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Cite this: DOI: 10.1039/c0xx00000x

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Communication

Cationic arene ruthenium(II) complexes with chelating *P*-functionalized alkyl phenyl sulfide and sulfoxide ligands as potent anticancer agents

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Synthesis and characterization of cationic ruthenium(II) complexes of the type [Ru(η⁶-*p*-cym)Cl{$Ph_2P(CH_2)_nS(O)_xPh$-κ*P*,κ*S*}][PF_6] (*n* = 1–3; *x* = 0, 1; *p*-cym = *p*-cymene) are presented. Furthermore, their high biological potential even against cisplatin-resistant tumor cell lines and structure–activity relationships are discussed.

The discovery of the chemotherapeutic activity of cisplatin by Barnett Rosenberg in 1965 was a milestone in the field of bioinorganic chemistry.[1,2] Cisplatin itself developed to be the "gold standard" by which all anticancer drugs should be judged.[3] However, drawbacks of cisplatin and other platinum-based anticancer agents are dose-depending toxic side effects as well as the occasional occurrence of resistances against cancer cells.[4–6] Thus, a manifold of transition metal complexes were screened for their cytotoxic activity, where some of them were able to enter clinical trials.[7–9] Major efforts were done in the field of ruthenium-based anticancer drugs, especially by the research groups of Sadler, Dyson and Keppler,[10–19] which may have not only a good cytotoxic activity, but also an antimetastatic activity.[20] Furthermore, the ruthenium complexes hardly affect normal cells and, in some cases, they can overcome the resistance of cancer cells against various platinum-based anticancer drugs.[21–23] The most prominent ruthenium complexes in the field of anticancer research are the octahedral ruthenium(III) complexes **I** and **II** (Fig. 1), which have entered clinical trials.[24–29] Unlike other anticancer drugs, complex **II** is not very toxic toward cancer cells, but the main effect that counts is the ability to stop the metastasis of the cancer. It is assumed that ruthenium(III) complexes underwent *in vivo* a reduction into the oxidation state +2,[30,31] which can be stabilized through π-bonded arene ligands.[32] Thus, arene ruthenium(II) complexes of type **III** (Fig. 1) showed both *in vitro* and *in vivo* promising anticancer activity with *in vitro* IC_{50} values (IC_{50} = concentration of compound that inhibits 50% of cell growth) in the range of 6–300 μM against human cancer cell lines.[32,33] So far, only a few examples of cytotoxic active ruthenium(II) complexes with phosphorus ligands are known. Examples are complexes **IV**–**VI**,[23,34] whereas complex **IV** exhibits nearly no cytotoxicity but a promising antimetastatic activity.[23] Recently, our group has investigated neutral arene ruthenium(II) complexes having κ*P*-coordinated ω-diphenylphosphino-functionalized alkyl phenyl sulfide, sulfoxide, and sulfone ligands (type **VII**, Fig. 1), whereas some of them showed *in vitro* cytotoxicities comparable to cisplatin.[35] Type **VII** complexes with κ*P*-coordinated ligands with pendant sulfide and sulfoxide groups (**1a**–**5a**) were prepared according to Scheme 1 starting from the dinuclear complex [{Ru(η⁶-*p*-cym)Cl_2)}$_2$] (reaction pathway **a**). Here, we report on the synthesis and characterization of cationic ruthenium(II) complexes with bidentately coordinated (κ*P*,κ*S*) ω-diphenylphosphino-functionalized alkyl phenyl sulfide and sulfoxide ligands $Ph_2P(CH_2)_nS(O)_xPh$ (*x* = 0, 1) as well as on their cytotoxic activity, particularly on the influence of the spacer length (*n* = 1–3) on it.

Reactions of neutral ruthenium complexes **1a**–**3a** bearing κ*P* coordinated ω-diphenylphosphino-functionalized alkyl phenyl sulfide ligands $Ph_2P(CH_2)_nSPh$ (*n* = 1–3) with [NH_4][PF_6] resulted under chloride abstraction in the formation of cationic complexes of the type [Ru(η⁶-*p*-cym)Cl{$Ph_2P(CH_2)_nSPh$-κ*P*,κ*S*}][PF_6] (**1b**–**3b**) having the ligands coordinated in a bidentate fashion (κ*P*,κ*S*), cf. Scheme 1 (path **b**).

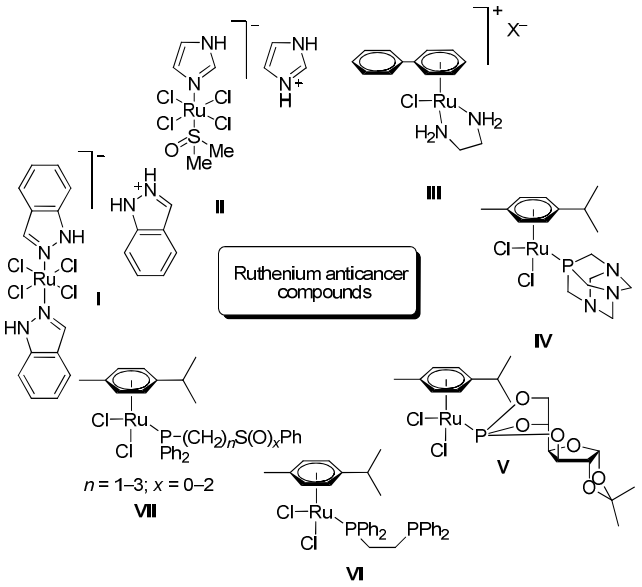
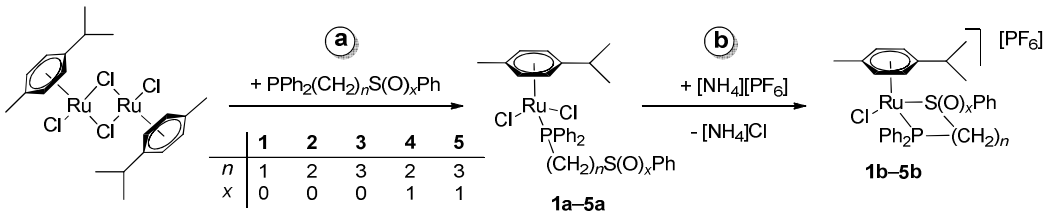


Fig. 1 Examples of ruthenium-based anticancer drugs.



Scheme 1 Synthetic route to ruthenium(II) complexes bearing $Ph_2P(CH_2)_nS(O)_xPh$-κ*P*,κ*S* ligands (**1b**–**5b**).

When the neutral complexes **1a**–**3a** were not isolated, i.e. following a one-pot reaction (path **a** + **b**), the cationic complexes **1b**–**3b** were obtained in good yields (67–83%) as yellow powders. Analogously, the neutral ruthenium complexes **4a** and **5a** with κ*P* coordinated ω-diphenylphosphino-functionalized alkyl phenyl sulfoxide ligands $Ph_2P(CH_2)_nS(O)Ph$ (*n* = 2, 3) were found to react with $[NH_4][PF_6]$ following one-pot procedure producing cationic complexes of the type $[Ru(\eta^6\text{-}p\text{-cym})Cl\{Ph_2P(CH_2)_n\text{-}S(O)Ph\text{-}\kappa P,\kappa S\}][PF_6]$ (**4b**, **5b**; Scheme 1) in yields between 74 and 78% as yellow powders. All complexes are stable on air over weeks and soluble in dimethylsulfoxide and in methylene chloride. The complexes **1b**–**5b** were characterized by elemental analyses, NMR spectroscopy (^1H, ^{13}C, ^{31}P) and single-crystal X-ray structure analyses.

Selected NMR spectroscopic parameters of complexes **1b**–**5b** are given in Table S1. Compared to the requisite neutral ruthenium complexes **1a**–**5a** having these ligands only κ*P* coordinated (Scheme 1), the formation of four- and five-membered ruthenacycles results in highfield (by 31 ppm, **1b**) and downfield shifts (44/49 ppm, **2b**, **4b**), respectively, in ^{31}P NMR spectra, whereas the formation of six-membered ruthenacycles (**3b**, **5b**) shifts the phosphorus resonances only marginally (< 5 ppm).[35] Furthermore, the formation of the $RuP(CH_2)_nS(O)_x$ cycles goes along with an increase of the $^1J_{P,C}$ coupling constants up to 10 Hz compared to the analogous neutral complexes.[35] Thus, the $^1J_{P,C}$ couplings of the cationic ruthenium(II) complexes **1b**–**5b** are generally in the range of 30 Hz, with the exception of **1b** (21.0 Hz) forming a four-membered RuPCS cycle. All proton resonances of the *p*-cymene ligand in complexes **1b**–**5b** were found to be in a narrow range (aromatic C*H*: 4.79–6.11 ppm; isopropyl C*H*/CH_3; 1.97–2.57/0.01–1.12 ppm; methyl CH_3: 1.23–2.07 ppm), largely independent from the type of the $S(O)_x$ function.

Crystals of $[Ru(\eta^6\text{-}p\text{-cym})Cl\{Ph_2PCH_2SPh\text{-}\kappa P,\kappa S\}][PF_6]\cdot CH_2Cl_2$ (**1b**·CH_2Cl_2), $[Ru(\eta^6\text{-}p\text{-cym})Cl\{Ph_2P(CH_2)_2SPh\text{-}\kappa P,\kappa S\}][PF_6]\cdot Me_2CO$ (**2b**·Me_2CO), $[Ru(\eta^6\text{-}p\text{-cym})Cl\{Ph_2P(CH_2)_3SPh\text{-}\kappa P,\kappa S\}][PF_6]$ (**3b**), $[Ru(\eta^6\text{-}p\text{-cym})Cl\{Ph_2P(CH_2)_2S(O)Ph\text{-}\kappa P,\kappa S\}][PF_6]\cdot CH_2Cl_2$ (**4b**·CH_2Cl_2) and $[Ru(\eta^6\text{-}p\text{-cym})Cl\{Ph_2P(CH_2)_3S(O)Ph\text{-}\kappa P,\kappa S\}][PF_6]$ (**5b**) suitable for X-ray diffraction analyses were obtained from methylene chloride/*n*-pentane or acetone solutions at room temperature. The compounds crystallized in discrete cations and anions. Between them weak C–H···F interactions ranging from 2.897(4) Å (C12···F3, **4b**·CH_2Cl_2) to 3.224(7) Å (C42···F41, **1b**·CH_2Cl_2) were found. The molecular structures of the cations are shown in Figures 2 and S1–S5 and selected structural parameters are given in the respective figure captions.

All the five complexes have a half sandwich ("piano stool") structure, in which the coordination spheres of ruthenium(II) are built up by a η^6-*p*-cymene, a chlorido as well as a P⌒S-κ*P*,κ*S* (**1b**–**3b**) and a P⌒S(O)-κ*P*,κ*S* (**4b**, **5b**) ligand, respectively. The angles at the ruthenium(II) atoms are close to 90° (81.4(2)–90.9(3)°), with the exception of complex **1b** (S–Ru–P 70.6(4)°), therefore the structures can be considered as slightly distorted octahedrons. The deviation of mentioned angle in **1b** can be likely attributed to the ring strain in the four-membered RuPCS cycle. The bite angles of the chelating ligands $P(CH_2)_nS(O)_xPh$-κ*P*,κ*S* are directly related to the chain length *n*. Thus, the bite angles range from 70.6(4)° for the ruthenium complex **1b** with a methylene spacer (*n* = 1) via 85.5(4)/81.4(2)° for complexes **2b**/**4b** with an dimethylene spacer (*n* = 2) up to 88.1(3)/88.8(2)° for complexes **3b**/**5b** with a trimethylene spacer (*n* = 3). The five-membered $RuPC_2S$ ruthenacycles adopt an envelope (**2b**) and a twist form (**4b**). The two six-membered $RuPC_3S$ ruthenacycles (**3b**, **5b**) possess a chair conformation. For all complexes, the Ru–Cl (2.381(1)–2.404(9) Å), Ru–P (2.312(7)–2.349(4) Å) as also the Ru–S bond lengths (2.262(7)–2.390(1) Å) are in the expected range (median Ru–Cl: 2.414 Å, lower/higher quartile: 2.389/2.442 Å, *n* = 5542; median Ru–P: 2.332 Å, lower/higher quartile: 2.287/2.375 Å, *n* = 2520; median Ru–S: 2.299 Å, lower/higher quartile: 2.266/2.352 Å, *n* = 678; *n* – number of observations). The Ru–P bonds are longer in complexes forming six-membered ruthenacycles (2.348(9)/2.349(4) Å) compared to those in complexes with four- and five-membered cycles (2.312(7)–2.318(1) Å). The Ru–$S_{sulfinyl}$ bonds (2.262(7)/2.285(4) Å, **4b**/**5b**) are significantly shorter than the Ru–$S_{sulfide}$ bonds (2.354(1)–2.390(1) Å, **1b**–**3b**).

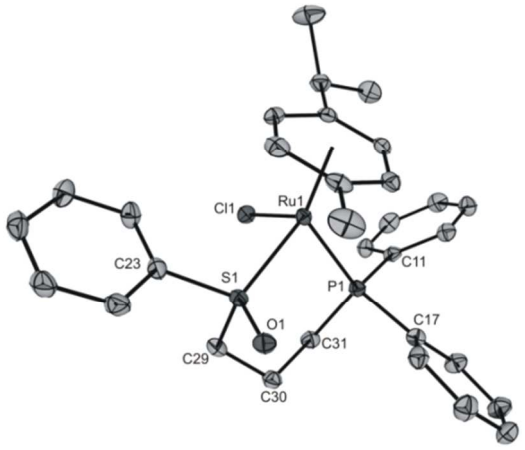


Fig. 2 Molecular structure of the cation in crystals of $[Ru(\eta^6\text{-}p\text{-cym})Cl\{Ph_2P(CH_2)_3S(O)Ph\text{-}\kappa P,\kappa S\}][PF_6]$, **5b**.‡ The ellipsoids are shown with a probability of 50%. H atoms have been omitted for clarity. Selected structural parameters (distances in Å, angles in °): Ru–Cl 2.400(4), Ru–P 2.349(4), Ru–S 2.285(4), Cl–Ru–P 83.4(2), Cl–Ru–S 89.4(2), S–Ru–P 88.8(2), C29–S–C23 100.6(8).

Table 1 IC_{50} values[a] (in μM) of the ruthenium(II) complexes **1b**–**5b** in comparison with cisplatin.

Compound	*n*/*x*	518A2	8505C	A253	MCF-7	SW480
1b	1/0	1.81 ± 0.11	1.81 ± 0.11	1.29 ± 0.09	0.41 ± 0.11	1.85 ± 0.02
2b	2/0	1.70 ± 0.06	1.70 ± 0.06	0.93 ± 0.04	0.26 ± 0.03	1.73 ± 0.14
3b	3/0	1.32 ± 0.10	1.32 ± 0.10	0.37 ± 0.06	0.17 ± 0.01	1.30 ± 0.05
4b	2/1	1.74 ± 0.09	1.53 ± 0.05	2.15 ± 0.22	0.39 ± 0.04	1.72 ± 0.02
5b	3/1	0.96 ± 0.12	0.96 ± 0.12	1.21 ± 0.03	0.14 ± 0.01	0.86 ± 0.04
cisplatin		1.52 ± 0.19	5.02 ± 0.23	0.81 ± 0.02	2.03 ± 0.11	3.24 ± 0.21

[a] Mean values ± SD (standard deviation) from three experiments.

In vitro cytotoxicity studies of the cationic ruthenium(II) complexes **1b**–**5b** were performed against 518A2 (melanoma), 8505C (anaplastic thyroid tumor), A253 (head and neck tumor), MCF-7 (breast), and SW480 (colon) cell lines. The results, based on the sulforhodamine-B (SRB) microculture colorimetric assay,[36] are shown in Table 1 in which, for comparison, the respective activities of cisplatin are included. The complexes of the type $[Ru(\eta^6\text{-}p\text{-cym})Cl\{Ph_2P(CH_2)_nS(O)_xPh\text{-}\kappa P,\kappa S\}][PF_6]$ (**1b**–**5b**; n = 1–3, x = 0, 1) show IC_{50} values in the same order of magnitude or, in some cases, even lower than cisplatin. Especially, the novel cationic ruthenium(II) complexes are highly active against cisplatin-resistant tumor cell lines 8505C, MCF-7 and SW480. The most active compound of this series is complex **5b** with an IC_{50} value of 0.1 μM against MCF-7 cell line (cisplatin: 2.0 μM).

Conclusions

In this study, cationic ruthenium(II) complexes of the type $[Ru(\eta^6\text{-}p\text{-cym})Cl\{Ph_2P(CH_2)_nS(O)_xPh\text{-}\kappa P,\kappa S\}][PF_6]$ (**1b**–**5b**; n = 1–3; x = 0, 1) were prepared by reactions of ω-diphenylphosphino-functionalized alkyl phenyl sulfides and sulfoxides with the dinuclear complex $[\{Ru(\eta^6\text{-}p\text{-cym})Cl_2\}_2]$ and $[NH_4][PF_6]$ (Scheme 1). The constitution of all these complexes, especially the κ*P*,κ*S* coordination of the ligands, was unequivocally confirmed by NMR studies and by single-crystal X-ray diffraction analyses, too. Investigations of the *in vitro* toxicity of these half sandwich ("piano stool") ruthenium(II) complexes against five different cell lines have shown high cytotoxicities. The following conclusions can be drawn:

1. Generally, in almost all cell lines, the cationic ruthenium complexes **1b**–**5b** with the κ*P*,κ*S* coordinated ligands show higher *in vitro* activities than the corresponding neutral ruthenium complexes $[Ru(\eta^6\text{-}p\text{-cym})Cl_2\{Ph_2P(CH_2)_nS(O)_xPh\text{-}\kappa P\}]$ (**1a**–**5a**) bearing the same, but only κ*P* coordinated ligands,[35] cf. the values given in Table 1 with those in Table S2. As an example, this is demonstrated in Fig. S7 for the most active complex **5b**.

2. The ligands themselves show moderate or only very weak cytotoxic activities (IC_{50}: 6–153 μM).[35]

3. The oxidation state of sulfur (–SPh vs. –S(O)Ph) in the ligands does not have a significant influence on the IC_{50} values of the cationic ruthenium complexes (cf. **2b**/**3b** vs. **4b**/**5b**).

4. A correlation between the spacer lengths $-(CH_2)_n-$ (n = 1–3) and cytotoxic activity (cell lines 518A2, 8505C, A253, MCF-7, SW480) has been observed, namely, the longer the spacer the higher the *in vitro* activity (cf. **1b** < **2b** < **3b** and **4b** < **5b**). This leads, for example, for the cell line A253 to a four times higher activity of complex **3b** having a trimethylene spacer (n = 3) compared to that of the respective complex **1b** having only a methylene spacer (n = 1).

5. *In vitro* anticancer activity investigations revealed that the most active ruthenium complex is compound **5b** (n = 3, x = 1) against the MCF-7 cell line with an IC_{50} value of 0.1 μM, thus, being more than one order of magnitude more active than cisplatin (IC_{50}: 2.0 μM).

Consequently, the cationic ruthenium(II) complexes presented here revealed high biological potential, especially against cisplatin-resistant tumor cell lines 8505C, MCF-7 and SW480. Furthermore, the correlation between the length of the spacer in the ligands and the cytotoxicity of the complexes can be traced back to an increasing hydrophobicity.

Acknowledgment

G. L. gratefully acknowledges financial support from the Graduate Scholarship of the State Saxony-Anhalt.

Notes and references

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† Electronic Supplementary Information (ESI) available: Complete experimental details, Tables and Figures of NMR spectroscopical data and molecular structures of **1b**–**5b**, crystallographic data for **1b**–**5b**. CCDC reference numbers 911007–911011. See DOI: 10.1039/b000000x/

‡ Crystallographic data for **5b**: $C_{31}H_{35}ClF_6OP_2RuS$, M = 768.11 g mol^{-1}, triclinic, P–1, a = 10.0603(2), b = 12.0758(3), c = 13.1404(3) Å, α = 83.783(2)°, β = 80.719(2)°, γ = 87.902(2)°, V = 1565.92(6) Å^3, Z = 2, T = 110 K, μ(MoKα) = 0.816 mm^{-1}. Using 388 parameters, $wR2$ = 0.0491 (6126 unique reflections), $R1$ = 0.0207 (5707 reflections with $I > 2\sigma(I)$).

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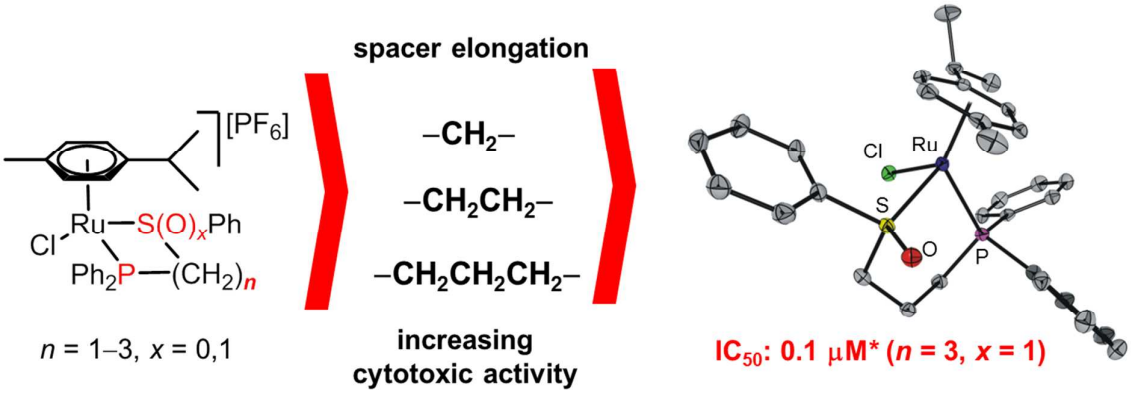
Graphical Abstract



* against the cisplatin-resistant cell line MCF-7

Synthesis and characterization of cationic ruthenium(II) complexes of the type [Ru(η^6-*p*-cym)Cl{$Ph_2P(CH_2)_nS(O)_xPh$-κ*P*,κ*S*}][PF_6] (*n* = 1–3; *x* = 0, 1) are presented. Furthermore, their high biological potential even against cisplatin-resistant tumor cell lines and structure–activity relationships are discussed.

Highlights

► Cationic ruthenium(II) complexes with *P*-functionalized alkyl phenyl sulfide and sulfoxide ligands of the type [Ru(η^6-*p*-cym)Cl{$Ph_2P(CH_2)_nS(O)_xPh$-κ*P*,κ*S*}][PF_6] (*n* = 1–3; *x* = 0, 1) are presented. ► These complexes proved to be potent inhibitors of cancer cell growth as active as cisplatin. ► Structure–activity relationships are discussed.

Keywords

- Ruthenium(II) complexes
- *P*,*S* ligands
- Cytotoxic activity