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trans-Thionate Derivatives of Pt(II) and Pd(II) with Water-Soluble Phosphane PTA and DAPTA Ligands: Antiproliferative Activity against Human Ovarian Cancer Cell Lines

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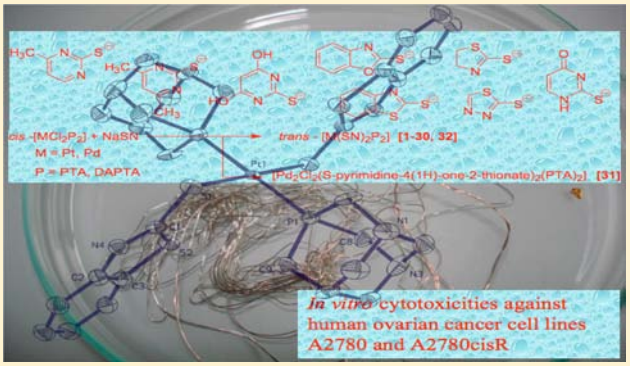
Supporting Information

ABSTRACT: A series of PTA and DAPTA platinum(II) and palladium(II) thionate complexes of the type *trans*-$[M(SN)_2P_2]$ were prepared from the reaction of *cis*-$[MCl_2P_2]$ [M = Pt, Pd; P = PTA (1,3,5-triaza-7-phosphaadamantane), DAPTA (3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane)] with the *in situ* generated sodium salts of the heterocyclic thiones *S*-*m*-methylpyrimidine-2-thione, *S*-4,6-dimethylpyrimidine-2-thione, *S*-4,6-dihydroxypyrimidine-2-thione, benzothiazole-2-thione, benzoxazole-2-thione, *S*-1,3,4,-thiadiazole-2-thione, *S*-4,5-*H*-thiazolan-2-thione, and *S*-pyrimidine-4(1*H*)-one-2-thione. The X-ray structures of six of the compounds confirm the *trans* disposition and, only in the case of $[Pd_2Cl_2(S\text{-pyrimidine-}4(1H)\text{-one-2-thionate})_2(PTA)_2]$, a dinuclear structure with a Pd−Pd distance of 3.0265(14)Å was observed. *In vitro* cytotoxicities against human ovarian cancer cell lines A2780 and A2780cisR were evaluated for ten complexes showing a high inhibition of cellular growth with a comparable inhibitory potency (IC_{50}) against A2780 cells to that of cisplatin. Notably, the compounds also show significant (up to 7-fold higher) activity in cisplatin-resistant A2780cisR cell lines.



INTRODUCTION

With the discovery of the anticancer activity of *cis*-diaminedichloroplatinum(II), cisplatin,[1,2] research of metallopharmaceuticals has increased dramatically. Cisplatin is still a widely used anticancer drug and is effective in treating a variety of cancers.[3] Cisplatin's cytotoxicity is caused by the formation of mainly 1,2-intrastrand d(GpG) DNA cross-links. The covalent cross-links cause a significant distortion of the helical structure and result in the inhibition of DNA replication and transcription.[4−6] The clinical success of cisplatin has proven to be limited because of significant side effects, poor solubility in water, and resistance that causes relapse.[3] Therefore, much effort has focused on developing new chemotherapeutic metal complexes with improved properties.[7−11] Second- and third-generation platinum-based anticancer drugs with significantly fewer side 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 further need for new and highly active cytotoxic platinum compounds. In a recent revision, Wang et al.[11] described three possible options for the design of new platinum drugs to avoid the systemic toxicity of and drug resistance to cisplatin. These options are the synthesis of complexes with different DNA-binding modes, exploiting prodrugs that can be activated only in tumor tissues, and improving drug accumulation at the tumor site by means of an accurate targeting and delivery strategy. The first category includes different types of derivatives, such as polynuclear platinum complexes, monofunctional platinum complexes, and *trans*-platinum complexes.[12] Some recent work has focused[13−15] 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 et al. showed that complexes with *trans* geometry were also cytotoxic.[16] Examples for such bioactive *trans*-platinum(II) complexes include *trans*-$[PtCl_2\{NH_2CH(CH_3)_2\}\{NH(CH_3)_2\}]$,[17] *trans*-$[PtCl_2(iminoether)_2]$,[18] and *trans*-$[PtCl_2(isopropylamine)(azole)_2]$[19] complexes or *trans*-$[Pt(O_2CR)_2(NH_3)(L)]$[20] with different proposals and studies

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about the chemistry and mechanisms around their biological activity.[21,22] In general, the low water solubility of *trans*-diaminedicholoroplatinum(II) and analogous complexes has limited their usefulness, and therefore, efforts have focused on modifying the nature of the anionic and neutral ligands.[23,24] Only recently have the biological activities of platinum complexes with other ligands such as phosphines and thiolates been investigated. Platinum(II) derivatives with aminodiphosphines,[25] as well as $[Pt(ts)(P)_2]$ (ts = thiosalicylate, P = PPh_3 or dppe) were reported to show significant biological activity.[26]

In parallel to the work on platinum complexes, the antitumor activity of other metal compounds also has been investigated. Some recent cytotoxicity studies of both gold(I) and gold(III) complexes have shown some promise.[27−34]

Recent work has also focused on medical applications of copper(I), silver(I), or gold(I) complexes containing diphosphines such as bis(diphenylphosphino)ethane and the study of the biological properties of ruthenium complexes containing water-soluble PTA.[35,36] While transition metals such as Ru, Rh, and Os bearing PTA or its derivatives have been extensively tested for their biological properties in the past few years with very promising results, metals of groups 11 and 12 have been studied to a much lesser extent.[37]

In addition, recent studies have been focused on the preparation of water-soluble gold, platinum, and palladium complexes[38−48] with satisfactory cytotoxicity results. Therefore, we have been interested in synthesizing new water-soluble thionate palladium(II) and platinum(II) derivatives with PTA (1,3,5-triaza-7-phosphaadamantane) and DAPTA (3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane). We have previously reported water-soluble gold(I) and platinum(II) complexes containing heterocyclic thionates [Au(SN)(P)] and *trans*-$[Pt(SN)_2(P)_2]$ [SN = C_5H_4NS (pyridine-2-thionate) or $C_4H_3N_2S$ (pyrimidine-2-thionate); P = PTA], which showed interesting *in vitro* antitumor properties in a series of tested cancer cell lines.[43] Some of the authors have also studied the biological activity of other platinum−PTA derivatives.[49,50]

Here we present the preparation and characterization of a series of slightly water-soluble mononuclear thionate Pd(II) and Pt(II) complexes of the type *trans*-$[M(SN)_2(P)_2]$, **1**−**30** and **32**, as evidenced by the X-ray structures of six of them. Only $[Pd_2Cl_2(S\text{-}2\text{-mercaptopyrimidin-4-one})_2(PTA)_2]$ (**31**) shows a dinuclear structure. The antiproliferative properties of some of these complexes have been tested, and they show *in vitro* activities (IC_{50}) against a human ovarian cancer cell line A2780 that are comparable to cisplatin, although they are much more efficient against A2780cisR (cisplatin-resistant cell line).

EXPERIMENTAL SECTION

Chemicals. *S*-*m*-Methylpyrimidine-2-thione ($C_5H_6N_2S$), *S*-4,6-dimethylpyrimidine-2-thione ($C_6H_8N_2S$), *S*-4,6-dihydroxypyrimidine-2-thione ($C_4H_4N_2SO_2$), benzothiazole-2-thione ($C_7H_5NS_2$), benzoxazole-2-thione (C_7H_5NSO), *S*-1,3,4,-thiadiazole-2-thione ($C_2H_2N_2S_2$), *S*-4,5-*H*-thiazolan-2-thione ($C_3H_5NS_2$) and *S*-pyrimidine-4(1*H*)-one-2-thione ($C_4H_4N_2SO$) were purchased from Sigma-Aldrich and used as received. PTA[51] and DAPTA[42,52] were prepared by published procedures. The *cis*-$[MCl_2(P)_2]$ complexes (M = Pt, Pd; P = PTA, DAPTA) were prepared by the reaction of $[MCl_2]$ with the appropriate phosphine in CH_2Cl_2. Ethanol was deoxygenated with a N_2 purge. All other reagents and solvents were obtained commercially and used as received. All manipulations were performed under a nitrogen atmosphere using a Schlenk line and syringe techniques.

General Methods. ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra were recorded using Varian INNOVA spectrometers at 400, 100.58, and 161.92 MHz, respectively. Chemical shifts (δ) are quoted in parts per million relative to the external TMS (^1H, ^{13}C) or 85% H_3PO_4 (^{31}P); coupling constants are reported in hertz. FAB mass spectra were measured on a VG Autospec spectrometer in positive ion mode using *m*-nitrobenzyl alcohol (NBA) as the matrix. IR spectra were recorded as Nujol mulls on a Perkin-Elmer Spectrum One instrument, a Nicolet Impact 410 FTIR (4000−400 cm^{-1}), and a JASCO FT-IR 6300 (630−150 cm^{-1}) spectrophotometer. Elemental analyses were obtained in-house using a Perkin-Elmer 240B and a LECO CHNS 932 microanalyzer.

Preparation of *trans*-$[M_2(SN)_2(P)_2]$ Complexes. An ethanolic solution of NaSN (0.500 mmol) prepared *in situ* from equimolar amounts of HNS (0.500 mmol) and NaOEt (35.5 mg, 0.500 mmol) was added to a suspension of *cis*-$[MCl_2(P)_2]$ (0.210 mmol) in absolute EtOH (20 mL). After the mixture was stirred at room temperature under a nitrogen atmosphere for 24 h, the solvent was partially removed to concentrate the suspension to ca. 5 mL. The solid was isolated by filtration, and the residue was washed with absolute ethanol and dried in air.

***S*-*m*-Methylpyrimidine-2-thionate = $C_5H_5N_2S$.** *trans-[Pt(S-m-methylpyrimidine-2-thionate)$_2$(PTA)$_2$] (**1**).* Pale yellow solid in 82% yield. ^1H NMR ($CDCl_3$, 25 °C): δ = 2.43 (s, 6H, CH_3), 4.21 (s, 12H, CH_2P), 4.37 (m, 12H, CH_2N), 6.73 (d, J = 5.4 Hz, 2H, Me-pyrimidin-H^5), 8.25 (d, J = 5.4 Hz, 2H, Me-pyrimidin-H^6), ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ = −62.23 (J_{Pt-P} = 2578.3 Hz) ppm. IR (Nujol) ν (cm^{-1}): 385 (Pt−S), 253 (Pt−P). FAB MS: m/z 477 [M − (SN) − PTA]$^+$, 634 [M−(SN)]$^+$. $C_{22}H_{34}N_{10}P_2PtS_2$ (759.7): C 34.78, H 5.51, N 18.44, S 8.44; found C 34.57, H 5.37, N 18.13, S 8.18. $S_{25°C}(H_2O)$: 0.2 g L^{-1}.

*trans-[Pt(S-m-methylpyrimidine-2-thionate)$_2$(DAPTA)$_2$] (**2**).* Colorless solid in 62% yield. ^1H NMR ($CDCl_3$, 25 °C): δ = 1.72 (s, 3H, *Me*-DAPTA), 1.93 (s, 3H, *Me*-DAPTA), 2.05 (s, 3H, *Me*-DAPTA), 2.08 (s, 3H, *Me*-DAPTA), 2.43 (s, 6H, *Me*-pyrimidin), 3.69−4,15 (m, 4H, NCH_2P, NCH_2N), 4.20−4.56 (m, 4H, NCH_2P, NCH_2N), 4.57 (m, 4H, NCH_2P), 4.87 (d, J = 14.3 Hz, 2H, NCH_2P), 4.91 (d, J = 14.0 Hz, 2H, NCH_2N), 5.67 (d, J = 15.6 Hz, 2H, NCH_2P), 5.74 (d, J = 14.0 Hz, 2H, NCH_2N), 6.78 (d, J = 4.7 Hz, 2H, *m*-methyl-pyrimidin-H^5), 8.35 (d, J = 4.7 Hz, 2H, *m*-methyl-pyrimidin-H^6) ppm. ^{31}P $\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ = −39.28 (s, J_{Pt-P} = 2684.0 Hz), −40.81 (s, J_{Pt-P} = 2684.3 Hz) ppm. IR (Nujol) ν (cm^{-1}): 1607 (C═O), 363 (Pt−S), 278 (Pt−P). FAB MS: m/z 549 [M − (SN) − DAPTA]$^+$, 778 [M − (SN)]$^+$. $C_{28}H_{42}N_{10}P_2PtS_2O_4$ (903.9): C 37.21, H 4.68, N 15.50, S 7.09; found C 37.57, H 4.87, N 15.13, S 7.18. $S_{25°C}(H_2O)$: 0.1 g L^{-1}.

*trans-[Pd(S-m-methylpyrimidine-2-thionate)$_2$(PTA)$_2$] (**3**).* Pale light yellow solid in 77% yield. ^1H NMR ($CDCl_3$, 25 °C): δ = 2.42 (s, 6H, CH_3), 4.22 (s, 12H, CH_2P), 4.43 (s, 12H, CH_2N), 6.71 (d, J = 5.1 Hz, 2H, MSpyrimidin-H^5), 8.17 (d, J = 5.1 Hz, 2H, Me-pyrimidin-H^6), ppm. ^{31}P $\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ = −55.99 ppm. IR (Nujol) ν (cm^{-1}): 387 (Pd−S), 255 (Pd−P). FAB MS: m/z 388 [M − (SN) − PTA]$^+$, 545 [M − (SN)]$^+$. $C_{22}H_{34}N_{10}P_2PdS_2$ (671.1): C 39.38, H 5.11, N 20.87, S 9.56; found C 39.23, H 5.17, N 21.03, S 9.88. $S_{25°C}(H_2O)$: 23.4 g L^{-1}.

*trans-[Pd(S-m-methylpyrimidine-2-thionate)$_2$(DAPTA)$_2$] (**4**).* Yellow solid in 95% yield. ^1H NMR ($CDCl_3$, 25 °C): δ = 1.89 (s, 6H, *Me*-DAPTA), 2.04 (s, 6H, *Me*-DAPTA), 2.43 (s, 6H, *Me*-pyrimidin), 3.69 (d, J = 7.0 Hz, 2H, NCH_2P) 3.73 (d, J = 16.8 Hz, 2H, NCH_2P), 3.92 (d, J = 14.0, 2H, NCH_2N), 4.00 (d, J = 14.8 Hz, 2H, NCH_2P), 4.22 (d, J = 14.8 Hz, 2H, NCH_2P), 4.55 (t, J = 14.3 Hz, 4H, NCH_2P, NCH_2N), 4.87 (d, J = 14.0 Hz, 2H, NCH_2N), 5.57 (d, J = 15.6 Hz, 2H, NCH_2P), 5.71 (d, J = 14.0 Hz, 2H, NCH_2N), 6.73 (d, J = 4.7 Hz, 2H, *m*-methyl-pyrimidin-H^5), 8.21 (d, J = 4.7 Hz, 2H, *m*-methyl-pyrimidin-H^6) ppm. ^{31}P $\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ = −36.23 ppm. IR (Nujol) ν (cm^{-1}): 364 (Pd−S), 281 (Pd−P). FAB MS: m/z 460 [M − (SN) − DAPTA]$^+$, 689 [M − (SN)]$^+$. $C_{28}H_{42}N_{10}P_2PdS_2O_4$ 815.2: C 41.26, H 5.19, N 17.18, S 7.87; found C 41.57, H 4.98, N 17.43, S 8.08. $S_{25°C}(H_2O)$: 12.6 g L^{-1}.

***S*-4,6-Dimethylpyrimidine-2-thionate = $C_6H_7N_2S$.** *trans-[Pt(S-4,6-dimethylpyrimidine-2-thionate)$_2$(PTA)$_2$] (**5**).* Pale yellow solid in 83% yield. ^1H NMR ($CDCl_3$, 25 °C): δ = 2.38 (s, 12H, CH_3), 4.21 (s, 12H, CH_2P), 4.36 (m, 12H, CH_2N), 6.58 (s, 2H, 4,6-dimethyl-

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pyrimidin-3-thionate-H^5), ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −62.62 (s, J_{Pt-P} = 2601.7 Hz) ppm. IR (Nujol) ν (cm^{-1}): 388 (Pt−S), 275 (Pt−P). FAB MS: m/z 491 [M − (SN) − PTA]$^+$, 648 [M − (SN)]$^+$. $C_{24}H_{38}N_{10}P_2PtS_2$ (787.8): C 36.59, H 4.86, N 17.78, S 8.14; found C 36.73, H 5,15, N 18.13, S 8.36. $S_{25°C}(H_2O)$: 0.8 g L^{-1}. Crystals suitable for X-ray diffraction were grown by slow diffusion of hexane into a $CHCl_3$ solution at room temperature.

trans-[Pt(S-4,6-dimethylpyrimidine-2-thionate)$_2$(DAPTA)$_2$] ***(6)***. Pale yellow solid in 80% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.72 (s, 3H, *Me*-DAPTA), δ = 1.78 (s, 3H, *Me*-DAPTA), δ = 1.98 (s, 3H, *Me*-DAPTA), 2.01 (s, 3H, *Me*-DAPTA), 2.43 (s, 12H, *Me*-(4,6-dimethylpyrimidin-2-thion), 3.69 (d, J = 14.0 Hz, 2H, NCH_2P), 3.79 (m, 2H, NCH_2P), 3.91 (m, 2H, NCH_2N), 4.10 (d, J = 16.0 Hz, 2H, NCH_2P), 4.23 (d, J = 14.4 Hz, 2H, NCH_2P), 4.31 (d, J = 16.0 Hz, 2H, NCH_2N), 4.61 (m, 2H, NCH_2P), 4.86 (m, 2H, NCH_2N), 5.59 (m, 2H, NCH_2P), 5.72 (m, 2H, NCH_2N), 6.64 (s, 2H, 4,6-dimethyl-pyrimidin-2-thionate-H^5) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −38.65 (s, J_{Pt-P} = 2760.73 Hz), −39.91(s, J_{Pt-P} = 2760.74 Hz) ppm. IR (Nujol) ν (cm^{-1}): 1642 (C═O), 358 (Pt−S), 282 (Pt−P). FAB MS: m/z 563 [M − (SN) − DAPTA]$^+$, 792 [M − (SN)]$^+$. $C_{30}H_{46}N_{10}P_2PtS_2O_4$ (931.9): C 38.67, H 4.98, N 15.03, S 6.88; found C 39.03, H 5.23, N 15.36, S 7.01. $S_{25°C}(H_2O)$: 0.7 g L^{-1}.

trans-[Pd(S-4,6-dimethylpyrimidine-2-thionate)$_2$(PTA)$_2$] ***(7)***. Orange solid in 92% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.16 (s, 6H, CH_3), 2.34 (s, 6H, CH_3), 4.22 (s, 12H, CH_2P), 4.40 (s, 12H, CH_2N), 6.55 (s, 2H, 4,6-dimethyl-pyrimidin-2-thionate-H^5) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −56.69 ppm. IR (Nujol) ν (cm^{-1}): 392 (Pd−S), 278 (Pd−P). FAB MS: m/z 402 [M − (SN) − PTA]$^+$, 559 [M − (SN)]$^+$. $C_{24}H_{38}N_{10}P_2PdS_2$ (699.1): C 41.23, H 5.48, N 20.03, S 9.17; found C 41.18, H 5.54, N 20.16, S 9.42. $S_{25°C}(H_2O)$: 0.5 g L^{-1}. Crystals suitable for X-ray diffraction were grown by slow diffusion of hexane into a $CHCl_3$ solution at room temperature.

trans-[Pd(S-4,6-dimethylpyrimidine-2-thionate)$_2$(DAPTA)$_2$] ***(8)***. Pale yellow solid in 75% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.84 (s, 6H, *Me*-DAPTA), 2.02 (s, 6H, *Me*-DAPTA), 2.39 (s, 12H, *Me*-(4,6-dimethylpyrimidin-2-thionate)), 3.69 (d, J = 14.0 Hz, 2H, NCH_2P), 3.77 (d, J = 15.6 Hz, 2H, NCH_2P), 3.88 (d, J = 14.0 Hz, 2H, NCH_2N), 4.09 (d, J = 14.4 Hz, 2H, NCH_2P), 4.27 (d, J = 16.0 Hz, 2H, NCH_2P), 4.48 (d, J = 16.0 Hz, 2H, NCH_2N), 4.56 (d, J = 14.0 Hz, 2H, NCH_2P), 4.84 (d, J = 13.6 Hz, 2H, NCH_2N), 5.48 (d, J = 16.0 Hz, 2H, NCH_2P), 5.69 (d, J = 14.0 Hz, 2H, NCH_2N), 6.62 (s, 2H, 4,6-Dimethyl-pyrimidin-3-thionate-H^5) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −35.86 ppm. IR (Nujol) ν (cm^{-1}): 355 (Pd−S), 279 (Pd−P). FAB MS: m/z 474 [M − (SN) − DAPTA]$^+$, 703 [M − (SN)]$^+$. $C_{30}H_{46}N_{10}P_2PdS_2O_4$ (843.2): C 42.73, H 5.50, N 16.61, S 7.61; found C 42.32, H 5.33, N 16.93, S 8.01. $S_{25°C}(H_2O)$: 0.8 g L^{-1}.

S-4,6-Dihydroxypyrimidine-2-thionate = $C_4H_3N_2SO_2$. *trans-[Pt(S-4,6-dihydroxypyrimidine-2-thionate)$_2$(PTA)$_2$]* ***(9)***. Pale yellow solid in 78% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 4.38 (m, 12H, NCH_2P), 4.50 (m, 12H, NCH_2N), 7.20 (s, 2H, 4,6-dihidroxipyrimidin-2-thion-H^5), 11.46 (s, br, 2H, CH^4-OH) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −42.69 ppm. IR (Nujol) ν (cm^{-1}): 361 (Pt−S); 285(Pt−P). FAB MS: m/z 495 [M − (SN) − PTA]$^+$, 653 [M − (SN)]$^+$. $C_{20}H_{30}N_{10}P_2PtS_2O_4$ (795.7): C 30.19; H 3.80; N 17.60; S 8.06. Found: C 30.41; H 4.06; N 17.68; S 8.67. $S_{25°C}(H_2O)$: < 0.1 g L^{-1}. Crystals suitable for X-ray diffraction were grown by slow diffusion of hexane into a CH_2Cl_2 solution at room temperature.

trans-[Pt(S-4,6-dihydroxypyrimidine-2-thionate)$_2$(DAPTA)$_2$] ***(10)***. Colorless solid in 75% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.94 (s, 12H, *Me*-DAPTA), 3.74 (d, J = 16.0 Hz, 2H, NCH_2P), 4.04 (d, J = 14.0 Hz, 2H, NCH_2P), 4.13 (m, 4H, NCH_2N), 4.31 (d, J = 14.0 Hz, 2H, NCH$_2$P), 4.54 (d, J = 13.0 Hz, 2H, NCH_2N), 4.84 (d, J = 15.0 Hz, 2H, NCH_2P), 4.97 (d, J = 13.2 Hz, 2H, NCH_2N), 5.53 (d, J = 14.0 Hz 2H, NCH_2P), 5.60 (d, J = 13.2 Hz, 2H, NCH_2N), 7.83 (s, 2H, 4,6-dihidroxipyrimidin-2-thion-H^5), 11.80 (s, br, 2H, CH^4-OH) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −36.17 ppm. IR (Nujol) ν (cm^{-1}): 1646 (C═O), 364 (Pt−S); 282 (Pt−P). FAB MS: m/z 568 [M − (SN) − PTA]$^+$, 797 [M − (SN)]$^+$. $C_{26}H_{38}N_{10}P_2PtS_2O_8$ (939.80): C 33.23; H 4.08; N 14.90; S 6.82. Found: C 33.51; H 3.86; N 15.18; S 6.87. $S_{25°C}(H_2O)$: ≪0.1 g L^{-1}.

trans-[Pd(S-4,6-dihydroxypyrimidine-2-thionate)$_2$(PTA)$_2$] ***(11)***. Yellow solid in 93% yield. ^{1}H NMR ([D_6] DMSO, 25 °C): δ = 3.40 (m, 12H, NCH_2P), 4.41 (m, 12H, NCH_2N), 7.07 (s, 2H, 4,6-dihidroxipyrimidin-2-thion-H^5), 11.46 (s, br, 2H, CH^4-OH) ppm. ^{31}P {^{1}H} NMR (400 MHz, [D_6] DMSO, 25 °C): δ = −42.69 ppm. IR (Nujol) ν (cm^{-1}): 391 (Pd−S); 284 (Pd−P). FAB MS: m/z 407 [M − (SN) − PTA]$^+$, 564 [M − (SN)]$^+$. $C_{20}H_{30}N_{10}P_2PdS_2O_4$ (706.0): C 33.98; H 4.28; N 19.81; S 9.07. Found: C 33.84; H 4.36; N 19.93; S 9.19. $S_{25°C}(H_2O)$: < 0.1 g L^{-1}.

trans-[Pd(S-4,6-dihydroxypyrimidine-2-thionate)$_2$(DAPTA)$_2$] ***(12)***. Yellow solid in 68% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.11 (s, 12H, *Me*-DAPTA), 3.69 (d, J = 14.5 Hz, 2H, NCH_2P), 3.89 (d, J = 16.0 Hz, 2H, NCH_2P), 3.99 (m, 4H, NCH$_2$N), 4.21 (d, J = 13.6 Hz, 2H, NCH_2P), 4.59 (d, J = 13.5 Hz, 2H, NCH_2N), 4.68 (d, J = 14.7 Hz, 2H, NCH_2P), 4.94 (d, J = 16.0 Hz, 2H, NCH_2N), 5.65 (d, J = 14.7 Hz 2H, NCH_2P), 5.79 (d, J = 14.4 Hz, 2H, NCH_2N), 6.98 (s, 2H, 4,6-dihidroxipyrimidin-2-thion-H^5), 12.00 (brs, 2H, CH^4-OH) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −34.11 ppm. IR (Nujol) ν (cm^{-1}): 1627 (C═O); 363 (PdS); 278 (PdP). FAB MS: m/z 479 [M − (SN) − PTA]$^+$, 708 [M − (SN)]$^+$. $C_{26}H_{38}N_{10}P_2PdS_2O_8$ (851.1): C 36.69; H 4.50; N 16.46; S 7.53. Found: C 36.41; H 4.53; N 16.24; S 7.27. $S_{25°C}(H_2O)$: < 0.1 g L^{-1}.

benzothiazole-2-thionate = $C_7H_4S_2N$. *trans-[Pt(benzothiazole-2-thionate)$_2$(PTA)$_2$]* ***(13)***. Light yellow solid in 92% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 4.26 (s, 12H, CH_2P), 4.34 (m, 12H, CH_2N), 7.24 (t, J = 7.6 Hz, 2H, benzothiazol-H^3), 7.37 (t, J = 7.8 Hz, 2H, benzothiazol-H^2), 7.66 (d, J = 7.6 Hz, 2H, benzothiazol-H^4), 7.77 (d, J = 7.9 Hz, 2H, benzothiazol-H^1) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −62.11 ppm (J_{Pt-P} = 2425 Hz). IR (Nujol) ν (cm^{-1}): 391 (Pt−S), 277 (Pt−P). FAB MS: m/z 518 [M − (SN) − PTA]$^+$, 675 [M − (SN)]$^+$. $C_{26}H_{32}N_8P_2PtS_4$ (841.9): C 37.09, H 3.83, N 13.31, S 15.23; found C 36.86, H 3.89, N 12.95, S 15.09. $S_{25°C}(H_2O)$: < 0.1 g L^{-1}. Crystals suitable for X-ray diffraction were grown by slow diffusion of hexane into a $CHCl_3$ solution at room temperature.

trans-[Pt(benzothiazole-2-thionate)$_2$(DAPTA)$_2$] ***(14)***. Light yellow solid in 71% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.97 (s, 6H, CH_3), 2.07 (s, 6H, CH_3), 3.76 (d, J = 15.8 Hz, 2H, NCH_2N), 3.86 (m, 4H, NCH_2P), 4.01 (d, J = 15.5 Hz, 2H, NCH_2P), 4.25 (d, J = 15.4 Hz, 2H, NCH_2N), 4.48 (d, J = 13.9 Hz, 2H, NCH_2N), 4.78 (m, 2H, NCH_2P), 4.86 (d, J = 14.5 Hz, 2H, NCH_2N), 5.69 (d, J = 13.7 Hz, 2H, NCH_2P), 5.82 (d, J = 15.5 Hz, 2H, NCH_2N), 7.28 (t, J = 7.5 Hz, 2H, CH_2Ar), 7.41 (t, J = 7.5 Hz, 2H, CH_2Ar), 7.69 (d, J = 7.8 Hz, 2H, CH_2Ar), 7.85 (dd, J = 7.4 Hz, J = 4.9 Hz 2H, CH_2Ar). ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −37.85 ppm (J_{Pt-P} = 2604 Hz); δ = −38.03 ppm (J_{Pt-P} = 2604 Hz). IR (Nujol) ν (cm^{-1}): 397 (Pt−S), 282 (Pt−P). FAB MS: m/z 590 [M − (SN) − DAPTA]$^+$, 819 [M − (SN)]$^+$. $C_{32}H_{40}N_8P_2PtS_4O_4$ (986.0): C 38.98, H 4.09, N 11.36, S 13.01; found C 39.0, H 4.0, N 11.67, S 13.20. $S_{25°C}(H_2O)$: < 0.1 g L^{-1}.

trans-[Pd(benzothiazole-2-thionate)$_2$(PTA)$_2$] ***(15)***. Yellow solid in 94% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 4.30 (s, 12H, CH_2P), 4.38 (s, 12H, CH_2N), 7.24 (t, J = 7.4 Hz, 2H, benzothiazol-H^3), 7.36 (t, J = 7.4 Hz, 2H, benzothiazol-H^2), 7.65 (d, J = 8.2 Hz, 2H, benzothiazol-H^4), 7.76 (d, J = 8.2 Hz, 2H, benzothiazol-H^1) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −54.92 ppm. IR (Nujol) ν (cm^{-1}): 391 (Pd−S), 277 (Pd−P). FAB MS: m/z 429 [M − (SN) − PTA]$^+$, 586 [M − (SN)]$^+$. $C_{26}H_{32}N_8P_2PdS_4$ (753.2): C 41.46, H 4.28, N 14.88, S 17.03; found C 41.29, H 4.52, N 14.94, S 17.56. $S_{25°C}(H_2O)$: < 0.1 g L^{-1}.

trans-[Pd(benzothiazole-2-thionate)$_2$(DAPTA)$_2$] ***(16)***. Yellow solid in 58% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.82 (s, 6H, *Me*-DAPTA), 2.04 (s, 6H, *Me*-DAPTA), 3.73 (d, J = 16.0 Hz, 2H, CH_2P), 3.84 (d, J = 14.4 Hz, 4H, CH_2P), 3.95 (d, J = 15.6, 2H, CH_2P), 4.22 (dd, J = 15.6, 2.3 Hz, 2H, CH$_2$N), 4.47 (d, J = 13.6 Hz, 2H, CH_2N), 4.75 (d, J = 15.2 Hz, 2H, CH_2N), 4.85 (d, J = 13.6 Hz, 2H, CH_2N), 5.68 (d, J = 14.0 Hz, 2H, CH_2N), 5.77 (d, J = 15.6 Hz, 2H, CH_2N), 7.23 (dt, J = 8.2, 1.2 Hz, 2H, benzothiazol-H^3), 7.36 (dt, J = 8.2, 1.2 Hz, 2H, benzothiazol-H^2), 7.64 (d, J = 7.4 Hz, 2H, benzothiazol-H^4), 7.79 (d, J = 7.8 Hz, 2H, benzothiazol-H^1) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −33.80 ppm. IR (Nujol) ν (cm^{-1}): 370 (Pd−S), 282 (Pd−P). FAB MS: m/z 501 [M − (SN) − DAPTA]$^+$, 730 [M − (SN)]$^+$.

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$C_{32}H_{40}N_8P_2PdS_4O_4$ (897.3): C 42.83, H 4.49, N 12.49, S 14.29; found C 42.66, H 4.73, N 12.60, S 14.90. $S_{25°C}(H_2O)$: < 0.1 g L^{-1}.

Benzoxazole-2-thionate = C_7H_4NSO. *trans-[Pt(benzoxazole-2-thionate)$_2$(PTA)$_2$] (**17**).* Pale yellow solid in 80% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 4.31 (s, 12H, CH_2P), 4.36 (m, 12H, CH_2N), 7.17 (m, 4H, benzoxazole-H^2, H^3), 7.39 (m, 2H, benzoxazole-H^1), 7.54 (m, 2H, benzoxazole-H^4) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −63.19 ppm (J_{Pt-P} = 2443 Hz). IR (Nujol) ν (cm^{-1}): 393 (Pt−S), 281 (Pt−P). FAB MS: m/z 502 [M − (SN) − PTA]$^+$, 659 [M − (SN)]$^+$. $C_{26}H_{32}N_8P_2PtS_2O_2$ (809.8): C 38.57, H 3.98, N 13.84, S 7.92; found C 39.19, H 4.07, N 13.61, S 8.20. $S_{25°C}(H_2O)$: < 0.1 g L^{-1}. Crystals suitable for X-ray diffraction were grown by slow diffusion of hexane into a $CHCl_3$ solution at room temperature.

*trans-[Pt(benzoxazole-2-thionate)$_2$(DAPTA)$_2$] (**18**).* Colorless solid in 63% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.97 (s, 6H, *Me*-DAPTA), 2.08 (s, 6H, *Me*-DAPTA), 3.71 (d, J = 14.8 Hz, 2H, NCH_2P), 3.90 (m, 4H, NCH_2P), 4.00 (m, 4H, NCH_2P), 4.25 (d, J = 14.4 Hz, 2H, NCH_2P), 4.55 (d, J = 12.5 Hz, 2H, NCH_2P), 4.81 (d, J = 12.9 Hz, 2H, NCH_2P), 4.91 (d, J = 12.1 Hz, 2H, NCH_2P), 5.75 (d, J = 11.3 Hz, 2H, NCH_2P), 7.21 (m, 2H, benzoxazole-H^3), 7.27 (m, 2H, benzoxazole-H^2), 7.40 (dd, J = 7.4, 5.5 Hz, 2H, benzoxazole-H^1), 7.73 (d, J = 7.4 Hz, 2H, benzoxatol-H^4) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −37.14 ppm (J_{Pt-P} = 2580 Hz). IR (Nujol) ν (cm^{-1}): 1645 (C═O), 363 (Pt−S), 278 (Pt−P). FAB MS: m/z 574 [M−(SN)]$^+$, 803 [M−(SN)]$^+$. $C_{32}H_{40}N_8P_2PtS_2O_6$ (953.9): C 40.29, H 4.23, N 11.75, S 6.72; found C 39.94, H 4.17, N 12.00, S 6.70. $S_{25°C}(H_2O)$: < 0.2 g L^{-1}.

*trans-[Pd(benzoxazole-2-thionate)$_2$(PTA)$_2$] (**19**).* Pale yellow solid in 84% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 4.31 (s, 12H, CH_2P), 4.40 (m, 12H, CH_2N), 7.17−7.25 (m, 4H, benzoxazole-H^2, H^3), 7.36 (d, J = 7.0 Hz, 2H, benzoxazole-H^1), 7.50 (d, J = 7.0 Hz, 2H, benzoxazole-H^4) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −53.18 ppm. IR (Nujol) ν (cm^{-1}): 393 (Pd−S), 280 (Pd−P). FAB MS: m/z 413 [M − (SN) − PTA]$^+$, 570 [M − (SN)]$^+$. $C_{26}H_{32}N_8P_2PdS_2O_2$ (721.1): C 43.31, H 4.47, N 15.54, S 8.89; found C 43.58, H 4.62, N 15.27, S 9.10. $S_{25°C}(H_2O)$: < 0.1 g L^{-1}. Crystals suitable for X-ray diffraction were grown by slow diffusion of hexane into a $CHCl_3$ solution at room temperature.

*trans-[Pd(benzoxazole-2-thionate)$_2$(DAPTA)$_2$] (**20**).* Yellow solid in 88% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.18 (s, 12H, DAPTA-*Me*), 3.73 (d, J = 15.6 Hz, 2H, NCH_2P), 3.93 (s, 4H, NCH_2P), 4.01 (d, J = 14.4 Hz, 2H, NCH_2P), 4.25 (d, J = 12.9 Hz, 2H, NCH_2P), 4.55 (d, J = 12.9 Hz, 2H, NCH_2P), 4.84 (dd, J = 16.8, 10.1 Hz, 2H, NCH_2P), 4.91 (d, J = 13.3 Hz, 2H, NCH_2P), 5.74 (d, J = 12.1 Hz, 4H, NCH_2P), 7.21−7.29 (m, 4H, benzoxazole-H^2, H^3), 7.40 (dd, J = 6.6, 5.5 Hz, 2H, benzoxazole-H^1), 7.54 (d, J = 7.4 Hz, 2H, benzoxatol-H^4) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −33.78 ppm. IR (Nujol) ν (cm^{-1}): 366 (Pd−S), 278 (Pd−P). FAB MS: m/z 485 [M − (SN) − DAPTA]$^+$, 714 [M−(SN)]$^+$. $C_{32}H_{40}N_8P_2PdS_2O_6$ (865.2): C 44.42, H 4.66, N 12.95, S 7.41; found C 44.21, H 4.42, N 12.70, S 7.60. $S_{25°C}(H_2O)$: < 0.1 g L^{-1}.

S-1,3,4,-Thiadiazole-2-thionate = $C_2HN_2S_2$. *trans-[Pt(S-1,3,4,-thiadiazole-2-thionate)$_2$(PTA)$_2$] (**21**).* Pale yellow solid in 89% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 4.20 (s, 12H, CH_2P), 4.40 (m, 12H, CH_2N), 8.90 (s, 2H, thiadiazol-H^5) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −62.17 (J_{Pt-P} = 2461.2 Hz) ppm. IR (Nujol) ν (cm^{-1}): 392 (Pt−S), 283 (Pt−P). FAB MS: m/z 469 [M−(SN) − PTA]$^+$, 626 [M − (SN)]$^+$. $C_{16}H_{26}N_{10}P_2PtS_4$ (743.7): C 25.84, H 3.52, N 18.83, S 17.24; found C 25.82, H 3.40, N 18.47, S 17.63. $S_{25°C}(H_2O)$: < 0.2 g L^{-1}.

*trans-[Pt(S-1,3,4,-thiadiazole-2-thionate)$_2$(DAPTA)$_2$] (**22**).* Colorless solid in 81% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.01 (s, 6H, *Me*-DAPTA), 2.04 (s, 6H, *Me*-DAPTA), 3.59 (d, J = 16.0 Hz, 2H, NCH_2P), 3.72 (d, J = 15.6 Hz, 2H, NCH_2P), 3.91 (m, 4H, NCH_2N, NCH_2P), 4.22 (d, J = 12.9 Hz, 2H, NCH_2P), 4.46 (d, J = 14.0 Hz, 2H, NCH_2N), 4.51 (d, J = 13.6 Hz, 2H, NCH_2P), 4.86 (dd, J = 14.0 Hz, J = 16.0 Hz, 2H, NCH_2N), 5.57 (d, J = 15.6 Hz, 2H, NCH_2P), 5.71 (d, J = 13.6 Hz, 2H, NCH_2N), 8.88 (s, 2H, thiadiazol-H^5) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −37.72 ppm (J_{Pt-P} = 2624.7 Hz). IR (Nujol) ν (cm^{-1}): 1621 (C═O), 362 (Pt−S), 281 (Pt−P). FAB MS: m/z 541 [M−(SN) − DAPTA]$^+$, 770 [M − (SN)]$^+$. $C_{22}H_{34}N_{10}P_2PtS_4O_4$ (887.9): C 29.76, H 3.86, N 15.78, S 14.45; found C 29.96, H 3.89, N 16.03, S 14.75. $S_{25°C}(H_2O)$: 0.1 g L^{-1}.

*trans-[Pd(S-1,3,4,-thiadiazole-2-thionate)$_2$(PTA)$_2$] (**23**).* Pale yellow solid in 95% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 4.19 (d, J = 24.2 Hz, 12H, CH_2P), 4.40 (d, J = 16.8 Hz, 12H, CH_2N), 8.78 (s, 2H, thiadiazol-H^5) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −54.17 ppm. IR (Nujol) ν (cm^{-1}): 396 (Pd−S), 280 (Pd−P). FAB MS: m/z 380 [M−(SN) − PTA]$^+$, 537 [M − (SN)]$^+$. $C_{16}H_{26}N_{10}P_2PdS_4$ (655.0): C 29.34, H 4.00, N 21.38, S 19.58; found C 29.29, H 4.05, N 21.17, S 19.83. $S_{25°C}(H_2O)$: < 0.1 g L^{-1}.

*trans-[Pd(S-1,3,4,-thiadiazole-2-thionate)$_2$(DAPTA)$_2$] (**24**).* Yellow solid in 87% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.99 (s, 6H, *Me*-DAPTA), 2.03 (s, 6H, *Me*-DAPTA), 3.56 (m, 2H, NCH_2P), 3.73 (d, J = 15.6 Hz, 2H, NCH_2P), 3.84 (d, J = 15.6 Hz, 2H, NCH_2N), 3.90 (d, J = 14.0 Hz, 2H, NCH_2P), 4.19 (d, J = 16.0 Hz, 2H, NCH_2P), 4.44 (d, J = 14.0 Hz, 2H, NCH_2N), 4.75 (d, J = 15.6 Hz, 2H, NCH_2P), 4.85 (d, J = 13.6 Hz, 2H, NCH_2N), 5.52 (d, J = 15.6 Hz, 2H, NCH_2P), 5.68 (d, J = 14.0 Hz, 2H, NCH_2N), 8.82 (s, 2H, thiadiazol-H^5) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −33.24 ppm. IR (Nujol) ν (cm^{-1}): 363 (Pd−S), 278 (Pd−P). FAB MS: m/z 452 [M − (SN) − DAPTA]$^+$, 681 [M − (SN)]$^+$. $C_{22}H_{34}N_{10}P_2PdS_4O_4$ (799.2): C 33.06, H 4.29, N 17.53, S 16.05; found C 33.17, H 4.59, N 17.80, S 16.32. $S_{25°C}(H_2O)$: 0.4 g L^{-1}.

S-4,5-H-Thiazolan-2-thionate = $C_3H_4S_2N$. *trans-[Pt(S-4,5-H-thiazolan-2-thionate)$_2$(PTA)$_2$] (**25**).* Colorless solid in 80% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 3.38 (t, J = 7.9 Hz, 4H, CH_2^5), 4.23 (t, J = 7.9 Hz, 4H, CH_2^4), 4.31 (s, 12H, CH_2P), 4.45 (m, 12H, CH_2N) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −62.33 ppm. (J_{Pt-P} = 2486.5 Hz). IR (Nujol) ν (cm^{-1}): 389 (Pt−S), 279 (Pt−P). FAB MS: m/z 470 [[M − (SN) − PTA]$^+$, 627 [M − (SN)]$^+$. $C_{18}H_{32}N_8P_2PtS_4$ (745.8): C 28.99, H 4.32, N 15.02, S 17.20; found C 28.63, H 4.13, N 15.37, S 17.73. $S_{25°C}(H_2O)$: 0.5 g L^{-1}.

*trans-[Pt(S-4,5-H-thiazolan-2-thionate)$_2$(DAPTA)$_2$] (**26**).* Colorless solid in 83% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.01 (s, 12H, *Me*-DAPTA), 3.45 (t, J = 7.8 Hz/8.2 Hz, 4H, thiazolan-CH_2^5), 3.66 (d, J = 16.0 Hz, 2H, NCH_2P), 3.90 (d, J = 15.6 Hz, 2H, NCH_2P), 4.00 (d, J = 14.4, 4H, NCH_2N, NCH_2P), 4.23 (d, J = 16.4 Hz, 2H, NCH_2P), 4.28 (t, J = 7.8 Hz/8.2 Hz, 4H, thiazolan-CH_2^4), 4.56 (d, J = 14.0 Hz, 2H, NCH_2N), 4.80 (d, J = 16.4 Hz, 2H, NCH_2P), 4.93 (d, J = 14.0 Hz, 2H, NCH_2N), 5.68 (d, J = 16,0 Hz, 2H, NCH_2P), 5.77 (d, J = 14.0 Hz, 2H, NCH_2N) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −39.72 ppm (J_{Pt-P} = 2682.8 Hz). IR (Nujol) ν (cm^{-1}): 1607 (C═O), 363 (Pt−S), 278 (Pt−P). FAB MS: m/z 542 [M − (SN) − DAPTA]$^+$, 771 [M−(SN)]$^+$. $C_{24}H_{40}N_8O_4P_2PtS_4$ (889.9): C 32.39, H 4.53 N 12.59, S 14.41; found C 32.04, H 4.18, N 12.37, S 14.09. $S_{25°C}(H_2O)$: 0.1 g L^{-1}.

*trans-[Pd(S-4,5-H-thiazolan-2-thionate)$_2$(PTA)$_2$] (**27**).* Pale yellow solid in 85% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 3.38 (t, J = 7.8 Hz, 4H, CH_2^5), 4.15 (t, J = 7.8 Hz, 4H, CH_2^4), 4.30 (s, 12H, CH_2P), 4.47 (s, 12H, CH_2N) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −54.16 (s); −55.79 (s,) ppm. IR (Nujol) ν (cm^{-1}): 393 (Pd−S), 281 (Pd−P). FAB MS: m/z 381 [M − (SN) − PTA]$^+$, 538 [M−(SN)]$^+$. $C_{18}H_{32}N_8P_2PdS_4$ (657.1): C 32.90, H 4.91, N 17.05, S 19.52; found C 32.54, H 4.48, N 16.17, S 19.19. $S_{25°C}(H_2O)$: 0.2 g L^{-1}.

*trans-[Pd(S-4,5-H-thiazolan-2-thionate)$_2$(DAPTA)$_2$] (**28**).* Pale yellow solid in 73% yield. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.08 (s, 12H, *Me*-DAPTA), 3.43 (t, J = 7.8 Hz, 4H, thiazolan-CH_2^5), 3.63 (d, J = 14.8 Hz, 2H, NCH_2P), 3.85 (d, J = 15.2 Hz, 2H, NCH_2P), 3.97 (d, J = 14.0, 4H, NCH_2N, NCH_2P), 4.20 (d, J = 15.6 Hz, 2H, NCH_2P), 4.22 (t, J = 7.8 Hz, 4H, thiazolan-CH_2^4), 4.56 (d, J = 14.0 Hz, 2H, NCH_2N), 4.74 (d, J = 15.6 Hz, 2H, NCH_2P), 4.91 (d, J = 14.0 Hz, 2H, NCH_2N), 5.59 (d, J = 15.6 Hz, 2H, NCH_2P), 5.75 (d, J = 14.0 Hz, 2H, NCH_2N) ppm. ^{31}P {^{1}H} NMR ($CDCl_3$, 25 °C): δ = −35.35 ppm. IR (Nujol) ν (cm^{-1}): 367 (Pd−S), 254 (Pd−P). FAB MS: m/z 453 [M − (SN) − DAPTA]$^+$, 682 [M − (SN)]$^+$. $C_{24}H_{40}N_8O_4P_2PdS_4$ (801.2): C 35.98, H 5.03, N 13.98, S 16.00; found C 36.04, H 5.18, N 14.37, S 16.20. $S_{25°C}(H_2O)$: 0.1 g L^{-1}.

S-Pyrimidine-4(1*H*)-one-2-thionate = $C_4H_3N_2SO$. *trans-[Pt(S-pyrimidine-4(1H)-one-2-thionate)$_2$(PTA)$_2$] (**29**).* Pale brown solid in 77% yield. ^{1}H NMR ([D_6] DMSO, 25 °C): δ = 4.39 (m, 12H, PTA), δ = 4.51 (m, 12H, PTA), 5.80 (d, J = 7.0 Hz, 2H, mercaptopyrimidinon-

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Table 1. Summary of Crystallographic Data for Complexes 5, 7, 9, 13, 17, 19, and 31

	5·CH_2Cl_2	**7**·$CHCl_3$	**9**·CH_2Cl_2	**13**·$CHCl_3$	**17**·$CHCl_3$	**19**	**31**·$CHCl_3$
formula	$C_{13}H_{21}Cl_2N_5PPt_{0.5}S$	$C_{13}H_{20}Cl_3N_5PPd_{0.5}S$	$C_{11}H_{17}Cl_2N_5O_2PPt_{0.5}S$	$C_{28}H_{34}Cl_6N_8P_2PtS_4$	$C_{14}H_{17}Cl_3N_4OPPt_{0.50}S$	$C_{13}H_{16}N_4OPPd_{0.5}S$	$C_{11}H_{16}Cl_4N_5OPPdS$
fw	478.82	468.92	482.77	1080.60	524.24	360.53	545.52
cryst syst	monoclinic	monoclinic	monoclinic	triclinic	monoclinic	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$C2/c$
a, Å	11.660(2)	12.0822(11)	11.6525(17)	6.3660(15)	15.3834(16)	15.3325(13) Å	20.372(7)
b, Å	22.327(4)	12.7210(12)	22.312(3)	10.743(3)	9.5940(10)	9.6087(8)	8.508(3)
c, Å	7.1416(12)	12.1166(11)	7.1349(10)	14.321(3)	13.0386(13)	12.9920(11)	23.688(8)
α, deg				99.225(4)			
β, deg	104.545(3)	96.9660(10)	104.499(2)	93.093(4)	93.082(2)	93.6380(10)	110.475(5)
γ, deg				98.438(4)			
V, Å^3	1799.7(5)	1848.5(3)	1795.9(4)	953.2(4)	1921.6(3)	1910.2(3)	3846(2)
Z	4	4	4	1	4	4	8
D_c (Mg/m^3)	1.767	1.685	1.786	1.882	1.812	1.254	1.884
μ, mm^{-1}	4.436	1.172	4.454	4.439	4.300	0.710	1.722
θ range, deg	2.02 to 27.99	2.33 to 28.06°	2.02 to 25.00°	2.22 to 27	2.5 to 26.00	2.50 to 27.00	2.13 to 26.99
no. data collect.	20297	20501	17467	10701	19608	21029	17933
no. unique data	4092 [R_{int} = 0.1309]	4230 [R_{int} = 0.1396]	3156 [R_{int} = 0.1609]	4058 [R_{int} = 0.1248]	3752 [R_{int} = 0.2328]	4158 [R_{int} = 0.1735]	4112 [R_{int} = 0.1183]
$R1$[a], $wR2$[b] [$I > 2\sigma(I)$]	0.0411, 0.1283	0.0413, 0.1116	0.0425, 0.0999	0.0542, 0.1248	0.0733, 0.1761	0.0793, 0.1745	0.0737, 0.1713
max,min $\Delta\rho$, e Å^{-3}	2.687, −3.165	0.591,-0.980	2.669, −1.681	2.101, −2.438	2.954, −2.036	0.932, −2.398	1.064, −1.680

[a] $R1 = \sum||F_o| - \sum|F_c|/|F_o|$. [b] $wR2 = \{\sum[w(F_o^2 - F_c^2)]/\sum[w(F_o^2)^2]\}^{1/2}$.

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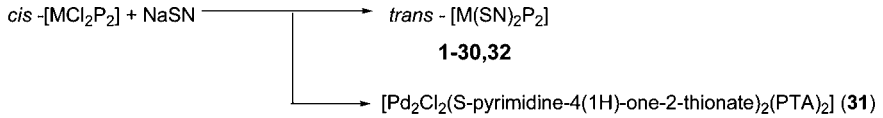
Scheme 1. Preparation of the Thionate Palladium and Platinum Derivatives[a]



M	P	S-*m*-Methyl pyrimidine-2-thionate $C_5H_5N_2S^-$	S-4,6-Dimethyl pyrimidine-2-thionate $C_6H_7N_2S^-$	S-4,6-dihydroxy pyrimidine-2-thionate $C_4H_3N_2O_2S^-$	Benzothiazole -2-thionate $C_7H_4NS_2^-$	Benzoxazole -2-thionate $C_7H_4NOS^-$	S-1,3,4,-thiadiazole-2-thionate $C_2HN_2S_2^-$	S-4,5 *H*-thiazolan-2-thionate $C_3H_4NS_2^-$	S-pyrimidine-4(1H)-one-2-thionate $C_4H_3N_2OS^-$
Pt	PTA	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**
Pt	DAPTA	**2**	**6**	**10**	**14**	**18**	**22**	**26**	**30**
Pd	PTA	**3**	**7**	**11**	**15**	**19**	**23**	**27**	**31**
Pd	DAPTA	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**

[a]PTA, 1,3,5-triaza-7-phosphaadamantane; DAPTA, 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane.

H^5), 7.51 (d, *J* = 7.0 Hz, 2H, mercaptopyrimidinon-*H*^{6}), 12.5 (s, 2H, N*H*) ppm. ^{31}P {^{1}H} NMR ([D$_6$] DMSO, 25 °C): δ = −30.4 ppm (s, J_{Pt-P} = 2510.2) Hz. IR (Nujol) ν (cm^{-1}): 1637 (C═O), 361 (Pt−S), 282 (Pt−P). MS: *m*/*z* 479 [M − (SN) − PTA]$^+$, 636 [M − (SN)]$^+$. $C_{20}H_{30}N_{10}P_2PtS_2O_2$ (763.7): C 31.46, H 3.96, N 18.34, S 8.40; found C 31.20, H 4.10, N 18.56, S 8.63. $S_{25°C}$(H$_2$O): < 0.1 g L^{-1}.

trans-[Pt(S-pyrimidine-4(1H)-one-2-thionate)$_2$(DAPTA)$_2$] (**30**). Pale brown solid in 71% yield. ^{1}H NMR (CDCl$_3$, 25 °C): δ = 2.01 (s, 6H, Me-DAPTA), 2.02 (s, 6H, Me-DAPTA), 3.71 (d, *J* = 14.4 Hz, 2H, NC*H*$_2$P), 3.77 (d, *J* = 15.6 Hz, 2H, NC*H*$_2$P), 3.88 (d, *J* = 14.0 Hz, 2H, NC*H*$_2$N), 4.05 (m, 4H, NC*H*$_2$P, NC*H*$_2$N), 4.37 (d, *J* = 11.2 Hz, 2H, NC*H*$_2$N), 4.59 (d, *J* = 14.4 Hz, 2H, NC*H*$_2$P), 4.99 (d, *J* = 13.6 Hz, 2H, NC*H*$_2$N), 5.66 (d, *J* = 16.0 Hz, 2H, NC*H*$_2$P), 5.75 (m, 2H, NC*H*$_2$N) ppm, 5.82 (d, *J* = 7,2 Hz, 2H, mercaptopyrimidinon-*H*^{5}), 7.43 (d, *J* = 7,2 Hz, 2H, mercaptopyrimidinon-*H*^{6}). ^{31}P {^{1}H} NMR (CDCl$_3$, 25 °C): δ = −30.48 (s, J_{Pt-P} = 2627.0 Hz), −30.56 (s, J_{Pt-P} = 2627.8 Hz) ppm. IR (Nujol) ν (cm^{-1}): 1619 (C═O), 364 (Pt−S), 282 (Pt−P). FAB MS: *m*/*z* 551 [M − (SN) − DAPTA]$^+$, 780 [M − (SN)]$^+$. $C_{26}H_{38}N_{10}P_2PtS_2O_6$ (907.8): C 34.40, H 4.22, N 15.43, S 7.06; found C 34.10, H 4.21, N 15.20, S 7.31. $S_{25°C}$(H$_2$O): < 0.1 g L^{-1}.

[Pd$_2$Cl$_2$(S-pyrimidine-4(1H)-one-2-thionate)$_2$] (**31**). It was prepared as described for complexes **1**−**30**. Yellow solid in 85% yield. ^{1}H NMR ([D$_6$] DMSO, 25 °C): δ = 4.37 (m, 24H, PTA), 5.80 (d, *J* = 7.0 Hz, 2H, mercaptopyrimidinon-*H*^{5}), 7.38 (d, *J* = 7.0 Hz, 2H, mercaptopyrimidinon-*H*^{6}), 12.3 (s, 2H, NH) ppm. ^{31}P {^{1}H} NMR (DMSO, 25 °C): δ = −23.4 ppm. IR (Nujol) ν (cm^{-1}): 477 (Pd−N), 390 (Pd−S), 278 (Pd−P), 328 (Pd−Cl). FAB MS: *m*/*z* 390 [Pd(SN)PTA]$^+$, 660 [M − Cl − PTA]$^+$, 817 [M − Cl]$^+$. Anal. Calcd for $C_{20}H_{30}Cl_2N_{10}P_2Pd_2S_2O_2$ (852.3): C 28.18; H 3.55; N, 16.43; S 7.52. Found: C 28.41; H 3.66; N 16.12; S 7.37. $S_{25°C}$(H$_2$O): 0.2 g L^{-1}. Crystals suitable for X-ray diffraction were grown by slow diffusion of hexane into a CHCl$_3$ solution at room temperature.

trans-[Pd(S-pyrimidine-4(1H)-one-2-thionate)$_2$(DAPTA)$_2$] (**32**). Yellow solid in 90% yield. ^{1}H NMR (CDCl3, 25 °C): δ = 2.01 (s, 6H, *Me*-DAPTA), 2.02 (s, 6H, *Me*-DAPTA), 3.68 (d, *J* = 14.4 Hz, 2H, NC*H*$_2$P), 3.73 (d, *J* = 15.6 Hz, 2H, NC*H*$_2$P), 4.05 (m, 4H, NC*H*$_2$P), 4.09 (d, *J* = 16.0 Hz, 2H, NC*H*$_2$P), 4.26 (d, *J* = 11.2 Hz, 2H, NC*H*$_2$N), 4.30 (d, *J* = 14.4 Hz, 2H, NC*H*$_2$P), 4.57 (d, *J* = 13.6 Hz, 4H, NC*H*$_2$N), 4.61 5.66 (d, *J* = 16.0 Hz, 2H, NC*H*$_2$P), 5.75 (m, 2H, NC*H*$_2$N) ppm 5.80 (d, *J* = 7.0 Hz, 2H, mercaptopyrimidinon-*H*^{5}), 7.38 (d, J = 7.0 Hz, 2H, mercaptopyrimidinon-*H*^{6}). ^{31}P {^{1}H} NMR (CDCl$_3$, 25 °C): δ = −32.21 (s), −32.5 (s) ppm. IR (Nujol) ν (cm^{-1}): 359 (Pd−S), 277 (Pd−P). FAB MS: *m*/*z* 462 [M − (SN) − DAPTA]$^+$, 691 [M − (SN)]$^+$ $C_{26}H_{38}N_{10}P_2PdS_2O_6$ (819.1): C 38.12, H 4.68, N 17.10, S 7.83. Found: C 38.05, H 4.80, N 16.83, S 8.05. $S_{25°C}$(H$_2$O): < 0.1 g L^{-1}.

Crystallographic Studies for 5, 7, 9, 13, 17, 19, and 31. Crystals suitable for X-ray diffraction were obtained by slow diffusion of hexane into chloroform (**5**, **7**, **13**, **17**, **19**, and **31**) or dichloromethane (**9**) solutions. The crystals were mounted on a glass fiber with inert oil and centered in a Bruker-Smart CCD diffractometer with graphite-monochromated Mo Kα (λ = 0.7107 Å) radiation for data collection. The diffraction frames were integrated by using the SAINT[53] package and corrected for absorption with SADABS.[54] The structures were solved by direct methods using SHELXS.[55] Full-matrix least-squares refinement was performed using SHELXL[56] minimizing $\omega(F_o^{2*} - F_c^2)^2$. Hydrogen atoms were included by using a riding model. Weighted *R* factors (R_w) and all goodness of fit *S* values are based on F^2; conventional *R* factors (*R*) are based on *F*. Eighteen restraints were applied in the case of **17** to refine the disordered chloroform. Weighted *R* factors (R_w) and all goodness-of-fit *S* values are based on F^2; conventional *R* factors (*R*) are based on *F*. The PLATON SQUEEZE algorithm was applied to **19** to model the diffuse contribution from a highly disordered solvent of crystallization to the electron density.[57,58] A summary of crystal and refinement data of the compounds is given in Table 1. For crystallographic data in CIF or another electronic format, see Supporting Information. The complete crystallographic data also have been deposited with the Cambridge Crystallographic Data Centre [deposition numbers are CCDC 928087−928093 for compounds **5**, **7**, **9**, **13**, **17**, **19**, and **31**, respectively]. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre or via www.ccdc.cam.ac.uk/data_request/cif.

Cytotoxicity Studies. The *in vitro* cytotoxicity experiments were performed at the Drugs Screening Platform Unit (USEF), Network Infrastructure Support for Research and Technological Development (RIAIDT), at the University of Santiago de Compostela (Spain). The human cancer ovarian cell lines, A2780 (cisplatin-sensitive) and A2780cisR (cisplatin-resistant), were grown in RPMI 1640 medium containing 10% fetal bovine serum (FBS) and 2 mM L-glutamine, under an atmosphere of 5% CO_2 at 37 °C. DMSO solutions of each

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complex were added to get a final constant proportion of DMSO (1%). For the cytotoxicity evaluation, 4000 cells per well were seeded in 100 μL of complete medium in 96-multiwell flat-bottom microtiter plates (Corning Costar). The plates were incubated at 37 °C in 5% CO_2 for 96 h prior to drug testing to allow cell adhesion. Then, 10 μL of a solution of 3-(4,5-dimethyl-2-thiazoyl)-2,5-diphenyltetrazolium bromide (MTT, 5 mg/mL in PBS, 0.136 M NaCl, 1.47 mM KH_2PO_4, 8 mM NaH_2PO_4, and 2.68 mM KCl) was added, and incubation was continued for 4 h. Next, 100 μL of SDS (10% in HCl 0.01 M) was added, and the plates were incubated for 12−14 h. Then, the cell culture supernatants were removed, the cell layer was dissolved in DMSO, and the absorbance at 595 nm was measured in a 96-well multiwell-plate reader (Tecan Ultra Evolution) and compared with the values of control cells incubated in the absence of complexes. Experiments were conducted in quadruplicate wells and repeated at least three times.

The measurement range of absorbance was evaluated between 1 point (triplicate) containing 4000 cells in RPMI 1640 in the absence of growth factors (stable cell concentration) and another point (triplicate) containing the usual growth medium (to measure the maximum growth at 96 h).

The % inhibition of cellular growth was calculated based on the following formula: % inhibition = $100 - \{(T \times 100)/C\}$ (T, observed absorption of the treated cells; C, observed absorption in control wells). The inhibitory potency was evaluated by using the concentration vs % inhibition of cellular growth curves. These curves were adjusted to the equation $E = E_{max}/\{1 + (IC_{50}/C)^n\}$ (E = percentage inhibition observed at C, n = slope of the semilogarithmic dose−response sigmoid curves, E_{max} = maximal effect, C = concentration of tested compounds). The nonlinear fitting was performed using GraphPad Prism 2.01, 1996 software. The cytotoxicity of cisplatin was also evaluated under the same experimental conditions for comparison.

All of the tested compounds showed a concentration-dependent inhibition of cell growth. The parameters used for evaluating compounds were inhibitory potency (the inverse of the IC_{50}) and efficiency (expressed as % maximum inhibition achieved by the compounds). Other values for cisplatin against A2780 and A2780cisR were as follows: 0.16 μM and 6.1 μM;[59] 1.2 μM and 10 μM,[60] or 2.3 μM and 7.8 μM.[61]

The tested compounds **6**, **9**, **13**, **14**, **15**, **19**, **21**, **22**, **25**, and **26** showed as high % cell growth inhibition (>50%) as was possible for curves of cell growth inhibition (see Tables 2 and 3).

RESULTS AND DISCUSSION

Synthesis and Spectroscopic Characterization of Complexes. The reaction of *cis*-$[MCl_2(P)_2]$ (M = Pt, Pd; P = PTA (1,3,5-triaza-7-phosphaadamantane) and DAPTA (3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane) with an ethanolic solution of NaSN in 1:2 molar ratio, prepared in situ from equimolar amounts of NaOEt and the eight HSN ligands shown in Scheme 1, afforded mononuclear derivatives of the type *trans*-$[M(SN)_2(P)_2]$ (**1**−**30** and **32**) and only one dinuclear $[Pd_2Cl_2(S\text{-pyrimidine-4(1}H\text{)-one-2-thionate})_2(PTA)_2]$ (**31**) derivative in good yields. These ligands have been selected because they show good antiproliferative properties when coordinated to gold(I) complexes.[43,48,62]

In all cases, the ^{1}H NMR spectra showed two sets of signals, one of them due to the protons of the thionate ligands and the other one due to the aliphatic protons of the coordinated phosphine ligand. The ^{1}H NMR spectra of PTA derivatives, except complex **31**, consisted of an AB system and a further signal, either singlet or multiplet resonance due to NCH_2N and NCH_2P protons, respectively. The $^1H\{^{31}P\}$ NMR spectroscopy could not resolve the $^{31}P-^1H$ coupling for the NCH_2P protons when multiplets were observed. In contrast, the lack of this $^{31}P-^1H$ coupling for the NCH_2P protons occurs also in other metal complexes containing PTA.[38,42,43] The assignments were further confirmed by using 2D NMR experiments. The ^{1}H NMR spectra of DAPTA complexes showed a complicated set of signals because of the ten different protons in NCH_2N and NCH_2P groups with some $^{31}P-^1H$ coupling being observed (see Experimental Section for details). A full discussion of the assignment of DAPTA signals was reported by us previously.[42] All the DAPTA complexes show only one resonance for the methyl protons with the exception of *trans*-[Pt(*S*-*m*-methylpyrimidine-2-thionate)$_2$(DAPTA)$_2$] (**2**), *trans*-[Pt(*S*-4,6-dimethylpyrimidine-2-thionate)$_2$(DAPTA)$_2$] (**6**), *trans*-[Pd(benzothiazole-2-thionate)$_2$(DAPTA)$_2$] (**16**), *trans*-[Pt(*S*-pyrimidine-4(1*H*)-one-2-thionate)$_2$(DAPTA)$_2$] (**30**), *trans*-[Pd(*S*-4,5-*H*-thiazolan-2-thionate)$_2$(PTA)$_2$] (**27**), and *trans*-[Pd(*S*-pyrimidine-4(1*H*)-one-2-thionate)$_2$(DAPTA)$_2$] (**32**), which show two very close singlets at room temperature that do not collapse when the spectra are recorded at lower temperatures and change to a singlet at higher temperatures. This behavior could be observed in the $^{31}P\{^1H\}$ NMR spectra of DAPTA in the corresponding complexes, which showed one or two singlets when one or two methyl resonances, respectively, are present, indicating the presence of two conformational isomers.[43] The dinuclear derivative $[Pd_2Cl_2(S\text{-pyrimidine-4(1}H\text{)-one-2-thionate})_2(PTA)_2]$ (**31**) shows a multiplet at 4.37 ppm for all the PTA protons; in this case, it was not possible to distinguish between NCH_2P or NCH_2N protons.

The $^{31}P\{^1H\}$ NMR spectra at room temperature show singlet resonances for all complexes with the commented exceptions for DAPTA derivatives of *trans*-[Pt(*S*-*m*-methylpyrimidine-2-thionate)$_2$(DAPTA)$_2$] (**2**), *trans*-[Pt(*S*-4,6-dimethylpyrimidine-2-thionate)$_2$(DAPTA)$_2$] (**6**), *trans*-[Pd(benzothiazole-2-thionate)$_2$(DAPTA)$_2$] (**16**), *trans*-[Pt(*S*-pyrimidine-4(1*H*)-one-2-thionate)$_2$(DAPTA)$_2$] (**30**), *trans*-[Pd(*S*-4,5-*H*-thiazolan-2-thionate)$_2$(PTA)$_2$] (**27**), and *trans*-[Pd(*S*-pyrimidine-4(1*H*)-one-2-thionate)$_2$(DAPTA)$_2$] (**32**), which show two very close singlets at room temperature that persist when the spectra are recorded at lower temperatures and change to a singlet at higher temperatures.

The platinum satellites $^{31}P-^{195}Pt$ of all thionate platinum complexes synthesized were consistent with a *trans* configuration of the ligands around the platinum center[40,41,43,63] in solution and ruled out the presence of *cis* isomers even at low temperatures. In addition, the presence of only one band each due to M−S and M−P (M = Pd, Pt) stretching vibrations in the far-IR spectra of complexes **1**−**30** and **32** in Nujol mulls also agrees with the proposed *trans* configuration. As previously reported by our group, *cis*-$[MCl_2(P)_2]$ that were used as precursors undergo an isomerization process during the course of the reaction. This is not typical behavior of platinum chemistry, and only a few examples in the preparation of palladium complexes, *trans*-$[PdI_2(PTA)_2]$ and *trans*-$[PdI_2(PTAH)_2]$ from *cis*-$[PdCl_2(PTA)_2]$, were described previously.[40,42,43,64] In the case of complex **31**, the far-IR spectrum also showed bands due to Pd−Cl and Pd−N stretching vibrations at 328 and 477 cm^{-1}, respectively. This is consistent with a bidentate coordination mode of the thionate ligand and a partial metathesis reaction from the chloride precursor.

The FAB+ spectra of complexes $[M(SN)_2(P)_2]$ (**1**−**30**, **32**) showed peaks corresponding to fragments resulting from the loss of one thionate ligand, $[M - (SN)]^+$, and one phosphine ligand, $[M - (SN) - (P)]^+$. The first usually is the base peak of

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the spectra because of the significant stability of the fragment. In the complex $[Pd_2Cl_2(S\text{-pyrimidine-4(1}H\text{)-one-2-thionate})_2(PTA)_2]$ (**31**), peaks at m/z 817 $[M - Cl]^+$, 660 $[M - Cl - PTA]^+$, and 390 $[Pd(SN)(PTA)]^+$ were identified. The experimental and calculated isotopical distribution of all commented fragments matched accurately.

Crystallographic Studies. Fortunately, the molecular structures of the complexes $[Pt(S\text{-4,6-dimethylpyrimidine-2-thionate})(PTA)_2]$ (**5**), $[Pd(S\text{-4,6-dimethylpyrimidine-2-thionate})_2(PTA)_2]$ (**7**), $[Pt(S\text{-4,6-dihydroxypyrimidine-2-thionate})_2(PTA)_2]$ (**9**), $[Pt(\text{benzothiazole-2-thionate})_2(PTA)_2]$ (**13**), $[Pt(\text{benzoxazole-2-thionate})_2(PTA)_2]$ (**17**), $[Pd(\text{benzoxazole-2-thionate})_2(PTA)_2]$ (**19**), and $[Pd_2(S\text{-pyrimidine-4(1}H\text{)-one-2-thionate})_2Cl_2(PTA)_2]$ (**31**) have been established by X-ray diffraction, confirming the *trans* configuration in $[M(SN)_2(P)_2]$ compounds or the dinuclear bridging thionate in the palladium derivative **31**. The structures are shown in Figures 1−7, and the crystallographic data are shown in Table 1.

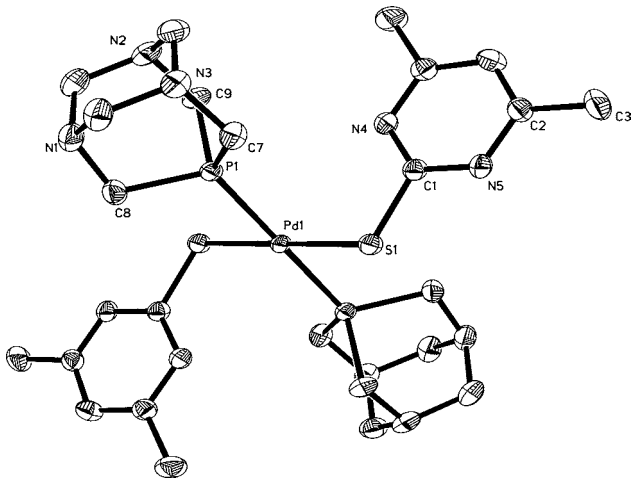

Figure 1. Molecular structure of complex **7**. Selected bond lengths [Å] and angles [deg]: #1 $-x, -y, -z + 2$; Pd(1)−P(1) 2.2895(8), Pd(1)−S(1) 2.3298(7), S(1)−C(1) 1.746(3), P(1)−C(7) 1.837(3), P(1)−C(9) 1.842(3), P(1)−C(8) 1.853(3), P(1)−Pd(1)−S(1)#1 86.96(3), P(1)#1-Pd(1)−S(1)#1 93.04(3). H atoms are omitted for clarity.

Figures 1−3 display the crystalline structures of the palladium (**7**) and the platinum (**5** and **9**) derivatives with *S*-4,6-dimethylpyrimidine-2-thionate and *S*-4,6-dihydroxypyrimidine-2-thionate ligands, respectively. In the three cases, the metallic atoms lie on a crystallographic center of inversion and within a *trans* N_2S_2 donor set, defining a square-planar geometry. Similar structures with pyridine and pyrimidine-2-thionate and PTA or DAPTA as phosphine ligands have been described previously[42,43] with the same *trans* disposition. In our structures, one of the nitrogen atoms from the thionate ligand is directed toward the metallic centers with separations that are too long (Pt1···N2 3.347 Å in **5**; Pd1···N4 3.331 Å in **7**, and Pt1···N4 3.355 Å in **9**) to be considered bonding interactions. This N atom displays an intramolecular C−H···N interaction with one of the methylene groups of the PTA molecule in both platinum structures (C8−H8a···N2 = 2.59 Å, C8···N2 = 3.324(6) Å and an angle at H8a of 132° in **5** and C5−H5a···$N4^i$ = 2.598 Å, $i = 1 - x, -y, -z$; C5···N4 = 3.331(6) Å and an angle at H5a of 132° in **9**). Two examples of mononuclear *S*-dimethylpyrimidine palladium and platinum X-ray structures

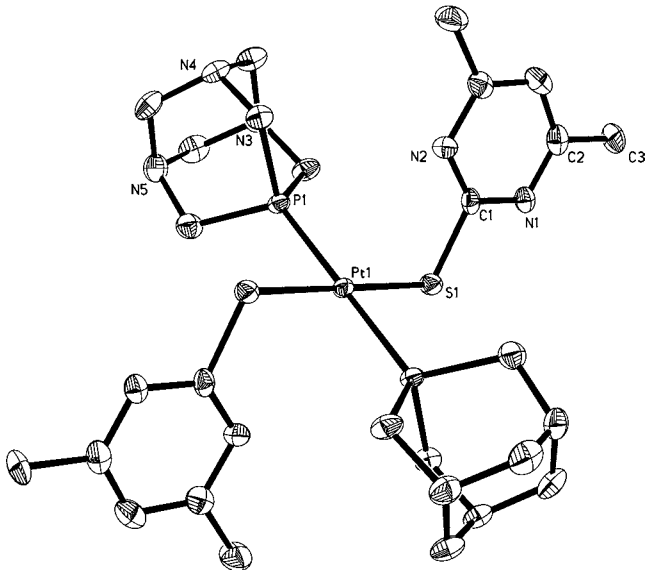

Figure 2. Molecular structure of complex **5**. Selected bond lengths [Å] and angles [deg]: #1 $-x + 1, -y + 1, -z + 2$; Pt(1)−P(1) 2.2884(10), Pt(1)−S(1) 2.3324(11), S(1)−C(1) 1.766(5), P(1)−C(10) 1.833(4), P(1)−C(8) 1.845(4), P(1)−C(7) 1.854(5), P(1)−Pt(1)−S(1) 92.99(4), P(1)−Pt(1)−S(1)#1 87.01(4). H atoms are omitted for clarity.

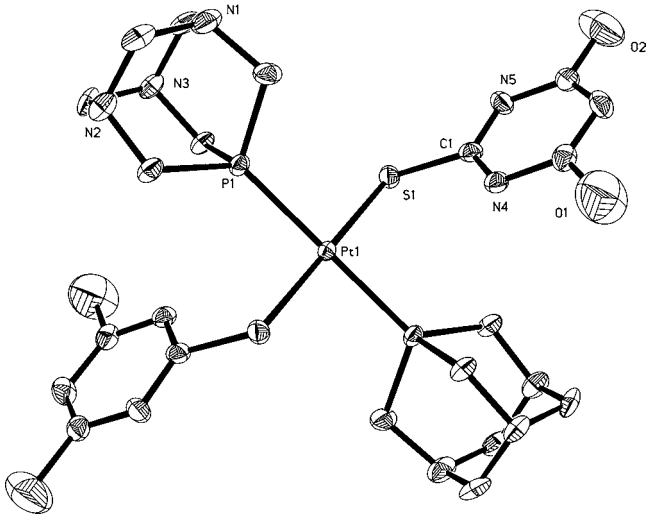

Figure 3. Molecular structure of complex **9** representing the thermal ellipsoids with 50% probabilities. Selected bond lengths [Å] and angles [deg]: #1 $-x + 1, -y + 1, -z + 1$; Pt(1)−P(1) 2.2860(12), Pt(1)−S(1) 2.3308(12), S(1)−C(1) 1.762(6), P(1)−C(8) 1.832(5), P(1)−C(5) 1.845(5), P(1)−C(6) 1.847(5), P(1)−Pt(1)−S(1)#1 92.93(4), P(1)−Pt(1)−S(1) 87.07(4). H atoms are omitted for clarity.

have been reported in the literature ($[M(S\text{-dimethylpyrimidine})_2]$, M = Pd, Pt),[65,66] and in both cases, the *S*-dimethylpyrimidine is acting as a chelate ligand with M−N distances of Pd−N 2.016(3)Å and Pt−N 2.006(4)Å. The M−S [Pd−S 2.3298(7) in **7**, Pt−S 2.3324(11) Å in **5**, and 2.3308(12) Å in **9**] bond lengths and M−P [Pd−P 2.2895(8) in **7**, Pt−S 2.2884(10) Å in **5**, and 2.2860(12) Å in **9**] distances are very close to those found in the reported complexes.[42,43] In both platinum complexes (**5** and **9**), long pyrimidine-2-thionate ring interactions of approximately 4.4 Å are observed (see the Supporting Information.)

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Complex **13** with benzothiazole-2-thionate as the thionate ligand and the isostructural complexes **17** and **19** with benzoxazole-2-thionate display the same *trans* disposition of the PTA ligands as in **5**, **7**, and **9** with square-planar geometry around the metallic center. There are only two examples of metallic derivatives with these thionate ligands described by X-ray analysis in the literature, as confirmed by a search in the *Cambridge Crystallographic Data Base* ([WCp(*S*-benzothiazole-2-thionate)$(CO)_3$][67] and [MoCp(*S*,*N*-benzothiazole-2-thionate)$(CO)_2$]),[68] and no examples of palladium or platinum compounds. In the crystal structure of **13**, the molecules associate through C−H···N interactions (C8−H8a···N1^i = 2.59 Å, i = 1 + x, y, z; C8···N1 = 3.539(12) Å and an angle at H8a of 164°) between two PTA molecules and an additional C−H···S interaction between the PTA and the S atom of the thionate molecule (C12−H12a···S1^i = 2.89 Å, i = −x, −y, −z; C12···S1 = 3.3429(6) Å and an angle at H12a of 122°). Only one significant intramolecular interaction is present in the structure of compound **17**, which corresponds to a C−H···S interaction between the PTA and the S atom of the thionate molecule with the parameters C10−H10a···S1^i = 2.83 Å, i x, 1/2 − y, −1/2 + z; C10···S1 = 3.693(11) Å and an angle at H10a of 149°. Comparison of the distances in the isostructural compounds **17** and **19** shows that the M−S (M = Pd 2.3206(13), Pt 2.325(2) Å) bond lengths are equal considering the standard deviation; however, it is noteworthy that the Pd−P (2.2949(14) Å) distance in **19** is longer than the Pt−P (2.288(3) Å) distance that is observed in **17**, which indicates similar ionic radii for both metallic centers. This observation is in contradiction with the usual previsions and with the features of the second and third transition rows. This fact agrees with the consideration of the relativistic effects.[69]

The molecular structure of complex **31** (Figure 7) has C_2 symmetry crystallographically imposed with two palladium atoms linked through two S−$C_4H_3N_2$(O) units in a head-to-tail fashion. The coordination around the metallic centers is distorted square-planar. The PTA molecules are oriented *trans* to the nitrogen atom, while the chlorine atoms are oriented *trans* to the sulfur of the thionate ligand. Similar dinuclear palladium derivatives with pyridine-2-thionate and different phosphines have been crystallographically characterized: [Pd-(μ−η^2-pySN,S)Cl(PR_3)]$_2$ (PR_3 = PMe_3,[70,71] PMe_2Ph,[71] and $PMePh_2$[71]). In the reported structures, the interatomic distances Pd···Pd in the range of 2.921(2)−2.982(3) Å are shorter than the distances found in **31** (3.0268(14)Å). The Pd−P, Pd−S, and Pd−Cl bond lengths of 2.223(2), 2.305(2), and 2.341(2) Å, respectively, are shorter than those observed in the reported derivatives; however, the Pd−N distance of 2.140(6) Å is slightly longer.

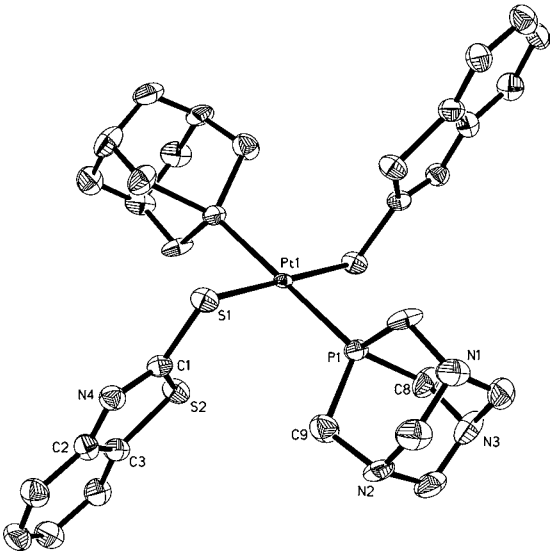

Figure 4. Molecular structure of complex **13**. Selected bond lengths [Å] and angles [deg]: #1 −x + 1, −y, −z; Pt(1)−P(1) 2.297(2), Pt(1)−S(1) 2.351(2), S(1)−C(1) 1.734(8), S(2)−C(1) 1.754(7), S(2)−C(3) 1.748(8), P(1)−C(9) 1.843(8), P(1)−C(12) 1.853(8), P(1)−C(8) 1.858(9), P(1)−Pt(1)−S(1)#1 91.45(8), P(1)−Pt(1)−S(1) 88.55(7). H atoms are omitted for clarity.

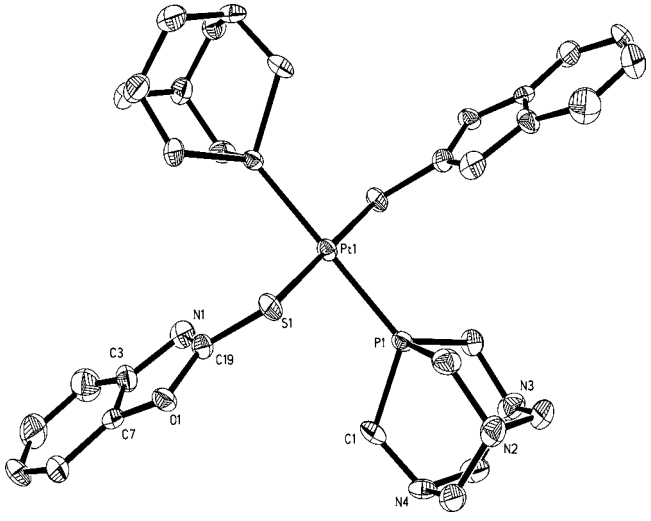

Figure 5. Molecular structure of complex **17**. Selected bond lengths [Å] and angles [deg]: #1 −x + 1, −y, −z + 1: Pt(1)−P(1) 2.288(3), Pt(1)−S(1) 2.325(2), P(1)−C(1) 1.835(11), P(1)−C(4) 1.840(10), P(1)−C(10) 1.832(10), S(1)−C(19) 1.735(11), O(1)−C(19) 1.386(12),O(1)−C(7) 1.382(13), P(1)−Pt(1)−S(1) 86.49(9), P(1)−Pt(1)−S(1)#1 93.51(9). H atoms are omitted for clarity.

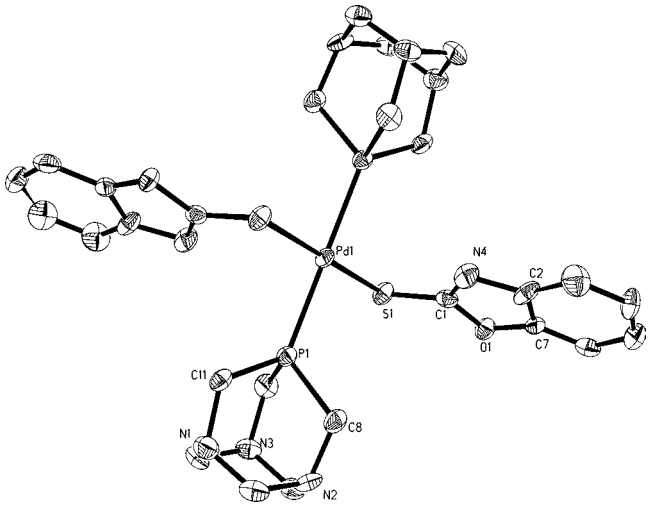

Figure 6. Structure of complex **19**. Selected bond lengths [Å] and angles [deg]: #1 −x, −y, −z + 1: Pd(1)−P(1) 2.2949(14), Pd(1)−S(1) 2.3206(13), S(1)−C(1) 1.716(6), P(1)−C(11) 1.836(5), P(1)#1−Pd(1)−S(1)#1 86.48(5), P(1)−Pd(1)−S(1)#1 93.52(5). H atoms are omitted for clarity.

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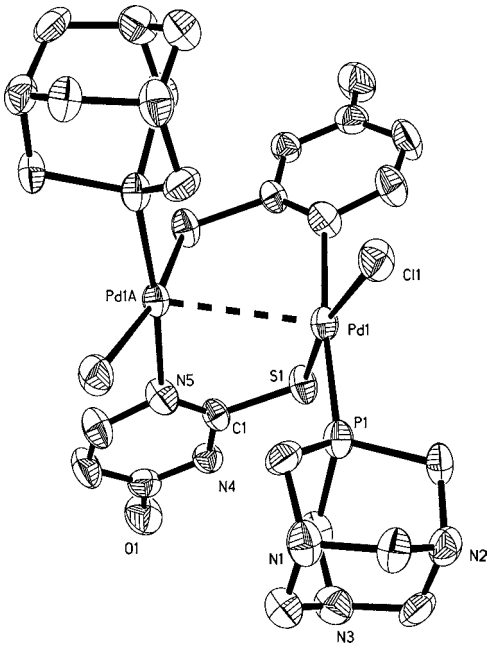

Figure 7. Molecular structure of complex **31**. Selected bond lengths [Å] and angles [deg]: #1 $-x + 1, y, -z + 1/2$; Pd(1)−N(5)#1 2.140(6), Pd(1)−P(1) 2.223(2), Pd(1)−S(1) 2.305(2), Pd(1)−Cl(1) 2.341(2), Pd(1)−Pd(1)#1 3.0268(14), O(1)−C(4) 1.244(10), P(1)−C(9) 1.835(8), P(1)−C(6) 1.844(7), P(1)−C(5) 1.840(8), S(1)−C(1) 1.740(7), N(5)#1−Pd(1)−P(1) 173.79(18), N(5)#1−Pd(1)−S(1) 89.10(18), P(1)−Pd(1)−S(1) 91.48(8), N(5)#1−Pd(1)−Cl(1) 91.66(18), P(1)−Pd(1)−Cl(1) 86.51(8), S(1)−Pd(1)−Cl(1) 168.23(7), N(5)#1−Pd(1)−Pd(1)#1 83.69(18), P(1)−Pd(1)−Pd(1)#1 102.51(5), S(1)−Pd(1)−Pd(1)#1 84.19(5), Cl(1)−Pd(1)−Pd(1)#1 107.57(5). H atoms are omitted for clarity.

Cytotoxicity Studies. All palladium and platinum complexes reported here are poorly water-soluble. In most cases, the water solubility values are in the 0.1−0.8 mg/mL range. The only ones that present a moderate water solubility at room temperature are *trans*-[Pd(*S*-*m*-methylpyrimidine-2-thionate)$_2$(PTA)$_2$] (**4**, 23.4 mg/mL) and *trans*-[Pd(*S*-*m*-methylpyrimidine-2-thionate)$_2$(DAPTA)$_2$] (**3**, 12.6 mg/mL). This fact has not prevented us from evaluating the *in vitro* activities of these complexes against the human ovarian cancer cell line A2780 and the cisplatin-resistant counterpart (A2780cisR) cell lines. It is known that a mere increase of the hydrophilicity is not a requirement for high activity in platinum complexes.[72]

All the tested compounds showed a high growth cell inhibition near 90% except for complexes **9** and **22**, very close to the value measured for cisplatin (see the corresponding cell growth inhibition curves in the Supporting Information). Tables 2 and 3 show the maximum effect (E_{max}) and IC_{50} to demonstrate the growth cell efficacy, maximum of inhibition by the compounds (expressed in percent %), and potency, respectively, against the human ovarian cell lines A2780 (sensible) and A2780cisR (resistant) after 96 h of drug exposure.

The data in Table 3 show the *in vitro* activities of the *trans*-platinum **6**, **9**, **13**, **15**, **19**, **21**, **22**, **25**, and **26** and *trans*-palladium **14** complexes studied and cisplatin as a reference in the human ovarian cancer cell lines A2780 and A2780cisR (cisplatin-resistant). The data about the cell growth inhibitory potency, IC_{50}, allowed understanding of the similar behavior of all the tested complexes, and no significant difference appeared

Table 2. Cell Growth Inhibitory Efficacy in the Human Ovarian Cancer Cell Lines A2780 and A2780cisR[a]

compound	A2780 E_{max} ± SE* (%)	A2780cisR E_{max} ± SE* (%)
trans-[Pt(*S*-4,6-dimethylpyrimidine-2-thionate)$_2$(DAPTA)$_2$] (**6**)	89 ± 2	89 ± 1
trans-[Pt(*S*-4,6-dihydroxypyrimidine-2-thionate)$_2$(PTA)$_2$] (**9**)	77 ± 3	85 ± 1
trans-[Pt(benzothiazole-2-thionate)$_2$(PTA)$_2$] (**13**)	91 ± 1	89 ± 1
trans-[Pt(benzothiazole-2-thionate)$_2$(DAPTA)$_2$] (**14**)	88 ± 1	86 ± 1
trans-[Pd(benzothiazole-2-thionate)$_2$(PTA)$_2$] (**15**)	85 ± 2	85 ± 1
trans-[Pt(benzoxazole-2-thionate)$_2$(PTA)$_2$] (**17**)	85 ± 3	91 ± 1
trans-[Pt(*S*-1,3,4,-thiadiazol-2-thionate)$_2$(PTA)$_2$] (**21**)	92 ± 1	84 ± 1
trans-[Pt(*S*-1,3,4,-thiadiazol-2-thionate)$_2$(DAPTA)$_2$] (**22**)	74 ± 2	86 ± 3
trans-[Pt(*S*-4,5-*H*-thiazolan-2-thionate)$_2$(PTA)$_2$] (**25**)	91 ± 1	89 ± 1
trans-[Pt(*S*-4,5-*H*-thiazolan-2-thionate)$_2$(DAPTA)$_2$] (**26**)	90 ± 1	85 ± 2
cisplatin	97 ± 1	92 ± 1

[a] E_{max}, maximun efficacy; SE*, standard error of the mean, % inhibition.

Table 3. IC_{50} Values of Palladium and Platinum Derivatives against Ovarian Carcinoma Cell Lines Sensitive (A2780) or Resistant to Cisplatin (A2780cisR) Compared with Cisplatin

compound	IC_{50} (μM)[a]		
	A2780	A2780cisR	RF[b]
trans-[Pt(*S*-4,6-dimethylpyrimidine-2-thionate)$_2$(DAPTA)$_2$] (**6**)	2.35 ± 0.01	1.71 ± 0.02	0.73
trans-[Pt(*S*-4,6-dihydroxypyrimidine-2-thionate)$_2$(PTA)$_2$] (**9**)	2.20 ± 0.04	0.85 ± 0.01	0.39
trans-[Pt(benzothiazole-2-thionate)$_2$(PTA)$_2$] (**13**)	3.10 ± 0.03	1.35 ± 0.02	0.43
trans-[Pt(benzothiazole-2-thionate)$_2$(DAPTA)$_2$] (**14**)	1.83 ± 0.02	0.99 ± 0.03	0.54
trans-[Pd(benzothiazole-2-thionate)$_2$(PTA)$_2$] (**15**)	3.12 ± 0.05	1.62 ± 0.03	0.52
trans-[Pt(benzoxazole-2-thionate)$_2$(PTA)$_2$] (**17**)	2.34 ± 0.02	0.93 ± 0.01	0.40
trans-[Pt(*S*-1,3,4,-thiadiazol-2-thionate)$_2$(PTA)$_2$] (**21**)	2.23 ± 0.07	0.96 ± 0.01	0.41
trans-[Pt(*S*-1,3,4,-thiadiazol-2-thionate)$_2$(DAPTA)$_2$] (**22**)	1.78 ± 0.01	1.32 ± 0.03	0.74
trans-[Pt(*S*-4,5-*H*-thiazolan-2-thionate)$_2$(PTA)$_2$] (**25**)	1.76 ± 0.04	0.70 ± 0.01	0.40
trans-[Pt(*S*-4,5-*H*-thiazolan-2-thionate)$_2$(DAPTA)$_2$] (**26**)	2.31 ± 0.01	1.80 ± 0.02	0.78
cisplatin	0.86 ± 0.02	5.02 ± 0.05	5.84

[a] Mean ± SE of at least three determinations. [b] RF, ratio between IC_{50} values for A2780cisR and A2780.

because of the nature of the thionate or phosphine ligand in the compounds. A cursory analysis of the response in the cell line A2780 allows some reflection. In the case of palladium or platinum center complexes, as in *trans*-[Pd(benzothiazole-2-thionate)$_2$(PTA)$_2$] (**15**) and *trans*-[Pt(benzothiazole-2-thionate)$_2$(PTA)$_2$] (**13**), which have the same thionate and phosphine ligands, their very similar responses made the comparative activity possible because of the nature of the metal center. The IC_{50} values, 3.12 and 3.10 μM, for complex **15** and

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13, respectively, indicate that *trans* palladium complexes can be good candidates to study the ability of their antitumor activity against isostructural platinum complexes. Both PTA compounds showed slightly higher values than that observed for the platinum DAPTA derivative **14**, 1.83 μM. This is not a typical behavior for the two different phosphine complexes. In the *S*-4,5-*H*-thiazolan-2-thionate derivatives, *trans*-[Pt(*S*-4,5-*H*-thiazolan-2-thionate)$_2$(PTA)$_2$] (**25**) and *trans*-[Pt(*S*-4,5-*H*-thiazolan-2-thionate)$_2$(DAPTA)$_2$] (**26**), the IC_{50} values are 1.76 and 2.31 μM, respectively, evidencing a slightly higher activity in the PTA derivative. In contrast, the 1,3,4-thiadiazole-2-thiolate derivatives, *trans*-[Pt(*S*-1,3,4,-thiadiazole-2-thionate)$_2$(PTA)$_2$] (**21**) and *trans*-[Pt(*S*-1,3,4,-thiadiazole-2-thionate)$_2$(DAPTA)$_2$] (**22**), behave as mentioned above with a lower activity in the case of the PTA derivative; IC_{50} values are 2.23 and 1.78 μM, respectively. It is possible to make the same comparisons about the activity against the A2780cisR cell line except for complexes **21** and **22** in which the PTA derivative presents a lower IC_{50} value than that observed for the DAPTA derivative. All the complexes are in the range of activity of cisplatin against the A2780 cell line; however, they are found to be more active, up to 7-fold in the best case, against the resistant cell line A2780cisR.

Recently, many platinum derivatives with *trans* geometry have been reviewed that exhibit significant *in vitro* antitumor activity against different tumor cells, including ones resistant to cisplatin.[13−15] In general and specifically to ovarian cancer cell lines, *trans*-platinum derivatives with iminoethers, planar amines (e.g., hydroxypyridine isomers, imidazole, imidazole-(1,2-α-pyridine)), carboxylates, nonplanar heterocyclic ligands (e.g., piperazine, piperidine), or aliphatic amines (e.g., propanamine, butanamine, *N*,*N*-dimethylamine) are found to be less active than cisplatin against A2780 cancer cells; however, they are sometimes found to be more active against the resistant cell lines than the parent cell line in comparison to cisplatin. The combination of one planar heterocyclic and one aliphatic ligand, such as (hydroxymethyl)pyridine and isopropylamine, creates *trans*-[PtCl$_2$(ipa)(py-Me-OH)] (py-Me-OH = 3-py-Me-OH and 4-py-Me-OH), which was found to be more cytotoxic than cisplatin in both cell lines (A2780 and A2780cisR).[73] Some recently reported examples of *trans* platinum complexes, such as *trans*-[PtCl$_2$((ferrocenymethylidene)(furan-2-ylethyl)-amine-kN))$_2$], *trans*-[PtCl$_2$((ferrocenymethylidene)(thiofen-2-ylmethyl)amine-kN))$_2$],[74] *trans*-[PtCl$_2$(NH$_3$)(2,3-diaminopyridine)], *trans*-[PtCl$_2$(2,3-diaminopyridine)$_2$],[75] *trans*-[Pt-(cyclohexanediamine)(pyrophosphato)],[76] *trans*-[PtCl$_2$(2-hydroxypyridine)$_2$],[77] or *trans*-[PtCl$_2$(thiazole)(L)] (L = imidazole, 3-hydroxypyridine),[78] display a high IC_{50} (>100 μM)[74] or lower cytotoxicity than cisplatin, with the ability to circumvent resistance to cisplatin in A2780cisR cells.[75−78]

In addition, only a few examples of mononuclear *trans*-palladium derivatives have been tested against ovarian cancer cells lines. Thus, *trans*-[PdCl$_2$L$_2$] complexes with L = 2-methylpyridine, imidazole, and 1,2-α-imidazopyridine[79] or *trans*-[PdCl$_2$(ferrocenylimine)$_2$][74] display a much lower cytotoxic activity against A2780 cancer cell lines in comparison to that of cisplatin. However, *trans*-palladium complexes with sterically hindered amines such as 3-hydroxypyridine, 2-hydroxypyridine, and 4-hydroxypyridine have shown significant antitumor activity against the same ovarian cancer cell lines and even more antitumor activity against cisplatin-resistant cell lines.[80]

In our case, only one example of a palladium derivative, *trans*-[Pd(benzothiazole-2-thionate)$_2$(PTA)$_2$] (**15**), has been evaluated with a similar behavior to that observed in the previously reported derivative with hydroxypyridine ligands with a IC_{50} value in the same range as that found in cisplatin against the sensitive A2780 cell line and an IC_{50} 3-fold lower than that of cisplatin against A2780cisR. It is noteworthy that these values are similar or even lower than those measured for gold(I) thionate compounds [Au(SN)(P)][44,47] (SN = pyridine-2-thionate, pyrimidine-2-thionate, methylpyrimidinthionate, thiazoline, benzoxazole or benzoimidazole, and P = PTA or DAPTA) against the same human ovarian cancer cell lines. Because in both type of derivatives the same type of thionates are employed, we can conclude that the corresponding thionate ligand could play an important role in the potential cytotoxic activity.

In addition, we have evaluated the cross-resistance profiles by means of the resistance factor (RF reported in Table 3), calculated as the ratio of IC_{50} values between the two cell lines. All the complexes display RF values ranging from 0.39 to 0.78, which are lower than that calculated for cisplatin (5.84) and are at least 2-fold less than the above referenced gold(I) derivatives.[47] Most of the reported *trans*-platinum compounds show much higher RF values than those described in this paper with the exception of complexes with carboxylato[81] or hydroxypyridine ligands[82] with values ranging from 0.9 to 1.7 and 0.5 to 1.2, respectively. This fact implies that all our *trans* derivatives tested in the current study are able to circumvent resistance to cisplatin in A2780cisR cells and present improved alternatives to cisplatin in second or third line treatment. These observations also agree with the IC_{50} values referenced in the literature for cisplatin against A2780 and A2780cisR: 0.16 and 6.1 μM,[59] RF 38.1; 1.2 and 10 μM,[60] RF 8.3; 2.3 and 7.8 μM,[61] RF 3.4.

CONCLUSIONS

All complexes [M(SN)$_2$(P)$_2$] (**1**−**30**, **32**) synthesized in this work have a *trans* disposition as deduced by different spectroscopic techniques and the X-ray structure of six of them, although the starting material has a *cis* disposition. Therefore, an isomerization occurs during the synthesis, which is noteworthy. In addition, the X-ray structures of the two isostructural complexes *trans*-[Pt(benzoxazole-2-thionate)$_2$(PTA)$_2$] (**17**) and *trans*-[Pd(benzoxazole-2-thionate)$_2$(PTA)$_2$] (**19**) show the ionic radii of Pt and Pd in these complexes to be nearly the same or for Pt to be slightly smaller than Pd, which is contrary to what is commonly accepted. Only in the case of [Pd$_2$Cl$_2$(*S*-pyrimidine-4(1*H*)-one-2-thionate)$_2$(PTA)$_2$] (**31**), the structure is dinuclear with a short Pd−Pd distance of 3.0265(14)Å.

The *in vitro* cytotoxicity against the human ovarian cancer cell lines A2780 and A2780cisR for ten compounds demonstrates considerable biological activity. Interestingly, it was observed that all complexes tested against the A2780 cell lines present an inhibitory potency comparable to cisplatin, and there were not any significant differences between the IC_{50} values for complexes with different thionate or phosphine groups as ligands. All ten complexes are even more active against the A2780cisR cell line (RF approximately 0.5) and overcome cisplatin resistance in a 7-fold factor. This result demonstrates the potential of these compounds as alternatives to cisplatin in second and third line treatment and is of fundamental importance, illustrating once more that platinum-

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(II) complexes with *trans* geometry also have *in vitro* activity in both cell lines. Currently studies are ongoing to gain a better insight into the nature of coordinated ligands to platinum or palladium centers in *trans*-thionate derivatives with *in vitro* cytotoxic properties in human cancer cell lines.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data for complexes **5**, **7**, **9**, **13**, **17**, **19**, and **31** in CIF format and cytotoxic data graphics for complexes **6**, **9**, **13**, **14**, **15**, **19**, **21**, **22**, **25**, and **26**, and view of the packing in the unit cell for complex **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Antonio Laguna on the occasion of his 65th birthday.

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