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

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SANOFI-AVENTIS U.S. LLC, SANOFI-AVENTIS, DEBIOPHARM S.A., Plaintiffs, v. SUN PHARMACEUTICAL INDUSTRIES LTD., CARACO PHARMACEUTICAL LABORATORIES, LTD. Defendants.	CIVIL ACTION NO.: 3:07-cv-03411-JAP-JJH

FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Sanofi-Aventis U.S. LLC, Sanofi-Aventis and Debiopharm S.A. (hereinafter, "Plaintiffs"), by way of their First Amended Complaint against Sun Pharmaceutical Industries Ltd. and Caraco Pharmaceutical Laboratories, Ltd., 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 the U.S. subsidiary of Sanofi-Aventis, and is a corporation incorporated 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, Sun Pharmaceutical Industries Ltd. ("Sun India") is a corporation organized under the laws of India, having corporate offices at Acme Plaza, Andheri-Kurla Road, Andheri (E), Mumbai, India 400 059.

5. On information and belief, Sun India conducts business through and with its subsidiary, Sun Pharmaceutical Industries, Inc. ("Sun USA"), which maintains a offices at 270 Prospect Plains Road, Cranbury, NJ 08512.

6. On information and belief, Caraco Pharmaceutical Laboratories, Ltd. ("Caraco") is a corporation registered to do business in New Jersey and maintaining an authorized agent at 820 Bear Tavern Road, West Trenton, NJ 08628.

7. On information and belief, Sun India owns a majority interest in Caraco.

8. On information and belief, Sun India is in the business of manufacturing generic pharmaceutical products, which are copies of products invented and developed by innovator pharmaceutical companies, and which include a generic version of Sanofi-Aventis's injectable oxaliplatin products.

9. On information and belief, Sun India assembled and caused to be filed with the United States Food and Drug Administration ("FDA"), pursuant to 21 U.S.C. § 355(j), Abbreviated New Drug Application ("ANDA") No. 78-818 concerning a proposed drug product, oxaliplatin for injection, containing 50 mg/vial and 100 mg/vial.

10. On information and belief, Caraco actively encouraged Sun India to file ANDA No. 78-818 with the FDA, and/or participated in the work related to submission of ANDA No. 78-818.

11. On information and belief, if ANDA No. 78-818 is approved, it is the intention of Sun India and Caraco that the product will be distributed in the United States by or through Caraco.

12. Sun India and Caraco are hereinafter referred to collectively as "Sun".

JURISDICTION AND VENUE

13. 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, 1338(a), 2201, and 2202.

14. Sun India is subject to personal jurisdiction in New Jersey because Sun India maintains continuous and systematic contacts with this judicial district. Sun India has conducted and continues to conduct business, directly, or through its subsidiaries, including Caraco and Sun USA, in this judicial district. On information and belief, Sun India, directly, or through its subsidiaries, manufactures, markets and sells generic drugs throughout the United States and the District of New Jersey. Sun has previously submitted to personal jurisdiction in New Jersey and has filed suit in New Jersey.

15. Caraco is subject to personal jurisdiction in New Jersey because it is registered to do business in New Jersey, and maintains an authorized agent in New Jersey.

16. 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

17. Plaintiffs repeat and reallege paragraphs 1-16 above as if fully set forth herein.

18. 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.

19. 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.

20. On information and belief, Sun submitted to the FDA ANDA No. 78-818 under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use and sale of injectable oxaliplatin formulations.

21. On information and belief, Sun submitted ANDA No. 78-818 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.

22. On information and belief, Sun made, and included in ANDA No. 78-818, a certification 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 June 8, 2007, Sun sent Plaintiffs notice of that certification pursuant to 21 U.S.C. § 355(j)(2)(B).

23. By filing its ANDA No. 78-818 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, Sun committed acts of infringement under 35 U.S.C. § 271(e)(2).

24. Further, the commercial manufacture, use, offer for sale, sale and/or importation of the generic oxaliplatin products for which Sun seeks approval in its ANDA No. 78-818 will infringe one or more claims of the '874 patent under 35 U.S.C. § 271.

25. 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. 78-818 relating to Sun '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:
DECLARATORY JUDGMENT OF
INFRINGEMENT OF U.S. PATENT NO. 5,959,133

26. Plaintiffs repeat and reallege paragraphs 1-25 above as if fully set forth herein.

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

28. The commercial manufacture, use, offer for sale, sale and/or importation of the generic oxaliplatin products for which Sun seeks approval in its ANDA No. 78-818 will infringe one or more claims of the '133 patent under 35 U.S.C. § 271.

29. Plaintiffs are entitled to a declaration of infringement against Sun and an order of this Court that Sun is 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 Sun India and Caraco have infringed one or more claims of the '874 patent by filing ANDA No. 78-818 relating to Sun's generic oxaliplatin products;

B. Judgment that Sun India and Caraco will infringe one or more claims of the '133 patent by engaging in the commercial manufacture, use, offer for sale, sale, or importation of generic oxaliplatin products before the expiration of the '133 patent;

C. A permanent injunction restraining and enjoining Sun and its officers, agents, attorneys and employees, and those acting in privity or concert with it, 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 patent and/or the '133 patent;

D. A declaration that the effective date of any approval of ANDA No. 78-818 relating to Sun 's generic oxaliplatin formulations be a date which is not earlier than the

expiration date of the '874 patent and/or the '133 patent 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.

Respectfully submitted,

Dated: August 15, 2008

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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

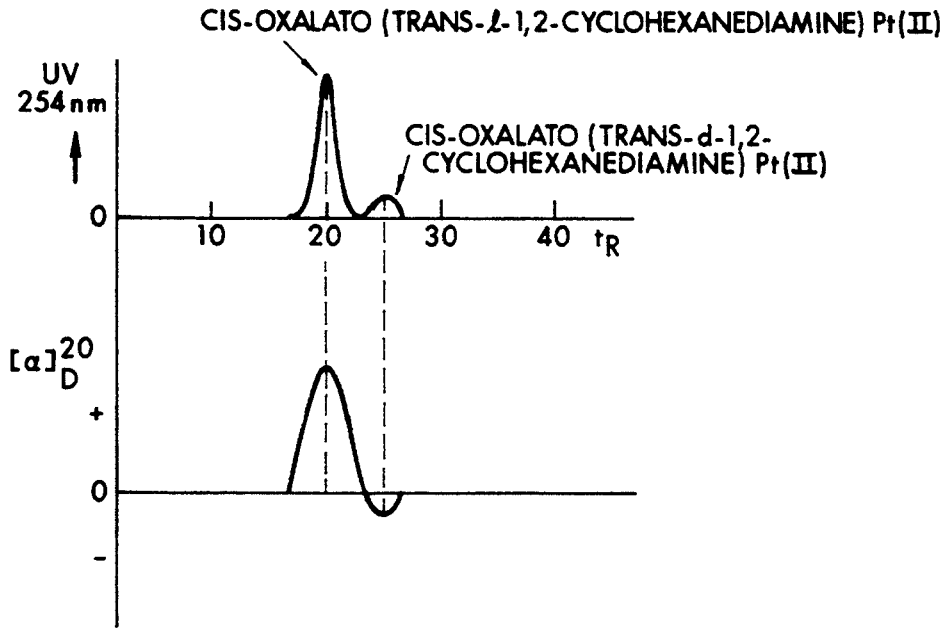
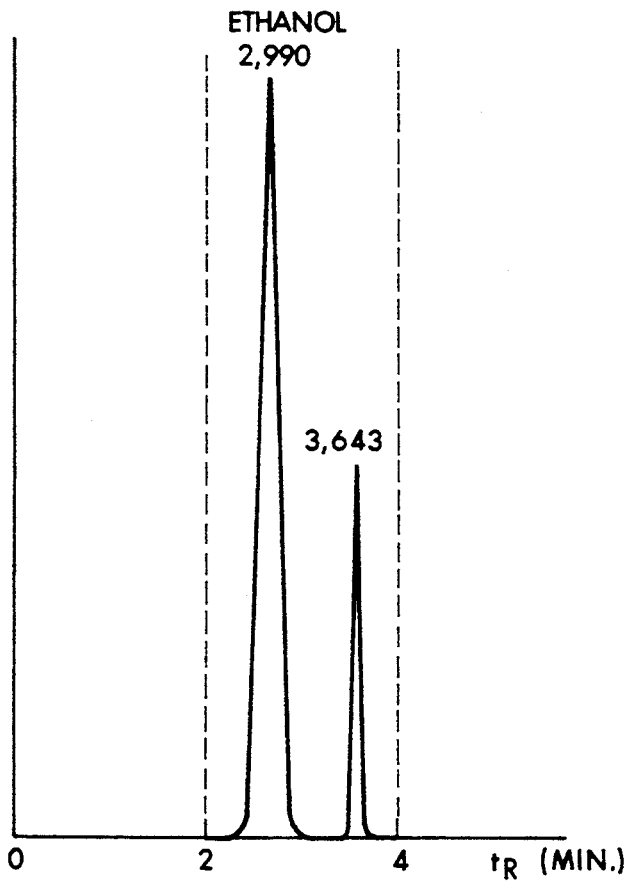


FIG. 2



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.

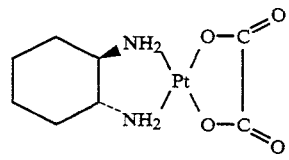
SUMMARY OF THE INVENTION

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.

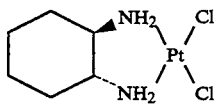
DETAILED DESCRIPTION OF THE INVENTION

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.

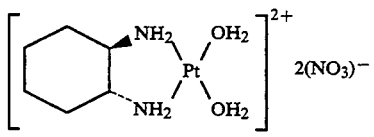
A crystal of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) represented in Formula **2** may be obtained

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-dlchloro(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. c. %) 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

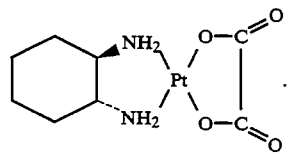
Acute Toxicity Test and Tumor Resistance Against L1210 of Cis-Oxalato(Trans-1-1,2-cyclohexamediamine) Pt(II)

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	311P	207P	158P	132P
Example 3*			(2/6)	(3/6)			
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

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

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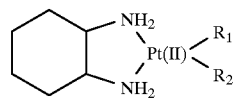
Primary Examiner—Gary Geist
Assistant Examiner—Jean F. Vollano
Attorney, Agent, or Firm—Jordan and Hamburg LLP

[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

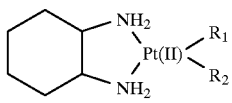
1. Field of the Invention

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

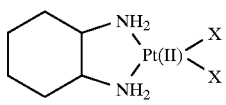
Platinum compounds represented by formula I

(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

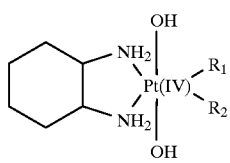
(II)



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.

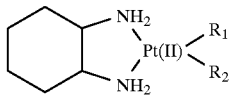
A purity analysis was carried out for cis-oxalato(trans-(-)-1,2-cyclohexanediamine)platinum(II) obtained from the working example of the present invention and for the corresponding complex obtained from the comparative example, through high-performance liquid chromatography (HPLC) (ODS column length, 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:

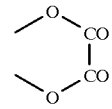
1. A process for a preparation of a platinum(II) complex of a 1,2-cyclohexanediamine isomer represented by formula I

(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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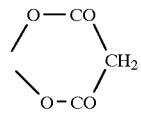

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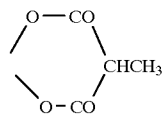

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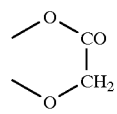
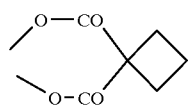


(VIII)



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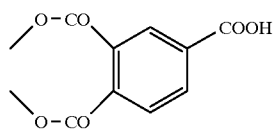
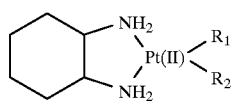


2. A process for a preparation of a platinum(II) complex of a 1,2-cyclohexanediamine isomer represented by formula I

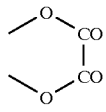
(I)



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)



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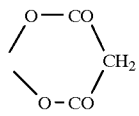

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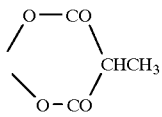

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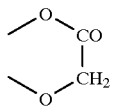

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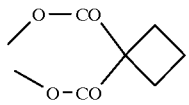
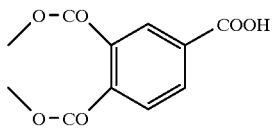
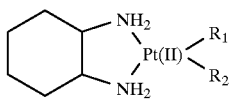


(IX)



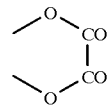
3. A process for the preparation of a platinum(II) complex of a 1,2-cyclohexanediamine isomer represented by formula I

(I)

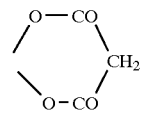


wherein the steric configuration of 1,2-cyclohexanediamine is cis, trans-d, or trans-l, and R_1 and R_2 form a cyclic structure with Pt(II) to represent a group of formula IV, formula V, formula VI, formula VII, formula VIII, or formula IX; the process comprising use of deoxygenating water in all steps 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

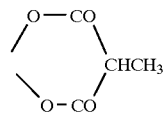
(IV)



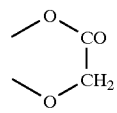
(V)



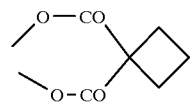
(VI)



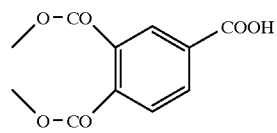
(VII)



(VIII)



(IX)



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