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Original paper

Synthesis and antitumor activity of platinum(II) complexes containing substituted ethylenediamine ligands

Henri BRUNNER[1]*, Peter HANKOFER[1], Ulrich HOLZINGER[1], Barbara TREITTINGER[1] and Helmut SCHÖNENBERGER[2]

[1]*Institut für Anorganische Chemie, University of Regensburg, Universitätsstraße 31, D-8400 Regensburg; and*
[2]*Institut für Pharmazie, University of Regensburg, Universitätsstraße 31, D-8400 Regensburg, FRG*

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Summary – The synthesis of substituted ethylenediamines, their reactions with K_2PtCl_4 to give the dichloroplatinum(II) complexes, and the exchange of the chloro ligands for other leaving groups are described. The new compounds have been tested as antitumor agents both *in vitro* using the hormone independent human mammary carcinoma cell line MDA-MB 231 as well as *in vivo* using the lymphocytic P388 leukemia of the CD_2F_1-mouse. In the P388 test, 53 of the 55 tested complexes fulfill the minimum activity of 125% T / C required for a substance to be active.

Résumé – **Synthèse et activité antitumorale des complexes du platine(II) renfermant des ligands éthylènediamine substituée.** *La synthèse d'éthylènediamines substituées, leur réaction avec K_2PtCl_4 donnant les complexes dichlorés du platine(II), et le remplacement des ligands chlorés par d'autres groupes anioniques partants sont décrits. L'activité antitumorale de ces nouveaux complexes a été examinée, non seulement* in vitro, *en utilisant la ligne de cellules MDA-MB 231 du cancer hormone-indépendant du sein humain, mais également* in vivo *en utilisant la leucémie lymphocytique P388 de la Souris CD_2F_1. Dans le test P388, 53 des 55 complexes dépassent le minimum de l'activité antitumorale nécessaire de 125% T / C.*

1,2-diaminoethanes / platinum(II) complexes / antitumor activity / MDA-MB 321 cell line / P388 leukemia

Introduction

Ethylenediamines, obtained from α-amino acids, were used as ligands for the synthesis of antitumor active platinum complexes [1]. Benzylethylenediamine-dichloroplatinum(II) in particular caused a strong *in vitro* inhibition of the tumor growth, which could be increased by phenyl substitution or leaving group exchange [2]. The purpose of this work is to extend these investigations by testing 66 new platinum(II) complexes both *in vitro* and *in vivo*, to determine the influence of structure and configuration of these complexes on tumor inhibition.

In Schemes 1–4 the ligands and platinum complexes are shown which were prepared and tested in the present study [3, 4]. In Scheme 3 and in the text for a given compound only part of the N-substituents R^1–R^4 are specified, invariably all the other N-substituent are H. The symbols used in Scheme 4 for the complexes with leaving groups other than chloride may imply different bonding situations, *e.g.* in 4-Pt($C_3H_2O_4$) the malonate is bonded to the platinum atom as a chelate ligand, whereas in 4-Pt(NO_3)$_2$ there are 2 H_2O ligands bonded in the platinum complex and the NO_3^- anions are the counter ions.

Synthesis of the ligands and platinum complexes

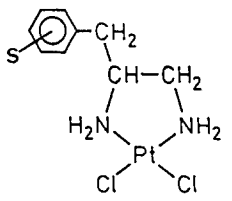
Ligands ***1–38***

Some of the amino acids needed to prepare the ligands of the platinum complexes were synthesized by the hydantoin route [4, 5]. Suitably substituted benzaldehydes were reacted with hydantoin under "Knoevenagel" conditions, the base being molten anhydrous sodium acetate. The benzylidenehydantoins were transferred into amino acids by reduction and hydrolysis with concentrated ammonium sulfide solution in an autoclave at 100°C.

Other amino acids were prepared by the modified Sörensen procedure [6], in which diethyl acetamidomalonate was alkylated by the corresponding benzylhalides in the presence of sodium ethanolate. The malonic acid derivatives were hydrolyzed and decarboxylated in one step by refluxing in 20% hydrochloric acid.

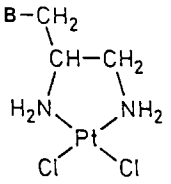
The amino acids were converted into their methylesterhydrochlorides by reaction with thionylchloride in methanol. The amino acid amides were obtained by stirring the esters in a methanolic solution of ammonia. Reduction with $LiAlH_4$ in THF gave the 1,2-ethylenediamine derivatives.

*Author to whom correspondence should be addressed.



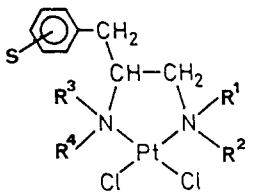
substituent	lig.	complex	substituent	lig.	complex
S = H	R,S-1	R,S-1-$PtCl_2$	S = 2,4-F_2	14	14-$PtCl_2$
S = H	R-1	R-1-$PtCl_2$	S = 3,4-F_2	15	15-$PtCl_2$
S = H	S-1	S-1-$PtCl_2$	S = 2-Cl,4-F	16	16-$PtCl_2$
S = 2-Cl	2	2-$PtCl_2$	S = 2-Cl,6-F	17	17-$PtCl_2$
S = 3-Cl	3	3-$PtCl_2$	S = 4-Cl,2-F	18	18-$PtCl_2$
S = 4-Cl	R,S-4	R,S-4-$PtCl_2$	S = 2-Br	19	19-$PtCl_2$
S = 4-Cl	R-4	R-4-$PtCl_2$	S = 3-Br	20	20-$PtCl_2$
S = 4-Cl	S-4	S-4-$PtCl_2$	S = 4-Br	21	21-$PtCl_2$
S = 2,3-Cl_2	5	5-$PtCl_2$	S = 3-CH_3	22	22-$PtCl_2$
S = 2,4-Cl_2	6	6-$PtCl_2$	S = 4-CH_3	23	23-$PtCl_2$
S = 2,5-Cl_2	7	7-$PtCl_2$	S = 4-CF_3	24	24-$PtCl_2$
S = 2,6-Cl_2	8	8-$PtCl_2$	S = 4-phenyl	25	25-$PtCl_2$
S = 3,4-Cl_2	9	9-$PtCl_2$	S = 4-OCH_3	26	26-$PtCl_2$
S = 3,5-Cl_2	10	10-$PtCl_2$	S= 3,4-O-CH_2-O-	27	27-$PtCl_2$
S = 2-F	11	11-$PtCl_2$	S=4-OCH_2CH_2-OCH_3	28	28-$PtCl_2$
S = 3-F	12	12-$PtCl_2$	S=2,6-Cl_2-4-OCH_3	29	29-$PtCl_2$
S = 4-F	13	13-$PtCl_2$	S=2,6-Cl_2-4-OH	30	30-$PtCl_2$

Scheme 1.



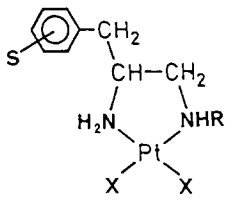
substituent	lig.	complex	substituent	lig.	complex
B= phenyl	31	31-$PtCl_2$	B= 1-naphthylmethyl	35	35-$PtCl_2$
B= α-phenylethyl	32	32-$PtCl_2$	B= 2-naphthylmethyl	36	36-$PtCl_2$
B= ß-phenylethyl	33	33-$PtCl_2$	B= cyclohexylmethyl	37	37-$PtCl_2$
B= 3-phenylpropyl	34	34-$PtCl_2$	B=pentafluorobenzyl	38	38-$PtCl_2$

Scheme 2.



substituent	lig.	complex	substituent	lig.	complex
R^1 = CH_3 S = H	39	39-$PtCl_2$	R^3 = H, CH_3, R^4 = CH_3 S = H	47	47-$PtCl_2$
R^1 = CH_3 S = 4-Cl	40	40-$PtCl_2$	R^1, R^2, R^3, R^4 = CH_3 S = H	48	48-$PtCl_2$
R^1 = CH_3 S=3,4-O-CH_2-O-	41	41-$PtCl_2$	R^1 = isopropyl S = H	49	49-$PtCl_2$
R^3 = CH_3 S = H	42	42-$PtCl_2$	R^3 = isopropyl S = H	50	50-$PtCl_2$
R^3 = CH_3 S = 4-Cl	43	43-$PtCl_2$	R^1, R^3 = isopropyl S = H	51	51-$PtCl_2$
R^3 = CH_3 S=3,4-O-CH_2-O-	44	44-$PtCl_2$	R^1=α-phenylethyl, R^3=CH_3 S = H	52	52-$PtCl_2$
R^1=CH_3, R^3=CH_3 S = H	45	45-$PtCl_2$	R^3 = α-phenylethyl S = H	53	53-$PtCl_2$
R^1=CH_3, R^2=CH_3 S = H	46	46-$PtCl_2$	R^3 = benzyl S = H	54	54-$PtCl_2$

Scheme 3.



substituent	lig.	complex	substituent	lig.	complex
S = H, R = H X = $(OH_2)^*(NO_3)$	1	1-$Pt(NO_3)_2$	S = H, R = CH_3 X = $(OH_2)^*(NO_3)$	39	39-$Pt(NO_3)_2$
S=H, R=H, 2X=4-carboxyphthalate	1	1-$Pt(C_9H_4O_6)$	S X = $(OH_2)^*(NO_3)$	4	4-$Pt(NO_3)_2$
S=H, R=H, X = monothiobenzoate	1	1-$Pt(C_7H_5OS)_2$	S = 4-Cl, R = H 2 X = malonate	4	4-$Pt(C_3H_2O_4)$
S = H, R = H 2X = $(OH_2)^*(S_2O_3)$	1	1-$Pt(S_2O_3)$	S = 4-Cl, R = H 2X=hydroxymalonate	4	4-$Pt(C_3H_2O_5)$
S = H, R = H 2X = $(OH_2)^*(SO_3)$	1	1-$Pt(SO_3)$	S = 4-Cl, R = H 2X = $(OH_2)^*(SO_4)$	4	4-$Pt(SO_4)$
S = H, R = CH_3 2 X = oxalate	39	39-$Pt(C_2O_4)$	S = 4-Cl, R = H X = nitrite	4	4-$Pt(NO_2)_2$

Scheme 4.

As in the preparation of the bromine substituted benzylethylenediamines the bromine substituents were lost during reflux with $LiAlH_4$ in THF, we used weaker reducing agents such as $Al(BH_4)_3$ [7], prepared *in situ* from $NaBH_4$ and $AlCl_3$, to synthesize the bromine substituted diamines **19**–**21**.

The 2,6-dichloro-4-hydroxy substituted ligand **30** is obtained by ether cleavage of the corresponding methylether **29** in CH_2Cl_2 solution using BCl_3 [8].

The optically pure benzylethylenediamines ***R-1, S-1, R-4 and S-4***

During the ligand synthesis, racemisation did not occur [5]. Therefore, *(R)*- and *(S)*-1,2-benzylethylenediamine stereospecifically could be derived from D- and L-phenylalanine. All the other amino acids were used as racemic mixtures, except 4-chlorophenylalanine, the methylester of which was resolved by enzymatic hydrolysis with α-chymotrypsin [9]. At pH 5, stereospecifically only the ester group of the L-isomer was hydrolyzed. The L-amino acid crystallized from the concentrated solution: the D-amino acid ester was obtained by extraction with ethyl acetate and processed as described above.

The N*-alkyl substituted ligands* ***39–54***

Subsequently, the nitrogen atom bound to the methylene group is designated by N^1 and the nitrogen atom bound to the benzyl substituted carbon atom by N^2.

Diamines with alkyl groups attached to N^1 could be prepared by using alkylamines instead of ammonia in the amidation step. The α-amino group of the amino acid was protected by a benzyloxycarbonyl group [10] to avoid the self-condensation of the amino acids, when bulky amines with low reactivity were used. To increase the rate of the amidation reaction, the protected amino acid was activated by *in situ* formation of an ester with *N*-hydroxysuccinimide [11] and by using the coupling agent dicyclohexylcarbodiimide. The protecting group was removed by hydrogen bromide in glacial acetic acid [12], followed by

reduction with $LiAlH_4$ in THF to give the *N*-alkylated benzylethylenediamine.

If the reduction was carried out with the benzyloxycarbonyl derivatives, the diamines with a methyl group bound to the nitrogen atom N^2 were obtained [13].

Diamines with alkyl groups attached to N^2 could be prepared by alkylating the α-amino group of the amino acid amide with ethyl chloroformate [14] and subsequent reduction with $LiAlH_4$ in THF. Dimethylation was achieved by an Eschweiler–Clarke alkylation with formaldehyde in the presence of formic acid [15]. Monoalkyl groups were introduced by condensation of the α-amino acid derivative with an aldehyde or a ketone. The Schiff base was subsequently reduced with $LiAlH_4$ transforming the imine function and the amide function into amino groups. In order to attach the same alkyl groups to both nitrogen atoms N^1 and N^2, the benzylethylenediamines were alkylated according to the procedures given above.

Synthesis of the platinum complexes ***1-PtCl₂-54-PtCl₂***

The diamines **1**–**54** were used as ligands to prepare the corresponding dichloro-platinum(II) complexes by addition to an aqueous solution of K_2PtCl_4 [16, 17], the pH of which was kept constant at 5.0 by addition of 1 N NaOH. The complexes precipitated after a short time as yellow solids.

On complexation of the *N*-alkyl substituted ligands with K_2PtCl_4 a new asymmetric centre resulted at the monosubstituted N atoms. As the benzyl group acted as a conformation anchor, invariably being in an equatorial position [18], the equatorial and axial positions of the alkyl groups at the N atoms could be differentiated by ^1H NMR spectroscopy. For **40-PtCl₂**, the *N*-methyl doublets appeared at 2.65 and 2.71 ppm (J_{CH-NH} = 5.66 Hz and 5.86 Hz) with a relative intensity of 52.7:47.3. The separation of the diastereomers could be achieved by preparative HPLC. The mixture of 18% acetonitrile and 82% H_2O with 0.0025 M decyltrimethylammoniumbromide proved to be the most suitable liquid phase, the solid phase being a 250 mm Li-Chrospher 100 CH-18/2 column with 4 mm diameter [4].

Leaving group exchange

In order to exchange the chloride ligands for other leaving groups, the diaqua-diamine-platinum(II)-dinitrate complexes had to be prepared. This was achieved by treatment of a suspension of the corresponding dichloro complex with an equivalent amount of an $AgNO_3$ solution. The water-soluble "nitrate complex" could be filtered off from the precipitated AgCl. After stoichiometric addition of the new anion, the complex containing the new leaving group was obtained. This procedure was especially suitable for organic dicarboxylic acids such as oxalic acid or malonic acid.

Another possibility to vary the leaving groups was to pass an aqueous solution of the diamine-diaqua-platinum(II)-dinitrate through a column with an anion exchange resin [19], in which the nitrate groups were replaced by hydroxy groups. The resulting aqueous solution was allowed to react with an equimolar amount of the corresponding acid to give the complex with the new leaving group.

Antitumor tests

All the complexes have been tested both *in vitro* using the human mammary cell line MDA-MB 231 as well as *in vivo* using the lymphocytic P388 leukemia of the CD_2F_1-mouse.

MDA-MB 231 in vitro *test*

The MDA-MB 231 *in vitro* test was performed as outlined previously [5, 20]. The complexes were added to the medium as freshly prepared solutions in absolute DMF as indicated in Table I. Due to solubility reasons, 7 complexes were used in DMSO solution. The solutions were added to the medium immediately after preparation to minimize solvolysis of the chloride ligands which can occur quickly in most cases. Two independent parameters, the inhibition of the cell proliferation and of the [^3H]-thymidine incorporation were determined. The pure solvents DMF and DMSO did not show any inhibition. All complexes were tested in three concentrations. For each concentration 6 measurements were made. In most cases the test series were reproduced 3 times. Table I gives the average values and the standard deviations.

The results obtained for the inhibition of the cell growth were in good agreement with the values of the inhibition of the ^3H-thymidine incorporation. For the 14 most active compounds the inhibition exceeded 30% at the concentration 1.0×10^{-6} mol/l. Benzylethylenediamine-dichloro-platinum(II) complexes, especially the derivatives with 4-fluoro, 3-bromo, 3-chloro, and 4-chloro substituents and their combinations with other halogen substituents, exhibited the highest tumor inhibition. Obviously, halogen substituents in the 3- and 4-position of the benzylethylenediamine skeleton result in highly active complexes.

The complexes 29-$PtCl_2$ and 30-$PtCl_2$ contain the 2,6-dichloro-4-methoxy and the 2,6-dichloro-4-hydroxy substituent, respectively. It is striking that these complexes differ only very little in their activity.

In the MDA-MB 231 *in vitro* test, complexes with one *N*-methyl substituent showed an increased antitumor activity, the substitution at N^1 being superior to that at N_2. A further introduction of methyl groups on one side or on both sides of the benzylethylenediamine decreased the *in vitro* activity in the same way as the replacement of the methyl substituents by isopropyl or α-phenylethyl groups.

P388 in vivo *test*

In order to determine the *in vivo* antitumor activity with the P388 test, 1.0×10^6 P388 leukemia cells, suspended in 0.1 ml phosphate buffered saline, were implanted intraperitoneally *(i.p.)* into female CD_2F_1 mice (Zentralinstitut für Versuchstiere, Hannover) with a body weight of *ca.* 18 g [21]. The animals were randomized in groups of 6. The therapy started 24 h after the transplantation (= day 1) with *i.p.* application of a solution of 1.0×10^{-5}, 2.0×10^{-5} or 4.0×10^{-5} mol/kg complex, dissolved or suspended

in a 1:1 mixture of polyethyleneglycol 400 and physiological saline. The therapy was repeated at day 5 and day 9. Animal deaths were recorded daily. Each experiment included 2 groups of 6 animals as untreated controls and one group with 6 animals, treated with *cis*-platinum at 1.5 mg/kg, as positive control. For the evaluation of the T/C-value the median survival time of the treated animals was compared with that of the untreated control animals:

$$T/C\ (\%) = \frac{\text{median survival time of the treated animals}}{\text{median survival time of the control animals}} \times 100$$

The T/C-values and the changes in animal weight are shown in Table II. An increase in animal weight d1–d5 (positive values in Table II) indicates toxicity. 53 of the 55 compounds, submitted to this test, exceeded the minimum activity of 125% T/C, required for a substance to be considered active [21].

Table I. *In vitro* inhibition of cell proliferation and ^{3}H-thymidine incorporation in the hormone independent human mammary carcinoma cell line MDA-MB 231 by the platinum(II) complexes prepared in the present study.

compound	conc. [* 10^{-6} mol/l]	inhibition [%] cell prolif.	inhibition [%] thym. incorp.	remarks	solvent
S = H	10	81.0 ± 0.7	86.7 ± 2.1	x3	DMSO
	5	72.8 ± 3.6	82.1 ± 2.9	x3	
(R,S)-1-$PtCl_2$	1	27.2 ± 9.0	35.0 ± 13.3	x3	
S = H	10	84.6 ± 3.5	90.8 ± 2.9	x3	DMSO
	5	65.5 ± 6.9	79.4 ± 1.2	x3	
(R)-1-$PtCl_2$	1	19.8 ± 6.9	31.0 ± 1.3	x3	
S = H	10	66.4 ± 9.4	91.7 ± 2.4	x3	DMSO
	5	44.1 ± 9.0	76.7 ± 4.0	x3	
(S)-1-$PtCl_2$	1	11.9 ± 7.5	31.9 ± 9.6	x3	
S = 2-Cl	10	77.8 ± 3.8	81.4 ± 6.2	x2	DMF
	5	62.9 ± 16.4	81.9 ± 11.7	x3	
2-$PtCl_2$	1	22.4 ± 4.9	66.6 ± 35.2	x3	
S = 3-Cl	5	80	77	x1	DMF
	1	54.2 ± 12.6	77.5 ± 21.2	x4	
3-$PtCl_2$	0.5	32.4 ± 27.5	50.8 ± 30.8	x2	
S = 4-Cl	5	73.1 ± 10.7	88.6 ± 3.8	x4	DMF
	1	30.3 ± 10.3	56.5 ± 28.5	x5	
(R,S)-4-$PtCl_2$	0.5	14.1 ± 7.4	41.2 ± 29.5	x3	
S = 4-Cl	10	75	98	x1	DMF
	5	65	97	x1	
(R)-4-$PtCl_2$	1	13.2 ± 7.8	85.0 ± 1.4	x2	
S = 4-Cl	5	55	96	x1	DMF
	2	31	74	x1	
(S)-4-$PtCl_2$	1	23.7 ± 5.9	70.1 ± 22.1	x2	
S = 2,3-Cl_2	10	66.5 ± 7.1	91.8 ± 2.1	x1	DMF
	5	51.6 ± 8.5	85.2 ± 3.7	x1	
5-$PtCl_2$	1	15.0 ± 7.8	62.9 ± 10.0	x2	
S = 2,4-Cl_2	5	72.8 ± 9.5	88.3 ± 6.6	x3	DMF
	2	49	83	x1	
6-$PtCl_2$	1	44.6 ± 14.2	64.2 ± 14.5	x4	
S = 2,5-Cl_2	10	68.9 ± 4.1	90.6 ± 3.2	x1	DMF
	5	46.1 ± 6.8	73.1 ± 5.3	x1	
7-$PtCl_2$	1	12.2 ± 1.2	32.5 ± 4.3	x2	
S = 2,6-Cl_2	10	86.6 ± 1.6	97.4 ± 0.7	x1	DMF
	5	80.3 ± 0.8	97.0 ± 0.7	x1	
8-$PtCl_2$	1	20.8 ± 6.6	80.0 ± 1.8	x2	
S = 3,4-Cl_2	5	72.2 ± 7.6	80.2 ± 13.4	x3	DMF
	2	47.3 ± 17.5	71.3 ± 19.3	x2	
9-$PtCl_2$	1	28.5 ± 4.5	57.6 ± 23.7	x4	
S = 3,5-Cl_2	10	82.8 ± 1.9	96.3 ± 1.0	x1	DMF
	5	56.5 ± 6.1	90.9 ± 2.2	x1	
10-$PtCl_2$	1	12.4 ± 3.6	68.5 ± 10.0	x2	
S = 2-F	10	83.5 ± 2.6	93.9 ± 1.0	x1	DMF
	5	74.4 ± 3.4	96.3 ± 1.6	x1	
11-$PtCl_2$	1	12.7 ± 1.8	72.9 ± 4.1	x2	
S = 3-F	5	72	99	x1	DMF
	2	36	96	x1	
12-$PtCl_2$	1	20.9 ± 9.8	86.2 ± 6.4	x2	

The most active complexes were *(R)*- and *(S)*-benzylethylenediamine-dichloro-platinum(II), **(R)-1-$PtCl_2$** and **(S)-1-$PtCl_2$**, both with a T/C value of 300%. However, these values were obtained at concentrations, which already showed signs of toxicity, *e.g.* a decrease in body weight of the mice between day 1 and day 5.

For the following structure/activity discussion, the complexes were compared at the concentration of 1.0×10^{-5} mol/kg. The *in vivo* antitumor activity was dependent on the substituent *S* in the phenyl ring of the benzylethylenediamine-platinum(II) complexes. In general, the activities of compounds substituted in *para*-position by halogens were better than those of alkyl and aryl substituted complexes. Within the halogen series the T/C values increased from chlorine to bromine and fluorine. However, with increasing activity also the toxicity increased.

Table I. *Continued.*

compound	conc. [* 10^{-6} mol/l]	inhibition [%] cell prolif.	inhibition [%] thym. incorp.	remarks	solvent
S = 4-F	5	79.3 ± 10.3	85.0 ± 7.2	x2	DMF
	1	63.2 ± 13.7	57.7 ± 24.8	x4	
13-$PtCl_2$	0.5	38.2 ± 22.2	58.3 ± 38.2	x2	
S = 2,4-F_2	5	44	98	x1	DMF
	2	30	97	x1	
14-$PtCl_2$	1	14.0 ± 12.9	81.0 ± 14.8	x2	
S = 3,4-F_2	5	37	98	x1	DMF
	2	24	97	x1	
15-$PtCl_2$	1	21.7 ± 5.7	76.0 ± 19.6	x2	
S = 2-Cl,4-F	10	28.8 ± 7.9		x1	DMF
	5	9.5 ± 6.1		x1	
16-$PtCl_2$	1	12.0 ± 8.2		x2	
S = 2-Cl,6-F	10	85.9 ± 1.7	98.2 ± 0.5	x1	DMF
	5	80.0 ± 0.9	97.3 ± 1.1	x1	
17-$PtCl_2$	1	22.5 ± 0.2	83	x1	
S = 4-Cl,2-F	2	61	96	x1	DMF
	1	46.7 ± 1.9	89.1 ± 1.6	x2	
18-$PtCl_2$	0.5	21	69	x1	
S = 2-Br	5	75.6 ± 9.3	91.0 ± 4.2	x2	DMF
	2	53.2 ± 7.4	66.9 ± 11.4	x2	
19-$PtCl_2$	1	41.0 ± 12.1	55.0 ± 4.0	x3	
S = 3-Br	1	58.6 ± 13.1	31.4 ± 18.8	x2	DMF
	0.5	36.1 ± 14.7	11.2 ± 22.8	x1	
20-$PtCl_2$	0.1	29.2 ± 19.2	0	x1	
S = 4-Br	5	83.6 ± 2.0	87.4 ± 3.7	x1	DMF
	2	45.8 ± 5.3	44.0 ± 7.6	x1	
21-$PtCl_2$	1	33.9 ± 5.8	31.7 ± 3.8	x2	
S = 3-CH_3	5	47.7 ± 5.1	59.2 ± 8.0	x1	DMF
	2	43.1 ± 8.9	42.4 ± 7.0	x1	
22-$PtCl_2$	1	18.6 ± 9.5	56.2 ± 16.0	x2	
S = 4-CH_3	5	72.8 ± 1.7	84.2 ± 2.5	x1	DMF
	2	21.7 ± 1.5	34.3 ± 11.7	x1	
23-$PtCl_2$	1	15.7 ± 1.3	46.9 ± 28.6	x2	
S = 4-CF_3	10	68.7 ± 6.8	88.7 ± 1.1	x2	DMSO
	5	43.5 ± 6.6	66.2 ± 4.4	x2	
24-$PtCl_2$	1	12.1 ± 10.2	21.9 ± 11.0	x2	
S = 4-phenyl	2	72.7 ± 5.2	56.1 ± 11.6	x1	DMF
	1	54.0 ± 5.6	61.1 ± 32.8	x2	
25-$PtCl_2$	0.5	22.9 ± 6.3	17.1 ± 16.7	x1	
S = 4-OCH_3	10	72.7 ± 12.0	89.4 ± 2.5	x2	DMSO
	5	57.3 ± 6.9	80.6 ± 1.2	x2	
26-$PtCl_2$	1	14.2 ± 67.5	31.3 ± 6.8	x2	
S=3,4-O-CH_2-O-	10	84.0 ± 5.5	89.1 ± 2.0	x2	DMSO
	5	55.0 ± 7.5	72.2 ± 4.5	x2	
27-$PtCl_2$	1	16.8 ± 0.2	26.8 ± 1.1	x2	
S=4-O-CH_2-CH_2-OCH_3 28-$PtCl_2$	1	14.0	17.4	x1	DMF
S = 2,6-Cl_2-4-OCH_3 29-$PtCl_2$	10	34.4 ± 2.6	68.3 ± 9.8	x2	DMSO
	5	23.1 ± 4.1	52.7 ± 0.2	x2	
	1	10.7 ± 0.3	33.1 ± 0.1	x2	
S = 2,6-Cl_2-4-OH 30-$PtCl_2$	10	32.2 ± 6.0		x1	DMF
	5	21.3 ± 6.1		x1	
	1	11.7 ± 5.6		x2	

An important result was that the *(R)*-configurated complexes were less toxic than the *(S)*-configurated complexes. The activity of the chloro substituted derivatives rose in the series:

3,4-dichloro < 4-chloro < 3-chloro < 3,5-dichloro < 2,5-dichloro < 2,4-dichloro < 2,3-dichloro < 2-chloro,

showing that *ortho*-substitution was better than *meta*- and *para*-substitution. This trend was valid for all the halogen substituted complexes. A higher activity could be achieved by combining a chlorine substituent in 2-position with a fluorine substituent in the 4- or 6-position. The most active complexes were obtained with 2-fluoro or 2,4-difluoro substituents:

2-chloro < 2-chloro, 4-fluoro < 2-chloro, 6-fluoro < 4-chloro, 2-fluoro < 2,4-difluoro < 2-fluoro.

These examples demonstrated that the effects of the subtituents were not additive.

In another test series the influence of the chain length, *i.e.* the number of methylene groups between the phenyl ring and the ethylenediamine moiety, was examined. In the low concentration 1.0×10^{-5} mol/kg the activities of the dichloro-complexes rose from 3 to 0 methylene groups:

3-phenylpropyl-ethylenediamine < 2-phenylethyl-ethylenediamine < benzyl-ethylenediamine < phenyl-ethylenediamine.

In higher concentrations the toxicities of these compounds must be taken into account. The activity increased from 3-phenylpropyl-ethylenediamine to β-phenylethyl-ethylenediamine and benzyl-ethylenediamine, but it decreased to phenyl-ethylenediamine. Therefore,

Table I. *Continued.*

compound	conc. [* 10^{-6} mol/l]	inhibition [%] cell prolit.	thym. incorp.	remarks	solvent
B = phenyl 31-$PtCl_2$	10 5 1	39.7 ± 11.0 15.6 ± 7.7 6.4 ± 4.4		×1 ×1 ×2	DMF
B = α-phenyl-ethyl 32-$PtCl_2$	5 2 1	73.7 ± 4.0 55.0 ± 11.3 37.3 ± 10.4	71.9 ± 7.8 0 0	×1 ×1 ×2	DMF
B = β-phenyl-ethyl 33-$PtCl_2$	1 0.5 0.1	28.6 ± 10.1 17.7 ± 16.5 0	10.8 ± 31.5 11.0 ± 17.6 14.5 ± 30.1	×1 ×1 ×1	DMF
B = 3-phenyl-propyl 34-$PtCl_2$	5 2 1	60.9 ± 9.4 32.1 ± 13.3 27.3 ± 15.6	91.9 ± 1.6 57.9 ± 9.7 38.6 ± 12.2	×1 ×1 ×1	DMF
B = 1-naphthyl-methyl 35-$PtCl_2$	5 2 1	55.8 ± 6.0 32.6 ± 7.0 36.6 ± 7.6	82.8 ± 3.1 54.5 ± 4.4 67.1 ± 27.0	×1 ×1 ×2	DMF
B = 2-naphthyl-methyl 36-$PtCl_2$	10 5 1	84.7 ± 6.2 47.0 ± 9.3 7.0 ± 1.4		×1 ×1 ×2	DMF
B = cyclohexyl-methyl 37-$PtCl_2$	5 2 1	59.4 ± 5.7 36.2 ± 6.4 21.6 ± 7.9	86.9 ± 2.6 47.2 ± 8.8 60.0 ± 34.2	×1 ×1 ×2	DMF
B =pentafluoro-benzyl 38-$PtCl_2$	10 5 1	18.3 ± 13.5 3.1 ± 17.2 0		×1 ×1 ×2	DMF
N^1-CH_3 S = H 39-$PtCl_2$	10 5 1	88.6 ± 2.0 83.4 ± 2.5 40.5 ± 11.5	95.7 ± 1.1 89.9 ± 2.9 46.0 ± 19.4	×2 ×2 ×2	DMF
N^1-CH_3 S = 4-Cl 40-$PtCl_2$	5 1 0.5	78.2 ± 2.5 45.6 ± 3.1 37	88.7 ± 1.5 40.2 ± 12.2 33	×2 ×2 ×1	DMF
N^1-CH_3 S=3,4-O-CH_2-O- 41-$PtCl_2$	1	39		×1	DMF
N^2-CH_3 S = H 42-$PtCl_2$	10 5 1	90 88 35	97 95 65	×1 ×1 ×1	DMF
N^2-CH_3 S = 4-Cl 43-$PtCl_2$	10 5 1	29.1 ± 8.8 36.1 ± 15.4 17.1 ± 8.3		×1 ×1 ×2	DMF
N^2-CH_3 S=3,4-O-CH_2-O- 44-$PtCl_2$	10 5 1	56.0 ± 8.2 32.9 ± 10.0 11.7 ± 3.0		×1 ×1 ×2	DMF
N^1-CH_3,N^2-CH_3 S = H 45-$PtCl_2$	10 5 1	88 55 13	99 91 49	×1 ×1 ×1	DMF
N^1-$(CH_3)_2$ S = H 46-$PtCl_2$	10 5 1	79 68 17	76 72 30	×1 ×1 ×1	DMF
N^2-$(CH_3)_2$ S = H 47-$PtCl_2$	10 5 1	73 54 11	74 53 0	×1 ×1 ×1	DMF
N^1,N^2-$(CH_3)_4$ S = H 48-$PtCl_2$	10 5 1	33 14 0	27 20 2	×1 ×1 ×1	DMF

Table I. *Continued.*

compound	conc. [* 10^{-6} mol/l]	inhibition [%] cell prolif.	thym. incorp.	remarks	solvent
N^1-isopropyl S = H 49-$PtCl_2$	10 5 1	80 78 20	85 79 50	×1 ×1 ×1	DMF
N^2-isopropyl S = H 50-$PtCl_2$	10 5 1	91 77 24	97 93 46	×1 ×1 ×1	DMF
N^1,N^2-diiso-propyl, S = H 51-$PtCl_2$	10 5 1	84 76 26	98 80 29	×1 ×1 ×1	DMF
N^1-α-phenylethyl N^2-CH_3, S = H 52-$PtCl_2$	10 5 1	92 89.0 ± 0.3 26.1 ± 1.5	98 96.2 ± 1.5 53.8 ± 5.9	×1 ×2 ×2	DMF
N^2-α-phenyl-ethyl, S = H 53-$PtCl_2$	10 5 1	98 91 0	99 98 6	×1 ×1 ×1	DMF
N^2-benzyl S = H 54-$PtCl_2$	10 5 1	98 98 0	99 99 16	×1 ×1 ×1	DMF
2 X = 4-carb-oxyphthalate S = H, R = H 1-Pt($C_9H_4O_6$)	1	13	75	×1	DMF
X = monothio-benzoate S = H, R = H 1-Pt(C_7H_5OS)$_2$	10	0	0	×1	DMF
2 X = thio-sulfate S = H, R = H 1-Pt(S_2O_3)	10	0	0	×1	DMF
2 X = sulfite S = H, R = H 1-Pt(SO_3)	10 5 1	52.9 ± 21.5 31.7 ± 12.3 6.2 ± 6.2	91.6 ± 6.1 76.5 ± 13.5 32.0 ± 29.5	×2 ×2 ×2	DMF
2 X = oxalate S = H, R = CH_3 39-Pt(C_2O_4)	10 5 1	46.5 ± 6.8 34.3 ± 4.5 6.9 ± 1.2	84.1 ± 3.4 70.0 ± 4.2 49.5 ± 21.9	×1 ×1 ×2	DMF
X = nitrate S = H, R = CH_3 39-Pt(NO_3)$_2$	10 5 1	35.1 ± 8.8 26.8 ± 6.3 14.7 ± 7.5	75.8 ± 3.1 35.8 ± 5.6 49.9 ± 21.4	×1 ×1 ×2	DMF
X = nitrate S = 4-Cl, R = H 4-Pt(NO_3)$_2$	10 5 1	62.5 ± 8.0 46.2 ± 6.3 9.2 ± 9.1	91.4 ± 1.2 88.4 ± 2.1 57.1 ± 9.5	×1 ×1 ×2	DMF
2 X = hydroxy-malonate S = 4-Cl, R = H 4-Pt($C_3H_2O_5$)	10 5 1	74.8 ± 4.3 35.3 ± 19.9 9.7 ± 5.7	81.0 ± 4.5 41.0 ± 14.0 28.2 ± 25.7	×2 ×2 ×3	DMF
2 X = sulfate S = 4-Cl, R = H 4-Pt(SO_4)	10 5 1	50.3 ± 16.0 9.4 ± 17.2 7.3 ± 19.7	47.1 ± 25.7 11.1 ± 40.0 37.7 ± 30.4	×1 ×1 ×2	DMF
X = nitrite S = 4-Cl, R = H 4-Pt(NO_2)$_2$	10 5 1	16.2 ± 8.8 15.4 ± 9.1 6.9 ± 6.9	65.0 ± 7.1 44.2 ± 10.8 37.9 ± 6.8	×1 ×1 ×2	DMF

×1: one test series; ×2: average of 2 test series; ×3: average of 3 test series; ×4: average of 4 test series; ×5: average of 5 test series.

the most effective complexes were benzylethylenediamine- and β-phenylethyl-ethylenediamine-dichloro-platinum(II), if administered in optimal concentrations.

A large influence of *N*-alkyl substituents in benzylethylenediamine-dichloro-platinum(II) complexes on the antitumor activity was expected, because the substituents should affect the steric and electronic situation of the platinum atom and as a consequence the dissociation of the leaving groups. However, a methyl group attached to N^2 gave only a small increase in activity, whereas a methyl group attached to N^1 resulted in an activity decrease. With larger *N*-alkyl groups no increase could be obtained.

Experimental protocols

Synthesis of α-amino acids

All the α-amino acids were synthesized starting from suitably substituted benzaldehydes *via* the "hydantoin route" as reported previously [22], except those which were prepared as described below.

Synthesis of 4-chlorophenylalanine-hydrochloride via *the Sörensen procedure*

To a solution of 200 mmol (4.6 g) of sodium in 300 ml of absolute ethanol 200 mmol (43.2 g) of diethyl acetamidomalonate and 200 mmol (32.2 g) of 4-chlorobenzylchloride were added. The yellow solution was stirred under reflux for 12 h. The hot reaction mixture was filtered and the precipitate was washed with hot absolute ethanol. The combined filtrates were evaporated and the residue was washed with ether. After drying, the product was refluxed for 12 h with 500 ml of 20% hydrochloric acid. Then, most of the solvent was removed and the residue was kept at −5°C for 12 h. The solid was collected, washed with little cold ethanol, and dried. Colorless crystals, mp: 235°C, yield: 44.8 g (95%), anal. $C_9H_{10}ClNO_2$. HCl (calcd. C: 45.79; H: 4.70; N: 5.93; found: C: 45.68; H: 4.96; N: 5.79); IR (KBr): 3200−2400 cm^{-1} (br, ν_{NH}), 1735 cm^{-1} (s, ν_{COOH}).

Other α-amino acids prepared by the Sörensen procedure:
2,3-dichlorophenylalanine-hydrochloride from 2,3-dichlorobenzylbromide, prepared from 2,3-dichlorotoluene and bromine according to [23], bp: 80°C / 10^{-4} Torr, yield: 97%;
2,5-dichlorophenylalanine-hydrochloride from 2,5-dichlorobenzyl-

Table II. *In vivo* antitumor activity of the platinum(II) complexes, prepared in the present study, in the P388 lymphocytic leukemia of the CD_2F_1 mouse.

compound	conc.±5 [* 10 mol/kg]	change in animal weight d_1-d_5 [g]	median survival time [d]	T/C-value [%]	remarks
S = H	1	-0.5	15.0	167	×5
	2	-0.7	21.0	233	×5
(R,S)-1-$PtCl_2$	4	+4.3	7.5	83	×5 tox
S = H	1	-0.1	23.5	196	×4
	2	-0.1	36.0	300	×4
(R)-1-$PtCl_2$	4	+2.0	32.0	266	×4
S = H	1	+1.3	31.5	263	×4
	2	+4.1	36.0	300	×4 tox
(S)-1-$PtCl_2$	4	+4.6	8.5	70	×4 tox
S = 2-Cl	1	+0.2	17.0	179	×2
	2	+1.2	19.5	205	×2
2-$PtCl_2$	4	+2.9	22.0	232	×2
S = 3-Cl	1	-0.8	15.5	148	×1
	2	-0.5	17.0	162	×1
3-$PtCl_2$	4	-0.4	18.0	171	×1
S = 4-Cl	1	-0.4	13.5	142	×2
	2	-0.3	16.5	174	×2
(R,S)-4-$PtCl_2$	4	-0.1	19.0	200	×2
S = 4-Cl	2	-1.1	17.0	189	×6
	4	-1.1	20.0	222	×6
(R)-4-$PtCl_2$	8	+0.5	22.0	244	×6
S = 4-Cl	2	-0.5	20.0	222	×6
	4	+0.9	22.5	250	×6
(S)-4-$PtCl_2$	8	+3.4	12.0	133	×6 tox
S = 2,3-Cl_2	1	-0.8	16.0	178	×7
	2	+0.2	16.5	183	×7
5-$PtCl_2$	4	+1.7	19.5	217	×7
S = 2,4-Cl_2	1	-0.3	16.0	168	×2
	2	-0.1	17.0	179	×2
6-$PtCl_2$	4	+0.9	18.5	195	×2
S = 2,5-Cl_2	1	-0.9	15.0	167	×7
	2	-0.3	16.0	178	×7
7-$PtCl_2$	4	+1.2	18.0	200	×7
S = 3,4-Cl_2	1	-0.8	9.5	100	×2
	2	0	12.0	126	×2
9-$PtCl_2$	4	-0.5	13.0	137	×2
S = 3,5-Cl_2	1	-1.1	14.5	161	×7
	2	-0.1	17.0	189	×7
10-$PtCl_2$	4	+0.9	18.0	200	×7
S = 2-F	1	+0.1	21.0	233	×6
	2	+3.9	8.5	94	×6 tox
11-$PtCl_2$	4	+5.0	6.0	66	×6 tox
S = 3-F	1	-1.0	20.5	228	×6
	2	+4.1	24.0	267	×6 tox
12-$PtCl_2$	4	+4.6	6.5	72	×6 tox
S = 4-F	1	+0.1	18.5	205	×6
	2	+3.3	22.5	250	×6
13-$PtCl_2$	4	+5.1	6.0	67	×6 tox

Table II. *Continued.*

compound	conc.±5 [* 10 mol/kg]	change in animal weight d_1-d_5 [g]	median survival time [d]	T/C-value [%]	remarks
S = 2,4-F_2	1	-1.4	19.0	211	×6
	2	+3.5	24.0	267	×6
14-$PtCl_2$	4	+5.1	7.0	78	×6 tox
S = 3,4-F_2	1	+0.3	19.0	211	×6
	2	-0.2	22.5	250	×6
15-$PtCl_2$	4	+3.9	8.0	89	×6 tox
S = 2-Cl,4-F	1	-0.5	17.0	189	×7
	2	-0.1	17.0	189	×7
16-$PtCl_2$	4	+2.7	23.0	256	×7
S = 2-Cl,6-F	1	-0.9	17.5	194	×6
	2	-0.6	20.0	222	×6
17-$PtCl_2$	4	+4.7	14.5	161	×6 tox
S = 4-Cl,2-F	1	-1.2	18.0	200	×6
	2	+0.9	18.5	206	×6
18-$PtCl_2$	4	+1.1	22.0	244	×6
S = 2-Br	1	+0.2	19.0	211	×6
	2	+1.7	22.0	244	×6
19-$PtCl_2$	4	+4.4	26.0	289	×6 tox
S = 3-Br	1	-1.3	17.5	194	×6
	2	-0.7	20.0	222	×6
20-$PtCl_2$	4	+2.4	22.0	244	×6
S = 4-Br	1	-2.1	16.0	178	×6
	2	-1.1	17.0	189	×6
21-$PtCl_2$	4	-0.7	19.0	211	×6
S = 3-CH_3	1	+0.2	23.5	196	×4
22-$PtCl_2$	2	+0.7	27.0	225	×4
S = 4-CH_3	1	+0.1	20.5	171	×4
	2	-0.1	28.0	233	×4
23-$PtCl_2$	4	+1.7	30.0	250	×4
S = 4-CF_3	1	-0.6	15.0	143	×1
	2	+0.5	16.0	152	×1
24-$PtCl_2$	4	+0.7	17.0	162	×1
S = 4-phenyl	1	-1.3	13.0	144	×5
	2	-0.5	14.0	156	×5
25-$PtCl_2$	4	+1.0	16.5	183	×5
S = 4-OCH_3	1	-0.7	15.0	167	×7
	2	-0.5	16.5	183	×7
26-$PtCl_2$	4	+2.7	22.5	250	×7
S=3,4-O-CH_2-O-	1	-0.3	15.0	166	×3
	2	+0.2	19.0	211	×3
27-$PtCl_2$	4	+1.8	21.0	233	×3
S=4-O-CH_2-CH_2-OCH_3	1	-1.4	11.0	122	×7
	2	-1.9	9.0	100	×7
28-$PtCl_2$	4	-2.2	11.0	122	×7
S = 2,6-Cl_2-4-OH	1	-0.7	15.5	172	×7
	2	-0.7	16.0	178	×7
30-$PtCl_2$	4	-0.3	16.0	178	×7

bromide, prepared from 2,5-dichlorotoluene and bromine according to [23], bp: 70°C / 10^{-4} Torr, yield: 93%;
2,6-dichlorophenylalanine-hydrochloride from 2,6-dichlorobenzylbromide (Janssen);
3,5-dichlorophenylalanine-hydrochloride from 3,5-dichlorobenzylchloride, prepared from 3,5-dichlorobenzylalcohol and $SOCl_2$ according to [24], bp: 79°C / 10^{-4} Torr, yield: 70%;
2-chloro-4-fluorophenylalanine-hydrochloride from 2-chloro-4-fluorobenzylbromide, prepared from 2-chloro-4-fluorotoluene and bromine according to [23], mp: 35°C, yield: 97%;
2-chloro-6-fluorophenylalanine-hydrochloride from 2-chloro-6-fluorobenzylchloride (Aldrich);
4-chloro-2-fluorophenylalanine-hydrochloride from 4-chloro-2-fluorobenzylbromide, prepared from 4-chloro-2-fluorotoluene and bromine according to [23], bp: 70°C / 10^{-4} Torr, yield: 97%;
2-bromophenylalanine-hydrochloride from 2-bromobenzylbromide, prepared from 2-bromotoluene and bromine according to [23], bp: 75°C / 10^{-4} Torr, yield: 99%;
3-bromophenylalanine-hydrochloride from 3-bromobenzylbromide, prepared from 3-bromotoluene and bromine according to [23], mp: 41°C, yield: 87%;
4-bromophenylalanine-hydrochloride from 4-bromobenzylbromide, prepared from 4-bromotoluene and bromine according to [23], mp: 59°C, yield: 95%;
4-phenylphenylalanine-hydrochloride from 4-phenylbenzylchloride, prepared from 4-hydroxymethylbiphenyl and $SOCl_2$ according to [24], mp: 71°C, yield: 62%;

Table II. *Continued.*

compound	conc.·5 [* 10^{-5} mol/kg]	change in animal weight d_1–d_5 [g]	median survival time [d]	T/C-value [%]	remarks
B = phenyl 31-$PtCl_2$	1 2 4	-0.3 +2.5 +4.5	16.0 19.0 13.0	178 211 144	×5 ×5 ×5 tox
B = α-phenyl-ethyl 32-$PtCl_2$	1 2 4	-0.8 -0.7 +1.7	13.5 17.0 21.0	150 189 233	×5 ×5 ×5
B = β-phenyl-ethyl 33-$PtCl_2$	1 2 4	+0.1 +0.4 +1.8	14.5 18.0 21.5	161 200 239	×5 ×5 ×5
B = 3-phenyl-propyl 34-$PtCl_2$	1 2 4	-0.9 -0.6 +0.1	13.5 16.0 17.0	150 178 189	×5 ×5 ×5
B = 1-naphthyl-methyl 35-$PtCl_2$	2 4	-0.1 +1.9	16.5 16.5	183 183	×3 ×3
B = 2-naphthyl-methyl 36-$PtCl_2$	1 2 4	-0.3 +0.3 +1.0	18.0 23.5 26.0	150 196 216	×4 ×4 ×4
B = cyclohexyl-methyl 37-$PtCl_2$	1 2 4	-0.8 -0.2 -0.2	23.0 24.0 24.5	192 200 204	×4 ×4 ×4
B =pentafluoro-benzyl 38-$PtCl_2$	1 2 4	-1.8 -1.6 -1.2	10.0 10.0 11.0	111 111 122	×7 ×7 ×7
N^1-CH_3 S = H 39-$PtCl_2$	1 2 4	-0.5 -0.1 0	14.5 15.0 17.0	153 158 179	×2 ×2 ×2
N^1-CH_3 S = 4-Cl 40-$PtCl_2$	1 2 4	-0.9 -0.6 +0.5	13.5 16.0 14.5	142 168 153	×2 ×2 ×2
N^2-CH_3 S = H 42-$PtCl_2$	1 2 4	+0.5 +0.8 +3.5	16.0 20.5 24.5	177 227 272	×3 ×3 ×3
N^2-CH_3 S = 4-Cl 43-$PtCl_2$	1 2 4	-0.2 +1.0 +0.7	15.5 16.0 16.0	172 178 178	×7 ×7 ×7
N^2-CH_3 S=3,4-O-CH_2-O- 44-$PtCl_2$	1 2 4	-0.6 -0.4 -0.5	14.5 15.5 16.5	161 172 183	×7 ×7 ×7
N^1-isopropyl S = H 49-$PtCl_2$	1 2 4	-0.5 -0.4 +1.4	13.0 14.0 16.5	144 155 183	×3 ×3 ×3
N^1-α-phenyl-ethyl, N^2-CH_3 S = H 52-$PtCl_2$	1 2 4	-0.6 -0.5 +0.1	11.5 13.5 14.0	121 142 147	×2 ×2 ×2

3,4-methylenedioxyphenylalanine-hydrochloride (cleavage of ethyl acetylamido-(3,4-methylenedioxybenzyl)malonate with 1 M HCl 5 d), from 3,4-methylenedioxybenzylchloride prepared from 3,4-methylenedioxybenzylalcohol and $SOCl_2$ according to [24], bp: 85°C / 10^{-4} Torr, yield: 90%;
4-(2-methoxyethoxy)phenylalanine-hydrochloride from 4-(2-methoxyethoxy)benzylbromide, prepared from 4-(2-methoxyethoxy)toluene and bromine according to [23], bp: 125°C / 10^{-4} Torr, yield: 95%;
(1-phenylethyl)glycine-hydrochloride from α-phenylethylbromide (Ega);
(2-phenylethyl)glycine-hydrochloride from β-phenylethylbromide (Janssen);

Table II. *Continued.*

compound	conc.·5 [* 10^{-5} mol/kg]	change in animal weight d_1–d_5 [g]	median survival time [d]	T/C-value [%]	remarks
2X = 4-carboxy-phthalate S = H, R = H 1-Pt($C_9H_4O_6$)	1	-0.7	14.0	156	×5
2 X = sulfite S = H, R = H 1-Pt(SO_3)	1 2 4	+1.6 +0.4 -0.5	12.0 12.0 16.0	120 120 160	×5 ×5 ×5
2 X = oxalate S = H, R=CH_3 39-Pt(C_2O_4)	1 2	-1.1 -0.7	11.0 14.5	122 161	×5 ×5
X = nitrate S = H, R=CH_3 39-Pt(NO_3)$_2$	1 2 4	-0.6 -0.3 +3.0	14.0 16.5 31.0	116 138 258	×4 ×4 ×4
2 X = malonate S = 4-Cl, R=H 4-Pt($C_3H_2O_4$)	1 2 4	-0.6 -0.5 -0.6	10.5 11.5 15.0	111 121 158	×2 ×2 ×2
2 X = hydroxy-malonate S = 4-Cl, R=H 4-Pt($C_3H_2O_5$)	1 2 4	-1.5 -0.2 -0.4	9.5 12.5 16.5	100 132 174	×2 ×2 ×2
2 X = sulfate S = 4-Cl, R=H 4-Pt(SO_4)	1 2 4	-0.8 -0.3 +1.4	15.0 17.0 19.5	167 189 217	×5 ×5 ×5
X = nitrite S = 4-Cl, R=H 4-Pt(NO_2)$_2$	1 2 4	-1.7 -0.6 -0.3	10.0 10.0 12.0	111 111 133	×5 ×5 ×5

×1: neg. control: solvent, median survival time = 9 d
change in animal weight d1–d5 = −1.2 g
pos. control: *cis*platinum, c = 5 · 10^{-6} mol / kg,
m.s.t. = 20.5 d, T / C = 195%, d1–d5 = +1.3 g

×2: neg. control: solvent, median survival time = 9.5 d
change in animal weight d1–d5 = −1.6 g
pos. control: *cis*platinum, c = 5 · 10^{-6} mol / kg,
m.s.t. = 22.5 d, T / C = 237%, d1–d5 = +2.2 g

×3: neg. control: solvent, median survival time = 9.0 d
change in animal weight d1–d5 = −2.4 g
pos. control: *cis*platinum, c = 5 · 10^{-6} mol / kg,
m.s.t. = 18.5 d, T / C = 206%, d1–d5 = +4.0 g

×4: neg. control: solvent, median survival time = 12.0 d
change in animal weight d1–d5 = −0.8 g
pos. control: *cis*platinum, c = 5 · 10^{-6} mol / kg,
m.s.t. = 23.0 d, T / C = 192%, d1–d5 = +1.0 g

×5: neg. control: solvent, median survival time = 9.0 d
change in animal weight d1–d5 = −1.6 g
pos. control: *cis*platinum, c= 5 · 10^{-6} mol / kg
m.s.t. = 16.0 d, T / C = 178%, d1–d5 = 0.0 g

×6: neg. control: solvent, median survival time = 9.0 d
change in animal weight d1–d5 = − 3.3 g
pos. control: *cis*platinum, c = 5 · 10^{-6} mol / kg,
m.s.t. = 23.0 d, T / C = 256%, d1–d5 = +1.0 g

×7: neg. control: solvent, median survival time = 9.0 d
change in animal weight d1–d5 = −1.6 g
pos. control: *cis*platinum, c = 5 · 10^{-6} mol / kg,
m.s.t. = 21.0 d, T / C = 233%, d1–d5 = +0.7 g

(3-phenylpropyl)glycine-hydrochloride from 3-phenylpropylbromide (Ega).

Resolution of 4-chlorophenylalanine

37.9 mmol (7.55 g) of D,L-4-chlorophenylalanine were added to the solution of 41.6 mmol (3.0 ml) of thionylchloride in 100 ml of ethanol at −5°C. The solution was heated under reflux for 15 h. After removal of the solvent the white solid ethyl 4-chlorophenylalaninate-hydrochloride was dissolved in 100 ml of water. The pH of the solution was adjusted to 5.0 with 0.2 M LiOH. 100 mg of α-chymotrypsin (Sigma, from bovine pancreas, 41 u/mg solid) were added and the temperature was held at 37°C during the reaction. The pH was kept constant by the automatic addition of 0.2 M LiOH from a pH-stat titrator. After 24 h consumption of LiOH had stopped. The mixture was concentrated until crystals appeared, cooled for 1 h and filtered. The precipitated L-amino acid was washed with ethanol and recrystallized from hot water.

The filtrate obtained after the removal of the L-amino acid was brought to pH 9.0 with 0.2 M LiOH and extracted with ethyl acetate (3 × 50 ml). The organic layer was dried over $MgSO_4$. The solvent was evaporated and the remaining oil was distilled at 110°C/10^{-4} Torr. Yield: 2.3 g L-4-chlorophenylalanine (61%), $[\alpha]_D^{30}$ +1.7° (c = 1, 1 N NaOH),optical purity 98.7% ee; 3.6 g ethyl D-4-chlorophenylalaninate (83%), $[\alpha]_{578}^{20}$ −31.55° (c = 2, EtOH), otpical purity 97.1% ee. The optical purity was determined after derivatization with trifluoroacetanhydride by gaschromatography with a 50-m Chirasil-L-val column: T_c = 130°C, T_i = 250°C, pH_2 = 2.0 bar.

Conversion of α-amino acids into 1,2-diamines

The conversion of α-amino acids into 1,2-diamines was carried out according to established procedures [1, 25]. Only additions and deviations necessary for specific compounds are given below.

Optical purity of benzylethylenediamines

(S)-Benzylethylenediamine, synthesized from L-phenylalanine (Janssen, 99% ee), was derivatized with trifluoroacetic anhydride. The derivative was chromatographed on a 50-m Chirasil-L-val column (T_c = 135°C, T_i = 250°C, pH_2 = 2.0 bar, R_t = 3.9 min). No impurity of the *(R)*-isomer could be detected. The same result was obtained when *(R)*-benzylethylenediamine (from D-phenylalanine, Janssen, 99% ee) was used (R_t = 4.1 min). Optical rotations of the optically pure benzylethylenediamines: ***(R)*−1:** $[\alpha]_{578}^{20}$ +19.3° (neat, ρ = 1), ***(S)*−1:** $[\alpha]_{578}^{20}$ −21.7° (neat, ρ = 1).

Optical rotations of *(R)*− and *(S)*-4-chlorobenzylethylenediamine, obtained from the optically active amino acids as described above: ***(R)*−4:** $[\alpha]_{578}^{20}$ +13.1° (c = 2, EtOH), ***(S)*−4:** $[\alpha]_{578}^{20}$ −12.2° (c = 2, EtOH).

Reduction of 2-bromophenylalanine amide

300 mmol (11.35 g) of $NaBH_4$ and 60 mmol (14.6 g) of 2-bromophenylalanine amide were suspended in 150 ml of absolute diglyme. A freshly prepared suspension of 100 mmol (13.3 g) of anhydrous $AlCl_3$ in 30 ml of absolute diglyme was slowly added at 0°C and the reaction mixture was stirred at 60°C for 15 h. The excess of reducing agent was hydrolyzed by slowly adding 20 ml of water. The solvent was removed and the white solid was extracted with ethanol in a Soxhlet apparatus. After the ethanol was distilled off, the diamine-dihydrochloride was left as an oil. It was dissolved in 30 ml of 2 M NaOH solution and extracted with 100 ml of ether in a liquid/liquid extraction apparatus for 12 h. The organic layer was dried over Na_2SO_4. After removal of the solvent, the diamine **19** was distilled at 120°C/10^{-4} Torr. Colorless liquid yield: 4.6 g (40%).

The same reduction procedure was applied to 3-bromophenylalanine amide to give **20** (colorless liquid, bp: 105°C/10^{-4} Torr, yield: 3.44 g (25%), and 4-bromophenylalanine amide to give **21** (colorless liquid, bp: 110°C/10^{-4} Torr, yield: 3.16 g (23%)).

*Ether cleavage in the 1,2-diamine **29***

*(2,6-Dichloro-4-hydroxybenzyl)-ethylendiamine-dihydrochloride **30** 2 HCl*

5.0 mmol (1.25 g) of (2,6-dichloro-4-methoxybenzyl)-ethylenediamine **29** were dissolved in 100 ml of absolute CH_2Cl_2 and cooled to −70°C. 25 ml of a 1 M solution of BCl_3 in CH_2Cl_2 were added dropwise and the reaction temperature was allowed to rise to room temperature within 12 h. The excess of BCl_3 was destroyed by a dropwise addition of 3.0 ml of methanol. Most of the solvent was removed. At −15°C 150 ml of ether were added. The dihydrochloride of the diamine **30** precipitated as a white solid. It was filtered off, washed with ether, and dried. Colorless, moisture sensitive crystals, mp: 145°C, dec. 254°C, yield: 1.23 g (73%); anal. $C_9H_{12}Cl_2N_2O \cdot 2\,HCl$ calcd.: C: 21.57; H: 2.41; N: 5.59; found: C: 21.12; H: 2.94; N: 5.27.

Synthesis of the N-alkyl substituted 1,2-diamines

*2-Amino-1-N-methylamino-3-phenylpropane **39***

10 mmol (1.78 g) of phenylalanine methylamide, obtained from L-methyl phenylalaninate and methylamine; colorless solid, mp: 57°C, yield: 7.75 g (87%) [3], were added in small portions to a stirred suspension of 30 mmol (1.14 g) of $LiAlH_4$ in 50 ml of dry THF at 0°C. The mixture was refluxed for 24 h. After cooling to 0°C 120 mmol (2.16 ml) of water were added dropwise to hydrolyze excess $LiAlH_4$. The mixture was filtered and the residue was extracted with 150 ml of THF in a Soxhlet apparatus. The extract was combined with the filtrate and the solvent was evaporated. The light yellow crude product was distilled at 75°C/10^{-4} Torr. Colorless liquid, mp of the dihydrochloride: 89°C, yield 1.26 g (76%).

The following 1,2-diamines were synthesized in the same way.

*2-Amino-1-N-methylamino-3-(4-chlorophenyl)-propane **40.*** This was synthesized using 4-chlorophenylalanine methylamide; colorless liquid, bp: 100°C/10^{-4} Torr, yield: 1.43 g (74%).

*2-Amino-1-N-methylamino-3-(3,4-methylendioxyphenyl)-propane **41.*** This was synthesized using 3,4-methylendioxyphenylalanine methylamide; colorless liquid, bp: 145°C/10^{-4} Torr, yield: 1.03 g (53%).

*2-Amino-1,1-N-dimethylamino-3-phenylpropane **46.*** This was synthesized *via* *N*-benzyloxycarbonylphenylalanine dimethylamide (obtained from *N*-benzyloxycarbonylphenylalanine [12], *N*-hydroxysuccinimide, dicyclohexylcarbodiimide and dimethylamine [3] and phenylalaninedimethylamide-hydrobromide (obtained from *N*-benzyloxycarbonylphenylalanine dimethylamide and hydrogenbromide); colorless liquid, bp; 100°C/10^{-4} Torr, yield: 1.62 g (73%).

*2-Amino-1-N-isopropylamino-3-phenylpropane **49.*** This was synthesized *via* *N*-benzyloxycarbonylphenylalanine isopropylamide (obtained from *N*-benzyloxycarbonylphenylalanine [12], *N*-hydroxysuccinimide, dicyclohexylcarbodiimide and isopropylamine) and phenylalanine isopropylamide-hydrobromide (obtained from *N*-benzyloxycarbonylphenylalanine isopropylamide and hydrogenbromide [3]); colorless liquid, bp: 145°C/10^{-4} Torr, yield: 2.85 g (74%).

*2-N-Methylamino-1-[N-(S)-1-phenylethylamino]-3-phenyl-propane **52.*** This was synthesized *via* *N*-benzyloxycarbonylphenylalanine *(S)*-1-phenylethylamide (obtained from *N*-benzyloxycarbonylphenylalanine [12], *N*-hydroxysuccinimide, dicyclohexylcarbodiimide, and *(S)*-1-phenylethylamine); colorless liquid, bp: 150°C/10^{-4} Torr, mp of the dihydrochloride: 203°C, yield: 4.05 g (83%).

*1-Amino-2-N-methylamino-3-phenylpropane **42.*** This was synthesized *via* *N*-ethyloxycarbonylphenylalanine (obtained from phenylalanine and ethyl chloroformate in the presence of Na_2CO_3); colorless liquid, bp: 75°C/10^{-4} Torr, mp of the dihydrochloride: 160°C, yield: 0.85 g (52%).

*1-Amino-2-N-methylamino-3-(4-chlorophenyl)-propane **43.*** This was synthesized *via* *N*-ethyloxycarbonyl-4-chlorophenylalanine (obtained from 4-chlorophenylalanine and ethyl chloroformate in the presence of Na_2CO_3); colorless liquid, bp: 110°C/10^{-4} Torr, yield: 1.04 g (52%).

*1-Amino-2-N-methylamino-3-(3,4-methylenedioxyphenyl)-propane **44.*** This was synthesized *via* *N*-ethyloxycarbonyl-3,4-methylenedioxyphenylalanine (obtained from 3,4-methylenedioxyphenylalanine and ethyl chloroformate in the presence of Na_2CO_3); colorless liquid, bp: 150°C/10^{-4} Torr, yield: 0.86 g (42%).

*1-Amino-2-N,N-dimethylamino-3-phenylpropane **47.*** This was synthesized *via* *N,N*-dimethylamino-phenylalanine amide (obtained from phenylalanine amide, 98% formic acid, and 37% aqueous formaldehyde solution); colorless liquid, bp: 90°C/10^{-4} Torr, yield: 2.17 g (54%).

*1-Amino-2-N-isopropylamino-3-phenylpropane **50.*** This was synthesized *via* *N*-isopropylimine-phenylalanine amide (obtained from phenyl-

alanine amide, acetone, and *p*-toluenesulfonic acid); colorless liquid, bp: 80°C / 10^{-4} Torr, yield: 2.30 g (60%).

*1-Amino-2-[*N*-1-phenylethylamino]-3-phenylpropane* **53.** This was synthesized *via* *N*-1-phenylethylimine-phenylalanine amide (obtained from phenylalanine amide, acetophenone, and *p*-toluenesulfonic acid); colorless liquid, bp: 150°C / 10^{-4} Torr, yield: 1.73 g (34%).

*1-Amino-2-*N*-benzylamino-3-phenylpropane* **54.** This was synthetized *via* *N*-benzylimine-phenylalanine amide (obtained from phenylalanine amide, benzaldehyde, and *p*-toluenesulfonic acid); colorless liquid, bp: 145°C / 10^{-4} Torr, yield: 2.12 g (44%).

*1,2-*Bis(N-*methylamino)-3-phenylpropane* **45.** This was synthesized *via* 1,2-*bis*-*N*-ethoxycarbonylamino-3-phenylpropane (obtained from benzylethylenediamine **1**, NaOH, and ethyl chloroformate); colorless liquid, bp: 85°C / 10^{-4} Torr, yield: 5.68 g (64%).

*1,2-*Bis(N-*isopropylamino)-3-phenylpropane* **51**
21.2 mmol (3.18 g) of benzylethylenediamine **1,** dissolved in 125 ml of benzene, were treated with 42.4 mmol (3.11 ml) of acetone and a catalytic amount of *p*-toluenesulfonic acid. The mixture was heated for 12 h in a Soxhlet apparatus which was equipped with $CaSO_4 \cdot 1/2\ H_2O$ as drying agent. After removal of the solvent a light yellow oil was obtained which was dissolved in 50 ml of methanol, cooled to −10°C, and treated with 80.0 mmol (3.03 g) of $NaBH_4$. The reaction mixture was refluxed for 12 h. The solvent was removed and the residue was hydrolyzed with 30 ml of water. Extraction with 150 ml of ether after drying over Na_2SO_4 and evaporation of the solvent gave a brown oil which was distilled at 100°C / 10^{-4} Torr. Colorless oil, yield: 2.23 g (48%).

Preparation of platinum complexes **1-$PtCl_2$–54-$PtCl_2$**

1.0 mmol (415 mg) of K_2PtCl_4 was dissolved in 5 ml of water and added dropwise to a solution of 1 mmol of ligand **1**–**54** in 5 ml of water, adjusted to pH 6. The solution was protected from light and heated to 50°C. The pH was kept constant by addition of 1 M NaOH. After 3–6 h the precipitated solids were filtered, washed successively with water and ethanol, and dried. The yields were almost quantitative.

Properties of platinum complexes **1-$PtCl_2$–54-$PtCl_2$**
All diamine-dichloro-platinum(II) complexes were light-yellow to yellow powders. The ν_{Pt-Cl} stretching frequency appeared at 300 cm^{-1} (br, m). ν_{Pt-N} varied from 520 to 470 cm^{-1} (w). ν_{N-H} was diminished to 3270 and 3195 cm^{-1} (s) compared to the ligand (3370 and 3290 cm^{-1} (b)) and a new band appeared at 3110 cm^{-1} (KBr).

The complexes were insoluble in water and the usual organic solvents. They were slightly soluble in diglyme, nitromethane, and acetonitrile and easily soluble in dimethylformamide, dimethylsulfoxide, monomethylformamide, and dimethylacetamide.

They had melting points between 240–270°C, however, at temperatures higher than 200–250°C, they irreversibly turned dark yellow to brown.

The CHN analyses of the 70 Pt complexes, including stereoisomers, fit the calculated values within ± 0.4%, except for 17 Pt compounds, which could not be purified due to their insolubility [4]. For the latter compounds the presence of impurities, particularly those of a polymeric nature, cannot be excluded. The organic precursors and the Pt complexes were routinely analyzed by ^1H NMR and FAB-MS spectroscopy, the spectra being in agreement with the proposed structures [4]. Details and spectral data of the parent compounds have been published in this journal [5].

Exchange of chloride for other anions

Benzylethylenediamine-diaqua-platinum(II)-dinitrate **1-$Pt(NO_3)_2$**
1.0 mmol (416.2 mg) of benzylethylenediamine-dichloro-platinum(II) **1-$PtCl_2$** was suspended in 10 ml of water with the help of ultrasound and treated with 2.0 mmol (339.7 mg) of $AgNO_3$, dissolved in 5 ml of water. The reaction mixture was stirred at 35°C excluding light. After a few hours, the initial yellow color of the dichloro complex changed to the white-grey color of the silver chloride formed. After 7 days the AgCl was filtered off. The solvent was removed from the colorless filtrate leaving a white viscous residue which solidified on addition of ether. The product was recrystallized from ethanol / water 1:1. Colorless solid, mp: 250°C, yield: 235 mg (50%).

In the same way 2-amino-1-methylamino-3-phenylpropane-diaqua-platinum(II)-dinitrate **39-$Pt(NO_3)_2$** and 4-chlorobenzylethylenediamine-diaqua-platinum(II)-dinitrate **4-$Pt(NO_3)_2$** were synthesized.

Benzylethylenediamine-4-carboxyphthalato-platinum(II) **1-$Pt(C_9H_4O_6)$**
The solution of **1-$Pt(NO_3)_2$** obtained as described above by filtering off AgCl was brought to pH 4.5 by addition of 0.5 M ammonia solution. A few minutes after addition of 1.0 mmol (210.1 mg) of 4-carboxyphthalic acid a white solid began to precipitate. The solid was filtered after 6 h, washed with cold water, and dried. Colorless solid, mp: 204°C, yield: 359.7 g (65%).

In the same way the following compounds were synthesized. Benzylethylenediamine-aqua-sulfito-platinum(II) **1-$Pt(SO_3)$**. This was synthesized from benzylethylenediamine-dichloro-platinum(II) **1-$PtCl_2$** and Na_2SO_3 [26].

2-Amino-1-methylamino-3-phenylpropane-oxalato-platinum(II) **39-$Pt(C_2O_4)$.** This was synthesized from 2-amino-1-methylamino-3-phenylpropane-dichloro-platinum(II) **39-$PtCl_2$** and oxalic acid.

4-Chlorobenzylethylenediamine-malonato-platinum(II) **4-Pt-($C_3H_2O_4$).** This was synthesized from 4-chlorobenzylethylenediamine-dichloro-platinum(II) **4-$PtCl_2$** and malonic acid.

4-Chlorobenzylethylenediamine-hydroxymalonato-platinum(II) **4-$Pt(C_3H_2O_5)$.** This was synthesized from 4-chlorobenzylethylenediamine-dichloro-platinum(II) **4-$PtCl_2$** and tartronic acid.

4-Chlorobenzylethylenediamine-aqua-sulfato-platinum(II) **4-$PtSO_4 \cdot H_2O$**
A strongly basic anion exchange resin in the OH^--form was charged with 30 ml of an aqueous solution of 1 mmol 4-chloro-benzylethylenediamine-diaqua-platinum(II)-dinitrate **4-$Pt(NO_3)_2$,** the filtrate of the $AgNO_3$-reaction (see above). 200 ml of water were allowed to pass through the column (0.5–10 cm). The eluate was collected in 1.0 mmol (103.2 mg) of 95% H_2SO_4. The viscous residue obtained by removal of the solvent was repeatedly washed with ether. Colorless crystals, mp: 205°C, yield: 380.3 mg (77%).

In the same way benzylethylenediamine-di(monothiobenzoato)-platinum(II) **1-$Pt(C_7H_5OS)_2$** from benzylethylenediamine-dichloro-platinum(II) **1-$PtCl_2$** and sodium monothiobenzoate, and benzylethylenediamine-aqua-thiosulfato-platinum(II) **1-$Pt(S_2O_3)$** from benzylethylenediamine-dichloro-platinum(II) **1-$PtCl_2$** and sodium thiosulfate were synthesized [26].

4-Chlorobenzylethylenediamine-dinitrito-platinum(II) **4-$Pt(NO_2)_2$**
The eluate, obtained in the ion exchange as described above, was collected in a solution of 2.0 mmol (138.0 mg) of $NaNO_2$ in 5 ml of water. After filtration, the filtrate was concentrated and the viscous residue was poured into 20 ml of ethanol. An insoluble red material was separated by filtration from the soluble platinum complex. After removing the ethanol, the solid was washed with ether and dried at 80°C. Colorless microcrystalline powder, yield: 330 mg (70%).

The good water solubility of the complexes, described above, disappeared when they were dried in a high vacuum, an effect, which was reported earlier [27].

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