

Research Article

Spectroscopic Characterization, *In Vitro* Cytotoxicity, and Antioxidant Activity of Mixed Ligand Palladium(II) Chloride Complexes Bearing Nucleobases

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Mixed-ligand palladium(II) chloride complexes bearing the nucleobases, adenine (Ad), cytosine (Cyt), and guanine (Gua), have been synthesized and characterized by UV-vis spectrophotometric methods, magnetic susceptibility, molar conductivity, elemental analysis, FTIR, and ¹H-NMR. The complexes were found to have the composition cis-[PdCl₂(Gua)(Cyt)], cis-[PdCl₂(Ad)(Cyt)], and cis-[PdCl₂(Ad)(Gua)]. A four-coordinated 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 were tested for their *in vitro* cytotoxicity on human promyelocytic leukemia (HL60) and human histiocytic leukemia (U937) cell lines. cis-[PdCl₂(Ad)(Gua)] showed IC₅₀ values of 11.29 ± 2.91 and 8.31 ± 1.44 μM against HL60 and U937, respectively, which was higher than that of the positive control (curcumin) against U937. The complexes also showed significant antioxidant activity when tested against 2,2-diphenyl-1-picrylhydrazylradical (DPPH).

1. Introduction

The versatility of nucleobases has made them suitable ligands for the synthesis of numerous transition metal complexes [1–5]. In particular, palladium complexes of nucleobases and their derivatives have been of current interest since these complexes form faster than their platinum analogues and produce analogous products in solution [6, 7]. The mode of bonding and structure of these and related ligands have been exhaustively studied, both spectroscopically and crystallographically [8–11] and have been shown to be monodentate via the N3 of the pyrimidine and N7 of the purine ligand (as shown in Figure 2). In view of the strong electron withdrawing ability of these metal ions, there is a drift of electron density onto the metal centre and in effect ligand hydrogens are easily lost in the presence of a free radical. This makes these metal complexes act as better antioxidants as compared to the free ligand [12, 13].

Mixed-ligand complexes play a key role in biological chemistry [14] because mixed chelation occurs commonly in

biological fluids as millions of potential ligands are likely to compete for metal ions *in vivo* [15]. Because of this profound role, mixed-ligand complexes have been extensively studied for their thermodynamic [16–18] as well as kinetic stability [19–23]. These complexes have received tremendous attention in the search for novel drugs against drug resistant diseases [24–27] with cisplatin being a classic example [28].

Metal based antioxidants have received recent attention for their capacity to protect organisms and cells from damage induced by oxidative stress [12]. An effective antioxidant, however, should be able to terminate the attack of reactive species like free radicals and prevent them from attacking body cells. The antioxidant activity of a synthetic compound can be measured using the scavenging ability of that compound to trap free radicals [13]. Although some palladium(II) complexes of pyrimidine and pyridine derivatives have been synthesized and characterized [1, 29], not much has been reported about the antioxidant activity as well as the *in vitro* cytotoxicity of these complexes. In this study we present the synthesis, spectroscopic characterization, and

antioxidant as well as *in vitro* cytotoxicity of palladium(II) complexes with purine and pyrimidine nucleobases as ligands on human promyelocytic leukemia (HL60) and human histiocytic leukemia (U937) cell lines.

2. Materials and Methods

2.1. Materials. All the ligands were purchased from Molekula (UK) and the palladium(II) chloride was 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 were of analytical grade and obtained from standard suppliers. Palladium content was analysed spectroscopically using dimethylglyoxime and a modification of the method described by Khader and Prasad [30]. Free radical scavenging ability of the complexes was used as a measure of the antioxidant activity of the complexes. Thiazoyl blue tetrazolium bromide (MTT) assay was used to determine the cytotoxicity of the complexes against U937 and HL60 cell lines.

2.2. Instrumentation and Methods. Chloride content was determined by the Mohr method. $^1\text{H-NMR}$ was recorded in DMSO-d_6 on a Gemini 2000 instrument (400 MHz) at room temperature and the ^1H 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 [31, 32].

2.3. Synthesis of the Palladium(II) Complexes. The complexes were prepared in a general way as follows: to a 10% HCl ethanolic solution (10 mL) of PdCl_2 (0.354 g, 2 mmol) was added 2 mmol of one nucleobase ligand in 20 mL of boiling ethanol. After stirring the mixture at 100°C for 30 minutes, 2 mmol of the other ligand dissolved in 20 mL of boiling ethanol was then added. The resulting solution was refluxed at 100°C with stirring for further 45 minutes. The yellow to orange precipitates were suction-filtered and washed with hot ethanol and dried over anhydrous CaCl_2 .

2.4. Procedure for MTT In Vitro Cytotoxicity. The *in vitro* cytotoxicity of the compounds was performed on HL60 and U937 cells as described [33]. The cells were maintained in RPMI 1640 medium (containing 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 using DMSO as the solvent. Negative control (untreated) and positive control (curcumin) experiments were included.

After 72 hours 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 were kept in the dark for further 4 hours. 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.

2.5. Procedure for Antioxidant Activity. The antioxidant activity of the complexes was determined as described [12, 34] with slight modifications 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 100 μL of each concentration of the test compounds using DMSO as the solvent. For positive control, 2,6-di-tert-butyl-4-methylphenol (BHT) was used at a concentration range of 0.0625–2 mM in methanol. The solvents, DMSO and methanol, were used as blanks. Duplicate experiments were performed. The plates were covered with aluminum foil and kept in the dark for 20 minutes 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:

$$\left[\text{Percent antioxidant} = \frac{A_0 - A_1}{A_0} \right], \quad (1)$$

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

3. Results and Discussion

3.1. *cis*-[PdCl₂(Gua)(Cyt)]. Yield = 0.6905 g (78.5%). M.p (dec) = 250°C . Colour = yellowish brown. Anal. Calcd. for $\text{C}_9\text{H}_{10}\text{N}_8\text{O}_2\text{PdCl}_2$ (%): Pd, 24.21; Cl, 16.16. found: Pd, 23.91; Cl, 15.81. UV-Vis λ (nm) (ϵ): 286($19007 \text{ M}^{-1} \text{ cm}^{-1}$), 331($3819 \text{ M}^{-1} \text{ cm}^{-1}$), 403($871 \text{ M}^{-1} \text{ cm}^{-1}$), 531($624 \text{ M}^{-1} \text{ cm}^{-1}$). Λ_m (R^2): $13.58 \Omega^{-1} \text{ cm}^{-2} \text{ mol}^{-1}$ (0.987). $\mu_{\text{eff}} = 0$.

3.2. *cis*-[PdCl₂(Ad)(Cyt)]. Yield = 0.6905 g (81.5%). M.p (dec) = 250°C . Colour = yellowish brown. Anal. Calcd. for $\text{C}_9\text{H}_{10}\text{N}_8\text{OPdCl}_2$ (%): Pd, 26.13; Cl, 16.77. found: Pd, 26.10; Cl, 16.12. UV-Vis λ (nm) (ϵ): 280($5149 \text{ M}^{-1} \text{ cm}^{-1}$), 331($2326 \text{ M}^{-1} \text{ cm}^{-1}$), 406($1111 \text{ M}^{-1} \text{ cm}^{-1}$), 531($503 \text{ M}^{-1} \text{ cm}^{-1}$). Λ_m (R^2): $18.48 \Omega^{-1} \text{ cm}^{-2} \text{ mol}^{-1}$ (0.983). $\mu_{\text{eff}} = 0$.

3.3. *cis*-[PdCl₂(Gua)(Ad)]. Yield = 0.6812 g (73.5%). M.p (dec) = 250°C . Colour = yellowish brown. Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_{10}\text{OPdCl}_2$ (%): Pd, 22.96; Cl, 15.32. found: Pd,

TABLE 1: Major IR/cm⁻¹ absorption bands of the palladium(II) complexes and the nucleobase ligands.

Complex	ν_{as} (NH ₂)	ν_s (NH ₂)	ν_s (C=O)	ν_s (C=N)	δ_s (NH ₂)	H-bonding
cis-[PdCl ₂ (cyt)(gua)]	3424 w	3286 s	1705 s	1634 s	1605 m	3625–2662 br
cis-[PdCl ₂ (cyt)(ad)]	3416 w	3271 w	1672 s	1638 w	1590 m	3663–2800 br
cis-[PdCl ₂ (cyt)(gua)]	3323 w	3170 w	1698 s	1638 s	1567 m	3618–2587 br
Cytosine	3372 w	3166 w	1668 s	1620 s	1534 m	3500–2500 br
Adenine	3364 w	3230 w	—	1672 s	1601 m	3394–2500 br
Guanine	3308 w	3114 w	1705 s	1631 s	1563 m	3390–2500 br

ν_{as} : antisymmetric stretching, ν_s : symmetric stretching, δ_s : symmetric bending, s: strong, w: weak, br: broad, and m: medium.

TABLE 2: Far IR/cm⁻¹ bands for the palladium(II) complexes.

Complex	ν_s (Pd-Cl)	ν_s (Pd-N)
cis-[PdCl ₂ (cyt)(gua)]	389 w, 312 w	282 w, 238 w
cis-[PdCl ₂ (cyt)(ad)]	386 w, 311 w	281 w, 227 w
cis-[PdCl ₂ (cyt)(gua)]	364 w, 339 w	283 w, 248 w

22.85; Cl, 15.33. UV-Vis λ (nm) (ϵ): 290(14001 M⁻¹ cm⁻¹), 333(3071 M⁻¹ cm⁻¹), 407(784 M⁻¹ cm⁻¹), 531(761 M⁻¹ cm⁻¹). Λ_m (R^2): 15.32 Ω^{-1} cm⁻² mol⁻¹ (0.925). μ_{eff} = 0.

3.4. IR Spectra. Important vibrational bands were selected by comparing the FTIR spectra of the complexes with those of the respective free nucleobase ligands. The symmetric and antisymmetric N-H stretching frequencies of the complexes were observed in the range of 3424–3170 cm⁻¹. These peaks were compared with those of the free ligands which appear between 3372 and 3114 cm⁻¹. The observed shifts can be attributed to hydrogen bonding and other noncovalent interactions in the solid state of these metal complexes [35, 36]. These observations are supported by the broadening of the spectra observed at 3663–2500 cm⁻¹ [36]. Also observed around 1605–1567 cm⁻¹ are important symmetric NH₂ bending vibrations of the ligands which showed slight shifts as compared to those of the free ligands. Furthermore, peaks corresponding to the ring stretching frequencies ν_s C=N between 1620–1567 cm⁻¹ in the free ligands were found to have shifted to 1634–1638 cm⁻¹ in the metal complexes, suggesting the involvement of the ring C=N group in coordinating to the metal center [25, 36]. The far-IR region also revealed bands corresponding to ν (Pd-Cl) and ν (Pd-N) vibrations which are absent in the spectra of the free ligands. The FTIR spectra of the complexes are summarized in Tables 1 and 2.

3.5. ¹H-NMR Spectra. A comparison of the ¹H-NMR spectra of the complexes with those of the free ligands show downfield shifts in the proton signals upon complexation to the palladium(II) ion. As shown in Table 3, the NH₂ cytosine protons of cis-[PdCl₂(Gua)(Cyt)] which are directly adjacent to the coordinating N3 ring nitrogen show a downfield shift from 7.06 to 7.70 ppm in the complex. Similarly, the NH₂ protons of guanine observed in the free ligand at 5.57 ppm was shifted to 5.95 ppm showing that these protons

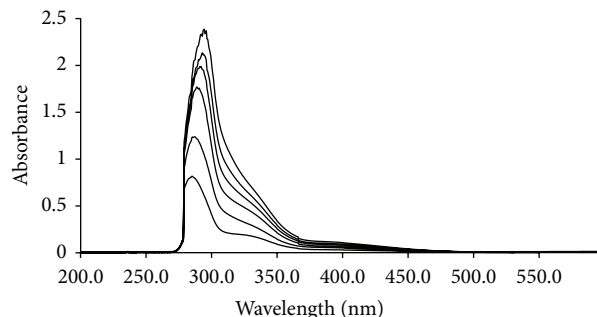
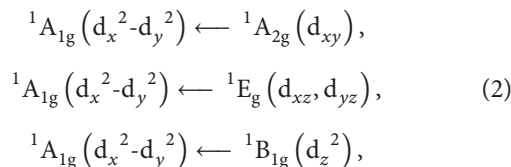


FIGURE 1: Electronic absorption spectra of cis-[PdCl₂(Cyt)(Gua)] showing bathochromism with increasing concentration.

experienced strong deshielding effects upon complexation [37]. Similar chemical shifts were observed for the remaining protons as shown in Table 3. Figure 2 shows the proposed structures of the complexes with labeled atoms.

3.6. Electronic Absorption Spectra, Conductivity, and Magnetic Measurements. The electronic spectra of the complexes were recorded in DMSO (10⁻³ M). This was used to study the effect of complexation on the splitting of the d orbitals in the Pd(II) ion. Significant absorption bands were observed in the region of 280–290, 331–333, 403–407, and 531 nm. These transitions may be attributed to intraligand π - π^* as well as the spin allowed LMCT d-d transitions of



respectively [37]. These transitions confirm the square planar (D_{4h}) geometry of the Pd(II) ion [31]. Bathochromism was also observed in the spectra of these complexes with increasing concentration as exemplified in Figure 1. This shift in wavelength can be attributed to strong intermolecular hydrogen bonding, a phenomenon which can be likened to the intercalative mode of bonding involving a strong π - π^* stacking interaction between aromatic chromophores and DNA bases [38–40].

The molar conductivities of the complexes measured in DMSO (10⁻³ M) was between 13.58 and 18.48 Ω^{-1} cm⁻² mol⁻¹

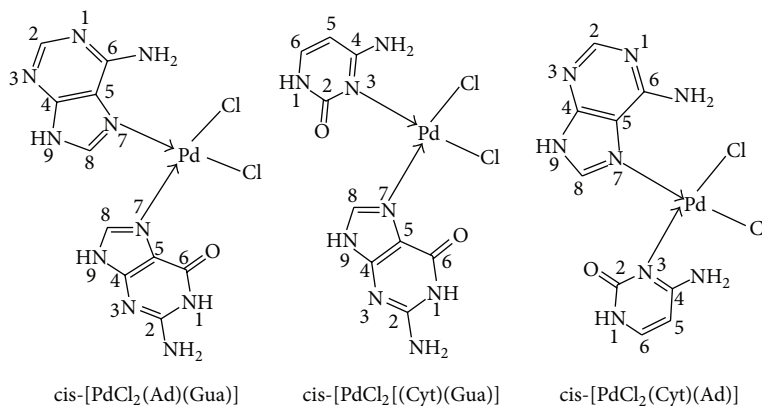


FIGURE 2: Proposed structures of the palladium(II) chloride complexes.

TABLE 3: $^1\text{H-NMR}$ data of the complexes and the free nucleobase ligands.

Complex	H-NMR ^a
$\text{cis-[PdCl}_2(\text{cyt})(\text{gua})]$	5.56 (1H, s, H-5(cyt)), 7.40 (1H, s, H-6(cyt)), 7.70 (s, NH ₂ (cyt)), 11.27 (1H, s, H-1(cyt)), 5.95 (s, NH ₂ (gua)), 8.83 (1H, s, H-8(gua)), 9.40 (1H, s, H-9(gua)), 12.03 (1H, s, H-1(gua)).
$\text{cis-[PdCl}_2(\text{cyt})(\text{ad})]$	5.90 (1H, s, H-5(cyt)), 7.71 (s, NH ₂ (cyt)), 8.13 (1H, s, H-6(cyt)), 2.01 (1H, s, H-1(cyt)), 7.70 (s, NH ₂ (ad)), 8.38 (1H, s, H-2(ad)), 9.37 (1H, s, H-8(ad)), 12.00 (1H, s, H-9(ad))
$\text{cis-[PdCl}_2(\text{ad})(\text{gua})]$	8.33 (s, NH ₂ (ad)), 8.78 (1H, s, H-8(ad)), 9.20 (1H, s, H-2(ad)), 13.45 (1H, s, H-9(ad)), 6.63 (s, NH ₂ (gua)), 8.29 (1H, s, H-8(gua)), 11.17 (1H, s, H-9(gua)), 14.06 (1H, s, H-1(gua))
Cytosine	5.56 (1H, s, H-5), 7.06 (s, NH ₂), 7.32 (1H, s, H-6), 10.56 (1H, s, H-9)
Adenine	7.11 (s, NH ₂), 8.10 (2H, s, H-2 and H-8), 12.86 (1H, s, H-9)
Guanine	5.57 (s, NH ₂), 7.08 (1H, s, H-8), 10.55 (1H, s, H-9)

^a25°C in DMSO-*d*₆ δ [ppm].

indicating the nonelectrolyte nature of these complexes [41–43]. The effective magnetic moment measurement at room temperature confirmed their diamagnetic characters of these complexes thus square-planar geometry.

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 Figure 2.

3.7. In Vitro Cytotoxicity. The growth inhibition effect of the complexes as well as the free ligands was measured on two leukemia cell lines (human promyelocytic leukemia (HL60) and human histiocytic leukemia (U937)) with curcumin as a positive control. The results as expressed by IC₅₀ values (μM) are presented in Table 4. Of the three nucleobase ligands, guanine was the only cytotoxin on HL60 within the working concentration of 0–200 μM . It reported an IC₅₀ value of $71.38 \pm 9.01 \mu\text{M}$. Guanine was also cytotoxic against U937, recording a value of $53.53 \pm 8.55 \mu\text{M}$.

All the three mixed ligand complexes were significantly cytotoxic with the exception of $\text{cis-[PdCl}_2(\text{Cyt})(\text{Ad})]$ which did not show any activity on HL60 within the working concentration. From Table 4, $\text{cis-[PdCl}_2(\text{Ad})(\text{Gua})]$ was the most cytotoxic against both cell lines with IC₅₀ values of 11.45 ± 2.91 and $8.31 \pm 1.44 \mu\text{M}$ on the respective cell lines. It was more cytotoxic than the positive control (curcumin)

TABLE 4: IC₅₀ values of the complexes tested on the respective cell lines.

Complex	Cell line	
	HL60	U937
$\text{cis-[PdCl}_2(\text{Cyt})(\text{Gua})]$	132.01 ± 3.44	17.63 ± 1.25
$\text{cis-[PdCl}_2(\text{Cyt})(\text{Ad})]$	>200	34.56 ± 2.02
$\text{cis-[PdCl}_2(\text{Ad})(\text{Gua})]$	11.45 ± 2.91	8.31 ± 1.44
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

on U937 cell line. The high activity of $\text{cis-[PdCl}_2(\text{Ad})(\text{Gua})]$ could be attributed to the bulkiness of the nucleobase ligands which has the tendency to significantly reduce the rate of deactivation by sulphur-containing molecules within the cell [44, 45].

3.8. Antioxidant Activity. Various researchers have used scavenging effect of a chemical on DPPH radical as a quick and reliable parameter to measure the *in vitro* antioxidant activity [12, 13, 46]. This assay is based on the measurement of the decrease in molar absorptivity of DPPH at 517 nm after reaction with the test compound.

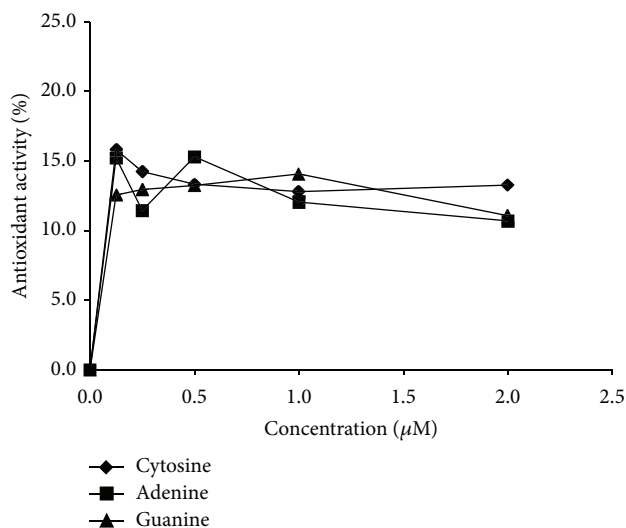


FIGURE 3: Percent antioxidant activity of the free ligands.

From Figure 3, the antioxidant activity of the free ligands was found to be between 10 and 15% but, upon complexation, it increased significantly (Figure 4). The increased antioxidant activity of these complexes can be attributed to the downfield shift of the $^1\text{H-NMR}$ signals (Table 3). As reported [12, 13], this phenomenon is as a result of the electron withdrawing effect of the Pd(II) ion which facilitates the release of hydrogen to reduce the DPPH radical. These proton shifts were very profound in $\text{cis-}[\text{PdCl}_2(\text{Ad})(\text{Gua})]$ with the H-1 proton of guanine absorbing at a chemical shift of 14.06 ppm. This could contribute to the higher activity of $\text{cis-}[\text{PdCl}_2(\text{Ad})(\text{Gua})]$ with an EC_{50} (concentration of complexes needed to scavenge 50% of the initial DPPH concentration) value of 1.00 mM.

4. Conclusion

In this study, we reported the synthesis and spectroscopic characterization of mixed ligand Pd(II) chloride complexes bearing the nucleobases cytosine, adenine, and guanine. A four-coordinated square-planar geometry was proposed for these complexes based on spectroscopic and magnetic measurements. The ligands and the metal complexes were tested for their antioxidant and *in vitro* cytotoxic activities. All the complexes were significantly cytotoxic with $\text{cis-}[\text{PdCl}_2(\text{Ad})(\text{Gua})]$ showing higher activity than the positive control (curcumin) on U937 cell line. All the complexes also show significant free radical scavenging ability when tested against DPPH.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

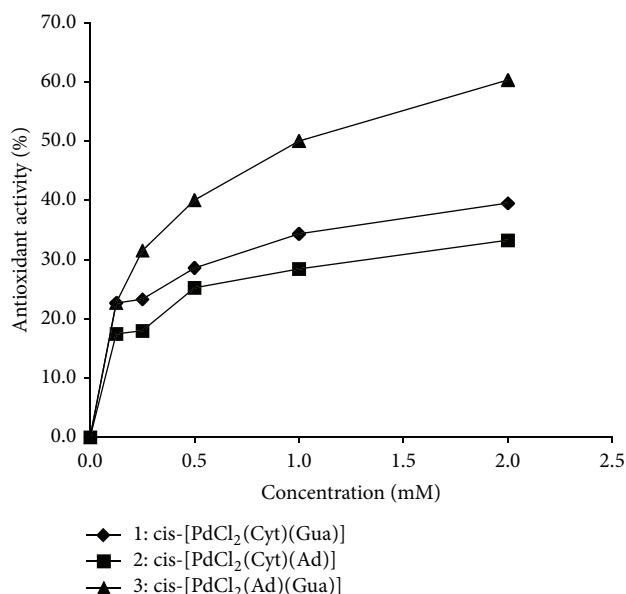


FIGURE 4: Percent antioxidant activity of the mixed ligand complexes.

Acknowledgments

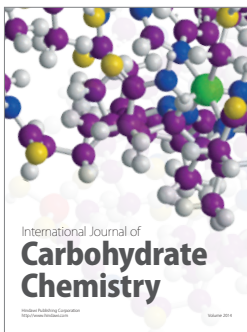
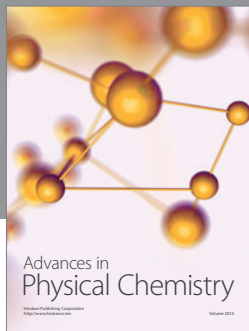
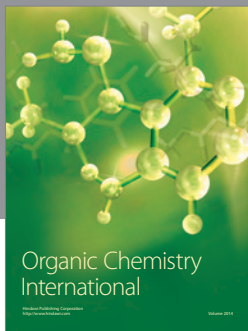
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