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Supporting Information

Minor Structural Variations of Small Molecules Tune Regulatory Activities toward Pathological Factors in Alzheimer's Disease

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Experimental Section

Preparation of 1-4 and 7

1-**4** and **7** were obtained as previously reported.[1, 2]

Preparation of 5

The compound was purchased from Ryan Scientific (Mt. Pleasant, SC) and was purified by column chromatography (Al_2O_3, 3:1 hexanes : ethyl acetate (EtOAc), R_f = 0.51). Yellow oil. ^{1}H NMR [400 MHz; $(CD_3)_2SO$] δ (ppm): 8.51 (1H, dd, *J* = 4 Hz), 7.72 (1H, t, *J* = 8 Hz), 7.37 (1H, dd, *J* = 8 Hz), 7.23 (1H, t, *J* = 8 Hz), 6.54 (4H, q, *J* = 12 Hz), 5.67 (1H, t, *J* = 8 Hz), 4.28 (2H, d, *J* = 4 Hz), 3.10 (4H, q, *J* = 8 Hz), 0.96 (6H, t, *J* = 8 Hz). ^{13}C NMR (100 MHz; $(CD_3)_2SO$) δ (ppm): 160.3, 148.7, 140.5, 139.8, 136.5, 121.8, 121.1, 116.5, 113.6, 49.47, 44.81, 12.37. HRMS Calcd for $C_{16}H_{22}N_3$ $[M+H]^+$: 256.1814; found 256.1808.

Preparation of 6

The compound was purchased from Ryan Scientific, dried under vacuum to remove all traces of solvents, and used without any further purification (tan powder). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ (ppm): 8.51 (d, 1H, *J* = 4 Hz), 7.71 (t, 1H, *J* = 8 Hz), 7.21 (d, 1H, *J* = 8 Hz), 7.24 (d, 1H, *J* = 8 Hz), 6.73 (d, 2H, *J* = 8 Hz), 6.51 (d, 2H, *J* = 8 Hz), 5.93 (t, 1H, *J* = 8 Hz), 4.29 (d, 2H, J = 4 Hz), 3.68 (t, 4H, *J* = 4 Hz), 2.86 (t, 4H, *J* = 4 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2) δ (ppm): 159.2, 149.5, 144.1, 142.8, 136.7, 122.3, 121.89, 118.4, 114.2, 67.39, 51.5, 50.2. HRMS (*m/z*): $[M+H]^+$ Calcd for $C_{16}H_{20}N_3O$, 270.1601; found, 270.1595.

Preparation of 8

The compound was purchased from Ryan Scientific and was recrystallized from 1:1 CH_2Cl_2 : hexanes 1x and washed 2x with hexanes. Light brown powder. ^{1}H NMR (400 MHz; CD_2Cl_2) δ (ppm): 8.55 (d, 1H, *J* = 4 Hz), 7.61 (t, 1H, *J* = 8 Hz), 7.33 (d, 1H, *J* = 4 Hz), 6.63 (d, 2H, *J* = 8 Hz), 6.53 (d, 2H, *J* = 8 Hz), 4.52 (m, 1H), 4.15 (s, 1H), 2.76 (s, 6H), 1.49 (d, 3H, *J* = 4 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2) δ (ppm): 165.1, 149.7, 144.7, 140.1, 137.0, 122.3, 120.9, 115.8, 115.4, 56.0, 42.3,

23.6. HRMS Calcd for $C_{15}H_{20}N_3$ $[M+H]^+$: 242.1652; found 242.1649.

Preparation of 9

The compound was purchased from Ryan Scientific (Mt. Pleasant, SC) and was recrystallized from EtOAc, CH_2Cl_2/hexanes, and washed twice with hexanes or dissolved in EtOAc and filtered over a neutral aluminum oxide plug. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ (ppm): 7.04 (d, 1H, *J* = 4 Hz), 6.76 (d, 1H, *J* = 4 Hz), 6.63 (m, 4H), 5.36 (t, 1H, *J* = 4 Hz), 4.18 (d, 2H, *J* = 4 Hz), 3.62 (s, 3H), 2.70 (s, 6H). ^{13}C NMR (100 MHz; CD_2Cl_2) δ (ppm): 146.2, 145.2, 140.7, 127.5, 121.9, 115.8, 151.2, 42.5, 42.3, 30.0. HRMS Calcd for $C_{13}H_{19}N_4$ $[M+H]^+$: 231.1604; found 231.1603.

Calculation of ionization potentials

First-principles calculations using Gaussian09[3] were performed using previously reported procedures.[1] Oxidation potentials were calculated using only thermodynamic parameters due to the difficulty of computing the kinetics of electron transfer steps. All the relevant chemical species were optimized at M06/6-31G(d) level, and their thermodynamic parameters were calculated at M06/6-311+G(2df,2p) level. All compounds were assumed to oxidize through the same pathway.

Electrochemistry

Cyclic voltammograms were recorded under N_2 (g) with a CHI620E model potentiostat (Qrins, Seoul, Republic of Korea). A three-electrode setup was utilized, consisting of a $Ag/AgNO_3$ reference electrode (Qrins, Seoul, Republic of Korea), a Pt wire auxiliary electrode (SPTE Platinum electrode; Qrins, Seoul, Republic of Korea), and a glassy carbon working electrode (Qrins, Seoul, Republic of Korea). The supporting electrolyte was 0.1 M $(Bu_4N)(ClO_4)$ in DMSO.

Parallel artificial membrane permeability assay adapted for blood-brain barrier (PAMPA-BBB)

PAMPA-BBB experiments were carried out using the PAMPA Explorer kit (*p*ION Inc., Billerica, MA, USA) using previously reported protocols.[1, 2, 4] UV−Vis absorbance values of the solutions in the reference, acceptor, and donor plates were measured using a microplate reader. The PAMPA Explorer software v. 3.5 (*p*ION) was used to calculate the $-\log P_e$ values for the compounds. CNS± designations were assigned by comparison to compounds that were identified in previous reports.[2, 5-7]

Aβ aggregation experiments

Aβ experiments were performed according to previously published methods.[1, 2, 4] Prior to experiments, $A\beta_{40}$ or $A\beta_{42}$ was dissolved in ammonium hydroxide (NH_4OH; 1% v/v, aq). The resulting solution was aliquoted, lyophilized overnight, and stored at −80 °C. A stock solution of Aβ was then prepared by dissolving lyophilized peptide in 1% NH_4OH (10 μL) and diluting with ddH_2O. The concentration of the solution was determined by measuring the absorbance of the solution at 280 nm (ε = 1450 $M^{-1}cm^{-1}$ for $A\beta_{40}$; ε = 1490 $M^{-1}cm^{-1}$ for $A\beta_{42}$). The peptide stock solution was diluted to a final concentration of 25 μM in Chelex-treated buffered solution containing HEPES [20 μM, pH 6.6 (for Cu^{II} samples) or pH 7.4 (for metal-free and Zn^{II} samples)] and NaCl (150 μM). For the inhibition studies, compounds (final concentration 50 μM, 1% v/v DMSO) were added to the sample of Aβ (25 μM) in the absence and presence of a metal chloride salt ($CuCl_2$ or $ZnCl_2$; 25, 50, 100 or 250 μM) followed by incubation at 37 °C with constant agitation for 4 or 24 h. For the disaggregation studies, Aβ with and without a metal chloride salt was incubated for 24 h at 37 °C with constant agitation to generate preformed Aβ aggregates. The resulting samples were then treated with compounds (50 μM) and incubated with constant agitation for additional 4 or 24 h.

Gel electrophoresis and Western blotting

The samples from the inhibition and disaggregation experiments were analyzed

by gel electrophoresis followed by Western blotting using an anti-Aβ antibody (6E10) using previously established procedures.[1, 2, 4] Samples (10 μL) were separated on a 10-20% Tris-tricine gel (Invitrogen, Grand Island, NY, USA). Following separation, the proteins were transferred onto nitrocellulose membranes and blocked with bovine serum albumin (BSA, 3% w/v, Sigma-Aldrich, St. Louis, MO, USA) in Tris-buffered saline (TBS) containing 0.1% Tween-20 (TBS-T) for 2 h at room temperature or overnight at 4 °C. The membranes were incubated with an anti-Aβ antibody (6E10, 1:2,000, Covance, Princeton, NJ, USA) in a solution of 2% BSA (w/v in TBS-T) for 4 h at room temperature or overnight at 4 °C. After washing with TBS-T (3x, 10 min), a horseradish peroxidase-conjugated goat antimouse secondary antibody (1:5,000 in 2% BSA w/v in TBS-T; Cayman Chemical Company, Ann Arbor, MI, USA) was added for 1 h at room temperature. The Thermo Scientific SuperSignal West Pico Chemiluminescent Substrate (Thermo Scientific, Rockford, IL, USA), Biosesang ECL Plus kit (Biosesang, Gyeonggi-do, Republic of Korea), or a homemade ECL kit[8] was used to visualize the results on a ChemiDoc MP Imaging System (Bio-Rad, Hercules, CA, USA).

Transmission electron microscopy (TEM)

Samples for TEM were prepared according to a previously reported method using glow-discharged grids (Formar/Carbon 300-mesh, Electron Microscopy Sciences, Hatfield, PA, USA).[1, 2, 4] Images for each sample were taken on a JEOL JEM-2100 transmission electron microscope [Ulsan National Institute of Science and Technology (UNIST) Central Research Facilities, UNIST, Ulsan, Republic of Korea].

Determination of solution speciation for the Zn^{II}–1 Complex

The acidity and stability constants values for Zn^{II}–**1** complex were determined by UV−Vis variable-pH titrations as previously reported.[2] A solution (100 mM NaCl, 10 mM NaOH, pH 12) containing $ZnCl_2$ and **1** (100 μM) in a metal to ligand ratio of 1:2 was titrated with small additions of HCl and at least 30 spectra were

recorded over the range pH 2−8. The acidity and stability constants were calculated by using the HypSpec program (Protonic Software, UK).[9] Speciation diagrams were modeled in the HySS2009 program (Protonic Software).[10]

2D NMR spectroscopy

The interaction of $A\beta_{40}$ with compounds were monitored by 2D band-Selective Optimized Flip-Angle Short Transient Heteronuclear Multiple Quantum Coherence (SOFAST-HMQC) at 8 °C.[11] Uniformly-^{15}N-labeled $A\beta_{40}$ (rPeptide, Bogart, GA, USA) was first dissolved in 1% NH_4OH and lyophilized. The peptide was re-dissolved in 3 μL of DMSO-d_6 (Cambridge Isotope, Tewksbury, MA, USA) and diluted with phosphate buffer, NaCl, D_2O, and ddH_2O to a final peptide concentration of 80 μM (20 mM PO_4^{3-}, pH 7.4, 50 mM NaCl, 7% v/v D_2O). Ligands were dissolved in DMSO-d_6 (50 mM) and titrated into the solution of $A\beta_{40}$. Each spectrum was obtained using 64 complex t_1 points and a 0.1 sec recycle delay. The interaction of the tested compounds with Zn^{II}–$A\beta_{40}$ was also explored by SOFAST-HMQC at 8 °C. Uniformly-^{15}N-labeled $A\beta_{40}$ was treated as described above, but diluted into buffer containing 20 mM Tris, rather than PO_4^{3-}, to avoid complex formation with the Zn^{II}. To the solution of $A\beta_{40}$ was first added 1 equiv $ZnCl_2$ and then 1 equiv ligand was introduced to this solution. Each spectrum was obtained using 96 complex t_1 points and a 0.1 sec recycle delay. All data were acquired on a Bruker Avance 600 MHz spectrometer equipped with a cryoprobe. The 2D data were processed using TOPSPIN 2.1 (Bruker). Resonance assignment was performed with SPARKY 3.1134 using published assignments for $A\beta_{40}$ as a guide.[12-14] Chemical shift perturbation (CSP) was calculated using the following equation:

$$\Delta\delta_{NH} = \sqrt{(\Delta\delta H^2 + \left(\frac{\Delta\delta N}{5}\right)^2}$$

Ion mobility–mass spectrometry (IM–MS)

All IM–MS experiments were carried out on a Synapt G2 (Waters, Milford, MA).[15,

[16] Samples were ionized using a nano-electrospray ionization (nESI) source operated in positive ion mode. MS instrumentation was operated at a backing pressure of 2.7 mbar and sample cone voltage of 40 V. The *m*/*z* scale was calibrated using 20 mg/mL aqueous cesium iodide. For peptide-derivative-metal ligation studies aliquots of $A\beta_{40}$ peptides (final concentration 18 μM) were sonicated for 5 sec prior to preincubation with or without Cu^{II} (copper(II) acetate) at 37 °C for 10 min. After preincubation, samples were titrated with or without **5**-**9** (20, 40, and 200 μM) and incubated in the absence of light at 37 °C for 30 min prior to analysis. Solution conditions were 100 mM ammonium acetate (pH 7.5) with 1% v/v DMSO. The *m*/*z* scale was calibrated using 20 mg/mL aqueous cesium iodide. Accurate mass values for covalently modified species were calculated using the monoisotopic peak difference between the apo and modified states. All other conditions are consistent with previously published methods.[1, 17]

Antioxidant assay

The antioxidant activity of the compounds was determined by the TEAC assay employing N2a cell line (ATCC, Manassas, VA, USA) lysates following the previous reported procedures.[1, 2, 4] The percent inhibition [% inhibition = 100 x $(A_0 – A)/A_0$] was calculated using the absorbance of the samples with compound (A) compared to the absorbance of control samples lacking compound (A_0) and was plotted as a function of compound concentration. The TEAC value of ligands were calculated as a ratio of the slope of the standard curve of the compound to the slope of Trolox (Sigma-Aldrich; Trolox = 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid; dissolved in DMSO). Duplicate measurements were conducted in three different experiments.

2-Deoxyribose assay

The ability of compounds to control free radical formation from Fenton-like chemistry by $Cu^{I/II}$ was determined using previously reported procedures.[1, 18, 19]

Cell viability studies

The human neuroblastoma M17 cell line was purchased from the American Type Culture Collection (ATCC). The cell line was maintained in media containing 50% minimum essential medium (MEM) and 50% F12 (GIBCO, Grand Island, NY, USA), supplemented with 10% fetal bovine serum (FBS, Sigma), 100 U/mL penicillin, and 100 mg/mL streptomycin (GIBCO). The cells were grown and maintained at 37 °C in a humidified atmosphere with 5% CO_2. Cell viability upon treatment of compounds was determined using the MTT assay (Sigma). M17 cells were seeded in a 96 well plate (15,000 cells in 100 μL per well). The cells were treated with Aβ (20 μM) with or without $CuCl_2$ or $ZnCl_2$ (20 μM), followed by the addition of compound (20 μM, 1% v/v final DMSO concentration) and incubated for 24 h with the cells. After incubation, 25 μL MTT (5 mg/mL in phosphate buffered saline (PBS, pH 7.4, GIBCO) was added to each well and the plate was incubated for 4 h at 37 °C. Formazan produced by the cells was solubilized using an acidic solution of *N*,*N*-dimethylformamide (DMF, 50%, v/v aq) and sodium dodecyl sulfate (SDS, 20%, w/v) overnight at room temperature in the dark. The absorbance was measured at 600 nm using a microplate reader. Cell viability was calculated relative to cells containing an equivalent amount of DMSO.

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Table S1. Electrochemical parameters of **1**-**9**. All compounds showed irreverisble waves with the exception of **7** which did not exhibit an observable electrochemical behavior.

ν (mV/s)[a]	E_{pa1} (V)[b]	E_{pa2} (V)[c]	E_{pc1} (V)[d]	i_{pa1} (μA)[e]	i_{pa2} (μA)[f]	I_{pc1} (μA)[g]
			Compound 1			
25	0.246	0.489	0.328	15.12	8.28	-8.78
50	0.250	0.501	0.319	24.97	9.27	-11.12
100	0.255	0.508	0.311	34.55	10.17	-13.91
150	0.256	0.508	0.307	41.86	10.35	-17.91
200	0.260	0.516	0.311	47.14	9.76	-17.63
250	0.262	0.521	0.295	59.93	9.35	-22.11
			Compound 2			
25	0.862	–	–	53.59	–	–
50	0.878	–	–	71.74	–	–
100	0.897	–	–	93.80	–	–
150	0.903	–	–	116.05	–	–
200	0.911	–	–	134.45	–	–
250	0.923	–	–	139.63	–	–
			Compound 3			
25	0.224	–	–	36.22	–	–
50	0.242	–	–	52.57	–	–
100	0.257	–	–	70.64	–	–
150	0.271	–	–	88.35	–	–
200	0.280	–	–	98.62	–	–
250	0.284	–	–	115.8	–	–
			Compound 4			
25	0.207	–	–	37.1	–	–
50	0.221	–	–	54.08	–	–
100	0.224	–	–	88.45	–	–
150	0.240	–	–	102.78	–	–
200	0.246	–	–	123.67	–	–
250	0.240	–	–	143.98	–	–

Compound 5						
25	0.175			31.70		
50	0.187			43.38		
100	0.203			59.57		
150	0.209			70.47		
200	0.212			80.40		
250	0.228			83.83		
Compound 6						
25	0.327	–	–	46.87	–	–
50	0.353	–	–	69.48	–	–
100	0.374	–	–	91.93	–	–
150	0.382	–	–	111.20	–	–
200	0.398	–	–	130.13	–	–
250	0.388	–	–	153.04	–	–
Compound 8						
25	0.245	–	–	75.85	–	–
50	0.257	–	–	105.26	–	–
100	0.272	–	–	124.44	–	–
150	0.279	–	–	150.26	–	–
200	0.284	–	–	169.06	–	–
250	0.286	–	–	186.9	–	–
Compound 9						
25	0.213	–	–	41.01	–	–
50	0.227	–	–	61.15	–	–
100	0.241	–	–	82.11	–	–
150	0.247	–	–	99.11	–	–
200	0.249	–	–	113.79	–	–
250	0.238	–	–	142.15	–	–

[a] ν, scan rate (mV/s); [b] E_{pa1}, first peak anodic potential (V); [c] E_{pa2}, second peak anoidic potential (V); [d] E_{pc1}, first peak cathodic potential (V); [e] i_{pa1}, first peak anodic current (μA); [f] i_{pa2}, second peak anodic current (μA); [g] i_{pc1}, first peak cathodic current (μA).

Table S2. Values (MW, *c*logP, HBA, HBD, PSA, logBB, and logP_e) of **1**-**9**.

Compound/ Parameters	MW[a]	*c*logP[b]	HBA[c]	HBD[d]	PSA (Å^2)[e]	logBB[f]	−logP_e[g]	CNS +/– Prediction[h]	Ref.
1	199	1.96	3	3	50.9	−0.563	5.0(1)	CNS+	1
2	244	1.73	4	1	43.4	−0.249	4.2(8)	CNS+	1
3	277	3.14	3	1	28.2	0.191	4.2(2)	CNS+	1
4	215	1.86	3	2	31.1	−0.047	4.9(0)	CNS+	1
5	255	2.82	3	1	28.2	0.141	4.4(2)	CNS+	this work
6	269	1.05	4	1	37.9	−0.272	4.6(5)	CNS+	this work
7	229	1.98	5	3	4	−0.696	4.2(1)	CNS+	this work
8	241	2.07	1	1	1	0.0273	4.3(7)	CNS+	this work
9	230	1.10	76.2	28.2	33.1	−0.193	4.7(3)	CNS+	this work
Lipinski's rules & Others	≤ 450	≤ 5.0	≤ 10	≤ 5	≤ 90	< −1.0 poorly distributed in the brain	−logP_e < 5.4 (CNS+); −logP_e > 5.7 (CNS-)		

[a]MW, molecular weight; [b]*c*logP, calculated log of water–octanol partition coefficient; [c]HBA, hydrogen bond acceptor; [d]HBD, hydrogen bond donor; [e]PSA, polar surface area; [f]logBB = −0.0148 × PSA + 0.152 × *c*logP × 0.130; [g]Determined using the Parallel Artificial Membrane Permeability Assay adapted for BBB (PAMPA-BBB). [h]Compounds categorized as CNS+ have the possibility to penetrate the BBB and are available in the CNS. Compounds assigned as CNS– have poor permeability through the BBB; therefore, their bioavailability into the CNS is considered to be minimal.

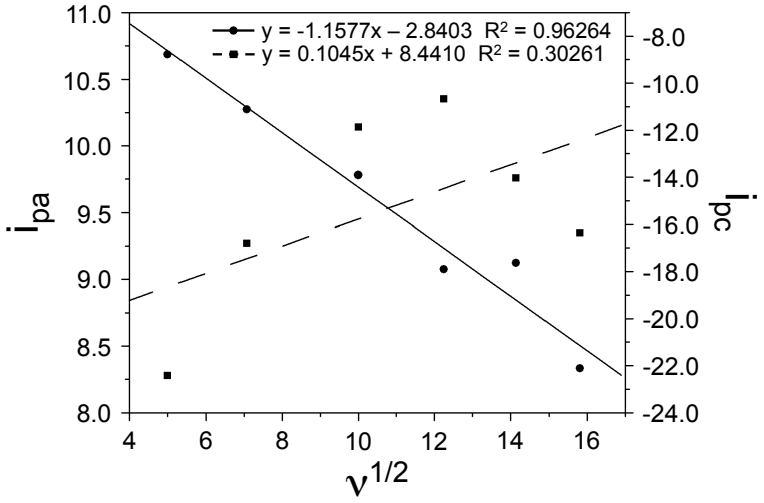


Figure S1. Cyclic voltametric analysis of **1**. Plot of the current (i_{pa} and i_{pc}) as a function of the (scan rate)$^{1/2}$ (*i.e.*, $\nu^{1/2}$), indicating the irreversible oxidation of **1**. Conditions: [**1**] = 1 mM; scan rate = 25, 50, 100, 150, 200, and 250 mV/s; room temperature; supporting electrolyte, 0.1 M (Bu_4N)(ClO_4) in DMSO.

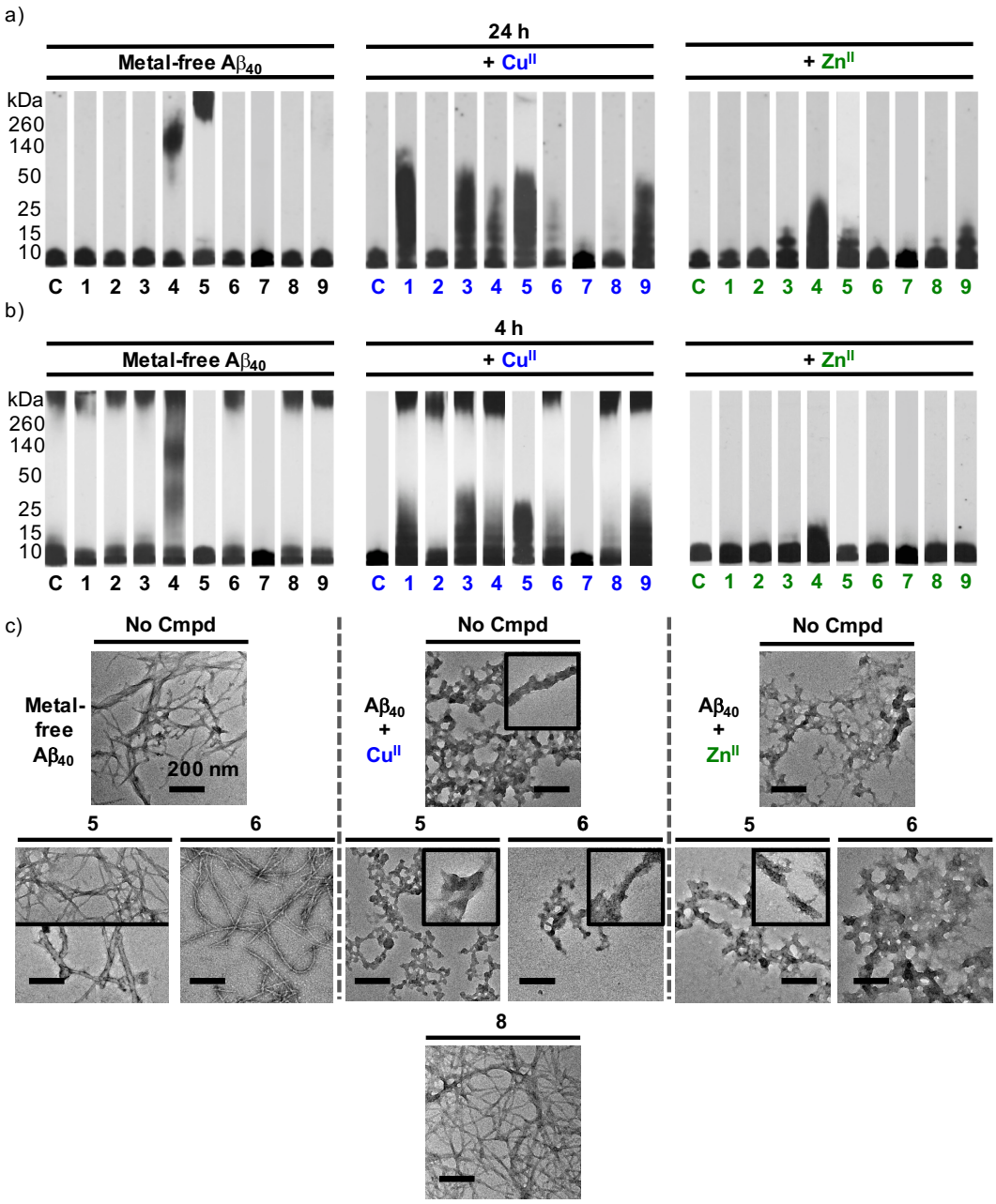


Figure S2. Inhibition of $A\beta_{40}$ aggregation by **1**-**9**. Analysis of the molecular weight of the resultant Aβ species after (a) 24 h or (b) 4 h treatment in the absence (left) or presence of Cu^{II} (middle; blue) or Zn^{II} (right; green) by gel electrophoresis and subsequent Western blotting (gel/Western blot) with an anti-Aβ antibody (6E10). (c) Morphologies of metal-free Aβ (left), Cu^{II}–Aβ (center), and Zn^{II}–Aβ (right) after 24 h incubation with the compounds, observed by TEM. Conditions: [Aβ] = 25 μM; [Cu^{II} or Zn^{II}] = 25 μM; [compound] = 50 μM; pH 6.6 (for Cu^{II}-containing samples) or pH 7.4 (for metal-free and Zn^{II}-containing samples); 37 °C; constant agitation.

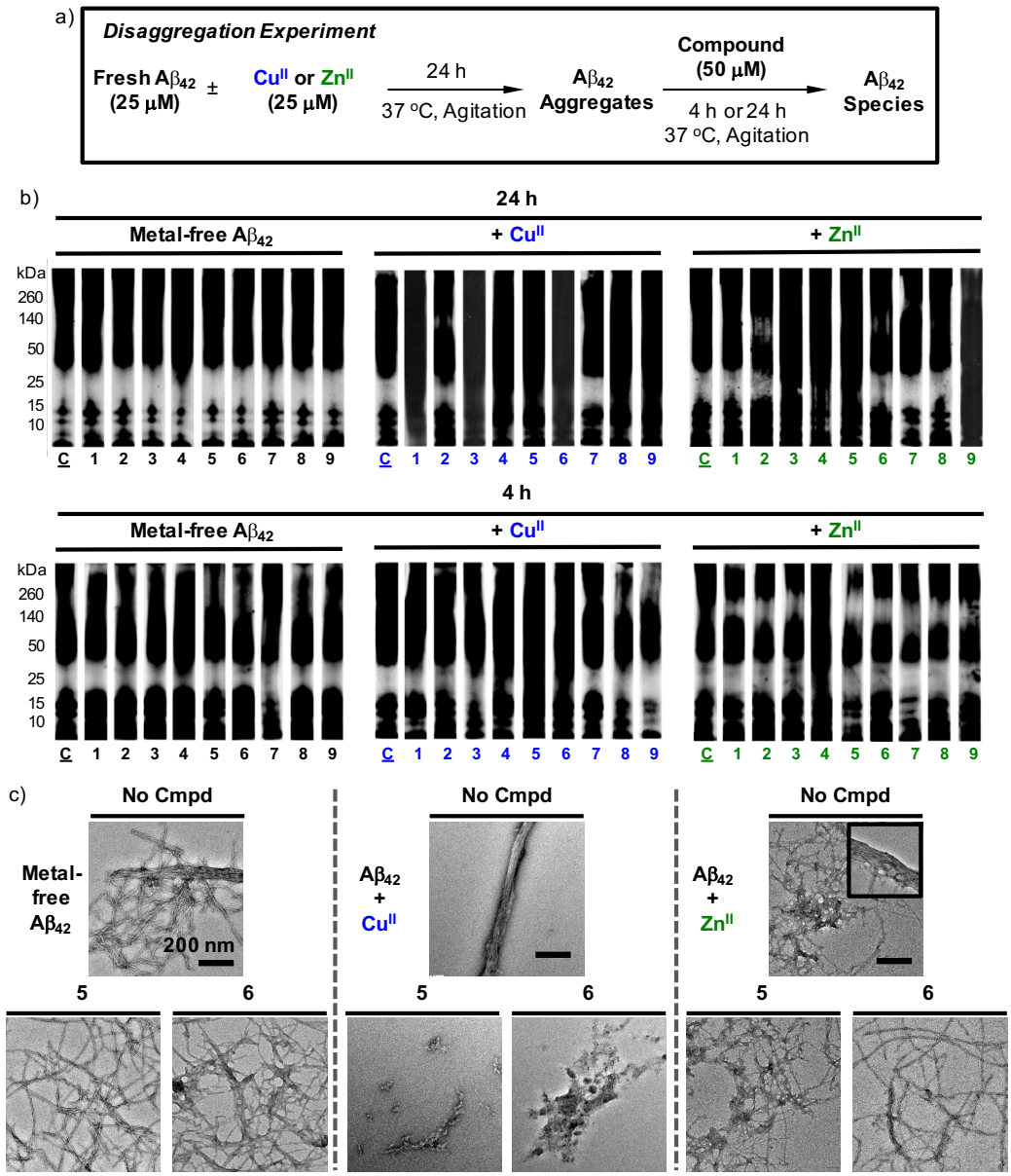


Figure S3. Disaggregation of preformed $A\beta_{42}$ aggregates by **1**-**9**. (a) Scheme of the disaggregation experiments. Mixtures of freshly prepared Aβ with or without Cu^{II} (blue) or Zn^{II} (green) were treated with compounds (**1**-**9**) and incubated for 4 h or 24 h before analysis. Samples excluding compounds (lane C) were also prepared as a control. Conditions: [Aβ] = 25 μM; [M^{II}] = 25 μM; [compound] = 50 μM; pH 6.6 (for Cu^{II}-containing samples) or pH 7.4 (for metal-free and Zn^{II}-containing samples); 37 °C; constant agitation. (b) Analysis of the molecular weight of the resultant Aβ species after 4 h or 24 h incubation in the absence (left) or presence of Cu^{II} (middle) or Zn^{II} (right) by gel electrophoresis and subsequent Western blotting (gel/Western blot) with an anti-Aβ antibody (6E10). (c) TEM images of the Aβ aggregates before (top) and after treatment with **5** and **6** (bottom) (scale bar = 200 nm).

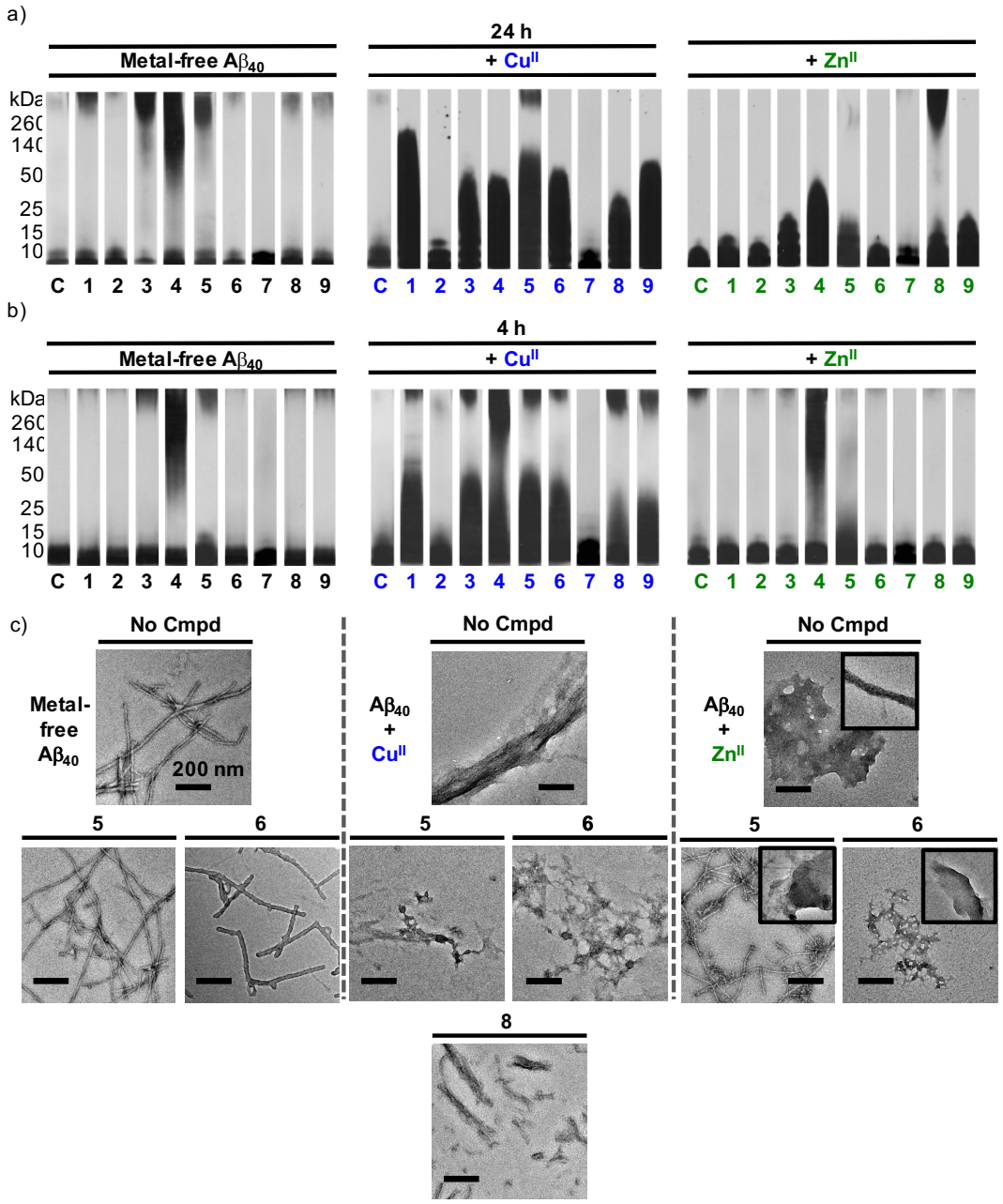


Figure S4. Disaggregation of preformed $A\beta_{40}$ aggregates by **1**-**9**. Analysis of the molecular weight of the resultant Aβ species after (a) 24 h or (b) 4 h treatment in the absence (left) or presence of Cu^{II} (middle; blue) or Zn^{II} (right; green) by gel electrophoresis and subsequent Western blotting (gel/Western blot) with an anti-Aβ antibody (6E10). (c) Morphologies of metal-free Aβ (left), Cu^{II}–Aβ (center), and Zn^{II}–Aβ (right) after 24 h incubation with the compounds, visualized by TEM. Conditions: [Aβ] = 25 μM; [Cu^{II} or Zn^{II}] = 25 μM; [compound] = 50 μM; pH 6.6 (for Cu^{II}-containing samples) or pH 7.4 (for metal-free and Zn^{II}-added samples); 37 °C; constant agitation.

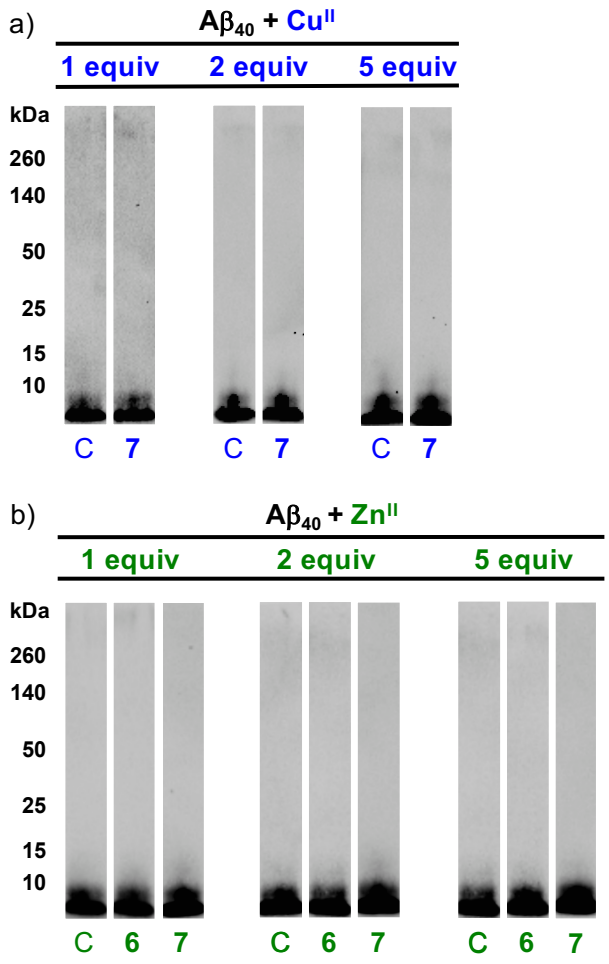


Figure S5. Inhibitory activity of compounds on $A\beta_{40}$ aggregation at higher ratios of metal to compound under the conditions of the inhibition experiments (Figure 2a) employing 1 equiv (left; 50 μM), 2 equiv (middle; 100 μM), and 5 equiv (right; 250 μM) of (a) Cu^{II} and (b) Zn^{II}.

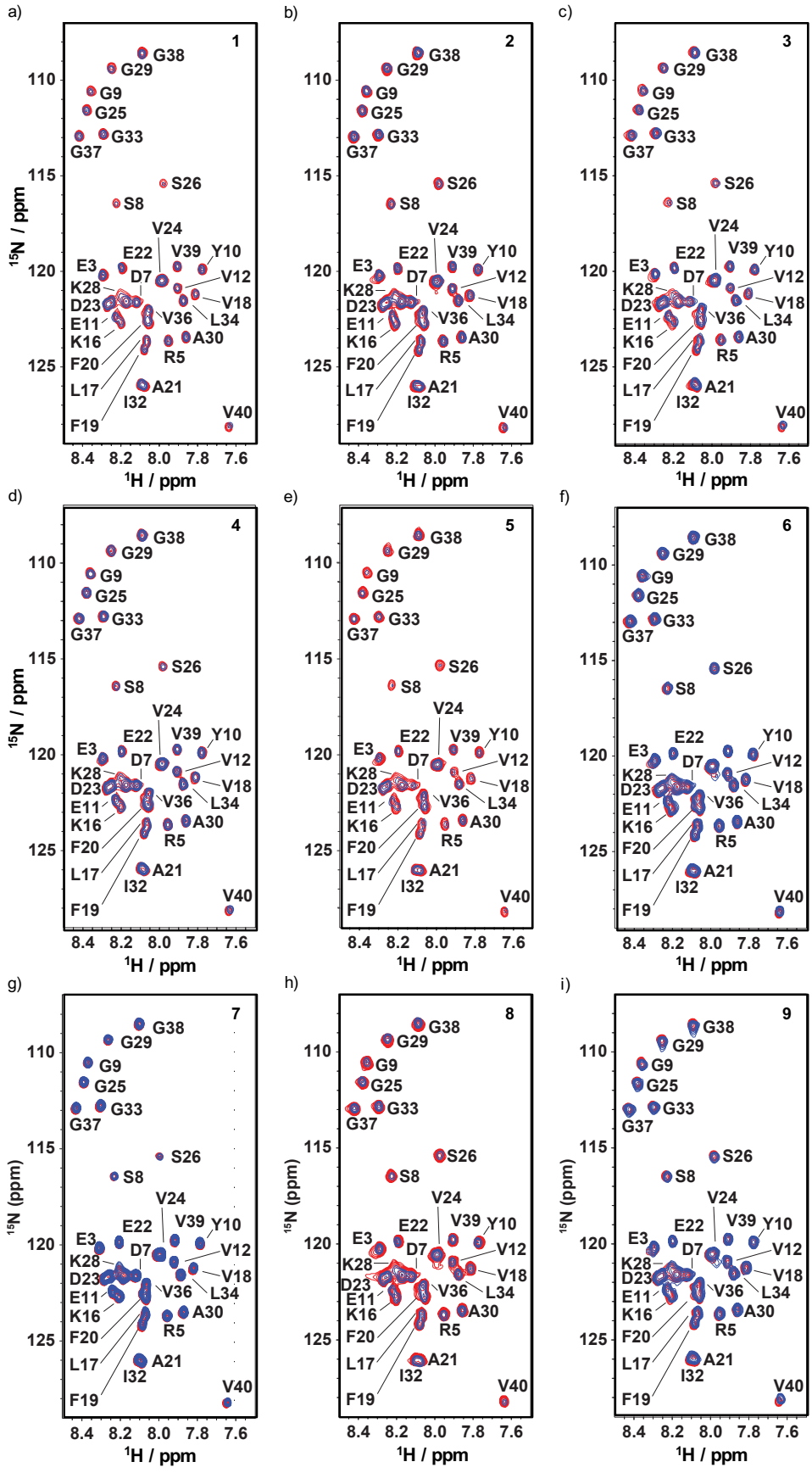

a)
1
b)
2
c)
3
d)
4
e)
5
f)
6
g)
7
h)
8
i)
9
G38
G29
G9
G25
G33
G37
S26
S8
V24
E22
V39
Y10
E3
D7
V12
K28
D23
V18
E11
V36
L34
K16
A30
R5
F20
L17
A21
I32
F19
V40
110
115
120
125
8.4
8.2
8.0
7.8
7.6
15N / ppm
15N (ppm)
1H / ppm

Figure S6. Interactions of compounds with ^{15}N-labeled Aβ_{40}. SOFAST-HMQC NMR (600 MHz) spectra before (blue) and after (red) addition of 10 equiv of (a) **1**, (b) **2**, (c) **3**, (d) **4**, (e) **5**, (f) **6**, (g) **7**, (h) **8**, and (i) **9**. Conditions: [^{15}N-labeled Aβ_{40}] = 80 μM; [compound] = 800 μM; 20 mM PO_4^{3-}, pH 7.4, 50 mM NaCl, 7% v/v D_2O; 8 °C.

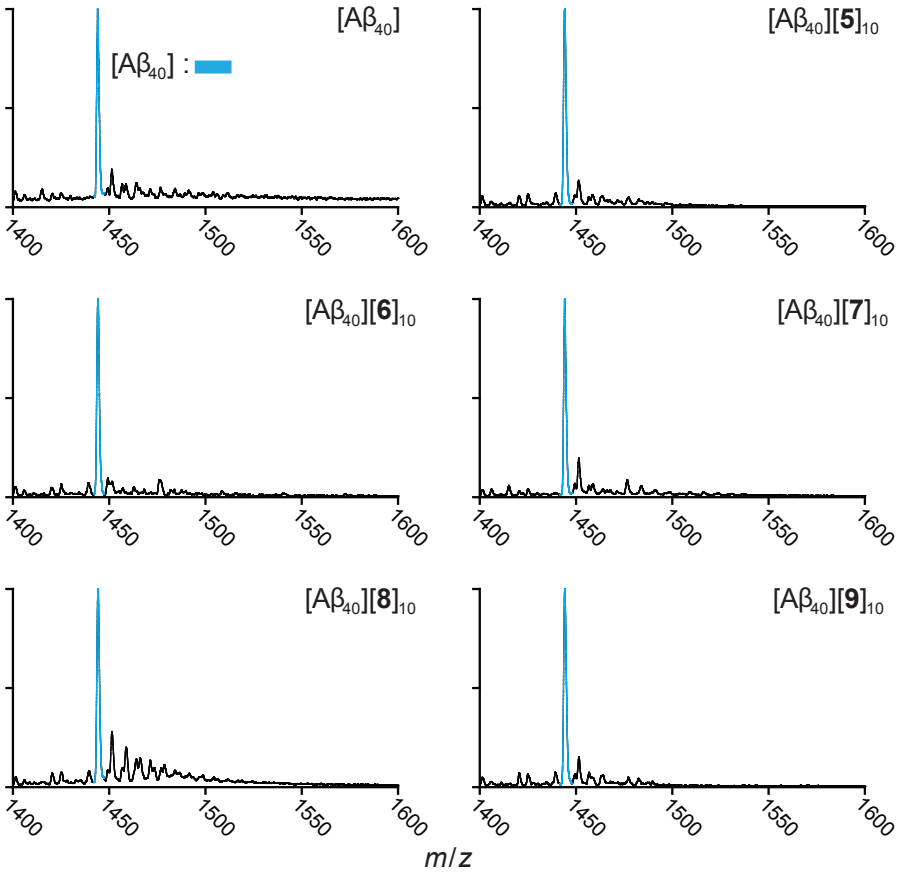
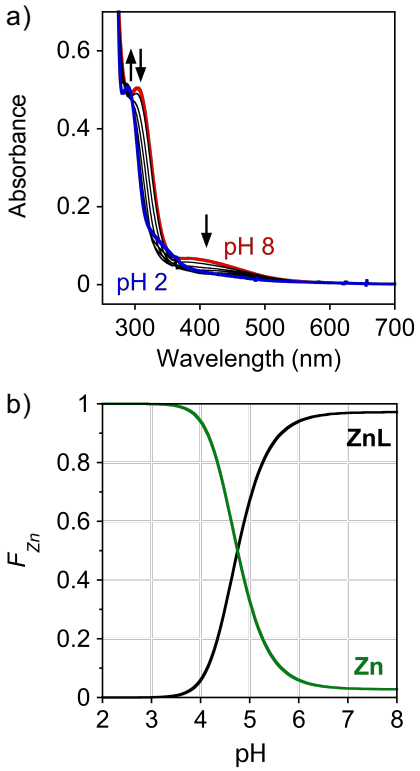


Figure S7. Mass spectrometric analysis of $A\beta_{40}$ incubated with **5-9** in the absence of a source of Cu^{II}. In the absence of Cu^{II}, no evidence of interactions between small molecules and metal-free $A\beta$ was observed with all data consistent with compound-free controls. Conditions: $[A\beta_{40}]$ = 20 μM (3+ charge state shown); [compound] = 200 μM.



c)

	logβ
L =	**1**
Zn + L ⇌ ZnL	5.5(3)
pZn (=−log[Zn^{II}]$_{free}$; pH 7.4)	5.54

Figure S8. Solution speciation studies of the Zn^{II}–**1** complex. (a) Variable pH UV-Vis titration spectra for Zn^{II}–**1** to determine stability constants (c, logβ) of Zn^{II}–L species and generate speciation diagrams (b, F_{Zn} = Fraction of free Zn^{II} and Zn^{II}–L). Parenthesis indicates that the error is in the last digit of the values. Conditions: Zn^{II}:L = 1:2; [**1**] = 100 μM; samples were incubated at room temperature for 24 h before titrations. Charges omitted for clarity.

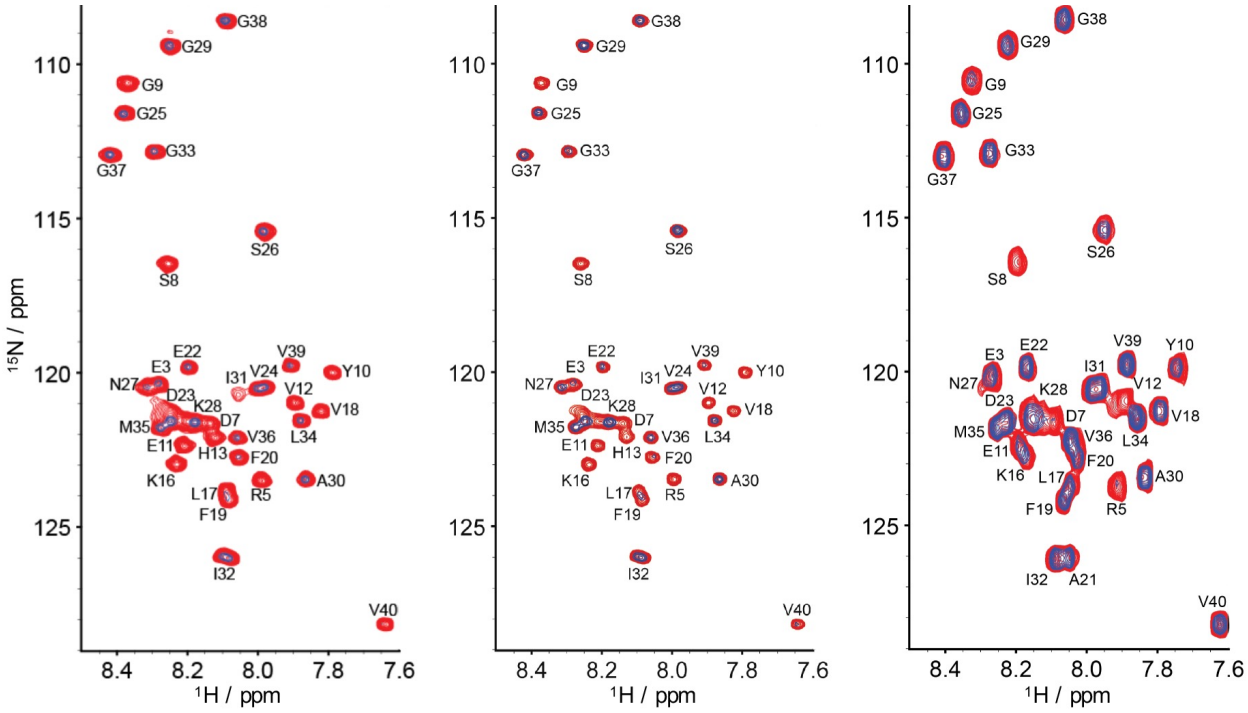


Figure S9. SOFAST-HMQC NMR (900 MHz) spectra of ^{15}N-labeled Aβ_{40} before (red) and after addition of Zn^{II} (blue) for the experiments with (left) **1**, (middle) **4**, and (right) **5**. Conditions: [^{15}N-labeled Aβ_{40}] = 80 μM; [$ZnCl_2$] = 80 μM; [compound] = 80 μM; 20 mM PO_4^{3-}, pH 7.4, 50 mM NaCl, 7% v/v D_2O; 8 °C.