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Highly active neutral ruthenium(II) arene complexes: Synthesis, characterization, and investigation of their anticancer properties☆

Gerd Ludwig [a], Goran N. Kaluđerović [a,b], Martin Bette [a], Michael Block [a], Reinhard Paschke [b], Dirk Steinborn [a,*]

[a] Institute of Chemistry, Martin Luther University of Halle-Wittenberg, Kurt-Mothes-Straße 2, D-06120 Halle, Germany
[b] Biocenter, Martin Luther University of Halle-Wittenberg, Weinbergweg 22, D-06120 Halle, Germany

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ABSTRACT

Reactions of ω-diphenylphosphino-functionalized alkyl phenyl sulfides $Ph_2P(CH_2)_nSPh$ ($n=1$, **L1**; 2, **L2**; 3, **L3**), sulfoxides $Ph_2P(CH_2)_nS(O)Ph$ ($n=1$, **L4**; 2, **L5**; 3, **L6**) and sulfones $Ph_2P(CH_2)_nS(O)_2Ph$ ($n=1$, **L7**; 2, **L8**; 3, **L9**) with the dinuclear chlorido bridged ruthenium(II) complex $[\{Ru(\eta^6\text{-}p\text{-cymene})Cl_2\}_2]$ afforded mononuclear ruthenium(II) complexes of the type $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2\{Ph_2P(CH_2)_nS(O)_xPh\text{-}\kappa P\}]$ ($n/x=1/0$, **1**; 2/0, **2**; 3/0, **3**; 1/1, **4**; 2/1, **5**; 3/1, **6**; 1/2, **7**; 2/2, **8**; 3/2, **9**) having the $P^{\cap}S(O)_x$ ligands κ*P* coordinated. The complexes were characterized by ^1H, ^{13}C and ^{31}P NMR spectroscopy. The crystal structures of complexes **2**, **7**·CH_2Cl_2 and **8** were determined by X-ray diffraction analysis. All complexes have been screened for cytostatic activity against cell lines 518A2, 8505C, A253, MCF-7, and SW480. In vitro biological experiments demonstrate that these compounds are active toward the used cell lines. The ruthenium(II) complex $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2\{Ph_2P(CH_2)_2SPh\text{-}\kappa P\}]$ (**2**) is the most active compound in the human cancer cell line MCF-7 with the IC_{50} value 1.4 μM lower than cisplatin (2.0 μM).

1. Introduction

Medicinal inorganic chemistry is a field of fast growth, increasing prominence, and fascinating opportunities enabled by the design and tuning of metal-based compounds as therapeutic agents [1–5]. Since the discovery of the cytostatic activity of cisplatin by Rosenberg in 1965 [6,7], metal complexes are in common use as anticancer drugs. Cisplatin itself, the prototype of a metal-based anticancer agent, is still the most widely used chemotherapeutic agent in clinical use [8]. The major disadvantage of cisplatin is the high toxicity, causing dose-depending side effects such as neuro-, hepto- and nephrotoxicity and thus limits the clinical application [9]. Another major problem in clinical use of cisplatin is the resistance of some carcinomas against different platinum based drugs [10,11]. Stimulated by the success and also by the disadvantages of cisplatin and related platinum complexes, a wide range of other transition metal complexes was screened for their cytostatic activities where some of them entered clinical trials [12–14]. Ruthenium complexes deserve special interest not only because of anticancer properties, but also because of antimetastatic activity [15]. An advantage of ruthenium complexes is on the one hand their cytotoxic activity, but on the other hand the fact that they only hardly attack normal cells [16–18]. Since the first discovery of ruthenium complexes for cancer research, a large number of ruthenium-based compounds have been investigated and reported in literature by the research groups of Sadler, Dyson and Keppler [19–28]. Thus, octahedral ruthenium(III) complexes [imiH]*trans*-[Ru(*N*-imi)(*S*-dmso)Cl_4] (imi = imidazole; type **I** in Fig. 1) and [indH]*trans*-[Ru(*N*-ind)$_2Cl_4$] (ind = indazole; type **II**) have reached clinical trials for cancer treatment [29–34]. Ruthenium complexes of the oxidation state +3 are thought to undergo a reduction into the oxidation state +2 in vivo [35,36]. By introducing a π-bonded arene ligand it is possible to stabilize the oxidation state +2 of ruthenium [37]. Thus, ruthenium(II) arene complexes of the type $[Ru(\eta^6\text{-arene})(N^{\cap}N)Cl]X$ ($N^{\cap}N$ = diamine chelating ligand; X = Cl, PF_6, BPh_4; type **III** in Fig. 1) showed both in vitro and in vivo promising anticancer activity. Complexes of this type exhibited IC_{50} values (IC_{50} = concentration of compound that inhibits 50% of cell growth) in vitro in the range of 6–300 μM against human cancer cell lines [37,38]. Recent research focused the synthesis and cytostatic activity of ruthenium(II) complexes with phosphorus ligands such as $[Ru(\eta^6\text{-arene})Cl_2(PTA)]$ (type **IV**; PTA: 1,3,5-triaza-7-phosphaadamantane) [18]. However, only a few examples of ruthenium complexes with mentioned coordination exhibit a cytostatic activity against human cancer cell lines in the range of cisplatin activity [39]. Here, we report on the cytotoxic activity of ruthenium(II) complexes of the type $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2\{Ph_2P(CH_2)_nS(O)_xPh\text{-}\kappa P\}]$, on the influence of the oxidation state of the sulfur atom ($x=0$–2), and the spacer length ($n=1$–3) on the cytotoxic activity of these ruthenium(II) complexes, respectively.

☆ Dedicated to Professor Wolfgang Beck on the occasion of his 80th birthday.

* Corresponding author. Fax: +49 34 5 5527028.
E-mail address: dirk.steinborn@chemie.uni-halle.de (D. Steinborn).

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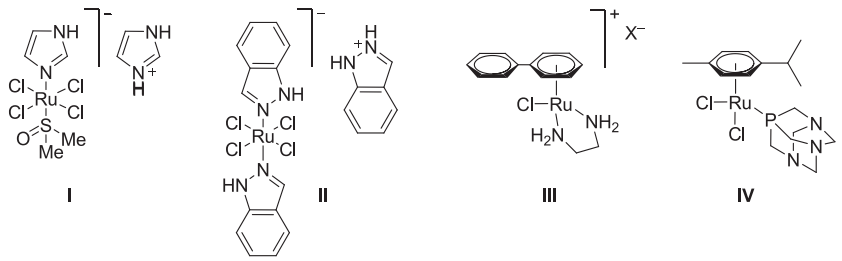


Fig. 1. Examples of ruthenium-based anticancer drugs.

2. Results and discussion

2.1. Syntheses and spectroscopic investigation

Reactions of the dinuclear complex [{Ru(η⁶-*p*-cymene)Cl₂)}₂] with ω-diphenylphosphino-functionalized alkyl phenyl sulfides, $Ph_2P(CH_2)_n$SPh ($n=1$, **L1**; 2, **L2**; 3, **L3**) afforded in toluene with cleavage of the Ru–Cl–Ru bridges the formation of mononuclear complexes of the type [Ru(η⁶-*p*-cymene)Cl₂{$Ph_2P(CH_2)_n$SPh-κ*P*}] (**1**−**3**; Scheme 1). Analogously, the ω-diphenylphosphino-functionalized alkyl phenyl sulfoxides $Ph_2P(CH_2)_n$S(O)Ph ($n=1$, **L4**; 2, **L5**; 3, **L6**) and sulfones $Ph_2P(CH_2)_n$S(O)₂Ph ($n=1$, **L7**; 2, **L8**; 3, **L9**) were found to react with the starting dinuclear ruthenium complex in methylene chloride and in refluxing methanol, respectively, to yield mononuclear complexes of the type [Ru(η⁶-*p*-cymene)Cl₂{$Ph_2P(CH_2)_n$S(O)$_x$Ph-κ*P*}] (**4**−**9**; Scheme 1). The complexes **1**−**9** were obtained as orange powders in yields between 67−91%. The solids are stable to air over weeks. All complexes are soluble in dimethylsulfoxide and, except for **7**, also in methylene chloride, in which they were found to decompose within 1–2 weeks, even under anaerobic conditions. The complexes **1**−**9** were characterized by elemental analyses, NMR spectroscopy (^{1}H, ^{13}C, ^{31}P), and X-ray single-crystal structure analyses (**2**, **7**, **9**).

Selected NMR spectroscopic parameters of complexes **1**−**9** are given in Table 1. Coordination of the ligands to Ru(II) gives rise to strong downfield shifts of the phosphorus resonances δ_P up to 50 ppm. The resulting singlet resonances between 21.8 and 31.3 ppm were found to be indicative of a κ*P* coordination of $Ph_2P(CH_2)_n$S(O)$_x$Ph to Ru(II) [40]. Coordination-induced shifts of the aliphatic carbon atoms ($\delta_{C(coord.)} - \delta_{C(uncoord.)}$) of the ligands $Ph_2P(CH_2)_n$S(O)$_x$Ph (**L1**−**L9**) were detected up to −11 ppm; the highest value (−11.2 ppm) was found in complex **7**. The $^1J_{P,C}$ couplings are generally in the range of 20–30 ppm, with the exception of **4** and **7**, caused by the direct influence of the sulfinyl or sulfonyl group on the α-carbon atom. All proton resonances of the *p*-cymene ligand in complexes **1**−**9** were found to be in a narrow range, largely independent from the type of the S(O)$_x$ function. The proton chemical shifts were detected between 4.95−5.22 ppm (aromatic C*H*), 2.44–2.49/0.78–0.86 ppm (isopropyl C*H*/C*H*$_3$), and 1.81–1.87 ppm (methyl C*H*$_3$). Because of the chirality of the *P*-functionalized sulfoxide, for the proton and the carbon atoms of the *p*-cymene ligand in the complexes **4**–**6** two sets of signals for the diastereotopic atoms (aromatic CH and isopropyl CH$_3$) could be detected.

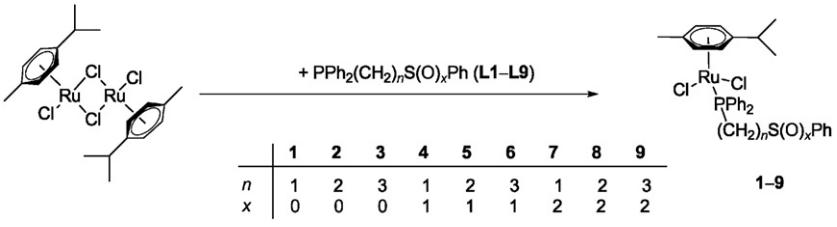
Table 1
Selected NMR spectroscopic data (δ in ppm, *J* in Hz) of [Ru(η⁶-*p*-cymene)Cl₂{$Ph_2P(CH_2)_n$S(O)$_x$Ph-κ*P*}] (**1**−**9**).

x		$Ph_2PC_\alpha H_2S(O)_xPh$			$Ph_2PC_\beta H_2C_\alpha H_2S(O)_xPh$				$Ph_2PC_\gamma H_2C_\beta H_2C_\alpha H_2S(O)_xPh$			
		$\delta_{\alpha\text{-}C}$ ($^1J_{P,C}$)	δ_P		$\delta_{\alpha\text{-}C}$ ($^2J_{P,C}$)	$\delta_{\beta\text{-}C}$ ($^1J_{P,C}$)	δ_P		$\delta_{\alpha\text{-}C}$ ($^3J_{P,C}$)	$\delta_{\gamma\text{-}C}$ ($^1J_{P,C}$)	δ_P
0	**1**	27.2 (21.0)	31.3	**2**	28.0 (5.8)	25.2 (23.2)	22.6	**3**	34.2 (13.2)	22.3 (28.8)	24.5
1	**4**	53.3 (10.3)	22.6	**5**	50.7 (4.5)	20.0 (27.6)	23.7	**6**	50.6 (11.4)	22.0 (22.7)	24.7
2	**7**	48.2 (11.8)	21.8	**8**	51.2	20.0 (27.0)	23.1	**9**	56.5 (12.1)	22.2 (29.1)	24.5

2.2. Molecular structures

Crystals of [Ru(η⁶-*p*-cymene)Cl₂{$Ph_2PCH_2CH_2SPh$-κ*P*}] (**2**), [Ru(η⁶-*p*-cymene)Cl₂{$Ph_2PCH_2S(O)_2Ph$-κ*P*}]·CH_2Cl_2 (**7**·CH_2Cl_2) and [Ru(η⁶-*p*-cymene)Cl₂{$Ph_2PCH_2CH_2S(O)_2Ph$-κ*P*}] (**8**) suitable for X-ray diffraction analysis were obtained from solutions of methylene chloride/*n*-pentane at room temperature. The compounds crystallized as isolated molecules without unusual intermolecular interactions (shortest distance between non-hydrogen atoms: 3.173(2) Å, C3···C4', **2**; 3.242(4) Å, C6···O1', **7**·CH_2Cl_2; 3.233(5) Å, C29···O2', **8**). The molecular structures are shown in Figs. 2–4 and selected structural parameters are given in the figure captions.

All the three complexes have a half sandwich (piano stool) structure, in which ruthenium(II) has coordinated a η⁶-cymene ligand, two chlorido ligands as well as a P∩S-κ*P* (**2**) and a P∩SO_2-κ*P* (**7**, **8**) ligand, respectively. The angles at the ruthenium(II) atom are close to 90° (85.9(3)–88.5(2)°), so that the structure can be viewed as a distorted octahedron. For all complexes, the Ru–Cl bond lengths (2.408(7)–2.423(7) Å) as also the Ru–P bond length (2.349(6)–2.371(4) Å) are in the expected range (median Ru–Cl: 2.422 Å, lower/higher quartile: 2.393/2.469 Å, $n=1153$; median Ru–P: 2.316 Å, lower/higher quartile: 2.275/2.359 Å, $n=1153$; *n* – number of observations). For the ruthenium(II) complexes with the ω-diphenylphosphino-functionalized alkyl phenyl sulfone ligands the O–S–O (119.6(2)°, **7**; 119.4(2)°, **8**) and C–S–C (100.5(1)°, **7**; 105.4(1)°, **8**) angles were found to be as anticipated (median O–S–O: 118.4°, lower/higher quartile: 117.6/119.2°, $n=3010$; median C–S–C: 104.7°, lower/higher quartile: 102.8/106.3°, $n=3010$).



Scheme 1. Synthetic routes to ruthenium(II) complexes bearing $Ph_2P(CH_2)_n$S(O)$_x$Ph-κ*P* ligands (**1**–**9**).

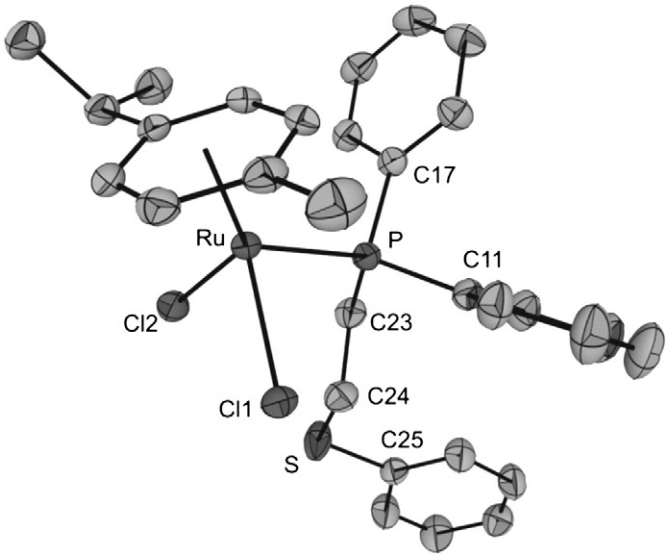


Fig. 2. Molecular structure of [Ru(η^6-*p*-cymene)Cl_2{$Ph_2PCH_2CH_2SPh$-κ*P*}] in crystals of **2**. The ellipsoids are shown with a probability of 50%. H atoms have been omitted for clarity. Selected structural parameters (distances in Å, angles in °): Ru–Cl1 2.410(4), Ru–Cl2 2.421(4), Ru–P 2.371(4), Cl1–Ru–Cl2 88.5(2), Cl1–Ru–P 87.6(1), Cl2–Ru–P 89.0(2), C24–S–C25 105.7(9).

2.3. Biological studies

In vitro cytotoxic studies of synthesized ruthenium(II) complexes were performed against 518A2 (melanoma), 8505C (anaplastic thyroid tumor), A253 (head and neck tumor), MCF-7 (breast), and SW480 (colon) cells lines. The cells were cultured in the presence of various concentrations of **L1**–**L9** and of corresponding ruthenium(II) complexes (**1**−**9**) for 96 h. The cell viability was analyzed by a sulforhodamine-B (SRB) microculture colorimetric assay [41]. Cell viability was determined by quantitative measurement of SRB incorporation in the cell and the results were normalized with respect to the viability rate in untreated cells. After a 96-h incubation period, increasing concentrations of **L1**–**L9** and **1**–**9** (0–300 μM) were able to inhibit cell growth of 518A2, 8505C, A253, MCF-7, and SW480 cells in a dose-dependent manner (Fig. 5). The results are shown in Table 2 in which, for comparison, the activity of cisplatin is included.

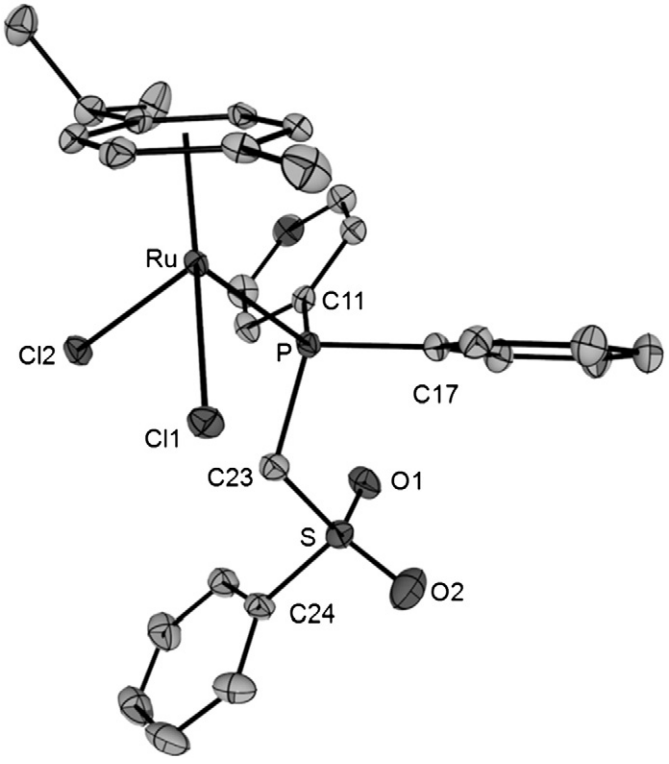


Fig. 3. Molecular structure of [Ru(η^6-*p*-cymene)Cl_2{$Ph_2PCH_2S(O)_2Ph$-κ*P*}] (**7**) in crystals of **7**·CH_2Cl_2. The ellipsoids are shown with a probability of 50%. H atoms have been omitted for clarity. Selected structural parameters (distances in Å, angles in °): Ru–Cl1 2.408(7), Ru–Cl2 2.423(7), Ru–P 2.360(7), Cl1–Ru–P 86.0(2), Cl2–Ru–P 85.9(3), Cl1−Ru−Cl2 87.7(3), C24–S–C23 100.5(1), O1−S−O2 119.6(2).

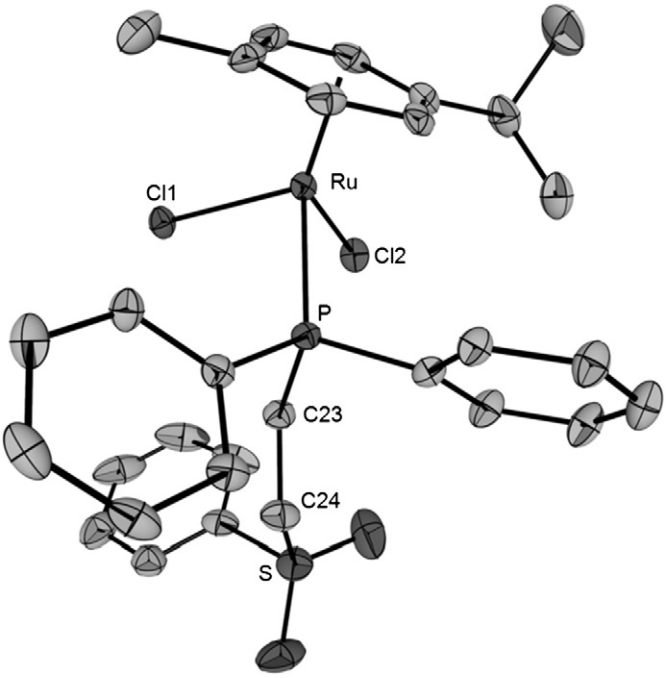


Fig. 4. Molecular structure of [Ru(η^6-*p*-cymene)Cl_2{$Ph_2PCH_2CH_2S(O)_2Ph$-κ*P*}] in crystals of **8**. The ellipsoids are shown with a probability of 50%. H atoms have been omitted for clarity. Selected structural parameters (distances in Å, angles in °): Ru–Cl1 2.417(6), Ru–Cl2 2.410(6), Ru–P 2.349(6), Cl1–Ru–P 87.5(2), Cl2–Ru–P 86.5(2), Cl1−Ru−Cl2 87.4(2), C24–S–C23 105.4(1), O1−S−O2 119.4(2).

Generally, with the exception of **L7**, ligands (**L1**–**L9**) show lower in vitro activities than the corresponding ruthenium(II) complexes on almost all cell lines. The most effective ligand was found to be **L2** (2.8–8.0 times less active than **2**). The ligands with the lowest influence on cell inhibition are **L6** and **L9**. In almost every case, with exception of complex **6**, the ruthenium(II) compounds with sulfinyl- (**4**–**6**) or sulfonyl-functionalized ligands (**7**–**9**) exhibited lower cytotoxicity than cisplatin. Only the ruthenium complexes [Ru(η^6-*p*-cymene)Cl_2{$Ph_2P(CH_2)_nSPh$-κ*P*}] (**1**–**3**; $n=1$–3) having a pendant thioether group in the ligand show IC_{50} values in the same order of magnitude or, in some cases, even lower than cisplatin. The most active compound of the series examined in the current study is compound **2** with an IC_{50} value of 1.4 μM against cell line MCF-7. Contrary, ruthenium(II) complex **7** with a sulfonyl-functionalized ligand on the same cell line showed IC_{50} value of 115.0 μM. The ruthenium(II) complex **1** ($n/x=1/0$) which has a κ*P* coordinated ligand and a sulfide group is four times more active against the cell line MCF-7 than the ruthenium(II) complex **4** ($n/x=1/1$) having a κ*P* coordinated ligand with a pendant sulfinyl group is eighteen times more active against the cell line MCF-7 than the ruthenium(II) complex **7** ($n/x=1/2$) with a κ*P* coordinated ligand having a pendant sulfonyl group. In general, the cytotoxic activity was found to increase with decreasing oxidation of the pendant $S(O)_xPh$ ($x=0$–2) group of the ligand.

Furthermore, within the ruthenium(II) complexes [Ru(η^6-*p*-cymene)Cl_2{$Ph_2P(CH_2)_nS(O)_xPh$-κ*P*}] having pendant sulfinyl ($x=1$) and sulfonyl ($x=2$) groups, a relationship between the spacer length ($n=1$–3) and cytotoxic activity could be derived: With increasing

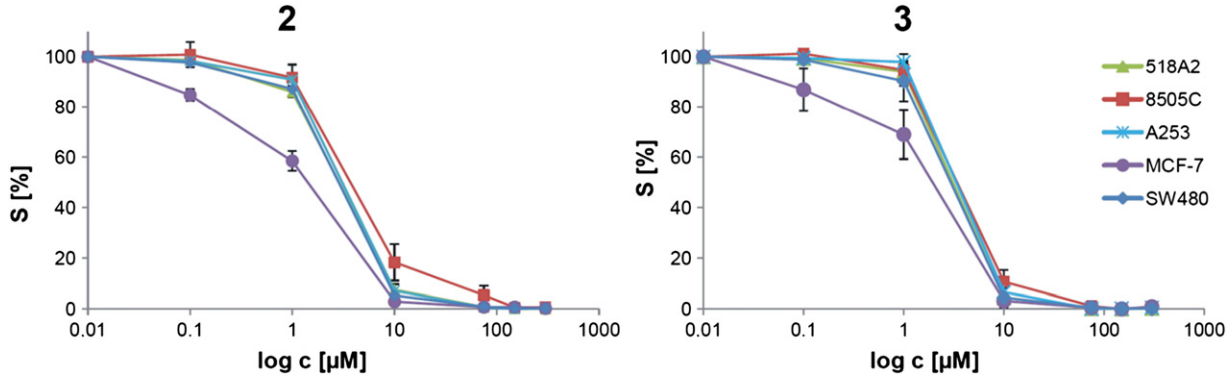


Fig. 5. Representative graphs showing survival (in %) of cells grown for 96 h in the presence of increasing concentrations of compounds **2** and **3**.

Table 2
IC_{50} values (in µM[a)]) of new ruthenium(II) derivatives (**1**–**9**) and the corresponding ligands (**L1**–**L9**). The values for cisplatin are given for comparison.

Compound	*n*/*x*	518A2	8505C	A253	MCF-7	SW480
L1	1/0	93.9 ± 1.9	76.9 ± 3.0	76.5 ± 3.8	64.8 ± 2.6	99.4 ± 1.9
L2	2/0	20.5 ± 1.9	11.0 ± 1.2	9.5 ± 1.1	6.3 ± 0.2	11.3 ± 1.2
L3	3/0	26.8 ± 3.8	18.3 ± 3.7	25.1 ± 2.7	10.7 ± 1.8	23.5 ± 1.9
L4	1/1	50.8 ± 2.9	72.2 ± 3.5	55.0 ± 1.4	31.7 ± 2.0	78.5 ± 0.7
L5	2/1	33.9 ± 4.0	32.7 ± 3.7	27.1 ± 3.2	55.6 ± 3.4	35.6 ± 1.5
L6	3/1	153.3 ± 5.8	96.8 ± 2.0	105.8 ± 6.3	23.0 ± 0.9	151.2 ± 2.5
L7	1/2	5.5 ± 2.0	28.2 ± 2.1	50.4 ± 2.4	46.8 ± 7.2	37.1 ± 2.6
L8	2/2	29.8 ± 1.5	33.5 ± 4.2	27.8 ± 2.7	31.1 ± 2.8	38.1 ± 2.6
L9	3/2	147.6 ± 2.0	128.0 ± 3.3	114.7 ± 3.4	85.3 ± 0.9	149.7 ± 1.9
1	1/0	1.8 ± 0.5	2.9 ± 0.1	1.7 ± 0.3	6.6 ± 0.5	3.5 ± 0.1
2	2/0	2.6 ± 0.1	3.9 ± 0.4	3.0 ± 0.1	1.4 ± 0.3	2.6 ± 0.1
3	3/0	3.0 ± 0.1	3.6 ± 0.1	3.9 ± 0.1	1.8 ± 0.5	2.7 ± 0.1
4	1/1	26.1 ± 1.2	27.2 ± 4.5	12.7 ± 0.8	31.7 ± 2.0	19.7 ± 1.6
5	2/1	18.6 ± 0.4	28.6 ± 0.8	26.8 ± 0.4	10.5 ± 1.2	19.5 ± 1.4
6	3/1	14.3 ± 3.6	12.0 ± 1.0	13.9 ± 1.5	1.8 ± 0.4	11.9 ± 3.3
7	1/2	26.1 ± 1.3	44.6 ± 4.4	30.9 ± 3.1	115.0 ± 0.6	25.2 ± 3.3
8	2/2	22.5 ± 2.1	21.1 ± 1.6	20.1 ± 1.7	21.3 ± 1.1	12.5 ± 1.0
9	3/2	11.7 ± 1.2	11.8 ± 2.5	11.6 ± 2.4	14.1 ± 2.3	10.9 ± 1.1
cisplatin		1.5 ± 0.2	5.0 ± 0.2	0.8 ± 0.1	2.0 ± 0.1	3.2 ± 0.2

a) Mean value ± standard deviation.

spacer length, an increasing cytotoxic activity against the cell lines 518A2, 8505C, MCF-7, and SW480 was observed. Thus, the cytotoxic activity against MCF-7 cell line of the ruthenium(II) complex **6** with the trimethylene spacer ($n = 3$; $x = 1$) is about 18 times higher than that of complex **4** having only the methylene spacer ($n = 1$; $x = 1$). An overview about the cytotoxic activity of the ruthenium(II) complexes, in comparison with cisplatin, is given in Fig. 6.

2.4. Conclusion

In summary, the in vitro toxicity of a series of half sandwich ruthenium(II) complexes, containing ligands with variable hydrophobic and polar groups, of the type [Ru(η^6-*p*-cymene)Cl_2{$Ph_2P(CH_2)_n S(O)_x$Ph-κ*P*}] (*n*/*x* = 1/0, **1**; 2/0, **2**; 3/0, **3**; 1/1, **4**; 2/1, **5**; 3/1, **6**; 1/2, **7**; 2/2, **8**; 3/2, **9**) having the P^S(O)$_x$ ligands κ*P* coordinated, has been assessed. The noncoordinated ligands are active against the studied cell lines, but when coordinated to the Ru(η^6-*p*-cymene)Cl_2 moiety activity is strongly increased in most cases. Furthermore, the functionalization of the ligands on the metal complex play a significant role in modulating the activity. It was found that ruthenium(II) complexes containing the ligands **L1**, **L2**, and **L3** are potent inhibitors of cancer cell growth. In vitro anticancer activity tests revealed that the most active ruthenium complex is compound **2** against the MCF-7 cell line with an IC_{50} value of 1.4 µM. Furthermore, the influences on the cytotoxic activity of the κ*P* coordinated phosphorous ligands have been pointed out. The elongation of the spacer from a methylene to a trimethylene spacer has a positive effect on the cytotoxic activity of the ruthenium(II) complexes **4**–**9** especially against the cell lines 518A2, 8505C, MCF-7, and SW480. On the other hand, the reduction of the sulfur functionalization, from the sulfonyl via sulfinyl to a sulfide group, increased the anticancer activity of the ruthenium(II) complexes **1**–**9** against all the used cell lines.

3. Experimental part

3.1. General comments

All reactions and manipulations were carried out under argon using standard Schlenk techniques. Diethyl ether, toluene, and *n*-pentane were dried over Na/benzophenone and methylene chloride over CaH_2 and freshly distilled prior to use. NMR spectra (^{1}H, ^{13}C, ^{31}P) were recorded at 27 °C on Varian Gemini 200 and VXR 400 spectrometers. Chemical shifts are relative to solvent signals ($CDCl_3$, δ_H 7.24, δ_C 77.0) as internal references; $\delta(^{31}P)$ is relative to external H_3PO_4 (85%). Microanalyses (C, H) were performed in the Microanalytical Laboratory of the University of Halle using a CHNS-932 (LECO) elemental analyzer. [{$RuCl_2$(η^6-*p*-cymene)}$_2$] and the starting compounds **L1**–**L9** were prepared according to literature procedure [40,42].

3.2. Preparation of [$RuCl_2$(η^6-*p*-cymene){$Ph_2P(CH_2)_n$SPh-κ*P*}] (1–3)

To a toluene solution (30 mL) of [{$RuCl_2$(η^6-*p*-cymene)}$_2$] (0.1 g, 0.16 mmol) the respective ligand (0.32 mmol) was added while

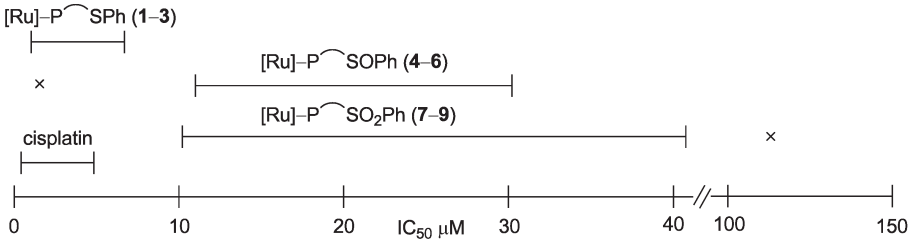


Fig. 6. Overview about the cytotoxic activity of the ruthenium(II) complexes (**1**–**9**) in comparison with cisplatin. [Ru] = Ru(η^6-*p*-cymene)Cl_2.

stirring. The solution was stirred at r.t. overnight, yielding an orange powder that was filtered off, washed with *n*-pentane (3×2 mL), and dried in vacuum.

1 (*n* = 1). Yield: 165 mg (84%). Anal. Found: C, 56.43; H, 4.82. Calcd for $C_{29}H_{31}Cl_2PRuS$ (614.03): C, 56.68; H, 5.08. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.78 (d, $^3J_{H,H}$ = 6.95 Hz, 6H, CH(CH_3)$_2$), 1.87 (s, 3H, CH_3), 2.33−2.56 (m, 1H, CH(CH$_3$)$_2$), 4.15 (d, $^2J_{P,H}$ = 3.63 Hz, 2H, PCH_2), 5.20 (AA'BB' spin system, 4H, C_{cym}-*H*), 6.80−7.85 (m, 15H, H_{Ph}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.2 (s, CCH_3), 21.2 (s, CH(CH_3)$_2$), 27.2 (d, $^1J_{P,C}$ = 21.0 Hz, CH_2PPh_2), 29.9 (s, CH(CH$_3$)$_2$), 85.7 (d, $^2J_{P,C}$ = 5.7 Hz, 2/6-C_{cym}), 90.4 (d, $^2J_{P,C}$ = 4.3 Hz, 3/5-C_{cym}), 94.1 (s, CCH_3), 108.0 (s, CCH(CH$_3$)$_2$), 125.6−136.3 (C_{Ph}). ^{31}P NMR (80 MHz, $CDCl_3$): δ 31.3 (s).

2 (*n* = 2). Yield: 179 mg (89%). Anal. Found: C, 57.98; H, 5.20. Calcd for $C_{30}H_{33}Cl_2PRuS$ (628.60): C, 57.94; H, 5.49. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.84 (d, $^3J_{H,H}$ = 6.93 Hz, 6H, CH(CH_3)$_2$), 1.84 (s, 3H, CH_3), 2.53−2.92 (m, 5H, CH(CH$_3$)$_2$ + SCH_2 + CH_2PPh_2), 5.12 (AA'BB' spin system, 4H, C_{cym}-*H*), 7.01−7.82 (m, 15H, H_{Ph}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.3 (s, CCH_3), 21.4 (s, CH(CH_3)$_2$), 25.2 (d, $^1J_{P,C}$ = 23.2 Hz, CH_2PPh_2), 28.0 (d, $^2J_{P,C}$ = 5.8 Hz, SCH_2), 29.9 (s, CH(CH$_3$)$_2$), 85.6 (d, $^2J_{P,C}$ = 5.8 Hz, 2/6-C_{cym}), 90.2 (d, $^2J_{P,C}$ = 4.1 Hz, 3/5-C_{cym}), 94.3 (s, CCH_3), 108.9 (s, CCH(CH$_3$)$_2$), 125.8−135.6 (C_{Ph}). ^{31}P NMR (80 MHz, $CDCl_3$): δ 22.6 (s).

3 (*n* = 3). Yield: 162 mg (0.79%). Anal. Found: C, 57.34; H, 5.16. Calcd for $C_{31}H_{35}Cl_2PRuS$ (642.62): C, 57.88; H, 5.45. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.78 (d, $^3J_{H,H}$ = 6.95 Hz, 6H, CH(CH_3)$_2$), 1.27−1.46 (m, 2H, CH_2PPh_2), 1.85 (s, 3H, CH_3), 2.44−2.73 (m, 5H, CH(CH$_3$)$_2$ + SCH_2 + $CH_2CH_2CH_2$), 5.14 (AA'BB' spin system, 4H, C_{cym}-*H*), 7.04−7.85 (m, 15H, H_{Ph}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.2 (s, CCH_3), 21.2 (s, CH(CH_3)$_2$), 22.3 (d, $^1J_{P,C}$ = 28.8 Hz, CH_2PPh_2), 23.0 (d, $^2J_{P,C}$ = 7.6, $CH_2CH_2CH_2$), 29.9 (s, CH(CH$_3$)$_2$), 34.2 (d, $^2J_{P,C}$ = 13.2 Hz, SCH_2), 85.6 (d, $^2J_{P,C}$ = 5.8 Hz, 2/6-C_{cym}), 90.4 (d, $^2J_{P,C}$ = 4.3 Hz, 3/5-C_{cym}), 93.7 (s, CCH_3), 108.1 (s, CCH(CH$_3$)$_2$), 125.6−136.1 (C_{Ph}). ^{31}P NMR (80 MHz, $CDCl_3$): δ 24.5 (s).

3.3. Preparation of [$RuCl_2$(η^6-*p*-cymene){$Ph_2P(CH_2)_nSOPh$-κP}] (4–6)

To a methylene chloride solution (25 mL) of [{$RuCl_2$(η^6-*p*-cymene)}$_2$] (0.1 g, 0.16 mmol) the respective ligand (0.32 mmol) was added while stirring. The solution was stirred at r.t. overnight, yielding an orange powder that was filtered off, washed with *n*-pentane (3×2 mL), and dried in vacuum.

4 (*n* = 1). Yield: 135 mg (0.67%). Anal. Found: C, 54.90; H, 4.69. Calcd for $C_{29}H_{31}Cl_2PRuSO$ (630.57): C, 55.24; H, 4.96. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0,70 (d, $^3J_{H,H}$ = 6.88 Hz, 3H, CH(CH_3)$_2$), 0,99 (d, $^3J_{H,H}$ = 6.97 Hz, 3H, CH(CH_3)$_2$), 1.84 (s, 3H, CH_3), 2.42−2.55 (m, 1H, CH(CH$_3$)$_2$), 3.88−4.19 (m, 2H, CH_2), 5.16 (AA'BB' spin system, 4H, C_{cym}-*H*), 7.30−8.22 (m, 15H, H_{Ph}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.3 (s, CCH_3), 20.5 (s, CH(CH_3)$_2$), 22.4 (s, CH(CH_3)$_2$), 30.1 (s, CH(CH$_3$)$_2$), 53.3 (d, $^1J_{P,C}$ = 10.3 Hz, CH_2PPh_2), 84.1 (d, 2/6-C_{cym}), 91.9 (d, 3/5-C_{cym}), 95.0 (s, CCH_3), 108.9 (s, CCH(CH$_3$)$_2$), 123.7−145.4 (C_{Ph}). ^{31}P NMR (80 MHz, $CDCl_3$): δ 22.6 (s).

5 (*n* = 2). Yield: 148 mg (0.72%). Anal. Found: C, 55.67; H, 4.90. Calcd for $C_{30}H_{33}Cl_2PRuSO$ (644.04): C, 55.90; H, 5.16. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0,85 (d, $^3J_{H,H}$ = 6.93 Hz, 3H, CH(CH_3)$_2$), 0,92 (d, $^3J_{H,H}$ = 6.94 Hz, 3H, CH(CH_3)$_2$), 1.82 (s, 3H, CH_3), 2.44−2.95 (m, 5H, CH(CH$_3$)$_2$ + SOCH_2 + CH_2PPh_2), 5.09 (AA'BB' spin system, 4H, C_{cym}-*H*), 7.30−7.81 (m, 15H, H_{Ph}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.4 (s, CCH_3), 20.0 (d, $^1J_{P,C}$ = 27.6 Hz, CH_2PPh_2), 21.4 (s, CH(CH_3)$_2$), 21.6 (s, CH(CH_3)$_2$), 30.0 (s, CH(CH$_3$)$_2$), 50.7 (d, $^2J_{P,C}$ = 4.5 Hz, SOCH_2), 85.6 (d, $^2J_{P,C}$ = 5.5 Hz, C_{cym}), 86.1 (d, $^2J_{P,C}$ = 5.9 Hz, C_{cym}), 89.7 (d, $^2J_{P,C}$ = 3.9 Hz, C_{cym}), 90.2 (d, $^2J_{P,C}$ = 4.4 Hz, C_{cym}), 95.2 (s, CCH_3), 109.5 (s, CCH(CH$_3$)$_2$), 128.1−133.5 (C_{Ph}). ^{31}P NMR (80 MHz, $CDCl_3$): δ 23.7 (s).

6 (*n* = 3). Yield: 143 mg (68%). Anal. Found: C, 56.48; H, 5.27. Calcd for $C_{31}H_{35}Cl_2PRuSO$ (658.06): C, 56.53; H, 5.36. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0,77 (d, $^3J_{H,H}$ = 6.87 Hz, 3H, CH(CH_3)$_2$), 0,80 (d, $^3J_{H,H}$ = 6.87 Hz, 3H, CH(CH_3)$_2$), 1.22−1.63 (m, 2H, CH_2PPh_2), 1.84 (s, 3H, CH_3), 2.41−2.71 (m, 5H, CH(CH$_3$)$_2$ + $CH_2CH_2CH_2$ + SOCH_2), 5.15 (AA'BB' spin system, 4H, C_{cym}-*H*), 7.37−7.89 (m, 15H, H_{Ph}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.6 (d, $^2J_{P,C}$ = 7.4 Hz, $CH_2CH_2CH_2$), 17.4 (s, CCH_3), 21.1 (s, CH(CH_3)$_2$), 21.3 (s, CH(CH_3)$_2$), 22.0 (d, $^1J_{P,C}$ = 22.7 Hz, CH_2PPh_2), 30.0 (s, CH(CH$_3$)$_2$), 50.6 (d, $^3J_{P,C}$ = 11.4 Hz, SOCH_2), 85.4 (d, $^2J_{P,C}$ = 5.6 Hz, C_{cym}), 85.8 (d, $^2J_{P,C}$ = 5.5 Hz, C_{cym}), 90.1 (d, $^2J_{P,C}$ = 3.9 Hz, C_{cym}), 90.6 (d, $^2J_{P,C}$ = 4.3 Hz, C_{cym}), 95.1 (s, CCH_3), 109.2 (s, CCH(CH$_3$)$_2$), 124.4−142.5 (C_{Ph}). ^{31}P NMR (80 MHz, $CDCl_3$): δ 24.7 (s).

3.4. Preparation of [$RuCl_2$(η^6-*p*-cymene){$Ph_2P(CH_2)_nSO_2Ph$-κP}] (7–9)

A solution of [{$RuCl_2$(η^6-*p*-cymene)}$_2$] (0.1 g, 0.16 mmol) and the respective ligand (0.32 mmol) in MeOH (15 mL) were heated to reflux for 3 h, during which time the initial orange-red solution became red in color. The solution had been concentrated under reduced pressure before *n*-pentane (5 mL) was added. The resulting precipitate was filtered off, washed with *n*-pentane (3×2 mL), and dried in vacuum.

7 (*n* = 1). Yield: 177 mg (86%). Anal. Found: C, 54.08; H, 5.09. Calcd for $C_{29}H_{31}Cl_2PRuSO_2$ (646.02): C, 53.87; H, 4.83. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.78 (d, $^3J_{H,H}$ = 6.87 Hz, 6H, CH(CH_3)$_2$), 1.83 (s, 3H, CH_3), 2.44−2.51 (m, 1H, CH(CH$_3$)$_2$), 4.66 (d, $^2J_{P,H}$ = 6.25 Hz, 2H, PCH_2), 5.16 (AA'BB' spin system, 4H, C_{cym}-*H*), 7.28−8.15 (m, 15H, H_{Ph}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.2 (s, CCH_3), 21.1 (s, CH(CH_3)$_2$), 29.9 (s, CH(CH$_3$)$_2$), 48.2 (d, $^1J_{P,C}$ = 11.8 Hz, CH_2PPh_2), 85.6 (d, $^2J_{P,C}$ = 6.2 Hz, 2/6-C_{cym}), 90.5 (d, $^2J_{P,C}$ = 4.4 Hz, 3/5-C_{cym}), 94.3 (s, CCH_3), 108.9 (s, CCH(CH$_3$)$_2$), 126.9−142.0 (C_{Ph}). ^{31}P NMR (80 MHz, $CDCl_3$): δ 21.8 (s).

8 (*n* = 2). Yield: 192 mg (91%). Anal. Found: C, 55.07; H, 5.38. Calcd for $C_{30}H_{33}Cl_2PRuSO_2$ (660.04): C, 54.54; H, 5.04. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (d, $^3J_{H,H}$ = 6.95 Hz, 6H, CH(CH_3)$_2$), 1.81 (s, 3H, CH_3), 2.42−2.56 (m, 1H, CH(CH$_3$)$_2$), 2.79−3.06 (m, 2H, SO_2CH_2), 3.46 (d, $^2J_{P,H}$ = 5.29 Hz, 2H, PCH_2), 5.09 (AA'BB' spin system, 4H, C_{cym}-*H*), 7.41−7.76 (m, 15H, H_{Ar}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.4 (s, CCH_3), 20.0 (s, $^1J_{P,C}$ = 27.0 Hz, CH_2PPh_2), 21.6 (s, CH(CH_3)$_2$), 30.0 (s, CH(CH$_3$)$_2$), 51.2 (s, SO_2CH_2), 85.9 (d, $^2J_{P,C}$ = 5.6 Hz, 2/6-C_{cym}), 89.8 (d, $^2J_{P,C}$ = 4.1 Hz, 3/5-C_{cym}), 95.2 (s, CCH_3), 109.5 (s, CCH(CH$_3$)$_2$), 128.1−133.5 (C_{Ph}). ^{31}P NMR (80 MHz, $CDCl_3$): δ 23.1 (s).

9 (*n* = 3). Yield: 187 mg (87%). Anal. Found: C, 55.16; H, 5.29. Calcd for $C_{31}H_{35}Cl_2PRuSO_2$ (674.05): C, 55.19; H, 5.23. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, $^3J_{H,H}$ = 6.94 Hz, 6H, CH(CH_3)$_2$), 1.43−1.56 (m, 2H, CH_2PPh_2), 1.85 (s, 3H, CH_3), 2.44−2.51 (m, 1H, CH(CH$_3$)$_2$), 2.54−261 (m, 2H, $CH_2CH_2CH_2$), 2.83−2.87 (m, 2H, SO_2CH_2), 5.13 (AA'BB' spin system, 4H, C_{cym}-*H*), 7.38−7.81 (m, 15H, H_{Ph}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9 (d, $^2J_{P,C}$ = 6.7 Hz, $CH_2CH_2CH_2$), 17.3 (s, CCH_3), 21.3 (s, CH(CH_3)$_2$), 22.2 (d, $^1J_{P,C}$ = 29.1 Hz, CH_2PPh_2), 30.0 (s, CH(CH$_3$)$_2$), 56.5 (d, $^3J_{P,C}$ = 12.1 Hz, SO_2CH_2), 85.6 (d, $^2J_{P,C}$ = 5.8 Hz, 2/6-C_{cym}), 90.2 (d, $^2J_{P,C}$ = 4.2 Hz, 3/5-C_{cym}), 94.2 (s, CCH_3), 108.4 (s, CCH(CH$_3$)$_2$), 127.7−138.9 (C_{Ph}). ^{31}P NMR (80 MHz, $CDCl_3$): δ 24.5 (s).

3.5. X-ray crystallography

Data for X-ray diffraction analyses of single crystals of **2** and **8** were collected on a Stoe-IPDS 2T diffractometer and of **7**·CH_2Cl_2 on a Stoe-IPDS diffractometer at 200(2) K using Mo-*K*α radiation (λ = 0.7103 Å, graphite monochromator). A summary of the crystallographic data, the data collection parameters and the refinement parameters is given in Table 3. Absorption corrections were applied numerically and by multi-scan with X-RED32 (T_{min}/T_{max}: 0.73/0.88, **2**; 0.53/0.63, **7**·CH_2Cl_2; 0.85/0.90, **8**) [43]. The structures were solved with direct methods using SHELXS-97 and refined using full-matrix least-square routines against F^2 with SHELXL-97 [44,45]. All non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms with isotropic ones. H atoms were placed in calculated positions according to the riding model. CCDC 870415 (**2**), 870416 (**7**·CH_2Cl_2), and 870417 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 3
Crystallographic data, data collection parameters, and refinement parameters for **2**, **7**·CH_2Cl_2, and **8**.

	2	**7**·CH_2Cl_2	**8**
Empirical formula	$C_{30}H_{33}Cl_2PRuS$	$C_{29}H_{31}Cl_2O_2PRuS{\cdot}CH_2Cl_2$	$C_{30}H_{33}Cl_2O_2PruS$
M_r	628.56	731.46	660.56
Crystal system	Orthorhombic	Monoclinic	Orthorhombic
Space group	*Pbca*	$P2_1/c$	$P2_12_12_1$
a/Å	10.4688(4)	9.6747(7)	12.9979(9)
b/Å	19.4369(9)	13.1189(10)	13.3661(9)
c/Å	27.3589(10)	25.491(2)	16.7576(9)
β/°		104.724(8)	
V/Å^3	5567.0(4)	3129.1(4)	2911.3(3)
Z	8	4	4
D_{cal}/g·cm^{-3}	1.500	1.553	1.507
μ(Mo-Kα)/mm^{-1}	0.906	0.987	0.875
F(000)	2576	1488	1352
θ range/°	2.66−28.00	2.27–26.05	2.87−28.00
Rfln collected	24985	23670	20662
Refln observed [$I>2\sigma(I)$]	5319	4930	5943
Rfln independent	6695 ($R_{int}=0.0227$)	6067 ($R_{int}=0.0614$)	7018 ($R_{int}=0.0314$)
Data/restraints/parameters	6695/0/319	6067/0/365	7018/0/337
Goodness-of-fit on F^2	0.941	1.001	0.847
*R*1, *wR*2 [$I>2\sigma(I)$]	0.0217, 0.0463	0.0333, 0.0806	0.0231, 0.0420
*R*1, *wR*2 (all data)	0.0337, 0.0490	0.0451, 0.0846	0.0313, 0.0431
Largest diff. peak and hole/e Å^{-3}	0.395/−0.376	0.554/−0.734	0.289/−0.477

3.6. Biological studies

3.6.1. Cell lines, culture conditions, and preparation of drug solutions

The cell lines 518A2, 8505C, A253, MCF-7, and SW480 were kindly provided by Dr. Thomas Müller, Department of Hematology/Oncology, Martin Luther University of Halle-Wittenberg, Halle (Saale), Germany. Cultures were maintained as monolayers in RPMI 1640 (PAA Laboratories, Pasching, Austria) supplemented with 5–10% heat-inactivated fetal bovine serum (Biochrom AG, Berlin, Germany) and penicillin/streptomycin (PAA Laboratories) at 37 °C in a humidified atmosphere with 5% CO_2. Stock solutions of investigated compounds were prepared in dimethylsulfoxide (DMSO, Sigma Aldrich) at a concentration of 20 mM, filtered through Millipore filter, 0.22 μm, before use, and diluted by nutrient medium to various working concentrations. Nutrient medium was RPMI-1640 (PAA Laboratories) supplemented with 10% fetal bovine serum (Biochrom AG) and penicillin/streptomycin (PAA Laboratories).

3.6.2. Cytotoxicity assay

The cytotoxic activities of all the compounds were evaluated using the SRB microculture colorimetric assay (Sigma Aldrich, Germany) [41]. The cells were treated with serial dilutions of the compounds (0–300 μM) for 96 h and assay was performed in repeated triplicate. The final concentration of DMSO solvent never exceeded 0.5%, at which it was non-toxic to the cells. Absorbance was measured at 570 nm using a 96-well plate reader (Tecan Spectra, Crailsheim, Germany). The IC_{50} value defined as the concentrations of the compound at which 50% cell inhibition is observed. The IC_{50} value was estimated from the semilogarithmic dose–response curves.

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