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Amide linkage isomerism as an activity switch for organometallic osmium and ruthenium anticancer complexes

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Contents

Preparation of the ligands: N-2,4-difluoride-Ph-picolinamide. Picolinic acid (3.0 g, 0.024 mol) was dissolved in pyridine (10 mL) with stirring. 2,4-Difluoroaniline (3.14 g, 0.024 mol) was added followed by triphenylphosphite (6.6 mL, 0.025 mol). The mixture was then refluxed (353 K, 24 h) and allowed to cool before distilled water (100 mL) was added. The solution was extracted into DCM (100 mL) and separated. The product was extracted with aqueous HCl (1:1 (v:v), 3 × 100 mL). The acidic solution was neutralised with $NaHCO_3$. The resulting solid was isolated by filtration and washed with distilled water. Finally the crude product was recrystallised from hot MeOH to yield white needles (5.36 g, 0.023 mol, 94%). ^{1}H NMR ($CDCl_3$, 300.13 MHz, 300 K) δ 10.27 (br.s., 1H, N<u>H</u>) δ 8.67 (d, 1H, $C_5\underline{H}_4N$), δ 8.56 (t, 1H, $C_5\underline{H}_4N$), δ 8.29 (d, 1H, $C_5\underline{H}_4N$), δ 7.95 (t, 1H, $C_5\underline{H}_4N$), δ 7.54 (d, 1H, $C_6\underline{H}_3F_2$), δ 6.98 (m, 2H, $C_6\underline{H}_3F_2$)

N-2-nitro-Ph-picolinamide. Picolinic acid (3.0 g, 0.024 mol) was dissolved in pyridine (10 mL) with stirring. 2-Nitroaniline (3.31 g, 0.024 mol) was added followed by triphenylphosphite (6.6 mL, 0.025 mol). The mixture was then refluxed (353 K, 24 h) and allowed to cool before distilled water (100 mL) was added. The solution was extracted into DCM (100 mL) and separated. The product was extracted with aqueous HCl (1:1 (v:v), 3 × 100 mL). The acidic solution was neutralised with $NaHCO_3$. The resulting solid was isolated by filtration and washed with distilled water. Finally the crude product was recrystallised from hot MeOH to yield yellow crystals (2.05 g, 0.008 mol, 35%). Anal. Calcd for [$C_{12}H_9N_3O_3$]: C 59.25; H 3.73; N 17.27 %. Found: C 58.95; H 3.80; N 17.25%. ^{1}H NMR: ($CDCl_3$, 300.13 MHz, 300 K) δ 12.79 (brs, 1H, NH), 8.93 (d, 1H, $^3J(^1H\text{-}^1H)$ =8.6 Hz, $C_6\underline{H}_4NO_2$), 8.79 (d, 1H, $^3J(^1H\text{-}^1H)$ =4.7 Hz, $C_5\underline{H}_4$), 8.35-8.30 (m, 2H, $C_5\underline{H}_4$), 7.97 (td, 1H, $^3J(^1H\text{-}^1H)$ =7.7 Hz, 1.65 Hz, $C_5\underline{H}_4$), 7.76 (td, 1H, $^3J(^1H\text{-}^1H)$ =8.6 Hz, 1.4 Hz, $C_6\underline{H}_4NO_2$), 7.59-7.55 (m, 1H, $C_6\underline{H}_4NO_2$), 7.26 (t, 1H, $^3J(^1H\text{-}^1H)$ =7.2 Hz, $C_6\underline{H}_4NO_2$) $^{13}C\{^1H\}$ NMR: ($CDCl_3$, 75 MHz, 298 K) δ 149.1 (CH of $\underline{C}_5H_4$), 138.0 (CH of $\underline{C}_5H_4$), 136.1 (CH of $\underline{C}_6H_4NO_2$), 127.37 (CH of $\underline{C}_5H_4$), 126.3 (CH of

$\underline{C}_6H_4NO_2$), 123.8 (CH of $\underline{C}_5H_4$), 123.2 (CH of $\underline{C}_6H_4NO_2$), 122.5 (CH of $\underline{C}_6H_4NO_2$); ES-MS (+) (MeOH): m/z 244 [M^+]

N-2,4-dimethoxide-Ph-picolinamide. Picolinic acid (3.0 g, 0.024 mol) was dissolved in pyridine (10 mL) with stirring. 2,4-Dimethoxyaniline (3.67 g, 0.024 mol) was added followed by triphenylphosphite (6.6 mL, 0.025 mol). The mixture was then refluxed (353 K, 24 h) and allowed to cool before distilled water (100 mL) was added. The solution was extracted into DCM (100 mL) and separated. The product was extracted with aqueous HCl (1:1 (v:v), 3 × 100 mL). The acidic solution was neutralised with $NaHCO_3$. The resulting solid was isolated by filtration and washed with distilled water. Finally the crude product was recrystallised from hot MeOH to yield pale green crystals (1.67 g, 0.01 mol, 40%) Anal. Calcd for [$C_{14}H_{14}N_2O_3$]: C 65.11; H 5.46; 10.85 %. Found: C 64.85; H 5.23; N 11.10 % ^{1}H NMR ($CDCl_3$, 300.13MHz, 300K) δ 10.38 [br. s, 1H, CON$\underline{H}$], 8.65 [d, 1H, $^3J(^1H\text{-}^1H)$= 6 Hz, $C_5\underline{H}_4N$], 8.55 [d, 1H, $^3J(^1H\text{-}^1H)$= 9 Hz, $C_6\underline{H}_3$], 8.29 [d, 1H, $^3J(^1H\text{-}^1H)$= 6 Hz, $C_5\underline{H}_4N$], [t, 1H, $^3J(^1H\text{-}^1H)$= 6 Hz, $C_5\underline{H}_4N$], 7.50 [m, 1H, $C_5\underline{H}_4N$], 6.51 [m, 2H, $C_6\underline{H}_3$], 3.94 [s, 3H, $C_6H_3(OC\underline{H}_3)_2$], 3.80 [s, 3H, $C_6H_3(OC\underline{H}_3)_2$]; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 62.90MHz, 300K) δ 162.0 [C of $\underline{C}ONH$], 157.0 [C of $\underline{C}_5H_4N$], 150.9 [C of $\underline{C}_6H_3(OMe)_2$], 150.5 [C of $\underline{C}_6H_3(OMe)_2$], 148.5 [CH of $\underline{C}_5H_4N$], 137.9 [CH of $\underline{C}_5H_4N$], 126.5 CH of $\underline{C}_5H_4N$], 122.6 [CH of $\underline{C}_5H_4N$], 121.6 [C of $\underline{C}_6H_3(OMe)_2$], 120.9 [CH of $\underline{C}_6H_3$], 104.2 [CH of $\underline{C}_6H_3$], 99.2 [CH of $\underline{C}_6H_3$], 56.3 [CH_3 of $C_6H_3(O\underline{C}H_3)_2$], 56.0 [$CH_3$ of $C_6H_3(O\underline{C}H_3)_2$].

N-2,4-6-trimethyl-Ph-picolinamide. Picolinic acid (3.0 g, 0.024 mol) was dissolved in pyridine (10 mL) with stirring. *2,4,6*-Trimethylaniline (3.29 g, 0.024 mol) was added followed by triphenylphosphite (6.6 mL, 0.025 mol). The mixture was then refluxed (353 K, 24 h) and allowed to cool before distilled water (100 mL) was added. The solution was extracted into DCM (100 mL) and separated. The product was extracted with aqueous HCl (1:1 (v:v), 3 × 100 mL). The acidic solution was neutralised with $NaHCO_3$. The resulting solid was isolated by

filtration and washed with distilled water. Finally the crude product was recrystallised from hot MeOH to yield white needles (2.60 g, 0.011 mol, 45%). Anal. Calcd for [$C_{15}H_{16}N_2O$]: C 74.97; H 6.71; N 11.66 %. Found: C 74.75; H 6.65; N 11.75 % ^{1}H NMR ($CDCl_3$, 300.13 MHz, 300 K) δ 9.45 [br. s, 1H, N*H*], 8.66 [d, 1H, ^{3}J(^{1}H-^{1}H)= 9.1Hz, CH of C_5H_4N], 8.34 [d, 1H, ^{3}J(^{1}H-^{1}H)= 9.1Hz, CH of C_5H_4N], 7.93 [t, 1H, ^{3}J(^{1}H-^{1}H)= 9.1Hz, CH of C_5H_4N], 7.50 [m, 1H, CH of C_5H_4N], 7.00 [s, 2H, 2 × CH of $C_6H_2(Me)_3$], 2.32 [s, 3H, CH_3 of $C_6H_2(CH_3)_3$], 2.30 [s, 6H, 2 × CH_3 of $C_6H_2(CH_3)_3$]; ^{13}C{^{1}H} NMR ($CDCl_3$, 75.47MHz, 300 K) δ 163.0 [C of *C*ONH], 150.3 [C of C_5H_4N], 148.6 [CH of C_5H_4N], 137.9 [CH of C_5H_4N], 137.2 [C of $C_6H_2(CH_3)_3$], 135.6 [C of $C_6H_2(CH_3)_3$], 131.5 [C of $C_6H_2(CH_3)_3$], 129.3 [2 × CH of $C_6H_2(CH_3)_3$], 126.8 [CH of C_5H_4N], 123.0 [CH of C_5H_4N], 21.4 [CH_3 of $C_6H_2(CH_3)_3$], 18.9 [2 × CH_3 of $C_6H_2(CH_3)_3$].

Spectroscopic data of the complexes: [(η^6-*p*-cym)Os(N-2,4-difluoro-Ph-picolinamide)Cl] (1). Anal. Calcd. for [$C_{22}H_{21}Cl_1F_2N_2OOs$] (593.09): C, 44.55; H, 3.57; N, 4.72 %. Found: C, 43.95; H, 3.55; N, 4.66 % ESI-MS (+ve): *m/z* 559.1, [(*p*-cym)Os(2,4-F-Ph-picolinamide)]$^+$. ^{1}H NMR (DMSO-d_6): δ = 9.25 (1H, d, J = 5.67 Hz), 8.14 (1H, tt, J = 7.56, 1.13 Hz), 7.91 (1H, d, J = 7.55 Hz), 7.68 (1H, td, J = 6.80, 1.51 Hz), 7.53 (1H, qw, J = 6.8 Hz), 7.26 (1H, td, J = 10.2, 3.0 Hz), 7.07 (1H, td, J = 8.69, 2.64 Hz), 6.04 (1H, d, J = 4.91 Hz), 5.67 (1H, d, J = 5.29 Hz), 5.51 (1H, d, J =5.29 Hz), 5.10 (1H, m), 2.42 (1H, q, J = 6.8 Hz), 2.19 (3H, s) 0.97 (6H, t, J = 6.8 Hz). ^{13}C{^{1}H} NMR (CD_3OD): δ 167.4 [*C*ONOs], 159.6 [C_5H_4N], 156.1 [C_6H_3], 140.5 [C_5H_4N], 130.1 [C_6H_3 or C_5H_4N], 129.3 [C_6H_3 or C_5H_4N], 126.9 [C_5H_4N], 112.4[C_6H_3], 105.8 [C_6H_3], 104.6 [C_6H_4], 77.3 [C_6H_4], 76.5 [C_6H_4], 74.9 [C_6H_4], 74.6 [C_6H_4], 32.6 [*C*H(CH_3)$_2$], 22.8 [CH(*C*H_3)$_2$], 22.6 [CH(*C*H_3)$_2$], 18.9 [$C_6H_4CH_3$].

[(η^6-*p*-cym)Ru(N-2,4-difluoro-Ph-picolinamide)Cl] (2). Anal. Calcd. for $C_{22}H_{21}ClF_2N_2ORu$ (503.09): C, 52.44; H, 4.20; N, 5.56 %. Found: C 52.65; H 4.40; N 5.35 %. ESI-MS (+ve): *m/z*, 469.1 [(*p*-cym)Ru(2,4-F-Ph-picolinamide)]$^+$. ^{1}H NMR (CD_3OD): δ = 9.31

(1H,d, J= 5.4Hz), 8.12 (1H, t, J = 7.7 Hz), 7.96 (1H, d, J = 7.8 Hz), 7.70 (2H, m), 7.10 (1H, m), 7.00 (1H, m), 5.68, (1H, d, J = 6.0 Hz), 5.43 (1H, d, J = 6.0 Hz), 5.36 (1H, d, J = 5.9 Hz), 4.97 (1H, d, J = 5.8 Hz)**,** 2.60 (1H, sept, J = 6.9 Hz), 2.15 (3H, s), 1.06 (6H, dd, J = 7.1 Hz). $^{13}C\{^{1}H\}$ NMR (CD_3OD): δ 169.9 [*C*ONRu], 156.2 [C_5H_4N], 155.8 [C_6H_3], 141.0 [C_5H_4N], 130.2 [C_6H_3 or C_5H_4N], 129.2 [C_6H_3 or C_5H_4N], 126.9 [C_5H_4N], 112.8 [d, 1C**,** $^{2}J(^{13}C\text{-}^{19}F)$ = 75.0Hz**,** C_6H_3], 105.3 [t**,** 1C $^{1}J(^{13}C\text{-}^{19}F)$ = 102.0Hz, C_6H_3], 104.1 [C_6H_4], 102.3 [C_6H_4], 87.0 [C_6H_4], 85.7[C_6H_4], 85.6 [C_6H_4], 85.5 [C_6H_4], 32.6 [$CH(CH_3)_2$], 23.2 [$CH(CH_3)_2$], 22.5 [$CH(CH_3)_2$], 19.4 [$C_6H_4CH_3$].

[(η^6-*p*-cym)Os(N-4-nitro-Ph-picolinamide)Cl] (3). Anal. Calcd. for [$C_{22}H_{22}Cl_1N_3O_3Os$] (602.11): C, 43.88; H, 3.68; N, 6.98 %. Found: C, 43.88; H, 3.43; N, 7.09 %. ESI-MS (+ve): *m/z* 568.1, [(*p*-cym)Os(4-NO_2-Ph-picolinamide)]$^{+}$. ^{1}H NMR (MeOD-d_4): δ = 9.20 (1H, d, J = 5.48 Hz), 8.30 (2H, m), 8.13 (1H, td, J = 7.68, 1.32 Hz), 8.06 (1H, m), 7.76 (2H, m), 7.68 (1H, m), 5.98 (1H, d, J = 5.64), 5.68 (1H, d, J = 5.60 Hz), 5.57 (1H, d, J = 5.56 Hz), 5.19 (1H, d, J = 5.52 Hz), 2.49 (1H, sep, J = 7.03 Hz), 2.32 (3H, s), 1.07 (6H, t, J = 7.03 Hz). $^{13}C\{^{1}H\}$ NMR (CD_3OD): δ 156.0 [*C*ONOs], 154.7 [C_5H_4N], 145.6 [$C_6H_4NO_2$], 140.5 [C_5H_4N], 134.3 [$C_6H_4NO_2$ or C_5H_4N], 130.5 [$C_6H_4NO_2$ or C_5H_4N], 129.4 [C_5H_4N], 129.1 [C_5H_4N], 126.1 [$C_6H_4NO_2$], 125.5 [$C_6H_4NO_2$], 96.9 [$C_6H_4NO_2$], 92.3 [$C_6H_4NO_2$], 77.7 [C_6H_4], 76.6 [C_6H_4], 76.0 [C_6H_4], 73.9 [C_6H_4], 32.5 [$CH(CH_3)_2$], 22.8 [$CH(CH_3)_2$], 22.7 [$CH(CH_3)_2$], 18.7 [$C_6H_4CH_3$].

[(η^6-*p*-cym)Os(N-2-nitro-Ph-picolinamide)Cl] (4). Anal. Calcd. for [$C_{22}H_{22}Cl_1N_3O_3Os$]·H_2O (620.13): C, 42.61; H, 3.90; N, 6.78 %. Found: C, 41.95; H, 3.56; N, 6.63 %. ESI-MS (+ve): *m/z* 568.1, [(*p*-cym)Os(2-NO_2-Ph-picolinamide)]$^{+}$. ^{1}H NMR ($CDCl_3$): δ = 8.94 (1H, d, J = 5.52 Hz), 8.07 (1H, d, J = 7.78 Hz), 7.92 (3H, m), 7.54 (2H, m), 7.30 (1H, t, J = 7.03 Hz), 5.73 (1H, d, J = 5.52 Hz), 5.61 (1H, d, J = 5.77), 5.56 (1H, d, J = 5.77 Hz), 5.07 (1H, d, J = 5.27 Hz), 2.61 (1H, q, J = 6.77 Hz), 2.24 (3H, s), 1.04 (6H, t, J = 6.77 Hz). $^{13}C\{^{1}H\}$

NMR (CD_3OD): δ 159.0 [*C*ONOs], 156.1 [C_5H_4N], 140.6 [C_6H_4], 140.5 [C_5H_4N], 129.5 [$C_6H_4NO_2$ or C_5H_4N], 129.4 [$C_6H_4NO_2$ or C_5H_4N], 128.6 [C_5H_4N], 128.5 [C_5H_4N], 127.1 [$C_6H_4NO_2$], 125.8 [$C_6H_4NO_2$], 121.0 [$C_6H_4NO_2$], 94.2 [C_6H_4], 77.6 [C_6H_4], 77.5 [C_6H_4], 74.6 [C_6H_4], 74.4 [C_6H_4], 32.7 [*C*H(CH_3)$_2$], 22.7 [CH(*C*H_3)$_2$], 22.6 [CH(*C*H_3)$_2$], 18.9 [C_6H_4*C*H_3].

[(η^6-*p*-cym)Os(N-2,4-dimethoxide-Ph-picolinamide)Cl]$_2$PF$_6$ (5). Anal. Calcd. for [$C_{22}H_{21}Cl_1F_2N_2OOs$]$_2PF_6$ (1382.24): C, 41.74; H, 4.09; N, 4.06 %. Found: C, 41.59; H, 3.89; N, 3.99 %. ESI-MS (+ve): *m/z* 583.1, [(*p*-cym)Os(2,4-OMe-Ph-picolinamide)]$^+$. ^{1}H NMR (DMSO-d_6): δ = 9.21 (1H, d, J = 5.48 Hz), 8.08 (1H, td, J = 7.62, 1.43Hz), 7.83 (1H, dd, J = 7.88, 1.12 Hz), 7.62 (1H, m), 7.18 (1H, d, J = 8.53 Hz), 6.64 (1H, d, J = 2.51 Hz), 6.48 (1H, dd, J = 2.51, 8.53 Hz), 5.89 (1H, d, J = 5.52 Hz), 5.54 (1H, d, J = 5.52), 5.43 (1H, d, J = 5.27 Hz) 4.85, (1H, d, J = 5.27 Hz) 2.41, (1H, q, J = 6.77 Hz) 2.10, (3H, s) 0.95, (6H, dd, J = 2.76, 4.27). ^{13}C{^{1}H} NMR (CD_3OD): δ 160.8 [*C*ONOs], 156.1 [C_5H_4N], 140.4 [C_6H_3], 140.3 [C_5H_4N], 129.4 [C_5H_4N], 127.9 [C_5H_4N], 127.8 [C_6H_3], 126.9 [C_6H_3], 105.9 [C_6H_4], 99.8 [C_6H_4], 95.1 [C_6H_3], 77.7 [C_6H_4], 76.0 [C_6H_4], 75.9 [C_6H_4], 75.1 [C_6H_4], 56.0 [C_6H_3(O*C*H_3)$_2$], 55.9 [C_6H_3(O*C*H_3)$_2$], 32.5 [*C*H(CH_3)$_2$], 22.9 [CH(*C*H_3)$_2$], 22.5 [CH(*C*H_3)$_2$], 18.9 [C_6H_4*C*H_3]. ^{31}P NMR (DMSO-d_6) δ = -143 ppm (septet).

[(η^6-*p*-cym)Ru(N-2,4-dimethoxide-Ph-picolinamide)Cl]$_2$PF$_6$ (6). Anal. Calcd. for [$C_{24}H_{27}ClN_2O_3Ru$]$_2HPF_6$·MeOH: C 47.69; H 4.82; N 4.54%. Found: C 47.30; H 4.55; N 4.75%. ESI-MS (+ve): *m/z* 493.1, [(*p*-cym)Ru(2,4-OMe-Ph-picolinamide)]$^+$. ^{1}H NMR (MeOD-d_4): δ 9.31 (d, 1H, J = 5.2 Hz), 8.10 (t, 1H, J = 7.6 Hz), 7.94 (d, 1H, J = 7.7 Hz), 7.70 (t, 1H, J = 6.9 Hz), 7.46 (d, 1H, J = 8.6 Hz), 6.75 (d, 1H, J = 2.4 Hz), 6.59, (dd, 1H, J = 8.6 Hz and J = 2.5 Hz), 5.63 (d, 1H, J = 6.1 Hz), 5.42 (d, 1H, J = 6.1 Hz), 5.38 (d, 1H, J = 5.9 Hz), 4.78 (masked, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 2.60 (sept, 1H, J = 6.9 Hz), 2.11 (s, 3H), 1.08 (d, 3H, J = 6.9 Hz), 1.03 (d, 3H, J = 6.9 Hz). ^{13}C{^{1}H} NMR (CD_3OD): δ 161.0 [*C*ONRu], 156.3 [C_5H_4N], 154.9 – 151.4 [3 x C_6H_3], 140.8 [C_5H_4N], 129.0 [C_5H_4N], 128.1 [C_5H_4N], 126.8

[C_6H_3], 106.3 [C_6H_3], 104.2 [C_6H_4], 101.5 [C_6H_4], 100.3 [C_6H_3], 87.4 [C_6H_4], 87.1 [C_6H_4], 85.8 [C_6H_4], 84.7 [C_6H_4], 56.5 [$C_6H_3(OCH_3)_2$], 56.4 [$C_6H_3(OCH_3)_2$], 32.6 [$CH(CH_3)_2$], 23.2 [$CH(CH_3)_2$], 22.2 [$CH(CH_3)_2$], 19.3 [$C_6H_4CH_3$].

[(η^6-*p*-cym)Os(N-2,4,6-trimethyl-Ph-picolinamide)Cl]PF_6 (7). Anal. Calcd. for $C_{25}H_{30}ClF_6N_2OOsP$ (745.17): C, 40.30; H, 4.06; N, 3.76 %. Found: C, 40.52; H, 3.78; N, 3.67 %. ESI-MS (+ve): *m/z* 601.2, [(*p*-cym)Os(2,4,6-Me-Ph-picolinamide)Cl]$^+$. ^{1}H NMR (DMSO-d_6): δ = 11.97 (1H, br), 9.55 (1H, br), 8.79 (1H, br), 8.49 (1H, br), 8.05 (1H, br), 7.09 (1H, br), 7.06 (1H, br), 6.49 (1H, br), 6.44 (2H, br), 6.24 (1H, br), 6.13 (1H, br), 2.58 (1H, m), 2.09(3H, s), 1.10 (6H, m). ^{13}C{^{1}H} NMR (MeOD): δ 175.6 [*C*ONH], 156.8 [C_5H_4N], 149.0 [C_5H_4N], 142.0 [C_5H_4N], 140.3 [$C_6H_2(Me)_3$], 132.4 [C_5H_4N], 130.3 [$C_6H_2(Me)_3$], 130.1 [C_5H_4N], 126.6 [$C_6H_2(Me)_3$], 95.4 [C_6H_4], 91.9 [C_6H_4], 76.3 [C_6H_4], 75.2 [C_6H_4], 74.9 [C_6H_4], 72.0 [C_6H_4], 32.9 [$C_6H_4CH_3$], 22.9 [$CH(CH_3)_2$], 22.5 [$CH(CH_3)_2$], 21.1 [$C_6H_2(CH_3)_3$], 18.9 [$C_6H_2(CH_3)_3$], 18.1 [$CH(CH_3)_2$]. ^{31}P NMR (DMSO-d_6) δ = -143 ppm (septet).

[(η^6-*p*-cym)Ru(N-2,4,6-trimethyl-Ph-picolinamide)Cl]PF_6 (8). Anal. Calcd. for $C_{25}H_{30}ClF_6N_2OPRu$ (656.01): C, 45.77; H, 4.61; N, 4.27 %. Found: C, 45.44; H, 4.51; N, 4.16 %. ESI-MS (+ve): *m/z* 511.1, [(*p*-cym)Ru(2,4,6-Me-Ph-picolinamide)Cl]$^+$. ^{1}H NMR (DMSO-d_6): δ = 11.72 (1H, s), 9.62 (1H, d, J = 4.95 Hz), 8.68 (1H, m), 8.47 (1H, m), 8.07 (1H, m), 7.08 (2H, m), 6.11 (2H, m), 5.86 (2H, m), 2.71 (1H, m), 2.33 (3H, s), 2.19 (9H, s), 1.15 (6H, dd, J = 6.76, 1.07 Hz). ^{13}C{^{1}H} NMR (MeOD): δ 173.4 [*C*ONH], 158.2 [C_5H_4N], 150.4 [C_5H_4N], 143.3 [C_5H_4N], 141.6 [$C_6H_2(Me)_3$], 133.2 [C_5H_4N], 132.1 [$C_6H_2(Me)_3$], 131.7 [C_5H_4N], 127.8 [$C_6H_2(Me)_3$], 106.3 [C_6H_4], 101.6 [C_6H_4], 86.1 [C_6H_4], 85.6 [C_6H_4], 84.7 [C_6H_4], 83.2 [C_6H_4], 34.0 [$C_6H_4CH_3$], 24.1 [$CH(CH_3)_2$], 23.6 [$CH(CH_3)_2$], 22.6 [$C_6H_2(CH_3)_3$], 20.2 [$C_6H_2(CH_3)_3$], 19.8 [$CH(CH_3)_2$].

[(η^6-bip)Os(N-Ph-picolinamide)Cl] (9). Anal. Calcd for $[C_{24}H_{19}ClN_2OOs]_2PF_6$ (1301.12): C, 44.34; H, 2.95; N, 4.31 %. Found: C, 44.33; H, 3.27; N, 4.07 % ESI-MS (+ve):

m/z 543.1, [(bip)Os(Ph-picolinamide)]$^+$. ^{1}H NMR (DMSO-d_6): δ = 9.01 (1H, d. J = 5.66 Hz), 8.04 (1H, t, J =7.93 Hz), 7.85 (1H, d, J =7.56 Hz), 7.53 (1H, m), 7.35 (3H, m), 7.30 (1H, m), 7.18 (1H, m), 7.08 (1H, s), 7.06 (1H, m), 6.99 (1H, s), 6.27 (1H, d, 5.29), 6.20 (1H, d, J =5.29 Hz), 5.98 (1H, t, J = 4.91 Hz), 5.90 (1H, t, J = 5.66 Hz), 5.79 (1H, t, J = 5.28 Hz), 3.43 (1H, m), 1.91 (3H, s), 1.05 (6H, t, J = 6.8 Hz). ^{13}C{^{1}H} NMR (CD_3OD): δ 155.4 [*C*ONOs], 140.5 [C_5H_4N], 130.1 [C_6H_5], 130.0 [C_5H_4N], 130.0 [C_6H_5 or C_5H_4N], 129.5 [C_6H_5 or C_5H_4N], 129.4 [C_5H_4N], 128.9 [C_5H_4N], 127.0 [C_6H_5], 126.9 [C_6H_5], 126.5 [C_6H_5], 80.2 [C_6H_4], 79.5 [C_6H_4], 75.5 [C_6H_4], 75.4 [C_6H_4], 66.9 [C_6H_4].

[(η^6-*p*-cym)Os(N-2-fluoro-Ph-picolinamide)Cl] (10). Anal. Calcd. for $[C_{22}H_{22}ClFN_2ORu]_2HPF_6$: C 47.28; H 4.06; N 5.01%, Found: C 47.50; H 4.35; N 5.00%. ^{1}H NMR (CD_3OD, 300.13MHz, 300K), δ 9.32 [d, 1H, ^{3}J(^{1}H-^{1}H) = 5.2Hz, CH of $C_5\underline{H_4}N$], 8.10 [t, 1H, ^{3}J(^{1}H-^{1}H) = 7.7Hz, CH of $C_5\underline{H_4}N$], 7.97 [d, 1H, ^{3}J(^{1}H-^{1}H) = 6.8Hz, CH of $C_5\underline{H_4}N$], 7.68 [t, 1H, ^{3}J(^{1}H-^{1}H) = 5.7Hz, CH of $C_5\underline{H_4}N$], 7.31-7.07 [m, 4H, 4 x CH of $C_6\underline{H_4}F$], 5.65 [d, 1H, ^{3}J(^{1}H-^{1}H) = 6.0Hz, CH of $C_6\underline{H_4}$], 5.42 [d, 1H, ^{3}J(^{1}H-^{1}H) = 6.8Hz, CH of $C_6\underline{H_4}$], 5.33 [d, 1H, ^{3}J(^{1}H-^{1}H) = 5.9Hz, CH of $C_6\underline{H_4}$], 4.90 [, 1H, CH of $C_6\underline{H_4}$**],** 2.60 [sept, 1H, ^{3}J(^{1}H-^{1}H) = 6.9Hz, CH of $C\underline{H}(CH_3)_2$], 2.13 [s, 3H, CH_3 of $C_6H_4C\underline{H_3}$], 1.07 [d, 3H, ^{3}J(^{1}H-^{1}H) = 7.1Hz, one CH_3 of $CH(C\underline{H_3})_2$], 1.04 [d, 3H, ^{3}J(^{1}H-^{1}H) = 7.1Hz, other CH_3 of $CH(C\underline{H_3})_2$].^{13}C{^{1}H} NMR (CD_3OD, 75.48MHz, 300K) δ 159.3 [CONRu], 155.8 [CH of $\underline{C_5}H_4N$], 155.7 [C of C_6H_4F], 140.4 [CH of $\underline{C_5}H_4N$], 140.3 [C of $\underline{C_5}H_4N$], 129.1 – 125.5 [5C, 5 x CH of $\underline{C_5}H_4N$ and $\underline{C_6}H_4F$], 116.9 [CH of $\underline{C_6}H_4F$], 103.8 [one C of $\underline{C_6}H_4$], 101.6 [other C of $\underline{C_6}H_4$], 86.5 [CH of $\underline{C_6}H_4$], 85.6 [CH of $\underline{C_6}H_4$], 85.3 [CH of $\underline{C_6}H_4$], 85.1 [CH of $\underline{C_6}H_4$], 32.1 [CH of $\underline{C}H(CH_3)_2$], 22.6 [one CH_3 of $CH(\underline{C}H_3)_2$], 22.0 [other CH_3 of $CH(\underline{C}H_3)_2$], 18.9 [CH_3 of $C_6H_4\underline{C}H_3$]. ES MS (+): m/z 451.1 $[M/2 – HPF_6Cl]^+$

Table S1. Crystallographic Data for [(η^6-*p*-cym)Os(N-2,4-difluoro-Ph-picolinamide)Cl] (**1**), [(η^6-*p*-cym)Ru(N-2,4-difluoro-Ph-picolinamide)Cl] (**2**), [(η^6-*p*-cym)Os(N-4-nitro-Ph-picolinamide)Cl]·MeOD (**3**·MeOD), [(η^6-*p*-cym)Ru(N-2,4-dimethoxide-Ph-picolinamide)Cl]$_2$HPF$_6$ (**[6-H-6]PF$_6$**), [(η^6-*p*-cym)Os(N-2,4,6-trimethyl-Ph-picolinamide)Cl]PF$_6$·CH$_2$Cl$_2$ (**7**·CH$_2$Cl$_2$) and [(η^6-*p*-cym)Ru(N-2,4,6-trimethyl-Ph-picolinamide)Cl]PF$_6$·CHCl$_3$ (**8**·CHCl$_3$).

	1	**2**	**3**·MeOD	**[6-H-6]PF$_6$**	**7**·CH$_2$Cl$_2$	**8**·CHCl$_3$
Formula	$C_{22}H_{21}ClF_2N_2$ OOs	$C_{22}H_{21}ClF_2N_2$ ORu	$C_{22}H_{22}ClN_3O_3$ Os	$C_{48}H_{55}Cl_2F_6$ $N_4O_6PRu_2$	$C_{26}H_{32}Cl_3F_6N$ $_2$OPOs	$C_{26}H_{31}Cl_4F_6N$ $_2$OPRu
Molecular weight	593.06	503.93	635.16	1201.97	830.07	775.37
Crystal description	Yellow needle	Yellow needle	Orange block	Orange fragment	Yellow block	Orange block
Size, mm	0.15 x 0.08 x 0.02	0.34 x 0.03 x 0.02	0.20 x 0.20 x 0.10	0.40 x 0.23 x 0.18	0.44 x 0.28 x 0.26	0.2 × 0.2 × 0.17
λ (Å)	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
T / K	120(2)	150(2)	100(2)	150(2)	150(2)	150(2)
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	P2(1)/c	P2(1)/c	P2(1)/c	*C*2	*Cc*	*Cc*
a (Å)	8.0430(4)	8.46490(10)	17.5297(3)	13.7640(3)	18.6715(4)	17.889(4)
b (Å)	29.2537(17)	29.1169(5)	9.61754(13)	13.3660(3)	10.7009(2)	11.419(2)
c (Å)	8.4770(5)	8.10670(10)	15.3795(4)	13.4540(3)	15.8714(3)	15.894(3)
α (°)	90	90°	90°	90°	90	90
β (°)	101.852(2)	101.8450(10)	115.341(3)	93.0780(10)	105.3730(10)	103.89(3
γ (°)	90	90°	90°	90°	90	90
Volume (Å^3)	1952.01(19)	1955.53(5)	2343.38(8)	2471.56(9)	3057.67(11)	3151.9(11)
Z	4	4	4	2	4	4
R	0.0425	0.0329	0.0175	0.0532	0.0211	0.0355
R_w	0.0920	0.0682	0.0379	0.1221	0.0540	0.0922
GOF	1.113	1.037	0.961	1.062	0.6380	1.053

Table S2. Selected Bond Lengths (Å) and Angles (°) for [(η^6-*p*-cym)Os(N-2,4-difluoro-Ph-picolinamide)Cl] (**1**), [(η^6-*p*-cym)Ru(N-2,4-difluoro-Ph-picolinamide)Cl] (**2**), [(η^6-*p*-cym)Os(N-4-nitro-Ph-picolinamide)Cl]·MeOD (**3**·MeOD), [(η^6-*p*-cym)Ru(N-2,4-dimethoxide-Ph-picolinamide)Cl]$_2$HPF$_6$ (**[6-H-6]PF$_6$**), [(η^6-*p*-cym)Os(N-2,4,6-trimethyl-Ph-picolinamide)Cl]PF$_6$·CH_2Cl_2 (**7**·CH_2Cl_2) and [(η^6-*p*-cym)Ru(N-2,4,6-trimethyl-Ph-picolinamide)Cl]PF$_6$·$CHCl_3$ (**8**·$CHCl_3$) where M is Os or Ru.

Bond length/ angle	**1**	**2**	**3**	**6**	**7**·CH_2Cl_2	**8**·$CHCl_3$
M-C(arene)	2.105(6)	2.219(2)	2.1640(19)	2.213(6)	2.216(4)	2.200(5)
	2.114(6)	2.193(2)	2.1864(18)	2.188(4)	2.161(4)	2.163(4)
	2.156(6)	2.155(2)	2.1872(18)	2.168(6)	2.158(4)	2.169(4)
	2.203(6)	2.193(2)	2.2048(18)	2.177(6)	2.203(4)	2.202(5)
	2.239(6)	2.188(2)	2.2127(18)	2.194(5)	2.170(4)	2.165(5)
	2.246(6)	2.217(2)	2.2274(19)	2.201(7)	2.196(4)	2.146(5)
M-O					2.117(2)	2.118(3)
M-N(amidinato)	1.969(5)	2.067(2)	2.1005(15)	2.072(3)		
M-N(pyridyl)	2.158(5)	2.0911(19)	2.0965(15)	2.089(4)	2.101(3)	2.104(3)
M-Cl	2.4434(14)	2.4050(6)	2.4126(4)	2.4114(11)	2.3878(10)	2.3853(11)
O-M-N(pyridyl)					75.77(10)	76.29(11)
N-M-N	77.2(2)	76.84(8)	76.34(6)	76.93(15)		
O-M-Cl					82.36(8)	82.78(8)
N(amidinato)-M-Cl	86.02(15)	86.13(6)	84.54(4)	85.90(10)		
N(pyridyl)-M-Cl	84.56(14)	82.93(5)	83.71(4)	87.15(10)	84.43(9)	84.97(10)

Table S3A. Crystallographic Data for [(η^6-*p*-cym)Ru(N-2-fluoro-Ph-picolinamide)Cl]$_2$HPF$_6$ (**10**).

	10
Formula	$C_{44}H_{45}Cl_2F_8N_4O_2PRu_2$
Molecular weight	1117.85
Crystal description	Orange plate
Size, mm	0.36 x 0.23 x 0.03
λ (Å)	0.71073
T / K	150(2)
Crystal system	Monoclinic
Space group	*P*2/*c*
a (Å)	16.9906(4)
b (Å)	9.1185(2)
c (Å)	14.4338(3)
α (°)	90°
β (°)	106.6470(8)
γ (°)	90°
Volume (Å^3)	2142.49(8)
Z	2
R	0.0508
R_w	0.1005
GOF	1.041

Table S3B. Selected Bond Lengths (Å) and Angles (°) for [(η^6-*p*-cym)Ru(N-2-fluoro-Ph-picolinamide)Cl] (**10**)

Bond length/ angle	(**TA3**)
C(Arene)-Ru(1) (mean)	2.206(3)
N(1)-Ru(1)	2.086(3)
N(8)-Ru(1)	2.112(3)
Cl(1)-Ru(1)	2.3978(8)
C(6)-N(1)	1.360(4)
C(6)-C(7)	1.485(4)
C(7)-N(8)	1.299(4)
C(7)-O(7)	1.286(4)
N(1)-C(6)-C(7)	114.2(3)
N(8)-C(7)-C(6)	114.9(3)
N(1)-Ru(1)-N(8)	76.19(10)
N(1)-Ru(1)-Cl(1)	85.55(7)
N(8)-Ru(1)-Cl(1)	85.10(8)

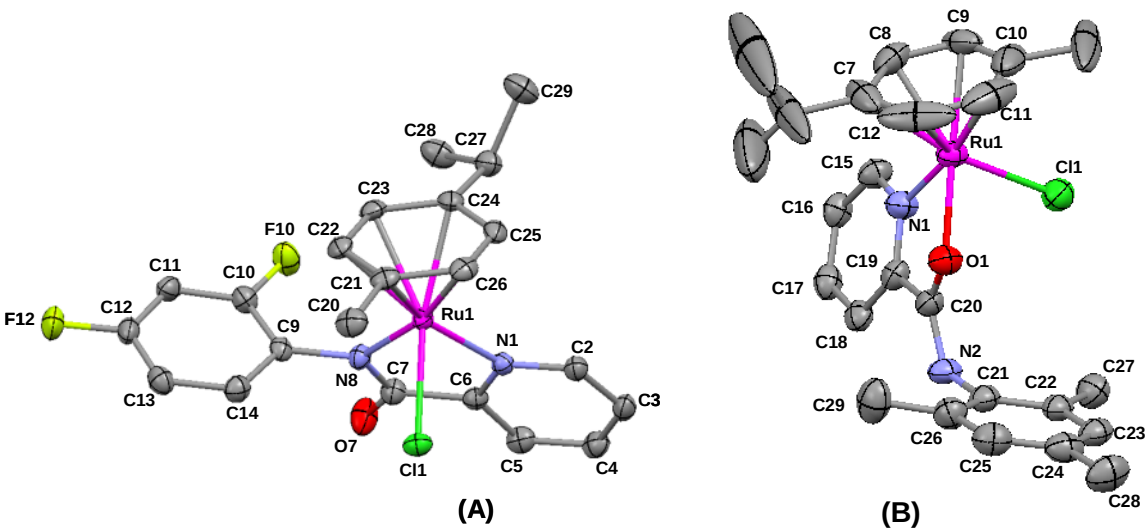

Figure S1. X-ray structures and atom numbering schemes for complexes (A) [(η^6-*p*-cym)Ru(N-2,4-difluoro-Ph-picolinamide)Cl] (**2**) and (B) [(η^6-*p*-cym)Ru(N-2,4,6-trimethyl-Ph-picolinamide)Cl]PF_6·$CHCl_3$ (**8**·$CHCl_3$). H atoms, solvent molecules and PF_6 anions are omitted for clarity.

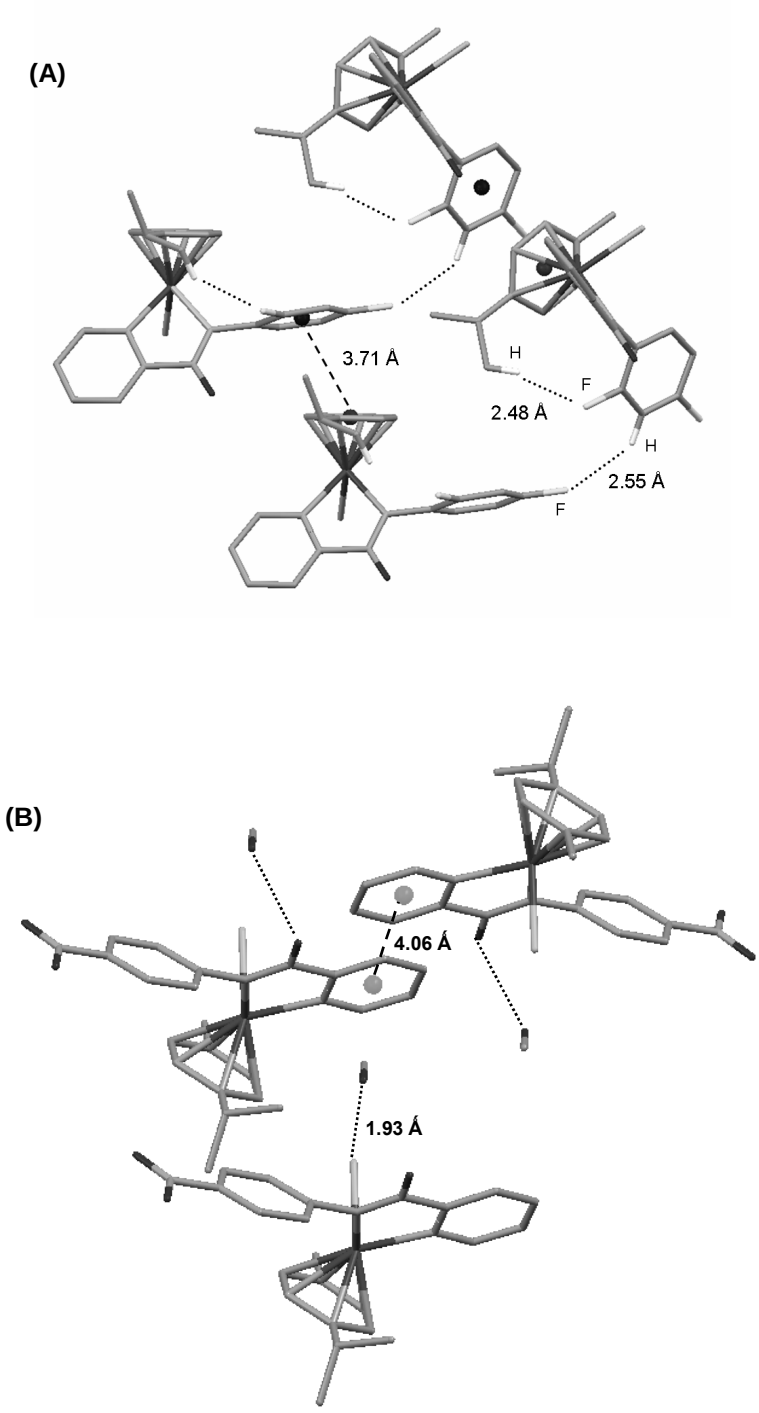

Figure S2. (A) X-ray structure of **1** showing intermolecular π-π stacking between the *p*-cymene arene and the substituted phenyl of an adjacent molecule (3.71 Å), and intermolecular H-bonding (C26-H···F17; 2.479 Å) and intramolecular H-bonding (C15-H···F14; 2.547 Å and C24-H···O8; 2.212 Å) and (B) X-ray structure of **3** showing intermolecular π-π stacking between two pyridyls of neighbouring molecules (4.06 Å), and H-bonding between the carboxylate and solvent molecule methanol (C=O···H; 1.93 Å)

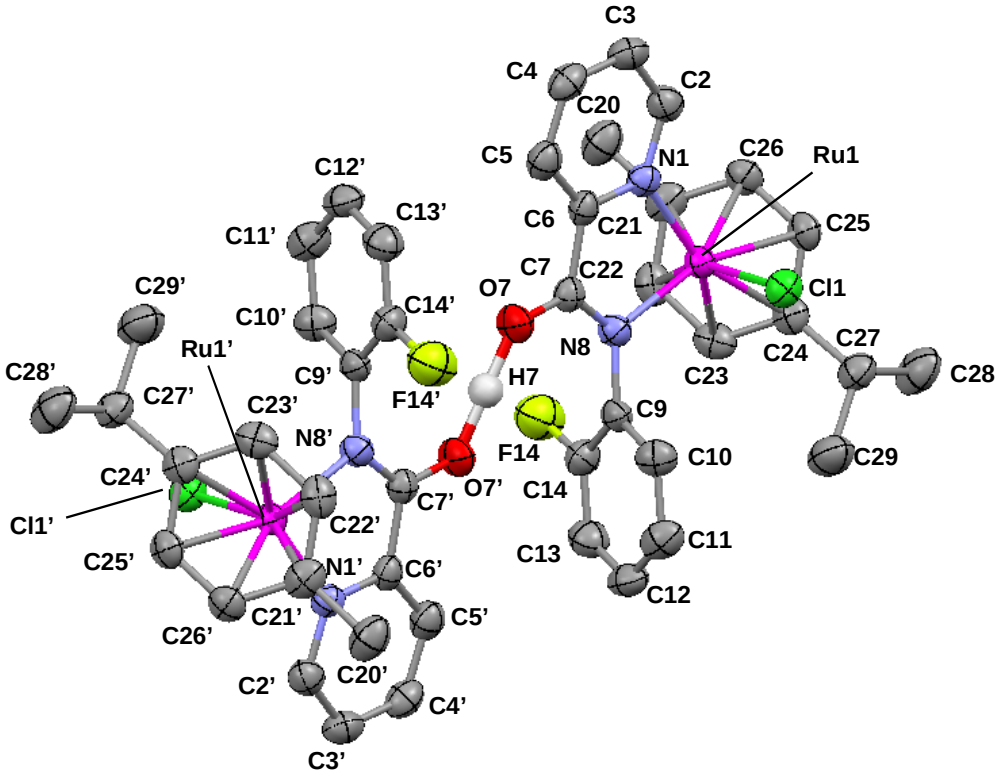

Figure S3. X-ray structure and atom numbering scheme for [(η^6-*p*-cym)Ru(N-2-fluoro-Ph-picolinamide)Cl] (**10**).

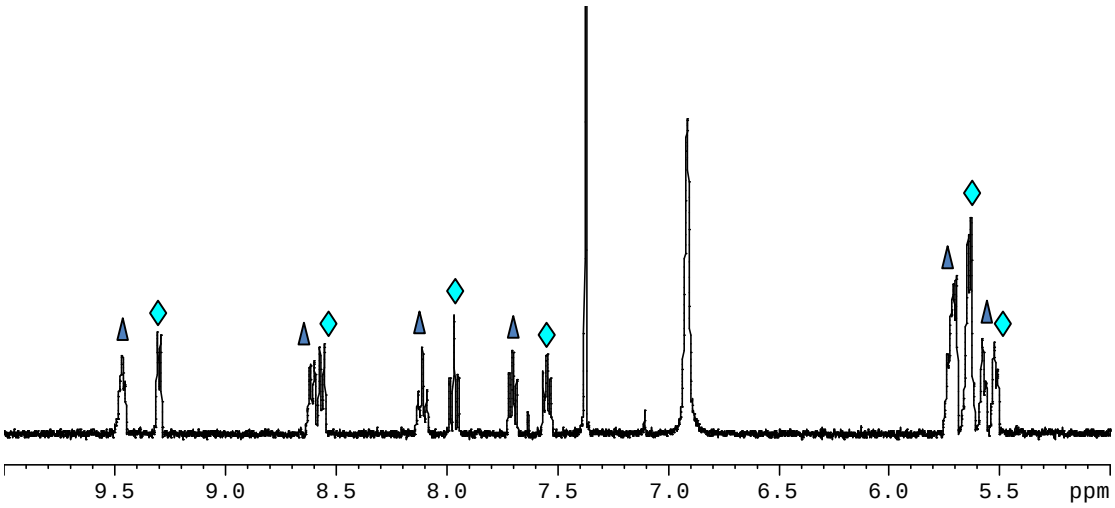

Figure S4. Low field region of the ^{1}H NMR spectrum of **7** in a 10% DMSO-d_6 / 90% $CDCl_3$ containing 3 mol equivalents of TRISPHAT showing the presence of two stereoisomers (◊,Δ) in a 50:50 ratio.

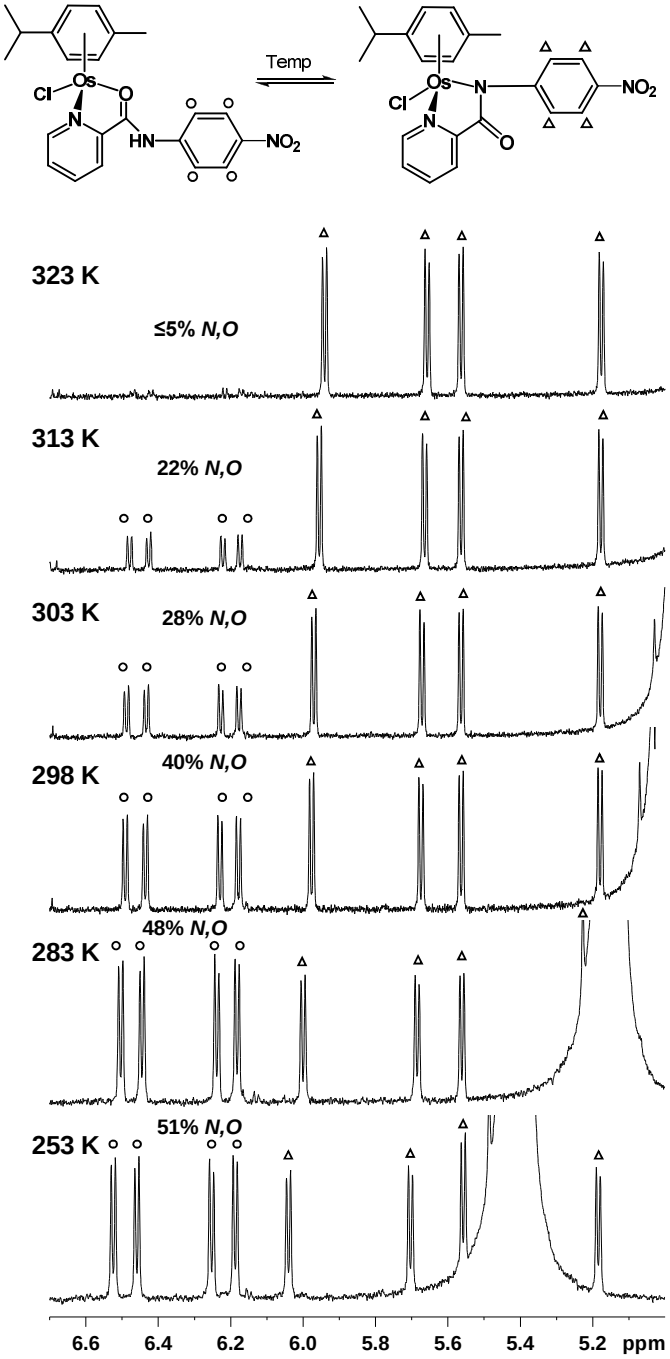

Figure S5. Low field region of the ^{1}H NMR spectrum of **3** in MeOD-d_4 at varying temperatures, where peaks labelled (○) are assigned to *p*-cymene arene peaks of the *N*,*O*-coordinated and (△) to the *N*,*N*-coordinated complex. The peaks around 8 ppm are not labelled due to peak overlap. The four peaks for both isomers arise from the four inequivalent *p*-cymene ring protons.

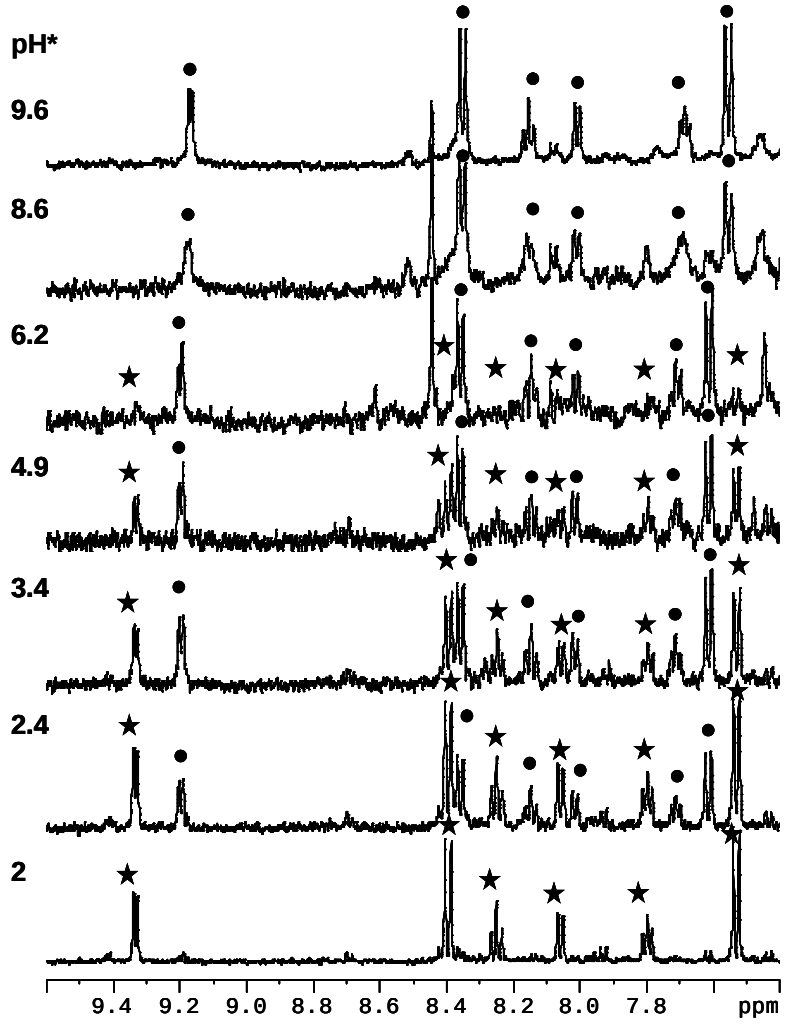

Figure S6. Low field region of the ^{1}H NMR spectrum of compound **3** in D_2O showing the dependence of an isomer mixture of **3** on pH* ranging from 2 to 9.6, where peaks labelled ● are assigned to the *N,O*-coordinated isomer, and labelled★ to the *N,N*-coordinated isomer.

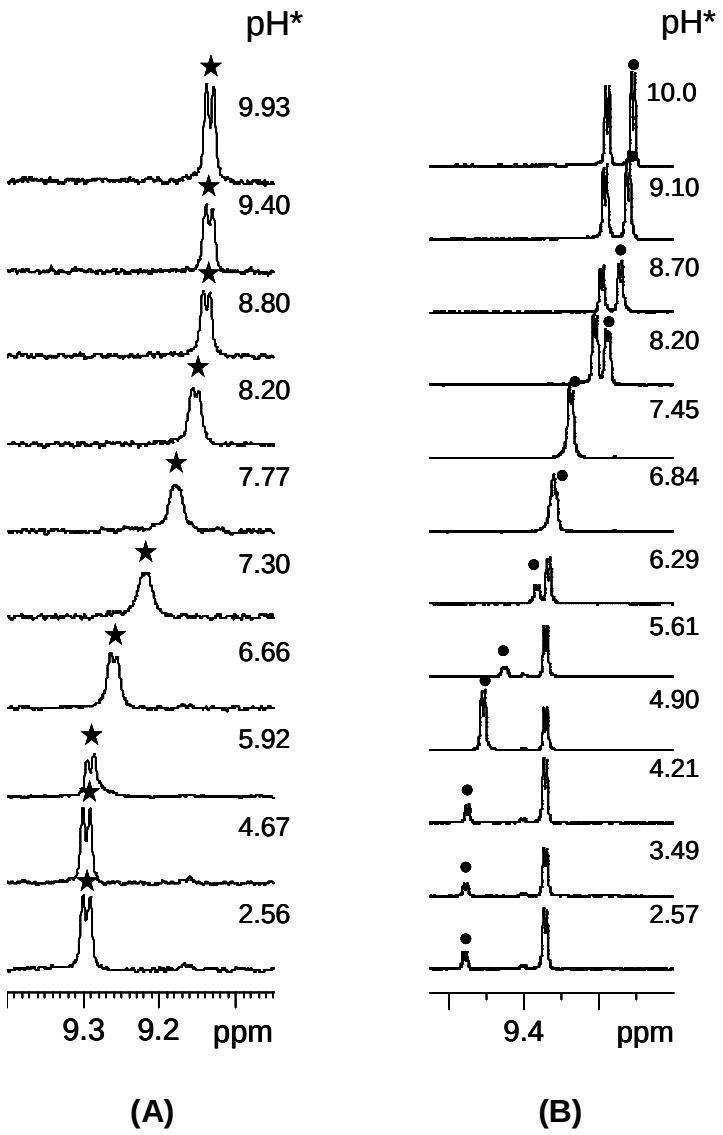

Figure S7. ^{1}H NMR spectra showing the dependence of A) the ortho-H of the picolinamide in N-2,4-difluoride-Ph-picolinamide of **1** and B) the ortho-H of the picolinamide in N-2,4,6-trimethyl-Ph-picolinamide of **7** in D_2O on pH*. A small amount of the complexes is also present as non-hydrolysed chlorido species **1** or **7** (their signals are unaffected by the pH* change.

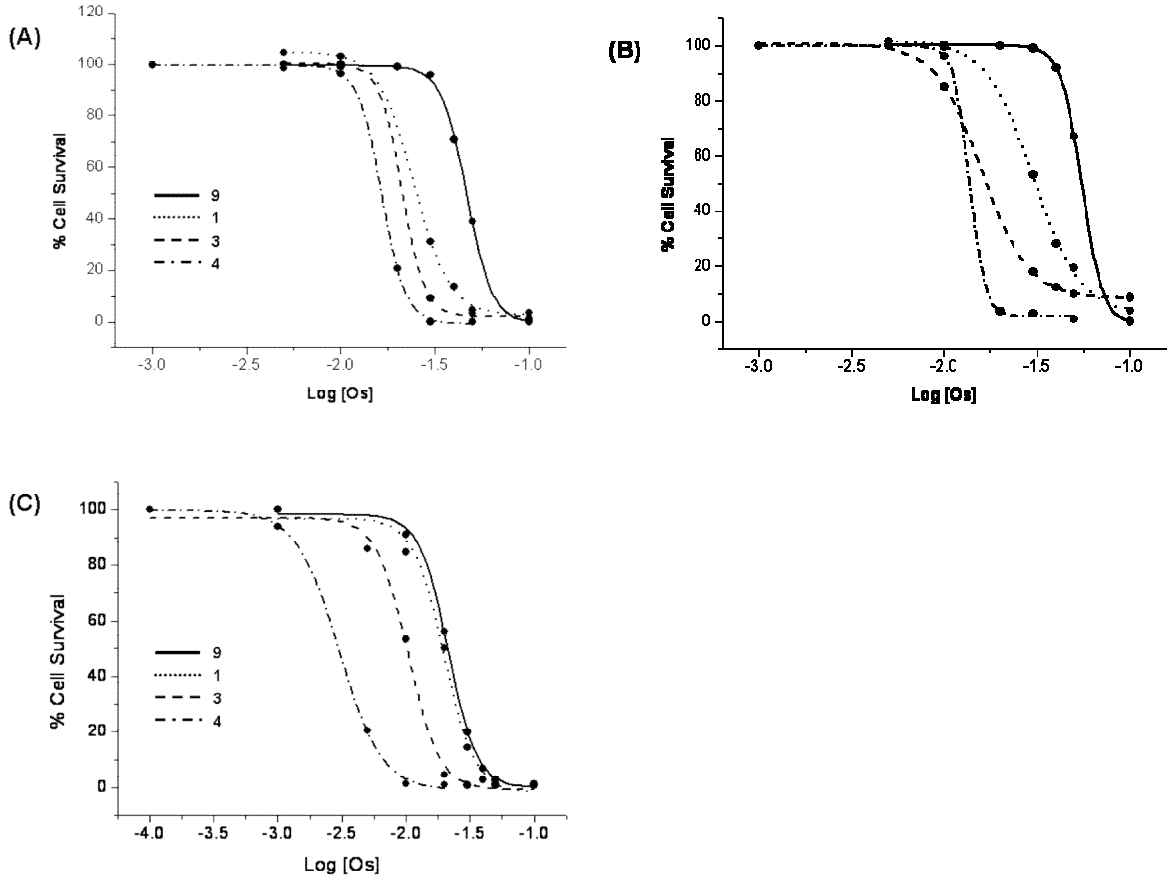

Figure S8. Cytotoxicity of [(η^6-*p*-cym)Os(N-2,4-difluoro-Ph-picolinamide)Cl] (**1**), [(η^6-*p*-cym)Os(N-4-nitro-Ph-picolinamide)Cl] (**3**), [(η^6-*p*-cym)Os(N-2-nitro-Ph-picolinamide)Cl] (**4**) and [(η^6-bip)Os(N-Ph-picolinamide)Cl] (**9**) towards A) human ovarian A2780 cancer cells, B) human ovarian cisplatin-resistant A2780cis cancer cells, and C) human colon HCT116 cancer cells. The IC_{50} values (concentrations that inhibits cell growth by 50%) obtained from these curves are given in Table 3.