Factor Analysis of *in Vitro* Antitumor Activities of Platinum Complexes

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Factor analysis was applied to the data matrix of *in vitro* growth inhibitory activities of 52 platinum complexes against 9 tumor cell lines, L1210, P388, Lewis lung, AH66, AH66F, HeLa S_3, KB, HT-1197 and HT-1376 cell lines. Three factors were obtained by the principal factor analysis method. After the varimax rotation of these three factors, tumor cell lines were classified into four groups according to their factor loadings. The platinum complexes were characterized by the factor scores. Cisplatin was situated in an extreme position as compared with the other platinum complexes. *In vivo* antitumor activities of the platinum complexes were tested against L1210 and LL murine tumor models. The *in vivo* activity against L1210 showed a negative correlation with that against LL. Factor 2 scores of the complexes obtained by factor analysis of *in vitro* antitumor activities showed a good correlation with these *in vivo* antitumor activities. Then, the structure-factor 2 score relationships among platinum complexes were analyzed by the Free–Wilson method. From this analysis, structure–activity relationships for carrier ligands and leaving groups are proposed. Factor analysis is suggested to be a useful method to establish an efficient screening system for platinum complexes.

Keywords Pt(II) complex; antitumor activity; factor analysis; structure–activity relationship

cis-Dichlorodiammineplatinum(II) (cisplatin) is a first-generation platinum complex that has antitumor activity against a variety of human solid tumors such as genito-urinary and gynecologic tumors as well as head, neck and lung tumors. It is currently one of the most important compounds used in the treatment of solid tumors.[1,2] However, its use is limited by severe side effects such as renal toxicity and emetic effect,[3] and some tumors exhibit natural or acquired resistance to cisplatin. Therefore, large numbers of cisplatin analogues have been tested for activity against transplanted animal tumors[4-6] and for renal toxicity to find compounds which have more favorable characteristics.

Cisplatin analogues have generally been screened using several mouse tumor lines, such as L1210 leukemia, P388 leukemia and Lewis lung carcinoma. However, the analogues that exhibited stronger antitumor activity against some tumor lines did not necessarily exhibit stronger activity against other tumor lines. Therefore, selected analogues were dependent upon the tumor lines used in the screening. It is important in analogue studies to use tumor lines which exhibit various responses to a group of compounds. Using such tumor lines, we are able to characterize analogues from a broader spectrum of activity. We present here a method of analysis in which tumor lines are characterized on the basis of their response pattern to platinum complexes and the complexes are classified on the basis of the antitumor spectrum. This method is based on factor analysis of data on the *in vitro* growth inhibitory activities of platinum complexes against 9 tumor cell lines and will be of help in establishing effective screening systems.

Experimental

Materials 1,4-Butanediamine and 2-methyl-1,4-butanediamine platinum(II) complexes were prepared as previously described.[7] Other platinum complexes were prepared as reported.[8-10] Methylene blue was purchased from Tokyo Kasei Kogyo Co., Ltd., Japan. Eagle's minimum essential medium (MEM) and fetal calf serum (FCS) were obtained from Gibco Laboratories Inc., U.S.A. RPMI 1640 medium and non-essential amino acids for MEM (NEAA) were obtained from Flow Laboratories Inc., U.S.A.

Determination of *in Vitro* Antitumor Activities of Platinum Complexes Tumor cell lines used in these experiments are catalogued in Table I. L1210, P388, AH66 and AH66F cell lines were maintained by intraperitoneal passage of ascites in mice or rats. For experiments, these cell lines were obtained from the peritoneal cavity of mice or rats on day 5 or 6 after inoculation. Other cell lines were grown continuously as monolayer cultures in Corning tissue culture flasks (25 cm^2 area) in each growth medium.

Drug treatment period was determined between 2 and 4 d according to cell doubling time, as shown in Table I. Growth inhibition in L1210, P388, Lewis lung (LL), AH66 and AH66F cell lines was estimated by cell number counting assay. Cells were cultured at an initial density of $(0.5—5) \times 10^4$ cells/ml/well in 24-well culture plates (Costar 3424). After preincubation at 37 °C for 2 h in a 5% CO_2 incubator, the drugs were added and the cultures were incubated for further 2 or 3 d. Cell numbers before and after treatment with drugs were counted by a Coulter counter, model ZBI. Growth inhibition in HeLa S_3, KB, HT-1197 and HT-1376 cell lines was estimated by dye staining assay.[11] Cells were cultured at an initial density of $(1.5—4) \times 10^3$ cells/0.2 ml/well in 96-well culture plates (Costar 3799). Following a 24-h preincubation, the drugs were added and the cultures were incubated for a further 3 or 4 d. Then, the culture medium (supernatant) was removed and 100 μl of methylene blue solution [5 g/l in ethanol–water (50%, v/v)] was added. After incubation at room temperature for 30 min, unbound dye was removed by washing with distilled water. Bound dye was solubilized by the addition of 100 μl of HCl solution (3%, v/v in water) to each well. Absorbance of wells were

TABLE I. Tumor Cell Lines Used in the Experiments

Cell line	Origin	Culture medium[a]	Period (d)[b]
L1210	Mouse leukemia	A	2
P388	Mouse leukemia	A	2
LL	Mouse lung carcinoma	B	3
AH66	Rat hepatoma	C	2
AH66F	Rat hepatoma	C	2
HeLa S_3	Human cervical carcinoma	C	3
KB	Human nasopharyngeal carcinoma	C	3
HT-1197	Human bladder carcinoma	D	4
HT-1376	Human bladder carcinoma	D	4

a) A, RPMI 1640+10% FCS+5 μM 2-ME; B, RPMI 1640+10% FCS; C, MEM+10% MEM; D, RPMI 1640+10% FCS+1% NEAA. *b*) Period of drug treatment.

measured at 660 nm with a Dynatech microplate reader MR600. The values of IC_{50}, the drug concentration at which 50% of cell growth was inhibited, were estimated from Probit plots of the data.

Determination of *in Vivo* Antitumor Activities of Platinum Complexes L1210 leukemia cells (10^5) and Lewis lung carcinoma cells (LL) (10^6) were inoculated i.p. into CDF_1 mice and BDF_1 mice, respectively, on day 0. The drug was administered i.p. once a day for 5 consecutive days from day 1. Antitumor activity was determined based on the percent increase in mean (L1210) or median (LL) survival time over controls (ILS). Since the *in vivo* antitumor activities showed considerable experimental variation, the activity of platinum complexes was compared with that of cisplatin on the basis of individual experiments involving concomitantly treated mice. The activity was expressed by the ratio of ILS of platinum complex to that of cisplatin.

Data Analysis IC_{50} values were transformed as follows. The ratios of IC_{50} values of platinum complexes to that of cisplatin (cisplatin-index) were calculated to correct the variation of IC_{50} values among individual experiments. The cisplatin-index was further transformed to log(1/cisplatin-index), since Hansch pointed out that $\log(1/LD_{50})$ or $\log(1/ED_{50})$ could be linearly related by regression analysis to various properties of the drugs.[12] Thus, we have applied factor analysis to the log(1/cisplatin-index) data to linearize the resulting functional equations. Factor analysis was carried out on the basis of the principal factor analysis method and varimax rotation method using the factor analysis program of IBC.[13] Analysis of structure–activity relationships in terms of the factor score obtained by factor analysis was carried out according to the Free–Wilson method.[14]

Results

Factor analysis was applied to the data matrix of growth-inhibitory activities of 52 platinum complexes against 9 tumor cell lines (Tables II and III). The principal factor analysis method was used for the determination of eigenvalues and eigenvectors. Three factors could be estimated, since the sum of three eigenvalues corresponded to 84% of the variance of data and the fourth eigenvalue was extremely small. Three factor loadings obtained were rotated orthogonally according to the varimax method. Figure 1 shows the plots of rotated factor loadings. Tumor cell lines are classified into four groups according to their factor loadings. The first group contains AH66F, L1210 and AH66 cell lines, which have higher factor 2 loadings and lower factor 1 and 3 loadings. The second group contains HT-1197 and LL cell lines, which have higher factor 3 loadings and relatively lower factor 1 and 2 loadings. The third group contains HeLa, P388 and KB cell lines, which have middle factor loadings. HT-1376 cell line is characterized by the highest factor 1 loading. By this analysis, tumor cell lines could be classified according to the response pattern to platinum complexes.

Factor scores of platinum complexes were estimated for the three factors and are plotted in Fig. 2. The platinum complexes were characterized by these scores, which revealed the spectrum of *in vitro* growth inhibitory activities. Namely, the spectrum of activities against 9 tumor cell lines could be expressed by three scores. By comparing the plots of factor scores with those of factor loadings, it is suggested that the higher the factor 1 score of platinum complexes, the stronger the activity against HT-1376 cell line, and the

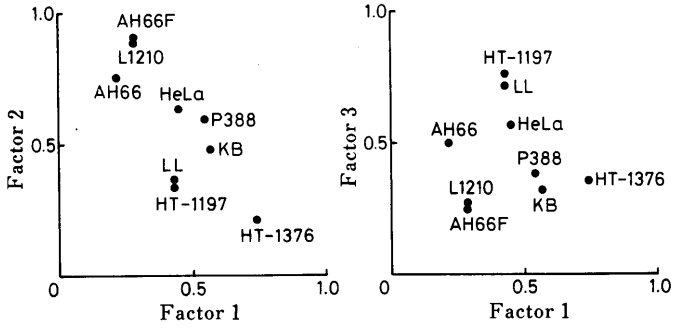
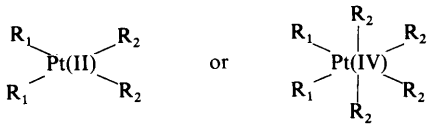


Fig. 1. Plots of the Rotated Factor Loadings

TABLE II. Structures of Platinum Complexes



Compound number	R_1: Carrier ligand	R_2: Leaving group	Pt
1[a]	Diamine	Dichloro	II
2	Diamine	Cyclobutane-1,1-dicarboxylato	II
3	(*R,R*)-1,2-Cyclohexanediamine	Oxalato	II
4	1,2-Cyclohexanediamine[b]	Carboxyphthalato	II
5	Diamine	2-Methylmalonato	II
6	Bis(isopropylamine)	Dihydroxydichloro	IV
7	1,1-Dimethylethylenediamine	Dichloro	II
8	1,1-Dimethylethylenediamine	Tetrachloro	IV
9	1,1-Diethylethylenediamine	Dichloro	II
10	1-(Aminomethyl)cyclohexylamine	Tetrachloro	IV
11	1-(Aminomethyl)cyclohexylamine	Di(chloroacetato)	II
12	1,1-Diethylethylenediamine	2-Ethylmalonato	II
13	2-Methyl-1,4-butanediamine	Cyclobutane-1,1-dicarboxylato	II
14	*N*-Cyclopentylethylenediamine	Sulfato	II
15	*N*-Cyclopentylethylenediamine	Dichloro	II
16	1-(Aminomethyl)cyclopentylamine	Tetrachloro	IV
17	1-(Aminomethyl)cyclopentylamine	Dihydroxydichloro	IV
18	1-(Aminomethyl)cyclopentylamine	Oxalato	II
19	1,1-Diethylethylenediamine	Dihydroxydichloro	IV
20	1-Methyl-1-ethylethylenediamine	Dichloro	II
21	1-(Aminomethyl)cyclohexylamine	Oxalato	II
22	*N,N*-Dimethylethylenediamine	Oxalato	II
23	1-(Aminomethyl)cyclohexylamine	Dihydroxydichloro	II
24	1-(Aminomethyl)cyclopentylamine	Dichloro	II
25	3,4-Diaminotetrahydropyran	Dichloro	II
26	1,1-Diethylethylenediamine	Tetrachloro	IV
27	1,2-Cyclohexanediamine	Cyclobutane-1,1-dicarboxylato	II
28	1,4-Butanediamine	Dichloro	II
29	1,3-Cyclohexanediamine	Dichloro	II
30	1-(Aminomethyl)cyclohexylamine	Sulfato	II
31	1,1-Diethylethylenediamine	Oxalato	II
32	1,1-Dimethylethylenediamine	1-Acetylaminopropane-1,3-dicarboxylato	II
33	1,2-Cyclohexanediamine	Selenato	II
34	1-(Aminomethyl)cyclohexylamine	Cyclobutane-1,1-dicarboxylato	II
35	1,1-Dimethylethylenediamine	Malonato	II
36	1,2-Cyclohexanediamine	1-Acetylaminopropane-1,3-dicarboxylato	II
37	1-(Aminomethyl)cyclopentylamine	Cyclobutane-1,1-dicarboxylato	II
38	1,1-Diethylethylenediamine	Sulfato	II
39	4,4-Bis(aminomethyl)tetrahydropyran	Dichloro	II
40	1-(Aminomethyl)cyclohexylamine	Malonato	II
41	3,4-Diaminotetrahydropyran	Oxalato	II
42	1,3-Propanediamine	Tetrahydropyran-1,1-dicarboxylato	II
43	1-Methylethylenediamine	Dichloro	II
44	1-Methylethylenediamine	Tetrachloro	IV
45	1,1-Dimethylethylenediamine	Cyclobutane-1,1-dicarboxylato	II
46	*N*-Methylethylenediamine	Tetrahydropyran-1,1-dicarboxylato	II
47	*N,N*-Dimethylethylenediamine	Dichloro	II
48	*N,N*-Dimethylethylenediamine	Dinitrato	II
49	*N,N*-Dimethylethylenediamine	Sulfato	II
50	*N,N*-Dimethylethylenediamine	Malonato	II
51	1,4-Butanediamine	Tetrahydropyran-1,1-dicarboxylato	II
52	2-Hydroxypropane-1,3-diamine	Tetrachloro	IV

a) Cisplatin. *b*) Mixture of isomers.

TABLE III. *In Vitro* and *in Vivo* Antitumor Activities of Platinum Complexes

Compound number	*In vitro* antitumor activity (cisplatin-index)									*In vivo*[a]	
	L1210	P388	LL	AH66	AH66F	HeLa	KB	HT-1197	HT-1376	L1210	LL
1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	11.87	18.65	12.48	8.91	17.74	15.25	15.51	11.56	6.45	0.48	0.81
3	0.14	1.98	3.52	0.20	0.19	0.55	3.14	1.36	1.83	2.38	0.15
4	0.16	1.65	2.65	0.16	0.19	0.67	2.51	1.44	2.20	1.58	0.54
5	5.43	10.74	13.26	11.48	10.26	8.48	9.62	12.50	4.43	0.61	1.00
6	5.42	7.55	26.81	11.99	3.45	10.73	11.45	11.00	13.71	0.63	0.39
7	1.17	5.12	3.69	6.24	1.63	8.04	3.39	6.23	4.61	1.03	0.50
8	1.11	4.25	10.56	5.71	1.87	5.40	3.63	7.87	5.56	0.60	0.35
9	0.29	4.23	6.58	2.89	0.67	3.95	3.64	6.94	5.43	1.85	0.25
10	0.11	2.02	4.34	1.01	0.11	1.43	0.97	4.17	2.22	1.54	0.28
11	0.07	1.60	2.51	0.20	0.07	0.94	2.15	1.89	2.09	1.93	0.34
12	2.23	13.20	10.30	3.96	2.82	10.56	15.78	15.54	14.71	1.02	0.35
13	4.39	6.99	6.89	6.76	3.89	7.71	11.21	10.87	11.62	0.53	1.27
14	3.91	9.78	24.76	7.41	1.91	9.31	14.16	20.59	9.84	0.58	0.35
15	3.12	10.11	18.32	5.44	2.72	10.95	11.58	19.31	11.85	0.62	0.37
16	0.23	3.37	4.81	0.88	0.19	2.06	0.92	8.04	5.48	2.72	0.15
17	5.86	10.43	29.64	11.25	2.28	18.18	11.82	36.23	13.85	1.64	0.57
18	0.39	5.65	7.92	1.53	0.76	4.96	4.78	8.91	8.58	0.86	n.t.
19	5.51	11.54	12.68	4.04	2.97	12.51	16.75	11.51	13.46	n.t.	0.61
20	0.54	2.82	4.88	1.25	0.75	3.25	4.63	8.28	10.10	n.t.	0.29
21	0.20	2.94	7.96	2.17	0.33	2.76	2.75	11.28	8.47	n.t.	n.t.
22	3.44	17.42	15.61	4.10	13.03	8.35	1.24	10.43	24.19	1.12	1.05
23	2.52	7.57	21.62	4.57	1.59	9.66	6.67	10.05	9.92	1.70	0.30
24	0.20	3.53	7.66	0.76	0.36	3.12	3.21	10.31	12.57	1.79	0.37
25	3.01	8.47	8.62	3.90	5.60	6.27	14.12	8.87	23.37	n.t.	0.63
26	0.42	2.05	3.41	0.68	0.67	3.75	4.25	5.60	13.03	1.68	0.35
27	0.76	8.25	2.32	1.75	1.39	1.26	10.69	1.45	11.18	2.31	0.40
28	0.55	2.15	2.10	1.19	0.86	1.99	1.53	2.00	2.16	0.79	0.38
29	0.57	1.46	1.16	0.77	0.55	2.26	1.83	3.29	5.20	1.30	0.51
30	0.10	2.34	4.54	1.69	0.16	1.06	11.54	3.51	3.27	n.t.	n.t.
31	0.47	5.50	12.30	6.77	1.31	4.78	4.98	6.56	12.86	1.19	n.t.
32	3.18	8.31	12.06	12.07	4.28	11.94	9.92	15.75	4.55	0.70	n.t.
33	0.16	1.26	2.41	0.43	0.19	0.56	1.45	0.68	2.93	2.14	n.t.
34	0.81	5.39	11.95	1.41	1.23	8.29	9.92	17.95	22.48	n.t.	n.t.
35	2.31	6.52	7.70	9.41	3.76	9.77	7.44	14.06	13.86	n.t.	n.t.
36	0.43	9.83	2.30	0.37	0.29	1.66	6.27	1.81	11.98	1.81	0.49
37	1.29	5.68	8.09	5.11	3.02	17.13	26.28	16.77	27.60	2.50	0.56
38	0.32	3.63	4.36	2.53	0.58	2.63	3.11	4.15	7.09	1.50	n.t.
39	1.20	4.26	6.10	4.08	1.00	8.87	5.82	4.12	13.04	n.t.	n.t.
40	0.27	1.65	5.09	0.49	0.18	2.30	3.39	3.97	8.22	n.t.	n.t.
41	3.30	10.23	10.63	14.02	3.43	11.49	15.90	9.57	18.80	n.t.	n.t.
42	5.63	5.73	7.87	3.39	6.20	8.97	8.76	4.76	8.26	0.36	0.63
43	6.12	7.72	5.12	4.53	5.15	7.88	5.66	6.12	6.01	0.30	0.81
44	2.57	3.58	4.90	5.64	1.57	7.61	5.31	6.37	8.86	0.30	n.t.
45	6.76	17.41	11.17	17.05	8.56	14.08	22.41	13.86	16.70	n.t.	0.49
46	11.76	13.40	17.98	15.82	18.01	11.24	16.61	12.24	9.39	0.29	0.20
47	5.14	10.36	12.11	13.01	11.01	14.71	11.00	13.16	12.03	0.42	n.t.
48	6.39	9.46	12.35	10.77	11.75	10.47	8.91	8.82	5.96	0.36	n.t.
49	5.75	8.30	11.17	18.10	12.25	12.26	9.69	9.52	5.60	0.38	n.t.
50	10.89	16.62	21.77	18.75	20.38	28.21	21.78	19.46	17.48	0.42	n.t.
51	0.93	3.15	3.05	2.60	1.63	2.58	2.63	3.29	4.03	0.36	0.35
52	2.96	3.03	4.28	4.58	3.56	12.02	9.47	7.69	7.51	0.23	0.56

a) Ratio of ILS of platinum complex to ILS of cisplatin.

higher the factor 2 score, the stronger the activity against AH66F, L1210 and AH66 cell lines. Cisplatin (**1**) is situated in an extreme position as compared with the other platinum complexes, and has the highest score of factor 1 and a high score of factor 3.

We investigated whether *in vivo* antitumor activities are predictable from *in vitro* antitumor activities. *In vivo* antitumor activities of platinum complexes against L1210 and LL tumors were graded according to ILS values. In Fig. 3A and B, *in vivo* antitumor activities of platinum complexes are superimposed on the plot of factor 1 *vs.* factor 2 obtained from *in vitro* antitumor activities. These figures show that *in vivo* antitumor activities against L1210 and LL have good positive and negative correlations, respectively, with factor 2. It should be noted that the platinum complexes having higher activity against L1210 exhibit less activity against LL and *vice versa*.

Since factor 2 scores correlated with *in vivo* antitumor activities and are considered to be quantitative values of *in vivo* antitumor activities, we investigated the structure–factor 2 relationships instead of the structure–activity relationships, using the Free–Wilson method. In general, the

platinum complexes which have antitumor activity consist of Pt and two substituted groups, a carrier ligand and a leaving group. This method assumes that some of the activity of complexes is due to the sum of contributions of the substituent groups. Table IV shows the contribution of each substituent group obtained by the analysis.

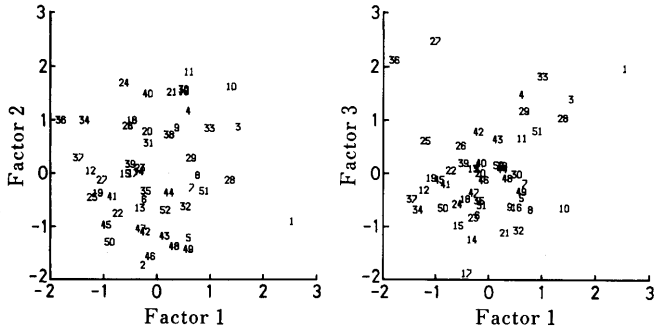


Fig. 2. Plots of the Factor Scores

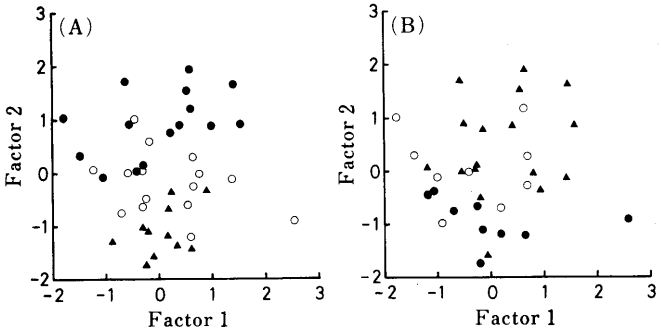


Fig. 3. *In Vivo* Antitumor Activities of Platinum Complexes against L1210 (A) and LL (B)

●, high activity; ○, moderate activity; ▲, low activity.

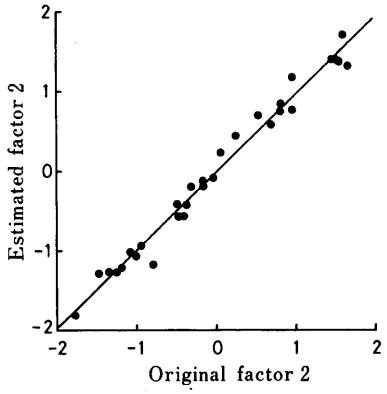


Fig. 4. The Correlation between Original Factor 2 Scores and Those Estimated by the Free–Wilson Method

The correlation coefficient between estimated and original factor 2 scores was 0.990, suggesting that this analysis is valid and the carrier ligand and leaving group contributed independently to the activity of each compound (Fig. 4). The range of contribution of the carrier ligand (-0.09 to 2.57) is more than that of the leaving group (-1.41 to 0.06). This indicates that the carrier ligand influences the activity of platinum complex more strongly than the leaving group. Since factor 2 was correlated with *in vivo* antitumor activity, it was suggested that the higher the contribution of substituent groups, the higher activity against L1210 leukemia the complex exhibited, and the lower the contribution of substituent groups, the higher activity against LL carcinoma the complex exhibited.

Discussion

It is the first step in an analogue study to establish an efficient screening system. In most cisplatin analogue studies reported so far, *in vivo* antitumor activities have been used to select analogues superior to cisplatin.[4,5] Several analogues have been found to have greater antitumor activity than cisplatin when evaluated against L1210 leukemia. Among them, analogues of 1,2-cyclohexanediamine platinum have been reported to show much greater activity against L1210 leukemia, and no-cross resistance to L1210 leukemia resistant to cisplatin.[4,5,15,16] In the factor analysis, L1210 cell line was clarified to have a biased character among 9 tumor cell lines.

A group of analogues containing a cyclohexane or cyclopentane structure, such as 1,2-cyclohexanediamine platinum, have higher factor 2 scores in contrast to cisplatin with a lower factor 2 score, and exhibit greater *in vivo* antitumor activity against L1210 leukemia than cisplatin. On the other hand, cisplatin exhibits greater *in vivo* antitumor activity against LL. The difference of antitumor activity between them should be due to the difference of factor 2. Thus, it is suggested that screening using only one tumor line or similar tumor lines, such as L1210 and AH66F, is not adequate for the screening of platinum complexes. We demonstrated in this study that factor analysis could provide a criterion to select tumor cell lines for the screening of platinum complexes, and the complexes were classified quantitatively according to the pattern of antitumor activity. In addition, *in vivo* antitumor activities were predictable from the combination of *in vitro* antitumor activities. Since *in vivo* antitumor activities are determined by the balance between the activity against tumor cells and the toxicity against host animals, it is

TABLE IV. Contributions of Carrier Ligands and Leaving Groups to Factor 2 Scores

Carrier ligand	Contribution	Leaving group	Contribution
1-(Aminomethyl)cyclohexylamine	2.5694	Tetrachloro	0.0599
1-(Aminomethyl)cyclopentylamine	2.2497	Dichloro	0.0
1,1-Diethylethylenediamine	1.7729	Oxalato	−0.1479
1,2-Cyclohexanediamine	1.6738	Malonato	−0.2581
1,4-Butanediamine	0.7494	Sulfato	−0.2438
1,1-Dimethylethylenediamine	0.7370	2-Methylmalonato	−0.3393
3,4-Diaminotetrahydropyran	0.5084	Cyclobutane-1,1-dicarboxylato	−0.8787
Diamine	0.0	Dihydroxydichloro	−1.4111
N,N-dimethylethylenediamine	−0.0895		

conceivable that *in vitro* tumor cell lines contain factors which influence not only *in vivo* antitumor activities, but also *in vivo* toxicity. This indicates that the combination of *in vitro* antitumor activities is useful for the first screening of platinum complexes. Thus, factor analysis makes it possible to select proper tumor cell lines and to use *in vitro* antitumor activity as the first screening.

The structure–activity relationships estimated by the Free–Wilson method clarified the effects of carrier ligands and leaving groups on *in vivo* antitumor activity. The contribution of the carrier ligand may be related to the number of carbons or the hydrophobicity, and that of the leaving group may be related to the dissociation rate from Pt, although there are some exceptions.[17] It is conceivable that the analysis of factor 2 will lead us the discovery of a highly effective platinum complex.

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