

Thiolato-Bridged Arene–Ruthenium Complexes: Synthesis, Molecular Structure, Reactivity, and Anticancer Activity of the Dinuclear Complexes $[(\text{arene})_2\text{Ru}_2(\text{SR})_2\text{Cl}_2]$

Anne-Flore Ibaou,^[a] Michaël Gras,^[a] Bruno Therrien,^[a] Georg Süß-Fink,^{*,[a]} Olivier Zava,^[b] and Paul J. Dyson^[b]

[a] Institut de Chimie, Université de Neuchâtel Avenue de Bellevaux 51, 2000 Neuchâtel, Switzerland; Fax: +41-32-7182511
E-mail: georg.suess-fink@unine.ch

[b] Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland

Dedicated to Dr. Hubert Le Bozec on the occasion of his 60th birthday

Keywords: Ruthenium / Arene ligands / Thiolato bridges / Cytotoxicity

Treatment of an arene–ruthenium dichloride dimer with thiols RSH to lead to cationic trithiolato complexes of the type $[(\text{arene})_2\text{Ru}_2(\text{SR})_3]^+$ was shown to proceed through the neutral thiolato complexes $[(\text{arene})_2\text{Ru}_2(\text{SR})_2\text{Cl}_2]$, which have been isolated and characterized for arene = *p*-MeC₆H₄iPr and R = CH₂Ph (**1**), CH₂CH₂Ph (**2**), CH₂C₆H₄-*p*-tBu (**3**), and C₆H₁₁ (**4**). The single-crystal X-ray structure analysis of the *p*-tert-butylbenzyl derivative **3** reveals that the two ruthenium

atoms are bridged by the two thiolato ligands without a metal–metal bond. The neutral dithiolato complexes $[(\text{arene})_2\text{Ru}_2(\text{SR})_2\text{Cl}_2]$ (**1–3**) are intermediates in the formation of the cationic trithiolato complexes $[(\text{arene})_2\text{Ru}_2(\text{SR})_3]^+$ (**5–7**). Of the new $[(\text{arene})_2\text{Ru}_2(\text{SR})_2\text{Cl}_2]$ complexes, derivative **2** is highly cytotoxic against human ovarian cancer cells, with IC₅₀ values of 0.20 μM for the A2780 cell line and 0.31 for the cisplatin-resistant cell line A2780cisR.

Introduction

The chemistry of arene–ruthenium complexes has been extensively studied,^[1] ever since G. Winkhaus and H. Singer reported in 1967 the synthesis of $[(\text{C}_6\text{H}_6)_2\text{Ru}_2\text{Cl}_4]$, which was at first considered to be a polymer^[2] but later shown to be a dimer.^[3,4] Thus, the dimeric arene–ruthenium dichloride complexes were found to react with thiols to give cationic trithiolato complexes of the type $[(\text{arene})_2\text{Ru}_2(\text{SR})_3]^+$, the first examples being the hexamethylbenzene derivative $[(\text{C}_6\text{Me}_6)_2\text{Ru}(\text{SC}_6\text{H}_5)_3]^+$ reported by H. T. Schacht et al.^[5] and the *p*-cymene derivative $[(p\text{-MeC}_6\text{H}_4\text{iPr})_2\text{Ru}(\text{SC}_6\text{H}_5)_3]^+$ reported by K. Mashima et al.,^[6] both of which contain three thiophenolato bridges. We completed this series in 2003 with the *p*-bromothiophenolato derivative $[(p\text{-MeC}_6\text{H}_4\text{iPr})_2\text{Ru}_2(\text{SC}_6\text{H}_4\text{-}p\text{-Br})_3]^+$,^[7] the *p*-methylthiophenolato and *p*-hydroxythiophenolato derivatives $[(\text{arene})_2\text{Ru}_2(\text{SC}_6\text{H}_4\text{-}p\text{-X})_3]^+$ (arene = C₆H₆, *p*-MeC₆H₄iPr, C₆Me₆; X = CH₃, OH),^[8] as well as the 2-hydroxyethanethiolato derivatives $[(\text{arene})_2\text{Ru}_2(\text{SCH}_2\text{CH}_2\text{OH})_3]^+$ (arene = C₆H₆, *p*-MeC₆H₄iPr, C₆Me₆).^[8] We also found that the chloride salts of the trithiolato complexes $[(\text{arene})_2\text{Ru}_2(\text{SR})_3]^+$ are highly cytotoxic toward human ovarian cancer cells.^[9] They are in fact among the most active ruthenium anticancer compounds.^[10]

With the exception of the 2-hydroxyethanethiolato complexes $[(\text{arene})_2\text{Ru}_2(\text{SCH}_2\text{CH}_2\text{OH})_3]^+$ (arene = C₆H₆, *p*-MeC₆H₄iPr, C₆Me₆),^[8] all these trithiolato complexes contain aromatic substituents at the sulfur atom. We therefore set out to synthesize $[(\text{arene})_2\text{Ru}_2(\text{SR})_3]^+$ complexes with aliphatic substituents R. When we treated $[(p\text{-MeC}_6\text{H}_4\text{iPr})_2\text{Ru}_2\text{Cl}_4]$ with *p*-tBuC₆H₄CH₂SH under the usual conditions in ethanol heated at reflux, we observed the formation of two complexes that were difficult to separate. One of them was the expected trithiolato complex $[(p\text{-MeC}_6\text{H}_4\text{iPr})_2\text{Ru}_2(\text{SCH}_2\text{C}_6\text{H}_4\text{-}p\text{-tBu})_3]^+$, the other one turned out to be the dithiolato complex $[(p\text{-MeC}_6\text{H}_4\text{iPr})_2\text{Ru}_2(\text{SCH}_2\text{C}_6\text{H}_4\text{-}p\text{-tBu})_2\text{Cl}_2]$. However, it was possible to direct the synthesis by choosing the reaction conditions to give exclusively either the cationic trithiolato complex or the neutral dithiolato complex. The new dithiolato complex is an organic derivative of the dihydrosulfido complex $[(p\text{-MeC}_6\text{H}_4\text{iPr})_2\text{Ru}_2(\text{SH})_2\text{Cl}_2]$ reported by M. Hidai and co-workers as a product of the reaction of the *p*-cymene dichloride dimer with hydrogen sulfide.^[11]

In this paper, we report the synthesis, characterization, molecular structure, and the anticancer activity of the neutral dithiolato complexes of the type $[(\text{arene})_2\text{Ru}_2(\text{SR})_2\text{Cl}_2]$, which are supposed to be intermediates in the synthesis of the cationic trithiolato complexes $[(\text{arene})_2\text{Ru}_2(\text{SR})_3]^+$.

Results and Discussion

Synthesis of the Neutral Dithiolato Complexes 1–4

The *p*-cymene–ruthenium dichloride dimer reacts in cold ethanol (0 °C) with phenylmethanethiol, 2-phenylethanethiol, and (4-*tert*-butylphenyl)methanethiol (2 equiv.) to give the neutral dithiolato complexes $[(p\text{-MeC}_6\text{H}_4i\text{Pr})_2\text{Ru}_2(\text{SCH}_2\text{Ph})_2\text{Cl}_2]$ (**1**), $[(p\text{-MeC}_6\text{H}_4i\text{Pr})_2\text{Ru}_2(\text{SCH}_2\text{CH}_2\text{Ph})_2\text{Cl}_2]$ (**2**), and $[(p\text{-MeC}_6\text{H}_4i\text{Pr})_2\text{Ru}_2(\text{SCH}_2\text{C}_6\text{H}_4\text{-}p\text{-}t\text{Bu})_2\text{Cl}_2]$ (**3**). In the case of the bulky cyclohexylthiol, the reaction is carried out in refluxing ethanol to yield the cyclohexylthiolato derivative $[(p\text{-MeC}_6\text{H}_4i\text{Pr})_2\text{Ru}_2(\text{SC}_6\text{H}_{11})_2\text{Cl}_2]$ (**4**) (see Scheme 1). The air-stable orange to red compounds were isolated by precipitation with diethyl ether. The spectroscopic and analytical data are given in the Experimental Section.

Molecular Structure of 3

Suitable crystals for X-ray analysis were obtained for the (4-*tert*-butylphenyl)methanethiolato derivative **3** by recrystallization from a chloroform/diethyl ether mixture. The molecular structure, shown in Figure 1, can be described in terms of two *p*-cymene–ruthenium units held together by two μ_2 -bridging thiolato units. Selected bond lengths and angles are listed in Figure 1. In accordance with the electron count, there is no metal–metal bond; the distance between two ruthenium atoms is 3.674(2) Å, which is, however, slightly shorter than the Ru···Ru distances in the halido-bridged complexes $[(p\text{-MeC}_6\text{H}_4i\text{Pr})_2\text{Ru}_2\text{Br}_4]$ [3.854(1) Å],^[12] $[(p\text{-MeC}_6\text{H}_4i\text{Pr})_2\text{Ru}_2\text{I}_4]$ [3.854(1) Å],^[12] and $[(\text{C}_6\text{H}_5)_2\text{Ru}_2\text{Cl}_4]$ [4.07 Å].^[13] The geometrical parameters of **3** are comparable to those of the halido-bridged complexes, but the Ru–S–Ru angles [100.49(9)°] are somewhat wider than the corresponding Ru–Cl–Ru [98.22°],^[13] Ru–Br–Ru [97.01(3)°],^[13] and Ru–I–Ru [96.96(2)°] angles.^[12]

In contrast to these dinuclear arene–ruthenium(II) complexes, which show a long Ru···Ru distance, the short Ru–Ru distances in the analogous pentamethylcyclopentadienyl–ruthenium(III) complexes $[(\text{C}_5\text{Me}_5)_2\text{Ru}_2(\text{SMe})_2\text{Cl}_2]$ (*syn* isomer 2.883 Å, *anti* isomer 2.889 Å),^[14] $[(\text{C}_5\text{Me}_5)_2\text{Ru}_2(\text{SPh})_2\text{Cl}_2]$ (*syn* isomer 2.881 Å, *anti* isomer 2.902 Å),^[14] and $[(\text{C}_5\text{Me}_5)_2\text{Ru}_2(\text{SEt})_2\text{Cl}_2]$ (2.850 Å)^[15] could be interpreted as a consequence of metal–metal bonding.

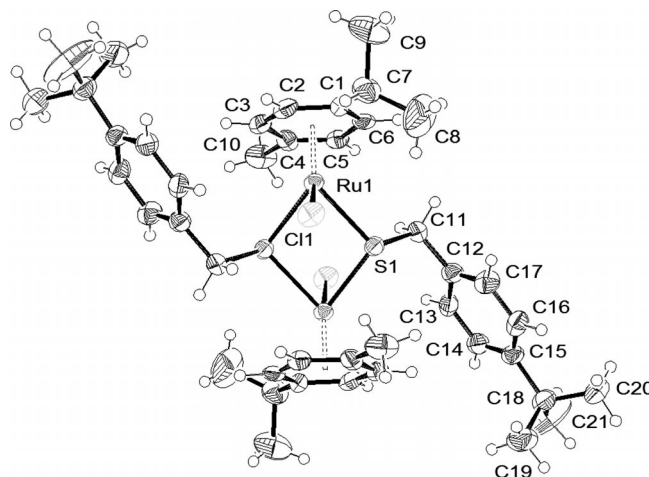


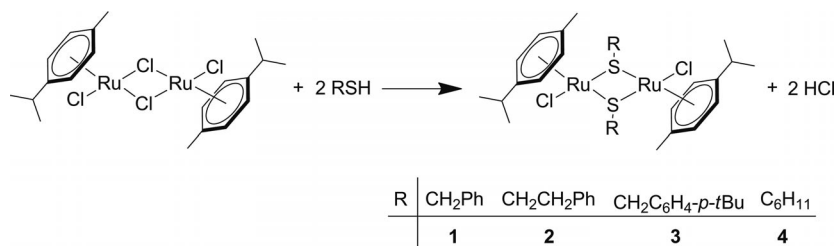
Figure 1. Molecular structure of **3** at 50% probability level ellipsoids. Selected bond lengths [Å] and angles [°]: Ru1–S1 2.384(2), Ru1–S1ⁱ 2.395(3), Ru1–Cl1 2.424(2), Ru1–Ru1ⁱ 3.674(2); S1–Ru1–S1ⁱ 79.51(9), S1–Ru1–Cl1 81.16(8), S1ⁱ–Ru1–Cl1 90.19(9), Ru1–S1–Ru1ⁱ 100.49(9). Symmetry operator: ⁱ 1 – *x*, –*y*, 1 – *z*.

Conversion into the Cationic Trithiolato Complexes 5–7

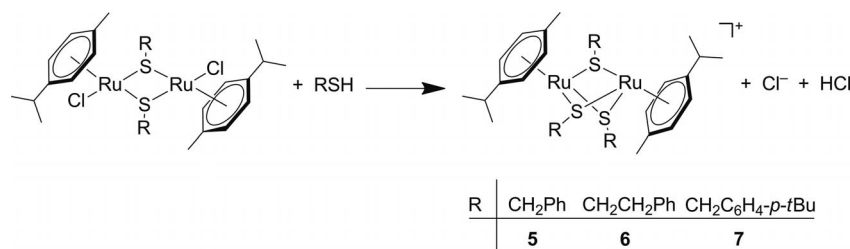
The neutral dithiolato complexes **1–3** react in ethanol heated at reflux with an excess amount of the corresponding thiol to give the cationic trithiolato complexes $[(p\text{-MeC}_6\text{H}_4i\text{Pr})_2\text{Ru}_2(\text{SCH}_2\text{Ph})_3]^+$ (**5**), $[(p\text{-MeC}_6\text{H}_4i\text{Pr})_2\text{Ru}_2(\text{SCH}_2\text{CH}_2\text{Ph})_3]^+$ (**6**), and $[(p\text{-MeC}_6\text{H}_4i\text{Pr})_2\text{Ru}_2(\text{SCH}_2\text{C}_6\text{H}_4\text{-}p\text{-}t\text{Bu})_3]^+$ (**7**), which were purified by column chromatography and isolated as the chloride salts (Scheme 2). The compounds **[5]Cl**, **[6]Cl**, and **[7]Cl** were obtained as air-stable orange to red crystalline solids, which were characterized by ¹H and ¹³C NMR spectroscopy, mass spectrometry, and elemental analysis.

The complexes **5–7** are also accessible by treating the *p*-cymene dichloride dimer with the corresponding thiol in ethanol heated at reflux; however, the direct reaction takes about 1 week and gives only poor yields (24–35%). This observation is consistent with the assumption that the neutral dithiolato complexes **1–3** are intermediates in the formation of the cationic trithiolato complexes **5–7**. Complex **4** does not react further in ethanol heated at reflux, presumably due to steric reasons.

In a similar fashion, the pentamethylcyclopentadienyl–ruthenium(III) complex $[(\text{C}_5\text{Me}_5)_2\text{Ru}_2\text{Cl}_4]$ was found to react with aromatic thiols to give the cationic trithiolato com-



Scheme 1. Synthesis of **1–4**.

Scheme 2. Synthesis of **5–7**.

plexes [(C₅Me₅)₂Ru₂(SR)₃]⁺, whereas aliphatic thiols gave neutral dithiolato complexes of the type [(C₅Me₅)₂Ru₂(SR)₂Cl₂]. However, conversion of the dithiolato complexes into the corresponding trithiolato with an excess amount of the thiol was not observed for these ruthenium(III) complexes.^[16,17]

Biological Activity

The antiproliferative activity of the dithiolato complexes **1–4** as well as of the trithiolato complexes **5–7** was evaluated against the human ovarian A2780 cancer cell line and its cisplatin-resistant derivative A2780cisR by using the MTT [MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide] assay, which measures mitochondrial dehydrogenase activity as an indication of cell viability. The IC₅₀ values of the complexes, which correspond to inhibition of cancer-cell growth at the 50% level, are reported in Table 1 together with those of cisplatin.

Table 1. Cytotoxicities of cisplatin, **1–4**, and [**5–7**]Cl towards A2780 and A2780cisR human ovarian cancer cells.

Compound	IC ₅₀ [μM] A2780	IC ₅₀ [μM] A2780cisR
1	2.94 ± 0.6	3.60 ± 0.8
2	0.20 ± 0.05	0.31 ± 0.08
3	>5	>5
4	0.46 ± 0.04	0.67 ± 0.08
[5]Cl	0.12 ± 0.04	0.11 ± 0.03
[6]Cl	0.17 ± 0.04	0.12 ± 0.02
[7]Cl	1.70 ± 0.2	3.40 ± 0.7
cisplatin	4.20 ± 0.5	15.2 ± 2.3

The neutral dithiolato complexes **1–3** are cytotoxic towards the cancer cell lines A2780 and A2780cisR, but the IC₅₀ values are always higher than those of the corresponding cationic trithiolato complexes **5–7** (Table 1). The substituent R has a strong influence on the cytotoxicity of the complexes. For the dithiolato complexes, the presence of two methylene groups in the aliphatic chain seems to be beneficial. Thus, the IC₅₀ values of 2.94 and 3.60 μM for **1** (with R = CH₂Ph) decrease to 0.20 and 0.31 μM for **2** (with R = CH₂CH₂Ph). This is in line with the submicromolar IC₅₀ values obtained for the cyclohexyl derivative **4** (0.46 and 0.67 μM). However, the *tert*-butyl group in the terminal position of the substituent (R = CH₂C₆H₄-*p*-tBu) in **3** has an opposite effect, which, to a lesser extent, is also exhibited by the corresponding cationic trithiolato complex **7**. The cytotoxicities of **2**, **4**, [**5**]Cl, and [**6**]Cl are remarkable, with

IC₅₀ values in the submicromolar range even for the cisplatin-resistant cell line A2780cisR.

A comparison of the neutral complexes **1–3** with their cationic analogues **5–7** shows that the [(arene)₂Ru₂(SR)₃]⁺ cations are more active than the corresponding neutral precursors [(arene)₂Ru₂(SR)₂Cl₂]. This may be due to a better uptake of charged complexes by living cells.^[18] As far as the mode of action is concerned, we have shown recently that the substitution-inert and stable complex [(*p*-MeC₆H₄-*i*Pr)₂Ru₂(SC₆H₄-*p*-Me)₃]⁺ efficiently catalyzes the oxidation of glutathione in water,^[19] which may account for the cytotoxicity of these complexes.

Conclusion

A new series of neutral dithiolato–diruthenium complexes has been prepared by the treatment of [(*p*-MeC₆H₄-*i*Pr)₂Ru₂Cl₄] with aliphatic thiols. These dithiolato complexes [(*p*-MeC₆H₄-*i*Pr)₂Ru₂(SR)₂Cl₂] were shown to react further to give the cationic trithiolato complexes [(*p*-MeC₆H₄-*i*Pr)₂Ru₂(SR)₃]⁺ with the exception of the cyclohexyl derivative, which remains as [(*p*-MeC₆H₄-*i*Pr)₂Ru₂(SC₆H₁₁)₂Cl₂], presumably for steric reasons. All compounds are highly cytotoxic toward human ovarian cancer cells.

Experimental Section

General: The starting material [(*p*-MeC₆H₄-*i*Pr)₂Ru₂Cl₄] was prepared according to published methods.^[20] 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- or negative-ion mode with an LCQ Finnigan mass spectrometer. Microanalyses were carried out by the Mikroelementaranalytisches Laboratorium, ETH Zürich (Switzerland).

Synthesis of 1–3: [(*p*-MeC₆H₄-*i*Pr)₂Ru₂Cl₄] (100 mg, 0.16 mmol) was dissolved in technical-grade EtOH (10 mL). When the compound had completely dissolved, the solution was cooled to 0 °C. After addition of the corresponding thiol RSH (0.32 mmol; R = CH₂Ph: 38 μL, R = CH₂CH₂Ph: 43 μL, R = CH₂C₆H₄-*p*-tBu: 60 μL), the solution was stirred at 0 °C for 2 h. Then the volume was reduced to 2 mL and diethyl ether (30 mL) added, which caused precipitation of the product. After cooling of the mixture to –18 °C for 24 h, the product was isolated by decantation using a cannula. The yellow to red product was washed with diethyl ether (2 times with 40 mL) and dried under vacuum.

Data for 1: Yield: 110 mg (86%). C₃₄H₄₂Cl₂Ru₂S₂ (787.87): calcd. C 51.83, H 5.37; found C 51.54, H 5.42. ESI MS (MeOH +

CH_2Cl_2): $m/z = 753.40$ $[\text{M} - \text{Cl}]^+$. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.44$ (m, 10 H, $\text{CH}_2\text{C}_6\text{H}_5$), 4.96 (m, 8 H, $H\text{-Ar}$), 4.19 (d, $^2J = 11.4$ Hz, 2 H, SCH_2), 3.31 (d, $^2J = 11.4$ Hz, 2 H, SCH_2), 2.86 [sept, $^3J = 6.8$ Hz, 2 H, $(\text{CH}_3)_2\text{CH}$], 1.88 (s, 6 H, CH_3), 1.21 [m, 12 H, $(\text{CH}_3)_2\text{CH}$] ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): $\delta = 142.0$, 130.6, 130.0, 129.3, 106.0, 100.0, 84.3, 83.2, 46.2, 32.2, 22.5, 18.0 ppm.

Data for 2: Yield: 70 mg (53%). $\text{C}_{36}\text{H}_{46}\text{Cl}_2\text{Ru}_2\text{S}_2$ (815.93): calcd. C 52.99, H 5.68; found C 52.77, H 5.71. ESI MS (MeOH + acetone): $m/z = 781.10$ $[\text{M} - \text{Cl}]^+$. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.29$ (m, 10 H, $\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$), 5.08 (m, 8 H, $H\text{-Ar}$), 3.15 (m, 4 H, SCH_2CH_2), 2.92 [sept, $^3J = 6.8$ Hz, 2 H, $(\text{CH}_3)_2\text{CH}$], 2.26 (m, 4 H, SCH_2CH_2), 2.17 (s, 6 H, CH_3), 1.24 [m, 12 H, $(\text{CH}_3)_2\text{CH}$] ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): $\delta = 141.5$, 128.9, 128.5, 126.14, 106.5, 96.5, 85.3, 85.1, 83.5, 80.8, 38.0, 35.4, 30.2, 23.0, 21.0, 18.9 ppm.

Data for 3: Yield: 100 mg (69%). $\text{C}_{42}\text{H}_{58}\text{Cl}_2\text{Ru}_2\text{S}_2 \cdot \text{CH}_2\text{Cl}_2$ (984.10): calcd. C 52.43, H 6.14; found C 51.88, H 6.16. ESI MS (MeOH + CH_2Cl_2): $m/z = 865.30$ $[\text{M} - \text{Cl}]^+$. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.49$ [d, $^3J = 8.0$ Hz, 4 H, $\text{CH}_2\text{C}_6\text{H}_4\text{C}(\text{CH}_3)_3$], 7.32 [d, $^3J = 8.0$ Hz, 4 H, $\text{CH}_2\text{C}_6\text{H}_4\text{C}(\text{CH}_3)_3$], 4.97 (m, 8 H, $H\text{-Ar}$), 4.11 (d, $^2J = 11.4$ Hz, 2 H, CH_2), 3.32 (d, $^2J = 11.4$ Hz, 2 H, CH_2), 2.82 [sept, $^3J = 6.8$ Hz, 2 H, $(\text{CH}_3)_2\text{CH}$], 1.89 (s, 6 H, CH_3), 1.38 [s, 18 H, $\text{CH}_2\text{C}_6\text{H}_4\text{C}(\text{CH}_3)_3$], 1.16 [m, 12 H, $(\text{CH}_3)_2\text{CH}$] ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): $\delta = 150.0$, 137.8, 130.2, 124.5, 105.7, 97.2, 83.4, 83.3, 82.8, 81.9, 36.5, 34.6, 31.5, 31.5, 31.5, 29.9, 23.3, 23.3, 18.7 ppm.

Synthesis of 4: Cyclohexanethiol (0.32 mmol, 38 mg) dissolved in EtOH (5 mL) was added to a solution of $[(p\text{-MeC}_6\text{H}_4\text{iPr})_2\text{Ru}_2\text{Cl}_4]$ (100 mg, 0.16 mmol) in technical-grade ethanol (50 mL). Then the solution was heated to reflux for 18 h, cooled to room temperature, and filtered through Celite. After evaporation of the solvent, the residue was purified by column chromatography on silica gel by using dichloromethane/ethanol (5:1) as eluent. The product was isolated as an orange powder and dried under vacuum.

Data for 4: Yield: 75 mg (61%). $\text{C}_{32}\text{H}_{50}\text{Cl}_2\text{Ru}_2\text{S}_2$ (771.86): calcd. C 49.79, H 6.53; found C 49.76, H 6.55. ESI MS (MeOH + CH_2Cl_2): $m/z = 736.30$ $[\text{M} - \text{Cl}]^+$. ^1H NMR (400 MHz, CDCl_3): $\delta = 5.70$ (d, $^3J = 8.0$ Hz, 4 H, $H\text{-Ar}$), 5.58 (d, $^3J = 8.0$ Hz, 4 H, $H\text{-Ar}$), 3.20 (m, 2 H, C_6H_{11}), 2.55 [sept, $^3J = 8.0$ Hz, 2 H, $(\text{CH}_3)_2\text{CH}$], 2.42 (m, 4 H, C_6H_{11}), 2.05 (s, 6 H, CH_3), 1.99 (m, 8 H, C_6H_{11}), 1.59 (m, 8 H, C_6H_{11}), 1.23 [d, $^3J = 8.0$ Hz, 12 H, $(\text{CH}_3)_2\text{CH}$] ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): $\delta = 82.3$, 82.2, 82.7, 39.2, 37.1, 33.0, 31.9, 31.7, 31.1, 29.6, 29.4, 27.3, 25.8, 24.1, 22.8, 22.6, 22.4, 18.4, 18.1, 14.2 ppm.

Synthesis of 5–7: The corresponding thiol (6 equiv.; $\text{R} = \text{CH}_2\text{Ph}$: 36 μL , $\text{R} = \text{CH}_2\text{CH}_2\text{Ph}$: 33 μL , $\text{R} = \text{CH}_2\text{C}_6\text{H}_4\text{-}p\text{-}t\text{-Bu}$: 99 μL) was added to a solution of the neutral dithiolato complexes (1 equiv.; **1**: 40 mg, **2**: 34 mg, **3**: 80 mg) in technical-grade ethanol (50 mL). Then the solution was heated to reflux for 12 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel by using dichloromethane/ethanol (9:1) as eluent. The yellow to brown product was isolated and dried under vacuum.

Data for [5]Cl: Yield: 25 mg (56%). $\text{C}_{41}\text{H}_{49}\text{ClRu}_2\text{S}_3$ (875.63): calcd. C 56.24, H 5.64; found C 55.64, H 5.85. ESI MS (MeOH): $m/z = 841.20$ $[\text{M} + \text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.55$ (m, 6 H, $\text{CH}_2\text{C}_6\text{H}_5$), 7.41 (m, 9 H, $\text{CH}_2\text{C}_6\text{H}_5$), 5.17 (d, $^3J = 6.0$ Hz, 2 H, $H\text{-Ar}$), 5.05 (d, $^3J = 6.0$ Hz, 2 H, $H\text{-Ar}$), 4.75 (d, $^3J = 6.0$ Hz, 2 H, $H\text{-Ar}$), 4.69 (d, $^3J = 6.0$ Hz, 2 H, $H\text{-Ar}$), 3.51 (s, 6 H, CH_2), 2.07 [sept, $^3J = 6.8$ Hz, 2 H, $(\text{CH}_3)_2\text{CH}$], 1.90 (s, 6 H, CH_3), 1.07 [d, $^3J = 6.8$ Hz, 6 H, $(\text{CH}_3)_2\text{CH}$], 1.02 [d, $^3J = 6.8$ Hz, 6 H, $(\text{CH}_3)_2\text{CH}$]

ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): $\delta = 139.7$, 129.3, 128.8, 128.1, 108.3, 100.4, 83.6, 83.5, 83.3, 81.9, 40.8, 31.5, 24.0, 23.6, 18.4 ppm.

Data for [6]Cl: Yield: 30 mg (78%). $\text{C}_{44}\text{H}_{55}\text{ClRu}_2\text{S}_3 \cdot \text{CH}_2\text{Cl}_2 \cdot \text{EtOH}$ (1049.12): calcd. C 53.83, H 6.06; found C 54.38, H 6.39. ESI MS (MeOH): $m/z = 883.20$ $[\text{M} + \text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.34$ (m, 15 H, $\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$), 5.16 (m, 8 H, $H\text{-Ar}$), 3.03 (t, $^3J = 7.6$ Hz, 6 H, SCH_2CH_2), 2.71 (t, $^3J = 7.6$ Hz, 6 H, SCH_2CH_2), 2.42 [sept, $^3J = 6.8$ Hz, 2 H, $(\text{CH}_3)_2\text{CH}$], 1.73 (s, 6 H, CH_3), 1.19 [m, 12 H, $(\text{CH}_3)_2\text{CH}$] ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): $\delta = 139.8$, 128.8, 126.9, 125.9, 106.8, 101.0, 83.7, 83.6, 83.6, 83.4, 41.4, 38.8, 31.4, 23.8, 22.6, 18.3 ppm.

Data for [7]Cl: Yield: 75 mg (82%). $\text{C}_{53}\text{H}_{73}\text{ClRu}_2\text{S}_3 \cdot 0.25\text{CH}_2\text{Cl}_2$ (1065.25): calcd. C 60.04, H 6.96; found C 59.94, H 7.18. MS (MeOH): $m/z = 1009.40$ $[\text{M}]^+$. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.45$ [s, 12 H, $\text{CH}_2\text{C}_6\text{H}_4\text{C}(\text{CH}_3)_3$], 5.13 (d, $^3J = 6.0$ Hz, 2 H, $H\text{-Ar}$), 5.07 (d, $^3J = 6.0$ Hz, 2 H, $H\text{-Ar}$), 4.80 (d, $^3J = 6.0$ Hz, 2 H, $H\text{-Ar}$), 4.61 (d, $^3J = 6.0$ Hz, 2 H, $H\text{-Ar}$), 3.50 (s, 6 H, CH_2), 2.04 [sept, $^3J = 6.8$ Hz, 2 H, $(\text{CH}_3)_2\text{CH}$], 1.72 (s, 6 H, CH_3), 1.35 [s, 18 H, $\text{C}(\text{CH}_3)_3$], 1.03 [d, $^3J = 6.8$ Hz, 6 H, $(\text{CH}_3)_2\text{CH}$], 0.97 [d, $^3J = 6.8$ Hz, 6 H, $(\text{CH}_3)_2\text{CH}$] ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): $\delta = 151.6$, 136.6, 129.1, 125.6, 108.1, 100.7, 83.4, 83.3, 82.8, 81.9, 40.4, 34.8, 31.5, 31.5, 31.3, 29.7, 23.6, 22.9, 18.5 ppm.

Single-Crystal X-ray Structure Analysis of 3

X-ray Data for $[(p\text{-MeC}_6\text{H}_4\text{iPr})_2\text{Ru}_2(\text{SCH}_2\text{C}_6\text{H}_4\text{-}p\text{-}t\text{-Bu})_2\text{Cl}_2]$ (3): $\text{C}_{42}\text{H}_{58}\text{Cl}_2\text{Ru}_2\text{S}_2$, $M_r = 900.04$, triclinic, space group $P\bar{1}$ (no. 2), cell parameters $a = 8.7997(18)$ Å, $b = 9.3427(18)$ Å, $c = 13.300(2)$ Å, $\alpha = 96.285(14)^\circ$, $\beta = 99.419(15)^\circ$, $\gamma = 102.542(16)^\circ$, $V = 1041.0(3)$ Å³, $T = 173(2)$ K, $Z = 1$, $D_{\text{calcd.}} = 1.430$ g cm⁻³, $\lambda(\text{Mo-K}\alpha) = 0.71073$ Å, 5540 reflections measured, 2577 unique ($R_{\text{int}} = 0.1440$), which were used in all calculations. The crystal was mounted on a Stoe image plate diffraction system equipped with a ϕ circle goniometer, and Mo-K α graphite-monochromated radiation ($\lambda = 0.71073$ Å) was used with a ϕ range of 0–200°. The structure was solved by direct methods with the program SHELXS-97, whereas the refinement and all further calculations were carried out by using SHELXL-97.^[21] The hydrogen atoms were included in calculated positions and treated as riding atoms by using the SHELXL default parameters. The non-hydrogen atoms were refined anisotropically by using weighted full-matrix least squares on F^2 . $R_1 = 0.0765$ [$I > 2\sigma(I)$] and $wR_2 = 0.1810$, GoF = 1.134; max./min. residual density 1.069/–0.743 e Å⁻³. Figure 1 was drawn with ORTEP.^[22] CCDC-846981 (3) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Cell Culture and Inhibition of Cell Growth: Human A2780 and A2780cisR ovarian carcinoma cells were obtained from the European Centre of Cell Cultures (ECACC, Salisbury, UK) and maintained in culture as described by the provider. The cells were routinely grown in RPMI 1640 medium with GlutaMAX that contained fetal calf serum (FCS) (5%) and antibiotic (penicillin and streptomycin) at 37 °C and CO₂ (5%). For the evaluation of growth-inhibition tests, the cells were seeded in 96-well plates (25×10^3 cells per well) and grown in complete medium for 24 h. The compounds were dissolved in DMSO and added to the required concentration to the cell culture for 72 h incubation. Solutions of compounds were applied by diluting a fresh stock solution of the corresponding compound in aqueous RPMI medium with GlutaMAX (20 mM). Following drug exposure, MTT was added to cells at a final concentration of 0.25 mg mL⁻¹ and incubated for 2 h. Then the culture medium was aspirated and the violet formazan

(artificial chromogenic precipitate of the reduction of tetrazolium salts by dehydrogenases and reductases) dissolved in DMSO. The optical density of each well (96-well plates) was quantified three times in triplicates at 540 nm with a multiwell plate reader (iEMS Reader MF, Labsystems, US), and the percentage of surviving cells was calculated from the ratio of absorbance of treated to untreated cells. The IC_{50} values for the inhibition of cell growth were determined by fitting the plot of the logarithmic percentage of surviving cells against the logarithm of drug concentration by using a linear regression function. The median value and the median absolute deviation were obtained from the Excel software (Microsoft), and those values are reported in Table 1.

Acknowledgments

Financial support of this work by the Swiss National Science Foundation and a generous loan of ruthenium(III) chloride hydrate from the Johnson Matthey Research Centre are gratefully acknowledged.

- [1] a) M. A. Bennett in *Comprehensive Organometallic Chemistry II*, vol. 7 (Eds.: E. W. Abel, F. G. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, p. 549–602; b) B. Therrien, *Coord. Chem. Rev.* **2009**, *253*, 493–519.
- [2] G. Winkhaus, H. Singer, *J. Organomet. Chem.* **1967**, *7*, 487–491.
- [3] R. A. Zelonka, M. C. Baird, *Can. J. Chem.* **1972**, *50*, 3063–3072.
- [4] M. A. Bennett, A. K. Smith, *J. Chem. Soc., Dalton Trans.* **1974**, 233–241.
- [5] H. T. Schacht, R. C. Haltiwanger, M. Rakovoski Dubois, *Inorg. Chem.* **1992**, *31*, 1728–1730.
- [6] K. Mashima, A. Mikami, A. Nakamura, *Chem. Lett.* **1992**, 1795–1798.
- [7] a) F. Chérioux, B. Therrien, G. Süss-Fink, *Eur. J. Inorg. Chem.* **2003**, 1043–1047; b) F. Chérioux, B. Therrien, G. Süss-Fink, *Inorg. Chim. Acta* **2004**, *357*, 834–838.
- [8] F. Chérioux, C. M. Thomas, T. Mounier, G. Süss-Fink, *Polyhedron* **2003**, *22*, 543–548.
- [9] M. Gras, B. Therrien, G. Süss-Fink, O. Zava, P. J. Dyson, *Dalton Trans.* **2010**, *39*, 10305–10313.
- [10] For reviews, see: a) G. S. Smith, B. Therrien, *Dalton Trans.* **2011**, *40*, 10793–10800; b) G. Süss-Fink, *Dalton Trans.* **2010**, *39*, 1673–1688; c) W. H. Ang, P. J. Dyson, *Eur. J. Inorg. Chem.* **2006**, 4003–4018; d) I. Kostova, *Curr. Med. Chem.* **2006**, *13*, 1085–1107; e) S. J. Dougan, P. J. Sadler, *Chimia* **2007**, *61*, 704–715.
- [11] H. Seino, Y. Mizobe, M. Hidai, *New J. Chem.* **2000**, *24*, 907–911.
- [12] A. Neels, H. Stoeckli-Evans, L. Plasseraud, E. Garcia Fidalgo, G. Süss-Fink, *Acta Crystallogr., Sect. C* **1999**, *55*, 2030–2032.
- [13] J. Canivet, B. Therrien, G. Süss-Fink, *Acta Crystallogr., Sect. E* **2005**, *61*, m1090–m1091.
- [14] Y. Nishibayashi, H. Imajima, G. Onodera, Y. Inada, M. Hidai, S. Uemura, *Organometallics* **2004**, *23*, 5100–5103.
- [15] K. Hashizume, Y. Mizobe, M. Hidai, *Organometallics* **1996**, *15*, 3303–3309.
- [16] M. Hidai, K. Imagawa, G. Cheng, Y. Mizobe, Y. Wakatsuki, H. Yamazaki, *Chem. Lett.* **1986**, 1299–1302.
- [17] S. Dev, K. Imagawa, Y. Mizobe, G. Cheng, Y. Wakatsuki, H. Yamazaki, M. Hidai, *Organometallics* **1989**, *8*, 1232–1237.
- [18] a) A. L. Harris, X. Yang, A. Hegmans, L. Povirk, J. L. Ryan, L. Kelland, N. P. Farrell, *Inorg. Chem.* **2005**, *44*, 9598–9600; b) Z. Ma, J. Roy Choudhury, M. W. Wright, C. S. Day, G. Saluta, G. L. Kucera, U. Bierbach, *J. Med. Chem.* **2008**, *51*, 7574–7580; c) A. V. Klein, T. W. Hambley, *Chem. Rev.* **2009**, *109*, 4911–4920; d) J. Mattsson, O. Zava, A. K. Renfrew, Y. Sei, K. Yamaguchi, P. J. Dyson, B. Therrien, *Dalton Trans.* **2010**, *39*, 8248–8255.
- [19] F. Giannini, G. Süss-Fink, J. Furrer, *Inorg. Chem.* **2011**, *50*, 10552–10554.
- [20] M. A. Bennett, T.-N. Huang, T. W. Matheson, A. K. Smith, *Inorg. Synth.* **1982**, *21*, 74–78.
- [21] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.
- [22] L. J. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565.