By either the pre- or postamputation schedules, both morpholinomethyl analogues inhibited metastases but *cis-syn-trans*-**4** was the more effective stereoisomer. Furthermore, in this study **4** significantly increased life span when employed in the postamputation schedule. Since the reverse stereoselective activity was observed for **1** and **2** when B16-F10 melanoma cells were pretreated in vitro, it may be that **4** is not primarily exerting its action following metabolic transformation to **2** but rather exhibits intrinsic antineoplastic properties possibly reflecting macromolecular alkylation by a compound possessing an appropriate geometry different from that required for the parent antimetastatic bis(dioxopiperazines).[1-4,7] This possibility requires further research, however, since morpholinomethyl derivatives are predictably unstable and undergo hydrolysis to the parent dioxopiperazines.[8]

To further investigate this effect, we compared the morpholinomethyl geometric isomers (**3** and **4**) with the parent compounds (**1** and **2**), using the postamputation schedule. Results are summarized in Table II. Again, the cis morpholinomethyl analogue **4** was the most effective inhibitor of metastasis and provided the greatest number of 50-day survivors. However, in this study the trans morpholinomethyl analogue **3** also exhibited significant activity, which was clearly better than that observed for parent trans-**1**. Interestingly, parent *cis*-**2** provided for a significant increase in life span of treated mice. Thus, the stereoselective effect in the LL model was reversed from that observed in the B16-F10 study.[4] These results are not in agreement with sructure–activity interpretations based on X-ray diffraction analyses of **1** and **2**.[7] Increased activity observed for the morpholinomethyl derivatives may reflect differences in solubility and delivery (prodrug) or an intrinsic antitumor activity of the morpholinomethyl–N functionality.

Experimental Section

All melting points are uncorrected and were taken on a Thomas-Hoover capillary melting point apparatus. Analyses were obtained from Galbraith Laboratories Inc., Knoxville, TN.

2,11-Bis(morpholinomethyl)-*trans*-tetrahydrodipyrazino[1,2-*a*:2′,1′-*c*]pyrazine-1,3,10,12(2*H*,4*H*,9*H*,11*H*)-tetrone (3). To a suspension of *trans-anti-trans*-**1**[4] (2.5 g, 9.9 × 10^{-3} mol) in 25 mL of Me_2SO was added 3 mL of morpholine and 3 mL of 37% HCHO. The mixture was heated at 55 °C for 5 h and the Me_2SO removed under reduced pressure. The residue was triturated with 20 mL of cold EtOH and the white solid filtered, washed with 20 mL of EtOH, and dried, affording 3.29 g (71.7%) of crystals, mp 216–218 °C. Anal. C, H, N.

2,11-Bis(morpholinomethyl)-*cis*-tetrahydrodipyrazino[1,2-*a*:2′,1′-*c*]pyrazine-1,3,10,12(2*H*,4*H*,9*H*,11*H*)-tetrone (4). This was prepared from *cis-syn-trans*-**2**[4] accordingg to the preparation of **3** from **1**, affording 3.4 g (76%) of white crystals, mp 212–214 °C. Anal. C, H, N.

Registry No. **1**, 79751-02-3; **2**, 79744-15-3; **3**, 96728-95-9; **4**, 96728-96-0; morpholine, 110-91-8.

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Activity of Platinum(II) Intercalating Agents against Murine Leukemia L1210

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Four series of intercalating, square-planar Pt(II) complexes derived from the ligands 2,2′-bipyridine, 2,2′:6′,2″-terpyridine, 1,10-phenanthroline, and 3,4,7,8-tetramethyl-1,10-phenanthroline were synthesized and aspects of their activity against murine leukemia L1210 cells investigated. The 2,2′:6′,2″-terpyridine–thiolato complexes are growth inhibitory in culture, with IC_{50} values in the range 6–32 μM, and cause cell lysis at high concentrations. Of the remaining three series, the 2,2′-bipyridine complexes are the least potent in their effects. There is a general enhancement in activity on moving from the 1,10-phenanthroline complexes to the 3,4,7,8-tetramethyl-1,10-phenanthroline analogues. Flow cytometric analysis on representative complexes shows that they are not cell cycle specific. Alkaline elution experiments indicate no damage to DNA of cells exposed to (thiophenolato)(2,2′:6′,2″-terpyridine)platinum(II) chloride monohydrate (**2a**) and (ethylenediamine)(1,10-phenanthroline)platinum(II) dichloride dihydrate (**5a**) although (ethylenediamine)(3,4,7,8-tetramethyl-1,10-phenanthroline)platinum(II) dichloride dihydrate (**6a**) causes both single-strand breaks and DNA cross-links. Compounds **2a**, **5a**, and **6a** showed no antitumor activity against L1210 in mice.

There are numerous antitumor agents capable of intercalative binding to DNA,[1] and an intercalating moiety is a structural feature of many naturally occurring, clinically useful drugs such as dactinomycin, adriamycin, ellipticine, bleomycin, and their analogues.[2] This observation can be exploited in the design of new antitumor agents. For example, starting with the intercalating chromophore, 9-aminoacridine, Cain and his colleagues have synthesized a large number of derivatives,[3] one of which, 4′-(9-acridinylamino)methanesulfon-*m*-aniside (amsacrine) (**1**), is a potent antitumor agent effective against both acute nonlymphoblastic leukemia and acute lymphoblastic leukemia.[4]

Although metallointercalators derived from 1,10-phenanthroline, 2,2′-bipyridine, 2,2′:6′,2″-terpyridine, and

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Table I. Chemical and Biological Data on (2,2′-Bipyridine)-, (2,2′:6′,2″-Terpyridine)-, (1,10-Phenanthroline)-, and (3,4,7,8-Tetramethyl-1,10-phenanthroline)platinum(II) Complexes

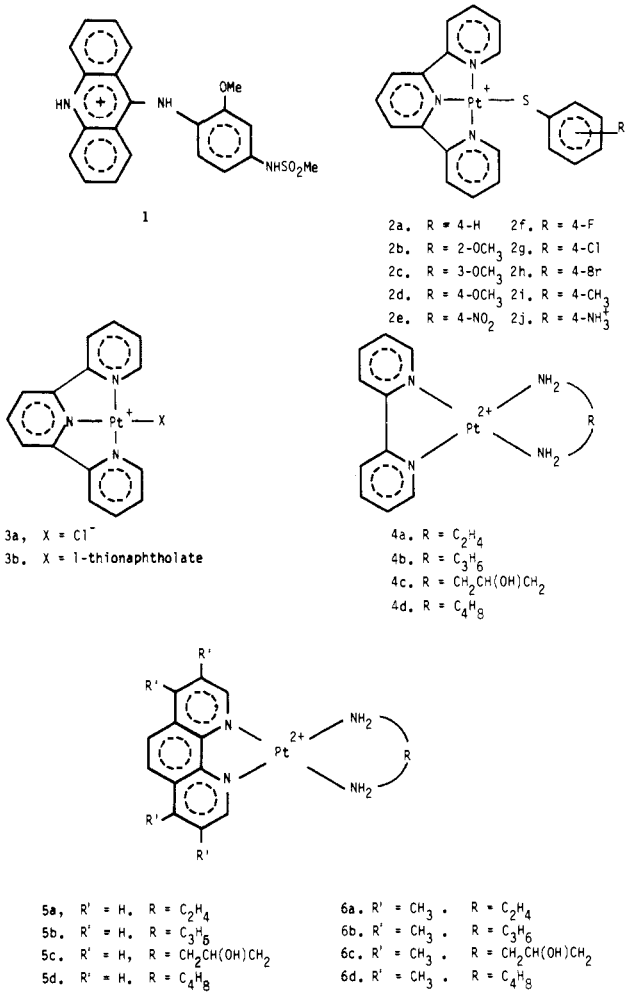
no.	R	formula	anal.[a]	growth Inhibn of L1210 in culture, IC_{50}, μM
2a	H	$C_{21}H_{16}N_3ClPtS·H_2O$	CHNClS	6
2b	2-OCH_3	$C_{22}H_{18}N_3ClOPtS·3H_2O$	CHNClS	10
2c	3-OCH_3	$C_{22}H_{18}N_3ClOPtS·2H_2O$	CHNClS	4
2d	4-OCH_3	$C_{22}H_{18}N_3ClOPtS·3H_2O$	CHNClS	9
2e	4-NO_2	$C_{21}H_{15}N_4ClO_2PtS·2H_2O$	CHNClS	13
2f	4-F	$C_{21}H_{15}N_3FClPtS·3H_2O$	CHNClS	13
2g	4-Cl	$C_{21}H_{15}N_3Cl_2PtS·3H_2O$	CHNClS	9
2h	4-Br	$C_{21}H_{15}N_3BrClPtS·2H_2O$	CHNBrS	9
2i	4-CH_3	$C_{22}H_{18}N_3ClPtS·2H_2O$	CHNClS	12
2j	4-NH_3^+	$C_{21}H_{18}N_4Cl_2PtS·2H_2O$	CHNClS	32
3a	x = Cl^-	$C_{15}H_{11}N_3Cl_2Pt·3H_2O$		450
3b	x = 1-thionaphtholate	$C_{25}H_{18}N_3ClPtS·2H_2O$	CHNClS	5
4a	C_2H_4	$C_{12}H_{16}N_4Cl_2Pt·2H_2O$		33
4b	C_3H_6	$C_{13}H_{18}N_4Cl_2Pt·0.5H_2O$	CHNCl	9
4c	$CH_2CH(OH)CH_2$	$C_{13}H_{18}N_4Cl_2OPt$	CHNCl	43
4d	C_4H_8	$C_{14}H_{20}N_4Cl_2Pt$	CHNCl	>500
5a	C_2H_4	$C_{14}H_{16}N_4Cl_2Pt·2H_2O$		2
5b	C_3H_6	$C_{15}H_{18}N_4Cl_2Pt·2H_2O$	CHNCl	14
5c	$CH_2CH(OH)CH_2$	$C_{15}H_{18}N_4Cl_2OPt$	CHNCl	11
5d	C_4H_8	$C_{16}H_{20}N_4Cl_2Pt·H_2O$	CHNCl	110
6a	C_2H_4	$C_{18}H_{24}N_4Cl_2Pt·2H_2O$	CHNCl	0.7
6b	C_3H_6	$C_{19}H_{26}N_4Cl_2Pt·H_2O$	CHN	1
6c	$CH_2CH(OH)CH_2$	$C_{19}H_{26}N_4Cl_2OPt·2H_2O$	CHN	5
6d	C_4H_8	$C_{20}H_{28}N_4Cl_2Pt$	CHN	50
$[Pt(phen)_2]Cl_2·3H_2O$		$C_{24}H_{16}N_4Cl_2Pt·3H_2O$		23

[a] Analyses for the elements as indicated were all within ±0.4% of the calculated values. A satisfactory analysis for C, H, N, and Cl was also obtained for $Pt(Me_4phen)Cl_2$.

porphyrin ligands have been reported,[5,6] their biological properties have not been investigated. Accordingly, we have prepared four series of square-planar platinum(II) complexes derived from 2,2′:6′,2″-terpyridine (**2a–j**, **3a–b**), 2,2′-bipyridine, (**4a–d**), 1,10-phenanthroline (**5a–d**), and 3,4,7,8-tetramethyl-1,10-phenanthroline (**6a–d**), and for each compound we have examined its growth inhibition effects against L1210 murine leukemia cells in culture. For selected compounds interaction with isolated and intracellular DNA has been studied and antitumor activity assessed against L1210 leukemia in mice. Impetus to this study is provided by the structural parallels that exist between the terpyridine series (**2a–j**) and amsacrine (**1**).

Chemistry. All of the complexes listed in Table I were isolated with chloride as counterion. This gives solids of generally good water solubility and also avoids the presence of anions that might themselves inhibit cell growth. The 1,10-phenanthroline complexes (**5a–d**) were prepared by reaction between $Pt(phen)Cl_2$[7] and the appropriate diamine in either water or DMF as solvent. The 2,2′-bipyridine complexes (**4a–d**) and the 3,4,7,8-tetramethyl-1,10-phenanthroline complexes (**6a–d**) were obtained in the same way, starting from either $Pt(bpy)Cl_2$[8] or (3,4,7,8-tetramethyl-1,10-phenanthroline)platinum(II) dichloride ($Pt(Me_4phen)Cl_2$), respectively. The compound $Pt(Me_4phen)Cl_2$ was prepared by reaction between the phenanthroline ligand and K_2PtCl_4 in Me_2SO–water. The thiolato complexes, **2a–i** and **3b**, were prepared by reaction between a suspension of $[Pt(terpy)Cl]Cl·2H_2O$[9] (**3a**) and a solution of the appropriate thiol in ethanol–water, under an atmosphere of nitrogen. The rate of dissolution of the suspended $[Pt(terpy)Cl]Cl·2H_2O$ to yield the product

Chart I



complex could be greatly enhanced by the addition of sufficient base to account for the proton release associated

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with coordination of the thiol. The complex [Pt(terpy)-$SC_6H_4NH_3$]$Cl_2 \cdot 2H_2O$ (**2j**) was obtained in a similar way using 4-ammoniothiophenol hydrochloride as a source of the thiol, in water as solvent. Protonation of the amino nitrogen in this complex is confirmed by its ^{13}C NMR spectrum[10] and elemental analysis.

Results and Discussion

Viscosity measurements with sonicated DNA have been used to establish intercalative binding to DNA by [Pt-(terpy)SC_6H_5]$Cl \cdot H_2O$ (**2a**),[11] [Pt(en)(Me_4phen)]$Cl_2 \cdot 2H_2O$ (**6a**), and the structurally related [Pt(phen)$_2$]$Cl_2 \cdot 3H_2O$.[12] Intercalative binding to DNA by [Pt(bpy)(en)]$Cl_2 \cdot 2H_2O$ (**4a**) and [Pt(en)(phen)]$Cl_2 \cdot 2H_2O$ (**5a**) has been previously established by demonstrating unwinding of covalently closed circular duplex DNA.[13]

Compounds were assayed for their ability to inhibit the growth of L1210 cells in culture. Cells were incubated with complex for a period of 48 h, and the IC_{50} concentration (the concentration required to inhibit the growth of cells by 50%) of each compound is given in Table I. For the terpyridine complexes the replacement of the coordinated chloride of **3a** by an aromatic thiol, **2a–j** and **3b**, leads to a considerable enhancement in activity. The terpyridine–thiolato complexes exert their effects rapidly since the IC_{50} for **2a** for a 2-h pulse (2-h exposure to drug followed by 48-h incubation) is the same, 6 μM, as that observed for continuous 48-h exposure. For the range of thiolato complexes at high concentration ($10IC_{50}$), final cell numbers are lower than the initial inoculum and microscopic examination reveals extensive cell lysis. Of the remaining three series the bipyridine complexes are the least potent, **4d** showing growth inhibition of only 20% at 500 μM and inhibition not exceeding 60% with **4a** and **4c** up to 300 μM. The 1,10-phenanthroline complexes appear to be cytostatic: the IC_{50} for a 2-h pulse of **5a** of 1000 μM is some 500-fold greater than that for continuous exposure for 48 h. Moreover, for continuous exposure at high drug doses for this and the other 1,10-phenanthroline complexes there is at least one doubling in cell number and no evidence of cell lysis. The same effects are observed for the 3,4,7,8-tetramethyl-1,10-phenanthroline complexes apart from **6a** where no intact cells remain at high concentrations ($10IC_{50}$). The IC_{50} value of 23 μM for [Pt(phen)$_2$]$Cl_2 \cdot 3H_2O$ indicates that replacement of the diamine ligand of **5a** by the far bulkier phenanthroline group has little effect on activity.

The free heterocyclic ligands, none of which are capable of intercalative binding at physiological pH,[12] are also growth inhibitory in the test system with the following IC_{50} values: 2,2′-bipyridine, 48 μM; 2,2′:6′,2″-terpyridine, 2.0 μM; 1,10-phenanthroline, 5 μM; 3,4,7,8-tetramethyl-1,10-phenanthroline, 1.5 μM. In the case of 2,2′:6′,2″-terpyridine the presence of equimolar amounts of thiophenol had no effect on the IC_{50} value. Similarly, the IC_{50} values of 2,2′-bipyridine, 1,10-phenanthroline, and 3,4,7,8-tetramethyl-1,10-phenanthroline were not influenced by the presence of equimolar amounts of ethylenediamine. The observation of growth inhibition of mammalian cells by chelating agents such as 1,10-phenanthroline is well documented.[14] The activity of the free ligands here may be due to their ability to induce metal-deficient states or to the formation of metal complexes that themselves are growth inhibitory.

Flow cytometric analysis of the DNA distributions of cells incubated with drug for 48 h at concentrations corresponding to $0.5IC_{50}$, IC_{50}, and $5IC_{50}$ indicates that the parental member of each series **2a**, **4a**, **5a**, and **6a** does not cause significant perturbation to the fraction of cells in $G_1 + G_0$, S, and G_2 + M phases of the cell cycle when compared to control populations. The mean phase fraction estimates for the five control populations were as follows: $G_0 + G_1$ = 44.2% (CV range 6.7–7.8); S, 37.2%; G_2 + M, 18.6%.

The alkaline elution technique[15] was used to assay for intracellular DNA damage by **2a**, **5a**, and **6a**. For both **2a** (100 μM complex concentration, 2- and 16-h exposure) and **5a** (1000 μM complex concentration, 2- and 16-h exposure) there was no evidence of single-strand breaks, interstrand cross-links, or protein–DNA linkages.[12] In the case of **6a** (100 μM complex concentration, 2-h exposure) both single-strand breaks and DNA interstrand cross-links were observed.[12] The possibility of intrastrand cross-linking cannot be detected by this technique.

The antitumor activity of **2a**, **5a**, and **6a** against L1210 in mice was investigated in a stringent assay in which the tumor was injected intraperitoneally on day 0 and the complex given over 5 days commencing on day 3. None of the complexes showed significant activity. In nontumor-bearing animals complex **2a** was toxic at a dose level of 5 mg/kg per day, with no mice surviving past day 9, whereas the phenanthroline complexes at the same dose caused no signs of toxicity up to day 16 when the mice were sacrificed.

It is apparent that despite their structural similarities the (terpyridine)-, (1,10-phenanthroline)-, and (3,4,7,8-tetramethyl-1,10-phenanthroline)platinum(II) complexes exert their biological effects in different ways. Moreover, there may well be a different mechanism of action when ligands and the corresponding complexes are compared. For instance, although 1,10-phenanthroline itself significantly alters distribution of cells in the cell cycle,[14] the phenanthroline complexes examined here do not. It is also worth noting that even though the cell cycle effects of *cis*-DDP[17] and the metallointercalators are similar, the structures of the latter agents are such that is unlikely they could react with intracellular amines to generate *cis*-DDP analogues.

The wide range of growth inhibitory properties observed within each series and the general enhancement in activity on moving from the 1,10-phenanthroline complexes to the 3,4,7,8-tetramethyl-1,10-phenanthroline analogues indicate that it is worth exploring the effects of both further changes to the phenanthroline moiety and more substantial alterations to the structure of the coordinated amine or thiol. Although no agent tested here showed antitumor activity against L1210 in mice, screening against other tumor models may be warranted.

Experimental Section

Chemistry. The data from NMR, UV, and IR spectra confirm the structures of the complexes as depicted. NMR spectra were obtained with a Jeol FX-200 NMR spectrometer. UV spectra were recorded on a Varian Cary 219 spectrophotometer. IR spectra were recorded on a Pye Unicam Model SP 1100 IR

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spectrophotometer. Microanalyses were performed by the Australian Microanalytical Service, Port Melbourne, Australis.

The following complexes were prepared as previously described: $[Pt(en)(phen)]Cl_2 \cdot 3H_2O$,[7] $[Pt(phen)_2]Cl_2 \cdot 3H_2O$,[7] $Pt(phen)Cl_2$,[7] $Pt(bpy)Cl_2$,[8] $[Pt(bpy)(en)]Cl_2 \cdot 2H_2O$ (**4a**),[8] $[Pt(terpy)Cl]Cl_2 \cdot 2H_2O$ (**3a**).[9]

Dichloro(3,4,7,8-tetramethyl-1,10-phenanthroline)platinum(II). A hot solution of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.08 g, 0.34 mmol) in 10 mL of Me_2SO was added to a hot solution of K_2PtCl_4 (0.140 g, 0.34 mmol) in 1 mL of water and 3 mL of Me_2SO. On cooling, fine yellow needles crystallized. These were collected, washed with Me_2SO and then acetone, and dried under vacuum at 100 °C for 2 h; yield 71%.

(1,3-Diamino-2-hydroxypropane)(1,10-phenanthroline)platinum(II) Dichloride (5c). A suspension of $Pt(phen)Cl_2$ (0.1 g, 0.22 mmol) and 1,3-diamino-2-hydroxypropane (0.078 g, 0.44 mmol) in 12 mL of DMF was stirred at 100 °C for 2 h during which time the starting complex was replaced by a pale yellow solid. The product was collected, washed with DMF and then acetone, and dried under vacuum at 100 °C for 2 h; yield 85%.

(Ethylenediamine)(3,4,7,8-tetramethyl-1,10-phenanthroline)platinum(II) Dichloride Dihydrate (6a). $Pt(Me_4phen)Cl_2$ (0.10 g, 0.2 mmol) and ethylenediamine (0.096 g, 1.6 mmol) were refluxed together in 20 mL of water until all the complex had dissolved to yield a pale yellow solution. The solution was concentrated to 3 mL, and then 6 mL of chilled 1 M HCl was added, which caused the product to precipitate as pale yellow crystals. The reaction mixture was cooled at 4 °C for 3 h, and then the product was collected, washed sparingly with chilled 1 M HCl and then acetone, and dried under vacuum at room temperature; yield 87%.

The remainder of the phenanthroline complexes listed in Table I were prepared by the same general method except that **5b** and **5d** were precipitated by addition of saturated aqueous NaCl and **6c** was precipitated by addition of acetone.

(2,2'-Bipyridine)(1,3-diamino-2-hydroxypropane)platinum(II) Dichloride (4c). A solution of 1,3-diamino-2-hydroxypropane (0.066 g, 0.73 mmol) in 6 mL of DMF was added to a hot solution of $Pt(bpy)Cl_2$ (0.150 g, 0.36 mmol) in 30 mL of DMF. The product quickly separated as a yellow solid, which was collected and dissolved in a minimum quantity of hot methanol. Slow addition of excess acetone to this solution caused the separation of yellow crystals that were collected, washed with acetone, and dried under vacuum at 100 °C for 2 h; yield 53%.

The bipyridine complex **4d** was prepared in the same way whereas **4b** was prepared by using the same procedure as reported for **4a**.[8]

(Thiophenolato)(2,2':6',2''-terpyridine)platinum(II) Chloride Monohydrate (2a). Thiophenol (0.093 g, 0.84 mmol) was added under nitrogen to a stirred suspension of **3a** (0.30 g, 0.56 mmol) in 35 mL of 95% v/v EtOH–H_2O. The $[Pt(terpy)Cl]Cl \cdot 2H_2O$ (**3a**) began to slowly dissolve to yield a purple solution. Methanolic tetraethylammonium hydroxide (1.52 μM, 368 μL, 0.56 mmol) was then added whereupon the remaining suspended $[Pt(terpy)Cl]Cl \cdot 2H_2O$ (**3a**) was rapidly replaced by a purple solid. The reaction mixture was stirred for a further 1 h under nitrogen. Subsequent operations were performed in air. Ethanol (25 mL) was then added and the reaction vessel gently warmed. The resultant solution was filtered and the product precipitated by slow addition of 50 mL of diethyl ether.

The reaction mixture was cooled at 4 °C for 1 h, and then the product was collected, washed with a small amount of 1:1 v/v EtOH–Et_2O, and dried under vacuum at room temperature; yield 85%.

(4-Ammoniothiophenolato)(2,2':6',2''-terpyridine)platinum(II) Dichloride Dihydrate (2j). A solution of **3a** (0.128 g, 0.24 mmol) in 6 mL of water was flushed with nitrogen, and then 4-ammoniothiophenol hydrochloride (0.077 g, 0.48 mmol) was added. Immediately the solution color changed from orange to intense red. Methanolic tetraethylammonium hydroxide (1.52 μM, 157 μL, 0.24 mmol) was then added. The solution was filtered in air and the product precipitated as red-purple crystals by the slow addition of 30 mL of acetone. The product was collected by filtration and washed with acetone and then while still wet with the wash liquid placed in a desiccator and dried under vacuum for 2 h; yield 78%. If allowed to stand in air while still wet, the complex is hygroscopic. However, once dry, it is stable in air.

The remainder of the terpyridine complexes listed in Table I were prepared by the same general procedure used for **2a** except that in the case of **2e**, **2f**, **2g**, and **2h** the solid formed after the addition of base was brought into solution using DMF.

Growth Inhibition of L1210 Cells in Vitro. L1210 cells in in vitro culture were obtained from the Ludwig Institute, Sydney, Australia, and grown in Minimum Essential Medium (Flow Laboratories, USA) supplemented with 15% fetal calf serum, glutamine (2 mM), and gentamycin (2 mg/100 mL). Cells were incubated without agitation in a 5% O_2–10% CO_2 atmosphere at 37 °C, and under those conditions the average doubling time was approximately 12 h. Drugs were diluted as required in sterile water, and then 40 μL of drug solution was dispensed into 2 mL of medium containing 5×10^4 cells/mL. Control cultures received 40 μL of sterile distilled water. After incubation at 37 °C for 48 h, cells were counted on a Coulter counter (Model ZM, Coulter Electronics Ltd., England). Cell growth as a percentage of control was plotted vs. drug concentration and the IC_{50} value determined. Each IC_{50} value quoted is the mean of at least two determinations.

Flow Cytometric DNA Analysis. The cells used in flow cytometric DNA analysis were incubated for 48 h with the appropriate complex at concentrations corresponding to $0.5IC_{50}$, IC_{50}, and $5IC_{50}$ and were prepared for analysis by fixation with sodium citrate followed by staining with propidium iodide according to the procedure of Krishnan.[16] Control cell populations were treated the same way. DNA distributions were determined on an Ortho-Diagnostic Systems System 50H cytofluorograph. The distributions were analyzed on an Ortho Diagnostic Systems 2150 computer using the Quickestimate cell cycle analysis algorithm as described in the Model 2150 computer system, Operator Reference Manual, Ortho Diagnostic Systems Inc.

Antitumor Testing. For each compound tested, five groups each containing eight CDF_1 male mice bearing L1210 lymphoid leukemia were injected ip with the appropriate complex on a qd 3–7 regime, day 0 being the day of tumor implant. Dose levels were arranged to span the maximum tolerated dose previously estimated with nontumor-bearing animals. The maximum dose level tested was fixed at 400 mg/kg. L1210 leukemia maintained in mice was obtained from the New Zealand Cancer Research Laboratory. For experiments mice were inoculated with 1×10^6 cells ip. Drug concentrations in water were chosen so that the volume injected was 0.01 mL/g of body weight. An extra group of eight mice was used as a control, receiving the same volume of sterile water. *cis*-Platinum was used as a positive control compound.

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Registry No. **2a**, 96728-97-1; **2b**, 96728-98-2; **2c**, 96745-76-5; **2d**, 96728-99-3; **2e**, 96729-00-9; **2f**, 96729-01-0; **2g**, 96729-02-1; **2h**, 96729-03-2; **2i**, 96729-04-3; **2j**, 96729-06-5; **3a**, 60819-00-3; **3b**, 96729-07-6; **4a**, 34409-74-0; **4b**, 96729-08-7; **4c**, 96729-09-8; **4d**, 96729-10-1; **5a**, 96729-11-2; **5b**, 96729-12-3; **5c**, 96729-13-4; **5d**, 96729-14-5; **6a**, 96729-15-6; **6b**, 96729-16-7; **6c**, 96729-17-8; **6d**, 96729-18-9.

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