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Tumor-inhibiting [1,2-bis(fluorophenyl)ethylenediamine]platinum(II) complexes

V. Synthesis and evaluation of enantiomeric [1,2-bis-(4-fluorophenyl)ethylenediamine]dichloroplatinum(II) complexes *

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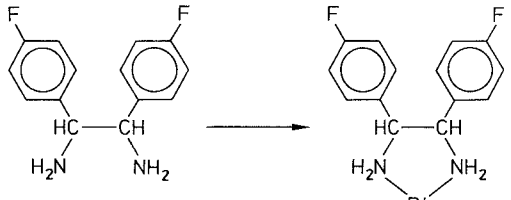
Summary. The enantiomeric [1,2-bis(4-fluorophenyl)ethylenediamine]dichloroplatinum(II) complexes were synthesized and tested on the hormone-sensitive human MCF7 breast cancer cell line and on the P388 leukemia of the mouse. They showed a strong and comparable activity on both tumor models.

Key words: (*R,R*)- and (*S,S*)-[1,2-bis(4-fluorophenyl)ethylenediamine]dichloroplatinum(II) – Synthesis – MCF7 breast cancer cell line – P388 murine leukemia

Introduction

R,S- and *R,R/S,S*-configurated diaqua[1,2-bis(4-fluorophenyl)ethylenediamine]platinum(II) sulfates and nitrates (**1–4**) display a strong growth inhibition of the hormone-dependent MXT-M3.2 mammary carcinoma of the mouse (Reile et al. 1990 b). Their effect is independent of the ligand configuration, *R,S* (meso) or *R,R/S,S* (racemate), and identical with that of cisplatin. In contrast to cisplatin, however, the diaqua [1,2-bis(4-fluorophenyl)-ethylenediamine]platinum(II) sulfates and nitrates cause a strong decrease in uterine weight of the adult but not of the juvenile mouse. This phenomenon is thought to be a consequence of an interference in the steroid biosynthesis. Therefore we assume that [1,2-bis(4-fluorophenyl)ethylenediamine]platinum(II) complexes exert their mammary-tumor-inhibiting properties by a decrease of the estrogen and progesterone level as well as by an interference with DNA replication in analogy to the mode of action of cisplatin. In fact, compound **2**, with *R,R/S,S* configuration, inhibits the [^{3}H]thymidine incorporation into hormone-independent human MDA-MB231 breast cancer cells to the same extent as cisplatin (Reile et al. 1990 b). Compound **1**, with *R,S*-configuration, is somewhat less active in this experiment. The same results were seen with the analogous dichloroplatinum(II) complexes (Reile et al. 1990 b). Platinum complexes that do not only act on the hormone-dependent but also on the hormone-independent mammary carcinoma (i.e. estrogen-receptor-positive and -negative, respectively) are of great therapeutic interest, since they delay or perhaps prevent the development of resistance, which originates from estrogen-receptor-negative mammary carcinoma clones.

The aim of this work was to show whether the effect of one enantiomer of [1,2-bis(4-fluorophenyl)ethylenediamine]dichloroplatinum(II) is superior to that of its racemic mixture (compound **8**). In the following we will describe the resolution of compound **8** into its enantiomers **9** and **10**, the determination of the absolute configuration by circular dichroism (CD) spectroscopy and the testing on the hormone-sensitive human MCF7 breast cancer cell line and on the P388 leukemia of the mouse.



Compound	Configuration
8a, 8	*R,R/S,S*
9a, 9	*R,R*
10a, 10	*S,S*

* Dedicated to Professor Dr. D. Schmähl on the occasion of his 65th birthday

Abbreviations. *R,R/S,S*, racemate; *R,S*, meso

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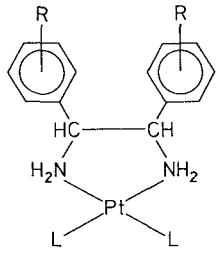
Table 1. ^{1}H–NMR data of enantiomeric [1,2-bis(4-fluorophenyl)ethylenediamine]dichloroplatinum(II) complexes and of their ligands

	Compound	Configuration	R	Leaving group (*L*)	Counter ion
	**1**	*R,S*	4-F	OH_2	SO_4
	2	*R,R/S,S*	4-F	OH_2	SO_4
	3	*R,S*	4-F	OH_2	$(NO_3)_2$
	4	*R,R/S,S*	4-F	OH_2	$(NO_3)_2$
	5	*R,R/S,S*	3-OH	Cl	–
	6	*R,R/S,S*	4-OH	Cl	–
	7	*R,S*	4-F	Cl	–
	8	*R,R/S,S*	4-F	Cl	–
	9	*R,R*	4-F	Cl	–
	10	*S,S*	4-F	Cl	–

Compound	δ (ppm) (tetramethylsilane, internal)		
	Aromatic H	CH (benzylic)	NH
9a[a]	6.90–6.99 (m, 4 H) 7.13–7.20 (m, 4 H)	4.01 (s, 2 H)	1.6 (s, br, 4 H)
10a[a]	6.89–6.99 (m, 4 H) 7.13–7.19 (m, 4 H)	4,01 (s, 2 H)	1.6 (s, br, 4 H)
9a · 2HCL[b]	7.01–7.61 (m, 8 H)	5.2 (s, 2 H)	
10a · 2HCl[b]	6.98–7.56 (m, 8 H)	5.2 (s, 2 H)	
9[c]	7.03–7.10 (m, 4 H) 7.75–7.80 (m, 4 H)	5.2 (m, br, 2 H)	6.0 (m, br, 2 H) 6.49–6.52 (m, 2 H)
10[c]	7.03–7.10 (m, 4 H) 7.75–7.81 (m, 4 H)	5.2 (m, br, 2 H)	5.97–6.03 (m, 2 H) 5.49–6.53 (m, 2 H)

[a] $CDCl_3$, 250 MHz
[b] CD_3OD, 60 MHz
[c] d_7-dimethylformamide, 250 MHz

Materials and methods

Chemistry

The synthesis of (±)-1,2-bis(4-fluorophenyl)ethylenediamine (**8a**) has been described in one of our previous publications (Müller et al. 1989). Since it turned out that neither ethylenediamine ligands nor dichloroplatinum(II) complexes were appreciably resolved by HPLC on triacetylcellulose, compound **8a** was resolved in MeOH by fractional crystallization of its diastereomeric salts with optically active tartaric acid (method A). This procedure leads to complete enantiomeric purity of the diamines [(+)**9a** and (−)**10a**]. For analytical characterization, the oily bases were transformed into their solid dihydrochlorides (+)**9a**·2HCl and (−)**10a**·2HCl (method B). The enantiomeric [1,2-bis(4-fluorophenyl)ethylenediamine] platinum(II) complexes [(+)**9** and (−)**10**] were synthesized by reacting K_2PtCl_4 with (+)**9a**·2HCl and (−)**10a**·2HCl, respectively, in aqueous solution (method C). ^{1}H-NMR data and elemental analyses of these substances are listed in Tables 1 and 2.

The absolute configuration of the enantiomeric [1,2-bis(4-fluorophenyl)ethylenediamine]dichloroplatinum(II) complexes (**9** and **10**) was determined by comparison of their CD spectra with those of (+)(*R,R*)- and (−)(*S,S*)-dichloro[1,2-diphenylethylenediamine]platinum(II), the structural assignment of which derives from the known absolute configuration of (+)-1,2-diphenylethylenediamine (*R,R*) (Meric and Vigneron 1974). In analogy to the 3- and 4-hydroxy-substituted (±)-dichloro[1,2-diphenylethylenediamine] platinum(II) complexes **5** (Jennerwein et al. 1989a) and **6** (Wappes et al. 1984), the dextrorotatory enantiomer of the (±)-[1,2-bis(4-fluorophenyl)ethylenediamine]dichloroplatinum(II) (**8**) has the *R,R*

Table 2. Enantiomeric [1,2-bis(4-fluorophenyl)ethylenediamine] dichloroplatinum(II) complexes, *9* and *10* and their ligands *9a* · 2HCl and *10a* · 2HCl: elemental analyses

Compound	C (%)		H (%)		N (%)	
	Calcd.	Found	Calcd.	Found	Calcd.	Found
9a·2HCl	52,4	52.4	5.02	4.91	8.7	8.5
10a·2HCl		52.4		4.87		8.5
9	32.7	33.2	2.75	2.83	5.5	5.3
10		33.0		2.90		5.2

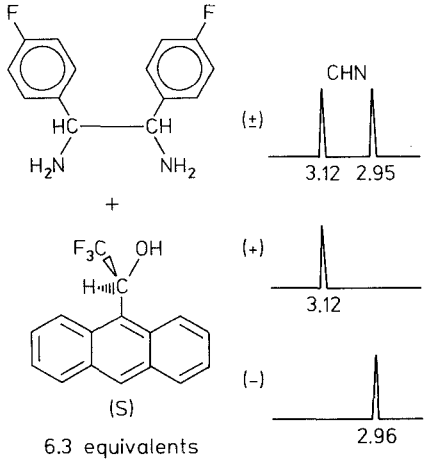


Fig. 1. ^{1}H-NMR benzyl signals of ligands in $CDCl_3$ at 250 MHz in the presence of 6.3 equivalents of an optically active auxiliary and of a small amount of D_2O. *Top:* (±)**8a** shows singlets for both enantiomers. *Center:* (+)**9a** shows one singlet only, i.e. an enantiomeric purity of approx. 100%. *Bottom:* (−)**10a** shows another singlet, exclusively (i.e. purity approx. 100%).

(compound **9**) and the levorotatory enantiomer *S,S* configuration (compound **10**).

*(±)-1,2-Bis(4-fluorophenyl)ethylenediamine [**8a**].* The synthesis of **8a** has been reported by Müller et al. (1989).

*(+)- and (−)-1,2-Bis(4-fluorophenyl)ethylenediamine [(+)**9a** and (−)**10a**], method A.* Compound **8a** (7.49 g, 30.17 mmol), dissolved in 35 ml MeOH, was added to the solution of L(+)-tartaric acid (13.58 g, 90.51 mmol) in 85 ml MeOH and boiled for 10 min. The solution was allowed to cool slowly. The tartrate of (−)**10a** crystallized at room temperature and was recrystallized from MeOH several times. The free base was obtained by treatment with 5% NaOH, extraction with CH_2Cl_2, washing with H_2O and drying over $MgSO_4$. The product was a colorless oil, yield 28%, $[\alpha]_{546}^{21} = -110$, $c = 1.0$, MeOH, enantiomeric purity approximately 100%. From the mother liquors of the precipitates the diamine, which contains an excess of (+)**9a**, was isolated as free base and purified in the same manner by crystallization of the D(−)-tartrate. The diamine was a colorless oil, yield 34%, $[\alpha]_{546}^{21} = +109$, $c = 1.0$, MeOH, enantiomeric purity: approximately 100%. The enantiomeric purity was determined by ^{1}H-NMR spectroscopy (250 MHz) by means of the formation of diastereomeric complexes with (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol. The molar ratio of this alcohol to compound (+)**9a** and compound (−)**10a**, respectively, was 6.3 [10.24 mg (+)**9a** or (−)**10a**, 71.87 mg (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol and two drops D_2O in 0.5 ml $CDCl_3$]. The enantiomeric purity was established by the integral ratio of the two singlets for the benzylic protons. The absorption band of compound (−)**10a** is shifted to higher field ($\delta = 2.96$ ppm) than that of (+)**9a** ($\delta = 3.12$ ppm) (Fig. 1).

*(+)-1,2-Bis(4-fluorophenyl)ethylenediaminedihydrochloride [(+)**9a**·2HCl], method B.* To compound (+)**9a**, dissolved in a small amount of MeOH, ethereal HCl was added dropwise under ice cooling. After addition of Et_2O to tarnish, the mixture was allowed to stand in the refrigerator. The precipitate was sucked off. Colorless crystals, m.p. 241.0–241.5° C (decomp.), yield 50%, $[\alpha]_{546}^{21} = +49$, $c = 1.0$, MeOH.

*(−)-1,2-Bis(4-fluorophenyl)ethylenediaminedihydrochloride [(−)**10a**·2HCl].* This was obtained as colorless crystals, m.p. 240.5–241.5° C (decomp.), yield 78%, $[\alpha]_{546}^{21} = -46$, $c = 1.0$, MeOH.

*[(±)-1,2-Bis(4-fluorophenyl)ethylenediamine] dichloroplatinum(II) (**8**), method C.* Synthesis has been described by Müller et al. (1989).

*[(+)-1,2-Bis(4-fluorophenyl)ethylenediamine] dichloroplatinum(II) ((+)**9**). Compound (+)**9*** was obtained as a yellow powder, yield 86%, $[\alpha]_{546}^{22} = +148$, $c = 0.5$, dimethylformamide.

*[(−)-1,2-Bis(4-fluorophenyl)ethylenediamine] dichloroplatinum(II) ((−)**10**).* Compound ((−)**10**) was a yellow powder, yield 88%, $[\alpha]_{546}^{22} = -144$, $c = 0.5$, dimethylformamide.

CD spectra

The spectra were obtained with a JASCO J-40 A spectropolarimeter (time constant 4 s; scan speed 50 nm/min) and recored in Me_2SO at room temperature in 0.2 cm quartz cells. The concentrations were 0.7 m*M* for (+)**9**, and 0.8 m*M* for (−)**10**, 2 m*M* for (*S,S*)-dichloro-[1,2-diphenylethylenediamine]platinum(II) and 4 m*M* for (*R,R*)-dichloro[1,2-diphenylethylenediamine]platinum(II).

General procedures

Melting points (uncorrected) were recorded in a Büchi 510 melting-point apparatus, ^{1}H-NMR spectra with a Varian EM 360 L (60 MHz) spectrometer and ^{1}H-NMR spectra of the platinum complexes with a Bruker PFT-NMR spectrometer WM 250 at 250 MHz. Elemental analyses were carried out by the Microlaboratory of the University of Regensburg. The polarimeter was a Perkin-Elmer 241 MC (Perkin-Elmer, Überlingen, FRG).

Biological methods

Hormone-sensitive human MCF7 breast cancer cell line. The MCF7 cell line was obtained from the pleural effusion of a patient with disseminated mammary carcinoma (Soule et al. 1973) and was obtained from the American Type Culture Collection, Rockville, USA. Cell line banking and quality control were performed according to the "seed stock concept" reviewed by Hay (1988). The cells were maintained in Eagle's minimum essential medium (Sigma) containing $NaHCO_3$ (2 g/l), gentamicin (50 mg/l), 10% fetal calf serum (Gibco) in 75-cm^2 flasks at 37° C in a H_2O-saturated atmosphere of 95% air and 5% CO_2. The cells were serially passaged weekly following trypsinization using trypsin/EDTA (Boehringer). For chemosensitivity testing the cells (in passage 155) were plated in 96-well microplates (100 µl/well) at a density of about 19 cells/microscopic field (Leitz Diavert, 320 ×) and were allowed to attach. After 73.5 h, the medium was removed by suction and replaced with fresh medium (200 µl/well) containing the drug (drugs were added as a 1000-fold stock solution in dimethylformamide or pure solvent. On every plate the rows 5 and 6 ($n = 16$) acted as controls, whereas two vertical rows ($n = 16$) per drug concentration and time point were used. After varying times of incubation the cells were fixed with glutaraldehyde and stored under phosphate-buffered saline at 4° C. All plates were stained with crystal violet simultaneously. The processing procedure and data analysis were performed as described by Reile et al. (1990a). Drug effects were calculated as corrected T/C values according to: $T/C_{corr.} = (T - C_0)/(C - C_0) \cdot 100[\%]$, where T is the absorbance of treated cells, C that of the controls and C_0 the absorbance at the time ($t = 0$) when drug was added. The calculated experimental errors for $T/C_{corr.}$ (according to the Gaussian formula) amount to about 10% after prolonged incubation.

P388 Leukemia. The P388 leukemia (Dawe and Potter 1957; Geran et al. 1972) was maintained by routine passage in female DBA/2 mice (Charles River Wiga, Sulzfeld, FRG). For determination of antitumor activity, female CDF_1 mice (18–22 g, Zentralinstitut für Versuchstiere Hannover, FRG), were inoculated i.p. with 10^6 leukemia cells in 0.1 ml phosphate-buffered saline (day 0). The animals were randomly assigned to groups of six (ten animals to the solvent control) and the complexes were administered i.p. on days 1–9 as a solution or suspension in polyethyleneglycol-400/1.8% NaCl in H_2O (1 : 1). The antitumor activity was evaluated as median survival time (days) compared to the untreated control.

Results and discussion

The strong effect of the diastereomeric [1,2-bis(4-fluorophenyl)ethylenediamine]platinum(II) complexes found on the hormone-dependent MXT mammary carcinoma of the mouse, was reevaluated in the experiment on the hormone-sensitive human MCF7 breast cancer cell line by means of the dichloroplatinum(II) derivatives **7**–**10** (Fig. 2).

In this test we studied the growth kinetics in the presence of increasing drug concentrations (0.5 µ*M*, 1 µ*M*, and 5 µ*M*) by staining with crystal violet. A microcomputer technique, which allows a large number of spectrophotometric measurements necessary for the construction of the growth curves, was used. In order to provide a maximum of information, the data are presented as cor-

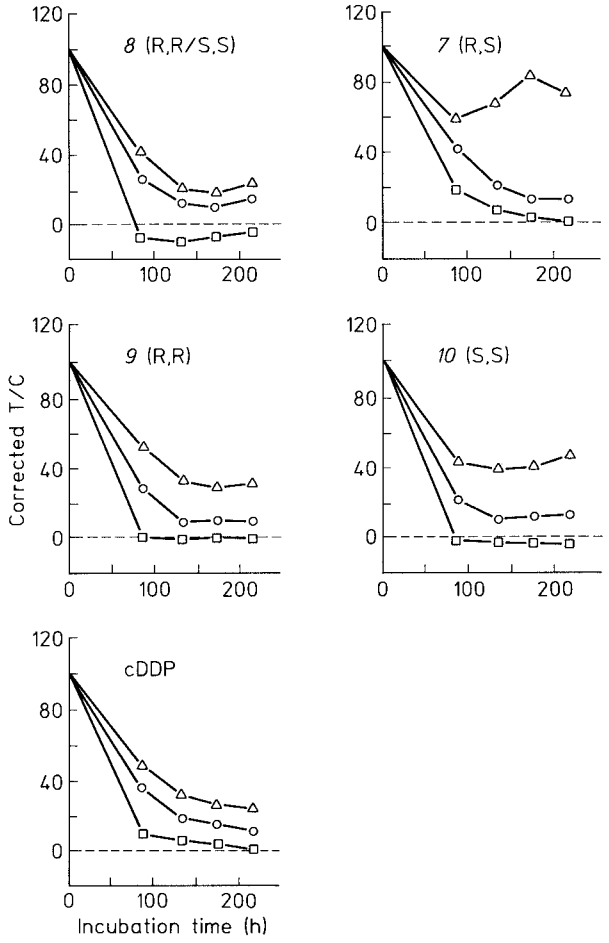


Fig. 2. Effect of compounds **7**–**10** and of cisplatin on MCF7 breast cancer cell line; plot of corrected T/C values versus time of drug exposure. △, 0.5 μ*M*; ○, 1 μ*M*; □, 5 μ*M*

rected T/C values versus time of drug exposure. A gradual decrease of $T/C_{corr.}$ values with time indicates an inhibition of cell growth (i.e. a slowing down or a cessation of cell proliferation = cytostatic drug action). An increase of $T/C_{corr.}$ values with time of drug exposure represents primary drug resistance or recovery of the cells from drug-induced damage, which may result in full reproductive integrity of the cells (see also Müller et al. 1990). $T/C_{corr.}$ values < 0 indicate cytocidal drug action.

On the MCF7 breast cancer cell line, the *R,S*-configurated complex (**7**) shows a similar effect to cisplatin in a concentration of 1 μ*M* and 5 μ*M*. At the lowest concentration (0.5 μ*M*) the cells are weakly inhibited initially but recover after about 150 h of drug exposure. This behavior can be explained by a development of resistance of the cell line against low concentrations of **7**. In the case of the more active complex **8**, with the *R,R/S,S* configuration, a clearcut dose-dependent inhibition is observed, producing a cytocidal effect in the highest concentration (5 μ*M*). Surprisingly, neither of the enantiomers (**9** and **10**) was more active than the racemate (**8**).

On the P388 leukemia of the mouse the enantiomeric [1,2-bis(4-fluorophenyl)ethylenediamine]dichloroplatinum(II) complexes (**9** and **10**) showed a strong but not dose-dependent inhibition of tumor growth, which probably results from their low water solubility (Table 3, compare also Reile et al. 1990c). In accordance with the results on the MCF7 breast cancer cell line, differences in activity between the two enantiomers (**9** and **10**) were not detectable. Further on, the antileukemic effect of **9** and **10** is similar to that of their racemate **8**.

Differences in the antitumor activity of *R,R*- and *S,S*-configurated [1,2-diphenylethylenediamine]platinum(II) complexes due to the chirality of DNA were postulated for the first time by Gulotti and coworkers (1982, 1984), but could not be proved so far in experiments on the P388 leukemia of the mouse. In contrast to these results Noji and coworkers (1984) reported on a different activity of enantiomeric [diaqua]1,2-diphenylethylenediamine] platinum(II) sulfates and nitrates in the L1210 mouse leukemia experiment. However, the significance of these data is questionable, since the order of activity changed depending on the nature of the counter ion. In the more meaningful in vitro experiment on the human MDA-MB231 breast cancer cell line we observed equal effects with both enantiomers of dichloro[1,2-diphenylethylenediamine]platinum(II), but marked differences between diastereomers (Wappes et al. 1984b). The complex with the *R,R/S,S* configuration was more active than its *R,S* counterpart.

However, small differences we observed with enantiomeric 3- and 4-hydroxy-substituted dichloro[1,2-diphenylethylenediamine]platinum(II) complexes (compare formulae of compounds **5** and **6**) (Wappes et al. 1984a;

Table 3. Antitumor effect of *R,R*- and *S,S*-configurated [1,2-bis(4-fluorophenyl)ethylenediamine]dichloroplatinum(II), compounds *9* and *10*, on the P388 leukemia of the CDF_1 mouse

Compound	Total dose[a] (μmol/kg)	Change of mean body weight (g)			Median survival days (range)	*T/C* (%)
		d5–d1	d9–d1	d16–d1		
Control		0.3	4.7	–	9.0 (9–11)	100
9	160	−0.9	−2.3	4.0	19.0 (17–22)	211
	120	−1.3	−1.4	–	19.5 (5–20)	217
	60	0.2	−0.7	–	17.5 (17–20)	194
10	160	−1.1	−1.2	3.9	18.5 (16–19)	206
	120	−0.3	−0.7	–	17.5 (16–20)	194
	60	−0.7	−0.3	–	16.5 (15–19)	183

[a] The compounds were administered intraperitoneally as polyethylene-glycol-400/1.8% NaCl solution on days 1–9

Jennerwein et al. 1989 b). The influence of steric factors on the antitumor activity of platinum complexes is thoroughly discussed in von Angerer et al. (1989).

Though the enantiomeric [1,2-bis(4-fluorophenyl) ethylenediamine]dichloroplatinum(II) complexes **9** and **10** show no difference in activity on the MCF7 breast cancer cell line, it is conceivable that under in vivo conditions the biological effects of the enantiomers **9** and **10** are different, since the discussed estrogen- and progesterone-lowering effects of these drugs (compare Müller et al. 1989) also influence the hormone-dependent mammary carcinoma. The steric factors are supposed to be more important for the activity of the enantiomeric [1,2-bis(4-fluorophenyl)ethylenediamine]dichloroplatinum(II) complexes on the steroid biosynthesis than on the DNA replication.

Whether enantiomeric [1,2-bis(4-fluorophenyl)ethylenediamine]dichloroplatinum(II) complexes have differing effects on the hormone-dependent mammary carcinoma in vivo will be studied on the estrogen-receptor-positive MXT mammary carcinoma of the mouse.

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