# Synthesis and Antitumor Activity of a Series of [2-Substituted-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) Complexes

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The synthesis, physical properties, antitumor activity, structure-activity relationships, and nephrotoxicity of a series of [2-substituted-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) complexes are described. The 42 platinum(II) complexes having a seven-membered ring structure in this series have been prepared and characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, FAB-MS, and elemental analysis. All members of the series were designed to have a 1,3-dioxolane ring moiety in their carrier ligands to increase water solubility. The solubility of platinum complexes was related to the nature of leaving ligands and 2-substituents in the 4,5-bis(aminomethyl)-1,3-dioxolane carrier ligands. In general, compounds having two different  $R_1$  and  $R_2$  substituents in the 4,5bis(aminomethyl)-1,3-dioxolane moiety were more water-soluble than those having the same substituents. Most members of this series showed the excellent antitumor activity against murine L1210 leukemia cells transplanted in mice and were superior to cisplatin and carboplatin. The (4R.5R)-stereoisomer 1a-h exhibited the higher antitumor activity than the corresponding (4S.5S)stereoisomer 2a-h in the (1,1-cyclobutanedicarboxylato)platinum(II) complexes. The (glycolato)platinum(II) complexes were highly cytotoxic toward four human stomach cancer cell lines. SNU-1, SNU-5, SNU-16, and NCI-N87, and among them, complexes 3d-g were even more cytotoxic than cisplatin. The (malonato)platinum(II) complex 1m and the (glycolato)platinum(II) complexes 3d-g were selected for further studies based on the greater in vivo and in vitro antitumor activity and desirable physical properties. The complexes 3e-g were almost equally cytotoxic to cisplatin toward human stomach cancer cell lines, KATO-III and MKN-45, and a human non-small cell lung cancer cell line, PC14. In contrast with cisplatin and carboplatin, five complexes selected significantly increased in life span in mice transplanted with cisplatin-resistant L1210 cells. Nephrotoxicity studies in ICR mice indicated that serum BUN and creatinine levels were not elevated when five complexes were given at a dose equal to 1.5 times the optimal dose determined in the *in vivo* L1210 screening system.

### Introduction

cis-Diamminedichloroplatinum(II) (cisplatin)<sup>1</sup> is one of the most effective anticancer agents currently available for the treatment of testicular, ovarian, and bladder carcinomas.<sup>2-8</sup> In addition, cisplatin is widely used in combination with other anticancer agents, such as doxorubicin, etoposide, bleomycin, and 5-fluorouracil, in treating head and neck cancer, lung carcinoma, stomach carcinoma, etc.<sup>9-12</sup> However, the clinical usefulness of cisplatin has been frequently limited by the following four drawbacks: (1) serious toxicities, such as nephrotoxicity, gastrointestinal toxicity, ototoxicity, and neurotoxicity, 3,13-14 (2) low activity for certain kinds of cancers, such as breast and colon cancers.<sup>2,15</sup> (3) development of acquired resistance,  $^{4,6,16-18}$  and (4) poor solubility in water. In an attempt to overcome these drawbacks of cisplatin, numerous analogues have been synthesized and evaluated in a search for alternative active agent.<sup>19-23</sup> Among them, cis-diammine(1,1-cyclobutanedicarboxylato)platinum(II) (carboplatin) has proven to be the only second-generation platinum complex commercially available at present.

and small-cell lung cancer,<sup>24,25</sup> is much less nephrotoxic and emetic than cisplatin,<sup>26,27</sup> and is sufficiently watersoluble. The spectrum of antitumor activity of carboplatin. however, does not seem to be expanded compared to that of cisplatin, possibly due to the same diamine carrier ligand.<sup>24,28</sup> Moreover, carboplatin is not effective in the treatment of cancer cells resistant to cisplatin, suggesting that cross-resistance exists between cisplatin and carboplatin.<sup>29,30</sup> The other promising second-generation platinum complexes under development are tetrachloro-((d,l-trans)-1,2-diaminocyclohexane)platinum(IV) (tetraplatin),<sup>31,32</sup> (glycolato-O.O') diammineplatinum(II) (254-S),<sup>33,34</sup> ((R)-2-methyl-1,4-butanediamine)(1,1-cyclobutanedicarboxylato)platinum(II) (NK-121),  $^{35,36}$  and [(-)-(R)-2-(aminomethyl)pyrrolidine](1,1-cyclobutanedicarboxylato)platinum(II) (DWA-2114R)<sup>37-39</sup> (Chart 1). Even though these second-generation platinum complexes show good activity and reduced renal toxicity, the antitumor spectrum is proven to be limited to cisplatin. Therefore, the search for the new potent platinum complexes that possess a broader spectrum of the antitumor activity, lower toxicity, lack of cross-resistance, and desirable physicochemical properties is continuing. Most of the platinum complexes reported to date have five-membered ring or

Carboplatin shows the same level of activity as cisplatin in treating some kinds of cancers, such as ovarian cancer

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Chart 1



six-membered ring structures between a bidentate carrier ligand and a platinum atom.<sup>40</sup> The reason why reports are scarce on the synthesis of seven-membered ring complexes seems to be that the chelate effect in a sevenmembered ring structure is considered to be weaker than that in a five- or six-membered ring structure.<sup>35</sup> Kaplan et al.<sup>41</sup> synthesized the seven-membered ring complex, (2-hydroxymalonato)[1,2-bis(aminomethyl)cyclohexane]platinum(II), for the first time and demonstrated that this complex and its sodium salt were sufficiently stable both as solid and in aqueous solution and more active than the corresponding (2-hydroxymalonato)(1,2-diaminocyclohexane)platinum(II) (five-membered ring) and its sodium salt against L1210 leukemia in mice in terms of % T/C value, the number of survivors, and potency. Very recently, Nowatari et al.35 reported that (1,4-butanediamine)platinum(II) complexes (seven-membered ring) have exhibited the higher antitumor activity against L1210 cells in vivo and in vitro than (ethylenediamine) platinum-(II) complexes (five-membered ring) and (1,3-propanediamine)platinum(II) complexes (six-membered ring) with the same types of leaving ligand. Moreover, NK-121 was proven to be highly active against a variety of human tumor cells and cisplatin-resistant murine leukemia cells in vitro and in vivo.<sup>36,42-43</sup> Haines et al.<sup>44</sup> also reported that the enantiomers of cis-dichloro(1,4-diamino-1,4-dideoxy-2,3-O-isopropylidenethreitol)platinum(II) showed a higher therapeutic index than cisplatin against the ADJ/PC6 plasmacytoma in vivo. If the platinum complexes have a seven-membered ring structure between a bidentate leaving ligand and a platinum atom, the antitumor activity is usually lower than those having a five- or six-membered ring structure. These studies indicate that complexes having a seven-membered ring structure between a bidentate carrier ligand and a platinum atom have desirable antitumor activity and sufficient stability in aqueous solution. On the basis of these findings, we have synthesized a series of [2-substituted-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) complexes having a sevenmembered ring structure, which are represented by the general structural formulas given (Chart 2). The 2-substituents,  $R_1$  and/or  $R_2$ , in this 4,5-bis(aminomethyl)-1,3dioxolane carrier ligand can be hydrogen, lower alkyl, or an alkylene unit. We envisioned that the 1,3-dioxolane ring moiety in the carrier ligands may render the organoplatinum species more water-soluble than the simple



cyclopentane-1,2-bis(aminomethane) complex,45 thereby facilitating intravenous administration and being possibly less toxic due to a more facile excretion via the kidney. It was well demonstrated that the antitumor activity of the platinum(II) complex was reduced by steric hindrance around the reactive center, platinum.<sup>46</sup> Therefore, the target compounds 1-3 have been designed to have trans stereochemistry in the 4,5-bis(aminomethyl)-1,3-dioxolane carrier ligands because trans isomers are less hindered than the corresponding *cis* isomers. In order to evaluate the differences in the antitumor activity between the trans isomers, as shown previously in the trans-1,2-diaminocyclohexane (DACH) complexes,<sup>47</sup> we have prepared both (4R,5R)-isomers 1a-h and the corresponding (4S,5S)isomers 2a-h. As leaving ligands, malonates (1, where  $R_3$  $= R_4 = H, R_3 = R_4 = Me, R_3 = H and R_4 = Et, or R_3, R_4$ =  $-(CH_2)_3$ -), glycolate (3, where  $R_5 = H$ ), and L-lactate (3, where  $R_5 = Me$ ) have been used because they were shown to be less nephrotoxic and more water-soluble than dichloride.<sup>40,48</sup> In this report we describe the chemistry, physical properties, antitumor activity, structure-activity relationships, and nephrotoxicity of a series of [2-substituted-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) complexes.

# Chemistry

The (malonato)platinum complexes 1a-t and 2a-h were prepared by reaction of the diiodoplatinum complexes 4a-h and 6a-h with the disilver salt of malonic acid 5a-d as shown in Schemes 1 and 2, respectively. The (glycolato)platinum complex 3a-g and (L-lactato)platinum complex 3h-n were prepared by two different methods, A and B, as shown in Scheme 3. In method A, the diiodoplatinum complex 4 was reacted with an aqueous silver nitrate solution to obtain an aqueous solution of a diaguo complex 7, which was then passed through a column packed with anion-exchange resin, Amberlite IRA-400(OH), to yield an aqueous solution of a dihydroxo complex 8. The aqueous eluate was allowed to react with glycolic acid and sodium glycolate, or L-lactic acid and sodium L-lactate to give the (glycolato)platinum complex 3a-g or (L-lactato)platinum complex 3h-n, respectively. In method B, treatment of complex 4 with glycolic acid or L-lactic acid in the presence of silver(I) oxide gave the complex 3a-gor 3h-n, respectively. Most of (glycolato)- and (L-lactato)platinum complexes were highly water-soluble; therefore, they were purified by preparative HPLC on Delta pak C<sub>18</sub>-100-Å reverse-phase bonded silica cartridge with  $MeOH-H_2O$  system as the mobile phase and freeze-dried. Method B was advantageous over method A in terms of yields and relatively easy preparation. The synthesized platinum complexes 1–3 were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, FAB-MS, and elemental analysis. The FAB (Substituted dioxolane)platinum(II) Complexes

Scheme 1



1a-t

**a**:  $R_1 = R_2 = H$ ,  $R_3$ ,  $R_4 = -(CH_2)_3$ **b**:  $R_1 = H$ ,  $R_2 = Me$ ,  $R_3$ ,  $R_4 = -(CH_2)_3$ c:  $R_1 = R_2 = Me$ ,  $R_3$ ,  $R_4 = -(CH_2)_3$ d:  $R_1 = Me, R_2 = CH_2OH, R_3, R_4 = -(CH_2)_3 - n: R_1, R_2 = -(CH_2)_4 -, R_3 = R_4 = H_3 - R_4 = H_3 - R_4 = H_3 - R_4 = H_3 - R_4 - R_4$ e:  $R_1 = H$ ,  $R_2 = Et$ ,  $R_3$ ,  $R_4 = -(CH_2)_3$ f:  $R_1 = H$ ,  $R_2 = i$ -Pr,  $R_3$ ,  $R_4 = -(CH_2)_3$ **g**:  $R_1$ ,  $R_2 = -(CH_2)_4$ ,  $R_3$ ,  $R_4 = -(CH_2)_3$ **h**:  $R_1$ ,  $R_2 = -(CH_2)_5^-$ ,  $R_3$ ,  $R_4 = -(CH_2)_3^ \mathbf{i}:\mathbf{R}_1=\mathbf{R}_2=\mathbf{R}_3=\mathbf{R}_4=\mathbf{H}$  $j: R_1 = R_3 = R_4 = H, R_2 = Me$ 

k: R<sub>1</sub> ≠ R<sub>2</sub> = Me, R<sub>3</sub> = R<sub>4</sub> = H I:  $R_1 = R_3 = R_4 = H$ ,  $R_2 = Et$  $\mathbf{m}$ :  $\mathbf{R}_1 = \mathbf{R}_3 = \mathbf{R}_4 = \mathbf{H}, \mathbf{R}_2 = i - Pr$ o: R<sub>1</sub> = H, R<sub>2</sub> = Et, R<sub>3</sub> = R<sub>4</sub> = Me  $\mathbf{p}$ :  $\mathbf{R}_1 = \mathbf{H}$ ,  $\mathbf{R}_2 = i$ -Pr,  $\mathbf{R}_3 \approx \mathbf{R}_4 = \mathbf{M}\mathbf{e}$ **q**:  $R_1, R_2 = -(CH_2)_4$ ,  $R_3 = R_4 = Me_1$  $r: R_1 = R_3 = H, R_2 = R_4 = Et$ **s**:  $R_1 = R_3 = H$ ,  $R_2 = iPr$ ,  $R_4 = Et$ t:  $R_1$ ,  $R_2 = -(CH_2)_4$ -,  $R_3 = H$ ,  $R_4 = Et$ 

Scheme 2



**a**:  $R_1 = R_2 = H$ **b**: R, = H, R<sub>2</sub> = Me c: R<sub>1</sub> = R<sub>2</sub> = Me **d**:  $R_1 = Me$ ,  $R_2 = CH_2OH$ e: R<sub>1</sub> = H, R<sub>2</sub> = Et f:  $R_1 = H, R_2 = i$ -Pr  $g: R_1, R_2 = -(CH_2)_4$ **h**:  $R_1, R_2 = -(CH_2)_5$ 

mass spectra of the platinum complexes 1-3 showed typical three protonated molecular ion peaks because of the isotopes <sup>194</sup>Pt (33%), <sup>195</sup>Pt (34%), and <sup>196</sup>Pt (25%). The (ethylmalonato)platinum complexes 1r and 1s may be considered to be a mixture of two diastereomers, and the (glycolato)- and (L-lactato)platinum complexes 3b, 3d, 3e, 3i, 3k, and 31 may be present as a mixture of two geometrical isomers (Chart 3). In all cases these diastereomers and geometrical isomers were shown to have a single peak in reverse-phase analytical HPLC analysis and were not readily distinguishable each other in their <sup>1</sup>H NMR spectra. However, the examination of the <sup>13</sup>C NMR spectra of these complexes clearly indicated that they were present as a mixture of two diastereomers or two geometrical isomers. For example, the <sup>13</sup>C NMR spectrum of (ethylmalonato)platinum complex 1r in DMSO- $d_6$ 

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Scheme 3<sup>a</sup>



exchange resin, H<sub>2</sub>O; (c) (i) glycolic acid, sodium glycolate (for 3a-g), 60 °C, 18 h, or (ii) L-lactic acid, sodium L-lactate (for 3h-n), 60 °C, 18 h; (d) (i) glycolic acid, Ag<sub>2</sub>O, (for 3a-g), 60 °C, 18 h, or (ii) L-lactic acid, Ag<sub>2</sub>O (for 3h-n), 60 °C, 18 h.





**1r** : 
$$R_1 = H, R_2 = Et$$
  
**1s** :  $R_1 = H, R_2 = iPr$ 



**3b** :  $R_1 = R_3 = H$ ,  $R_2 = Me$ **3d** :  $R_1 = R_3 = H, R_2 = Et$ **3e** :  $R_1 = R_3 = H, R_2 = i Pr$ 31 : R<sub>1</sub> = H, R<sub>2</sub> = R<sub>3</sub> = Me 3k : R<sub>1</sub> = H, R<sub>2</sub> = Et, R<sub>3</sub> = Me 3I : R, = H, R<sub>2</sub> = *i*-Pr, R<sub>3</sub> = Me

showed a pair of C-4 and C-4' resonances at 77.68, 77.80, 79.51, and 79.64 ppm and a pair of C-5 and C-5' resonances at 47.69, 47.81, 47.84, and 47.94 ppm. The (glycolato)platinum complex 3b in  $D_2O$  displayed a pair of C-5 and  $C\text{-}5^\prime$  resonances at 48.57, 48.73, 48.86, and 49.05 ppm. The antitumor activity of platinum complexes is frequently affected by the chirality of the carrier ligands as shown in the 1,2-diaminocyclohexane complexes and 2-(aminomethyl)cyclohexylamine complexes.<sup>46,47</sup> A recent study of Miyamoto et al.49 with the four optical isomers of (mandelato)(trans-1,2-diaminocyclohexane)platinum-(II) showed that the chirality of both carrier ligands and leaving ligands influenced the antitumor activity of platinum complexes. Thus, it seems necessary to separate afore-mentioned diastereomers and geometrical isomers before biological evaluation. However, since the separation of those isomers was practically difficult even by using HPLC, they were tested without further separation. The





**h**: 
$$R_{1}, R_{2} = -(CH_{2})_{5}$$

 $^a$  (a)  $R_1COR_2$  or  $R_1C(OEt)_2R_2$ , MsOH; (b) NaN3, DMF, 100 °C, 16 h; (c) ((*tert*-butyldiphenylsilyl)oxy)acetone, anhydrous CuSO4, MsOH, toluene, 45 °C, 16 h; (d) *n*-Bu4NF, THF, room temperature, 1 h; (e) 10% Pd-C, EtOH, H<sub>2</sub> (50 psi), 40 °C, 2 h; (f) K<sub>2</sub>PtCl<sub>4</sub>, KI, H<sub>2</sub>O, 60 °C, 3 h.

purity of the platinum complexes 1-3 were further determined by analytical reverse-phase HPLC analysis in two solvent systems (MeOH-H<sub>2</sub>O), and all complexes were found to be sufficiently pure (>98%) for biological evaluation. The synthesis of cis-diiodo[(4R,5R)-4,5-bis-(aminomethyl)-1,3-dioxolane]platinum(II) 4a-h from Dthreitol 1,4-bis(methanesulfonate) (9)<sup>50</sup> as chiral starting material is outlined in Scheme 4. Reaction of D-threitol 1,4-bis(methanesulfonate) (9) with an appropriate aldehyde, acetal, ketone, or ketal in the presence of an acid catalyst gave (4R,5R)-4,5-bis(((methylsulfonyl)oxy)methyl)-1,3-dioxolanes 10a-f. These were then reacted with sodium azide in DMF to give (4R, 5R)-4,5-bis(azidomethyl)-1,3-dioxolanes 12a-b and 12f-i. 2,2-Dimethyl-(4R,5R)-4,5-bis(azidomethyl)-1,3-dioxolane (12c)<sup>44</sup> was prepared by reaction of 2,2-dimethyl-1,3-dioxolane-(4R,5R)-4,5-bis-(methanesulfonate)<sup>50</sup> with sodium azide in DMF. For the synthesis of 2-(hydroxymethyl)-2-methyl-(4R,5R)-4,5-bis-(azidomethyl)-1,3-dioxolane (12e), D-threitol 1,4-bis-(methanesulfonate) (9) was reacted with sodium azide in DMF to give (2R.3R)-2.3-dihydroxy-1.4-diazidobutane (11), which was then treated with ((tert-butyldiphenyl-



<sup>a</sup> (a)  $R_1COR_2$  or  $R_1C(OEt)_2R_2$ , MsOH; (b) NaN<sub>3</sub>, DMF, 100 °C, 16 h; (c) ((*tert*-butyldiphenylsilyl)oxy)acetone, anhydrous CuSO<sub>4</sub>, MsOH, toluene, 45 °C, 16 h; (d) *n*-Bu<sub>4</sub>NF, THF, room temperature, 1 h; (e) 10% Pd-C, EtOH, H<sub>2</sub> (50 psi), 40 °C, 2 h; (f) K<sub>2</sub>PtCl<sub>4</sub>, KI, H<sub>2</sub>O, 60 °C, 3 h.

silyl)oxy)acetone and anhydrous CuSO<sub>4</sub> in the presence of methanesulfonic acid to afford 2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-(4R,5R)-4,5-bis(azidomethyl)-1,3-dioxolane (12d). Desilylation of 12d with tetrabutylammonium fluoride in THF finally gave 12e. The diazides 12a-c and 12e-i were reduced with hydrogen in the presence of 10% palladium on activated carbon in an alcoholic medium to afford (4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolanes 13a-h, which were then reacted with potassium tetraiodoplatinate(II) to give cis-diiodo[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) 4a-h. cis-Diiodo[(4S,5S)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) 6a-h, the enantiomers of 4a-h, were prepared from L-threitol 1,4-bis(methanesulfonate) (14)<sup>50</sup> as chiral starting material according to the same procedure described in Scheme 4, as shown in Scheme 5. The physical and spectral properties of new 1.3-dioxolane intermediates are listed in Table 1.

#### **Results and Discussion**

The complexes 1-3 were tested to evaluate the antitumor activity against L1210 leukemia (ip-ip system) in mice,

Table 1. Physical and Spectral Properties of New 1,3-Dioxolane Intermediates

			R1	_O.,,,H₃			$\sim$	H3		
			R <sub>2</sub>			R <sub>2</sub>	),/	Ba		
				(4 <i>R</i> ,5 <i>R</i> )		(4	4 <i>S</i> ,5 <i>S</i> )			
compd	R <sub>1</sub>	$R_2$	$R_3$	absolute config	% yield	$[\alpha]^{20}_{\rm D}, \deg$ (c = 0.04, acetone)	MS	formula	anal.ª	IR, cm <sup>-1</sup>
10c	н	Et	OMs	(4R, 5R)	78	······································	318	$C_9H_{18}O_8S_2$	C, H	1357, 1179
15c	н	$\mathbf{Et}$	OMs	(4S, 5S)	83		318	$C_9H_{18}O_8S_2$	С, Н	1357, 1179
10 <b>d</b>	н	i-Pr	OMs	(4R, 5R)	98		332	$C_{10}H_{20}O_8S_2$	С, Н	1360, 1182
1 <b>5d</b>	Н	i-Pr	OMs	(4S, 5S)	96		332	$C_{10}H_{20}O_8S_2$	С, Н	1360, 1182
10e	-(C]	H <sub>2</sub> ) <sub>4</sub> -	OMs	(4R, 5R)	89		344	$C_{11}H_{20}O_8S_2$	С, Н	1357, 1179
15e	-(C]	$(H_2)_4 -$	OMs	(4S, 5S)	96		344	$C_{11}H_{20}O_8S_2$	С, Н	1357, 1179
12a	н	Н	$N_3$	(4R, 5R)	95	+125.2	184	$C_5H_8N_6O_2$	C, H, N	2103
17a	н	Н	$N_3$	(4S, 5S)	<del>9</del> 6	-122.0	184	$C_5H_8N_6O_2$	C, H, N	2013
12b	н	Me	$N_3$	(4R, 5R)	93	+143.8	198	$C_6H_{10}N_6O_2$	C, H, N	2101
17 <b>b</b>	н	Me	$N_3$	(4S, 5S)	98	-140.7	198	$C_6H_{10}N_6O_2$	C, H, N	2101
12d	Me	$CH_2OTBDPS$	$N_3$	(4R, 5R)	90		467	$C_{23}H_{30}N_6O_3Si$	C, H, N	2099
17 <b>d</b>	Me	CH₂OTBDPS	$N_3$	(4S, 5S)	91		467	$C_{23}H_{30}N_6O_3Si$	C, H, N	2099
12e	Me	CH₂OH	$N_3$	(4R, 5R)	93	+108.6	228	$C_7H_{12}N_6O_3$	C, H, N	3425, 2103
17e	Me	CH₂OH	$N_3$	(4S, 5S)	92	-107.1	228	$C_7H_{12}N_6O_3$	C, H, N	3425, 2103
12f	н	Et	$N_3$	(4R, 5R)	92	+127.9	212	$C_7H_{12}N_6O_2$	C, H, N	2102
17f	н	Et	$N_3$	(4S, 5S)	90	-127.5	212	$C_7H_{12}N_6O_2$	C, H, N	2102
12g	Н	i-Pr	$N_3$	(4R, 5R)	97	+110.9	226	$C_8H_{14}N_6O_2$	C, H, N	2103
17g	Н	<i>i</i> -Pr	$N_3$	(4S, 5S)	97	-110.9	226	$C_8H_{14}N_6O_2$	C, H, N	2103
12h	-(Cl	$(H_2)_4 -$	$N_3$	(4R, 5R)	95	+125.4	238	$C_9H_{14}N_6O_2$	C, H, N	2101
17h	-(C]	$(H_2)_4 -$	$N_3$	(4S, 5S)	97	-122.9	238	$C_9H_{14}N_6O_2$	C, H, N	2101
12i	-(Cl	$H_{2})_{5}-$	$N_3$	(4R, 5R)	95	+120.4	252	$C_{10}H_{16}N_6O_2$	C, H, N	2100
17i	-(C]	$H_{2})_{5}-$	$N_3$	(4S, 5S)	98	-122.5	252	$C_{10}H_{16}N_6O_2$	C, H, N	2100
13 <b>a</b>	н	H	$\rm NH_2$	(4R, 5R)	97		132	$C_5H_{12}N_2O_2$	C, H, N	3370, 3307
18a	Н	Н	$\rm NH_2$	(4S, 5S)	99		132	$C_5H_{12}N_2O_2$	C, H, N	3370, 3307
13b	Н	Me	$\rm NH_2$	(4R, 5R)	97		146	$C_6H_{14}N_2O_2$	C, H, N	3375, 3304
18b	Н	Me	$\rm NH_2$	(4S, 5S)	99		146	$C_6H_{14}N_2O_2$	C, H, N	3375, 3304
13d	Me	CH <sub>2</sub> OH	$NH_2$	(4R, 5R)	99		176	$C_7H_{16}N_2O_3$	C, H, N	3366
18d	Me	CH₂OH	NH <sub>2</sub>	(4S, 5S)	99		176	$C_7H_{16}N_2O_3$	C, H, N	3366
13e	н	Et	$NH_2$	(4R,5R)	95		160	$C_7H_{16}N_2O_2$	C, H, N	3367
18e	н	Et	$NH_2$	(4S, 5S)	93		160	$C_7H_{16}N_2O_2$	C, H, N	3367
13f	H	i-Pr	$NH_2$	(4R,5R)	96		174	$C_8H_{18}N_2O_2$	C, H, N	3369, 3301
18f	Н	<i>i</i> -Pr	$NH_2$	(45,55)	96		174	$C_8H_{18}N_2O_2$	C, H, N	3369, 3301
13g	-(C)	H <sub>2</sub> ) <sub>4</sub>	$NH_2$	(4K, 5K)	96		186	$C_9H_{18}N_2O_2$	C, H, N	3370, 3302
18g	-(Cl	$H_{2}_{4}$	$NH_2$	(45,55)	95		186	$C_9H_{18}N_2O_2$	C, H, N	3370, 3302
13h	-(C)	H <sub>2</sub> ) <sub>5</sub> -	NH <sub>2</sub>	(4K,5K)	99		200	$C_{10}H_{20}N_2O_2$	U, H, N	3370, 3297
18h	-(Cl	H <sub>2</sub> } <sub>5</sub> -	NH <sub>2</sub>	(45,55)	98		200	$C_{10}H_{20}N_2O_2$	C, H, N	3370, 32 <b>9</b> 7

<sup>a</sup> Analytical results for the indicated elements are within  $\pm 0.4\%$  of theoretical values.

and the effects of their leaving ligands and 2-substituents in the 4,5-bis(aminomethyl)-1,3-dioxolane carrier ligands were examined (Table 2). In the (1,1-cyclobutanedicarboxylato)platinum(II) complexes, 1e ( $R_1 = H, R_2 = Et$ ) showed the most potent antitumor activity with a % T/C value of 391. Compounds 1b ( $R_1 = H, R_2 = Me$ ) and 1c  $(R_1 = R_2 = Me)$  also exhibited the potent activity with % T/C values of higher than 300. No antitumor activity of 1h ( $R_1$ ,  $R_2 = -(CH_2)_5$ -) might be attributed to very poor water solubility (0.9 mg/mL, 25 °C). It was demonstrated that the (4R,5R)-stereoisomers 1a-h had higher antitumor activities than the corresponding (4S,5S)-stereoisomers 2a-h. In the malonato-, (dimethylmalonato)-, and (ethylmalonato)platinum(II) complexes, all of the compounds except 1k and 1g showed the potent antitumor activity with % T/C values of higher than 200. Among the (glycolato)platinum(II) complexes, **3f** ( $R_1, R_2 = -(CH_2)_4$ -) exhibited the most potent antitumor activity with a % T/C value of 295. The next most potent was 3g (R<sub>1</sub>, R<sub>2</sub>  $= -(CH_2)_5$ ). In the (L-lactato)platinum(II) complexes, 3i ( $R_1 = H$ ,  $R_2 = Me$ ) showed the excellent antitumor activity with a % T/C value of 327, and all remaining compounds had potent activity with % T/C values above 200. As is evident from Table 2, most of platinum complexes in this series showed the excellent activity against mouse leukemia L1210 and were superior to

cisplatin and carboplatin. The solubility of platinum complexes was related to the nature of leaving ligands and 2-substituents in the 4,5-bis(aminomethyl)-1,3-dioxolane carrier ligands. The order of water solubility of the complexes having different leaving ligands was L-lactate >glycolate>malonate>dimethylmalonate>ethylmalonate > 1,1-cyclobutanedicarboxylate. In general, compounds having two different  $R_1$  and  $R_2$  substituents in the 4,5-bis(aminomethyl)-1,3-dioxolane moiety were more water-soluble than those having the same substituents. For example, compounds 1b and 1d ( $R_1 = Me$ ,  $R_2 = CH_2$ -OH) and 1e are highly water-soluble (24.9, 20.8, and 12.0 mg/mL at 25 °C, respectively), while compounds 1a ( $R_1$ =  $R_2$  = H) and 1c are less water-soluble (3.1 and 2.0 mg/ mL, respectively). The stability of the platinum complexes 1-3 in H<sub>2</sub>O was studied at room temperature by HPLC. All of the (malonato)- and (glycolato)platinum(II) complexes showed very little decomposition (<0.5%) over a period of 3 days; however, the (L-lactato)platinum(II) complexes were found to decompose to some extent (10-20%). Cytotoxicity of the compounds against four human stomach cancer cell lines, SNU-1, SNU-5, SNU-16, and NCl-N87,<sup>51</sup> were tested, and the results are shown in Table 3. We were particularly interested in testing this series of compounds toward those cell lines because stomach cancer is still a leading malignant disease in many

Table 2. Antitumor Activity of Platinum(II) Complexes against L1210 Leukemia in Mice<sup>a</sup>

	% 1/C at dose (mg/kg, ip, days 1, 5, 9)									
compd	100	50	25	12.5	6.25	3.1	1.5			
la	271 (2/7), <sup>b</sup> (2/7) <sup>c</sup>	193	137	187	122					
2a	179	123 (1/7) <sup>b</sup>	119	97	93					
1 <b>b</b>	382 (1/7). <sup>b</sup> (4/7) <sup>c</sup>	262 (2/7)°	247 (2/7)°	129 (1/7) <sup>b</sup>	125					
2b	254 (1/7)°	201 (1/7)°	150	115	108					
1c	317 (1/7). <sup>b</sup> (2/7) <sup>c</sup>	283 (2/7)°	217 (1/7)°	170 (1/7) <sup>b</sup>	124					
2c	142	148 (1/7)°	124	106	112					
1d	181 (1/7)	121	104	103	94					
2d	123	118	98	94	98					
1e	391 (5/7)°	208	193 (1/7) <sup>b</sup>	130	122					
2e	151	134	116	107	97					
lf	$130 (3/7)^{b}$	133	126	106	113					
2 <b>f</b>	120	112	104	100	96					
1g	185	148	110 (1/7)	122	109					
2g	117 (3/7)6	106	94	109	102					
-8 1h	108 (3/7)	101 (1/7)	120							
2h	toxic	95 (3/7)6	104							
11		276 (1/7)°	133 (3/7)	146						
15		241	156	140						
-, 1k		190	179	133						
11		245	204	144						
1m		220 (1/7)°	148	123 (1/7)°						
1n		203	169	217						
10	248 (1/7)°	165 (1/7)°	213 (1/7)							
10 1n	204	174	123							
10	150	160	172							
	97 (5/7). <sup>b</sup> (1/7) <sup>c</sup>	245	197							
18	243 (1/7) <sup>b</sup>	169	137							
1t	216	232 (1/7)	147							
3.9		toxic	129 (2/7)	137	132 (1/7)	95				
3b		toxic	$167 (2/7)^{b}$	154	136	104				
30		toxic	toxic	201	179	112				
3d		toxic	toxic	205	162	113				
3e		toxic	toxic	191 (1/7)b	166	155				
3f		toxic	toxic	295 (2/7)°	161	154				
3g		toxic	$231 (1/7)^{b}$	233 (1/7)°	146	102				
3h		92	207	178						
31		139 (5/7) <sup>b</sup>	327 (2/7)°	201						
31		toxic	toxic	213						
3k		toxic	$165 (2/7)^{b}$	206						
31		toxic	232 (2/7), <sup>b</sup> (1/7) <sup>c</sup>	208						
3m		192 (5/7). <sup>b</sup> (2/7) <sup>c</sup>	243 (1/7)°	225 (1/7)°						
3n		toxic	227	204						
cisplatin			-	toxic	82 (5/7) <sup>b</sup>	167 (2/7) <sup>b</sup>	142			
carboplatin	197 (1/7)6	196 (1/7)°	148	125	107					
		· · ·			-					

<sup>a</sup> See the Experimental Section for biological methods. <sup>b</sup> Values in parentheses = number of toxic death/number of animals tested. <sup>c</sup> Values in parentheses = number of cures/number of animals tested. Cures are defined as animals without gross evidence of tumor on the 50th day of evaluation.

countries, including Korea, Japan, eastern Europe, Iceland, and South Africa.<sup>52,53</sup> All of the tested (1,1-cyclobutanedicarboxylato)platinum(II) complexes except 1d exhibited higher cytotoxicity toward above cancer cell lines than carboplatin. The (glycolato)platinum(II) complexes were highly cytotoxic, and among them, compounds 3d ( $R_1 =$ H,  $R_2 = Et$ ), 3e ( $R_1 = H$ ,  $R_2 = i$ -Pr), 3f, and 3g were even more cytotoxic than cisplatin in terms of  $IC_{50}$ . Among the (L-lactato)platinum(II) complexes, compounds  $3\mathbf{k}$  ( $\mathbf{R}_1 =$ H,  $R_2 = Et$ ), 31 ( $R_1 = H$ ,  $R_2 = i$ -Pr), 3m ( $R_1$ ,  $R_2 = -(CH_2)_4$ -), and 3n (R<sub>1</sub>, R<sub>2</sub> = -(CH<sub>2</sub>)<sub>5</sub>-) displayed the cytotoxicity almost equal to cisplatin. It is noteworthy that the SNU-5 cells were particularly sensitive to this series of complexes compared to cisplatin and carboplatin. The order of  $IC_{50}$ values of the complexes having different leaving ligands was glycolate < L-lactate < malonate  $\simeq$  dimethylmalonate  $\simeq$  ethylmalonate < 1,1-cyclobutanedicarboxylate. The 2-substituents in the 4,5-bis(aminomethyl)-1,3-dioxolane carrier ligands considerably influenced their cytotoxicity, also. The substitution of a hydrogen by the isopropyl group remarkably increased the cytotoxicity. The order of cytotoxicity of the complexes with different 2-substituents seemed to be  $R_1 = H$ ,  $R_2 = i$ -Pr >  $R_1$ ,  $R_2 =$  $-(CH_2)_{4^-} > R_1, R_2 = -(CH_2)_{5^-} > R_1 = H, R_2 = Et > R_1$ =  $R_2 = Me > R_1 = H, R_2 = Me > R_1 = R_2 = H > R_1 =$ Me,  $R_2 = CH_2OH$ . The screening data presented in Tables 2 and 3 and the physical properties of this series of complexes will give the valuable information to choose the candidate for further evaluation for clinical use. Although the (1.1-cvclobutanedicarboxvlato) platinum(II) complexes 1b and 1e showed the excellent antitumor activity against L1210 leukemia in mice, they were not included in further screening because of the lower cytotoxicity toward four human stomach cancer cell lines compared to (glycolato)- and (L-lactato)platinum(II) complexes. On the basis of antitumor activity and cytotoxicity, the (glycolato)platinum(II) complexes 3d-g were selected as promising candidates. These four complexes also have good solubility and high stability in aqueous solution; therefore, they were chosen for further evaluation. While the (L-lactato)platinum(II) complexes 3k-n showed good combination of antitumor activity and cytotoxicity, they were not tested further due to the instability in aqueous solution. Among the (malonato)-,

 Table 3. Cytotoxicity of Platinum(II) Complexes against Human

 Stomach Cancer Cell Lines in Vitro<sup>a</sup>

	IC <sub>50</sub> (μg/mL)							
compd	SNU-1 <sup>b</sup>	SNU-5 <sup>b</sup>	SNU-16 <sup>b</sup>	NCI-N87 <sup>b</sup>				
1a	28.23	4.82	12.67	70.46				
1 <b>b</b>	28.02	4.77	8.69	87.55				
1c	24.64	3.94	9.40	54.39				
1 <b>d</b>	161.69	14.15	71.38	544.16				
1e	17.62	2.15	9.02	56.92				
1 <b>f</b>	16.64	1.21	10.09	60.61				
1 <b>g</b>	18.43	2.50	7.61	44.41				
11	8.96	2.42	9.72	43.46				
1j	26.99	1.84	13.59	25.04				
1 <b>k</b>	14.27	1.72	9.71	26.48				
11	11.34	1.67	9.73	22.45				
1 <b>m</b>	9.17	1.80	4.40	16.35				
1 <b>n</b>	8.82	1.02	3.80	14.90				
10	17.61	1.93	6.17	14.88				
1 <b>p</b>	8.70	0.18	4.42	12.00				
1 <b>q</b>	7.07	1.80	3.09	30.91				
1 <b>r</b>	11.05	0.51	8.63	14.20				
1s	8.09	1.82	4.25	15.19				
lt	9.48	0.50	3.75	20.86				
3a	4.93	0.88	3.93	17.10				
3b	8.42	0.29	4.64	13.49				
3c	7.50	1.04	1.96	16.20				
3d	3.63	0.22	3.14	5.69				
3e	2.49	0.17	1.62	4.83				
3f	1.75	0.05	1.58	5.50				
3g	2.39	0.81	1.24	11.09				
3h	11.75	0.84	5.59	13.43				
31	12.15	0.87	3.18	10.79				
3j	11.01	0.94	2.51	10.82				
3k	8.43	0.26	2.99	5.39				
31	5.17	0.30	2.26	14.42				
3m	4.08	0.63	1.79	17.42				
3n	2.88	0.87	2.24	16.57				
cisplatin	2.90	1.29	2.83	13.73				
carboplatin	37.78	10.75	34.02	153.38				

<sup>a</sup> See the Experimental Section for biological methods. <sup>b</sup> See ref 51.

 Table 4. Cytotoxicity of Selected Platinum(II) Complexes

 against Human Stomach and Lung Cancer Cell Lines in Vitro<sup>a</sup>

		IC <sub>50</sub> (µg/m	L)	
compd	KATO-III <sup>b</sup>	MKN-45 <sup>b</sup>	PC-9°	PC-14 <sup>c</sup>
1 <b>m</b>	1.98	1.96	5.02	0.82
3d	1.78	1.43	2.31	0.55
3e	0.98	0.57	1.99	0.56
3f	1.14	0.82	1.98	0.63
3g	0.92	0.88	2.07	0.87
cisplatin	0.83	0.51	1.03	0.77
carboplatin	10.50	6.40	19.00	5.80

<sup>a</sup> See the Experimental Section for biological methods. <sup>b</sup> Stomach adenocarcinoma. <sup>c</sup> Lung adenocarcinoma.

(dimethylmalonato), and (ethylmalonato)platinum(II) complexes, the compounds 1m, 1n, 1p, 1r-t showed good combination of antitumor activity and cytotoxicity. The (malonato)platinum(II) complex 1m was considered to be a good candidate for further studies because of very high stability in solution, showing very little decomposition (<1%) in H<sub>2</sub>O, 5% aqueous xylitol solution, and 5% aqueous mannitol solution, respectively, over a period of 6 months at 4 °C. Cytotoxicity of the selected five compounds 1m, 3d-g were further tested toward two human stomach cancer cell lines, KATO-III and MKN-45, and two human non-small cell lung cancer cell lines, PC-9 and PC-14, by MTT assay<sup>54,55</sup> (Table 4). It was found that the compounds 3e-g had the cytotoxicity almost equal to cisplatin against KATO-III, MKN-45, and PC-14. The selected compounds were tested for the antitumor activity

against cisplatin-resistant L1210 cells (ip-ip system) in mice (Table 5). The compounds 1m, 3d, 3f, and 3g exhibited the potent antitumor activity with % T/C values of around 200, whereas cisplatin had virtually no activity and carboplatin showed only marginal activity in this screening. Therefore, it has been demonstrated that cisplatin-resistant L1210 cells had lower cross-resistance to these compounds than to cisplatin and carboplatin. As a measure of nephrotoxicity, serum blood urea nitrogen (BUN) and creatinine levels<sup>56</sup> were monitored in ICR mice after the administration of the five compounds at a dose equal to 1.5 times the optimal dose determined in the *in* vivo L1210 screening system, and the results are summarized in Table 6. Cisplatin and carboplatin were also given at 2 and 1.5 times the optimal doses, respectively, as the control. As indicated from these data, the selected five compounds and carboplatin did not elevate serum levels of BUN and creatinine during the 8-day examination period, while cisplatin produced a significant rise in both BUN (43.1 mg/100 mL) on day 4 and serum creatinine (0.40 mg/100 mL) on day 8. In histopathological examinations, mild tubular degeneration in kidney was observed in cisplatin-treated group only, thus indicating that these five complexes were less nephrotoxic than cisplatin.

# Conclusion

It has been shown that almost all the members of this series of [2-substituted-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) complexes have the pronounced antitumor activity against L1210 cells in mice and exhibit the high cytotoxicity toward human stomach cancer cell lines, SNU-1, SNU-5, SNU-16, and NCI-N87 in vitro. Most of these complexes possess the desirable physical properties such as high solubility and stability in aqueous solution. The selected five complexes 1m, 3d-g have potent antitumor activity against cisplatin-resistant L1210 cells in mice, whereas carboplatin shows only marginal activity, demonstrating that these complexes are less cross-resistant to cisplatin than carboplatin. In addition, nephrotoxicity studies in ICR mice indicate serum BUN and creatinine levels are not elevated when five complexes are given at a dose equal to 1.5 times the optimal dose determined in the *in vivo* L1210 screening system, suggesting that these complexes be less nephrotoxic than cisplatin. Therefore, the results of these studies demonstrate that this series of platinum complexes has an extremely high potential to be developed as a clinically useful anticancer agent.

# **Experimental Section**

Melting points were determined on an Electrothermal F500MA digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. <sup>1</sup>H NMR spectra were recorded on either a Varian Unity 300 or a Bruker AM-100 spectrometer. The chemical shifts are reported in parts per million (ppm) relative to TMS in CDCl<sub>3</sub> or DMSO- $d_6$  and to DSS (0.015 ppm) in D<sub>2</sub>O. <sup>1</sup>H noise-decoupled  $^{13}\mathrm{C}\ \mathrm{NMR}$  spectra were recorded on either a Varian Unity 300 at 75.4 MHz or a Bruker AM-100 spectrometer at 25.1 MHz. When  $CDCl_3$  or  $DMSO-d_6$  was used as solvent, it served as the internal standard at  $\delta$  77.0 or 39.5, respectively. When D<sub>2</sub>O was used, DSS (-1.6 ppm) was added as the internal standard. UV spectra were measured in H<sub>2</sub>O with a Gilford Response UV-vis spectrophotometer. Electron impact mass spectra (EI-MS) and fastatom bombardment mass spectra (FAB-MS) were obtained on a VG Quattro mass spectrometer. Glycerol was used as FAB matrix. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60F-254 glass plates. Flash

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Table 5. Antitumor Activity of Selected Platinum(11) Complexes against Cisplatin-Resistant L1210 Leukemia	a Mice

	% T/C at dose (mg/kg, ip, days 1, 5, 9)							
compd	100	50	25	12.5	6.25	3.1	1.5	
lm	213 (1/7)°	205 (1/7)°	140					
3d				183 (2/7) <sup>c</sup>	121 (1/7)°	118 (1/7)°		
3e				164	135 (1/7)°	158		
3f				168 (3/7)°	213 (2/7)°	103		
3g				196 (3/7)°	189 (3/7)°	110		
cisplatin					toxic	109	86	
carboplatin	81 (2/7) <sup>b</sup>	132 (2/7)°	98					

<sup>a-c</sup> See corresponding footnotes of Table 2.

Table 6. Serum Levels of Blood Urea Nitrogen and Creatinine in Mice after a Singe ip Administration of Selected Platinum(II) Complexes<sup>a</sup>

		BUN (mg/100 mL)			creatinine (mg/100 mL)		
compd	dose (mg/kg)	day 1	day 4	day 8	day 1	day 4	day 8
control	_	25.9 ± 1.3 <sup>b</sup>	26.9 ± 1.1	24.9 ± 2.5	$0.27 \pm 0.01$	$0.26 \pm 0.01$	$0.28 \pm 0.01$
1m	75.0	$22.6 \pm 1.6$	$27.0 \pm 2.2$	$28.3 \pm 1.5$	$0.22 \pm 0.01$	$0.24 \pm 0.02$	$0.29 \pm 0.01$
3d	18.8	$24.9 \pm 1.1$	$19.0 \pm 1.0$	$19.9 \pm 1.6$	$0.28 \pm 0.02$	$0.26 \pm 0.02$	$0.26 \pm 0.01$
3e	18.8	$26.8 \pm 1.8$	$21.2 \pm 0.7$	$26.7 \pm 1.0$	$0.27 \pm 0.01$	$0.26 \pm 0.01$	$0.30 \pm 0.01$
3f	18.8	$26.7 \pm 2.8$	$20.7 \pm 1.1$	$24.7 \pm 2.8$	$0.27 \pm 0.01$	$0.24 \pm 0.02$	$0.29 \pm 0.02$
3g	18.8	$26.1 \pm 0.9$	$17.2 \pm 2.2$	$22.0 \pm 0.8$	$0.26 \pm 0.01$	$0.24 \pm 0.01$	$0.27 \pm 0.02$
cisplatin	6.0	$24.8 \pm 1.6$	43.1 ± 12.9°	$32.5 \pm 2.4^{d}$	$0.26 \pm 0.01$	$0.28 \pm 0.06$	$0.40 \pm 0.03$
carboplatin	150.0	$24.4 \pm 0.7$	$21.1 \pm 1.3$	$28.58 \pm 3.1$	$0.25 \pm 0.02$	$0.19 \pm 0.01$	$0.31 \pm 0.01$

<sup>a</sup> See the Experimental Section for biological methods. <sup>b</sup> The values represent the means plus or minus standard error. <sup>c</sup> Mean is significantly different from control group; p < 0.05. <sup>d</sup> Mean is significantly different from control group; p < 0.01.

chromatography was performed using Merck silica gel 60 (230-400 mesh). Purity and stability for tested platinum(II) complexes was assessed by analytical reverse-phase column chromatography (RPHPLC) on a Waters Associates system (consisting of a 600E pump, a 712WISP automated injector, and a Model 990 photodiode array detector), using  $\mu$ -Bondapak C<sub>18</sub>, 10- $\mu$ m particle size, 125-Å pore size columns,  $3.9 \times 300$  mm. The mobile phase utilized was a MeOH-H<sub>2</sub>O system, and the flow rate was 1.5 mL/min, with monitoring of the peak at 220 nm. Preparative RPHPLC was accomplished on a Waters Associates system (consisting of a 600E pump, a Prep LC 3000 system, and a Model 484 tunable absorbance detector), using Delta pak  $C_{18}$ , 15- $\mu$ m particle size, 100-Å pore size columns, 19 × 300 mm (UV detection at 220 nm). Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. Where indicated by the symbols of the elements, analyses were within  $\pm 0.4\%$  of theoretical values.

General Method for the Synthesis of (Malonato)platinum(II) Complexes 1a-t and 2a-h. A suspension of diiodoplatinum(II) complex (4a-h and 6a-h) (1.0 mmol) and the silver salt of a malonic acid (5a-d) (1.0 mmol) in H<sub>2</sub>O (100 mL) was stirred at 60 °C in the dark overnight. The resulting silver iodide was filtered through a pad of Celite, and the filtrate was again filtered using a millipore filter (0.22  $\mu$ m). The filtrate was concentrated under a reduced pressure to ~20 mL in volume. The white precipitates were filtered, and the mother liquor was purified by preparative HPLC on Delta pak C<sub>18</sub>-100-Å reversephase bonded silica cartridge with MeOH-H<sub>2</sub>O system as the mobile phase. The eluate was concentrated under a reduced pressure to a small volume and freeze-dried to give an additional product. Starting materials, mobile phase for preparative HPLC, yield, physical appearance, and spectral data are given below.

cis-(Cyclobutane-1,1-dicarboxylato)[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) (1a): 4a and 5a; MeOH-H<sub>2</sub>O (2:8); 46%; white crystals; IR (KBr) 3432, 3239, 3191, 3126, 1634, 1590 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.67 (quintet, J =7.8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.50-2.77 (m, 6 H, 2 CHNH<sub>2</sub> and CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.06 (m, 2 H, 2 CHNH<sub>2</sub>), 4.32 (m, 2 H, 2 CH), 4.93 (s, 2 H, OCH<sub>2</sub>O), 5.24-5.65 (m, 4 H, 4 NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  14.85, 30.32, 47.75, 55.43, 78.37, 93.87, 177.30; FAB-MS m/z 470 (MH)<sup>+</sup>. Anal. (C<sub>11</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4R,5R)-4,5-bis(aminomethyl)-2-methyl-1,3-dioxolane]platinum(II) (1b): 4b and 5a; MeOH-H<sub>2</sub>O (2:8); 55%; white powder; IR (KBr) 3447, 3218, 3132, 1634 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  1.26 (d, J = 4.9 Hz, 3 H, CH<sub>3</sub>), 1.67 (quintet, J = 7.8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.47-2.80 (m, 2 H, 2 CHNH<sub>2</sub> overlapped with CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.66 (t, J = 7.8 Hz,

4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.95 (m, 1 H, CHNH<sub>2</sub>), 3.08 (m, 1 H, CHNH<sub>2</sub>), 4.32 (m, 1 H, CH), 4.48 (m, 1 H, CH), 5.14 (q, J = 4.9 Hz, 1 H, CH), 5.32 (br s, 1 H, NH), 5.46 (br s, 3 H, 3 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  14.82, 19.49, 30.21, 30.39, 47.87, 47.98, 55.42, 77.61, 79.73, 100.44, 177.29; FAB-MS m/z 484 (MH)<sup>+</sup>. Anal. (C<sub>12</sub>H<sub>20</sub>-N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4R,5R)-4,5-bis(aminomethyl)-2,2-dimethyl-1,3-dioxolane]platinum(II) (1c): 4c and 5a; MeOH-H<sub>2</sub>O (4:6); 55%; white crystals; IR (KBr) 3424, 3239, 3084, 1616, 1587 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  1.33 (s, 6 H, 2 CH<sub>3</sub>), 1.67 (quintet, J = 7.8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.56 (m, 2 H, 2 CHNH<sub>2</sub>), 2.66 (t, J = 7.8 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.56 (m, 2 H, 2 CHNH<sub>2</sub>), 2.66 (t, J = 7.8 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.03 (m, 2 H, 2 CHNH<sub>2</sub>), 4.37 (m, 2 H, 2 CH), 5.43 (br s, 2 H, 2 NH), 5.51 (br s, 2 H, 2 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  14.86, 26.41, 30.29, 48.47, 55.44, 78.18, 108.32, 177.28; FAB-MS m/z 498 (MH)<sup>+</sup>. Anal. (C<sub>13</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4R,5R)-4,5-bis(aminomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane]platinum(II) (1d): 4d and 5a; MeOH-H<sub>2</sub>O (2:8); 67%; colorless crystals; IR (KBr) 3469, 3205, 3131, 1652, 1608 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  1.24 (s, 3 H, CH<sub>3</sub>), 1.67 (quintet, J = 7.8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.59 (m, 2 H, 2 CHNH<sub>2</sub>, overlapped with CH<sub>2</sub>-CH<sub>2</sub>CH<sub>2</sub>), 2.65 (t, J = 7.8 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>OH<sub>2</sub>), 3.03 (m, 2 H, 2 CHNH<sub>2</sub>), 3.27 (d, J = 11.7 Hz, 1 H, CH<sub>2</sub>OH), 3.34 (d, J = 11.7 Hz, 1 H, CH<sub>2</sub>OH), 4.36 (m, 1 H, CH), 4.53 (m, 1 H, CH), 4.94 (br s, 1 H, OH), 5.35 (br s, 2 H, 2 NH), 5.44 (br s, 2 H, 2 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  14.83, 22.11, 30.27, 48.17, 55.42, 65.47, 78.37, 78.85, 109.46, 177.25; FAB-MS m/z 514 (MH)<sup>+</sup>. Anal. (C<sub>13</sub>H<sub>22</sub>-N<sub>2</sub>O<sub>7</sub>Pt) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4R,5R)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (1e): 4e and 5a; MeOH-H<sub>2</sub>O (3:7); 57%; colorless crystals; IR (KBr) 3446, 3189, 3072, 1609 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_{\theta}$ )  $\delta$  0.86 (t, J = 7.5 Hz, 3 H, CH<sub>3</sub>), 1.57 (dq, J = 4.5 Hz, J = 7.5 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 2.65 (t, J = 7.8 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.97 (m, 1 H, CHNH<sub>2</sub>), 3.09 (m, 1 H, CHNH<sub>2</sub>), 4.28 (m, 1 H, CH), 4.45 (m, 1 H, CH), 4.99 (t, J = 4.5 Hz, 1 H, CH), 5.30 (br s, 1 H, NH), 5.44 (br s, 3 H, 3 NH); <sup>13</sup>C NMR (DMSO- $d_{\theta}$ )  $\delta$  7.63, 14.79, 26.33, 30.27, 47.90, 47.98, 55.40, 77.70, 79.52, 104.08, 177.24; FAB-MS m/z 498 (MH)<sup>+</sup>. Anal. (C<sub>13</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4R,5R)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (1f): 4f and 5a; MeOH-H<sub>2</sub>O (4:6); 51%; white crystals; IR (KBr) 3433, 3198, 3070, 1608, 1593 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  0.86 (d, J = 6.9 Hz, 6 H, 2 CH<sub>3</sub>), 1.67 (quintet, J = 7.8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.72 (m, 1 H, CH(CH<sub>3</sub>)<sub>2</sub>, overlapped with CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.57 (m,

#### (Substituted dioxolane)platinum(II) Complexes

2 H, 2 CHNH<sub>2</sub>, overlapped with CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>( $H_2$ ), 2.64 (t, J = 7.8 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.00 (m, 1 H, CHNH<sub>2</sub>), 3.10 (m, 1 H, CHNH<sub>2</sub>), 4.24 (m, 1 H, CH), 4.44 (m, 1 H, CH), 4.79 (d, J = 4.5 Hz, 1 H, CH), 5.30 (br s, 1 H, NH), 5.45 (br s, 3 H, 3 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  14.80, 16.39, 16.44, 30.17, 30.37, 31.32, 47.83, 48.03, 55.41, 77.92, 79.48, 106.83, 177.24; FAB-MS m/z 512 (MH)<sup>+</sup>. Anal. (C<sub>14</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclopentane]platinum-(II) (1g): 4g and 5a; MeOH-H<sub>2</sub>O (5:5); 45%; white powder; IR (KBr) 3445, 3190, 3085, 1615 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.47-1.85 (m, 8 H, cyclopentyl), 1.67 (quintet, J = 7.8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>-CH<sub>2</sub>, overlapped with cyclopentyl), 2.55 (m, 2 H, 2 CHNH<sub>2</sub>), 2.65 (t, J = 7.8 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.05 (m, 2 H, 2 CHNH<sub>2</sub>), 4.34 (m, 2 H, 2 CH), 5.38 (br s, 2 H, 2 NH), 5.47 (br s, 2 H, 2 NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  15.26, 23.30, 30.72, 36.58, 48.61, 55.84, 78.34, 118.69, 178.13; FAB-MS m/z 524 (MH)<sup>+</sup>. Anal. (C<sub>16</sub>H<sub>24</sub>-N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclohexane]platinum-(II) (1h): 4h and 5a; MeOH-H<sub>2</sub>O (5:5); 41%; white powder; IR (KBr) 3445, 3190, 3069, 1607 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  1.34 (br s, 2 H, cyclohexyl), 1.54 (br s, 8 H, cyclohexyl), 1.67 (quintet, J = 7.8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.55 (m, 2 H, 2 CHNH<sub>2</sub>), 2.65 (t, J = 7.8 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.10 (m, 2 H, 2 CHNH<sub>2</sub>), 2.65 (t, J = 7.8 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.10 (m, 2 H, 2 CHNH<sub>2</sub>), 4.36 (m, 2 H, 2 CH), 5.37 (br s, 2 H, 2 NH), 5.45 (br s, 2 H, 2 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  14.82, 23.32, 24.41, 30.26, 35.55, 48.60, 55.42, 77.84, 108.72, 117.24; FAB-MS m/z 538 (MH)<sup>+</sup>. Anal. (C<sub>16</sub>H<sub>26</sub>-N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Malonato)[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum)(II) (1i): 4a and 5b; MeOH-H<sub>2</sub>O (1:9), 81%; white crystals; IR (KBr) 3481, 3243, 3172, 3048, 1652, 1606 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  2.62 (m, 2 H, 2 CHNH<sub>2</sub>), 3.04 (m, 2 H, 2CHNH<sub>2</sub>), 3.26 (s, 2 H, CH<sub>2</sub>), 4.41 (m, 2 H, 2 CH), 4.94 (s, 2 H, OCH<sub>2</sub>O), 5.38 (br s, 2 H, 2 NH), 5.47 (br s, 2 H, 2 NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  47.54, 50.22, 78.30, 93.86, 174.01; FAB-MS m/z 430 (MH)<sup>+</sup>. Anal. (C<sub>8</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Malonato)[(4R,5R)-4,5-bis(aminomethyl)-2-methyl-1,3-dioxolane]platinum(II) (1j): 4b and 5b; MeOH-H<sub>2</sub>O (1: 9), 81%; white crystals; IR (KBr) 3454, 3383, 3214, 3065, 1643-1555 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  1.27 (d, J = 4.8 Hz, 3 H, CH<sub>3</sub>), 2.60 (m, 2 H, 2 CHNH<sub>2</sub>), 2.94 (m, 1 H, CHNH<sub>2</sub>), 3.05 (m, 1 H, CHNH<sub>2</sub>), 3.26 (s, 2 H, CH<sub>2</sub>), 4.36 (m, 1 H, CH), 4.61 (m, 1 H, CH), 5.16 (q, J = 4.8 Hz, 1 H, CH), 5.31 (br s, 1 H, NH), 5.48 (br s, 3 H, 3 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  19.54, 47.75, 47.81, 50.21, 77.50, 79.72, 100.44, 174.03; FAB-MS m/z 444 (MH)<sup>+</sup>. Anal. (C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Malonato)[(4R,5R)-4,5-bis(aminomethyl)-2,2-dimethyl-1,3-dioxolane]platinum(II) (1k): 4c and 5b; MeOH-H<sub>2</sub>O (3: 7); 89%; white crystals; IR (KBr) 3445, 3207, 3107, 1627 cm<sup>-1</sup>; <sup>1</sup>H NMR (DSMO- $d_6$ )  $\delta$  1.34 (s, 6 H, 2 CH<sub>3</sub>), 2.56 (m, 2 H, 2 CHNH<sub>2</sub>), 3.02 (m, 2 H, 2 CHNH<sub>2</sub>), 3.26 (s, 2 H, CH<sub>2</sub>), 4.45 (m, 2 H, 2 CH), 5.45 (br s, 2 H, 2 NH), 5.56 (br s, 2 H, 2 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  26.42, 48.33, 50.22, 78.10, 108.30, 174.00; FAB-MS m/z 458 (MH)<sup>+</sup>. Anal. (C<sub>10</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Malonato)[(4R,5R)-4,5-bis(aminomethyl)-2-ethyl-1,3dioxolane]platinum(II) (11): 4e and 5b; MeOH-H<sub>2</sub>O (3:7); 89%; white crystals; IR (KBr) 3447, 3214, 3120, 1628 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  0.87 (t, J = 7.5 Hz, 3 H, CH<sub>3</sub>), 1.58 (dq, J = 4.5 Hz, J = 7.5 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 2.59 (m, 2 H, 2 CHNH<sub>2</sub>), 2.97 (m, 1 H, CHNH<sub>2</sub>), 3.08 (m, 1 H, CHNH<sub>2</sub>), 3.26 (s, 2 H, CH<sub>2</sub>), 4.33 (m, 1 H, CH), 4.57 (m, 1 H, CH), 5.00 (t, J = 4.5 Hz, 1 H, CH), 5.29 (br s, 1 H, NH), 5.46 (br s, 3 H, 3 NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  7.65, 26.35, 47.74, 47.84, 50.21, 77.65, 79.50, 104.12, 174.04; FAB-MS m/z 458 (MH)<sup>+</sup>. Anal. (C<sub>10</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Malonato)[(4R,5R)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (1m): 4f and 5b: MeOH-H<sub>2</sub>O (4: 6); 89%; white crystals; IR (KBr) 3431, 3205, 3049, 1612 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  0.87 (d, J = 6.6 Hz, 6 H, 2 CH<sub>3</sub>), 1.75 (m, 1 H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.59 (m, 2 H, 2 CHNH<sub>2</sub>), 2.98 (m, 1 H, CHNH<sub>2</sub>), 3.09 (m, 1 H, CHNH<sub>2</sub>), 3.25 (s, 1 H, CH<sub>2</sub>), 3.26 (s, 1 H, CH<sub>2</sub>), 4.31 (m, 1 H, CH), 4.55 (m, 1 H, CH), 4.80 (d, J = 4.5 Hz, 1 H, CH), 5.31 (br s, 1 H, NH), 5.48 (br s, 3 H, 3 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  16.42, 16.45, 31.27, 47.72, 47.92, 50.22, 77.84, 79.42, 106.81, 173.99; FAB-MS m/z 472 (MH)<sup>+</sup>. Anal. (C<sub>11</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Malonato)[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclopentane]platinum(II) (1n): 4g and 5b; MeOH-H<sub>2</sub>O (4:6); 56%; white crystals; IR (KBr) 3433, 3200, 3053, 1613 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  1.45–1.90 (m, 8 H, cyclopentyl), 2.55 (m, 2 H, 2 CHNH<sub>2</sub>), 3.03 (m, 2 H, 2 CHNH<sub>2</sub>), 3.26 (s, 2 H, CH<sub>2</sub>), 4.41 (m, 2 H, 2 CH), 5.38 (br s, 2 H, 2 NH), 5.50 (br s, 2 H, 2 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  22.86, 36.23, 48.20, 50.21, 78.03, 118.10, 174.00; FAB-MS m/z 484 (MH)<sup>+</sup>. Anal. (C<sub>12</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Dimethylmalonato)[(4R,5R)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (10): 4e and 5c; MeOH-H<sub>2</sub>O (4:6); 83%; white crystals; IR (KBr) 3454, 3211, 3126, 1650-1597 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  0.86 (t, J = 7.4 Hz, 3 H, CH<sub>3</sub>), 1.53 (s, 3 H, CH<sub>3</sub>), 1.54 (s, 3 H, CH<sub>3</sub>), 1.58 (dq, J = 4.4 Hz, J = 7.4 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 2.59 (m, 2 H, 2 CHNH<sub>2</sub>), 2.98 (m, 1 H, CHNH<sub>2</sub>), 3.10 (m, 1 H, CHNH<sub>2</sub>), 4.29 (m, 1 H, CH), 4.47 (m, 1 H, CH), 5.00 (t, J = 4.4 Hz, 1 H, CH), 5.35 (br s, 1 H, NH), 5.48 (br s, 3 H, 3 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  7.68, 26.03, 26.38, 47.92, 48.01; 51.72, 77.79, 79.59, 104.15, 178.65; FAB-MS m/z 486 (MH)<sup>+</sup>. Anal. (C<sub>12</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Dimethylmalonato)[(4R,5R)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (1p): 4f and 5c; MeOH-H<sub>2</sub>O (5:5); 75%; white crystals; IR (KBr) 3449, 3216, 3130, 1630 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_{\theta}$ )  $\delta$  0.87 (d, J = 6.9 Hz, 6 H, 2 CH<sub>3</sub>), 1.53 (s, 3 H, CH<sub>3</sub>), 1.54 (s, 3 H, CH<sub>3</sub>), 1.74 (m, 1 H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.59 (m, 2 H, 2 CHNH<sub>2</sub>), 3.00 (m, 1 H, CHNH<sub>2</sub>), 3.11 (m, 1 H, CHNH<sub>2</sub>), 4.26 (m, 1 H, CH), 4.45 (m, 1 H, CH), 4.81 (d, J = 4.5Hz, 1 H, CH), 5.33 (br s, 1 H, NH), 5.48 (br s, 3 H, 3 NH); <sup>13</sup>C NMR (DMSO- $d_{\theta}$ )  $\delta$  16.44, 16.49, 26.00, 26.04, 31.36, 47.87, 48.06, 51.72, 78.00, 79.53, 106.89, 178.65; FAB-MS m/z 500 (MH)<sup>+</sup>. Anal. (C<sub>13</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Dimethylmalonato)[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclopentane]platinum(II) (1q): 4g and 5c; MeOH-H<sub>2</sub>O (5:5); 64%; white powder; IR (KBr) 3454, 3218, 3131, 1668–1652 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  1.50–1.85 (m, 8 H, cyclopentyl), 1.54 (s, 6 H, 2 CH<sub>3</sub>), 2.55 (m, 2 H, 2 CHNH<sub>2</sub>), 3.04 (m, 2 H, CHNH<sub>2</sub>), 4.36 (m, 2 H, 2 CH), 5.40 (br s, 2 H, 2 NH), 5.49 (br s, 2 H, 2 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  22.91, 26.01, 36.26, 48.38, 51.70, 78.15, 118.10, 178.59; FAB-MS m/z 512 (MH)<sup>+</sup>. Anal. (C<sub>14</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Ethylmalonato)[(4R,5R)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (1r): 4e and 5d; MeOH-H<sub>2</sub>O (4: 6); 95%; white crystals; IR (KBr) 3446, 3205, 3122, 1648, 1635 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  0.86 (t, J = 7.5 Hz, 3 H, CH<sub>3</sub>), 0.87 (t, J = 7.5 Hz, 3 H, CH<sub>3</sub>), 1.58 (dq, J = 4.2 Hz, J = 7.5 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 1.82 (dq, J = 7.1 Hz, J = 7.5 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 2.60 (m, 2 H, 2 CHNH<sub>2</sub>), 2.96 (m, 1 H, CHNH<sub>2</sub>), 3.08 (m, 1 H, CHNH<sub>2</sub>), 3.40 (t, J = 7.1 Hz, 1 H, CH), 4.30 (m, 1 H, CH), 4.50 (m, 1 H, CH), 5.00 (t, J = 4.2 Hz, 1 H, CH), 5.30 (br s, 1 H, NH), 5.48 (br s, 3 H, 3 NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  7.67, 7.69, 12.49, 22.52, 22.57, 26.38, 47.69, 47.81, 47.84, 47.94, 59.39, 77.68, 77.80, 79.51, 79.64, 104.13, 175.59, 175.62; FAB-MS m/z 486 (MH)<sup>+</sup>. Anal. (C<sub>12</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Ethylmalonato)[(4R,5R)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (1s): 4f and 5d; MeOH– H<sub>2</sub>O (5:5); 59%; white crystals; IR (KBr) 3448, 3202, 3126, 1617 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  0.86 (t, J = 7.5 Hz, 3 H, CH<sub>3</sub>), 0.87 (d, J = 6.9 Hz, 6 H, 2 CH<sub>3</sub>), 1.75 (m, 1 H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.82 (dq, J = 7.1 Hz, J = 7.5 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 2.58 (m, 2 H, 2 CHNH<sub>2</sub>), 2.98 (m, 1 H, CHNH<sub>2</sub>), 3.09 (m, 1 H, CHNH<sub>2</sub>), 3.41 (t, J = 7.1Hz, 1 H, CH), 4.28 (m, 1 H, CH), 4.50 (m, 1 H, CH), 4.81 (d, J = 4.5 Hz, 1 H, CH), 5.34 (br s, 1 H, NH), 5.52 (br s, 3 H, 3 NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  12.47, 12.51, 16.45, 16.52, 22.55, 31.35, 47.67, 47.83, 48.00, 48.02, 59.36, 59.41, 77.89, 78.04, 79.43, 79.57, 106.87, 175.63; FAB-MS m/z 500 (MH)<sup>+</sup>. Anal. (C<sub>13</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Ethylmalonato)[(4R,5R)-4,5-bis(aminomethyl)-1,3dioxolane-2-spiro-1'-cyclopentane]platinum(II) (1t): 4g and 5d; MeOH-H<sub>2</sub>O (5:5); 86%; white powder; IR (KBr) 3448, 3197, 3092, 1622 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  0.86 (t, J = 7.2 Hz, 3 H, CH<sub>3</sub>), 1.50–1.85 (m, 8 H, cyclopentyl), 1.83 (dq, J = 7.1 Hz, J = 7.5 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 2.55 (m, 2 H, 2 CHNH<sub>2</sub>), 3.04 (m, 2 H, 2 CHNH<sub>2</sub>), 3.40 (t, J = 7.1 Hz, 1 H, CH), 4.38 (m, 2 H, 2 CH), 5.41 (br s, 2 H, 2 NH), 5.52 (br s, 2 H, 2 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  12.49, 22.56, 22.90, 22.93, 36.24, 36.30, 48.12, 48.39, 59.44, 78.01, 78.24, 118.11, 175.58, 175.61; FAB-MS m/z 512 (MH)<sup>+</sup>. Anal. (C<sub>14</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4S,5S)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) (2a): 6a and 5a; MeOH-H<sub>2</sub>O (2:8); 48%; white crystals; spectral data were identical with that of 1a. Anal. ( $C_{11}H_{18}N_2O_6Pt$ ) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4S,5S)-4,5-bis(aminomethyl)-2-methyl-1,3-dioxolane]platinum(II) (2b): 6b and 5a; MeOH-H<sub>2</sub>O (2:8); 54%; white powder; spectral data were identical with that of 1b. Anal. ( $C_{12}H_{20}N_2O_6Pt$ ) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4S,5S)-4,5-bis(aminomethyl)-2,2-dimethyl-1,3-dioxolane]platinum(II) (2c): 6c and 5a; MeOH-H<sub>2</sub>O (4:6); 54%; white crystals; spectral data were identical with that of 1c. Anal. (C<sub>13</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>Pt) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4S,5S)-4,5-bis(aminomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane]platinum(II) (2d): 6d and 5a; MeOH-H<sub>2</sub>O (2:8); 65%; colorless crystals; spectral data were identical with that of 1d. Anal. ( $C_{13}H_{22}N_2O_7Pt$ ) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4S,5S)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (2e): 6e and 5a; MeOH-H<sub>2</sub>O (3:7); 56%; colorless crystals; spectral data were identical with that of 1e. Anal. ( $C_{13}H_{22}N_2O_6Pt$ ) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4S,5S)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (2f): 6f and 5a; MeOH-H<sub>2</sub>O (4:6); 46%; white crystals; spectral data were identical with that of 1f. Anal. ( $C_{14}H_{24}N_2O_6Pt$ ) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4S,5S)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclopentane]platinum-(II) (2g): 6g and 5a; MeOH-H<sub>2</sub>O (5:5); 54%; white powder; spectral data were identical with that of 1g. Anal. ( $C_{15}H_{24}N_2O_6$ -Pt) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4S,5S)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclohexane]platinum-(II) (2h): 6h and 5a; MeOH-H<sub>2</sub>O (5:5); 50%; white powder; spectral data were identical with that of 1h. Anal. ( $C_{16}H_{26}N_2O_6$ -Pt) C, H, N

General Procedure for the Synthesis of (Glycolato)platinum(II) Complexes (3a-g) and (L-Lactato)platinum-(II) Complexes (3h-n). Method A. To a stirred suspension of diiodoplatinum(II) complex (4a-c and 4e-h) (0.86 mmol) in H<sub>2</sub>O (15 mL) was added a solution of AgNO<sub>3</sub> (1.72 mmol) in H<sub>2</sub>O (15 mL). The mixture was heated at 60 °C for 2 h in the dark and filtered through a pad of Celite, and the filtered residue was washed with a small volume of  $H_2O$ . The combined filtrate and washing were concentrated under a reduced pressure to  $\sim 10 \text{ mL}$ in volume and passed through the column of anion exchange resin, Amberlite IRA-400 (OH- type, 20 mL), with  $H_2O$  as the eluent. To the alkaline eluate ( $\sim$ 30 mL) were added glycolic acid (0.92 mmol) and sodium glycolate (3.44 mL of 1 M aqueous solution) (for 3a-g), or L-lactic acid (0.92 mmol) and sodium L-lactate (3.44 mL of 1 M aqueous solution) (for 3h-n). The mixture was stirred at 60 °C in the dark overnight, concentrated under a reduced pressure to  $\sim 10$  mL in volume, and purified by preparative HPLC on Delta pak C<sub>18</sub>-100-Å reverse-phase bonded silica cartridge with MeOH-H<sub>2</sub>O system as the mobile phase. The eluate was concentrated under a reduced pressure to a small volume and freeze-dried to give the product as a white solid.

Method B. A mixture of diiodoplatinum(II) complex (4a-c and 4e-h) (0.86 mmol), glycolic acid (1.72 mmol, for 3a-g), or L-lactic acid (1.72 mmol, for 3h-n) and Ag<sub>2</sub>O (1.72 mmol) in H<sub>2</sub>O (30 mL) was stirred at 60 °C in the dark overnight. The reaction mixture was filtered through a pad of Celite, and the filtered residue was washed with a small volume of H<sub>2</sub>O. The combined filtrate and washing were concentrated under a reduced pressure to ~10 mL in volume. The concentrate was purified in the same manner as described in method A.

The mobile phase for preparative HPLC, yield, and spectral data are given below.

cis-(Glycolato-O, O')[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) (3a): H<sub>2</sub>O only; 56% (method A), 57% (method B); IR (KBr) 3445, 3222, 3069, 1645 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  2.87 (m, 2 H, 2 CHNH<sub>2</sub>), 3.38 (m, 2 H, 2 CHNH<sub>2</sub>), 4.10 (s, 2 H, CH<sub>2</sub>), 4.59 (m, 2 H, 2 CH), 5.05 (s, 2 H, OCH<sub>2</sub>O); <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  48.52, 48.82, 69.30, 79.49, 79.53, 95.42, 195.49; FAB-MS m/z 402 (MH)<sup>+</sup>. Anal. (C<sub>7</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N. cis (Glycolato-O,O')[(4R,5R)-4,5-bis(aminomethyl)-2-methyl-1,3-dioxolane]platinum(II) (3b): MeOH-H<sub>2</sub>O (1:19); 78% (method A), 64% (method B); IR (KBr) 3451, 3213, 3139, 1634 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.40 (d, J = 4.8 Hz, 3 H, CH<sub>3</sub>), 2.87 (m, 2 H, 2 CHNH<sub>2</sub>), 3.28 (m, 1 H, CHNH<sub>2</sub>), 3.39 (m, 1 H, CHNH<sub>2</sub>), 4.10 (s, 2 H, CH<sub>2</sub>), 4.64 (m, 1 H, CH), 4.71 (m, 1 H, CH, overlapped with HOD), 5.28 (q, J = 4.8 Hz, 1 H, CH); <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  19.51, 48.57, 48.73, 48.86, 49.05, 69.29, 78.82, 80.77, 102.70, 195.46; FAB-MS m/z 416 (MH)<sup>+</sup>. Anal. (C<sub>8</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N.

cis-(Glycolato-O, O')[(4R,5R)-4,5-bis(aminomethyl)-2,2dimethyl-1,3-dioxolane]platinum(II) (3c): MeOH-H<sub>2</sub>O (1: 9); 46% (method A), 42% (method B); IR (KBr) 3430, 3142, 3085, 1657 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.47 (s, 6 H, 2 CH<sub>3</sub>), 2.86 (m, 2 H, 2 CHNH<sub>2</sub>), 3.32 (m, 2 H, 2 CHNH<sub>2</sub>), 4.10 (s, 2 H, CH<sub>2</sub>), 4.71 (m, 2 H, 2 CH); <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  26.56, 49.36, 49.65, 69.27, 79.18, 111.35, 195.51; FAB-MS m/z 430 (MH)<sup>+</sup>. Anal. (C<sub>9</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N.

cis-(Glycolato-O,O')[(4R,5R)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (3d): MeOH-H<sub>2</sub>O (1:9); 54% (method A), 66% (method B); IR (KBr) 3431, 3132, 1650 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  0.93 (t, J = 7.5 Hz, 3 H, CH<sub>3</sub>), 1.72 (dq, J = 4.5 Hz, J = 7.5 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 2.88 (m, 2 H, 2 CHNH<sub>2</sub>), 3.29 (m, 1 H, CHNH<sub>2</sub>), 3.39 (m, 1 H, CHNH<sub>2</sub>), 4.10 (s, 2 H, CH<sub>2</sub>), 4.61 (m, 1 H, CH), 4.68 (m, 1 H, CH, overlapped with HOD), 5.15 (t, J = 4.5 Hz, 1 H, CH); <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  7.89, 26.90, 48.65, 48.70, 48.94, 49.00, 69.28, 78.85, 80.57, 106.43, 195.48; FAB-MS m/z 430 (MH)<sup>+</sup>. Anal. (C<sub>9</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N.

cis-(Glycolato-O,O')[(4R,5R)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (3e): MeOH-H<sub>2</sub>O (3:7); 29% (method A), 75% (method B); IR (KBr) 3425, 3218, 3143, 1634 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  0.94 (d, J = 6.9 Hz, 6 H, 2 CH<sub>3</sub>), 1.89 (m, 1 H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.86 (m, 2 H, 2 CHNH<sub>2</sub>), 3.30 (m, 1 H, CHNH<sub>2</sub>), 3.39 (m, 1 H, CHNH<sub>2</sub>), 4.10 (s, 2 H, CH<sub>2</sub>), 4.58 (m, 1 H, CH), 4.64 (m, 1 H, CH, overlapped with HOD), 4.98 (d, J =4.2 Hz, 1 H, CH); <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  16.69, 16.79, 32.02, 48.66, 48.72, 48.96, 49.02, 69.28, 78.97, 80.48, 109.26, 195.50; FAB-MS m/z 444 (MH)<sup>+</sup>. Anal. (C<sub>10</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N.

cis-(Glycolato-O,O')[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclopentane]platinum(II) (3f): MeOH-H<sub>2</sub>O (4:6); 50% (method A), 68% (method B); IR (KBr) 3409, 3211, 3143, 1635 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.60–2.00 (m, 8 H, cyclopentyl), 2.86 (m, 2 H, 2 CHNH<sub>2</sub>), 3.33 (m, 2 H, 2 CHNH<sub>2</sub>), 4.10 (s, 2 H, CH<sub>2</sub>), 4.66 (m, 2 H, 2 CH); <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  23.88, 37.11, 49.22, 49.50, 69.29, 79.05, 121.09, 195.51; FAB-MS m/z 456 (MH)<sup>+</sup>. Anal. (C<sub>11</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N.

cis-(Glycolato-O,O')[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclohexane]platinum(II) (3g): MeOH– H<sub>2</sub>O (4:6); 23% (method A), 48% (method B); IR (KBr) 3417, 3218, 3143, 1634 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  1.34 (br s, 2 H, cyclohexyl), 1.54 (br s, 8 H, cyclohexyl), 2.55 (m, 2 H, 2 CHNH<sub>2</sub>), 3.14 (m, 2 H, 2 CHNH<sub>2</sub>), 3.78 (s, 2 H, CH<sub>2</sub>), 4.40 (m, 2 H, 2 CH), 4.93 (br s, 1 H, NH), 5.15 (br s, 2 H, 2 NH); <sup>13</sup>C NMR (DMSO- $d_6$ )  $\delta$  23.79, 24.83, 35.96, 36.00, 48.92, 48.96, 69.70, 78.17, 78.21, 109.43, 191.91; FAB-MS m/z 470 (MH)<sup>+</sup>. Anal. (C<sub>12</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N.

cis-(L-Lactato-O, O')[(4R, 5R)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) (3h): MeOH-H<sub>2</sub>O (7:93); 24% (method A), 58% (method B); IR (KBr) 3426, 3209, 3132, 1628 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.34 (d, J = 6.9 Hz, 3 H, CH<sub>3</sub>), 2.89 (m, 2 H, 2 CHNH<sub>2</sub>), 4.17 (d, J = 6.9 Hz, 1 H, CHCH<sub>3</sub>), 4.60 (m, 2 H, 2 CH), 5.05 (s, 2 H, OCH<sub>2</sub>O); <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  22.62, 48.47, 48.82, 75.19, 79.53, 79.58, 95.43, 196.47; FAB-MS m/z 416 (MH)<sup>+</sup>. Anal. (C<sub>8</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N.

cis-(1-Lactato-O,O')[(4R,5R)-4,5-bis(aminomethyl)-2-methyl-1,3-dioxolane]platinum(II) (3i): MeOH-H<sub>2</sub>O (1:9); 76% (method A), 57% (method B); IR (KBr) 3426, 3214, 3143, 1623 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.30 (d, J = 6.9 Hz, 3 H, CH<sub>3</sub>), 1.40 (d, J = 4.8 Hz, 3 H, CH<sub>3</sub>), 2.88 (m, 2 H, 2 CHNH<sub>2</sub>), 3.30 (m, 1 H, CHNH<sub>2</sub>), 3.41 (m, 1 H, CHNH<sub>2</sub>), 4.17 (d, J = 6.9 Hz, 1 H, CHCH<sub>3</sub>), 4.63 (m, 1 H, CH), 4.70 (m, 1 H, CH, overlapped with HOD), 5.28 (q, J = 4.8 Hz, 1 H, CH); FAB-MS m/z 430 (MH)<sup>+</sup>. Anal. (C<sub>9</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N.

cis-(L-Lactato-O,O')[(4R,5R)-4,5-bis(aminomethyl)-2,2dimethyl-1,3-dioxolane]platinum(II) (3j): MeOH-H<sub>2</sub>O (3: 7); 56% (method A), 73% (method B); IR (KBr) 3419, 3216, 3131, 1634 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  1.14 (d, J = 6.9 Hz, 3 H,

#### (Substituted dioxolane)platinum(II) Complexes

CH<sub>3</sub>), 1.37 (s, 6 H, 2 CH<sub>3</sub>), 2.66 (m, 1 H, CHNH<sub>2</sub>), 2.80 (m, 1 H, CHNH<sub>2</sub>), 3.18 (m, 2 H, 2 CHNH<sub>2</sub>), 3.68 (d, J = 6.9 Hz, 1 H, CHCH<sub>3</sub>), 4.66 (m, 2 H, 2 CH), 6.16 (br s, 1 H, NH), 6.22 (br s, 1 H, NH), 6.48 (br s, 2 H, 2 NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  21.33, 26.39, 48.01, 48.29, 66.91, 77.49, 77.94, 108.74, 180.70; FAB-MS m/z 444 (MH)<sup>+</sup>. Anal. (C<sub>10</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N.

cis-(1-Lactato-O,O')[(4R,5R)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (3k): MeOH-H<sub>2</sub>O (2:8); 77% (method A), 73% (method B); IR (KBr) 3405, 3209, 3138, 1636 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  0.94 (t, J = 7.5 Hz, 3 H, CH<sub>2</sub>CH<sub>3</sub>), 1.30 (d, J = 6.9 Hz, 3 H, CH<sub>3</sub>), 1.73 (dq, J = 4.5 Hz, J = 7.5 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 2.88 (m, 2 H, 2 CHNH<sub>2</sub>), 3.31 (m, 1 H, CHNH<sub>2</sub>), 3.41 (m, 1 H, CHNH<sub>2</sub>), 4.17 (q, J = 6.9 Hz, 1 H, CHCH<sub>3</sub>), 4.62 (m, 1 H, CH), 4.70 (m, 1 H, CH, overlapped with HOD), 5.15 (t, J =4.5 Hz, 1 H, CH); FAB-MS m/z 444 (MH)<sup>+</sup>. Anal. (C<sub>10</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>-Pt) C, H, N.

cis-(L-Lactato-O, O')[(4R, 5R)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (31): MeOH-H<sub>2</sub>O (3:7); 85% (method A), 62% (method B); IR (KBr) 3425, 3212, 3136, 1634 cm<sup>-1</sup>; FAB-MS m/z 458 (MH)<sup>+</sup>. Anal. (C<sub>11</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N.

cis-(L-Lactato-O,O')[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclopentane]platinum(II) (3m): MeOH-H<sub>2</sub>O (4:6); 70% (method A), 47% (method B); IR (KBr) 3413, 3207, 3143, 1642 cm<sup>-1</sup>; FAB-MS m/z 470 (MH)<sup>+</sup>. Anal. (C<sub>12</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N.

cis-(L-Lactato-O, O')[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclohexane]platinum(II) (3n): MeOH-H<sub>2</sub>O (5:5); 47% (method A), 60% (method B); IR (KBr) 3425, 3219, 3137, 1630 cm<sup>-1</sup>; FAB-MS m/z 484 (MH)<sup>+</sup>. Anal. (C<sub>13</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>Pt) C, H, N.

General Method for the Synthesis of Diiodoplatinum-(II) Complexes (4a-h and 6a-h). To a stirred solution of KI (61.2 mmol) in H<sub>2</sub>O (20 mL) was added a filtered solution of K<sub>2</sub>PtCl<sub>4</sub> (10.2 mmol) in H<sub>2</sub>O (150 mL) that was stirred at room temperature for 40 min in the dark under a nitrogen atmosphere to obtain a black solution of K<sub>2</sub>PtI<sub>4</sub>. H<sub>2</sub>O (110 mL) was placed in a flask and stirred at 60 °C under a nitrogen atmosphere, and into this, the above obtained black solution of K<sub>2</sub>PtI<sub>4</sub> and a solution of 4,5-bis(aminomethyl)-1,3-dioxolane (13a-h and 18ah) (10.2 mmol) in H<sub>2</sub>O (170 mL) were simultaneously added dropwise over 2 h at a constant rate. After 1 h, the yellow precipitate was filtered, washed sequentially with H<sub>2</sub>O, EtOH, and Et<sub>2</sub>O, and dried *in vacuo*.

*cis*-Diiodo[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) (4a): yield 83%; IR (KBr) 3438, 3263, 3207, 3172, 3122, 1597 cm<sup>-1</sup>; FAB-MS *m/z* 582 (MH)<sup>+</sup>.

*cis*-Diiodo[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-methyl-1,3-dioxolane]platinum(II) (4b): yield 83%; IR (KBr) 3439, 3211, 3123, 1598 cm<sup>-1</sup>; FAB-MS *m/z* 596 (MH)<sup>+</sup>.

cis-Diiodo[(4R,5R)-4,5-bis(aminomethyl)-2,2-dimethyl-1,3-dioxolane]platinum(II) (4c): yield 88%; IR (KBr) 3439, 3206, 3170, 3124, 1595 cm<sup>-1</sup>; FAB-MS m/z 610 (MH)<sup>+</sup>.

cis-Diiodo[(4R,5R)-4,5-bis(aminomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane]platinum(II) (4d): yield 91%; IR (KBr) 3483, 3204, 3188, 3123, 1594 cm<sup>-1</sup>; FAB-MS m/z 626 (MH)<sup>+</sup>.

*cis*-Diiodo[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (4e): yield 86%; IR (KBr), 3439, 3206, 3172, 3124, 1597 cm<sup>-1</sup>; FAB-MS *m/z* 610 (MH)<sup>+</sup>.

*cis*-Diiodo[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3dioxolane]platinum(II) (4f): yield 88%; IR (KBr) 3446, 3207, 3172, 3124, 1597 cm<sup>-1</sup>; FAB-MS *m/z* 624 (MH)<sup>+</sup>.

cis-Diiodo[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane-2spiro-1'-cyclopentane]platinum(II) (4g): yield 90%; IR (KBr) 3446, 3203, 3122, 1591 cm<sup>-1</sup>; FAB-MS m/z 636 (MH)<sup>+</sup>.

*cis*-Diiodo[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane-2spiro-1'-cyclohexane]platinum(II) (4h): yield 88%; IR (KBr) 3457, 3206, 3129, 1587 cm<sup>-1</sup>; FAB-MS *m/z* 650 (MH)<sup>+</sup>.

cis-Diiodo[(4S,5S)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) (6a): yield 85%; spectral data were identical with that of 4a.

cis-Diiodo[(4S,5S)-4,5-bis(aminomethyl)-2-methyl-1,3-dioxolane]platinum(II) (6b): yield 84%; spectral data were identical with that of 4b. cis-Diiodo[(4S,5S)-4,5-bis(aminomethyl)-2,2-dimethyl-1,3dioxolane]platinum(II) (6c): yield 85%; spectral data were identical with that of 4c.

cis-Diiodo[(4S,5S)-4,5-bis(aminomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane]platinum(II) (6d): yield 90%; spectral data were identical with that of 4d.

cis-Diiodo[(4S,5S)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (6e): yield 84%; spectral data were identical with that of 4e.

cis-Diiodo[(4S,5S)-4,5-bis(aminomethyl)-2-isopropyl-1,3dioxolane]platinum(II) (6f): yield 79%; spectral data were identical with that of 4f.

cis-Diiodo[(4S,5S)-4,5-bis(aminomethyl)-1,3-dioxolane-2spiro-1'-cyclopentane]platinum(II) (6g): yield 88%; spectral data were identical with that of 4g.

cis-Diiodo[(4S,5S)-4,5-bis(aminomethyl)-1,3-dioxolane-2spiro-1'-cyclohexane]platinum(II) (6h): yield 86%; spectral data were identical with that of 4h.

General Procedure for the Preparation of Disilver Salts of Malonic Acids (5a-d). To a stirred 1 N NaOH solution (40 mL) were added a malonic acid (20 mmol) and AgNO<sub>3</sub> (40 mmol). The mixture was stirred at room temperature in the dark overnight. The resulting white silver salt was filtered and dried thoroughly *in vacuo* to give 5a-d in 90-96% yield.

2,3-O-Methylene-D-threitol 1,4-bis(methanesulfonate) (10a), 2,3-O-methylene-L-threitol 1,4-bis(methanesulfonate) (15a), 2,3-O-ethylidene-D-threitol 1,4-bis(methanesulfonate) (10b), 2,3-O-ethylidene-L-threitol 1,4-bis(methanesulfonate) (15b), 2,3-O-cyclohexylidene-D-threitol 1,4-bis(methanesulfonate) (15f), and 2,3-O-cyclohexylidene-L-threitol 1,4-bis(methanesulfonate) (16f), and 3,5-O-cyclohexylidene-L-threitol 1,4-bis(methanesulfo

2,3-O-Propionylidene-D-threitol 1,4-Bis(methanesulfonate) (10c). A mixture of D-threitol 1,4-bis(methanesulfonate) (9) (1.80 g, 6.5 mmol), propionaldehyde (0.41 g, 7.1 mmol, 0.51 mL), anhydrous CuSO<sub>4</sub> (1.55 g, 9.7 mmol), and CH<sub>3</sub>SO<sub>3</sub>H (2 drops) in anhydrous toluene (30 mL) was stirred at room temperature for 16 h under a nitrogen atmosphere. Anhydrous  $K_2CO_3$  (0.30 g) was added to the reaction mixture, and the resulting mixture was stirred for an additional 20 min. The reaction mixture was filtered and evaporated to dryness, and the oily residue was crystallized from a mixture of absolute EtOH and acetone to give 1.60 g (78%) of 10c as colorless crystals: mp 65-65.5 °C; IR (Nujol)  $1357, 1179 \text{ cm}^{-1}; {}^{1}\text{H} \text{ NMR} (\text{CDCl}_3) \delta 0.96 (t, J = 7.4 \text{ Hz}, 3 \text{ H}, \text{CH}_3),$ 1.71 (dq, J = 4.6 Hz, J = 7.4 Hz, 2 H, CH<sub>2</sub>), 3.09 (s, 6 H, 2 SO<sub>2</sub>-CH<sub>3</sub>), 4.09-4.29 (m, 2 H, 2 CH), 4.33 (m, 4 H, 2 CH<sub>2</sub>), 5.07 (t, J = 4.6 Hz, 1 H, CH);  ${}^{13}$ C NMR (CDCl<sub>3</sub>)  $\delta$  7.59, 26.89, 37.77, 67.78, 68.00, 75.18, 75.73, 106.38; EI-MS m/z 318 (M<sup>+</sup>). Anal. (C<sub>9</sub>H<sub>18</sub>O<sub>8</sub>S<sub>2</sub>) C, H.

2,3-O-Isobutylidene-D-threitol 1,4-Bis(methanesulfonate) (10d). A mixture of compound 9 (4.00 g, 14.4 mmol), isobutyraldehyde (1.14 g, 15.8 mmol), anhydrous CuSO<sub>4</sub> (3.44 g, 21.6 mmol), and CH<sub>3</sub>SO<sub>3</sub>H (2 drops) in anhydrous toluene (40 mL) was stirred at room temperature for 16 h under a nitrogen atmosphere. The reaction mixture turned to the solid mass, and to it were added EtOAc (50 mL) and anhydrous  $K_2CO_3$  (0.30 g). The reaction mixture was stirred for an additional 20 min, filtered, evaporated to dryness under a reduced pressure, and purified by flash column chromatography over silica gel with a mixture of EtOAc-hexane (1:1, v/v) as the eluent to give 4.70 g (98%) of 10d which was crystallized from absolute EtOH: mp 70-70.5 °C; IR (KBr) 1360, 1182 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.95 (d, J = 6.8 Hz, 6 H, 2 CH<sub>3</sub>), 1.82 (m, 1 H, CH), 3.08 (s, 6 H, 2 SO<sub>2</sub>CH<sub>3</sub>), 4.05-4.25 (m, 2 H, 2 CH), 4.25–4.45 (m, 4 H, 2 CH<sub>2</sub>), 4.86 (d, J = 4.6 Hz, 1 H, CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 16.50, 31.87, 37.75, 67.83, 67.91, 75.28, 75.66, 109.15; El-MS m/z 332 (M<sup>+</sup>). Anal. (C<sub>10</sub>H<sub>20</sub>O<sub>8</sub>S<sub>2</sub>) С, Н.

2,3-O-Cyclopentylidene-D-threitol 1,4-Bis(methanesulfonate) (10e). A mixture of compound 9 (10.00 g, 35.9 mmol), cyclopentanone (6.05 g, 71.8 mmol, 6.4 mL), and  $CH_3SO_3H$  (5 drops) in benzene (100 mL) was refluxed under a Dean–Stark continuous water separator for 16 h. The reaction mixture was cooled to room temperature, and to this clear solution was added anhydrous  $K_2CO_3$  (0.50 g). The reaction mixture was stirred for an additional 20 min, filtered, and evaporated under a reduced pressure, and the residue was crystallized from absolute EtOH to give 11.02 g (89%) of **10e** as white crystals: mp 89.5–90.5 °C; IR (Nujol) 1357, 1179 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.50–2.00 (m, 8 H, 4 CH<sub>2</sub>), 3.08 (s, 6 H, 2 SO<sub>2</sub>CH<sub>3</sub>), 4.10–4.25 (m, 2 H, 2 CH), 4.25–4.50 (m, 4 H, 2 CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  23.35, 37.15, 37.66, 68.03, 75.10, 120.80; EI-MS m/z 344 (M<sup>+</sup>). Anal. (C<sub>11</sub>H<sub>20</sub>O<sub>8</sub>S<sub>2</sub>) C, H.

2,3-O-Propionylidene-L-threitol 1,4-bis(methanesulfonate) (15c) was synthesized from L-threitol 1,4-bis(methanesulfonate) (14) by the same procedure as described above for the synthesis of 10c: yield 83%; mp 65–66 °C; spectral data were identical with that of 10c. Anal.  $(C_9H_{18}O_8S_2)$  C, H.

2,3-O-Isobutylidene-L-threitol 1,4-bis(methanesulfonate) (15d) was synthesized from compound 14 by the same procedure as described above for the synthesis of 10d: yield 96%; mp 70–71 °C; spectral data were identical with that of 10d. Anal. ( $C_{10}H_{20}O_8S_2$ ) C, H.

2,3-O-Cyclopentylidene-L-threitol 1,4-bis(methanesulfonate) (15e) was synthesized from compound 14 by the same procedure as described above for the synthesis of 10e: yield 96%; mp 90-91 °C; spectral data were identical with that of 10e. Anal.  $(C_{11}H_{20}O_8S_2)$  C, H.

(2R,3R)-2,3-Dihydroxy-1,4-diazidobutane (11). A mixture of compound 9 (31.71 g, 114.0 mmol) and sodium azide (44.45 g, 683.7 mmol) in anhydrous DMF (300 mL) was heated at 100 °C for 16 h under a nitrogen atmosphere. After the mixture was cooled to the room temperature, the precipitates obtained were filtered off and the filtrate was concentrated in vacuo. The oily residue was partitioned between EtOAc (200 mL) and brine (80 mL), and the aqueous phase was extracted with EtOAc ( $2 \times 50$ mL). The combined organic phase was dried over anhydrous MgSO<sub>4</sub>, evaporated to dryness, and purified by flash column chromatography over silica gel with a mixture of EtOAc-hexane (1:2, v/v) as the eluent to give 18.35 g (94%) of 11 as a pale yellow oil:  $[\alpha]^{20} = -13.4^{\circ}$  (c = 0.04, acetone); IR (neat) 3402, 2105 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.30 (br s, 2 H, 2 OH), 3.15–3.60 (m, 4 H, 2 CH<sub>2</sub>), 3.65-3.90 (m, 2 H, 2 CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 53.65, 70.49; EI-MS m/z 172 (M<sup>+</sup>). Anal. (C<sub>4</sub>H<sub>8</sub>N<sub>6</sub>O<sub>2</sub>) C, H, N.

2(S),3(S)-Dihydroxy-1,4-diazidobutane (16) was synthesized from compound 14 by the same procedure as described above for the synthesis of 11: yield 95%:  $[\alpha]^{20}_{D} = +13.1^{\circ}$  (c = 0.04, acetone); spectral data were identical with that of 11. Anal. (C<sub>4</sub>H<sub>8</sub>N<sub>6</sub>O<sub>2</sub>) C, H, N.

General Method for the Preparation of 4,5-Bis(azidomethyl)-1,3-dioxolanes (12a-b, 12f-i, 17a-b, and 17f-i). A mixture of 1,3-dioxolane-4,5-bis(methanesulfonate) (10a-f and 15a-f) (11.0 mmol) and NaN<sub>3</sub> (2.86 g, 44.0 mmol) in anhydrous DMF (15 mL) was heated at 100 °C for 16 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, diluted with H<sub>2</sub>O (20 mL), and extracted with Et<sub>2</sub>O (100 mL). The ethereal solution was washed with brine (20 mL), dried over anhydrous MgSO<sub>4</sub>, and evaporated to dryness under reduced pressure. The crude product was purified by flash column chromatography over silica gel with a mixture of Et<sub>2</sub>Ohexane (1:4, v/v) as the eluent to give a pale yellow oil.

(4R,5R)-4,5-Bis(azidomethyl)-1,3-dioxolane (12a): yield95%;  $[\alpha]^{20}_{D} = +125.2^{\circ} (c = 0.04, acetone); {}^{1}H NMR (CDCl_3) \delta$ 3.30-3.62 (m, 4 H, 2 CH<sub>2</sub>), 3.91-4.09 (m, 2 H, 2 CH), 5.08 (s, 2 H, OCH<sub>2</sub>O); {}^{13}C NMR (CDCl\_3) \delta 51.64, 77.14, 95.37; EI-MS m/z 184 (M<sup>+</sup>). Anal. (C<sub>5</sub>H<sub>8</sub>N<sub>6</sub>O<sub>2</sub>) C, H, N.

(4*R*,5*R*)-4,5-Bis(azidomethyl)-2-methyl-1,3-dioxolane (12b): yield 93%;  $[\alpha]^{20}_D$  = +143.8° (*c* = 0.04, acetone); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.42 (d, *J* = 4.8 Hz, 3 H, CH<sub>3</sub>), 3.24–3.63 (m, 4 H, 2 CH<sub>2</sub>), 3.93–4.13 (m, 2 H, 2 CH), 5.24 (q, *J* = 4.8 Hz, 1 H, CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  19.84, 51.76, 76.80, 77.96, 101.97; EI-MS *m/z* 198 (M<sup>+</sup>). Anal. (C<sub>6</sub>H<sub>10</sub>N<sub>6</sub>O<sub>2</sub>) C, H, N.

(4*R*,5*R*)-4,5-Bis(azidomethyl)-2-ethyl-1,3-dioxolane (12f): yield 92%;  $[\alpha]^{20}_D = +127.9^{\circ}$  (c = 0.04, acetone); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.98 (t, J = 7.5 Hz, 3 H, CH<sub>3</sub>), 1.72 (dq, J = 4.5 Hz, J = 7.5 Hz, 2 H, CH<sub>2</sub>), 3.34–3.54 (m, 4 H, 2 CH<sub>2</sub>), 3.97–4.07 (m, 2 H, 2 CH), 5.07 (t, J = 4.5 Hz, 1 H, CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ 7.64, 27.09, 51.88, 51.94, 77.94, 105.86; EI-MS m/z 212 (M<sup>+</sup>). Anal. (C<sub>7</sub>H<sub>12</sub>N<sub>6</sub>O<sub>2</sub>) C, H, N.

(4R,5R)-4,5-Bis(azidomethyl)-2-isopropyl-1,3-dioxolane (12g): yield 97%;  $[\alpha]^{20}_{D} = +110.9^{\circ}$  (c = 0.04, acetone); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.97 (d, J = 6.8 Hz, 6 H, 2 CH<sub>3</sub>), 1.65–2.05 (m, 1 H, CH), 3.20–3.60 (m, 4 H, 2 CH<sub>2</sub>), 3.85–4.15 (m, 2 H, 2 CH), 4.85 (d, J = 4.6 Hz, 1 H, CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.51, 16.56, 32.00, 51.81, 51.91, 77.10, 77.90, 108.69; EI-MS m/z 226 (M<sup>+</sup>). Anal. (C<sub>8</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub>) C, H, N.

(4R,5R)-4,5-Bis(azidomethyl)-1,3-dioxolane-2-spiro-1'-cyclopentane (12h): yield 95%;  $[\alpha]^{20}_{D} = +125.4^{\circ}$  (c = 0.04, acetone); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.50–2.05 (m, 8 H, 4 CH<sub>2</sub>), 3.25–3.60 (m, 4 H, 2 CH<sub>2</sub>), 3.89–4.09 (m, 2 H, 2 CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ 23.25, 37.07, 51.73, 76.83, 120.15; EI-MS m/z 238 (M<sup>+</sup>). Anal. (C<sub>9</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub>) C, H, N.

(4R,5R)-4,5-Bis(azidomethyl)-1,3-dioxolane-2-spiro-1'-cyclohexane (12i): yield 95%;  $[\alpha]^{20}_{D} = +120.4^{\circ}$  (c = 0.04, acetone); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.20–1.85 (m, 10 H, 5 CH<sub>2</sub>), 3.21–3.62 (m, 4 H, 2 CH<sub>2</sub>), 3.95–4.15 (m, 2 H, 2 CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  23.77, 24.93, 36.45, 51.70, 76.60, 110.99; EI-MS m/z 252 (M<sup>+</sup>). Anal. (C<sub>10</sub>H<sub>16</sub>N<sub>6</sub>O<sub>2</sub>) C, H, N.

(4S,5S)-4,5-Bis(azidomethyl)-1,3-dioxolane (17a): yield 96%;  $[\alpha]^{20}_{D} = -122.0^{\circ}$  (c = 0.04, acetone); spectral data were identical with that of 12a. Anal. (C<sub>5</sub>H<sub>8</sub>N<sub>6</sub>O<sub>2</sub>) C, H, N.

(4S,5S)-4,5-Bis(azidomethyl)-2-methyl-1,3-dioxolane (17b): yield 98%;  $[\alpha]^{20}_{D} = -140.7^{\circ}$  (c = 0.04, acetone); spectral data were identical with that of 12b. Anal. (C<sub>6</sub>H<sub>10</sub>N<sub>6</sub>O<sub>2</sub>) C, H, N.

(4S,5S)-4,5-Bis(azidomethyl)-2-ethyl-1,3-dioxolane (17f): yield 90%;  $[\alpha]^{20}_D = -127.5^\circ$  (c = 0.04, acetone); spectral data were identical with that of 12f. Anal. ( $C_7H_{12}N_6O_2$ ) C, H, N.

(48,58)-4,5-Bis(azidomethyl)-2-isopropyl-1,3-dioxolane (17g): yield 97%;  $[\alpha]^{20}_D = -110.9^\circ$  (c = 0.04, acetone); spectral data were identical with that of 12g. Anal. ( $C_8H_{14}N_8O_2$ ) C, H, N.

(4.5,5.5)-4,5-Bis(azidomethyl)-1,3-dioxolane-2-spiro-1'-cyclopentane (17h): yield 97%;  $[\alpha]^{20}_D = -122.9^\circ$  (c = 0.04, acetone); spectral data were identical with that of 12h. Anal. (C<sub>9</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub>) C, H, N.

 $\begin{array}{l} \textbf{(4S,5S)-4,5-Bis(azidomethyl)-1,3-dioxolane-2-spiro-1'-cy-clohexane (17i): yield 98\%; [$\alpha$]^{20}$_D = -122.5° ($c$ = 0.04, acetone$); spectral data were identical with that of 12i. Anal. ($C_{10}H_{16}N_6O_2$) C, H, N. \end{array}$ 

(4R,5R)-4,5-Bis(azidomethyl)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-1,3-dioxolane (12d). To a stirred solution of acetol (5.50 g, 74.2 mmol) and imidazole (9.19 g, 135.0 mmol) in anhydrous DMF (50 mL) was added tert-butylchlorodiphenylsilane (20.40 g, 74.2 mmol) dropwise at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 18 h, diluted with  $H_2O$  (100 mL), and extracted with  $Et_2O$  (3 × 100 mL). The organic phase was washed with cold H<sub>2</sub>O (100 mL), dried over anhydrous MgSO<sub>4</sub>, and evaporated under a reduced pressure to dryness. The crude product was purified by flash column chromatography over silica gel with a mixture of  $Et_2O$ -hexane (1:5, v/v) as the eluent to give 21.90 g (94%) of ((tert-butyldiphenylsilyl)oxy)acetone as a colorless oil: IR (neat) 3071, 1735, 1718, 1113 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.12 (s, 9 H, 3 CH<sub>3</sub>), 2.21 (s, 3 H, COCH<sub>3</sub>), 4.18 (s, 2 H, OCH<sub>2</sub>), 7.34-7.54 (m, 6 H, Ar H), 7.60–7.80 (m, 4 H, Ar H).

A mixture of compound 11 (7.13 g, 41.4 mmol), ((tertbutyldiphenylsilyl)oxy)acetone (11.77 g, 37.7 mmol), anhydrous CuSO<sub>4</sub> (18.03 g, 113.0 mmol), and CH<sub>3</sub>SO<sub>3</sub>H (5 drops) in anhydrous toluene (100 mL) was stirred at 45 °C for 16 h under a nitrogen atmosphere. Anhydrous K2CO3 (0.50 g) was added to the reaction mixture and stirred for an additional 20 min. The reaction mixture was filtered and evaporated to dryness under a reduced pressure. The crude product was purified by flash column chromatography over silica gel with a mixture of Et<sub>2</sub>Ohexane (1:5, v/v) as the eluent to give 15.75 g (90%) of 12d as a pale yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) & 1.07 (s, 9 H, 3 CH<sub>3</sub>), 1.43 (s,  $3 H, CH_3$ ,  $3.25-3.56 (m, 4 H, 2 CH_2)$ , 3.58 (d, J = 10.3 Hz, 1 H, J) $OCH_2$ ), 3.62 (d, J = 10.3 Hz, 1 H,  $OCH_2$ ), 3.92-4.06 (m, 2 H, 2 CH), 7.35-7.45 (m, 6 H, Ar H), 7.65-7.75 (m, 4 H, Ar H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) § 19.24, 22.63, 26.87, 51.54, 52.10, 68.00, 76.90, 78.40, 110.96, 127.69, 129.73, 133.20, 135.63; EI-MS m/z 467 (M<sup>+</sup>). Anal.  $(C_{23}H_{30}N_6O_3Si)$  C, H, N.

(4R,5R)-4,5-Bis(azidomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane (12e). To a stirred solution of compound 12d (14.96 g, 32.1 mmol) in THF (150 mL) was added tetrabutylammonium fluoride (64.2 mL, 1 M solution in THF) at 0 °C. The mixture was stirred at room temperature for 1 h and then concentrated under a reduced pressure. The oily residue was diluted with EtOAc (200 mL) and washed with H<sub>2</sub>O (50 mL) and brine (50 mL). The organic phase was dried over anhydrous MgSO<sub>4</sub> and evaporated to dryness, and the residue was purified by flash column chromatography over silica gel with a mixture of Et<sub>2</sub>O-hexane (1:3, v/v) as the eluent to give 6.82 g (93%) of 12e as a pale yellow oil:  $[\alpha]^{20}_{D} = +108.6^{\circ}$  (c = 0.04, acetone); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.43 (s, 3 H, CH<sub>3</sub>), 2.20 (t, J = 6.6 Hz, 1H, OH), 3.30–3.70 (m, 4 H, 2 CH<sub>2</sub>), 3.55–3.65 (m, 2 H, OCH<sub>2</sub>), 4.09–4.19 (m, 2 H, 2 CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  22.34, 51.29, 51.34, 67.15, 76.79, 77.87, 110.60; EI-MS m/z 228 (M<sup>+</sup>). Anal. (C<sub>7</sub>H<sub>12</sub>N<sub>6</sub>O<sub>3</sub>) C, H, N.

(4S,5S)-4,5-Bis(azidomethyl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methyl-1,3-dioxolane (17d) was synthesized from compound 16 by the same procedure as described above for the synthesis of 12d: yield 91%; spectral data were identical with that of 12d. Anal. (C<sub>22</sub>H<sub>30</sub>N<sub>6</sub>O<sub>8</sub>Si) C, H, N.

(4S,5S)-4,5-Bis(azidomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane (17e) was synthesized from compound 17d by the same procedure as described above for the synthesis of 12e: yield 92%;  $[\alpha]^{20}_{D} = -107.1^{\circ}$  (c = 0.04, acetone); spectral data were identical with that of 12e. Anal. (C<sub>7</sub>H<sub>12</sub>N<sub>6</sub>O<sub>3</sub>) C, H, N.

General Method for the Preparation of 4,5-Bis(aminomethyl)-1,3-dioxolanes (13a-h and 18a-h). A solution of 4,5bis(azidomethyl)-1,3-dioxolanes (12a-c, 12e-i, 17a-c, and 17ei) (10 mmol) in EtOH (20 mL) was hydrogenated in the presence of 10% Pd on activated carbon (0.2 g) at 50 psi at 40 °C for 2 h. The reaction mixture was filtered through a pad of Celite and evaporated to dryness under a reduced pressure to give the analytically pure product as a colorless oil.

(4R,5R)-4,5-Bis(aminomethyl)-1,3-dioxolane (13a): yield 97%; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.40 (s, 4 H, 2 NH<sub>2</sub>), 2.81–2.98 (m, 4 H, 2 CH<sub>2</sub>), 3.63–3.82 (m, 2 H, 2 CH), 5.01 (s, 2 H, OCH<sub>2</sub>O); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  43.81, 80.34, 94.34; EI-MS *m/z* 132 (M<sup>+</sup>). Anal. (C<sub>5</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N.

(4R,5R)-4,5-Bis(aminomethyl)-2-methyl-1,3-dioxolane (13b): yield 97%; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.37 (d, J = 4.8 Hz, 3 H, CH<sub>3</sub>), 1.41 (s, 4 H, 2 NH<sub>2</sub>), 2.65–3.04 (m, 4 H, 2 CH<sub>2</sub>), 3.65–3.87 (m, 2 H, 2 CH), 5.16 (q, J = 4.8 Hz, 1 H, CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  19.75, 43.76, 44.05, 80.16, 81.09, 100.35; EI-MS m/z 146 (M<sup>+</sup>). Anal. (C<sub>6</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N.

(4*R*,5*R*)-4,5-Bis(aminomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane (13d): yield 99%; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.33 (s, 3 H, CH<sub>3</sub>), 1.95 (br s, 3 H, NH<sub>2</sub> and OH), 2.77–3.10 (m, 6 H, 2 CH<sub>2</sub> and OCH<sub>2</sub>), 3.82–3.90 (m, 1 H, CH), 4.06–4.13 (m, 1 H, CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  23.14, 42.32, 44.12, 68.24, 79.33, 80.90, 109.76; EI-MS m/z 176 (M<sup>+</sup>). Anal. (C<sub>7</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>) C, H, N.

(4R,5R)-4,5-Bis(aminomethyl)-2-ethyl-1,3-dioxolane (13e): yield 95%; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.97 (t, J = 7.5 Hz, 3 H, CH<sub>3</sub>), 1.36 (s, 4 H, 2 NH<sub>2</sub>), 1.68 (dq, J = 4.5 Hz, J = 7.5 Hz, 2 H, CH<sub>2</sub>), 2.75-3.00 (m, 4 H, 2 CH<sub>2</sub>), 3.70-3.80 (m, 2 H, 2 CH), 5.00 (t, J = 4.5 Hz, 1 H, CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  7.83, 27.19, 44.05, 44.33, 80.34, 81.11, 104.59; EI-MS m/z 160 (M<sup>+</sup>). Anal. (C<sub>7</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N.

(4R,5R)-4,5-Bis(aminomethyl)-2-isopropyl-1,3-dioxolane (13f): yield 96%; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.96 (d, J = 6.9 Hz, 6 H, 2 CH<sub>3</sub>), 1.33 (s, 4 H, 2 NH<sub>2</sub>), 1.75–1.90 (m, 1 H, CH), 2.75– 2.98 (m, 4 H, 2 CH<sub>2</sub>), 3.67–3.77 (m, 2 H, 2 CH), 4.79 (d, J = 4.5Hz, 1 H, CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.65, 16.76, 32.06, 44.01, 44.25, 80.29, 80.91, 107.40; EI-MS m/z 174 (M<sup>+</sup>). Anal. (C<sub>8</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N.

 $\begin{array}{l} (4R,5R)-4,5-Bis(aminomethyl)-1,3-dioxolane-2-spiro-1'- \\ cyclopentane (13g): yield 96\%; ^{1}H NMR (CDCl_3) \delta 1.36 (s, 4 \\ H, 2 NH_2), 1.50-1.90 (m, 8 H, 4 CH_2), 2.77-2.95 (m, 4 H, 2 CH_2), \\ 3.68-3.78 (m, 2 H, 2 CH); ^{13}C NMR (CDCl_3) \delta 23.23, 37.30, 44.13, \\ 80.02, 118.45; EI-MS m/z 186 (M^+). Anal. (C_3H_{18}N_2O_2) C, H, N. \end{array}$ 

(4R,5R)-4,5-Bis(aminomethyl)-1,3-dioxolane-2-spiro-1'cyclohexane (13h): yield 99%; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.37 (s, 4 H, 2 NH<sub>2</sub>), 1.40–1.80 (m, 10 H, 5 CH<sub>2</sub>), 2.78–2.93 (m, 4 H, 2 CH<sub>2</sub>), 3.70–3.80 (m, 2 H, 2 CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  23.71, 25.00, 36.74, 44.20, 79.55, 109.06; EI-MS *m/z* 200 (M<sup>+</sup>). Anal. (C<sub>10</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N.

(4S,5S)-4,5-Bis(aminomethyl)-1,3-dioxolane (18a): yield 99%; spectral data were identical with that of 13a. Anal.  $(C_5H_{12}N_2O_2)$  C, H, N.

(4S,5S)-4,5-Bis(aminomethyl)-2-methyl-1,3-dioxolane (18b): yield 99%; spectral data were identical with that of 13b. Anal. (C<sub>6</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N.

(4.5,5.5)-4,5-Bis(aminomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane (18d): yield 99%; spectral data were identical with that of 13d. Anal. (C<sub>7</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>) C, H, N.

(4S,5S)-4,5-Bis(aminomethyl)-2-ethyl-1,3-dioxolane (18e): yield 93%; spectral data were identical with that of 13e. Anal.  $(C_7H_{16}N_2O_2)$  C, H, N.

(4S,5S)-4,5-Bis(aminomethyl)-2-isopropyl-1,3-dioxolane (18f): yield 96%; spectral data were identical with that of 13f. Anal. (C<sub>8</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N.

(4S,5S)-4,5-Bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclopentane (18g): yield 95%; spectral data were identical with that of 13g. Anal. (C<sub>9</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N.

(4.5,5.5)-4,5-Bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclohexane (18h): yield 98%; spectral data were identical with that of 13h. Anal.  $(C_{10}H_{20}N_2O_2)$  C, H, N.

Water Solubility. A standard solution was prepared by dissolving 1 mg of sample in 10 mL of H<sub>2</sub>O at 25 °C. The standard solution was diluted with H<sub>2</sub>O as necessary, and the diluted standard solutions were scanned by UV at 220 nm to obtain a standard curve. A saturated solution was prepared by vortex mixing in H<sub>2</sub>O for 60 s, then ultrasonification for 60 s, vortex mixing for 180 s, ultrasonification for 60 s, and finally vortex mixing for 5 min in the presence of excess compound. The solution was filtered to remove excess compound, using 0.45- $\mu$ m Millipore filters. The saturated solution was diluted to at least 2 mL and then scanned by UV at 220 nm. Total solubility was then determined by the comparison of the absorbance of the saturated solution with that of the standard curve.

In Vivo Antitumor Activity. L1210 leukemia cells were obtained from the American Type Culture Collection (Bethesda, MD) and maintained by serial passage in intraperitoneal cavities of DBA/2 mice.<sup>57</sup> Cisplatin-resistant L1210 cells were developed by continuously exposing L1210 cells to increasing concentrations of cisplatin<sup>58</sup> and were passaged in DBA/2 mice treated with cisplatin (5 mg/kg) ip as a single injection on day 1 and 5 after the tumor implantation.<sup>59</sup> BDF<sub>1</sub> male mice were inoculated ip with  $1 \times 10^6$  viable (those excluding trypan blue) L1210 or cisplatin-resistant L1210 cells on day 0. Test compounds were administered ip on day 1, 5, and 9 after the tumor implantation. Each drug-treated group for each dose level consisted of seven mice. All experiments were terminated on day 50. The in vivo antitumor activity was evaluated by comparing the mean survival time of treated groups (T) with that of control groups (C) and was expressed by percentage value of T/C (% T/C).

In Vitro Cytotoxicity. Eight human cancer cell lines (six stomach and two lung cancers) were tested in MTT assay. SNU-1, SNU-5, SNU-16, and NCI-N87 were obtained from Cancer Research Institute, Seoul National University College of Medicine, Korea. MKN-45, PC-9, and PC-14 were kindly provided by Dr. N. Saijo, National Cancer Center Hospital and Research Institute, Japan, and Kato-III was supplied by the American Type Culture Collection. These cell lines were grown in RPMI-1640 medium (GIBCO) supplemented with 10% heat-inactivated fetal calf serum, penicillin (100 units/mL), and streptomycin (100  $\mu$ g/mL) (RPMI-FCS) in a highly humidified atmosphere of 5%  $CO_2$  at 37 °C. Single-cell suspensions were prepared by pipette disaggregation and/or by trypsinization, and cells were counted with a hemocytometer. The number of cells for each cell line plated in 96-well microtiter plates was determined in the standard and growth curves of each cell line obtained in MTT assay. In all experimental conditions, cells untreated were in the exponential phase of growth at the completion of 4-day assay incubation. Cells were inoculated into each well in 0.18 mL of **RPMI-FCS** medium and 0.02 mL of 0.1, 0.3, 1.0, 3.0, 10.0, 30.0, or 100.0  $\mu$ g/mL of test compound was added to each well. Each test was done in triplicate. After 4 days of culture, 0.1 mg (50  $\mu$ L of 2 mg/mL) of MTT was added to each well. The plates were then incubated at 37 °C for an additional 4 h. After the plates were centrifuged at 450g for 5 min and the supernatant was aspirated, 150 µL of DMSO or acidified 2-propanol solution was added to each well to solubilize formazan crystals. The plates were read immediately at 540 nm on an Elisa reader (Dynatech, MR 5000). Data points in each experiment represent the arithmetic mean of the absorbances read. All experiments were done at least three times. The surviving fraction of cells was defined as the percent of optical density (OD) in treated wells to that of the control. The  $IC_{50}$  was defined as the concentration of compounds that produced a 50% reduction of the surviving fraction and calculated by quantal probit analysis of pharmacologic calculations with computer program.<sup>60</sup>

Nephrotoxicity Test. Test compounds dissolved or suspended in 0.5% carboxymethylcellulose sodium salt solution in water were administered ip in ICR male mice on day 0 at a dose equal to 1.5 times the optimal dose determined in the in vivo L1210 screening system. Cisplatin and carboplatin were also given at 2 and 1.5 times the optimal doses, respectively, as the control. Each treatment and control group consisted of six mice. On days 1, 4, and 8 after the administration, the mice were anesthetized and blood samples were collected from the posterior vena cava. The sample tubes were centrifuged at 1500g for 10 min, and the serum was collected and analyzed with a Ciba-Corning 550 Express biochemistry analyzer. Serum levels of BUN and creatinine were used as the indicator of nephrotoxicity.

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Supplementary Material Available: Analytical, physical, and spectral (analytical HPLC conditions, water solubilities, and FAB-MS) data for platinum(II) complexes 1a-t, 2a-h, and 3a-n (3 pages). Ordering information is given on any current masthead page.

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