# Chemical and Biological Properties of a New Series of *cis*-Diammineplatinum(II) Antitumor Agents Containing Three Nitrogen Donors: *cis*-$[Pt(NH_3)_2(N\text{-donor})Cl]^+$

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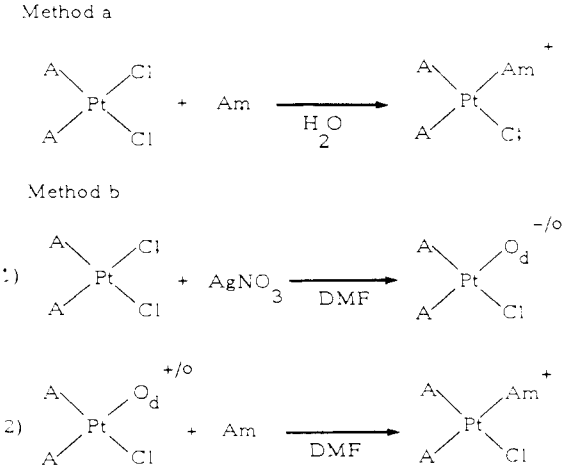
A series of 32 cationic platinum(II) complexes of the form *cis*-$[PtA_2(Am)Cl]^+$, where A is a monodentate ($NH_3$ or *i*-$PrNH_2$) or $A_2$ is a bidentate (ethylenediamine or 1,2-diaminocyclohexane) amine and Am is either a heterocyclic amine based on a pyridine, pyrimidine, purine, piperidine, or a saturated amine ($RNH_2$) ligand, was prepared and screened against in vivo murine tumor models. Each compound was tested against Sarcoma 180 ascites (S180a) in mice, with 20 members of the series showing activity (ILS >50%). Antitumor activity also was demonstrated in 4 of 16 compounds tested in the L1210 murine leukemia model (ILS > 25%) and in 3 of 3 tested in the P388 murine leukemia model (ILS > 30%). The most active and potent analogues of the series were obtained when A was $NH_3$ and Am was *N1*-pyridine, *N1*-4-methylpyridine, *N1*-4-bromopyridine, *N1*-4-chloropyridine, *N3*-cytosine, or *N7*-2′-deoxyguanosine. Complexes containing chelating and saturated amine ligands (A), as well as two trans isomers of active cis analogues (*trans*-$[Pt(NH_3)_2(Am)Cl]^+$, where Am = *N1*-pyridine or *N1*-4-methylpyridine), were inactive in the S180a screen. All complexes were characterized by means of elemental analysis, HPLC, and $^{195}Pt$ NMR spectroscopy, and the structure of one analogue, *cis*-$[Pt(NH_3)_2(N3\text{-cytosine})Cl](NO_3)$, was determined by using single-crystal X-ray diffraction methods. While members of this series of compounds demonstrate antitumor activity in vivo, these new agents are not classical analogues of cisplatin (i.e. *cis*-$[PtA_2X_2]$ complexes), as they contain three nitrogen donors and only one leaving group. The results of these studies suggest that further work should be conducted to better define the limits of the structure–activity relationships among platinum(II) complexes.

While cisplatin, *cis*-$[Pt(NH_3)_2Cl_2]$, has proven effective in treating a variety of forms of cancer,[1] a continuing effort is being made in analogue development programs to broaden the spectrum of activity and to improve the therapeutic properties of platinum-based antitumor agents. Specific goals in this area include developing agents that are active against unresponsive diseases, such as colon and breast cancer, improving the activity in tumor systems that presently respond to cisplatin, such as lung and bladder carcinomas, and reducing the major toxicities, such as myelosuppression and nephrotoxicity.[2] In our efforts to develop a new platinum-based antitumor agent that will display a different activity profile, we have chosen to investigate complexes that do not possess structural features that are characteristic of standard cisplatin analogues.[3]

The search for new platinum complexes that possess improved therapeutic properties has spanned a 15-year period. During this time, several thousand platinum complexes have been prepared and evaluated in animal tumor screens. While some success has been achieved in identifying compounds that are less toxic than cisplatin, little progress has been made toward improving the activity of platinum complexes against both responsive and unresponsive forms of the disease. The search for new agents has relied heavily on the structure–activity relationships that were first summarized by Cleare and Hoeschele in 1973[3] and, to date, these guidelines continue to influence synthetic efforts in this area. In general, the majority of the analogues that have been examined are neutral platinum(II) complexes of the form *cis*-$[PtA_2X_2]$, where A is an amine ligand and X is an anionic leaving group.[3,4] In all cases, the related *trans*-diamine complexes (*trans*-$[PtA_2X_2]$), which are simple isomers of active *cis*-diamine analogues, lack activity in animal tumor models. The importance of the cis geometry of the leaving groups (X) in these square-planar complexes has been stressed on the basis of mechanistic studies, which suggest that *cis*-$[PtA_2X_2]$ complexes produce bifunctional lesions on DNA that are capable of disrupting cellular replication processes.[5]

Scheme I




Excluding those complexes that conform to the *cis*-$[PtA_2X_2]$ structural class, relatively few platinum compounds have demonstrated activity in murine tumor sys-

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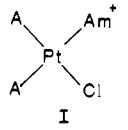
0022-2623/89/1832-0128$01.50/0 

Table I. $^{195}Pt$ Chemical Shift and $^{195}Pt$–$^{15}N$ Coupling Constant Data for the Products of the Reaction of *cis*-$[Pt(^{15}NH_3)_2Cl_2]$ with $AgNO_3$

| complex | concn,[a] % | δ (ppm)[b] | J,[c] Hz | J′, Hz |
|---|---|---|---|---|
| | In DMF | | | |
| *cis*-$[Pt(^{15}NH_3)_2Cl_2]$ | 12 | −2088 | 303 | |
| *cis*-$[Pt(^{15}NH_3)_2(O1\text{-DMF})Cl](NO_3)$ | 56 | −1808 | 364[d] | 338[e] |
| *cis*-$[Pt(^{15}NH_3)_2(NO_3)Cl]$ | 23 | −1794 | 341[f] | 335[e] |
| *cis*-$[Pt(^{15}NH_3)_2(O1\text{-DMF})_2](NO_3)_2$ | 3 | −1590 | 366[g] | |
| *cis*-$[Pt(^{15}NH_3)_2(NO_3)(O1\text{-DMF})](NO_3)$ | 5 | −1585 | 375[g,h] | |
| *cis*-$[Pt(^{15}NH_3)_2(NO_3)_2]$ | 1 | −1577 | 380[g] | |
| | In $H_2O$[g] | | | |
| *cis*-$[Pt(^{15}NH_3)_2Cl_2]$ | 4 | −2136 | 326 | |
| *cis*-$[Pt(^{15}NH_3)_2(H_2O)Cl](NO_3)$ | 57 | −1824 | 368[i] | 345[e] |
| *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2](NO_3)$ | 39 | −1580 | 388 | |

[a] Relative concentration as % total Pt based on integrated intensities. [b] Measured relative to $H_2PtCl_6$ at 0 ppm. [c] Coupling constants were measured from $^{15}N$ spectra, except were noted. [d] Trans to DMF. [e] Trans to Cl. [f] Trans to $NO_3$. [g] Coupling constants measured from $^{195}Pt$ spectrum. [h] Average value. [i] Trans to $H_2O$.

tems. In this report, we present chemical and biological data on a new series of platinum antitumor agents that violate some of the classical structure–activity relationships. These compounds are cationic triamine complexes of the form I, where A is ammonia and Am is either a




I

heterocyclic amine based on pyridine, pyrimidine, purine, or piperidine substituents or a saturated amine. Members of this series of compounds show activity in a number of murine tumor screens, including S180a, P388, and L1210. These complexes, which represent a potentially broad class of antitumor agents whose activity has been unsuspected until now, also possess desirable physical properties, such as high stability and solubility in aqueous media. The results of these studies suggest that the structure–activity relationships among platinum-based antitumor agents should be reexamined to determine if additional structural classes have been discounted as inactive, based on test results that were obtained on a limited number of example compounds.

## Results

**Chemical Studies of the *cis*-[Pt(diamine)(Am)Cl]$^+$ Complexes.** The platinum–triamine complexes were prepared by using one of the two general reaction sequences outlined in Scheme I. In method a, the starting materials, *cis*-$[PtA_2Cl_2]$ and the selected Am ligand, were heated in water at 50–60 °C for a period of 1–3 days to promote Am substitution. The desired products were typically recrystallized (from water or methanol) to remove unreacted starting materials and disubstituted byproducts of the form *cis*-$[PtA_2(Am)_2]^{2+}$. In method b, the reactive monochloro intermediates *cis*-$[PtA_2(O1\text{-DMF})Cl](NO_3)$ and *cis*-$[PtA_2(NO_3)Cl]$ were first prepared from the reaction of *cis*-$[PtA_2Cl_2]$ with 1 equiv of $AgNO_3$ in DMF (eq 1). In step 2, the oxygen-bound ligands (DMF and $NO_3^-$) were readily displaced by the nucleophilic Am ligand, yielding the desired platinum–triamine complex. After removing the DMF and extracting unreacted ligand with $CH_2Cl_2$, the products were purified by recrystallization from methanol or water.

While both reactions can be used to prepare platinum–triamine complexes, better overall yields were obtained by using the $AgNO_3$/DMF method. This procedure was first used by Lippert et al. to prepare the related thymine complex *cis*-$[Pt(NH_3)_2(N1\text{-thymine})Cl]$.[13] There are several reasons why this method provides higher yields. First, in aqueous solution (method a), the concentration of platinum during the reaction is limited by the relatively low solubility of the *cis*-$[PtA_2Cl_2]$ complexes. This leads to an increase in disubstituted products (*cis*-$[PtA_2(Am)_2]^{2+}$) as the Am to platinum ratio is large during the initial stages of the reaction. Second, the oxygen-bound ligands in the intermediate complexes, *cis*-$[PtA_2(O_d)Cl]^+$ ($O_d$ = *O1*-DMF and $NO_3^-$), are much better leaving groups than the chloride ligand. This leads to faster substitution kinetics and a reduction in the amount of disubstituted byproducts. Furthermore, as discussed below, a more favorable distribution of monochloro intermediates is obtained when DMF is used as the solvent.

$^{195}Pt$ NMR studies of the reaction between *cis*-$[Pt(^{15}NH_3)_2Cl_2]$ and 1 equiv of $AgNO_3$ in DMF (0.2 M) show that six platinum species remain in solution following AgCl filtration (after 24 h). As shown in Table I, the monochloro complexes, *cis*-$[Pt(^{15}NH_3)_2(O1\text{-DMF})Cl]^+$ and *cis*-$[Pt(^{15}NH_3)_2(NO_3)Cl]$, constitute ~80% of the platinum in solution under these conditions. The favorable distribution of these monochloro species improves the yield of the *cis*-$[PtA_2(Am)Cl]^+$ complex upon reaction with the chosen Am ligand. When the analogous reaction between $AgNO_3$ and *cis*-$[Pt(^{15}NH_3)_2Cl_2]$ is conducted in water, a lower yield of the reactive monochloro intermediate, *cis*-$[Pt(^{15}NH_3)_2(H_2O)Cl]^+$, is obtained (57%, see Table I). Furthermore, the relatively high concentration of the diaquadiammine complex, *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2]^{2+}$ (39%), produces a larger proportion of disubstituted byproducts when the reaction is conducted in water. The oxygen-bound nitrate complexes, *cis*-$[PtA_2(NO_3)Cl]^+$ and *cis*-$[PtA_2(NO_3)_2]$, are also formed to a lesser extent in water than in DMF (apparently a result of the enhanced ionic strength of the aqueous medium).

Using the methods described above, we have prepared a total of 34 platinum–triamine analogues of the form *cis*- or *trans*-$[PtA_2(Am)Cl]^+$ for evaluation in murine tumor screens. While a number of reports on triamine complexes of this type, where Am is a pyrimidine,[13,14] purine,[15] or a

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**Table II.** $^{195}$Pt NMR Data for *cis*-[Pt(RNH$_2$)$_2$(Am)Cl]$^+$ Complexes[a]

| compound | $\delta$ ($^{195}$Pt),[b] ppm |
|---|---|
| *cis*-[Pt(NH$_3$)$_2$(*N1*-pyridine)Cl]Cl (1) | −2289 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-2-OH-pyridine)Cl]Cl (2) | −2287 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-6-Me-2-OH-pyridine)Cl]Cl (3) | −2264 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-3-OH-pyridine)Cl]Cl (4) | −2291 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-6-Me-3-OH-pyridine)Cl]Cl (6) | −2277 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-4-Cl-pyridine)Cl]Cl (7) | −2279 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-4-Me-pyridine)Cl]Cl (11) | −2289 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-4-Et-pyridine)Cl]Cl (12) | −2290 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-4-Br-pyridine)Cl]Cl (13) | −2280 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-4-N(Me)$_2$-pyridine)Cl](NO$_3$) (14) | −2273 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-Me-isonicotinate)Cl]Cl (15) | −2285 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-4-Me-piperidine)Cl](NO$_3$) (24) | −2410 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-cyclohexylmethylamine)Cl](NO$_3$) (27) | −2408 |
| *cis*-[Pt(NH$_3$)$_2$(*N2*-isopropylamine)Cl](NO$_3$) (28) | −2410 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-octylamine)Cl](NO$_3$) (29) | −2406 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-quinuclidine)Cl](NO$_3$) (30) | −2304 |
| *cis*-[Pt(NH$_3$)$_2$(*N2*-1-MeO-isopropylamine)Cl](NO$_3$) (31) | −2407 |
| *cis*-[Pt(NH$_3$)$_2$(*N3*-cytosine)Cl]Cl (10) | −2379 |
| *cis*-[Pt(NH$_3$)$_2$(*N3*-1-Me-cytosine)Cl]Cl (16) | −2365 |
| *cis*-[Pt(NH$_3$)$_2$(*N3*-5-Me-cytosine)Cl]Cl (17) | −2358 |
| *cis*-[Pt(NH$_3$)$_2$(*N9*-DHPT)Cl](NO$_3$) (18) | −2234 |
| *cis*-[Pt(NH$_3$)$_2$(*N3*-cytidine)Cl](NO$_3$) (19) | −2358 |
| *cis*-[Pt(NH$_3$)$_2$(*N7*-guanosine)Cl](NO$_3$) (20) | −2290 |
| *cis*-[Pt(NH$_3$)$_2$(*N3*-2′-deoxycytidine)Cl]Cl (21) | −2357 |
| *cis*-[Pt(NH$_3$)$_2$(*N3*-ara-C)Cl](NO$_3$) (22) | −2355 |
| *cis*-[Pt(NH$_3$)$_2$(*N7*-2′-deoxyguanosine)Cl]Cl (23) | −2280 |
| *cis*-[Pt(NH$_3$)$_2$(*N1*-4-Me-pyridine)Br](NO$_3$) (33) | −2409 |
| [Pt(en)(*N1*-pyridine)Cl]Cl (8) | −2523 |
| [Pt(dach)(*N1*-pyridine)Cl](NO$_3$) (9) | −2465[c] |
| | −2490[c] |
| *cis*-[Pt(*i*-PrNH$_2$)$_2$(*N1*-4-Me-pyridine)Cl](NO$_3$) (25) | −2381 |
| [Pt(en)(*N1*-4-Me-pyridine)Cl](NO$_3$) (26) | −2517 |
| [Pt(*trans*-(*R,R*)-dach)(*N1*-4-Me-pyridine)Cl](NO$_3$) (32) | −2487 |
| *trans*-[Pt(NH$_3$)$_2$(*N1*-pyridine)Cl]Cl (5) | −2310 |
| *trans*-[Pt(NH$_3$)$_2$(*N1*-4-Me-pyridine)Cl](NO$_3$) (34) | −2312 |

[a] Abbreviations: DHPT = 7-(2,3-dihydroxypropyl)theophylline; ara-C = 1-β-D-arabinofuranosylcytosine. [b] Chemical shifts are referenced relative to $H_2PtCl_6$ at 0 ppm. [c] Unresolved cis and trans dach isomers.

pyridine[16] base, have appeared in the literature, these analogues do not appear to have been tested for antitumor activity. In this study, all platinum–triamine complexes were characterized by means of NMR ($^{195}$Pt and $^{13}$C), HPLC, and elemental analysis. HPLC and $^{195}$Pt NMR studies were conducted to insure that the samples were not contaminated with *cis*-[PtA$_2$Cl$_2$]-related products.

A listing of the $^{195}$Pt chemical shifts for each compound in this series is presented in Table II. Since the position of the $^{195}$Pt resonance is influenced by the donor strength of the ligands attached to platinum,[17] this information can be used to gauge the relative donor strengths of the amine ligands in this series. A comparison of the $^{195}$Pt NMR data for the various *cis*-[Pt(NH$_3$)$_2$(Am)Cl]$^+$ complexes shows that the analogues containing pyridine bases have chemical shifts that are ~100 ppm downfield relative to those containing pyrimidine bases (a result of the enhanced donor strength of the pyrimidine ligands). The ordering of ligand donor strengths for the Am series generally follows the sequence alkylamine > pyrimidine > purine ≈ pyridine. The $^{195}$Pt resonances of the alkylamine complexes, *cis*-[Pt(RNH$_2$)$_2$(Am)Cl]$^+$, also appear upfield, relative to the diammine analogues, as a result of the increased donor strength of the amine ligands (en > dach > *i*-PrNH$_2$ > NH$_3$). As discussed below, a clear relationship between the donor strength of the Am ligand and antitumor activity has not emerged from the results of these studies.

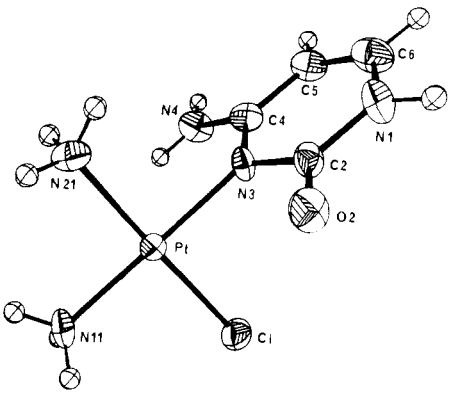


**Figure 1.** ORTEP illustration of the *cis*-[Pt(NH$_3$)$_2$(*N3*-cytosine)Cl]$^+$ cation in **10**. Non-hydrogen atoms are shown by using 40% probability thermal ellipsoids; hydrogen atoms are depicted as spheres, with *B* set to 1 Å$^2$ for clarity.

One member of the series, *cis*-[Pt(NH$_3$)$_2$(*N3*-cytosine)Cl]Cl (**10**), was chosen for X-ray crystallographic studies in an attempt to determine which of the two potential binding sites on the cytosine ligand, N1 or N3, is attached to platinum. As illustrated in Figure 1, the results of these studies show that the metal is bound to the N3 site. The structural data obtained on **10** are very similar to those reported for the related pyrimidine complexes: *cis*-[Pt(NH$_3$)$_2$(*N3*-1-methylcytosine)Cl](NO$_3$) (**16**),[14b] *cis*-[Pt(NH$_3$)$_2$(*N3*-1-methylcytosine)Cl]$_2$[Pt(CN)$_4$] (**36**),[14j] and [Pt(en)(*N3*-ara-C)Cl].[14i] The geometry of both the platinum coordination plane and the cytosine ligand in **10** compares favorably with that found in 1-methylcytosine complexes **16** and **36**. The N3 binding site on cytosine has also been implicated as a potential binding site for platinum on double-stranded DNA.[18] Further details of the X-ray crystallographic study on **10** are given as supplementary material in Tables S1–S3 and Figure S1.

**Biological Studies of the *cis*-[Pt(diamine)(Am)Cl]$^+$ Complexes.** All of the subject compounds were tested against Sarcoma 180 ascites (S180a) in female CFW mice

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**Table III.** Optimum Screening Results for Platinum–Triamine Complexes vs S180a

| compound | best %ILS | optimum dose,[a] mg/kg |
|---|---|---|
| *cis*-[$Pt(NH_3)_2$(*N1*-pyridine)Cl]Cl (1) | 103 | 40 |
| *cis*-[$Pt(NH_3)_2$(*N1*-2-OH-pyridine)Cl]Cl (2) | 97 | 160 |
| *cis*-[$Pt(NH_3)_2$(*N1*-6-Me-2-OH-pyridine)Cl]Cl (3) | 93 | 160 |
| *cis*-[$Pt(NH_3)_2$(*N1*-3-OH-pyridine)Cl]Cl (4) | 69 | 80 |
| *trans*-[$Pt(NH_3)_2$(*N1*-pyridine)Cl]Cl (5) | 26 | 80 |
| *cis*-[$Pt(NH_3)_2$(*N1*-6-Me-3-OH-pyridine)Cl]Cl (6) | 93 | 80 |
| *cis*-[$Pt(NH_3)_2$(*N1*-4-Cl-pyridine)Cl]Cl (7) | 77 | 40 |
| [Pt(en)(*N1*-pyridine)Cl]($NO_3$) (8) | 17 | 80 |
| [Pt(dach)(*N1*-pyridine)Cl]Cl (9) | 25 | 80 |
| *cis*-[$Pt(NH_3)_2$(*N3*-cytosine)Cl]Cl (10) | 92 | 80 |
| *cis*-[$Pt(NH_3)_2$(*N1*-4-Me-pyridine)Cl]Cl (11) | 83 | 40 |
| *cis*-[$Pt(NH_3)$(*N1*-4-Et-pyridine)Cl]Cl (12) | 24 | 80 |
| *cis*-[$Pt(NH_3)_2$(*N1*-4-Br-pyridine)Cl]Cl (13) | 102 | 80 |
| *cis*-[$Pt(NH_3)_2$(*N1*-4-$N(Me)_2$-pyridine)Cl]($NO_3$) (14) | 78 | 40 |
| *cis*-[$Pt(NH_3)_2$(*N1*-Me-isonicontinate)Cl]Cl (15) | 31 | 80 |
| *cis*-[$Pt(NH_3)_2$(*N3*-1-Me-cytosine)Cl]($NO_3$) (16) | 73 | 40 |
| *cis*-[$Pt(NH_3)_2$(*N3*-5-Me-cytosine)Cl]Cl (17) | 84 | 160 |
| *cis*-[$Pt(NH_3)_2$(*N9*-DHPT)Cl]($NO_3$) (18) | 95 | 320 |
| *cis*-[$Pt(NH_3)_2$(*N3*-cytidine)Cl]($NO_3$) (19) | 30 | 320 |
| *cis*-[$Pt(NH_3)_2$(*N7*-guanosine)Cl]($NO_3$) (20) | 79 | 160 |
| *cis*-[$Pt(NH_3)_2$(*N3*-2′-deoxycytidine)Cl]Cl (21) | 85 | 80 |
| *cis*-[$Pt(NH_3)_2$(*N3*-ara-C)Cl]($NO_3$) (22) | 51 | 160 |
| *cis*-[$Pt(NH_3)_2$(*N7*-2′-deoxyguanosine)Cl]Cl (23) | 88 | 80 |
| *cis*-[$Pt(NH_3)_2$(*N1*-4-Me-piperidine)Cl]($NO_3$) (24) | 76 | 80 |
| *cis*-[Pt(*i*-$PrNH_2)_2$(*N1*-4-Me-pyridine)Cl]($NO_3$) (25) | 16 | 80 |
| [Pt(en)(*N1*-4-Me-pyridine)Cl]($NO_3$) (26) | 14 | 10 |
| *cis*-[$Pt(NH_3)_2$(*N1*-cyclohexylmethylamine)Cl]($NO_3$) (27) | 61 | 80 |
| *cis*-[$Pt(NH_3)_2$(*N2*-isopropylamine)Cl]($NO_3$) (28) | 13 | 40 |
| *cis*-[$Pt(NH_3)_2$(*N1*-octylamine)Cl]($NO_3$) (29) | 25 | 20 |
| *cis*-[$Pt(NH_3)_2$(*N1*-quinuclidine)Cl]($NO_3$) (30) | 59 | 80 |
| *cis*-[$Pt(NH_3)_2$(*N2*-1-MeO-isopropylamine)Cl]($NO_3$) (31) | 34 | 40 |
| [Pt(*trans*-(*R,R*)-dach)(*N1*-4-Me-pyridine)Cl]($NO_3$) (32) | 42 | 160 |
| *cis*-[$Pt(NH_3)_2$(*N1*-4-Me-pyridine)Br]($NO_3$) (33) | 43 | 80 |
| *trans*-[$Pt(NH_3)_2$(*N1*-4-Me-pyridine)Cl]($NO_3$) (34) | 2 | 20 |
| cisplatin | 81 (12)[b] | 8 |

[a] Compounds given over 6 dose-doublings up to 320 mg/kg. [b] Average (std dev) for positive control.

(see Table III). Of the 34 compounds tested, 20 achieved an ILS of 50% or more in the S180a screen. While these compounds displayed activities comparable to or greater than that obtained with cisplatin, they were from 2.5 to 20 times less potent on a mole-equivalent basis. The compounds showing the best combination of activity and potency were *cis*-[$Pt(NH_3)_2$(*N1*-pyridine)Cl]Cl (1), *cis*-[$Pt(NH_3)_2$(*N1*-4-chloropyridine)Cl]Cl (7), *cis*-[$Pt(NH_3)_2$-(*N3*-cytosine)Cl]Cl (10), *cis*-[$Pt(NH_3)_2$(*N1*-4-methylpyridine)Cl]Cl (11), *cis*-[$Pt(NH_3)_2$(*N1*-4-bromopyridine)-Cl]Cl (13), and *cis*-[$Pt(NH_3)_2$(*N7*-2′-deoxyguanosine)Cl]Cl (23). In a few cases, relatively minor structural changes were found to produce inactivity in this series. For example, *cis*-[$Pt(NH_3)_2$(*N1*-4-ethylpyridine)Cl]Cl (12) and *cis*-[$Pt(NH_3)_2$(*N1*-4-methylpyridine)Br]($NO_3$) (33) were inactive while the related 4-methyl analogue, *cis*-[Pt-$(NH_3)_2$(*N1*-4-methylpyridine)Cl]Cl (11), was active. The corresponding trans isomers of active *cis*-diammine complexes, in which the Am ligand is pyridine (5) or 4-methylpyridine (34), as well as compounds containing chelating diamine ligands, [Pt(en)(*N1*-pyridine)Cl]($NO_3$) (8), [Pt(dach)(*N1*-pyridine)Cl]Cl (9), [Pt(en)(*N1*-4-methylpyridine)Cl]($NO_3$) (26), and [Pt(*trans*-(*R,R*)-dach)(*N1*-4-methylpyridine)Cl]($NO_3$) (32) or a saturated amine, *cis*-[Pt(*i*-$PrNH_2)_2$(*N1*-4-methylpyridine)Cl]($NO_3$) (25), also were inactive in the S180a screen.

A number of the compounds were evaluated in two murine leukemia screens (see Table IV). Of the 16 platinum–triamine complexes that were tested in the L1210 leukemia screen, 4 of these analogues, *cis*-[Pt-$(NH_3)_2$(*N3*-cytosine)Cl]Cl (10), *cis*-[$Pt(NH_3)_2$(*N1*-4-bromopyridine)Cl]Cl (13), *cis*-[$Pt(NH_3)_2$(*N1*-2′-deoxycytidine)Cl]Cl (21), *cis*-[$Pt(NH_3)_2$(*N1*-4-methylpiperidine)Cl]($NO_3$) (24), were active. Three platinum–triamine compounds, *cis*-[$Pt(NH_3)_2$(*N1*-pyridine)Cl]Cl (1), *cis*-[$Pt(NH_3)_2$(*N1*-2-hydroxypyridine)Cl]Cl (2), and *cis*-[$Pt(NH_3)_2$(*N3*-cytosine)Cl]Cl (10), were also screened and found active vs P388 leukemia. While all of the platinum–triamine complexes were less active and less potent than cisplatin in these screens, the best combination of activity and potency was observed with the pyridine (1), 4-bromopyridine (13), and 4-methylpiperidine (24) analogues.

Examination of the screening data presented in Tables III and IV shows that the observed activity is dependent on both the nature and the orientation of the amine ligands within the $[PtA_2(Am)X]^+$ series. In general, a cis configuration of $NH_3$ ligands is required for activity, as all chelating diamine ($A_2$ = dach and en) and *trans*-diammine analogues that have been tested to date are inactive. Both the amine ligand (Am) and the leaving group (X) also influence the antitumor activity. The active analogues contain heterocyclic, secondary, or tertiary Am ligands, while those containing primary Am ligands (28, 29, and 31) are inactive. Additional relationships between antitumor activity and nature of the Am ligand are not evident from the data that are currently available on these compounds. As for the effect of the leaving group, in the one case where the chloride ligand in the active complex *cis*-[$Pt(NH_3)_2$(*N1*-4-methylpyridine)Cl]$^+$ (11) was replaced with bromide, the resulting complex (33) was inactive. Clearly, further examples will be required to gain a better understanding of the structure–activity relationships within this series of complexes.

**Table IV.** Optimum Screening Results for Platinum–Triamine Complexes vs L1210 and P388

| compound | L1210 best %ILS | L1210 optimum dose,[a] mg/kg | P388 best %ILS | P388 optimum dose,[a] mg/kg |
|---|---|---|---|---|
| *cis*-[Pt($NH_3$)$_2$(*N1*-pyridine)Cl]Cl (1) | | | 72 | 80 |
| *cis*-[Pt($NH_3$)$_2$(*N1*-2-OH-pyridine)Cl]Cl (2) | | | 82 | 150 |
| *cis*-[Pt($NH_3$)$_2$(*N1*-4-Cl-pyridine)Cl]Cl (7) | 23 | 80 | | |
| [Pt(en)(*N1*-pyridine)Cl]($NO_3$) (8) | 7 | 80 | | |
| *cis*-[Pt($NH_3$)$_2$(*N3*-cytosine)Cl]Cl (10) | 38 | 160 | 90 | 300 |
| *cis*-[Pt($NH_3$)$_2$(*N1*-4-Me-pyridine)Cl]Cl (11) | 13 | 40 | | |
| *cis*-[Pt($NH_3$)$_2$(*N1*-4-Et-pyridine)Cl]Cl (12) | 21 | 80 | | |
| *cis*-[Pt($NH_3$)$_2$(*N1*-4-Br-pyridine)Cl]Cl (13) | 51 | 20 | | |
| *cis*-[Pt($NH_3$)$_2$(*N1*-4-*N*($Me$)$_2$-pyridine)Cl]($NO_3$) (14) | 6 | 20 | | |
| *cis*-[Pt($NH_3$)$_2$(*N1*-Me-isonicontinate)Cl]Cl (15) | −5 | 10 | | |
| *cis*-[Pt($NH_3$)$_2$(*N3*-5-Me-cytosine)Cl]Cl (17) | 9 | 20 | | |
| *cis*-[Pt($NH_3$)$_2$(*N9*-DHPT)Cl]($NO_3$)[b] (18) | 24 | 160 | | |
| *cis*-[Pt($NH_3$)$_2$(*N7*-guanosine)Cl]($NO_3$) (20) | 8 | 160 | | |
| *cis*-[Pt($NH_3$)$_2$(*N3*-2′-deoxycytidine)Cl]Cl (21) | 59 | 320 | | |
| *cis*-[Pt($NH_3$)$_2$(*N3*-ara-C)Cl]($NO_3$)[b] (22) | 10 | 160 | | |
| *cis*-[Pt($NH_3$)$_2$(*N1*-4-Me-piperidine)Cl]($NO_3$) (24) | 60 | 40 | | |
| *cis*-[Pt($NH_3$)$_2$(*N1*-cyclohexylmethylamine)Cl]($NO_3$) (27) | 5 | 10 | | |
| [Pt(*trans*-(*R*,*R*)-dach)(*N1*-4-Me-pyridine)Cl]($NO_3$) (32) | 9 | 160 | | |
| cisplatin | 87 (39)[c] | 8 | | |

[a] Compounds given over 6 dose-doublings (maximum dose was 320 mg/kg for L1210 and 300 mg/kg for P388). [b] See Table II for abbreviations. [c] Average (std dev) for positive control.

## Discussion

The majority of the active cisplatin analogues are neutral *cis*-[$PtA_2X_2$] complexes that are capable of binding to their proposed biological target, DNA, in a bidentate fashion.[5] While in vivo antitumor activity has been reported for a small number of charged platinum compounds, these complexes are typically anionic species of the form [Pt(amine)$Cl_3$]$^-$, where the amine ligand is ammonia[3c] or *tert*-butylamine.[19] A few cationic complexes, which contain three nitrogen donors, such as [Pt($NH_3$)$_3$Cl]Cl[3c] and [Pt(dien)Cl]Cl,[3a] also have been screened, but they were found to be inactive in the S180a and L1210 screens. In contrast, the complexes described in this report are cationic platinum–triamine analogues that display good activity in murine tumor screens, even though they contain only one leaving group and are expected to bind to DNA in a monodentate fashion. Most of what is known about monofunctional binding of platinum complexes to DNA has been elucidated by using [Pt(dien)Cl]$^+$ as a model compound.[18b,20] The results of these studies have served to help establish the importance of bidentate Pt–DNA lesions in the mechanism of action of cisplatin.[5] While it is generally believed that platinum–triamine complexes lack activity as a result of their inability to produce bidentate lesions on DNA, the data presented here suggest that further studies will be required to explore the mechanistic implications of active monofunctional agents.

With respect to a possible mechanism of action, three of the platinum–triamine complexes, *cis*-[Pt($NH_3$)$_2$(*N3*-cytosine)Cl]Cl (10), *cis*-[Pt($NH_3$)$_2$(*N1*-4-methylpyridine)Cl]Cl (11), and *cis*-[Pt($NH_3$)$_2$(*N1*-4-bromopyridine)Cl]Cl (13), have been found to bind to DNA in vitro,[21] and the details of this interaction are presently being examined. Since the *cis*-[$PtA_2$(Am)Cl]$^+$ complexes are expected to bind DNA in a monodentate fashion, and this type of binding is not expected to result in antitumor activity, it is tempting to speculate that these complexes could achieve bidentate binding to DNA through an ammonia loss pathway. While facile ammonia release has been reported to occur when *cis*-[Pt($NH_3$)$_2$(*N3*-1-methylcytosine)Cl]Cl is heated in aqueous solutions,[22] the ammonia loss occurs at the site trans to the chloride ligand. In this case, it is difficult to envision that the resulting complex, *trans*-[Pt($NH_3$)(*N3*-1-methylcytosine)$Cl_2$], would be responsible for the observed antitumor response as, historically, *trans*-diammine complexes are devoid of activity. One can also conceive of bifunctional lesions occurring as a result of ammonia release at the site cis to the chloride ligand. In this case, it would be expected that the donor strength of the Am ligand would affect the antitumor properties, as a better Am donor should promote ammonia release and thereby enhance the activity. However, no such correlation is evident when the screening data are examined in relation to the $^{195}$Pt NMR data, which can be used to gauge Am ligand donor strength. Furthermore, there is no indication that ammonia release occurs in the reaction between *cis*-[Pt($^{15}NH_3$)$_2$(*N1*-pyridine)Cl]$^+$ and 2′-deoxyguanosine, as determined by $^{15}$N NMR studies.[21]

It is possible that the cationic *cis*-[$PtA_2$(Am)Cl]$^+$ complexes produce monofunctional lesions on DNA that are cytotoxic as a result of the interaction between the Am ligand and DNA. Perhaps an Am ligand, such as cytosine or pyridine, is positioned externally in the major grove of DNA, as a result of monofunctional binding at N7 sites of guanine bases, in such a fashion as to produce a disruptive and nonrepairable lesion on DNA. Or, perhaps these complexes act on intracellular targets other than DNA, and a different mechanism of antitumor activity is operative in this case. Further experiments that are designed to shed light on the possible mechanism of action of these novel complexes are in progress.

## Conclusion

Chemical and biological studies have been presented on a new series of platinum(II) antitumor agents that appear to violate some of the classical structure–activity relationships that have been established for platinum compounds. These new agents, which have demonstrated

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activity against S180a, P388, and L1210 in mice, are *cis*-$[Pt(NH_3)_2(Am)Cl]^+$ complexes, where Am is a heterocyclic amine based on pyridine, pyrimidine, purine, or piperidine substituents.

## Experimental Section

**Physical Methods.** NMR spectra were recorded with a Varian XL-200 spectrometer by using a 10-mm tunable probe (20–80 MHz). $^{195}Pt$ spectra (42.935 MHz) were collected by using a 9 μs (70°) pulse and a 0.06-s acquisition time with a spectral width of 80 kHz (19.6k data points). Spectra were processed with line broadening (200 Hz) and zero filling (64k). $^{195}Pt$ chemical shifts were referenced relative to an external sample of 0.1 M $K_2[PtCl_4]$ in $D_2O$ at −1624 ppm. The position of $K_2[PtCl_4]$ was measured relative to $H_2PtCl_6$ (1 g/3 mL $D_2O$) at 0 ppm. A Waters HPLC system, equipped with a Model 440 UV–vis detector system, was used to check sample purity. Analytical samples were run in water or 0.1 M ammonium acetate (pH 6), at a flow rate of 6 mL/min using a Novapak $C_{18}$ radial compression column (Z module), and absorbance was monitored at 254 nm. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

**X-ray Crystallography.** The unit cell parameters and intensity data for compound **10** were measured with an Enraf-Nonius CAD-4F single-crystal diffractometer. Compound **10** crystallizes in the monoclinic space group $P2_1/c$ ($C_{2h}^5$, No. 14),[6] as determined from systematic absences and axial photographs, with the following unit cell parameters: $a = 6.6708$ (4), $b = 7.6446$ (5), and $c = 20.340$ (2) Å; $\beta = 98.470$ (5)°; $V = 1025.9$ Å$^3$; $Z = 4$. Full details of the data collection and refinement are presented as supplementary material (Table S1). The structure was solved, by means of standard Patterson and Fourier methods, using 2122 unique reflections ($2\theta < 50°$). Neutral atom scattering factors, anomalous dispersion corrections,[7] and hydrogen atom scattering factors[8] were used in conjunction with SHELX-76[9] for structure refinement. Anisotropic thermal parameters were used for all non-hydrogen atoms. Hydrogen atoms were placed at calculated positions and constrained to "ride" on the atoms to which they are attached, using a common thermal parameter for N-H and C-H hydrogen atoms. Full-matrix least-squares refinement using 138 parameters converged at $R_1 = 0.038$ and $R_2 = 0.045$.[10] The function minimized during refinement was $\sum w(|F_o| - |F_c|)^2$, where $w = 0.408/[\sigma^2(F_o) + 0.000\,625F_o^2]$. The largest peaks (<2.1 e Å$^{-3}$) on the final difference map were in the vicinity of the Pt atom (<1.0 Å). Further details on the refinement, including a complete listing of atomic positional and thermal parameters, a table of interatomic bond lengths and angles, a crystal packing diagram, and a listing of observed and calculated structure factors are availabe as supplementary material (Tables S1–S3, Figure S1).

**Compound Preparation.** All *cis*-$[Pt(amine)_2Cl_2]$ starting materials were prepared from $K_2[PtCl_4]$ (Engelhard) by using the method of Dhara.[11] All other reagents were obtained from commercial sources. All compounds were analyzed by using HPLC techniques to insure that the products were free of *cis*-$[Pt(amine)_2Cl_2]$ starting materials. Compounds were considered to be pure when less than 0.1% impurity was detected by HPLC.

***cis*-[Pt(NH$_3$)$_2$(*N1*-pyridine)Cl]Cl (1).** *cis*-$[Pt(NH_3)_2Cl_2]$ (6.00 g) and pyridine (1.6 mL) were added to 1 L of water and heated to 60 °C with stirring for 2 h. The reaction mixture was cooled to room temperature and stirred for 72 h. The volume was then reduced to 100 mL, at which time unreacted *cis*-$[Pt(NH_3)_2Cl_2]$ was removed by filtration. The filtrate was taken to dryness and the resulting yellowish white solid was recrystallized once from 0.1 N HCl, once from 0.5 N HCl, and once from methanol (yield 1.92 g, white crystals). Anal. ($PtC_5H_{11}N_3Cl_2$) Pt, C, H, N, Cl.

***cis*-[Pt(NH$_3$)$_2$(*N1*-hydroxypyridine)Cl]Cl·H$_2$O (2).** *cis*-$[Pt(NH_3)_2Cl_2]$ (15.0 g) and 2-hydroxypyridine (10.7 g) were stirred in 1.35 L of water at 60 °C for 48 h. The resulting solution was cooled and evaporated to a volume of ~150 mL and filtered to remove a greenish solid. The solution was then evaporated to dryness and the solid was stirred in 500 mL of $CH_2Cl_2$ to remove unreacted ligand. After the solid was filtered and air-dried, the crude product was dissolved in 650 mL of methanol, and a small amount of yellow solid was removed by filtration. The filtrate was evaporated to dryness and the solid was recrystallized from 30 mL of 0.1 N HCl (yield 6.2 g, white crystals). Anal. ($PtC_5H_{13}N_3O_2Cl_2$) C, H, N, Cl.

***cis*-[Pt(NH$_3$)$_2$(*N1*-6-methyl-2-hydroxypyridine)Cl]Cl (3).** *cis*-$[Pt(NH_3)_2Cl_2]$ (10.0 g) and 6-methyl-2-hydroxypyridine (5.0 g) were stirred in 900 mL of water at 60 °C for 48 h. A dark brown solid was filtered from the reaction mixture and the filtrate was evaporated to a volume of ~450 mL. The yellow precipitate that formed was removed by filtration, and the filtrate was evaporated to dryness. The crude product was treated with methanol (500 mL) and the insoluble portion was removed by filtration. The filtrate was taken to dryness and the resulting solid was treated with $CHCl_3$ (100 mL). The chloroform-insoluble portion was collected and air-dried. The resulting product (6.4 g of khaki green solid) was recrystallized from methanol/0.1 N HCl (yield 2.6 g, white crystals). Anal. ($PtC_6H_{13}N_3OCl_2$) Pt, C, H, N, Cl.

***cis*-[Pt(NH$_3$)$_2$(*N1*-3-hydroxypyridine)Cl]Cl (4).** *cis*-$[Pt(NH_3)_2Cl_2]$ (10.0 g) and 3-hydroxypyridine (7.2 g) were stirred in 900 mL of water at 60 °C until the solution became clear (48 h). The solution was evaporated to a volume of ~450 mL, and a yellow solid was removed by filtration. The filtrate was taken to dryness and the solid was dissolved in methanol (25 mL). The insoluble portion was removed by filtration and the methanol solution was evaporated to dryness. The remaining solid was recrystallized from hot 0.1 N HCl (yield 3.30 g, white crystals). Anal. ($PtC_5H_{11}N_3OCl_2$) Pt, C, H, N, Cl.

***trans*-[Pt(NH$_3$)$_2$(*N1*-pyridine)Cl]Cl (5).** *trans*-$[Pt(NH_3)_2Cl_2]$ (2.05 g) and pyridine (0.66 mL) were stirred in 500 mL of water at 60 °C for 24 h. The resulting solution was evaporated to dryness under vacuum. The remaining solid was dissolved in 30 mL of hot water (steam bath). After the solution was cooled to 5 °C for 1 h, a white solid was collected by filtration and it was washed with a small quantity of cold water and methanol (yield 1.3 g, white crystals). Anal. ($PtC_5H_{11}N_3Cl_2$) Pt, C, H, N, Cl.

***cis*-[Pt(NH$_3$)$_2$(*N1*-6-methyl-3-hydroxypyridine)Cl]Cl (6).** A mixture of 6.0 g of *cis*-$[Pt(NH_3)_2Cl_2]$ and 2.4 g of 6-methyl-3-hydroxypyridine in 1 L of water was heated at 55 °C for 3 days. The resulting solution was cooled to room temperature and then evaporated to a volume of 35 mL on a rotary evaporator. This solution was mixed with 100 mL of methanol and filtered to remove unreacted *cis*-$[Pt(NH_3)_2Cl_2]$. The filtrate was evaporated at room temperature, which produced a white crystalline solid. This material was further recrystallized from methanol (yield 1.4 g). Anal. ($PtC_6H_{13}N_3OCl_2$) Pt, C, H, N, Cl.

***cis*-[Pt(NH$_3$)$_2$(*N1*-4-chloropyridine)Cl]Cl (7).** *cis*-$[Pt(NH_3)_2Cl_2]$ (6.0 g) and 4-chloropyridine (3.1 g) were added to 1 L of water and the mixture was stirred at 60 °C for 48 h. After cooling the mixture on ice, the unreacted cisplatin was removed by filtration and the filtrate was concentrated and refiltered. The filtrate was taken to dryness and the residue was recrystallized from hot methanol (yield 2.1 g, white crystals). Anal. ($PtC_5H_{10}N_3Cl_3$) Pt, C, H, N, Cl.

**[Pt(en)(*N1*-pyridine)Cl]Cl (8).** A mixture of 6.52 g of $[Pt(en)Cl_2]$ and 3.38 g of $AgNO_3$ was stirred in 200 mL of DMF for 16 h at room temperature. The resulting solution was filtered to remove the AgCl precipitate and the filtrate was treated with 1.1 mL of pyridine. After stirring the solution for 16 h under $N_2$, it was added to 500 mL of ether and the resulting mixture was stirred for an additional 30 h. The solvent was then decanted, leaving a gummy solid which was recrystallized once from 0.1 M HCl (20 mL) and twice from water (20 mL). The resulting solid was dissolved in 20 mL of methanol, filtered, and evaporated to dryness (yield 1.1 g, white crystals). Anal. ($PtC_7H_{13}N_4O_3Cl$) Pt, C, H, N, Cl.

**[Pt(dach)(*N1*-pyridine)Cl]Cl (9).** $[Pt(dach)Cl_2]$ (3.8 g) and $AgNO_3$ (1.7 g) were stirred in 100 mL of DMF for 2 h at room temperature. The AgCl precipitate was removed by filtration and 0.8 g of pyridine was added to the filtrate. After stirring the solution for 18 h, it was refiltered and the filtrate was poured into 300 mL of ether. The supernatant was decanted and the oily precipitate was stirred in 2-propanol and filtered. The filtrate was evaporated to dryness and the resulting solid was washed with ethanol. The product was recrystallized from methanol (yield 0.6 g, white solid). Anal. ($PtC_{11}H_{19}N_3Cl_2$) Pt, C, H, N, Cl.

***cis*-[Pt(NH$_3$)$_2$(*N3*-cytosine)Cl]Cl (10).** A solution of 6.0 g of *cis*-$[Pt(NH_3)_2Cl_2]$ and 2.3 g of cytosine in 1 L of water was stirred at 60 °C for 2 days. The solution was then cooled to room temperature and filtered, and the filtrate was evaporated to a

volume of 30 mL using a rotary evaporator. A light purple solid was removed from this solution after cooling at 4 °C for 2 h. The solid (**10**) was recrystallized two times from 0.5 M HCl (15 mL) and once from water (yield 1.1 g). Anal. ($PtC_4H_{11}N_5OCl_2$) Pt, C, H, N, Cl.

***cis*-[Pt($NH_3$)$_2$(*N1*-4-methylpyridine)Cl]Cl (11).** *cis*-[Pt($NH_3$)$_2$Cl$_2$] (6.0 g) and 4-methylpyridine (1.95 mL) were stirred in 750 mL of water at 55 °C for 36 h. The volume of the solution was then reduced under vacuum to 50 mL and the insoluble material was removed by filtration. The filtrate was taken to dryness and the residue was stirred in 20 mL of ethanol. The resulting mixture was filtered and the filtrate was evaporated to dryness, leaving 2.1 g of product, which was recrystallized from water and methanol. Anal. ($PtC_6H_{13}N_3Cl_2$) Pt, C, H, N, Cl.

***cis*-[Pt($NH_3$)$_2$(*N1*-4-ethylpyridine)Cl]Cl (12).** Cisplatin (6.0 g) and 4-ethylpyridine (2.14 g) were stirred in water (750 mL) for 20 h at 50 °C. After cooling the solution, it was reduced to dryness under vacuum, and the residue was extracted with 100 mL of hot methanol. The methanol solution was filtered while hot and taken to dryness, and the remaining solid was stirred under 150 mL of $CH_2Cl_2$ for 15 min. The solid was filtered, air-dried, and recrystallized twice from a small volume of hot water (yield 0.97 g, white solid). Anal. ($PtC_7H_{15}N_3Cl_2$) C, H, N.

***cis*-[Pt($NH_3$)$_2$(*N1*-4-bromopyridine)Cl]Cl (13).** Cisplatin (6.0 g) and 4-bromopyridine hydrochloride (3.89 g) were stirred in water (750 mL) for 36 h at 50 °C. The solution was cooled and the volume was reduced to ~30 mL. The unreacted cisplatin was removed by filtration, and the filtrate was taken to dryness. The residue was extracted with 100 mL of hot methanol, and the extract was filtered and evaporated to dryness under vacuum. The remaining solid was stirred under $CH_2Cl_2$ (150 mL) for 30 min, filtered, and air-dried. The product was recrystallized from 20 mL of hot water (yield 2.34 g, light yellow solid). Anal. ($PtC_5H_{10}N_3Cl_2Br$) C, H, N.

***cis*-[Pt($NH_3$)$_2$(*N1*-4-(*N*,*N*-dimethylamino)pyridine)Cl]($NO_3$) (14).** Cisplatin (6.0 g) and $AgNO_3$ (3.39 g) were stirred in 100 mL of DMF for 24 h at room temperature. The resulting AgCl precipitate was removed by filtration and 4-(*N*,*N*-dimethylamino)pyridine (2.443 g) was added to the filtrate. After the solution was stirred for an additional 24 h, the DMF was removed under vacuum, and the remaining oil was stirred under 150 mL of $CH_2Cl_2$ for 1 h. The resulting solid was filtered and extracted with hot methanol (100 mL). The methanol extract was filtered while hot and the filtrate was refrigerated at 4 °C. After 24 h, a white crystalline product was collected by filtration, washed with a small quantity of methanol, and vacuum-dried (yield 3.10 g). Anal. ($PtC_7H_{16}N_5O_3Cl$) C, H, N.

***cis*-[Pt($NH_3$)$_2$(*N1*-methyl isonicotinate)Cl]Cl (15).** Cisplatin (6.0 g) and methyl isonicotinate (2.74 mL) were stirred in 750 mL of water at 60 °C for 24 h. Upon cooling, the mixture was filtered and the filtrate was concentrated to a volume of ~30 mL under vacuum. After a second filtration, the remaining filtrate was taken to dryness. The resulting solid was treated with 100 mL of hot methanol and the solution was filtered while hot. The filtrate was evaporated to dryness under vacuum and the solid that remained was shaken with 50 mL of $CH_2Cl_2$ for 30 min. The product was then filtered and recrystallized from 10 mL of hot water (yield 1.05 g, white solid). Anal. ($PtC_7H_{13}N_3O_2Cl_2$) C, H, N.

***cis*-[Pt($NH_3$)$_2$(*N3*-1-methylcytosine)Cl]($NO_3$) (16).** Cisplatin (3.0 g) and $AgNO_3$ (1.69 g) were stirred in 50 mL of DMF at room temperature for 24 h. After the AgCl was removed by filtration, 1-methylcytosine (1.25 g) was added to the filtrate and the mixture was stirred for 24 h. During this period, a white solid formed. The solid was collected by filtration and it was recrystallized once from hot methanol and three times from hot water (yield 0.75 g). An additional 1.34 g of crude product was obtained by taking the DMF filtrate to dryness and shaking the residue with 150 mL of $CH_2Cl_2$. Anal. ($PtC_5H_{13}N_6O_4Cl$) C, H, N.

***cis*-[Pt($NH_3$)$_2$(*N3*-5-methylcytosine)Cl]Cl (17).** Cisplatin (6.0 g) and 5-methylcytosine (3.25 g) were stirred in 600 mL of water at 60 °C for 72 h. The mixture was cooled, filtered, and taken to dryness under vacuum. The residue was extracted once with $CHCl_3$ and three times with 100 mL of methanol. The remaining solid was treated with 10 mL of hot water and stirred briefly with decolorizing carbon, and the solution was filtered. The filtrate was refrigerated overnight and the resulting yellow solid was removed by filtration. The remaining filtrate was treated with 75 mL of ethanol and the white solid that formed after refrigeration at 4 °C for 5 days was collected by filtration and recrystallized from 10 mL of hot water. The yield was 1.2 g. Anal. ($PtC_5H_{13}N_5OCl_2$) C, H, N.

***cis*-[Pt($NH_3$)$_2$(*N9*-7-(2,3-dihydroxypropyl)theophylline)Cl]($NO_3$)·0.5 $H_2O$ (18).** Cisplatin (6.0 g) and $AgNO_3$ (3.39 g) were stirred in 100 mL of DMF at room temperature for 24 h. The mixture was filtered and 7-(2,3-dihydroxypropyl)theophylline (5.08 g) was added to the filtrate. After stirring the solution for 24 h, it was taken to dryness under vacuum. The residue was shaken with 100 mL of methylene chloride. A yellowish white solid was collected by filtration and it was extracted with ~100 mL of hot methanol. The methanol filtrate was taken to dryness and the residue, which contained solid and oil, was converted to a white solid by stirring under ethanol and removing the ethanol under vacuum (yield 2.58 g). Anal. ($PtC_{10}H_{21}N_7O_{7.5}Cl$) C, H, N.

***cis*-[Pt($NH_3$)$_2$(*N3*-cytidine)Cl]($NO_3$) (19).** Cisplatin (6.0 g) and $AgNO_3$ (3.39 g) were stirred in 100 mL of DMF at room temperature for 24 h. The AgCl precipitate was removed by filtration, cytidine (4.86 g) was added to the filtrate, and the mixture was stirred for 24 h. The DMF was removed under vacuum, and the residue was stirred in 150 mL of $CH_2Cl_2$. The resulting solid, which was collected by filtration, was dissolved in 20 mL of hot water and the solution was cooled to room temperature. A small amount of yellow solid was removed by filtration and ethanol was added to the filtrate. The resulting white solid was collected by filtration, and recrystallized from 10 mL of hot water (yield 2.00 g). Anal. ($PtC_9H_{19}N_6O_8Cl$) C, H, N.

***cis*-[Pt($NH_3$)$_2$(*N7*-guanosine)Cl]($NO_3$) (20).** Cisplatin (6.0 g) and $AgNO_3$ (3.39 g) were stirred in 100 mL of DMF at room temperature for 24 h. Silver chloride was removed by filtration, guanosine (5.66 g) was added to the filtrate, and the mixture was stirred for 24 h. Silver chloride was removed by filtration, guanosine (5.66 g) was added to the filtrate, and the mixture was stirred for 24 h. The DMF was removed under vacuum, and the residue was shaken in 150 mL of $CH_2Cl_2$ for 1 h. The resulting solid was filtered, air-dried, and recrystallized from 50 mL of hot water (yield 4.88 g). Anal. ($PtC_{10}H_{19}N_8O_8Cl$) C, H, N.

***cis*-[Pt($NH_3$)$_2$(*N3*-2′-deoxycytidine)Cl]Cl (21).** Cisplatin (3.0 g) and 2′-deoxycytidine (2.27 g) were stirred in 500 mL of water at 60 °C for 16 h. After the solution was cooled, unreacted cisplatin was filtered off and the volume was reduced to ~50 mL. Following a second filtration, the solution was taken to dryness and the residue was extracted with 200 mL of hot methanol. The extract was refrigerated overnight, and the resulting solid was collected by filtration and dried (yield 1.41 g). Anal. ($PtC_9H_{20}N_5O_5Cl_2$) C, H, N.

***cis*-[Pt($NH_3$)$_2$(*N3*-1-β-D-arabinofuranosylcytosine)Cl]($NO_3$)·$H_2O$ (22).** Cisplatin (3.0 g) and $AgNO_3$ (1.69 g) were stirred in 50 mL of DMF for 24 h. After the AgCl was filtered, 1-β-D-arabinofuranosylcytosine (1.11 g) was added to the filtrate and stirring was resumed for 24 h. The mixture was taken to low volume under vacuum, and 150 mL of $CH_2Cl_2$ was added to the concentrated mixture. The product was filtered off and dissolved in 10 mL of water, and the solution was filtered. The filtrate was treated with ethanol and the resulting precipitate was collected by filtration (yield 0.63 g). Anal. ($PtC_9H_{21}N_6O_9Cl$) C, H, N: calcd, 15.12; found, 14.70.

***cis*-[Pt($NH_3$)$_2$(*N7*-2′-deoxyguanosine)Cl]($NO_3$)·$H_2O$ (23).** Cisplatin (1.01 g) and $AgNO_3$ (0.571 g) were stirred in 25 mL of DMF for 24 h. The resulting AgCl precipitate was filtered off and 2′-deoxyguanosine (0.90 g) was added to the filtrate. After the mixture was stirred for 24 h, the DMF was removed under vacuum and the residue was stirred for 2 h in 100 mL of $CH_2Cl_2$. The resulting solid was collected by filtration and recrystallized once from hot water. This material was added to 5 mL of cold water and the undissolved cisplatin was removed by filtration. The product was recovered by removing the water as an azeotrope with ethanol (yield 0.28 g). Anal. ($PtC_{10}H_{21}N_8O_8Cl$) C, H, N.

***cis*-[Pt($NH_3$)$_2$(*N1*-4-methylpiperidine)Cl]($NO_3$) (24).** Cisplatin (6.0 g) and $AgNO_3$ (3.39 g) were stirred in 100 mL of DMF for 48 h at room temperature. After the precipitate was filtered, 4-methylpiperidine (2.28 mL) was added to the filtrate and the solution was stirred for 72 h at room temperature. The

solution was then filtered and taken to dryness under vacuum. The residue was stirred in $CH_2Cl_2$ for 4 h. A yellow solid was filtered off and recrystallized from 30 mL of hot water. The resulting crystals were treated with 100 mL of hot methanol and the solution was filtered while hot. Evaporation of the filtrate gave a white solid (yield 2.25 g). Anal. ($PtC_6H_{19}N_4O_3Cl$) C, H, N.

***cis*-[Pt(*i*-PrNH$_2$)$_2$(*N1*-4-methylpyridine)Cl](NO$_3$)·0.5H$_2$O (25).** *cis*-[Pt(*i*-PrNH$_2$)$_2$Cl$_2$] (2.0 g) and $AgNO_3$ (0.88 g) were stirred in 40 mL of DMF for 24 h at room temperature. The resulting AgCl was removed by filtration and 0.51 mL of 4-methylpyridine was added to the filtrate. After 24 h, the DMF was removed under vacuum and the remaining yellow oil was stored under vacuum (0.1 mm Hg) for 3 days. This material was recrystallized from 15 mL of hot water (yield 1.02 g). Anal. ($PtC_{12}H_{26}N_4O_{3.5}Cl$) C, H, N.

**[Pt(en)(*N1*-4-methylpyridine)Cl](NO$_3$) (26).** [Pt(en)Cl$_2$] (3.26 g) and $AgNO_3$ (1.69 g) were stirred in 50 mL of DMF for 24 h at room temperature. After the precipitate was filtered, 4-methylpyridine (0.97 mL) was added to the filtrate. After 24 h, the DMF was removed under vacuum, and the residue was shaken in 150 mL of $CH_2Cl_2$ overnight. The resulting solid was recrystallized twice from hot methanol (yield 0.69 g, white solid). Anal. ($PtC_8H_{15}N_4O_3Cl$) C, H, N.

***cis*-[Pt(NH$_3$)$_2$(*N1*-cyclohexylmethylamine)Cl](NO$_3$) (27).** *cis*-[Pt(NH$_3$)$_2$Cl$_2$] (6.0 g) and $AgNO_3$ (3.39 g) were stirred in 100 mL of DMF for 24 h at room temperature. The solution was filtered to remove AgCl, and cyclohexylmethylamine (2.60 mL) was added to the filtrate, and the mixture was stirred for 24 h at room temperature. The resulting solution was taken to dryness under vacuum and the remaining yellow solid was stirred for 2 h in 100 mL of $CH_2Cl_2$. The solid collected on a filter and this material was extracted with 200 mL of hot methanol. The methanol was evaporated under vacuum and the residue was recrystallized once from hot water and once from hot methanol (yield 0.82 g). Anal. ($PtC_7H_{21}N_4O_3Cl$) C, H, N.

***cis*-[Pt(NH$_3$)$_2$(*N2*-isopropylamine)Cl](NO$_3$) (28).** *cis*-[Pt(NH$_3$)$_2$Cl$_2$] (6.0 g) and $AgNO_3$ (3.39 g) were stirred in 100 mL of DMF for 24 h at room temperature. After the AgCl was filtered off, isopropylamine (1.7 mL) was added to the filtrate and the solution was stirred for an additional 24 h. The DMF was then removed under vacuum and the residue was stirred in 150 mL of $CH_2Cl_2$ for 1.5 h. A yellow solid was collected and it was dissolved in 10 mL of water and this solution was filtered to remove cisplatin. The filtrate was treated with 150 mL of ethanol and the volume was reduced to ~20 mL under vacuum. The white solid that formed after 18 h at 4 °C was collected by filtration. The solid was recrystallized twice from hot water (yield 1.67 g, white solid). Anal. ($PtC_3H_{15}N_4O_3Cl$) C, H, N.

***cis*-[Pt(NH$_3$)$_2$(*N1*-octylamine)Cl](NO$_3$) (29).** *cis*-[Pt(NH$_3$)$_2$Cl$_2$] (6.0 g) and $AgNO_3$ (3.39 g) were stirred for 24 h in 100 mL of DMF at room temperature. After AgCl filtration, 1-octylamine (3.3 mL) was added to the filtrate and the reaction mixture was stirred for 24 h. The DMF was removed under vacuum and the residue was shaken in 150 mL of $CH_2Cl_2$ for 3 h. The resulting solid was extracted with 100 mL of hot methanol. Upon evaporation of the methanol filtrate, a precipitate formed and it was collected by filtration. Further concentration of the filtrate (~30 mL) gave 2.36 g of **29**. Anal. ($PtC_8H_{25}N_4O_3Cl$) C, H, N.

***cis*-[Pt(NH$_3$)$_2$(*N1*-quinuclidine)Cl](NO$_3$) (30).** *cis*-[Pt(NH$_3$)$_2$Cl$_2$] (6.0 g) and $AgNO_3$ (3.39 g) were stirred in 100 mL of DMF for 72 h at room temperature. The resulting AgCl precipitate was removed by filtration and quinuclidine (2.22 g) was added to the filtrate. The reaction mixture was stirred at room temperature for 24 h. The DMF was removed under vacuum and the residue was stirred in 100 mL of $CH_2Cl_2$ for 2 h. The crude product was collected by filtration and it was extracted with 200 mL of hot methanol. Upon cooling the extract, a solid crystallized and it was removed by filtration (a second crop of solid was obtained from the filtrate). The crude product was recrystallized from water/ethanol and methanol (yield 0.46 g). Anal. ($PtC_7H_{19}N_4O_3Cl$) C, H, N.

***cis*-[Pt(NH$_3$)$_2$(*N2*-1-methoxyisopropylamine)Cl](NO$_3$) (31).** *cis*-[Pt(NH$_3$)$_2$Cl$_2$] (6.0 g) and $AgNO_3$ (3.39 g) were stirred in 100 mL of DMF for 24 h. After the AgCl was removed by filtration, 2-amino-1-methoxypropane (2.1 mL) was added to the filtrate and stirring was continued for 24 h. The DMF was removed under vacuum and the residue was shaken in $CH_2Cl_2$ for 2 h. The crude product was filtered and dissolved in 15 mL of water and refiltered. Ethanol (150 mL) was added to the filtrate and the volume was reduced under vacuum. The solution was cooled to 4 °C (18 h) and the solid was collected by filtration and recrystallized twice from hot methanol/decolorizing charcoal (yield 0.98 g, white needles). Anal. ($PtC_4H_{17}N_4O_4Cl$) C, H, N.

**[Pt(*trans*-(*R*,*R*)-dach)(*N1*-4-methylpyridine)Cl](NO$_3$) (32).** [Pt(*trans*-(*R*,*R*)-dach)Cl$_2$] (3.4 g) and $AgNO_3$ (1.52 g) were stirred in 50 mL of DMF for 24 h. After filtering the solution to remove the AgCl precipitate, 4-methylpyridine (0.87 mL) was added to the filtrate and the mixture was stirred for 24 h. A small amount of precipitate was removed, and the filtrate was reduced to a volume of ~15 mL under vacuum. This residue was treated with 150 mL of $CH_2Cl_2$ and the resulting yellow precipitate was filtered. Upon evaporating the $CH_2Cl_2$ filtrate to dryness and shaking the residue in an additional 150 mL of $CH_2Cl_2$ for 3 h, a white solid formed. This was collected and recrystallized from 10 mL of hot methanol/decolorizing charcoal. The yield was 0.83 g. Anal. ($PtC_{12}H_{21}N_4O_3Cl$) C, H, N.

***cis*-[Pt(NH$_3$)$_2$(*N1*-4-methylpyridine)Br](NO$_3$) (33).** *cis*-[Pt(NH$_3$)$_2$Br$_2$] (3.9 g) and $AgNO_3$ (1.69 g) were stirred in 50 mL of DMF for 24 h. The resulting AgBr was removed by filtration, 4-methylpyridine (0.98 mL) was added to the filtrate, and the mixture was stirred for 24 h. After the volume was reduced to ~5 mL under vacuum, 150 mL of $CH_2Cl_2$ was added and the mixture was stirred for 1 h. The resulting precipitate was collected by filtration and it was extracted with 100 mL of hot methanol. The methanol extract was evaporated under vacuum and the residue was dissolved in 10 mL of water. The solution was filtered and the filtrate was treated with ethanol. The volume was reduced under vacuum and the resulting solid was collected by filtration and washed with $CH_2Cl_2$ (yield 0.61 g). Anal. ($PtC_6H_{13}N_4O_3Br$) C, H, N: calcd, 12.07; found, 12.52.

***trans*-[Pt(NH$_3$)$_2$(*N1*-4-methylpyridine)Cl](NO$_3$) (34).** *trans*-[Pt(NH$_3$)$_2$Cl$_2$] (3.0 g) and $AgNO_3$ (1.69 g) were stirred in 50 mL of DMF for 16 h. After the AgCl precipitate was filtered, 4-methylpyridine (0.98 mL) was added to the filtrate and the mixture was stirred for 1 h. The solution was then filtered to remove a small quantity of solid and the filtrate was stirred for an additional 7 h. The volume of the solution was reduced to ~5 mL under vacuum and 100 mL of $CH_2Cl_2$ was added. The light yellow precipitate that formed was collected by filtration. The product was recrystallized from water/ethanol (yield 0.93 g). Anal. ($PtC_6H_{13}N_4O_3Cl$) C, H, N.

**Antitumor Screening. L1210 Leukemia.** L1210 screening was conducted according to previously described methods.[12] Female $CDF_1$ mice (16–22 g) were implanted with $1 \times 10^6$ tumor cells ip on day 0 and compounds were administered ip (in 0.5 mL of water) on day 1. Tests were conducted by using groups of 6 mice for each dose, with a control group of 6 mice receiving only tumor cells and 0.5 mL of water. A positive control group received tumor cells and 8 mg/kg of cisplatin in 0.5 mL of 0.15 M NaCl. The test was terminated after three times the mean survival time (MST) of the control group; surviving mice were counted as dying on that day. Activity was determined based on the percent increase in MST of test mice over controls (% ILS). An ILS of ≥25% represents activity. The tumor line was maintained through weekly transfers of $5 \times 10^4$ tumor cells in DBA/2 mice.

**Sarcoma 180 Ascites.** Female CFW mice (18–25 g) were implanted with $2 \times 10^6$ tumor cells ip on day 0. Compounds were administered in 0.5 mL of water ip on day 1. Groups of 6 mice were used for each test dose, by using control groups as defined above. The test was run for twice the MST of the control group, with survivors counted as dying on that day. An ILS of ≥50% indicates activity. The tumor line was maintained through weekly transfers of $4 \times 10^6$ tumor cells in CFW mice.

**P388 Leukemia.** $BDF_1$ mice (female, 5 weeks of age) were implanted with $2 \times 10^5$ tumor cells ip on day 0. Compounds were administered ip on days 1, 5, and 9. Groups of 5 mice were used for each dose, with a control group of 10 mice receiving tumor cells but no drug. An ILS of >30% indicates activity in this screen. The tumor line was maintained through weekly transfers of tumor cells in $BDF_1$ mice. P388 testing was conducted by Mitsubishi

Chemical Industries Limited, Tokyo, Japan.

**Acknowledgment.** We thank Gary Gramiccioni and Linda Murphy for their assistance with compound preparation and animal screening studies.

**Registry No.** 1, 106343-59-3; **2**, 85336-86-3; **3**, 106344-30-3; **4**, 106343-49-1; **5**, 106343-54-8; **6**, 106343-51-5; **7**, 106343-52-6; **8**, 49792-58-7; **9**, 117269-11-1; **10**, 99466-88-3; **11**, 106343-50-4; **12**, 117251-14-6; **13**, 117251-15-7; **14**, 117251-17-9; **15**, 117251-18-0; **16**, 75659-46-0; **17**, 117251-19-1; **18**, 117307-55-8; **19**, 117251-20-4; **20**, 117269-12-2; **21**, 117307-56-9; **22**, 117307-58-1; **23**, 98064-87-0; **24**, 117251-22-6; **25**, 117251-24-8; **26**, 117228-71-4; **27**, 117228-73-6; **28**, 117228-75-8; **29**, 117228-77-0; **30**, 117228-79-2; **31**, 117228-81-6; **32**, 117228-83-8; **33**, 117228-85-0; **34**, 117306-65-7; $^{195}$Pt, 14191-88-9; *cis*-[Pt($^{15}NH_3$)$_2$Cl$_2$], 78017-69-3; *cis*-[Pt($^{15}NH_3$)$_2$(O1-DMF)Cl](NO$_3$), 117228-87-2; *cis*-[Pt($^{15}NH_3$)$_2$(NO$_3$)Cl], 117228-88-3; *cis*-[Pt($^{15}NH_3$)$_2$(O1-DMF)$_2$](NO$_3$)$_2$, 117228-90-7; *cis*-[Pt($^{15}NH_3$)$_2$(NO$_3$)(O1-DMF)](NO$_3$), 117228-92-9; *cis*-[Pt($^{15}NH_3$)$_2$(NO$_3$)$_2$], 117228-93-0; *cis*-[Pt($^{15}NH_3$)$_2$(H$_2$O)Cl](NO$_3$), 78039-63-1; *cis*-[Pt($^{15}NH_3$)$_2$(H$_2$O)$_2$](NO$_3$)$_2$, 78022-63-6; *trans*-[Pt(NH$_3$)$_2$Cl$_2$], 14913-33-8; [Pt(en)Cl$_2$], 14096-51-6; [Pt(dach)Cl$_2$], 52691-24-4; *cis*-[Pt(*i*-PrNH$_2$)$_2$Cl$_2$], 41637-05-2; [Pt(*trans*-(*R*,*R*)-dach)Cl$_2$], 61848-66-6; *cis*-[Pt(NH$_3$)$_2$Br$_2$], 15978-91-3; *cis*-[Pt(NH$_3$)$_2$Cl$_2$], 15663-27-1; *cis*-[Pt(NH$_3$)$_2$(O1-DMF)Cl](NO$_3$), 79084-71-2; *cis*-[Pt(NH$_3$)$_2$(NO$_3$)Cl], 117228-94-1; *cis*-[Pt(NH$_3$)$_2$(O1-DMF)$_2$](NO$_3$)$_2$, 79084-73-4; *cis*-[Pt(NH$_3$)$_2$(NO$_3$)(O1-DMF)](NO$_3$), 117228-96-3; *cis*-[Pt(NH$_3$)$_2$(NO$_3$)$_2$], 41575-87-5; *cis*-[Pt(NH$_3$)$_2$(H$_2$O)Cl](NO$_3$), 117228-97-4; *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$](NO$_3$)$_2$, 52241-26-6.

**Supplementary Material Available:** X-ray crystallographic data on compound **10** (6 pages); structure factor tables for **10** (7 pages). Ordering information is given on any current masthead page.

# Studies on Antitumor Agents. 8.[1] Antitumor Activities of *O*-Alkyl Derivatives of 2′-Deoxy-5-(trifluoromethyl)uridine and 2′-Deoxy-5-fluorouridine

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*O*-Benzyl and *O*-ethyl derivatives of 2′-deoxy-5-(trifluoromethyl)uridine ($F_3$Thd) and 2′-deoxy-5-fluorouridine (FUdR) were synthesized. The oral antitumor activity of the compounds against sarcoma 180 in mice was examined. The 5′-*O*-ethyl (**3b**), 3′-*O*-ethyl (**3c**), 5′-*O*-benzyl (**3e**), and 3′-*O*-benzyl (**3f**) derivatives of $F_3$Thd were 4-fold more active than $F_3$Thd itself. Among the substituted-benzyl derivatives of $F_3$Thd, 3′-*O*-(*p*-chlorobenzyl)-$F_3$Thd (**3h**) showed the highest activity, with an $ED_{50}$ less than one-tenth of that of $F_3$Thd. The activities of 5′-*O*-benzyl (**7c**) and 3′-*O*-benzyl (**7d**) derivatives of FUdR were equal to those of the effective *O*-alkyl derivatives of $F_3$Thd.

2′-Deoxy-5-(trifluoromethyl)uridine ($F_3$Thd) was first synthesized by Heidelberger and his co-workers in 1962.[2] It has shown considerable biological activity through the actions of its metabolites in a number of systems.[3-7] For example, the antitumor activity of $F_3$Thd against transplanted tumors such as adenocarcinoma 755 and L 1210 leukemia is equal to or higher than that of 2′-deoxy-5-fluorouridine (FUdR).[7]

However, $F_3$Thd showed unsatisfactory results in clinical cancer chemotherapy, because of its short half-life in plasma.[8] Rapid metabolic degradation by thymidine phosphorylase has been reported.[8,9] Thus, depot forms of $F_3$Thd which resist degradation by the enzyme would be expected to maintain higher concentrations of $F_3$Thd in plasma and thus show greater antitumor activities in vivo.

Recently, we have reported the synthesis and antitumor activity of acyl derivatives[10] and *O*-alkoxyalkyl derivatives[1] of $F_3$Thd. Acylation of $F_3$Thd has been shown to enhance antitumor activity, but the acyl derivatives were easily hydrolyzed to $F_3$Thd by intestinal homogenate. *O*-Alkoxyalkyl derivatives of $F_3$Thd resisted degradation by thymidine phosphorylase, were activated by NADP-dependent microsomal drug-metabolizing enzymes after absorption, and thus showed greater antitumor activity. O-Ethoxymethylation and O-benzyloxymethylation increased the in vivo antitumor activity of $F_3$Thd 6-fold. Closer studies of the metabolic pathway of these derivatives suggested that *O*-benzyl or *O*-ethyl derivatives of $F_3$Thd might also be activated by the NADP-dependent microsomal drug-metabolizing enzymes.

If the depot form of $F_3$Thd were activated slowly after absorption, it would be expected to decrease toxicity to the gastrointestinal tract and give rise to an increase in the area under the curve for the $F_3$Thd concentration in plasma. The overall result would be an improved therapeutic index. Since FUdR has a similar disadvantage in vivo,[11] because of its short half-life in plasma,[12] O-alkylation of FUdR might also be effective in enhancing the antitumor activity of FUdR in vivo.

On this basis, various *O*-benzyl and *O*-ethyl derivatives of $F_3$Thd and FUdR were synthesized, and their antitumor

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