Electronic Supplementary Material (ESI) for Chemical Science.

SUPPLEMENTARY INFORMATION

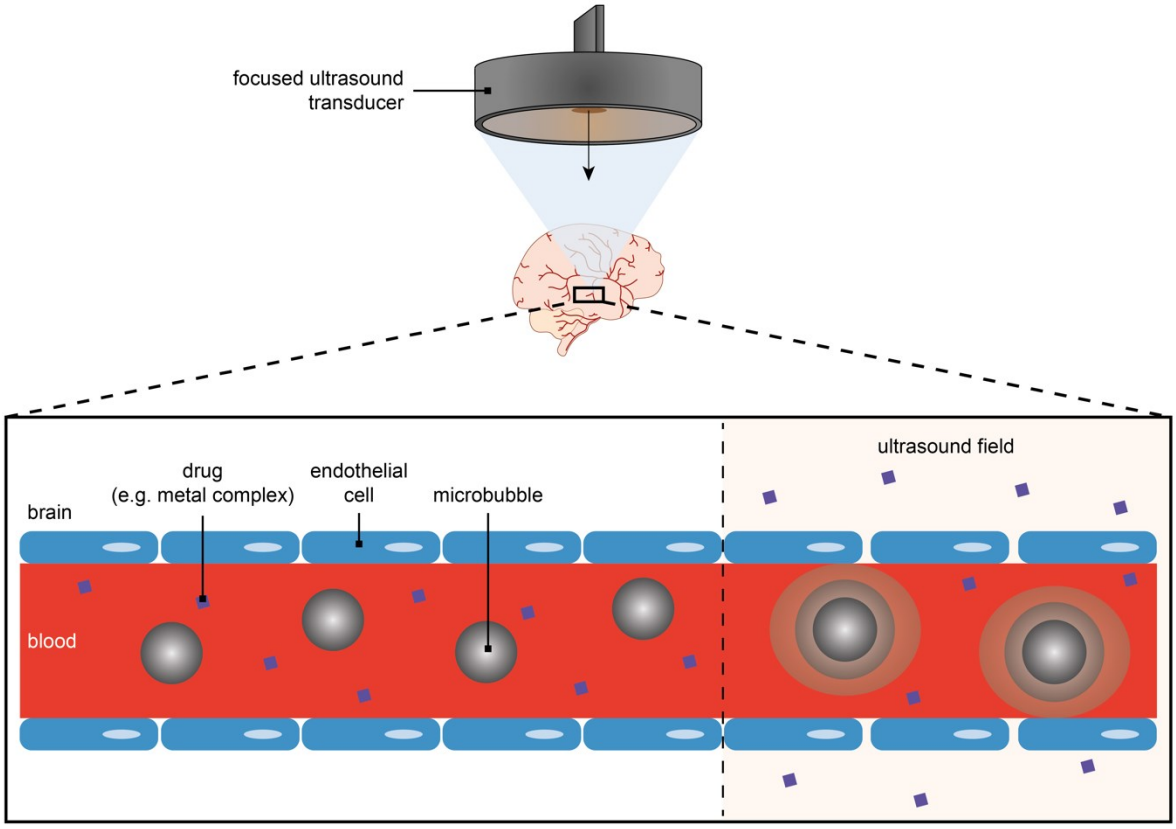


Figure S1. Schematic representation of focused ultrasound-mediated blood-brain barrier opening. Microbubbles and the compound of choice are injected intravenously, and the target region of the brain is then exposed to ultrasound. In an ultrasound field, microbubbles radially oscillate, exerting mechanical stress to their surroundings and resulting in delivery of the compound to the brain.

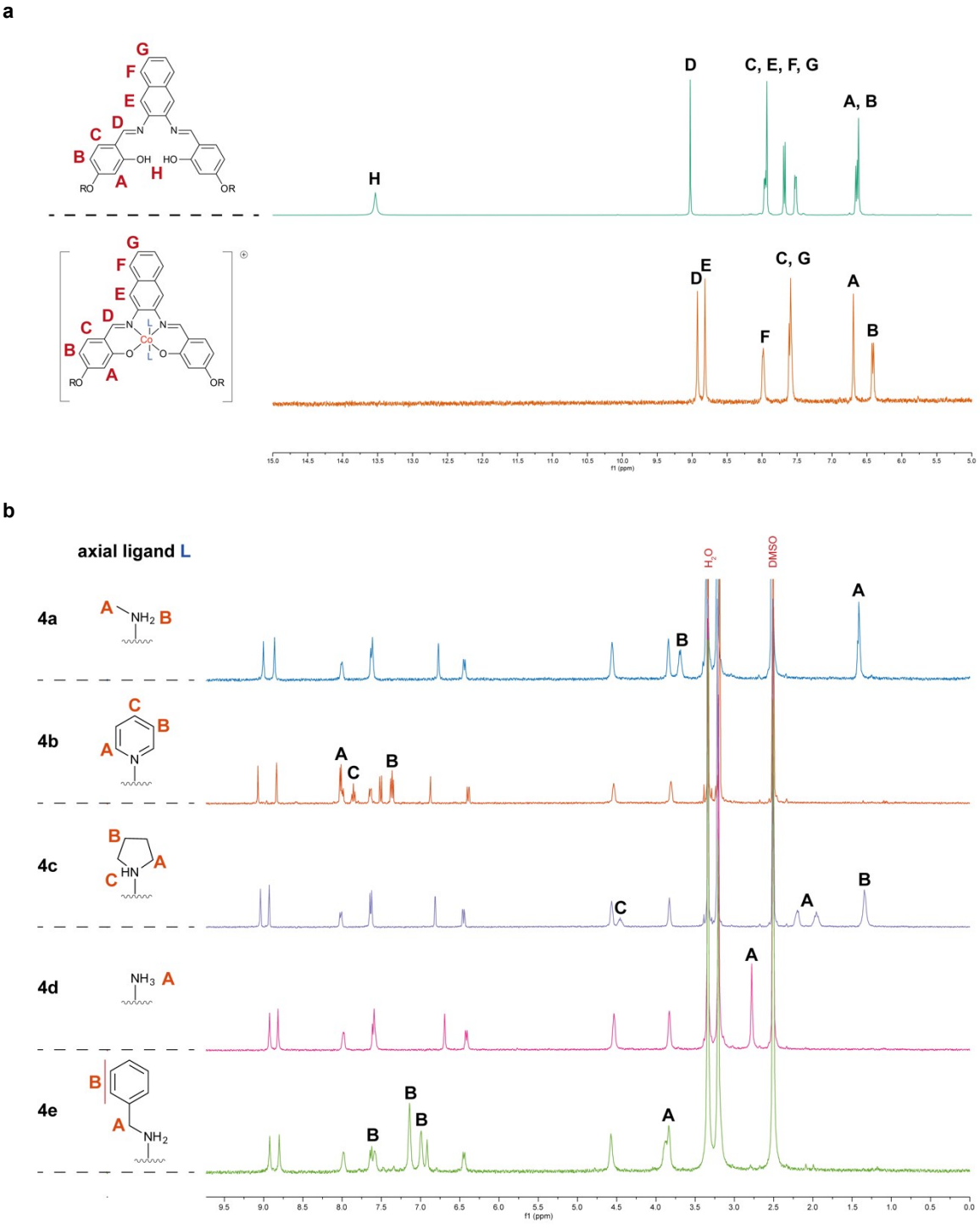


Figure S2. [a] Aromatic region of the ^{1}H NMR spectrum of the salnaph ligand recorded before and after cobalt complexation (L = NH_3). Disappearance of the -O<u>H</u> (H_H) signal is clearly observed, as well as shifts in the aromatic protons. [b] ^{1}H NMR spectra of cobalt salnaphs **4a-4e**. Peaks labelled are those that correspond to the attached axial ligands.

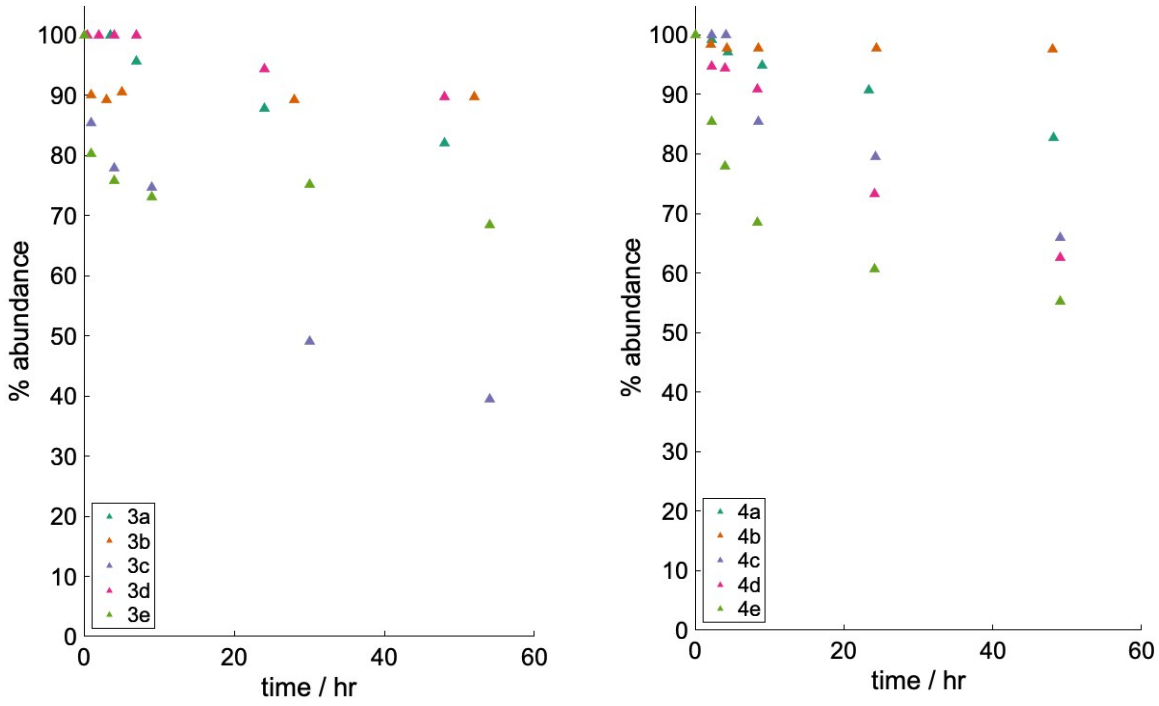


Figure S3. Stability of complexes **3a-4e** in aqueous solution. The % abundance over time was calculated from ^{1}H NMR spectra of the complexes recorded at various time-points. All spectra were recorded in D_2O:aqueous buffer (1:9, pH 7.2-7.4) using standard water suppression techniques. For complexes **3a-3e**, spectra were recorded in 10 mM to 1 M Tris-100 mM KCl. For complexes **4a-4e**, spectra were recorded in phosphate buffered saline. For complex **3d**, DMSO (1:1) was added to aid solubility.

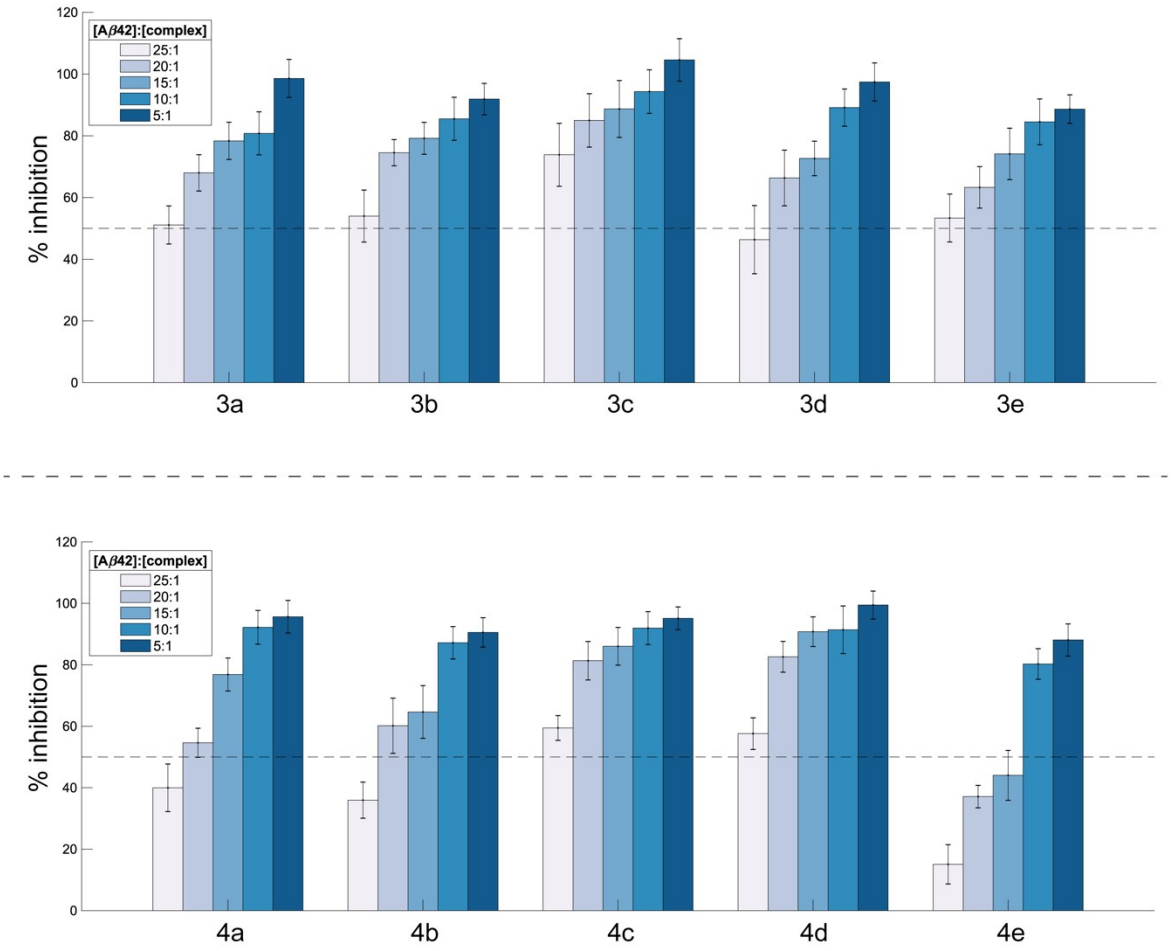


Figure S4. Inhibition of Aβ1-42 aggregation (%) induced by cobalt salphens **3a-3e** (top) and cobalt salnaphs **4a-4e** (bottom) determined using the Thioflavin-T assay. Complexes were tested at [Aβ42]:[complex] = 25:1, 20:1, 15:1, 10:1 and 5:1, and all samples were incubated at 37 °C with shaking. The dotted line represents the half-inhibition point and all data is reported as the mean ± standard deviation of three independent experiments.

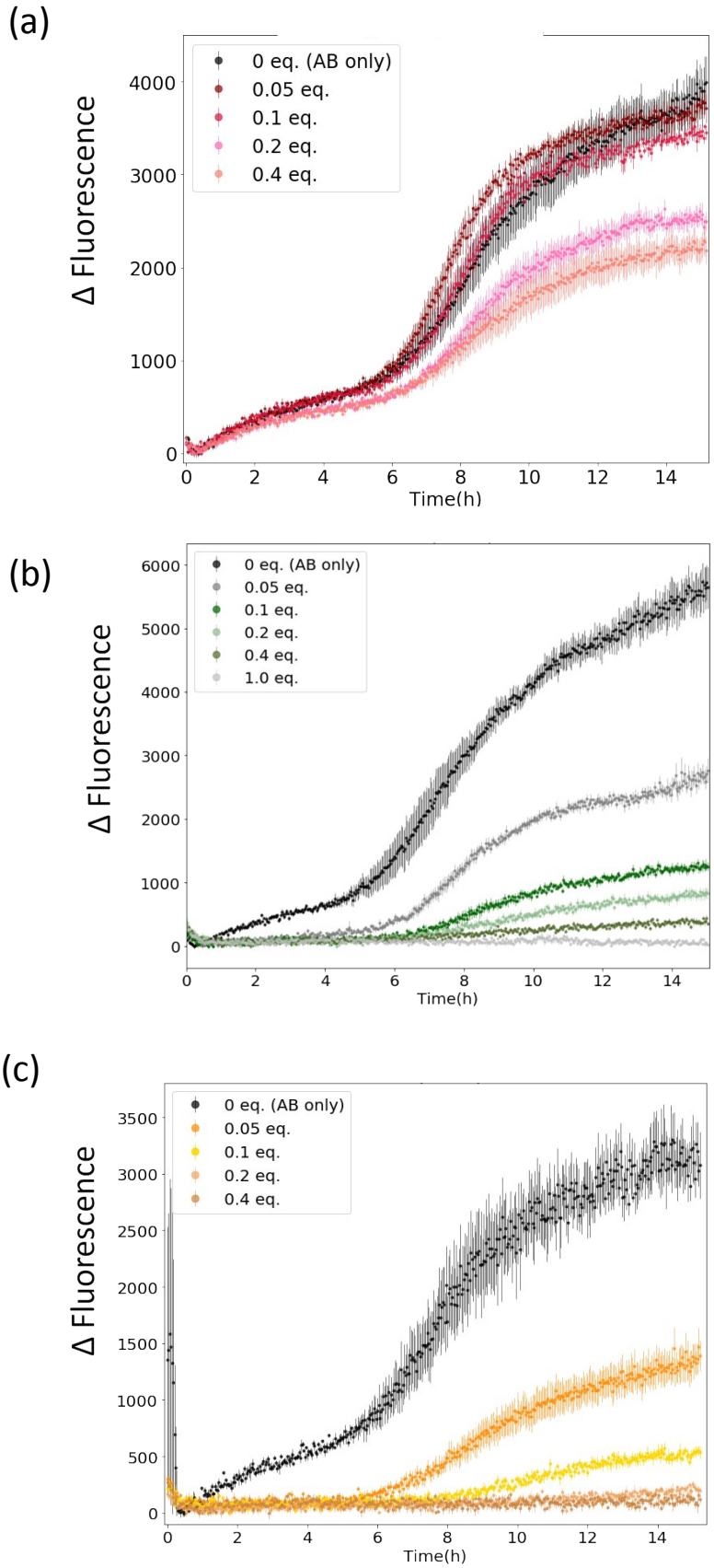


Figure S5. Plots showing the ThT ΔFluorescence over time of 5 μM Aβ1-42 at increasing concentrations of (a) compound **1**; (b) compound **3c**; (c) compound **4c**. Those curves with a sigmoidal profile are also shown as normalized kinetics in Figure 3.

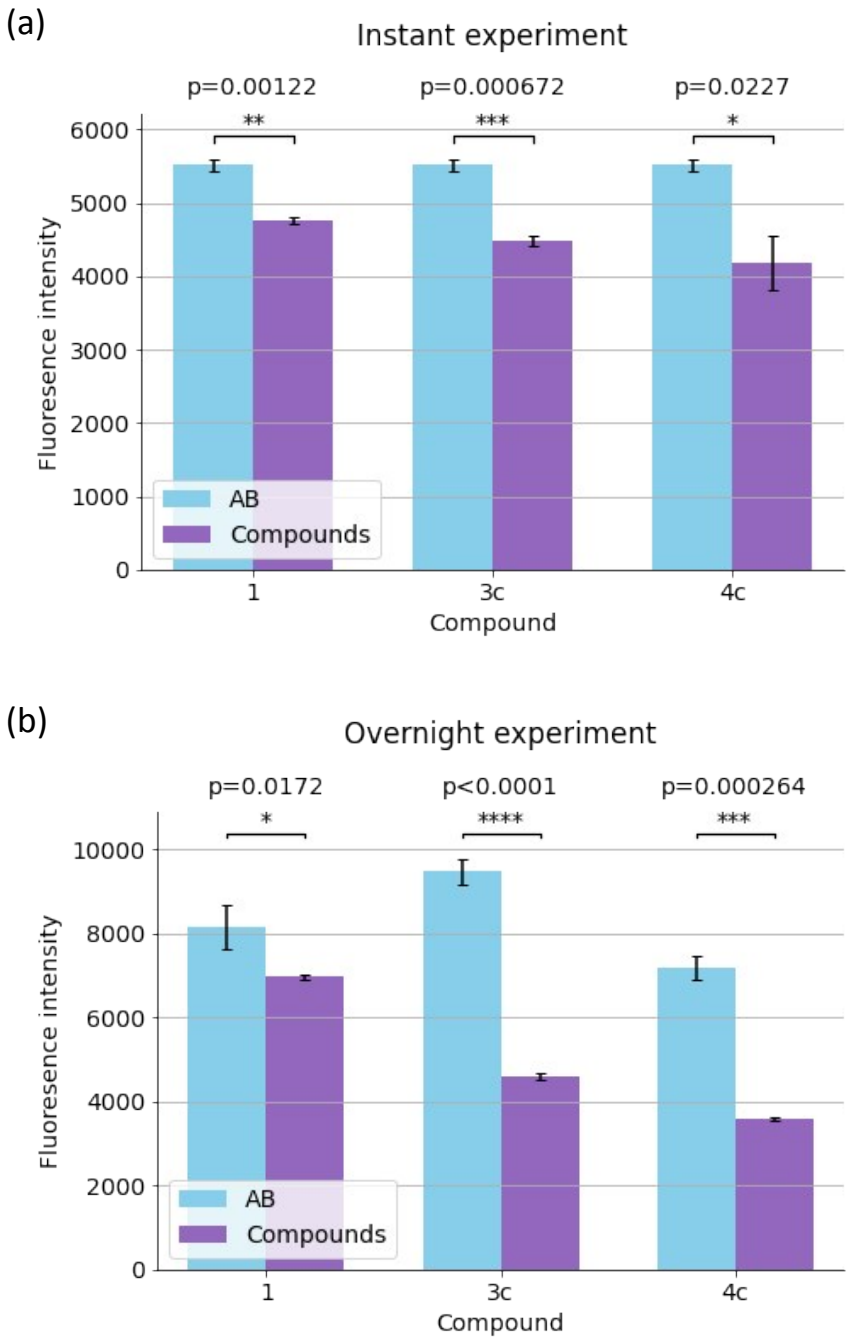


Figure S6. (a) Bar plot showing the ThT fluorescence of 5 μM Aβ1-42 preformed fibrils alone (cyan) or upon addition of 0.1 equivalents of metal complexes (violet). (b) Bar plot showing the ThT fluorescence recorded at the endpoint of the aggregation kinetics (Figures 3 and S5) of 5 μM Aβ1-42 alone (cyan) and in the presence of 0.1 equivalents of metal complexes (violet). Bars represent the mean of n=3 replicas and the error bars are the standard deviation of the mean. Statistical analysis was performed using t-test (* 0.05≥p>0.01, ** 0.01≥p>0.001, *** 0.001≥p>0.0001, **** p<0.0001).

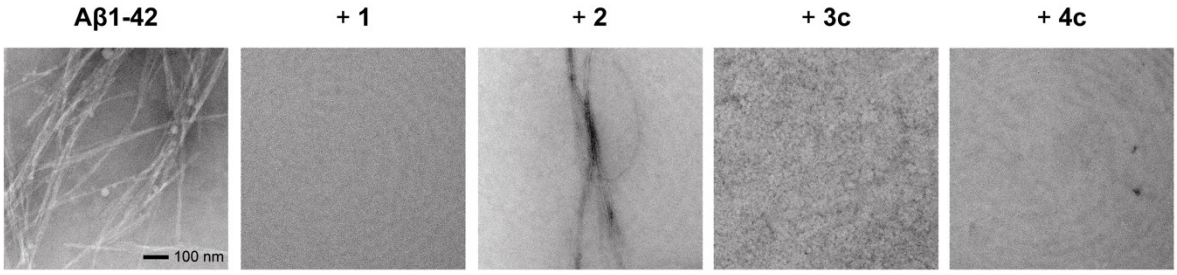
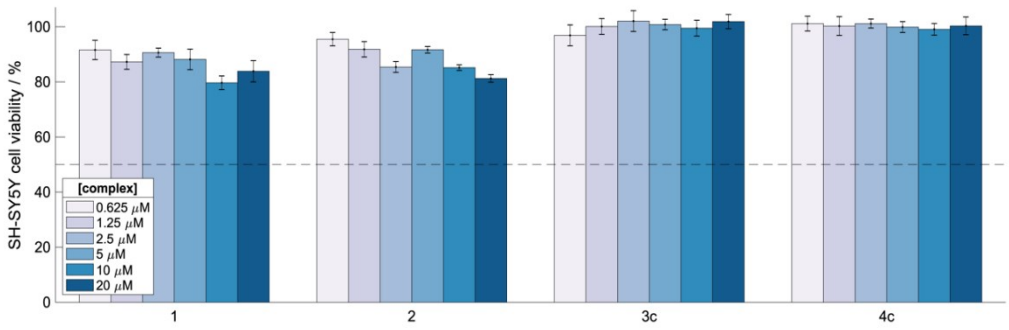


Figure S7. Representative TEM images of Aβ1-42 incubated by itself or with **1, 2, 3c** or **4c** for 48 hr at 37 °C (1:1 ratio). Clear fibril formation can be observed in the sample of Aβ1-42 incubated by itself. Reduced fibril formation is observed when Aβ1-42 is incubated with **2**, while no evidence of fibril formation is observed with complexes **1, 3c** and **4c**.

a



b

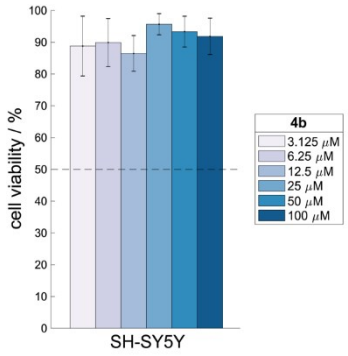


Figure S8. [a] Cytotoxicity of complexes **1**, **2**, **3c** and **4c** against human neuroblastoma SH-SY5Y cells determined using an MTS assay. [b] Cytotoxicity of complex **4b** against human neuroblastoma SH-SY5Y cells determined using an MTS assay. For all experiments, cells were incubated for 24 hrs at 37 °C in the presence of the complex of interest. The IC50 for **4b** was determined to be > 100 μM, indicating a lack of cytotoxicity. All data is reported as the mean ± standard deviation of three independent experiments.

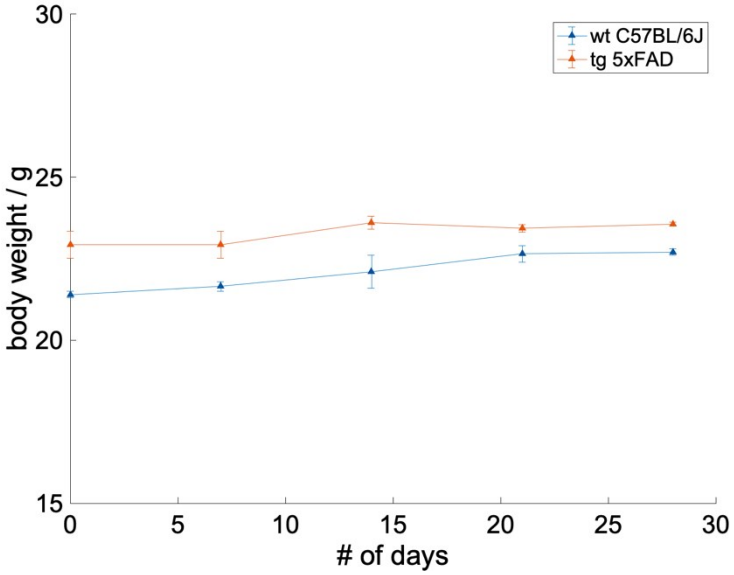


Figure S9. Body weight of wild-type C57BL/6J and transgenic 5xFAD mice treated with ultrasound + complex **4b** over a five week period. Treatment was given weekly on day 0, 7, 14 and 21. The dose of complex **4b** administered was 20 mg/kg for all mice (number of mice per model = 3).

Experimental Methods

1. Synthesis of Metal Complexes

Complexes **1**, **3a** and **3d** were synthesised as previously reported.[1,2] Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Elemental analyses (C, H, N) are reported as the average of two independent measurements and were obtained by Mr. A. Dickerson (University of Cambridge). ^{1}H NMR spectra were recorded on a 400 MHz Bruker Avance III HD NMR spectrometer at 298 K. Chemical shifts are given in parts per million (ppm, δ) and are reported relative to TMS and referenced to the residual deuterated solvent. Splitting patterns are designated as s for singlet, d for doublet, t for triplet and m for multiplet. Liquid chromatography electrospray (LC-ES) mass spectra were obtained on a Waters LCT Premier (ES-TOF)/Acquity i-Class spectrometer by Dr. L. Haigh (Imperial College London).

1.1 General Procedure for Synthesis of Salphen and Salnaph Ligands

4-(4-formyl-3-hydroxyphenoxy)-N,N,N-trimethylethan-1-ammonium bromide was synthesised via a procedure reported by Rakers et al.[1] 4-(4-formyl-3-hydroxyphenoxy)-N,N,N,-trimethylethan-1-ammonium bromide (800 mg, 2.63 mmol, 2 eq.) was dissolved in absolute ethanol (50 mL). 1,2-phenylenediamine (142.1 mg, 1.31 mmol, 1 eq.) or 2,3-diaminonaphthalene (207.7 mg, 1.31 mmol, 1 eq.) was added and the reaction was refluxed for 5 hours under an inert atmosphere. The precipitated product was filtered and washed with EtOAc, DCM and Et_2O (3 x 5 mL) to give the desired product as a yellow solid.

1.1.1 Salphen Ligand:

Yellow solid, 739.9 mg, 83%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.19 (s, 18H, NMe_3), 3.80-3.82 (m, 4H, -CH_2N-), 4.53-4.55 (m, 4H, -OCH_2-), 6.57 (d, 2H, J = 8.0 Hz, Ar-H), 6.62 (dd, 2H, J = 8.0, 4.0 Hz, Ar-H), 7.36-7.39 (m, 2H, Ar-H), 7.44-7.46 (m, 2H, Ar-H), 7.61 (d, 2H, J = 8.0 Hz, Ar-H), 8.89 (s, 2H, -CH=N-), 13.57 (s, 2H, -OH); ^{13}C NMR (400 MHz, DMSO-d_6) δ 53.1, 61.8, 63.8, 101.8, 107.2, 113.8, 119.5, 127.4, 134.2, 141.6, 161.7, 162.9, 163.4; MS (ES$^+$) m/z calcd for $C_{30}H_{40}BrN_4O_4^+$ (M^+): 599.22; found: 599.22.

1.1.2 Salnaph Ligand:

Bright yellow solid, 770.7 mg, 80%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.52 (s, 2H, -OH), 9.02 (s, 2H, -N=CH-), 7.97 – 7.90 (m, 4H, Ar-H), 7.67 (d, J = 8.6 Hz, 2H, Ar-H), 7.52 (dd, J = 6.2, 3.4 Hz, 2H, Ar-H), 6.68 – 6.58 (m, 4H, Ar-H), 4.56 (t, J = 4.7 Hz, 4H, -O-CH_2-), 3.85 (t, J = 4.8 Hz, 4H, -CH_2-NMe_3), 3.22 (s, 18H, -$(CH_3)_3$); ^{13}C NMR (400 MHz, DMSO-d_6) δ 163.5, 163.1, 161.9, 141.8, 134.8, 132.2, 127.6, 126.2, 116.4, 113.9, 107.3, 101.8, 63.9, 61.9, 53.1; MS (ES$^+$) m/z 285.1594 ([M+2H]$^{2+}$, 100%), where M = $C_{34}H_{42}N_4O_4^{2+}$.

1.2 Synthesis of Platinum(II) Salphen (2)

The salphen ligand (150 mg, 0.22 mmol, 1 eq.) was first dissolved in a mixture of DMSO (12 mL) and MeCN (30 mL), and then NaOAc (48 mg, 0.59 mmol, 2.7 eq.) was added. The yellow mixture was stirred at 70 °C under N_2 for 30 min. K_2PtCl_4 (108 mg, 0.26 mmol, 1.2 eq.) was dissolved in DMSO (ca. 0.7 mL) and added to the reaction mixture which turned red immediately. The mixture was heated to 65 °C under N_2 for 18 h to give an orange solid precipitate, which was isolated by filtration, washed with MeCN (3 x 10 mL) and diethyl ether (3 x 10 mL) and dried under reduced pressure (198 mg, 0.227 mmol, quant.). For further purification, the obtained product was dissolved in distilled H_2O (7 mL) and MeCN (8-10 eq.) was slowly added to precipitate out a bright-orange powder. The precipitate was isolated by filtration, washed with MeCN (3 x 10 mL) and diethyl ether (3 x 10 mL) before drying under reduced pressure.

Elem. Anal. Found: C, 41.51; H, 4.85; N, 6.30. $C_{30}H_{38}N_4O_4PtBr_2$ requires C, 41.25; H, 4.38; N, 6.41%; ^{1}H NMR (400 MHz, 50% DMSO-d_6, 50% D_2O): δ 3.11 (s, 18H, -$(CH_3)_3$, 3.71 (t, $^3J_{HH}$ = 4 Hz, 4H, -(CH_2)), 4.36 (br s, 4H, -(CH_2)), 6.43 – 6.37 (m, 2H, ArH), 7.21 – 7.10 (m, 2H, ArH), 7.45 (d, $^3J_{HH}$ = 8 Hz, 2H, ArH), 7.89 – 7.79 (m, 2H, ArH), 8.63 (s, 2H, -CH=N-); MS (ES^+) m/z 758.31 ([M-2Br^- + $HCOO^-$]$^+$, 100%), where M = $C_{30}H_{38}N_4O_4PtBr_2$.

1.3 Synthesis of Cobalt(III) Salphens (3) and Salnaphs (4)

Cobalt(II) acetate tetrahydrate (17 mg, 0.07 mmol, 1 eq.) was added to a solution of salphen or salnaph ligand (50 mg, 0.07 mmol, 1 eq.) in methanol (10 mL), resulting in a colour change from yellow to dark red. The desired axial ligand (0.70 mmol, 10 eq.) was added, and the mixture was stirred for 5 hr in air. NH_4PF_6 (> 10 eq.) was then added, resulting in the formation of a precipitate which was separated via centrifugation and washed with water and DCM (3 x 5 mL) to give the desired product.

3b: L = pyridine
Red-brown solid, 105 mg, 60%
Elem. Anal. Found: C, 38.44; H, 4.02; N, 6.55. $C_{40}H_{52}CoF_{18}N_6O_6P_3$ requires C, 39.81; H, 4.34; N, 6.96%; ^{1}H NMR (400 MHz, MeOD-d_4) δ 3.29 (s, 18H, NMe_3), 3.91 (s, 4H, -CH_2N-), 4.60 (m, 4H, -OCH_2-), 6.42 (s, 2H, ArH), 6.95 (s, 2H, ArH), 7.30 (s, 4H, ArH), 7.48 (s, 4H, ArH), 7.81 (s, 2H, ArH), 8.10 (s, 4H, ArH), 8.24 (s, 2H, ArH), 8.75 (s, 2H, -CH=N-); ^{13}C NMR (400 MHz, MeOD-d_4) δ 54.7, 63.2, 66.3, 106.4, 109.4, 115.3, 118.6, 126.6, 130.1, 138.5, 141.2, 144.3, 153.2, 161.1, 166.7, 169.6; MS(ES^+) m/z calcd for $C_{41}H_{49}CoF_6N_6O_6P$ (M^+): 925.27; found: 925.27.

3c: L = pyrrolidine
Red-brown solid, 134 mg, 75%.
Elem. Anal. Found: C, 42.24; H, 5.49; N, 7.52. $C_{38}H_{62}Br_2CoF_6N_6O_7P$ requires C, 42.31; H, 5.79; N, 7.79%; ^{1}H NMR (400 MHz, MeOD-d_4) δ 1.43 (8H, $CH_{2,pyrr}$), 1.97 (4H, $CH_{2,pyrr}$), 2.30 (4H, $CH_{2,pyrr}$), 3.29 (s, 18H, NMe_3), 3.94 (s, 4H, -CH_2N-), 4.63 (m, 4H, -OCH_2-), 6.50 (d, 2H, J = 8.0 Hz, ArH), 6.96 (s, 2H, ArH), 7.52 (s, 2H, ArH), 7.60 (d, 2H, J = 8.0 Hz, ArH), 8.35 (s, 2H, -CH=N-); ^{13}C NMR (400 MHz, DMSO-d_6) δ 23.7, 48.5, 49.6, 54.8, 63.3, 66.5, 105.8, 108.6, 114.6, 118.0, 129.5, 138.8, 145.0, 160.3, 166.5, 170.6; MS(ES^+) m/z calcd for $C_{38}H_{56}CoF_{12}N_6O_4P_2^+$ (M^+): 1009.30; found: 1009.30.

3e: L = benzylamine
Red-brown solid, 126 mg, 69%.
Elem. Anal. Found: C, 43.95; H, 4.79; N, 6.82. $C_{44}H_{58}BrCoF_{12}N_6O_6P_2$ requires C, 44.20; H, 4.89; N, 7.03%; ^{1}H NMR (400 MHz, MeOD-d_4) δ 3.08 (s, 4H, $CH_{2,\ bzlan}$), 3.29 (s, 18H, NMe_3), 3.92 (s, 4H, -CH_2N-), 4.65 (m, 4H, -OCH_2-), 6.53 (d, 2H, J = 8.0 Hz, ArH), 6.92 (s, 4H, ArH), 7.03 (s, 2H, ArH), 7.14 (s, 6H, ArH), 7.47 (s, 2H, ArH), 7.56 (s, J = 8.0 Hz, 2H, ArH), 8.20 (s, 2H, ArH), 8.63 (s, 2H, -CH=N-); ^{13}C NMR (400 MHz, MeOD-d_4) δ 46.7, 54.8, 63.3, 66.5, 106.0, 108.5, 115.0, 118.0, 128.9, 129.1, 129.4, 129.7, 138.6, 138.9, 144.9, 160.7, 166.3, 169.8; MS(ES^+) m/z calcd for $C_{41}H_{48}CoF_6N_6O_6P$ (M^{2+}): 417.22; found: 417.18.

4a: L = methylamine
Yellow-orange solid, 74 mg, 96%.
Elem. Anal. Found: C, 36.6; H, 4.39; N, 7.48. $C_{36}H_{49}CoN_6O_4P_3F_{18}\cdot 3H_2O$ requires C, 36.72; H, 4.71; N, 7.14%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 2H, -N=CH-), 8.85 (s, 2H, Ar-H), 8.03 – 7.95 (m, 2H, Ar-H), 7.61 (m, 4H, Ar-H), 6.76 (s, 2H, Ar-H), 6.43 (d, J = 8.9 Hz, 2H, Ar-H), 4.55 (br, 4H, -O-CH_2-), 3.83 (br, 4H, -CH_2-NMe_3), 3.71 – 3.65 (m, 4H, -NH_2CH_3), 3.21 (s, 18H, -(CH_3)$_3$), 1.40 (t, J = 6.4 Hz, 6H, -NH_2CH_3); MS (ES$^+$) m/z 417.1392 ([M+PF_6^-+2H]$^{2+}$, 45%), 367.1545 ([M+2Na]$^{2+}$, 100%), where M = $C_{36}H_{49}CoN_6O_4^{3+}$.

4b: L = pyridine
Dark red solid, 63 mg, 74%.
Elem. Anal. Found: C, 41.75; H, 4.13; N, 6.45. $C_{44}H_{50}CoN_6O_4P_3F_{18}\cdot 3H_2O$ requires C, 41.46; H, 4.43; N, 6.59%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 2H, -N=CH-), 8.84 (s, 2H, Ar-H), 8.06 – 7.96 (m, 6H, Ar-H), 7.90 – 7.81 (m, 2H, Ar-H), 7.64 (dd, J = 6.3, 3.1 Hz, 2H, Ar-H), 7.51 (d, J = 9.1 Hz, 2H, Ar-H), 7.36 (m, 4H, Ar-H), 6.88 (s, 2H, Ar-H), 6.39 (d, J = 9.1 Hz, 2H, Ar-H), 4.54 (t, 4H, -O-CH_2-), 3.81 (t, 4H, -CH_2-NMe_3), 3.19 (s, 18H, -(CH_3)$_3$); MS (ES$^+$) m/z 465.1379 ([M+PF_6^-+2H]$^{2+}$, 70%), 415.1526 ([M+2Na]$^{2+}$, 100%), where M = $C_{44}H_{50}CoN_6O_4^{3+}$.

4c: L = pyrrolidine
Yellow-orange solid, 65 mg, 79%.
Elem. Anal. Found: C, 41.68; H, 4.75; N, 6.87. $C_{42}H_{58}CoN_6O_4P_3F_{18}$ requires C, 41.87; H, 4.85; N, 6.98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 2H, -N=CH-), 8.93 (s, 2H, Ar-H), 8.01 (m, 2H, Ar-H), 7.67-7.59 (m, 4H, Ar-H), 6.81 (d, J = 2.4 Hz, 2H, Ar-H), 6.45 (dd, J = 8.8 Hz, 2.4 Hz, 2H, Ar-H), 4.56 (s, 4H, -O-CH_2-), 4.45 (s, 4H, -NH-), 3.83 (s, 4H, -CH_2-NMe_3), 3.21 (s, 18H, -(CH_3)$_3$), 2.19 (m, 4H, -NH-CH_2-), 1.96 (m, 4H, -NH-CH_2-), 1.34 (br, 6H, -NH-CH_2-CH_2-); MS (ES$^+$) m/z 407.2071 ([M+2Na]$^{2+}$, 100%), where M = $C_{42}H_{58}CoN_6O_4^{3+}$.

4d: L = ammonia
Yellow-orange solid, 56 mg, 75%.
Elem. Anal. Found: C, 37.12; H, 4.18; N, 7.56. $C_{34}H_{46}CoN_6O_4P_3F_{18}$ requires C, 37.24; H, 4.23; N, 7.66%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 2H, -N=CH-), 8.82 (s, 2H, Ar-H), 7.99-7.96 (m, 2H, Ar-H), 7.61-7.57 (m, 4H, Ar-H), 6.69 (d, J = 2.2 Hz, 2H, Ar-H), 6.42-6.39 (m, 2H, Ar-H), 4.53 (s, 4H, -O-CH_2-), 3.82 (s, 4H, -CH_2-NMe_3), 3.20 (s, 18H, -(CH_3)$_3$), 2.77 (s, 6H, -NH_3); MS (ES$^+$) m/z 403.1255 ([M+PF_6^-+2H]$^{2+}$, 35%), 353.1585 ([M+2Na]$^{2+}$, 100%), where M = $C_{34}H_{46}CoN_6O_4^{3+}$.

4e: L = benzylamine
Brown solid, 81 mg, 92%.
Elem. Anal. Found: C, 44.58; H, 4.58; N, 6.35. $C_{48}H_{58}CoN_6O_4P_3F_{18}\cdot H_2O$ requires C, 44.52; H, 4.67; N, 6.49%; ^{1}H NMR (400 MHz, DMSO-d_6)) δ 8.92 (s, 2H, -N=CH-), 8.80 (s, 2H, Ar-H), 7.98 (s, 2H, Ar-H), 7.67-7.56 (m, 4H, Ar-H), 7.14 (s, 6H, Ar-H), 6.99 (s, 4H, Ar-H), 6.92 (s, 2H, Ar-H), 6.45 (d, J = 8.7 Hz, 2H, Ar-H), 4.57 (s, 4H, -O-CH_2-), 3.86 (m, 8H, -CH_2-NMe_3, -NH_2-CH_2-), 3.21 (s, 18H, -(CH_3)$_3$); MS (ES$^+$) m/z 443.1873 ([M+2Na]$^{2+}$, 100%), 280.4556 ([M+3H]$^{3+}$, 80%), where M = $C_{48}H_{58}CoN_6O_4^{3+}$.

2. Stability of Complexes in Aqueous Solution

The ^{1}H NMR spectra of each complex were recorded at 0, 2, 4, 8, 24 and 48 hrs in D_2O:aqueous buffer (1:9, pH 7.2-7.4) using standard water suppression techniques. For complex **3d**, DMSO-d_6 was added (1:1) to allow for solubility. The ratio of complex with axial ligands:complex without axial ligands was

determined by comparing the integrals of the relevant peaks and used to calculate the abundance of each species over time.

3. Preparation of Amyloid Beta Peptides

All Aβ peptides (Aβ1-42, Aβ1-28, H6R Aβ1-28 and Aβ1-16; > 95% purity – see below for exact sequences) were bought from either Discovery Peptides or rPeptide and treated with 10% (w/v) NH_4OH to remove any preformed aggregates following reported protocols.[3] Briefly, 1 mg of lyophilised peptide was dissolved in 200 µL of NH_4OH, incubated at 25 °C for 10 mins, sonicated for 5 mins and then aliquoted. The NH_4OH was removed by lyophilisation to give a white solid. The dry peptide was stored at -80 °C and each aliquot was used only once. Before use, peptide aliquots were dissolved in 60 mM NaOH to a stock concentration of 200 µM and then diluted to the desired concentration with PBS. Peptide concentrations were determined by UV-Vis spectroscopy using an extinction coefficient of 1490 cm^{-1} M^{-1} at 280 nm.[4,5]

Aβ sequences used in this work:

Aβ1-42: DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA
Aβ1-28: DAEFRHDSGYEVHHQKLVFFAEDVGSNK
H6R Aβ1-28: DAEFR**R**DSGYEVHHQKLVFFAEDVGSNK
Aβ1-16: DAEFRHDSGYEVHHQK

4. End-point Thioflavin-T Assay

Complexes were dissolved in DMSO:PBS (1x PBS: 137 mM NaCl, 2.7 mM KCl, 4.3 mM Na_2HPO_4 and 1.47 mM KH_2PO_4) to give stock solutions of the required concentrations. The final percentage of DMSO was 1% in all cases. The corresponding metal complex (20 µL) was added to Aβ1-42 (10 µL, 20 µM) and ThT (10 µL, 80 µM). The final concentrations of ThT and Aβ1-42 were 20 µM and 5 µM respectively, and final [Aβ1-42]:[complex] ratios were 25:1, 20:1, 15:1, 10:1 and 5:1. Samples were incubated for 24 hr at 37 °C with shaking in a 384 well-plate. After incubation, the fluorescence emission at 485 nm when excited at 442 nm was recorded using a Perkin Elmer EnVision plate reader. All samples were run in triplicate. The % inhibition in each case was calculated as $[1 - (X - F_{ThT\_alone})/(F_{ThT\_fibrils} - F_{ThTalone})] * 100$. For all complexes, the data reported is the mean ± standard deviation of three independent experiments.

5. Aggregation Kinetic and ThT Quenching/Displacement Assays

A BMG Labtech CLARIOstar Plus plate reader was used for the kinetic experiments. The excitation and emission filters used were 440 nm and 480 nm respectively and the fluorescence was measured via bottom optics. A Corning black polystyrene 96-well half-area, clear bottom, low binding microplate with a polyethylene glycol coating was used. Plates were kept at 37 ^{0}C during measurements without shaking and sealed to prevent evaporation. Each condition was made up in low binding Eppendorf tubes before being transferred to the plate and measured in quintuplicate. Each tube contained 5 µM Aβ1-42 in PBS, 20 µM ThT and compounds of varying concentrations (dissolved in DMSO:PBS to give stock solutions of the required concentrations). The final proportion of DMSO was kept constant at 1%. Control conditions were also measured in quintuplicate. Data are represented in terms of ΔFluorescence and normalized fluorescence. Error bars represent the standard deviation of the mean.

ThT quenching/displacement assay was performed as it follows. Solutions of 5 μM monomeric Aβ1-42 were incubated in PBS and 20 μM ThT at 37 ^{0}C for 24 h to form fibrils. The ThT fluorescence of these samples was measured and compared to that one of samples also containing 0.1 equivalents of metal complexes **1**, **3c**, and **4c**. The final proportion of DMSO was kept constant at 0.8%. As a reference, we compared the endpoint ThT fluorescence of aggregation kinetics containing 5 μM Aβ1-42 alone with the endpoint ThT fluorescence of aggregation kinetics also containing 0.1 equivalents of metal complexes **1**, **3c**, and **4c**. Each experiment was carried out in triplicate.

6. Transmission Electron Microscopy

A solution of 10 μM Aβ1-42 was incubated with 10 μM of complexes **1, 2, 3c** or **4c** for 48 hrs at 37 °C. 5 μL of the mixture was drop-casted onto a carbon-coated grid and then negatively-stained with 5 μL of uranyl acetate. Images were acquired on a Tecnai Spirit TWIN TEM microscope at 52,000x magnification and with -2 micron defocus. All grid screening was conducted blind to avoid bias.

7. Fluorescence Titrations

The truncated peptide Aβ1-16 is intrinsically fluorescent due to its Tyr10 residue and can be used to study non-covalent interactions following reported methods.[6] Briefly, a solution of 150 μM Aβ1-16 was titrated with increasing concentrations of metal complex **1, 3c** or **4c** (11.3 μM to 112.5 μM; 0 to 0.75 eq.) After each addition, the fluorescence emission between 285-400 nm was recorded using a Cary Eclipse Fluorescence Spectrophotometer using an excitation wavelength of 280 nm. Emission values at 310 nm (λ_{max}) were normalised to the emission recorded for Aβ1-16 without any complex added. All samples were measured in triplicate, with cisplatin included as a negative control.

8. ^{1}H NMR Spectroscopy of Aβ

^{1}H NMR spectroscopy was run with the wild-type (WT) Aβ1-28 peptide and the H6R point-mutated Aβ1-28 peptide. In both cases, the N-terminal metal ion binding site of Aβ (residues 1-16) is conserved. Truncated peptides were used to simplify NMR analyses following reported methods.[6] Samples of WT Aβ1-28 or H6R Aβ1-28 (100 μM) in D_2O:phosphate buffer (1:9, pH 7.4) were incubated at 37 °C in the presence and absence of metal complexes **1, 2, 3c** or **4c** (100 μM). ^{1}H NMR spectra were recorded at three time-points (t = 0, 1 and 24 hr) on a 600 MHz Bruker Avance III HD NMR spectrometer at 298 K using standard water suppression techniques.

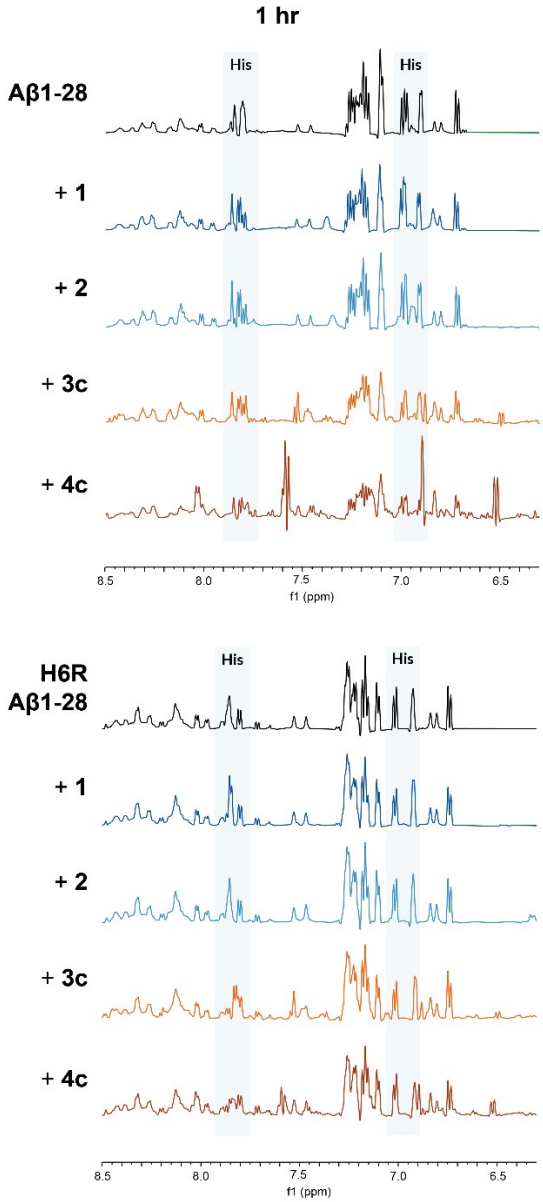


Figure S10. ^{1}H NMR spectra of Aβ1-28 (top) or H6R Aβ1-28 (bottom) incubated by itself (black), with square planar **1** and **2** (blue) or octahedral **3c** and **4c** (orange) complexes (in a 1-to-1 peptide:complex ratio). All spectra were recorded in D_2O:phosphate buffer (1:9, pH 7.4) at 37 ^{0}C; the spectra shown are at 1 hr incubation time. Peaks corresponding to the Aβ histidine residues are highlighted in blue.

9. MTS Assay

Human neuroblastoma (SH-SY5Y) were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with F-12 nutrient mix and 10% foetal calf serum (FBS) at 37 °C and 5% CO_2. Before each assay, cells were seeded at a density of 2,500 cells/well in a 96-well plate and incubated for 24 hrs.

SH-SY5Y cells were incubated with differing concentrations of the compound under study (complexes **1**, **2**, **3c**, **4c** and **4b**) for 24 hrs. Cytotoxicity was evaluated using a colorimetric MTS assay following

manufacturer's protocols (CellTiter 96 Aqueous One Solution Cell Proliferation Assay). Briefly, 1.5 mL of [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium, inner salt] (MTS) was first mixed with 75 µL of phenazine methosulphate (PMS). 1.5 mL of the MTS/PMS mixture was then added to 7.5 mL DMEM/F-12. Cell media was removed from each well and replaced with 100 µL of the MTS/PMS-containing media to minimise interference from the added complexes. Plate was then incubated for 2 hrs. The absorbance at 492 nm was recorded using a Thermo Scientific Varioskan LUX multimode microplate reader. All data is reported as the mean ± standard deviation of three independent experiments.

10. In Vivo Experiments

Focused ultrasound experiments were conducted using the setup depicted below. Briefly, the desired ultrasound pulse sequence and shape were defined using two 33500B Series Agilent Technologies function generators, passed through a 50 dB Precision Acoustics power amplifier and then emitted from a 1 MHz Sonic Concepts single-element, spherical-segment focused ultrasound transducer. The 1 MHz focused ultrasound transducer was mounted onto a programmable 3D positioning system to allow the transducer to be moved to the target location. A 7.5 MHz Olympus Industrial focused passive cavitation detector was used during ultrasound treatment to detect the presence of the microbubbles in the sonicated region. To avoid significant attenuation or distortion of the emitted ultrasound, water baths and coupling gel were used in between the skull of the mouse and the transducer.

Before in vivo experiments, pressure amplitudes were measured using a Precision Acoustics needle hydrophone (diameter: 0.2 mm) in a degassed water tank. Peak-positive and peak-negative values were attenuated by 11% to correct for skull attenuation.[7]

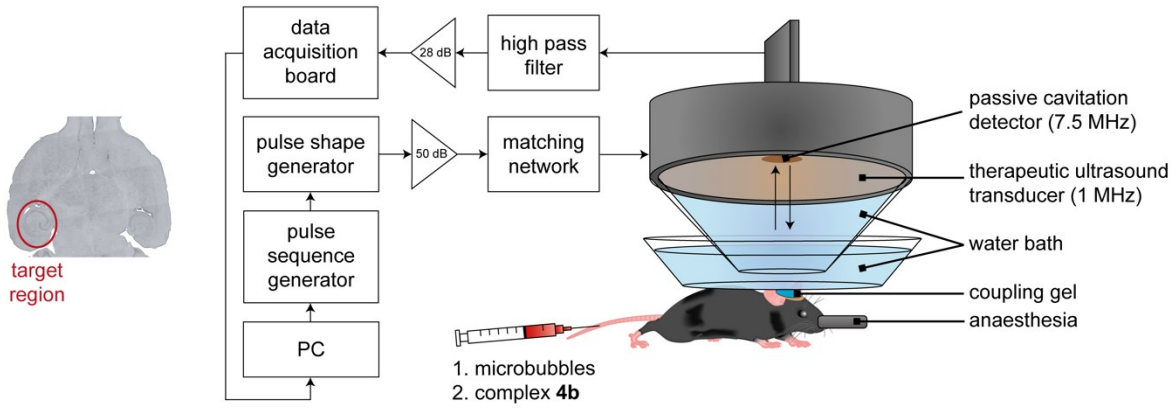


Figure S11. Schematic of ultrasound setup used for *in vivo* experiments.

10.1 General Procedure for Focused Ultrasound-Mediated Drug Delivery to the Brain

All animal procedures were performed in compliance with the European Directive 63/2010/EU and the UK Animals (Scientific Procedures) Act 1986. All protocols were approved by Imperial College London's Animal Welfare and Ethical Review Body. Before every experiment, the fur from the head of the mouse was removed using an electric razor and depilatory cream. The mouse was then anaesthetised with 98% O_2 / 2% isoflurane and its head was fixed using a stereotaxic frame. The transducer was moved to target the left hippocampus following reported protocols and sonicated over 250 s (frequency = 1

MHz; peak-negative pressure = 350 kPa; pulse length = 5 cycles; pulse repetition frequency = 1.25 kHz burst length = 10 ms; burst repetition frequency = 0.5 Hz).[7,8] After five bursts, SonoVue microbubbles (100 µL, 5 µL/g) were administered intravenously via a tail vein catheter, followed by the metal complex. At the study end-point, mice were transcardially perfused with PBS (20 mL) with added heparin (10 units/mL) and then fixed by perfusing with 4% paraformaldehyde (20 mL). Brains were extracted, submerged in 4% paraformaldehyde overnight and then cryoprotected by immersing in graded sucrose solutions (15% to 30%). Samples were cryosectioned at a thickness of 20 µm, mounted onto microscope slides and allowed to air-dry before staining.

10.2 Laser Ablation Inductively Coupled Plasma Mass Spectrometry

Platinum(II) complex **2** (30 mg/kg) or cobalt(III) complex **4c** (30 mg/kg) were administered intravenously via a tail vein catheter. Brain sections were analysed using an Agilent 7900 quadrupole-based inductively coupled plasma mass spectrometer coupled to a New Wave UP213 laser ablation system. Laser ablation was performed using a focused laser beam in scanning mode with a series of ~65 lines of ~10 mm long, giving a total ablated area of approximately 10 mm x 10 mm. Spot size was 65 µm. Distribution maps of the isotopes of interest were plotted using MATLAB.

10.3 Safety Evaluation

Complex **4b** in 5% DMSO at a concentration of 20 mg/kg was delivered to the left hippocampus of wild-type C57BL/6J or transgenic 5xFAD mice (4-5 months, number of mice = 3 per mouse model) on a weekly basis for four weeks using focused ultrasound. The body weight and behaviour of the mice were monitored according to standard procedures. Brain sections were stained with H&E to assess whether there were any changes in morphology due to the treatment. Briefly, slides were first cleared by submerging in Histoclear II for 5 mins and then again for 10 mins. Sections were then hydrated in water and immersed in Harris Haematoxylin solution for 5 mins. Following rinsing with tap water, slides were dipped 3x in 1% acid-alcohol solution (1% HCl in 70% ethanol) and rinsed. Sections were then dipped in Eosin Y for 50 secs and rinsed with water again. Stained slides were dehydrated by placing in 90% ethanol for 30 secs, followed by 100% ethanol for 30 secs and then left in Histoclear II for mounting. Slides were mounted with DPX, coverslipped and imaged.

References

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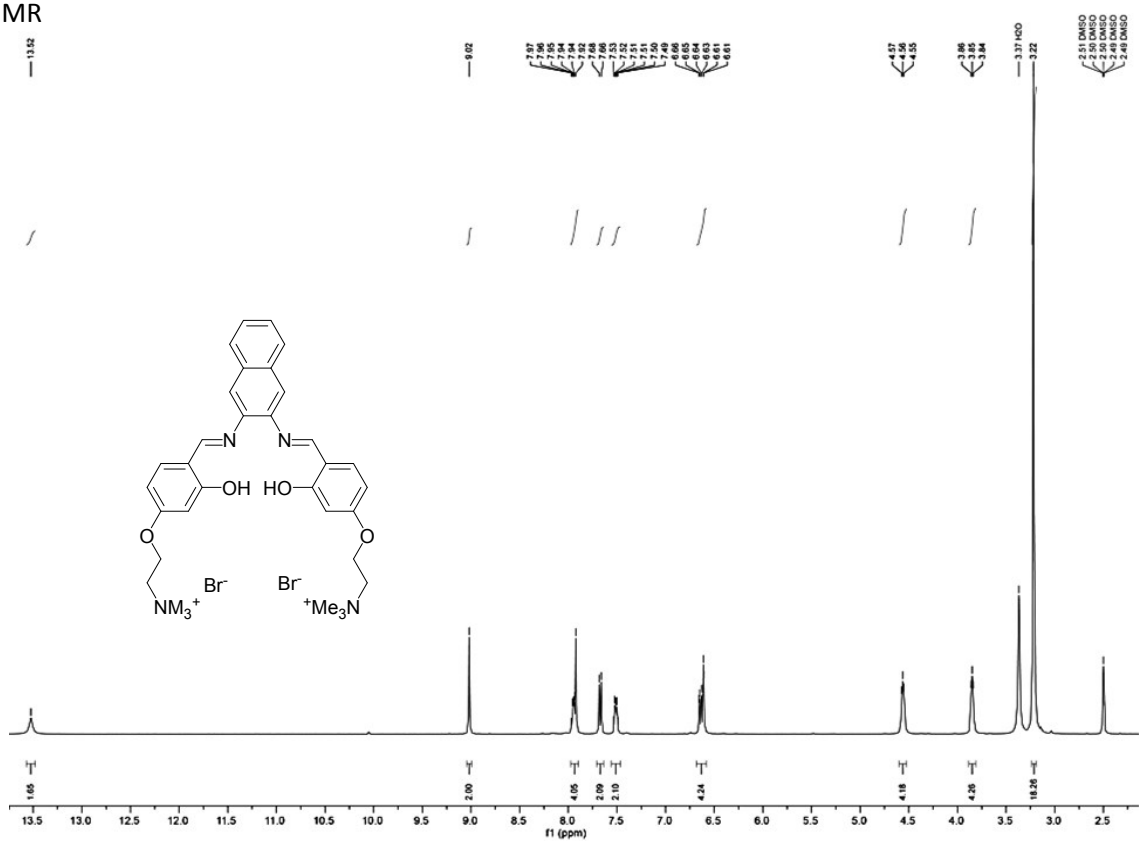
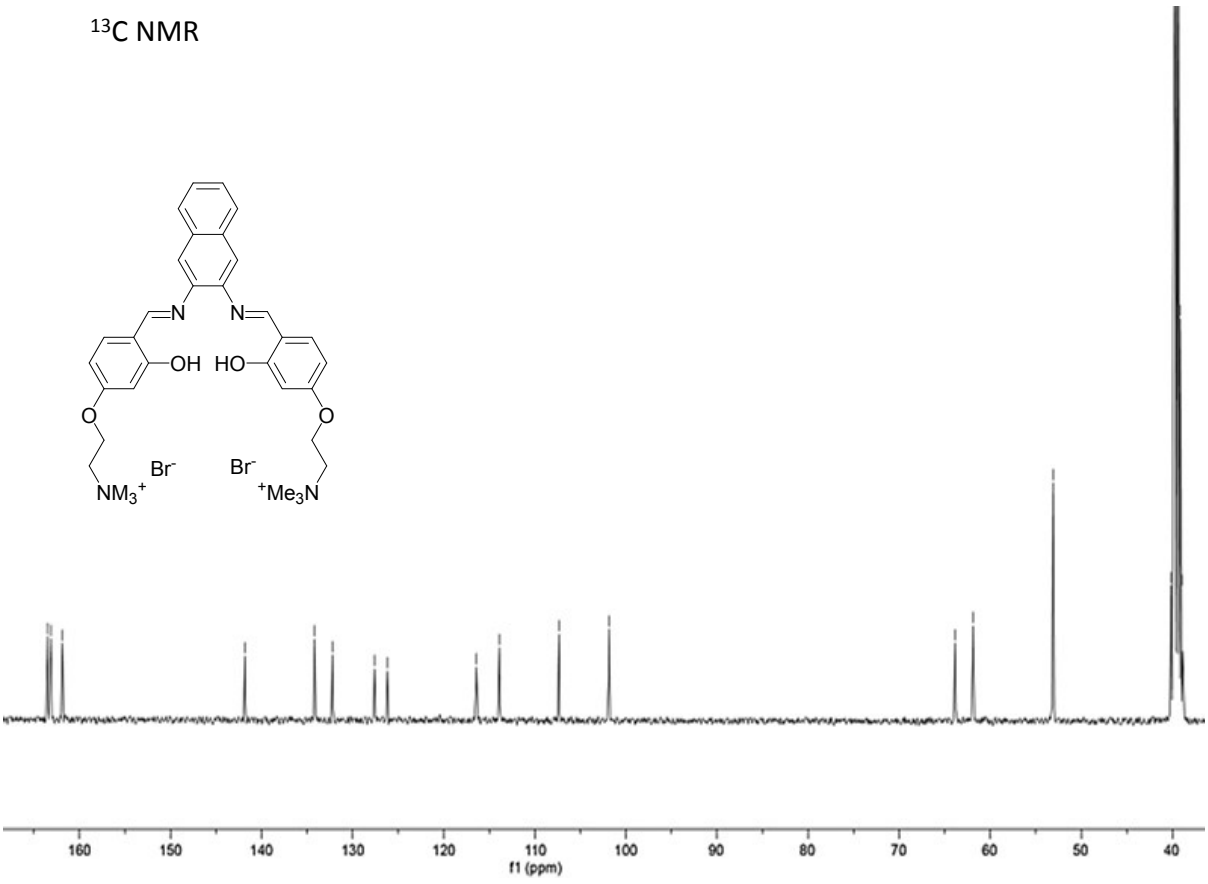
Characterisation Data for Metal Complexes 2, 3b, 3c, 3d and 4a-4e

Salnaph Ligand

^{1}H NMR



^{13}C NMR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HO
O
O
Br-
Br-
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140
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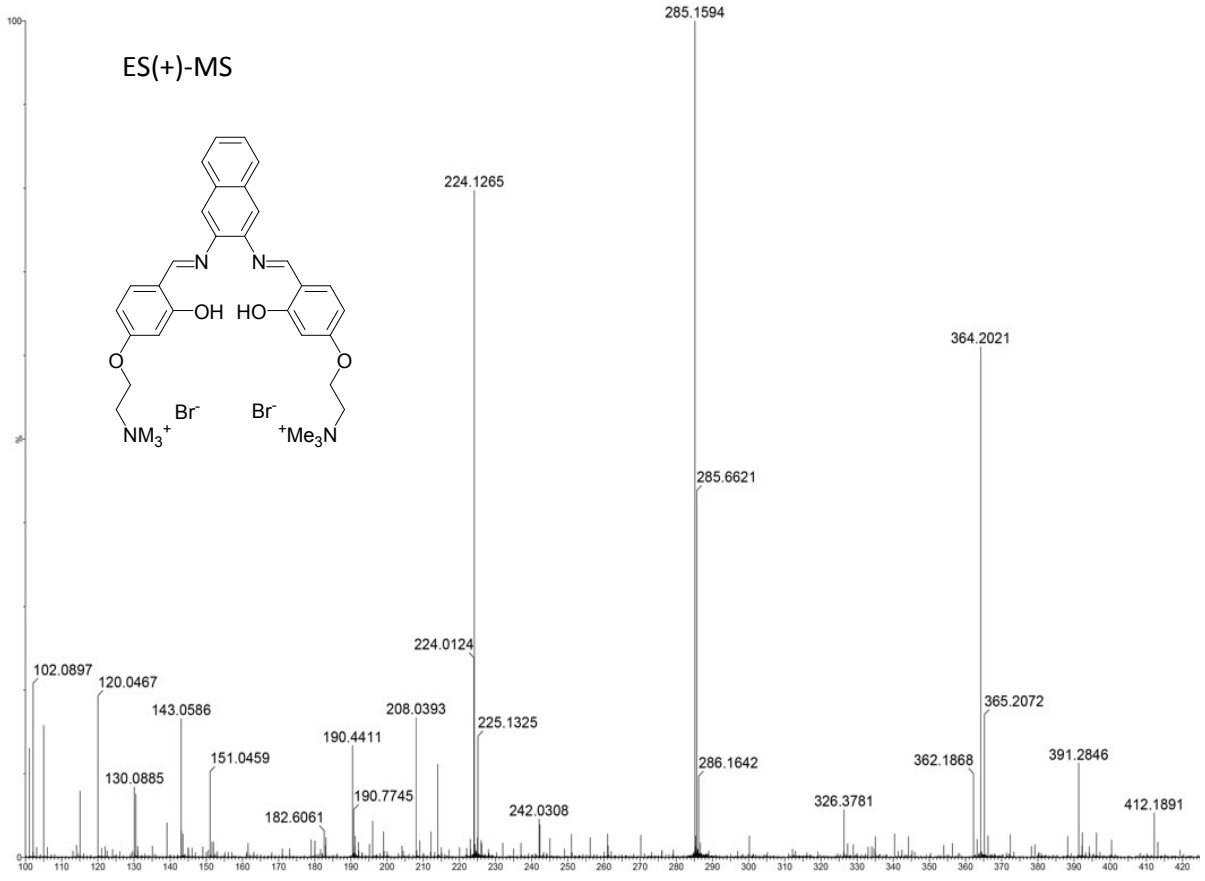
110
100
90
80
70
60
50
40
f1 (ppm)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Br-
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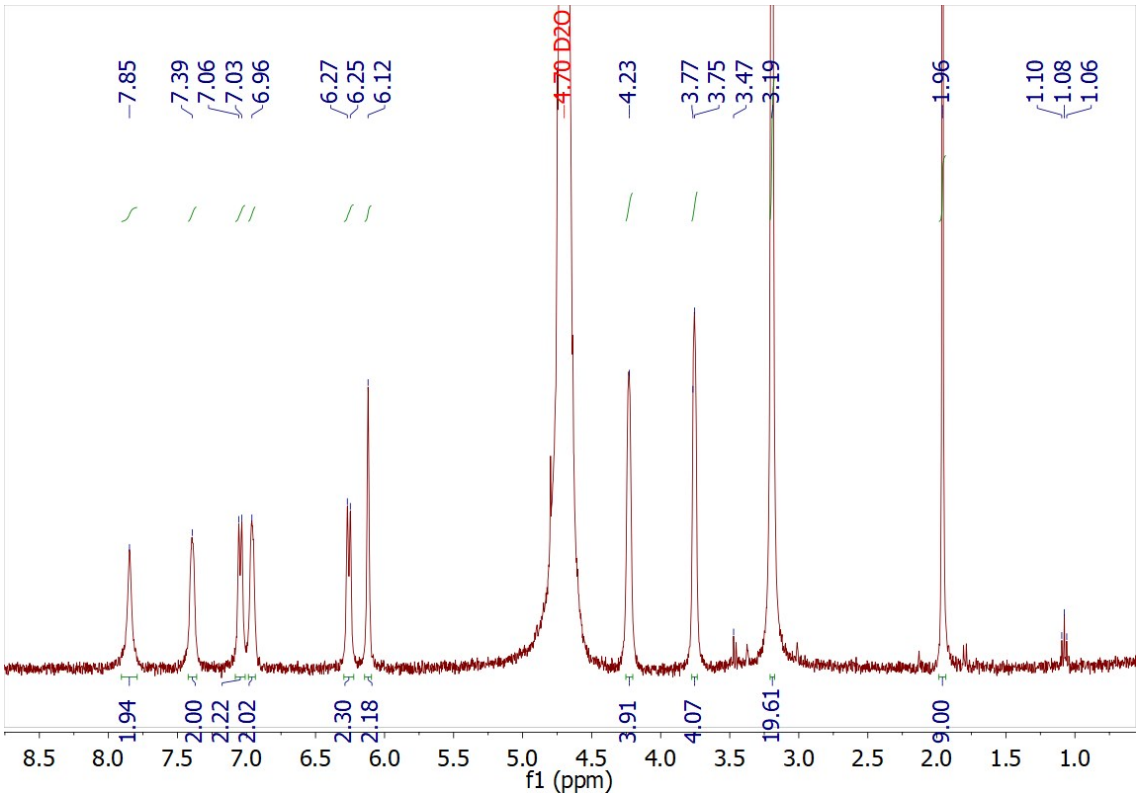
+Me3N

Complex 2

^{1}H NMR



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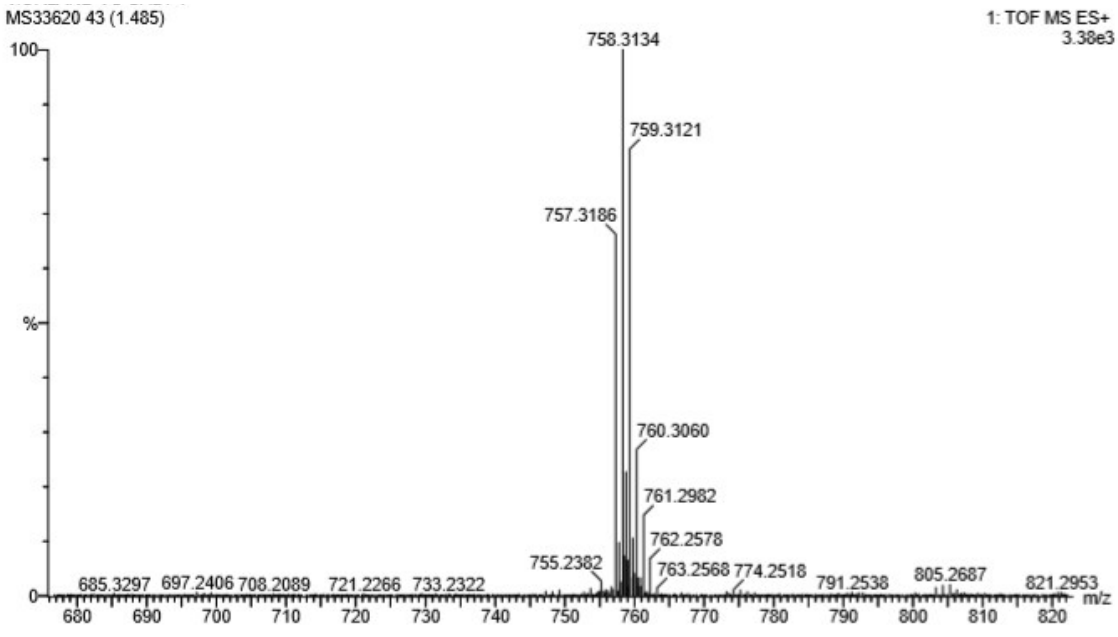
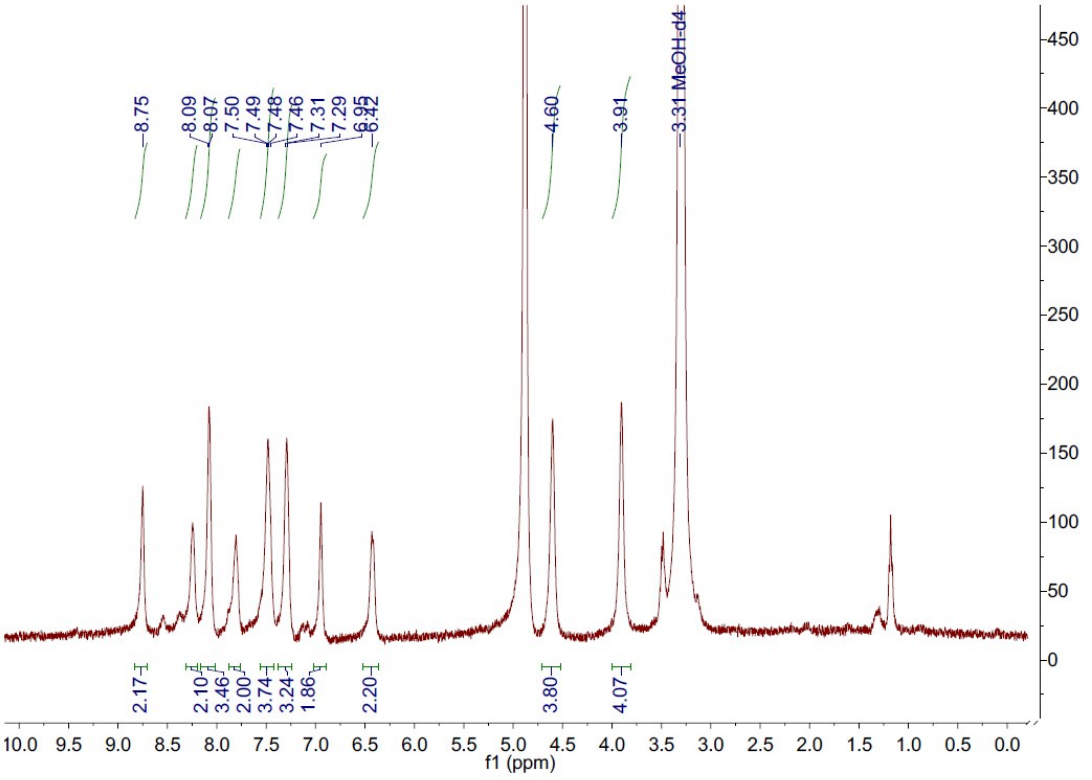


Complex 3b: L = pyridine

^{1}H NMR



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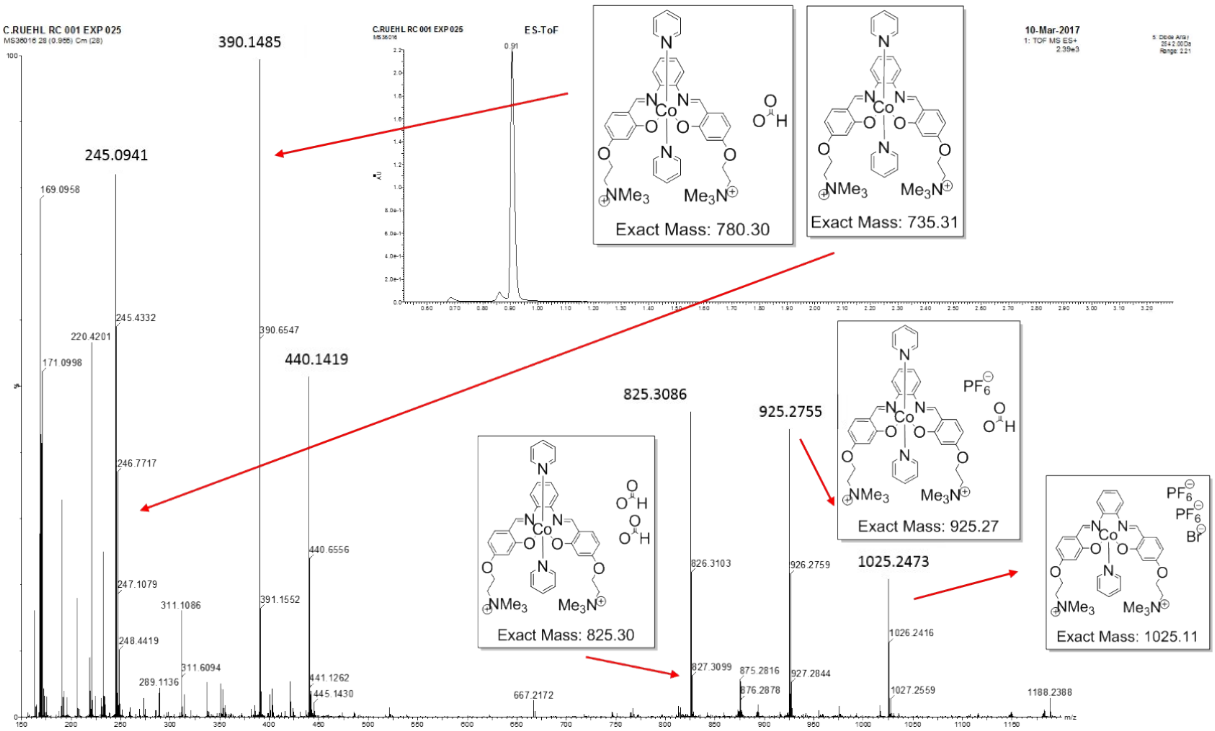
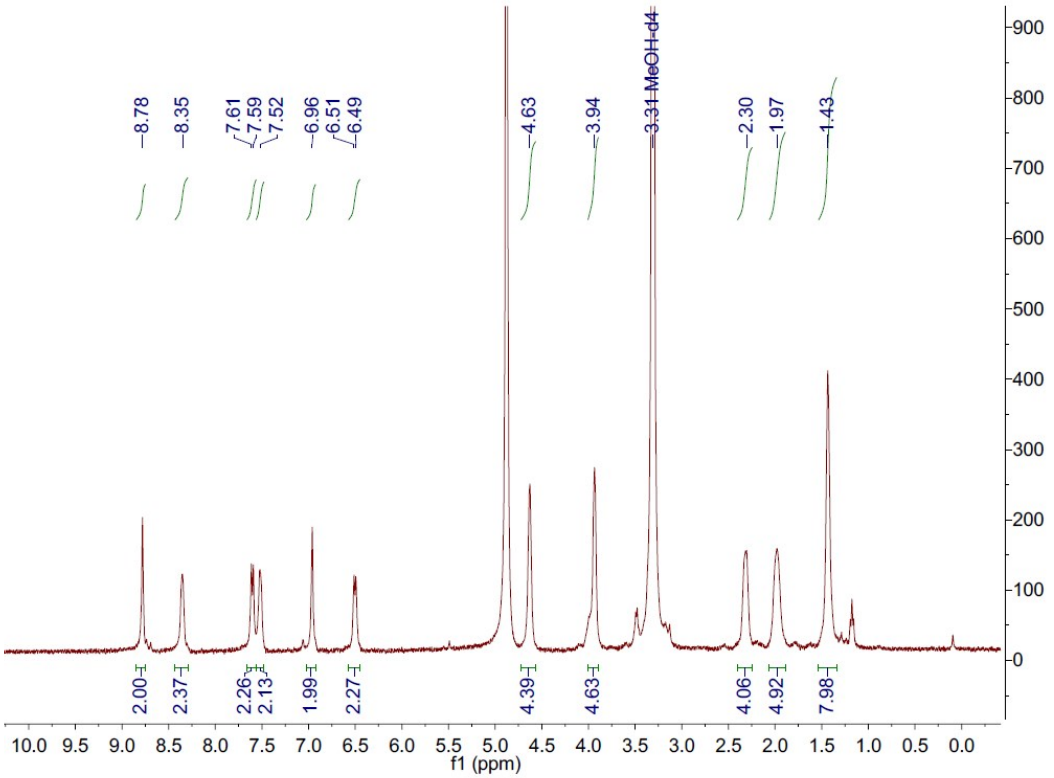


Complex 3c: L = pyrrolidine

^{1}H NMR



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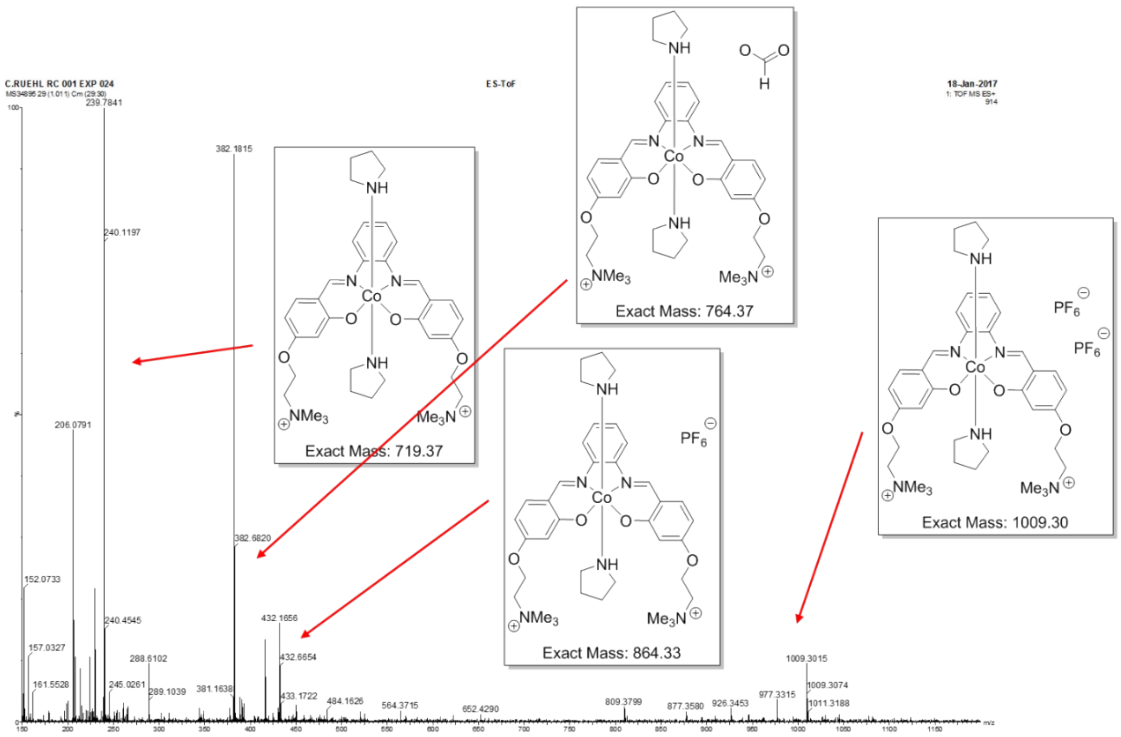
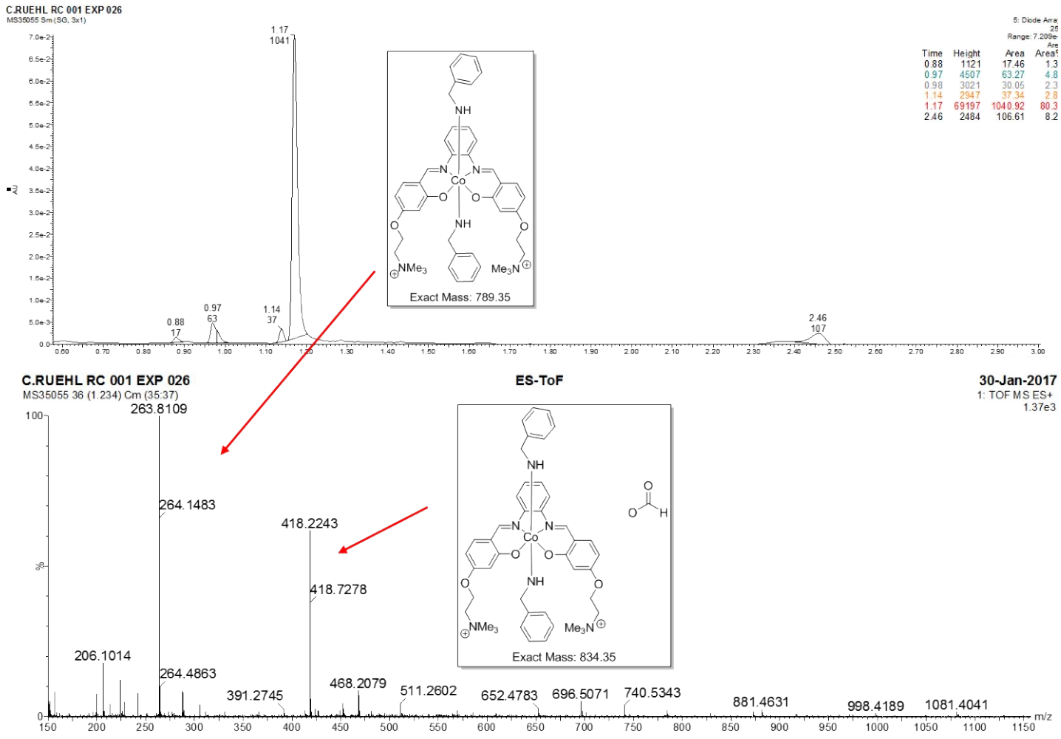


Complex 3e: L = benzylamine

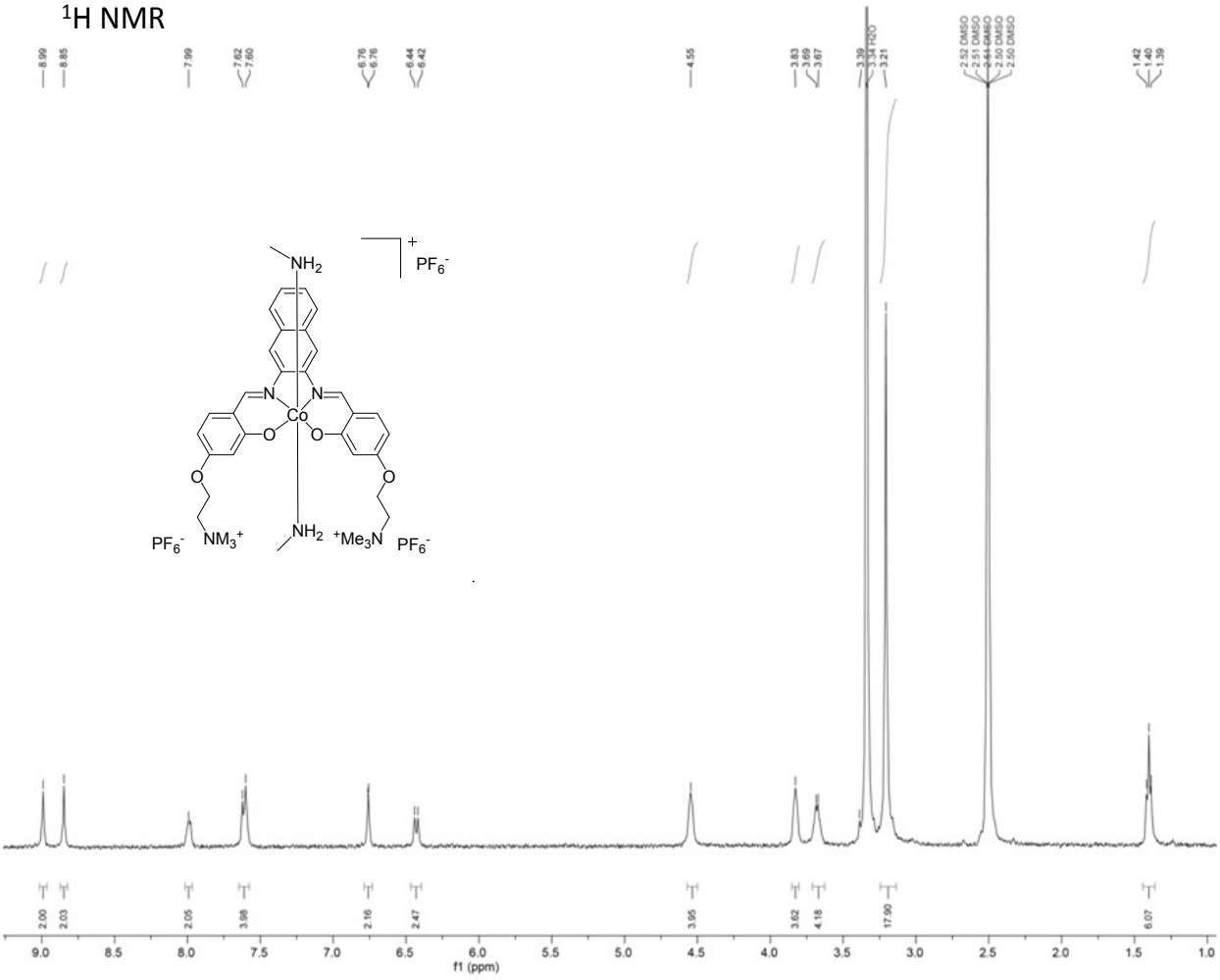
^{1}H NMR

ES(MS$^+$)



Complex 4a: L = methylamine

^{1}H NMR



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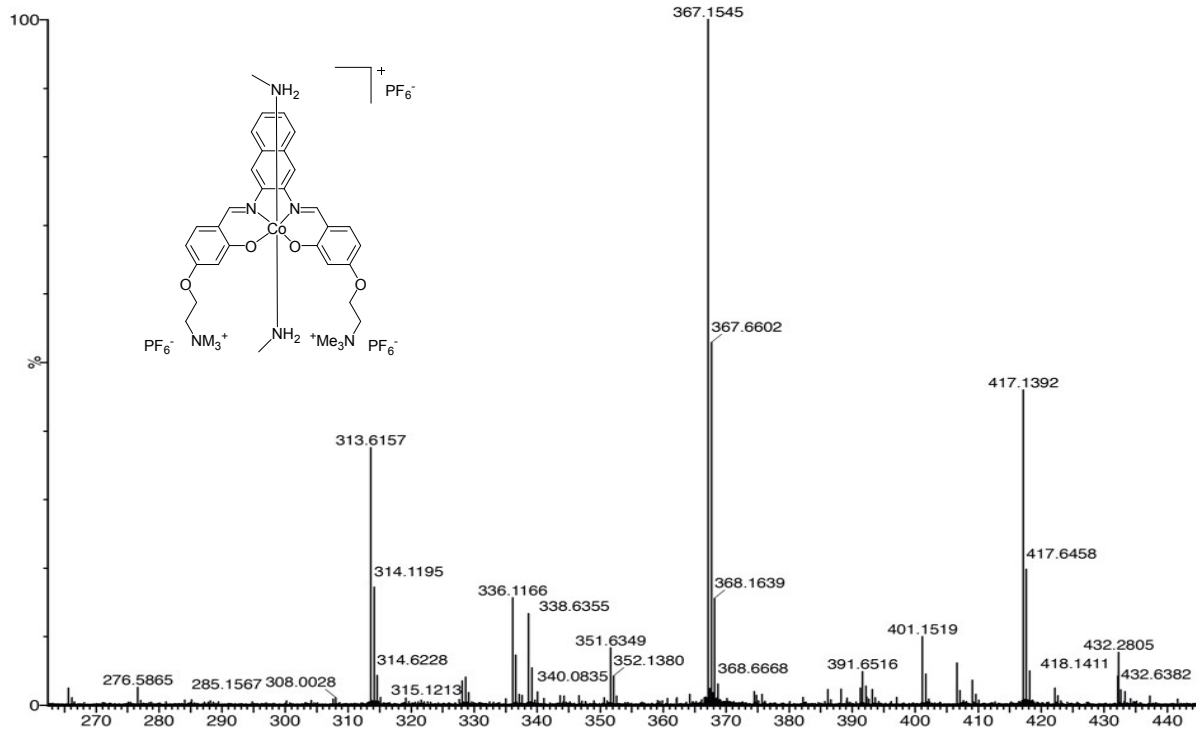
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314.1195
368.1639
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338.6355
401.1519
351.6349
352.1380
432.2805
314.6228
340.0835
368.6668
391.6516
418.1411
276.5865
285.1567
308.0028
315.1213
432.6382
270
280
290
300
310
320
330
340
350
360
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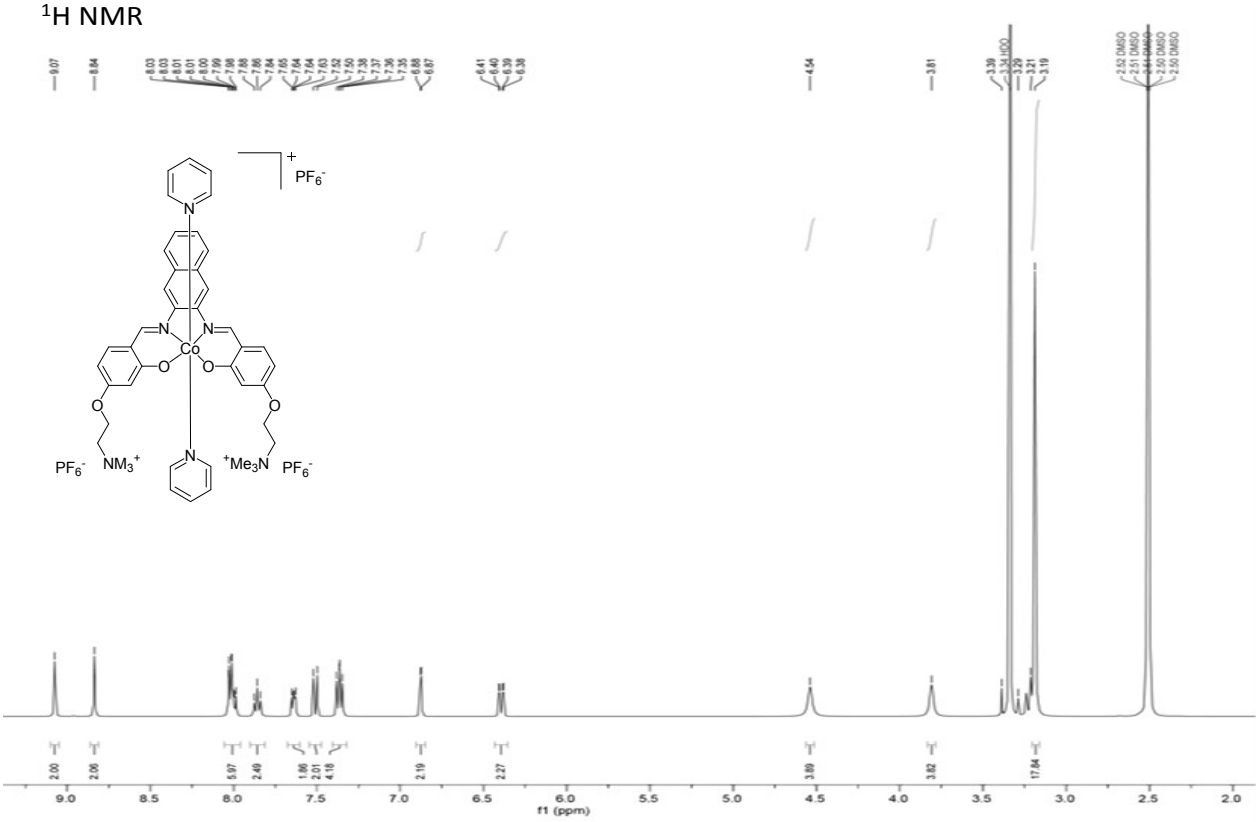
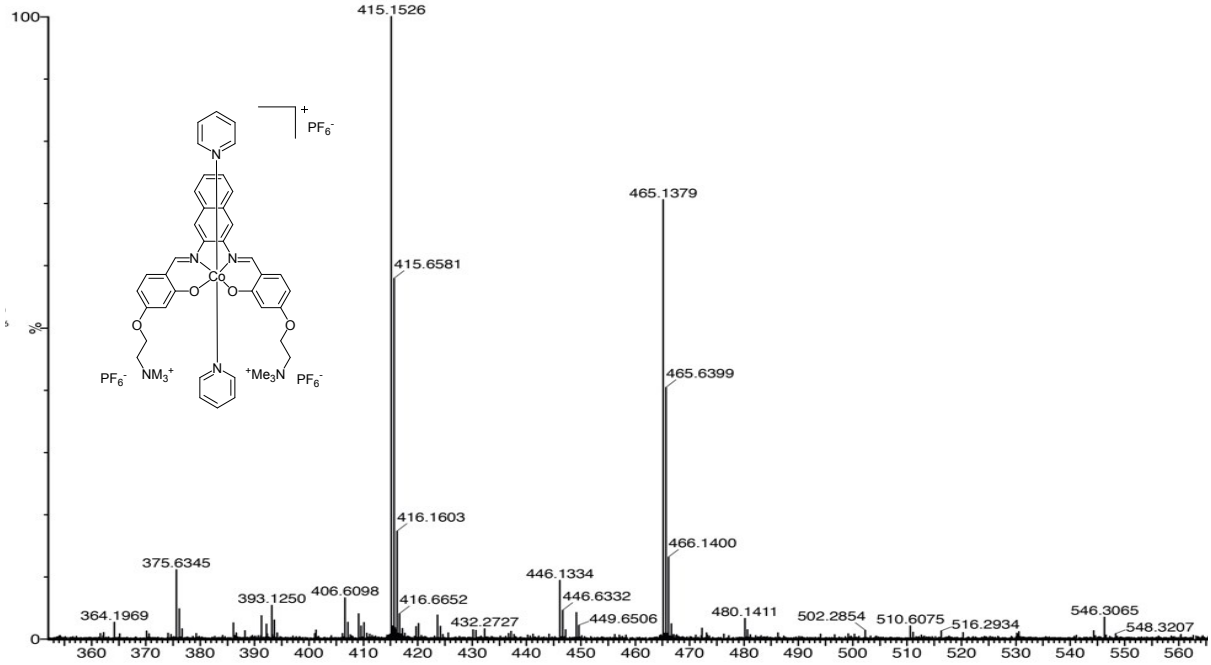
400
410
420
430
440

Complex 4b: L = pyridine

^{1}H NMR

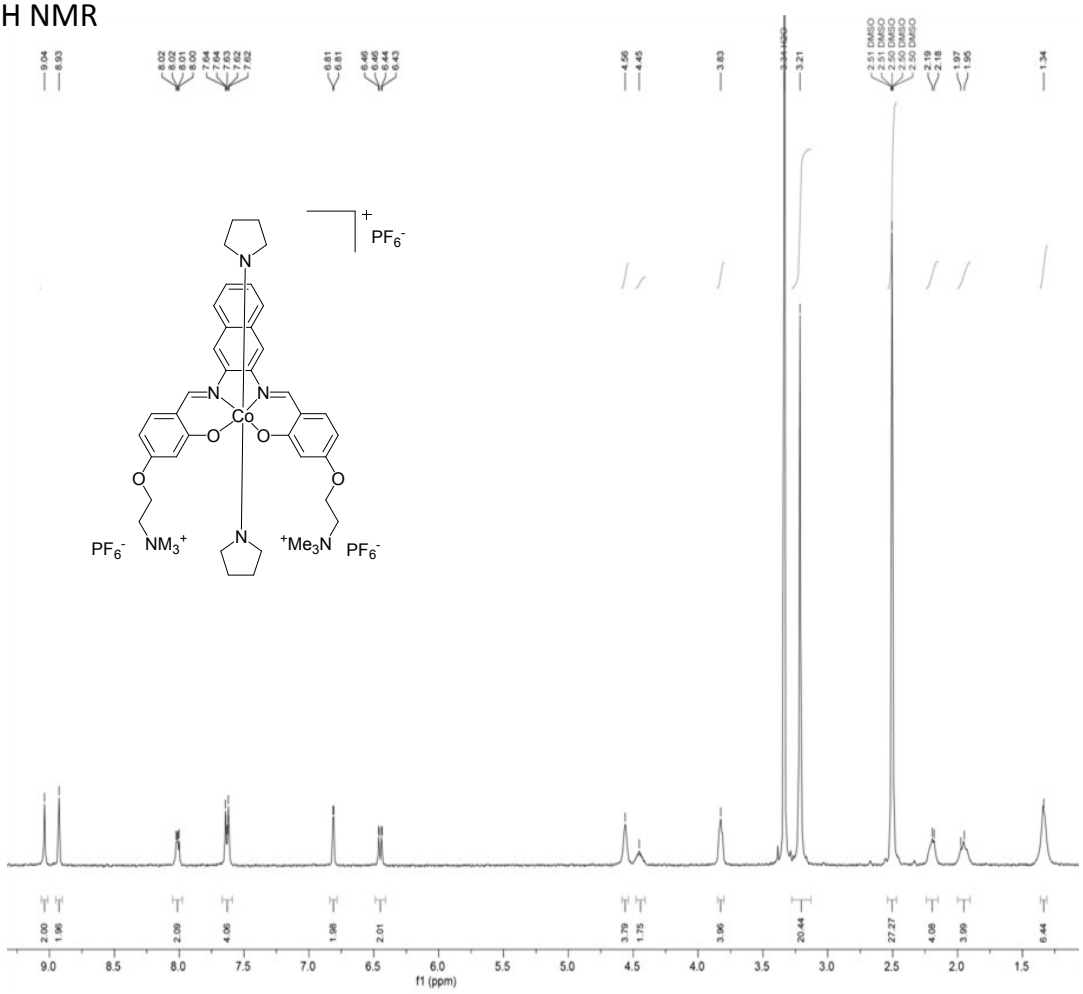


ESI(+)-MS



Complex 4c: L = pyrrolidine

^{1}H NMR



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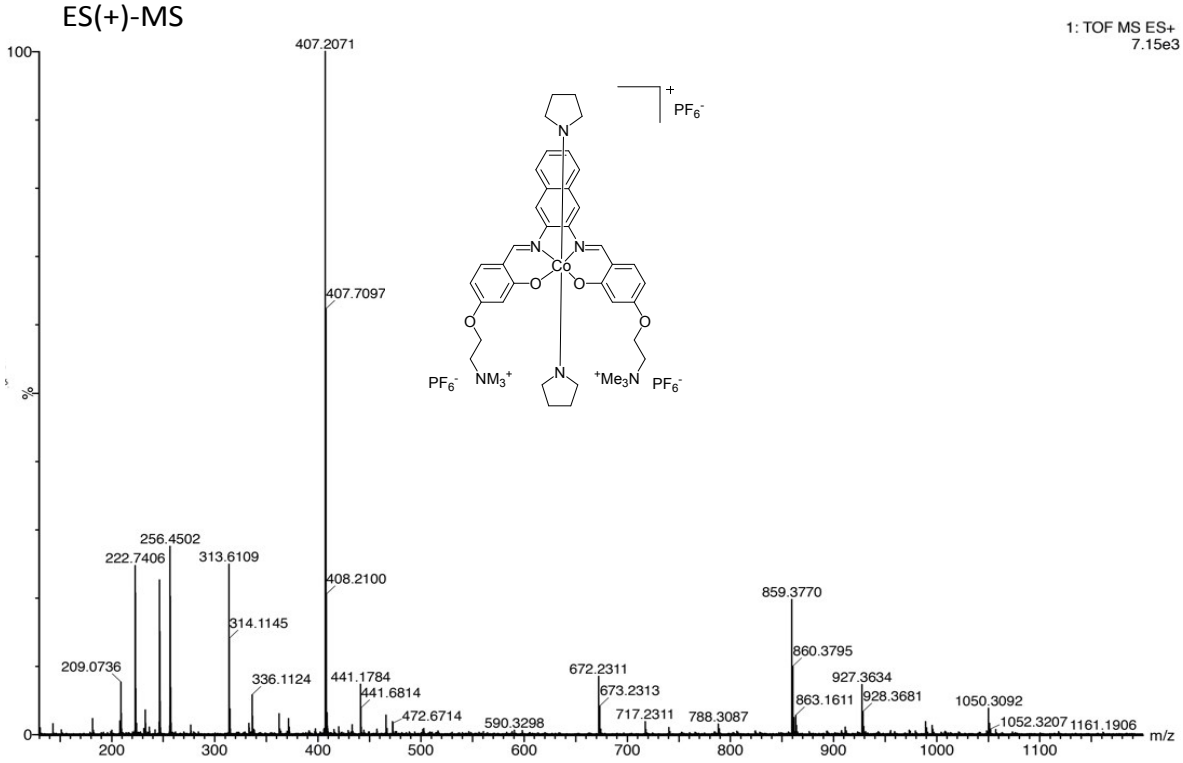
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m/z
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300
400
500
600
700
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900
1000
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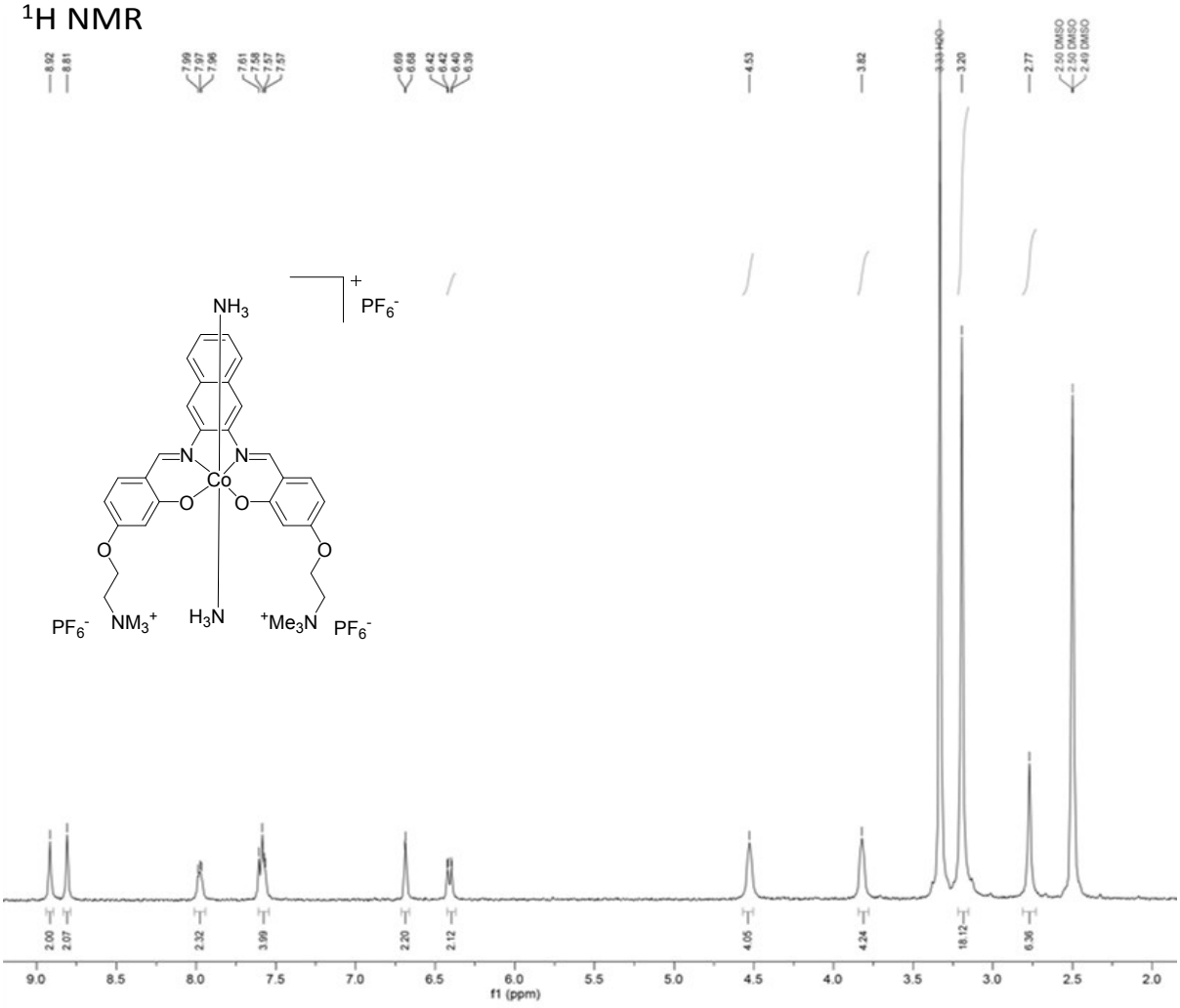
PF6-
PF6-

Complex 4d: L = ammonia

^{1}H NMR



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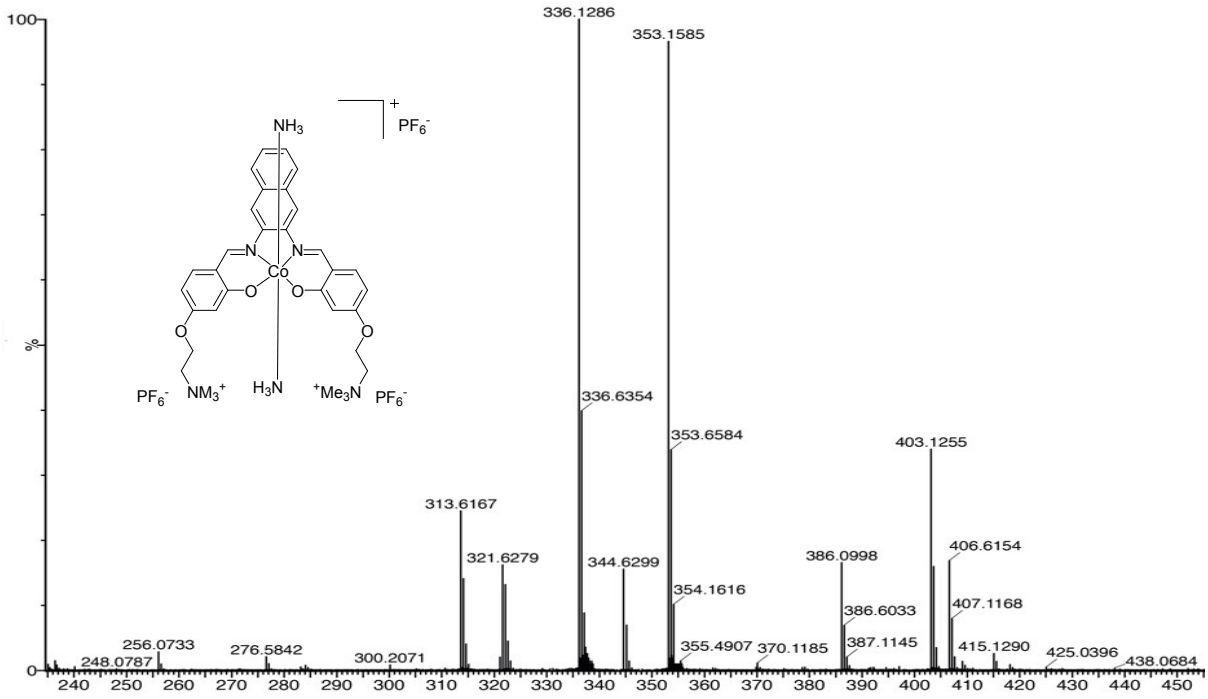
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276.5842
300.2071
240 250 260 270 280 290 300 310 320 330 340 350 360 370 380 390 400 410 420 430 440 450
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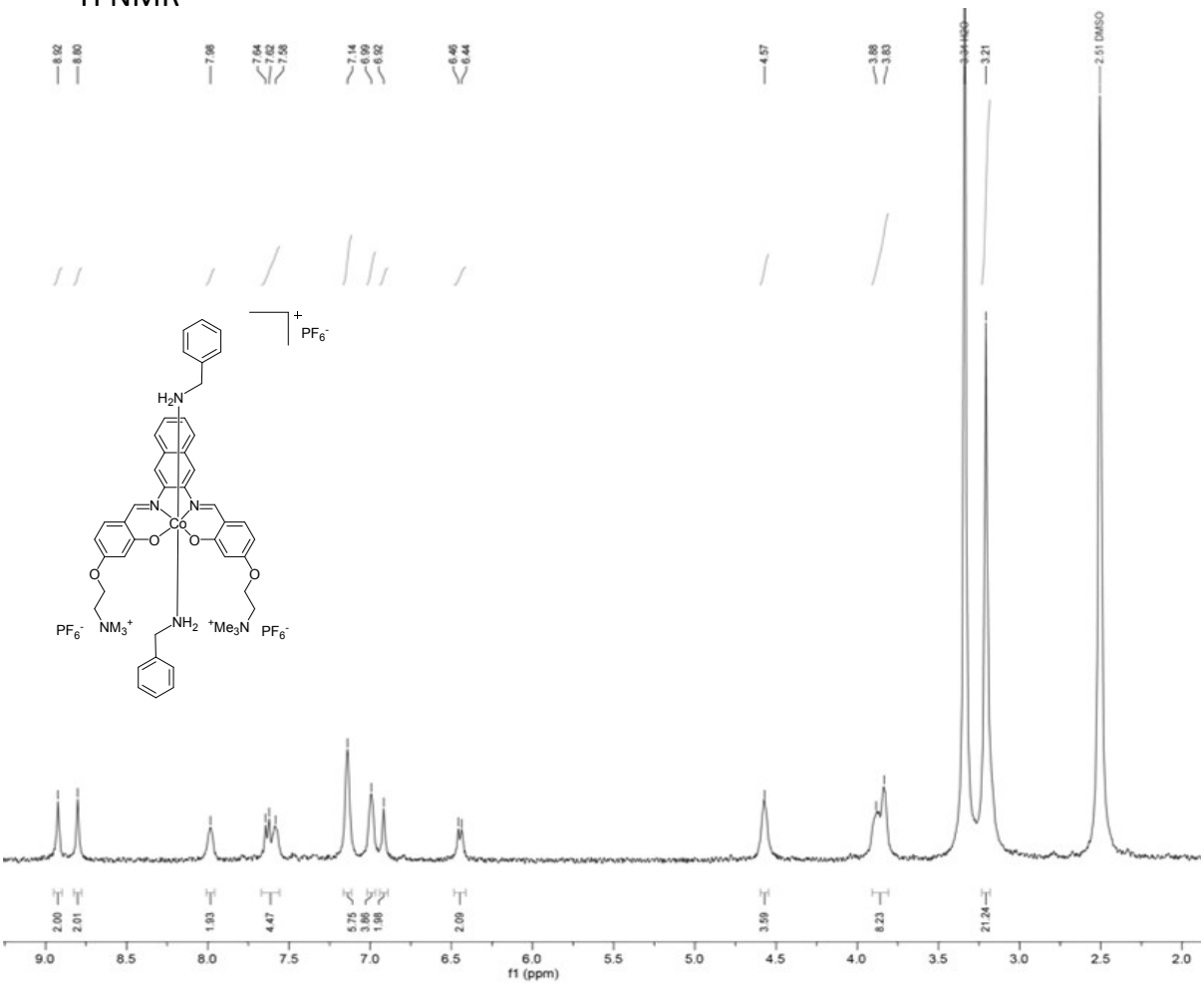
+Me3N

Complex 4e: L = benzylamine

^{1}H NMR



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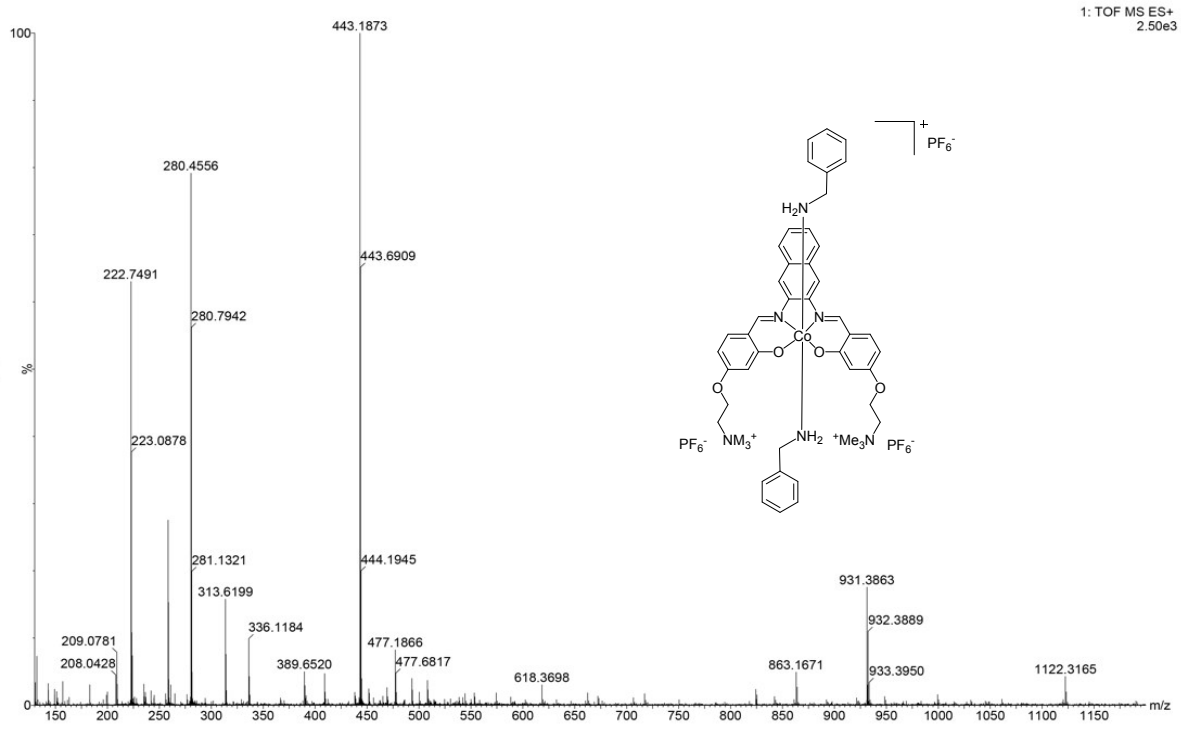
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m/z
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N
N
Co
O
O
O
O
PF6-
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+Me3N
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