the isomers mentioned in the Japanese patent publication No. 60-41077.

In the cis-oxalate (trans-1-1,2-cyclohexanediamine) Pt(II) conventionally reported, the isolation of the complex consisting of two trans-dl isomers is insufficient so that the question of the purity of the isolated Pt(II) complex remains.

Large differences in connection with a carcinostatic activity and a secondary effect between isomers of many optically active medicines, and their optical purity is especially important when they are employed as medicines.

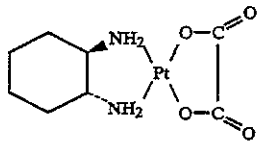
SUMMARY OF THE INVENTION

The present invention has been made in view of this standpoint.

An object of the present invention is to provide a platinum complex compound having optically high purity.

Another object of the invention is to provide a platinum complex compound which is useful as raw material of a pharmaceutically active agent because of its high purity.

The present invention is cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) of optically high purity having a general formula of Formula (1).



(1)

The cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) of optically high purity of the present invention may be prepared by completely and optically resoluting the Pt(II) optical isomers by means of a process of optically resoluting an optically active platinum complex compound disclose in an application of the same Applicant of the same date.

Since the complex compound of the present invention contains no cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) of optically isomer thereof, the excellent results of acute toxicity can be obtained in comparison with cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) conventionally obtained contaminated with an optical isomer so that it is effective for providing medicines on higher safety.

The boiling point of the cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) is, because of the absence of impurities, lower than of that of conventionally prepared cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II).

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a chromatogram obtained in HPLC of cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) before optical obtained in Example 1, Example 2 and Example 3. The upper portion shows an amount of elution per unit time as a relative absorption amount of ultraviolet ray at 254 nm, and the lower portion 1 shows an amount of elution per unit time as a relative degree of rotation.

FIG. 2 is a chromatogram of trans-dl-1,2-cyclohexanediamine obtained in (1) of Example 2.

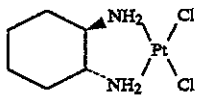
DETAILED DESCRIPTION OF THE INVENTION

The cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) of optically high purity represented by Formula (1) of this invention may be prepared in accordance with a following illustrative method.

Commercially available 1,2-cyclohexanediamine (for instance, trans-1-1,2-cyclohexanediamine made by Aldrich, cis and trans-dl mixed 1,2-cyclohexanediamine made by Tokyo Kasei K.K.) may be employed. The compounds made by Aldrich and Wako Junyaku were employed without further treatment because of their relatively high purity, and the geometrical isomers of cis and trans that made by Tokyo Kasei may be resoluted and purified in accordance with such a known process as that disclosed in Japanese patent publication No. 61-4827. The optical resolution of the trans isomer may be conducted by forming a diastereoisomer in accordance with a normal method by means of tartaric acid and employing a recrystallization method.

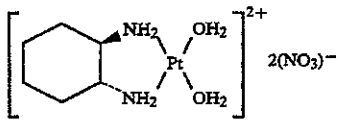
A crystal of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) represented in Formula 2 may be obtained

by a reaction between the trans-1-1,2-cyclohexanediamine previously obtained and an equivalent weight of potassium tetrachloroplatinate [K_2PtCl_4] dissolved in water at room temperature over 10 hours.



(2)

After the compound represented in Formula 2 is suspended in water followed by the addition of two equivalent weights of an aqueous solution of silver nitrate, the reaction is allowed to proceed over 24 hours in the dark followed by the removal of silver chloride by means of filtration to produce an aqueous solution of cis-diaquo(trans-1-1,2-cyclohexanediamine) Pt(II) nitrate represented in Formula 3. After potassium iodide is added to this solution followed by the removal of the excess silver ion as silver iodide by means of filtration and the decolorization and purification by active carbon, an equivalent weight of oxalic acid in respect to the potassium tetrachloroplatinate is added to produce a crude crystal of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) after the two hours' reaction. Cis-oxalato(-trans-1-1,2-cyclohexanediamine) Pt(II) obtained by the recrystallization of the said crude crystal from hot water is a mixture with cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II) which is an optical isomer thereof.



(3)

Then, the recrystallized crystal is completely isolated as cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) in accordance with the process of resoluting and purifying the optically active Pt(II) isomers after the crystal is dissolved in water. That is, the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) contaminated with no optical isomers can be obtained by freeze-drying an aqueous solution separately eluted by means of high peformance liquid chromatography (hereinafter referred to as "HPLC"), for example, under the following conditions.

Separation column: 4.6 mm of inner diameter and 25 cm of height packed with OC of Daicel Chemical Industries, Ltd.

Mobile phase: othanol/methanol=30:70 (volume ratio)

Flow rate: 0.2 ml/min.

Column temperature: 40° C.

Detector:

ultraviolet ray 254 nm

optical rotation 580 nm.

the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) having the high optical purity in accordance with the present invention is active against a tumor "leukomia L1210" and effective as a carcinostatic agent.

EXAMPLES

Then, a representative process of preparing the cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) of this invention, its properties and biological activities will be described in Examples. Further, in fact, that compound prepared by a conventional method is a mixture of optical isomers will be shown contrary to a known fact.

EXAMPLE 1

① Preparation of cis-dichloro(trans-1-1,2-cyclohexanodiamine) Pt(II)

A reaction between 46.8 g of trans-1-1,2-cyclohexanediamine made by Aldrich ($[\alpha]^{19}_D=-35.6°$, 4% H_2O) and 170 g of potassium tetrachloroplatinate (made by Tanaka Kikinzoku Kogyo K.K.) in an aqueous solution at room temperature over 10 hours yielded needles of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II). Yield: 99%.

② Preparation of cis-diaquo(trans-1-1,2-cyclohexanediamine) Pt(II) nirtrate

The cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) obtained above was suspended in 1.6 liters of water to which was added two molar volumes of silver nitrate for proceeding a reaction in the dark over 24 hours, and the silver chloride produced during the reaction was filtered off. After 4.8 g of potassium iodide was added to this filtrate followed by the precipitation of the excess silver ion as silver iodide produced during the reaction of over 12 hours, 1 g of active carbon for purification and decolorization was added which was then filtered off together with the silver iodide.

③ Preparation of cis-oxalate(trans-1-1,2-cyclohexanediamine) Pt(II)

To the filtrate obtained above was added 48 g of oxalic acid dihydrate to yield 90 g of a white crude crystal after a two hours' reaction.

Then, 80 g of this crude crystal was recrystallized from three liters of hot water, and 45 g of the obtained crystal was dissolved into 9 liters of water. HPLC was conducted employing the solution under the following conditions to obtain a chromatogram of FIG. 1.

Column for optical resolution: Column having a length of 50 cm and an inner diameter of 5 cm packed with OC (Daicel Chemical Industries, Ltd., a filler prepared by adsorbing a cellulose carbamate derivative to silica gel)

Mobile phase: ethanol/methanol=30:70 (volume ratio)

Flow rate: 2.0 ml/min.

Column temperature: 40° C.

Detection:

ultraviolet ray 254 nm

optical rotation 589 nm.

The upper portion of FIG. 1 shows an amount of elution per unit time as a relative absorption amount of ultraviolet ray at 254 nm, and the lower portion of FIG. 1 shows an amount of elution per unit time as a relative degree of rotation. At a retention time (t_R) of 25 minutes, cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II) was found to be contaminated. The optical purity of the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) prepared by employing the trans-1-1,2-cyclohexanediamine made by Aldrich ($[\alpha]^{19}_D=-35.6°$, 4% H_2O) was calculated in accordance with a below equation to be 88.5% of an enantiomer excess rate (Table 1). Then, cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) of 100% of an optical purity (e.e.) was obtained by collecting an aqueous solution eluted in fractions from 15 minutes to 22 minutes (t_R) followed by freeze drying. Yield: 39.8 g 50% (based on the crude crystal).

[Equation for calculating optical purity]

Optical purity (%) . . . e.e (%) =

{([content of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II)] − [content of [cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II)])/ ([content of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II)] + [content of [cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II)])} × 100

(e.e.: enantiomer excess rate)

EXAMPLE 2

① Resolution of cis and trans geometrical isomers

To a solution prepared by dissolving 100 g of cis, trans-dl-mixed-1,2-cyclohexanediamine into 640 ml of methanol was added a solution prepared by dissolving 104 g of nickel chloride [$NiCl_2.6H_2O$] into 1760 ml of methanol which was then reacted at room temperature for 2 hours under stirring. A precipitated yellow crystal [Ni(cis-1,2-cyclohexanediamine)Cl_2 (31.6 g) was filtered and washed with methanol and air-dried. To this crystal was added 140 ml of 6-normal hydrochloric acid and then its pH was adjusted to 4.2~4.5 with a 15% sodium hydroxide aqueous solution. After a precipitated royal purple crystal [Ni(trans-dl-1,2-cyclohexanediamine)-$(II_2O)_2Cl_2$] (72.0 g) was filtered and washed, 120 ml of 6-normal hydrochloric acid was added thereto. It was concentrated under a reduced pressure followed by addition of 600 ml of ethanol and 600 ml of acetone to obtain colorless precipitate [trans-dl-1,2-cyclohexanediamine.2HC.] (42.54 g) after filtration which was then wased with ethanol-acetone. After this was extracted with chloroform and dried with potassium carbonate, a colorless liquid [trans-dl-1,2-cyclohexanediamine (35.5 g)] ($[\alpha]^{19}_D$=0°, 4% H_2O) was obtained. A single peak appeared on a gas chromatogram at t_R=3.043 minutes.

FIG. 2 is a gas chromatogram of trans-dl-1,2-cyclohexanediamine.

The gas chromatography was conducted under the following conditions.

Column: CP-Cyclodextrin-B-236-M-19 50 m×0.25 mm (inner diameter) df=0.25 μm

Column temperature: 200° C.

Carrier gas: N_2, 2 kg/cm^2

Injector temperature: 200° C.

Detector: FID (200° C.)

Sample volume: 1 μl.

② Optical resolution of trans-dl-1,2-cyclohexanediamine

To 35.5 g of the trans-dl-1,2-cyclohexanediamine previously obtained was added 671 ml of water for dissolving under heating at 90° C. The standing thereof for 12 hours after the gradual addition of 22.10 g of d-tartaric acid and 13.4 ml of glacial acetic acid produced 16.23 g of a diastereoisomer (trans-1-1,2-cyclohoxanediamine (1) tartaric acid. This was recrystallized from water twice. No further change of the rotation of angle was observed after the repeated recrystallization as shown in FIG. 2.

After 9.23 g of the diastereoisomer obtained was dissolved into a small amount of water followed by the addition of 5.64 g of sodium hydroxide, it was extracted with ether and was distilled under a reduced pressure to obtain 3.20 g of a colorless liquid, trans-1-1,2-cyclohexanediamine.

③ Preparation of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II)

In accordance with the same procedures as those of ① of Example 1 except that the trans-1-1,2-cyclohexanediamine obtained in ② of Example 2 was employed as raw material in place of the trans-1-1,2-cyclohexanediamine made by Aldrich of ① of Example 1, 9 g of the corresponding Pt(II) complex was obtained.

④ Preparation of cis-diaquo(trans-1-1,2-cyclohexanediamine) Pt(II) nitrate

In accordance with the same procedures as those of ② of Example 1 except that the Pt(II) complex obtained in ③ of Example 2 was employed in place of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) obtained in ① of Example 1, an aqueous solution of the desired Pt(II) complex was obtained.

⑤ Preparation of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt (II)

In accordance with the same procedures as those of ③ of Example 1 except that the aqueous solution of the Pt (II) complex obtained in ④ of Example 2 was employed in place of the aqueous solution of the Pt(II) complex obtained in ② of Example 1, 7 g of a crude crystal of cis-oxalato(trans-1-1,2-cyclohexancdiamine) Pt(II) was obtained. After the recrystallization of this crude crystal from hot water was conducted, 4 g of the recrystallized crystal was dissolved into 800 ml of water. Th HPLC of this solution under the same conditions of those of ③ of Example 1 revealed that cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II) which was an optical isomer was apparently contaminated at t_R=25 minutes as shown in FIG. 1.

The optical pority of the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) synthesized by employing the raw material isolated in accordance with a process of resoluting and purifying isomers (Japanese patent application No. 61-4827) was e.e.=90.0% in accordance with the equations of ③ of Example 1 as shown in Table 1. Then, cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) of 100% of an optical purity (e.e.) was obtained by collecting an aqueous solutioneluted in fractions from 15 minutes to 22 minutes (t_R) followed by freeze drying. Yield: 3.6 g, 51% (based on the crude crystal).

EXAMPLE 3

① Preparation of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II)

In accordance with the same procedures as those of ① of Example 1 except that the trans-1-1,2-cyclohexanediamine made by Wako Junyaku K.K. ($[\alpha]^{19}_D$=34.9°, 4% H_2O) was employed in place of the trans-1-1,2-cyclohexanediamine made by Aldrich of ① of Example 150 g of the corresponding Pt(II) complex was obtained.

② Preparation of cis-diaquo(trans-1-1,2-cyclohexanediamine) Pt(II) anitrate

In accordance with the same procedures as those of ② of Example 1 except that the Pt(II) complex obtained in ① of Example 3 was employed in place of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) obtained in ① of Example 1, an aqueous solution of the desired cis-diaquo(trans-1-1,2-cyclohexanediamine) Pt(II) nitrate was obtained.

③Preparation of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II)

In accordance with the same procedures as those of ③ of Example 1 except that the aqueous solution of the Pt(II) complex obtained in ② of Example 3 was employed in place of the aqueous solution of the Pt(II) complex obtained in ② of Example 1, 90 g of a crude crystal of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) was obtained. After the recrystallization of this crude crystal from hot water was conducted, 45 g of the recrystallized crystal was dissolved into 9 liters of water. The HPLC of this solution under the same conditions of those of ③ of Example 1 revealed that cis-oxalato(trans-d-1,2-cyclohexanediamine) PT(II) which was an optical isomer was apparaently contaminated at t_R=25 minutes as shown in FIG. 1. The optical purity of the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) synthesized by employing trans-1-1,2-cyclohexanediamine made by Wako Junyaku K.K. as raw material was e.e.=86.8% in accordance with the equation of ③ of Example 1 as shown in Table 1. Then, cis-oxalato(trans-1-1,2 cyclohexanediamine) Pt(II) of 100% of an optical purity (e.e.) was obtained by collecting an aqueous solution eluted in fractions from 15 minutes to 22 minutes (t_R) followed by freeze drying. Yield: 39.1 g, 43% (based on the crude crystal).

COMPARATIVE EXAMPLE

For comparing and evaluating the optical purity, the physicochemical properties and the biological properties obtained in accordance with the present invention, the cis-oxalate(trans-1-1,2-cyclohexanediamine) Pt(II) was synthesized as Comparative Example by employing the raw material made by Tokyo Kasei K.K. in accordance with the following procedures disclosed Japanese patent publication No. 60-41077.

To 3 g of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) was added 500 ml of water followed by the boiling thereof for dissolution. After two moles of $AgNo_3$ (2.6 g) were added and was stireed for 2 to 3 hours in the dark, the filtrations were repeated until the filtrate became transparent. After the filtrate was concentrated under a reduced pressure to 100 ml, 1.3 g of potassium oxalate was added to the concentrated solution followed by standing for 8 hours at room tempeature. The solution was again concentrated at a reduced pressue to produce white crystalline precipitate. The precipitated was recrystallized from water.

The comparisons of the optical purity between the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) of Examples and Comparative Example, that of the physicochemical properties and that of the biological properties are shown in Table 1, Table 3 and Table 4, respectively.

No difference is recognized between the compounds of Examples and Comparative Examples in connection with their properties, elemental analysis (C,H,N) and infrared spectra in Table 3. However, the melting points of the compounds of Examples 1 to 3 are lower than that of Comparative Example. This fact indicates that while the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) conventionally obtained is contaminated with such an impurity of its optical isomer, the cis-oxalato(-trans-1-1,2-cyclohexanediamine) Pt(II) obtained in Examples of the present invention is contaminated with no impurities.

Table 4 shows an acute toxicity test (LD_{60}) and a resistance against a tumor of L1210 of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II). The test was conducted by prescribing L1210 in a peritoneal cavity of six CDF_1 mice/one group (the number of transplanted cells is 10^n per mouse and prescribing the medicine in the poritoncal cavity on a first day, a fifth day and a ninth day.

TABLE 1

Optical Purity of Cis-Oxalato(Trans-1-1,2-Cyclohexanediamine) Pt(II)

Experiment	Raw Material	Optical Purity (e. e. %) Before Resolution By HPLC	→	After Resolution By HPLC
Example 1	Aldrich	88.5	→	100
Example 2	Tokyo Kasei	90.0	→	100
Example 3	Wako Junyaku	86.8	→	100
Com. Ex.	Tokyo Kasei	90.0	→	100

TABLE 2

Angle of Rotation of trans-1-1,2-cyclohexanediamine-(+)-tartaric acid

Tokyo Kasei (Lot No. FBZ01)	$[\alpha]_n^{10}$ (1% H_2O)
Before Recrystallization	+12.0+ ± 0.1°
After One Recrystallization	+12.1° ± 0.1°
After two Recrystallizations	+12.1° ± 0.1°

TABLE 3

Physicochemical Properties of cis-oxalato(trans1-1,2-cyclohexanediamine)Pt(II)

Experiment	Melting Point	CD (Δε)	$[\alpha]_n^{20}$ (0.5%, H_2O)
Example 1*	198.3~	255 nm	
Example 2*	291.7° C.	+0.67 ± 0.19	>74.5° C.
Example 3*		324 nm +0.61 ± 0.10	
Comp. Ex. (JP Publi. No. 60-41077)	>300° C.	not mentioned	not mentioned

*High Purity Sample Prepared by HPLC

TABLE 4

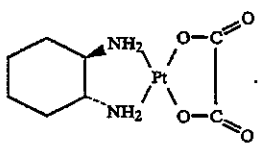
Acute Toxicity Test and Tumor Resistance Against L1210 of Cis-Oxalato(Trans-1-1,2-cyclohexamediamine) Pt(II)

Experiment	Acute Toxicity Test LD_{50}	Tumor Resistance T/C (%) (mg/kg) 25	12.5	6.25	3.12	1.56	0.78
Example 1*	18.2~20.8	T					
Example 2*	mouse IP	129P	280P (2/6)	311P (3/6)	207P	158P	132P
Example 3*							
Comp. Ex.	14.8~19.0 mouse IP	T 81	308P (4/6)	253P (1/6)	191P	158P	

*High Purity Sample Prepared by HPLC
P: Effective (Over 125%)
T: Toxic (Large Weight Loss)
(3/6): This means that three out of six was cured.

What is claimed is:

1. Optically pure cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) having a general formula of Formula (1).



(1)

2. Cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) as claimed in claim 1, wherein the melting point thereof is between 198° C. and 292° C.

* * * * *

EXHIBIT B

US005420319A

United States Patent [19]

Okamoto et al.

[11] **Patent Number: 5,420,319**

[45] **Date of Patent: * May 30, 1995**

[54] **CIS-OXALATO(TRANS-1-1,2-CYCLOHEXANEDIAMINE) PT(II) COMPLEX HAVING HIGH OPTICAL PURITY AND PROCESS OF PREPARING SAME**

[75] Inventors: **Koji Okamoto; Chihiro Nakanishi; Junichi Taniuchi; Junji Ohnishi; Yasunobu Komoda**, all of Kanagawa, Japan

[73] Assignee: **Tanaka Kikinzoku Kogyo K.K.**, Japan

[*] Notice: The portion of the term of this patent subsequent to Aug. 16, 2011 has been disclaimed.

[21] Appl. No.: **117,892**

[22] Filed: **Sep. 7, 1993**

[30] **Foreign Application Priority Data**

May 21, 1993 [JP] Japan 5-142824

[51] **Int. Cl.**[6] **G07F 15/00**

[52] **U.S. Cl.** **556/137**

[58] **Field of Search** 556/137

[56] **References Cited**

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OTHER PUBLICATIONS

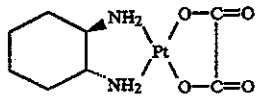
Chemical Abstracts, vol. 87, No. 1, issued Jul. 4, 1977, Kidani et al., "Synthesis and anti-tumor activities of platinum (II) complexes of 1,2-diaminocyclohexane isomers and their related isomers," p. 28, column 2, abs. No. 298z, J. Clin. Hematol. Oncol, 1977, 7(1), 197–209.

Primary Examiner—Paul J. Killos
Assistant Examiner—Porfirio Nazario-Gonzalez
Attorney, Agent, or Firm—Klauber & Jackson

[57] **ABSTRACT**

Disclosed is cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) complex having high optical purity and no toxicity and exhibiting anticancer performance, as shown in the below Formula.

Cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) complex of the invention possesses high optical purity or 99.94% or more e.e. and a melting point of 198.3° to 199.7° C. The complex is synthesized employing as starting material trans-1-1,2-cyclohexamediamine or a derivative of the trans-1-1,2-cyclohexanediamine optically resoluted by means of a high performance liquid chromatography.



13 Claims, 3 Drawing Sheets

FIG. 1

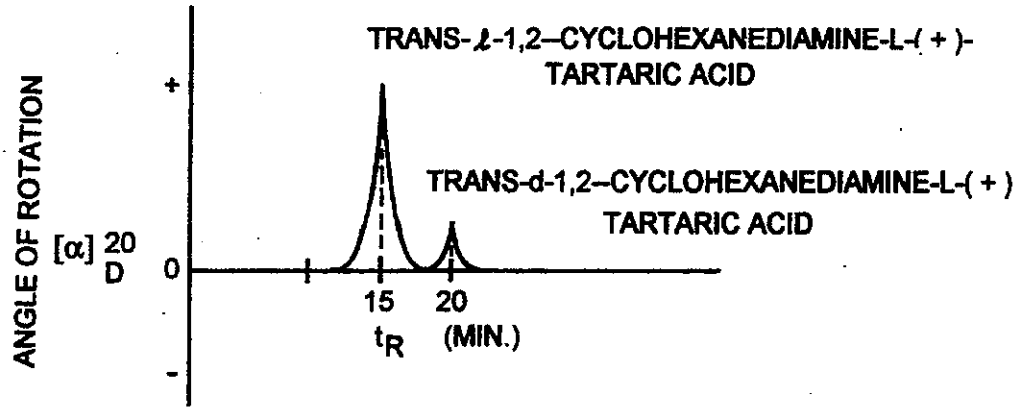

TRANS-ℓ-1,2–CYCLOHEXANEDIAMINE-L-(+)-
TARTARIC ACID
TRANS-d-1,2–CYCLOHEXANEDIAMINE-L-(+)
TARTARIC ACID
ANGLE OF ROTATION
[α] 20 D
+
0
-
15
20
tR
(MIN.)

FIG. 2

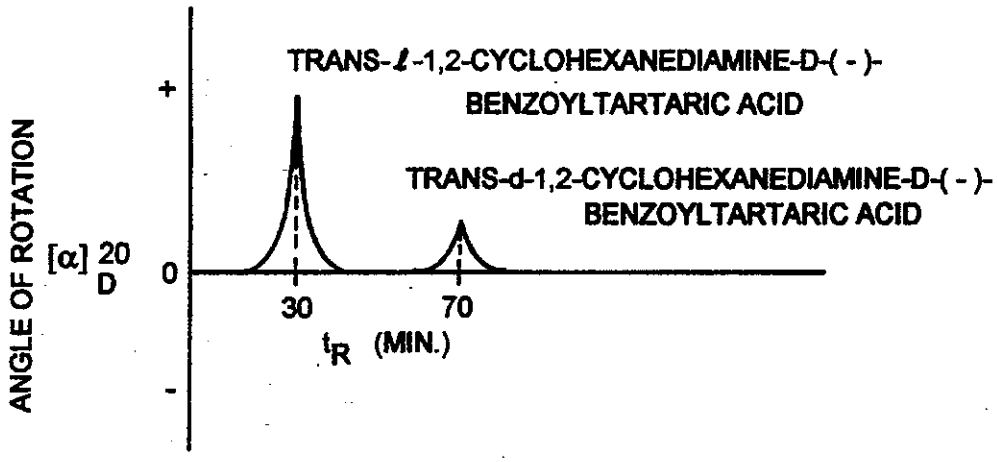

TRANS-ℓ-1,2-CYCLOHEXANEDIAMINE-D-(-)-
BENZOYLTARTARIC ACID
TRANS-d-1,2-CYCLOHEXANEDIAMINE-D-(-)-
BENZOYLTARTARIC ACID
ANGLE OF ROTATION
[α] 20 D
+
0
-
30
70
tR
(MIN.)

FIG. 3

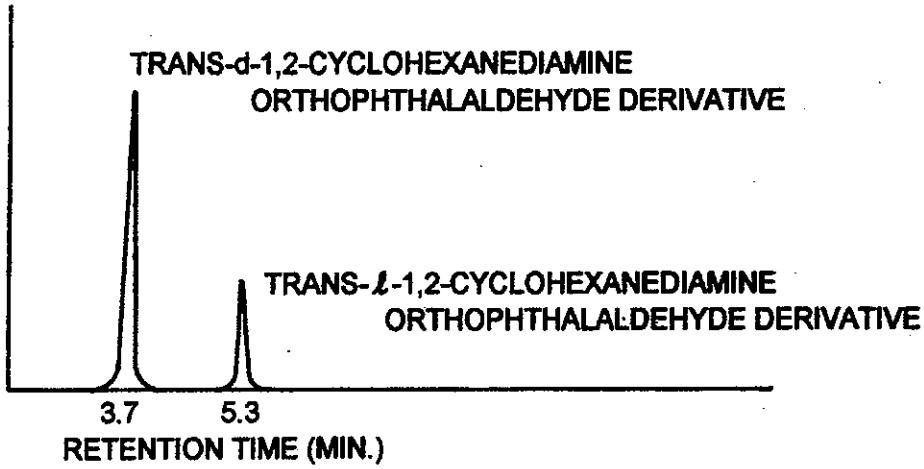

TRANS-d-1,2-CYCLOHEXANEDIAMINE
ORTHOPHTHALALDEHYDE DERIVATIVE
TRANS-ℓ-1,2-CYCLOHEXANEDIAMINE
ORTHOPHTHALALDEHYDE DERIVATIVE
3.7
5.3
RETENTION TIME (MIN.)

FIG. 4

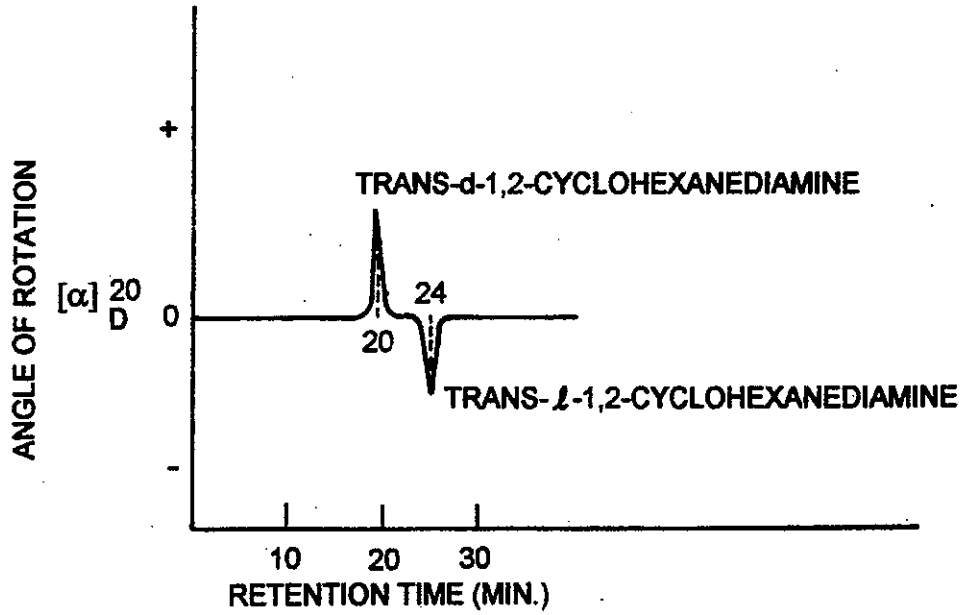

ANGLE OF ROTATION
[α] 20 D
+
0
-
TRANS-d-1,2-CYCLOHEXANEDIAMINE
24
20
TRANS-ℓ-1,2-CYCLOHEXANEDIAMINE
10
20
30
RETENTION TIME (MIN.)

FIG. 5

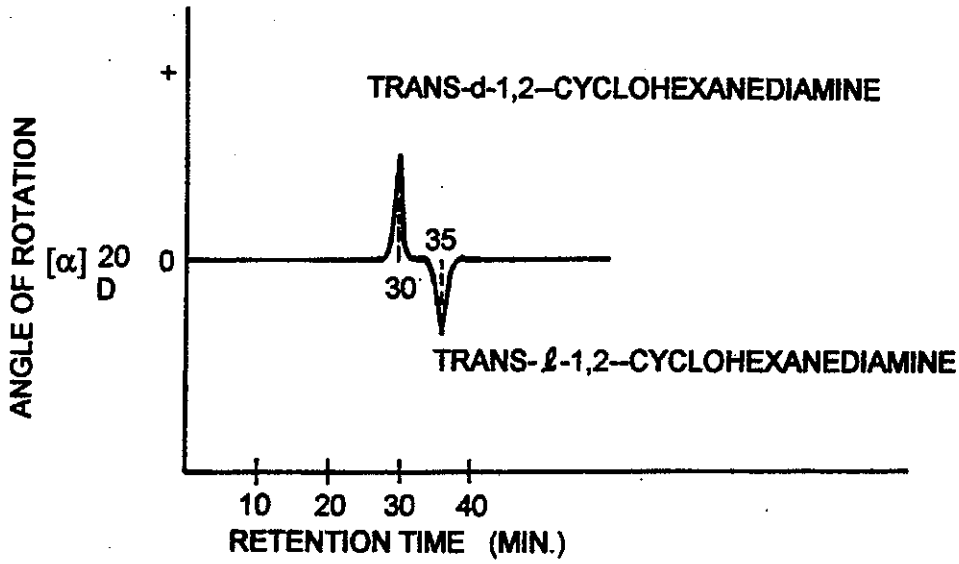
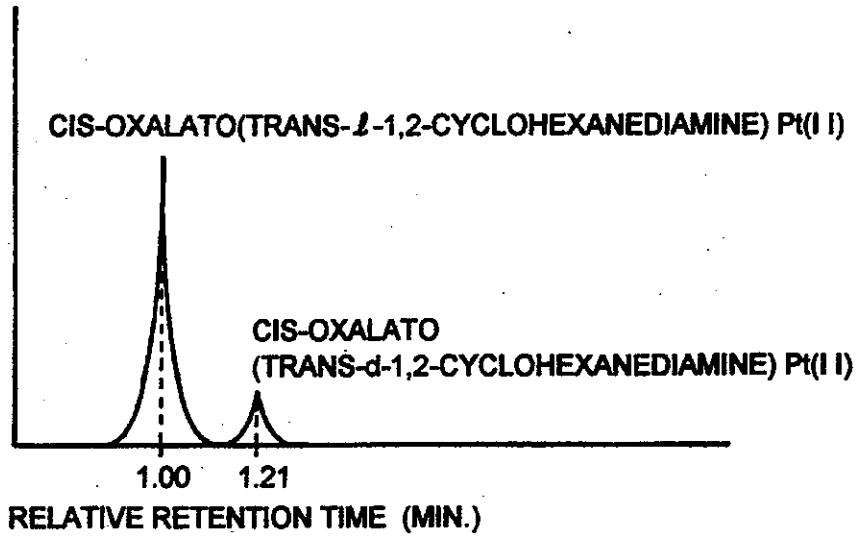

ANGLE OF ROTATION
[α] 20 D
+
0
TRANS-d-1,2--CYCLOHEXANEDIAMINE
35
30
TRANS-ℓ-1,2--CYCLOHEXANEDIAMINE
10
20
30
40
RETENTION TIME (MIN.)

FIG. 6


CIS-OXALATO(TRANS-ℓ-1,2-CYCLOHEXANEDIAMINE) Pt(I I)
CIS-OXALATO
(TRANS-d-1,2-CYCLOHEXANEDIAMINE) Pt(I I)
1.00
1.21
RELATIVE RETENTION TIME (MIN.)

CIS-OXALATO(TRANS-1-1,2-CYCLOHEXANEDIAMINE) PT(II) COMPLEX HAVING HIGH OPTICAL PURITY AND PROCESS OF PREPARING SAME

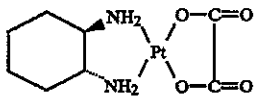
BACKGROUND OF THE INVENTION

The present invention relates to cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) complex having high optical purity which may be employed as starting material of carcinostatic substance and a process of preparing same.

Trans-1-1,2-cyclohexanediamine can be obtained by reacting trans-dl-1,2-cyclohexanediamine with tartaric acid to form diastereomers and optically resoluting the respective diastereomers by means of a recrystallization method utilizing the difference of solubilities of the respective diastereomers. However, this method possesses a limitation because the solubility difference is not large so that it is reported that optical purity of 99.5 % or more cannot be industrially attained.

Accordingly, in order to obtain a platinum complex represented by Formula 1 having high optical purity, after the resolution of cis-trans stereoisomers of 1,2-cyclohexanediamine which is starting material for the preparation of the platinum complex in accordance with a resolution refining process

[Formula]

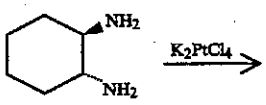


(Japanese patent publication No.61-4827), the optical resolution of the trans isomer is conducted by, in accordance with a normal process, forming a diastereomer by means of tartaric acid followed by its recrystallization. A platinum complex prepared by employing this resoluted isomer is further optically resoluted by means of high performance liquid chromatography (hereinafter referred to as "HPLC method") to produce the platinum complex (Formula 1) having the high optical purity (U.S. patent application Ser. No. 08/043,901 and European patent application No.93830160.3). The optical resolution of the final product is conventionally required because the resolution and refining of the trans-1-1,2-cyclohexanediamine is insufficient. Since the trans-1-1,2-cyclohexanadiamine is the important starting material of cis-oxalato(trans-1-1,2-cyclohexanadiamine) Pt(II) complex which is the starting material of a carcinostatic agent, the trans-1-1,2-cyclohexanediamine having stably higher optical purity has been required.

The platinum complex (Formula 1) has been synthesized in accordance with a preparation process shown as the below equation (Formula 2).

Many optically active pharmaceuticals may have a considerable difference in carcinostatic activities and their side effects due to their isomerism so

[Formula 2]



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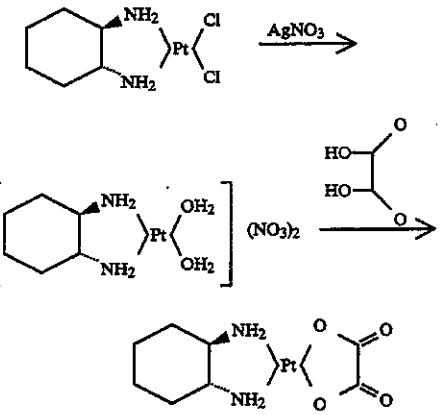


that their optical purity is important when they are utilized as the pharmaceuticals.

SUMMARY OF THE INVENTION

In these viewpoints, an object of the present invention is to provide cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) complex having high optical purity through complete optical resolution and its preparation process.

Another object of the invention is to provide the Pt (II) complex having the optical purity of 99.94 % or more and its preparation process.

Tile cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) complex having the high optical purity represented by Formula 1 of the invention can be obtained in accordance with one of the following processes.

Commercially available 1,2-cyclohexanediamine (for example, trans-1-1,2-cyclohexanediamine made by Aldrich, cis, trans-dl-mixed-1,2-cyclohexanediamine made by Tokyo Kasei K.K., and trans-1-1, 2-cyclohexanediamine made by Wako Junyaku K.K.) is employed. After the cyclohexanediamine made by Tokyo Kasei is resoluted into its cis and trans-stereoisomers in accordance with the above resolution refining process, trans-1-1,2-cyclohexanediamine having the high optical purity can be obtained employing the trans-isomer through one of the below three processes of optical resolution.

(1) The trans-1-1,2-cyclohexanediamine is reacted with L-(+)-tartaric acid to form a diastereomer. A filler prepared by, for example, chemically bonding (1R,2S)-2-carboxymethylamino-1,2-diphenylethanol to silica gel to which a metal ion (Cu^{2+}) is coordinated is packed in a column having, for example, an inner diameter of 4.6 mm and a height of 25 cm which is then employed as a resolution column. The resolution may be carried out by employing the column through which the diastereomer passes in accordance with the HPLC method. The mobile phase may be water and the detection may be performed by employing a polarimeter detecting 589 nm as a detector. An alkaline solution is added to the aqueous solution eluted to obtain the trans-1-1,2-cyclohexanediamine completely resoluted.

(2) The trans-1-1,2-cyclohexanediamine is reacted with a benzoyl derivative, preferably orthophthalaldehyde, to form a diastereomer. As a resolution column, ULTRON ES-OVM having an inner diameter of 4.6 mm and a height of 15 cm made by Shinwa Kako K.K. is, for example, employed. The resolution may be car-

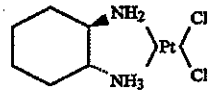
ried out by employing the column through which the diastereomer passes in accordance with the HPLC method. The mobile phase may be 20 nM of potassium dihydrogen phosphate (pH 5.6) and ethanol in a volume ratio of 100:7, and the detection may be performed by employing ultraviolet ray at 220 nm. Then, 1-N hydrochloric acid is added to the aqueous solution eluted to obtain the trans-1-1, 2-cyclohexanediamnie completely resoluted.

③ The trans-1-1,2-cyclohexanediamnie is dissolved in water. A filler prepared by, for example, chemically bonding L-proline to silica gel to which a metal ion (Cu^{2+}) is coordinated is packed in a column which is then employed as a resolution column. The resolution may be carried out by employing the column through which the diastereomer passes in accordance with the HPLC method. The mobile phase may be water and the detection may be performed by employing a polarimeter detecting 589 nm as detector. The water is removed from the aqueous solution eluted to obtain the trans-1-1,2-cyclohexanediamnie completely resoluted.

All the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) represented as Formula 1 obtained by employing the trans-1-1,2-cyclohexanediamine having the high optical purity obtained in the above respective procedures ①, ② and ③ possesses high optical purity so that the optical resolution thereafter described in U.S. patent application Ser. No. 08/043,901 or European patent application No. 93830160.3 can be omitted. The preparation process of the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) described therein is as follows.

Trans-1-1,2-cyclohexanediamine and equimolar potassium tetrachloroplatinate [K_2PtCl_4] are dissolved in water and reacted for over 10 hours at room temperature to produce the crystal of the cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) represented as Formula 3.

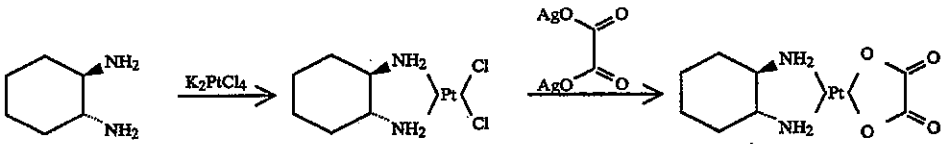
[Formula 3]



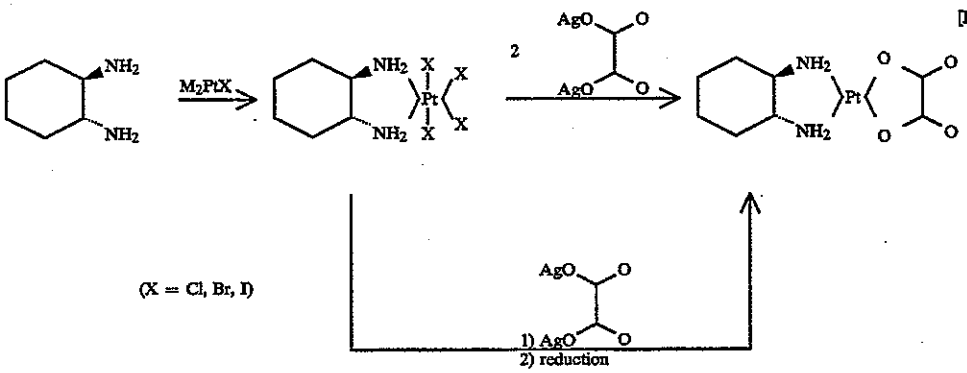
Then, water is added to the compound of Formula 3 for suspending to which is added a silver nitrate (2 mols) aqueous solution. The both are allowed to react in dark for over 24 hours and silver nitrate is removed by filtration to obtain an aqueous solution of cis-diaquo(trans-1-1,2-cyclohexanediamine) Pt(II) nitrate. After potassium iodide is added to this aqueous solution for removing the excess silver ion as silver iodide by mean of filtration and the aqueous solution is refined and decolorized with active carbon, equimolar oxalic acid in respect of the potassium tetrachloroplatinate is added to the aqueous solution to obtain the crude crystal of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) after a two hour reaction. By recrystallizing this crude crystal from hot water, the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) having high purity can be obtained.

The preparation process of this invention is as follows.

[Formula 4]



[Formula 5]



According to the present invention, cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) having high optical purity represented by Formula 1 is provided. Since this isomer contains no cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II) which is an optical isomer, the former exhibits remarkably excellent results in connection with acute toxicity compared with that of the prior art and effective for providing pharmaceuticals having safety.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a chromatogram of isomers obtained by optical resolution of dl-1,2-cyclohexanediamine-L-(+)-tartaric acid by means of an HPLC method in Example 1 which shows a volume of elution at 589 nm of angle of rotation;

FIG. 2 is a chromatogram of isomers obtained by optical resolution of trans-dl-1,2-cyclohexanediamine-

D-(−)-benzoyltartaric acid by means of an HPLC method in Example 2;

FIG. 3 is a chromatogram of isomers obtained by optical resolution of a trans-dl-1,2-cyclohexanediamine orthophthalaldehyde derivative by means of an HPLC method in Example 3 which shows a volume of elution as its relative absorption volume of ultraviolet ray of angle of rotation at 220 nm of angle of rotation;

FIG. 4 is a chromatogram of isomers obtained by optical resolution of trans-dl-1,2-cyclohexanediamine by means of an HPLC method in Example 4;

FIG. 5 is a chromatogram of isomers obtained by optical resolution of trans-dl-1,2-cyclohexanediamine by means of an HPLC method in Example 5; and

FIG. 6 is a chromatogram of isomers obtained by optical resolution of the mixture of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) which is a standard sample and cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II) which shows a volume of elution as its relative absorption volume of ultraviolet ray of angle of rotation at 254 nm of angle of rotation.

DETAILED DESCRIPTION OF THE INVENTION

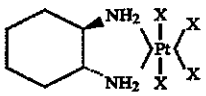
The preparation process of this invention will be described more in detail.

The cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) (Formula 3) obtained by reacting the trans-1-1,2-cyclohexanediamine obtained in the above procedures ①, ② and ③ with potassium tetrachloroplatinate [K_2PtCl_4] is suspended in water and equimolar silver oxalate is added thereto and reacted at a temperature of 0° to 100° C., preferably in a range of 20° to 60° C. for, generally, 0.5 to 4 hours. After silver chloride is removed by filtration and the filtrate is concentrated under a reduced pressure, a precipitated product is washed to obtain cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) represented by Formula 1.

The cis-tetrahalogeno(trans-1-1,2-cyclohexanediamine) Pt(IV) (Formula 6) obtained by reacting the trans-1-1,2-cyclohexanediamine obtained in the above procedures ①, ② and ③ with a platinum (IV) acid salt is suspended in water and two moles of silver oxalate is added thereto and reacted at a temperature range of 60° to 100° C. for, generally, 1 to 2 hours.

After silver halogenide is removed by filtration and the filtrate is concentrated under a reduced pressure, a precipitated product is washed to

[Formula 6]

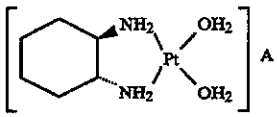


obtain the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) represented by Formula 1.

After, on the other hand, the intermediate obtained above, the cis-tetrahalogeno(trans-1-1,2-cyclohexanediamine) Pt(IV) (Formula 6) is suspended in water and equimolar silver oxalate is added thereto for proceeding the reaction, it is reduced with a suitable reducing agent to also obtain the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II).

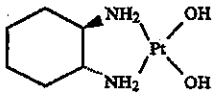
The cis-dihalogeno(trans-1-1,2-cyclohexanediamine) Pt(II) synthesized employing as starting material the trans-1-1,2-cyclohexanediamine obtained in the above procedures ①, ② and ③ having high optical purity is suspended in water and silver nitrate or silver sulfate is added thereto for proceeding the reaction. The resulting aqueous solution of the compound of Formula 7 is passed through a column packed with such anion exchange resin as Amberlite IRA-400, Dowex I and Diaion SA-10A to obtain the compound of Formula 8. By reacting this with oxalic acid to obtain the cis-oxalato(-trans-1-1,2-cyclohexanediamine) Pt(II) represented by Formula 1.

[Formula 7]



A: $(NO_3)_2$ or SO_4

[Formula 8]



EXAMPLES

Then, a typical preparation process of the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) of the present invention and its properties will be described in Examples, and Comparative Examples will be also presented which show that the compound is the mixture of optical isomers though it is well known. These Examples are not construed to limit the scope of the present invention.

EXAMPLE 1

Optical Resolution of Trans-dl-1,2-cyclohexanediamine-L-(+)-Tartaric Acid by Means of HPLC

After 6.71 ml of water was added to 3.55 g of trans-dl-1,2-cyclohexanediamine to dissolve it under heating at 90° C. and then 2.21 g of L-(+)-tartaric acid and 1.34 ml of glacial acetic acid were gradually added and stirred, an aqueous solution of trans-dl-1,2-cyclohexanediamine-(+)-tartaric acid which was a diastereomer was obtained. The HPLC separation procedure was conducted under the following conditions employing the above solution.

Column: Filler prepared by chemically bonding (1R,2S)-2-carboxymethylamino-1,2-diphenylethanol to silica gel to which a metal ion (Cu^{2+}) was coordinated. Inner diameter: 4.6 mm Height: 25 cm Mobile phase: Water Column temperature: 40° C. Flow rate: 1.8 ml/min. Detector: Polarimeter 589 nm

As shown in FIG. 1, the retention time (t_R) of trans-1-1,2-cyclohexanediamine-(+)-tartaric acid was 15 minutes and the retention time (t_R) of trans-d-1,2-cyclohexanediamine-(+)-tartaric acid was 20 minutes so that both were completely isolated. After sodium hydroxide was added to the respective diastereomers to make its pH alkaline, the diastereomers were extracted with ether and distilled under reduced pressure to produce as colorless liquid trans-1-1,2-cyclohexanediamine and trans-d-1,2-cyclohexanediamine.

EXAMPLE 2

Optical Resolution of Trans-dl-1,2-cyclohexanediamine-D-(−)-Benzol-Tartaric Acid by Means of HPLC

An aqueous solution of trans-dl-1,2-cyclohexanediamine-D-(−)-bonzoyltartaric acid was obtained in accordance with the procedures of Example 1 except that D-(−)-benzoyltartaric acid and ethanol were employed

in place of the L-(+)-tartaric acid and the water of Example 1, respectively. The HPLC separation procedure was conducted under the following conditions employing the above solution.

Column: Octadecylsilane Inner diameter: 4.6 mm Height: 25 cm Mobile phase: Water:Methanol=3:7 (volume ratio) Column temperature: 40° C. Flow rate: 1.0 ml/min. Detector: Polarimeter 589 nm

As shown in FIG. 2, the retention time (t_R) of trans-1-1,2-cyclohexanediamine-D-(−)-benzoyltartaric acid was 30 minutes and the retention time (t_R) of trans-d-1,2-cyclohexanediamine-D-(−)-benzoyltartaric acid was 70 minutes so that both were completely isolated. After the isolation procedures the same as those of Example 1, trans-1-1,2-cyclohexanediamine and trans-d-1,2-cyclohexanediamine were obtained.

EXAMPLE 3

Optical Resolution of Trans-dl-1,2-cyclohexanediamine Orthophthal-Aldehyde Derivative by Means of HPLC

After 11.4 mg of trans-dl-1,2-cyclohexanediamine was dissolved in 44 ml of phosphoric acid buffer (pH 7) and 20.1 g of orthophthalaldehyde was added thereto, the reaction was allowed to proceed at room temperature for a whole day and night to produce a solution of a trans-dl-1,2-cyclohexanediamine orthophthalaldehyde derivative. The HPLC separation procedure was conducted under the following conditions employing the above solution.

Column: ULTRON ES-OVM made by Shinwa Kako K.K. (filler prepared by chemically bonding acidic glycoprotein to aminated silica gel) Inner diameter: 4.6 mm Height: 15 cm Mobile phase: 20 mM potassium dihydrogen phosphate (pH 5.6):ethanol=100:7 (volume ratio) Column temperature: 40° C. Flow rate: 2.0 ml/min. Detector: UV 220 nm

As shown in FIG. 3, the retention time (t_R) of the trans-1-1,2-cyclohexanediamine orthophthalaldehyde derivative is 5.3 minutes and that of the trans-d-1,2-cyclohexanediamine orthophthalaldehyde was 3.7 minutes so that both were completely isolated. After 1-N hydrochloric acid was added to the respective derivatives and reacted at room temperature for 30 minutes, the derivatives were extracted with ether and distilled under reduced pressure to produce as colorless liquid trans-1-1,2-cyclohexanediamine and trans-d-1,2-cyclohexanediamine.

EXAMPLE 4

Optical Resolution of Trans-dl-1,2-cyclohexanediamine by Means of HPLC

In 100 ml of water was dissolved 1.00 g of trans-dl-1,2-cyclohexanediamine. The HPLC separation procedure was conducted under the following conditions employing the above solution.

Column: Filler prepared by chemically bonding L-prolin to silica gel to which a metal ion (Cu^{2+}) was coordinated. Inner diameter: 4.6 mm Height: 25 cm Mobile phase: Water Column temperature: 40° C. Flow rate: 1.8 ml/min. Detector: Polarimeter 589 nm

As shown in FIG. 4, the retention time (t_R) of the trans-d-1,2-cyclohexanediamine was 20 minutes and that of the trans-1-1,2-cyclohexanediamine was 24 minutes so that both were completely isolated.

EXAMPLE 5

The HPLC separation procedure was conducted under the following conditions employing the solution of Example 4.

Column: Filler prepared by adsorbing cellulose trisphenyl carbamate to silica gel Inner diameter: 4.6 mm Height: 25 cm Mobile phase: Ethanol:Methanol=50:50 (volume ratio) Column temperature: 40° C. Flow rate: 2.0 ml/min. Detector: Polarimeter 589 nm

As shown in FIG. 5, the retention time (t_R) of the trans-d-1,2-cyclohexanediamine was 30 minutes and that of the trans-1-1,2-cyclohexanediamine was 35 minutes so that both were completely isolated.

Comparative Example 1

The diastereomer obtained in Example 1 was optically resoluted by means of recrystallization in place of the HPLC method. That is, when 67 ml of water was added to 35.5 g of trans-dl-1,2-cyclohexanediamine to dissolve it under heating at 90° C. and then 22.10 g of L-(+)-tartaric acid and 13.4 ml of glacial acetic acid were gradually added and stirred, an aqueous solution of trans-1-1,2-cyclohexanediamine-L-(+)-tartaric acid which was a diastereomer was obtained. After 9.23 g of this diastereomer was dissolved in a small amount of water, 5.64 g of sodium hydroxide was added, extracted with ether and distilled under reduced pressure to produce as colorless liquid 3.2 g of trans-1-1,2-cyclohexanediamine.

Comparative Example 2

The trans-1-1,2-cyclohexanediamine was obtained in accordance with the same procedures as those of Comparative Example 1 except that D-(−)-benzoyl tartaric acid and ethanol were employed in place of the L-(+)-tartaric acid and the water of Comparative Example 1, respectively.

EXAMPLE 6

Comparison of Optical Purity of Trans-1-1,2-cyclohexanediamine

The cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) was synthesized from the respective trans-1-1,2-cyclohexanediamine prepared in Examples 1, 2, 3, 4 and 5 and Comparative Examples 1 and 2 in accordance with a conventional method. The optical purity of the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) after the below HPLC procedures was compared with an authentic sample.

Column: OC made by Daicel K.K. (filler prepared by adsorbing a cellulose carbamate derivative to silica gel) Inner diameter: 4.6 mm Height: 25 cm Mobile phase: Ethanol:Methanol=30:70 (volume ratio) Column temperature: 40° C. Flow rate: 2.0 ml/min. Detector: UV 254 nm

The determination of the optical purity was conducted as follows. From an authentic sample, cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) (100% e.e.), a calibration curve was prepared. The mixed ratio of the optical isomer of the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) obtained in Examples 1, 2, 3, 4 and 5 and Comparative Examples 1 and 2 was measured referring to the calibration curve and the optical purity was determined in accordance with the following equations.

Optical purity (%) = e.e. (%)
= [{cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) content}
− {cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II) content}/
{cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) content}
+ {cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II) content}] × 100
(e.e.: enantiomer excess)

As shown in FIG. 6, while the relative retention time of the cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) was 1.00 minute, that of the cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II) was 1.21 minutes. The relative standard deviation of the repeated HPLC injection precision was satisfactorily 0.04% or less.

The results of the determination of the optical purity are as shown in Table 1. The cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) synthesized from the trans-1-1,2-cyclohexanediamine optically resoluted by means of the HPLC method possesses higher optical purity than that of the cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) obtained through the recrystallization.

TABLE 1

		Optical Purity e.e. (%)
Example	1	100.0
	2	100.0
	3	100.0
	4	100.0
	5	100.0
Comparative Example	1	99.0
		99.0

EXAMPLE 7

① Preparation of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II)

After 46.8 g (0.41 mol) of the trans-1-1,2-cyclohexanediamine obtained in Examples 1 to 5 was reacted with 170 g (0.41 mol) of potassium tetrachloroplatinate in an aqueous solution at room temperature over 10 hours, 154.1 g (yield: 99%) of yellow needles of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) were precipitated.

② Preparation of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II)

After 10.00 g (26.3 mmol) of the cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) obtained above was suspended in 800 ml of water, 7.99 g (26.3 mmol) of silver oxalate was added thereto and stirred for 2 hours at room temperature. After the precipitated silver chloride was removed, the obtained solution was concentrated to 100 ml. The deposited crystal was collected by filtration to obtain 8.3 g of crystals of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) (yield: 80%). Optical purity: 100% e.e. Melting point: 198.3° to 199.7° C.

EXAMPLE 8

① Preparation of cis-tetrachloro(trans-1-1,2-cyclohexanediamine) Pt(IV)

After 45.7 g (0.40 mol) of the trans-1-1,2-cyclohexanediamine obtained in Examples 1 to 5 and 194.4 g (0.4 mol) of potassium hexachloroplatinate (IV) were dissolved in water and reacted for over 10 hours, 171.4 g (yield: 95%) of cis-tetrachloro(trans-1-1,2-cyclohexanediamine) Pt (IV) was obtained.

② Preparation of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II)

After 4.51 g (10.0 mmol) of the cis-tetrachloro(trans-1-1,2-cyclohexanediamine) Pt(IV) obtained ① of Example 8 was suspended in 800 ml of water, 6.08 g (20.0 mmol) of silver oxalate was added thereto and reacted for 1 hour under reflux. After insoluble substance was removed, the obtained solution was concentrated to 80 ml under reduced pressure, the deposited crystal was collected by filtration to obtain 3.18 g of cis-oxalato(-trans-1-1,2-cyclohexanediamine) Pt(II) (yield: 80%). Optical purity: 100% e.e. Melting point: 198.3° to 199.° C.

③ Preparation of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II)

After 4.51 g (10.0 mmol) of the cis-tetrachloro(trans-1-1,2-cyclohexanediamine) Pt(IV) obtained ① of Example 8 was suspended in 800 ml of water, 3.04 g (10.0 mmol) of silver oxalate was added thereto and reacted for 10 hours under reflux. After insoluble substance was removed, 3.40 g (20.0 mmol) of silver nitrate was added to the obtained solution. After, further, 250 mg (5 mmol) of hydrazine hydrate was added thereto and reacted for 3 hours at room temperature, 20 ml of an aqueous solution of 1-N sodium hydroxide was added and reacted for 1 hour. After insoluble substance was removed, the obtained solution was concentrated to 80 ml under reduced pressure, the deposited crystal was collected by filtration to obtain 1.59 g of cis-oxalato(-trans-1-1,2-cyclohexanediamine) Pt(II) (yield: 40%). Optical purity: 100% e.e. Melting point: 198.3° to 199.7° C.

EXAMPLE 9

① Preparation of cis-diaquo(trans-1-1,2-cyclohexanediamine) Pt(II)

After 4.00 g (10.5 mmol) of the cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) obtained in ① of Example 7 was suspended in 100 ml of distilled water, two moles of silver nitrate was added and reduced in dark for over 24 hours and silver chloride produced in the reaction was removed by filtration. After 0.12 g of potassium iodide was added to the filtrate and reacted for over 12 hours for precipitating excess silver ions as silver iodide, 10 mg of active carbon was added thereto for refining and decolorizing which was then removed by filtration.

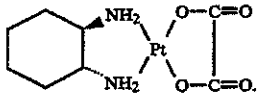
② Preparation of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II)

A solution of a nitrate of cis-diaquo(trans-1-1,2-cyclohexane-diamine) Pt(II) thus obtained was passed through a column packed with 160 ml of Amberlite IRA-400 and eluted with distilled water. After 1.32 g (10.5 mmol) of oxalic acid dihydrate was added to this solution and reacted for 2 hours to obtain 3.33 g of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) (yield: 80%) was obtained. Optical purity: 100% e.e. Melting point: 198.3° to 199.7° C.

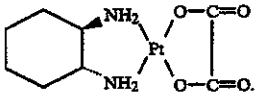
What is claimed is:

1. Cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) complex having high optical purity represented by Formula 1 which possesses optical purity of 99.94% or more and a melting point between 198.3° C. and 199.7° C.

[Formula 1]



2. In a process for the preparation of cis-oxalato(-trans-1-1,2-cyclohexanediamine) Pt(II) complex of high optical purity and a melting point between 198.3° C. and 199.7° C., the improvement which comprises utilizing as the starting material for the synthesis of the complex trans-1-1,2-cyclohexanediamine or a derivative thereof which has been optically resoluted by high performance liquid chromatography, said complex being represented by the Formula:



3. The process of claim 2 wherein the optically resoluted trans-1-1,2-cyclohexanediamine or derivative thereof is dissolved in water and reacted with a tetrahalogenoplatinum (IV) acid salt to produce cis-tetrahalogeno(trans-1-1,2-cyclohexanediamine) Pt(IV).

4. The process of claim 2 wherein the tetrahalogenoplatinum (IV) salt comprises potassium tetrachloroplatinate and the cis-tetratetrahalogeno(trans-1-1,2-cyclohexanediamine) Pt(IV) comprises cis-tetrachloro(-trans-1-1,2-cyclohexanediamine) Pt(IV).

5. The process of claim 4 wherein the cis-tetrachloro(trans-1-1,2-cyclohexanediamine) Pt(IV) is reacted with 2 moles of silver oxalate per mole of cis-tetrachloro(trans-1-1,2-cyclohexane-diamine) Pt(IV) to produce cis-oxalato(trans-1-1,2-cyclohexane-diamine) Pt(II) complex.

6. The process of claim 4 wherein the cis-tetrachloro(trans-1-1,2-cyclohexanediamine) Pt(IV) is reacted with equimolar silver oxalate and thereafter reduced with a suitable reducing agent to produce cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) complex.

7. The process of claim 2 wherein the optically resoluted trans-1-1,2-cyclohexanediamine or derivative thereof is dissolved in water and reacted with potassium tetrachloroplatinate to produce cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(IV).

8. The process of claim 7 wherein the cis-dichloro(-trans-1-1,2-cyclohexanediamine) Pt(IV) is suspended in water and reacted with equimolar silver oxalate to produce cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) complex.

9. The process of claim 7 wherein the cis-dichloro(-trans-1-1,2-cyclohexanediamine) Pt(IV) is suspended in water and reacted with silver nitrate or silver sulfate followed by elution with an anion exchange resin (OH form) to produce cis-dihydroxy(trans-1-1,2-cyclohexanediamine) Pt(IV) which is thereafter reacted with oxalic acid to produce cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) complex.

10. The process of claim 2 wherein the high performance liquid chromatography is carried out in a column packed with a filler comprised of a material selected from the group consisting of cellulose, a cellulose ester derivative, a cellulose carbamate derivative, an amylose carbamate derivative, a polymethacryl acid ester, β- and γ-cyclodextrin, a polymethacrylamide derivative, an acidic glycoprotein, L-proline, hydroxyproline, L-valine, a material prepared by adsorbing or binding (1R,2S)-2-carboxy-methylamino-1,2-diphenylethanol to silica gel, a material prepared by coordinating a metal ion to one of the aforesaid materials, a material prepared by adsorbing or binding a protein to aminated silica gel, a crown ether, a urea derivative chiral to silica gel treated with (3-aminopropyl)triethoxysilane, N(3,5-dinitrobenzoyl)-(R)-phenylglycine, a material chemically bonded to DNB-L-leucine and (S)-1-(α-naphthyl)-ethylamino-(S)-2-(4-chlorophenyl)isovaleric acid, an octadecylsilane and a silica gel.

11. The process of claim 2 wherein the optically resoluted trans-1-1,2-cyclohexanediamine derivative is prepared by reacting 1,2-cyclohexanediamine with a compound selected from the group consisting of L-(+)-tartaric acid, D-(−)-tartaric acid, L-(+)-benzoyltartaric acid and D-(−)-benzoyltartaric acid to form the diastereomer and optically resoluting the diastereomer by high performance liquid chromatography.

12. The process of claim 2 wherein derivative utilized as the optically resoluted trans-1-1,2-cyclohexane-diamine derivative is selected from the group consisting of an isoindolin derivative, a benzoyl derivative, an acetyl derivative, a 3,5-dinitrobenzoyl derivative and a para-nitrobenzoyl derivative.

13. The process of claim 2 wherein the high performance liquid chromatography is carried out by utilizing a column packed with a chiral filler and a polarimeter as a detector.

* * * * *

EXHIBIT C

US005290961A

United States Patent [19]

Okamoto et al.

[11] Patent Number: 5,290,961

[45] Date of Patent: Mar. 1, 1994

[54] PLATINUM COMPOUND AND PROCESS OF PREPARING SAME

[75] Inventors: Koji Okamoto; Yuko Hoshi; Chihiro Nakanishi, all of Kanagawa, Japan

[73] Assignee: Tanaka Kikinzoku Kogyo K.K., Japan

[21] Appl. No.: 3,306

[22] Filed: Jan. 12, 1993

[30] Foreign Application Priority Data

Jan. 13, 1992 [JP] Japan 4-23219

[51] Int. Cl.[5] C07F 15/00

[52] U.S. Cl. 556/137

[58] Field of Search 556/137

[56] References Cited

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Primary Examiner—José G. Dees
Assistant Examiner—Porfirio Nazario-Gonzalez
Attorney, Agent, or Firm—Klauber & Jackson

[57] ABSTRACT

Disclosed herein are a platinum compound employed as raw material of medicines having carcinostatic effects, and a process of preparing the platinum compound. The platinum compound (I) substantially free from impurities can be prepared through a reaction between the corresponding dihalogen compound and an organic dibasic acid employing an iodine compound utilizing the difference of solubilities between the desired compound and the iodine compounds.

2 Claims, No Drawings

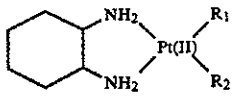
PLATINUM COMPOUND AND PROCESS OF PREPARING SAME

BACKGROUND OF THE INVENTION

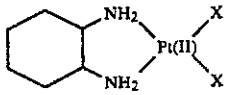
The present invention relates to a platinum compound and a process of preparing the same.

Heretofore, compounds (I) and (II) have been known as platinum compounds having carcinostatic effects. The compound (I) has been obtained by means of the following procedures. At first, the compound (II) is prepared by reacting $K_2Pl(II)X_4$ (X is Cl or Br) with a 1,2-cyclohexanediamine isomer. A silver nitrate solution of two equivalents in respect to the compound (II) is added to a solution prepared by dissolving the compound (II) into water under boiling to precipitate chlorine or bromine as silver chloride or silver bromide which is then filtered off. To the filtrate is added an organic dibasic acid to obtain the desired compound (I).

I



II



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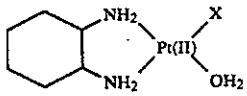

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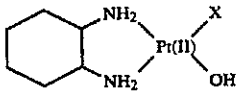


However, this preparation process possesses a disadvantage that many impurities such as the unreacted compound (II), compounds (III) and (IV) which are by-products of the compound (II) and an unreacted silver ion remain in the compound (I) prepared according to the above process.

One of the reasons the impurities are contaminated in the desired compound (I) is the low solubility of the compound (II) in water. For example, when the compound (II) is a chloride of a trans-1 isomer, its considerably low solubility in water is about 0.26 mg/ml and oven if dissolved under boiling, only about 0.5 mg/ml of the compound (II) dissolves. Because of the low solubility of the compound (II), it is quite difficult to completely dechlorinate the compound (II) from the viewpoint of its characteristics resulting in the contamination of the above impurities.

A remarkable problem also remains in the removal of the silver chloride formed as a result of the above reaction. The solubility of the silver chloride is relatively low so that almost all the silver chloride formed can be removed in ordinary conditions. However, in the above reaction, a large amount of water is required due to the low solubility of the compound (II) so that the complete removal of the silver chloride may be impossible in such a reaction employing a large amount of water.

This tendency becomes worse when the bromide is employed.

Many platinum compounds may possess physiologic activities such as cytotoxicity, and the contamination of the above unreacted compound (II) and the by-products (III) and (IV) is not allowed in the raw material for medicines having carcinostatic effects even if a trace amount. The unreacted silver ion which may exist in the medicines is regulated in a heavy metal test method, but no satisfactory value in connection with the silver ion has been obtained in conventional methods.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a process of preparing a compound (I) which can be employed for raw material of a medicine having carcinostatic effects.

Another object of the invention is to provide a process of preparing a compound (I) which is not contaminated with such impurities as the above compounds (II), (III) and (IV) and an unreacted silver ion.

A further object of the invention is to provide the compound (I) substantially free from the above impurities.

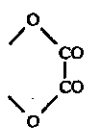
The present invention has been made to overcome the above-mentioned drawbacks of the prior art. The objects can be attained by adding to a compound (II) a silver ion solution containing not less than two equivalents of silver in respect to the compound (II), removing silver chloride and/or silver bromide formed, adding to the solution sodium iodide and/or potassium iodide to covert the unreacted compound (II), the by-products of the compound (II) and an unreacted silver ion into their iodine compounds followed by the removal thereof and thereafter adding an organic dibasic acid thereto to form the platinum complex (I).

DETAILED DESCRIPTION OF THE INVENTION

In the above preparation process, after the removal, preferably the filtration of the silver chloride and/or the silver bromide, such impurities as the unreacted compound (II), the compounds (III) and (IV) are converted into the corresponding iodine compounds by adding sodium iodide and/or potassium iodide thereto. Since the solubility of these iodine compounds in water is remarkably low so as to make a large difference between the said solubility and that of the desired compound (I), the iodide compounds can be completely removed, for example, by filtration to provide the final desired compound (I) contaminated with substantially no impurities.

In the formula (I), R_1 and R_2 form with each other a circular group selected from the formulae (V), (VI), (VII), (VIII), (IX) and (X). In other words, R_1 and R_2 form with each other an aliphalic dibasic acid residue. Almost all the platinum compounds shown in the formula (I) and prepared in accordance with the process of the present invention possess carcinostatic effects which are not depressed because of no contamination with impurities.

V



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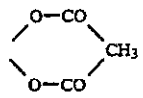
VI



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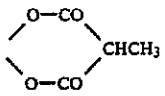
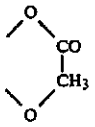
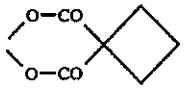


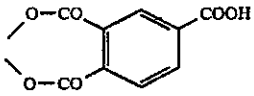
VIII



IX



X



EXAMPLE

A preferred Example of this invention will be hereinafter described. Although a process of preparing cis-oxalate (trans-1-1,2-cyclohexanediamine) platinum (II) as a representative of the compound (I) will be illustrated, the Example does not intend to restrict the present invention.

EXAMPLE

562.5 g of potassium chloroplatinate and 154.8 g of trans 1-1,2-cyclohexanediamine were dissolved and mixed in 3.5 liters of water to obtain cake-like cis-dichloro (trans-1-1,2-cyclohexanediamine) platinum (II) without recrystallization with a yield of 96%. This compound was suspended in 5.7 liters of water to which was added a solution which had been prepared by dissolving 386.4 g of silver nitrate in 2.8 liters of water. After this solution was stirred in the dark at a room temperature for three days, most of the precipitate of the silver chloride was removed by filtration. After the filtrate was concentrated under a reduced pressure, a solution consisting of 45 ml of water and 3.85 g of potassium iodide dissolved therein was added followed by one hour stirring, and then active carbon was added. Silver iodido and iodine compounds of (II), (III) and (IV) then formed and the active carbon were completely removed by filtration. To the remaining filtrate was added 146.3 g of oxalic acid which was allowed to stand for two hours to obtain crude crystal of desired cis-oxalate (trans 1-1,2-cyclohexanediamine) platinum (II) with a yield of 80%. Then, 70 g of this crude crystal was dissolved under heating in 2.7 liters of water, filtered and cooled to a room temperature. The platinum crystal precipitated was collected by filtration and washed with a small amount of water. The crystal obtained was dried to obtain the desired platinum complex. These experiments were repeated five times of which yields were 49 g, 45 g, 50 g, 48 g and 47 g.

COMPARATIVE EXAMPLE

After the cake-like cis-dichloro (trans-1-1,2-cyclohexanediamine) platinum (II) was obtained under the same conditions as those of Example, this cake like substance was dissolved in 5.7 liters of water under boiling to which was added a solution consisting of 2.8 liters of water and 386.4 g of silver nitrate dissolved therein, the solution being stirred in the dark for three hours. The reaction solution was filtered after cooling and the filtrations were repeated until the filtrate became transparent. After the concentration of the filtrate under a reduced pressure, 140.3 g of oxalic acid was added and the solution was allowed to stand overnight at a room temperature to obtain cis oxalate (trans 1 1,2-cyclohexanediamino) platinum (II) with a yield of 80% by means of the concentration under a reduced pressure. These experiments were repeated five times of which yields were 300 g, 280 g, 310 g, 290 g and 300 g.

The purity test for detecting the impurities contained in the cis-oxalate (trans-1 1,2-cyclohexanediamine) platinum (II) prepared in Example and Comparative Example was carried out by means of a high performance liquid chromatography (HPLC) method. The results are shown in Table 1.

The purity test was carried out in accordance with an absolute analytical curve method.

In other words, an analytical curve was prepared by stepwise introducing standard known amounts of the unreacted components supposed to be impurities, measuring the peak areas of the respective chromatograms and plotting the amounts of the components on the abscissa axis and the peak areas on the ordinate axis. The contents of the cis-oxalate (trans-1-1,2-cyclohexanediamine) platinum (II) in the samples respectively prepared in the above Example and Comparative Example were measured under the same conditions employing HPLC and calculated by determining the amounts of the components to be tested from the peak areas referring to the analytical curve.

The operation conditions of the chromatography were as follows.

TABLE 1

Component	Relative Retention Time 'R	Purity Test, Content (%) Example	Comp. Example	Chromat. Condition
cis-oxalate (trans-1-1,2-cyclohexanediamine) platinum (II)	1.00	100.0	98.0	1.2
cis dichloro (trans-1-1,2-cyclohexanediamine) platinum (II)	0.92	0	0.5	1
cis-monochloro-monoaquo (trans-1-1,2-cyclohexanediamine) platinum (II)	0.87	0	0.3	2
cis-diaquo (trans-1-1,2-cyclohexanediamine) platinum (II) nitrate	0.82	0	0.3	3
cis-diiodo (trans-1-1,2-cyclohexanediamine) platinum (II)	1.73	0	0	2

Chromatography Operation Conditions 1:
Detector: Ultraviolet absorption photometer: 220 nm

Column: Stainless tube having an inner diameter of about 4.6 mm and a length of 15 cm packed with octadecylsilicated silica gel having a particle size of 5 to 10 μm

Column Temperature: 40° C.

Moving phase: Mixed solution of water and methanol (97:3)

Flow rate: 0.7 ml/min.

Chromatography Operation Conditions 2:

Moving phase: Mixed solution of water and methanol (85:15)

The other operation conditions were the same as those of Conditions 1.

Chromatography Operation Conditions 3:

Moving phase: Mixed solution of water and methanol (85:15)

The other operation conditions were the same as those of Conditions 1.

The purity test of silver impurities contained in the cis-oxalate trans-1-1,2-cyclohexanediamino) platinum (II) prepared above was carried out in accordance with an atomic absolute method. The results are shown in Table 2.

Operation Conditions of Atomic Absorption:

Employed gas:

Combustible gas: Acetylene

Combustion supporting gas Air

Lamp: Hollow silver cathode lamp

Wavelength: 328.1 nm.

TABLE 2

	Example		Comparative Example	
Lot No.	Silver (ppm)	Halogen (ppm)	Silver (ppm)	Halogen (ppm)
1	0.3	2.2	31.6	5.0
2	0.6	3.5	1.3	28.2
3	0.9	2.2	36.2	7.3
4	0.3	2.9	0.9	65.3
5	0.7	2.2	25.4	10.3

The purity test was performed in accordance with a standard addition method. Three sample solutions were taken and a standard solution was added to each of the solutions in which the concentrations of the elements to be detected were stepwise distributed to which was added a solvent to make the volumes of the solutions identical. The absorption was measured for each of the solutions for plotting the amounts (concentrations) of the added standard element on the abscissa axis and the values of the absorption on the ordinate axis. The amount of the element to be detected (concentration of silver atom) was determined, after extending a regression line obtained by the plotting, by a distance between the intersecting point with the abscissa axis and the origin.

The concentration of halogen impurities was measured in accordance with a potentiometric titration method employing a flask in which oxygen burns. The results thereof are shown in Table 2.

Potentiometric titration employing flask in which oxygen burns

Flow rate of oxygen: 200 ml/min.

Flow rate of argon: 250 ml/min.

Temperature of electric furnace: 850° to 950° C.

Final Potential: 293 mV

Titration Current: 1.0 mA.

The halogen content was determined as chlorine concentration in accordance with the following equation.

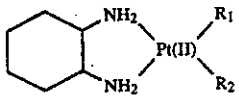
$$\text{Halogen content} = \text{Chlorine concentration (ppm)} - [\text{Measured value } (\mu g) \times 1000]/[\text{Sample amount (mg)} \times \text{Recovery Rate}]$$

As apparent from the Tables 1 and 2, no impurities were contained in the cis-oxalate (trans-1,1,2-cyclohexanediamino) platinum (II) prepared in Example.

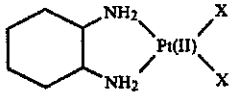
What is claimed is:

1. A process of preparing a cis-platinum (II) complex of a 1,2-cyclohexanediamine isomer designated by a general formula (I)

I

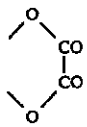


II

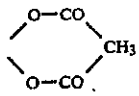


(in the formula, the conformation of 1,2-cyclohexanediamine is cis, trans-d or trans-1-isomer, and R_1 and R_2 form with each other a circular group selected from the group consisting of the formulae (V), (VI), (VII), (VIII), (IX) and (X))

V



VI



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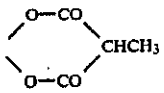
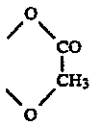
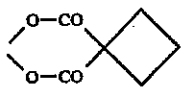


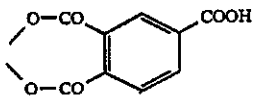
VIII



IX



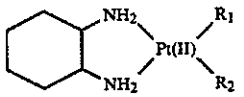
X



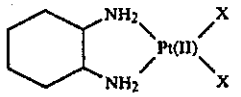
which comprises adding to a dihalogen compound of a cis-platinum (II) complex of a 1,2-cyclohexanediamine

isomer designated by a general formula (II), wherein X is a halogen, a silver ion solution containing not less than two equivalents of silver in respect to the compound (II), removing silver chloride and/or silver bromide, adding to the solution sodium iodide and/or potassium iodide to convert the unreacted compound (II), the by-products of the compound (II) and an unreacted silver ion to their iodine compounds followed by the removal thereof and thereafter adding the corresponding organic dibasic acid of the formulae (V), (VI), (VII), (VIII), (IX) and (X) to the remaining platinum complex.

2. A platinum compound (I)

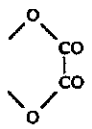


I

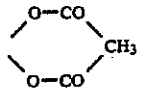


II

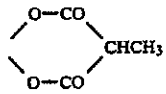
(in the formula, the conformation of 1,2-cyclohexanediamine is cis, trans-d or trans-l-isomer, and R_1 and R_2 form with each other a circular group selected from the group consisting of the formulae (V), (VI), (VII), and (X))



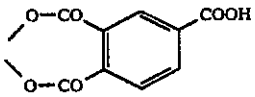
V



VI



VII



X

substantially free from impurities prepared by reacting a dihalogen compound of a cis-platinum (II) complex of a 1,2-cyclohexanediamine isomer (II) with a silver compound to form silver iodide and/or silver bromide which is then removed, converting the unreacted compound (II), the by-products of the compound the corresponding organic dibasic acid of the formulae (V), (VI), (VII), and (X) and an unreacted silver to their corresponding iodine compounds by adding sodium iodide and/or potassium iodide which are then removed, and reacting the remaining platinum complex with an organic dibasic acid.

* * * * *

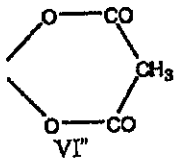
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,290,961
APPLICATION NO. : 08/003306
DATED : March 1, 1994
INVENTOR(S) : Koji Okamoto et al.

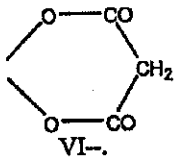
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 3, Lines 3-6, please delete "



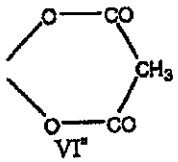
VI"

and insert --



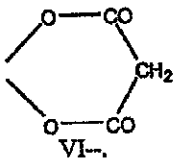
VI--.

Claim 1, Col. 6, Lines 42-45, please delete "



VI"

and insert --



VI--.

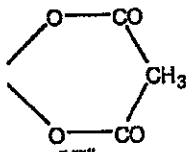
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,290,961
APPLICATION NO. : 08/003306
DATED : March 1, 1994
INVENTOR(S) : Koji Okamoto et al.

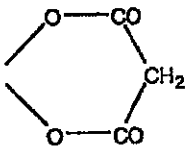
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 2, Col. 8, Lines 8 -11, please delete "



VI"

and insert --



VI–.

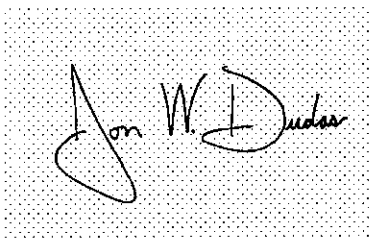
Claim 2, Col. 8, Line 25 of the text, please delete "(II)" and insert --designated by a general formula (II), wherein X is a halogen,--.

Claim 2, Col. 8, Lines 28-30 of the text, please delete "the corresponding organic dibasic acid of the formulae (V), (VI), (VII), and (X)" and insert --(II)--.

Claim 2, Col. 8, Lines 33-34 of the text, please delete "an organic dibasic acid." and insert -- the corresponding organic dibasic acid of the formulae (V), (VI), (VII), and (X).--.

Signed and Sealed this

Twenty-first Day of November, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT D

US005959133A

United States Patent [19]

Ohnishi

[11] **Patent Number: 5,959,133**

[45] **Date of Patent: Sep. 28, 1999**

[54] **PROCESS FOR THE PREPARATION OF PLATINUM COMPOUNDS**

[75] Inventor: **Yuko Ohnishi**, Kanagawa-ken, Japan

[73] Assignee: **Tanaka Kikinzoku Kogyo K.K.**, Tokyo, Japan

[21] Appl. No.: **09/029,682**

[22] PCT Filed: **Jul. 4, 1997**

[86] PCT No.: **PCT/JP97/02332**

§ 371 Date: **Mar. 3, 1998**

§ 102(e) Date: **Mar. 3, 1998**

[87] PCT Pub. No.: **WO98/01454**

PCT Pub. Date: **Jan. 15, 1998**

[30] **Foreign Application Priority Data**

Jul. 4, 1996 [JP] Japan 8-174788

[51] **Int. Cl.**^{6} **C07F 15/00**

[52] **U.S. Cl.** **556/137**

[58] **Field of Search** 556/137

[56] **References Cited**

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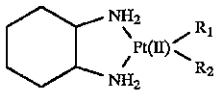
Inorg Chem vol. 27 No. 23 Synthesis and characterization of Diasteromeric (1,2–diaminocyclohexane) platinum (II) complexes, by Hoeschele pp. 4106–4113, 1988.

Primary Examiner—Gary Geist
Assistant Examiner—Jean F. Vollano
Attorney, Agent, or Firm—Jordan and Hamburg LLP

[57] **ABSTRACT**

A process for the preparation of cis-platinum(II) complexes of 1,2-cyclohexanediamine isomers, represented by formula I, containing substantially no dihydroxoplatinum(IV) complex as an impurity.

(I)



Deoxygenated water is used in all steps of the process, from charging of the starting materials; i.e., potassium tetrachloroplatinate and trans-(-)-1,2-cyclohexanediamine, to the acquisition of target complexes. In addition, a low-oxygen content atmosphere is applied as an operational environment to prevent deoxygenated water from degradation through oxygen absorption and to eliminate the possibility of direct oxidation of a platinum compound due to atmospheric oxygen.

3 Claims, No Drawings

PROCESS FOR THE PREPARATION OF PLATINUM COMPOUNDS

This application is the national stage of PCT/JP97/02332 filed Jul. 4, 1997.

BACKGROUND OF THE INVENTION

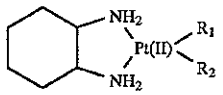
1. Field of the Invention

The present invention relates to a process for the preparation of cis-platinum(II) complexes of 1,2-cyclohexanediamine isomers that serve as active components of carcinostatic drugs.

2. Background Art

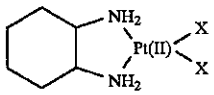
Platinum compounds represented by formula I

(I)



are generally known to have carcinostaticity. They have conventionally been prepared by the following steps: reacting $K_2Pt(II)X_4$ (X is Cl or Br) with a 1,2-cyclohexanediamine isomer to form an intermediate compound represented by formula II

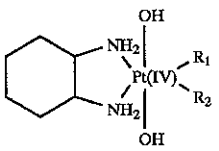
(II)



dissolving the intermediate compound in water under boiling; adding thereto a solution of $AgNO_3$ in an amount of twice the mol equivalent of the intermediate compound represented by formula II so as to cause chlorine or bromine contained in the compound to precipitate in the form of silver chloride or bromide; separating the precipitates through filtration; and adding a dibasic organic acid to the filtrate.

However, the platinum compounds represented by formula I obtained through the customary process contain as an impurity about 0.1–5% of a dihydroxoplatinum(IV) complex—a platinum compound represented by formula III—which is produced through oxidation of the platinum compounds represented by formula I.

(III)



SUMMARY OF THE INVENTION

In view of the foregoing, a general object of the present invention is to provide a process for a preparation of cis-platinum(II) complexes of 1,2-cyclohexanediamine isomers that contain substantially no dihydroxoplatinum(IV) complex as an impurity.

To achieve the above object, the inventor of the present invention has conducted careful studies of a process for a preparation of cis-platinum (II) complexes of 1,2-cyclohexanediamine isomers to overcome the aforementioned problems and has developed a process which does not produce the aforementioned impurity, i.e., dihydroxoplatinum(IV) complex, by satisfactorily eliminating factors that cause oxidation during the preparation.

According to the present invention, the target compounds which serve as active components of carcinostatic drugs, i.e., cis-platinum(II) complexes of 1,2-cyclohexanediamine isomers, are prepared from potassium tetrachloroplatinate and trans-(-)-1,2-cyclohexanediamine, and oxidation of the target complexes is prevented by the process described below.

The preparation steps of the present invention have two characteristics. Firstly, deoxygenated water is used to prevent oxidation caused by dissolved oxygen in the solution where cis-platinum(II) complexes of 1,2-cyclohexanediamine isomers are being formed. Secondly, the oxygen content in the operational atmosphere involved in the preparation of the platinum compounds is reduced in order to eliminate possibility of direct oxidation of cis-platinum(II) complexes of 1,2-cyclohexanediamine isomers due to atmospheric oxygen as well as to prevent degradation of deoxygenated water. Deoxygenated water degrades as it absorb oxygen.

The process of the present invention provides cis-platinum(II) complexes of 1,2-cyclohexanediamine isomers which contain substantially no physiologically active dihydroxoplatinum(IV) complex as an impurity.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

According to the process of the present invention for preparing platinum(II) complexes of 1,2-cyclohexanediamine isomers represented by formula I, there is employed deoxygenated water in all steps of preparing a platinum compound from the starting materials, i.e, potassium tetrachloroplatinate and trans-(-)-1,2-cyclohexanediarnine, and substituting nitrogen or an inert gas for air of the operational environment or alternatively degassing under vacuum to thereby produce a low-oxygen content atmosphere so as to prevent degradation of deoxygenated water and to eliminate a possibility of direct oxidation of a platinum compound due to oxygen contained in air of the operational environment.

In the process, deoxygenated water is consistently used in all steps from the placement of the starting materials, i.e., potassium tetrachloroplatinate and trans-(-)-1,2-cyclohexanediamine, to the target cis-platinum(II) complexes of 1,2-cyclohexanediamine isomers. Therefore, oxidation due to oxygen dissolved in the deoxygenated water is prevented, and dihydroxoplatinum(IV) complex, an impurity, is not formed.

It has empirically been determined that the oxygen content in an operational environment should be adjusted to 5% or less in order to prevent deoxygenated water from absorbing oxygen and being degraded by atmospheric oxygen. To attain this oxygen content, air of the operational environment is preferably evacuated through degassing under vacuum or replacement with nitrogen or an inert gas.

The best mode of the embodiments of the present invention will now be described. In the process of the present invention for the preparation of platinum(II) complexes of 1,2-cyclohexanediamine isomers, deoxygenated water was used consistently as water participating in the reactions, and the atmosphere of operational chamber having the oxygen

content level of 1% adjusted through nitrogen-substitution was provided during all steps of preparing cis-platinum(II) complexes of 1,2-cyclohexanediamine isomers—active components of carcinostatic drugs—from the starting materials, i.e., potassium tetrachloroplatinate and trans-(-)-1,2-cyclohexanediamine.

Potassium tetrachloroplatinate (562.5 g) and trans-(-)-1,2-cyclohexanediamine (154.8 g) were dissolved and mixed in deoxygenated water (3.5 l) to thereby obtain cis-dichloro(trans-(-)-1,2-cyclohexanediamine)platinum(II) without recrystallization (cake-like, yield 96%). The resultant material was suspended in deoxygenated water (5.7 l) and the resulting suspension was mixed with a solution of silver nitrate (386.4 g) dissolved in deoxygenated water (2.8 l). This solution was stirred in the dark at room temperature for three days, then silver chloride that precipitated was mostly removed through filtration. The filtrate was concentrated under reduced pressure, and subsequently, a solution of potassium iodide (3.85 g) dissolved in deoxygenated water (45 ml) was added thereto. The resultant solution was stirred for one hour, after which activated carbon was added thereto. Formed precipitates and activated carbon were completely removed through filtration. Oxalic acid (146.3 g) was added to the filtrate, then the solution was allowed to stand for 2 hours to thereby obtain cis-oxalato(trans-(-)-1,2-cyclohexanediamine)platinum(II) (crude crystals, yield 50%). The crude crystals (270 g) were dissolved in deoxygenated water (12 l) with heat, then the solution was filtered and cooled to room temperature. White crystals that precipitated were collected by filtration, washed with a small amount of deoxygenated water, and dried to thereby obtain the target complex, cis-oxalato(trans-(-)-1,2-cyclohexanediamine)platinum(II) (160 g).

In a comparative example, the same procedure as described above was performed except that oxygen-containing water was used during all steps until the target cis-platinum(II) complexes of 1,2-cyclohexanediamine isomers are obtained from potassium tetrachloroplatinate and trans-(-)-1,2-cyclohexanediamine as starting materials, and that the reactions were carried out in the atmosphere.

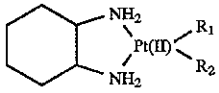
A purity analysis was carried out for cis-oxalato(trans-(-)-1,2-cyclohexanediamine)platinum(II) obtained from the working example of the present invention and for the corresponding complex obtained from the comparative example, through high-performance liquid chromatography (HPLC) (ODS column length, 50 cm; mobile phase, water-acetonitrile mixture; flow of eluent, 5 ml/min).

From the results of the HPLC purity analysis, a dihydroxoplatinum(IV) complex was detected in an amount of 1.5% in the cis-oxalato(trans-(-)-1,2-cyclohexanediamine)platinum(II) prepared in the comparative example, whereas no dihydroxoplatinum(IV) complex was detected in the corresponding compound prepared in the working example of the present invention.

What is claimed is:

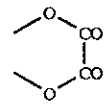
1. A process for a preparation of a platinum(II) complex of a 1,2-cyclohexanediamine isomer represented by formula I

(I)



wherein the steric configuration of 1,2-cyclohexanediamine is cis, trans-d, or trans-l and R_1 and R_2 form a cyclic structure with Pt(II) to represent a group of formula IV, formula V, formula VI, formula VII, formula VIII, or formula IX; the process comprising use of deoxygenating water in all steps for obtaining a platinum compound from potassium tetrachloroplatinate and trans-(-)-1,2-cyclohexanediamine serving as starting materials, and substituting nitrogen for air of an operational environment to thereby produce a low-oxygen content atmosphere so as to prevent degradation of deoxygenated water and to eliminate a possibility of direct oxidation of a platinum compound due to oxygen contained in air of the operational environment

(IV)



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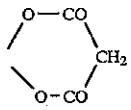

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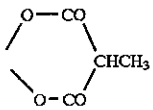
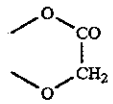
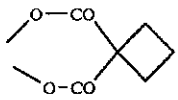


(VII)



(VIII)



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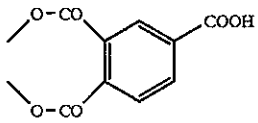
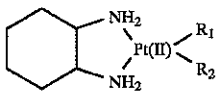


2. A process for a preparation of a platinum(II) complex of a 1,2-cyclohexanediamine isomer represented by formula I

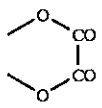
(I)



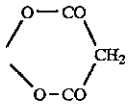
wherein the steric configuration of 1,2-cyclohexanediamine is cis, trans-d, or trans-l, and R_1 and R_2 form a cyclic structure with PT(II) to represent a group of formula IV, formula V, formula VI, formula VII, formula VIII, or formula IX; the process comprising use of deoxygenating water in all steps for obtaining a platinum compound from potassium tetrachloroplatinate and trans-(-)-1,2-cyclohexanediamine serving as starting materials, and substituting an inert gas for air of an operational environment to thereby produce a low-oxygen content atmosphere so as to prevent degradation of deoxygenated water and to eliminate

a possibility of direct oxidation of a platinum compound due to oxygen contained in air of the operational environment

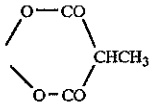
(IV)



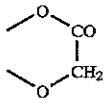
(V)



(VI)



(VII)



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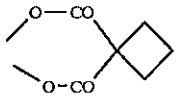
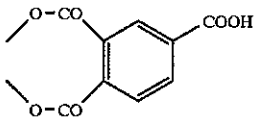
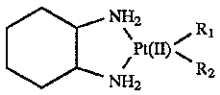


(IX)



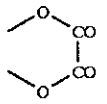
3. A process for the preparation of a platinum(II) complex of a 1,2-cyclohexanediamine isomer represented by formula I

(I)

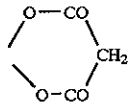


wherein the steric configuration of 1,2-cyclohexanediamine is cis, trans-d, or trans-l, and R_1 and R_2 form a cyclic structure with Pt(II) to represent a group of formula IV, formula V, formula VI, formula VII, formula VIII, or formula IX; the process comprising use of deoxygenating water in all steps for obtaining a platinum compound from potassium tetrachloroplatinate and trans-(-)-1,2-cyclohexanediamine serving as starting materials, and degassing under vacuum air of an operational environment to thereby produce a low-oxygen content atmosphere so as to prevent degradation of deoxygenated water and to eliminate a possibility of direct oxidation of a platinum compound due to oxygen contained in air of the operational environment

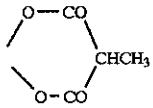
(IV)



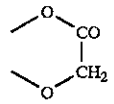
(V)



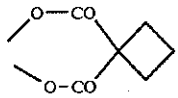
(VI)



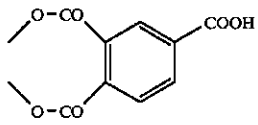
(VII)



(VIII)



(IX)



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