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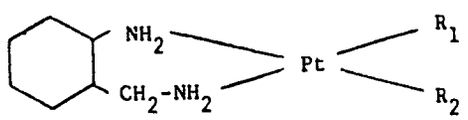
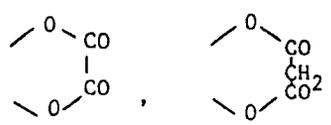
(54) **Platinum complexes, processes for their preparation, pharmaceutical compositions containing them and their use as medicaments.**

(57) Platinum complexes of the general formula:



(wherein a) R_1 and R_2 are the same and each represents a halogen atom or NO_3;
or b) R_1 is SO_4 and R_2 is H_2O;
or c) R_1 and R_2 together represent



or a glucuronate moity), the configuration of the 1-aminomethyl-2-aminocyclohexane being selected from *trans*-1, *trans*-d, *cis*-1 and *cis*-d have been found to exhibit antitumour activity together with low toxicity and are thus of potential interest as medicament.

Processes for the preparation of the platinum complexes are described and exemplified and pharmaceutical compositions comprising the platinum complexes as active ingredient are described.

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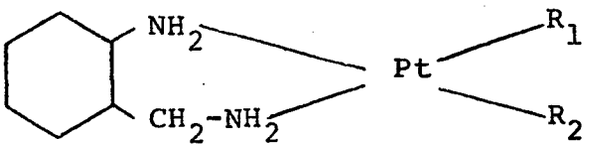
Platinum complexes, processes for their preparation, pharmaceutical compositions containing them and their use as medicaments

This invention relates to platinum complexes, processes for their preparation, pharmaceutical compositions containing them and their use as medicaments.

It is known that certain platinum complexes are active against tumour cells [for example, Nature, 222, 385 (1969); Platinum Metal Rev., 15, No. 2, 42-51 (1971); ibid. 17, No. 1, 2-13 (1973) and US Patent 4,115,418 (1978)].

The present invention is based on the discovery that certain 1-aminomethyl-2-aminocyclohexane platinum complexes exhibit good anti-tumour activity and low toxicity.

Thus, the present invention provides a platinum complex of the general formula:

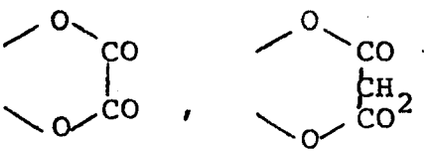


I

(wherein a) R_1 and R_2 are the same and each represent a halogen atom or NO_3;

or b) R_1 is SO_4 and R_2 is H_2O;

or c) R_1 and R_2 together represent:-



or a glucuronate moiety),

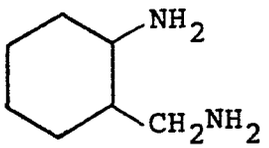
the configuration of the 1-aminomethyl-2-aminocyclohexane being selected from trans-l, trans-d, cis-l and cis-d.

The platinum complexes of formula [I] exhibit anti-tumour activity and are potentially of interest as medicaments.

The platinum complexes of the present invention may, for example, be produced by any of the following

processes, which processes constitute further features of the invention:-

a) for the preparation of a platinum complex as hereinbefore defined (wherein R_1 and R_2, which are the same, each represents a halogen atom), the reaction of a compound of the formula:-



II

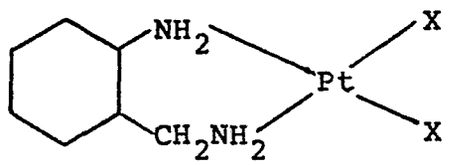
with a compound of the formula

$$M^{n\oplus}[PtX_4]^{\ominus}_n \qquad \text{III}$$

(wherein X represents a halogen atom, M represents a stabilising metal cation and n is the charge on the cation).

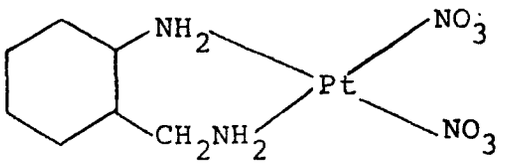
A compound of formula III is preferably used in which X represents chlorine. The stabilising metal cation is preferably an alkali metal or an alkaline earth metal cation e.g. a sodium or potassium cation.

b) for the preparation of a platinum complex as hereinbefore defined (wherein R_1 and R_2, which are the same, each represent a group NO_3), the reaction of a platinum complex of the formula:-



IV

(wherein X represents a halogen atom) with a compound of the formula $B(NO_3)_n$ (in which n represents the charge on B and B is a cation whose halide is insoluble in water) whereby a platinum complex of the formula:-



V

is obtained.

The cation B is preferably a silver cation

c) for the preparation of a platinum complex as hereinbefore defined (wherein R_1 and R_2, which are the same, each represent a bromine or iodine atom or R_1 and R_2 together form an oxalate, malonate or glucuronate moiety), the reaction of a compound of formula V (as hereinbefore defined) with a compound of the formula:

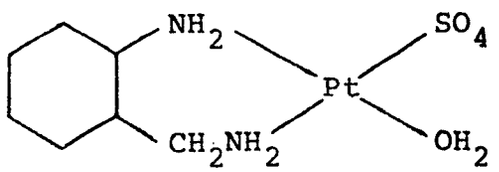
MX_n or $M_2(R_1R_2)_n$

(VII) (VIII)

(wherein X represents a bromide or iodide anion, M represents a stabilising metal cation, n represents the charge on the cation and R_1 and R_2 are as hereinbefore defined) whereby a platinum complex of formula I is obtained.

A compound of formula VII or formula VIII is preferably used in which M represents an alkali metal or alkaline earth metal cation e.g. a potassium or sodium cation.

d) for the preparation of a platinum complex as hereinbefore defined (wherein R_1 is SO_4 and R_2 is H_2O), the reaction of a compound of formula IV with a compound of the formula:- $B_2(SO_4)_n$ (wherein B and n are as hereinbefore defined) whereby a compound of the formula:



VI

is obtained.

The cation B is preferably a heavy metal cation e.g. a silver cation.

The 1-aminomethyl-2-aminocyclohexane is conveniently prepared as follows:

Racemic (Rac) modification of trans (or cis)-cyclohexane-1,2-dicarboxylic acid

↓ Step I — Introduction of amino group

Rac-trans (or cis)-2-aminocyclohexanecarboxylic acid

↓ Step II — Conversion into ester

Rac-trans (or cis)-2-aminocyclohexanecarboxylic ethyl ester

↓ Step III — Conversion into hydrazide

Rac-trans (or cis)-2-aminocyclohexanecarbohydrazide

↓ Step IV — Conversion into aminomethyl-compound

Rac-trans (or cis)-1-aminomethyl-2-aminocyclohexane
[hereinafter referred to as rac-trans (or cis)-aamch]

↓ Step V — Optical resolution

Trans-d-aamch·diastereomer and trans- l-aamch·diastereomer
[or cis-d-aamch·diastereomer and cis-l-aamch.diastereomer]

↓ Step VI — Decomposition of diastereomer

Trans-l-aamch (absolute configuration: 1R, 2S)
Trans-d-aamch (" : 2S, 2R)
Cis-l-aamch (" : 1R; 2R)
Cis-d-aamch (" : 1S, 2S)

The above-mentioned steps may, for example, be effected as follows:-

[Step I]

A racemic modification of trans (or cis)-cyclohexane-1,2-dicarboxylic acid is dissolved in a suitable solvent such as, for example, chloroform, added with an acid and the reaction is carried out to introduce an amino group by using a suitable agent such as. for example, sodium azide. After completion of the reaction, the solvent is removed from the reaction mixture which is then added with a neutralizing agent. After the neutralizing, the solution is filtered and the filtrate is concentrated under reduced pressure to dryness, and if desired, recrystallized from ethanol. As the starting material, one of the market grade may be used.

[Step II]

The racemic modification of trans (or cis)-2-amino-cyclohexanecarboxilic acid prepared by Step I is dissolved in a suitable solvent such as, for example, ethanol. The solution is saturated with hydrogen chloride and at the same time the refluxing ethanol is removed. After this, water is added to the solution which is neutralized with a neutralizing agent and is extracted with ether. Ether is distilled off from the extract to obtain the desired product.

[Step III]

Hydrazine hydrate is added to the trans (or cis)-2-aminocyclohexanecarboxylic acid prepared by Step II. The solution is refluxed to complete the reaction, and the reaction mixture is concentrated to dryness under reduced pressure to obtain the desired product which may, if desired, be washed with an organic solvent.

[Step IV]

The trans (or cis)-2-aminocyclohexanecarbohydrazide is dissolved in a suitable solvent such as, for example, benzene, ether, tetrahydrofuran and the like. The solution is added with a reducing agent such as,for example, lithium alminium hydride and refluxed for 4 to 7 days. After completion of the reaction, the excessive lithium aluminium hydride is decomposed and the solvent is distilled off, followed by concentration to dryness under reduced pressure to obtain the desired product.

[Step V]

Equimolar amounts of rac-trans (or cis)-aamch prepared by Step IV and (+) [or (-)]-dibenzoyltartaric acid are suspended in water and stirred. After completion of the reaction, the resultant diastereomer is dissolved in a solvent of water/methanol (1:1 volume by volume)and allowed to stand for a night to obtain the needles of the desired product.

[Step VI]

Each isomeric diastereomer prepared by Step V is suspended or dissolved in water and is then added with conc. hydrochloric acid. The reaction solution is filtered to give a filtrate which is then neutralized to liberate the desired product. This product is, if desired, extracted with an organic solvent and the solvent is evaporated off to obtain the desired product i.e. trans-d, trans-l, cis-d or cis-l-aamch.

[Step VII]

The production of platinum complexes from the diamines prepared by Step VI may be carried out in a similar manner to that described, for example, in Journal of Pharmaceutical Sciences, vol. 65, 315-328 (1976) by the following procedures which are as described above:-

1) $PtHal_2$(aamch) especially $PtCl_2$(aamch) may for example be produced by the reaction of K_2PtX_4 (wherein X is halogen e.g. chlorine) with aamch.

2) The $PtHal_2$(aamch) e.g. $PtCl_2$(aamch) prepared by (1) may for example be reacted with $AgNO_3$ and then filtered to obtain a filtrate. This filtrate is concentrated to dryness to obtain $Pt(NO_3)_2$(aamch).

3) $Pt(NO_3)_2$(aamch) may, for example, be dissolved in water and then treated with KI, KBr, potassium oxalate, sodium malonate or sodium glucuronate to effect the reaction, resulting in PtI_2(aamch), $PtBr_2$(aamch), Pt(oxalate)(aamch), Pt(malonate)(aamch) or Pt(glucuronate)(aamch) respectively.

4) $PtCl_2$(aamch) may for example be treated with $AgSO_4$ to carry out the reaction. The resultant AgCl is removed by filtration, and the filtrate is evaporated off to obtain $Pt(OH_2)(SO_4)$-(aamch).

These reactions may for example be effected in the presence of water, if desired, at an elevated temperature and/or in darkness and may be completed in 3 to 48 hours to give precipitates coloured usually in white to yellow. The resultant precipitates may be recrystallized from 0.1N hydrochloric acid to obtain the desired products in the form of crystals.

According to a further feature of the present invention there is provided a pharmaceutical composition comprising as active ingredient at least one platinum complex as hereinbefore defined in association with a pharmaceutical carrier or excipient.

The compositions may be presented in a form suitable for oral, rectal or parenteral administration. Thus, for example, compositions for oral administration may be solid or liquid and may take the form of granules, tablets, coated tablets, capsules, syrups, emulsions, suspensions or drops, such compositions comprising carriers or excipients conventionally used in the pharmaceutical art. Thus, for example, suitable tabletting excipients include lactose, potato and soluble starches and magnesium stearate.

For parenteral administration, the carrier may be a sterile, parenterally acceptable liquid such as sterile water, or a parenterally acceptable oil e.g. arachis oil, contained in ampoules. Compositions

for rectal administration may take the form of suppositories, the carrier comprising a suppository base.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Tablets, coated tablets, capsules, suppositories and ampoules are examples of suitable dosage unit forms.

The present invention also provides platinum complexes of formula I as hereinbefore defined when used as a medicament.

The compounds of the present invention may be prepared by the processes of the examples as hereinafter described which are provided by way of illustration only. The physical characteristics of complexes of the invention are indicated in the following table. Malonate, glucuronate and oxalate are hereinafter abbreviated as mal, gluc and OX respectively.

TABLE I

W: white, LY: light yellow, Y: yellow,

No.	Compound	Colour	Elemental Analysis Found H	C	N
1	$PtCl_2$(trans-d-aamch)	W	4.10	21.32	7.11
2	$PtCl_2$(trans-ℓ-aamch)	W	4.10	21.32	7.11
3	$PtCl_2$(cis-d-aamch)	W	4.10	21.32	7.11
4	$PtCl_2$(cis-ℓ-aamch)	W	4.10	21.32	7.11
5	$PtBr_2$(trans-d-aamch)	LY	3.34	17.40	5.80
6	$PtBr_2$(trans-ℓ-aamch)	LY	3.34	17.40	5.80
7	$PtBr_2$(cis-d-aamch)	LY	3.34	17.40	5.80
8	$PtBr_2$(cis-ℓ-aamch)	LY	3.34	17.40	5.80
9	PtI_2(trans-d-aamch)	Y	2.80	14.57	4.85
10	PtI_2(trans-ℓ-aamch)	Y	2.80	14.57	4.85
11	PtI_2(cis-d-aamch)	Y	2.80	14.57	4.85
12	PtI_2(cis-ℓ-aamch)	Y	2.80	14.57	4.85
13	Pt(OX)(trans-d-aamch)	W	3.93	26.28	6.81
14	Pt(OX)(trans-ℓ-aamch)	W	3.93	26.28	6.81

TABLE I (continued)

W: white, LY: light yellow, Y: yellow,

No.	Compound	Colour	Elemental Analysis Calculated H	C	N
1	$PtCl_2$(trans-d-aamch)	W	4.18	20.98	6.88
2	$PtCl_2$(trans-l-aamch)	W	3.96	21.09	6.97
3	$PtCl_2$(cis-d-aamch)	W	4.14	21.71	7.20
4	$PtCl_2$(cis-l-aamch)	W	3.98	21.20	6.96
5	$PtBr_2$(trans-d-aamch)	LY	3.45	18.13	5.97
6	$PtBr_2$(trans-l-aamch)	LY	3.27	17.62	5.69
7	$PtBr_2$(cis-d-aamch)	LY	3.36	17.75	5.95
8	$PtBr_2$(cis-l-aamch)	LY	3.28	17.60	5.74
9	PtI_2(trans-d-aamch)	Y	2.95	15.93	5.45
10	PtI_2(trans-l-aamch)	Y	2.88	15.32	4.90
11	PtI_2(cis-d-aamch)	Y	2.88	14.75	4.64
12	PtI_2(cis-l-aamch)	Y	2.80	14.75	4.88
13	Pt(OX)(trans-d-aamch)	W	3.84	26.50	6.89
14	Pt(OX)(trans-l-aamch)	W	3.78	25.82	6.82

TABLE I (continued)

W: white, LY light yellow, Y: yellow,

No.	Compound	Colour	Elemental analysis Found		
			H	C	N
15	Pt(OX)(cis-d-aamch)	W	3.93	26.28	6.81
16	Pt(OX)(cis-ℓ-aamch)	W	3.93	26.28	6.41
17	Pt(OH_2)(SO_4)(trans-d-aamch)	W	4.16	19.22	6.41
18	Pt(OH_2)(SO_4)(trans-ℓ-aamch)	W	4.16	19.22	6.41
19	Pt(OH_2)(SO_4)(cis-d-aamch)	W	4.16	19.22	6.41
20	Pt(OH_2)(SO_4)(cis-ℓ-aamch)	W	4.16	19.22	6.41
21	Pt(NO_3)$_2$(cis-d-aamch)	W	3.61	18.79	12.53
22	Pt(NO_3)$_2$(cis-ℓ-aamch)	W	3.61	18.79	12.53
23	Pt(NO_3)$_2$(trans-d-aamch)	W	3.61	18.79	12.53
24	Pt(NO_3)$_2$ (trans-ℓ-aamch)	W	3.61	18.79	12.53
25	Pt(mal)(trans-d-aamch)	W	4.27	28.23	6.59
26	Pt(mal) (trans-ℓ-aamch)	W	4.27	28.23	6.59
27	Pt(mal)(cis-d-aamch)	W	4.27	28.23	6.59
28	Pt(mal)(cis-ℓ-aamch)	W	4.27	28.23	6.59
29	Pt(gluc)(trans-d-aamch)	LY			
30	Pt(gluc)(trans-ℓ-aamch)	LY			
31	Pt(gluc)(cis-d-aamch)	LY			
32	Pt(gluc)(cis-ℓ-aamch)	LY			

Table I (continued)

W: white, LY: light yellow, Y: yellow,

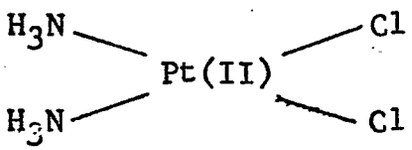
No.	Compound	Colour	Elemental analysis Calculated H	C	N
15	Pt(OX)(cis-d-aamch)	W	3.32	26.12	7.00
16	Pt(OX)(cis-ℓ-aamch)	W	3.90	26.02	6.84
17	$Pt(OH_2)(SO_4)$(trans-d-aamch)	W			
18	$Pt(OH_2)(SO_4)$(trans-ℓ-aamch)	W	4.14	19.15	6.10
17	$Pt(OH_2)(SO_4)$(cis-d-aamch)	W	4.00	19.35	6.08
20	$Pt(OH_2)(SO_4)$(cis-ℓ-aamch)	W	4.22	19.25	6.61
21	$Pt(NO_3)_2$(cis-d-aamch)	W	3.40	18.76	12.44
22	$Pt(NO_3)_2$(cis-ℓ-aamch)	W	3.57	18.91	12.38
23	$Pt(NO_3)_2$(trans-d-aamch)	W			
24	$Pt(NO_3)_2$ (trans-ℓ-aamch)	W			
25	Pt(mal)(trans-d-aamch)	W	4.08	28.05	6.62
26	Pt(mal) (trans-ℓ-aamch)	W			
27	Pt(mal)(cis-d-aamch)	W			
28	Pt(mal)(cis-ℓ-aamch)	W			
29	Pt(gluc)(trans-d-aamch)	LY			
30	Pt(gluc)(trans-ℓ-aamch)	LY			
31	Pt(gluc)(cis-d-aamch)	LY			
32	Pt(gluc)(cis-ℓ-aamch)	LY			

The following experiments were conducted to investigate the anti-tumour activities of the compounds provided by the present invention.

Experiments

CDF_1 mouse (each group consisting of 6 mice) were used as test animals. A physiological sodium chloride solution containing 10^6 cells of Leukemia P-388 was administered to each mice intraperitoneally. On the first and fifth days after this, each mouse was intraperitoneally administered with a given amount of the test compound contained in physiological sodium chloride solution to obtain the results shown in Table 2 wherein the effect is indicated by T/C % (the ratio of the median survival days of the test animal to the control mice).

For comparison purpose, PDD i.e. cis— dichlorodiammine platinum (II) which is represented by the following formula:



and which is known as being active against tumour cells is treated in a similar manner to that described above to obtain the results shown as Reference in the following tables, from which it is apparent that the platinum complexes provided by the present invention are superior to the known platinum complex with respect to T.I., toxicity and other properties.

TABLE 2

D : Doses (mg/kg)
No. : Compound number

No. \ D	T/C %								
	100	50	25	12.5	6.25	3.12	1.56	0.78	0.39
1		61	68	226	174	157	156	138	123
2		62	81	197	177	162	159	140	118
3				106	243	187	166	147	135
4				90	240	203	157	138	110
5	70	194(1)	188	175	161	145	134	133	
6	80	186	178	178	166	164	135	130	
7	75	190	196	161	161	147	144	125	
8	67	99	181	178	176	147	154	135	
9	160	160	143	145					
10	0	153	158	138	128				
11	0	73	160	158	141				
12	0	80	141	148					
13			171	168	139	131	112		
14			83	245	200	151	128	128	
15			90	184	184	131	128	128	
16		70	193	163	137	146	131		
17		215	196	179	185	166	140	129	
18			80	181	181	151	158	146	
19		59	83	189	178	152	159		
20		59	88	189	178	159	133		
21				248	228	197			
22				92	240	220			
29			170	170	148				
30			200	173	158				
31			180	179	167				
32			208	184	173				
Ref.		0	0	67	121	230	165	134	118

The toxic dose (T.D), optimal dose (O.D), minimal effective dose (MED), each T/C% corresponding to O.D or MED respectively, and therapeutic index (T.I) of each compound are calculated on the basis of Table 2 and shown in Table 3.

TABLE 3

No.	T. D	O.D		MED		T. I
	mg/Kg	mg/Kg	T/C%	mg/Kg	T/C %	
1	25	12.5	226	0.39	123	32
2	25	12.5	197	0.78	126	16
3	25	6.25	242	0.39	135	16
4	25	6.25	240	0.78	138	8
5	100	50	194(1)	0.78	133	64
6	100	50	186	0.78	130	64
7	100	25	196	0.78	125	32
8	100	25	181	0.78	135	32
9	≧200	100	160	12.5	145	8
10	100	25	158	6.25	128	4
11	50	25	160	6.25	141	4
12	50	12.5	148	12.5	148	1
13	≧50	25	171	3.12	131	≧8
14	25	12.5	243	0.78	128	16
15	50	12.5	184	0.78	128	16
16	50	25	193	1.56	131	16
17	≧100	50	215	0.78	129	64
18	75	12.5	181	0.78	146	16
19	25	6.25	189	≦0.78	159	≧8
20	25	6.25	189	0.78	138	8
Ref	12.5	3.12	230	0.78	134	4

With reference to the accompanying drawings, Figs. 1-6 show respectively infrared absorption spectra of $PtCl_2$(trans-d-aamch), $PtCl_2$(cis-l-aamch), $PtBr_2$(trans-d-aamch), $PtBr_2$(cis-l-aamch), PtI_2(trans-d-aamch) and PtI_2(cis-l-aamch). Fig. 7 shows CD spectrum of $Pt(NO_3)_2$-(trans-l-aamch). Fig. 8 shows CD spectrum of $Pt(NO_3)_2$-(cis-l-aamch). Fig. 9 shows electron spectrum of $Pt(OH_2)$-(SO_4)(trans-l-aamch). Fig. 10 (1) and Fig. 10 (2) show respectively CD spectra of $Pt(OH_2)(SO_4)$(trans-l-aamch) and $Pt(OH_2)(SO_4)$(trans-d-aamch). Figs. 11 and 12 show respectively electron spectrum and CD spectrum of $Pt(OH_2)$-(SO_4)(cis-l-aamch).

The following non-limitative examples illustrate the invention.

Example 1

(A) Trans-cyclohexane-1,2-dicarboxylic acid (8.105 g; racemic modification) is dissolved in conc. sulfuric acid (25 ml) and chloroform (50 ml) and kept at a temperature of 45°C, to which is added sodium azide (3.6 g) in one hour. After this, the solution is stirred for 90 minutes, added with ice water (25 ml) and is added with ether to remove chloroform. Barium carbonate (90 g) is added to the water layer of the solution to effect the neutralization. Barium sulfate is removed from the solution by

filtration and the filtrate is concentrated to dryness to result in needle crystals of rac-trans-2-aminocyclohexanecarboxylic acid (referred to as A) having the following characteristics. When a corresponding rac-cis-compound is used as starting material, there is obtained the corresponding cis-compound i.e. rac-cis-aminocyclohexanecarboxylic acid, referred to as B).

Elemental analysis(calculated as $C_7H_{13}NO_2$):

	H	C	N
Calculated:	58.7%	9.15%	9.8%
Found (A):	58.79%	9.27%	9.06%
(B):	58.45%	9.14%	9.42%

Melting point: (A) 273°C (B) 238°C

(B) The thus-obtained rac-trans-2-aminocyclohexanecarboxylic acid (1.8 g) is dissolved in ethanol. This solution is saturated with hydrogen chloride and refluxed for 7 hours under conditions for saturation with hydrogen chloride. Ethanol is removed from the solution by distillation, and a small amount of water is added to the reaction solution. Ether is distilled off from the reaction solution which is then evaporated under reduced pressure to obtain ethyl ester of rac-trans-2-aminocyclohexanecarboxylic acid having a melting point of 120-122°C/2 mmHg. When a corresponding cis-compound is used as starting material, there is obtained the corresponding cis-compound having a melting point of 75°C/2 mmHg.

(C) The thus-obtained ester (trans form; 1.54 g) is mixed with hidrazine hydrate (20 ml) and the mixture is refluxed for one hour. After completion of the reaction, the reaction solution is concentrated under reduced pressure to dryness, resulting in needle crystals of rac-trans-2-aminocyclohexanecarbohydrazide having a melting point of 166-167°C. When an ester of the corresponding cis-compound is used as starting material, there is obtained rac-cis-2-aminocyclohexanecarbohydrazide.

(D) The thus-obtained trans-compound (1.57 g) is dissolved in a mixture of benzene (100 ml) and tetrahydrofuran (150 ml), added with lithium alminium hydride, and refluxed for 7 days. After completion of the reaction, the reaction solution is added with a saturated solution of potassium carbonate to decompose the excess of lithium alminium hydride. After refluxing for 30 minutes, the solution is filtered and the filtrate is distilled under reduced pressure to remove excessive benzene and tetrahydrofuran, resulting in rac-trans-1-aminomethyl-2-aminocyclohexane.

(E) The cis-compound obtained by (C) (3.5 g) is dissolved in a mixture of benzene (150 ml) and ether (150 ml). The mixed solution is added with lithium aluminium hydride (2g) and ether (50 ml) and refluxed for 7 days. After completion of the reaction, lithium aluminium hydride is decomposed. After this, the reaction solution is filtered and the filtrate is distilled to obtain rac-cis-1-aminomethyl-2-aminocyclohexane (melting point: 86°C/5 mmHg).

(F) Rac-trans-aamch thus-obtained (17.6521 g) and (+)-dibenzoyltartaric acid (51.7520 g) in an equimolar amount are suspended in water (100 ml) and stirred to prepare a diastereomer which is washed with water several times and is then dissolved in a solvent of water/ethanol (1:1 v/v) at an elevated temperature. The reaction solution is allowed to stand for a night to give needles of trans-1-aamch having a specific rotation of $[\alpha]_D^{23}$=-95.2° which is recrystallized by using a similar mixed solvent to the above-mentioned to a furtherly purified trans-1-aamch-diastereomer having a specific rotation of $[\alpha]_D^{23}$= -97.78°. When the rac-trans-aamch and (-)-dibenzoyltartaric acid are used in a similar manner to that described above, it is possible to obtain trans-d-aamch-diastereomer having a specific rotain of $[\alpha]_D^{23}$= + 99.06°.

There is also obtained cis- aamch-diastereomer having a specific rotation of $[\alpha]_D^{23}$= +91.2° or cis-d-aamch-diastereomer having a specific rotation of $[\alpha]_D^{23}$ = - 88.7° respectively by using rac-cis-aamch in combination with either (-)-dibenzoyltartaric acid or (+)-dibenzoyltartaric acid.

(G) Each isomer of the diastereomers thus-obtained is suspended or dissolved in water and added with conc. hydrochloric acid to liberate benzoyltartaric acid which is then removed by filtration. With addition of sodium hydroxide, the filtrate is neutrallized to liberate diamine. The filtrate is then extracted with ether, and ether is removed by distillation to obtain each of the following

isomers:

Trans-l-aamch (absolute configuration: 1R,2S)

Trans-d-aamch (" : 1S,2R)

Cis-l-aamch (" : 1R,2R)

Cis-d-aamch (" : 1S,2S)

By the use of the isomers thus-obtained, it is possible to obtain the platinum complexes of the present invention in the following manner.

(H) Synthesis of $PtCl_2$(aamch):

Aamch (1.28259 g) and K_2PtCl_4 (4.1511 g) are dissolved in water (50 ml) and is allowed to stand for some time to give crystlline precipitates coloured in light yellow to white which represent $PtCl_2$(aamch) corresponding to the aamch used as the starting material. The infrared absorption spectrum of $PtCl_2$(trans-d-aamch) shown in Fig. 1 is identical with that of $PtCl_2$(trans-l-aamch), and the infrared absorption spectrum of $PtCl_2$(cis-l-aamch) shown in Fig. 2 is identical with that of $PtCl_2$(cis-d-aamch).

(I) Synthesis of $Pt(NO_3)_2$(aamch), $PtBr_2$(aamch) and PtI_2-(aamch):

$PtCl_2$(aamch) (3.9424 g) and $AgNO_3$ (3.3974 g) are suspended in water (100 ml) and stirred for a night. The AgCl formed is removed from the solution by filtration and the filtrate is evaporated under reduced pressure to dryness, resulting in $Pt(NO_3)_2$(aamch) which is dissolved in water at an elevated temperature and is then added with an excessive amount of KI or KBr to obtain a desired product coloured in light yellow corresponding to the starting $PtBr_2$(aamch) or a yellow product corresponding to the starting PtI_2(aamch).

The infrared absorption spectra of the thus-obtained $PtBr_2$-(trans-d-aamch), $PtBr_2$(cis-l-aamch), PtI_2(trans-d-aamch) and PtI_2(cis-l-aamch) shown in Figs. 3-6 respectively are identical with the individual infrared spectra of the corresponding optical antipodes. Fig. 7 shows CD spectrum of $Pt(NO_3)_2$(trans-l-aamch) measured at a concentration of 1.788×10^{-2} mol ($\Delta\varepsilon_{323} = +0.025$, $\Delta\varepsilon_{275} = -0.032$). Fig. 8 shows CD spetrum of $Pt(NO_3)_2$(cis-l-aamch) measured at a concentration of 3.721×10^{-2} mol ($\Delta\varepsilon_{355} = +0.020$).

(J) Synthesis of Pt(OX)(aamch), Pt(mal)(aamch) and Pt(gluc)(aamch):

$Pt(NO_3)_2$(aamch) (4.4736 g) and potassium oxalate (1.8424 g) are dissolved in water (10 ml) at an elevated temperature and allowed to stand at ambient temperature to obtain platy crystals of Pt(OX)(aamch) coloured in white.

$Pt(NO_3)_2$(aamch) (4.4736 g) and sodium malonate (1.6604 g) are dissolved in water (10 ml) at an elevated temperature and the solution is concentrated by heating to make up the amount to 5 ml. By allowing the solution to stand at room temperature for a night, white needles of Pt(mal)(aamch) are obtained.

$Pt(NO_3)_2$(aamch) (1.1184 g) and sodium D-glucuronate (0.63049 g) are dissolved in water (5 ml) at an elevated temperature. The solution is allowed to stand at room temperature for a week and is then concentrated under reduced pressure to obtain Pt(gluc)(aamch).

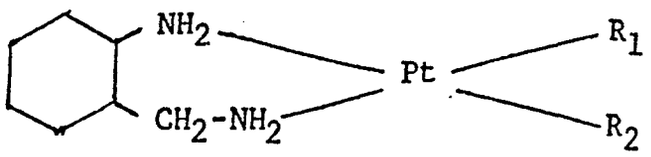
(K) Synthesis of $Pt(OH_2)(SO_4)$(aamch):

$PtCl_2$(aamch) (3.9424 g) and $AgSO_4$ (3.1183 g) are suspended in water (100 ml) and the solution is stirred for a night. After this, the solution is filtered to remove AgCl and the filtrate is concentrated under reduced pressure, followed by addition of acetone to result in white crystals of $Pt(OH_2)(SO_4)$(aamch).

Figs. 9 and 10(1) show respectively the electron spetrum of $Pt(OH_2)(SO_4)$(trans-l-aamch) [measured at a concentration of 1.163×10^{-3} mol by using a quartz cell (length of the optical pass: 1 cm)] and its CD spectrum [measure at a concentration of 1.163×10^{-2} mol; $\Delta\varepsilon_{321}$= + 0.039; $\Delta\varepsilon_{272}$ = - 0.030]. Fig. 10(2) shows the CD spectrum of $Pt(OH_2)(SO_4)$(trans-d-aamch) [measured at a concentration of 2.027×10^{-2} mol; $\Delta\varepsilon_{321}$ = - 0.061; $\Delta\varepsilon_{272}$= + 0.045]. Figs. 11 and 12 show respectively the electron spectrum of $Pt(OH_2)(SO_4)$(cis-l-aamch) [measured at a concentration of 7.86×10^{-4} mol by using a quartz cell (length of the optical pass: 1 cm)] and its CD spectrum [measured at a concentration of 7.86×10^{-3} mol; $\Delta\varepsilon_{340}$= + 0.021; $\Delta\varepsilon_{265}$= + 0.068).

Claims

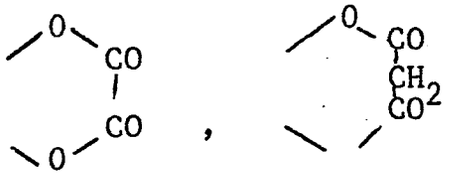
1. A platinum complex of the general formula:



(wherein a) R_1 and R_2 are the same and each represents a halogen atom or NO_3;

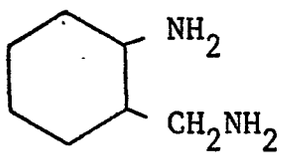
or b) R_1 is SO_4 and R_2 is H_2O;

or c) R_1 and R_2 together represent



or a glucuronate moiety), the configuration of the 1-aminomethyl-2-aminocyclohexane being selected from trans-1, trans-2, cis-1 and cis-d.

2. A process for the preparation of a platinum complex as defined in claim 1 (wherein R_1 and R_2, which are the same, each represents a halogen atom) which comprises reacting a compound of the formula:-



II

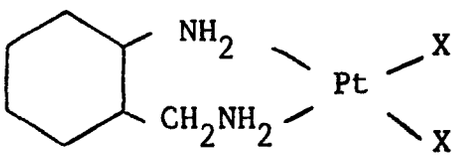
with a compound of the formula:-

$$M^{n\oplus}[Pt\ X_4]^{\ominus}_n \qquad \text{III}$$

(wherein X represents a halogen atom, M represents a stabilising metal cation and n is the charge on the

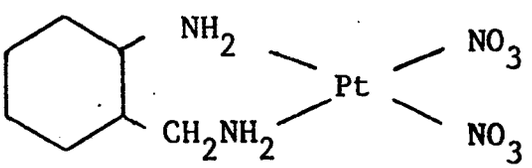
cation).

3. A process for the preparation of a platinum complex as defined in claim 1 (wherein R_1 and R_2, which are the same, each represent a group NO_3), which comprises reacting a platinum complex of the formula:-



IV

(wherein X represents a halogen atom) with a compound of the formula $B(NO_3)_n$ (in which n represents the charge on B and B is a cation whose halide is insoluble in water) whereby a platinum complex of the formula:-



V

is obtained).

4. A process for the preparation of a platinum complex as defined in claim 1 (wherein R_1 and R_2, which are the same, each represent a bromine or iodine atom or R_1 and R_2 together form an oxalate, malonate or glucuronate moiety) which process comprises reacting a compound of formula V (as defined in claim 3) with a

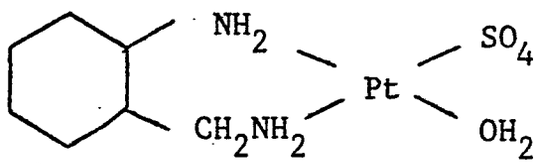
compound of the formula:-

MX_n or $M_2(R_1R_2)_n$

(VII) (VIII)

(wherein X represents a bromide or iodide anion, M represents a stabilising metal cation, n represents the charge on the cation and R_1 and R_2 are as defined in claim 1) whereby a platinum complex of formula I is obtained.

5. A process for the preparation of a platinum complex as defined in claim 1 (wherein R_1 is SO_4 and R_2 is H_2O) which process comprises reacting a compound of formula IV with a compound of the formula:- $B_2(SO_4)_n$ (wherein B and n are as defined in claim 3) whereby a compound of the formula:-



VI

is obtained.

6. A process as claimed in claim 2 or claim 4 wherein a compound III, VII or VIII is used in which M represents an alkali metal.

7. A process as claimed in claim 6 wherein M represents sodium or potassium.

8. A process as claimed in any one of claims 2, 4, 6 and 7 wherein X represents chlorine.

9. A process as claimed in claim 3 or claim 5 wherein B represents a silver cation.

10. A pharmaceutical composition comprising as active ingredient at least one platinum complex as defined in claim 1 in association with a pharmaceutical carrier or excipient.

11. A platinum complex as defined in claim 1 when used as a medicament.

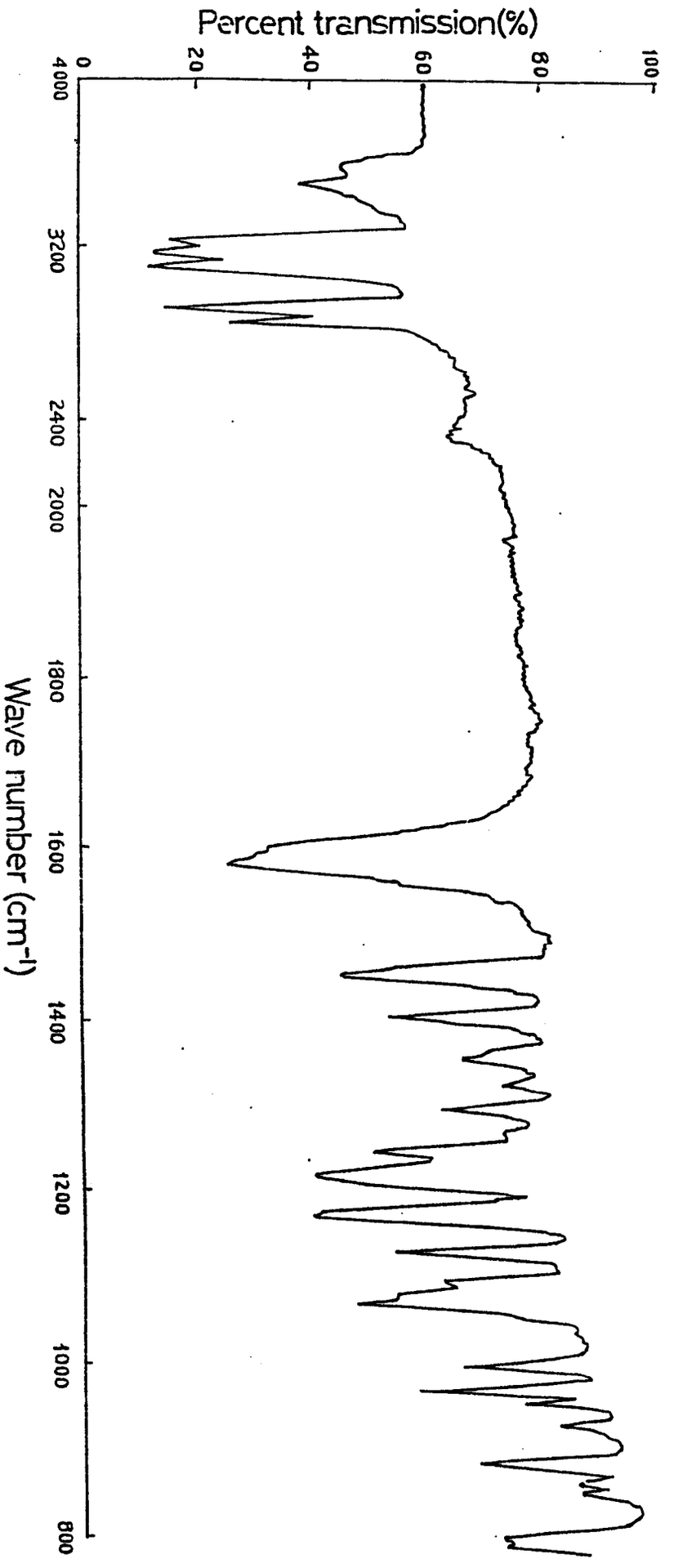

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FIG. 1

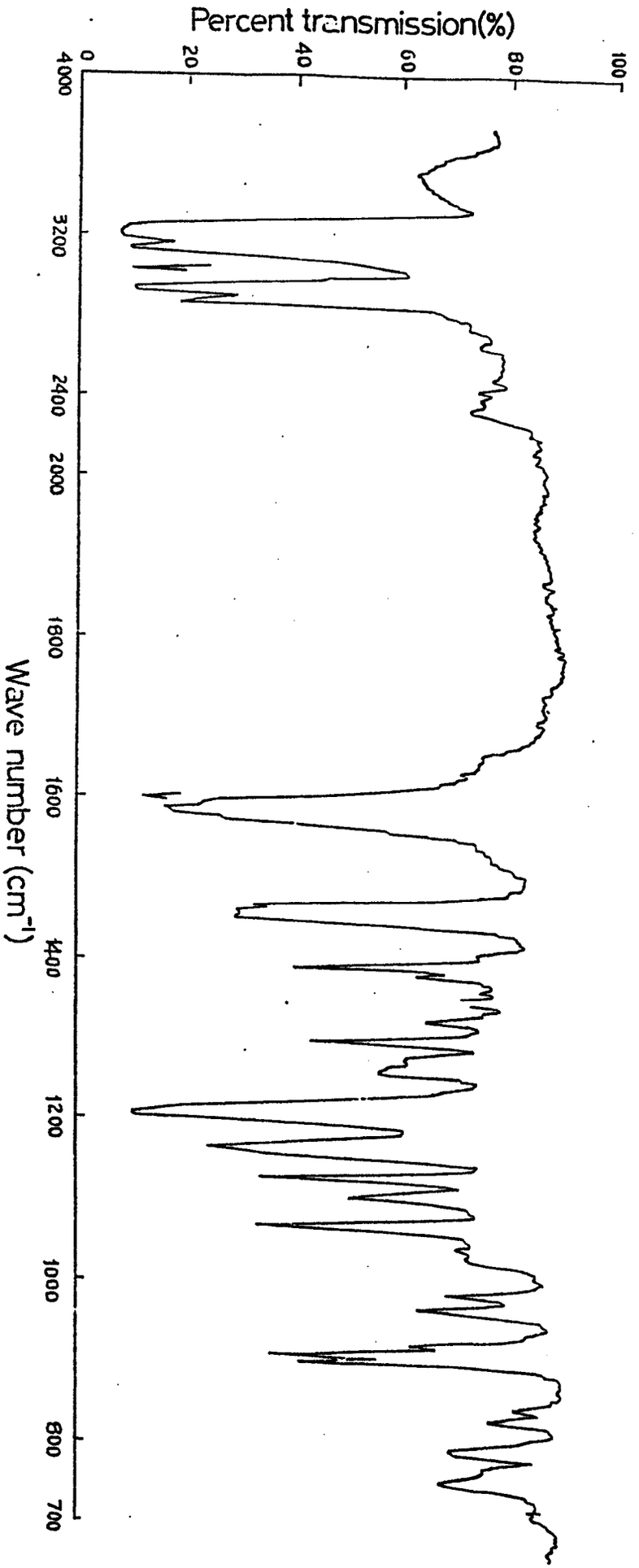
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FIG. 2

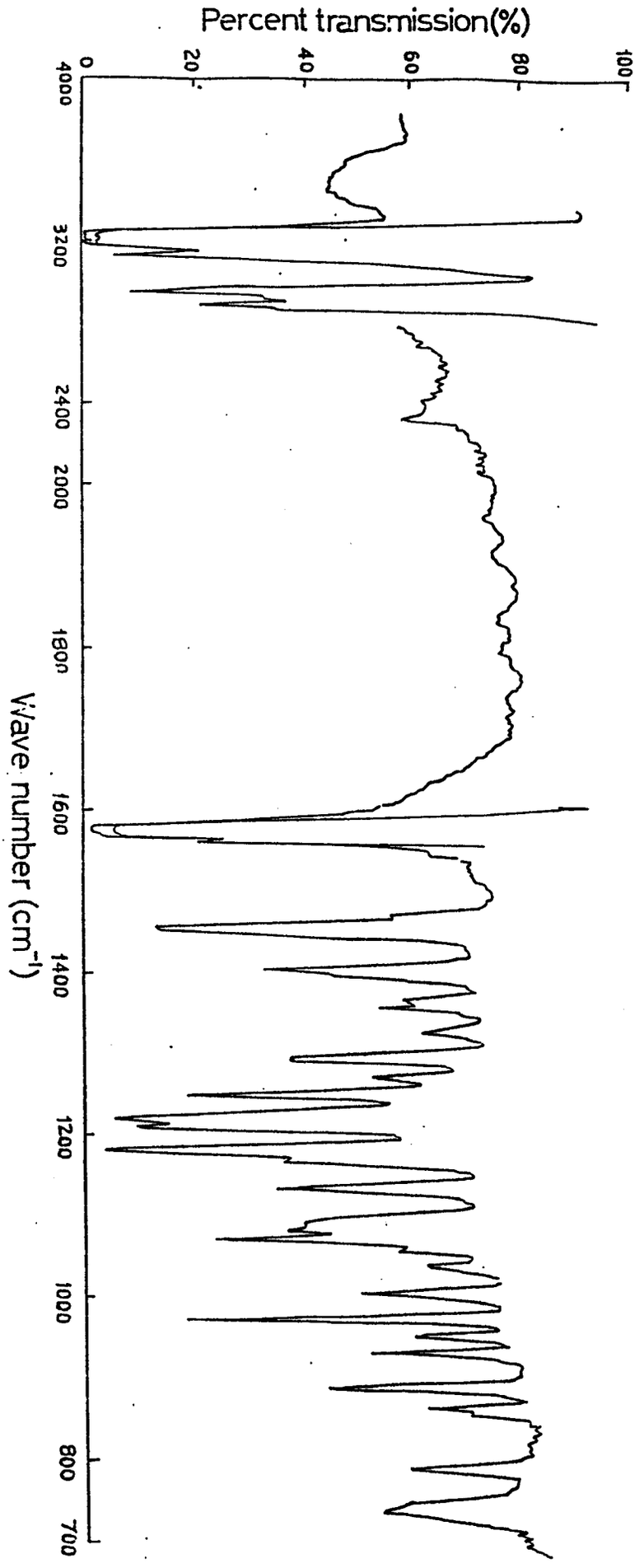
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FIG. 3

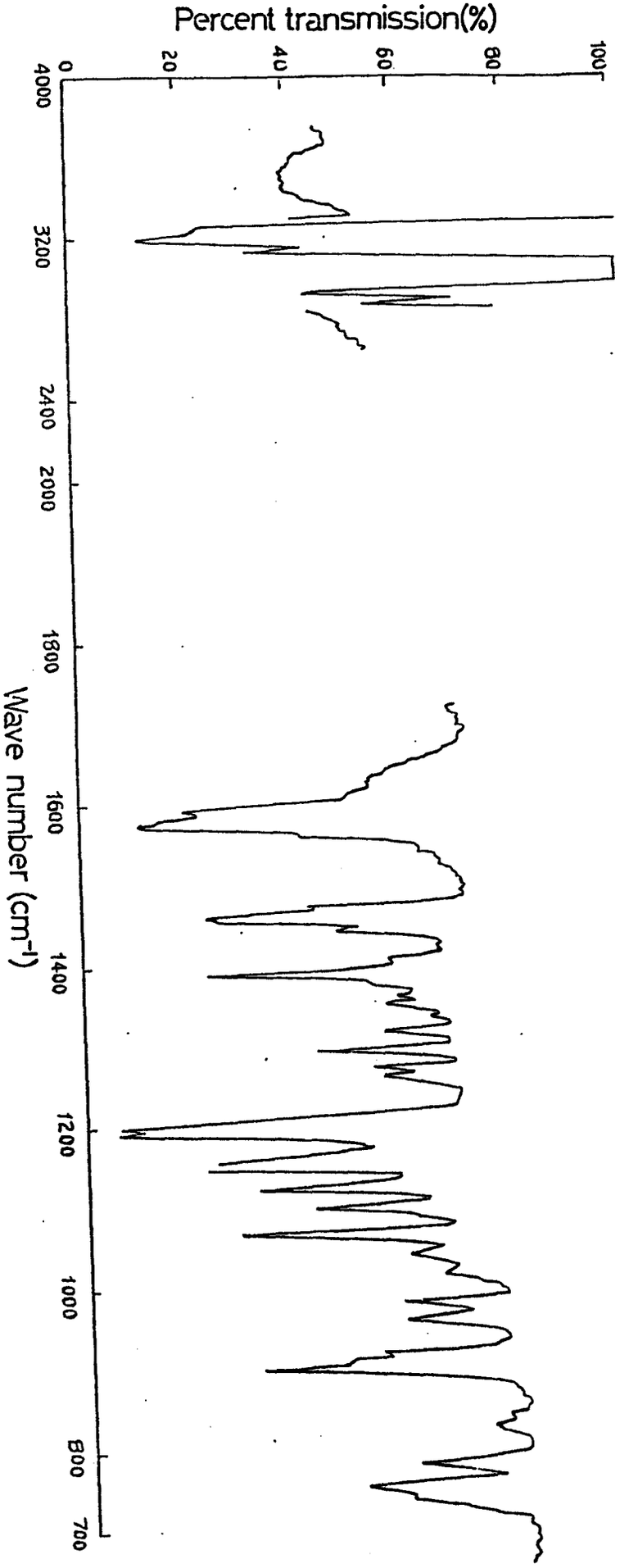
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FIG. 4

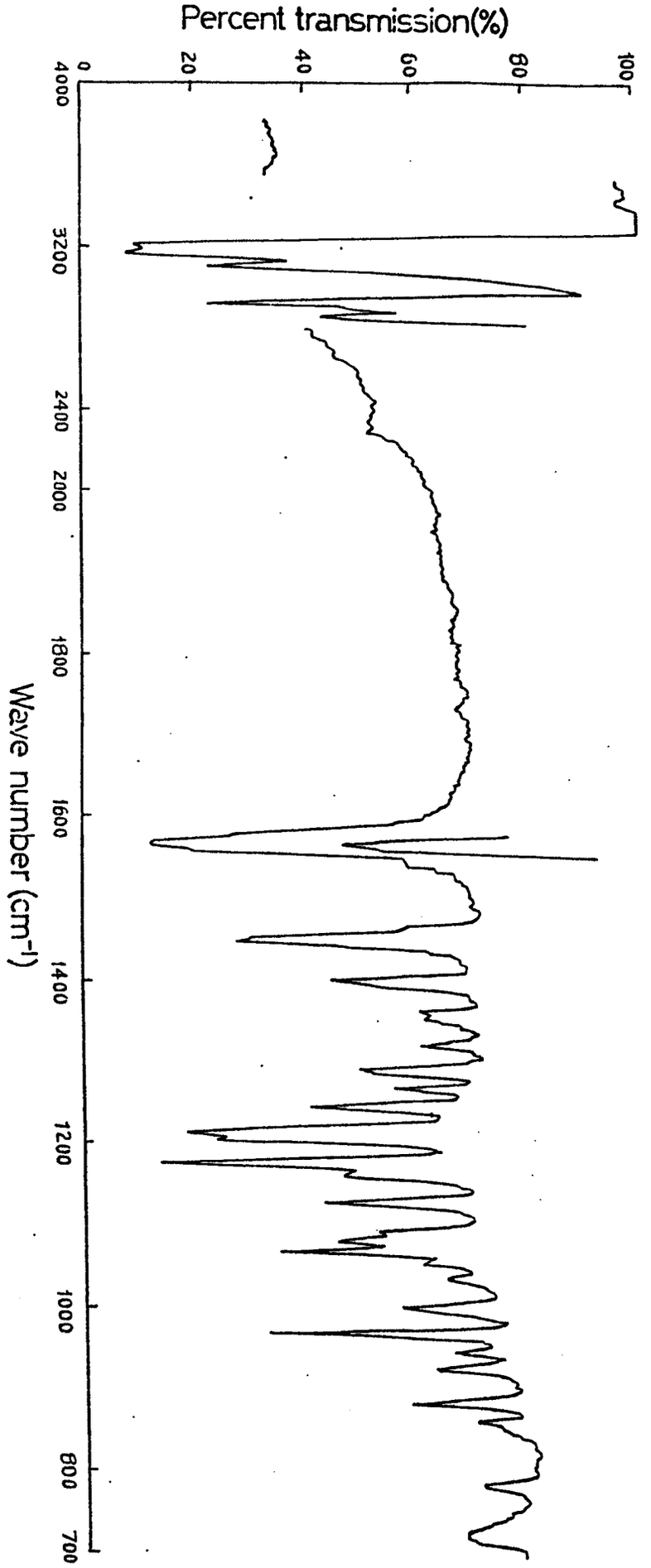
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FIG. 5

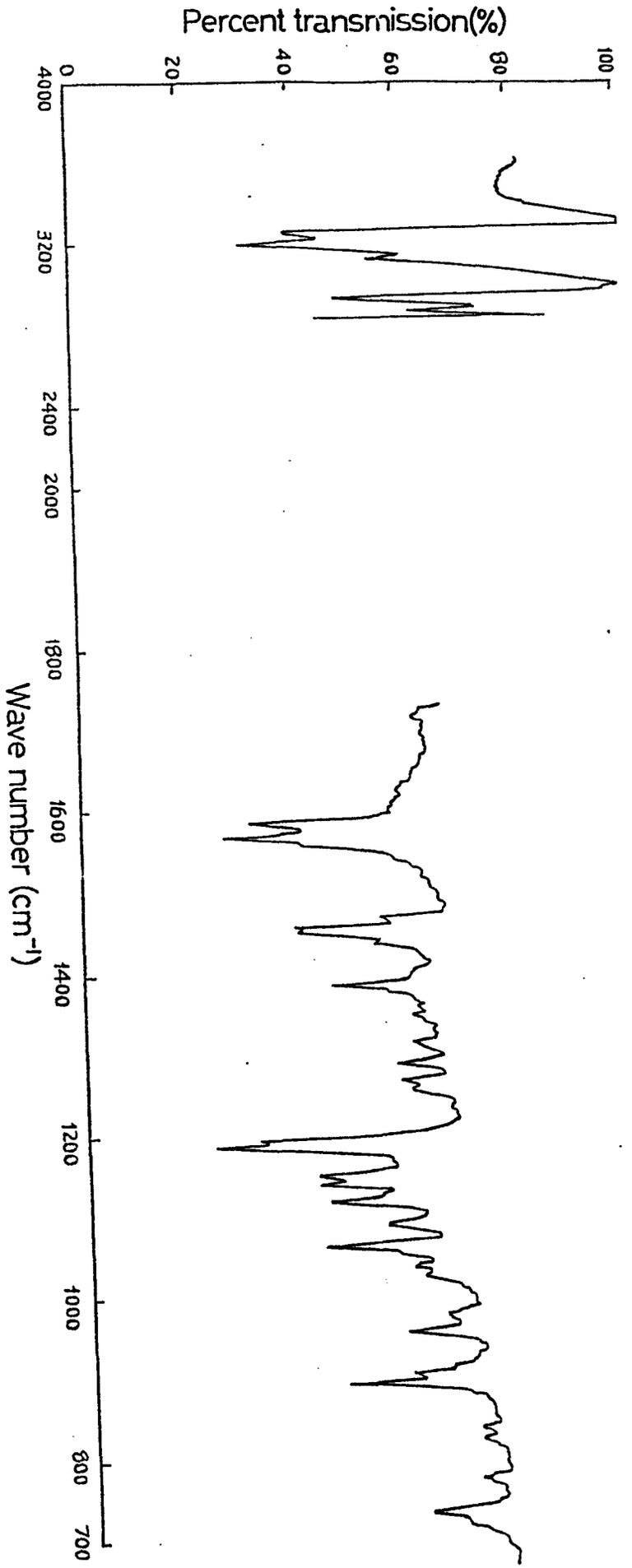
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FIG. 6

FIG. 7

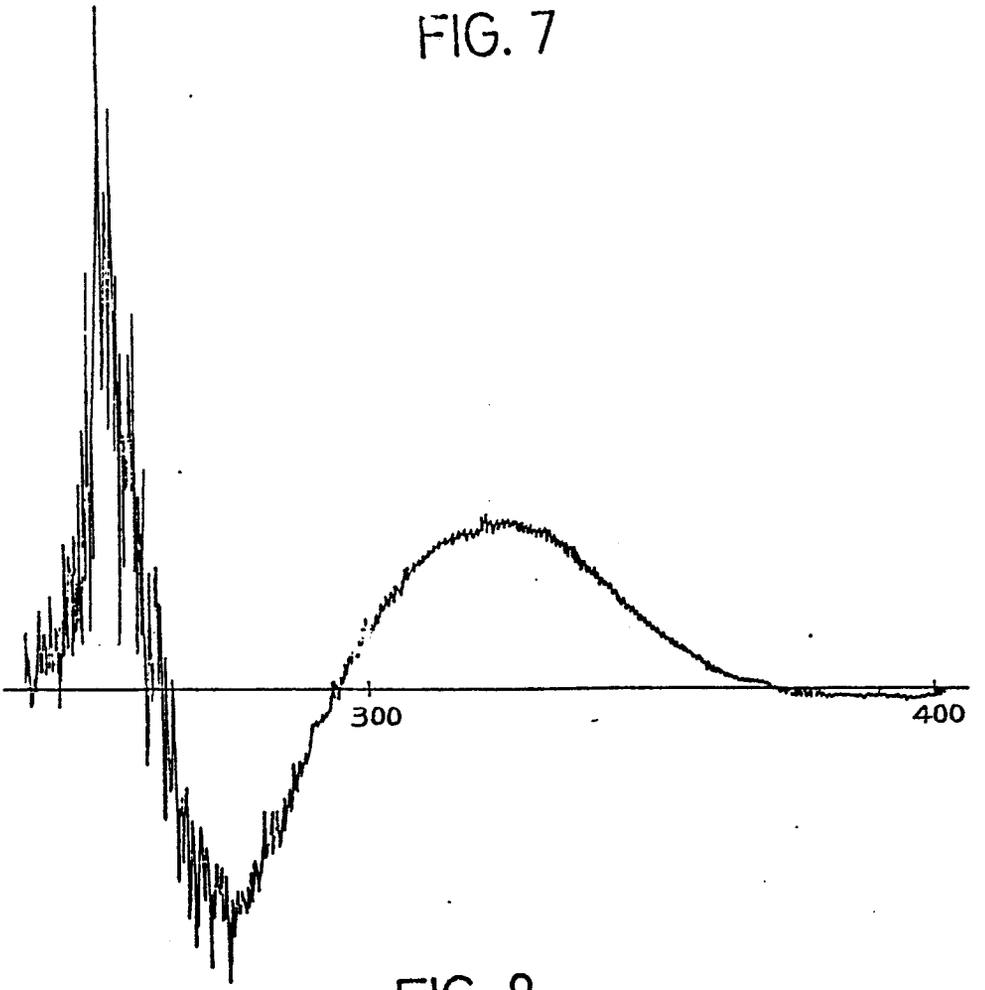
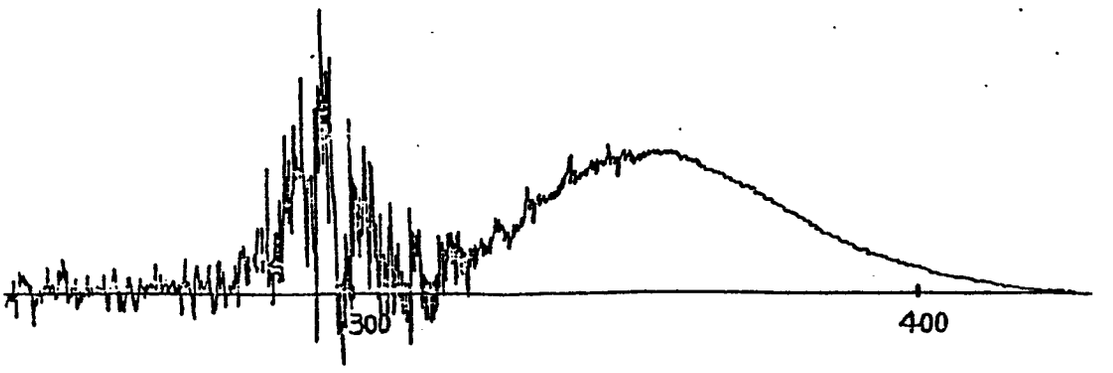


FIG. 8



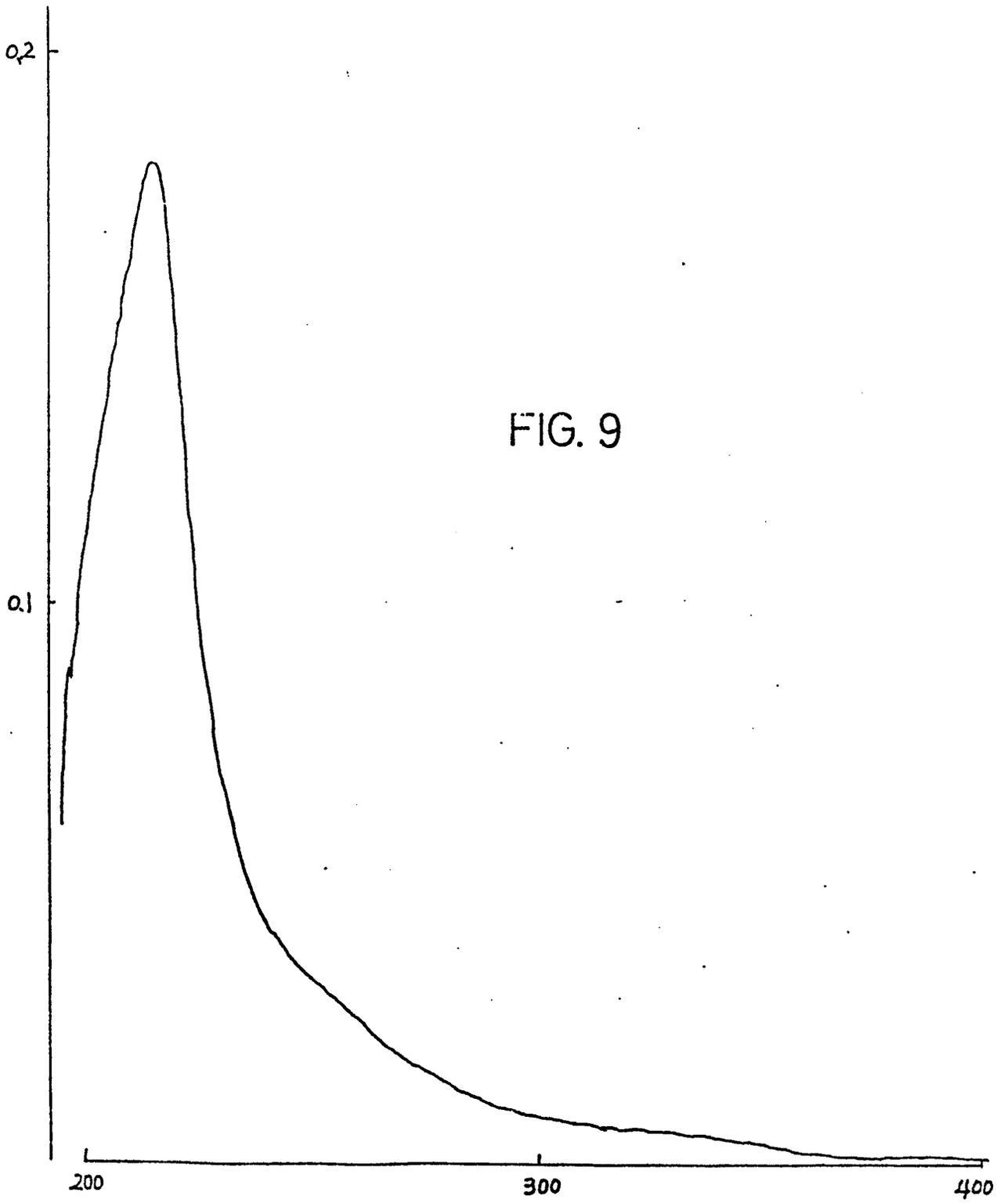


FIG. 9

FIG. 10

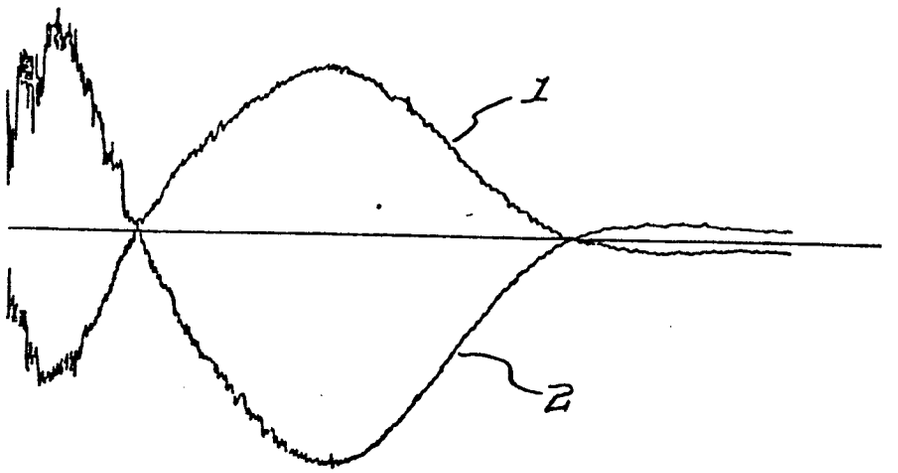
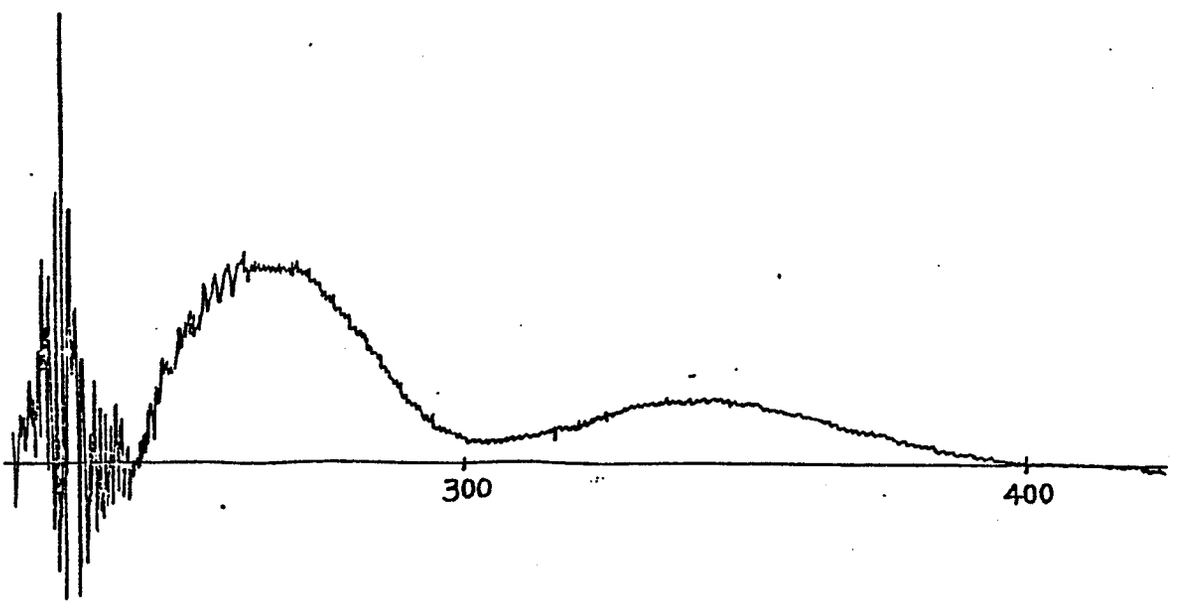


FIG. 12



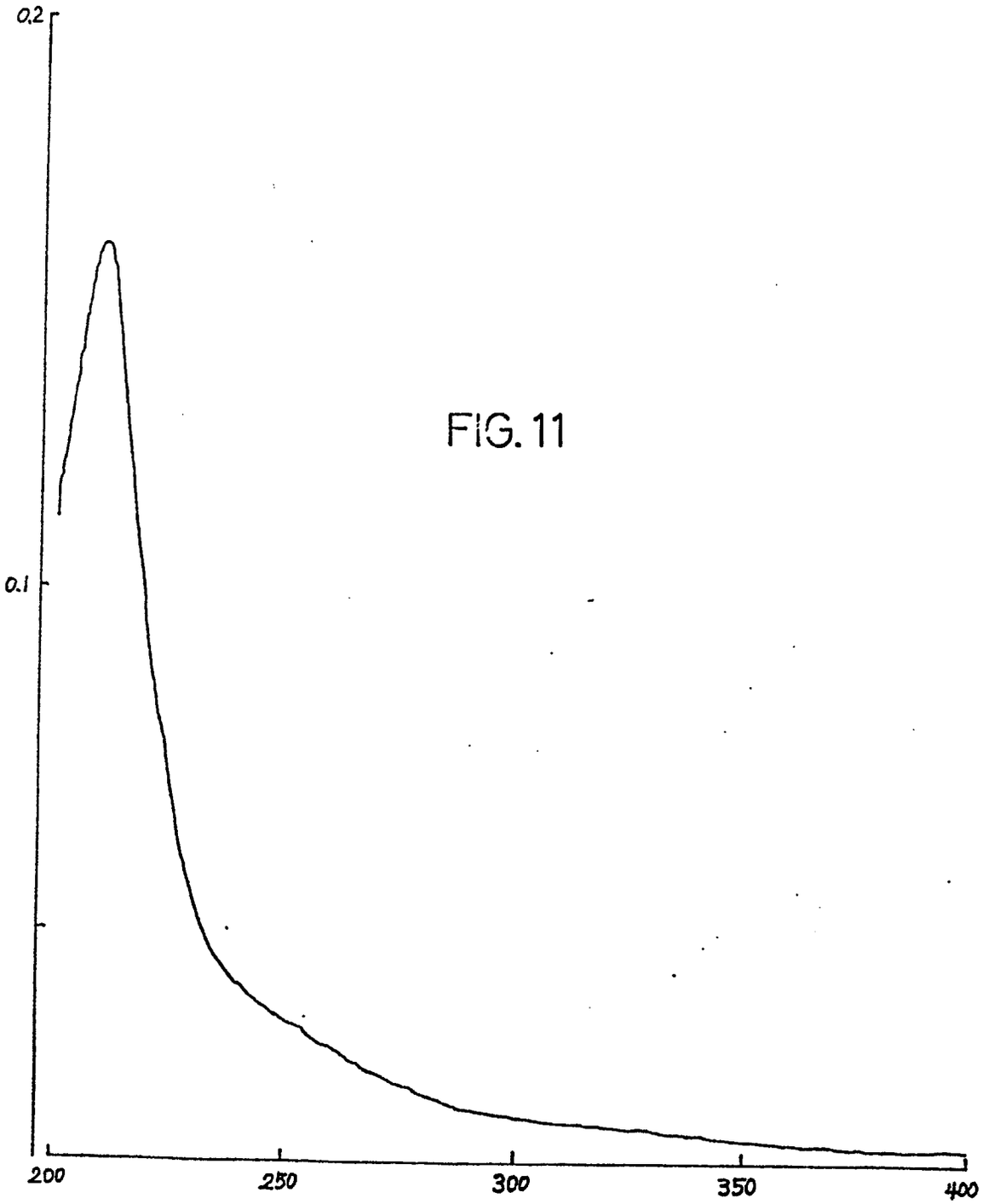


FIG. 11

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application number EP 79 30 1803

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	14(2), 117-125 (Eng.) * Abstract * -- CHEMICAL ABSTRACTS, Chemical Substance Index, vol. 87, July-December 1977, page 1766, Columbus, Ohio, U.S.A. * Second and third column * --		
P,D	US - A - 4 115 418 (G.R. GALE and S.J. MEISCHEN) * Claim; columns 2-3 * ----	1,10-11	TECHNICAL FIELDS SEARCHED (Int. Cl.³)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number 0008936

EP 79 30 1803

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
	FR - A - 2 187 345 (RESEARCH CORPORATION) * Claims 1,9 * & GB - A - 1 380 228 --	1,10, 11
	CHEMICAL ABSTRACTS, vol. 84, no.9, 1st March 1976, page 44, no. 54030n Columbus, Ohio, U.S.A. R.J. SPEER et al.: "Malonato-1,2-diaminocyclohexaneplatinum(II), a potential antitumor agent" & WADLEY MED. BULL. 1975, 5(4), 335-348 (Eng.) * Abstract * --	1,10, 11
	CHEMICAL ABSTRACTS, vol. 87, no. 19, 7th November 1977, page 14, no. 145547q Columbus, Ohio, U.S.A. Z. SIMON et al.: "Quantitative structure-antitumor activity relations for complex platinum (II) compounds with amine ligands" & REV. ROUM. BIOCHIM. 1977 ./.	1,10, 11

CLASSIFICATION OF THE APPLICATION (Int Cl.)

C 07 F 15/00 // C 07 C 87/36

TECHNICAL FIELDS SEARCHED (Int Cl.)

C 07 F 15/00
C 07 C 87/36

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-10

Claims searched incompletely:

Claims not searched: 11

Reason for the limitation of the search: Method for treatment of the human or animal body by surgery or therapy (See article 52(4) of the European Patent Convention).

CATEGORY OF CITED DOCUMENTS

- X. particularly relevant
- A. technological background
- O. non-written disclosure
- P. intermediate document
- T. theory or principle underlying the invention
- E. conflicting application
- D. document cited in the application
- L. citation for other reasons

&. member of the same patent family, corresponding document

Place of search	Date of completion of the search	Examiner
The Hague	29-11-1979	MOREAU