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Platinum(IV) Complexes Featuring One or Two Axial Ferrocene Bearing Ligands – Synthesis, Characterization, and Cytotoxicity

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Ferrocenyl compounds show interesting antiproliferative properties. Consequently, ferrocene bearing moieties were prepared and coupled for the first time to anticancer platinum(IV) complexes. The compounds, featuring either one or two axially coordinated ferrocene-containing ligands, were fully characterized by ESI-MS and multinuclear (^{1}H, ^{13}C, ^{15}N, and ^{195}Pt) one- and two-dimensional NMR spectroscopy. Their cytotoxicity was investigated in three human cancer cell lines deriving from ovarian carcinoma (CH1), colon carcinoma (SW480), and non-small-cell lung carcinoma (A549) by means of the colorimetric MTT assay. Promising IC_{50} values in the low micromolar range in CH1 and SW480 human cancer cells were found.

Introduction

In 1965, Barnett Rosenberg discovered accidentally the ability of cisplatin to inhibit cell proliferation.[1] After cisplatin had been granted approval in 1978 as a chemotherapeutic,[2] many efforts have been made to develop novel platinum compounds with anti-proliferative potential. Besides cisplatin, two so-called second- and third-generation platinum drugs, namely carboplatin and oxaliplatin, gained worldwide approval as antineoplastic drugs (Figure 1). Three other platinum-based compounds, nedaplatin, lobaplatin, and heptaplatin, gained regional approval in Japan, China, and South Korea, respectively.[3] Due to severe side-effects of cisplatin and its analogues and tumor resistance, and due to the fact that platinum(II) compounds are kinetically labile agents, the investigation of platinum(IV) compounds has recently received more and more interest. Platinum(IV) agents are kinetically inert, thus opening up the possibility of being administered orally and thereby enabling chemotherapy to become a more convenient treatment. Furthermore, six instead of only four coordination sites may be varied, facilitating a better fine-tuning of the pharmacological properties of the drug. By now, four platinum(IV) compounds have found their way into clinical trials, namely tetraplatin, iproplatin, satraplatin, and LA-12.[4]

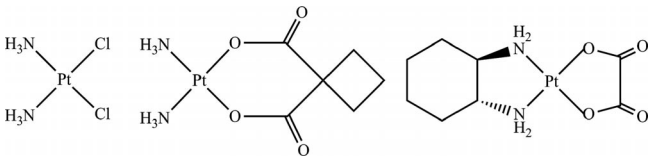

Figure 1. Worldwide approved platinum-based drugs: cisplatin (left), carboplatin (middle), and oxaliplatin (right).

Tetraplatin was abandoned due to its high toxicity in vivo, whereas iproplatin showed a lack of activity on account of its slow reduction rate.[5] Satraplatin failed to gain approval by the FDA but is still being investigated in combination therapy, while its derivative, LA-12 was in phase I clinical trials after having shown good in vivo results in mice.[4] Besides platinum-based metallodrugs, transition-metal-based complexes, such as ferrocene-bearing compounds, have shown strong antiproliferative effects in vitro as well as antitumor effects in vivo.[6,7] The most intensively investigated ferrocene-based compounds with anticancer potential are ferrocifens, prepared by replacing a phenyl group with ferrocene in tamoxifen, a selective estrogen receptor modulator (SERM) used in hormone-dependent (ER+) breast cancer treatment. In 1996, Jaouen et al. coupled ferrocene to 4-hydroxytamoxifen and modified the length of the carbon chain in order to optimize its pharmacological properties (Figure 2).[8] The hydroxyferrocifens show antiproliferative activity in hormone-dependent and in hormone-independent cells, whereas tamoxifen and hydroxytamoxifen are inactive in the latter.[9] Investigation of ferrocene-based anticancer agents ranged from design of ferrocenium salts (first investigated by Köpf-Maier et al. in

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1984)[10] over combination of ferrocenyl groups with transition-metal complexes and to coupling of ferrocene moieties to drug delivery systems, such as polymers and nanoparticles.[9] During the past two decades, the synthesis of several platinum(II) compounds bearing ferrocene moieties has been accomplished.[9,11–13] Some of these compounds have shown promising IC_{50} values (Figure 3): (i) Nieto et al. recently published the successful synthesis and first cell culture tests of a *cis*-configured ferrocene-platinum derivative, which showed in vitro activity in human breast, cervix, lung and colon cancer cells in the low micromolar range (partially exceeding the antiproliferative activity of cisplatin);[11] (ii) a *trans*-dichloridoplatinum(II) complex featuring two ferrocene-bound phosphane units was designed by Schulz et al., which yielded low IC_{50} values in the micromolar range in the ovarian cancer cell line A2780.[13] A platinum(IV)-ferrocenyl system was described recently.[14] However, with the aim of combining the advantages of anticancer platinum(IV) complexes with the therapeutic potential of ferrocene-based compounds, we report here the synthesis, characterization, and antiproliferative potential of the first anticancer platinum(IV) complexes bearing ferrocene moieties as axial ligands.

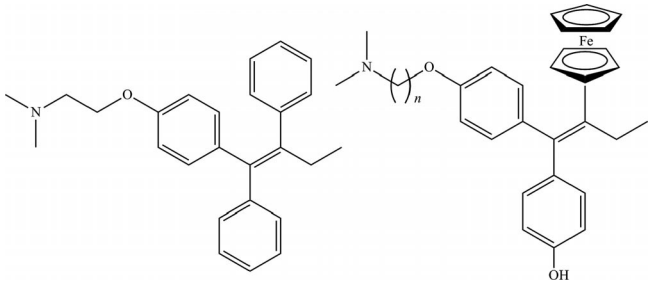
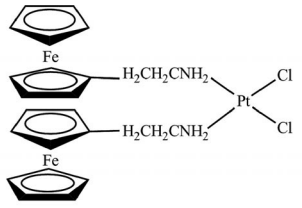


Figure 2. Molecular structures of SERM tamoxifen (left) and hydroxyferrocifens (right).



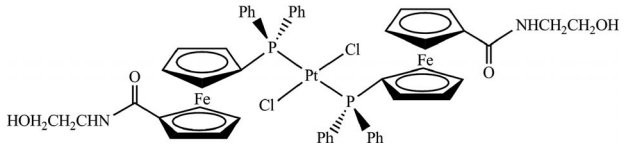


Figure 3. Cytotoxic platinum(II) complexes with ferrocene-bearing ligands.

Results and Discussion

Synthesis

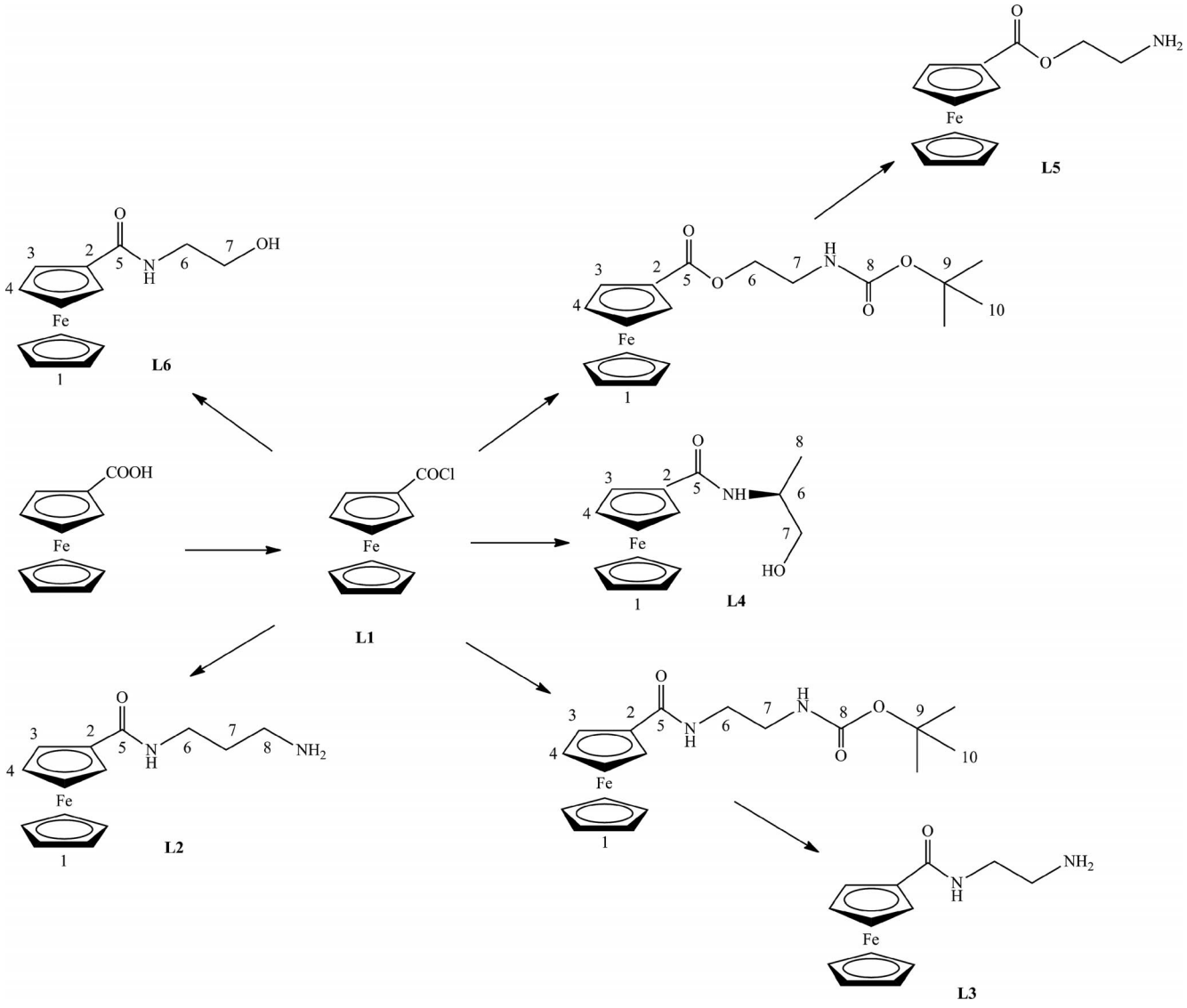
For generation of ferrocene precursors **L2**–**L6**, the synthesis started with preparation of ferrocenecarboxylic acid according to literature methods (Scheme 1).[15] The acid was converted into the acyl chloride, subsequently brought to reaction with the desired diamine, *N*-*boc*-ethylenediamine, *N*-*boc*-ethanolamine or amino alcohol, and characterized by ^{1}H NMR spectroscopy. Precursors **L2**, **L4**, and **L6** could directly be used without further purification for coupling with compounds **2**, **8**, and **10** (Schemes 2 and 3), respectively. Before amidation, the *N*-*boc* protecting groups were removed from precursors of **L3** and **L5** by reaction with conc. trifluoroacetic acid (TFA).

All investigated complexes were prepared from $K_2[PtCl_4]$ according to literature methods by conversion into two different platinum(II) precursors, dichlorido(ethane-1,2-diamine) platinum(II) and (*1R*,*2R*-diaminocyclohexane)(oxalato)platinum(II). Both complexes were oxidized subsequently in the presence of hydrogen peroxide to yield dihydroxidoplatinum(IV) complexes **1** and **7** (Schemes 2 and 3). Preparation of dicarboxylic acids **2** and **8** was performed with succinic anhydride. Activation of the uncoordinated carboxylic acid groups followed by conversion into amides was accomplished by 1,1′-carbonyldiimidazole (CDI). The formed platinum(IV) imidazolides were brought to reaction in situ with ferrocene-bearing amines **L2**, **L3**, and **L5**, which resulted in amides **4**, **3**, and **11**, respectively. Synthesis of esters **5** and **12** was carried out by using the peptide coupling reagent *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine. Since complexes **3**, **4**, **5**, **11**, and **12** show only poor solubility in water, analogous complexes with only one axial ferrocene fragment were prepared. For that purpose, (1*R*,2*R*-diaminocyclohexane)oxalatoplatinum(II) was oxidized with peracetic acid in acetic acid, which yielded acetato(1*R*,2*R*-diaminocyclohexane)hydroxido(oxalato)platinum(IV) (**9**). Thus, carboxylation with succinic anhydride of only one axial coordination site was facile, which resulted in an enhanced solubility in water of the substance when converted into esters and amides, respectively. Esterification and amidation were achieved by the same reaction pathways as described above. The final products **13**, **14**, and **15** were isolated in moderate yields of 20–41%.

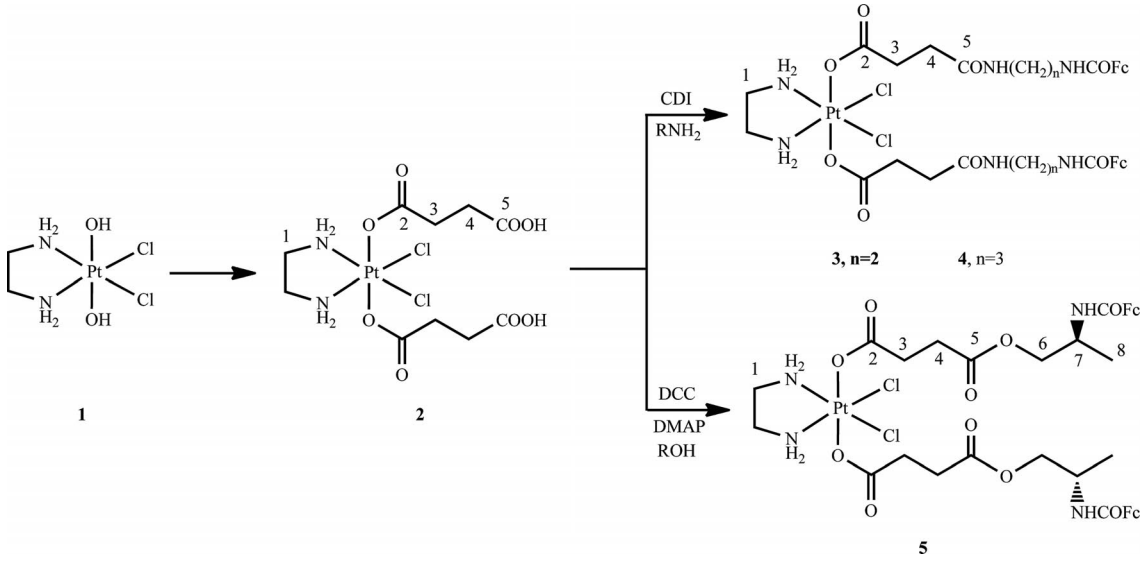
Spectroscopic Characterization

The final products **3**–**5** and **11**–**15** were fully characterized by elemental analysis, ESI-MS and multinuclear (^{1}H, ^{13}C, ^{15}N, ^{195}Pt) 1D and 2D NMR spectroscopy, whereas structures of ferrocene precursors **L2**–**L6** were verified by ^{1}H NMR spectroscopy. Carboxylation and further derivatization can best be judged by NMR spectroscopy.

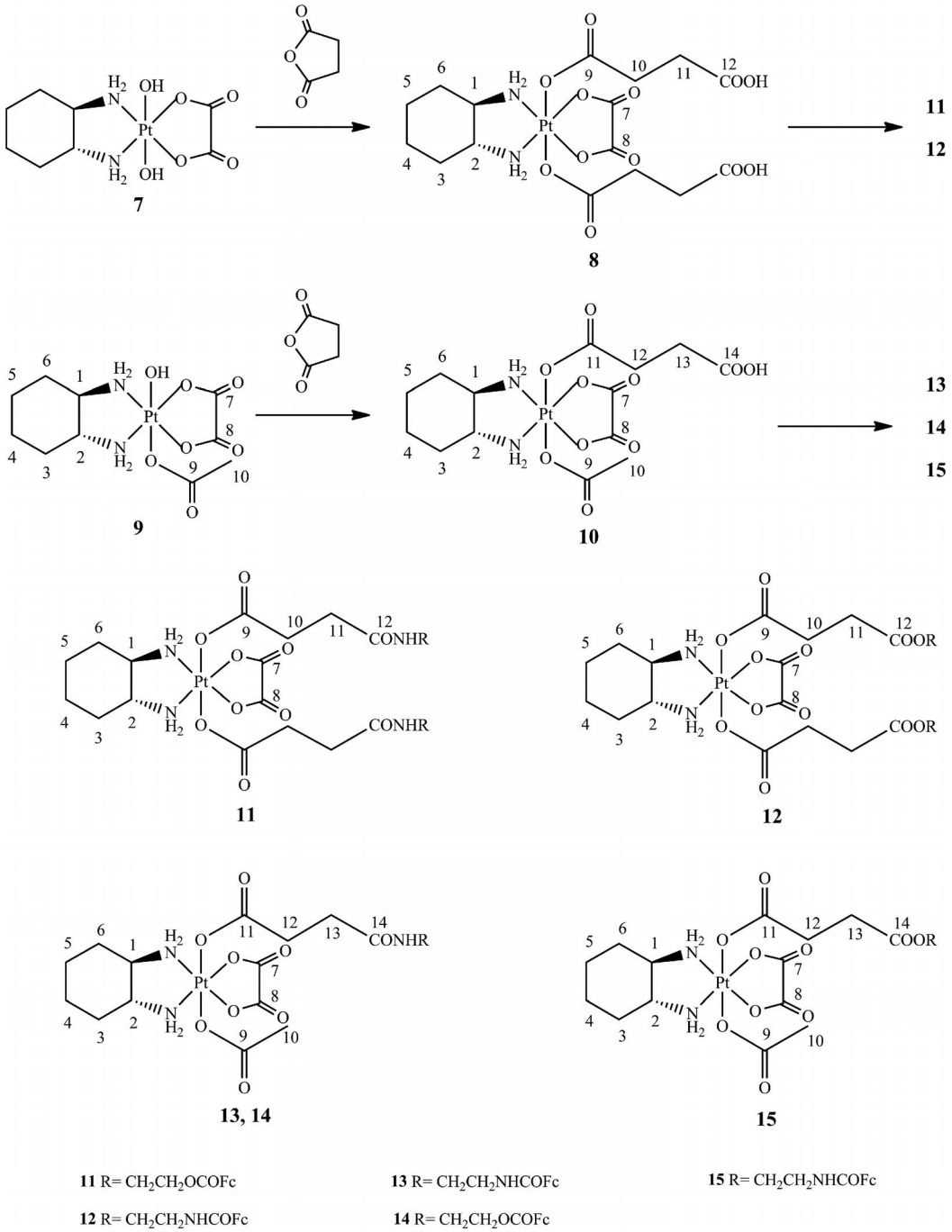
By analysis of the 2D NMR spectra, all protons of the final products could be assigned except for the two methylene groups in the axial position nearest to the platinum nucleus because of several overlaps. It was possible to distinguish between the three quaternary C=O carbon atoms because of the long-range shift correlation signals arising from the carbon atoms and protons of the cyclopentyl ring or protons belonging to the residue of the coupled ligand.



Scheme 1. Synthesis of ferrocene precursors **L2**–**L6** and NMR numbering scheme.



Scheme 2. Synthesis of complexes **3**–**5** and NMR numbering scheme.



Scheme 3. Synthesis of platinum(IV) complexes **11**–**15** and NMR numbering scheme.

As described in the literature,[16] novel Pt^{IV} complexes with the $Cl_2N_2O_2$ coordination sphere show ^{195}Pt resonances in the region around 2656 ppm, whereas resonances for oxaliplatin-type platinum(IV) complexes appear in the region of 3230 ppm. As anticipated, the ^{195}Pt resonances are comparable for oxaliplatin-based Pt^{IV} complexes **13**, **14**, and **15** with one acetato and one derivatized carboxylato ligand in the axial position to those for their biscarboxylated analogues. ESI-MS spectra were measured in the positive as well as in the negative mode. The highest peak observed in each spectrum in the positive mode is $[M + Na]^+$, which is also in accordance with the calculated values.

Cytotoxicity

The cytotoxicity of dichlorido(ethane-1,2-diamine)platinum(IV) complexes **3**–**5**, as well as of the oxaliplatin derivatives **11**–**15**, was determined in cisplatin-sensitive CH1 (ovarian carcinoma) and in intrinsically cisplatin-resistant SW480 (colon carcinoma) as well as in A549 (non-small-cell lung carcinoma) cancer cells by means of the MTT colorimetric assay (Table 1). In general, the antiproliferative potency of novel ferrocene-containing complexes is highest in the ovarian carcinoma cell line CH1 with promising IC_{50} values in the low micromolar range (0.84–2.3 μM). Remark-

ably, the equatorial ligand sphere and the number of ferrocene moieties of the platinum compounds seem to have no pronounced influence on these properties. In contrast, the cytotoxicity of all tested complexes in the lung carcinoma cell line A549 is only moderate with IC_{50} values well above 20 μM. Antiproliferative potency in SW480 colon carcinoma cells was observed in an intermediate range, and a clear-cut structure–activity relationship in this cell line could be drawn. Compounds **3**–**5** featuring more cisplatin-like equatorial ligands, i.e. ethane-1,2-diamine and dichlorido, were less cytotoxic (IC_{50} = 32–46 μM) than oxaliplatin-type complexes **11**–**15** (IC_{50} = 2.7–5.6 μM).

Table 1. Cytotoxicity of complexes **3**–**5** and **11**–**15** in CH1, A549, and SW480 cancer cells.

IC_{50} [μM][a]			
Compound	CH1	SW480	A549
3	1.5 ± 0.4	43 ± 5	69 ± 15
4	1.6 ± 0.4	32 ± 11	65 ± 8
5	2.3 ± 0.5	46 ± 9	84 ± 1
11	0.86 ± 0.20	4.4 ± 1.4	>50
12	1.2 ± 0.1	3.9 ± 1.3	38 ± 4
13	0.84 ± 0.13	2.7 ± 1.0	24 ± 6
14	1.6 ± 0.1	4.8 ± 1.3	48 ± 2
15	1.3 ± 0.0	5.6 ± 0.9	49 ± 12
cisplatin[b]	0.14 ± 0.03	3.3 ± 0.4	1.3 ± 0.4
oxaliplatin	0.18 ± 0.01	0.29 ± 0.05	0.98 ± 0.21
8[c]	55 ± 28	44 ± 9	–
L6	>280	>320	>320

[a] 50% inhibitory concentrations in the MTT assay (96 h exposure). Values are means (± standard deviations) obtained from at least three independent experiments. [b] Data taken from ref.[17] [c] Data taken from ref.[18].

The latter behavior was expected, since oxaliplatin is approved for clinical treatment of metastatic colorectal carcinoma and shows above-average in vitro activity in many intrinsically cisplatin-resistant colon carcinoma cell lines such as SW480. As could be shown by evaluating monoacetato complexes **13**, **14**, and **15**, the linking fragment between the carboxylatoplatinum(IV) moiety and the ferrocene part (NH–CH_2–CH_2–NH vs. NH–CH_2–CH_2–O vs. O–CH_2–CH_2–NH) has nearly no influence on cytotoxicity. Furthermore, no substantial differences in the antiproliferative behavior of bis- and mono(ferrocene) derivatives (**11** vs. **14** and **12** vs. **15**) could be observed.

There is also no difference depending on the length of the linking methylene moiety (NH–CH_2–CH_2–NH vs. NH–CH_2–CH_2–CH_2–NH) when comparing the cytotoxicity of compounds **3** and **4**. Generally, all complexes are less active by factors of 6–16 in the cisplatin-sensitive cell line CH1 than cisplatin. Likewise, oxaliplatin derivatives **11**–**15** are by an order of magnitude less potent than oxaliplatin in SW480 cells. All novel complexes presented in this manuscript are hence less effective than cis- and oxaliplatin, but it should be kept in mind that cis- and oxaliplatin are platinum(II) complexes, whereas the central platinum ion in complexes **3**–**5** and **11**–**15** has the oxidation state +4. This means that they act as prodrugs and, consequently, have to be activated in the organism by reduction. Therefore, their suitability according to the prodrug concept cannot be assessed based on these in vitro investigations alone. Further experiments, especially in vivo, are warranted.

Exemplarily, one of the ferrocene compounds, namely **L6**, was tested for its antiproliferative potential. IC_{50} values were mostly not reached with maximum tested concentrations of 320 μM, attesting a very low cytotoxicity. The platinum(IV) precursor **8** shows also a low antiproliferative activity (Table 1), however, when **L6** and **8** were brought to reaction resulting in ester **12**, a significant increase in cytotoxicity (one order of magnitude as compared to **8**) was observed, warranting further studies.

Conclusions

Platinum(IV) complexes featuring axially coordinated ferrocene-bearing ligands were synthesized for the first time and fully characterized by multinuclear NMR spectroscopy. Taking into account that platinum(IV) complexes act as prodrugs, which have to be activated in the organism, they show promising IC_{50} values in the low micromolar range in CH1 and SW480 human cancer cells.

Experimental Section

$K_2[PtCl_4]$ was obtained from Johnson Matthey (Switzerland), ferrocenecarboxylic acid from Alfa Aesar. All other chemicals were purchased from Aldrich, Fluka, Acros, or Fisher and used without further purification. When platinum(II) complexes were involved, syntheses were carried out under light protection; glass-coated magnetic stirring bars were used for each synthesis. For reactions in water, doubly distilled osmosis water was used.

Starting compounds **L1**–**L6** and precursors,[19–22] (SP-4–2)-(*trans*-1R,2R-diaminocyclohexane)oxalatoplatinum(II) (**6**), (*OC*-6–33)-bis(3-carboxypropanoato)dichlorido(ethane-1,2-diamine)platinum(IV) (**2**), (*OC*-6–33)-bis(3-carboxypropanoato)(*trans-1R,2R*-diaminocyclohexane)oxalatoplatinum(IV) (**8**), **9**, and **10**,[23–26] were synthesized according to literature methods.

Physical Measurements: Elemental Analysis was carried out by the Microanalytical Laboratory of the University of Vienna with a 2400 CHN Elemental Analyzer manufactured by Perkin–Elmer. For each submitted substance, the percentage of the elements carbon, hydrogen, and nitrogen was determined. Electrospray ionization mass spectra were recorded with a Bruker Esquire3000 ion trap spectrometer with MeOH as solvent, the molecular mass was determined in the positive as well as in the negative mode. NMR spectra were recorded on a Bruker FT-NMR Avance III 500 MHz instrument at 500.32 (^{1}H), 125.81 (^{13}C), 50.70 (^{15}N), and 107.55 (^{195}Pt) MHz. 2D NMR measurements were recorded by using standard pulse programs. Chemical shifts were referenced relative to the solvent signal for ^{1}H and ^{13}C spectra; for ^{15}N and ^{195}Pt spectra, the external standards $^{15}NH_4Cl$ and $K_2[PtCl_4]$ were used, respectively.

Synthesis of Ferrocene Precursors

Ferrocenyl Chloride (L1): Ferrocenecarboxylic acid was dissolved in abs. CH_2Cl_2 (typically 700 mg in 5 mL of abs. CH_2Cl_2) under an argon atmosphere, and oxalyl chloride (2 equiv.) was added. The solution was stirred for 20 min at room temperature, and the solvent was removed under reduced pressure. The obtained dark red

substance was dissolved in CH_2Cl_2 and used without purification for subsequent reactions.

***N*-3-(Aminopropyl)ferrocenecarboxamide (L2):** Compound **L1** (3.04 mmol) was dissolved in abs. CH_2Cl_2 (5 mL) and added slowly over 2 h at –23 °C to a solution of 1,3-diaminopropane (2.5 mL, 30.4 mmol) in abs. CH_2Cl_2 (50 mL). The solution was filtered (in order to get rid of the dimer) and extracted three times with water; the organic phase was dried with $MgSO_4$. After removal of the solvent under reduced pressure, the product was suspended in diethyl ether and filtered through a G-4 glass filter. The product was dried in vacuo. Yield: 235 mg, 33%. ^{1}H NMR ($CDCl_3$): δ = 6.82 (br. s, 1 H, NH), 4.69 (t, ^3J = 1.9 Hz, 2 H, H3), 4.35 (t, ^3J = 1.9 Hz, 2 H, H4), 4.22 (s, 5 H, H1), 3.53 (m, 2 H, CH_2), 2.94 (m, 2 H, CH_2), 1.76 (m, 2 H, CH_2) ppm.

***N*-2-(Aminoethyl)ferrocenecarboxamide (L3):** Compound **L1** (3.48 mmol) was dissolved in abs. CH_2Cl_2 (6 mL) and then added via a Teflon cannula to a stirred solution of *N*-*boc*-ethylenediamine (826 µL, 5.22 mmol) and triethylamine (964.7 µL 6.96 mmol) in abs. CH_2Cl_2 under an argon atmosphere and left to stir for 1 h. The solution was extracted three times with water, the organic phase was dried with $MgSO_4$, and the solvent was removed under reduced pressure. Yield: 512 mg, 33% of the *N*-*boc*-protected product. ^{1}H NMR ($CDCl_3$): δ = 6.30 (br. s, 1 H, NH), 4.67 (t, ^3J = 1.8 Hz, 2 H, H3), 4.31 (t, ^3J = 1.9 Hz, 2 H, H4), 4.18 (s, 5 H, H1), 3.42 (m, 2 H, CH_2), 2.90 (m, 2 H, CH_2), 1.63 (s, 9 H, H10) ppm. The product was dissolved in trifluoroacetic acid (4 mL) and left to stir for 5 min. Subsequently, trifluoroacetic acid was removed under reduced pressure, and the crude product was extracted three times with CH_2Cl_2 and with a saturated $NaHCO_3$ solution. The organic phase was dried again over $MgSO_4$, and the solvent was removed under reduced pressure.

(*S*)-*N*-(1-Hydroxypropan-2-yl)ferrocenecarboxamide (L4): Compound **L1** (2.17 mmol) was dissolved in abs. CH_2Cl_2 (4 mL) and then added via a teflon cannula to a stirred solution of (*S*)-2-amino-1-propanol (606 µL, 4.34 mmol) and triethylamine (604.9 µL 4.34 mmol) in abs. CH_2Cl_2 under an argon atmosphere and left to stir for 1 h. The solution was extracted three times with water, and the organic phase dried with $MgSO_4$. The solvent was removed under reduced pressure. Yield: 171 mg, 28%. ^{1}H NMR ($CDCl_3$): δ = 5.83 (m, 1 H, NH), 4.72 (m, 1 H, H3), 4.69 (m, 1 H, H3), 4.39 (s, 2 H, H4), 4.25 (s, 5 H, H1), 3.79 (m, 1 H, H6/H7), 3.65 (m, 1 H, H6/H7), 2.96 (m, 1 H, H6/H7), 1.30 (d, ^3J = 6.9 Hz, 3 H, H8) ppm.

[(2-Aminoethoxy)carbonyl]ferrocene (L5): Compound **L1** (3.04 mmol) was dissolved in abs. CH_2Cl_2 (6 mL) and then added via a teflon cannula to a stirred solution of *N*-*boc*-ethylenediamine (705.4 µL, 4.56 mmol) and triethylamine (847 µL 6.04 mmol) in abs. CH_2Cl_2 under an argon atmosphere and left to stir for 1 h. The solution was extracted three times with water, and the organic phase dried over $MgSO_4$. The solvent was removed under reduced pressure. Yield: 384 mg, 32.5% of the *N*-*boc*-protected product. ^{1}H NMR ($CDCl_3$): δ = 4.85 (t, ^3J = 1.8 Hz, 2 H, H3), 4.45 (t, ^3J = 1.8 Hz, 2 H, H4), 4.32 (m, 2 H, CH_2), 4.24 (s, 5 H, H1), 3.52 (m, 2 H, CH_2), 1.48 (s, 9 H, H10) ppm. The product was dissolved in trifluoroacetic acid (4 mL) and left to stir for 5 min. Subsequently, trifluoroacetic acid was removed under reduced pressure, and the crude product was extracted three times with CH_2Cl_2 and with a saturated $NAHCO_3$ solution. The organic phase was dried again over $MgSO_4$, and the solvent removed under reduced pressure.

{[(2-Hydroxyethyl)amino]carbonyl}ferrocene (L6): Compound **L1** (3.04 mmol) was dissolved in abs. CH_2Cl_2 (6 mL) and then added via a teflon cannula to a stirred solution of ethanolamine (550.4 µL, 9.12 mmol) and triethylamine (847 µL 6.04 mmol) in abs. CH_2Cl_2 under an argon atmosphere and left to stir for 1 h. The solution was filtered and extracted three times with water. The organic phase was dried with $MgSO_4$, and the solvent was removed under reduced pressure. Yield: 380 mg, 50%. ^{1}H NMR ($CDCl_3$): δ = 6.15 (br. s, 1 H, NH), 4.71 (t, ^3J = 1.5 Hz, 2 H, H3), 4.40 (t, ^3J = 1.6 Hz, 2 H, H4), 4.25 (s, 5 H, H1), 3.84 (t, ^3J = 4.9 Hz, 2 H, CH_2), 3.59 (m, 2 H, CH_2) ppm.

Synthesis of precursors 9 and 10

(*OC*-6–44)-Acetato(*1R*,*2R*-diaminocyclohexane)hydroxido(oxalato)platinum(IV) (9): Compound **6** (3 g, 7.6 mmol) was suspended in acetic acid (60 mL), peracetic acid (3.3 mL, 2.5 equiv.) was added, and the solution stirred for 30 min. The solution turned clear and was left to stir for 24 h. Acetic acid was removed under reduced pressure; the residue was dissolved in acetic acid (20 mL) and evaporated again. The product was suspended in ethyl acetate, methanol was added until the appearance of the suspension did not change any more, and the suspension was filtered. Solvents were removed on a rotary evaporator, and the white solid was dried in vacuo. Yield: 2.43 g, 66%. ^{1}H NMR ([D$_6$]DMSO) = 8.59 (br. m, 1 H, NH_2), 8.18 (br. m, 1 H, NH_2), 7.80 (br. m, 1 H, NH_2), 7.10 (m, 1 H, NH_2), ≈2.55 (H1/H2, underneath the DMSO peak), 2.07 (m, 2 H, H3/4/5/6), 1.92 (s, 3 H, H10), 1.54–1.29 (br. m, 4 H, H3/4/5/6); 1.13 (m, 2 H, H3/4/5/6) ppm.

(*OC*-6–44)-Acetato(3-carboxypropanoato)(*1R*,*2R*-diaminocyclohexane)oxalatoplatinum(IV) (10): Compound **9** (1 g, 2.04 mmol) and succinic anhydride (306.2 mg, 3.06 mmol) were suspended in abs. DMF (15 mL) and stirred for 24 h at 50 °C. The solvent was removed under reduced pressure, and the crude product was suspended in acetone. Methanol was added stepwise until the amount of insoluble solid did not change any more. The solution was filtered, the solvents were removed under reduced pressure, the residue was dissolved in acetone again, and ethyl acetate was added until no further precipitation was observed. The product was filtered, washed with diethyl ether, and dried in vacuo. Yield: 945 mg, 79%. ^{1}H NMR ([D$_6$]DMSO): δ = 12.13 (br. m, 1 H, OH), 8.11–8.52 (br. m, 4 H, NH_2), 2.58 (m, H1/H2), 2.40 (m, 2 H, H12/H13), 2.12 (m, 2 H, H3/H4/H5/H6), 1.97 (s, 3 H, H10), 1.51 (m, 2 H, H3/H4/H5/H6), 1.41 (m, 2 H, H3/H4/H5/H6), 1.17 (m, 2 H, H3/H4/H5/H6) ppm.

General Procedure for the Synthesis of Complexes 3, 4, 11, 13, and 14: 1,1′-Carbonyldiimidazole and the prevailing complex (**2**, **8** or **10**) were dissolved in abs. DMF stirred for 10 min at 60 °C and simultaneously flushed with argon. The solution was cooled down to room temperature, the required amine was added (**L2**, **L3** or **L5**), and the solution was left to stir for 24 h. The solvent was removed under reduced pressure; the crude product was dissolved in acetone and precipitated with diethyl ether. The product was filtered and subsequently purified by column chromatography.

General Procedure for the Synthesis of Complexes 5, 12, and 15: To a stirred solution of 4-dimethylaminopyridine, carboxylic acid (**2**, **8** or **10**), and the alcohol (**L4** or **L6**) was added *N*,*N*′-dicyclohexylcarbodiimide over 100 min. under an argon atmosphere. The solution was left to stir for 24 h at room temperature. The volume was reduced to 3 mL, and the suspension was filtered. The remaining solution was evaporated, and the crude product was purified by column chromatography.

(*OC*-6–33)-Dichlorido(ethane-1,2-diamine)bis(4-{[2-ferrocenoylamino]ethyl}amino)-4-oxobutanoatoplatin(IV) (3): 1,1′-Carbonyldiimidazole (92 mg, 0.57 mmol), **2** (144 mg, 0.26 mmol) in abs. DMF (6 mL), **L3** (175 mg, 0.64 mmol) in abs. DMF (2 mL). The

crude product was purified by column chromatography (EtOAc/MeOH, 2:1). The obtained product was dried in vacuo. Yield: 69 mg, 26%, yellow powder. $C_{36}H_{46}Cl_2Fe_2N_6O_8Pt·4H_2O$: calcd. C 37.91, H 4.77, N 7.37; found C 37.69, H 4.25, N 7.11. ^{1}H NMR ([D$_6$]DMSO): δ = 8.45 (br. s, 2 H, NH$_2$), 7.94 (br. m, 2 H, NH), 7.83 (br. m, 2 H, NH–COCp), 4.76 (br. m, 4 H, H10), 4.34 (br. m, 4 H, H11), 4.16 (s, 10 H, H12), 3.22 (m, 4 H, H7), 3.18 (m, 4 H, H6), 2.67 (br. m, 4 H, H1), ≈2.5 (H3/H4, underneath the DMSO peak), 2.32 (t, ^3J = 7.3 Hz, 4 H, H3/H4) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 181.7 (C2), 172.0 (C5), 169.6 (C8), 77.0 (C9), 70.4 (C11), 69.9 (C12), 68.6 (C10), 49.2 (C1), 39.3 (C6/7), 39.1 (C6/7), 32.2 (C3/C4), 31.8 (C3/C4) ppm. ^{15}N NMR ([D$_6$]DMSO): δ = 91.4 (NH), 85.8 (NH–COCp), –4.4 (NH$_2$) ppm. ^{195}Pt NMR ([D$_6$]-DMSO): δ = 2655 ppm. MS (180 °C): *m*/*z* = 1091 [M + Na$^+$].

(*OC*-6–33)-Dichlorido(ethane-1,2-diamine)bis(4-{[3-ferrocenoylamino]propyl}amino)-4-oxobutanoatoplatin(IV) (4): 1,1′-Carbonyldiimidazole (109 mg, 0.67 mmol), **2** (184 mg, 0.33 mmol) in abs. DMF (7 mL), **L2** (235 mg, 0.82 mmol) in abs. DMF (2 mL). The crude product was purified by column chromatography (CHCl$_3$/MeOH, 5:1). The obtained product was dried in vacuo. Yield: 73 mg, 20%, yellow powder. $C_{38}H_{50}Cl_2Fe_2N_6O_8Pt·3H_2O$: calcd. C 39.67, H 4.91, N 7.30; found C 39.55, H 4.57, N 7.20. ^{1}H NMR ([D$_6$]DMSO): δ = 8.45 (br. s, 2 H, NH$_2$), 7.85 (br. m, 2 H, NH), 7.75 (br. m, 2 H, NH–COCp), 4.77 (br. m, 4 H, H11), 4.34 (br. m, 4 H, H12), 4.16 (s, 10 H, H13), 3.18 (m, 4 H, H8), 3.12 (m, 4 H, H6), 2.66 (br. m, 4 H, H1), ≈2.5 (H3/H4, underneath the DMSO peak), 2.31 (t, ^3J = 7.1 Hz, 4 H, H3/H4), 1.61 (m, 4 H, H7) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 181.7 (C2), 171.7 (C5), 169.3 (C9), 77.3 (C10), 70.3 (C12), 69.8 (C13), 68.5 (C11), 49.1 (C1), 36.8 (C6/C8), 36.8 (C6/C8), 32.3 (C3/C4), 31.8 (C3/C4), 30.1 (C7) ppm. ^{15}N NMR ([D$_6$]DMSO): δ = 94.1 (NH), 87.9 (NHCOCp), –4.8 (NH$_2$) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 2656 ppm. MS (180 °C): *m*/*z* = 1119 [M + Na$^+$], 1095 [M – H$^+$].

(*OC*-6–33)-Dichlorido(ethane-1,2-diamine)bis(4-{*S*-2-[ferrocenoylamino]propoxy})-4-oxobutanoatoplatin(IV) (5): 4-Dimethylaminopyridine (4.9 mg, 0.04 mmol), *N*,*N*′-dicyclohexylcarbodiimide (84.2 mg, 0.41 mmol) in abs. DMF (5 mL), **2** (111.4 mg, 0.20 mmol) in abs. DMF (7 mL), **L4** (171.4 mg, 0.60 mmol). The crude product was purified by column chromatography (EtOAc/MeOH, 2:1). The obtained product was dried in vacuo. Yield: 55 mg, 26%, yellow powder. $C_{38}H_{48}Cl_2Fe_2N_4O_{10}Pt·3H_2O$: calcd. C 39.60, H 4.72, N 4.86; found C 39.67, H 4.31, N 4.82. ^{1}H NMR ([D$_6$]DMSO): δ = 8.46 (br. s, 2 H, NH$_2$), 8.43 (br. s, 2 H, NH$_2$), 7.58 (d, ^3J = 8.3 Hz, 2 H, NH), 4.84 (br. m, 2 H, H11), 4.80 (br. m, 2 H, H11), 4.35 (br. m, 4 H, H12), 4.21 (m, 2 H, H7), 4.17 (s, 10 H, H13), 4.11 (m, 2 H, H6), 3.95 (m, 2 H, H6), 2.65 (br. s, 4 H, H1), 2.56 (m, 2 H, H3/H4), 2.50 (H3/H4, underneath the DMSO peak), 1.15 (d, ^3J = 6.7 Hz, 6 H, H8) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 180.0 (C2), 172.7 (C5), 169.1 (C9), 76.8 (C10), 70.5 (C12), 70.4 (C12), 69.9 (C13), 68.9 (C11), 68.5 (C11), 67.0 (C6), 49.2 (C1), 43.9 (C7), 31.3 (C3/C4), 30.1 (C3/C4), 17.7 (C8) ppm. ^{15}N NMR ([D$_6$]-DMSO): δ = 96.3 (NH), –5.1 (NH$_2$) ppm. ^{195}Pt NMR ([D$_6$]-DMSO): δ = 2658 ppm. MS (180 °C): *m*/*z* = 1121 [M + Na$^+$].

(*OC*-6–33)-(trans-*1R*,*2R*-Diaminocyclohexane)bis{4-[2-(ferrocenoyloxy)ethylamino]-4-oxobutanoato}oxalatoplatin(IV) (11): 1,1′-Carbonyldiimidazole (85.6 mg, 0.53 mmol), **8** (151.8 mg, 0.24 mmol) in abs. DMF (6 mL), **L5** (234 mg, 0.6 mmol) in abs. DMF (2 mL). The crude product was purified by column chromatography (CHCl$_3$/MeOH, 8:1). The obtained product was dried in vacuo. Yield: 112 mg, 41%, yellow powder. $PtC_{42}H_{50}Fe_2N_4O_{10}$: calcd. C 44.18, H 4.41, N 4.91; C 43.86, H 4.11, N 4.74. ^{1}H NMR ([D$_6$]-DMSO): δ = 8.36 (br. m, 2 H, NH$_2$), 8.15 (br. m, 2 H, NH$_2$), 8.07 (t, ^3J = 5.5 Hz, 2 H, NH), 4.77 (m, 4 H, H17), 4.50 (m, 4 H, H18), 4.23 (s, 10 H, H19), 4.13 (t, ^3J = 5.8 Hz, 2 H, H14), 3.37 (m, 2 H, H13), 2.69 (m, 2 H, H1/H2), ≈2.5 (H10/H11 underneath the DMSO peak), 2.35 (m, 2 H, H10/H11), 2.10 (m, 2 H, H3/H6), 1.50 (m, 2 H, H4/H5), 1.40 (m, 2 H, H3/H6), 1.18 (m, 2 H, H4/H5) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 180.7 (C9), 172.0 (C12), 171.1 (C15), 163.8 (C7/C8), 71.8 (C18), 71.1 (C16), 70.3 (C17), 70.1 (C17/C19), 62.9 (C14), 61.2 (C1/C2), 38.3 (C13), 31.6 (C3/C6/C10/C11), 31.4 (C3/C6/C10/C11), 24.0 (C4/C5) ppm. ^{15}N NMR ([D$_6$]DMSO): δ = 88.8 (NH), –6.3 (NH$_2$) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3233 ppm. MS (180 °C): *m*/*z* = 1164 [M + Na$^+$], 1040 [M – H$^+$].

(*OC*-6–33)-(trans-*1R*,*2R*-Diaminocyclohexane)bis[4-(2-ferrocenoylamino)ethoxy]-4-(oxobutanoato)oxalatoplatin(IV) (12): 4-Dimethylaminopyridine (7.3 mg, 0.06 mmol), *N*,*N*′-dicyclohexylcarbodiimide (136.2 mg, 0.66 mmol) in abs. DMF (5 mL), **8** (190.4 mg, 0.30 mmol) in abs. DMF (8 mL), **L6** (247 mg, 0.90 mmol). The crude product was purified by column chromatography (CHCl$_3$/MeOH, 8:1). The obtained product was dried in vacuo. Yield: 67 mg, 20%, yellow powder. $C_{42}H_{50}Fe_2N_4O_{10}Pt·H_2O$: calcd. C 43.50, H 4.52, N 4.83; found C 43.27, H 4.21, N 4.78. ^{1}H NMR ([D$_6$]DMSO): δ = 8.35 (br. m, 2 H, NH$_2$), 8.17 (br. m, 2 H, NH$_2$), 7.89 (t, ^3J = 5.5 Hz, 2 H, NH), 4.79 (m, 4 H, H17), 4.35 (s, 4 H, H18), 4.23 (s, 10 H, H19), 4.12 (t, ^3J = 5.7 Hz, 2 H, H13), 3.42 (m, 2 H, H14), 2.69 (m, 2 H, H1/H2), ≈2.5 (H10/H11, underneath the DMSO peak), 2.15 (m, 2 H, H10/H11), 2.10 (m, 2 H, H3/H6), 1.50 (m, 2 H, H4/H5), 1.38 (m, 2 H, H3/H6), 1.13 (m, 2 H, H4/H5) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 179.9 (C9), 172.8 (C12), 169.8 (C15), 163.9 (C7/C8), 76.8 (C16), 70.5 (C18), 69.9 (C19), 68.7 (C17), 63.3 (C13), 61.3 (C1/C2), 38.2 (C14), 31.4 (C3/C6), 30.9 (C10/C11), 30.0 (C10/C11), 24.0 (C4/C5) ppm. ^{15}N NMR ([D$_6$]-DMSO): δ = 82.9 (NH), –6.4 (NH$_2$) ppm. ^{195}Pt NMR ([D$_6$]-DMSO): δ = 3238 ppm. MS (180 °C): *m*/*z* = 1164 [M + Na$^+$].

(*OC*-6–44)-Acetato(trans-*1R*,*2R*-diamminocyclohexane)[4-(2-ferrocenoylamino)ethylamino]-4-(oxobutanoato)oxalatoplatin(IV) (13): 1,1′-Carbonyldiimidazole (63.4 mg, 0.40 mmol), **10** (216.8 mg, 0.36 mmol) in abs. DMF (9 mL), **L3** (250 mg, 0.92 mmol) in abs. DMF (2 mL). The crude product was purified by column chromatography (CHCl$_3$/MeOH, 8.5:1). The obtained product was dried in vacuo. Yield: 100 mg, 34%, yellow powder. $C_{27}H_{35}Fe_2N_3O_{11}Pt·2H_2O$: calcd. C 37.55, H 4.67, N 6.49; found C 37.34, H 4.27, N 6.30. ^{1}H NMR ([D$_6$]DMSO): δ = 8.41 (br. m, 1 H, NH$_2$), 8.31 (br. m, 1 H, NH$_2$), 8.26 (m, 1 H, NH$_2$), 8.20 (m, 1 H, NH$_2$), 7.93 (br. m, 2 H, NH), 7.80 (br. m, 2 H, NH), 4.75 (br. m, 4 H, H19), 4.35 (br. m, 4 H, H20), 4.15 (s, 10 H, H21), 3.22 (br. m, 2 H, H15), 3.18 (bm, 2 H, H16), 2.67 (m, 1 H, H1/H2), 2.55 (m, H1/H2), ≈2.5 (H12/H13, underneath the DMSO peak), 2.31 (m, 2 H, H12/H13), 2.11 (m, 2 H, H3/H6), 1.96 (s, 3 H, H10), 1.50 (m, 2 H, H4/H5), 1.41 (m,2 H, H3/H6), 1.17 (m, 2 H, H4/H5) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 180.6 (C11), 179.1 (C9), 172.0 (C14), 169.6 (C17), 163.9 (C7/C8), 163.8 (C7/C8), 77.0 (C18), 70.4 (C20), 69.9 (C21), 68.6 (C19), 61.5 (C1/C2), 61.2 (C1/C2), 39.2 (C15), 39.1 (C16), 31.6 (C12/C13), 31.5 (C12/C13), 31.3 (C3/C6), 24.0 (C4/C5), 23.9 (C4/C5), 23.4 (C10) ppm. ^{15}N NMR ([D$_6$]DMSO): δ = 91.3 (NH), 85.4 (NH), –6.3 (NH$_2$) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3236 ppm. MS (180 °C): *m*/*z* = 850 [M + Na$^+$].

(*OC*-6–44)-Acetato(trans-*1R*,*2R*-diaminocyclohexane)[4-(2-ferrocenoyloxy)ethylamino]-4-(oxobutanoato)oxalatoplatin(IV) (14): 1,1′-Carbonyldiimidazole (60.6 mg, 0.37 mmol), **10** (201.1 mg, 0.34 mmol) in abs. DMF (9 mL), **L5** (200 mg, 0.51 mmol) in abs. DMF (2 mL). The crude product was purified by column chromatography (CHCl$_3$/MeOH, 7:1). The obtained product was dried in vacuo. Yield: 78 mg, 28%, yellow powder.

$C_{27}H_{36}Fe_2N_4O_{10}Pt·H_2O$: calcd. C 38.31, H 4.41, N 5.07; found C 38.41, H 4.01, N 4.95. ^{1}H NMR ([D$_6$]DMSO): δ = 8.42 (br. m, 1 H, NH_2), 8.31 (br. m, 1 H, NH_2), 8.25 (br. m, 1 H, NH_2), 8.24 (br. s, 1 H, NH_2), 8.07 (t, ^3J = 5.6 Hz, 2 H, NH), 4.77 (t, ^3J = 1.9 Hz, 2 H, H19), 4.50 (t, ^3J = 1.9 Hz, 2 H, H20), 4.23 (s, 5 H, H21), 4.13 (t, ^3J = 5.8 Hz, 2 H, H16), 3.37 (m, 2 H, H15), 2.71 (br. s, 1 H, H1/H2), ≈2.55 (m, H1/H2, underneath the DMSO peak), ≈2.50 (H12/H13, underneath the DMSO peak), 2.35 (m, 2 H, H12/H13), 2.11 (m, H3/H6), 1.96 (s, 3 H, H10), 1.50 (m, 2 H, H4/H5), 1.41 (m, 2 H, H3/H6), 1.17 (m, 2 H, H4/H5) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 180.6 (C11), 179.0 (C9), 172.0 (C14), 171.1 (C17), 163.9 (C7/C8), 163.8 (C7/C8), 71.9 (C20), 71.1 (C18), 70.3 (C19), 70.1 (C21), 62.9 (C16), 61.4 (C1/C2), 61.2 (C1/C2), 38.3 (C15), 31.5 (C3/C6/C12/C13), 31.4 (C3/C6/C12/C13), 24.1 (C4/C5), 23.9 (C4/C5), 23.4 (C10) ppm. ^{15}N NMR ([D$_6$]DMSO): δ = 87.6 (NH), –6.6 (NH_2) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3236 ppm. (180 °C): *m*/*z* = 851 [M + Na^+], 826 [M – H^+].

(*OC*-6–44)-Acetato(trans-*1R*,*2R*-diaminocyclohexane)[4-(2-ferrocenoylamino)ethoxy]-4-(oxobutanoato)oxalatoplatin(IV) (15): 4-Dimethylaminopyridine (6.6 mg, 0.05 mmol), *N*,*N*′-dicyclohexylcarbodiimide (61.3 mg, 0.30 mmol) in abs. DMF (5 mL), **10** (160 mg, 0.27 mmol) in abs. DMF (8 mL), **L6** (133 mg, 0.49 mmol). The crude product was purified by column chromatography ($CHCl_3$/MeOH, 8:1). The obtained product was dried in vacuo. Yield: 67 mg, 30%, yellow powder. $C_{27}H_{35}Fe_2N_3O_{11}Pt·1.5H_2O$: calcd. C 37.91, H 4.48, N 4.91; found C 37.73, H 4.05, N 4.82. ^{1}H NMR ([D$_6$]DMSO): δ = 8.41 (br. m, 1 H, NH_2), 8.33 (br. m, 1 H, NH_2), 8.26 (br. m, 1 H, NH_2), 8.21 (br. s, 1 H, NH_2), 7.89 (t, ^3J = 5.7 Hz, 2 H, NH), 4.79 (br. m, 2 H, H19), 4.35 (br. m, 2 H, H20), 4.16 (s, 5 H, H21), 4.11 (m, 2 H, H15), 3.41 (m, 2 H, H16), 2.57 (br. s, 2 H, H1/H2), ≈2.5 (m, H12/H13, underneath the DMSO peak), 2.10 (br. s, 2 H, H3/H6), 1.50 (m, 2 H, H4/H5), 1.40 (m, 2 H, H3/H6), 1.15 (m, 2 H, H4/H5) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 179.8 (C11), 179.0 (C9), 172.8 (C14), 169.8 (C17), 163.9 (C7/C8), 163.8 (C7/C8), 76.8 (C18), 70.5 (C20), 69.9 (C21), 68.6 (C19), 63.3 (C15), 61.4 (C1/C2), 61.2 (C1/C2), 38.2 (C16), 31.4 (C3/C6), 31.3 (C3/C6), 31.0 (C3/C6/C12/C13), 30.0 (C12/C13), 24.0 (C4/C5), 23.9 (C4/C5), 23.4 (C10) ppm. ^{15}NNMR ([D$_6$]DMSO): δ = 82.7 (NH), –6.7 (NH_2) ppm. ^{195}Pt NMR ([D$_6$]DMSO): δ = 3238 ppm. MS (180 °C): *m*/*z* = 851 [M + Na^+].

Evaluation of Biological Activity

Cell Lines and Cultivation Conditions: The cytotoxicity tests were performed in three cancer cell lines: CH1 (ovarian carcinoma), SW480 (colon carcinoma), and A549 (non-small cell lung cancer). Adherent cell monolayer cultures were grown in 75 cm^2 culture flasks (CytoOne, Starlab, UK) in complete medium [i.e. minimal essential medium (MEM) supplemented with 10% heat-inactivated fetal bovine serum, 1 mM sodium pyruvate, 4 mM L-glutamine, and 1% nonessential amino acids from 100× ready-to-use stock (all purchased from Sigma–Aldrich, Austria)]. Cell cultures were incubated at 37 °C in a moist atmosphere containing 5% CO_2.

Cytotoxicity Tests in Cancer Cell Lines: The cytotoxic activity of the compounds was determined by means of the MTT-based colorimetric microculture assay [MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide]. The cells were harvested from culture flasks by trypsinization and passaged into 96-well microculture plates (CytoOne, Starlab, UK) in densities of 1×10^3 cells per well (CH1), 2×10^3 cells per well (SW480), and 3×10^3 cells per well (A549) in volumes of 100 µL per well. The cells were preincubated for 24 h before exposure to the drugs. Stock solutions of each complex were prepared in DMSO. These stock solutions were diluted in complete medium and then added in aliquots of 100 µL per well (final DMSO concentration 0.5%). After continuous exposure for 96 h, drug solutions were replaced with 100 µL of a RPMI/MTT mixture (6 parts RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum and 2 mM L-glutamine; 1 part MTT solution in phosphate-buffered saline [5 mg/mL]). After incubation for 4 h, the medium/MTT mixtures were removed, and the formazan crystals formed by viable cells were dissolved in 150 µL of DMSO per well. Optical densities at 550 nm were measured with a microplate reader (ELx808 Absorbance Microplate Reader, Bio-Tek, USA), by using a reference wavelength of 690 nm to correct for unspecific absorption. The quantities of viable cells were expressed in terms of T/C values by comparison to untreated control microcultures, and 50% inhibitory concentrations (IC_{50}) were calculated from concentration-effect curves by interpolation. Evaluation is based on means from at least three independent experiments, each comprising triplicates per concentration level.

Stability in DMSO/H_2O: Since the complexes had to be dissolved in DMSO and then diluted in aqueous medium for biological evaluation, stability under these conditions was addressed by NMR spectroscopy. In deuterated DMSO, all complexes were stable during the acquisition of the data (24–60 h), which is in accord with previous findings in the case of analogous platinum(IV) complexes. The stability of a representative complex (compound **3**) in a mixture of DMSO/D_2O was investigated by ^{1}H NMR spectroscopy. For this purpose, 0.5 mg of complex **3** was dissolved in 0.5 mL of DMSO mixed with 0.1 mL of D_2O. ^{1}H NMR spectra were measured from time to time. After sequential intervals of 24, 23.5, 8.5, and 14 h, 0.1 mL of D_2O was added, and the mixtures were investigated in the same way. The last mixture, consisting of 0.5 mL of DMSO and 0.5 mL of D_2O, was investigated for 48 h during which the signals broadened as a result of crystallization of **3**. However, a change in the NMR spectra could not be observed; in sum, **3** proved to be stable over 118 h under these conditions. In order to exclude precipitation of a decomposition product, 0.5 mL of the final suspension was mixed with 0.5 mL of DMSO. The clear solution was investigated by ^{1}H NMR spectroscopy, which proved the stability of **3** (significant amounts of hydrolysis products could not be detected).

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