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\textsubscript{ow} values to determine BBB permeability of cyclen.

**Figure S6.** HSQC spectra of 15\textsuperscript{N}-Aβ\textsubscript{1-40} (black) and 15\textsuperscript{N}-Aβ\textsubscript{1-40} and 1 (1.5 eq.) (red). (a) full spectrum, (b) zoom of 15\textsuperscript{N} 120-125 ppm region and (c) change in intensity for residues in Aβ\textsubscript{1-40} peptide in the presence of 1 when compared to 15\textsuperscript{N}-Aβ\textsubscript{1-40} signal intensities alone.

**Experimental:** Details of Spectrophotometric determination of K (mM\textsuperscript{-1}) for cyclen and 1.
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<table>
<thead>
<tr>
<th>Log $K_{ow}$ fragment description</th>
<th>Coefficient</th>
<th>Value obtained for 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CH2- [aliphatic carbon]</td>
<td>0.4911</td>
<td>3.9288</td>
</tr>
<tr>
<td>-NH- [aliphatic attach]</td>
<td>-1.4962</td>
<td>-5.9848</td>
</tr>
<tr>
<td>Equation Constant</td>
<td></td>
<td>0.2290</td>
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<tr>
<td>Log$K_{ow}$</td>
<td></td>
<td>-1.8270</td>
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</table>

Table S1. Calculated $K_{ow}$ values to determine BBB permeability of cyclen.
Figure S6. HSQC spectra of $^{15}$N-Aβ$_{1-40}$ (black) and $^{15}$N-Aβ$_{1-40}$ 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 Aβ$_{1-40}$ peptide caused by addition of 1 (1.5 eq.). The ratios between the cross-peak intensities of the Aβ$_{1-40}$ peptide plus 1.5 eq. of 1 (I) and those of the Aβ$_{1-40}$ 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: $M + L \rightleftharpoons ML$, 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:

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

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

In order to express $[M]$ as a function of $K$, $C_M$ and $C_L$, it is useful to start by relating the fraction of copper-ligand complex, $\frac{[ML]}{C_L}$, to the binding constant using equation 1 and the previous mass balances:

$$\frac{C_M - [M]}{C_L} = \frac{K[M]}{1 + K[M]} \quad (2)$$

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

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

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

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

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

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

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

$$\alpha_{\text{free}} = \frac{-(1 - K C_M + K C_L) + \sqrt{(1 - K C_M + K C_L)^2 + 4 K C_M}}{2 K C_M} \quad (4)$$

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 $\hat{f} C_L'$, where $C_L'$ is the measured 1 concentration by weight and $\hat{f}$ is a corrective factor that takes into account that part of the total weighed material is impurity; hence, $\hat{f} \leq 1$. This value of $\hat{f}$ 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.

<table>
<thead>
<tr>
<th></th>
<th>Cyclen$^1$</th>
<th>1$^1$</th>
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<tbody>
<tr>
<td>$K$/mM$^{-1}$</td>
<td>&gt;100</td>
<td>6.4±1.7</td>
</tr>
<tr>
<td>$R$</td>
<td>179±1</td>
<td>14.7±0.2</td>
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<tr>
<td>$\hat{f}$</td>
<td>1.05±0.01</td>
<td>0.88±0.02</td>
</tr>
</tbody>
</table>

$^1$the uncertainties are standard deviations.