A New Family of Water-Soluble, Third Generation Antitumor Platinum Complexes

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[1,1-Cyclobutanedicarboxylato(2–)-*O,O'*](1,3-dioxane-5,5-dimethanamine-*N,N'*)platinum(II), **3a**, a third generation, very water-soluble platinum complex, has been synthesized along with several of its analogues. All members of the new family contain a 1,3-dioxane or 1,3-dioxolane-1,3-diamine as their basic ligand, a moiety which contributes to their increased water solubility, and a bidentate acid ligand, which is responsible for their good stability. They were all easily crystallized and characterized by ^{1}H NMR and elemental analysis, and the parent complex **3a** was further characterized by ^{13}C NMR. Their very desirable physical properties combined with their broad spectrum of antitumor activity and reduced toxicity make them good candidates of further development.

In a previous report[1] we discussed a new class of water-soluble, third generation platinum(II) complexes derived from either hydroxylated aliphatic amines or carbocyclic amino ligands bearing one oxygen atom in their ring and a malonate derivative for the carboxylate ligand. All these complexes, in addition to their good water solubilities, exhibited excellent activity against a variety of leukemias and solid tumors, low nephrotoxicity, pharmakokinetic stability, and a lack of cross resistance with *cis*-diamminedichloroplatinum(II) (cisplatin).[2-8] They are, therefore, superior to cisplatin, a first generation platinum complex; *cis*-diammine[1,1-cyclobutanedicarboxylato-(2–)-*O,O'*]platinum(II) (carboplatin),[9-13] a second generation platinum complex; and some third generation platinum complexes.[14-17]

In this report we describe the synthesis and antitumor activity of a new class of third generation, water-soluble platinum complexes with 1,3-dioxanes or 1,3-dioxolanes as their amine-bearing ligand.

Results and Discussion

I. Chemistry. The malonatoplatinum complexes **3** of 1,3-diamines **4** were prepared by two different methods (Scheme I). These methods are (1) reaction of dichloroplatinum complex **1** (n = 0, 1) with the silver salt of a malonic acid **2**[18] and (2) reaction of the dimethyl sulfoxide–platinum complex **5**[19] with 1,3-diamine **4**. The first method is generally used for the preparation of water-soluble platinum complexes and was the method of choice for most of the platinum complexes synthesized in this report. The second method, which is the most general one, can be used for both water-soluble and water-insoluble platinum complexes and it was used to synthesize **3a**. The dichloroplatinum complex **1** (n = 0, 1) was synthesized by reaction of potassium tetrachloroplatinate with 1,3-diamine **4** (n = 0, 1). The dimethyl sulfoxide–platinum complex **5** was prepared by reaction of potassium tetrachloroplatinate with dimethyl sulfoxide followed by reaction of the resulting intermediate with the disilver salt of a malonic acid **2**. The synthesized platinum complexes **3** were supported by ^{1}H NMR and elemental analysis. The structure of the platinum complex **3a** was further confirmed by ^{13}C NMR.

The syntheses of the two different diamines **4** (n = 1, 0) are outlined in Schemes II and III, respectively. Reaction of 2,2-bis(bromomethyl)-1,3-propanediol with an acetal **6** in acetic acid gave the 1,3-dioxanes **7**. These then reacted with sodium azide in *N,N*-dimethylformamide to give 5-bis(azidomethyl)-1,3-dioxanes **8**, which were reduced with 5% Pd/$CaCO_3$ to give the 5,5-bis(aminomethyl)-1,3-dioxanes **4** (n = 1). This general procedure was slightly modified for the synthesis of 3,3-bis(bromomethyl)-1,5-dioxaspiro[5.5]undecane (**7d**, R_1,R_2 = C_5H_{10}), where 2,2-(dibromomethyl)-1,3-propanediol reacted with 2,2-pentamethylene-1,3-dioxolane in concentrated hydrochloric acid at room temperature instead of by heating the corre-

(1) Bitha, P.; Carvajal, S. G.; Citarella, R. V.; Child, R. G.; Delos Santos, E.; Durr, F. E.; Hlavka, J. J.; Lang, S. A., Jr.; Lindsay, H. L.; Thomas, J. P.; Wallace, R. E.; Lin, Y.-i *J. Med. Chem.* In press.
(2) Rosenberg, B.; VanCamp, L.; Trosco, J. F.; Mansour, V. H. *Nature (London)* **1969**, *222*, 385.
(3) Holland, J. F.; Bruckner, H. W.; Cohen, C. J.; Walleck, R. C.; Brushberth, S. B.; Greenspan, E. M.; Goldberg, J. In *Cisplatin Current Status and New Developments*: *Cisplatin Therapy of Ovarian Cancer*; Prestayco, A. W., Crook, S. T., Carter, S. K., Eds.; Academic Press, Inc.: New York, 1980.
(4) Williams, S. D.; Einhorn, L. H. In *Cisplatin Current Status and Developments*: *Cisplatin Chemotherapy of Testicular Cancer*; Prestayko, A. W., Crook, S. T., Carter, S. K., Eds.; Academic Press, Inc.: New York, 1980.
(5) Loehrer, P. J.; Einhorn, L. H. *Ann. Intern. Med.* **1984**, *100*, 704.
(6) Krakoff, I. H. *Cancer Treat. Rep.* **1979**, *63*, 1523.
(7) Vermorken, J. B.; Pinedos, H. M. *Neth. J. Med.* **1982**, *25*, 270.
(8) Vonhoff, D. D.; Scilsky, R.; Reichert, C. M. *Cancer Treat. Rep.* **1979**, *63*, 1527.
(9) Calvert, A. H.; Harland, S. J.; Newell, D. R.; Siddik, Z. H.; Jones, A. C.; McElwain, T. J.; Raju, S.; Wilkshaw, E.; Smith, I. E.; Baker, J. M.; Peckham, M. J.; Harrap, K. R. *Cancer Chemother. Pharmacol.* **1982**, *9*, 140.
(10) Harland, S. J.; Smith, I. E.; Smith, N.; Alison, D. L. In *Platinum Coordination Complexes in Cancer Chemotherapy*; Hacker, M. P., Douple, E. B., Krakoff, I. H., Eds.; Martinus Nihoff Publishing: Boston, MA, 1984; p 352.
(11) Egorin, M. J.; Van Echo, D. A.; Olman, E. A.; Whitacre, M. Y.; Forest, A.; Aisner, J. *Cancer Res.* **1985**, *45*, 6502.
(12) Harland, S. J.; Newell, D. R.; Siddik, Z. H.; Chadwick, R.; Calvert, A. H.; Harrap, K. R. *Cancer Res.* **1984**, *44*, 1693.
(13) Mauldin, S. K.; Husain, I.; Sancar, A.; Chaney, S. G. *Cancer Res.* **1986**, *46*, 2876.
(14) Cleare, M. J.; Hydes, P. C.; Hepburn, D. R.; Malerbi, B. W. In *Cisplatin Current Status and New Developments*; Prestayko, A. W., Crook, S. T., Carter, S. K., Eds.; Academic Press, Inc.: New York, 1980, p 149.
(15) Vermorken, J. B.; ten Bokkel Huinink, W. W.; McVie, J. G.; Van der Vijh, W. J. F.; Pinedo, H. M. In *Platinum Coordination Complexes in Cancer Chemotherapy*; Hacker, M. P., Douple, E. B., Krakoff, I. H., Eds.; Martinus Nihoff Publishing: Boston, MA, 1984; p 330.
(16) Kelser, D. P.; Scher, H.; Berchenal, J. In *Platinum Coordination Complexes in Cancer Chemotherapy*; Hacker, M. P., Douple, E. B., Krakoff, I. H., Eds.; Martinus Nihoff Publishing: Boston, MA, 1984; p 310.
(17) Gonyette, A.; Ducret, J. P.; Caille, P.; Amiel, J. L.; Ronesse, J.; Foka, M.; Carde, P.; Hayat, M.; Sancho-Garnier, H. *Anticancer Res.* **1986**, *6*, 1127.
(18) Schwartz, P.; Meischen, S. J.; Gale, G. R.; Atkins, L. M.; Smith, A. B.; Walker, E. M., Jr. *Cancer Treat. Rep.* **1977**, *61*, 1519.
(19) Bitha, P.; Dunne, T. S.; Morton, G. O.; Lin, Y.-i. Unpublished results.
(20) Bitha, P.; Child, R. G.; Hlavka, J. J.; Lang, S. A., Jr.; Lin, Y.-i; Haltiwanger, R. C.; Pierpont, C. G. *Inorg. Chim. Acta* **1988**, *151*, 89.

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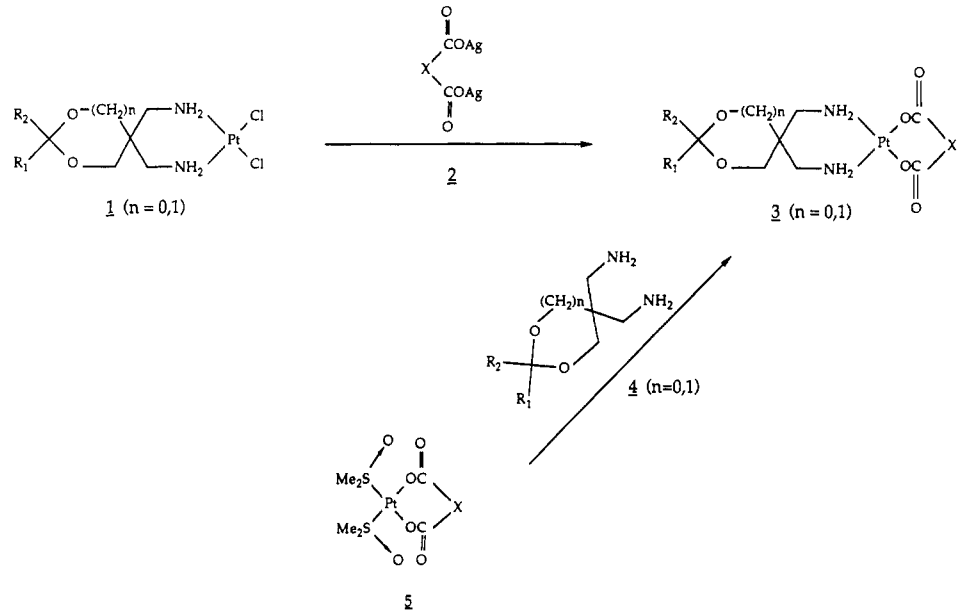
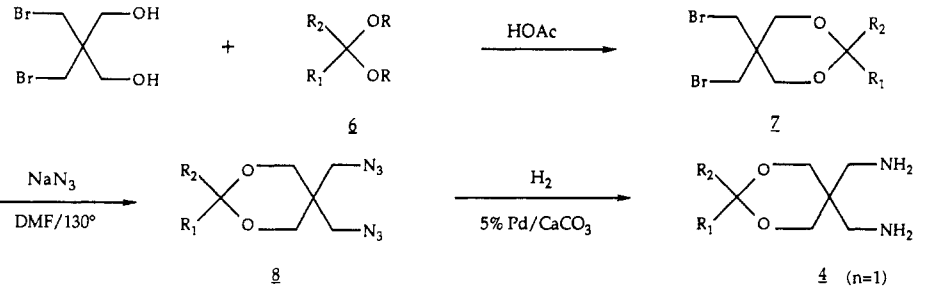
Scheme I



Scheme II



sponding reagents in acetic acid.

1,3-Dioxolane-4,4-dimethanamine (**4**, n = 0) was prepared from 3-chloro-2-(chloromethyl)-1,2-propanediol[21] (**9**) by reaction with formaldehyde in concentrated hydrochloric acid to give 4,4-bis(chloromethyl)-1,3-dioxolane (**10**). This compound further reacted with lithium azide in *N*,*N*-dimethylformamide to give 4,4-bis(azidomethyl)-1,3-dioxolane (**11**) and, after reduction with 5% $Pd/CaCO_3$, 1,3-dioxolane-4,4-dimethanamine (**4e**, n = 0). Finally, 5,5-bis(bromomethyl)-1,3-dioxane (**7a**, $R_1 = R_2 = H$) was prepared by heating 2,2-bis(bromomethyl)-1,3-propanediol and 37% formaldehyde in concentrated hydrochloric acid.

It is evident from our previous work[1] and this report that the incorporation of oxygen in the amino moiety of the platinum complex enhances water solubility. For example, the solubilities of three different platinum complexes a, b, and c which contain 1,1-cyclobutanedicarboxylic acid as their carboxylate ligand and (a) 1,1-cyclohexanedimethanamine, (b) tetrahydro-4*H*-pyran-4,4-dimethanamine,[1] and (c) 1,1-dioxane-5,5-dimethanamine (**3a**) are 1, 90, and 100 mg/mL, respectively. For comparison, the solubilities of cisplatin and carboplatin are 1 and 10 mg/mL, respectively.

The stability of platinum complex **3a** in both D_2O and 0.9% saline at room temperature was studied by ^1H NMR. The complex was found to be stable in water but slightly decomposed to produce 1.5% of free 1,1-cyclobutanedicarboxylic acid in 0.9% saline after 24 h. ^1H NMR spectral data for several compounds are listed in Tables I and II.

II. Biology. The combined results from all biological testing are given in Tables III and IV. As is evident from Table III, all water-soluble (malonato)platinum(II) complexes (**3a–l**) showed excellent activity against mouse leukemia P388. Of these complexes, **3a**, which was tested more extensively, showed excellent activity against mouse L1210 and L1210CPR leukemias. The antitumor activity of complex **3a** was compared with that of cisplatin and carboplatin. Complex **3a** was comparable to cisplatin and carboplatin with respect to activity against P388 leukemia and B-16 melanoma. It was significantly better than both drugs against L1210, L1210CPR, a subline resistant to cisplatin, and Colon 26 adenocarcinoma. In addition, when given ip, **3a** was significantly more active (119% ILS) against sc implanted L1210 cells than either cisplatin (33% ILS) or carboplatin (19% ILS).

Similar evaluations of drug activity were made with human breast (MX-1) and ovarian (H207) xenografts in athymic mice[1] (Table IV). The activity of **3a** against these solid tumors was similar to that of cisplatin and carboplatin.

The potency of **3a** was the same as that of carboplatin (50 mg/kg) but significantly less than that of cisplatin (2 mg/kg) (Table IV). However, the safety margin (maximum effective dose divided by minimum effective dose) of **3a** was 16-fold better (64) than cisplatin (4) and 4-fold better than carboplatin (16).

Kidney damage, which occurs in 28–36% of patients taking cisplatin, is a major dose-limiting factor. For this reason, **3a** and cisplatin were compared with respect to blood urea nitrogen (BUN) elevation potential in the rat.

(21) Ridley, H. F.; Charttergee, S. S.; Moran, J. F.; Triggle, D. J. *J. Med. Chem.* **1969**, *2*, 931.

(22) Geran, R. I.; Greenberg, N. R.; Macdonald, M. M.; Schumacher, A. M.; Abbott, B. J. Protocols for Screening Chemical Agents and Natural Products Against Animal Tumors and Other Biological Systems. *Cancer Chemother. Rep. Part 3* **1972**, *3*, 1–103.

Table I. ^1H NMR[a] Spectral Data of Intermediates 1, 4, 7, 8, 10, and 11

no.	substituents R	R_1	R_2	n	δ (J, Hz) R_1, R_2	OCH_2C	CH_2R	NH_2
1a	$(NH_2)_2PtCl_2$	H	H	1	4.68 (2 H, s)	3.60 (4 H, s)	2.37 (4 H, br s)	5.03 (4 H, br s)
1b	$(NH_2)_2PtCl_2$	H	CH_3	1	1.16 (3 H, d, J = 5.0), 4.53 (1 H, q, J = 5.0)	3.38 (2 H, d, J = 11.3), 3.88 (2 H, d, J = 11.3)	2.08 (2 H, br s), 2.62 (2 H, br s)	4.98 (2 H, br s), 5.06 (2 H, br s)
1c	$(NH_2)_2PtCl_2$	CH_3	CH_3	1	1.28 (6 H, s)	3.56 (4 H, s)	2.38 (4 H, br s)	5.01 (4 H, br s)
1d	$(NH_2)_2PtCl_2$	$-CH_2(CH_2)_3CH_2-$		1	1.39 (6 H, br s), 1.63 (4 H, br s)	3.58 (4 H, s)	2.39 (4 H, br s)	5.00 (4 H, br s)
1e	$(NH_2)_2PtCl_2$	H	H	0	4.87 (2 H, s)	3.61 (2 H, s)	2.43 (2 H, m), 3.55 (2 H, m)	4.90 (2 H, br s), 5.27 (2 H, br s)
4a	NH_2	H	H	1	4.81 (2 H, s)	3.73 (4 H, s)	2.81 (4 H, s)	1.51 (4 H, br s)
4b	NH_2	H	CH_3	1	4.58 (1 H, q, J = 5.0), 1.33 (3 H, d, J = 5.0)	3.46 (2 H, d, J = 11.8), 3.98 (2 H, d, J = 11.8)	2.52 (2 H, s), 3.10 (2 H, s)	1.68 (4 H, br s)
4c	NH_2	CH_3	CH_3	1	1.40 (6 H, s)	3.68 (4 H, s)	2.72 (4 H, s)	2.08 (4 H, br s)
4d	NH_2	$-CH_2(CH_2)_2CH_2-$		1	1.3–2.0 (10 H, br m)	3.65 (4 H, s)	2.75 (4 H, s)	1.26 (4 H, br s)
4e	NH_2	H	H	0	4.81 (2 H, s)	3.73 (4 H, s)	2.81 (4 H, s)	1.51 (4 H, br s)
7a	Br	H	H	1	4.79 (2 H, s)	3.84 (4 H, s)	3.58 (4 H, s)	
7b	Br	H	CH_3	1	1.35 (3 H, d, J = 5.0), 4.58 (1 H, q, J = 5.0)	3.61 (2 H, d, J = 11.8), 4.07 (2 H, d, J = 11.8)	3.23 (2 H, s), 3.89 (2 H, s)	
7c	Br	CH_3	CH_3	1	1.40 (6 H, s)	3.75 (4 H, s)	3.52 (4 H, s)	
7d	Br	$-CH_2(CH_2)_3CH_2-$		1	1.2–2.0 (10 H, br m)	3.69 (4 H, s)	3.56 (4 H, s)	
8a	N_3	H	H	1	4.79 (2 H, s)	3.67 (4 H, s)	3.46 (4 H, s)	
8b	N_3	H	CH_3	1	1.33 (3 H, d, J = 5.0), 4.58 (1 H, q, J = 5.0)	3.51 (2 H, d, J = 11.6), 3.86 (2 H, d, J = 11.6)	3.16 (2 H, s), 3.75 (2 H, s)	
8c	N_3	CH_3	CH_3	1	1.41 (6 H, s)	3.65 (4 H, s)	3.45 (4 H, s)	
8d	N_3	$-CH_2(CH_2)_3CH_2-$		1	1.2–2.0 (10 H, br m)	3.65 (4 H, s)	3.45 (4 H, s)	
10	Cl	H	H	0	5.07 (2 H, s)	3.95 (2 H, s)	3.73 (4 H, s)	
11	N_3	H	H	0	5.09 (2 H, s)	3.85 (2 H, s)	3.45 (4 H, s)	

[a] NMR spectra for compounds 1a–e were taken in DMSO-d_6. All other spectra were taken in $CDCl_3$.

Preliminary experiments[23] indicated a lower propensity to cause elevation of BUN levels for **3a**.

Complexes **3b–e** also show interesting activities against B16 melanoma and C26 adenocarcinoma and in most cases appear to be more active or at least as active as cisplatin and carboplatin. However, they are all less active than **3a**, the parent complex in this series.

The dichloroplatinate complexes **1a–e** are very water insoluble and presumably they are as nephrotoxic as cisplatin and for this reason were tested only against P388 leukemia.

In conclusion, the third generation platinum complexes described in this report exhibit good water solubility, excellent activity against murine tumors, and reduced toxicity.

Experimental Section

Chemistry. Unless otherwise noted, all carboxylic acids and potassium tetrachloroplatinate were obtained from commercial suppliers and were used without further purification. Tetrahydro-4*H*-pyran-4,4-dicarboxylic acid[24] and 3-chloro-2-(chloromethyl)-1,2-propanediol[21] (**9**) were synthesized by literature procedures. Silver salts of carboxylic acids were prepared by reactions of sodium carboxylates with an equimolar amount of silver nitrate at room temperature in the dark overnight. NMR spectra were determined with a Nicolet NT-300 WB (^1H at 300 MHz, ^{13}C at 75 MHz) spectrometer and chemical shifts (δ) are in parts per million relative to internal tetramethylsilane. All platinum complexes spectra were taken in DMSO-d_6 and were run as soon as solutions were prepared. The spectra of all nonplatinum intermediates were taken in $CDCl_3$ and all intermediates were used "as is" without purification to avoid decomposition, which was evident when distillation of oil intermediates was attempted.

1,3-Dioxane-5,5-dimethanamine (4a). Step A. 5,5-Bis(bromomethyl)-1,3-dioxane (7a). A suspension of 2,2-bis(bromomethyl)-1,3-propanediol (26.2 g, 0.1 mol) and 37% formaldehyde solution (50 mL) in concentrated hydrochloric acid was stirred in an oil bath at 50 °C overnight. The reaction mixture was cooled to room temperature and filtered. The filtrate was extracted with three 100-mL portions of ether. The combined ether phase was dried over magnesium sulfate and evaporated to give 26.9 g (98%) of **7a** as colorless oil, which was used directly in step B.

Step B. 5,5-Bis(azidomethyl)-1,3-dioxane (8a). Typical Procedure for 8a–d. A suspension of **7a** (26.9 g, 0.098 mol) and sodium azide (38 g, 0.59 mol) in DMF (250 mL) was stirred in an oil bath at 130 °C overnight. The reaction mixture was cooled to room temperature and the solid was removed by filtration. The filtrate was evaporated to an oily residue. The residue was slurried in water (100 mL) and extracted with three 100-mL portions of ether. The combined either phase was washed with water (25 mL), dried over magnesium sulfate, and evaporated to give 18.7 g (96%) of **8a** as a yellow oil. IR: strong stretching at 2120 cm^{-1}. The oil was used immediately in step C.

Step C. The oil **8a** (18.6, 0.044 mol) was dissolved in ethanol (180 mL) and mixed with a 5% $Pd/CaCO_3$ catalyst (5 g). The mixture was first purged with argon and then hydrogen was bubbled through for 5 h (or until no azido stretching was present in the IR spectrum). The catalyst was filtered, after the reaction mixture was purged again with argon, and the filtrate was evaporated to give 13.2 g (96.4%) of 1,3-dioxane-5,5-dimethanamine (**4a**) as colorless oil. The oil was used directly for the preparation of **1a**.

5,5-Bis(bromomethyl)-2-methyl-1,3-dioxane (7b). Typical Procedure for 7b,c. A solution of 2,2-bis(bromomethyl)-1,3-propanediol (5.25 g, 0.020 mol) and acetal (10 mL, 0.102 mol) in glacial acetic acid (40 mL) was refluxed for 1 h and evaporated to give 5.7 g (100%) of **7b** as a colorless oil. The compound **7b** was used directly for the preparation of **8b**.

3,3-Bis(bromomethyl)-1,5-dioxaspiro[5.5]undecane (7d). A solution of 2,2-bis(bromomethyl)-1,3-propanediol (5.24 g, 0.020 mol) and 2,2-pentamethylene-1,3-dioxolane (5 mL, 0.036 mol) in concentrated hydrochloric acid was stirred at room temperature for 2 h and at 45 °C for 1 h. The two-phase solution was cooled to room temperature and extracted with ether to give, after evaporation and distillation at 1.8 mm, 5.87 g (85.8%) of **7d** as a colorless oil.

4,4-Bis(chloromethyl)-1,3-dioxolane (10). A solution of 3-chloro-2-(chloromethyl)-1,2-propanediol (**9**)[21] (11.8 g, 0.074 mol) and 37% formaldehyde (37 mL) in concentrated hydrochloric acid (37 mL) was heated in an oil bath at 50 °C for 17 h. The two-phase solution was cooled to room temperature and extracted with two 100-mL portions of ether. The combined ether phase was washed with water, dried over magnesium sulfate, and evaporated to give, after distillation at 0.4 mm and 55 °C, 6.8 g (53.7%) of **10** as a colorless oil. Anal. Calcd for $C_5H_8Cl_2O_2$: C, 35.1; H, 4.71; Cl, 41.5. Found: C, 34.9; H, 4.78; Cl, 41.5.

4,4-Bis(azidomethyl)-1,3-dioxolane (11). A solution of **10** (8.05 g, 0.047 mol) and lithium azide (7.0 g, 0.143 mol) in DMF

(23) Unpublished results.
(24) Stanfield, J. A.; Daugherty, P. M. *J. Am. Chem. Soc.* **1959**, *81*, 5167.

Table II. ^{1}H NMR[a] Spectral Data of (Carboxylato)platinum(II) Complexes

	substituents				δ (J, Hz)						
no.	R_1	R_2	n	X	R_1, R_2	OCH_2C	CH_2N	NH_2	X	formula	anal.[b]
3a	H	H	1		4.69 (2 H, s)	3.60 (4 H, s)	3.31 (4 H, br s)	5.34 (4 H, br s)	1.65 (2 H, quintet, J = 7.7), 2.67 (4 H, t, J = 7.8)	$C_{12}H_{20}N_2O_6Pt\cdot 2H_2O$	CHN
3b	H	CH_3	1		1.17 (1 H, q, J = 5.0), 4.55 (3 H, d, J = 4.9)	3.36 (2 H, d, J = 11.6), 3.84 (2 H, d, J = 11.6)	2.05 (2 H, br s), 2.56 (2 H, br s)	5.28 (2 H, br s), 5.36 (2 H, br s)	1.64 (2 H, quintet, J = 7.7), 2.64 (4 H, t, J = 7.7)	$C_{13}H_{22}N_2O_6Pt\cdot H_2O$	CHN
3c	CH_3	CH_3	1		1.29 (6 H, s)	3.56 (4 H, s)	2.33 (4 H, br s)	5.31 (4 H, br s)	1.64 (2 H, quintet, J = 7.7), 2.67 (4 H, t, J = 7.7)	$C_{14}H_{24}N_2O_6Pt$	CHN
3d	$-CH_2(CH_2)_3CH_2-$				1.39 (6 H, br s), 1.64 (4 H, br m)	3.56 (4 H, s)	2.33 (4 H, br s)	5.30 (4 H, br s)	1.64 (2 H, quintet, J = 7.7), 2.67 (4 H, t, J = 7.7)	$C_{17}H_{28}N_2O_6Pt\cdot {}^1/_2H_2O$	CHN
3e	H	H	0								
3f	H	H	1	CH_2OH	4.73 (2 H, q, J = 5.2)	3.76 (4 H, br s)	2.57 (4 H, br s)	4.99 (2 H, br s), 5.24 (2 H, br s)	3.46 (2 H, s), 3.82 (2 H, s), 4.04 (2 OH, m)	$C_{10}H_{20}N_2O_8Pt$	CHN
3g	H	H	1	$-(CH_2)_3-$	4.74 (2 H, m)	3.76 (4 H, br s)	2.40 (4 H, br s)	5.84 (2 H, br s), 6.22 (2 H, br s)	1.65 (2 H, m), 2.09 (4 H, m)	$C_{11}H_{20}N_2O_6Pt\cdot H_2O$	CHN
3h	H	H	1		4.70 (2 H, s)	3.60 (4 H, d, J = 1.7)	2.33 (4 H, br q, J = 9.4)	5.4 (4 H, d, J = 4.9)	0.84 (3 H, t, J = 7.3), 1.80 (2 H, quintet, J = 7.3), 3.42 (1 H, t, J = 7.0)	$C_{11}H_{20}N_2O_6Pt\cdot H_2O$	CHN
3i	H	H	1		4.70 (2 H, s)	3.60 (4 H, s)	2.34 (4 H, br s)	5.38 (4 H, br s)	1.55 (6 H, s)	$C_{11}H_{20}N_2O_6Pt$	CHN
3j	H	H	1	$-(CH_2)_3-$	4.74 (2 H, q, J = 4.2)	3.75 (4 H, m)	2.23 (4 H, br s)	5.81 (2 H, br s), 6.31 (2 H, br s)	2.62 (4 H, s)	$C_{10}H_{18}N_2O_6Pt\cdot H_2O$	CHN
3k	H	H	1	$-(CH_2)-$	4.49 (2 H, s)	3.39 (4 H, s)	2.12 (4 H, br s)	5.18 (4 H, br s)	2.99 (2 H, s)	$C_9H_{16}N_2O_6Pt$	CHN
3l	H	H	1		4.69 (2 H, s)	3.59 (4 H, br s)	2.32 (4 H, br s)	5.42 (4 H, br s)	2.42 (4 H, br s), 3.56 (4 H, br s)	$C_{13}H_{22}N_2O_7Pt\cdot H_2O$	CHN

[a] All NMR spectra were taken in DMSO-d_6. Complexes **3f–k** are not very stable in DMSO and the spectra must be taken as soon the solutions are prepared. [b] The microanalyses were all within 0.4% of the calculated values.

Scheme III

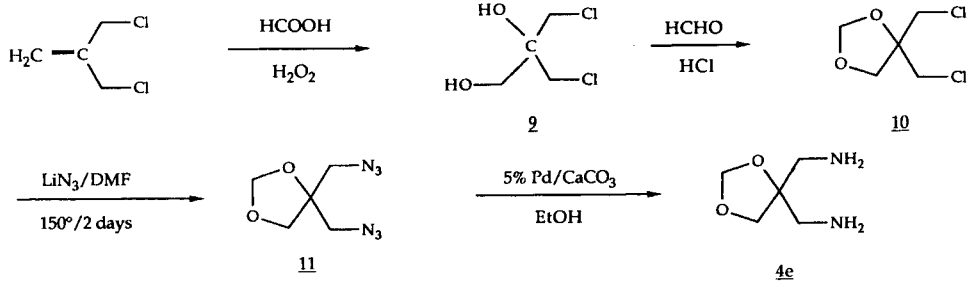


Table III. Activity of Platinum Complexes against Murine Tumors

complex	water solub, mg/mL	media % increase in life span (optimal dose, mg/kg; % survivors)				
		P388[a]	L1210[a]	L1210CPR[a,b]	B-16[c]	C26[d]
1a	0.5	173 (6.2; 3)			27 (0.4; 0)	41 (3.1; 0)
1b	0.1	136 (12.5; 1)				
1c	0.1	141 (6.2; 2)				
1d	0.2					
1e	≤0.2	160 (25.5; 0)	44 (12.5; 0)			50 (6.2; 0)
3a	100	>195 (50; 33)	172 (50; 50)	168 (50; 33)	61 (12.5; 3)	153 (50; 0)
3b	100	173 (100; 5)			62 (25; 0)	
3c	100	173 (25; 5)			68 (25; 0)	
3d	10	190 (50; 2)	117 (100; 0)		36 (25; 0)	30 (100; 0)
3e	100	138 (100; 0)	28 (50; 0)			41 (25; 0)
3f	100	142 (6.2; 3)	56 (6.2; 0)	21 (6.2; 0)	35 (3.1; 0)	79 (6.2; 0)
3g	50	119 (25; 2)				
3h	17	146 (50; 3)			64 (25; 0)	127 (100; 3)
3i	100	146 (50; 3)			84 (25; 0)	61 (50; 0)
3j	100	146 (25; 2)			14 (12.5; 0)	20 (25; 0)
3k	10	120 (25; 1)	110 (25; 1)	44 (25; 0)	56 (12.5; 0)	46 (25; 0)
3l	5	125 (50; 0)				
cisplatin		140 (6.2; 17)	96 (6.2; 4)	IA[e]	36 (0.4; 0)	47 (1; 17)
carboplatin		144 (100; 6)	35 (100; 0)	IA[e]	43 (12.5; 0)	85 (50; 17)

[a] With BDF_1 mice; the test compounds were administered ip on days 1, 5, and 9 relative to tumor inoculation and the mice were observed for 30 days. [b] L1210 cisplatin-resistant leukemia. [c] With C57BC/6 mice; the test compounds were administered ip on days 1–9 relative to tumor inoculation and the mice were observed for 60 days. [d] With Balb/C mice; the test compounds were administered ip on days 1, 5, and 9 relative to tumor inoculation and the mice were observed for 30 days. [e] Inactive.

Table IV. Activity of **3a** against Human Tumors in Athymic Mice

drug	optimal dose,[a] mg/kg	% tumor weight inhibn (TWI)[b]	
		MX-1	H207
3a	50	159	198
cisplatin	2	86	200
carboplatin	50	90	200

[a] IP on days 8, 12, and 16 after sc tumor implantation. [b] TWI ≥ 58% is considered necessary to demonstrate activity.

(35 mL) was heated in an oil bath at 150 °C for 2 days. The solution was then evaporated to dryness and the oil was dissolved in water and extracted with two 100-mL portions of ether. The combined ether phase was washed with water, dried over magnesium sulfate, and evaporated to give 3.3 g (37%) of **11** as a colorless oil. IR (KBr): 2120 cm^{-1}. The oil was used immediately for the preparation of **4e**.

Dichloro(1,3-dioxane-5,5-dimethanamine-*N*,*N*′)platinum(II) (1a). Typical Procedure for 1a–e. To a stirred solution of potassium tetrachloroplatinate (3.62 g, 8.73 mmol) in water (20 mL) was added a solution of **4a** in 5 mL of water. Within 0.5 h crystals precipitated out. After stirring overnight at room temperature, the crystals were collected by filtration, washed well with water, and dried to give 2.9 g (81%) of **1a**.

[1,1-Cyclobutanedicarboxylato(2−)-*O*,*O*′](1,3-dioxane-5,5-dimethanamine-*N*,*N*′)platinum(II) (3a). Procedure A. Typical Procedure for 3a–e. A suspension of **1a** (27.41 g, 0.067 mol) and 1,1-cyclobutanedicarboxylic acid disilver salt (23.9 g, 0.067 mol) in water (2.9 L) was stirred in the dark for 17 h. The resulting silver chloride was removed by filtration and the light yellow filtrate was evaporated to dryness. The residue was recrystallized from 400 mL of hot water to give 19.0 g (59%) of **3a** as colorless crystals. ^{13}C NMR (DMSO-d_6): δ 15.02 (CCH_2C, 1 C), 30.43 (CH_2-*t*-$CC{=}O$, 2 C), 37.33 (*t*-CCH_2O, 1 C), 45.71 (CH_2N, 2 C), 55.64 (*t*-$CC{=}O$, 1 C), 69.72 (OCH_2-*t*-C, 2 C), 93.27 (OCH_2O, 1 C), 177.47 ($OC{=}O$, 2 C).

Procedure B. Applicable to 3a–e and 3g–l. A solution of [1,1-cyclobutanedicarboxylato(2−)-*O*,*O*′]bis[sulfinylbis(methane)-*S*]platinum(II)[1] (1.97 g, 0.04 mol) in water (48 mL) was added to a solution of **1a** (0.585 g, 0.04 mol) in water (12 mL). The mixture was kept in an oil bath at 100 °C for 6 h and was then evaporated to dryness. The residue was recrystallized from a small amount of water to give 0.787 g (41%) of **3a** as colorless crystals.

Biology. The platinum compounds were dissolved or suspended in 0.85% saline or 0.2% Klucel in water or saline. Klucel HF (lot 4830) was obtained from Hercules, Inc., Wilmington, DE.

The transplantable mouse tumors P388 and L1210 leukemia and B-16 melanoma were obtained through the Drug Evaluation branch of the National Cancer Institute. Mouse colon tumor 26 was obtained from Dr. T. H. Corbett, Southern Research Institute, Birmingham, AL. The mouse L1210 cisplatin-resistant leukemia (L1210CPR) and the human mammary MX-1 and human ovarian H207 xenografts were obtained from the Mason Research Institute, Worchester, MA.

All tumors were propagated and used for testing in general accordance with protocols described by the National Cancer Institute.[22]

In all mouse tumor systems, an increase in life span (ILS) ≥25% over controls was considered necessary to demonstrate activity. With human tumor xenografts, a tumor weight inhibition (TWI) ≥58% was considered necessary to demonstrate activity. Only treatment that reduced ILS or body weight by ≥15% over control mice was rated toxic.

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Registry No. **1a**, 104844-74-8; **1b**, 121705-26-8; **1c**, 104844-76-0; **1d**, 121705-27-9; **1e**, 121705-28-0; **2** (X = $(CH_2)_0$), 533-51-7; **2** (X = $(-CH_2OH)_2$), 18971-60-3; **2** (X = $(CH_2)_3$), 117091-70-0; **2** (X = CH_2), 57421-56-4; **3a**, 121705-29-1; **3b**, 121705-30-4; **3c**, 121705-31-5; **3d**, 121705-32-6; **3e**, 121705-33-7; **3f**, 121705-34-8; **3g**, 121705-35-9; **3k**, 104844-53-3; **4a**, 104275-08-3; **4b**, 121705-18-8; **4c**, 104275-10-7; **4d**, 121705-19-9; **4e**, 121705-20-2; **5** (X = $(CH_2)_0$), 121730-28-7; **5** (X = $(CH_2)_3$), 121730-29-8; **5** (X = CH_2), 119759-75-0; **6** (R = Et, R_1 = R_2 = Me), 4744-08-5; **6** (R = Et, R_1 = H, R_2 = Me), 105-57-7; **7a**, 22633-46-1; **7b**, 13727-36-1; **7c**, 43153-20-4; **7d**, 121705-21-3; **8a**, 104274-96-6; **8b**, 121705-22-4; **8c**, 104274-87-5; **8d**, 121705-23-5; **9**, 23787-74-8; **10**, 121705-24-6; **11**, 121705-25-7; K_2PtCl_4, 10025-99-7; HCHO, 50-00-0; 2,2-bis(bromomethyl)-1,3-propanediol, 3296-90-0; 2,2-pentamethylene-1,3-dioxolane, 177-10-6.