2 H, CHCH_2), 4.17 (septet, J = 6.6 Hz, 1 H, CH), 5.36 (br d, J = 7 Hz, 1 H, NH); CI MS m/z 250 (2, M + H), 194 (5, $C_7H_{16}NO_3S$), 150 (34, $C_6H_{16}NOS$), 57 (100, C_4H_9), 44 (32, CO_2); $[\alpha]^{20}_D$ +40.8 (c 0.12, MeOH). CD spectrum (MeCN), at 216 nm a single positive Cotton effect was observed ($\Delta\epsilon$ = +0.31). Anal. ($C_{11}H_{23}NO_3S$) C, H, N.

For the S_CR_S compound: mp 131–132 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.37 (d, J = 6.7 Hz, 3 H, $CHCH_3$), 1.41 (s, 9 H, t-Bu), 1.63–2.03 (m, 2 H, CH_2CH_3), 2.76 (t, J = 8 Hz, 2 H, S(O)CH_2CH$_2$), 2.89 (d, J = 6.6 Hz, 2 H, CHCH_2), 4.88 (septet, J = 6.8 Hz, 1 H, CH), 4.96 (br d, J = 6.6 Hz, 1 H, NH); CI MS m/z 250 (1, M + H), 194 (1, $C_7H_{16}NO_3S$), 150 (22, $C_6H_{16}NOS$), 57 (100, C_4H_9), 44 (23, CO_2); $[\alpha]^{20}_D$ +20.7° (c 0.135, MeOH); CD spectrum (MeCN), at 221 nm a single negative Cotton effect was observed ($\Delta\epsilon$ = −0.21). Anal. ($C_{11}H_{23}NO_3S$) C, H, N.

(S_CS_S)-1-(*n*-Propylsulfinyl)-2-[(*E*)-β-(6-methyl-5-uracilyl)acrylamido]propane (38). The *N*-Boc protecting group of **37** (530 mg, 2.13 mmol) was removed by stirring with 10 mL of TFA for 30 min at 0 °C. After evaporation of the excess TFA, stripping twice with EtOH and drying in vacuo, the amine was dissolved in 20 mL of DMF and the solution was neutralized with Et_3N. Subsequently, Et_3N (0.3 mL, 1 equiv) and the pentafluorophenyl ester of **2** (771 mg, 2.13 mmol), which was prepared in situ by reaction of **2** with pentafluorophenol and DCC in DMF,[24] were added, and the reaction mixture was stirred in the dark for 18 h at room temperature. Concentration in vacuo and gel filtration of the crude reaction product on Fractogel (eluent MeOH/H_2O, 1:1) afforded 502 mg (72% yield) of a white material after lyophilization from HOAc and drying in an exsiccator on KOH: TLC R_f 0.39 (eluent MeOH/$CHCl_3$, 1:4); ^{1}H NMR (D_2O) δ 1.04 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.36 (d, J = 6.7 Hz, 3 H, $CHCH_3$), 1.77 (sextet, J = 7.4 Hz, 2 H, CH_2CH_3), 2.34 (s, 3 H, C(6)-CH_3), 2.89 (t, J = 7.4 Hz, 2 H, S(O)CH_2CH$_2$), 3.06 (d, J = 6.7 Hz, 2 H, CHCH_2), 4.42 (quintet, J = 6.6 Hz, 1 H, CH), 6.96 and 7.30 (AB q, J_{AB} = 15.4 Hz, 2 H, CH=CH); FAB MS m/z 328 (7, M + H, $C_{14}H_{22}N_3O_4S$), 179 (11, $C_8H_7N_2O_3$), 150 (53, $C_6H_{16}NOS$); $[\alpha]^{20}_D$ +98.3° (c 0.115, MeOH).

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Water-Soluble Third Generation Antitumor Platinum Complexes, [2,2-Bis(aminomethyl)-1,3-propanediol-*N*,*N*']-[1,1-cyclobutanedicarboxylato(2-)-*O*,*O*']platinum(II) and [1,1-Cyclobutanedicarboxylato(2-)-*O*,*O*'][tetrahydro-4*H*-pyran-4,4-dimethanamine-*N*,*N*']platinum(II)

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The synthesis, stability, and antitumor activity of a series of water-soluble third generation platinum(II) complexes have been described. Among these complexes, [2,2-bis(aminomethyl)-1,3-propanediol-*N*,*N*'][1,1-cyclobutanedicarboxylato(2-)-*O*,*O*']platinum(II) and [1,1-cyclobutanedicarboxylato(2-)-*O*,*O*'](tetrahydro-4*H*-pyran-4,4-dimethanamine-*N*,*N*')platinum(II) have shown the greatest promise for further investigation and are currently under clinical evaluation.

cis-Diamminedichloroplatinum(II) (cisplatin)[1] is one of the most effective oncolytic agents against cancers of the testes, ovaries, bladder, and head and neck.[2-4] It is also an important adjunct for cancers of cervix, lung, and breast.[2] Its most spectacular success has been in the treatment of testicular cancer,[3] a form of cancer previously resistant to any therapy but now considered to be curable in most cases. However, cisplatin has three drawbacks which limit its usefulness: (1) it has severe toxicities[5-7] such as nephrotoxicity, nausea/vomiting, myelosuppression, ototoxicity, and neuologic complications, (2) it only affects a narrow range of tumors, and (3) it causes the develop-

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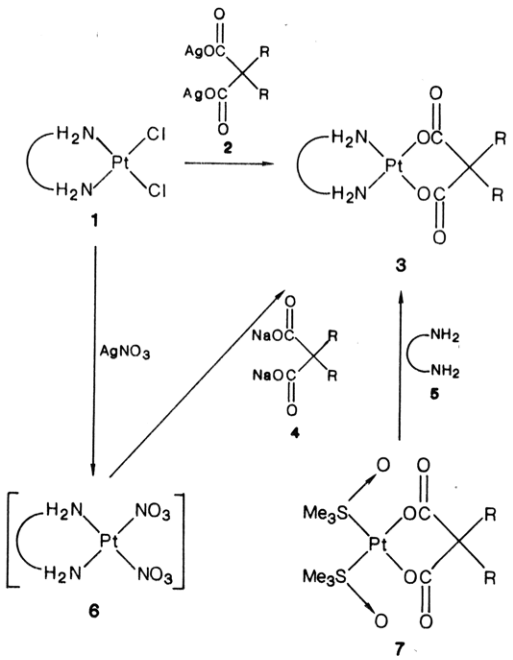
Scheme I



ment of resistance in the tumor cell.

cis-Diammine(1,1-cyclobutanedicarboxylato)platinum-(II) (carboplatin)[8-10] is the only clinically successful second generation platinum complex. It does not exhibit significant nephrotoxicity and emesis, and its relatively lower toxicities as compared to those of cisplatin have been related to the greater pharmacokinetic stability of its 1,1-cyclobutanecarboxylate ligand in solution.[11,12] Nevertheless, it still has two other drawbacks. Just like cisplatin, it only effects a narrow range of tumors and causes the development of resistance in the tumor cell.

In recent years, there has been an intense interest in developing third generation platinum complexes with a broader spectrum of activity, improved clinical effectiveness, lack of cross-resistance to cisplatin, and enhanced water solubility.[13,14] Several third generation platinum complexes having 1,2-cyclohexanediamine or 1,1-cyclohexanedimethanamine as the stable amine ligand have entered clinical trials. These complexes are (1,2-cyclohexanediamine)(malonato)platinum,[15] (aqua)[1,1-bis-(aminomethyl)cyclohexane](sulfato)platinum (spiroplatin),[15,16] (4-carboxyphthalato)(1,2-cyclohexanediamine)platinum,[15,17] and (1,2-cyclohexanediamine)(isocitrato)platinum (PHIC).[18] Although these compounds exhibited excellent antitumor activity and lack of cross-resistance with cisplatin, none of them appear to have any future for further clinical evaluation. The major difficulties encountered to date are insufficient water solubility, excessive host toxicity, inadequate purity, and lack of acceptable formulation. In order to improve on these drawbacks, we have used a malonate derivative for the carboxylate ligand and incorporated oxygen into the amine ligand and/or the carboxylate ligand in the synthesis of third generation platinum complexes.

In this report, we describe the synthesis, stability, and antitumor activity of these water-soluble third generation platinum(II) complexes. Among these, [2,2-bis(aminomethyl)-1,3-propanediol-*N*,*N*′][1,1-cyclobutanedicarboxylato(2−)-*O*,*O*′]platinum(II) (CL 286,558; **3h**) and [1,1-cyclobutanedicarboxylato(2−)-*O*,*O*′](tetrahydro-4*H*-pyran-4,4-dimethanamine-*N*,*N*′)platinumn(II) (CL 287,110; **3c**) have shown the greatest promise for further investigation and are currently under clinical evaluation.

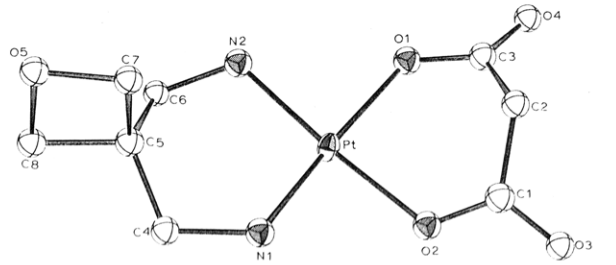
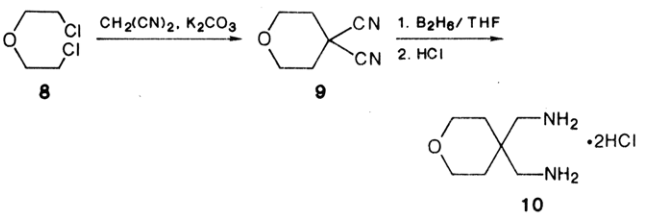
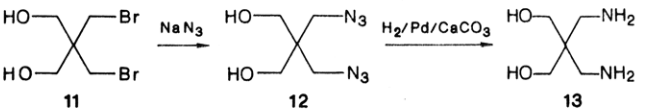


Figure 1. Drawing showing the *cis*-[Pt(OXTDMA)($CH_2(CO_2)_2$] (**3b**) molecule.

Scheme II



Scheme III



Results and Discussion

I. Chemistry. Malonatoplatinum complexes **3** of 1,2- or 1,3-diamines **5** were prepared by three different methods (Scheme I): (1) reaction of dichloroplatinum complex **1** with the disilver salt of a malonic acid, **2**,[19] (2) reaction of **1** with silver nitrate followed by reaction of the resulting (dinitrato)platinum complex **6** with the disodium salt of

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Table I. Data for All Platinum(II) Complexes Synthesized

complex[a]	formula	mp, °C	anal.[b]	H_2O solubility, mg/mL	^1H NMR [DMSO-d_6/TMS, δ, J (Hz)]
1a, *cis*-[Pt(OXTDMA)Cl_2]	$C_5H_{12}Cl_2N_2OPt$	270–273	C, H, Cl, N, Pt	0.3	5.14 (4 H, s, NH_2), 4.28 (4 H, s), 2.64 (4 H, t, J = 5.5)
1b, *cis*-[Pt(THPDMA)Cl_2]	$C_7H_{16}Cl_2N_2OPt$	290–292	C, H, Cl, N, Pt	0.3	3.99 (4 H, br s, NH_2), 3.47 (4 H, m), 2.22 (4 H, m), 1.35 (4 H, m)
1c, *cis*-[Pt(THFDA)Cl_2]	$C_4H_{10}Cl_2N_2OPt$	246–249	C, H, Cl, N, Pt	1	5.32 (2 H, m), 5.22 (2 H, m), 3.59 (2 H, m), 3.45 (2 H, m), 3.32 (2 H, m)
1d, *cis*-[Pt(BAMPDO)Cl_2]	$C_5H_{14}Cl_2N_2O_2Pt$	215–218	C, H, Cl, N, Pt	1.7	5.58 (2 H, br s), 5.48 (2 H, br s), 4.92 (2 H, t, J = 4.5), 3.35 (4 H, m), 2.43 (4 H, t)
1e, *cis*-[Pt(DABDO)Cl_2]	$C_4H_{12}Cl_2N_2O_2Pt$	290–294	C, H, Cl, N, Pt	1	3.48 (4 H, s), 2.57 (2 H, br s)
3a, *cis*-[Pt(OXTDMA)(CBCD)]·H_2O	$C_{11}H_{18}N_2O_5Pt·H_2O$	280–284	C, H, N, Pt	3.5	5.48 (4 H, br s, NH_2), 4.29 (4 H, s), 2.65 (4 H, t, J = 7.6), 2.63 (4 H, s), 1.64 (2 H, m, J = 7.6)
3b, *cis*-[Pt(OXTDMA($OOCCH_2COO$)]	$C_8H_{14}N_2O_5Pt$	275–279	C, H, N, Pt	3.5	5.49 (4 H, broadened t, NH_2), 4.28 (4 H, s), 3.18 (2 H, s), 2.61 (4 H, t, J = 5.2)
3c, *cis*-[Pt(THPDMA)(CBDC)]	$C_{13}N_{22}N_2O_5Pt$	260–263	C, H, N, Pt	450 (90)[c]	5.29 (4 H, s, NH_2), 3.48 (4 H, s), 2.69 (4 H, t, J = 7.6), 2.19 (4 H, s), 1.64 (2 H, m, J = 7.6), 1.35 (4 H, s)
3d, *cis*-[Pt(THPDMA)($OOCCH_2COO$)]·$2H_2O$	$C_{10}H_{18}N_2O_5Pt·2H_2O$	250–253	C, H, N, Pt	25	5.35 (4 H, br s), 3.49 (4 H, s), 3.19 (2 H, s), 2.21 (4 H, s), 1.35 (4 H, s)
3e, *cis*-[Pt(THPDMA)(THPDC)]	$C_{14}H_{24}N_2O_6Pt$	295–297	C, H, N, Pt	15	5.43 (4 H, s), 3.61 (4 H, s), 3.52 (4 H, s), 2.54 (4 H, s), 2.25 (4 H, s), 1.34 (4 H, s)
3f, *cis*-[Pt(THFDA)(CBDC)]	$C_{10}H_{16}N_2O_5Pt$	215–218	C, H, N, Pt	3.3	3.4 (2 H, m), 3.15 (2 H, m), 2.97 (2 H, m), 2.34 (4 H, t, J = 7.6), 1.34 (2 H, m, J = 7.6)[d]
3g, *cis*-[Pt(THFDA)($OOCCH_2COO$)]	$C_7H_{12}N_2O_5Pt$	250–253	C, H, N, Pt	8.3	5.58 (4 H, br s, NH_2), 3.65 (2 H, s), 3.33 (4 H, m), 3.25 (2 H, s)
3h, *cis*-[Pt(BAMPDO)(CBDC)]	$C_{11}H_{20}N_2O_6Pt$	210–212	C, H, N, Pt	7.0	5.15 (4 H, br s, NH_2), 4.57 (2 H, br s, OH), 3.28 (4 H, s), 2.67 (4 H, t, J = 7.6), 2.24 (4 H, br s), 1.64 (2 H, m, J = 7.6)
3i, *cis*-[Pt(BAMPDO)(THPDC)]	$C_{12}H_{22}N_2O_7Pt$	198–200	C, H, N, Pt	100	5.23 (4 H, br s, NH_2), 4.61 (2 H, br s, OH), 3.61 (4 H, s), 3.31 (4 H, s), 2.58 (4 H, s), 2.28 (4 H, s)
3j, *cis*-[Pt(DABDO)(CBDC)]·H_2O	$C_{10}H_{18}N_2O_6Pt·H_2O$	197–200	C, H, N, Pt	4	5.85 (2 H, m), 4.98 (2 H, m), 4.87 (2 H, t), 3.48 (4 H, br s), 2.69 (4 H, t, J = 7.6), 2.5 (2 H), 1.65 (2 H, m, J = 7.6)
3k, *cis*-[Pt(DABDO)($OOCCH_2COO$)]·H_2O	$C_7H_{14}N_2O_6Pt·H_2O$	170–173	C, H, N, Pt	50	5.9 (2 H, d), 5.05 (2 H, br s), 4.86 (2 H, br s), 3.64 (4 H, s), 3.17 (2 H, s), 2.51 (2 H, s)
3l, *cis*-[Pt(CBDMA)(CBDC)]		245–247		2.0	
3m, *cis*-[Pt(CHDMA)(CBDC)]		221–225		1.0	
3n, *cis*-[Pt(CHDA)(CBDC)]		–		1.0	
3o, *cis*-[Pt(DMPDA)(CBDC)]		–		–	

[a] OXTDMA = 3,3-Oxetanedimethanamine; THPDMA = tetrahydro-4*H*-pyran-4,4-dimethanamine; THFDA = *trans*-(±)-tetrahydro-3,4-furandiamine; BAMPDP = 2,2-bis(aminomethyl)-1,3-propanediol; DABDO = 2,3-diamino-1,4-butanediol; CBDMA = 1,1-cyclobutanedimethanamine; CHDMA = 1,1-cyclohexanedimethanamine; CHDA = *trans*-(+)-1,2-cyclohexanediamine; DMPDA = 2,2-dimethyl-1,3-propanediamine; CBDC = 1,1-cyclobutanedicarboxylate; THPDC = tetrahydro-4*H*-pyran-4,4-dicarboxylate. [b] The microanalyses were all within 0.4% of the calculated values. [c] The solubility of the hydrate. [d] Taken in D_2O.

a malonic acid, **4**,[19] and (3) reaction of the dimethyl sulfoxide–platinum complex **7** with 1,2- or 1,3-diamine **5**.[20] Most of the complexes **3** prepared in this report were synthesized by the first method, which is applicable to the synthesis of water-soluble platinum complexes. The platinum complexes **3l–o** with low water solubilities were prepared by the second method. The third method is the most general one in that it is useful for the synthesis of both water-soluble and water-insoluble platinum complexes. The dichloroplatinum complex **1** was prepared by reaction of potassium tetrachloroplatinate with an appropriate 1,2- or 1,3-diamine **5**. The dimethyl sulfoxide–platinum complex **7** 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 structures of the antitumor platinum complexes **3** synthesized in this study were all supported by NMR, IR, and elemental analyses (Table I). The structures of the platinum complexes **3b**, **3c**, **3h**, and **3k** were further confirmed by single-crystal X-ray analyses.

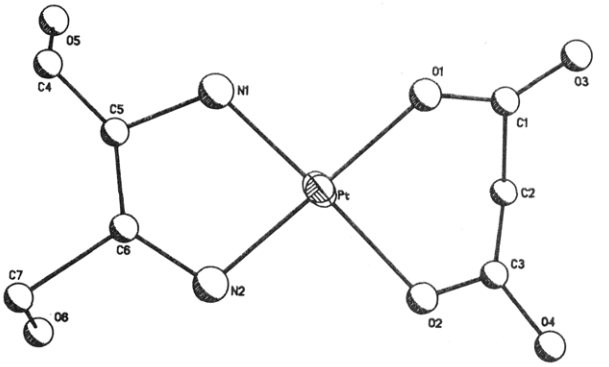


Figure 2. Drawing showing the *cis*-[Pt(DABDO)($CH_2(CO_2)_2$] (**3k**) molecule.

(20) Manuscript in preparation.

Table II. Crystal Data of the Structure Determination for *cis*-[Pt(OXTDMA)($CH_2(CO_2)_2$)] (**3b**)

formula	$PtO_5N_2C_8H_{14}$	volume, Å^3	737.3
MW	413.29	Z	2
space group[a]	Pm	d_{calcd}, g cm^{-3}	1.862
crystal system	monoclinic	d_{exptl}, g cm^{-3}	1.84 (2)
a[b], Å	6.138 (1)	$F(000)$	388
b, Å	5.925 (2)	μ, cm^{-1}	137.9
c, Å	20.327 (2)	crystal	0.44 ×
β, deg	94.17 (2)	dimensions, mm	0.15 × 0.11

[a] *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1965; Vol. 1. [b] Cell dimensions were determined by least-squares fit of the setting angles of 25 reflections with 2θ in the range 15–25°.

Table III. Crystal Data of the Structure Determination for *cis*-[Pt(DABDO)($CH_2(CO_2)_2$)] (**3k**)

formula	$PtO_6N_2C_7H_{14}$	Z	4
MW	417.27	d_{calcd} g cm^{-3}	2.589
space group[a]	$Pn2_1a$	d_{exptl} g cm^{-3}	2.60 (2)
crystal system	orthorhombic	$F(000)$	784
a[b], Å	9.018 (1)	μ, cm^{-1}	137.9
b, Å	12.637 (3)	crystal	0.37 ×
c, Å	9.393 (2)	dimensions, mm	0.28 × 0.25
volume, Å^3	1070.43 (8)		

[a] *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1965; Vol. 1. [b] Cell dimensions were determined by least-squares fit of the setting angles of 20 reflections with 2θ in the range 20–30°.

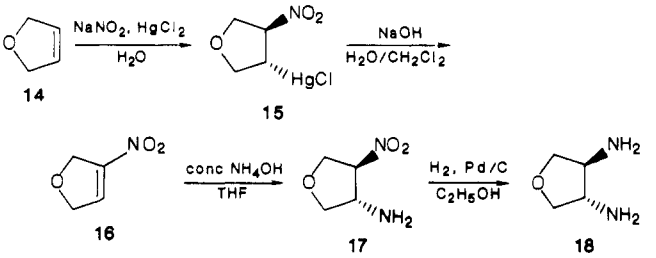
Details of the structures of **3c** and **3h** appeared in an earlier publication.[25] Drawings of compounds **3b** and **3k** are shown in Figures 1 and 2, and Tables II and III contain crystal data for the compounds. Tables containing bond distances and angles, details of the structure determination and refinement, and atomic parameters for both structure determinations are available as supplementary material.

The synthesis of two new 1,3-diamines, **10** and **13**, are outlined in Schemes II and III, respectively. Reaction of 2-chloroethyl ether (**8**) with malononitrile in acetonitrile in the presence of potassium carbonate gave dicarbonitrile **9**, which was reduced with borane in tetrahydrofuran followed by treatment with hydrochloric acid to give dimethanamine dihydrochloride **10**. Reaction of 2,2-bis(bromomethyl)-1,3-propanediol (**11**) with sodium azide in *N*,*N*-dimethylformamide gave 2,2-bis(azidomethyl)-1,3-propanediol (**12**), which was reduced with hydrogen and 5% Pd/$CaCO_3$ to give 2,2-bis(aminomethyl)-1,3-propanediol (**13**).

A previously described synthesis[21] of 1,2-diamine **18** was not satisfactory, so a new method[22] was developed as outlined in Scheme IV. Nitromercuration of 2,5-dihydrofuran (**14**) with sodium nitrite and mercuric chloride in aqueous solution gave the adduct **15**, which was treated with sodium hydroxide to give nitroolefin **16**. Addition of ammonia to the nitroolefin **16** gave nitroamine **17**, which was catalytically reduced to the desired 1,2-diamine **18**. This is a highly efficient synthesis and gives an overall yield of 40%.

2,3-Diamino-1,4-butanediol,[21] 3,3-oxetanedimethanamine,[23] 1,1-cyclobutanedimethanamine,[24] and 1,1-cyclohexanedimethanamine[24] were prepared by literature procedures.

Scheme IV



II. Solubility and Stability in Water. As is evident from Table I, the cyclic ether and hydroxyl functional groups of the diamine and carboxylate ligands enhance water solubility. For example, the analogue **3m** with a cyclohexyl ring has a solubility of only 1.0 mg/mL in water, while the solubility of **3c** with a tetrahydropyran group exceeds 90 mg/mL. The unusually high solubility of **3c** appears partially related to water solvate molecules which cocrystallize with the complex. Dehydration of **3c** by heating solid samples in vacuo leads to a lower solubility of 45 mg/mL. In the crystal structure of **3c**,[25] four water molecules located on a crystallographic mirror plane bridge adjacent complex molecules by hydrogen bonding with carboxylate oxygen atoms and with one another. The presence of water molecules of hydration was confirmed by elemental analysis.

The stability of four complexes, **3c**, **3h**, **3j**, and **3k**, in both D_2O and 0.9% saline at room temperature has been studied by ^1H and ^{13}C NMR. The complexes are all stable in D_2O but decompose to produce 1–2% of free 1,1-cyclobutanedicarboxylic acid or malonic acid in 0.9% NaCl/D_2O after 24 h. In the case of **35** in D_2O, 80% of the malonate protons disappear in 24 h, indicating that the compound tautomerized to the enolate in solution. Apparently, the kinetic stability of these complexes is due to the absence of strain in the malonate–Pt chelate ring.

III. Biology. As is evident from Table IV, all water-soluble (malonato)platinum(II) complexes (**3a–k**) showed excellent activity against mouse P388 leukemia, but only those in the tetrahydropyran series (**3c–e**) showed excellent activity against mouse L1210 and L1210 CPR leukemias. Of these, the complex **3c** is most active overall against all three leukemias and is significantly more active than cisplatin and carboplatin. The activity of **3c** against solid tumors was at least as good as that of both clinical drugs. In contrast, the complex **3h** was somewhat less active than the clinical drugs against the leukemias but had better activity against solid tumors, B-16 melanoma, and M5076 reticulum cell sarcoma. Furthermore, **3h** is about 10 times as potent as **3c**.

The complexes **3c** and **3h** were further evaluated in human breast (MX-1) and ovarian (H207) tumors in athymic mice. The activity of these two complexes against these two human tumors is as good as that of both clinical drugs. Again, **3h** is almost as potent as cisplatin and about 10 times more potent than **3c** and carboplatin (Table V). During the course of our platinum studies, we have altogether synthesized more than 500 platinum complexes and have not seen any (carboxylato)platinum(II) complexes as potent as **3h**. Since the cost of carboplatin treatment may be a problem due to its lack of potency, the high potency of **3h** may be a very significant factor to the success of drug development.

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

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Table IV. Activity of Platinum Complexes against Murine Tumors

complex	median % increase in life span (optimal dose, mg/kg; % survivors)					
	P388[a]	L1210[a]	L1210 CPR[a,b]	B16[c]	Colon 26[d]	M5076[e]
1a	93 (12.5; 0)	39 (3.1; 0)		36 (1.5; 0)		128 (3; 67)
1b	122 (12.5; 0)	50 (6.2; 0)		53 (6; 0)		
1c	132 (25; 17)	50 (25; 0)		35 (12.5; 0)	75 (12.5; 0)	
1d	173 (3.2; 83)	38 (1.5; 0)		43 (0.2; 0)	39 (0.8; 0)	138 (0.8; 83)
1e	136 (6.2; 0)	IA[f]		43 (0.4; 0)	59 (3.1; 0)	
3a	118 (50; 0)	56 (50; 0)		53 (6; 0)		
3b	153 (50; 0)	50 (50; 0)		76 (12; 0)		
3c	145 (50; 50)	142 (100; 33)	>275 (100; 67)	48 (25; 0)	121 (100; 0)	>114 (25; 80)
3d	113 (50; 0)	80 (50; 0)	36 (100; 0)	102 (25; 33)	79 (100; 0)	
3e	100 (100; 0)	213 (50; 33)	57 (50; 0)	109 (50; 0)	42 (50; 0)	
3f	82 (100; 0)	IA	IA	64 (100; 0)		
3g	84 (100; 0)	37 (50; 0)	IA			
3h	91 (6.2; 6)	36 (6.2; 0)	IA	135 (3.2; 25)	70 (6.2; 0)	>140 (3; 90)
3i	175 (12.5; 0)	28 (12.5; 0)			68 (12.5; 0)	
3j	131 (50; 17)	IA		77 (25; 17)	85 (50; 0)	
3k	136 (50; 17)	33 (25; 0)	IA	59 (3; 0)	108 (12; 17)	
3l	186 (50; 83)	106 (100; 0)	72 (50; 0)			
3m	83 (100; 0)	106 (100; 67)	89 (100; 0)			
3n	126 (25; 0)	148 (50; 0)	181 (50; 67)	64 (6; 0)		
3o	154 (25; 50)	154 (25; 25)	71 (25; 0)	58 (6; 0)		
cisplatin	140 (3; 17)	96 (6.2; 4)	IA	36 (0.4; 0)	47 (1; 17)	73 (1.6; 37)
carboplatin	144 (100; 6)	35 (100; 0)	IA	43 (12.5; 0)	85 (50; 17)	>115 (25; 80)

[a] With BDF_1 mice; the test compounds were administered ip on days 1, 5, and 9 relative to tumor inoculation; 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; 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; observed for 30 days. [e] With BDF_1 mice; the test compounds were administered ip on days 1, 5, 9, 13, and 17 relative to tumor inoculation; observed for 60 days. [f] Inactive.

Table V. Activity of **3c** and **3h** against Human Tumors in Athymic Mice

drug	optimal dose, mg/kg	% tumor weight inhibn (TWI)[a]	
		breast MX-1	ovarian H207
3c	100	92	200
3h	6	85	200
cisplatin	3	86	200
carboplatin	50	90	200

[a] TWI ≥ 58% is considered necessary to demonstrate activity.

at doses greater than optimal therapeutic levels did not induce elevated BUN levels.[26]

In summary, **3c** and **3h** exhibit excellent antitumor activities, low renal toxicity, and good stability and solubility in water. Furthermore, **3c** shows lack of cross-resistance with cisplatin, and **3h** is almost as potent as cisplatin and about 10 times more potent than carboplatin. Therefore, both **3c** and **3h** were selected for further development and are currently under clinical evaluation.[27]

Experimental Section

Chemistry. 1,1-Cyclobutanedicarboxylic acid (CBDCA), malonic acid, *trans*-(−)-cyclohexanediamine (CHDA), 2,2-dimethyl-1,3-propanediamine (DMPDA), and potassium tetrachloroplatinate were commercially available. Tetrahydro-4*H*-pyran-4,4-dicarboxylic acid (THPDCA),[28] *cis*-dichlorobis[sulfinylbis[methane]-*S*]platinum,[20] *trans*-(+)-tetrahydro-3,4-furandiamine (THFDA) (**18**),[21,22] 2,3-diamino-1,4-butanediol (DABDO),[21] 3,3-oxetanedimethanamine (OXTDMA)[23] 1,1-cyclobutanedimethanamine (CBDMA),[24] and 1,1-cyclohexanedimethanamine (CHDMA)[24] were prepared 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.

All melting points were taken on a Mel-Temp apparatus. 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 ppm relative to internal tetramethylsilane.

Dichloro(tetrahydro-4*H*-pyran-4,4-dimethanamine-*N*,*N*′)platinum(II) (1b). Typical Procedure for 1a–e. To a stirred solution of potassium tetrachloroplatinate (4.15 g, 0.010 mol) in water (20 mL) was added a solution of **10** (2.17 g, 0.010 mol) in a mixture of water (10 mL) and 5 N sodium hydroxide solution (4 mL, 0.020 mol).[29] Within a few minutes, gray crystals precipitated. After stirring at room temperature overnight, the crystals were collected by filtration to give 3.44 g (84%) of **1b**; mp 290–292 °C dec.

[1,1-Cyclobutanedicarboxylato(2−)-*O*¹,*O*¹](tetrahydro-4*H*-pyran-4,4-dimethanamine-*N*,*N*′)platinum(II) (3c). Procedure A: Typical Procedure for 3a–k. A suspension of **1b** (13.6 g, 0.0332 mol) and 1,1-cyclobutanedicarboxylic acid disilver salt (11.9 g, 0.0332 mol) in water (1450 mL) 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 (13.2 g) was recrystallized from water to give 9.41 g (60%) of **3c** as colorless crystals; mp 260–263 °C dec.

Procedure B: Applicable to 3a–o. A mixture of *cis*-[Pt(Me$_2$SO)$_2$Cl$_2$] (12.7 g, 0.030 mol), the disilver salt of 1,1-cyclobutanedicarboxylic acid (10.7 g, 0.030 mol), and water (900 mL) was stirred at room temperature in the dark for 22 h and then filtered. The filtrate was concentrated to ca. 25 mL and the precipitate was collected, giving 14.5 g (90%) of [1,1-cyclobutanedicarboxylato(2−)-*O*,*O*′]bis[sulfinylbis[methane]-*S*]platinum(II) as colorless crystals; mp 201 °C dec.

To a hot solution of [1,1-cyclobutanedicarboxylato(2−)-*O*,*O*′]-bis[sulfinylbis[methane]-*S*]platinum(II) (4.93 g, 0.010 mol) in water (120 mL) was added a solution of tetrahydro-4*H*-pyran-

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(29) When a diamine free base was used, sodium hydroxide solution was omitted.

4,4-dimethanamine (1.44 g, 0.010 mol) in water (30 mL). The mixture was kept at 100 °C in an oil bath for 6 h and then evaporated to dryness. The residue was recrystallized from a small amount of water to give 2.34 g (47%) of **3c** as colorless crystals; mp 260–263 °C dec.

(1,1-Cyclobutanedicarboxylato)(2,2-dimethyl-1,3-propanediamine)platinum(II) (3o).[30] **Typical Procedure for 3l–o.** To a stirred solution of potassium tetrachloroplatinate (12.4 g, 0.030 mol) in water (75 mL) was added 2,2-dimethyl-1,3-propanediamine (3.06 g, 0.030 mol). After standing at room temperature overnight, the tan crystals were collected by filtration to give 7.0 g (64%) of dichloro(2,2-dimethyl-1,3-propanediamine)platinum(II).

To a suspension of the above platinum complex (3.68 g, 0.010 mol) in water (30 mL) was added a solution of silver nitrate (3.40 g, 0.020 mol) in water (30 mL). The resulting mixture was stirred at room temperature for 3 h and, after removal of the insoluble precipitate of silver chloride by filtration, a solution of 1,1-cyclobutanedicarboxylic acid (1.44 g, 0.010 mol) in 1 N NaOH solution (20 mL) was added to the filtrate. After setting aside the reaction mixture for 3 h, it was concentrated under reduced pressure at room temperature to about 30 mL. The white precipitate was collected by filtration to give 2.4 g (55%) of **3o**.

Tetrahydro-4*H*-pyran-4,4-dicarbonitrile (9). A suspension of 2-chloroethyl ether (**8**, 28.6 g, 0.200 mol), potassium carbonate (55.3 g, 0.400 mol), and malononitrile (13.2 g, 0.200 mol) in acetonitrile (800 mL) was refluxed at 100 °C for 24 h and the hot reaction mixture was filtered. The filtrate was evaporated to dryness. The residue was recrystallized from ethanol to give 11.2 g (41%) of **9** as colorless crystals: mp 113–114 °C; ^{1}H NMR ($CDCl_3$) δ 2.22 (4 H, t, J = 5.2 Hz), 3.86 (4 H, t, J = 5.2 Hz). Anal. ($C_7H_8N_2O$) C, H, N.

Tetrahydro-4*H*-pyran-4,4-dimethanamine Dihydrochloride (10). To a solution of **9** (9.53 g, 0.070 mol) in tetrahydrofuran (175 mL) at 0 °C was added slowly a 0.98 M solution of borane in tetrahydrofuran (214 mL). The reaction mixture was then stirred at room temperature overnight. Ethanol (100 mL) was added to the reaction mixture and the resultant solution was stirred at room temperature for 4 h and then evaporated to dryness. The white residue was slurried in water (100 mL) and 6 N HCl (50 mL) was added slowly to the suspension. After most of the solid had dissolved, the reaction mixture was filtered and the filtrate was extracted with ether (3 × 75 mL). The aqueous phase was evaporated to dryness. The resultant amorphous solid was then crystallized from methanol to give 8.26 g (54%) of **10** as colorless crystals: mp 258–262 °C; ^{1}H NMR (DMSO-d_6) δ 1.55 (4 H, br s), 3.1 (4 H, s), 3.6 (4 H, br s), 8.35 (6 H, br s). Anal. ($C_7H_{16}N_2O$·2HCl) C, H, N.

2,2-Bis(aminomethyl)-1,3-propanediol (13). A mixture of 2,2-bis(bromomethyl)-1,3-propanediol (**11**, 26.2 g, 0.100 mol) and sodium azide (26.0 g, 0.400 mol) in *N*,*N*-dimethylformamide (600 mL) was heated at 120 °C with stirring for 20 h and filtered. The filtrate was evaporated under reduced pressure to dryness. The residue was then taken up in dichloromethane (200 mL) and the dichloromethane solution was filtered. The filtrate was evaporated to dryness to give 18.6 g (100%) of 2,2-bis(azidomethyl)-1,3-propanediol (**12**) as a colorless oil.

Nitrogen was bubbled through a mixture of **12** (18.6 g, 0.100 mol) and 5% Pd/$CaCO_3$ (5.0 g) in ethanol (250 mL) for 5 min. Hydrogen was then bubbled through the stirred mixture for 6 h with a resultant rise in the temperature of the reaction mixture. After bubbling nitrogen through the reaction mixture for 5 min, the mixture was filtered, and the filtrate was evaporated to dryness to give 13.0 g (93%) of **13** as a colorless oil, which crystallized on standing; mp 165–166 °C. This material was used in the next reaction without further purification.

Biology. Platinum compounds were dissolved or suspended in 0.85% saline or 0.2% Klucel in water or in 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 reticulum cell sarcoma M5076 was obtained from the A. D. Little Co., Cambridge, MA. The mouse L1210 cisplatin-resistant leukemia (L1210 CPR) and the human mammary MX-1 and human ovarian H207 xenografts were obtained from the Mason Research Institute, Worcester, MA.

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

In all mouse tumor systems, an increase in life span (ILS) >25% over controls was considered necessary to demonstrate activity. Any treatment that reduced ILS or body weight by >15% over control mice was rated toxic.

Human Tumor Xenograft Tests. To evaluate the sensitivity of tumors to drugs, female athymic mice were implanted subcutaneously with five (2 mm)^3 tumor fragments in the axillary region. Mice were randomized and used when tumors were 100–350 mg (staging day). Drugs were administered intraperitoneally (ip) at several dose levels once each 4 days for three total injections starting on staging day, with five or six mice per test and 10–12 mice in control groups. To estimate drug toxicity, mice were weighed on staging day and days 5 and 10 post staging and were monitored daily for deaths. Tumors were measured on days 11, 15, and 21 post staging by means of vernier calipers and tumor weights were estimated from tumor diameters by the following formula:

$$\text{tumor weight (mg)} = \frac{L\ (\text{mm}) \times W^2\ (\text{mm})}{2}$$

The change (Δ) in tumor weight was calculated for each group by subtracting the initial mean group weight on staging day from the mean group weight on the day of evaluation. The percentage of treated divided by control weight change (%T/C) [or percentage of mean weight change over initial mean weight for groups showing a negative number (regression)] was calculated for test groups with >65% survivors. For the plotting of tumor growth, actual mean tumor weights were used. T/C was then converted into TWI (tumor weight inhibition); for example, T/C of 40% = 60% TWI, T/C of 0% = 100% TWI, and TC of −100% (complete regression) = 200% TWI. A tumor weight inhibition ≥58% was necessary to demonstrate activity.

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Supplementary Material Available: Tables containing the details of the structure determination and refinement of **3b** and **3k**, bond distances and angles for both structure determinations, and atomic positional and thermal parameters (6 pages). Ordering information is given on any current masthead page.

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