

Novel coumarin rhenium(I) and -(V) complexes: Formation, DFT and DNA binding studies

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ABSTRACT

Herein, we report the formation and characterisation of novel rhenium(I) and -(V) compounds with coumarin bidentate chelates: *trans*-[ReOBr₂(PPh₃)(hbc)] (**1**) (Hhbc = 7-(2-hydroxybenzylideneamino)-4-(trifluoromethyl)-2H-chromen-2-one), *fac*-[Re(CO)₃Cl(aomc)] (**2**) (aomc = 7-(((2-amino-4-oxo-4H-chromen-3-yl)methylene)amino)-4-(trifluoromethyl)-2H-chromen-2-one) and *fac*-[Re(CO)₃Cl(moac)] (**3**) (moac = 7-(((2-methoxy-4-oxochroman-3-yl)methylene)amino)-4-(trifluoromethyl)-2H-chromen-2-one). The coumarin free-ligands and the metal complexes **1–3** were characterized by NMR, UV–Vis and FTIR spectroscopy, melting point and molar conductivity measurements as well as time-of-flight mass spectrometry. Their structural elucidations were supported by the respective solid state structures of **1**, Hhbc and moac. DNA binding studies conducted using the *facial* tricarbonylrhenium(I) complexes **2** and **3**, revealed that they are DNA groove binders with intrinsic binding constants in the order of 10⁵ and 10⁴ M bp, respectively. This study was also complemented using density functional theory (DFT) and time-dependent DFT methods to attain a deeper understanding into the structural parameters, infrared and electronic spectra of these coumarin free-ligands and their metal complexes **1–3**.

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1. Introduction

The design of new target-specific rhenium radiopharmaceuticals necessitates exploring the coordination susceptibility of rhenium towards multidentate chelators encompassing various biologically relevant moieties [1,2]. Rhenium naturally occurs as a mixture of two non-radioactive isotopes ¹⁸⁵Re and ¹⁸⁷Re while the rhenium radionuclides used in nuclear medicine are ¹⁸⁶Re and ¹⁸⁸Re have β -emission energies and half-lives adequate for therapeutic treatment of cancer [3,4]. Schiff bases have shown to exhibit high coordination affinities towards rhenium(I) and -(V) cores and moreover, their metal complexes have shown to exhibit a wide array of physical properties culminating into applications including chemical sensing, DNA interaction, cell imaging and catalysis [5–8].

Recent studies shows that transition metal complexes with chromone Schiff base chelates have been isolated and many of these metal complexes have shown optimal *in vitro* anticancer

activities [9]. However, the formation of coumarin Schiff bases remains relatively unexplored despite the facts that the isostructural benzopyranes; coumarin and chromones are secondary metabolites and that they are building blocks of various drugs [10]. Among the few examples of *d*-block metal complexes of coumarin Schiff bases include the [M(II)(L)2H₂O] {M = Ni, Cu or Co} complexes (L = (*E*)-*N*-(3-chlorophenyl)-2-(1-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)ethylidene)hydrazinocarbothioamide) where a synergistic effect is observed based on the higher antimicrobial effects of the metal complexes compared to their free-ligands [11].

A combination drug, coumarin/troloxerutine have shown therapeutic application in the perseverance of the salivary glands and mucosa in patients who underwent head and neck radiotherapy [12]. The results also suggest that the co-drug, coumarin has a defined biodistribution pattern and this provides impetus in developing coumarin Schiff base rhenium compounds which can be potential therapeutic radiopharmaceutical for salivary gland cancer. In this research study, we report the formation of [Re^{VO}]³⁺ and *fac*-[Re^I(CO)₃]⁺ compounds with bidentate coumarin ligands derived from 7-amino-4-(trifluoromethyl)coumarin. The rhenium complexes, *trans*-[ReOBr₂(PPh₃)(hbc)] (**1**), *cis*-[Re(CO)₃Cl(aomc)] (**2**) and *cis*-[Re(CO)₃Cl(moac)] (**3**) were each synthesized from the

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coordination reactions of rhenium(V) and -(I) precursors with the coumarin free-ligands: 7-(2-hydroxybenzylideneamino)-4-(trifluoromethyl)-2H-chromen-2-one (Hhbc), 7-(((2-amino-4-oxo-4H-chromen-3-yl)methylene)amino)-4-(trifluoromethyl)-2H-chromen-2-one (aomc) and 7-(((2-methoxy-4-oxochroman-3-yl)methylene)amino)-4-(trifluoromethyl)-2H-chromen-2-one (moac), respectively (see Fig. 1). Furthermore, a detailed understanding of the electronic structures and spectroscopic properties are important to aid in the interpretation of the experimental findings. There are reports on the use of density functional theory (DFT) methods to complement experimental research involving rhenium(I) [13] and -(V) complexes [14]. Consequently, computational methods were employed to aid in the interpretation of experimental data.

2. Experimental

2.1. Materials and methods

The following chemicals: 7-amino-4-(trifluoromethyl)-coumarin, salicylaldehyde, 3-formylchromone, 2-amino-3-formylchromone, pentacarbonylchlororhenium(I), calf thymus DNA (CT-DNA) and phosphate buffered saline (PBS) tablets were purchased from Sigma-Aldrich and used as received. The oxorhenium(V) precursors were synthesized *via* methods obtained from literature [15,16]. All solvents were obtained from Merck SA. Reagent grade toluene was dried over sodium wire while other solvents and chemicals were used without any further purification. Ultrapure water was produced from an Elga Purelab Ultra system. Infrared spectra (IR) were recorded on a Perkin Elmer Spectrum 100 spectrometer in the 4000–200 cm^{-1} range. The IR spectra of all the compounds were attained in the solid state using the Perkin Elmer Universal ATR Accessory (UATR). The ^1H and ^{13}C NMR spectra were obtained at 295 K using a Bruker Avance 400 or 500 MHz spectrometer. All NMR spectra were recorded in DMSO- d_6 . UV-Vis spectra were recorded using a Perkin Elmer Lambda 25 spectrometer. The extinction coefficients (ϵ) are given in $\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$. The melting points were obtained using a Stuart SMP3 apparatus. The conductivity measurements were determined at 295 K on a Radiometer R21M127 CD 230 conductivity and pH meter. Mass spectrometry was conducted in both the positive and negative

modes *via* direct injection of the samples into a Waters Micromass LCT Premier mass spectrometer equipped with an electrospray ionization (ESI) source and a time-of-flight (TOF) mass analyser.

2.2. Synthesis of ligands

2.2.1. 7-(2-Hydroxybenzylideneamino)-4-(trifluoromethyl)-2H-chromen-2-one (Hhbc)

The two reactants, 7-amino-4-(trifluoromethyl)coumarin (0.3305 g; 1.440 mmol) and salicylaldehyde (0.15 cm^3 ; 1.440 mmol) were heated until reflux in methanol (20 cm^3) for 3 h. The resultant yellow solution was allowed cool down to room temperature and afterwards further cooled down in an ice bath which resulted in the formation of orange crystals. These crystals were filtered, washed with methanol and petroleum ether. Yield = 50%; Melting point: 189.5–191.6 $^\circ\text{C}$; Infrared ($\nu_{\text{max}}/\text{cm}^{-1}$): $\nu(\text{O}-\text{H})$ 3109 (br, w), $\nu(\text{C}=\text{O})$ 1730 (s), $\nu(\text{C}=\text{N})$ 1595 (s), $\nu(\text{C}-\text{O}-\text{C})$ 1268 (s); ^1H NMR (d_6 -DMSO/295 K/ppm): 12.37 (s, 1H, OH), 9.07 (s, 1H, H11), 7.80–7.71 (m, 2H, H13, H15), 7.62–7.60 (d, $J = 2.0$ Hz, 1H, H9), 7.51–7.44 (m, 2H, H6, H8), 7.05–6.97 (t, $J = 9.0$ Hz, 3H, H3, H14, H16); ^{13}C NMR (d_6 -DMSO/295 K/ppm): 165.55 (C17), 160.36 (C4), 159.35 (C11), 156.54 (C2), 154.84 (C7), 154.07 (C5), 152.70 (C15), 134.22 (C13), 132.49 (C9), 125.72 (C1), 125.70 (C14), 119.35 (C10), 116.77 (C8), 112.18 (C12), 109.44 (C16), 101.72 (C6), 98.95 (C3); UV-Vis (Methanol, λ_{max} (ϵ , $\text{M}^{-1} \text{cm}^{-1}$): 373 nm (36997), 277 nm (sh, 10671), 232 nm (24033); TOF-MS (m/z): Calcd: 333.0613, Found: 332.0537 $[\text{M}-\text{H}]^-$, 333.0613 $[\text{M}]^-$.

2.2.2. 7-(((2-Amino-4-oxo-4H-chromen-3-yl)methylene)amino)-4-(trifluoromethyl)-2H-chromen-2-one (aomc)

The Schiff base was synthesized from the condensation reaction between 7-amino-4-(trifluoromethyl)coumarin (0.2684 g; 1.171 mmol) and 2-amino-3-formylchromone (0.2216 g; 1.171 mmol) in methanol (20 cm^3) which was heated under reflux for 3 h. The resultant yellow solution was allowed to cool to room temperature before the light yellow precipitate was filtered and washed using cold methanol and petroleum ether. Yield = 50%; Melting point: 239.9–244.8 $^\circ\text{C}$; Infrared ($\nu_{\text{max}}/\text{cm}^{-1}$): $\nu(\text{N}-\text{H})$ 3242, 3093 (br), $\nu(\text{C}=\text{O})$ 1679 (s), $\nu(\text{C}=\text{N})$ 1610 (s), $\nu(\text{C}-\text{O}-\text{C})$ 1334 (s); ^1H NMR (d_6 -DMSO/298 K/ppm): 10.09 (s, 1H, H11), 9.59 (s, 2H, NH_2),

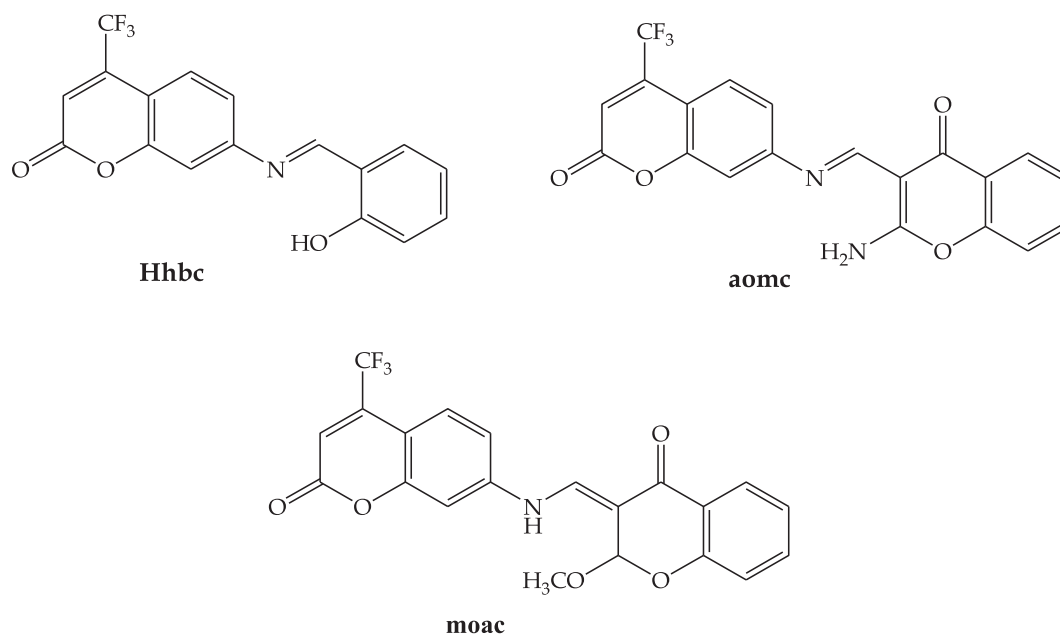


Fig. 1. Structures of the coumarin free-ligands considered within this study.

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