Chem. Pharm. Bull. 37(9) 2406—2409 (1989) Vol. 37, No. 9

Synthesis and Antitumor Activities of Alkyl-1,4-butanediamine Pt(II) Complexes Having Seven-Membered Ring Structure

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Novel alkyl-1,4-butanediamine Pt(II) complexes having a seven-membered ring structure were synthesized and characterized by fast atom bombardment mass and infrared spectra and elemental analysis. Their antitumor activities *in vivo* toward lymphoid leukemia L1210 and Lewis lung carcinoma LL were studied in the case where the leaving group was either dichloride or cyclobutane-1,1-dicarboxylate. 1,4-Butanediamine Pt(II) complexes (seven-membered ring) showed higher antitumor activities than those of ethylenediamine Pt(II) (five-membered ring) and 1,3-propanediamine Pt(II) (six-membered ring) complexes toward L1210 for both leaving groups. Alkyl-1,4-butanediamine Pt(II) complexes showed high antitumor activities toward L1210, except for 1,1-dimethyl-1,4-butanediamine Pt(II) complexes. In particular, 2,2-dimethyl-1,4-butanediamine and 2,3-dimethyl-1,4-butanediamine Pt(II) complexes exhibited excellent antitumor activities with *T/C* % values higher than 300. None of the dichloro Pt(II) complexes showed antitumor activities toward LL, but the cyclobutane-1,1-dicarboxylato Pt(II) complexes, which were moderately active toward L1210 with *T/C* % values around 200, also showed high antitumor activities toward LL with *T/C* % values of more than 200. Alkyl-1,4-butanediamine Pt(II) complexes with a seven-membered ring structure were found to be stable and to have antitumor activities *in vivo*.

Keywords alkyl-1,4-butanediamine; platinum(II) complex; seven-membered ring structure; antitumor activity; structure–activity relationship

cis-Diamminedichloroplatinum(II) (CDDP) which is effective in the treatment of human tumor also cause severe renal toxicity, nausea and vomiting.[1] Therefore, a number of Pt(II) complexes, such as diammine-cyclobutane-1,1-dicarboxylato Pt(II), [(1*R*,2*R*)-1,2-cyclohexanediamine]-oxalato Pt(II),[2] and others[3] have been prepared in attempts to find platinum complexes with lower toxicity. In general, platinum complexes possessing antitumor activity consist of a carrier ligand (which is neutral), a leaving group (which is negatively charged) and a Pt atom. Many kinds of diamine other than ammonia molecules have been used as a carrier ligand, but few platinum complexes having a linear alkyl diamine have been reported, compared to those having a five-membered ring or six-membered ring structure. Antitumor activities of platinum complexes having a seven-membered ring structure have not been reported, because of difficulties in synthesis. The chelate effect, where the structure of the diamine complexes is stabilized owing to ring formation, is well known. However, it is considered that in the case of a seven-membered ring structure, the chelate effect is weaker than in the case of a five- or six-membered ring structure. This seems to be the reason why reports are scarce on the synthesis of seven-membered ring complexes in which diamine coordinates to a platinum atom with both N atoms. We now report a new class of Pt(II) complexes of 1,4-butanediamine or its derivatives in which the diamine is bound to platinum ion as a bidentate ligand forming a seven-membered ring structure. In this paper, the synthesis and the antitumor activities of alkyl-1,4-butanediamine Pt(II) complexes are described in comparison with those of ethylenediamine Pt(II) or 1,3-propanediamine Pt(II) complexes.

Experimental

Materials Ethylenediamine and 1,4-butanediamine were purchased from Tokyo Kasei Co., and purified by distillation. The other chemicals were obtained from Kojima Chemical Co., Wako Junyaku Co., and Tokyo Kasei Co., and were used without purification.

Analyses Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-GX270 (270 MHz) and mass spectra (MS) were recorded on a JEOL JMS-D300. For the measurement of fast atom bombardment mass spectra (FAB-MS), glycerol was used as a matrix substance. Infrared (IR) spectra were recorded on a JASCO IR-810 (Nujol or KBr). Elemental analyses were performed by a Yanagimoto MT-3. Scanning electron microscopy and electron probe micro analyses (EPMA) were performed with JEOL JSM-840 and LINS SYSTEM 860 instruments. The content of platinum in the complexes was determined with a Hitachi L-6000 high performance liquid chromatogrphy (HPLC) system, according to the method of Ebina *et al.*[4] Purity of the Pt(II) complexes was determined with a HPLC. Nucleosil $5C_8$ was used in the case of dicarboxylatodiamine complexes (mobile phase: 1% KH_2PO_4/methanol = 1/5), and Shodex AD803/S and AD802/S were used in the case of diiododiamine complexes and dichlorodiamine complexes (mobile phase: *N*,*N*-dimethylformamide).

Preparation of Carrier Ligands 1-Methyl-1,4-butanediamine was prepared from 2-methyladipic acid by means of the Schmidt reaction.[5] 2-Methyl-1,4-butanediamine, 1,1-dimethyl-1,4-butanediamine, 2,2-dimethyl-1,4-butanediamine and 1-ethyl-1,4-butanediamine were prepared from the corresponding dicarboxylic acids in a similar manner. 2-Ethyl-1,4-butanediamine and 2,3-dimethyl-1,4-butanediamine were prepared by hydrogenation in liquid ammonia over Raney cobalt from 2-ethylsuccinonitrile and 2,3-dimethylsuccinonitrile, respectively.[6]

1-Methyl-, 2-methyl- and 2-ethyl-1,4-butanediamine were racemic, and were used without resolution. 2,3-Dimethyl-1,4-butanediamine was the mixture of isomers (*meso*-, (*R*,*R*)- and (*S*,*S*)-form) and was used without separation.

These carrier ligands were characterized by MS and NMR(^{13}C and ^{1}H) analyses.

Preparation of Pt(II) Complexes Ethylenediamine Pt(II) complexes and 1,3-propanediamine Pt(II) complexes were prepared by the usual method.[7] Alkyl-1,4-butanediamine Pt(II) complexes were prepared by utilizing a modified reaction method, as shown in Chart 1. All reactions were carried out in water and diamines were treated under nitrogen.

Aqueous solutions of potassium tetrachloroplatinate and potassium iodide were mixed to obtain a solution of potassium tetraiodoplatinate (**1**). This solution and a solution of a diamine were added simultaneously and at constant rates to water. The reaction was conducted at low concentration with the reactant solutions added slowly over more than 1 h to reduce the formation of by-products. The resulting crude diiododiamine Pt(II) was purified by reacting it with silver nitrate to convert it into the diaquadiamine Pt(II) (**4**), and then allowed to react with potassium iodide

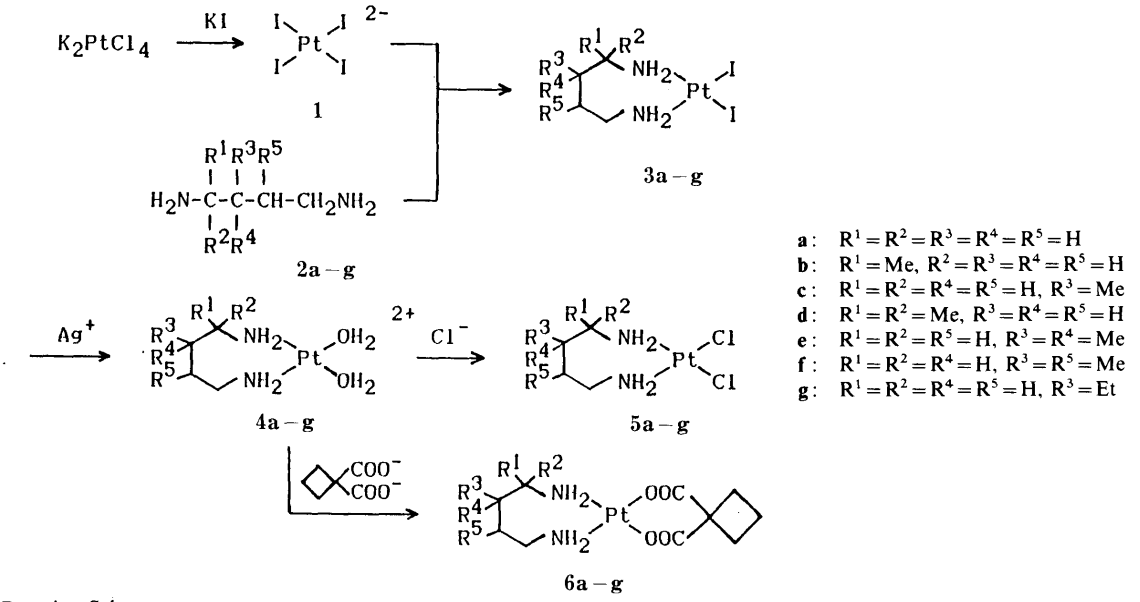

Chart 1. Reaction Scheme

TABLE I. Dichloro and Cyclobutane-1,1-dicarboxylato Diamine Pt(II) Complexes

Compd. No.	Carrier ligand	Leaving group	FAB[a] MS *m/z*	Yield[b] (%)	Elemental analysis (%) Calcd C	H	N	Pt	Found C	H	N	Pt
5a	bn	Cl_2	353	76.6	13.57	3.42	7.91	55.1	13.44	3.56	8.04	54.8
5b	1-Methyl-bn	Cl_2	367	52.5	16.31	3.83	7.61	53.0	16.57	3.98	7.81	53.0
5c	2-Methyl-bn	Cl_2	367	47.9	16.31	3.83	7.61	53.0	16.15	3.70	7.44	53.1
5d	1,1-Dimethyl-bn	Cl_2	381	60.2	18.86	4.22	7.33	51.0	18.77	4.33	7.58	50.7
5e	2,2-Dimethyl-bn	Cl_2	381	75.8	18.86	4.22	7.33	51.0	19.12	4.03	7.01	50.8
5f	2,3-Dimethyl-bn	Cl_2	381	73.2	18.86	4.22	7.33	51.0	18.63	4.39	7.18	50.6
5g	2-Ethyl-1,4-bn	Cl_2	381	82.0	18.86	4.22	7.33	51.0	19.00	4.35	7.16	51.0
6a	bn	cbdca	425	60.0	28.24	4.27	6.59	45.9	28.56	4.41	6.48	45.2
6b	1-Methyl-bn	cbdca	439	51.5	30.07	4.59	6.38	44.4	29.88	4.44	6.53	44.1
6c	2-Methyl-bn	cbdca	439	83.2	30.07	4.59	6.38	44.4	30.20	4.31	6.15	44.5
6d	1,1-Dimethyl-bn	cbdca	453	86.3	31.79	4.89	6.18	43.0	32.02	5.11	6.01	44.2
6e	2,2-Dimethyl-bn	cbdca	453	79.4	31.79	4.89	6.18	43.0	31.81	5.01	6.36	43.2
6f	2,3-Dimethyl-bn	cbdca	453	53.0	31.79	4.89	6.18	43.0	32.01	4.67	6.34	44.0
6g	2-Ethyl-bn	cbdca	453	77.9	31.79	4.89	6.18	43.0	31.51	4.67	6.22	42.1

bn = 1,4-butanediamine. cbdca = cyclobutane-1,1-dicarboxylato ion. *a*) Protonated molecular ion peaks of all complexes, $(M+H)^+$, were observed by means of FAB-MS. All masses are referenced to the isotopes ^{194}Pt and ^{35}Cl. *b*) The isolated yields were calculated based on the diiodo-diamine Pt(II), **3**.

to obtain pure diiododiamine Pt(II). According to this scheme, various kinds of *cis*-diiodo-alkyl-1,4-butanediamine Pt(II) were obtained in yields higher than 70%. The purified diiododiamine Pt(II) complex (**3**) was converted into dichlorodiamine Pt(II) (**5**) or dicarboxylatodiamine Pt(II) (**6**) in the usual way.[7a,8] Typical examples of the synthesis of 2-methyl-1,4-butanediamine Pt(II) complexes are presented below.

Synthesis of *cis*-Diiodo(2-methyl-1,4-butanediamine)platinum(II) (3c) A solution of 24 g (145 mmol) of potassium iodide in 50 ml of H_2O was added to 10 g (24 mmol) of potassium tetrachloroplatinate(II) dissolved in 350 ml of H_2O, with stirring. Stirring was continued for 10 min at 40 °C to obtain a black solution of potassium tetraiodoplatinate(II), and this solution was stored at 0 °C [solution A]. Separately, 2.46 g (24 mmol) of 2-methyl-1,4-butanediamine was dissolved in 400 ml of H_2O [solution B]. Next, 250 ml of water was placed in a flask and stirred at 60 °C under nitrogen, and into this, solution A and solution B were simultaneously added dropwise over 2 h at a constant rate. The resulting reddish-brown crystals were collected by filtration and washed with water, ethanol and ether. The crystals were then dried to obtain 12.62 g of crude *cis*-diiododiamine complex. For purification, 10 g of these crystals was suspended in 200 ml of H_2O, to which a solution of 6.04 g of silver nitrate in 100 ml of H_2O was added. After stirring for 20 min at 60 °C, the mixture was cooled and the silver iodide was filtered off to obtain a solution of the diaqua complex, **4c**. To this, a solution of 18.07 g of potassium iodide in 50 ml of H_2O was added. The resulting yellow crystals were filtered off and washed with water, ethanol and ether, and then dried under vacuum of obtain 8.32 g of pure *cis*-diiodo (2-methyl-1,4-butanediamine)platinum (II) (**3c**) (yield 79.3%).

Synthesis of *cis*-Dichloro(2-methyl-1,4-butanediamine)platinum(II) (5c) **3c** (1 g, 1.81 mmol) was suspended in 20 ml of H_2O and a solution of 0.604 g (3.56 mmol) of silver nitrate in 10 ml of H_2O was added. By the same procedure as above, a solution of **4c** was obtained, and into this solution was added a solution of 0.636 g (10.9 mmol) of sodium chloride in 5 ml of H_2O, with stirring at 40 °C. The resulting yellow crystals were filtered off, washed with water and ethanol, and then dried to give 0.320 g of *cis*-dichloro (2-methyl-1,4-butanediamine)platinum(II) (**5c**).

Synthesis of *cis*-Cyclobutane-1,1-dicarboxylato(2-methyl-1,4-butanediamine)platinum(II) (6c) **3c** (1 g, 1.81 mmol) was used and a solution of **4c** was obtained by the same procedure as above. Into this solution was added a solution of 0.523 g (3.62 mmol) of cyclobutane-1,1-dicarboxylic acid dissolved in 7.29 ml of 1 N NaOH. The mixed solution was stirred at 50 °C for 2 h. The solution was concentrated to 5 ml and then cooled to 0 °C. The resulting white crystals were filtered off and washed with a small amount of chilled water and ethanol, and then dried to obtain 0.663 g of *cis*-cyclobutane-1,1-dicarboxylato(2-methyl-1,4-butanediamine)platinum(II) (**6c**).

The yield of the complexes and the results of elemental analyses are listed in Table I.

All of the dichloride complexes, **5a**—**g**, have a solubility higher than 2 mg/ml in physiological saline solution at 25 °C (**5c**; 5.2 mg/ml), and these

dichloride complexes were readily soluble in dimethylsulfoxide. The dicarboxylate complexes, **6a**—**g**, have a solubility higher than 4 mg/ml in H_2O at 25 °C (**6c**; 7.2 mg/ml).

All of the complexes were very stable in air at room temperature: no change was observed in any of the complexes by HPLC analysis after standing for one year.

The binuclear complex, [LPt(diamine)$_2$PtL] and the ion-pair complex, [Pt(diamine)$_2$][PtL$_2$] (L = leaving group), which gave the same calculated values of elemental analysis as those listed in Table I, were liable to be formed as well. However, peaks due to these by-products were not observed by FAB-MS analysis. A typical FAB-MS of *cis*-cyclobutane-1,1-dicarboxylato-2-methyl-1,4-butanediamine Pt(II) is shown in Fig. 1.

Growth-Inhibitory Effect against Murine Lymphoid Leukemia L1210 Cells Murine lymphoid leukemia L1210 cells were treated with various concentrations of complexes in RPMI 1640 medium supplemented with 10% fetal calf serum, and cultured for 2 d in a 5% CO_2 humidified incubator at 37 °C. Growth inhibitory activities of the test complexes were measured in term of the ratio of cell numbers in treated and control groups. The IC_{50} values (the concentrations in μg/ml required for 50% inhibition of growth) were calculated from log-probability graphs. The IC_{50} value of CDDP was 0.12 μg/ml in this test.

Antitumor Activities *in Vivo* Antitumor activities of the synthesized Pt(II) complexes were evaluated in terms of the life span prolongation of tumor-bearing mice.

Antitumor Activity toward Murine Lymphoid Leukemia L1210 in Mice Six-week-old female DBA/2 mice were intraperitoneally inoculated with 1×10^5 L1210 cells and after 5 d the ascites were collected from these mice. The cells were suspended in Hank's balanced salt solution (HBSS) ant the number was counted with a Coulter counter. The cell suspension was adjusted with HBSS to the concentration of 5×10^5 cells/ml, the 0.2 ml of the suspension was intraperitoneally injected into six-week-old female CDF_1 mice on day 0. These mice were divided into groups of 5 mice into which the Pt(II) complexes were intraperitoneally injected once a day for 5 consecutive days from day 1. The complexes were dissolved in the solvents (saline for dichlorodiamine Pt(II) complexes and 5% glucose solution for dicarboxylatodiamine Pt(II) complexes). Mice in the control group were injected with solvent only in the same manner. The mice were observed for 30 d and antitumor activities were evaluated in terms of the $T/C\%$ values calculated from the mean survival time (t) of the drug-treated group and that (c) of the control group [$T/C\% = (t/c) \times 100$]. Mean survival times of the control group ranged from 6.8 to 8.3 d.

Antitumor Activity toward Lewis Lung Carcinoma LL in Mice Six-week-old male C57BL/6 mice were inoculated with 5×10^5 Lewis lung carcinoma (LL) cells in the muscles of the rear limbs and after 10 d the tumor was obtained surgically, finely chopped with scissors and suspended in HBSS. Viable cells were counted by use of the trypan blue dye exclusion test. The viable cell suspension was adjusted with HBSS to the concentration of 5×10^6 cells/ml. Then 0.2 ml of this suspension was intraperitoneally injected into six-week-old male BDF_1 mice on day 0. These mice were divided into groups consisting of 5 mice. The complexes were administered in the same manner as in the case of the L1210 system. The observation period was 30 d and antitumor activities were evaluated in terms of $T/C\%$ values calculated from the median survival time (t) of the drug-treated group and that (c) of the control group. Median survival times of the control group ranged from 12.5 to 16.3 d.

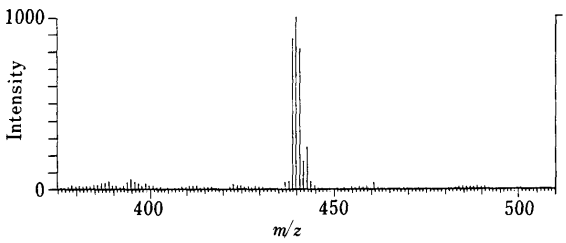

Fig. 1. FAB-MS of *cis*-Cyclobutane-1,1-dicarboxylato-2-methyl-1,4-butanediamine Pt(II) Complex

Results and Discussion

Cytotoxicities and antitumor activities toward L1210 cells of Pt(II) complexes having various ring structures were tested, and the results are shown in Table II.

The order of IC_{50} values of the complexes having five-, six- and seven-membered ring structures (which are abbreviated as 5-R, 6-R and 7-R, respectively), was 6-R > 5-R > 7-R with both types of leaving group. Among these complexes, 7-R had the highest cytotoxic activity. Additionally, seven-membered ring complexes exhibited high activity with $T/C\%$ values of more than 200, while the others exhibited lower activity with $T/C\%$ values of less than 144. The order of activity of these complexes was 7-R ≫ 6-R > 5-R with both types of leaving group. Though 6-R exhibited lower cytotoxic acitivities than 5-R, they exhibited slightly higher antitumor activities than those of 5-R. Morikawa *et al.*[9] reported that five-membered ring complexes exhibited higher activity than six-membered ring complexes toward P388 cells in the case of 2-aminoalkylpyridine Pt(II) complexes. In general, the steric hindrance effect is moderately high when the carrier ligand contains bulky groups, such pyridine. This might be why the more distorted 6-R were less active than 5-R in the case of the 2-aminoalkylpyridine Pt(II) complexes. In contrast, the results in this study showed that the steric effect was not so large as to reduce the antitumor activities of our complexes, since the most distorted 7-R exhibited the highest cytotoxicities and antitumor activities (Table II). As mentioned below, 1,1-dimethyl-1,4-butanediamine Pt(II) complexes were less active than the other 7-R. In the case of a carrier ligand where two alkyl groups are bonded to the carbon atom adjacent to NH_2, it seems that the antitumor activities were reduced by steric effects. The 7-R are not so stabilized by the chelate effect as 5-R or 6-R, and therefore it is possible that 7-R exhibit activities by different mechanisms from tose of 5-R or 6-R.

Antitumor activies of various alkyl-1,4-butanediamine Pt(II) complexes were tested toward L1210 and LL cells in

Table II. Cytotoxicity and Antitumor Activity of Diamine Pt(II) Complexes Having Various Ring Structures on L1210 Cells

Carrier ligand	Ring[a] structure	Leaving group	IC_{50} (μg/ml)	T/C (%) Dose (mg/kg) 64	32	16	8	4	2	1	0.5
en	5	Cl_2	0.51				113	136	128	126	118
pn	6	Cl_2	0.88				85	118	141	115	
bn	7	Cl_2	0.21				62	79	210	144	159
en	5	cbdca	2.27	79	97	126	121	110			
pn	6	cbdca	2.95	77	90	144	121	113			
bn	7	cbdca	1.55	115	231	146	126	115			

en = ethylenediamine. pn = 1,3-propanediamine. bn = 1,4-butanediamine. cbdca = cyclobutane-1,1-dicarboxylato ion. *a*) Each numeral in this column represents the number of atoms forming the ring structure resulting from the coordination of a diamine to the Pt atom.

TABLE III. Antitumor Activity of Alkyl-1,4-butanediamine Pt(II) Complexes toward L1210 Cells in Mice

Compd. No.	Carrier ligand	Leaving group	T/C (%) Dose (mg/kg) 128	64	32	16	8	4	2	1	0.5
5a	bn	Cl_2					62	79	210	144	159
5b	1-Methyl-bn	Cl_2						98	225	145	
5c	2-Methyl-bn	Cl_2			87	161	187	145	134		
5d	1,1-Dimethyl-bn	Cl_2			86	119	150	136	131		
5e	2,2-Dimethyl-bn	Cl_2			82	359	224	190	137		
5f	2,3-Dimethyl-bn	Cl_2			83	123	323	264			
5g	2-Ethyl-1,4-bn	Cl_2			81	111	261	169			
6a	bn	cbdca		115	231	146	126	115			
6b	1-Methyl-bn	cbdca		176	135	124	116	111			
6c	2-Methyl-bn	cbdca	82	168	182	147	135				
6d	1,1-Dimethyl-bn	cbdca	111	111	111	108	114				
6e	2,2-Dimethyl-bn	cbdca	320	183	152	125	113				
6f	2,3-Dimethyl-bn	cbdca		213	328	203	173	141			
6g	2-Ethyl-bn	cbdca		175	275	222	153	125			

bn = 1,4-butanediamine. cbdca = cyclobutane-1,1-dicarboxylato ion.

TABLE IV. Antitumor Activity of Alkyl-1,4-butanediamine Pt(II) Complexes toward LL Cells in Mice

Compd. No.	Carrier ligand	Leaving group	T/C (%) Dose (mg/kg) 128	64	32	16	8	4	2	1	0.5
5b	1-Methyl-bn	Cl_2							120	108	103
5c	2-Methyl-bn	Cl_2				66	117	103	110		
5f	2,3-Dimethyl-bn	Cl_2			56	86	133	118			
6a	bn	cbdca		238	184	166	128	114	98		
6b	1-Methyl-bn	cbdca	204	142	115	88	101	108			
6c	2-Methyl-bn	cbdca			222	157	122	119			
6e	2,3-Dimethyl-bn	cbdca		131	101	102	86	106	114		
6f	2,3-Dimethyl-bn	cbdca		85	144	118	111	107			
6g	2-Ethyl-bn	cbdca		88	129	107	106	102			

bn = 1,4-butanediamine. cbdca = cyclobutane-1,1-dicarboxylato ion.

mice, and the results are given in Table III and Table IV.

It was demonstrated, with either type of leaving group, that all of the complexes had high antitumor activities toward L1210 cells, except for **5d** and **6d**. In particular, the 2,2-dimethyl- and 2,3-dimethyl-1,4-butanediamine Pt(II) complexes (**5e**, **5f**, **6e** and **6f**) had excellent antitumor activities with $T/C\%$ values higher than 300. Activity reduction due to steric effects was observed only in the case of **d** and the other complexes can be divided into two groups independently of the kind of leaving groups. One is a group which showed moderate antitumor activities with $T/C\%$ values around 200 (**a**,**b** and **c**), and the other is a group which showed excellent activities with $T/C\%$ values higher than 250 (**e**, **f** and **g**), *i.e.*, more active than CDDP.

None of the dichloro Pt(II) complexes exhibited a marked antitumor activity toward LL cells ($T/C\% < 135$). Among the dicarboxylato Pt(II) complexes, one group of the complexes, which had excellent activities toward L1210 cells ($T/C\% > 250$), was less active toward LL cells with $T/C\%$ values lower than 145. However, the other group of dicarboxylato Pt(II) complexes, which showed moderate activities toward L1210 cells, exhibited high activities toward LL cells with $T/C\%$ values higher than 200. These $T/C\%$values are comparable to that of CDDP. The dicarboxylato Pt(II) complexes which are less active toward LL cells, are those having as a carrier ligand methyl-disubstituted or ethyl-substituted 1,4-butanediamine. As these complexes are very active toward L1210 cells, this difference of activity seems to be caused by a difference of affinity to tumor cells, rather than by steric effects.

We are now studying the antitumor activities of the complexes toward other kinds of tumor cells.

References

1) A. W. Prestayko, S. T. Crooke and S. K. Carter (eds.), "Cisplatin," Academic Press Inc., New York, 1980.
2) M. J. Clear and J. H. Hoeschle, *Bioinorg. Chem.*, **2**, 187 (1973); M. Noji, K. Suzuki, T. Tashiro, M. Suzuki, K. Harada, K. Masuda and Y. Kidani, *Chem. Pharm. Bull.*, **35**, 221 (1987).
3) Y. Kidani, *Yakugaku Zassi*, **105**, 909 (1985); A. Pasini and F. Zunino, *Angew. Chem. Int. Ed. Eng.*, **26**, 615 (1987); T. Shimura, T. Tomohiro, K. Maruno, Y. Fujimoto and Y. Okuno, *Chem. Pharm. Bull.*, **35**, 5028 (1987); T. S. Hollis, A. R. Amundsen and E. W. Stern, *J. Med. Chem.*, **32**, 128 (1989); K. Okude, H. Ichida, T. K. Miyamoto, Y. Sasaki and T. Tashiro, *Chem. Lett.*, **1989**, 119.
4) T. Ebina, H. Suzuki and T. Yotsuyanagi, *Bunseki Kagaku*, **32**, 575 (1983).
5) H. Wolff, "Organic Reactions," Vol. 3, John Wiley & Sons Inc., London, 1946, p. 307.
6) H. P. Schultz, *J. Am. Chem. Soc.*, **70**, 2666 (1948).
7) *a*) F. K. V. Leh and W. Wolf, *J. Pharm. Sci.*, **65**, 315 (1976); *b*) S. C. Dhara, *Indian J. Chem.*, **8**, 193 (1970).
8) T. Totani, K. Aono, M. Komura and Y. Adachi, *Chem. Lett.*, **1986**, 429.
9) K. Morikawa, M. Honda, K. Endoh, T. Matsumoto, K. Akamatsu and H. Mitsui, *Yakugaku Zassi*, **108**, 317 (1988).