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Arene ruthenium dichloro complexes containing isonicotinic ester ligands: Synthesis, molecular structure and cytotoxicity

Farooq-Ahmad Khan [a], Bruno Therrien [a], Georg Süss-Fink [a,*], Olivier Zava [b], Paul J. Dyson [b]

[a] Institut de Chimie, Université de Neuchâtel, Avenue de Bellevaux 51, CH-2000 Neuchâtel, Switzerland
[b] Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

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ABSTRACT

A series of *p*-cymene ruthenium dichloro complexes containing isonicotinic ester ligands, [(arene)$RuCl_2NC_5H_4$-4-COO$-C_6H_4-p$-O-$(CH_2)_n$-CH_3] (n = 1: **1**, n = 3: **2**, n = 5: **3**, n = 7: **4**, n = 9: **5**, n = 11: **6**, n = 13: **7**, n = 15: **8**), were prepared from *p*-cymene ruthenium dichloro dimer and the corresponding isonicotinic ester ligand. The single-crystal X-ray analysis of **1** shows the molecule to adopt the usual pseudo-tetrahedral piano-stool geometry, the isonicotinic ester ligand being coordinated through the nitrogen atom. The cytotoxicity of all complexes and of the free ligands was studied towards human ovarian cancer cells; high activities were observed only for n = 9 (presenting a chain with ten carbon atoms), both as far as the free ligands and the complexes are concerned. Based on this result, a new isonicotinic ester ligand with a C_{10} substituent containing a terminal alcohol function, NC_5H_4-4-COO$-C_6H_4-p$-O-$(CH_2)_{10}$-OH, was synthesized by a four-step method, and arene ruthenium complexes thereof, [(arene)$RuCl_2NC_5H_4$-4-COO$-C_6H_4-p$-O-$(CH_2)_{10}$-OH] (arene = C_6H_6: **9a**, arene = *p*-$MeC_6H_4Pr^i$: **9b**, arene = C_6Me_6: **9c**) were prepared. The complexes **9a** and **9b** show indeed remarkable anticancer activities, the IC_{50} values for human ovarian cancer cells being in the submicromolar range. The highest cytotoxicity was observed for complex **9b**, with IC_{50} values of 0.18 μM for A2780 and 3.04 μM for the cisplatin-resistant mutant A2780cisR.

1. Introduction

Arene ruthenium complexes containing chlorido ligands are often both lipophilic and water-soluble, which preconditions these organometallics for bio-medical applications, in particular as anticancer agents [1]. The field of antitumoral and antimetastatic arene ruthenium complexes has, in recent years, received considerable attention [2,3], following the first *in vitro* study of arene ruthenium compounds as anticancer agents by Tocher et al. in 1992, who observed a cytotoxicity enhancement by coordinating the anticancer agent metronidazole [1-β-(hydroxyethyl)-2-methyl-5-nitro-imidazole] to a benzene ruthenium dichloro fragment [4]. Prototype arene ruthenium(II) complexes evaluated for anticancer properties include [(*p*-$MeC_6H_4Pr^i$)$RuCl_2$(*P*-pta)] (pta = 1,3,5-triaza-7-phospha-tricyclo-[3.3.1.1]decane), termed RAPTA-C [5], and [(C_6H_5Ph)RuCl(*N*,*N*-en)][PF_6] (en = 1,2-ethylenediamine) [6], although many different classes have since been reported [7]. Recently, we reported highly cytotoxic diruthenium compounds such as [(*p*-$MeC_6H_4Pr^i$)Ru_2(S-*p*-$C_6H_4Me)_3$]Cl [8].

Isonicotinic acid (pyridine-4-carboxylic acid), an isomer of nicotinic acid (pyridine-3-carboxylic acid), is widely used for the synthesis of antibiotics and antituberculosis preparations [9], and it has strong bactericide effects [10]. The encouraging pharmacological profile of isonicotinic acid derivatives coupled with amphiphilic arene ruthenium moieties makes this combination promising for drug design. Thus, Liu et al. recently reported arene ruthenium complexes containing isonicotinic acid, methyl isonicotinate and 5-fluorouracil-1-methyl isonicotinate (5-Fu) ligands, a synergistic effect was observed in the case of the 5-Fu ligand and the *p*-cymene ruthenium fragment [11]. Similar effect was observed by Schobert et al. in a series of arene ruthenium dichloro complexes containing *N*-coordinated oestrogen and androgen isonicotinates [12]. However, Šipka et al. reported only low cytotoxic activity for a series of arene ruthenium complexes with functionalized pyridines including a *p*-cymene ruthenium derivative containing an isonicotinic acid ligand *viz.* [(*p*-$MeC_6H_4Pr^i$)$RuCl_2NC_5H_4COOH$] [13]. Another arene ruthenium complex containing isonicotinic acid as a ligand, namely [(C_6H_6)$RuCl_2NC_5H_4COOH$], was synthesized by Małecki et al., but the biological properties of this complex were not reported [14]. We have been interested in the use of long-chain isonicotinic esters as lipophilic components in order to increase

* Corresponding author. Tel.: +41 32 718 2405; fax: +41 32 718 2511.
E-mail address: georg.suess-fink@unine.ch (G. Süss-Fink).

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the anticancer activity of arene ruthenium complexes. Recently, we found that long-chain isonicotinic ester ligand-stabilized ruthenium(0) nanoparticles, derived from the precursor complex [(*p*-$MeC_6H_4Pr^i$)$RuCl_2NC_5H_4$-4-COO–C_6H_4–*p*-O–$(CH_2)_9$–CH_3] (**5**) show *in vitro* anticancer activity against human ovarian cancer cells [15].

In this paper we report a systematic study of this type of complexes: the synthesis and characterization of *p*-cymene ruthenium complexes containing isonicotinic ester ligands, (arene) $RuCl_2[NC_5H_4$-4-COO–C_6H_4–*p*-O-$(CH_2)_n$-$CH_3]$ (n = 1: **1**, n = 3: **2**, n = 5: **3**, n = 7: **4**, n = 9: **5**, n = 11: **6**, n = 13: **7**, n = 15: **8**) with an even number of carbon atoms in the aliphatic chain (including the known complex **5** [15]), the synthesis and characterization of a new long-chain isonicotinic ester ligand with a C_{10} substituent containing a terminal alcohol function, NC_5H_4-4-COO–C_6H_4–*p*-O–$(CH_2)_{10}$–OH, and of the corresponding ruthenium complexes thereof, [(arene) $RuCl_2NC_5H_4$-4-COO–C_6H_4–*p*-O–$(CH_2)_{10}$–OH] (arene = C_6H_6: **9a**, arene = *p*-$MeC_6H_4Pr^i$: **9b**, arene = C_6Me_6: **9c**) as well as the cytotoxicities of these compounds for human ovarian cancer cells.

2. Results and discussion

2.1. Synthesis of the p-cymene ruthenium complexes 1–8

The dinuclear complex [(*p*-$MeC_6H_4Pr^i$)$RuCl_2]_2$ reacts in dichloromethane with two equivalents of the isonicotinic ester ligands NC_5H_4-4-COO–C_6H_4–*p*-O-$(CH_2)_n$-CH_3 at room temperature to give the neutral complexes [(*p*-$MeC_6H_4Pr^i$)$RuCl_2NC_5H_4$-4-COO–C_6H_4–*p*-O-$(CH_2)_n$-CH_3] (n = 1: **1**, n = 3: **2**, n = 5: **3**, n = 7: **4**, n = 9: **5**, n = 11: **6**, n = 13: **7**, n = 15: **8**) in quantitative yield, see Scheme 1.

All the complexes are obtained as air-stable yellow to yellow-brownish powders, which are soluble in polar organic solvents, in particular in dichloromethane and in chloroform. The complexes are also sparingly soluble in water.

2.2. Single-crystal X-ray structure analysis of 1

Orange crystals of **1** with X-ray diffraction quality were obtained by slow evaporation of a dichloromethane solution. This compound crystallizes in the monoclinic centrosymmetric space group $P2_1/c$. The structure of this complex can be described as pseudo-tetrahedral, having a "piano stool"-like geometry, in which the ruthenium atom is coordinated to the *p*-$MeC_6H_4Pr^i$ ligand, the two chlorido ligands and to the nitrogen atom of the isonicotinic ester ligand. The molecular structure of **1** is shown in Fig. 1, and characteristic distances and angles are summarized in Table 1.

2.3. Anticancer properties of complexes 1–8 and of the free ligands

The *in vitro* cytotoxicity of the complexes [(*p*-$MeC_6H_4Pr^i$) $RuCl_2NC_5H_4$-4-COO–C_6H_4–*p*-O-$(CH_2)_n$-CH_3] (**1**–**8**) and of the corresponding free isonicotinic ester ligands NC_5H_4-4-COO–C_6H_4–*p*-O-$(CH_2)_n$-CH_3 (n = 1, 3, 5, 7, 9, 11, 13, 15) was studied towards the A2780 ovarian cancer cell line and cisplatin-resistant variant A2780cisR using the MTT assay. It was found that the IC_{50} values for both cell lines depend strongly on the length of the carbon chain in the isonicotinic ester ligand (Fig. 2). In particular, complex **5** containing a ten-carbon-atom chain (n = 9) exhibits a very high cytotoxicity towards both cell lines, the IC_{50} values being comparable to those of cisplatin [16]. Indeed, it has been shown previously that arene ruthenium complexes with long aliphatic chains [17] or long perfluorous chains [18] are often very cytotoxic.

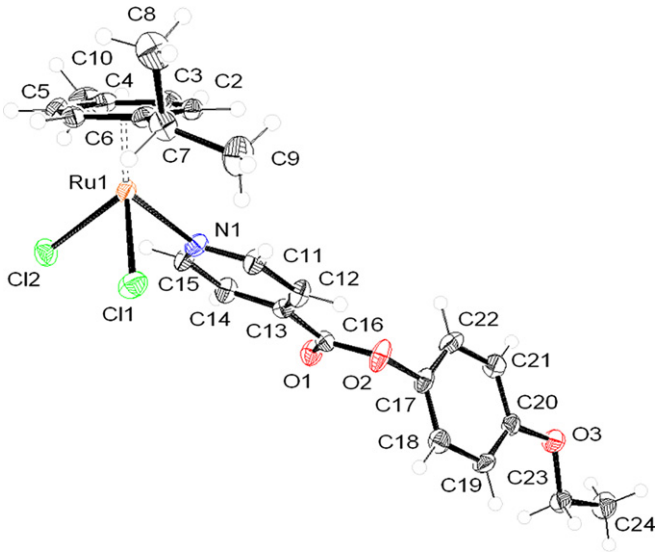


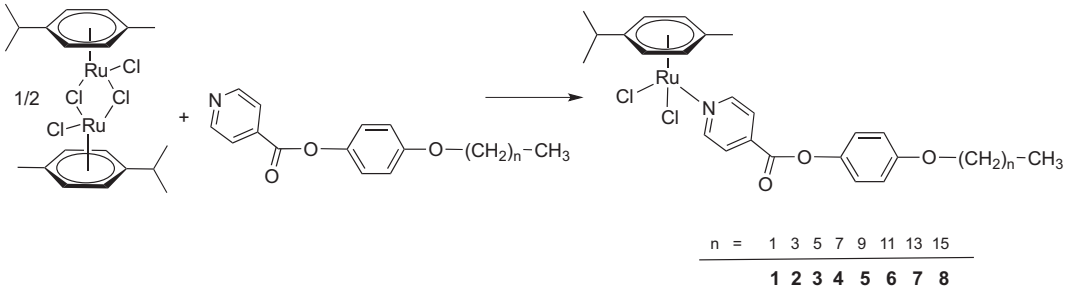
Fig. 1. OREP diagram of complex **1** with 50% probability thermal ellipsoids.

Interestingly, the analogous pyridine complex [(*p*-$MeC_6H_4Pr^i$) $RuCl_2$(py)] is essentially inactive (IC_{50} = 750 μM) under comparable conditions in these cancer cell lines [19], suggesting that the cytotoxicity of isonicotinic ester complexes may be due to the long-chain isonicotinic ligand. This is supported by the low IC_{50} values observed for the free ligands (Fig. 3).

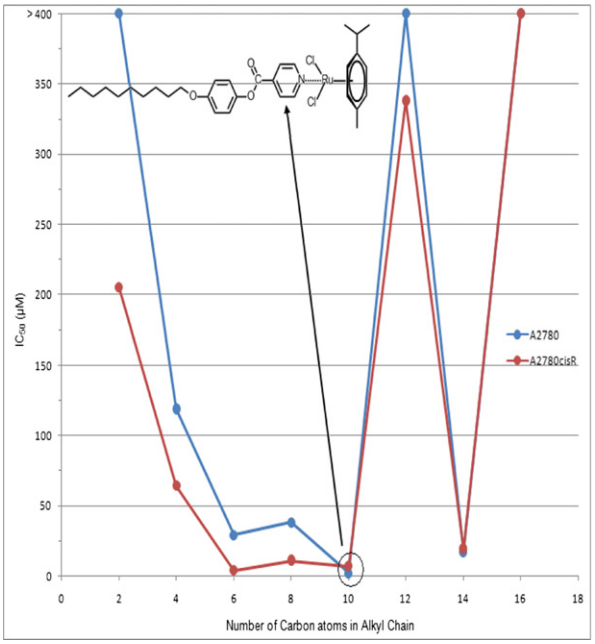
The remarkable dependence of the IC_{50} values on the length of the carbon chain in both, the free isonicotinic ester ligands and of the *p*-cymene ruthenium complexes thereof suggests that for the highest anticancer activity ten carbon atoms in the substituent of the isonicotinic ester are required. This observation prompted us to synthesize a new isoniconitic ester containing a ten-carbon-atom chain with an alcoholic function at the terminal carbon atom in order to increase the hydrophilicity of the complex.

2.4. Synthesis of the isonicotinic ester NC_5H_4-4-COO–C_6H_4–p-O–$(CH_2)_{10}$–OH

The long-chain isonicotinic ester NC_5H_4-4-COO–C_6H_4–*p*-O–$(CH_2)_{10}$–OH was synthesized using a classical four-step method,



Scheme 1.



Compound	A2780 IC_{50} [μM]	A2780cisR IC_{50} [μM]
1 (n = 1)	>400	205
2 (n = 3)	119	64
3 (n = 5)	29	4
4 (n = 7)	38	11
5 (n = 9)	2	7
6 (n = 11)	>400	338
7 (n = 13)	17	19.3
8 (n = 15)	>400	>400
cisplatin [16]	1.6	8.6

Fig. 2. Cytotoxicities of arene ruthenium complexes 1–8 containing isonicotinic ester ligands and graphical representation of carbon atom chain length effect on IC_{50} values of these complexes.

see Scheme 2: Starting by selective bromination of 1,10-decanediol using 48% HBr solution in a liquid–liquid extractor to give 10-bromodecanol [20] (Step 1), the corresponding benzyl ether was obtained by reaction with benzyl hydroquinone in the presence of potassium carbonate and 18-crown-6, according to a literature-modified etherification process [21] (Step 2). The benzyl group was then removed with molecular hydrogen under pressure in the presence of palladium on carbon [22] (Step 3). The isonicotinic ester NC_5H_4-4-COO–C_6H_4–*p*-O–$(CH_2)_{10}$–OH was obtained by reacting isonicotinoyl chloride hydrochloride with the alcohol *viz.* 4-(10-hydroxydecyloxy)phenol (Step 4) [22]. The reaction is done in the presence of triethylamine to bind the HCl eliminated. The full characterization of this new isonictonic ester is presented in the Experimental Part.

2.5. Synthesis of the arene ruthenium complexes **9a**–**c**

The precursors $[(C_6H_6)RuCl_2]_2$, $[(p\text{-}MeC_6H_4Pr^i)RuCl_2]_2$ and $[(C_6Me_6)RuCl_2]_2$ react in dichloromethane as expected with two equivalents of the new isonicotinic ester ligand NC_5H_4-4-COO–C_6H_4–*p*-O–$(CH_2)_{10}$–OH to give the complexes [(arene)Ru-4-COO–C_6H_4–*p*-O–$(CH_2)_{10}$–OH] (arene = C_6H_6: **9a**, arene = *p*-$MeC_6H_4Pr^i$: **9b**, arene = C_6Me_6: **9c**) in quantitative yield, see Scheme 3.

The coordination of the ligand to the ruthenium centre can be concluded from the ^{1}H NMR spectra of the complexes **9a**–**c**, in which the signals for the α-protons in the pyridine ring appear at lower field as compared to those of the corresponding protons in the free ligand. All complexes are obtained as air-stable yellow to brownish-yellow powders, which are soluble in polar organic solvents, in particular in dichloromethane and chloroform. The complexes are also soluble in DMSO and sparingly soluble in water.

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

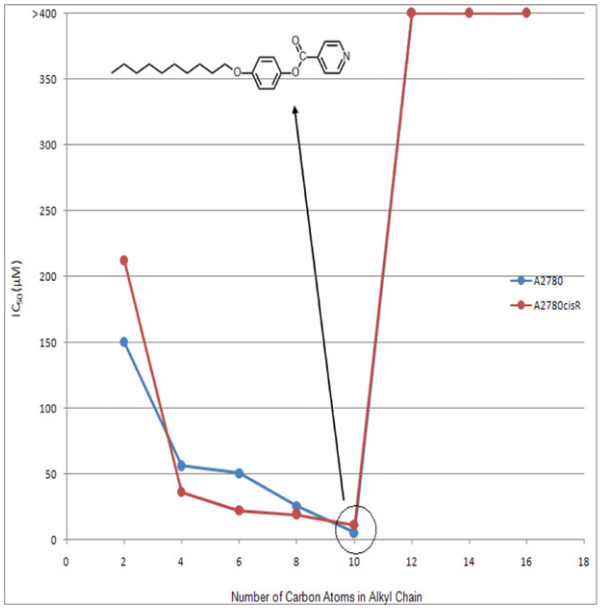
Bond lengths (Å)		Angles (°)	
Ru1–N1	2.142(3)	Cl1–Ru1–N1	85.53(11)
Ru1–C1	2.216(4)	Cl2–Ru1–N1	86.13(9)
Ru1–C2	2.181(4)	Cl1–Ru1–Cl2	88.02(4)
Ru1–C3	2.144(5)	–	–
Ru1–C4	2.177(4)	–	–
Ru1–C5	2.153(4)	–	–
Ru1–C6	2.188(4)	–	–
Ru1–Cl1	2.4251(12)	–	–
Ru1–Cl2	2.3934(11)	–	–

2.6. Anticancer properties of complexes **9a**–**c** and of the free ligand

The *in vitro* cytotoxicity of the complexes [(arene)$RuCl_2NC_5H_4$-4-COO–C_6H_4–*p*-O–$(CH_2)_{10}$–OH] (arene = C_6H_6: **9a**, arene = *p*-$MeC_6H_4Pr^i$: **9b**, arene = C_6Me_6: **9c**) and of the corresponding free isonicotinic ester ligand NC_5H_4-4-COO–C_6H_4–*p*-O–$(CH_2)_{10}$–OH was studied towards the A2780 ovarian cancer cell line and cisplatin-resistant variant A2780cisR using the MTT assay. Surprisingly, the free ligand NC_5H_4-4-COO–C_6H_4–*p*-O–$(CH_2)_{10}$–OH is almost inactive (IC_{50} = 162 μM for A2780 and IC_{50} = 208 μM for A2780cisR), in contrast to its non-hydroxylated analogue NC_5H_4-4-COO–C_6H_4–*p*-O–$(CH_2)_9$–CH_3 (IC_{50} = 5 μM for A2780 and IC_{50} = 11 μM for A2780cisR). However, the arene ruthenium complexes containing the hydroxylated C_{10} ligand are very active, see Table 2. In particular, the *p*-cymene ruthenium complex **9b** containing the hydroxylated C_{10} ligand is, towards the A2780 cell line, ten times more active than the corresponding *p*-cymene ruthenium complex **5** containing the non-hydroxylated C_{10} ligand; towards the cisplatin-resistant A2780 cell line, the introduction of a terminal hydroxyl function into the C_{10} isonicotinic ester ligand increases the anticancer activity by a factor of 2.

3. Conclusions

A systematic series of *p*-cymene ruthenium dichloro complexes containing an isonicotinic ester ligand, the carbon chain length of which varying from 2 to 16 were prepared and evaluated for anticancer activity towards human ovarian cancer cells (A2780 and A2780cisR). A striking activity increase was observed for the complex containing a C_{10} aliphatic chain. A new isonicotinic ester was synthesized by introducing a terminal



Free Ligand	A2780 IC_{50} [μM]	A2780cisR IC_{50} [μM]
n = 1	150	212
n = 3	56	36
n = 5	50	22
n = 7	25	19
n = 9	5	11
n = 11	>400	>400
n = 13	>400	>400
n = 15	>400	>400

Fig. 3. Cytotoxicity values of isonicotinic ester ligands NC_5H_4-4-COO–C_6H_4–*p*-O-$(CH_2)_n$-CH_3 (n = 1, 3, 5, 7, 9, 11, 13, 1) and correlation of IC_{50} values and carbon chain length.

hydroxy group at the end of the C_{10} chain, and the corresponding *p*-cymene ruthenium dichloro complex turned indeed out to be the most active compound. It is too early to say whether these ruthenium compounds exert their cytotoxic effect via a similar mechanism to cisplatin or whether different mechanisms are in operation.

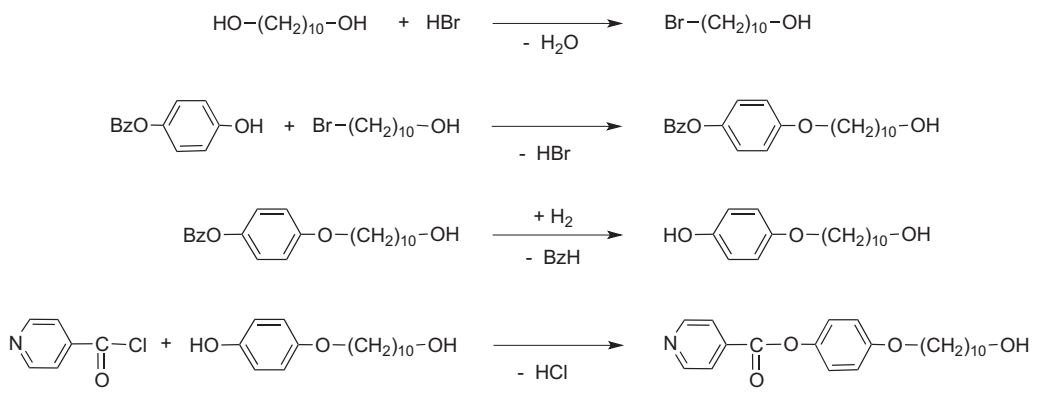
4. Experimental section

4.1. General procedures

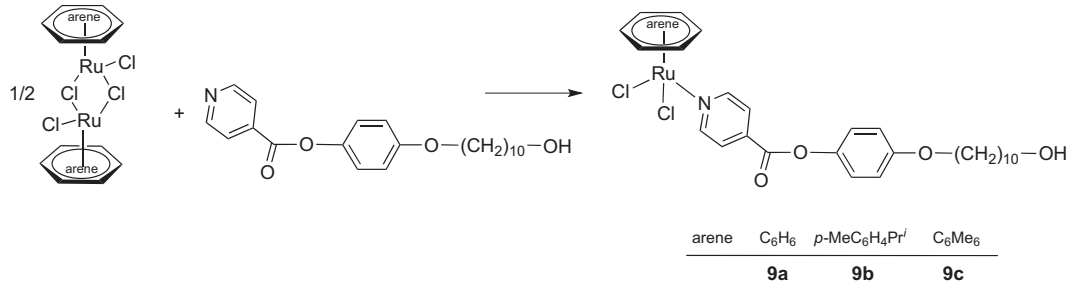
Solvents were dried using appropriate drying agents and distilled prior to use. $RuCl_3 \cdot n\ H_2O$ (Johnson-Matthey), 1-bromoalkanes (Sigma Aldrich), isonicotinoyl chloride hydrochloride (Sigma Aldrich), 4-benzyloxyphenol (Sigma Aldrich) were used as received. NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer at 400.13 (^{1}H) with $SiMe_4$ as internal references and coupling constants are given in Hz. Infrared spectra were recorded on Perkin–Elmer FT-IR spectrometer as KBr pellets. UV–Vis studies were recorded on a UVIKON 930 spectrometer. The compounds $[(C_6H_6)RuCl_2]_2$ [24], $[(p\text{-}MeC_6H_4Pr^i)RuCl_2]_2$ [25], $[(C_6Me_6)RuCl_2]_2$ [26], the 4-(alkyloxy)phenyl isonicotinate ligands [27] (except the new derivative for n = 7, see below) and $[(p\text{-}MeC_6H_4Pr^i)RuCl_2NC_5H_4\text{-}4\text{-}COO\text{–}C_6H_4\text{–}p\text{-}O\text{–}(CH_2)_9\text{–}CH_3]$ (**5**) [15] were prepared according to published methods.

4.2. Cytotoxicity tests (MTT assay)

The cytotoxicity was determined using the MTT assay (MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide). Cells were seeded in 96-well plates as monolayers with 100 μl of cell solution (approximately 20,000 cells) per well and pre-incubated for 24 h in medium supplemented with 10% FCS. Compounds were added as DMSO solutions and serially diluted to the appropriate concentration (to give a final DMSO concentration of 0.5%). 100 μl of drug solution was added to each well and the plates were incubated for another 72 h. Subsequently, MTT (5 mg/ml solution in phosphate buffered saline) 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



Scheme 2.



Scheme 3.

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 is based on means from two independent experiments, each comprising three microcultures per concentration level.

4.3. Crystal structure determination of compound **1**

Single crystal X-ray data for **1** were collected at 173 K (−100 °C) on a Stoe Mark II-Image Plate Diffraction System equipped with a two-circle goniometer and using MoKα graphite monochromated radiation (λ = 0.71073 Å). The structure was solved by direct methods using the program SHELXS-97 [28]. The refinement and all further calculations were carried out using SHELXL-97 [28]. The C-bound H-atoms were included in calculated positions and treated as riding atoms. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2. Crystallographic details are summarized in Table 3. Fig. 1 was drawn with ORTEP [29]. CCDC 853079 (**1**) contains 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.

4.4. Synthesis of the isonicotinic ester NC_5H_4-4-COO—C_6H_4—p-O—$(CH_2)_7$—CH_3

4-Benzyloxyphenol (3 g, 15 mmol) and aqueous potassium hydroxide (0.84 g, 15 mmol in 30 mL water) were stirred in ethanol (125 mL). Then octyl bromide (15 mmol) was added dropwise, and the mixture was refluxed overnight. The following day, water and ethanol were removed under reduced pressure. Dichloromethane (100 mL) was added to the residue, the insoluble potassium bromide was filtered off and discarded. The filtrate was purified by flash chromatography using dichloromethane as mobile phase. The solvent was then removed by evaporation under reduced pressure in order to get a brown residue of 1-(benzyloxy)-4-(octyloxy)benzene, yield: 3.2 g, 68%. ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 7.48–7.35 (m, 5H, C_6H_5), 6.91 (d, ^3J = 9 Hz, 2H, C_6H_4), 6.84 (d, ^3J = 9 Hz, 2H, C_6H_4), 5.01 (s, 2H, CCH_2), 3.91 (t, ^3J = 7 Hz, 2H, OCH_2), 1.75 (quin, ^3J = 7 Hz, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.28 (m, 8H, $(CH_2)_4$), 0.89 (t, ^3J = 7 Hz, 3H, CH_3). 1-(Benzyloxy)-4-(octyloxy)benzene (3.2 g, 10.2 mmol) was deprotected using 10% Pd/C (0.4 mol eq) in a CH_2Cl_2/EtOH mixture (9:1). This mixture was stirred overnight under H_2 pressure (4 bar) at room temperature. Then, Pd/C was removed by filtration, and the solvents were evaporated under reduced pressure in order to give a pale-white residue of 4-octyloxyphenol, yield: 2.1 g, 91%. ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 6.77 (m, 4H, C_6H_4), 4.57 (s, 1H, OH), 3.98 (t, ^3J = 7 Hz, 2H, OCH_2), 1.75 (quin, ^3J = 7 Hz, 2H, CH_2), 1.44 (m, 2H, CH_2), 1.28 (m, 8H, $(CH_2)_4$), 0.89 (t, ^3J = 7 Hz, 3H, CH_3). 4-Octyloxyphenol (1.26 g, 5.7 mmol) and Et_3N (0.8 mL) were dissolved in CH_2Cl_2 (100 mL). Isonicotinoyl chloride hydrochloride (1.06 g, 5.09 mmol) was then added. The reaction mixture was stirred overnight at room temperature. The precipitate was filtered off and discarded, and the solution was evaporated to dryness under reduced pressure. The yellow residue obtained was recrystallized several times from ethanol to give a white product, *viz*. 4-(octyloxy)phenyl isonicotinate, yield: 1.04 g, 56%. (Found: C, 73.26; H, 7.68; N, 4.31. Calc. for $C_{20}H_{25}NO_3$ (M = 327.42): C, 73.37; H, 7.70; N, 4.28%). IR (KBr, cm^{-1}): 3476(m), 2933(s, νCH_2CH_3), 2856(m, νCH_2), 1738(s, $\nu C=O$), 1596(w), 1563(w), 1514(s, νCN_{py}), 1410(m), 1296(m), 1254(m, νOCH_2), 1207(m), 1103(m), 1050(m), 877(m), 821(m), 753(m), 701(m, νNC_5H_4), 553(w), 456(w). UV–vis: (2.30 × 10^{-5} M, CH_2Cl_2, 298 K): λ_{max} 419 nm (ε = 1094 M^{-1} cm^{-1}), λ_{max} 277 nm (ε = 6660 M^{-1} cm^{-1}), λ_{max} 229 nm (ε = 8557 M^{-1} cm^{-1}) ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 8.87 (d, ^3J = 6 Hz, 2H, NC_5H_4), 8.01 (d, ^3J = 6 Hz, 2H, NC_5H_4), 7.13

Table 2
Cytotoxicity values of the arene ruthenium complexes **9a**–**c**.

Complex	A2780 IC_{50} [μM]	A2780cisR IC_{50} [μM]
9a	0.60 ± 0.24	3.56 ± 1.43
9b	0.18 ± 0.07	3.04 ± 1.12
9c	3.00 ± 1.23	9.57 ± 2.14

Table 3
Crystallographic and structure refinement parameters for complex **1**.

Chemical formula	$C_{24}H_{27}Cl_2NO_3Ru$
Formula weight	549.44
Crystal system	Monoclinic
Space group	$P2_1/c$
Crystal colour and shape	Orange block
Crystal size (mm)	0.18 × 0.15 × 0.13
a (Å)	14.3079(9)
b (Å)	8.4712(4)
c (Å)	19.3588(9)
β (°)	99.463(4)
V (Å^3)	2314.5(2)
Z	4
T (K)	173(2)
D_c (g cm^{-3})	1.577
μ (mm^{-1})	0.934
Scan range (°)	$1.44 < \theta < 25.11$
Unique reflections	4107
Observed refls [$I > 2\sigma(I)$]	2909
R_{int}	0.1062
Final R indices [$I > 2\sigma(I)$][a]	R_1 0.0489, wR_2 0.0563
R indices (all data)	R_1 0.0877, wR_2 0.0620
Goodness-of-fit	0.978
Max., min. Δρ (e Å^{-3})	0.566, −0.699

[a] Structures were refined on F_0^2: $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR_2 = [\Sigma[w(F_0^2 - F_c^2)^2]/\Sigma w(F_0^2)^2]^{1/2}$, where $w^{-1} = [\Sigma(F_0^2) + (aP)^2 + bP]$ and $P = [\max(F_0^2, 0) + 2F_c^2]/3$.

(d, ^3J = 9 Hz, 2H, C_6H_4), 6.95 (d, ^3J = 9 Hz, 2H, C_6H_4), 3.98 (t, ^3J = 7 Hz, 2H, OCH_2), 1.83 (quin, ^3J = 7 Hz, 2H, CH_2), 1.46–1.30 (m, 10H, $(CH_2)_5$), 0.91 (t, ^3J = 7 Hz, 3H, CH_3) ppm. $^{113}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.1 (1C, C═O), 157.2 (1C, C–O), 150.8 (2C, NCH), 143.7 (1C, C–O), 136.9 (1C, C_{py}), 123.0 (2C, CH_{py}), 122.0 (2C, CH), 115.1 (2C, CH), 68.4 (1C, OCH_2), 31.8–22.6 (6C, $(CH_2)_6$), 14.1 (1C, CH_3) ppm. MS (ESI) *m/z*: 327 $[M + H]^+$.

4.5. Synthesis of the isonicotinic ester NC_5H_4-4-COO–C_6H_4–p-O–$(CH_2)_{10}$–OH

10-Bromodecanol was synthesized by reported procedures [23]. A typical procedure for the synthesis of 10-bromodecanol is as follows: 1,10-decandiol (25 g, 0.14 mol) and 48% HBr solution (125 mL, 2.2 mol) in 380 mL ligroin were distilled in a liquid–liquid extractor. After 3 days, the organic layer was separated. The solvent was then removed by evaporation under reduced pressure in order to get a dark brown oily residue of 10-bromodecanol, yield: 22.9 g, 67.1%. ^1H NMR (400 MHz, *CDCl*$_3$) δ ppm 3.64 (t, ^3J = 4 Hz, 2H, CH_2Br), 3.41 (t, ^3J = 4 Hz, 2H, CH_2OH), 1.88 (quin, ^3J = 8 Hz, 2H, CH_2), 1.59 (quin, ^3J = 8 Hz, 2H, CH_2), 1.52–1.29 (m, 12H, $(CH_2)_6$). A mixture of 4-benzyloxyphenol (5.0 g, 21 mmol), potassium carbonate (5.6 g, 41 mmol) and 18-crown-6 ether (0.2 g, 0.7 mmol) was stirred in dry acetone (125 mL) for 30 min at room temperature. Then, 1-bromodecanol (2.8 g, 14 mmol) in acetone (25) was added dropwise. This mixture was refluxed under inert atmosphere. After four days, the solution was filtered to eliminate potassium carbonate, and the solvent was removed by evaporation under reduced pressure. The product was further purified by CH_2Cl_2/H_2O extraction, followed by recrystallization in isopropanol, which affords a light brown product, *viz*. 10-(4-(benzyloxy)phenoxy)decanol, yield: 4.46 g, 88.9%. ^1H NMR (400 MHz, *CDCl*$_3$) δ ppm 7.43–7.31 (m, 5H, C_6H_5), 6.91 (d, ^3J = 9 Hz, 2H, C_6H_4), 6.84 (d, ^3J = 9 Hz, 2H, C_6H_4), 5.01 (s, 2H, $C_6H_5CH_2O$), 3.91 (t, ^3J = 6 Hz, 2H, OCH_2), 3.66 (m, 2H, CH_2OH), 1.78 (quin, ^3J = 7 Hz, 2H, CH_2), 1.60 (quin, ^3J = 7 Hz, 2H, CH_2), 1.44–1.31 (m, 12H, $(CH_2)_6$). 10-(4-(Benzyloxy)phenoxy)decanol (0.21 g, 0.6 mmol) was deprotected using 10% Pd/C (0.4 mol eq) in a CH_2Cl_2/EtOH mixture (9:1). This mixture was stirred overnight under H_2 pressure (4 bar) at room temperature. Then, Pd/C was removed by filtration, and the solvents were evaporated under reduced pressure in order to give the white residue of 4-(10-hydroxydecyloxy)phenol, yield: 0.15 g, 95.4%. ^1H NMR (400 MHz, *CDCl*$_3$) δ ppm 6.77 (m, 4H, C_6H_4), 4.48 (s, 1H, OH), 3.91 (t, ^3J = 6, 2H, OCH_2), 3.67 (m, 2H, CH_2OH), 1.76 (quin, ^3J = 6 Hz, 2H, CH_2), 1.58 (m, 2H, CH_2), 1.48–1.21 (m, 12H, $(CH_2)_6$). 4-(10-Hydroxyde)phenol (0.15 g, 0.6 mmol) and Et_3N (0.08 mL) were dissolved in $CHCl_3$ (20 mL). Isonicotinoyl chloride hydrochloride (0.1 g, 0.6 mmol) was then added. The reaction mixture was stirred overnight at room temperature. The yellow precipitate was filtered off and discarded, and the solution was evaporated to dryness. The yellow residue obtained was recrystallized several times from ethanol to give a white product, *viz*. 4-(10-hydroxydecyloxy)phenyl isonicotinate, yield: 1.04 g, 61.4%. (Found: C, 71.05; H, 7.95; N, 3.78. Calc. for $C_{22}H_{29}NO_4$ (*M* = 371.48): C, 71.13; H, 7.87; N, 3.77%). IR (KBr, cm^{-1}): 3471(m), 2934(s, νCH_2CH_3), 2856(m, νCH_2), 2346(w), 1738(s, $\nu C=O$), 1611(w), 1564(w), 1514(s, νCN_{py}), 1410(m), 1295(m), 1255(m, νOCH_2), 1207(m), 1103(m), 1052(m), 877(m), 824(m), 754(m), 701(m, νNC_5H_4), 607(w), 483(w).UV–vis: (1.5×10^{-5} M, CH_2Cl_2, 298 K): λ_{max} 277 nm (ε = 7386 M^{-1} cm^{-1}), λ_{max} 229 nm (ε = 8395 M^{-1} cm^{-1}). ^1H NMR (400 MHz, *CDCl*$_3$) δ ppm 8.86 (s, 2H, NC_5H_4), 8.03 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.13 (d, ^3J = 9 Hz, 2H, C_6H_4), 6.95 (d, ^3J = 9 Hz, 2H, C_6H_4), 3.98 (t, ^3J = 7 Hz, 2H, OCH_2), 3.66 (t, ^3J = 7 Hz, 2H, CH_2OH), 1.83 (quin, ^3J = 7 Hz, 2H, CH_2), 1.9 (quin, ^3J = 7 Hz, 2H, CH_2), 1.46–1.30 (m, 12H, $(CH_2)_6$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.9 (1C, C═O), 157.2 (1C, C–O), 150.3 (2C, NCH), 143.7 (1C, C–O), 137.3 (1C, C_{py}), 123.4 (2C, CH_{py}), 122.0 (2C, CH), 115.1 (2C, CH), 68.4 (1C, OCH_2), 63.0 (1C, CH_2OH), 32.7–25.7 (8C, $(CH_2)_8$) ppm. MS (ESI) *m/z*: 372.4 $[M + H]^+$.

4.6. Synthesis of the arene ruthenium dichloro isonicotinic ester complexes

A mixture of the appropriate $[(arene)RuCl_2]_2$ and 2 equivalents of the isonicotinic ester ligand in CH_2Cl_2 solution (25 mL) was stirred for 3 h at room temperature. The solvent was then removed under reduced pressure, and the residue was re-dissolved in EtOH (30 mL). The solution was filtered and then evaporated to dryness, and the final product was collected and dried *in vacuo*.

4.6.1. $[(p\text{-}MeC_6H_4Pr^i)RuCl_2NC_5H_4\text{-}4\text{-}COO\text{–}C_6H_4\text{–}p\text{-}O\text{–}CH_2\text{–}CH_3]$ (**1**)

Yield: 0.0816 g, >99%. (Found: C, 52.59; H, 5.08; N, 2.54. Calc. for $C_{24}H_{27}NO_3Cl_2Ru$ (*M* = 549.46): C, 52.46; H, 4.95; N, 2.55%). IR (KBr, cm^{-1}): 3481(s), 2935(m, νCH_2CH_3), 2868(w, νCH_2), 2363(w), 1748(s, $\nu C=O$), 1613(m), 1589(w), 1507(s, νCN_{py}), 1417(m), 1273(m), 1190(s, νOCH_2), 1100(s), 1089(s), 878(m), 826(m), 768(m), 696(w, νNC_5H_4), 607(w), 483(w). UV–vis: (1.0×10^{-5} M, CH2Cl2, 298 K): λ_{max} 337 nm (ε = 5552 M^{-1} cm^{-1}), λ_{max} 277 nm (ε = 10,259 M^{-1} cm^{-1}), λ_{max} 229 nm (ε = 21,320 M^{-1} cm^{-1}). ^1H NMR (400 MHz, *CDCl*$_3$) δ ppm 9.32 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.99 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.12 (d, ^3J = 8 Hz, 2H, C_6H_4), 6.95 (d, ^3J = 8 Hz, 2H, C_6H_4), 5.48 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 5.26 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 4.05 (q, ^3J = 6 Hz, 2H, OCH_2), 3.01 (sept, ^3J = 7 Hz, 1H, CH), 2.12 (s, 3H, CH_3), 1.42 (t, ^3J = 7 Hz, 3H, CH_3), 1.32 (d, ^3J = 7 Hz, 6H, $(CH_3)_2$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9 (1C, C═O), 157.2 (1C, C–O), 156.0 (2C, NCH), 143.6 (1C, C–O), 138.3 (1C, C_{py}), 123.8 (2C, CH_{py}), 122.0 (2C, CH), 115.3 (2C, CH), 103.9 (1C, C_{arene}), 97.5(1C, C_{arene}), 83.2(2C, CH_{arene}), 82.4(2C, CH_{arene}), 63.9 (1C, OCH_2), 30.8 (1C, $CH(CH_3)_2$), 22.3 (2C, $(CH_3)_2$) 18.3(1C, CH_3),14.8 (1C, CH_3) ppm.

4.6.2. $[(p\text{-}MeC_6H_4Pr^i)RuCl_2NC_5H_4\text{-}4\text{-}COO\text{–}C_6H_4\text{–}p\text{-}O\text{–}(CH_2)_3\text{–}CH_3]$ (**2**)

Yield: 0.0908 g, >99%. (Found: C, 53.79; H, 5.50; N, 2.41. Calc. for $C_{26}H_{31}NO_3Cl_2Ru$ (*M* = 577.51): C, 54.07; H, 5.41; N, 2.43. IR (KBr, cm^{-1}): 3480(s), 2935(s, νCH_2CH_3), 2867(m, νCH_2), 2366(w), 1748(s, $\nu C=O$), 1611(m), 1592(w), 1505(s, νCN_{py}), 1488(m), 1406(m), 1251(m), 1194(s, νOCH_2), 1100(s), 1094(s), 878(m), 826(s), 691(w, νNC_5H_4), 607(w), 487(w). UV–vis: (1.1×10^{-5} M, CH_2Cl_2, 298 K): λ_{max} 337 nm (ε = 4740 M^{-1} cm^{-1}), λ_{max} 278 nm (ε = 7900 M^{-1} cm^{-1}), λ_{max} 229 nm (ε = 18,544 M^{-1} cm^{-1}). ^1H NMR (400 MHz, *CDCl*$_3$) δ ppm 9.32 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.99 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.12 (d, ^3J = 8 Hz, 2H, C_6H_4), 6.95 (d, ^3J = 8 Hz, 2H, C_6H_4), 5.48 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 5.26 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 3.97 (t, ^3J = 6 Hz, 2H, OCH_2), 3.01 (sept, ^3J = 7 Hz, 1H, CH), 2.13 (s, 3H, CH_3), 1.81 (quin, ^3J = 6 Hz, 2H, CH_2), 1.49 (m, 2H, CH_2), 1.34 (d, ^3J = 7 Hz, 6H, $(CH_3)_2$), 1.00 (t, ^3J = 7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9 (1C, C═O), 157.4 (1C, C–O), 156.0 (2C, NCH), 143.5 (1C, C–O), 138.4 (1C, C_{py}), 123.8 (2C, CH_{py}), 122.0 (2C, CH), 115.3 (2C, CH), 103.9 (1C, C_{arene}), 97.5(1C, C_{arene}), 83.2(2C, CH_{arene}), 82.4(2C, CH_{arene}), 68.2 (1C, OCH_2), 31.3 (1C, $CH(CH_3)_2$), 30.7 (1C, CH_2), 22.3 (2C, $(CH_3)_2$), 19.2 (1C, CH_2), 18.3 (1C, CH_3), 14.8 (1C, CH_3) ppm.

4.6.3. $[(p\text{-}MeC_6H_4Pr^i)RuCl_2NC_5H_4\text{-}4\text{-}COO\text{–}C_6H_4\text{–}p\text{-}O\text{–}(CH_2)_5\text{–}CH_3]$ (**3**)

Yield: 0.0964 g, >99%. (Found: C, 55.75; H, 5.85; N, 2.34. Calc. for $C_{28}H_{35}NO_3Cl_2Ru$ (*M* = 605.56): C, 55.54; H, 5.83; N, 2.31%). IR (KBr, cm^{-1}): 3489(m), 2937(s, νCH_2CH_3), 2867(m, νCH_2), 2373(w), 1748(s, $\nu C=O$), 1611(m), 1592(w), 1505(s, νCN_{py}), 1488(m), 1417(m), 1251(m), 1190(s, νOCH_2), 1099(s), 1089(s), 878(m), 826(s), 691(w, νNC_5H_4), 607(w), 486(w). UV–vis: (0.7×10^{-5} M, CH_2Cl_2, 298 K): λ_{max} 337 nm (ε = 7176 M^{-1} cm^{-1}), λ_{max} 278 nm (ε = 11,960 M^{-1} cm^{-1}), λ_{max}

229 nm ($\varepsilon = 28{,}073\ M^{-1}\ cm^{-1}$). ^1H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.31 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.99 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.12 (d, ^3J = 8 Hz, 2H, C_6H_4), 6.95 (d, ^3J = 8 Hz, 2H, C_6H_4), 5.48 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 5.26 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 3.96 (t, ^3J = 6 Hz, 2H, OCH_2), 3.01 (sept, ^3J = 7 Hz, 1H, CH), 2.12 (s, 3H, CH_3), 1.79 (quint, ^3J = 6 Hz, 2H, CH_2), 1.47 (m, 2H, CH_2), 1.34–1.29 (m, 10H, $(CH_3)_2$ and $(CH_2)_2$), 0.92 (t, ^3J = 7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9 (1C, C=O), 157.4 (1C, C–O), 156.0 (2C, NCH), 143.5 (1C, C–O), 138.4 (1C, C_{py}), 123.8 (2C, CH_{py}), 122.0 (2C, CH), 115.3 (2C, CH), 103.9 (1C, C_{arene}), 97.5(1C, C_{arene}), 83.2(2C, CH_{arene}), 82.4(2C, CH_{arene}), 68.5 (1C, OCH_2), 31.6 (1C, $CH(CH_3)_2$), 30.7–22.6 (4C, $(CH_2)_4$), 22.3 (2C, $(CH_3)_2$), 18.3 (1C, CH_3), 14.1 (1C, CH_3) ppm.

4.6.4. [(p-$MeC_6H_4Pr^i$)$RuCl_2NC_5H_4$-4-COO–C_6H_4–p-O–$(CH_2)_7$–CH_3] (**4**)

Yield: 0.1052 g, >99%. (Found: C, 57.08; H, 6.23; N, 2.23. Calc. for $C_{30}H_{39}NO_3Cl_2Ru$ (M = 633.62): C, 56.87; H, 6.20; N, 2.21%). IR (KBr, cm^{-1}): 3477(s), 2933(s, νCH_2CH_3), 2865(m, νCH_2), 2367(w), 1748(s, νC = O), 1613(m), 1589(w), 1496(s, νCN_{py}), 1456(m), 1405(m), 1251(m), 1192(s, νOCH_2), 1099(s), 1086(s), 878(m), 826(s), 691(w, νNC_5H_4), 607(w), 488(w). UV–vis: (0.8×10^{-5} M, CH_2Cl_2, 298 K): λ_{max} 337 nm ($\varepsilon = 3747\ M^{-1}\ cm^{-1}$), λ_{max} 278 nm ($\varepsilon = 6673\ M^{-1}\ cm^{-1}$), λ_{max} 229 nm (ε = 16,052 $M^{-1}\ cm^{-1}$). ^1H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.31 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.98 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.12 (d, ^3J = 8 Hz, 2H, C_6H_4), 6.94 (d, ^3J = 8 Hz, 2H, C_6H_4), 5.49 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 5.26 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 3.95 (t, ^3J = 6 Hz, 2H, OCH_2), 3.01 (sept, ^3J = 7 Hz, 1H, CH), 2.12 (s, 3H, CH_3), 1.80 (quin, ^3J = 6 Hz, 2H, CH_2), 1.47 (m, 2H, CH_2), 1.32–1.26 (m, 14H, $(CH_3)_2$ and $(CH_2)_4$), 0.91 (t, ^3J = 7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9 (1C, C=O), 157.4 (1C, C–O), 156.0 (2C, NCH), 143.5 (1C, C–O), 138.4 (1C, C_{py}), 123.8 (2C, CH_{py}), 122.0 (2C, CH), 115.3 (2C, CH), 103.9 (1C, C_{arene}), 97.5(1C, C_{arene}), 83.2(2C, CH_{arene}), 82.4(2C, CH_{arene}), 68.5 (1C, OCH_2), 31.8 (1C, $CH(CH_3)_2$), 30.7–22.7 (6C, $(CH_2)_6$), 22.3 (2C, $(CH_3)_2$), 18.3 (1C, CH_3), 14.1 (1C, CH_3) ppm.

4.6.5. [(p-$MeC_6H_4Pr^i$)$RuCl_2NC_5H_4$-4-COO–C_6H_4–p-O–$(CH_2)_{11}$–CH_3] (**6**)

Yield: 0.1087 g, >99%. (Found: C, 59.27; H, 6.81; N, 2.04. Calc. for $C_{34}H_{47}NO_3Cl_2Ru$ (M = 689.73): C, 59.21; H, 6.87; N, 2.03%). IR (KBr, cm^{-1}): 3485(s), 2927(s, νCH_2CH_3), 2862(m, νCH_2), 2362(w), 1749(m, νC = O), 1611(m), 1591(w), 1496(s, νCN_{py}), 1454(m), 1405(m), 1251(m), 1192(s, νOCH_2), 1099(s), 1088(s), 878(m), 826(s), 691(w, νNC_5H_4), 607(w), 485(w). UV–vis: (0.7×10^{-5} M, CH_2Cl_2, 298 K): λ_{max} 337 nm (ε = 6535 $M^{-1}\ cm^{-1}$), λ_{max} 277 nm (ε = 13,238 $M^{-1}\ cm^{-1}$), λ_{max} 229 nm (ε = 25,689 $M^{-1}\ cm^{-1}$). ^1H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.31 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.99 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.12 (d, ^3J = 8 Hz, 2H, C_6H_4), 6.95 (d, ^3J = 8 Hz, 2H, C_6H_4), 5.48 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 5.26 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 3.96 (t, ^3J = 6 Hz, 2H, OCH_2), 3.01 (sept, ^3J = 7 Hz, 1H, CH), 2.13 (s, 3H, CH_3), 1.79 (quin, ^3J = 6 Hz, 2H, CH_2), 1.46 (m, 2H, CH_2), 1.33–1.26 (m, 22H, $(CH_3)_2$ and $(CH_2)_8$), 0.88 (t, ^3J = 7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9 (1C, C=O), 157.4 (1C, C–O), 156.0 (2C, NCH), 143.5 (1C, C–O), 138.4 (1C, C_{py}), 123.8 (2C, CH_{py}), 122.0 (2C, CH), 115.3 (2C, CH), 103.9 (1C, C_{arene}), 97.5(1C, C_{arene}), 83.2(2C, CH_{arene}), 82.4(2C, CH_{arene}), 68.5 (1C, OCH_2), 31.8 (1C, $CH(CH_3)_2$), 30.7–22.7 (10C, $(CH_2)_{10}$), 22.3 (2C, $(CH_3)_2$), 18.3 (1C, CH_3), 14.2 (1C, CH_3) ppm.

4.6.6. [(p-$MeC_6H_4Pr^i$)$RuCl_2NC_5H_4$-4-COO–C_6H_4–p-O–$(CH_2)_{13}$–CH_3] (**7**)

Yield: 0.1237 g, >99%. (Found: C, 60.30; H, 7.08; N, 1.98. Calc. for $C_{36}H_{51}NO_3Cl_2Ru$ (M = 717.78): C, 60.24; H, 7.16; N, 1.95%). IR (KBr, cm^{-1}): 3476(m), 2927(s, νCH_2CH_3), 2858(m, νCH_2), 2359(w), 1749(m, νC = O), 1612(m), 1589(w), 1505(s, νCN_{py}), 1456(m), 1405(m), 1251(m), 1192(s, νOCH_2), 1097(s), 1087(s), 877(m), 826(s), 795(w), 691(w, νNC_5H_4), 607(w), 483(w). UV–vis: (0.7×10^{-5} M, CH_2Cl_2, 298 K): λ_{max} 337 nm ($\varepsilon = 5098\ M^{-1}\ cm^{-1}$), λ_{max} 277 nm ($\varepsilon = 9253\ M^{-1}\ cm^{-1}$), λ_{max} 229 nm ($\varepsilon = 19{,}935\ M^{-1}\ cm^{-1}$). ^1H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.32 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.99 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.12 (d, ^3J = 8 Hz, 2H, C_6H_4), 6.95 (d, ^3J = 8 Hz, 2H, C_6H_4), 5.48 (d, ^3J = 5 Hz, 2H, RuC_6H_4), 5.26 (d, ^3J = 5 Hz, 2H, RuC_6H_4), 3.96 (t, ^3J = 6 Hz, 2H, OCH_2), 3.01 (sept, ^3J = 7 Hz, 1H, CH), 2.13 (s, 3H, CH_3), 1.79 (quin, ^3J = 6 Hz, 2H, CH_2), 1.46 (m, 2H, CH_2), 1.34–1.26 (m, 26H, $(CH_3)_2$ and $(CH_2)_{10}$), 0.88 (t, ^3J = 7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9 (1C, C=O), 157.4 (1C, C–O), 156.0 (2C, NCH), 143.5 (1C, C–O), 138.4 (1C, C_{py}), 123.8 (2C, CH_{py}), 122.0 (2C, CH), 115.3 (2C, CH), 103.9 (1C, C_{arene}), 97.5(1C, C_{arene}), 83.2(2C, CH_{arene}), 82.4(2C, CH_{arene}), 68.5 (1C, OCH_2), 31.8 (1C, $CH(CH_3)_2$), 30.7–22.7 (12C, $(CH_2)_{12}$), 22.3 (2C, $(CH_3)_2$), 18.3 (1C, CH_3), 14.2 (1C, CH_3) ppm.

4.6.7. [(p-$MeC_6H_4Pr^i$)$RuCl_2NC_5H_4$-4-COO–C_6H_4–p-O–$(CH_2)_{15}$–CH_3] (**8**)

Yield: 0.1219 g, >99%. (Found: C, 61.33; H, 7.34; N, 1.89. Calc. for $C_{38}H_{55}NO_3Cl_2Ru$ (M = 745.83): C, 61.20; H, 7.43; N, 1.88%). IR (KBr, cm^{-1}): 3481(m), 2926(s, νCH_2CH_3), 2856(m, νCH_2), 2361(w), 1749(s, νC = O), 1612(m), 1587(w), 1506(s, νCN_{py}), 1417(m), 1251(m), 1191(s, νOCH_2), 1097(m), 1087(m), 877(m), 826(m), 766(w), 691(w, νNC_5H_4), 607(w), 472(w). UV–vis: (0.8×10^{-5} M, CH_2Cl_2, 298 K): λ_{max} 337 nm ($\varepsilon = 4118\ M^{-1}\ cm^{-1}$), λ_{max} 277 nm ($\varepsilon = 7569\ M^{-1}\ cm^{-1}$), λ_{max} 229 nm (ε = 17,483 $M^{-1}\ cm^{-1}$). ^1H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.32 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.99 (d, ^3J = 5 Hz, 2H, NC_5H_4), 7.12 (d, ^3J = 8 Hz, 2H, C_6H_4), 6.95 (d, ^3J = 8 Hz, 2H, C_6H_4), 5.48 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 5.26 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 3.96 (t, ^3J = 6 Hz, 2H, OCH_2), 3.01 (sept, ^3J = 7 Hz, 1H, CH), 2.13 (s, 3H, CH_3), 1.79 (qint, ^3J = 6 Hz, 2H, CH_2), 1.46 (m, 2H, CH_2), 1.34–1.26 (m, 30H, $(CH_3)_2$ and $(CH_2)_{12}$), 0.88 (t, ^3J = 7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9 (1C, C=O), 157.4 (1C, C–O), 156.0 (2C, NCH), 143.5 (1C, C–O), 138.4 (1C, C_{py}), 123.8 (2C, CH_{py}), 122.0 (2C, CH), 115.3 (2C, CH), 103.9 (1C, C_{arene}), 97.5(1C, C_{arene}), 83.2(2C, CH_{arene}), 82.4(2C, CH_{arene}), 68.5 (1C, OCH_2), 31.8 (1C, $CH(CH_3)_2$), 30.7–22.7 (14C, $(CH_2)_{14}$), 22.3 (2C, $(CH_3)_2$), 18.3 (1C, CH_3), 14.2 (1C, CH_3) ppm.

4.6.8. [$(C_6H_6)RuCl_2NC_5H_4$-4-COO–C_6H_4–p-O–$(CH_2)_{10}$–OH] (**9a**)

Yield: 0.2536 g, >99%. (Found: C, 52.70; H, 5.62; N, 2.25. Calc. for $C_{28}H_{35}NO_4Cl_2Ru \cdot 0.25\ CH_2Cl_2$ (M = 642.09): C, 52.79; H, 5.57; N, 2.18%). IR (KBr, cm^{-1}): 3471(s), 2931(s, νCH_2CH_3), 2862(m, νCH_2), 2361(w), 1743(m, νC = O), 1613(m), 1583(w), 1496(s, νCN_{py}), 1405(m), 1253(m), 1192(s, νOCH_2), 1096(s), 1053(s), 877(m), 825(s), 691(w, νNC_5H_4), 607(w), 486(w). UV–vis: (0.8×10^{-5} M, CH_2Cl_2, 298 K): λ_{max} 328 nm (ε = 4937 $M^{-1}\ cm^{-1}$), λ_{max} 277 nm ($\varepsilon = 6502\ M^{-1}\ cm^{-1}$), λ_{max} 229 nm ($\varepsilon = 19{,}597\ M^{-1}\ cm^{-1}$). ^1H NMR (400 MHz, *CD_2Cl_2*) δ ppm 9.38 (d, ^3J = 7 Hz, 2H, NC_5H_4), 8.01 (d, ^3J = 7 Hz, 2H, NC_5H_4), 7.13 (d, ^3J = 9 Hz, 2H, C_6H_4), 6.95 (d, ^3J = 9 Hz, 2H, C_6H_4), 5.71 (s, 6H, C_6H_6), 3.98 (t, ^3J = 7 Hz, 2H, OCH_2), 3.67 (dt, ^3J = 6 Hz, ^3J = 7 Hz, 2H, CH_2OH), 1.79 (quin, ^3J = 7 Hz, 2H, CH_2), 1.58 (m, 2H, CH_2), 1.46–1.33 (m, 12H, $(CH_2)_6$), 1.20 (t, ^3J = 6 Hz, 1H, OH). $^{13}C\{^1H\}$ NMR (100 MHz, CDCl3): δ 162.8 (1C, C=O), 157.5 (1C, C–O), 156.4 (2C, NCH), 143.5 (1C, C–O), 128.4 (1C, C_{py}), 124.2 (2C, CH_{py}), 122.0 (2C, CH), 115.3 (2C, CH), 85.0 (6C, C_6H_6), 68.5 (1C, OCH_2), 63.1 (1C, CH_2OH), 32.8–25.8 (8C, $(CH_2)_8$) ppm.

4.6.9. [(p-$MeC_6H_4Pr^i$)$RuCl_2NC_5H_4$-4-COO–C_6H_4–p-O–$(CH_2)_{10}$–OH] (**9b**)

Yield: 0.2219 g, >99%. (Found: C, 56.13; H, 6.29; N, 2.08. Calc. for $C_{32}H_{43}NO_4Cl_2Ru \cdot 0.1\ CH_2Cl_2$ (M = 685.56): C, 56.19; H, 6.35; N, 2.04%). IR (KBr, cm^{-1}): 3474(s), 2930(s, νCH_2CH_3), 2862(m, νCH_2), 2367(w), 1747(s, νC = O), 1612(m), 1589(w), 1496(s, νCN_{py}), 1454(m), 1404(m), 1251(m), 1192(s, νOCH_2), 1100(s), 1054(s), 877(m), 825(s),

691(w, νNC_5H_4), 608(w), 484(w). UV–vis: (0.6×10^{-5} M, CH_2Cl_2, 298 K): λ_{max} 329 nm (ε = 5530 M^{-1} cm^{-1}), λ_{max} 277 nm (ε = 9914 M^{-1} cm^{-1}), λ_{max} 229 nm (ε = 24,297 M^{-1} cm^{-1}). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.32 (d, ^3J = 6 Hz, 2H, NC_5H_4), 8.00 (d, ^3J = 6 Hz, 2H, NC_5H_4), 7.13 (d, ^3J = 9 Hz, 2H, C_6H_4), 6.95 (d, ^3J = 9 Hz, 2H, C_6H_4), 5.49 (d, ^3J = 6 Hz, 2H, RuC_6H_4), 5.26 (d,^3J = 6 Hz, 2H, RuC_6H_4), 3.98 (t, ^3J = 6 Hz, 2H, OCH_2), 3.66 (dt, ^3J = 6 Hz, ^3J = 7 Hz, 2H, CH_2OH), 3.02 (sept, ^3J = 7 Hz, 1H, CH), 2.13 (s, 3H, CH_3), 1.79 (quin, ^3J = 6 Hz, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.48–1.28 (m, 18H, $(CH_3)_2$ and $(CH_2)_6$), 1.21 (t, ^3J = 6 Hz, 1H, OH). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9 (1C, C=O), 157.4 (1C, C–O), 156.1 (2C, NCH), 143.5 (1C, C–O), 138.3 (1C, C_{py}), 123.9 (2C, CH_{py}), 122.0 (2C, CH), 115.3 (2C, CH), 103.8 (1C, C_{arene}), 97.6(1C, C_{arene}), 83.3(2C, CH_{arene}), 82.6(2C, CH_{arene}), 85.0 (6C, C_6H_6), 68.5 (1C, OCH_2), 63.1 (1C, CH_2OH), 32.8–25.8 (8C, $(CH_2)_8$), 30.8 (1C, $CH(CH_3)_2$), 22.4 (2C, $(CH_3)_2$), 18.4 (1C, CH_3) ppm.

4.6.10. [(C_6Me_6)$RuCl_2NC_5H_4$-4-COO–C_6H_4–p-O–$(CH_2)_{10}$–OH] (**9c**)

Yield: 0.2136 g, >99%. (Found: C, 57.16; H, 6.70; N, 2.02. Calc. for $C_{34}H_{47}NO_4Cl_2Ru \cdot 0.1\ CH_2Cl_2$ (M = 714.21): C, 57.35; H, 6.66; N, 1.96%). IR (KBr, cm^{-1}): 3481(s), 2929(s, νCH_2CH_3), 2861(m, νCH_2), 2356(w), 1746(s, $\nu C=O$), 1611(m), 1587(w), 1496(s, νCN_{py}), 1454(m), 1404(m), 1278(m), 1250(m), 1188(s, νOCH_2), 1090(s), 1053(s), 877(m), 825(s), 689(w, νNC_5H_4), 607(w), 482(w). UV–vis: (1.0×10^{-5} M, CH_2Cl_2, 298 K): λ_{max} 329 nm (ε = 2318 M^{-1} cm^{-1}), λ_{max} 277 nm (ε = 5422 M^{-1} cm^{-1}), λ_{max} 229 nm (ε = 14,890 M^{-1} cm^{-1}). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.10 (d, ^3J = 6 Hz, 2H, NC_5H_4), 7.97 (d, ^3J = 6 Hz, 2H, NC_5H_4), 7.13 (d, ^3J = 9 Hz, 2H, C_6H_4), 6.95 (d, ^3J = 9 Hz, 2H, C_6H_4), 3.98 (t, ^3J = 6 Hz, 2H, OCH_2), 3.66 (dt, ^3J = 5 Hz, ^3J = 6 Hz, 2H, CH_2OH), 2.02 (s, 18H, $C_6(CH_3)_6$), 1.79 (quin, ^3J = 6 Hz, 2H, CH_2), 1.59 (m, 2H, CH_2), 1.47–1.26 (m, 12H, $(CH_2)_6$), 1.22 (t, ^3J = 5 Hz, 1H, OH). $^{13}C\{^1H\}$ NMR (100 MHz, CDCl3): δ 163.0 (1C, C=O), 157.3 (1C, C–O), 155.7 (2C, NCH), 143.2 (1C, C–O), 137.6 (1C, C_{py}), 123.6 (2C, CH_{py}), 121.9 (2C, CH), 115.2 (2C, CH), 91.6 (6C, (C_6)), 68.4 (1C, OCH_2), 63.0 (1C, CH_2OH), 32.8–25.7 (8C, $(CH_2)_8$), 15.4 (6C, $(CH_3)_6$) ppm.

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