Electronic Supplementary Material (ESI) for Inorganic Chemistry Frontiers.

Supporting Information

for

Reactivities of Cyclam Derivatives with Metal–Amyloid-β

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Table S1 Summary of the X-ray crystallographic data for **1**.

Empirical formula	$C_{14}H_{28}N_4O$
Formula weight	268.4
Temperature	170 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P-1
Unit cell dimensions	a = 8.4724(6)Å b = 8.8104(6)Å β = 95.879(6)° c = 10.4428(7)Å
Volume	715.16(9) $Å^3$
Z	2
Density (calculated)	1.246 mg/m^3
Absorption coefficient	0.081 mm^{-1}
F(000)	296
Crystal size	0.37 x 0.12 x 0.05 mm^3
θ range for data collection	3.46 to 26.37°
Index ranges	-10<=h<=10, -11<=k<=10, -12<=l<=13
Reflections collected	5561
Independent reflections	2904 [R(int) = 0.0256]
Completeness to θ = 25.242°	99.6%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9960 and 0.9707
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2904 / 0 / 173
Goodness-of-fit on F^2	0.883
Final R indices [I>2σ(I)]	R1 = 0.0428, wR2 = 0.0874
R indices (all data)	R1 = 0.0847, wR2 = 0.0974
Extinction coefficient	n/a
Largest diff. peak and hole	0.243 and -0.159 e·$Å^{-3}$

Table S2 Summary of the acidity constants (pK_as) of **DMC**, **DMC-E**, **TMC**, and **TMC-E**.

	pK_a[a]					
L=	**Cyclam**[b]	**Cyclam-E**[b]	**DMC**	**DMC-E**	**TMC**	**TMC-E**
$LH \rightleftharpoons L + H$	11.54	11.16(1)	10.61(2)	10.88(2)	9.45(3)	9.69(2)
$LH_2 \rightleftharpoons LH + H$	10.35	10.14(2)	9.02(4)	8.89(4)	9.13(2)	9.13(2)
$LH_3 \rightleftharpoons LH_2 + H$	2.43	-	-	-	2.75(6)	2.27(3)
$LH_4 \rightleftharpoons LH_3 + H$	1.97	-	-	-	2.1(9)	-

Charges are omitted for clarity. Conditions: [compound] = 2 mM; 25 °C; I = 0.10 M in KNO_3. [a]Values in parentheses are standard derivations in the last significant digit. [b]The values are obtained from reference 1.

Reference

1. N. Camus, Z. Halime, N. le Bris, H. Bernard, M. Beyler, C. Platas-Lglesias and R. Tripier, A [two-step/one week] synthesis of *C*-functionalized homocyclens and cyclams. Application to the preparation of conjugable BCAs without chelating properties alteration, *RSC Adv.*, 2015, **5**, 85898–85910.

Table S3 Summary of the X-ray crystallographic data for [Cu(**DMC**)$(Cl)_2$].

Empirical formula	$C_{12}H_{28}Cl_2CuN_4$
Formula weight	362.82
Temperature	153(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 6.813(2) Å b = 12.552(5) Å β = 103.241(12)° c = 10.796(4) Å
Volume	898.6(6) $Å^3$
Z	2
Density (calculated)	1.341 mg/m^3
Absorption coefficient	1.507 mm^{-1}
F(000)	382
Crystal size	0.471 x 0.121 x 0.098 mm^3
θ range for data collection	3.620 to 27.999°
Index ranges	-8<=h<=8, -16<=k<=16, -13<=l<=14
Reflections collected	9934
Independent reflections	2133 [R(int) = 0.0586]
Completeness to θ = 25.242°	98.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7457 and 0.5275
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2133 / 0 / 92
Goodness-of-fit on F^2	1.038
Final R indices [I>2σ(I)]	R1 = 0.0510, wR2 = 0.1163
R indices (all data)	R1 = 0.0672, wR2 = 0.1284
Extinction coefficient	n/a
Largest diff. peak and hole	0.855 and -0.514 $e·Å^{-3}$

Table S4 Summary of the X-ray crystallographic data for [Zn(**DMC**)$(Cl)_2$].

Empirical formula	$C_{12}H_{28}N_4Cl_2Zn$
Formula weight	364.65
Temperature	100(2) K
Wavelength	0.700 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 16.424(3) Å b = 6.4810(13) Å β = 112.23(3)° c = 16.486(3) Å
Volume	1624.4(6) $Å^3$
Z	4
Density (calculated)	1.491 mg/m^3
Absorption coefficient	1.755 mm^{-1}
F(000)	768
Crystal size	0.034 x 0.032 x 0.012 mm^3
θ range for data collection	1.314 to 24.975°
Index ranges	-19<=h<=19, -7<=k<=7, -19<=l<=19
Reflections collected	8024
Independent reflections	2121 [R(int) = 0.0675]
Completeness to θ = 25.242°	97.1%
Absorption correction	Empirical
Max. and min. transmission	1.000 and 0.896
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2121 / 288 / 171
Goodness-of-fit on F^2	1.034
Final R indices [I>2σ(I)]	R1 = 0.0825, wR2 = 0.2324
R indices (all data)	R1 = 0.1133, wR2 = 0.2644
Largest diff. peak and hole	1.760 and –0.955 $e·Å^{-3}$

Table S5 Selected bond lengths (Å) and angles (°) for [Cu(**DMC**)$(Cl)_2$] and [Zn(**DMC**)$(Cl)_2$].

[Cu(**DMC**)$(Cl)_2$]		[Zn(**DMC**)$(Cl)_2$]	
Cu1–N1	1.987(3)	Zn1–N1	2.268(19)
Cu1–N2	2.066(3)	Zn1–N2	2.11(4)
Cu1–N3	1.987(3)	Zn1–N3	2.11(4)
Cu1–N4	2.066(3)	Zn1–N4	2.268(19)
Cu1–Cl1	2.982(1)	Zn1–Cl1	2.461(6)
Cu1–Cl2	2.982(1)	Zn1–Cl2	2.461(6)
N1–Cu1–N2	93.50(12)	N1–Zn1–N2	79.3(12)
N2–Cu1–N3	86.50(12)	N2–Zn1–N3	84.8(18)
N3–Cu1–N4	93.50(12)	N3–Zn1–N4	87.3(12)
N4–Cu1–N1	86.50(12)	N4–Zn1–N1	161.9(8)
N1–N2–N3–N4[a]	0	N1–N2–N3–N4[a]	80.59

[a]This angle was obtained by averaging the dihedral angles obtained from the two measurements.

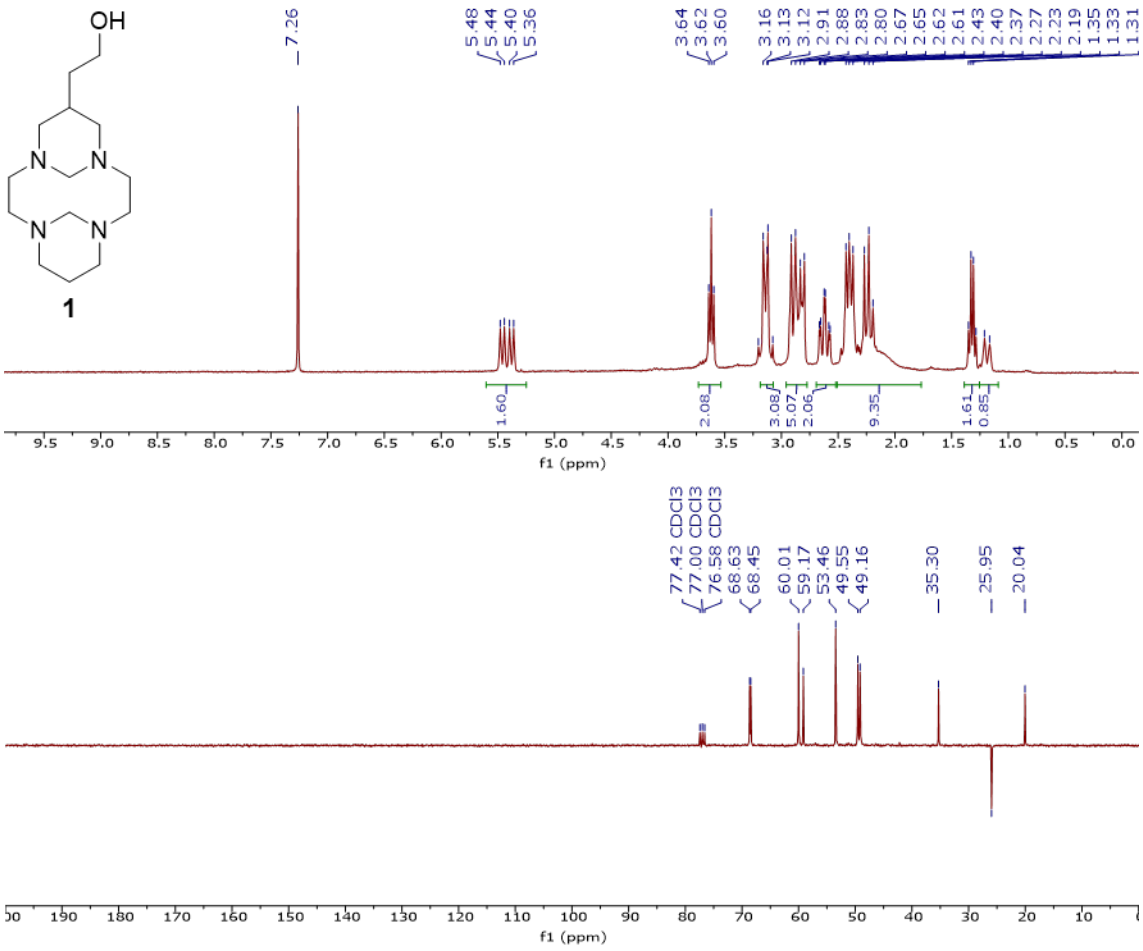

Fig. S1 NMR [^{1}H (300 MHz) and ^{13}C (75 MHz)] spectra of **1**.

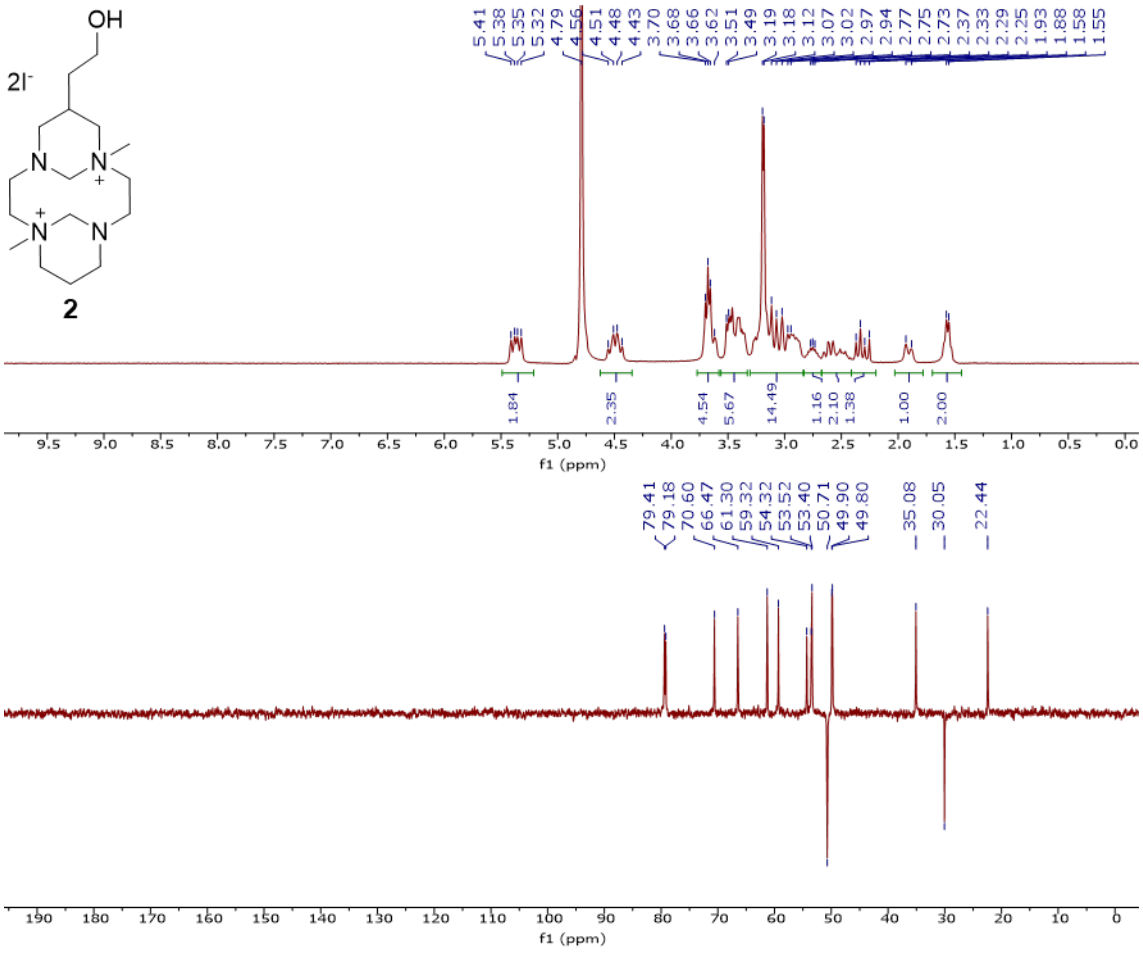

Fig. S2 NMR [^{1}H (300 MHz) and ^{13}C (75 MHz)] spectra of **2**.

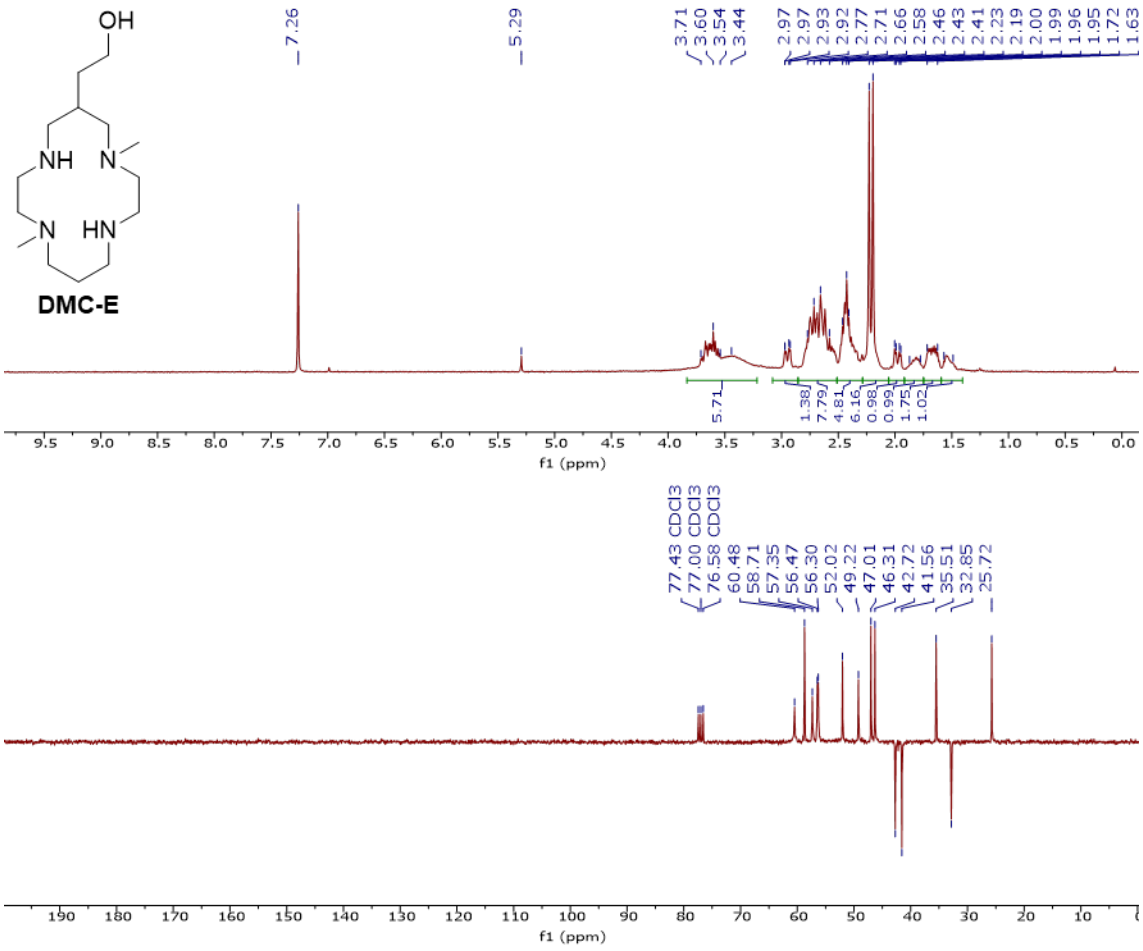

Fig. S3 NMR [^{1}H (300 MHz) and ^{13}C (75 MHz)] spectra of **DMC-E**.

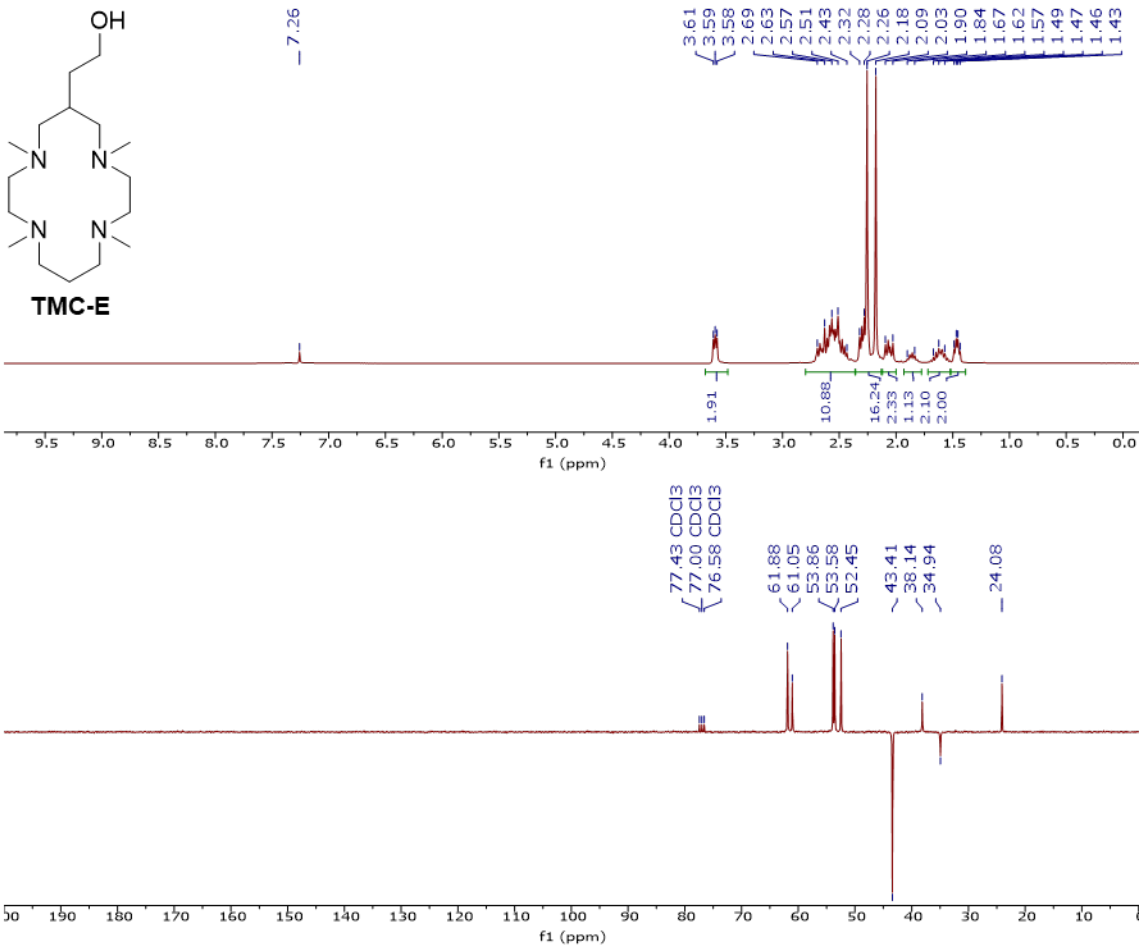

Fig. S4 NMR [^{1}H (300 MHz) and ^{13}C (75 MHz)] spectra of **TMC-E**.

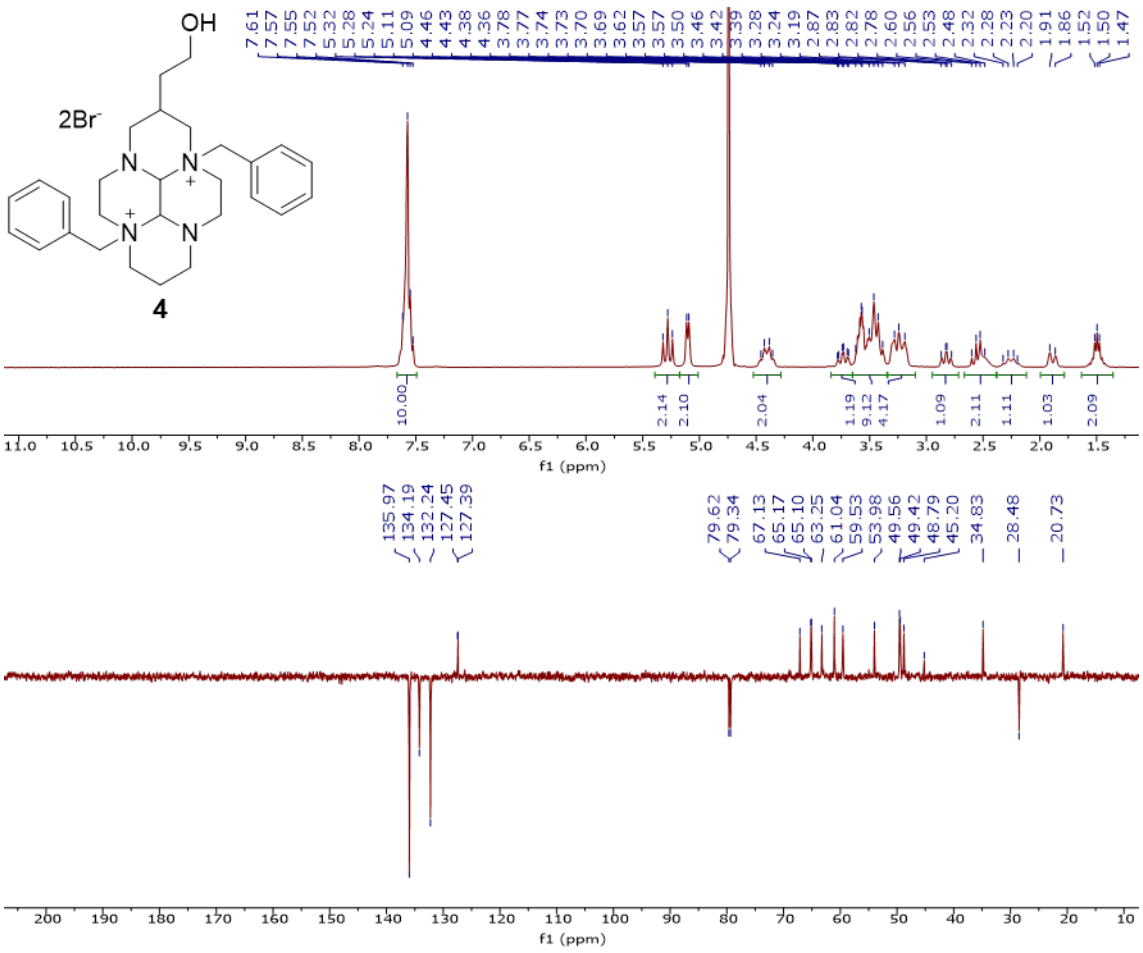

Fig. S5 NMR [^{1}H (300 MHz) and ^{13}C (75 MHz)] spectra of **4**.

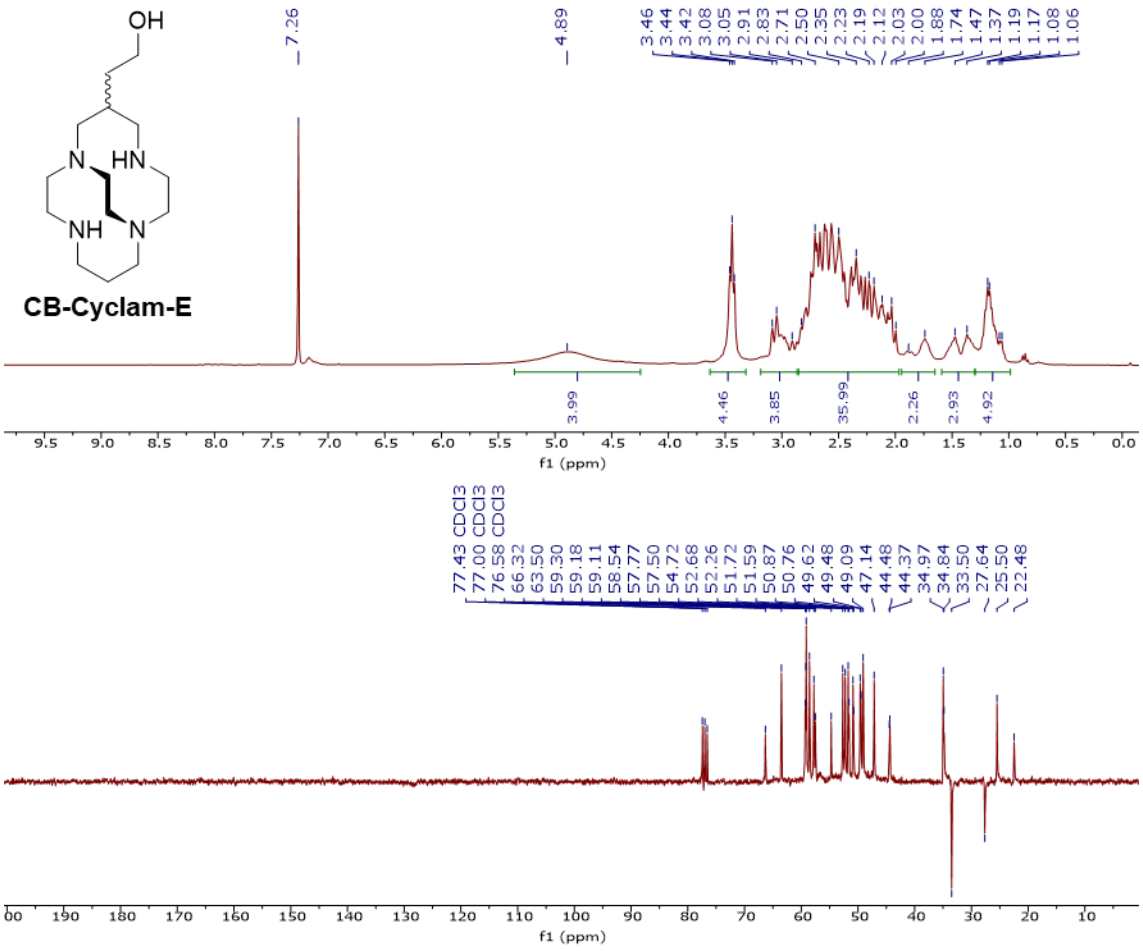

Fig. S6 NMR [^{1}H (300 MHz) and ^{13}C (75 MHz)] spectra of **CB-Cyclam-E**.

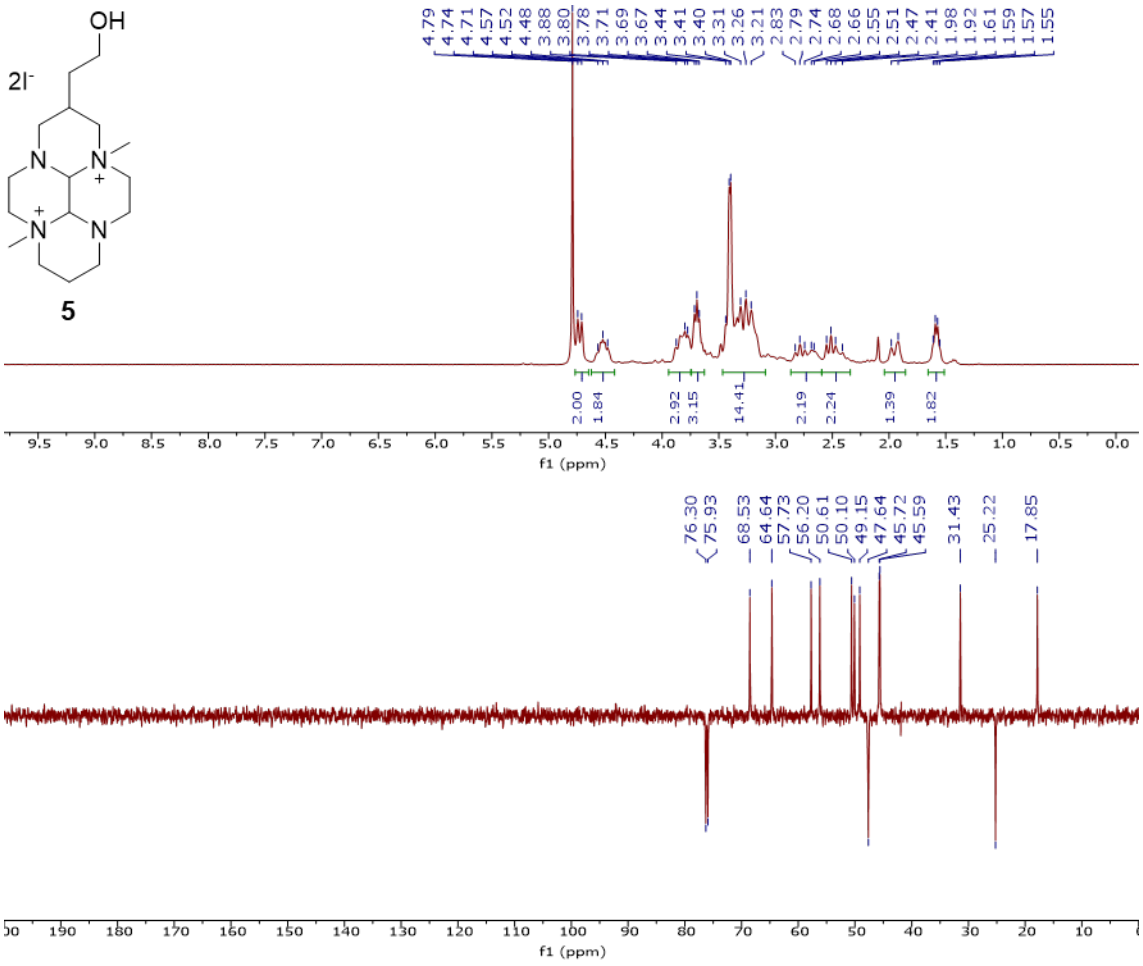

Fig. S7 NMR [^{1}H (300 MHz) and ^{13}C (75 MHz)] spectra of **5**.

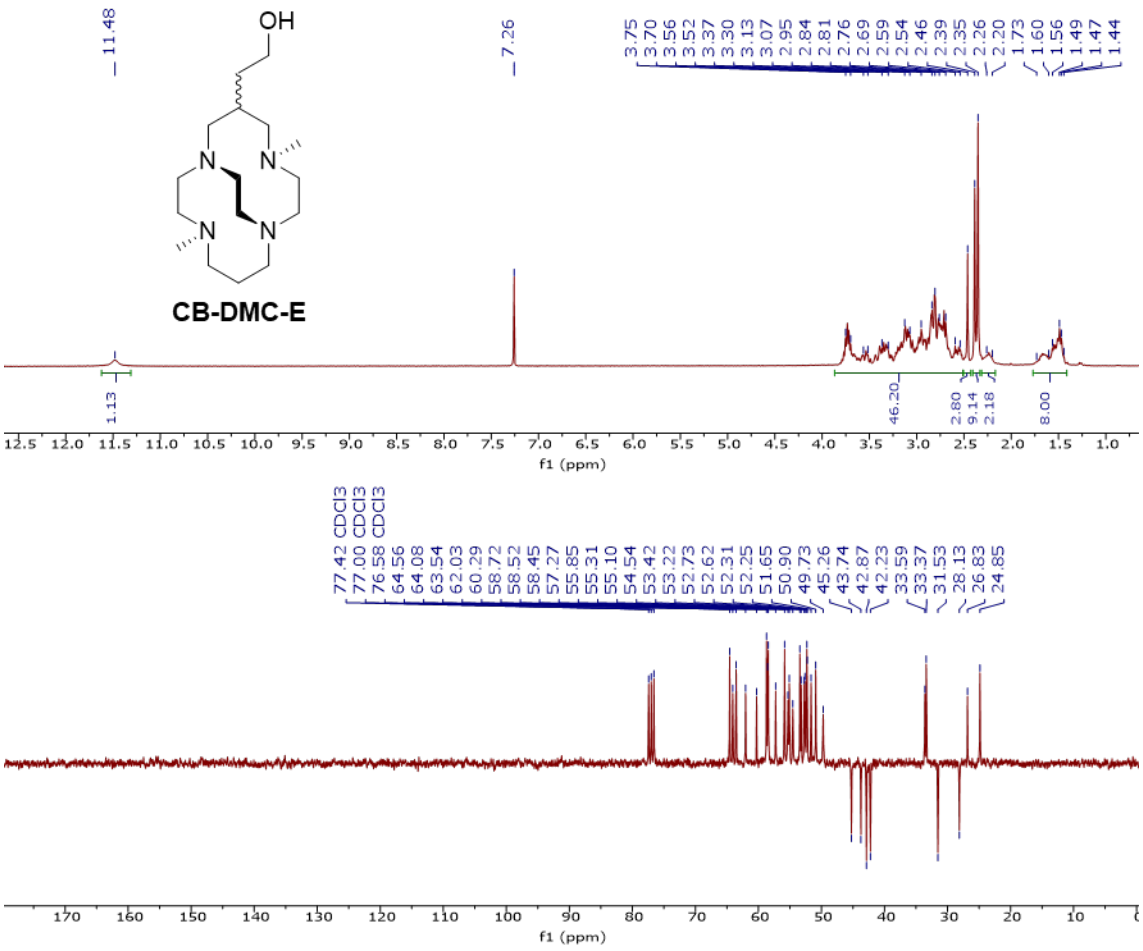

Fig. S8 NMR [^{1}H (300 MHz) and ^{13}C (75 MHz)] spectra of **CB-DMC-E**.

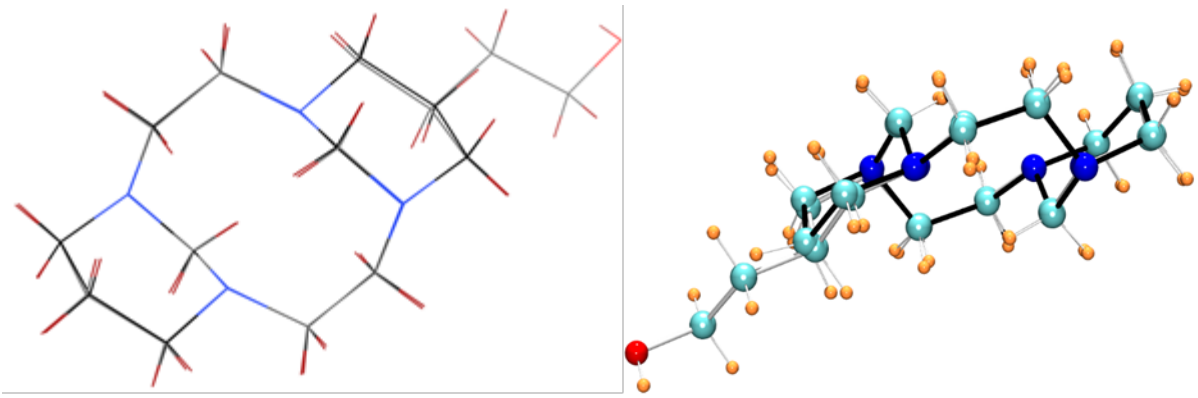

Fig. S9 Superposition of the X-ray crystal structures of cyclam-hydroxyethyl-bisformyl **1** (grey bonds) and cyclam-bisformyl (black bonds).[2] The X-ray crystallographic data were summarized in Table S1.

Reference

2. G. Royal, V. Dahaoui-Gindrey, S. Dahaoui, A. Tabard, R. Guilard, P. Pullumbi and C. Lecomte, New synthesis of *trans*-disubstituted cyclam macrocycles – elucidation of the disubstitution mechanism on the basis of X-ray data and molecular modeling, *Eur. J. Org. Chem.*, 1998, 1971–1975.

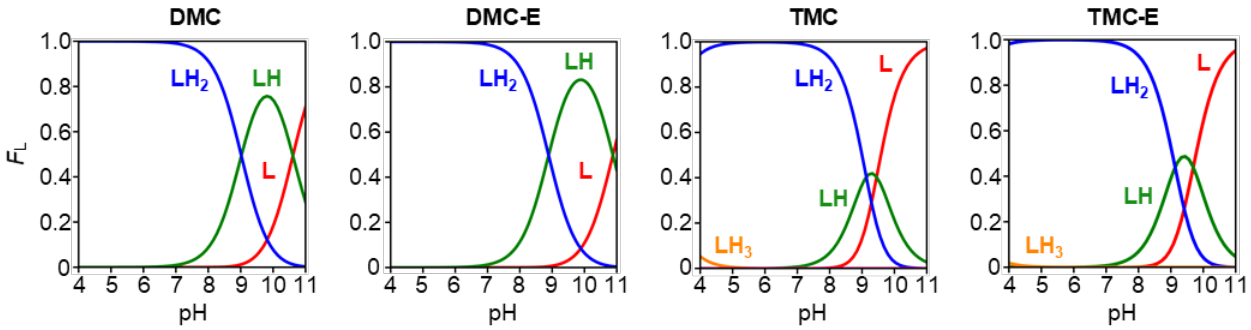

Fig. S10 Solution speciation studies of **DMC**, **DMC-E**, **TMC**, and **TMC-E** by potentiometry. Solution speciation diagrams of the compounds (F_L = fraction of species at given pH) were summarized. Charges are omitted for clarity. Conditions: [compound] = 2 mM; 25 °C; I = 0.10 M in KNO_3.

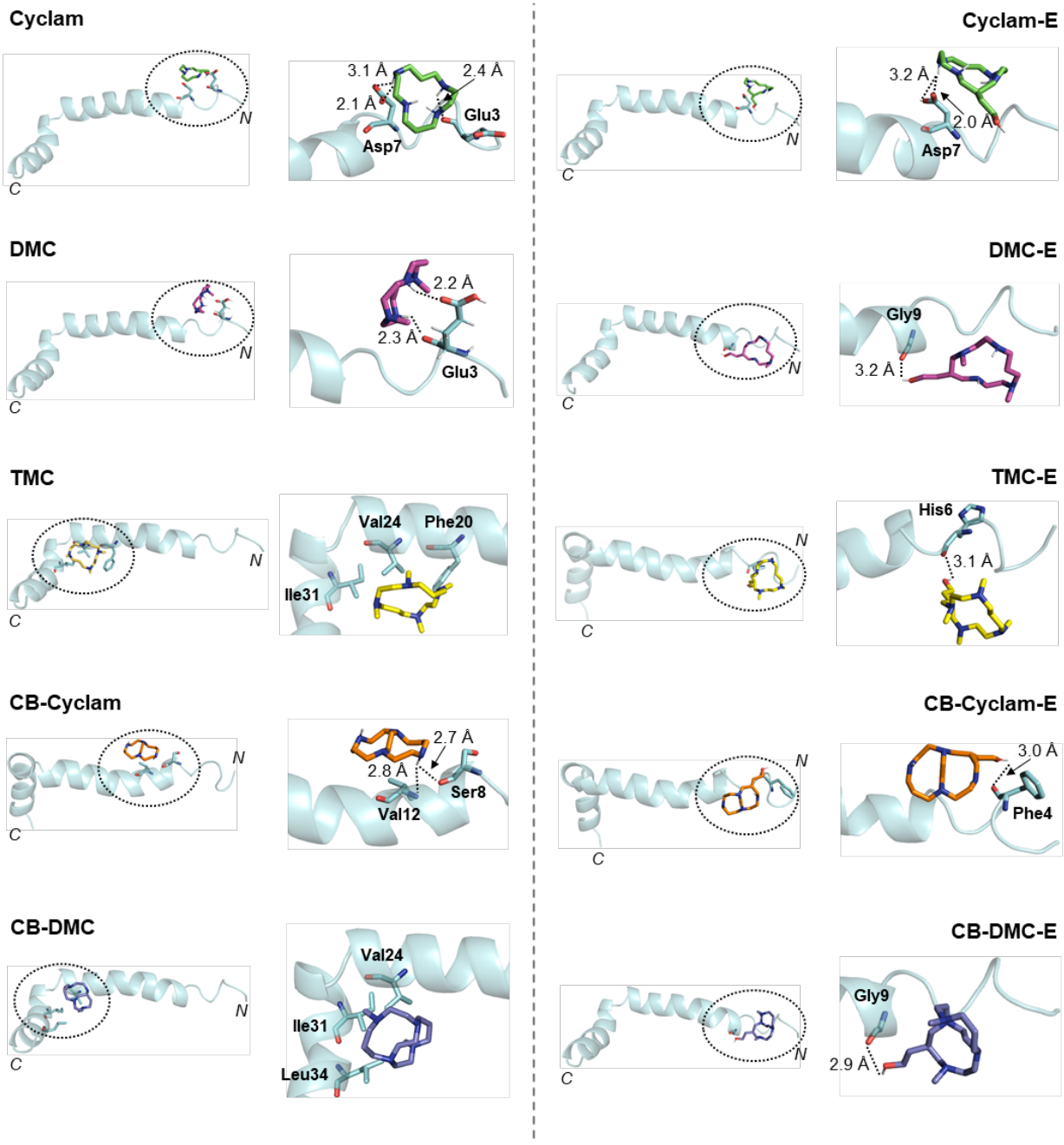

Fig. S11 Possible interactions of **Cyclam** and its derivatives with the $A\beta_{42}$ monomer (PDB 1IYT) visualized by docking studies. The structure of compounds and amino acid residues in $A\beta_{42}$ adjacent to the compounds are indicated in stick representation. Distances of hydrogen bonding (within 3.2 Å) are labeled in Å with dashed lines.

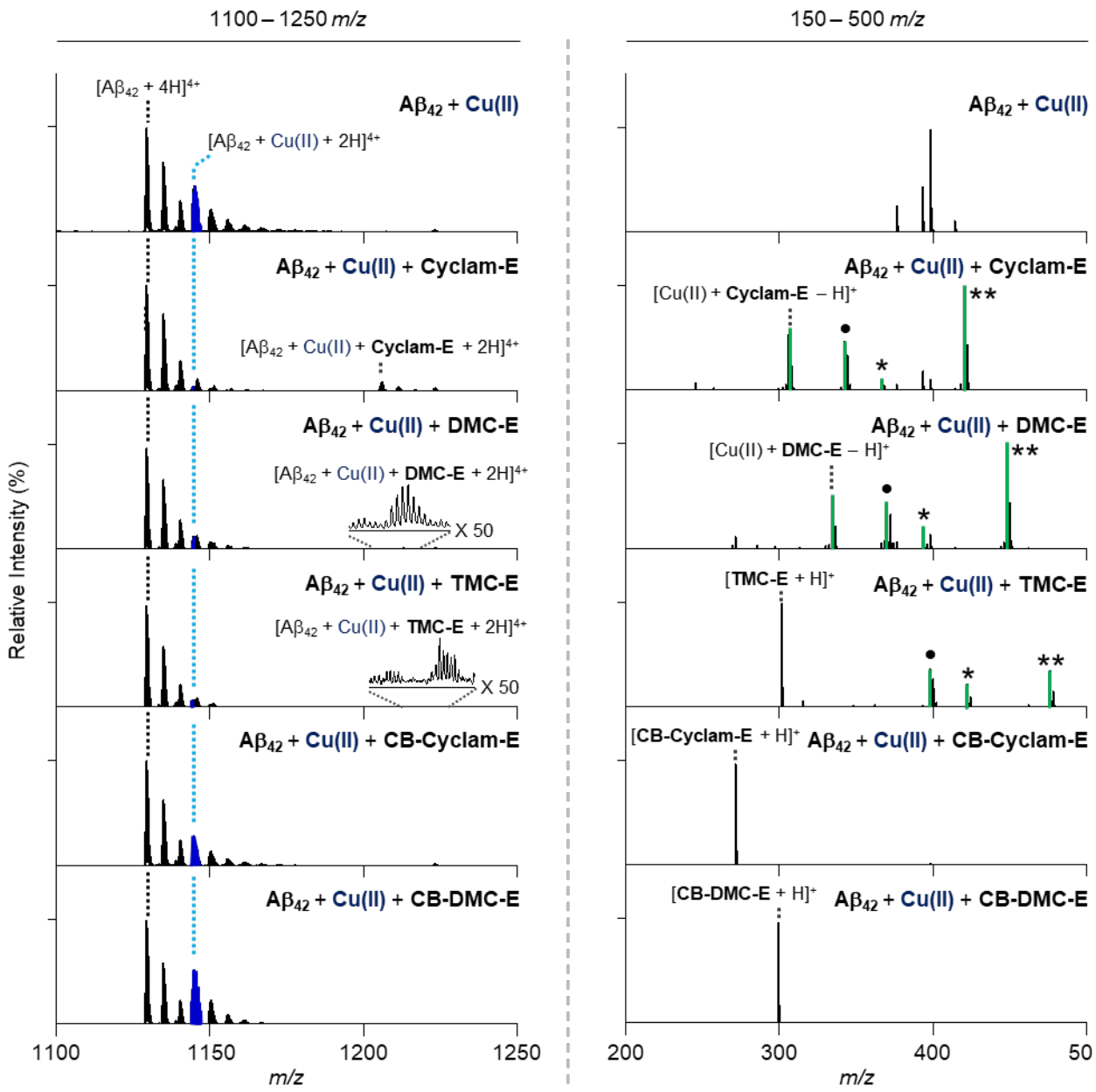

Fig. S12 Interactions of Cu(II)-treated $A\beta_{42}$ with **Cyclam-E**, **DMC-E**, **TMC-E**, **CB-Cyclam-E**, or **CB-DMC-E** detected by ESI-MS. Blue dashed line indicates the peak corresponding to $[A\beta_{42} + Cu(II) + 2H]^{4+}$. Green peaks denote the adducts of cyclam derivatives with Cu(II) (• = $[Cu(II) + compound + Cl)]^+$; ⋆ = $[Cu(II) + compound + CH_3COO]^+$; ⋆⋆ = $[Cu(II) + compound + CF_3COO]^+$). Conditions: $[A\beta_{42}]$ = 25 μM; $[CuCl_2]$ = 25 μM; [compound] = 25 μM; 20 mM ammonium acetate, pH 7.3; 37 °C; 3 h incubation. The relative intensity of each spectrum was normalized based on the highest peak in the spectrum. Note that the trifluoroacetate moiety was originated from $A\beta_{42}$.

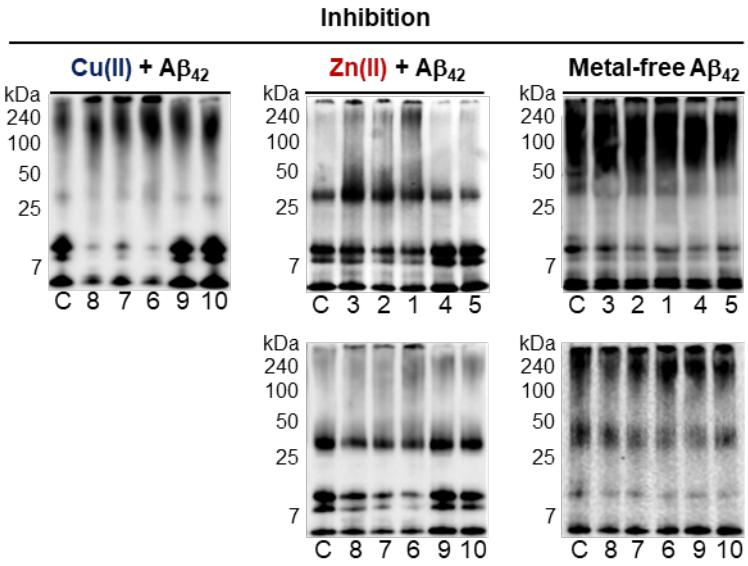

Fig. S13 Original gel/Western blot data of Fig. 5. Detailed conditions are described in Fig. 5.

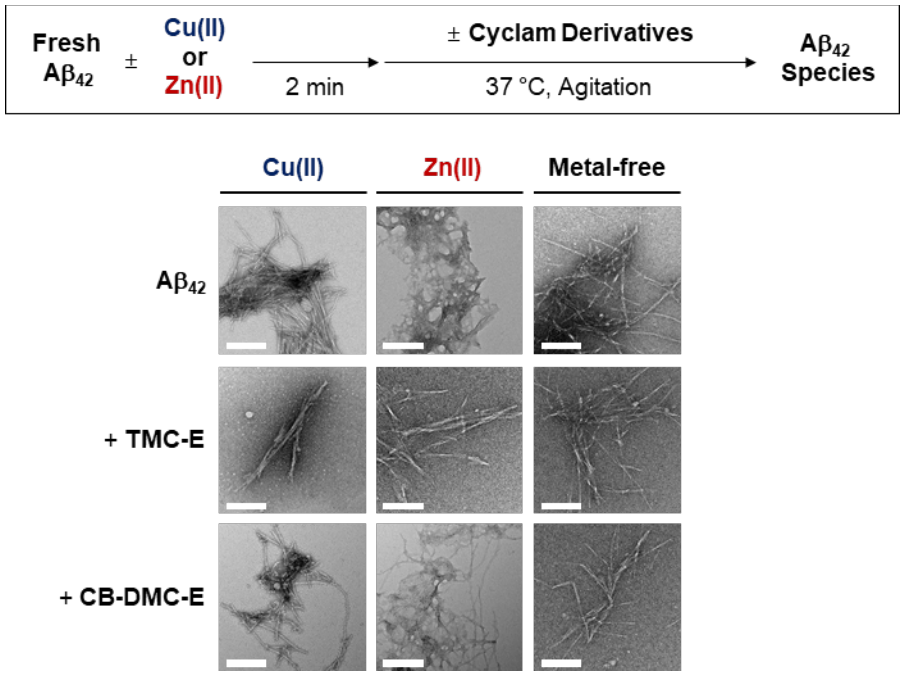

Fig. S14 Morphologies of the resultant metal-free and metal-treated $A\beta_{42}$ aggregates generated upon incubation with **TMC-E** and **CB-DMC-E** observed by TEM. Conditions: [$A\beta_{42}$] = 25 μM; [$CuCl_2$ or $ZnCl_2$] = 25 μM; [compound] = 25 μM; pH 7.4. Scale bar = 200 nm.

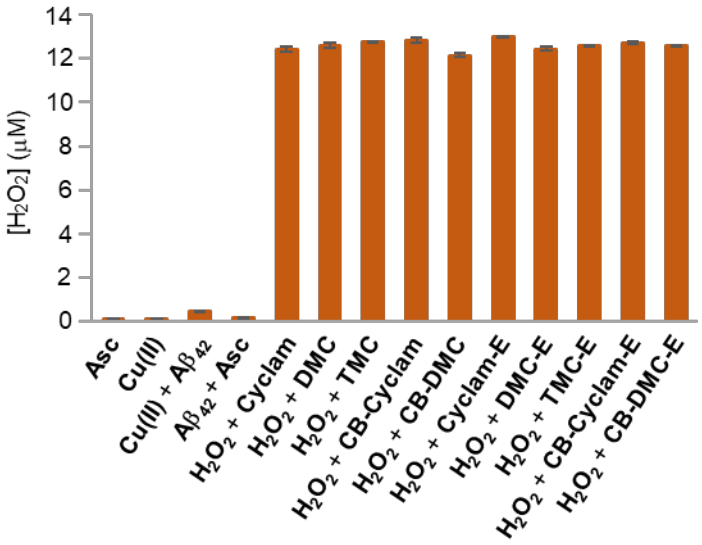

Fig. S15 Ability of **Cyclam** and its derivatives to remove H_2O_2. The concentration of H_2O_2 presented from the samples [*L*-ascorbate (Asc) only; Cu(II) only; Cu(II) + $A\beta_{42}$; $A\beta_{42}$ + Asc; H_2O_2 + compound] was detected by an Amplex Red H_2O_2/peroxidase assay. Conditions: [$A\beta_{42}$] = 12.5 μM; [$CuCl_2$] = 12.5 μM; [Asc] = 500 μM; [H_2O_2] = 12.5 μM; [compound] = 12.5 μM; 37 °C; 1 h incubation. Error bars represent the standard error of the mean from two independent experiments.

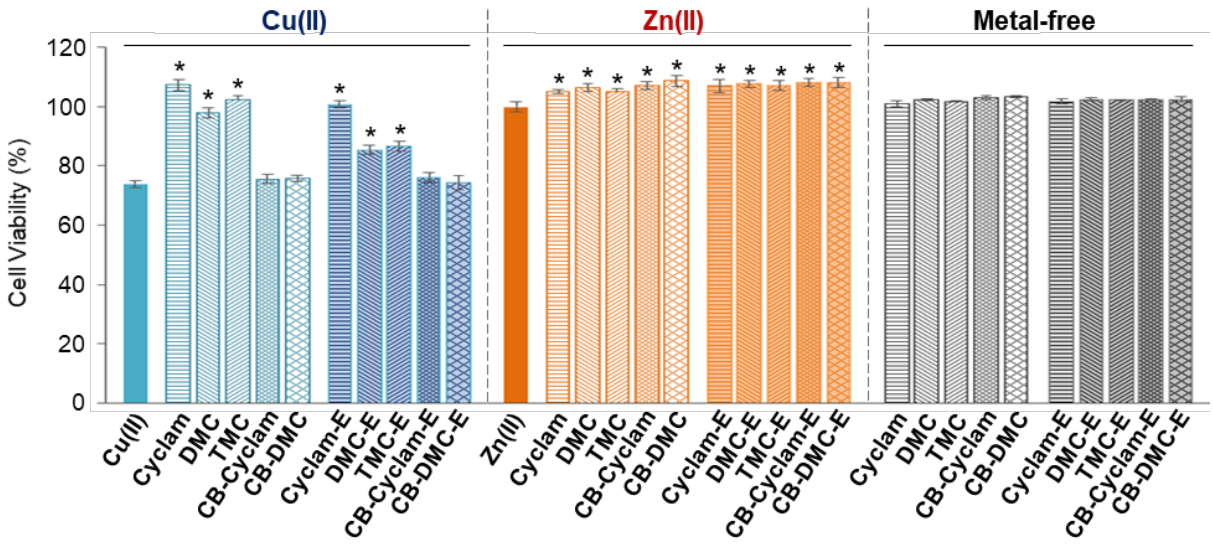

Fig. S16 Cytotoxicity of **Cyclam** and its derivatives in the absence and presence of metal ions. Cell viability, determined by the MTT assay, was calculated in comparison to that obtained upon treatment with an equivalent amount of H_2O. Conditions: [$CuCl_2$ or $ZnCl_2$] = 50 μM; [compound] = 50 μM; 37 °C; 24 h incubation. Error bars represent the standard error of the mean from three independent experiments. *P < 0.05.