Supplementary Information

Small Bifunctional Chelators that Do Not Disaggregate Amyloid Fibrils Exhibit Reduced Cellular Toxicity

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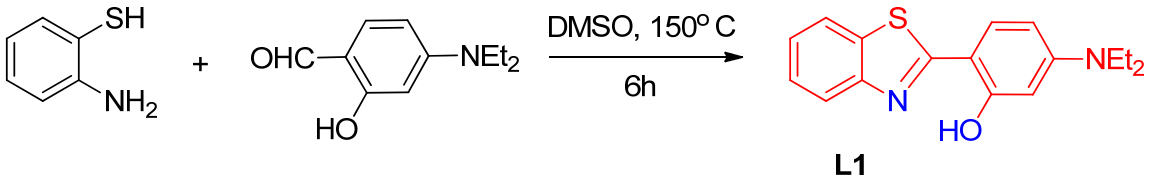
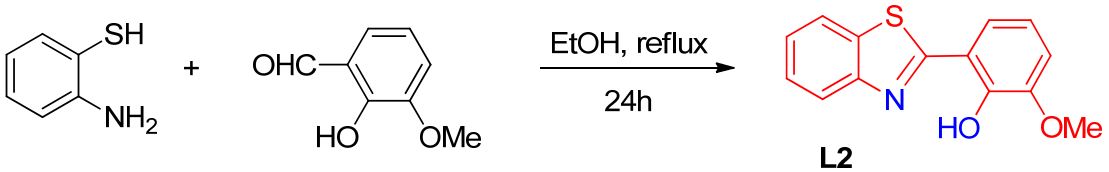
I. Synthetic schemes for L1 and L2.



L1



L2

II. UV-vis Spectra of L1 and L2.

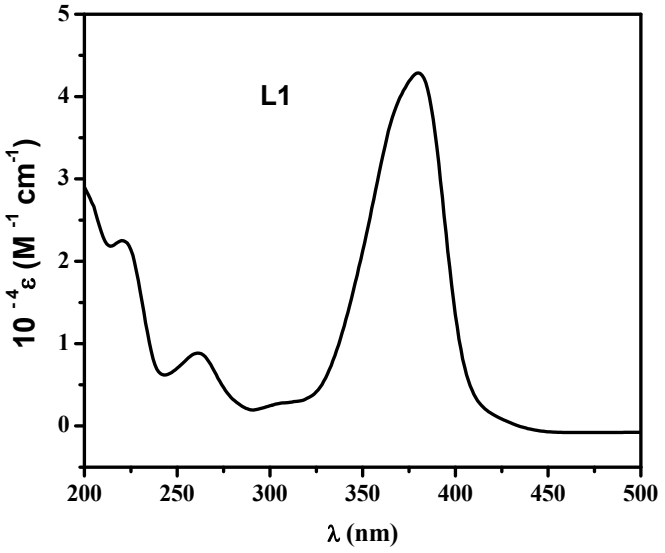


Figure S1. Absorption spectrum of L1 in MeCN.

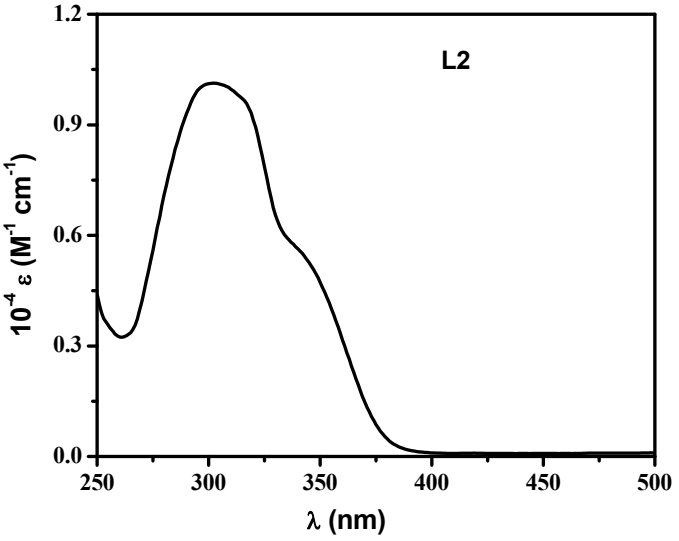


Figure S2. Absorption spectrum of L2 in MeCN.

III. Fluororescence Spectra of L1 and L2.

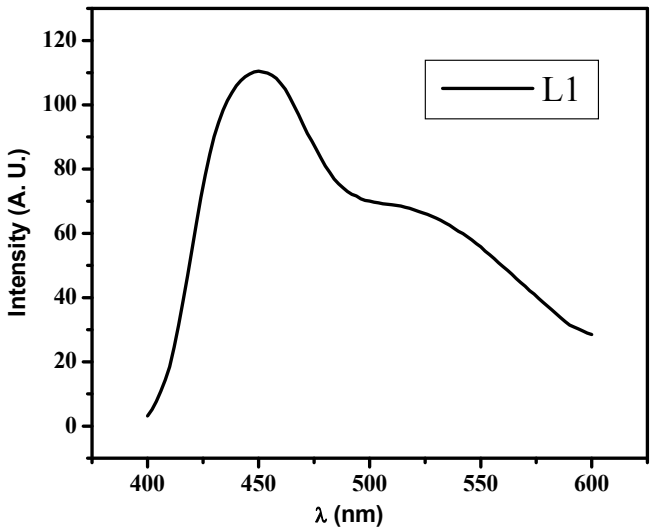


Figure S3. Emission spectrum of L1 in PBS (λ_{ex} = 380 nm).

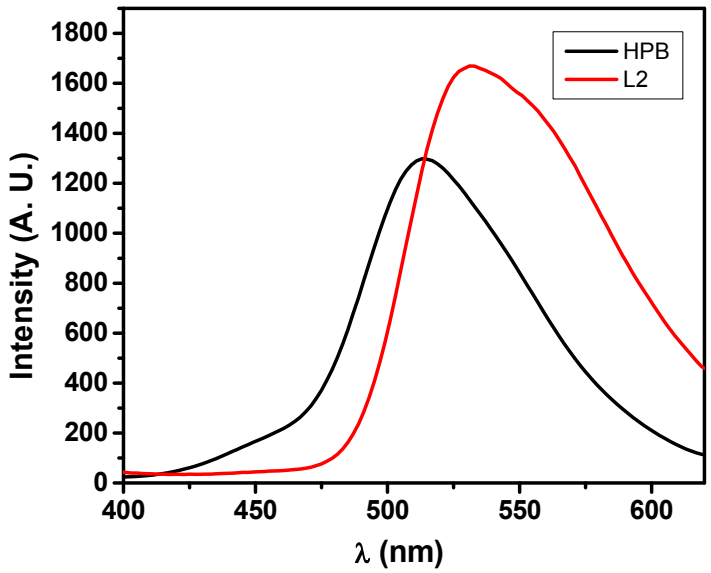


Figure S4. Emission spectrum of L2 and 2-(2-hydroxyphenyl)benzothiazole (HPB) in PBS (λ_{ex} = 320 nm).

IV. Job's Plot Analysis of L1 and Metal Ions.

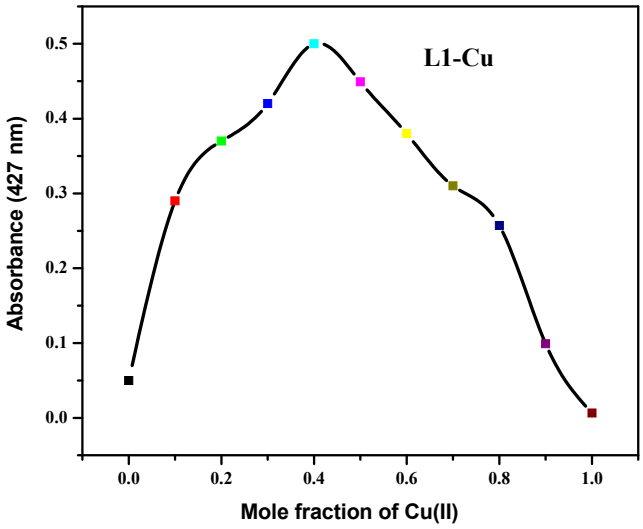


Figure S5. Job's plot for L1 and Cu^{2+} in MeCN.

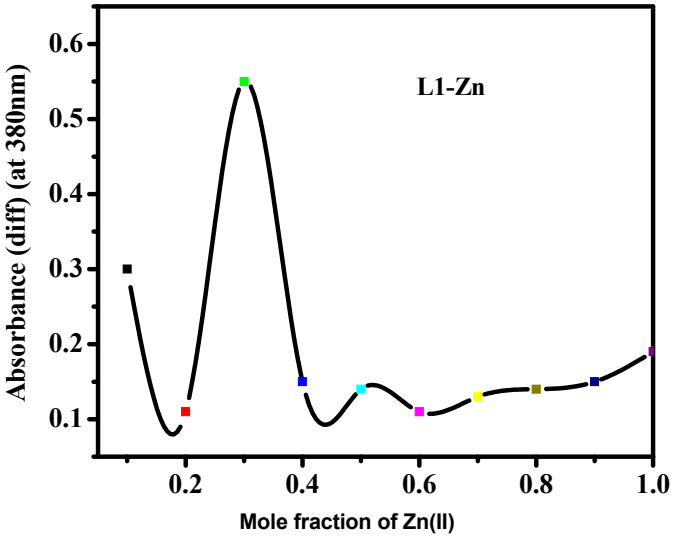


Figure S6. Job's plot for L1 and Zn^{2+} in MeCN.

V. UV-vis Spectra of Metal Complexes.

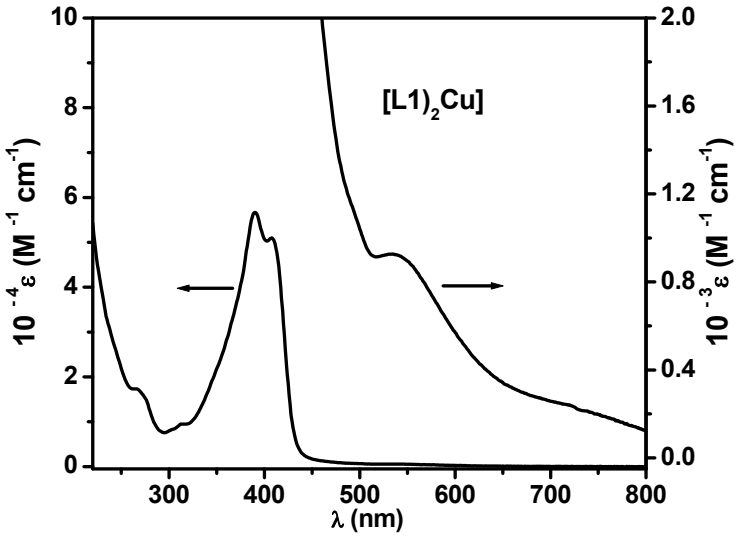


Figure S7. Absorption spectrum of $[(L1)_2Cu^{II}]$ in CH_2Cl_2.

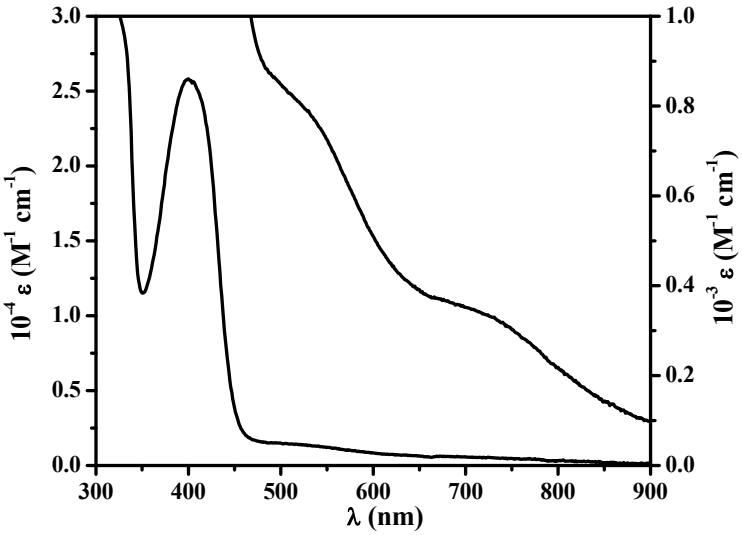


Figure S8. Absorption spectrum of $[(L2)_2Cu^{II}]$ in CH_2Cl_2.

VI. Inhibition of Aβ$_{40}$ Aggregation by L1 and L2.

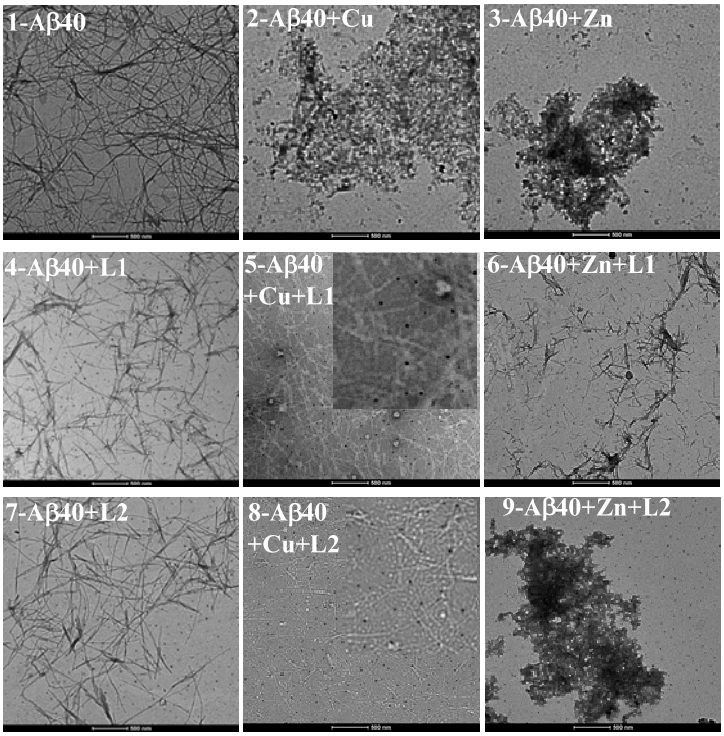


Figure S9. TEM images of the inhibition of Aβ$_{40}$ aggregation by L1 and L2, in the presence or absence of metal ions ([Aβ$_{42}$] = [M^{2+}] = 25 μM, [compound] = 50 μM, PBS, 37 °C, 24 h, scale bar = 500 nm). Panels are as follows: (1) Aβ$_{40}$; (2) Aβ$_{40}$ + Cu^{2+}; (3) Aβ$_{40}$ + Zn^{2+}; (4) Aβ$_{40}$ + L1; (5) Aβ$_{40}$ + L1 + Cu^{2+}(inset is an enlarged image to show fibrillar structures) (6) Aβ$_{40}$ + L1 + Zn^{2+}; (7) Aβ$_{40}$ + L2; (8) Aβ$_{40}$ + L2 + Cu^{2+} (inset is an enlarged image to show fibrillar structures); (9) Aβ$_{40}$ + L2 + Zn^{2+}.

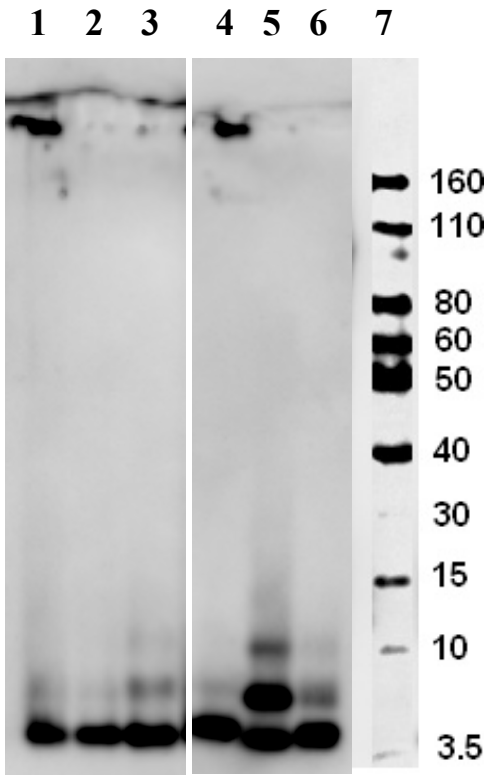


Figure S10. Native gel electrophoresis/Western blot analysis of the inhibition of $A\beta_{40}$ aggregation by L1 and L2, in the presence or absence of metal ions. Panels and lanes are as follows: (1) $A\beta_{40}$ + L1; (2) $A\beta_{40}$ + Cu^{2+} + L1; (3) $A\beta_{40}$ + Zn^{2+} + L1; (4) $A\beta_{40}$ + L2; (5) $A\beta_{40}$ + Cu^{2+} + L2; (6) $A\beta_{40}$ + Zn^{2+} + L2.

VII. Cellular Toxicity of Compounds.

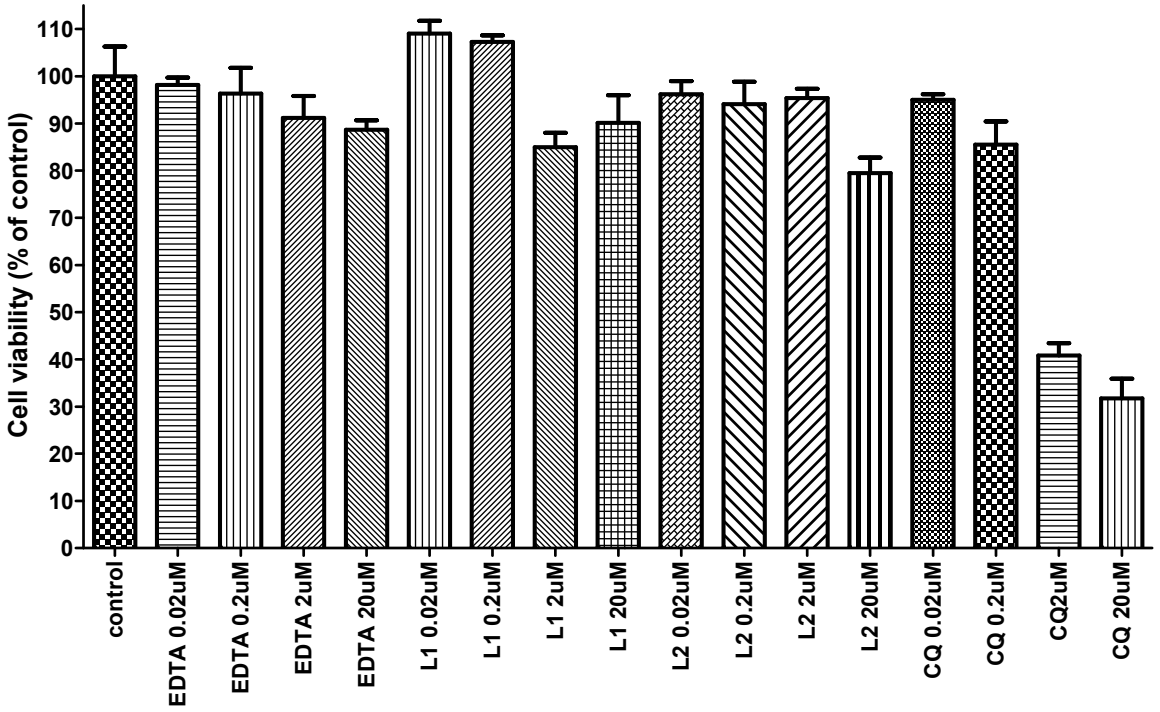


Figure S11. Cell viability (% control) of Neuro2A cells incubated with various amounts of ligands ranging from 0.2 to 20 μM.

VIII. X-ray Data for 1, 2, and-3.

Table S1. Crystal data and structure refinement for complex **1**.

Identification code	l3010/lt//lt/AS-NEt2-Cu	
Empirical formula	C_{34} H_{34} Cu N_4 O_2 S_2	
Formula weight	658.31	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 19.8642(16) Å	α = 90°
	b = 13.1133(11) Å	β = 116.072(4)°
	c = 12.7539(10) Å	γ = 90°
Volume	2984.1(4) $Å^3$	
Z	4	
Density (calculated)	1.465 Mg/m^3	
Absorption coefficient	0.911 mm^{-1}	
F(000)	1372	
Crystal size	0.30 x 0.19 x 0.16 mm^3	
Theta range for data collection	1.93 to 27.90°.	
Index ranges	$-26 \leq h \leq 25$, $-17 \leq k \leq 17$, $-16 \leq l \leq 16$	
Reflections collected	43481	
Independent reflections	3472 [R(int) = 0.084]	
Completeness to theta = 25.00°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8686 and 0.7691	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3472 / 4 / 205	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2sigma(I)]	R1 = 0.0493, wR2 = 0.1206	
R indices (all data)	R1 = 0.0723, wR2 = 0.1378	
Largest diff. peak and hole	0.984 and -0.932 e.$Å^{-3}$	

Table S2. Crystal data and structure refinement for **2**.

Identification code	l35409/lt/AKS-1-Zn	
Empirical formula	C_{23} H_{33} Cl_2 N_3 O S Zn	
Formula weight	535.85	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	$I4_1/a$	
Unit cell dimensions	a = 25.5583(11) Å	α = 90°
	b = 25.5583(11) Å	β = 90°
	c = 15.3021(7) Å	γ = 90°
Volume	9995.7(8) $Å^3$	
Z	16	
Density (calculated)	1.424 Mg/m^3	
Absorption coefficient	1.300 mm^{-1}	
F(000)	4480	
Crystal size	0.38 x 0.16 x 0.15 mm^3	
Theta range for data collection	2.22 to 27.57°.	
Index ranges	$-33 \leq h \leq 33$, $-33 \leq k \leq 33$, $-19 \leq l \leq 19$	
Reflections collected	185322	
Independent reflections	5779 [R(int) = 0.0516]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8268 and 0.6364	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5779 / 0 / 285	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0230, wR2 = 0.0553	
R indices (all data)	R1 = 0.0305, wR2 = 0.0594	
Largest diff. peak and hole	0.935 and -0.211 e.$Å^{-3}$	

Table S3. Crystal data and structure refinement for **3**.

Identification code	l2013/rt/smart/AS-L6-Cu	
Empirical formula	C_{28} H_{20} Cu N_2 O_4 S_2	
Formula weight	576.12	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1/n	
Unit cell dimensions	a = 8.3782(3) Å	α = 90°
	b = 22.6181(8) Å	β = 91.914(2)°
	c = 12.9135(4) Å	γ = 90°
Volume	2445.73(14) $Å^3$	
Z	4	
Density (calculated)	1.565 Mg/m^3	
Absorption coefficient	1.104 mm^{-1}	
F(000)	1180	
Crystal size	0.127 x 0.078 x 0.059 mm^3	
Theta range for data collection	1.801 to 24.999°.	
Index ranges	$-9 \leq h \leq 9$, $-26 \leq k \leq 26$, $-15 \leq l \leq 15$	
Reflections collected	45293	
Independent reflections	4299 [R(int) = 0.1176]	
Completeness to theta = 25.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9377 and 0.8726	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4299 / 1 / 341	
Goodness-of-fit on F^2	1.010	
Final R indices [I>2sigma(I)]	R1 = 0.0534, wR2 = 0.1142	
R indices (all data)	R1 = 0.1264, wR2 = 0.1474	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.821 and -0.353 $e.Å^{-3}$	