Thermoresponsive Organometallic Arene Ruthenium Complexes for Tumour Targeting

Catherine M. Clavel, Emilia Păunescu, Patrycja Nowak-Sliwinska and Paul J. Dyson

C. M. Clavel, Dr. E. Păunescu, Dr. P. Nowak-Sliwinska, Prof. P. J. Dyson
Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne (Switzerland)
Dr. P. Nowak-Sliwinska
Department of Urology, University Hospital (CHUV), Lausanne, Switzerland

Supplementary Information

Synthesis and characterization of the compounds

$RuCl_3 \cdot 3H_2O$ was obtained from Precious Metals Online. All other reagents were purchased from Aldrich, AlfaAesar, and Acros Chemicals and used without further purification. Reactions were performed with solvents dried using dry-columns and collected and used under a N_2 atmosphere. The $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ dimer was prepared and purified according to a literature procedure.[1] Reactions were performed under N_2 using conventional Schlenk techniques and complexation reactions with $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ were performed in the absence of light. During the synthesis of the ligands the reactions were monitored by TLC using Merck TLC Silicagel coated aluminium sheets 60 F_{254} and hexane/EtOAc (2:3) as the eluent and visualized with a UV lamp at 254 nm following staining with $KMnO_4$. Purification of the ligands was carried out using flash column chromatography using a Varian 971-FP Autocolumn purification machine and pre-packed Silicagel columns (Luknova flash columns, 40–60 μm) with a hexane/EtOAc mixture in gradient as eluent.

^1H (400.13 MHz), ^{19}F (188.30 MHz) and ^{13}C (100.62 MHz) NMR spectra were recorded on a Bruker Avance II 400 spectrometer at 298 K. The chemical shifts are reported in parts per million (ppm) and referenced to deuterated solvent residual peaks for ^1H and ^{13}C ($CDCl_3$: ^1H δ 7.26, $^{13}C\{^1H\}$ δ 77.16 ppm)[2] and coupling constants (J) are reported in Hertz (Hz). IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR Spectrometer at room temperature. Electrospray ionization mass spectra (ESI-MS) were obtained on a Thermo-Finnigan LCQ Deca XP Plus quadropole ion-trap instrument operated in positive-ion mode. Elemental analysis was carried out by the microanalytical laboratory at the Institute of Chemical Sciences and Engineering (EPFL). Melting points were determined using a SMP3 Stuart Melting Point Apparatus and are uncorrected.

General procedure for the synthesis of the ligands ester derivatives L1a-L1d and L2a-L2c

To a suspension of 3-(pyridin-3-yl)propanoic acid (1 equiv.) in CH_2Cl_2 (50 mL), EDCI (*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride) (1 equiv.) was added and the mixture stirred at r.t. for 15 min. The appropriate alcohol (1 equiv.) and DMAP (4-(dimethylamino)pyridine) (0.2 equiv.) were added and the reaction mixture was stirred at r.t. for about 7 days. The mixture was diluted with CH_2Cl_2 (100 mL) washed with H_2O (200 mL), then the aqueous phase re-extracted with CH_2Cl_2 (2 x 100 mL), and the organic phases washed with brine (200 mL), and dried over

anhydrous Na_2SO_4 and concentrated under reduced pressure. Solid deposition on Celite and purification by flash column chromatography afforded the desired compounds in good yield.

Octyl-3-(pyridin-3-yl)propanoate (L1a)

3-(Pyridin-3-yl)propanoic acid (0.650 g, 4.30 mmol, 1 equiv.), 1-octanol (0.683 mL, 4.30 mmol, 1 equiv.), EDCI (0.824 g, 4.30 mmol, 1 equiv.) and DMAP (0.111 g, 0.860 mmol, 0.2 equiv.) in CH_2Cl_2 (50 mL). The product was isolated as a pale yellow oil (1.097 g, η = 97%).

R_f (Hex/EtOAc 6:4 (v/v)) = 0.28.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.48 (1H, s, N_{py}-C*H*-C), 8.46 (1H, d, N_{py}-C*H*-CH, $^3J_{H,H}$ = 4.7 Hz), 7.53 (1H, d, N_{py}-CH-C-C*H*, $^3J_{H,H}$ = 7.7 Hz), 7.21 (1H, dd, N_{py}-CH-C*H*-CH, $^3J_{H,H}$ = 7.7Hz, $^3J_{H,H}$ = 4.7 Hz), 4.06 (2H, t, O-C*H*$_2$-CH_2, $^3J_{H,H}$ = 6.7 Hz), 2.95 (2H, t, C*H*$_2$-CH_2-C=O, $^3J_{H,H}$ = 7.5 Hz), 2.64 (2H, t, CH_2-C*H*$_2$-C=O, $^3J_{H,H}$ = 7.5 Hz), 1.56-1.61 (2H, m, O-CH_2-C*H*$_2$), 1.20-1.38 (10H, m br, O-$(CH_2)_2$-C*H*$_2$, O-$(CH_2)_3$-C*H*$_2$, C*H*$_2$-$(CH_2)_2$-CH_3, C*H*$_2$-CH_2-CH_3, C*H*$_2$-CH_3), 0.88 (3H, t, CH_2-C*H*$_3$, $^3J_{H,H}$ = 6.9 Hz).

^{13}C-NMR ($CDCl_3$) δ_C, ppm: 172.2 (1C, CH_2-*C*=O), 149.8 (1C, N_{py}-*C*H-C), 147.7 (1C, N_{py}-*C*H-CH), 135.8 (1C, N_{py}-CH-*C*-CH), 135.7 (1C, N_{py}-CH-C-*C*H), 123.2 (1C, N_{py}-CH-*C*H), 64.7 (1C, O-*C*H_2-CH_2), 35.3 (1C, CH_2-C*H*$_2$-C=O), 31.7 (1C, *C*H_2-CH_2-C=O), 29.1 (1C, O-$(CH_2)_3$-*C*H_2), 29.1 (1C, *C*H_2-$(CH_2)_2$-CH_3), 28.5 (1C, *C*H_2-CH_2-CH_3), 28.0 (1C, O-CH_2-*C*H_2), 25.8 (1C, O-$(CH_2)_2$-*C*H_2), 22.5 (1C, *C*H_2-CH_3), 14.0 (1C, CH_2-*C*H_3).

IR (ν, cm^{-1}): 2925-2855 (CH_2, CH_3), 1731 (C=O), 1575, 1424-1479 (*Py* C=C, C=N), 1177 (C-O).

ESI-MS(+): *m/z* found 264.33 $[M+H]^+$, calcd. for $C_{16}H_{25}NO_2$ 263.38.

Anal. (%) calcd. for $C_{16}H_{25}NO_2$: C 72.96, H 9.57, N 5.32; found: C 73.13, H 9.55, N, 5.59.

Decyl-3-(pyridin-3-yl)propanoate (L1b)

3-(pyridin-3-yl)propanoic acid (0.650 g, 4.30 mmol, 1 equiv.), 1-decanol (0.820 mL, 4.30 mmol, 1 equiv.), EDCI (0.824 g, 4.30 mmol, 1 equiv.) and DMAP (0.111 g, 0.860 mmol, 0.2 equiv.) in CH_2Cl_2 (50 mL). The product was isolated as a pale yellow oil (1.067 g, η = 85%).

R_f (Hex/EtOAc 6:4 (v/v)) = 0.29.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.48 (1H, s, N_{py}-C*H*-C), 8.46 (1H, d, N_{py}-C*H*-CH, $^3J_{H,H}$ = 4.6 Hz), 7.52 (1H, d, N_{py}-CH-C-C*H*, $^3J_{H,H}$ = 7.7 Hz), 7.21 (1H, dd, N_{py}-CH-C*H*-CH, $^3J_{H,H}$ = 7.7 Hz, $^3J_{H,H}$ = 4.6 Hz), 4.05 (2H, t, O-C*H*$_2$-CH_2, $^3J_{H,H}$ = 6.8 Hz), 2.95 (2H, t, C*H*$_2$-CH_2-C=O, $^3J_{H,H}$ = 7.6 Hz), 2.64 (2H, t, CH_2-C*H*$_2$-C=O, $^3J_{H,H}$ = 7.6 Hz), 1.54-1.61 (2H, m, O-CH_2-C*H*$_2$), 1.19-1.37 (14H, m br, O-CH_2-CH_2-C*H*$_2$, O-CH_2-$(CH_2)_2$-C*H*$_2$, OCH_2-$(CH_2)_3$-C*H*$_2$, C*H*$_2$-$(CH_2)_3$-CH_3, C*H*$_2$-$(CH_2)_2$-CH_3, C*H*$_2$-CH_2-CH_3, C*H*$_2$-CH_3), 0.88 (3H, t, CH_2-C*H*$_3$, $^3J_{H,H}$ = 6.7 Hz).

^{13}C-NMR ($CDCl_3$) δ_C, ppm: 172.1 (1C, CH_2-*C*=O), 149.7 (1C, N_{py}-*C*H-C), 147.6 (1C, N_{py}-*C*H-CH), 135.7 (1C, N_{py}-CH-*C*-CH), 135.6 (1C, N_{py}-CH-C-*C*H), 123.1 (1C, N_{py}-CH-*C*H), 64.6 (1C, O-*C*H_2-CH_2), 35.2 (1C, CH_2-C*H*$_2$-C=O), 31.7 (1C, *C*H_2-CH_2-C=O), 29.3 (1C, O-$(CH_2)_4$-*C*H_2), 29.3 (1C, *C*H_2-$(CH_2)_3$-CH_3), 29.1 (1C, O-$(CH_2)_3$-*C*H_2), 29.0 (1C, *C*H_2-$(CH_2)_2$-CH_3), 28.4 (1C, *C*H_2-CH_2-*C*H_3), 27.9 (1C, O-CH_2-*C*H_2), 25.7 (1C, O-$(CH_2)_2$-*C*H_2), 22.5 (1C, *C*H_2-CH_3), 13.9 (1C, CH_2-*C*H_3).

IR (ν, cm^{-1}): 2922-2853 (CH_2, CH_3), 1732 (C=O), 1575, 1479-1424 (*Py* C=C, C=N), 1179 (C-O).

ESI-MS(+): *m/z* found 292.33 $[M+H]^+$, calcd. for $C_{18}H_{29}NO_2$ 291.43.

Anal. (%) calcd. for $C_{18}H_{29}NO_2$ C 74.18, H 10.03, N 4.81; (found) C 74.22, H 9.87, N 5.14.

Dodecyl-3-(pyridin-3-yl)propanoate (L1c)

3-(Pyridin-3-yl)propanoic acid (0.650 g, 4.30 mmol, 1 equiv.), 1-dodecanol (0.960 mL, 4.30 mmol, 1 equiv.), EDCI (0.824 g, 4.30 mmol, 1 equiv.) and DMAP (0.111 g, 0.860 mmol, 0.2 equiv.) in CH_2Cl_2 (50 mL). The product was isolated as a pale yellow oil (1.196 g, η = 87%).

R_f (Hex/EtOAc 6:4 (v/v)) = 0.32.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.47 (1H, s, N_{py}-C*H*-C), 8.45 (1H, d, N_{py}-C*H*-CH, $^3J_{H,H}$ = 4.7 Hz), 7.52 (1H, d, N_{py}-CH-C-C*H*, $^3J_{H,H}$ = 7.8 Hz), 7.20 (1H, dd, N_{py}-CH-C*H*-CH, $^3J_{H,H}$ = 7.8 Hz, $^3J_{H,H}$ = 4.7 Hz), 4.05 (2H, t, O-C*H*$_2$-CH_2, $^3J_{H,H}$ = 6.8 Hz), 2.95 (2H, t, C*H*$_2$-CH_2-C=O, $^3J_{H,H}$ = 7.5 Hz), 2.63 (2H, t, CH_2-C*H*$_2$-C=O, $^3J_{H,H}$ = 7.5 Hz), 1.54-1.61 (2H, m, -O-CH_2-C*H*$_2$), 1.28-1.35 (18H, m br, O-$(CH_2)_2$-C*H*$_2$, O-$(CH_2)_3$-C*H*$_2$, O-$(CH_2)_4$-C*H*$_2$, O-$(CH_2)_5$-C*H*$_2$, C*H*$_2$-$(CH_2)_4$-CH_3, C*H*$_2$-$(CH_2)_3$-CH_3, C*H*$_2$-$(CH_2)_2$-CH_3, C*H*$_2$-CH_2-CH_3, C*H*$_2$-CH_3), 0.87 (3H, t, CH_2-C *H*$_3$, $^3J_{H,H}$ = 6.9 Hz).

^{13}C-NMR ($CDCl_3$) δ_C, ppm: 172.5 (1C, CH_2-*C*=O), 150.0 (1C, N_{py}-*C*H-C), 147.9 (1C, N_{py}-*C*H-CH), 136.2 (1C, N_{py}-CH-*C*-CH), 135.9 (1C, N_{py}-CH-C-*C*H), 123.5 (1C, N_{py}-CH-*C*H), 65.0 (1C, O-*C*H_2-CH_2), 35.5 (1C, CH_2-*C*H_2-C=O), 32.0 (1C, *C*H_2-CH_2-C=O), 29.8 (2C, O-$(CH_2)_5$-*C*H_2, *C*H_2-$(CH_2)_4$-*C*H_3), 29.7 (1C, O-$(CH_2)_4$-*C*H_2), 29.6 (1C, *C*H_2-$(CH_2)_3$-CH_3), 29.5 (1C, O-$(CH_2)_3$-*C*H_2), 29.3 (1C, *C*H_2-$(CH_2)_2$-CH_3), 28.7 (1C, *C*H_2-CH_2-*C*H_3), 28.3 (1C, O-CH_2-*C*H_2), 26.0 (1C, O-$(CH_2)_2$-*C*H_2), 22.8 (1C, *C*H_2-CH_3), 14.2 (1C, CH_2-*C*H_3).

IR (ν, cm^{-1}): 2922-2852 (CH_2, CH_3), 1733 (C=O), 1575, 1479-1424 (*Py* C=C, C=N), 1178 (C-O).

ESI-MS(+): *m/z* found 320.42 $[M+H]^+$, calcd. for $C_{20}H_{33}NO_2$ 319.48.

Anal. (%) calcd. for $C_{20}H_{33}NO_2$ C 75.19, H 10.41, N 4.38; (found) C 75.13, H 10.24, N 4.76.

Octadecyl-3-(pyridin-3-yl)propanoate (L1d)

3-(Pyridin-3-yl)propanoic acid (0.800 g, 5.29 mmol, 1equiv.), 1-octadecanol (1.432 g, 5.29 mmol, 1 equiv.), EDCI (1.015 g, 5.29 mmol, 1 equiv.) and DMAP (0.065 g, 0.53 mmol, 0.1 equiv.) in CH_2Cl_2 (250 mL). The product was isolated as a white solid (1.658 g, η = 78%).

M.p. (^{o}C): 47.5-48.5.

R_f (Hex/EtOAc 8:2 (v/v)) = 0.29.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.49 (2H, m, N_{py}-C*H*-C, N_{py}-C*H*-CH), 7.51 (1H, d, N_{py}-CH-C-C*H*, $^3J_{H,H}$ = 7.6 Hz), 7.20 (1H, m, N_{py}-CH-C*H*), 4.04 (2H, t, O-C*H*$_2$-CH_2, $^3J_{H,H}$ = 6.7 Hz), 2.94 (2H, t, C*H*$_2$-CH_2-C=O, $^3J_{H,H}$ = 7.5 Hz), 2.62 (2H, t, CH_2-C*H*$_2$-C=O, $^3J_{H,H}$ = 7.5 Hz), 1.56 (2H, m, O-CH_2-C*H*$_2$), 1.15-1.35 (30H, m br, O-$(CH_2)_2$-C*H*$_2$, O-$(CH_2)_3$-C*H*$_2$, O-$(CH_2)_4$-C*H*$_2$, O-$(CH_2)_5$-C*H*$_2$, O-$(CH_2)_6$-C*H*$_2$, O-$(CH_2)_7$-C*H*$_2$, C*H*$_2$-$(CH_2)_8$-CH_3, C*H*$_2$-$(CH_2)_7$-CH_3, C*H*$_2$-$(CH_2)_6$-CH_3, C*H*$_2$-$(CH_2)_5$-CH_3, C*H*$_2$-$(CH_2)_4$-CH_3, C*H*$_2$-$(CH_2)_3$-CH_3, C*H*$_2$-$(CH_2)_2$-CH_3, C*H*$_2$-CH_2-CH_3, C*H*$_2$-CH_3), 0.86 (3H, t, CH_2-C*H*$_3$, $^3J_{H,H}$ = 6.8 Hz).

^{13}C-NMR ($CDCl_3$) δ_C, ppm: 172.5 (1C, CH_2-*C*=O), 150.0 (1C, N_{py}-*C*H-C), 147.9 (1C, N_{py}-*C*H-CH), 136.1 (1C, N_{py}-CH-*C*-CH), 135.9 (1C, N_{py}-CH-C-*C*H), 123.5 (1C, N_{py}-CH-*C*H), 65.0 (1C, O-*C*H_2-CH_2), 35.5 (1C, CH_2-*C*H_2-C=O), 32.0 (1C, *C*H_2-CH_2-C=O), 29.8 (8C, O-$(CH_2)_5$-*C*H_2, O-$(CH_2)_6$-*C*H_2, O-$(CH_2)_7$-*C*H_2, O-$(CH_2)_8$-*C*H_2, *C*H_2-$(CH_2)_7$-*C*H_3), *C*H_2-$(CH_2)_6$-*C*H_3), *C*H_2-$(CH_2)_5$-*C*H_3), *C*H_2-$(CH_2)_4$-*C*H_3), 29.7 (1C, O-$(CH_2)_4$-*C*H_2), 29.6 (1C, *C*H_2-$(CH_2)_3$-CH_3), 29.5 (1C, O-$(CH_2)_3$-*C*H_2), 29.3 (1C, *C*H_2-$(CH_2)_2$-CH_3), 28.7 (1C, *C*H_2-CH_2-*C*H_3), 28.2 (1C, O-CH_2-*C*H_2), 26.0 (1C, O-$(CH_2)_2$-*C*H_2), 23.0 (1C, *C*H_2-CH_3), 14.2 (1C, CH_2-*C*H_3).

IR (ν, cm^{-1}): 2953-2848 (CH_2, CH_3), 1726 (C=O), 1575, 1474-1425 (*Py* C=C, C=N), 1188 (C-O).

ESI-MS(+) *m/z* found 404.35 $[M+H]^+$, calcd. for $C_{26}H_{45}NO_2$ 403.64.

Anal. (%) calcd. for $C_{26}H_{45}NO_2$ C 77.37, H 11.24, N 3.47; found C 77.32, H 11.06, N 3.43.

1*H*,1*H*,2*H*,2*H*-Perfluorooctyl-3-(pyridin-3-yl)propanoate (L2a)

3-(Pyridin-3-yl)propanoic acid (0.650 g, 4.30 mmol, 1 equiv.), 1*H*,1*H*,2*H*,2*H*-perfluoro-1-octanol (0.932 mL, 4.30 mmol, 1 equiv.), EDCI (0.824 g, 4.30 mmol, 1 equiv.) and DMAP (0.111 g, 0.860 mmol, 0.2 equiv.) in CH_2Cl_2 (50 mL). The product was isolated as a pale yellow oil (2.057 g, η = 96%).

R_f (Hex/EtOAc 5:5 (v/v)) = 0.2.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.40 (1H, s, N_{py}-C*H*-C), 8.38 (1H, d, N_{py}-C*H*-CH, $^3J_{H,H}$ = 4.8 Hz), 7.44 (1H, d, N_{py}-CH-C-C*H*, $^3J_{H,H}$ = 7.6 Hz), 7.12 (1H, dd, N_{py}-CH-C*H* , $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 4.8 Hz), 4.29 (2H, t, O-CH_2-CH_2, $^3J_{H,H}$ = 6.4 Hz), 2.88 (2H, t, CH_2-CH_2-C=O, $^3J_{H,H}$ = 7.5 Hz), 2.59 (2H, t, CH_2-CH_2-C=O, $^3J_{H,H}$ = 7.5 Hz), 2.29-2.41 (2H, m, O-CH_2-CH_2).

^{13}C-NMR ($CDCl_3$) δ_C, ppm: 171.9 (1C, CH_2-*C*=O), 149.8 (1C, N_{py}-*C*H-C), 147.9 (1C, N_{py}-*C*H-CH), 135.7 (1C, N_{py}-CH-C-*C*H), 135.6 (1C, N_{py}-CH-*C*-CH), 123.3 (1C, N_{py}-CH-*C*H), 105.8-121.5 (6C, m series, CH_2-*C*F_2-CF_2, CH_2-CF_2-*C*F_2 , CH_2-$(CF_2)_2$-*C*F_2, *C*F_2-CF_2-CF_3, CF_2-*C*F_2-CF_3, CF_2-CF_2-*C*F_3), 56.4 (1C, t, O-*C*H_2-CH_2, $^3J_{C,F}$ = 4 Hz), 35.0 (1C, CH_2-*C*H_2-C=O), 30.6 (1C, t, O-CH_2-*C*H_2, $^2J_{C,F}$ = 22 Hz), 28.1 (1C, *C*H_2-CH_2-C=O).

^{19}F-NMR ($CDCl_3$) δ_F, ppm: -80.77 (3F, t, C*F*$_3$, $^3J_{F,F}$ = 9.6 Hz), -113.63 (2F, m, CH_2-C*F*$_2$-CF_2), -121.87 (2F, m, CH_2-$(CF_2)_2$-C*F*$_2$), -122.88 (2F, m, C*F*$_2$-CF_2-CF_3), -123.59 (2F, m, CH_2-CF_2-C*F*$_2$), -126.11 (2F, m, C*F*$_2$-CF_3).

IR (ν, cm^{-1}): 2953-2931 (CH_2), 1740 (C=O), 1576, 1480, 1425 (*Py* C=C, C=N), 1232-1081 (CF_2, CF_3), 1187 (C-O).

ESI-MS(+) *m/z* found 498.06 $[M+H]^+$, calcd. for $C_{16}H_{12}F_{13}NO_2$ 497.25.

Anal. (%) calcd. for $C_{16}H_{12}F_{13}NO_2$ C 38.65, H 2.43, N 2.82; found C 39.01, H 2.76, N 2.88.

1*H*,1*H*,2*H*,2*H*-Perfluorodecyl-3-(pyridin-3-yl)propanoate (L2b)

3-(Pyridin-3-yl)propanoic acid (0.650 g, 4.30 mmol, 1 equiv.), 1*H*,1*H*,2*H*,2*H*-perfluoro-1-decanol (1.996 g, 4.30 mmol, 1 equiv.), EDCI (0.824 g, 4.30 mmol, 1 equiv.) and DMAP (0.111 g, 0.860 mmol, 0.2 equiv.) in CH_2Cl_2 (50 mL). The product was isolated as a pale yellow solid (2.124 g, η = 83%).

M.p. (^{o}C): 39.5-41.5.

R_f (Hex/EtOAc 5:5 (v/v)) = 0.24.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.47-8.48 (2H, m, N_{py}-C*H*-C, N_{py}-C*H*-CH), 7.54 (1H, d, N_{py}-CH-C-C*H*, $^3J_{H,H}$ = 7.7 Hz), 7.23 (1H, dd, N_{py}-CH-C*H*, $^3J_{H,H}$ = 7.7 Hz, $^3J_{H,H}$ = 4.8 Hz), 4.38 (2H, t, O-CH_2-CH_2, $^3J_{H,H}$ = 6.4 Hz), 2.97 (2H, t, CH_2-CH_2-C=O, $^3J_{H,H}$ = 7.5 Hz), 2.68 (2H, t, CH_2-CH_2-C=O, $^3J_{H,H}$ = 7.5 Hz), 2.37-2.50 (2H, m, O-CH_2-CH_2).

^{13}C-NMR ($CDCl_3$) δ_C, ppm: 171.9 (1C, CH_2-*C*=O), 149.9 (1C, N_{py}-*C*H-C), 148.0 (1C, N_{py}-*C*H-CH), 135.8 (1C, N_{py}-CH-C-*C*H), 135.6 (1C, N_{py}-CH-*C*-CH), 123.7 (1C, N_{py}-CH-*C*H), 104.8-121.8 (8C, m series, CH_2-*C*F_2-CF_2, CH_2-CF_2-*C*F_2, CH_2-$(CF_2)_2$-*C*F_2, CH_2-$(CF_2)_3$-*C*F_2, *C*F_2-$(CF_2)_2$-CF_3, *C*F_2-CF_2-CF_3, CF_2-*C*F_2-CF_3, CF_2-CF_2-*C*F_3), 56.5 (1C, t, O-*C*H_2-CH_2, $^3J_{C,F}$ = 4 Hz), 35.1 (1C, CH_2-*C*H_2-C=O), 30.5 (1C, t, O-CH_2-*C*H_2, $^2J_{C,F}$ = 22 Hz), 27.9 (1C, *C*H_2-CH_2-C=O).

^{19}F-NMR ($CDCl_3$) δ_F, ppm: -80.73 (3F, t, C*F*$_3$, $^3J_{F,F}$ = 9.7Hz), -113.62 (2F, m, CH_2-C*F*$_2$-CF_2), -121.85 (6F, m, CH_2-$(CF_2)_2$-C*F*$_2$, CH_2-$(CF_2)_3$-C*F*$_2$, C*F*$_2$-$(CF_2)_2$-CF_3), -122.69 (2F, m, C*F*$_2$-CF_2-CF_3), -123.53 (2F, m, CH_2-CF_2-C*F*$_2$), -126.08 (2F, m, C*F*$_2$-CF_3).

IR (ν, cm^{-1}): 2951-2935 (CH_2), 1730 (C=O), 1574, 1482, 1425 (*Py* C=C, C=N), 1242-1116 (CF_2, CF_3), 1198 (C-O).

ESI-MS(+) *m/z* found 598.08 $[M+H]^+$, calcd. for $C_{18}H_{12}F_{17}NO_2$ 597.27.

Anal. (%) calcd. for $C_{18}H_{12}F_{17}NO_2$ C 36.20, H 2.03, N 2.35; found C 35.85, H 2.08, N 2.29.

1*H*,1*H*,2*H*,2*H*-Perfluorododecyl-3-(pyridin-3-yl)propanoate (L2c)

3-(pyridin-3-yl)propanoic acid (0.263 g, 1.74 mmol, 1 equiv.), 1*H*,1*H*,2*H*,2*H*-perfluoro-1-dodecanol (0.983 g, 1.74 mmol, 1 equiv.), EDCI (0.334 g, 1.74 mmol, 1 equiv.) and DMAP (0.021 g, 0.174 mmol, 0.1 equiv.) in CH_2Cl_2 (250 mL). The product was isolated as a pale yellow solid (0.884 g, η = 73%).

M.p. (°C): 78.5-79.5.

R_f (Hex/EtOAc 4:6 (v/v)) = 0.33.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.47 (2H, m, N_{py}-C*H*-C, N_{py}-C*H*-CH), 7.50 (1H, d, N_{py}-CH-C-C*H*, $^3J_{H,H}$ = 7.6 Hz), 7.19 (1H, dd, N_{py}-CH-C*H*, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 4.8 Hz), 4.36 (2H, t, O-C*H*$_2$-CH_2, $^3J_{H,H}$ = 6.5 Hz), 2.94 (2H, t, C*H*$_2$-CH_2-C=O, $^3J_{H,H}$ = 7.5 Hz), 2.65 (2H, t, CH_2-C*H*$_2$-C=O, $^3J_{H,H}$ = 7.5 Hz), 2.34-2.47 (2H, m, O-CH_2-C*H*$_2$).

^{13}C-NMR ($CDCl_3$) δ_C, ppm: 172.0 (1C, CH_2-*C*=O), 150.0 (1C, N_{py}-*C*H-C), 148.1 (1C, N_{py}-*C*H-CH), 135.9 (1C, N_{py}-CH-C-*C*H), 135.6 (1C, N_{py}-CH-*C*-CH), 123.5 (1C, N_{py}-CH-*C*H), 105.3-122.0 (10C, m series, CH_2-*C*F_2-CF_2, CH_2-CF_2-*C*F_2, CH_2-$(CF_2)_2$-*C*F_2, CH_2-$(CF_2)_3$-*C*F_2, CH_2-$(CF_2)_4$-*C*F_2, *C*F_2-$(CF_2)_3$-CF_3, *C*F_2-$(CF_2)_2$-CF_3, *C*F_2-CF_2-CF_3, CF_2-*C*F_2-CF_3, CF_2-CF_2-*C*F_3), 56.6 (1C, t, O-*C*H_2-CH_2, $^3J_{C,F}$ = 4 Hz), 35.4 (1C, CH_2-*C*H_2-C=O), 30.8 (1C, t, O-CH_2-*C*H_2, $^2J_{C,F}$ = 22 Hz), 28.2 (1C, *C*H_2-CH_2-C=O).

^{19}F-NMR ($CDCl_3$) δ_F, ppm: -80.70 (3F, t, C*F*$_3$, $^3J_{F,F}$ = 9.7 Hz), -113.59 (2F, m, CH_2-C*F*$_2$-CF_2), -121.85 (10F, m, CH_2-$(CF_2)_2$-C*F*$_2$, CH_2-$(CF_2)_3$-C*F*$_2$, CH_2-$(CF_2)_4$-C*F*$_2$, C*F*$_2$-$(CF_2)_3$-CF_3, C*F*$_2$-$(CF_2)_2$-CF_3), -122.65 (2F, m, C*F*$_2$-CF_2-CF_3), -123.51 (2F, m, CH_2-CF_2-C*F*$_2$), -126.06 (2F, m, C*F*$_2$-CF_3).

IR (ν, cm^{-1}): 2930-2983 (CH_2), 1729 (C=O), 1574, 1483, 1425 (*Py* C=C, C=N), 1252-1115 (CF_2, CF_3), 1200 (C-O).

ESI-MS(+) *m/z* found 698.25 $[M+H]^+$, calcd. for $C_{20}H_{12}F_{21}NO_2$ 697.28.

Anal. (%) calcd. for $C_{20}H_{12}F_{21}NO_2$ C 34.45, H 1.73, N 2.01; found C 34.42, H 1.75, N 2.08.

General procedure for the synthesis of the ruthenium(II)-arene complexes 1a-1d and 2a-2c

To a solution of [Ru(η^6-*p*-cymene)Cl_2]$_2$ (1 equiv.) in CH_2Cl_2 (10 mL) a solution of the appropriate ligand ester (2.1 equiv.) was added and the reaction mixture stirred at r.t. in the dark for 3 to 5 days. The reaction mixture was concentrated under reduced pressure almost to dryness and a few drops of MeOH or Et_2O were added and the mixture maintained at 0°C in the dark overnight. The obtained precipitate was triturated with diethyl ether and hexane and then removed by filtration and dried under vacuum.

[Ru(η^6-*p*-cymene)Cl_2(octyl-3-(pyridin-3-yl)propanoate)] (1a)

[Ru(η^6-*p*-cymene)Cl_2]$_2$ (0.250 g, 0.408 mmol, 1 equiv.), octyl-3-(pyridin-3-yl)propanoate) (**L1a**) (0.215 g, 0.816 mmol, 2.1 equiv.), in CH_2Cl_2 (30 mL), 5 d. The product was isolated as an orange solid (0.389 g, η = 84%).

M.p. (°C): 136.5-137.5.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.92 (1H, s, N_{py}-C*H*-C), 8.89 (1H, d, N_{py}-C*H*-CH, $^3J_{H,H}$ = 5.6 Hz), 7.58 (1H, d, N_{py}-CH-C-C*H*, $^3J_{H,H}$ = 7.5 Hz), 7.23 (1H, dd overlapped, N_{py}-CH-C*H*, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,H}$ = 5.6 Hz), 5.43 (2H, d, 2xCH_3-C-CH-C*H*(*Ar*), $^3J_{H,H}$ = 5.5 Hz), 5.21 (2H, d, 2xCH_3-C-C*H*(*Ar*), $^3J_{H,H}$ = 5.5 Hz), 4.06 (2H, t, O-C*H*$_2$-CH_2, $^3J_{H,H}$ = 6.7 Hz), -2.93-3.00 (1H, m, *Ar*-C*H*$(CH_3)_2$), 2.95 (2H, t, C*H*$_2$-CH_2-C=O, $^3J_{H,H}$ = 7.4 Hz), 2.64 (2H, t, CH_2-C*H*$_2$-C=O, $^3J_{H,H}$ = 7.4 Hz), 2.08 (3H, s, *Ar*-C*H*$_3$), 1.60 (2H, m, O-CH_2-C*H*$_2$), 1.30 (6H, d, *Ar*-CH(C*H*$_3$)$_2$, $^3J_{H,H}$ = 6.3 Hz), 1.20-1.40 (10H, m br, O-$(CH_2)_2$-C*H*$_2$, O-$(CH_2)_3$-C*H*$_2$, C*H*$_2$-$(CH_2)_2$-CH_3, C*H*$_2$-CH_2-CH_3, C*H*$_2$-CH_3), 0.87 (3H, t, CH_2-C*H*$_3$, $^3J_{H,H}$ = 6.6 Hz).

^{13}C-NMR ($CDCl_3$) δ_C, ppm: 172.1 (1C, CH_2-*C*=O), 154.9 (1C, N_{py}-*C*H-C), 152.7 (1C, N_{py}-*C*H-CH), 137.6 (1C, N_{py}-CH-C-*C*H), 137.1 (1C, N_{py}-CH-*C*-CH), 124.1 (1C, N_{py}-CH-*C*H), 103.3 (1C, (*Ar*)CH-*C*-CH$(CH_3)_2$), 97.1 (1C, CH_3-*C*-CH(*Ar*)), 82.8 (2C, 2xCH_3-C-*C*H(*Ar*)), 82.1 (2C, 2x(*Ar*)*C*H-C-CH$(CH_3)_2$), 64.9 (1C, O-*C*H_2-CH_2), 34.7 (1C, CH_2-*C*H_2-C=O), 31.7 (1C, *C*H_2-CH_2-C=O), 30.6 (1C, *Ar*-*C*H$(CH_3)_2$), 29.1 (1C, O-$(CH_2)_3$-*C*H_2), 29.1 (1C, *C*H_2-$(CH_2)_2$-

CH_3), 28.5 (1C, $\underline{C}H_2$-CH_2-CH_3), 27.7 (1C, O-CH_2-$\underline{C}H_2$), 25.8 (1C, O-$(CH_2)_2$-$\underline{C}H_2$), 22.5 (1C, $\underline{C}H_2$-CH_3), 22.2 (2C, *Ar*-CH($\underline{C}H_3$)$_2$), 18.1 (1C, *Ar*-$\underline{C}H_3$), 14.0 (1C, CH_2-$\underline{C}H_3$).

IR (ν, cm^{-1}): 3062 (CH *Ar*), 2958-2855 (CH_2, CH, CH_3), 1724 (C=O), 1577, 1481-1421 (Py C=C, C=N), 1194 -1165 (C-O).

ESI-MS(+) *m/z* found 534.12 $[M-Cl]^+$, calcd. for $C_{26}H_{39}ClNO_2Ru$ 534.17, the experimental isotopic pattern fits well the calculated one.

Anal. (%) calcd. for $C_{26}H_{39}Cl_2NO_2Ru$ C 54.83, H 6.90, N 2.46; found C 54.76, H 6.76, N 2.76.

[Ru(η^6-*p*-cymene)Cl_2(decyl-3-(pyridin-3-yl)propanoate)] (1b)

[Ru(η^6-*p*-cymene)Cl_2]$_2$ (0.250 g, 0.408 mmol, 1 equiv.), decyl-3-(pyridin-3-yl)propanoate (**L1b**) (0.238 g, 0.816 mmol, 2.1 equiv.), in CH_2Cl_2 (30 mL), 5 d. The product was isolated as an orange solid (0.383 g, η = 79%).

M.p. (°C): 114.5-115.5.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.92 (1H, s, N_{py}-C$\underline{H}$-C), 8.88 (1H, d, N_{py}-C$\underline{H}$-CH, $^3J_{H,H}$ = 5.3 Hz), 7.58 (1H, d, N_{py}-CH-C-C$\underline{H}$, $^3J_{H,H}$ = 7.3 Hz), 7.22 (1H, dd overlapped, N_{py}-CH-C$\underline{H}$, $^3J_{H,H}$ = 7.3 Hz, $^3J_{H,H}$ = 5.3 Hz), 5.43 (2H, d, 2xCH_3-C-CH-C$\underline{H}$(*Ar*), $^3J_{H,H}$ = 5.4 Hz), 5.21 (2H, d, 2xCH_3-C-C$\underline{H}$(*Ar*), $^3J_{H,H}$ = 5.4 Hz), 4.05 (2H, t, O-C$\underline{H_2}$-CH_2, $^3J_{H,H}$ = 6.6 Hz), 2.93-2.98 (1H, m, *Ar*-C$\underline{H}$(CH_3)$_2$), 2.95 (2H, t, C$\underline{H_2}$-CH_2-C=O, $^3J_{H,H}$ = 7.1 Hz), 2.64 (2H, t, CH_2-C$\underline{H_2}$-C=O, $^3J_{H,H}$ = 7.1 Hz), 2.07 (3H, s, *Ar*-C$\underline{H_3}$), 1.60 (2H, m, O-CH_2-C$\underline{H_2}$), 1.30 (6H, d, *Ar*-CH(C$\underline{H_3}$)$_2$, $^3J_{H,H}$ = 6.9 Hz), 1.18-1.41 (14H, m br, O-CH_2-CH_2-C$\underline{H_2}$, O-CH_2-$(CH_2)_2$-C$\underline{H_2}$, OCH_2-$(CH_2)_3$-C$\underline{H_2}$, C$\underline{H_2}$-$(CH_2)_3$-CH_3, C$\underline{H_2}$-$(CH_2)_2$-CH_3, C$\underline{H_2}$-CH_2-CH_3, C$\underline{H_2}$-CH_3),

0.87 (3H, t, CH_2-C$\underline{H_3}$, $^3J_{H,H}$ = 6.1Hz).

^{13}C-NMR ($CDCl_3$) δ_C, ppm: 172.1 (1C, CH_2-$\underline{C}$=O), 154.9 (1C, N_{py}-$\underline{C}$H-C), 152.8 (1C, N_{py}-$\underline{C}$H-CH), 137.6 (1C, N_{py}-CH-C-$\underline{C}$H), 137.1 (1C, N_{py}-CH-$\underline{C}$-CH), 124.1 (1C, N_{py}-CH-$\underline{C}$H), 103.3 (1C, (*Ar*)CH-$\underline{C}$-CH(CH_3)$_2$), 97.2 (1C, CH_3-$\underline{C}$-CH(*Ar*)), 82.9 (2C, 2xCH_3-C-$\underline{C}$H(*Ar*)), 82.2 (2C, 2x(*Ar*)$\underline{C}$H-C-CH(CH_3)$_2$), 64.9 (1C, O-$\underline{C}H_2$-CH_2), 34.7 (1C, CH_2-$\underline{C}H_2$-C=O), 31.8 (1C, $\underline{C}H_2$-CH_2-C=O), 30.6 (1C, *Ar*-$\underline{C}$H(CH_3)$_2$), 29.5 (1C, O-$(CH_2)_4$-$\underline{C}H_2$, $\underline{C}H_2$-$(CH_2)_3$-CH_3), 29.2 (1C, O-$(CH_2)_3$-$\underline{C}H_2$), 29.2 (1C, $\underline{C}H_2$-$(CH_2)_2$-CH_3), 28.6 (1C, $\underline{C}H_2$-CH_2-CH_3), 27.8 (1C, O-CH_2-$\underline{C}H_2$), 25.9 (1C, O-$(CH_2)_2$-$\underline{C}H_2$), 22.6 (1C, $\underline{C}H_2$-CH_3), 22.3 (2C, *Ar*-CH($\underline{C}H_3$)$_2$), 18.1 (1C, *Ar*-$\underline{C}H_3$), 14.1 (1C, CH_2-$\underline{C}H_3$).

IR (ν, cm^{-1}): 3045 (CH *Ar*), 2958-2853 (CH_2, CH, CH_3), 1725 (C=O), 1578, 1466-1421 (*Py* C=C, C=N), 1182-1158 (C-O).

ESI-MS(+) *m/z* found 562.18 $[M-Cl]^+$, calcd. for $C_{28}H_{43}ClNO_2Ru$ 562.20, the experimental isotopic pattern fits well the calculated one.

Anal. (%) calcd. for $C_{28}H_{43}Cl_2NO_2Ru$ C 56.27, H 7.25, N 2.34, found C 56.05, H 7.16, N 2.62.

[Ru(η^6-*p*-cymene)Cl_2(dodecyl-3-(pyridin-3-yl)propanoate)] (1c)

[Ru(η^6-*p*-cymene)Cl_2]$_2$ (0.250 g, 0.408 mmol, 1 equiv.), dodecyl-3-(pyridin-3-yl)propanoate (**L1c**) (0.261 g, 0.816 mmol, 2.1 equiv.), in CH_2Cl_2 (30 mL), 5 d. The product was isolated as an orange solid (0.414 g, η = 81%).

M.p. (°C): 112.5-113.5.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.91 (1H, s, N_{py}-C$\underline{H}$-C), 8.88 (1H, d, N_{py}-C$\underline{H}$-CH, $^3J_{H,H}$ = 5.5 Hz), 7.57 (1H, d, N_{py}-CH-C-C$\underline{H}$, $^3J_{H,H}$ = 7.6 Hz), 7.21 (1H, dd overlapped, N_{py}-CH-C$\underline{H}$, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 5.5 Hz), 5.42 (2H, d, 2xCH_3-C-CH-C$\underline{H}$(*Ar*), $^3J_{H,H}$ = 5.7 Hz), 5.20 (2H, d, 2xCH_3-C-C$\underline{H}$(*Ar*), $^3J_{H,H}$ = 5.7 Hz), 4.05 (2H, t, O-C$\underline{H_2}$-CH_2, $^3J_{H,H}$ = 6.7 Hz), -2.92-3.00 (1H, m, *Ar*-C$\underline{H}$(CH_3)$_2$), 2.94 (2H, t, C$\underline{H_2}$-CH_2-C=O, $^3J_{H,H}$ = 7.3 Hz), 2.63 (2H, t, CH_2-C$\underline{H_2}$-C=O, $^3J_{H,H}$ = 7.3 Hz),

2.07 (3H, s, *Ar*-C$\underline{H_3}$), 1.56-1.59 (2H, m, O-CH$_2$-C$\underline{H_2}$), 1.29 (6H, d, *Ar*-CH(C$\underline{H_3}$)$_2$, $^3J_{H,H}$ = 7.0 Hz), 1.18-1.35 (18H, m br, O-(CH$_2$)$_2$-C$\underline{H_2}$, O-(CH$_2$)$_3$-C$\underline{H_2}$, O-(CH$_2$)$_4$-C$\underline{H_2}$, O-(CH$_2$)$_5$-C$\underline{H_2}$, C$\underline{H_2}$-(CH$_2$)$_4$-CH$_3$, C$\underline{H_2}$-(CH$_2$)$_3$-CH$_3$, C$\underline{H_2}$-(CH$_2$)$_2$-CH$_3$, C$\underline{H_2}$-CH$_2$-CH$_3$, C$\underline{H_2}$-CH$_3$), 0.86 (3H, t, CH$_2$-C$\underline{H_3}$, $^3J_{H,H}$ = 6.2 Hz).

^{13}C-NMR (CDCl$_3$) δ_C, ppm: 172.1 (1C, CH$_2$-$\underline{C}$=O), 155.0 (1C, N$_{py}$-$\underline{C}$H-C), 152.8 (1C, N$_{py}$-$\underline{C}$H-CH), 137.7 (1C, N$_{py}$-CH-C-$\underline{C}$H), 137.2 (1C, N$_{py}$-CH-$\underline{C}$-CH), 124.2 (1C, N$_{py}$-CH-$\underline{C}$H), 103.4 (1C, (*Ar*)CH-$\underline{C}$-CH(CH$_3$)$_2$), 97.2 (1C, CH$_3$-$\underline{C}$-CH(*Ar*)), 82.9 (2C, 2xCH$_3$-C-$\underline{C}$H(*Ar*)), 82.2 (2C, 2x(*Ar*)$\underline{C}$H-C-CH(CH$_3$)$_2$), 65.0 (1C, O-$\underline{C}$H$_2$-CH$_2$), 34.8 (1C, CH$_2$-$\underline{C}$H$_2$-C=O), 31.9 (1C, $\underline{C}$H$_2$-CH$_2$-C=O), 30.7(1C, *Ar*-$\underline{C}$H(CH$_3$)$_2$), 29.6 (2C, O-(CH$_2$)$_5$-$\underline{C}$H$_2$, $\underline{C}$H$_2$-(CH$_2$)$_4$-CH$_3$), 29.6 (1C, O-(CH$_2$)$_4$-$\underline{C}$H$_2$), 29.5 (1C, $\underline{C}$H$_2$-(CH$_2$)$_3$-CH$_3$), 29.3 (1C, O-(CH$_2$)$_3$-$\underline{C}$H$_2$), 29.3 (1C, $\underline{C}$H$_2$-(CH$_2$)$_2$-CH$_3$), 28.6 (1C, $\underline{C}$H$_2$-CH$_2$-CH$_3$), 27.8 (1C, O-CH$_2$-$\underline{C}$H$_2$), 25.9 (1C, O-(CH$_2$)$_2$-$\underline{C}$H$_2$), 22.7 (1C, $\underline{C}$H$_2$-CH$_3$), 22.3 (2C, *Ar*-CH($\underline{C}$H$_3$)$_2$), 18.2 (1C, *Ar*-$\underline{C}$H$_3$), 14.1 (1C, CH$_2$-$\underline{C}$H$_3$).

IR (ν, cm^{-1}): 3047 (CH *Ar*), 2957-2853 (CH$_2$, CH, CH$_3$), 1723 (C=O), 1579, 1466-1428 (*Py* C=C, C=N), 1185-1151 (C-O).

ESI-MS(+) *m/z* found 590.23 [M-Cl]$^+$, calcd. for $C_{30}H_{47}ClNO_2Ru$ 590.23, the experimental isotopic pattern fits well the calculated one;

Anal. (%) calcd. for $C_{30}H_{47}Cl_2NO_2Ru$ C 57.59, H 7.57, N 2.24, found C 57.66, H 7.52, N 2.54.

[Ru(η^6-*p*-cymene)Cl$_2$(octadecyl-3-(pyridin-3-yl)propanoate)] (1d)

[Ru(η^6-*p*-cymene)Cl$_2$]$_2$ (0.137 g, 0.224 mmol, 1 equiv.), octadecyl-3-(pyridin-3-yl)propanoate (**L1d**) (0.190 g, 0.471 mmol, 2.1 equiv.), in CH$_2$Cl$_2$ (30 mL), 3 d. The product was isolated as an orange solid (0.280 g, η = 88%).

M.p. (^{o}C): 105.5-106.5.

^{1}H-NMR (CDCl$_3$) δ_H, ppm: 8.93 (1H, s, N$_{py}$-C$\underline{H}$-C), 8.89 (1H, d, N$_{py}$-C$\underline{H}$-CH, $^3J_{H,H}$ = 5.6 Hz), 7.58 (1H, d, N$_{py}$-CH-C-C$\underline{H}$, $^3J_{H,H}$ = 7.4 Hz), 7.23 (1H, dd overlapped, N$_{py}$-CH-C$\underline{H}$, $^3J_{H,H}$ = 7.4Hz, $^3J_{H,H}$ = 5.6 Hz), 5.43 (2H, d, 2xCH$_3$-C-CH-C$\underline{H}$(*Ar*), $^3J_{H,H}$ = 5.4 Hz), 5.21 (2H, d, 2xCH$_3$-C-C$\underline{H}$(*Ar*), $^3J_{H,H}$ = 5.4 Hz), 4.06 (2H, t, O-C$\underline{H_2}$-CH$_2$, $^3J_{H,H}$ = 6.6 Hz), 2.94-2.99 (1H, m, *Ar*-C$\underline{H}$(CH$_3$)$_2$), 2.95 (2H, t, C$\underline{H_2}$-CH$_2$-C=O, $^3J_{H,H}$ = 7.3 Hz), 2.64 (2H, t, CH$_2$-C$\underline{H_2}$-C=O, $^3J_{H,H}$ = 7.3 Hz),

2.08 (3H, s, *Ar*-C$\underline{H_3}$), 1.54-1.62 (2H, m, O-CH$_2$-C$\underline{H_2}$), 1.30 (6H, d, *Ar*-CH(C$\underline{H_3}$)$_2$, $^3J_{H,H}$ = 6.9 Hz), 1.25 (30H, m br, O-(CH$_2$)$_2$-C$\underline{H_2}$, O-(CH$_2$)$_3$-C$\underline{H_2}$, O-(CH$_2$)$_4$-C$\underline{H_2}$, O-(CH$_2$)$_5$-C$\underline{H_2}$, O-(CH$_2$)$_6$-C$\underline{H_2}$, O-(CH$_2$)$_7$-C$\underline{H_2}$, C$\underline{H_2}$-(CH$_2$)$_8$-CH$_3$, C$\underline{H_2}$-(CH$_2$)$_7$-CH$_3$, C$\underline{H_2}$-(CH$_2$)$_6$-CH$_3$, C$\underline{H_2}$-(CH$_2$)$_5$-CH$_3$, C$\underline{H_2}$-(CH$_2$)$_4$-CH$_3$, C$\underline{H_2}$-(CH$_2$)$_3$-CH$_3$, C$\underline{H_2}$-(CH$_2$)$_2$-CH$_3$, C$\underline{H_2}$-CH$_2$-CH$_3$, C$\underline{H_2}$-CH$_3$), 0.88 (3H, t, CH$_2$-C$\underline{H_3}$, $^3J_{H,H}$ = 6.4 Hz).

^{13}C-NMR (CDCl$_3$) δ_C, ppm: 172.1 (1C, CH$_2$-$\underline{C}$=O), 155.0 (1C, N$_{py}$-$\underline{C}$H-C), 152.7 (1C, N$_{py}$-$\underline{C}$H-CH), 137.6 (1C, N$_{py}$-CH-C-$\underline{C}$H), 137.2 (1C, N$_{py}$-CH-$\underline{C}$-CH), 124.1 (1C, N$_{py}$-CH-$\underline{C}$H), 103.4 (1C, (*Ar*)CH-$\underline{C}$-CH(CH$_3$)$_2$), 97.1 (1C, CH$_3$-$\underline{C}$-CH(*Ar*)), 82.9 (2C, 2xCH$_3$-C-$\underline{C}$H(*Ar*)), 82.2 (2C, 2x(*Ar*)$\underline{C}$H-C-CH(CH$_3$)$_2$), 64.9 (1C, O-$\underline{C}$H$_2$-CH$_2$), 34.7 (1C, CH$_2$-$\underline{C}$H$_2$-C=O), 31.9 (1C, $\underline{C}$H$_2$-CH$_2$-C=O), 30.6 (1C, *Ar*-$\underline{C}$H(CH$_3$)$_2$), 29.6 (8C, O-(CH$_2$)$_5$-$\underline{C}$H$_2$, O-(CH$_2$)$_6$-$\underline{C}$H$_2$, O-(CH$_2$)$_7$-$\underline{C}$H$_2$, O-(CH$_2$)$_8$-$\underline{C}$H$_2$, $\underline{C}$H$_2$-(CH$_2$)$_7$-CH$_3$), $\underline{C}$H$_2$-(CH$_2$)$_6$-CH$_3$), $\underline{C}$H$_2$-(CH$_2$)$_5$-CH$_3$), $\underline{C}$H$_2$-(CH$_2$)$_4$-CH$_3$), 29.6 (1C, O-(CH$_2$)$_4$-$\underline{C}$H$_2$), 29.5 (1C, $\underline{C}$H$_2$-(CH$_2$)$_3$-CH$_3$), 29.3 (1C, O-(CH$_2$)$_3$-$\underline{C}$H$_2$), 29.2 (1C, $\underline{C}$H$_2$-(CH$_2$)$_2$-CH$_3$), 28.6 (1C, $\underline{C}$H$_2$-CH$_2$-CH$_3$), 27.8 (1C, O-CH$_2$-$\underline{C}$H$_2$), 25.9 (1C, O-(CH$_2$)$_2$-$\underline{C}$H$_2$), 22.6 (1C, $\underline{C}$H$_2$-CH$_3$), 22.3 (2C, *Ar*-CH($\underline{C}$H$_3$)$_2$), 18.1 (1C, *Ar*-$\underline{C}$H$_3$), 14.1 (1C, CH$_2$-$\underline{C}$H$_3$).

IR (ν, cm^{-1}): 3057 (CH *Ar*), 2962-2850 (CH$_2$, CH, CH$_3$), 1723 (C=O), 1577, 1471-1428 (*Py* C=C, C=N), 1151-1179 (C-O).

ESI-MS(+) *m/z* found 674.33 [M-Cl]$^+$, calcd. for $C_{36}H_{59}ClNO_2Ru$ 674.33, the experimental isotopic pattern fits well the calculated one.

Anal. (%) calcd. for $C_{36}H_{59}Cl_2NO_2Ru$ C 60.91, H 8.38, N 1.97, found C 60.95, H 8.63, N 1.88.

[Ru(η^6-*p*-cymene)Cl_2(1*H*,1*H*,2*H*,2*H*-perfluorooctyl-3-(pyridin-3-yl)propanoate)] (2a)

[Ru(η^6-*p*-cymene)Cl_2]$_2$ (0.200 g, 0.327 mmol, 1 equiv.), 1*H*,1*H*,2*H*,2*H*-perfluorooctyl-3-(pyridin-3-yl)propanoate (**L2a**) (0.325 g, 0.653 mmol, 2.1 equiv.), in CH_2Cl_2 (30 mL), 5 d. The product was isolated as an orange solid (0.456 g, η = 87%).

M.p. (°C): 113.5-114.5.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.93 (1H, s, N_{py}-C*H*-C), 8.89 (1H, d, N_{py}-C*H*-CH, $^3J_{H,H}$ = 5.5 Hz), 7.58 (1H, d, N_{py}-CH-C-C*H*, $^3J_{H,H}$ = 7.6 Hz), 7.23 (1H, dd overlapped, N_{py}-CH-C*H*, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 5.5 Hz), 5.42 (2H, d, 2xCH_3-C-CH-C*H*(*Ar*), $^3J_{H,H}$ = 5.7 Hz), 5.21 (2H, d, 2xCH_3-C-C*H*(*Ar*), $^3J_{H,H}$ = 5.7 Hz), 4.39 (2H, t, O-C*H*$_2$-CH_2, $^3J_{H,H}$ = 6.4 Hz), 2.94-3.01 (1H, m, *Ar*-C*H*(CH_3)$_2$), 2.96 (2H, t, C*H*$_2$-CH_2-C=O, $^3J_{H,H}$ = 7.2 Hz), 2.66 (2H, t, CH_2-C*H*$_2$-C=O, $^3J_{H,H}$ = 7.2 Hz), 2.41-2.53 (2H, m, O-CH_2-C*H*$_2$), 2.08 (3H, s, *Ar*-C*H*$_3$), 1.29 (6H, d, *Ar*-CH(C*H*$_3$)$_2$, $^3J_{g',f'}$ = 6.9Hz).

^{13}C-NMR ($CDCl_3$) δ_C, ppm: 171.6 (1C, CH_2-*C*=O), 154.9 (1C, N_{py}-*C*H-C), 153.0 (1C, N_{py}-*C*H-CH), 137.7 (1C, N_{py}-CH-C-*C*H), 136.9 (1C, N_{py}-CH-*C*-CH), 124.2(1C, N_{py}-CH-*C*H), 105.2-121.9 (6C, m series, CH_2-*C*F_2-CF_2, CH_2-CF_2-*C*F_2, CH_2-$(CF_2)_2$-*C*F_2, *C*F_2-CF_2-CF_3, CF_2-*C*F_2-CF_3, CF_2-CF_2-*C*F_3), 103.5 (1C, CH_3-C-CH-CH-*C*(*Ar*)), 97.2 (1C, CH_3-*C*-CH(*Ar*)), 82.8 (2C, 2xCH_3-C-CH-*C*H(*Ar*), 82.3 (2C, 2xCH_3-C-*C*H(*Ar*), 56.5 (1C, t, O-*C*H_2-CH_2, $^3J_{C,F}$ = 4 Hz), 34.5 (1C, CH_2-*C*H_2-C=O), 30.7 (1C, *Ar*-*C*H(CH_3)$_2$), 30.5 (1C, t, O-CH_2-*C*H_2, $^2J_{C,F}$ = 22 Hz), 27.6 (1C, *C*H_2-CH_2-C=O), 22.3 (2C, *Ar*-CH(*C*H_3)$_2$), 18.1 (1C, *Ar*-*C*H_3).

^{19}F-NMR ($CDCl_3$) δ_F, ppm: -80.72 (3F, t, C*F*$_3$, $^3J_{F,F}$ = 9.3 Hz), -113.69 (2F, m, CH_2-C*F*$_2$-CF_2), -121.83 (2F, m, CH_2-$(CF_2)_2$-C*F*$_2$), -122.82 (2F, m, C*F*$_2$-CF_2-CF_3), -123.53 (2F, m, CH_2-CF_2-C*F*$_2$), -126.08 (2F, m, C*F*$_2$-CF_3).

IR (ν, cm^{-1}): 3053 (CH *Ar*), 2967-2930 (CH_2, CH, CH_3), 1736 (C=O), 1578, 1473, 1427 (*Py* C=C, C=N), 1231-1115 (CF_2, CF_3), 1186 (C-O).

ESI-MS(+) *m/z* found 768.06 [M-Cl]$^+$, calcd. for $C_{26}H_{26}ClF_{13}NO_2Ru$ 768.05, the experimental isotopic pattern fits well the calculated one.

Anal. (%) calcd. for $C_{26}H_{26}Cl_2F_{13}NO_2Ru$ C 38.87, H 3.26, N 1.74, found C 39.01, H 3.15, N 1.73.

[Ru(η^6-*p*-cymene)Cl_2(1*H*,1*H*,2*H*,2*H*-perfluorodecyl-3-(pyridin-3-yl)propanoate)] (2b)

[Ru(η^6-*p*-cymene)Cl_2]$_2$ (0.220 g, 0.359 mmol, 1 equiv.), 1*H*,1*H*,2*H*,2*H*-perfluorodecyl-3-(pyridin-3-yl)propanoate (**L2b**) (0.450 g, 0.753 mmol, 2.1 equiv.), in CH_2Cl_2 (35 mL), 5 d. The product was isolated as an orange solid (0.558 g, η = 86%).

M.p. (°C): 101.5-102.5.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.93 (1H, s, N_{py}-C*H*-C), 8.89 (1H, d, N_{py}-C*H*-CH, $^3J_{H,H}$ = 5.5 Hz), 7.58 (1H, d, N_{py}-CH-C-C*H*, $^3J_{H,H}$ = 7.7 Hz), 7.22 (1H, dd overlapped, N_{py}-CH-C*H*, $^3J_{H,H}$ = 7.7 Hz, $^3J_{H,H}$ = 5.5Hz), 5.42 (2H, d, 2xCH_3-C-CH-C*H*(*Ar*), $^3J_{H,H}$ = 5.9 Hz), 5.21 (2H, d, 2xCH_3-C-C*H*(*Ar*), $^3J_{H,H}$ = 5.9 Hz), 4.39 (2H, t, O-C*H*$_2$-CH_2, $^3J_{H,H}$ = 6.4Hz), 2.94-3.01 (1H, m, *Ar*-C*H*(CH_3)$_2$), 2.96 (2H, t, C*H*$_2$-CH_2-C=O, $^3J_{H,H}$ = 7.2 Hz), 2.67 (2H, t, CH_2-C*H*$_2$-C=O, $^3J_{H,H}$ = 7.2 Hz), 2.41-2.53 (2H, m, O-CH_2-C*H*$_2$), 2.08 (3H, s, *Ar*-C*H*$_3$), 1.29 (6H, d, *Ar*-CH(C*H*$_3$)$_2$, $^3J_{H,H}$ = 6.6 Hz).

^{13}C-NMR ($CDCl_3$) δ_C, ppm: 171.6 (1C, CH_2-*C*=O), 154.9 (1C, N_{py}-*C*H-C), 153.0 (1C, N_{py}-*C*H-CH), 137.7 (1C, N_{py}-CH-C-*C*H), 136.9 (1C, N_{py}-CH-*C*-CH), 124.2(1C, N_{py}-CH-*C*H), 104.8-121.7 (8C, m series, CH_2-*C*F_2-CF_2, CH_2-CF_2-*C*F_2, CH_2-$(CF_2)_2$-*C*F_2, CH_2-$(CF_2)_3$-*C*F_2, *C*F_2-$(CF_2)_2$-CF_3, *C*F_2-CF_2-CF_3, CF_2-*C*F_2-CF_3, CF_2-CF_2-*C*F_3), 103.5 (1C, CH_3-C-CH-CH-*C*(*Ar*)), 97.2 (1C, CH_3-*C*-CH(*Ar*)), 82.9 (2C, 2xCH_3-C-CH-*C*H(*Ar*), 82.3 (2C, 2xCH_3-C-*C*H(*Ar*), 56.6 (1C, t, O-*C*H_2-CH_2, $^3J_{C,F}$ = 4 Hz), 34.5 (1C, CH_2-*C*H_2-C=O), 30.7 (1C, *Ar*-*C*H(CH_3)$_2$), 30.5 (1C, t, O-CH_2-*C*H_2, $^2J_{C,F}$ = 22 Hz), 27.6 (1C, *C*H_2-CH_2-C=O), 22.3 (2C, *Ar*-CH(*C*H_3)$_2$), 18.2 (1C, *Ar*-*C*H_3).

^{19}F-NMR ($CDCl_3$) δ_F, ppm: -80.70 (3F, t, C$\underline{F_3}$, $^3J_{F,F}$ = 9.7 Hz), -113.59 (2F, m, CH_2-C$\underline{F_2}$-CF_2), -121.82 (6F, m, CH_2-$(CF_2)_2$-C$\underline{F_2}$, CH_2-$(CF_2)_3$-C$\underline{F_2}$, C$\underline{F_2}$-$(CF_2)_2$-CF_3), -122.66 (2F, m, C$\underline{F_2}$-CF_2-CF_3), -123.49 (2F, m, CH_2-CF_2-C$\underline{F_2}$), -126.05 (2F, m, C$\underline{F_2}$-CF_3).

IR (ν, cm^{-1}): 3075 (CH *Ar*), 2967-2932 (CH_2, CH, CH_3), 1740 (C=O), 1578, 1473, 1430 (*Py* C=C, C=N), 1242-1115 (CF_2, CF_3), 1198 (C-O).

ESI-MS(+) m/z found 868.05 $[M\text{-}Cl]^+$, calcd. for $C_{28}H_{26}ClF_{17}NO_2Ru$ 868.04, the experimental isotopic pattern fits well the calculated one.

Anal (%) calcd. for $C_{28}H_{26}Cl_2F_{17}NO_2Ru$ C 37.22, H 2.90, N 1.55, found C 36.87, H 2.96, N 1.58.

[Ru(η^6-*p*-cymene)Cl_2(1*H*,1*H*,2*H*,2*H*-perfluorododecyl-3-(pyridin-3-yl)propanoate)] (2c)

[Ru(η^6-*p*-cymene)Cl_2]$_2$ (0.105 g, 0.171 mmol, 1 equiv.), 1*H*,1*H*,2*H*,2*H*-perfluorododecyl-3-(pyridin-3-yl)propanoate (**L2c**) (0.250 g, 0.359 mmol, 2.1 equiv.), in CH_2Cl_2 (30 mL), 3 d. The product was isolated after precipitation with methanol, trituration with hexane (20 mL), Et_2O (3x20 mL) as an orange solid (0.257 g, η = 71%).

M.p. (^{o}C): 76.5-77.5.

^{1}H-NMR ($CDCl_3$) δ_H, ppm: 8.92 (1H, s, N_{py}-C$\underline{H}$-C), 8.88 (1H, d, N_{py}-C$\underline{H}$-CH, $^3J_{H,H}$ = 5.5 Hz), 7.57 (1H, d, N_{py}-CH-C-C$\underline{H}$, $^3J_{H,H}$ = 7.7 Hz), 7.22 (1H, dd overlapped, N_{py}-CH-C$\underline{H}$, $^3J_{H,H}$ = 7.7 Hz, $^3J_{H,H}$ = 5.5 Hz), 5.41 (2H, d, 2xCH_3-C-CH-C$\underline{H}$(*Ar*), $^3J_{H,H}$ = 5.6 Hz), 5.20 (2H, d, 2xCH_3-C-C$\underline{H}$(*Ar*), $^3J_{H,H}$ = 5.6 Hz), 4.38 (2H, t, O-C$\underline{H_2}$-CH_2, $^3J_{H,H}$ = 6.4 Hz), -2.93-3.00 (1H, m, *Ar*-C$\underline{H}$(CH_3)$_2$), 2.95 (2H, t, C$\underline{H_2}$-CH_2-C=O, $^3J_{H,H}$ = 7.2 Hz), 2.66 (2H, t, CH_2-C$\underline{H_2}$-C=O, $^3J_{H,H}$ = 7.2 Hz), 2.41-2.51 (2H, m, O-CH_2-C$\underline{H_2}$), 2.07 (3H, s, *Ar*-C$\underline{H_3}$), 1.28 (6H, d, *Ar*-CH(C$\underline{H_3}$)$_2$, $^3J_{H,H}$ = 7.1 Hz).

^{13}C-NMR ($CDCl_3$) δ_C, ppm: 171.7 (1C, CH_2-$\underline{C}$=O), 155.0 (1C, N_{py}-$\underline{C}$H-C), 153.1 (1C, N_{py}-$\underline{C}$H-CH), 137.7 (1C, N_{py}-CH-C-$\underline{C}$H), 136.9 (1C, N_{py}-CH-$\underline{C}$-CH), 124.2 (1C, N_{py}-CH-$\underline{C}$H), 106.9-121.4 (10C, m series, CH_2-$\underline{C}F_2$-CF_2, CH_2-CF_2-$\underline{C}F_2$, CH_2-$(CF_2)_2$-$\underline{C}F_2$, CH_2-$(CF_2)_3$-$\underline{C}F_2$, CH_2-$(CF_2)_4$-$\underline{C}F_2$, $\underline{C}F_2$-$(CF_2)_3$-CF_3, $\underline{C}F_2$-$(CF_2)_2$-CF_3, $\underline{C}F_2$-CF_2-CF_3, CF_2-$\underline{C}F_2$-CF_3, CF_2-CF_2-$\underline{C}F_3$), 103.6 (1C, CH_3-C-CH-CH-$\underline{C}$(*Ar*)), 97.3 (1C, CH_3-$\underline{C}$-CH(*Ar*)), 82.9 (2C, 2xCH_3-C-CH-$\underline{C}$H(*Ar*)), 82.3 (2C, 2xCH_3-C-$\underline{C}$H(*Ar*)), 56.7 (1C, t, O-$\underline{C}H_2$-CH_2, $^3J_{C,F}$ = 4 Hz), 34.6 (1C, CH_2-$\underline{C}H_2$-C=O), 30.7 (1C, *Ar*-$\underline{C}$H(CH_3)$_2$), 30.6 (1C, t, O-CH_2-$\underline{C}H_2$, $^2J_{C,F}$ = 22 Hz), 27.7 (1C, $\underline{C}H_2$-CH_2-C=O), 22.3 (2C, *Ar*-CH($\underline{C}H_3$)$_2$), 18.2 (1C, *Ar*-$\underline{C}H_3$).

^{19}F-NMR ($CDCl_3$) δ_F, ppm: -80.69 (3F, t, C$\underline{F_3}$, $^3J_{F,F}$ = 9.8 Hz), -113.58 (2F, m, CH_2-C$\underline{F_2}$-CF_2), -121.70 (10F, m, CH_2-$(CF_2)_2$-C$\underline{F_2}$, CH_2-$(CF_2)_3$-C$\underline{F_2}$, CH_2-$(CF_2)_4$-C$\underline{F_2}$, C$\underline{F_2}$-$(CF_2)_3$-CF_3, C$\underline{F_2}$-$(CF_2)_2$-CF_3), -122.65 (2F, m, C$\underline{F_2}$-CF_2-CF_3), -123.48 (2F, m, CH_2-CF_2-C$\underline{F_2}$), -126.06 (2F, m, C$\underline{F_2}$-CF_3).

IR (ν, cm^{-1}): 3057 (CH-Ar), 2965-2930 (CH_2, CH, CH_3), 1735 (C=O), 1472-1432 (*Py* C=C, C=N), 1231-1112 (CF_2, CF_3), 1197 (C-O).

ESI-MS(+) *m/z* found 967.99 $[M\text{-}Cl]^+$, calcd. for $C_{30}H_{26}ClF_{21}NO_2Ru$ 968.04, the experimental isotopic pattern fits well the calculated one.

Anal. (%) calcd. for $C_{30}H_{26}Cl_2F_{21}NO_2Ru$ C 35.91, H 2.61, N 1.40, found C 35.43, H 2.64, N 1.43.

Cell culture and evaluation of the anticancer activity

Human A2780 and A2780R ovarian carcinoma cells, A549 lung cancer cells, MCF-7 and MDA-MB-231 breast cancer cells and HEK (human embryo kidney) cells were obtained from the European Collection of Cell Cultures (Salisbury, UK). A2780, A2780R and A549 cells were grown routinely in RPMI-1640 and MCF-7, MDA-MB-231 and HEK cells in 4.5 g/L glucose DMEM medium, both containing 10% foetal calf serum (FCS) and antibiotics at 37°C and 5% CO_2. All cell culture reagents were obtained from Gibco, Basel, Switzerland. Cells were grown in 96-well plates in 100 µL of

cell culture medium for 24 h. Compounds were freshly dissolved in DMSO and immediately diluted in complete medium containing HEPES (6 g/L) and added to each well to give a maximum concentration of DMSO of 0.5% (NMR spectra of the complexes and the corresponding free ligands in pure DMSO show different shifts for the pyridine protons of the complexes from the ones of the corresponding free ligands, indicating the complexes remain stable in pure DMSO in the time course used for these experiments). The plates were incubated for another 72 h at 37°C or 2 h at 41°C followed by a 70 h incubation at 37°C. A solution (20 µL) of MTT (3-(4,5-dimethyl-2-thiazoyl)-2,5-diphenyltetrazolium bromide, Sigma-Aldrich, 200 µg/ml final concentration) was added to the cells and the plates were incubated for a further 2 h. The culture medium was aspirated, and the purple formazan crystals formed by the mitochondrial dehydrogenase activity of vital cells were dissolved in DMSO. The optical density, directly proportional to the number of surviving cells, was quantified at 590 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.

Cell uptake studies

Cells were seeded in 6-well plates, grown to approximately 50% confluency and incubated with the corresponding compound (from a DMSO solution dissolved to obtain a final concentration of 0.5% in DMSO) in the medium, for the incubation time (24 hours for temperature-dependent tests and 1 h in PBS and at the required temperature). After incubation, cells were subsequently detached using an enzyme free dissociation solution (Millipore) and pelleted for 10 min at 100 g and 4°C and washed twice with ice cold PBS. Cell lysis was achieved using a freeze-thaw technique. All samples were analyzed for their protein content prior to ICP-MS determination using a bicinchoninic acid (BCA) assay (Sigma Aldrich). All determinations described above were carried out as at least two independent experiments. Sample digestion was carried out in concentrated nitric acid for 3 h. Samples were then filled to a total volume of 8 ml with water. Indium was added as an internal standard at a concentration of 0.5 ppb. Determination of the internalized metal content was achieved on an Elan DRC II ICP-MS instrument (Perkin Elmer, Switzerland) equipped with a Meinhard nebulizer and a cyclonic spray chamber. The ICP-MS instrument was tuned using a solution provided by the manufacturer containing 1 ppb of each element Mg, In, Ce, Ba, Pb and U. External standards were prepared gravimetrically in identical matrix to the samples (with regard to internal standard and nitric acid) with single element standards obtained from CPI International (Amsterdam, The Netherlands).

References

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