Inorg. Chem. **2008**, *47*, 5641−5648

Synthesis, Characterization, and in Vitro Cytotoxicity of Some Gold(I) and Trans Platinum(II) Thionate Complexes Containing Water-Soluble PTA and DAPTA Ligands. X-ray Crystal Structures of $[Au(SC_4H_3N_2)(PTA)]$, *trans*-$[Pt(SC_4H_3N_2)_2(PTA)_2]$, *trans*-$[Pt(SC_5H_4N)_2(PTA)_2]$, and *trans*-$[Pt(SC_5H_4N)_2(DAPTA)_2]$

Susana Miranda,[†] Elena Vergara,[‡] Fabian Mohr,*[,†,§] Dick de Vos,[||] Elena Cerrada,[‡] Aránzazu Mendía,*[,†] and Mariano Laguna*[,‡]

Departamento de Química, Facultad de Ciencias, Universidad de Burgos, 09001 Burgos, Spain, Departamento de Química Inorgánica, Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain, Bergische Universität Wuppertal, Fachbereich C Anorganische Chemie, 42119 Wuppertal, Germany, and PCH Pharmachemie, Haarlem 2003, The Netherlands

Received November 7, 2007

A series of gold(I) and platinum(II) complexes of the type [Au(SR)(P)] and *trans*-$[Pt(SR)_2(P)_2]$ [SR = 2-thiopyridine (SPy), 2-thiopyrimidine (SPyrim); P = 1,3,5-triaza-7-phosphaadamantane (PTA), 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (DAPTA)] were prepared and characterized, and their in vitro cytotoxicities against a panel of seven human cancer cell lines were evaluated. The highly water soluble gold(I) complexes [Au(SR)(P)] [P = PTA and SR = SPy (**1**), SPyrim (**2**); P = DAPTA and SR = SPy (**3**), SPyrim (**4**)] showed low cytotoxicity, while the platinum(II) complexes *trans*-$[Pt(SR)_2(P)_2]$ [P = PTA and SR = SPyrim (**5**), SPy (**6**); P = DAPTA and SR = SPyrim (**7**), SPy (**8**)] demonstrated potent cytotoxicity for ovarian, colon, renal, and melanoma cancer cell lines on the basis of a comparison with ID_{50} values for some established cytotoxic drugs. Single crystals of **2**, **5**, **6**, and **8** suitable for X-ray structural characterization were obtained, and the study revealed the trans configuration for **5**, **6**, and **8** in their solid states.

Introduction

Metal compounds are widely used in medicine as magnetic resonance imaging (MRI) contrast agents, radiopharmaceuticals, antiarthritis drugs, antiulcer drugs, and cancer chemotherapy agents.[1–9] Metallic gold and gold compounds, in particular, have had a long history of use in medicine,[10] and several gold complexes are on the market as antiarthritic drugs (e.g., Solganol, Myocrisin, and Auranofin).[10–17] The serendipitous discovery of the cytotoxicity of *cis*-$[PtCl_2(NH_3)_2]$ ("cisplatin") and its successful use in cancer therapy since the 1970s have led to an enormous amount of research in this area.[18–21] Second- and third-generation platinum-based anticancer drugs with significantly fewer side

* To whom correspondence should be addressed. E-mail: fmohr@uni-wuppertal.de (F.M.), amendia@ubu.es (A.M.), mlaguna@posta.unizar.es (M.L.).
[†] Universidad de Burgos.
[‡] Universidad de Zaragoza.
[§] Bergische Universität Wuppertal.
[||] PCH Pharmachemie.

(1) Orvig, C., Abrams, M. J., Eds. *Chem. Rev.* **1999**, *99*, 2201–2842.
(2) (a) Sadler, P. J.; Guo, Z. *Pure Appl. Chem.* **1998**, *70*, 863–871. (b) Guo, Z. J.; Sadler, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1513–1531. (c) Sadler, P. J.; Li, H. Y.; Sun, H. Z. *Coord. Chem. Rev.* **1999**, *186*, 689–709. (d) Guo, Z. J.; Sadler, P. J. *Adv. Inorg. Chem.* **2000**, *49*, 183–306.
(3) *Metal Compounds in Cancer Therapy*; Fricker, S. P., Ed.; Chapman & Hall: London, 1994.
(4) *Metal Complexes in Cancer Therapy*; Keppler, B. K., Ed.; VCH: Weinheim, Germany, 1993.
(5) (a) Farrel, N. P. In *Uses of Inorganic Chemistry in Medicine*; Farrel, N., Ed.; RSC Publishing: Cambridge, U.K., 1999, p 208. (b) Farrel, N. *Coord. Chem. Rev.* **2002**, *232*, 1–4.
(6) (a) *Metal Ions and Their Complexes in Medication*; Sigel, A., Sigel, H., Eds.; Metal Ions in Biological Systems, Vol. *41*; Marcel Dekker: New York, 2004. (b) *Metal Complexes in Tumor Diagnosis and As Anticancer Agents*; Sigel, A., Sigel, H., Eds.; Metal Ions in Biological Systems, Vol. *42*; Marcel Dekker: New York, 2004.
(7) (a) Thompson, K. H.; Orvig, C. *Dalton Trans.* **2006**, 761–764. (b) Storr, T.; Thompson, K. H.; Orvig, C. *Chem. Soc. Rev.* **2006**, *35*, 534–544.

10.1021/ic7021903 CCC: $40.75
Published on Web 04/30/2008

effects than cisplatin have since been developed. One major problem with platinum-based anticancer drugs is the development of cell resistance, and thus, there is a continuing need for new and highly active cytotoxic platinum compounds. Some recent work has focused on the development of trans platinum complexes, which were initially neglected after it was reported that *trans*-$[PtCl_2(NH_3)_2]$ is not cytotoxic.

Traditionally, it was believed that only complexes of platinum(II) containing two inert and two semilabile and mutually cis ligands display antitumor activity until Farrel and coworkers[22] showed that complexes with trans geometry are also cytotoxic. Examples of such bioactive trans platinum(II) complexes include *trans*-$[PtCl_2\{NH_2CH(CH_3)_2\}\{NH(CH_3)_2\}]$[23] and *trans*-$[PtCl_2(iminoether)_2]$.[24] In general, the low water solubilities of *trans*-diaminedichloroplatinum(II) and analogous complexes have limited their usefulness, and efforts have therefore focused on modifying the nature of the anionic and neutral ligands.[25,26] Only relatively recently have the biological activities of platinum complexes with other neutral ligands such as phosphines and thiolates been investigated. Platinum(II) derivatives with aminodiphosphines[27] or lipophilic PPh_3 and/or hydrophilic 1,3,5-triaza-7-phosphaadamantane (PTA) and thiotheophyllines as anionic ligands[28] as well as $[Pt(ts)(P)_2]$ (ts = thiosalicylate; P = PPh_3, dppe) were reported to show significant biological activity.[29]

In parallel to the work on platinum complexes, the antitumor activities of other metal compounds have also been investigated. Thus, over the past 20 years, work has also focused on medical applications of copper(I), silver(I), and gold(I) complexes containing diphosphines such as bis(diphenylphosphino)ethane,[30] and some more-recent cytotoxicity studies of both gold(I) and gold(III) complexes have shown some promise.[31–35] Recently, a new type of water-soluble mixed-metal complex containing platinum(II) and ruthenium(III) was assessed for its effects on DNA and showed an intermediate toxicity compared with cisplatin.[36] In the past few years, studies of the biological anticancer properties of ruthenium complexes containing water-soluble PTA[37,38] as well as the osmium[38,39] and rhodium[39] derivatives have caused the coordination chemistry of PTA and its phosphine derivatives to receive a great deal of attention.[40] We have been interested in the preparation and applications of water-soluble gold, palladium, and platinum complexes containing thionate ligands.[41–45] As an extension of this work, we present here the preparation, characterization, and

(8) (a) Allardyce, C. S.; Dorcier, A.; Scolaro, C.; Dyson, P. J. *Appl. Organomet. Chem.* **2005**, *19*, 1–10. (b) Allardyce, C. S.; Dyson, P. J. *Bioorganomet. Chem.* **2006**, *17*, 177–210.

(9) *Applications of Coordination Chemistry*; Ward, M. D., Ed.; Comprehensive Coordination Chemistry II: From Biology to Nanotechnology, McCleverty, J. A., Meyer, T. J., Eds., Vol. *9*; Elsevier Pergamon: Oxford, U.K., 2004.

(10) Huaizi, Z.; Yuantao, N. *Gold Bull.* **2001**, *34*, 24–29.

(11) Higby, G. J. *Gold Bull.* **1982**, *15*, 130–140.

(12) Parish, R. V. *Interdiscip. Sci. Rev.* **1992**, *17*, 221–228.

(13) Parish, R. V.; Cottrill, S. M. *Gold Bull.* **1987**, *20*, 3–12.

(14) Sadler, P. J.; Sue, R. E. *Met.-Based Drugs* **1994**, *1*, 107–144.

(15) Best, S. L.; Sadler, P. J. *Gold Bull.* **1996**, *29*, 87–93.

(16) Shaw, C. F., III *Chem. Rev.* **1999**, *99*, 2589–2600.

(17) Zou, J.; Taylor, P.; Dornan, J.; Robinson, S. P.; Walkinshaw, M. D.; Sadler, P. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 29–31.

(18) Lippert, B. *Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug*; Wiley-VCH: Weinheim, Germany, 1999.

(19) Wong, E. W.; Giandomenico, C. M. *Chem. Rev.* **1999**, *99*, 2451–2466.

(20) Galanski, M.; Jakupec, M. A.; Keppler, B. K. *Curr. Med. Chem.* **2005**, *12*, 2075–2094.

(21) Berners-Price, S. J.; Ronconi, L.; Sadler, P. J. *Prog. Nucl. Magn. Reson. Spectrosc.* **2006**, *49*, 65–98.

(22) Bierbach, U.; Qu, Y.; Hambley, T. W.; Peroutka, J.; Nguyen, H. L.; Doedee, M.; Farrel, N. *Inorg. Chem.* **1999**, *38*, 3535–3542.

(23) Montero, E. I.; Diaz, S.; González-Vadillo, A. M.; Pérez, J. M.; Alonso, C.; Navarro-Ranninger, C. *J. Med. Chem.* **1999**, *42*, 4264–4268.

(24) Coluccia, M.; Nassi, A.; Boccarelli, A.; Giordano, D.; Cardellicchio, N.; Locker, D.; Leng, M.; Sivo, M.; Intini, F. P.; Natile, G. *J. Inorg. Biochem.* **1999**, *77*, 31–35.

(25) Bierbach, U.; Sabat, M.; Farrel, N. *Inorg. Chem.* **2000**, *39*, 1882–1890.

(26) Barenholz, Y.; Khazanov, E.; Najajreh, Y.; Gibson, D. US 2005090478, WO 030117998.

(27) (a) Habtemariam, A.; Parkinson, J. A.; Margiotta, N.; Hambley, T. W.; Parsons, S. P. J. *J. Chem. Soc., Dalton Trans.* **2001**, *36*, 2–372. (b) Margiotta, N.; Habtemariam, A.; Sadler, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1185–1187. (c) Habtemariam, A.; Sadler, P. J. *Chem. Commun.* **1996**, 1785–1786.

(28) (a) Romerosa, A.; Bergamini, P.; Bertolasi, V.; Canella, A.; Cattabriga, M.; Gavioli, R.; Mañas, S.; Mantovani, N.; Pellacani, L. *Inorg. Chem.* **2004**, *43*, 905–913. (b) Bergamini, P.; Bertolasi, V.; Marvellli, L.; Canella, A.; Gavioli, R.; Mantovani, N.; Mañas, S.; Romerosa, A. *Inorg. Chem.* **2007**, *46*, 4267–4276.

(29) Henderson, W.; McCaffrey, L. J.; Nicholson, B. K. *J. Chem. Soc., Dalton Trans.* **2000**, 2753–2760.

(30) Berners-Price, S. J.; Sadler, P. J. *Struct. Bonding (Berlin)* **1988**, *70*, 27–102.

(31) Fricker, S. P. *Gold Bull.* **1996**, *29*, 53–60.

(32) (a) Tiekink, E. R. T. *Crit. Rev. Oncol. Hematol.* **2002**, *42*, 225–248. (b) Tiekink, E. R. T. *Gold Bull.* **2003**, 117–124.

(33) Messori, L.; Marcon, G.; Orioli, P. *Bioinorg. Chem. Appl.* **2003**, *1*, 177–187.

(34) Messori, L.; Marcon, G. Gold Complexes As Anti-Tumor Agents. In *Metal Ions in Biological Systems*; Sigel, A., Sigel, H., Eds.; Marcel Dekker: New York, 2004; Vol. *42*, pp 385−424.

(35) Krpetic, Z.; Porta, F.; Scari, G. *Gold Bull.* **2006**, *39*, 66–68.

(36) Herman, A.; Tanski, J. M.; Tibbetts, M. F.; Anderson, C. M. *Inorg. Chem.* **2008**, *47*, 274–280.

(37) (a) Phillips, A. D.; Gonsalvi, L.; Romerosa, A.; Vizza, F.; Peruzzini, M. *Coord. Chem. Rev.* **2004**, *248*, 955–993. (b) Romerosa, A.; Campos-Malpartida, T.; Lidrissi, C.; Saoud, M.; Serrano-Ruiz, M.; Peruzzini, M.; Garrido-Cárdenas, J. A.; García-Maroto, F. *Inorg. Chem.* **2006**, *45*, 1289–1298. (c) Romerosa, A.; Saoud, M.; Campos-Malpartida, T.; Lidrissi, C.; Serrano-Ruiz, M.; Peruzzini, M.; Garrido, J. A.; García-Maroto, F. *Eur. J. Inorg. Chem.* **2007**, 2803–2812. (d) Ang, W. H.; Dyson, P. J. *Eur. J. Inorg. Chem.* **2006**, 4003–4018. (e) Allardyce, C. S.; Dyson, P. J.; Ellis, D. J.; Heath, S. L. *Chem. Commun.* **2001**, 1396–1397. (f) Scolaro, C.; Bergamo, A.; Brescacin, L.; Delfino, R.; Cocchietto, M.; Laurenczy, G.; Geldbach, T. J.; Sava, G.; Dyson, P. J. *J. Med. Chem.* **2005**, *48*, 4161–4171.

(38) Dorcier, A.; Dyson, P. J.; Gossens, C.; Rothlisberger, U.; Scopelliti, R.; Tavernelli, I. *Organometallics* **2005**, *24*, 2114–2123.

(39) Dorcier, A.; Ang, W. H.; Bolaño, S.; Gonsalvi, L.; Juillerat-Jeannerat, L.; Laurenczy, G.; Peruzzini, M.; Phillips, A. D.; Zanobini, F.; Dyson, P. J. *Organometallics* **2006**, *25*, 4090–4096.

(40) (a) Erlandsson, M.; Gonsalvi, L.; Lenco, A.; Peruzzini, M. *Inorg. Chem.* **2008**, *47*, 8–10. (b) Wong, G. W.; Lee, W.-C.; Frost, B. J. *Inorg. Chem.* **2008**, *47*, 612–620. (c) Wong, G. W.; Harkreader, J. L.; Mebi, C. A.; Frost, B. J. *Inorg. Chem.* **2006**, *45*, 6748–6755. (d) Frost, B. J.; Bautista, C. M.; Huang, R.; Shearer, J. *Inorg. Chem.* **2006**, *45*, 3481–3483. (e) Mebi, C. A.; Frost, B. J. *Inorg. Chem.* **2007**, *46*, 7115–7120. (f) Mebi, C. A.; Frost, B. J. *Z. Anorg. Allg. Chem.* **2007**, *633*, 368–371. (g) Mebi, C. A.; Fair, R. P.; Frost, B. J. *Organometallics* **2007**, *26*, 429–438.

(41) Mohr, F.; Cerrada, E.; Laguna, M. *Organometallics* **2006**, *25*, 644–648.

(42) Mohr, F.; Sanz, S.; Tiekink, E. R. T.; Laguna, M. *Organometallics* **2006**, *25*, 3084–3087.

(43) Mendía, A.; Cerrada, E.; Arnáiz, F. J.; Laguna, M. *Dalton Trans.* **2006**, 609–616.

(44) Mohr, F.; Mendía, A.; Laguna, M. *Eur. J. Inorg. Chem.* **2007**, 3115–3123.

(45) Vergara, E.; Miranda, S.; Mohr, F.; Cerrada, E.; Tieknik, E. R. T.; Romero, M. P.; Mendía, A.; Laguna, M. *Eur. J. Inorg. Chem.* **2007**, 2926–2933.

cytotoxicity studies of some gold(I) and trans platinum(II) complexes containing the water-soluble phosphine ligands PTA and 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]-nonane (DAPTA) as well as the thionate ligands 2-pyridinethione (SPy) and 2-thiopyrimidine (SPyrim).

Experimental Section

General Methods and Materials. ^{1}H, ^{13}C, and ^{31}P{^{1}H} NMR spectra, respectively, were recorded using 400, 100.58, and 161.92 MHz Bruker Avance and Varian INOVA spectrometers. Chemical shifts (δ) are quoted in parts per million relative to external TMS (^{1}H, ^{13}C) or 85% H_3PO_4 (^{31}P); coupling constants (J) are reported in hertz. Liquid secondary-ion mass spectrometry (LSIMS) mass spectra were measured using a VG Autospec spectrometer in positive-ion mode with *m*-nitrobenzyl alcohol (NBA) as the matrix. IR spectra were recorded as Nujol mulls using a PerkinElmer Spectrum One instrument and Nicolet Impact 410 FTIR (4000–400 cm^{-1}) and JASCO FT-IR 6300 (630–150 cm^{-1}) spectrophotometers. Elemental analyses were obtained in-house using PerkinElmer 240B and LECO CHNS 932 microanalyzers. PTA,[46] DAPTA,[47] and [AuCl(PTA)][48] were prepared using published procedures. The platinum(II) complexes *cis*-[$PtCl_2(P)_2$] (P = PTA, DAPTA) were prepared using slight modifications of the pathways described in the literature.[49–51] All of the other reagents and solvents were obtained commercially and used as received.

Preparation of [Au(SR)(P)] Complexes. To a solution of KOH (0.022 g, 0.385 mmol) in MeOH (10 mL) containing the thiol compound (0.308 mmol) was added [AuCl(P)] (0.257 mmol). After the mixture was stirred for 20 h, the solution was evaporated to dryness in vacuum and the residue extracted into CH_2Cl_2 (3 × 10 mL). The combined extracts were passed through Celite and concentrated in vacuum to a volume of 5 mL. Addition of pentane or Et_2O precipitated the products, which were isolated by filtration and dried in air.

[Au(SPy)(PTA)] (1). 78% yield, pale-yellow solid. ^{1}H NMR (D_2O): δ 4.28 (q, J = 13.6 Hz, 6H, CH_2N), 4.30 (s, 6H, CH_2P), 7.05 (dt, J = 5.3, 1.3 Hz, 1H, py-H_4), 7.48 (dt, J = 7.8, 1.8 Hz, 1H, py-H_5), 7.63 (d, J = 8.0 Hz, 1H, py-H_6), 8.21 (dd, J = 4.8, 1.0 Hz, 1H, py-H_3). ^{31}P{^{1}H} NMR (D_2O): δ −46.72. FAB MS: *m*/*z* 465 $[M]^+$, 818 $[M + AuPTA]^+$. Anal. Calcd for $C_{11}H_{16}AuN_4PS$ (mol wt 464.3): C, 28.46; H, 3.47; N, 12.07. Found: C, 28.50; H, 3.32; N, 11.56.

[Au(SPyrim)(PTA)] (2). 72% yield, pale-yellow solid. ^{1}H NMR (D_2O): δ 4.39 (m, 12H, TPA), 7.09 (t, J = 4.8 Hz, 1H, pyrim-H_5), 8.39 (d, J = 5.1 Hz, 2H, pyrim-H_4, H_6). ^{31}P{^{1}H} NMR (D_2O): δ −46.50. FAB MS: *m*/*z* 466 $[M]^+$, 819 $[M + AuPTA]^+$. Anal. Calcd for $C_{10}H_{15}AuN_5PS$ (mol wt 465.3): C, 25.81; H, 3.25; N, 15.05. Found: C, 25.75; H, 3.30; N, 15.27. Crystals suitable for X-ray diffraction were grown by slow diffusion of diethyl ether into a CH_2Cl_2 solution at room temperature (rt).

[Au(SPy)(DAPTA)] (3). 75% yield, pale-yellow solid. ^{1}H NMR ($CDCl_3$): δ 2.08 (s, 6H, Me), 3.04 (dd, J = 14.6, 7.3 Hz, 1H, NCH_2P), 3.99 (s, 2H, NCH_2P), 4.03 (d, J = 14.3 Hz, 1H, NCH_2N), 4.32 (d, J = 15.5 Hz, 1H, NCH_2P), 4.61 (d, J =14.4 Hz, 1H, NCH_2N), 4.73 (dd, J = 15.5, 9.5 Hz, 1H, NCH_2P), 4.91 (d, J = 14.3 Hz, 1H, NCH_2N), 5.63 (dd, J = 16.1, 7.5 Hz, 1H, NCH_2P), 5.74 (d, J = 14.3 Hz, 1H, NCH_2N), 6.90 (t, J = 6.8 Hz, 1H, py-H_5), 7.38 (t, J = 7.9 Hz, 1H, py-H_4), 7.44 (d, J = 8.1 Hz, 1H, py-H_3), 8.19 (d, J = 5.1 Hz, 1H, py-H_6). ^{31}P{^{1}H} NMR ($CDCl_3$): δ –26.95. IR (Nujol) ν (cm^{-1}): 1642 (C═O). FAB MS: *m*/*z* 537 $[M]^+$, 963 $[M + AuDAPTA]^+$; Anal. Calcd for $C_{14}H_{20}AuN_4O_2PS$ (mol wt 536.3): C, 31.35; H, 3.76; N, 10.45. Found: C, 30.87; H, 3.77; N, 10.32.

[Au(SPyrim)(DAPTA)] (4). 49% yield, pale-yellow solid. ^{1}H NMR ($CDCl_3$): δ 2.07 (s, 3H, Me), 2.08 (s, 3H, Me), 3.84 (dt, J = 15.8 Hz, 1H, NCH_2P), 4.05–4.09 (m, 3H, NCH_2P, NCH_2N), 4.43 (dt, J = 15.6, 2.8 Hz, 1H, NCH_2P), 4.66 (d, J = 14.1 Hz, 1H, NCH_2N), 4.81–4.91 (m, 2H, NCH_2N, NCH_2P), 5.63 (d, J = 15.9 Hz, 1H, NCH_2P), 5.65 (d, J = 15.9 Hz, 1H, NCH_2P), 5.72 (d, J = 14.2 Hz, 1H, NCH_2N), 7.01 (t, J = 5.1 Hz, 1H, pyrim-H_5), 8.48 (d, J = 5.1 Hz, 2H, pyrim-H_4, H_6). ^{31}P{^{1}H} NMR ($CDCl_3$): δ –27.14. IR (Nujol) ν (cm^{-1}): 1629 (C═O). FAB MS: *m*/*z* 538 $[M]^+$, 964 $[M + AuDAPTA]^+$; Anal. Calcd for $C_{13}H_{19}AuN_5O_2PS$ (mol wt 537.3): C, 29.06; H, 3.56; N, 13.03. Found: C, 28.78; H, 3.20; N, 13.12.

Preparation of *trans*-[$Pt(SR)_2(P)_2$] Complexes. To a solution of NaOEt (0.035 g, 0.500 mmol) in EtOH (20 mL) containing the thiol compound (0.450 mmol) was added *cis*-[$PtCl_2(P)_2$] (0.170 mmol). After the mixture was stirred at room temperature under nitrogen for 16 h, the precipitated solid was isolated by filtration and the residue washed with EtOH and Et_2O and dried in air.

***trans*-[$Pt(SPyrim)_2(PTA)_2$] (5).** 84% yield, yellow solid. ^{1}H NMR ($CDCl_3$): δ 4.23 (s, 12H, CH_2P), 4.35 and 4.41 (AB system, J_{AB} = 13.1 Hz, 12H, CH_2N), 6.85 (t, J = 4.7 Hz, 2H, pyrim-H_5), 8.38 (d, J = 4.7 Hz, 4H, pyrim-H_4, H_6). ^{31}P{^{1}H} NMR ($CDCl_3$): δ −63.27 (J_{Pt-P} = 2565 Hz). IR (Nujol) ν (cm^{-1}): 1533, 1558 (C═C + C═N), 392 (Pt−S), 281 (Pt−P). FAB MS: *m*/*z* 620 $[M - SPyrim]^+$, 575 $[M - PTA + H]^+$, 463 $[M - SPyrim - PTA]^+$. Anal. Calcd for $C_{20}H_{30}N_{10}P_2PtS_2$ (mol wt 731.7): C, 32.83; H, 4.13; N, 19.14; S 8.76. Found: C, 32.58; H, 4.13; N, 18.87; S, 8.75.

***trans*-[$Pt(SPy)_2(PTA)_2$] (6).** 82% yield, colorless solid. ^{1}H NMR ($CDCl_3$): δ 4.14 (s, 12H, CH_2P), 4.37 and 4.31 (AB system, J_{AB} = 13.1 Hz, 12H, CH_2N), 6.88 (dt, J = 5.0, 1.0 Hz, 2H, py-H_4), 7.32 (dt, J = 7.7, 2.0 Hz, 2H, py-H_5), 7.55 (d, J = 8.0 Hz, 2H, py-H_6), 8.32 (d, J = 5.0 Hz, 2H, py-H_3). ^{31}P{^{1}H} NMR ($CDCl_3$): δ –62.7 (J_{Pt-P} = 2559 Hz). IR (Nujol) ν (cm^{-1}): 1546, 1571 (C═C + C═N), 391 (Pt−S), 275 (Pt−P). FAB MS: *m*/*z* 618 $[M - SPy]^+$. Anal. Calcd for $C_{22}H_{32}N_8P_2PtS_2$ (mol wt 729.7): C, 36.21; H, 4.42; N, 15.36; S, 8.79. Found: C, 35.96; H, 4.07; N, 14.78; S, 8.52. Crystals suitable for X-ray diffraction were grown by slow diffusion of hexane into a $CHCl_3$ solution at room temperature.

***trans*-[$Pt(SPyrim)_2(DAPTA)_2$] (7).** 71% yield, brownish solid. ^{1}H NMR ($CDCl_3$): δ 1.79 (s, 6H, Me), 2.06 (s, 6H, Me), 3.80–3.74 (m, 6H, NCH_2P, NCH_2N), 3.94 (d, J = 14.1 Hz, 2H, NCH_2N), 4.16 (d, J = 15.6 Hz, 2H, NCH_2P), 4.28 (m, 2H, NCH_2N), 4.59 (d, J = 13.6 Hz, 2H, NCH_2N), 4.66 (d, J = 14.1 Hz, 2H, NCH_2P), 4.88 (d, J = 13.6 Hz, 2H, NCH_2N), 5.74 (m, 4H, NCH_2N, NCH_2P), 6.94 (t, J = 4.8 Hz, 2H, pyrim-H_5), 8.45 (d, J = 4.8 Hz, 4H, pyrim-H_4, H_6). ^{31}P{^{1}H} NMR ($CDCl_3$, rt): δ –40.19 (s, J_{Pt-P} = 2721 Hz), −40.28 (s, J_{Pt-P} = 2724 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$, 303 K): δ −40.14 (s, J_{Pt-P} = 2724 Hz). IR (Nujol) ν (cm^{-1}): 1626 (C═O), 1534, 1557 (C═C + C═N), 369 (Pt−S), 282 (Pt−P). FAB MS: *m*/*z* 876 $[M + H]^+$, 764 $[M - SPyrim]^+$, 647 $[M - DAPTA +$

(46) Daigle, D. J. *Inorg. Synth.* **1998**, *32*, 40–45.
(47) Darensbourg, D. J.; Ortiz, C. G.; Kamplain, J. W. *Organometallics* **2004**, *23*, 1747–1754.
(48) Assefa, Z.; McBurnett, B. G.; Staples, R. J.; Fackler, J. P., Jr.; Assmann, B.; Angermaier, K.; Schmidbaur, H. *Inorg. Chem.* **1995**, *34*, 75–83.
(49) Darensbourg, D. J.; Decuir, T. J.; Stafford, N. W.; Robertson, J. B.; Draper, J. D.; Reibenspies, J. *Inorg. Chem.* **1997**, *36*, 4218–4226.
(50) Alyea, E. C.; Ferguson, G.; Shanmugaperumal, K. *Polyhedron* **1998**, *17*, 2727–2732.
(51) Otto, S.; Roodt, A.; Purcell, W. *Inorg. Chem. Commun.* **1998**, *1*, 415–417.

H]$^+$, 535 [M − Spyrim − DAPTA]$^+$, Anal. Calcd for $C_{26}H_{42}N_{10}O_4P_2PtS_2$ (mol wt 875.8): C, 35.66; H, 4.37; N, 15.99; S, 7.32. Found: C, 35.26; H, 4.32; N, 14.78; S, 6.87.

***trans*-[Pt(SPy)$_2$(DAPTA)$_2$] (8).** 92% yield, colorless solid. ^{1}H NMR ($CDCl_3$): δ 1.81 (s, 6H, Me), 1.85 (s, 6H, Me), 3.72 (m, 4H, NCH_2P), 3.88 (dd, J = 14.0 Hz, 2H, NCH_2N), 4.00 (d, J = 14.8 Hz, 2H, NCH_2P), 4.19 (d, J = 15.6 Hz, 2H, NCH_2P), 4.50 (d, J =14.0 Hz, 2H, NCH_2N), 4.63 (d, J = 15.1 Hz, 2H, NCH_2P), 4.86 (d, J = 13.8 Hz, 2H, NCH_2N), 5.70 (d, J = 14.0 Hz, 4H, NCH_2P, NCH_2N), 6.94 (t, J = 5.5 Hz, 2H, py-H_5), 7.36 (t, J = 8.3 Hz, 2H, py-H_4), 7.52 (d, J = 8.1 Hz, 2H, py-H_3), 8.39 (d, J = 4.6 Hz, 2H, py-H_6). ^{31}P{^{1}H} NMR ($CDCl_3$, rt) δ –38.73 (s, J_{Pt-P} = 2731 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$, 253 K): –38.89 (s, J_{Pt-P} = 2701 Hz), –38.94 (s, J_{Pt-P} = 2701 Hz). IR (Nujol) ν (cm^{-1}): 1640 (C═O), 1550, 1567 (C═C + C═N), 361 (Pt−S), 278 (Pt−P). FAB MS: m/z 763 [M − SPy]$^+$, 645 [M − DAPTA + H]$^+$, 535 [M − Spy − DAPTA + H]$^+$. Anal. Calcd for $C_{28}H_{40}N_8O_4P_2PtS_2$ (mol wt 873.8): C, 38.49; H, 4.61; N, 12.82; S, 7.34. Found: C, 38.46; H, 4.47; N, 12.69; S, 7.01.

Cytotoxicity Studies. The in vitro cytotoxicity experiments were performed at the Laboratory of Translational Pharmacology, Department of Medical Oncology, Erasmus Medical Center, Rotterdam, The Netherlands. The test and reference compounds were dissolved at a concentration of 0.25 mg/mL in full medium by 20-fold dilution of a stock solution containing 1 mg of compound/200 μL. The test complexes **1–8** were dissolved in water. The compounds were taken into dimethyl sulfoxide (DMSO). Cytotoxicity was estimated using the microculture sulforhodamine B (SRB) test.[52] The human cancer cell lines examined in the present study were A498 (renal cancer), MCF-7 [estrogen receptor (ER)+/progesterone receptor (PgR)+ breast cancer], EVSA-T (ER−/PgR− breast cancer), H226 (non-small-cell lung cancer), IGROV (ovarian cancer), M19 MEL (melanoma), and WIDR (colon cancer).[53]

The experiment was started on day 0, when 10 000 cells per well were seeded into 96-well flat-bottom microtiter plates (Falcon 3072, DB). The plates were incubated overnight at 37 °C, using 5% CO_2 to allow the cells to adhere to the bottom. On day 1, a 3-fold dilution sequence of ten steps was carried out in full medium, starting with the 250 μg/mL stock solution. Every dilution was used in quadruplicate through addition of 200 μL to a column of four wells. This procedure resulted in a highest concentration of 62 500 ng/mL being present in column 12. Column 2 was used for the blank. After incubation for 3 days, the plates were washed twice with PBS. A fluorescein diacetate (FDA) stock solution was diluted to 2 μg/mL using PBS, and 200 μL of this solution was added to each of the control, experimental, and blank wells. The plates were incubated for 30 min at 37 °C, and the fluorescence generated from each well was measured at an excitation wavelength of 485 nm and an emission wavelength of 535 nm using an automated microplate reader (Labsystems Multiskan MS). PBS was added to column 1 in order to diminish interfering evaporation. On day 7, the incubation was terminated by washing the plate twice with PBS. Subsequently, the cells were fixed with 10% trichloroacetic acid in PBS and kept at 4 °C for 1 h. After five washes with tap water, the cells were stained for at least 15 min with 0.4% SRB dissolved in 1% acetic acid. The cells were stained and then washed with 1% acetic acid to remove the unbound stain. The plates were air-dried, and the bound stain was dissolved in 150 μL of 10 mM Tris base. The absorbance was read at 540 nm using an automated microplate reader. Data were used for construction of concentration−response curves and for determination of the ID_{50} value through use of Deltasoft 3 software.[54]

The variability of the in vitro cytotoxicity test depends on the cell lines used and the serum applied. With the same batch of cell lines and the same batch of serum, the interexperimental coefficient of variation (CV) was 1–11%, depending on the cell line, and the intraexperimental CV was 2–4%. These values may have been higher if other batches of cell lines and/or serum had been used.

X-Ray Structure Determination for 2, 5, 6, and 8. Crystals suitable for X-ray diffraction were obtained by slow diffusion of diethyl ether or hexane into dichloromethane or $CHCl_3$ solutions. A summary of the fundamental crystal data and refinement parameters for compounds **2**, **5**, **6**, and **8** is given in Table 1. The crystals were mounted on glass fiber with inert oil and centered on a Bruker-Siemens Smart CCD diffractometer (for **2**) or a Bruker SMART CCD area-detector diffractometer (for **5**, **6**, or **8**); in either case, monochromated Mo Kα radiation (λ = 0.7107 Å) and the $\theta-2\theta$ scan type were used. Intensities were integrated[55] over several series of exposures, with each exposure covering 0.3° in ω and the total data set being a sphere. Absorption corrections were applied on the basis of multiple and symmetry-equivalent measurements.[56] The structures were solved using direct methods[57] and refined by least-squares on weighted F^2 values for all reflections. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included at geometrically determined positions, riding on their respective carbon atoms. All of the calculations were performed using the SHELXTL program package.[57] In the case of **6**, the diffraction data were weak, having a mean $I/\sigma(I)$ value of 4.81 in the data set before averaging of equivalents, an R_{int} value of 29.29%, and only 38% of the data with $I > 3\sigma(I)$; thus, they did not give a completely acceptable resolution.

Results and Discussion

Gold(I) and Platinum(II) Complexes. The gold(I) complexes [Au(SR)(P)] [P = PTA and SR = SPy (**1**), SPyrim (**2**); P = DAPTA and SR = SPy (**3**), SPyrim (**4**)] were prepared in good yields by reaction of the appropriate chlorogold(I) precursors with the thiol derivatives in the presence of base (Scheme 1). The Pt(II) complexes *trans*-[Pt(SR)$_2$(P)$_2$] [P = PTA and SR = SPyrim (**5**), SPy (**6**); P = DAPTA and SR = SPyrim (**7**), SPy (**8**)] were prepared by an analogous route, as shown in Scheme 2.

The new complexes **1**−**8** were fully characterized using various spectroscopic techniques. Complexes **1**−**4** showed singlet resonances in their ^{31}P{^{1}H} NMR spectra, the chemical shifts of which were consistent with coordination of the phosphine ligands to a gold(I) center.[45] The same was observed for the platinum PTA complexes **5** and **6**, which showed singlet resonances with platinum satellites in their ^{31}P{^{1}H} NMR spectra. In the case of the platinum DAPTA complex **7**, two singlets appeared at room temperature and were converted into one singlet at 305 K. Complex **8** showed similar behavior, although at lower temperatures, with one singlet at room temperature that became two singlets at 253

(52) Keepers, Y. P.; Pizao, P. E.; Peters, G. J.; Van Ark-Otte, J.; Winograd, B.; Pinedo, H. M. *Eur. J. Cancer* **1991**, *27*, 897–900.

(53) (a) Boyd, M. R. *Princ. Pract. Oncol.* **1989**, *3*, 1–12. (b) Boyd, M. R. The NCI in Vitro Anticancer Drug Discovery Screen: Concept, Implementation, and Operation, 1985−1995. In *Anticancer Drug Development Guide: Preclinical Screening, Clinical Trials, and Approval*; Teicher, B. A., Ed.; Humana Press: Totowa, NJ, 1997; Vol. *23*, p 42.

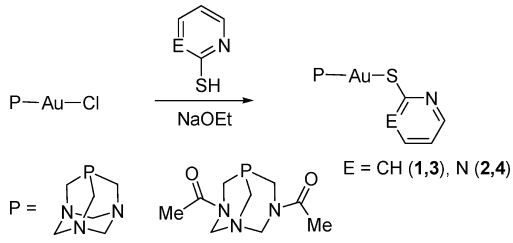
(54) Delta/3 GO2280; http://www.qontinuum-plus.com/esp/soptec/actualizaciones/actu_delta3.htm.

Table 1. Crystal Data and Data Collection and Refinement Parameters for the Complexes [Au(SPyrim)(PTA)] (**2**), *trans*-[Pt(SPyrim)$_2$(PTA)$_2$] (**5**), *trans*-[Pt(SPy)$_2$(PTA)$_2$] (**6**), and *trans*-[Pt(SPy)$_2$(DAPTA)$_2$] (**8**)

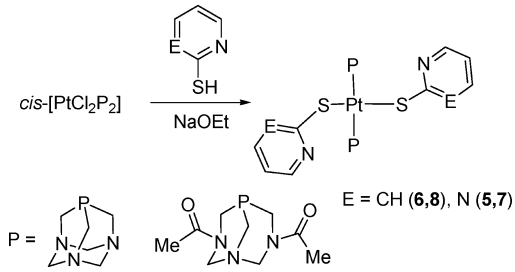
	2	**5**	**6**	**8**
empirical formula	$C_{10}H_{15}Cl_3AuN_5PS$	$C_{20}H_{30}N_{10}P_2PtS_2$	$C_{24}H_{34}Cl_6N_8P_2PtS_2$	$C_{28}H_{40}N_8O_4P_2PtS_2$
mol wt	465.27	731.7	968.46	873.83
color, shape	colorless, needles	colorless, prism	colorless, prism	colorless, prism
space group	monoclinic, *C*2/*c*	triclinic, $P\bar{1}$	monoclinic, $P2_1/c$	monoclinic, $P2_1/c$
a (Å)	20.889(3)	6.271(5)	6.0782(12)	10.047(7)
b (Å)	6.2438(10)	10.186(5)	27.124(5)	10.559(7)
c (Å)	20.699(3)	11.126(5)	10.990(2)	15.598(11)
α (deg)	90	66.214(5)	90	90
β (deg)	95.791(3)	82.432(5)	103.30(3)	100.878(12)
γ (deg)	90	72.388(5)	90	90
V (Å^3)	2685.9(7)	619.8(6)	1763.2(6)	1625(2)
T (K)	100(2)	173(2)	293(2)	173(2)
Z	8	2	4	2
D_{calc} (g cm^{-3})	2.301	1.960	1.824	1.786
size (mm^3)	0.3 × 0.06 × 0.04	0.4 × 0.05 × 0.05	0.1 × 0.4 × 0.05	0.5 × 0.5 × 0.5
μ (mm^{-1})	11.218	5.990	4.674	4.593
θ range (deg)	1.96−24.00	2.00−27.92	2.95−17.50	2.06−28.03
no. of data collected	6415	7036	6762	17 512
no. of unique data	2100 [R_{int} = 0.0386]	2701 [R_{int} = 0.1508]	1122 [R_{int} = 0.2929]	3667 [R_{int} = 0.1954]
R_1[a] [$F^2 > 2\sigma(F^2)$]	0.0307	0.0486	0.0628	0.0628
wR_2[b] (all data)	0.0702	0.1558	0.1288	0.1354
S[c] (all data)	1.007	1.060	1.051	0.971

[a] $R_1(F) = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR_2(F^2) = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$, where $w = [\sigma^2(F_o^2) + (\alpha P)^2 + bP]^{-1}$ with $P = [\max(F_o^2, 0) + 2F_c^2]/3$. [c] $S = [\sum(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$, where *n* is the number of reflections and *p* is the number of refined parameters.

Scheme 1



Scheme 2



K. This behavior could be seen in the methyl resonances of DAPTA in complexes **7** and **8**, which showed two or one methyl resonance when two or one phosphorus resonance was present, respectively, indicating that they corresponded to conformational isomers. The platinum satellites of complexes **5**−**8** (J_{Pt-P} = 2565, 2559, 2724, and 2731 Hz, respectively) were consistent with a trans configuration of ligands about the platinum center[28b,43,44,58] and ruled out the presence of cis isomers even at low temperatures. In addition, the presence of only one band each due to Pt−S and Pt−P stretching vibrations in the IR spectra of complexes **5**−**8** also agreed with the proposed trans configuration in the solid state. Given that *cis*-[PtCl$_2$(P)$_2$] starting materials were used, an isomerization process must have occurred during the course of the reaction. Such isomerization is not unusual for platinum complexes and may be expected since the chloride ligands are being replaced by the larger SR$^-$ anions. Similar isomerization reactions occur in the preparation of *trans*-[PdI$_2$(PTA)$_2$] and *trans*-[PdI$_2$(PTAH)$_2$]$^{2+}$ from *cis*-[PdCl$_2$(PTA)$_2$].[59]

For complexes **5**, **6**, and **8**, the trans configuration was confirmed by an X-ray diffraction experiment. In the case of complex **6**, the low quality of the data precluded any acceptable discussion of the structure. The molecular structures of **5** and **8** are shown in Figures 1 and 2, respectively. In both of these complexes, the platinum atom lies on a crystallographic inversion center with the two thiolate and two phosphine ligands mutually trans to each other, resulting in a distorted square-planar geometry. The bond angles P1−Pt1−P1#1 [180.0(2)° in **5** and 180.00(14)° in **8**] and S1#1−Pt1−S1 [180.00(2) and 180.00(9)°, respectively] are perfectly linear, while the bond angles P1−Pt1−S1#1 [86.89(10)° in **5** and 92.84(9)° in **8**], P1#1−Pt1−S1#1 [93.11(10)° in **5** and 87.16(9)° in **8**], P1−Pt1−S1 [93.11(10)° in **5** and 87.16(9)° in **8**], and P1#1−Pt1−S1 [86.89(10)° in **5** and 92.84(9)° in **8**] deviate slightly from 90°. The pyridine nitrogen atom in **8** and one of the pyrimidine nitrogen atoms in **5** are directed toward the central platinum atom, but the Pt···N4 separations [3.389(9) and 3.266(7) Å, respectively] are not considered to represent significant bonding interactions. In the case of complex **8**, the COCH$_3$ groups of the

(55) *SAINT Integration Software*; Siemens Analytical X-ray Instruments Inc.: Madison, WI, 2000.
(56) Sheldrick, G. M. *SADABS: A Program for Absorption Correction with the Siemens SMART System*; Universität Göttingen: Göttingen, Germany, 2001.
(57) Sheldrick, G. M. *SHELXTL-NT*, version 6.1; Universität Göttingen: Göttingen, Germany, 1998.
(58) (a) Narayan, S.; Jain, V. K. *Transition Met. Chem.* **1999**, *24*, 409–413. (b) Jain, V. K.; Kannan, S.; Tienkink, E. R. T. *J. Chem. Res., Synop.* **1994**, 85. (c) Jain, V. K.; Kannan, S.; Tienkink, E. R. T. *J. Chem. Res., Miniprint* **1994**, 501.
(59) Meij, A. M. M.; Otto, S.; Roodt, A. *Inorg. Chim. Acta* **2005**, *358*, 1005–1011.

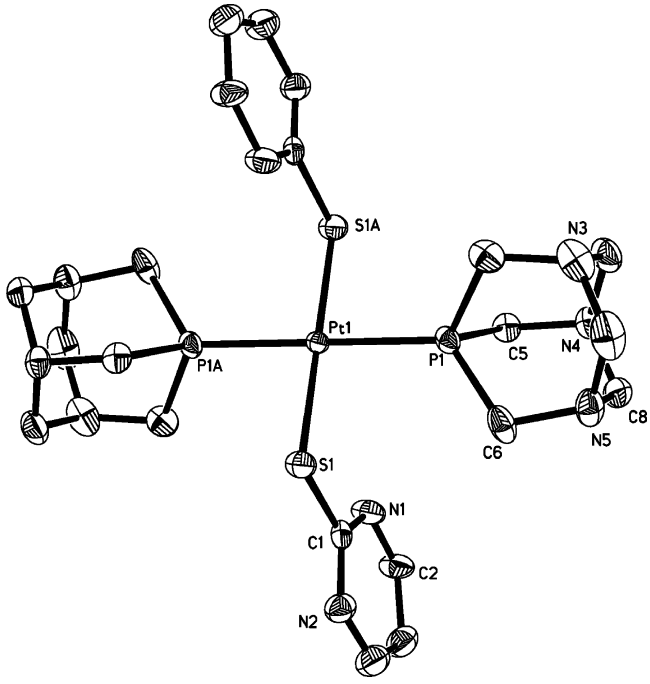


Figure 1. Molecular structure of complex **5**. Thermal ellipsoids are drawn at the 50% probability level, and H atoms have been omitted for clarity. Selected bond distances (Å): Pt1−P1#1, 2.280(3); Pt1−P1, 2.280(3); Pt1−S1, 2.329(3); Pt1−S1#1, 2.329(3); S1−C1, 1.768(10). Selected bond angles (deg): P1#1−Pt1−P1, 180.0(2); P1#1−Pt1−S1, 86.89(10); P1−Pt1−S1, 93.11(10); P1#1−Pt1−S1#1, 93.11(10); P1−Pt1−S1#1, 86.89(10); S1−Pt1−S1#1, 180.00(12). (Atoms labeled #1 are related to the corresponding unlabeled atoms by the symmetry operation *i*: $-x + 2$, $-y + 1$, $-z$.)

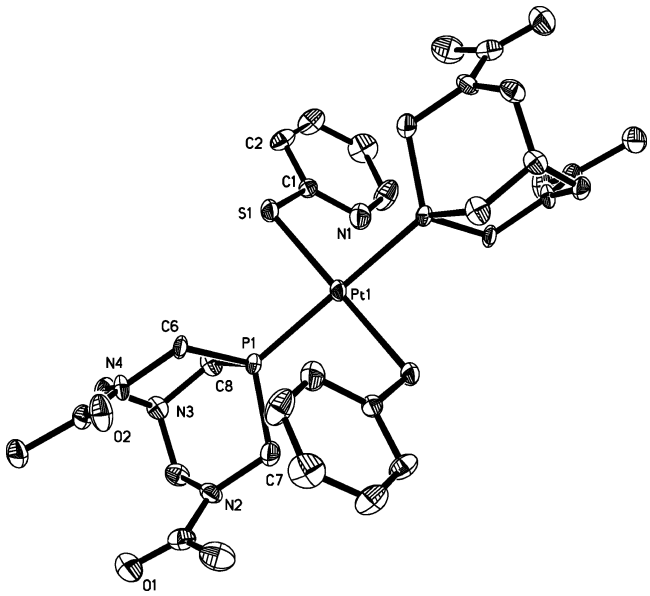


Figure 2. Molecular structure of complex **8**. Thermal ellipsoids are drawn at the 50% probability level, and H atoms have been omitted for clarity. Selected bond distances (Å): Pt1−P1#1, 2.301(2); Pt1−P1, 2.301(2); Pt1−S1, 2.350(2); Pt1−S1#1, 2.350(2); S1−C1, 1.753(7). Selected bond angles (deg): P1#1−Pt1−P1, 180.00(14); P1#1−Pt1−S1, 92.84(9); P1−Pt1−S1, 87.16(9); P1#1−Pt1−S1#1, 87.16(9); P1−Pt1−S1#1, 92.84(9); S1−Pt1−S1#1, 180.00(9). (Atoms labeled #1 are related to the corresponding unlabeled atoms by the symmetry operation *i*: $-x$, $-y$, $-z$.)

DAPTA ligand are anti with respect to each other, as they are in the free phosphine.[47] Overall, these structures are similar to those previously reported for the platinum phosphine thionate complexes *trans*-$[Pt(SPy)_2(PPh_3)_2]$[60] and *trans*-$[Pt(SPy)_2(PPh_2Me)_2]$.[43] The Pt−P distances in complexes **5** and **8** [2.280(3) and 2.301(2) Å, respectively], while comparatively longer, are very similar to those observed in the PPh_3 analogues and in other trans platinum complexes containing the PTA ligand, such as *trans*-$[PtX_2(PTA)_2]$ (X = I,[61] CN[62]), *trans*-$[Pt(PTA)_3(PTAH)]Cl$,[63] *trans*-$[Pt(SCN)(PTA)_3](SCN)$,[64] and *trans*-$[Pt(C{\equiv}C(CH_2)_3NH_3)_2(PTA)_2]Br_2$.[65] While the Pt−P distances in **8** are longer, the Pt−S distances [2.329(3) Å in **5** and 2.350(2) Å in **8**] are considerably shorter than those in the other complexes.

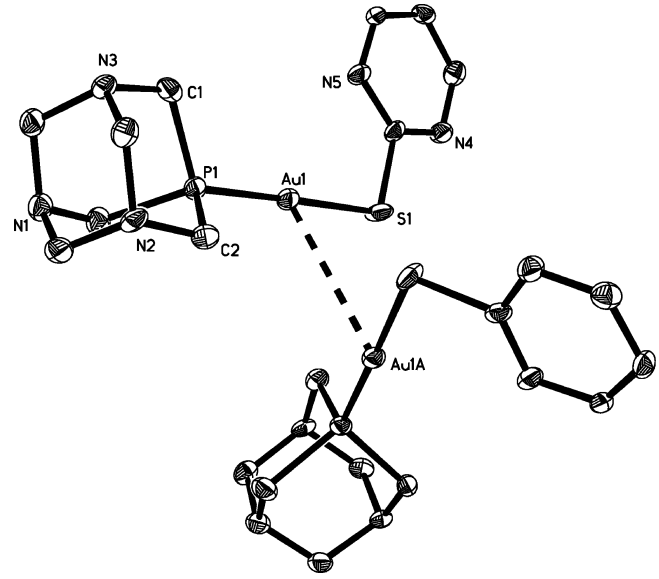


Figure 3. Molecular structure of complex **2**. Thermal ellipsoids are drawn at the 50% probability level, and H atoms have been omitted for clarity. Selected bond distances (Å): Au1−P1, 2.2527(18); Au1−S1, 2.3085(18); Au1−Au1#1, 3.3536(7). Selected bond angles (deg): P1−Au1−P1, 180.0(2); P1−Au1−Au1#1, 102.39(4); S1−Au1−Au1#1, 75.27(4). (Atoms labeled #1 are related to the corresponding unlabeled atoms by the symmetry operation *i*: $-x + 1$, y, $-z + {}^3/_2$.)

The structure of complex **2** was also obtained by X-ray analysis. The molecule, whose structure is shown in Figure 3, displays a typical linear geometry about the gold center, with an S1−Au1−P1 angle of 177.33(6)°. The molecule is associated with an additional unit related by symmetry in a nearly perpendicular arrangement (torsion angle of 70.2°) through a gold−gold interaction with a distance of 3.3536(7) Å. This interaction distance is longer than those observed in other gold complexes with PTA as a ligand[42,66,67] (3.047−3.1164 Å), probably as a result of steric effects. The Au−P

(60) Lobana, T. S.; Verma, R.; Castineiras, A. *Polyhedron* **1998**, *17*, 3753–3758.
(61) Otto, S.; Roodt, A. *Acta Crystallogr.* **2001**, *C57*, 540–541.
(62) Assefa, Z.; McBurnett, B. G.; Staples, R. J.; Fackler, J. P., Jr. *Acta Crystallogr.* **1995**, *C51*, 1742–1743.
(63) Darensbourg, D. J.; Robertson, J. B.; Larkins, D. L.; Reibenspies, J. H. *Inorg. Chem.* **1999**, *38*, 2473–2481.
(64) Sam, Z. A.; Roodt, A.; Otto, S. *J. Coord. Chem.* **2006**, *59*, 1025–1036.
(65) Krogstad, D. A.; Cho, J.; DeBoer, A. J.; Klitzke, J. A.; Sanow, W. R.; Williams, H. A.; Halfen, J. A. *Inorg. Chim. Acta* **2006**, *358*, 136–148.
(66) Assefa, Z.; McBurnett, B. G.; Staples, R. J.; Fackler, J. P., Jr. *Inorg. Chem.* **1995**, *34*, 4965–4972.
(67) Forward, J. M.; Bohmann, D.; Fackler, J. P., Jr.; Staples, R. J. *Inorg. Chem.* **1995**, *34*, 6330–6336.

Table 2. ID_{50} Values (ng/mL) for Complexes **1–8** in Vitro Using SRB as a Cell Viability Test[a]

complex	A498	EVSA-T	H226	IGROV	M19 MEL	MCF-7	WIDR
1	*1097*	983	8211	349	1681	2651	*401*
2	*1055*	1073	8089	302	1642	3519	*392*
3	*1115*	1745	23914	457	3392	6427	*355*
4	*1182*	3996	45691	348	6551	22983	*417*
5	**118**	5868	**146**	**5**	**207**	62500	**39**
6	**43**	2137	**59**	**<3.2**	**151**	4739	**17**
7	**963**	58474	**174**	**18**	2789	>62500	**68**
8	**635**	1382	**180**	**16**	1722	7133	**62**

[a] Human tumor cell lines used: A498 (renal cancer), EVSA-T (breast cancer), H226 (non-small-cell lung cancer), IGROV (ovarian cancer), M19 MEL (melanoma), MCF-7 (breast cancer), and WIDR (colon cancer).

Table 3. ID_{50} Values (ng/mL) of Some Established Cytotoxic Drugs: Doxorubicin (DOX), Cisplatin (CPT), 5-Fluorouracil (5-FU), Metotrexato (MTX), Etopoxide (ETO), and Taxol (TAX)

drug	A498	EVSA-T	H226	IGROV	M19 MEL	MCF-7	WIDR
DOX	90	8	199	60	16	10	11
CPT	**2253**	**422**	**3269**	**169**	**558**	**699**	**967**
5-FU	143	475	340	297	442	750	225
MTX	37	5	2287	7	23	18	<3.2
ETO	1314	317	3934	580	505	2594	150
TAX	3.2	<3.2	<3.2	<3.2	<3.2	<3.2	<3.2

and Au−S bond lengths of 2.2527(18) and 2.3085(18) Å, respectively, are in the same range as those found in gold−PTA complexes[42,66,68] and gold−thiolate complexes with PTA as a ligand.[67]

The ^{1}H NMR spectra of the gold−PTA complexes consisted of an AB system and a singlet resonance due to the NCH_2N and NCH_2P protons, respectively. The lack of P−H coupling for the NCH_2P protons was somewhat surprising but has been observed previously in various other gold−PTA complexes.[41,45] The assignments were confirmed unambiguously using $^1H\{^{31}P\}$ NMR spectroscopy as well as $^1H/^{13}C$ correlation experiments. In some of the complexes (**2**, **5**, and **6**), only one multiplet was observed for the PTA protons. The ^{1}H NMR spectra of the DAPTA proton resonances were much more complex than those for PTA because of the reduced symmetry of DAPTA. In some of the complexes, two separate signals for the acetate methyl groups were seen. A detailed discussion of the assignment of the DAPTA signals was recently reported by us.[45]

The LSIMS+ spectra for the gold complexes **1**−**4** showed molecular-ion peaks as well as higher *m*/*z* signals corresponding to $[M + AuPTA]^+$ or $[M + AuDAPTA]^+$ adducts of the complexes. Such behavior is frequently seen in mass spectra of gold(I)−phosphine complexes.[69,70] In contrast, the LSIMS+ spectra of the platinum derivatives **5**−**8** showed peaks corresponding only to fragments resulting from loss of either a thiolate ligand, a phosphine ligand, or both.

Both the gold and platinum complexes reported here are water-soluble, with solubilities up to 120 g/L for the gold derivatives **1**−**4** and less than 10 g/L for the platinum analogues **5**−**8**. The cytotoxicities of complexes **1**−**8** were evaluated in vitro against a panel of seven standard cell lines: A498 (renal cancer), EVSA-T (breast cancer), H226 (non-small-cell lung cancer), IGROV (ovarian cancer), M19 MEL (melanoma), MCF-7 (breast cancer), and WIDR (colon cancer). The results of this study are compiled in Table 2, and ID_{50} values for some standard antitumor drugs (with values for cisplatin in bold) are given in Table 3. It can be seen that the gold complexes showed low to moderate cytotoxicities across all of the cell lines tested. In the best cases, the gold complexes **1**−**4** displayed ID_{50} values (italic in Table 2) similar to or better than those for cisplatin for the A498 and WIDR cell lines, respectively. Our hope that the high water solubilities of the gold complexes might improve their cytotoxicities compared to those of the water-insoluble Et_3P or Ph_3P derivatives was not realized for this set of compounds. In contrast, the results for the platinum complexes were significantly better. For all but the EVSA-T and MCF-7 cell lines, the Pt complexes **5**−**8** showed significantly higher cytotoxicities than cisplatin (see the bold ID_{50} values in Table 2). For complex **6**, the ID_{50} values were roughly 130-fold less than those for cisplatin for the A498, H226, IGROV, and WIDR cell lines. Furthermore, for the IGROV and WIDR cell lines, all four of the platinum complexes also showed lower ID_{50} values (<3.2 to –70 ng/mL), i.e., higher cytotoxicities, than the established anticancer drugs doxorubicin, 5-fluorouracil, methotrexate, and etoposide. These values are comparable to those reported for *all-trans*-$[PtCl_2(OH)_2(amine)(NHMe_2)]$[71] and *trans*-$[PtCl_2(iPram)(Mepz)]$, *trans*-$[PtCl_2(iPram)(Meim)]$, and *trans*-$[PtCl_2(iPram)(HPz)]$ (iPram = isopropylamine; Mepz = 1-methylpyrazole; Meim = 1-methylimidazole; HPz = pyrazole).[72] The best IC_{50} values for the last of these compounds, *trans*-$[PtCl_2(IPram)(HPz)]$, were 160, 340, and 430 times higher than those for complex **6** for the A498 and H226, WIDR, and IGROV cell lines, respectively. In addition, complexes **5**−**8** showed higher in vitro cytotoxicities in the IGROV and WIDR cell lines than the trans

(68) Assefa, Z.; Staples, R. J.; Fackler, J. P., Jr. *Acta Crystallogr.* **1996**, *C52*, 305–307.
(69) Gimeno, M. C.; Jones, P. G.; Laguna, A.; Laguna, M.; Terroba, R. *Inorg. Chem.* **1994**, *33*, 3932–3938.
(70) Cerrada, E.; Jones, P. G.; Laguna, A.; Laguna, M. *Inorg. Chem.* **1996**, *35*, 2995–3000.
(71) Navarro-Ranninger, C.; González-Vadillo, A. M. ES 2214138.
(72) Pantoja, E.; Gallipoli, A.; van Zutphen, S.; Komeda, S.; Reddy, D.; Jaganyi, D.; Lutz, M.; Tooke, D. M.; Spek, A. L.; Navarro-Ranninger, C.; Reedijk, J. *J. Inorg. Biochem.* **2006**, *100*, 1955–1964.

platinum complexes described by Reedijk et al.[72] In the case of the trans Pt(IV) derivatives cited above, IC_{50} values ranging from 2.5 to 35 μM were observed. For comparison, complex **6** and cisplatin had ID_{50} values in the ranges <1 to 6.4944 μM and 0.56 to 0.89 μM, respectively, in the same cancer cell lines. Other trans platinum derivatives, such as [Pt(X)(Y)(Am1)(Am2)] (X and Y = halogen, carboxylate, phosphate, or sulfate; Am1 = primary or secondary amine, nonplanar heterocyclic aliphatic amine, or heterocyclic aromatic amine; Am2 = nonplanar heterocyclic aliphatic amine),[26] showed IC_{50} values in the ranges 0.4–7 and 0.9–14 μM for the human colon (C-26) and human ovarian (OV-1063) carcinoma cell lines, respectively.

The complexes presented here are the first examples of trans platinum(II) complexes with S- and P-donor ligands that demonstrate considerable biological activity. The ultimate goal is to use the new compounds in clinical anticancer therapy, and whenever an anticancer drug is to be used in the clinic, it must be soluble in water. The in vitro activities of these complexes against the IGROV ovarian cancer and WIDR colon cancer cell lines are promising and clearly warrant further systematic studies of this class of compounds, which are currently ongoing in our groups.

Acknowledgment. We thank the Spanish Ministry for Education and Science, Junta de Castilla y León, as well as the University of Burgos for generous financial support (Grants BQU2005-0899-CO3-01, BU033A06, and 112-541A-487.01).

Note Added after ASAP Publication. This paper was released ASAP on April 30, 2008, without one of the authors indicated as a corresponding author. The correct version was posted on June 7, 2008.

Supporting Information Available: Crystallographic data for complexes **2**, **5**, **6**, and **8** in CIF format and cytotoxic data for complexes **4**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

IC7021903