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Biologically Active Platinum Complexes Containing 8-Thiotheophylline and 8-(Methylthio)theophylline

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Complexes [Pt(μ-N,S-8-TT)(PPh_3)$_2$]$_2$ (**1**), [Pt(μ-S,N-8-TT)(PTA)$_2$]$_2$ (**2**), [Pt(8-TTH)(terpy)]BF_4 (**3**), *cis*-[PtCl(8-MTT)(PPh_3)$_2$] (**4**), *cis*-[Pt(8-MTT)$_2$(PPh_3)$_2$] (**5**), *cis*-[Pt(8-MTT)(8-TTH)(PPh_3)$_2$] (**6**), *cis*-[PtCl(8-MTT)(PTA)$_2$] (**7**), *cis*-[Pt(8-MTT)$_2$(PTA)$_2$] (**8**), and *trans*-[Pt(8-MTT)$_2$(py)$_2$] (**9**) (8-TTH_2 = 8-thiotheophylline; 8-MTTH = 8-(methylthio)theophylline; PTA = 1,3,5-triaza-7-phosphaadamantane) are presented and studied by IR and multinuclear (^{1}H, ^{31}P{^{1}H}) NMR spectroscopy. The solid-state structure of **4** and **9** has been authenticated by X-ray crystallography. Growth inhibition of the cancer cells T2 and SKOV3 induced by the above new thiopurine platinum complexes has been investigated. The activity shown by complexes **4** and **9** was comparable with cisplatin on T2. Remarkably, **4** and **9** displayed also a valuable activity on cisplatin-resistant SKOV3 cancer cells.

Introduction

The success of cisplatin and related platinum complexes as anticancer agents has stimulated a diffuse search for other active transition metal anticancer complexes.[1] Cisplatin is a highly effective antitumor agent used, in particular, to treat genitourinary and head and neck cancers.[1] Despite its remarkable pharmacological activity, the drug cisplatin presents heavy disadvantages such as a relatively limited spectrum of activity and high toxicity; moreover, some cancer cells develop resistance to the drug. A large number of modifications of the basic structure *cis*-[PtX_2L_2] (X = halides; L = nitrogen, sulfur, phosphorus, etc., neutral ligand) have been made in the attempt to overcome these clinical limitations.[1] These modifications have allowed one to reduce the toxicity and to alter the modes of delivery, but a very small number of analogues of cisplatin has been able to surpass the parent drug in efficacy and convenience.[1]

A few natural purines are building blocks of nucleic acids. Methylxanthines such as caffeine, theophylline, and theobromine are voluptuary substances with a variety of mild pharmacological actions (stimulant, cardiotonic, diuretic); some thiopurines (e.g. mercaptopurine, 6-thioguanine) are currently exploited in the clinical practice for the treatment of leukaemia, and more functionalized purines such as acyclovir, vidarabine, and didanosine are widely used for their antiviral activity including anti-HIV action.[2,3] It is reasonable to forecast that the binding of platinum to thiopurines could enhance the pharmacological activity of

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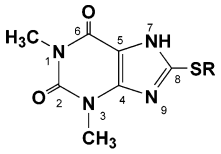
Chart 1



R= H; 8-thiotheophylline (8-TTH_2).
R= CH_3; 8-(methylthio)theophylline (8-MTTH).

the two species through a synergic action and could affect the metal distribution in the body exploiting a ligand "carrier effect".

Another item to consider in the design of new platinum-based drugs is the solubility both in the body fluids, constituted essentially by water, and in the cell membrane, a hydrophobic system. Therefore, the adequate choice of ligands to be bonded to platinum appears crucial not only for improving the activity but also for modulating the solubility to allow both the drug migration through the body and the reaching of DNA, the drug target, inside the cell nucleus.

In this paper we present the synthesis and characterization of new platinum complexes containing thiopurine molecules together with ligands modulating the solubility of the complexes in water and in a lipophilic medium. These complexes constitute a new family of compounds suitable to undergo citotoxicity tests and to be used as models for clarifying the interaction between platinum and biomolecules containing purines.

The selected purine molecules were 8-thiotheophylline (8-TTH_2) and 8-(methylthio)theophylline (8-MTTH) (Chart 1). For 8-TTH_2, both N7H and SH can be deprotonated leading to the formation of a bianionic bidentate ligand. The 8-MTTH coordination chemistry is also expected to be rich and versatile due to the presence of two potentially coordinating functions: the hard N7 and the soft S−Me site. Moreover the relative position of these two sites should allow bidentate coordination in a bridging (M−N−C−S−M) and/or chelating mode (N−C−S−M). It has also been reported that palladium complexes with 8-MTTH provide a pathway to C8 coordination to palladium by elimination of the S−CH_3 group.[4]

We tried to modulate the complexes solubility by choosing as ancillary ligands the lipophilic phosphane PPh_3 or, alternatively, the water-soluble phosphane PTA (PTA = 1,3,5-triaza-7-phosphaadamantane) both providing a NMR-active label that allowed us to study the reactions by $^{31}P\{^1H\}$ NMR spectroscopy. Finally, pyridine and terpyridine were also used to understand how a non-phosphorate ligand affects the chemical and biological properties of the thiopurine−platinum complexes.

Experimental Section

Ligands 8-thiotheophylline (8-TTH_2), 8-(methylthio)theophylline (8-MTTH),[5,6] and 1,3,5-triaza-7-phosphaadamantane (PTA)[7] and complexes *cis*-$[PtCl_2(PPh_3)_2]$,[8] *cis*-$[PtCl_2(PTA)_2]$,[9] $[PtOH(terpy)]BF_4$,[10] and *trans*-$[PtCl_2py_2]$[11] have been prepared by following the procedure described by literature methods. All the other chemicals and solvents were used as purchased (reagent grade). Elemental analyses (C, H, N, S) were performed using a Carlo Erba model EA1110 instrument. FT-IR spectra were recorded on a Nicolet 510P FT-IR instrument (4000−200 cm^{-1}) using CsI or KBr. NMR spectra were recorded on a Bruker AM spectrometer 200 MHz for ^1H NMR (TMS internal reference) and 81.15 MHz for $^{31}P\{^1H\}$ NMR (H_3PO_4 85% external reference).

The molecular weights were measured by mass spectroscopy using a Maldi Toff Hewlett-Packard G2025A LD/TOFF mass spectrometer with α-cyano-4-hydroxycynnamic acid as matrix for complexes **1** and **2**, while that for **3** was determined by a Hewlett-Packard MS Engine HP 5989 A, equipped with a FAB source, using 3-nitrobenzyl alcohol as matrix.

Synthesis of $[Pt(\mu\text{-N,S-8-TT})(PPh_3)_2]_2$ (1). The ligand 8-TTH_2 (0.013 g, 0.06 mmol) was dissolved in 1.2 mL of aqueous NaOH (0.1 M), and the solution was added to a solution of *cis*-$[PtCl_2(PPh_3)_2]$ (0.05 g, 0.06 mmol) in 10 mL of CH_2Cl_2. The double-layered mixture was stirred at room temperature for 1 h, and afterward the organic phase was separated, washed three times with water, and dried over Na_2SO_4. The solvent was removed under vacuum to leave the complex as a pale yellow powder.

Yield: 0.051 g, 88%. Anal. Found: C, 54.93; H, 3.85; N, 5.60; S, 3.03. Calcd for $C_{86}H_{72}N_8O_4P_4Pt_2S_2$: C, 55.49; H, 3.87; N, 6.02; S, 3.45. MW by MS Maldi Toff: 1860 Da. IR (KBr, cm^{-1}) selected data: ν(C6═O) 1686 (s); ν(C2═O) 1643 (s); ν(C═C) + ν(C═N) 1531 (s). ^1H NMR ($CDCl_3$; δ (ppm)): 3.0 (s, N1−CH_3, 3H), 3.2 (s, N3−CH_3, 3H), 6.9−8.2 (m, Ph, 30H). $^{31}P\{^1H\}$ NMR ($CDCl_3$; δ (ppm)): 7.9 (d, P_A, $^2J_{P_BP_A}$ = 20.7 Hz, $^1J_{PtP_A}$ = 3427 Hz), 17.5 (d, P_B, $^2J_{P_AP_B}$ = 20.7 Hz, $^1J_{PtP_B}$ = 3035 Hz).

Synthesis of $[Pt(\mu\text{-S,N-8-TT})(PTA)_2]_2$ (2). The biphase system obtained by adding 8-TTH_2 (0.017 g, 0.08 mmol), 1.6 mL of NaOH (0.1 M), *cis*-$[PtCl_2(PTA)_2]$ (0.046 g, 0.08 mmol), and 8 mL of CH_2Cl_2 was stirred at room temperature for 1 h. The pale yellow water solution was separated out and the organic phase evaporated under vacuum. The solid product was extracted with 15 mL of $CHCl_3$ for 30 min and then the insoluble residue filtered out. The pale yellow product was obtained by removing the solvent and dried on P_2O_5.

Yield: 0.052 g, 90%. Anal. Found: C, 31.02; H, 4.37; N, 18.97; S, 4.11. Calcd for $C_{38}H_{60}N_{20}O_4P_4Pt_2S_2$: C, 31.71; H, 4.17; N, 19.46; S, 4.45. MW by MS Maldi Toff: 1438 Da. IR (KBr, cm^{-1}) selected data: ν(C6═O) 1683 (s); ν(C2═O) 1635 (s); ν(C═C) + ν(C═N) 1530, 1509 (s). ^1H NMR ($CDCl_3$; δ (ppm)): 3.0 (s, N1−CH_3, 6H), 3.4 (s, N3−CH_3, 6H), 4.0−4.5 (m, PTA, 48H). $^{31}P\{^1H\}$ NMR ($CDCl_3$; δ (ppm)): −57.1 (d, P_A, $^2J_{P_BP_A}$ = 22.8 Hz, $^1J_{PtP_A}$ = 2649 Hz), −72.6 (d, P_B, $^2J_{P_AP_B}$ = 22.8 Hz, $^1J_{PtP_B}$ = 3028 Hz).

Synthesis of $[Pt(8\text{-TTH})(terpy)]BF_4$ (3). Stirring a suspension of 8-TTH_2 (0.038 g, 0.18 mmol) and $[PtOH(terpy)]BF_4$ (0.096 g, 0.18 mmol) in 40 mL of MeOH at room temperature for 3 h produced a purple mixture. The purple solid residue was isolated by filtration and then dried over P_2O_5.

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Yield: 0.113 g, 86%. Anal. Found: C, 36.11; H, 2.34; N, 13.02; S, 4.25. Calcd for $C_{22}H_{18}BF_4N_7O_2PtS$: C, 36.34; H, 2.48; N, 13.49; S, 4.40. IR (KBr, cm^{-1}) selected data: ν(N−H) 2500−3300 3135; ν(C6═O) 1694 (s); ν(C2═O) 1660 (s); ν(C═C) + ν(C═N) 1602 (m), 1541 (s). ^{1}H NMR (CD_3NO_2; δ (ppm)): 3.1(s, N1−CH_3, 3H), 3.6 (s, N3−CH_3, 3H), 8.0−9.0 (m, Ph, 9H), 9.0 (d, H_6, $^3J_{PtH}$ = 41 Hz, $^3J_{HH}$ = 9 Hz, 2H), 13 (s, N_7H, 1H, DMSO-d_6). FAB: 639 (*m*/*z*).

Synthesis of *cis*-[PtCl(8-MTT)(PPh_3)$_2$] (4). The ligand 8-MTTH (0.113 g, 0.5 mmol) was dissolved in 5 mL of aqueous NaOH (0.1 M), and the resulting solution was mixed with 60 mL of CH_2Cl_2 containing *cis*-[$PtCl_2(PPh_3)_2$] (0.394 g, 0.5 mmol). The double-layered system was refluxed for 4 h, and the yellow organic phase was separated and dried over Na_2SO_4. A yellow powder was obtained by removing the solvent under reduced pressure.

Crystals for X-ray determination of complex **4** were obtained by recrystallization of the crude product from $CHCl_3$ and Et_2O.

Yield: 0.48 g, 97%. Anal. Found: C, 53.76; H, 3.80; N, 5.75; S, 3.24. Calcd for $C_{44}H_{39}ClN_4O_2P_2PtS$: C, 53.85; H, 3.98; N, 5.71; S, 3.26. IR (CsI, cm^{-1}) selected data: ν(C6═O) 1688 (s); ν(C2═O) 1649 (s); ν(C═C) + ν(C═N) 1584 (m), 1526 (s), ν(PtCl) 311. ^{1}H NMR ($CDCl_3$; δ (ppm)): 2.7 (s, S−CH_3, 3H), 3.3 (s, N1−CH_3, 3H), 3.4 (s, N3−CH_3, 3H), 7.0−8.0 (m, Ph, 30H). ^{31}P{^{1}H} NMR ($CDCl_3$; δ (ppm)): 8.1 (d, P_A, $^2J_{P_BP_A}$ = 20 Hz, $^1J_{PtP_A}$ = 3233 Hz), 13.7 (d, P_B, $^2J_{P_AP_B}$ = 20 Hz, $^1J_{PtP_B}$ = 3836 Hz).

Synthesis of *cis*-[Pt(8-MTT)$_2$(PPh_3)$_2$] (5). Into a bilayered mixture containing 2.5 mL of NaOH (0.1 M) and 15 mL of CH_2Cl_2 was introduced 8-MTTH (0.057 g, 0.25 mmol) and *cis*-[$PtCl_2(PPh_3)_2$] (0.100 g, 0.125 mmol). After 24 h at refluxing temperature the organic phase was separated and dried over Na_2SO_4. Under vacuum the organic solvent was removed leaving a clear-yellow powder.

Yield: 0.13 g, 89%. Anal. Found: C, 53.07; H, 4.09; N, 9.05; S, 5.56. Calcd for $C_{52}H_{48}N_8O_4P_2PtS_2$: C, 53.37; H, 4.13; N, 9.57; S, 5.48. IR (CsI, cm^{-1}) selected data: ν(C6═O) 1690 (s); ν(C2═O) 1648 (s); ν(C═C) + ν(C═N) 1586 (m), 1525 (s). ^{1}H NMR ($CDCl_3$; δ (ppm)): 2.2 (s, S−CH_3, 3H), 3.25 (s, N1−CH_3, 3H), 3.35 (s, N3−CH_3, 3H), 6.4−7.9 (m, Ph, 15H). ^{31}P{^{1}H} NMR ($CDCl_3$; δ (ppm)): −0.75 (s, $^1J_{PtP}$ = 3479 Hz).

Synthesis of *cis*-[Pt(8-MTT)(8-TTH)(PPh_3)$_2$] (6). 8-TTH_2 (0.022 g, 0.10 mmol) was dissolved in 1 mL of NaOH (0.1 M), and the solution was added to a solution of **4** (0.1 g, 0.10 mmol) in 8 mL of CH_2Cl_2. The mixture was refluxed for 3 days, the organic layer appearing bright yellow. A further 5 mL of CH_2Cl_2 was added to dissolve a small amount of solid product in the interphase; the organic phase was then separated and dried on Na_2SO_4. The filtered organic phase was evaporated to leave the product as a yellow powder.

Yield: 0.11 g, 90%. Anal. Found: C, 52.01; H, 4.03; N, 8.84; S, 5.81. Calcd for $C_{51}H_{46}N_8O_4P_2PtS_2$: C, 52.93; H, 3.98; N, 9.69; S, 5.53. IR (KBr, cm^{-1}) selected data: ν(N−H) 3050; ν(C6═O) 1692 (s); ν(C2═O) 1653 (s); ν(C═C) + ν(C═N) 1582 (m), 1531 (s). ^{1}H NMR ($CDCl_3$; δ (ppm)): 2.7 (s, SCH_3, 3H), 3.3 (s, N1−CH_3, 8-TT^- + 8-MTT^-, 6H), 3.4 and 3.5 (2 s, each 3H; 8-TT^- + 8-MTT^-, N3−CH_3), 7.0−8.0 (m, Ph, 30H), 11.7 (s, N7H, 1H). ^{31}P{^{1}H} NMR ($CDCl_3$; δ (ppm)): 18.9 (d, P_A, $^2J_{P_BP_A}$ = 18 Hz, $^1J_{PtP_A}$ = 3127 Hz), 5.1 (d, P_B, $^2J_{P_AP_B}$ = 18 Hz, $^1J_{PtP_B}$ = 3250 Hz).

Synthesis of *cis*-[PtCl(8-MTT)(PTA)$_2$] (7). The solution obtained by dissolving 8-MTTH (0.039 g, 0.17 mmol) in 1.7 mL of NaOH (0.1 M) was added to a suspension of *cis*-[$PtCl_2(PTA)_2$] (0.099 g, 0.17 mmol) in 15 mL of CH_2Cl_2. The biphase system obtained was stirred at room temperature for 1 h. The aqueous phase was separated and reextracted with CH_2Cl_2 (3 × 10 mL). The organic fractions were dried on Na_2SO_4, and the solvent was removed under vacuum. The yellow powder obtained was dried on P_2O_5.

Yield: 0.093 g, 70%. Anal. Found: C, 30.73; H, 4.33; N, 18.32; S, 4.08. Calcd for $C_{20}H_{33}ClN_{10}O_2$ P_2PtS: C, 31.21; H, 4.29; N, 18.19; S, 4.16. IR (KBr, cm^{-1}) selected data: ν(C6═O) 1684 (s); ν(C2═O) 1653 (s); ν(C═C) + ν(C═N) 1580 (m), 1526 (s). ^{1}H NMR ($CDCl_3$; δ (ppm)): 2.7 (s, S−CH_3, 3H), 3.4 (s, N1−CH_3, 3H), 3.55 (s, N3−CH_3, 3H), 3.9−4.6 (m, PTA, 24H). ^{31}P{^{1}H} NMR ($CDCl_3$; δ (ppm)): −69.5 (d, P_A, $^2J_{P_BP_A}$ = 20.5 Hz, $^1J_{PtP_A}$ = 2962 Hz), −58.4 (d, P_B, $^2J_{P_AP_B}$ = 20.5 Hz, $^1J_{PtP_B}$ = 3369 Hz).

Synthesis of *cis*-[Pt(8-MTT)$_2$(PTA)$_2$] (8). The solution obtained by dissolving 8-MTTH (0.077 g, 0.34 mmol) in 3.4 mL of an aqueous solution of NaOH (0.1 M) was added to a suspension of *cis*-[$PtCl_2(PTA)_2$] (0.099 g, 0.17 mmol) in 25 mL of CH_2Cl_2. After 1 h at refluxing temperature a colorless biphasic system was obtained. The aqueous phase was separated and reextracted with CH_2Cl_2 (3 × 10 mL). The organic fractions were collected and dried on Na_2SO_4. Evaporation of the solvent gave a pale yellow powder which was dried on P_2O_5.

Yield: 0.132 g, 81%. Anal. Found: C, 34.89; H, 4.97; N, 19.86; S, 6.93. Calcd for $C_{28}H_{42}N_{14}O_4P_2PtS_2$: C, 35.05; H, 4.38; N, 20.43; S, 6.67. IR (KBr, cm^{-1}) selected data: ν(C6═O) 1687 (s); ν(C2═O) 1650 (s); ν(C═C) + ν(C═N) 1586 (m), 1522 (s). ^{1}H NMR ($CDCl_3$; δ (ppm)): 2.4 (s, S−CH_3, 6H), 3.5 (s, N1−CH_3, 6H), 3.5 (s, N3−CH_3, 6H), 4.1−4.3 (two dd, CH_AH_B−P, $^2J_{H_AH_B}$ = 15 Hz, $^2J_{HP}$ = 2 Hz, 12H), 4.4−4.5 (two broad d, CH_AH_B−N, $^2J_{H_AH_B}$ = 13.5 Hz, 12H). ^{31}P{^{1}H} NMR ($CDCl_3$; δ (ppm)): −68.8 (s, $^1J_{PtP}$ = 3066 Hz).

Synthesis of *trans*-[Pt(8-MTT)$_2$(py)$_2$] (9). Into a light-protected vessel, $AgBF_4$ (0.17 g, 0.87 mmol) and *trans*-[$PtCl_2(Py)_2$] (0.15 g, 0.35 mmol) in 25 mL of acetone were stirred for 24 h. After AgCl removing by filtration, a solution of 8-MTTH (0.16 g, 0.70 mmol) in 7 mL of NaOH (0.1 M) was added producing a white suspension which was stirred at room temperature for 4 h. The precipitated product was separated out by centrifugation, washed with H_2O (2 × 3 mL), and dried over P_2O_5.

Yield: 0.17 g, 60%. Anal. Found: C, 38.20; H, 3.19; N, 17.31; S, 8.45. Calcd for $C_{26}H_{28}N_{10}O_4PtS_2$: C, 38.81; H, 3.48; N, 17.42; S, 7.96. IR (KBr, cm^{-1}) selected data: ν(C6═O) 1694 (s); ν(C2═O) 1657 (s); ν(C═C) + ν(C═N) 1586 (m), 1526 (s). ^{1}H NMR ($CDCl_3$; δ (ppm)): 2.6 (s, S−CH_3, 6H), 3.4 (s, N1−CH_3, 6H), 3.5 (s, N3−CH_3, 6H), 7.2 (m, 4 H_2), 7.6 (t, 2 H_3, $^3J_{H_2H_3}$ = 7.4 Hz), 9.0 (d, 4 H_1, $^3J_{H_2H_1}$ = 5.2 Hz; $^3J_{PtH_1}$ = 34 Hz).

X-ray Structure Determinations. Data for compounds **4** and **9** were collected on a Nonius Kappa CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.7107 Å) at room temperature (295 K). The data were corrected for Lorentz−polarization and absorption (SORTAV)[12] effects. The crystal parameters and other experimental details of the data collections are summarized in Table 1. The structures were solved by direct methods (SIR92)[13] and refined by full-matrix least-squares methods with all non-hydrogen atoms anisotropic. The carbon atom of the solvent molecule ($CHCl_3$) for **4** was found to be disordered over two sites and refined isotropically, each with an occupancy of 0.5. All hydrogens were included in calculated positions and refined using a riding model. Selected bond distances and angles are shown in Table 2. All calculations were performed using SHELXL-97[14] and PARST.[15]

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Table 1. Crystallographic Data

	4	**9**
formula	$PtC_{44}H_{39}ClN_4O_2P_2S{\cdot}CHCl_3$	$PtC_{26}H_{28}N_{10}O_4S_2$
M_r	1099.70	803.782
space group	$P2_1/c$	$P2_1/a$
cryst system	monoclinic	monoclinic
a/Å	9.5816(1)	8.6483(2)
b/Å	27.2650(6)	16.5361(4)
c/Å	17.6174(4)	10.8846(3)
α/deg	90	90
β/deg	99.512(1)	106.781(1)
γ/deg	90	90
V/Å^3	4539.1(2)	1490.48(7)
Z	4	2
D_c/g cm^{-3}	1.609	1.791
F(000)	2184	792
μ(Mo Kα)/cm^{-1}	34.85	48.99
measd reflcns	28 728	24 532
unique reflcns	10 538	4343
R_{int}	0.045	0.052
obsd reflcns [$I \geq 2\sigma(I)$]	8584	3071
$\theta_{min}-\theta_{max}$/°	3.3−28	3.5−30
hkl ranges	−12, 12; −36, 36; −23, 22	−12, 12; −23, 23; −15, 14
R(F^2) (obsd reflcns)	0.0420	0.0396
wR(F^2) (all reflcns)	0.0941	0.0895
no. of variables	534	199
goodness of fit	1.084	1.182
ρ_{min}, ρ_{max}/e Å^{-3}	−1.08, 1.80	−1.28, 0.97

Table 2. Selected Bond Distances (Å) and Angles (deg)

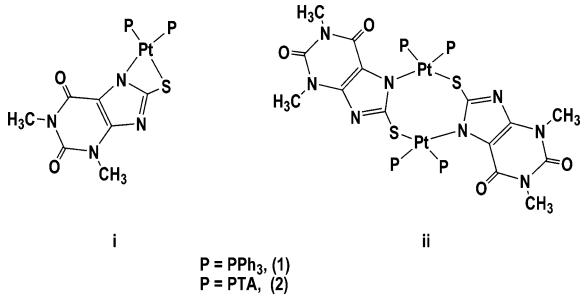
	4	**9**
Pt1−P1	2.257(1)	
Pt1−P2	2.272(1)	
Pt1−N7	2.054(4)	2.026(4)
Pt1−Cl1	2.337(1)	
Pt1−N10		2.009(4)
N7−C8	1.348(6)	1.336(7)
N7−C5	1.374(7)	1.394(6)
P1−Pt1−P2	99.1(1)	
P1−Pt1−N7	90.6(1)	
P1−Pt1−Cl1	174.9(1)	
P2−Pt1−N7	170.4(1)	
P2−Pt1−Cl1	86.0(5)	
N7−Pt1−Cl1	84.4(1)	
N7−Pt1−N10		88.9(2)
N7−Pt1−N10′		91.1(2)
C5−N7−C8	104.0(4)	104.4(4)

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications nos. CCDC 209304 and 209305. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax +44 1223 336033 or e-mail deposit@ccdc.cam.ac.uk).

Growth Inhibition Assays. Cell growth inhibition assays were carried out using the cisplatin-sensitive T2 human cell line and the cisplatin-resistant SKOV3 cell line. T2 is a cell hybrid obtained by the fusion of the human lymphoblastoid line 174 (B lymphocyte transformed by the Epstein−Barr virus) with the CEM human cancer line (leukemia T) while SKOV3 is derived from an human ovarian tumor.

The cells were seeded in triplicate in 96-well trays at a density of 50×10^3 in 50 μL of AIM-V medium for T2 and 25×10^3 in 50 μL of AIM-V medium for SKOV3.

Chart 2



Stock solutions (10 mM) of the Pt(II) complexes were made in DMSO and diluted in AIM-V medium to give final concentration of 2, 10, and 50 μM.

Cisplatin was employed as a control for the cisplatin-sensitive T2 cell line and for the cisplatin-resistant SKOV3. Untreated cells were placed in every plate as a negative control. The cells were exposed to the compounds for 72 h, and then 25 μL of a 4,5-(dimethylthiozol-2-yl)-2,5-diphenyltetrazolium bromide solution (12 mM) was added. After 2 h of incubation, 100 μL of lysing buffer (50% DMF + 20% SDS, pH 4.7) were added to convert 4,5-(dimethylthiozol-2-yl)-2,5-diphenyltetrazolium bromide into a brown colored formazane. After an additional 18 h the solution absorbance, proportional to the number of live cells, was measured by spectrophotometer and converted in % of growth inhibition.

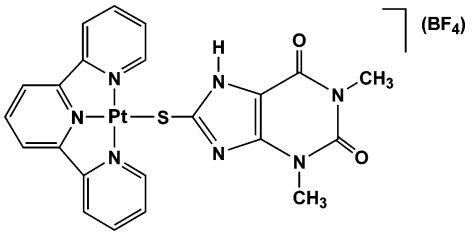
Results and Discussion

Reactivity of 8-TTH$_2$ with *cis*-[PtCl$_2$(PPh$_3$)$_2$], *cis*-[PtCl$_2$(PTA)$_2$], and [Pt(OH)(terpy)]BF$_4$. The reaction of 8-TTH$_2$ with 2 equiv of NaOH and 1 equiv of *cis*-[PtCl$_2$(PPh$_3$)$_2$] in the biphasic CH_2Cl_2/H_2O system gave the pale yellow complex [Pt(μ-N,S-8-TT)(PPh$_3$)$_2$]$_2$ (**1**). The IR spectrum showed the characteristic absorptions of PPh$_3$ and of the purine ligands [ν(C6═O) 1686 (s); ν(C2═O) 1643 (s)]. These observations were also supported by ^{1}H NMR spectroscopy: no resonances for N7−H were observed, while the signals integrals for PPh$_3$ and purine were consistent with a 2:1 ratio. The elemental analysis was in agreement with a 1:1:2 Pt/8-TT^{2-}/PPh$_3$ molar ratio. The ^{31}P{^{1}H} NMR pattern presented two doublets ($^2J_{P_AP_B}$ = 20.7 Hz) at 7.9 (P$_A$) and 17.5 ppm (P$_B$) with satellites due to the coupling with the Pt atom. The platinum−phosphorus coupling constants ($^1J_{PtP_A}$ = 3427 Hz; $^1J_{PtP_B}$ = 3035 Hz) seem to indicate that P$_A$ is trans to nitrogen and P$_B$ is trans to sulfur.[16]

It can be concluded that in complex **1** platinum must be coordinated to two magnetically different PPh$_3$ ligands and one 8-TT^{2-} anion bonded to the metal through both the S atom and the imidazole N7 atom. This formulation is consistent with two possible structures (Chart 2): (i) a mononuclear complex where a 8-TT^{2-} acts as a N7−S bidentate chelating ligand; (ii) a binuclear complex containing two 8-TT^{2-} anions bridging to two different Pt atoms by their N7 and S. Although the first hypothesis seems disfavored because the four member ring strain would destabilized the product, it cannot be excluded a priori; in fact a few complexes containing NCSM rings are known.[17]

(14) Sheldrick, G. M. *SHELXL-97, Program for Crystal Structure Refinement*; University of Gottingen: Gottingen, Germany, 1997.
(15) Nardelli, M. *J. Appl. Crystallogr.* **1995**, *28*, 659.
(16) Appleton, T. G.; Bennett, M. A. *Inorg. Chem.* **1978**, *17*, 738.
(17) Wang, S.; Staples, R. J.; Fackler J. R., J. P. *Acta Crystallogr.* **1994**, *C50*, 889.

Chart 3



3

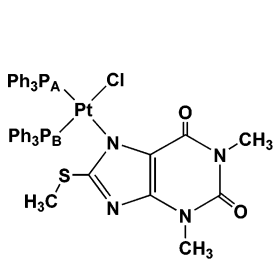
To elucidate the right structure, a molecular weight measurement was performed. The data obtained by Maldi Toff MS (MW = 1860 Da) confirmed that complex **1** has the binuclear structure ii.

In a similar way, the reaction of 8-TTH_2 with NaOH and *cis*-[$PtCl_2(PTA)_2$] in the biphasic system H_2O/CH_2Cl_2 at room temperature leads to [Pt(μ-S,N-8-TT)$(PTA)_2]_2$ (**2**), recovered as a pale yellow powder. This water-soluble complex showed an elemental analysis consistent with a 1:2:1 Pt/(PTA)/(8-TT^{2-}) molar ratio. The ^{1}H NMR supported the indications of the elemental analysis and, in combination with the IR spectroscopy, suggested that the N7 atom of the purine was deprotonated. The $^{31}P\{^1H\}$ NMR displayed two different doublets ($^2J_{PP}$ = 22.8 Hz) at −57.1 (P_A) and −72.6 ppm (P_B) both coupled to platinum ($^1J_{PtP_A}$ = 2649 Hz and $^1J_{PtP_B}$ = 3028 Hz, respectively). Also for this complex two different structures (Chart 2) are consistent with the data. In this case we did not succeed in obtaining crystals adequate for X-ray determination, but a measure of the molecular weight by Maldi Toff MS (MW = 1438 Da) allowed us to unequivocally identify **2** as a binuclear complex (Chart 2, ii).[18]

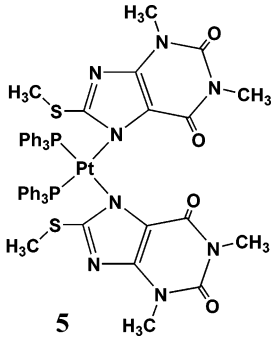
The reaction of 8-TTH_2 with [PtOH(terpy)]BF_4 in MeOH at room temperature gave the yellow product **3**, which was characterized as a mononuclear Pt/8-TTH complex (Chart 3). The ^{1}H NMR spectrum indicated the persistence of the N7 proton in the complex [N7−H = 13 ppm (DMSO-d_6)], suggesting that the monodeprotonated 8-TTH^- acts as a monodentate anionic ligand through the sulfur atom. The other key points to define the composition of **3** are (a) the integrals ratio between the purine N−CH_3 and the terpyridine aromatic signals suggested a 1:1:1 Pt/terpyridine/purine molar proportion, which was also supported by the elemental analysis, (b) the monocationic charge of the platinum complex was indicated by the presence of a single BF_4^- anion in the complex composition (elemental analysis), (c) the FAB analysis showed a signal at 639 *m*/*z*, in agreement with the formula weight of the mononuclear cation, and (d) in the ^{1}H NMR spectrum of the complex the terpyridine protons showed Pt satellites indicating that terpy is acting as a terdentate ligand.

In the three complexes **1**−**3**, the signals produced by the purine N−CH_3 groups are in the range found for other similar complexes.[19] Nevertheless, it is important to point out that

Chart 4



4



5

the N3−CH_3 signal moves downfield in the series **1**, **2**, **3** (**1**, 3.2 ppm; **2**, 3.4 ppm; **3**, 3.6 ppm) showing that the electronic distribution inside the coordinated thiopurine is affected by the nonpurinic ligand.

Reaction of 8-MTTH with *cis*-[$PtCl_2(PPh_3)_2$], *cis*-[$PtCl_2$-$(PTA)_2$], and *trans*-[$PtCl_2(py)_2$]. Synthesis and Characterization of the Heteropurine Complex *cis*-[Pt(8-MTT)(8-TTH)$(PPh_3)_2$] (6). When the ligand 8-MTTH was treated with NaOH and *cis*-[$PtCl_2(PPh_3)_2$] in molar ratios 1:1:1 and 2:2:1, the new complexes *cis*-[PtCl(8-MTT)$(PPh_3)_2$] (**4**) and *cis*-[Pt(8-MTT)$_2(PPh_3)_2$] (**5**) were formed, respectively. The reactions were performed either in a water/CH_2Cl_2 double-phase system or in 95% EtOH.

The elemental analysis and spectroscopic data were in agreement with the proposed composition (Chart 4) for **4** and **5**. The $^{31}P\{^1H\}$ NMR of **4** showed two doublets with satellites at 8.1 (P_A) and 13.7 ppm (P_B), due to the reciprocal coupling among the two magnetically different phosphorus atoms ($^2J_{P_AP_B}$ = 20 Hz) and to platinum. The Pt−P_A coupling constant ($^1J_{PtP_A}$ = 3233 Hz) was smaller than the corresponding for P_B ($^1J_{PtP_B}$ = 3836 Hz), in agreement with a minor trans effect for chloride than for N.

Complex **5** showed a $^{31}P\{^1H\}$ NMR containing a single signal at −0.75 ppm with a $^1J_{PtP}$ of 3479 Hz, supporting the disposition of the PPh_3 trans to the thiopurine N7.[20]

A platinum phosphane complex containing two different purine ligands could provide important information about how the presence of a Pt-bonded purine influences the coordination of a second one.

The reaction between the 8-MTTH complex **4** and 8-TTH_2 in refluxing aqueous NaOH/CH_2Cl_2 gave *cis*-[Pt(8-MTT)-(8-TTH)$(PPh_3)_2$] (**6**) (Chart 5). This complex contains two different thiopurines bonded to the same platinum nucleus in two different coordination modes: 8-MTT^- and 8-TTH^- coordinated via N7 and S^-, respectively. It has been isolated and fully characterized.

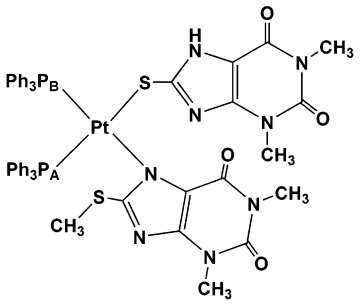
The ^{1}H NMR of **6** showed signals belonging to both purines. The resonance at 2.7 ppm was easily assigned to the S−CH_3 group of 8-MTT^-, but it was not possible to assign unequivocally the other three signals at 3.3, 3.4, and 3.5 in a 2:1:1 ratio. The highest field peak was tentatively assigned to the two coincident N1−CH_3 of the two purines on the basis of the chemical shift for that group in other

(18) Colacio, E.; Cuesta, R.; Ghazi, M.; Huertas, M. A.; Moreno, J. M.; Navarrete, A. *Inorg. Chem.* **1997**, *36*, 1652.

(19) Romerosa, A.; López-Magaña, C.; Saoud, M.; Mañas-Carpio, S. *Eur. J. Inorg. Chem.* **2003**, 348.

(20) Pregosin, P. S.; Kunz, R. W. *31P and 13C NMR of Transition Metal Phosphine Complexes*; Springer-Verlag: Berlin, 1979.

Chart 5



6

thiopurine complexes: in fact the N1−CH_3 chemical shift arises in a narrow range, at higher field and is less sensitive than the N3−CH_3 to the purine coordination. The residual signals at 3.4 and 3.5 were consequently assigned to the two N3−CH_3 groups.[4,5] The signal at 11.7 ppm is due to a residual N7-bonded proton belonging to S-coordinated 8-TTH^-, at appreciably higher field than the corresponding signal in noncoordinated 8-TTH_2 (13.36 ppm) or in the gold complex [Au(8-TTH)PPh_3] (12.89 ppm).[21]

The $^{31}P\{^1H\}$ NMR was in agreement with the proposed structure. Two doublets with satellites were observed at 18.9 (P_A) and 5.1 ppm (P_B), ($^2J_{P_AP_B}$ = 18 Hz). Both signals were coupled to platinum with different coupling constants: 3127 Hz for the phosphorus trans to the S thiopurine atom (P_A) and 3250 Hz for the other, trans to the N7 purine atom (P_B).

The reaction of 8-MTTH with NaOH and *cis*-[$PtCl_2$-$(PTA)_2$] in H_2O/CH_2Cl_2 in 1:1:1 molar proportion gave the complex *cis*-[PtCl(8-MTT)$(PTA)_2$] (**7**) while in 2:2:1 molar ratio gave *cis*-[Pt(8-MTT)$_2(PTA)_2$] (**8**) (Chart 6)

Complex **7** and **8** are soluble in H_2O (2.6 and 4.1 mM, respectively) as well as in organic solvents (CH_2Cl_2 and $CHCl_3$). The spectroscopic properties and elemental analysis are in agreement with the proposed composition for both compounds and are presented in the Experimental Section.

The $^{31}P\{^1H\}$ NMR spectrum for **7** displayed two doublets (P_A = −69.5 ppm; P_B = −58.4 ppm; $^2J_{PP}$ = 20.5 Hz). The coupling constant between P_A and Pt was 2962 Hz, which is adequate for a P trans to a N, while the corresponding value for P_B ($^1J_{PPt}$ = 3369 Hz) was in agreement with a P trans to a Cl.[20] Complex **8** showed a singlet at −68.8 ppm with a PtP coupling constant similar in value (3066 Hz) to P_A of complex **7**.

Finally, we intended to complete this series of potentially antiproliferative thiopurine/platinum complexes designing a comparative complex with no phosphane ligands. Because the anticancer activity of trans platinum complexes bearing aromatic flat molecules as neutral ligands has been described,[22,23] complex *trans*-[Pt(8-MTT)$_2$(py)$_2$] (**9**) (Chart 7) is likely to be active too: it was synthesized by a two-step reaction from *trans*-[$PtCl_2(Py)_2$], which was treated in acetone with 2 equiv of $AgBF_4$ and then with 8-MTTH in aqueous NaOH (0.1 M). The complex was fully characterized by spectroscopic techniques (see Experimental Section) and X-ray diffraction (see further).

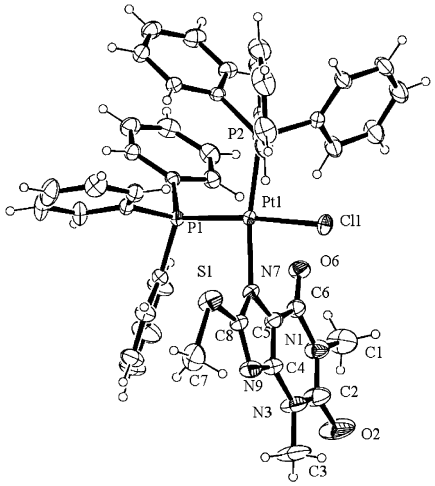


Figure 1. ORTEP view and atom numbering of compound **4** showing the thermal ellipsoids at 30% probability.

The comparative analysis of the thiopurine transitions in ^1H NMR for the above 8-MTT^- complexes showed that while there is no evident correlation between the complex structure and the N1−CH_3 and the N3−CH_3 chemical shifts, a trend can be sketched for the S−CH_3 chemical shift: this signal arises at lower field for monopurine complexes (2.7 ppm in **4** and in **7**) than for those containing two purine bases (2.2 in **5**; 2.4 in **8**, 2.6 ppm in **9**).

Crystal Structure of 4. Crystals of complex **4** were obtained by recrystallization of the crude product from $CHCl_3$ and Et_2O. An ORTEP [24] view is displayed in Figure 1; the crystallographic data are given in Table 1, and a list of selected bond distances and angles appears in Table 2.

The asymmetric unit contains one $CHCl_3$ molecule and one *cis*-[PtCl(8-MTT)$(PPh_3)_2$] molecule. In this compound the platinum(II) atom is coordinated to the phosphorus atoms of two triphenylphosphane ligands, to a chloride, and to a 8-MTT^- anion through the N7 atom. As anticipated by NMR analysis, the two triphenylphosphane are cis to each other. The coordination polyhedron of the metal atom adopts a marked distorted square-planar geometry (P2−Pt−P1 = 99.06(4)°, N7−Pt−Cl = 84.40(1)°) likely caused by the steric repulsion between the two triphenylphosphane ligands. The biggest deviation from the coordination plane of 0.032(2) Å corresponds to Cl1 atom [$\Sigma(d/\sigma)^2$ = 459.5 for the coordination plane]. The Pt1−Cl1 and Pt1− N1 distances are 2.337(1) and 2.054(4) Å, respectively, as expected when Cl and N(sp^2) are trans to a phosphane group[18,25−27] and are in agreement with other similar thiopurine−metal complexes.[4,5,19,21] The purine molecule is roughly planar

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(22) Van Beusichem, M.; Farrell, N. *Inorg. Chem.* **1992**, *31*, 634.
(23) Kharatishvili, M.; Mathieson, M.; Farrell, N. *Inorg. Chim. Acta* **1997**, *255*, 1.
(24) Johnson, C. K. *ORTEP II. Report ORNL-5138*; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.
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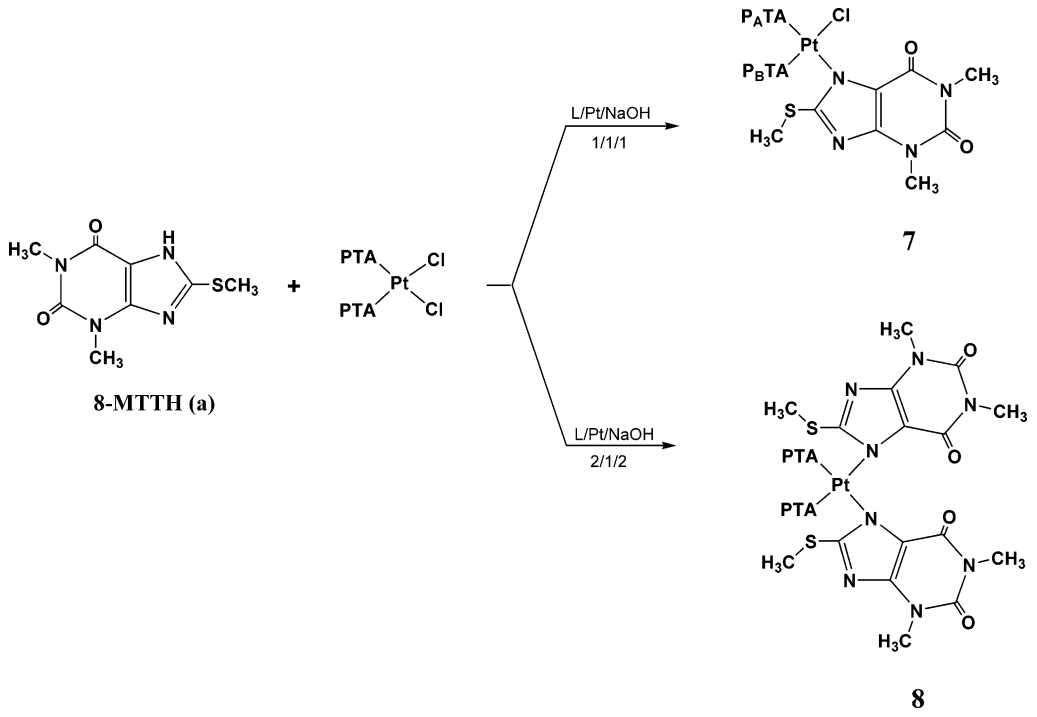
(26) Garcia-Sejio, M. I.; Castineiras, A.; Mahieu, B.; Janosi, L.; Berente, Z.; Kollar, L.; Garcia-Fernandez, M. E. *Polyhedron* **2001**, *20*, 855.
(27) Lee, C.; Kang, Y.; Kang, S. O.; Ko, J.; Yoo, J. W.; Cho, M. H. *J. Organomet. Chem.* **1999**, 587.

Chart 6



8-MTTH (a)

7

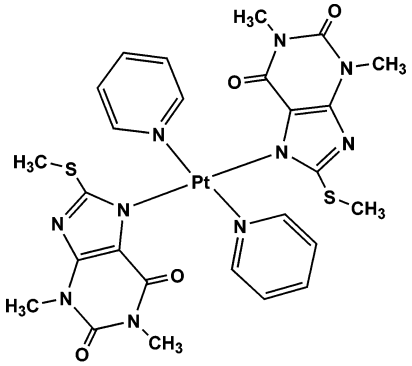
8

$[\Sigma(d/\sigma)^2 = 101.0]$ with maximum deviation from the plane for C8 atom of 0.0305 Å while the exocyclic groups do not show any significant deviation from the purine plane. The purine is twisted away from the metal coordination mean plane. The mean plane of the purine is rotated with respect to the coordination metal plane by an angle of 88.4(1)° likely to minimize the steric repulsions between the bulky triphenylphosphane ligands and the thiomethyl group of the purine ligands.

Finally, the rest of bond distances and angles are similar to those found in other N(7)-bonded purine complexes[4,5,19,21] and there are no significant intra- and intermolecular interactions, less than the sum of the van der Waals radii, between molecules.

Crystal Structure of 9. Crystals of **9** adequate for X-ray diffraction determination were obtained from a $CHCl_3$ solution by slow diffusion of Et_2O. An ORTEP[24] view is displayed in Figure 2. The crystallographic data are given in Table 1, and a list of selected bond distances and angles appears in Table 2.

Chart 7



9

In complex **9**, platinum is bonded to two 8-MTT$^-$ ligands trans to each other by the deprotonated N7 atoms and to two pyridine molecules. The complex is located on a crystallographic center of symmetry coincident with the Pt atom. The angles of the coordination square planar geometry around the metal are 88.9(2) and 91.1(2)°. The Pt1−N7 distances (2.026(4) Å) are in agreement with those found in Pt(II) complexes with N(sp^2) atoms in mutual trans position and in particular with the imidazolic N7 purine atoms. Pt square complexes containing purine derivatives in trans positions display Pt−N distances in the range 1.996−2.033 Å.[18,25−27] The distances of 2.009(4) Å between Pt1 and pyridine-N5 are in agreement with the values observed in other similar Pt(II) square planar complexes where the pyridine, not contained in a strained multidentate ligand, is in trans position to a N(sp^2) atom.[28] The square coordination plane is somewhat regular and perfectly planar for symmetry reasons. Also the purine molecule is practically planar

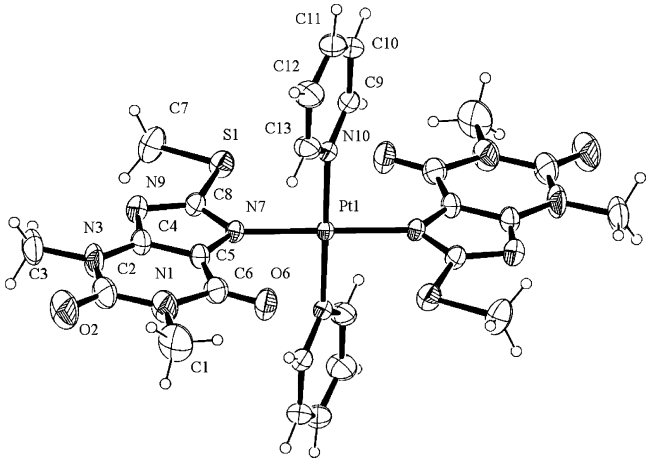


Figure 2. ORTEP view and atom numbering of compound **9** showing the thermal ellipsoids at 30% probability.

Table 3. Percentage (±SD) of Growth Inhibition of T2 Cells

complex	50 μM	10 μM	5 μM
1	68 ± 1.0	32 ± 1.5	15 ± 1.5
2	16 ± 1.5	5 ± 1.0	2 ± 1.5
3	20 ± 0.5	7 ± 1.5	5 ± 1.0
4	92 ± 0.5	90 ± 0.5	53 ± 2.0
5	76 ± 1.5	25 ± 3.0	20 ± 2.5
6	71 ± 0.5	42 ± 1.5	2 ± 1.0
7	16 ± 0.5	1 ± 0.5	1 ± 0.5
8	20 ± 6.0	14 ± 4.0	10 ± 2.0
9	92 ± 1.5	68 ± 2.0	10 ± 2.0
cis-Pt	90 ± 2.5	79 ± 1.5	62 ± 2.5

Table 4. Percentage (±SD) of Growth Inhibition of SKOV-3 Cells

complex	50 μM	10 μM	5 μM
1	64 ± 2.0	30 ± 1.0	10 ± 1.5
2	32 ± 2.5	24 ± 1.0	15 ± 2.0
3	16 ± 1.5	10 ± 2.0	10 ± 2.0
4	57 ± 3.0	22 ± 3.5	4 ± 1.5
5	20 ± 3.0	14 ± 1.5	10 ± 1.0
6	35 ± 3.0	21 ± 5.0	1 ± 0.5
7	18 ± 1.5	7 ± 2.0	1 ± 0.5
8	23 ± 1.5	15 ± 2.5	10 ± 3.0
9	81 ± 2.0	43 ± 2.0	10 ± 2.5
cis-Pt	18 ± 1.5	10 ± 2.0	5 ± 1.5

Chart 8. T2 Cell Line Growth Inhibition

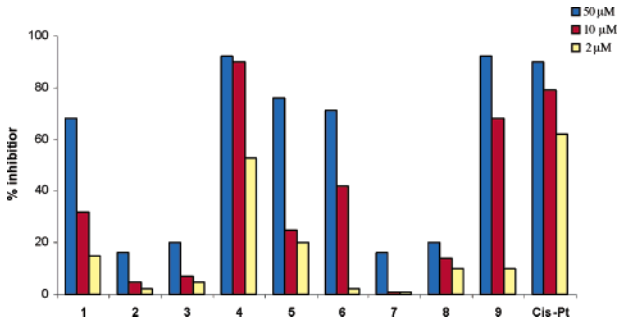
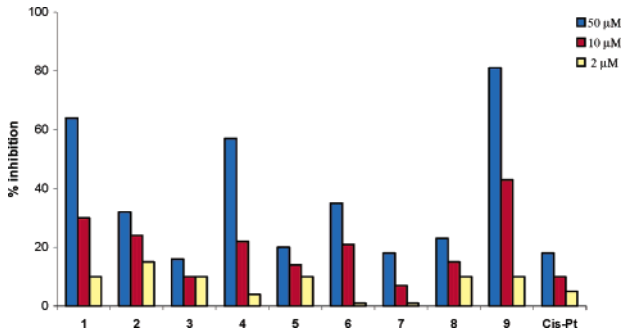


Chart 9. SKOV-3 Cell Line Growth Inhibition



$[\Sigma(d/\sigma)^2 = 11.48]$, the maximum deviation from the mean plane being 0.010(6) Å for C5 atom, while the exocyclic groups do not show any significant deviation from the purine plane. The ligands mean plane is rotated by an angle of 86.0(1)° with respect to the platinum coordination plane. The rest of distances and angles are similar to those found in other N(7)-bonded purine complexes [4,5,19,21] and do not deserve any additional comments. No significant intra- and intermolecular short interactions, less than the sum of van der Waals radii, are present in the crystal.

Cell Growth Inhibition. Complexes **1**−**9** have been tested for their capacity to inhibit the cell growth of two human cancer cell lines: the cisplatin-sensitive T2 (results reported in Table 3 and Chart 8) and the cisplatin-resistant SKOV3 (results reported in Table 4 and Chart 9). In both diagrams the activity of cisplatin was included for comparison. Each complex was dissolved in DMSO and diluted in AIM-V medium to obtain final concentrations of 50, 10, and 2 μM solutions. The chemical stability of the complexes in water/DMSO solutions was verified by $^{31}P\{^1H\}$ NMR.

The results clearly show that the activity of complexes **1**−**9** on cisplatin-sensitive T2 cells is strongly affected by the nature of the neutral ligands. The complexes containing PPh_3 (**1** and **4**−**6**) or pyridine (**9**) display a significantly better activity than those containing PTA (**2, 7,** and **8**) or terpyridine (**3**).

The tests performed with the cisplatin-sensitive T2 cells show that **4**, **9**, and cisplatin complexes have a comparable inhibitory activity at 50 μM. In particular, complex **4** shows the highest inhibitory capacity, similar to cisplatin activity.

The tests performed with the cisplatin-resistant SKOV3 cell line show that the 8-TTH_2 complex **1** and the 8-MTTH complex **4,** both containing triphenylphosphane, and the trans pyridine/8-MTTH complex **9** have the ability to induce inhibition, in contrast to cisplatin. The highest inhibition was obtained with complex **9.** Complexes containing PTA (**2**, **7**, **8**) and terpyridine (**3**) show a low activity, similarly to cisplatin.

Although a more exhaustive number of structures and experiments would be required for defining a complete structure−activity relationship, some observations can be attempted:

(a) The most active complexes on the cisplatin-sensitive T2 human cells are **4** and **9**. In the case of **9** it is known that the parent complex *trans*-$[PtCl_2py_2]$ is active[29] and therefore complex **9** could simply act as a prodrug, the active moiety being the $Pt(py)_2$ group. On the contrary, the precursor of **4**, *cis*-$[PtCl_2(PPh_3)_2]$, has been reported as nonactive[30] and therefore in this case the thiopurines are not innocent ligands and may have a role in determining the drug distribution and its interactions with biomolecules.

(b) The most active complexes on the cisplatin-resistant SKOV3 cells are **1**, **4**, and **9**, this last being the best one. The three complexes are more active than cisplatin at 50 and 10 μM concentrations. This fact supports the hypothesis that the complexes containing thiopurines and PPh_3 or pyridine act by a mechanism different from that accepted for cisplatin.

(c) Surprisingly very low activity has been found for the more water soluble PTA complexes. Although a more detailed investigation is required to correlate the PTA properties and the biological activity of its Pt complexes, this observation indicates that the activity is not improved by a mere increase of hydrophilicity, although the presence

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of hydrophilic ligands could be convenient in terms of drug administration and distribution.

Conclusion

We have synthesized and characterized nine new thiotheophylline platinum complexes containing deprotonated 8-TTH_2 and 8-MTTH ligands. The structure of the complexes *cis*-[PtCl(8-MTT)(PPh_3)$_2$] (**4**) and *trans*-[Pt(8-MTT)$_2$(py)$_2$] (**9**) have been also characterized by monocrystal X-ray diffraction.

The cancer cell growth inhibition activity of the above new platinum complexes have been tested on the cisplatin-sensitive T2 human cell line and the cisplatin-resistant SKOV3 cell line, and it has been observed that most of these compounds show some inhibitory activity on T2, although not as strong as cisplatin. Complexes **4** and **9** showed a appreciable activity also on cisplatin-resistant SKOV3 cells, which suggests that their activity is produced by a mechanism different from that consolidated for cisplatin.

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