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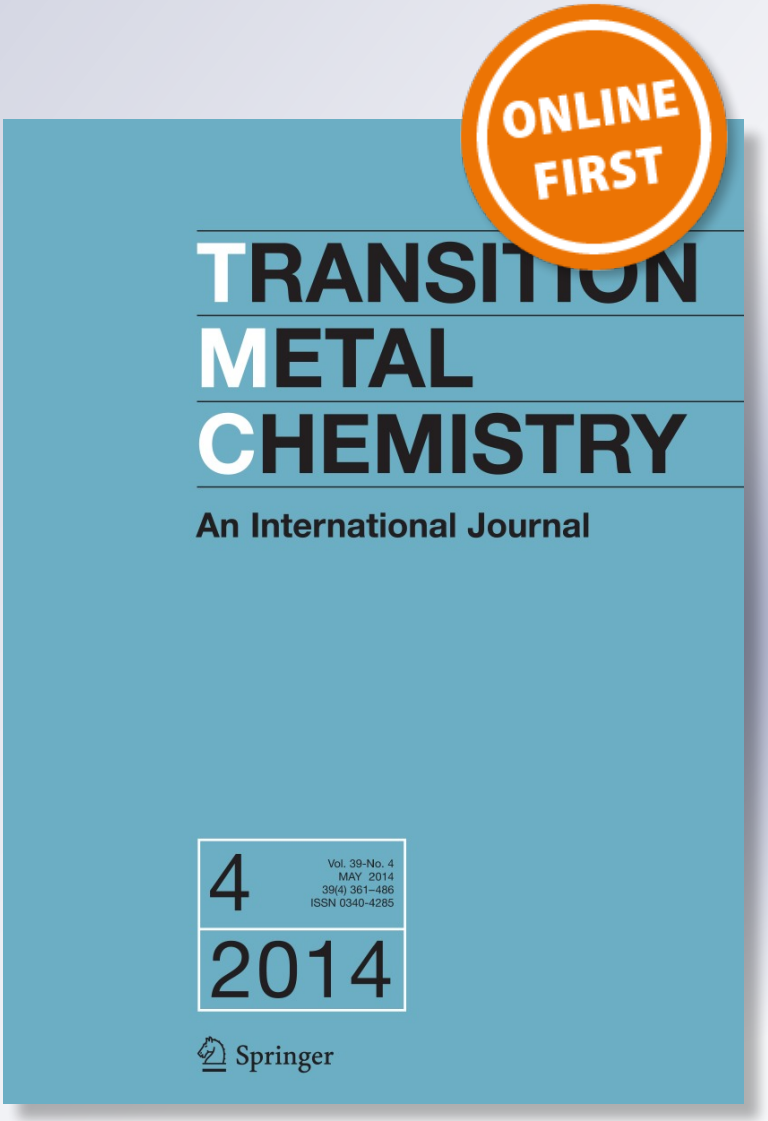

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Cytotoxicity, antioxidant and glutathione *S*-transferase inhibitory activity of palladium(II) chloride complexes bearing nucleobase ligands

Samuel Tetteh · David. K. Dodoo · Regina Appiah-Opong · Isaac Tuffour

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Abstract Palladium(II) chloride complexes bearing the nucleobases, adenine, cytosine and guanine, have been synthesized and characterized by UV–vis spectrophotometric methods, magnetic susceptibility, molar conductivity, elemental analysis, FTIR and ^{1}H-NMR. The complexes were found to have the general composition $PdCl_2(NH_3L)$ (where L = adenine, cytosine or guanine). Square-planar geometry is proposed for these Pd(II) complexes based on magnetic evidence and electronic spectra. The complexes as well as the free nucleobase ligands show varying degrees of cytotoxicity on human promyelocytic leukemia (HL60) and human histiocytic leukemia (U937) cell lines, with *cis*-$[PdCl_2(NH_3)(Gua)]$ showing IC_{50} values of 48.03 ± 9.67 and 11.12 ± 3.42 μM against HL60 and U937, respectively. The complexes as well as the ligands did not show anti-proliferative activity against a normal human cell line (NB1RGB). The complexes also show significant antioxidant activity against 2,2-diphenyl-1-picrylhydrazyl radical as well as glutathione *S*-transferase inhibitory activity.

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Introduction

The introduction of a bulky heterocyclic planar ligand (2-methylpyridine) significantly reduced the rate of deactivation of picoplatin (ZD0473) by sulfur-containing molecules within the cell as compared to cisplatin. This has made picoplatin a clinically promising candidate against cisplatin-resistant cell lines and cell lines that have enhanced mechanisms for removing platinum from cells, complexing platinum to cellular thiols or removing platinum from DNA [1, 2]. This clinical success has advocated the synthesis of metal-based anticancer drugs with bulky heterocyclic ligands which have shown significant in vitro as well as in vivo cytotoxicities in given cell lines [3–7].

Comparatively, cispalladium, *cis*-$[PdCl_2(NH_3)_2]$ does not show antitumor activity [8]. It is well known that it transforms to an inactive trans conformation and that the two compounds hydrolyze very fast as well as interacting in vivo with a lot of molecules, particularly proteins, thus preventing these complexes from reaching the DNA, their pharmacological target [9]. Relatively, palladium complexes hydrolyze too rapidly: 10^5 times faster than their corresponding palladium analogs and thus dissociate rapidly in solution leading to very reactive species that are unable to reach their pharmacological target [10]. This relatively high activity can be reduced by the introduction of a bulky monodentate N-heterocyclic ligand as in the case of picoplatin [8, 10].

Glutathione *S*-transferases (GSTs) are a family of phase II detoxifying enzymes that function to protect cellular macromolecules from attack by a wide variety of endogenous and exogenous electrophilic compounds [11]. According to Parker et al. [12], the effectiveness of several chemotherapeutic agents such as cisplatin is greatly limited by drug resistance which in some cancers has been

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associated with an overexpression of π-class glutathione *S*-transferase (GST P1-1), an important enzyme in the mercapturic acid detoxifying pathway. This led to the design of ethacraplatin (EA-CPT), a *trans*-Pt(IV) carboxylate complex containing ethacrynate ligand, a platinum cancer metallodrug that can also target cytosolic GST enzymes is able to tremendously inhibit GST activity in live mammalian cells compared with either cisplatin or ethacrynic acid [12]. Salazer-Medina et al. [13] also reported an overexpression of bacterial protein when they investigated the inhibition of a μ-class GST of the marine shrimp *Litopenaeus vannamei* by copper (Cu^{2+}) and cadmium (Cd^{2+}). The inhibition of GSTs is therefore an important pathway for enhancing the cytotoxic activity of these anticancer drugs.

Studies into metal–nucleobase-binding properties have also been of great interest in recent times since metal ions play a crucial role in the structure and function of nucleic acids and genetic information transfer [14, 15]. The mode of bonding and structure of these adducts have been exhaustively studied both spectroscopically and crystallographically [16–21] and have been shown to be monodentate via the N3 of the pyrimidine and N7 of the purine ligand [22–28]. In view of the strong electron withdrawing ability of these metal ions, there is a shift of electron density onto the metal center meaning that ligand hydrogens are easily lost in the presence of a free radical. This makes metal complexes act as better antioxidants as compared to the free ligand [29–31].

Several researchers have reported on the synthesis and characterization of transition metal complexes bearing nucleobases as ligands [17, 18, 20, 32–36]. However, as far as we know, the antioxidant activity, GST inhibition and cytotoxic activity of palladium(II) chloride complexes with nucleobases and ammonia ligands have not been investigated. Based on the geometrical resemblance of this group of compounds to picoplatin, it is hoped that interesting chemical as well as biochemical characteristics will be discovered in this study.

Experimental

Physical measurements

Palladium content was analyzed spectroscopically using dimethylglyoxime and a modification of the method described by Khader and Prasad [37]. Chlorido ligand content was determined by the Mohr method. ^{1}H-NMR was recorded in DMSO-d_6 on a Gemini 2000 instrument (400 MHz) at room temperature and the ^{1}H chemical shifts referenced to the residual signals of the protons of the NMR solvent quoted in ppm. The IR spectra (KBr disks) were recorded on an Interspec 200-X spectrophotometer. Molar conductivity was recorded on a Wagtech 4510 conductivity meter. Electronic absorbance of the complexes was recorded in DMSO on a T70 UV/Vis spectrometer. Melting points of the complexes were determined with a Thermo Scientific Electrothermal Digital Melting Point Apparatus IA9100. Magnetic susceptibility was determined using a modification of the Gouy method [38, 39].

All the ligands were purchased from Molekula (UK) and the palladium(II) chloride purchased from Merck KGaA (Germany). These were used without further purification. The DPPH was purchased from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals and cell lines were of analytical grade and obtained from standard suppliers. Free radical scavenging ability of the complexes was used as a measure of the antioxidant activity of the complexes. Thiazolyl blue tetrazolium bromide (MTT) assay was used to determine the cytotoxicity of the complexes against human histiocytic leukemia cell line (U937), human promyelocytic leukemia cell line (HL60) and normal human skin fibroblast cell line (NB1RGB). GST inhibition was determined by a method similar to those reported by Habig et al. [40].

Synthesis of the Pd(II) complexes

All the complexes were prepared by a general method as follows: Exactly 0.15 mL (2 mmol) of ammonia solution was added to 0.354 g (2 mmol) of $PdCl_2$ dissolved in 10 mL of 10 % concentrated HCl in ethanol and kept in ice for 30 min. Two millimolar of each nucleobase ligand, respectively, dissolved in 40 mL of boiling methanol, was added. The resulting solution was heated with stirring at 50 °C for 45 min. The yellow precipitate formed was collected by filtration under suction, washed repeatedly with ethanol and dried in a dessicator over anhydrous $CaCl_2$.

Cis-[$PdCl_2$(Ad)(NH_3)]. Yield = 0.6385 g(96.9 %). M.p(dec) = 250 °C. Color = yellow. Anal. Calcd. for $C_5H_8N_6PdCl_2$(%): Pd, 32.30; Cl, 21.55. Found: Pd, 32.00; Cl, 22.03. IR(KBr)ν(cm^{-1}): 3,304, 3,173, 1,642, 1,632, 3,000, 1,530, 3,637–3,043, 1,056, 1,625, 3,226, 3,420, 250, 281. UV–vis λ(nm)(ε): 286(5,496 M^{-1} cm^{-1}), 331(3,321 M^{-1} cm^{-1}), 403(1,025 M^{-1} cm^{-1}), 531 (227 M^{-1} cm^{-1}). $\Lambda_m(R^2)$: 20.12 Ω^{-1} cm^{-2} mol^{-1}(0.987). μ_{eff} = 0. ^{1}H-NMR (DMSO-d_6): δ_{ppm} 8.00(s, NH_2), 8.50(2H, s, H-2, H-8), 7.02–7.28(t, NH_3).

Cis-[$PdCl_2$(Cyt)(NH_3)]. Yield = 0.3958 g(64.8 %). M.p(dec) = 250 °C. Color = yellow. Anal. Calcd. for $C_4H_8N_4PdCl_2$(%): Pd, 34.84; Cl, 23.25. Found: Pd, 34.62; Cl, 22.46. IR(KBr)ν(cm^{-1}): 3,424, 3,203, 1,664, 1,623, 1,537, 3,020, 1,507, 3,660–2,695, 1,055, 1,647, 3,099, 3,312, 235, 296. UV–vis λ(nm)(ε): 280(12,398 M^{-1} cm^{-1}), 331(2,470 M^{-1} cm^{-1}),

406(691.3 M^{-1} cm^{-1}), 531(300.9 M^{-1} cm^{-1}). $\Lambda_m(R^2)$: 35.89 Ω^{-1} cm^{-2} mol^{-1}(0.996). $\mu_{eff} = 0$. ^{1}H-NMR(DMSO-d_6): δ_{ppm} 5.95(1H, s, H-5), 8.50(s, NH_2), 7.75(1H, s, H-6), 12.09(1H, s, H-1), 7.09–7.35(t, NH_3).

Cis-[$PdCl_2$(Gua)(NH_3)]. Yield = 0.6159 g(89.1 %). M.p(dec) = 250 °C. Color = yellow. Anal. Calcd. for $C_5H_8N_4OPdCl_2$(%): Pd, 30.80; Cl, 20.56. Found: Pd, 31.22; Cl, 20.10. IR(KBr)ν(cm^{-1}): 3,312, 3,165, 1,690, 1,631, 1,563, 3,005, 1,534, 3,622–2,553, 238, 310. UV–vis λ(nm)(ε): 290(9,024 M^{-1} cm^{-1}), 333(2,261 M^{-1} cm^{-1}), 407(640.2 $M^{-1}cm^{-1}$), 531(187.4 M^{-1} cm^{-1}). $\Lambda_m(R^2)$: 9.4 Ω^{-1} cm^{-2} mol^{-1}(0.983). $\mu_{eff} = 0$. ^{1}H-NMR(DMSO-d_6): δ_{ppm} 6.65(s, NH_2), 8.83(1H, s, H-8), 11.92(1H, s, H-9), 7.00–7.26(m, NH_3).

Procedure for cytotoxicity

The in vitro cytotoxicities of the compounds were assayed on HL60 (human promyelocytic leukemia) and U937 (human histiocytic leukemia) cells as described [41]. The cells were maintained in RPMI 1640 medium. Normal human skin fibroblast (NB1RGB) cells were grown in α-MEM medium. All cultures were supplemented with 10 % FBS and 0.01 % kanamycin. Cells in exponential growth were seeded into 96-well plates at a concentration of 1×10^4 cells/100 μL/well. The cells were then treated with various concentrations of the test compounds at a concentration range of 0–200 μM for HL60 and 0–100 μM for U937. Negative control (untreated) and positive control (curcumin) experiments were included.

After 72 h of incubation at 37 °C under 5 % CO_2 in humidified atmosphere, 20 μL of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added to each well and the plates kept in the dark for further 4 h. Subsequently, 150 μL of acidified isopropanol containing Triton-X 100 was added to stop the reaction and also solubilize the formazan crystals formed. Absorbance readings were taken at 570 nm on a Tecan-PC infinite M200 Pro Plate reader after overnight incubation of the plates. Triplicate experiments were performed. Dose-response curves were plotted as percentages of cell viability against concentration. Drug sensitivity was expressed in terms of the concentration of drug required for a 50 % reduction of cell viability (IC_{50}). The IC_{50} values were determined by nonlinear regression analysis.

Procedure for antioxidant activity

The antioxidant activity of the complexes was determined as described [30, 42] as follows: on a 96-well plate, the compounds were serially diluted in DMSO to obtain a concentration range of 1.25–20 mM. The reaction mixture consisted of 100 μL of 0.5 mM 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) and 100μL of each concentration of the test compounds. For positive control, 2,6-di-*tert*-butyl-4-methylphenol (BHT) was used at a concentration range of 0.0625–2 mM. The solvents, DMSO and methanol, were used as blanks. Triplicate experiments were performed. The plates were covered with aluminum foil and kept in the dark for 20 min after which the absorbance was read on a Tecan-PC infinite M200 Pro Plate reader at the absorbance wavelength of 517 nm. The percent antioxidant activity was calculated as follows:

$$\left[\text{Percent Antioxidant Activity} = \frac{A_0 - A_1}{A_0} \times 100\ \%\right]$$

where A_0 is the absorbance of the blank, and A_1 is the absorbance in the presence of the sample or positive control.

Procedure for glutathione *S*-transferase (GST) inhibition

Exactly 160 μL of KPI buffer was pipetted into each of the wells on the 96-well plate according to the number of compounds, positive controls and negative controls. 10 μL of GSH was then added to each buffer followed by 20 μL of enzyme after which 2 mM of 5 μL of the compounds were added. 5 μL of 0.25 mM ethacrynic acid (ETA) was used as the positive control. 5 μL of 1-chloro-2,4-dinitrobenzene (CDNB) was added to each compound well and also to the positive control wells. Two sets of negative controls were prepared with one set containing 160 μL of KPI buffer, 10 μL GSH and 20 μL enzymes with no CDNB, whereas the other set contained 160 μL of KPI buffer, 10 μL GSH and 5 μL CDNB with no enzymes. Triplicate measurements were made in all cases. The absorbance was read immediately at 340 nm on a Tecan-PC infinite M200 Pro Plate reader.

These experiments were performed to deduce the structures of the complexes as well as to determine their activity on cancerous and normal body cell lines. Part of the experiment was also to determine the free radical scavenging as well as the GST activities of the complexes.

Results and discussion

Characterization of complexes

Upon careful comparison between the FTIR spectra of the nucleobase ligands and those of their respective complexes, characteristic vibrations were identified. The strong bands at 1,623–1,642 cm^{-1} are assigned to the ν(C=N) stretching mode of the pyrimidine or purine ring. These bands are significantly shifted in *cis*-[$PdCl_2$(NH_3)(Ad)] and *cis*-

[$PdCl_2(NH_3)$(Cyt)] compared to *cis*-[$PdCl_2(NH_3)$(Gua)]. These shifts support the participation of the N3(cytosine) and N7 (adenine and guanine) in binding to the Pd(II) ion which have previously been reported [20, 22–24, 43–46]. Also conspicuous in the spectra of the complexes are the asymmetric and symmetric (NH_2) stretching modes of the nucleobase ligands which were identified at 3,165–3,424 cm^{-1}. Comparatively, these bands showed slight shifts as a result of their involvement in hydrogen bonding interactions [43, 47, 48].

Due to the strong intermolecular and intramolecular hydrogen bonding interaction between the ligands, broadening of the spectra, similar to those reported by Khan and Zakeerudin [43], was observed at 2,500–3,500 cm^{-1} in all the complexes. Also observed in the spectra are important N–H deformations of the NH_3 ligand which were absent in the spectrum of the free nucleobase ligands. These are the symmetric bending (1,055–1,115 cm^{-1}), degenerate bending (1,625–1,647 cm^{-1}), symmetric stretch (3,099–3,226 cm^{-1}) and the antisymmetric stretch (3,289–3,420 cm^{-1}). Weak Pd–N stretching vibrational peaks were also observed at 235–310 cm^{-1}. These peaks can be attributed to the A_1 and B_1, symmetric and antisymmetric vibrations of the C_{2V} point group, which are both IR active [32]. Thus, cis geometry is proposed for the local PdNN group based on the far FTIR data.

A comparison between the ^{1}H-NMR spectra of the complexes and those of the free nucleobase ligands shows a downfield shift in the signals of the ligand protons upon complexation to the palladium(II) ion. The $-NH_2$ cytosine protons of *cis*-[($PdCl_2(NH_3)$(cyt)], which are directly adjacent to the coordinating N3 ring nitrogen, show a marked downfield shift from 7.06 in the free ligand to 8.50 ppm in the complex. The H-1, H-5 and H-6 protons also show downfield shifts upon complexation. All the ligand protons of the other complexes show similar change in chemical shift. Similar results were observed by Coletta et al. [22].

The electronic spectra of the complexes were measured in DMSO and showed four significant absorption bands. These bands were observed in the regions 280–290, 331–333, 403–407 and 530–535 nm. These may, respectively, be attributed to intraligand $\pi \rightarrow \pi^*$ excitation as well as the spin allowed d–d transitions of $^1A_{1g}(d_{x^2-y^2}) \leftarrow {}^1A_{2g}(d_{xy})$, $^1A_{1g}(d_{x^2-y^2}) \leftarrow {}^1E_g(d_{xz}, d_{yz})$ and $^1A_{1g}(d_{x^2-y^2}) \leftarrow {}^1B_{1g}(d_{z^2})$. These confirm the square-planar (D_{4h}) geometry of the Pd(II) ion.

As shown in Fig. 1, the strong intramolecular and intermolecular hydrogen bonding in these complexes resulted in a bathochromic shift in wavelength with increasing concentration, a phenomenon that can be likened to the intercalative mode of bonding involving a strong $\pi \leftarrow \pi^*$ stacking interaction between aromatic chromophores and DNA bases [28, 49, 50].

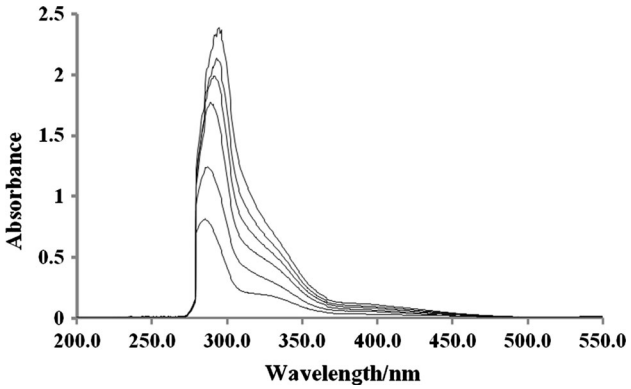


Fig. 1 Absorption spectra of *cis*-[$PdCl_2$(cyt)(NH_3)] showing bathochromic shifts with increasing concentration

Based on the above discussion of results and the analytical data obtained from the metal and chloride content analyses, we suggest that the structural formulae of the complexes are as given in Fig. 2.

The molar conductivities of the complexes (Fig. 3) measured in DMSO (10^{-3} M) show their nonelectrolyte nature [51, 52] as values between 9.40 and 35.89 Ω^{-1} - cm^{-2} mol^{-1} were recorded.

These low molar conductivity values suggest that the complexes do not dissociate in solution and have the potential of reaching their pharmacological target as undissociated species.

The room temperature magnetic moments of the complexes were zero, confirming the diamagnetic properties of these complexes and hence the square-planar geometry of the Pd(II) ion [32].

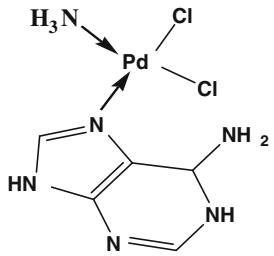
Biochemical characterization of the complexes

In vitro cytotoxicity

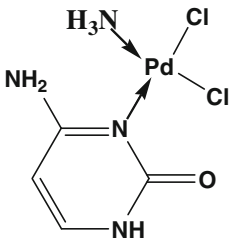
The growth inhibition effect of the complexes as well as the free nucleobase ligands was tested on two leukemia cell lines (human promyelocytic leukemia cell line (HL60) and human histiocytic leukemia cell line (U937) as well as on normal human skin fibroblast cell line (NB1RGB) with curcumin as a positive control. The results as expressed by IC_{50} values (μM) are presented in Table 1. The ligands adenine and cytosine failed to show IC_{50} values on HL60 within the working concentration (0–200 μM), whilst guanine gave values of 71.38 ± 9.01 μM and 53.53 ± 8.55 μM, respectively, on HL60 and U937.

Of the three complexes, *cis*-[$PdCl_2(NH_3)$(Gua)] was the most cytotoxic with values of 48.03 ± 9.67 and 11.12 ± 3.42 μM against HL60 and U937, respectively. The higher activity of the guanine complex could be attributed to its bulkiness as compared to adenine and cytosine, since this

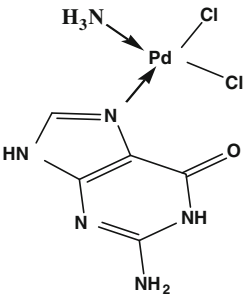
Fig. 2 Proposed structures of the palladium(II) chloride complexes



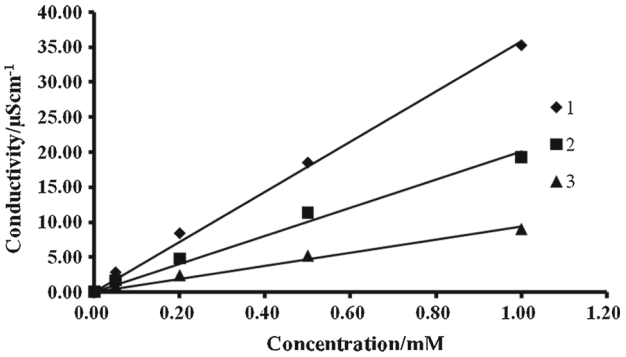
Cis-[$PdCl_2(Ad)(NH_3)$]



Cis-[$PdCl_2(Cyt)(NH_3)$]



Cis-[$PdCl_2(Gua)(NH_3)$]



1 = cis-[$PdCl_2(cyt)(NH_3)$], 2 = cis-[$PdCl_2(ad)(NH_3)$], 3 = cis-[$PdCl_2(gua)(NH_3)$]

Fig. 3 A plot of conductivity in DMSO(10^{-3}) against concentration

Table 1 IC_{50} values of the complexes and the nucleobase ligands as measured against the respective cell lines

Complex	IC_{50} values/μM	
	HL60	U937
Cis-[$PdCl_2(NH_3)(Ad)$]	139.26 ± 9.25	21.90 ± 9.45
Cis-[$PdCl_2(NH_3)(Cyt)$]	>200	46.50 ± 6.13
Cis-[$PdCl_2(NH_3)(Gua)$]	48.03 ± 9.67	11.12 ± 3.42
Adenine	>200	>100
Cytosine	>200	44.95 ± 7.11
Guanine	71.38 ± 9.01	53.53 ± 8.55
Curcumin	5.40 ± 2.55	8.63 ± 1.94

has a tendency of significantly reducing the rate of deactivation by sulfur-containing molecules within the cell [1–3, 10]. In addition, guanine derivatives have been shown to inhibit cell cycle cyclin-dependent kinases (CDKs) by reducing antitumor selectivity [53–55].

According to Arris et al. [56] and Davies et al. [57], guanine derivatives form important interactions with CDK2 which include a triplet of hydrogen bonds (i.e., purine NH-9 to glu 81, purine N-3 to leu 83 and 2-NH_2 to leu 83) that confers specificity for CDK1 and 2 over CDK4. This can be supported by the observed broadening of the FTIR spectra as well as the bathochromic shift in λ_{max} of the electronic spectra (Fig. 1), which were attributed to hydrogen bonding interactions in the complexes. The IC_{50} values are summarized in Table 1.

In an attempt to investigate the selectivity index of the complexes in leukemia cell lines and a normal skin fibroblast cell line, we treated the cells using 0–200 μM of each complex as well as the free ligand for 72 h followed by MTT assay (Fig. 4). The complexes and one of the ligands (guanine) significantly suppressed cell growth in the leukemia cell lines. However, none of the complexes nor the free ligands inhibited cell proliferation in NB1RGB remarkably.

Antioxidant activity

Free radicals such as reactive oxygen and nitrogen species are the main agents that trigger the growth of cancer cells [30]. Therefore, a cytotoxic drug that has an antioxidant activity will have an added advantage since it possess the ability to stop the growth of cancer cells and also prevent free radical damage to normal body cells.

The ability of the complexes as well as the free nucleobase ligands to quench free radicals was determined by the decrease in the molar absorptivity of DPPH at 517 nm. The activity of the free ligand was found to be between 10 and 15 % [8], but upon complexation, it increased significantly to 20–60 % (as shown in Fig. 5). With *cis*-[$PdCl_2(Ad)(NH_3)$] and *cis*-[$PdCl_2(Gua)(NH_3)$], EC_{50} (concentration of the complexes needed to scavenge 50 % of the initial DPPH concentration) values of 1.36 and 1.00 mM, respectively, were recorded. These values are in agreement with reported studies [8, 29, 58] in which metal complexes showed higher antioxidant activities as compared to their free ligands. The increased antioxidant activity of the complexes can be explained by the downfield shift of the ^{1}H-NMR signals of the complexes. The electron withdrawing effect of the Pd(II) ion facilitates the release of hydrogen as a free radical in the presence of DPPH [29, 30, 58].

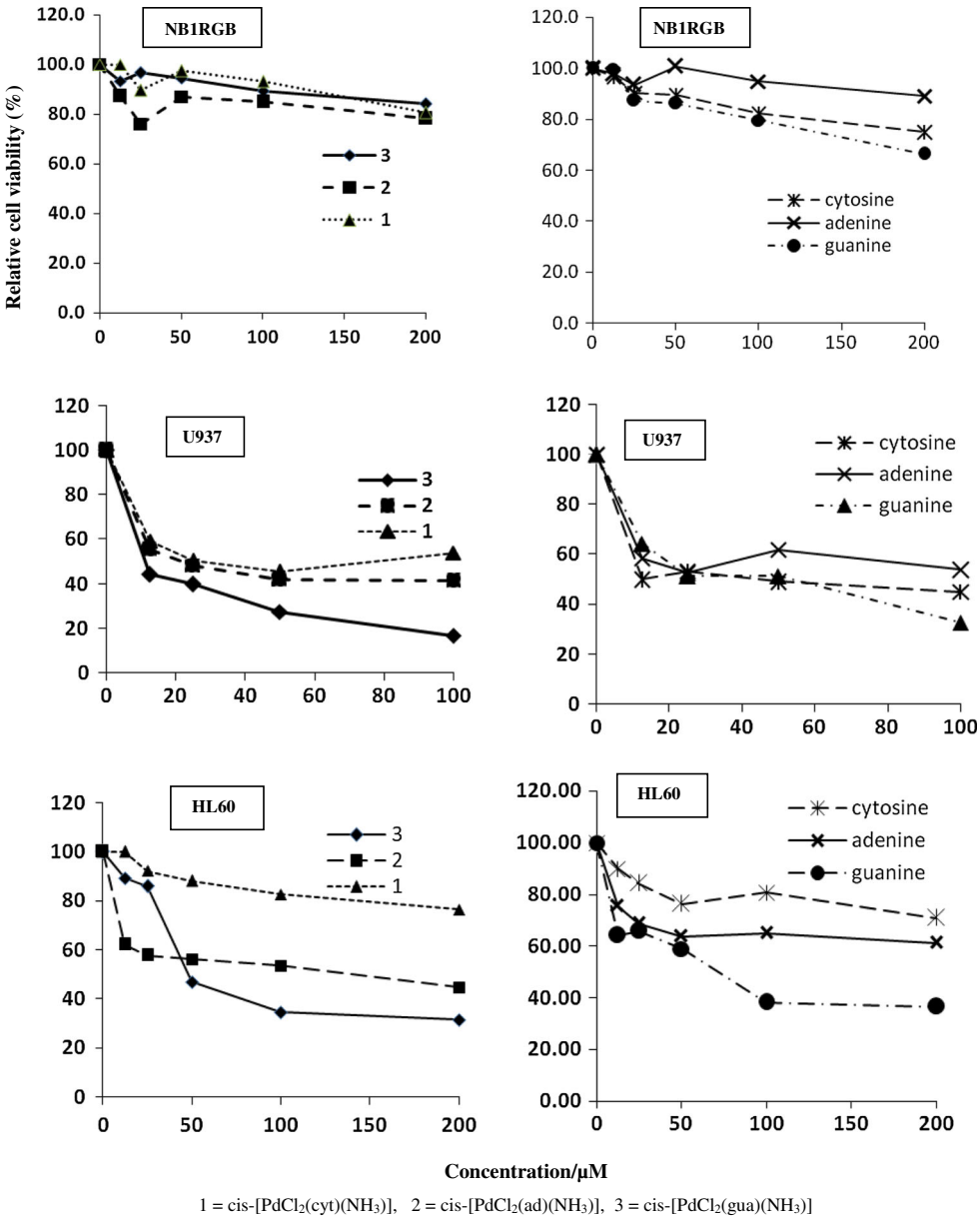
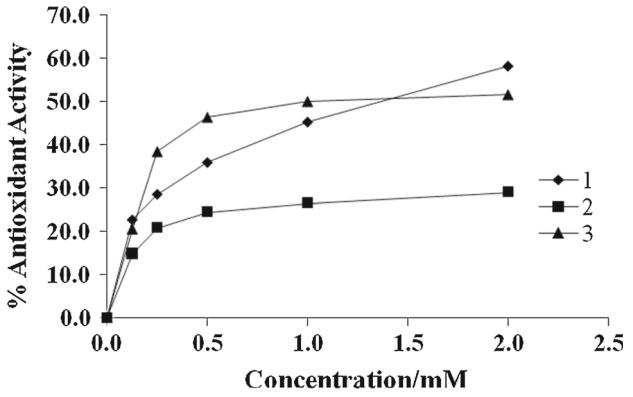


Fig. 4 Cytotoxic activity of the Pd(II) complexes and the free nucleobase ligands on human leukemia and normal skin fibroblast cell lines

Glutathione S-transferase (GST) activity

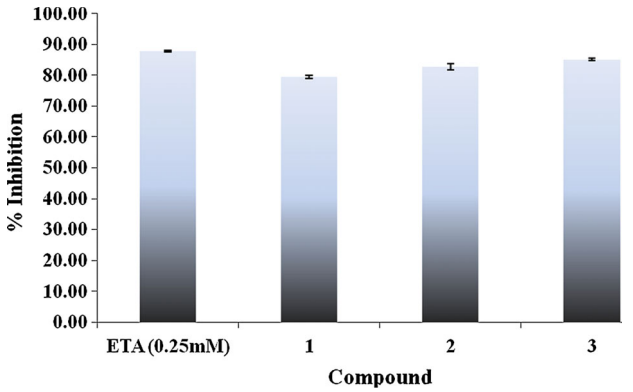
The percentage GST inhibitory activity of the complexes is illustrated in Fig. 6. *cis*-$[PdCl_2(Gua)(NH_3)]$ showed the highest activity of 85.12 % with *cis*-$[PdCl_2(Gua)(NH_3)]$ showing 79.36 % inhibition. IC_{50} values of 0.03 ± 0.01 mM, 0.09 ± 0.00 mM and 0.11 ± 0.01 mM were, respectively, obtained for *cis*-$[PdCl_2(cyt)(NH_3)]$, *cis*-$[PdCl_2(ad)(NH_3)]$ and *cis*-$[PdCl_2(gua)(NH_3)]$. The positive control (ethacrynic acid) recorded an IC_{50} of 0.03 ± 0.01 mM.

Moreover, the GST activity showed a positive correlation with the cytotoxicity of the complexes [59]. Therefore, the high cytotoxic activity of the complexes could be attributed to their ability to inhibit glutathione *S*-transferase activity, thus significantly reducing its conjugation to glutathione to prevent detoxification. GSTs have been extensively studied as prognostic agents in cancer chemotherapy [60]. These enzymes are overexpressed in cancerous cells in an attempt to catalyze the conjugation of exogenous and endogenous xenobiotics to cellular guardians such as glutathione. Cytotoxic drugs that have the ability to inhibit GST activity are more likely to get to their pharmacological targets without detoxification. These complexes could therefore be used in combination therapy to reduce cell resistance to certain anticancer drugs such as cisplatin.



1 = cis-[$PdCl_2$(cyt)(NH_3)], 2 = cis-[$PdCl_2$(ad)(NH_3)], 3 = cis-[$PdCl_2$(gua)(NH_3)]

Fig. 5 Percent antioxidant activity of the complexes



1 = cis-[$PdCl_2$(cyt)(NH_3)], 2 = cis-[$PdCl_2$(ad)(NH_3)], 3 = cis-[$PdCl_2$(gua)(NH_3)]

Fig. 6 Glutathione *S*-transferase (GST) inhibitory activity of the complexes

Conclusion

In this study, we have reported the synthesis of palladium(II) chloride complexes containing the nucleobases, adenine, cytosine and guanine, as ligands. The complexes were characterized using elemental analysis, spectroscopic methods, magnetic and molar conductivity measurements. All the complexes have square-planar geometry and are nonelectrolytes in DMSO. The ligands and the respective complexes show varying degrees of cytotoxicity against HL60 and U937 cell lines, with guanine and its corresponding complex being the most cytotoxic. The complexes also show higher antioxidant activity as compared to the free ligands. Finally, the complexes were able to inhibit glutathione *S*-transferase activity and have the potential of being used in combination therapy.

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