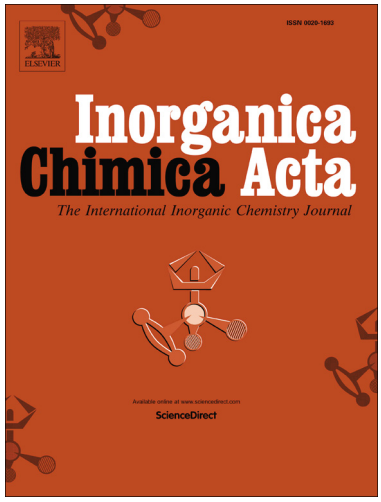

Synthesis, characterization, lipophilicity and cytotoxic properties of novel bis(carboxylato)oxalatobis(1-propylamine)platinum(IV) complexes

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Synthesis, characterization, lipophilicity and cytotoxic properties of novel bis(carboxylato)oxalatobis(1-propylamine)platinum(IV) complexes

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Abstract

A series of novel bis(carboxylato)oxalatobis(1-propylamine)platinum(IV) complexes as well as an ethylamine analog were synthesized. The compounds are either symmetrical with both axial ligands consisting of monoesters of succinic acid, or unsymmetrical, with one axial ligand being acetate. The compounds were characterized in detail by elemental analysis, mass spectrometry and multinuclear (^{1}H, ^{13}C, ^{15}N, ^{195}Pt) NMR spectroscopy. The reduction behavior was followed by NMR spectroscopy, while lipophilicity was determined by analytical reversed-phase HPLC measurements. The capacity of inhibiting proliferation of the human cancer cell lines A549 (non-small cell lung cancer), CH1(PA-1) (ovarian teratocarcinoma) and SW480 (colon carcinoma) was evaluated by the MTT assay. In the most sensitive cell line CH1(PA-1), all compounds exhibited IC_{50} values in the lower µM range. In general, within the two compound series, the IC_{50} values decreased with increasing lipophilicity. Nevertheless, replacing one of the succinic ester ligands with acetate has a rather marginal impact on antiproliferative activity and is hardly disadvantageous.

Keywords: platinum; anticancer agents; synthesis; cytotoxicity; NMR spectroscopy

1. Introduction

Chemotherapy involving metal complexes is a rewarding and widely accepted mode of treatment. Specifically, the platinum complexes cisplatin, carboplatin and oxaliplatin (Figure 1), bearing ligands of a varying nature, are often administered intravenously to patients with different forms of neoplasms.

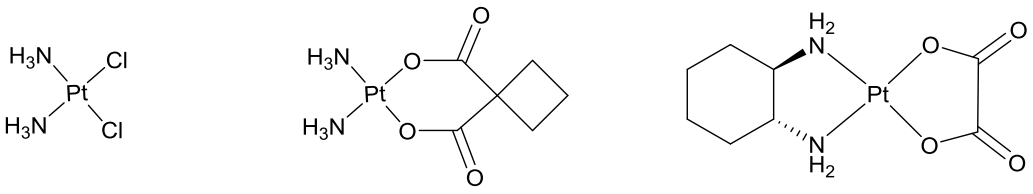


Figure 1. Chemical structures of cisplatin, carboplatin and oxaliplatin.

The platinum(II)-based agents are taken up from the blood stream by tissue and ultimately bind to the cellular DNA (cisplatin, carboplatin, and oxaliplatin) [1] or additionally cause ribosome biogenesis stress (oxaliplatin) [2], preferably in the cancer cell; in last consequence, apoptotic mechanisms are initiated, leading to the death of the cell. Cisplatin has a broad spectrum of application and is used in many chemotherapies [3]. In spite of its success in the treatment of tumors, this drug has various side-effects such as nephrotoxicity, nausea and neurotoxicity. Only a certain proportion of the administered drug reaches the DNA and a significant amount binds to functional proteins, causing systemic toxicity [4] or leading to detoxification of cisplatin. Modification of the leaving ligands leads to a different bio-distribution profile and change of toxic side effects (e.g., carboplatin and oxaliplatin). Carboplatin, bearing a more inert chelate ligand, causes much less nephrotoxicity than cisplatin. Modification of the non-leaving ammine ligand as is the case in oxaliplatin, however, leads to an altered anticancer profile. Oxaliplatin is active in colorectal carcinomas, which are known to be resistant to cis- and carboplatin.

During the last two decades, octahedrally coordinated platinum(IV) complexes have been developed, which are kinetically inert compared to their platinum(II) counterparts [5]. They act as pro-drugs and have to be reduced inside or outside the tumor cell to the respective platinum(II) complexes to be activated [6]. The reduction process may be favored by the hypoxic medium of the tumor cell [7], so that the inert platinum(IV) complex is activated preferably at the site of the tumor, where the active form of the drug is desired. Thus, selectivity over healthy tissue is achieved. One positive consequence of the kinetic inertness outside of the tumor tissue is that systemic toxicity is reduced. In addition, delivery of the intact drug at the target site is improved as a result of decreased deactivation by binding, e.g., to glutathione, which helps to overcome platinum resistance [8]. Further, platinum(IV) drugs can be administered orally, which could be much more convenient for the patient. In terms of drug design, the octahedral coordination sphere offers a broad range of possibilities

for the fine-tuning of pharmacological properties of the compound. Nevertheless, no Pt(IV) complex has gained clinical approval up to now [9] .

As can be deduced from the mechanism of activation, the drug's anticancer efficacy depends strongly on the reduction potential [10,11]. Complexes with axial carboxylato ligands possess an intermediate redox potential in comparison to analogs with chlorido or hydroxido ligands [12], conferring the drug sufficient stability to reach the target site but also an appropriate degree of therapeutic activity without causing severe systemic toxicity. In fact, the promising results obtained in clinical evaluation of satraplatin, (*OC*-43)-bis(acetato)amminedichlorido(cyclohexylamine)platinum(IV), can be explained in part by this combination of properties [13,14].

Bulky amine ligands such as isopropylamine or cyclohexylamine, however, would contribute to faster reduction by destabilizing the platinum(IV) center [15,16]. The 1-propylamine ligand employed here is sterically less demanding so that a positive effect in terms of stability and, consequently, of anticancer properties is expected.

Lipophilicity is an important parameter for the bioavailability of a compound, as the passage through cell membranes is facilitated [9]. With regard to platinum drugs, an increased lipophilicity frequently correlates with enhanced cytotoxicity [11]. Our group has previously investigated the influence of lipophilicity on cytotoxicity by varying axial and equatorial ligands within a series of dicarboxylatoplatinum(IV) complexes [13,17,18,19] , some of which have IC_{50} values in the micromolar range. A rough correlation was demonstrated between the IC_{50} values of such complexes and their lipophilicity [17].

In this work, we present a series of novel platinum(IV) complexes with 1-propylamine and oxalate as equatorial ligands and succinic esters of varying chain length (or acetate in the case of unsymmetric complexes) as axial ligands. Compared to typical am(m)ine ligands, the presence of two equatorial 1-propylamine ligands renders these compounds significantly more lipophilic, which might allow a higher accumulation even after reduction to the corresponding platinum(II) species.

2. Experimental

2.1 Materials and Methods: All chemicals were obtained from commercial suppliers and used as received. $K_2[PtCl_4]$ was purchased from Johnson Matthey (Switzerland), potassium iodide (99%) from Alfa Aesar, oxalic acid (99%) from Fluka, silver nitrate (99.85%) from Acros, 1-propylamine (98%) from TCI Europe, succinic anhydride (99%) from Acros Fisher, hydrogen peroxide (30% solution) from Sigma-Aldrich, dimethyl formamide (99.8%) from Acros Organics, propanol (99.5%) and butanol (99%) from Sigma-Aldrich. Methanol and ethanol were dried before use. Water was purified by reversed osmosis and double distillation before use. Reactions involving platinum compounds were performed under light protection and with glass-coated magnetic stirring bars. NMR spectroscopy measurements were performed with a Bruker AVANCE NEO 500 MHz spectrometer at 500.32 (^{1}H), 125.81 (^{13}C), 50.70 (^{15}N), and 107.38 (^{195}Pt) MHz at 25 °C. The solvent resonances were used as internal references for ^{1}H {DMSO-d_6, δ = 2.51 ppm, $CDCl_3$, δ = 7.26 ppm, DMF-d_7, δ = 2.75 ppm} and ^{13}C (DMSO-d_6, 40.0 ppm, $CDCl_3$, δ = 77.4 ppm, DMF-d_7, δ = 29.76 ppm). The ^{195}Pt and ^{15}N NMR resonances were referenced relative to external $K_2[PtCl_4]$ or NH_4Cl, respectively. High-resolution electrospray ionization mass spectra were measured with a Bruker maXis ESI-QqTOF (electrospray ionization quadrupole–quadrupole time-of-flight) spectrometer in the positive mode with ACN/MeOH 1 % H_2O as the solvent (ACN = acetonitrile). Elemental analyses were performed at the microanalytical laboratory of the Faculty of Chemistry of the University of Vienna with a Eurovector EA3000 elemental analyzer.

2.2 Synthesis

The diiodidoplatinum(II) precursors **1** and **7** (Schemes 1 and 2) were prepared by reacting $K_2[PtCl_4]$ with an excess of KI and the respective amines, namely 1-propylamine or ethylamine. Iodido ligands were removed with $AgNO_3$ according to Dhara's method [20], and replaced by adding oxalic acid to obtain the oxalatoplatinum(II) complexes **2** and **8**. Oxidation with 30% hydrogen peroxide in aqueous solution yielded the corresponding dihydroxido

species **3** and **9**. Oxidation of **2** in a mixture of acetic acid and 30% hydrogen peroxide in aqueous solution yielded the asymmetric precursor *(OC*-6-44*)*-acetatohydroxidooxalatobis(1-propylamine)platinum(IV) (**5**). The respective noncyclic anhydride of the succinic monoester (2-4 eq) in absolute DMF was added to the respective platinum(IV) precursor (**3**, **5** or **9**) in an oven-dried nitrogen flask flushed with argon and the suspension was stirred at 70 °C until a clear solution formed. Afterwards the solution was stirred at room temperature overnight. DMF was removed under reduced pressure and the crude product was purified by HPLC.

General procedure for the synthesis of succinic acid monoesters L1-L4

Succinic anhydride was refluxed in an excess of the respective alcohol under anhydrous conditions and the remaining alcohol was removed under reduced pressure. Chloroform was added to precipitate remaining succinic acid, which was subsequently removed by filtration. The succinic acid mono ester was dried in vacuo and was used without further purification.

3-(Methoxycarbonyl)propanoic acid (L1). Methanol (10 mL, 0.25 mol, 10 eq), succinic anhydride (2.5 g, 0.025 mol), 2 h at 70 °C. The colorless liquid was cooled to -18 °C for 15 min to give a white crystalline solid which was dried in vacuo. Yield 3.237 g (98%), ^{1}H NMR ($CDCl_3$): δ 3.74 (s, 3H, H5), 2.74–2.71 (m, 2H, H2/H3), 2.68–2.65 (m, 2H, H2/H3) ppm.

3-(Ethoxycarbonyl)propanoic acid (L2). Ethanol (15 mL, 0.25 mol, 10 eq), succinic anhydride (2.5 g, 0.025 mol), 2 h at 80 °C. Yield 2.885 g (79%), colorless liquid. ^{1}H NMR ($CDCl_3$): δ = 4.19 (q, 2H, H5, $^{3}J_{H,H}$ = 7.1 Hz), 2.72–2.70 (m, 2H, H2/H3), 2.66–2.63 (m, 2H, H2/H3), 1.28 (t, 3H, H6, $^{3}J_{H,H}$ = 7.1 Hz) ppm.

3-(Propoxycarbonyl)propanoic acid (L3). Propanol (18.70 mL, 0.25 mol, 10 eq), succinic anhydride (2.5 g, 0.025 mol), 2 h at 100 °C. Yield 3.323 g (83%), colorless liquid. ^{1}H NMR ($CDCl_3$): δ = 4.06 (t, 2H, H5, $^{3}J_{H,H}$ = 6.7 Hz), 2.70–2.68 (m, 2H, H2/H3), 2.64–2.61 (m, 2H, H2/H3), 1.65 (m, 2H, H6), 0.93 (t, 3H, H7, $^{3}J_{H,H}$ = 7.5 Hz) ppm.

3-(Butoxycarbonyl)propanoic acid (L4). Butanol (22.87 mL, 0.25 mol, 10 eq), succinic anhydride (2.5 g, 0.025 mol), 2 h at 127 °C. Yield 3.715 g (85%), colorless liquid. ^{1}H NMR

($CDCl_3$): δ = 4.10 (t, 2H, H5, $^3J_{H,H}$ = 6.7 Hz), 2.70–2.68 (m, 2H, H2/H3), 2.64–2.61 (m, 2H, H2/H3), 1.61 (m, 2H, H6), 1.37 (m, 2H, H7), 0.92 (t, 3H, H8, $^3J_{H,H}$ = 7.1 Hz) ppm.

General procedure for the synthesis of anhydrides L5-L8 of succinic acid mono esters

Acetic anhydride and the corresponding succinic acid mono ester were heated to 110 °C for 1.5 h under anhydrous conditions. The clear solution was allowed to cool down to room temperature and acetic acid and the unreacted excess of acetic anhydride were distilled off in vacuo.

3-(Methoxycarbonyl)propanoic anhydride (L5). Acetic anhydride (6.0 mL, 63.60 mmol, 4.55 eq), L1 (1.850 g, 14.00 mmol). Yield 1.568 (91%) colorless liquid. ^{1}H NMR (CDCl3): δ = 3.74 (s, 6H, H5), 2.83 (t, 2H, H2/H3, $^3J_{H,H}$ = 6.6 Hz), 2.70 (t, 2H, H2/H3, $^3J_{H,H}$ = 6.6 Hz) ppm.

3-(Ethoxycarbonyl)propanoic anhydride (L6). Acetic anhydride (7.0 mL, 74.2 mmol, 4 eq), L2 (2.711 g, 18.55 mmol). Yield 2.490 g (98%) colorless liquid. ^{1}H NMR ($CDCl_3$): δ = 4.19 (q, 4H, H5, $^3J_{H,H}$ = 7.1 Hz), 2.82 (t, 2H, H2/H3, $^3J_{H,H}$ = 6.6 Hz), 2.69 (t, 2H, 2H/3H, $^3J_{H,H}$ = 6.5 Hz), 1.29 (t, 6H, H6, $^3J_{H,H}$ = 7.1 Hz) ppm.

3-(Propoxycarbonyl)propanoic anhydride (L7). Acetic anhydride (9.0 mL, 95.40 mmol, 4.6 eq), L3 (3.310 g, 20.66 mmol). Yield 3.885 g (97%) colorless liquid. ^{1}H NMR ($CDCl_3$): δ = 4.06 (t, 4H, H5, $^3J_{H,H}$ = 6.7 Hz), 2.79 (t, 2H, H2/H3, $^3J_{H,H}$ = 6.6 Hz), 2.67 (t, 2H, 2H/3H, $^3J_{H,H}$ = 6.5 Hz), 1.65 (m, 4H, H6), 0.93 (t, 6H, H7, $^3J_{H,H}$ = 7.5 Hz) ppm.

3-(Butoxycarbonyl)propanoic anhydride (L8). Acetic anhydride (8.1 mL, 85.5 mmol, 4 eq), L3 (3.700 g, 21.24 mmol). Yield 3.885 g (97%) colorless liquid. ^{1}H NMR ($CDCl_3$): δ = 4.10 (t, 4H, H5, $^3J_{H,H}$ = 6.73 Hz), 2.79 (t, 2H, H2/H3, $^3J_{H,H}$ = 6.6 Hz), 2.66 (t, 2H, 2H/3H, $^3J_{H,H}$ = 6.5 Hz), 1.61 (m, 4H, H6), 1.37 (m, 4H, H7), 0.92 (t, 6H, H8, $^3J_{H,H}$ = 7.1 Hz) ppm.

***(SP*-4-2*)*-Diiodidobis(1-propylamine)platinum(II) (1):** Potassium tetrachloroplatinate (900 mg, 2.17 mmol) was dissolved in 20 mL H_2O and potassium iodide (1800 mg, 10.84 mmol, 5 eq) was added. The mixture was stirred at rt for 20 min. A solution of 1-propylamine (513 mg,

8.67 mmol, 4 eq) in 5 mL of H_2O were added and stirred at rt for 3h. The precipitate was collected by filtration. Yield: 1073.5 mg (87%), yellow solid.

***(SP*-4-2*)*-Oxalatobis(1-propylamine)platinum(II) (2):** *(SP*-4-2*)*-Diiodidobis(1-propylamine)platinum(II) (**1**) (1070.0 mg, 1.88 mmol) and $AgNO_3$ (609 mg, 3.58 mmol) were suspended in 20 mL of H_2O and stirred overnight at rt. AgI was filtered off twice using a MN-GF-3 filter paper and oxalic acid (169.2 mg, 1.88 mmol) was added. The mixture was stirred for 2h at rt, cooled and the precipitate collected by filtration. The filtrate was concentrated and the precipitate filtered two more times. Yield: 531.6 mg (70%), pale yellow solid. HRMS: (pos) m/z 424.0796 $[M+Na^+]^+$.

***(OC*-6-33*)*-Dihydroxidooxalatobis(1-propylamine)platinum(IV) (3):** *(SP*-4-2*)*-Oxalatobis(1-propylamine)platinum(II) (**2**) (505 mg, 1.31 mmol) was suspended in 15 mL of a 30% hydrogen peroxide solution and stirred at 50°C for 2 h, whereas the solution became clear. Then, the solution was lyophilized. Yield: 545.1 mg (95%), pale yellow solid. ^{1}H NMR (DMF-d_7): δ = 6.69 (bs, 4H, NH_2), 2.85 (m, 4H, H1), 1.79 (m, 4H, H2), 0.94 (t, $^3J_{H,H}$ = 7.4 Hz, 6H, H3). ^{13}C NMR (DMF-d_7): δ = 162.1 (C4), 46.3 (C1), 22.2 (C2), 10.7 (C3) ppm. ^{195}Pt NMR (DMF-d_7): δ = 3081 ppm. ^{15}N NMR (DMF-d_7): δ = -31.6 ppm. HRMS (ACN/MeOH 1% H_2O): calcd. 435.10, found (pos) m/z 458.0859 $[M+Na^+]^+$.

***(OC*-6-33*)*-Bis((4-methoxy)-4-oxobutanoato)oxalatobis(1-propylamine)platinum(IV) (4a):** In an oven-dried 50 mL nitrogen flask flushed with argon, **3** (510.4 mg, 1.17 mmol) and **L5** (1155.0 mg, 4.69 mmol, 4 eq.) were suspended in 9 mL of DMF. The suspension was stirred at 70 °C for 15 min and a clear solution was obtained, which was stirred at 45 °C overnight. DMF was removed in vacuo and the residue was purified via prep-HPLC (20-25% ACN:H2O). Yield: 241.7 mg (31%), white solid. ^{1}H NMR (DMSO-d_6): δ = 7.23 (bs, 4H, NH_2), 3.56 (s, 6H, H9), 2.61 (m, 4H, H1), 2.55 (m, 4H, H6), 2.45 (m, 4H, H7), 1.61 (m, 4H, H2), 0.92 (t, $^3J_{H,H}$ = 7.4 Hz, 6H, H3) ppm. ^{13}C NMR (DMSO-d_6): δ = 179.1 (C5), 173.1 (C8), 163.9 (C4), 51.8 (C9), 46.6 (C1), 30.6 (C6), 29.8 (C7), 22.4 (C2), 11.4 (C3) ppm. ^{195}Pt NMR (DMSO-d_6): δ = 3371 ppm. ^{15}N NMR (DMSO-d_6): δ = -33.8 ppm. HRMS (ACN/MeOH 1%

H_2O): calcd. 663.16, found (pos) m/z 686.1480 $[M+Na^+]^+$, 664.1661 $[M+H^+]$. $C_{18}H_{32}N_2O_{12}Pt$: calcd. C 32.58, H 4.86, N 4.22; found C 32.62, H 5.00, N 4.06.

***(OC*-6-33*)*-Bis((4-ethoxy)-4-oxobutanoato)oxalatobis(1-propylamine)platinum(IV) (4b)** In an oven-dried 50 mL nitrogen flask flushed with argon, **3** (545.0 mg, 1.25 mmol) and **L6** (1030 mg, 3.75 mmol, 3 eq.) were suspended in 9 mL of DMF. The suspension was stirred at 70 °C for 15 min and a clear solution was obtained, which was stirred at 45 °C overnight. DMF was removed in vacuo and the crude was purified via prep-HPLC (20-33% ACN:H_2O). Yield: 275.5 mg (32%), white solid. ^{1}H NMR (DMSO-d_6): δ = 7.24 (bs, 4H, NH_2), 4.02 (q, $^3J_{H,H}$ = 7.1 Hz, 4H, H9), 2.61 (m, 4H, H1), 2.54 (m, 4H, H6), 2.44 (m, 4H, H7), 1.61 (m, 4H, H2), 1.16 (t, , $^3J_{H,H}$ = 7.1 Hz, 6H, H10), 0.92 (t, , $^3J_{H,H}$ = 7.4 Hz, 6H, H3) ppm. ^{13}C NMR (DMSO-d_6): δ = 179.6 (C5), 172.7 (C8), 163.9 (C4), 60.3 (C9), 46.6 (C1), 30.5 (C6), 29.8 (C7), 22.3 (C2), 14.4 (C10), 11.3 (C3) ppm. ^{195}Pt NMR (DMSO-d_6): δ = 3371 ppm. ^{15}N NMR (DMSO-d_6): δ = -33.5 ppm. HRMS (ACN/MeOH 1% H_2O): calcd. 691.19, found (pos) m/z 692.1990 $[M+H^+]^+$. $C_{20}H_{36}N_2O_{12}Pt$: calcd. C 34.73, H 5.25, N 4.05; found C 34.77, H 4.99, N 3.99.

***(OC*-6-33*)*-Oxalatobis((4-propoxy)-4-oxobutanoato)bis(1-propylamine)platinum(IV) (4c):** In an oven-dried 50 mL nitrogen flask flushed with argon, **3** (285.1 mg, 0.655 mmol) and **L7** (396,0 mg, 1,31 mmol, 2 eq.) were suspended in 7 mL of DMF. The suspension was stirred at 70 °C for 1 h and a clear solution was obtained, which was stirred at rt overnight. DMF was removed in vacuo and the residue purified via preparative HPLC (23-49% ACN:H_2O). The combined product fractions were lyophilized. Yield: 163.0 mg (34%), white solid. ^{1}H NMR (DMSO-d_6): δ = 7.25 (bs, 4H, NH_2), 3.94 (q, $^3J_{H,H}$ = 6.7 Hz, 4H, H9), 2.62 (m, 4H, H1), 2.54 (m, 4H, H6), 2.44 (m, 4H, H7), 1.61 (m, 4H, H2), 1.57 (m, 4H, H10), 0.92 (t, $^3J_{H,H}$ = 7.3 Hz, 6H, H3), 0.87 (t, $^3J_{H,H}$ = 7.4 Hz, 6H, H11) ppm. ^{13}C NMR (DMSO-d_6): δ = 179.6 (C5), 172.7 (C8), 163.9 (C4), 65.8 (C9), 46.5 (C1), 30.6 (C6), 29.9 (C7), 22.4 (C2), 21.9 (C10), 11.4 (C3), 10.7 (C11) ppm. ^{195}Pt NMR (DMSO-d_6): δ = 3372 ppm. ^{15}N NMR (DMSO-d_6): δ = -34.1 ppm. HRMS (ACN/MeOH 1% H_2O): calcd. 719.22, found (pos) m/z 742.2113 $[M+Na^+]^+$. $C_{22}H_{40}N_2O_{12}Pt$: calcd. C 36.72, H 5.60, N 3.89; found C 36.58, H 5.78, N 3.97.

***(OC*-6-44*)*-Acetato(hydroxido)oxalatobis(1-propylamine)platinum(IV) (5):** *(SP*-4-2*)*-Oxalatobis(1-propylamine)platinum(II) (**2**) (676,0 mg, 1,68 mmol) was suspended in 10 mL of acetic acid and 500 µl of a 30% H_2O_2 solution were added. The solution was stirred for 20 min before another 500 µl portion of 30% H_2O_2 was added. After stirring for 20 min, further 1.4 mL of 30% H_2O_2 were added and the mixture was stirred at rt overnight. Acetic acid and hydrogen peroxide were removed under reduced pressure. The crude product was used without further purification. Yield: 365.5 mg (45%), pale yellow solid. ^{1}H NMR (DMF-d_7): δ = 7.67 (bs, 4H, NH_2), 2.87 (m, 4H, H1), 1.99 (s, 3H, H6), 1.73 (m, 4H, H2), 0.97 (t, $^{3}J_{H,H}$ = 7.4 Hz, 6H, H3). ^{13}C NMR (DMF-d_7): δ = 179.1 (C5), 162.1 (C4), 46.5 (C1), 22.3 (C2), 21.9 (C6), 10.7 (C3) ppm. ^{195}Pt NMR (DMF-d_7): δ = 3370 ppm. ^{15}N NMR (DMF-d_7): δ = -35.8 ppm. HRMS: (ACN/MeOH 1% H_2O): calcd. 477.11, found (pos) m/z 500.0961 $[M+Na^+]^+$.

General procedure for the synthesis of complexes 6a-6d

In an oven-dried 100 mL flask flushed with argon, (OC-6-44)-acetato(hydroxido)oxalatobis(1-propylamine)platinum(IV) (**5**) and the respective anhydride were suspended in DMF. The suspension was stirred at 70 °C for several hours and a clear solution was obtained, which was stirred at rt overnight. DMF was removed in vacuo and the residue purified via preparative HPLC (13-35% ACN/H_2O). The combined product fractions were lyophilized.

***(OC*-6-44*)*-Acetatooxalato(4-methoxy-4-oxobutanoato)bis(1-propylamine)platinum(IV) (6a):** **5** (245.1 mg, 0.514 mmol), **L5** (253.5 mg, 1.026 mmol, 2 eq.) 5 mL of DMF, 70 °C for 7 h. Yield: 174.0 mg (57%) , white powder. ^{1}H NMR (DMSO-d_6): δ = 7.38 (bs, 2H, NH_2), 7.17 (bs, 2H, NH_2), 3.56 (s, 6H, H11), 2.63 (m, 4H, H1), 2.55 (m, 2H, H8), 2.45 (m, 2H, H9), 1.96 (s, 3H, H6), 1.63 (m, 4H, H2), 0.92 (t, $^{3}J_{H,H}$ = 7.4 Hz, 6H, H3) ppm. ^{13}C NMR (DMSO-d_6): δ = 179.4 (C7), 178.8 (C5), 173.2 (C10), 163.9 (C4), 51.8 (C11), 46.6 (C1), 30.6 (C8), 29.8 (C9), 23.1 (C6), 22.4 (C2), 11.5 (C3) ppm. ^{195}Pt NMR (DMSO-d_6): δ = 3373 ppm. ^{15}N NMR (DMSO-d_6): δ = -34.1 ppm. HRMS (ACN/MeOH 1% H_2O): calcd. 591.14, found (pos) m/z

614.1266 $[M+Na^+]^+$, 1205.2631 $[2M+Na^+]^+$. $C_{15}H_{28}N_2O_{10}Pt$: calcd. C 30.46, H 4.77, N 4.74; found C 30.17, H 4.75, N 4.62.

***(OC*-6-44)-Acetato(4-ethoxy-4-oxobutanoato)oxalatobis(1-propylamine)platinum(IV)**

(6b): 5 (360.1 mg, 0.754 mmol), **L6** (310.5 mg, 1.131 mmol, 1.5 eq.), 7 mL of DMF, 70 °C for 2 h. Yield: 347.28 mg (76%), white powder. ^{1}H NMR (DMSO-d_6): δ = 7.38 (bs, 2H, NH_2), 7.17 (bs, 2H, NH_2), 4.02 (q, , $^3J_{H,H}$ = 7.1 Hz, 2H, H11), 2.63 (m, 4H, H1), 2.54 (m, 2H, H8), 2.44 (m, 2H, H9), 1.96 (s, 3H, H6), 1.61 (m, 4H, H2), 1.16 (t, , $^3J_{H,H}$ = 7.1 Hz, 3H, H12), 0.92 (t, $^3J_{H,H}$ = 7.4 Hz, 6H, H3) ppm. ^{13}C NMR (DMSO-d_6): δ = 179.5 (C7), 178.8 (C5), 172.7 (C10), 163.9 (C4), 60.3 (C11), 46.6 (C1), 30.6 (C8), 29.9 (C9), 23.1 (C6), 22.3 (C2), 14.5 (C12), 11.5 (C3) ppm. ^{195}Pt NMR (DMSO-d_6): δ = 3373 ppm. ^{15}N NMR (DMSO-d_6): δ = -34.20 ppm. HRMS (ACN/MeOH 1% H_2O): calcd. 605.15, found (pos) m/z 628.1435 $[M+Na^+]^+$, 1233.2971 $[2M+Na^+]^+$. $C_{16}H_{30}N_2O_{10}Pt$: calcd. C 31.74, H 4.99, N 4.63; found C 31.44, H 4.96, N 4.54.

***(OC*-6-44)-Acetatooxalato(4-propoxy-4-oxobutanoato)bis(1-propylamine)platinum(IV)**

(6c): 5 (120.1 mg, 0.251 mmol), **L7** (114.0 mg, 0.377 mmol, 1.5 eq.), 7 mL of DMF, 70 °C for 3 h. Yield: 53 mg (34%), white solid. ^{1}H NMR (DMSO-d_6): δ = 7.38 (bs, 2H, NH_2), 7.17 (bs, 2H, NH_2), 3.94 (q, $^3J_{H,H}$ = 6.7 Hz, 2H, H11), 2.63 (m, 4H, H1), 2.55 (m, 2H, H8), 2.45 (m, 2H, H9), 1.96 (s, 3H, H6), 1.61 (m, 4H, H2), 1.57 (m, 2H, H12), 0.92 (t, $^3J_{H,H}$ = 7.3 Hz, 6H, H3), 0.87 (t, $^3J_{H,H}$ = 7.4 Hz, 3H, H13) ppm. ^{13}C NMR (DMSO-d_6): δ = 179.6 (C7), 178.8 (C5), 172.7 (C10), 163.9 (C4), 65.7 (C11), 46.5 (C1), 30.6 (C8), 29.9 (C9), 23.1 (C6), 22.4 (C2), 21.9 (C12), 11.4 (C3), 10.7 (C13) ppm. ^{195}Pt NMR (DMSO-d_6): δ = 3373 ppm. ^{15}N NMR (DMSO-d_6): δ = -33.9 ppm. HRMS (ACN/MeOH 1% H_2O): calcd. 619.17, found (pos) m/z 642.1917 $[M+Na^+]^+$. $C_{17}H_{32}N_2O_{10}Pt$: calcd. C 32.96, H 5.21, N 4.52; found C 32.78, H 5.07, N 4.49.

***(OC*-6-44)-Acetato(4-butoxy-4-oxobutanoato)oxalatobis(1-propylamine)platinum(IV)**

(6d): **5** (365.1 mg, 0.764 mmol), **L8** (505.12 mg, 0.377 mmol, 2 eq.), 7 mL of DMF, 70 °C for 3 h. Yield: 280.5 mg (58%), white powder. ^{1}H NMR (DMSO-d_6): δ = 7.38 (bs, 2H, NH_2), 7.17 (bs, 2H, NH_2), 3.98 (s, 2H, H11), 2.63 (m, 4H, H1), 2.55 (m, 2H, H8), 2.45 (m, 2H, H9), 1.96 (s, 3H, H6), 1.62 (m, 4H, H2), 1.53 (m, 2H, H12), 1.32 (m, 2H, H13), 0.93 (t, $^3J_{H,H}$ = 7.4 Hz,

6H, H3), 0.89 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H, H14) ppm. ^{13}C NMR (DMSO-d_6): δ = 179.5 (C7), 178.8 (C5), 172.7 (C10), 163.9 (C4), 64.1 (C11), 46.6 (C1), 30.6 (C8), 30.2 (C12), 29.9 (C9), 23.1 (C6), 22.4 (C2), 19.08 (C13), 14.0 (C14), 11.5 (C3) ppm. ^{195}Pt NMR (DMSO-d_6): δ = 3373 ppm. ^{15}N NMR (DMSO-d_6): δ = -34.1 ppm. HRMS (ACN/MeOH 1% H_2O): calcd. 633.19, found (pos) m/z 656.1746 $[M+Na^+]^+$, 1289.3606 $[2M+Na^+]^+$. $C_{18}H_{34}N_2O_{10}Pt$: calcd. C 34.12, H 5.41, N 4.42; found C 33.81, H 5.14, N 4.34.

***(SP*-4-2*)*-Bis(ethylamine)diiodoplatinum(II) (7):** Potassium tetrachloroplatinate (1300.6 mg, 3.13 mmol) was dissolved in 20 mL of H_2O and potassium iodide (3000 mg, 15.65 mmol, 5 eq) was added. The mixture was stirred at rt for 20 min. A solution of ethylamine (564.4 mg, 12.52 mmol, 4 eq) in 5 mL of H_2O were added and stirred at rt for 3h. The precipitate was collected by filtration. Yield: 1575.5 mg (93%), yellow solid.

***(SP*-4-2*)*-Bis(ethylamine)oxalatoplatinum(II) (8):** (*SP*-4-2*)*-Diiodobis(ethylamine)platinum(II) (1484.5 mg, 2.75 mmol, 1 eq) and $AgNO_3$ (887.54 mg, 5.22 mmol, 1.9 eq) were suspended in 20 mL of H_2O and stirred overnight at rt. AgI was filtered off twice using a MN-GF-3 filter paper and oxalic acid (247.58 mg, 2.75 mmol, 1 eq) was added. The mixture was stirred for 2h at rt, cooled and the precipitate collected by filtration. The filtrate was concentrated and the precipitate filtered two more times. Yield: 719.2 mg (70%), yellow solid.

***(OC*-6-33*)*-Bis(ethylamine)dihydroxidooxalatoplatinum(IV) (9):** (*SP*-4-2*)*-Bis(ethylamine)oxalatoplatinum(II) (705 mg, 1,75 mmol) was suspended in 15 mL of a 30% hydrogen peroxide solution and stirred at rt for 4 h, whereas the solution became clear. Then, the solvent was removed in vacuo. Yield: 679.4 mg (95%), pale yellow solid.

***(OC*-6-33*)*-Bis(ethylamine)oxalatobis((4-propoxy)-4-oxobutanoato)platinum(IV) (10):** In an oven-dried 50 mL nitrogen flask flushed with argon, *(OC*-6-33*)*-bis(ethylamine)dihydroxidooxalatoplatinum(IV) (415.4 mg, 1.02 mmol) and 4-propoxy-4-oxobutanoic anhydride (1233.5 mg, 4.08 mmol, 2 eq.) were suspended in 8 mL DMF (dry). The suspension was stirred at 70 °C for 3 h and a clear solution was obtained, which was stirred at rt overnight. DMF was removed in vacuo and the residue purified via prep-HPLC

(20-37% ACN:H_2O). The combined product fractions were lyophilized. Yield: 236.3 mg (33%), white powder. ^{1}H NMR (DMSO-d_6): δ = 7.20 (bs, 4H, NH_2), 3.94 (t, $^{3}J_{H,H}$ = 6.7 Hz, 4H, H8), 2.68 (m, 4H, H9), 2.55 (m, 4H, H5), 2.46 (m, 4H, H6), 1.57 (m, 4H, H1), 1.19 (t, $^{3}J_{H,H}$ = 7.3 Hz, 6H, H10), 0.87 (t, $^{3}J_{H,H}$ = 7.4 Hz, 6H, H2) ppm. ^{13}C NMR (DMSO-d_6): δ = 179.4 (C4), 172.7 (C7), 164.0 (C3), 65.8 (C8), 30.6 (C5), 29.9 (C6), 21.9 (C1), 14.4 (C10), 10.7 (C2). ^{195}Pt NMR (DMSO-d_6): δ = 3374 ppm. ^{15}N NMR (DMSO-d_6): δ = -30.3 ppm. HRMS (ACN/MeOH 1% H_2O): calcd. 691.19, found (pos) m/z 714.1906 $[M+Na^{+}]^{+}$. $C_{20}H_{36}N_2O_{12}Pt$: calcd. C 34.73, H 5.25, N 4.05; found C 34.52, H 4.90, N 3.93.

2.3 Determination of lipophilicity

Lipophilicity of all compounds was determined via their chromatographic retention factors k´ using reverse-phase HPLC and expressed as k_w (the retention time in 100% aqueous solvent). The analysis was performed on an Ultimate 3000 Dionex system controlled by the Dionex Chromeleon 7.0 software. A reversed phase Acquity BEH C18 column (3.0 × 50 mm, 1.7 µm) from Waters served as stationary phase. The mobile phase consisted of different ratios of methanol and water (Milli-Q, 18.2 MΩ cm, Milli-Q Advantage A10, Darmstadt, Germany) with 0.1% TFA, ranging from 20% MeOH for the most hydrophilic to 70% MeOH for the most lipophilic compound. Samples were prepared as 0.5 mM solutions in a 10% mixture of MeOH and H_2O and filtered through 0.45 µm nylon filters (Minisart RC 25, Sartorius AG, Göttingen, Germany) before injection. A solution of potassium iodide (0.3 mM) was used as external dead volume marker. The chromatographic conditions were as follows: column temperature 25 °C, flow rate 0.6 mL/min, injection volume 10 µL, UV–vis detection at 210, 230, 252 and 318 nm. The capacity factor k′ is defined as the partition of a compound between a stationary (apolar) and a mobile phase (polar) and can be determined via $k' = (t_R - t_0) / t_0$ where t_R denotes the retention time of the analyte and t_0 the retention time of the external dead volume marker. Retention time of each analyte was determined for at least 3 different mobile phase compositions to obtain capacity factors k' in the linear range of $0.5 < \log k' < 1.5$. A linear plot of $\log k'$ versus mobile phase composition follows the equation $\log k'$

$= log k_w - S_{MeOH} \cdot \phi$ where S is a specific constant for an analyte and a certain HPLC system, and ϕ is the percentage of the organic component of the mobile phase [21]. Comparison of different substances analyzed at various amounts of organic phase is possible by extrapolation of the equation to the same mobile phase concentration. The y-intercept of the linear log k′ correlation affords $log k_w$ values, which are the retention factors in 100% aqueous phase.

2.4 Reduction behavior

Reduction of complexes **4a-c**, **6a-d** and the ethylamine complex **10** by ascorbic acid was monitored by ^{1}H NMR spectroscopy at ambient temperature. 0.5 mM (0.25 mM in case of **4c** and **10**) solutions of the compounds were prepared in 50 mM phosphate buffer (in D_2O, pD =7.4) and ^{1}H NMR spectra were measured over a period of 24 h and the stability of the complexes in aqueous solution was confirmed. Then, ascorbic acid (12.5 mM or 6.25 mM, 25 equiv.) was added and ^{1}H NMR spectra were recorded for several days. Reduction was monitored either by following the decrease of intensity of triplets of the terminal methyl groups of the propylamine moieties in Pt(IV) and Pt(II) species (0.86 ppm versus 0.82 ppm) in case of complexes **4a**, **4b** and **6b** or by the ratio of $CH_2C(O)O$ protons of the coordinated or free succinato ligand (2.49 ppm versus 2.33 ppm) in case of complexes **4c, 6a, 6c, 6d, 10**.

2.5 Cytotoxicity tests in human cancer cell lines

CH1(PA-1) (provided by L. R. Kelland, CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, UK; confirmed by STR profiling as PA-1 ovarian teratocarcinoma cells at Multiplexion, Heidelberg, Germany), as well as SW480 colon carcinoma and A549 non-small cell lung cancer cells (both provided by B. Marian, Institute of Cancer Research, Department of Medicine I, Medical University of Vienna, Austria) were grown as monolayer cultures in 75 cm^2 culture flasks (Starlab) in complete medium, i.e., minimal essential medium (MEM) supplemented with 1 mM sodium pyruvate, 4 mM L-glutamine, 1% (v/v) nonessential amino acids from 100-fold stock solution (all purchased from Sigma-Aldrich)

and 10% heat-inactivated fetal bovine serum (BioWest). Cultures were maintained at 37 °C in a humidified atmosphere containing 5% CO_2 in air.

Cytotoxicity of the compounds was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay in at least three independent experiments as follows: Cells were harvested from culture flasks by using trypsin-EDTA (Sigma-Aldrich), and the following cell numbers were seeded into 96-well microculture plates (Starlab): 1×10^3 (CH1(PA-1)), 2×10^3 (SW480), 3×10^3 (A549) cells per well (each in 100 µL). Plates were incubated for 24 h, then the test compounds were dissolved and serially diluted in complete MEM and each dilution added to plates in triplicate (100 µL per well). After exposure for 96 h, the medium was replaced with 100 µL of drug-free RPMI 1640 medium (Sigma-Aldrich) and 20 µL of MTT solution (5 mg/mL) in phosphate-buffered saline (Sigma-Aldrich). After incubation for 4 h, these mixtures were removed, and the formazan products were dissolved in 150 µl of DMSO per well. Optical densities at 550 nm (and at 690 nm as a reference) were measured with a microplate reader (Biotek ELx808), and IC_{50} values were calculated from concentration–effect curves by interpolation.

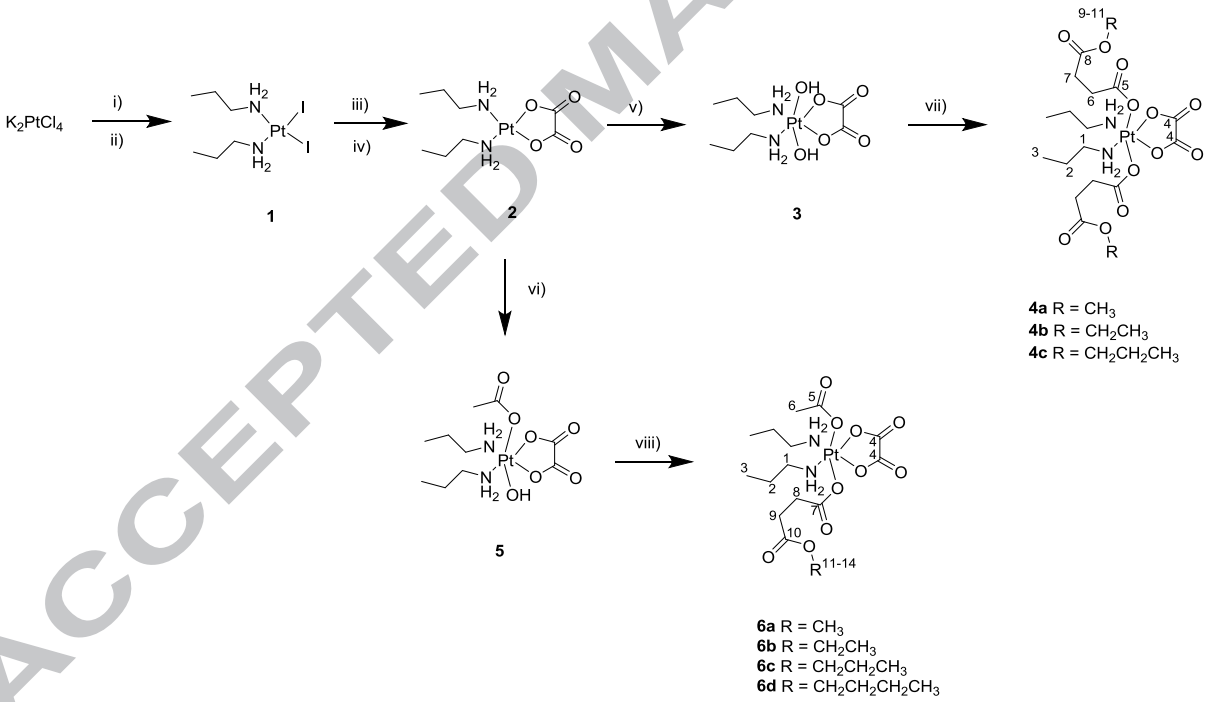
3. Results and Discussion

3.1 Synthesis

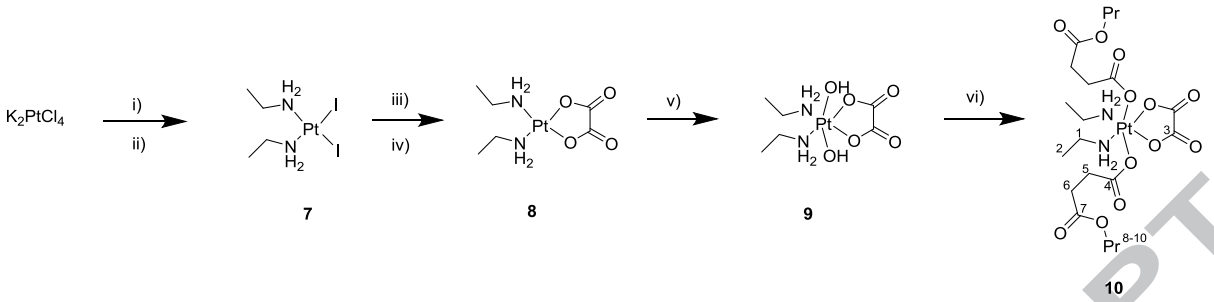
Platinum(IV) complexes were synthesized as shown in Schemes 1 and 2. The platinum(II) precursor *(SP-4-2)*-diiodobis(1-propylamine)platinum(II) (**1**) was prepared by reacting $[PtCl_4]^{2-}$ with an excess of KI forming $[PtI_4]^{2-}$ and further addition of 1-propylamine (Scheme 1). According to Dhara's method [20], iodide ligands in **1** were removed with $AgNO_3$; subsequently, oxalic acid was added to obtain the oxalato complex **2**.

Oxidation of **2** with 30% hydrogen peroxide in aqueous solution yielded the dihydroxidoplatinum(IV) complex (**3**)**.** Oxidation of **2** in a mixture of acetic acid and 30% hydrogen peroxide in aqueous solution, however, gave the unsymmetric acetatohydroxidoplatinum(IV) species **5**.

Noncyclic anhydrides used for carboxylation of hydroxidoplatium(IV) complexes were synthesized by mono-esterification of succinic anhydride with the corresponding anhydrous alcohols (methanol, ethanol, 1-propanol or 1-butanol) and subsequent heating under reflux in acetic anhydride. Carboxylation reactions were performed according to the following general procedure to obtain final compounds **4a-4c, 6a-6d.** The anhydride (2-3 eq) in absolute DMF was added to the respective platinum(IV) precursor (**3, 5 or 9**) and the suspension was heated until a clear solution was formed and stirred at room temperature overnight. DMF was removed under reduced pressure and the crude product was purified via preparative HPLC and dried in vacuo. The bis(ethylamine) analog **10** was synthesized in the same manner (Scheme 2).



Scheme 1. Synthesis of novel bis(carboxylato)oxalatobis(1-propylamine)platinum complexes together with the NMR numbering scheme. i) KI, 5 eq.; ii) 1-propylamine, 4 eq.; iii) $AgNO_3$, 1.90 eq.; iv) $C_2H_2O_4$, 1 eq.; v) 30% H_2O_2/H_2O; vi) CH_3COOH/H_2O_2; vii) $(ROCOCH_2CH_2CO)_2O$/DMF, 3 eq.; viii) $(ROCOCH_2CH_2CO)_2O$/DMF, 1.5 eq.



Scheme 2. Synthesis of *(OC*-6-33*)*-bis(ethylamine)oxalatobis((4-propoxy)-4-oxobutanoato)oxalatoplatinum(IV). i) KI, 5 eq.; ii) ethylamine, 4 eq.; iii) $AgNO_3$, 1.90 eq.; iv) $C_2H_2O_4$, 1 eq.; v) 30% H_2O_2/H_2O; vi) $(CH_3CH_2CH_2OCOCH_2CH_2CO)_2O$/DMF, 2 eq.

3.2 Characterization

The novel complexes were fully characterized by elemental analysis, one and two dimensional multinuclear NMR spectroscopy (^{1}H, ^{13}C, ^{15}N, ^{195}Pt) and ESI-MS. The ^{195}Pt resonance for the platinum(II) complex **2** was detected at −263 ppm (measured relative to K_2PtCl_4). Upon oxidation to the corresponding hydroxidoplatinum(IV) analogue **3** or **5**, the chemical shift was found at 3081 or 3370 ppm, respectively. Carboxylation of **3** or **5** resulted in signals for complexes **4a-c** and **6a-d** at 3372 ppm, the ethylamine complex **10** resonated at 3374 ppm. The symmetric complexes **4a–c** displayed NH_2 proton resonances as a broad multiplet at around 7.24 ppm, whereas unsymmetric complexes **6a-d** featured a marked splitting of this signal, giving two broad multiplets at 7.38 and 7.17 ppm.

3.3 Lipophilicity

Determining major pharmacokinetic processes such as membrane and cell permeation, biotransformation and clearance of a drug, lipophilicity is an essential physico-chemical parameter [22].

In addition to its role in solubility as well as tissue distribution and metabolism, lipophilicity can be a relevant factor modulating the cytotoxic properties of a platinum drug. As has been shown for various types of platinum complexes, a good correlation exists between IC_{50} and log *P* values [19,23]. Herein, we have determined the lipophilicity of all new compounds by RP-HPLC, using isocratic methods and varying compositions of water/MeOH as the mobile

phase. In contrast to the classical shake-flask method, modern HPLC instrumentation is sensitive, and providing fast results in parallel. Further, chromatographic retention factors as a measure of partitioning between the mobile phase and the stationary phase (C18) can be used as a direct measure of lipophilicity, without the need of converting them into log *P* values [21]. The obtained retention factors are summarized in Table 1 as log k_w values (retention factor extrapolated to purely aqueous mobile phase). There is an unambiguous correlation between IC_{50} and log k_w values: the higher the lipophilicity, the higher the cytotoxicity (the lower the IC_{50} value).

	IC_{50} [µM]			log k_w	reduction half-life [h]
	A549	CH1(PA-1)	SW480		
4a	> 400	12 ± 4	188 ± 33	1.5	150
4b	291 ± 32	8.1 ± 1.1	119 ± 15	2.42	120
4c	153 ± 35	4.0 ± 0.1	52 ± 15	2.88	78
6a	> 300	13 ± 1	103 ± 25	1.82	116
6b	270 ± 107	9.1 ± 1.0	81 ± 11	2.13	111
6c	202 ± 77	5.9 ± 2.2	61 ± 29	2.57	53
6d	119 ± 42	2.8 ± 0.9	42 ± 15	2.84	55
10	173 ± 32	2.0 ± 0.3	73 ± 3	2.73	72

Table 1. *In vitro* cytotoxicity, log k_w and reduction half-lives of the new platinum(IV) complexes. IC_{50} values (in µM, means ± standard deviations) of **4a–c**, **6a–d** and **10** were determined by the MTT assay (exposure time: 96 h) in three human cancer cell lines.

3.4 Reduction by ascorbic acid

Since activation of platinum(IV) compounds by reduction is critical for their activity, the rate of reduction was studied by incubating the synthesized platinum(IV) complexes with a 25-fold excess of ascorbic acid in phosphate buffered D_2O solution (pD 7.4). At that point it should be emphasized, that in living systems a series of reductants is available, one of which is ascorbic acid, which was chosen for the present study. A clear trend is visible for the symmetrical as well as the unsymmetrical complexes: With increasing chain length of the succinic ester, the reduction of the platinum(IV) compound to platinum(II) is facilitated. Reduction half-lives of the presented platinum(IV) compounds are in the range of 2.5 to 5 days, which is slow but not unexpected for platinum(IV) compounds with such a type of N_2O_4 coordination sphere [24].

3.5 Cytotoxicity in cancer cell lines

Compounds **4a–c**, **6a–d** and **10** were tested for their capacity of inhibiting proliferation of the human cancer cell lines A549 (non-small cell lung cancer), CH1(PA-1) (ovarian teratocarcinoma) and SW480 (colon carcinoma) by the MTT assay, with CH1(PA-1) cells

being the most sensitive, the P-glycoprotein-expressing SW480 cells intermediately and the highly multidrug-resistant A549 cells the least sensitive of these cell lines, as expected. Concentration–effect curves (Figures 2 and 3) and the corresponding IC_{50} values (listed in Table 1) reveal the following structure–activity relationships: Within each of the two compound series, cytotoxic potency increases with the length of the terminal alkyl chain of the axial ligand(s) (Figure 4). For each CH_2 group subtracted, the IC_{50} values increase on average 1.8–1.9 times within series **4a–c** (containing two identical variable ligands) and 1.4–1.7 times within series **6a–d** (containing just one variable ligand), depending on the cell line (and except for two cases where the IC_{50} value is either higher than the tested range or varies around the maximum concentration applied). In each cell line, the ranges of IC_{50} values of the two series overlap largely. Hence, replacing one of the identical axial ligands of **4a–c** with an acetato ligand is not necessarily disadvantageous and often has negligible effect. Overall, **6d** is the most cytotoxic within these series of compounds, reaching an IC_{50} value as low as 2.8 µM in CH1(PA-1) cells, second only to compound **10** (IC_{50} = 2.0 µM), which, however, shows only intermediate potency in the other two cell lines. Despite its higher potency in CH1(PA-1) cells, the overall activity of compound **10** is quite well comparable with that of its analog **4c**, from which it differs only by the presence of two equatorial ethylamine instead of propylamine ligands.

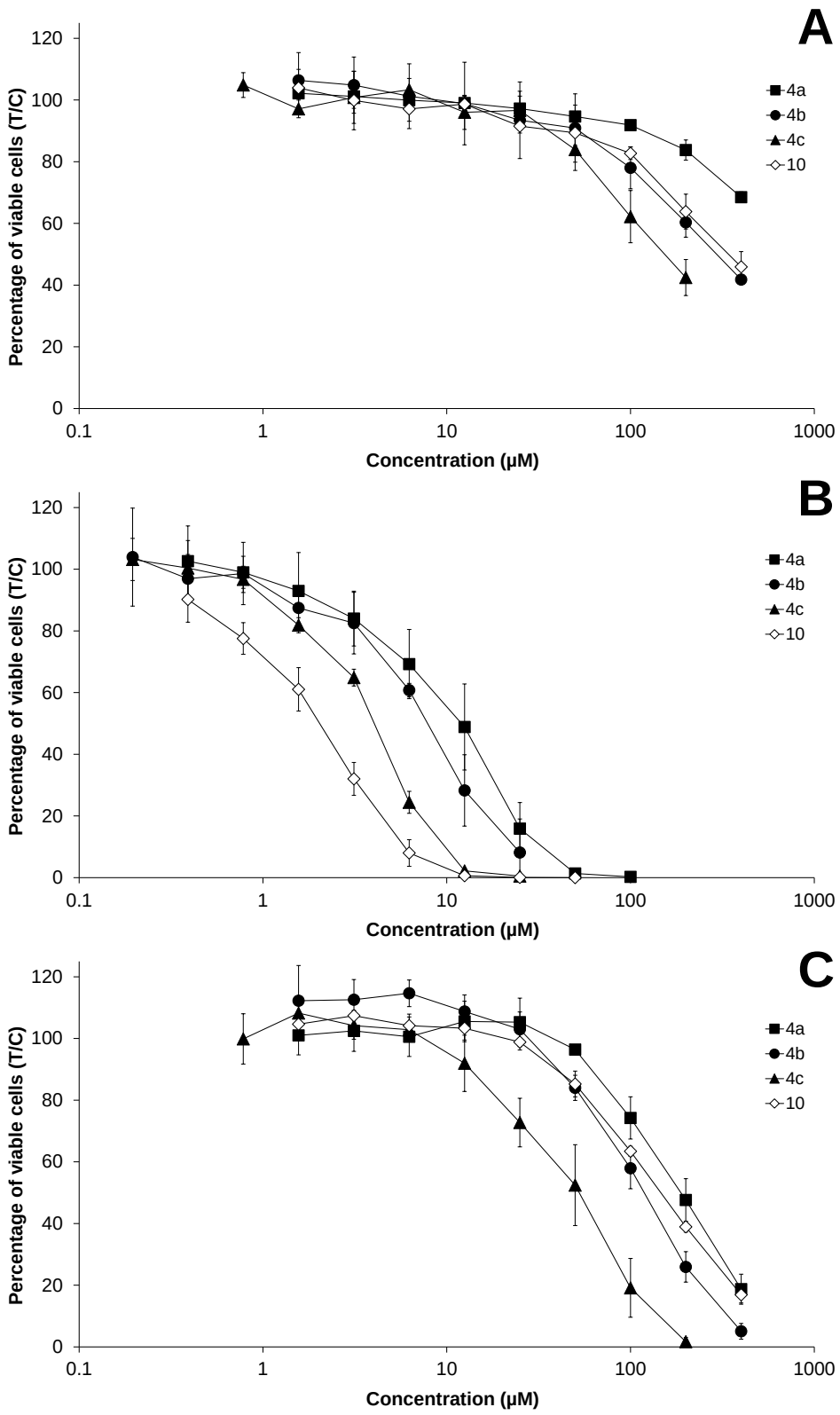


Figure 2. Concentration–effect curves based on the MTT assay (exposure time: 96 h) of compounds **4a–c** and **10** in A549 (A), CH1(PA-1) (B) and SW480 (C) cells.

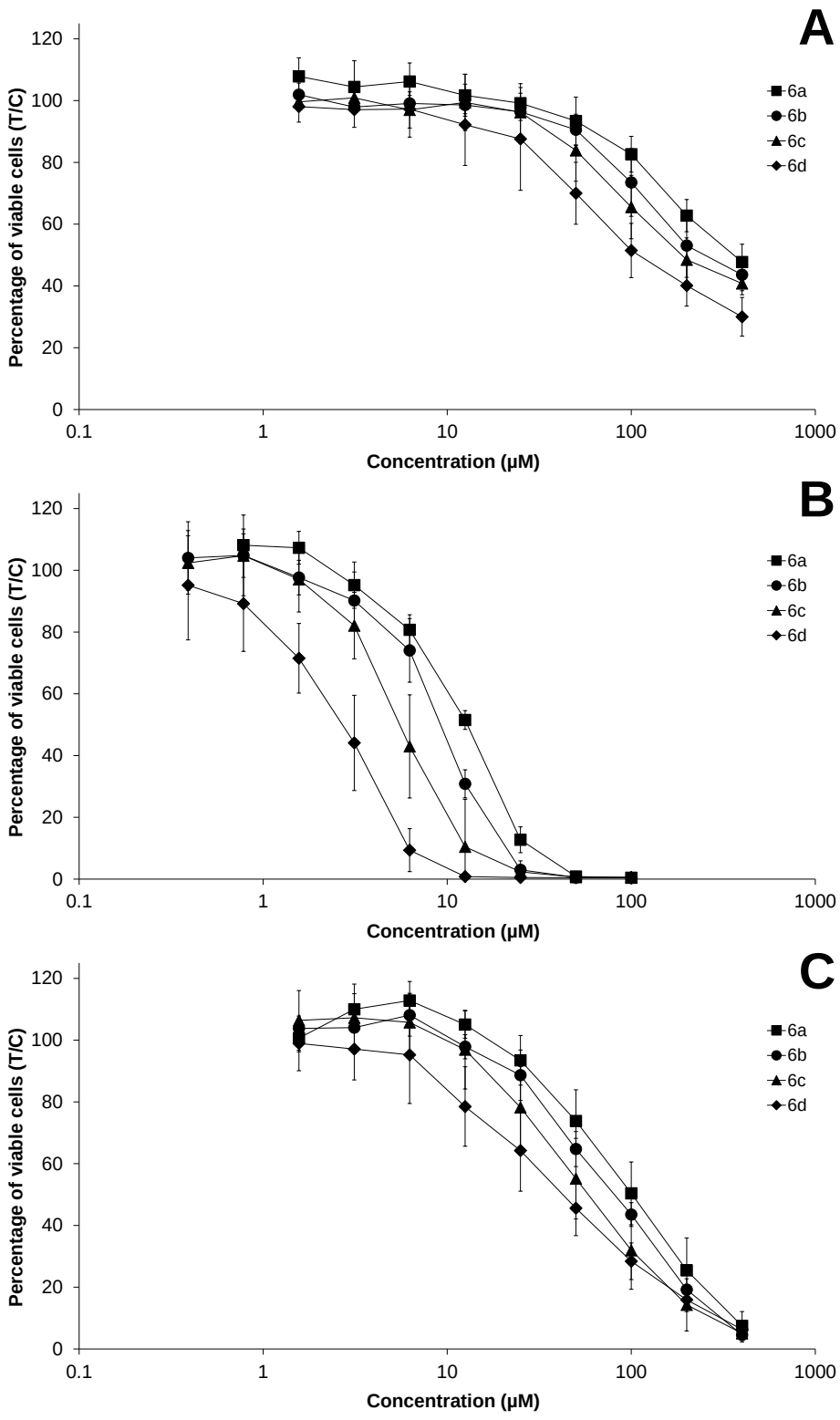


Figure 3. Concentration–effect curves based on the MTT assay (exposure time: 96 h) of compounds **6a–d** in A549 (A), CH1(PA-1) (B) and SW480 (C) cells.

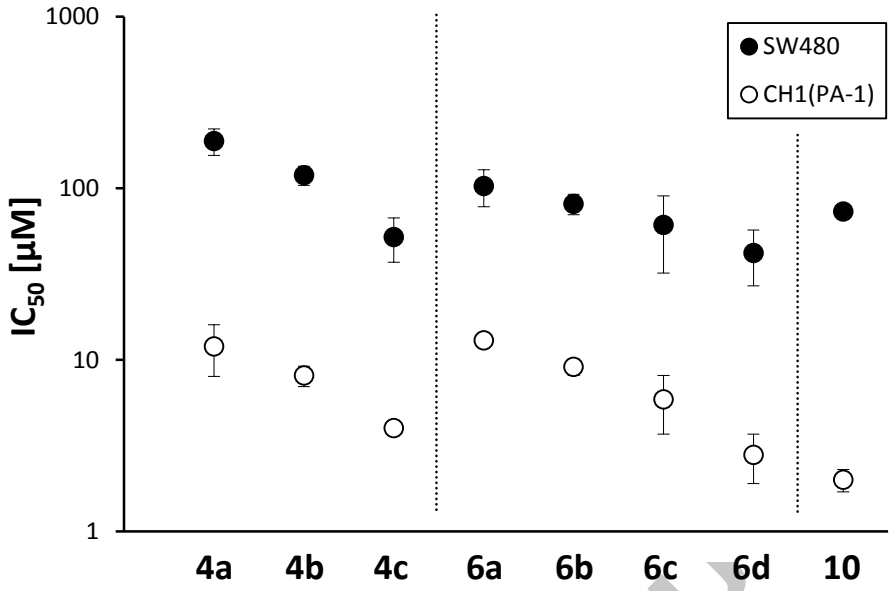
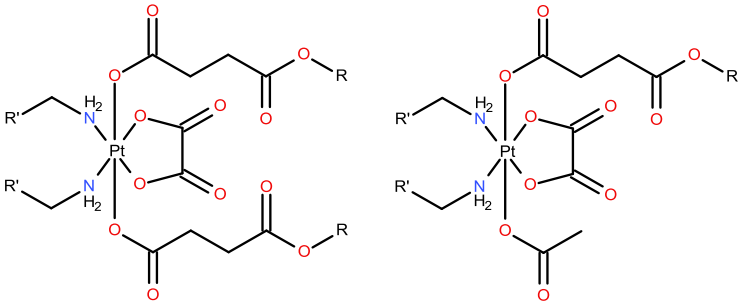


Figure 4. Structure–activity relationships in CH1(PA-1) and SW480 cells. Dependence of IC_{50} values (means ± standard deviations) on the axial ligands for compound series **4a–4c** and **6a–6d**, compared to compound **10**.

5. Conclusion

Seven novel oxalatobis(1-propylamine)platinum(IV) complexes comprising three symmetrical and four unsymmetrically coordinated complexes were synthesized and fully characterized; additionally, a bis(ethylamine)oxalatoplatinum(IV) analogue was synthesized and investigated for comparison in order to judge the influence of the length/lipophilicity of the equatorial amine ligand. Lipophilicity of the compounds in either series as determined by reverse-phase HPLC corresponds to the length of the alkyl chain of the succinic ester. In general, there is a good correlation between the lipophilicity and cytotoxic potency: the longer the terminal alkyl chain, the lower the IC_{50} value. As expected for such type of complexes featuring a N_2O_4 coordination sphere, an overall slow rate of reduction was found, which was further influenced by the length of the axial ligands (esters). However, the cytotoxic properties of the complexes could not further be increased since higher lipophilicity results in a lack of solubility in aqueous media.



Highlights

Diaminetetracarboxylatoplatinum(IV) complexes are potential anticancer prodrugs.

Novel complexes exhibited IC_{50} values down to the low micromolar range.

Lipophilicity and reduction for two compound series was determined.

Lipophilicity as well as reduction were found to parallel the cytotoxic properties.

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