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Bis- and Tris(carboxylato)platinum(IV) Complexes with Mixed Am(m)ine Ligands in the *trans* Position Exhibiting Exceptionally High Cytotoxicity

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A series of seven diam(m)inebis(carboxylato)dihydroxidoplatinum(IV) and eleven diam(m)inetris(carboxylato)hydroxidoplatinum(IV) complexes with am(m)ine ligands in the *trans* position was synthesized and characterized by multinuclear ^{1}H, ^{13}C, ^{15}N, ^{195}Pt NMR spectroscopy. IC_{50} values for all eighteen substances were determined by means of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay for three human cancer cell lines. In cisplatin-sensitive CH1(PA-1) cancer cells, diam(m)inebis(carboxylato)dihydroxidoplatinum(IV) complexes displayed 50% inhibitory concentrations in the micromolar range, whereas for the most lipophilic compounds of the diam(m)inetris(carboxylato)hydroxidoplatinum(IV) series, promising IC_{50} values in the nanomolar range were found.

Introduction

Besides cisplatin, whose antiproliferative properties were discovered in 1965 by Rosenberg,[1] only two more platinum-based agents, namely carboplatin and oxaliplatin (Figure 1), are in worldwide clinical use.[2–5]

The major drawbacks of these platinum-based drugs are (1) dose-limiting severe systemic toxicity and (2) intrinsic or acquired resistance of various tumors. A possible way to reduce side effects is the development of kinetically inert platinum(IV) complexes, being reduced to the more reactive platinum(II) species (prodrug concept, activation by reduction), preferentially in the oxygen-deficient milieu of solid tumors by release of the axial ligands.[6–8] Additionally, octahedrally configured platinum(IV) compounds are accessible for carboxylation at the axially coordinated hydroxido ligands.[9–12] By use of a cyclic anhydride for the carboxylation reaction, a free carboxylic acid moiety is obtained, which can be further derivatized. Following this pathway, series of platinum(IV) complexes have been synthesized in recent years by transferring the peripheral carboxylic acid group into esters or amides.[13–22] It was observed that the antiproliferative potency of these platinum(IV) agents was enhanced with increasing lipophilicity, and for the most lipophilic compounds 50% inhibitory concentrations in the nanomolar range were found.

As enhanced removal of cisplatin-induced DNA adducts has been reported to play a main role in tumor cell resistance in case of platinum-based drugs,[23] the development of agents that bind differently to DNA is believed to be a possible strategy to circumvent resistance. One platinum complex known to possess distinct DNA-binding behavior is transplatin [*SP*-4-1-diamminedichloridoplatinum(II)], which was shown to form mainly 1,3-intrastrand and 1,3-interstrand cross-links with DNA as opposed to the 1,2-intrastrand cross-links mainly formed by cisplatin.[24,25]

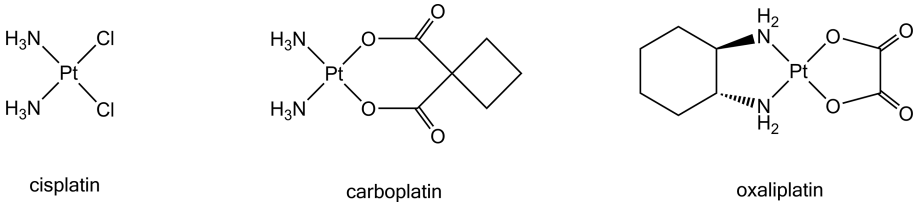

Figure 1. Chemical structures of platinum(II) complexes in worldwide clinical use.

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While transplatin showed no antiproliferative properties,[26] Farrell and co-workers reported that exchange of one ammine ligand with a planar amine yielded *trans*-configured platinum(II) complexes exhibiting IC_{50} values in the micromolar range.[27–29] Subsequently, platinum(II) compounds of *trans* geometry with different kinds of amines (*trans* to the ammine) and their dihydroxido platinum(IV) analogues have been investigated.[30–32] Navarro-Ranninger and co-workers reported on *trans*-configured platinum(II) complexes with mixed amines,[33] and their corresponding dihydroxido platinum(IV) species, which showed IC_{50} values in the micromolar range and exhibited high activity for cisplatin-resistant cell lines.[34–36] An advantage of the dihydroxido platinum(IV) complexes, which showed similar or even higher cytotoxic activity than their platinum(II) counterparts, is the higher water solubility they provide. A strategy to obtain more water soluble *trans*-configured platinum(II) compounds was introduced by Farrell and co-workers, who exchanged chloride ligands with acetato[37,38] or various carboxylato[39–41] ligands, to obtain diam(m)inebis(carboxylato)platinum(II) complexes showing promising IC_{50} values and small resistance factors for cisplatin-resistant cell lines.[42]

The aim of the present work was to combine the possible advantages of *trans*-configured complexes featuring carboxylato ligands with those of platinum(IV) compounds. Here, we report on a series of novel diam(m)inebis- and diam(m)inetris(carboxylato)platinum(IV) complexes with am(m)ine ligands in the *trans* position. The target compounds were characterized in detail by multinuclear NMR spectroscopy and elemental analysis and were evaluated regarding their cytotoxic potential for three human cancer cell lines. Additionally, the rate of reduction of four complexes (two of each kind) in the presence of an excess amount of ascorbic acid was investigated by means of ^{1}H NMR spectroscopy.

Results and Discussion

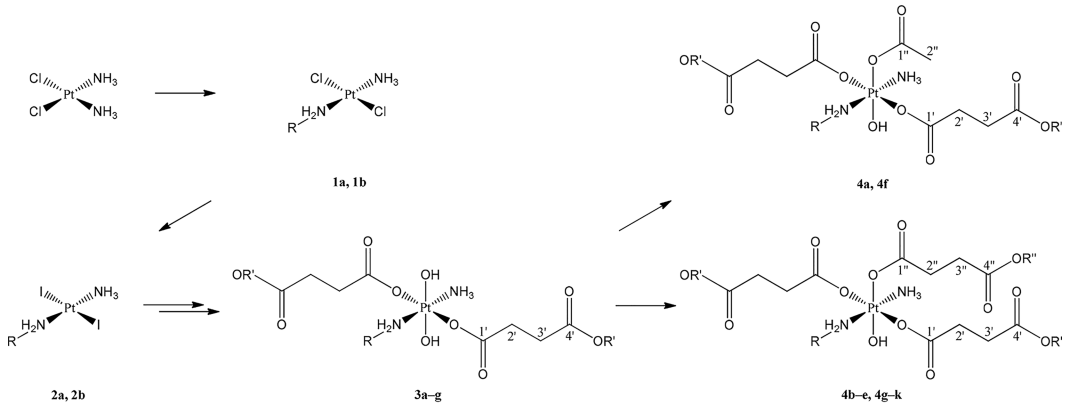
trans-Configured (*SP*-4-1)-ammine(dichlorido)(cyclopentylamine)platinum(II) (**1a**) and (*SP*-4-1)-ammine(dichlorido)(methylamine)platinum(II) (**1b**) were prepared by reaction of (*SP*-4-2)-diammine(dichlorido)platinum(II) with cyclopentylamine and methylamine, respectively, followed by heating under reflux of the tetramine intermediate formed with an excess amount of HCl. Subsequent exchange of the chlorido ligands for iodido ligands was achieved by reaction with potassium iodide in acetone to yield precursors (*SP*-4-1)-ammine(cyclopentylamine)diiodidoplatinum(II) (**2a**) and (*SP*-4-1)-ammine(diiodido)(methylamine)platinum(II) (**2b**) (Figure 2). By reaction of **2a** and **2b** with silver 4-alkoxy-4-oxobutanoates and subsequent oxidation of the bis(carboxylato)platinum(II) intermediates with hydrogen peroxide in water, compounds **3a**–**g** were obtained. The latter were carboxylated with either acetic anhydride or 4-alkoxy-4-oxobutanoic anhydrides, resulting in tris(carboxylato)hydroxidoplatinum(IV) complexes **4a**–**k**.

Using 1.2–1.5 equiv. of anhydride for the carboxylation leads almost exclusively to the formation of tris(carboxylato) species. The tetrakis(carboxylato) complex, which is also obtained in a small amount, is soluble in diethyl ether, unlike the main product, and can therefore be easily removed. Synthesis of the tetrakis(carboxylato) complexes has not been carried out, as (1) the separation is not easy, and, even if the separation were accomplished, (2) the tetrakis(carboxylato) products could only be obtained as an oily residue.

Bis(carboxylato)dihydroxidoplatinum(IV) complexes **3a**–**3g** and tris(carboxylato)hydroxidoplatinum(IV) complexes **4a**–**4k** were characterized by elemental analysis and multinuclear one- and two-dimensional ^{1}H, ^{13}C, and ^{195}Pt NMR spectroscopy; for compounds **4a**–**4k**, ^{15}N NMR chemical shifts were detected additionally by ^{1}H,^{15}N correlation measurements. Complexes **3a**–**3c** and **3e**–**3g** were dissolved in [D_4]MeOH, complex **3d** was dissolved in D_2O, and complexes **4a**–**4k** were dissolved in [D_6]DMSO for the spectroscopic measurements. ^{195}Pt NMR chemical signals of complexes **3a**–**3c** were observed at δ = 3645 ppm; **3d**, which was dissolved in D_2O, showed a ^{195}Pt NMR shift of 3629 ppm, whereas signals of **3e**–**3g** were observed at δ = 3601 ppm. All these signals are indicative of a PtN_2O_2 coordination sphere. ^{195}Pt NMR chemical shifts of complexes **4a**–**4h** (detected between 3790 and 3792 ppm), and those of complexes **4i**–**4k** (observed between 3755 and 3756 ppm) were shifted downfield by around 55 ppm. C=O resonances of C-1′ and C-4′ in **3a**–**3g** were detected at around 182 (182.4–182.9) and 175 (174.9–176.2) ppm. Chemical shifts of carbonyl C-atoms C-1′ and C-4′ as well as C-1′′ and C-4′′ in **4a**–**4k** were observed at around 179 (178.6–179.4) and 172 (172.2–172.9) ppm, whereas the C=O chemical shift of the acetato ligand in **4a** and **4f** was detected at δ = 177.9 ppm. ^{1}H,^{15}N shift correlation signals for coordinated ammonia were found in the range from 6.11 to 6.14 (^{1}H) and from –43.8 to –43.0 ppm (^{15}N) in **4a**–**4k**. For coordinated cyclopentylamine in **4a**–**4h** ^{1}H,^{15}N cross peaks ranging from 6.84 to 6.89 and from –8.8 to –8.1 ppm were observed, whereas coordinated methylamine in **4i**–**4k** showed ^{1}H,^{15}N correlation signals between 6.69 and 6.70 and from –34.2 to –34.1 ppm.

The cytotoxicity of complexes **3a**–**3g** and **4a**–**4k** was investigated by means of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay for three human cancer cell lines representing ovarian teratocarcinoma [CH1(PA-1)], non-small cell lung cancer (A549), and colon carcinoma (SW480) (Table 1).

IC_{50} values of bis(carboxylato)dihydroxidoplatinum(IV) complexes **3a**–**3g** in cisplatin-sensitive CH1(PA-1) cells varied in a wide range from 53 to 0.25 μM, whereas complexes **4a**–**4k** featuring only one hydroxido ligand showed even lower half maximal inhibitory concentrations between 6.5 and 0.016 μM. The majority of IC_{50} values for the intrinsically cisplatin-resistant cell lines A549 and SW480 were at least an order of magnitude higher; in some cases, cytotoxicity was even decreased by a factor of > 100 for A549 cells compared to that for the CH1(PA-1) cell line.



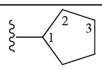
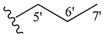
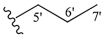
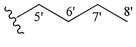
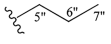
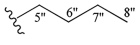
Complex	R	R'	R''
1a, 2a		–	–
1b, 2b		–	–
3a			–
3b			–
3c			–
3d			–
3e			–
3f			–
3g			–
4a			–
4b			
4c			
4d			
4e			
4f			–
4g			
4h			
4i			
4j			
4k			

Figure 2. Synthesis and chemical structures of the bis- and tris(carboxylato)platinum(IV) complexes with NMR numbering schemes.

Table 1. 50% inhibitory concentrations of complexes **3a**–**4k** in CH1(PA-1), A549, and SW480 cancer cells.

Compound	IC_{50} [μM][a]		
	CH1(PA-1)	A549	SW480
3a (58)[b]	3.5 ± 0.2	58 ± 17	25 ± 6
3b	1.7 ± 0.2	61 ± 19	18 ± 2
3c	0.25 ± 0.05	19 ± 2	5.9 ± 1.0
3d (55)[b]	53 ± 7	> 400	175 ± 23
3e	24 ± 4	> 400	136 ± 20
3f	7.3 ± 1.8	207 ± 15	45 ± 8
3g	1.9 ± 0.4	91 ± 17	21 ± 5
4a	0.087 ± 0.021	5.8 ± 0.6	1.4 ± 0.2
4b (17)[b]	0.15 ± 0.01	13 ± 5	1.8 ± 0.4
4c	0.046 ± 0.014	6.1 ± 0.8	0.87 ± 0.23
4d	0.026 ± 0.002	3.3 ± 0.2	0.56 ± 0.11
4e	0.016 ± 0.004	2.0 ± 0.1	0.39 ± 0.05
4f	0.030 ± 0.006	1.9 ± 0.6	0.42 ± 0.11
4g	0.034 ± 0.006	3.4 ± 1.1	0.69 ± 0.19
4h	0.016 ± 0.003	1.2 ± 0.4	0.23 ± 0.08
4i (13)[b]	6.5 ± 0.8	> 200	40 ± 5
4j	0.69 ± 0.14	39 ± 5	4.6 ± 0.4
4k	0.051 ± 0.012	4.9 ± 1.4	0.52 ± 0.14
Cisplatin[43]	0.077 ± 0.006	6.2 ± 1.2	3.3 ± 0.2
Oxaliplatin[44]	0.18 ± 0.01	4.9 ± 0.2	0.52 ± 0.05

[a] 50% inhibitory concentrations in the MTT assay (96 h exposure). Values are means and ± standard deviations obtained from at least three independent experiments. [b] Half-lives of reduction by ascorbic acid in minutes.

Compounds **4e** and **4h** displayed an exceptionally high antiproliferative potential in CH1(PA-1) cells with an IC_{50} value of 0.016 μM, being more active than clinically administered cisplatin (0.077 μM) or oxaliplatin (0.18 μM). Furthermore, both complexes, **4e** and **4h**, showed a cytotoxic potency comparable to oxaliplatin for the intrinsically cisplatin-resistant cell line SW480. Independently from the chosen cancer cells or the axial ligands, complexes featuring a cyclopentylamine ligand were more active than their methylamine analogues. In the same line, an increase in the lipophilicity of the ester moieties in each sub series (**3a**–**3c**, **3d**–**3g**, **4b**–**4e**, **4g**–**4h**, and **4i**–**4k**) resulted in decreased IC_{50} values. Simultaneous variation of both equatorial and axial ligands (as in series **4i**–**4k**) has an even stronger impact on cytotoxic potency than changing the equatorial ligands only (Figure 3).

Consequently, the following conclusions can be drawn on structure–activity relationships: (1) tris(carboxylato)hydroxidoplatinum(IV) complexes display a considerably higher cytotoxicity than their bis(carboxylato)dihydroxidooplatinum(IV) counterparts; (2) cyclopentylamine complexes are more active than analogues featuring a methylamine ligand; and (3) IC_{50} values decrease with increasing lipophilicity of the compounds.

In order to study the rate of reduction of the novel platinum(IV) complexes, compounds **3a**, **3d**, **4b**, and **4i** were incubated with a 25-fold excess amount of ascorbic acid in a D_2O buffered solution (pD = 7.4) and ^1H NMR spectra were recorded until no starting material could be detected anymore (Figure 4). Before addition of ascorbic acid, ^1H NMR spectra were recorded over a period of 24 h in order to check the stability of the complexes; changes in the NMR spectra could generally not be seen. Additionally, the rate of reduction of two platinum(IV) complexes with *cis*-configured ammine ligands, (*OC*-6-44)-acetato(diammine)-hydroxido(malonato)platinum(IV) and (*OC*-6-33)-diammine(malonato)bis[(4-methoxy)-4-oxobutanoato]platinum(IV), was determined in the same manner for comparison.

Complexes **3a** and **3d**, featuring two hydroxido, two carboxylato, and two am(m)ine ligands, showed half-lives of 58 min and 55 min, respectively. For complexes **4b** and

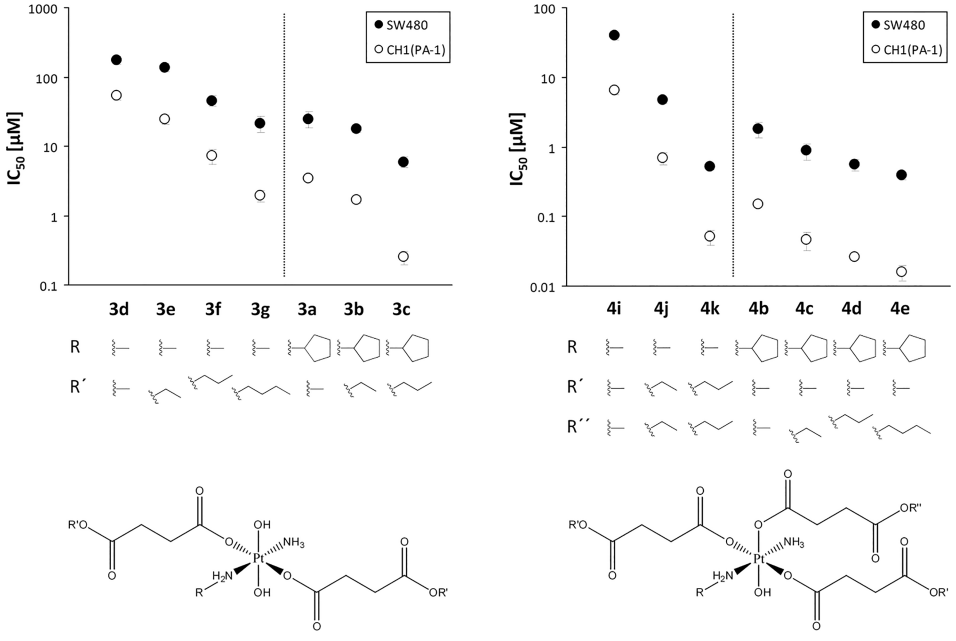


Figure 3. Dependence of IC_{50} values (means ± standard deviations) in CH1(PA-1) and SW480 cells on the variable ligand residues for compound series **3a**–**3c**, **3d**–**3g** (left) and **4b**–**4e**, **4i**–**4k** (right). Note the different logarithmic scales.

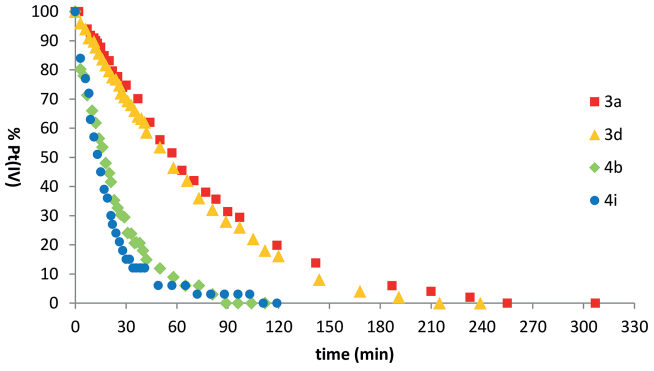


Figure 4. Time-dependent reduction of complexes **3a**, **3d**, **4b**, and **4i** (1 mM) in the presence of ascorbic acid (25 mM) at ambient temperature.

4i, having only one hydroxido, but three carboxylato, and two am(m)ine ligands, half-lives were found to be 17 min and 13 min, respectively.

These values are not unexpectedly low and are in general agreement with the reduction rate of the *cis*-configured monohydroxido complex (*OC*-6-44)-acetato(diammine)-hydroxido(malonato)platinum(IV) with a half-life of 27 min. In contrast, the reduction of a *cis*-configured tetrakis(carboxylato) analogue, (*OC*-6-33)-diammine-(malonato)bis[(4-methoxy)-4-oxobutanoato]platinum(IV), is comparably slow; only 50% of the complex was reduced after 33 h. It seems that the *cis*- or *trans*-configuration of am(m)ine ligands has no significant influence on the reduction rate. The fast reduction of the investigated platinum(IV) complexes featuring one or two hydroxide ligands is in accord with recent findings.[45,46] Gibson and coworkers showed that tris(carboxylato)monohydroxidoplatinum(IV) complexes were reduced significantly faster than the tetracarboxylato species. It is likely that the reduction process (transfer of electrons) is easier via coordinated hydroxide ligands and is hampered by carboxylato ligands. This would also explain why a difference between *cis*- and *trans*-configured complexes was not detected.

Conclusions

A series of 18 diam(m)inebis(carboxylato)dihydroxidoplatinum(IV) and diam(m)inetris(carboxylato)hydroxidoplatinum(IV) complexes with am(m)ine ligands in the *trans* position were synthesized and characterized by one- and two-dimensional NMR spectroscopy, and elemental analysis. The most lipophilic complexes featuring a cyclopentylamine ligand showed the highest cytotoxic activity in vitro. IC_{50} values of complexes **4e** and **4h** in CH1(PA-1) cells were markedly lower than those of clinically established agents cisplatin and oxaliplatin, whereas their activity for the cisplatin-resistant cell line SW480 was comparable to that of oxaliplatin. Therefore, compounds **4e** and **4h** are interesting candidates for further investigations and will be tested for their in vivo behavior in future work.

Experimental Section

All chemicals and solvents were obtained from commercial suppliers and used without further purification. Doubly distilled osmosis water was used for the synthesis, methanol and ethanol were dried according to standard procedures, and column chromatography was carried out with aluminum oxide 90 (Merck). The starting compound, (*SP*-4-2)-diammine(dichlorido)platinum(II), was synthesized by Dhara's method.[47]

^{1}H, ^{13}C, ^{15}N, ^{195}Pt, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, ^{1}H-^{15}N HSQC, and ^{1}H-^{13}C HMBC NMR spectra were recorded with a Bruker Avance III 500 MHz spectrometer at 500.32 (^{1}H), 125.81 (^{13}C), 107.55 (^{195}Pt), and 50.70 MHz (^{15}N) at ambient temperature. Precursors **1a**, **1b**, **2a**, and **2b** were dissolved in [D_6]acetone, complexes **3a**–**c** and **3e**–**g** in [D_4]MeOH, **3d** in D_2O, and **4a**–**k** in [D_6]DMSO for the measurements. For ^{1}H and ^{13}C NMR spectroscopy measurements, the solvent residual peaks were used as internal reference, whereas ^{15}N and ^{195}Pt NMR chemical shifts were referenced relative to external NH_4Cl or K_2PtCl_4. Elemental analyses were carried out by the Microanalytical Laboratory of the University of Vienna using a Carlo Erba EA 1108 CHNS-O or a Perkin–Elmer 2400 CHN elemental analyzer.

General Procedure for Obtaining the Succinic Acid Monoesters (4-Alkoxy-4-oxobutanoic Acids): Succinic anhydride was suspended in an excess amount of an alcohol and stirred at 68 °C under argon overnight; subsequently, the excess amount of alcohol was evaporated by use of an oil pump to yield the respective succinic acid monoester, which was used without further purification.

General Procedure for Preparing the Silver Salts of the Succinic Acid Monoesters (Silver 4-Alkoxy-4-oxobutanoates): The respective succinic acid monoester was dissolved in water (in case of the propyl ester, acetone was added to obtain a clear solution). Silver nitrate (1 equiv.) was added, the solution was stirred for a couple of minutes, and then ammonium hydroxide (1 equiv.) was added, upon which a white product precipitated; the silver 4-alkoxy-4-oxobutanoate was collected by filtration and washed with ethanol and diethyl ether.

General Procedure for Synthesizing the Anhydrides of the Succinic Acid Monoesters (4-Alkoxy-4-oxobutanoic Anhydrides): The respective succinic acid monoester was heated to reflux with an excess amount of acetic acid anhydride under argon overnight to obtain the corresponding succinic acid monoester anhydride; the excess amount of acetic acid anhydride and the acetic acid formed were evaporated by use of an oil pump.

(*SP*-4-1)-Ammine(dichlorido)(cyclopentylamine)platinum(II) (1a): (*SP*-4-2)-Diammine(dichlorido)platinum(II) (2.193 g, 7.31 mmol) was suspended in H_2O (20 mL), cyclopentylamine (2.171 mL, 21.93 mmol) was added, and the suspension was stirred at 40 °C until a clear, almost colorless solution was obtained. Concentrated hydrochloric acid (9 mL, in excess) was added, and the reaction mixture was heated to reflux for 16 h. Upon cooling down, the yellow product precipitated, which was collected by filtration and washed with H_2O and diethyl ether. Yield: 1.996 g, 74%. ^{1}H NMR ([D_6]acetone): δ = 3.99 (br. s, 2 H, NH_2), 3.50 (m, 1 H, 1-H), 3.39 (br. s, 3 H, NH_3), 2.04 (m, 2 H, 2-H/3-H), 1.78 (m, 4 H, 2-H/3-H), 1.59 (m, 2 H, 2-H/3-H) ppm. $C_5H_{14}Cl_2N_2Pt$ (368.18): calcd. C 16.31, H 3.83, N 7.61; found C 16.56, H 3.94, N 7.42.

(*SP*-4-1)-Ammine(dichlorido)(methylamine)platinum(II) (1b): The synthesis was carried out as described for **1a** by using (*SP*-4-2)-diammine(dichlorido)platinum(II) (1.920 g, 6.4 mmol), methylamine (41% solution in H_2O, 2.2 mL, 25.4 mmol), and hydro-

chloric acid (9 mL, in excess). Yellow solid. Yield: 1.512 g, 75%. ^{1}H NMR ([D$_6$]acetone): δ = 4.00 (br. s, 2 H, NH$_2$), 3.39 (br. s, 3 H, NH$_3$), 2.45 [t($^3J_{HH}$ = 6.4 Hz) + d($^3J_{HPt}$ = 32 Hz), 3 H, 1-H] ppm. $CH_8Cl_2N_2Pt$ (314.08): calcd. C 3.82, H 2.57, N 8.92; found C 3.83, H 2.56, N 8.54.

(*SP*-4-1)-Ammine(cyclopentylamine)diiodidoplatinum(II) (2a): (*SP*-4-1)-Ammine(dichlorido)(cyclopentylamine)platinum(II) (1.613 g, 4.38 mmol) was dissolved in acetone (30 mL), and KI (1.819 g, 10.96 mmol) was added. After stirring at room temp. for 4 h, H_2O (30 mL) was added, and the acetone was evaporated to yield the product as an orange solid (suspension in H_2O), which was collected by filtration and washed with H_2O. Yield: 2.341 g, 97%. ^{1}H NMR ([D$_6$]acetone): δ = 4.00 (br. s, 2 H, NH$_2$), 3.68 (m, 1 H, 1-H), 3.48 (br. s, 3 H, NH$_3$), 1.96 (m, 2 H, 2-H/3-H), 1.76 (m, 4 H, 2-H/3-H), 1.59 (m, 2 H, 2-H/3-H) ppm. $C_5H_{14}I_2N_2Pt$ (551.08): calcd. C 10.90, H 2.56, N 5.08; found C 11.13, H 2.62, N 4.81.

(*SP*-4-1)-Ammine(diiodido)(methylamine)platinum(II) (2b): The synthesis was carried out as described for **2a** by using (*SP*-4-1)-ammine(dichlorido)(methylamine)platinum(II) (1.563 g, 4.98 mmol) and KI (2.065 g, 12.44 mmol). Orange solid. Yield: 2.399 g, 97%. ^{1}H NMR ([D$_6$]acetone): δ = 3.99 (br. s, 2 H, NH$_2$), 3.46 (br. s, 3 H, NH$_3$), 2.53 [t($^3J_{HH}$ = 6.4 Hz) + d($^3J_{HPt}$ = 34 Hz), 3 H, 1-H] ppm. $CH_8I_2N_2Pt$ (496.99): calcd. C 2.42, H 1.62, N 5.64; found C 2.46, H 1.53, N 5.37.

(*OC*-6-12)-Ammine(cyclopentylamine)dihydroxidobis[(4-methoxy)-4-oxobutanoato]platinum(IV) (3a): Compound **2a** (533.7 mg, 0.968 mmol) was dissolved in acetone (150 mL), and silver 4-methoxy-4-oxobutanoate (462.9 mg, 1.937 mmol) was added. After 24 h of stirring at 50 °C, the silver iodide formed was filtered off, and the filtrate was concentrated to dryness. H_2O (30 mL) and H_2O_2 (5 mL, 30%) were added to the residue. After 16 h of stirring at room temp., most of the H_2O/H_2O_2 mixture was evaporated, a bit of acetone and then Et_2O were added to precipitate the white product, which was subsequently collected by filtration and purified by column chromatography (CH_2Cl_2/MeOH, 6:1). Yield: 269 mg, 47%. ^{1}H NMR ([D$_4$]MeOH): δ = 3.66 (s, 6 H, 5′-H), 3.44 (m, 1 H, 1-H), 2.67 [t($^3J_{HH}$ = 6.7 Hz), 4 H, 2′-H], 2.58 [t ($^3J_{HH}$ = 6.7 Hz), 4 H, 3′-H], 2.04 (m, 2 H, 2-H), 1.77 (m, 2 H, 3-H), 1.70 (m, 2 H, 2-H), 1.61 (m, 2 H, 3-H) ppm. ^{13}C NMR ([D$_4$]MeOH): δ = 182.9 (C-1′), 175.3 (C-4′), 56.7 (C-1), 52.2 (C-5′), 33.8 (C-2), 32.0 [s + d($^3J_{CPt}$ = 40 Hz), C-2′], 30.7 (C-3′), 25.1 (C-3) ppm. ^{195}Pt NMR ([D$_4$]MeOH): δ = 3645 ppm. $C_{15}H_{30}N_2O_{10}Pt$ (593.50): calcd. C 30.36, H 5.10, N 4.72; found C 30.34, H 4.98, N 4.67.

(*OC*-6-12)-Ammine(cyclopentylamine)bis[(4-ethoxy)-4-oxobutanoato]dihydroxidoplatinum(IV) (3b): The synthesis was carried out as described for **3a** by using **2a** (572 mg, 1.04 mmol) and silver 4-ethoxy-4-oxobutanoate (525 mg, 2.08 mmol). The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 6:1). Yield: 390 mg, 61%. ^{1}H NMR ([D$_4$]MeOH): δ = 4.13 (m, 4 H, 5′-H), 3.44 (m, 1 H, 1-H), 2.67 [t($^3J_{HH}$ = 6.7 Hz), 4 H, 2′-H], 2.57 [t($^3J_{HH}$ = 6.7 Hz), 4 H, 3′-H], 2.04 (m, 2 H, 2-H), 1.77 (m, 2 H, 3-H), 1.70 (m, 2 H, 2-H), 1.61 (m, 2 H, 3-H), 1.25 [t($^3J_{HH}$ = 7.1 Hz), 6 H, 6′-H] ppm. ^{13}C NMR ([D$_4$]MeOH): δ = 182.9 (C-1′), 174.9 (C-4′), 61.7 (C-5′), 56.7 (C-1), 33.8 (C-2), 31.9 [s + d($^3J_{CPt}$ = 40 Hz), C-2′], 30.9 (C-3′), 25.1 (C-3), 14.5 (C-6′) ppm. ^{195}Pt NMR ([D$_4$]MeOH): δ = 3645 ppm. $C_{17}H_{34}N_2O_{10}Pt$ (621.55): calcd. C 32.85, H 5.51, N 4.51; found C 32.77, H 5.48, N 4.32.

(*OC*-6-12)-Ammine(cyclopentylamine)dihydroxidobis[(4-propoxy)-4-oxobutanoato]platinum(IV) (3c): The synthesis was carried out as described for **3a** by using **2a** (406 mg, 0.74 mmol) and silver 4-propoxy-4-oxobutanoate (393 mg, 1.47 mmol). The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 6:1). Yield: 126 mg, 26%. ^{1}H NMR ([D$_4$]MeOH): δ = 4.04 [t($^3J_{HH}$ = 6.7 Hz), 4 H, 5′-H], 3.44 (m, 1 H, 1-H), 2.67 [t ($^3J_{HH}$ = 6.7 Hz), 4 H, 2′-H], 2.58 [t($^3J_{HH}$ = 6.7 Hz), 4 H, 3′-H], 2.04 (m, 2 H, 2-H), 1.77 (m, 2 H, 3-H), 1.70 (m, 2 H, 2-H), 1.66 (m, 4 H, 6′-H), 1.61 (m, 2 H, 3-H), 0.95 [t($^3J_{HH}$ = 7.4 Hz), 6 H, 7′-H] ppm. ^{13}C NMR ([D$_4$]-MeOH): δ = 182.9 (C-1′), 175.0 (C-4′), 67.3 (C-5′), 56.7 (C-1), 33.8 (C-2), 32.0 [s + d($^3J_{CPt}$ = 40 Hz), C-2′], 30.9 (C-3′), 25.1 (C-3), 23.0 (C-6′), 10.7 (C-7′) ppm. ^{195}Pt NMR ([D$_4$]MeOH): δ = 3645 ppm. $C_{19}H_{38}N_2O_{10}Pt$ (649.61): calcd. C 35.13, H 5.90, N 4.31; found C 35.12, H 5.99, N 4.19.

(*OC*-6-12)-Ammine(dihydroxido)bis[(4-methoxy)-4-oxobutanoato]-methylamineplatinum(IV) (3d): The synthesis was carried out as described for **3a** by using **2b** (500 mg, 1.01 mmol) and silver 4-methoxy-4-oxobutanoate (480 mg, 2.01 mmol). The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 6:1). Yield: 284 mg, 52%. ^{1}H NMR (D_2O): δ = 3.73 (s, 6 H, 5′-H), 2.76 [t ($^3J_{HH}$ = 6.5 Hz), 4 H, 2′-H], 2.67 [t ($^3J_{HH}$ = 6.6 Hz), 4 H, 3′-H], 2.25 [s + d($^3J_{HPt}$ = 22.8 Hz), 3 H, 1-H] ppm. ^{13}C NMR (D_2O): δ = 182.4 (C-1′), 176.2 (C-4′), 52.3 (C-5′), 30.4 [s + d($^3J_{CPt}$ = 40 Hz), C-2′], 29.5 (C-3′), 28.5 (C-1) ppm. ^{195}Pt NMR (D_2O): δ = 3629 ppm. $C_{11}H_{24}N_2O_{10}Pt$ (539.41): calcd. C 24.49, H 4.48, N 5.19; found C 24.33, H 4.74, N 5.24.

(*OC*-6-12)-Amminebis[(4-ethoxy)-4-oxobutanoato]dihydroxido-(methylamine)platinum(IV) (3e): The synthesis was carried out as described for **3a** by using **2b** (504 mg, 1.01 mmol) and silver 4-ethoxy-4-oxobutanoate (513 mg, 2.03 mmol). The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 6:1). Yield: 386 mg, 67%. ^{1}H NMR ([D$_4$]MeOH): δ = 4.12 (m, 4 H, 5′-H), 2.67 [t($^3J_{HH}$ = 6.8 Hz), 4 H, 2′-H], 2.58 [t($^3J_{HH}$ = 6.8 Hz), 4 H, 3′-H], 2.24 [s + d($^3J_{HPt}$ = 23.5 Hz), 3 H, 1-H], 1.24 [t($^3J_{HH}$ = 7.1 Hz), 6 H, 6′-H] ppm. ^{13}C NMR ([D$_4$]MeOH): δ = 182.8 (C-1′), 175.0 (C-4′), 61.7 (C-5′), 31.9 (C-2′), 30.9 (C-3′), 29.2 (C-1), 14.5 (C-6′) ppm. ^{195}Pt NMR ([D$_4$]MeOH): δ = 3601 ppm. $C_{13}H_{28}N_2O_{10}Pt$ (567.46): calcd. C 27.52, H 4.97, N 4.94; found C 27.26, H 4.72, N 4.87.

(*OC*-6-12)-Ammine(dihydroxido)methylaminebis[(4-propoxy)-4-oxobutanoato]platinum(IV) (3f): The synthesis was carried out as described for **3a** by using **2b** (757 mg, 1.52 mmol) and silver 4-propoxy-4-oxobutanoate (813 mg, 3.04 mmol). The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 6:1). Yield: 399 mg, 44%. ^{1}H NMR ([D$_4$]MeOH): δ = 4.03 [t($^3J_{HH}$ = 6.7 Hz), 4 H, 5′-H], 2.68 [t ($^3J_{HH}$ = 6.6 Hz), 4 H, 2′-H], 2.59 [t($^3J_{HH}$ = 6.6 Hz), 4 H, 3′-H], 2.24 [s + d($^3J_{HPt}$ = 24.0 Hz), 3 H, 1-H], 1.65 (m, 4 H, 6′-H), 0.95 [t($^3J_{HH}$ = 7.4 Hz), 6 H, 7′-H] ppm. ^{13}C NMR ([D$_4$]MeOH): δ = 182.8 (C-1′), 175.0 (C-4′), 67.3 (C-5′), 31.9 [s + d($^3J_{CPt}$ = 40 Hz), C-2′], 30.9 (C-3′), 29.2 (C-1), 23.0 (C-6′), 10.7 (C-7′) ppm. ^{195}Pt NMR ([D$_4$]MeOH): δ = 3601 ppm. $C_{15}H_{32}N_2O_{10}Pt$ (595.52): calcd. C 30.25, H 5.42, N 4.70; found C 30.37, H 5.39, N 4.66.

(*OC*-6-12)-Amminebis[(4-butoxy)-4-oxobutanoato]dihydroxido-(methylamine)platinum(IV) (3g): The synthesis was carried out as described for **3a** by using **2b** (702 mg, 1.41 mmol) and silver 4-butoxy-4-oxobutanoate (794 mg, 2.83 mmol). The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 6:1). Yield: 314 mg, 36%. ^{1}H NMR ([D$_4$]MeOH): δ = 4.08 [t($^3J_{HH}$ = 6.6 Hz), 4 H, 5′-H], 2.67 [t ($^3J_{HH}$ = 6.7 Hz), 4 H, 2′-H], 2.58 [t($^3J_{HH}$ = 6.6 Hz), 4 H, 3′-H], 2.24 [s + d($^3J_{HPt}$ = 23.6 Hz), 3 H, 1-H], 1.61 (m, 4 H, 6′-H), 1.40 (m, 4 H, 7′-H), 0.95 [t($^3J_{HH}$ = 7.4 Hz), 6 H, 8′-H] ppm. ^{13}C NMR ([D$_4$]MeOH): δ = 182.8 (C-1′), 175.0 (C-4′), 65.5 (C-5′), 31.9 [s + d($^3J_{CPt}$ = 40 Hz, C-2′)], 31.8 (C-6′), 30.9 (C-3′), 29.2 (C-1), 20.2 (C-7′), 14.2 (C-8′) ppm. ^{195}Pt NMR ([D$_4$]-

MeOH): δ = 3601 ppm. $C_{17}H_{36}N_2O_{10}Pt$ (623.57): calcd. C 32.74, H 5.82, N 4.49; found C 32.53, H 5.84, N 4.41.

(*OC*-6-13)-Acetato(ammine)cyclopentylamine(hydroxido)bis[(4-methoxy)-4-oxobutanoato]platinum(IV) (4a): Compound **3a** (60 mg, 0.10 mmol) was suspended in DMF (5 mL), and acetic anhydride (12 μL, 0.13 mmol) was added. After 2.5 h of stirring at room temp., a clear solution was obtained, and DMF was evaporated by use of an oil pump. The residue was suspended in diethyl ether, and the white product was collected by filtration and washed with diethyl ether. Yield: 58 mg, 71%. ^{1}H NMR ([D$_6$]DMSO): δ = 6.88 (br. s, 2 H, NH_2), 6.13 (br. s, 3 H, NH_3), 3.57 (s, 6 H, 5′-H), 3.25 (m, 1 H, 1-H), 2.51 (m, 4 H, 2′-H), 2.46 (m, 4 H, 3′-H), 1.86 (s, 3 H, 2′′-H), 1.85 (m, 2 H, 2-H), 1.64 (m, 4 H, 2-H + 3-H), 1.47 (m, 2 H, 3-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 179.3 (C-1′), 177.9 (C-1′′), 172.7 (C-4′), 54.3 (C-1), 51.2 (C-5′), 31.9 (C-2), 30.5 (C-2′), 29.5 (C-3′), 23.7 (C-2′′), 23.6 (C-3) ppm. ^{15}N NMR ([D$_6$]-DMSO): –8.6 (NH_2), –43.2 (NH_3) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3792 ppm. $C_{17}H_{32}N_2O_{11}Pt$ (635.54): calcd. C 32.13, H 5.08, N 4.41; found C 32.09, H 5.03, N 4.30.

(*OC*-6–21)-Ammine(cyclopentylamine)hydroxidotris[(4-methoxy)-4-oxobutanoato]platinum(IV) (4b): The synthesis was carried out as described for **4a** by using **3a** (152 mg, 0.26 mmol) and 4-methoxy-4-oxobutanoic anhydride (94 mg, 0.38 mmol), with 3 h of stirring. White solid. Yield: 159 mg, 88%. ^{1}H NMR ([D$_6$]DMSO): δ = 6.84 (br. s, 2 H, NH_2), 6.11 (br. s, 3 H, NH_3), 3.57 (s, 6 H, 5′-H), 3.56 (s, 3 H, 5′′-H), 3.24 (m, 1 H, 1-H), 2.49 (m, 4 H, 2′-H), 2.46 (m, 4 H, 3′-H), 2.44 (m, 2 H, 2′′/-H3′′-H), 2.42 (m, 2 H, 2′′/-H3′′-H), 1.85 (m, 2 H, 2-H), 1.64 (m, 4 H, 2-H + 3-H), 1.47 (m, 2 H, 3-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 179.3 (C-1′), 178.8 (C-1′′), 172.8 (C-4′′), 172.7 (C-4′), 54.4 (C-1), 51.2 (C-5′), 51.1 (C-5′′), 31.9 (C-2), 31.3 (C-2′′), 30.6 (C-2′), 29.8 (C-3′′), 29.4 (C-3′), 23.6 (C-3) ppm. ^{15}N NMR ([D$_6$]DMSO): –8.5 (NH_2), –43.0 (NH_3) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3791 ppm. $C_{20}H_{36}N_2O_{13}Pt$ (707.60): calcd. C 33.95, H 5.13, N 3.96; found C 33.86, H 4.74, N 3.92.

(*OC*-6-32)-Ammine(cyclopentylamine)[(4-ethoxy)-4-oxobutanoato]-hydroxidobis[(4-methoxy)-4-oxobutanoato]platinum(IV) (4c): The synthesis was carried out as described for **4a** by using **3a** (50 mg, 0.08 mmol) and 4-ethoxy-4-oxobutanoic anhydride (29 mg, 0.12 mmol), with 2.5 h of stirring. White solid. Yield: 50 mg, 82%. ^{1}H NMR ([D$_6$]DMSO): δ = 6.86 (br. s, 2 H, NH_2), 6.12 (br. s, 3 H, NH_3), 4.02 (m, 4 H, 5′′-H), 3.57 (s, 6 H, 5′-H), 3.24 (m, 1 H, 1-H), 2.49 (m, 4 H, 2′-H), 2.46 (m, 4 H, 3′-H), 2.43 (m, 2 H, 2′′-H/-H3′′-H), 2.41 (m, 2 H, 2′′-H/3′′-H), 1.84 (m, 2 H, 2-H), 1.64 (m, 4 H, 2-H + 3-H), 1.47 (m, 2 H, 3-H), 1.16 [t($^3J_{HH}$ = 7.1 Hz), 3 H, 6′′-H] ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 179.4 (C-1′), 178.9 (C-1′′), 172.7 (C-4′), 172.4 (C-4′′), 59.7 (C-5′′), 54.4 (C-1), 51.3 (C-5′), 31.9 (C-2), 31.3 (C-2′′), 30.6 (C-2′), 30.0 (C-3′′), 29.5 (C-3′), 23.6 (C-3), 14.1 (C-6′′) ppm. ^{15}N NMR ([D$_6$]DMSO): –8.4 (NH_2), –43.1 (NH_3) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3791 ppm. $C_{21}H_{38}N_2O_{13}Pt$ (721.63): calcd. C 34.95, H 5.31, N 3.88; found C 34.93, H 5.27, N 3.86.

(*OC*-6-32)-Ammine(cyclopentylamine)hydroxidobis[(4-methoxy)-4-oxobutanoato][(4-propoxy)-4-oxobutanoato]platinum(IV) (4d): The synthesis was carried out as described for **4a** by using **3a** (50 mg, 0.08 mmol) and 4-propoxy-4-oxobutanoic anhydride (32 mg, 0.12 mmol), with 2.5 h of stirring. White solid. Yield: 43 mg, 73%. ^{1}H NMR ([D$_6$]DMSO): δ = 6.86 (br. s, 2 H, NH_2), 6.14 (br. s, 3 H, NH_3), 3.94 [t($^3J_{HH}$ = 6.7 Hz), 2 H, 5′′-H], 3.57 (s, 6 H, 5′-H), 3.25 (m, 1 H, 1-H), 2.49 (m, 4 H, 2′-H), 2.46 (m, 4 H, 3′-H), 2.44 (m, 2 H, 2′′-H/3′′-H), 2.42 (m, 2 H, 2′′-H/3′′-H), 1.85 (m, 2 H, 2-H), 1.64 (m, 4 H, 2-H + 3-H), 1.57 (m, 2 H, 6′′-H), 1.47 (m, 2 H, 3-H), 0.87 [t($^3J_{HH}$ = 7.4 Hz), 3 H, 7′′-H] ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 179.3 (C-1′), 178.9 (C-1′′), 172.7 (C-4′), 172.4 (C-4′′), 65.2 (C-5′′), 54.4 (C-1), 51.2 (C-5′), 31.9 (C-2), 31.4 (C-2′′), 30.5 (C-2′), 30.0 (C-3′′), 29.4 (C-3′), 23.6 (C-3), 21.5 (C-6′′), 10.2 (C-7′′) ppm. ^{15}N NMR ([D$_6$]DMSO): –8.4 (NH_2), –43.3 (NH_3) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3792 ppm. $C_{22}H_{40}N_2O_{13}Pt$ (735.65): calcd. C 35.92, H 5.48, N 3.81; found C 35.96, H 5.50, N 3.68.

(*OC*-6-32)-Ammine[(4-butoxy)-4-oxobutanoato](cyclopentylamine)-hydroxidobis[(4-methoxy)-4-oxobutanoato]platinum(IV) (4e): The synthesis was carried out as described for **4a** by using **3a** (60 mg, 0.10 mmol) and 4-butoxy-4-oxobutanoic anhydride (42 mg, 0.13 mmol), with 2 h of stirring. White solid. Yield: 57 mg, 76%. ^{1}H NMR ([D$_6$]DMSO): δ = 6.86 (br. s, 2 H, NH_2), 6.13 (br. s, 3 H, NH_3), 3.98 [t($^3J_{HH}$ = 6.7 Hz), 2 H, 5′′-H], 3.57 (s, 6 H, 5′-H), 3.24 (m, 1 H, 1-H), 2.49 (m, 4 H, 2′-H), 2.46 (m, 4 H, 3′-H), 2.43 (m, 2 H, 2′′-H/3′′-H), 2.41 (m, 2 H, 2′′-H/3′′-H), 1.85 (m, 2 H, 2-H), 1.64 (m, 4 H, 2-H + 3-H), 1.53 (m, 2 H, 6′′-H), 1.47 (m, 2 H, 3-H), 1.32 (m, 2 H, 7′′-H), 0.88 [t($^3J_{HH}$ = 7.4 Hz), 3 H, 8′′-H] ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 179.3 (C-1′), 178.9 (C-1′′), 172.7 (C-4′), 172.4 (C-4′′), 63.4 (C-5′′), 54.4 (C-1), 51.2 (C-5′), 31.9 (C-2), 31.3 (C-2′′), 30.5 (C-2′), 30.2 (C-6′′), 30.0 (C-3′′), 29.4 (C-3′), 23.6 (C-3), 18.6 (C-7′′), 13.5 (C-8′′) ppm. ^{15}N NMR ([D$_6$]DMSO): –8.1 (NH_2), –43.2 (NH_3) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3792 ppm. $C_{23}H_{42}N_2O_{13}Pt$ (749.68): calcd. C 36.85, H 5.65, N 3.74; found C 36.76, H 5.36, N 3.72.

(*OC*-6-13)-Acetato(ammine)cyclopentylaminebis[(4-ethoxy)-4-oxobutanoato]hydroxidoplatinum(IV) (4f): The synthesis was carried out as described for **4a** by using **3b** (60 mg, 0.10 mmol) and acetic anhydride (11 μL, 0.12 mmol), with 3 h of stirring. White solid. Yield: 46 mg, 71%. ^{1}H NMR ([D$_6$]DMSO): δ = 6.89 (br. s, 2 H, NH_2), 6.14 (br. s, 3 H, NH_3), 4.04 (m, 4 H, 5′-H), 3.25 (m, 1 H, 1-H), 2.48 (m, 4 H, 2′-H), 2.43 (m, 4 H, 3′-H), 1.86 (s, 3 H, 2′′-H), 1.85 (m, 2 H, 2-H), 1.64 (m, 4 H, 2-H + 3-H), 1.47 (m, 2 H, 3-H), 1.17 [t($^3J_{HH}$ = 7.1 Hz), 6 H, 6′-H] ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 179.4 (C-1′), 177.9 (C-1′′), 172.2 (C-4′), 59.8 (C-5′), 54.3 (C-1), 31.9 (C-2), 30.5 (C-2′), 29.7 (C-3′), 23.7 (C-2′′), 23.6 (C-3), 14.1 (C-6′) ppm. ^{15}N NMR ([D$_6$]DMSO): –8.8 (NH_2), –43.1 (NH_3) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3791 ppm. $C_{19}H_{36}N_2O_{11}Pt$ (663.59): calcd. C 34.39, H 5.47, N 4.22; found C 34.33, H 5.61, N 4.19.

(*OC*-6-13)-Ammine(cyclopentylamine)bis[(4-ethoxy)-4-oxobutanoato]hydroxido[(4-methoxy)-4-oxobutanoato]platinum(IV) (4g): The synthesis was carried out as described for **4a** by using **3b** (50 mg, 0.08 mmol) and 4-methoxy-4-oxobutanoic anhydride (29 mg, 0.12 mmol), with 2 h of stirring. White solid. Yield: 44 mg, 73%. ^{1}H NMR ([D$_6$]DMSO): δ = 6.86 (br. s, 2 H, NH_2), 6.13 (br. s, 3 H, NH_3), 4.04 (m, 4 H, 5′-H), 3.56 (s, 3 H, 5′′-H), 3.25 (m, 1 H, 1-H), 2.49 (m, 4 H, 2′-H), 2.44 (m, 4 H, 3′-H), 2.43 (m, 2 H, 2′′-H/3′′-H), 2.42 (m, 2 H, 2′′-H/3′′-H), 1.85 (m, 2 H, 2-H), 1.64 (m, 4 H, 2-H + 3-H), 1.47 (m, 2 H, 3-H), 1.17 [t($^3J_{HH}$ = 7.1 Hz), 6 H, 6′-H] ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 179.4 (C-1′), 178.9 (C-1′′), 172.8 (C-4′′), 172.2 (C-4′), 59.8 (C-5′′), 54.4 (C-1), 51.1 (C-5′′), 31.9 (C-2), 31.3 (C-2′′), 30.5 (C-2′), 29.8 (C-3′′), 29.6 (C-3′), 23.6 (C-3), 14.0 (C-6′) ppm. ^{15}N NMR ([D$_6$]DMSO): –8.7 (NH_2), –43.2 (NH_3) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3790 ppm. $C_{22}H_{40}N_2O_{13}Pt$ (735.65): calcd. C 35.92, H 5.48, N 3.81; found C 35.85, H 5.62, N 3.77.

(*OC*-6–21)-Ammine(cyclopentylamine)tris[(4-ethoxy)-4-oxobutanoato]hydroxidoplatinum(IV) (4h): The synthesis was carried out as described for **4a** by using **3b** (75 mg, 0.12 mmol) and 4-ethoxy-4-oxobutanoic anhydride (42 mg, 0.15 mmol), with 2 h of stirring. White solid. Yield: 74 mg, 82%. ^{1}H NMR ([D$_6$]DMSO): δ = 6.87 (br. s, 2 H, NH_2), 6.13 (br. s, 3 H, NH_3), 4.03 (m, 4 H, 5′-H), 4.02

(m, 2 H, 5′′-H), 3.25 (m, 1 H, 1-H), 2.49 (m, 4 H, 2′-H), 2.44 (m, 4 H, 3′-H), 2.42 (m, 2 H, 2′′-H/3′′-H), 2.41 (m, 2 H, 2′′-H/3′′-H), 1.84 (m, 2 H, 2-H), 1.64 (m, 4 H, 2-H + 3-H), 1.47 (m, 2 H, 3-H), 1.17 [t($^3J_{HH}$ = 7.1 Hz), 6 H, 6′-H], 1.16 [t($^3J_{HH}$ = 7.1 Hz), 3 H, 6′′-H] ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 179.4 (C-1′), 178.9 (C-1′′), 172.3 (C-4′′), 172.2 (C-4′), 59.8 (C-5′), 59.7 (C-5′′), 54.4 (C-1), 31.9 (C-2), 31.3 (C-2′′), 30.5 (C-2′), 30.0 (C-3′′), 29.6 (C-3′), 23.6 (C-3), 14.0 (C-6′ + C-6′′) ppm. ^{15}N NMR ([D$_6$]DMSO): –8.6 (NH$_2$), –43.0 (NH$_3$) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3790 ppm. $C_{23}H_{42}N_2O_{13}Pt$ (749.68): calcd. C 36.85, H 5.65, N 3.74; found C 36.83, H 5.80, N 3.61.

(*OC*-6–21)-Ammine(hydroxido)tris[(4-methoxy)-4-oxobutanoato]-methylamineplatinum(IV) (4i): Compound **3d** (50 mg, 0.09 mmol) was suspended in $CHCl_3$ (5 mL), and 4-methoxy-4-oxobutanoic anhydride (29 mg, 0.12 mmol) was added. After 72 h of stirring at room temp., a clear solution was obtained, diisopropyl ether was added, and $CHCl_3$ was evaporated to yield a white solid (suspension in diisopropyl ether), which was collected by filtration and washed with diethyl ether. Yield: 54 mg, 89%. ^{1}H NMR ([D$_6$]-DMSO): δ = 6.69 (br. s, 2 H, NH$_2$), 6.14 (br. s, 3 H, NH$_3$), 3.57 (s, 6 H, 5′-H), 3.56 (s, 3 H, 5′′-H), 2.49 (m, 4 H, 2′-H), 2.46 (m, 4 H, 3′-H), 2.44 (m, 2 H, 2′′-H/3′′-H), 2.42 (m, 2 H, 2′′-H/3′′-H), 2.02 [t($^3J_{HH}$ = 6.2 Hz), 3 H, 1-H] ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 179.1 (C-1′), 178.6 (C-1′′), 172.9 (C-4′′), 172.3 (C-4′), 51.3 (C-5′), 51.1 (C-5′′), 31.3 (C-2′′), 30.5 (C-2′), 29.8 (C-3′′), 29.5 (C-3′), 27.7 (C-1) ppm. ^{15}N NMR ([D$_6$]DMSO): –34.2 (NH$_2$), –43.6 (NH$_3$) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3756 ppm. $C_{16}H_{30}N_2O_{13}Pt$ (653.51): calcd. C 29.41, H 4.63, N 4.29; found C 29.10, H 4.70, N 4.23.

(*OC*-6–21)-Amminetris[(4-ethoxy)-4-oxobutanoato](hydroxido)methylamineplatinum(IV) (4j): The synthesis was carried out as described for **4i** by using **3e** (80 mg, 0.14 mmol) and 4-ethoxy-4-oxobutanoic anhydride (48 mg, 0.18 mmol), with 2.5 h of stirring. White solid. Yield: 92 mg, 94%. ^{1}H NMR ([D$_6$]DMSO): δ = 6.70 (br. s, 2 H, NH$_2$), 6.13 (br. s, 3 H, NH$_3$), 4.04 (m, 4 H, 5′-H), 4.03 (m, 2 H, 5′′-H), 2.49 (m, 4 H, 2′-H), 2.44 (m, 4 H, 3′-H), 2.43 (m, 2 H, 2′′-H/3′′-H), 2.41 (m, 2 H, 2′′-H/3′′-H), 2.02 [t($^3J_{HH}$ = 6.1 Hz), 3 H, 1-H], 1.17 [t($^3J_{HH}$ = 7.1 Hz), 6 H, 6′-H], 1.16 [t($^3J_{HH}$ = 7.1 Hz), 3 H, 6′′-H] ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 179.2 (C-1′), 178.6 (C-1′′), 172.4 (C-4′′), 172.2 (C-4′), 59.8 (C-5′), 59.7 (C-5′′), 31.3 (C-2′′), 30.5 (C-2′), 30.0 (C-3′′), 29.7 (C-3′), 27.7 (C-1), 14.1 (C-6′ + C-6′′) ppm. ^{15}N NMR ([D$_6$]DMSO): –34.2 (NH$_2$), –43.8 (NH$_3$) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3755 ppm. $C_{19}H_{36}N_2O_{13}Pt$ (695.59): calcd. C 32.81, H 5.22, N 4.03; found C 32.52, H 5.38, N 3.99.

(*OC*-6–21)-Ammine(hydroxido)methylaminetris[(4-propoxy)-4-oxobutanoato]platinum(IV) (4k): The synthesis was carried out as described for **4a** by using **3f** (60 mg, 0.10 mmol) and 4-propoxy-4-oxobutanoic anhydride (38 mg, 0.13 mmol), with 2.5 h of stirring. White solid. Yield: 59 mg, 79%. ^{1}H NMR ([D$_6$]DMSO): δ = 6.70 (br. s, 2 H, NH$_2$), 6.14 (br. s, 3 H, NH$_3$), 3.95 [t($^3J_{HH}$ = 6.5 Hz), 4 H, 5′-H], 3.94 [t($^3J_{HH}$ = 6.4 Hz), 2 H, 5′′-H], 2.49 (m, 4 H, 2′-H), 2.46 (m, 4 H, 3′-H), 2.44 (m, 2 H, 2′′-H/3′′-H), 2.42 (m, 2 H, 2′′-H/3′′-H), 2.02 [t($^3J_{HH}$ = 6.2 Hz), 3 H, 1-H], 1.57 (m, 4 H, 6′-H), 1.56 (m, 2 H, 6′′-H), 0.873 [t($^3J_{HH}$ = 7.4 Hz), 6 H, 6′-H], 1.16 [t($^3J_{HH}$ = 7.4 Hz), 3 H, 6′′-H] ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 179.2 (C-1′), 178.6 (C-1′′), 172.4 (C-4′′), 172.3 (C-4′), 65.3 (C-5′), 65.2 (C-5′′), 31.3 (C-2′′), 30.5 (C-2′), 30.0 (C-3′′), 29.6 (C-3′), 27.7 (C-1), 21.5 (C-6′ + C-6′′), 10.2 (C-7′ + C-7′′) ppm. ^{15}N NMR ([D$_6$]DMSO): –34.1 (NH$_2$), –43.7 (NH$_3$) ppm. ^{195}Pt NMR ([D$_6$]-DMSO): δ = 3756 ppm. $C_{22}H_{42}N_2O_{13}Pt$ (737.67): calcd. C 35.82, H 5.74, N 3.80; found C 35.64, H 5.41, N 3.82.

Incubation with Ascorbic Acid: Reduction of complexes **3a**, **3d**, **4b**, **4i**, (*OC*-6-44)-acetato(diammine)hydroxido(malonato)platinum-(IV), and (*OC*-6-33)-diammine(malonato)bis[(4-methoxy)-4-oxobutanoato]platinum(IV) by ascorbic acid was monitored by ^{1}H NMR spectroscopy at ambient temperature. 1 mM solutions of the compounds were prepared in 50 mM phosphate buffer (in D_2O, pD = 7.4), and ^{1}H NMR spectra were recorded over a period of 24 h in order to check the stability of the complexes; changes in the NMR spectra could generally not be seen [with the exception of (*OC*-6-44)-acetato(diammine)hydroxido(malonato)platinum(IV), showing a small amount of hydrolysis]. Subsequently, ascorbic acid (25 mM) was added and ^{1}H NMR spectra were recorded until complete reduction of the platinum(IV) complex was observed. The process was monitored by following the decrease in intensity of the CH_2 signals of the coordinated succinic acid methyl ester chains, or in the case of (*OC*-6-44)-acetato(diammine)hydroxido(malonato)platinum(IV), by following the decrease in intensity of the CH_3 signal of the acetato ligand. In all cases, integration of the signals was performed relative to the sum of all signals deriving from the respective (coordinated and non-coordinated) ligands.

Biological Tests

Cell lines and culture conditions: CH1 cells (identified by STR profiling as PA-1 ovarian teratocarcinoma cells by Multiplexion, Heidelberg, Germany; see also ref.[48]) were provided by Lloyd R. Kelland, CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, UK. SW480 colon carcinoma and A549 non-small cell lung cancer cells were provided by Brigitte Marian, Institute of Cancer Research, Department of Medicine I, Medical University of Vienna, Austria, and authenticated by Multiplexion, Heidelberg, Germany. All cells were grown as monolayer cultures in 75 cm^2 culture flasks (CytoOne, Starlab, UK) in complete medium, that is, minimal essential medium (MEM) supplemented with 10% heat-inactivated fetal bovine serum, 1 mM sodium pyruvate, 4 mM L-glutamine, and 1% v/v nonessential amino acids from 100× ready-to-use stock solution (all purchased from Sigma–Aldrich, Austria). Cultures were maintained at 37 °C in a moist atmosphere containing 5% CO_2 in air.

Cytotoxicity tests in cancer cell lines: Cytotoxicity was determined by the colorimetric 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay in at least three independent experiments. For this purpose, cells were harvested from culture flasks by using trypsin-EDTA solution (Sigma–Aldrich, Austria) and seeded into 96-well microculture plates (CytoOne, Starlab, UK) in the following cell numbers per well (in 100 µL each): 1×10^3 (CH1), 2.5×10^3 (SW480), 3×10^3 (A549). Plates were incubated for 24 h, after which the test compounds were dissolved and serially diluted in complete medium and dilutions added in triplicates of 100 µL per well. After exposure for 96 h, drug solutions were replaced with 100 µL RPMI 1640 medium and 20 µL MTT in phosphate-buffered saline (5 mg/mL). After incubation for 4 h, the liquid was removed and the solid formazan product was dissolved in 150 µL of DMSO per well. Optical densities at 550 nm (and a reference wavelength of 690 nm) were measured with a microplate reader (Biotek ELx808), and IC_{50} values were calculated from concentration-effect curves by interpolation.

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