Cytotoxicity of 2,2′:6′,2″-Terpyridineplatinum(II) Complexes against Human Ovarian Carcinoma

Gordon Lowe,*,† Anne Sophie Droz,† Tirayut Vilaivan,† George W. Weaver,† Jenny J. Park,† Jonathan M. Pratt,† Lindsay Tweedale,† and Lloyd R. Kelland§

Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, U.K., and CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Block E, 15 Cotswold Road, Belmont, Sutton, Surrey SM2 5NG, U.K.

Received April 13, 1999

2,2′:6′,2″-Terpyridineplatinum(II) complexes are shown to possess cytotoxicity against a number of human ovarian tumor cell lines. Many of the complexes show similar activity against cisplatin- and doxorubicin-resistant cell lines as the parental cells suggesting that there is little or no cross-resistance with cisplatin or doxorubicin. The cytotoxicity of bis[2,2′:6′,2″-terpyridineplatinum(II)] complexes is strongly dependent on the nature of the linker. Bis[2,2′:6′,2″-terpyridineplatinum(II)] complexes with a flexible linker at the 4′-position show poor cytotoxicity; by contrast bis[2,2′:6′,2″-terpyridineplatinum(II)] complexes with rigid and short linkers at platinum(II) are strikingly effective. Several of the compounds show greater cytotoxicity against human ovarian cell lines than carboplatin, the therapeutic agent currently advocated for the treatment of human ovarian cancers.

Introduction

It has been known for more than 20 years that 2-hydroxyethanethiolato-2,2′:6′,2″-terpyridineplatinum(II) nitrate (**1**) (Chart 1) intercalates into DNA with a binding constant of 0.83×10^5 M^{-1}.[1] Recently we have shown that 4-picoline 2,2′:6′,2″-terpyridineplatinum(II) bis(tetrafluoroborate) (**2**, L = 4-Me-C_5H_4N) is a more potent intercalator of DNA ($K = 2 \times 10^7$ M^{-1}) and have ascribed this to the retention of the double positive charge on platinum.[2] In addition this complex platinates guanosine residues at N-7 in double-stranded DNA.[3] Moreover, in a polymerase termination assay we have shown that there is sequence selectivity of guanosine residues and that this is different from that of *cis*-diamminedichloroplatinum(II) (cisplatin).[4] In view of these observations, we have synthesized and investigated the in vitro cytotoxicity of a range of 2,2′:6′,2″-terpyridineplatinum(II) complexes against five human ovarian carcinoma cell lines. Synthesis of the 4′-substituted 2,2′:6′,2″-terpyridineplatinum(II) complexes was made possible by the development of a very mild and efficient method of platination.[5]

Results and Discussion

Synthesis of 4′-Substituted 2,2′:6′,2″-Terpyridines. The 4′-substituted 2,2′:6′,2″-terpyridines were synthesized by one of two strategies. The first was based on a one-pot Hantzsch method[6,7] used extensively by Collin et al.[8] The second involves nucleophilic substitution of 4′-chloro-2,2′:6′,2″-terpyridine. With good nucleophiles such as hydrazine and alkoxide ions, this can be achieved directly. With less effective nucleophiles, the reactivity can be enhanced by forming the Fe(II) complex.[9] When the product has formed, the terpyridine can be decomplexed by oxidation of the Fe(II) to Fe(III) and precipitation as ferric oxide.

Synthesis of Unsubstituted and Substituted 2,2′:6′,2″-Terpyridineplatinum(II) Complexes. The standard platination procedure using potassium chloroplatinate worked well for the preparation 4-picoline 2,2′:6′,2″-terpyridineplatinum(II) bis(tetrafluoroborate)[2] but was unsatisfactory for all other 2,2′:6′,2″-terpyridine ligands described here. A new and highly efficient preparative procedure has been developed[5] which enabled all the 2,2′:6′,2″-terpyridineplatinum(II) complexes to be prepared under mild conditions in good yield.

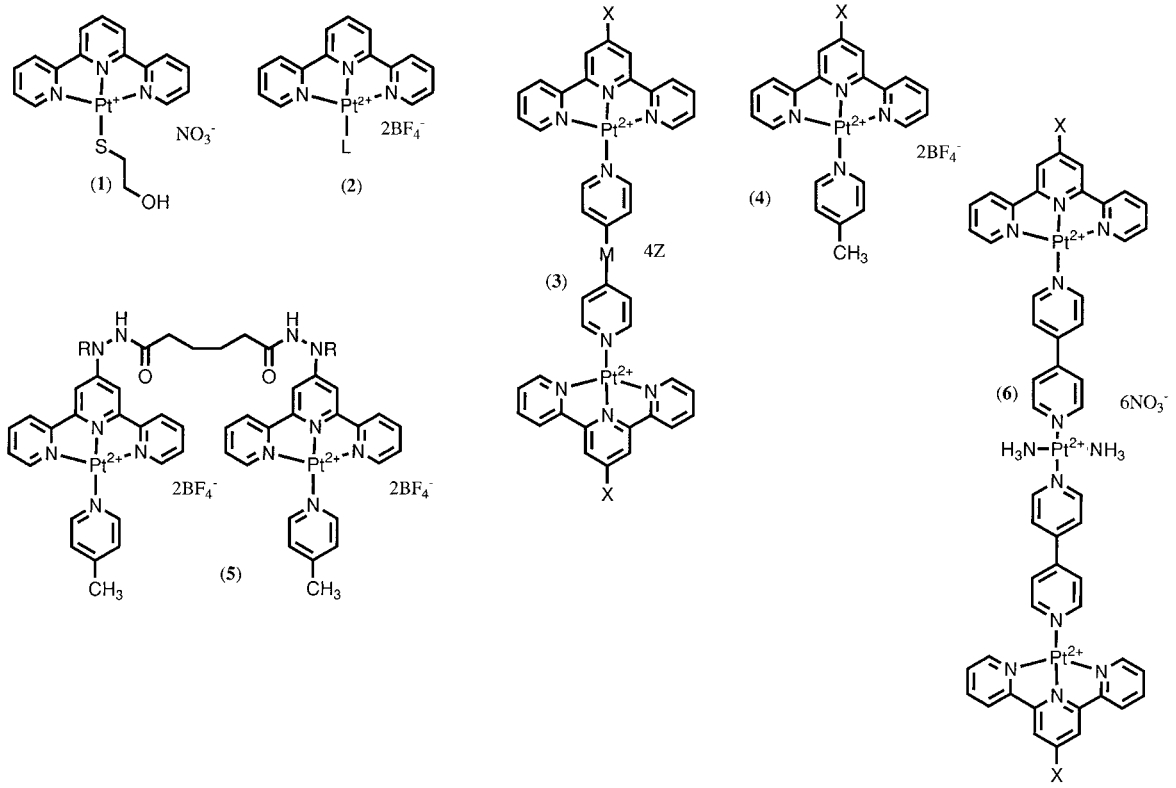
Synthesis of Rigid and Extended Linkers. The three rigid linkers containing ethynyl bonds were prepared using standard palladium-catalyzed coupling procedures (Scheme 1). Concern, however, that linkers with an increasingly lengthy hydrophobic core would lack sufficient water solubility as their bis[2,2′:6′,2″-terpyridineplatinum(II)] complexes (**3**) led us to consider ways of generating more hydrophilic linear rigid linkers. By treating *trans*-diamminedichloroplatinum(II) (transplatin) with 4,4′-dipyridyl, the *trans*-diammine bis(4,4′-dipyridyl)platinum(II) complex was obtained (Scheme 2).

Antitumor Activity. 2,2′:6′,2″-Terpyridineplatinum(II) complexes are known to intercalate into DNA,[1] and the chloro,[10] hydroxy,[11] and picoline complexes[3,4] also platinate DNA. A number of 2,2′:6′,2″-terpyridineplatinum(II) complexes (**2**) were prepared in order to investigate the effect of the leaving group (L) on antitumor activity. The compounds were evaluated for in vitro cytotoxicity against five human ovarian carcinoma cell lines which included two selected for resistance to cisplatin (CHlcis^R and A2780cis^R) and one for resistance to doxorubicin (CHldox^R). The cell lines were selected primarily to search for agents which would circumvent acquired cisplatin and doxorubicin resistance. The mechanism of resistance in the CH1/CH1cis^R pair is due to increased DNA damage repair/tolerance,[12,13] in CH1/CH1dox^R it is due to P-glycoprotein

† Oxford University.
§ CRC Centre for Cancer Therapeutics.

10.1021/jm991053y CCC: $18.00
Published on Web 07/24/1999

Chart 1



overexpression, and in A2780/A2780cis^R it is due to elevated glutathione levels, reduced drug accumulation, and increased DNA damage repair/tolerance.[14−16] The SKOV3 cell line was included because it is one of the most resistant to platinum drugs. The compounds were exposed to cells for 96 h and growth inhibition assessed using the sulforhodamine B protein staining assay.[17] The IC_{50} values are shown in Table 1. Cisplatin and carboplatin are included for comparison. In a recent clinical trial a combination therapy of three drugs (cyclophosphamide, doxorubicin, and cisplatin) was compared with the optimal dose of a single agent, carboplatin, for patients with advanced ovarian cancer. No difference was found in survival between groups on the combination therapy regimen and those on carboplatin. Carboplatin, however, had fewer side effects and was advocated as the standard treatment for advanced ovarian cancer.[18]

It is noteworthy that the bis-intercalator **3**, (X = H, M = *trans*-CH=CH−, Z = BF_4^-) has the lowest IC_{50} against CHl, A2780, and SKOV3 cell lines. Moreover, it is slightly more effective than cisplatin against the cisplatin-resistant cell lines (CHlcis^R and A2780cis^R) indicating a lack of or low level of cross-resistance. The explanation of the antitumor activity is the subject of a continuing investigation, and it would be premature to speculate about the reasons for its effectiveness.

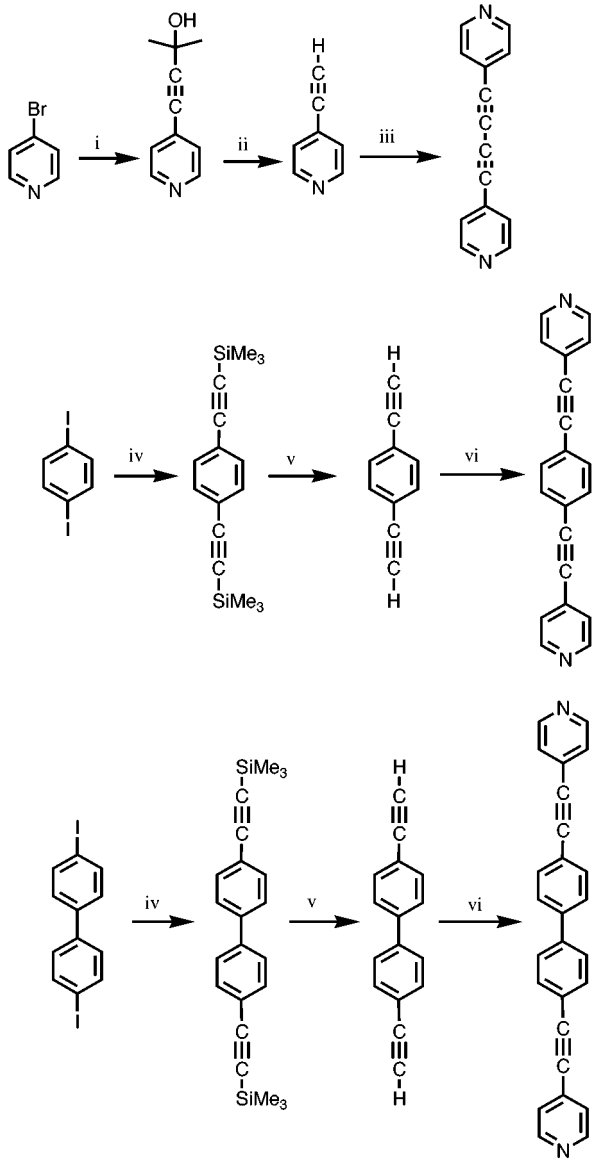
Inspection of Table 1 shows that several of the platinum(II) complexes are more effective than carboplatin against the human ovarian cell lines investigated. The effect of substituents on the pyridine ligand L in **2** (L = 4-Br-C_5H_4N, 4-MeCO-C_5H_4N, 4-Me_2N-C_5H_4N, 2-F-C_5H_4N, 3-F-C_5H_4N, 4-(HOCH$_2$)-C_5H_4N) is relatively small as might be expected from the relative weakness of the Pt(II)−pyridine bond caused by the *trans*-influence of the 2,2′:6′,2″-terpyridine ligand.[19] Although the aqua complex **2** (L = H_2O) and the chloro complex **2** (L = Cl^-) are known to platinate DNA faster than the picoline complex **2** (L = 4-Me-C_5H_4N),[4] they are not, in general, significantly more cytotoxic. This suggests that, at least during the 96-h incubation period used in this assay, the rate of platination is not the most significant parameter in determining cytotoxicity.

The effect of substituents at the 4′-position in 2,2′:6′,2″-terpyridine-Pt(II) complexes is shown in Table 2. It would appear that large and electron-donating substituents as in **4** (X = N(CH$_2$CH$_2$OH)$_2$) lead to a significant loss of activity, although with SKOV3 it is very effective. Bis-intercalators with a flexible linker at the 4′-position, **5** (R = H and R = Me), also show relatively low cytotoxicity. This is particularly pertinent since bis-intercalators which are capable of 'stapling' DNA by intramolecular bis-intercalation have been sought by many, as they were considered to have higher antitumor potential. Indeed, this is considered to be the basis of the antitumor activity of the quinoxaline antibiotics, echinomycin and triostin A, which bis-intercalate into DNA in this way.[20]

Introducing the 4′-chloro group into the 2,2′:6′,2″-terpyridine tridendate ligand as in complex **4** (X = Cl) provides an effective increase in activity, notably against the CH1dox^R cell line where a submicromolar IC_{50} (0.425 μM) was observed. Complex **4** (*X* = 4-Br-C_6H_4) is effective against CH1 and CH1cis^R cell lines and is especially effective against CH1dox^R cells, whereas compound **4** (X = NMeNH$_2$) is effective against CH1, CH1cis^R, CH1dox^R, A2780, and A2780cis^R cell lines.

We next investigated the effect of linker length in analogues of the bis-intercalators **3** (X = H or Cl). The data are shown in Table 3. Against the CH1 cell line three of the bis[terpyridine-Pt(II)] complexes show submicromolar IC_{50} values (**3**, X = H, M = butadiyne, Z =

Scheme 1. Synthetic Routes to the Three Dipyridyl Linkers Containing Ethynyl Bonds[a]

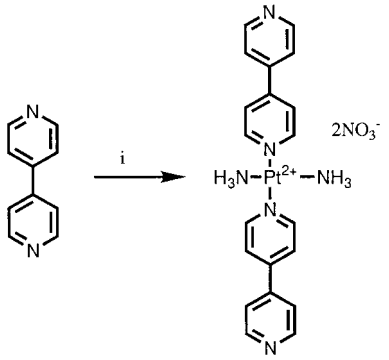


[a] Reagents: (i) 3-methyl-3-hydroxybut-1-yne, Cu_2Cl_2, $(Ph_3P)_2PdCl_2$, $NHEt_2$; (ii) NaOH, toluene; (iii) Cu_2Cl_2, O_2, pyridine; (iv) trimethylsilylacetylene, Cu_2Cl_2, $(Ph_3P)_2PdCl_2$, NEt_3; (v) aq KOH; (vi) $(Ph_3P)_2PdCl_2$, $NHEt_2$, Cu_2I_2, 4-bromopyridine.

NO_3^-; **3**, X = Cl, M = nothing, Z = NO_3^-; and **6**, X = Cl); all are comparable in activity to cisplatin. Against the cisplatin-resistant CH1 cell line ($CH1cis^R$) three compounds (**3**, X = H, M = butadiyne, NO_3^-; **3**, X = Cl, M = nothing, Z = NO_3^-; and **6**, X = Cl) have submicromolar IC_{50} values and are now more effective than cisplatin. It is clear from the resistance factors (RF) that there is little or no cross-resistance with cisplatin. Against the doxorubicin-resistant CH1 ($CH1dox^R$) cell line all of the bis[terpyridine-Pt(II)] complexes tested have submicromolar IC_{50} values with resistant factors close to or less than 1. The most effective complexes, **3** (X = H, M = butadiyne, Z = NO_3^-) and **6** (X = Cl), have similar IC_{50} values and RF values of 0.6 and 0.8, respectively.

Against the cell line A2780 one complex, **3** (X = Cl, M = butadiyne, Z = NO_3^-), has a submicromolar IC_{50} value and is comparable in activity to cisplatin. Against

Scheme 2. Synthesis of *trans*-Diammine Bis(4,4′-dipyridyl)platinum(II) Dinitrate[a]



[a] Reagent: (i) *trans*-diamminedichloroplatinum(II), $AgNO_3$.

the $A2780cis^R$ cell line it retains this level of activity (RF 1.1) but is now 13 times more effective than cisplatin.

Against the cell line SKOV3 six of the bis[terpyridine-Pt(II)] complexes are more effective than cisplatin, the most effective being **3** (X = Cl, M = butadiyne, Z = NO_3^-) and **3** (X = Cl, M = nothing, Z = NO_3^-) each with comparable antitumor activity to **3** (X = H, M = *trans*-CH=CH−, Z = BF_4^-) (Table 1).

Since complexes with longer linkers such as **3** (X = Cl, M = 1,4-diethynylbenzene, Z = NO_3^-) and **3** (X = Cl, M = 4,4′-diethynylbiphenyl, Z = NO_3^-) are not among the most effective agents against any of the cell lines, longer chain lengths do not apparently improve antitumor activity. By contrast, compounds with the shortest linker length are among the most effective against several cell lines, e.g. **3** (X = Cl, M = nothing, Z = NO_3^-) against CH1, $CH1cis^R$, $CH1dox^R$, and SKOV3. The exceptions to this conclusion are **6** (X = H and Cl) which have long linkers and yet are very effective against most cell lines. This suggests that activity may correlate with charge density and/or the electrostatic stress within these molecules caused by the double positive charge on each Pt(II). In general the shorter the chain length the higher the charge density and the electrostatic stress will be within the molecule. Since this is expected to increase binding and the rate of platination of DNA for these antitumor agents, this could account for the effectiveness of the bis[terpyridine-Pt(II)] complexes. Although **6** (X = H and Cl) have long linkers, the charge density and electrostatic stress is high in these molecules since they possess a third Pt(II) in the middle of the chain and thus carry six positive charges. Indeed the charge density and electrostatic stress is expected to be similar to that in **3** (X = H, M = nothing, Z = NO_3^-) and **3** (X = Cl, M = nothing, Z = NO_3^-) where the distance between Pt(II)s is comparable.

The counterions used for these bis[2,2′:6′,2″-terpyridine-Pt(II)] complexes is significant. First, the counterion has a dramatic influence on the solubility of the complexes in different solvents. For good solubility in water, nitrate ions are a suitable choice. All of the bis-(terpyridine) complexes reported in Table 3 have nitrate ions as the counterions, and they are all sufficiently water soluble for adminstration in this solvent alone. Second, the counterion appears to influence the antitumor activity. This is being investigated with a variety of counterions which give complexes with good water

Table 1. 96-h IC_{50} Values (μM) for the in Vitro Growth Inhibition of Human Ovarian Cell Lines by 2,2′:6′,2″-Terpyridineplatinum(II) Complexes[a]

2, L	CH1	CH1cis^R	RF	CH1dox^R	RF	A2780	A2780cis^R	RF	SKOV3
4-Me-C_5H_4N	14	11	0.8	4.4	0.3	17	>100		20
4-Br-C_5H_4N	2.1	2.1	1.0	0.85	0.41	5.8	6.7	1.16	9.2
4-MeCO-C_5H_4N	2.2	2.3	1.05	1.18	0.54	5.9	7.5	1.25	11.1
4-Me_2N-C_5H_4N	6.1	7.5	1.2	3.95	0.6	16	21.5	1.3	13
2-F-C_5H_4N	15.5	14	0.9	5.4	0.3	21.5	>100		>100
3-F-C_5H_4N	17	17	1	6.1	0.3	19.5	>100		>100
thiazole	17	17	1	6.3	0.4	18.6	>100	1	>100
imidazole	16.5	15.5	0.9	6.1	0.4	17	>100		>100
Me-CN	18	18.5	1	13	0.7	50	100	2	>100
4-(HO-CH_2)C_5H_4N	14	12.5	0.9	5	0.3	40	92	2.3	17
C_5H_5N	17.5	18	1	5.7	0.3	40	>100		24
H_2O	12	18	1.5	14	1.2	8.8	7.0	0.9	9.2
NH_3	5.2	4.5	0.9	3.75	0.7	11.5	23.5	2	15
Cl^-	6.6	6.4	1	3.75	0.6	49	41	0.8	19.5
3, X = H, M = *trans*-CH=CH−, Z = BF_4^-	1.35	0.63	0.46	5.1	3.8	1.6	2.4	1.5	1.3
cisplatin	0.4	1.2	3.0	0.5	1.2	0.53	8.8	16.6	2.25
carboplatin	6.2	14.0	2.3	6.0	1.0	35	>100		>100

[a] Two of the cell lines are resistant to cisplatin and one to doxorubicin. RF is the resistance factor: IC_{50} resistant line/IC_{50} parent line.

Table 2. 96-h IC_{50} Values (μM) for the in Vitro Growth Inhibition of Human Ovarian Cell Lines by 4′-Substituted 2,2′:6′,2″-Terpyridineplatinum(II) Picoline Complexes[a]

4, X	CH1	CH1cis^R	RF	CH1dox^R	RF	A2780	A2780cis^R	RF	SKOV3
N(CH_2CH_2OH)$_2$	19.5	22	1.1			31.5	56	1.8	1.8
NMe(CH_2CH_2OH)	>100	>100		17.5		40	>100		>100
Cl	6.35	6.4	1	0.425	0.07	14.5	14.5	1	5.6
Br	5.4	5.5	1	1.5	0.3	44	50	1.1	50
OMe	15.5	16	1	5.1	0.3	25.5	94	3.7	45
4-Me-C_6H_4	7.2	8.9	1.2	1.5	0.2	27	25	0.9	13.5
4-Br-C_6H_4	5.0	5.8	1.2	1.05	0.2	39	29.5	0.8	>100
N(CH_2CH_2)	16	13.5	0.8	5.3	0.3	39	89	2.3	80
$NHNH_2$	65	>100		14.5	0.2	18	62	3.4	>100
$NMeNH_2$	4.6	3.7	0.8	4.2	0.9	7.7	20	2.6	19
NH_2	15.1	16.5	1.1	17	1.1	25	21	0.8	25
5, R = H	48	42	0.9	40	0.8	19	40	2.1	98
5, R = Me	48	46	0.9	58	1.2	17	10.5	0.6	>100

[a] Two of the cell lines are resistant to cisplatin and one to doxorubicin. RF is the resistance factor: IC_{50} resistant line/IC_{50} parent line.

Table 3. 96-h IC_{50} Values (μM) for the in Vitro Growth Inhibition of Human Ovarian Cell Lines by Bis[unsubstituted and 4′-chloro-2,2′:6′,2″-terpyridineplatinum(II)] Complexes[a]

3, X, M, Z = NO_3	CH1	CH1cis^R	RF	CH1dox^R	RF	A2780	A2780cis^R	RF	SKOV3
X = H, M = *trans*-CH=CH−	2.05	2.15	1	0.71	0.3	>25	11		3.5
X = H, M = butadiyne	0.73	0.73	1	0.44	0.6	2	1.8	0.9	1.7
X = Cl, M = butadiyne	1.3	1.75	1.3			0.62	0.68	1.1	1.4
X = Cl, M = 1, 4-diethynylbenzene	2.15	2.15	1			4.75	6.6	1.4	1.8
X = Cl, M= 4, 4′-diethynylbiphenyl	2.5	3.1	1.2			8.6	12.5	1.4	2.2
X = H, M = nothing	1.55	2.05	1.3	0.56	0.4	>25	9.6		3.1
X = Cl, M = nothing	0.59	0.87	1.5	0.69	1.1	>25	18.5		1.3
6, X = H	1.4	1.8	1.3	0.46	0.3	2.4	1.4	0.6	5.1
6, X = Cl	0.55	0.81	1.5	0.42	0.8	13.5	20.5	1.5	1.7

[a] Two of the cell lines are resistant to cisplatin and one to doxorubicin. RF is the resistance factor: IC_{50} resistant line/IC_{50} parent line.

solubility and is part of a continuing investigation of the antitumor activity of the 2,2′:6′,2″-terpyridine-Pt(II) complexes.

Summary

2,2′:6′,2″-Terpyridine-Pt(II) complexes are cytotoxic against several human ovarian cell lines including cell lines resistant to cisplatin and doxorubicin. Bis-intercalators with a rigid and extended linker, particularly a short linker, are very effective antitumor agents. Several bis[2,2′:6′,2″-terpyridine-Pt(II)] complexes have been identified which are more effective than cisplatin against some human ovarian cell lines investigated and both cisplatin-resistant cell lines, indicating that a new class of platinum antitumor agents has been found which show little or no cross-resistance to cisplatin. These complexes are much more effective than carboplatin, the therapeutic agent currently advocated for the treatment of human ovarian cancers,[18] and AMD473, which was recently selected for phase I clinical trials in the U.K.[21]

Experimental Section

General Methods and Materials. Thin-layer chromatography was performed on aluminum sheets precoated with neutral alumina (0.2 mm, Merck aluminum oxide, 60 F254)

and unless otherwise indicated eluted with diethyl ether. Plates were visualized under UV light and stained to detect terpyridine with $FeCl_2$ solution (saturated solution in 1 M HCl). Melting points were recorded on a Kofler block apparatus and are uncorrected.

Mass spectra were recorded by Dr. R. T. Aplin on a V. G. Biotech Bio-Q spectrometer [electrospray ionization (ESI)]; the samples were dissolved in methanol:water (1:1 v/v). Values are quoted in *m*/*z* with only the molecular $[M]^+$ fragments of molecular ions and major peaks being quoted. Routine mass spectra were obtained on a Micromass platform APCI spectrometer. Samples were run in $MeOH/CH_2Cl_2$ (1:1). Routine proton magnetic resonance spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer. Higher-field spectra were recorded at 500 MHz by Mrs. E. McGuinness on a Bruker AM500 spectrometer. Coupling constants (*J*) are recorded in hertz to one decimal place. Samples were judged pure by the absence of nonassignable peaks in the high-field ^1H NMR spectrum and a molecular ion peak in the ESI mass spectrum with the correct isotope distribution.

Chemicals were purchased from Sigma Chemical Co. Ltd. and Aldrich Chemical Co. and were used without further purification. Solvents were obtained from BDH and Fisons at reagent grade and used without distillation.

All compounds were dissolved in water for biological evaluation. The method used to determine in vitro antitumor activity was as previously described.[22] Briefly, single viable cells were seeded into 96-well microtiter plates at 4000−5000/well in 160 μL of growth medium (10% fetal calf serum in Dulbecco's modified Eagle's medium) and allowed to attach overnight. Drugs were dissolved in water and then immediately added to wells (4 wells/concentration; 10 concentrations/drug) and incubated for 96 h. Cell number in treated versus control wells was then assessed using sulforhodamine B (SRB) staining as outlined previously.[22] Comparative potency was determined using IC_{50} (concentration required to reduce the absorbance compared to the controls by 50%) values. No result was more than a factor of 2 from the average values quoted in the tables.

4′-Chloro-2,2′:6′,2″-terpyridine and 4′-bromo-2,2′:6′,2″-terpyridine were prepared by literature methods.[23,24] 4′-*p*-Tolyl-2,2′:6′,2″-terpyridine and 4′-*p*-bromophenyl-2,2′:6′,2″-terpyridine were prepared by the method of Spahni and Calzaferri.[7] 4′-[*N*,*N*-Bis(2-hydroxyethyl)amino]-2,2′:6′,2″-terpyridine, 4′-methoxy-2,2′:6′,2″-terpyridine, 4′-amino-2,2′:6′,2″-terpyridine, 4′-[*N*-(2-hydroxyethyl)-*N*-methylamino]-2,2′:6′,2″-terpyridine, 4′-(1-methylhydrazino)-2,2′:6′,2″-terpyridine, 4′-hydrazino-2,2′:6′,2″-terpyridine, 4′-[*N*-(2-hydroxyethyl)amino]-2,2′:6′,2″-terpyridine, 4′-aziridino-2,2′:6′,2″-terpyridine, and their platinated complexes (**2**) were described previously.[25] The platinum(II) complexes reported in Table 1 except **3** (X = H, M = *trans*-CH=CH−, Z = BF_4^-) and **5** (R = H and Me) were prepared as described previously.[25]

***trans*-4,4′-Vinylidenedipyridine Bis[2,2′:6′,2″-terpyridineplatinum(II)] Tetrafluoroborate (3, X = H, M = *trans*-CH=CH−, Z = BF_4^-).** Diiodo-1,5-cyclooctadieneplatinum(II) (0.292 g, 0.53 mmol) was treated with a solution of silver tetrafluoroborate (0.214 g, 1.1 mmol) in acetone (1.5 mL). The mixture was centrifuged to remove precipitated silver iodide and the supernatant solution added to a solution of 2,2′:6′,2″-terpyridine (0.117 g, 0.5 mmol) in dichloromethane (0.25 mL) and acetonitrile (0.25 mL). A yellow-orange solid was immediately precipitated, collected by centrifugation, and washed with ether:acetonitrile (2:1, 2 × 1.0 mL). The solid was then suspended in acetonitrile (0.5 mL) and the mixture treated with a solution of *trans*-4,4′-vinylidenedipyridine (0.046 g, 0.25 mmol) in dichloromethane (0.25 mL). The mixture was kept at room temperature with occasional shaking for 5 h. The solid changed to a pale-yellow color. The product was collected by centrifugation and dried over P_2O_5 in vacuo to give the title compound (0.123 g, 35%): mp >230 °C; δ_H (ppm) {500 MHz, CD_3CN) 9.05, AA′m, 4H, H2‴, H6‴; 8.56, t, J = 8.2 Hz, 2H, H4′; 8.46−8.37, series of m, 12H, H4, H4″, H3, H3″, H3′, H5′; 8.16, BB′m, 4H, H3‴, H5‴; 7.95, s, 2H, Ha; 7.88, d, J = 5.3 Hz, 4H, H6, H6″; 7.76−7.73, m, 4H, H5, H5″; MS (ESI) *m*/*z* 259.7 (M^{4+}), 305.1 {$[M - Pt(terpy)]^{2+}$}.

1,4-Bis(4-pyridyl)butadiyne. This was prepared by the method of Della Ciana and Haim[26] as white crystalline plates: mp 208−209 °C (lit.[26] mp 203−205 °C); δ_H (ppm) {200 MHz, $CDCl_3$} 8.63, AA′m, 4H, H2, H6; 7.38, BB′m, 4H, H3, H5.

Preparation of 4,4″-Dipyridyl-1′,4′-diethynylbenzene. 1,4-Diethynylbenzene. 1,4-Bis(trimethylsilylethynyl)benzene[27] (1.00 g, 3.71 mmol) was dissolved in dichloromethane (15 mL) and methanol (15 mL). Aqueous potassium hydroxide (1 M, 3 mL) was added dropwise with stirring. The mixture was stirred at room temperature for 2.5 h. The organic solvent was removed under reduced pressure. Water (25 mL) was added, and the mixture was extracted with ether (3 × 30 mL). The combined ether extracts were dried ($MgSO_4$) and decolorized with activated charcoal, and the solvent was removed under reduced pressure to yield 1,4-diethynylbenzene (367 mg, 78%) as a white solid which was used immediately without further purification: mp 95−96 °C; δ_H (ppm) {200 MHz, $CDCl_3$} 7.46, s, 4H, C_6H_4; 3.18, s, 2H, acetylenic H.

4,4″-Dipyridyl-1′,4′-diethynylbenzene. Bis(triphenylphosphine)palladium(II) chloride (70.2 mg, 0.10 mmol) was added to a stirred suspension of 4-bromopyridine hydrochloride (778 mg, 4.0 mmol), 1,4-diethynylbenzene (252 mg, 2.0 mmol), copper(I) iodide (28.6 mg, 0.15 mmol), and dry diethylamine (15 mL) under an atmosphere of argon. The reaction was stirred for 36 h at room temperature under argon. A further portion of bis(triphenylphosphine)palladium(II) chloride (16.3 mg, 0.023 mmol) was added. The reaction was stirred for a further 48 h. The mixture was filtered through Celite using ethyl acetate and concentrated under reduced pressure. The residue was chromatographed on flash silica gel using 5% methanol/dichloromethane as eluant and further purified by chromatography on alumina (grade IV) using 50% ethyl acetate/petroleum ether (40−60 °C) as eluant to yield 4,4″-dipyridyl-1′,4′-diethynylbenzene (284 mg, 51%) as a pale-yellow solid: mp 185−203 °C; δ_H (ppm) {200 MHz, $CDCl_3$} 8.64, AA′m, 4H, H2, H6, H2″, H6″; 7.58, s, 4H, C_6H_4; 7.41, BB′m, 4H, H3, H5, H3″, H5″.

Synthesis of 4″,4‴-Dipyridyl-4,4′-diethynylbiphenyl. 4,4′-Diethynylbiphenyl. 4,4′-Bis(trimethylsilylethynyl)biphenyl[27] (1.04 g, 2.99 mmol) was dissolved in dichloromethane (15 mL) and methanol (15 mL). Aqueous potassium hydroxide (1 M, 3 mL) was added dropwise with stirring. The mixture was stirred at room temperature for 2.5 h. The organic solvent was removed under reduced pressure. Water (25 mL) was added, and the mixture was extracted with ether (3 × 30 mL). The combined ether extracts were dried ($MgSO_4$) and decolorized with activated charcoal, and the solvent was removed under reduced pressure to yield 4,4′-diethynylbiphenyl (562 mg, 93%) as a white solid which was used immediately without further purification: mp 167−169 °C; δ_H (ppm) {200 MHz, $CDCl_3$} 7.57, s, 8H, 2xC_6H_4; 3.15, s, 2H, acetylenic H.

4,4′-Diethynyl-4″,4‴-dipyridylbiphenyl. Bis(triphenylphosphine)palladium(II) chloride (78.2 mg, 0.11 mmol) was added to a stirred suspension of 4-bromopyridine hydrochloride (846 mg, 4.35 mmol), 4,4′-diethynylbiphenyl (440 mg, 2.18 mmol), copper(I) iodide (29.2 mg, 0.15 mmol), and dry diethylamine (30 mL) under an atmosphere of argon. The reaction was stirred for 48 h at room temperature under argon. The mixture was filtered through Celite using ethyl acetate and concentrated under reduced pressure. The residue was chromatographed on flash silica gel using 5% methanol/dichloromethane as eluant and further purified by chromatography on alumina (grade IV) using 50% ethyl acetate/petroleum ether (40−60 °C) as eluant to yield 4,4′-diethynyl-4″,4‴-dipyridylbiphenyl (310 mg, 20%) as a pale-yellow solid: mp 205−275 °C; δ_H (ppm) {200 MHz, $CDCl_3$} 8.63, AA′m, 4H, H2″, H6″, H2‴, H6‴; 7.65, s, 8H, 2xC_6H_4; 7.41, BB′m, 4H, H3″, H5″, H3‴, H5‴.

2,2′:6′,2″-Terpyridineplatinum(II) Acetonitrile Dinitrate. A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0.5 mL) was added dropwise to a suspen-

sion of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.75 mL). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2′:6′,2″-terpyridine (33.6 mg, 0.144 mmol) in acetonitrile (0.3 mL). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet of 2,2′:6′,2″-terpyridineplatinum(II) acetonitrile dinitrate (0.144 mmol) was washed with acetonitrile/ether (1:3, 3 × 1.5 mL) and then dissolved in water (1.5 mL).

4,4′-Dipyridine Bis[2,2′:6′,2″-terpyridineplatinum(II)] Tetranitrate (3, X = H, M = nothing, Z = NO_3^-). A solution of 4,4′-dipyridine (11.3 mg, 0.072 mmol) in acetone (0.75 mL) was added to a solution of 2,2′:6′,2″-terpyridineplatinum(II) acetonitrile dinitrate (0.144 mmol) in water (1.5 mL). The mixture was vortexed and sonicated for 1 h. The mixture was added to ether/acetone (3:7, 25 mL) to precipitate the complex. The mixture was centrifuged and the pellet washed with ether/acetone (3:1, 3 × 20 mL) to yield 4,4′-dipyridine bis[2,2′:6′,2″-terpyridineplatinum(II)] tetranitrate (86 mg, 95%) as a yellow solid. The product was purified by reprecipitation from ether/acetone (1:1, 20 mL): δ_H (ppm) {500 MHz, D_2O} 9.43, AA′m, 4H, H2‴, H6‴; 8.55, t, *J* 8.2 Hz, 2H, H4′; 8.40−8.47, series of multiplets, 16H, H3‴, H5‴, H3′, H5′, H3, H3″, H4, H4″; 7.90, d, *J* 5.6 Hz, 4H, H6, H6″; 7.74, m, 4H, H5, H5″; ESMS (CV = 5 V) *m*/*z* 253.2 (M^{4+}, 100%), 292.2 {$[M - Pt(terpy)]^{2+}$, 52%}.

***trans*-4,4′-Vinylidenedipyridine Bis[2,2′:6′,2″-terpyridineplatinum(II)] Tetranitrate (3, X = H, M = *trans*-CH=CH−, Z = NO_3^-).** A solution of *trans*-4,4′-vinylidenedipyridine (13.1 mg, 0.072 mmol) in acetone (0.75 mL) was added to a solution of 2,2′:6′,2″-terpyridineplatinum(II) acetonitrile dinitrate (0.144 mmol) in water (1.5 mL). The mixture was vortexed and sonicated for 1 h. The mixture was added to ether/acetone (3:7, 25 mL) to precipitate the complex. The mixture was centrifuged and the pellet washed with ether/acetone (3:1, 3 × 20 mL) to yield *trans*-4,4′-vinylidenedipyridine bis[2,2′:6′,2″-terpyridineplatinum(II)] tetranitrate (90.6 mg, 98%) as an apricot-colored solid. The product was purified by reprecipitation from ether/acetone (1:1, 20 mL): δ_H (ppm) {500 MHz, D_2O} 9.18, AA′m, 4H, H2‴, H6‴; 8.53, t, *J* 8.2 Hz, 2H, H4′; 8.16, BB′m, 4H, H3‴, H5‴; 7.89−7.91, s and d, 6H, vinylic-H, H6, H6″; 8.38−8.45, series of multiplets, 12H, H3′, H5′, H3, H3″, H4, H4″; 7.74, m, 4H, H5, H5″; ESMS (CV = 5 V): *m*/*z* 259.7 (M^{4+}, 100%), 305.2 {$[M - Pt(terpy)]^{2+}$, 15%}.

1,4-Bis(4-pyridyl)butadiyne Bis[2,2′:6′,2″-terpyridineplatinum(II)] Tetranitrate (3, X = H, M = butadiyne, Z = NO_3^-). A solution of 1,4-bis(4-pyridyl)butadiyne (14.7 mg, 0.072 mmol) in acetone (0.75 mL) was added to a solution of 2,2′:6′,2″-terpyridineplatinum(II) acetonitrile dinitrate (0.144 mmol) in water (1.5 mL). The mixture was vortexed and sonicated for 1 h. The mixture was added to ether/acetone (3:7, 25 mL) to precipitate the complex. The mixture was centrifuged and the pellet washed with ether/acetone (3:1, 3 × 20 mL) to yield 1,4-bis(4-pyridyl)butadiyne bis[2,2′:6′,2″-terpyridineplatinum(II)] tetranitrate (92.7 mg, 98%) as a light-brown solid. The product was purified by reprecipitation from ether/acetone (1:1, 20 mL): δ_H (ppm) {500 MHz, D_2O} 9.23, AA′m, 4H, H2‴, H6‴; 8.53, t, *J* 8.2 Hz, 2H, H4′; 8.40−8.45, series of multiplets, 12H, H3′, H5′, H3, H3″, H4, H4″; 8.08, BB′m, 4H, H3‴, H5‴; 7.86, d, *J* 5.6 Hz, 4H, H6, H6″; 7.73, m, 4H, H5, H5″; ESMS (CV = 5 V): *m*/*z* 265.2 (M^{4+}, 100%), 316.2 {$[M - Pt(terpy)]^{2+}$, 58%}.

4′-Chloro-2,2′:6′,2″-terpyridineplatinum(II) Acetonitrile Dinitrate. A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0. 5 mL) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.75 mL). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4′-chloro-2,2′:6′,2″-terpyridine (38.6 mg, 0.144 mmol) in acetonitrile (0.3 mL). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet of 4′-chloro-2,2′:6′,2″-terpyridineplatinum(II) acetonitrile dinitrate (0.144 mmol) was washed with acetonitrile/ether (1:3, 3 × 1.5 mL) and then dissolved in water (1.5 mL).

4,4′-Dipyridine Bis[4′-chloro-2,2′:6′,2″-terpyridineplatinum(II)] Tetranitrate (3, X = Cl, M = nothing, Z = NO_3^-). A solution of 4,4′-dipyridine (11.3 mg, 0.072 mmol) in acetone (0.75 mL) was added to a solution of 4′-chloro-2,2′:6′,2″-terpyridineplatinum(II) acetonitrile dinitrate (0.144 mmol) in water (1.5 mL). The mixture was vortexed and sonicated for 1 h. The mixture was added to ether/acetone (3:7, 25 mL) to precipitate the complex. The mixture was centrifuged and the pellet washed with ether/acetone (3:1, 3 × 20 mL) to yield 4,4′-dipyridine bis[2,2′:6′,2″-terpyridineplatinum(II)] tetranitrate (95.0 mg, 99%) as a yellow solid. The product was purified by reprecipitation from ether/acetone (1:1, 20 mL): δ_H (ppm) {500 MHz, D_2O} 9.42, AA′m, 4H, H2‴, H6‴; 8.60, s, 4H, H3′, H5′; 8.43−8.48, series of multiplets, 12H, H3‴, H5‴, H3, H3″, H4, H4″; 7.93, d, *J* 5.6 Hz, 4H, H6, H6″; 7.78, m, 4H, H5, H5″; ESMS (CV = 10 V) *m*/*z* 270.4 (M^{4+}, 100%).

1,4-Bis(4-pyridyl)butadiyne Bis[4′-chloro-2,2′:6′,2″-terpyridineplatinum(II)] Tetranitrate (3, X = Cl, M = butadiyne, Z = NO_3^-). A solution of the 1,4-bis(4-pyridyl)-butadiyne (8.7 mg, 0.043 mmol) in methanol (0.75 mL) was added to a solution of 4′-chloro-2,2′:6′,2″-terpyridineplatinum(II) acetonitrile dinitrate (0.82 mmol) in water (0.75 mL). The mixture was vortexed and sonicated for 15 min and allowed to stand at room temperature for 30 min. The solution was added dropwise to ether/acetone (1:1, 20 mL) to precipitate the complex. The mixture was centrifuged. The pellet was washed with ether/acetone (1:1, 4 × 20 mL) and then dried to yield the desired complex (58.4 mg, 99%) as a dusky orange solid: δ_H (ppm) {500 MHz, D_2O} 9.22, AA′ m, 4H, H2‴, H6‴; 8.58, s, 4H, H3′, H5′; 8.48−8.34, series of multiplets, 8H, H3, H3″, H4, H4″; 8.08, BB′ m, 4H, H3‴, H5‴; 7.89, d, *J* 5.7 Hz, 4H, H6, H6″; 7.76, m, 4H, H5, H5″; ESMS (CV = 10 V) *m*/*z* 282.7 (M^{4+}, 100%), 333.8 {$[M - Pt(Cl\text{-}terpy)]^{2+}$, 80%}.

4,4″-Dipyridyl-1′,4′-diethynylbenzene Bis[4′-chloro-2,2′:6′,2″-terpyridineplatinum(II)] Tetranitrate (3, X = Cl, M = 1,4-diethynylbenzene, Z = NO_3^-). A solution of the 4,4″-dipyridyl-1′,4′-diethynylbenzene (11.3 mg, 0.043 mmol) in methanol (0.75 mL) was added to a solution of 4′-chloro-2,2′:6′,2″-terpyridineplatinum(II) acetonitrile dinitrate (0.0.82 mmol) in water (0.75 mL). The mixture was vortexed and sonicated for 15 min and allowed to stand at room temperature for 30 min. A yellow precipitate formed. The mixture was centrifuged and the pellet washed with ether/acetone (1:1, 3 × 20 mL) to yield the desired complex (33.4 mg) as a yellow solid. The supernatant was added dropwise to ether/acetone (1:1, 20 mL) to precipitate more of the complex which was washed with ether/acetone (1:1, 4 × 20 mL) and then dried to yield the desired complex (22.2 mg) as a yellow solid. The total yield of the product was 55.6 mg (96%): δ_H (ppm) {500 MHz, D_2O} 9.16, AA′ m, 4H, H2‴, H6‴; 8.58, s, 4H, H3′, H5′; 8.48−8.40, series of multiplets, 8H, H3, H3″, H4, H4″; 8.02, BB′ m, 4H, H3‴, H5‴; 7.93, d, *J* 5.7 Hz, 4H, H6, H6″; 7.80, s, 4H, H2⁗, H3⁗, H5⁗, H6⁗; 7.77, m, 4H, H5, H5″; ESMS (CV = 10 V) *m*/*z* 301.7 (M^{4+}, 100%), 371.8 {$[M - Pt(Cl\text{-}terpy)]^{2+}$, 38%}.

4,4′-Diethynyl-4″,4‴-dipyridylbiphenyl Bis[4′-chloro-2,2′:6′2″-terpyridineplatinum(II)] Tetranitrate (3, X = Cl, M = 4,4′-diethynylbiphenyl, Z = NO_3^-). A solution of the 4,4′-diethynyl-4″,4‴-dipyridylbiphenyl (14.3 mg, 0.040 mmol) in methanol (1.5 mL) was added to a solution of 4′-chloro-2,2′:6′,2″-terpyridineplatinum(II) acetonitrile dinitrate (0.0.82 mmol) in water (0.75 mL). The mixture was vortexed and sonicated for 15 min and allowed to stand at room temperature for 30 min. The dark solution was added dropwise to ether/acetone (1:1, 20 mL) to precipitate the complex which was washed with ether/acetone (1:1, 4 × 20 mL) and then dried to yield the desired complex (37.6 mg, 61%) as a yellow solid: δ_H (ppm) {500 MHz, D_2O} 9.10, AA′ m, 4H, H2‴, H6‴; 8.56, s, 4H, H3′, H5′; 8.45−8.38, series of multiplets, 8H, H3, H3″, H4, H4″; 8.02, BB′ m, 4H, H3‴, H5‴; 7.92, d, *J* 5.7 Hz, 4H, H6, H6″; 7.80, m, 4H, H5, H5″; 7.79, s, 8H, H2⁗, H3⁗, H5⁗, H6⁗;

ESMS (CV = 10 V) *m/z* 320.8 (M^{4+}, 100%), 410.0 {[M − Pt(Cl-terpy)]$^{2+}$, 69%}.

***trans*-Diammine Bis(4,4′-dipyridyl)platinum(II) Dinitrate.** A solution of silver nitrate (36.3 mg, 0.200 mmol) in acetone/water (1:1, 0.5 mL) was added to a suspension of transplatin (30.0 mg, 0.100 mmol) in acetone/water (1:1, 0.5 mL) and sonicated for 24 h. The mixture was centrifuged, and the supernatant was added to a solution of 4,4′-dipyridyl (31.2 mg, 0.200 mmol) in acetone (0.5 mL), maintaining an excess of 4,4′-dipyridyl. The mixture was sonicated for 24 h and then centrifuged to yield *trans*-diammine bis(4,4′-dipyridyl)platinum(II) dinitrate (64.9 mg, 97%) as a white solid: δ_H (ppm) {500 MHz, DMSO} 8.90, AA′m, 4H, H2, H6; 8.84, AA′m, 4H, H2′, H6′; 8.25, BB′m, 4H, H3, H5; 7.98, BB′m, 4H, H3′, H5′; 4.73, b s, 6H, NH_3; ESMS (CV = 30 V) *m/z* 270.8 (M^{2+}, 60%), 540.3 [$(M - H)^+$, 33%].

***trans*-Diammine Bis(4,4′-dipyridyl)platinum(II) Bis-[2,2′:6′,2″-terpyridineplatinum(II)] Hexanitrate (6, X = H).** A suspension of *trans*-diammine bis(4,4′-dipyridyl)platinum(II) nitrate (23.0 mg, 0.035 mmol) in methanol (0.75 mL) was added to a solution of 2,2′:6′,2″-terpyridineplatinum(II) acetonitrile dinitrate (0.0.82 mmol) in water (0.75 mL). The mixture was vortexed and sonicated for 5 days at room temperature. The mixture was centrifuged. The supernatant was added dropwise to ether/acetone (1:1, 20 mL) to precipitate the complex. Centrifugation yielded a purple solid (30.1 mg), which dissolved in water to give a yellow solution. Reprecipitation (5 times) from ether/acetone (1:1, 20 mL) gave the desired complex (8.3 mg) as a pale-yellow solid: δ_H (ppm) {500 MHz, D_2O} 9.38, AA′m, 4H, H2‴, H6‴; 9.15, AA′m, 4H, H2⁗, H6⁗; 8.54, t, *J* 8.2 Hz, 2H, H4′; 8.46−8.41, series of multiplets, 12H, H3′, H5′, H3, H3″, H4, H4″; 8.35, BB′m, H3‴, H5‴; 8.20, BB′m, 4H, H3⁗, H5⁗; 7.86, d, *J* 5.6 Hz, 4H, H6, H6″; 7.72, m, 4H, H5, H5″; ESMS (CV = 10 V) *m/z* 242.5 {[M − Pt(terpy)]$^{4+}$, 9%}, 279.4 [$(M - H)^{5+}$, 100%], 292.2 {[(terpy)Pt-(bip)]$^{2+}$, 35%}, 322.9 {[M − Pt(terpy) − H]$^{3+}$, 20%}.

***trans*-Diammine Bis(4,4′-dipyridyl)platinum(II) Bis[4′-chloro-2,2′:6′,2″-terpyridineplatinum(II)] Hexanitrate (6, X = Cl).** A suspension of *trans*-diammine bis(4,4′-dipyridyl)-platinum(II) nitrate (23.0 mg, 0.035 mmol) in methanol (0.75 mL) was added to a solution of 4′-chloro-2,2′:6′,2″-terpyridine-platinum(II) acetonitrile dinitrate (0.0.82 mmol) in water (0.75 mL). The mixture was vortexed and sonicated for 5 days at room temperature. The mixture was centrifuged. The supernatant was added dropwise to ether/acetone (1:1, 20 mL) to precipitate the complex. Centrifugation yielded a mauve solid (28.4 mg), which dissolved in water to give a yellow solution. Reprecipitation (4 times) from ether/acetone (1:1, 20 mL) gave the desired complex (12.1 mg) as a pale-yellow solid: δ_H (ppm) {500 MHz, D_2O} 9.37, AA′m, 4H, H2‴, H6‴; 9.15, AA′m, 4H, H2⁗, H6⁗; 8.60, s, 4H, H3′, H5′; 8.47−8.41, series of multiplets, 8H, H3, H3″, H4, H4″; 8.36, BB′m, H3‴, H5‴; 8.20, BB′m, 4H, H3⁗, H5⁗; 7.89, d, *J* 5.7 Hz, 4H, H6, H6″; 7.76, m, 4H, H5, H5″; ESMS (CV = 5 V) *m/z* 270.4 {[$Pt(bip)_2$-$(NH_3)_2$]$^{2+}$, 28%}, 293.2 [$(M - H)^{5+}$, 100%], 309.3 {[(Cl-terpy)-Pt(bip)]$^{2+}$, 22%}, 334.2 {[M − Pt(Cl-terpy) − H]$^{3+}$, 48%}.

Acknowledgment. Support for this work from the BBSRC and EPSRC (G.W.W., J.J.P., and J.M.P.), the Institute for Promotion of Science and Technology Teaching (Thailand) and the Thai Government for a DPST Scholarship (T.V.), and the Fondation Suisse d'Etudes (A.S.D.) is gratefully acknowledged.

References

(1) Jennette, K.; Lippard, S. J.; Vassiliades, G.; Bauer, W. Metallo-intercalation Reagents. 2-Hydroxyethanethiolato(2,2′,2″-terpyridine)-platinum (II) monocation binds strongly to DNA by Intercalation. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 3839−3843.

(2) McCoubrey, A.; Latham, H. C.; Cook, P. R.; Rodger, A.; Lowe, G. 4-Picoline 2,2′:6′,2″-terpyridine-platinum (II) − a Potent Intercalator of DNA. *FEBS Lett.* **1996**, *380*, 73−78.

(3) Lowe, G.; McCloskey, J.; Ni, J.; Vilaivan, T. A Mass Spectroscopic Investigation of the Reaction between 4,4′-Vinylenedipyridine Bis[2,2′:6′,2″-terpyridine-platinum (II)] and the Self-complementary Oligonucleotide d(CpGpTpApCpG). *Bioorganic Med. Chem.* **1996**, *4*, 1007−1013.

(4) Lowe, G.; Hartley, J.; et al. Unpublished work.

(5) Lowe, G.; Vilaivan, T. An improved method for the synthesis of 2,2′:6′,2″-terpyridine-platinum (II) complexes. *J. Chem. Res. (S)* **1996**, 386−387.

(6) Case, F. H.; Kaspen, T. J. The Preparation of some Substituted 2,6-Bis-(2-pyridyl)-pyridines. *J. Am. Chem. Soc.* **1956**, *78*, 5842.

(7) Spahni, W.; Calzaferri, G. Synthese von para-substituierten Phenyl-Terpyridin Liganden. *Helv. Chim. Acta* **1984**, *67*, 450−453.

(8) Collin, J.-P.; Guillerez, S.; Sauvage, J.-P.; Barigelletti, F.; De Cola, L.; Flamigni, L.; Balzani, V. Photoinduced Processes in Dyads and Triads Containing a Ruthenium (II)-Bis(terpyridine) Photosensitizer Covalently Linked to Electron Donor and Acceptor Groups. *Inorg. Chem.* **1991**, *30*, 4230−4238.

(9) Constable, E. C.; Cargill Thompson, A. M. W.; Tocher, D. A.; Daniels, M. A. M. Synthesis, Characterisation and Spectroscopic Properties of Ruthenium(II)-2,2′:6′,2″-terpyridine Coordination Triades. X-ray structure of 4′-(N,N-Dimethylamino)-2,2′:6′,2″-terpyridine and Bis(4′-(N,N-Dimethylamino)-2,2′:6′,2″-terpyridine)-ruthenium(II) Hexafluorophosphate Acetonitrile Solvate. *New J. Chem.* **1992**, *16*, 855−867.

(10) Howe-Grant, M.; Wu, K. C.; Bauer, W. R.; Lippard, S. J. Binding of Platinum and Palladium Metallointercalation Reagents and Antitumour Drugs to Closed and Open DNAs. *Biochemistry* **1976**, *15*, 4339−4346.

(11) Peyratout, C. S.; Aldridge, T. K.; Crites, D. K.; McMillin, D. R. DNA-Binding Studies of a Bifunctional Platinum Complex that is a Luminescent Intercalator. *Inorg. Chem.* **1994**, *34*, 4484−4489.

(12) Kelland, L. R.; Mistry, P.; Abel, G.; Loh, S. Y.; O'Neill, C. F.; Murrer, B. A.; Harrap, K. R. Mechanism-related circumvention of cis-diamminedichloroplatinum(II) acquired resistance using two pairs of human ovarian cancer cell lines by ammine/amine platinum(IV) dicarboxylates. *Cancer Res.* **1992**, *52*, 3857−3864.

(13) O'Neill, C. F.; Orr, R. M.; Kelland, L. R.; Harrap, K. R. Comparison of platinum (Pt) binding to DNA and removal of total Pt adducts and interstrand cross-links in three human ovarian carcinoma cell lines sensitive and resistant to cisplatin. *Cell Pharmacol.* **1995**, *2*, 1−7.

(14) Behrens, B. C.; Hamilton, T. C.; Masuda, H.; Grotsinger, K. R.; Whang-Peng, J.; Louie, K. G.; Knutsen, T.; McKoy, W. M.; Young, R. C.; Ozols, R. F. Charcterisation of cis-diamminedichloroplatinum(II)-resistant human ovarian carcinoma cell line and its use in evaluation of platinum analogues. *Cancer Res.* **1987**, *47*, 414−418.

(15) Johnson, S. W.; Perez, R. P.; Godwin, A. K.; Yeung, A. T.; Handel, L. M.; Ozols, R. F.; Hamilton, T. C. Role of platinum-DNA adduct formation and removal in cisplatin resistace in human ovarian cancer cell lines. *Biochem. Pharmacol.* **1994**, *47*, 689−697.

(16) Kelland, L. R.; Barnard, C. F. J.; Mellish, K. J.; Jones, M.; Goddard, P. M.; Valenti, M.; Murrer, B. A.; Harrap, K. R. A novel trans-platinum coordination complex possessing in vitro and in vivo antitumour activity. *Cancer Res.* **1994**, *54*, 5618−5622.

(17) Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J.; Bokesch, H.; Kennedy, S.; Boyd, M. R. New colorimetric cytotoxicity assay for anticancer drug screening. *J. Natl. Cancer Inst.* **1990**, *82*, 1107−1112.

(18) ICON Collaborators. ICON 2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. *Lancet* **1998**, *352*, 1571−1576.

(19) Chernega, A.; Droz, A. S.; Prout, K.; Vilaivan, T.; Weaver, G. W.; Lowe, G. Structural Evidence for the Reactivity of 4-Picoline 2,2′:6′,2″-terpyridine (II) Complexes and Evidence for π-stacking in the Crystal Lattice. *J. Chem. Res. (S)* **1996**, 402−403.

(20) Blackburn, G. M.; Gait, M. J. *Nucleic Acids in Chemistry and Biology*, 2nd ed.; IRL Press: Oxford University, 1996; pp 352−357.

(21) Holford, J.; Sharp, S. Y.; Murrer, B. A.; Abrams, M.; Kelland, L. R. In vitro circumvention of cisplatin resistance by the novel sterically hindered platinum complex AMD473. *Br. J. Cancer* **1998**, *77*, 366−373.

(22) Kelland, L. R.; Abel, G.; McKeage, M. J.; Jones, M.; Goddard, P. M.; Valenti, M.; Murrer, B. A.; Harrap, K. R. Preclinical antitumour evaluation of bis-acetato-ammine-dichloro-cyclohexylamine platinum (IV), an orally active platinum drug. *Cancer Res.* **1993**, *53*, 2581−2586.

(23) Constable, E. C.; Ward, M. D. Synthesis and Coordination Behaviour of 6′,6″-Bis(2-pyridyl)-2,2′:4,4″:2″,2‴-quaterpyridine; 'Back-to-back' 2,2′:6′,2″-Terpyridine. *J. Chem. Soc., Dalton Trans.* **1990**, 1405−1409.
(24) Lehn, J.-M.; Sauvage, J.-P.; Simon, J.; Ziessel, R.; Piccinni-Leopardi, C.; Germain, G.; Declercq, J.-P.; Van Meerssche, M. Synthesis and Metal Complexes of a Conformationally Restricted Quaterpyridine. Crystal Structure of its Dimeric Dinuclear Cu(I) Complex, $[Cu_2(pQP)_2]^{2+}$. *Nouv. J. Chim.* **1983**, *7*, 413−420.
(25) Lowe, G.; Droz, A. S.; Vilaivan, T.; Weaver, G. W.; Tweedale, L.; Pratt, J. M.; Rock, P.; Yardley, V.; Croft, S. L. Cytotoxicity of 2,2′:6′,2″-Terpyridine Pt(II) Complexes to Leishmania donovani, *Trypanosoma cruzi* and *Trypanosoma brucei*. *J. Med. Chem.* **1999**, *42*, 999−1006.
(26) Della Ciana, L.; Haim, A. Synthesis of 1,4-Bis(4-pyridyl)-butadiyne. *J. Heterocyl. Chem.* **1984**, *21*, 607−608.
(27) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. A Convenient Synthesis of Ethynylarenes and Diethynylarenes. *Synthesis* **1980**, *8*, 627−630.

JM991053Y