**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 ($L = \text{NH}_3$). Disappearance of the -OH (H$_2$O) 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$_2$O: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 salphen 3a-3e (top) and cobalt salnaph 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.

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). 1H 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 Et2O (3 x 5 mL) to give the desired product as a yellow solid.

1.1.1 Salphen Ligand:

Yellow solid, 739.9 mg, 83%.

1H NMR (400 MHz, DMSO-d6) δ 3.19 (s, 18H, NMe3), 3.80-3.82 (m, 4H, -CH2N-), 4.53-4.55 (m, 4H, -OCH2-), 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); 13C NMR (400 MHz, DMSO-d6) 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 C30H40BrN4O4+ (M+): 599.22; found: 599.22.

1.1.2 Salnaph Ligand:

Bright yellow solid, 770.7 mg, 80%.

1H NMR (400 MHz, DMSO-d6) δ 13.52 (s, 2H, -OH), 9.02 (s, 2H, -N=CH-), 7.97 – 7.90 (m, 4H, Ar-H), 7.68 – 7.60 (m, 4H, 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, -OCH2-), 3.85 (t, J = 4.8 Hz, 4H, -CH2-NMe3), 3.22 (s, 18H, -(CH3)3); 13C NMR (400 MHz, DMSO-d6) 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 = C34H46BrN4O42+.

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 N₂ for 30 min. K₂PtCl₄ (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 N₂ 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 H₂O (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. C₃₀H₃₅N₂O₄PtBr₂ requires C, 41.25; H, 4.38; N, 6.41%; ¹H NMR (400 MHz, 50% DMSO-d₆, 50% D₂O): δ 3.11 (s, 18H, -(CH₃)₃), 3.71 (t, 3J_HH = 4 Hz, 4H, -(CH₂)₃), 4.36 (br s, 4H, -(CH₂)), 6.43 – 6.37 (m, 2H, ArH), 7.21 – 7.10 (m, 2H, ArH), 7.45 (p, 3J_HH = 8 Hz, 2H, ArH), 7.09 – 7.01 (m, 2H, ArH), 8.63 (s, 2H, -CH=N-); MS (ES⁺) m/z 758.31 ([M-2Br + HCOO⁺]⁺, 100%).

where M = C₃₀H₃₅N₂O₄PtBr₂.

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 h in air. NH₄PF₆ (> 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. C₄₅H₃₂CoF₁₈N₂O₄P₃ requires C, 39.81; H, 4.34; N, 6.96%; ¹H NMR (400 MHz, MeOD-d₆) δ 3.29 (s, 18H, NMe₃), 3.91 (s, 4H, -CH₂N-), 4.60 (m, 4H, -OCH₂-), 6.42 (2H, ArH), 6.95 (2H, ArH), 7.30 (4H, ArH), 7.48 (4H, ArH), 7.81 (2H, ArH), 8.10 (4H, ArH), 8.24 (2H, ArH), 8.75 (2H, -CH=N-); ¹³C NMR (400 MHz, MeOD-d₆) δ 54.7, 63.3, 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 C₅₁H₄₀CoF₁₈N₂O₄P (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. C₃₈H₃₀Br₂CoF₆N₂O₄P requires C, 42.31; H, 5.79; N, 7.79%; ¹H NMR (400 MHz, MeOD-d₆) δ 1.43 (8H, CH₂-pyr), 1.97 (4H, CH₂-pyr), 2.30 (4H, CH₂-pyr), 3.29 (18H, NMe₃), 3.94 (4H, -CH₂N-), 4.63 (m, 4H, -OCH₂-), 6.50 (2H, J = 8.0 Hz, ArH), 6.96 (2H, ArH), 7.52 (2H, ArH), 7.60 (2H, J = 8.0 Hz, ArH), 8.35 (2H, -CH=N-); ¹³C NMR (400 MHz, DMSO-d₆) 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 C₃₈H₃₀CoF₁₆N₂O₄P₂⁺ (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. C₄₄H₃₆Br₂CoF₁₂N₂O₄P₂ requires C, 44.20; H, 4.89; N, 7.03%; ¹H NMR (400 MHz, MeOD-d₆) δ 3.08 (s, 4H, CH₂-bzten), 3.29 (18H, NMe₃), 3.92 (4H, -CH₂N-), 4.65 (m, 4H, -OCH₂-), 6.53 (2H, J = 8.0 Hz, ArH), 6.92 (2H, ArH), 7.03 (2H, ArH), 7.14 (2H, ArH), 7.47 (2H, ArH), 7.56 (s, J = 8.0 Hz, 2H, ArH), 8.20 (2H, ArH), 8.63 (2H, -CH=N-); ¹³C NMR (400 MHz, MeOD-d₆) 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 C₄₁H₄₈CoF₁₂N₂O₄P (M⁺): 417.22; found: 417.18.
4a: L = methyamine
Yellow-orange solid, 74 mg, 96%. 
Elem. Anal. Found: C, 36.6; H, 4.39; N, 7.48. C$_{39}$H$_{59}$CoN$_{9}$O$_{4}$P$_{2}$F$_{18}$·3H$_{2}$O 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), 4.56 (br, 4H, -O-CH$_2$-), 3.83 (br, 4H, -CH$_2$-NMe$_3$), 3.71–3.65 (m, 4H, -NH$_2$CH$_3$), 3.21 (s, 18H, -(CH$_3$)$_3$). 1.40 (t, J = 6.4 Hz, 6H, -NH$_2$CH$_3$); MS (ES$^+$) m/z 417.1392 ([M+PF$_6$+2H]$^{2+}$, 45%), 367.1545 ([M+2Na]$^{2+}$, 100%), where $M$ = C$_{39}$H$_{59}$CoN$_{9}$O$_{4}$P$_{2}$.$^3$$^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$_{9}$O$_{4}$P$_{2}$F$_{18}$·3H$_{2}$O 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$_2$), 3.85 (s, 2H, -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$_{9}$O$_{4}$.$^3$$^3$.

4c: L = pyrrolidine
Yellow-orange solid, 65 mg, 79%. 
Elem. Anal. Found: C, 41.68; H, 4.75; N, 6.87. C$_{44}$H$_{50}$CoN$_{9}$O$_{4}$P$_{2}$F$_{18}$ 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), 6.46 (dd, J = 8.8 Hz, 2.4 Hz, 2H, Ar-H), 4.56 (s, 4H, -O-CH$_2$), 4.45 (s, 4H, -NH$_2$), 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$_{44}$H$_{50}$CoN$_{9}$O$_{4}$.$^3$$^3$.

4d: L = ammonia
Yellow-orange solid, 56 mg, 75%. 
Elem. Anal. Found: C, 37.12; H, 4.18; N, 7.56. C$_{44}$H$_{50}$CoN$_{9}$O$_{4}$P$_{2}$F$_{18}$ 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$_2$); MS (ES$^+$) m/z 403.1255 ([M+PF$_6$+2H]$^{2+}$, 35%), 353.1585 ([M+2Na]$^{2+}$, 100%), where $M$ = C$_{44}$H$_{50}$CoN$_{9}$O$_{4}$.$^3$$^3$.

4e: L = benzylamine
Brown solid, 81 mg, 92%. 
Elem. Anal. Found: C, 44.58; H, 4.58; N, 6.35. C$_{48}$H$_{60}$CoN$_{9}$O$_{4}$P$_{2}$F$_{18}$·H$_2$O 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-), 8.00 (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$_{60}$CoN$_{9}$O$_{4}$.$^3$$^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$_2$O: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) NH₄OH to remove any preformed aggregates following reported protocols.[3] Briefly, 1 mg of lyophilised peptide was dissolved in 200 μL of NH₄OH, incubated at 25 °C for 10 mins, sonicated for 5 mins and then aliquoted. The NH₄OH 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: DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVIA
Aβ1-28: DAEFRHDSGYEVHHQKLVFFAEDVGSNK
H6R Aβ1-28: DAEFRHDRDSGYEVHHQKLVFAEDVGSNK
Aβ1-16: DAEFRHDRDSGYEVHHQK

4. End-point Thioflavin-T Assay

Complexes were dissolved in DMSO:PBS (1x PBS: 137 mM NaCl, 2.7 mM KCl, 4.3 mM Na₂HPO₄ and 1.47 mM KH₂PO₄) 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 \(\left(1 - \frac{X - F_{\text{ThT alone}}}{F_{\text{ThT fibrils}} - F_{\text{ThT alone}}}\right) \times 100\). 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 °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 °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 (λmax) 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. 1H NMR Spectroscopy of Aβ

1H 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 D2O: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). 1H 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$_2$O:phosphate buffer (1:9, pH 7.4) at 37 °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.](image)

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

All animal studies were conducted according to UK Home Office regulations and institutional guidelines. 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% O₂ / 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). 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

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

Salnaph Ligand
$^{13}$C NMR

![Chemical structure](image)
Complex 2

$^1$H NMR

ES( MS$^+$ )
Complex 3b: $L = \text{pyridine}$

$^1H\text{ NMR}$

$\text{ES(MS}^+\text{)}$
Complex 3c: L = pyrrolidine

$^1$H NMR

ES(MS$^+$)
Complex 3e: L = benzylamine

$^1$H NMR

ES(MS$^+$)
Complex 4a: L = methylamine

$^{1}$H NMR

[Diagram of the complex with labels for NH$_3$, Me$_3$N, PF$_6^-$]
ES(\text{+})-MS
Complex 4b: $L = \text{pyridine}$
Complex 4c: $L = \text{pyrrolidine}$

$^1$H NMR

[Diagram of the complex with labeled peaks]
ES(+) - MS

\[
\begin{align*}
\text{Me}_3\text{NM}_3 + \text{Me}_3\text{NM}_3 \\
\text{Co} & \text{NH} \quad \text{PF}_6^- \\
\end{align*}
\]
Complex 4d: $L = \text{ammonia}$

$^1H$ NMR
Complex 4e: L = benzylamine

$^1$H NMR
ES(+)•MS

1. TOP MS ES+
2. 30e4