Monatshefte für Chemie 136, 693–700 (2005)
DOI 10.1007/s00706-004-0241-3

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Synthesis, Cytotoxicity, and Structure-Activity Relationships of New Oxaliplatin Derivatives

Markus Galanski[1,*], **Afshin Yasemi**[1], **Michael A. Jakupec**[1], **Nikolai Graf v. Keyserlingk**[2], and **Bernhard K. Keppler**[1]

[1] Institute of Inorganic Chemistry, University of Vienna, A-1090 Vienna, Austria
[2] Faustus Forschungs Compagnie Translational Cancer Research GmbH, D-04109 Leipzig, Germany

Received June 18, 2004; accepted June 28, 2004
Published online March 11, 2005

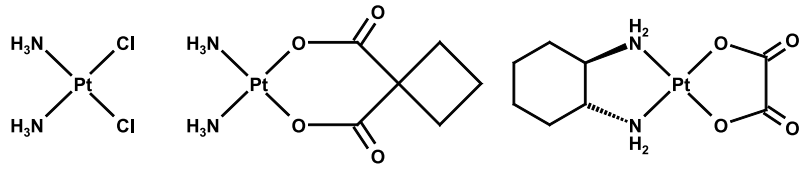
Summary. In order to setup structure-activity relationships and to explore the possibilities of improving the anticancer activity of oxaliplatin, which was recently approved for combination chemotherapy of metastatic colorectal cancer, new oxaliplatin analogues have been synthesized. The cytotoxicity was determined in nine human tumor cell lines and revealed a comparable or even higher cytotoxic potency in leukemia, ovarian and colon cancer cell lines in the case of small substituents at position 4 of the cyclohexane-1,2-diamine ligand. Introduction of bigger substituents at this position and thereby increasing the steric demand of the diamine ligands and the lipophilicity of the oxaliplatin derivatives resulted in platinum complexes with reduced cytotoxic properties.

Keywords. Drug research; Antitumor agent; Bioinorganic chemistry; Metal complexes; Coordination chemistry.

Introduction

Cisplatin and carboplatin (**1** and **2**, Fig. 1) are in worldwide clinical use as anticancer complexes since 1978 and 1985, respectively [1–5]. Today, 50% of all antitumor therapies are platinum-based. Cisplatin and carboplatin are especially used against urogenital tumors, and in the case of testicular cancer, cisplatin-based therapy is known to result in cure rates of more than 90%. During the last 20 years, thousands of platinum complexes have been synthesized and tested with respect to their cytotoxic and tumor inhibiting properties, but only oxaliplatin (**3**, Fig. 1), developed by *Kidani et al.* [6], could be approved as third generation platinum drug.

* Corresponding author. E-mail: markus.galanski@univie.ac.at



1 **2** **3**

Fig. 1. Platinum(II) complexes in clinical use, cisplatin (**1**), carboplatin (**2**), and oxaliplatin (**3**)

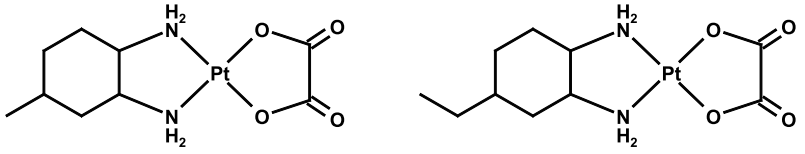
Oxaliplatin (Eloxatin®, Sanofi-Synthelabo) was first approved in 1998 in France and subsequently in the rest of Europe and, more recently, in 2002 by the Food and Drug Administration in the United States. Oxaliplatin is active against certain tumors which are primarily resistant to cisplatin and carboplatin, and it is used in the clinics in combination with 5-fluorouracil and leukovorin [7] for the treatment of patients with colorectal cancer [8, 9], which is the second leading cause of cancer death in developed countries.

The mode of action of platinum-based anticancer drugs has been investigated in detail during the last decades and is therefore very well understood [10]. It is known that *DNA* of tumor cells is the ultimate target of platinum chemotherapy and that in the case of cisplatin and carboplatin as well as of oxaliplatin two neighboring guanine nucleobases at one *DNA* strand are crosslinked by the diamineplatinum(II) unit through coordination of N7 of each purine base [11]. The resulting platinum–*DNA* bisadduct, the 1,2-d(*G*p*G*) intrastrand crosslink, leads in last consequence to the induction of programmed cell death (apoptosis). The anionic leaving ligands (chloro, 1,1-cyclobutanedicarboxylato, or oxalato) play an important role in determining the general toxicity as well as the pharmacokinetics of the platinum complexes.

The striking difference between cisplatin and carboplatin *DNA* adducts on the one hand and oxaliplatin *DNA* adducts on the other is the presence of the cyclohexane ring in the latter, resulting in a marked unpolar region at the *DNA*, which is processed differently by the cellular machinery [12–14]. Moreover, contrary to the diamineplatinum(II) complexes, oxaliplatin displays a higher lipophilicity, resulting in significant differences in the volume of distribution from plasma ultrafiltrate [15]. This observation implies that oxaliplatin is efficiently cleared from the blood plasma through enhanced tissue penetration. Consequently, substitution at the nonleaving cyclohexane-1,2-diamine ligand should have a marked influence on the tumor inhibiting activity of oxaliplatin derivatives and, in addition, would lead to an increased lipophilicity.

Preliminary results with 4-methyl- and 4-ethyl substituted (*trans*-cyclohexane-1,2-diamine)oxalatoplatinum(II) complexes (**4** and **5**, Fig. 2) demonstrated a comparable cytotoxic potency to oxaliplatin in the SW480 colon carcinoma cell line [16].

Based on these results, we have focused on (i) the synthesis of further oxaliplatin derivatives with more lipophilic substituents in the 4-position and (ii) on an extensive investigation of oxaliplatin analogues in comparison to oxaliplatin in a panel of nine tumor cell lines in order to explore structure-activity relationships.



4 **5**

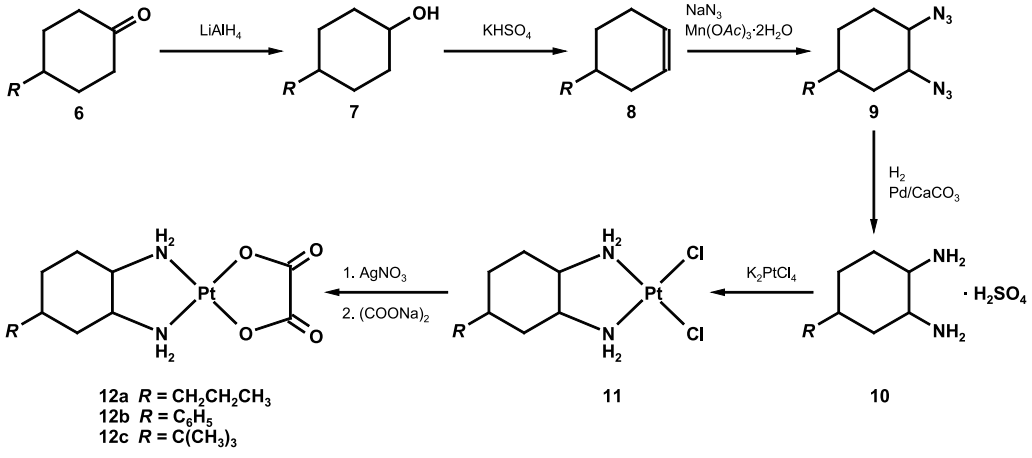
Fig. 2. Structure of 4-methyl- and 4-ethyl substituted (*trans*-cyclohexane-1,2-diamine)oxalatoplatinum(II) complexes (**4** and **5**)

Results and Discussions

Synthesis and Characterization

The ligands were synthesized in analogy to methods described by *Snyder* [17] and *Corey* [18], starting from the ketones **6a**–**6c** or the alcohols **7a**–**7c**, if commercially available. After dehydration, the cyclohexene derivatives were transformed to the diazides (**8a**–**8c**) in the presence of $Mn(OAc)_3 \cdot 2H_2O$. The new 4-substituted cyclohexane-1,2-diamine compounds were obtained by catalytic hydrogenation over $Pd/CaCO_3$ (*Lindlar* catalyst) and isolated as dihydrogen sulfates **10a**–**10c**. Reaction of these with K_2PtCl_4 in the presence of NaOH afforded the diaminedichloroplatinum(II) complexes (**11a**–**11c**). Abstraction of the chloro ligands by using silver nitrate resulted in the corresponding diaminediaquaplatinum(II) species which were directly converted into the oxalato complexes (**12a**–**12c**) by reaction with sodium oxalate. The target compounds precipitated and were obtained as white solids without further purification.

The *trans*-cyclohexane-1,2-diamine derivatives **10a**–**10c** have been characterized by ^1H and ^{13}C NMR spectroscopy as well as elemental analysis. They were obtained as bisequatorially substituted (1*R*,2*R*/1*S*,2*S*) 1:1-mixtures, with the substituents at position 4 mainly being in the axial position. Consequently, the ^{13}C–N resonances of C(1) and C(2) of the uncoordinated ligands (major isomers, Table 1,



Scheme 1

Table 1. ^{13}C chemical shifts of C(1) and C(2) as well as substitution at position 4 in complexes **12a**–**12c** in comparison to the uncoordinated ligands[a]

	Complexes		
	12a	**12b**	**12c**
Chemical shifts (δ/*ppm*)			
Major isomer	58.6/63.5 (48.8/51.3)	59.0/63.3 (48.7/49.1)	59.9/62.6 (47.4/48.9)
Minor isomer	63.0/63.3 (52.6/52.8)	62.7/63.0 (52.2/52.5)	63.1/63.6 (52.7/53.2)
Axial substitution (%)			
	81 (82)	91 (93)	74 (89)

[a] Values for the uncoordinated ligands are given in parentheses

values in parentheses) show a marked splitting ($\Delta\delta = 2.5$–0.4 ppm) in comparison to the equatorially substituted counterparts ($\Delta\delta = 0.5$–0.2 ppm, minor isomer). Furthermore, ^{13}C chemical shifts of C(1) and C(2) of the major isomers (axial substitution) are found upfield from those of the minor isomers. The quantity of axial substitution in **10a**–**10c** was determined by integration of NMR spectra; values between 82 and 93% were determined.

These data are in accord with those found for the uncoordinated ligands of **4** and **5** [16]. In the case of the 4-methyl- and 4-ethyl-*trans*-cyclohexane-1,2-diamine dihydrogensulfates, the quantity of axial substitution was 85 and 82%, respectively.

The title complexes **12a**–**12c** were obtained with moderate yields of 49 to 62% and characterized by NMR spectroscopy and elemental analysis. In the oxalatoplatinum(II) complexes, the ^{13}C–N resonances of C(1) and C(2) display a marked downfield shift of about 10 ppm in comparison to the corresponding uncoordinated diamine dihydrogensulfate ligands. Consequently, the major isomers exhibit axial substitution at position 4 of the cyclohexane ring (quantity 74–91%) with a splitting of the C(1) and C(2) resonance of $\Delta\delta = 4.9$–2.7 ppm (Table 1). This difference is notably increased in comparison to the uncoordinated ligand, whereas in the case of the minor oxalatoplatinum(II) isomers with equatorial substituents at position 4 the difference between C(1) and C(2) ($\Delta\delta = 0.5$–0.3 ppm) is in the same range as detected for the diamine dihydrogensulfates. Again, the data is in accord with previous observations for complexes **4** and **5**.

Cytotoxicity and Structure-Activity Relationships

Cytotoxicity was determined in nine human tumor cell lines (originating from colon and ovarian carcinoma, leukemia, and melanoma) by means of the resazurin assay after drug exposure for 48 hours, and IC_{50} values are listed in Table 2.

The following structure-activity relationships can be deduced from these data: The oxaliplatin derivatives carrying small substituents at position 4 of the cyclohexane ring (**4**, **5**) exhibit a higher cytotoxic potency in both leukemia cell lines, but a lower cytotoxicity in SK-MEL-5 melanoma cells than the parent compound, whereas in colon and ovarian cancer cells IC_{50} values are comparable or slightly higher than those of oxaliplatin (**3**). The cytotoxic potency of the derivatives carrying bigger substituents at the same position (**12a**, **12b**, **12c**) is by one to two

Table 2. Cytotoxicity of oxaliplatin and analogues in nine human tumor cell lines[a]

		Complexes					
		3	**4**	**5**	**12a**	**12b**	**12c**
Tumor cell line							
Colon	SW480	2.19	5.90	3.67	142	157	140
	SW620	2.27	3.24	7.53	87.7	103	136
	HCT-15	10.8	9.86	24.3	63.8	107	117
	COLO 205	1.50	1.03	3.8	164	164	208
	HT-29	1.93	2.40	1.31	26.3	24.8	147
Ovarian	NIH-OVCAR-3	5.57	5.90	2.18	78.9	68.5	175
Leukemia	MOLT-4	38.9	1.42	1.91	39.3	41.7	128
	HL-60	4.07	1.38	1.23	5.69	5.50	19.8
Melanoma	SK-MEL-5	4.58	33.9	15.8	76.6	82.2	136

[a] IC_{50} values (μM) of oxalatoplatinum(II) complexes after exposure for 48 h, determined by resazurin assay

orders of magnitude lower than that of oxaliplatin in colon, ovarian, and melanoma cancer cells and lower than that of **4** and **5** in all cell lines. Only in leukemia cells, the cytotoxicity of oxaliplatin is not affected by the introduction of a propyl or a phenyl group, but still markedly lowered in the case of a *tert*-butyl group.

These results are even more remarkable, considering the fact that in this work *trans-R,R/trans-S,S* isomeric mixtures have been investigated. Since *trans-R,R*-cyclohexane-1,2-diamine-containing platinum complexes are usually more active than their *trans-S,S* isomers or their *trans-R,R/trans-S,S* isomeric mixtures, a markedly improved antitumor activity of the pure *trans-R,R* isomers should be expected.

In preliminary *in vivo* experiments in mice bearing L1210 leukemia, complexes **4** and **5** displayed a higher anticancer activity and were found to be more tolerable in comparison to oxaliplatin at analogous dosage.

Conclusion

The attempt to develop more cytotoxic oxaliplatin derivatives by increasing the steric demand and the lipophilicity of the amine ligand, which are thought to be decisive for the cellular processing of the platinum–*DNA* adducts, is partially successful in the case of small substituents such as methyl and ethyl, but fails in the case of bigger substituents bound to C(4) of the cyclohexane-1,2-diamine ligand.

Based on these findings, we focus on the synthesis of (i) *trans*-cyclohexane-1,2-diamine derivatives bearing methyl and ethyl substituents with exclusive axial and equatorial substitution and (ii) on the optical resolution of the *trans-R,R/trans-S,S* isomeric mixtures with respect to optimization of structure-activity relationships.

Experimental

Potassium tetrachloroplatinate(II) was obtained from Degussa (Germany). All other chemicals (Sigma-Aldrich, Austria) were used as received and were of analytical grade. Water was used doubly distilled.

The synthetic procedures were carried out in a light protected environment when platinum complexes were involved. ^{1}H, ^{13}C{^{1}H}, ^{1}H,^{1}H-COSY, and ^{13}C,^{1}H-COSY spectra were recorded in D_2O or *DMF*-d_7 at 298 K (2D in a gradient enhanced mode) using a Bruker Avance DPX 400 instrument (Ultra-Shield^{TM} Magnet) and standard pulse programs at 400.13 (^{1}H) and 100.62 MHz (^{13}C). Chemical shifts were measured relative to the solvent peak. Elemental analyses (C, H, N) were performed by the microanalytical laboratory at the University of Vienna; their results were found to be in good agreement with the calculated values.

The substituted *trans*-cyclohexane-1,2-diamine dihydrogensulfates **10a**–**10c** have been synthesized according to standard literature procedures.

4-Propyl-trans-cyclohexane-1,2-diamine dihydrogensulfate (**10a**, $C_9H_{20}N_2 \cdot H_2SO_4$)

^{1}H NMR (D_2O): $\delta = 0.78$ [m, 3H, H(9)], 0.88–2.15 [m, 11H, H(3), H(4), H(5), H(6), H(7), H(8)], 3.39 [m, 1H, H(1) or H(2)], 3.52 [m, 1H, H(1) or H(2)]; ^{13}C NMR (D_2O): $\delta = 13.6$ [C(9)], 20.0 [C(8)], 24.2 [C(7)], 26.0 [C(5)], 30.5 [C(4)], 32.1 [C(6)], 34.0 [C(3)], 48.8 [C(1) or C(2)], 51.3 [C(1) or C(2)]; minor isomer: $\delta = 52.6$ [C(1′) or C(2′)], 52.8 [C(1′) or C(2′)].

4-Phenyl-trans-cyclohexane-1,2-diamine dihydrogensulfate (**10b**, $C_{12}H_{18}N_2 \cdot H_2SO_4$)

^{1}H NMR (D_2O): $\delta = 1.45$–2.40 [m, 7H, H(3), H(4), H(5), H(6)], 3.60–3.72 [m, 2H, H(1), H(2)], 7.20–7.39 [m, 5H, H(8), H(9), H(10)]; ^{13}C NMR (D_2O): $\delta = 24.2$, 26.1, 31.2 [C(3), C(5), C(6)], 35.6 [C(4)], 48.7 [C(1) or C(2)], 49.1 [C(1) or C(2)], 127.28, 127.31, 129.3 [C(8), C(9), C(10)], 143.4 [C(7)]; minor isomer: $\delta = 52.2$ [C(1′) or C(2′)], 52.5 [C(1′) or C(2′)].

4-(1,1-Dimethylethyl)-trans-cyclohexane-1,2-diamine dihydrogensulfate
(**10c**, $C_{10}H_{22}N_2 \cdot H_2SO_4$)

^{1}H NMR (D_2O): $\delta = 0.80$ [s, 9H, H(8)], 0.93–2.21 [m, 7H, H(3), H(4), H(5), H(6)], 3.62 [m, 1H, H(1) or H(2)], 3.75 [m, 1H, H(1) or H(2)]; ^{13}C NMR (D_2O): $\delta = 19.7$ [C(5)], 23.8 [C(3) or (C6)], 24.7 [C(3) or C(6)], 26.6 [C(8)], 31.8 [C(7)], 39.9 [C(4)], 47.4 [C(1) or C(2)], 48.9 [C(1) or C(2)]; minor isomer: $\delta = 52.7$ [C(1′) or C(2′)], 53.2 [C(1′) or C(2′)].

General Procedure for Diaminedichloroplatinum(II) Complexes

To a solution of K_2PtCl_4 (1 equiv) in 50 cm^3 of water, the diamine dihydrogensulfate (1 equiv) was added. The *pH* was adjusted to 7 with 0.5 *M* NaOH and was kept constant during the reaction at this value using 0.1 *M* NaOH. A yellow precipitate formed, which was filtered off and dried under reduced pressure over P_2O_5.

(SP-4-3)-Dichloro(4-propyl-trans-cyclohexane-1,2-diamine)platinum(II)
(**11a**, $C_9H_{20}Cl_2N_2Pt$)

K_2PtCl_4 (2.50 g, 6.02 mmol) was converted according to the above procedure to give 1.83 g of **11a** (72%) as a yellow solid.

(SP-4-3)-Dichloro(4-phenyl-trans-cyclohexane-1,2-diamine)platinum(II)
(**11b**, $C_{12}H_{18}Cl_2N_2Pt$)

K_2PtCl_4 (2.00 g, 4.82 mmol) was converted according to the above procedure to give 1.20 g of **11b** (55%) as a yellow solid.

(SP-4-3)-Dichloro(4-(1,1-dimethylethyl)-trans-cyclohexane-1,2-diamine)platinum(II)
(**11c**, $C_{10}H_{22}Cl_2N_2Pt$)

K_2PtCl_4 (2.50 g, 6.02 mmol) was converted according to the above procedure to give 1.80 g of **11c** (70%) as a yellow solid.

General Procedure for Diamineoxalatoplatinum(II) Complexes

To a suspension of the diaminedichloroplatinum(II) complex (1 equiv) in 15 cm^3 of water, $AgNO_3$ (1.9 equiv) was added in one portion. The mixture was stirred for a period of 24 hours at room temperature, and the precipitated silver chloride was filtered off. Oxalic acid (2 equiv) and 1 *M* NaOH (2 equiv) were added to the remaining solution. After stirring for 5 minutes at 50°C and one hour at room temperature, a white precipitate formed, which was filtered off and dried under reduced pressure over P_2O_5.

(SP-4-3)-(4-Propyl-trans-cyclohexane-1,2-diamine)oxalatoplatinum(II)
(**12a**, $C_{11}H_{20}N_2O_4Pt$)

Complex **11a** (1.0 g, 2.37 mmol) was converted according to the above procedure to give 488 mg of **12a** (49%) as a white solid. ^{1}H NMR (*DMF*-d_7): $\delta = 1.07$ [t, $^3J_{H,H} = 7$ Hz, 3H, H(9)], 1.38–1.52 [m, 4H, H(7), H(8)], 1.55–1.70 [m, 5H, H(3), H(4), H(5), H(6)], 2.06 [m, 1H, H(6)], 2.17 [m, 1H, H(3)], 2.52 [m, 1H, H(1) or H(2)], 2.73 [m, 1H, H(1) or H(2)], 5.49 [m, 2H, NH_2], 6.20 [m, 1H, NH_2], 6.33 [m, 1H, NH_2]; ^{13}C NMR (*DMF*-d_7): $\delta = 14.3$ [C(9)], 21.1 [C(8)], 27.7 [C(6)], 28.8 [C(5)], 33.3 [(C4)], 33.6 [C(7)], 36.1 [C(3)], 58.6 [C(1) or C(2)], 63.5 [C(1) or C(2)], 167.0 [C(10)]; minor isomer: $\delta = 63.0$ [C(1′) or C(2′)], 63.3 [C(1′) or C(2′)].

(SP-4-3)-(4-Phenyl-trans-cyclohexane-1,2-diamine)oxalatoplatinum(II)
(**12b**, $C_{14}H_{18}N_2O_4Pt$)

Complex **11b** (1.2 g, 2.63 mmol) was converted according to the above procedure to give 734 mg of **12b** (62%) as a white solid. ^{1}H NMR (*DMF*-d_7): $\delta = 1.60$ [m, 1H, H(5)], 1.77 [m, 1H, H(6)], 1.90–2.06 [m, 2H, H(6), H(3)], 2.19 [m, 1H, H(5)], 2.54 [m, 2H, H(1), H(2)], 2.67 [m, 1H, H(3)], 3.12 [m, 1H, H(4)], 5.36 [m, 1H, NH_2], 5.45 [m, 1H, NH_2], 6.14 [m, 2H, NH_2], 7.25 [t, $^3J_{H,H} = 7$ Hz, 1H, H(10)], 7.38 [t, $^3J_{H,H} = 8$ Hz, 1H, H(8)], 7.44 [d, $^3J_{H,H} = 8$ Hz, 1H, H(9)]; ^{13}C NMR (*DMF*-d_7): $\delta = 28.2$ [C(6)], 29.0 [C(5)], 35.6 [C(3)], 36.7 [(C4)], 59.0 [C(1) or C(2)], 63.3 [C(1) or C(2)], 126.2 [C(10)], 127.7 [C(8)], 128.9 [C(9)], 143.0 [C(7)], 166.8 [C(11)]; minor isomer: $\delta = 62.7$ [C(1′) or C(2′)], 63.0 [C(1′) or C(2′)].

(SP-4-3)-(4-(1,1-Dimethylethyl)-trans-cyclohexane-1,2-diamine)oxalatoplatinum(II)
(**12c**, $C_{12}H_{22}N_2O_4Pt$)

Complex **11c** (1.50 g, 3.44 mmol) was converted according to the above procedure to give 834 mg of **12c** (55%) as a white solid. ^{1}H NMR (*DMF*-d_7): $\delta = 1.04$ [s, 9H, H(8)], 1.60 [m, 2H, H(4), (H6)], 1.72–1.99 [m, 3H, H(3), (H5), H(6)], 2.12 [m, 1H, H(5)], 2.28 [m, 1H, H(3)], 2.48–2.69 [m, 1H, H(1) or H(2)], 2.86 [m, 1H, H(1) or H(2)], 5.42 [m, 1H, NH_2], 5.59 [m, 1H, NH_2], 6.28 [m, 2H, NH_2]; ^{13}C NMR (*DMF*-d_7): $\delta = 24.9$ [(C6], 29.7 [C(5)], 29.8 [C(8)], 32.9 [C(3)], 34.0 [C(7)], 42.5 [(C4)], 59.9 [C(1) or C(2)], 62.6 [C(1) or C(2)], 167.0 [C(11)]; minor isomer: $\delta = 63.1$ [C(1′) or C(2′)], 63.6 [C(1′) or C(2′)].

Cytotoxicity Tests in Cancer Cell Lines

SW480, SW620, HCT-15, COLO 205, HT-29 (all colon carcinoma), NIH-OVCAR-3 (ovarian carcinoma), MOLT-4, HL-60 (both leukemia), and SK-MEL-5 (melanoma) cells were obtained from the

American Type Culture Collection (ATCC) and propagated in cell culture medium, *i.e.* RPMI 1640, except for SW480 and SW620: Iscove's Modified Dulbecco's Medium (IMDM), HT-29 and SK-MEL-5: Dulbecco's Modified Eagle Medium (DMEM), supplemented with 10% heat-inactivated fetal calf serum (FCS) in every case.

Cells were harvested by trypsinization (except for the non-adherent lines MOLT-4 and HL-60 cells), seeded in 100 mm^3 of cell culture medium in defined densities (ranging from 7×10^3 to 2×10^4 living cells per well, depending on the cell line) into 96-well tissue culture plates and incubated at 37°C in a humidified atmosphere containing 5% CO_2 for 24 hours. Stock solutions of the test substances in water were sterilized by filtration (0.2 μm) and serially diluted (1:2) in cell culture medium. 100 mm^3 of each dilution were added to the cells in quadruples. For a negative control, 100 mm^3 of cell culture medium were added to four wells (100% value). For a positive control, all cells were deadened with sodium selenite (0% value). After drug exposure for 48 hours at 37°C and 5% CO_2, cells were incubated with resazurin (Sigma-Aldrich) (100 μM in *PBS*, added in aliqots of 50 μl per well) for further 4 hours at 37°C and 5% CO_2. Resazurin is metabolized by living cells from its oxidized form (blue) to a fluorescent intermediate (red). The development of the fluorescent intermediate was quantified in a fluorescence microplate reader (Genios, Tecan) at 590 nm using an excitation of 560 nm. The raw data were normalized to the positive control of deadened cells and set into relation to the metabolic activity of the untreated control cells. IC_{50} values were calculated by four parametric nonlinear regression using Graph Pad Prism 3.0 software.

Acknowledgements

The support of the FWF (Fonds zur Foerderung der wissenschaftlichen Forschung) and COST is gratefully acknowledged.

References

[1] Rosenberg B (1978) Interdiscip Sci Rev **3**: 134
[2] Lippert B (ed) (1999) Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug. Verlag Helvetica Chimica Acta, Zürich, and Wiley-VCH, Weinheim
[3] O'Dwyer PJ, Stevenson JP, Johnson SW (2000) Drugs **59**: 19
[4] O'Dwyer PJ, Stevenson JP, Johnson SW (1999) Clinical status of cisplatin, carboplatin, and other platinum-based antitumor drugs. In: Lippert B (ed) Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug. Verlag Helvetica Chimica Acta, Zürich, and Wiley-VCH, Weinheim, p 31
[5] Jakupec MA, Galanski M, Keppler BK (2003) Rev Physiol Biochem Pharmacol **146**: 1
[6] Kidani Y, Noji M, Tashiro T (1980) Gann **71**: 637
[7] Cvitkovic E, Bekradda M (1999) Semin Oncol **26**: 647
[8] O'Dwyer PJ, Johnson SW (2003) Semin Oncol **30**: 78
[9] Graham J, Muhsin M, Kirkpatrick P (2004) Nat Rev Drug Discov **3**: 11
[10] Reedijk J (1996) Chem Commun 801
[11] Jamieson ER, Lippard SJ (1999) Chem Rev **99**: 2467
[12] Scheeff ED, Briggs JM, Howell SB (1999) Mol Pharmacol **56**: 633
[13] Spingler B, Whittington DA, Lippard SJ (2001) Inorg Chem **40**: 5596
[14] Malina J, Kasparkova J, Natile G, Brabec V (2002) Chemistry and Biology **9**: 629
[15] Graham MA, Lockwood GF, Greenslade D, Brienza S, Bayssas M, Gamelin E (2000) Clin Cancer Res **6**: 1205
[16] Galanski M, Yasemi A, Slaby S, Jakupec MA, Arion VB, Rausch M, Nazarov AA, Keppler BK (2004) Eur J Med Chem **39**: 707
[17] Snyder BB, Lin H (1998) Synth Commun **28**: 1913
[18] Corey EJ, Nicolaou KC, Balanson RD, Machida Y (1975) Synthesis **9**: 590