RECEIPT NUMBER

560032

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IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

SANOFI-AVENTIS U.S. LLC,
SANOFI-AVENTIS,
DEBIOPHARM, S.A.,

Plaintiffs,

v.

SUN PHARMACEUTICAL INDUSTRIES, LTD. and CARACO PHARMACEUTICAL LABORATORIES, LTD.,

Defendants.

Case: 2:07-cv-13107
Assigned To: Cox, Sean F
Referral Judge: Whalen, R. Steven
Filed: 07-24-2007 At 03:38 PM
CMP SANOFI AVENTIS ET AL V. SUN PHARMACEUTICAL IND ET AL (DA)

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SANOFI-AVENTIS and DEBIOPHARM, S.A.

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Sanofi-Aventis U.S. LLC, Sanofi-Aventis and Debiopharm, S.A. (hereinafter "Plaintiffs"), by way of 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 its place of business at Acme Plaza, Andheri Kurla Road, Mumbai, India 400059.

5. On information and belief, Sun India conducts business through and with its subsidiary, Sun Pharmaceutical Industries, Inc. ("Sun USA"), which is incorporated under the laws of the state of Michigan and maintains a registered office at 29714 Orion Court, Farmington Hills, MI 48334.

6. On information and belief, Caraco Pharmaceutical Laboratories, Ltd. ("Caraco") is a corporation organized under the laws of the state of Michigan, having a place of business at 1150 Elijah McCoy Drive, Detroit, MI 48202.

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 referred to hereinafter, 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 and 1338(a).

14. Sun India is subject to personal jurisdiction in the Eastern District of Michigan because Sun India consented to jurisdiction in this 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, including within Michigan.

15. Caraco is subject to personal jurisdiction in the Eastern District of Michigan because it is incorporated in Michigan and maintains a place of business in Michigan.

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.

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. 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;

C. 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 plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

D. 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

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

Respectfully submitted,

By: _____

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Dated: July 24, 2007

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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 Okuishi; Junji Okuishi; Junichi Tsubuchi; Koji Okamoto; Takashi Tomwe, all of Kanagawa, Japan

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

[21] Appl. No.: 48,901

[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—Joseph C. 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

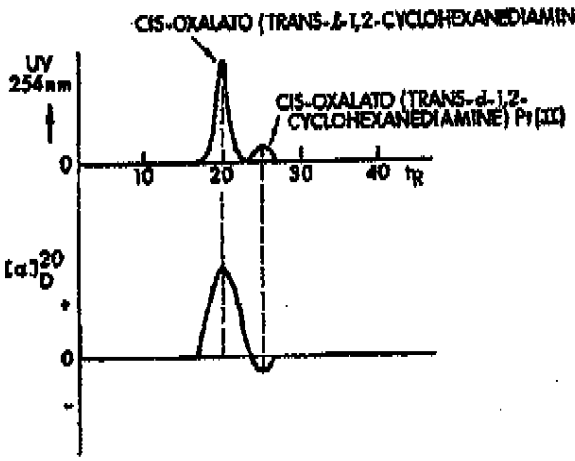
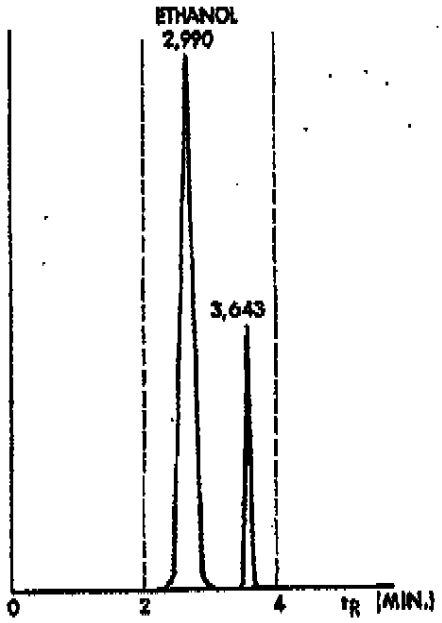


FIG. 2



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-l-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 resolved 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-l-1,2-cyclohexanediamine) Pt(II) was synthetically obtained through a reaction between the trans-l-1,2-cyclohexanediamine obtained in accordance with the above method and K_2PtCl_4 (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-l-1,2-cyclohexanediamine) Pt(II) and relate to circular dochroism (CD) exhibiting its steric configuration and to an angle of rotation ([α]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-oxalato (trans-l-1,2-cyclohexanediamine) Pt(II) conventionally reported, the isolation of the complex consisting of two trans-di 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.

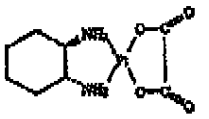
SUMMARY OF THE INVENTION

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-l-1,2-cyclohexanediamine) Pt(II) of optically high purity having a general formula of Formula (I).



(I)

The cis-oxalato (trans-l-1,2-cyclohexanediamine) Pt(II) of optically high purity of the present invention may be prepared by completely and optically resolving the Pt(II) optical isomers by means of a process of optically resolving 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-l-1,2-cyclohexanediamine) Pt(II) of optically isomer thereof, the excellent results of acute toxicity can be obtained in comparison with cis-oxalato (trans-l-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-l-1,2-cyclohexanediamine) Pt(II) is, because of the absence of impurities, lower than of that of conventionally prepared cis-oxalato (trans-l-1,2-cyclohexanediamine) Pt(II).

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a chromatogram obtained in HPLC of cis-oxalato (trans-l-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 shows an amount of elution per unit time as a relative degree of rotation.

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

DETAILED DESCRIPTION OF THE INVENTION

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

Commercially available 1,2-cyclohexanediamine (for instance, trans-l-1,2-cyclohexanediamine made by Aldrich, cis and trans-di 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 resolved 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 diastereomer in accordance with a normal method by means of tartaric acid and employing a recrystallization method.

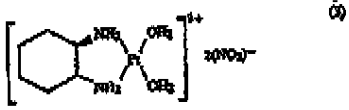
A crystal of cis-dichloro(trans-l-1,2-cyclohexanediamine) Pt(II) represented in Formula 3 may be obtained

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 decoloration 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 resolving 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 performance 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: ethanol/methanol=30:70 (volume ratio)

Flow rate: 0.2 ml/min.

Column temperature: 40° C.

Detection:

ultraviolet ray 254 nm

optical rotation 589 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 "leukemia 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-cyclohexanediamine) Pt(II)

A reaction between 46.3 g of trans-d-1,2-cyclohexanediamine made by Aldrich ($[\alpha]^{19}_D$=−39.6°, 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) nitrate

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 decoloration was added which was then filtered off together with the silver iodide.

③ Preparation of cis-oxalato(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 mm 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 ($[\alpha]^{19}_D$=−39.6°, 4% H_2O) was calculated in accordance with a below equation to be 88.5% of an equimolar 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 (%) ... ee (%) =

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

(e.e.: enantiomer excess ratio)

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)-$(H_2O)_2Cl_2$] (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.2HCl] (42.54 g) after filtration which was then washed 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)] ($[\alpha]^{20}_D=0°$, 4% H_2O) was obtained. A single peak appeared on a gas chromatogram at t_R=1.043 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/cm²

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 16.2[illegible] g of a diastereoisomer (trans-l-1,2-cyclohexanediamine (l) 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-l-1,2-cyclohexanediamine.

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

In accordance with the same procedures as those of ① of Example 1 except that the trans-l-1,2-cyclohexanediamine obtained in ② of Example 2 was employed as raw material in place of the trans-l-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-l-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-l-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-l-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-l-1,2-cyclohexanediamine) 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. The HPLC of this solution under the same conditions of those of ⑤ 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 purity of the cis-oxalato(trans-l-1,2-cyclohexanediamine) Pt(II) synthesized by employing the raw material isolated in accordance with a process of resolving and purifying isomers (Japanese patent application No. 61-4827) was e.e.=90.0% in accordance with the equations of ⑤ of Example 1 as shown in Table 1. Then, cis-oxalato(trans-l-1,2-cyclohexanediamine) Pt(II) of 100% of an optical purity (e.e.) was obtained by collecting an aqueous solution eluted in fractions from 13 minutes to 21 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-l-1,2-cyclohexanediamine) Pt(II)

In accordance with the same procedures as those of ① of Example 1 except that the trans-l-1,2-cyclohexanediamine made by Wako Junyaku K.K. ($[\alpha]^{20}_D$=34.9°, 4% H_2O) was employed in place of the trans-l-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-l-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 ① of Example 3 was employed in place of cis-dichloro(trans-l-1,2-cyclohexanediamine) Pt(II) obtained in ① of Example 1, an aqueous solution of the desired cis-diaquo(trans-l-1,2-cyclohexanediamine) Pt(II) nitrate was obtained.

③ Preparation of cis-oxalato(trans-l-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 systemically 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 Jouyaku 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-oxalato(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 300 ml of water followed by the boiling thereof for dissolution. After two moles of $AgNO_3$ (2.6 g) were added and was stirred for 2 to 3 hours in the dark, the filtration was 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 3 hours at room temperature. The solution was again concentrated at a reduced pressure 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_{50}) 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 10^5 per mouse and prescribing the medicine in the peritoneal 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	86.5	→	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. FIM20I)	$(\alpha)_D^{20}$ (1% H_2O)
Before Recrystallization	+13.0(+ ± 0.1°
After One Recrystallization	+12.3° ± 0.1°
After two Recrystallization	+11.9° ± 0.1°

TABLE 3

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

Experiment	Melting Point	CD (Δε)	$(\alpha)_D^{20}$ (0.5% H_2O)
Example 1*	193.1°~	253 nm	
Example 2*	191.7° C.	+0.67 ± 0.19	>+74.5° C.
Example 3*		326 nm +0.61 ± 0.18	
Comp. Ex. (JP Pub. No. 60-41077)	>300° C.	not mentioned	not mentioned

*High Purity Sample Prepared by HPLC

TABLE 4

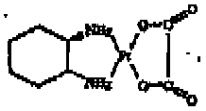
Acute Toxicity Test and Tumor Resistance Against L1210 of Cis-Oxalato(Trans-1-1,2-cyclohexanediamine) Pt(II)

Experiment	Acute Toxicity Test LD_{50}	Tumor Resistance T/C (%) for/to 25	12.5	6.25	3.12	1.56	0.78
Example 1*	18.5—22.5 mg/kg	7					
Example 2*		136%* (2/6)	136%* (2/6)	211%* (1/6)	207%* (1/6)	134%*	133%*
Example 3*							
Comp. Ex.	14.6—19.0 mg/kg	T 83	83%* (4/6)	125%* (1/6)	99%*	134%*	

*High Purity Sample Prepared by HPLC
†: Effective (Over 125%)
T: Toxic (Large Weight Loss)
(1/6): This means that three out of six were cured.

What is claimed is:

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



(I)

2. Cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) as claimed in claim 1, wherein the melting point thereof is between 195° C. and 202° C.

* * * * *

CIVIL COVER SHEET

JS 44

)COUNTY IN WHICH ACTION AROSE WAYNE

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS
SANOFI-AVENTIS U.S. LLC, SANOFI-AVENTIS and DEBIOPHARM, S.A.

(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF Somerset, NJ
(EXCEPT IN U.S. PLAINTIFF CASES)

DEFENDANTS
SUN PHARMACEUTICAL INDUSTRIES LTD. and CARACO PHARMACEUTICAL LABORATORIES, LTD.
COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT Mumbai, India
(IN U.S. PLAINTIFF CASE ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

(c) ATTORNEYS (FIRM NAME, ADDRESS, AND TELEPHONE NUMBER)
Edward H. Pappas (P23224), D. Lee Khachaturian (P59966)
Dickinson Wright PLLC
38525 Woodward Ave., Suite 2000
Bloomfield Hills, MI 48304
(248) 433-7200

ATTORNEYS (IF KNOWN)

Case: 2:07-cv-13107
Assigned To: Cox, Sean F
Referral Judge: Whalen, R. Steven
Filed: 07-24-2007 At 03:38 PM
CMP SANOFI AVENTIS ET AL V. SUN PHA
RMACEUTICAL IND ET AL (DA)

II. BASIS OF JURISDICTION (PLACE AN "X" IN ONE BOX ONLY)

- ☐ 1 U.S. Government Plaintiff
- ■ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

II (F DEFENDANT)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporation or Principal Place of Business in This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporation or Principal Place of Business in Another State	☐ 5	☐ 5
Citizen of Subject of a Foreign County	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

VI. ORIGIN (PLACE AN "X" IN ONE BOX ONLY)

■ 1 Original ☐ 2 Removed from ☐ 3 Remanded from ☐ 4 Reinstated or ☐ 5 Transferred from another district ☐ 6 Multidistrict ☐ 7 Appeal of District Judge from Magistrate Judgment

V. NATURE OF SUIT (PLACE AN "X" IN ONE BOX ONLY)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Exc. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury-Med. Malpractice
- ☐ 365 Personal Injury-Product Liability
- ☐ 368 Injury Med. Malpractice

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

HABEAS CORPUS:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copy Rights
- ■ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUIT
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS - Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce/ICC Rates/etc.
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 810 Selective Services
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of States
- ☐ 890 Other Statutory Actions

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE BRIEF STATEMENT OF CAUSE. DO NOT CITE JURISDICTIONAL UNLESS DIVERSITY.)

21 U.S.C. § 355; 35 U.S.C. § 271. This is an action for patent infringement arising under the Patent Laws of the United States, title 35 of the U.S. Code and the Federal Food, Drug and Cosmetic Laws, title 21 of the U.S. Code.

VII. REQUEST IN COMPLAINT: ☐ CHECK IF THIS IS A CLASS ACTION **DEMAND** _____ **CHECK** YES only if demanded in complaint **JURY DEMAND:** ☐ YES ■ NO

VIII. RELATED CASE(S) IF ANY JUDGE See Ex. A, attached DOCKET NUMBER

DATE July 24, 2007

SIGNATURE OF ATTORNEY OF RECORD D. Lee Khachaturian (P59966)

MAG.RECEIPT # AMOUNT APPLYING IFP JUDGE JUDGE

PURSUANT TO LOCAL RULE 83.11

1. Is this a case that has been previously discontinued or dismissed? ☐ YES ☐ NO

   If **yes**, give the following information:

   Court:_____

   Case No.:_____

   Judge:_____

2. Other than stated above, are there any pending or previously discontinued or dismissed companion cases in this or any other court, including state court? (Companion cases are matters in which it appears substantially similar evidence will be offered or the same or related parties are present and the cases arise out of the same transaction or occurrence.) ☒ YES ☐ NO

   If **yes**, give the following information:

   Court: See Ex. A, attached

   Case No.: _____

   Judge:_____

NOTES

EXHIBIT A

The following case was filed July 23, 2007 in the United States District Court, District of New Jersey:

Sanofi-Aventis U.S. LLC, Sanofi-Aventis and Debiopharm, S.A. v. Sun Pharmaceutical Industries, Ltd. and Caraco Pharmaceutical Laboratories, Ltd.

The following cases are pending before the Honorable Freda L. Wolfson in the United States District Court, District of New Jersey:

Sanofi-Aventis U.S. LLC, Sanofi-Aventis and Debiopharm, S.A. v. Sandoz, Inc., Civ. Docket No. 07-cv-02762 (FLW) (JJH);

Sanofi-Aventis U.S. LLC, Sanofi-Aventis and Debiopharm, S.A. v. Teva Parenteral Medicines, Inc., Teva Pharmaceuticals USA, Inc. and Teva Industries, Ltd., Civ. Docket No. 07-cv-02837 (FLW) (JJH);

Sanofi-Aventis U.S. LLC, Sanofi-Aventis and Debiopharm, S.A. v. Dabur Oncology Plc. and Dabur Pharma Limited, Civ. Docket No. 07-cv-02854 (FLW) (JJH);

Sanofi-Aventis U.S. LLC, Sanofi-Aventis and Debiopharm, S.A. v. Actavis Totowa LLC, Actavis, Inc., Actavis Group hf, Civ Docket No. 07-cv-03142 (FLW) (JJH);

Sanofi-Aventis U.S. LLC, Sanofi-Aventis and Debiopharm, S.A. v Mustafa Nevzat Ilac Sanayii A.S. (a.k.a. "MN Pharmaceuticals"), Par Pharmaceutical Companies, Inc. and Par Pharmaceutical, Inc., Civ. Docket No. 07-cv-03143 (FLW) (JJH);

Sanofi-Aventis U.S. LLC, Sanofi-Aventis and Debiopharm, S.A. v. Pharmachemie B.V., Teva Parenteral Medicines, Inc., Teva Pharmaceuticals USA, Inc., and Teva Industries, Ltd., Civ. Docket No. 07-cv-03144 (FLW) (JJH);

Sanofi-Aventis U.S. LLC, Sanofi-Aventis and Debiopharm, S.A. v. Abraxis Bioscience, Inc., Civ. Docket No. 07-cv-03163 (FLW) (JJH); and

Sanofi-Aventis U.S. LLC, Sanofi-Aventis and Debiopharm, S.A. v. Ebewe Pharma Ges.m.b.H.Nfg.KG, Civ. Docket No. 07-cv-03164 (FLW) (JJH).