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Synthetic, characterization and cytotoxic studies of ruthenium complexes with Schiff bases encompassing biologically relevant moieties

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ABSTRACT

This research study describes the formation and characterization of novel paramagnetic ruthenium complexes, *cis*-Cl, *trans*-P-$[Ru^{II}Cl_2(carboim)(PPh_3)_2]$ with bidentate chelating carbohydrazide Schiff bases (carboim = bpc for **1**, ttc for **2** and tpc for **3**). These metal complexes were synthesized by the equimolar coordination reactions of *trans*-$[RuCl_2(PPh_3)_3]$ with *N*-[1,3-benzothiazole-2-ylmethylidene]pyridine-2-carbohydrazide (Hbpc), *N*-((uracil-5-yl)methylene)thiophene-2-carbohydrazide (Httc) and *N*-[(uracil-5-yl)methylidene]pyridine-2-carbohydrazide (Htpc), respectively. Physicochemical techniques including nuclear magnetic resonance-, electron-spin resonance- and infrared spectroscopy, UV–Vis spectrophotometry, voltammetry as well as molar conductivity measurements provided definitive determinations of the respective ruthenium compounds' structures. The DPPH and NO radical scavenging capabilities of **1**–**3** and two previously reported ruthenium(II) complexes, *trans*-$[RuCl(PPh_3)_2(Htdp)]$ (H_2tdp = 5-((thiophen-3-yl)methyleneamino)-6-amino-1,3-dimethyluracil) (**4**) and $[RuCl(PPh_3)(H_3ucp)]$ (H_4ucp = 2,6-*bis*-((6-amino-1,3-dimethyluracilimino)methylene)pyridine) (**5**), were investigated. The calf-thymus DNA binding capabilities of **1**–**5** were explored using electronic spectroscopy and gel electrophoresis. In vitro anticancer studies showed that **1** and **2** were not active in the range tested, while **3**–**5** were toxic to HCC70 breast carcinoma cells, with **4** showing promising IC_{50} at 3.4 μM.

1. Introduction:

Current widespread interests in the bioinorganic chemistry of ruthenium stems largely from its diverse coordination chemistry and the fact that selected ruthenium complexes have afforded fewer side effects than established platinum-based chemotherapeutic agents [1]. The optimal activities of the ruthenium anticancer agents have been ascribed to their capabilities to mimic the biodistribution patterns of iron-containing biomolecules [2]. For instance, mechanistic studies have revealed that many ruthenium complexes have high affinity for transferrin receptors on malignant growths [3].

Recent progress to enhance drug efficacies of metallopharmaceuticals embrace the hypothesis of designing them with biologically active chaperones [4]. The versatility of this drug design approach is elaborated by the wide range of potential ligands that can function as variable site-specific chaperones while improving the pharmacodynamics and pharmacokinetics of the resultant ruthenium complexes [5]. For example, metal complex cations of ruthenium coordinated to the biologically active components, ibuprofen or diclofenac, displayed generally improved or comparable cytotoxicity than Cisplatin [6].

Herein, we consider carbohydrazide Schiff bases incorporating benzothiazole and uracil moieties, as stabilizing scaffolds for the *trans*-$[Ru^{II}(PPh_3)_2]$ core. Moreover, uracil and benzothiazole derivatives are essential pharmacophores in various antitumor agents and sensors [7–10]. The latter is illustrated in the organic compounds, *N*-formyl-2-(5-nitrothiophen-2-yl)benzothiazole-6-carbohydrazide and 1-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl) uracil which presented anticancer effects towards MCF7 breast cancer cells where the mechanism of activities are largely facilitated by inhibition of various enzymatic pathways [11,12]. In addition, synergistic effects between ruthenium complexes with benzothiazole or uracil chelating polypyridyl ligands have shown to result in optimal structure–activity relationships [13,14]. For instance, the diamagnetic ruthenium complex salts, *cis*-$[Ru(bpy)_2(uip)]^{2+}$ (bpy = 2,2′-bipyridyl, uip is 2-(5-uracil)-1*H*-imidazo[4,5-*f*][1,10]phenanthroline) and *cis*-$[Ru(bpy)_2(5\text{-}bbtb)]^{2+}$ (bbtb = *bis*

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