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Ruthenium Selenoquinone Complexes

Selenoquinones Stabilized by Ruthenium(II) Arene Complexes: Synthesis, Structure, and Cytotoxicity

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Abstract: A new series of monoselenoquinone and diselenoquinone π complexes, [(η^6-*p*-cymene)Ru(η^4-C_6R_4SeE)] (R = H, E = Se (**6**); R = CH_3, E = Se (**7**); R = H, E = O (**8**)), as well as selenolate π complexes [(η^6-*p*-cymene)Ru(η^5-$C_6H_3R_2Se$)][SbF_6] (R = H (**9**); R = CH_3 (**10**)), stabilized by arene ruthenium moieties were prepared in good yields through nucleophilic substitution reactions from dichlorinated-arene and hydroxy-monochlorinated-arene ruthenium complexes [(η^6-*p*-cymene)Ru(C_6R_4XCl)][SbF_6]$_2$ (R = H, X = Cl (**1**); R = CH_3, X = Cl (**2**); R = H, X = OH (**3**)) as well as the monochlorinated π complexes [(η^6-*p*-cymene)Ru(η^5-$C_6H_3R_2Cl$)][SbF_6]$_2$ (R = H (**4**); R = CH_3 (**5**)). The X-ray crystallographic structures of two of the compounds, [(η^6-*p*-cymene)Ru(η^4-$C_6Me_4Se_2$)] (**7**) and [(η^6-*p*-cymene)Ru(η^4-C_6H_4SeO)] (**8**), were determined. The structures confirm the identity of the target compounds and ascertain the coordination mode of these unprecedented ruthenium π complexes of selenoquinones. Furthermore, these new compounds display relevant cytotoxic properties towards human ovarian cancer cells.

Introduction

Unlike quinones, which are a prominent class of compounds that play an important role in chemistry and biology, the related selenium quinones "$C_6H_4Se_2$" are unstable and consequently do not exist in nature, and hence their chemical and biological properties remain unknown.[1] In fact, the replacement of the oxygen atoms in quinone by the heavier chalcogen atoms, sulfur or selenium, leads to highly reactive intermediates that cannot be isolated in pure form due to the instability of the unnatural functional groups C=E (E = S, Se).[2] Thus, examples of isolated thioquinones are scarce and the parent compound has been generated and characterized spectroscopically only at low temperature (10 K) in an argon matrix.[3] These procedures illustrate the difficulty in isolating and stabilizing thioquinones. As for the hypothetical selenoquinone molecule (Figure 1), it is even less stable. Our group has demonstrated that group 9 transition metal complexes and in particular the Cp*Ir moiety (Cp* = pentamethylcyclopentadienyl) have profound stabilizing properties towards reactive intermediates.[4] Indeed, *ortho*-quinone methides as well as *ortho*- and *para*-dithiobenzoquinones were isolated as π complexes of Cp*Ir and their molecular structures were determined.[5] More recently, the first molecular structure of a diselenoquinone π complex stabilized by Cp*Ir was confirmed by a single-crystal X-ray diffraction study.[6] Furthermore, this organometallic π complex exhibits interesting anticancer activity towards human A2780 ovarian cancer cells with a cytotoxicity (IC_{50} = 5 μM) comparable to that of the benchmark metallodrug cisplatin (IC_{50} = 3 μM).[6] Indeed, metallocenes and organometallic π complexes are currently being extensively studied as putative anticancer agents as potential substitutes for the well-known clinically applied platinum-based drugs.[7]

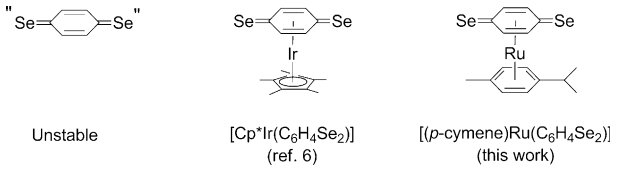

Figure 1. Schematic drawing of the parent diselenoquinone molecule (reactive intermediate), the only known iridium-stabilized diselenoquinone (our previous work, Ref. [6]), and the ruthenium-stabilized diselenoquinone (current work).

Pursuing our research in the area of metal-stabilized reactive intermediates, we investigated other organometallic moieties that might stabilize the diselenoquinone reactive species. In this context, the (*p*-cymene)Ru moiety appeared to be of interest. In addition to forming stable π complexes, this metal fragment is frequently encountered in the development of metal

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complexes with pharmacologically relevant properties.[8] In this context, the most widely studied compounds are the half-sandwich complexes with either one or two chloride (leaving group) ligands. Various techniques have been used to show that these types of complexes can bind to biomolecular targets, and crystal structures confirming the loss of the chloride ligands on binding to cancer-relevant targets have been reported.[9] Full-sandwich complexes comprising an arene ring and a cyclopentadienyl or Cp* ring have also been evaluated, and the complexes with the more lipophilic Cp* group display cytotoxicites equivalent to cisplatin.[10]

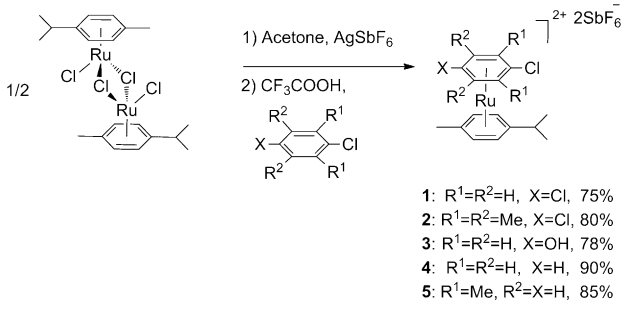
Herein, we describe the synthesis and characterization of a novel family of mono- and diselenoquinone complexes. The X-ray molecular structures of two compounds of the above series are also presented. Furthermore, the cytotoxicity of the new complexes were investigated and compared to that of the iridium compound.

Results and Discussion

Synthesis and characterization of chlorinated-arene ruthenium π complexes 1–5

The coordination and activation of electron-poor halogenated arenes by reaction with $[Cp^*Ru(CH_3CN)_3][OTf]$ (Tf = trifluoromethanesulfonyl) have been widely studied;[11] however, the related complexes with the (*p*-cymene)Ru moiety are less well investigated.[12] Hence, the synthesis of the novel organometallic mono- and dichlorinated-arene and hydroxymonochlorinated-arene π complexes [(*p*-cymene)Ru(arene-(X)(Cl))][SbF_6]$_2$ (**1**–**5**) (X = OH, Cl) was realized according to the following procedure. A solvated [(η^6-*p*-cymene)Ru(solvent)$_3$][SbF_6]$_2$ compound was generated in situ from the dimeric compound [(η^6-*p*-cymene)-$RuCl_2$]$_2$ and silver salt $AgSbF_6$ in acetone, the filtered solution was poured into an excess of the desired halogenated arene ligand, and the mixture was stirred. The solvent was then evaporated to dryness, trifluoroacetic acid was added, and the mixture was heated to 90 °C for 2 h. Complexes **1** to **5** were isolated as white air-stable powders in good yields (75 to 90%; Scheme 1).

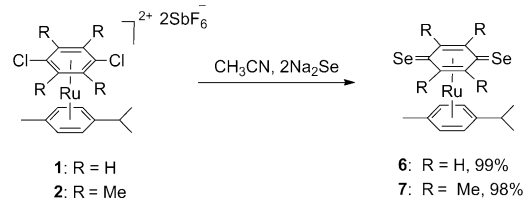
All of the dicationic sandwich complexes were fully characterized by NMR spectroscopy and elemental analysis (see the Experimental Section). ^{1}H and ^{13}C NMR spectra, recorded in CD_3NO_2, showed the coordination of the halogenated arene ring to the (*p*-cymene)Ru moiety. For instance, complex **1** exhibits a singlet at $\delta = 7.39$ ppm, attributed to the halogenated aromatic protons slightly downfield relative to the free aromatic ligand, and a doublet of doublets due to the (*p*-cymene)Ru unit at $\delta = 7.10$ ppm, which is downfield relative to the starting material ruthenium dimer [(*p*-cymene)$_2$Ru(μ-Cl)$_2$Cl$_2$]. Furthermore, three signals for the alkyl protons of the (*p*-cymene)Ru moiety are displayed at $\delta = 2.97$, 2.49, and 1.42 ppm, respectively, which are also downfield relative to the starting material. Full spectroscopic data of complexes **1**–**5** are given in the Experimental Section.



Scheme 1. Synthesis of (*p*-cymene)ruthenium halogenated-arene complexes **1**–**5**.

Synthesis and characterization of mono- and diselenoquinone ruthenium π complexes 6–8 and the selenolate ruthenium complexes 9 and 10

Organometallic sandwich and half-sandwich complexes are well known to drastically modify the electrophilicity and hence the reactivity of the aromatic unit coordinated to the metal center.[5,11] The arene rings are mostly susceptible to nucleophilic additions and halogen-substitution reactions as illustrated in our complexes (see below). The preparation of the novel family of selenoquinone π compounds followed the path already described by us for the synthesis of the *para*-diselenobenzoquinone–iridium complex.[6] Thus, the white dihalogenated Ru^{II} complexes **1** and **2** were reacted in acetonitrile with Na_2Se through a double nucleophilic substitution reaction to afford the neutral ruthenium diselenobenzoquinone π complexes **6** and **7** as deep-red powders in almost quantitative yields (Scheme 2).



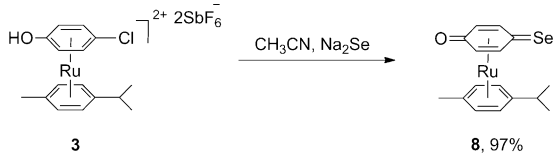
Scheme 2. Preparation of diselenoquinone π complexes [(*p*-cymene)Ru-($C_6H_4Se_2$)] (**6**) and [(*p*-cymene)Ru($C_6Me_4Se_2$)] (**7**).

Complexes **6** and **7** were fully characterized by spectroscopic methods and elemental analysis. For instance, the ^{1}H NMR spectrum of [(*p*-cymene)Ru($C_6H_4Se_2$)] (**6**) recorded in CD_2Cl_2 showed an upfield shift of the four protons of the π-bonded selenoquinone "η-$C_6H_4Se_2$" unit relative to that of starting complex [(*p*-cymene)Ru($C_6H_4Cl_2$)][SbF_6]$_2$ (**1**), which appeared as a singlet at $\delta = 6.40$ ppm. In a similar fashion the four aromatic protons of the (*p*-cymene)Ru unit appeared as a doublet of doublets centered at $\delta = 6.30$ ppm upfield relative to that of **1**. Moreover, the three alkyl signals of the (*p*-cymene)Ru unit appeared at $\delta = 2.65$, 2.13, and 1.36 ppm, respectively, and were also upfield relative to the dihalogenated π complex **1**. Full characterization details of both complexes are given in the Experimental Section. Furthermore, after many attempts, crystals

of **7** were grown from CH_2Cl_2/Et_2O and the structure was determined by X-ray diffraction, which confirmed the formation of the target complex (see below).

To probe the effect of the selenium center on the anticancer activity of this kind of complex, we attempted the synthesis of a mixed selenoquinone π complex [(*p*-cymene)Ru(C_6H_4SeO)] (**8**) starting from the complex **3** carrying a π-bonded *para*-chlorophenol. We anticipated that chloride substitution by a selenide anion and subsequent phenol deprotonation should give the target mixed selenoquinone π complex [(*p*-cymene)Ru-(C_6H_4SeO)] (**8**).

Thus, in a similar way to that described for **1** and **2**, complex **3** reacted with $NaSe_2$ through nucleophilic substitution of one chloride ligand with the simultaneous deprotonation of the phenol leading to the desired monoselenoquinone complex [(*p*-cymene)Ru(C_6H_4SeO)] (**8**) in 97% yield (Scheme 3). As

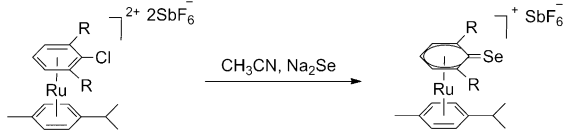


3 **8**, 97%

Scheme 3. Preparation of monoselenoquinone mixed complex [(*p*-cymene)Ru(C_6H_4SeO)] (**8**).

expected, the ^{1}H NMR spectrum of **8** recorded in CD_2Cl_2 showed a general upfield shift relative to **3**. For instance, the four protons of the monoselenoquinone unit "η-C_6H_4SeO" appear as two doublets at $\delta = 5.66$ and 5.01 ppm, and the aromatic protons of the (*p*-cymene)Ru unit give rise to a pair of doublets at $\delta = 6.08$ and 5.94 ppm. As described previously, the three signals attributed to the alkyl protons of the (*p*-cymene)Ru unit are all upfield relative to the starting material **3**. Furthermore, crystals of **8** were grown from a solution of CH_2Cl_2/Et_2O and the structure was determined by X-ray diffraction to confirm the formation of this unique complex displaying both quinone and selenoquinone functions (see below).

The preparation of the cationic ruthenium selenolate π complexes **9** and **10** was also carried out to probe the charge effect of these compounds on their antitumor activities relative to the neutral complexes. The halogen precursors **4** and **5** were then treated with Na_2Se in acetonitrile in a similar way to that described for **1**–**3** and provided, following purification, the ruthenium selenolate arene salts [(*p*-cymene)Ru(η^5-C_6H_5Se)]-[SbF_6] (**9**) and [(*p*-cymene)Ru(η^5-$C_6H_3Me_2Se$)][SbF_6] (**10**) as red microcrystalline powders (Scheme 4).



4: R=H
5: R=Me

9: R=H
10: R=Me

Scheme 4. Preparation of cationic selenolate π complexes [(*p*-cymene)Ru(η^5-C_6H_5Se)][SbF_6] (**9**) and [(*p*-cymene)Ru(η^5-$C_6H_3Me_2Se$)][SbF_6] (**10**).

Molecular structures of diselenobenzoquinone [(*p*-cymene)Ru($C_6Me_4Se_2$)] (7) and monoselenoquinone [(*p*-cymene)Ru(C_6H_4SeO)] (8)

Single crystals suitable for X-ray diffraction analysis of complexes **7** and **8** were obtained at room temperature by vapor diffusion of diethyl ether into a dichloromethane solution. Crystal data are given in Table 1, the molecular structures of **7** and **8** are depicted in Figure 2, and key bond parameters are listed in Table 2. The crystal structure of **7** contains partial disorder for the π-bonded diselenoquinone unit. This disorder was successfully modeled by using two orientations with a ratio of 60:40, in which the positions of all six carbon atoms of the ring remain unchanged. Four of these atoms (C1, C3, C4, and C6) are bound alternatively to a methyl group or to selenium and their positions are averaged. However, the structure clearly indicates that the (*p*-cymene)Ru moiety is coordi-

Table 1. Crystallographic data for [(η^6-*p*-cymene)Ru(η^4-$C_6Me_4Se_2$)] (**7**) and [(η^6-*p*-cymene)Ru(η^4-C_6H_4SeO)] (**8**).

Compound	**7**	**8**
chemical formula	$C_{20}H_{26}RuSe_2$	$C_{16}H_{18}ORuSe$
formula weight	525.40	406.33
crystal system	trigonal	monoclinic
space group	$R\bar{3}$	$P21/c$
a [Å]	34.1673(9)	7.3345(2)
b [Å]	34.1673(9)	9.5268(3)
c [Å]	11.2302(3)	20.9231(6)
α [°]	90	90
β [°]	90	97.0860(10)
γ [°]	120	90
V [Å^3]	8637.9(5)	1450.82(7)
Z	18	4
ρ_{calcd} [Mg m^{-3}]	1.818	1.860
T [K]	200(1)	200(1)
λ [Å]	1.54178	1.54178
μ [mm^{-1}]	10.902	11.512
F(000)	4644	800
crystal size [mm^3]	0.2×0.05×0.05	0.25×0.15×0.15
θ range for data collection [°]	2.55 to 66.42	4.26 to 66.48
index ranges	$-39 \le h \le 40$ $-40 \le k \le 36$ $-10 \le l \le 8$	$-8 \le h \le 8$ $-11 \le k \le 9$ $-24 \le l \le 24$
reflections collected	8594	10389
independent reflections	3201 [R(int) = 0.0349]	2521 [R(int) = 0.0227]
completeness	95.7% to $\theta = 65.91°$	98.1% to $\theta = 66.48°$
absorption correction	semiempirical from equivalents	semiempirical from equivalents
max. and min. transmission	0.5186 and 0.7527	0.3182 and 0.1570
refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
data/restraints/parameters	3201/1/253	2521/0/176
goodness-of-fit on F^2	1.030	1.142
final R indices [$I > 2\sigma(I)$]	$R1 = 0.0324$, $wR2 = 0.0753$	$R1 = 0.0216$, $wR2 = 0.0602$
R indices (all data)	$R1 = 0.0443$, $wR2 = 0.0806$	$R1 = 0.0219$, $wR2 = 0.0604$
largest diff. peak and hole [e Å^{-3}]	0.621 and −0.327	0.514 and −0.402

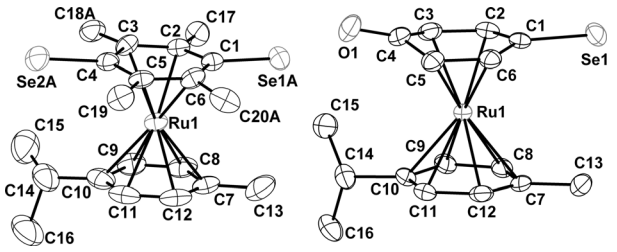


Figure 2. Molecular structures of [(η^6-*p*-cymene)Ru(η^4-$C_6Me_4Se_2$)] (**7**; left) and [(η^6-*p*-cymene)Ru(η^4-C_6H_4SeO)] (**8**; right) with atom numbering systems. Hydrogen atoms are omitted for clarity.

Table 2. Selected bond lengths and angles for [(η^6-*p*-cymene)Ru(η^4-$C_6Me_4Se_2$)] (**7**) and [(η^6-*p*-cymene)Ru(η^4-C_6H_4SeO)] (**8**).

Lengths [Å]/Angles [°]	**7**	**8**
Ru–C2	2.217(4)	2.188(2)
Ru–C5	2.219(4)	2.203(2)
Ru–C3	2.275(4)	2.215(2)
Ru–C6	2.260(4)	2.195(2)
Ru–C1	2.283(4)	2.295(2)
Ru–C4	2.270(4)	2.496(2)
C4–O1	–	1.237(3)
C1–Se1A	1.838(4), 1.919(4)	–
C4–Se2A	1.957(4), 1.890(4)	–
C1–Se1	–	1.873(3)
C2-C1-C6	118.7(4)	114.8(2)
C3-C4-C5	118.9(4)	110.6(2)
C8-C7-C12	117.1(5)	117.5(2)
C9-C10-C11	116.7(5)	117.3(2)
C15-C14-C16	110.9(5)	110.2(3)

nated to only four diene carbon atoms of the π-diselenoquinone unit. The average Ru–C=(Se/C) distance of 2.272(4) Å is significantly longer than the Ru–C=C distances, average 2.218(4) Å (C2, C5), yet shorter than the Ir–C=Se distance, average 2.359 Å, for the only known compound [Cp*Ir($C_6H_4Se_2$)] reported previously by us.[6] Moreover, the C–Se bond lengths for **7** average 1.901(4) Å, which is slightly longer than that reported for the iridium selenoquinone complex, that is, 1.870 Å. The structure also shows that the η^4-selenoquinone ligand adopts a boatlike conformation, although the angles between the selenoquinonoid carbon atoms and the diene plane could not be determined precisely for **7** due to the partial disorder.

The molecular structure of **8** confirmed the formation of the target complex and shows that the (*p*-cymene)Ru moiety is indeed coordinated to only four diene carbon atoms. The Ru–C=C bond lengths average 2.200(2) Å and are shorter than the Ru–C=Se distance, 2.295(2) Å, and that of Ru–C=O, 2.496(2) Å. Remarkably, the boatlike conformation displayed by the monoselenoquinonoid unit is nonsymmetric with hinge angles of $\theta = 6.4(3)^\circ$ for C–Se and $\theta = 19.7(2)^\circ$ for C–O, consistent with the electronic nature of each of the chalcogen atoms attached to the ring. The C–Se distance determined for **8** is 1.873(3) Å, which is indicative of partial double-bond character and comparable (C=Se, 1.870 Å) to that found for the related iridium selenoquinone compound [Cp*Ir($C_6H_4Se_2$)].[6] These bond lengths are shorter than that reported for diselenocin with a C–Se single bond of 1.924(8) Å[13] and are closer in value to the C=Se double bond of 1.857(9) Å reported for 2-selenoxoperhydro-1,3-selenazin-4-one.[14] The C=Se bond in **8** is slightly longer than that reported for seleno-acrylamide with a C=Se double-bond length of 1.837(4) Å,[15] selenobenzyl amide of length 1.830(2) Å,[16] and 4,4′-dimethoxy-selenobenzophenone with a C=Se bond length of 1.79 Å.[17] However, the reported bond length for a selenoaldehyde–tungsten complex is 1.854 Å,[18] which is comparable to that found in **8**. Consequently, the free C=Se bond is expected to be shorter than that present in a metal complex.

Anticancer activity of complexes 6–10 towards human ovarian cancer cells

The cytotoxicity of the compounds was evaluated against human ovarian cancer cells, cisplatin-sensitive A2780 cells and A2780R cells with acquired resistance to cisplatin, by using the MTT assay (see the Experimental Section). IC_{50} values of complexes **6**–**10**, that is, the drug concentration killing 50% of the cells, are listed in Table 3.

Table 3. IC_{50} values of complexes **6**–**10** against A2780 and A2780R human ovarian cancer cells at 72 h.

Complex	IC_{50} in A2780 [μM]	IC_{50} in A2780R [μM]
6	25 ± 1	51 ± 2
7	41 ± 3	61 ± 3
8	75 ± 1	74 ± 2
9	19 ± 1	36 ± 6
10	49 ± 3	240 ± 46
cisplatin[a]	3	25 ± 2
[Cp*Ir($C_6H_4O_2$)][a]	93	–
[Cp*Ir($C_6H_4Se_2$)][a]	5	–

[a] Taken from Ref. [6].

The ruthenium selenolate arene salt [(η^6-*p*-cymene)Ru(η^5-C_6H_5Se)][SbF_6] (**9**) is the most cytotoxic compound in both cell lines with an IC_{50} of 19 μM in A2780 and 36 μM in A2780R cells, followed closely by the neutral ruthenium diselenobenzoquinone π complex **6** (IC_{50} = 25 μM in A2780 and 51 μM in A2780R cells). Previously, we also found the diselenobenzoquinone of iridium to be more cytotoxic than the oxygen-containing analogues (see Table 3), although the cytotoxicity of [Cp*Ir($C_6H_4Se_2$)] is closer in value to that of cisplatin in the A2780 cell line.[6] With methyl substituents on the selenium-bearing arene, complex **10** exhibits a lower cytotoxicity (IC_{50} = 49 μM in cisplatin-sensitive cancer cells and IC_{50} = 240 μM in cisplatin-resistant cells). The same trend is observed for **6** and **7**, with **7** being less cytotoxic against both cell lines, although to a lesser extent (IC_{50} = 41 and 61 μM in A2780 and A2780R, respectively). Bulkier arenes therefore appear to lower the activity of these complexes, possibly by reducing their stability in the pharmacological environment so that less of the intact compound enters the cells. Lastly, compound **8** is the least active com-

pound against A2780 cells ($IC_{50}=75$ μM) although it maintains the same level of activity in cisplatin-resistant cells ($IC_{50}=74$ μM). The trends observed here contrast somewhat with previous studies on full-sandwich (arene)Ru complexes combined with cyclopentadienyl or Cp* rings, in which the more hydrophilic cyclopentadienyl-containing complexes are considerably less cytotoxic than the more lipophilic complexes containing the Cp* ring.[10]

Conclusion

We have reported the preparation of a unique family of organometallic ruthenium complexes that stabilize selenolate, diselenobenzoquinone, and monoselenoquinone entities through π-bonding interactions to a (*p*-cymene)Ru^{II} moiety. Selenium compounds have a number of important biological functions,[19] so we assessed the possible cytotoxicity of these unique compounds on cancer cells. Indeed, it is expected that the selenoarene ring would slowly dissociate inside the cells and induce a cytotoxic effect—the presumably solvated (*p*-cymene)Ru byproduct is known to exert negligible cytotoxicity. The complexes display moderate cytotoxicities although clear structure–activity correlations could not be gauged. Nevertheless, these compound display interesting properties and in the future mechanistic studies will be required to delineate their precise mechanism of action.

Experimental Section

General experimental methods

Glassware was oven-dried prior to use. All reactions were carried out using Schlenk techniques for synthesis of the complexes under an argon atmosphere. THF and diethyl ether were distilled from sodium benzophenone. CH_2Cl_2 was distilled from CaH_2. Other reagents were obtained from commercial suppliers and used as received. ^{1}H NMR spectra were recorded at 300 or 400 MHz in CD_2Cl_2 and CD_3NO_2. Data are reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as an internal standard (CD_2Cl_2 $\delta=5.32$ ppm, CD_3NO_2 $\delta=4.33$ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances). ^{13}C NMR spectra were recorded at 75 or 100 MHz in CD_2Cl_2 and CD_3NO_2. Data are reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as an internal standard (CD_2Cl_2 $\delta=54.0$ ppm, CD_3NO_2 $\delta=62.0$ ppm). Infrared spectra were measured using a Tensor 27 (ATR diamond) Bruker spectrometer. IR data are reported as characteristic bands (cm^{-1}). The dimer $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ was synthesized according to a literature report.[20]

General procedure for the preparation of $[(\eta^6\text{-}p\text{-cymene})Ru(\eta^6\text{-chloroarene})][SbF_6]_2$ complexes

A Schlenk flask under argon was charged with $AgSbF_6$ (449 mg, 1.306 mmol) and $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ (200 mg, 0.326 mmol). Once dissolved in acetone (10 mL), the reaction mixture was stirred at room temperature in the dark during 20 min. AgCl precipitate was removed by filtration and the filtrate was directly poured onto a large excess of the desired chloroarene (ca. 10 equiv). The acetone was evaporated until dryness. The resulting orange paste was dissolved in a minimum of trifluoroacetic acid (ca. 2–3 mL). The resulting mixture was heated at reflux during 90 min. After cooling, the filtrate was removed and the precipitate was washed with small portions of diethyl ether to provide a white air-stable powder.

Synthesis of $[(\eta^6\text{-}p\text{-cymene})Ru(\eta^6\text{-1,4-dichlorobenzene})][SbF_6]_2$ (1)

1,4-Dichlorobenzene (white crystalline solid) was used as ligand to provide complex **1** as a white air-stable powder. Yield: 75%. ^{1}H NMR (CD_3NO_2): $\delta=7.39$ (s, H π-dichlorobenzene, 4H), 7.12 (d, $^3J=7.0$ Hz, H π-cymene, 2H), 7.08 (d, $^3J=7.0$ Hz, H π-cymene, 2H), 2.99 (sept, $^3J=6.8$ Hz, H *i*Pr, 1H), 2.49 (s, Me, 3H), 1.42 ppm (d, $^3J=6.8$ Hz, Me *i*Pr, 6H); ^{13}C NMR (CD_3NO_2): $\delta=122.4$ (2C-Cl), 113.9, 112.9 (2C, *p*-cymene), 95.2 (2CH, *p*-cymene), 93.3 (4CH, dichlorobenzene), 92.8 (2CH, *p*-cymene), 29.2 (1Me), 19.3 (2Me), 15.6 ppm (CH); elemental analysis calcd (%) for $C_{16}H_{18}Cl_2F_{12}RuSb_2$ (853.79 g mol^{-1}): C 22.51, H 2.12; found: C 22.42, H 2.07.

Synthesis of $[(\eta^6\text{-}p\text{-cymene})Ru(\eta^6\text{-1,4-dichloro-tetramethylbenzene})][SbF_6]_2$ (2)

1,4-Dichloro-tetramethylbenzene (white crystalline solid) was used as ligand to provide complex **2** as a white air-stable powder. Yield: 80%. ^{1}H NMR (CD_3NO_2): $\delta=6.78$ (d, $^3J=6.8$ Hz, H π-cymene, 2H), 6.67 (d, $^3J=6.8$ Hz, H π-cymene, 2H), 2.97 (sept, $^3J=6.8$ Hz, H *i*Pr, 1H), 2.84 (s, 4Me, 12H), 2.44 (s, Me, 3H), 1.40 ppm (d, $^3J=6.8$ Hz, Me *i*Pr, 6H); ^{13}C NMR (CD_3NO_2): $\delta=122.4$ (2C-Cl), 115.8, 113.6 (2C, *p*-cymene), 110.2 (4C, chloroarene), 97.3 (2CH, *p*-cymene), 94.7 (2CH, *p*-cymene), 20.7 (1Me), 29.9 (4Me), 21.3 (1Me), 18.6 (2Me), 16.9 ppm (CH); elemental analysis calcd (%) for $C_{20}H_{26}Cl_2F_{12}RuSb_2$ (909.90 g mol^{-1}): C 26.40, H 2.88; found: C 26.45, H 2.89.

Synthesis of $[(\eta^6\text{-}p\text{-cymene})Ru(\eta^6\text{-4-chlorophenol})][SbF_6]_2$ (3)

4-Chlorophenol (white solid) was used as ligand to provide complex **3** as a pale-yellow air-stable powder. Yield: 78%. ^{1}H NMR (CD_3NO_2): $\delta=7.05$ (d, $^3J=6.9$ Hz, H π-chlorophenol, 2H), 6.92 (d, $^3J=6.3$ Hz, H π-cymene, 2H), 6.85 (d, $^3J=6.3$ Hz, H π-cymene, 2H), 6.66 (d, $^3J=6.9$ Hz, H π-chlorophenol, 2H), 3.86 (s, OH, 1H), 2.95 (sept, $^3J=6.9$ Hz, H *i*Pr, 1H), 2.42 (s, 1Me, 3H), 1.38 ppm (d, $^3J=6.9$ Hz, Me *i*Pr, 6H); ^{13}C NMR (CD_3NO_2): $\delta=142.5$ (1C-OH), 122.4 (1C-Cl), 113.5, 109.8 (2C *p*-cymene), 97.1, 95.2 (2CH *p*-cymene), 94.7 (2CH chlorophenol), 94.1, 92.4 (2CH *p*-cymene), 83.1, 80.7 (2CH chlorophenol), 32.9 (1Me), 22.7 (2Me), 16.9 ppm (CH); elemental analysis calcd (%) for $C_{16}H_{19}ClF_{12}ORuSb_2$ (835.35 g mol^{-1}): C 23.01, H 2.29; found: C 23.05, H 2.30.

Synthesis of $[(\eta^6\text{-}p\text{-cymene})Ru(\eta^6\text{-chlorobenzene})][SbF_6]_2$ (4)

Chlorobenzene (liquid) was used as ligand to provide complex **4** as a white air-stable powder. Yield: 90%. ^{1}H NMR (CD_3NO_2): $\delta=7.34$ (d, $^3J=6.6$ Hz, H π-chloroarene, 2H), 7.15 (d, $^3J=6.3$ Hz, H π-cymene, 2H), 7.04 (m, 2H π-cymene and 2H π-chloroarene, 4H), 6.97 (t, $^3J=6.0$ Hz, H π-chloroarene, 1H), 3.08 (sept, $^3J=6.9$ Hz, H *i*Pr, 1H), 2.56 (s, Me, 3H), 1.40 ppm (d, $^3J=6.9$ Hz, Me *i*Pr, 6H); ^{13}C NMR (CD_3NO_2): $\delta=125.0$ (C-Cl), 116.3, 115.7 (2C *p*-cymene), 96.8, 96.2, 95.6, 95.0, 94.4 (4CH *p*-cymene, 5CH chlorobenzene), +32.8 (1Me), 22.3 (2Me), 18.9 ppm (CH); ^{13}C NMR (CD_3NO_2): $\delta=$ 125.0 (C-Cl), 116.3, 115.7 (2C *p*-cymene), 96.8, 96.2, 95.6, 95.0, 94.4 (4CH *p*-cymene, 5CH chlorobenzene), 32.8 (1Me), 22.3 (2Me), 18.9 ppm (CH); elemental analysis calcd (%) for $C_{16}H_{19}ClF_{12}RuSb_2$ (819.35 g mol^{-1}): C 23.45, H 2.34; found: C 23.15, H 2.24.

Synthesis of [(η^6-*p*-cymene)Ru(η^6-2-chloro-1,3-dimethylbenzene)][SbF_6]$_2$ (5)

1,4-Dichlorobenzene (white crystalline solid) was used as ligand to provide complex **5** as a white air-stable powder. Yield: 85%. ^{1}H NMR (CD_3NO_2): δ = 7.07 (d, ^3J = 6.0 Hz, H π-chloroarene, 2H), 6.93 (d, ^3J = 6.8 Hz, H π-cymene, 2H), 6.82 (d, ^3J = 6.0 Hz, H π-chloroarene, 1H), 6.80 (d, ^3J = 6.8 Hz, H π-cymene, 2H), 3.05 (sept, ^3J = 7.2 Hz, H *i*Pr, 1H), 2.74 (s, 2Me, 6H), 2.52 (s, Me, 3H), 1.39 ppm (d, ^3J = 7.2 Hz, Me *i*Pr, 6H); ^{13}C NMR (CD_3NO_2): δ = 123.1 (C-Cl), 116.7, 114.2 (2C, *p*-cymene), 113.3 (2C-Me, chloroarene), 96.4, 94.5, 93.4 (7CH), 32.3 (2Me, chloroarene), 21.9 (1Me, *p*-cymene), 19.2 (2Me, *p*-cymene), 17.7 ppm (CH, *p*-cymene); elemental analysis calcd (%) for $C_{18}H_{23}ClF_{12}RuSb_2$ (847.40 g mol^{-1}): C 25.51, H 2.74; found: C 25.58, H 2.78.

General procedure for the preparation of selenium-derived complexes

Treatment at room temperature of the appropriate dicationic ruthenium sandwich complex (0.2 mmol) with an excess of Na_2Se (ca. 10 equiv) in CH_3CN (15 mL) provided the desired selenium-derived complex after filtration through celite with dichloromethane.

Synthesis of [(η^6-*p*-cymene)Ru(η^4-1,4-diselenobenzoquinone)] (6)

Treatment of complex **1** provided the red neutral complex **6**. Yield: 99%. ^{1}H NMR (CD_2Cl_2): δ = 6.40 (s, H π-quinone, 2H), 6.39 (s, H π-quinone, 2H), 6,36 (d, ^3J = 6.8 Hz, H π-cymene, 2H), 6.25 (d, ^3J = 6.8 Hz, H π-cymene, 2H), 2.65 (sept, ^3J = 6.8 Hz, H *i*Pr, 1H), 2.14 (s, Me, 3H), 1.37 ppm (d, ^3J = 6.8 Hz, Me *i*Pr, 6H); elemental analysis calcd (%) for $C_{16}H_{18}RuSe_2$ (469.30 g mol^{-1}): C 40.95, H 3.87; found: C 40.91, H 3.91.

Synthesis of [(η^6-*p*-cymene)Ru(η^4-1,4-diseleno-tetramethylbenzoquinone)] (7)

Treatment of complex **2** provided the red neutral complex **7**. Yield: 98%. ^{1}H NMR (CD_2Cl_2): δ = 5.33 (d, ^3J = 6.4 Hz, H π-cymene, 2H), 5.07 (d, ^3J = 6.4 Hz, H π-cymene, 2H), 2.70 (sept, ^3J = 7.2 Hz, H *i*Pr, 1H), 2.64 (s, 4Me, 12H), 2.05 (s, Me, 3H), 1.27 ppm (d, ^3J = 7.2 Hz, Me *i*Pr, 6H); ^{13}C NMR (CD_2Cl_2): δ = 140.9 (C=Se), 111.9, 106.1, 101.5 (3C Ar), 92.0, 89.2 (4CH Ar), 26.1 (Me), 25.0 (4Me), 21.7 (2Me), 12.8 ppm (CH); elemental analysis calcd (%) for $C_{20}H_{26}RuSe_2{\cdot}H_2O$ (543.43 g mol^{-1}): C 44.20, H 5.19; found: C 44.28, H 4.93.

Synthesis of [(η^6-*p*-cymene)Ru(η^4-1-oxo-4-selenobenzoquinone)] (8)

Treatment of complex **3** provided the red neutral complex **8**. Yield: 95%. ^{1}H NMR (CD_2Cl_2): δ = 6.08 (d, ^3J = 7.2 Hz, H π-quinone, 2H), 5.95 (d, ^3J = 6.3 Hz, H π-cymene, 2H), 5.66 (d, ^3J = 6.3 Hz, H π-cymene, 2H), 5.01 (d, ^3J = 7.2 Hz, H π-quinone, 2H), 2.85 (sept, ^3J = 7.2 Hz, H *i*Pr, 1H), 2.20 (s, Me, 3H), 1.33 ppm (d, ^3J = 7.2 Hz, Me *i*Pr, 6H); elemental analysis calcd (%) for $C_{16}H_{18}ORuSe$ (406.34 g mol^{-1}): C 47.29, H 4.46; found: C 47.35, H 4.49.

Synthesis of [(η^6-*p*-cymene)Ru(η^5-phenseleno)][SbF_6] (9)

Treatment of complex **4** provided the orange monocationic complex **9**. Yield: 90%. ^{1}H NMR (CD_2Cl_2): δ = 6.57 (d, ^3J = 7.2 Hz, H π-phenseleno, 2H), 6.37 (m, H π-phenseleno and H π-cymene, 3H), 6.30 (m, H π-phenseleno and H π-cymene, 4H), 2.91 (sept, ^3J = 7.2 Hz, H *i*Pr, 1H), 2.28 (s, Me, 3H), 1.36 ppm (d, ^3J = 7.2 Hz, Me *i*Pr, 6H); elemental analysis calcd (%) for $C_{16}H_{19}F_6RuSbSe$ (627.10 g mol^{-1}): C 30.64, H 3.05; found: C 30.59, H 3.06.

Synthesis of [(η^6-*p*-cymene)Ru(η^5-1,3-dimethyl-phenseleno)]-[SbF_6] (10)

Treatment of complex **5** provided the orange monocationic complex **10**. Yield: 90%. ^{1}H NMR (CD_2Cl_2): δ = 6.57 (d, ^3J = 7.2 Hz, H π-phenseleno, 2H), 6.37 (m, H π-phenseleno and H π-cymene, 3H), 6.30 (m, H π-phenseleno and H π-cymene, 4H), 2.91 (sept, ^3J = 7.2 Hz, H *i*Pr, 1H), 2.28 (s, Me, 3H), 1.36 ppm (d, ^3J = 7.2 Hz, Me *i*Pr, 6H); ^{13}C NMR (CD_2Cl_2): δ = 157.6 (C=Se), 117.3, 111.3, 106.5 (4C), 94.6, 90.0, 89.2, 85.1 (7CH), 31.7 (1Me, *p*-cymene), 26.0, 23.2 (4Me), 17.7 ppm (CH, *p*-cymene); elemental analysis calcd (%) for $C_{16}H_{19}F_6RuSbSe$ (627.10 g mol^{-1}): C 30.64, H 3.05; found: C 30.66, H 3.01.

X-ray crystal structure determination of [(η^6-*p*-cymene)-Ru(η^4-1,4-diseleno-tetramethylbenzoquinone)] (7) and [(η^6-*p*-cymene)Ru(η^4-1-oxo-4-selenobenzoquinone)] (8)

Data were collected on a Bruker Kappa-APEXII instrument. Unit-cell parameter determination, data collection strategy, and integration were carried out with the Bruker APEX2 suite of programs. Multiscan absorption correction was applied[21] and the structures were solved using SIR92[22] and refined anisotropically by full-matrix least-squares methods using SHELXL-2013.[23] CCDC-964943 (**7**) and 964944 (**8**) contain the supplementary crystallographic data (excluding structure factors) 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 cancer cells were obtained from the European Collection of Cell Cultures (Salisbury, UK). Cells were grown routinely in RPMI-1640 medium supplemented with 10% fetal calf serum (FCS) and antibiotics at 37 °C and 5% CO_2. Cytotoxicity was determined using the MTT assay (MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide). Cells were seeded in 96-well plates as monolayers with cell solution (100 μL, approximately 20000 cells) per well and preincubated for 24 h in medium supplemented with 10% FCS. Compounds were prepared as a DMSO solution, then dissolved in the culture medium and serially diluted to the appropriate concentration to give a final DMSO concentration of 0.5%. Drug solution (100 μL) was added to each well and the plates were incubated for another 72 h. Subsequently, MTT solution (5 mg mL^{-1}) was added to the cells and the plates were incubated for a further 2 h. The culture medium was aspirated, and the purple formazan crystals formed by the mitochondrial dehydrogenase activity of vital cells were dissolved in DMSO. The optical density, directly proportional to the number of surviving cells, was quantified at 540 nm using a multiwell plate reader and the fraction of surviving cells was calculated from the absorbance of untreated control cells. Evaluation was based on means from two independent experiments, each comprising three microcultures per concentration level.

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