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Synthesis, spectral characterization, DNA interaction, radical scavenging and cytotoxicity studies of ruthenium(II) hydrazone complexes

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ABSTRACT

Three new ruthenium(II) complexes with hydrazone ligands, furan-2-carboxylic acid (2,4-dihydroxy-benzylidene)-hydrazide (**HL^1**), furan-2-carboxylic acid [4-(ethyl-propyl-amino)-2-hydroxy-benzylidene]-hydrazide (**HL^2**) and furan-2-carboxylic acid (3-ethoxy-2-hydroxy-benzylidene)-hydrazide (**HL^3**) were synthesized and characterized by various spectro-analytical techniques. The hydrazone ligands act as a tridendate ligand with ONO as the donor sites and are preferably found in the enol form in all the complexes. The molecular structure of the ligands was determined by single crystal X-ray diffraction technique. The interaction of the ligands and the complexes with CT-DNA were evaluated by an absorption titration method which revealed that the compounds interact with CT-DNA through intercalation. Gel electrophoresis assay demonstrated the ability of the complexes to cleave the calf thymus DNA hydrolytically. Antioxidant studies showed that the ruthenium(II) complexes have a strong radical-scavenging properties. Further, the cytotoxic effect of the compounds examined on cancerous cell lines showed that the complexes exhibited substantial anticancer activity.

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1. Introduction

In recent years, there has been growing interest pertaining to the synthesis of metal based chemotherapeutic agents in the field of inorganic medicinal chemistry [1]. The major focus on this field combines the elements of chemistry, pharmacology and biochemistry. Transition metal complexes have been utilized for the design and development of metal based chemotherapeutic agents that are capable of binding and cleaving nucleic acid under physiological conditions. Metal based compound cisplatin is one of the most widely used anticancer drug [2–5].

The applicability of these drugs is associated with high toxicity leading to severe side effects and acquired drug resistance. This in turn affects the administration of the drugs. To overcome these limitations, attempts are being made to develop alternatives for platinum based drugs which are less toxic and more effective for the chemotherapeutic application [6]. In this respect, ruthenium complexes are better suited because of its variable oxidation states, low toxicity, selectivity for cancer cells and ability to mimic iron in binding to biomolecules [7]. Ruthenium complexes are currently investigated because of their utility as DNA structural probes, DNA foot printing and sequence specific cleavage agents and potential anticancer drug. Interaction of small molecules with DNA has been studied extensively, since DNA is the material of inherence and controls the structure and functions [8]. Many ruthenium complexes were recently shown to possess encouraging cytotoxic and antitumor properties in preclinical models. The entrance of two Ru based drugs, NAMI-A and KP1019 into clinical trials for the treatment of metastatic tumors increased the interest on this metal [9,10]. NAMI-A has been used as an antimetastatic drug and KP1019 has been employed as colon carcinoma drug [11,12]. In addition, hydrazones are versatile ligands occupying a unique position in drug discovery and offer different modes of coordination towards metal ions and display wide range of biological properties, such as anti-inflammatory, antioxidant and anticancer [13–16]. Studies have demonstrated that hydrazones are potent inhibitors for the cancer cells. Incorporation of hydrazone and their corresponding metal complexes can result in alteration and enhancement of their biological activity [17,18]. In the field of pharmacy, the binding capacity is further increased by condensation of hydrazide with a salicylaldehyde derivative [19–21]. This aroused our interest in the design of ruthenium(II) salicylaldehyde hydrazone complexes with a view point towards evaluating biological properties such as DNA binding, DNA cleavage, antioxidant and cytotoxicity. Herein, we report the synthesis, characterization of ruthenium(II) complexes containing hydrazone ligands derived from condensing furan-2-carboxylic acid hydrazide with 2,4-dihydroxybenzaldehyde/4-diethylaminosalicylaldehyde/3-ethoxy salicylaldehyde. The crystal structure of the hydrazone ligands has been determined by X-ray crystallography. The investigation of the biological properties of the ligands and ruthenium(II) complexes has been focused on the binding properties with CT-DNA, DNA cleavage properties, antioxidant properties against DPPH, OH and NO radicals and *in vitro* anticancer activity against HeLa and MCF-7 cancer cell lines.

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2. Experimental Details

2.1. Materials and Instrumentation

All the chemicals used were of chemically pure and AR grade. Solvents were purified and dried according to the standard procedure [22]. The metal precursor $[RuHCl(CO)(PPh_3)_3]$ was prepared by literature method [23]. Melting points were recorded with Veego VMP-DS heating table and elemental analysis (C, H and N) were performed on a Perkin Elmer 240C elemental analyzer at University of Hyderabad, Hyderabad, India. Infrared spectra were recorded as a KBr pellets method in the range of 400–4000 cm^{-1} using a Perkin Elmer FT-IR 8000 spectrophotometer. Electronic spectra were recorded in DMSO solution with a systronics double beam UV–Vis spectrophotometer 2202 in the range of 200–800 nm. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV III 500 MHZ instrument using TMS as an internal reference. ^{31}P NMR spectra were recorded on a Bruker AV III 500 MHZ instrument using ortho phosphoric acid as an internal reference. The EI mass spectrum of the complexes was recorded on a JEOL GCMATE II mass spectrometer. Calf-thymus (CT-DNA) was purchased from Bangalore Genei, Bangalore, India. DNA cleavage studies were carried out using Gelstan, Gel documentation system. Antioxidant and anticancer studies were carried out at the Kovai Medical Centre and Hospital Pharmacy College, Coimbatore, Tamil Nadu.

2.2. Preparation of Hydrazone Ligands

A methanolic solution (50 mL) of furan-2-carboxylic acid hydrazide (0.01 mol) was added to a methanol solution (25 mL) containing 2, 4-dihydroxybenzaldehyde/4-diethylaminosalicylaldehyde/3-ethoxy salicylaldehyde (0.01 mol). The mixture was refluxed for an hour, which results in the formation of a precipitate. The reaction mixture was cooled to room temperature and the solid compound was filtered, washed and recrystallized from ethanol. Needle shaped crystals suitable for X-ray diffraction analysis were formed (Scheme 1).

Furan-2-carboxylic acid (2,4-dihydroxy-benzylidene)-hydrazide **HL¹**(1): Color: Yellow; Yield: 89%; M.P: 207 °C. Anal. calcd. for $C_{12}H_{10}N_2O_4$ (%): C, 58.54; H, 4.09; N, 11.38; O, 25.99. Found (%): C, 58.51; H, 4.15; N, 11.31; O, 25.93. IR (KBr, cm^{-1}): 1615 $\nu(C = N)$; 1632 $\nu(C = O)$; 3177 $\nu(NH)$; 3325 $\nu(Ph–OH)$. UV–vis (DMSO), λ_{max} (nm): 264, 313 ($\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$). ^1H NMR (DMSO-d_6); δ 9.97 (s, 1H,–NH); δ 8.50 (s, 1H, H–C = N); δ 11.33 (s, 1H,C8–OH); δ 11.94 (s, 1H, C10–OH); δ 6.31–7.94 (m, 6H, aromatic).^{13}C NMR (DMSO-d_6); δ 162 (C = O); δ 149 (C = N); δ 102–139 (aromatic).

Furan-2-carboxylic acid [4-(ethyl-propyl-amino)-2-hydroxy-benzylidene]-hydrazide (**HL²**) (2): Color: Pale yellow; Yield: 85%; M.P: 216 °C. Anal. calcd. for $C_{16}H_{19}N_3O_3$ (%): C, 63.77; H, 6.36; N, 13.94; O, 15.93. Found (%): C, 63.81; H, 6.30; N, 13.90; O, 15.98. IR (KBr, cm^{-1}): 1600 $\nu(C = N)$; 1631 $\nu(C = O)$; 3123 $\nu(NH)$; 3433 $\nu(Ph–OH)$. UV–vis (DMSO), λ_{max} (nm): 265, 373 ($\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$). ^1H NMR (DMSO-d_6); δ 9.59 (s, 1H,–NH); δ 8.41 (s, 1H, H–C = N); δ 11.79 (s, 1H, OH); δ 6.10–7.91 (m, 6H, aromatic); δ 1.10 (m, 6H, CH_3), 4.49 (m, 4H, CH_2).^{13}C NMR (DMSO-d_6); δ 160 (C = O); δ 144 (C = N); δ 102–139 (aromatic); δ 47 (CH_2); δ 12.65 (CH_3).

Furan-2-carboxylic acid (3-ethoxy-2-hydroxy-benzylidene)-hydrazide (**HL³**) (3): Color: Yellow; Yield: 87%; M.P: 213 °C. Anal. calcd. for $C_{14}H_{14}N_2O_4$ (%): C, 61.31; H, 5.14; N, 10.21; O, 23.33. Found (%): C, 61.38; H, 5.19; N, 10.28; O, 23.39. IR (KBr, cm^{-1}): 1605 $\nu(C = N)$; 1636 $\nu(C = O)$; 3137 $\nu(NH)$; 3456 $\nu(Ph-OH)$. UV–vis (DMSO), λ_{max} (nm) 261, 377 ($\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$). ^1H NMR (DMSO-d_6); δ 9.60 (s, 1H,–NH); δ 8.64 (s, 1H, H–C = N); δ 10.81 (s, 1H, OH); δ 6.60–7.91 (m, 6H, aromatic); δ 1.35 (m, 3H, CH_3), 4.0 (m, 2H, CH_2).^{13}C NMR (DMSO-d_6); δ 164 (C = O); δ 148 (C = N); δ 112–138 (aromatic); δ 62 (OCH_2); δ 15 (CH_3).

2.3. Preparation of Ruthenium(II) Complexes

The dibasic tridentate ligands (**HL¹–HL³**) (0.5 mmol) were added to a solution of $[RuHCl(CO)(PPh_3)_3]$ in 1:1 M ratio in ethanol-benzene and the reaction mixture was refluxed for 6 h. The progress of the reaction was monitored using TLC. At the end of the reaction the solution was concentrated to about 3 mL and petroleum ether (60–80 °C) was added whereby the solid separated out. The obtained solid were recrystallized from CH_2Cl_2/petroleum ether and dried under vacuum (Scheme 2). Extensive efforts to obtain single crystals of the complexes were unsuccessful.

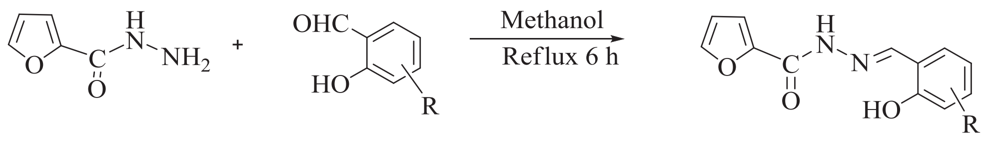
$[Ru(CO)(PPh_3)_2L^1]$ (4): Color: Yellow; Yield: 82%; M.P: 221–227 °C. Anal. calcd. for $C_{49}H_{38}N_2O_5P_2Ru$ (%): C, 65.55; H, 4.27; N, 3.12; O, 8.91. Found (%): C, 65.48; H, 4.25; N, 3.17; O, 8.87. EI–MS: Found m/z = 898.1289 (M^+) (calculated m/z = 898.1299 for (M^+). IR (KBr, cm^{-1}): 1601 $\nu(C{=}N)$; 1332 $\nu(C\text{-}O)$; 1950 $\nu(C{\equiv}O)$ cm^{-1}. UV–vis (DMSO), λ_{max} (nm): 269, 312 (ILCT), 418 (MLCT). ^1H NMR (DMSO-d_6); δ 9.02 (s, 1H, H–C=N); δ 11.75 (s, 1H, C10–OH); δ 6.45–7.75 (m, 36H, aromatic).^{13}C NMR (DMSO-d_6); δ 158 (C–O); δ 152 (C=N); δ 193 (C≡O); δ 120–138 (aromatic).^{31}P NMR (DMSO-d_6); δ 37.12.

$[Ru(CO)(PPh_3)_2L^2]$ (5): Color: Brown; Yield: 84%; M.P: 229–235 °C. Anal. calcd. for $C_{53}H_{47}N_3O_4P_2Ru$ (%): C, 66.80; H, 4.97; N, 4.41; O, 6.72. Found (%): C, 66.85; H, 4.91; N, 4.49; O, 6.77. EI-MS: Found m/z = 953.2036 (M^+) (calculated m/z = 953.2085 for (M^+). IR (KBr, cm^{-1}): 1594 $\nu(C{=}N)$; 1357 $\nu(C–O)$; 1947 $\nu(C{\equiv}O)$ cm^{-1}. UV–vis (DMSO), λ_{max} (nm): 267, 321 (ILCT), 412 (MLCT). ^1H NMR (DMSO-d_6); δ 9.32 (s, 1H, H–C=N); δ 6.66–7.97 (m, 36H, aromatic); δ 1.14 (m, 6H, CH_3), 4.32 (m, 4H, N–CH_2).^{13}C NMR (DMSO-d_6); δ 156 (C–O); δ 149 (C=N); δ 197 (C≡O); δ 120–140 (aromatic); δ 48.10 (CH_2); δ 16.01 (CH_3).^{31}P NMR (DMSO-d_6); δ 37.43.

$[Ru(CO)(PPh_3)_2L^3]$(6): Color: Brown; Yield: 85%; M.P: 227–239 °C. Anal. calcd. for $C_{51}H_{42}N_2O_5P_2Ru$ (%): C, 66.16; H, 4.57; N, 3.03; O, 8.64. Found (%): C, 66.21; H, 4.52; N, 3.10; O, 8.61. EI–MS: Found m/z = 926.1629 (M^+) (calculated m/z = 926.1612 for (M^+). IR (KBr, cm^{-1}): 1598 $\nu(C{=}N)$; 1374 $\nu(C\text{-}O)$; 1952 $\nu(C{=}O)$ cm^{-1}. UV–vis (DMSO), λ_{max} (nm): 263, 323 (ILCT), 410 (MLCT). ^1H NMR (DMSO-d_6); δ 9.36 (s, 1H, H–C=N); δ 6.58–7.98 (m, 36H, aromatic); δ 1.30 (m, 3H, CH_3), 4.04 (m, 2H, CH_2).^{13}C NMR (DMSO-d_6); δ 158 (C–O); δ 153 (C=N); δ 192 (C≡O); δ 129–138 (aromatic); δ 60 (OCH_2); δ 14 (CH_3).^{31}P NMR (DMSO-d_6); δ 38.02.

2.4. Single Crystal X-Ray Diffraction Studies

Single crystal X-ray diffraction data of ligands HL^1, HL^2 and HL^3 were collected at room temperature on a Bruker AXS KAPPA APEX2 CCD diffractometer equipped with a fine focused sealed tube. The unit cell parameters were determined and the data collections of ligands HL^1, HL^2 and HL^3 were performed using a graphite-mono chromate Mo Kα (λ = 0.71073 Å) radiation by φ and Ω scans. The data collected were reduced by SAINT program [24] and the empirical absorption corrections



Scheme 1. Synthetic route of the hydrazone ligands. Where, **HL¹**: R = 4-OH, **HL²**: R = 4 N(CH_2–CH_3)$_2$, **HL³**: R = 3-OC_2H_5.

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