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Dinuclear arene ruthenium thiolato complexes with fluorous side-chains

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ABSTRACT

Four complexes of the general formula $[(\eta^6\text{-}p\text{-}MeC_6H_4Pr^i)_2Ru_2(\mu\text{-}SC_2H_4R)_3]^+$, R = $(CF_2)_7CF_3$ (**1**), $(CF_2)_5CF_3$ (**2**), $(CF_2)_3CF_3$ (**3**) and $(CH_2)_5CH_3$ (**4**) were synthesized and characterized. The molecular structures of complexes **1** and **3** were confirmed by single crystal X-ray diffraction analysis of their chloride salts. Complexes **3** and **4** were evaluated for their antiproliferative activity against human ovarian cancer A2780 and A2780cisR cell lines and against the non-tumorigenic HEK293 cell line. Complexes **3** and **4** are highly cytotoxic (IC_{50} values in the nanomolar range) and exhibit a slight selectivity for cancer cells over the model healthy cells.

1. Introduction

Following the discovery of the anticancer properties of *cis*-diamminedichloridoplatinum(II) (cisplatin) [1] and its clinical success in the treatment of testicular cancer [2], the research of anticancer metal-based drugs has flourished. Due to the well-known limitations of cisplatin and the two other platinum-based anticancer agents carboplatin and oxaliplatin [3,4], considerable efforts have been focused on finding anticancer agents based on other metals, in the hope that they will possess higher selectivity to cancer cells and will therefore have less severe side-effects. Ruthenium complexes tend to have a low general toxicity [5] and several ruthenium(III) complexes, i.e., NAMI-A, KP1019 and NKP1339 have been evaluated in clinical trials [6–8], while other complexes are currently in preclinical development [5].

In cancer treatments, 5-fluorouracil occupies a special place [9], like many fluorine-containing compounds. Indeed, fluorine-containing compounds are frequently encountered in medicinal chemistry with ca. 20% of all pharmaceuticals containing fluorine substituents, due to the unique properties of fluorine atom(s) or fluorinated group(s) [10,11]. The electronegativity, size, lipophilicity, and electrostatic interactions of fluorine can dramatically influence the reactivity and properties of compounds [12]. Bioisosterism of chemical groups with fluorine-containing substituents is often exploited in the search for more active or more selective compounds in medicinal chemistry [13]. Thus, C—H, C—F, C—Cl, C—OH, and C—OMe bonds can sometimes be interchanged without a major influence on the biological behavior of the compound [10]. The C—CF_3 fragment can be used as a substitute for the C=O group [14], and the CF_3 group is regularly used as a bioisoster of the CH_3 group or as a variation of halide groups. The fluorovinyl group (C=CHF) has been used as a replacement for peptide bonds [15].

The limited selectivity of many of the currently used anticancer agents is manifested by their severe side-effects. In the search for more selective cancer treatments, many new approaches have been devised such as phototherapy, treatment with magnetic nanoparticles or thermotherapy. During these therapies, a non-toxic agent (photosensitizer, magnetic nanoparticles or thermo-responsive drug, respectively) is introduced into the tumor tissue, followed by the application of an external inducer such as light [16], magnetic field [17] or hyperthermia [18], which then activates the agent, thus locally increasing its cytotoxicity. Since these external inducers can be applied specifically on the area containing the tumor tissue, the selectivity of such treatments is significantly increased and side-effects are reduced. Recently, the thermo-responsive properties of organic compounds with long fluorous alkyl chains [19], and of organometallic complexes with perfluorinated phosphines [20], have been investigated. In addition, the thermo-responsive properties of arene ruthenium complexes of the general formula $[(\eta^6\text{-}p\text{-}MeC_6H_4Pr^i)Ru(\mu\text{-}NC_5H_4\text{-}m\text{-}C_2H_5COOC_2H_5(CF_2)_nCF_3]$ (n = 5, 7, 9) were studied (Fig. 1), with certain complexes being two orders of magnitude more toxic to cancer cells under mild hyperthermia (40–42 °C) than under normal conditions (37 °C), while being

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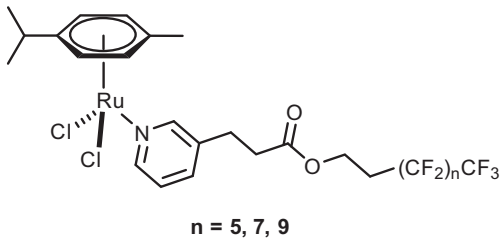
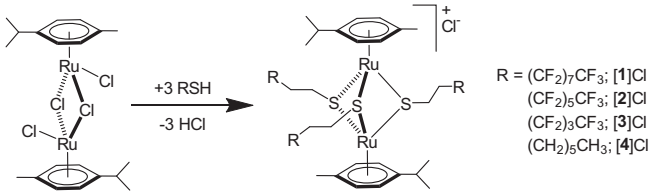


Fig. 1. Examples of thermo-responsive arene ruthenium(II) complexes containing fluorous chains.



Scheme 1. Synthesis of trithiolato complexes **1**–**4**, isolated as chloride salts.

non-toxic to healthy HEK293 cells. This behavior was attributed to the long fluorous alkyl chains [21]. The benefits of thermotherapy with the lead compound [(η^6-*p*-$MeC_6H_4Pr^i$)Ru(μ-NC_5H_4-*m*-$C_2H_5COOC_2H_5(CF_2)_9CF_3$] were later confirmed *in vivo*, showing a 90% decrease in tumor growth after the application of the complex in combination with local hyperthermia.

Over the last five years, we have published series of articles describing the synthesis and antiproliferative properties of thiolato-bridged arene ruthenium complexes of the general formula [(η^6-arene)$_2$Ru$_2$(μ-SR)$_3$]$^+$ [22–26]. The chloride salts of these complexes were found to be highly cytotoxic to human ovarian cancer cells, their IC_{50} values being in the lower nanomolar range on A2780 and A2780cisR cell lines [23–26]. The cytotoxicity of the arene ruthenium thiolato-bridged complexes was shown to depend on the lipophilicity of the complexes, the most active compound [(*p*-$MeC_6H_4Pr^i$)$_2$Ru$_2$(μ-SC_6H_4-*p*-Bu^t)$_3$]Cl (IC_{50} = 30 nM for both A2780 and A2780cisR cell lines) being also one of the most lipophilic derivatives [23]. The lipophilicity of long fluorous chains on the dinuclear ruthenium core could therefore have a positive effect on the anticancer activity of the resulting compounds. Thus, in order to investigate the effects of fluorous alkyl chains on the solubility, cytotoxicity and thermo-responsiveness of thiolato-bridged arene ruthenium complexes, we synthesized a new series of complexes of the general formula [(η^6-*p*-$MeC_6H_4Pr^i$)$_2$Ru$_2$(μ-SC_2H_4R)$_3$]$^+$, R = $(CF_2)_7CF_3$ (**1**), $(CF_2)_5CF_3$ (**2**), $(CF_2)_3CF_3$ (**3**) and $(CH_2)_5CH_3$ (**4**). The structure, stability and anticancer activity of these complexes were studied under normal and mild hyperthermia conditions.

2. Results and discussion

The dinuclear *p*-cymene complex [(η^6-*p*-$MeC_6H_4Pr^i$)$_2$Ru$_2$Cl$_2$(μ-Cl)$_2$] reacts with the RSH thiols [R = $CH_2CH_2(CF_2)_7CF_3$, $CH_2CH_2(CF_2)_5CF_3$, $CH_2CH_2(CF_2)_3CF_3$ and $(CH_2)_7CH_3$] to give the cationic trithiolato arene ruthenium complexes **1**–**4** (Scheme 1). All four complexes are isolated as chloride salts, as light orange crystalline powders, and are soluble in chlorinated solvents and in polar organic solvents such as DMSO, methanol and ethanol. The complexes were characterized by spectroscopic methods and by elemental analyses. The analytical data are given in Section 4. The dinuclear nature of the trithiolato-bridged complexes was further confirmed by the single-crystal X-ray structure analysis of [**1**]Cl and [**3**]Cl.

Crystals of [**1**]Cl and [**3**]Cl were obtained by a slow diffusion of diethyl ether vapors in a dichloromethane solution of the salt. In both crystals, the fluorous alkyl chains were highly disordered and did not allow a complete resolution of the structure. Nevertheless, the dinuclear nature of the complexes, bridged by three thiolato-ligands, was clearly confirmed. The Ru···Ru distances were respectively 3.35(1) Å in **1** and 3.34(1) Å in **3**, while the average Ru–S distance was 2.39 Å. These values were in accordance with

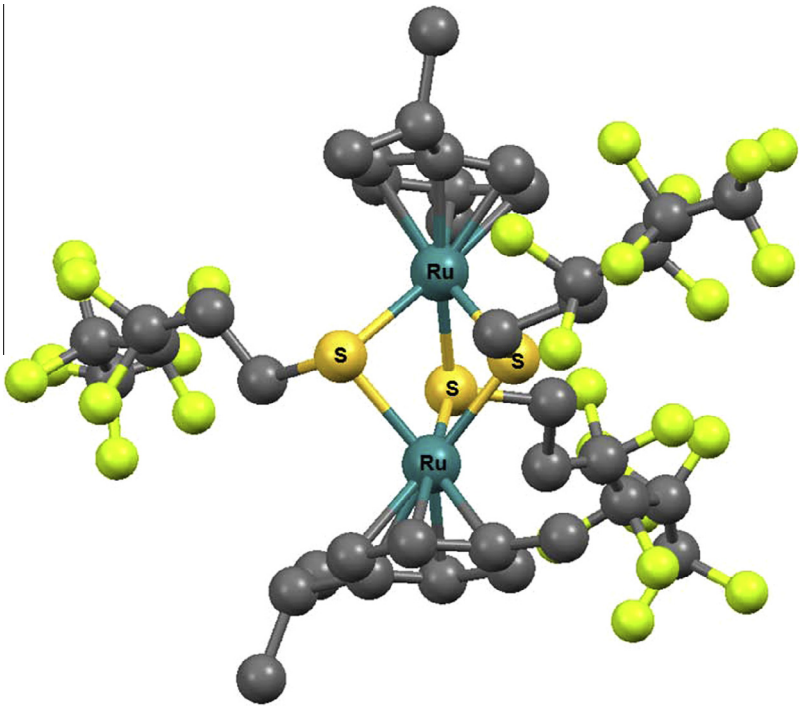


Fig. 2. Molecular structure of [**3**]$^+$, with the hydrogen and chloride atoms being omitted for clarity.