APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. 2007; **21**: 626–632
Published online 4 May 2007 in Wiley InterScience
(www.interscience.wiley.com) DOI:10.1002/aoc.1227

Synthesis, characterization and *in vitro* cytotoxicity of homobimetallic complexes of palladium(II) with 2-thiouracil ligands. Crystal structure of $[Pd_2(TU)(PPh_3)_3Cl_2]$

Farkhanda Shaheen[1]*, Amin Badashah[1], Marcel Gielen[2]*, L. Marchio[3], Dick de Vos[4] and M. Kaleem Khosa[5]

[1]Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan
[2]Vrije Universiteit Brussel, Faculty of Engineering, HNMR Unit, B-1050 Brussels, Belgium
[3]Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica, Universitia de Parma, 17/A 43100, Parma, Italy
[4]Pharmachemie BV, PO Box 552, 2003 RN Haarlem, The Netherlands
[5]Department of Chemistry, Government College University Faisalabad, Pakistan

Received 17 January 2007; Revised 7 February 2007; Accepted 9 February 2007

Square planar metallic and homonuclear bimetallic complexes of Pd(II) with 2-thiouracil (HTU) and organophosphines have been synthesized and characterized by FT-IR and multinuclear ^{1}H, ^{13}C, ^{31}P NMR spectroscopy. The thiouracil ligand TU acts as bidentate, is bound through the thioxo moiety and the endo amino group and forms a bridge between a $PdCl(R_3P)$ and a $PdCl(R_3P)_2$ moiety [R_3P = Ph_3P (*o*-tolyl)$_3P$, $ClPh_2P$] in the homonuclear bimetallic complexes. The square planar geometry around Pd(II) has been confirmed for these complexes by a single-crystal X-ray diffraction study of compound 1, $[Pd_2(TU)(PPh_3)_3Cl_2]$. These compounds were also screened against human tumor cell lines and showed promising *in vitro* cytotoxicity. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: palladium; organophosphines; thiouracil; cytotoxicity.

INTRODUCTION

The heterocyclic thiones exist as tautomeric thiol and thione forms and their anions are referred to as thionates. When coordinating to a metal centre, they may act as bidentate and ambidentate ligands.[1,2] Palladium(II) and platinum(II) complexes with N and S donor and bridging chelates find extensive applications as industrial biological detoxicants[1] against intoxication by heavy metals.[3] Palladium(II) and platinum(II) compounds are not only cytotoxic but also show radio-sensitizing activity.[4–8] Cisplatin complexes and a few carboxylato analogs are effective antitumor drugs.[9–11] In order to modulate cisplatin activity and toxicity, a new strategy was designed for the synthesis of new molecules containing either N or S donors.[12–14] Various thiosemicarbazone Pd(II) complexes have been synthesized and tested against different cell lines. They inhibit DNA synthesis in P338 leukemia cells[15] and induce apoptosis in tumor cells (*pam-ras*) transformed by *ras* oncogenes and expressing resistance to cisplatin.[16] The 2-mercaptopyrimidine and 4,6-dimethylpyrimidine-2-thione belong to the same class of bases and behave as unsymmetrical ambidentate ligands. When coordinated to a metal, they generate linkage isomerism due to steric repulsions/interactions and act as antitumor/antithyroid agents.[17] A similar inhibitory effect has been found for pyrimidine-2-thione that also exhibits pronounced *in vitro* bacteriostatic activity.[18] Palladium-based drugs, in contrast to platinum references, were non-mutagenic in the *Ames* test and therefore exhibit a lower potential health risk.[19,20] A number of mixed ligand complexes of phosphines/amines

*Correspondence to: Marcel Gielen, Vrije Universiteit Brussel, Faculty of Engineering, HNMR Unit, B-1050 Brussels, Belgium and Farkhanda Shaheen, Department of Chemistry, Quaid-I-Azam University, Islamabad 45320, Pakistan.
E-mail: mgielen@vub.ac.be; fshaheenpk@yahoo.com
Contract/grant sponsor: Quaid-e-Azam University, Islamabad, Pakistan.
Contract/grant sponsor: National Science Foundation Islamabad, Pakistan.

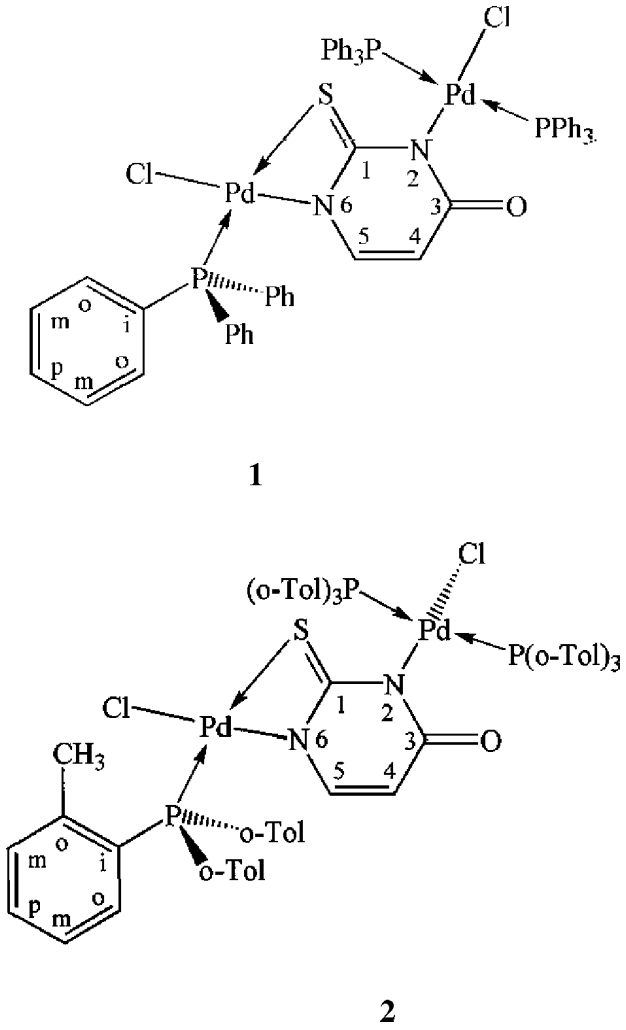

Figure 1. Structures of compounds **1** and **2**.

have been reported.[21] The coordination of metal ions to heterocyclic thiones is of current interest because these complexes are used in the synthesis of clinically useful drugs. Palladium(II) complexes containing heterocyclic thione ligands have attracted considerable attention due to significant palladium–sulfur interactions in biological systems.[22] In order to investigate the structure–activity relationship in biological systems and the anticancer activity of palladium(II) complexes, we have synthesized some complexes of Pd(II) with mixed organophosphine/2-thiouracil ligands, compounds **1**–**5** (see Figs 1 and 2).

EXPERIMENTAL

Reagents

All reagents, 2-thiouracil, triphenylphosphine, tris-*o*-tolylphosphine, chlorodiphenylphosphine and palladium(II) chloride, were of analytical grade and purchased from Aldrich, USA. All the organic solvents were dried before use according to standard procedures.[23,24]

Instrumentation

Elemental analyses were carried out on a Fisons EA1108 CHNS-O microanalyzer. FT-IR spectra were recorded on a Bio-Rad Excalibure FT-IR, model FTS 3000 MX instrument with KBr discs from 4000 to 400 cm^{-1} and on a Perkin-Elmer FT-IR Nexus spectrometer with CsI discs from 500 to 200 cm^{-1}.

The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solutions on a Bruker 300 MHz spectrometer operating at 300 and 75.5 MHz, respectively. The ^{31}P NMR spectra were recorded in $CDCl_3$ solutions on a Bruker AMX-400 MHz spectrometer operating at 160 MHz.

Cytotoxicity screenings

The test and reference compounds were dissolved to a concentration of 250 000 ng ml^{-1} in full medium, by 20-fold dilution of a stock solution which contained 1 mg compound per 200 µl. The compounds were taken into dimethylsulfoxide. *In vitro* cytotoxicity was estimated by the microculture sulforhodamine B (SRB) test.[46] 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, estrogen receptor (ER)−/progesterone receptor (PgR)− breast cancer, H226, non-small cell lung cancer; IGROV, ovarian cancer; M19 MEL, melanoma; and WIDR, colon cancer.

The experiment was started on day 0. On day 0, 10 000 cells per well were seeded into 96-well flat-bottomed microtiter

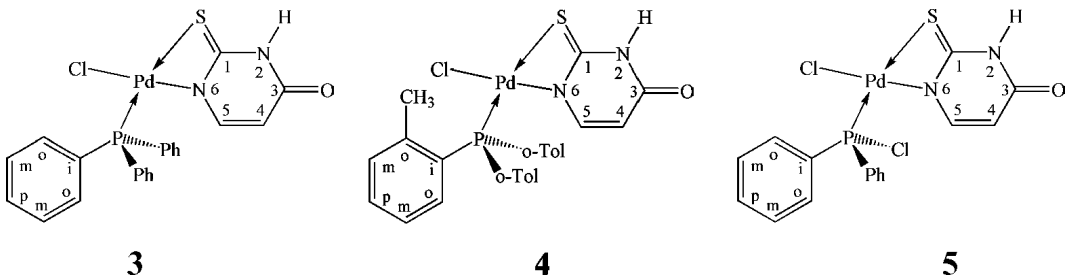

Figure 2. Structures of compounds **3**–**5**.

DOI: 10.1002/aoc

plates (falcon 3072, DB). The plates were incubated overnight at 37 °C in 5% CO_2 to allow the cells to adhere to the bottom. On day 1, a 3-fold dilution sequence of 10 steps was made in full medium, starting with the 250 000 ng ml^{-1} stock solution. Every dilution was used in quadruplicate by adding 200 µl to a column of four wells. This procedure results in a highest concentration of 625 000 ng ml^{-1} present in column 12. Column 2 was used for the blank. After incubation of 3 days, the plates were washed with PBS twice. Fluorescein diacetate (FDA) stock solution was diluted to 2 µg ml^{-1} with 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 micro-plate reader (Labsystems Multiskan MS). Data were used for construction of concentration–response curves and determination of the ID_{50} value by use of Deltasoft 3 software. The variability of the *in vitro* cytotocicity test depends on the cell lines used and the serum applied, amongst other factors. With the same batch of cell lines and the same batch of serum, the inter-experimental CV (coefficient of variation) is 1–11% depending on the cell line, and the intra-experimental CV is 2–4%. These values may be higher with other batches of cell lines and/or serum.

Synthesis

Synthesis of [Pd(PR$_2$R′)Cl$_2$]

The [Pd(PR$_2$R′)$_2$Cl$_2$] compounds were synthesized according to literature methods[15,23,24] by mixing a solution of palladium chloride in 25 cm^3 of ethanol with a few drops of 1 M hydrochloric acid with 25 cm^3 of a PR$_2$R′ acetone solution ($PdCl_2$: $PR_2R' = 1:2$). The reaction mixture was refluxed for 2 h to yield a pale-yellow precipitate that was filtered, washed with an excess of ethanol and dried in air. The compound was crystallized from THF: light yellow crystals were obtained after 48 h.

*Synthesis of 3-[chlorobis(triphenylphosphino)] palladium-1- [chloro(triphenylphosphino)](2-thiouracil)palladium(II) (**1**)*

2-Thiouracil was mixed with a suspension of $PdCl_2(PPh_3)_2$ (1 : 2 molar ratio) in 25 cm^3 of CH_2Cl_2. The reaction mixture was refluxed for 1 h to yield a clear solution. The solvent was evaporated under reduced pressure. The obtained product was crystallized from CH_2Cl_2. Compound **2** was prepared similarly. Crystals suitable for X-ray diffraction were obtained by dissolving 0.5 g of the sample in a small quantity of CH_2Cl_2 and submitting to a slow evaporation at room temperature for several days to yield small orange crystals. Yield: 80%. Anal. calcd for $C_{58}H_{47}Cl_2N_2OP_3Pd_2S$: calcd (obs.) C = 58.14 (58.12), H = 3.92 (3.92), N = 2.33 (2.34), S = 2.67 (2.64); FT-IR: 1630,

Table 1. Crystal data and structure refinement for compound **1**

Identification code	far10
Empirical formula	$C_{58}H_{47}Cl_2N_2OP_3Pd_2S$
Formula weight	1196.65
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	$a = 11.845(1)$ Å $\alpha = 69.592(2)°$
	$b = 15.590(2)$ Å $\beta = 75.495(2)°$
	$c = 15.697(2)$ Å $\gamma = 80.831(2)°$
Volume	2621.8(5) $Å^3$
Z, Calculated density	2, 1.516 mg m^{-3}
Absorption coefficient	0.962 mm^{-1}
F(000)	1208
Crystal size	0.25 × 0.15 × 0.08 mm
Theta range for data collection	1.64–27.10°
Limiting indices	$-15 \le h \le 15, 19 \le k \le 19, 20 \le l \le 20$
Reflections collected/unique	28623/11291 [R(int) = 0.0567]
Completeness to theta = 27.10	97.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.830
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	11291/0/622
Goodness-of-fit on F^2	0.936
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0428$, $wR_2 = 0.0551$
R indices (all data)	$R_1 = 0.1053$, $wR_2 = 0.0605$
Largest difference peak and hole	0.861 and −0.759 e $Å^{-3}$

DOI: 10.1002/aoc

Table 2. Inhibition doses ID_{50} *in vitro* cytotoxicity of compounds **1** and **3** and of six reference compounds using SRB as cell viability test

Compound	A498	EVSA-T	H226	IGROV	M19MEL	MCF-7	WiDr
1	1526	8322	2093	631	30062	25153	1409
3	2335	1097	5166	192	3382	2338	2890
DOX	90	8	199	60	16	10	11
CPT	2253	422	3269	169	558	699	967
5FU	143	475	340	297	442	750	225
MTX	37	5	2287	7	23	18	<3
ETO	1314	317	3934	580	505	2594	150
TAX	<3	<3	<3	<3	<3	<3	<3

ν(C═N); 320, ν(Pd–S); 451, ν(Pd ← N); ^{1}H NMR (DMSO-d_6): δ 5.87(d, 1H4), 5.95(d, 1H5), 7.4–7.6(m, 45H, Ph). ^{13}C NMR (DMSO-d_6): δ 177.97(C1), 176.44(C3), 106.1(C4), 161.24(C5): ^{31}P{^{1}H} NMR ($CDCl_3$): δ 27.50(s, PPh_3).

*Synthesis of 3-[chlorobis(tri-o-tolylphosphino)] palladium-1-[chloro(tri-o-tolylphosphino)](2-thiouracil)palladium(II), **2***

Yield: 85%. Anal. calcd for $C_{67}H_{65}Cl_2N_2OP_3Pd_2S$; calcd (obs) C = 60.77 (60.73), H = 4.91(4.90), N = 2.11 (2.00), S = 2.41 (2.43); FT-IR: 1630, ν(C═N); 423, ν(Pd–S); 449, ν(Pd ← N); ^{1}H NMR (DMSO-d_6): δ 5.84(d, 1H4), 5.95(d,1H5), 7.1–7.7(m, 36H, Ph); 2.4–2.9(m, 27H,–CH_3). ^{13}C NMR (DMSO-d_6): δ 177.35(C1), 176.23(C3), 105.99(C4), 160.24(C5); ^{31}P{^{1}H} NMR ($CDCl_3$): δ 31.85, 29.79, 28.18[3 s, P(*o*-Tol)$_3$]

*Synthesis of chloro[(2-thiouracil)(triphenyl-phosphino)] palladium(1I), **3***

2-Thiouracil was mixed with a suspension of $PdCl_2(PPh_3)_2$ in 25 cm^3 of CH_2Cl_2 (1 : 1 molar ratio). The reaction mixture was refluxed for half an hour to obtain a clear solution. The solvent was evaporated under reduced pressure. The obtained product was crystallized from CH_2Cl_2 by a slow evaporation at room temperature. Compounds **4** and **5** were synthesized similarly.

Yield: 85%. Anal. calcd for $C_{21}H_{18}ClN_2OPPdS$; calcd (obs) C = 48.50 (48.50), H = 3.46 (3.45), N = 5.38 (5.38), S = 6.15 (6.05); FT-IR: 1629, ν(C═N); 3066, ν(N–H); 321, ν(Pd–S); 471, ν(Pd ← N); ^{1}H NMR (DMSO-d_6): δ 12.5(s,H1, –NH), 5.9[d,1H4, 7.65(m, 1H5) 7.4–7.8(m, 15H, Ph)]. ^{13}C NMR (DMSO-d_6): δ 172.3(C1), 161.2(C3), 106.1(C4), 158.24 (C5): ^{31}P{^{1}H} NMR ($CDCl_3$): δ 28.6(s, PPh_3).

*Synthesis of chloro[(2-thiouracil)(tris-o-tolyl-phosphino)]palladium(1I), **4***

Yield: 80%. Anal. calcd for $C_{24}H_{24}ClN_2OPPdS$; calcd (obs) C = 51.29 (51.30), H = 4.27 (4.28), N = 4.98 (4.97), S = 5.69 (5.68); FT-IR: 1630, ν(C═N); 3058, ν(N–H); 401, ν(Pd–S); 473, ν(Pd ← N); ^{1}H NMR (DMSO-d_6): δ 12.5(s, H1, –NH), 5.85(d, 1H4), 5.95(d, 1H5), 7.4–7.6(m, 12H, Ph), 2.4–2.9(m, 9H,–CH_3). ^{13}C NMR (DMSO-d_6): δ 175.3(C1), 165.2(C3), 106.2(C4), 159.94 (C5): ^{31}P{^{1}H} NMR ($CDCl_3$): δ 31.4[s, P(*o*-Tol)$_3$].

*Synthesis of chloro[(2-thiouracil)(chlorodiphenyl-phosphino)]palladium(1I), **5***

Yield: 80%. Anal. calcd for $C_{16}H_{13}Cl_2N_2OPPd$ S; calcd (obs) C = 39.18(39.08), H = 2.65 (2.64), N = 5.71 (5.69), S = 6.53 (6.54); FT-IR: 1628, ν(C═N); 3064, ν(N–H); 320, ν(Pd–S); 473, ν(Pd ← N); ^{1}H NMR (DMSO-d_6): δ 8.72(H1, –NH), 5.86(d, 1H4), 5.97(d, 1H5), 7.1–7.8(m, 10H, Ph). ^{13}C NMR (DMSO-d_6): δ 172.3(C1), 165.2(C3), 106.3(C4), 158.24 (C5): ^{31}P{^{1}H} NMR ($CDCl_3$): δ 34.0(s, $PClPh_2$).

X-ray crystallography

A summary of data collection and structure refinement for [Pd_2(μ-thiouracyl)(PPh_3)$_3Cl_2$] is reported in Table 1. The crystal was mounted on a glass capillary and the crystal data were collected with a Bruker AXS Smart 1000 area detector diffractometer (Mo Kα; λ = 0.71073 Å). Cell parameters were refined from the observed setting angles and detector positions of selected strong reflections.[25] No crystal decay was observed and an absorption correction was applied using the program SADABS,[26] which gave min. and max. transmission factors of 0.729 and 0.926, respectively. The structures were solved by direct methods (SIR97)[27] and refined with full-matrix least-squares (SHELXL-97)[28] using the Wingx software package.[29] Non-hydrogen atoms were refined anisotropically and the H atoms were placed at their calculated positions. Graphical material was prepared using the program ORTEP-3 for Windows.[30]

RESULTS AND DISCUSSION

^{1}H, ^{13}C and ^{31}P NMR studies

A significant downfield shift is observed for the ^{1}H and ^{13}C NMR resonances of the complexes **1–5** when compared with the uncoordinated free 2-thiouracil, which is confirmed by the data reported for complexes of 2-mercapto-4-pyrimidone.[31]

In the ^{1}H NMR spectrum of free 2-thiouracil, the (N2-)H2 and (N6-)H6 resonances appear as singlets at 12.52 and 12.34 ppm. Both signals have disappeared in the complexes **1** and **2**. The complexation of two Pd atoms with one ligand through both N atoms is confirmed by the absence

DOI: 10.1002/aoc

of the (N6-)H6 and (N2-)H2 signals that were present in the spectrum of 2-thiouracil, whereas the (N2-)H2 singlet appears at 12.54 ppm in the one Pd atom complexes **3–5**. The (C4-)H4 and (C5-)H5 protons resonances are shifted downfield at 5.97 ppm (unresolved doublet) and 5.86 ppm (well resolved doublet) as compared with the free 2-thiouracil ($\Delta\delta = 0.026$, $^3J_{H,H} = 7.8$ Hz), respectively, in the complexes **1–5,**[32] implying a lowering of the bond order as a consequence of the thione → thiol tautomerization during complexation.[33]

During complexation, 2-thiouracil behaves as bidentate via S/N in one-Pd complexes **3–5** and as a bridging moiety coordinated to palladium via N and S/N atoms in complexes **1** and **2**. The ^{13}C NMR spectra of these complexes show a downfield shift of the C1 and C3 signal (177.97 and 176.44 ppm, respectively) of the bridging moiety as compared with the free 2-thiouracil, due to coordination of Pd(II) in complexes **1** and **2**. In the case of complexes **3–5**, the C3 signal appears at 165.53 ppm, and the C4 and C5 resonances are observed downfield at 106.20 and 161.24 ppm, respectively. The phenyl resonances of PPh_3 are observed at 129.32 (*i*), 134.46 (*o*), 132.17 (*m*) and 128.56 ppm (*p*).

The $^{31}P\{^1H\}$ room temperature NMR spectrum in $CDCl_3$ shows only a sharp singlet at 27.50 ppm for complex **1**, which does not seem in accord with the solid-state structure. This could be due to a dynamic fluxional behavior, so that all the phosphorus atoms appear as magnetically equivalent in solution and their signals, as averaged.[34] In $CDCl_3$ at −40 °C, a single resonance is observed at 27.99 ppm. The phosphorus atoms could be almost isochronous in that compound. In contrast, the spectrum of complex **2** exhibits three sharp signals at 31.85, 29.79 and 28.18 ppm, respectively, in agreement with the solid-state structure of compound **1**. Complexes **3–5** showed a single resonance at 34.0, 31.4 and 28.6 ppm, respectively, in accordance with the structures proposed.

Molecular structure

The molecular structure of $[Pd_2(\mu\text{-thiouracil})(PPh_3)_3Cl_2]$, compound **1**, is shown in Fig. 3. The complex exhibits a dinuclear structure in which the two metals present different coordination environments: Pd(1) is coordinated by a PPh_3, a chloride ion and the *N*,*S* chelating 2-thiouracyl ligand, whereas the Pd(2) is bound by two PPh_3 in *trans* position, a chloride ion and the N(2) nitrogen atom of the 2-thiouracyl molecule. The two metals adopt a square planar geometry and the dihedral angle between the two coordination planes is of 67.5(1)°. The Pd(1)–P(1) bond distance [2.231(2) Å] is significantly shorter than the Pd(2)–P(2) and Pd(2)–P(3) ones [2.329(1) and 2.307(1) Å, respectively] as a consequence of the greater *trans* influence exerted by the PPh_3 [P(1)] with respect to the N(6) atom. This is reflected also in the Pd(1)–N(6) bond distance, which is significantly longer [2.102(4) Å] than the Pd(2)–N(2) one [2.024(4) Å]. The 2-thiouracyl ligand is bridging the two metal centers through the N(2) and S(1)/N(6) atoms. This is an unprecedented mode of coordination of the thiouracyl ligand since usually it behaves as a monodentate ligand (S coordinated),[35–38] as a *N*,*S* chelate[39,40] or bridging *N*,*S* chelate.[41,42]

FT-IR studies

The FT-IR spectral data of compounds **1–5** do not show the strong absorption band at 3066 cm^{-1} due to the –N(2)–H(2) group which was present in the spectrum of the free 2-thiouracil, while the medium absorption band at 3066 cm^{-1} for the –N(6)–H(6) group in the uncomplexed 2-thiouracil has completely disappeared in complexes **1** and **2**. These results indicate the replacement of the acidic hydrogen(s) by palladium[43] and are also indicative of *N*,*S*-coordination and forming a four-membered chelate rings around the central metal through a donor atom set comprising the imine-nitrogen and thiolate sulfur, respectively, while a new absorption band due to Pd–Cl appeared at 305–321 cm^{-1}. The weak- or medium-intensity absorptions in the regions 448–473 cm^{-1} and 330–385 cm^{-1} in all complexes have been assigned to ν(Pd ← N) and ν(Pd–S) vibrations,[44,45] respectively. The replacement of triphenylphosphine in complexes **2** and **4** by tris(*o*-tolylphosphine) and in complex **5**, by chlorodiphenylphosphine, is expected to result in a greater drift of electrons from the remaining 2-mercapto-4-pyrimidone to the metal. The effect of PR_3 is also observed in some dithiocarbamate complexes.[47] The metallation is confirmed by the absence of acidic hydrogens of ν(N–H)/ν(S–H). The shifts in the ligand vibrations observed upon coordination, with respect to the free uncomplexed ligand, are similar in all complexes.

In vitro cytotoxicity screenings

The results of the *in vitro* cytoxicity tests of compounds **1–7** are given in Table 1 as the inhibition doses ID_{50} observed against a panel of seven human tumor cell lines; MCF-7 and EVSA-T, two breast cancers; WiDr, a colon cancer; IGROV, an ovarian cancer; M19 MEL, a melanoma; A248, a renal cancer;

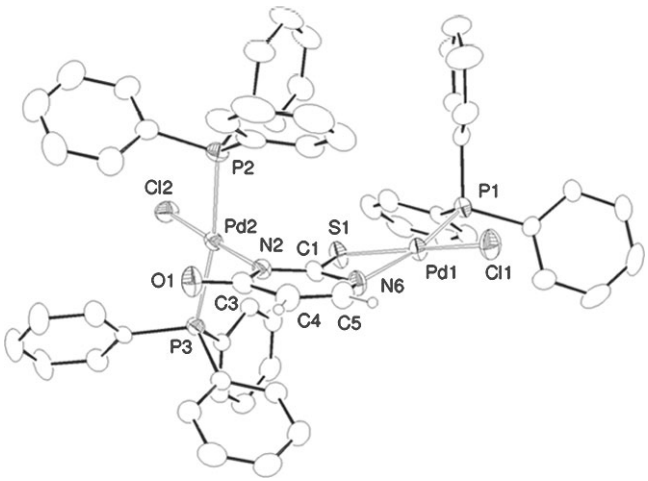

Figure 3. ORTEP diagram of the $[Pd_2(\mu\text{-thiouracil})(PPh_3)_3Cl_2]$ complex.

DOI: 10.1002/aoc

and H226, a non-small cell lung cancer. The cytotoxicity results were compared with those obtained for clinically used reference compounds like doxorubicin (DOX), cisplatin (CPT), 5-fluorouracil (5FU), methotrexate (MTX), etoposide (ETO) and taxol (TAX).

It is evident from Table 2 that the studied compounds exhibit *in vitro* cytotoxic activity in some cases comparable to those of cisplatin.

CONCLUSION

The complexes **1–5** have been synthesized and characterized by FT-IR and multinuclear NMR spectroscopy, and compound **1** also by single-crystal X-ray diffraction. Each technique suggests that the structural changes occurring in 2-thiouracil upon deprotonation and coordination to palladium take place through S, N(2) and N(6) atoms, the remaining coordination positions being occupied by a chloride ion and one or two phosphines to achieve a square planar geometry around palladium. The coordination positions have been confirmed by the novel crystal structure of [3-(chloro-bistriphenylphosphino)palladium-1-(chlorotriphenylphosphino)](μ-2-thiouracil)palladium(II), complex **1**. Such coordination Pd(II) complexes with thiouracil and organophosphine show promising *in vitro* cytotoxicity. These active compounds may serve as a starting point for further studies on anti-tumor palladium compounds.

Acknowledgments

This work was supported by Quaid-e-Azam University, Islamabad, Pakistan and National Science Foundation Islamabad, Pakistan. The *in vitro* cytotoxicity experiments were carried out by Ms P. F. van Cuijk in the Laboratory of Translational Pharmacology, Department of Medical Oncology, Erasmus Medical Center, Rotterdam, The Netherlands, under the supervision of Dr E. A. C. Wiemer and Professor G. Stoter.

Supplementary data

The crystallographic data of the compounds have been deposited with the Cambridge Crystallographic Data Centre as CCDC number 296399. Copies of the data can be obtained on request to CCDC, 12 Union Road, Cambridge CB21 EZ, UK. E-mail: deposited@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk.

REFERENCES

1. Sorenson JRJ. *Free Rad. Biol. Med.* 1992; **13**: 593.
2. Criado JJ, Lopez Aria JA, Marcias B, Fernandez Lago LR. *Inorg. Chim. Acta.* 1992; **193**: 229.
3. Duboy SK, Roy U. *Appl. Organometal. Chem.* 2003; **17**: 3.
4. Skov KA, Adomat H, Konway DC, Farrell NP. *Chem. Biol. Interact.* 1987; **62**: 117.
5. Farrell N, Gomes de Carneiro TM. *Inorg. Chim. Acta.* 1987; **126**: 137.
6. Kuduk-Jaworska J. *Wiadomosci Chemicze* 1999; **53**: 349.
7. Gradzka I, Buraczewska I, Kuduk-Jaworska J, Romaniewska A, Szumiel I. *Chem. Biol. Interact.* 2003; **146**: 165.
8. Ali H, Van Lier JE. *Chem. Rev.* 1999; **99**: 2379.
9. Wong E, Giandomenico CM. *Chem. Rev.* 1999; **99**: 2451.
10. Guo Z, Sadler PJ. *Adv. Inorg. Chem.* 2000; **49**: 183.
11. Lippert B. *Coord. Chem. Rev.* 1999; **182**: 263.
12. Landi J, Hacker MP, Farrel N. *Inorg. Chim. Acta.* 1992; **202**: 79.
13. Ling ECH, Allen GW, Hambley TW. *J. Chem. Soc., Dalton Trans.* 1993; 3705.
14. Pasini A, Alfonso GD, Manzotti C, Moret M. *Inorg. Chem.* 1994; **33**: 4140.
15. Demertzi DK, Domopoulou A, Demertizis MA, Valle G, Papageorgoiu A. *J. Inorg. Biochem.* 1997; **68**: 147.
16. Quiroga AG, Perez JM, Montero EI, West DX, Alonso C, Ranninger CN. *J. Inorg. Biochem.* 1999; **75**: 293.
17. Carbon JA, David HM, Studier H. *Science.* 1968; **161**: 1146.
18. Holly A, Votruba I, Jost K. *Coll. Czech Chem. Commun.* 1974; **39**: 634.
19. Bunger J, Stocrk J, Stalder K. *Int. Arch. Occup. Environ. Health* 1996; **69**: 33.
20. Raper ES. *Coord. Chem. Rev.* 1985; **61**: 115.
21. Belykh LB, Goremyka TV, Zinchenko SV, Rokhin AV, Ratovshii GV, Schmidt FK. *Russ. J. Coord. Chem.* 2002; **28**: 664.
22. Montoya V, Pons J, Solans X, Font-bardia M, Ros J. *Inorg. Chim. Acta.* 2005; **358**: 2312.
23. Parrin DD, Armarego WLF. *Purification of Laboratory Chemicals*, 3rd edn. Butterworth Heinemann: Oxford, 1997.
24. Kitanto Y, Kinoshita Y, Nakamura R, Ashida T. *Acta Crystallogr.* 1983; **C39**: 1015.
25. SMART (control) and SAINT (integration) software for CCD systems, Bruker AXS, Madison, WI, 1994.
26. SADABS : Area-Detector Absorption Correction. Siemens Industrial Automation, Inc.: Madison, WI, 1996.
27. Altomare A, Burla MC, Camalli M, Cascarano GL, Giacovazzo C, Guagliardi A, Moliterni GG, Polidori G, Spagna R. *J. Appl. Crystallogr.* 1999; **32**: 115.
28. Sheldrick GM. SHELX 97. *Programs for Crystal Structure Analysis*. 1997; (Release 97-2). University of Göttingen: Göttingen.
29. Farrugia LJ. *J. Appl. Crystallogr.* 1999; **32**: 837.
30. Farrugia LJ. *J. Appl. Crystallogr.* 1997; **30**: 565.
31. Sasaki S-I. *Handbook of Proton-NMR Spectra and Data*, Vol. I. Asahi Research Center: Tokyo, 1985; 129–142.
32. Casas JS, Castineriras A, Rodriguez-Arguelles MC, Sanchez A, Sordo J, Vazquez-Lopez A. Vazquez-Lopez EM. *J. Chem. Soc., Dalton Trans.* 2000; 4056.
33. Rodriguez-Arguelles MC, Sanchez A, Ferrari MB, Fava GG, Pelizzi C, Pelosi G, Albertini R, Lunghi P and Pinelli S. *J. Inorg. Biochem.* 1999; **73**: 7.
34. Crociani L, Tisato F, Refosco F, Bandoli G, Corain B. *Eur. J. Inorg. Chem.* 1998; 1655.
35. Hunt GW, Griffith EAH, Amma ELA. *Inorg. Chem.* 1976; **15**: 2993.
36. Harker CSW, Tiekink ERT, Whitehouse MW. *Inorg. Chim. Acta.* 1991; **181**: 23.
37. Darensbourg DJ, Frost BJ, Derecskei-Kovacs A, Reibenspies JH. *Inorg. Chem.* 1999; **38**: 4715.
38. Hoskins BF, Zhenrong L, Tiekink ERT. *Inorg. Chim. Acta.* 1989; **158**: 7.
39. Yamanari K, Okusako K, Kushi Y, Kaizaki S. *J. Chem. Soc., Dalton Trans.* 1992; 1621.
40. Dias AR, Duarte MT, Galvao AM, Garcia MH, Marques MM, Salema MS, Mealli C. *Polyhedron* 1995; 14675.
41. Goodgame DML, Rollins RW, Slawin AMZ, Williams DJ, Zard PW. *Inorg. Chim. Acta* 1986; **120**: 91.
42. Casas JS, Castellano EE, Garcia-Tasende MS, Sanchez A, Sordo J, Vazquez-Lopez EM, Zukerman-Schpector J. *J. Chem. Soc., Dalton Trans.* 1996; 1973.

43. Bravo J, Cordero MB, Casas JS, Castano MV, Sanchez A, Sordo J. *J. Organomet. Chem.* 1996; **513**: 63.
44. Bellamy LJ. *The Infrared Spectra of Complex Molecule*. Methuen: London, 1985; 353–358.
45. Garcia-Tojal J, Lezama L, Pizaro JL, Insausti M, Arriortua MI, Rojo T. *Polyhedron* 1999; **18**: 3703.
46. Keepers YP, Pizao PE, Peters GJ, van Ark-Otte J, Winograd B, Pinedo HM. *Eur. J. Cancer* 1991; **27**: 897.
47. Manav N, Mishra AK, Kaushik NK. *Spectrochim Acta Part A*: 2004; **60**: 3087.

DOI: 10.1002/aoc