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Organometallic ruthenium(II) complexes containing NS donor Schiff bases: Synthesis, structure, electrochemistry, DNA/BSA binding, DNA cleavage, radical scavenging and antibacterial activities

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ABSTRACT

Four new cyclopentadienylruthenium(II)-acetophenone-4(*N*)-substituted thiosemi-carbazone complexes, with the general formula [Ru(η^5-C_5H_5)(H-Aptsc)PPh_3].Cl (**1**), [Ru(η^5-C_5H_5)(H-Apmtsc)PPh_3].Cl (**2**), [Ru(η^5-C_5H_5)(H-Ap-etsc)PPh_3].Cl (**3**) and [Ru(η^5-C_5H_5)(H-Ap-ptsc)PPh_3].Cl (**4**) were synthesised and characterised (^{1}H NMR, ^{13}C NMR, IR and electronic spectroscopy). The molecular structure of representative complexes **2** and **3** was confirmed by single crystal X-Ray diffraction technique. The binding ability of complexes (**1**–**4**) to calf-thymus DNA (CT DNA) and Bovine Serum Albumin (BSA) has been explored by absorption and emission titration methods. Based on the observations, an electrostatic and an intercalative binding mode have been proposed for the complexes with CT-DNA. The BSA protein binding studies have been monitored by quenching of tryptophan and tyrosine residues in the presence of complexes and static type of quenching mechanism has been proposed. *In vitro* free radical scavenging activity was performed by DPPH radical. The complexes (**1**–**4**) exhibited highest scavenging activity than conventional standard vitamin C ($IC_{50} = 5.65 \pm 0.12$). Further, antibacterial activity of the complexes has been screened against four pathogenic bacteria such as *Salmonella paratyphi*, *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis*. From the results it is found that all the complexes exhibited significant activity against the pathogens and among them, complex **3** exhibited higher activity.

1. Introduction

Thiosemicarbazones (TSCs) have attracted extensive attention by chemists and biologists due to their broad spectrum of pharmacological effects; these compounds and their metal complexes revealed significant antibacterial, antiviral, antifungal and particularly antitumor activity [1–3]. In recent years, a number of thiosemicarbazone derivatives have been synthesized, and their antitumor activity and a broad spectrum of chemotherapeutic properties were also evaluated [4–6]. Besides, the complexes contain transition metals and thiosemicarbazone ligands generally showed more potent pharmacological effects than the thiosemicarbazone ligands alone [7–9]. The biological properties of the thiosemicarbazone ligands can be modified and improved by linking to transition metal ions [10,11]. The ruthenium-based complexes, showed significant antiproliferation activity and lesser toxicity as compared to that of platinum drugs, which were developed in the last two decades [12–15]. In specific, the Ru(III) complexes, [HIm][*trans*-$RuCl_4$(DMSO)(Im)] (NAMI-A) and [ImH][*trans*-$RuCl_4(Im)_2$] (KP1019), have entered into clinical trials with very promising results [16–18]. The organometallic Ru(II) arene complexes, with the half-sandwich type structure, have demonstrated their potential [19–21]. Their coordination sites can be filled with various ligands, which offer several possibilities to modify biological and pharmacological activities by proper ligand selection [22, 23]. The complexes incorporated with 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]-decane (PTA) ligand, is exhibited significant activity against metastases [24–27]. The Ru(II)-arene complexes of thiosemicarbazones have also emerged as an approach to develop promising Ru-based therapeutic agents. Beckford et al. reported the structurally characterized ruthenium-arene half-

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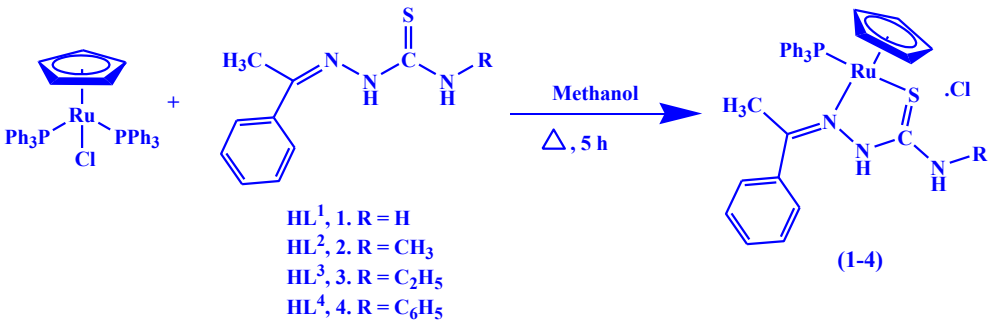
sandwich complexes with thiosemicarbazone ligands exhibiting good cytotoxic profiles against different human cancer cell lines, and their biological activities were apparently modified by the thiosemicarbazone coligand [10, 28]. In this line, Smith et al. demonstrated the cytotoxicity and antiparasitic activity of a set of thiosemicarbazone derivatives and their corresponding Ru(II)-arene complexes [29,30]. Moreover, the pharmacological activity of the binuclear thiosemicarbazone Ru-arene complexes were also demonstrated by Gambino and his co-workers [31, 32]. Even though the thiosemicarbazone Ru-arene complexes have been proven to have potential as effective anticancer drugs, their different modes of action and biological targets are still the focus of active research. In this paper, a series of acetophenone-4(*N*)-substituted thiosemicarbazone derivatives (**HL$^{1-4}$**) and their corresponding Ru(II)-cyclopentadienyl complexes(**1**–**4**) were synthesized and characterized by various spectroscopic techniques, and their DNA/BSA binding, DNA cleavage, Antioxidant studies, electrochemistry and antibacterial activity has been studied systematically.

2. Results and discussion

The reactions of [RuCl(PPh$_3$)$_2$(η^5-C$_5$H$_5$)] with an equimolar amount of various 4(*N*)-substituted thiosemicarbazones (**HL^1**–**HL^4**) in methanol resulted in the formation of new complexes (Scheme 1), the analytical data of which confirmed the stoichiometry of the complexes (**1**–**4**). The structure of the complexes **2** and **3** were confirmed by X-ray crystallographic studies and attempts were made to grow single crystals of complex **1** and **4** suitable for X-ray studies in various organic solvents were unsuccessful. The complexes are soluble in common organic solvents such as dichloromethane, chloroform, benzene, acetonitrile, ethanol, methanol, dimethylformamide and dimethylsulfoxide.

3. Spectroscopic studies

The IR spectra of the ligands [**HL^1-HL^4**] and their complexes provide information about the metal ligand bonding. A strong absorption at 1534-1596 cm^{-1} in the ligands [**HL^1-HL^4**] is assigned to the presence of $\upsilon_{(C=N)}$ group and this was found at 1535-1600 cm^{-1} in the complexes indicate the interaction of azomethine nitrogen with metal ion [33, 34]. The ligand may exist in thione-thiol tautomerization since it contains a thioamide (-NH-C=S) functional group. The absence of the $\upsilon_{(S-H)}$ stretching frequency in the region 2500-2600 cm^{-1} and the presence of $\upsilon_{(N-H)}$ stretching frequency in the region 3221-3316 cm^{-1} in the IR spectrum of the ligands indicating thione form in the solid state. This is further inferred from the presence of a strong band in the region 810-842 cm^{-1} corresponding to the presence of $\upsilon_{(C=S)}$ stretching frequency. However, in complexes **1**–**4** the absence of the $\upsilon_{(S-H)}$ stretching frequency and presence of $\upsilon_{(N-H)}$ stretching frequency at 3051-3055 cm^{-1} indicate the involvement of the thione sulphur in the coordination rather than thiolate [35, 36]. This is further supported by the presence of a strong band in the region 814-849 cm^{-1} corresponding to $\upsilon_{(C=S)}$ stretching frequency [37, 38]. The characteristic absorption band for triphenylphosphine are present in the expected region [39]. The electronic spectra of the complexes in CH_2Cl_2 showed one to two bands in the region 393–238 nm. The ground state of ruthenium(II) is $^1A_{1g}$, arising from the t^6_{2g} configuration in an octahedral environment. Excited state corresponding to the $t^5_{2g}e^1_g$ configuration are $^3T_{1g}$, $^3T_{2g}$, $^1T_{1g}$, $^1T_{2g}$. Hence, four bands corresponding to the transitions $^1A_{1g}\rightarrow{}^3T_{1g}$, $^1A_{1g}\rightarrow{}^3T_{2g}$, $^1A_{1g}\rightarrow{}^1T_{1g}$ and $^1A_{1g}\rightarrow{}^1T_{2g}$ are possible, in order of increasing energy. The bands in the 329–393 nm region present in all the complexes may be assigned to the Ru(4dπ)$\rightarrow\pi^*$ (ligand) (MLCT) transition [40–42]. The other high intensity bands in the 300–238 nm region were characterized by ligand-centred (LC) transitions and have been designated as $\pi-\pi^*$ and $n-\pi^*$ transitions for the electrons localized on the azomethine group of the Schiff bases. The ^{1}H NMR spectra of the ligands [**HL^1-HL^4**] showed a singlet at δ 8.61–9.41 ppm corresponding to (N(2)H-C=S) group, [43] whereas in the complexes (**1**–**4**), a singlet occurred at δ 8.92–11.54 ppm due to (N(2)H-C=S-) group indicating that the ligand remains in its thionic form (Figure S1-S12) [44]. This shift showed that the thiosemicarbazone is coordinated to the ruthenium through thione sulphur atom rather than thiolate sulphur [45, 46]. In complexes (**1**–**4**) a sharp singlet appeared at δ 4.10–4.62 ppm due to cyclopentadienyl protons [47]. A singlet observed in the ligand **HL^1** at δ 6.38 ppm due to terminal (-NH$_2$) was appeared at 8.49 ppm in the complex **1** [44]. A singlet observed in the ligands **HL^2**, **HL^3** and **HL^4**at δ 7.26, 7.00 and 8.75 ppm due to the presence of terminal (-NH) was appeared in the complexes **2, 3** and **4** as a singlet at δ 11.54, 9.52 and 10.65 ppm respectively [44]. A doublet observed in **HL^2** at δ 3.26–3.27 ppm due to the presence of terminal methyl protons was appeared as a singlet in the complex **2** at δ 2.94 ppm. For **HL^3** methylene protons of ethyl group appeared as a pentet at δ 3.73–3.79 ppm in the ligand was appeared as a multiplet in the complex **3** at δ 1.58–1.60 ppm and methyl protons of ethyl group appeared as a triplet in both the ligand and complex at δ 1.04–1.33 ppm [48]. A singlet appeared at δ 2.28–2.70 ppm of the ligands and complexes were assigned to the presence of methyl group protons of acetophenone [44]. The ^{13}C {^{1}H} NMR spectra of the complexes (**1**–**4**) (Figs. 9–12) contain resonances for the cyclopentadienyl ring carbons around δ 81.43–83.81 ppm [47]. The resonance observed around δ 159.14–170.28 ppm assigned to the (C=N) carbon of the ligands [45]. In complexes (**1**–**3**) resonances observed around δ 179.31–179.88 ppm as more deshielded indicating the thione sulphur coordination to ruthenium [35, 36]. The



Scheme 1. Synthesis of new ruthenium(II) complexes.