Diamminetetrakis(carboxylato)platinum(IV) Complexes – Synthesis, Characterization, and Cytotoxicity

by Björn R. Hoffmeister*)+, Mahsa S. Adib-Razavi*)+, Michael A. Jakupec+)−), Markus Galanski*)+, and Bernhard K. Keppler*)+−)

*) University of Vienna, Institute of Inorganic Chemistry, Währinger Strasse 42, AT-1090 Vienna
(phone: +43-1-427752600; fax: +43-1-427752680; markus.galanski@univie.ac.at, bernhard.keppler@univie.ac.at)
−) Research Platform ‘Translational Cancer Therapy Research’ University of Vienna, Währinger Strasse 42, AT-1090 Vienna

A series of eight novel diamminetetrakis(carboxylato)platinum(IV) complexes was synthesized and characterized by multinuclear ¹H-, ¹³C-, ¹⁵N-, and ¹⁹⁵Pt-NMR spectroscopy. Their antiproliferative potency was evaluated in three human cancer cell lines representing ovarian (CH1), lung (A549), and colon carcinoma (SW480). In cisplatin-sensitive CH1 cancer cells, cytotoxicity was found in the low micromolar range, whereas, in inherently cisplatin-resistant A549 and SW480 cells, the activity was very low or negligible. Astonishingly, raise in lipophilicity of the complexes, as found in the case of cisplatin analogs, did not result in a significant enhancement of the cytotoxic effect.

Introduction. – Cisplatin, carboplatin, and oxaliplatin (Fig. 1) are worldwide the mainstream as chemotherapeutics in the fight against cancer [1–3]. These three Pt-based agents are used in more than 50% of all anticancer regimens mainly in combination with other antiproliferative drugs [4–6].

Fig. 1. Chemical structures of cisplatin, carboplatin, and oxaliplatin being approved worldwide for clinical use. Tetraplatin, iproplatin and satraplatin are Pt⁰° complexes which were investigated in clinical trials.

© 2012 Verlag Helvetica Chimica Acta AG, Zurich
Cisplatin, carboplatin, and oxaliplatin are administered intravenously against a series of solid tumors. However, some tumors are not accessible due to intrinsic resistance or develop resistance during therapy. Additionally, platinum chemotherapy is accompanied by a set of side effects that are, to some extent, severe and dose-limiting. Despite the development of organic compounds used in that field and the approval of monoclonal antibodies (targeted therapy), Pt-based treatment still builds the basis for combination cancer therapy.

During the last decades, different strategies were pursued with the aim of reducing side effects and accumulating or activating Pt drugs at the tumor site [7]; additionally, oral administration of the complexes would be advantageous with respect to the acceptance of chemotherapy, improving the quality of life and reducing hospitalization costs. Along that line, the development of octahedrally configured PtIV complexes seems to be most promising [8][9]. Consequently, it is not surprising that so far four complexes, namely tetraplatin, iproplatin, satraplatin (Fig. 1), and LA-12 (a close analog of satraplatin, but featuring an adamantylamine ligand instead of cyclohexylamine) have been evaluated in phase I–III clinical trials.

Platinum(IV) complexes are kinetically inert. i) Therefore, they can be administered orally via absorption through the gastrointestinal tract, if lipophilic enough. ii) Platinum(IV) complexes act as prodrugs which can be reduced to the PtII species featuring a higher reactivity/activity (activation by reduction) in the hypoxic (oxygen deficiency) milieu of many solid tumors, accompanied by release of the axial ligands [10][11]. iii) Platinum(IV) complexes can be derivatized more easily at coordinated OH [12–15] or peripheral functional groups [16–18] compared to their PtII counterparts.

With respect to the latter aspect, PtIV complexes were coupled to small molecules such as ethacrynic acid [19], endothall [20], dichloroacetate [21], or estrogen [22], which act either as enzyme inhibitor or sensitize cancer cells to platinum treatment. Additionally, PtIV constructs tethered to peptides [23][24], single walled carbon nanotubes [25][26], or as part of nanoparticles [27][28] were developed for targeted delivery.

In a more basic approach, we recently reported on a series of diamine(dicarboxylato)dichloridoplatinum(IV) complexes which were investigated with regard to their cytotoxicity, lipophilicity, and cellular accumulation [29–33]. It was found that, with increasing lipophilicity, the cellular accumulation and the antiproliferative potency were enhanced as well. IC_{50} Values in the low nanomolar range, and therefore significantly better compared to those of cisplatin, were observed for the most lipophilic agents.

In case that this behavior is a general characteristic, it should then be possible to improve the cytotoxicity of kinetically more inert diaminetetrakis(carboxylato)platinum(IV) complexes just by increasing their lipophilicity. To validate this hypothesis, eight novel (OC-6-33)-diamminebis(carboxylato)malonatoplatinum(IV) complexes were synthesized, characterized, and their cytotoxicity was evaluated in three human cancer cell lines.

**Results and Discussion.** – The PtII precursor, (SP-4-2)-diammine(malonato)platinum(II) (I), was prepared starting from the diamminediiodido complex via reaction
with AgNO₃ and subsequent coordination of malonate. Oxidation with 30% H₂O₂ was performed in aqueous solution at ambient temperature resulting in the octahedrally configured dihydroxido compound 2 (Scheme). The latter was carboxylated with succinic anhydride in DMF as published recently [17]. The terminal and uncoordinated carboxylic acid groups were activated with 1,1’-carbonyldiimidazole (CDI), and converted to the corresponding esters or amides, respectively.

Scheme. Synthesis of Novel Diamminetetrakis(carboxylato)platinum(IV) Complexes with NMR Numbering Scheme

Novel tetrakis(carboxylato)platinum(IV) complexes 3 and 4a–4h were characterized by elemental analysis and multinuclear 1D and 2D ¹H-, ¹³C-, ¹⁵N-, and ¹⁹⁵Pt-NMR spectroscopy. The ¹⁹⁵Pt chemical shifts were found in a narrow range between 3541 and 3544 ppm, and are in accord with an N₂O₄ donor set. The H-atom resonances of H/C₀C(1) in 4a–4h were detected at 3.61 or 3.62 ppm as singlets, reflecting the symmetrical character of the molecule. The CO C-atoms C(2) resonated at 172.4 or 172.5 ppm, respectively, whereas the C=O chemical shifts of C(3) and C(6) were observed at ca. 179 (179.2–180.3) and 172 (171.1–172.5) ppm. ¹H,¹⁵N cross peaks for coordinated NH₃.
were found at 6.77 and −54 ppm in 4a–4h; in the case of amides, further 1H,15N shift-correlation signals at 7.80/93.6 and 7.79/106.7 were assigned to the CONH moiety of 4g and 4h, respectively.

Cytotoxicity of complexes 4a–4h was studied in three human cancer cell lines representing ovarian (CH1), lung (A549), and colon carcinoma (SW480) by means of the MTT (= 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) assay (Table and Fig. 2).

Table. Cytotoxicity of Complexes 4a–4h in CH1, A549, and SW480 Cancer Cells

| Compound | IC\textsubscript{50} [\mu\text{M}] | CH1 | A549 | SW480 |
|----------|------------------|-----|------|-------|
| 4a       | 15±2             | >250| 298±34|
| 4b       | 12±2             | >250| 240±17|
| 4c       | 6.7±2.1          | >500| 119±8 |
| 4d       | 5.9±0.9          | >500| 94±23 |
| 4e       | 8.2±0.2          | >250| 199±41|
| 4f       | 30±4             | >500| >500  |
| 4g       | 14±2             | >250| 359±40|
| 4h       | 12±1             | >500| 320±47|

\textsuperscript{a}) 50\% Inhibitory concentrations in the MTT assay (96-h exposure). Values are means±standard deviations obtained from at least three independent experiments.

Precursor 3 was not evaluated, since it is known that analogous complexes featuring free carboxylic acid moieties have low antiproliferative potency due to their relatively high solubility in H\textsubscript{2}O [33].

In cisplatin-sensitive CH1 cells, IC\textsubscript{50} values were between 5.9 and 30 \mu\text{M}. However, cytotoxicity in the inherently cisplatin-resistant A549 and SW480 cell lines was negligible or very low. The following structure–activity relationships could be drawn from the results in CH1 and SW480 cancer cells: i) IC\textsubscript{50} values of 4a–4d decrease parallel to an increasing lipophilicity (methyl, ethyl, propyl, and butyl ester), ii) an iPr residue (i.e., 4e) is not favorable compared to Pr (i.e., 4c), iii) exchange of a CH\textsubscript{2} fragment in 4d by oxygen (i.e., 4f) is clearly unfavorable in terms of cytotoxicity due to a lower lipophilicity of the latter, iv) amides 4g and 4h display relatively high IC\textsubscript{50} values.

The finding that IC\textsubscript{50} values in CH1 cells are in the low micromolar range, but not well below 1 \mu\text{M} (cisplatin, 0.16 \mu\text{M} [30]), is not astonishing at first sight, since release of a chelating dicarboxylato ligand (e.g., carboplatin) is rather slow compared to coordinated chloride (e.g., cisplatin). However, it was envisaged to significantly improve the cytotoxic potency by enhancing lipophilic properties and thereby increasing cellular accumulation [32]. In the case of close analogs featuring the same axial ligands, but ethane-1,2-diamine and two chlorido ligands in the equatorial coordination sphere, an improvement of the cytotoxicity by a factor of 40 (0.68 \mu\text{M} vs. 0.018 \mu\text{M}) was achieved comparing the methyl ester derivative with its butyl ester counterpart [30]. On the contrary, in the case of 4a–4d, cytotoxicity could only be
raised by a factor of less than 3. Obviously, besides lipophilicity, factors such as the redox potential and the rate of reduction play a crucial role in the mode of action of PtIV complexes.

This assumption was confirmed very recently by Hambley, Gibson and co-workers [34], who showed that coordinated am(m)ines and carboxylates are unfavorable for facilitated electron transfer. They concluded that reduction potentials not necessarily reflect the rates of reduction.

Whether their findings can be generalized will be subject of further investigations. Especially correlation of lipophilicity and reduction potential with cellular accumulation and cytotoxicity of tetrakis(carboxylato)platinum(IV) complexes will be investigated in more detail.
The authors are indebted to the FFG – Austrian Research Promotion Agency, the Austrian Council for Research and Technology Development, the FWF (Austrian Science Fund, P20683-N19), and COST D39.

Experimental Part

General. All chemicals and solvents were obtained from commercial suppliers and used without further purification. MeOH and EtOH were dried according to standard procedures, and reverse osmosis water was doubly distilled before use. For column chromatography (CC), silica gel 60 (SiO2; Fluka) was used. (SP-4-2)-Diamminediiodidoplatinum(II) was synthesized by Dhara’s method [35].

The 1H-, 13C-, 15N-, and 195Pt-NMR, 1H,1H-COSY, 1H,13C-HSQC, 1H,15N-HSQC, and 1H,13C-HMBC spectra were recorded with a Bruker Avance III 500 MHz spectrometer at 500.32 (1H), 125.81 (13C), 107.38 (195Pt), and 50.70 MHz (15N) in (D7)DMF at ambient temp. For 1H and 13C, the solvent residual peaks were used as internal reference. 13C and 195Pt chemical shifts were referenced relative to external NH4Cl or K2PtCl4. Elemental analyses were carried out by the Microanalytical Laboratory of the University of Vienna using a Perkin-Elmer 2400 CHN elemental analyzer.

Synthesis. (SP-4-2)-Diamminediodidoplatinum(II) (3.091 g, 6.40 mmol) was suspended in 70 ml of H2O. AgNO3 (2.065 g, 12.16 mmol) was added, and the suspension was stirred at r.t. for 24 h. The formed AgI was filtered off, and the filtrate was added to a soln. of malonic acid (668 mg, 6.42 mmol) and NaOH (512 mg, 12.80 mmol) in 10 ml of H2O. After stirring for 90 min at 50° and for 16 h at r.t., the white solid was collected by filtration and washed with cold H2O and acetone. Yield: 1.469 g (73%). Anal calc. for C13H18N2O4Pt (331.18): C 10.88, H 2.43, N 8.46; found C 25.10, H 4.27, N 4.44. (OC-6-33)-Diammine(dihydroxido)malonatoplatinum(IV) (2). Compound 1 (1.294 g, 3.91 mmol) was suspended in 15 ml of H2O and 15 ml of 30% H2O2. The mixture was stirred for 48 h at r.t. The white solid was collected by filtration and washed with cold H2O and acetone. Yield: 1.322 g (84%). Anal. calc. for C29H32N2O12Pt·2 H2O (565.34): C 23.73, H 2.30, N 8.25; found C 23.29, H 2.43, N 4.45.

(OC-6-33)-Diammined(malonato)bis{(4-ethoxy)-4-oxobutanoato}(malonato)platinum(IV) (3). A mixture of 2 (910 mg, 2.49 mmol) and succinic anhydride (1.00 g, 9.99 mmol) in 5 ml of DMF was stirred at 50° until the solid material dissolved to form a clear soln. The soln. was removed under reduced pressure and acetone was added to the residue to yield a white solid, which was collected by filtration and washed with cold H2O and acetone. Yield: 1.233 g (88%). 1H-NMR: 12.40 (br. s, 2 COOH); 6.77 (m, 2 CH2); 3.64 (s, CH3(1)); 2.50 (m, 2 CH2(5)); 2.50 (m, 2 CH2(7)); 2.61 (m, 2 CH2(1)); 2.61 (m, 2 CH2(4)); 2.52 (m, 2 CH2(5)); 1.21 (t, J = 7.1, 2 Me(8)); 1.21 (t, J = 7.1, 2 Me(8)). 13C-NMR: 179.7 (C(3)); 173.9 (C(6)); 172.5 (C(2)); 46.9 (C(1)); 30.4 (C(4)); 29.7 (C(5)). 195Pt-NMR: – 55.3. Anal. calc. for C15H26N2O12Pt·2 H2O (629.43): C 24.81, H 3.52, N 6.98; found: C 23.73, H 2.30, N 8.25.

(OC-6-33)-Diammined(malonato)bis{(4-methoxy)-4-oxobutanoato}platinum(IV) (4a). A soln. of CDI (237 mg, 1.46 mmol) in abs. DMF (8 ml) was added to a soln. of 3 (400 mg, 0.71 mmol) in abs. DMF (8 ml). The mixture was stirred at 60° for 15 min, then cooled down to r.t., and flushed with Ar to remove the formed CO2. MeONa (15 mg Na in 10 ml of abs. MeOH) in abs. MeOH was added, and the soln. was stirred for 48 h at r.t. MeOH and DMF were removed under reduced pressure, and the crude product was purified by CC (AcOEt/MeOH 2:1) to yield a white solid, which was dried in vacuo. Yield: 110 mg (25%). 1H-NMR: 6.67 (s, 2 H2); 3.64 (s, 2 MeO), 3.61 (s, CH3(1)); 2.51 (m, 2 CH2(4)); 2.52 (m, 2 CH2(5)); 1.21 (t, J = 7.1, 2 Me(8)); 1.21 (t, J = 7.1, 2 Me(8)). 13C-NMR: 179.5 (C(3)); 172.9 (C(6)); 172.4 (C(2)); 51.1 (C(7)); 46.8 (C(1)); 30.3 (C(4)); 29.6 (C(5)). 195Pt-NMR: – 55.2. Anal. calc. for C13H22N2O12Pt·2 H2O (629.43): C 25.10, H 4.27, N 4.44; found: C 24.81, H 4.27, N 4.44.

(OC-6-33)-Diammined(malonato)bis{(4-ethoxy)-4-oxobutanoato}platinum(IV) (4b). The synthesis was carried out as described for 4a. CDI (237 mg, 1.46 mmol) in abs. DMF (8 ml), EtONa (10 mg Na in 15 ml of abs. EtOH). The crude product was purified by CC (AcOEt/MeOH 3:1) to yield a white solid, which was dried in vacuo. Yield: 138 mg (30%). 1H-NMR: 6.77 (m, 2 NH2); 4.09 (m, 2 CH2(7)); 3.61 (s, CH3(1)); 2.51 (m, 2 CH2(4)); 2.51 (m, 2 CH2(5)); 1.21 (t, J = 7.1, 2 Me(8)); 1.21 (t, J = 7.1, 2 Me(8)). 13C-NMR: 179.4 (C(3)); 172.5 (C(6)); 172.4 (C(2)); 60.1 (C(7)); 46.8 (C(1)); 30.3 (C(4)); 29.9 (C(5)); 13.8 (C(8)). 195Pt-NMR: – 53.6. Anal. calc. for C13H22N2O12Pt·2 H2O (657.48): C 24.70, H 4.60, N 4.26; found C 25.27, H 4.60, N 4.22.
(OC-6-33)-Diammine(malonato)bis[(4-propyloxy)-4-oxobutanoato]platinum(IV) (4e). The synthesis was carried out as described for 4a: CDI (297 mg, 1.83 mmol) in abs. DMF (8 ml), 3 (500 mg, 0.88 mmol) in abs. DMF (8 ml), PrONa (15 mg Na in 10 ml of PrOH). The crude product was purified by CC (AcOEt/MeOH 4 :1) to yield a white solid, which was dried in vacuo. Yield: 219 mg (40%). 1H-NMR: 6.77 (m, 2 NH3); 4.00 (t, J = 6.7, 2 CH2(7)); 3.61 (s, CH3(1)); 2.61 (m, 2 CH2(4)); 2.53 (m, 2 CH2(5)); 1.62 (m, 2 CH2(6)); 0.91 (t, J = 7.4, 2 Me(9)). 13C-NMR: 179.4 (C(3)); 172.5 (C(6)); 172.4 (C(2)); 65.6 (C(7)); 46.9 (C(1)); 30.3 (C(14)); 29.8 (C(5)); 21.8 (C(8)); 9.9 (C(9)). 15N-NMR: – 54.6. 195Pt-NMR: 3544. Anal. calc. for C17H30N2O12Pt·H2O (667.52): C 30.59, H 4.83, N 4.20; found C 30.82, H 4.93, N 4.11.

(OC-6-33)-Diammine(malonato)bis[(4-prop-2-yloxy)-4-oxobutanoato]platinum(IV) (4d). The synthesis was carried out as described for 4a: CDI (297 mg, 1.83 mmol) in abs. DMF (8 ml), 3 (500 mg, 0.88 mmol) in abs. DMF (8 ml), BuONa (15 mg Na in 10 ml of BuOH). The crude product was purified by CC (AcOEt/MeOH 4 :1) to yield a white solid, which was dried in vacuo. Yield: 260 mg (44%). 1H-NMR: 6.77 (m, 2 NH3); 4.05 (t, J = 6.7, 2 CH2(7)); 3.61 (s, CH3(1)); 2.61 (m, 2 CH2(4)); 2.52 (m, 2 CH2(5)); 1.58 (m, 2 CH2(8)); 1.36 (m, 2 CH2(9)); 0.91 (t, J = 7.4, 2 Me(10)). 13C-NMR: 179.4 (C(3)); 172.5 (C(6)); 172.4 (C(2)); 63.9 (C(7)); 46.9 (C(1)); 30.6 (C(8)); 30.3 (C(4)); 29.8 (C(5)); 18.9 (C(9)); 13.3 (C(10)). 15N-NMR: – 54.8. 195Pt-NMR: 3543. Anal. calc. for C17H30N2O12Pt·H2O (677.56): C 33.68, H 5.08, N 4.13; found C 33.72, H 5.20, N 4.02.

(OC-6-33)-Diammine(malonato)bis[(4-(2-methoxyethoxy)-4-oxobutanoato)platinum(IV) (4f). The synthesis was carried out as described for 4a: CDI (297 mg, 1.83 mmol) in abs. DMF (8 ml), 3 (500 mg, 0.88 mmol) in abs. DMF (8 ml), 2-methoxyethanolate (15 mg Na in 10 ml 2-methoxyethanol). The crude product was purified by CC (AcOEt/MeOH 3 :1) to yield a white solid, which was dried in vacuo. Yield: 130 mg (21%). 1H-NMR: 6.76 (m, 2 NH3); 4.02 (m, 2 H–C(7)); 3.62 (s, CH3(1)); 2.60 (m, 2 CH2(4)); 2.48 (m, 2 CH2(5)); 1.20 (d, J = 6.3, 4 Me(8)). 13C-NMR: 179.4 (C(3)); 172.4 (C(2)); 171.9 (C(6)); 67.4 (C(7)); 46.9 (C(1)); 30.3 (C(4)); 30.2 (C(5)); 21.3 (C(8)). 15N-NMR: – 54.4. 195Pt-NMR: 3543. Anal. calc. for C17H30N2O14Pt·H2O (667.52): C 30.59, H 4.83, N 4.11; found C 30.82, H 4.93, N 4.11.

(OC-6-33)-Diammine(malonato)bis[(4-(2-methoxyethyl)-4-oxobutanoato)platinum(IV) (4g). The synthesis was carried out as described for 4a: CDI (297 mg, 1.83 mmol) in abs. DMF (8 ml), 3 (500 mg, 0.88 mmol) in abs. DMF (8 ml), 2-methoxyethanolate (15 mg Na in 10 ml 2-methoxyethanol). The crude product was purified by CC (AcOEt/MeOH 2 :1) to yield a white solid, which was dried in vacuo. Yield: 100 mg (14%). 1H-NMR: 6.75 (m, 2 NH3); 3.94 (m, 2 H–C(7)); 3.63 (s, CH3(1)); 2.62 (m, 2 CH2(4)); 2.54 (m, 2 CH2(5)); 1.56 (m, 2 CH2(8)); 1.36 (m, 2 Me(9)); 0.87 (t, J = 7.4, 2 Me(10)). 13C-NMR: 179.2 (C(3)); 172.5 (C(6)); 172.4 (C(2)); 171.9 (C(6)); 67.4 (C(7)); 46.9 (C(1)); 30.3 (C(4)); 30.2 (C(5)); 21.3 (C(8)). 15N-NMR: – 54.9. 195Pt-NMR: 3542. Anal. calc. for C17H30N2O14Pt·2 H2O (699.52): C 29.19, H 4.61, N 4.00; found C 29.10, H 4.33, N 4.00.
(C(8)); 31.6 (C(4)); 31.3 (C(5)); 23.6 (C(9)). $^{15}$N-NMR: 106.7 (CONH); 54.4 (NH$_3$). $^{195}$Pt-NMR: 3541.

**Cell Lines and Culture Conditions.** CH1 (ovarian carcinoma, human) cells were a generous gift from Lloyd R. Kelland (CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, U.K.). A549 (non-small-cell lung cancer, human) and SW480 (colon carcinoma, human) cells were kindly provided by Brigitte Marian (Institute of Cancer Research, Department of Medicine I, Medical University of Vienna, Austria). All cell lines were grown in 75-cm$^2$ culture flasks in Minimal Essential Medium (MEM) containing 10% heat-inactivated fetal bovine serum, 1 mM sodium pyruvate, 2 mM L-glutamine and 1% (v/v) non-essential amino acids (from 100× stock as obtained from commercial supplier) at 37°C in a humidified atmosphere of 95% air and 5% CO$_2$.

**Cytotoxicity Tests in Cancer Cell Lines.** The cells were harvested from culture flasks by using 0.25% trypsin. Then, 100 μl of cell suspensions in MEM were seeded in densities of 1.0×10$^4$ (CH1), 4.0×10$^4$ (A549), and 2.5×10$^4$ (SW480) cells per well into 96-well microculture plates and incubated for 24 h to restore adherent growth. After dissolving and serially diluting the test compounds in MEM, 100 μl of these solns. were added to each well, and plates were incubated for 96 h at 37°C. Thereafter, the MEM containing the test compounds was replaced with 100 μl of RPMI 1640 medium and 20 μl 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) in phosphate-buffered saline (PBS, 5 mg/ml). After 24 h incubation at 37°C, the mixture was aspirated, and the purple formazan product was dissolved in 150 μl of DMSO per well. The absorbance of the resulting colored solns. was quantified spectrophoto-

**REFERENCES**

[1] 'Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug’, Ed. B. Lippert, Verlag Helvetica Chimica Acta, Zürich, Switzerland, 1999.
[2] P.J. O’Dwyer, J. P. Stevenson, S. W. Johnson, *Drugs* 2000, 59, 19.
[3] M. Galanski, M. A. Jakupec, B. K. Keppler, in ‘Metal Compounds in Cancer Chemotherapy’, Eds. J. M. Pérez, M. A. Fuertes, C. Alonso, Research Signpost, Kerala, 2005, pp. 155–185.
[4] M. A. Jakupec, M. Galanski, B. K. Keppler, *Rev. Physiol. Biochem. Pharmacol*. 2003, 146, 1.
[5] M. Galanski, M. A. Jakupec, B. K. Keppler, *Curr. Med. Chem.* 2005, 12, 2075.
[6] M. A. Jakupec, M. Galanski, V. B. Arion, C. G. Hartinger, B. K. Keppler, *Dalton Trans.* 2008, 183.
[7] M. Galanski, B. K. Keppler, *Anti-Cancer Agents Med. Chem.* 2007, 7, 55.
[8] M. D. Hall, T. W. Hambley, *Coord. Chem. Rev.* 2002, 232, 49.
[9] M. Galanski, M. A. Jakupec, B. K. Keppler, *Recent Pat. Anti-Cancer Drug Discovery* 2006, 1, 285.
[10] M. Galanski, B. K. Keppler, *Inorg. Chim. Acta* 2000, 300–302, 783.
[11] M. D. Hall, H. R. Mellor, R. Callaghan, T. W. Hambley, *J. Med. Chem.* 2007, 50, 3403.
[12] C. M. Giandomenico, M. J. Abrams, B. A. Murrer, J. F. Vollano, M. I. Rheinheimer, S. B. Wyer, G. E. Bossard, J. D. Higgins, *Inorg. Chem.* 1995, 34, 1015.
[13] M. Galanski, B. K. Keppler, *Inorg. Chem.* 1996, 35, 1709.
[14] M. Galanski, B. K. Keppler, *Inorg. Chim. Acta* 1997, 265, 271.
[15] J. J. Wilson, S. J. Lippard, *Inorg. Chem.* 2011, 50, 3103.
[16] M. Galanski, W. Zimmermann, M. Berger, C. Baumgartner, G. Giester, B. K. Keppler, *Eur. J. Inorg. Chem.* 2002, 417.
[17] M. Reithofer, M. Galanski, A. Roller, B. K. Keppler, *Eur. J. Inorg. Chem.* 2006, 2612.
[18] V. Pichler, S. M. Valiahdi, M. A. Jakupec, V. B. Arion, M. Galanski, B. K. Keppler, *Dalton Trans.* 2011, 40, 8187.
[19] W. H. Ang, I. Khalaila, C. S. Allardyce, L. Juillerat-Jeanneret, P. J. Dyson, *J. Am. Chem. Soc.* 2005, 127, 1382.
[20] M. R. Reithofer, S. M. Valiahdi, M. Galanski, M. A. Jakupec, V. B. Arion, B. K. Keppler, *Chem. Biodiversity* 2008, 5, 2160.
[21] S. Dhar, S. J. Lippard, *Proc. Natl. Acad. Sci. U.S.A.* 2009, 106, 22199.
