Dinuclear arene ruthenium thiolato complexes with fluororous side-chains

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ABSTRACT

Four complexes of the general formula $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu\text{-SC}_2\text{H}_4\text{R})_3]^+$, $\text{R} = (\text{CF}_2)_7\text{CF}_3$ (**1**), $(\text{CF}_2)_5\text{CF}_3$ (**2**), $(\text{CF}_2)_3\text{CF}_3$ (**3**) and $(\text{CH}_2)_5\text{CH}_3$ (**4**) were synthesized and characterised. 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.

Keywords: Bioorganometallic chemistry; Arene ruthenium complexes; Dinuclear complexes; Thiolato ligands; Metal-based drugs; Fluorine chemistry; Hyperthermia

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–CF₃ fragment can be used as a substitute for the C=O group [14], and the CF₃ group is regularly used as a bioisoster of the CH₃ 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 tumour 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 tumour tissue, the selectivity of such treatments is significantly increased and side-effects are reduced. Recently, the thermo-

responsive properties of organic compounds with long fluoruous 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 $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^i)\text{Ru}(\mu\text{-NC}_5\text{H}_4\text{-}m\text{-C}_2\text{H}_5\text{COOC}_2\text{H}_5(\text{CF}_2)_n\text{CF}_3)]$ ($n = 5, 7, 9$) were studied (Figure 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 non-toxic to healthy HEK293 cells. This behaviour was attributed to the long fluoruous alkyl chains [21]. The benefits of thermotherapy with the lead compound $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^i)\text{Ru}(\mu\text{-NC}_5\text{H}_4\text{-}m\text{-C}_2\text{H}_5\text{COOC}_2\text{H}_5(\text{CF}_2)_9\text{CF}_3)]$ were later confirmed *in vivo*, showing a 90% decrease in tumour growth after the application of the complex in combination with local hyperthermia.

Figure 1. Examples of thermo-responsive arene ruthenium(II) complexes containing fluoruous chains.

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 $[(\eta^6\text{-arene})_2\text{Ru}_2(\mu\text{-SR})_3]^+$ [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 $[(p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu\text{-SC}_6\text{H}_4\text{-}p\text{-Bu}^t)_3]\text{Cl}$ ($\text{IC}_{50} = 30 \text{ nM}$ for both A2780 and A2780cisR cell lines) being also one of the most lipophilic derivatives [23]. The lipophilicity of long fluoruous 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 $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu\text{-SC}_2\text{H}_4\text{R})_3]^+$, R = $(\text{CF}_2)_7\text{CF}_3$ (**1**), $(\text{CF}_2)_5\text{CF}_3$ (**2**), $(\text{CF}_2)_3\text{CF}_3$ (**3**) and $(\text{CH}_2)_5\text{CH}_3$ (**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 $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2\text{Cl}_2(\mu\text{-Cl})_2]$ reacts with the RSH thiols [R = $\text{CH}_2\text{CH}_2(\text{CF}_2)_7\text{CF}_3$, $\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3$, $\text{CH}_2\text{CH}_2(\text{CF}_2)_3\text{CF}_3$ and $(\text{CH}_2)_7\text{CH}_3$] 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 the Experimental. 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**.

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

Crystals of **[1]Cl** and **[3]Cl** were obtained by a slow diffusion of diethyl ether vapours in a dichloromethane solution of the salt. In both crystals, the fluorous alkyl chains were highly disordered and did not allowed 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 those found in analogous trithiolato-bridged arene ruthenium complexes [23]. The molecular structure of the dinuclear cation **3** is presented in Figure 2.

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

The stability of **[1]Cl** - **[4]Cl** was tested at 37°C in a DMSO- d_6 /D $_2$ O (1:1) solution by ^1H NMR spectroscopy. As can be seen in Figure 3 (for **[2]Cl**), no changes were observed in the NMR spectra after a week of incubation at 37°C. We therefore considered the compounds stable and studied their cytotoxicity under various conditions.

Figure 3. ^1H NMR spectra of [2]Cl in a DMSO- $\text{d}_6/\text{D}_2\text{O}$ (1:1) solution over 7 days.

Compounds [1]Cl and [2]Cl were insoluble in water even in the presence of 1% DMSO and, hence, could not be studied in cell culture; subsequent experiments were performed with [3]Cl and [4]Cl only. Initial experiments were performed with A2780 human ovarian cancer cells at 37°C and 41°C. Although the IC_{50} values of compounds [3]Cl and [4]Cl are in the nanomolar range, no difference was observed when the experiments were performed at 41°C, indicating that the fluorine chains on [3]Cl do not lead to thermo-responsive activity, in contrast to previously reported compounds [19-21]. Therefore, the cytotoxicity on A2780cisR (human ovarian cancer cells with acquired resistance to cisplatin) and HEK293 (human embryonic kidney cells) was

studied only at 37°C. The two compounds were found to be highly cytotoxic to both cell lines, although slightly less cytotoxic (by a factor of two) to the non-tumorigenic HEK293 cells (Table 1). The cytotoxicity of [3]Cl and [4]Cl to the A2780 and A2780cisR cells matches well with those observed for previously reported trithiolato complexes of the type $[(p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu\text{-SC}_6\text{H}_4\text{-}p\text{-X})_3]^+$ (X = H, Me, Ph, Br, OH, NO₂, OMe, CF₃, F, Prⁱ or Bu^t), where the most lipophilic compound $[(p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu\text{-SC}_6\text{H}_4\text{-}p\text{-Bu}^t)_3]\text{Cl}$ ([5]Cl) was found to be the most cytotoxic, with an IC₅₀ value of 30 nM for A2780 and A2780cisR [25-27]. Compound [3]Cl is therefore as active for the cisplatin sensitive cell line A2780 and only slightly less active for the cisplatin resistant cell line A2780cisR, which makes it one of the most active ruthenium complexes reported to date.

Table 1. Cytotoxicity of [3]Cl and [4]Cl against cancerous cell lines (A2780 and A2780cisR) and non-cancerous cells (HEK293) after 72 hours (nd = not determined).

Compound	A2780 (37°C) [nM]	A2780 (41°C) [nM]	A2780cisR [nM]	HEK293 [nM]
[3]Cl	30 ± 10	30 ± 10	40 ± 20	80 ± 50
[4]Cl	100 ± 20	100 ± 20	80 ± 20	170 ± 30
[5]Cl	30 ± 10	nd	30 ± 10	nd

3. Conclusions

Dinuclear arene ruthenium complexes [1]Cl – [4]Cl were prepared and fully characterized. As expected, the long fluororous chains lead to highly lipophilic compounds. Compounds [3]Cl and [4]Cl are both highly cytotoxic towards human ovarian cancer cell lines, with their IC₅₀ values being similar to that of $[(p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu\text{-SC}_6\text{H}_4\text{-}p\text{-Bu}^t)_3]\text{Cl}$, the most active thiolato-bridged compound evaluated so far. Unfortunately, the thermo-responsive activity anticipated for these compounds, by virtue of the perfluorous chain, was not observed. Nevertheless, these compounds display modest cancer cell selectivity although it is lower than that required for useful therapeutic windows.

4. Experimental

4.1. General remarks

The starting material $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2\text{Cl}_2(\mu\text{-Cl})_2]$ was prepared according to the published method [28]. All other reagents were commercially available and were used without further purification. NMR spectra were recorded with a Bruker 400 MHz spectrometer. Electrospray mass spectra were obtained in positive mode with an LCQ Finnigan mass spectrometer. Microanalyses were carried out by the group of Dr. Stefan Schürch at the University of Bern (Switzerland).

4.2. Synthetic procedures

4.2.1. Synthesis of **[1 – 3]Cl**

In a Schlenk tube was introduced 0.153 mmol (93.8 mg) of $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2\text{Cl}_2(\mu\text{-Cl})_2]$ in 20 mL of distilled methanol. Then, 0.919 mmol of the corresponding thiol were dissolved in 10 mL of distilled methanol and added dropwise to the Schlenk tube. The reaction mixture was refluxed under inert atmosphere for 40 hours (complexes **1** and **3**) or for 5 days (complex **2**). Afterwards the solvent was evaporated *in vacuo* and the mixture was separated by column chromatography on silica gel (eluents $\text{CH}_2\text{Cl}_2/\text{EtOH}$ 7 : 1). The red band was collected, solvents evaporated *in vacuo* and the product was recrystallized from a $\text{CH}_2\text{Cl}_2/(\text{C}_2\text{H}_5)_2\text{O}$ mixture. The resulting orange crystalline solids were collected and dried under reduced pressure.

4.2.2. Data for **[1]Cl**

Yield: 267.9 mg (90%). $\text{C}_{50}\text{H}_{40}\text{ClF}_{51}\text{Ru}_2\text{S}_3$ (1943.56): calcd. C, 30.90; H, 2.07; found C, 30.62; H, 1.94. ESI MS: ($\text{MeOH} + \text{CH}_2\text{Cl}_2$): $m/z = 1908.1$ $[\text{M-Cl}]^+$, ^1H NMR (400 MHz, CDCl_3): $\delta = 5.72 - 5.48$ [broad, 8H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 2.84 – 2.47 [broad, 12H, $\text{S-C}_2\text{H}_4\text{C}_8\text{F}_{17}$, 2H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 2.22 [s, 6H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 1.27 [m, 12H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$] ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 108.03, 101.92, 84.02, 83.72, 83.52, 33.55, 31.72, 29.13, 23.52, 22.37, 18.31$ ppm.

4.2.3. Data for **[2]Cl**

Yield: 75.3 mg (34%). $\text{C}_{38}\text{H}_{40}\text{ClF}_{27}\text{Ru}_2\text{S}_3$ (1343.46): calcd. C, 33.37; H, 2.98; found C, 33.47; H, 2.85. ESI MS: ($\text{MeOH} + \text{CH}_2\text{Cl}_2$): $m/z = 1308.7$ $[\text{M-Cl}]^+$, ^1H NMR (400 MHz, CDCl_3): $\delta = 5.72 - 5.48$ [broad, 8H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 2.84 – 2.47 [broad, 12H, $\text{S-C}_2\text{H}_4\text{C}_8\text{F}_{17}$, 2H, $p\text{-}$

$\text{CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 2.22 [s, 6H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 1.27 [m, 12H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$] ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 108.03, 101.92, 84.02, 83.72, 83.52, 33.55, 31.72, 29.13, 23.52, 22.37, 18.31 ppm.

4.2.4. Data for [3]Cl

Yield: 236.6 mg (94%). $\text{C}_{44}\text{H}_{40}\text{ClF}_{39}\text{Ru}_2\text{S}_3$ (1643.51): calcd. C, 31.70; H, 2.45; found C, 31.73; H, 2.16. ESI MS: ($\text{MeOH} + \text{CH}_2\text{Cl}_2$): m/z = 1608.98 $[\text{M}-\text{Cl}]^+$, ^1H NMR (400 MHz, CDCl_3): δ = 5.72 – 5.48 [broad, 8H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 2.84 – 2.47 [broad, 12H, $\text{S-C}_2\text{H}_4\text{C}_8\text{F}_{17}$, 2H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 2.22 [s, 6H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 1.27 [m, 12H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$] ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 108.03, 101.92, 84.02, 83.72, 83.52, 33.55, 31.72, 29.13, 23.52, 22.37, 18.31 ppm.

4.2.5. Synthesis of [4]Cl

In a Schlenk tube was introduced 0.153 mmol (93.8 mg) of $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2\text{Cl}_2(\mu\text{-Cl})_2]$ in 20 mL of distilled methanol. Then, 1.632 mmol of 1-octanethiol were dissolved in 10 mL of distilled methanol and added dropwise to the reaction mixture. The mixture was refluxed under inert atmosphere for 7 days. Afterwards, 5 grams of activated charcoal were added, the suspension was stirred for 1 hour and filtered. The solvent was evaporated *in vacuo* and the mixture was separated by column chromatography on silica gel (eluent $\text{CH}_2\text{Cl}_2/\text{EtOH}$ 9 : 1). The red band was collected, solvent evaporated *in vacuo* and the product washed thoroughly with diethyl ether and pentane. The resulting orange powder was dried under reduced pressure.

4.2.6. Data for [4]Cl

Yield 40.4 mg (28%). $\text{C}_{44}\text{H}_{79}\text{ClRu}_2\text{S}_3 \cdot 0.75 \text{CH}_2\text{Cl}_2 \cdot 0.5 \text{C}_5\text{H}_{12}$ (1041.66): calcd.: C, 54.48; H, 8.37 found: C, 54.58; H, 8.65 ESI MS: ($\text{MeOH} + \text{CH}_2\text{Cl}_2$): m/z = 906.20 $[\text{M}-\text{Cl}]^+$, ^1H NMR (400 MHz, CDCl_3): δ = 5.46 [t, 3J = 6 Hz, 4H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 5.32 [d, 3J = 5 Hz, 2H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 5.24 [d, 5 Hz, 2H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 2.55 [sept, 3J = 7 Hz, 2H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 2.34 [m, 6H, $\text{S-C}_8\text{H}_{17}$], 2.17 [s, 6H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 1.79 – 1.62 [m, 6H, $\text{S-C}_8\text{H}_{17}$], 1.54 – 1.42 [m, 6H, $\text{S-C}_8\text{H}_{17}$], 1.40 – 1.26 [m, 24H, $\text{S-C}_8\text{H}_{17}$], 1.29 [d, 3J = 7 Hz, 6H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 1.23 [d, 3J = 7 Hz, 6H, $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$], 0.95 – 0.86 [m, 9H, $\text{S-C}_8\text{H}_{17}$] ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 106.41, 101.27, 83.60, 83.14, 82.98, 82.87, 77.30, 76.98, 76.66, 38.96, 32.78, 31.73, 31.52, 29.34, 29.14, 23.89, 22.58, 22.36, 18.14, 14.02 ppm.

4.3. Stability in DMSO/D₂O mixtures

Stability was studied by dissolving the complex [2]Cl in DMSO-d₆/D₂O (1:1) solution and recording the 1D ¹H-NMR spectrum every 24 hours. Between the NMR measurements, the sample was stored in the dark at 37°C.

4.4. Cell culture and cytotoxicity measurements

Human A2780 and A2780cisR ovarian carcinoma cells were obtained from the European Centre of Cell Cultures (ECACC, Salisbury, UK). Non-tumorigenic HEK-293 cells were obtained from ATCC (Sigma, Switzerland). A2780 and A2780cisR cells were routinely grown in RPMI 1640 medium with GlutaMAX containing 5% fetal bovine serum (FBS) and 1% antibiotics (penicillin and streptomycin) at 37°C and 5% CO₂. HEK-293 cells were grown in DMEM medium containing 5% fetal bovine serum (FBS) and 1% antibiotics (penicillin and streptomycin) at 37°C and 5% CO₂. In order to keep the A2780cisR cells resistant to cisplatin the cells were monthly treated with 2 µM cisplatin for one passage. Cytotoxicity was determined using the MTT assay (MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide)]. Briefly, the cells were seeded in 96 well plates (10'000 cells per well) and grown for 24 h in complete medium. For each testing, compounds were freshly prepared as DMSO stock solution, then dissolved in the culture medium and immediately serially diluted to the appropriate concentration, to give a final DMSO concentration of 0.5% v/v. Drug solution (100 µL) was added to each well and the plates were incubated at 37°C for 72 h or 2 h at 41.5°C followed by a 68 h incubation at 37°C. Following drug exposure, 20 µL of MTT (5 mg/mL solution in PBS) were added to the cells and incubated for 4 h, then the culture medium was aspirated and the violet formazan crystals were dissolved in DMSO (100 µL). The optical density of each well (96 well plates) was quantified at 590 nm using a multiwell plate reader (Molecular Devices, UK), and the percentage of surviving cells was calculated from the ratio of absorbance of treated to untreated cells. The IC₅₀ values for the inhibition of cell growth were determined by fitting the plot of the logarithmic percentage of surviving cells against the logarithm of the drug concentration using a linear regression function. Mean values and standard deviations computed from two independent experiments, each comprising four microcultures per concentration level, are reported in Table 1.

4.5. X-ray crystallography

Crystals of [1]Cl and [3]Cl were mounted on a Stoe Image Plate Diffraction system equipped with a ϕ circle goniometer, using Mo-K α graphite monochromatic radiation ($\lambda = 0.71073 \text{ \AA}$) with ϕ range 0-200°. The structures were solved by direct methods using the program SHELXS-97, while the refinement and all further calculations were carried out using SHELXL-97 [29]. Despite using different crystals of [1]Cl and [3]Cl, and collecting the data at different temperatures, only poor quality data were obtained. In both cases, the best data set was used, and the two structures show as expected the dinuclear arene ruthenium trithiolato-bridged cores. The fluorous alkyl chains are highly disordered and did not allow full convergence. Therefore, the data sets were not deposited to Cambridge Structural Database. However, the parametrical data of the dinuclear cores were good enough for discussion and compare well with those observed for analogous trithiolato-bridged arene ruthenium complexes [24].

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References

- [1] B. Rosenberg, L. VanCamp, *Cancer Res.*, **1970**, 30, 1799.
- [2] J. Cassidy, D. Bissett, R. A. J. Spence, M. Payne, G. Morris-Stiff (eds.), *Oxford Handbook of Oncology*, Oxford University Press, **2015**, 928 pages.
- [3] E. Wong, C. M. Giandomenico, *Chem. Rev.*, **1999**, 99, 2451.
- [4] M. Galanski, M. A. Jakupiec, B. K. Keppler, *Curr. Med. Chem.*, **2005**, 12, 2075.
- [5] G. Süss-Fink, *Dalton Trans.*, **2010**, 39, 1673.
- [6] S. Leijen, S. A. Burgers, P. Baas, D. Pluim, M. Tibben, E. van Werkhoven, E. Alessio, G. Sava, J. H. Beijnen J. H. M. Schellens, *Invest. New Drug.*, **2015**, 33, 201.
- [7] C. G. Hartinger, M. A. Jakupiec, S. Zorbas-Seifried, M. Groessler, A. Egger, A. Berger, H. Zorbas, P. J. Dyson, B. K. Keppler, *Chem. Biodiversity*, **2008**, 5, 2140.

- [8] R. Trondl, P. Heffeter, C. R. Kowol, M. A. Jakupec, W. Berger, B. K. Keppler, *Chem. Sci.*, **2014**, 5, 2925.
- [9] D. B. Longley, D. P. Harkin, P. G. Johnston, **2003**, *Nat. Rev. Cancer*, 3, 330.
- [10] Fluorine in Medicinal Chemistry and Chemical Biology, I. Ojima (ed.), John Wiley & Sons, **2009**, 640 pages.
- [11] K. Müller, C. Faeh, F. Diederich, *Science*, **2007**, 317, 5846, 1881.
- [12] J. Wang, M. Sanchez-Rosello, J. Luis Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, 114, 2432.
- [13] G. A. Patani, E. J. LaVoie, *Chem. Rev.* **1996**, 96, 3147.
- [14] W. C. Black, C. I. Bayly, D. E. Davis, S. Desmarais, J.-P. Falgueyret, S. Léger, C. S. Li, F. Massé, D. J. McKay, J. T. Palmer, M. D. Percival, J. Robichaud, N. Tsou, R. Zamboni, *Bioorg. Med. Chem. Lett.*, **2005**, 15, 4741.
- [15] J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley-Interscience, **2008**, 366 pages.
- [16] For reviews see for example: a) Z. Huang, *Technol. Cancer Res. Treat.*, **2005**, 4, 283; b) P. Rai, S. Mallidi, X. Zheng, R. Rahmzadeh, Y. Mir, S. Elrington, A. Khurshid, T. Hasan, *Adv Drug Deliv Rev*, **2010**, 62, 1094; c) Q. Shao, B. Xing, *Chem. Soc. Rev.*, **2010**, 39, 2835; d) B. Therrien, *Chem. Eur. J.*, **2013**, 19, 8378.
- [17] For reviews see for example: a) A. J. Giustini, A. A. Petryk, S. M. Cassim, J. A. Tate, I. Baker, P. J. Hoopes, *Nano Life*, **2010**, 1, 17; c) T. Kobayashi, *Biotechnology Journal*, **2011**, 6, 1342; c) A. Hervault, N. T. K. Thanh, *Nanoscale*, **2014**, 6, 11553;
- [18] For reviews see for example: a) M. Urano, M. Kuroda, Y. Nishimura, *Int. J. Hyperthermia*, **1999**, 15, 79; b) M A. Ward, T. K. Georgiou, *Polymers*, **2011**, 3, 1215; c) J. R. McDaniel, M. W. Dewhirst, A. Chilkoti, *Int J Hyperthermia*, **2013**, 29, 501; d) C. M. Clavel, P. Nowak-Sliwinska, E. Păunescu, P. J. Dyson, *MedChemComm*, **2015**, 6, 2054..
- [19] C. M. Clavel, O. Zava, F. Schmitt, B. H. Kenzaoui, A. A. Nazarov, L. Juillerat-Jeanneret, P. J. Dyson, *Angew. Chem. Int. Ed.*, **2011**, 50, 7124.
- [20] A. K. Renfrew, R. Scopelliti, P. J. Dyson, *Inorg. Chem.*, **2010**, 49, 2239.
- [21] a) C. M. Clavel, E. Păunescu, P. Nowak-Sliwinska, P. J. Dyson, *Chem. Sci.*, **2014**, 5, 1097; b) C. M. Clavel, P. Nowak-Sliwinska, E. Păunescu, A. W. Griffioen, P. J. Dyson, *Chem. Sci.*, **2015**, 6, 2795.

- [22] F. Giannini, G. Süss-Fink, J. Furrer, *Inorg. Chem.*, **2011**, 50, 10552.
- [23] F. Giannini, J. Furrer, A.-F. Ibaó, G. Süss-Fink, B. Therrien, O. Zava, M. Baquie, P. J. Dyson, P. Štěpnička, *J. Bio. Inorg. Chem.*, **2012**, 17, 951.
- [24] a) M. Gras, B. Therrien, G. Süss-Fink, O. Zava, P. J. Dyson, *Dalton Trans.*, **2010**, 39, 10305; b) G. Gupta, P. Nowak-Sliwinska, N. Herrero, P. J. Dyson, B. Therrien, *Inorg. Chim. Acta*, **2014**, 423, 524; c) F. Giannini, L. Geiser, L. E. H. Paul, T. Roder, B. Therrien, G. Süss-Fink, J. Furrer, *J. Organomet. Chem.*, **2015**, 783, 40.
- [25] F. Giannini, J. Furrer, G. Süss-Fink, C. M. Clavel, P. J. Dyson, *J. Organomet Chem.*, **2013**, 744, 41.
- [26] F. Giannini, L. E. H. Paul, J. Furrer, B. Therrien, G. Süss-Fink, *New J. Chem.*, **2013**, 37, 3503.
- [27] A.-F. Ibaó, M. Gras, B. Therrien, G. Süss-Fink, O. Zava, P. J. Dyson, *Eur. J. Inorg. Chem.*, **2012**, 1531.
- [28] M. A. Bennett, T.-N. Huang, T. W. Matheson, A. K. Smith, *Inorg. Synth.* **1982**, 21, 74.
- [29] G. M. Sheldrick, *Acta Cryst.*, **2008**, A64, 112.

GRAPHICAL ABSTRACT

Dinuclear arene ruthenium thiolato-bridged complexes were synthesized and isolated as their chloride salts. All complexes were fully characterized by standard techniques. The antiproliferative activity against cancerous and non-cancerous cell lines was evaluated. Two complexes are highly cytotoxic, and they both possess a slight selectivity for cancer cells over healthy cells.