In vitro assessment of cytotoxicity, anti-inflammatory, antifungal properties and crystal structures of metallacyclic palladium(II) complexes

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ABSTRACT

Metallacyclic palladium(II) complexes [Pd(L)(R$_3$P)Cl], L = TIQDTC (1,2,3,4-tetrahydroisoquinolinedithio-carbamate), 4MpipDTC (4-methylpipradinedithiocarbamate), MPizDTC (*N*-methylpiperazinedithio-carbamate), R$_3$P = Ph$_3$P, (*o*-tolyl)$_3$P, Ph$_2$ClP, were synthesized in a 1:1 molar metal–ligand ratio. These complexes were characterized by elemental analyses, FT-IR, multinuclear (^{1}H, ^{13}C and ^{31}P) NMR. The X-ray crystal structures of [Pd(TIQDTC)(Ph$_3$P)Cl] and [Pd(TIQDTC)((*o*-tolyl)$_3$P)Cl] show a slightly distorted square planar environment around the Pd(II) ion with S–Pd–S and P–Pd–Cl average bond angles of 74.51 and 92.41, respectively. These complexes were screened for cytotoxic, antifungal, anti-inflammatory and antibacterial activity. Some complexes exhibit a significant activity against fungi.

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1. Introduction

Metal-containing compounds offer certain advantages over purely organic compounds in drug therapy and broad applications in the field of material sciences. Metal-based sulfur-containing molecules like dithiocarbamates are currently under study as adsorbents for the preparation of gold nanoparticles, stimulated by the numerous nanotechnological possibilities for the developments of nanoscale optoelectronic devices, sensors and biosensors, corrosion resistant materials and new catalysts. The interest in the synthesis of functionalised monolayer protected metal nanoparticles is expanding with an exponential rate [1–3], also used as chemoprotectants in platinum-based chemotherapy [4]. Cisplatin is one of the most effective drugs used not only in the treatment of head and neck cancer, lung carcinoma, stomach carcinoma, testicular, ovarian, bladder, oesophageal, small and non-small cell lung [5], breast, cervical and prostate cancers but also to treat Hodgkin's and non-Hodgkin's lymphomas, neuroblastomas, sarcomas, multiple myelomas, melanomas and mesotheliomas [6,7]. However, the clinical usefulness of cisplatin has been frequently limited by its severe side effects such as nephrotoxicity (kidney damage), neurotoxicity (nervous system damage), ototoxicity (hearing loss) and myelotoxicity (bone marrow suppression) [8,9], and by the development of acquired resistance against breast and colon cancer [10]. Continuous efforts are still being made to reduce the toxicity of platinum anticancer complexes towards normal cells, circumventing acquired resistance to cisplatin and decreasing its side effects. The interest in the chemical and biochemical properties of platinum and palladium complexes with thiocarbonyl and thiol donors has been increased because sulfur-containing ligands are used as detoxicant agents against metal-containing drugs [11]. Dithiocarbamates have been used for their efficacy as inhibitors of cisplatin-induced side effects [12]. In particular, dithiocarbamates selectively remove platinum from the enzyme–thiol complexes by nucleophilic attack of the chelating sulfur atoms to the platinum moiety [13]. Moreover the selectivity protects normal tissues without inhibiting the antitumour effect [14]. Their biological as well as catalytic activities are enhanced by complexation with Pd(II) [15]. The dithiocarbamate moiety can bind (chelate) palladium by a (–S:S′–) coordination mode [11]. Several Pd dithiocarbamates complexes [Pd(ESTD)(2-pic)CL], [Pd(MSDTM)Br]$_n$ and [Pd(ESTD)CL]$_n$ are known to exhibit cytotoxic activities against HeLa, HL60, lung, ovarian melanoma, colon, renal, prostate and breast cancer cell lines [17–21,50].

During the last few years, we have been studying palladium(II) complexes with dithiocarbamates [20] and some mixed ligands

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dithicarbamate and organophosphines, such as [Pd(L)(PR$_3$)Cl] [L = DCHDTC (*N,N′*-dicyclohexyldithiocarbamate), MCyHDTC (*N*-methyl-*N*-cyclohexyldithiocarbamate); PR$_3$ = PPh$_3$, P(*o*-tolyl)$_3$, PPh$_2$Cl] [16]. The new series of palladium metallacyclic complexes with mixed tertiary phosphines/dithiocarbamate ligands described in this paper is the continuation of our previous work: we have selected the three ligands 1,2,3,4-tetrahydroisoquinolinedithiocarbamate (TIQDTC), 4-methylpiperidinedithiocarbamate (4MpipDTC) and *N*-methylpiperazinedithiocarbamate (MPizDTC) to synthesize a series of complexes, [Pd(L)(PR$_3$)Cl] (L = TIQDTC, 4MpipDTC, MPizDTC; R$_3$P = Ph$_3$P, (*o*-tolyl)$_3$P, ClPh$_2$P). We characterized these by elemental analyses, FT-IR, multinuclear (^{1}H, ^{13}C and ^{31}P) NMR and single X-ray crystallography, and screened them for cytotoxic, antifungal, anti-inflammatory and antibacterial activity.

2. Materials and instrumentation

Elemental analyses were carried out on a Fisons EA1108 CHNS-O microanalyser. Melting points were determined with a Mitamura Riken Kogyo (Japan) instrument. The FT-IR spectra of the synthesized complexes were recorded on two instruments: a Nicolet 5SXC FT-IR spectrometer, using KBr discs from 4000 to 400 cm^{-1} and a Perkin–Elmer FT-IR Nexus spectrometer by using CsI discs from 500 to 200 cm^{-1}.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer with CDCl$_3$ as a solvent and TMS as reference, operating at 300 and 75.5 MHz, respectively. ^{31}P NMR spectra were recorded on Bruker WM-300 and AM-400 spectrometers operating at 121.51 and 162.40 MHz, respectively. Spectra were run in CDCl$_3$ solution at ambient temperature and referenced to external 85% phosphoric acid with downfield shifts defined as positive.

Secondary amines such as 1,2,3,4-tetrahydroisoquinoline, 4-methylpiperidine and methylpiperazine were purchased from Aldrich (USA) and distilled before use. All reagents were of analytical grade and used without further purification. The organic solvents

were dried before use over sodium benzophenone by the standard method [22].

3. Syntheses and characterizations

3.1. Synthesis of PdCl$_2$(PR$_3$)$_2$ and of the dithiocarbamate ligands

The complexes [PdCl$_2$(PR$_3$)$_2$] (R$_3$P = Ph$_3$P, (*o*-tolyl)$_3$P, ClPh$_2$P) were prepared by a literature method [23a]. The dithiocarbamates [RDTC] (R = 1,2,3,4-tetrahydroisoquinoline (TIQH), 4-methylpiperidine (4MpipH), methylpiperazine (MPizH)) were prepared by the reactions of secondary amines with carbon disulfide at 0 °C [23b].

3.2. General synthetic procedure of Pd(II) complexes with mixed ligands

Pd(II) complexes of mixed ligands were synthesized by suspending [PdCl$_2$(PR$_3$)$_2$] (1.14 mmol) in 15 cm^3 of CH$_2$Cl$_2$ and adding to it a solution of substituted dithiocarbamate ligand (1.14 mmol) in 15 cm^3 CH$_2$Cl$_2$ in a two neck flask fitted with a reflux condenser at 40 °C. The reaction mixture was refluxed for 1 h to obtain a clear solution and then cooled down to room temperature. The solvent was removed under reduced pressure. The resultant solid was recrystallized from CH$_2$Cl$_2$/*n*-hexane (3:1) (see Scheme 1).

3.2.1. [Pd(TIQDTC)(PPh$_3$)Cl] (**1**)

[Pd(TIQDTC)(PPh$_3$)Cl] was synthesized by the method as described above and recrystallized from a mixture of dichloromethane (20 cm^3) and *n*-hexane (5 cm^3). Orange crystals were obtained after 15 days by slow evaporation at room temperature. Data (85% yield). M.P.: 301–303 °C. Anal. Calc. for C$_{28}$H$_{26}$ClNPPdS$_2$: C, 54.82; H, 4.27; N, 2.28; P, 5.05 S, 10.45; Cl, 5.78. Found: C, 54.80; H, 4.25; N, 2.30; P, 5.08; S, 10.43; Cl, 5.77%. ^{1}H NMR (CDCl$_3$): 4.28 (d, $^2J_{HH}$ = 7.6 Hz, 1H, H$_A$C(1)–N), 4.21 (d, $^2J_{HH}$ = 7.6 Hz, 1H, H$_B$C(1)–N), 3.94–4.01 (m, 4H, HC4 and HC5); 7.47–7.67 (m, 15H, Ph); ^{13}C NMR (CDCl$_3$): 208.6 (CSS–), 42.9 (C1–N), 41.9 (C5–N), 35.0 (C4–
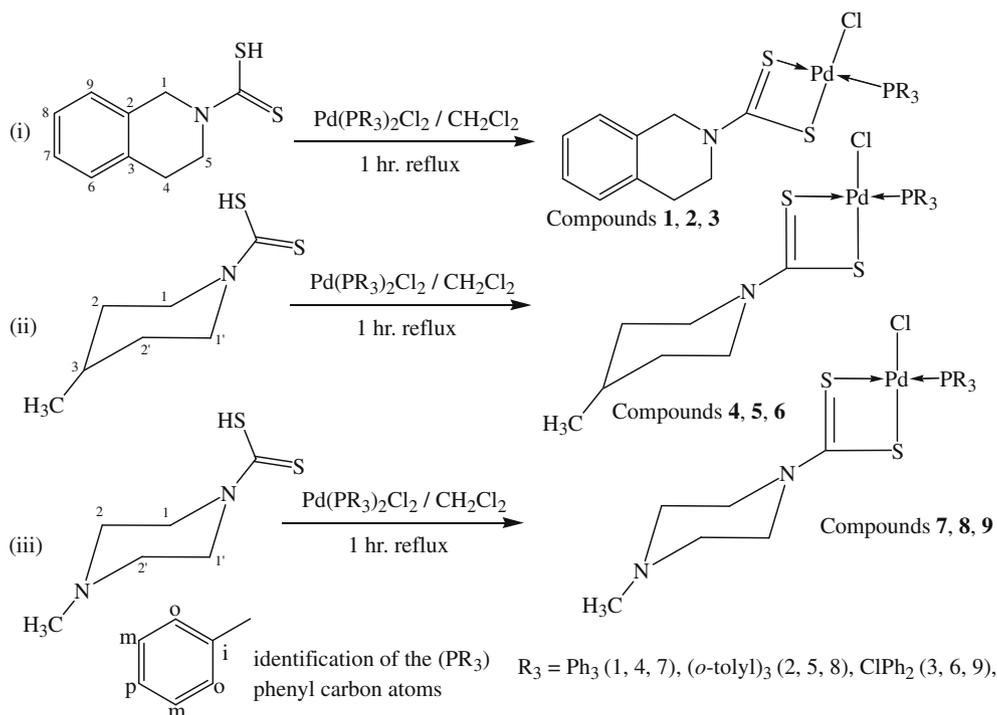
Scheme 1. General synthetic pathway of the palladium(II) complexes.

N), 142.5 (C2), 140.9 (C3), 132.8 (C6), 128.2 (C7), 129.1(C8), 138.1 (C9), 130.5 (iC, $^1J_{CP}$ = 109 Hz), 134.5 (oC, $^2J_{CP}$ = 11.5 Hz), 133.2 (mC, $^3J_{CP}$ = 14.9 Hz), 129.2 (pC, $^4J_{CP}$ = 4.5 Hz); ^{31}P NMR (CDCl$_3$): 34.1 (s).

3.2.2. [Pd(TIQDTC)(P(o-tolyl)$_3$)Cl] (2)

A suspension of [PdCl$_2$(P(o-tolyl)$_3$)$_2$] (1.14 mmol) in 20 cm^3 of CH$_2$Cl$_2$ and a solution of TIQDTC (1.14 mmol) in 15 cm^3 CH$_2$Cl$_2$ were reacted according to the above mentioned method. Orange crystals were obtained after recrystallization from a mixture of dichloromethane and n-hexane. Data: (60% yield). M.P. 293–295 °C. Anal. Calc. for C$_{31}$H$_{32}$ClNPPdS$_2$: C, 56.80; H, 4.92; N, 2.14; P, 4.72; S, 9.78; Cl, 5.41. Found: C, 56.79; H, 4.93; N, 2.13; P, 4.72; S, 9.78; Cl, 5.40%. ^{1}H NMR (CDCl$_3$): 4.31 (d, $^2J_{HH}$ = 7.6 Hz, 1H, H$_A$C(1)–N), 4.27 (d, $^2J_{HH}$ = 7.6 Hz, 1H, H$_B$C(5)–N), 2.30 (s, 9H, –CH$_3$), 7.28–7.48 (m, 12H, Ph); ^{13}C NMR (CDCl$_3$): 206.4 (CSS–), 47.3 (C1–N), 49.3 (C5–N), 38.5 (C4–N), 141.2 (C2), 139.9 (C3), 129.8 (C6), 125.1 (C7), 125.3 (C8), 134.4 (C9), 129.7 (iC, $^1J_{CP}$ = 112 Hz), 133.2 (oC, $^2J_{CP}$ = 10.5 Hz), 131.5 (mC, $^3J_{CP}$ = 12.9 Hz), 128.4 (pC, $^4J_{CP}$ = 5.5 Hz); ^{31}P NMR (CDCl$_3$): 32.3 (s).

3.2.3. [Pd(TIQDTC)(ClPh$_2$P)Cl] (3)

A suspension of [PdCl$_2$(P(Ph)$_2$Cl)$_2$] (1.14 mmol) in 20 cm^3 of methanol was reacted with a solution of TIQDTC (1.14 mmol) in 15 cm^3 acetone. By adopting the method mentioned above, a yellow crystalline product was obtained at room temperature from a mixture of CH$_2$Cl$_2$/OEt$_2$ (1:1). Data: (73% yield). M.P. 241–243 °C. Anal. Calc. for C$_{22}$H$_{21}$Cl$_2$PPdNS$_2$: C, 46.21; H, 3.70; N, 2.45; P, 5.42; S, 11.21; Cl, 12.39. Found: C, 46.21; H, 3.68; N, 2.45; P, 5.40; S, 11.20; Cl, 12.40%. ^{1}H NMR (CDCl$_3$): 4.33 (d, $^2J_{HH}$ = 7.8 Hz, 1H, H$_A$C(1)–N), 4.27 (d, $^2J_{HH}$ = 7.6 Hz, 1H, H$_B$C(5)–N), 7.52–7.61 (m, 10H, Ph); ^{13}C NMR (CDCl$_3$): 206.5 (CSS–), 59.3 ((H$_2$C)$_2$–N); 208.6 (CSS–), 53.9 (C1–N), 59.9 (C5–N), 30.9 (C4–N), 136.2 (C2), 131.9 (C3), 129.8 (C6), 127.1 (C7), 128.3(C8), 130.0 (C9), 129.6 (iC, $^1J_{CP}$ = 120 Hz), 132.0 (oC, $^2J_{CP}$ = 16.5 Hz), 130.5 (mC, $^3J_{CP}$ = 18.5 Hz), 128.3 (pC, $^4J_{CP}$ = 6.5 Hz); ^{31}P NMR (CDCl$_3$): 33.7(s).

3.2.4. [Pd(4MpipDTC)(PPh$_3$)Cl] (4)

A complex prepared by above mentioned method. An orange crystalline product was obtained at room temperature from a mixture of CH$_2$Cl$_2$/n-hexane (3:1). Data: (81% yield). M.P. 238–240 °C (decomposed). Anal. Calc. for C$_{25}$H$_{27}$NClPPdNS$_2$: C, 50.68; H, 4.59; N, 4.73; P, 5.23; S, 10.82; Cl, 5.98. Found: C, 50.67; H, 4.57; N, 4.72; P, 5.22; S, 10.83; Cl, 5.97%. ^{1}H NMR (CDCl$_3$): 3.93–4.36 (m, 4H, H$_2$C(1,1')–N); 0.92–2.35 (m, 5H, H$_2$C(2,2',3), 7.52–7.54 (m, 15H, Ph), ^{13}C NMR (CDCl$_3$): 207.8 (CSS–), 49.9 (C1–N), 35.0 (C2–N), 29.5 (C3–N), 130.6 (iC, $^1J_{CP}$ = 110.5 Hz), 133.4 (oC, $^2J_{CP}$ = 15.5 Hz),135.0 (mC, $^3J_{CP}$ = 18.7 Hz), 129.3 (pC, $^4J_{CP}$ = 6.3 Hz); ^{31}P NMR (CDCl$_3$): 38.2 (s).

3.2.5. [Pd(4MpipDTC))(P(o-tolyl)$_3$)Cl] (5)

Data: (78% yield). M.P. 293–295 °C. Anal. Calc. for C$_{28}$H$_{33}$ClPPdN$_2$: C, 54.20; H, 5.36; N, 2.26; P, 4.99; S, 10.33; Cl, 5.71. Found: C, 54.21; H, 5.35; N, 2.25; P, 4.98; S, 10.34; Cl, 5.71%. ^{1}H NMR (CDCl$_3$): 3.97–4.48 (m, 4H, H$_2$C(1,1')–N), 0.98–2.05 (m, 5H, H$_2$C(2,2',3)–), 7.52–7.54 (m, 12H, Ph), ^{13}C NMR (CDCl$_3$): 207.3 (CSS–), 51.2 (C1–N), 30.1 (C2–N), 34.5 (C3–N), 129.5 (iC, $^1J_{CP}$ = 114.0 Hz), 134.0 (oC, $^2J_{CP}$ = 13.5 Hz), 132.5 (mC, $^3J_{CP}$ = 17.9 Hz), 127.7 (pC, $^4J_{CP}$ = 4.9 Hz); ^{31}P NMR (CDCl$_3$): 38.9 (s).

3.2.6. [Pd(4MpipDTC)(ClPh$_2$P)Cl] (6)

Data: (80% yield). M.P. 281–284 °C (decomposed). Anal. Calc. for C$_{19}$H$_{22}$Cl$_2$PPdNS$_2$: C, 42.51; H, 4.13; N, 2.61; P, 5.77; S, 11.94; Cl, 13.21. Found: C, 42.52; H, 4.12; N, 2.61; P, 5.76; S, 11.93; Cl, 13.20%. ^{1}H NMR (CDCl$_3$): 3.99–4.46 (m, 4H, H$_2$C(1,1')–N), 0.90–2.25 (m, 5H, H$_2$C(2,2',3)–), 7.31–7.54 (m, 10H, Ph), ^{13}C NMR

(CDCl$_3$): 207.2 (CSS–), 50.6 (C1–N), 29.7 (C2–N), 35.2 (C3–N), 129.6 (iC, $^1J_{CP}$ = 121.0 Hz), 132.0 (oC, $^2J_{CP}$ = 19.5 Hz), 130.5 (mC, $^3J_{CP}$ = 19.9 Hz), 128.3 (pC, $^4J_{CP}$ = 7.5 Hz); ^{31}P NMR (CDCl$_3$): 41.2(s).

3.2.7. [Pd(MPizDTC)(PPh$_3$)Cl] (7)

The complex [Pd(MCHDTC)(PPh$_3$)Cl] was synthesized by the method described above. Data: (85% yield). M.P. 341–343 °C. Anal. Calc. for C$_{24}$H$_{26}$ClN$_2$PPdS$_2$: C, 49.75; H, 4.52; N, 4.83; P, 5.35; S, 11.07; Cl, 6.12. Found: C, 49.74; H, 4.52; N, 4.82; P, 5.33; S, 11.08; Cl, 6.11%. ^{1}H NMR (CDCl$_3$): 3.96–4.10 (m, 8H, H$_2$C (1,1',2,2')-N), 2.20, s (s, 3H, –CH$_3$), 7.09–7.21 (m, 15H, Ph), ^{13}C NMR (CDCl$_3$): 209.3 (CSS–), 58.9 (C1–N), 56.9 (C2–N), 32.2 (CH$_3$), 125.5 (iC, $^1J_{CP}$ = 111.0 Hz), 129.3 (oC, $^2J_{CP}$ = 12.5 Hz), 127.5 (mC, $^3J_{CP}$ = 15.6 Hz), 124.5 (pC, $^4J_{CP}$ = 5.5 Hz); ^{31}P NMR (CDCl$_3$): 28.8 (s).

3.2.8. [Pd(MPizDTC)(P(o-tolyl)$_3$)Cl] (8)

The complex [Pd(MPizDTC)(P(o-tolyl)$_3$)Cl] was synthesized by adopting the above method. Data: (89% yield). M.P. 323–325 °C. Anal. Calc. for C$_{27}$H$_{32}$ClN$_2$PPdS$_2$: C, 52.18; H, 5.19; N, 4.51; P, 4.98; S, 10.32; Cl, 5.70. Found: C, 52.17; H, 5.15; N, 4.53; P, 4.96; S, 10.31; Cl, 5.69%. ^{1}H NMR (CDCl$_3$): 3.93–4.09 (m, 8H, H$_2$C((1,1',2,2')–N), 2.25 (s, 12H, –CH$_3$), 7.08–7.16 (m, 12H, Ph), ^{13}C NMR (CDCl$_3$): 207.2 (CSS–), 63.0 (C1–N), 59.0 (C2–N), 29.8 (CH$_3$), 124.2 (iC, $^1J_{CP}$ = 114.2 Hz), 129.2 (oC, $^2J_{CP}$ = 13.5 Hz), 127.3 (mC, $^3J_{CP}$ = 16.5 Hz), 123.3 (pC, $^4J_{CP}$ = 6.2 Hz); ^{31}P NMR (CDCl$_3$): 31.2 (s).

3.2.9. [Pd (MPizDTC)(ClPh$_2$P)Cl] (9)

[Pd(MPizDTC)(PPh$_2$Cl)Cl] was also prepared as described above. Data: (85% yield). M.P. 265–267 °C. Anal. Calc. for C$_{18}$H$_{21}$Cl$_2$N$_2$PPdS$_2$: C, 40.20; H, 3.94; N, 5.21; P, 5.76; S, 11.92; Cl, 13.18. Found: C, 40.19; H, 3.92; N, 5.23; P, 5.75; S, 11.91; Cl, 13.16%. ^{1}H NMR (CDCl$_3$): 3.99–4.04 (m, 8H, H$_2$C(1,1',2,2')–N), 2.23 (s, 3H, –CH$_3$), 7.31–7.39 (m, 10H, Ph), ^{13}C NMR (CDCl$_3$): 206.5 (CSS–), 58.6 (C1–N), 55.6 (C2–N), 31.5 (CH$_3$), 129.5 (iC, $^1J_{CP}$ = 119.5 Hz), 134.2 (oC, $^2J_{CP}$ = 15.5 Hz), 132.6 (mC, $^3J_{CP}$ = 18.5 Hz), 127.5 (pC, $^4J_{CP}$ = 7.2 Hz); ^{31}P NMR (CDCl$_3$): 29.4 (s).

3.3. X-ray structure determination

3.3.1. X-ray structure determination of compound 1

An orange X-ray quality crystal of compound **1** was selected with a dimension 0.30 × 0.20 × 0.05 mm and single crystal diffraction data was collected on an Oxford Xcalibur CCD area detector diffractometer, using graphite monochromatic Mo Kα = 0.71069 Å radiation. Reflection data was collected by using limits −15 ⩽ h ⩽ 17, −9 ⩽ k ⩽ 10, −18 ⩽ l ⩽ 11, out of 7866 reflections 3099 were considered observed with I > 2σ(I). Data reduction and absorption correction were performed using CrysAlisPro 171.29.9 (Oxford Diffraction). The structure was solved by direct methods using SIR2004 [24], refined by full-matrix least-squares using SHELX-97 and hydrogen atoms were generated in calculated position using SHELX-97 [25].

3.3.2. X-ray structure determination of compound 2

A prism shaped orange single crystal of compound **2**, (0.45 × 0.30 × 0.30 mm) was mounted on a Philips PW 1000 diffractometer, equipped with graphite monochromator and Mo Kα radiation. Unit cell dimensions were obtained by a least-square refinement of the setting angles of 24 randomly distributed and carefully centred reflections (6.00 < 2θ < 18.00). Empirical absorption correction was applied using the local program based on Walker and Stuart [26]. The structure was solved by direct method by SIR97 [27] and refined by SHELXL-97, Full-matrix least-squares on F^2 method [23]. All the calculations were performed using the WinGX System, Ver 1.61. [28]: molecular graphics: ORTEP-3 for

Windows [29] The choice of space group $P2_1/n$ involves a structural disorder of the phenyl rings, the Pd(phen) moiety being located on a symmetry mirror, cell refinement, data reduction calculations were carried out by using local programs; Reflection data collected by using index limits $-12 \leqslant h \leqslant 12, -1 \leqslant k \leqslant 28, 0 \leqslant l \leqslant 17$, refinement of non-H atoms was done anisotropically.

4. Biological assays

4.1. Antibacterial assays

The antibacterial activity of all the synthesized metal complexes has been investigated against six strains of bacteria (*Escherichia coli, Bacillus subtilis, Shigella flexenari, Staphylococcus aureus, Samonella typhi, Pseudomonas aeruginosa* by the agar well diffusion method [30,31]. Imipenum was used as standard antibiotic. Three milligrams of the complexes were dissolved in 1 mL of DMSO. Centrifuged pellets of bacteria from a 24 h old culture containing approximately 10^4–10^6 colony forming unit (CFU) per ml were spread on the surface of Muller Hinton Agar (MHA) plates. Wells were created in the medium with the help of a sterile metallic borer and nutrients agar medium were prepared by suspending nutrient agar (Merck) (20 g/l) of distilled water (pH 7.0), autoclaved and cooled down to 45 °C. Then it was seeded with 10 ml of prepared inocula to have 10^6 CFU/ml. Petri plates were prepared by pouring 75 ml of seeded nutrients agar. Experimental plates were incubated for 24 h and zones of inhibition (%) were measured and compared with standard antibiotic Imipenum with zone inhibition of 20 and 22 mm, respectively [32,33]. The results are shown in Table 5.

4.2. Antifungal assay

The agar tube dilution method [34a,34b] was used for the determination of the antifungal activity of compound with some modifications. The compounds were solubilized in dimethylsulfoxide and a dilution was performed in Sabouraud dextrose agar (SDA) (Merck) medium. Media with acidic pH (pH 5.5–5.6) containing relatively a high concentration of glucose (40%) were prepared by mixing (SDA) 6.5 g/mL distilled water. The contents were dissolved and dispensed as 4 mL volumes into screw-capped tubes and autoclaved at 121 °C for 20 min. Tubes were allowed to cool down to 50 °C and the non-solidified SDA is loaded with 67 μL of compound pipette out from the stock solution. This gave the final concentration of 200 μg/mL of the compound in media. Tubes were allowed to solidify in slanting position at room temperature and prepared in triplicate for each fungus species. Other media supplemented with dimethylsulfoxide and reference antifungal drugs were used as negative and positive control, respectively. Each tube was inoculated with 4 mm diameter piece of inoculums, removed from a seven days old culture of fungus. The tubes were incubated at 28 °C for 7 days. Cultures were examined twice weekly during the incubation. The growth in the media was determined by measuring the linear growth (mm) and the growth inhibition was calculated with reference to the negative control. A growth control of the test strains and a susceptibility standard test using Terbinafine 200 μg/ml as the reference system were performed applying the same technique.

4.3. Anti-inflammatory activity

4.3.1. Test samples

Adult male Sprague–Dawley rats (180–230 g) were used in all the experiments. The animals were housed under optimum conditions of light and temperature (12 h light and dark cycle and 22–38 °C), with food and water provided *ad libitum*. The animals were divided into eleven groups (1 control, 1 standard and 9 test). Test samples were suspended in 0.75% sodium carboxymethylcellulose (CMC) and were given orally to the test animals. The animals of the control group received the same experimental handling except that the drug treatment was replaced with appropriate volumes of the dosing vehicle. Nine groups of three animals each received one compounds i.e. 25 mg/kg. The standard drug declofenac potassium 10 mg/5 ml was used as reference drug.

4.3.2. Carrageenan-induced hind paw oedema test

The rat paw oedema was induced by subcutaneous injection of 0.1% carrageenan (50 μl) into the sub plantar region of each animal left hind paw [35]. The measurement of paw volumes was carried out by the plythesmographic method [36]. It was done by recording the rat paw volume before the carrageenan injection at 0 h and then at 1 h intervals for 4 h. Nine groups of three animals were given compounds **1**–**9** (25 mg/kg), each group given one compound. The standard drug declofenac potassium 10 mg/5 ml was used as a positive control. The negative control group received 0.75% sodium CMC, one hour before receiving carrageenan injection. The percentage oedema inhibition was calculated for each animal group in comparison with its control treated group.

4.4. Cytotoxicity of compound **5** against seven human tumour cell lines

The cytotoxicity of compound **5** was tested *in vitro* by applying seven well characterized human tumour cell lines [MCF-7 and EVSA-T (breast cancers), WIDR (colon cancer), IGROV (ovarian cancer), M19 MEL (melanoma), A498 (renal cancer), H226 (non-small cell lung cancer)] and the microculture sulforhodamine B (SRB) test of which the protocol was described elsewhere [21a].

Cell lines WIDR, M19 MEL, A498, IGROV and H226 belong to the currently used anticancer screening panel of the National Cancer Institute, USA.

The cell line EVSA-T is (ER)-/(PgR)- and the MCF-7 cell line is estrogen receptor (ER)+/ progesterone receptor (PgR)+.

The variability of the *in vitro* cytotoxicity test depends on i.a. the cell lines used and the serum applied. 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.

5. Discussion

5.1. Molecular structure determination

In the asymmetric unit of [Pd(TIQDTC)((PPh$_3$)Cl], compound **1**, the central Pd atom is coordinated with chloride and two molecules dithiocarbamate and triphenylphosphine. The dithiocarbamate acts as a bidentate chelate coordinating to Pd via both S atoms, and is disordered in two positions related to the bond distances between sulfur and palladium, S1–Pd1 = 2.2865(10), S2–Pd1 = 2.3462(9), the deviation of the Pd1 atom from the mean plane through the ligand donor atoms is only 0.060(4) Å. The bond distances in the S1–C28 = S2 chain indicate the greater delocalization of electron, S1–C28 = 1.731(3) Å, C28–S2 = 1.710(4) Å. The dithiocarbamate fragment S1–C28–S2 is essentially planar, the maximum deviation being 0.401 Å for N1 and 0.021 Å for the sulfur atoms. Because of these deviations the molecule exhibits a slightly distorted square planar geometry shown in Fig. 1. The average torsion angle deviations of the dithiocarbamate fragment and coordinated phosphine with the phenyl group are $-0.07°$ and $-1.11°$, respectively. This is the result of steric hindrance of bulky
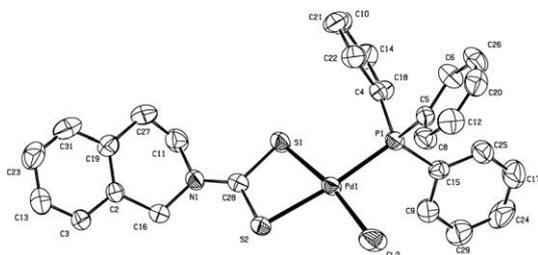
Fig. 1. ORTEP diagram of [Pd(TIQDTC)(PPh$_3$)Cl].

Scheme 2. Dithiocarbamate disordered at a local plane of symmetry.

dithiocarbamate and triphenylphosphine groups, which also effect on the geometry of the compounds.

Selected bonds orders and angles of compound **1** between Pd1–P1 = 2.2936(9) Å, Pd1–Cl2 = 2.2936(9) Å, Pd1–S1 = 2.2865(10) Å, Pd1–S2 = 2.3462(9) Å, N1–C28 = 1.314(4) Å, bonds angle: S1–Pd1–P1 = 95.37(4)°, S1–Pd1–Cl2 = 169.72(3)°, P1–Pd1–Cl2 = 94.72(4)°, S1–Pd1–S2 =75.29(3)°, P1–Pd1–S2 = 170.08(3)°.

5.2. Molecular structure of compound 2

The molecular structure of [Pd(TIQDTC)((o-tolyl)$_3$P)Cl] compound **2**, is shown in Fig. 2. The geometry around the Pd(II) centre is a slightly distorted square planar geometry, with the metal coordinated by the S,S-chelating bidentate dithiocarbamate, a chloride and a tris(o-tolyl)phosphine. The dithiocarbamate is disordered in two positions related by a local plane of symmetry with site occupancy factor of 0.66 and 0.44, respectively, see Scheme 2.

Selected bond orders and angles of compound **2** between S11–Pd = 2.3636(11) Å, S21–Pd = 2.2933(11) Å, Pd–P1 = 2.3085(10) Å, Pd–Cl = 2.3282(11) Å, N15–C25 = 1.491(17), C11–N11 = 1.315(13) Å, bonds angles: P1–Pd–S21 = 97.46, P1–Pd–S11 = 171.55(3), S21–Pd–S11 = 74.71, P1–Pd–Cl = 92.43(4), S21–Pd–P1 = 97.46(4), S21–Pd–Cl = 169.16 (3), S11–Pd–Cl = 95.15 (4) (see Table 1).

5.3. Infrared study

FT-IR spectroscopy has been used mainly to understand the geometry of the molecule by hunting out the band that belongs to the different types of metal–ligand coordinations. The most significant bands of all the synthesized complexes are listed in Table 2. The dithiocarbamate compounds exhibit a characteristic band in the range (1580–1425) cm^{-1} assignable to the v(C–N) [37]. The absence of v(S–H) vibrations, (which were observed in the parent dithiocarbamates in the range of 2734–2664 cm^{-1}) in the synthe-

Table 1
Crystal data and structure refinement for compounds **1** and **2**.

	Compound **1**	Compound **2**
Empirical formula	C$_{28}$H$_{25}$ClNPPdS$_2$	C$_{31}$H$_{31}$ClNPPdS$_2$
Formula weight	613.44	654.51
Temperature (K)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	P2(1)/c	P2$_1$/n
Unit cell dimensions		
a (Å)	15.903	9.810(3)
b (Å)	22.233(2)	22.336(8)
c (Å)	13.836(2)	13.867(5)
α (°)	90.00	90
β (°)	108.07(2)	103.49(2)
γ (°)	90.00	90
V (Å^3)	2649.4 (8)	2954.7(18)
Z	4	4
Density (calculated) (Mg/m^3)	1.538	1.471
Absorption coefficient (mm^{-1})	1.037	0.935
F(0 0 0)	1244	1336
Crystal size (mm^3)	0.30 × 0.20 × 0.05	0.45 × 0.30 × 0.30
Theta range for data collection (°)	0.814–23.26	3.02–27.00
Index ranges	$-15 \leqslant h \leqslant 17$, $-9 \leqslant k \leqslant 10$, $-18 \leqslant l \leqslant 11$,	$-12 \leqslant h \leqslant 12$, $-1 \leqslant k \leqslant 28$, $0 \leqslant l \leqslant 17$
Reflections collected	3099	
Independent reflections [R$_{(int)}$]	3099 [0.0220]	6998/6433 [0.0319]
Reflections [$I > 2\sigma(I)$]	2568	
Completeness to theta = 23.26°	99.9%	99.7%
Absorption correction	Empirical	Empirical
Maximum and minimum transmission	1.000 and 0.945	1.000 and 0.945
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	3099/0/407	6433/5/404
Goodness-of-fit (GOF) on F^2	1.029	1.013
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0238, wR2 = 0.0493	R1 = 0.0379, wR2 = 0.0889
R indices (all data)	R1 = 0.0353, wR2 = 0.0539	R1 = 0.0632, wR2 = 0.0982
Largest difference in peak and hole (e Å^{-3})	0.395 and −0.252	0.512 and −1.040

Fig. 2. ORTEP diagram of [Pd(TIQDTC)((o-tolyl)$_3$P)Cl] molecule.

Table 2
Principal FT-IR Spectral data (cm^{-1}) of [(*L) Pd (PR$_3$)Cl] complexes by using KBr pellets.

Complexes	IR (v, cm^{-1})			
	v(C–N)	v(CSS)sy	v(Pd–Cl)	v(Pd–S)
Compound 1	1436 s	1026 m	303 m	358 m
Compound 2	1475 s	1034 m	298 m	382 m
Compound 3	1470 s	1055 w	330 w	392 w
Compound 4	1498 s	1092 m	311 s	372 m
Compound 5	1483 s	1075 br	316 m	377 m
Compound 6	1431 s	1066 br	312 s	374 m
Compound 7	1461 s	1020 w	299 w	379 w
Compound 8	1467 s	1037 m	315 m	349 m
Compound 9	1486 s	1021 m	323 m	368 m

s = sharp, m = medium, w = weak, br = broad; R$_3$P = Ph$_3$P, (o-tolyl)$_3$P, ClPh$_2$P.
*L = 1,2,3,4-tetrahydroisoquinolinedithiocarbamate, 4-methylpiperidinedithiocarbamate, methylpiperazinedithiocarbamate.

sized complexes indicate that the S–H proton is replaced by a metal ion. The C–N and C–S stretching frequencies can be used to differentiate between mono- and bidentate modes of binding of dithiocarbamate ligands [38]. The position of the v(C–N) absorption is at 1446–1435 cm^{-1} in the free ligands and complexes. In the complexes showing an S–S chelate to metal coordination, the v(C–N) stretching frequencies are shifted to higher frequency by about $\sim$40 cm^{-1} on coordination with palladium. The v(C–N) stretching vibration appears in the region 1475–1486 cm^{-1} for both ligands and its complexes, which indicates the non-involvement of C–N bond in the formation of the metal complexes due to hindrance of sulfur atoms and owing to the increased double bond character in the CS group, caused by electron delocalization towards the metal centre [39,40]. In the case of a single coordination with the thiocarbonyl sulfur, the shift is approximately 10–20 cm^{-1} [41]. This suggests that the C–N bonds in the complexes have some partial double bond character. Partial double bond character for the C–N bond would result in some partial double bond character for the C–S bonds [41,42]. Further evidence of dithiocarbamate-metal coordination can be deduced from the presence of only one band in the region 1053–900 cm^{-1} that is assumed to indicate a completely symmetrically bonding of the dithiocarbamate ligand, acting in a bidentate fashion, while a split band is indicative of an unsymmetrically bound bidentate ligand [39,43]. This single band observed in the 1053–900 cm^{-1} region which is characteristic of CS$_2$ group vibrations due to sulfur chelation attributed the band of v_{asym} CSS and v_{sym} CSS at 1023 cm^{-1} and 973 cm^{-1} [44]. A characteristic band of the PPh$_3$ ligand was observed around 1448 cm^{-1} and assigned to the symmetric and asymmetric stretching and bending of P–Ph bonds [45].

In the complexes reported in this paper, the presence of only one band in the region of 1053–940 cm^{-1}, the v(CSS) mode, suggests a symmetrical behaviour of the bidentate dithiocarbamate moiety. According to the literature [42,46,47], for complexes, the Δv values v(CSS)$_{asym}$–v(CSS)$_{sym}$ are 125–139 cm^{-1}, indicating that the sulfur atoms of the dithiocarbamate group are linked to the central metal atom in a bidentate fashion. A new Pd–S band appeared in the region of 400–300 cm^{-1} after complexation [48].

5.4. NMR study

Generally, the absence of S–H protons and a slight downfield shift of the protons in the NMR spectra of all complexes were observed, which indicates that the ligands are coordinated to palladium through sulfur atoms [49]. The mode of coordination has also been confirmed by single crystal X-ray diffraction. In the ^{1}H NMR spectra of the synthesized [Pd(TIQDTC)(R$_3$P)Cl] complexes **1–3** recorded in CDCl$_3$, the broad signal of the methylene protons of (CH$_2$)$_2$N at C4/C5 moiety appeared at 3.94–4.01 ppm exhibit downfield shifts. These signals for the N–CH$_2$ methylene protons of (CH$_2$)$_2$N originated from the different position (*syn* or *anti*) with respect to the thiocarbonyl group in the square planar molecule, the separation being larger than in the free dithiocarbamic acids due to coordination and barrier of rotation about the C–N bond [50], which makes the nitrogen substituents magnetically non-equivalent [50]. The N–CH$_2$ protons at C1 are non-equivalent and appear as two doublets at 4.28 ($\Delta\delta$ = 0.03 ppm, $^2J_{HH}$ = 7.6 Hz) and at 4.21 ppm ($\Delta\delta$ = 0.03 ppm, $^2J_{HH}$ = 7.6 Hz). A similar behaviour for N–CH$_2$ is observed in the complexes **2** and **3**. One signal is present in the spectrum of complex **2** for the methyl proton of (*o*-tolyl)P at 1.97 ppm. The proton resonances of the phenyl group of the tertiary phosphines of all compounds appear as complex patterns in the range δ = 7.28–7.67 ppm. In the complexes **4–6**, the methylene protons (H, 2, 2′, 3) belonging to the –CH$_2$/CH moiety exhibit downfield shifts in the range of δ = 0.92–2.35 ppm and two signals appeared around δ = 3.93–4.36 ppm for the

H$_2$C(1,1′)–N methylene protons. For the complexes **7–9**, the resonances of the methylene protons N–(CH$_2$)$_2$ near to the thiocarbonyl will show a slight downfield shift in the range of δ = 3.61–4.07 ppm rather than (CH$_2$)$_2$N methylene proton. The signal of methyl proton (singlet) CH$_3$–N appears at 2.20–2.25 ppm in the complexes **7–9**. The proton resonances of the phenyl group of the tertiary phosphine of all compounds appear as complex patterns in the range 7.05–7.67 ppm.

The ^{13}C{^{1}H} NMR spectra of all the complexes were recorded for CDCl$_3$ solutions. The resonance of the –CSS carbon was observed around 206.4–209.3 ppm, the number of signals found corresponds with the presence of magnetically non-equivalent carbon atoms, that were assigned by comparison with literature values [51]. The resonance of the C≡S carbon at δ (189.6–195.3 ppm) in the free dithiocarbamic acids. The significant downfield shift in the thiocarbonyl carbon can be due to a strong deshielding effect after complexation. Moreover, a significant downfield shift was observed for the C–N carbons. The downfield shift is consistent with an increase in the double bond character of the C–N bond. The other resonances were only slightly shifted.

The ^{31}P NMR spectra of the complexes **1–9** were run in CDCl$_3$ solutions at ambient temperature and are referenced to external standard 85% phosphoric acid with downfield shifts defined as positive. According to the ^{31}P NMR spectra, the tertiary phosphines are symmetrically bounded to the central palladium atom and exhibit a low-field resonance due to the trans-influence of S-bonded to dithiocarbamate ligand and interaction with palladium(II), while a high-field resonance is generally observed for the free phospho-

Table 3
Antifungal activity of palladium(II) complexes. Terbinafine, used as control, inhibited all fungi at 200 µg/ml.

Compounds	Growth effect% inhibition (fungi)				
	F. moniliformes	*F. solani*	*Mucor sp.*	*A. niger*	*A. fumigatus*
Compound **1**	69	48	20	53	33
Compound **2**	77	29	19	40	45
Compound **3**	66	33	9	59	39
Compound **4**	30	78	41	10	43
Compound **5**	31	69	39	09	59
Compound **6**	27	62	49	05	43
Compound **7**	63	45	11	68	54
Compound **8**	78	50	23	42	52
Compound **9**	59	59	20	61	49
Linear length in −ve control	45	25	100	90	39

−ve Control group with 0.75% CMC (carboxymethylcellulose) sodium.

Table 4
Anti-inflammatory activity of palladium(II) compounds of [Pd^{II}(*L)(R$_3$P)Cl] on carrageenan induced rat paw oedema.

Sample name	% Oedema inhibition at time (h)			
	First hour	Second hour	Third hour	Fourth hour
Standard drug	2.32 ± 4.52	3.49 ± 4.32	68.70 ± 3.05	74.14 ± 2.72
Compound **1**	28.71 ± 2.34	35.91 ± 4.06	55.19 ± 20.78	70.41 ± 6.35
Compound **2**	18.45 ± 3.78	38.15 ± 3.65	72.65 ± 2.99	88.68 ± 1.08
Compound **3**	29.84 ± 3.51	46.28 ± 6.13	79.57 ± 2.84	93.87 ± 2.35
Compound **4**	18.51 ± 2.51	49.7 ± 6.23	65.33 ± 2.12	87.46 ± 3.53
Compound **5**	15.84 ± 2.23	25.99 ± 6.32	58.66 ± 1.72	97.46 ± 2.25
Compound **6**	27.73 ± 3.23	55.38 ± 4.32	89.47 ± 1.52	92.48 ± 1.25
Compound **7**	25.51 ± 1.51	39.7 ± 6.13	55.33 ± 3.12	89.46 ± 3.53
Compound **8**	23.84 ± 3.23	35.99 ± 5.32	78.66 ± 2.72	95.46 ± 2.25
Compound **9**	25.73 ± 4.23	45.38 ± 5.32	79.47 ± 2.52	94.48 ± 2.25

Values are mean ± SEM; n = 3 in each group. *L = 1,2,3,4-tetrahydroisoquinolinedithiocarbamate, methylpiperazinedithiocarbamate; R$_3$P = Ph$_3$P, (*o*-tolyl)$_3$P, ClPh$_2$P.

Table 5
Antibacterial activity of the [Pd^{II}(L)(R$_3$P)Cl]complexes: zones of inhibition (in%).

Name of bacteria	% Zone of inhibition of samples (mm)									% Zone of inhibition of std drug (mm)
	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5	Compound 6	Compound 7	Compound 8	Compound 9	
Escherichia coli	30	25	26	30	31	27	29	28	24	33
Bacillus subtilis	19	20	18	10	14	21	19	14	22	30
Shigella flexenari	09	11	07	14	09	14	15	05	13	35
S. aureus[a]	24	27	23	10	18	10	29	28	20	43
Samonella typhi	23	21	18	17	09	16	39	20	33	25
P. aeruginosa[b]	30	18	29	09	09	13	26	22	31	40

Concentration of the standard drug ("Imipenum") = 10 μg/disc. Concentration of sample = 3 mg/mL, (–) no activity.

[a] S = *Staphylococcus*.
[b] P = *Pseudomonas*.

rus ligand [52]. The ^{31}P NMR spectra of all complexes displayed a singlet at δ 29.4–31.8 ppm.

5.5. Biological assays

5.5.1. Antifungal activity
The results of antifungal assay given in Table 3 show that the compounds 1–9 possess antifungal activity against the following five fungi *Fusarium moniliformes*, *Fusarium saolani*, *Mucor* sp., *Aspergillus niger*, *Aspergillus fumigatus*. At the concentration of 200 μg/ml compounds 1–9 inhibited the growth of *F. moniliformes* from 78% to 60%, respectively. The compounds show minimum activity against the *Mucor* sp. i.e. 09–23%. The inhibition growth of all compounds against *F. moniliformes* is maximum, while, against *Mucor* sp., the activity of all compounds is not significant; the compounds showed a moderate activity against *A. niger*, *A. fumigatus*. The rank-order of growth effect of % inhibition of fungi is *F. moniliformes* > *F. saolani* > *A. fumigatus* ≈ *A. niger* > *Mucor* sp. which clearly indicates that palladium(II) complexes are significantly active against these fungi.

5.5.2. Anti-inflammatory activity
The *in vitro* pharmacological assessment of compounds 1–9 (see table 4) exhibit a significant inhibition of cyclooxygenase (COX-1 and COX-2) enzyme relative to other NSAIDs, the injection of carrageenan induces the liberation of bradykinin, which later induces the biosynthesis of prostaglandin and other autacoids, which are responsible for the formation of the inflammatory exudates [53]. The constitutive isoform of COX, COX-1 has clear physiological functions and inducible isoform COX-2 was discovered few years ago, and induced in a number of cells by pro-inflammatory stimuli. The carrageenan-induced oedema tests involving both COX-1 and COX-2 activities [54], it is not as clear whether the complexes of palladium(II) with dithiocarbamate/tertiary phosphine acts by inhibiting COX-1 alone or by inhibiting both COX-1 and COX-2. Therefore, it is suggested that the mechanism of action of synthesized compounds may be related to the anti-inflammatory mechanism of declofenac potassium in the inhibition of the inflammatory process by carrageenan [55].

5.5.3. Antibacterial activity
Metal dithiocarbamates are capable of inhibiting bacterial growth and activity by interfering with the metabolic processes in the bacteria. In the present work, we have synthesized Pd(II) complexes with mixed ligands dithiocarbamate/organophosphine. The antibacterial activity of the Pd(II) complexes have been determined against six strains of bacteria: *E. coli*, *B. subtilis*, *S. flexenari*, *S. aureus*, *S. typhi*, *P. aeruginosa*.

The results are given in Table 5. Significant antibacterial activities were observed when compared to a standard drug "Imipen-

Table 6
Inhibition doses ID$_{50}$ *in vitro* cytotoxicities of compound 5 and of six reference compounds doxorubicin (DOX), cisplatin (CPT), 5-fluorouracil (5-FU), methotrexate (MTX), etoposide (ETO) and taxol (TAX) using SRB as cell viability test. The concentrations were 83×10^3, 27×10^3, 9×10^3, 3×10^3, 1×10^3, 330, 100, 33, 10, 3 ng/ml.

Cpd.	A498	EVSA-T	H226	IGROV	M19MEL	MCF-7	WIDR
5	22,074	7474	22,089	8371	10,628	11,782	14,245
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

um". The metal complexes 1–3 containing TIQDTC, 4–6 containing 4MpipDTC and 7–9 containing MPizDTC with tertiary phosphines exhibit a low activity against "*S. flexenari*" and a significant activity against "*E. coli*". The complexes 1–9 exhibit a moderate activity against *B. subtilis, S. aureus, S. typhi, P. aeruginosa* bacteria.

5.5.4. Cytotoxicity of compound 5 against seven human tumour cell lines
The cytotoxicity of compound 5 was tested *in vitro* by applying seven well characterized human tumour cell lines (MCF-7, EVSA-T, WIDR, IGROV, M19 MEL, A498, H226). Table 6 shows the experimental results.

Compound 5 showed mostly moderate to low cytotoxicity against the seven human tumour cell lines (ID$_{50}$ 2500–20,000 ng/ml).

6. Conclusions

The spectroscopic (IR, NMR) and single crystal X-ray diffraction techniques suggest that the coordination in all the [Pd(L)(R$_3$P)Cl] complexes is square planar through the sulfur donating atoms, the NCSS group coordinating the metal centre acting as a bidentate symmetrical mode. This study provides useful information about the bonding nature and potential of Pd(II) complexes as cross-linking agents. These synthesized Pd(II) complexes form adducts with DNA bases (guanine or adenine) at N-7 and N-4 positions, respectively. The *in vitro* bioassays of the synthesized complexes have been studied by testing them in various strains of bacteria and fungi. Against bacteria, the complexes exhibit a low inhibitory effect as compared to their antifungal and anti-inflammatory effect. It is important to observe that this antibacterial effect is not accompanied by cytotoxicity. This indicates a certain degree of specificity of the compounds studied.

7. Supplementary material

CCDC 644064 and 611785 contain the supplementary crystallographic data for **1** and **2**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

References

[1] S.V. Matthew, J. Cookson, D.B. Paul, T.B. Peter, B. Thiebaut, J. Mater. Chem. 16 (2006) 209.
[2] N.I. Dodoff, D. Kovala-Demertzi, M. Kubiak, J. Kuduk-Jaworska, A. Kochel, G.A. Gorneva, Z. Naturforsch., B: Chem. Sci. 61 (2006) 1110.
[3] (a) M.C. Daniel, D. Astruc, Chem. Rev. 104 (2004) 293;
    (b) C.G. Hartinger, P.J. Dyson, Chem. Soc. Rev. 38 (2009) 391.
[4] V. Alverdi, L. Giovagnini, C. Marzano, R. Seraglia, F. Bettio, S. Sitran, R. Graziani, D. Fregona, J. Inorg. Biochem. 98 (2004) 1117.
[5] C. Marzano, F. Bettio, F. Baccichetti, A. Trevisan, L. Giovagnini, D. Fregona, Chem.-Biol. Interact. 148 (2004) 37.
[6] M.S. Soloway, J. Urol. 120 (1978) 716.
[7] M.V. Fiorentino, C. Ghiotto, in: M. Nicolini (Ed.), Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy, Martinus Nijhoff, Boston, 1988, p. 415.
[8] D.J. Wagener, S.H. Yap, T. Wobbes, J.T. Burghouts, F.E. van Dam, H.F. Hillen, G.J. Hogendoorn, H. Scheerder, V. van der, Cancer Chemother. Pharmacol. 15 (1985) 86.
[9] D.D. Von Hoff, R. Schilsky, C.M. Reichert, R.L. Reddick, M. Rozencweig, R.C. Young, F.M. Muggia, Cancer Treat. Rep. 63 (1979) 1527.
[10] I.H. Krakoff, Cancer Treat. Rep. 63 (1979) 1523.
[11] G. Faraglia, L. Giovagnini, L. Ronconi, C. Marzano, A. Trevisan, S. Sitran, B. Biondi, F. Bordin, J. Inorg. Biochem. 93 (2003) 181.
[12] S. Hidaka, M. Tsuruoka, T. Funakoshi, H. Shimmada, M. Kiyozumi, S. Kojima, Renal Failure 16 (1994) 337.
[13] G. Faraglia, D. Fregona, S. Sitran, L. Giovagnini, C. Marzano, F. Baccichetti, U. Cesellato, J. Inorg. Biochem. 83 (2001) 31.
[14] C. Marzano, A. Trevisan, L. Giovagnini, D. Fregona, Toxicol. In Vitro 16 (2002) 413.
[15] D.L. Bodenner, P.C. Dedon, D.C. Keng, R.F. Borch, Cancer Res. 46 (1986) 2745.
[16] (a) F. Shaheen, M. Najam-ul-Haq, K. Wurst, A. Badshah, S. Ali, Acta Crystallogr. E 62 (2006) m136.
[17] P.I. O'Dwyer, J.P. Stevenson, S.W. Johnson, in: B. Lippert (Ed.), Cisplatin. Chemistry and Biochemistry of a Leading Anticancer Drug, Wiley-VCH, Weinheim, 1999, p. 31.
[18] A. Scozzafava, A. Mastrolorenzo, T.C. Supuran, Bioorg. Med. Chem. Lett. 10 (2000) 1887.
[19] F. Shaheen, A. Badshah, M. Gielen, C. Gieck, M. Jamil, D. de Vos, J. Organomet. Chem. 693 (2008) 1117.
[20] F. Shaheen, A. Badshah, M. Gielen, M. Dusek, K. Fejfarova, D. de Vos, B. Mirza, J. Organomet. Chem. 692 (2007) 3019.
[21] (a) S. Farkhanda, A. Badshah, M. Gielen, C. Gieck, Dick de Vos, Appl. Organomet. Chem. 21 (2007) 633.
[22] D.D. Perrin, W.L.F. Armarego, Purification of Laboratory Chemicals, 4th ed., Butterword, Oxford, 1997.
[23] (a) K.Y. Kinoshita, R. Nakamura, T. Ashida, Acta Crystallogr. C 39 (1983) 1015;
    (b) A.I. Vogel, A Textbook of Practical Organic Chemistry, ELBS Publication, London, 1968. p. 499.
[24] M.C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G.L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna, J. Appl. Crystallogr. 38 (2005) 381.
[25] G.M. Sheldrick, SHELXL97, University of Göttingen, Germany, 1997.
[26] N. Walker, D. Stuart, Acta Crystallogr. A 39 (1983) 158.
[27] A. Altomare, C.M. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, G.G.A. Moliterni, G. Polidori, R. Spagna, J. Appl. Crystallogr. 32 (1999) 115.
[28] M. Nardelli, J. Appl. Crystallogr. 28 (1995) 659.
[29] L.J. Farrugia, J. Appl. Crystallogr. 30 (1997) 565.
[30] R. Carran, A. Maran, J.M. Montero, L. Fernadozlago, A. Dominguez, Plants Med. Phyto. 21 (1987) 195.
[31] S.U. Kazmi, S.N. Ali, S.A. Jamal, J. Pharm. Sci. 4 (1991) 113.
[32] S.S. Shaukat, N.A. Khan, F. Ahmad, Pakistan J. Bot. 12 (1980) 97.
[33] M.I. Choudhary, Dur-e-Shahwar, Z. Parveen, A. Jabbar, I. Ali, Atta-ur-Rahman, Phytochemistry 40 (4) (1995) 1243.
[34] (a) C.A. Winter, E.A. Risley, G.W. Nuss, Proc. Soc. Exp. Biol. Med. 111 (1962) 544;
    (b) A. Garoufis, S.K. Hadjikakou, N. Hadjiliadis, Coord. Chem. Rev. 253 (2009) 1384.
[35] J.M. Harris, P.S.J. Spencer, J. Pharm. Pharmacol. 14 (1962) 464.
[36] G. Faraglia, S. Sitran, D. Montagner, Inorg. Chim. Acta 358 (2005) 971.
[37] J.J. Criado, J.A. Lopez Aria, B. Marcias, L.R. Fernandez Lago, Inorg. Chim. Acta 193 (1992) 229.
[38] O. Pivoesana, G. Cappuccilli, Inorg. Chem. 11 (1972) 1543.
[39] D. Fregona, S. Tenconi, G. Faragila, S. Sitran, Polyhedron 16 (1997) 3795.
[40] H.D. Yin, C.H. Wang, C.L. Ma, Y. Wang, R.F. Zhang, Chin. J. Inorg. Chem. 18 (2002) 347.
[41] H.D. Yin, C.H. Wang, C.L. Ma, Y. Wang, R.F. Zhang, Chin. J. Org. Chem. 22 (2002) 183.
[42] (a) L. Ronconi, C. Maccata, D. Barreca, R. Saini, M. Zancato, D. Fregona, Polyhedron 24 (2005) 521;
    (b) L. Ronconi, P.J. Sadler, Coord. Chem. Rev. 252 (2008) 2239;
    (c) L. Ronconi, P.J. Sadler, Coord. Chem. Rev. 251 (2007) 1633.
[43] K. Nakamoto, Infrared and Raman Spectra of Inorganic and Coordination Compounds, Part B, 5th ed., John Wiley and Sons, USA, 1997. p. 137.
[44] K. Nag, D.S. Joardar, Inorg. Chem. Acta 14 (1975) 133.
[45] C.V.R. de Moura, A.P.G. De Sousa, R.M. Silva, A. Abras, M. Horner, A.J. Bortoluzzi, C.A.L. Filgueiras, J.L. Wardell, Polyhedron 18 (1999) 2961.
[46] E.R.T. Tiekink, V.J. Hall, M.A. Buntine, Z. Kristallogr. 214 (1999) 124.
[47] R.V. Parish, B.P. Howe, J.P. Wright, J. Mack, R.C. Pritchard, R.G. Buckley, A.M. Elsome, S.P. Fricker, Inorg. Chem. 35 (1996) 1659.
[48] G. Faraglia, S. Sitran, Inorg. Chim. Acta 176 (1990) 67.
[49] (a) A.E. Lemire, J.C. Thompson, Can. J. Chem. 48 (1970) 824;
    (b) C.H. Yoder, A. Komoriya, J.E. Kochanowsky, F.H. Suydam, J. Am. Chem. Soc. 93 (1971) 6515.
[50] L. Giovagnini, C. Marzano, F. Bettio, D. Fregona, J. Inorg. Biochem. 99 (2005) 2139.
[51] S.J. Anderson, A.L. Goggin, R.J. Goodfellow, J. Chem. Soc., Dalton Trans (1976) 1959.
[52] A. Ueno, H. Naraba, Y. Ikeda, F. Ushikubi, T. Murata, S. Naramiya, S. Ohishi, Life Sci. 66 (2000) 155.
[53] (a) F. Nantel, D. Denis, R. Gordon, A. Northey, M. Cirino, K.M. Metters, C.C. Chan, Braz. J. Pharmacol. 128 (1999) 853;
    (b) K. Seibert, Y. Zhang, K. Leahy, S. Hauser, J. Masferrer, W. Perkins, L. Lee, P. Isakson, Proc. Natl. Acad. Sci. USA 91 (1994) 12013.
[54] M. Di Rosa, J.P. Papadimitrion, D.A. Willoughby, J. Pathol. 104 (1971) 15.
[55] Y. Zhang, A. Shaffer, J. Portanova, K. Seiber, P.C. Isakson, J. Pharmacol. Exp. Ther. 283 (1997) 1069.