Electronic Supplementary Information (ESI)

Rhenium(I) complexes of *N*-heterocyclic carbene ligands that bind to amyloid plaques of Alzheimer's disease

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Experimental details

General procedures: All reagents were purchased from Sigma Aldrich or Alfa Aesar and were used without further purification unless otherwise stated. All manipulations were performed under nitrogen unless otherwise stated. NMR spectra were recorded on either a Bruker Avance ARX-300 (300.14 MHz for ^{1}H, 75.48 MHz for ^{13}C), a Bruker Avance ARX-400 (400.13 MHz for ^{1}H, 100.61 MHz for ^{13}C), or a Bruker Avance ARX-500 (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C) spectrometer and were internally referenced to solvent resonances. Mass spectra were obtained using a Bruker Esquire6000 mass spectrometer fitted with an Agilent electrospray ion (ESI) source. UV−visible spectra were recorded using an Agilent Technologies Cary 300 UV−visible spectrophotometer using quartz cuvettes (1 cm). Fluorescence spectra were recorded on a Varian Cary Eclipse spectrofluorimeter (5 nm bandpass, 1 nm data interval, PMT voltage: 600 V) using quartz cuvettes (1 cm). Microanalyses were performed by the Campbell Microanalytical Laboratory, Department of Chemistry, The University of Otago, New Zealand.

Reverse Phase High Performance Liquid Chromatography (HPLC). RP-HPLC analyses and purifications were performed using a Shimadzu HPLC fitted with two Shimadzu LC-20AD pumps, a SIL-20AHT autosampler, a SPD-M20A photodiode array detector and a FRC-10A fraction collector. For all HPLC methods chromatograms were obtained by monitoring absorbance at 258 nm. Elution was carried out as follows: *Method 1*: Alltima C18 semi-preparative column (22 × 250 mm), flow rate of 3 mL min^{-1}, mobile phase: (A) 0.1% trifluoroacetic acid (TFA) in water and (B) 0.1% TFA in methanol. Gradient elution: 30% (B) 0 – 1 min, 30-80% (B) 1 – 5 min, 80-90% (B) 5 – 10 min, 90 – 30% (B) 10 – 12 min and stop at 16 min. *Method 2*: Atlantis T3 DC_{18} analytical column (4.6 × 150 mm), flow rate of 1 mL min^{-1}, mobile phase: (A) 0.1% trifluoroacetic acid (TFA) in water and (B) 0.1% TFA in methanol. Gradient elution: 30% (B) 0 – 1 min, 30-90% (B) 1 – 5 min, 90% (B) 5 – 10 min, 90 – 30% (B) 10 – 12 min, stop at 16 min.

Preparation of Aβ(1-42) peptide stock solution:

AB_{1-42} was synthesized using solid phase peptide synthesizer (liberty peptide synthesiser, Biostage) using Fmoc chemistry on a 0.1 mM scale. Synthetic peptide was dissolved in HFIP (1 mg per 221.7 µL HFIP) and was allowed to evaporate overnight followed by drying by high speed vacuum centrifugation to remove residual HFIP and moisture then stored at -80^{o}C. For a 1 mg/mL stock solution, the HFIP treated peptide was dissolved in 2 parts of 60 mM NaOH and incubated for 3 min at room temperature. To this solution 7 parts of de-ionized water was added and vortex briefly followed by ultrasoniacation for 5 minutes on ice. Added 1part of 10x PBS, vortex briefly and centrifuged for 5 min.

Supernatant was transfered to a fresh tube and kept on ice. The initial concentration of the Aβ(1-42) solution (Day 0) was determined by its absorbance at 214 nm (ε = 75 887 M^{-1} cm^{-1}).

ThT Fluorescence Aβ binding Assays. Stock solutions of ThT (1 mM in PBS), conjugated Re(I) complexes (**7a**·PF_6, **8a**·PF_6, **15**·PF_6 or **16**·PF_6) (1 mM in DMSO) and Aβ(1-42) peptide (100 μM) were used for the ThT fluorescence assays. All samples were prepared on ice, by mixing Aβ(1-42) (final concentration: 10 μM), ThT (final concentration: 40 μM) and the chosen Re(I) complex (final concentration: 20 μM), and the control consisting of Aβ (1-42) (final concentration: 10 μM) and ThT (final concentration: 40 μM). All samples were made up to the final volume to 350 μL using PBS solution having 2% DMSO in each well. The ThT fluorescence intensity of each sample was recorded every 12.5 min at 37 ^oC using an OPTIMA fluorescent plate reader with 440/490 nm excitation/emission filters over a period of 51 h.

Staining of Human AD Brain Tissues.[1] The Health Sciences Human Ethics Sub-committee, The University of Melbourne, approved all experiments using human brain tissue (Ethics Approval No. 1341145). Brain tissue was collected at autopsy. Brain tissue from the frontal cortex was preserved by formalin fixation and paraffin embedding. AD pathology was confirmed according to standard National Institute of Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease (1997) criteria. The brain tissue samples of age-matched Human controls (HC) were subject to the above criteria. The AD and HC brain tissue sections (7 μm) were first deparaffined (xylene, 3 × 2 min) followed by rehydration (soaking for 2 min in a series of 100%, 90%, 70%, and 0% v/v ethanol/water). The hydrated tissue sections were washed in phosphate buffer saline (PBS, 5 min). Autofluorescence of the tissue was quenched using potassium permanganate ($KMnO_4$) (0.25% in PBS, 20 min) and the sections were further washed with PBS (2 × 2 min) to remove the excess $KMnO_4$. The brown-coloured sections were washed with potassium metabisulfite and oxalic acid (1% in PBS) until the brown colour was removed followed by washing with PBS (3 × 2 min). The sections were blocked with bovine serum albumin (2% BSA in PBS, pH 7.0, 10 min) and covered with a solution of the chosen Re(I) complex (50 μM in 15% v/v DMSO/PBS, 60 min). The sections were treated with BSA again (4 min) to remove any Re(I) complex non-specifically bound to the tissue. Finally, the sections were washed with PBS (3 × 2 min), DI water, and mounted with non-fluorescent mounting media (Dako). Fluorescence images were visualized using a Leica (Bannockburn, IL) DM1RB microscope.

X-ray Crystallography

Data Collection:

Single crystals suitable for X-ray diffraction were obtained as follows: **15**·PF_6, **16**·PF_6 and **17**·PF_6: diffusion of vapors between diethyl ester and solutions of the title compounds in a mixture of methanol and acetone. Crystallographic data for all structures determined are given in Tables S1. For all samples, crystals were removed from the crystallization vial and immediately coated with paratone oil on a glass slide. A suitable crystal was mounted in Paratone oil on a glass fiber and cooled rapidly to 173 K in a stream of cold N_2 using an Oxford low temperature device. Diffraction data were measured using an Oxford Gemini diffractometer mounted with Mo-Kα λ = 0.71073 Å and Cu-Kα λ = 1.54184 Å. Data were reduced and corrected for absorption using the CrysAlis Pro program.[2] The SHELXL2013-2[3] program was used to solve the structures with Direct Methods, with refinement by the Full-Matrix Least-Squares refinement techniques on F^2. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed geometrically and refined using the riding model. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. All calculations were carried out using the program Olex2.[4] Images were generated by using ORTEP-3.[5] Further XRD details are provided in the ESI. CCDC 1498857-1498859 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Data Refinement Details:

15·PF_6: Solved in the triclinic space group *P*-1. The asymmetric unit contains one molecule of the title compound, a PF_6^- counter ion and a co-crystallized molecule of acetone. Disorder was identified in the positions of the fluorine atoms of the PF_6^- counter ion, with each of the disordered atoms occupying two crystallographically independent positions that could be located from the additional residual electron density. Refinement of the site occupancy factors for the disordered atoms gave the values of 0.80 and 0.20 respectively.

16·PF_6: Solved in the triclinic space group *P*-1. The asymmetric unit contains one molecule of the title compound and a PF_6^- counter ion. Disorder was identified in the positions of one of the ethylene linker groups between the NHC and amine units, with each of the disordered atoms occupying two crystallographically independent positions that could be located from the additional residual electron density. Refinement of the site occupancy factors for the disordered atoms gave the values of 0.85 and 0.15 respectively.

17·PF_6: Solved in the monoclinic space group $P2_1/c$. The asymmetric unit contains one molecule of the title compound, a PF_6^- counter ion and a co-crystallized molecule of acetone. Disorder was identified in the positions of each of the ethylene linker groups between the NHC and amine units, with each of the disordered atoms occupying two crystallographically independent positions that could be located from the additional residual electron density. Refinement of the site occupancy factors for the disordered atoms gave the values 0.64 and 0.36 and 0.78 and 0.22 for each of the ethylene linker groups respectively. CheckCIF report alerts: (1) Short Intra H...H Contact H13B .. H12C .. 1.29 Ang. Response - this intramollecular H···H contact results from the significant levels of dissorder associated with the ethylene linker groups (2) ADDSYM Detects New (Pseudo) Symm. Elem. A 94 % fit. Response – analysis with ADDSYM and CALC NEWSYM in PLATON suggests that $P2_1/c$ is the space group for this structure.

Table S1. Refinement data

	15·PF_6	**16**·PF_6	**17**·PF_6
Empirical formula	$C_{36}H_{41}F_6N_7O_5PRe$	$C_{32}H_{32}F_6N_8O_4PReS$	$C_{21}H_{27}F_6N_5O_6PRe$
Formula weight	982.93	955.88	776.64
Temperature/K	173	150	173
Crystal system	triclinic	triclinic	monoclinic
Space group	*P*-1	*P*-1	$P2_1/c$
a/Å	11.3606(5)	8.7659(3)	10.2779(4)
b/Å	12.7288(4)	12.9987(7)	8.9789(3)
c/Å	14.7762(6)	16.3263(11)	28.8091(10)
α/°	108.108(3)	68.155(6)	90
β/°	103.558(4)	76.597(4)	94.652(4)
γ/°	100.145(3)	81.414(4)	90
Volume/$Å^3$	1901.26(13)	1675.61(17)	2649.86(17)
Z	2	2	4
$\rho_{calc}g/cm^3$	1.717	1.895	1.947
μ/mm^{-1}	3.32	3.823	4.735
F(000)	980	944	1520
Crystal size/mm^3	0.8 × 0.4 × 0.12	0.1 × 0.03 × 0.03	0.12 × 0.1 × 0.07
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.586 to 49.424	5.956 to 52.744	5.676 to 52.744
Index ranges	$-13 \le h \le 12$, $-14 \le k \le 14$, $-17 \le l \le 14$	$-10 \le h \le 10$, $-16 \le k \le 16$, $-20 \le l \le 16$	$-11 \le h \le 12$, $-11 \le k \le 11$, $-36 \le l \le 32$
Reflections collected	16341	15862	17197
Independent reflections	6461 [R_{int} = 0.0293, R_{sigma} = 0.0367]	6840 [R_{int} = 0.0301, R_{sigma} = 0.0406]	5403 [R_{int} = 0.0241, R_{sigma} = 0.0254]
Data/restraints/parameters	6461/0/509	6840/4/484	5403/12/379
Goodness-of-fit on F^2	1.035	1.043	1.132
Final R indexes [I>=2σ (I)]	R_1 = 0.0267, wR_2 = 0.0623	R_1 = 0.0264, wR_2 = 0.0622	R_1 = 0.0259, wR_2 = 0.0574
Final R indexes [all data]	R_1 = 0.0302, wR_2 = 0.0647	R_1 = 0.0302, wR_2 = 0.0644	R_1 = 0.0293, wR_2 = 0.0587
Largest diff. peak/hole / e $Å^{-3}$	1.51/-0.71	1.30/-0.81	0.79/-0.69

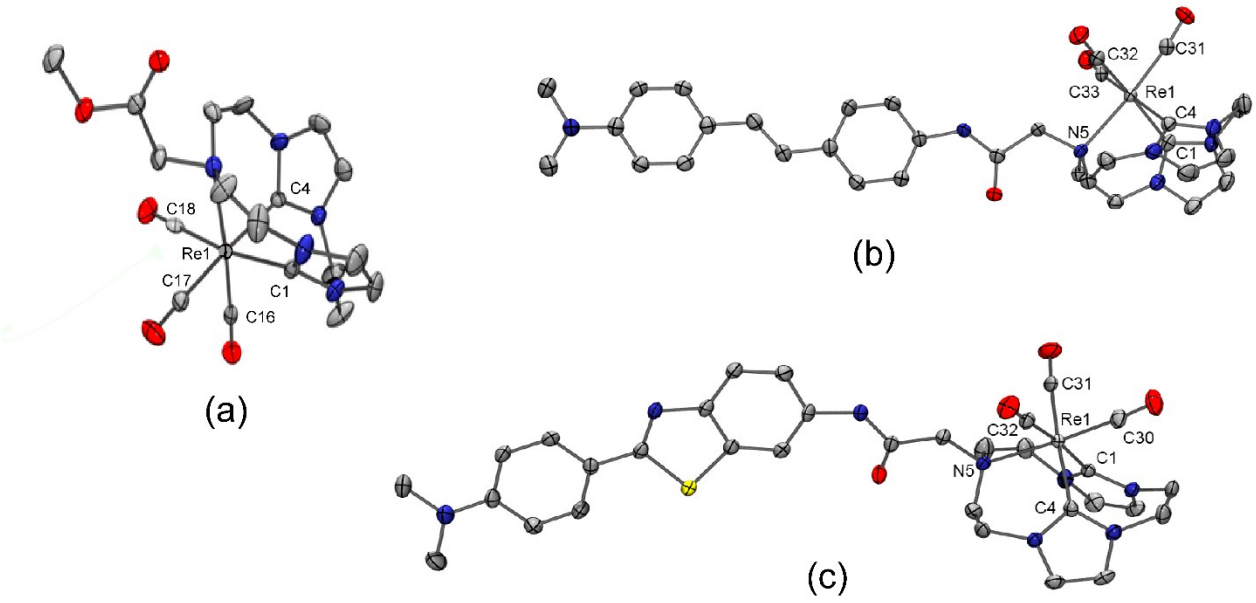
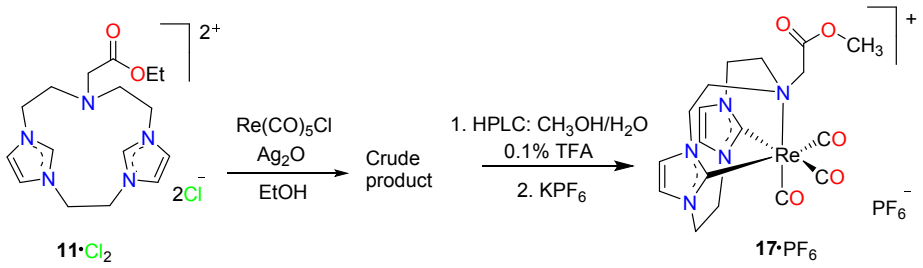
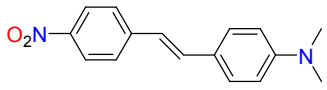


Figure S1. ORTEP-3[5] structures of (a) **17**$^+$ and alternative views of cationic complexes **15**$^+$ (b) and **16**$^+$ (b) (PF_6^- counter ions, hydrogen atoms and a co-crystallized solvent molecule omitted for clarity). Ellipsoids are shown 50% probability. Selected bond lengths: **17**$^+$: Re1-C1 = 2.159(4) Å, Re1-C4 = 2.152(4) Å, Re1-N5 = 2.369(3) Å, Re1-C16 = 1.894(4) Å, Re1-C17 = 1.943(4) Å, Re1-C18 = 1.957(4) Å; **15**$^+$: Re1-N5 = 2.351(3)Å, Re1-C1 = 2.182(3) Å, Re1-C4 = 2.126(3) Å, Re1-C31 = 1.907(4) Å, Re1-C32 = 1.958(4) Å, Re1-C33 = 1.941(3) Å; **16**$^+$: Re1-N5 = 2.341(3) Å, Re1-C1 = 2.156(3) Å, Re1-C30 = 1.896(4) Å, Re1-C32 = 1.935(3) Å, Re1-C31 = 1.948(4) Å, Re1-C4 = 2.146(3) Å.



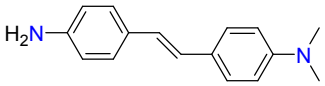
Scheme S1. Synthesis of complex **17**·PF_6.

Synthesis

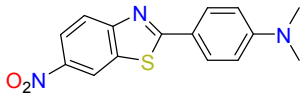


(*E*)-N,N-dimethyl-4-(4-nitrostyryl)aniline: This compound was prepared according to a literature procedure[6] from *p*-nitro-phenylacetic acid (5.46 g, 30.15 mmol), *p*-dimethylaminobenzaldehyde (3.00 g, 20.11 mmol) and piperidine (2.55 g, 30.11 mmol). The product was obtained as crystalline red solid. (Yield: 4.75 g, 89%). ^{1}H NMR (400 MHz) ($CDCl_3$): δ (ppm) 8.15 (d, $^3J_{HH}$ = 8.36 Hz, 2H, 2H_{Ar}), 7.54 (d, $^3J_{HH}$ = 8.36 Hz, 2H, 2H_{Ar}), 7.42 (d, $^3J_{HH}$

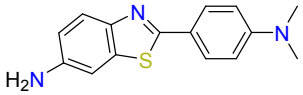
= 8.40 Hz, 2H, 2H_{Ar}), 7.19 (d, $^3J_{HH}$ = 16.00 Hz, 1H, HC=C*H*), 6.90 (d, $^3J_{HH}$ = 16.00 Hz, 1H, *H*C=CH), 6.69 (d, $^3J_{HH}$ = 8.36 Hz, 2H, 2H_{Ar}), 3.00 (s, 6H, 2NCH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) 150.8 C_q, 145.9 C_q, 145.0 C_q, 133.6 HC=*C*H, 128.3 2C_{Ar}, 126.0 2C_{Ar}, 124.3 C_q, 124.1 2C_{Ar}, 121.5 H*C*=CH, 112.1 2C_{Ar}, 40.2 2N*C*H$_3$.



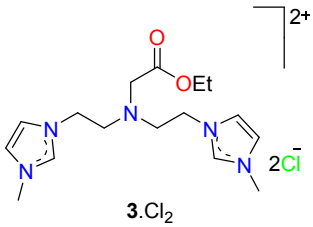
(*E*)-4-(4-aminostyryl)-N,N-dimethylaniline (**I**): This compound was prepared according to a literature procedure[7] from (*E*)-N,N-dimethyl-4-(4-nitrostyryl)aniline (0.40 g, 1.49 mmol) and $SnCl_2.2H_2O$ (1.34 g, 5.95 mmol). The product was obtained as yellow solid. (Yield: 0.30 g, 84%). ^{1}H NMR (400 MHz) ($CDCl_3$): δ (ppm) 7.35 (d, $^3J_{HH}$ = 8.84 Hz, 2H, 2H_{Ar}), 7.28 (d, $^3J_{HH}$ = 8.52 Hz, 2H, 2H_{Ar}), 6.86 (d, $^3J_{HH}$ = 16.32 Hz, 1H, HC=C*H*), 6.81 (d, $^3J_{HH}$ = 16.32 Hz, 1H, *H*C=CH), 6.70 (d, $^3J_{HH}$ = 8.84 Hz, 2H, 2H_{Ar}), 6.64 (d, $^3J_{HH}$ = 8.52 Hz, 2H, 2H_{Ar}), 3.69 (s, 2H, NH_2), 2.95 (s, 6H, 2NCH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) 149.8 C_q, 145.5 C_q, 129.1 C_q, 127.3 2C_{Ar}, 127.2 2C_{Ar}, 126.8 C_q, 125.5 HC=*C*H, 124.8 H*C*=CH, 115.4 2C_{Ar}, 112.8 2C_{Ar}, 40.8 2N*C*H$_3$.



N,N-dimethyl-4-(6-nitrobenzo[*d*]thiazol-2-yl)aniline: This compound was prepared according to a literature procedure[8] from 2-amino-5-nitrothiophenol (1.70 g, 10.00 mmol), *p*-dimethylaminobenzaldehyde (1.49 g, 10.00 mmol) and pyridine (20 mL). The product was obtained as crystalline dark red solid. (Yield: 1.20 g, 39%). ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 9.07 (d, $^4J_{HH}$ = 2.40 Hz, 1H, $H_{benzothi}$), 8.28 (dd, $^3J_{HH}$ = 9.04 Hz, $^4J_{HH}$ = 2.40 Hz, 1H, 1$H_{benzothi}$), 8.04 (d, $^3J_{HH}$ = 9.04 Hz, 1H, $H_{benzothi}$), 7.95 (d, $^3J_{HH}$ = 8.92 Hz, 2H, 2H_{Ar}), 6.84 (d, $^3J_{HH}$ = 8.92 Hz, 2H, 2H_{Ar}), 3.04 (s, 6H, 2NCH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 170.7 C_q, 154.5 C_q, 149.3 C_q, 139.8 C_q, 130.8 C_q, 125.5 2C_{Ar}, 118.2 $C_{benzothi}$, 118.1 $C_{benzothi}$, 115.5 C_q, 115.3 $C_{benzothi}$, 108.1 2C_{Ar}, 39.5 2N*C*H$_3$.



2-(4-(dimethylamino)phenyl)benzo[*d*]thiazol-6-amine (**II**) This compound was prepared according to a literature procedure[7] from N,N-dimethyl-4-(6-nitrobenzo[*d*]thiazol-2-yl)aniline (0.50g, 1.64 mmol) and $SnCl_2.2H_2O$ (1.36 g, 6.00 mmol). The product was obtained as dark yellow solid. (Yield: 0.38 g, 84%). ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 7.74 (d, $^3J_{HH}$ = 9.04 Hz, 2H, 2H_{Ar}), 7.56 (d, $^3J_{HH}$ = 8.68 Hz, 1H, $H_{benzothi}$), 7.03 (d, $^4J_{HH}$ = 2.08 Hz, 1H, $H_{benzothi}$), 6.78 (d, $^3J_{HH}$ = 9.04 Hz, 2H, 2H_{Ar}), 6.71 (dd, $^3J_{HH}$ = 8.68 Hz, $^4J_{HH}$ = 2.08 Hz, 1H, 1$H_{benzothi}$), 5.30 (s, 2H, NH_2), 2.98 (s, 6H, 2NCH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 161.4 C_q, 151.4 C_q, 146.5 C_q, 145.4 C_q, 135.4 C_q, 127.6 2C_{Ar}, 122.2 $C_{benzothi}$, 121.0 C_q, 114.5 $C_{benzothi}$, 111.8 2C_{Ar}, 104.0 $C_{benzothi}$, 39.5 2N*C*H$_3$.



3.Cl_2 This compound was prepared according to a literature procedure[9] from **9** (3.08 g, 13.50 mmol). The isolated crude product was obtained as an oil, which was triturated with acetone (5 × 20 mL). (Yield: 2.96 g, 56%). ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 9.20 (s, 2H, H_{imi}(NC*H*N)), 7.69 (dd, $^3J_{HH}$ = 1.60 Hz, $^4J_{HH}$ = 1.60 Hz, 2H, H_{imi}), 7.66 (dd, $^3J_{HH}$ = 1.60 Hz, $^4J_{HH}$ = 1.60 Hz, 2H, H_{imi}), 4.20 (t, $^3J_{HH}$ = 6.40 Hz, 4H, 2CH_2CH$_2$), 4.08 (q, $^3J_{HH}$ = 7.20 Hz, 2H, OCH_2), 3.85 (s, 6H, imi-CH_3), 3.54 (s, 2H, CH_2CO), 3.06 (t, $^3J_{HH}$ = 6.40 Hz, 4H, 2CH$_2$CH_2), 1.19 (t, $^3J_{HH}$ = 7.20 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 170.8 *C*O, 136.7 2C_{imi} (N*C*HN), 122.9 2C_{imi}, 122.4 2C_{imi}, 60.0 CH$_3$*C*H$_2$, 52.7 2CH$_2$*C*H$_2$ and *C*H$_2$CO 46.5 2*C*H$_2$CH$_2$, 35.7 2imi-*C*H$_3$, 14.0 *C*H$_3$.

4·Cl_3: This compound was prepared according to a literature procedure[9] from **3**·Cl_2 (1.00 g, 2.55 mmol) and 5 M HCl (20 mL). The product was obtained as a hygroscopic white crystalline solid. (Yield: 0.68 g, 67%). ^{1}H NMR (500 MHz) (DMSO-d_6): δ (ppm) 9.31 (s, 2H, 2H_{imi}(NC*H*N)), 7.76 (dd, $^3J_{HH}$ = 1.50 Hz, $^4J_{HH}$ = 1.50 Hz, 2H, H_{imi}), 7.68 (dd, $^3J_{HH}$ = 1.50 Hz, $^4J_{HH}$ = 1.50 Hz, 2H, H_{imi}), 4.26 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2CH_2CH$_2$), 3.85 (s, 6H, 2imi-CH_3), 3.51 (s, 2H, CH_2CO), 3.13 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2CH$_2$CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 172.0 *C*O, 136.9 2C_{imi} (N*C*HN), 122.9 2C_{imi}, 122.4 2C_{imi}, 53.2 *C*H$_2$CO, 52.7 2*C*H$_2$CH$_2$, 46.3 2CH$_2$*C*H$_2$, 35.7 2*C*H$_3$.

5·Br_2: To a mixture of **I** (65 mg, 0.27 mmol) and DIPEA (70 mg, 0.54 mmol) in acetone (~10 mL) was added a solution of **4**·Cl_3 (98 mg, 0.27 mmol), DIPEA (70 mg, 0.54 mmol) and HOBt (36 mg, 0.27 mmol) in a 1:1 mixture of DMF/H_2O (2 mL). The mixture was cooled to 10 °C and EDC (103 mg, 0.54 mmol) was added and stirring was continued for 24 h. The mixture was concentrated on a rotatory evaporator and the resulting residue was dissolved in water (20 mL) and filtered through a plug of Celite and a solution of KPF_6 (199 mg, 1.08 mmol) in water (5 mL) was added. After stirring for 30 min, a yellow solid separated, which was isolated by centrifugation and redissolved in acetone (5 mL). A solution of tetrabutylammonium bromide (348 mg, 1.08 mmol) in a 7:3 mixture of acetone and ether (5 mL) was then added and a yellow oil formed. The oil was isolated by centrifugation and resuspended in a 9:1 mixture of dichloromethane and methanol, and acetone was then added drop-wise until the product precipitated. The product was isolated as hygroscopic yellow solid. (Yield: 57 mg, 31%). ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 10.21 (s, 1H, N*H*), 9.17 (s, 2H, 2H_{imi}(NC*H*N)), 7.71 (dd, $^3J_{HH}$ = 1.60 Hz, $^4J_{HH}$ = 1.80 Hz, 2H, 2H_{imi}), 7.64 (dd, $^3J_{HH}$ = 1.60 Hz, $^4J_{HH}$ = 1.80 Hz, 2H, 2H_{imi}), 7.59 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.46 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.38 (d, $^3J_{HH}$ = 8.40 Hz, 2H, 2H_{Ar}), 7.02 (d, $^3J_{HH}$ = 16.00 Hz, 1H, C*H*=CH), 6.91 (d, $^3J_{HH}$ = 16.00 Hz, 1H, CH=C*H*), 6.71 (d, $^3J_{HH}$ = 8.40 Hz, 2H, 2H_{Ar}), 4.28 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2CH_2CH$_2$), 3.82 (s, 6H, 2imi-CH_3), 3.51

(s, 2H, COCH_2), 3.09 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2CH$_2$CH_2), 2.91 (s, 6H, 2NCH_3). ^{13}C NMR (DMSO-d$_6$): δ (ppm) 168.9 *C*O, 137.3 C_q, 136.8 2C_{imi} (N*C*HN), 133.1 C_q, 130.8 C_q, 127.4 *C*H=CH, 127.2 2C_{Ar}, 126.1 2C_{Ar}, 123.2 CH=*C*H, 123.0 2C_{imi}, 122.5 2C_{imi}, 119.3 2C_{Ar}, 118.9 C_q, 112.3 2C_{Ar}, 55.8 CO*C*H$_2$, 53.2 2*C*H$_2$CH$_2$, 46.5 2CH$_2$*C*H$_2$, 39.5 2N*C*H$_3$, 35.7 2imi-*C*H$_3$. Anal. Calcd for $C_{30}H_{39}N_7OBr_2.2H_2O$: N, 13.82. C, 50.78. H, 6.11%. Found: N, 13.72. C, 50.92. H, 6.17%.

6·Br$_2$: This compound was prepared as described for **5**·Br$_2$ from **II** (142 mg, 0.53 mmol). The product was obtained as hygroscopic yellow solid. (Yield: 0.17 g, 64%). ^{1}H NMR (400 MHz) (DMSO-d$_6$): δ (ppm) 10.06 (s, 1H, N*H*), 9.04 (s, 2H, 2H_{imi} (NC*H*N)), 8.39 (s, 1H, $H_{benzothi}$), 7.87-7.83 (m, 3H, 2H_{Ar} and 1$H_{benzothi}$) 7.68 (dd, $^3J_{HH}$ = 1.50 Hz, $^4J_{HH}$ = 1.75 Hz, 2H, 2H_{imi}), 7.64 (dd, $^3J_{HH}$ = 1.50 Hz, $^4J_{HH}$ = 1.75 Hz, 2H, 2H_{imi}), 7.51 (d, $^3J_{HH}$ = 9.00 Hz, 1H, $H_{benzothi}$), 6.81 (d, $^3J_{HH}$ = 9.50 Hz, 2H, 2H_{Ar}), 4.24 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2C*H*$_2$CH$_2$), 3.83 (s, 6H, 2imi-C*H*$_3$), 3.51 (s, 2H, COC*H*$_2$), 3.09 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2CH$_2$C*H*$_2$), 3.01 (s, 6H, 2NC*H*$_3$). ^{13}C NMR (DMSO-d$_6$): δ (ppm) 169.6 *C*O, 167.1 C_q, 152.5 C_q, 150.6 C_q, 137.2 2C_{imi} (N*C*HN), 135.9 C_q, 134.8 C_q, 128.7 2C_{Ar}, 123.6 2C_{imi}, 123.0 2C_{imi}, 122.3 $C_{benzothi}$, 120.6 C_q, 119.2 $C_{benzothi}$, 112.3 2C_{Ar}, 112.1 $C_{benzothi}$, 56.8 CO*C*H$_2$, 53.9 2*C*H$_2$CH$_2$, 47.1 2CH$_2$*C*H$_2$, 39.5 2N*C*H$_3$, 36.2 2imi-*C*H$_3$. Anal. Calcd for $C_{29}H_{36}N_8OSBr_2.H_2O$: N, 15.51. C, 48.21. H, 5.30%. Found: N, 15.30. C, 48.24. H, 5.29%.

7a·PF$_6$ and **7b**·PF$_6$: A solution of **5**·Br$_2$ (57 mg, 0.08 mmol) and Ag$_2$O (19 mg, 0.08 mmol) in a 1:9 mixture of methanol and dichloromethane (30 mL) was stirred for 24 h and then filtered through a plug of Celite and the filtrate was concentrated to dryness on a rotatory evaporator. The residual solid was then dissolved in dichloromethane and Re(CO)$_5$Cl (29 mg, 0.08 mmol) was added in one portion. The reaction mixture was heated to 60 ^{o}C for 24 h and after cooling to RT, the mixture was filtered through a plug of Celite and the solvent removed on a rotatory evaporator. The residual solid was dissolved in a minimum volume of a 1:1 mixture of acetone and methanol. The linkage isomer forms of the complex **7**$^+$, were separated using HPLC (HPLC *Method 1*, Experimental section). The compound containing fractions were concentrated under a stream of N$_2$ gas, followed by adding a solution of KPF$_6$ (15 mg, 0.082 mmol) in water (3 mL). The yellow precipitate, **7a**·PF$_6$ (HPLC R_T = 10.12 min) was collected via centrifugation and resuspended in a 9:1 mixture of methanol and acetone and precipitation was induced by the addition of ether. The product was obtained as yellow crystalline solid. (Yield: 8 mg, 10%): ^{1}H NMR (400 MHz) (DMSO-d$_6$): δ (ppm) 10.38 (s, 1H, N*H*), 7.58 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.49 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.46 (s, 4H, 4H_{imi}), 7.40 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.05 (d, $^3J_{HH}$ = 16.40 Hz, 1H, $H_{c=c}$), 6.92 (d, $^3J_{HH}$ = 16.40 Hz, 1H, $H_{c=c}$), 6.73 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 4.36 (s, 2H, OC*H*$_2$), 4.25-4.19 (m, 2H, 2C*H*$_2$CH$_2$), 3.63-3.57 (m, 8H, 2C*H*$_2$CH$_2$ and 2imi-C*H*$_3$), 3.40-3.38 (m, 4H, 2C*H*$_2$CH$_2$), 2.92 (s, 6H, 2NC*H*$_3$). ^{13}C NMR (DMSO-d$_6$): δ (ppm)

195.4 C_q, 195.3 C_q, 190.0 C_q, 174.2 2C_{imi} (N*C*N), 166.5 C_q, 136.9 C_q, 133.5 C_q, 127.7 *C*=C, 127.6 C_q, 127.3 2C_{Ar}, 126.2 2C_{Ar}, 123.5 2C_{imi}, 123.2 C=*C*, 122.4 2C_{imi}, 119.7 2C_{Ar}, 112.4 2C_{Ar}, 71.8 O*C*H_2, 59.7 2*C*H_2CH$_2$, 49.2 2CH$_2$*C*H$_2$, 39.5 2N*C*H$_3$, 37.8 2imi-*C*H$_3$. ESI-MS: m/z = 782.2 $[C_{33}H_{37}N_7O_4Re]^+$. Anal. Calcd for $C_{33}H_{37}F_6N_7O_4PRe$.MeOH: N, 10.22. C, 42.59. H, 4.31%. Found: N, 9.98. C, 42.64. H, 4.15%.

The yellow precipitate of **7b**·PF_6 (HPLC R_T = 9.58 min, *HPLC method 1*) was collected via centrifugation and dissolved in a solution of chloroform and precipitation was induced by the addition of ether. The product was obtained as yellow crystalline solid. (Yield: 12 mg, 16%): ^{1}H NMR (400 MHz) (CD_3CN): δ (ppm) 8.80 (s, 1H, NC*H*N), 7.57 (dd, $^3J_{HH}$ = 1.60 Hz, $^4J_{HH}$ = 1.60 Hz, 1H, H_{imi}), 7.51 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.46 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.42-7.40 (m, 3H, 2H_{Ar} and 1H_{imi}), 7.16 (d, $^3J_{HH}$ = 1.60 Hz, 1H, H_{imi}), 7.12 (d, $^3J_{HH}$ = 1.60 Hz, 1H, 1H_{imi}), 7.09 (d, $^3J_{HH}$ = 16.40 Hz, 1H, C*H*=CH), 6.93 (d, $^3J_{HH}$ = 16.40 Hz, 1H, CH=C*H*), 6.73 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 4.71-4.54 (m, 3H, CH_2CH_2), 4.24-4.07 (m, 3H, 1H CH_2CH_2, 2H NCH_2), 4.00 (t, $^3J_{HH}$ = 7.20 Hz, 2H, CH_2CH_2), 3.97 (s, 3H, imi-CH_3), 3.90 (s, 3H, imi-CH_3), 3.48-3.44 (m, 1H, CH_2CH_2), 3.05-3.00 (m, 1H, CH_2CH_2), 2.95 (s, 6H, 2NCH_3). ESI-MS: m/z = 928.6 $[C_{33}H_{37}N_7O_4RePF_6]H^+$. Anal. Calcd for $C_{33}H_{37}F_6N_7O_4PRe$.1.5 $CHCl_3$: N, 8.87. C, 37.47. H, 3.51%. Found: N, 9.10. C, 37.39. H, 3.71%.

8a·PF_6 and **8b**·PF_6: This compound was prepared using the same procedure described for **7a**·PF_6 and **7b**·PF_6 from **6**·Br_2 (58 mg, 0.082 mmol) in a 9:1 mixture of chloroform and methanol (30 mL). The yellow precipitate of **8a**·PF_6 (HPLC R_T = 11.03 min, *HPLC method 1*) was collected via centrifugation and re-supended in a mixture of 9:1 methanol and acetone and precipitation was induced by the addition of ether. The product was obtained as yellow crystalline solid. (Yield: 4 mg, 5%): ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 10.56 (s, 1H, N*H*), 8.40 (d, $^3J_{HH}$ = 1.60 Hz, 1H, $H_{benzothi}$), 7.89-7.83 (m, 3H, 1$H_{benzothi}$ and 2H_{Ar}), 7.54 (d, $^3J_{HH}$ = 8.80 Hz, 1H, $H_{benzothi}$), 7.46 (s, 4H, 4H_{imi}), 6.81 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 4.40 (s, 2H, OCH_2), 4.25-4.21 (m, 2H, 2CH_2CH$_2$), 3.64-3.56 (m, 2H, 2CH_2CH$_2$), 3.57 (s, 6H, 2imi-CH_3), 3.41-3.36 (m, 4H, 2CH_2CH$_2$), 3.01 (s, 6H, 2NCH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 197.2 C_q, 195.3 C_q, 174.2 2C_{imi} (N*C*N), 166.9 C_q, 166.7 C_q, 152.1 C_q, 150.3 C_q, 135.1 C_q, 134.4 C_q, 128.3 2C_{Ar}, 123.5 2C_{imi}, 122.4 2C_{imi}, 121.9 $C_{benzothi}$, 120.1 C_q, 118.9 $C_{benzothi}$, 112.0 $C_{benzothi}$, 111.8 2C_{Ar}, 64.9 O*C*H_2, 59.7 2*C*H_2CH$_2$, 49.2 2CH$_2$*C*H$_2$, 39.5 2N*C*H$_3$, 37.8 2imi-*C*H$_3$. ESI-MS: m/z = 813.1 $[C_{32}H_{34}N_8SO_4Re]^+$. Anal. Calcd for $C_{32}H_{34}N_8O_4SPF_6Re$: N, 11.70. C, 40.12. H, 3.58%. Found: N, 11.42. C, 39.85. H, 3.64%.

The yellow precipitate of **8b**·PF_6 (HPLC R_T = 10.36 min) was collected by centrifugation and resuspended in a mixture of 9:1 chloroform and acetone and precipitation was induced with the

addition of ether. The product was obtained as bright yellow crystalline solid. (Yield: 9.5 mg, 12%): ^{1}H NMR (400 MHz) (Acetone-d_6): δ (ppm) 9.22 (s, 1H, NC*H*N), 8.23 (d, $^{3}J_{HH}$ = 2.40 Hz, 1H, $H_{benzothi}$), 7.97 (t, $^{3}J_{HH}$ = 1.60 Hz, $^{4}J_{HH}$ = 1.60 Hz, 1H, H_{imi}), 7.93-7.88 (m, 3H, 2H_{Ar} and 1$H_{benzothi}$), 7.80 (t, $^{3}J_{HH}$ = 1.60 Hz, $^{4}J_{HH}$ = 1.60 Hz, 1H, H_{imi}), 7.53 (d, $^{3}J_{HH}$ = 8.80 Hz, 1H, $H_{benzothi}$), 7.43 (d, $^{3}J_{HH}$ = 2.00 Hz, 1H, 1H_{imi}), 7.40 (d, $^{3}J_{HH}$ = 2.00 Hz, 1H, 1H_{imi}), 6.84 (d, $^{3}J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 5.17-5.07 (m, 2H, CH_2CH_2), 4.93-4.81 (m, 2H, OCH_2), 4.55-4.37 (m, 4H, CH_2CH_2), 4.10 (s, 3H, imi-CH_3), 4.09 (s, 3H, imi-CH_3), 3.39-3.88 (m, 1H, CH_2CH_2), 3.53-3.48 (m, 1H, CH_2CH_2), 3.08 (s, 6H, 2NCH_3). ^{13}C NMR (Acetone-d_6): δ (ppm) 208.9 C_q, 180.6 C_q, 178.6 C_q, 172.1 C_{imi} (N*C*N), 170.3 C_q, 162.5 C_q, 153.9 C_q, 153.7 C_q, 138.6 C_{imi} (N*C*HN), 136.0 C_q, 132.6 C_q, 129.6 2C_{Ar}, 129.2 C_q, 125.3 C_{imi}, 124.3 C_{imi}, 124.0 C_{imi}, 123.8 C_{imi}, 123.2 $C_{benzothi}$, 121.4 C_q, 121.0 $C_{benzothi}$, 115.3 $C_{benzothi}$, 112.6 2C_{Ar}, 66.1 O*C*H$_2$ and *C*H$_2$*C*H$_2$, 59.4 *C*H$_2$*C*H$_2$, 48.5 *C*H$_2$*C*H$_2$, 45.4 *C*H$_2$*C*H$_2$, 40.2 2N*C*H$_3$, 39.5 imi-*C*H$_3$, 37.0 imi-*C*H$_3$. ESI-MS: m/z = 958.9 [$C_{32}H_{34}F_6N_8O_4PSRe$.]$H^+$. Anal. Calcd for $C_{32}H_{34}F_6N_8O_4PSRe$.1.5 $CHCl_3$: N, 10.03. C, 35.39. H, 3.15%. Found: N, 10.09. C, 35.03. H, 3.23%.

9: This compound was prepared according to a literature procedure [9] from *bis*(2-chloroethyl)amine hydrochloride (9.55 g, 53.53 mmol) and ethyl-2-bromoacetate (8.94 g, 53.53 mmol) and was obtained as a colourless oil after purification on silica, with a 1:8 mixture of ethyl acetate and hexane as the eluent. (Yield: 8.64 g, 78%). ^{1}H NMR (300 MHz) ($CDCl_3$): δ (ppm) 4.07 (q, $^{3}J_{HH}$ = 7.08 Hz, 2H, OCH_2), 3.58 (t, $^{3}J_{HH}$ = 6.90 Hz, 4H, 2CH_2CH_2), 3.54 (s, 2H, CH_2CO), 2.97 (t, $^{3}J_{HH}$ = 6.90 Hz, 4H, 2CH_2CH_2), 1.18 (t, $^{3}J_{HH}$ = 7.08 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) 171.1 *C*O, 59.8 CH_3*C*H_2, 55.7 2CH_2*C*H_2, 54.4 *C*H_2CO, 42.6 2*C*H_2CH_2, 14.0 *C*H_3.

10: This compound was prepared according to a modified literature procedure.[10] A mixture of imidazole (1.36 g, 20.00 mmol), powdered KOH (1.34 g, 24.00 mmol) and tetrabutylammonium bromide (0.19 g, 0.59 mmol) was stirred for 1 h at RT. After the addition of 1,2-dichloroethane (0.80 mL, 10.10 mmol) the resultant viscous mixture was heated to 40 °C and stirred for 24 h. Further additions of KOH (0.67 g, 12.00 mmol) and 1,2-dichloroethane (0.80 mL, 10.10 mmol) were then made, and the mixture was stirred for a further 24 h at the same temperature. The mixture was extracted with chloroform (3 × 20 mL) and the organic extracts were concentrated on a rotatory evaporator and a small amount (~ 5 mL) of hexane was added. The product precipitated as an off white crystalline solid. (Yield: 0.86 g, 53%). ^{1}H NMR (500 MHz) (DMSO-d_6): δ (ppm) 8.17 (s, 2H, 2H_{imi} (NC*H*N)), 7.30 (s, 2H, 2H_{imi}), 7.27 (s, 2H, 2H_{imi}), 4.52 (s, 4H, CH_2CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 136.4 2C_{imi} (N*C*HN), 124.3 2C_{imi}, 120.5 2C_{imi}, 47.3 *C*H_2*C*H_2.

11·Cl_2: A solution of **9** (360 mg, 1.58 mmol) and **10** (256 mg, 1.58 mmol) in acetonitrile (300 mL) was refluxed for 5 days. The mixture was then cooled to RT and concentrated on a rotatory evaporator and dichloromethane (50 mL) was added to the crude residue. After 24 h the dichloromethane layer was decanted leaving a residual oil, which was re-suspended in a minimum amount of methanol and re-precipitated by the addition of ether. The product was obtained as brown oil. (Yield: 0.23 g, 37%). ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 8.30 (s, 2H, 2H_{imi} (NC*H*N)), 7.87-7.85 (m, 4H, 4H_{imi}), 4.63 (s, 4H, imi-CH_2CH_2-imi), 4.20 (t, $^3J_{HH}$ = 5.20 Hz, 4H, 2CH_2CH$_2$), 4.12 (q, $^3J_{HH}$ = 7.20 Hz, CH_2CH$_3$), 3.54 (s, 2H, COCH_2), 3.01 (t, $^3J_{HH}$ = 5.20 Hz, 4H, 2CH$_2$CH_2), 1.22 (t, $^3J_{HH}$ = 7.20 Hz, CH$_2$CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 170.6 *C*O, 135.9 2C_{imi} (N*C*HN), 124.1 2C_{imi}, 122.0 2C_{imi}, 60.1 *C*H$_2$CH$_3$, 53.1 2CH$_2$*C*H$_2$, 49.7 CO*C*H$_2$, 48.9 2*C* (imi-*C*H$_2$*C*H$_2$-imi) 46.5 2*C*H$_2$CH$_2$, 14.1 *C*H$_3$. This compound was obtained as an oil and was characterised by HPLC, ESI-MS and ^{1}H and ^{13}C NMR spectroscopy. NMR spectra, ESI-MS and HPLC chromatogram are provided in the ESI (Figure S2) as evidence of purity.

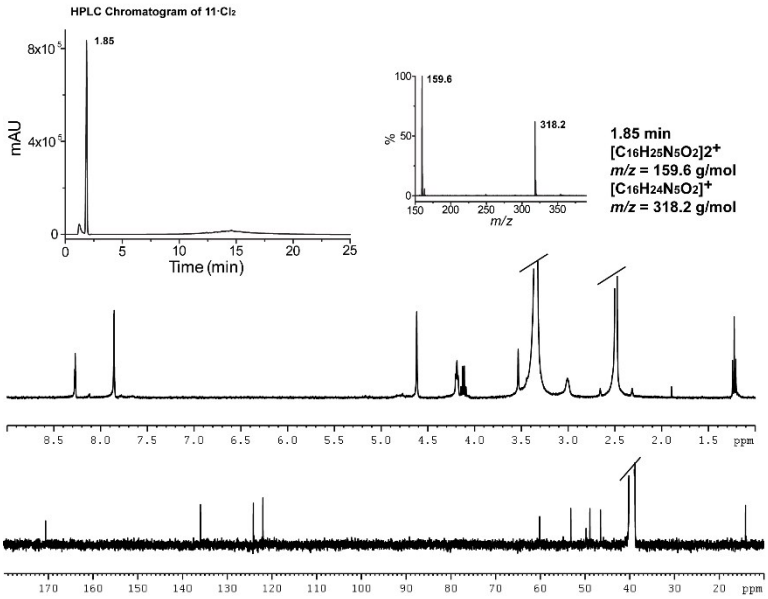


Figure S2. ^{1}H and ^{13}C NMR spectra for **11**.Cl_2. Spectra were recorded at 400.14 MHz for ^{1}H, 100.03 MHz for ^{13}C from a DMSO-d_6 solution and were internally referenced to solvent resonances. (inset) HPLC Chromatogram of **11**.Cl_2 (Eluent: MeOH/H_2O with 0.1% formic acid) and the ESI-MS spectrum corresponding to main peak.

12·Cl_3: A solution of **11**·Cl_2 (137 mg, 0.35 mmol) in 5 M HCl (10mL) was heated at 110 ^{o}C for 2 h. After cooling to RT, the solvent was removed on a rotatory evaporator. The crude product was dissolved in a minimum amount of methanol followed by addition of acetone until the product crystallized as a hygroscopic white powder. (Yield: 105 mg, 75%). ^{1}H NMR (500 MHz) (DMSO-d_6): δ (ppm) 8.32 (s, 2H, 2H_{imi} (NC*H*N)) , 7.86 (dd, $^3J_{HH}$ = 1.50 Hz, $^4J_{HH}$ = 1.50 Hz, 4H, 4H_{imi}), 4.62 (s, 4H,

imi-CH_2CH_2-imi), 4.19 (t, $^3J_{HH}$ = 5.50 Hz, 4H, 2CH_2CH$_2$), 3.45 (s, 2H, COCH_2), 3.01 (t, $^3J_{HH}$ = 5.50 Hz, 4H, 2CH$_2$CH_2). ^{13}C NMR (DMSO-d$_6$): δ (ppm) 172.1 *C*O, 136.0 2C_{imi} (N*C*HN), 124.1 2C_{imi}, 121.9 2C_{imi}, 53.1 2*C*H$_2$CH$_2$, 49.6 CO*C*H$_2$, 48.8 2*C* (imi-*C*H$_2$*C*H$_2$-imi), 46.5 2CH$_2$*C*H$_2$. This compound was obtained as a hygroscopic solid and was characterised by HPLC, ESI-MS and ^{1}H and ^{13}C NMR spectroscopy. NMR spectra, ESI-MS and HPLC chromatogram are provided in the ESI (Figure S3) as evidence of purity.

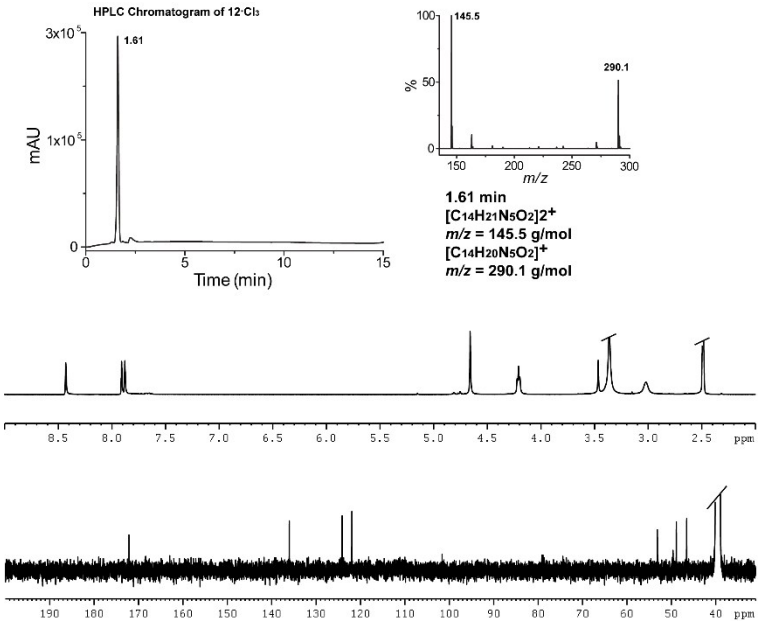


Figure S3. ^{1}H and ^{13}C NMR spectra for **12**·Cl$_3$. Spectra were recorded at 400.14 MHz for ^{1}H, 100.03 MHz for ^{13}C from a DMSO-d$_6$ solution and were internally referenced to solvent resonances. (inset) HPLC Chromatogram of **12**·Cl$_3$ (Eluent: MeOH/H$_2$O with 0.1% formic acid) and the ESI-MS spectrum corresponding to main peak.

13·Br$_3$: This compound was prepared as described for **5**·Br$_2$ from **I** (107 mg, 0.45 mmol) and **12**·Cl$_3$ (179 mg, 0.45 mmol). The product was obtained as extremely hygroscopic yellow solid. (Yield: 81 mg, 27%). ^{1}H NMR (400 MHz) (DMSO-d$_6$): δ (ppm) 10.18 (s, 1H, N*H*), 8.41 (s, 2H, 2H_{imi} (NC*H*N)), 7.86 (dd, $^3J_{HH}$ = 1.60 Hz, $^4J_{HH}$ = 1.60 Hz, 2H, 2H_{imi}), 7.82 (dd, $^3J_{HH}$ = 1.60 Hz, $^4J_{HH}$ = 1.60 Hz, 2H, 2H_{imi}), 7.58 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.48 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.39 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.03 (d, $^3J_{HH}$ = 16.80 Hz, 1H, C*H*=CH), 6.91 (d, $^3J_{HH}$ = 16.80 Hz, 1H, CH=C*H*), 6.70 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 4.62 (s, 4H, im-CH_2CH_2-im), 4.24 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2CH_2CH$_2$), 3.46 (s, 2H, COCH_2), 2.98 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2CH$_2$CH_2), 2.92 (s, 6H, 2NCH_3). ^{13}C NMR (DMSO-d$_6$): δ (ppm) 169.1 *C*O, 149.8 C_q, 137.0 C$_q$, 136.1 2C_{imi} (N*C*HN), 127.6 *C*H=CH, 127.3 2C_{Ar}, 126.1 2C_{Ar}, 125.0 C_q, 124.3 2C_{imi}, 123.0 CH=*C*H, 121.8 2C_{imi}, 119.7 2C_{Ar}, 117.8 C_q, 112.2 2C_{Ar}, 54.8 2*C*H$_2$CH$_2$, 54.2 CO*C*H$_2$, 49.2 2*C*(imi-*C*H$_2$*C*H$_2$-imi), 46.9 2CH$_2$*C*H$_2$, 39.5 2N*C*H$_3$. This compound was obtained

as a hygroscopic solid and was characterised by HPLC, ESI-MS and ^{1}H and ^{13}C NMR spectroscopy. NMR spectra, ESI-MS and HPLC chromatogram are provided in the ESI (Figure S4) as evidence of purity.

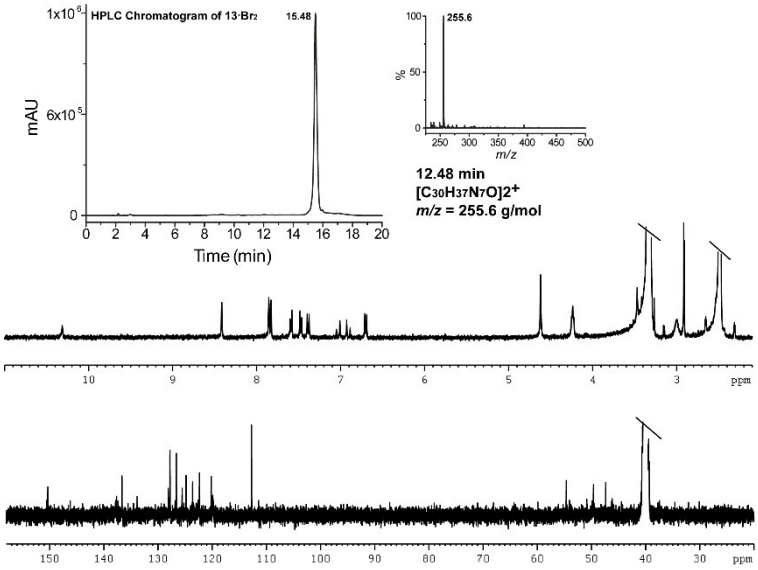


Figure S4. ^{1}H and ^{13}C NMR spectra for **13**·Br_2. Spectra were recorded at 400.14 MHz for ^{1}H, 100.03 MHz for ^{13}C from a DMSO-d_6 solution and were internally referenced to solvent resonances. (inset) HPLC Chromatogram of **13**·Br_2 (Eluent: MeOH/H_2O with 0.1% formic acid) and the ESI-MS spectrum corresponding to main peak.

14·Br_2: This compound was prepared as described for **5**·Br_2 from **II** (101 mg, 0.38 mmol) and **12**·Cl_3 (152 mg, 0.38 mmol). The product was obtained as extremely hygroscopic green/yellow solid. (Yield: 56 mg, 21%). ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 10.40 (s, 1H, N*H*), 8.42 (s, 2H, 2H_{imi} (NC*H*N)), 8.41 (s, 1H, $H_{benzothi}$), 7.90-7.78 (m, 7H, 4H_{imi}, 2H_{Ar} and 1$H_{benzothi}$), 7.57 (d, $^{3}J_{HH}$ = 8.80 Hz, 1H, 1$H_{benzothi}$), 6.81 (d, $^{3}J_{HH}$ = 9.20 Hz, 2H, 2H_{Ar}), 4.63 (s, 4H, im-CH_2CH_2-im), 4.25 (t, $^{3}J_{HH}$ = 4.80 Hz, 4H, 2CH_2CH$_2$), 3.51 (s, 2H, COCH_2), 3.01 (s, 10H, 2NCH_3 and 2CH$_2$CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 169.4 *C*O, 152.1 C_q, 150.3 C_q, 136.3 C_q, 136.2 2C_{imi} (N*C*HN), 135.3 C_q, 134.9 C_q, 134.3 C_q, 128.3 2C_{Ar}, 124.5 $C_{benzothi}$, 124.4 2C_{imi}, 121.9 C_{imi}, 119.1 $C_{benzothi}$, 112.0 $C_{benzothi}$, 111.8 C_{Ar}, 54.4 2*C*H$_2$CH$_2$ and CO*C*H$_2$, 49.2 2*C*(imi-*C*H$_2$*C*H$_2$-imi), 47.0 2CH$_2$*C*H$_2$, 39.5 2N*C*H$_3$. This compound was obtained as a hygroscopic solid and was characterised by HPLC, ESI-MS and ^{1}H and ^{13}C NMR spectroscopy. NMR spectra, ESI-MS and HPLC chromatogram are provided in the ESI (Figure S5) as evidence of purity.

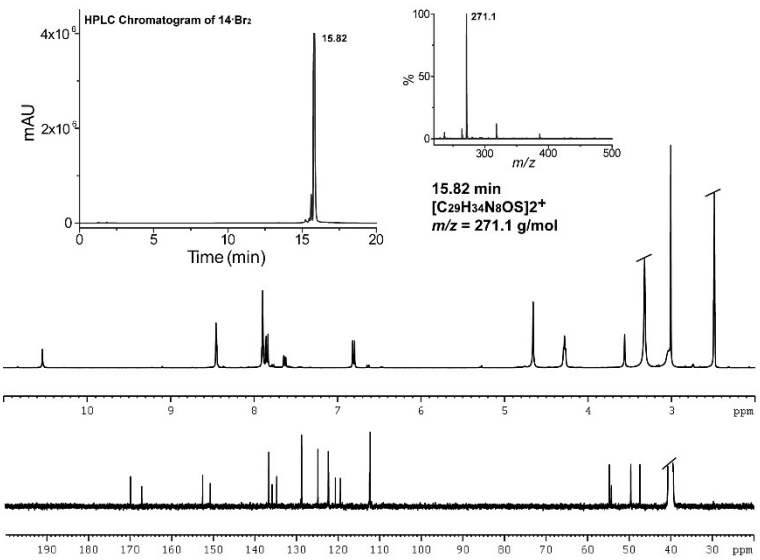


Figure S5. ^{1}H and ^{13}C NMR spectra for **14**·Br_2. Spectra were recorded at 400.14 MHz for ^{1}H, 100.03 MHz for ^{13}C from a DMSO-d_6 solution and were internally referenced to solvent resonances. (inset) HPLC Chromatogram of **14**·Br_2 (Eluent: MeOH/H_2O with 0.1% formic acid) and the ESI-MS spectrum corresponding to main peak.

15·PF_6: A mixture of **13**·Br_3 (53 mg, 0.08 mmol), Ag_2O (37 mg, 0.16 mmol) and $Re(CO)_5Cl$ (29 mg, 0.08 mmol) in methanol was heated at 85 °C for 24 h. The mixture was then filtered through a plug of Celite and the solvent was removed on a rotatory evaporator. The resulting crude residue was dissolved in a minimum volume of a 1:1 mixture of acetone and methanol. Complex, **15**$^{+}$, was then purified using semi-preparative RP-HPLC (HPLC *Method 1*). The compound containing fraction was collected and lyophilized. The residue was re-suspended in a minimum volume of a 1:1 mixture of acetone and water, followed by adding a solution of KPF_6 (141 mg, 0.77 mmol) in water (3 mL). The yellow precipitate, **15**·PF_6, was collected via centrifugation and dissolved in a minimum volume of a 9:1 mixture of methanol and acetone with addition of ether. The product was obtained as yellow/green solid. (Yield: 15 mg, 20%) (RP-HPLC R_T = 10.61 min): ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 10.46 (s, 1H, N*H*), 7.60 (d, $^{3}J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.50 (d, $^{3}J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.43 (d, $^{3}J_{HH}$ = 2.00 Hz, 2H, 2H_{imi}), 7.38 (d, $^{3}J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 7.37 (d, $^{3}J_{HH}$ = 2.00 Hz, 2H, 2H_{imi}), 7.05 (d, $^{3}J_{HH}$ = 16.00 Hz, 1H, $H_{c=c}$), 6.91 (d, $^{3}J_{HH}$ = 16.00 Hz, 1H, $H_{c=c}$), 6.70 (d, $^{3}J_{HH}$ = 8.80 Hz, 2H, 2H_{Ar}), 4.86-4.80 (m, 2H, imi-CH_2CH$_2$-imi), 4.64-4.55 (m, 2H, imi-CH$_2$CH_2-imi), 4.51 (s, 2H, OCH_2), 4.31-4.29 (m, 4H, 2CH_2CH$_2$), 4.10-4.02 (m, 2H, 2CH$_2$CH_2), 2.55-2.54 (m, 2H, 2CH$_2$CH_2), 2.91 (s, 6H, 2NCH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 197.1 C_q, 196.7 C_q, 174.2 2C_{imi} (N*C*N), 166.6 C_q, 149.9 C_q, 141.8 C_q, 136.8 C_q, 133.7 C_q, 127.9 *C*=C, 127.4 2C_{Ar}, 126.3 2C_{Ar}, 125.1 C_q, 124.5 2C_{imi}, 123.0 C=*C*, 122.0 2C_{imi}, 119.7 2C_{Ar}, 112.2 2C_{Ar}, 67.6 O*C*H$_2$, 60.0 2*C*H$_2$CH$_2$, 49.1 2CH$_2$*C*H$_2$, 46.4 imi-*C*H$_2$*C*H$_2$-imi, 39.5 2N*C*H$_3$. ESI-MS: m/z = 780.2 $[C_{33}H_{35}N_7O_4Re]^{+}$. Anal. Calcd for

$C_{33}H_{35}N_7O_4RePF_6$.0.5 $(CH_3)_2CO$. 1 CH_3OH: N, 9.94. C, 43.25. H, 4.29%. Found: N, 9.71. C, 43.09. H, 4.17%.

16·PF_6: This compound was prepared as described for **15**·PF_6 from **14**·Br_2 (41 mg, 0.06 mmol). The complex, **16**$^+$, was purified using semi-preparative RP-HPLC (HPLC *Method 1*). The yellow precipitate, **16**·PF_6, was collected via centrifugation and dissolved in a minimum volume of a 9:1 mixture of methanol and acetone. Precipitation was induced by the addition of ether. The product was obtained as yellow solid. (Yield: 11 mg, 19%) (RP-HPLC R_T = 13.83 min): ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 10.64 (s, 1H, N*H*), 8.43 (d, $^3J_{HH}$ = 2.00 Hz, 1H, $H_{benzothi}$), 7.90-7.83 (m, 3H, 1$H_{benzothi}$ and 2H_{Ar}), 7.57 (d, $^3J_{HH}$ = 8.40 Hz, 1H, $H_{benzothi}$), 7.44 (d, $^3J_{HH}$ = 1.60 Hz, 2H, 2H_{imi}), 7.38 (d, $^3J_{HH}$ = 1.60 Hz, 2H, 2H_{imi}), 6.81 (d, $^3J_{HH}$ = 8.80 Hz, 2H, 2H_{imi}), 4.86-4.81 (m, 2H, imi-CH_2CH$_2$-imi), 4.62-4.56 (m, 2H, imi-CH$_2$CH_2-imi), 4.52 (s, 2H, OCH_2), 4.32-4.31 (m, 4H, 2CH_2CH$_2$), 4.09-4.05 (m, 2H, 2CH$_2$CH_2), 3.01 (s, 6H, 2NCH_3), 2.57-2.52 (m, 2H, 2CH$_2$CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 196.8 C_q, 195.2 C_q, 174.2 2C_{imi} (N*C*N), 167.0 C_q, 165.6 C_q, 162.3 C_q, 135.1 C_q, 134.4 C_q, 128.3 2C_{Ar}, 124.4 2C_{imi}, 122.0 $C_{benzothi}$ and 2C_{imi}, 119.0 $C_{benzothi}$, 112.1 $C_{benzothi}$, 111.8 2C_{Ar}, 67.8 O*C*H$_2$, 60.0 2*C*H$_2$CH$_2$, 49.1 2CH$_2$*C*H$_2$, 46.4 imi-*C*H$_2$*C*H$_2$-imi, 39.5 2N*C*H$_3$. ESI-MS: m/z = 811.1 $[C_{32}H_{32}N_8SO_4Re]^+$. Anal. Calcd for $C_{32}H_{32}N_8SO_4RePF_6$: N, 11.72. C, 40.21. H, 3.37%. Found: N, 11.64. C, 40.10. H, 3.25%.

17·PF_6: This compound was prepared as described for **15**·PF_6 from a mixture of **11**·Cl_2 (60 mg, 0.15 mmol), Ag_2O (71 mg, 0.31 mmol) and $Re(CO)_5Cl$ (56 mg, 0.15 mmol) in ethanol. The complex, **17**$^+$, was then purified using semi-preparative RP-HPLC (HPLC *Method 1*). The white precipitate, **17**·PF_6, was collected via centrifugation and dissolved in a minimum volume of a 9:1 mixture of dichloromethane and acetone. Precipitation was induced by the addition of ether. The product was obtained as colourless crystalline solid. (Yield: 18 mg, 16%) (RP-HPLC R_T = 9.84 min): ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 7.44 (d, $^3J_{HH}$ = 1.84 Hz, 2H, 2H_{imi}), 7.38 (d, $^3J_{HH}$ = 1.84 Hz, 2H, 2H_{1mi}), 4.87-4.82 (m, 2H, imi-CH_2CH$_2$-imi), 4.59-4.54 (m, 2H, imi-CH$_2$CH_2-imi), 4.45 (s, 2H, NCH_2), 4.29-4.18 (m, 4H, 2CH_2CH$_2$), 3.83-3.80 (m, 2H, 2CH$_2$CH_2), 2.91 (s, 3H, CH_3), 2.43-2.36 (m, 2H, 2CH$_2$CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 196.5 C_q, 195.6 C_q, 174.1 2C_{imi} (N*C*N), 168.8 C_q, 124.3 2C_{imi}, 122.0 2C_{imi}, 66.3 N*C*H$_2$, 61.2 2CH$_2$*C*H$_2$, 52.0 *C*H$_3$, 49.7 2*C*H$_2$CH$_2$, 46.6 imi-*C*H$_2$*C*H$_2$-imi. ESI-MS: m/z = 574.1 $[C_{18}H_{21}N_5O_5Re]^+$. Anal. Calcd for $C_{15}H_{19}N_5O_3RePF_6$.0.5 CH_2Cl_2.0.5 $(C_2H_5)O$: N, 8.78. C, 30.85. H, 3.41%. Found: N, 8.61. C, 30.99. H, 3.26%.

Photophysical studies

The electronic absorption and emission properties of the imidazolium salts (**5**·Br_2, **6**·Br_2, **13**·Br_2 and **14**·Br_2) and the Re(I) complexes (**7**·PF_6, **8**·PF_6, **15**·PF_6 and **16**·PF_6) are summarized in Table S2. The spectra were obtained from 10 μM solutions (acetonitrile or methanol), depending on the solubility of the compounds. In addition, the electronic absorption and emission properties of the Re(I) complexes **7a**·PF_6, **8a**·PF_6, **15**·PF_6 and **16**·PF_6 were evaluated in phosphate-buffered saline (PBS) solution, as this buffer was used in the ThT fluorescence assays and the human brain tissues staining studies. All UV-visible and fluorescence spectra for these compounds are given in Figures S6-S13 (ESI).

Table S2. UV-visible absorption and fluorescence spectroscopic data for compounds: **5**·Br_2, **6**·Br_2, **13**·Br_2, **14**·Br_2, **7**·PF_6, **8**·PF_6, **15**·PF_6 and **16**·PF_6.

	Compound (Solvent)	λ_{max}/nm (ε/M^{-1} cm^{-1})	Photoluminescence λ_{max}/nm
NH_2-bearing Aβ binding moeities	**II** (10 μM, Acetonitrile)	362 (34880)	427
	I (10 μM, Acetonitrile)	358 (35480)	419
Bis(NHC)-amine pro-ligands conjugated to Aβ binding moieties	**5**·Br_2 (10 μM, Methanol)	359 (78100)	461
	6·Br_2 (10 μM, Methanol)	368 (57840)	435
	13·Br (10 μM, Methanol)	358 (28440)	460
	14·Br_2 (10 μM, Methanol)	368 (44450)	436
Re(I) complexes conjugated to Aβ binding moieties	**7a**·PF_6 (10 μM, Acetonitrile)	362 (51810)	455
	7b·PF_6 (10 μM, Acetonitrile)	372 (60480)	446
	8a·PF_6 (10 μM, Acetonitrile)	368 (11950)	428
	8b·PF_6 (10 μM, Acetonitrile)	372 (80340)	434
	15·PF_6 (10 μM, Acetonitrile)	363 (45210)	459
	16·PF_6 (10 μM, Acetonitrile)	365 (22030)	429
	7a·PF_6 (5 μM, PBS buffer)	350 (97220)	467
	8a·PF_6 (5 μM, PBS buffer)	361 (221190)	454
	15·PF_6 (5 μM, PBS buffer)	355 (129440)	467
	16·PF_6 (5 μM, PBS buffer)	365 (32910)	450

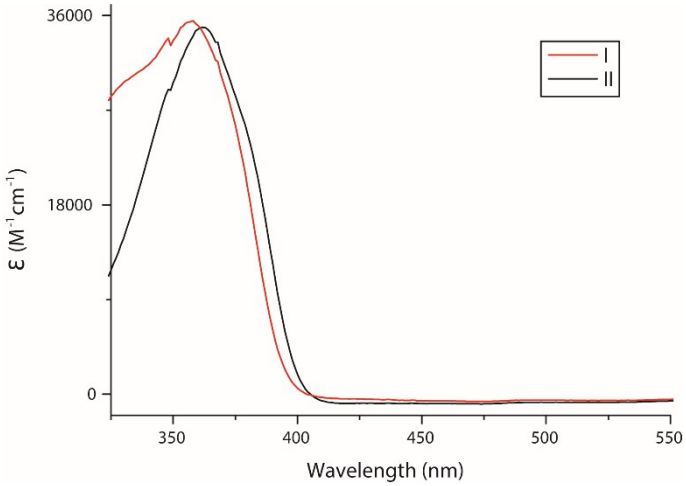


Figure S6. Ultra violet-visible spectrum of acetonitrile (10 μM) solutions of amine bearing amyloid binding moieties **I** and **II**.

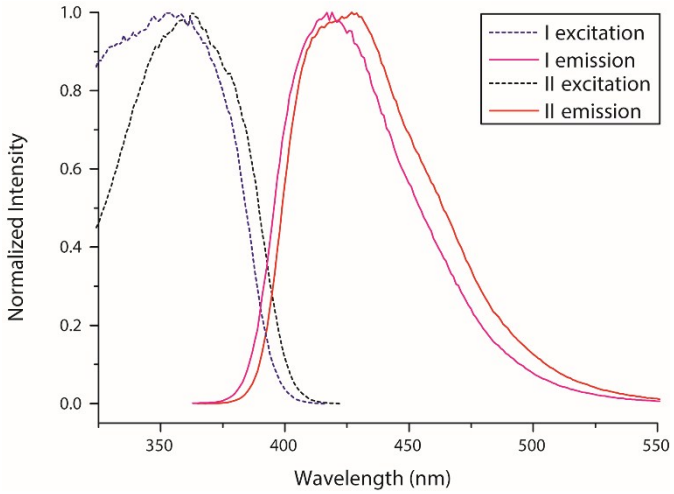


Figure S7. Excitation and emission spectra for acetonitrile solutions (10 μM) of amine bearing amyloid binding moieties **I** and **II**.

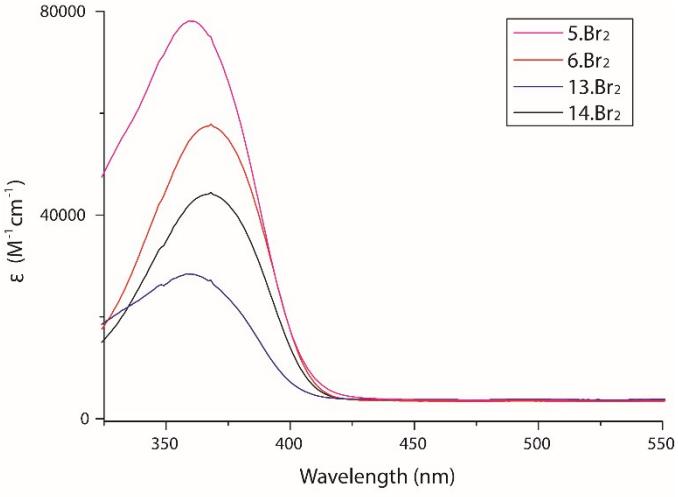


Figure S8. UV-visible spectra of methanol solutions (10 μM) of diimidazolium salts **5**·Br_2, **6**·Br_2, **13**·Br_2 and **14**·Br_2.

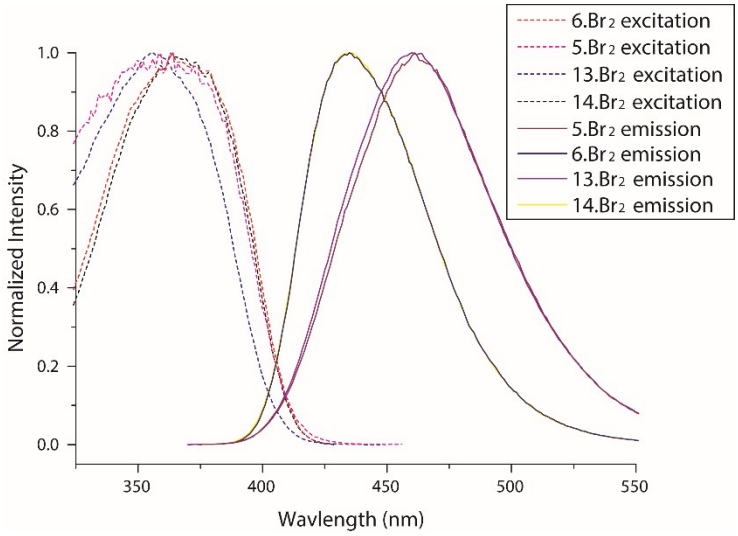


Figure S9. Excitation and emission spectra for methanol solutions (10 μM) of diimidazolium salts **5**·Br_2, **6**·Br_2, **13**·Br_2 and **14**·Br_2.

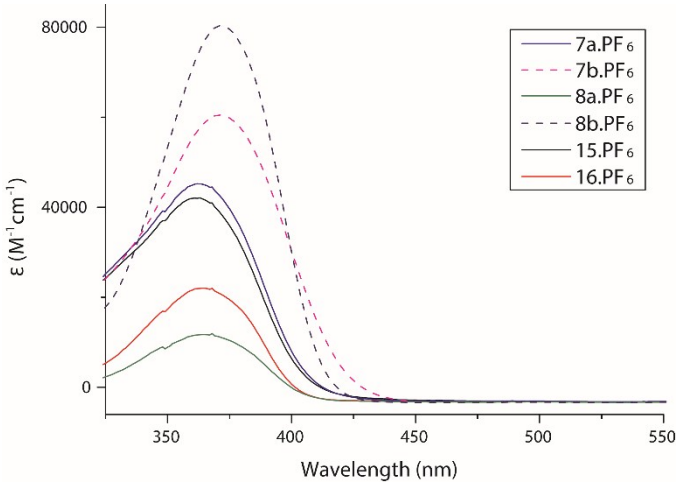


Figure S10. UV-visible spectra of acetonitrile solutions (10 μM) of Re(I) complexes **7a**·PF_6, **7b**·PF_6, **8a**·PF_6, **8b**·PF_6, **15**·PF_6 and **16**·PF_6.

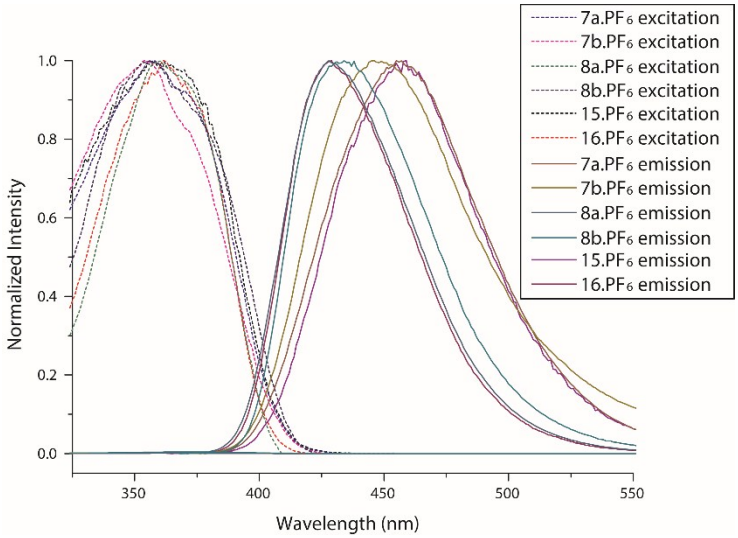


Figure S11. Excitation and emission spectra for acetonitrile solutions (10 μM) of Re(I) complexes **7a**·PF_6, **7b**·PF_6, **8a**·PF_6, **8b**·PF_6, **15**·PF_6 and **16**·PF_6.

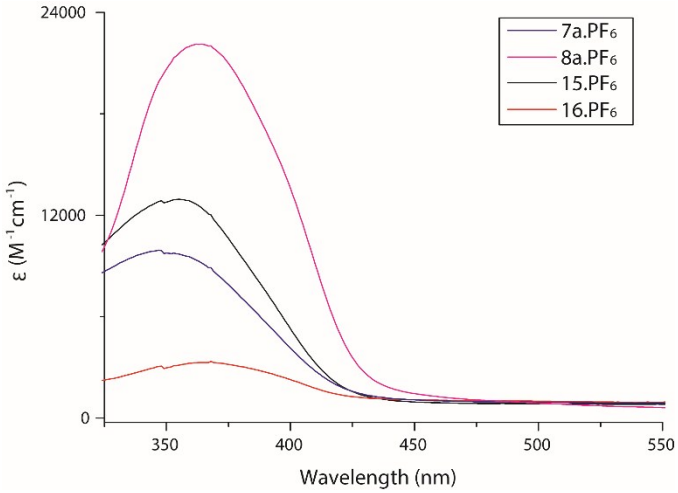


Figure S12. UV-visible spectra of PBS solutions (5 μM) of Re(I) complexes **7a**·PF_6, **8a**·PF_6, **15**·PF_6 and **16**·PF_6.

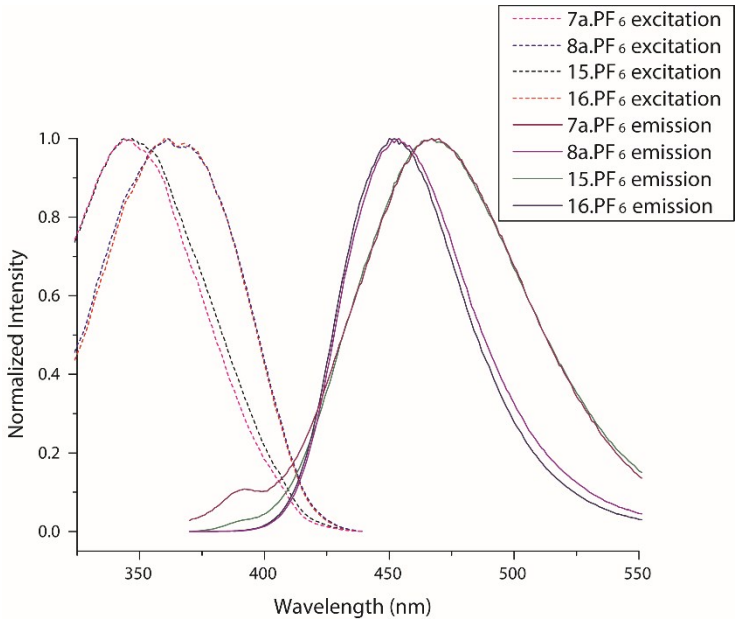


Figure S13. Excitation and emission spectra for PBS solutions (5 μM) of Re(I) complexes **7a**·PF_6, **8a**·PF_6, **15**·PF_6 and **16**·PF_6.

Stability studies

The stability of complexes **8a**·PF_6 **8b**·PF_6 and **16**·PF_6 were evaluated in ligand challenge experiments using the metal binding amino acids: L-histidine and L-cysteine. These complexes were chosen for these studies as they represent examples of complexes bearing acyclic and cyclic tridentate ligand systems and different ligand coordination modes. Stock solutions of either **8a**·PF_6, **8b**·PF_6 or **16**·PF_6 (10 mM in DMSO) were reconstituted in phosphate buffered saline (pH = 7) (final complex concentration = 0.33 mM) containing either: no addition (control), L-cysteine (3.33 mM) or L-histidine (3.33 mM). These solutions were incubated in the dark at 37 °C ± 1°C for at least 24 h after mixing. The complex stability was monitored by recording HPLC chromatograms of the reaction

mixtures (S14 – S17) over the course of the incubation period. To identify the *trans*-chelation reaction products, the HPLC peaks were collected and the positive ion mass spectra recorded. For all complexes, HPLC *Method 2* was used. In order to obtain acceptable peak shape in the HPLC analysis of the cationic complexes (**8a**·PF_6 **8b**·PF_6 and **16**·PF_6) 0.1% trifluoroacetic acid (TFA) was added to the eluent as an organic modifier. HPLC analysis of the reaction mixtures for complexes **8a**·PF_6 and **16**·PF_6 showed no evidence for *trans*-chelation in the presence of these competing ligands (Figures S14-S17). HPLC chromatograms obtained for complex **8b**·PF_6 L-histidine and L-cysteine (not shown) showed that the complex was unstable and decomposed within 4 h.

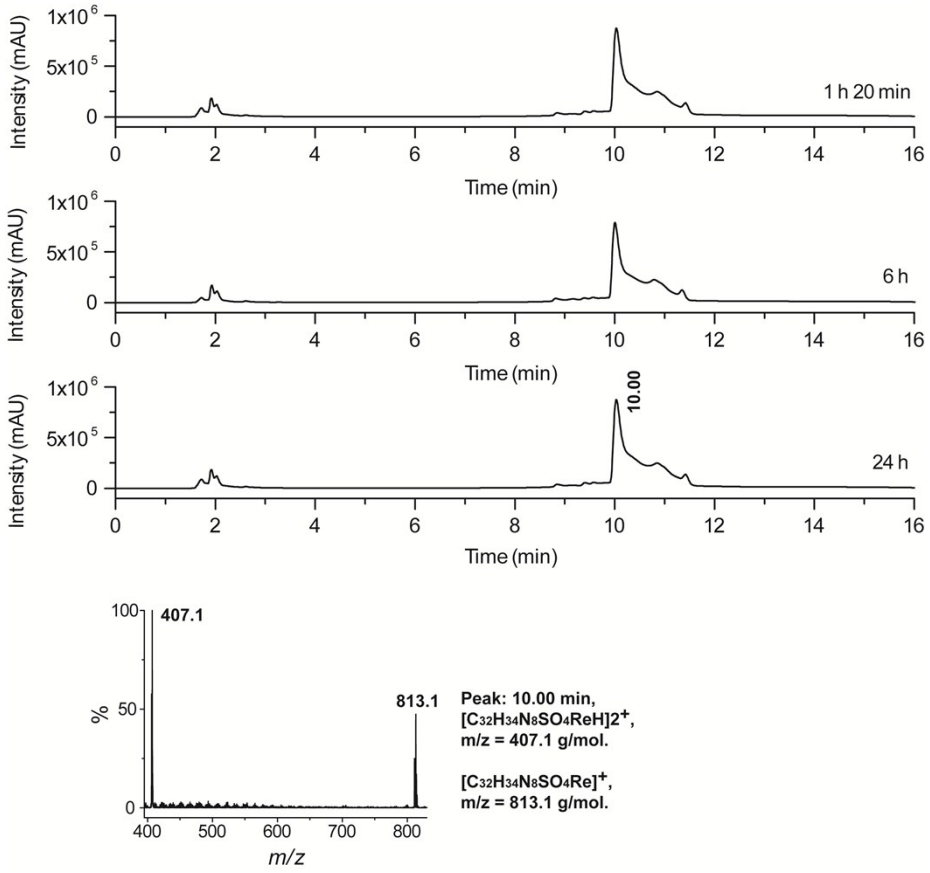


Figure S14. HPLC chromatograms obtained for **8a**·PF_6 (0.33 mM) in phosphate buffered saline (PBS) containing cysteine (3.33 mM), recorded at 1 h 20 min, 6 h and 24 h after mixing. Inset (lower panel): ESI-mass spectrum corresponding to the main peaks.

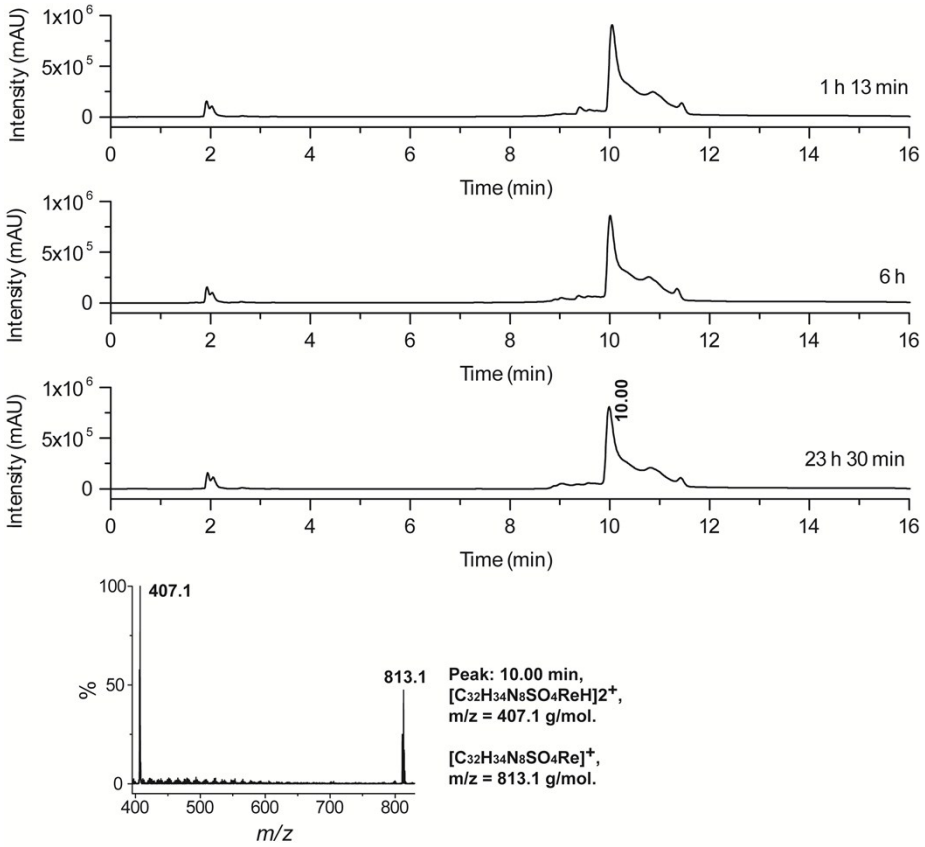


Figure S15. HPLC chromatograms obtained for **8a**·PF_6 (0.33 mM) in phosphate buffered saline (PBS) containing histidine (3.33 mM), recorded at 1 h 13 min, 6 h and 23 h 30 min after mixing. Inset (lower panel): ESI-mass spectrum corresponding to the main peak (10.00 min).

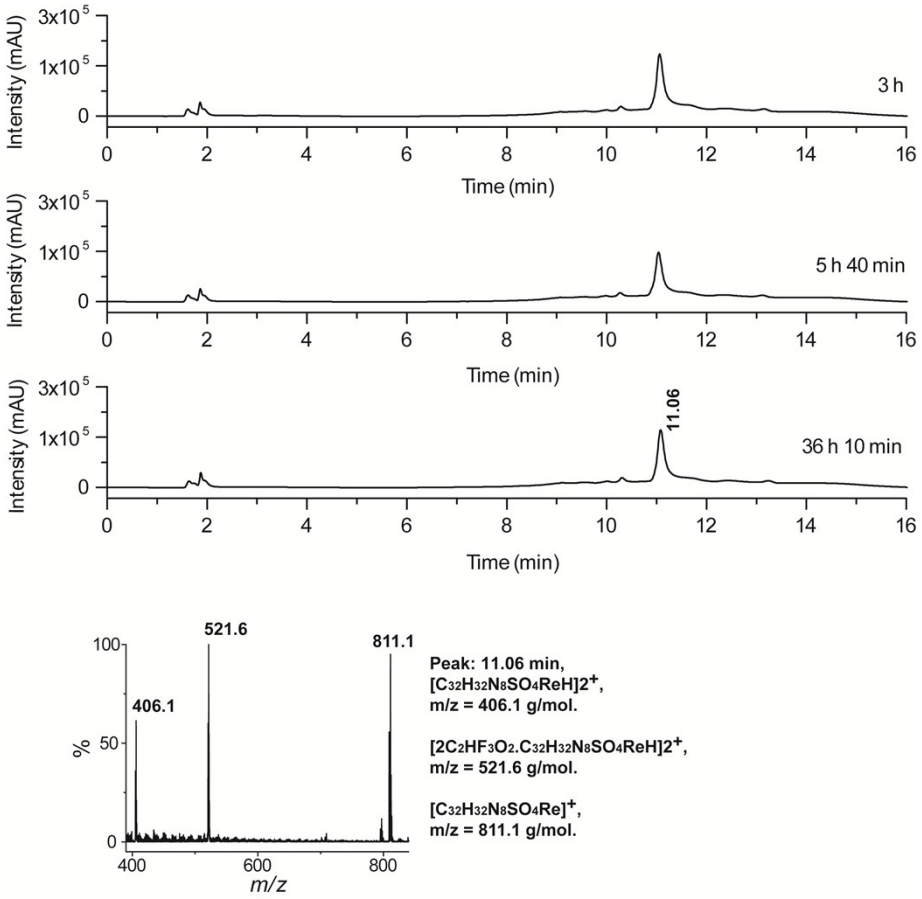


Figure S16. HPLC chromatograms obtained for **16**·PF_6 (0.33 mM) in phosphate buffered saline (PBS) containing cysteine (3.33 mM), recorded at 3 h, 5 h 40 min and 36 h 10 min after mixing. Insets (lower panel): ESI-mass spectrum corresponding to the main peak (11.06 min).

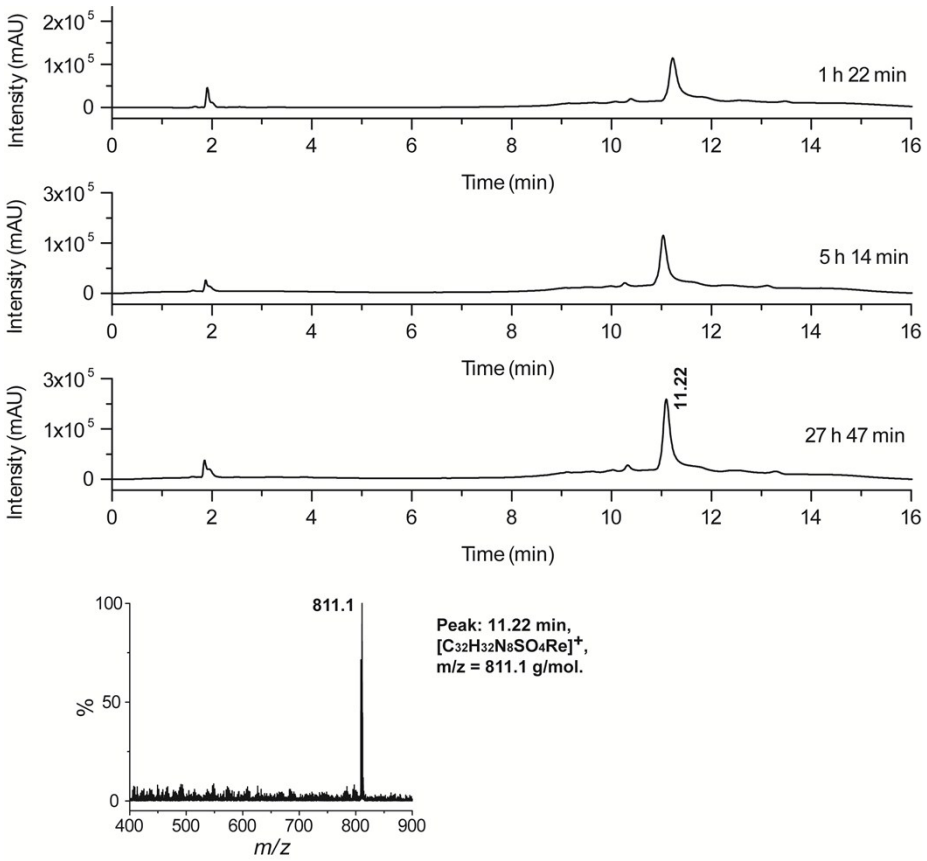


Figure S17. HPLC chromatograms obtained for **16**·PF_6 (0.33 mM) in phosphate buffered saline (PBS) containing histidine (3.33 mM), recorded at 1 h 22 min, 5 h 14 min and 27 h 47 min after mixing. Inset (lower panel): ESI-mass spectrum corresponding to the main peak (11.22 min).

Microscopy images

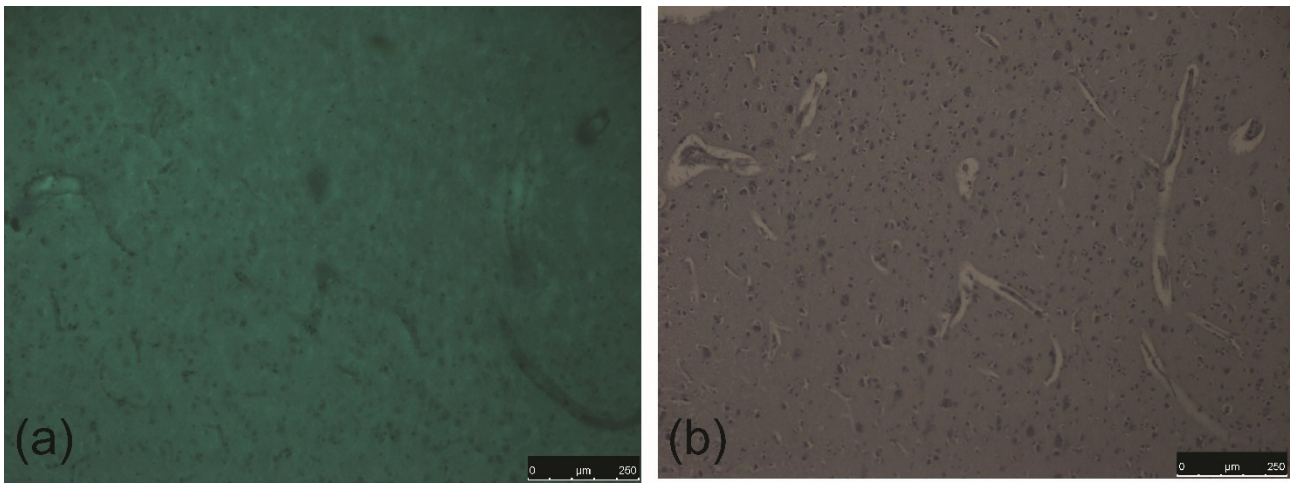


Figure S18. (a) Epi-fluorescence microscopy image of age matched control frontal cortex brain tissue treated with the Re(I) complex **15**·PF_6 (λ_{ex} = 359 nm, λ_{em} = 461 nm) and (b) microscopy image of the contiguous section immune-stained with an anti-amyloid β peptide antibody 1E8.

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