Synthesis and antitumor activity of water-soluble 2-benzyl-1,2-diaminobutane-α-oxycarboxylatoplatinum(II) complexes

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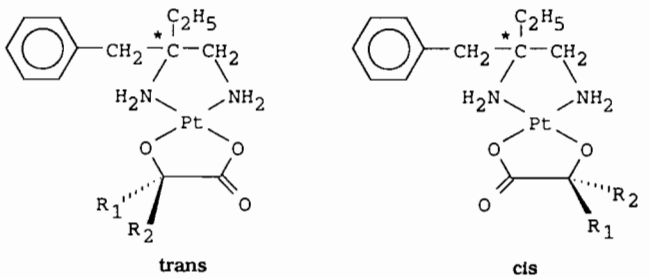
Abstract

Nine new water-soluble platinum(II) complexes were synthesized and characterized. *Racemic* (±)-2-benzyl-1,2-diaminobutane or the corresponding enantiomers (+)-2-benzyl-1,2-diaminobutane and (−)-2-benzyl-1,2-diaminobutane were used as nitrogen chelate ligands. The chloride leaving groups of the resulting *N,N'*-2-benzyl-1,2-diaminobutanedichloroplatinum(II) complexes were replaced by the anions of four α-hydroxycarboxylic acids to increase the water solubility. As α-hydroxycarboxylic acids, lactic acid, glycolic acid, mandelic acid and α-hydroxyisobutyric acid were used. For *N,N'*-2-benzyl-1,2-diaminobutane-*O,O'*-lactatoplatinum(II), the different geometrical and optical isomers were separated. The antitumor activity of the platinum(II) complexes was examined *in vitro* towards the MDA-MB 231 breast cancer cell line and *in vivo* towards the P 388 leukemia of the CD_2F_1 mouse. Contrary to the insoluble dichloro complexes, the α-oxycarboxylatoplatinum(II) complexes exhibited good water solubility associated with a high antitumor activity.

Introduction

In a previous paper we reported the synthesis and the high antitumor activity towards P 388 leukemia of *N,N'*-(±)-2-benzyl-1,2-diaminobutanedichloroplatinum(II) [1]. The antitumor activity is accompanied by a low toxicity compared to *cis*-platinum [2]. However, in view of the application, the solubility in water has to be increased. It is known, that α-oxycarboxylate ligands render diamineplatinum complexes water soluble [3–5]. Therefore in the present study, the anions of lactic acid, glycolic acid, mandelic acid and α-hydroxyisobutyric acid were used as leaving groups in *N,N'*-(±)-2-benzyl-1,2-diaminobutaneplatinum(II) complexes [6]. For the lactate derivatives, the different isomers **1–6** were synthesized and separated (Scheme 1), respectively. The antitumor activity of the water-soluble platinum(II) compounds **1–9** towards the MDA-MB 231 mammary tumor and the P 388 leukemia is reported in the present paper.



trans cis

	Coordination of α-hydroxycarboxylate	R_1	R_2	2-Benzyl-1,2-diaminobutane
1	*cis*	H	CH_3	(±)
2	*trans*	H	CH_3	(±)
3	*cis*	H	CH_3	(−)
4	*trans*	H	CH_3	(−)
5	*cis*	H	CH_3	(+)
6	*trans*	H	CH_3	(+)
7	*cis/trans*	H	H	(±)
8	*cis/trans*	H	Ph	(±)
9	*cis/trans*	CH_3	CH_3	(±)

Scheme 1.

Synthesis of ligands and complexes

Starting from benzylethylketone, (±)-2-benzyl-1,2-diaminobutane is synthesized. The ketone is converted to (±)-2-amino-2-benzyl-1-butanenitrile in a Strecker-type reaction [7, 8]. The aminonitrile is reduced to (±)-2-benzyl-1,2-diaminobutane with $LiAlH_4$ and the product is purified by distillation.

The optically pure diamines (+)- and (−)-2-benzyl-1,2-diaminobutane are obtained by fractional crystallization, using (+)- or (−)-dibenzoyltartaric acid.

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Racemic (±)-2-benzyl-1,2-diaminobutane and the corresponding enantiomers are used as ligands to prepare the dichloroplatinum(II) complexes by reaction with K_2PtCl_4 [9, 10]. For the preparation of the complexes, water serves as the solvent. The pH is kept constant at 6 during the reaction by adjustment with 1 N NaOH. The complexes precipitate after some time as yellow solids.

In order to exchange the chloride ligands for α-oxycarboxylate, the diaminediaquaplatinum(II)–dinitrate complexes have to be prepared. This is achieved by treatment of an aqueous suspension of the corresponding dichloro complex with an equivalent amount of an aqueous $AgNO_3$ solution. The resulting solution is filtered off from the precipitated AgCl. To replace the nitrate groups by hydroxy groups, the aqueous solution of the diaminediaquaplatinum(II)–dinitrate is passed through a strongly basic anion exchange resin [11].

The resulting aqueous solution is treated with an equimolar amount of the corresponding α-hydroxycarboxylic acid. To isolate the product, the solvent is evaporated completely, the residue is dissolved in methanol and precipitated with ether to give the colorless complexes. The *cis*- and *trans*-isomers **1–6** of the lactate complexes are obtained after passing the crude product, dissolved in methanol, through a silica gel chromatography column. The *cis*- and *trans*-isomers of the compounds **7–9** cannot be separated by the same technique.

Antitumor tests

The cytotoxic effects of the water-soluble complexes **1–9** were examined *in vitro* using the MDA-MB 231 mammary tumor. The antitumor activity of the compounds **1**, **2** and **7–9** was also investigated *in vivo* towards the P 388 leukemia of the CD_2F_1 mouse.

The tumor-inhibiting effect of the platinum complexes **1–9** was tested towards the MDA-MB 231 breast cancer cell line [12], which was derived from the pleural effusion of a patient with a poorly differentiated papillary carcinoma [13].

The MDA-MB 231 cells are grown in a humified incubator in a 5% CO_2 atmosphere at 37 °C. Richter's medium, supplemented with 10% NCS (newborn calf serum), is used as a culture medium. The cells are harvested with trypsin/EDTA, diluted in 10% NCS medium. 100 μl of the cell suspension are inoculated into 96-well-plates. Then, the plates are incubated at 37 °C in a humified 5% CO_2 atmosphere to ensure growth of the monolayer. Two days later, the medium is changed and the platinum complexes are added as freshly prepared 1000-fold concentrated solutions in methanol, leading to a final solvent concentration of 0.1%. After an incubation time of 2 days, the cells are fixed for 15 min with 1% glutardialdehyde solution in PBS (phosphate buffered saline, pH 7.4). After this time, the cell nuclei are colored with 0.05% crystal violet solution in deionized water. Afterwards, the cell membranes are destroyed with 75% aqueous ethanol and the cell growth inhibition is monitored by measuring the decreasing optical density of the ethanolic solutions [14]. The absorbance of the colored ethanolic solutions are measured directly with a spectrophotometer (BIO TEK 309-Tecnorama) at 25 °C and 590 nm. Control: methanol in Richter's medium 1:1000. *T/C* (%): (extinction test compound/extinction control) × 100.

The most active compound towards MDA-MB 231 was **7** with a growth inhibition of 87.7% (*T/C* 22.3%, 10^{-5} mol/l, Table 1). However, the activity of the other compounds was only marginally lower. Surprisingly, there was no significant difference in the cytotoxic activity of the isomers **1–6** of *N,N'*-2-benzyl-1,2-diaminobutanelactatoplatinum(II).

The water-soluble complexes **1**, **2** and **7–9** were tested *in vivo* towards the P 388 lymphatic leukemia of the CD_2F_1 mouse [15, 16], which is known to be very sensitive to platinum complexes.

TABLE 1. Cell growth inhibition of MDA-MB 231 cells (*in vitro*) by compounds **1–9**

Compound	Concentration (mol/l) × 10^6	*T/C* (%)
1	10	29.7(±)10.3
	5	56.8(±)9.8
	1	79.9(±)9.9
2	10	35.3(±)11.2
	5	58.6(±)10.8
	1	83.8(±)14.7
3	10	28.3(±)7.8
	5	50.8(±)8.3
	1	80.4(±)11.3
4	10	26.2(±)8.9
	5	50.2(±)7.7
	1	74.5(±)9.8
5	10	30.1(±)6.2
	5	57.3(±)8.9
	1	78.2(±)11.2
6	10	33.9(±)8.9
	5	53.1(±)13.1
	1	73.7(±)14.6
7	10	22.3(±)7.2
	5	48.7(±)9.1
	1	70.1(±)6.8
8	10	39.8(±)10.2
	5	63.7(±)9.7
	1	90.1(±)10.8
9	10	36.2(±)7.2
	5	61.3(±)12.4
	1	87.2(±)14.9

TABLE 2. Antitumor activity towards P 388 leukemia of compounds **1**, **2**, **7**, **8** and **9**

Compound	Concentration (mol/kg)	Weight difference (d5 − d1) (g)	*T/C* (%)
1	4.0×10^{-5}	−0.3	282
2	4.0×10^{-5}	−0.5	188
7	4.0×10^{-5}	−0.4	300
8	4.0×10^{-5}	0.7	268
9	4.0×10^{-5}	0.2	261

In order to determine the antitumor activity, 1.0×10^{6} P 388 leukemia cells, suspended in 0.1 ml of PBS, are implanted intraperitoneally into female CD_2F_1 mice with a body weight of *c.* 18 g. The animals are randomized in groups of six. The therapy starts 24 h after the transplantation (day 1) with an intraperitoneal application of a solution of 4.0×10^{-5} mol/kg body weight of the respective complex, dissolved in distilled water. The therapy is repeated at day 5 and day 9. Animal deaths are recorded daily. Each experiment includes a group with six animals as untreated control and a group with six animals, treated with *cis*-platinum at 1.5 mg/kg as positive control. For the evaluation of the *T/C* value, the median survival time of the treated animals is compared with that of the untreated control animals, which is about 10 days. The *T/C* value (%) = (median survival time of the treated animals/median survival time of the untreated animals) × 100 of the *cis*-platinum group is about 180. In addition to the survival time, the change in the animal's weight from day 1 to day 5 (d5 − d1) is of interest.

All the complexes **1**, **2**, **7**, **8** and **9** were more active than *cis*-platinum, without any toxicity showing up in the body weights of the mice (Table 2). Complex **7** had the highest antitumor activity (*T/C* = 300%). Remarkably, there was a difference in the antitumor activity of the *cis*- and *trans*-isomers **1** and **2** of the lactate complex. The antitumor effect of complex **1** (*cis*-isomer, *T/C* = 282%) was much better than that of complex **2** (*trans*-isomer, *T/C* = 188%).

Experimental

(±)-2-Amino-2-benzyl-1-butanenitrile

5.88 g (0.11 mol) of NH_4Cl are dissolved in 20 ml of water and mixed with 20 ml of conc. NH_3 solution. To this solution first 5.39 g (0.11 mol) of NaCN in 50 ml of water and then 14.8 g (0.10 mol) of benzylethylketone in 20 ml of methanol are added dropwise. The mixture is stirred for 15 h at 50 °C. To isolate the product, the reaction mixture is adjusted to pH = 6 with 1 N HCl and extracted with ether. The aqueous layer is made alkaline with conc. NH_3 solution, and the product is extracted with ether. After drying the ethereal layer over Na_2SO_4 and evaporation of the solvent, the product is obtained and used for the next step without further purification.

Yellow oil, yield 60–64%. IR (film): 3320, 3280 (NH), 3040 (aromat. CH), 2980, 2940 (aliphat. CH), 2020 (CN) cm^{-1}.

(±)-2-Benzyl-1,2-aminobutane

To a suspension of 7.60 g (0.20 mol) of $LiAlH_4$ in 100 ml of anhydrous THF a solution of 8.01 g (0.05 mol) of (±)-2-amino-2-benzyl-1-butanenitrile in 70 ml of THF is added dropwise while cooling the mixture to 0 °C. The reaction mixture is heated at reflux for 15 h. On cooling to 0 °C, 14.4 ml (0.80 mol) of water are added dropwise for hydrolysis with stirring. The solid is filtered off and extracted in a Soxhlet apparatus with 250 ml of THF for 15 h. The extract is combined with the filtrate of the reaction mixture, the solvent is evaporated and the residue is distilled at reduced pressure (10^{-4} torr). A byproduct is distilled off and discarded, before the product is collected.

Colorless oil, b.p. 95 °C (10^{-4} torr), yield 29%. IR (film): 3390, 3300 (NH), 3020 (aromat. CH), 2920, 2860 (aliphat. CH), 1610, 1590 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): 7.33–7.17 (m, 5H, aromat. H), 2.66 (s, 2H, benzyl. H) 2.54 (AB, 2H, ^2J = 13.0 Hz, CH_2N), 1.37 (q, 2H, ^3J = 7.3 Hz, CH_2), 1.15 (m, 4H, NH_2), 0.94 (t, 3H, ^3J = 7.3 Hz, CH_3) ppm.

(−)-2-Benzyl-1,2-diaminobutane and (+)-2-benzyl-1,2-diaminobutane

To a solution of 16.40 g (0.10 mol) of (±)-2-benzyl-1,2-diaminobutane in 250 ml of aqueous ethanol (75% ethanol), 35.80 g (0.10 mol) of (−)-dibenzoyl tartaric acid are added and the mixture is stirred at 70 °C until a colorless solution is obtained. The solution is filtered and slowly cooled to 4 °C. The crystals are filtered off and recrystallized four times from ethanol/water 3:1. Then, the resulting product is dissolved in aqueous NaOH (6%) and extracted with benzene for 24 h in a liquid/liquid extraction apparatus. The organic layer is dried over Na_2SO_4 and the solvent is evaporated. The residue is distilled at 95 °C (10^{-4} torr).

Colorless oil, b.p. 95 °C (10^{-4} torr), yield 11%. $[\alpha]_D^{20}$ −18.0 (*c* = 3, EtOH). IR (film): 3390, 3300 (NH), 3020 (aromat. CH), 2920, 2860 (aliphat. CH), 1610, 1590 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): 7.33–7.17 (m, 5H, aromat. H), 2.66 (s, 2H, benzyl. H), 2.54 (AB, 2H, ^2J = 13.0 Hz, CH_2N), 1.37 (q, 2H, ^3J = 7.3 Hz, CH_2), 1.15 (m, 4H, NH_2), 0.94 (t, 3H, ^3J = 7.3 Hz, CH_3) ppm. ^1H NMR ($CDCl_3$, 250 MHz, 4 equiv. (*S*)-9-anthryl-2,2,2-trifluoroethanol): 2.16, 2.15 (2s, 2H, benzyl. H), 1.94 (AB, 2H, ^2J = 13.5 Hz, CH_2N), 0.93 (q, 2H, ^3J = 7.3 Hz, CH_2), 0.53 (t, 3H, ^3J = 7.3 Hz, CH_3) ppm.

The filtrates of the crystallizations are combined, the solvent is evaporated and the residue is dissolved in aqueous NaOH (6%). After liquid/liquid extraction with benzene for 24 h in an extraction apparatus, the benzene layer is dried over Na_2SO_4 and the solvent is evaporated. The resulting oil is distilled at 95 °C (10^{-4} torr). After addition of 30.43 g (0.85 mol) of (+)-dibenzoyl tartaric acid, the product is obtained via the same recrystallizing and extracting procedure as described before.

Colorless oil, b.p. 95 °C (10^{-4} torr), yield 13%. $[\alpha]_D^{20}$ 17.4 ($c=3$, EtOH). IR (film): 3390, 3300 (NH), 3020 (aromat. CH), 2920, 2860 (aliphat. CH), 1610, 1590 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): 7.33–7.17 (m, 5H, aromat. H), 2.66 (s, 2H, benzyl. H), 2.54 (AB, 2H, $^2J=13.0$ Hz, CH_2N), 1.37 (q, 2H, $^3J=7.3$ Hz, CH_2), 1.15 (m, 4H, NH_2), 0.94 (t, 3H, $^3J=7.3$ Hz, CH_3) ppm. ^1H NMR ($CDCl_3$, 250 MHz, 4 equiv. (*S*)-9-anthryl-2,2,2-trifluoroethanol): 2.20, 2.19 (2s, 2H, benzyl. H). 1.94 (AB, 2H, $^2J=13.5$ Hz, CH_2N), 0.91 (q, 2H, $^3J=7.3$ Hz, CH_2), 0.50 (t, 3H, $^3J=7.3$ Hz, CH_3) ppm.

N,N'-2-Benzyl-1,2-diaminobutanedichloroplatinum(II) compounds

891.5 mg (5.00 mmol) of the corresponding 2-benzyl-1,2-diaminobutane are dissolved in 20 ml of water. The solution is adjusted to pH = 6 using 1 N HCl. 2.08 g (5.00 mmol) of K_2PtCl_4, dissolved in 50 ml of water, are added to the solution. The pH is kept constant by addition of 1 N NaOH. The reaction is finished, if the pH does not change anymore. The complexes precipitate as yellow solids which are filtered off, washed with water and ethanol, and dried.

N,N'-(±)-2-Benzyl-1,2-diaminobutanedichloroplatinum(II)

Yellow solid, m.p. 300 °C (dec.), yield 60%. IR (KBr): 3280, 3200, 3140 (NH), 2960, 2940 (aliphat. CH), 1610, 1580 (NH), 320 (PtCl) cm^{-1}. ^1H NMR (DMF-d_7, 250 MHz): 7.51–7.28 (m, 5H, aromat. H), 5.58, 5.12, 4.80 (3m, 4H, NH_2), 3.27 (AB, 2H, $^2J=13.7$ Hz, benzyl. H), 2.81–2.73 (obscured by solvent peaks, 2H, CH_2N), 1.77 (m, 2H, $^3J=7.5$ Hz, CH_2), 1.09 (t, 3H, $^3J=7.5$ Hz, CH_3) ppm.

Anal. Calc. for $C_{11}H_{18}Cl_2N_2Pt$ (444.3): C, 29.74; H, 4.08; N, 6.31. Found: C, 29.87; H, 3.96; N, 6.42%.

N,N'-(−)-2-Benzyl-1,2-diaminobutanedichloroplatinum(II)

Yellow solid, m.p. 300 °C (dec.), yield 58%. IR (KBr): 3280, 3200, 3140 (NH), 2960, 2940 (aliphat. CH), 1610, 1580 (NH), 320 (PtCl) cm^{-1}. ^1H NMR (DMF-d_7, 250 MHz): 7.51–7.28 (m, 5H, aromat. H), 5.58, 5.12, 4.80 (3m, 4H, NH_2), 3.27 (AB, 2H, $^2J=13.7$ Hz, benzyl. H), 2.81–2.73 (obscured by solvent peaks, 2H, CH_2N), 1.77 (m, 2H, $^3J=7.5$ Hz, CH_2), 1.09 (t, 3H, $^3J=7.5$ Hz, CH_3) ppm.

Anal. Calc. for $C_{11}H_{18}Cl_2N_2Pt$ (444.3): C, 29.74; H, 4.08; N, 6.31. Found: C, 29.93, H, 4.03; N, 6.26%.

N,N'-(+)-2-Benzyl-1,2-diaminobutanedichloroplatinum(II)

Yellow solid, m.p. 300 °C (dec.), yield 60%. IR (KBr): 3280, 3200, 3140 (NH), 2960, 2940 (aliphat. CH), 1610, 1580 (NH), 320 (PtCl) cm^{-1}. ^1H NMR (DMF-d_7, 250 MHz): 7.51–7.28 (m, 5H, aromat. H), 5.58, 5.12, 4.80 (3m, 4H, NH_2), 3.27 (AB, 2H, $^2J=13.7$ Hz, benzyl. H), 2.81–2.73 (obscured by solvent peaks, 2H, CH_2N), 1.77 (m, 2H, $^3J=7.5$ Hz, CH_2), 1.09 (t, 3H, $^3J=7.5$ Hz, CH_3) ppm.

Anal. Calc. for $C_{11}H_{18}Cl_2N_2Pt$ (444.3): C, 29.74; H, 4.08; N, 6.31. Found: C, 29.95; H, 4.00; N, 6.27%.

N,N'-2-Benzyl-1,2-diaminobutane-O,O'-α-oxycarboxylatoplatinum(II) complexes

5.0 mmol of the corresponding *N,N'*-2-benzyl-1,2-diaminobutanedichloroplatinum(II) compound are suspended in 50 ml of water. A solution of 1.9 g (10.0 mmol) of $AgNO_3$ in 10 ml of water is added, and the mixture is stirred, excluding light, at 25 °C for one week. 25 g of a strongly basic anion exchange resin (Merck, Ionenaustauscher III; exchanging capacity 4 mval/g) are filled into a chromatography column and the resin is treated with 100 ml of 2 N NaOH. Then, it is washed with water until the pH of the eluate is 9. The suspension is filtered and the filtrate is passed through the column, dropping into a solution of 5.0 mmol of the corresponding α-hydroxycarboxylic acid in 10 ml of water. To isolate the complex, the water is evaporated completely. The residue is dissolved in 5 ml of methanol. 100 ml of ether are added to this solution, precipitating a colorless solid, which is filtered off. To prevent decomposition, the solid is dried immediately. 100 mg of the lactate complexes are dissolved in 5 ml of methanol, and by passing through a chromatography column (Merck, size B (25×2.5 cm), LiChroprep Si 60 (40–60 μm)) the *cis*- and *trans*-isomers of the complexes are separated.

cis-N,N'-(±)-2-Benzyl-1,2-diaminobutane-O,O'-(S)-lactatoplatinum(II) (1)

Colorless solid, yield 56%. IR (KBr): 3220, 3110 (NH), 3040 (aromat. CH), 2980, 2940 (aliphat. CH), 1740, 1630 (C=O), 375 (PtO) cm^{-1}. ^1H NMR (CD_3OD, 250 MHz): 7.32 (m, 5H, aromat. H), 4.06 (2q, 1H, $^3J=6.9$ Hz, CH), 3.02 (s, 2H, benzyl. H), 2.49 (s, 2H, CH_2N), 1.78, 1.58 (2m, 2H, $^3J=7.5$ Hz, CH_2), 1.32, 1.30 (2d, 3H, $^3J=6.9$ Hz, CH_3), 1.03 (t, 3H, $^3J=7.5$ Hz, CH_3) ppm. HPLC (Merck, RP 18-column, methanol): $t_R=4.9$ min. FAB-MS: $m/z=462$ (MH^+).

Anal. Calc. for $C_{14}H_{22}N_2O_3Pt$ (461.4) ($\cdot H_2O$): C, 35.07; H, 5.06; N, 5.84. Found: C, 34.81; H, 5.18; N, 5.57%.

trans-N,N'-(±)-2-Benzyl-1,2-diaminobutane-O,O'-(S)-lactatoplatinum(II) (2)

Colorless solid, yield 51%. IR (KBr): 3220, 3110 (NH), 3040 (aromat. CH), 2980, 2940 (aliphat. CH), 1740, 1630 (C=O), 375 (PtO) cm^{-1}. ^1H NMR (CD_3OD, 250 MHz): 7.33 (m, 5H, aromat. H), 4.07, 4.06 (2q, 1H, $^3J=6.9$ Hz, CH), 3.02 (m, 2H, benzyl. H), 2.52 (m, 2H, CH_2N), 1.87, 1.58 (2m, 2H, $^3J=7.5$ Hz, CH_2), 1.32, 1.29 (2d, 3H, $^3J=6.9$ Hz, CH_3), 1.06 (t, 3H, $^3J=7.5$ Hz, CH_3) ppm. HPLC (Merck, RP 18-column, methanol): $t_R=5.2$ min. FAB-MS: $m/z=462$ (MH^+).

Anal. Calc. for $C_{14}H_{22}N_2O_3Pt$ (461.4) ($\cdot H_2O$): C, 35.07; H, 5.06; N, 5.84. Found: C, 34.90; H, 5.16; N, 5.61%.

cis-N,N'-(−)-2-Benzyl-1,2-diaminobutane-O,O'-(S)-lactatoplatinum(II) (3)

Colorless solid, yield 46%. IR (KBr): 3220, 3110 (NH), 3040 (aromat. CH), 2980, 2940 (aliphat. CH), 1740, 1630 (C=O), 375 (PtO) cm^{-1}. ^1H NMR (CD_3OD, 250 MHz): 7.33 (m, 5H, aromat. H), 4.08 (q, 1H, $^3J=6.8$ Hz, CH), 3.02 (s, 2H, benzyl. H), 2.49 (s, 2H, CH_2N), 1.78, 1.58 (2m, 2H, $^3J=7.5$ Hz, CH_2), 1.30 (d, 3H, $^3J=6.8$ Hz, CH_3), 1.06 (t, 3H, $^3J=7.5$ Hz, CH_3) ppm.

Anal. Calc. for $C_{14}H_{22}N_2O_3Pt$ (461.4) ($\cdot H_2O$): C, 35.07; H, 5.06; N, 5.84. Found: C, 34.95; H, 5.12; N, 5.54%.

trans-N,N'-(−)-2-Benzyl-1,2-diaminobutane-O,O'-(S)-lactatoplatinum(II) (4)

Colorless solid, yield 52%. IR (KBr): 3220, 3110 (NH), 3040 (aromat. CH), 2980, 2940 (aliphat. CH), 1740, 1630 (C=O), 375 (PtO) cm^{-1}. ^1H NMR (CD_3OD, 250 MHz): 7.33 (m, 5H, aromat. H), 4.06 (q, 1H, $^3J=6.8$ Hz, CH), 3.01 (s, 2H, benzyl. H), 2.49 (AB, 2H, $^2J=12.7$ Hz, CH_2N), 1.84, 1.58 (2m, 2H, $^3J=7.5$ Hz, CH_2), 1.32 (d, 3H, $^3J=6.8$ Hz, CH_3), 1.06 (t, 3H, $^3J=7.5$ Hz, CH_3) ppm.

Anal. Calc. for $C_{14}H_{22}N_2O_3Pt$ (461.4) ($\cdot H_2O$): C, 35.07; H, 5.06; N, 5.84. Found: C, 34.80; H, 5.00; N, 5.43%.

cis-N,N'-(+)-2-Benzyl-1,2-diaminobutane-O,O'-(S)-lactatoplatinum(II) (5)

Colorless solid, yield 48%. IR (KBr): 3220, 3110 (NH), 3040 (aromat. CH), 2980, 2940 (aliphat. CH), 1740, 1630 (C=O), 375 (PtO) cm^{-1}. ^1H NMR (CD_3OD, 250 MHz): 7.33 (m, 5H, aromat. H), 4.07 (q, 1H, $^3J=6.8$ Hz, CH), 3.02 (s, 2H, benzyl. H), 2.49 (2s, 2H, CH_2N), 1.79, 1.58 (2m, 2H, $^3J=7.5$ Hz, CH_2), 1.32 (d, 3H, $^3J=6.8$ Hz, CH_3), 1.06 (t, 3H, $^3J=7.5$ Hz, CH_3) ppm.

Anal. Calc. for $C_{14}H_{22}N_2O_3Pt$ (461.4) ($\cdot H_2O$): C, 35.07; H, 5.06; N, 5.84. Found: C, 35.39; H, 5.14; N, 5.63%.

trans-N,N'-(+)-2-Benzyl-1,2-diaminobutane-O,O'-(S)-lactatoplatinum(II) (6)

Colorless solid, yield 60%. IR (KBr): 3220, 3110 (NH), 3040 (aromat. CH), 2980, 2940 (aliphat. CH), 1740, 1630 (C=O), 375 (PtO) cm^{-1}. ^1H NMR (CD_3OD, 250 MHz): 7.33 (m, 5H, aromat. H), 4.07 (q, 1H, $^3J=6.8$ Hz, CH), 2.99 (AB, 2H, $^2J=14.0$ Hz, benzyl. H), 2.50 (AB, 2H, $^2J=12.7$ Hz, CH_2N), 1.89, 1.57 (2m, 2H, $^3J=7.5$ Hz, CH_2), 1.29 (d, 3H, $^3J=6.8$ Hz, CH_3), 1.06 (t, 3H, $^3J=7.5$ Hz, CH_3) ppm.

Anal. Calc. for $C_{14}H_{22}N_2O_3Pt$ (461.4) ($\cdot H_2O$): C, 35.07; H, 5.06; N, 5.84. Found: C, 34.80; H, 4.87; N, 5.34%.

cis,trans-N,N'-(±)-2-Benzyl-1,2-diaminobutane-O,O'-glycolatoplatinum(II) (7)

Colorless solid, yield 58%. IR (KBr): 3220, 3110 (NH), 3040 (aromat. CH), 2980, 2950 (aliphat. CH), 1640 (C=O), 370 (PtO) cm^{-1}. ^1H NMR (D_2O, 250 MHz): 7.31 (m, 5H, aromat. H), 3.96, 3.92 (2s, 2H, CH_2O), 2.97 (AB, 2H, $^2J=14.0$ Hz, benzyl. H), 2.48 (m, 2H, CH_2N), 1.76, 1.57 (2m, 2H, $^3J=7.5$ Hz, CH_2), 0.96 (t, 3H, $^3J=7.5$ Hz, CH_3) ppm. FAB-MS: $m/z=448$ (MH^+).

Anal. Calc. for $C_{13}H_{20}N_2O_3Pt$ (447.4) ($\cdot H_2O$): C, 33.55; H, 4.77; N, 6.02. Found: C, 33.83; H, 4.80; N, 5.77%.

cis,trans-N,N'-(±)-2-Benzyl-1,2-diaminobutane-O,O'-(S)-mandelatoplatinum(II) (8)

Colorless solid, yield 47%. IR (KBr): 3220, 3100 (NH), 3060, 3040 (aromat. CH), 2980, 2940 (aliphat. CH), 1640 (C=O), 360 (PtO) cm^{-1}. ^1H NMR (CD_3OD, 250 MHz): 7.72, 7.31 (2m, 10H, aromat. H), 4.88–4.86 (1H, obscured by solvent peaks, CH), 3.04 (m, 2H, benzyl. H), 2.47 (m, 2H, CH_2N), 1.79, 1.61 (2m, 2H, $^3J=7.5$ Hz, CH_2), 1.07, 1.06 (2t, 3H, $^3J=7.5$ Hz, CH_3) ppm. HPLC (Merck, RP 18-column, methanol): $t_R=4.8$ (*cis*), 5.6 (*trans*) min. FAB-MS: $m/z=525$ (MH^+).

Anal. Calc. for $C_{19}H_{24}N_2O_3Pt$ (523.5): C, 43.59; H, 4.63; N, 5.35. Found: C, 43.56; H, 4.88; N, 5.49%.

cis,trans-N,N'-(±)-2-Benzyl-1,2-diaminobutane-O,O'-α-oxyisobutyratoplatinum(II) (9)

Colorless solid, yield 62%. IR (KBr): 3220, 3120 (NH), 3040 (aromat. CH), 2980, 2940 (aliphat. CH), 1640 (C=O), 370 (PtO) cm^{-1}. ^1H NMR (CD_3OD, 250 MHz): 7.33 (m, 5H, aromat. H), 3.02 (s, 2H, benzyl. H), 2.50 (m, 2H, CH_2N), 1.79, 1.58 (2m, 2H, $^3J=7.5$ Hz, CH_2) 1.33, 1.30 (2s, 6H, CH_3), 1.06 (t, 3H, $^3J=7.5$ Hz, CH_3) ppm.

Anal. Calc. for $C_{15}H_{24}N_2O_3Pt$ (475.4) ($\cdot H_2O$): C, 36.51; H, 5.32; N, 5.67. Found: C, 36.33; H, 5.46; N, 5.44%.

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