Electronic Supporting Information

The Contrasting Chemical Reactivity of Potent Isoelectronic Iminopyridine and Azopyridine Osmium(II) Arene Anticancer Complexes

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1. EXPERIMENTAL

Materials. $OsCl_3{\cdot}3H_2O$ was purchased from Alfa-Aesar. Ethanol and methanol were dried over Mg/I_2 or anhydrous quality was used (Aldrich). All other reagents were obtained from commercial suppliers and used as received. The preparations of the starting materials $[Os(\eta^6\text{-bip})Cl_2]_2$, $[Os(\eta^6\text{-bip})I_2]_2$, $[Os(\eta^6\text{-p-cym})Cl_2]_2$ and $[Os(\eta^6\text{-p-cym})I_2]_2$ were based on a previous report.[1] The A2780 human ovarian carcinoma cell line A549 human lung cancer cell line were purchased from European Collection of Cell Cultures, RPMI-1640 media and trypsin from Invitrogen, bovine serum was from Biosera, penicillin, streptomycin, TCA and SRB from Sigma–Aldrich, and tris[hydroxymethyl]aminomethane from Formedium.

Synthesis of iminopyridine ligands. Syntheses of iminopyridine ligand were based on literature reports.[2]

(1) $[Os(\eta^6\text{-bip})(Impy)I]PF_6{\cdot}H_2O$. $[Os(\eta^6\text{-bip})I_2]_2$ (50.0 mg, 0.042 mmol) was dissolved in methanol (30 mL) at 353 K. The Impy ligand (15.3 mg, 0.84 mmol) in methanol (10 mL) was added dropwise, the solution-colour changed from orange to red immediately. The reaction mixture was stirred at 353 K for 3 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (27.4 mg, 0.17 mmol) was added and the solution left in a freezer for 24 h. Dark coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 51.0 mg (78.1%). ESI-MS Calcd for $C_{24}H_{20}IN_2Os$: m/z 655.0, found 655.3. ^{1}H NMR($(CD_3)_2CO$): δ 9.38 (d, 1H, J=5 Hz), 9.19 (s, 1 H), 8.55 (d, 1H, J=8 Hz), 8.25 (t, 1H, J=8 Hz), 7.70 (d, 2H, J=9 Hz),7.55-7.48 (m, 7H). 7.40 (d, 2H, J=9 Hz), 6.68 (d, 1H, J=6 Hz), 6.63 (t, 1H, J=6 Hz), 6.58 (t, 1H, J=6 Hz), 6.47 (t, 1H, J=6 Hz),), 6.34 (t, 1H, J=6 Hz). CHN analysis: Found: C, 34.91%; H, 2.41%; N, 3.34%. Calcd. for $C_{24}H_{20}F_6IN_2OsP{\cdot}H_2O$: C, 35.24%; H, 2.71%; N, 3.42%.

(2) $[Os(\eta^6\text{-p-cym})(Impy)I]PF_6$. $[Os(\eta^6\text{-}p\text{-cym})I_2]_2$ (30.0 mg, 0.026 mmol) was dissolved in methanol (20 mL) at 313 K. The Impy ligand (9.4 mg, 0.052 mmol) in methanol (10 mL) was added dropwise; the solution-colour changed from orange to red immediately. The reaction mixture was stirred at ambient temperature for 2 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (17.0

mg, 0.1 mmol) was added and the solution left in a freezer for 24 h. Dark coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 30.2 mg (74.8 %). ESI-MS Calcd for $C_{22}H_{24}IN_2Os$: m/z 635.1, found 635.0. ^{1}H NMR($(CD_3)_2CO$): δ 9.65 (d, 1H, J=6 Hz), 9.31 (s, 1 H), 8.59 (d, 1H, J=8 Hz), 8.32 (t, 1H, J=8 Hz), 7.97-7.95 (m, 2H), 7.86 (t, 1H, J=8 Hz), 7.68-7.65 (m, 2H), 6.37 (d, 1H, J=8 Hz), 6.08 (d, 1H, J=6 Hz), 5.98 (d, 1H, J=6 Hz), 5,83 (d, 1H, J=6 Hz), 2.81 (s, 3H), 2.75-2.68 (m, 1H), 2.63 (s, 6H), 1.09 (d, 3H, J=7 Hz) 1.07 (d, 3H, J=7 Hz). CHN analysis: Found: C, 34.29%; H, 3.10%; N, 3.57%. Calcd for $C_{22}H_{24}F_6IN_2OsP$: C, 33.94%; H, 3.11%; N, 3.60%.

(3) [Os(η^6-bip)(Impy-OH)I]PF_6·0.5H_2O. [Os(η^6-bip)I_2]$_2$ (50.0 mg, 0.042 mmol) was dissolved in methanol (30 mL) and water (10 mL) mixture at 353 K. The Impy-OH ligand (16.6 mg, 0.084mmol) in methanol (10 mL) was added dropwise and the solution was stirred at 353 K for 4 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (52.2 mg, 0.32 mmol) was added. Then the solution was left in a fridge for 24 h. Dark coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 29.0 mg (17.2 %). ^{1}H NMR($(CD_3)_2CO$): δ 9.37 (d, 1H, J=6 Hz), 9.10 (s, 1 H), 8.49 (d, 1H, J=8 Hz), 8.20 (t, 1H, J=8 Hz), 7.66 (t, 1H, J=9 Hz),7.59 (d, 2H, J=8 Hz), 7.49-7.41 (m, 5H), 6.91 (d, 2H, J=9 Hz), 6.89 (d, 1H, J=6 Hz), 6.65 (t, 1H, J=6 Hz), 6.55 (d, 1H, J=6 Hz), 6.48 (t, 1H, J=6 Hz), 6.34 (t, 1H, J=6 Hz). CHN analysis: Found: C, 34.92%; H, 2.65%; N, 3.29%. Calcd for $C_{24}H_{20}F_6IN_2OOsP\cdot 0.5H_2O$: C, 34.94%; H, 2.56%; N, 3.39%.

(4) [Os(η^6-p-cym)(Impy-OH)I]PF_6. [Os(η^6-*p*-cym)I_2]$_2$ (50.0 mg, 0.043 mmol) was dissolved in methanol (30 mL) at 313 K The Impy-OH. ligand (17.1 mg, 0.086 mmol) in methanol (10 mL) was added dropwise, the solution-colour changed from orange to red immediately. The reaction mixture was stirred at ambient temperature for 48 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (26.1 mg. 0.16 mmol) was added and the solution was left in a freezer for 24 h. Dark coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 43.7 mg (64.0 %). ESI-MS Calcd for $C_{22}H_{24}IN_2OOs$: m/z 651.0, found 651.1. ^1H NMR($(CD_3)_2CO$): δ 9.61 (d, 1H, J=5 Hz), 9.22 (s, 1 H), 8.51 (d, 1H, J=7 Hz), 7.85(t, 1H, J=6 Hz), 7.80 (t, 1H, J=7 Hz), 7.07 (d, 2H, J=9 Hz), 6.40 (d, 1H, J=6 Hz), 6.07 (d, 1H, J=6 Hz), 5.97 (d, 1H, J=6 Hz), 5.88 (d, 1H, J=6 Hz), 5.66 (s, 1H), 2.81 (s, 3H), 2.74-2.66 (m, 1H), 2.09 (s, 6H), 1.13 (d, 3H, J=7 Hz) 1.09 (d, 3H, J=7 Hz). CHN analysis: Found: C, 33.01%; H, 3.15%; N, 3.41%. Calcd for $C_{22}H_{24}F_6IN_2OOsP$: C, 33.26%; H, 3.04%; N, 3.53%. Crystals for X-ray diffraction were obtained by crystallization of a concentrated solution of [(η^6-*p*-cym)Os(Impy-OH)I]PF_6 in a mixture of DCM and MeOH at 253K.

(5) [Os(η^6-bip)(Impy-NMe$_2$)I]PF$_6$. [Os(η^6-bip)I_2]$_2$ (50.0 mg, 0.042 mmol) was dissolved in methanol (30 mL) at 353 K. The Impy-NMe$_2$ ligand (18,8 mg, 0.84 mmol) in methanol (10 mL) was added dropwise, the solution-colour changed from orange to red immediately. The solution was stirred at 353K for 4 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (27.3 mg. 0.17 mmol) was added. Then the solution was left in a freezer for 24 h. Red coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 35.1 mg (49.8 %). ESI-MS Calcd for $C_{26}H_{25}IN_3Os$: m/z 698.1, found 698.1. ^1H NMR($(CD_3)_2CO$): δ 9.29 (d, 1H, J=5 Hz), 9.02 (s, 1 H), 8.42 (d, 1H, J=8 Hz), 8.18 (t, 1H, J=8 Hz), 7.65 (d, 2H, J=9 Hz), 7.51-7.38 (m, 7H). 6.88 (d, 1H, J=6 Hz), 6.74 (d, 2H, J=9 Hz), 6.62 (t, 1H, J=6 Hz), 6.55 (d, 1H, J=6 Hz), 6.50 (t, 1H, J=6 Hz), 6.34 (t, 1H, J=6 Hz), CHN analysis: Found: C, 41.54%; H, 3.31%; N, 5.61%. Calcd for $C_{24}H_{29}ClF_6N_3OsP$: C, 41.63% H, 3.36% N, 5.60%.

(6) [Os(η^6-*p*-cym)(Impy-NMe$_2$)I]PF$_6$·0.5H$_2$O. [Os(η^6-*p*-cym)I_2]$_2$ (50.0 mg, 0.043 mmol) was dissolved in methanol (30 mL) at 313 K. The Impy-NMe$_2$ ligand (19.5 mg, 0.086 mmol) in methanol (10 mL) was added dropwise, the solution-colour changed from orange to red immediately. The solution was stirred at ambient temperature for 2 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (141.8 mg, 0.87 mmol) was added. Then the solution was left in a freezer for 24 h. Dark coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 50.7 mg (72.9 %). ESI-MS Calcd for $C_{24}H_{29}IN_3Os$: m/z 678.1, found 678.0. ^{1}H NMR(($(CD_3)_2CO$)): δ 9.55 (d, 1H, J=5 Hz), 9.12 (s, 1 H), 8.45 (d, 1H, J=7 Hz), 8.24 (t, 1H, J=7 Hz), 7.83 (d, 2H, J=9 Hz), 7.73 (t, 1H, J=5 Hz), 6.89 (d, 2H, J=9 Hz), 6.38 (d, 1H, J=6 Hz), 6.04 (d, 1H, J=6 Hz), 5.92-5.87 (m, 2H), 3.15 (s, 6H), 2.65 (s, 3H), 2.21-2.13 (m, 1H), 1.09 (d, 3H, J=6 Hz) 1.07 (d, 3H, J=6 Hz). CHN analysis: Found: C, 34.53%; H, 3.36%; N, 5.06%. Calcd for $C_{24}H_{29}F_6IN_3OsP{\cdot}0.5H_2O$: C, 34.64%; H, 3.63%; N, 5.05%.

(7) [Os(η^6-bip)(OMe-Impy-NMe$_2$)I]PF$_6$. [Os(η^6-bip)I_2]$_2$ (50.0 mg, 0.042 mmol) was dissolved in methanol (30 mL) and water (10 mL) mixture at 353 K. The OMe-Impy-NMe$_2$ ligand (21.3 mg, 0.84 mmol) in methanol (10 mL) was added dropwise, the solution-colour changed from orange to red immediately. The reaction mixture was stirred at 353 K for 4 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (27.3 mg, 0.17 mmol) was added. Then the solution was left in a freezer for 24 h. Red-coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 18.0 mg (24.0 %). ESI-MS Calcd for $C_{27}H_{27}IN_3OOs$: m/z 728.08, found 727.9. ^{1}H NMR(($(CD_3)_2CO$)): δ 9.00 (s, 1H), 8.18 (t, 1H, J=8 Hz), 7.99 (d, 1H, J=8 Hz), 7.60 (d, 2H, J=9 Hz), 7.49-7.39 (m, 5H), 7.34 (d, 1H, J=8 Hz), 6.91 (d, 1H, J=6 Hz), 6.74 (d, 2H, J=9 Hz), 6.56 (d, 1H, J=6 Hz), 6.51 (d, 1H, J=6 Hz), 6.48 (d, 1H, J=6 Hz), 6.21 (d, 1H, J=6 Hz), 4.10 (s, 3H), 3.12 (s, 6H), CHN analysis: Found: C, 37.17%; H, 2.98%; N, 5.04%. Calcd for $C_{27}H_{27}F_6IN_3OOsP$: C, 37.21% H, 3.12% N, 4.82%.

(8) [Os(η^6-*p*-cym)(OMe-Impy-NMe$_2$)I]PF$_6$. [Os(η^6-*p*-cym)I_2]$_2$ (50.0 mg, 0.043 mmol) was dissolved in methanol (30 mL) at 313 K. The OMe-Impy-NMe$_2$ ligand (22.0 mg, 0.086 mmol) in methanol (10 mL) was added dropwise, the solution-colour changed from orange to red immediately. The reaction mixture was stirred at ambient temperature for 2 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (28.0 mg, 0.172 mmol) was added. Then the solution was left in a freezer for 24 h. Dark-coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 35.2 mg (49.2 %). ESI-MS Calcd for $C_{25}H_{31}IN_3OOs$: m/z 708.1, found 708.0. ^{1}H NMR($(CD_3)_2CO$): δ 9.10 (s, 1 H), 8.23 (t, 1H, J=8 Hz), 8.03 (d, 1H, J=8 Hz), 7.83 (d, 2H, J=8 Hz), 7.64 (d, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 6.51 (d, 1H, J=6 Hz), 5.96 (d, 1H, J=6 Hz), 5.91(d, 1H, J=6 Hz), 5.75 (d, 1H, J=6 Hz), 4.40 (s, 3H), 3.16 (s, 6H), 2.84 (s, 3H), 2.70-2.61 (m, 1H), 1.11 (d, 3H, J=6 Hz) 1.09 (d, 3H, J=6 Hz).. CHN analysis: Found: C 35.20%, H 3.61%, N 5.01%. Calcd for $C_{25}H_{31}F_6IN_3OOsP$: C, 35.26 % H, 3.67 % N, 4.93 %.

(9) [Os(η^6-bip)(Impy)Cl]PF_6. [Os(η^6-bip)Cl_2]$_2$ (50.0 mg, 0.060 mmol) was dissolved in methanol (30 mL) at 353 K. The Impy ligand (21.9 mg, 0.12 mmol) in methanol (10 mL) was added dropwise, the solution-colour changed from orange to red immediately. The reaction mixture was stirred at 353 K for 4 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (39.1 mg. 0.24 mmol) was added. Then the solution was left in a freezer for 24 h. Dark-coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 64.0 mg (75.3 %). ESI-MS Calcd for $C_{24}H_{20}ClN_2Os$: m/z 563.1, found 563.0. ^{1}H NMR($(CD_3)_2CO$): δ 9.42 (d, 1H, J=5 Hz), 9.28 (s, 1 H), 8.53 (d, 1H, J=8 Hz), 8.34 (t, 1H, J=8 Hz), 7.80 (t, 1H, J=8 Hz), 7.62 (d, 2H, J=9 Hz), 7.58(d, 2H, J=9 Hz), 7.54-7.45 (m, 6H). 6.71 (d, 1H, J=6 Hz), 6.45 (d, 1H, J=6 Hz), 5.45-5.40 (m, 2H). 6.36 (t, 1H, J=6 Hz), CHN analysis: Found: C, 40.77%; H, 2.79%; N, 3.91%. Calcd for $C_{24}H_{20}ClF_6N_2OsP$: C, 40.77% H, 2.85% N, 3.96%.

(10) [Os(η^6-*p*-cym)(Impy)Cl]PF_6. [Os(η^6-*p*-cym)Cl_2]$_2$ (30.0 mg, 0.042 mmol) was dissolved in methanol (30 mL) at 313 K. The Impy ligand (15.2 mg, 0.085 mmol) in methanol (10 mL) was added dropwise, the solution-colour changed from yellow to red immediately. The reaction mixture was stirred at ambient temperature for 2 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (27.6 mg. 0.17 mmol) was added. Then the solution was left in a freezer for 24 h. Dark-coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 27.4 mg (77.4%). ESI-MS Calcd for $C_{22}H_{24}ClN_2Os$: m/z 543.1, found 543.1. ^1H NMR($(CD_3)_2CO$): δ 9.63 (d, 1H, J=6 Hz), 9.37 (s, 1 H), 8.54 (d, 1H, J=8 Hz), 8.37 (t, 1H, J=8 Hz), 7.90 (d, 2H, J=9 Hz), 7.66 (d, 2H, J=8 Hz), 7.86 (d, 2H, J=8 Hz), 6.44 (d, 1H, J=6 Hz), 6.02 (d, 1H, J=6 Hz), 5,96 (d, 1H, J=6 Hz), 5,79 (d, 1H, J=6 Hz), 2.79 (s, 3H), 2.69-2.55 (m, 1H), 2.39 (s, 6H), 1.09 (d, 3H, J=7 Hz) 1.07 (d, 3H, J=7 Hz). CHN analysis: Found: C 38.44%; H 3.38%; N 4.06% Calcd. for $C_{22}H_{24}ClF_6N_2OsP$: C, 38.46%; H, 3.52%; N, 4.08%.

(11) [Os(η^6-bip)(Impy-OH)Cl]PF_6·0.5H_2O. [Os(η^6-bip)Cl_2]$_2$ (50.0 mg, 0.060 mmol) was dissolved in methanol (20 mL) and water (10 mL) mixture at 353 K. The Impy-OH ligand (23.8mg, 0.012mmol) in methanol (10 mL) was added dropwise. The reaction mixture was stirred at 353 K for 4 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (97.8 mg, 0.6 mmol) was added. Then the solution was left in a freezer for 24 h. Dark-coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 15.3 mg (17.2 %). ESI-MS Calcd for $C_{24}H_{20}ClN_2OOs$: m/z 579.1, found 579.0. ^1H NMR($(CD_3)_2CO$): δ 9.36 (d, 1H, J=6 Hz), 9.18 (s, 1 H), 8.47 (d, 1H, J=8 Hz), 8.29 (t, 1H, J=8 Hz), 7.76 (t, 1H, J=9 Hz),7.58 (d, 2H, J=8 Hz), 7.54-7.43 (m, 5H), 6.92 (d, 2H, J=9 Hz), 6.74 (d, 1H, J=6 Hz), 6.64 (d, 1H, J=6 Hz), 6.45 (t, 1H, J=6 Hz), 6.42 (t, 1H, J=6 Hz), 6.35 (t, 1H, J=6 Hz), CHN analysis: Found: C, 39.44%; H, 2.84%; N, 3.71%. Calcd for $C_{24}H_{20}ClF_6N_2OOsP·0.5H_2O$: C, 39.32%; H, 2.89%; N, 3.82%.

(12) [Os(η^6-p-cym)(Impy-OH)Cl]PF_6. [Os(η^6-*p*-cym)Cl_2]$_2$ (50.0 mg, 0.063 mmol) was dissolved in methanol (30 mL) at 313 K. The Impy-OH ligand (25.0 mg, 0.12 mmol) in methanol (10 mL) was added dropwise, the solution-colour changed from orange to red immediately. The reaction mixture was stirred at ambient temperature for 2 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (41.2 mg, 0.25 mmol) was added. Then the solution was left in a freezer for 24 h. Dark-coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 53.8 mg (63.7 %). ESI-MS

Calcd for $C_{22}H_{24}ClN_2OOs$: m/z 559.1, found 559.1. ^{1}H NMR(($(CD_3)_2CO$): δ 9.60 (d, 1H, J=5 Hz), 9.35 (s, 1 H), 8.50 (d, 1H, J=7 Hz), 8.34 (t, 1H, J=7 Hz), 7.84(t, 1H, J=6 Hz), 7.75 (d, 2H, J=9 Hz), 7.08 (d, 2H, J=9 Hz), 6.46 (d, 1H, J=6 Hz), 6.00 (d, 1H, J=6 Hz), 5.84 (d, 1H, J=6 Hz), 2.81 (s, 3H), 2.65-2.55 (m, 1H), 2.41 (s, 6H), 1.10 (d, 3H, J=7 Hz) 1.08 (d, 3H, J=7 Hz). CHN analysis: Found: C, 37.82%; H, 3.33%; N, 3.91%. Calcd for $C_{22}H_{24}ClF_6N_2OOsP$: C, 37.58% H, 3.44% N, 3.98%.

(13) [Os(η^6-bip)(Impy-NMe$_2$)Cl]PF$_6$. [Os(η^6-bip)Cl$_2$]$_2$ (50.0 mg, 0.060 mmol) was dissolved in methanol (20 mL) at 313 K. The Impy-NMe$_2$ ligand (27.1mg, 0.12 mmol) in methanol (10 mL) was added dropwise; the solution-colour changed from orange to red immediately. The reaction mixture was stirred at 353K for 12 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (39.1 mg, 0.24 mmol) was added. Then the solution was left in a freezer for 24 h. Red-coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 52.0 mg (57.8 %). ^{1}H NMR($(CD_3)_2CO$): δ 9.31 (d, 1H, J=5 Hz), 9.09 (s, 1 H), 8.39 (d, 1H, J=8 Hz), 8.25 (t, 1H, J=8 Hz), 7.70 (t, 1H, J=9 Hz),7.61-7.44 (m, 7H). 6.77 (d, 2H, J=9 Hz), 6.74 (d, 1H, J=6 Hz), 6.62 (d, 1H, J=6 Hz), 6.63-6.45 (m, 2H), 6.34 (t, 1H, J=6 Hz), CHN analysis: Found: C, 41.54%; H, 3.31%; N, 5.61%. Calcd for $C_{26}H_{25}ClF_6N_3OsP$: C, 41.63%; H, 3.36%; N, 5.60%.

(14) [Os(η^6-*p*-cym)(Impy-NMe$_2$)Cl]PF$_6$. [Os(η^6-*p*-cym)Cl$_2$]$_2$ (50.0 mg, 0.063 mmol) was dissolved in methanol (30 mL) at 313 K. The Impy-NMe$_2$ ligand (28.5mg, 0.126 mmol) in methanol (10 mL) was added dropwise, the solution-colour changed from orange to red immediately. The reaction mixture was stirred at ambient temperature for 2 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (41.2 mg, 0.253 mmol) was added. Then the solution was left in a freezer for 24 h. Dark-coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 67.2 mg (85.6 %). ESI-MS Calcd for $C_{24}H_{29}ClN_3Os$: m/z 586.2, found 586.1. ^{1}H NMR($(CD_3)_2CO$): δ 9.55 (d, 1H, J=5 Hz), 9.20 (s, 1 H), 8.44 (d, 1H, J=7 Hz), 8.31 (t, 1H, J=7 Hz), 7.82(t, 1H, J=6 Hz), 7.76 (d, 2H, J=9 Hz), 6.92 (d, 2H, J=9 Hz), 6.44 (d, 1H, J=6 Hz), 6.04 (d, 1H, J=6 Hz), 5.97 (d, 1H, J=6 Hz), 5.85 (d, 1H, J=6 Hz), 3.16 (s, 6H), 2.42 (s, 3H), 2.21-2.11 (m, 1H), 1.09 (d, 3H, J=7 Hz) 1.07 (d, 3H, J=7 Hz). CHN analysis: Found: C, 39.43%; H, 3.89%; N, 5.75%. Calcd. for $C_{24}H_{29}ClF_6N_3OsP$: C, 39.48%; H, 4.00% N, 5.75%.

(15) [Os(η^6-bip)(OMe-Impy-NMe$_2$)Cl]PF$_6$·0.5H$_2$O. [Os(η^6-bip)Cl$_2$]$_2$ (50.0 mg, 0.060 mmol) was dissolved in methanol (20 mL) and water (10 mL) at 313 K. The OMe-Impy-NMe$_2$ ligand (30.6 mg, 0.12 mmol) in methanol (10 mL) was added dropwise, the solution-colour changed from orange to red immediately. The reaction mixture was stirred at 353K for 12 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (39.1 mg. 0.24 mmol) was added. Then the solution was left in a freezer for 24 h. Red-coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 72.1 mg (77.0 %). ESI-MS Calcd for $C_{27}H_{27}ClN_3OOs$: m/z 636.2, found 636.0. ^{1}H NMR((CD_3)$_2$CO): δ 9.00 (s, 1H), 8.24 (t, 1H, J=8 Hz), 7.95 (d, 1H, J=8 Hz), 7.60-7.56 (m, 5H), 7.50-7.41 (m, 5H), 6.77 (d, 2H, J=9 Hz), 6.60 (d, 1H, J=6 Hz), 6.37-6.32 (m, 2H), 4.14 (s, 3H), 3.12 (s, 6H), CHN analysis: Found: C, 41.04%; H, 3.32%; N, 5.28%. Calcd for $C_{27}H_{27}ClF_6N_3OOsP{\cdot}0.5H_2O$: C, 41.04 %; H, 3.57 %; N, 5.32 %.

(16) [Os(η^6-*p*-cym)(OMe-Impy-NMe$_2$)Cl]PF$_6$·H$_2$O. [Os(η^6-*p*-cym)Cl$_2$]$_2$ (50.0 mg, 0.063 mmol) was dissolved in methanol (30 mL) at 313 K. The OMe-Impy-NMe$_2$ ligand (32.2 mg, 0.126 mmol) in methanol (10 mL) was added dropwise, the solution-colour changed from orange to red immediately. The reaction mixture was stirred at ambient temperature for 2 h. The volume was reduced to about 10 mL by removal of methanol on a rotary evaporator, and ammonium hexafluorophosphate (41.2 mg, 0.253 mmol) was added. Then the solution was left in a freezer for 24 h. Dark-coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 58.7 mg (61.3 %). ESI-MS Calcd for $C_{25}H_{31}ClN_3OOs$: m/z 616.2, found 616.0. ^{1}H NMR((CD_3)$_2$CO): δ 9.10 (s, 1 H), 8.25 (t, 1H, J=8 Hz), 7.98 (d, 1H, J=8 Hz), 7.72 (d, 2H, J=8 Hz), 7.53 (d, 1H, J=8 Hz), 6.90 (d, 2H, J=8 Hz), 6.54 (d, 1H, J=6 Hz), 5.98 (d, 1H, J=6

Hz), 5.82 (dd, 2H, J=6 Hz), 4.38 (s, 3H), 2.86 (s, 6H), 2.61-2.51 (m, 1H), 2.38 (s, 3H), 1.11 (d, 3H, J=7 Hz) 1.08 (d, 3H, J=7 Hz). CHN analysis: Found: C 38.66%, H 4.00%, N 5.29%. Calcd. for $C_{25}H_{31}ClF_6N_3OOsP{\cdot}H_2O$: C, 38.54%; H, 4.27%; N, 5.39%.

(14A) [Os(η^6-*p*-cym)(Impy-NMe$_2$)OH]PF$_6$·H$_2$O. [Os(η^6-*p*-cym)Cl$_2$]$_2$ (100.0 mg, 0.126 mmol) and $AgNO_3$ (85.9 mg, 0.506 mmol) was stirred in water (20 mL) at 313 K for 12 h, a white precipitate was filtered off. The Impy-NMe$_2$ ligand (57.0 mg, 0.25 mmol) was added to the yellow clear solution, the solution-colour changed from yellow to red immediately. The reaction mixture was stirred at ambient temperature for 12 h. Ammonium hexafluorophosphate (205 mg, 1.26 mmol) was added. Then the solution was left in a fridge for 24 h. Dark-coloured powder precipitated which was collected by filtration, washed with cold ethanol and diethyl ether, and finally dried in vacuum. Yield: 105 mg (58.5 %). ESI-MS Calcd for $C_{24}H_{30}N_3OOs$: m/z 568.2, found 569.1. ^{1}H NMR(D_2O): δ 9.29 (d, 1H, J=5 Hz), 8.98 (s, 1 H), 8.15 (d, 1H, J=7 Hz), 8.12 (t, 1H, J=7 Hz), 7.67 (t, 1H, J=6 Hz), 7.52 (d, 2H, J=9 Hz), 6.96 (d, 2H, J=9 Hz), 6.17 (d, 1H, J=6 Hz), 5.81 (d, 1H, J=6 Hz), 5.66 (d, 1H, J=6 Hz), 5.54 (d, 1H, J=6 Hz), 2.98 (s, 6H), 2.25 (s, 3H), 2.23-2.16 (m, 1H), 0.83 (d, J=7 Hz, 3H), 0.74 (d, J=7 Hz, 3H). CHN analysis: Found: C, 39.59%, H, 3.87%, N, 6.23%. Calcd. for $C_{24}H_{30}F_6N_3OOsP{\cdot}H_2O$: C, 39.42%, H, 4.41%, N, 5.74%.

Methods

Electrochemistry. The electrochemical study was carried out using similar conditions to those used for the ruthenium analogues reported previously:[3] Electrochemical studies were performed with a CHI730A bipotentiostat (CH Instrument, USA) system, and a three-electrode configuration with all the electrodes in solution. A 2 mm diameter platinum disc electrode was used as the working electrode with a chloridized silver wire as the quasi-reference electrode and a Pt counter electrode (CH Instrument, USA). The reference electrode was Ag/AgCl in a solution of 0.1 M [TBA][BF_4] in DMF, against which $E_{1/2}$ for the ferrocenium/ferrocene couple was measured to be +0.55 V.

High resolution Liquid Chromatography–Mass Spectrometry (LC-MS) Analysis. LC-MS analysis was carried with a Dionex 3000RS UHPLC coupled with a Bruker MaXis Q-TOF mass spectrometer. A Sigma Ascentis Express column (C18, 150x2.1 mm, 2.7 µm) was used. Mobile phases are consisted of A (water with 0.1% formic acid) and B (as methanol with 0.1% formic acid). A gradient of 5% B to 100% B in 15 minutes was employed with flow rate at 0.2 mL/min, UV detection wavelength 210 nm. The mass spectrometer was operated in electrospray positive mode with a scan range 50-2,000 m/z. Source conditions: end plate offset at -500 V; capillary at -4500 V; nebulizer gas (N_2) at 1.6 bar; dry gas (N_2) at 8 L/min; dry temperature at 453 K. Ion tranfer conditions: ion funnel RF at 200 Vpp; multiple RF at 200 Vpp; quadruple low mass set at 55 m/z; collision energy at 5.0 eV; collision RF at 600 Vpp; ion cooler RF at 50-350 Vpp; transfer time 121 µs; pre-pulse storage time 1 µs. Calibration was made with sodium formate (10 mM) through a loop injection of 20 µL of standard solution at the beginning of each run.

NADH (0.5 mM) with or without complex **14A** (0.5 mM) was incubated at 310 K for 24 h; NADH and NAD^+ were incubated under the same conditions and LC-MS was employed to analyze the 3 samples.

Detection of H_2 by Gas Chromatography (GC). Solutions containing complex **14** [(η^6-*p*-cym)Os(Impy-NMe_2)OH]PF_6 and NADH (Os 100 µM, NADH, 2 mM, 100 mM phosphate buffer, pH 7.4, 10% MeOH/90% H_2O) were incubated at 310 K for 18 h before sampling.

Aliquots of the headspace (10 μl) were removed by using a gas-tight syringe and analyzed on an Agilent GC 7890A instrument equipped with a thermal conductivity detector, using N2 as the carrier gas. Under these conditions H_2 had a retention time of 0.4 min and O_2 a retention time of 0.8 min.

X-ray Crystallography. X-ray diffraction data for [Os(η^6-*p*-cym)(Impy-OH)I]PF_6 (**3**) were obtained on an Oxford Diffraction Gemini four-circle system with a Ruby CCD area detector using Mo K_α radiation.[4] Absorption corrections were carried out using ABSPACK. The crystals were mounted in oil and held at 100(2) K with the Oxford Cryosystem Cryostream Cobra. The structure was solved by direct methods using SHELXS (TREF) with additional light atoms found by Fourier methods[5] and refined with SHELXL 97[6] (refinement of F^2 against ALL reflections). Hydrogen atoms were added at calculated positions and refined using a riding model except the phenol OHs and the hydrogens on O200 which were located in a difference map. Anisotropic displacement parameters were used for all non-H atoms. H-atoms were given isotropic displacement parameter equal to 1.2 (or 1.5 for methyl or OH H-atoms) times the equivalent isotropic displacement parameter of the atom to which they are attached. No hydrogens were located for water O300. One of the PF_6 counter ions was modelled as disordered around the phosphorus in the ratio 43:57 P10(F11-F16):P10(F11A-F16A). DFIX, DANG and ISOR restraints were used to maintain sensible bonds, angles and thermal parameters of the disordered components P10 F11-F16 and F11A-F16A. Drawings were made with Ortep-3 and Mercury 2.4.

Cell Culture and IC_{50} determinations. Human ovarian A2780 cells were obtained from ECACC (Salisbury, UK). The cells were maintained in RPMI-1640 supplemented with 10% (v/v) foetal calf serum, 1% L-glutamine, and 1% penicillin/streptomycin at 310 K in a humidified atmosphere containing 5% CO_2. The concentrations of the osmium complexes that inhibit 50% of the proliferation of human ovarian A2780, MRC-5 human fetal lung fibroblast cells and human lung cancer A549 cancer cells were determined using the sulforhodamine B assay. Cancer cells were seeded in 96-well plates (Falcon) at 5000 cells/well, after incubation for 48 h. The complexes were solubilised in DMSO (Sigma) to provide 10 mM stock solutions. These were serially diluted with cell culture media to give concentrations four-fold greater than the final concentrations for the assay. The complexes diluted in cell culture media were added to the 96-well plates with cells in triplicate. The final DMSO concentration in each well was no more than 1% (v/v). The media containing the complexes were removed after 24 h. The cells were washed with phosphate buffered saline once and cell culture medium was added (200 µL/well). The cells were then allowed to grow for a further 72 h. The surviving cells were fixed by adding 50 µL/well of 50% (w/v) trichloroacetic acid and incubated for 1 h in a refrigerator (277 K). The plates were washed with tap water three times and dried under a flow of warm air, 0.4% sulforhodamine B (Sigma) solution (50 µL/well) was added for 30 min, followed by washing with 1% acetic acid five times and drying under a flow of warm air. The dye was dissolved in 10 mM Tris buffer (150 µL/well). The absorbance of each well was determined using a Multiskan Ascent plate reader (Labsystems) at 540 nm. The absorbance of SRB in each well is directly proportional to the cell number. Then the absorbance was plotted against concentration and the IC_{50} determined by using Origin software (version 7.5).

ROS detection. The vial of DCFH-DA was opened under N_2 protection, and contents were dissolved in DMSO to give a 10 mM stock solution. A549 cells were seeded (5000 cells/well) into black 96-well plates and incubated for 24 h at 310 K, 5% CO_2, high humidity. Cells were loaded with DCFH-DA (10 µM) and incubated for 30 min. The probe was removed and PBS was used to wash the cells twice. The cells were then kept in PBS solution then treated with **6** (4 µM), **14** (4 µM), L-BSO (50 µM), **6** or **14** combined with L-BSO (50 µM), and H_2O_2 (10 µM, positive control). The fluorescence was recorded over a period of 4 h at 310 K by excitation at 480 nm and emission at 530 nm on a TECAN plate reader (TECAN, USA).

NAD^+/NADH Ratio in Cells. Determination of the nicotinamide adenine dinucleotide NAD^+/NADH ratio in cellular lysates was carried out using a Biovision NAD^+ and NADH quantification kit according to the manufacturer's specifications. A stock solution of the Os^{II} complex **14** was prepared in DMSO to assist dissolution and then diluted into medium (maximum final DMSO concentration 0.25%). A2780 cells (400,000) were seeded in 6-well plates and cultured in complete medium for one day.

Cancer cells were treated with 1.5 μM of complex **14** for 6 h, washed with PBS, trypsinised, counted and lysed for extraction. Briefly, lysates of 200,000 S7 cells were extracted by freeze/thaw two cycles (20 min on dry ice, then 10 min at room temperature). Extracted samples were filtered through 10 kDa molecular weight cut-off filters to remove enzymes consuming NADH. Samples were stored at -80 ^{o}C until the assay was performed. To detect total NADH plus NAD^+ (NADt), the samples and NADH standards were incubated directly with NAD cycling mix (cycling buffer and enzyme mix). To detect NADH, samples were heated to 60°C for 30 min to decompose NAD^+ before incubating with NAD cycling mix.

Duplicated samples and standards were then mixed with NADH developer and incubated at room temperature for 4 h before recording the absorbance at 450nm. The amount of NAD^+ in samples was calculated by subtracting NADH from NADt (NADH + NAD^+).

Instrumentation

NMR Spectroscopy. ^{1}H NMR spectra were acquired in 5 mm NMR tubes at 298 K or 310 K on either Bruker DPX-400, Bruker DRX-500, Bruker AV III 600 or Bruker AV II 700 spectrometers. ^{1}H NMR chemical shifts were internally referenced to TMS using acetone (2.09 ppm), 1, 4-dioxane (3.71 ppm), $CHCl_3$ (7.27 ppm) or DMSO (2.50 ppm). To minimize the effect of HOD signal overlapping with other proton peaks in ^{1}H NMR experiments using 10%D_2O/90%H_2O, the HOD signal was suppressed using presaturation methods. All data processing was carried out using MestReC or TOPSPIN version 2.0 (Bruker U.K. Ltd.).

pH* Measurements. pH* values (pH meter reading from D_2O solution without correction for effects of deuterium on glass electrode) were measured at ambient temperature before the NMR spectra were recorded, using a Corning 240 pH meter equipped with a microcombination electrode calibrated with Aldrich buffer solutions at pH 4, 7 and 10. The pH* values were adjusted with dilute NaOH or HNO_3 solutions in D_2O.

Calculation of pK_a^* values. The chemical shift of the ^{1}H NMR signals were plotted against pH* values. The curve from the pH* titration was fitted to the Henderson-Hasselbalch equation using ORIGIN 7.5. The pK_a^* values were converted to pK_a values by using the equation $pK_a = 0.929 \cdot pK_a^* + 0.42$.[7]

Electrospray Ionisation Mass Spectrometry (ESI-MS). Spectra were obtained by preparing the samples in 50% CH_3CN and 50% H_2O (v/v) and infusing into the mass spectrometer (Bruker Esquire 2000). The mass spectra were recorded with a scan range of m/z 500-1000 for positive ions. Data were processed using Data Analysis version 3.3 (Bruker Daltonics).

Elemental Analysis. Elemental analysis (carbon, hydrogen, and nitrogen) was carried out through Warwick Analytical Service using an Exeter analytical elemental analyzer (CE440).

UV-Vis Spectroscopy. UV-Vis spectra were recorded on a Cary 300-Bio spectrophotometer using 1-cm path-length quartz cuvettes (0.5 mL) and a PTP1 Peltier temperature controller.

Spectra were recorded at 310 K from 800 to 200 nm. All data processing was carried out using Excel 2007 (Microsoft, USA) or Origin 7.5 (Origin, USA).

Table S1: Crystal data and structure refinement for [Os(η^6-*p*-cym)(Impy-OH)I]PF_6 $\cdot 0.5CH_2Cl_2 \cdot H_2O$ (**4** $\cdot 0.5CH_2Cl_2 \cdot H_2O$)

	4 $\cdot 0.5CH_2Cl_2 \cdot H_2O$
Empirical formula	$C_{22.50}H_{27}ClF_6IN_2O_2OsP$
Crystal size [mm]	0.20×0.20×0.20
Formula weight	854.98
Crystal system	Triclinic
Space group	P-1
a [Å]	11.3168(3)
b [Å]	13.0498(3)
c [Å]	19.2278(4)
α [°]	95.3980(19)
β [°]	103.654(2)
γ [°]	97.2625(19)
Volume [Å^3]	2714.50(11)
Temperature [K]	100(2)
Z	4
μ [mm^{-1}]	6.057
Reflections collected	12572
Independent reflections [Rint]	9981 [0.0222]
*R*1, *wR*2 [$I>2\sigma(I)$]	0.0332, 0.0793
*R*1, *wR*2 (all data)	0.0450, 0.0817
GOF	1.061
$\Delta\rho$ max and min /eÅ^{-3}	4.429, -1.365

Table S2: Selected bond lengths[a] [Å] and angles [°] for [Os(η^6-*p*-cym)(Impy-OH)I]PF_6 ·$0.5CH_2Cl_2·H_2O$ (**4**·$0.5CH_2Cl_2·H_2O$)

4·$0.5CH_2Cl_2·H_2O$					
Os1-N108	2.077(4)	Os2-N208	2.078(4)	Os1- η^6-arene centroid	1.6962(2)
Os1-N101	2.087(4)	Os2-N201	2.080(4)	Os2- η^6-arene centroid	1.6845(2)
Os1-C120	2.182(5)	Os2-C220	2.169(5)	N108-Os1-N101	76.05(14)
Os1-C116	2.189(5)	Os2-C216	2.184(5)	N101-Os1-I1	84.80(11)
Os1-C117	2.206(5)	Os2-C221	2.201(6)	N208-Os2-N201	76.59(15)
Os1-C121	2.209(5)	Os2-C217	2.209(5)	N208-Os2-I2	85.06(12)
Os1-C119	2.219(4)	Os2-C219	2.212(5)		
Os1-C118	2.256(4)	Os2-C218	2.245(5)		
Os1-I1	2.7091(4)	Os2-I2	2.7247(4)		

[a] Intermolecular hydrogen bonds are observed between one water molecule and both PF_6^- counterions [O300-H30A···F33 2.10(3) Å, x+1, y, z; O300-H30B···F21 2.36(3) Å, -x+1, -y, -z]

Table S3. NCI 60-cell line test data: (A) [Os(η^6-*p*-cym)(Impy-NMe$_2$)I]PF$_6$(**6**); (B) [Os(η^6-*p*-cym)(Impy-NMe$_2$)Cl]PF$_6$ (**14**).

(A)

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 755639 / 1	Experiment ID : 1102NS99	Test Type : 08	Units : Molar
Report Date : April 09, 2011	Test Date : February 14, 2011	QNS :	MC :
COMI : FY092 (102118)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0Y4T	

Log10 Concentration

Panel/Cell Line	Time Zero	Ctrl	Mean Optical Densities -8.0	-7.0	-6.0	-5.0	-4.0	Percent Growth -8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.405	1.448	1.267	1.323	1.302	0.514	0.342	83	88	86	10	-16	2.99E-6	2.52E-5	> 1.00E-4
HL-60(TB)	0.773	1.450	1.474	1.514	1.067	0.340	0.271	104	109	43	-56	-65	7.94E-7	2.73E-6	8.70E-6
K-562	0.272	1.159	1.248	1.266	0.571	0.305	0.226	110	112	34	4	-17	6.20E-7	1.51E-5	> 1.00E-4
MOLT-4	0.584	1.276	1.315	1.401	1.410	0.469	0.360	106	118	119	-20	-38	3.16E-6	7.22E-6	> 1.00E-4
RPMI-8226	0.845	2.098	2.049	2.075	1.385	0.692	0.541	96	98	43	-18	-36	7.49E-7	5.06E-6	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.331	1.323	1.286	1.304	1.313	0.437	0.218	96	98	99	11	-34	3.58E-6	1.73E-5	> 1.00E-4
EKVX	0.583	1.555	1.545	1.569	1.492	0.839	0.337	99	101	93	26	-42	4.44E-6	2.42E-5	> 1.00E-4
HOP-62	0.420	1.142	1.118	1.176	1.023	0.543	0.076	97	105	83	17	-82	3.19E-6	1.48E-5	4.76E-5
HOP-92	1.156	1.652	1.601	1.524	1.522	0.729	0.214	90	74	74	-37	-81	1.64E-6	4.64E-6	1.96E-5
NCI-H226	0.749	1.533	1.481	1.437	1.475	0.998	0.086	93	88	93	32	-89	5.01E-6	1.84E-5	4.78E-5
NCI-H23	0.479	1.428	1.399	1.278	1.278	0.631	0.232	97	84	84	16	-52	3.17E-6	1.72E-5	9.45E-5
NCI-H322M	0.824	1.665	1.643	1.713	1.763	1.016	0.300	97	106	112	23	-64	4.94E-6	1.84E-5	6.96E-5
NCI-H460	0.265	1.917	1.971	1.877	1.739	0.496	0.122	103	98	89	14	-54	3.32E-6	1.61E-5	8.74E-5
NCI-H522	0.865	2.102	2.097	2.085	1.907	0.745	0.285	100	99	84	-14	-67	2.23E-6	7.21E-6	4.77E-5
Colon Cancer															
COLO 205	0.271	1.131	1.144	1.103	0.756	0.065	0.033	101	97	56	-76	-88	1.12E-6	2.66E-6	6.34E-6
HCC-2998	0.632	2.139	2.073	2.051	2.001	0.728	0.119	96	94	91	6	-81	3.04E-6	1.18E-5	4.40E-5
HCT-116	0.227	1.423	1.412	1.465	1.171	0.251	0.027	99	104	79	2	-88	2.38E-6	1.05E-5	3.78E-5
HCT-15	0.244	1.481	1.485	1.392	1.338	1.459	0.885	100	93	88	98	52	> 1.00E-4	> 1.00E-4	> 1.00E-4
HT29	0.335	1.498	1.556	1.505	1.397	0.284	0.067	105	101	91	-15	-80	2.44E-6	7.18E-6	3.42E-5
KM12	0.468	2.068	2.156	2.140	2.054	0.245	0.059	105	104	99	-48	-87	2.16E-6	4.73E-6	1.15E-5
SW-620	0.282	1.649	1.593	1.518	1.422	0.375	0.050	96	90	83	7	-82	2.73E-6	1.19E-5	4.33E-5
CNS Cancer															
SF-268	0.474	1.340	1.373	1.410	1.322	0.458	0.110	104	108	98	-3	-77	2.97E-6	9.26E-6	4.31E-5
SF-295	0.718	2.339	2.314	2.378	2.380	2.231	0.502	98	102	103	93	-30	2.24E-5	5.70E-5	> 1.00E-4
SF-539	0.634	2.016	1.932	1.891	1.857	0.745	0.188	94	91	88	8	-70	3.01E-6	1.27E-5	5.50E-5
SNB-19	0.463	1.446	1.483	1.463	1.414	0.672	0.100	104	102	97	21	-79	4.16E-6	1.63E-5	5.18E-5
SNB-75	0.753	1.256	1.190	1.265	1.230	0.604	0.086	87	102	95	-20	-89	2.46E-6	6.71E-6	2.75E-5
U251	0.412	1.374	1.397	1.369	1.206	0.407	0.034	102	99	82	-1	-92	2.44E-6	9.64E-6	3.45E-5
Melanoma															
LOX IMVI	0.296	1.904	1.783	1.747	1.829	0.418	0.112	92	90	95	8	-62	3.28E-6	1.28E-5	6.69E-5
MALME-3M	0.685	1.415	1.389	1.379	1.255	0.680	0.202	96	95	78	-1	-71	2.27E-6	9.77E-6	5.07E-5
M14	0.301	1.083	1.056	1.045	0.857	0.464	0.062	97	95	71	21	-79	2.63E-6	1.61E-5	5.09E-5
MDA-MB-435	0.489	1.801	1.870	1.882	1.551	0.397	0.100	105	106	81	-19	-80	2.04E-6	6.47E-6	3.25E-5
SK-MEL-2	0.887	1.716	1.745	1.747	1.706	0.557	0.223	103	104	99	-37	-75	2.28E-6	5.32E-6	2.18E-5
SK-MEL-28	0.521	1.368	1.412	1.403	1.335	0.582	0.025	105	104	96	7	-95	3.30E-6	1.18E-5	3.61E-5
SK-MEL-5	0.607	1.726	1.720	1.675	1.531	0.070	0.008	100	95	83	-89	-99	1.55E-6	3.04E-6	5.95E-6
UACC-257	0.749	1.345	1.303	1.290	1.116	0.552	0.134	93	91	62	-26	-82	1.35E-6	5.01E-6	2.65E-5
UACC-62	0.799	2.207	2.192	2.252	2.121	0.671	0.144	99	103	94	-16	-82	2.51E-6	7.14E-6	3.27E-5
Ovarian Cancer															
IGROV1	0.580	1.751	1.854	1.953	1.743	0.775	0.237	109	117	99	17	-59	3.95E-6	1.66E-5	7.58E-5
OVCAR-3	0.518	1.585	1.618	1.657	1.423	0.349	0.030	103	107	85	-33	-94	1.98E-6	5.27E-6	1.91E-5
OVCAR-4	0.497	1.371	1.367	1.391	1.249	0.523	0.164	100	102	86	3	-67	2.72E-6	1.10E-5	5.70E-5
OVCAR-5	0.430	1.098	1.030	1.044	1.062	0.494	0.079	90	92	95	10	-82	3.34E-6	1.27E-5	4.50E-5
OVCAR-8	0.281	0.852	0.842	0.843	0.795	0.353	0.137	98	98	90	13	-51	3.28E-6	1.57E-5	9.56E-5
NCI/ADR-RES	0.417	1.470	1.517	1.415	1.411	1.442	1.242	104	95	94	97	78	> 1.00E-4	> 1.00E-4	> 1.00E-4
SK-OV-3	0.413	0.887	0.869	0.871	0.853	0.494	0.183	96	97	93	17	-56	3.67E-6	1.71E-5	8.32E-5
Renal Cancer															
786-0	0.450	1.570	1.534	1.522	1.472	1.267	0.113	97	96	91	73	-75	1.43E-5	3.11E-5	6.78E-5
A498	1.424	2.132	1.976	1.974	1.923	1.523	0.663	78	78	70	14	-53	2.30E-6	1.61E-5	8.89E-5
ACHN	0.300	1.235	1.152	1.164	1.240	1.158	0.452	91	92	101	92	16	3.57E-5	> 1.00E-4	> 1.00E-4
CAKI-1	0.910	2.174	2.231	2.228	2.251	2.552	2.263	105	104	106	130	107	> 1.00E-4	> 1.00E-4	> 1.00E-4
RXF 393	0.629	1.161	1.173	1.130	1.128	1.079	0.039	102	94	94	84	-94	1.56E-5	2.98E-5	5.67E-5
SN12C	0.919	2.529	2.536	2.525	2.383	1.136	0.289	100	100	91	13	-69	3.38E-6	1.46E-5	5.93E-5
TK-10	0.686	1.233	1.197	1.243	1.224	0.991	0.088	94	102	98	56	-87	1.10E-5	2.46E-5	5.50E-5
UO-31	0.536	1.737	1.658	1.632	1.662	1.773	1.265	93	91	94	103	61	> 1.00E-4	> 1.00E-4	> 1.00E-4
Prostate Cancer															
PC-3	0.559	1.700	1.687	1.610	1.510	0.659	0.197	99	92	83	9	-65	2.80E-6	1.31E-5	6.30E-5
DU-145	0.399	1.311	1.394	1.402	1.378	0.597	0.026	109	110	107	22	-93	4.67E-6	1.54E-5	4.19E-5
Breast Cancer															
MCF7	0.609	2.562	2.504	2.547	2.089	0.890	0.118	97	99	76	14	-81	2.63E-6	1.42E-5	4.76E-5
MDA-MB-231/ATCC	0.466	0.839	0.881	0.903	0.950	0.338	0.130	111	117	130	-27	-72	3.21E-6	6.69E-6	3.20E-5
HS 578T	0.904	1.376	1.302	1.296	1.233	0.700	0.586	84	83	70	-23	-35	1.63E-6	5.69E-6	> 1.00E-4
T-47D	0.615	1.295	1.242	1.229	1.091	0.566	0.075	92	90	70	-8	-88	1.81E-6	7.90E-6	3.36E-5
MDA-MB-468	0.470	1.007	0.978	0.951	0.632	0.412	0.056	95	90	30	-12	-88	4.64E-7	5.11E-6	3.14E-5

(B)

National Cancer Institute Developmental Therapeutics Program In-Vitro Testing Results

NSC : D - 755640 / 1	Experiment ID : 1102NS99	Test Type : 08	Units : Molar
Report Date : April 09, 2011	Test Date : February 14, 2011	QNS :	MC :
COMI : FY095 (102119)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0Y4T	

			Log10 Concentration												
	Time		Mean Optical Densities					Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.405	1.623	1.419	1.438	1.333	0.635	0.359	83	85	76	19	-11	2.86E-6	4.21E-5	> 1.00E-4
HL-60(TB)	0.773	1.619	1.610	1.552	1.560	0.450	0.354	99	92	93	-42	-54	2.08E-6	4.90E-6	4.59E-5
K-562	0.272	1.348	1.253	1.279	0.959	0.336	0.227	91	94	64	6	-17	1.73E-6	1.83E-5	> 1.00E-4
MOLT-4	0.584	1.315	1.327	1.353	1.382	0.972	0.404	102	105	109	53	-31	1.09E-5	4.29E-5	> 1.00E-4
RPMI-8226	0.845	2.160	2.206	2.029	1.722	0.758	0.606	103	90	67	-10	-28	1.65E-6	7.35E-6	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.331	1.363	1.444	1.419	1.412	1.185	0.282	108	105	105	83	-15	2.16E-5	7.03E-5	> 1.00E-4
EKVX	0.583	1.522	1.526	1.521	1.594	1.124	0.629	100	100	108	58	5	1.39E-5	> 1.00E-4	> 1.00E-4
HOP-62	0.420	1.269	1.302	1.319	1.236	0.710	0.409	104	106	96	34	-3	5.54E-6	8.43E-5	> 1.00E-4
HOP-92	1.156	1.616	1.568	1.577	1.596	1.297	0.580	90	91	96	31	-50	5.03E-6	2.40E-5	> 1.00E-4
NCI-H226	0.749	1.590	1.574	1.534	1.559	1.285	0.705	98	93	96	64	-6	1.57E-5	8.22E-5	> 1.00E-4
NCI-H23	0.479	1.428	1.373	1.324	1.344	0.987	0.466	94	89	91	54	-3	1.15E-5	8.91E-5	> 1.00E-4
NCI-H322M	0.824	1.768	1.624	1.611	1.714	1.514	0.698	85	83	94	73	-15	1.82E-5	6.71E-5	> 1.00E-4
NCI-H460	0.265	2.028	2.158	2.080	2.031	0.997	0.130	107	103	100	42	-51	7.17E-6	2.81E-5	9.72E-5
NCI-H522	0.865	2.249	2.137	2.118	2.188	1.314	0.304	92	91	96	32	-65	5.27E-6	2.15E-5	7.03E-5
Colon Cancer															
COLO 205	0.271	1.306	1.338	1.304	1.281	0.066	0.050	103	100	98	-76	-82	1.88E-6	3.65E-6	7.10E-6
HCC-2998	0.632	2.112	2.157	2.065	1.991	1.156	0.386	103	97	92	35	-39	5.50E-6	2.99E-5	> 1.00E-4
HCT-116	0.227	1.584	1.583	1.505	1.611	0.474	0.064	100	94	102	18	-72	4.18E-6	1.59E-5	5.72E-5
HCT-15	0.244	1.603	1.577	1.511	1.589	1.363	1.093	98	93	99	82	62	> 1.00E-4	> 1.00E-4	> 1.00E-4
HT29	0.335	1.734	1.792	1.740	1.821	1.057	0.161	104	100	106	52	-52	1.04E-5	3.15E-5	9.58E-5
KM12	0.468	2.216	2.258	2.298	2.187	0.801	0.041	102	105	98	19	-91	4.07E-6	1.49E-5	4.22E-5
SW-620	0.282	1.737	1.752	1.680	1.649	0.590	0.065	101	96	94	21	-77	4.01E-6	1.64E-5	5.30E-5
CNS Cancer															
SF-268	0.474	1.402	1.342	1.337	1.365	0.675	0.027	93	93	96	22	-94	4.15E-6	1.54E-5	4.15E-5
SF-295	0.718	2.417	2.243	2.172	2.302	2.077	0.614	90	86	93	80	-14	2.08E-5	7.03E-5	> 1.00E-4
SF-539	0.634	2.120	2.016	2.117	2.114	1.151	0.553	93	100	100	35	-13	5.82E-6	5.37E-5	> 1.00E-4
SNB-19	0.463	1.496	1.479	1.398	1.456	0.834	0.299	98	91	96	36	-36	5.83E-6	3.18E-5	> 1.00E-4
SNB-75	0.753	1.299	1.222	1.205	1.243	0.999	0.493	86	83	90	45	-35	7.77E-6	3.68E-5	> 1.00E-4
U251	0.412	1.380	1.397	1.450	1.396	0.582	0.031	102	107	102	18	-92	4.11E-6	1.44E-5	4.11E-5
Melanoma															
LOX IMVI	0.296	1.944	1.866	1.883	1.870	1.337	0.309	95	96	95	63	1	1.63E-5	> 1.00E-4	> 1.00E-4
MALME-3M	0.685	1.494	1.352	1.402	1.291	0.651	0.175	82	89	75	-5	-74	2.05E-6	8.65E-6	4.44E-5
M14	0.301	1.206	1.154	1.159	1.154	0.596	0.209	94	95	94	33	-31	5.22E-6	3.27E-5	> 1.00E-4
MDA-MB-435	0.489	2.030	1.964	1.947	1.948	0.820	0.123	96	95	95	21	-75	4.08E-6	1.67E-5	5.52E-5
SK-MEL-2	0.887	2.026	1.988	1.985	2.059	1.740	0.340	97	96	103	75	-62	1.52E-5	3.53E-5	8.21E-5
SK-MEL-28	0.521	1.433	1.441	1.444	1.424	0.730	0.039	101	101	99	23	-93	4.40E-6	1.58E-5	4.28E-5
SK-MEL-5	0.607	1.840	1.705	1.810	1.724	0.176	-0.002	89	98	91	-71	-100	1.78E-6	3.63E-6	7.41E-6
UACC-257	0.749	1.410	1.394	1.441	1.406	0.788	0.146	98	105	99	6	-81	3.38E-6	1.17E-5	4.44E-5
UACC-62	0.799	2.292	2.244	2.174	2.265	1.341	0.219	97	92	98	36	-73	6.01E-6	2.15E-5	6.20E-5
Ovarian Cancer															
IGROV1	0.580	1.788	1.747	1.789	1.884	1.160	0.510	97	100	108	48	-12	9.25E-6	6.28E-5	> 1.00E-4
OVCAR-3	0.518	1.602	1.589	1.561	1.505	0.580	0.034	99	96	91	6	-94	3.02E-6	1.14E-5	3.64E-5
OVCAR-4	0.497	1.440	1.395	1.385	1.371	0.839	0.483	95	94	93	36	-3	5.71E-6	8.47E-5	> 1.00E-4
OVCAR-5	0.430	1.173	1.179	1.156	1.210	0.865	0.372	101	98	105	58	-13	1.31E-5	6.49E-5	> 1.00E-4
OVCAR-8	0.281	0.881	0.874	0.906	0.865	0.379	0.230	99	104	97	16	-18	3.83E-6	2.97E-5	> 1.00E-4
NCI/ADR-RES	0.417	1.489	1.495	1.459	1.477	1.423	1.291	100	97	99	94	81	> 1.00E-4	> 1.00E-4	> 1.00E-4
SK-OV-3	0.413	0.995	0.980	0.961	0.961	0.879	0.272	98	94	94	80	-34	1.84E-5	5.03E-5	> 1.00E-4
Renal Cancer															
786-0	0.450	1.676	1.396	1.645	1.747	1.318	0.702	77	97	106	71	21	2.59E-5	> 1.00E-4	> 1.00E-4
A498	1.424	2.276	2.121	2.114	2.142	1.897	1.028	82	81	84	56	-28	1.16E-5	4.63E-5	> 1.00E-4
ACHN	0.300	1.343	1.386	1.322	1.354	1.203	0.724	104	98	101	87	41	6.26E-5	> 1.00E-4	> 1.00E-4
CAKI-1	0.910	2.252	2.252	2.265	2.439	2.484	2.152	100	101	114	117	92	> 1.00E-4	> 1.00E-4	> 1.00E-4
RXF 393	0.629	1.183	1.174	1.147	1.178	1.057	0.666	98	94	99	77	7	2.43E-5	> 1.00E-4	> 1.00E-4
SN12C	0.919	2.650	2.558	2.501	2.606	1.689	0.772	95	91	97	44	-16	7.87E-6	5.44E-5	> 1.00E-4
TK-10	0.686	1.401	1.353	1.388	1.423	1.208	0.839	93	98	103	73	21	2.79E-5	> 1.00E-4	> 1.00E-4
UO-31	0.536	1.788	1.657	1.638	1.720	1.612	1.203	90	88	95	86	53	> 1.00E-4	> 1.00E-4	> 1.00E-4
Prostate Cancer															
PC-3	0.559	1.812	1.833	1.823	1.704	1.190	0.626	102	101	91	50	5	1.02E-5	> 1.00E-4	> 1.00E-4
DU-145	0.399	1.456	1.446	1.462	1.427	0.871	0.222	99	100	97	45	-44	7.89E-6	3.17E-5	> 1.00E-4
Breast Cancer															
MCF7	0.609	2.611	2.442	2.392	2.599	1.727	0.452	92	89	99	56	-26	1.18E-5	4.82E-5	> 1.00E-4
MDA-MB-231/ATCC	0.466	0.862	0.895	0.882	0.931	0.848	0.219	108	105	118	97	-53	2.05E-5	4.42E-5	9.53E-5
HS 578T	0.904	1.501	1.448	1.420	1.464	1.008	0.644	91	86	94	17	-29	3.74E-6	2.38E-5	> 1.00E-4
T-47D	0.615	1.418	1.380	1.409	1.364	0.761	0.420	95	99	93	18	-32	3.77E-6	2.31E-5	> 1.00E-4
MDA-MB-468	0.470	1.034	1.036	0.999	0.872	0.489	0.100	100	94	71	3	-79	2.06E-6	1.10E-5	4.46E-5

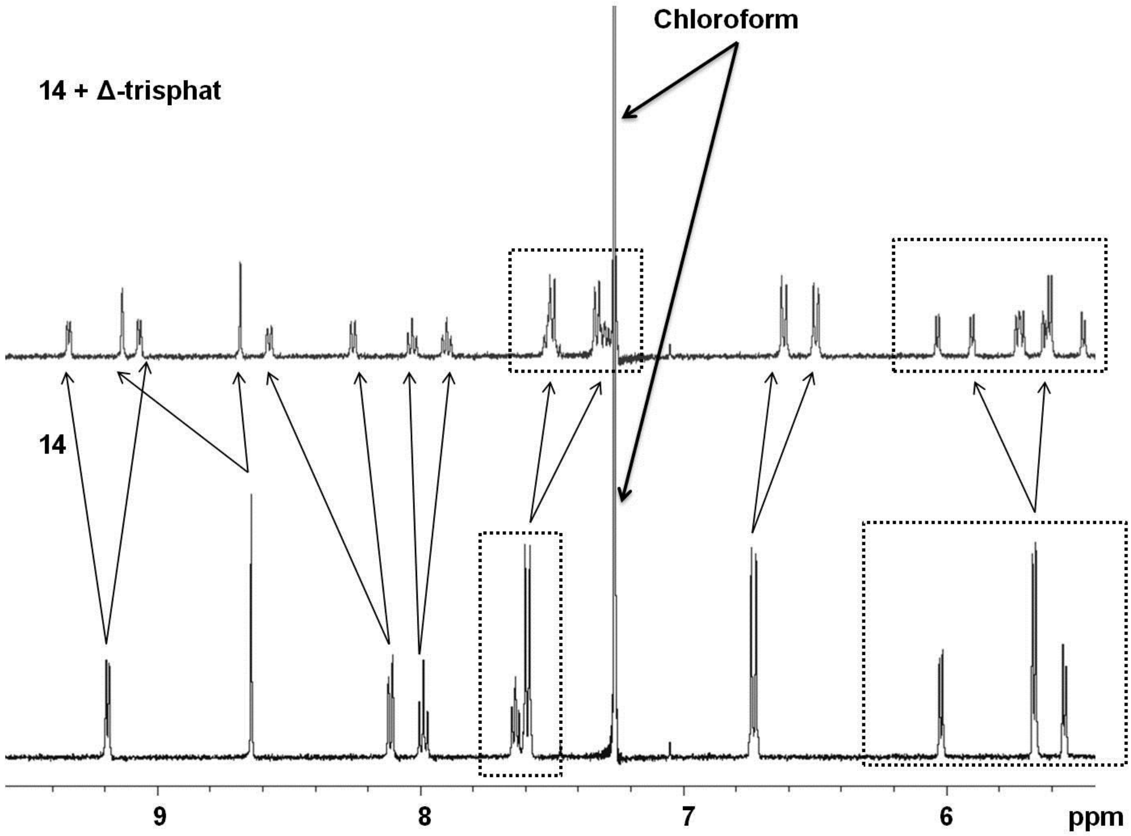
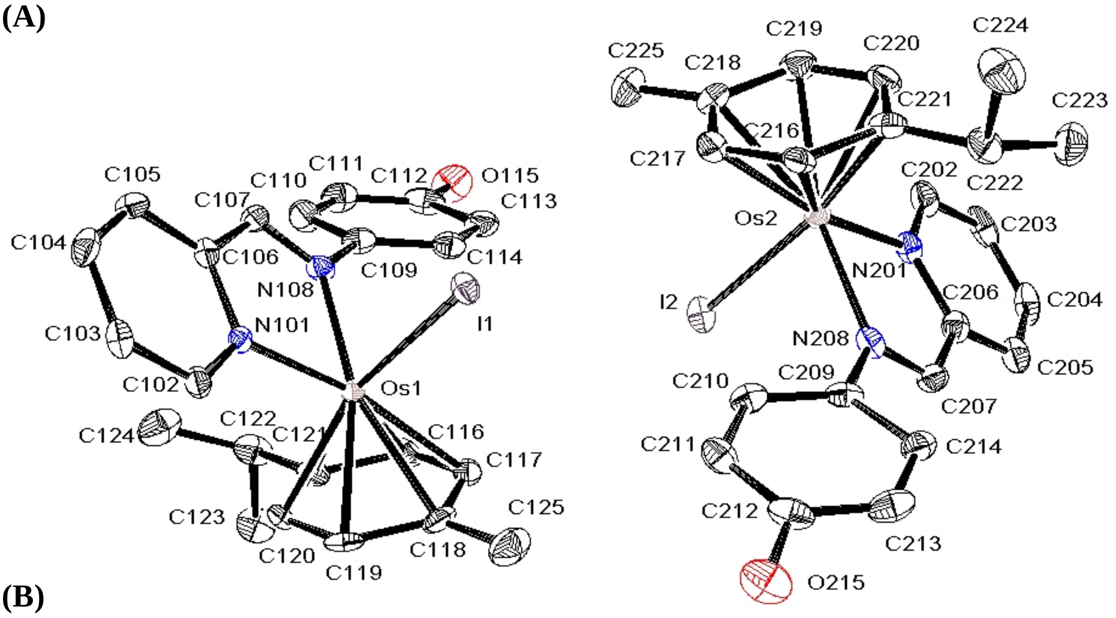


Figure S1. [1]H NMR spectrum of complex **14** before and after adding 2 mol equivalents of Δ-trisphat in $CDCl_3$, showing the presence of two enantiomers.

(A)



(B)

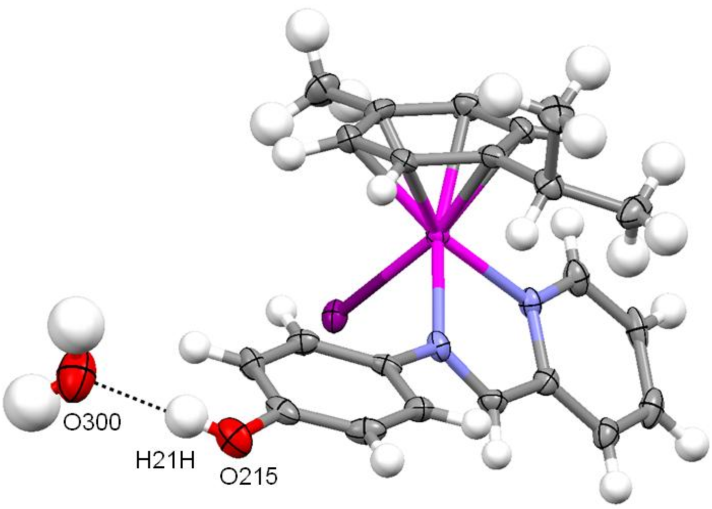


Figure S2. (A) Solid state structure of the two crystallographically-independent cations found in the asymmetric unit of complex **4**·0.5CH_2Cl_2·H_2O consisting of enantiomers (S)-[Os(η^6-*p*-cym)(Impy-OH)I]PF_6 (left) and (R)-[Os(η^6-*p*-cym)(Impy-OH)I]PF_6 (right), showing the atomic numbering scheme. Thermal ellipsoids are drawn at the 50% probability level. Lattice CH_2Cl_2 and H_2O molecules are not shown. Hydrogen atoms and PF_6^- counterions are omitted for clarity. **(B)** Hydrogen bond interaction between the phenol group of the chelating iminopyridine ligand in the enantiomer (R)-[Os(η^6-*p*-cym)(Impy-OH)I]PF_6 and a water molecule. The (R)- and (S)- configurations at the osmium metal centre were assigned according to Cahn–Ingold–Prelog priority rules (CIP system**)** for defining the priority sequence of ligands attached to osmium: I > η^6-C_6H_6 > N (imine) > N (pyridine).

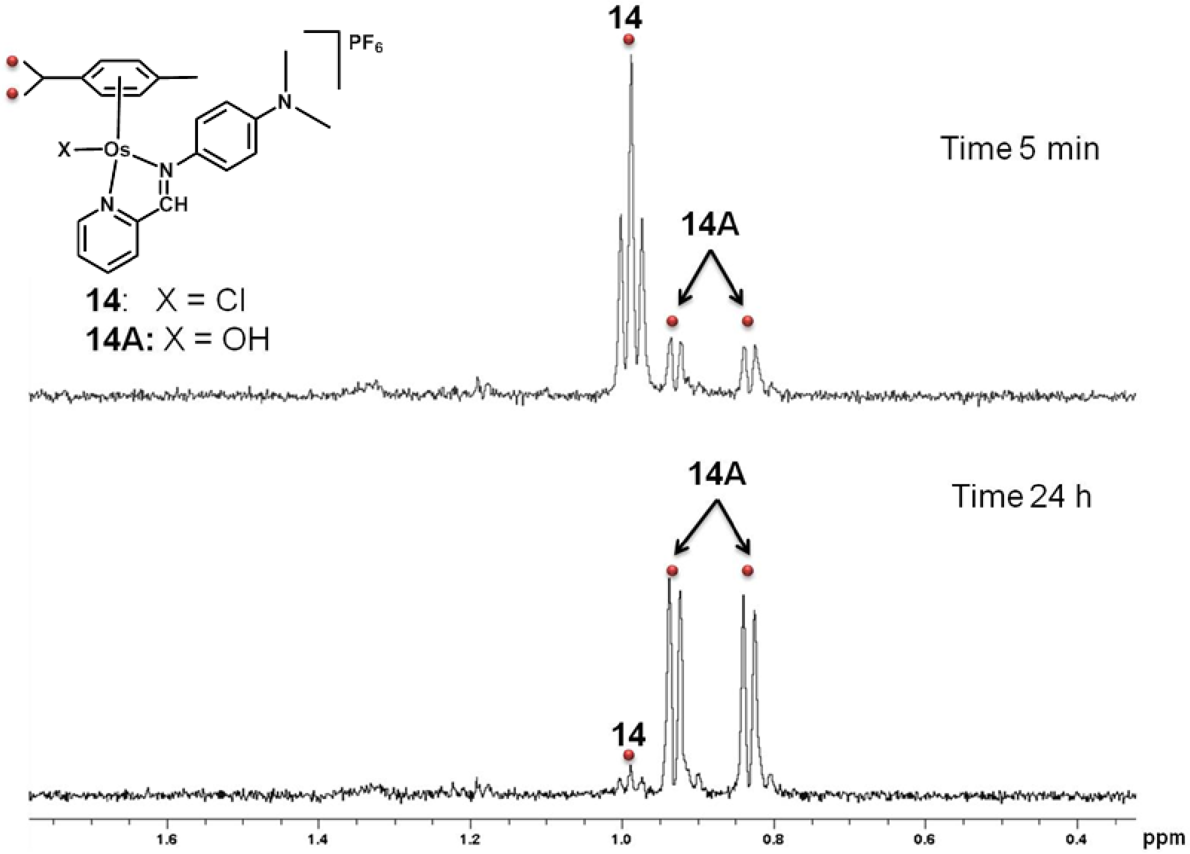


Figure S3. ^{1}H NMR spectra of complex **14** (0.1 mM) in MeOD/D_2O (10%/90%) recorded soon after preparing the sample (top spectrum) and after 24 h incubation at 310 K (bottom spectrum), showing the increase in intensity of peaks for the aqua adduct **14A**.

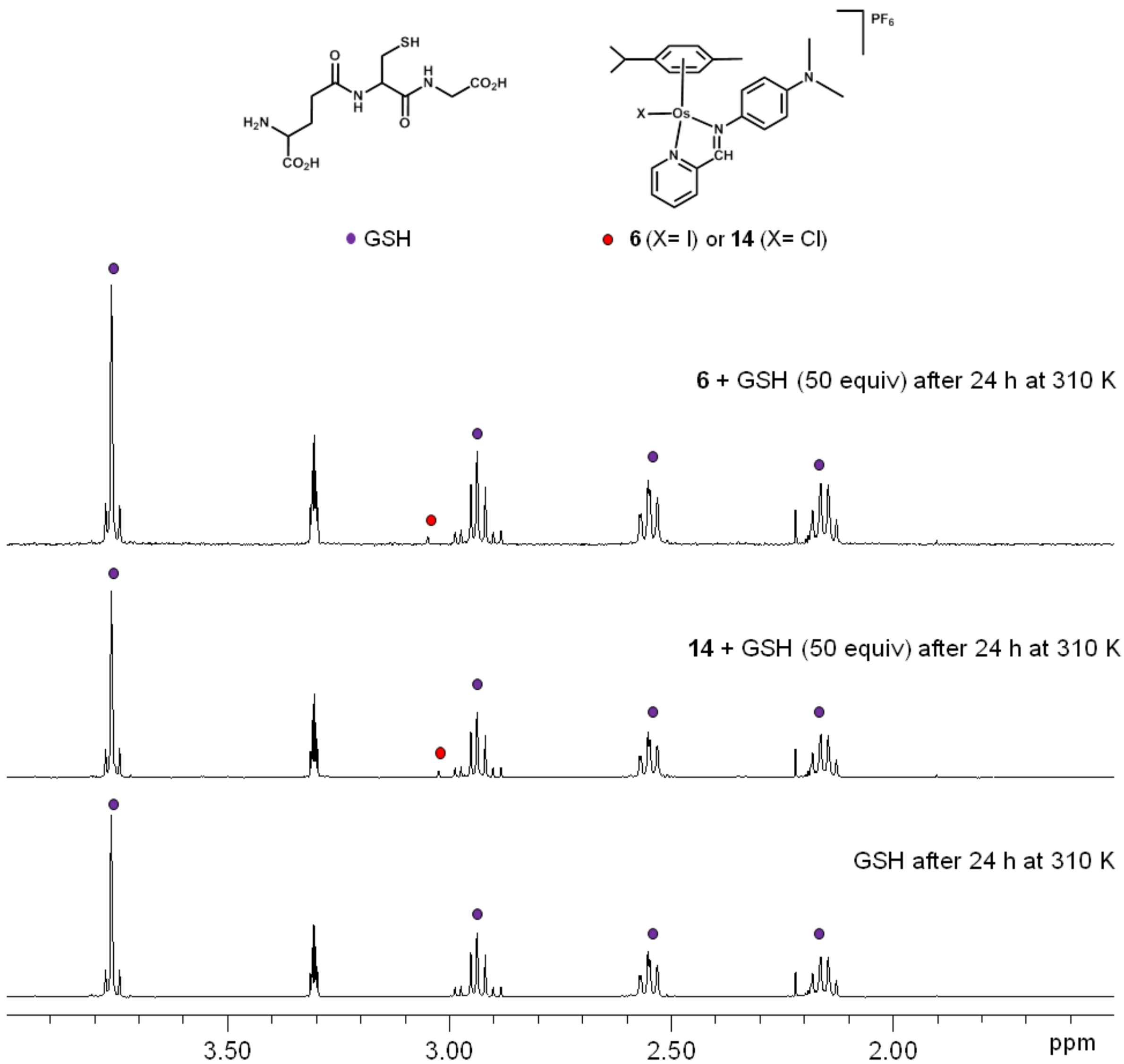
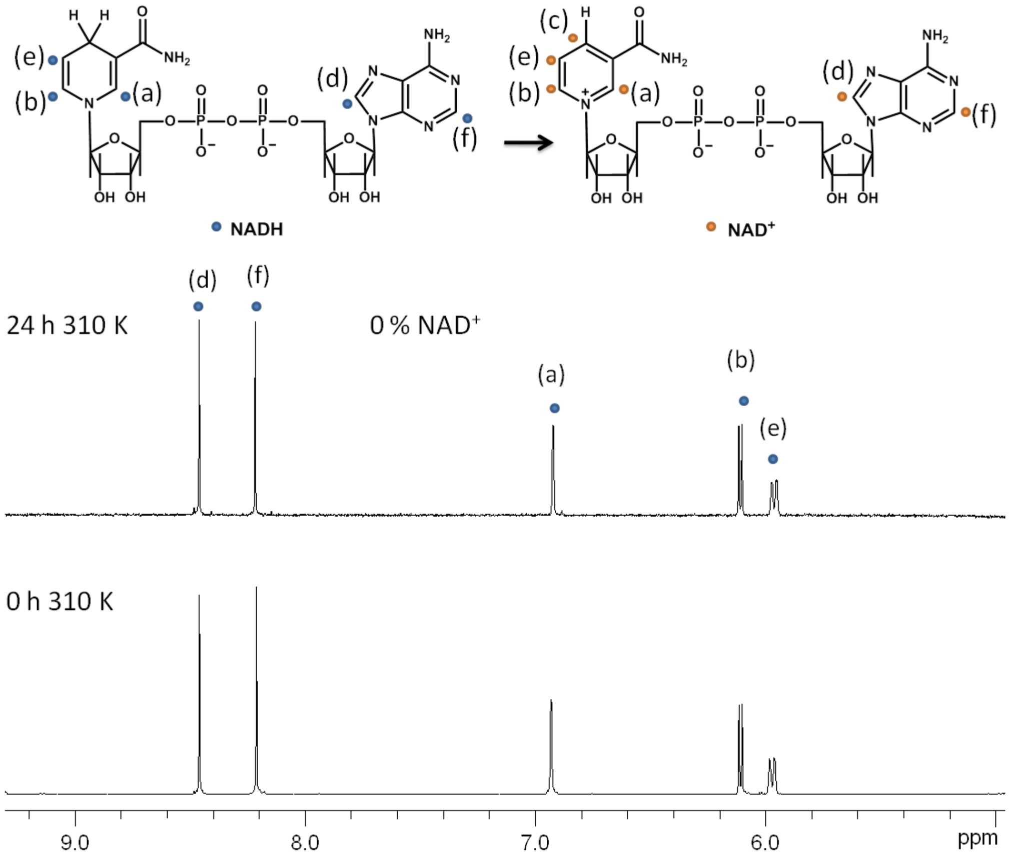


Figure S4. ^{1}H NMR spectra of solutions containing osmium complex **6** or **14** (0.1 mM) and GSH (5 mM). Samples were prepared in a 10%MeOD/90%D_2O phosphate buffer solution (pH* = 7.4) and spectra recorded after 24 h of incubation of the sample at 310 K. Bottom spectrum: GSH after incubation at 310 K for 24 h; middle spectrum: (**14**) [Os(η^6-*p*-cym)(Impy-NMe$_2$)Cl]PF$_6$ with GSH; top spectrum: (**6**) [Os(η^6-*p*-cym)(Impy-NMe$_2$)I]PF$_6$ with GSH, 1 µL of acetone/sample was added as the reference of chemical shifts.

(A)


(e)
(b)
(a)
(d)
(f)
NADH
(c)
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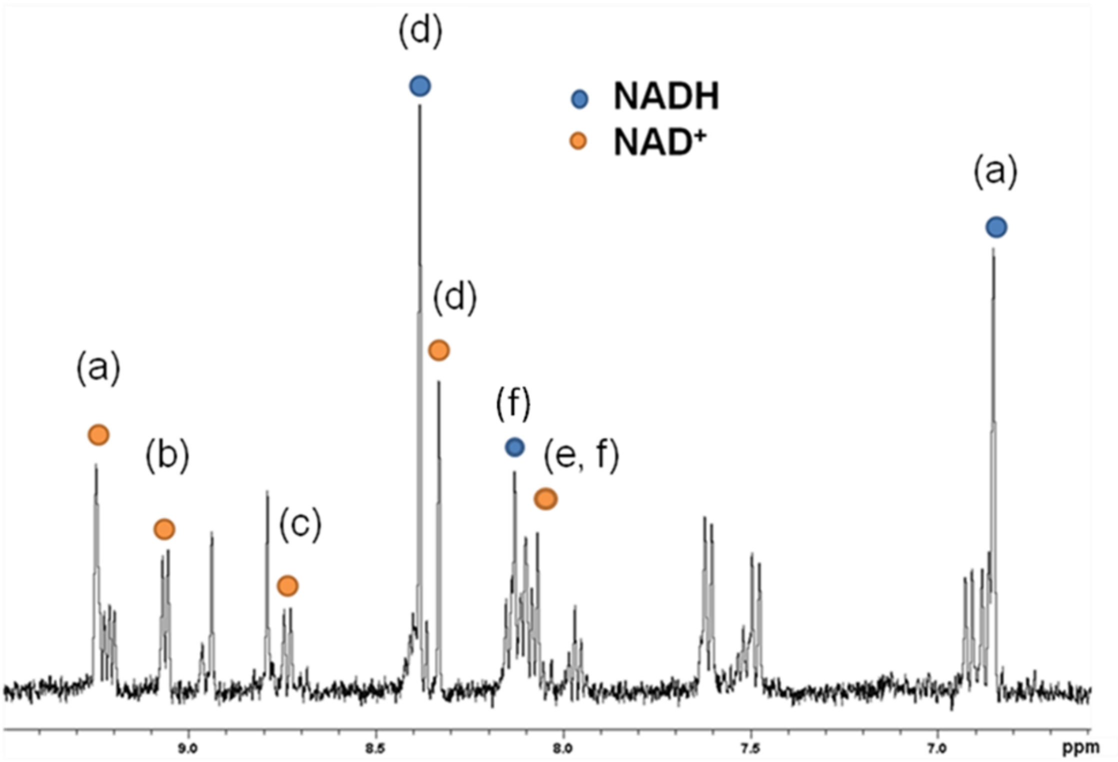
0 % NAD⁺
0 h 310 K
9.0
8.0
7.0
6.0
ppm

(B)


NADH
NAD⁺
(a)
(b)
(c)
(d)
(f)
(e, f)
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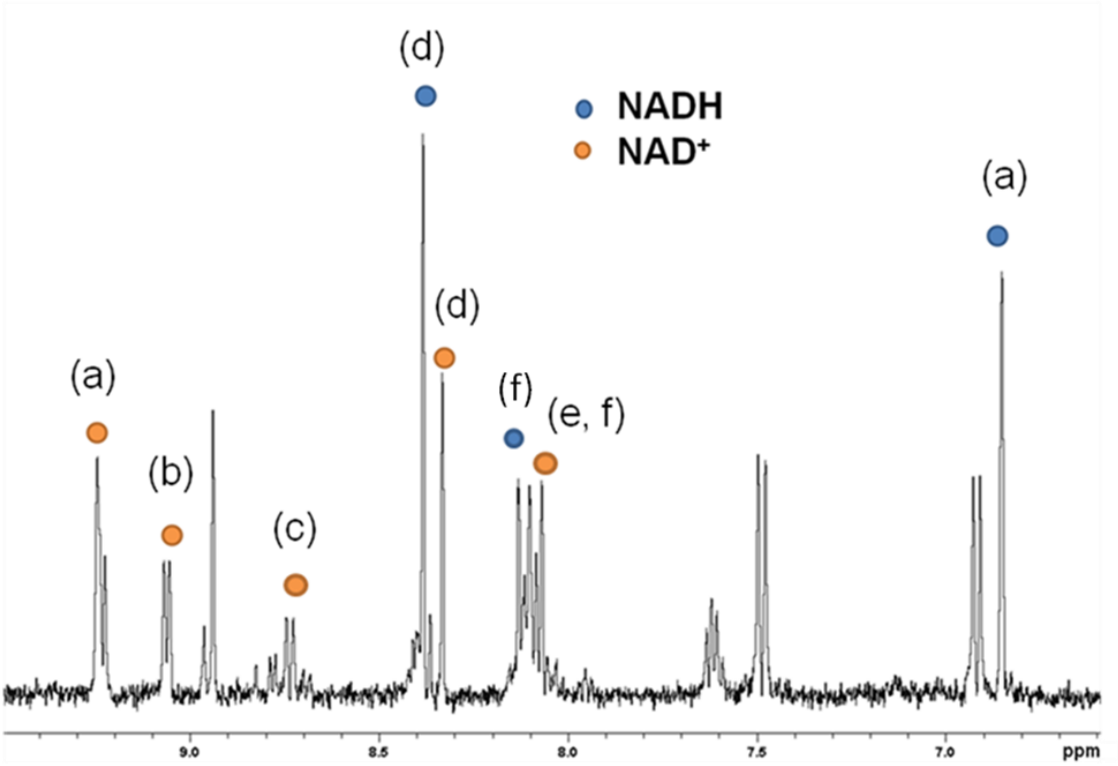
8.5
8.0
7.5
7.0
ppm

(C)


(d)
NADH
NAD+
(a)
(d)
(a)
(f)
(e, f)
(b)
(c)
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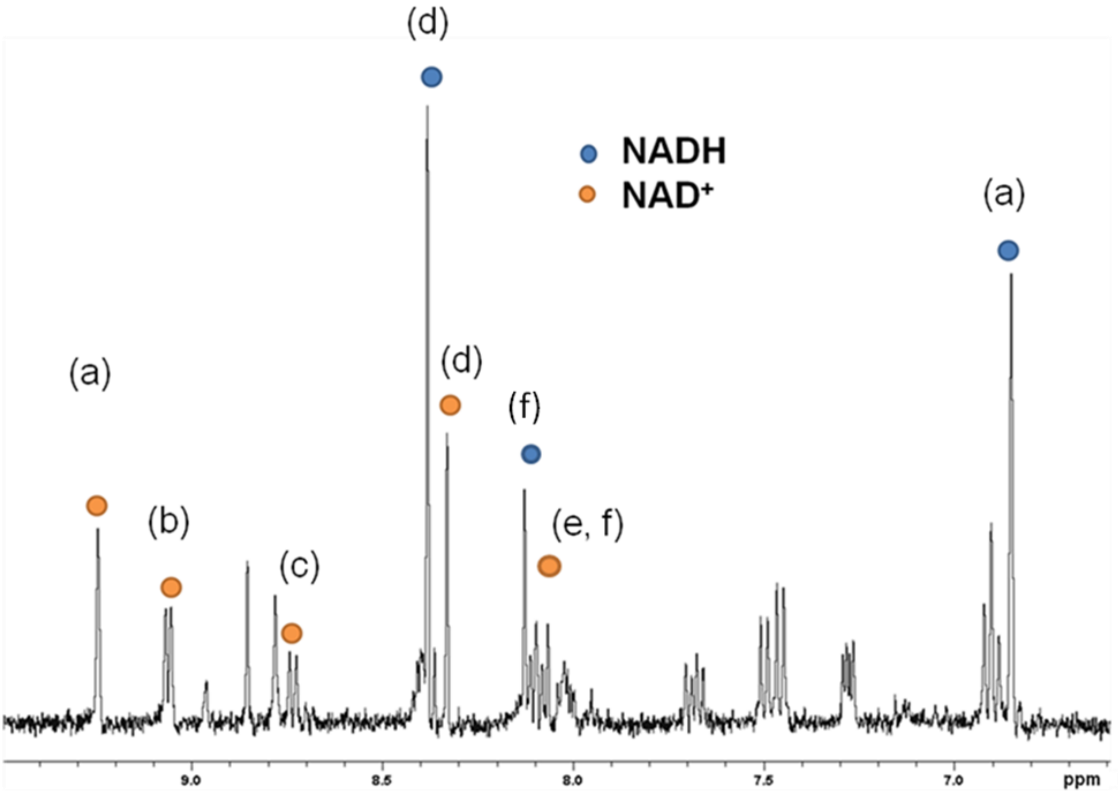
8.5
8.0
7.5
7.0
ppm

(D)


(d)
NADH
NAD+
(a)
(a)
(d)
(f)
(b)
(e, f)
(c)
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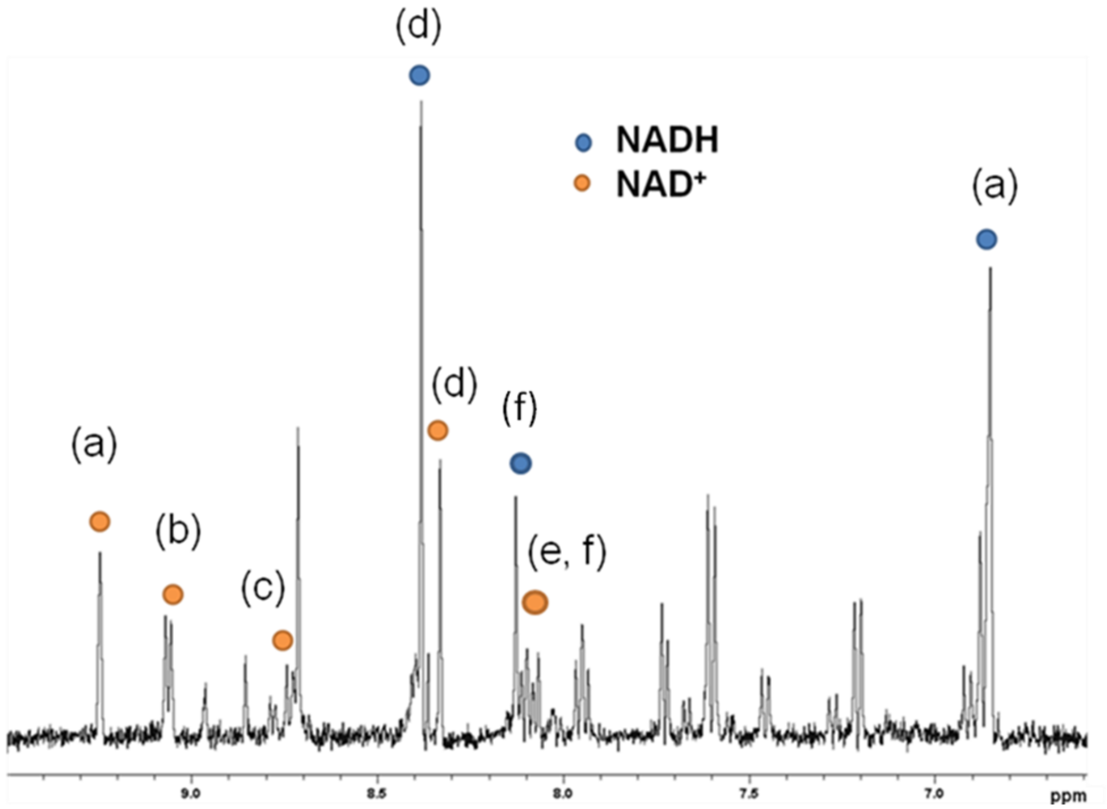
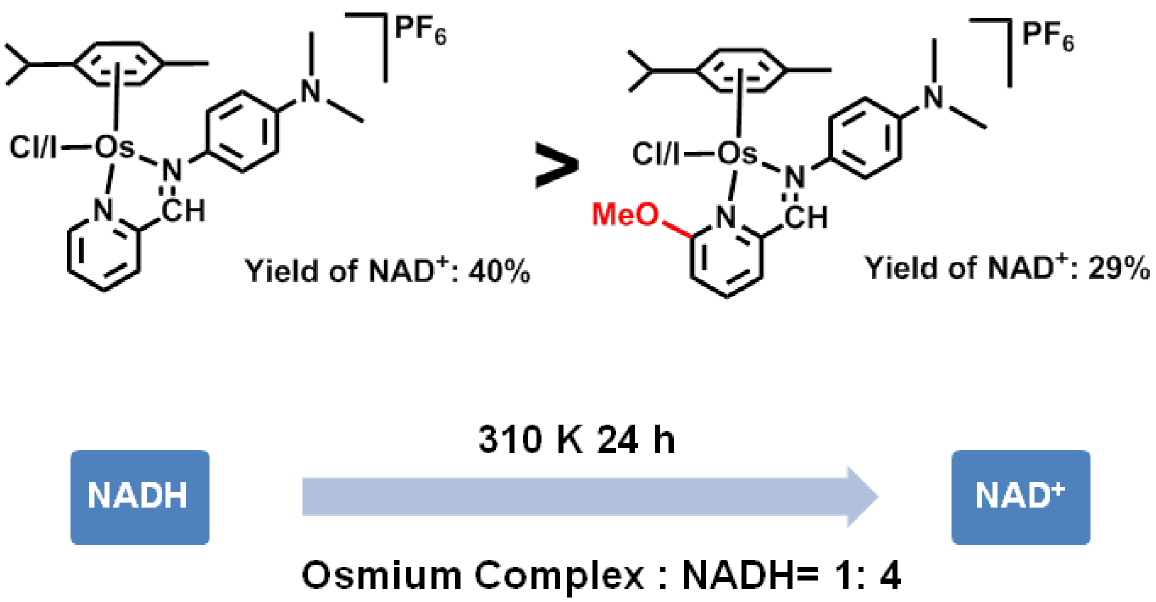
8.5
8.0
7.5
7.0
ppm

(E)


(d)
NADH
NAD+
(a)
(d)
(f)
(a)
(b)
(e, f)
(c)
9.0
8.5
8.0
7.5
7.0
ppm

(F)


PF6
Cl/I—Os
N
N
CH
Yield of NAD+: 40%
>
PF6
Cl/I—Os
MeO
N
N
CH
Yield of NAD+: 29%
310 K 24 h
NADH
NAD+
Osmium Complex : NADH= 1: 4

(G)

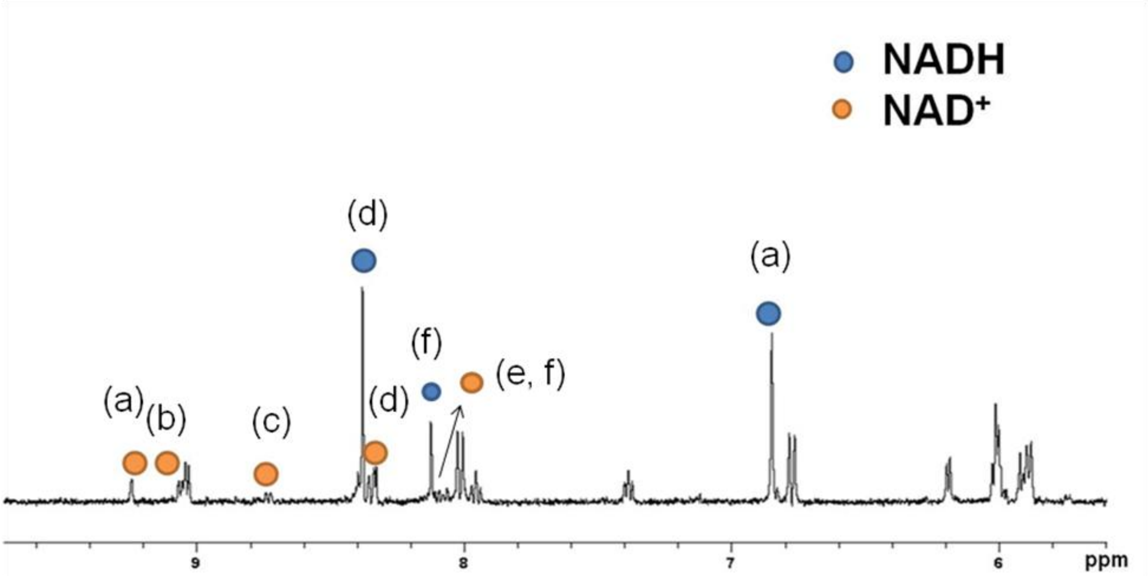


Figure S5. ^{1}H NMR spectra for the reaction between the osmium complex (0.1 mM) and NADH (0.4 mM, 4 mol equivalents). The spectra were recorded in a 10%MeOD/90%D_2O phosphate buffer solution (pH* = 7.4) after 24 h of incubation of the sample at 310 K. (A) Control: NADH at time 0 and time 24 h (310 K oven). (B) (**6**) [Os(η^6-*p*-cym)(Impy-NMe$_2$)I]PF$_6$. (C) (**14**) [Os(η^6-*p*-cym)(Impy-NMe$_2$)Cl]PF$_6$. (D) (**8**) [Os(η^6-*p*-cym)(Ome-Impy-NMe$_2$)I]PF$_6$. (E) (**16**) [Os(η^6-*p*-cym)(OMe-Impy-NMe$_2$)Cl]PF$_6$. (F) NADH Extent of oxidation by osmium iminopyridine complexes: **6**, **8**, **14**, and **16**. (G) [Os(η^6-*p*-cym)(Azpy-NMe$_2$)I]PF$_6$ (**FY026**). The control (NADH) was stable towards the NAD$^+$ formation under the same conditions at millimolar concentrations.

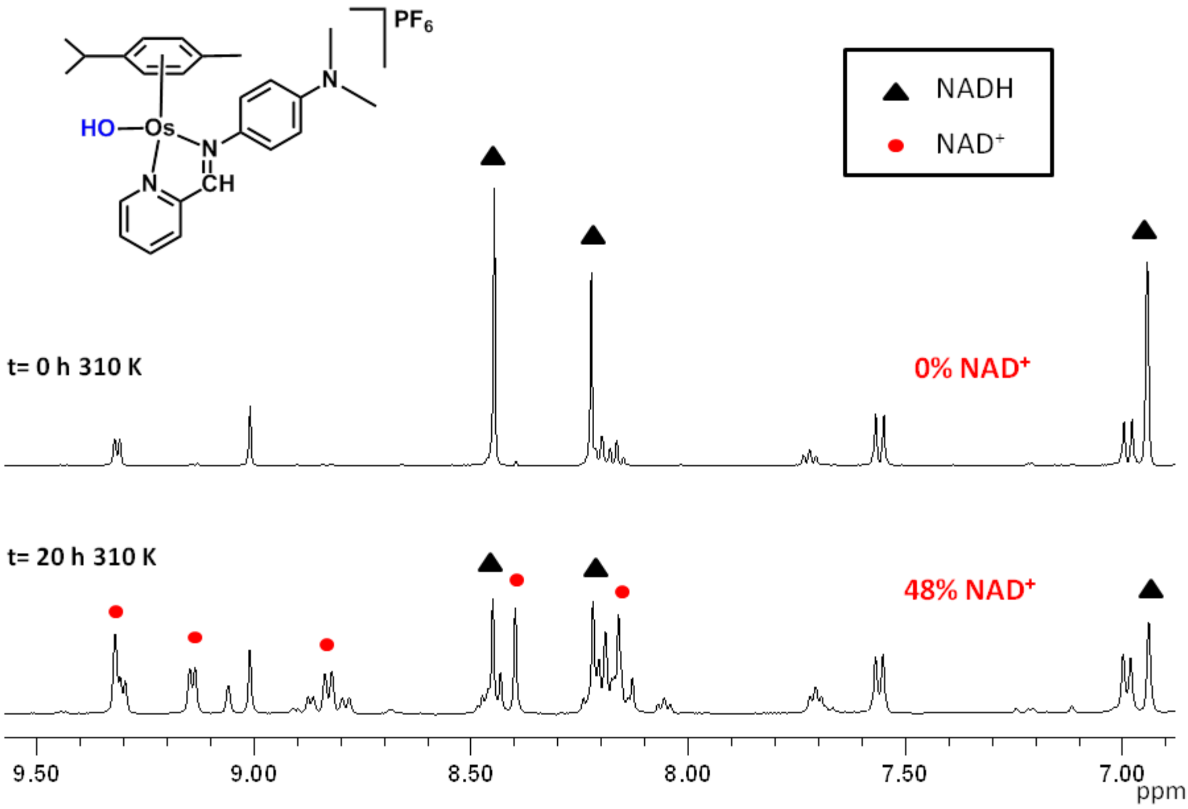
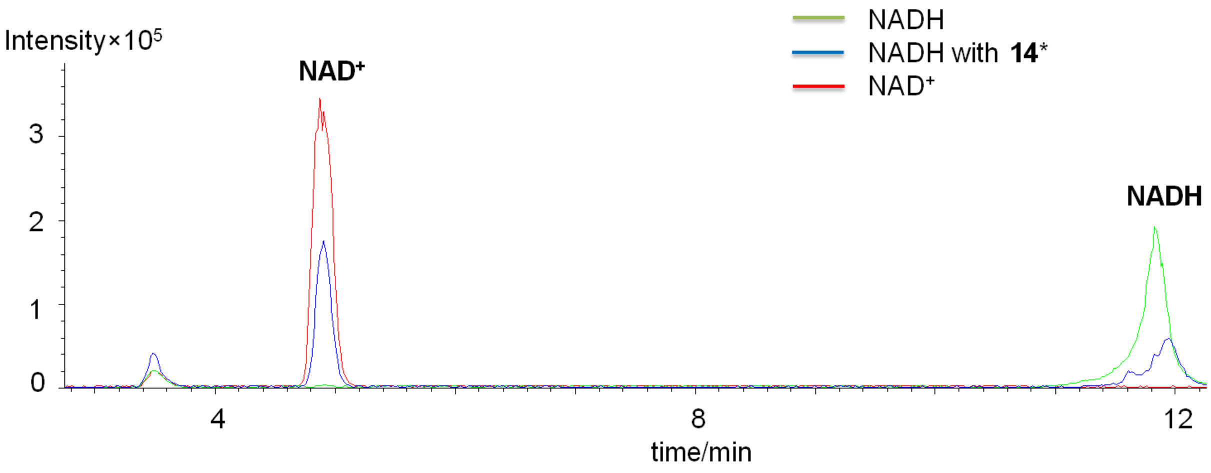
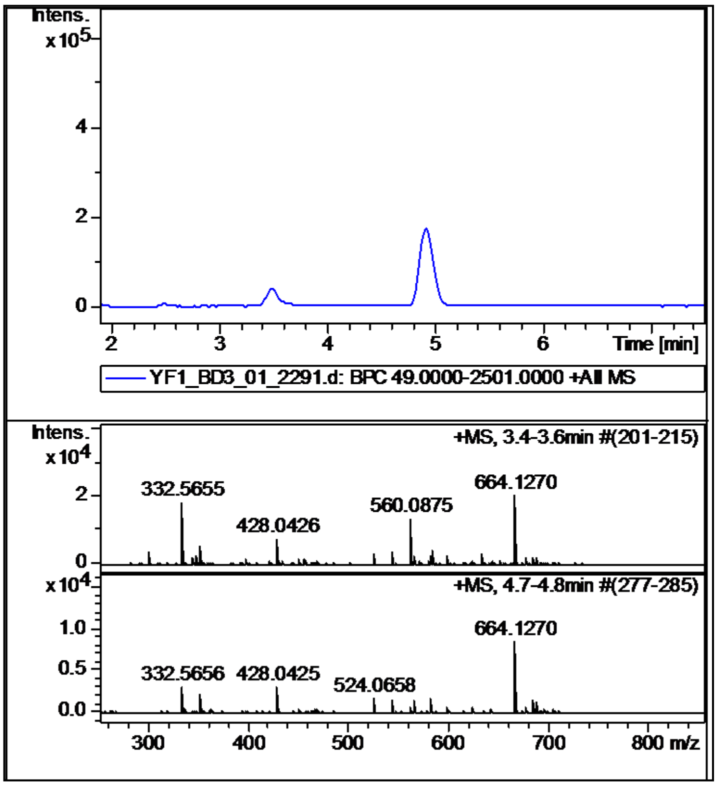


Figure S6. [1]H NMR spectra for the reaction between the hydroxido complex **14A** (2 mM) and NADH (8 mM, 4 mol equivalents). The samples were prepared in a 10%D_2O/90%H_2O phosphate buffer solution (pH^* = 7.4) and spectra recorded at t= 0 h and 20 h after incubation of the sample at 310 K.

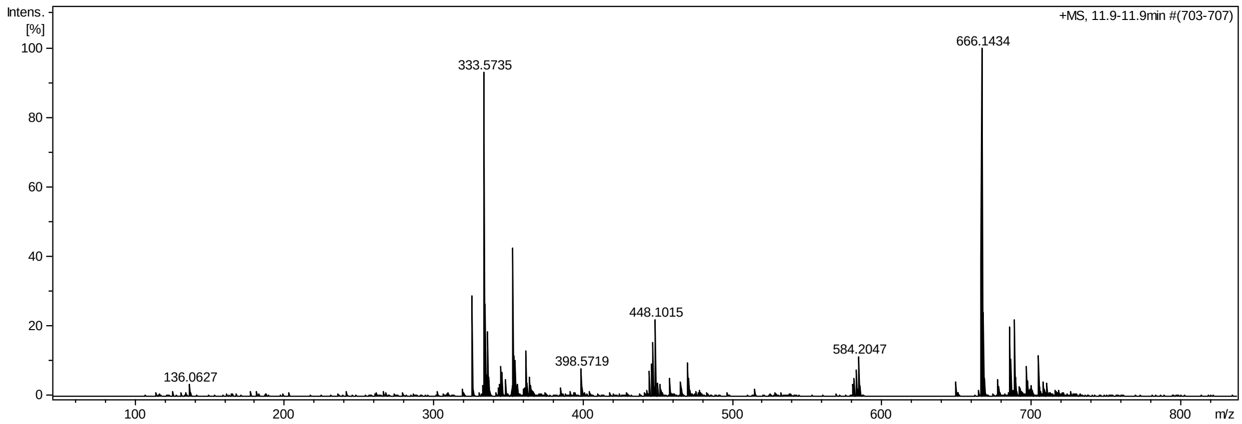
(A)


NADH
NADH with **14***
NAD+
Intensity×10^5
NAD+
NADH
3
2
1
0
4
8
12
time/min

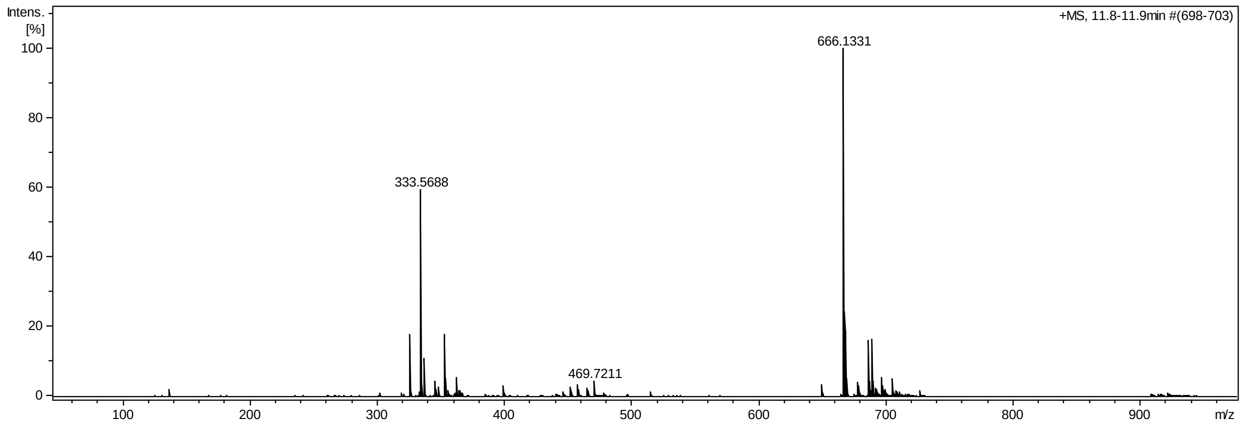
(B)


Intens.
x10^5
4
2
0
2
3
4
5
6
Time [min]
YF1_BD3_01_2291.d: BPC 49.0000-2501.0000 +All MS
Intens.
x10^4
2
0
+MS, 3.4-3.6min #(201-215)
332.5655
428.0426
560.0875
664.1270
x10^4
1.0
0.5
0.0
+MS, 4.7-4.8min #(277-285)
332.5656
428.0425
524.0658
664.1270
300
400
500
600
700
800 m/z

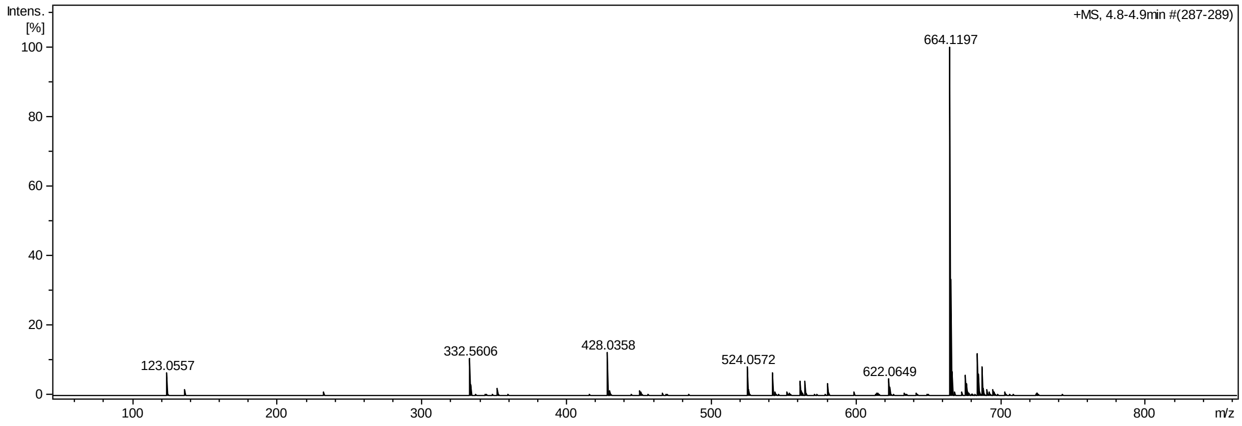
(C)


Intens.
[%]
+MS, 11.9-11.9min #(703-707)
666.1434
333.5735
448.1015
584.2047
398.5719
136.0627
m/z

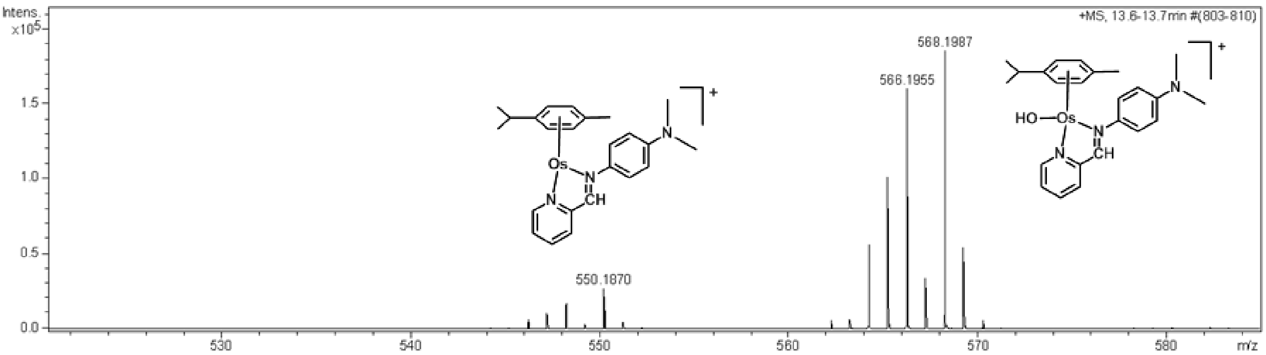
(D)


Intens.
[%]
+MS, 11.8-11.9min #(698-703)
666.1331
333.5688
469.7211
m/z

(E)


Intens.
[%]
+MS, 4.8-4.9min #(287-289)
664.1197
428.0358
332.5606
524.0572
123.0557
622.0649
m/z

(F)



(G)

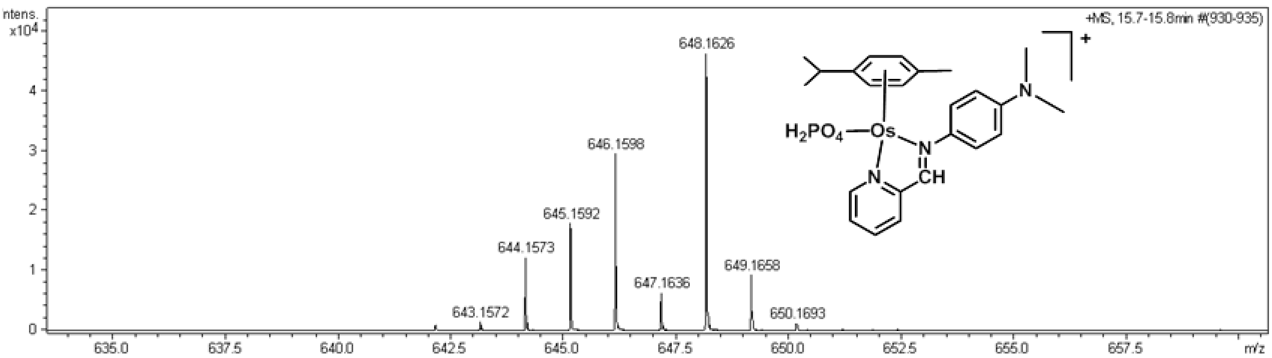


Figure S7. NADH (0.5 mM) with or without complex **14A** (0.5 mM) was incubated at 310 K for 24 h; NADH and NAD^+ were incubated under the same conditions and LC-MS was employed to analyze the 3 samples. (A) HPLC separation of NADH (0.5 mM, green line), NADH with complex **14A** (blue line) and NAD^+ (0.5 mM, red line). (B) MS of first two appearing peaks from HPLC of NADH with complex **14A** (blue line). (C) MS of second peak appearing from HPLC (green line). (D) MS of third peak appearing from HPLC of NADH with complex **14A** (blue line), (E) MS of NAD^+, (F) MS of **14A**, (G) MS of phosphate adduct of **14A**.

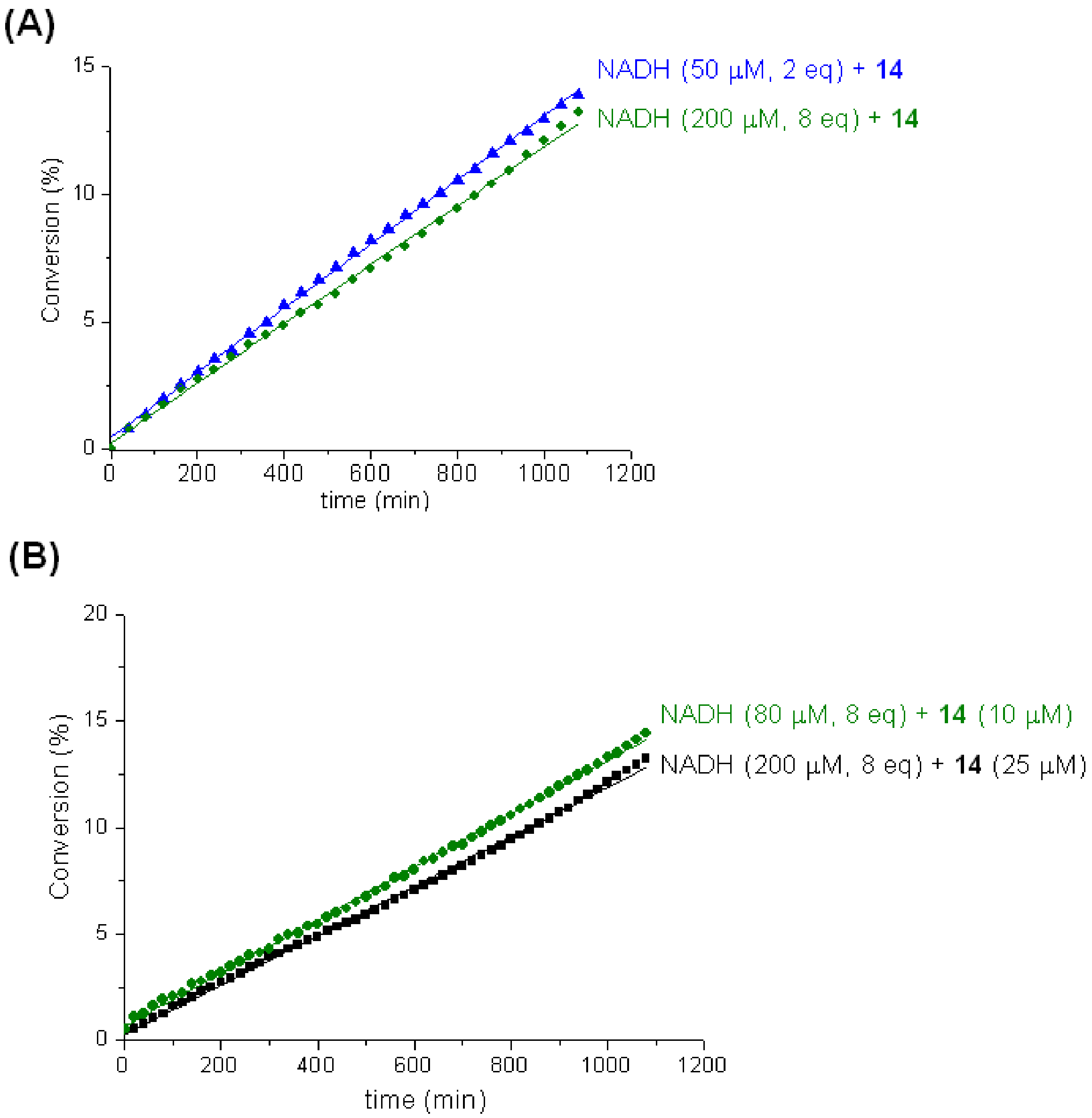
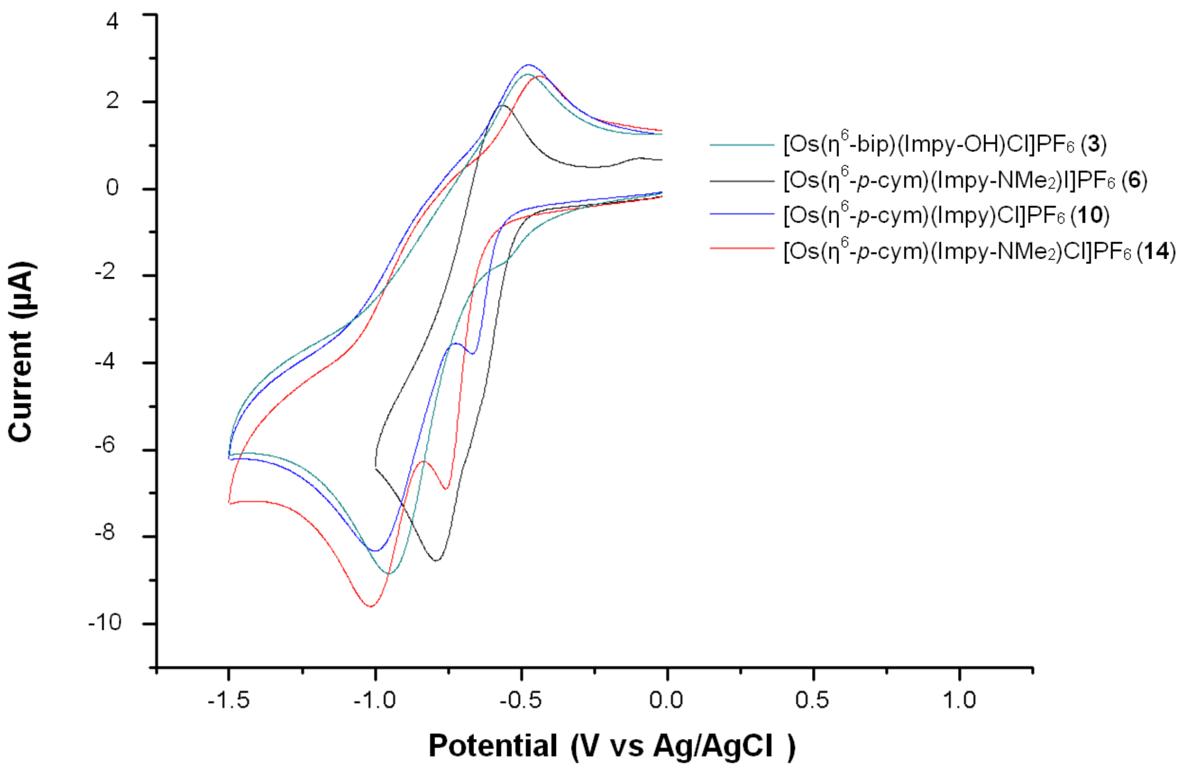


Figure S8. Kinetic experiments monitored by UV-Vis spectroscopy for samples in a 1 mM phosphate buffer solution (H_2O, pH 7.4). All the data were obtained monitoring the NADH absorption band at 338 nm and recording the spectra at intervals of 20 min during 18 h at 310 K. **(A)** Percentage of conversion of 2 and 8 mol equiv of NADH to NAD^+ in the presence of complex **14** (0.025 mM) plotted against time. **(B)** Percentage of conversion of 8 mol equiv of NADH to NAD+ plotted against time. The experiments were carried out using different concentrations of complex **14**, 0.01 mM (green line, y = 0.67379+ 0.01245x, R^2= 0.99885) and 0.025 mM (black line, y = 0.28163+ 0.01159x, R^2= 0.99787) respectively.



Complex	Reduction Peak /V
(**3**) $[Os(\eta^6$-bip)(Impy-OH)I]PF_6	-0.58, -0.95
(**6**) $[Os(\eta^6$-*p*-cym)(Impy-NMe_2)I]PF_6	-0.65, -0.82
(**10**) $[Os(\eta^6$-*p*-cym)(Impy)Cl]PF_6	-0.67, -1.0
(**14**) $[Os(\eta^6$-*p*-cym)(Impy-NMe_2)Cl]PF_6	-0.76, -1.0

Figure S9. Cyclic voltammograms for **3**, **6**, **10** and **14** (in 0.1 M tetrabutylammonium BF_4, sweep width from 0 to -1.5 to 0 V or 0 to -1.0 to 0 V at scan rate 0.1 V/s). Reduction peaks for **3**, **6**, **10** and **14** are listed.

Notes and references

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