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 ^{1}H NMR, ^{13}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 4,5-bis(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 (4*R*,5*R*)-stereoisomer **1a–h** exhibited the higher antitumor activity than the corresponding (4*S*,5*S*)-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)[1] is one of the most effective anticancer agents currently available for the treatment of testicular, ovarian, and bladder carcinomas.[2–8] 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.[9–12] 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,[2,15] (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.[19–23] Among them, *cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II) (carboplatin) has proven to be the only second-generation platinum complex commercially available at present. Carboplatin shows the same level of activity as cisplatin in treating some kinds of cancers, such as ovarian cancer and small-cell lung cancer,[24,25] is much less nephrotoxic and emetic than cisplatin,[26,27] and is sufficiently water-soluble. 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.[24,28] Moreover, carboplatin is not effective in the treatment of cancer cells resistant to cisplatin, suggesting that cross-resistance exists between cisplatin and carboplatin.[29,30] The other promising second-generation platinum complexes under development are tetrachloro((*d,l-trans*)-1,2-diaminocyclohexane)platinum(IV) (tetraplatin),[31,32] (glycolato-*O,O'*)diammineplatinum(II) (254-S),[33,34] ((*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)[37–39] (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

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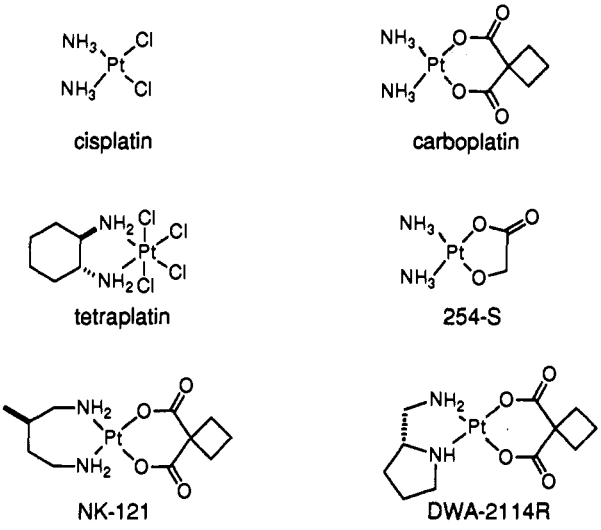
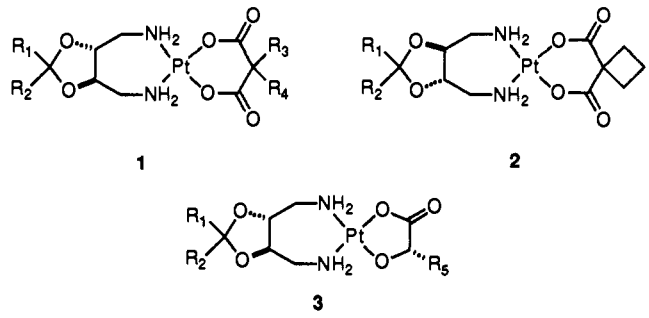
Chart 1



six-membered ring structures between a bidentate carrier ligand and a platinum atom.[40] The reason why reports are scarce on the synthesis of seven-membered ring complexes seems to be that the chelate effect in a seven-membered ring structure is considered to be weaker than that in a five- or six-membered ring structure.[35] Kaplan *et al.*[41] 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*.[36,42-43] Haines *et al.*[44] 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 seven-membered 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)-1,3-dioxolane 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

Chart 2

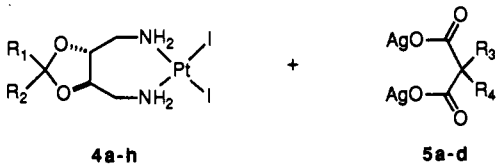


cyclopentane-1,2-bis(aminomethane) complex,[45] thereby facilitating intravenous administration and being possibly less toxic due to a more facile excretion *via* the kidney. It was well demonstrated that the antitumor activity of the platinum(II) complex was reduced by steric hindrance around the reactive center, platinum.[46] 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,[47] we have prepared both (4*R*,5*R*)-isomers **1a–h** and the corresponding (4*S*,5*S*)-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.[40,48] 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 diaquo 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–g** or **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_{18}-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 ^1H NMR, ^{13}C NMR, IR, FAB-MS, and elemental analysis. The FAB

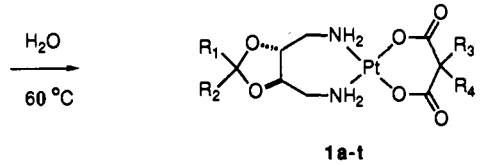
Scheme 1



4a-h + 5a-d

a: $R_1 = R_2 = H$
b: $R_1 = H$, $R_2 = Me$
c: $R_1 = R_2 = Me$
d: $R_1 = Me$, $R_2 = CH_2OH$
e: $R_1 = H$, $R_2 = Et$
f: $R_1 = H$, $R_2 = i\text{-Pr}$
g: $R_1, R_2 = -(CH_2)_4-$
h: $R_1, R_2 = -(CH_2)_5-$

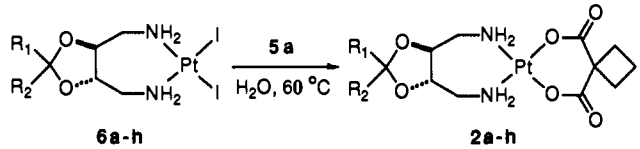
a: $R_3, R_4 = -(CH_2)_3-$
b: $R_3 = R_4 = H$
c: $R_3 = R_4 = Me$
d: $R_3 = H$, $R_4 = Et$



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: $R_1 = Me$, $R_2 = CH_2OH$, $R_3, R_4 = -(CH_2)_3-$
e: $R_1 = H$, $R_2 = Et$, $R_3, R_4 = -(CH_2)_3-$
f: $R_1 = H$, $R_2 = i\text{-Pr}$, $R_3, R_4 = -(CH_2)_3-$
g: $R_1, R_2 = -(CH_2)_4-$, $R_3, R_4 = -(CH_2)_3-$
h: $R_1, R_2 = -(CH_2)_5-$, $R_3, R_4 = -(CH_2)_3-$
i: $R_1 = R_2 = R_3 = R_4 = H$
j: $R_1 = R_3 = R_4 = H$, $R_2 = Me$
k: $R_1 = R_2 = Me$, $R_3 = R_4 = H$
l: $R_1 = R_3 = R_4 = H$, $R_2 = Et$
m: $R_1 = R_3 = R_4 = H$, $R_2 = i\text{-Pr}$
n: $R_1, R_2 = -(CH_2)_4-$, $R_3 = R_4 = H$
o: $R_1 = H$, $R_2 = Et$, $R_3 = R_4 = Me$
p: $R_1 = H$, $R_2 = i\text{-Pr}$, $R_3 = R_4 = Me$
q: $R_1, R_2 = -(CH_2)_4-$, $R_3 = R_4 = Me$
r: $R_1 = R_3 = H$, $R_2 = R_4 = Et$
s: $R_1 = R_3 = H$, $R_2 = i\text{-Pr}$, $R_4 = Et$
t: $R_1, R_2 = -(CH_2)_4-$, $R_3 = H$, $R_4 = Et$

Scheme 2

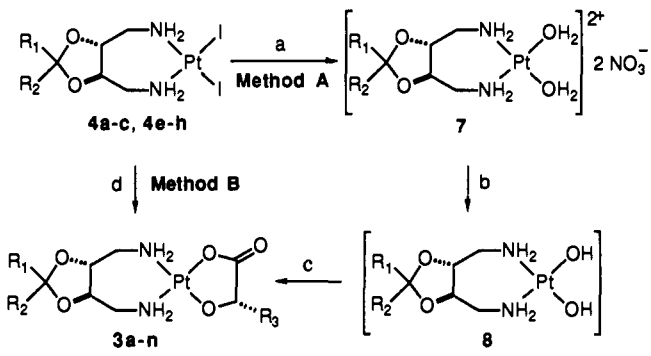


6a-h → (5a, H_2O, 60 °C) → 2a-h

a: $R_1 = R_2 = H$
b: $R_1 = H$, $R_2 = Me$
c: $R_1 = R_2 = Me$
d: $R_1 = Me$, $R_2 = CH_2OH$
e: $R_1 = H$, $R_2 = Et$
f: $R_1 = H$, $R_2 = i\text{-Pr}$
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 ^{194}Pt (33%), ^{195}Pt (34%), and ^{196}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 **3l** 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 ^1H NMR spectra. However, the examination of the ^{13}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 ^{13}C NMR spectrum of (ethylmalonato)platinum complex **1r** in DMSO-d_6

Scheme 3[a]

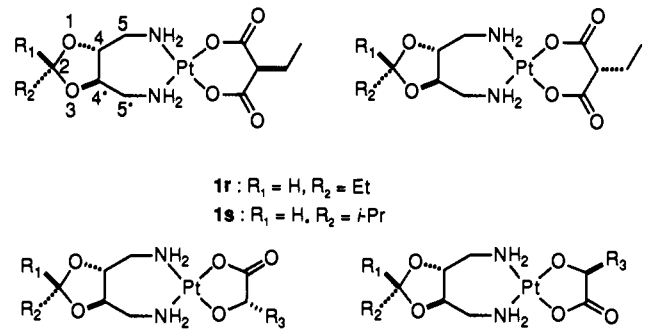


4a-c, 4e-h → (a, Method A) → 7 ($2NO_3^-$)
4a-c, 4e-h → (d, Method B) → 3a-n
7 → (b) → 8 → (c) → 3a-n

a: $R_1 = R_2 = R_3 = H$
b: $R_1 = R_3 = H$, $R_2 = Me$
c: $R_1 = R_2 = Me$, $R_3 = H$
d: $R_1 = R_3 = H$, $R_2 = Et$
e: $R_1 = R_3 = H$, $R_2 = i\text{-Pr}$
f: $R_1, R_2 = -(CH_2)_4-$, $R_3 = H$
g: $R_1, R_2 = -(CH_2)_5-$, $R_3 = H$
h: $R_1 = R_2 = H$, $R_3 = Me$
i: $R_1 = H$, $R_2 = R_3 = Me$
j: $R_1 = R_2 = R_3 = Me$
k: $R_1 = H$, $R_2 = Et$, $R_3 = Me$
l: $R_1 = H$, $R_2 = i\text{-Pr}$, $R_3 = Me$
m: $R_1, R_2 = -(CH_2)_4-$, $R_3 = Me$
n: $R_1, R_2 = -(CH_2)_5-$, $R_3 = Me$

[a] (a) $AgNO_3$, H_2O, 60 °C, 2 h; (b) Amberlyte IRA-400(OH) ion-exchange resin, H_2O; (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_2O, (for **3a-g**), 60 °C, 18 h, or (ii) L-lactic acid, Ag_2O (for **3h-n**), 60 °C, 18 h.

Chart 3

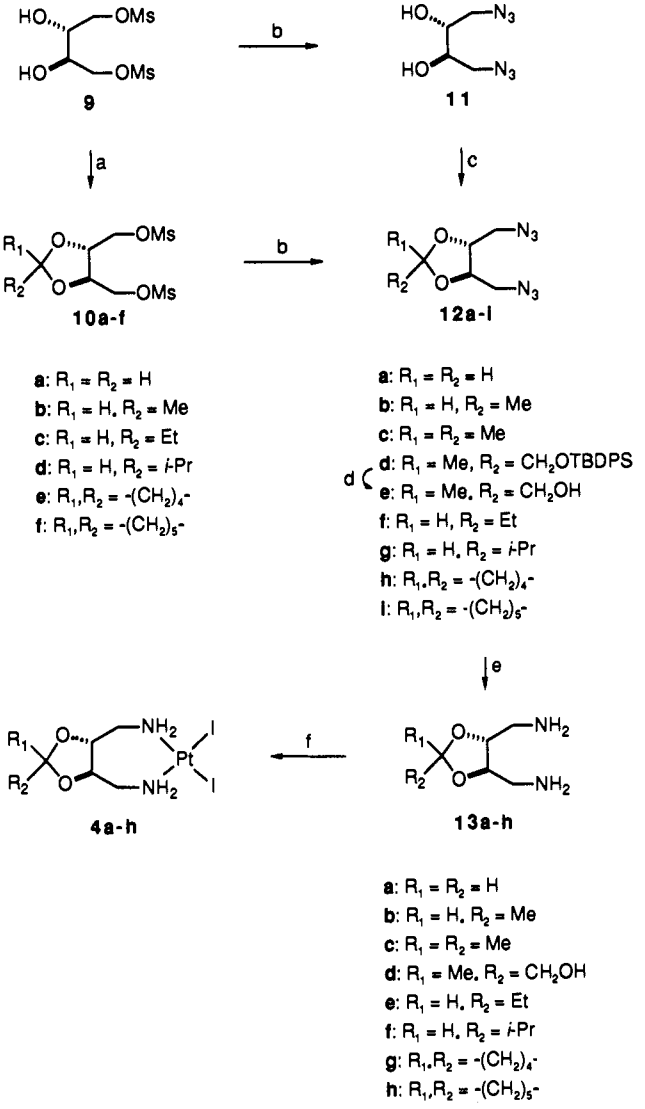


1r: $R_1 = H$, $R_2 = Et$
1s: $R_1 = H$, $R_2 = i\text{-Pr}$

3b: $R_1 = R_3 = H$, $R_2 = Me$
3d: $R_1 = R_3 = H$, $R_2 = Et$
3e: $R_1 = R_3 = H$, $R_2 = i\text{-Pr}$
3i: $R_1 = H$, $R_2 = R_3 = Me$
3k: $R_1 = H$, $R_2 = Et$, $R_3 = Me$
3l: $R_1 = H$, $R_2 = i\text{-Pr}$, $R_3 = Me$

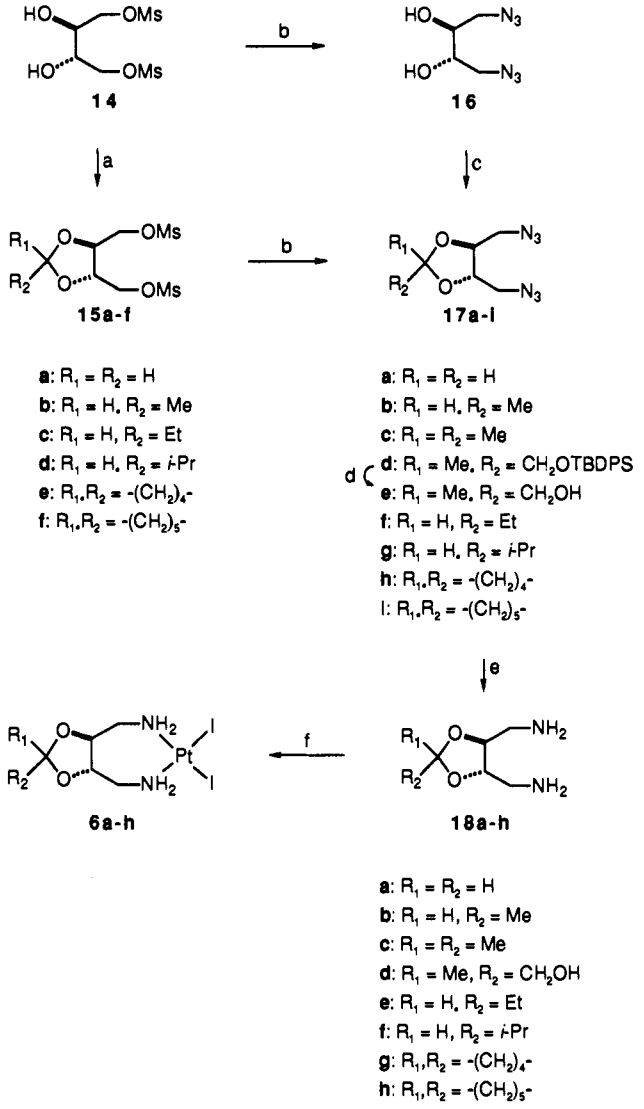
showed a pair of C-4 and C-4′ resonances at 77.68, 77.80, 79.51, and 79.64 ppm and a pair of C-5 and C-5′ resonances at 47.69, 47.81, 47.84, and 47.94 ppm. The (glycolato)-platinum complex **3b** in D_2O displayed a pair of C-5 and C-5′ resonances at 48.57, 48.73, 48.86, and 49.05 ppm. The antitumor 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.[46,47] 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

Scheme 4[a]



[a] (a) R_1COR_2 or $R_1C(OEt)_2R_2$, MsOH; (b) NaN_3, DMF, 100 °C, 16 h; (c) ((*tert*-butyldiphenylsilyl)oxy)acetone, anhydrous $CuSO_4$, MsOH, toluene, 45 °C, 16 h; (d) *n*-Bu_4NF, THF, room temperature, 1 h; (e) 10% Pd–C, EtOH, H_2 (50 psi), 40 °C, 2 h; (f) K_2PtCl_4, KI, H_2O, 60 °C, 3 h.

Scheme 5[a]



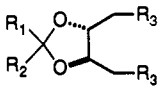
[a] (a) R_1COR_2 or $R_1C(OEt)_2R_2$, MsOH; (b) NaN_3, DMF, 100 °C, 16 h; (c) ((*tert*-butyldiphenylsilyl)oxy)acetone, anhydrous $CuSO_4$, MsOH, toluene, 45 °C, 16 h; (d) *n*-Bu_4NF, THF, room temperature, 1 h; (e) 10% Pd–C, EtOH, H_2 (50 psi), 40 °C, 2 h; (f) K_2PtCl_4, KI, H_2O, 60 °C, 3 h.

purity of the platinum complexes **1–3** were further determined by analytical reverse-phase HPLC analysis in two solvent systems (MeOH–H_2O), and all complexes were found to be sufficiently pure (>98%) for biological evaluation. The synthesis of *cis*-diiodo[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) **4a–h** from D-threitol 1,4-bis(methanesulfonate) (**9**)[50] 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 (4*R*,5*R*)-4,5-bis(((methylsulfonyl)oxy)methyl)-1,3-dioxolanes **10a–f**. These were then reacted with sodium azide in DMF to give (4*R*,5*R*)-4,5-bis(azidomethyl)-1,3-dioxolanes **12a–b** and **12f–i**. 2,2-Dimethyl-(4*R*,5*R*)-4,5-bis(azidomethyl)-1,3-dioxolane (**12c**)[44] was prepared by reaction of 2,2-dimethyl-1,3-dioxolane-(4*R*,5*R*)-4,5-bis(methanesulfonate)[50] with sodium azide in DMF. For the synthesis of 2-(hydroxymethyl)-2-methyl-(4*R*,5*R*)-4,5-bis(azidomethyl)-1,3-dioxolane (**12e**), D-threitol 1,4-bis(methanesulfonate) (**9**) was reacted with sodium azide in DMF to give (2*R*,3*R*)-2,3-dihydroxy-1,4-diazidobutane (**11**), which was then treated with ((*tert*-butyldiphenylsilyl)oxy)acetone and anhydrous $CuSO_4$ in the presence of methanesulfonic acid to afford 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methyl-(4*R*,5*R*)-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 (4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolanes **13a–h**, which were then reacted with potassium tetraiodoplatinate(II) to give *cis*-diiodo[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) **4a–h**. *cis*-Diiodo[(4*S*,5*S*)-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**)[50] 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.

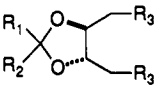
Results and Discussion

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



(4R,5R)



(4S,5S)

compd	R_1	R_2	R_3	absolute config	% yield	$[\alpha]^{20}_D$, deg (c = 0.04, acetone)	MS	formula	anal.[a]	IR, cm^{-1}
10c	H	Et	OMs	(4*R*,5*R*)	78		318	$C_9H_{13}O_8S_2$	C, H	1357, 1179
15c	H	Et	OMs	(4*S*,5*S*)	83		318	$C_9H_{13}O_8S_2$	C, H	1357, 1179
10d	H	*i*-Pr	OMs	(4*R*,5*R*)	98		332	$C_{10}H_{20}O_8S_2$	C, H	1360, 1182
15d	H	*i*-Pr	OMs	(4*S*,5*S*)	96		332	$C_{10}H_{20}O_8S_2$	C, H	1360, 1182
10e	$-(CH_2)_4-$		OMs	(4*R*,5*R*)	89		344	$C_{11}H_{20}O_8S_2$	C, H	1357, 1179
15e	$-(CH_2)_4-$		OMs	(4*S*,5*S*)	96		344	$C_{11}H_{20}O_8S_2$	C, H	1357, 1179
12a	H	H	N_3	(4*R*,5*R*)	95	+125.2	184	$C_5H_8N_6O_2$	C, H, N	2103
17a	H	H	N_3	(4*S*,5*S*)	96	−122.0	184	$C_5H_8N_6O_2$	C, H, N	2013
12b	H	Me	N_3	(4*R*,5*R*)	93	+143.8	198	$C_6H_{10}N_6O_2$	C, H, N	2101
17b	H	Me	N_3	(4*S*,5*S*)	98	−140.7	198	$C_6H_{10}N_6O_2$	C, H, N	2101
12d	Me	$CH_2OTBDPS$	N_3	(4*R*,5*R*)	90		467	$C_{23}H_{30}N_6O_3Si$	C, H, N	2099
17d	Me	$CH_2OTBDPS$	N_3	(4*S*,5*S*)	91		467	$C_{23}H_{30}N_6O_3Si$	C, H, N	2099
12e	Me	CH_2OH	N_3	(4*R*,5*R*)	93	+108.6	228	$C_7H_{12}N_6O_3$	C, H, N	3425, 2103
17e	Me	CH_2OH	N_3	(4*S*,5*S*)	92	−107.1	228	$C_7H_{12}N_6O_3$	C, H, N	3425, 2103
12f	H	Et	N_3	(4*R*,5*R*)	92	+127.9	212	$C_7H_{12}N_6O_2$	C, H, N	2102
17f	H	Et	N_3	(4*S*,5*S*)	90	−127.5	212	$C_7H_{12}N_6O_2$	C, H, N	2102
12g	H	*i*-Pr	N_3	(4*R*,5*R*)	97	+110.9	226	$C_8H_{14}N_6O_2$	C, H, N	2103
17g	H	*i*-Pr	N_3	(4*S*,5*S*)	97	−110.9	226	$C_8H_{14}N_6O_2$	C, H, N	2103
12h	$-(CH_2)_4-$		N_3	(4*R*,5*R*)	95	+125.4	238	$C_9H_{14}N_6O_2$	C, H, N	2101
17h	$-(CH_2)_4-$		N_3	(4*S*,5*S*)	97	−122.9	238	$C_9H_{14}N_6O_2$	C, H, N	2101
12i	$-(CH_2)_5-$		N_3	(4*R*,5*R*)	95	+120.4	252	$C_{10}H_{16}N_6O_2$	C, H, N	2100
17i	$-(CH_2)_5-$		N_3	(4*S*,5*S*)	98	−122.5	252	$C_{10}H_{16}N_6O_2$	C, H, N	2100
13a	H	H	NH_2	(4*R*,5*R*)	97		132	$C_5H_{12}N_2O_2$	C, H, N	3370, 3307
18a	H	H	NH_2	(4*S*,5*S*)	99		132	$C_5H_{12}N_2O_2$	C, H, N	3370, 3307
13b	H	Me	NH_2	(4*R*,5*R*)	97		146	$C_6H_{14}N_2O_2$	C, H, N	3375, 3304
18b	H	Me	NH_2	(4*S*,5*S*)	99		146	$C_6H_{14}N_2O_2$	C, H, N	3375, 3304
13d	Me	CH_2OH	NH_2	(4*R*,5*R*)	99		176	$C_7H_{16}N_2O_3$	C, H, N	3366
18d	Me	CH_2OH	NH_2	(4*S*,5*S*)	99		176	$C_7H_{16}N_2O_3$	C, H, N	3366
13e	H	Et	NH_2	(4*R*,5*R*)	95		160	$C_7H_{16}N_2O_2$	C, H, N	3367
18e	H	Et	NH_2	(4*S*,5*S*)	93		160	$C_7H_{16}N_2O_2$	C, H, N	3367
13f	H	*i*-Pr	NH_2	(4*R*,5*R*)	96		174	$C_8H_{18}N_2O_2$	C, H, N	3369, 3301
18f	H	*i*-Pr	NH_2	(4*S*,5*S*)	96		174	$C_8H_{18}N_2O_2$	C, H, N	3369, 3301
13g	$-(CH_2)_4-$		NH_2	(4*R*,5*R*)	96		186	$C_9H_{18}N_2O_2$	C, H, N	3370, 3302
18g	$-(CH_2)_4-$		NH_2	(4*S*,5*S*)	95		186	$C_9H_{18}N_2O_2$	C, H, N	3370, 3302
13h	$-(CH_2)_5-$		NH_2	(4*R*,5*R*)	99		200	$C_{10}H_{20}N_2O_2$	C, H, N	3370, 3297
18h	$-(CH_2)_5-$		NH_2	(4*S*,5*S*)	98		200	$C_{10}H_{20}N_2O_2$	C, H, N	3370, 3297

[a] Analytical results for the indicated elements are within ±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 (4*R*,5*R*)-stereoisomers **1a–h** had higher antitumor activities than the corresponding (4*S*,5*S*)-stereoisomers **2a–h**. In the malonato-, (dimethylmalonato)-, and (ethylmalonato)platinum(II) complexes, all of the compounds except **1k** and **1q** 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_1, R_2 = $-(CH_2)_5-$). 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_2OH) 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_2O 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 NCI-N87,[51] 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[a]

	% T/C at dose (mg/kg, ip, days 1, 5, 9)						
compd	100	50	25	12.5	6.25	3.1	1.5
1a	271 (2/7),[b] (2/7)[c]	193	137	187	122		
2a	179	123 (1/7)[b]	119	97	93		
1b	382 (1/7),[b] (4/7)[c]	262 (2/7)[c]	247 (2/7)[c]	129 (1/7)[b]	125		
2b	254 (1/7)[c]	201 (1/7)[c]	150	115	108		
1c	317 (1/7),[b] (2/7)[c]	283 (2/7)[c]	217 (1/7)[c]	170 (1/7)[b]	124		
2c	142	148 (1/7)[c]	124	106	112		
1d	181 (1/7)[b]	121	104	103	94		
2d	123	118	98	94	98		
1e	391 (5/7)[c]	208	193 (1/7)[b]	130	122		
2e	151	134	116	107	97		
1f	130 (3/7)[b]	133	126	106	113		
2f	120	112	104	100	96		
1g	185	148	110 (1/7)[b]	122	109		
2g	117 (3/7)[b]	106	94	109	102		
1h	108 (3/7)[b]	101 (1/7)[b]	120				
2h	toxic	95 (3/7)[b]	104				
1i		276 (1/7)[c]	133 (3/7)[b]	146			
1j		241	156	140			
1k		190	179	133			
1l		245	204	144			
1m		220 (1/7)[c]	148	123 (1/7)[c]			
1n		203	169	217			
1o	248 (1/7)[c]	165 (1/7)[c]	213 (1/7)[c]				
1p	204	174	123				
1q	150	160	172				
1r	97 (5/7),[b] (1/7)[c]	245	197				
1s	243 (1/7)[b]	169	137				
1t	216	232 (1/7)[c]	147				
3a		toxic	129 (2/7)[b]	137	132 (1/7)[b]	95	
3b		toxic	167 (2/7)[b]	154	136	104	
3c		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)[c]	161	154	
3g		toxic	231 (1/7)[b]	233 (1/7)[c]	146	102	
3h		92	207	178			
3i		139 (5/7)[b]	327 (2/7)[c]	201			
3j		toxic	toxic	213			
3k		toxic	165 (2/7)[b]	206			
3l		toxic	232 (2/7),[b] (1/7)[c]	208			
3m		192 (5/7),[b] (2/7)[c]	243 (1/7)[c]	225 (1/7)[c]			
3n		toxic	227	204			
cisplatin				toxic	82 (5/7)[b]	167 (2/7)[b]	142
carboplatin	197 (1/7)[b]	196 (1/7)[c]	148	125	107		

[a] See the Experimental Section for biological methods. [b] Values in parentheses = number of toxic death/number of animals tested. [c] 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.[52,53] 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 **3k** (R_1 = H, R_2 = Et), **3l** (R_1 = H, R_2 = *i*-Pr), **3m** (R_1, R_2 = $-(CH_2)_4-$), and **3n** (R_1, R_2 = $-(CH_2)_5-$) 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 ≃ dimethylmalonate ≃ 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-cyclobutanedicarboxylato)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*[a]

compd	IC_{50} (μg/mL)			
	SNU-1[b]	SNU-5[b]	SNU-16[b]	NCI-N87[b]
1a	28.23	4.82	12.67	70.46
1b	28.02	4.77	8.69	87.55
1c	24.64	3.94	9.40	54.39
1d	161.69	14.15	71.38	544.16
1e	17.62	2.15	9.02	56.92
1f	16.64	1.21	10.09	60.61
1g	18.43	2.50	7.61	44.41
1i	8.96	2.42	9.72	43.46
1j	26.99	1.84	13.59	25.04
1k	14.27	1.72	9.71	26.48
1l	11.34	1.67	9.73	22.45
1m	9.17	1.80	4.40	16.35
1n	8.82	1.02	3.80	14.90
1o	17.61	1.93	6.17	14.88
1p	8.70	0.18	4.42	12.00
1q	7.07	1.80	3.09	30.91
1r	11.05	0.51	8.63	14.20
1s	8.09	1.82	4.25	15.19
1t	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
3i	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
3l	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

[a] See the Experimental Section for biological methods. [b] See ref 51.

Table 4. Cytotoxicity of Selected Platinum(II) Complexes against Human Stomach and Lung Cancer Cell Lines *in Vitro*[a]

compd	IC_{50} (μg/mL)			
	KATO-III[b]	MKN-45[b]	PC-9[c]	PC-14[c]
1m	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

[a] See the Experimental Section for biological methods. [b] Stomach adenocarcinoma. [c] 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_2O, 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[54,55] (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[56] 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. ^1H 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 $CDCl_3$ or DMSO-d_6 and to DSS (0.015 ppm) in D_2O. ^1H noise-decoupled ^{13}C 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 δ 77.0 or 39.5, respectively. When D_2O was used, DSS (−1.6 ppm) was added as the internal standard. UV spectra were measured in H_2O with a Gilford Response UV–vis spectrophotometer. Electron impact mass spectra (EI-MS) and fast-atom 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

Table 5. Antitumor Activity of Selected Platinum(II) Complexes against Cisplatin-Resistant L1210 Leukemia in Mice[a]

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

[a-c] 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[a]

		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[b]	26.9 ± 1.1	24.9 ± 2.5	0.27 ± 0.01	0.26 ± 0.01	0.28 ± 0.01
1m	75.0	22.6 ± 1.6	27.0 ± 2.2	28.3 ± 1.5	0.22 ± 0.01	0.24 ± 0.02	0.29 ± 0.01
3d	18.8	24.9 ± 1.1	19.0 ± 1.0	19.9 ± 1.6	0.28 ± 0.02	0.26 ± 0.02	0.26 ± 0.01
3e	18.8	26.8 ± 1.8	21.2 ± 0.7	26.7 ± 1.0	0.27 ± 0.01	0.26 ± 0.01	0.30 ± 0.01
3f	18.8	26.7 ± 2.8	20.7 ± 1.1	24.7 ± 2.8	0.27 ± 0.01	0.24 ± 0.02	0.29 ± 0.02
3g	18.8	26.1 ± 0.9	17.2 ± 2.2	22.0 ± 0.8	0.26 ± 0.01	0.24 ± 0.01	0.27 ± 0.02
cisplatin	6.0	24.8 ± 1.6	43.1 ± 12.9[c]	32.5 ± 2.4[d]	0.26 ± 0.01	0.28 ± 0.06	0.40 ± 0.03
carboplatin	150.0	24.4 ± 0.7	21.1 ± 1.3	28.58 ± 3.1	0.25 ± 0.02	0.19 ± 0.01	0.31 ± 0.01

[a] See the Experimental Section for biological methods. [b] The values represent the means plus or minus standard error. [c] Mean is significantly different from control group; $p < 0.05$. [d] 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 μ-Bondapak C_{18}, 10-μm particle size, 125-Å pore size columns, 3.9 × 300 mm. The mobile phase utilized was a MeOH–H_2O 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-μm 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 ±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_2O (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 μm). 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_{18}-100-Å reverse-phase bonded silica cartridge with MeOH–H_2O 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)[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) (1a)**: **4a** and **5a**; MeOH–H_2O (2:8); 46%; white crystals; IR (KBr) 3432, 3239, 3191, 3126, 1634, 1590 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.67 (quintet, J = 7.8 Hz, 2 H, $CH_2CH_2CH_2$), 2.50–2.77 (m, 6 H, 2 $CHNH_2$ and $CH_2CH_2CH_2$), 3.06 (m, 2 H, 2 $CHNH_2$), 4.32 (m, 2 H, 2 CH), 4.93 (s, 2 H, OCH_2O), 5.24–5.65 (m, 4 H, 4 NH); ^{13}C NMR (DMSO-d_6) δ 14.85, 30.32, 47.75, 55.43, 78.37, 93.87, 177.30; FAB-MS m/z 470 $(MH)^+$. Anal. ($C_{11}H_{18}N_2O_6Pt$) C, H, N.

***cis*-(Cyclobutane-1,1-dicarboxylato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-methyl-1,3-dioxolane]platinum(II) (1b)**: **4b** and **5a**; MeOH–H_2O (2:8); 55%; white powder; IR (KBr) 3447, 3218, 3132, 1634 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.26 (d, J = 4.9 Hz, 3 H, CH_3), 1.67 (quintet, J = 7.8 Hz, 2 H, $CH_2CH_2CH_2$), 2.47–2.80 (m, 2 H, 2 $CHNH_2$ overlapped with $CH_2CH_2CH_2$), 2.66 (t, J = 7.8 Hz, 4 H, $CH_2CH_2CH_2$), 2.95 (m, 1 H, $CHNH_2$), 3.08 (m, 1 H, $CHNH_2$), 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); ^{13}C NMR (DMSO-d_6) δ 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 $(MH)^+$. Anal. ($C_{12}H_{20}N_2O_6Pt$) C, H, N.

***cis*-(Cyclobutane-1,1-dicarboxylato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2,2-dimethyl-1,3-dioxolane]platinum(II) (1c)**: **4c** and **5a**; MeOH–H_2O (4:6); 55%; white crystals; IR (KBr) 3424, 3239, 3084, 1616, 1587 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33 (s, 6 H, 2 CH_3), 1.67 (quintet, J = 7.8 Hz, 2 H, $CH_2CH_2CH_2$), 2.56 (m, 2 H, 2 $CHNH_2$), 2.66 (t, J = 7.8 Hz, 4 H, $CH_2CH_2CH_2$), 3.03 (m, 2 H, 2 $CHNH_2$), 4.37 (m, 2 H, 2 CH), 5.43 (br s, 2 H, 2 NH), 5.51 (br s, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 14.86, 26.41, 30.29, 48.47, 55.44, 78.18, 108.32, 177.28; FAB-MS m/z 498 $(MH)^+$. Anal. ($C_{13}H_{22}N_2O_6Pt$) C, H, N.

***cis*-(Cyclobutane-1,1-dicarboxylato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane]platinum(II) (1d)**: **4d** and **5a**; MeOH–H_2O (2:8); 67%; colorless crystals; IR (KBr) 3469, 3205, 3131, 1652, 1608 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.24 (s, 3 H, CH_3), 1.67 (quintet, J = 7.8 Hz, 2 H, $CH_2CH_2CH_2$), 2.59 (m, 2 H, 2 $CHNH_2$, overlapped with $CH_2CH_2CH_2$), 2.65 (t, J = 7.8 Hz, 4 H, $CH_2CH_2CH_2$), 3.03 (m, 2 H, 2 $CHNH_2$), 3.27 (d, J = 11.7 Hz, 1 H, CH_2OH), 3.34 (d, J = 11.7 Hz, 1 H, CH_2OH), 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); ^{13}C NMR (DMSO-d_6) δ 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 $(MH)^+$. Anal. ($C_{13}H_{22}N_2O_7Pt$) C, H, N.

***cis*-(Cyclobutane-1,1-dicarboxylato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (1e)**: **4e** and **5a**; MeOH–H_2O (3:7); 57%; colorless crystals; IR (KBr) 3446, 3189, 3072, 1609 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.86 (t, J = 7.5 Hz, 3 H, CH_3), 1.57 (dq, J = 4.5 Hz, J = 7.5 Hz, 2 H, CH_2CH_3), 2.65 (t, J = 7.8 Hz, 4 H, $CH_2CH_2CH_2$), 2.97 (m, 1 H, $CHNH_2$), 3.09 (m, 1 H, $CHNH_2$), 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); ^{13}C NMR (DMSO-d_6) δ 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 $(MH)^+$. Anal. ($C_{13}H_{22}N_2O_6Pt$) C, H, N.

***cis*-(Cyclobutane-1,1-dicarboxylato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (1f)**: **4f** and **5a**; MeOH–H_2O (4:6); 51%; white crystals; IR (KBr) 3433, 3198, 3070, 1608, 1593 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.86 (d, J = 6.9 Hz, 6 H, 2 CH_3), 1.67 (quintet, J = 7.8 Hz, 2 H, $CH_2CH_2CH_2$), 1.72 (m, 1 H, $CH(CH_3)_2$, overlapped with $CH_2CH_2CH_2$), 2.57 (m,

2 H, 2 C*H*NH$_2$, overlapped with CH_2CH_2CH_2), 2.64 (t, J = 7.8 Hz, 4 H, CH_2CH_2CH_2), 3.00 (m, 1 H, C*H*NH$_2$), 3.10 (m, 1 H, C*H*NH$_2$), 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); ^{13}C NMR (DMSO-d_6) δ 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)$^+$. Anal. ($C_{14}H_{24}N_2O_6Pt$) C, H, N.

***cis*-(Cyclobutane-1,1-dicarboxylato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1′-cyclopentane]platinum(II) (1g)**: **4g** and **5a**; MeOH–H_2O (5:5); 45%; white powder; IR (KBr) 3445, 3190, 3085, 1615 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.47–1.85 (m, 8 H, cyclopentyl), 1.67 (quintet, J = 7.8 Hz, 2 H, CH_2CH_2-CH_2, overlapped with cyclopentyl), 2.55 (m, 2 H, 2 C*H*NH$_2$), 2.65 (t, J = 7.8 Hz, 4 H, CH_2CH_2CH_2), 3.05 (m, 2 H, 2 C*H*NH$_2$), 4.34 (m, 2 H, 2 CH), 5.38 (br s, 2 H, 2 NH), 5.47 (br s, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 15.26, 23.30, 30.72, 36.58, 48.61, 55.84, 78.34, 118.69, 178.13; FAB-MS m/z 524 (MH)$^+$. Anal. ($C_{15}H_{24}$-N_2O_6Pt) C, H, N.

***cis*-(Cyclobutane-1,1-dicarboxylato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1′-cyclohexane]platinum(II) (1h)**: **4h** and **5a**; MeOH–H_2O (5:5); 41%; white powder; IR (KBr) 3445, 3190, 3069, 1607 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.34 (br s, 2 H, cyclohexyl), 1.54 (br s, 8 H, cyclohexyl), 1.67 (quintet, J = 7.8 Hz, 2 H, CH_2CH_2CH_2), 2.55 (m, 2 H, 2 C*H*NH$_2$), 2.65 (t, J = 7.8 Hz, 4 H, CH_2CH_2CH_2), 3.10 (m, 2 H, 2 C*H*NH$_2$), 4.36 (m, 2 H, 2 CH), 5.37 (br s, 2 H, 2 NH), 5.45 (br s, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 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)$^+$. Anal. ($C_{16}H_{26}$-N_2O_6Pt) C, H, N.

***cis*-(Malonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum)(II) (1i)**: **4a** and **5b**; MeOH–H_2O (1:9), 81%; white crystals; IR (KBr) 3481, 3243, 3172, 3048, 1652, 1606 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.62 (m, 2 H, 2 C*H*NH$_2$), 3.04 (m, 2 H, 2C*H*NH$_2$), 3.26 (s, 2 H, CH$_2$), 4.41 (m, 2 H, 2 CH), 4.94 (s, 2 H, OCH$_2$O), 5.38 (br s, 2 H, 2 NH), 5.47 (br s, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 47.54, 50.22, 78.30, 93.86, 174.01; FAB-MS m/z 430 (MH)$^+$. Anal. ($C_3H_{14}N_2O_6Pt$) C, H, N.

***cis*-(Malonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-methyl-1,3-dioxolane]platinum(II) (1j)**: **4b** and **5b**; MeOH–H_2O (1:9), 81%; white crystals; IR (KBr) 3454, 3383, 3214, 3065, 1643–1555 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.27 (d, J = 4.8 Hz, 3 H, CH$_3$), 2.60 (m, 2 H, 2 C*H*NH$_2$), 2.94 (m, 1 H, C*H*NH$_2$), 3.05 (m, 1 H, C*H*NH$_2$), 3.26 (s, 2 H, CH$_2$), 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); ^{13}C NMR (DMSO-d_6) δ 19.54, 47.75, 47.81, 50.21, 77.50, 79.72, 100.44, 174.03; FAB-MS m/z 444 (MH)$^+$. Anal. ($C_9H_{16}N_2O_6Pt$) C, H, N.

***cis*-(Malonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2,2-dimethyl-1,3-dioxolane]platinum(II) (1k)**: **4c** and **5b**; MeOH–H_2O (3:7); 89%; white crystals; IR (KBr) 3445, 3207, 3107, 1627 cm^{-1}; ^{1}H NMR (DSMO-d_6) δ 1.34 (s, 6 H, 2 CH$_3$), 2.56 (m, 2 H, 2 C*H*NH$_2$), 3.02 (m, 2 H, 2 C*H*NH$_2$), 3.26 (s, 2 H, CH$_2$), 4.45 (m, 2 H, 2 CH), 5.45 (br s, 2 H, 2 NH), 5.56 (br s, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 26.42, 48.33, 50.22, 78.10, 108.30, 174.00; FAB-MS m/z 458 (MH)$^+$. Anal. ($C_{10}H_{13}N_2O_6Pt$) C, H, N.

***cis*-(Malonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (1l)**: **4e** and **5b**; MeOH–H_2O (3:7); 89%; white crystals; IR (KBr) 3447, 3214, 3120, 1628 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.87 (t, J = 7.5 Hz, 3 H, CH$_3$), 1.58 (dq, J = 4.5 Hz, J = 7.5 Hz, 2 H, CH_2CH$_3$), 2.59 (m, 2 H, 2 C*H*NH$_2$), 2.97 (m, 1 H, C*H*NH$_2$), 3.08 (m, 1 H, C*H*NH$_2$), 3.26 (s, 2 H, CH$_2$), 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); ^{13}C NMR (DMSO-d_6) δ 7.65, 26.35, 47.74, 47.84, 50.21, 77.65, 79.50, 104.12, 174.04; FAB-MS m/z 458 (MH)$^+$. Anal. ($C_{10}H_{13}N_2O_6Pt$) C, H, N.

***cis*-(Malonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (1m)**: **4f** and **5b**: MeOH–H_2O (4:6); 89%; white crystals; IR (KBr) 3431, 3205, 3049, 1612 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.87 (d, J = 6.6 Hz, 6 H, 2 CH$_3$), 1.75 (m, 1 H, CH(CH$_3$)$_2$), 2.59 (m, 2 H, 2 C*H*NH$_2$), 2.98 (m, 1 H, C*H*NH$_2$), 3.09 (m, 1 H, C*H*NH$_2$), 3.25 (s, 1 H, CH$_2$), 3.26 (s, 1 H, CH$_2$), 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); ^{13}C NMR (DMSO-d_6) δ 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)$^+$. Anal. ($C_{11}H_{20}N_2O_6Pt$) C, H, N.

***cis*-(Malonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1′-cyclopentane]platinum(II) (1n)**: **4g** and **5b**; MeOH–H_2O (4:6); 56%; white crystals; IR (KBr) 3433, 3200, 3053, 1613 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.45–1.90 (m, 8 H, cyclopentyl), 2.55 (m, 2 H, 2 C*H*NH$_2$), 3.03 (m, 2 H, 2 C*H*NH$_2$), 3.26 (s, 2 H, CH$_2$), 4.41 (m, 2 H, 2 CH), 5.38 (br s, 2 H, 2 NH), 5.50 (br s, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 22.86, 36.23, 48.20, 50.21, 78.03, 118.10, 174.00; FAB-MS m/z 484 (MH)$^+$. Anal. ($C_{12}H_{20}N_2O_6Pt$) C, H, N.

***cis*-(Dimethylmalonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (1o)**: **4e** and **5c**; MeOH–H_2O (4:6); 83%; white crystals; IR (KBr) 3454, 3211, 3126, 1650–1597 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J = 7.4 Hz, 3 H, CH$_3$), 1.53 (s, 3 H, CH$_3$), 1.54 (s, 3 H, CH$_3$), 1.58 (dq, J = 4.4 Hz, J = 7.4 Hz, 2 H, CH_2CH$_3$), 2.59 (m, 2 H, 2 C*H*NH$_2$), 2.98 (m, 1 H, C*H*NH$_2$), 3.10 (m, 1 H, C*H*NH$_2$), 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); ^{13}C NMR (DMSO-d_6) δ 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)$^+$. Anal. ($C_{12}H_{22}N_2O_6Pt$) C, H, N.

***cis*-(Dimethylmalonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (1p)**: **4f** and **5c**; MeOH–H_2O (5:5); 75%; white crystals; IR (KBr) 3449, 3216, 3130, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.87 (d, J = 6.9 Hz, 6 H, 2 CH$_3$), 1.53 (s, 3 H, CH$_3$), 1.54 (s, 3 H, CH$_3$), 1.74 (m, 1 H, CH(CH$_3$)$_2$), 2.59 (m, 2 H, 2 C*H*NH$_2$), 3.00 (m, 1 H, C*H*NH$_2$), 3.11 (m, 1 H, C*H*NH$_2$), 4.26 (m, 1 H, CH), 4.45 (m, 1 H, CH), 4.81 (d, J = 4.5 Hz, 1 H, CH), 5.33 (br s, 1 H, NH), 5.48 (br s, 3 H, 3 NH); ^{13}C NMR (DMSO-d_6) δ 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)$^+$. Anal. ($C_{13}H_{24}N_2O_6Pt$) C, H, N.

***cis*-(Dimethylmalonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1′-cyclopentane]platinum(II) (1q)**: **4g** and **5c**; MeOH–H_2O (5:5); 64%; white powder; IR (KBr) 3454, 3218, 3131, 1668–1652 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.50–1.85 (m, 8 H, cyclopentyl), 1.54 (s, 6 H, 2 CH$_3$), 2.55 (m, 2 H, 2 C*H*NH$_2$), 3.04 (m, 2 H, C*H*NH$_2$), 4.36 (m, 2 H, 2 CH), 5.40 (br s, 2 H, 2 NH), 5.49 (br s, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 22.91, 26.01, 36.26, 48.38, 51.70, 78.15, 118.10, 178.59; FAB-MS m/z 512 (MH)$^+$. Anal. ($C_{14}H_{24}N_2O_6Pt$) C, H, N.

***cis*-(Ethylmalonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (1r)**: **4e** and **5d**; MeOH–H_2O (4:6); 95%; white crystals; IR (KBr) 3446, 3205, 3122, 1648, 1635 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J = 7.5 Hz, 3 H, CH$_3$), 0.87 (t, J = 7.5 Hz, 3 H, CH$_3$), 1.58 (dq, J = 4.2 Hz, J = 7.5 Hz, 2 H, CH_2CH$_3$), 1.82 (dq, J = 7.1 Hz, J = 7.5 Hz, 2 H, CH_2CH$_3$), 2.60 (m, 2 H, 2 C*H*NH$_2$), 2.96 (m, 1 H, C*H*NH$_2$), 3.08 (m, 1 H, C*H*NH$_2$), 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); ^{13}C NMR (DMSO-d_6) δ 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)$^+$. Anal. ($C_{12}H_{22}N_2O_6Pt$) C, H, N.

***cis*-(Ethylmalonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (1s)**: **4f** and **5d**; MeOH–H_2O (5:5); 59%; white crystals; IR (KBr) 3448, 3202, 3126, 1617 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J = 7.5 Hz, 3 H, CH$_3$), 0.87 (d, J = 6.9 Hz, 6 H, 2 CH$_3$), 1.75 (m, 1 H, CH(CH$_3$)$_2$), 1.82 (dq, J = 7.1 Hz, J = 7.5 Hz, 2 H, CH_2CH$_3$), 2.58 (m, 2 H, 2 C*H*NH$_2$), 2.98 (m, 1 H, C*H*NH$_2$), 3.09 (m, 1 H, C*H*NH$_2$), 3.41 (t, J = 7.1 Hz, 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); ^{13}C NMR (DMSO-d_6) δ 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)$^+$. Anal. ($C_{13}H_{24}N_2O_6Pt$) C, H, N.

***cis*-(Ethylmalonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1′-cyclopentane]platinum(II) (1t)**: **4g** and **5d**; MeOH–H_2O (5:5); 86%; white powder; IR (KBr) 3448, 3197, 3092, 1622 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.50–1.85 (m, 8 H, cyclopentyl), 1.83 (dq, J = 7.1 Hz, J = 7.5 Hz, 2 H, CH_2CH$_3$), 2.55 (m, 2 H, 2 C*H*NH$_2$), 3.04 (m, 2 H, 2 C*H*NH$_2$), 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); ^{13}C NMR (DMSO-d_6) δ 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 $(MH)^+$. Anal. ($C_{14}H_{24}N_2O_6Pt$) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4*S*,5*S*)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) (2a): 6a and 5a; MeOH–H_2O (2:8); 48%; white crystals; spectral data were identical with that of 1a. Anal. ($C_{11}H_{13}N_2O_6Pt$) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4*S*,5*S*)-4,5-bis(aminomethyl)-2-methyl-1,3-dioxolane]platinum(II) (2b): 6b and 5a; MeOH–H_2O (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)[(4*S*,5*S*)-4,5-bis(aminomethyl)-2,2-dimethyl-1,3-dioxolane]platinum(II) (2c): 6c and 5a; MeOH–H_2O (4:6); 54%; white crystals; spectral data were identical with that of 1c. Anal. ($C_{13}H_{22}N_2O_6Pt$) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4*S*,5*S*)-4,5-bis(aminomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane]platinum(II) (2d): 6d and 5a; MeOH–H_2O (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)[(4*S*,5*S*)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (2e): 6e and 5a; MeOH–H_2O (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)[(4*S*,5*S*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (2f): 6f and 5a; MeOH–H_2O (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)[(4*S*,5*S*)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1′-cyclopentane]platinum(II) (2g): 6g and 5a; MeOH–H_2O (5:5); 54%; white powder; spectral data were identical with that of 1g. Anal. ($C_{15}H_{24}N_2O_6Pt$) C, H, N.

cis-(Cyclobutane-1,1-dicarboxylato)[(4*S*,5*S*)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1′-cyclohexane]platinum(II) (2h): 6h and 5a; MeOH–H_2O (5:5); 50%; white powder; spectral data were identical with that of 1h. Anal. ($C_{16}H_{26}N_2O_6Pt$) 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_2O (15 mL) was added a solution of $AgNO_3$ (1.72 mmol) in H_2O (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 ~10 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 (~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 ~10 mL in volume, and purified by preparative HPLC on Delta pak C_{18}-100-Å reverse-phase bonded silica cartridge with MeOH–H_2O 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_2O (1.72 mmol) in H_2O (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_2O. 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*′)[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) (3a): H_2O only; 56% (method A), 57% (method B); IR (KBr) 3445, 3222, 3069, 1645 cm^{-1}; ^1H NMR (D_2O) δ 2.87 (m, 2 H, 2 C*H*NH_2), 3.38 (m, 2 H, 2 C*H*NH_2), 4.10 (s, 2 H, CH_2), 4.59 (m, 2 H, 2 CH), 5.05 (s, 2 H, OCH_2O); ^{13}C NMR (D_2O) δ 48.52, 48.82, 69.30, 79.49, 79.53, 95.42, 195.49; FAB-MS m/z 402 $(MH)^+$. Anal. ($C_7H_{14}N_2O_5Pt$) C, H, N.

cis-(Glycolato-*O*,*O*′)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-methyl-1,3-dioxolane]platinum(II) (3b): MeOH–H_2O (1:19); 78% (method A), 64% (method B); IR (KBr) 3451, 3213, 3139, 1634 cm^{-1}; ^1H NMR (D_2O) δ 1.40 (d, J = 4.8 Hz, 3 H, CH_3), 2.87 (m, 2 H, 2 C*H*NH_2), 3.28 (m, 1 H, C*H*NH_2), 3.39 (m, 1 H, C*H*NH_2), 4.10 (s, 2 H, CH_2), 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); ^{13}C NMR (D_2O) δ 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 $(MH)^+$. Anal. ($C_8H_{16}N_2O_5Pt$) C, H, N.

cis-(Glycolato-*O*,*O*′)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2,2-dimethyl-1,3-dioxolane]platinum(II) (3c): MeOH–H_2O (1:9); 46% (method A), 42% (method B); IR (KBr) 3430, 3142, 3085, 1657 cm^{-1}; ^1H NMR (D_2O) δ 1.47 (s, 6 H, 2 CH_3), 2.86 (m, 2 H, 2 C*H*NH_2), 3.32 (m, 2 H, 2 C*H*NH_2), 4.10 (s, 2 H, CH_2), 4.71 (m, 2 H, 2 CH); ^{13}C NMR (D_2O) δ 26.56, 49.36, 49.65, 69.27, 79.18, 111.35, 195.51; FAB-MS m/z 430 $(MH)^+$. Anal. ($C_9H_{18}N_2O_5Pt$) C, H, N.

cis-(Glycolato-*O*,*O*′)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (3d): MeOH–H_2O (1:9); 54% (method A), 66% (method B); IR (KBr) 3431, 3132, 1650 cm^{-1}; ^1H NMR (D_2O) δ 0.93 (t, J = 7.5 Hz, 3 H, CH_3), 1.72 (dq, J = 4.5 Hz, J = 7.5 Hz, 2 H, C$H_2$$CH_3$), 2.88 (m, 2 H, 2 C*H*$NH_2$), 3.29 (m, 1 H, C*H*$NH_2$), 3.39 (m, 1 H, C*H*$NH_2$), 4.10 (s, 2 H, CH_2), 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); ^{13}C NMR (D_2O) δ 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 $(MH)^+$. Anal. ($C_9H_{18}N_2O_5Pt$) C, H, N.

cis-(Glycolato-*O*,*O*′)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (3e): MeOH–H_2O (3:7); 29% (method A), 75% (method B); IR (KBr) 3425, 3218, 3143, 1634 cm^{-1}; ^1H NMR (D_2O) δ 0.94 (d, J = 6.9 Hz, 6 H, 2 CH_3), 1.89 (m, 1 H, C*H*(CH_3)$_2$), 2.86 (m, 2 H, 2 C*H*NH_2), 3.30 (m, 1 H, C*H*NH_2), 3.39 (m, 1 H, C*H*NH_2), 4.10 (s, 2 H, CH_2), 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); ^{13}C NMR (D_2O) δ 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 $(MH)^+$. Anal. ($C_{10}H_{20}N_2O_5Pt$) C, H, N.

cis-(Glycolato-*O*,*O*′)[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1′-cyclopentane]platinum(II) (3f): MeOH–H_2O (4:6); 50% (method A), 68% (method B); IR (KBr) 3409, 3211, 3143, 1635 cm^{-1}; ^1H NMR (D_2O) δ 1.60–2.00 (m, 8 H, cyclopentyl), 2.86 (m, 2 H, 2 C*H*NH_2), 3.33 (m, 2 H, 2 C*H*NH_2), 4.10 (s, 2 H, CH_2), 4.66 (m, 2 H, 2 CH); ^{13}C NMR (D_2O) δ 23.88, 37.11, 49.22, 49.50, 69.29, 79.05, 121.09, 195.51; FAB-MS m/z 456 $(MH)^+$. Anal. ($C_{11}H_{20}N_2O_5Pt$) C, H, N.

cis-(Glycolato-*O*,*O*′)[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1′-cyclohexane]platinum(II) (3g): MeOH–H_2O (4:6); 23% (method A), 48% (method B); IR (KBr) 3417, 3218, 3143, 1634 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.34 (br s, 2 H, cyclohexyl), 1.54 (br s, 8 H, cyclohexyl), 2.55 (m, 2 H, 2 C*H*NH_2), 3.14 (m, 2 H, 2 C*H*NH_2), 3.78 (s, 2 H, CH_2), 4.40 (m, 2 H, 2 CH), 4.93 (br s, 1 H, NH), 5.15 (br s, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 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 $(MH)^+$. Anal. ($C_{12}H_{22}N_2O_5Pt$) C, H, N.

cis-(L-Lactato-*O*,*O*′)[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) (3h): MeOH–H_2O (7:93); 24% (method A), 58% (method B); IR (KBr) 3426, 3209, 3132, 1628 cm^{-1}; ^1H NMR (D_2O) δ 1.34 (d, J = 6.9 Hz, 3 H, CH_3), 2.89 (m, 2 H, 2 C*H*NH_2), 4.17 (d, J = 6.9 Hz, 1 H, C*H*CH_3), 4.60 (m, 2 H, 2 CH), 5.05 (s, 2 H, OCH_2O); ^{13}C NMR (D_2O) δ 22.62, 48.47, 48.82, 75.19, 79.53, 79.58, 95.43, 196.47; FAB-MS m/z 416 $(MH)^+$. Anal. ($C_8H_{18}N_2O_5Pt$) C, H, N.

cis-(L-Lactato-*O*,*O*′)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-methyl-1,3-dioxolane]platinum(II) (3i): MeOH–H_2O (1:9); 76% (method A), 57% (method B); IR (KBr) 3426, 3214, 3143, 1623 cm^{-1}; ^1H NMR (D_2O) δ 1.30 (d, J = 6.9 Hz, 3 H, CH_3), 1.40 (d, J = 4.8 Hz, 3 H, CH_3), 2.88 (m, 2 H, 2 C*H*NH_2), 3.30 (m, 1 H, C*H*NH_2), 3.41 (m, 1 H, C*H*NH_2), 4.17 (d, J = 6.9 Hz, 1 H, C*H*CH_3), 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 $(MH)^+$. Anal. ($C_9H_{18}N_2O_5Pt$) C, H, N.

cis-(L-Lactato-*O*,*O*′)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2,2-dimethyl-1,3-dioxolane]platinum(II) (3j): MeOH–H_2O (3:7); 56% (method A), 73% (method B); IR (KBr) 3419, 3216, 3131, 1634 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.14 (d, J = 6.9 Hz, 3 H,

CH_3), 1.37 (s, 6 H, 2 CH_3), 2.66 (m, 1 H, C*H*NH_2), 2.80 (m, 1 H, C*H*NH_2), 3.18 (m, 2 H, 2 C*H*NH_2), 3.68 (d, J = 6.9 Hz, 1 H, C*H*CH_3), 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); ^{13}C NMR (DMSO-d_6) δ 21.33, 26.39, 48.01, 48.29, 66.91, 77.49, 77.94, 108.74, 180.70; FAB-MS m/z 444 $(MH)^+$. Anal. ($C_{10}H_{20}N_2O_5Pt$) C, H, N.

***cis*-(L-Lactato-*O*,*O*')[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-ethyl-1,3-dioxolane]platinum(II) (3k)**: MeOH–H_2O (2:8); 77% (method A), 73% (method B); IR (KBr) 3405, 3209, 3138, 1636 cm^{-1}; ^1H NMR (D_2O) δ 0.94 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.30 (d, J = 6.9 Hz, 3 H, CH_3), 1.73 (dq, J = 4.5 Hz, J = 7.5 Hz, 2 H, CH_2CH_3), 2.88 (m, 2 H, 2 C*H*NH_2), 3.31 (m, 1 H, C*H*NH_2), 3.41 (m, 1 H, C*H*NH_2), 4.17 (q, J = 6.9 Hz, 1 H, C*H*CH_3), 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 $(MH)^+$. Anal. ($C_{10}H_{20}N_2O_5Pt$) C, H, N.

***cis*-(L-Lactato-*O*,*O*')[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (3l)**: MeOH–H_2O (3:7); 85% (method A), 62% (method B); IR (KBr) 3425, 3212, 3136, 1634 cm^{-1}; FAB-MS m/z 458 $(MH)^+$. Anal. ($C_{11}H_{22}N_2O_5Pt$) C, H, N.

***cis*-(L-Lactato-*O*,*O*')[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclopentane]platinum(II) (3m)**: MeOH–H_2O (4:6); 70% (method A), 47% (method B); IR (KBr) 3413, 3207, 3143, 1642 cm^{-1}; FAB-MS m/z 470 $(MH)^+$. Anal. ($C_{12}H_{22}N_2O_5Pt$) C, H, N.

***cis*-(L-Lactato-*O*,*O*')[(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-1'-cyclohexane]platinum(II) (3n)**: MeOH–H_2O (5:5); 47% (method A), 60% (method B); IR (KBr) 3425, 3219, 3137, 1630 cm^{-1}; FAB-MS m/z 484 $(MH)^+$. Anal. ($C_{13}H_{24}N_2O_5Pt$) 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_2O (20 mL) was added a filtered solution of K_2PtCl_4 (10.2 mmol) in H_2O (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_2PtI_4. H_2O (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_2PtI_4 and a solution of 4,5-bis(aminomethyl)-1,3-dioxolane (**13a–h** and **18a–h**) (10.2 mmol) in H_2O (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_2O, EtOH, and Et_2O, 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^{-1}; FAB-MS m/z 582 $(MH)^+$.

***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^{-1}; FAB-MS m/z 596 $(MH)^+$.

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

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

***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^{-1}; FAB-MS m/z 610 $(MH)^+$.

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

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

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

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

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

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

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

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

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

***cis*-Diiodo[(4*S*,5*S*)-4,5-bis(aminomethyl)-1,3-dioxolane-2-spiro-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 $AgNO_3$ (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) (10f), and 2,3-*O*-cyclohexylidene-L-threitol 1,4-bis(methanesulfonate) (15f) were synthesized according to the published procedure[50] in 61%, 63%, 95%, 96%, 92%, and 95% yields, respectively.

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 $CuSO_4$ (1.55 g, 9.7 mmol), and CH_3SO_3H (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 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3 H, CH_3), 1.71 (dq, J = 4.6 Hz, J = 7.4 Hz, 2 H, CH_2), 3.09 (s, 6 H, 2 SO_2CH_3), 4.09–4.29 (m, 2 H, 2 CH), 4.33 (m, 4 H, 2 CH_2), 5.07 (t, J = 4.6 Hz, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 7.59, 26.89, 37.77, 67.78, 68.00, 75.18, 75.73, 106.38; EI-MS m/z 318 (M^+). Anal. ($C_9H_{13}O_3S_2$) 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 $CuSO_4$ (3.44 g, 21.6 mmol), and CH_3SO_3H (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^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6.8 Hz, 6 H, 2 CH_3), 1.82 (m, 1 H, CH), 3.08 (s, 6 H, 2 SO_2CH_3), 4.05–4.25 (m, 2 H, 2 CH), 4.25–4.45 (m, 4 H, 2 CH_2), 4.86 (d, J = 4.6 Hz, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 16.50, 31.87, 37.75, 67.83, 67.91, 75.28, 75.66, 109.15; El-MS m/z 332 (M^+). Anal. ($C_{10}H_{20}O_3S_2$) C, H.

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^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–2.00 (m, 8 H, 4 CH_2), 3.08 (s, 6 H, 2 SO_2CH_3), 4.10–4.25 (m, 2 H, 2 CH), 4.25–4.50 (m, 4 H, 2 CH_2); ^{13}C NMR ($CDCl_3$) δ 23.35, 37.15, 37.66, 68.03, 75.10, 120.80; EI-MS *m/z* 344 (M^+). Anal. ($C_{11}H_{20}O_3S_2$) 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. ($C_9H_{13}O_3S_2$) 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. ($C_{10}H_{20}O_3S_2$) 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. ($C_{11}H_{20}O_3S_2$) C, H.

(2*R*,3*R*)-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 × 50 mL). The combined organic phase was dried over anhydrous $MgSO_4$, 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: $[\alpha]^{20}_D$ = −13.4° (*c* = 0.04, acetone); IR (neat) 3402, 2105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (br s, 2 H, 2 OH), 3.15–3.60 (m, 4 H, 2 CH_2), 3.65–3.90 (m, 2 H, 2 CH); ^{13}C NMR ($CDCl_3$) δ 53.65, 70.49; EI-MS *m/z* 172 (M^+). Anal. ($C_4H_8N_6O_2$) 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° (*c* = 0.04, acetone); spectral data were identical with that of **11**. Anal. ($C_4H_8N_6O_2$) 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_3 (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_2O (20 mL), and extracted with Et_2O (100 mL). The ethereal solution was washed with brine (20 mL), dried over anhydrous $MgSO_4$, and evaporated to dryness under reduced pressure. The crude product was purified by flash column chromatography over silica gel with a mixture of Et_2O–hexane (1:4, v/v) as the eluent to give a pale yellow oil.

(4*R*,5*R*)-4,5-Bis(azidomethyl)-1,3-dioxolane (12a): yield 95%; $[\alpha]^{20}_D$ = +125.2° (*c* = 0.04, acetone); ^1H NMR ($CDCl_3$) δ 3.30–3.62 (m, 4 H, 2 CH_2), 3.91–4.09 (m, 2 H, 2 CH), 5.08 (s, 2 H, OCH_2O); ^{13}C NMR ($CDCl_3$) δ 51.64, 77.14, 95.37; EI-MS *m/z* 184 (M^+). Anal. ($C_5H_8N_6O_2$) 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); ^1H NMR ($CDCl_3$) δ 1.42 (d, *J* = 4.8 Hz, 3 H, CH_3), 3.24–3.63 (m, 4 H, 2 CH_2), 3.93–4.13 (m, 2 H, 2 CH), 5.24 (q, *J* = 4.8 Hz, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 19.84, 51.76, 76.80, 77.96, 101.97; EI-MS *m/z* 198 (M^+). Anal. ($C_6H_{10}N_6O_2$) C, H, N.

(4*R*,5*R*)-4,5-Bis(azidomethyl)-2-ethyl-1,3-dioxolane (12f): yield 92%; $[\alpha]^{20}_D$ = +127.9° (*c* = 0.04, acetone); ^1H NMR ($CDCl_3$) δ 0.98 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.72 (dq, *J* = 4.5 Hz, *J* = 7.5 Hz, 2 H, CH_2), 3.34–3.54 (m, 4 H, 2 CH_2), 3.97–4.07 (m, 2 H, 2 CH), 5.07 (t, *J* = 4.5 Hz, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 7.64, 27.09, 51.88, 51.94, 77.94, 105.86; EI-MS *m/z* 212 (M^+). Anal. ($C_7H_{12}N_6O_2$) C, H, N.

(4*R*,5*R*)-4,5-Bis(azidomethyl)-2-isopropyl-1,3-dioxolane (12g): yield 97%; $[\alpha]^{20}_D$ = +110.9° (*c* = 0.04, acetone); ^1H NMR ($CDCl_3$) δ 0.97 (d, *J* = 6.8 Hz, 6 H, 2 CH_3), 1.65–2.05 (m, 1 H, CH), 3.20–3.60 (m, 4 H, 2 CH_2), 3.85–4.15 (m, 2 H, 2 CH), 4.85 (d, *J* = 4.6 Hz, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 16.51, 16.56, 32.00, 51.81, 51.91, 77.10, 77.90, 108.69; EI-MS *m/z* 226 (M^+). Anal. ($C_8H_{14}N_6O_2$) C, H, N.

(4*R*,5*R*)-4,5-Bis(azidomethyl)-1,3-dioxolane-2-spiro-1′-cyclopentane (12h): yield 95%; $[\alpha]^{20}_D$ = +125.4° (*c* = 0.04, acetone); ^1H NMR ($CDCl_3$) δ 1.50–2.05 (m, 8 H, 4 CH_2), 3.25–3.60 (m, 4 H, 2 CH_2), 3.89–4.09 (m, 2 H, 2 CH); ^{13}C NMR ($CDCl_3$) δ 23.25, 37.07, 51.73, 76.83, 120.15; EI-MS *m/z* 238 (M^+). Anal. ($C_9H_{14}N_6O_2$) C, H, N.

(4*R*,5*R*)-4,5-Bis(azidomethyl)-1,3-dioxolane-2-spiro-1′-cyclohexane (12i): yield 95%; $[\alpha]^{20}_D$ = +120.4° (*c* = 0.04, acetone); ^1H NMR ($CDCl_3$) δ 1.20–1.85 (m, 10 H, 5 CH_2), 3.21–3.62 (m, 4 H, 2 CH_2), 3.95–4.15 (m, 2 H, 2 CH); ^{13}C NMR ($CDCl_3$) δ 23.77, 24.93, 36.45, 51.70, 76.60, 110.99; EI-MS *m/z* 252 (M^+). Anal. ($C_{10}H_{16}N_6O_2$) C, H, N.

(4*S*,5*S*)-4,5-Bis(azidomethyl)-1,3-dioxolane (17a): yield 96%; $[\alpha]^{20}_D$ = −122.0° (*c* = 0.04, acetone); spectral data were identical with that of **12a**. Anal. ($C_5H_8N_6O_2$) C, H, N.

(4*S*,5*S*)-4,5-Bis(azidomethyl)-2-methyl-1,3-dioxolane (17b): yield 98%; $[\alpha]^{20}_D$ = −140.7° (*c* = 0.04, acetone); spectral data were identical with that of **12b**. Anal. ($C_6H_{10}N_6O_2$) C, H, N.

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

(4*S*,5*S*)-4,5-Bis(azidomethyl)-2-isopropyl-1,3-dioxolane (17g): yield 97%; $[\alpha]^{20}_D$ = −110.9° (*c* = 0.04, acetone); spectral data were identical with that of **12g**. Anal. ($C_8H_{14}N_6O_2$) C, H, N.

(4*S*,5*S*)-4,5-Bis(azidomethyl)-1,3-dioxolane-2-spiro-1′-cyclopentane (17h): yield 97%; $[\alpha]^{20}_D$ = −122.9° (*c* = 0.04, acetone); spectral data were identical with that of **12h**. Anal. ($C_9H_{14}N_6O_2$) C, H, N.

(4*S*,5*S*)-4,5-Bis(azidomethyl)-1,3-dioxolane-2-spiro-1′-cyclohexane (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.

(4*R*,5*R*)-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_2O (100 mL), dried over anhydrous $MgSO_4$, 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^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 9 H, 3 CH_3), 2.21 (s, 3 H, $COCH_3$), 4.18 (s, 2 H, OCH_2), 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), ((*tert*-butyldiphenylsilyl)oxy)acetone (11.77 g, 37.7 mmol), anhydrous $CuSO_4$ (18.03 g, 113.0 mmol), and CH_3SO_3H (5 drops) in anhydrous toluene (100 mL) was stirred at 45 °C for 16 h under a nitrogen atmosphere. Anhydrous K_2CO_3 (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_2O–hexane (1:5, v/v) as the eluent to give 15.75 g (90%) of **12d** as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 1.07 (s, 9 H, 3 CH_3), 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, 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); ^{13}C NMR ($CDCl_3$) δ 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^+). Anal. ($C_{23}H_{30}N_6O_3Si$) C, H, N.

(4*R*,5*R*)-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_2O (50 mL) and brine (50 mL). The organic phase was dried over anhydrous $MgSO_4$ and evaporated to dryness, and the residue was purified by flash column chromatography over silica gel with a mixture of Et_2O–hexane (1:3, v/v) as the eluent to give 6.82 g (93%) of **12e** as a pale yellow oil: $[\alpha]^{20}_D = +108.6°$ (c = 0.04, acetone); ^1H NMR ($CDCl_3$) δ 1.43 (s, 3 H, CH_3), 2.20 (t, J = 6.6 Hz, 1H, OH), 3.30–3.70 (m, 4 H, 2 CH_2), 3.55–3.65 (m, 2 H, OCH_2), 4.09–4.19 (m, 2 H, 2 CH); ^{13}C NMR ($CDCl_3$) δ 22.34, 51.29, 51.34, 67.15, 76.79, 77.87, 110.60; EI-MS m/z 228 (M^+). Anal. ($C_7H_{12}N_6O_3$) C, H, N.

(4*S*,5*S*)-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. ($C_{23}H_{30}N_6O_3Si$) C, H, N.

(4*S*,5*S*)-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%; $[\alpha]^{20}_D = -107.1°$ (c = 0.04, acetone); spectral data were identical with that of **12e**. Anal. ($C_7H_{12}N_6O_3$) C, H, N.

General Method for the Preparation of 4,5-Bis(aminomethyl)-1,3-dioxolanes (13a–h and 18a–h). A solution of 4,5-bis(azidomethyl)-1,3-dioxolanes (**12a–c, 12e–i, 17a–c,** and **17e–i**) (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.

(4*R*,5*R*)-4,5-Bis(aminomethyl)-1,3-dioxolane (13a): yield 97%; ^1H NMR ($CDCl_3$) δ 1.40 (s, 4 H, 2 NH_2), 2.81–2.98 (m, 4 H, 2 CH_2), 3.63–3.82 (m, 2 H, 2 CH), 5.01 (s, 2 H, OCH_2O); ^{13}C NMR ($CDCl_3$) δ 43.81, 80.34, 94.34; EI-MS m/z 132 (M^+). Anal. ($C_5H_{12}N_2O_2$) C, H, N.

(4*R*,5*R*)-4,5-Bis(aminomethyl)-2-methyl-1,3-dioxolane (13b): yield 97%; ^1H NMR ($CDCl_3$) δ 1.37 (d, J = 4.8 Hz, 3 H, CH_3), 1.41 (s, 4 H, 2 NH_2), 2.65–3.04 (m, 4 H, 2 CH_2), 3.65–3.87 (m, 2 H, 2 CH), 5.16 (q, J = 4.8 Hz, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 19.75, 43.76, 44.05, 80.16, 81.09, 100.35; EI-MS m/z 146 (M^+). Anal. ($C_6H_{14}N_2O_2$) C, H, N.

(4*R*,5*R*)-4,5-Bis(aminomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane (13d): yield 99%; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3 H, CH_3), 1.95 (br s, 3 H, NH_2 and OH), 2.77–3.10 (m, 6 H, 2 CH_2 and OCH_2), 3.82–3.90 (m, 1 H, CH), 4.06–4.13 (m, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 23.14, 42.32, 44.12, 68.24, 79.33, 80.90, 109.76; EI-MS m/z 176 (M^+). Anal. ($C_7H_{16}N_2O_3$) C, H, N.

(4*R*,5*R*)-4,5-Bis(aminomethyl)-2-ethyl-1,3-dioxolane (13e): yield 95%; ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 7.5 Hz, 3 H, CH_3), 1.36 (s, 4 H, 2 NH_2), 1.68 (dq, J = 4.5 Hz, J = 7.5 Hz, 2 H, CH_2), 2.75–3.00 (m, 4 H, 2 CH_2), 3.70–3.80 (m, 2 H, 2 CH), 5.00 (t, J = 4.5 Hz, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 7.83, 27.19, 44.05, 44.33, 80.34, 81.11, 104.59; EI-MS m/z 160 (M^+). Anal. ($C_7H_{16}N_2O_2$) C, H, N.

(4*R*,5*R*)-4,5-Bis(aminomethyl)-2-isopropyl-1,3-dioxolane (13f): yield 96%; ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 6.9 Hz, 6 H, 2 CH_3), 1.33 (s, 4 H, 2 NH_2), 1.75–1.90 (m, 1 H, CH), 2.75–2.98 (m, 4 H, 2 CH_2), 3.67–3.77 (m, 2 H, 2 CH), 4.79 (d, J = 4.5 Hz, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 16.65, 16.76, 32.06, 44.01, 44.25, 80.29, 80.91, 107.40; EI-MS m/z 174 (M^+). Anal. ($C_8H_{18}N_2O_2$) C, H, N.

(4*R*,5*R*)-4,5-Bis(aminomethyl)-1,3-dioxolane-2-spiro-1′-cyclopentane (13g): yield 96%; ^1H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 23.23, 37.30, 44.13, 80.02, 118.45; EI-MS m/z 186 (M^+). Anal. ($C_9H_{18}N_2O_2$) C, H, N.

(4*R*,5*R*)-4,5-Bis(aminomethyl)-1,3-dioxolane-2-spiro-1′-cyclohexane (13h): yield 99%; ^1H NMR ($CDCl_3$) δ 1.37 (s, 4 H, 2 NH_2), 1.40–1.80 (m, 10 H, 5 CH_2), 2.78–2.93 (m, 4 H, 2 CH_2), 3.70–3.80 (m, 2 H, 2 CH); ^{13}C NMR ($CDCl_3$) δ 23.71, 25.00, 36.74, 44.20, 79.55, 109.06; EI-MS m/z 200 (M^+). Anal. ($C_{10}H_{20}N_2O_2$) C, H, N.

(4*S*,5*S*)-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.

(4*S*,5*S*)-4,5-Bis(aminomethyl)-2-methyl-1,3-dioxolane (18b): yield 99%; spectral data were identical with that of **13b**. Anal. ($C_6H_{14}N_2O_2$) C, H, N.

(4*S*,5*S*)-4,5-Bis(aminomethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxolane (18d): yield 99%; spectral data were identical with that of **13d**. Anal. ($C_7H_{16}N_2O_3$) C, H, N.

(4*S*,5*S*)-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.

(4*S*,5*S*)-4,5-Bis(aminomethyl)-2-isopropyl-1,3-dioxolane (18f): yield 96%; spectral data were identical with that of **13f**. Anal. ($C_8H_{18}N_2O_2$) C, H, N.

(4*S*,5*S*)-4,5-Bis(aminomethyl)-1,3-dioxolane-2-spiro-1′-cyclopentane (18g): yield 95%; spectral data were identical with that of **13g**. Anal. ($C_9H_{18}N_2O_2$) C, H, N.

(4*S*,5*S*)-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_2O at 25 °C. The standard solution was diluted with H_2O 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_2O 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-μm 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.[57] Cisplatin-resistant L1210 cells were developed by continuously exposing L1210 cells to increasing concentrations of cisplatin[58] 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.[59] BDF_1 male mice were inoculated ip with 1×10^6 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 μg/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 μg/mL of test compound was added to each well. Each test was done in triplicate. After 4 days of culture, 0.1 mg (50 μL 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 450*g* 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.[60]

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 1500*g* 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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