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Enantiomerically Pure [1,2-Diamino-1-(4-fluorophenyl)butane]platinum(II) Complexes: Synthesis and Antitumor Activity against MCF-7 and MDA-MB 231 Breast Cancer and LnCaP/FGC Prostate Cancer Cell Lines

Enantiomerically pure 1,2-diamino-1-(4-fluorophenyl)butanes were synthesized by stereoselective procedures. The enantiomeric purity was determined by ^{1}H NMR spectroscopy after derivatization with (*1R*)-myrtenal. For the coordination to platinum, the diamines were reacted with K_2PtI_4. Reaction with Ag_2SO_4 yielded the respective sulfatoplatinum(II) complexes, which were converted into the dichloroplatinum(II) complexes by treatment with 2 N HCl. The influence of the configuration and the kind of leaving group on the antitumor activity was studied on the MCF-7 and MDA-MB 231 breast cancer cell lines, as well as on the LnCaP/FGC prostate cancer cell line. It was demonstrated that the dichloroplatinum(II) complexes were more active than the respective diiodoplatinum(II) derivatives. Conversion into the sulfatoplatinum(II) complexes further enhanced the antiproliferative effects. The configuration determined the antitumor effects, dependent on the cell line used: MCF-7: (*R,R*) > (*S,S*) > (*R,S*) > (*S,R*); MDA-MB 231: (*S,S*) > (*R,R*) > (*R,S*) = (*S,R*); LnCaP/FGC: (*S,S*) > (*R,R*) > (*R,S*) > (*S,R*).

Keywords: Platinum Complexes; MCF-7 and MDA-MB 231 Breast Cancer Cell Lines; LnCaP/FGC Prostate Cancer Cell Line; Antitumor Activity; Enantiomers

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Introduction

Since the discovery of the cytotoxicity of platinum complexes by Rosenberg et al. [1], numerous diaminedichloroplatinum(II) complexes have been synthesized and tested for antitumor activity.

Cisplatin exhibits high antitumor activity, but its clinical use is mostly limited by toxic side effects [2]. Exchange of both chlorides by cyclobutane-1,1-dicarboxylate led to carboplatin, which showed higher water solubility and reduced toxic side effects; however, myelosuppression and the development of resistance are intolerable disadvantages [3].

In order to overcome these drawbacks and to enhance the tumor selectivity, many carrier ligands were developed and coordinated to platinum. The most successful ligand, the 1,2-diaminocyclohexane (DACH), made oxaliplatin to the first platinum-based drug licensed for the therapy of colorectal cancer [4]. It has also shown efficacy in the treatment of patients with advanced ovarian [5] and small cell lung cancer [6]. Preliminary results further indicate that it might be also useful in the therapy of breast cancer [7].

The mode of action includes the building of intrastrand cross links comparable to other platinum compounds [8], but DACH-platinum DNA adducts formed by oxaliplatin are generally associated with greater cytoxicity and inhibition of DNA synthesis.

The stereochemistry of the 1,2-diaminocyclohexane moiety significantly influences the toxicity of the platinum complexes. Complexes of the two *trans* isomers (*R,R* and *S,S*) exhibit higher activities than the *meso* (*R,S* and *S,R*) adducts, and the *R,R*-complex is more effective than the *S,S* one [9–12].

These results encouraged us to investigate the enantioselective antitumor activity of [1,2-diamino-1,2-diarylethane]dichloroplatinum(II) complexes [13–15]. On the human MCF-7 breast cancer cell line, the *R,S*-configurated complexes were distinctly less active than their *R,R/S,S*-diastereomers. Optimization of the antitumor activity due to a separation of the enantiomers

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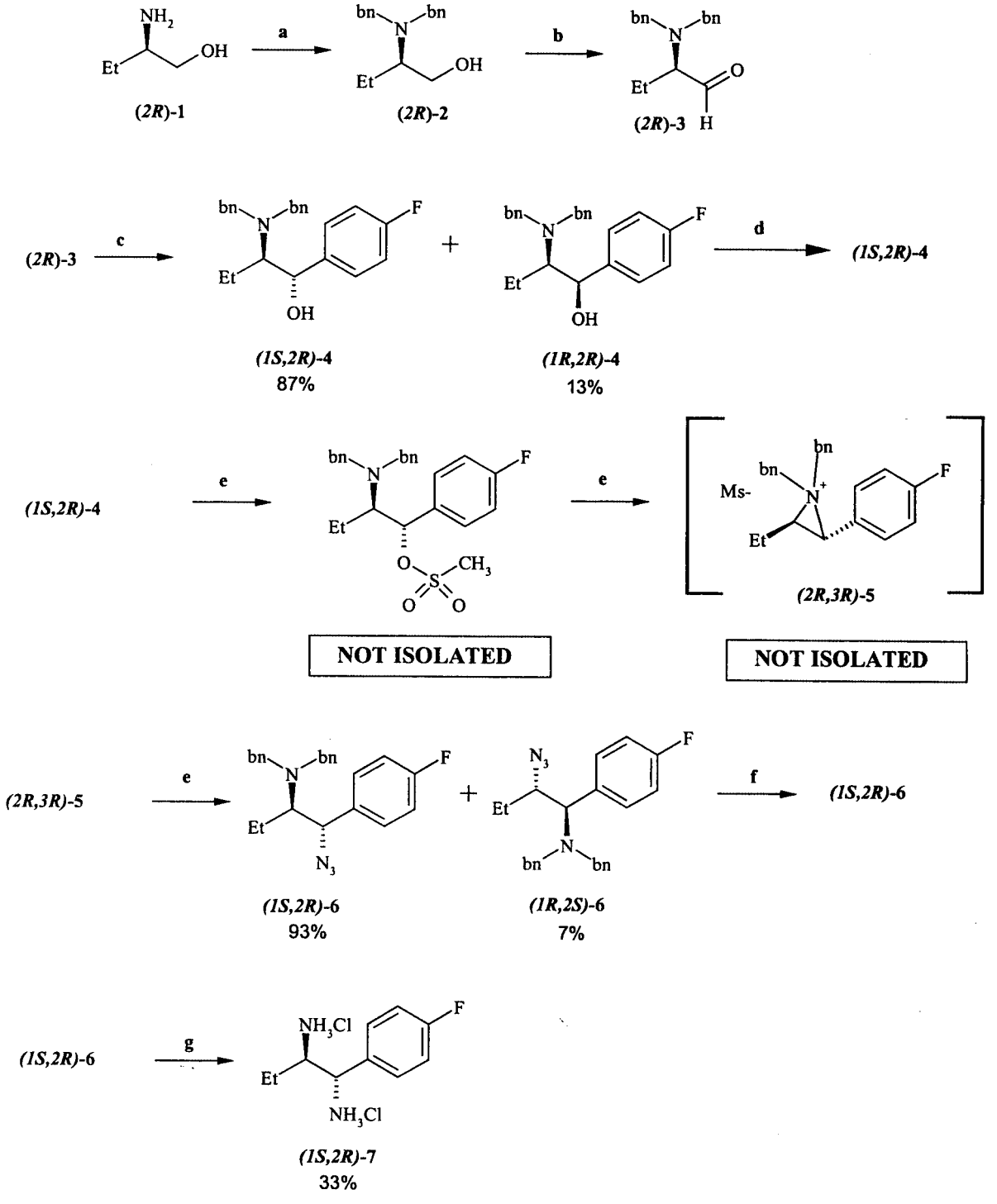

Scheme 1. Synthesis of *1S,2R*-configurated 1,2-diamino-1-(4-fluorophenyl)butanes. Reagents and conditions: **a**: BnBr (2 eq.), KI (0.1 eq.), Na_2CO_3 (2 eq.), THF, reflux; **b**: DMSO (2 eq.), oxalyl chloride (1.1 eq.), TEA (5 eq.), CH_2Cl_2, −60 °C; **c**: 4F-phenylmagnesium bromide (1.1 eq.), THF, 0 °C; **d**: column chromatography, petroleum ether$_{(40\text{-}60)}$/acetone (9 : 1); **e**: 1. MsCl (1.5 eq.), TEA (3 eq.), Et_2O, O °C to room temperature; 2. NaN_3 (2 eq.), H_2O; **f**: column chromatography, petroleum ether$_{(40\text{-}60)}$/acetone (98 : 2); **g**: 1. $HCOONH_4$ (4 eq.), Pd on C (10 %), MeOH, reflux ; 2. HCl/Et_2O.

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was less successful. Only small differences between the enantiomers exist if the aryl rings are unsubstituted, 3-OH, 4-OH or 4-F substituted.

To get more insight into the structural dependence of enantiomerically pure [1,2-diaminoethane]dichloroplatinum(II) complexes, we determined the antiproliferative effects of [1,2-diamino-1-phenylpropane]dichloroplatinum(II) (**Ph/Me-PtCl$_2$**) and [1,2-diamino-1-(4-fluorophenyl)propane]dichloroplatinum(II) (**4F-Ph/Me-PtCl$_2$**) isomers on the MCF-7 cell line [16, 17].

The cytotoxic potency of **Ph/Me-PtCl$_2$** decreased in the series (*R,R*) > (*S,S*) > (*S,R*) = (*R,S*), while in the case of **4F-Ph/Me-PtCl$_2$**, the *S,S*-enantiomer is more active than its isomers.

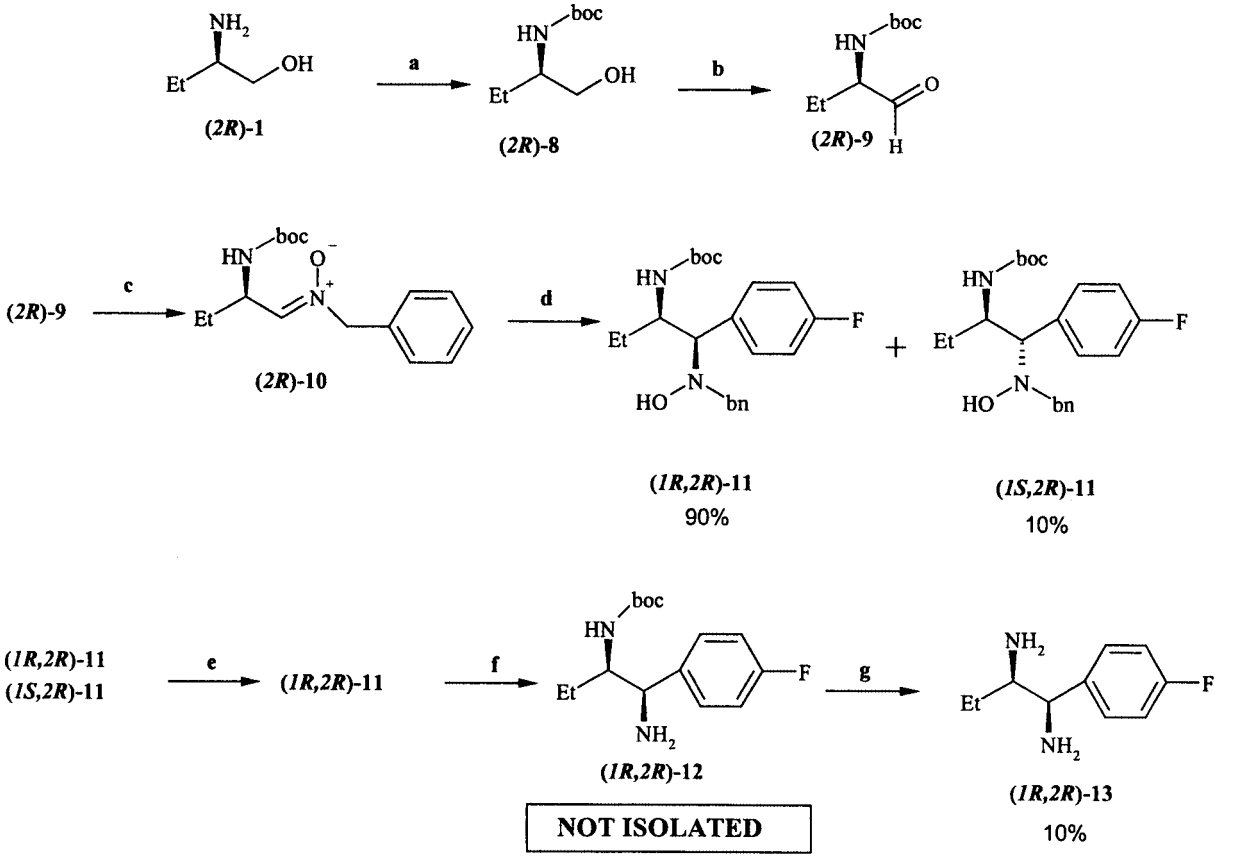
Because of these studies, we focussed our attention on the 4-F derivatives and determined the influence of the elongation of the C2-alkyl chain (methyl → ethyl), as well as the significance of the leaving groups, on the antiproliferative effects against human breast (MCF-7 and MDA-MB 231) and prostate (LnCaP/FGC) cancer cell lines.

Results

Synthesis

The *1S,2R*-configurated 1,2-diamino-1-(4-fluorophenyl)butane **(*1S,2R*)-7** was obtained by an already published modified method of O'Brien [18] (Scheme 1).

(*2R*)-2-Aminobutanol **(*2R*)-1** was first N-protected by two benzyl groups and transformed into the aldehyde **(*2R*)-3** [19], which was reacted with 4-fluorophenylmagnesiumbromide to give a mixture of the diastereomeric aminoalcohols **(*1S,2R*)-4**/**(*1R,2R*)-4** in a ratio of about 87:13 [20]. After separation by column chromatography, the alcoholic function of **(*1S,2R*)-4** was activated via mesylate formation. This resulting



Scheme 2. Synthesis of *1R,2R*-configurated 1,2-diamino-1-(4-fluorophenyl)butanes. Reagents and conditions: **a**: BOC anhydride (1.1 eq.), TEA (1.1 eq.), CH_2Cl_2, O °C to room temperature; **b**: DMSO (2 eq.), oxalyl chloride (1 eq.), TEA (5 eq.), CH_2Cl_2, −60 °C; **c**: benzylhydroxylamine (1 eq.), $MgSO_4$ (1 eq.), CH_2Cl_2, room temperature; **d**: 4F-phenylmagnesium bromide (3 eq.), THF, −50 °C; **e**: column chromatography, petroleum ether$_{(40\text{-}60)}$/acetone (95:5); **f**: $HCOONH_4$ (4 eq.), Pd on C (10%), MeOH; **g**: 1. HCl/MeOH ; 2. NaOH; 3. D-(−)-(*2S,3S*)-tartaric acid.

unstable intermediate could not be isolated because it cyclized readily to afford an aziridinium ion **(*2R,3R*)-5**. Ring opening with N_3^- yielded mainly the azidoamine **(*1S,2R*)-6** (93%), which was separated, reduced and deprotected to obtain the diamine **(*1S,2R*)-7** with an overall yield of 33% [21]. **(*1R,2S*)-7** was available by the same reaction course starting from **(*2S*)-1**.

The synthesis of the *1R,2R*-configurated 1,2-diamino-1-(4-fluorophenyl)butane **(*1R,2R*)-13** is presented in Scheme 2 [22].

(*2R*)-1 protected with a *tert*-butoxycarbonyl group (BOC) [23] was oxydized to the aldehyde **(*2R*)-9** [19], which reacted with N-benzylhydroxylamine to give the N-oxide **(*2R*)-10**. Addition of 4-fluorophenylmagnesiumbromide resulted in the diastereoisomeric mixture of **(*1R,2R*)-11** and **(*1S,2R*)-11** in a ratio of about 90:10. Separation of **(*1R,2R*)-11**, reduction and deprotection gave **(*1R,2R*)-13** in an overall amount of 10%.

Using the (*2S*)-2-aminobutanol **(*2S*)-1**, diamine **(*1S,2S*)-13** was available.

The optical purity of the diamines has been determined by ^{1}H NMR using (*1R*)-(−)-myrtenal as chiral derivatizing agent, following already published procedures [24].

K_2PtI_4 was used for the coordination of the enantiomerically pure 1,2-diaminobutanes **7** and **13** (Scheme 3). The reaction with Ag_2SO_4 yielded the respective sulfatoplatinum(II) complexes, which were transformed into the dichloroplatinum(II) complexes by addition of 2 N HCl (Scheme 3).

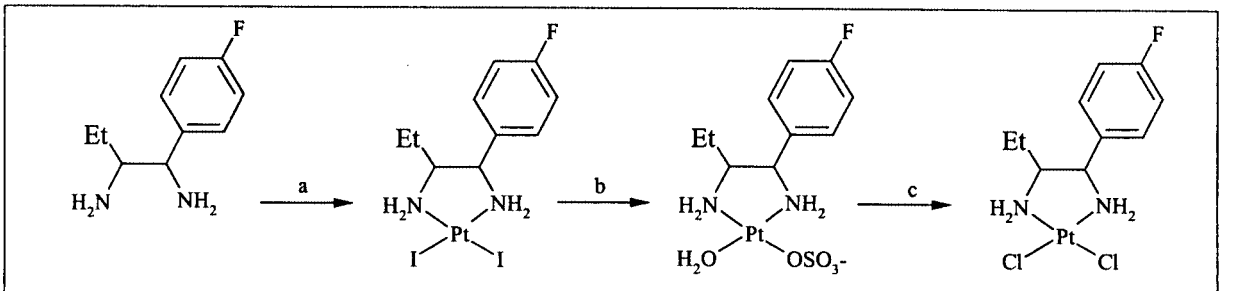
Spectroscopic characterization

The coordination to platinum was confirmed by NMR spectroscopy. The NH_3^+ resonances of the free 1,2-diaminoethanes were replaced by four resonances due to a diastereotopically split resulting from the coordination to platinum.

A reciprocal coupling and the coupling to the amine protons split the methine protons. The signals were further broadened by platinum satellites ($^3J_{CH\text{-}Pt}$). If the coordination to platinum of the 1,2-diaminoethanes was performed with K_2PtI_4 in D_2O, an NH/ND-exchange took place and the $^3J_{CH\text{-}CH}$ and the $^3J_{CH\text{-}Pt}$ could be calculated from the spectra. The coupling constants depended on the dihedral angle and allowed an insight into the conformational behavior of the platinum complexes [25–27].

The five-membered chelate ring was puckered and could exist in two possible conformations, the δ- and the λ-form. An exclusive equatorial orientation of the C1-aryl and the C2-alkyl substituents was realized in the RR/SS-series, resulting in coupling constants of $^3J_{CH\text{-}CH} \approx 12.0$ Hz and $^3J_{CH\text{-}Pt} = 0$ Hz.

On the contrary, the *R,S/S,R*-configuration enhanced the dynamic properties. In the spectra of the *R,S*- and *S,R*-configurated complexes, the methine proton at C_2 was split by couplings to the benzylic proton ($^3J_{CH\text{-}CH} \approx 4.5$ Hz) and to ^{195}Pt ($^3J_{CH\text{-}Pt} = 60$ Hz). The CH-Pt coupling showed a maximum of 80 Hz if the proton was exclusively equatorially arranged, and a minimum of $^3J_{CH\text{-}Pt} = 0$ Hz if the CH was axial standing [25]. The coupling constant of $^3J_{CH\text{-}Pt} = 60$ Hz indi-



(*1S,2R*)-7	(*RS*)-4F-Ph/Et-PtI_2	(*RS*)-4F-Ph/Et-$PtSO_4$	(*RS*)-4F-Ph/Et-$PtCl_2$
(*1R,2S*)-7	(*SR*)-4F-Ph/Et-PtI_2	(*SR*)-4F-Ph/Et-$PtSO_4$	(*SR*)-4F-Ph/Et-$PtCl_2$
(*1R,2R*)-13	(*RR*)-4F-Ph/Et-PtI_2	(*RR*)-4F-Ph/Et-$PtSO_4$	(*RR*)-4F-Ph/Et-$PtCl_2$
(*1S,2S*)-13	(*SS*)-4F-Ph/Et-PtI_2	(*SS*)-4F-Ph/Et-$PtSO_4$	(*SS*)-4F-Ph/Et-$PtCl_2$

Scheme 3. Synthesis of [1,2-diamino-1-(4-fluorophenyl)butane]platinum(II) complexes. Reagents and conditions: **a**: K_2PtI_4 (1.1 eq.) at 40 °C in aqueous solution; **b**: Ag_2SO_4 (0.95 eq.) in aqueous solution with protection from light; **c**: 2 N HCl.

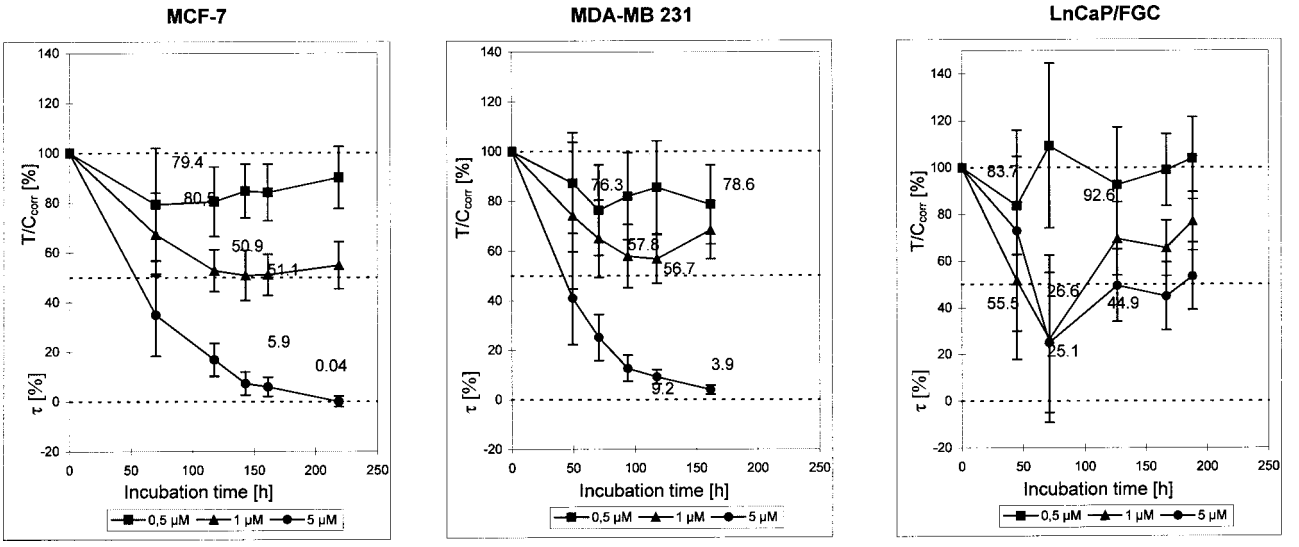


Figure 1. Antiproliferative effects of cisplatin on the human MCF-7 and MDA-MB 231 breast cancer cell lines and on the LnCaP/FGC prostate cancer cell line.

cated an interconversion of the five-membered chelate ring with a displaced equilibrium in favor of a conformation with an axial-standing aryl ring.

The leaving groups influenced the chemical shifts of the signals. The NH_2 as well as the $CH_{methine}$ signals of the diiodoplatinum(II) complexes were diamagnetically shifted compared to their dichloroplatinum(II) derivatives. This was the consequence of stronger *trans* effects of the iodides labilizing the Pt-N bonds.

The spectra of the sulfatoplatinum(II) complexes showed a strong low-field shift of the same protons, due to the positive charge on the platinum central atom. The measurement of the complexes had to be done in DMSO, since usable spectra were only available in this solvent [28]. DMSO coordinated to platinum and gave a well-defined sulfato[sulfinylbismethane-S]platinum(II) complex.

Antiproliferative effects

The platinum complexes were tested on the MCF-7 and MDA-MB 231 mammary carcinoma cell lines as well as the LwCaP/FGC prostate cancer cell line. Cisplatin was used as reference (Figure 1).

Cisplatin reduced the growth of the tumor cells, in a concentration-dependent way. At 5 µM, it suppressed the proliferation of MDA-MB 231 and MCF-7 cells completely ($T/C_{corr} \approx 0\%$; see Figure 1). On the LnCaP/FGC cell line, it was by far less active. At a concentration of 5 µM, a cell mass reduction of about 75% was achieved after an incubation of 75 h. The following onset of proliferation indicated the development of drug resistance [29].

[1,2 diamino-1-(4-fluorophenyl)butane]platinum(II) complexes showed antiproliferative effects, depending on the configuration and the kind of leaving group. As described in Figures 2 and 3, the diiodoplatinum(II) complexes were less active on the MCF-7 breast cancer cell line than the sulfatoplatinum(II) and the dichloroplatinum(II) derivatives.

At the highest concentration, **(*SS*)-** and **(*RR*)-4F-Ph/Et-PtI$_2$** significantly reduced cell growth by 70% and about 100%, respectively, while **(*SR*)-** and **(*RS*)-4F-Ph/Et-PtI$_2$** were inactive. Exchange of the I^- leaving groups increased the antitumor activity in the *erythro*-series. In the case of **(*RS*)-4F-Ph/Et-PtCl$_2$**, a concentration-dependent antiproliferative effect was observed (see Figure 3), even comparable to that of cisplatin. It should be mentioned that the *R,S*-configurated complexes were distinctly more active than their *S,R*-enantiomers.

The variation of the leaving groups in the *threo*-series led to complexes that were by far more active than cisplatin. **(*RR*)-4F-Ph/Et-PtSO$_4$** and **(*SS*)-4F-Ph/Et-PtSO$_4$** showed cytocidal effects even at the low concentration of 0.5 µM. Conversion of both complexes into the dichloroplatinum(II) compounds (**(*RR*)-** and **(*SS*)-4F-Ph/Et-PtCl$_2$**) decreased the cytotoxicity. **(*RR*)-4F-Ph/Et-PtCl$_2$** reduced cell growth significantly stronger than **(*SS*)-4F-Ph/Et-PtCl$_2$** and achieved cytocidal effects at concentrations of 1 and 5 µM.

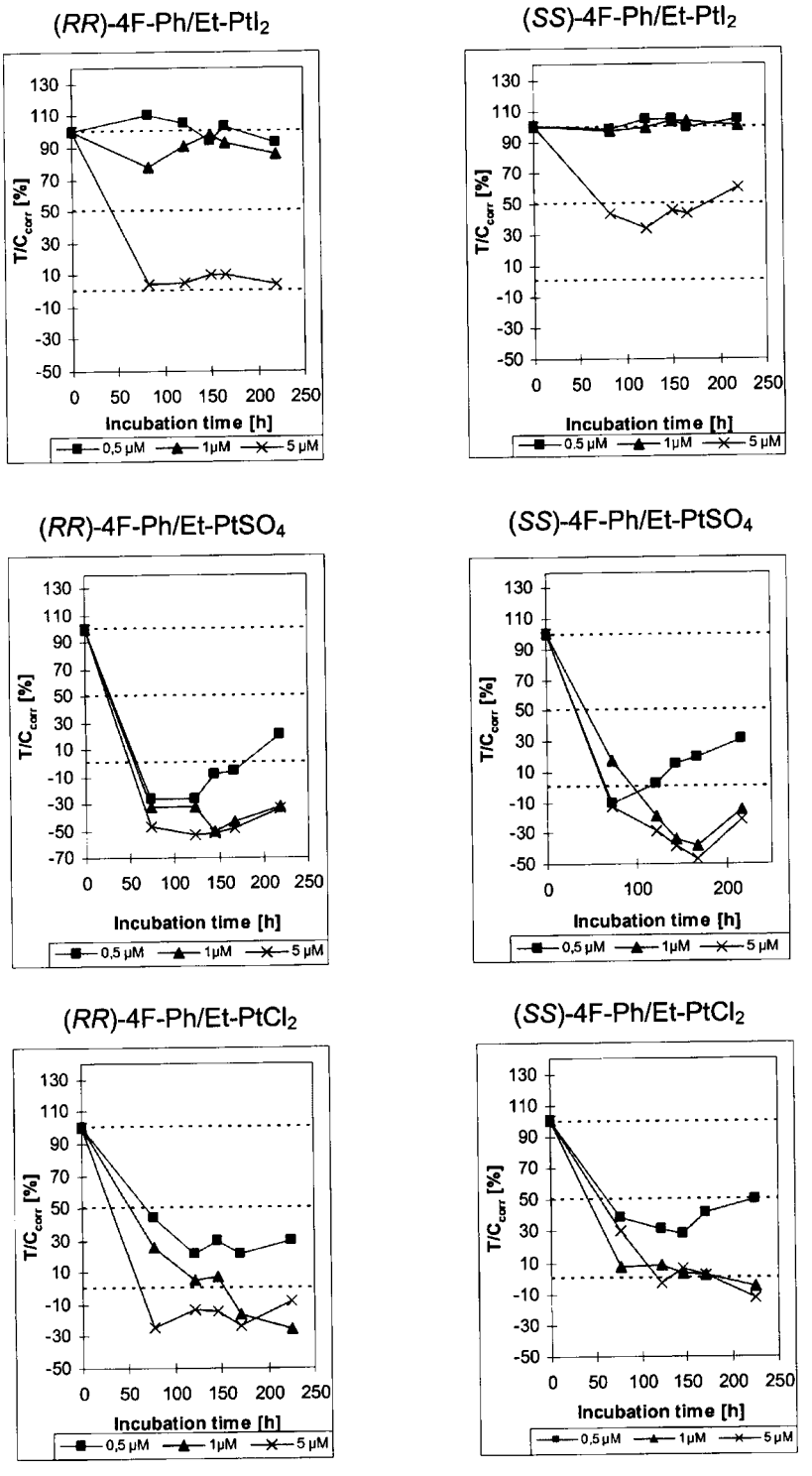


Figure 2. Antiproliferative effects of *R,R*- and *S,S*-configurated [1,2-diamino-1-(4-fluorophenyl)butanes]platinum(II) complexes on MCF-7 cells.

[1,2-Diamino-1-(4-fluorophenyl)butane]platinum(II) complexes also caused antiproliferative effects against MDA-MB 231 cells. **(*SR*)-** and **(*RS*)-4F-Ph/Et-PtCl$_2$** reduced the cell growth at the highest concentration used to about T/C$_{corr}$ = 10% (see Figure 4). Their diastereomeres were distinctly more active and reached

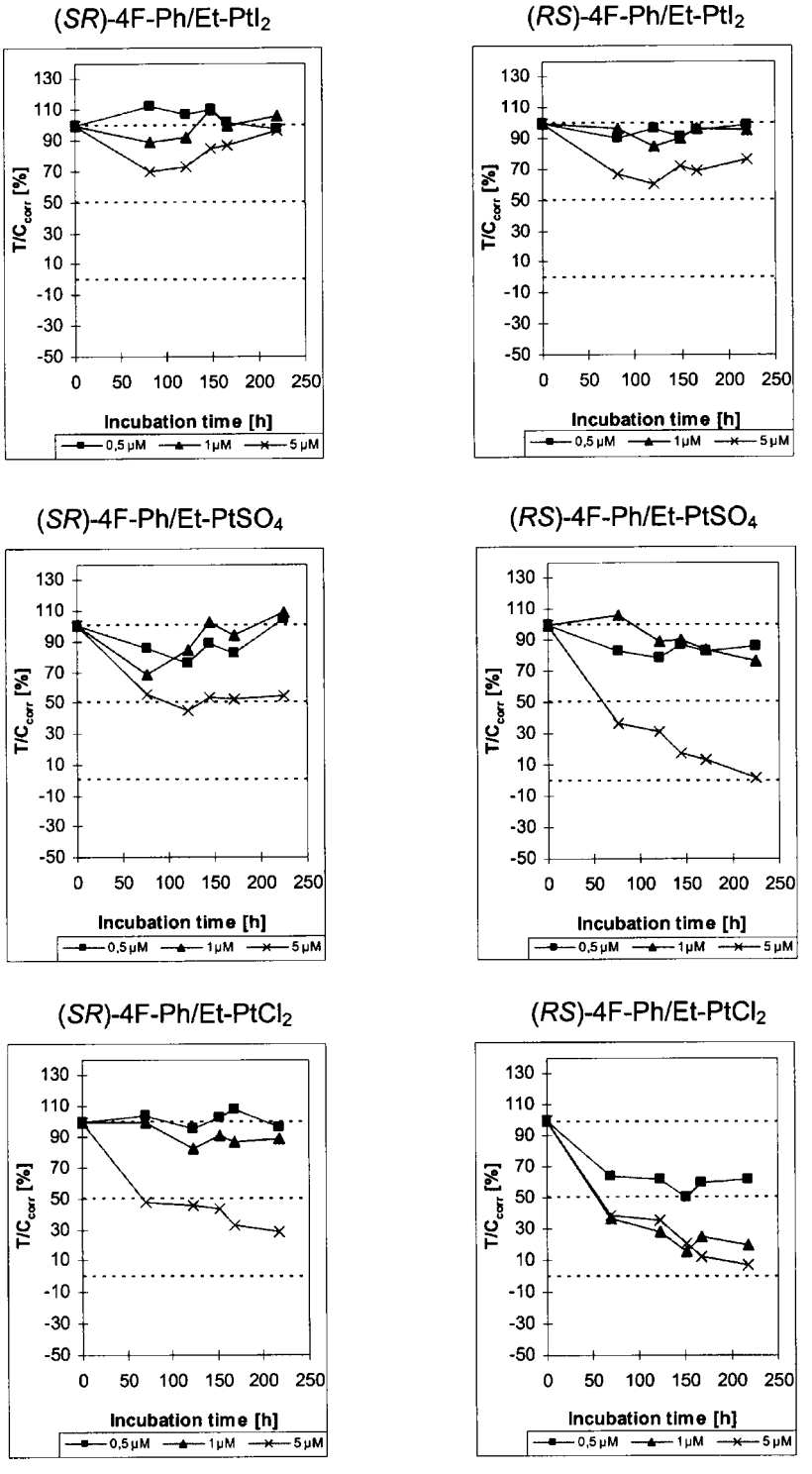


Figure 3. Antiproliferative effects of *R,S*- and *S,R*-configurated [1,2-diamino-1-(4-fluorophenyl)butane]platinum(II) complexes on MCF-7 cells.

cytostatic potency ($T/C_{corr} \approx 0\%$). In this test, **(*SS*)-4F-Ph/Et-PtCl$_2$** showed slightly better effects than **(*RR*)-4F-Ph/Et-PtCl$_2$**, especially at lower concentrations.

On the LnCaP/FGC cell line, **(*RS*)-**, **(*SS*)-** and **(*RR*)-4F-Ph/Et-PtCl$_2$** were more active than cisplatin (Figure 5). **(*SS*)-** and **(*RR*)-4F-Ph/Et-PtCl$_2$** demonstrated cytocidal effects at each concentration used. A some-

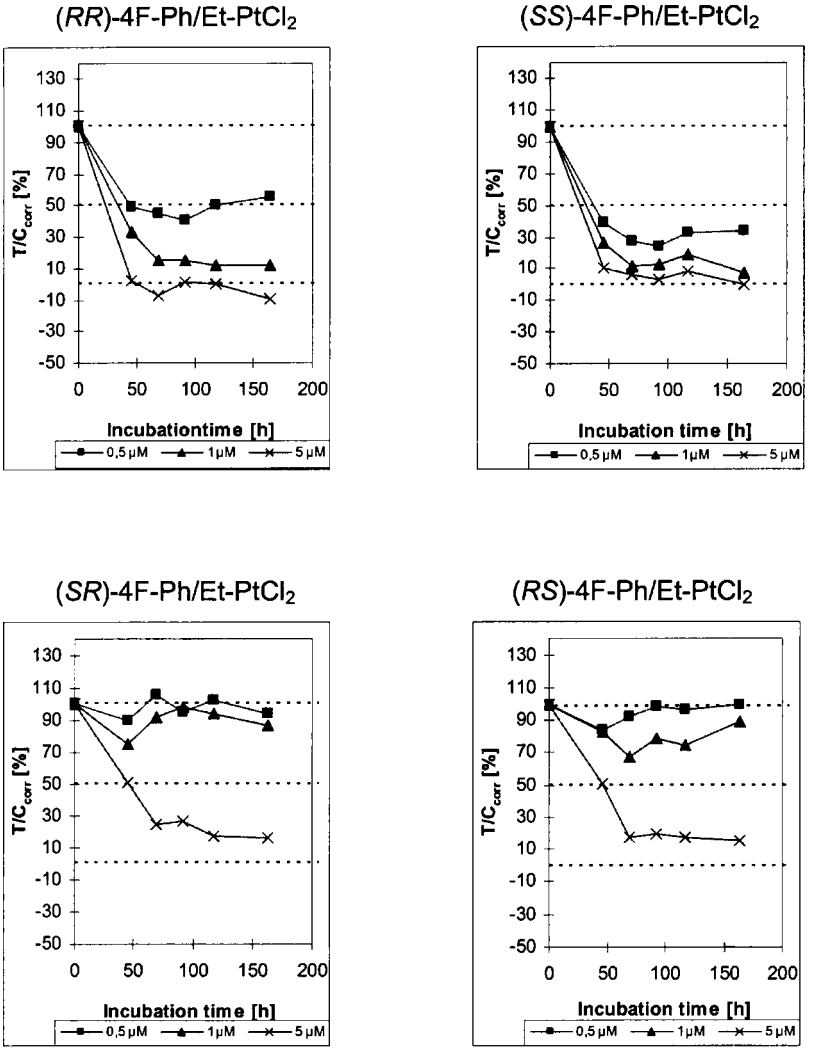


Figure 4. Antiproliferative effects of *R,S*- and *S,R*-configured [1,2-diamino-1-(4-fluorophenyl)butane]dichloroplatinum(II) complexes on the MDA-MB 231 cell line.

what higher cytotoxicity of **(*SS*)-4F-Ph/Et-PtCl$_2$** was deduced from the time activity curves.

Discussion

The investigations presented in this paper continue the structure activity relationship study on [1,2-diamino-1-(4-fluorophenyl)ethane]dichloroplatinum(II) complexes [16, 17] that were synthesized to optimize the antitumor activity of the parent compounds [(*R,S*)- and (*R,R/S,S*)-1,2-diamino-1,2-bis(4-fluorophenyl)-ethane]dichloroplatinum(II) (**(*RS*)-4F-Ph-PtCl$_2$** and **(*RR/SS*)-4F-Ph-PtCl$_2$**) [14].

The **4F-Ph-PtCl$_2$** complexes are cisplatin derivatives with high selectivity for mammary carcinoma cells [30]. It was demonstrated in various pharmacological studies that the complexes possessed high antiproliferative effects against MCF-7 and MDA-MB 231 breast cancer cells and were also active on the LnCaP/FGC prostate cancer cell line [30, 31]. The *R,R/S,S*-configurated compound was by far more active than its diastereomer. This finding was explained by an accumulation in the cytoplasm by a stereospecific transport through the cell membrane [32] and different attachment at the DNA due to the spatial structure of the diamine ligand.

The separation of the enantiomers did not optimize the antitumor activity [15], although the binding of enantiomeric compounds to the double-helical DNA as a chiral structure should lead to diastereomeric adducts. Furthermore, it has been verified that DNA cross-links

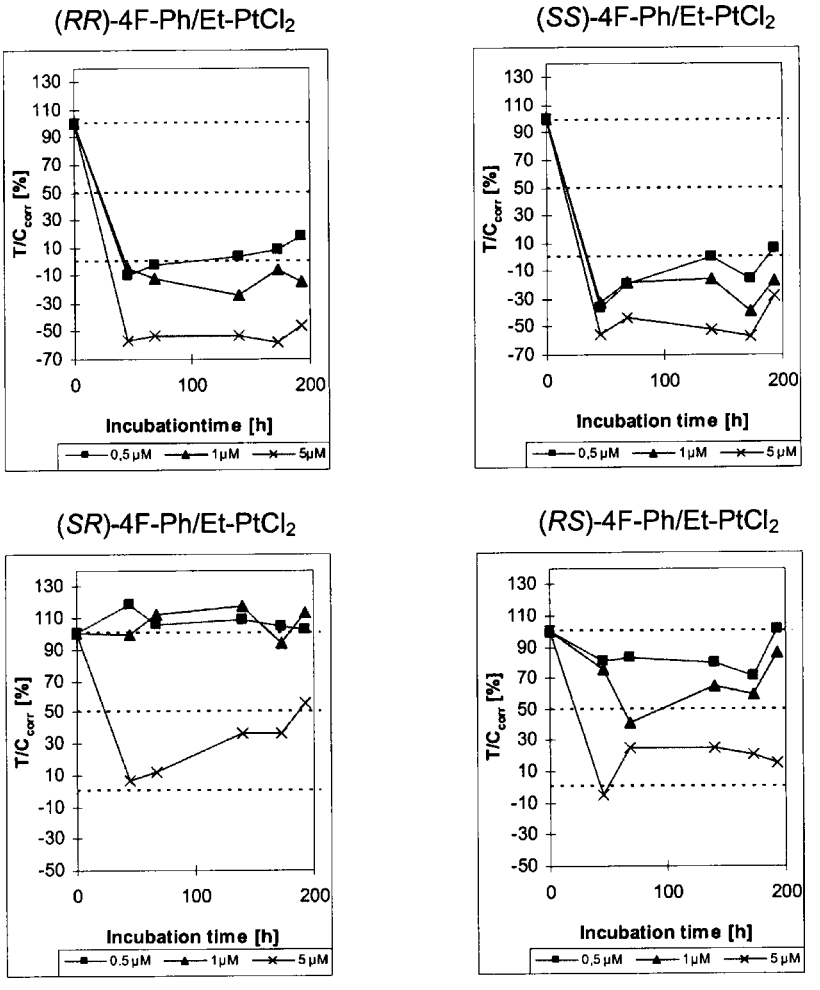


Figure 5. Antiproliferative effects of [1,2-diamino-1-(4-fluorophenyl)butane]dichloroplatinum(II) complexes on the LnCaP/FGC cell line.

of platinum complexes with enantiomeric amine ligands can not only exhibit different conformational features but also be differently processed by the cellular machinery. These results expand the general knowledge about the influence of the stereochemistry on the platinum-DNA adduct can influence the cell response, and contribute to the understanding of the processes that are crucial for antitumor activity [33].

In another study, molecular modeling techniques were used to investigate the role of steric interactions between the ligands at the platinum and the DNA in influencing the bifunctional binding of two enantiomers. It was calculated that the *S*-configured [3-aminohexahydroazepine]dichloroplatinum(II) should bind more readily. Indeed, the binding of the *S*-enantiomer to calf thymus DNA was slightly greater than the binding of the R-enantiomer and slightly less than the binding of cisplatin. Assays of the proportion of monofunctional adducts showed that a substantially greater proportion of monofunctional adducts remained for the *R*-enantiomer and cisplatin than for the *S*-enantiomer [34].

4F-Ph-PtCl$_2$ represents a compound with two asymmetric centres. It is supposed that the identically substituted benzylic C-atoms might be the reason for the missing enantioselectivity. Therefore, we tried to optimize the antiproliferative activity by exchanging a 4-fluorophenyl moiety for an alkyl chain. In a previously published SAR study [16, 17], we demonstrated a marginal loss of cytotoxicity for the MCF-7 cell line but an increase of stereoselectivity by use of a C2-methyl substituent: **(*SS*)-4F-Ph/Me-PtCl$_2$** > **(*RR*)-4F-Ph/Me-PtCl$_2$** > **(*SR*)-4F-Ph/Me-PtCl$_2$** = **(*RS*)-4F-Ph/Me-PtCl$_2$**. These positive results encouraged us to elongate the C-alkyl chain. A comparison with the antitumor activity of [1,2-diamino-1-(4-fluorophenyl)propane]platinum(II) complexes indicated a distinct increase of activity due

to the elongation of the C2-alkyl chain by a methylene group. However, it is obvious that this modification also changed the series of activity: **(*RR*)-4F-Ph/Et-PtCl$_2$** > **(*SS*)-4F-Ph/Et-PtCl$_2$** > **(*RS*)-4F-Ph/Et-PtCl$_2$** > **(*SR*)-4F-Ph/Et-PtCl$_2$**. Interestingly, the cytotoxicity of **(*RS*)-4F-Ph/Me-PtCl$_2$** and **(*SR*)-4F-Ph/Me-PtCl$_2$** was identical for the MDA-MB 231 cell line.

It should be noted that the antitumor activity depended on the kind of cells used in the *in vitro* assays. The **4F-Ph/Et-PtCl$_2$** complexes showed the highest activity against LnCaP/FGC prostate cancer cells, superior to cisplatin. The hormone-dependent MCF-7 cells were more sensitive to **4F-Ph/Et-PtCl$_2$** complexes than the hormone-independent MDA-MB 231 cells. With the exception of **(*SR*)-4F-Ph-PtCl$_2$** on the MCF-7 cell line and both **(*SR*)-4F-Ph-PtCl$_2$** and **(*RS*)-4F-Ph-PtCl$_2$** on the MDA-MB 231 cell line, the complexes were more active than cisplatin.

The antitumor activity was determined, besides the asymmetric C-atoms, by the kind of leaving group. It is expected that after the transport into the cytoplasm, the platinum complexes hydrolize into the aqua- and the diaquaplatinum(II) complexes, which then bind to nucleobases [35].

In previous studies [28, 36–38] on the leaving group derivatives of [1,2-diamino-1,2-bis(4-fluorophenyl)-ethane]platinum(II), we demonstrated a correlation between the strength of the Pt-X bond (X = leaving group) and the cytotoxic properties. The same trend can be estimated from the time activity curves depicted in Figures 2 and 3. **(*SS*)-** and **(*RR*)-4F/Et-PtI$_2$** were marginally active. The exchange of I- by Cl- enhanced the influence on tumor cell growth. Iodide is a leaving group that is strongly bound to platinum.

The hydrolysis as prerequisite for DNA binding is retarded. In contrast, the Pt-Cl bond is hydrolyzed in the cytoplasm in sufficient amounts to achieve high cytotoxicity. Interestingly, the aquasulfatoplatinum(II) complexes which are rapidly transformed into the diaquaplatinum(II) form [39] were more active than the dichloroplatinum(II) complexes. This correlates very well with the findings obtained with the parent compound **4F-Ph-PtSO$_4$**. **(*RR/SS*)-4F-Ph-PtSO$_4$** was enriched in the MCF-7 cells, although it represented a cationic Pt(H$_2$O)$_2$ form under the conditions used (Cl-free medium) [32]. It was proposed that the platinum complex was accumulated by an active transport. This might also be possible for [1,2-diamino-1-(4-fluorophenyl)-butane]platinum(II) complexes, which will be evaluated in a further study.

Acknowledgments

The technical assistance of S. Bergemann and I. Schnautz is acknowledged. Thanks are due to the Deutsche Forschungsgemeinschaft for financial support (Gu 284/4-1 and FOR 463).

Experimental

^{1}H and ^{13}C NMR spectra were taken at 293 K on a Bruker Avance 300 MHz spectrometer with TMS as internal standard. IR analyses were performed with a Shimadzu IR-470 spectrophotometer. Melting points (uncorrected) were measured with a Mettler FP1 apparatus. All CC purifications were done using silica gel Kieselgel® 100 (Merck). TLC was performed on Kieselgel® 60 F_{254} plates (Merck). Mass spectra were recorded on a Thermo-Fisons VG Auto Spec (70 eV). Specific rotations were measured with a Perkin-Elmer 141 polarimeter. All reagents were obtained from Aldrich, except benzylhydroxylamine which was synthesized following published procedures [40, 41]. Experimental procedures were performed with either (*2R*)- or (*2S*)-2-aminobutane-1-ol (**(*2R*)-1** or **(*2S*)-1**) as starting material. The synthesis was described on the example of **(*2R*)-1**.

Synthesis

*(2R)-N,N-dibenzyl-2-aminobutan-1-ol (**(*2R*)-2**)*

To a solution of (*2R*)-2-aminobutan-1-ol (**(*2R*)-1**) (10 g, 0.112 mol) in THF (200 mL), Na_2CO_3 (23.7 g, 0.224 mol), KI (1.9 g, 11.2 mmol) and benzyl bromide (38.3 g, 0.224 mol) were added. The suspension was stirred and refluxed for 10 h. After cooling and filtration, the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL). This solution was washed with NaOH 10% (wt/vol) (100 mL), brine (50 mL), then dried over $MgSO_4$, filtered and evaporated under reduced pressure. Yellow oil: 30.2 g (yield: quantitative).

^{1}H NMR ($CDCl_3$) (base): δ = 0.88 (t, 3H, J = 7.5 Hz, CH_3), 1.21 and 1.76 (m and m, 1H and 1H, CH_3CH_2), 2.69 (m, 1H, C*H*N), 3.14 (bs, 1H, OH), 3.38 (superimposed) and 3.50 (dd and dd, 1H and 1H, J = 5.0 and 10.6 Hz, CH_2OH), 3.40 and 3.79 (d and d, 2H and 2H, J = 13.2 Hz, $ArCH_2$), 7.18–7.32 (10H, Ar). ^{13}C NMR ($CDCl_3$) (base): δ = 12.3 (CH_3CH_2), 18.5 (CH_3CH_2), 53.8 ($ArCH_2$), 61.1 (CH_2OH), 61.2 (CHN), 127.7 ($C_{4'}$), 129.5 ($C_{2'}C_{6'}$), 129.6 ($C_{3'}C_{5'}$), 140 ($C_{1'}$). IR (film) (base): 3410 (ν O-H), 2840, 1445, 1044, 744, 692 cm^{-1}.

*(2R)-N,N-dibenzyl-2-aminobutanal (**(*2R*)-3**)*

In a three-necked flask maintained under N_2, oxalyl chloride (11 g, 87 mmol) was dissolved in dry CH_2Cl_2 (100 mL) and cooled to −60 °C. At this temperature, a solution of anhydrous DMSO (12.3 g, 157 mmol) in dry CH_2Cl_2 (25 mL) was added. After 2 min of stirring, a solution of (*2R*)-N,N-dibenzyl-2-aminobutan-1-ol (**(*2R*)-2**) (21.2 g, 79 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise during 5 min. This mixture was stirred for 15 min, and TEA (40 g, 395 mmol) was added. The suspension formed was stirred at about −30 °C for 5 min and then warmed to room temperature. Water (200 mL) was added, and the mixture was decanted. The organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product (dark

yellow oil: 19.4 g) (yield: 92% estimated by ^{1}H NMR) was not purified before analysis and directly used for the next step.

^{1}H NMR ($CDCl_3$) (base): δ = 0.95 (t, 3H, *J* = 7.4 Hz, CH_3), 1.67 (m, 2H, CH_3CH_2), 3.06 (t, 1H, *J* = 6.8 Hz, NC*H*C=O), 3.69 and 3.78 (d and d, 2H and 2H, *J* = 13.7 Hz, $ArCH_2$), 7.18–7.38 (10H, Ar), 9.70 (s, 1H, CH=O). ^{13}C NMR ($CDCl_3$) (base): δ = 12.3 (CH_3), 18.0 (CH_3CH_2), 55.4 ($ArCH_2$), 69.0 (CHN), 127.8 ($C_{4'}$), 128.9 ($C_{2'}C_{6'}$), 129.4 ($C_{3'}C_{5'}$), 139.8 ($C_{1'}$), 204.2 (C=O). IR (film) (base): 2795, 2690, 1712 (C=O), 1444, 1361, 1135, 1066, 730, 692 cm^{-1}.

(1S,2R)-N,N-dibenzyl-2-amino-1-(4-fluorophenyl)butan-1-ol ***((1S,2R)-4)***

To a solution of (*2R*)-N,N-dibenzyl-2-aminobutanal (**(*2R*)-3**) (10 g, 37.4 mmol) cooled to 0 °C, an 1 M solution of 4-fluorophenylmagnesium bromide in THF (41 mL, 41 mmol) was added dropwise. The solution was stirred for 2 h at 0 °C and poured into saturated NH_4Cl solution (100 mL). The mixture was extracted twice with diethyl ether (100 mL). The organic layers were collected, washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure (viscous yellow oil, 13.52 g). The diastereoisomeric mixture (87 : 13) was separated by column chromatography (petroleum $ether_{40\text{-}60}$/acetone 95 : 5). Light yellow viscous oil, 9.6 g (**(*1S,2R*)-4**, yield: 81%).

^{1}H NMR ($CDCl_3$) (base): δ = 0.99 (t, 3H, *J* = 7.4 Hz, CH_3), 1.20 and 1.42 (m and m, 1H and 1H, CH_3CH_2), 2.70 (dt, 1H, C*H*N), 3.57 and 3.71 (d and d, 2H and 2H, *J* = 13.8 Hz, $ArCH_2$), 4.94 (d, 1H, *J* = 3.9 Hz, ArCH), 6.92 (m, 2H, F-ArH3′H5′), 7.12 (m, 2H, F-ArH2′H6′), 7.17–7.31 (10H, Ar). IR (film) (base): 3220 (ν O-H), 2915, 1455, 1219 (ν C-F), 842 (ν ArF), 740, 695 cm^{-1}. α_{20}^D: (base): **(*1R,2S*)-4**: α_{20}^D = +36.3 (c = 0.6, MeOH), **(*1S,2R*)-4**: α_{20}^D = −37 (c = 1, MeOH).

(1S,2R)-N,N-dibenzyl-2-amino-1-azido-1-(4-fluorophenyl)-butane ***((1S,2R)-6)***

(*1S,2R*)-N,N-dibenzyl-2-amino-1-(4-fluorophenyl)butan-1-ol (**(*1S,2R*)-4**) (9.6 g, 26.4 mmol) and TEA (8.02 g, 79.2 mmol) were dissolved in diethyl ether (200 mL). This solution was cooled in an ice bath. Methanesulfonyl chloride (4.5 g, 39.6 mmol) was added dropwise. The mixture was stirred for 10 h at room temperature. Water (100 mL) and sodium azide (3.4 g, 52.8 mmol) were added. After 12 h, the organic layer was taken up and washed with brine (50 mL). After drying over $MgSO_4$ and filtration, the solvent was evaporated *in vacuo*. The mixture of regioisomers (**(*1S,2R*)-6** and **(*1R,2S*)-6**) (93 : 7) was separated by column chromatography (petroleum $ether_{40\text{-}60}$/acetone, 98 : 2). White solid, 6.25 g; mp: 84 °C. (yield: 61%).

^{1}H NMR ($CDCl_3$) (base): δ = 0.97 (t, 3H, *J* = 7.3 Hz, CH_3), 1.46 and 1.81 (m and m, 1H and 1H, CH_3CH_2), 2.73 (dt, 1H, C*H*NBn_2), 3.60 and 3.92 (d and d, 2H and 2H, *J* = 13.8 Hz, CH_2Ar), 4.77 (d, 1H, *J* = 5.5 Hz, ArCH), 6.94–7.05 (m, 2H, F-ArH3′H5′), 7.18–7.37 (m, 12H, Ar + 4F-Ar). ^{13}C NMR ($CDCl_3$) (base): δ = 13.2 (CH_3), 19.6 (CH_3CH_2), 54.8 ($ArCH_2$), 64.2 (CH_2CHN), 67.1 (ArCH), 116.0 (d, $J_{C\text{-}F}$ = 21 Hz, F-ArC3′C5′), 127.7 (ArC4′), 128.9 (ArC2′C6′), 129.5 (ArC3′C5′), 129.6 (d, $J_{C\text{-}F}$ = 8 Hz, F-ArC2′C6′), 139.8 (F-ArC1′), 140.2 (ArC1′), 162.8 (d, $J_{C\text{-}F}$ = 246 Hz, F-ArC4′). IR (film) (base): 2900, 2075 (ν N_3), 1591, 1496, 1444, 1220 (C-F), 823 (ν ArF), 737, 694 cm^{-1}. α_{20}^D (base); **(*1R,2S*)-6**: α_{20}^D = +17.4 (c = 0.2, MeOH), **(*1S,2R*)-6**: α_{20}^D = −17.9 (c = 0.4, MeOH).

(1S,2R)-1,2-diamino-1-(4-fluorophenyl)butane ***((1S,2R)-7)***

To a solution of (*1S,2R*)-N,N-dibenzyl-2-azido-1-(4-fluorophenyl)butane (**(*1S,2R*)-6**) (1.4 g, 3.6 mmol) in MeOH (75 mL) was added palladium on charcoal 10% (0.3 g). This suspension was stirred and refluxed for 30 min. Afterwards ammonium formate (0.45 g, 7.2 mmol) was added, and the mixture was stirred for an additional 10 h. An equal amount of ammonium formate was then added, and the reaction was carried on for 10 h. The reaction medium was filtered on celite, and the solvent evaporated under reduced pressure. The oily residue was dissolved in CH_2Cl_2 (100 mL). This solution was washed with a solution of sodium carbonate 20% (wt/vol) (50 mL) and brine (50 mL). It was further dried over $MgSO_4$, filtered and evaporated under reduced pressure to give 0.51 g of yellow oil. Upon addition of HCl in diethyl ether, a yellowish solid precipitated. It was filtered and recrystallized from iPrOH/MeOH/Et_2O (5:5:20). White solid, 0.66 g (dihydrochloride); mp: 290.1 °C with some decomposition. (Yield: 72%). ee (%) for the two enantiomers: 98.

^{1}H NMR ([D_6]-DMSO) (hydrochloride): δ = 1.01 (t, 3H, *J* = 7.3 Hz, CH_3), 1.60 and 1.73 (m and m, 1H and 1H, CH_3-CH_2), 3.66 (m, 1H, CH_2CHN), 4.73 (d, 1H, *J* = 4.5 Hz, ArCH), 7.35 (m, 2H, ArH3′H5′), 7.74 (m, 2H, ArH2′H6′), 8.65 and 9.14 (bs and bs, 3H and 3H, NH_3+). ^{13}C NMR ([D_6]-DMSO) (hydrochloride): δ = 9.4 (CH_3), 21.7 (CH_2), 53.8 (CH_2CHN), 54.4 (ArCH), 115.5 (d, $J_{C\text{-}F}$ = 22 Hz, ArC3′C5′), 129 (d, $J_{C\text{-}F}$ = 3Hz, ArC1′), 130.3 (d, $J_{C\text{-}F}$ = 9 Hz, ArC2'C6'), 162.2 (d, $J_{C\text{-}F}$ = 245 Hz, ArC4′). IR (KBr, 1%) (hydrochloride): 2905 (ν N-H), 2720 (ν C-H), 1603, 1230 (ν C-F), 1075, 852 (ν Ar-F) cm^{-1}. α_{20}^D (hydrochloride): **(*1R,2S*)-7**: α_{20}^D = +24.4 (c = 0.8, MeOH), **(*1S,2R*)-7**: α_{20}^D = −24.2 (c = 2, MeOH). MS (base): *m/z* (%) = 183 (41) [M+], 166 (30), 124 (21), 97 (6), 58 (100).

(2R)-N-(tert-butoxycarbonyl)-2-aminobutan-1-ol ***((2R)-8)***

A solution of (*2R*)-2-aminobutan-1-ol (**(*2R*)-1**) (5 g, 56.1 mmol) and TEA (6.24 g, 62 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C. A solution of di-*tert*-butyl dicarbonate (13.5 g, 62 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The reaction was carried on for 12 h at room temperature. The solvents and reagents were evaporated under reduced pressure (60 °C/66 Pa). Yellow oil: 10.6 g (yield: quantitative).

^{1}H NMR ($CDCl_3$): δ = 0.96 (t, 3H, *J* = 7.4 Hz, CH_3CH_2), 1.45 (s, 9H, $C(CH_3)_3$), 1.54 (m, 2H, CH_3CH_2), 3.56 (m, 2H superimposed, C*H*N and CH_2OH), 3.66 (m, 1H, CH_2OH), 4.67 (bs, 1H, O=CNH). ^{13}C NMR ($CDCl_3$): δ = 11.2 (CH_3CH_2), 25.2 (CH_3CH_2), 29.0 ($C(CH_3)_3$), 55.0 (*C*HN), 66.2 (COH), 80.2 ($C(CH_3)_3$), 157.3 (C=O).

(2R)-N-(tert-butoxycarbonyl)-2-aminobutanal ***((2R)-9)***

Oxalyl chloride (13.4 g, 106 mmol) in dry CH_2Cl_2 (200 mL) was placed into a three-necked flask under N_2 and cooled to −60 °C. This temperature was maintained during all the reaction. Anhydrous DMSO (15 g, 193 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise. After 2 min of stirring, a solution of (*2R*)-N-(*tert*-butoxycarbonyl)-2-aminobutan-1-ol (**(*2R*)-8**) (18.23 g, 96 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise during 5 min. After 5 min of stirring, TEA (48.8 g, 483 mmol) was added. The suspension was stirred at −30 °C for 5 min, then allowed to warm to room temperature. Water (200 mL) was added. After decantation, the organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The yellowish oil

(16.91 g, yield: 90% estimated by ^{1}H NMR) was not purified before analysis and directly used for the next step.

^{1}H NMR ($CDCl_3$): δ = 0.97 (t, 3H, *J* = 7.5 Hz, C*H*$_3$CH$_2$), 1.46 (s, 9H, C(CH$_3$)$_3$), 1.67 and 1.95 (m and m, 1H and 1H, CH$_3$CH$_2$), 4.20 (m, 1H, CHN), 5.12 (bs, 1H, O=CNH), 9.58 (s, 1H, O=CH). IR (film): 3320 (ν N-H), 2940 (ν C-H), 2705 (ν C-H), 1680 large (ν C=O aldehyde and carbamate), 1502, 1159 cm^{-1}.

*(2R)-[N-(tert-butoxycarbonyl)-2-aminobutylidene]benzylamine N-oxide (**(2R)-10**)*

To a solution of (*2R*)-N-(*tert*-butoxycarbonyl)-2-aminobutanal (**(*2R*)-9**) (5.92 g, 31.6 mmol) and benzylhydroxylamine (3.9 g, 31.7 mmol) in dry CH_2Cl_2 (150 mL) $MgSO_4$ was added (3.8 g, 31.7 mmol). The suspension was stirred for 15 h at room temperature. After filtration, the solvent was evaporated under reduced pressure, and the obtained yellow solid was purified by column chromatography (diethyl ether) to afford 6.14 g of yellow solid; mp: 129.2 °C (yield: 66%).

^{1}H NMR ($CDCl_3$): δ =0.91 (t, 3H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 1.41 (s, 9H, C(CH$_3$)$_3$), 1.78 (m, 2H, CH$_3$CH$_2$), 4.32 (m, 1H, C*H*NBOC), 4.87 (s, 2H, ArCH$_2$), 5.89 (bs, 1H, O=CN*H*), 6.82 (bs, 1H, N=CH), 7.39−7.42 (5H, Ar). ^{13}C NMR ($CDCl_3$): δ = 11.1 (*C*H$_3$CH$_2$), 24.6 (CH$_3$*C*H$_2$), 30.0 (C(*C*H$_3$)$_3$), 50.6 (CH$_2$*C*HN), 70.4 (ArCH$_2$), 80.2 (*C*(CH$_3$)$_3$), 129.7 (ArC2′C6′), 129.9 (ArC3′C4′C5′), 133.3 (ArC1′), 139.0 (C=N), 156.1 (C=O). IR (KBr, 1%): 3323 (ν N-H), 2922 (ν C-H), 1677 (ν C=O, C=N), 1518, 1250, 1163, 700 cm^{-1}.

*(1R,2R)-N^1-benzyl-N^2-(tert-butoxycarbonyl)-2-amino-1-(4-fluorophenyl)-1-hydroxyaminobutane (**(1R,2R)-11**)*

A solution of (*2R*)-[N-(*tert*-butoxycarbonyl)-2-aminobutylidene]benzylamine N-oxide (**(*2R*)-10**) (6.14 g, 21 mmol) in anhydrous THF (100 mL) was cooled to −40 °C. A 2 M solution of 4-fluorophenylmagnesium bromide in diethyl ether (31.5 mL, 63 mmol) was added dropwise at −40 °C. The reaction medium was stirred at this temperature for 4 h. Then, it was let to warm to room temperature and poured into a saturated solution of NH_4Cl (200 mL). After three extractions with diethyl ether (100 mL), the organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The brown solid obtained (8.49 g: mixture of diastereoisomers **(*1R,2R*)-11** and **(*1S,2R*)-11**: 90:10) from which **(*1R,2R*)-11** was separated by column chromatography (petroleum ether$_{(40\text{-}60)}$/acetone, 95:5). Yellow solid, 4.5 g; mp: 127.5 °C (yield: 68%).

^{1}H NMR ($CDCl_3$): δ = 0.86 (t, 3H, *J* = 7.6 Hz, C*H*$_3$CH$_2$), 1.35 (m, 2H, CH$_3$CH$_2$), 1.53 (s, 9H, C(CH$_3$)$_3$), 3.24 (d, 1H, *J* = 10.2 Hz, ArCH), 3.55 and 3.60 (d and d, 1H and 1H, *J* = 13.9 Hz, ArCH$_2$), 4.06 (m, 1H, CH$_2$C*H*N), 4.47 (d, 1H, *J* = 9.7, O=CNH), 6.82 (bs, 1H, NOH), 7.06 (m, 2H, F-ArH3′H5′), 7.20−7.35 (7H, Ar). ^{13}C NMR ($CDCl_3$): δ = 11.0 (*C*H$_3$CH$_2$), 25.4 (CH$_3$*C*H$_2$), 29.2 (C(*C*H$_3$)$_3$), 54.3 (CH$_2$*C*HN), 61.0 (ArCH$_2$), 74.2 (ArCH), 80.9 (*C*(CH$_3$)$_3$), 115.7 (d, J$_{C\text{-}F}$ = 21 Hz, F-ArC3′C5′), 127.5 (ArC4′), 128.8 (ArC2′C6′), 129.1 (ArC3′C5′), 131.0 (d, *J* = 3Hz, F-ArC1′), 132.2 (ArC1′), 132.3 (d, $J_{C\text{-}F}$ = 8 Hz, F-ArC2′C6′), 159.1 (C=O), 163.2 (d, $J_{C\text{-}F}$ = 246 Hz, F-ArC4′). IR (KBr, 1%): 3350 (ν N-H O-H), 2960 (ν C-H), 1677 (ν C=O), 1538, 1219 (ν C-F), 1155, 728 cm^{-1}. α^D_{20}; **(*1R,2R*)-11**: α^D_{20} = +2.3 (c = 0.9, MeOH), **(*1S,2S*)-11**: α^D_{20} = −2.1 (c = 0.5, MeOH).

*(1R,2R)-N^2-(tert-butoxycarbonyl)-1,2-diamino-1-(4-fluorophenyl)butane (**(1R,2R)-12**)*

(*1R,2R*)-N^1-benzyl-N^2-(*tert*-butoxycarbonyl)-2-amino-1-(4-fluorophenyl)-1-hydroxyaminobutane **(*1R,2R*)-11** (8.26 g, 21.3 mmol) was dissolved in MeOH (250 mL), and palladium on charcoal 10% (0.8 g) was added. The suspension was refluxed for 30 min. Ammonium formate (2.68 g, 42.5 mmol) was added. The suspension was refluxed for 12 h. An equal amount of ammonium formate was then added, and the reaction was carried on for 12 h. The cooled reaction mixture was filtered on celite, and the solvent evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (100 mL). This solution was washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The oily residue (6 g) was directly used for the next step.

*(1R,2R)-1,2-diamino-1-(4-fluorophenyl)butane (**(1R,2R)-13**)*

(*1R,2R*)-12 was dissolved in a solution of HCl in anhydrous MeOH (10%, wt/vol) (50 mL). This solution was stirred at room temperature for 8 h. Then, the solvent was evaporated under reduced pressure. The yellow solid obtained was treated with water (50 mL), NaOH 40% (wt/vol) (10 mL) and extracted two times with CH_2Cl_2 (100 mL). The organic solution was washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The liquid obtained was dissolved in MeOH (20 mL) and a solution of D-(−)-(*2S,3S*)-tartaric acid (1.54 g, 10.3 mmol) in MeOH (20 mL) was added. This mixture was heated to reflux for 10 min and then let to cool to room temperature. The white crystals (1.41 g) were collected by filtration, washed two times with MeOH and dried at 60 °C under 13.3 kPa. White crystals (yield: 20%); mp: 281.7 °C with some decomposition. A small fraction of these salts were transformed into base and hydrochloride for analysis. ee (%) for the two enantiomers: 98.

^{1}H NMR ([D$_6$]-DMSO) (hydrochloride): δ = 1.01 (t, 3H, *J* = 5.5 Hz, CH$_3$), 1.62 and 1.73 (m and m, 1H and 1H, CH$_2$), 3.67 (m, 1H, CH$_2$C*H*N), 4.76 (d, 1H, *J* = 4.1 Hz, ArCH), 7.34 (m, 2H, ArH3'H5'), 7.76 (m, 2H, ArH2H6'), 8.59 and 9.32 (bs and bs, 3H and 3H, NH$_3$+). ^{13}C NMR ([D$_6$]-DMSO) (hydrochloride): δ = 9.4 (CH$_3$), 21.7 (CH$_2$), 53.8 (CH$_2$*C*HN), 54.4 (ArCH), 115.5 (d, $J_{C\text{-}F}$ = 22 Hz, ArC3′C5′), 129.0 (d, $J_{C\text{-}F}$ = 3 Hz, ArC1′), 130.3 (d, $J_{C\text{-}F}$ = 9 Hz, ArC2′C6′), 162.2 (d, $J_{C\text{-}F}$ = 246 Hz, ArC4′). IR (KBr, 1%) (hydrochloride): 2905 (ν N-H), 2720 (ν C-H), 1603, 1230 (ν C-F), 1075, 852 (ν Ar-F) cm^{-1}. α^D_{20} (hydrochloride), **(*1R,2R*)-13**: α^D_{20} = +7.5 (c = 0.4, MeOH), **(*1S,2S*)-13**: α^D_{20} = −7.7 (c = 0.2, MeOH). MS (base): *m/z* (%) = 183 (41) [M+], 166 (30), 124 (21), 97 (6), 58 (100).

[1,2-Diamino-1-(4-fluorphenyl)butane]diiodoplatinum(II)

To an aqueous solution (5 mL) of the diamine (0.25 mmol), K_2PtI_4 (0.25 mmol) dissolved in 5 mL water was added after the pH was adjusted to 6.5−7.5 with 0.1 N NaOH. The reaction mixture was stirred in the dark for 24 h. Subsequently, it was acidified with 0.1 N HCl, and the yellow precipitate was sucked off and dried over P_2O_5 *in vacuo*.

(*RR*)-4F-Ph/Et-PtI$_2$/(*SS*)-4F-Ph/Et-PtI$_2$

^{1}H NMR ([D7]-DMF): δ = 0.85 (t, 3H, CH$_3$), 1.30−1.51 (m, 2H, CH$_2$), 3.15 (1H, CH-alkyl), 3.80 (m, 1H, Ar-H), 5.05 (br, 1H, NH), 5.38 (br, 1H, NH), 5.72 (br, 1H, NH), 6.00 (br, 1H, NH), 7.21−7.32 (m, 2H, H3'H5'), 7.67−7.79 (m, 2H, H2'H6'). Brownish powder. **(*RR*)-4F-Ph/Et-PtI$_2$**; yield: 29%. **(*SS*)-4F-Ph/Et-PtI$_2$**; yield: 29%. $C_{10}H_{15}N_2FPtI_2$ (633.0): calc: C 18.95, H 2.37, N 4.43; found: C 18.47, H 2.19, N 4.16 (**(*RR*)-4F-Ph/**

Et-PtI$_2$); found: C 18.55, H 2.36, N 4.16 (**(*SS*)-4F-Ph/Et-PtI$_2$**).

(*RS*)-4F-Ph/Et-PtI$_2$/(*SR*)-4F-Ph/Et-PtI$_2$
^{1}H NMR ([D7]-DMF): δ = 0.95 (t, 3H, CH_3), 1.52 (m, 2H, CH_2), 3.19 (1H, CH-alkyl), 4.13 (m, 1H, Ar-H), 4.80 (br, 1H, NH), 5.50 (br, 2H, NH), 6.00 (br, 1H, NH), 7.20−7.29 (m, 2H, H3′H5′), 8.12−8.24 (m, 2H, H2'H6'). Brownish powder. **(*RS*)-4F-Ph/Et-PtI$_2$**; yield: 29%. **(*SR*)-4F-Ph/Et-PtI$_2$**; yield: 30%. $C_{10}H_{15}N_2FPtI_2$ (633.0): calc: C 18.95, H 2.37, N 4.43; found: C 18.55, H 2.35, N 4.20 (**(*RS*)-4F-Ph/Et-PtI$_2$**); found: C 18.57, H 2.21, N 4.78 (**(*SR*)-4F-Ph/Et-PtI$_2$**).

Aqua[1,2-diamino-1-(4-fluorphenyl)butane]sulfatoplatinum(II)

The corresponding sulfatoplatinum(II) complexes were obtained by addition of Ag_2SO_4 (0.195 mmol) to the aqueous suspensions (30 mL) of the diiodoplatinum(II) complexes (0.2 mmol). After stirring for 3 days, the precipitated AgI was separated by filtration and the resulting clear solution was lyophilized.

(*RR*)-4F-Ph/Et-PtSO$_4$/(*SS*)-4F-Ph/Et-PtSO$_4$
^{1}H NMR ([D$_6$]-DMSO): δ = 0.68 (t, 3H, CH_3), 1.20−1.35 (m, 2H, CH_2), 3.20 (1H, CH-alkyl), 3.77 (m, 1H, Ar-H), 5.82 (br, 1H, NH), 6.17 (br, 1H, NH), 6.30 (br, 1H, NH), 6.42 (br, 1H, NH), 7.21−7.30 (m, 2H, H3′H5′), 7.45−7.58 (m, 2H, H2′H6′). Colorless powder. **(*RR*)-4F-Ph/Et-PtSO$_4$**; yield: 20%. **(*SS*)-4F-Ph/Et-PtSO$_4$**; yield: 21%. $C_{10}H_{15}N_2FPtSO_5 \times {}^1/_2$ H_2O (500.3): calc: C 23.98, H 3.20, N 5.60, found: C 24.22, H 3.40, N 5.40 (**(*RR*)-4F-Ph/Et-PtSO$_4$**); found: C 24.06, H 3.50, N 5.64 (**(*SS*)-4F-Ph/Et-PtSO$_4$**).

(*RS*)-4F-Ph/Et-PtSO$_4$/(*SR*)-4F-Ph/Et-PtSO$_4$
^{1}H NMR ([D$_6$]-DMSO): δ = 0.85 (t, 3H, CH_3), 1.23 (m, 2H, CH_2), 3.16 (1H, CH-alkyl), 4.20 (m, 1H, Ar-H), 6.05 (br, 1H, NH), 6.26 (br, 1H, NH), 6.52 (br, 2H, NH), 7.21−7.32 (m, 2H, H3'H5'), 7.51−7.60 (m, 2H, H2'H6'). Colorless powder. **(*RS*)-4F-Ph/Et-PtSO$_4$**; yield: 29%. **(*SR*)-4F-Ph/Et-PtSO$_4$**; yield: 25%. $C_{10}H_{15}N_2FPtSO_5$ (491.3): calc: C 24.42, H 3.05, N 5.69; found: C 23.71, H 3.75, N 5.53 (**(*RS*)-4F-Ph/Et-PtSO$_4$** $\times$ 1 H_2O); found: C 24.28, H 3.24, N 5.56 (**(*SR*)-4F-Ph/Et-PtSO$_4$** $\times$ $^1/_2$ H_2O).

[1,2-Diamino-1-(4-fluorphenyl)butane]dichloroplatinum(II)

The respective sulfatoplatinum(II) complex (0.2 mmol) was converted into the dichloroplatinum(II) complex by treatment with 2 N HCl in aqueous solution. The yellow precipitate was collected and dried over P_2O_5 *in vacuo*.

(*RR*)-4F-Ph/Et-PtCl$_2$/(*SS*)-4F-Ph/Et-PtCl$_2$
^{1}H NMR ([D7]-DMF): δ = 0.85 (t, 3H, CH_3), 1.30 (m, 2H, CH_2), 3.30 (1H, CH-alkyl), 4.15 (m, 1H, Ar-H), 5.21 (br, 1H, NH), 5.50 (br, 1H, NH), 5.89 (br, 1H, NH), 6.08 (br, 1H, NH), 7.21−7.30 (m, 2H, H3′H5′), 7.70−7.80 (m, 2H, H2′H6′). Yellow powder. **(*RR*)-4F-Ph/Et-PtCl$_2$**; yield: 38%. **(*SS*)-4F-Ph/Et-PtCl$_2$**; yield: 31%. $C_{10}H_{15}FCl_2N_2Pt$ (450.1): calc: C 26.66, H 3.33, N 6.22; found: C 26.64, H 3.36, N 6.42 (**(*RR*)-4F-Ph/Et-PtCl$_2$**); found: C 26.69, H 3.32, N 6.33 (**(*SS*)-4F-Ph/Et-PtCl$_2$**).

(*RS*)-4F-Ph/Et-PtCl$_2$/(*SR*)-4F-Ph/Et-PtCl$_2$
^{1}H NMR ([D7]-DMF): δ = 0.95 (t, 3H, CH_3), 1.48 (m, 2H, CH_2), 3.50 (1H, CH-alkyl), 4.20 (m, 1H, Ar-H), 4.89 (br, 1H, NH), 5.72 (br, 2H, NH), 6.15 (br, 1H, NH), 7.21−7.33 (m, 2H, H3′H5′), 8.20−8.32 (m, 2H, H2'H6'). Yellow powder. **(*RS*)-4F-Ph/Et-PtCl$_2$**; yield: 36%. **(*SR*)-4F-Ph/Et-PtCl$_2$**; yield: 38%. $C_{10}H_{15}FCl_2N_2Pt$ (450.1): calc: C 26.66, H 3.33, N 6.22; found: C 26.76, H 3.29, N 6.43 (**(*RS*)-4F-Ph/Et-PtCl$_2$**); found: C 26.74, H 3.37, N 6.11 (**(*SR*)-4F-Ph/Et-PtCl$_2$**).

Biological methods

Cell culture

The human MCF-7 and MDA-MB 231 breast cancer cell lines as well as the LwCaP/FGC cell line were obtained from the American Type Culture Collection (ATCC, USA). Cell line banking and quality control were performed according to the seed stock concept reviewed by Hay [42]. The MCF-7 cells were maintained in L-glutamine containing Eagle's MEM (Sigma, Germany) supplemented with $NaHCO_3$ (2.2 g/L), sodium pyruvate (110 mg/L), gentamycin (50 mg/L) and 10% fetal calf serum (FCS; Gibco, Germany), using 75-cm^2 culture flasks in a humidified atmosphere (95% air/5% CO_2) at 37°C. The MDA-MB 231 cells (McCoy's 5A medium supplemented with $NaHCO_3$ (2.2 g/L), sodium pyruvate (110 mg/L), gentamycin (50 mg/L), 5% FCS) and the LwCaP/FGC cells (L-glutamine-containing RPMI 1640 supplemented with $NaHCO_3$ (2.0 g/L), gentamycin (50 mg/L), 7.5% FCS) were maintained under the same conditions. The cell lines were weekly passaged after treatment with 0.05% trypsin/0.02% ethylenediaminetetraacetic acid (EDTA; Boehringer, Germany). Mycoplasma contamination was regularly monitored, and only mycoplasma-free cultures were used.

In vitro chemosensitivity assays

The *in vitro* testing of the platinum complexes for antitumor activity was carried out on exponentially dividing human cancer cells, according to a previously published microtiter assay [29, 43]. Briefly, in 96-well microtiter plates, 100 μL of a cell suspension at 7700 cells/mL culture medium (MCF-7) or 3200 cells/mL (MDA-MB 231) or 2700 cells/mL (LwCaP/FGC) was plated into each well and incubated at 37°C for 3 days (MCF-7, MDA-MB 231) or 5 days (LwCaP/FGC) in a humidified atmosphere (5% CO_2). By addition of an adequate volume of a stock solution of the respective compound (solvent: DMF) to the medium, the aimed test concentration was obtained. For each test concentration and for the control, which contained the corresponding amount of DMF, 16 wells were used. After the proper incubation time, the medium was removed, the cells were fixed with a glutardialdehyde solution and stored under phosphate buffered saline (PBS) at 4°C. Cell biomass was determined by a crystal violet staining technique, as described earlier [29, 43]. The efficiency of the complexes is expressed as corrected% T/C_{corr} values according to the following equations:
Cytostatic effect: T/C_{corr} [%] = $[(T-C_o)/(C-C_o)] \times 100$
where T (test) and C (control) were the optical densities at 590 nm of the crystal violet extract of the cells in the wells (i.e. the chromatin-bound crystal violet extracted with ethanol 70%), and C_o was the density of the cell extract immediately before treatment.
Cytocidal effect: τ [%] = $[(T-C_o)/C_o] \times 100$.
A microplate reader at 590 nm (Flashscan AnalytikJena AG) was used for the automatic estimation of the optical density of the crystal violet extract in the wells.

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