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# Thiophenolato-bridged dinuclear arene ruthenium complexes: a new family of highly cytotoxic anticancer agents

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New cationic diruthenium complexes of the type $[(arene)_2Ru_2(SPh)_3]^+$, arene being $C_6H_6$, *p*-$^i$Pr$C_6H_4$Me, $C_6Me_6$, $C_6H_5R$, where R = $(CH_2)_nOC(O)C_6H_4$-*p*-$O(CH_2)_6CH_3$ or $(CH_2)_nOC(O)CH{=}CHC_6H_4$-*p*-$OCH_3$ and *n* = 2 or 4, are obtained from the reaction of the corresponding precursor $[(arene)RuCl_2]_2$ and thiophenol and isolated as their chloride salts. The complexes have been fully characterised by spectroscopic methods and the solid state structure of $[(C_6H_6)_2Ru_2(SPh)_3]^+$, crystallised as the hexafluorophosphate salt, has been established by single crystal X-ray diffraction. The complexes are highly cytotoxic against human ovarian cancer cells (cell lines A2780 and A2780cisR), with the $IC_{50}$ values being in the submicromolar range. In comparison the analogous trishydroxythiophenolato compounds $[(arene)_2Ru_2(S\text{-}p\text{-}C_6H_4OH)_3]Cl$ ($IC_{50}$ values around 100 μM) are much less cytotoxic. Thus, it would appear that the increased antiproliferative effect of the arene ruthenium complexes is due to the presence of the phenyl or toluyl substituents at the three thiolato bridges.

## 1. Introduction

Water-soluble arene ruthenium complexes such as the prototype (*p*-$^i$Pr$C_6H_4$Me)Ru(*P*-pta)$Cl_2$ (pta = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane) (termed RAPTA-C)[1] and lipophilic compounds such as the benchmark $[(C_6H_5Ph)Ru(N,N\text{-en})Cl]^+$ (en = 1,2-ethylenediamine)[2] have antitumoral or antimetastatic properties *in vitro* and *in vivo*. The anticancer potential of these types of compounds has been explained by their dual character, with the hydrogen bonding capacity of the pta or en ligands counterbalanced by the lipophilicity of the arene ligand,[3] while the mechanism of cytotoxic action is thought to involve hydrolysis of the Ru–Cl bond followed by reaction with the biomolecular target or targets.[4] The underlying design of arene ruthenium anticancer agents and the current understanding of their mode of action is summarised in several review articles.[5–9]

While most cytotoxicity studies with arene ruthenium compounds have been concerned with mononuclear complexes, the question of applying the multinuclearity concept to arene ruthenium complexes was recently raised,[10] in the light of an increased cytotoxicity of trinuclear arene ruthenium cluster cations.[11] This is indeed confirmed by recent findings with highly active dinuclear arene ruthenium complexes: the dinuclear arene ruthenium complexes (*p*-$^i$Pr$C_6H_4$Me)Ru(*O*,*O*-$C_6H_5O_2N(CH_2)_nNC_6H_5O_2$-*O*,*O*)Ru(*p*-$^i$Pr$C_6H_4$Me) containing a pyridone-derived linker (Fig. 1) reported by Hartinger show relevant cytotoxic effects against human ovarian (A2780) and colon (SW480) cancer cell lines. A pronounced influence of the spacer length and cytotoxicity was found (A2780 $IC_{50}$ 25 μM for *n* = 3, 30 μM for *n* = 6, 1.5 μM for *n* = 12, SW480 $IC_{50}$ 62 μM for *n* = 3, 26 μM for *n* = 6, 0.3 μM for *n* = 12), with the cytotoxicity being correlated with lipophilicity and water solubility.[12,13] A detailed structure–activity relationship was established based on water/octanol partition and hydrolytic stability, showing that only the most lipophilic (long) chain (*n* = 12) is highly active, due to the ability of the compound to cross-link with biomolecules.[14] This is in agreement with the cytotoxicities we observed for dinuclear ferrocenyl pyridine arene ruthenium complexes $[(arene)RuCl_2]_2(NC_5H_4OOCC_5H_4FeC_5H_4COOC_5H_4N)$, arene being *p*-$^i$Pr$C_6H_4$Me (Fig. 1) or $C_6Me_6$.[15]

Dinuclear arene ruthenium complexes containing 2,3-bis(2-pyridyl)pyrazine (bpp) as a doubly chelating ligand in the *N*,*N*:*N*,*N*-bridge have been synthesised and studied for photoactivation by Sadler in view of their potential in photodynamic therapy. The benzene and indane derivatives $[\{(C_6H_6)RuCl\}_2(N,N{:}N,N\text{-bpp})]^{2+}$ and $[\{(C_9H_{10})RuCl\}_2(N,N{:}N,N\text{-bpp})]^{2+}$ (Fig. 1) readily undergo arene loss upon UV irradiation whereas the *p*-cymene and hexamethylbenzene derivatives do not. The indane derivative undergoes aquation in the dark, and UV or visible light leads to a dissociation of the indane ligand and to the formation of strong diruthenium DNA adducts.[16]

Based on our earlier work on dinuclear arene ruthenium complexes of the type $[(arene)_2Ru_2(SX)_3]^+$ (arene = $C_6H_6$, *p*-$^i$Pr$C_6H_4$Me or $C_6Me_6$ and X = *p*-$C_6H_4$-OH, *p*-$C_6H_4Br$, *p*-$C_6H_4$-3′-$C_4H_3S$, *p*-$C_6H_4$–$C_6H_5$, *p*-$C_6H_4$-(*m*-$C_6H_4C_6H_5$), *p*-$C_6H_4C_{10}H_7$, $C_6H_4$-*p*-$CH_3$ or $C_2H_4$-OH),[17–21] we now report on the synthesis of new trithiophenolato-bridged dinuclear arene ruthenium complexes $[(arene)_2Ru_2(SPh)_3]^+$, which in the form of their chloride salts proved to be highly active against human ovarian cancer cell lines, with the cytotoxicity being in the submicromolar range.

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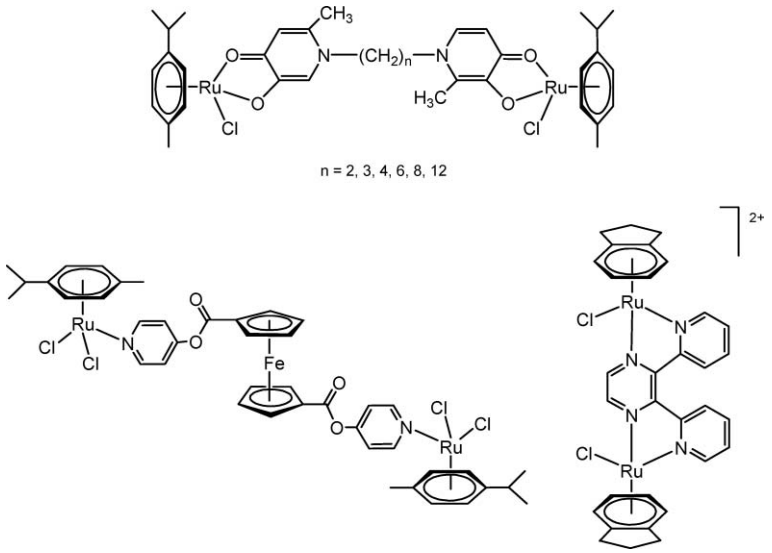
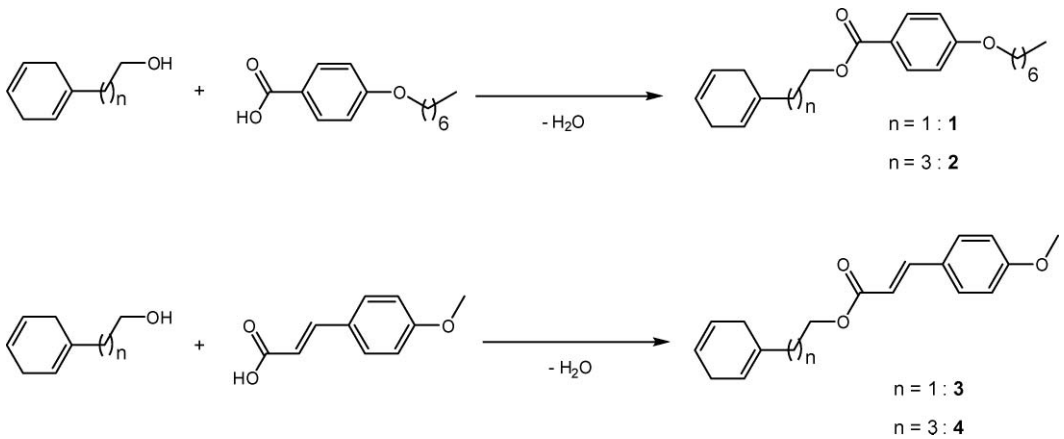



**Fig. 1** Cytotoxic dinuclear arene ruthenium complexes.




**Scheme 1** Synthesis of the diene precursors **1**–**4**.

## 2. Results and discussion

### Synthesis and characterisation of the diene precursors 1–4

The compounds 2-(cyclohexa-1,4-dienyl)ethanol and 4-(cyclohexa-1,4-dienyl)butanol, accessible by Birch reduction of the corresponding benzene derivatives,[22,23] react in the presence of 4-(dimethylamino)pyridine, *N*,*N*′-dicyclohexylcarbodiimide and 4-pyrrolidinopyridine as coupling reagents, with 4-(heptyloxy)benzoic acid to give the functionalised dienes **1** and **2**, using conditions similar to those reported previously.[24] The coupling with 4-methoxycinnamic acid under the same conditions yields to the functionalised dienes **3** and **4** (Scheme 1). The new compounds, obtained as colorless oils, were characterised by NMR spectroscopy, mass spectrometry and elemental analysis (see Experimental).

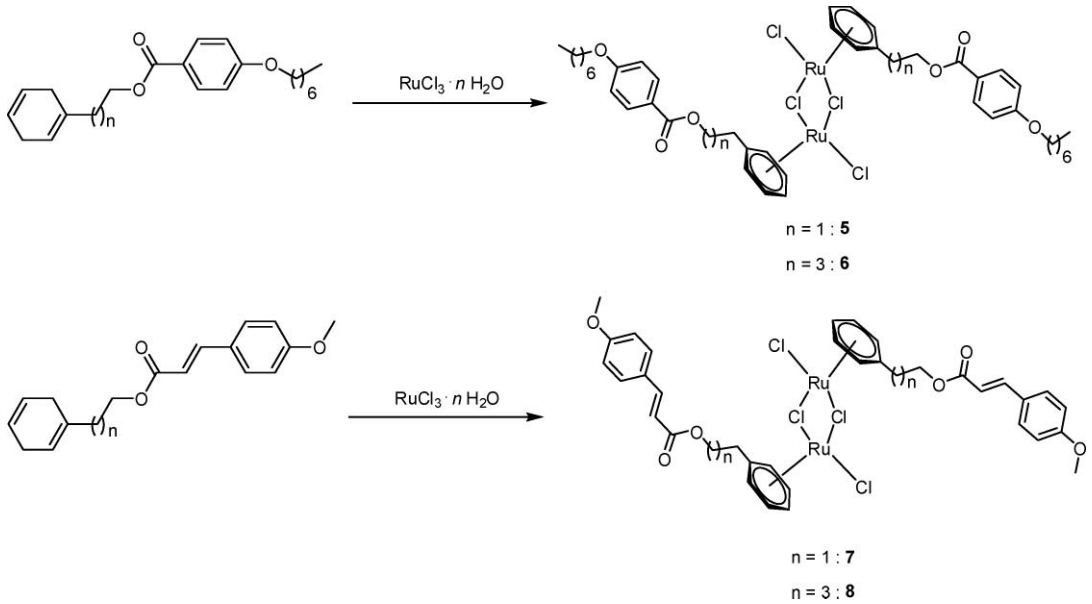
### Synthesis and characterisation of the functionalised arene ruthenium chloro intermediates 5–8

The complexes $[(C_6H_5R)RuCl_2]_2$ (where R = $(CH_2)_2OC(O)$-$C_6H_4$-*p*-$O(CH_2)_6CH_3$: **5**, $(CH_2)_4OC(O)C_6H_4$-*p*-$O(CH_2)_6CH_3$: **6**, $(CH_2)_2OC(O)CH{=}CHC_6H_4$-*p*-$OCH_3$: **7**, $(CH_2)_4OC(O)$-$CH{=}CHC_6H_4$-*p*-$OCH_3$: **8**), are accessible from the reaction of the corresponding dienes **1**, **2**, **3** and **4** with ruthenium(III) chloride hydrate in refluxing acetone/water (5 : 1), see Scheme 2. Complexes **5**–**8** are air-stable brown to orange crystalline solids (see Experimental for spectroscopic and analytical data), which are soluble in dichloromethane and chloroform.

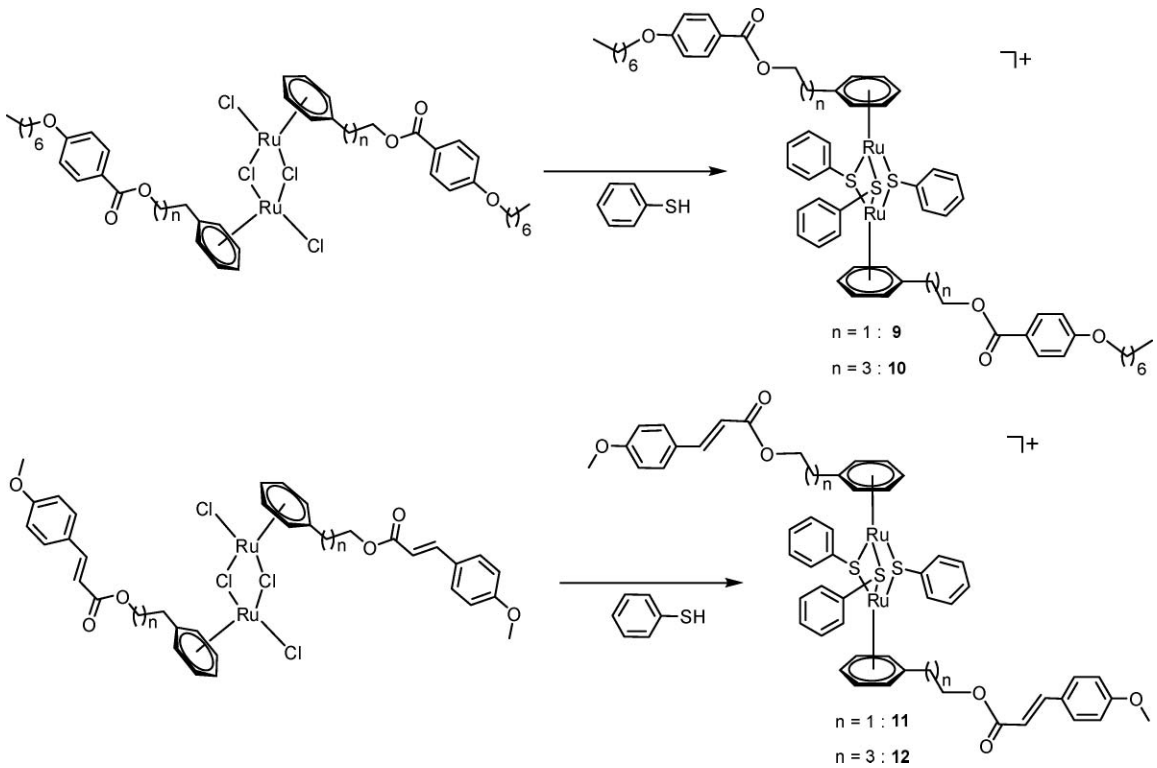
### Synthesis and characterisation of the functionalised arene ruthenium thiophenolato complexes 9–12

The arene ruthenium chloro intermediates **5**–**8** react with thiophenol in refluxing ethanol to give the dinuclear arene ruthenium thiophenolato complexes $[(arene)_2Ru_2(SPh)_3]^+$, arene being $C_6H_5R$ (R = $(CH_2)_2OC(O)C_6H_4$-*p*-$O(CH_2)_6CH_3$: **9**, $(CH_2)_4OC(O)C_6H_4$-*p*-$O(CH_2)_6CH_3$: **10**, $(CH_2)_2OC(O)CH{=}CHC_6H_4$-*p*-$OCH_3$: **11**, $(CH_2)_4OC(O)CH{=}CHC_6H_4$-*p*-$OCH_3$: **12**), according to Scheme 3.

The chloride salts of **9**–**12** are obtained as air-stable orange to red crystalline solids which are soluble in methanol, dichloromethane and chloroform. The $^1$H NMR spectra




**Scheme 2** Synthesis of the functionalised arene ruthenium chloro intermediates **5–8**.

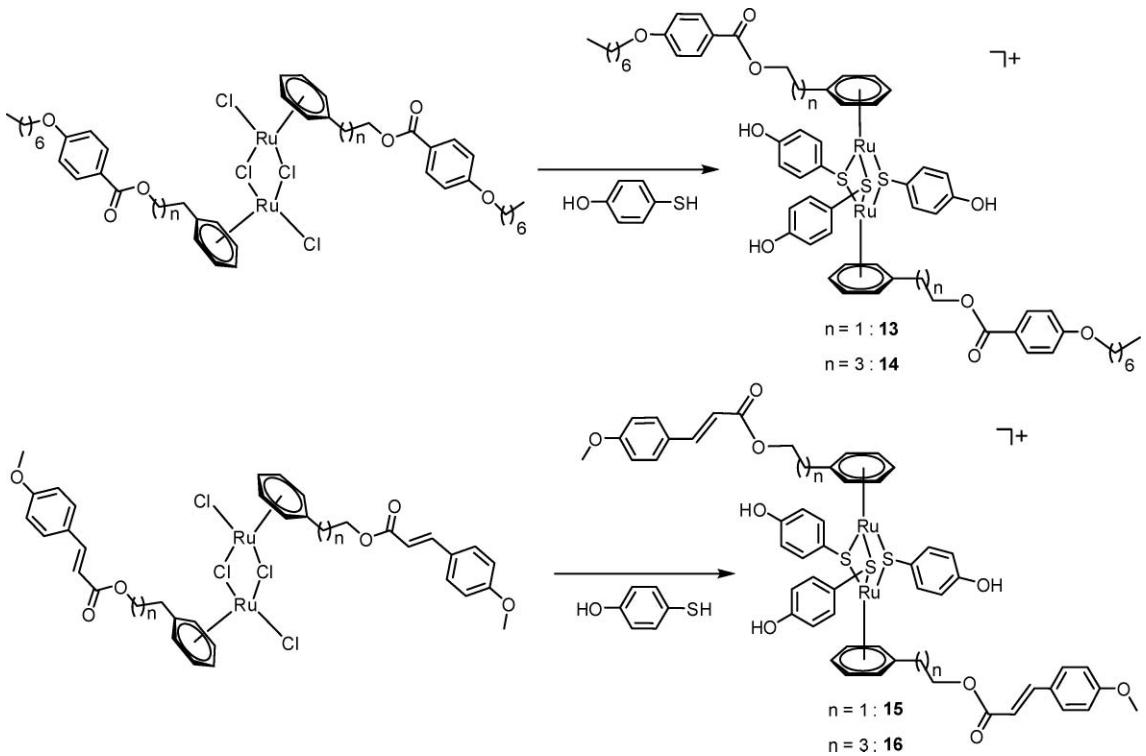



**Scheme 3** Synthesis of the functionalised arene ruthenium thiophenolato complexes **9–12**.

of the dinuclear arene ruthenium thiophenolato complexes $[(arene)_2Ru_2(SPh)_3]^+$ **9–12** in $CDCl_3$ give rise to two signals for the three equivalent thiophenolato groups (**9**: 7.37 m, 7.88 d ppm; **10**: 7.36 m, 7.92 d ppm; **11**: 7.42 m, 7.88 d ppm; **12**: 7.41 m, 7.85 d ppm), and to the characteristic arene ligand signals (see Experimental for further details). The ESI mass spectra of **9–12** contain molecular ion peaks at $m/z$ 1211, 1267, 1095 and 1151, respectively.

## Synthesis and characterisation of the functionalised arene ruthenium hydroxythiophenolato complexes 13–16

Since the anticancer activity of arene ruthenium complexes depends to some extent on their lipophilic and on their hydrophilic properties,[1,2,12,13] the thiolato bridges in the $[(arene)_2Ru_2(SPh)_3]^+$ complexes were modified by the introduction of a *p*-hydroxy function onto the phenyl substituent to increase water




**Scheme 4** Synthesis of the functionalised arene ruthenium hydroxythiophenolato complexes **13–16**.

solubility. This was achieved by reacting the $[(arene)RuCl_2]_2$ intermediates **5–8** with *p*-hydroxythiophenol in a similar fashion to the method outlined above, to afford the dinuclear arene ruthenium complexes $[(C_6H_5R)_2Ru_2(S\text{-}p\text{-}C_6H_4OH)_3]^+$ (where R = $(CH_2)_2$–O–C(O)–$C_6H_4$-*p*-$O(CH_2)_6CH_3$: **13**, $(CH_2)_4$–O–C(O)–$C_6H_4$-*p*-$O(CH_2)_6CH_3$: **14**, $(CH_2)_2$–O–C(O)–CH═CH–$C_6H_4$-*p*-$OCH_3$: **15**, $(CH_2)_4$–O–C(O)–CH═CH–$C_6H_4$-*p*-$OCH_3$: **16**), see Scheme 4.

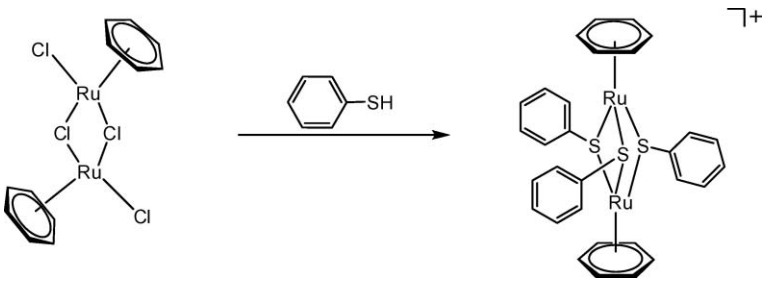
The chloride salts of **13–16**, which are soluble in dichloromethane, chloroform and in other polar organic solvents, are obtained as air-stable yellow to orange crystalline solids. The $^1$H NMR spectra of **13–16** in $CDCl_3$ provide the two signals of the three equivalent hydroxythiophenolato groups (**13**: 7.01 d, 7.63 d ppm; **14**: 6.93 d, 7.52 d ppm; **15**: 6.90 d, 7.62 d ppm; **16**: 6.82 d, 7.47 d ppm), and the characteristic arene ligand signals (see Experimental). In the ESI mass spectra, the molecular peaks of **13–16** are observed at *m/z* 1259, 1315, 1143 and 1199, respectively.

**Synthesis and characterisation of the unfunctionalised arene ruthenium thiophenolato complexes 17–19**

In order to study the influence of the lipophilic chains in the arene ligands on the biological activity, we also synthesised the unfunctionalised cation $[(C_6H_6)_2Ru_2(SPh)_3]^+$ (**17**) that was prepared from the reaction of thiophenol with $[(C_6H_6)RuCl_2]_2$ in refluxing ethanol (Scheme 5).

The known *p*-cymene and hexamethylbenzene analogs $[(p\text{-}^iPrC_6H_4Me)_2Ru_2(SPh)_3]^+$ (**18**),[25] $[(C_6Me_6)_2Ru_2(SPh)_3]^+$ (**19**)[26] (Fig. 2) and $[(p\text{-}^iPrC_6H_4Me)_2Ru_2(S\text{-}p\text{-}C_6H_4Me)_3]^+$ (**20**)[18] (Fig. 2) were also synthesised according to this method which gives much better yields than the reported procedures. All the complexes were isolated as the chloride salts.

Compound [**17**]Cl, an air-stable yellow solid soluble in water and in organic solvents, gives rise to two signals for the three equivalent thiophenolato groups (7.37 m and 7.83 d ppm) and to a singlet for the two equivalent benzene



**Scheme 5** Synthesis of the unfunctionalised diruthenium complex **17**.

**Table 1** Selected bond lengths (Å) and angles (°) for cation **17**

| | Molecule A | Molecule B |
|---|---|---|
| *Interatomic distances* | | |
| Ru–S | 2.3764(12) | 2.3823(13) |
| | 2.3858(12) | 2.3828(13) |
| | 2.4014(12) | 2.3866(14) |
| | 2.4019(13) | 2.3961(13) |
| | 2.4112(12) | 2.4043(13) |
| | 2.4239(12) | 2.4119(14) |
| $S–C_{ph}$ | 1.793(5) | 1.792(5) |
| | 1.795(5) | 1.795(5) |
| | 1.798(5) | 1.796(6) |
| Ru-centroid | 1.704 | 1.695 |
| | 1.705 | 1.698 |
| *Angles* | | |
| Ru–S–Ru | 88.17(4) | 88.58(4) |
| | 88.48(4) | 88.67(4) |
| | 89.67(4) | 88.96(4) |

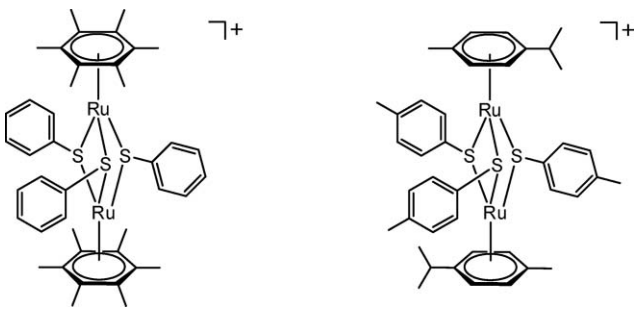



**Fig. 2** Diruthenium complexes **19** (left) and **20** (right).

ligands (5.44 ppm) in the $^1$H NMR spectrum (in $CDCl_3$). The ESI mass spectrum shows the molecular peak at *m/z* 686.94. The spectroscopic data for the analogues [**18**]Cl, [**19**]Cl and [**20**]Cl are in excellent agreement with those reported previously.[25,26,18]

The molecular structure of **17** was established by single-crystal X-ray diffraction analysis of the $PF_6^-$ salt. The unit cell contains two independent cations (molecules A and B), the bond distances and angles being similar. An ORTEP drawing with the atom labelling scheme for molecule A of cation **17** is shown in Fig. 3 and selected bond lengths and angles are given in Table 1. The structure contains a trigonal bipyramidal $Ru_2S_3$ framework, in which each ruthenium atom adopts a pseudo-octahedral geometry due to the three sulfur atoms and the benzene ligand that formally occupies three coordination sites.

The Ru–S bond distances in the cation **17** range from 2.3764(12) to 2.4239(12) Å and the Ru–S–Ru angles range from 88.17(4) to 89.67(4)°, similar to those found in the known *p*-cymene and hexamethylbenzene derivatives $[(p\text{-}^i\text{PrC}_6\text{H}_4\text{Me})_2\text{Ru}_2(\text{SPh})_3]^+$ (**18**)[25] and $[(C_6Me_6)_2Ru_2(SPh)_3]^+$ (**19**),[26] but slightly longer than in a thiopyrone complex.[27] In accordance with the electron count, the Ru–Ru distances (3.3576(5) and 3.3481(6) Å) are clearly outside of the range for a metal-metal single bond (2.28–2.95 Å).[24] The three phenyl groups are not in the plane formed by the three sulfur atoms. The difference between the two independent molecules resides in the relative tilt of the phenyl groups with respect to this plane; in molecule A two phenyl groups are tilted to the right and the third phenyl group is tilted to the left whereas the tilts are opposite in molecule B.

**Table 2** $IC_{50}$ values of complexes **9**–**20** towards A2780 and A2780cisR human ovarian cancer cells

| Compound | $IC_{50}$/μM A2780 | $IC_{50}$/μM A2780cisR |
|---|---|---|
| [**9**]Cl | 2.2 | 2.7 |
| [**10**]Cl | 4.9 | 5.6 |
| [**11**]Cl | 0.82 | 1.36 |
| [**12**]Cl | 0.49 | 0.56 |
| [**13**]Cl | 127 | 132 |
| [**14**]Cl | 130 | 126 |
| [**15**]Cl | 113 | 104 |
| [**16**]Cl | 13.6 | 27.2 |
| [**17**]Cl | 0.38 | 0.48 |
| [**18**]Cl | 0.24 | 0.25 |
| [**19**]Cl | 0.4 | 1.2 |
| [**20**]Cl | 0.13 | 0.08 |

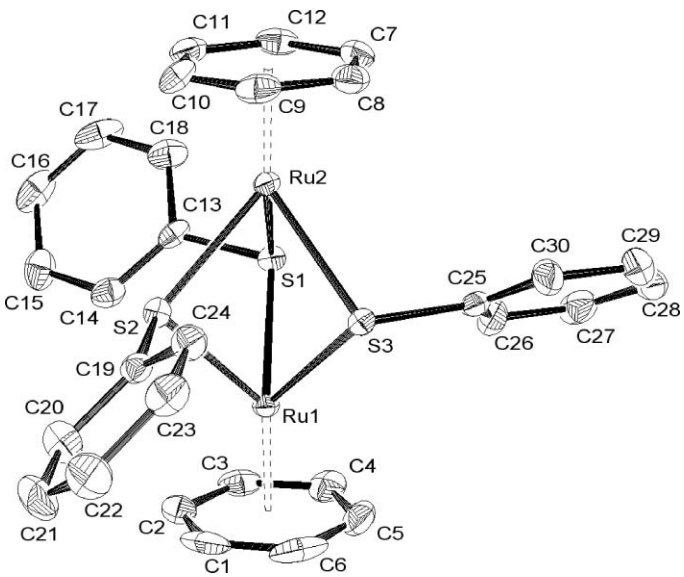



**Fig. 3** Molecular structure of cation **17**, thermal ellipsoids are drawn at 50% probability level and hydrogen atoms are omitted for clarity.

## 3. Biological activity towards human ovarian cancer cells

The antiproliferative activity of complexes **9**–**20** was evaluated against the human ovarian A2780 cancer cell line and its cisplatin-resistant derivative A2780cisR using the MTT assay, which measures mitochondrial dehydrogenase activity as an indication of cell viability. The $IC_{50}$ values of **9**–**20**, corresponding to inhibition of cancer cell growth at the 50% level, are listed in Table 2.

The complexes tested show a broad range of cytotoxicities, depending on both the thiophenyl and arene substituents, but with comparable effects on both the cisplatin sensitive and resistant cell lines. More precisely, two general tendencies can be appreciated from the data. First, the arene ruthenium thiophenato complexes (**9** to **12**) are systematically more cytotoxic than their hydroxyl-thiophenato analogues (**13** to **16**). Second, the arene moiety has an effect, as shown by the diversity of toxicities observed for compounds **9**, **10**, **17**, **18**, **19** and **20**, although the $IC_{50}$ values obtained cannot be precisely correlated to the lipophilicity or the

size of the substituents. It is worth noting that the sub-micromolar cytotoxicities observed for some of these compounds place them amongst the most cytotoxic arene ruthenium compounds reported, even based on the fact that two ruthenium centers are present.

The stability of the most active complex [(*p*-$^{i}$PrC$_6$H$_4$Me)$_2$Ru$_2$(S-*p*-C$_6$H$_4$Me)$_3$]$^+$ (**20**) was assessed using $^1$H NMR spectroscopy over 12 h at 37 °C in DMSO-d$_6$, in D$_2$O/DMSO-d$_6$ (95 : 5), and in DMSO-d$_6$ in the presence of two drops of RPMI 1640 medium with GlutaMAX™ containing 5% foetal calf serum and penicillin and streptomycin antibiotics to mimic pseudo-physiological conditions. The $^1$H NMR signals of **20** did not change at all during 12 h period which indicates that it is stable under these conditions.

In conclusion, a series of highly cytotoxic cationic diruthenium complexes of general formula [(arene)$_2$Ru$_2$(SPh)$_3$]$^+$ have been prepared. The high *in vitro* anticancer activity of these complexes must be ascribed, at least in part, to the presence of the thiophenolato groups. Further work is required to delineate the mode of action of these compounds and to develop further derivatives in order to understand the role of the bridging thiophenolato ligands.

## 4. Experimental

### General comments

All reagents were purchased either from Aldrich or Fluka and used as received. The dimers [(arene)$_2$RuCl$_2$]$_2$ [28] were prepared according to literature methods. Reactions were carried out under nitrogen. NMR spectra were recorded on a Bruker AMX 400 spectrometer using the residual protonated solvent as internal standard. Micro-analyses were performed by the Laboratory of Pharmaceutical Chemistry, University of Geneva (Switzerland) or by Mikroelementaranalytisches Laboratorium, ETH Zürich (Switzerland). Electrospray ionisation mass spectra were obtained in positive-ion mode with an LCQ Finnigan mass spectrometer or performed at the Department of Chemistry of the University of Fribourg (Switzerland).

### Preparation of the diene precursors 1–4

To a Schlenk tube, the corresponding acid (5.2 mmol, 1.24 g for **1**; 4.3 mmol, 1.01 g for **2**; 5.2 mmol, 934 mg for **3**; 4.3 mmol, 761 mg for **4**), in the presence of the coupling reagents 4-(dimethylamino)pyridine (4 mmol, 492 mg for **1** and **3**; 3.3 mmol, 401 mg for **2** and **4**), *N*,*N*′-dicyclohexylcarbodiimide (8 mmol, 1.66 g for **1** and **3**; 6.6 mmol, 1.36 g for **2** and **4**) and 4-pyrrolidinopyridine (4 mmol, 597 mg for **1** and **3**; 3.3 mmol, 497 mg for **2** and **4**) were dissolved in $CH_2Cl_2$ (100 mL). After the addition of a solution of the diene (4 mmol, 500 mg for **1** and **3**; 3.3 mmol, 500 mg for **2** and **4**) in $CH_2Cl_2$ (10 mL), the reaction was stirred at 20 °C during 18 h. Then resulting mixture was filtered through Celite and the solvent was removed under reduced pressure. The resulting oil was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH 4.8 : 0.2); compounds **1**–**4** were isolated as colorless oils and dried *in vacuo*.

**1.** Colorless oil, yield: 1.15 g, 84%. $^1$H NMR (400 MHz, $CDCl_3$): 0.91 (t, 3H, –C*H*$_3$), 1.44 (m, 8H, –CH$_2$–(C*H*$_2$)$_4$–CH$_3$), 1.80 (q, 2H, –O–CH$_2$–C*H*$_2$–(CH$_2$)$_4$–CH$_3$), 2.42 (t, 2H, C$_6$H$_7$–C*H*$_2$–CH$_2$–O–(CO)–Ar), 2.69 (s, 4H, C*H*$_2$diene), 3.99 (t, 2H, –O–C*H*$_2$–(CH$_2$)$_5$–CH$_3$), 4.38 (t, 2H, C$_6$H$_7$–CH$_2$–C*H*$_2$–O–(CO)–Ar), 5.55 (s, 1H, C*H*diene), 5.71 (t, 2H, C*H*diene), 6.89 (d, $^3J$ = 6.8 Hz, 2H, *H*–Ar), 7.98 ppm (d, $^3J$ = 6.8 Hz, 2H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 14.18, 22.70, 26.05, 26.88, 29.13, 29.22, 29.26, 31.86, 35.42, 36.73, 60.66, 63.08, 65.23, 68.28, 114.09, 120.98, 124.17, 126.61, 131.64, 138.15, 163.07, 166.38 ppm. Mass (ESI, *m*/*z*): 365.18 [M+Na$^+$]. Anal Calc. for (%): $C_{22}H_{30}O_3$ : C, 77.16; H, 8.83. Found: C, 77.25; H, 8.69.

**2.** Colorless oil, yield: 1.16 g, 95%. $^1$H NMR (400 MHz, $CDCl_3$): 0.91 (t, 3H, –C*H*$_3$), 1.33 (m, 10H, –CH$_2$–(C*H*$_2$)$_4$–CH$_3$, C$_6$H$_7$–CH$_2$–C*H*$_2$–CH$_2$–CH$_2$–O–(CO)–Ar), 1.79 (m, 4H, C$_6$H$_7$–CH$_2$–CH$_2$–C*H*$_2$–CH$_2$–O–(CO)–Ar, –O–CH$_2$–C*H*$_2$–(CH$_2$)$_4$–CH$_3$), 2.05 (t, 2H, C$_6$H$_7$–C*H*$_2$–(CH$_2$)$_3$–O–(CO)–Ar), 2.62 (m, 2H, C*H*$_2$diene), 2.70 (m, 2H, C*H*$_2$diene), 4.01 (t, 2H, –O–C*H*$_2$–(CH$_2$)$_5$–CH$_3$), 4.31 (t, 2H, C$_6$H$_7$–(CH$_2$)$_3$–C*H*$_2$–O–(CO)–Ar), 5.46 (s, 1H, C*H*diene), 5.72 (t, 2H, C*H*diene), 6.91 (d, $^3J$ = 6.8 Hz, 2H, *H*–Ar), 8.00 ppm (d, $^3J$ = 6.8 Hz, 2H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 14.10, 22.62, 25.26, 25.98, 26.78, 27.87, 28.46, 28.88, 29.06, 29.15, 31.79, 37.05, 64.61, 68.21, 114.05, 118.73, 124.30, 124.32, 125.84, 128.36, 131.53, 134.53, 162.93, 166.48 ppm. Mass (ESI, *m*/*z*): 393.10 [M+Na$^+$]. Anal Calc. for (%): $C_{24}H_{34}O_3$ : C, 77.80; H, 9.25. Found: C, 77.91; H, 9.39.

**3.** Colorless oil, yield: 1.02 g, 89%. $^1$H NMR (400 MHz, $CDCl_3$): 2.37 (t, 2H, C$_6$H$_7$–C*H*$_2$–CH$_2$–O–(CO)–CH═CH–), 2.69 (m, 4H, C*H*$_2$diene), 3.82 (s, 3H, –O–C*H*$_3$), 4.29 (t, 2H, C$_6$H$_7$–CH$_2$–C*H*$_2$–O–(CO)–CH═CH–), 5.53 (s, 1H, C*H*diene), 5.71 (t, 2H, C*H*diene), 6.30 (d, $^3J$ = 16 Hz, 1H, –C*H*═CH–), 6.91 (d, 2H, *H*–Ar), 7.47 (d, 2H, *H*–Ar), 7.64 ppm (d, $^3J$ = 16 Hz, 1H, –CH═C*H*–). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 26.85, 36.64, 55.42, 62.78, 64.93, 114.38, 115.83, 120.88, 124.21, 126.61, 129.11, 129.76, 129.81, 144.43, 161.44, 161.48, 167.27, 167.34 ppm. Mass (ESI, *m*/*z*): 307.20 [M+Na$^+$]. Anal Calc. for (%): $C_{18}H_{20}O_3$ : C, 77.03; H, 7.09. Found: C, 77.26; H, 7.15.

**4.** Colorless oil, yield: 870 mg, 84%. $^1$H NMR (400 MHz, $CDCl_3$): 1.54 (m, 2H, C$_6$H$_7$–CH$_2$–C*H*$_2$–(CH$_2$)$_2$–O–(CO)–CH═CH–), 1.71 (m, 2H, C$_6$H$_7$–(CH$_2$)$_2$–C*H*$_2$–CH$_2$–O–(CO)–CH═CH–), 2.03 (t, 2H, C$_6$H$_7$–C*H*$_2$–(CH$_2$)$_3$–O–(CO)–CH═CH–), 2.61 (m, 2H, C*H*$_2$diene), 2.69 (m, 2H, C*H*$_2$diene), 3.84 (s, 3H, –O–C*H*$_3$), 4.21 (t, 2H, C$_6$H$_7$–(CH$_2$)$_3$–C*H*$_2$–O–(CO)–CH═CH–), 5.45 (m, 1H, C*H*diene), 5.72 (m, 2H, C*H*diene), 6.32 (d, $^3J$ = 16 Hz, 1H, –C*H*═CH–), 6.91 (d, 2H, *H*–Ar), 7.49 (d, 2H, *H*–Ar), 7.65 ppm (d, $^3J$ = 16 Hz, 1H, –CH═C*H*–). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 23.68, 26.78, 28.22, 28.88, 37.04, 53.45, 55.37, 64.39, 114.33, 115.75, 118.71, 124.32, 125.84, 127.23, 128.43, 129.71, 134.54, 144.27, 161.37, 167.42 ppm. Mass (ESI, *m*/*z*): 335.07 [M+Na$^+$]. Anal Calc. for (%): $C_{20}H_{24}O_3$ : C, 76.89; H, 7.74. Found: C, 76.95; H, 7.62.

### Preparation of the arene ruthenium chloro intermediates 5–8

To a solution of $RuCl_3 \cdot nH_2O$ (0.8 mmol, 209 mg for **5** and **7**; 0.6 mmol, 155 mg for **6** and **8**) in degassed acetone/water 5 : 1 (100 mL) a solution of the corresponding diene (4 mmol, 1.37 g for **5**, 1.14 g for **7**; 3 mmol, 1.10 g for **6**, 937 mg for **8**) in degassed acetone/water 5 : 1 (10 mL) was added and the mixture was refluxed for 18 h. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (5 mL). Then

the product was precipitated by addition of diethyl ether (50 mL), isolated by filtration and dried *in vacuo*.

**5.** Orange solid, yield: 380 mg, 93%. $^1$H NMR (400 MHz, $CDCl_3$): 0.83 (t, 6H, –C$H_3$), 1.37 (m, 16H, –CH$_2$–(C$H_2$)$_4$–CH$_3$), 1.79 (q, 4H, –O–CH$_2$–C$H_2$–(CH$_2$)$_4$–CH$_3$), 3.04 (t, 4H, C$_6$H$_5$–C$H_2$–CH$_2$–O–(CO)–Ar), 3.98 (t, 4H, –O–C$H_2$–(CH$_2$)$_5$–CH$_3$), 4.54 (t, 4H, C$_6$H$_5$–CH$_2$–C$H_2$–O–(CO)–Ar), 5.50 (d, 4H, C$H_{arene}$), 5.66 (m, 6H, C$H_{arene}$), 6.86 (d, $^3J$ = 6.8 Hz, 4H, *H*–Ar), 7.86 ppm (d, $^3J$ = 6.8 Hz, 4H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 14.19, 22.46, 22.72, 26.06, 29.13, 29.21, 31.87, 33.70, 34.25, 62.91, 68.40, 80.48, 81.37, 84.22, 97.68, 114.35, 121.73, 131.67, 163.38, 165.95 ppm. Mass (ESI, *m/z*): 977.20 [M–2Cl$^-$+Na$^+$]. Anal Calc. for (%): $C_{44}H_{56}Cl_4O_3Ru_2$ : C, 51.56; H, 5.51. Found: C, 51.50; H, 5.34.

**6.** Orange solid, yield: 290 mg, 90%. $^1$H NMR (400 MHz, $CDCl_3$): 0.87 (t, 6H, –C$H_3$), 1.37 (m, 16H, –CH$_2$–(C$H_2$)$_4$–CH$_3$), 1.75 (m, 12H, C$_6$H$_5$–CH$_2$–C$H_2$–C$H_2$–CH$_2$–O–(CO)–Ar, –O–CH$_2$–C$H_2$–(CH$_2$)$_4$–CH$_3$), 2.60 (t, 4H, C$_6$H$_5$–C$H_2$–(CH$_2$)$_3$–O–(CO)–Ar), 3.97 (t, 4H, –O–C$H_2$–(CH$_2$)$_5$–CH$_3$), 4.26 (t, 4H, C$_6$H$_5$–(CH$_2$)$_3$–C$H_2$–O–(CO)–Ar), 5.38 (d, 4H, C$H_{arene}$), 5.60 (m, 6H, C$H_{arene}$), 6.87 (d, $^3J$ = 8.8 Hz, 4H, *H*–Ar), 7.92 ppm (d, $^3J$ = 8.8 Hz, 4H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 14.15, 22.65, 26.00, 26.35, 28.56, 29.08, 29.17, 31.81, 33.25, 64.00, 68.29, 79.86, 80.46, 84.22, 100.99, 114.16, 122.38, 131.62, 163.06, 166.37 ppm. Mass (ESI, *m/z*): 1033.20 [M–2Cl$^-$+Na$^+$]. Anal Calc. for (%): $C_{48}H_{64}Cl_4O_6Ru_2$ : C, 53.33; H, 5.97. Found: C, 53.51; H, 5.94.

**7.** Brown solid, yield: 216 mg, 72%. $^1$H NMR (400 MHz, $CDCl_3$): 2.85 (t, 4H, C$_6$H$_5$–C$H_2$–CH$_2$–O–(CO)–CH═CH–), 3.67 (s, 6H, –O–C$H_3$), 4.35 (t, 4H, C$_6$H$_5$–CH$_2$–C$H_2$–O–(CO)–CH═CH), 5.59 (d, 4H, C$H_{arene}$), 5.77 (m, 6H, C$H_{arene}$), 6.10 (d, $^3J$ = 16 Hz, 2H, –C*H*═CH–), 6.74 (d, 4H, *H*–Ar), 7.31 (d, 4H, *H*–Ar), 7.44 ppm (d, $^3J$ = 16 Hz, 2H, –CH═C*H*–). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 35.60, 55.12, 62.10, 84.34, 86.65, 88.48, 103.57, 114.10, 114.33, 126.45, 129.43, 144.93, 157.74, 161.30, 166.42, 172.13 ppm. Mass (ESI, *m/z*): 861.13 [M–2Cl$^-$+Na$^+$]. Anal Calc. for (%): $C_{36}H_{36}Cl_4O_2Ru_2$ : C, 47.59; H, 3.99. Found: C, 47.71; H, 4.06.

**8.** Brown solid, yield: 252 mg, 82%. $^1$H NMR (400 MHz, $CDCl_3$): 1.73 (m, 8H, C$_6$H$_5$–CH$_2$–C$H_2$–C$H_2$–CH$_2$–O–(CO)–CH═CH–), 2.61 (t, 4H, C$_6$H$_5$–C$H_2$–(CH$_2$)$_3$–O–(CO)–CH═CH), 3.83 (s, 6H, –O–C$H_3$), 4.19 (t, 4H, C$_6$H$_5$–(CH$_2$)$_3$–C$H_2$–O–(CO)–CH═CH–), 5.39 (d, 4H, C$H_{arene}$), 5.60 (m, 6H, C$H_{arene}$), 6.28 (d, $^3J$ = 16 Hz, 2H, –C*H*═CH–), 6.90 (d, 4H, *H*–Ar), 7.48 (d, 4H, *H*–Ar), 7.62 ppm (d, $^3J$ = 16 Hz, 2H, –CH═C*H*–). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 26.41, 28.58, 33.31, 55.52, 63.85, 79.93, 80.56, 84.28, 101.08, 114.47, 115.58, 127.26, 129.91, 144.69, 161.56, 167.40 ppm. Mass (ESI, *m/z*): 917.07 [M–2Cl$^-$+Na$^+$]. Anal Calc. for (%): $C_{40}H_{44}Cl_4O_2Ru_2$ : C, 49.80; H, 4.60. Found: C, 49.87; H, 4.66.

**Preparation of the arene ruthenium thiophenolato complexes 9–12**

The dinuclear dichloro complex [(arene)$_2$RuCl$_2$]$_2$ (0.15 mmol, 150 mg for **9**, 162 mg for **10**, 136 mg for **11**, 144 mg for **12**) was refluxed in technical grade EtOH (50 mL). As soon as the starting material was completely dissolved, a solution of thiophenol (0.9 mmol, 99 mg, 92 µL) in technical grade EtOH (5 mL) was added dropwise to the hot solution. The resulting mixture was refluxed in EtOH for 18 h. After cooling to 20 °C, the solvent was removed under reduced pressure. The mixture was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH 5 : 1), and the compounds [**9**–**12**]Cl were isolated as air-stable orange to red crystalline solids and dried *in vacuo*.

[**9**]Cl. Red solid, yield: 174 mg, 93%. $^1$H NMR (400 MHz, $CDCl_3$): 0.88 (t, 6H, –C$H_3$), 1.30 (m, 16H, –CH$_2$–(C$H_2$)$_4$–CH$_3$), 1.78 (q, 4H, –O–CH$_2$–C$H_2$–(CH$_2$)$_4$–CH$_3$), 2.12 (m, 4H, C$_6$H$_5$–C$H_2$–CH$_2$–O–(CO)–Ar), 2.36 (m, 4H, C$_6$H$_5$–C$H_2$–CH$_2$–O–(CO)–Ar), 3.98 (t, 4H, –O–C$H_2$–(CH$_2$)$_5$–CH$_3$), 4.13 (m, 4H, C$_6$H$_5$–CH$_2$–C$H_2$–O–(CO)–Ar), 5.62 (m, 4H, C$_6$H$_5$–CH$_2$–C$H_2$–O–(CO)–Ar), 5.13 (d, 2H, C$H_{arene}$), 5.38 (m, 4H, C$H_{arene}$), 5.62 (m, 4H, C$H_{arene}$), 6.86 (d, $^3J$ = 9.2 Hz, 4H, *H*–Ar), 7.37 (m, 9H, *H*–Ar), 7.78 (d, $^3J$ = 9.2 Hz, 4H, *H*–Ar), 7.88 ppm (d, 6H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 14.20, 22.71, 26.05, 29.13, 29.20, 31.87, 32.18, 63.01, 68.45, 85.57, 86.03, 86.08, 86.35, 87.56, 99.80, 114.38, 121.58, 128.63, 129.59, 131.64, 132.23, 138.55, 163.42, 165.81 ppm. Mass (ESI, *m/z*): 1211.26 [M+H$^+$]. Anal Calc. for (%): $C_{62}H_{71}ClO_6Ru_2S_3$ : C, 59.76; H, 5.74. Found: C, 59.81; H, 5.80.

[**10**]Cl. Red solid, yield: 169 mg, 91%. $^1$H NMR (400 MHz, $CDCl_3$): 0.88 (t, 6H, –C$H_3$), 1.30 (m, 16H, –CH$_2$–(C$H_2$)$_4$–CH$_3$), 1.55 (m, 12H, C$_6$H$_5$–CH$_2$–C$H_2$–C$H_2$–CH$_2$–O–(CO)–Ar, –O–CH$_2$–C$H_2$–(CH$_2$)$_4$–CH$_3$), 1.80 (t, 4H, C$_6$H$_5$–C$H_2$–(CH$_2$)$_3$–O–(CO)–Ar), 3.99 (t, 4H, –O–C$H_2$–(CH$_2$)$_5$–CH$_3$), 4.11 (t, 4H, C$_6$H$_5$–(CH$_2$)$_3$–C$H_2$–O–(CO)–Ar), 4.97 (d, 2H, C$H_{arene}$), 5.27 (m, 4H, C$H_{arene}$), 5.59 (m, 4H, C$H_{arene}$), 6.88 (d, $^3J$ = 8 Hz, 4H, *H*–Ar), 7.36 (m, 9H, *H*–Ar), 7.84 (d, $^3J$ = 8 Hz, 4H, *H*–Ar), 7.92 ppm (d, 6H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 14.19, 22.71, 26.06, 26.20, 28.42, 29.14, 29.23, 31.87, 32.09, 63.76, 68.41, 85.40, 86.28, 86.34, 103.70, 114.24, 122.36, 128.48, 129.47, 131.66, 132.24, 138.87, 163.20, 166.44 ppm. Mass (ESI, *m/z*): 1267.32 [M+H$^+$]. Anal Calc. for (%): $C_{66}H_{79}ClO_6Ru_2S_3$ : C, 60.88; H, 6.12. Found: C, 60.81; H, 5.98.

[**11**]Cl. Orange solid, yield: 148 mg, 87%. $^1$H NMR (400 MHz, $CDCl_3$): 2.76 (t, 4H, C$_6$H$_5$–C$H_2$–CH$_2$–O–(CO)–CH═CH–), 3.83 (s, 6H, –O–C$H_3$), 4.06 (t, 4H, C$_6$H$_5$–CH$_2$–C$H_2$–O–(CO)–CH═CH–), 5.12 (d, 2H, C$H_{arene}$), 5.36 (m, 4H, C$H_{arene}$), 5.61 (m, 4H, C$H_{arene}$), 6.14 (d, $^3J$ = 16 Hz, 2H, –C*H*═CH–), 6.89 (d, 4H, *H*–Ar), 7.42 (m, 13H, *H*–Ar), 7.53 (d, $^3J$ = 16 Hz, 2H, –CH═C*H*–), 7.88 ppm (d, 6H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 32.12, 55.57, 62.73, 85.53, 86.07, 86.13, 86.37, 87.56, 99.84, 114.54, 114.61, 126.88, 128.63, 129.61, 130.06, 132.26, 138.60, 145.47, 161.79, 166.79 ppm. Mass (ESI, *m/z*): 1095.09 [M+H$^+$]. Anal Calc. for (%): $C_{54}H_{51}ClO_6Ru_2S_3$ : C, 57.41; H, 4.55. Found: C, 57.52; H, 4.47.

[**12**]Cl. Orange solid, yield: 152 mg, 86%. $^1$H NMR (400 MHz, $CDCl_3$): 1.83 (m, 8H, C$_6$H$_5$–CH$_2$–C$H_2$–C$H_2$–CH$_2$–O–(CO)–CH═CH–), 2.01 (m, 4H, C$_6$H$_5$–C$H_2$–(CH$_2$)$_3$–O–(CO)–CH═CH–), 3.82 (s, 6H, –O–C$H_3$), 4.02 (t, 4H, C$_6$H$_5$–(CH$_2$)$_3$–C$H_2$–O–(CO)–CH═CH–), 4.97 (d, 2H, C$H_{arene}$), 5.26 (m, 4H, C$H_{arene}$), 5.59 (m, 6H, C$H_{arene}$), 6.25 (d, $^3J$ = 16 Hz, 2H, –C*H*═CH–), 6.89 (d, 4H, *H*–Ar), 7.41 (m, 13H, *H*–Ar), 7.60 (d, $^3J$ = 16 Hz, 2H, –CH═C*H*–), 7.85 ppm (d, 6H, *H*–Ar),. $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 15.29, 26.05, 28.26, 31.97, 55.30, 55.45, 63.42, 65.86, 84.71, 85.28, 86.18, 86.21, 103.62, 113.91, 114.41, 115.32, 127.01, 128.39, 129.24, 129.27, 132.15, 138.78, 144.65, 161.53, 167.27 ppm. Mass (ESI, *m/z*): 1151.15 [M+H$^+$]. Anal Calc. for (%): $C_{58}H_{59}ClO_6Ru_2S_3$ : C, 58.74; H, 5.01. Found: C, 58.82; H, 4.85.

**Preparation of the arene ruthenium thiophenolato complexes 13–16**

The dinuclear dichloro complex $[(arene)_2RuCl_2]_2$ (0.05 mmol, 50 mg for **13**, 54 mg for **14**, 45 mg for **15**, 48 mg for **16**) was refluxed in technical grade EtOH (50 mL). As soon as the starting material was completely dissolved, a solution of *p*-hydroxythiophenol (0.3 mmol, 38 mg) in technical grade EtOH (5 mL) was added dropwise to the hot solution. The resulting mixture was refluxed in EtOH for 18 h. After cooling to 20 °C, the solvent was removed under reduced pressure. The mixture was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH 5 : 1) and [**13**–**16**]Cl were isolated as air-stable yellow to orange crystalline solids and dried *in vacuo*.

[**13**]Cl. Orange solid, yield: 52 mg, 82%. $^1$H NMR (400 MHz, $CDCl_3$): 0.83 (t, 6H, –C$H_3$), 1.35 (m, 16H, –$CH_2$–(C$H_2$)$_4$–$CH_3$), 1.71 (q, 4H, –O–$CH_2$–C$H_2$–$(CH_2)_4$–$CH_3$), 2.30 (m, 8H, $C_6H_5$–C$H_2$–$CH_2$–O–(CO)–Ar, $C_6H_5$–C$H_2$–$CH_2$–O–(CO)–Ar), 3.92 (t, 4H, –O–C$H_2$–$(CH_2)_5$–$CH_3$), 4.19 (m, 4H, $C_6H_5$–$CH_2$–C$H_2$–O–(CO)–Ar), 5.05 (d, 2H, C$H_{arene}$), 5.17 (m, 2H, C$H_{arene}$), 5.25 (m, 2H, C$H_{arene}$), 5.38 (m, 4H, C$H_{arene}$), 6.82 (d, 4H, *H*–Ar), 7.01 (d, 6H, *H*–Ar), 7.63 (d, 6H, *H*–Ar), 7.74 ppm (d, 4H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 14.17, 22.67, 26.01, 29.17, 29.79, 31.82, 32.28, 63.47, 68.44, 84.60, 85.93, 85.97, 86.54, 100.01, 114.41, 116.95, 121.46, 127.46, 131.64, 133.25, 158.29, 163.40, 166.12 ppm. Mass (ESI, *m*/*z*): 1259.23 [M+H$^+$]. Anal Calc. for (%): $C_{62}H_{71}ClO_9Ru_2S_3$ : C, 57.55; H, 5.53. Found: C, 57.68; H, 5.59.

[**14**]Cl. Orange solid, yield: 60 mg, 89%. $^1$H NMR (400 MHz, $CDCl_3$): 0.83 (t, 6H, –C$H_3$), 1.37 (m, 16H, –$CH_2$–(C$H_2$)$_4$–$CH_3$), 1.52 (m, 12H, $C_6H_5$–$CH_2$–C$H_2$–C$H_2$–$CH_2$–O–(CO)–Ar, –O–$CH_2$–C$H_2$–$(CH_2)_4$–$CH_3$), 1.95 (t, 4H, $C_6H_5$–C$H_2$–$(CH_2)_3$–O–(CO)–Ar), 3.94 (t, 4H, –O–C$H_2$–$(CH_2)_5$–$CH_3$), 4.12 (t, 4H, $C_6H_5$–$(CH_2)_3$–C$H_2$–O–(CO)–Ar), 4.85 (d, 2H, C$H_{arene}$), 5.04 (m, 4H, C$H_{arene}$), 5.29 (m, 4H, C$H_{arene}$), 6.83 (d, 4H, *H*–Ar), 6.93 (d, 6H, *H*–Ar), 7.52 (d, 6H, *H*–Ar), 7.87 ppm (d, 4H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 14.09, 22.57, 25.92, 26.43, 28.30, 29.00, 29.08, 31.72, 32.13, 63.81, 68.25, 83.57, 84.70, 86.05, 86.10, 103.81, 114.09, 116.74, 122.19, 127.20, 131.55, 132.93, 158.53, 163.03, 166.36 ppm. Mass (ESI, *m*/*z*): 1315.30 [M+H$^+$]. Anal Calc. for (%): $C_{66}H_{79}ClO_9Ru_2S_3$ : C, 58.71; H, 5.90. Found: C, 58.83; H, 5.84.

[**15**]Cl. Yellow solid, yield: 49 mg, 83%. $^1$H NMR (400 MHz, $CDCl_3$): 2.29 (m, 4H, $C_6H_5$–C$H_2$–$CH_2$–O–(CO)–CH=CH–), 3.79 (s, 6H, –O–C$H_3$), 4.09 (t, 4H, $C_6H_5$–$CH_2$–C$H_2$–O–(CO)–CH=CH–), 5.02 (d, 2H, C$H_{arene}$), 5.21 (m, 4H, C$H_{arene}$), 5.40 (m, 4H, C$H_{arene}$), 6.13 (d, $^3J$ = 16 Hz, 2H, –C*H*=CH–), 6.90 (d, 6H, *H*–Ar), 7.42 (m, 8H, *H*–Ar), 7.48 (d, $^3J$ = 16 Hz, 2H, –CH=C*H*–), 7.62 ppm (d, 6H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 32.13, 55.47, 63.03, 85.81, 85.95, 96.06, 86.46, 99.86, 114.46, 116.65, 126.77, 127.52, 129.25, 130.03, 133.23, 145.58, 158.11, 161.73, 167.13 ppm. Mass (ESI, *m*/*z*): 1143.09 [M+H$^+$]. Anal Calc. for (%): $C_{54}H_{51}ClO_9Ru_2S_3$ : C, 55.07; H, 4.36. Found: C, 55.16; H, 4.44.

[**16**]Cl. Yellow solid, yield: 54 mg, 88%. $^1$H NMR (400 MHz, $CDCl_3$): 1.43 (m, 8H, $C_6H_5$–$CH_2$–C$H_2$–C$H_2$–$CH_2$–O–(CO)–CH=CH–), 1.89 (m, 4H, $C_6H_5$–C$H_2$–$(CH_2)_3$–O–(CO)–CH=CH–), 3.71 (s, 6H, –O–C$H_3$), 3.96 (t, 4H, $C_6H_5$–$(CH_2)_3$–C$H_2$–O–(CO)–CH=CH–), 4.78 (d, 2H, C$H_{arene}$), 4.98 (m, 4H, C$H_{arene}$), 5.24 (m, 6H, C$H_{arene}$), 6.15 (d, $^3J$ = 16 Hz, 2H, –C*H*=CH–), 6.77 (d, 4H, *H*–Ar), 6.82 (d, 6H, *H*–Ar), 7.34 (d, 4H, *H*–Ar), 7.47 (d, 6H, *H*–Ar), 7.52 ppm (d, $^3J$ = 16 Hz, 2H, –CH=C*H*–). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 15.26, 26.12, 28.12, 31.92, 55.27, 63.32, 77.37, 83.40, 84.51, 84.84, 85.98, 114.23, 115.17, 116.44, 129.61, 132.84, 144.43, 158.32, 161.32, 167.03 ppm. Mass (ESI, *m*/*z*): 1199.14 [M+H$^+$]. Anal Calc. for (%): $C_{58}H_{59}ClO_9Ru_2S_3$ : C, 56.46; H, 4.82. Found: C, 56.51; H, 4.85.

**Preparation of the arene ruthenium thiophenolato complexes 17–19**

The dinuclear dichloro complex $[(arene)_2RuCl_2]_2$ (0.20 mmol, 100 mg for **17**; 122 mg for **18**; 133 mg for **19**) was refluxed in technical grade EtOH (50 mL). As soon as the starting material was dissolved, a solution of thiophenol (1.2 mmol, 132 mg, 123 µL) in technical grade EtOH (5 mL) was added dropwise to the hot solution. The resulting mixture was refluxed in EtOH for 18 h. After cooling to 20 °C, the solvent was removed under reduced pressure. The mixture was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH 5 : 1) and [**17**–**19**]Cl were isolated as air-stable yellow to red crystalline solids and dried *in vacuo*.

[**17**]Cl. Yellow solid, yield: 129 mg, 88%. $^1$H NMR (400 MHz, $CDCl_3$): 5.44 (s, 12H, *H*–Ar), 7.37 (m, 9H, *H*–Ar), 7.83 ppm (d, 6H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 86.55, 128.32, 129.61, 132.05, 139.22 ppm. Mass (ESI, *m*/*z*): 686.94 [M+H$^+$]. Anal Calc. for (%): $C_{30}H_{27}ClRu_2S_3$ : C, 49.95; H, 3.77. Found: C, 49.85; H, 3.70.

[**18**]Cl. Orange solid, yield: 155 mg, 93%. $^1$H NMR (400 MHz, $CDCl_3$): 0.78 (d, $^3J$ = 8 Hz, 12H, $(CH_3)_2$CH), 1.57 (s, 6H, C$H_3$), 1.86 (sept, $^3J$ = 7.2 Hz, 2H, $(CH_3)_2$C*H*), 5.05 (d, $^3J$ = 8 Hz, 2H, *H*–Ar), 5.08 (d, $^3J$ = 8 Hz, 2H, *H*–Ar), 5.19 (d, 2H, *H*–Ar), 5.36 (d, 2H, *H*–Ar), 7.34 (m, 9H, *H*–Ar), 7.84 ppm (d, 6H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 17.71, 21.95, 22.53, 30.58, 83.65, 84.76, 85.03, 85.37, 99.97, 107.39, 128.45, 129.19, 132.57, 137.81 ppm. Mass (ESI, *m*/*z*): 799.07 [M+H$^+$]. Anal Calc. for (%): $C_{38}H_{43}ClRu_2S_3$ : C, 54.76; H, 5.20. Found: C, 54.69; H, 5.32.

[**19**]Cl. Red solid, yield: 162 mg, 91%. $^1$H NMR (400 MHz, $CDCl_3$): 2.02 (s, 36H, C$H_3$), 7.36 (m, 9H, *H*–Ar), 7.87 ppm (d, 6H, *H*–Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): 14.99, 97.82, 128.42, 129.53, 132.15, 138.32 ppm. Mass (ESI, *m*/*z*): 855.13 [M+H$^+$]. Anal Calc. for (%): $C_{42}H_{51}ClRu_2S_3$ : C, 56.70; H, 5.78. Found: C, 56.65; H, 5.70.

**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™ containing 5% foetal calf serum (FCS) and antibiotics (penicillin and streptomycin) at 37 °C and 5% $CO_2$. For the evaluation of growth inhibition tests, the cells were seeded in 96-well plates ($25 \times 10^3$ cells per well) and grown for 24 h in complete medium. Complexes were dissolved in DMSO and added to the required concentration to the cell culture for 72 h incubation. Solutions of the compounds were applied by diluting a freshly prepared stock solution of the corresponding compound in aqueous RPMI medium with GlutaMAX™ (20 mM). Following drug exposure, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to the cells at a final concentration of 0.25 mg mL$^{-1}$ and incubated for 2 h,

**Table 3** Crystallographic and structure refinement parameters for [**17**]$PF_6$

| | [**17**]$PF_6$ |
|---|---|
| Chemical formula | $C_{30}H_{27}F_6PRu_2S_3$ |
| Formula weight | 830.81 |
| Crystal system | Monoclinic |
| Space group | *C* 2/*c* (no. 15) |
| Crystal colour and shape | Yellow block |
| Crystal size | $0.23 \times 0.18 \times 0.15$ |
| *a*/Å | 39.0178(15) |
| *b*/Å | 10.4836(3) |
| *c*/Å | 30.5653(13) |
| $\beta$ (°) | 106.929(3) |
| *V*/Å$^3$ | 11960.9(8) |
| *Z* | 16 |
| *T*/K | 173(2) |
| $D_c$/g cm$^{-3}$ | 1.845 |
| $\mu$/mm$^{-1}$ | 1.332 |
| Scan range (°) | $1.50 < \theta < 29.28$ |
| Unique reflections | 16075 |
| Observed refls [$I > 2\sigma(I)$] | 11044 |
| $R_{int}$ | 0.1253 |
| Final *R* indices [$I > 2\sigma(I)$]* | 0.0688, $wR_2$ 0.0812 |
| *R* indices (all data) | 0.1153, $wR_2$ 0.0892 |
| Goodness-of-fit | 1.116 |
| Max, Min $\Delta\rho$/e (Å$^{-3}$) | 1.149, – 1.232 |

Structures were refined on $F_0^2$: $wR_2 = [\Sigma[w\ (F_0^2 - F_c^2)^2]/\Sigma w\ (F_0^2)^2]^{1/2}$, where $w^{-1} = [\Sigma(F_0^2) + (aP)^2 + bP]$ and $P = [\max(F_0^2, 0) + 2F_c^2]/3$

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 using a multiwall 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 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 2.

### Single-crystal X-ray structure analysis

A crystal of [**17**]$PF_6$, prepared by diffusion of a dichloromethane solution of [**17**]Cl in the presence of $KPF_6$ into a diethyl ether layer, was mounted on a Stoe Image Plate Diffraction system equipped with a $\phi$ circle goniometer, using Mo-K$\alpha$ graphite monochromated radiation ($\lambda$ = 0.71073 Å) with $\phi$ range 0–200°. The structure was solved by direct methods using the program SHELXS-97, while the refinement and all further calculations were carried out using SHELXL-97.[29] The H-atoms were included in calculated positions and treated as riding atoms using the SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-square on $F^2$. Crystallographic details are summarised in Table 3. Fig. 2 was drawn with ORTEP.[30]

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