Supporting Information

Novel phthiocol based organometallics with tridentate coordination sphere and their unexpected cytotoxic behavior

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Materials and methods

2-Hydroxy-3-methyl-1,4-dione **L**[1,2], $[RuCl_2(p\text{-cym})]_2$[3], $[OsCl_2(p\text{-cym})]_2$[4] and 4-amino-1*H*-pyrazole[5] were synthesized according to literature known procedures. Following chemicals and solvents were used without further purification for the syntheses: ruthenium(III) chlorid hydrate, osmium tetroxide (Johnson Matthey), 1*H*-pyrazole, triethylamine (Acros Organics), 2-methyl-naphthalene-1,4-dione, 4-methyl-1*H*-pyrazole, Pd on activated charcoal, 6-amino-1*H*-indazole (Aldrich), 4-nitro-1*H*-pyrazole (Flourochem), α-terpinene (Alfa Aesar), sodium carbonate (Merck), hydrazine dihydrochloride (Sigma-Aldrich), hydrogen (Messer), hydrochloric acid (37%), sulfuric acid (95%), silica gel (mesh 40-63 μm), ethyl acetate (Reag.Ph.Eur.ACS), *n*-hexane (Reag.Ph.Eur.ACS), dichloromethane (stabilized with 0.2% ethanol) (VWR), methanol (HPLC grade), ethanol absolute (Laboratory reagent grade) (Fluka), ammonia hydroxide solution (20-24%) (W.Neubus Enkel GmbH) and 1*H*-indazole (Polivalent-95). Microwave reactions were performed with a Biotage® Initiator+ system. Elemental analysis were conducted by the microanalytical laboratory of the faculty of chemistry of the University of Vienna with a Perkin Elmer 2400 CHN elemental analyzer

^{1}H-, ^{13}C- and 2D-NMR spectra were recorded at 298 K on a Bruker Avance III HD 700 MHz or Bruker Avance III 600 MHz spectrometers at 600.25/700.40 MHz (^{1}H) and 150.95/176.13 MHz (^{13}C). UV-Vis stability measurements were performed on a Perkin Elmer lambda 35 photometer with PTP (Peltier Temperature Programmer) and Julabo AWC 100 recirculating cooler.

Cell culture. In this study, the following human cancer cell lines were used: A549 (non-small cell lung carcinoma), SW480 and HCT-116 (both colon carcinoma) were kindly provided by Brigitte Marian, Institute of Cancer Research, Department of Medicine I, Medical University of Vienna. The cell line CH1/PA-1 (ovarian teratocarcinoma) was kindly provided by Lloyd R. Kelland (CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, UK). HCT-15 (colon carcinoma, CCL-247™) were obtained from ATCC®.

All cell culture media (including supplements) and reagents were obtained from Sigma-Aldrich, and all plasticware from StarLab, unless stated otherwise. A549, CH1/PA-1 and SW480 cells were grown in MEM supplemented with 10% fetal calf serum (FCS; from BioWest), 1 mM sodium pyruvate, 4 mM L-glutamine and 1% v/v nonessential amino acids (from 100× solution) and L-glutamine. HCT-116 and HCT-15 cells were maintained in McCoy's 5a and RPMI 1640 medium,

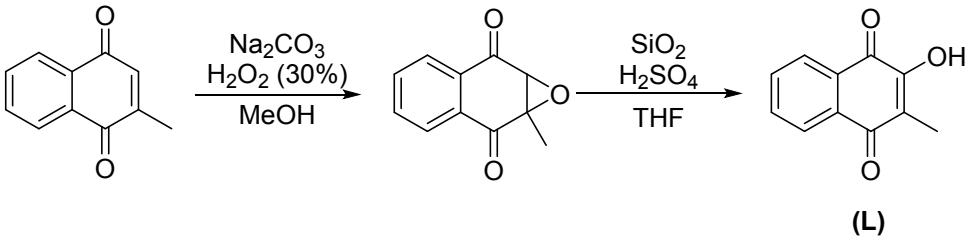
respectively, each supplemented with 10% FCS and L-glutamine. All cells were cultured as adherent monolayers in 75 cm^2 flasks and kept in a humidified incubator at 37 °C with 5% CO_2.

MTT assay. Cytotoxicity of the compounds was determined by using the colorimetric MTT assay (MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide). 1×10^3 CH1/PA-1, 2×10^3 SW480 and 3×10^3 A549 cells were seeded in 100 µL per well into 96-well microculture plates. After 24 h, test compounds were dissolved in DMSO (Fisher Scientific), serially diluted in complete MEM (to final DMSO content not exceeding 0.5% v/v) and added in 100 µL per well. After 96 h, the drug-containing medium was replaced with 100 µL of RPMI 1640/MTT mixture [6 parts of RPMI 1640 medium (supplemented with 10% heat-inactivated fetal bovine serum and 4 mM L-glutamine), 1 part of MTT solution in phosphate-buffered saline (5 mg/mL)]. After incubation for 4 h, the MTT-containing medium was replaced with 150 µL DMSO per well to dissolve the formazan product formed by viable cells. Optical densities at 550 nm (and at a reference wavelength of 690 nm) were measured with a microplate reader (ELx808, Bio-Tek). The 50% inhibitory concentrations (IC_{50}) relative to untreated controls were interpolated from concentration–effect curves. At least three independent experiments were performed, each with triplicates per concentration level.

Spheroid formation. For spheroid generation, HCT-116, HCT-15, CH1/PA-1 and A549 cells were harvested from culture flasks by trypsinization, resuspended in their respective supplemented medium and seeded in ultra-low attachment round-bottom 96-well plates (Nunclon Sphera™, Thermo Fisher Scientific) at a density of 500 viable cells per well. Plates were incubated at 37 °C with 5% CO_2 for 96 hours to allow spheroid formation and then used for the experiments.

Alamar Blue assay. The test compounds were first dissolved in DMSO, and stock solutions were prepared in appropriate medium according to the cell line and diluted stepwise to obtain a serial dilution. 100 µl of the respective dilutions were added to each well, and the plates were incubated for 96 hours at 37 °C with 5% CO_2. A 440 µM resazurin sodium salt solution in PBS was prepared and 20 µl were added to each well. The plates were incubated for 16 hours at 37 °C with 5% CO_2. Fluorescence was measured and recorded with a Synergy HT reader (BioTek). All the results originate from at least three technical and biological replicates.

Synthesis of 2-hydroxy-3-methylnaphthalene-1,4-dione (L)



(L)

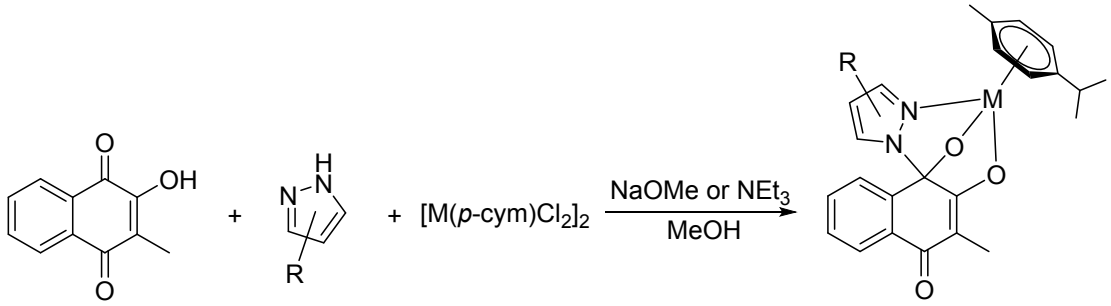
Scheme S1: Synthetic pathway to phthiocol (**L**)

The 2-hydroxy-3-mehtylnaphtalene-1,4-dione (Phthiocol, **L**) was prepared as described in literature with minor modifications.[1]

2-Methyl-1,4-naphthoquinone (1.54 g, 8.933 mmol, 1 eq.) was suspended in 100 mL methanol and cooled with an ice bath. Sodium carbonate (0.28 g, 2.680 mmol, 0.3 eq.) and hydrogen peroxide solution (30%, 1.72 mL, 517 mg, 15.186 mmol, 1.7 eq.) were dissolved in 10 mL water and added to the yellow suspension. The mixture was stirred for 0.5 h with ice cooling and for further 3 h at room temperature. The mixture was diluted with water and the volume of methanol was reduced by evaporation. The white precipitate was separated, washed with water and dried *in vacuo*. The epoxide was suspended in THF and ca. 4 g of silica gel and conc. H_2SO_4 (1.76 mL, 3.24 g, 33.052 mmol, 3.7 eq.) were added. The suspension was evaporated with 500 mbar and 70 °C until dryness. The formed yellow solid was dissolved in dichloromethane, filtrated and washed with saturated sodium bicarbonate solution. The dark red aqueous layers were combined and acidified with concentrated HCl. The yellow suspension was extracted with dichloromethane, dried over Na_2SO_4, evaporated and dried *in vacuo*. Yield: 1.33 g yellow powder (7.068 mmol, 79 %). ^{1}H NMR (500.10 MHz, $CDCl_3$) δ 8.13 (dd, J = 7.8, 1.1 Hz, 1H, $H_{5/8}$), 8.08 (dd, J = 7.7, 1.7 Hz, 1H, $H_{5/8}$), 7.75 (ddd, J = 7.6, 7.5, 1.4 Hz, 1H, $H_{6/7}$), 7.68 (ddd, J = 7.6, 7.5, 1.3 Hz, 1H, $H_{6/7}$), 7.29 (s, 1H, H_{OH}), 2.11 (s, 3H, H_9). Anal. Calc. for $C_{11}H_8O_3$: C 70.21%, H 4.29%. Found: C: 69.82%, H 4.23%

Synthesis of complexes (1a-e, 2a-c)

General procedure



(L)

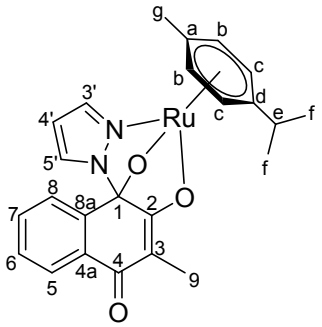
R = H; 1*H*-Pyrazole
R = CH_3(4) = 4-Methyl-1*H*-pyrazole
R = C_6H_4 = 1*H*-Indazole
R = NH_2(4) = 4-Amino-1*H*-pyrazole
R = C_6H_5N = 6-Amino-1*H*-indazole

1a: M = Ru; R = 1*H*-Pyrazole (41%)
1b: M = Ru; R = 1*H*-Indazole (63%)
1c: M = Ru; R = 4-Methyl-1*H*-pyrazole (84%)
1d: M = Ru; R = 4-Amino-1*H*-pyrazole (55%)
1e: M = Ru; R = 6-Amino-1*H*-indazole (45%)
2a: M = Os; R = 1*H*-Pyrazole (65%)
2b: M = Os; R = 1*H*-Indazole (56%)
2c: M = Os; R = 4-Methyl-1*H*-pyrazole (46%)

Scheme S2: Synthetic pathway to Ru^{II} and Os^{II} complexes (**1a-c**, **2a-c**)

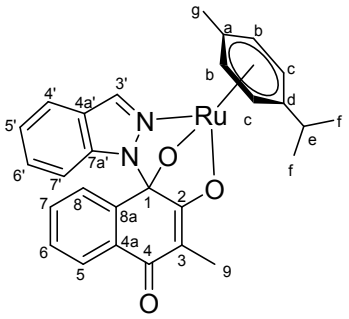
The respective metal dimer (1eq.), 1,2-diazole (1.9 – 2.2 eq.), 1,4-naphthoquinone (L) (2.1-2.2 eq.) and sodium methoxide (4.5 eq.) or triethylamine (10 eq.) were dissolved in 12 mL methanol and stirred under microwave irradiation at 50-60 °C for 6-12 minutes. Afterwards, the mixture was evaporated, the remaining residue was dissolved in dichloromethane and filtered. The solution was purified by column chromatography (Eluent: EtOAC/*n*-hexane/NEt_3 or EtOAc/MeOH/NH_4OH). The fractions were combined, evaporated and the oily residue was dissolved in dichloromethane. For precipitation, excess of diethyl ether and *n*-hexane were added until precipitation started and the mixture was stored at 4 °C overnight for complete precipitation. The solid was separated and washed twice with diethyl ether and once with *n*-hexane. The yellowish powder was dried *in vacuo*. Yield: 41–84%.

[3-Methyl-4-oxo-(1*H*-κN^2-pyrazol-1-yl)-1,4-dihydronaphtalene-1,2-bis(olato)-κO^1-κO^2)(η^6-*p*-cymene)ruthenium(II)] **(1a)**



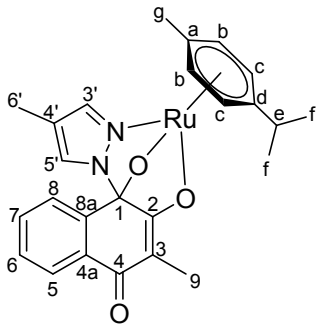
The reaction was performed according to the general procedure, using bis[dichlorido(η^6-*p*-cymene)ruthenium(II) (150 mg, 0.245 mmol, 1 eq.), 1*H*-pyrazole (35 mg, 0.514 mmol, 2.1 eq.), 2-hydroxy-3-methylnaphthalene-1,4-dione (**L**) (97 mg, 0.514 mmol, 2.1 eq.), sodium methoxide (60 mg, 1.102 mmol, 4.5 eq.). The mixture was stirred at 60 °C for 8 minutes under microwave irradiation. Flash column chromatography with EtOAc/*n*-hexane/NEt_3 (90/5/5). Yield: 99 mg yellow powder(0.202 mmol, 41%). ^{1}H NMR (600.25 MHz, MeOD) δ 8.33 (dd, *J* = 2.2, 0.7 Hz, 1H, $H_{3'}$), 8.12 – 8.07 (m, 1H, $H_{arom.}$), 7.62 – 7.57 (m, 3H, $H_{arom.}$), 6.68 (dd, *J* = 2.6, 0.7 Hz, 1H, $H_{5'}$), 6.34 (t, *J* = 2.4 Hz, 1H, $H_{4'}$), 5.98 (d, *J* = 5.8 Hz 1H, H_c), 5.87 (d, *J* = 5.8 Hz, 1H, H_c), 5.63 – 5.58 (m, 2H, H_b), 2.86 (hept, *J* = 6.9 Hz, 1H, H_e), 2.33 (s, 3H, H_g), 1.74 (s, 3H, H_9), 1.33 (dd, *J* = 6.9, 1.3 Hz, 3H, H_f). ^{13}C NMR (150.95 MHz, MeOD) δ 183.9 (C2), 183.6 (C4), 141.5 (C3‘), 137.8 ($C_{arom.}$), 134.1 ($C_{arom.}$), 132.3 ($C_{arom.}$), 131.2 ($C_{arom.}$), 127.9 (C5’), 127.7 ($C_{arom.}$), 127.1 ($C_{arom.}$), 108.7 (C4’), 105.6 (C3), 101.0 (Cd), 98.7 (Ca), 94.8 (C1), 83.3 (Cc), 83.1 (Cc), 80.2 (Cb), 80.1 (Cb), 32.7 (Ce), 23.0 (Cf), 22.8 (Cf), 18.3 (Cg), 8.1 (C9). Anal. Calc. for $C_{24}H_{24}N_2O_3Ru$: C 58.88%, H 4.94%, N 5.72%. Found: C: 58.53%, H 5.16%.

[3-Methyl-4-oxo-(1*H*-κN^2-indazolyl-1-yl)-1,4-dihydronaphtalene-1,2-bis(olato)-κO^1-κO^2)(η^6-*p*-cymene)ruthenium(II)] (**1b**)



The reaction was performed according to the general procedure, using bis[dichlorido(η^6-*p*-cymene)ruthenium(II) (40 mg, 0.065 mmol, 1 eq.), 1*H*-indazole (15 mg, 0.130 mmol, 2 eq.), 2-hydroxy-3-methylnaphthalene-1,4-dione (**L)** (27 mg, 0.143 mmol, 2.2. eq), triethylamine (90.5 µL, 66 mg, 0.650 mmol, 10 eq.). The mixture was stirred at 50 °C for 12 minutes under microwave irradiation. Flash column chromatography with EtOAc/*n*-hexane/NEt_3 (90/5/5). Yield: 44 mg yellow powder (0.082 mmol, 63%). ^{1}H NMR (600.25 MHz, DMSO-d_6) δ 9.18 (d, J = 0.9 Hz, 1H, $H_{3'}$), 8.07 – 8.04 (m, 1H, $H_{arom.}$), 7.80 – 7.77 (m, 1H, $H_{arom.}$), 7.66 – 7.60 (m, 2H, $H_{arom.}$), 7.56 – 7.53 (m, 1H, $H_{arom.}$), 7.07 – 7.03 (m, 1H, $H_{arom.}$), 7.01 – 6.97 (m, 1H, $H_{arom.}$), 6.14 (d, J = 5.9 Hz, 1H, H_b), 6.08 (d, J = 5.9 Hz, 1H, H_b), 5.77 (d, J = 5.9 Hz, 1H, H_c), 5.68 (d, J = 5.9 Hz, 1H, H_c), 5.22 (dd, J = 8.7, 0.9 Hz, 1H, $H_{arom.}$), 2.83 (hept, J = 6.9 Hz, 1H, H_e), 2.28 (s, 3H, H_g), 1.54 (s, 3H, H_9), 1.27 (d, J = 6.9 Hz, 6H, H_f). ^{13}C NMR (150.95 MHz, DMSO) δ 180.8 (C2), 180.2 (C4), 137.0 ($C_{arom.}$), 135.2 (C3'), 135.1 ($C_{arom.}$), 132.7 ($C_{arom.}$), 130.6 ($C_{arom.}$), 129.8 ($C_{arom.}$), 127.8 ($C_{arom.}$), 127.0 ($C_{arom.}$), 125.4 ($C_{arom.}$), 124.2 ($C_{arom.}$), 121.7 ($C_{arom.}$), 121.5 ($C_{arom.}$), 109.5 ($C_{arom.}$), 102.6 (C3), 98.6 (Cd), 97.3 (Ca), 95.8 (C_1), 82.6 (Cb), 82.3 (Cb), 79.0 (Cc), 78.2 (Cc), 30.9 (Ce), 22.6 (Cf), 22.3 (Cf), 17.6 (Cg), 8.1 (C9). Anal. Calc. for $C_{28}H_{26}N_2O_3Ru$ • 0.25 H_2O: C 61.80%, H 4.91%, N 5.15%. Found: C 61.62%, H 5.16%, N 5.41%.

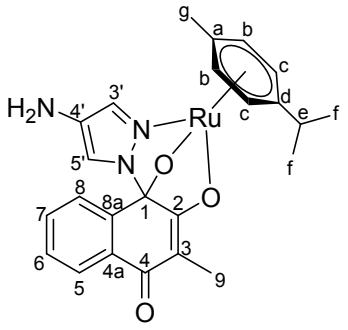
[3-Methyl-4-oxo-(4-methyl-1*H*-κN^2-pyrazol-1-yl)-1,4-dihydronaphtalene-1,2-bis(olato)-κO^1-κO^2)(η^6-*p*-cymene)ruthenium(II)] (**1c**)



The reaction was performed according to the general procedure, using bis[dichlorido(η^6-*p*-cymene)ruthenium(II) (50 mg, 0.082 mmol, 1 eq.), 4-methyl-1*H*-pyrazole (13.64 µL, 14 mg, 0.164 mmol, 2 eq.), 2-hydroxy-3-methylnaphthalene-1,4-dione (**L)** (34 mg, 0.180 mmol, 2.2 eq.), triethylamine (114.3 µL, 83 mg 0.820 mmol, 10 eq.). The mixture was stirred at 50 °C for 10 minutes under microwave irradiation. Flash column chromatography with EtOAc/*n*-hexane/NH_4OH (88/10/2). Yield: 69 mg yellow powder (0.137 mmol, 84%).

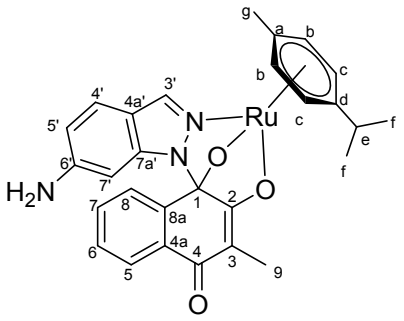
^{1}H NMR (600.25 MHz, MeOD) δ 8.14 (s, 1H, $H_{3'}$), 8.11 – 8.07 (m, 1H, $H_{arom.}$), 7.62 – 7.55 (m, 3H, $H_{arom.}$), 6.47 (s, 1H, $H_{5'}$), 5.94 (d, *J* = 5.9 Hz, 1H, H_c), 5.85 (d, *J* = 5.9 Hz, 1H, H_c), 5.60 – 5.55 (m, 2H, H_b), 2.86 (hept, *J* = 6.9 Hz, 1H, H_e), 2.32 (s, 3H, H_g), 1.97 (s, 3H, $H_{6'}$), 1.74 (s, 3H, H_9), 1.34 (d, *J* = 2.1 Hz, 3H, H_f), 1.33 (d, *J* = 2.1 Hz, 3H; H_f). ^{13}C NMR (151 MHz, MeOD) δ 183.9 (C2), 183.8 (C4), 141.3 (C3‘), 137.9 ($C_{arom.}$), 134.1 ($C_{arom.}$), 132.2 ($C_{arom.}$), 131.1 ($C_{arom.}$), 127.8 ($C_{arom.}$), 127.0 ($C_{arom.}$), 126.9 (C5’), 119.9 (C4’), 105.5 (C3), 101.0 (Cd), 98.6 (Ca), 94.5 (C1), 83.3 (Cc), 83.0 (Cc), 80.2 (Cb), 80.0 (Cb), 32.7 (Ce), 23.0 (Cf), 22.8 (Cf), 18.3 (Cg), 8.9 (C6’), 8.1 (C9). Anal. Calc. for $C_{25}H_{26}N_2O_3Ru$: C 59.63%, H 5.20%, N 5.56%. Found: C: 59.68%, H 5.44%, N 5.64%.

[3-Methyl-4-oxo-(4-amino-1*H*-κN^2-pyrazol-1-yl)-1,4-dihydronaphtalene-1,2-bis(olato)-κO^1-κO^2)(η^6-*p*-cymene)ruthenium(II)] (**1d**)



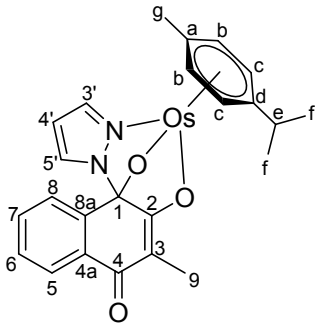
The reaction was performed according to the general procedure, using bis[dichlorido(η^6-*p*-cymene)ruthenium(II) (50 mg, 0.082 mmol, 1 eq.), 4-amino-1*H*-pyrazole (14 mg, 0.164 mmol, 2 eq.), 2-hydroxy-3-methylnaphthalene-1,4-dione (**L)** (34 mg, 0.180 mmol, 2.2 eq.), triethylamine (114.3 µL, 83 mg 0.820 mmol, 10 eq.). The mixture was stirred at 50 °C for 12 minutes under microwave irradiation. Flash column chromatography with EtOAc/*n*-hexane/NH_4OH (88/10/2). Yield: 46 mg brown powder (0.091 mmol, 55%) ^{1}H NMR (600.25 MHz, MeOD) δ 8.10 – 8.05 (m, 1H, $_{Harom.}$), 7.91 (d, *J* = 0.9 Hz, 1H, $H_{3'}$), 7.63 – 7.55 (m, 3H, $H_{arom.}$), 6.21 (d, *J* = 0.9 Hz, 1H, $H_{5'}$), 5.92 (d, *J* = 5.9 Hz, 1H, H_c), 5.83 (d, *J* = 5.8 Hz 1H, H_c), 5.56 (dd, *J* = 6.4 Hz,6.3 Hz, 2H, H_b), 2.86 (hept, *J* = 6.9 Hz, 1H, H_e), 2.32 (s, 3H, H_g), 1.73 (s, 3H, H_9), 1.35 – 1.32 (m, 6H, H_f). ^{13}C NMR (150.95 MHz, MeOD) δ 183.9 (C4), 183.7 (C2), 138.0 (Carom.), 134.1 (Carom.), 132.9 (C4'), 132.3 (C3'), 132.1 (Carom.), 131.1 (Carom.), 127.8 (Carom.), 127.0 (Carom.), 116.9 (C5'), 105.4 (C3), 100.9 (Cd), 98.6 (Ca), 94.6 (C1), 83.3 (Cc), 82.9 (Cc), 80.1 (Cb), 80.0 (Cb), 32.7 (Ce), 23.0 (Cf), 22.8 (Cf), 18.3 (Cg), 8.1 (C9). $C_{24}H_{25}N_3O_3Ru$ • 0.3 H_2O: C 56.53%, H 5.06%, N 8.26%. Found: C 56.21%, H 4.99%, N 8.64%.

[3-Methyl-4-oxo-(6-Amino-1*H*-κN^2-indazolyl-1-yl)-1,4-dihydronaphtalene-1,2-bis(olato)-κO^1-κO^2)(η^6-*p*-cymene)ruthenium(II)] (**1e**)



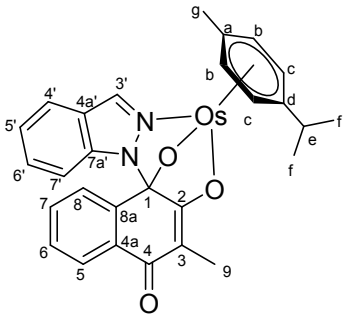
The reaction was performed according to the general procedure, using bis[dichlorido(η^6-*p*-cymene)ruthenium(II) (100 mg, 0.163 mmol, 1 eq.), 6-amino-1*H*-indazole (41 mg, 0.310 mmol, 1.9 eq.), 2-hydroxy-3-methylnaphthalene-1,4-dione (**L)** (64 mg, 0.342 mmol, 2.1 eq.), triethylamine (227.3 µL, 165 mg 1.630 mmol, 10 eq.). The mixture was stirred at 50 °C for 6 minutes under microwave irradiation. Flash column chromatography with EtOAc/*n*-hexane/NH_4OH (88/10/2). Yield: 77 mg yellow/greenish crystals (0.091 mmol, 45%). ^{1}H NMR (600.25 MHz, MeOD) δ 8.66 (d, *J* = 0.9 Hz, 1H, $H_{7'}$), 8.17 (ddd, *J* = 7.9, 1.4, 0.5 Hz, 1H, H_5), 7.72 (ddd, *J* = 7.6, 1.4, 0.5 Hz, 1H, H_8), 7.66 (ddd, *J* = 7.7, 7.6, 1.4 Hz, 1H, $H_{arom.}$), 7.59 (ddd, *J* = 7.5, 7.5, 1.4 Hz, 1H, $H_{arom.}$), 7.40 (dd, *J* = 8.8, 0.7 Hz, 1H, $H_{4'}$), 6.50 (dd, *J* = 8.8, 1.8 Hz, 1H, $H_{5'}$), 5.98 (d, *J* = 5.6 Hz, 1H, H_b), 5.87 (d, *J* = 5.6 Hz,1H, H_b), 5.61 (dd, *J* = 5.60, 5.61 Hz, 2H, H_c), 4.47 (dd, *J* = 1.8, 0.9 Hz, 1H, $H_{3'}$), 2.88 (hept, *J* = 6.9 Hz, 1H, H_e), 2.34 (s, 3H, H_g), 1.71 (s, 3H, H_9), 1.37 – 1.33 (m, 6H, H_e).^{13}C NMR (150.95 MHz, MeOD) δ 184.4 (C2), 184.2 (C4), 150.5 (C3a'), 139.8 (C6'), 138.4 (C7a'), 137.0 (C7'), 134.3 (C8a), 132.2 (Carom.), 131.3 (Carom.), 128.47 (C8), 127.1 (C5), 122.7 (C4'), 119.3 (C4a), 115.8 (C5'), 106.8 (C3), 101.1 (Cd), 98.7 (Ca), 94.0 (C1), 92.1 (C3'), 83.6 (Cb), 83.3 (Cb), 80.6 (Cc), 80.5 (Cc), 32.69 (Ce), 23.1 (Cf), 22.9 (Cf), 18.3 (Cg), 8.0 (C9). $C_{28}H_{27}N_3O_3Ru$ • 0.5 CH_2Cl_2: C 57.33%, H 4.73%, N 7.04%. Found: C 56.99%, H 4.97%, N 7.09%.

[3-Methyl-4-oxo-(1*H*-κN^2-pyrazol-1-yl)-1,4-dihydronaphtalene-1,2-bis(olato)-κO^1-κO^2)(η^6-*p*-cymene)osmium(II)] (**2a**)



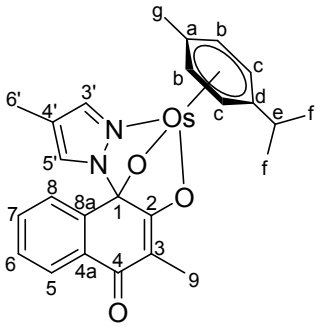
The reaction was performed according to the general procedure, using bis[dichlorido(η^6-*p*-cymene)osmium(II) (200 mg, 0.253 mmol, 1 eq.), 1*H*-pyrazole (34 mg, 0.506 mmol), 2-hydroxy-3-methylnaphthalene-1,4-dione (**L)** (105 mg, 0.557 mmol, 2.2 eq.), sodium methoxide (60 mg, 1.113 mmol, 4.4 eq.). The mixture was stirred at 60 °C for 8 minutes under microwave irradiation. Flash column chromatography with EtOAc/*n*-hexane/NEt_3 (90/5/5). Yield: 190 mg yellow powder (0.328 mmol, 65 %). ^{1}H NMR (700.40 MHz, MeOD) δ 8.29 (d, *J* = 2.2 Hz, 1H, $H_{3'}$), 8.17 – 8.11 (m, 1H, $H_{arom.}$), 7.66 – 7.60 (m, 3H, $H_{arom.}$), 6.87 (d, *J* = 2.6 Hz, 1H, $H_{5'}$), 6.39 (t, *J* = 2.4 Hz, 1H, $H_{4'}$), 6.19 (d, *J* = 5.5 Hz, 1H, H_c), 6.09 (d, *J* = 5.5 Hz, 1H, H_c), 5.85 (d, *J* = 5.4 Hz, 1H, H_b), 5.80 (d, *J* = 5.5 Hz, 1H, H_b), 2.74 (hept, *J* = 6.9 Hz, 1H, H_e), 2.40 (s, 3H, H_g), 1.75 (s, 3H, H_9), 1.31 (d, *J* = 6.9 Hz, 6H, H_f).^{13}C NMR (176.13 MHz, MeOD) δ 184.6 (C2), 183.1 (C4), 141.4 (C3‘), 136.7 ($C_{arom.}$), 134.3 ($C_{arom.}$), 132.5 ($C_{arom.}$), 131.5 ($C_{arom.}$), 127.8 ($C_{arom.}$), 127.6 (C5’), 127.3 ($C_{arom.}$), 109.4 (C4’), 105.4 (C3), 98.1 (C1), 90.8 (Cd), 89.1 (Ca), 73.9 (Cc), 73.4 (Cc), 70.4 (Cb), 70.3 (Cb), 33.1 (Ce), 23.4 (Cf), 23.2 (Cf), 18.6 (Cg), 8.1 (C9). Anal. Calc. for $C_{24}H_{24}N_2O_3Os$•0.25CH_2Cl_2: C 48.55%, H 4.12%, N 4.67%. Found: C 48.40%, H 4.12%, N 4.67%.

[3-Methyl-4-oxo-(1*H*-κ*N*^{2}-indazolyl-1-yl)-1,4-dihydronaphtalene-1,2-bis(olato)-κ*O*^{1}-κ*O*^{2})(η^6-*p*-cymene)osmium(II)] (**2b**)



The reaction was performed according to the general procedure, using bis[dichlorido(η^6-*p*-cymene)osmium(II) (200 mg, 0.253 mmol, 1 eq.), 1*H*-indazol (60 mg, 0.506 mmol), 2-hydroxy-3-methylnaphthalene-1,4-dione (**L)** (105 mg, 0.557 mmol, 2.2 eq.), sodium methoxide (60 mg, 1.113 mmol, 4.4 eq.). The mixture was stirred at 60 °C for 8 minutes under microwave irradiation. Flash column chromatography with EtOAc/*n*-hexane/NEt_3 (90/5/5). Yield: 178 mg yellow powder (0.283 mmol 56 %). ^{1}H NMR (700.40 MHz, DMSO-d_6) δ 9.17 (s, 1H, H3'), 8.11 (dd, *J* = 7.8, 1.4 Hz, 1H, $H_{arom.}$), 7.83 – 7.80 (m, 1H, $H_{arom.}$), 7.70 – 7.65 (m, 2H, $H_{arom.}$), 7.62 – 7.57 (m, 1H, $H_{arom.}$), 7.13 – 7.02 (m, 2H, $H_{arom.}$), 6.33 (d, *J* = 5.4 Hz, 1H, H_c), 6.26 (d, *J* = 5.5 Hz, 1H, H_c), 5.98 (d, *J* = 5.4 Hz, 1H, H_c), 5.89 (d, *J* = 5.4 Hz, 1H, H_c), 5.29 (d, *J* = 8.5 Hz, 1H, $H_{arom.}$), 2.72 (hept, *J* = 6.9 Hz, 1H, H_e), 2.34 (s, 3H, H_g), 1.56 (s, 3H, H_9), 1.27 – 1.23 (m, 6H, H_f). ^{13}C NMR (176.13 MHz, DMSO) δ 181.0 (C4), 180.3 (C2), 135.9 ($C_{arom.}$), 135.5 (C3'), 134.4 ($C_{arom.}$), 132.8 ($C_{arom.}$), 130.9 ($C_{arom.}$), 130.1 ($C_{arom.}$), 128.5 ($C_{arom.}$), 127.0 ($C_{arom.}$), 125.6 ($C_{arom.}$), 124.6 ($C_{arom.}$), 122.1 ($C_{arom.}$), 121.9 ($C_{arom.}$), 109.6 ($C_{arom.}$), 102.51 (C3), 98.8 (C1), 88.8 (Cd), 87.9 (Ca), 72.9 (Cc), 72.6 (Cc), 69.2 (Cb), 68.5 (Cb), 31.3 (Ce), 23.0 (Cf), 22.6 (Cf), 17.8 (Cg), 8.2 (C9). Anal. Calc. for $C_{28}H_{26}N_2O_3Os$•0.1H_2O: C 53.33%, H 4.19%, N 4.44%. Found: C 52.92%, H 4.15%, N 4.39%.

[3-Methyl-4-oxo-(4-methyl-1*H*-κN^2-pyrazol-1-yl)-1,4-dihydronaphtalene-1,2-bis(olato)-κO^1-κO^2)(η^6-*p*-cymene)osmium(II)] (**2c**)



The reaction was performed according to the general procedure, using bis[dichlorido(η^6-*p*-cymene)osmium(II) (200 mg, 0.253 mmol, 1 eq.), 4-methyl-1*H*-pyrazole (41.9 µL, 42 mg, 0.506 mmol), 2-hydroxy-3-methylnaphthalene-1,4-dione (**L)** (105 mg, 0.557 mmol, 2.2 eq.), sodium methoxide (60 mg, 1.113 mmol, 4.4 eq.). The mixture was stirred at 60 °C for 8 minutes under microwave irradiation. Flash column chromatography with EtOAc/*n*-hexane/NEt_3 (90/5/5). Yield: 137 mg yellow powder (0.231 mmol 46 %). ^{1}H NMR (700.40 MHz, MeOD) δ 8.16 – 8.11 (m, 1H, $H_{arom.}$), 8.10 (s, 1H, $H_{3'}$), 7.66 – 7.59 (m, 3H, $H_{arom.}$), 6.67 (s, 1H, $H_{5'}$), 6.15 (d, *J* = 5.4 Hz, 1H, H_b), 6.07 (d, *J* = 5.4 Hz, 1H, H_b), 5.82 (d, *J* = 5.5 Hz, 1H, H_c), 5.77 (d, *J* = 5.5 Hz, 1H, H_c), 2.73 (hept, *J* = 6.9 Hz, 1H, H_e), 2.39 (s, 3H, H_g), 1.98 (s, 3H, $H_{6'}$), 1.75 (s, 3H, H_9), 1.31 (d, *J* = 6.9 Hz, 6H, H_f).^{13}C NMR (176.12 MHz, MeOD) δ 183.2 (C4), 181.9 (C2), 139.8 (C3‘), 135.5 ($C_{arom.}$), 132.9 ($C_{arom.}$), 131.0 ($C_{arom.}$), 130.0 ($C_{arom.}$), 126.4 ($C_{arom.}$), 125.8 ($C_{arom.}$), 125.2 (C5’), 119.2 (C4’), 103.8 (C3), 96.5 (C1), 89.4 (Cd), 87.6 (Ca), 72.4 (Cb), 71.9 (Cb), 69.0 (Cc), 68.8 (Cc), 31.7 (Cg), 22.0 (Cf), 21.8 (Cf), 17.2 (Ce), 7.5 (C6’), 6.7 (C9). Anal. Calc. for $C_{25}H_{26}N_2O_3Os$: C 50.66%, H 4.42%, N 4.73%. Found: C 50.46%, H 4.40%, N 4.72%.

NMR Spectra

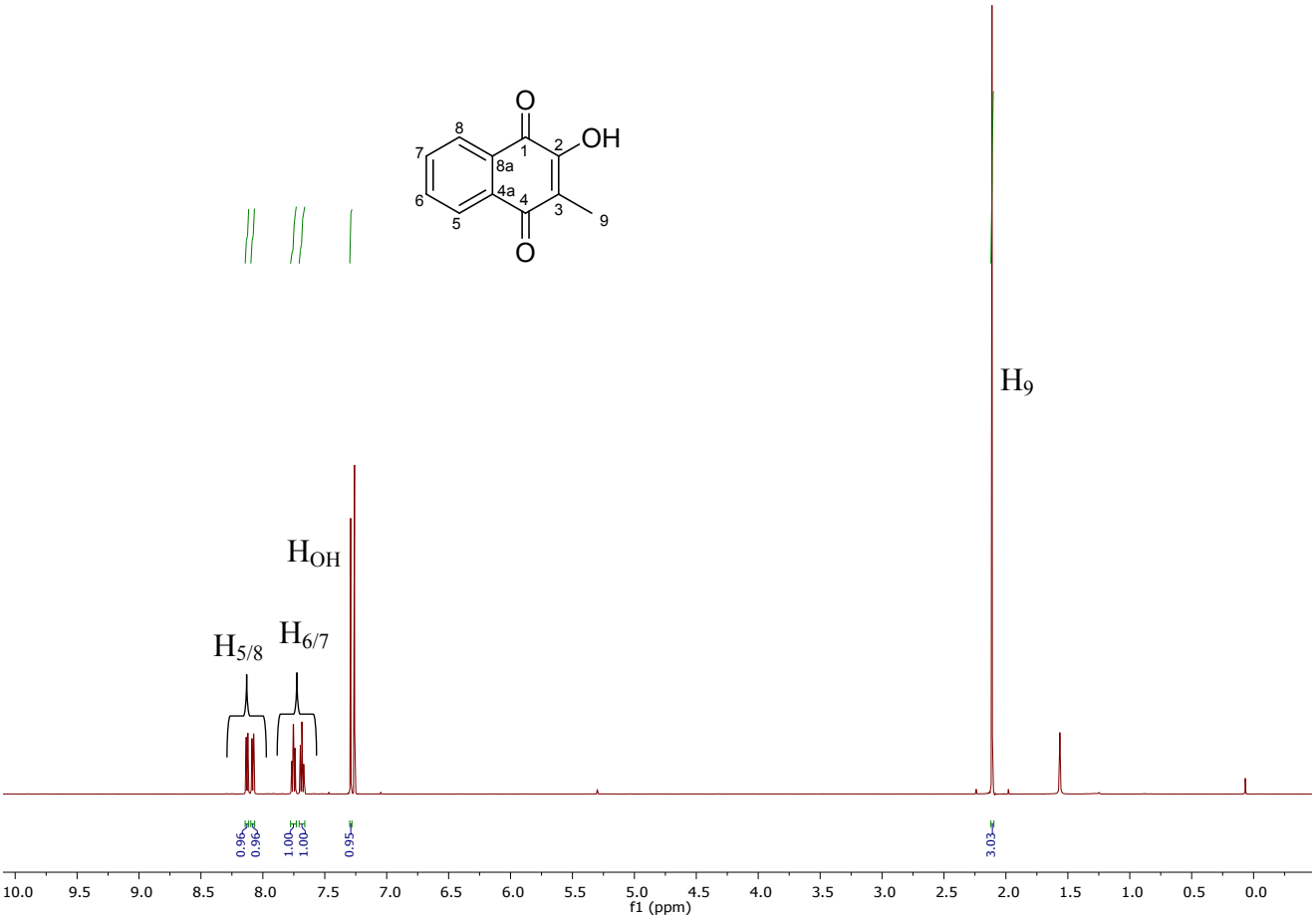


Figure S1: ^{1}H-NMR spectrum of compound **L**

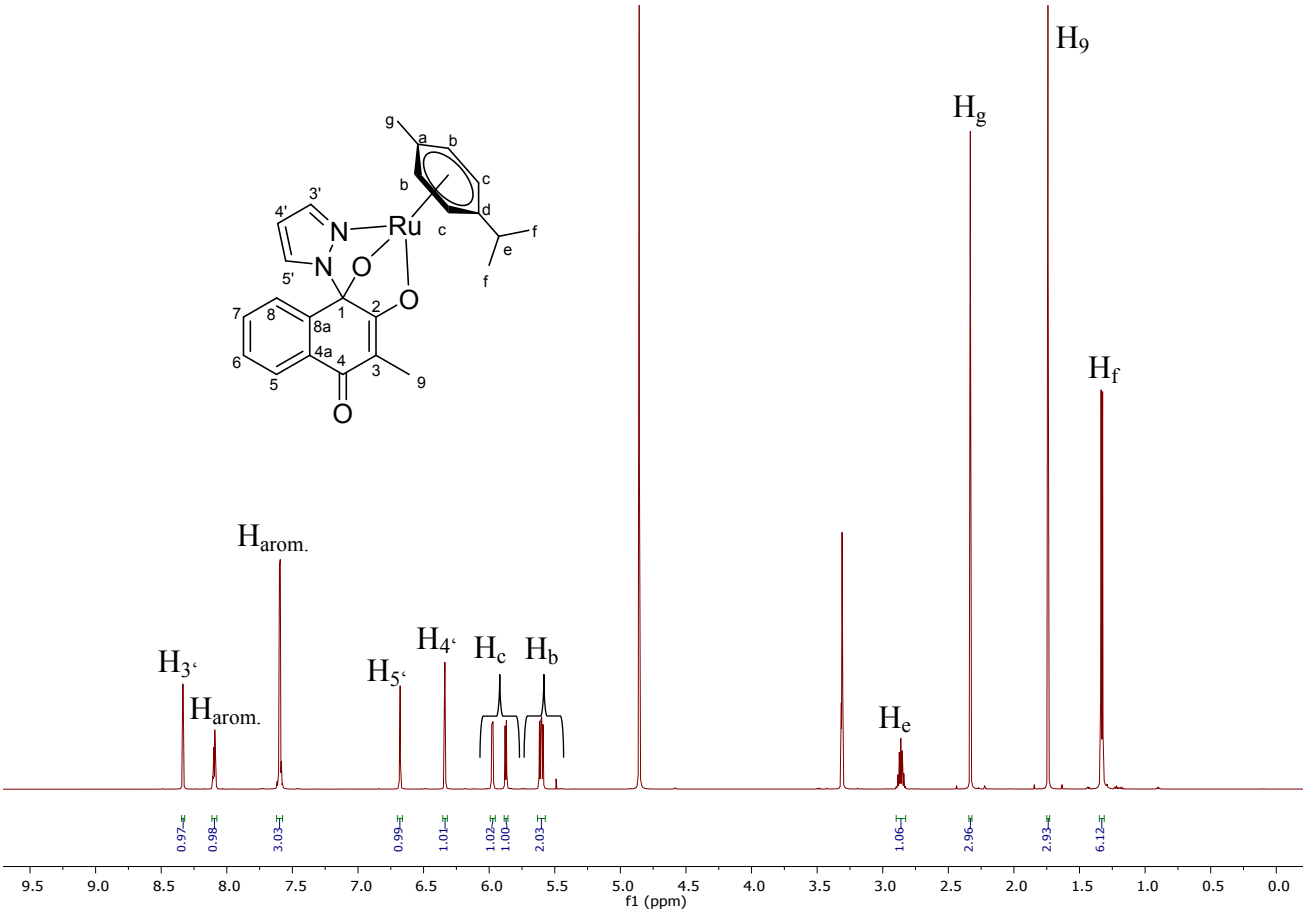


Figure S2: ^{1}H-NMR spectrum of compound **1a**

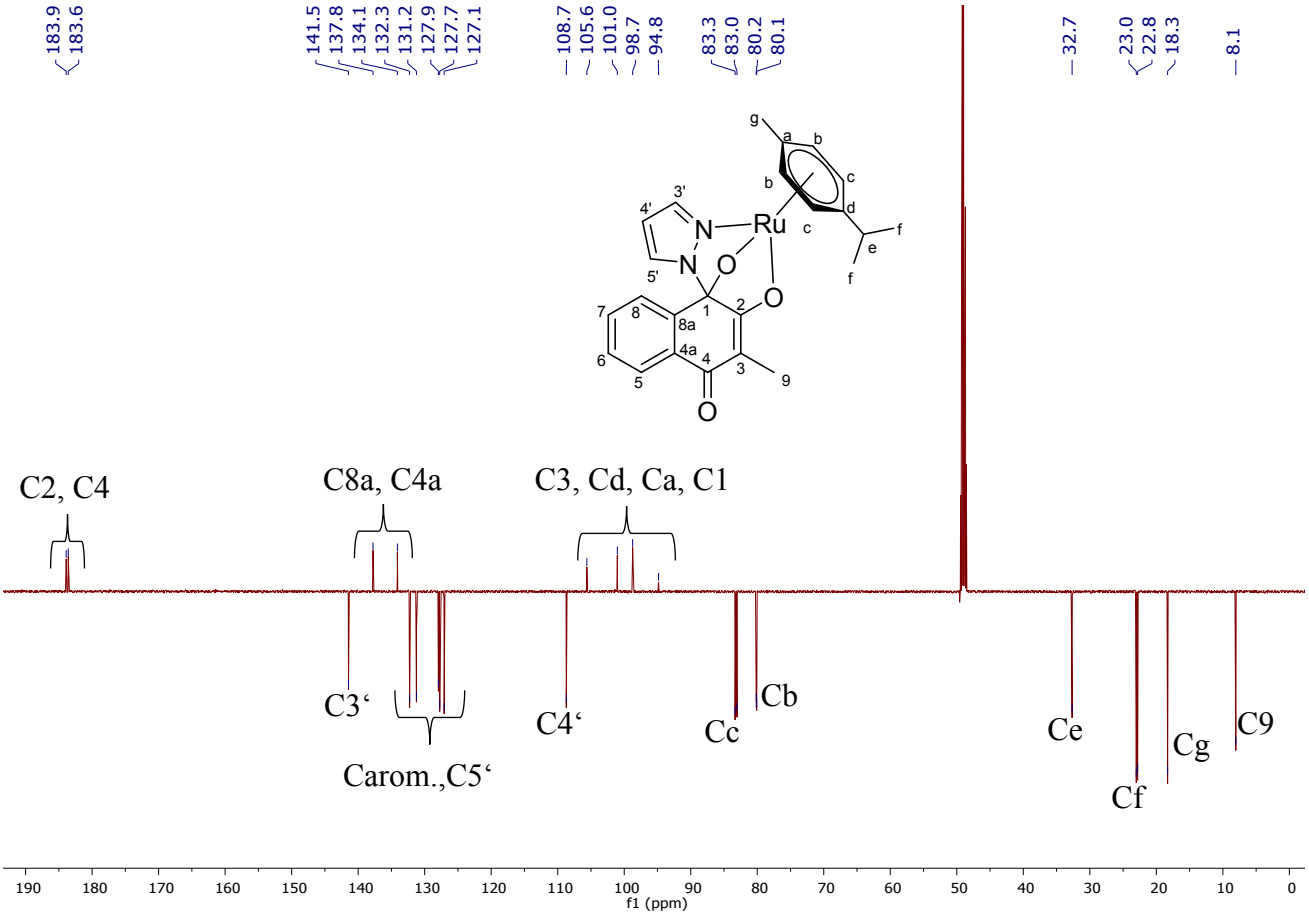


Figure S3: ^{13}C-NMR spectrum of compound **1a**

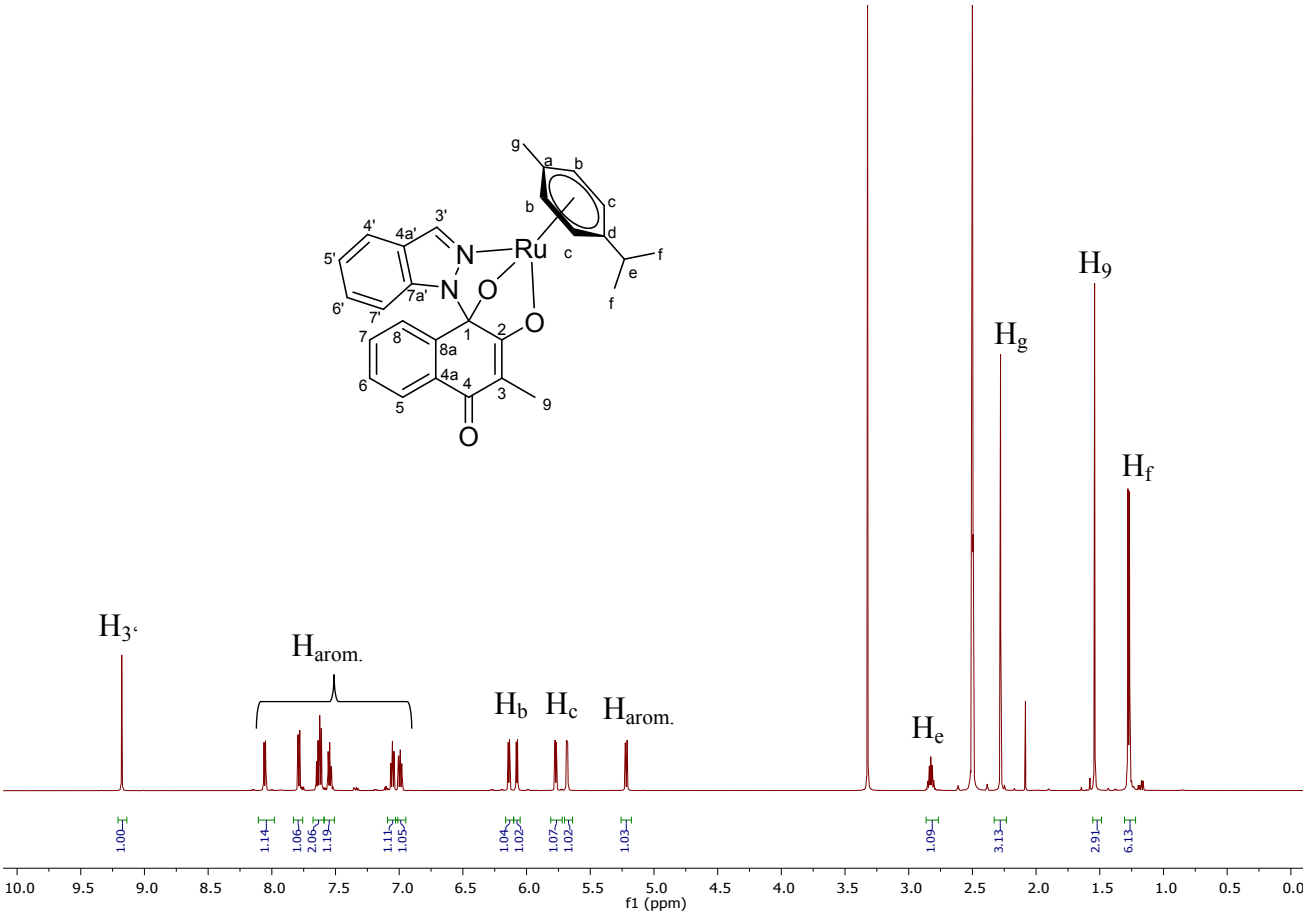


Figure S4: [1]H-NMR spectrum compound **1b**

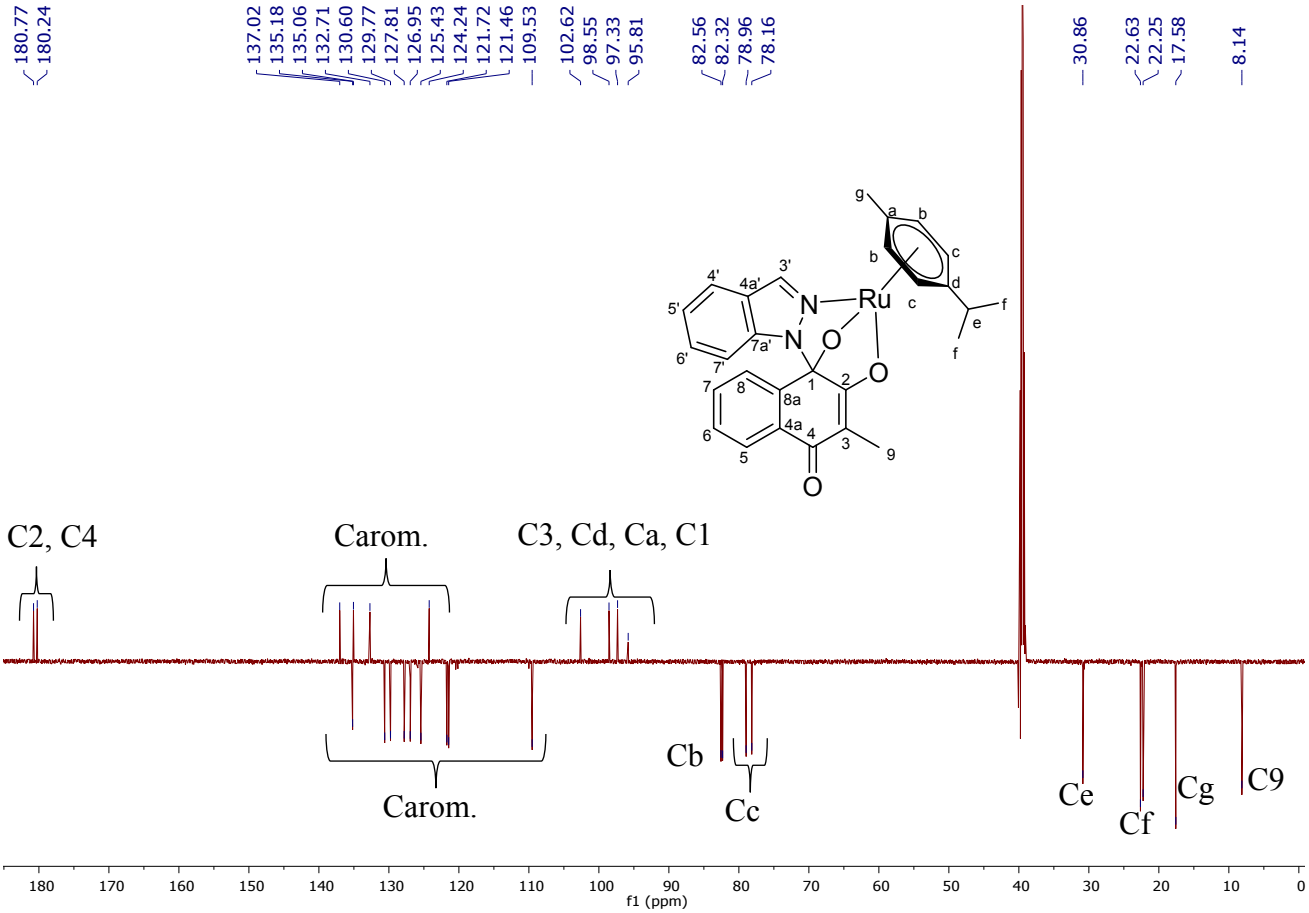


Figure S5: ^{13}C-NMR spectrum of compound **2b**

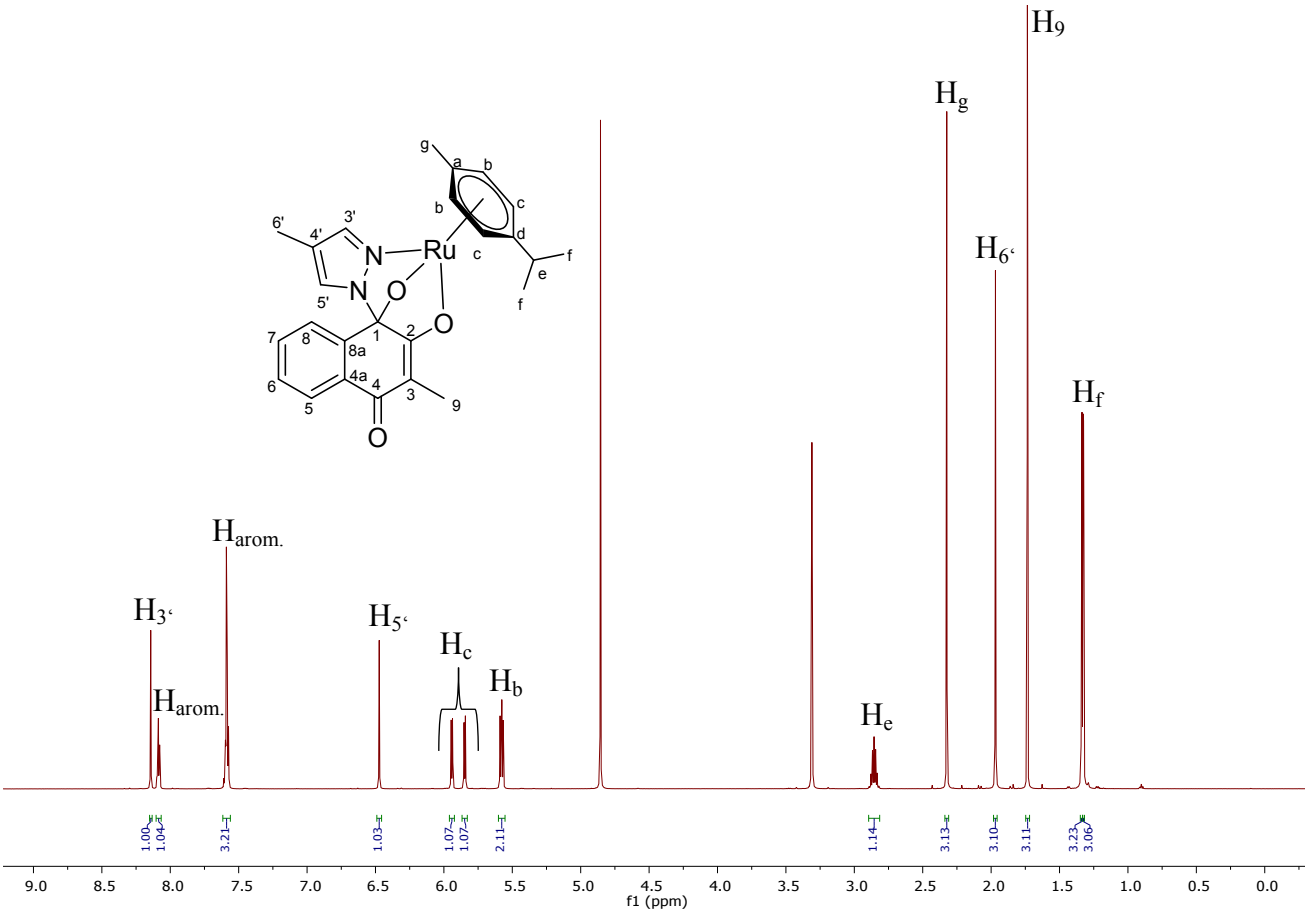


Figure S6: ^{1}H-NMR spectrum of compound **1c**

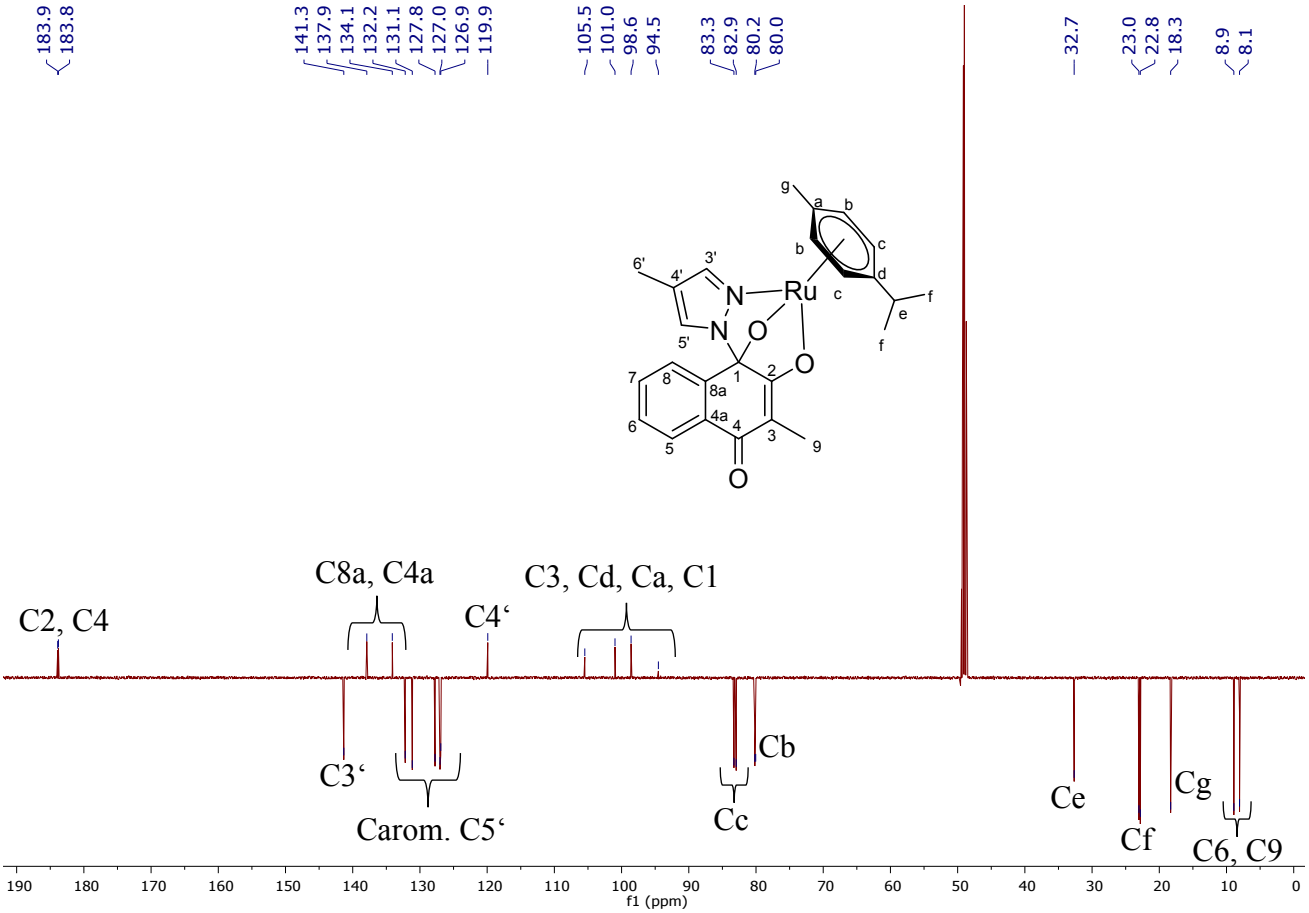


Figure S7: ^{13}C-NMR spectrum of compound **1c**

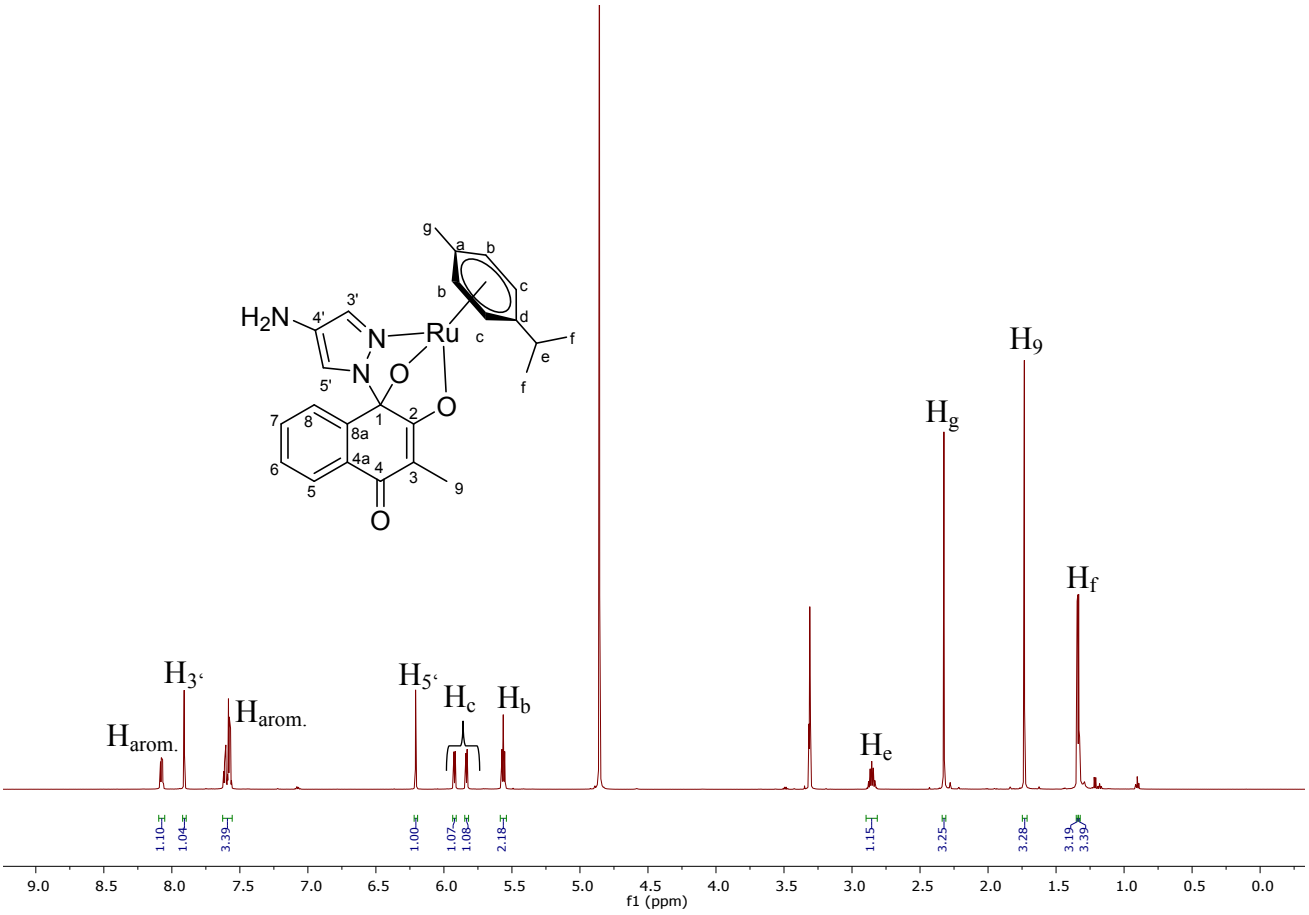


Figure S8: ^{1}H-NMR spectrum of compound **1d**

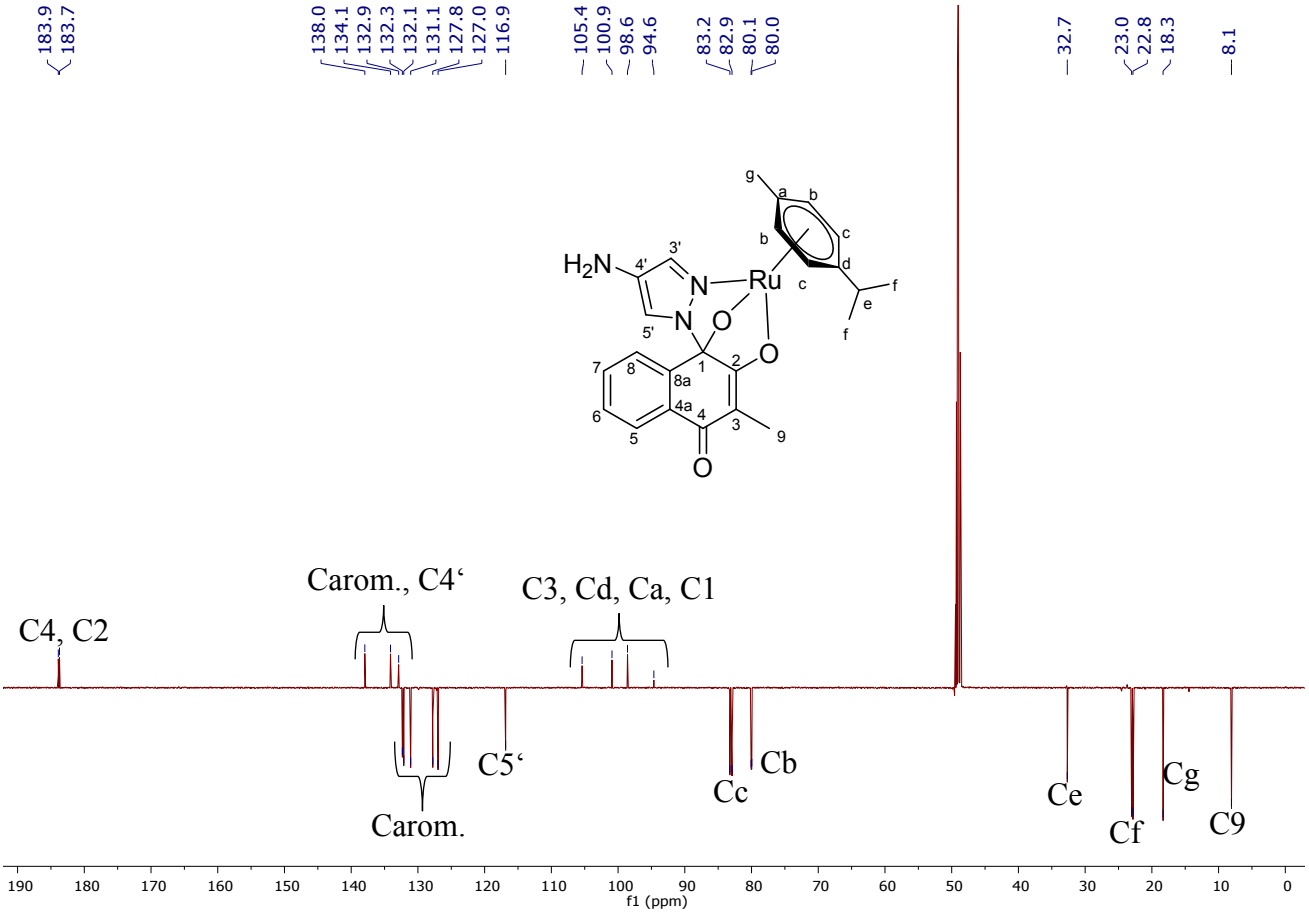


Figure S9: ^{13}C-NMR spectrum of compound **1d**

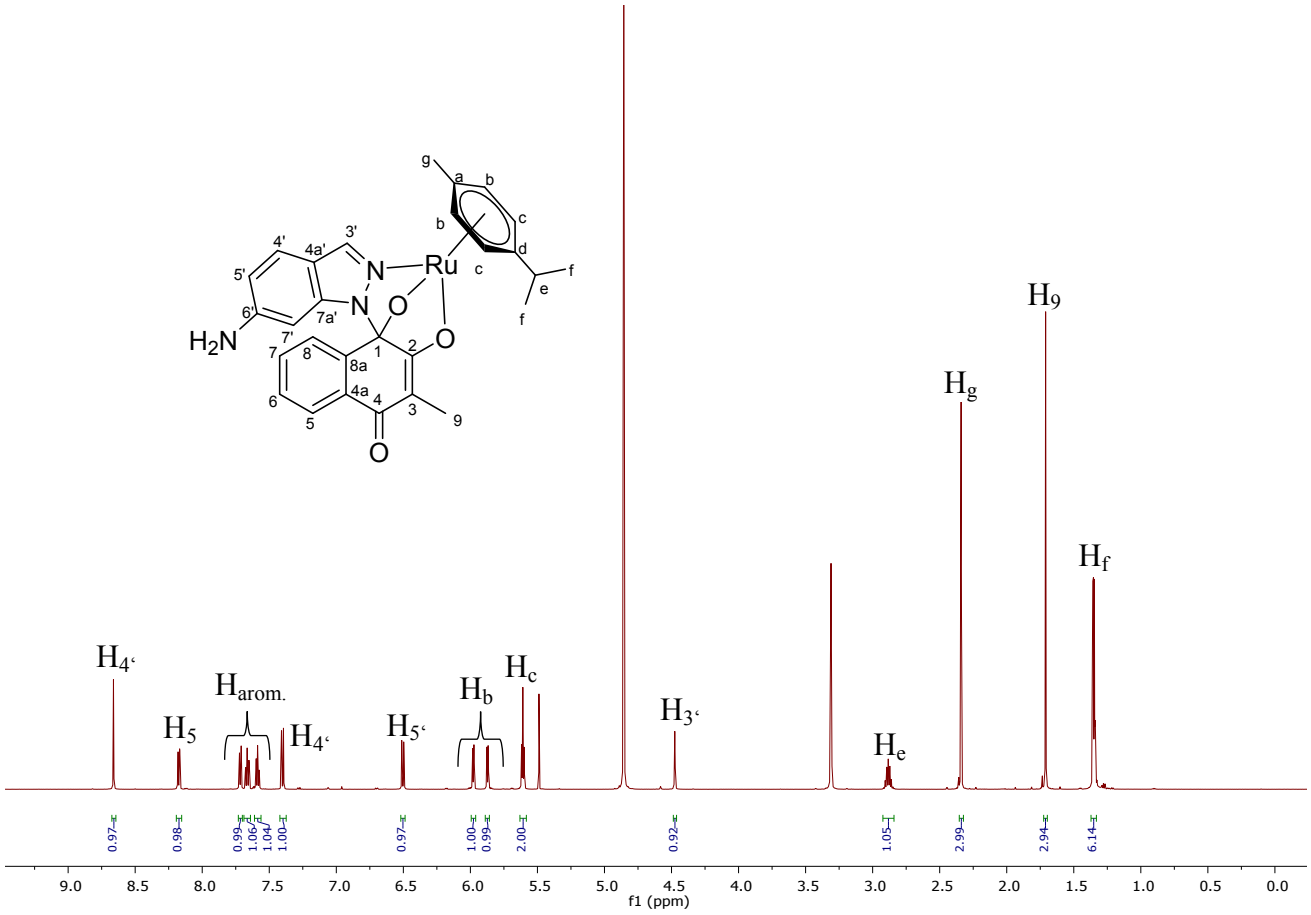


Figure S10: ^{1}H-NMR spectrum of compound **1e**

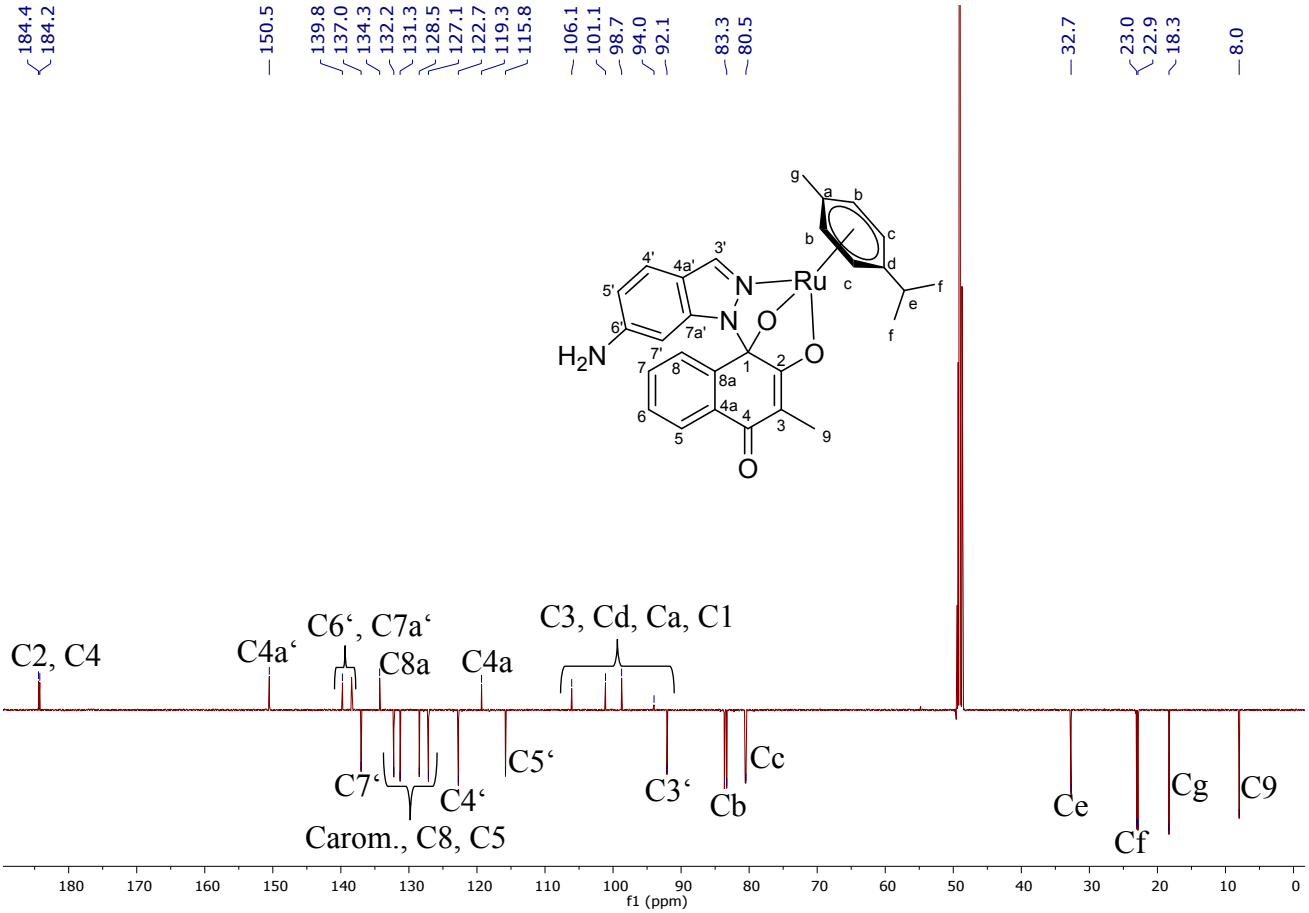


Figure S11: ^{13}C-NMR spectrum of compound **1e**

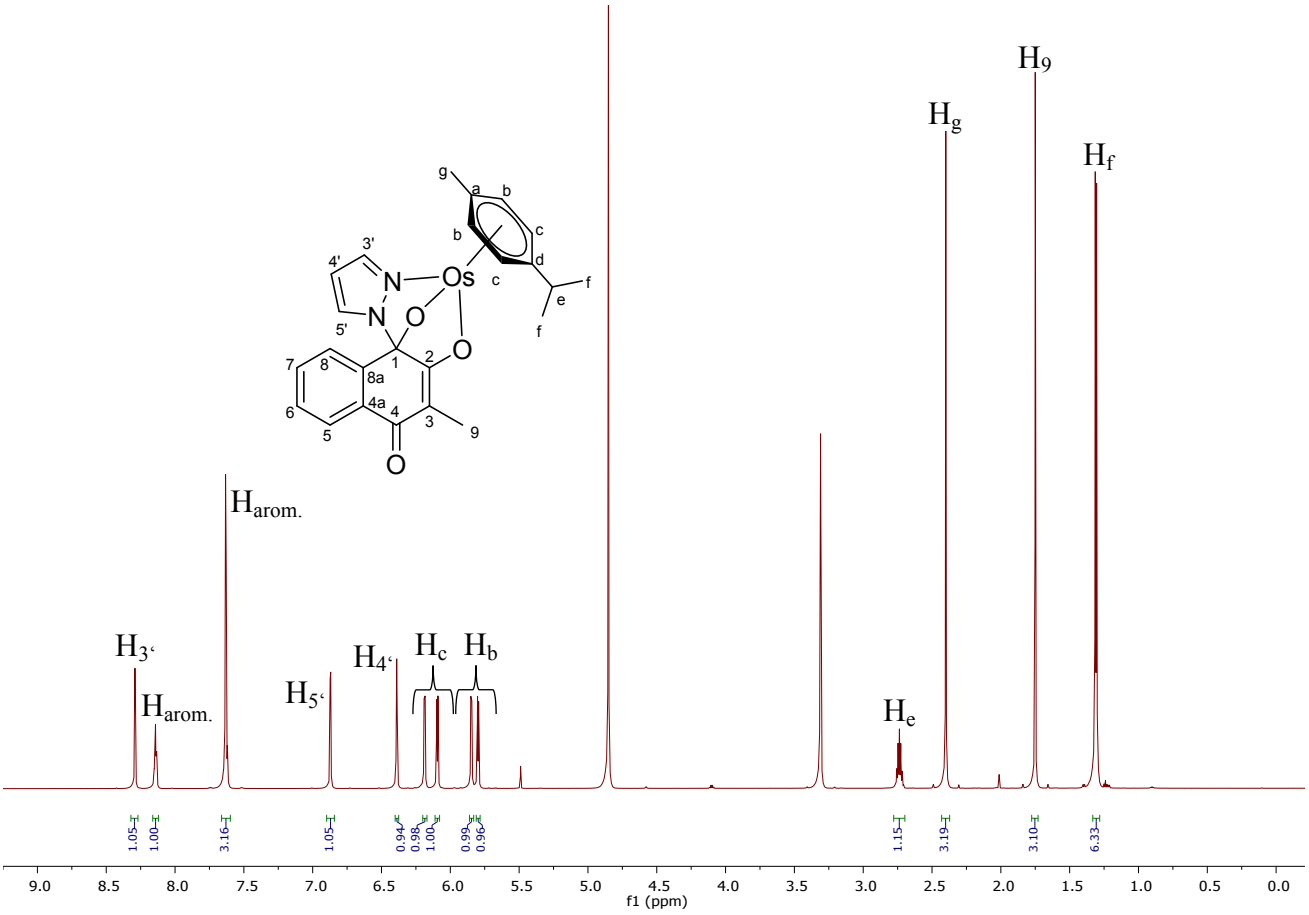


Figure S12: ^{1}H-NMR spectrum of compound **2a**

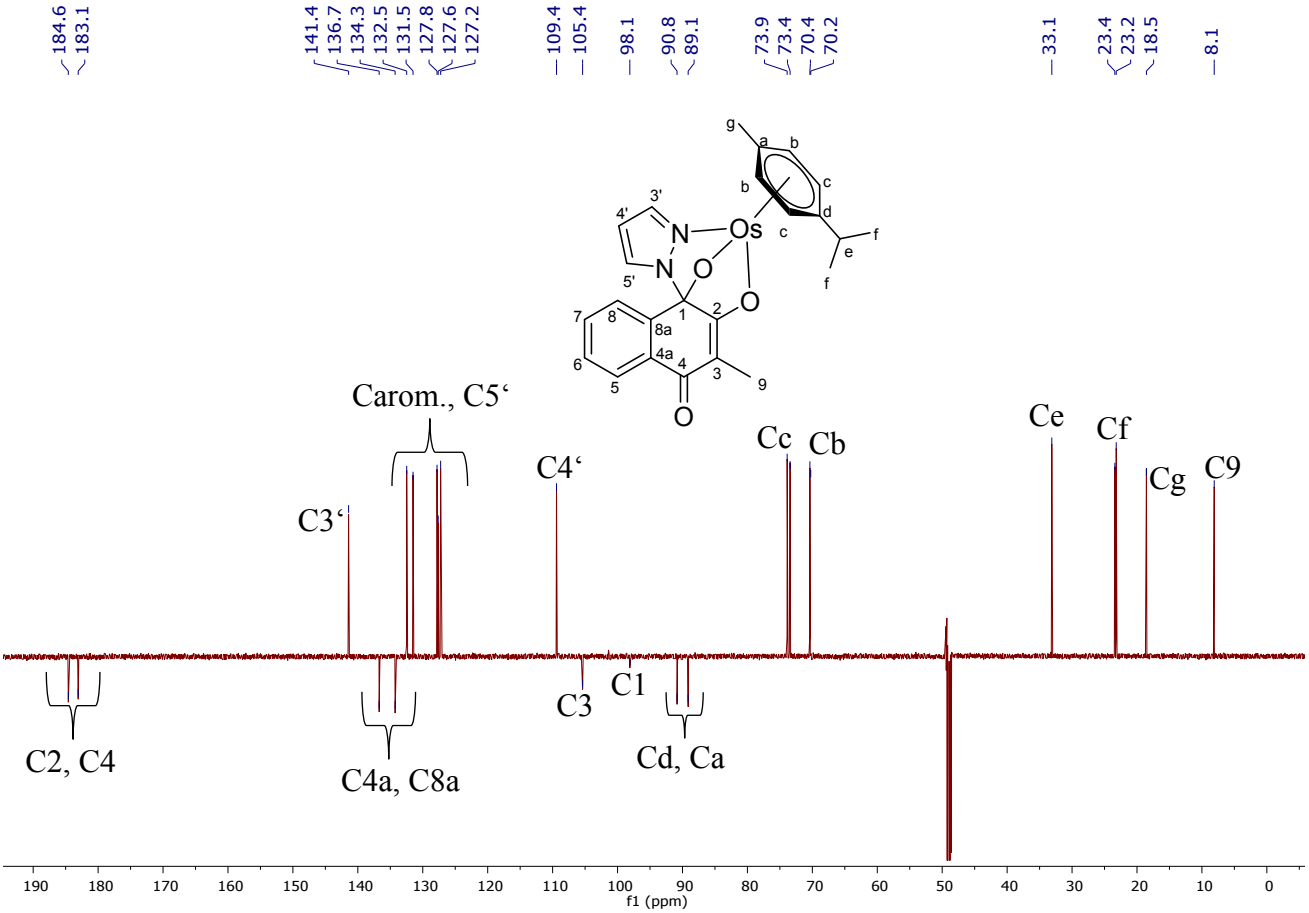


Figure S13: ^{13}C-NMR spectrum of compound **2a**

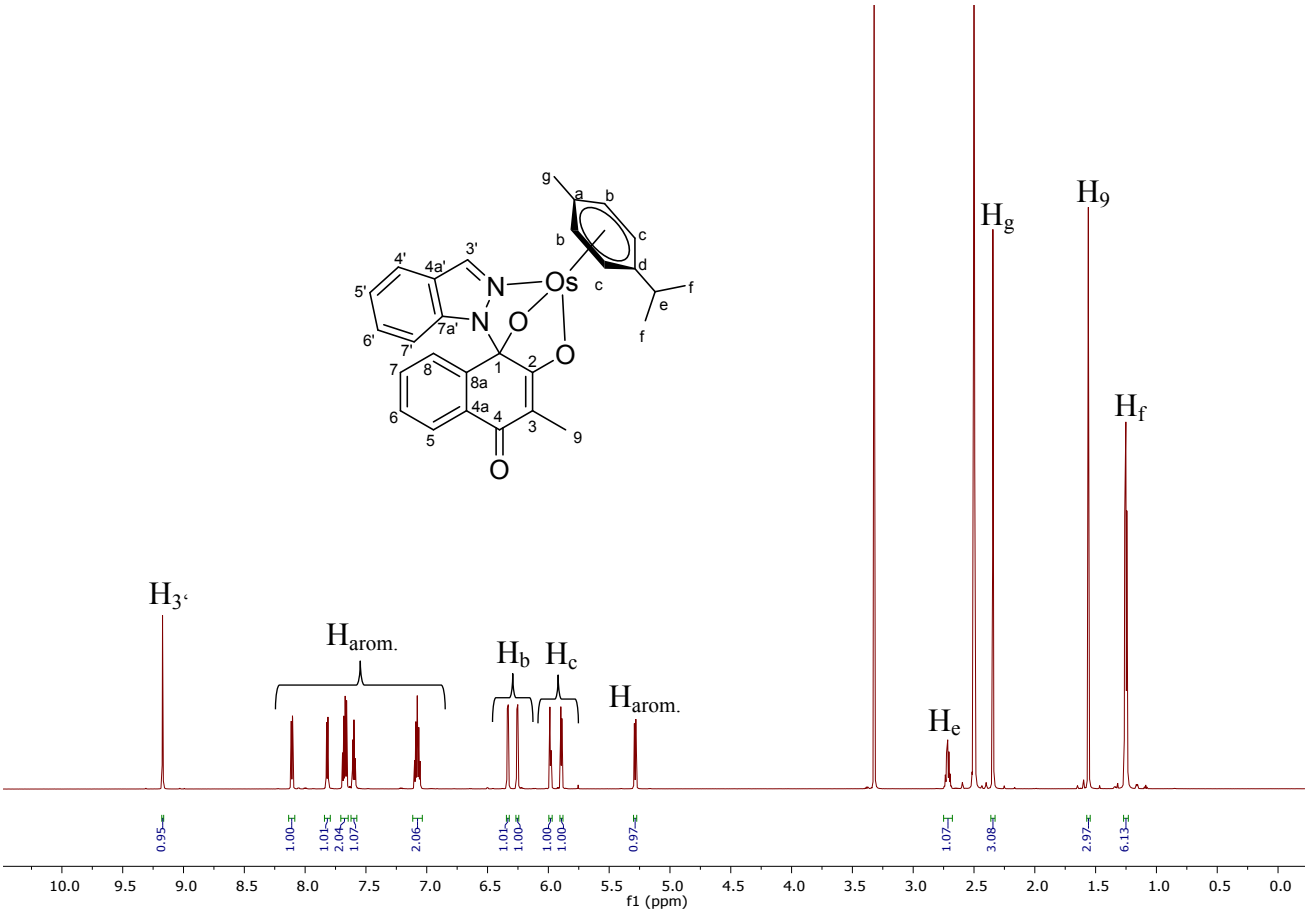


Figure S14: ^{1}H-NMR spectrum of compound **2b**

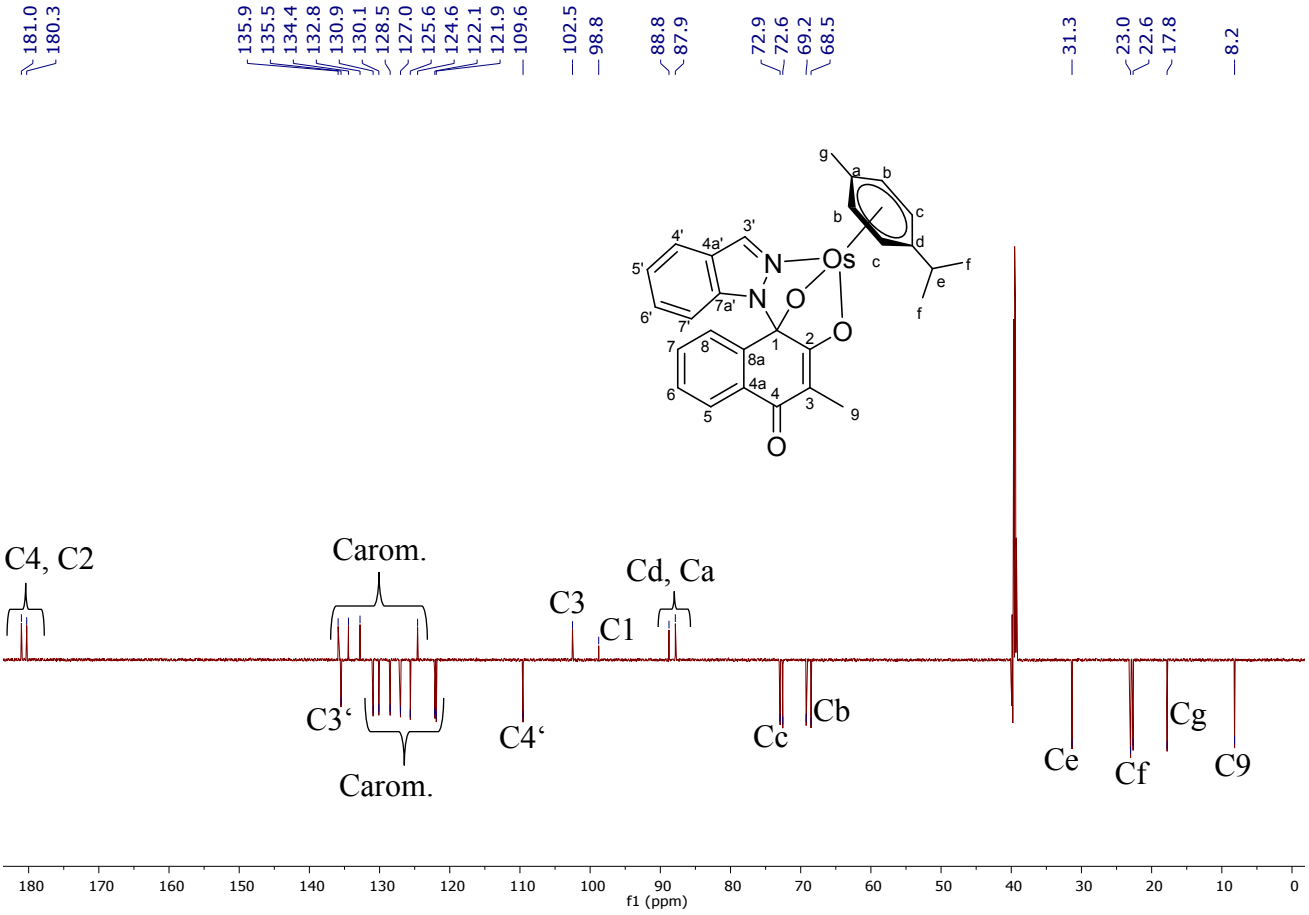


Figure S15: 13C-NMR spectrum of compound **2b**

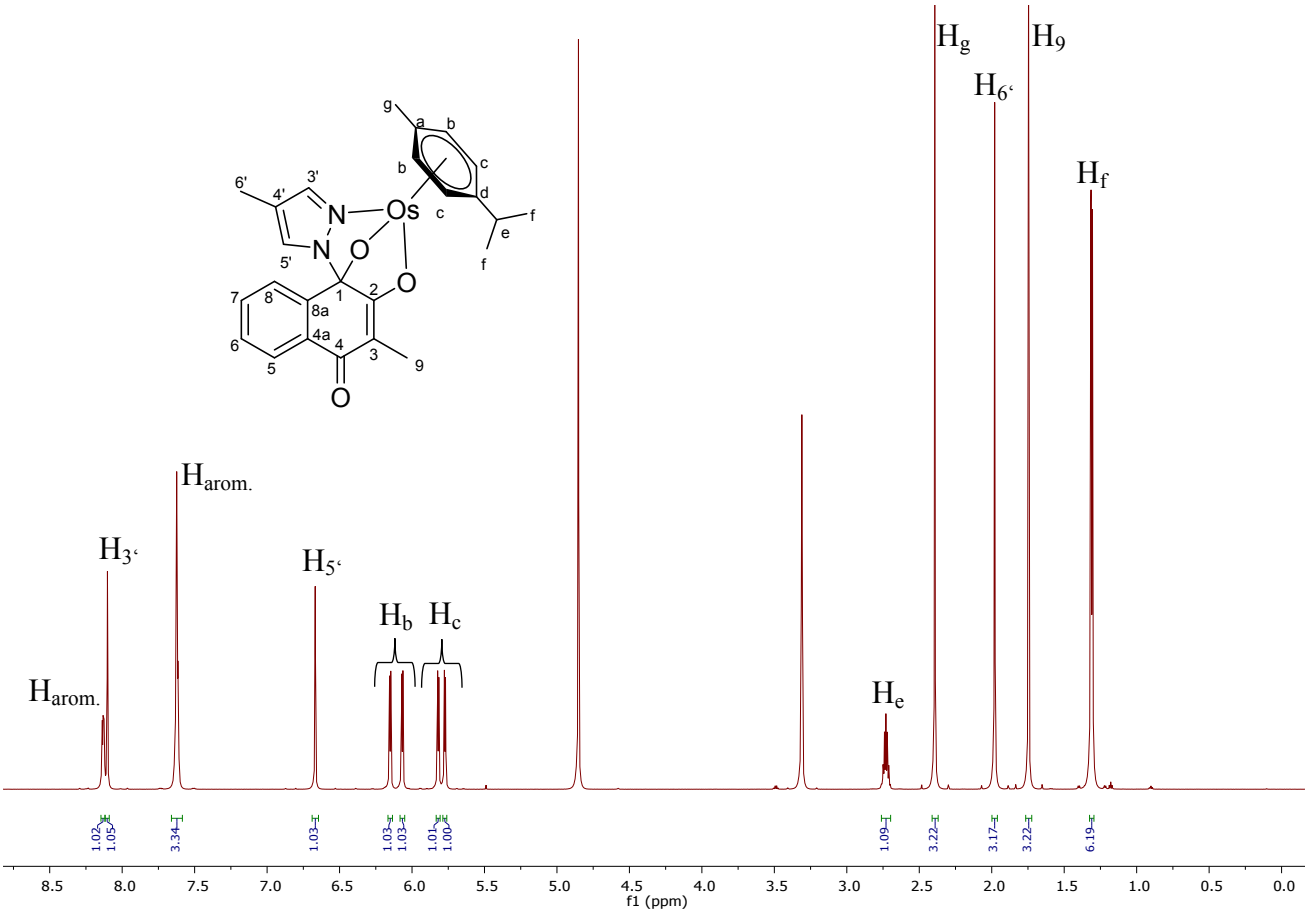


Figure S16: ^{1}H-NMR spectrum of compound **2c**

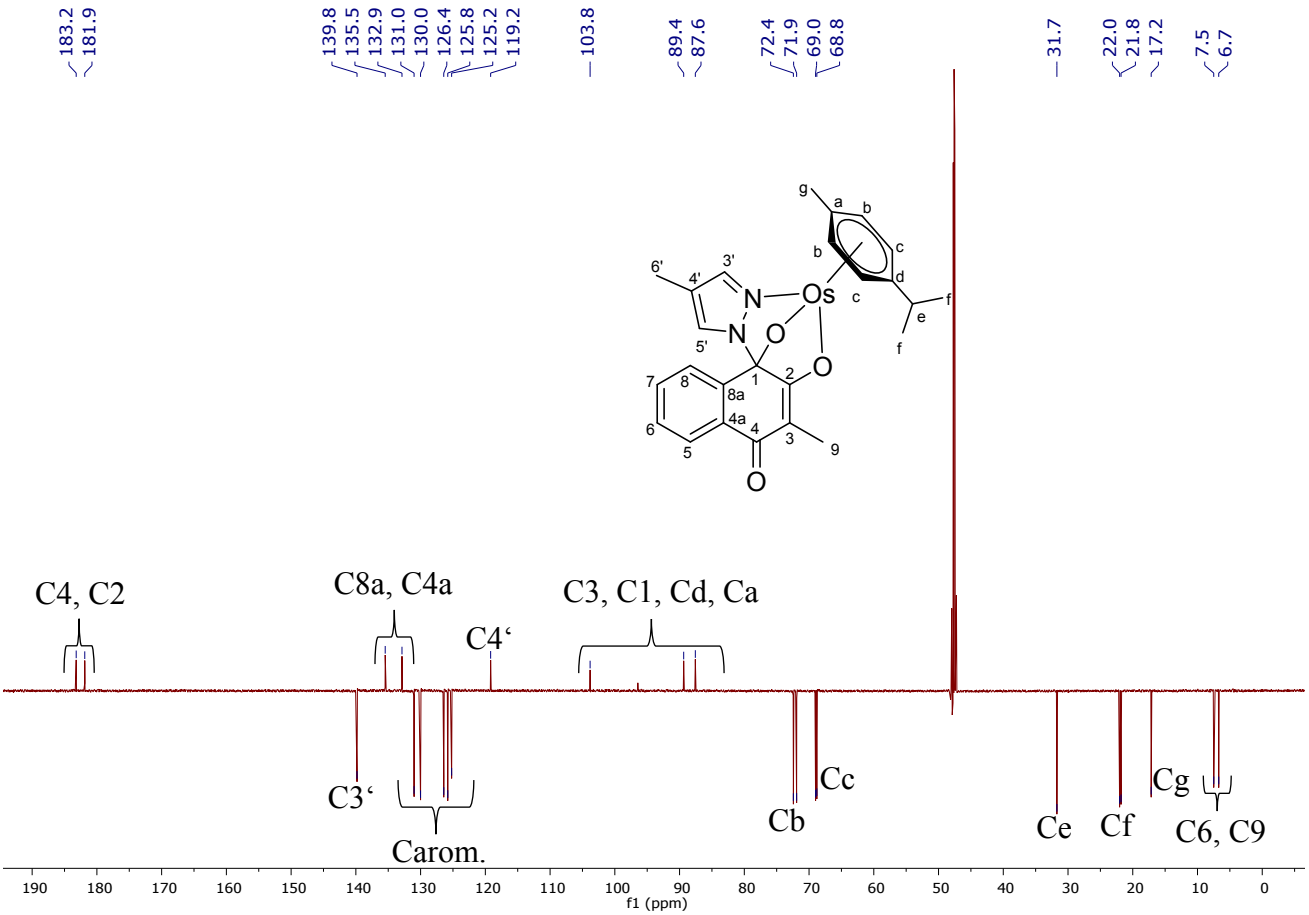


Figure S17: ^{13}C-NMR spectrum of compound **2c**

X-ray analysis

The X-ray intensity data were measured on Bruker D8 Venture diffractometer equipped with multilayer monochromators, Cu/Mo K/α INCOATEC micro focus sealed tubes and Oxford cooling system. The structures were solved by *direct methods or charge flipping* and refined by *full-matrix least-squares techniques*. Non-hydrogen atoms were refined with *anisotropic displacement parameters*. Hydrogen atoms were inserted at calculated positions and refined with riding model. The following software was used: *Bruker SAINT software package*[6] using a narrow-frame algorithm for frame integration, *SADABS*[7] for absorption correction, *OLEX2*[8] for structure solution, refinement, molecular diagrams and graphical user-interface, *Shelxle*[9] for refinement and graphical user-interface *SHELXS-2015*[10] for structure solution, *SHELXL-2015*[11] for refinement, *Platon*[12] for symmetry check and π-π Interactions calculations. Experimental data and CCDC-Codes Experimental data and CCDC-Code (Available online: http://www.ccdc.cam.ac.uk/conts/retrieving.html) can be found in Table S1. Crystal data, data collection parameters, and structure refinement details are given in Table S2 to Table S17. Crystal structures and π-π Interactions are visualized in Figure S18 to Figure S27.

Table S1: Experimental parameter and CCDC-Codes.

Sample	**Machine**	**Source**	**Temp.**	**Detector Distance**	**Time/ Frame**	**#Frames**	**Frame width**	**CCDC**
	Bruker		[K]	[mm]	[s]		[°]	
417 1a	D8	Mo	100	30	15	752	0.400	1955180
576 1b	D8	Mo	100	30	2	765	0.400	1955183
542 1c	D8	Cu	100	30	26	2037	0.500	1955182
640 1d	D8	Mo	100	30	5	816	1.000	1955187
636 1e	D8	Cu	100	30	20	2533	1.000	1955186
510 2a	D8	Mo	100	40	1.5	1214	0.500	1985181
579 2b	D8	Mo	100	30	0.5	1200	0.500	1955184
580 2c	D8	Cu	100	30	3	2281	1.000	1955185

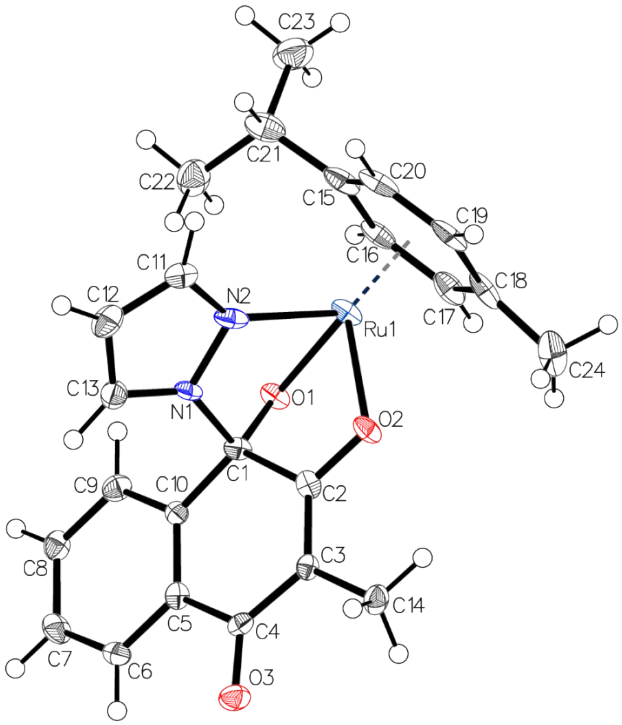


Figure S18: Crystal structure of **1a**. C-C- Bond precision: 0.0068 Å. Solvent and counter ion omitted for clarity.

Table S2: Sample and crystal data (**1a**).

Chemical formula	C27H32N2O5Ru	**Crystal system**	monoclinic	
Formula weight [g/mol]	565.61	**Space group**	*C2/c*	
Temperature [K]	100	**Z**	8	
Measurement method	\f and \w scans	**Volume [Å^3]**	5052.2(4)	
Radiation (Wavelength [Å])	MoKα (λ = 0.71073)	**Unit cell dimensions [Å] and [°]**	32.8559(11)	90
Crystal size / [mm^3]	0.316 × 0.053 × 0.034		8.4989(4)	96.9960(17)
Crystal habit	clear yellow needle		18.2283(7)	90
Density (calculated) / [g/cm^3]	1.487	**Absorption coefficient / [mm^{-1}]**	0.661	
Abs. correction Tmin	0.6285	**Abs. correction Tmax**	0.746	
Abs. correction type	multiscan	**F(000) [e$^-$]**	2336	

Table S3: Data collection and structure refinement (**1a**).

Index ranges	$-39 \le h \le 30$, $-8 \le k \le 10$, $-21 \le l \le 21$	**Theta range for data collection [°]**	4.502 to 50.692	
Reflections number	10516	**Data / restraints / parameters**	4622/0/325	
Refinement method	Least squares	**Final R indices**	all data	R1 = 0.0658, wR2 = 0.1218
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$		I>2σ(I)	R1 = 0.0478, wR2 = 0.1130
Goodness-of-fit on F^2	1.048	**Weighting scheme**	w=1/[σ2(Fo2)+(0.0001P)2 +32.9719P]	
Largest diff. peak and hole [e $Å^{-3}$]	2.44/-1.33		where $P=(F_o^2+2F_c^2)/3$	

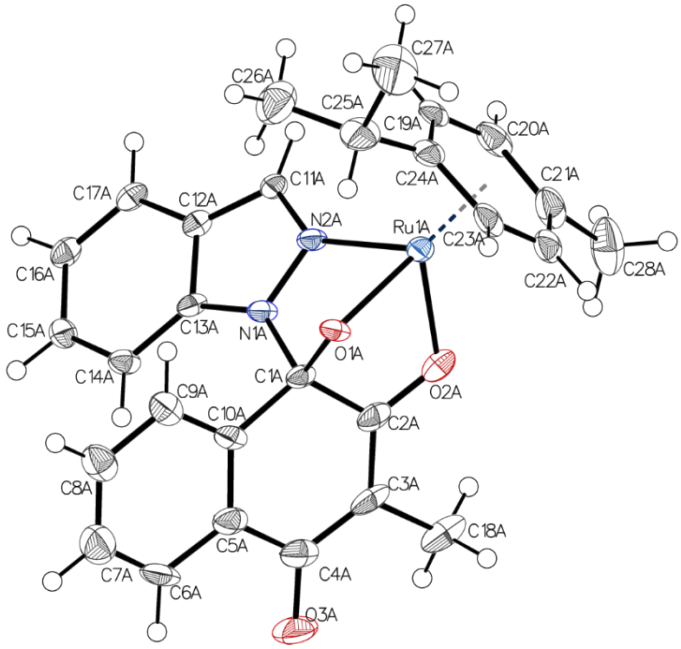


Figure S19: Crystal structure of **1b**. C-C- Bond precision: 0.0073Å. Second independent moiety B and solvent omitted for clarity. Squeeze was used to cut the volume and the corresponding electron densities, because small electron densities in excluded volumes could not be matched. Details see cif-code.

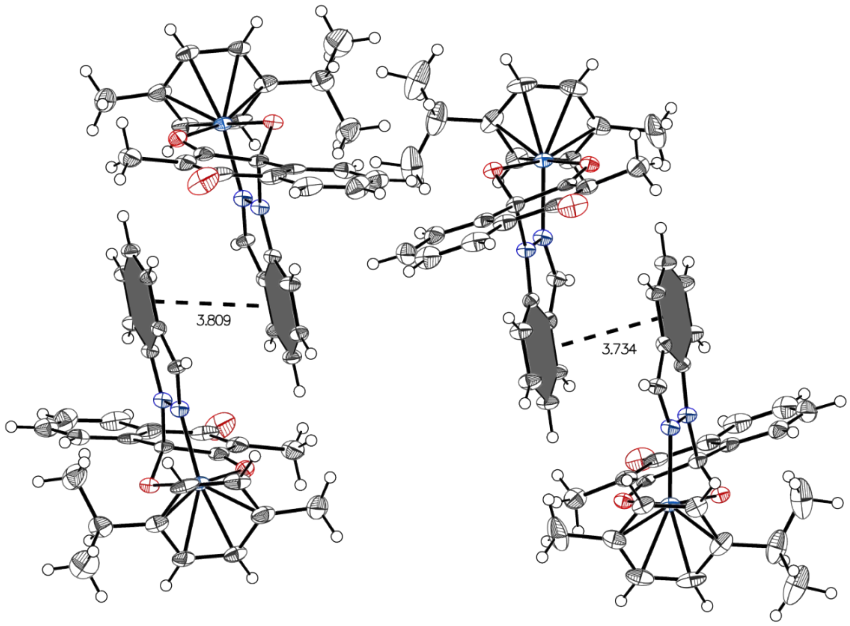


Figure S20: Analysis of π-π Interactions. The distance of Cg-Cg amounts 3.809Å and 3.734 Å. Solvent and hydrogen omitted for clarity.

Table S4: Sample and crystal data (**1b**).

Chemical formula	C28.7H27.75N2O3.17Ru	**Crystal system**	triclinic	
Formula weight [g/mol]	552.55	**Space group**	*P-1*	
Temperature [K]	100	**Z**	4	
Measurement method	\f and \w scans	**Volume [Å^3]**	2687.88(9)	
Radiation (Wavelength [Å])	MoKα (λ = 0.71073)	**Unit cell dimensions [Å] and [°]**	11.4410(2)	107.7827(7)
Crystal size / [mm^3]	0.2 × 0.06 × 0.04		15.6073(3)	99.4000(7)
Crystal habit	clear yellow needle		17.4184(3)	108.5729(6)
Density (calculated) / [g/cm^3]	1.365	**Absorption coefficient / [mm^{-1}]**	0.615	
Abs. correction Tmin	0.2162	**Abs. correction Tmax**	0.259	
Abs. correction type	multiscan	**F(000) [e$^-$]**	1133	

Table S5: Data collection and structure refinement (**1b**).

Index ranges	$-13 \leq h \leq 13$, $-18 \leq k \leq 18$, $-20 \leq l \leq 20$	**Theta range for data collection [°]**	4.652 to 50.68	
Reflections number	28022	**Data / restraints / parameters**	9774/40/662	
Refinement method	Least squares	**Final R indices**	all data	R1 = 0.0651, wR2 = 0.1049
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$		$I>2\sigma(I)$	R1 = 0.0455, wR2 = 0.0934
Goodness-of-fit on F^2	1.039	**Weighting scheme**	w=1/[σ2(Fo2)+(0.0260P)2 +3.1126P]	
Largest diff. peak and hole [e $Å^{-3}$]	0.95/-0.68		where $P=(F_o^2+2F_c^2)/3$	

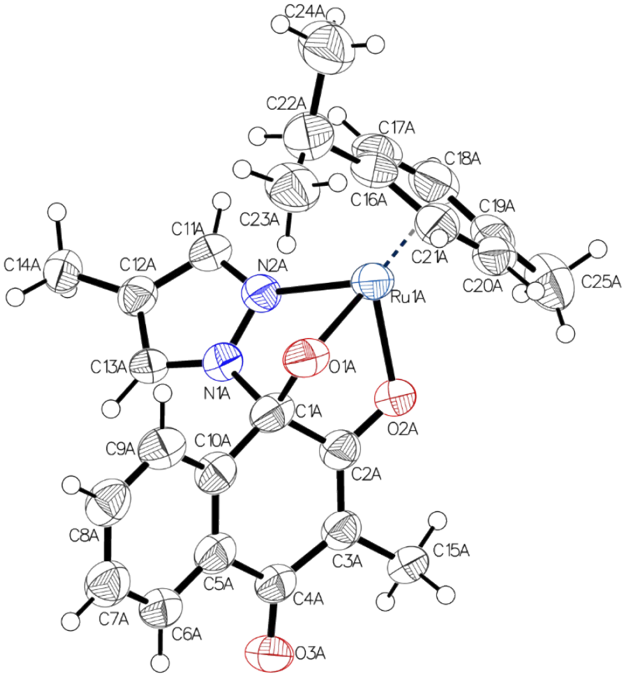


Figure S21: Crystal structure of **1c**. C-C- Bond precision: 0.0105 Å. Second independent moiety B omitted for clarity. Squeeze was used to cut the volume and the corresponding electron densities, because small electron densities in excluded volumes could not be matched. Details see cif-code.

Table S6: Sample and crystal data (**1c**).

Chemical formula	C25H26N2O3Ru	**Crystal system**	triclinic	
Formula weight [g/mol]	503.55	**Space group**	*P-1*	
Temperature [K]	100	**Z**	4	
Measurement method	\f and \w scans	**Volume [Å^3]**	2233.61(9)	
Radiation (Wavelength [Å])	CuKα (λ = 1.54178)	**Unit cell dimensions [Å] and [°]**	9.6758(2)	71.6959(13)
Crystal size / [mm^3]	0.05 × 0.025 × 0.025		14.2466(3)	84.0849(14)
Crystal habit	clear yellow block		17.8729(4)	72.7405(13)
Density (calculated) / [g/cm^3]	1.497	**Absorption coefficient / [mm^{-1}]**	5.914	
Abs. correction Tmin	0.0245	**Abs. correction Tmax**	0.1163	
Abs. correction type	multiscan	**F(000) [e$^-$]**	1032	

Table S7: Data collection and structure refinement (**1c**).

Index ranges	$-10 \leq h \leq 11$, $-16 \leq k \leq 16$, $-20 \leq l \leq 18$	**Theta range for data collection [°]**	5.208 to 127.366	
Reflections number	15128	**Data / restraints / parameters**	7170/0/569	
Refinement method	Least squares	**Final R indices**	all data	R1 = 0.0730, wR2 = 0.1754
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$		$I>2\sigma(I)$	R1 = 0.0650, wR2 = 0.1663
Goodness-of-fit on F^2	1.058	**Weighting scheme**	$w=1/[\sigma 2(Fo2)+(0.1130P)2 +3.2250P]$	
Largest diff. peak and hole [e $Å^{-3}$]	2.84/-0.42		where $P=(F_o^2+2F_c^2)/3$	

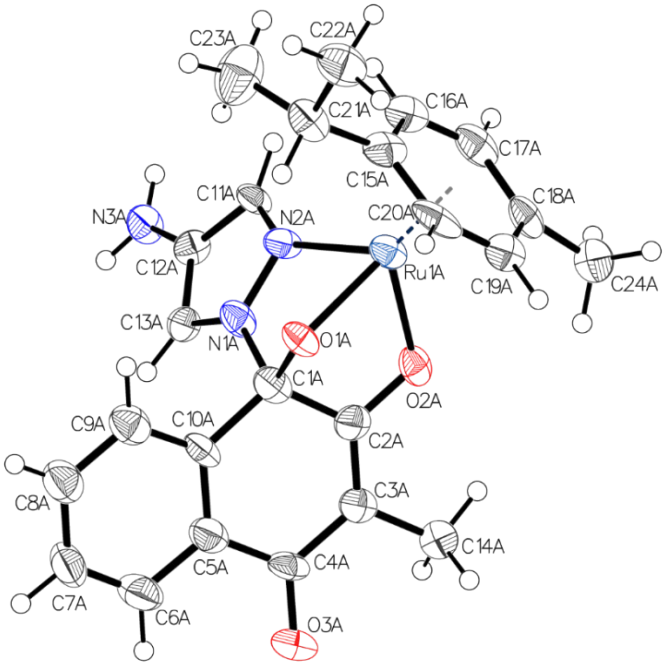


Figure S22: Crystal structure of **1d**. C-C- Bond precision: 0.0135 Å. Second independent molecule omitted for clarity. Squeeze was used to cut the volume and the corresponding electron densities, because small electron densities in excluded volumes could not be matched. Details see cif-code.

Table S8: Sample and crystal data (**1d**).

Chemical formula	C24H25N3O3Ru	**Crystal system**	monoclinic	
Formula weight [g/mol]	504.54	**Space group**	*P21/n*	
Temperature [K]	100	**Z**	8	
Measurement method	\f and \w scans	**Volume [Å^3]**	4641.7(6)	
Radiation (Wavelength [Å])	MoKα (λ = 0.71073)	**Unit cell dimensions [Å] and [°]**	11.3136(9)	90
Crystal size / [mm^3]	0.1 × 0.05 × 0.02		23.5155(17)	102.414(3)
Crystal habit	clear orange plate		17.8647(15)	90
Density (calculated) / [g/cm^3]	1.444	**Absorption coefficient / [mm^{-1}]**	0.705	
Abs. correction Tmin	0.0635	**Abs. correction Tmax**	0.0916	
Abs. correction type	multiscan	**F(000) [e$^-$]**	2064	

Table S9: Data collection and structure refinement (**1d**).

Index ranges	$-13 \leq h \leq 13$, $-28 \leq k \leq 28$, $0 \leq l \leq 21$	**Theta range for data collection [°]**	4.768 to 50.77	
Reflections number	16802	**Data / restraints / parameters**	8522/6/569	
Refinement method	Least squares	**Final R indices**	all data	R1 = 0.1232, wR2 = 0.2108
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$		$I>2\sigma(I)$	R1 = 0.0884, wR2 = 0.1915
Goodness-of-fit on F^2	1.07	**Weighting scheme**	w=1/[σ2(Fo2)+(0.0714P)2 +38.3513P]	
Largest diff. peak and hole [e $Å^{-3}$]	1.34/-0.93		where $P=(F_o^2+2F_c^2)/3$	

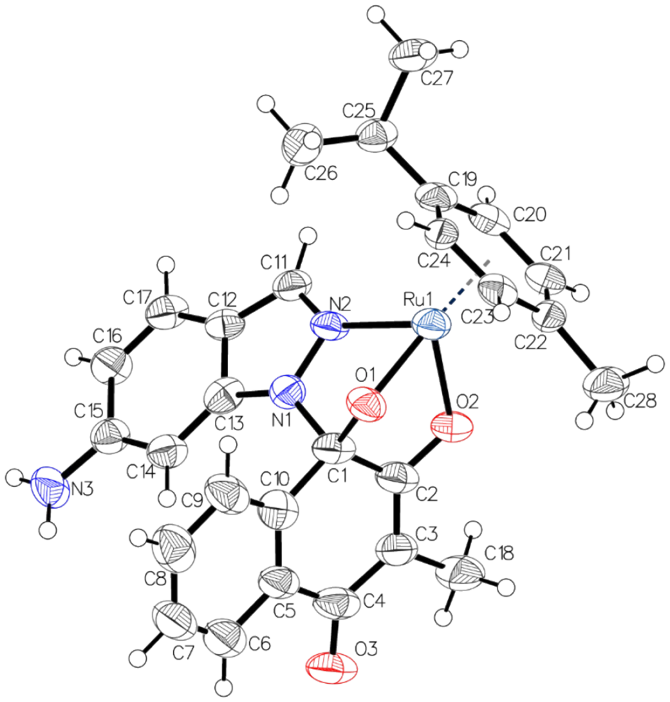


Figure S23: Crystal structure of **1e**. C-C- Bond precision: 0.0144 Å. Squeeze was used to cut the volume and the corresponding electron densities, because small electron densities in excluded volumes could not be matched. Details see cif-code.

Table S10: Sample and crystal data (**1e**).

Chemical formula	C28H27N3O3Ru	**Crystal system**	monoclinic	
Formula weight [g/mol]	554.59	**Space group**	*P21/c*	
Temperature [K]	100	**Z**	4	
Measurement method	\f and \w scans	**Volume [Å^3]**	2853.5(4)	
Radiation (Wavelength [Å])	CuKα (λ = 1.54178)	**Unit cell dimensions [Å] and [°]**	10.9871(9)	90
Crystal size / [mm^3]	0.1 × 0.1 × 0.03		9.5021(7)	98.361(3)
Crystal habit	clear yellow block		27.626(2)	90
Density (calculated) / [g/cm^3]	1.291	**Absorption coefficient / [mm^{-1}]**	4.691	
Abs. correction Tmin	0.0625	**Abs. correction Tmax**	0.1665	
Abs. correction type	multiscan	**F(000) [e$^-$]**	1136	

Table S11: Data collection and structure refinement (**1e**).

Index ranges	$-13 \leq h \leq 13$, $-10 \leq k \leq 11$, $-32 \leq l \leq 33$	**Theta range for data collection [°]**	8.134 to 136.47	
Reflections number	38659	**Data / restraints / parameters**	5217/0/320	
Refinement method	Least squares	**Final R indices**	all data	R1 = 0.0979, wR2 = 0.2271
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$		$I>2\sigma(I)$	R1 = 0.0974, wR2 = 0.2269
Goodness-of-fit on F^2	1.244	**Weighting scheme**	w=1/[σ2(Fo2)+37.2588P]	
Largest diff. peak and hole [e $Å^{-3}$]	1.80/-1.65		where $P=(F_o^2+2F_c^2)/3$	

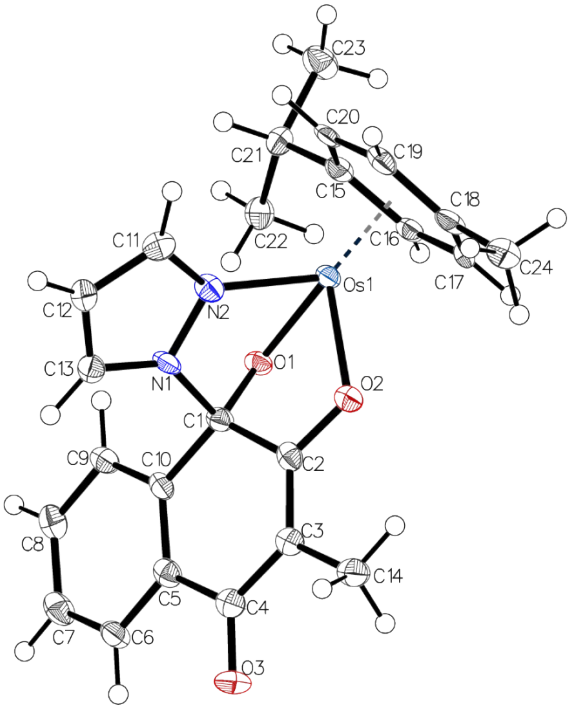


Figure S24: Crystal structure of **2a**. C-C- Bond precision: 0.0070Å. Counter ion omitted for clarity

Table S12: Sample and crystal data (**2a**).

Chemical formula	C24H26N2O4Os	**Crystal system**	monoclinic	
Formula weight [g/mol]	596.67	**Space group**	*P21/n*	
Temperature [K]	100	**Z**	4	
Measurement method	\f and \w scans	**Volume [Å^3]**	2052.02(17)	
Radiation (Wavelength [Å])	MoKα (λ = 0.71073)	**Unit cell dimensions [Å] and [°]**	11.8354(6)	90
Crystal size / [mm^3]	0.41 × 0.22 × 0.2		14.6547(7)	110.4966(15)
Crystal habit	clear yellow block		12.6306(6)	90
Density (calculated) / [g/cm^3]	1.931	**Absorption coefficient / [mm^{-1}]**	6.25	
Abs. correction Tmin	0.0887	**Abs. correction Tmax**	0.2651	
Abs. correction type	multiscan	**F(000) [e$^-$]**	1168	

Table S13: Data collection and structure refinement (**2a**).

Index ranges	$-14 \leq h \leq 14$, $-17 \leq k \leq 17$, $-15 \leq l \leq 15$	**Theta range for data collection [°]**	4.424 to 50.698	
Reflections number	22678	**Data / restraints / parameters**	3762/3/287	
Refinement method	Least squares	**Final R indices**	all data	R1 = 0.0323, wR2 = 0.0803
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$		$I>2\sigma(I)$	R1 = 0.0306, wR2 = 0.0792
Goodness-of-fit on F^2	1.103	**Weighting scheme**	w=1/[σ2(Fo2)+(0.0343P)2 +4.0645P]	
Largest diff. peak and hole [e $Å^{-3}$]	2.16/-1.12		where $P=(F_o^2+2F_c^2)/3$	

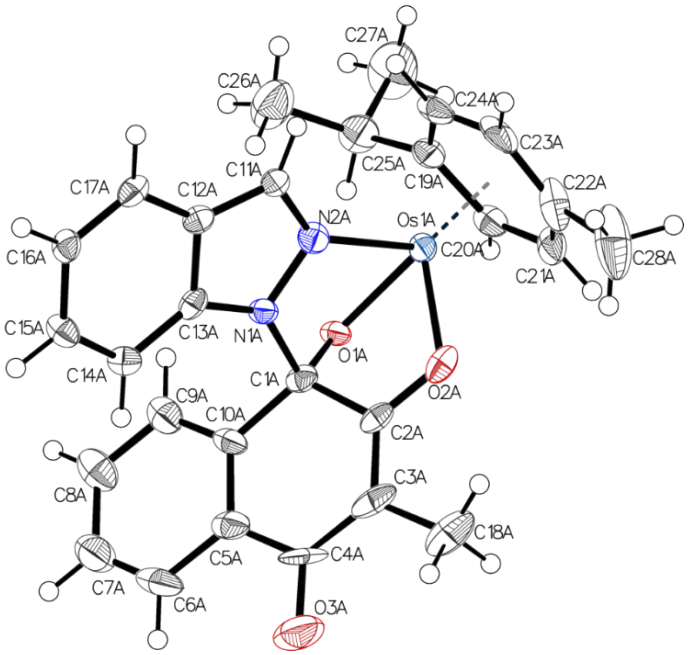


Figure S25: Crystal structure of **2b**. C-C- Bond precision: 0.0142 Å. Second independent moiety B omitted for clarity. Squeeze was used to cut the volume and the corresponding electron densities, because small electron densities in excluded volumes could not be matched. Details see cif-code.

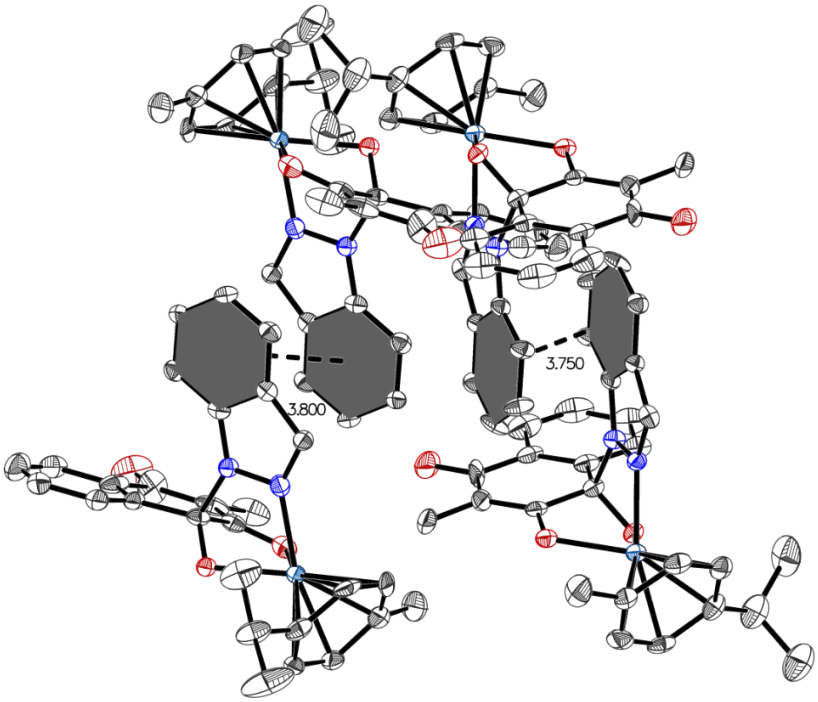


Figure S26: Analysis of π-π Interactions. The distance of Cg-Cg amounts 3.800Å and 3.750 Å. Hydrogen omitted for clarity.

Table S14: Sample and crystal data (**2b**).

Chemical formula	C28H26N2O3Os	**Crystal system**	triclinic	
Formula weight [g/mol]	628.71	**Space group**	*P-1*	
Temperature [K]	100	**Z**	4	
Measurement method	\f and \w scans	**Volume [Å^3]**	2702.76(13)	
Radiation (Wavelength [Å])	MoKα (λ = 0.71073)	**Unit cell dimensions [Å] and [°]**	11.4724(3)	107.6878(10)
Crystal size / [mm^3]	0.2 × 0.15 × 0.1		15.5715(4)	99.3524(10)
Crystal habit	clear yellow block		17.4570(5)	108.3467(10)
Density (calculated) / [g/cm^3]	1.545	**Absorption coefficient / [mm^{-1}]**	4.747	
Abs. correction Tmin	0.0294	**Abs. correction Tmax**	0.099	
Abs. correction type	multiscan	**F(000) [e$^-$]**	1232	

Table S15: Data collection and structure refinement (**2b**).

Index ranges	$-14 \le h \le 14$, $-19 \le k \le 19$, $-22 \le l \le 22$	**Theta range for data collection [°]**	4.6 to 54.206	
Reflections number	72850	**Data / restraints / parameters**	11905/0/621	
Refinement method	Least squares	**Final R indices**	all data	R1 = 0.0623, wR2 = 0.1242
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$		I>2σ(I)	R1 = 0.0509, wR2 = 0.1186
Goodness-of-fit on F^2	1.052	**Weighting scheme**	w=1/[σ2(Fo2)+(0.0237P)2 +45.5397P]	
Largest diff. peak and hole [e Å^{-3}]	3.65/-1.69		where $P=(F_o^2+2F_c^2)/3$	

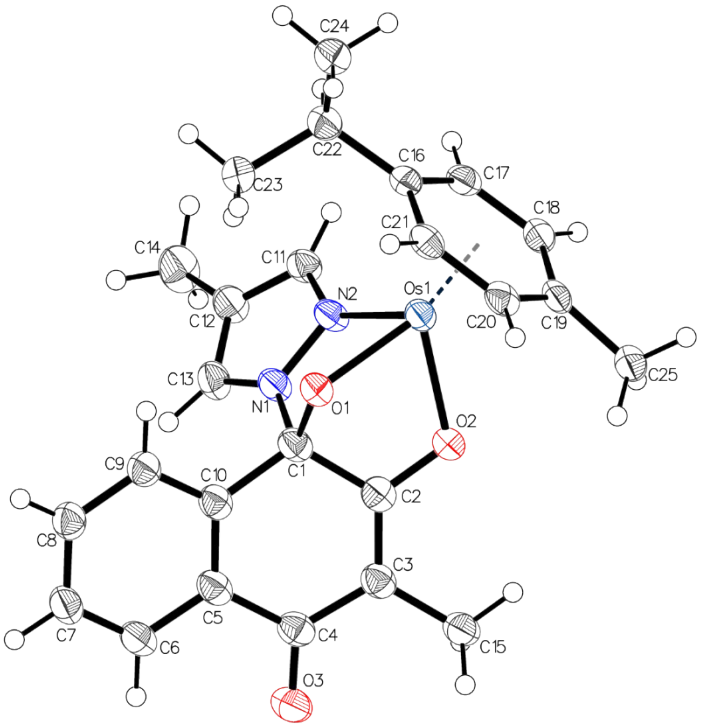


Figure S27: Crystal structure of **2c**. C-C- Bond precision: 0.0054Å

Table S16: Sample and crystal data (**2c**).

Chemical formula	C25H26N2O3Os	**Crystal system**	monoclinic	
Formula weight [g/mol]	592.68	**Space group**	*P21/c*	
Temperature [K]	100	**Z**	4	
Measurement method	\f and \w scans	**Volume [Å^3]**	2131.7(2)	
Radiation (Wavelength [Å])	CuKα (λ = 1.54178)	**Unit cell dimensions [Å] and [°]**	16.3690(9)	90
Crystal size / [mm^3]	0.1 × 0.05 × 0.02		7.6784(4)	110.5999(13)
Crystal habit	clear yellow block		18.1186(10)	90
Density (calculated) / [g/cm^3]	1.847	**Absorption coefficient / [mm^{-1}]**	11.544	
Abs. correction Tmin	0.042	**Abs. correction Tmax**	0.1665	
Abs. correction type	multiscan	**F(000) [e$^-$]**	1160	

Table S17: Data collection and structure refinement (**2c**).

Index ranges	$-19 \leq h \leq 19$, $-8 \leq k \leq 9$, $-21 \leq l \leq 21$	**Theta range for data collection [°]**	10.432 to 137.18	
Reflections number	31965	**Data / restraints / parameters**	3888/0/285	
Refinement method	Least squares	**Final R indices**	all data	R1 = 0.0301, wR2 = 0.0796
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$		$I>2\sigma(I)$	R1 = 0.0298, wR2 = 0.0794
Goodness-of-fit on F^2	1.11	**Weighting scheme**	w=1/[σ2(Fo2)+(0.0451P)2 +2.5141P]	
Largest diff. peak and hole [e $Å^{-3}$]	1.81/-0.80		where $P=(F_o^2+2F_c^2)/3$	

UV-Vis stability measurements

DMSO/DMF was obtained from VWR. PBS buffer solution was adjusted with NaOH or HCl to pH 7.4. Stock solutions with a concentration of 10 mM in DMSO/DMF were prepared. 1980 µL PBS buffer solution, 12 µL DMSO/DMF and 8 µL of the stock solution were added to a quartz cuvette (d=1cm) to obtain a concentration of 40 µM with 1% DMSO/DMF. The UV-Vis spectra were recorded in the range of 200-750 nm at 20 °C on a Perkin Elmer lambda 35 photometer with PTP (Peltier Temperature Programmer) and Julabo AWC 100 recirculating cooler.

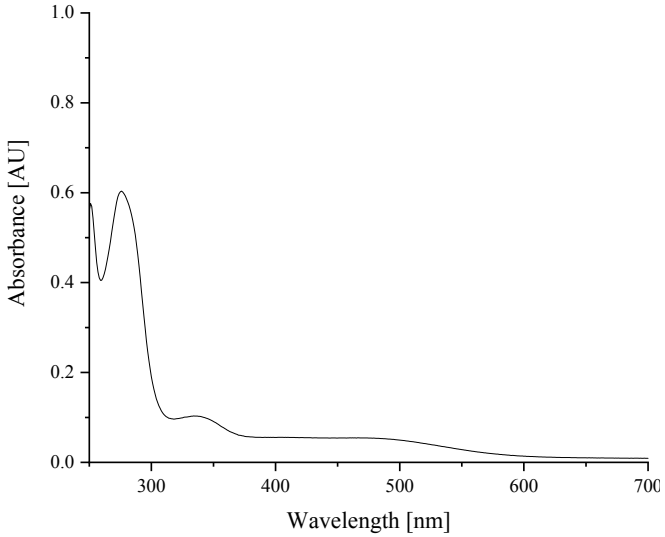


Figure S28: UV-Vis spectrum of phthiocol **L**, with 40 µM in PBS/1% DMF (pH= 7.4), 24 h

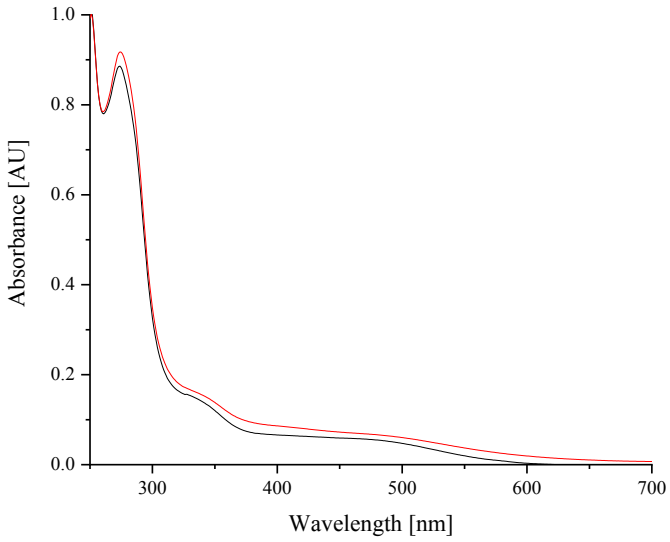


Figure S29: UV-Vis spectrum of KP2048 **1**, with 40 µM in PBS/1% DMF (pH= 7.4), 24 h. Red: t = 0; black: t = 24 h

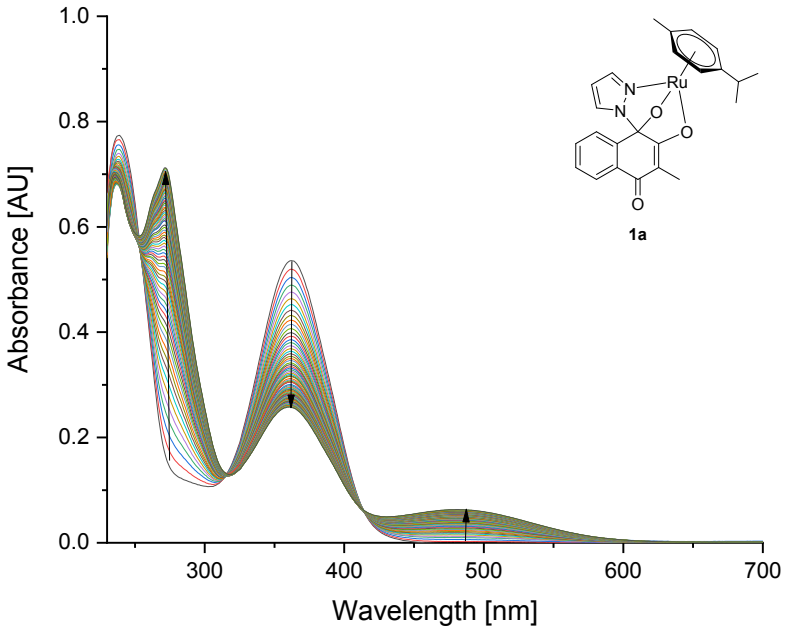


Figure S30. UV-Vis spectrum of **1a**, with 40 µM in PBS/1% DMSO (pH= 7.4), 72 h

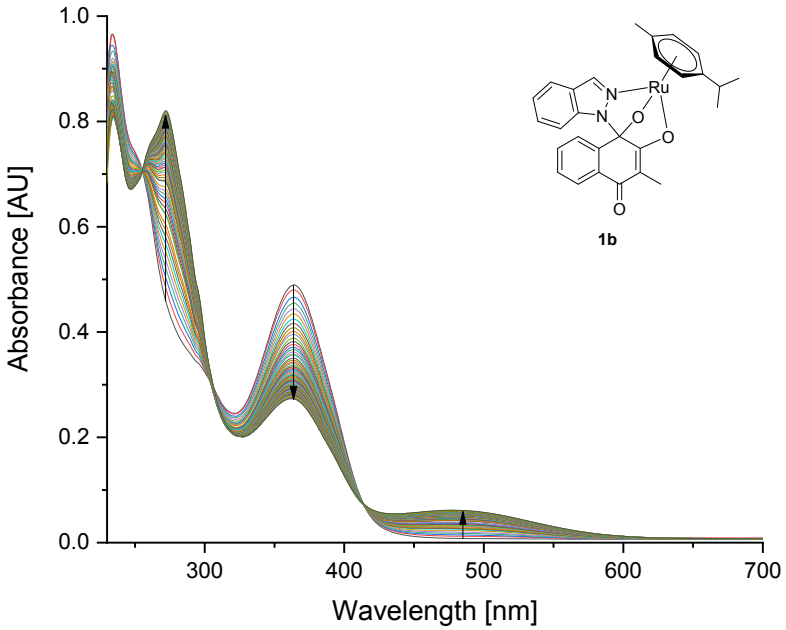


Figure S31: UV-Vis spectrum of **1b**, with 40 µM in PBS/1% DMSO (pH= 7.4), 72 h

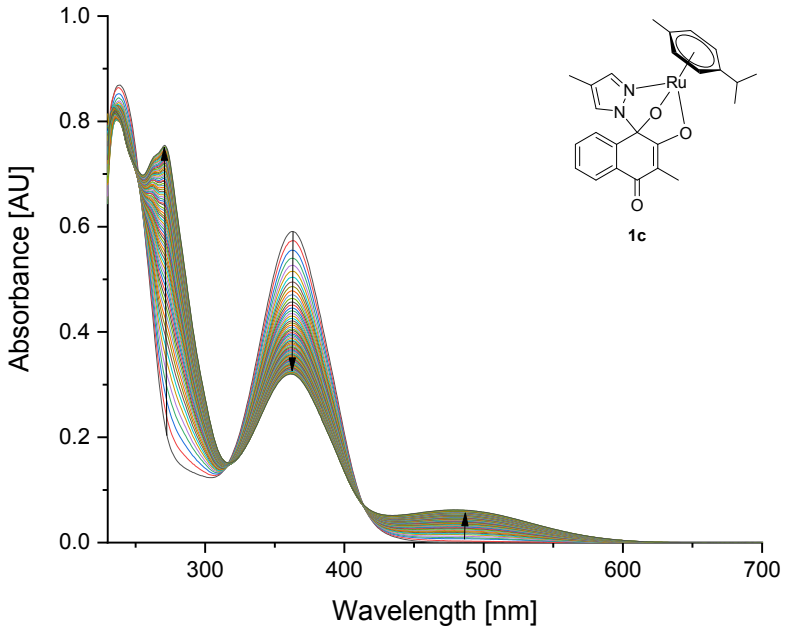


Figure S32: UV-Vis spectrum of **1c**, with 40 µM in PBS/1% DMSO (pH= 7.4), 72 h

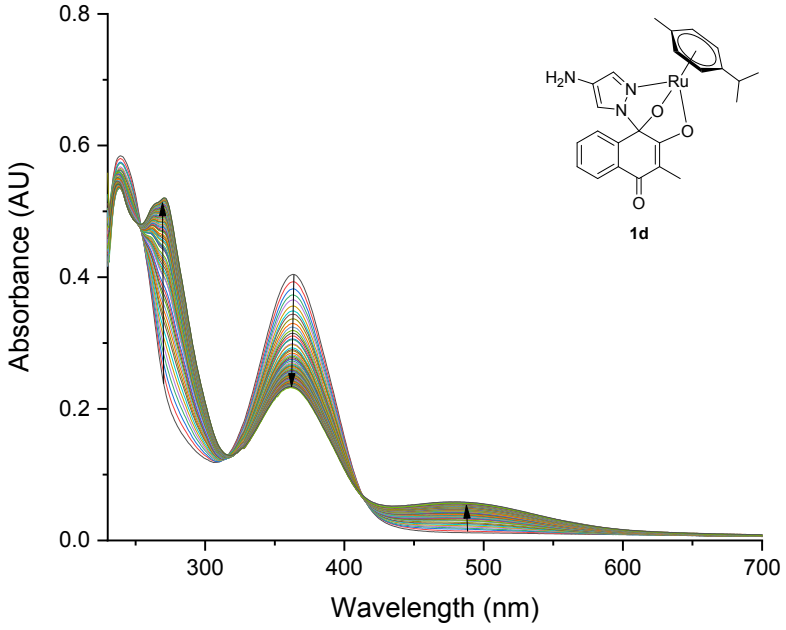


Figure S33: UV-Vis spectrum of **1d**, with 40 µM in PBS/1% DMSO (pH= 7.4), 72 h

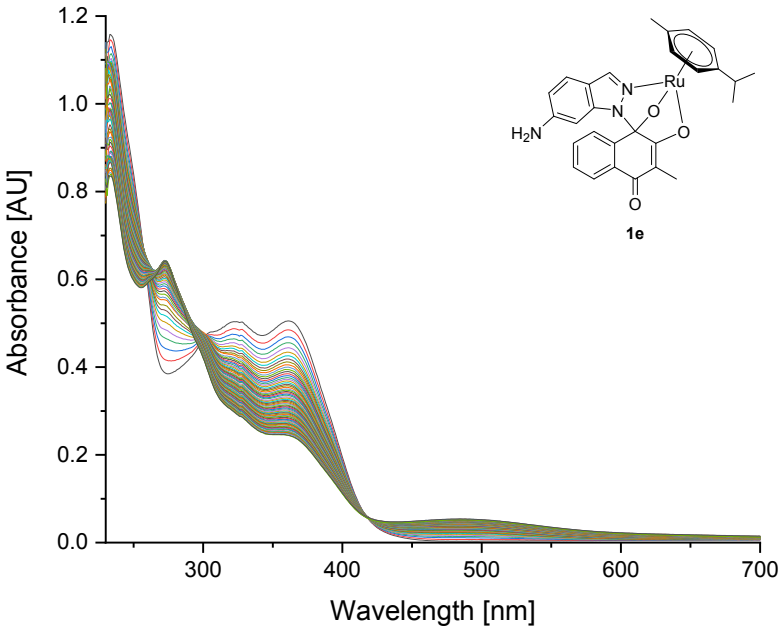


Figure S34: UV-Vis spectrum of **1e**, with 40 µM in PBS/1% DMSO (pH= 7.4), 72 h

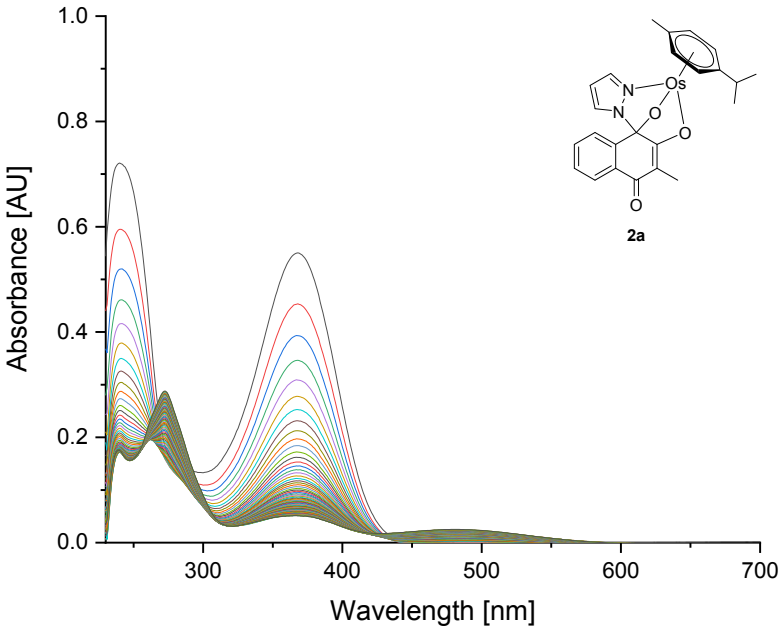


Figure S35: UV-Vis spectrum of **2a**, with 40 µM in PBS/1% DMSO (pH= 7.4), 72 h

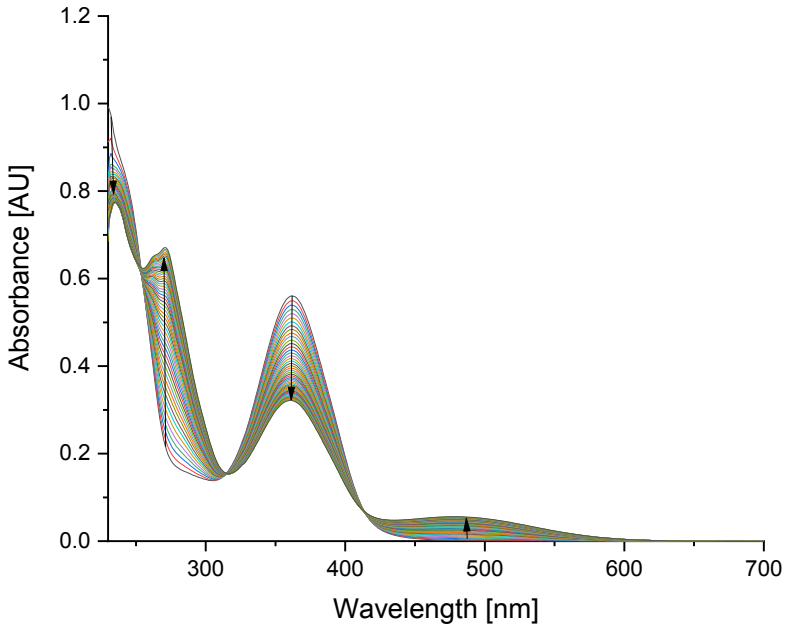


Figure S36: UV-Vis spectrum of **1a**, with 40 µM in PB/1% DMSO (20mM, pH = 5.8), 48 h

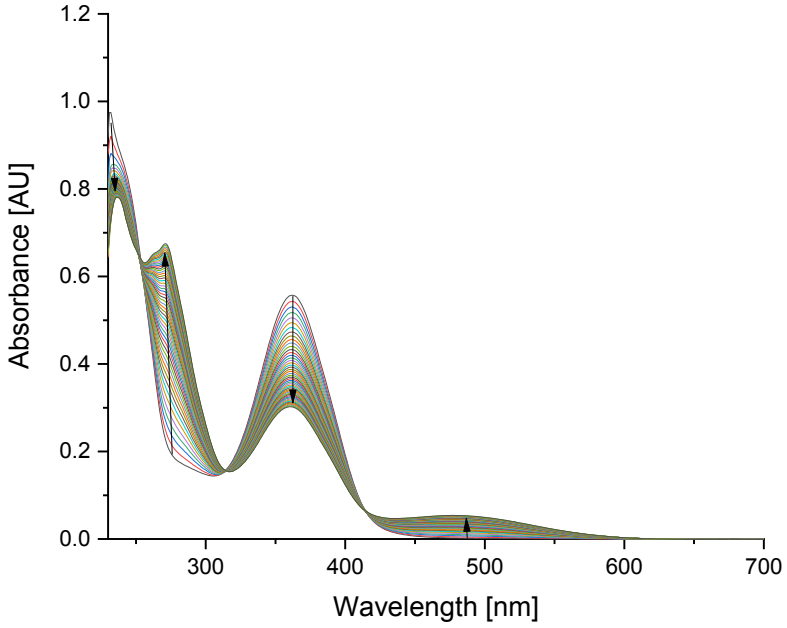


Figure S37: UV-Vis spectrum of **1a**, with 40 µM in PB PB/1% DMSO (20mM, pH = 6.2), 48 h

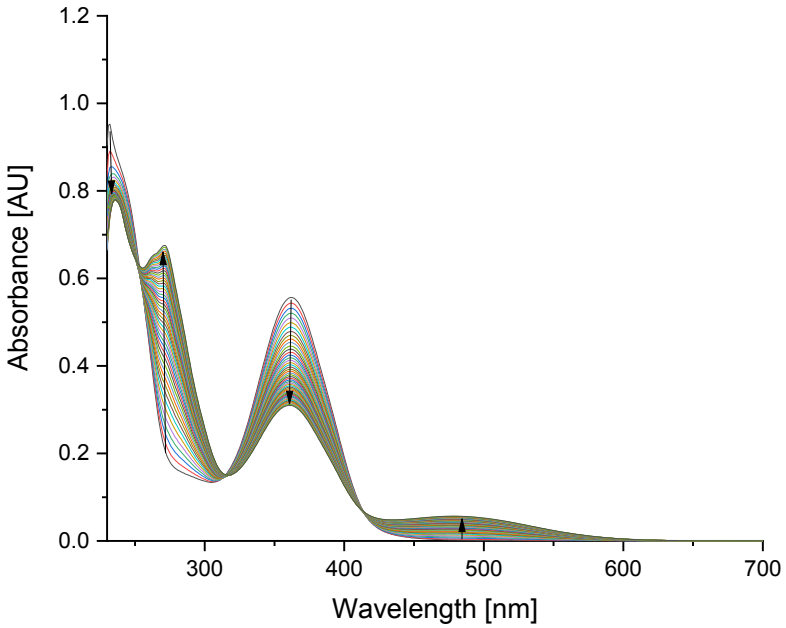


Figure S38: UV-Vis spectrum of **1a**, with 40 µM in PB PB/1% DMSO (20mM, pH = 6.7), 48 h

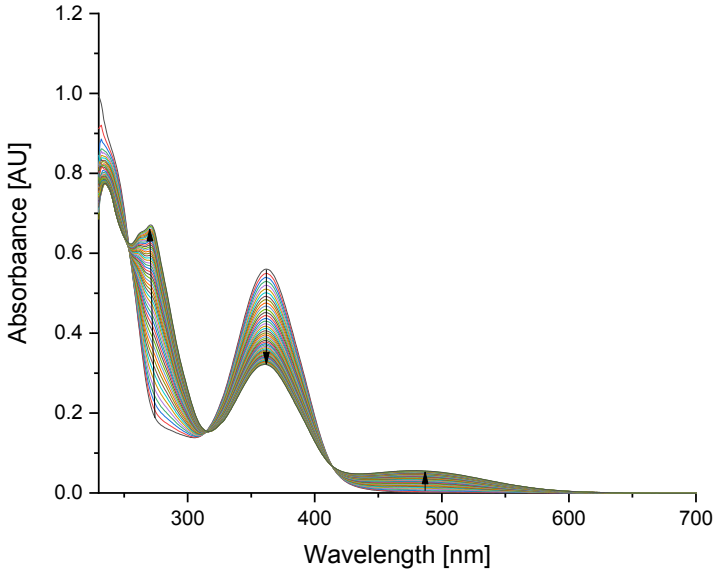


Figure S39: UV-Vis spectrum of **1a**, with 40 µM in PB PB/1% DMSO (20mM, pH = 7.9, 48 h

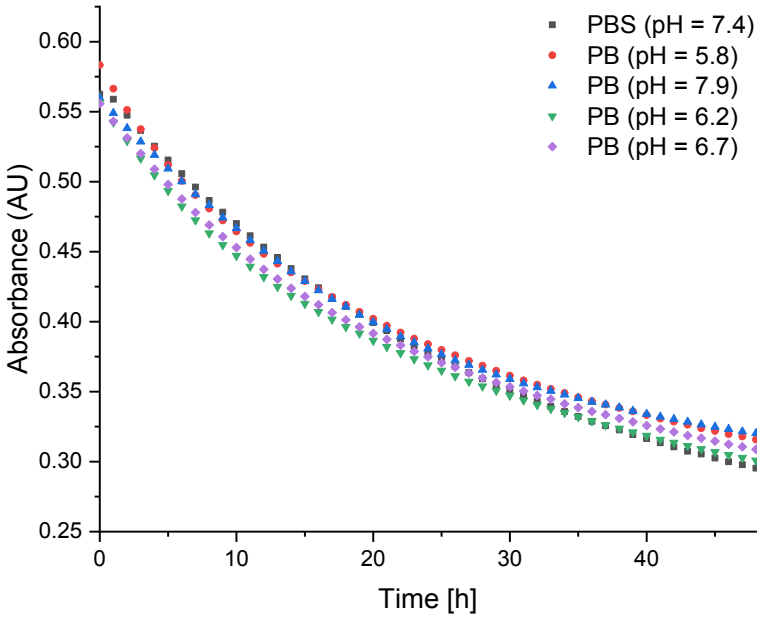


Figure S40: Absorption vs. time at 363 nm at different pH values (5.8–7.9) of compound **1a**

Cytotoxicity in Cell Cultures

Table S18: *In vitro* anticancer activity (IC_{50} values) of 1,2-diazoles

Compound	**IC_{50} [µM]**		
	A549	**SW480**	**CH1/PA-1**
HPz	> 200	> 200	> 200
HInd	> 200	> 200	> 200
4-MeHPz	> 200	> 200	> 200
4-NH_2-HPz	> 200	> 200	> 200
6-NH_2-HInd	> 200	> 200	> 200

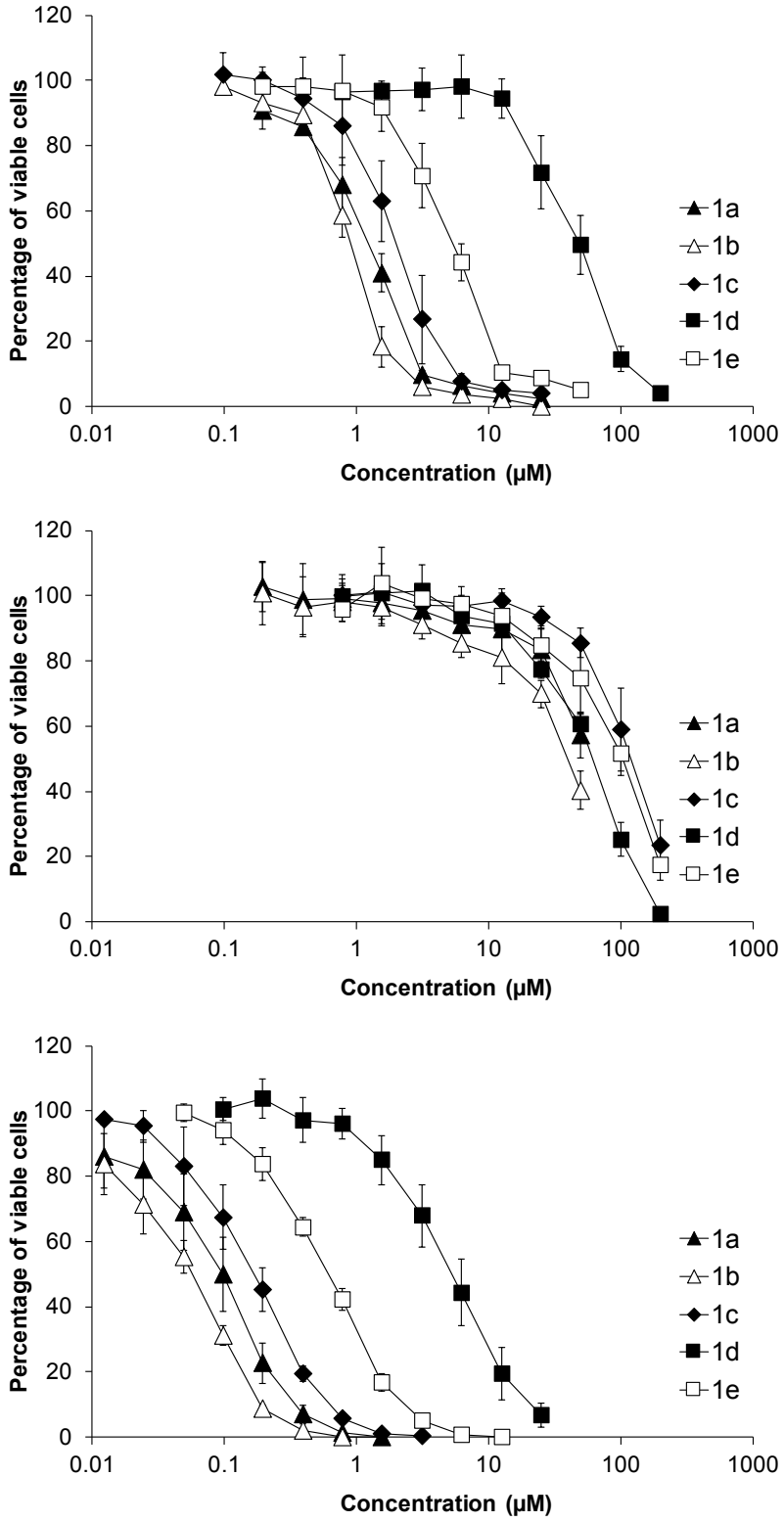


Figure S41: Concentration–effect curves of Ru compounds **1a–1e** in monolayer cultures of the cancer cell lines A549 (top), PA-1/CH1 (middle) and SW480 (bottom) in the MTT assay (exposure time: 96 h). Values are means ± standard deviations of at least three independent experiments.

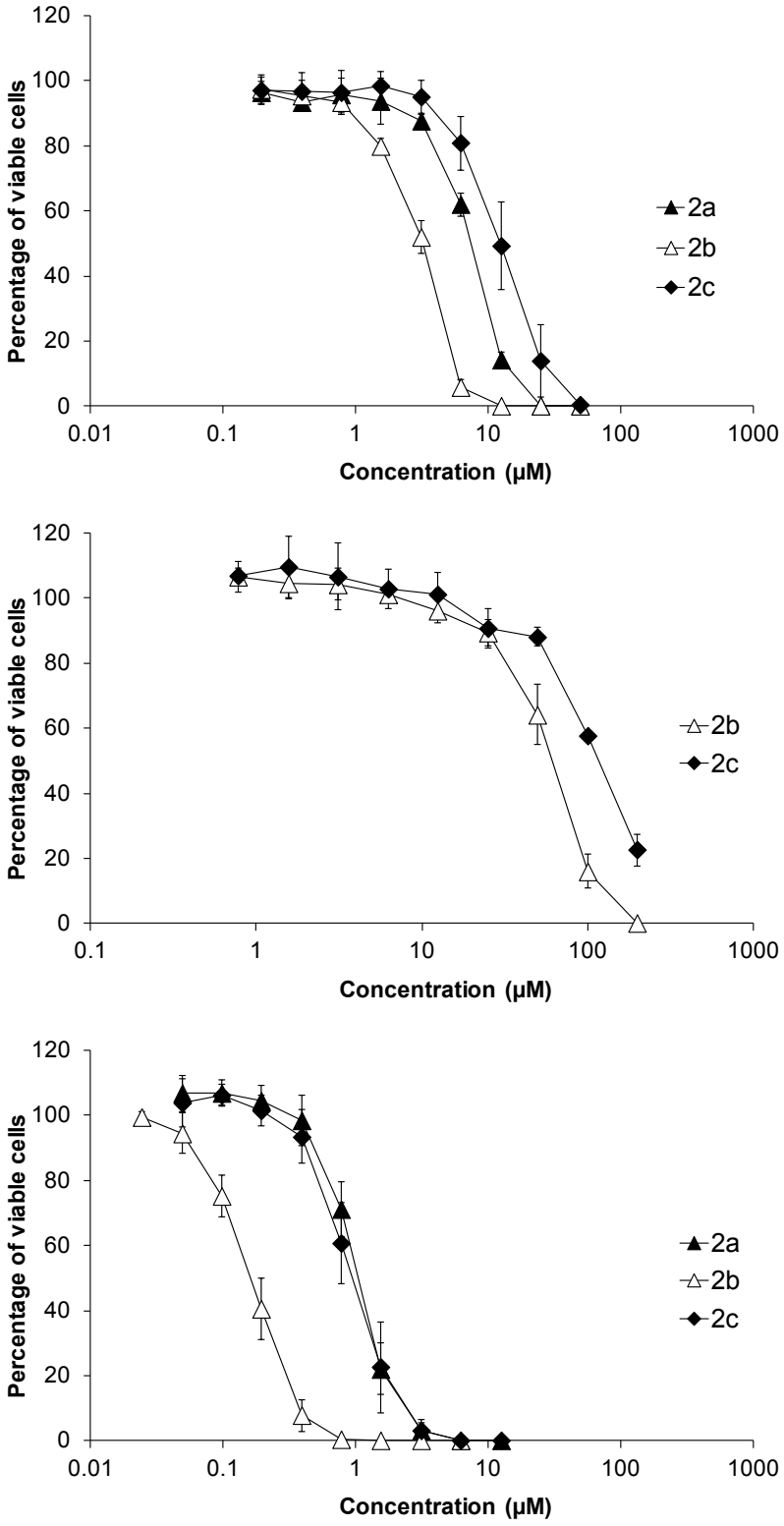


Figure S42: Concentration–effect curves of Os compounds **2a–2c** in monolayer cultures of the cancer cell lines A549 (top), PA-1/CH1 (middle) and SW480 (bottom) in the MTT assay (exposure time: 96 h). Values are means ± standard deviations of at least three independent experiments.

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