Lipophilicity *vs.* Antitumor Activity of Carboxylatoplatinum(IV) Complexes

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Acylation of an intermediate tetrahydroxoplatinum(IV) complex, [Pt(OH)$_4$(dach)] (dach = *trans*-(±)-1,2-diaminocyclohexane), with one or two kinds of carboxylic anhydrides in stepwise manner afforded various carboxylatoplatinum(IV) complexes, [Pt(O$_2$CR)$_x$(OR')$_{4-x}$(dach)] (R = (CH$_2$)$_3$CH$_3$ or C(CH$_3$)$_3$, R' = H or OCCH$_3$, and x = 1-4) with a wide range of lipophilicity. The title complexes were subjected to bioassay using the murine leukemia L1210 cell line, and in particular, their *in vivo* oral antitumor activity was attempted to correlate with their lipophilicity and water solubility. The most orally active complex exhibited intermediate lipophilicity and water solubility, but it has been found that an exact relationship between the lipophilicity and oral anticancer activity could not be established, since the lipophilicity of the complexes is not the sole parameter to determine the oral activity. One of the important intermediate complexes partially substituted was subjected to X-ray analysis for positional assignment of the substituted group: [Pt(OPiv)$_3$(OH)(dach)] crystallizes in the tetragonal system, space group $P\bar{4}2_1c$ with a = 21.161(3) Å, b = 21.161(6) Å, c = 12.816(3) Å, $\alpha = \beta = \gamma = 90^o$, V = 5739(2) Å^3 and Z = 8.

Introduction

The oral antitumor activity of platinum(IV) complexes is known to be dependent on the kinds of axial and equatorial ligands relevant to their reduction potential as well as on the balance of the lipophilicity and hydrophilicity of the complexes. In particular, lipophilicity is an important factor for bioavailability by oral administration,[1,2] although the action mechanism of the Pt(IV) complexes has not been yet fully understood.[3] The majority of platinum(IV) complexes have been synthesized by reacting carboxylic anhydrides or acyl chloride with hydroxo platinum(IV) complexes, for example, *cis-trans-cis*-(diamine)Pt(OH)$_2$X$_2$ (X = halides or dicarboxylates).[4-9] Recently we have reported a facile synthetic method and antitumor activity of lipophilic (diamine)tetracarboxylatoplatinum(IV) complexes obtained by electrophilic substitution of (diamine)tetrahydroxoplatinum(IV) complexes with carboxylic anhydrides.[10,11] Above-mentioned studies suggested that the complexes with appropriate 1-octanol/water partition coefficient exhibited good antitumor activity. In order to examine the relationship between the lipophilicity and oral antitumor activity of Pt(IV) complexes, we have prepared Pt(IV) complexes of mixed carboxylates showing a wide range of lipophilicity. In the present study, the carrier amine ligand was fixed to *trans*-(±)-1,2-diaminocyclohexane (dach), which is known to afford nearly no cross-resistance,[12,13] and the lipophilicity of Pt(IV) complexes was modulated by appropriate combination of different carboxylate ligands.

Experimental Section

Materials and instrumentation. Potassium tetrachloroplatinate(II) from Kojima, and pivalic anhydride ((Piv)$_2$O), valeric anhydride ((Val)$_2$O), acetic anhydride (Ac$_2$O) and *trans*-(±)-1,2-diaminocyclohexane (dach) from Aldrich were used as received. The starting material, (dach)Pt(OH)$_4$ was prepared by the literature method.[4] For analytical HPLC, samples were chromatographed on Capcell PAK C$_{18}$ using aqueous acetonitrile solutions as eluent. Elemental analyses were carried out at the Advanced Chemical Analysis Center, KIST. ^{1}H NMR spectra were recorded on a 300 MHz Varian Gemini NMR spectrometer. IR spectra were measured as KBr pellets on a MIDAC 101025 FT-IR spectrometer. The mass analyses were performed by HP5989A equipped with HP59987A as an electron-spray source. A mixture of methanol and water (80 : 20) containing 1% formic acid was used as solvent for the mass analysis. Water solubility of the complexes was measured by the literature method.[2]

Synthesis of [Pt(OPiv)$_3$(OH)(dach)] (1). To a suspension of (dach)Pt(OH)$_4$ (0.379 g, 1 mmol) in acetone (10 mL) was added pivalic anhydride (609 μL, 3 mmol), and the reaction mixture was stirred for 6 h under protection from light. The solution mixture was evaporated to dryness under reduced pressure. The solid product was eluted through a silica gel column using a mixed solvent of acetone/hexane (70/30, v/v), and the product was recovered with methanol. Yield, 35%. Anal. Calcd for C$_{21}$H$_{42}$N$_2$O$_7$Pt · H$_2$O: C, 40.1; H, 6.68; N, 4.45. Found: C, 39.1; H, 6.68; N, 4.31. IR (KBr, cm^{-1}): ν_{max}, 1635, 1364, 1311, 1270, 1204, 598. ^{1}H NMR (acetone-d$_6$, ppm): δ 2.85 (br, NCH, 2H), 2.58 (br, 2H, CH$_2$), 1.65 (br, 2H, CH$_2$), 1.35 (br, 2H, CH$_2$), 1.21 (br, 2H, CH$_2$). 1.18 (s, 9H, CH$_3$), 1.14 (s, 9H, O$_2$CC(CH$_3$)$_3$).

Synthesis of [Pt(OVal)$_3$(OH)(dach)] (2). The procedure was the same as described for **1** except that valeric anhydride (593 μL, 3 mmol) instead of pivalic anhydride was used. Yield: 35%. Anal. Calcd for C$_{21}$H$_{42}$N$_2$O$_7$Pt · H$_2$O: C, 40.1; H, 6.68; N, 4.45. Found: C, 39.8; H, 6.53; N, 4.39. IR (KBr, cm^{-1}): ν_{max}, 1624, 1372, 1278, 588. ^{1}H NMR (acetone-d$_6$, ppm): δ 2.85 (br, 2H, NCH), 2.45 (br, 2H, CH$_2$), 2.21-2.35 (m, 6H, O$_2$CCH$_2$), 1.50-1.70 (m, 10H, CH$_2$), 1.28-1.45 (m, 8H, CH$_2$), 0.92-0.98 (m, 9H, CH$_3$).

Synthesis of [Pt(OPiv)(OAc)$_3$(dach)] (3), [Pt(OPiv)$_2$ (OAc)$_2$-(dach)] (4), [Pt(OPiv)$_3$(OAc)(dach)] (5), and [Pt(OPiv)$_4$-(dach)](6). These complexes were prepared according to our previous method.[14]

Synthesis of [Pt(OVal)(OAc)$_3$(dach)] (7). To a suspension of (dach)Pt(OH)$_4$ (0.379 g, 1 mmol) in acetone was added valeric anhydride (198 μL, 1 mmol), and the reaction mixture was stirred for 1 day under protection from light. Acetic anhydride (330 μL, 3 mmol) was added to the reaction mixture, which was further stirred for 1 day. The solution mixture was evaporated to dryness under reduced pressure. The solid product was eluted through a silica gel column using a mixed solvent of acetone/hexane (35/75 to 70/30, v/v). The product was obtained as a mixture of two stereoisomers. Yield: 25%. Anal. Calcd for $C_{17}H_{32}N_2O_8Pt \cdot 4H_2O$: C, 40.0; H, 6.07; N, 4.25. Found C, 41.0; H, 6.37; N, 4.12. IR (KBr, cm^{-1}): ν_{max}, 2954, 1654, 1627, 1300, 1212. ^{1}H NMR ($CDCl_3$, ppm): δ 2.90 (br, 2H, CH_2), 2.49 (br, 2H, CH_2), 2.21-2.47 (m, 2H, O_2CCH_2), 1.93-2.00 (s, 9H, O_2CCH_3), 1.69 (br, 2H, CH_2), 1.45-1.62 (m, 4H, CH_2) 1.29-1.43 (m, 4H, CH_2), 0.92-0.98 (m, 3H, CH_3).

Synthesis of [Pt(OVal)$_2$(OAc)$_2$(dach)] (8). This compound was synthesized using the corresponding mole ratio of valeric and acetic anhydrides by the same procedure for **7**. The product was obtained as a mixture of three stereoisomers. Yield: 15%. Anal. Calcd for $C_{20}H_{38}N_2O_8Pt \cdot 4H_2O$: C, 34.2; H, 6.56; N, 3.99. Found: C, 35.1; H, 6.49; N, 4.22. IR (KBr, cm^{-1}): ν_{max}, 2954, 1654, 1632, 1300, 1212. ^{1}H NMR ($CDCl_3$, ppm): δ 2.90 (br, 2H, CH_2), 2.51 (br, 2H, CH_2), 2.21-2.46 (m, 4H, O_2CCH_2), 1.92-2.00 (s, 6H, O_2CCH_3), 1.71 (br, 2H, CH_2), 1.45-1.62 (m, 6H, CH_2) 1.30-1.43 (m, 6H, CH_2), 0.92-0.98 (m, 6H, CH_3).

Synthesis of [Pt(OVal)3(OAc)(dach)] (9). This compound was synthesized using the corresponding mole ratio of valeric and acetic anhydrides by the same procedure for **7**. The product was obtained as a mixture of two stereoisomers. Yield: 28%. Anal. Calcd for $C_{23}H_{44}N_2O_8Pt \cdot H_2O$: C, 40.0; H, 6.68; N, 4.06. Found C, 39.6; H, 6.87; N, 3.93. IR (KBr, cm^{-1}): ν_{max}, 2924, 1658, 1630, 1300. ^{1}H NMR ($CDCl_3$, ppm): δ 2.90 (br, 2H, CH_2), 2.51 (br, 2H, CH_2), 2.21-2.46 (m, 6H, O_2CCH_2), 1.92-2.00 (s, 3H, O_2CCH_3), 1.71 (br, 2H, CH_2), 1.45-1.62 (m, 8H, CH_2) 1.30-1.43 (m, 8H, CH_2), 0.92-0.98 (m, 9H, CH_3).

Bioassay. The antitumor activity of the compounds was assayed *in vitro* and *in vivo* at the Korea Research Institute of Chemical Technology (KRICT).

***In vitro* assay**: These tests were carried out using the ascites cell form of L1210 lymphoid leukemia, which was obtained from DBA/2 donor mice bearing 3-5 day tumor growth. L1210 leukemia cells were maintained in RPMI 1640 medium supplemented with 10% fatal bovine serum (GIBCO). Cells were adjusted to 1×10^6 cells/mL and distributed to 24 well tissue culture plates (0.5 mL/well). Following 48 hrs incubation in a 5% CO_2 atmosphere at 37 °C, cell counts were determined with a Coulter Model ZM cell counter. Cell growth in the presence of test compounds was expressed as a percentage of growth in untreated control wells and the concentration of compound producing 50% inhibition of cell growth was determined (ED_{50}).

***In vivo* assay**: These tests were carried out using the ascites cell form of L1210 lymphoid leukemia, which was obtained from DBA/2 donor mice bearing 3-5 day tumor growth. L1210 leukemia cells (10^6) were inoculated i.p. in BDF mice (6-8 weeks old, 20-25 g, 8 mices per group), and 24 hrs later, compounds were administered orally once a day for 5 consecutive days at a dose of 150 mg/kg per administration. Mortality was recorded and mean survival time was calculated for each group. *In vivo* activity of the title complexes was expressed as a survival effect (T/C % value), where T is the mean survival time of the drug treated mice and C is that of control mice.

X-ray structure determination. All the X-ray data were collected on an Enraf-Nonius CAD4 automated diffractometer equipped with a Mo X-ray tube and a graphite crystal monochromator. The orientation matrix and unit cell dimensions were determined from 25 machine centered reflections in the 2θ range of 15 to 25°. The variation of intensities was monitored by repeated check of intensities of three reflections every 1 h during the data collection period. Absorption corrections were applied by empirical psi scan on 3 reflection planes with a chi value of near 90°. A direct or Patterson method (SHELXS-97)[15] was employed to locate the platinum atom. Subsequent cycles of Fourier map and least square refinements located other atoms (SHELXL-93).[16] All the nonhydrogen atoms were refined anisotropically. Hydrogen atoms were included in the structure factor calculation using a riding model. All the calculations were carried out using VAX and PC computers.

Results and Discussion

Synthesis and characterization. Acylation of tetrahydroxoplatinum(IV) complex, [Pt(OH)$_4$(dach)], with one or two kinds of carboxylic anhydrides in stepwise manner afforded various carboxylatoplatinum(IV) complexes, [Pt(O_2CR)$_x$-(OR')$_{4-x}$(dach)] (R = $(CH_2)_3CH_3$ or $C(CH_3)_3$, R' = H or $OCCH_3$, and x = 1-4). Each compound was separated by silica gel column chromatography and obtained as a mixture of stereoisomers. Even when [Pt(OH)$_4$(dach)] was reacted with equivalent pivalic or valeric anhydride only, various partially carboxylated products such as [Pt(O_2CR)$_3$(OH)(dach)], [Pt-(O_2CR)$_2$(OH)$_2$(dach)] and [Pt(O_2CR)(OH)$_3$(dach)] were formed along with the fully carboxylated [Pt(O_2CR)$_4$(dach)]. Among these products [Pt(O_2CR)$_4$(dach)] and [Pt(O_2CR)$_3$-(OH)(dach)] could be purely isolated by two successive elutions from silica gel column (acetone/hexane, 70/30, v/v % and methanol). The tricarboxylated product, [Pt(OPiv)$_3$-(OH)(dach)], obtained from the second fraction, was recrystallized and subjected to X-ray crystallography. These trisubstituted complexes may be used as a new precursor for other mixed carboxylatoplatinum(IV) complexes by reacting with another second carboxylic anhydride. For example, further reaction of the tris(pivalato)platinum(IV) complex with acetic anhydride afforded [Pt(OPiv)$_3$(OAc)(dach)] in quanti-

Table 1. Physico-chemical properties of Pt(IV) complexes and their antitumor activity against murine leukemia L1210

	in vitro ED_{50} (μg/mL)	*in vivo* T/C (%)	HPLC T_R (min)	solubility (mg/mL)
1 [Pt(OPiv)$_3$(OH)(dach)]	5.9	101	17.5	0.73
2 [Pt(OVal)$_3$(OH)(dach)]	1.1	113	15.6	3.31
3 [Pt(OPiv)(OAc)$_3$(dach)]	8.6	108	6.9	17.3
4 [Pt(OPiv)$_2$(OAc)$_2$(dach)]	1.3	137	13.2	3.24
5 [Pt(OPiv)$_3$(OAc)(dach)]	1.5	125	21.5	1.01
6 [Pt(OPiv)$_4$(dach)]	> 40	101	28.9	0.12
7 [Pt(OVal)(OAc)$_3$(dach)]	5.0	125	7.5	15.5
8 [(Pt(OVal)$_2$(OAc)$_2$(dach)]	4.2	95	13.3	11.6
9 [Pt(OVal)$_3$(OAc)(dach)]	8.6	95	18.5	0.97
[Pt(OAc)$_4$(dach)][11]	25.8	100	3.1	20.7
[Pt(OVal)$_4$(dach)][11]	6.2	toxic	23.8	0.43
JM216[11]	1.2	160	11.0	0.51

tative yield. In its ^{1}H NMR spectrum, the resonance of the methyl protons of the axial pivalate group appeared in more upfield region by 0.08 ppm compared with those of the equatorial ones. The mobility of the complexes in the HPLC column was monitored at 210 nm and their retention times are listed in Table 1. The lipophilicity of the complexes is generally known to be approximately proportional to their retention time.[17] Tetrakis(acetato)platinum(IV) complex is the most hydrophilic and eluted at first of all (T_R = 3.2 min), and tetrakis(pivalato)platinum(IV) complex was the most lipophilic (T_R = 28 min). It is seen in the table that the lipophilicity of the complexes increases with increasing number of the pivalate or valerate group substituted. Such characteristics seem to be related to their anticancer activity, which will be discussed later. In the IR spectra of (dach)Pt(IV) complexes of mixed carboxylates showed two distinguished asymmetric carboxylate stretching bands at 1658 and 1622 cm^{-1} in the case of **3**-**5**, and at 1654 and 1626 cm^{-1} in the case of **7**-**9**, respectively. The partially acylated complexes **1** and **2** showed a characteristic Pt-O stretching band in the region 588-598 cm^{-1} in addition to the asymmetric carboxylate stretching bands.

Crystal structure of [Pt(OPiv)$_3$(OH)(dach)]. An ORTEP drawing of the complex is shown in Figure 1. The crystallographic data and selected bond lengths and angles are listed in Table 2 and Table 3, respectively. The terminal methyl groups of the pivalate ligand are crystallographically disordered. Four oxygen atoms in the crystal structure around the platinum(IV) atom are positioned in a distorted octahedral geometry, in which the hydroxo ligand occupies the axial position. The distances of Pt-N(1) and Pt-N(2) bonds are 2.04(2) and 1.989(19) Å, respectively, which fall in the range of the normal Pt-N bond.[18,19] The distances of Pt-O(1) (2.007(17) Å) and Pt-O(3) (2.026(18) Å) are slightly longer than axial ones (1.968(13) Å and 2.00(2) Å), being consistent with the case of tetracarboxylatoplatinum(IV) complexes in the literature.[8,14] In addition, these Pt-O bond lengths (2.007(17), 2.026(18) and 2.00(2) Å) between the platinum atom and the carboxylate oxygens are slightly longer than

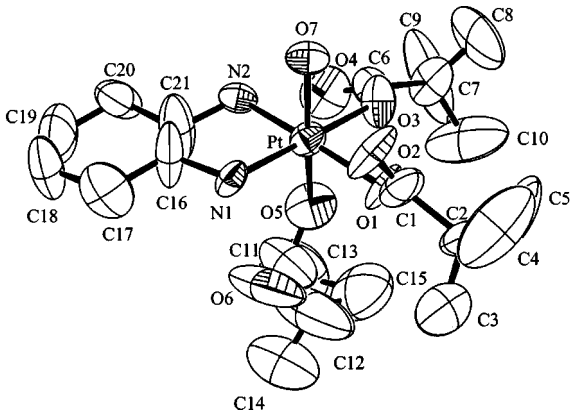

Figure 1. ORTEP drawing of [Pt(OPiv)$_3$(OH)(dach)] with an atomic labeling scheme.

Table 2. Crystallographic data for [Pt(OPiv)$_3$(OH)(dach)]

empirical formula	C_{21} H_{42} N_2 O_7 Pt
formula weight	629.65
temperature	293(2) K
wavelength	0.71073 Å
crystal system, space group	*tetragonal*, $P\bar{4}2_1c$
unit cell dimensions	a = 21.161(3) Å, α = 90°.
	b = 21.161(6) Å, β = 90°.
	c = 12.816(3) Å, γ = 90°.
V	5739(2) Å^3
Z, calculated density	8, 1.448 g/cm^3
absorption coefficient	4.925 mm^{-1}
F(000)	2496
θ range for data collection	1.36 to 24.95°.
reflections collected/unique	3047/1849 [R(int) = 0.1836]
refinement method	Full-matrix least-squares on F^2
data/restraints/parameters	1849/6/280
goodness-of-fit on F^2	1.031
final R indices [$I > 2\sigma(I)$]	R_1 = 0.0639, wR_2 = 0.1043
R indices (all data)	R_1 = 0.0703, wR_2 = 0.1087
largest diff. peak and hole	1.433 and -1.589 e. Å^{-3}

$^aR_1 = \Sigma\ ||F_o| - |F_c||/|F_o|$. $^bwR_2 = \{\Sigma\ w(F_o^2 - F_c^2)^2/\Sigma\ wF_o^4\}^{1/2}$, where $w = 1/\{\sigma^2F_o^2 + (0.0197P)^2 + 0.00P\}$, and where $P = \{\max(F_o^2,0)\} + 2F_c^2\}/3$.

Table 3. Selected bond lengths [Å] and angles [°] for [Pt(OPiv)$_3$-(OH)(dach)]^a

Distances			
Pt(1)-O(7)	1.968(13)	Pt(1)-N(2)	1.989(19)
Pt(1)-O(5)	2.00(2)	Pt(1)-O(1)	2.007(17)
Pt(1)-O(3)	2.026(18)	Pt(1)-N(1)	2.04(2)
Angles			
O(7)-Pt(1)-N(2)	87.6(7)	O(7)-Pt(1)-O(5)	169.4(10)
O(7)-Pt(1)-O(1)	97.8(7)	N(2)-Pt(1)-O(1)	174.6(7)
O(7)-Pt(1)-O(3)	89.9(7)	O(1)-Pt(1)-N(1)	95.9(7)
O(1)-Pt(1)-O(3)	84.4(8)	O(7)-Pt(1)-N(1)	89.4(7)
N(2)-Pt(1)-N(1)	84.4(7)	O(5)-Pt(1)-N(1)	99.0(9)
Hydrogen bonds			
N(2)-O(4)	2.68	N(1)-O(6)	2.68
O(7)-O(2)	2.85	N(1)-O(7)$^{\#1}$	2.75
N(2)-O(2)$^{\#2}$	2.87		

Symmetry transformations used to generate equivalent atoms: (#1) 1-y, x, 1-z; (#2) y, 1-x, 1-z.

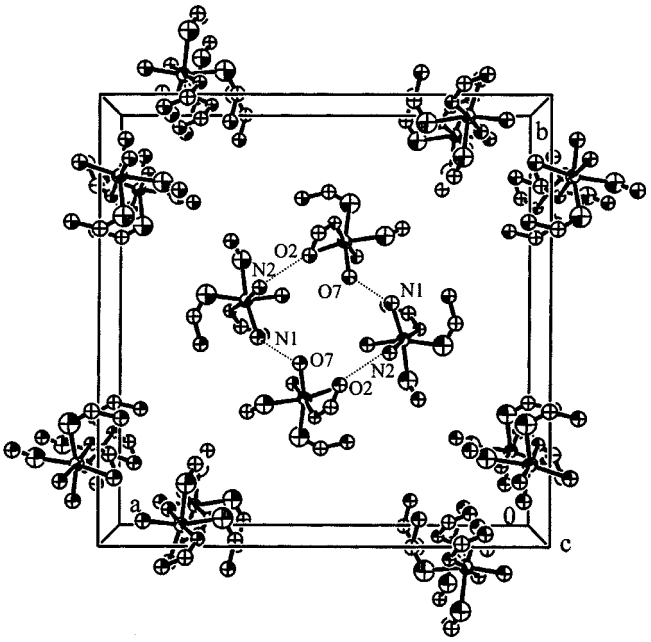

Figure 2. Molecular packing diagram of $[Pt(OPiv)_3(OH)(dach)]$.

the Pt-OH bond (1.968(13) Å). Nitrogen atoms of dach and the oxygen atom of the hydroxo ligand are involved in intramolecular hydrogen bonding with three pivalate oxygens ((NH(1)---O(6) (2.668 Å), NH(2)---O(4) (2.676 Å), OH(7)---O(2) (2.848 Å)). The oxygen atom of the axial hydroxo ligand (O7) involved in the hydrogen bonding makes a difference from other tetracarboxylatoplatinum(IV) complexes which have no free hydroxo ligand. These hydrogen bondings may be responsible for the distortion of the coordination angle of O(1)-Pt-O(3) (84.4(8)). The packing diagram of the complex is shown in Figure 2, in which *tert*-butyl groups of the complex are omitted for clarity. Two nitrogen atoms of dach interact with oxygen atoms of neighboring molecules through hydrogen bonding $N(1)---OH(7)^{\#1}$ (2.752 Å) and $NH(2)---O(2)^{\#2}$ (2.872 Å). In the solid state, the molecules of symmetry code (x, y, z), (1-y, x, 1-z), (1-x, 1-y, z) and (y, 1-x, 1-z) showed a tetrameric interaction disposed like as a millwind through intermolecular hydrogen bonding. Intermolecular hydrogen bonding interactions are shown by dotted lines in the figure.

Antitumor Activity. The *in vitro* cytotoxicity and *in vivo* oral antitumor activitiy of the title complexes were assayed against the murine leukemia L1210 cell line and the results are listed in Table 1. Dosage and schedule for oral administration were 150 mg/kg and five consecutive daily treatments (Q1D × 5). The antitumor activity of the present complexes was compared with that of JM216, which has undergone extensive clinical studies.[20,21] *In vitro* activity of some complexes (1.1, 1.3 and 1.5 mg/mL for the complexes **2**, **4**, and **5,** respectively) was almost the same as that of JM216 (1.2 mg/mL), but their *in vivo* activity was inferior to that of JM216. However, among the present complexes, compound **4** with an intermediate lipophilicity (T_R = 13.2) and moderate water solubility (3.24 mg/mL) exhibit the highest oral activity. It seems to be noteworthy that the lipophilicity of compound **4** is comparable to that of JM 216 (T_R = 11.0). The pivalate complexes (**1**, **3**-**6**) were generally more active than the valerate complexes, although they exhibit similar behavior in HPLC or water solubility. The pivalate group has been widely used to obtain lipophilic derivatives of too hydrophillic drugs so as to enhance their bioavailabilty.[22] This ligand seems to afford more bioavailability of its metal complexes than valerate. The complexes substituted by more than two valerates are inactive and even toxic in the case of the complex fully substituted by valerate. The complexes of too hydrophilic or too hydrophobic character showed no or only marginal oral activity. The inactivity of too hydrophilic complexes such as $[Pt(OAc)_4(dach)]$ may be ascribed to fast elimination in the gastro-intestinal tract or difficulty to pass biological membrane. On the other hand, highly lipophilic complexes are practically insoluble in water, which prohibits from molecular absorption through the biological membrane even though their lipophilicity is high. The water solubility of the present complexes was measured and also listed in Table 1. The water solubility of the title complexes decreases in the order of increasing lipophilicity as expected. The complex **4**, the most active among the present complexes, showed a moderate water solubility (3.4 mg/mL) higher than JM216 (0.5 mg/mL), although its hydrophobicity is comparable to that of JM216 as above-mentioned. Other orally active complexes **5** and **7** showed considerably different lipophilicity and solubility compared with the complex **4**. However, such an ampiphilic character seems to be an important factor for diffusion or partition of a drug through the biological membranes. The lipophilicity *vs.* anticancer activity relationship is, however, not easy to generalize because the antitumor activity also depends upon other factors such as reduction potential and molecular geometry of the complexes.

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Supplementary Material. Tables of crystallographic details, non-hydrogen positional parameters, bond distances and angles, anisotropic and isotropic thermal parameters for the present compounds (7 pages). The Supporting materials will be given upon your request to the correspondance author. (Tel: +82-2-958-5081, Fax: +82-2-958-5089, E-mail: yssohn @kistmail.kist.re.kr)

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