Full Paper

Applied Organometallic Chemistry

Received: 15 August 2014 Revised: 20 September 2014 Accepted: 29 September 2014 Published online in Wiley Online Library: 6 November 2014

(wileyonlinelibrary.com) DOI 10.1002/aoc.3238

Binuclear dichlorido(η⁶-*p*-cymene)ruthenium(II) complexes with bis(nicotinate)- and bis(isonicotinate)-polyethylene glycol ester ligands

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Neutral binuclear ruthenium complexes 1–8 of the general formula [{$RuCl_2(\eta^6$-*p*-cym)}$_2$ μ-(N^N)] (N^N = bis(nicotinate)- and bis(isonicotinate)-polyethylene glycol esters: (3-py)$COO(CH_2CH_2O)_n$CO(3-py) and (4-py)$COO(CH_2CH_2O)_n$CO(4-py), *n* =1–4), as well as mononuclear [$RuCl_2(\eta^6$-*p*-cym)((3-py)$COO(CH_2CH_2OCH_3)$-κ*N*)], complex 9, were synthesized and characterized using elemental analysis and electrospray ionization high-resolution mass spectrometry, infrared, ^{1}H NMR and ^{13}C NMR spectroscopies. Stability of the binuclear complexes in the presence of dimethylsulfoxide was studied. Furthermore, formation of a cationic complex containing bridging pyridine-based bidentate ligand was monitored using ^{1}H NMR spectroscopy. Ligand precursors, polyethylene glycol esters of nicotinic (L1 · 2HCl–L4 · 2HCl and L9 · HCl) and isonicotinic acid dihydrochlorides (L5 · 2HCl–L8 · 2HCl), binuclear ruthenium(II) complexes 1–8 and mononuclear complex 9 were tested for *in vitro* cytotoxicity against 518A2 (melanoma), 8505C (anaplastic thyroid cancer), A253 (head and neck tumour), MCF-7 (breast tumour) and SW480 (colon carcinoma) cell lines. Copyright © 2014 John Wiley & Sons, Ltd.

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Keywords: ruthenium(II) complexes; nicotinic acid; isonicotinic acid; polyethylene glycol esters; cytotoxicity

Introduction

As 'drug of the twentieth century', cisplatin stimulated many scientists in search for new metal-based antitumor drugs.[1–6] Successful application of cisplatin has been found against head and neck, testicular, cervical, bladder, ovarian and small-cell lung cancers.[6,7] Besides its effectiveness, cisplatin expresses unfavourable severe impacts on various organs (causing neurotoxicity, nephrotoxicity, ototoxicity, vomiting and nausea),[8] thus restricting its therapeutic applications.[9] Therefore, *in vitro* examination of the cytotoxic activity of diverse transition metal complexes has been, and still is, a very important and active field in medicinal chemistry during the last two decades.[10–13] Ruthenium-based anticancer drugs deserve a special position in research not only because of their good cytotoxicity[14–20] but also because of their antimetastatic activity.[21] Especially, several ruthenium complexes combine good selectivity between normal and tumour cells with activity against cisplatin-resistant tumour cell lines.[22–24] Some of the *in vitro* active ruthenium(II) complexes are depicted in Fig. 1. Arene ruthenium(II) complexes (Fig. 1A) bearing ethylenediamine ligand demonstrated favourable *in vitro* and *in vivo* anticancer activity.[25,26] RAPTA-C (Fig. 1B), a ruthenium(II) complex with 1,3,5-triaza-7-phosphaadamantane, exhibited moderate cytotoxicity but expressed promising *in vivo* antimetastatic activity.[27] A ruthenium(II) complex having isonicotinate ester moiety (Fig. 1C) showed a high anticancer activity towards human ovarian cell line A2780.[28] Recently, Steinborn *et al.* investigated neutral and cationic arene ruthenium(II) complexes having κ*P* and κ*P*,κ*S* respectively coordinated ω-diphenylphosphino-functionalized alkylphenyl sulfide, sulfoxide and sulfone ligands (Fig. 1D and E).[19,20] Several complexes from both groups exhibited *in vitro* cytotoxicities similar to or greater than that of cisplatin.

In order to investigate how less lipophilic substituents, compared to complexes having alkyl moieties (see Fig. 1C),[28] and the presence of two ruthenium(II) centres affect cytotoxic activity, herein is described the synthesis and characterization of new ruthenium(II) complexes **1–8** of the general formula [{$RuCl_2(\eta^6$-*p*-cym)}$_2$ (N^N)] with polyethylene glycol esters of nicotinic (**L1–L4**) and isonicotinic acids (**L5–L8**) as ligands in bridging mode. Also, a ruthenium(II) complex containing ethylene glycol monomethyl ether nicotinate (**L9**), complex **9**, was prepared and characterized.

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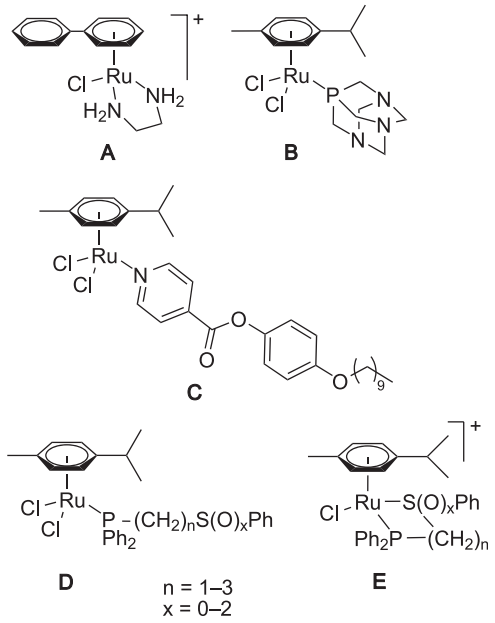


Figure 1. Some ruthenium-based *in vitro* active compounds.

The reactivity of novel ruthenium(II) complex **4** against DMSO and the formation of cationic complex **10** were studied. Ligand precursors and the corresponding ruthenium(II) complexes were tested against cancer cell lines.

Experimental

Materials and Methods

All reactions and manipulations were carried out under argon using standard Schlenk techniques. Toluene was dried over Na/benzophenone, dichloromethane over CaH_2 and isopropanol over 3 Å molecular sieve and degassed with argon prior to use. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded at 300 K with Inova 500 (500 MHz) or VXR (400 MHz) spectrometers. Chemical shifts were recorded relative to solvent signals ($CDCl_3$: δ_H 7.26 ppm, δ_C 77.16 ppm; D_2O: δ_H 4.79 ppm) as internal references and $\delta(^{31}P)$ relative to external H_3PO_4 (85%). Microanalyses (C, H, N) were performed at the Microanalytical Laboratory of the University of Halle using a CHNS-932 (LECO) elemental analyser. Electrospray high-resolution mass spectrometry (ESI HRMS) was carried out in positive- and negative-ion modes with a Bruker Apex III (FTR-ICR) mass spectrometer. IR spectra were measured from 250 to 4000 cm^{-1} with a Bruker Tensor 27 FT-IR spectrometer with diamond ATR.

The starting compounds $[\{RuCl_2(\eta^6\text{-}p\text{-cym})\}_2]$, $[RuCl_2(\eta^6\text{-}p\text{-cym})(nic)]$ and $[RuCl_2(\eta^6\text{-}p\text{-cym})(inic)]$ were prepared according to literature procedures.[29,30] Thionyl chloride, nicotinic acid, isonicotinic acid and polyethylene glycols were commercially available. Ethane-1,2-diol was distilled prior to use and all other polyethylene glycols were dried with sodium sulfate.

Preparation of ligand precursors (L1 · 2HCl–L8 · 2HCl, L9 · HCl)

Ligand precursors were prepared using an adapted literature procedure. Firstly, nicotinic and isonicotinic acid chloride hydrochlorides were synthesized by reaction of the appropriate acid with thionyl chloride in the presence of DMF.[31] The aroyl chloride hydrochloride was suspended in toluene and the appropriate polyethylene glycol was added and the mixture was stirred overnight at room temperature.[31] Details are given in the supporting information.

Preparation of $[\{RuCl_2(\eta_6\text{-p-cym})\}_2\mu\text{-(3-py)COO(CH}_2\text{CH}_2\text{O)}_n\text{CO(3-py)-}\kappa N,\kappa N'\text{)}]$ (1–4), $[\{RuCl_2(\eta_6\text{-p-cym})\}_2\mu\text{-(4-py)COO(CH}_2\text{CH}_2\text{O)}_n\text{CO(4-py)-}\kappa N,\kappa N'\text{)}]$ (5–8) and $[RuCl_2(\eta^6\text{-}p\text{-cym})((3\text{-py})\text{COO(CH}_2\text{CH}_2\text{OCH}_3\text{)-}\kappa N\text{)}]$ (9)

$[\{RuCl_2(\eta^6\text{-}p\text{-cym})\}_2]$ (for the synthesis of **1**, **2**, **5**, **6**: 0.20 mmol; **3**: 0.18 mmol; **4**: 0.15 mmol; **7**: 0.23 mmol; **8**: 0.19 mmol; **9**: 0.13 mmol) and 1 equiv. of the appropriate ligand precursor **L1** · 2HCl–**L8** · 2HCl or 2 equiv. of **L9** · HCl were suspended in isopropanol (20 ml). The reaction mixture was heated to 40 °C and stirred for 4 h for binuclear complexes or 2 h for mononuclear complexes and then was stored at −47 °C. The product precipitated as orange powder, which was filtered off, washed with small amounts of isopropanol and diethyl ether (4 × 2 ml) and dried in air.

1, n = 1. Yield 106 mg (60%). Anal. Found (%): C, 44.72; H, 4.29; N, 3.09. Calcd for $C_{34}H_{40}Cl_4N_2O_4Ru_2$ (884.65) (%): C, 46.16; H, 4.56; N, 3.17. ESI HRMS (CH_3OH), positive mode: calcd for $[C_{34}H_{40}Cl_4N_2O_4^{102}Ru_2Na]^+$ 906.97214, *m/z* 906.97186 $[M+Na]^+$. ESI HRMS (CH_3OH), negative mode: calcd for $[C_{34}H_{40}Cl_5N_2O_4^{102}Ru_2]^-$ 918.95232, *m/z* 918.95438 $[M+Cl]^-$. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.28 (d, ^3J(H,H) = 6.9 Hz, 12H, C^gH_3), 2.08 (s, 6H, C^eH_3), 2.96 (sept, ^3J(H,H) = 6.9 Hz, 2H, C^fH), 4.73 (s, 4H, OCH_2), 5.27 (d, ^3J(H,H) = 5.7 Hz, 4H, C^bH), 5.45 (d, ^3J(H,H) = 5.7 Hz, 4H, C^cH), 7.46 (dd, ^3J(H^5,H^4) = 7.5 Hz, ^3J(H^5,H^6) = 5.5 Hz, 2H, H^5), 8.42 (d, ^3J(H,H) = 7.5 Hz, 2H, H^4), 9.22 (d, ^3J(H,H) = 5.5 Hz, 2H, H^6), 9.61 (s, 2H, H^2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 18.3 (C^e), 22.2 (C^g), 30.7 (C^f), 63.3 (CH_2O), 82.5 (C^c), 82.6 (C^b), 97.1 (C^a), 103.8 (C^d), 124.4 (C^5), 126.7 (C^3), 138.9 (C^4), 156.0 (C^2), 158.2 (C^6), 163.4 (*COO*). IR (ATR, cm^{-1}): 3060(w), 2962(w), 1724(s), 1604(w), 1470(w), 1430(w), 1351(w), 1270(s), 1195(w), 1112(m), 1053(m), 1031(w), 875(w), 835(w), 744(s), 691 (m), 624(w), 396(w), 288(s).

2, n = 2. Yield: 148 mg (80%). Anal. Found (%): C, 46.38; H, 4.73; N, 3.02. Calcd for $C_{36}H_{44}Cl_4N_2O_5Ru_2$ (928.71) (%): C, 46.56; H, 4.78; N, 3.02. ESI HRMS (CH_3OH), negative mode: calcd for $[C_{36}H_{44}Cl_5N_2O_5^{102}Ru_2]^-$ 962.97744, *m/z* 962.97853 $[M+Cl]^-$. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.30 (d, ^3J(H,H) = 7.0 Hz, 12H, C^gH_3), 2.07 (s, 6H, C^eH_3), 2.96 (sept, ^3J(H,H) = 7.0 Hz, 2H, C^fH), 3.86 (m, 4H, OCH_2), 4.53 (m, 4H, $COOCH_2$), 5.24 (d, ^3J(H,H) = 6.0 Hz, 4H, C^bH), 5.44 (d, ^3J(H,H) = 6.0 Hz, 4H, C^c), 7.34 (dd, ^3J(H^5,H^4) = 7.9 Hz, ^3J(H^5, H^6) = 5.8 Hz, 2H, H^5), 8.16 (d(b), ^3J(H,H) = 7.9 Hz, 2H, H^4), 9.14 (d(b), ^3J(H,H) = 5.8 Hz, 2H, H^6), 9.61 (s, 2H, H^2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 18.4 (C^e), 22.4 (C^g), 30.8 (C^f), 64.9 (CH_2COO), 69.1 (CH_2O), 82.4 (C^c), 82.9 (C^b), 97.3 (C^a), 103.8 (C^d), 124.7 (C^5), 127.1 (C^3), 138.5 (C^4), 155.8 (C^2), 158.4 (C^6), 163.6 (*COO*). IR (ATR, cm^{-1}): 3066(w), 3046(w), 2966(w), 1732(s), 1602(w), 1470(m), 1429(w), 1376(m), 1290(s), 1140(m), 1122(s), 1054(m), 1023(w), 872(m), 842(w), 748 (s), 691(m), 457(w), 282(s), 229(s).

3, n = 3. Yield: 138 mg (78%). Anal. Found (%): C, 45.97; H, 4.69; N, 2.80. Calcd for $C_{38}H_{48}Cl_4N_2O_6Ru_2$ (972.76) (%): C, 46.92; H, 4.97; N, 2.88. ESI HRMS (CH_3OH), negative mode: calcd for $[C_{38}H_{48}Cl_5N_2O_6^{102}Ru_2]^-$ 1007.00475, *m/z* 1007.01415 $[M+Cl]^-$. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.31 (d, ^3J(H,H) = 6.9 Hz, 12H, C^gH_3), 2.11 (s, 6H, C^eH_3), 2.98 (sept, ^3J(H,H) = 6.9 Hz, 2H, C^fH), 3.73 (s, 4H, OCH_2), 3.84 (m, 4H, OCH_2), 4.51 (m, 4H, $COOCH_2$), 5.26 (d, ^3J(H,H) = 6.0 Hz, 4H, C^b), 5.46 (d, ^3J(H,H) = 6.0 Hz, 4H, C^c), 7.39 (dd, ^3J(H^5,H^4) = 7.8 Hz, ^3J

(H^5,H^6) =5.8 Hz, 2H, H^5), 8.16 (d, ^3J(H,H) =7.8 Hz, 2H, H^4), 9.14 (d, ^3J(H,H) =5.8 Hz, 2H, H^6), 9.61 (s, 2H, H^2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 18.4 (C^e), 22.4 (C^g), 30.8 (C^f), 65.4 (CH_2COO), 69.1, 71.1 (CH_2O), 82.4 (C^c), 82.9 (C^b), 97.3 (C^a), 103.8 (C^d), 124.4 (C^5), 127.4 (C^3), 138.7 (C^4), 156.1 (C^2), 158.2 (C^6), 163.7 (*COO*). IR (ATR, cm^{-1}): 3064(w), 2964(w), 2874(w), 1722(s), 1600(w), 1428(w), 1376(w), 1284(s), 1198(w), 1105(s), 1053 (m), 870(w), 750(s), 693(m), 284(s), 234(s).

4, *n* =4. Yield: 119 mg (77%). Anal. Found (%): C, 46.03; H, 4.93; N, 2.70. Calcd for $C_{40}H_{52}Cl_4N_2O_7Ru_2$ (1016.81) (%): C, 47.25; H, 5.15; N, 2.76. ESI HRMS (CH_3OH), negative mode: calcd for [$C_{40}H_{52}Cl_5N_2O_7^{102}Ru_2$]$^-$ 1051.02987, *m/z* 1051.03641 [M + Cl]$^-$. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.33 (d, ^3J(H,H) =6.9 Hz, 12H, C^gH_3), 2.13 (s, 6H, C^eH_3), 2.99 (sept, ^3J(H,H) =6.9 Hz, 2H, C^fH), 3.69 (m, 8H, OCH_2), 3.84 (m, 4H, OCH_2), 4.52 (m, 4H, $COOCH_2$), 5.27 (d, ^3J(H,H) =6.0 Hz, 4H, C^bH), 5.47 (d, ^3J(H,H) =6.0 Hz, 4H, C^cH), 7.43 (dd, ^3J(H^5,H^4) =7.7 Hz, ^3J(H^5,H^6) =5.8 Hz, 2H, H^5), 8.34 (d, ^3J(H,H) =7.7 Hz, 2H, H^4), 9.23 (d, ^3J(H,H) =5.8 Hz, 2H, H^6), 9.62 (s, 2H, H^2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 18.4 (C^e), 22.4 (C^g), 30.8 (C^f), 65.3 (CH_2COO), 69.0, 70.8, 70.9 (CH_2O), 82.4 (C^c), 82.9 (C^b), 97.4 (C^a), 103.8 (C^d), 124.4 (C^5), 127.4 (C^3), 138.8 (C^4), 156.1 (C^2), 158.1 (C^6), 163.6 (*COO*). IR (ATR, cm^{-1}): 3065(w), 2960(w), 2873(w), 1724(s), 1600(w), 1468(w), 1424(w), 1377(w), 1284(s), 1199(w), 1111(s), 1053(m), 1028(m), 940(w), 867(m), 802(w), 746(s), 692(m), 451(w), 397(w), 284(s), 232(s).

5, *n* =1. Yield: 166 mg (94%). Anal. Found (%): C, 45.44; H, 4.41; N, 3.31. Calcd for $C_{34}H_{40}Cl_4N_2O_4Ru_2$ (884.65) (%): C, 46.16; H, 4.56; N, 3.17. ESI HRMS (CH_3OH), positive mode: calcd for [$C_{34}H_{40}Cl_4N_2O_4^{102}Ru_2Na$]$^+$ 906.97214, *m/z* 906.97214 [M + Na]$^+$. ESI HRMS (CH_3OH), negative mode: calcd for [$C_{34}H_{40}Cl_5N_2O_4^{102}Ru_2$]$^-$ 918.95232, *m/z* 918.95401 [M + Cl]$^-$. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.31 (d, ^3J(H,H) =6.9 Hz, 12H, C^gH_3), 2.11 (s, 6H, C^eH_3), 3.00 (sept, ^3J(H,H) =6.9 Hz, 2H, C^fH), 4.73 (s, 4H, OCH_2), 5.25 (d, ^3J(H,H) =5.9 Hz, 4H, C^bH), 5.46 (d, ^3J(H,H) =5.9 Hz, 4H, C^cH), 7.81 (d, ^3J(H,H) =6.2 Hz, 4H, H^3), 9.24 (d, ^3J(H,H) =6.2 Hz, 4H, H^2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 18.5 (C^e), 22.2 (C^g), 30.9 (C^f), 67.7 (CH_2O), 82.6 (C^c), 83.1 (C^b), 97.6 (C^a), 104.2 (C^d), 123.4 (C^3), 138.1 (C^4), 156.1 (C^2), 163.7 (*COO*). IR (ATR, cm^{-1}): 3056(w), 2963(w), 1726(s), 1600 (w), 1468(w), 1429(w), 1270(s), 1197(w), 1111(s), 1056(m), 878(w), 746(s), 689(m), 626(w), 396(w), 289(s), 234(s).

6, *n* =2. Yield: 139 mg (76%). Anal. Found (%): C, 45.76; H, 4.72; N, 2.81. Calcd for $C_{36}H_{44}Cl_4N_2O_5Ru_2$ (928.71) (%): C, 46.56; H, 4.78; N, 3.02. ESI HRMS (CH_3OH), positive mode: calcd for [$C_{36}H_{44}Cl_3N_2O_5^{102}Ru_2$]$^+$ 893.03973, *m/z* 893.04128 [M − Cl]$^+$. ESI HRMS (CH_3OH), negative mode: calcd for [$C_{36}H_{44}Cl_5N_2O_5^{102}Ru_2$]$^-$ 962.97744, *m/z* 962.97962 [M + Cl]$^-$. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.31 (d, ^3J(H,H) =6.9 Hz, 12H, C^gH_3), 2.08 (s, 6H, C^eH_3), 2.98 (sept, ^3J(H,H) =6.9 Hz, 2H, C^fH), 3.83 (m, 4H, OCH_2), 4.52 (m, 4H, $COOCH_2$), 5.34 (d, ^3J(H,H) =6.0 Hz, 4H, C^bH), 5.54 (d, ^3J(H,H) =6.0 Hz, 4H, C^cH), 7.76 (d, ^3J(H,H) =6.6 Hz, 4H, H^3), 9.27 (d, ^3J(H,H) =6.6 Hz, 4H, H^2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 18.4 (C^e), 22.5 (C^g), 30.9 (C^f), 65.0 (CH_2OOC), 69.0 (CH_2O), 82.3 (C^c), 83.6 (C^b), 97.8 (C^a), 103.6 (C^d), 123.6 (C^3), 138.6 (C^4), 156.1 (C^2), 163.9 (*COO*). IR (ATR, cm^{-1}): 3060(w), 2964(w), 2875(w), 1730(s), 1416(m), 1377(w), 1284(s), 1228(m), 1129(s), 1059(m), 865(m), 769(s), 696(m), 452(w), 287(s), 234(s).

7, *n* =3. Yield: 188 mg (84%). Anal. Found (%): C, 45.65; H, 4.78; N, 2.76. Calcd for $C_{38}H_{48}Cl_4N_2O_6Ru_2$ (972.76) (%): C, 46.92; H, 4.97; N, 2.88. ESI HRMS (CH_3OH), negative mode: calcd for [$C_{38}H_{48}Cl_5N_2O_6^{102}Ru_2$]$^-$ 1007.00475, *m/z* 1007.00303 [M + Cl]$^-$. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.31 (d, ^3J(H,H) =6.9 Hz, 12H, C^gH_3), 2.09 (s, 6H, C^eH_3), 2.98 (sept, ^3J(H,H) =6.9 Hz, 2H, C^fH), 3.68 (s, 4H, OCH_2), 3.82 (m, 4H, OCH_2), 4.51 (m, 4H, $COOCH_2$), 5.26 (d, ^3J(H,H) =6.0 Hz, 4H, C^bH), 5.48 (d, ^3J(H,H) =6.0 Hz, 4H, C^cH), 7.83 (d, ^3J(H,H) =6.5 Hz, 4H, H^3), 9.23 (d, ^3J(H,H) =6.5 Hz, 4H, H^2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 18.4 (C^e), 22.4 (C^g), 30.9 (C^f), 65.4 (CH_2OOC), 69.0, 70.9 (CH_2O), 82.5 (C^c), 83.3 (C^b), 97.6 (C^a), 103.9 (C^d), 123.7 (C^3), 138.7 (C^4), 156.0 (C^2), 164.0 (*COO*). IR (ATR, cm^{-1}): 3063(w), 2962(w), 2874(w), 1729(s), 1412(m), 1278(s), 1119(s), 1056(m), 864(m), 769(s), 694(m), 449(w), 283(s).

8, *n* =4. Yield: 180 mg (91%). Anal. Found (%): C, 47.41; H, 4.90; N, 2.83. Calcd for $C_{40}H_{52}Cl_4N_2O_7Ru_2$ (1016.81) (%): C, 47.25; H, 5.15; N, 2.76. ESI HRMS (CH_3OH), negative mode: calcd for [$C_{40}H_{52}Cl_5N_2O_7^{102}Ru_2$]$^-$ 1051.02987, *m/z* 1051.03653 [M + Cl]$^-$. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.31 (d, ^3J(H,H) =7.0 Hz, 12H, C^gH_3), 2.09 (s, 6H, C^eH_3), 2.98 (sept, ^3J(H,H) =7.0 Hz, 2H, C^fH), 3.65 (m, 8H, OCH_2), 3.82 (m, 4H, OCH_2), 4.52 (m, 4H, $COOCH_2$), 5.25 (d, ^3J(H,H) =5.6 Hz, 4H, C^bH), 5.47 (d, ^3J(H,H) =5.6 Hz, 4H, C^cH), 7.84 (d, ^3J(H,H) =6.4 Hz, 4H, H^3), 9.22 (d, ^3J(H,H) =6.4 Hz, 4H, H^2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 18.5 (C^e), 22.5 (C^g), 30.9 (C^f), 65.6 (CH_2OOC), 69.1, 70.9, 71.0 (CH_2O), 82.6 (C^c), 83.4 (C^b), 97.7 (C^a), 104.0 (C^d), 123.8 (C^3), 138.9 (C^4), 156.0 (C^2), 164.1 (*COO*). IR (ATR, cm^{-1}): 3060(w), 2964(w), 2874(w), 1730(s), 1416(m), 1279(s), 1118(s), 1058(m), 864(m), 766(s), 696(m), 452(w), 286(s), 233(s).

9. Yield: 122 mg (96%). Anal. Found (%): C, 46.56; H, 4.85; N, 2.86. Calcd for $C_{19}H_{25}Cl_2NO_3Ru$ (487.38) (%): C, 46.82; H, 5.17; N, 2.78. ESI HRMS (CH_3OH), positive mode: calcd for [$C_{19}H_{25}ClNO_3^{96}Ru$]$^+$ 446.05936, *m/z* 446.05947 [M − Cl]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.32 (d, ^3J(H,H) =6.9 Hz, 6H, C^gH_3), 2.14 (s, 3H, C^eH_3), 3.00 (sept, ^3J(H,H) =6.9 Hz, 1H, C^fH), 3.43 (s, 3H, OCH_3), 3.73 (t, ^3J(H,H) =5.0 Hz, 2H, OCH_2), 4.51 (t, ^3J(H,H) =5.0 Hz, 2H, $COOCH_2$), 5.26 (d, ^3J(H,H) =6.0 Hz, 2H, C^bH), 5.45 (d, ^3J(H,H) =6.0 Hz, 2H, C^cH), 7.41 (dd, ^3J(H^5,H^4) =7.7 Hz, $^3J_{H5,H6}$ = 5.7 Hz, 1H, H^5), 8.36 (d, ^3J(H,H) =7.7 Hz, 1H, H^4), 9.23 (d, ^3J(H,H) =5.7 Hz, 1H, H^6), 9.63 (s, 1H, H^2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 18.4 (C^e), 22.4 (C^g), 30.8 (C^f), 59.2 (CH_3O), 65.1 (CH_2OOC), 70.3 (CH_2O), 82.5 (C^c), 82.7 (C^b), 97.4 (C^a), 104.0 (C^d), 124.2 (C^5), 127.4 (C^3), 138.7 (C^4), 156.3 (C^2), 158.0 (C^6), 163.6 (*COO*). IR (ATR, cm^{-1}) 3062(w), 2962(w), 2880(w), 1726(s), 1604(w), 1451(w), 1425(w), 1370(w), 1282(s), 1198(m), 1125(s), 1100 (m), 1053(m), 1028(m), 867(m), 802(w), 747(s), 695(m), 666(w), 542 (w), 455(w), 374(w), 284(s), 228(s).

Preparation of {di-μ-[(3-py)COO(C_2H_4O)$_4$CO(3-py)-κ*N*,κ*N*′][RuCl(η^6-*p*-cym)]$_2$} hexafluorido phosphate (10)

The ligand precursor **L4**·2HCl (0.2 mmol, *n* =4) and lithium hydroxide (0.4 mmol) were suspended in isopropanol (20 ml). The reaction mixture was stirred for 1 h at 40 °C. Dichlorido(η^6-*p*-cymene)ruthenium(II) dimer (76 μmol) was added and the orange reaction mixture stirred for an additional 4 h and cooled to room temperature. Dichloromethane (10 ml) was added until the precipitated neutral ruthenium(II) complex was redissolved. Excess ammonium hexafluoridophosphate (1.5 mmol) was added in one portion and solid lithium hydroxide (8 μmol) was added in small portions over 2 h. The crude product precipitated out of the reaction mixture at −47 °C and was redissolved in dichloromethane, filtered and the product was then obtained by evaporation of dichloromethane.

Yield: 40 mg (39%). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.15 (d, ^3J(H,H) =6.9 Hz, 12H, C^gH_3), 1.75 (s, 6H, C^eH_3), 2.58 (sept, ^3J(H,H) =6.9 Hz, 2H, C^fH), 3.68 (m, 16H, OCH_2), 3.78 (m, 8H, OCH_2), 4.49 (m, 8H, $COOCH_2$), 5.72 (d, ^3J(H,H) =5.9 Hz, 4H, C^bH), 5.96 (d, ^3J(H,H) =5.9 Hz, 4H, C^cH), 7.74 (dd, ^3J(H^5,H^4) =7.8 Hz, ^3J(H^5,H^6) =5.8 Hz, 4H, H^5), 8.46 (d, ^3J(H,H) =7.8 Hz, 2H, H^4), 9.43 (m,8H, H^2,H^6). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 18.0 (C^e), 22.4 (C^g), 31.1 (C^f), 66.2 (CH_2COO), 68.9, 70.8, 71.6

(CH_2O), 82.4 (C^c), 88.8 (C^b), 102.1 (C^a), 103.0 (C^d), 127.1 (C^5), 128.4 (C^3), 140.5 (C^4), 153.2 (C^2), 159.3 (C^6), 163.2 (COO). ^{31}P NMR (162 MHz, $CDCl_3$, δ, ppm): −141.7 (sept, J(P,F) =713 Hz, PF_6^-).

In vitro study

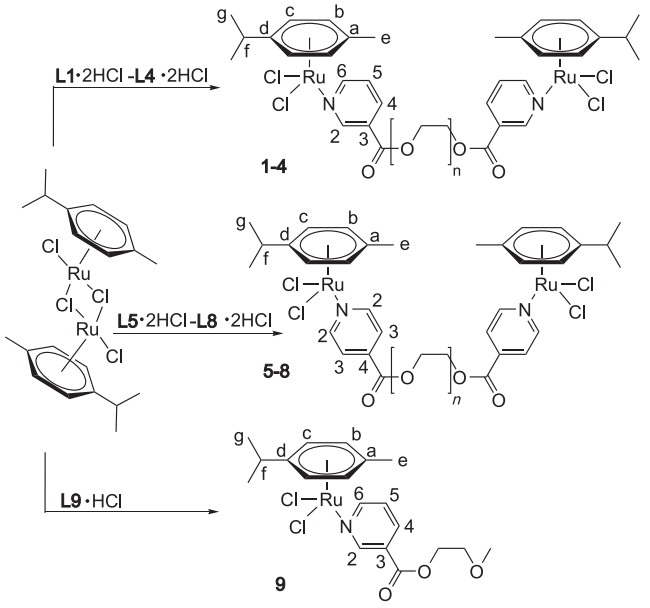
Foetal calf serum, RPMI-1640, phosphate-buffered saline and DMF were obtained from Sigma (St. Louis, MO). Human thyroid carcinoma 8505C, submandibular gland carcinoma A253, breast adenocarcinoma MCF7, melanoma 518A2 and colon cancer SW480 cell lines were obtained from ATCC. Cells were routinely maintained in HEPES-buffered RPMI-1640 medium supplemented with 10% foetal calf serum, 2 mM L-glutamine, 0.01% sodium pyruvate and antibiotics (culture medium) at 37 °C in a humidified atmosphere with 5% CO_2. After standard trypsinization, cells were seeded at a density of 1×10^3–2.5×10^3 cells per well in 96-well plates for viability. Stock solutions of investigated compounds (20 mM) were freshly prepared in DMF and diluted to various working concentrations with medium.

The viability of adherent viable cells was measured using sulforhodamine-B (SRB) assay.[32] Cells were exposed to a wide range of doses of the compounds for 96 h and then fixed with 10% trichloroacetic acid for 2 h at 4 °C. After fixation, cells were washed in distilled water, stained with 0.4% SRB solution for 30 min at room temperature, washed and dried overnight. The dye was dissolved in 10 mM Tris buffer and the absorbance was measured at 540 nm with a reference wavelength of 640 nm. Results are expressed as percentage of control that was arbitrarily set to 100%.

Results and Discussion

Syntheses and Characterization

The reaction of dichlorido(η^6-*p*-cym)ruthenium(II) dimer with one equivalent of ligand precursor, N^N · 2HCl, polyethylene glycol bis(nicotinate) ester dihydrochlorides ((3-py)COO(CH_2CH_2O)$_n$CO(3-py); n =1, **L1** · 2HCl; 2, **L2** · 2HCl; 3, **L3** · 2HCl; 4, **L4** · 2HCl) and polyethylene glycol bis(isonicotinate) dihydrochlorides ((4-py)COO(CH_2CH_2O)$_n$CO(4-py); n =1, **L5** · 2HCl; 2, **L6** · 2HCl; 3, **L7** · 2HCl; 4, **L8** · 2HCl), previously used for the preparation of silver and copper coordination networks,[31,33] affords binuclear ruthenium(II) complexes **1–8** with the general formula [{$RuCl_2(\eta^6$-*p*-cym)}$_2$ μ-(N^N)] (Scheme 1), while starting binuclear ruthenium(II) dimer reacts with ethylene glycol monomethyl ether nicotinate hydrochloride (**L9** · HCl, Scheme 1), in molar ratio 1:2, yielding mononuclear [$RuCl_2(\eta^6$-*p*-cym)((3-py)COO($CH_2CH_2OCH_3$)-κN)] complex. The complexes **1–9** are obtained as orange powders in good to very good yields (60–96%). Compounds **1–9** are stable in air over weeks and are soluble in dichloromethane, acetonitrile and DMF. Slow decomposition occurs in all these solvents and resonances of free *p*-cymene were detected in ^{1}H NMR and ^{13}C NMR spectra.



Scheme 1. Synthesis of binuclear (**1–8**; for *n* see text) and mononuclear (**9**) arene ruthenium(II) complexes and assignment of pyridine part of coordinated ligands (see NMR data in text).

Elemental analyses of all complexes were carried out to prove the composition. ESI MS, recorded in methanol as solvent, gives evidence for molecular composition. Namely, $[M+Na]^+$ ions (for **1**, **5**) or $[M-Cl]^+$ ions (for **9**) in positive mode and $[M+Cl]^-$ ions (for **1–8**) in negative mode are formed.

Ruthenium(II) complexes **1–9** show comparable NMR spectra. The polyethylene oxide spacer protons of bridging ligands give resonances in ^{1}H NMR spectra in the range 4.7–3.5 ppm and pyridine resonances are found from 7.2 to 9.7 ppm. The hydrogen atoms belonging to *p*-cymene ligand give chemical shifts similar to literature values.[29] The *N*-coordination of ligands **L1–L9** generates a strong downfield shift of all proton resonances of the pyridine ring. For instance, the resonances of the protons in o-positions to the coordinated nitrogen atom shift up to 9.6 ppm ($\Delta\delta$ =0.2 ppm) for nicotinate ester ligands and up to 9.3 ppm ($\Delta\delta$ =0.2 ppm) for the isonicotinate moiety (see Experimental section). The same tendencies are observed in ^{13}C NMR spectra and the resonances of the carbon atoms bound to coordinated nitrogen are shifted downfield and found at 158 and 156 ppm for complexes with nicotinate moieties and at 156 ppm for isonicotinate moieties. The region with all the resonances of the polyethylene glycol bridging group remains unchanged below 4.7 ppm in ^{1}H NMR spectra and between 60 and 75 ppm in ^{13}C NMR spectra. Additionally, in ^{13}C NMR spectra of complexes **1–9** the resonances of the carbon atoms from *p*-cymene ligand can be assigned.

In the IR spectra of **1–9** characteristic and most prominent bands are seen and discussed herein. All observed bands in the spectra of the ruthenium(II) complexes remain unchanged in comparison to ligand precursors. Weaker bands are observed near 3020 cm^{-1} for heteroaromatic and aromatic vibrations of C–H bonds of the pyridine ring and the *p*-cymene ligand. The bands near 2980 cm^{-1} are assigned to the C–H vibrations of the alkyl groups. Strong absorption at 1730 cm^{-1} is assigned to the C=O from the ester function, while those found at approximately 1280 and 1110 cm^{-1} are typical bands for carbon–oxygen single bonds.[34] The band at around 750 cm^{-1} also remains unchanged in the same region upon coordination. Those absorptions are slightly stronger than in the ligand precursors, due to the presence of the additional aromatic moiety. The band at 285 cm^{-1} is assigned to the ruthenium–chlorine vibration.[30,35]

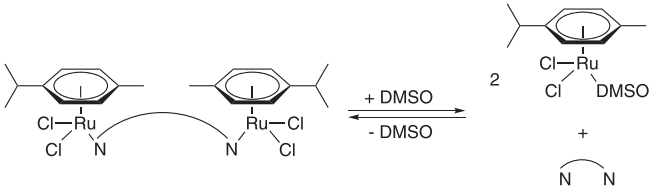
Reversible Dissociation in DMSO

All complexes **1–9** dissociate in DMSO (Scheme 2) and ^{1}H NMR and ^{13}C NMR resonances of the corresponding free ligands and dichlorido(η^6-*p*-cymene)ruthenium(II) were monitored. Partial dissociation is observed if small amounts of DMSO are added to chloroform solutions of the complexes. A higher molar ratio of DMSO in

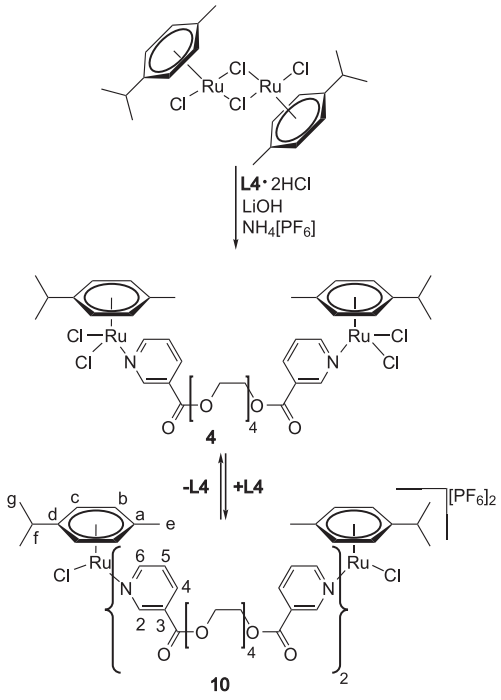
solution corresponds to higher resonance intensities of the dissociated complexes. The complexes are recovered by decreasing the concentration of DMSO (addition of toluene and pentane, cooling to −47 °C, DMSO precipitates) or by precipitation of complex (addition of EtOH, pentane and diethyl ether) from the reaction mixture. Results from this study are in agreement with similar findings for (arene)ruthenium(II) complexes containing *N*-heterocyclic ligands.[36]

Synthesis of cationic binuclear complex 10

Further attempts were made to synthesize a cationic N^N bridged ruthenium(II) complex. After neutralization of ligand precursor **L4** · 2HCl and addition of dichlorido(η^6-*p*-cymene)ruthenium(II), excess of ammonium hexafluoridophosphate and lithium hydroxide, new cationic complex **10** is obtained. The first attempts to synthesize cationic ruthenium(II) complex (Scheme 3) yielded mixtures of complexes with one (**4**) or two coordinated **L4** ligands (**10**). The ratio of product formation was determined using the intensities of the *p*-cymene and pyridine-based ligand resonances. The fast direct reaction to cationic complex **10** and a slow back reaction to the neutral complex **4** are identified using ^{1}H NMR spectroscopy (Fig. S37). A chemical equilibrium is formed in solution between **4** and **10**. This equilibrium is shifted to the formation of cationic complex **10** by multiple additions of lithium hydroxide, in order to neutralize the formed HCl, and complex **10** can be precipitated



Scheme 2. Dissociation and recovery of ruthenium(II) complexes in DMSO.



Scheme 3. Synthesis of cationic complex **10** and assignment of pyridine part of coordinated **L4** ligand (see NMR data in text).

from the reaction mixture. The formation of derivative of complex **4** with just one pyridine-based ligand is also observed, if the isolated cationic ruthenium(II) complex **10** is dissolved in alcohols.

The formation of cationic ruthenium(II) complex **10** is confirmed using multinuclear NMR spectroscopy. The ^{1}H NMR spectrum shows the expected chemical shift pattern as already discussed above for neutral complexes. With reaction **4** → **10** the most prominent changes in the ^{1}H NMR spectra are observed for bound *p*-cymene moiety; thus the proton resonances for the methyl and isopropyl groups are shifted to higher field while those arising from the aromatic protons are shifted downfield. The ^{13}C NMR spectrum shows also the resonance differences for carbon atoms from *p*-cymene moiety in comparison to neutral complexes ($\Delta\delta$ up to 5 ppm). All other carbon resonances are found to be nearly unshifted. The carbon atom resonances of the coordinated *p*-cymene are found at approximately 82.4, 88.8, 102.1 and 103.0 ppm. The ^{31}P NMR spectrum shows the expected septet for the hexafluoridophosphate ion at −141.7 ppm.

Biological Studies

The biological activity of the bidentate ligand precursors **L1** · 2HCl–**L8** · 2HCl, **L9** · HCl and the prepared ruthenium(II) complexes **1–9** was studied *in vitro*. The cells were cultured in the presence of increasing concentrations (up to 100 μM) of the ligand precursors or corresponding ruthenium(II) complexes for 96 h. Afterwards the cell viability was analysed using a sulforhodamine-B (SRB) assay.[32] Results are summarized in Table 1 along with the cytotoxicity data of ruthenium(II) complexes containing nicotinic (nic) and isonicotinic acid (inic) ligands, [$RuCl_2$(η^6-*p*-cym)(nic)] and [$RuCl_2$(η^6-*p*-cym)(inic)], as well as of cisplatin for comparison.

Tested ligand precursors show no cytotoxic activity at investigated concentrations (IC_{50} > 100 μM). Similar results are observed when cells are treated with binuclear complexes **2–8**. Only ruthenium(II) complex **1** shows moderate activity against the investigated cell lines. Complex **1** exhibits higher activity than ruthenium (II) complexes containing nicotinic or isonicotinic acid, but lower activity than cisplatin. Complex **1**, as well as **2–8**, has two equivalents of metal per complex unit relative to cisplatin. Furthermore, mononuclear complex **9**, which possesses a methyl group instead of the second [$RuCl_2$(η^6-*p*-cym)(nic)] moiety in binuclear complex **1** shows no activity against the selected cell lines (IC_{50} > 100 μM). The *in vitro* activity of [$RuCl_2$(η^6-*p*-cym)(nic)] and [$RuCl_2$(η^6-*p*-cym)(inic)] was investigated recently (IC_{50} > 200 μM).[29] Comparing previous results of [$RuCl_2$(η^6-*p*-cym)(nic)] and **1**, it is obvious that the activity of **1** is greater because of the presence of derivatized nicotinic acid ligand. Moreover, the cytotoxicity is influenced by the presence of two ruthenium(II) centres (**1** versus **9**). In comparison to complex **1**, introducing two to four ethylene oxide units in binuclear ruthenium(II) complexes decreases the activity which might be related to the lower lipophilicity of **2–4** than **1**. Furthermore, the use of the isonicotinate instead of nicotinate esters does not result in more active ruthenium(II) complexes. In contrast to these findings, ruthenium(II) complexes with substituted isonicotinates shown in Fig. 1C show much higher activity (2–7 μM).[28] These results give evidence for the importance of the effect of lipophilicity of the tested compounds on the biological activity. Thus, ruthenium(II) complexes containing ligands with more lipophilic side chains, such as alkyl[28] in comparison to polyethylene glycol moieties, are found to be superior in cytotoxic activity than those with more hydrophilic chains.

Table 1. IC_{50} values[a] (in μM) of investigated compounds **L1** · 2HCl–**L8** · 2HCl, **L9** · HCl, **1–9**, $[RuCl_2(\eta^6\text{-}p\text{-cym})(nic)]$ (nic = nicotinic acid), $[RuCl_2(\eta^6\text{-}p\text{-cym})(inic)]$ (inic = isonicotinic acid) and cisplatin

Compound	518A2	8505C	A253	MCF-7	SW480
L1 · 2HCl–**L8** · 2HCl, **L9** · HCl	> 100	> 100	> 100	> 100	> 100
1	53 ± 1	> 100	57 ± 10	80 ± 16	92 ± 11
2	> 100	> 100	> 100	> 100	> 100
3	> 100	> 100	> 100	> 100	> 100
4	> 100	> 100	> 100	> 100	> 100
5	> 100	> 100	> 100	> 100	> 100
6	> 100	> 100	> 100	> 100	> 100
7	> 100	> 100	> 100	> 100	> 100
8	> 100	> 100	> 100	> 100	> 100
9	> 100	> 100	> 100	> 100	> 100
$[RuCl_2(\eta^6\text{-}p\text{-cym})(nic)]$	> 100	> 100	> 100	> 100	> 100
$[RuCl_2(\eta^6\text{-}p\text{-cym})(inic)]$	> 100	> 100	> 100	> 100	> 100
Cisplatin	1.5 ± 0.2	5.0 ± 0.2	20.8 ± 0.1	2.0 ± 0.1	3.2 ± 0.2

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

Conclusions

A series of binuclear dichlorido(η^6-*p*-cymene)ruthenium(II) complexes $[\{RuCl_2(\eta^6\text{-}p\text{-cym})\}_2\ \mu\text{-}(N^{\frown}N)]$ with bridging $N^{\frown}N$ bis(nicotinate)- and bis(isonicotinate)-polyethylene glycol ester ligands, (3-py)COO$(CH_2CH_2O)_n$CO(3-py) and (4-py)COO$(CH_2CH_2O)_n$CO(4-py) respectively (n =1–4), as well as a mononuclear $[RuCl_2(\eta^6\text{-}p\text{-cym})$((3-py)COO$(CH_2CH_2OCH_3)$-$\kappa N$)] complex were synthesized and characterized. Dissociation of the Ru–N bond was observed for all complexes in DMSO and initial complexes were recovered by dilution of DMSO solution. Corresponding cationic complexes containing two bridging $N^{\frown}N$ ligands can be formed as proved by NMR monitoring for complex **10**. The *in vitro* cytotoxicity of ligand precursors and corresponding ruthenium(II) complexes was tested against five human cancer cell lines. From the tested compounds, only complex **1**, with the shortest oxyethylene spacer and nicotinate moieties, exhibited moderate activity (e.g. against 518A2: $IC_{50} = 53 \pm 1$ μM).

Acknowledgements

EHH and GNK gratefully acknowledge the European Union and the Free State of Saxony (project no. 100099597) and DMI, MM and SM the Ministry of Education, Science and Technological Development (project no. 173013).

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