

SYNTHESIS, CHARACTERISATION, AND ANTICANCER AND ANTIOXIDANT ACTIVITIES OF NOVEL COMPLEXES OF PALLADIUM AND AN ORGANIC SCHIFF-BASE LIGAND

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ABSTRACT. Treatment of the Schiff base 2-N-(salicylidene) benzothiazole (SabtH) with palladium chloride afforded the neutral 2-N-(salicylidene) benzothiazole palladium(II) complex. This was then treated with one molar equivalent of either ethylenediamine or 1,10-phenanthroline, yielding the neutral mixed ligand complexes **1** and **2**, respectively. The prepared organic ligand and its mixed ligand complexes were characterised via UV-Vis, FTIR, ¹H-NMR, and ¹³C-NMR spectroscopy. The antiproliferative activities of **1** and **2** were tested against MCF-7 (breast) and HT-29 (colon) cancer cells using an MTT assay. **1** showed strong antiproliferative activity against both MCF-7 and HT-29 cancer cells, with IC₅₀ values of 74.6 ± 8.35 and 174 ± 20.28 µg/mL, respectively. In addition, **2** exhibited the maximum antioxidant activity, with an EC₅₀ value of 1029 ± 196.76 µg/mL.

KEY WORDS: 2-N-(Salicylidene) benzothiazole, 1,10-Phenanthroline, Palladium mixed ligand complexes, Anticancer, Antioxidant activity

INTRODUCTION

In the synthesis of transition metal complexes, the ability of nitrogen to act as a donor atom and coordinate metal ions has greatly enriched the field of coordination chemistry. Drugs and fungicidal agents can be produced from coordination compounds that contain organic ligands [1-3]. The Schiff bases typically exhibit bidentate ligand behaviour and interact with metallic cations to produce neutral metal complexes; notably, numerous studies have investigated the metal complexes of Schiff bases [4-6]. Most transition metal ions form stable complexes with Schiff-base ligands, which can coordinate to the metal through both nitrogen and oxygen. Biological features play a major role in the significance of the Schiff-base complexes involving Pd(II) ions [7]. Recent studies [8] have been conducted on the coordination chemistry and biological effects of mixed ligand complexes of Pd(II), Zn(II), and Cd(II); research also exists on the coordination chemistry and thermal analysis of Hg(II) with a mixed ligand comprising a Schiff-base anion, phosphine, pyridine, and bipyridine as co-ligands [4, 9-11]. These ligands are adaptable and exist in both neutral and anionic forms. Due to their significance in biology and medicine, the metal complexes of ethylenediamine, phenanthroline, and Schiff bases have attracted significant attention [12]. Notably, palladium(II) complexes involving Schiff bases, phosphines, pyridine, ethylenediamine, bipyridine, and 1,10-phenanthroline have attracted much interest because of their numerous antibacterial [13-15], antifungal [16-18], chemical sensing [19, 20], antiviral [6, 21, 22], and catalytic [17, 23, 24] applications. They have additionally been applied in the management of several cancers, including Hodgkin's disease. The current inquiry aims to introduce novel palladium(II) complexes (involving phenanthroline and Schiff mixed ligands) and examine their antioxidant and anticancer properties.

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EXPERIMENTAL

Materials and instrumentation

The following chemicals were used as received from suppliers: sodium tetrachloropalladate(II), salicylaldehyde, 2-aminobenzothiazole, ethylenediamine, and 1,10-phenanthroline. KBr discs were prepared for Fourier-transform infrared (FTIR) spectroscopy, and the spectra were recorded using the Shimadzu 24 FTIR 8400s spectrophotometer. Electronic spectra of the prepared complexes were measured in the region of 200–800 nm for 10^{-3} M solutions in DMSO at 25 °C using the Shimadzu UV-160A ultraviolet-visible (UV-Vis) spectrophotometer with a 1.000 ± 0.001 cm matched quartz cell. Electrical conductivity measurements of the complexes were recorded at room temperature for 10^{-3} M sample solutions in DMSO using a PW9527 digital conductivity meter (Philips). Melting points were recorded using the Stuart melting point apparatus.

Synthesis of the organic ligand 2-N-(salicylidene) benzothiazole (SabtH)

The ligand 2-N-(salicylidene) benzothiazole (SabtH) was prepared by mixing an absolute ethanolic solution of 2-aminobenzothiazole (4506 mg, 30 mmol) with 3663.6 mg (30 mmol) of salicylaldehyde in 20 mL of ethanol. The mixture was refluxed for approximately 1–3 h. Upon cooling, a yellow precipitate was formed; this was filtered off, washed with the same solvent, and dried in a vacuum over anhydrous CaCl_2 to form the product in a 91% yield [25].

Synthesis of palladium complexes

In separate flasks, a solution of ethylenediamine (10.22 mg, 0.17 mmol) or 1,10-phenanthroline (31 mg, 0.17 mmol) in CHCl_3 (6 mL) was added to a suspension of the complex $[\text{Pd}(\text{SabtH})_2] \cdot 2\text{H}_2\text{O}$ (110.34 mg, 0.17 mmol) in CHCl_3 (8 mL). The reaction mixture was stirred at 30 °C for 3 h, and the yellow and orange precipitates were filtered off, washed with CHCl_3 , and dried under vacuum [9].

Antioxidant activity

The sample preparation for the antioxidant activity measurements was carried out using the DPPH assay [26–28]. First, the sample was dissolved in DMSO to a suitable concentration (1 to 5 mg/mL). Different volumes of the sample (100, 50, 25, and 12.5 μL) were then diluted with DMSO to a final volume of 100 μL . Next, 1900 μL of the DPPH reagent (final concentration of 1/10 mM dissolved in ethanol) was added to reach the final volume of 2 mL. The samples were subsequently incubated in the dark for 20 min. The control group was prepared with 100 μL of DMSO and 1900 μL of the DPPH reagent. After centrifugation at 12000 rpm for 2 min, the absorption of all samples was recorded at 517 nm. The results were reported as the mean \pm the standard deviation (SD).

Anticancer activity

The MTT method was utilised for the determination of cell viability [29, 30]. Briefly, 1×10^4 cells were seeded into each well of a 96-well plate for 24 h. Different concentrations (15.625, 31.25, 62.5, 125, 250, and 500 $\mu\text{g/mL}$) of the samples were added separately to the plate (six replicates), which was then incubated for 48 h. Subsequently, 100 μL of the MTT solution (at a final concentration of 0.05 mg/well) was added, and the plate was incubated for 4 h. Thereafter, 100 μL /well of DMSO (Merck, Germany) was used to solubilise the formazan crystals formed in

the cells. Finally, the absorbance was measured at 570 nm. For the statistical analysis, the test was performed in triplicate to obtain the standard deviation.

RESULTS AND DISCUSSION

Synthesis and characterisation of complexes

The general synthetic route for the metal–ligand complexes is provided in Scheme 1. The synthesised compounds are coloured powders, stable in air, nonhygroscopic, and easily soluble in DMF and DMSO. The melting points reveal that all the complexes decompose before melting. The analytical data (Table 1) indicate a metal-to-ligand ratio of 1:1 for all the complex systems.

Table 1. Physical properties and electrical conductivities of the metal–ligand complexes.

Compound	Formula	F. Wt (g)	Colour	Yield (%)	Decomp. Temp., °C	Conductance ($\mu\text{S}\cdot\text{cm}^{-1}$)
SabtH	$\text{C}_{14}\text{H}_{10}\text{ON}_2\text{S}$	254.32	Yellow	91	145–147	-
1	$\text{C}_{30}\text{H}_{26}\text{O}_2\text{N}_6\text{S}_2\text{Pd}$	673.14	Yellow	95	>180	26.5
2	$\text{C}_{40}\text{H}_{26}\text{O}_2\text{N}_6\text{S}_2\text{Pd}$	793.26	Orange	91.6	>230	19.6

The organic ligand was successfully synthesised, as confirmed by the ^1H - and ^{13}C -NMR spectra [31]. The ligand was then mixed with palladium to form complex **1**; according to its ^1H -NMR spectrum, the resonances related to the aromatic protons appear as multiplets in the 6.80–8.90 ppm range. The signals related to the ethylene moiety in the ethylenediamine ligand appear as multiplets between 3 and 4 ppm. In the ^{13}C -NMR spectrum of complex **1**, the aliphatic carbon signals appear in the 46.0–62.6 ppm range, and multiple signals related to the aromatic ring carbons appear in the 114–167 ppm range. In the ^1H -NMR spectrum of complex **2**, multiplets related to the aromatic protons appear at 5.70–11.50 ppm; in its ^{13}C -NMR spectrum, the expected aromatic-only carbon signals appear at 120–190 ppm. The FTIR spectra of complexes **1** and **2** also support their formation. The FTIR spectrum of the ligand alone was first analysed, and characteristic peaks corresponding to functional groups likely to coordinate with a metal centre were identified. These included, for example, peaks corresponding to C=O (carbonyl) stretches (~ 1700 – 1750 cm^{-1}) or N-H (amine) stretches (~ 3300 – 3500 cm^{-1}). Metal coordination typically leads to shifts in the stretching frequencies; for instance, a carbonyl peak might shift to lower wavenumbers upon coordination to a metal centre. In the FTIR spectrum of complex **1**, sharp signals related to aliphatic C-H stretching appear just below 3000 cm^{-1} , while aromatic C-H stretching frequencies appear above 3000 cm^{-1} as sharp signals. In the FTIR spectrum of complex **2**, only signals related to aromatic C-H stretching appear above 3000 cm^{-1} (Table 2). The ^1H -NMR spectra of the ligands and complexes can be compared to identify the functional groups coordinated to the metal centre. In this regard, chemical shifts, peak multiplicity, signal integration, splitting patterns, peak broadening, saturation effects, and resonance enhancement are key features. The proton chemical shifts in ligands may shift upon coordination to a metal centre, while the peak multiplicity may change due to decoupling. Integration values should correlate with the expected number of protons on each ligand in the complex. Notably, the free ligand chemical shift at 7.94 ppm (s, 1H, -N=CH-) is shifted to 7.64 ppm in the complexes. Furthermore, ^{13}C -NMR spectroscopy was used to confirm the formation of the complexes. Coordination to a metal centre often induces changes in the electronic environment around the coordinated atoms, leading to changes in the chemical shifts of the corresponding carbon nuclei in the free ligands and complexes. These shifts can, thus, be indicative of coordination and aid in identifying the functional groups involved. Furthermore, the multiplicity (singlet, doublet, triplet, etc.) and coupling constants observed in the ^{13}C -NMR spectra of ligands and complexes can provide

valuable information. Notably, coordination can alter the spin-spin coupling patterns and coupling constants of nearby carbon atoms, which can aid in identifying the coordination environment.

Table 2. Infrared spectral data of the mixed complexes (cm^{-1}).

Compound	ν C=N	ν C-O	ν O-H	ν C=N	ν Pd-N	ν Pd-O
1	1604	1365	3170	1533	578	514
2	1604	1340	3284	1533	750	510

Electronic spectra

The UV-Vis spectra of the free mixed ligands L_1 and L_2 and their complexes were recorded in DMF solution over the range of 230–900 nm, as presented in Table 3. The absorption spectra of L_1 and L_2 consist of intense bands centred at 300 and 316 nm, respectively, attributed to $n-\pi^*$ transitions of the azomethine group [32]. These transitions are also found in the spectra of the complexes, though they are shifted towards lower frequencies, confirming the coordination of the ligands to the metallic ions [33]. The UV-Vis spectra for both complexes also confirm the formation of the structures; these were recorded in DMF changes to DMSO medium at room temperature (Figures 1 and 2). UV-Vis (DMSO, $C = 1 \times 10^{-6} \text{ mol dm}^{-3}$) λ_{max} (ϵ), nm ($\text{mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$): 265 nm (37736 cm^{-1}) and 265.5 nm (37665 cm^{-1}) for complexes **1** and **2**, respectively.

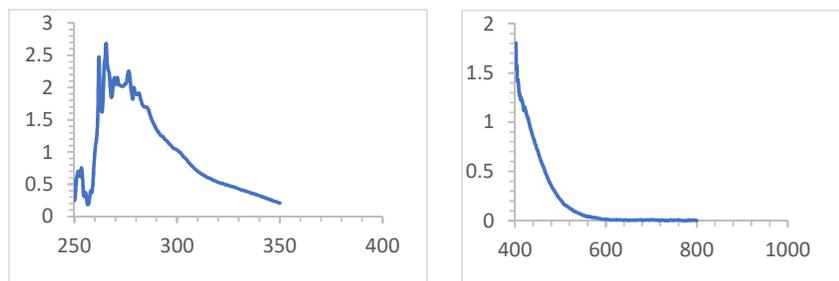


Figure 1. UV-Vis spectrum of $\text{C}_{30}\text{H}_{26}\text{O}_2\text{N}_6\text{S}_2\text{Pd}$ (**1**) in the range 250–900 nm.

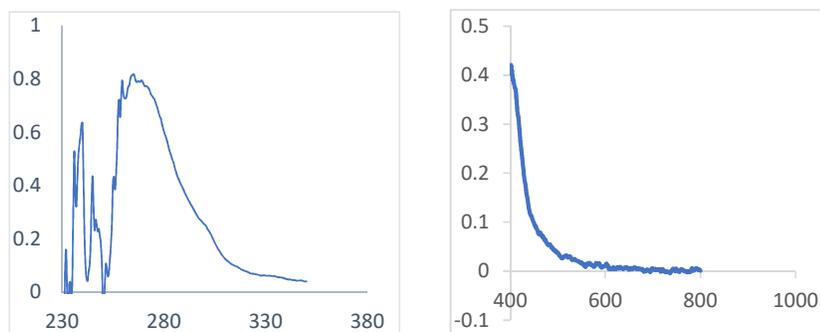


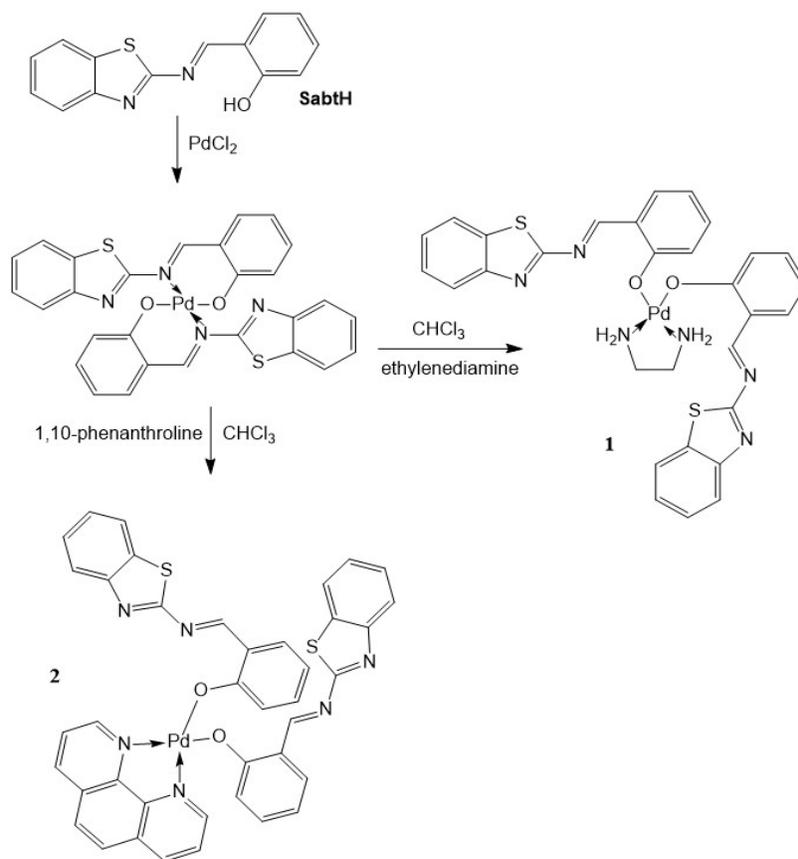
Figure 2. UV-Vis spectrum of $\text{C}_{40}\text{H}_{26}\text{O}_2\text{N}_6\text{S}_2\text{Pd}$ (**2**) in the 250–900 nm range.

Metal-to-ligand and ligand-to-metal charge transfer imply the transfer of electrons between the metal and ligand. $^1A_{1g} \rightarrow ^1B_{1g}$ represents a d-d transition, where electrons are transferred

between d orbitals from the ground state to the excited state; this transition is primarily responsible for the colour of the metal complexes. The nature of the ligand field around the metal ion was deduced from the band assignments of the complexes, presented in Table 3. The electronic spectra of the mixed ligand Pd(II) complexes **1** and **2** in DMSO solution reveal absorption bands at 401.5 and 401 nm, respectively. The bands can be assigned to the $^1A_{1g} \rightarrow ^1B_{1g}$ transition, suggesting a square planar geometry around the Pd(II) ion [34, 35].

Table 3. Electronic (UV-Vis) spectral data of the mixed ligand Pd(II) complexes.

Compounds	Band assignments			
	Charge transfer			$^1A_{1g} \rightarrow ^1B_{1g}$
1	(262 nm) 38168 cm^{-1}	(265.5 nm) 37665 cm^{-1}	(276.5 nm) 36166 cm^{-1}	(401.5 nm) 24907 cm^{-1}
2	(239.5 nm) 41754 cm^{-1}	(260 nm) 38476 cm^{-1}	(266 nm) 37594 cm^{-1}	(401 nm) 24938 cm^{-1}



Scheme 1. Synthesis of the palladium complexes.

Antioxidant activity

It is well documented that reactive oxygen species (ROS) are involved in the etiopathogenesis of numerous chronic diseases, such as atherosclerosis, hypertension, and coronary heart disease. In addition, combining the redox properties of metal ions and various ligands is a noteworthy method to develop antioxidant compounds [36]. Considering the above, the antioxidant activities of the Pd(II)–SabtH complexes **1** and **2** towards DPPH were evaluated and compared with that of the well-known antioxidant compound vitamin C, which is the most commonly used reference standard [37]. The EC₅₀ results (μg/mL) for the synthesised ligand and complexes are summarised in Table 4, with complex **2** showing stronger antioxidant activity (1029 ± 96.76 μg/mL) than the ligand and complex **1** (1128 ± 95.71 and 1846 ± 94.79 μg/mL, respectively). Overall, the ligand and complexes exhibit low DPPH scavenging capacities and lower antioxidant activities compared to the reference compound vitamin C.

Table 4. Antioxidant activities of the metal–ligand complexes.

Compound	Molecular formula	EC ₅₀ (μg/mL)
SabtH	C ₁₄ H ₁₀ ON ₂ S	1128 ± 95.71
1	C ₃₀ H ₂₆ O ₂ N ₆ S ₂ Pd	1846 ± 94.79
2	C ₄₀ H ₂₆ O ₂ N ₆ S ₂ Pd	1029 ± 96.76
vitamin C	C ₆ H ₈ O ₆	21.44 ± 2.06

Anticancer activity

The structure–activity relationship and anticancer activity of the ligand and complexes **1** and **2** were evaluated via an MTT assay using the MCF-7 (breast) and HT-29 (colon) cancer cell lines; the measured half-maximal inhibitory concentration (IC₅₀) values are given in Table 5. Complex **1** shows strong anticancer activity against the MCF-7 and HT-29 cancer cells, with IC₅₀ values of 74.6 ± 8.35 and 174 ± 20.28 μg/mL, respectively (i.e., the overall order of activity is MCF-7 > HT-29). The biochemical effects could be due to the active functional groups and bridge spacer, ethylenediamine, which could play a vital role in the anticancer potential of the C₃₀H₂₆O₂N₆S₂Pd and C₄₀H₂₆O₂N₆S₂Pd complexes. Notably, the synthesised complexes exhibit stronger in vitro anticancer activities against the tested cancer cell lines compared with the ligand before the addition of palladium.

Table 5. Anticancer activities of the metal–ligand complexes.

Compounds	Molecular formula	IC ₅₀ (μg/mL)	
		HT-29	MCF-7
SabtH	C ₁₄ H ₁₀ ON ₂ S	1153 ± 87.91	707.5 ± 96.99
1	C ₃₀ H ₂₆ O ₂ N ₆ S ₂ Pd	174 ± 20.28	74.6 ± 8.35
2	C ₄₀ H ₂₆ O ₂ N ₆ S ₂ Pd	346 ± 33.63	374.6 ± 40.61

CONCLUSION

In this study, novel palladium complexes were successfully prepared and characterised via various spectroscopic techniques. The anticancer and antioxidant activities of the ligand and mixed ligand metal complexes were also investigated, with the latter showing favourable activities. The ¹H- and ¹³C-NMR spectral results, physical properties, and conductivity measurements confirmed that the ligand adopts a bidentate behaviour and bonds with the metal through its nitrogen and oxygen atoms. Furthermore, the in vitro anticancer activity results indicated that, among the tested

compounds, the $C_{30}H_{26}O_2N_6S_2Pd$ complex shows the highest activity against MCF-7 and HT-29 cells. Notably, palladium played a vital role in enhancing the biological activity against the selected human cell lines. Further syntheses of other transition metal complexes with the ligand SabtH are in progress.

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