Supporting Information

Bimodal-hybrid heterocyclic amine targeting oxidative pathways and copper mis-regulation in Alzheimer's disease.

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Table S1. Calculated K_{ow} values to determine BBB permeability of **cyclen**.

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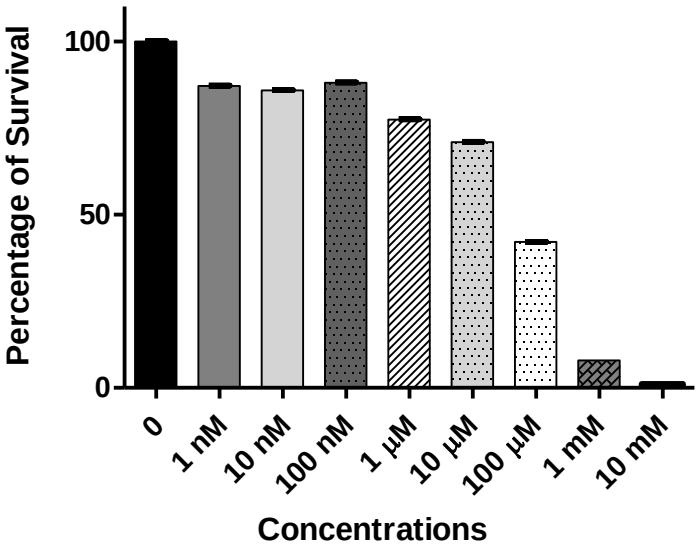
Experimental: Details of Spectrophotometric determination of K (mM^{-1}) for **cyclen** and **1**.



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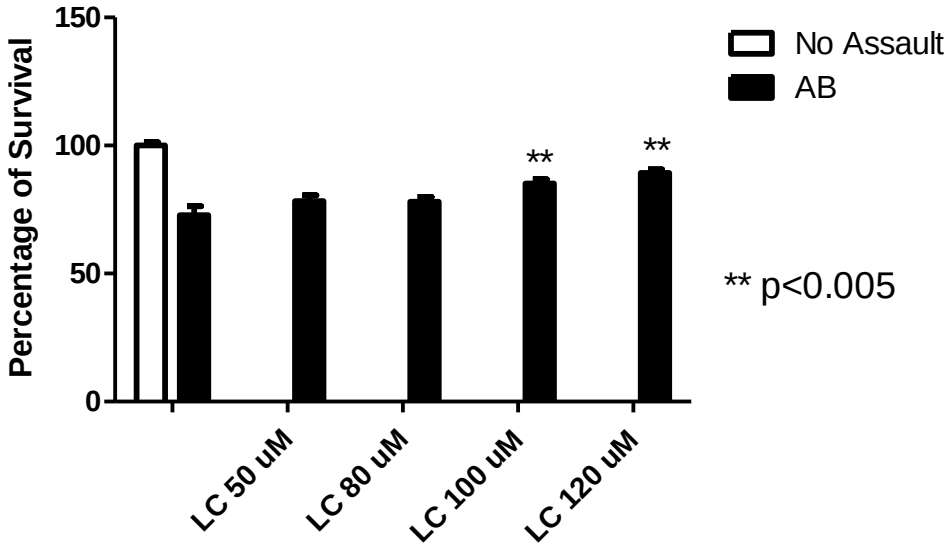


Figure S2. Protective effect of **1** against Aβ associated neurotoxicity in HT-22 cells in a 48 h. treatment using MTT assay. Aβ 15 µM; **1** 50, 80, 100, 120 µM.

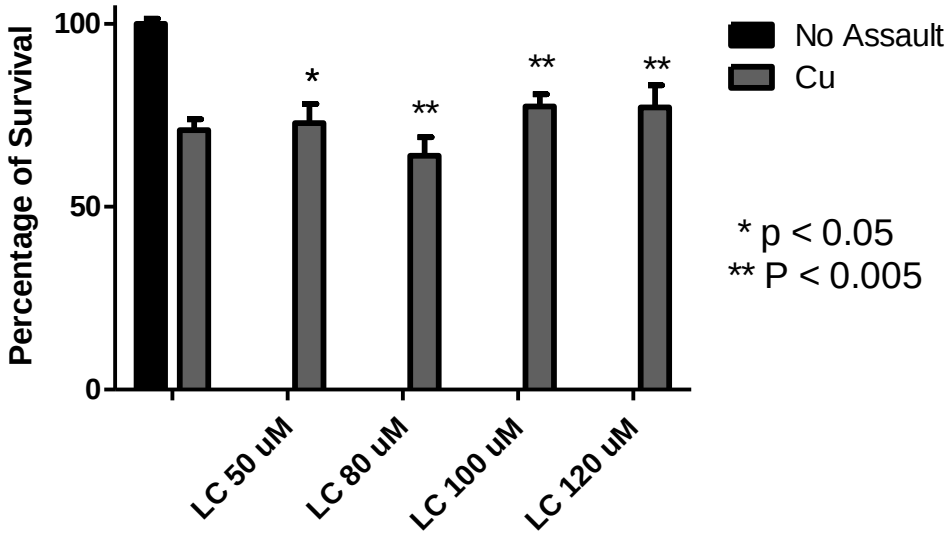
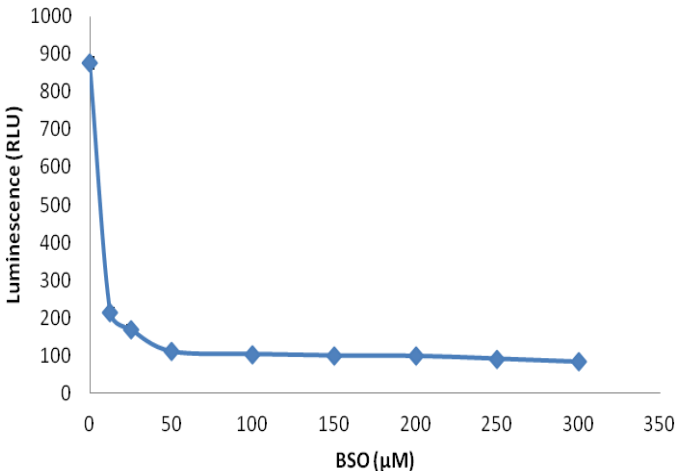
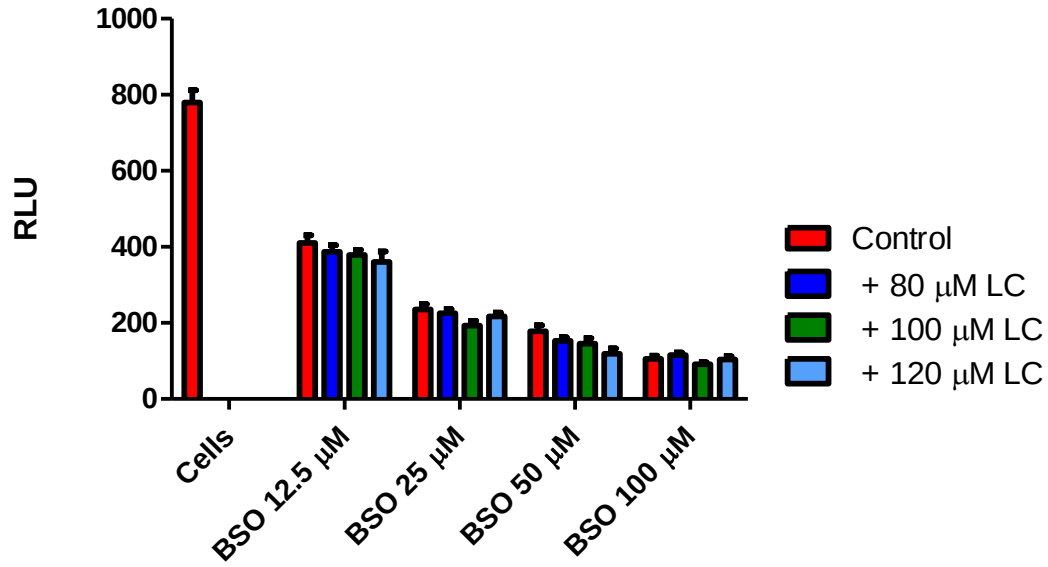


Figure S3. Protective effect of **1** against copper associated neurotoxicity in HT-22 cells in a 48 h. treatment using MTT assay. $CuCl_2$ 15 µM; **1** 50, 80, 100, 120 µM.



(a)



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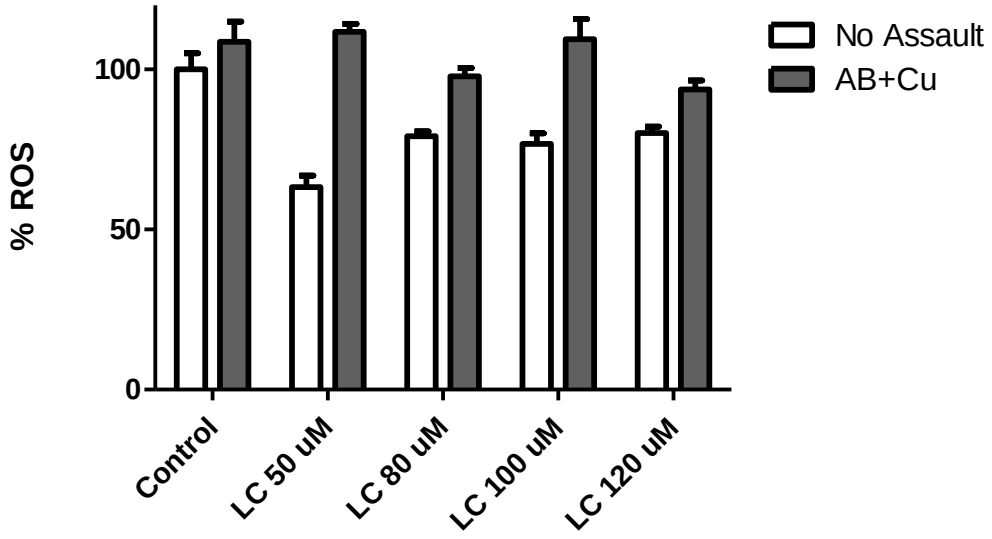

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Log K_{ow} fragment description	**Coefficient**	**Value obtained for 1**
| -CH2- [aliphatic carbon]	0.4911	3.9288
-NH- [aliphatic attach]	-1.4962	-5.9848
Equation Constant		0.2290
LogK_{ow}		**-1.8270**

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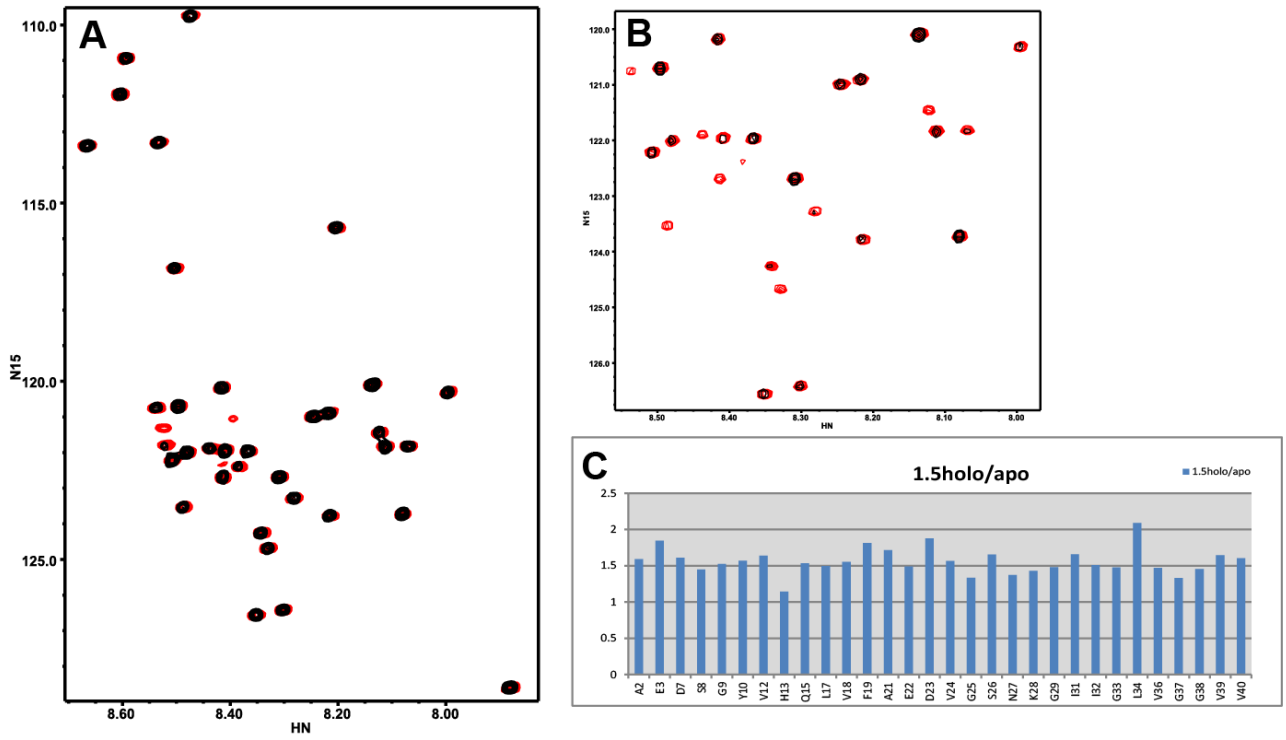

Figure S6. HSQC spectra of ^{15}N-A$\beta_{1\text{-}40}$ (black) and ^{15}N-A$\beta_{1\text{-}40}$ plus **1** (1.5 eq.) (red). (a) Full spectrum. (b) Expansion of the central region of the spectrum, plotted at higher contour levels than in panel (a) to emphasize the stronger intensities of the red cross-peaks compared to the corresponding black cross-peaks. (c) Changes in the HSQC cross-peak intensities of the A$\beta_{1\text{-}40}$ peptide caused by addition of **1** (1.5 eq.). The ratios between the cross-peak intensities of the A$\beta_{1\text{-}40}$ peptide plus 1.5 eq. of **1** (I) and those of the A$\beta_{1\text{-}40}$ peptide alone (I_0) are plotted as a function of the residue number.

Details of Spectrophotometric determination of K (mM^{-1}) for cyclen and 1.

Our data were examined using the one-to-one binding stoichiometry model: $\mathbf{M + L \rightleftharpoons ML}$, where M, L and ML represent free copper, free ligand and copper-ligand complex, respectively. The binding constant, *K*, can then be expressed in terms of molar concentrations of each component:

$$K = \frac{[\mathbf{ML}]}{[\mathbf{M}][\mathbf{L}]} \quad (1)$$

where [M], [L] and [ML] are the corresponding molar concentrations. The total copper concentration, C_M, is related to [M] by the mass balance $C_{\mathbf{M}} = [\mathbf{M}] + [\mathbf{ML}]$ and the total ligand concentration C_L to [L] by the mass balance $C_{\mathbf{L}} = [\mathbf{L}] + [\mathbf{ML}]$.

In order to express [M] has a function of *K*, C_M and C_L, it is useful to start by relating the fraction of copper-ligand complex, $\left([\mathbf{ML}]/C_{\mathbf{L}}\right)$, to the binding constant using equation 1 and the previous mass balances:

$$\frac{C_{\mathbf{M}} - [\mathbf{M}]}{C_{\mathbf{L}}} = \frac{K[\mathbf{M}]}{1 + K[\mathbf{M}]} \quad (2)$$

Equation 2 can be rearranged as a quadratic equation with respected to [M] and its positive root can be calculated:

$$[\mathbf{M}] = \frac{-(1 - KC_{\mathbf{M}} + KC_{\mathbf{L}}) + \sqrt{(1 - KC_{\mathbf{M}} + KC_{\mathbf{L}})^2 + 4KC_{\mathbf{M}}}}{2K} \quad (3)$$

At a given wavelength, the copper extinction coefficient, ε, in the presence of ligand, can be expressed as the weighted average between that of the free copper ions, ε_{free}, and bound copper, ε_{bound}, according to:

$$\varepsilon = \frac{[\mathbf{M}]}{C_{\mathbf{M}}}\varepsilon_{\mathbf{free}} + \frac{[\mathbf{ML}]}{C_{\mathbf{M}}}\varepsilon_{\mathbf{bound}} \quad (4)$$

In equation 4, it is useful to define $[M]/C_M$ has the fraction of free copper ions in solution, α_{free}. Therefore, we can rewrite equation 4 and express $\varepsilon/\varepsilon_{free}$ has a function of α_{free}.

$$\frac{\varepsilon}{\varepsilon_{\mathbf{free}}} = \alpha_{\mathbf{free}} + (1 - \alpha_{\mathbf{free}})R \quad (3)$$

where and $R=\varepsilon_{bound}/\varepsilon_{free}$ and

$$\alpha_{\mathbf{free}} = \frac{-(1 - KC_{\mathbf{M}} + KC_{\mathbf{L}}) + \sqrt{(1 - KC_{\mathbf{M}} + KC_{\mathbf{L}})^2 + 4KC_{\mathbf{M}}}}{2KC_{\mathbf{M}}} \quad (4)$$

The method of least squares (using KaleidaGraph software) based on equations 3 and 4 was applied to our experimental data to determine *K* and *R* (Table S3). The accuracy of the prepared **1** solutions concentration was assessed by substituting in equation (4) C_L with $fC_{\mathbf{L}}'$, where $C_{\mathbf{L}}'$ is the measured **1** concentration by weight and *f* is a corrective factor that takes into account that part of the total weighed material is impurity; hence, $f \leq 1$. This value of *f* is consistent with the actual concentration value extracted from NMR, being approximately 10% lower than that determined by sample weight.

Table S3. Fitting model parameters associated with copper-ligand binding.

	Cyclen[1]	**1**[1]
K **/mM^{-1}**	>100	6.4±1.7
R	179±1	14.7±0.2
f	1.05±0.01	0.88±0.02

[1]the uncertainties are standard deviations**.**