Electronic Supplementary Material (ESI) for Dalton Transactions

Supporting Information

for

Exploring the Reactivity of Flavonoid Compounds with Metal-Associated Amyloid-β Species

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Table S1. Values (MW, clogP, HBA, HBD, PSA, and logBB) of **FL1** – **FL4**.[a]

	MW	HBD	HBA	PSA	*c*logP	logBB
FL1	238.24	1	3	50.44	4.11	0.008
FL2	281.31	1	4	53.68	4.29	–0.012
FL3	281.31	1	4	53.68	3.23	–0.174
FL4	239.23	1	4	63.33	1.83	–0.529

[a] Molecular weight (MW) ≤ 450, calculated logarithm of the octanol-water partition coefficient (*c*logP) ≤ 5, hydrogen bond donor (HBD) atoms ≤ 5, hydrogen bond acceptor (HBA) atoms ≤ 10, polar surface area (PSA) ≤ 90 $Å^2$. The log BB is calculated from the equation logBB = −0.0148 × PSA + 0.152 × *c*logP + 0.130. If the log BB value is > 0.3, the molecule can pass the BBB; if the value is < −1.0, then it will poorly cross the BBB.

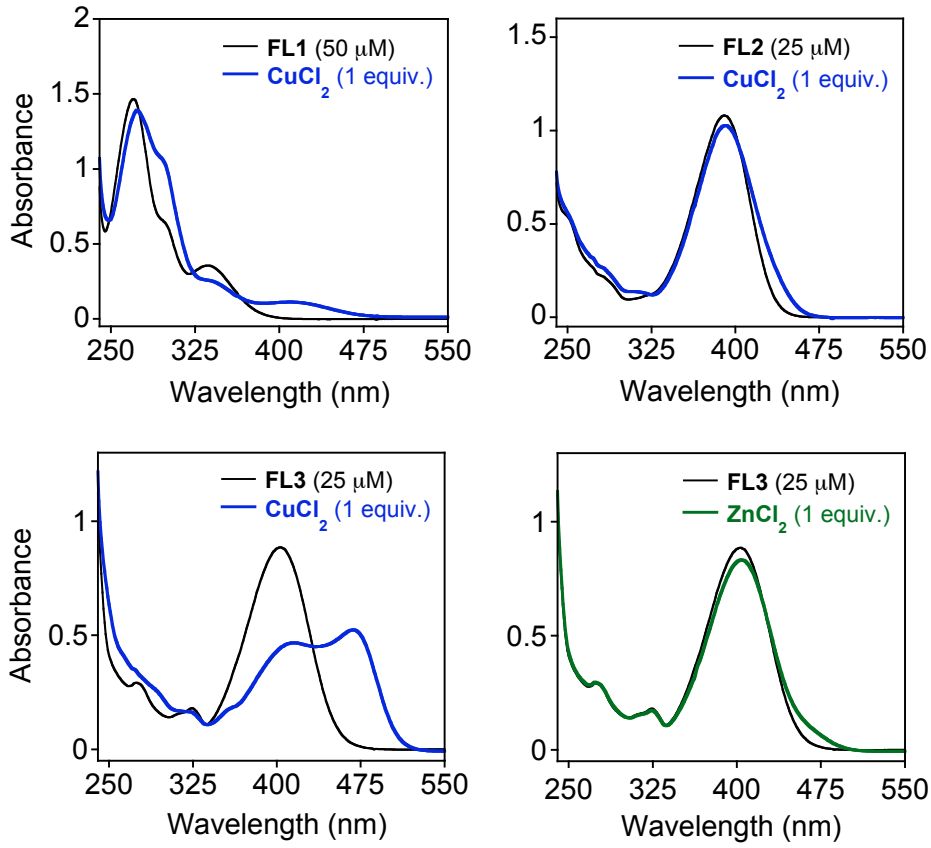

Fig. S1 UV-Vis spectra of **FL1** – **FL3** before (black) and after incubation with 1 equivalent of $CuCl_2$ (blue) or $ZnCl_2$ (green) for 5 min in EtOH.

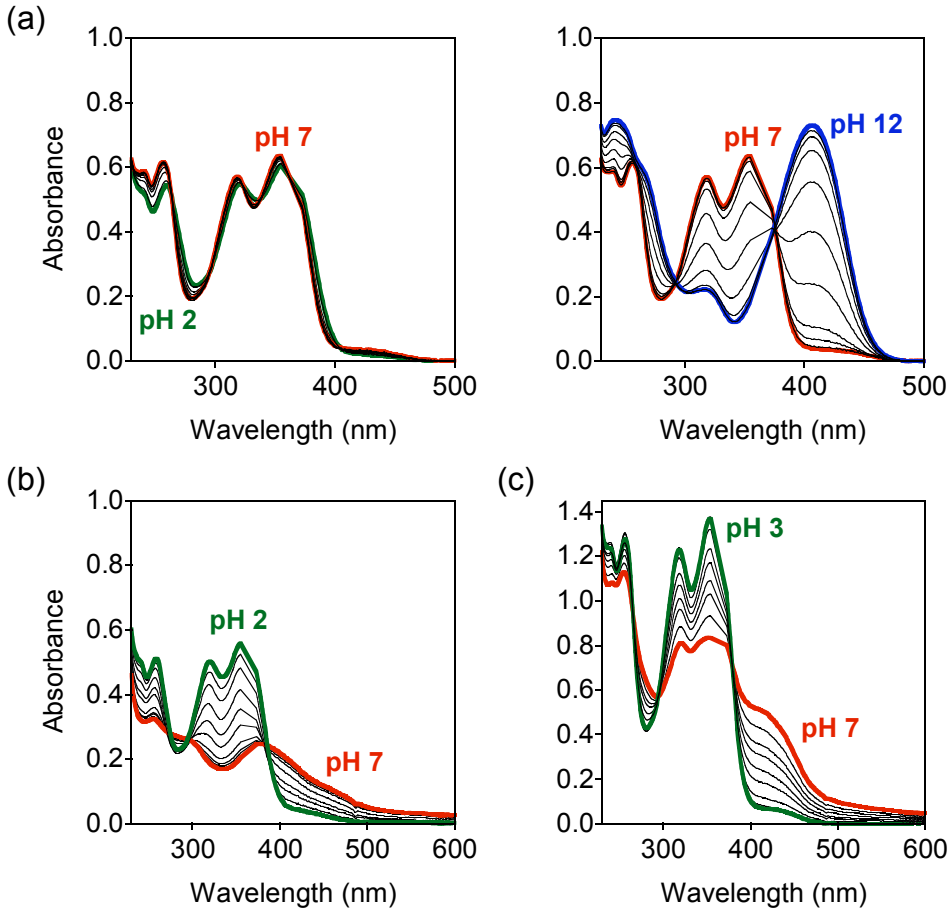

Fig. S2 UV-Vis variable-pH titration spectra of (a) **FL4** (left, pH 2.0 to 7.0; right, pH 7.0 to 12; [**FL4**] = 50 μM), (b) **FL4** with Cu^{2+} (pH 2.0 to 7.0; [**FL4**] = 50 μM, [$CuCl_2$] = 25 μM), and (c) **FL4** with Zn^{2+} (pH 3.0 to 7.0; [**FL4**] = 100 μM, [$ZnCl_2$] = 50 μM).

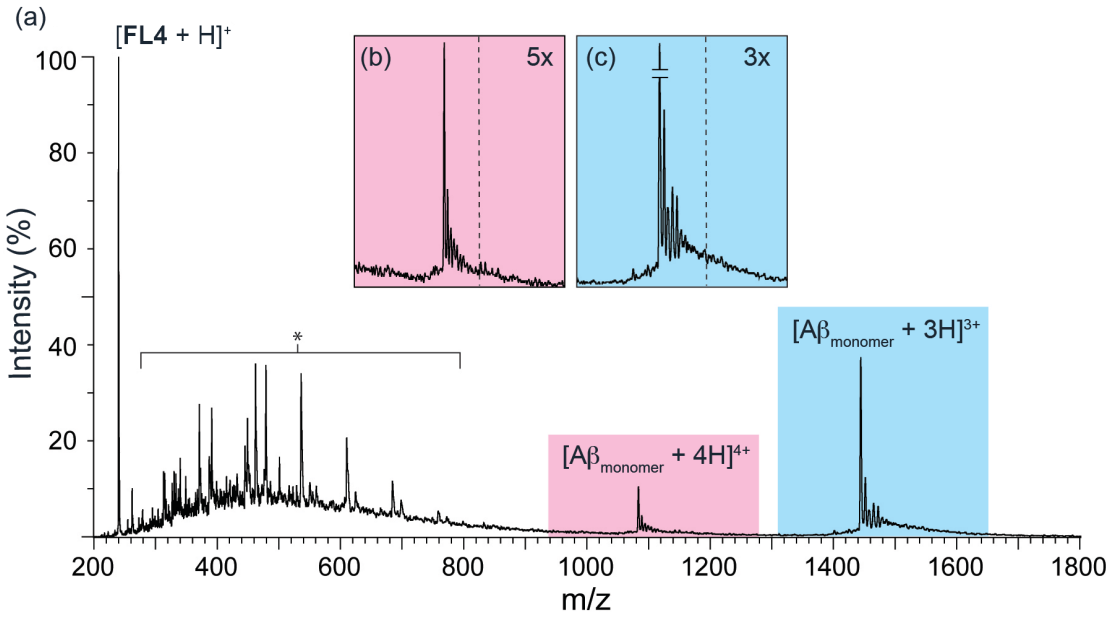

Fig. S3 Determination of the interaction of **FL4** with $A\beta_{1\text{-}40}$ monomer by mass spectrometry. (a) A mass spectrum of a sample containing **FL4** and $A\beta_{1\text{-}40}$ in a 5:1 molar ratio. Free ligand signal (observed as an $[M+H]^+$ ion) is observed in high abundance, as are signals for the monomeric Aβ peptide. Control data acquired for these experiments showed clear evidence for larger oligomers, as reported previously (data not shown). The peaks within the region marked with an * correspond to chemical noise peaks, primarily arising from the ammonium acetate buffer used to prepare the samples. (b) Inset showing ion intensity magnified by 5x for the region surrounding the 4+ charge state of the $A\beta_{1\text{-}40}$ peptide. The dashed line represents the region of the spectrum where a signal corresponding to the protein-ligand complex would be expected to appear. (c) Inset showing ion intensity magnified by 3x for the region surrounding the 3+ charge state of the $A\beta_{1\text{-}40}$ peptide. As in (b), the dashed line represents the region of the spectrum where a signal corresponding to the protein-ligand complex would be expected to appear. In both (b) and (c), no clear evidence of ligand binding to monomeric $A\beta_{1\text{-}40}$ is observed at the 5:1 molar ratio used here.

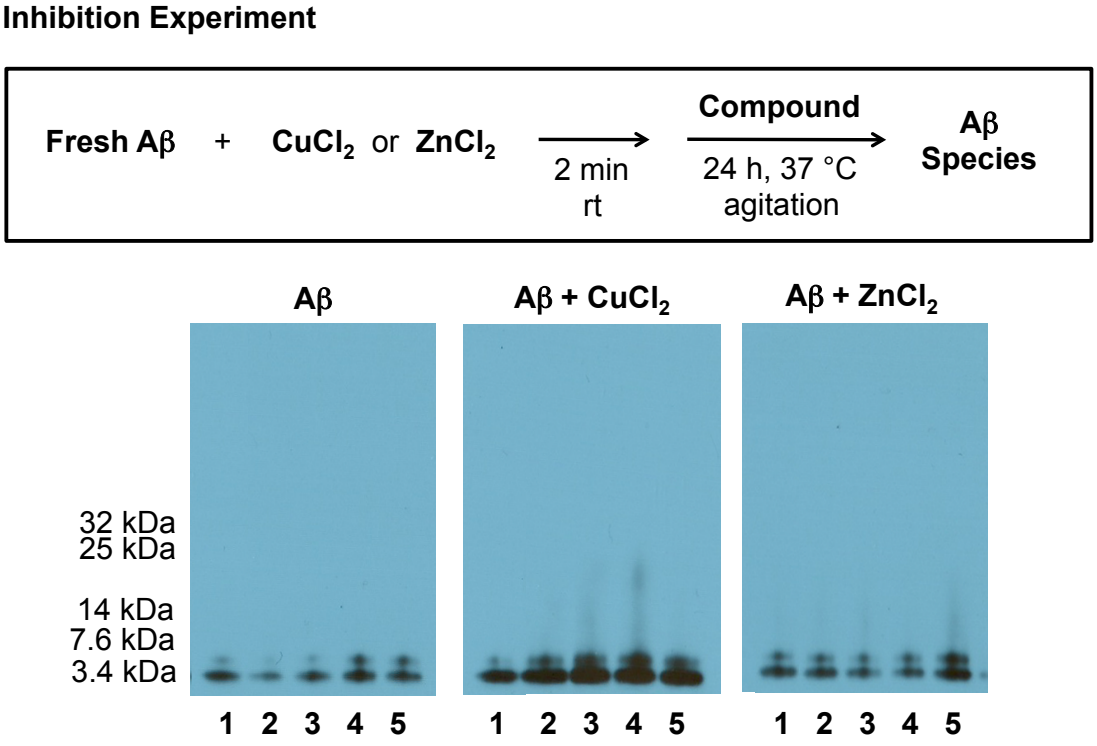

Fig. S4 Inhibition experiment. Top: Scheme of the inhibition experiment. Bottom: Results visualized by native gel electrophoresis followed by Western blotting (6E10). The samples include Aβ (10 μM) incubated with or without $CuCl_2$ or $ZnCl_2$ (10 μM) and ligand (20 μM) for 24 h at 37 °C with agitation (buffer condition: 20 μM HEPES, pH 6.6 for $CuCl_2$ or pH 7.4 for $ZnCl_2$, 150 μM NaCl). Lanes: 1) Aβ ± $CuCl_2$ or $ZnCl_2$; 2) 1 + **FL1**; 3) 1 + **FL2**; 4) 1 + **FL3**; 5) 1 + **FL4**.

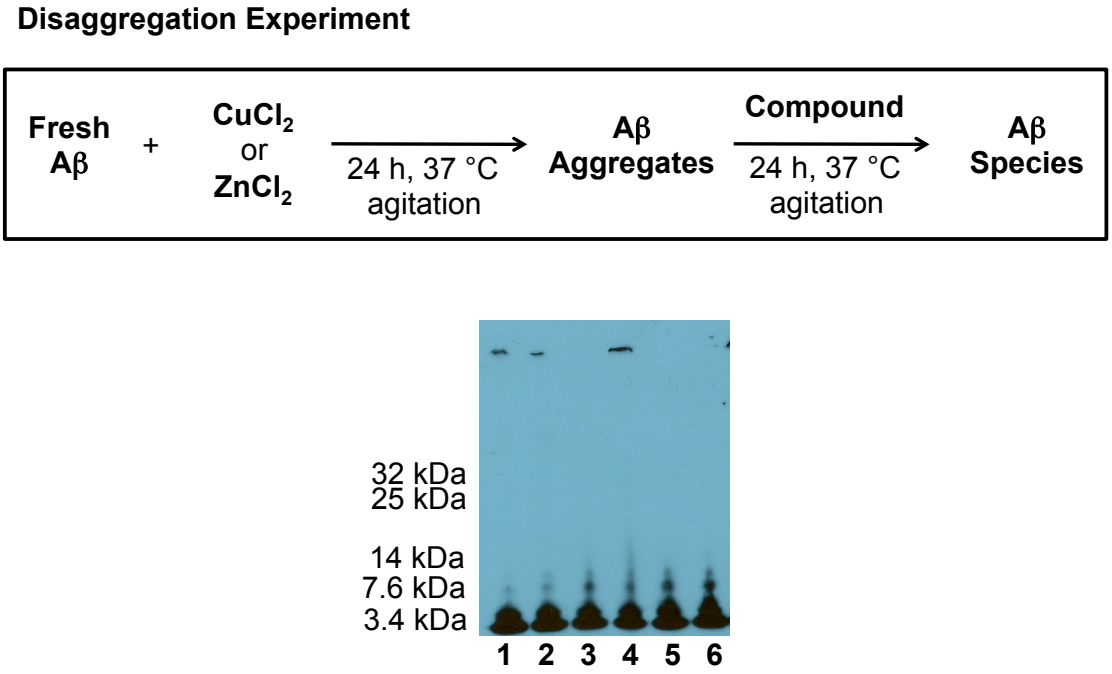

Fig. S5 Disaggregation experiment using **FL4**. Top: Scheme of the disaggregation experiment. Bottom: Results visualized by native gel electrophoresis followed by Western blotting (6E10). The samples include Aβ (25 μM) incubated with or without $CuCl_2$ or $ZnCl_2$ (25 μM) and **FL4** (50 μM) for 24 h at 37 °C with agitation (buffer condition: 20 μM HEPES, pH 6.6 for $CuCl_2$ or pH 7.4 for $ZnCl_2$, 150 μM NaCl). Lanes: 1) Aβ; 2) 1 + **FL4**; 3) Aβ + $CuCl_2$; 4) 3 + **FL4**; 4) Aβ + $ZnCl_2$ + **FL4**; 5) 4 + **FL4**.