18251/88

[illegible]
30-7-90

FORM 1

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

602589

APPLICATION FOR A STANDARD PATENT

American Cyanamid Company, of One Cyanamid Plaza, Wayne, New Jersey, UNITED STATES OF AMERICA, hereby apply for the grant of a standard patent for an invention entitled:

Synthesis of Cisplatinum Analogs

which is described in the accompanying complete specification.

Details of basic application(s):-

Basic Applic. No:	Country:	Application Date:
065441	US	23 June 1987

The address for service is:-

Spruson & Ferguson
Patent Attorneys
Level 33 St Martins Tower
31 Market Street
Sydney New South Wales Australia

DATED this TWENTY SECOND day of JUNE 1988

American Cyanamid Company

By:

Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
OUR REF: 56674
S&F CODE: 50380

5845/2

REPRINT OF RECEIPT
5000500 22/06/88

~~7,510~~

COMMONWEALTH OF AUSTRALIA
DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made for a patent patent for an invention entitled:

SYNTHESIS OF CISPLATINUM ANALOGS

I/~~We~~ ALPHONSE R. NOE

of 470 Haviland Road, Stamford, State of Connecticut,
United States of America

do solemnly and sincerely declare as follows:-

1. I AM/~~WE ARE~~ authorised by

AMERICAN CYANAMID COMPANY

the applicant~~(s)~~ for the patent to make this declaration on its/~~their~~ behalf.

2. The basic application~~(s)~~ as defined by Section 141 of the Act was/~~were~~ made

in the United States of America

on June 23, 1987

by PANAYOTA BITHA, JOSEPH JOHN HLAVKA and YANG-I LIN

3. ~~I am/we are the actual inventor(s) of the invention referred to in the basic application(s)~~

3. PANAYOTA BITHA, JOSEPH JOHN HLAVKA and YANG-I LIN citizens of the United States of America,

of 287 Treetop Circle, Nanuet, State of New York 10954;
Tower Hill Road, Tuxedo Park, State of New York 10987;
and 35 Constitution Drive, Tappan, State of New York 10983; United States of America respectively

~~is~~/are the actual inventor(s) of the invention and the facts upon which the applicant(s) is/~~are~~ entitled to make the application are as follows: 1 Assignment~~(s)~~ dated June 18, 1987 assigning said invention from the said inventors to the said company.

4. The basic application~~(s)~~ referred to in paragraph 2 of this Declaration was/~~were~~ the first application~~(s)~~ made in a Convention country in respect of the invention~~(s)~~ the subject of the application.

Signed at Stamford, Connecticut U.S.A. this 4th

day of April 1988.

AMERICAN CYANAMID COMPANY
BY:
Alphonse R. Noe, Manager
Patent Law Department

To: Commissioner of Patents

(12) PATENT ABRIDGMENT (11) Document No. AU-B-18251/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 602589

(54) Title
SYNTHESIS OF CISPLATINUM ANALOGS

International Patent Classification(s)
(51)[4] C07C 147/14 C07C 053/10 C07C 055/08 C07C 061/04
C07C 085/24 C07C 087/18 C07C 087/38 C07C 089/00
C07C 091/12 C07C 091/14 C07D 207/09 C07D 211/26
C07D 307/14 C07D 309/04 C07D 317/28 C07D 319/06
C07D 319/12 C07D 333/48 C07D 335/02
(51)[5] C07C 209/68 C07C 211/36 C07C 213/08 C07C 215/18
C07C 317/04

(21) Application No. : 18251/88 (22) Application Date : 22.06.88

(30) Priority Data

(31) Number (32) Date (33) Country
065441 23.06.87 US UNITED STATES OF AMERICA

(43) Publication Date : 05.01.89

(44) Publication Date of Accepted Application : 18.10.90

(71) Applicant(s)
AMERICAN CYANAMID COMPANY

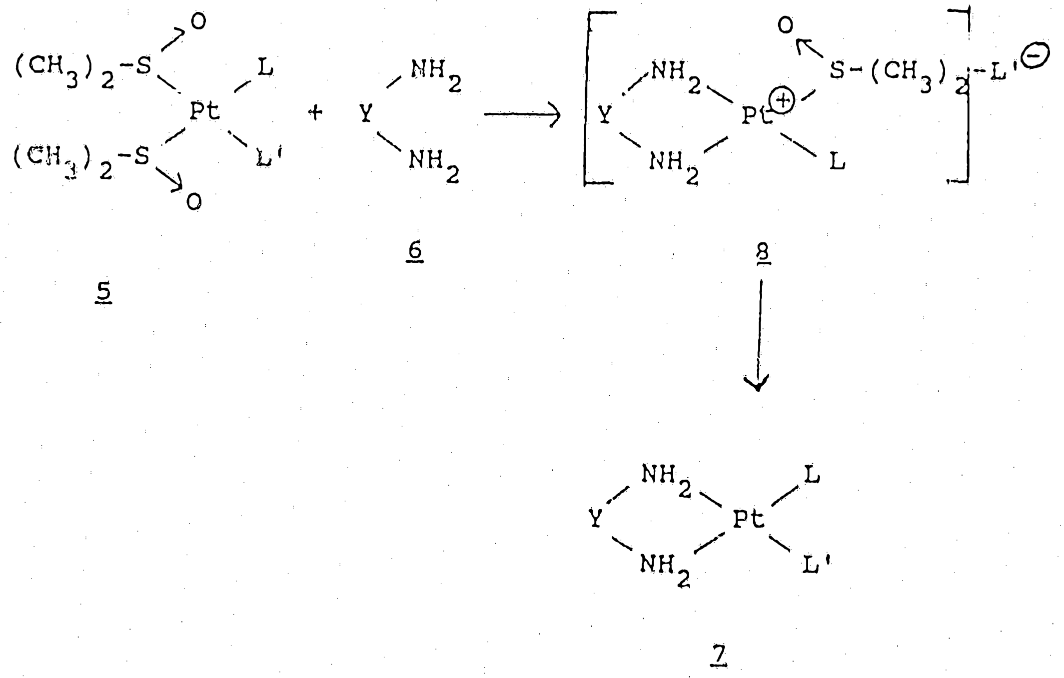
(72) Inventor(s)
YANG-I LIN; JOSEPH JOHN HLAVKA; PANAYOTA BITHA

(74) Attorney or Agent
SPRUSON & FERGUSON, GPO Box 3898, SYDNEY NSW 2001

(56) Prior Art Documents
AU 594099 65748/86 C07C 087/38

(57)

Flowchart B



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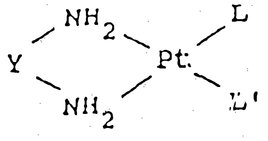
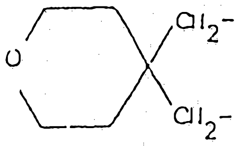
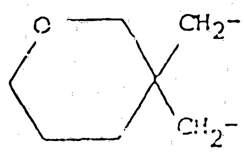
CLAIM

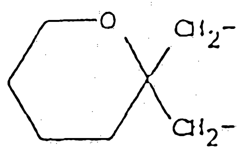
1. A process for producing a compound of the formula:

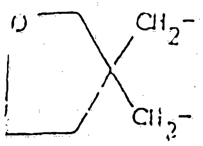


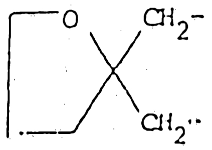
wherein Y is

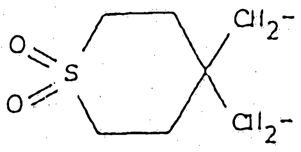
 ,

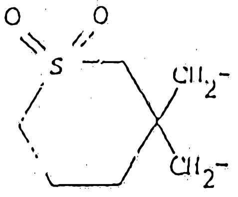
 ,

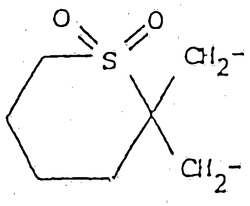
 ,

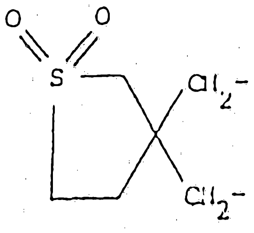
 ,

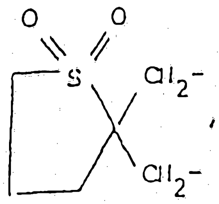
 ,

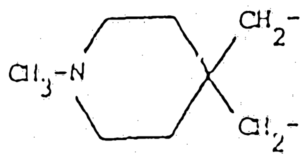
 ,

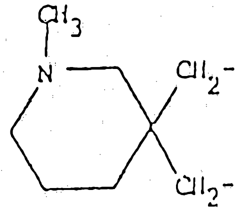
 ,

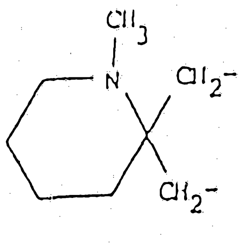
 ,

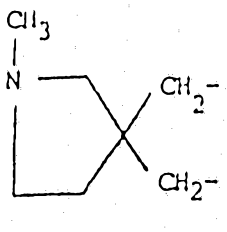
 ,

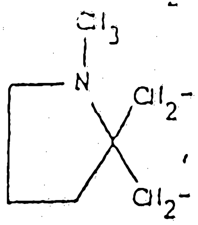
 ,

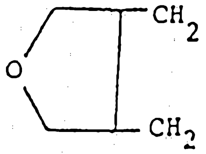
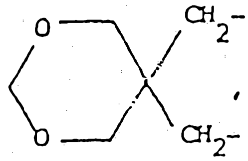
 ,

 ,

 ,

 ,

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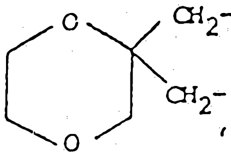
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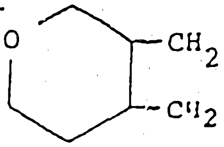
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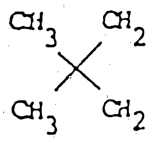
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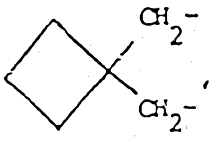
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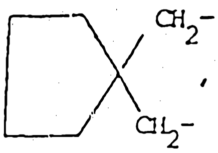
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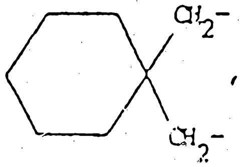
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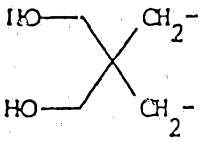
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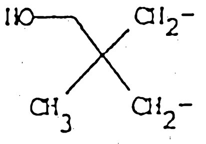
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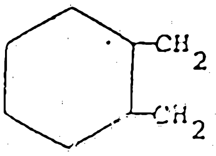
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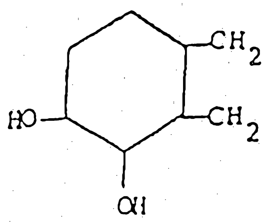
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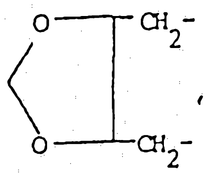
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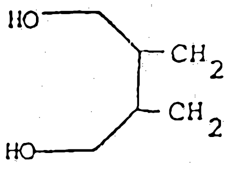
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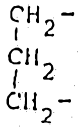
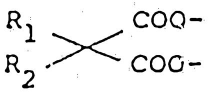
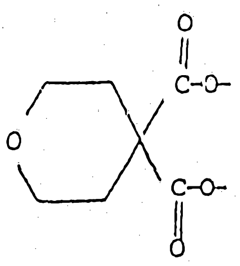
or  $-CH_2-CH_2-CH_2-$; and L and L′ are monobasic carboxylates consisting of acetate, hydroxyacetate and propionate, or L and L′ taken together are a dibasic carboxylate consisting of  $R_1R_2C(COO-)_2$, where R_1 and R_2 are hydrogen or lower alkyl-(C_1-C_5), or R_1 and R_2 taken together is $(CH_2)_n$, where n is 2 to 5,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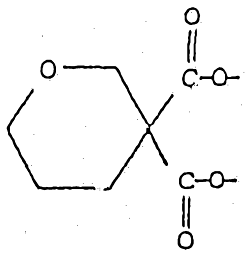
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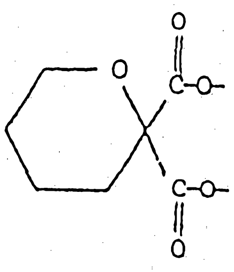

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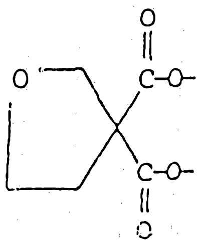

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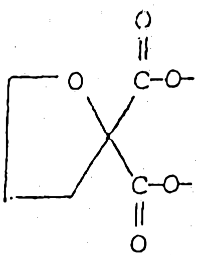

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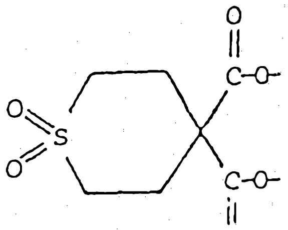

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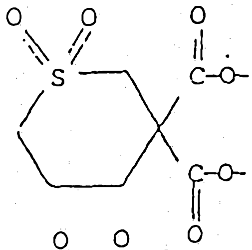

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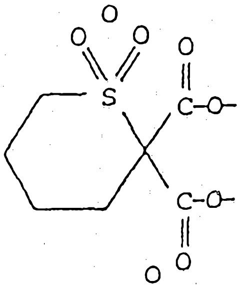

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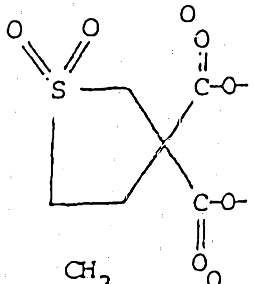

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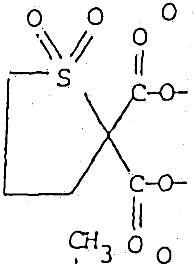

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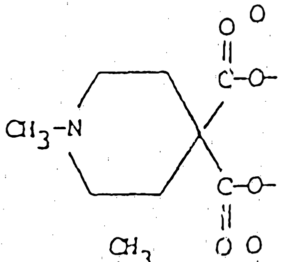

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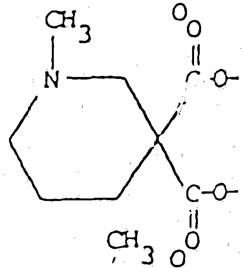

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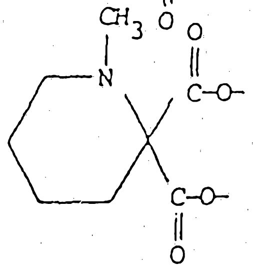

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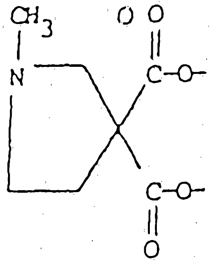

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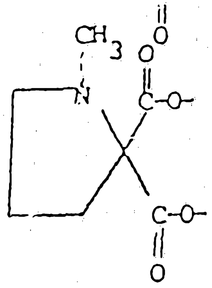

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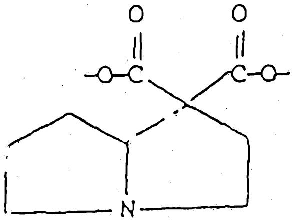

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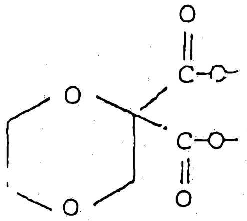
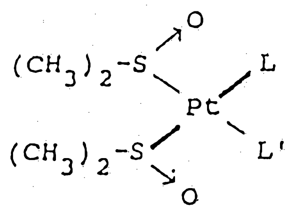
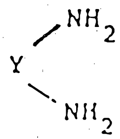


which comprises reacting sulfinylbismethane, compound with platinum chloride with mono- or dicarboxylic acid in aqueous solution, protected from the light, giving a carboxylic acid-bis[sulfinylbis[methane]-S]platinum

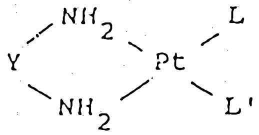
compound of the formula



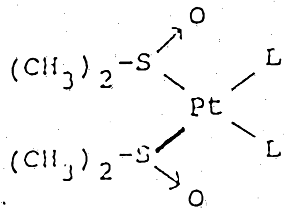
$$\begin{matrix} (CH_3)_2\text{-}\overset{\nearrow O}{S} & & L \\ & Pt & \\ (CH_3)_2\text{-}\underset{\searrow O}{S} & & L' \end{matrix}$$

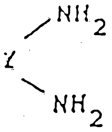
, where L and L'are as described above, which is then reacted with an amine of the formula  , where Y is as described above, in a hot aqueous solution.

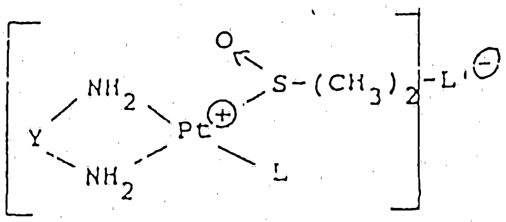
2. A process for producing a compound of the formula:



wherein Y,L and L' are as defined in Claim 1, which comprises reacting a carboxylic acid-bis[sulfinylbis[methane]-S]platinum compound of the formula

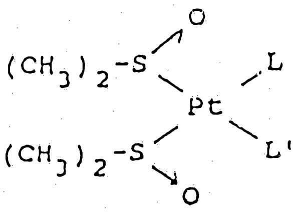


where L and L' are as defined in Claim 1, in warm aqueous solution with an amine of the formula  , where Y is as defined in Claim 1, giving a compound of the formula:



which is further reacted in a hot aqueous solution.

3. A compound of the formula:



wherein L and L' are as defined in Claim 1.

S & F Ref: 56674

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:
Accepted:
Published:

602589

Priority:

Related Art:

Name and Address of Applicant:	American Cyanamid Company One Cyanamid Plaza Wayne New Jersey UNITED STATES OF AMERICA
Address for Service:	Spruson & Ferguson, Patent Attorneys Level 33 St Martins Tower, 31 Market Street Sydney, New South Wales, 2000, Australia

Complete Specification for the invention entitled:

Synthesis of Cisplatinum Analogs

The following statement is a full description of this invention, including the best method of performing it known to me/us

Title: SYNTHESIS OF CISPLATIN ANALOGS

DESCRIPTION OF THE INVENTION

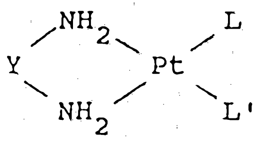
ABSTRACT OF THE DISCLOSURE

This disclosure sets forth a novel process for producing cisplatin analogs which possess antitumor activity.

Title: SYNTHESIS OF CISPLATIN ANALOGS

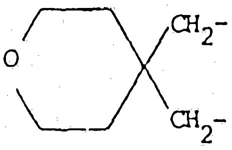
DESCRIPTION OF THE INVENTION

This invention is concerned with a process for producing compounds of The formula I:



Formula I

wherein Y is selected from the group consisting of



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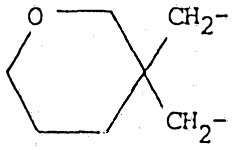

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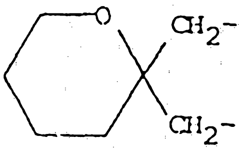

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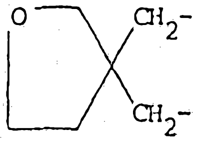

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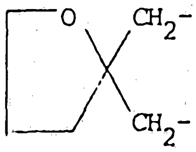

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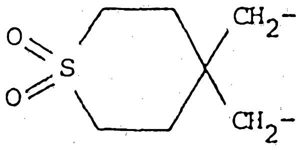

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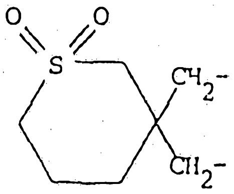

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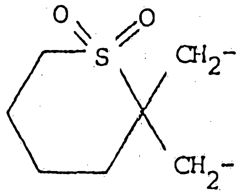

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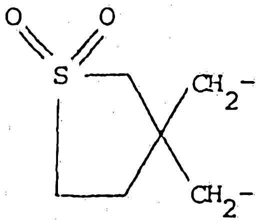

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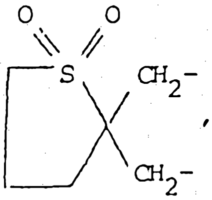
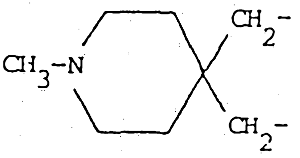
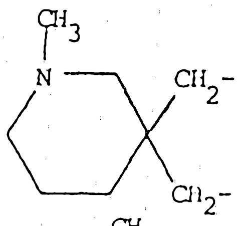
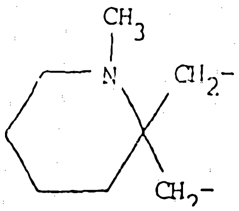
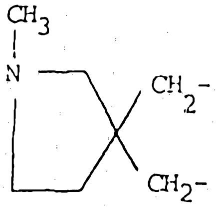
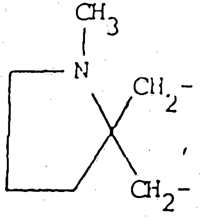
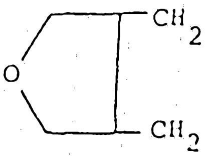
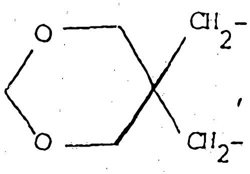
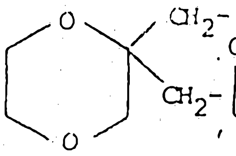
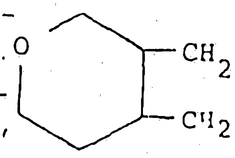
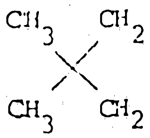
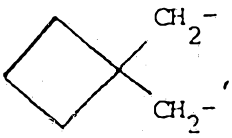
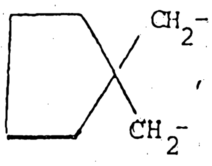
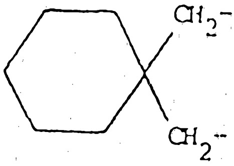
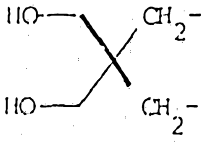
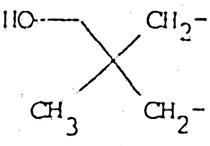
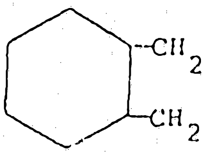
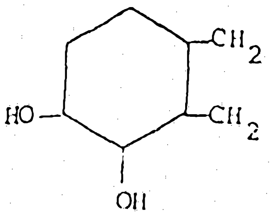
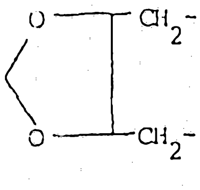
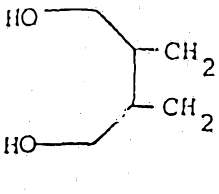
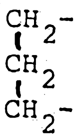
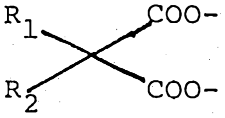
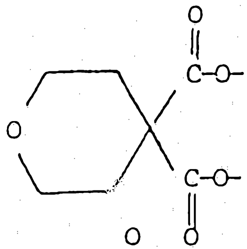
,
,
,
,
,
,
.
,
,

,
,
,
,
,
,
,
,
,
,

or 
$\begin{array}{c} CH_2- \\ | \\ CH_2 \\ | \\ CH_2- \end{array}$; and L and L' are monobasic carboxylates consisting of acetate, hydroxyacetate or propionate, or L and L' taken together are a dibasic carboxylate consisting of



, wherein R_1 and R_2 are hydrogen or lower alkyl(C_1-C_5) or R_1 and R_2 taken together is $(CH_2)_n$, wherein n is 2 to 5,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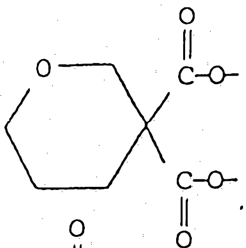
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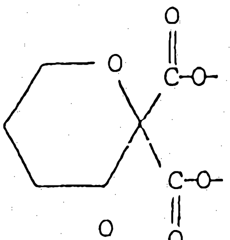
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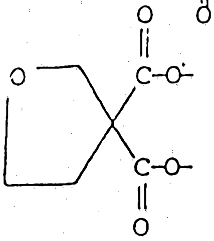
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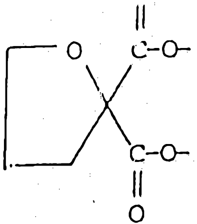
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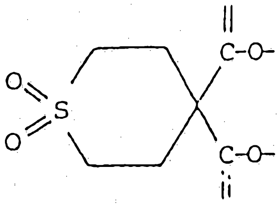
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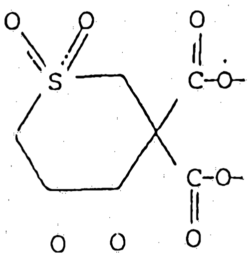
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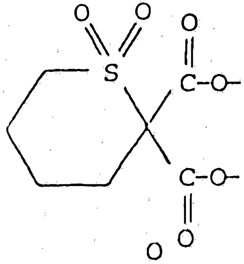
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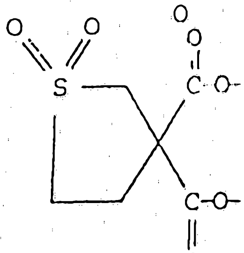
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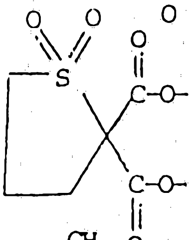
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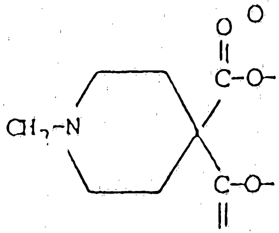
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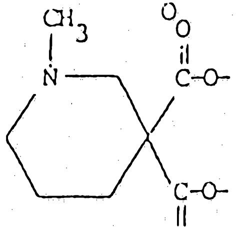
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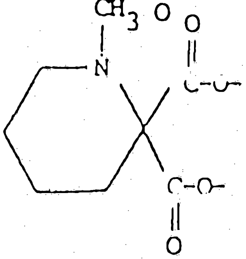
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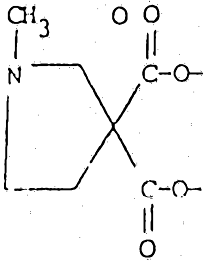
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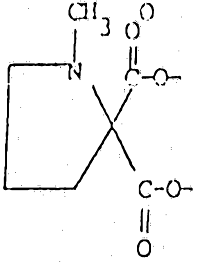
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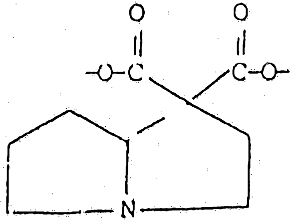

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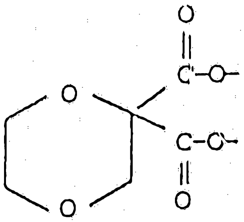
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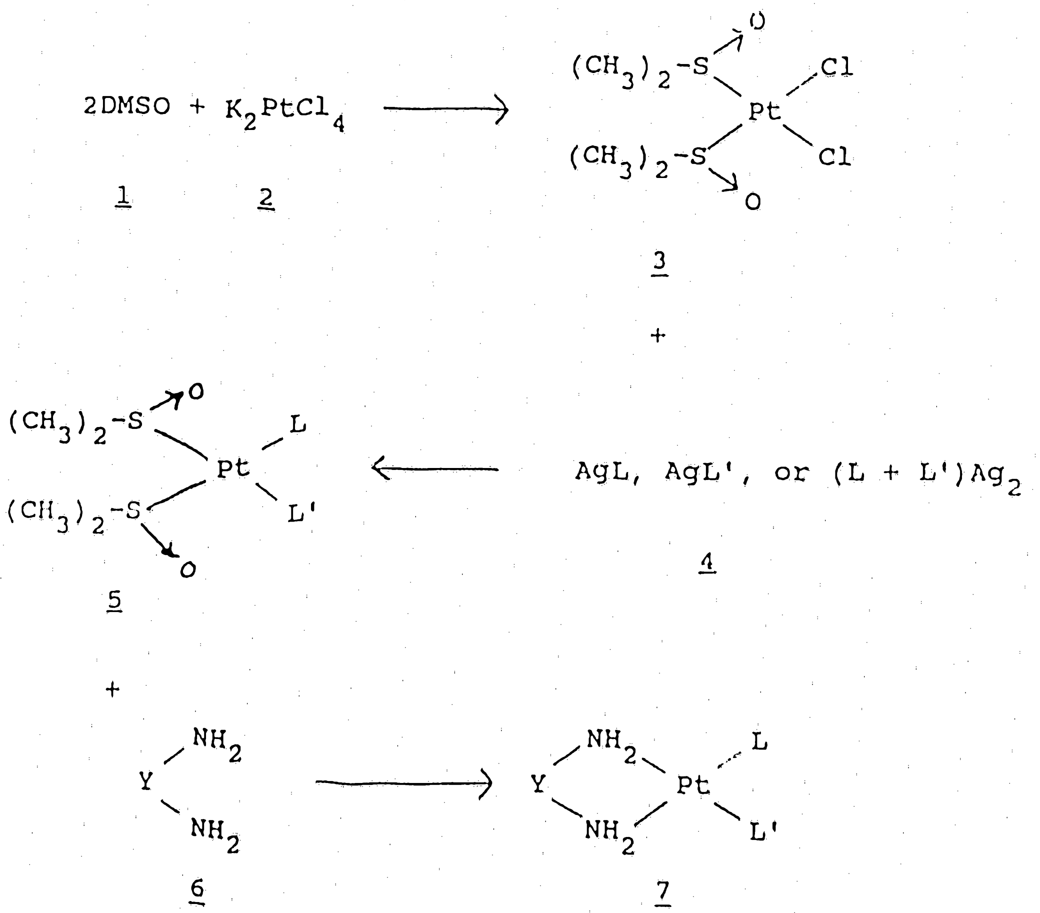
The compounds described in Formula I are highly active antitumor agents. Their activity as such has been disclosed in the following South African patents 87/0714, issued September 30, 1987 and 87/0713, issued January 1, 87.

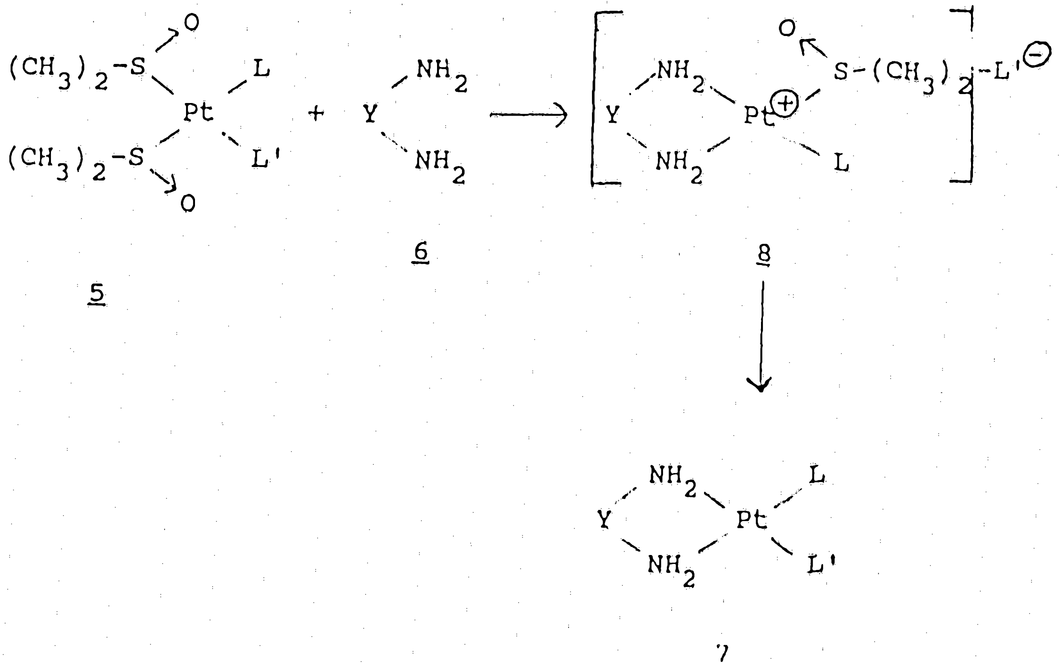
The process, with which the current invention is concerned, is described below by flowchart and text.

Flowchart A



In accordance with flowchart A, dimethyl sulfoxide 1 is reacted with potassium tetrachloroplatinate 2 in aqueous solution to produce sulfinyl bismethane, compound with platinum dichloride (2:1) 3. Compound 3 is then reacted with a mono- or dicarboxylic acid silver salt (L, L' or L + L') 4 in aqueous solution, protected from light, giving carboxylic acid-bis[sulfinylbis[methane]-S]platinum derivative 5. Compound 5 is then reacted with an amine 6 giving the final, pharmacologically active product 7 (Formula I).

Flowchart B



In accordance with Flowchart B, a carboxylic acid-bis[sulfinylbis[methane]-S]platinum derivative 5 is reacted with an amine 6, giving an amine, carboxylic acid [sulfinylbis[methane]-S]platinum derivative 8, which on heating in aqueous solution gives the biologically active derivative 7.

The intermediates 5 and 8 are unknown in the art and since they are integral in the preparation of pharmaceutically useful products, they will be claimed as new compounds as a part of this invention.

The invention will be described further in conjunction with the following specific examples.

Example 1

[1,1-Cyclobutanedicarboxylato(2-)-O,O^1]bis[sulfinylbis-[methane]-S]platinum

To a solution of 41.5 g of potassium tetrachloroplatinate in 330 ml of water was added 21.3 ml of dimethyl sulfoxide. The mixture was allowed to stand 12 hours, then the solid was collected, washed with water, ethanol and ether, giving 38.0 g of sulfinyl bismethane, compound with platinum chloride (2:1), mp 222°C (dec.).

A mixture of 12.66 g of the above compound, 10.74 g of the disilver salt of 1,1-cyclobutanedicarboxylic acid and 900 ml of water was stirred in the dark for 22 hours and then filtered. The filtrate was concentrated to 40 ml and the precipitate collected, giving 12.4 g of [1,1-cyclobutanedicarboxylato(2-)-O,O^1]bis[sulfinylbis[methane]-S]platinum, mp 208°C (dec.).

This compound (494 mg) in a hot solution of 12 ml of water, was reacted with a hot solution of 114 mg of trans-(-)-1,2-cyclohexandiamine in 3 ml of water. The mixture was kept at 100°C for 6 hours, then cooled, giving 360 mg of biologically active trans-(-)-1,2-cyclohexanediamine, compound with [1,1-cyclobutanedicarboxylato(2-)-O,O^1]platinum (1:1).

Example 2

Preparation of [1,1-Cyclobutanedicarboxylato(2-)-O,O^1](1,3-dioxane-5,5-dimethanamine-N,N')platinum

A suspension of 26.2 g of 2,2-bis(bromomethyl)-1,3-propanediol, 50 ml of concentrated hydrochloric acid and 50 ml of 38% formaldehyde was stirred in a 50°C oil bath overnight, then cooled to room temperature and filtered. The filtrate was extracted with three 100 ml portions of ether. The ether extracts were combined, washed with water, dried and evaporated to an oil. A small amount of solid which formed was removed by filtration and washing with ether. The combined filtrate and wash was evaporated under reduced pressure, giving 26.9 g of 5,5-bis(bromomethyl)-1,3-dioxane as a clear oil.

A suspension of 2.69 g of 5,5-bis(bromomethyl)-1,3-dioxane, 3.8 g of sodium azide and 50 ml of dimethylformamide was heated at 130°C in an oil bath overnight, then cooled and filtered. The filtrate was evaporated to an oily suspension which was diluted with 30 ml of water. The oily phase was extracted with three 25 ml portions of ether. The ether extracts were combined, dried and evaporated, giving 1.95 g of 5,5-bis(azidomethyl)-1,3-dioxane.

A mixture of 1.95 g of 5,5-bis(azidomethyl)-1,3-dioxane, 0.5 g of 10% palladium on calcium carbonate and 40 ml of ethanol was reduced for 2 hours and then filtered. The filtrate was evaporated, giving 1.41 g of 1,3-dioxane-5,5-dimethanamine as an oil.

A 1.97 g portion of [1,1-cyclobutanedicarboxylato(2-)-O,O^1]bis[sulfinylbis[methane]-S]platinum was dissolved in 48 ml of hot (100°C) water. To this was added a solution of 585 mg of 1,3-dioxane-5,5-dimethanamine in 12 ml of water. The mixture was stirred at 100°C for 6 hours and then evaporated to dryness. The residue was dissolved in 2 ml of hot water and filtered. The filtrate was cooled, then refrigerated for 2 hours and the solid collected, giving 606 mg of biologically active [1,1-cyclobutanedicarboxylato(2-)-O,O^1](1,3-dioxane-5,5-dimethanamine-N,N')platinum.

Example 3

Preparation of [1,1-Cyclobutanedicarboxylato(2-)-O^1,O^1]-(tetrahydro-4H-pyran-4,4-dimethanamine-N,N')platinum

A mixture of 28.6 g of dichloroethyl ether, 13.2 g of malononitrile, 55.28 g of potassium carbonate and 800 ml of acetonitrile was refluxed on a steam bath for 24 hours, then filtered while hot. The filtrate was evaporated and the residue crystallized, with charcoal treatment, from 100 ml of ethanol, giving 9.5 g of tetrahydro-4H-pyran-4,4-dicarbonitrile as colorless plates, mp 110-112^{o}C.

A 180 ml portion of 1N borane in tetrahydrofuran was added rapidly, dropwise to a solution of 8.18 g of tetrahydro-4H-pyran-4,4-dicarbonitrile in 150 ml of tetrahydrofuran. This mixture was warmed, then cooled to room temperature in an ice bath and then stirred for 64 hours at room temperature. A 100 ml portion of ethanol was added dropwise, then the mixture was stirred 4 hours and evaporated to dryness. The residue was taken up in 100 ml of water, acidified with 50 ml of 6N hydrochloric acid and extracted three times with ether. The remaining aqueous layer was evaporated to dryness. The residue was boiled in 300 ml of methanol and filtered while hot. The filtrate was treated with 200 ml of ether and cooled. The resulting solid was collected, washed with ether and dried, giving 8.31 g of tetrahydro-4H-pyran-4,4-dimethanamine, dihydrochloride.

An ion exchange resin (Dowex, 1-X4) was slurried in 10N sodium hydroxide and then packed into a 3/4 inch column. The column was washed with water until the pH was neutral. An aqueous solution of 2.17 g of tetrahydro-4H-pyran-4,4-dimethanamine, dihydrochloride was added to the column at a slow flow rate. The column cut containing the free base was evaporated, giving 1.48 g of tetrahydro-4H-pyran-4,4-dimethanamine as a colorless oil.

A 4.9 g portion of [1,1-cyclobutanedicarboxylato-(2-)-O,O^{1}]bis[sulfinylbis[methane]-S]platinum was dissolved in 120 ml of water at 100^{o}C. A solution of 1.4 g of tetrahydro-4H-pyran-4,4-dimethanamine in 30 ml of water was added and the mixture was heated at 100^{o}C for 6 hours. The mixture was filtered and the filtrate evaporated to dryness. The residue was slurried in 30 ml of water, heated to 95^{o}C and filtered. The filtrate was concentrated to about 10 ml and the resulting solid collected, washed with water and dried, giving 1.34 g of biologically active [1,1-cyclobutanedicarboxylato(2-)-O^1,O^1](tetrahydro-4_H_-pyran-4,4-dimethanamine-_N_,_N_']platinum.

Example 4

Preparation of [2,2-Bis(aminomethyl)-1,3-propanediol-_N_,_N_'][1,1-cyclobutanedicarboxylato(2-)-O^1,O^1]platinum

To a solution of 1.0 g of [1,1-cyclobutanedicarboxylato(2-)-O,O^1]bis[sulfinylbis[methane]-S]platinum in 25 ml of water at 100°C was added a solution of 272 mg of 2,2-bis(aminomethyl)-1,3-propanediol in 5 ml of water. The mixture was heated at 100°C for 6 hours and then filtered. The filtrate was evaporated to about 3 ml and the resulting solid collected, giving 100 mg of biologically active [2,2-bis(aminomethyl)-1,3-propanediol-_N_,_N_'][1,1-cyclobutanedicarboxylato(2-)-O^1,O^1]platinum.

Example 5

Preparation of 2,2-Dimethyl-1,3-propanediamine, compound with [1,1-cyclobutanedicarboxylato(2-)-O,O^1]platinum

To a warm solution of 1.24 g of [1,1-cyclobutanedicarboxylato(2-)-O,O^1]bis[sulfinylbis[methane]-S]platinum in 60 ml of water was added 0.26 g of 2,2-dimethyl-1,3-propanediamine. The mixture was kept at 100°C for 20 hours and then evaporated under reduced pressure. The residue was recrystallized from 10 ml of water, giving 510 mg of biologically active 2,2-dimethyl-1,3-propanediamine, compound with [1,1-cyclobutanedicarboxylato(2-)-O,O^1]platinum.

Example 6

Bis(Acetato-O)bis[sulfinylbis[methane]-S]platinum

A 20.75 g portion of potassium tetrachloroplatinate was added to 165 ml of water, stirred for a few minutes and then filtered. To the filtrate was added 10.65 g of dimethyl sulfoxide. The suspension was allowed to stand for 14 hours, then the crystals were collected, washed with water, ethanol and ether and dried, giving 18.57 g of sulfinylbismethane, compound with platinum chloride.

A suspension of 1.27 g of sulfinylbismethane, compound with platinum chloride, 1.0 g of silver acetate and 70 ml of water was stirred in the dark overnight, then filtered and the filtrate evaporated to dryness. The residue was slurried in methanol, diluted with ether and the solid collected and dried, giving 1.2 g of bis(acetato-O)-bis[sulfinylbis[methane]-S]platinum.

Example 7

[Propanedioato(2-)-O^1,O^3]bis[sulfinylbis[methane]-S]platinum

A suspension of 1.27 g of sulfinylbismethane, compound with platinum chloride, 953 mg of the disilver salt of malonic acid and 70 ml of water was stirred in the dark overnight, then filtered and the filtrate evaporated to dryness. The residue was slurried in methanol, diluted with ether and the solid collected and dried, giving 1.15 g of [propanedioato(2-)-O^1,O^3]bis[sulfinylbis[methane]-S]-platinum.

Example 8

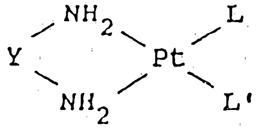
trans-(-)-[1,1-Cyclobutanedicarboxylato(2-)-O,O^1]-(1,2-cyclohexanediamine-N,N')[sulfinylbis[methane]-S]platinum

To a solution of 1.24 g of [1,1-cyclobutanedicarboxylato(2-)-O,O^1]bis[sulfinylbis[methane]-S]platinum in 40 ml of water at 40°C was added 285 mg of trans-(-)-1,2-cyclohexanediamine. The mixture was heated at 40°C for 1 hour, then evaporated at 40°C under reduced pressure. The residue was triturated with ethanol and ether, giving 1.15 g of trans-(-)-[1,1-cyclobutanedicarboxylato(2-)-O,O^1](1,2-cyclohexanediamine-N,N')[sulfinylbis[methane]-S]-platinum.

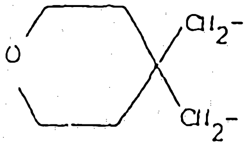
A 200 mg portion of the above compound in 5 ml of water was heated at 100°C for 6 hours, then cooled and the solid collected and dried, giving 130 mg of biologically active trans-(-)-1,2-cyclohexanediamine, compound with [1,1-cyclobutanedicarboxylato(2-)-O,O^1]platinum.

~~We claim:~~The claims defining the invention are as follows:

1. A process for producing a compound of the formula:



wherein Y is



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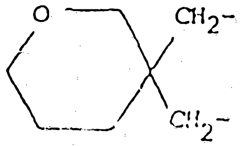

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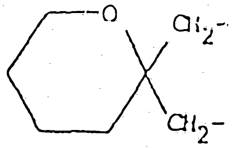

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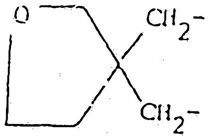

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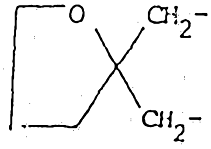

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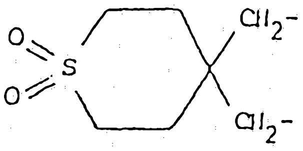

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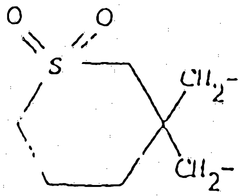

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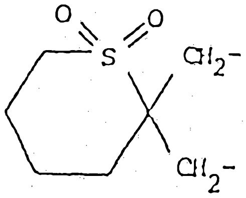

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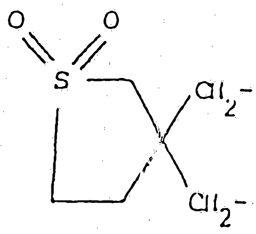

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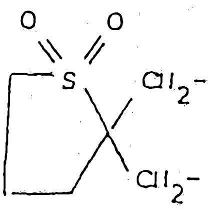

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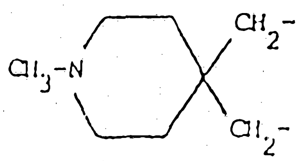

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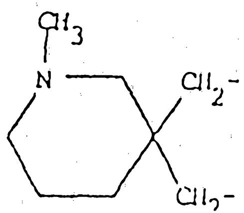

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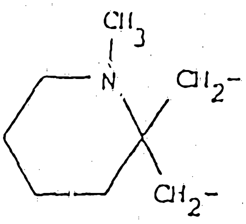

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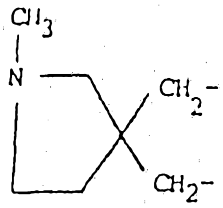

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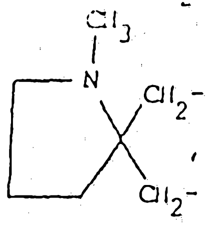

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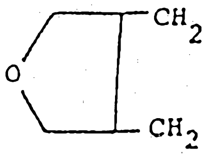
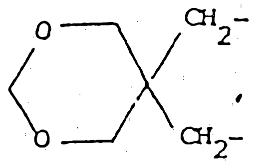
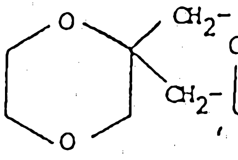
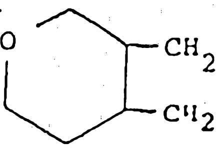
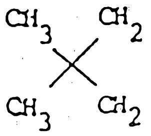
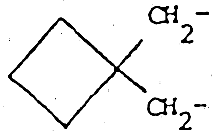
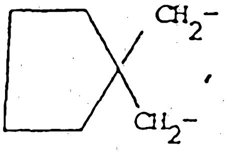
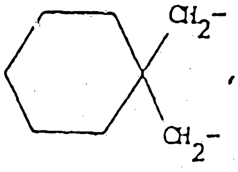
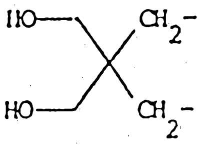
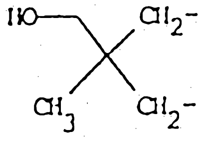
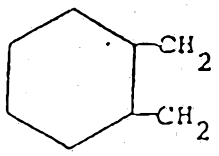
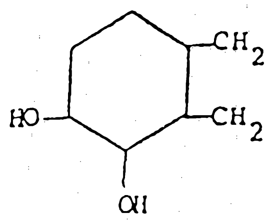
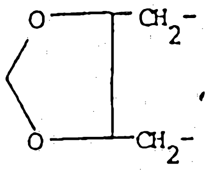
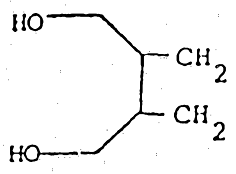
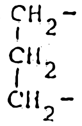
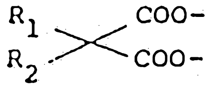
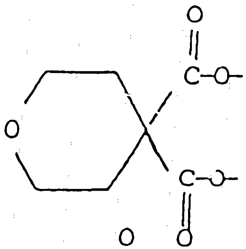
 , , 

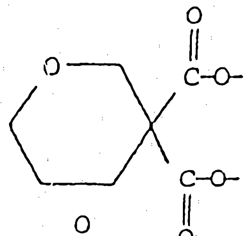
, , , ,

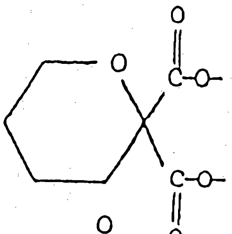
, , , ,

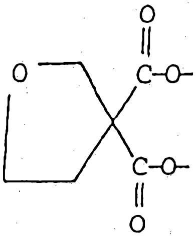
, ,

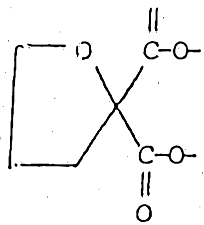
or  $-CH_2-CH_2-CH_2-$; and L and L′ are monobasic carboxylates consisting of acetate, hydroxyacetate and propionate, or L and L′ taken together are a dibasic carboxylate consisting of  $R_1R_2C(COO-)_2$, where R_1 and R_2 are hydrogen or lower alkyl-(C_1-C_5), or R_1 and R_2 taken together is $(CH_2)_n$, where n is 2 to 5,

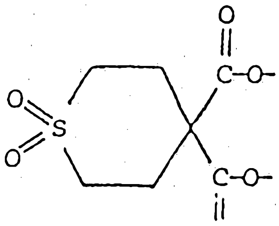
 ,

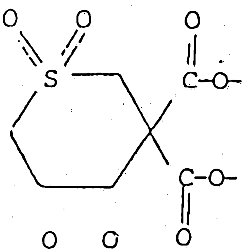
 ,

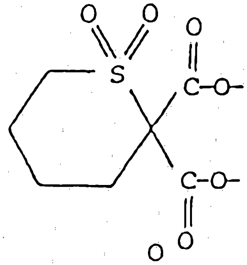
 ,

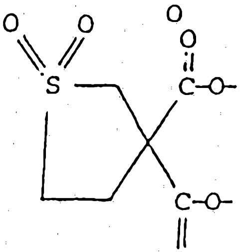
 ,

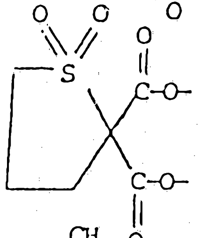
 ,

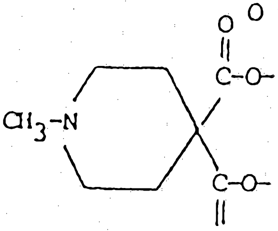
 ,

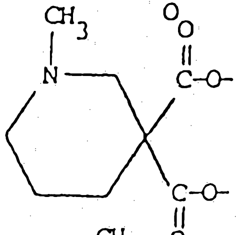
 ,

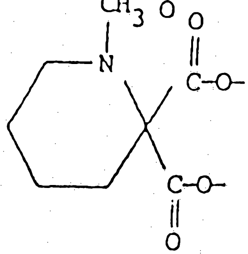
 ,

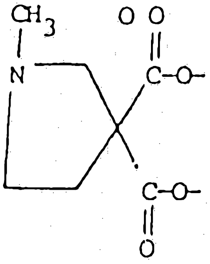
 ,

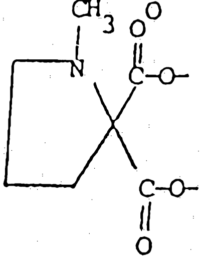
 ,

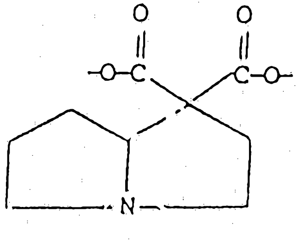
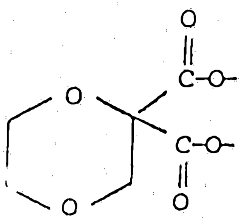
 ,

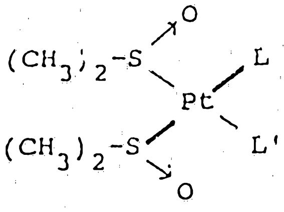
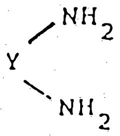
 ,

 ,

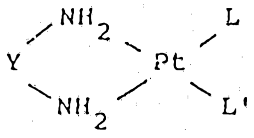
 ,

 ,

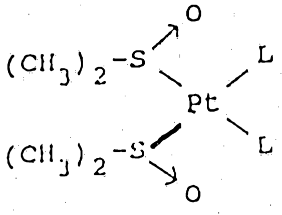
 or 

which comprises reacting sulfinylbismethane, compound with platinum chloride with mono- or dicarboxylic acid in aqueous solution, protected from the light, giving a carboxylic acid-bis[sulfinylbis[methane]-S]platinum compound of the formula  , where L and L′are as described above, which is then reacted with an amine of the formula  , where Y is as described above, in a hot aqueous solution.

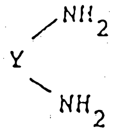
2. A process for producing a compound of the formula:



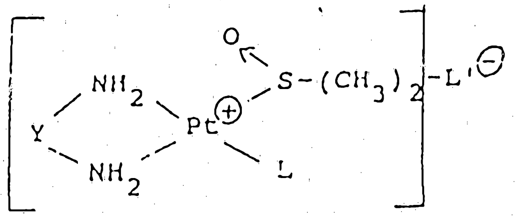
wherein Y,L and L′ are as defined in Claim 1, which comprises reacting a carboxylic acid-bis[sulfinylbis [methane]-S]platinum compound of the formula



where L and L′ are as defined in Claim 1, in warm aqueous solution with an amine of the formula

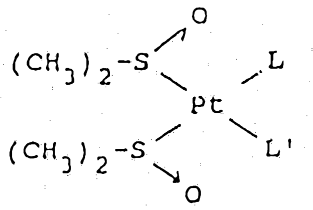


, where Y is as defined in Claim 1, giving a compound of the formula:



which is further reacted in a hot aqueous solution.

3. A compound of the formula:



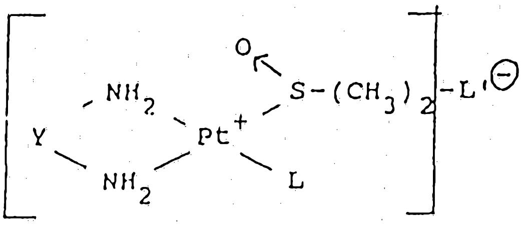
wherein L and L' are as defined in Claim 1.

4. [1,1-Cyclobutanedicarboxylato(2-)-O,O^1]bis[sulfinylbis[methane]-S]platinum.

5. Bis(aceto-O)bis[sulfinylbis[methane]-S]-platinum.

6. [Propanedioato(2-),-O^1,O^3]bis-[sulfinylbis[methane]-S]platinum.

7. ..pound of the formula :



wherein Y, L and L′ are as defined in Claim 1.

8. Trans-(-)-[1,1-cyclobutanedicarboxylato-(2-)-O,O^{1}](1,2-cyclohexanediamine-N,N')[sulfinylbis-[methane]-S]platinum.

9. The product of the process of any one of claim 1 or claim 2.

10. A process for synthesis of cisplatin analogs substantially as hereinbefore described with reference to any one of the Examples.

DATED this TWENTY-SIXTH day of APRIL 1988
American Cyanamid Company

Patent Attorneys for the Applicant
SPRUSON & FERGUSON