tonation of the complex is only achieved in strong acid. Remembering that inversion must have taken place during the dechlorination process (acidic solution), and not during the initial chlorination (neutral solution), it is clear that the pK_a values of the present platinum(IV) complexes are also quite low.

The complex *trans*-$[Pt(\mathbf{2})Cl_2]^{2+}$ was found to be quite stable in acetonitrile, since the crystal used in the X-ray structure was grown over a period of several weeks. However, it was found that the pendent chloroamine groups slowly dechlorinated in acid, resulting in the complex *trans*-$[Pt(\mathbf{1})Cl_2]^{4+}$. Recall that the chloroamine complex was stable in aqueous solution for at least 1 day before it precipitated as the perchlorate salt, so although the decomposition is not rapid, dechlorination of both pendent amines does occur over a period of a couple of weeks in acidic solution. Rapid precipitation of *trans*-$[Pt(\mathbf{2})Cl_2]^{2+}$ was avoided by acidificiation of the reaction mixture with hydrochloric acid instead of perchloric acid, and it was apparent that the chloride salt of *trans*-$[Pt(\mathbf{2})Cl_2]^{2+}$ was sufficiently soluble that precipitation did not occur before dechlorination. Acid-catalyzed dechlorination of chloroamines is well-known,[17] and the observed reaction of *trans*-$[Pt(\mathbf{2})Cl_2]^{2+}$ is in accord with this. Despite the observed acid-catalyzed decomposition of *trans*-$[Pt(\mathbf{2})Cl_2]^{2+}$, the stability of the complex was still remarkable by comparison with most chloroamine compounds. An extensive pyrolytic study[18] revealed that chloroamines possessing α-hydrogen atoms generally decompose by elimination of HCl to generate either a chloroimine or a nitrile depending on the whether one or two molecules of HCl are eliminated, respectively. It has been found that the presence of a tertiary carbon adjacent to the chloroamine group acts to stabilize the compound. For example, *N,N*-dichloro-*tert*-butylamine may be safely distilled without noticeable decomposition.[19] The pendent methyl groups in *trans*-$[Pt(\mathbf{2})Cl_2]^{2+}$ evidently act to stabilize the dichloroamine groups in a similar manner.

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Registry No. **1**, 138383-04-7; *trans*-$[Pt(\mathbf{1}\text{-H})](ClO_4)_3$, 131076-94-3; *trans*-$[Pt(\mathbf{1})Cl_2]Cl_2(ClO_4)_2 \cdot 4H_2O$, 138333-51-4; *trans*-$[Pt(\mathbf{2})Cl_2](ClO_4)_2$, 138353-16-9.

Supplementary Material Available: Tables of complete crystal data, thermal parameters, and derived hydrogen positional and thermal parameters for *trans*-$[Pt(\mathbf{1})Cl_2]Cl_2(ClO_4)_2 \cdot 4H_2O$ and *trans*-$[Pt(\mathbf{2})Cl_2](ClO_4)_2$ (4 pages); listings of structure factors for the same compounds (34 pages). Ordering information is given on any current masthead page.

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Activation of the Trans Geometry in Platinum Antitumor Complexes. Synthesis, Characterization, and Biological Activity of Complexes with the Planar Ligands Pyridine, *N*-Methylimidazole, Thiazole, and Quinoline. Crystal and Molecular Structure of *trans*-Dichlorobis(thiazole)platinum(II)

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The presence of planar ligands in *trans*-$[PtCl_2(py)_2]$ (py = pyridine) greatly enhances the cytotoxicity of such species, with respect both to their corresponding cis isomer and also to *trans*-$[PtCl_2(NH_3)_2]$. The cytotoxicity of *trans*-$[PtCl_2(py)_2]$ in murine tumor cell lines is equivalent to the anticancer drug cisplatin, *cis*-$[PtCl_2(NH_3)_2]$ (*J. Med. Chem.* **1989**, *32*, 2240). The generality of this effect has been studied for a range of structures with planar ligands of formula *trans*-$[PtCl_2(L)(L')]$. Three distinct series have been examined—(i) L = L' = pyridine (py), *N*-methylimidazole (*N*-MeIm), and thiazole (Tz), (ii) L = quinoline (quin) and L' = substituted sulfoxide R'R''SO, where R' = Me and R'' = Me, CH_2Ph, and Ph, and (iii) L = quinoline and L' = NH_3. The synthesis and chemical characterization of all new complexes are described. An X-ray crystal structure determination for *trans*-$[PtCl_2(Tz)_2]$ confirmed the geometry with N-bound thiazole. The crystals are monoclinic, space group $C2/c$, with cell dimensions a = 8.088 (3) Å, b = 14.964 (4) Å, c = 8.847 (2) Å, and Z = 4. Platinum has the expected square planar coordination with l(Pt–Cl) = 2.300 (5) Å and l(Pt–N) = 2.024 (18) and 2.077 (17) Å. Bond angles are normal with N(1)–Pt–N(2) = 180.0 (1)°, N(1)–Pt–Cl(1) = 904 (1)°, and N(2)–Pt–Cl(1A) = 89.6 (1)°. The intensity data were collected with Mo Kα radiation with λ = 0.710 73 Å. Refinement was by full-matrix least-squares methods to a final R value of 5.45%. The thiazole rings are not coplanar but slightly tilted to each other at an angle of 14.3°. The dihedral angles between the Pt coordination plane and the thiazole rings are 119.3 and 105.0°. The biological studies confirm the generality of activation of the trans geometry using planar ligands. Cytotoxicity tests in murine leukemia (L1210) cell lines both sensitive and rendered resistant to cisplatin show that the complexes show equivalent cytostatic activity to that of cisplatin. Thus the activity is an order of magnitude greater than *trans*-$[PtCl_2(NH_3)_2]$. The cytotoxicity is further marked by consistent activity in the cisplatin-resistant cell line. Contrary to the well-established but empirical structure–activity relationships, the trans geometry can give platinum complexes with cytotoxicity equivalent to that of the analogous cis isomer. The results point to a further source of platinum antitumor complexes acting by a different molecular mechanism to cisplatin with potential for antitumor activity complementary to that of the clinically used drug.

The clinical utility of platinum anticancer agents is by now well established.[1] The empirical structure–activity relationships delineated for platinum complexes state that the cis geometry, e.g. *cis*-$[PtX_2(NH_3)_2]$, where X = Cl or X_2 = 1,1-cyclobutanedicarboxylate, is necessary for antitumor activity. When the ammine is changed to a planar ligand such as pyridine (py) in *trans*-$[PtCl_2(py)_2]$, the cytotoxicity of the trans complex is dramatically enhanced in comparison to that of both its cis isomer and *trans*-$[PtCl_2(NH_3)_2]$, which is inactive at biologically relevant concentrations.[2] The generality of this effect has been studied

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Table I. Spectral Properties of New Quinoline Complexes of the General Formula $[PtCl_2L(L')]$

			IR[a], cm^{-1}		NMR[b] (δ), ppm				
					$^1H(L)$[c]				
L	L'	geometry	ν(S–O)	ν(Pt–Cl)	H(8)	H(2)	H(4)	$^1H(L')$	^{195}Pt
quin	Me_2SO	cis	1120	340,310	9.77	9.85 (47)	9.01	3.78 (23.5)[d]	−2871
quin	Me_2SO	trans	1128	340	9.41	9.25 (27.4)	8.75	3.60 (19.7)	−3016
quin	MeBzSO	trans	1115	339	9.30	8.82 (35)	9.26	3.36 (19.7) 5.15 (dd) 7.60 (m)	−3033
quin	MePhSO	trans	1145	335	9.41	8.82 (31)	9.33	3.66 (17.5) 7.66 (m)	−3047
quin	NH_3	cis		315 (br)	9.86	8.67 (44.4)	9.51	4.48[e]	−2035
quin	NH_3	trans		325	9.81	8.64 (35.4)	9.37	4.19	−2029

[a] IR done on KBr disks. [b] Chemical shifts are relative to TMS (^1H) and $PtCl_6^{2-}$ (^{195}Pt). All complexes were dissolved in DMF-d_7. [c] All (H8), H(2), and H(4) resonances are doublets. $^3J(^{195}Pt\text{-}^1H)$ are given in parentheses. Other quinoline resonances are between 7.66 and 8.75 ppm. [d] Singlets except where stated. $^3J(^{195}Pt\text{–}^1H)$ for the methyl protons is given in parentheses. The resonance at 5.15 ppm is a doublet of doublets (dd) separated by 20 and 13 Hz due to the diastereotopic benzyl protons. [e] NH_3 resonances are broad singlets.

with three classes of compounds of general structure $[PtCl_2(L)(L')]$—(i) L = L' = pyridine (py), *N*-methylimidazole (*N*-MeIm), and thiazole (Tz), (ii) L = quinoline (quin) and L' = substituted sulfoxide R'R''SO, where R' = Me and R'' = Me, CH_2Ph, and Ph, and (iii) L = quinoline and L' = NH_3. This paper reports on the synthesis, characterization, and cytotoxicity of these novel platinum antitumor complexes. The results confirm the general utility of activation of the trans-platinum structure by use of planar ligands.

Experimental Section

Starting Materials and Physical Methods. The starting complexes *cis*-$[PtCl_2(NH_3)_2]$ and $K[PtCl_3(NH_3)]$ were prepared by the methods of Dhara[3] and Abrams[4] respectively. *trans*-$[PtCl_2(NH_3)_2]$ was prepared by the published method.[5] The complexes *cis*-$[PtCl_2(R'R''SO)_2]$ were prepared by the procedure of Wayland for R' = R'' = Me.[6] Similarly, the known complexes *cis*- and *trans*-$[PtCl_2L_2]$, where L = py[7] and *N*-MeIm,[8,9] were prepared by literature methods. Thiazole and quinoline were from Aldrich and were used without further purification. IR spectra were obtained as KBr disks on Nicolet FT6000 Series and Perkin-Elmer 1430 spectrophotometers. NMR spectra were run on Bruker 250- and 270-MHz spectrometers. ^{195}Pt NMR spectra were run on the 250-MHz machine in DMF-d_7 or D_2O with reference to a Na_2PtCl_6 solution in D_2O as external reference. Samples were run at a pulse width of 10 μs with a relaxation delay of 0.5 s. Usually a sweep width of 30 KHz was used and 5000–10000 scans were adequate. All shifts are positive to lower shielding. Elemental analyses were by Robertson Laboratories, Madison, NJ.

Cytotoxicity Assays. These were performed as described previously.[39] The complexes were dissolved in DMF and diluted by serial dilution in saline to a final concentration of 0.5% DMF.

***cis*-[PtCl$_2$(thiazole)$_2$].** The complex was prepared by a modified procedure of Kauffman.[7] To a solution of K_2PtCl_4 (0.5 g, 1.2 mmol) dissolved in 5 mL of H_2O was added a solution of thiazole (0.17 mL, 0.205 g, 2.4 mmol) dissolved in 1.25 mL of EtOH with continuous stirring. The solution was stirred for several hours and then refrigerated overnight. The product was filtered, washed with acetone and ether (diethyl ether), and dried in vacuo with heat; yield 87%. Anal. Calcd for $C_6H_6N_2Cl_2S_2Pt$: C, 16.52; H, 1.39; N, 6.42; Cl, 16.25. Found: C, 16.81; H, 1.41; N, 6.25; Cl, 16.19.

[Pt(thiazole)$_4$]Cl$_2$. *cis*-$[PtCl_2(Tz)_2]$ (1.0 g, 2.30 mmol) was suspended in 10 mL of H_2O. A solution of thiazole (1.2 mL, 0.98 g, 11.47 mmol) dissolved in 6.9 mL of EtOH was added with gentle heating until the reaction mixture became clear and colorless. The solution was evaporated to dryness, and the resulting solid was recrystallized from water/acetone and the product filtered and washed with acetone and ether. $[Pt(Tz)_4]Cl_2$ was dried in air; yield 93%. Anal. Calcd for $C_{12}H_{12}N_4Cl_2S_4Pt.2H_2O$: C, 22.43; H, 2.51; N, 8.72; Cl, 11.37. Found: C, 22.40; H, 2.39; N, 8.54; Cl, 11.94.

***trans*-[PtCl$_2$(thiazole)$_2$].** $[Pt(Tz)_4]Cl_2$ (0.65 g, 1.08 mmol) was placed in a 100-mL round-bottom flask and heated at 100 °C under vacuum for 2 h. After this time the yellow powder was washed with water to ensure removal of unreacted $[Pt(Tz)_4]Cl_2$; yield 90%. (Note: A large flask is best; the reaction goes to completion faster if $[Pt(Tz)_4]Cl_2$ is in a thin layer and can be heated evenly.) Anal. Calcd for $C_6H_6N_2Cl_2S_2Pt$: C, 16.52; H, 1.39; N, 6.42; Cl, 16.25. Found: C, 16.78; H, 1.37; N, 6.31; Cl, 16.37.

***trans*-[PtCl$_2$(R'R''SO)(quinoline)] (R' = Methyl; R'' = Methyl, Phenyl, Benzyl).** To a suspension of *cis*-$[PtCl_2(R'R''SO)_2]$ (1 mmol) in 25 mL of MeOH was added quinoline (1 mmol). The reaction mixture was stirred overnight. After filtration, the product was washed with MeOH, acetone, and ether and dried in vacuo without heat. The product was recrystallized from hot MeOH; yields 56–65%. Anal. Calcd for R' = R'' = Me, $C_{11}H_{13}NCl_2OSPt$: C, 27.90; H, 2.75; N, 2.96; Cl, 15.01. Found: C, 27.92; H, 2.56; N, 2.71; Cl, 15.29. Calcd for R' = Me and R'' = Ph, $C_{16}H_{15}NCl_2OSPt$: C, 35.89; H, 2.82; N, 2.62; Cl, 13.24. Found: C, 35.85; H, 2.65; N, 2.49; Cl, 13.41. Calcd for R' = Me and R'' = Bz, $C_{17}H_{17}NCl_2OSPt$: C, 37.16; H, 3.09; N, 2.55; Cl, 12.91. Found: C, 37.11; H, 3.04; N, 2.38; Cl, 13.88.

***cis*-[PtCl$_2$(Me$_2$SO)(quinoline).** *trans*-$[PtCl_2(Me_2SO)(quin)]$ (0.24 g, 0.51 mmol) was dissolved in 2 mL of Me_2SO and stirred overnight. The white precipitate was filtered off and washed with acetone and ether. The product was dried in vacuo with heat; yield 54%. Anal. Calcd for $C_{11}H_{13}NCl_2OSPt$: C, 27.90; H, 2.75; N, 2.96; Cl, 15.01. Found: C, 27.96; H, 2.65; N, 2.73; Cl, 15.00.

***cis*-[PtCl$_2$(NH$_3$)(quinoline)].** To a solution of $K[PtCl_3(NH_3)]$ (0.40 g, 1.1 mmol) dissolved in 6 mL of water was added quinoline (0.12 mL, 0.13 g, 1.1 mmol) diluted to 0.5 mL with EtOH with constant stirring. The mixture was allowed to stir at room temperature overnight and filtered and the filtrate washed with EtOH and ether and dried in vacuo with heat; yield 56%. Anal. Calcd for $C_9H_{10}N_2Cl_2Pt$: C, 26.23; H, 2.45; N, 6.80; Cl, 17.20. Found: C, 26.00; H, 2.25; N, 6.53; Cl, 16.97.

***trans*-[PtCl$_2$(NH$_3$)(quinoline)].** *cis*-$[Pt(NH_3)_2Cl_2]$ (1.0 g, 3.33 mmol) was suspended in 175 mL of water. Silver nitrate (1.33 g, 6.67 mmol) and quinoline (0.79 mL, 0.86 g, 6.67 mmol) diluted to 5 mL with EtOH were added with constant stirring. The mixture was stirred at room temperature overnight. To dissolve the *cis*-$[Pt(NH_3)_2(quin)_2](NO_3)_2$ that had formed, the mixture was heated before filtering through Celite to remove silver chloride. To the filtrate was added 10 mL of 1 N HCl to remove any residual silver, and this mixture was filtered immediately through Celite. Concentrated HCl (5 mL) was added, and the solution was heated until a yellow precipitate formed. The precipitate was filtered off, washed with hot water, acetone and ether, and dried in vacuo with heat. A second crop can be obtained by further heating of the filtrate; yield 23%. Anal. Calcd for $C_9H_{10}N_2Cl_2Pt$: C, 26.23; H, 2.45; N, 6.80; Cl, 17.20. Found: C, 26.29; H, 2.24; N, 6.62; Cl, 16.91.

Crystal Structure Determination. The experimental details are given in the supplementary material. The structure was solved by a combination of direct methods and heavy-atom Fourier techniques using the standard Siemens SHELXTL PLUS crystallographic package. Full-matrix least-squares refinement was carried out with anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms were placed in calculated positions. The molecule contains a crystallographically imposed C_2 axis of symmetry through the N–Pt–N vector, which creates a symmetry-imposed disorder of the S atoms and one of the C atoms attached to S. At the resolution of this determination, the separate electron density peaks for the discrete S and C atoms were not resolved.

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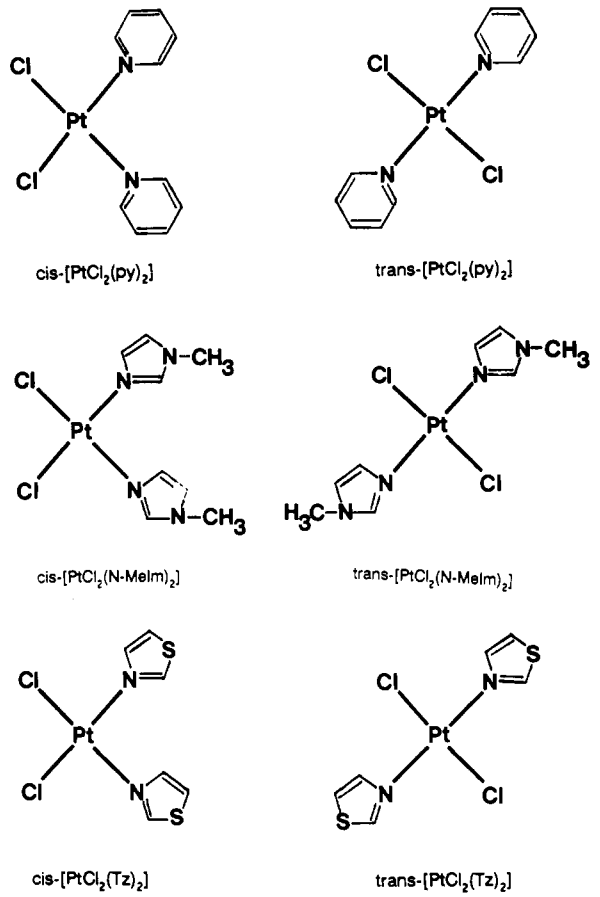

Figure 1. Structures of complexes $[PtCl_2(L)(L')]$ examined for cytotoxicity.

The Fourier map showed single peaks at distances of 1.58 (2) Å from C1 and 1.62 (2) Å from C2, which are close to an average of the C–C and S–C distances. These peaks were refined as S. The symmetry generated positions of S(1) and S(2) were labeled as C′ and C″ respectively. The maximum shift/esd in the last refinement cycle was less than 0.4, and the maximum residual electron density in the final difference Fourier map was 2.2 e/Å^3 near the C1 atom.

Results and Discussion

The structures of all complexes prepared are given in Figures 1 and 2. Spectral and characterization data for new quinoline complexes are summarized in Table I.

Complexes of the Type $[PtCl_2(L)(L')]$. L = L′. To extend our reported studies on pyridine complexes we examined *N*-MeIm and thiazole complexes. The biological activity of imidazole complexes in the cis configuration has been previously examined.[8] Thiazole was chosen as a further example of a planar ligand due to its accepted chemical similarity with pyridine. The known DNA-binding of the dithiazole unit in the antibiotic bleomycin[10] and of simple dithiazole ligands[11] also made study of these complexes attractive. For the series $[PtCl_2(L)(L')]$ the synthesis of the known complexes with L = L′ = py or *N*-MeIm followed standard procedures.[7-9] The trans isomer is usually prepared by formation of $[Pt(amine)_4]Cl_2$, which with excess acid and heating is converted to *trans*-$[PtCl_2(amine)_2]$. When the amine is NH_3, this transformation also occurs simply by heating the tetraamine complex in the solid state in vacuo. The temperature required for the conversion is high (150 °C) in the case of NH_3.[12] This solid-state conversion is effected smoothly at much lower temperatures for the heterocyclic amines pyridine,[13] *N*-methylimidazole, and thiazole. For example, when $[Pt(Tz)_4]Cl_2$ is heated under vacuum

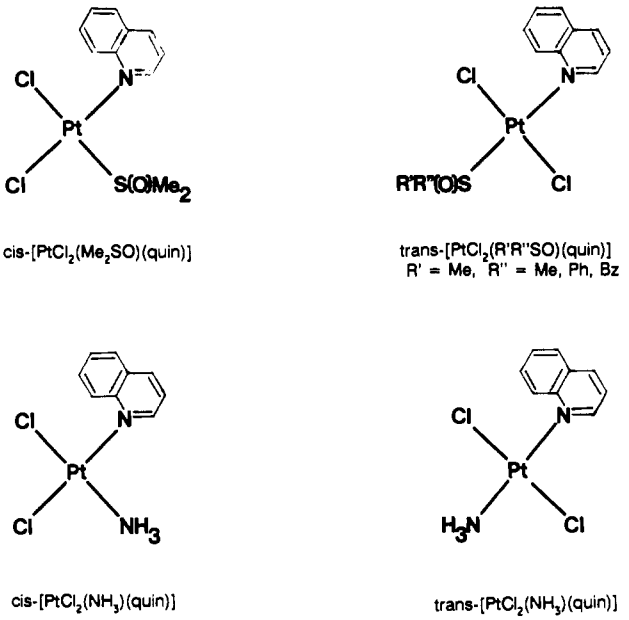

Figure 2. Structures of complexes $[PtCl_2(quinoline)(L')]$, L′ = R′R″SO or NH_3, examined for cytotoxicity.

at 100 °C, reaction can be observed as the color of the powder changes from white to yellow. Spectroscopic data confirmed the formation of the trans derivative, identical to that formed by the HCl method. Subsequent studies confirmed the generality of this reaction for the pyridine and *N*-methylimidazole derivatives. The reaction is clean and proceeds in nearly quantitiative yields. The milder conditions required for this solid-state transformation in comparison to NH_3 imply that the tertiary amine ligands are significantly more labile than NH_3. On the basis of ease of transformation of the tetrakis(amine) complex to the corresponding *trans*-$[PtCl_2(amine)_2]$, thiazole is the most labile ligand, followed by *N*-methylimidazole and pyridine.

The spectral parameters obtained for the thiazole derivatives are as follows (see Experimental Section):

	$\delta(^{195}Pt)$, ppm	$\delta(^1H)$, ppm (J(Pt–H), Hz)	ν(Pt–Cl), cm^{-1}
cis-$[PtCl_2(Tz)_2]$	−1918	9.57 (d, 25.0) 8.05 (m)	320
trans-$[PtCl_2(Tz)_2]$	−1969	9.38 (s, 26.0) 8.03 (d) 7.91 (d)	330
$[Pt(Tz)_4]Cl_2$	−2524	9.69 (d) 8.31 (d) 8.05 (m)	...

The ^{195}Pt NMR chemical shifts for the thiazole derivatives relative to $PtCl_6^{2-}$ confirm that the ligand is bound through the nitrogen.[14] In both *cis*- and *trans*-$[PtCl_2(Tz)_2]$ the lowest field resonance in the ^1H NMR spectrum is the H_2 proton, with *trans*-$[PtCl_2(Tz)_2]$ being slightly more downfield with respect to the cis isomer. The value of $^3J(^{195}Pt-^1H)$ for the H2 proton is similar in both complexes (cis, 25 Hz; trans, 26 Hz). In *cis*-$[PtCl_2(Tz)_2]$, the peaks due to the H4 and H5 resonances are not resolved at 250 MHz. In the trans complex, these peaks are resolved, and evidence for Pt–H coupling (as indicated by small broad shoulders at the base of the central peak) can also be seen in the H4 resonance. The coupling does not exhibit the theoretical 1:4:1 pattern because of the effects of chemical shift anisotropy at the field strengths used.[15]

Calculations of the electronic structure of thiazole confirm that the net charge of the thioether-type sulfur is positive, with the negative charge residing on the nitrogen.[16] Thus, nitrogen is

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Table II. Crystallographic Data for *trans*-$[PtCl_2(Tz_2]$

formula	$C_6H_6Cl_2N_2PtS_2$
fw	436.2
space group	monoclinic $C2/c$
a, Å	8.088 (3)
b, Å	14.964 (4)
c, Å	8.847 (2)
β, deg	99.50 (2)
V, Å^3	1056.1 (5)
Z	4
D_c, Mg m^{-3}	2.744
diffractometer	Siemens R3m/v
radiation	Mo Kα (λ = 0.71073 Å)
scan mode $2\theta/\theta$, deg	$4 < \theta < 55$
μ(Mo Kα), mm^{-1}	10.51
T, °C	295
tot. no. of reflcns	2756
no. of indep reflcns	1227
no. of observed reflcns ($I > 3\sigma(I)$)	1105
R, %	5.45
R_w, %	6.55

Table III. Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Coefficients (Å^2 × 10^3) for *trans*-$[PtCl_2(Tz)_2]$

	x	y	z	U(eq)[a]
Pt(1)	0	1278 (1)	2500	25 (1)
Cl(1)	7167 (6)	1267 (1)	2558 (7)	45 (1)
S(1)	10525 (13)	4175 (5)	3547 (12)	46 (3)
S(2)	10687 (14)	1626 (5)	−1613 (11)	51 (3)
N(1)	0	2631 (12)	2500	52 (7)
N(2)	0	−110 (11)	2500	41 (6)
C(2)	10947 (21)	−556 (11)	3624 (20)	49 (5)
C(1)	10602 (19)	3126 (12)	3728 (24)	54 (6)

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized U_{ij} tensor.

expected to be a better donor to transition metals. Previous studies on platinum thiazoles had indicated the N as the donor atom.[17,18] An X-ray crystal structure determination of $[PtBr_3(nsb)]$ (nsb = 2-(2-chloro-5-nitrostyryl)benzothiazole) confirmed the N-coordination of the thiazole ring.[19] To confirm the structure of *trans*-$[PtCl_2(Tz)_2]$, an X-ray crystal structure determination was carried out.

Description of the Structure of *trans*-$[PtCl_2(Tz)_2]$. The full structure collection data are given in the supplementary material. Table II gives the crystallographic data summary while Table III gives the atomic coordinates. The complex displays the expected square-planar configuration about platinum (Figure 3). Despite the symmetry imposed disorder (see Experimental Section) the thiazole is clearly N-bound with Pt–N distances of 2.024 (18) and 2.077 (17) Å. The Pt–Cl distance is 2.300 (5) Å. All other bond lengths and angles are normal (see abstract and Table SV). The thiazole ligands are at dihedral angles of 119.3 and 105° to the PtN_2Cl_2 coordination plane and are thus slightly tilted to each other at a dihedral angle of 14.3°.

Complexes of the Type $[PtCl_2(L)(L')]$. L ≠ L'. Consideration of the geometry and possible mechanism of action of these complexes (see also below) indicate that the trans-planar ligands may act as one unit. This point can be examined by studying the effect of planar rings of larger size than pyridine. Thus, we set out to prepare complexes with quinoline containing two fused planar rings. In this case it is desirable to have simply one planar ligand present to examine the effect of the increased ring size on activity.

$[PtCl_2(R'R''SO)(L)]$. Mixed amine–Me_2SO complexes of this type have been extensively studied with NH_3 or pyridine and we wished to examine this series with quinoline because of their

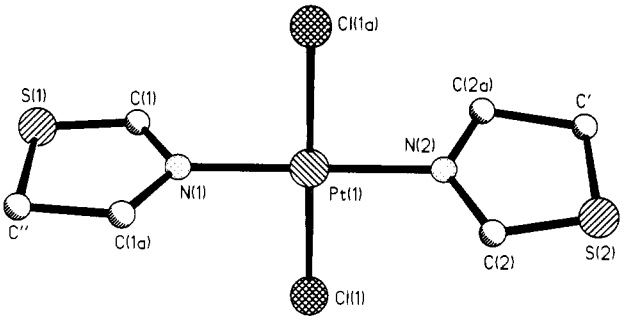

Figure 3. ORTEP diagram of *trans*-$[PtCl_2(Tz)_2]$.

well-defined structures. The compound initially formed from the reaction of either $K[PtCl_3(Me_2SO)]$ or *cis*-$[PtCl_2(Me_2SO)_2]$ with pyridine or purine nucleosides (L') is in fact *trans*-$[PtCl_2(Me_2SO)(L')]$, which isomerizes readily to the cis form in Me_2SO solution.[20-23] The behavior of quinoline as a ligand is consistent with these findings. Using MeOH as solvent, the products of the reaction of quinoline with either $K[PtCl_3(Me_2SO)]$ or *cis*-$[PtCl_2(Me_2SO)_2]$ were identical and thus the *trans*-$[PtCl_2(Me_2SO)(quin)]$ formulation is indicated. Dissolution of this complex in a concentrated solution of Me_2SO gives overnight a precipitate characterized as *cis*-$[PtCl_2(Me_2SO)(quin)]$.

The ^{195}Pt chemical shifts of *cis*- and *trans*-$[PtCl_2(Me_2SO)(py)]$ have been assigned as −2856 and at −2957 ppm respectively.[23] The corresponding values for $[PtCl_2(Me_2SO)(quin)]$ are −2871 (cis) and −3016 ppm (trans). The complexes with substituted sulfoxides give similar chemical shifts but which are slightly upfield to that of the Me_2SO derivative. The sulfoxide is S-bonded in all cases. An independent X-ray crystal structure determination of *cis*-$[PtCl_2(Me_2SO)(acridine)]$ shows that the acridine ring is tilted so that the hydrogen atoms of the C4 and C5 carbons are approximately 2.8 Å from the platinum atom and occupy the axial positions above and below the square plane. This results in a significant deshielding of 1.5–1.7 ppm for these protons.[24] These positions are equivalent to the H8 protons of the quinoline ring, which also undergo significant deshielding upon complexation. The signals of the H2, H4, and H8 protons in free quinoline appear at 8.81 (doublet of doublets), 8.0, and 8.05 ppm (overlapping doublets) respectively. These are the three protons most affected by steric (H8, H2) and electronic (H2, H4) effects upon platination (Table I). In the cisplatin adduct of chloroquine, a substituted quinoline, the H8 proton is shifted downfield by 1.73 ppm.[25] The weak Pt–H–C interactions of axially positioned hydrogens have been a subject of recent study with a series of substituted quinolines.[26] In all the quinoline complexes described here the H8 and H2 protons undergo downfield shifts of 1.3–1.5 and 0.4–0.8 ppm, respectively. The electronic effect of Pt binding is further reflected in a deshielding of the H4 protons by 0.5–1 ppm. In the isomeric pair of $[PtCl_2(Me_2SO)(quin)]$ the protons of the cis isomer are shifted more downfield than those of the trans isomer. No J(Pt–H) coupling was observed for H8 at the field strength of 250 MHz. A value of $^3J(^{195}Pt-^1H)$ of 24.6 Hz is obtained for the H2 proton of *trans*-$[PtCl_2(Me_2SO)(quin)]$. This value is within the range observed for other quinoline species.[26] The sharp signals observed for all sulfoxide and quinoline protons indicate that there is no restricted rotation in these molecules, even with the asymmetric sulfoxides. In *cis*-$[PtCl_2(Me_2SO)(quin)]$, the furthest downfield resonance is the quinoline H2 proton, as

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Table IV. Cytotoxicity of Trans Platinum(III) Complexes in L1210 Leukemia Cells[a]

complex	ID_{50}, μM		
	L1210/0	L1210/DDP	L1210/dach
cis-$[PtCl_2(py)_2]$	4.36	3.3 (0.76)[b]	2.89 (0.66)
trans-$[PtCl_2(py)_2]$	1.2	1.1 (0.92)	2.26 (1.88)
cis-$[PtCl_2(Tz)_2]$	2.8	7.34 (2.62)	5.62 (2.01)
trans-$[PtCl_2(Tz)_2]$	1.6	7.4 (4.63)	5.96 (3.73)
cis-$[PtCl_2(N\text{-MeIm})_2]$	8.77	>23.36 (>2.66)	>23.36 (>2.66)
trans-$[PtCl_2(N\text{-MeIm})_2]$	6.00	5.45 (0.91)	5.34 (0.89)
cis-$[PtCl_2(Me_2SO)(quin)]$	0.70	5.08 (7.25)	7.82 (11.2)
trans-$[PtCl_2(Me_2SO)(quin)]$	0.36	0.38 (1.06)	0.39 (1.08)
trans-$[PtCl_2(MePhSO)(quin)]$	3.5	2.4 (0.69)	1.33 (0.38)
trans-$[PtCl_2(MeBzSO)(quin)]$	0.67	0.99 (1.48)	0.90 (1.34)
cis-$[PtCl_2(NH_3)(quin)]$	0.48	2.75 (5.73)	3.00 (6.25)
trans-$[PtCl_2(NH_3)(quin)]$	0.51	1.35 (2.65)	0.96 (1.88)
cis-$[PtCl_2(NH_3)_2]$	0.33	9.22 (28)	1.81 (5.48)
trans-$[PtCl_2(NH_3)_2]$	15.7	22.0 (1.40)	19.6 (1.25)
$[Pt(R,R\text{-dach})SO_4]$	0.23	0.75 (3.26)	5.65 (25)

[a] All complexes in 0.5% DMF except *cis*-$[Pt(NH_3)_2Cl_2]$ and $[Pt(R,R\text{-dach})SO_4]$ which were in saline. Assays were run according to ref 39. All values are averages of at least three independent experiments. [b] Resistance factor, defined as ID_{50} (resistant)/ID_{50} (sensitive), is given in parentheses.

evidenced by the Pt–H2 coupling. The trans–cis isomerization of $[PtCl_2(Me_2SO)(quin)]$ is solvent dependent. Rapid isomerization is observed in d_6-Me_2SO but in DMF-d_7 no change in the ^1H NMR spectrum of *trans*-$[PtCl_2(Me_2SO)(quin)]$ was observed over the temperature range 28–118 °C or with time at 37 °C.

The infrared spectra of this series of complexes were as expected. ν(S–O) ranges from 1115 to 1145 cm^{-1} and is increased from the respective free sulfoxide. All trans complexes show sharp bands for ν(Pt–Cl) ranging from 335 to 340 cm^{-1}. The asymmetric and symmetric stretches for ν(Pt–Cl) are resolved in *cis*-$[PtCl_2(Me_2SO)(quin)]$ at 340 and 310 cm^{-1}.

The detailed chemical and spectroscopic properties of the series $[PtCl_2(R'R''SO)(quin)]$ will be the subject of a further report—here we wish to establish the general utility of planar ligands in producing biologically active trans-platinum complexes.

$[PtCl_2(NH_3)(quinoline)]$. Reaction of amine with $K[PtCl_3(NH_3)]$ gives the *cis*-$[PtCl_2(NH_3)(amine)]$ product. The trans effect of Cl^- ensures that the incoming amine will be cis to the NH_3.[27]

Because of the similar trans effects of amines such as py and NH_3, general methods for the synthesis of mixed amine complexes in the trans configuration, *trans*-$[PtCl_2(L)(L')]$, are not common. One route is the displacement of NH_3 trans to Cl in the reaction

$$cis\text{-}[PtCl(NH_3)_2(amine)]^+ + HCl \rightarrow trans\text{-}[PtCl_2(NH_3)(amine)]$$

This scheme has been reported for amine = 1-methylcytosine[28] and 4-bromopyridine.[29] However, while this method is the most obvious, it is not necessarily the most general one because of the necessity to displace the relatively inert NH_3 and the reaction times involved. Possible side reactions of *cis*-$[PtCl(NH_3)_2(amine)]^+$ include protonation of a labile amine to produce *cis*-$[PtCl_2(NH_3)_2]$.[27] Further, the preparation of *cis*-$[PtCl(NH_3)_2(amine)]^+$ by selective displacement of one chloride from *cis*-$[PtCl_2(NH_3)_2]$ is not always straightforward because of the formation of side products involving displacement of both chlorides. To overcome these disadvantages we studied the formation of *trans*-$[PtCl_2(NH_3)(L')]$ from $[Pt(NH_3)_2(L')_2]^{2+}$. The latter cation is easily prepared by the reaction

$$cis\text{-}[PtCl_2(NH_3)_2] + \text{excess } L' \rightarrow cis\text{-}[Pt(NH_3)_2(L')_2]Cl_2$$

Treatment with HCl gives the desired product. Using this scheme, it is not necessary to isolate the intermediate tetrakis(amine) species because whichever amine is displaced first the trans effect of chloride guarantees the desired final product

$$cis\text{-}[Pt(NH_3)_2(L')_2]Cl_2 + HCl \rightarrow trans\text{-}[PtCl_2(NH_3)(L')]$$

The spectral data for $[PtCl_2(NH_3)(quinoline)]$ are consistent with their structural assignments. The ^{195}Pt NMR chemical shifts are indicative of $[PtCl_2(amine)_2]$ coordination spheres.[14] In both complexes the chemical shift of the H8 proton is shifted to lowest field, while the H8 proton of *cis*-$[PtCl_2(NH_3)(quin)]$ is downfield from that of the trans isomer. No Pt–H coupling is seen for this proton. The value of $^3J(^{195}Pt\text{–}^1H)$ for the H2 proton is greater for the cis isomer than for the trans isomer (44 and 35 Hz, respectively).

Cytotoxicity Studies. The cytotoxicity of all complexes was studied in murine L1210 leukemia cells sensitive to cisplatin and resistant to either cisplatin or the complex with 1,2-diaminocyclohexane, $[Pt(R,R\text{-dach})SO_4]$.[39]

The results confirm the generality of activation of the trans geometry by use of bulky planar ligands (Table IV). Thus, in L1210/0 (sensitive to cisplatin), all pairs of cis/trans isomers to $[PtCl_2(L')(L'')]$ series where L' = L'' show at least equivalent cytotoxicity in distinct contrast to $[PtCl_2(NH_3)_2]$. There is in general an approximate order of magnitude increase in cytotoxicity for all trans complexes in comparison to *trans*-$[PtCl_2(NH_3)_2]$. In the $[PtCl_2(R'R''SO)(quin)]$ series, the activity is dependent on the nature of R'R''SO and for Me_2SO and MeBzSO the complexes are as equipotent as cisplatin itself. It is of interest to note that in the series $[PtCl(R'R''SO)(diamine)]^+$ the highest antitumor activity is found with more labile sulfoxides.[30] In the present case the more inert sulfoxides such as Me_2SO and MeBzSO give the most toxic compounds. In the cationic series the adducts are similar to that of cisplatin with loss of sulfoxide.[31] The advantage of inert sulfoxides in the trans series implies that, at least initially, it is advantageous to maintain the Pt–R'R''SO bond. Finally, for the cis/trans pair of $[PtCl_2(NH_3)(quin)]$ both isomers show equivalent cytotoxicity, again similar to that of cisplatin. In this case, we may note the remarkable increase in cytotoxicity of trans complexes caused by a simple substitution of NH_3 by quinoline.

Examination of the results in the cisplatin resistant line, L1210/DDP, is instructive. For all series, the activity is characterized by remarkably low resistance factors with the values of ID_{50} in some cases at least equivalent to the corresponding value in the sensitive cell line (see *trans*-$[PtCl_2(R'R''SO)(quin)]$ and *trans*-$[PtCl_2(py)_2]$). Thus, the general feature of a trans complex with a bulky planar ligand gives complexes with no cross resistance to cisplatin—the trans complexes are active in cisplatin-resistant cells. Similarly, the trans complexes are also non-cross-resistant to $[Pt(R,R\text{-dach})SO_4]$.

By definition, trans complexes must act by a different molecular mechanism to that of cisplatin. The persistence of cytotoxicity in cisplatin-resistant cells and independent analysis using the

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COMPARE program of NCI support this contention.[32] The factors which affect cytotoxicity and cellular resistance to cisplatin include altered uptake, altered reactivity of endogenous thiols such as glutathione and metallothionein, and altered rates of DNA repair.[33,34] Any or all of the factors could be affected by the structural modifications we have made on the basic $[PtCl_2(NH_3)_2]$ structure. The complex *trans*-$[PtCl_2(py)_2]$ inhibits intracellular DNS synthesis (as measured by the incorporation of labelled thymidine),[35] and thus a role for DNA binding is implicated in the mechanism of action. This is noteworthy in view of the absence of H-bond donor ligands in this complex. The presence of a H-bonding group such as NH_3 has been hitherto considered a necessary feature for DNA binding and antitumor activity. Differential DNA repair is implicated as a mechanism of cisplatin resistance in both the L1210 lines studied here[36] and in a range of human tumor cell lines rendered resistant to cisplatin.[33,34] It is appealing to consider that the reason for activity in cisplatin-resistant cells also lies at the DNA level. The sequence specificity of *trans*-$[PtCl_2(NH_3)_2]$ is somewhat different to cisplatin with increased binding to –GC– sites.[37,38] The presence of planar ligands may accentuate this difference with subsequent effects on adduct structure and conformational changes. Other possible contributions to overcoming cisplatin resistance include differential reactivity with endogenous S-donors such as glutathione.

With respect to altered modes of DNA binding, it is relevant that bis(platinum) complexes of general formula $[\{PtCl_m(NH_3)_{3-m}\}_2(\text{diamine})]^{2(2-m)+}$ (m = usually 1 or 2 and where diamine is $H_2N(CH_2)_nNH_2$) are also highly active in cisplatin-resistant lines in both murine and human tumor cell lines.[39,40] We have shown in related studies that these complexes induce a different array of lesions in comparison to cisplatin.[41,42] Altered modes of DNA binding may be inherently more cytotoxic or may be more difficult to repair than the lesions induced by cisplatin. The complexes discussed here are also examples of a structural class capable of molecular interactions not accessible to cisplatin. Indeed the structures are not expected to produce cytotoxicity of the order shown. Indeed, with respect to the original structure-activity relationships for cisplatin, there is now a compelling body of evidence that these relationships are limited in scope. Although the neutral *cis*-$[PtCl_2(\text{amine})_2]$ structure gives highly antitumor active compounds, useful antitumor activity has also been demonstrated in cationic complexes[29,30] and bis(platinum) complexes with monodentate coordination spheres[41] as well as the enhancement of cytotoxicity in trans complexes we report here.

Two principal questions arising from this work are why the presence of a planar ligand makes such a dramatic difference to cytotoxicity in comparison to *trans*-$[PtCl_2(NH_3)_2]$ and how to improve in vivo antitumor activity. Both these aspects are under investigation. The new complexes discussed here are also being surveyed for in vivo activity. Preliminary in vivo studies indicated that *trans*-$[PtCl_2(py)_2]$ was inactive in both L1210 and P388 leukemia.[2] These disappointing results could be due to pharmacokinetic factors such as considerably reduced water solubility or metabolic deactivation. The demonstration of a general method to increase cytotoxicity of trans complexes in cells, especially cisplatin-resistant cells, commonly used for mechanistic work is of considerable significance. The potential for biological activation of trans-platinum compounds needs to be explored to delineate fully the validity of the standard structure–activity relationships for platinum antitumor complexes.

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Supplementary Material Available: Tables of crystallographic data (Table SI), anisotropic displacement coefficients (Table SII), H-atom coordinates (Table SIII), bond lengths and angles (Table SV), and weighted least-squares planes (Table SVI) and a packing diagram for *trans*-dichlorobis(thiazole)platinum(II) (Figure S1) (4 pages); a complete list of observed and calculated structure factors (Table SIV) (5 pages). Ordering information is given on any current masthead page.

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