Electronic Supplementary Information (ESI)

1. General Materials

All reactions except solid phase peptide synthesis were carried out with continuous magnetic stirring in ordinary glassware; solid phase peptide synthesis was performed in 10 mL polypropylene syringes with filters, purchased from Torviq, on an IKA® VXR basic Vibrax® shaker. Heating of reactions was conducted with a paraffin oil bath; cooling of reactions was achieved using an ice or ice-salt bath. All reagents and solvents were purchased from Sigma-Aldrich, Alfa Acer, Merck, Mimotopes, GL Biochem or Ajax Finechem. Wang resin was purchased from Novabiochem. Reagents were used as received unless otherwise specified. Hexane and ethyl acetate were distilled before use. Dichloromethane and ethanol were distilled over calcium hydride and stored over activated 4 Å molecular sieves. Chloroform was passed through a column of basic alumina prior to use. Diethyl ether, methanol, acetonitrile and *N*,*N*-dimethylformamide were collected freshly from a PureSolv MD 7 solvent purification system having been passed through anhydrous alumina columns.

2. Instrumentation and Methods

^{1}H and ^{13}C NMR spectra were recorded at 300 K on a Bruker AVANCE 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), a Bruker AVANCE 300 spectrometer (^{1}H at 300.13 MHz and ^{13}C at 75.47 MHz) or a Bruker DRX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.61 MHz). ^{1}H and ^{13}C NMR spectra are referenced to ^{1}H signals of residual nondeuterated solvents (or tetramethylsilane) and ^{13}C signals of the deuterated solvents respectively. ^{1}H NMR signals are reported with chemical shift values δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, m = multiplet and br = broad), relative integral, coupling constants J (Hz) and assignments. Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer. UV-Vis spectra were recorded on a Varian Cary 4000 or Varian Cary 1E UV-visible spectrophotometer. Temperature control for UV-visible spectrophotometer was provided by a Varian Cary PCB water peltier system. Low resolution and high resolution mass spectra were recorded on a Finnigan LCQ mass spectrometer and a Bruker 7T Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer respectively. Ionisation of all samples was carried out using ESI. Optical rotation α was measured on

a PerkinElmer 341 polarimeter with a sodium lamp in a semi-micro fused silica polarimeter cell (length: 100 mm, capacity: 3.0 mL) at 589 nm and 20 °C using spectroscopic grade solvents. Temperature was controlled by a Julabo F12-ED refrigerated/heating circulator connected directly to the polarimeter cell. Melting points were determined on an OptiMelt 100 automated melting point apparatus and are uncorrected. Elemental analyses were carried out by the Campbell Microanalytical Laboratory (University of Otago, New Zealand) on a Carlo Erba EA 1108 Elemental Analyser. Analytic reverse phase high performance liquid chromatography (RP-HPLC) was carried out on a Waters 2695 separations module with a Waters 2996 photodiode array detector and an Alliance series column heater. A Waters SunFire™ C18 column (5 µm, 2.1 × 150 mm) was used at 30 °C at a flow rate of 0.2 mL/min. Preparative RP-HPLC was carried out on a Waters 600 controller with a Waters 600 pump and a 2998 photodiode array detector. A Waters SunFire™ C18 OBD™ column (5 µm, 19 × 150 mm) was used at a flow rate of 7 mL/min. Mobile phases of 0.1% TFA in Milli-Q water (solvent A) and 0.1% TFA in acetonitrile (solvent B) in different ratios was used in both analytic and preparative HPLC. The fractions from preparative HPLC were lyophilized using a Labconco FreeZone 6 liter console freeze dry system. Data acquired from both analytic and preparative HPLC were processed using Waters Empower 2 software. Liquid chromatography mass spectrometry (LCMS) was performed on a Thermo Separation Products: Spectra System consisting of a P400 pump and a UV6000LP photodiode array detector coupled to a Thermoquest Finnigan LCQ Deca mass spectrometer (ESI). A Phenomenex Jupiter C18 column (5 µm, 2.1 × 150 mm) was eluted at a flow rate of 0.2 mL/min with a mobile phase of 0.1% formic acid in Milli-Q water and 0.1% formic acid in acetonitrile. Analytical TLC was performed on Merck silica gel 60 F_{254} pre-coated aluminium plates (0.2 mm) and visualized under UV light (254 nm), followed by staining with ninhydrin. Flash column chromatography was carried out using Merck silica gel 60 (0.040-0.063 mm).

3. General Synthetic Procedures

General Synthetic Procedure A: SPPS of Peptides following the Fmoc Strategy[59,60]

Pre-loading of Wang Resin

Wang resin (1.0 eq.) was washed with DMF (5 ×), DCM (5 ×) and DMF (5 ×), and swelled in DMF for 30 min before use. Fmoc-Phe-OH (10.0 eq.) was dissolved in anhydrous DCM (0.1 M) and cooled to 0 °C. DIC (5.0 eq.) was added dropwise. The reaction mixture was stirred for 30 min at 0 °C and concentrated under reduced pressure. The residue and DMAP (0.1 eq.) were dissolved in DMF (final concentration 0.1 M) and added immediately to the pre-swelled Wang resin. The resin was shaken for 2 h and washed with DMF (5 ×), DCM (5 ×) and DMF (5 ×). Capping with acetic anhydride/pyridine (1:9, v/v) (2 × 5 min) was followed by washing with DMF (5 ×), DCM (5 ×) and DMF (5 ×). Treatment of the resin with 10% piperidine/DMF (2 × 5 min) and measurement of the absorbance of the resulting piperidine-fulvene adduct at λ = 301 nm showed that the resin loading was quantitative.

Iterative Peptide Assembly

Deprotection: The resin was treated with 10% piperidine/DMF (2 × 5 min) and washed with DMF (5 ×), DCM (5 ×) and DMF (5 ×).

Amino acid coupling: A pre-activated solution of Fmoc-protected amino acid (4.0 eq.), PyBOP (4.0 eq.) and NMM (8.0 eq.) in DMF (final concentration 0.1 M) was added to the resin. After shaking for 1 h, the resin was washed with DMF (5 ×), DCM (5 ×) and DMF (5 ×).

Capping: The resin was treated with acetic anhydride/pyridine (1:9, v/v) (2 × 5 min) and washed with DMF (5 ×), DCM (5 ×) and DMF (5 ×).

Acetic acid derivative coupling: A pre-activated solution of an acetic acid derivative (**9**, **10**, **11** or **12**) (4.0 eq.), PyBOP (4.0 eq.) and NMM (8.0 eq.) in DMF (final concentration 0.1 M) was added to the resin. After shaking for 1 h, the resin was washed with DMF (5 ×) and DCM (10 ×) and dried *in vacuo*. The capping and deprotection steps were omitted.

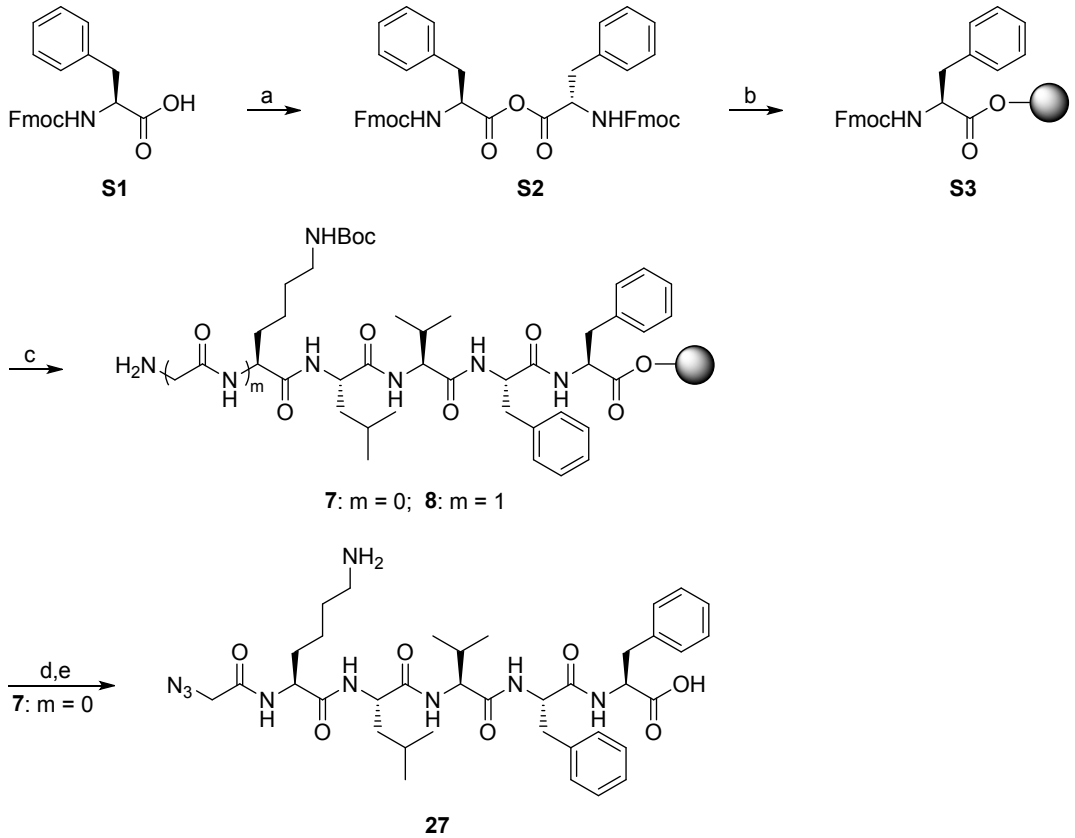
Cleavage: A mixture of TFA/TIS/H_2O (90:5:5, v/v/v) was added to the resin. After shaking for 2 h, the resin was washed with TFA (3 × 5 mL).

Work-up: The combined cleavage solution and TFA washings were concentrated under reduced pressure, and the residue was purified by preparative RP-HPLC.

General Synthetic Procedure B: Metal Complexation[25]

To a solution of *N*-functionalized cyclam trifluoroacetate (1.0 eq.) in EtOH (0.1 M) was added dropwise a solution of $CuCl_2 \cdot 2H_2O$ or $ZnCl_2$ (1.0 eq.) in EtOH (0.1 M) at room temperature. The reaction mixture was heated at reflux for 6 h and cooled on an ice bath. The desired metal complex was isolated from the suspension by centrifugation.

4. Synthesis of Precursors 7-12 and the Control Compound 27

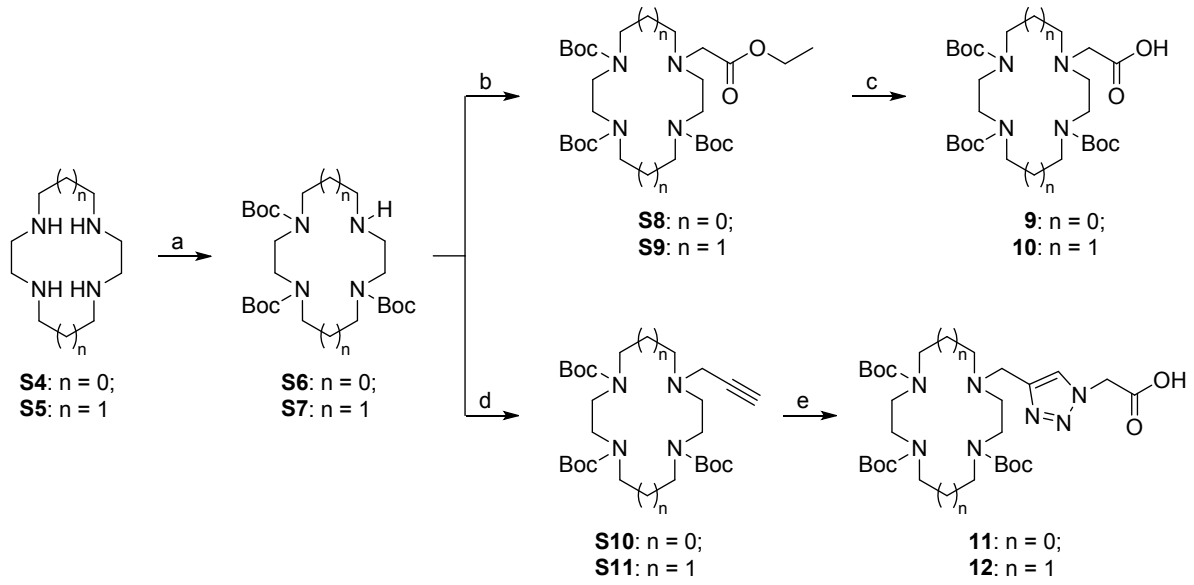


Scheme S1. Synthesis of resin-bound oligopeptides **7** and **8** as well as the control compound **27**. Reagents and conditions: (a) DIC, DCM, 0 °C, 1 h; (b) Wang resin, DMAP, DMF, rt, 2 h; (c) iterative Fmoc strategy SPPS (4 times for **7** and 5 times for **8**): (1) Fmoc removal: 10% piperidine/DMF, rt, 2 × 5 min; (2) amino

acid coupling: Fmoc-X_{aa}-OH (X_{aa} = Phe, Val, Leu, Lys(Boc) and Gly), PyBOP, NMM, DMF, rt, 1 h; (3) capping: 10% Ac_2O/pyridine, rt, 2 × 5 min; (d) only for **7**, 2-azidoacetic acid, PyBOP, NMM, DMF, rt, 1 h; (e) TFA/TIS/H_2O (90:5:5), rt, 2 h, followed by RP-HPLC purification, 72%.

(2*S*,5*S*,8*S*,11*S*,14*S*)-14-(4-Aminobutyl)-17-azido-2,5-dibenzyl-11-isobutyl-8-isopropyl-4,7,10,13,16-pentaoxo-3,6,9,12,15-pentaazaheptadecan-1-oic acid (27).

Wang resin (100-200 mesh, loading 1.1 mmol/g, 182 mg, 0.200 mmol) was pre-loaded with Fmoc-Phe-OH (**S1**) and azide-capped pentapeptide **27** was assembled using general synthetic procedure A. The combined cleavage solution and TFA washings were concentrated under reduced pressure, and the residue was purified by preparative RP-HPLC (gradient 10% to 50% B over 45 min) to give **27** as a white solid (106 mg, 72%). **m.p.** 238-239 °C. **$[\alpha]_D^{20}$** -22.5 (*c* 1.0, DMSO). **IR** ν_{max}/cm^{-1} 3277, 3074, 3028, 2956, 2875, 2108, 1630, 1540, 1429, 1399, 1281, 1198, 1137, 1036, 694. **^{1}H NMR** (500 MHz, CD_3OD) δ 0.78 (d, 3H, *J* 7.0, CH_3), 0.83 (d, 3H, *J* 6.5, CH_3), 0.88 (d, 3H, *J* 6.0, CH_3), 0.93 (d, 3H, *J* 6.5, CH_3), 1.39-1.46 (m, 2H), 1.46-1.51 (m, 1H), 1.55-1.60 (m, 1H), 1.60-1.72 (m, 4H), 1.78-1.86 (m, 1H), 1.91-1.99 (m, 1H) (total 10H, CHC*H*$(CH_3)_2$ & CH_2C*H*$(CH_3)_2$ & CH_2CH_2C$H_2$$CH_2NH_2$), 2.85 (dd, 1H, *J* 14.0 & 9.5, C*H*HPh), 2.89 (t, 2H, *J* 7.5, CH_2NH_2), 3.00 (dd, 1H, *J* 14.0 & 8.0, CH*H*Ph), 3.09 (dd, 1H, *J* 14.0 & 5.5, C*H*HPh), 3.17 (dd, 1H, *J* 14.0 & 5.5, CH*H*Ph), 3.90 (s, 2H, N_3CH_2), 4.16 (t, 1H, *J* 8.0, NHC*H*CO), 4.41-4.50 (m, 2H, 2 × NHC*H*CO), 4.62-4.71 (m, 2H, 2 × NHC*H*CO), 7.15-7.45 (m, 10H, Ph-H), 7.99 (d, 1H, *J* 8.5, CONH), 8.11 (d, 1H, *J* 8.0, CONH), 8.20 (d, 1H, *J* 7.5, CONH), 8.28 (d, 1H, *J* 7.5, CONH) (two primary amine proton signals (NH_2), one amide proton signal (CONH) and one carboxylic acid proton signal (COOH) not observed due to H/D exchange). **^{13}C NMR** (75 MHz, CD_3OD) δ 18.8, 19.8, 22.0, 23.5, 23.6, 25.8, 28.1, 32.3, 32.7, 38.5, 39.1, 40.5, 41.7, 52.7, 53.4, 54.3, 55.1, 55.6, 60.1, 127.7, 127.8, 129.4, 129.5, 130.3, 138.2, 170.2, 172.9, 173.0, 173.6, 174.2, 174.5 (six carbon signals overlapping or obscured). **MS** (ESI) *m/z* 736.1 ($[M+H]^+$, 100%), 758.2 ($[M+Na]^+$, 6%), 1471.1 ($[2M+H]^+$, 19%). **HRMS** (ESI) 736.41304 ($[M+H]^+$); calcd. for $C_{37}H_{54}N_9O_7$ ($[M+H]^+$) 736.41407. **Anal.** Calcd. for $C_{37}H_{53}N_9O_7 \cdot CF_3COOH \cdot H_2O$: C 53.97, H 6.50, N 14.52; Found: C 54.06, H 6.51, N 14.49.



Scheme S2. Synthesis of precursors **9**-**12**. Reagents and conditions: (a) Boc_2O, Et_3N, $CHCl_3$ for **S4** and DCM for **S5**, 0 °C to rt, o/n, **S6**: 72%, **S7**: 77%; (b) $BrCH_2COOCH_2CH_3$, Na_2CO_3, CH_3CN, reflux, o/n, **S8**: 100%, **S9**: 91%; (c) 1 M NaOH, CH_3OH, rt, 2 h for **9** and 2.5 h for **10**, **9**: 100%, **10**: 93%; (d) propargyl bromide, Na_2CO_3, CH_3CN, reflux, o/n, **S10**: 96%, **S11**: 95%; (e) 2-azidoacetic acid, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, *t*-BuOH/H_2O (1:1), rt, o/n, **11**: 100%, **12**: 98%.

Tri-*tert*-butyl 1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (S6).[61-63]

To a solution of cyclen (**S4**, 1.73 g, 10.0 mmol) and triethylamine (4.20 mL, 30.1 mmol) in $CHCl_3$ (120 mL, freshly passed through Al_2O_3 (activated, neutral, Brockmann I)) at 0 °C was added dropwise a solution of di-*tert*-butyl dicarbonate (6.55 g, 30.0 mmol) in $CHCl_3$ (100 mL, freshly passed through Al_2O_3 (activated, neutral, Brockmann I)) under N_2. After the addition was complete, the resulting solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, EtOAc:hexane = 3:2 ramping to EtOAc) to give **S6** as a white foam (3.41 g, 72%). $\boldsymbol{R_F}$ (EtOAc:hexane = 4:1) 0.63. **IR** ν_{max}/cm^{-1} 3313, 2974, 2931, 2818, 1679, 1463, 1412, 1365, 1313, 1247, 1156, 1046, 771, 736. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.45 (s, 18H, 2 × $C(CH_3)_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.78-2.92 (m, 4H, CH_2NHCH_2), 3.16-3.34 (m, 6H), 3.34-3.50 (m, 2H), 3.55-3.75 (m, 4H) (total 12H, 3 × $CH_2N(Boc)CH_2$) (one secondary amine proton signal (NH) not observed). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.1, 28.2, 28.3, 28.4, 28.5, 44.7, 45.7, 48.8, 49.2, 50.3, 50.8, 78.9, 79.1, 155.1, 155.4 (eight carbon signals overlapping or obscured). **MS** (ESI) *m/z* 472.9 ($[M+H]^+$, 27%), 495.0 ($[M+Na]^+$, 99%),

967.1 ([2M+Na]$^+$, 100%). The spectroscopic data were in agreement with those in the literature.[61-63]

Tri-*tert*-butyl 1,4,8,11-tetraazacyclotetradecane-1,4,8-tricarboxylate (S7).[64]

To a solution of cyclam (**S5**, 1.51 g, 7.54 mmol) and triethylamine (5.20 mL, 37.3 mmol) in anhydrous DCM (300 mL) was added dropwise di-*tert*-butyl dicarbonate (2.95 g, 13.5 mmol) in anhydrous DCM (90 mL) under N_2. After the addition was complete, the reaction mixture was cooled to -15 °C, and a second portion of di-*tert*-butyl dicarbonate (1.96 g, 8.98 mmol) in anhydrous DCM (60 mL) was added. The reaction mixture was stirred at room temperature overnight and washed with 0.5 M Na_2CO_3 (2 × 150 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc ramping to EtOAc:CH_3OH = 9:1) to give **S7** as a white foam (2.91 g, 77%). $\boldsymbol{R_F}$ (EtOAc:CH_3OH = 9:1) 0.54. **m.p.** 46-47 °C. **IR** ν_{max}/cm^{-1} 2973, 2932, 2818, 1681, 1464, 1409, 1389, 1364, 1239, 1158. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.46 (s, 27H, 3 × C(CH_3)$_3$), 1.60-1.80 (m, 2H, $CH_2CH_2CH_2$), 1.80-2.10 (m, 2H, $CH_2CH_2CH_2$), 2.62 (t, 2H, *J* 5.6, CH_2NHCH_2), 2.78 (t, 2H, *J* 5.4, CH_2NHCH_2), 3.20-3.50 (m, 12H, 3 × CH_2N(Boc)CH_2) (one secondary amine proton signal (NH) not observed). **MS** (ESI) *m/z* 501.3 ([M+H]$^+$, 100%), 523.5 ([M+Na]$^+$, 17%). The spectroscopic data were in agreement with those in the literature.[64]

Tri-*tert*-butyl 10-(2-ethoxy-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (S8).[65]

To a solution of tri-Boc cyclen **S6** (6.04 g, 12.8 mmol) in anhydrous CH_3CN (120 mL) were added Na_2CO_3 (1.63 g, 15.4 mmol) and ethyl bromoacetate (1.70 mL, 15.3 mmol). The reaction mixture was stirred at reflux under N_2 overnight. The insoluble salts were filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc:hexane = 1:2 ramping to 1:1) to give **S8** as a white foam (7.14 g, 100%). $\boldsymbol{R_F}$ (EtOAc:hexane = 1:1) 0.71. **IR** ν_{max}/cm^{-1} 2975, 2932, 1735, 1682, 1459, 1413, 1364, 1312, 1248, 1156, 1030, 770. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, *J* 6.8, $COOCH_2CH_3$), 1.45 (s, 18H, 2 × C(CH_3)$_3$), 1.48 (s, 9H, C(CH_3)$_3$), 2.85-3.02 (m, 4H, CH_2N($CH_2COOCH_2CH_3$)CH_2), 3.20-3.65 (br m, 12H, 3 ×

CH_2N(Boc)CH_2), 3.51 (s, 2H, NCH_2COOCH_2CH_3), 4.15 (q, 2H, *J* 6.8, COOCH_2CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 28.1, 28.3, 46.7, 47.0, 47.3, 49.5, 50.7, 53.2, 54.5, 59.8, 78.7, 79.0, 79.1, 154.9, 155.3, 155.6, 170.1 (nine carbon signals overlapping or obscured). **MS** (ESI) *m/z* 581.0 ([M+Na]$^+$, 100%), 1139.0 ([2M+Na]$^+$, 98%). The spectroscopic data were in agreement with those in the literature.[65]

Tri-*tert*-butyl 11-(2-ethoxy-2-oxoethyl)-1,4,8,11-tetraazacyclotetradecane-1,4,8-tricarboxylate (S9).[66,67]

To a solution of tri-Boc cyclam **S7** (3.80 g, 7.59 mmol) in anhydrous CH_3CN (160 mL) were added Na_2CO_3 (0.956 g, 9.10 mmol) and ethyl bromoacetate (1.00 mL, 9.02 mmol). The reaction mixture was stirred at reflux under Ar overnight. The insoluble salts were filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc:hexane = 1:2 ramping to 1:1) to give **S9** as a white foam (4.06 g, 91%). $\boldsymbol{R_F}$ (EtOAc:hexane = 1:1) 0.67. **IR** ν_{max}/cm^{-1} 2974, 2933, 2869, 1737, 1685, 1465, 1411, 1366, 1292, 1240, 1154, 1032, 772, 731. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, *J* 7.2, COOCH_2CH_3), 1.46 (s, 27H, 3 × C(CH_3)$_3$), 1.60-1.78 (m, 2H, CH_2C$H_2$$CH_2$), 1.85-2.00 (m, 2H, CH_2C$H_2$$CH_2$), 2.60-2.72 (m, 2H, C$H_2$N($CH_2$COOC$H_2$$CH_3$)$CH_2$), 2.80-2.90 (m, 2H, CH_2N(CH_2COOC$H_2$$CH_3$)C$H_2$), 3.22-3.65 (m, 14H, 3 × CH_2N(Boc)CH_2 & NCH_2COOC$H_2$$CH_3$), 4.14 (q, 2H, *J* 7.2, COOC$H_2$$CH_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 14.2, 27.0, 28.4, 45.2, 46.8, 47.1, 47.3, 48.3, 51.8, 52.9, 53.6, 55.3, 60.1, 79.4, 155.4, 155.6, 170.9 (twelve carbon signals overlapping or obscured). **MS** (ESI) *m/z* 587.0 ([M+H]$^+$, 6%), 609.1 ([M+Na]$^+$, 100%), 1194.9 ([2M+Na]$^+$, 47%). The spectroscopic data were in agreement with those in the literature.[66,67]

2-(4,7,10-Tris(*tert*-butoxycarbonyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid (9).[65]

To a solution of ester **S8** (559 mg, 1.00 mmol) in CH_3OH (10 mL) was added 1 M NaOH (10 mL). The resulting cloudy reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was dissolved in 10% citric acid, taken to pH 5 and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give **9** as a white foam

(531 mg, 100%). The product was of sufficient purity to be used directly in the next step, but an analytical sample could be obtained by flash column chromatography (silica gel, EtOAc:hexane = 1:1 ramping to EtOAc). $\boldsymbol{R_F}$ (EtOAc:CH_3OH = 9:1) 0.54. **m.p.** 98-99 °C (lit.[68] **m.p.** 138 °C). **IR** ν_{max}/cm^{-1} 3505, 2974, 2931, 2869, 1738, 1682, 1462, 1414, 1366, 1250, 1156, 1115, 1038, 976, 856, 770. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.45 (s, 18H, 2 × $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 2.85-3.05 (m, 4H, $CH_2N(CH_2COOH)CH_2$), 3.25-3.50 (m , 8H), 3.50-3.65 (m, 6H) (total 14 H, 3 × $CH_2N(Boc)CH_2$ & NCH_2COOH), 9.90 (br s, 1H, COOH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.3, 28.5, 47.2, 47.5, 49.7, 51.0, 54.0, 79.4, 79.7, 155.3, 155.9, 172.8 (thirteen carbon signals overlapping or obscured). **MS** (ESI+) *m/z* 531.0 ($[M+H]^+$, 22%), 553.1 ($[M+Na]^+$, 65%), 1083.0 ($[2M+Na]^+$, 100%); (ESI-) *m/z* 529.2 ($[M-H]^-$, 50%), 1059.3 ($[2M-H]^-$, 100%), 1081.7 ($[2(M-H)+Na]^-$, 14%). The spectroscopic data were in agreement with those in the literature.[65,68,69]

2-(4,8,11-Tris(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-yl)acetic acid (10).[66,67]

To a solution of ester **S9** (3.20 g, 5.45 mmol) in CH_3OH (64 mL) was added 1 M NaOH (40 mL). The reaction mixture was stirred at room temperature for 2.5 h and concentrated under reduced pressure. The residue was dissolved in 10% citric acid, taken to pH 5 and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc ramping to EtOAc:CH_3OH = 9:1) to give **10** as a white foam (2.83 g, 93%). $\boldsymbol{R_F}$ (EtOAc:CH_3OH = 8:2) 0.17. **m.p.** 65-66 °C (lit.[67] **m.p.** 89-91 °C). **IR** ν_{max}/cm^{-1} 2974, 2932, 1680, 1468, 1413, 1367, 1304, 1242, 1154, 1060, 912, 727. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.46 (s, 27H, 3 × $C(CH_3)_3$), 1.75-1.85 (m, 2H, $CH_2CH_2CH_2$), 1.85-2.00 (m, 2H, $CH_2CH_2CH_2$), 2.75-2.85 (m, 2H, $CH_2N(CH_2COOH)CH_2$), 2.90-3.05 (m, 2H, $CH_2N(CH_2COOH)CH_2$), 3.25-3.55 (m, 14H, 3 × $CH_2N(Boc)CH_2$ & NCH_2COOH), 9.06 (br s, 1H, COOH). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 26.5, 28.5, 45.9, 46.5, 47.5, 47.7, 52.5, 53.8, 56.4, 79.8, 80.4, 155.6, 156.3, 172.1 (thirteen carbon signals overlapping or obscured). **MS** (ESI) *m/z* 559.0 ($[M+H]^+$, 45%), 581.1 ($[M+Na]^+$, 100%), 1139.2 ($[2M+Na]^+$, 88%). The spectroscopic data were in agreement with those in the literature.[66,67]

Tri-*tert*-butyl 10-(prop-2-yn-1-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (S10).[51]

To a solution of tri-Boc cyclen **S6** (3.17 g, 6.71 mmol) in anhydrous CH_3CN (200 mL) were added Na_2CO_3 (2.85 g, 26.9 mmol) and propargyl bromide (~80% in toluene, 1.20 mL, 8.07 mmol). The reaction mixture was stirred at reflux under N_2 overnight. The insoluble salts were filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc:hexane = 1:1) to give **S10** as a white solid (3.28 g, 96%). $\boldsymbol{R_F}$ (EtOAc:hexane = 1:1) 0.78. **m.p.** 127-128 °C. **IR** ν_{max}/cm^{-1} 3303, 3251, 2974, 2930, 2831, 1677, 1460, 1413, 1365, 1313, 1250, 1157, 1035, 731. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.45 (s, 18H, 2 × $C(CH_3)_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.21 (s, 1H, C≡CH), 2.65-2.85 (m, 4H, $CH_2N(CH_2C{\equiv}CH)CH_2$), 3.20-3.45 (m, 8H), 3.45-3.65 (m, 4H) (total 12H, 3 × $CH_2N(Boc)CH_2$), 3.53 (s, 2H, $NCH_2C{\equiv}CH$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.5, 28.7, 39.0, 46.5, 47.0, 47.7, 47.8, 49.8, 49.9, 53.1, 54.3, 73.7, 77.6, 79.2, 79.4, 79.7, 155.2, 155.7, 156.0 (seven carbon signals overlapping or obscured). **MS** (ESI) *m/z* 533.0 ([M+Na]$^+$, 41%), 1043.1 ([2M+Na]$^+$, 100%). **HRMS** (ESI) 533.33145 ([M+Na]$^+$); calcd. for $C_{26}H_{46}N_4NaO_6$ ([M+Na]$^+$) 533.33096. The spectroscopic data were in agreement with those in the literature.[51]

Tri-*tert*-butyl 11-(prop-2-yn-1-yl)-1,4,8,11-tetraazacyclotetradecane-1,4,8-tricarboxylate (S11).[49,70]

To a solution of tri-Boc cyclam **S7** (437 mg, 0.873 mmol) in anhydrous CH_3CN (26 mL) were added Na_2CO_3 (370 mg, 3.49 mmol) and propargyl bromide (~80% in toluene, 156 μL, 1.05 mmol). The reaction mixture was heated at reflux under N_2 overnight. The insoluble salts were filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc:hexane = 7:3) to give **S11** as a white foam (446 mg, 95%). $\boldsymbol{R_F}$ (EtOAc:hexane = 7:3) 0.58. **m.p.** 47-48 °C (lit.[49,70] **m.p.** 47-49 °C). **IR** ν_{max}/cm^{-1} 3305, 3243, 2976, 2932, 2871, 2826, 1681, 1463, 1410, 1365, 1240, 1150. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.40 (s, 27H, 3 × $C(CH_3)_3$), 1.55-1.75 (m, 2H, $CH_2CH_2CH_2$), 1.75-1.95 (m, 2H, $CH_2CH_2CH_2$), 2.12 (s, 1H, C≡CH), 2.46 (t, 2H, *J* 5.4, $CH_2N(CH_2C{\equiv}CH)CH_2$), 2.55-2.70 (m, 2H, $CH_2N(CH_2C{\equiv}CH)CH_2$), 3.10-3.50 (br m, 14H, 3 × $CH_2N(Boc)CH_2$ & $NCH_2C{\equiv}CH$). **MS** (ESI) *m/z* 539.4 ([M+H]$^+$, 100%),

561.5 ([M+Na]$^+$, 28%). The spectroscopic data were in agreement with those in the literature.[49,70]

2-(4-((4,7,10-Tris(*tert*-butoxycarbonyl)-1,4,7,10-tetraazacyclododecan-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)acetic acid (11).

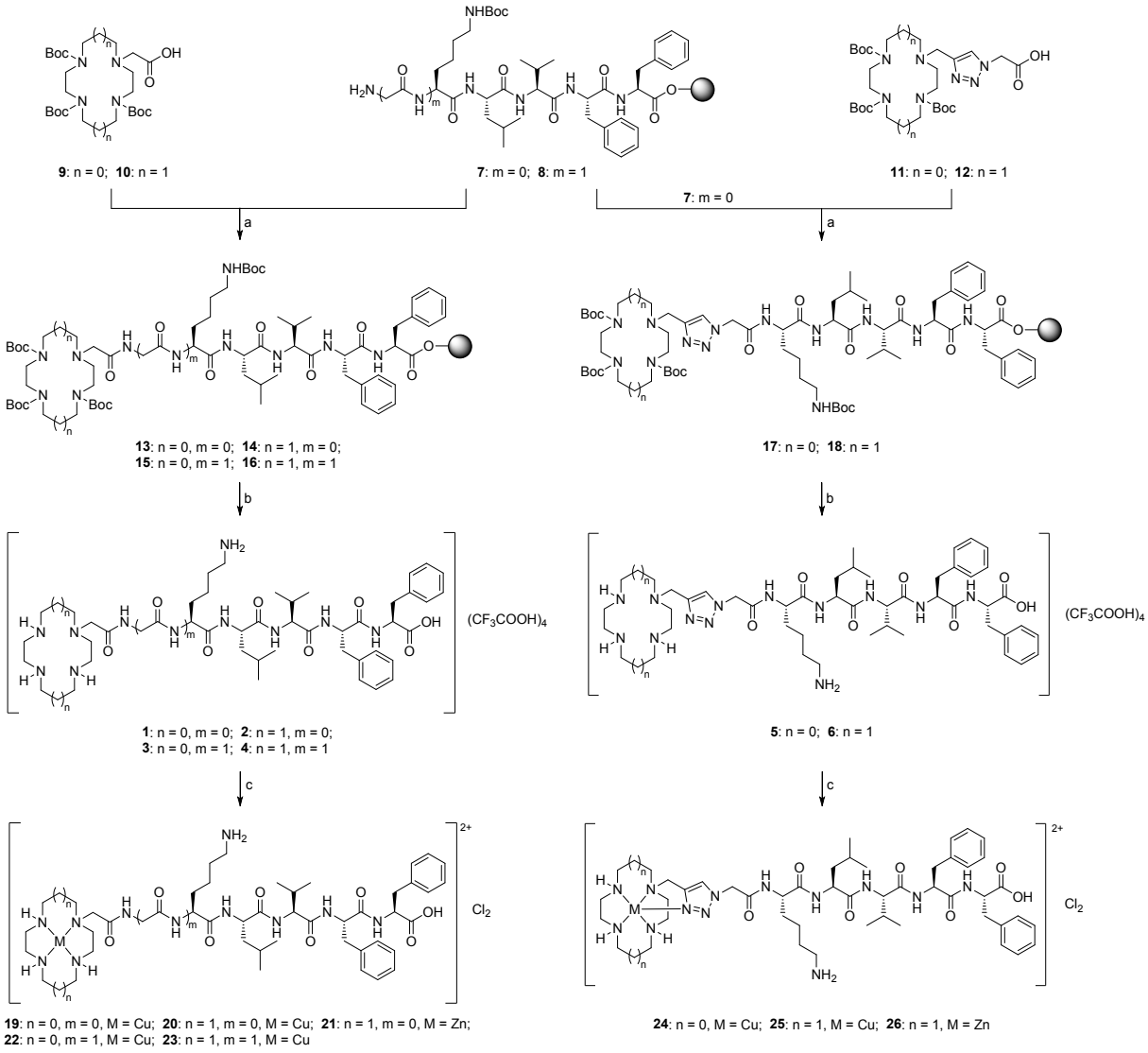
Propargyl-tri-Boc cyclen **S10** (1.02 g, 2.00 mmol) and 2-azidoacetic acid[25] (0.202 g, 2.00 mmol) were dissolved in *t*-BuOH/H_2O (1:1, 40 mL). A brown cloudy solution of $CuSO_4 \cdot 5H_2O$ (25 mg, 0.10 mmol, 5 mol%) and sodium ascorbate (40 mg, 0.20 mol, 10 mol%) in H_2O (4 mL) was added. The reaction mixture was stirred under Ar at room temperature overnight, quenched with 5% $NaHCO_3$ (10 mL), taken to pH 4-5 with 10% citric acid and extracted with EtOAc (3 × 80 mL). The combined organic extracts were concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, EtOAc ramping to EtOAc:CH_3OH = 7:3) to give the **11** as a white foam (1.22 g, 100%). $\boldsymbol{R_F}$ (EtOAc:CH_3OH = 9:1) 0.13. **IR** ν_{max}/cm^{-1} 3478, 2974, 2932, 2827, 1679, 1462, 1413, 1364, 1247, 1156, 1048, 772. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.44 (s, 18H, 2 × C(CH_3)$_3$), 1.46 (s, 9H, C(CH_3)$_3$), 2.75-2.95 (m, 4H, CH_2N(CH_2-triazole)CH_2), 3.25-3.65 (br m, 12H, 3 × CH_2N(Boc)CH_2), 4.05 (br s, 2H, NCH_2-triazole), 5.10 (s, 2H, triazole-CH_2COOH), 6.48 (br s, 1H, COOH), 7.80 (br s, 1H, triazole-H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 28.2, 28.4, 45.3, 46.7, 47.8, 49.4, 51.3, 52.0, 79.6, 79.9, 125.8, 140.0, 155.5, 155.9, 168.9 (thirteen carbon signals overlapping or obscured). **MS** (ESI) *m/z* 610.2 ([M-H]$^-$, 100%), 1221.5 ([2M-H]$^-$, 55%). **HRMS** (ESI) 612.37210 ([M+H]$^+$); calcd. for $C_{28}H_{50}N_7O_8$ ([M+H]$^+$) 612.37154.

2-(4-((4,8,11-Tris(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)acetic acid (12).

Propargyl-tri-Boc cyclam **S11** (1.08 g, 2.00 mmol) and 2-azidoacetic acid[25] (0.203 g, 2.01 mmol) were dissolved in *t*-BuOH/H_2O (1:1, 40 mL). A brown cloudy solution of $CuSO_4 \cdot 5H_2O$ (25 mg, 0.10 mmol, 5 mol%) and sodium ascorbate (40 mg, 0.20 mol, 10 mol%) in H_2O (4 mL) was added. The reaction mixture was stirred under Ar at room temperature overnight, quenched with saturated NH_4Cl (10 mL) and extracted with EtOAc (3 × 80 mL). The combined organic extracts were concentrated under reduced

pressure, and the residue was purified by flash column chromatography (silica gel, EtOAc ramping to EtOAc:CH_3OH = 7:3) to give the **12** as a white foam (1.26 g, 98%). $\boldsymbol{R_F}$ (EtOAc:CH_3OH = 9:1) 0.13. **IR** ν_{max}/cm^{-1} 3454, 2974, 2934, 2108, 1684, 1626, 1468, 1413, 1370, 1302, 1241, 1157, 1055, 734. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.43 (s, 18H, 2 × $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$), 1.70-1.83 (m, 2H, $CH_2CH_2CH_2$), 1.83-2.00 (m, 2H, $CH_2CH_2CH_2$), 2.50-2.70 (m, 2H, $CH_2N(CH_2$-triaozle)CH_2), 2.70-2.90 (m, 2H, $CH_2N(CH_2$-triazole)CH_2), 3.15-3.55 (m, 12H, 3 × $CH_2N(Boc)CH_2$), 3.93 (br s, 2H, NCH_2-triazole), 4.96 (s, 2H, triazole-CH_2COOH), 7.09 (br s, 1H, COOH), 7.76 (br s, 1H, triazole-H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 25.2, 28.4, 45.3, 46.4, 46.9, 47.3, 48.3, 50.4, 51.4, 52.8, 79.6, 79.8, 125.5, 140.8, 155.4, 155.7, 171.5 (thirteen carbon signals overlapping or obscured). **MS** (ESI) *m/z* 638.3 ($[M-H]^-$, 100%), 1277.5 ($[2M-H]^-$, 48%). **HRMS** (ESI) 662.38603 ($[M+Na]^+$); calcd. for $C_{30}H_{53}N_7NaO_8$ ($[M+Na]^+$) 662.38478.

5. Synthesis of Tetraazamacrocycle-(G)KLVFF Hybrids 1-6 and Metal Complexes 19-26



Scheme S3. Synthesis of tetraazamacrocycle-(G)KLVFF hybrids **1**-**6** and their metal complexes **19-26**. Reagents and conditions: (a) appropriate carboxylic acid (**9**, **10**, **11** or **12**), PyBOP, NMM, DMF, rt, 1 h; (b) TFA/TIS/H_2O (90:5:5), rt, 2 h, followed by RP-HPLC purification, **1**: 53%, **2**: 63%, **3**: 52%, **4**: 60%, **5**: 60%, **6**: 58%; (c) $CuCl_2{\cdot}2H_2O$ or $ZnCl_2$, EtOH, reflux, 6 h, **19**: 94%, **20**: 81%, **21**: 54%, **22**: 85%, **23**: 88%, **24**: 67%, **25**: 53%, **26**: 69%.

10-((4*S*,7*S*,10*S*,13*S*,16*S*)-4-(4-Ammoniobutyl)-13-benzyl-16-carboxy-7-isobutyl-10-isopropyl-2,5,8,11,14-pentaoxo-17-phenyl-3,6,9,12,15-pentaazaheptadecyl)-10-aza-1,4,7-triazoniacyclododecane-1,4,7-triium 2,2,2-trifluoroacetate (1).

Wang resin (100-200 mesh, loading 1.1 mmol/g, 227 mg, 0.250 mmol) was pre-loaded with Fmoc-Phe-OH (**S1**) and cyclen-pentapeptide conjugate **1** was assembled using

general synthetic procedure A. The combined cleavage solution and TFA washings were concentrated under reduced pressure, and the residue was purified by preparative RP-HPLC (gradient 0% to 50% B over 45 min) to give **1** as a white solid (174 mg, 53%). **m.p.** 169-170 °C. **$[\alpha]_D^{20}$** -42.6 (*c* 1.0, H_2O). **IR** ν_{max}/cm^{-1} 3273, 3074, 2961, 2871, 1672, 1630, 1539, 1420, 1362, 1184, 1131, 707. **^{1}H NMR** (400 MHz, D_2O) δ 0.68 (d, 3H, *J* 6.4, CH_3), 0.76 (d, 3H, *J* 7.2, CH_3), 0.78 (d, 3H, *J* 6.4, CH_3), 0.84 (d, 3H, *J* 6.0, CH_3), 1.25-1.44 (m, 3H), 1.44-1.55 (m, 2H), 1.55-1.65 (m, 2H), 1.65-1.77 (m, 2H), 1.77-1.90 (m, 1H) (total 10H, C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$NH$_3^+$ & C*H*$_2$C*H*(CH$_3$)$_2$ & CHC*H*(CH$_3$)$_2$), 2.70-2.84 (m, 2H), 2.84-3.03 (m, 10H), 3.03-3.30 (m, 10H) (total 22H, 2 × C*H*$_2$Ph & C*H*$_2$NH$_3^+$ & 3 × C*H*$_2$NH$_2^+$C*H*$_2$ & C*H*$_2$N(CH$_2$CONH)C*H*$_2$), 3.44 (s, 2H, NC*H*$_2$CONH), 4.04 (d, 1H, *J* 8.0, NHC*H*CO), 4.23 (t, 1H, *J* 6.8, NHC*H*CO), 4.28-4.38 (m, 1H, NHC*H*CO), 4.52-4.64 (m, 2H, 2 × NHC*H*CO), 7.08 (d, 2H, *J* 7.2, Ph-H), 7.12 (d, 2H, *J* 7.2, Ph-H), 7.14-7.25 (m, 6H, Ph-H) (nine ammonium proton signals (3 × NH_2^+ & NH_3^+), five amide proton signals (5 × CONH) and one carboxylic acid proton signal (COOH) not observed due to H/D exchange). **^{13}C NMR** (100 MHz, D_2O) δ 17.7, 18.5, 21.2, 22.0, 24.3, 26.4, 30.6, 30.8, 36.7, 37.6, 39.1, 39.8, 42.1, 42.5, 44.3, 49.6, 52.3, 53.8, 53.9, 54.4, 55.1, 59.0, 116.3 (q, $J_{C\text{-}F}$ 290.0, 4 × CF_3), 127.1, 128.6, 129.1, 129.2, 136.1, 136.3, 162.7 (q, $J_{C\text{-}F}$ 40.0, 4 × CF_3*C*OOH), 172.0, 172.1, 173.1, 173.4, 173.6, 174.0 (eleven carbon signals overlapping or obscured). **MS** (ESI) *m/z* 866.0 ([M-4TFA+H]$^+$, 100%). **HRMS** (ESI) 865.56469 ([M-4TFA+H]$^+$); calcd. for $C_{45}H_{73}N_{10}O_7$ ([M-4TFA+H]$^+$) 865.56582. **Anal.** Calcd. for $C_{53}H_{76}F_{12}N_{10}O_{15}$: C 48.18, H 5.80, N 10.60; Found: C 48.44, H 6.06, N 10.82.

11-((4*S*,7*S*,10*S*,13*S*,16*S*)-4-(4-Ammoniobutyl)-13-benzyl-16-carboxy-7-isobutyl-10-isopropyl-2,5,8,11,14-pentaoxo-17-phenyl-3,6,9,12,15-pentaazaheptadecyl)-11-aza-1,4,8-triazoniacyclotetradecane-1,4,8-triium 2,2,2-trifluoroacetate (2).

Wang resin (100-200 mesh, loading 1.1 mmol/g, 227 mg, 0.250 mmol) was pre-loaded with Fmoc-Phe-OH (**S1**) and cyclam-pentapeptide conjugate **2** was assembled using general synthetic procedure A. The combined cleavage solution and TFA washings were concentrated under reduced pressure, and the residue was purified by preparative RP-HPLC (gradient 0% to 50% B over 45 min) to give **2** as a white solid (213 mg, 63%). **m.p.** 155-156 °C. **$[\alpha]_D^{20}$** -43.4 (*c* 1.0, H_2O). **IR** ν_{max}/cm^{-1} 3272, 3074, 2959, 2865, 1672, 1628, 1544, 1428, 1364, 1185, 1128, 833, 797, 706. **^{1}H NMR** (400 MHz, D_2O) δ 0.69 (d,

3H, *J* 6.4, CH_3), 0.77 (d, 3H, *J* 7.2, CH_3), 0.79 (d, 3H, *J* 5.6, CH_3), 0.84 (d, 3H, *J* 5.2, CH_3), 1.26-1.54 (m, 5H), 1.54-1.66 (m, 2H), 1.66-1.76 (m, 2H), 1.76-2.10 (m, 5H) (total 14H, 2 × $NCH_2CH_2CH_2N$ & $CH_2CH_2CH_2CH_2NH_3^+$ & $CH_2CH(CH_3)_2$ & $CHCH(CH_3)_2$), 2.60-3.50 (br m, 24H, 2 × CH_2Ph & $CH_2NH_3^+$ & 3 × $CH_2NH_2^+CH_2$ & $CH_2N(CH_2CONH)CH_2$), 4.07 (d, 1H, *J* 8.0, NHC*H*CO), 4.24 (t, 1H, *J* 6.8, NHC*H*CO), 4.28-4.36 (m, 1H, NHC*H*CO), 4.54-4.63 (m, 2H, 2 × NHC*H*CO), 7.09 (d, 2H, *J* 7.2, Ph-H), 7.14 (d, 2H, *J* 7.2, Ph-H), 7.15-7.26 (m, 6H, Ph-H) (nine ammonium proton signals (3 × NH_2^+ & NH_3^+), five amide proton signals (5 × CONH) and one carboxylic acid proton signal (COOH) not observed due to H/D exchange). **^{13}C NMR** (75 MHz, D_2O) δ 17.8, 18.5, 21.4, 22.0, 22.5, 23.5, 24.3, 26.4, 30.7, 36.7, 37.7, 39.0, 40.2, 42.9, 44.5, 45.5, 46.7, 52.2, 53.5, 53.9, 54.3, 54.6, 58.9, 116.3 (q, $J_{C\text{-}F}$ 292.5, 4 × CF_3), 127.0, 128.5, 129.0, 129.1, 136.1, 136.3, 162.6 (q, $J_{C\text{-}F}$ 37.5, 4 × CF_3CCOOH), 171.9, 173.2, 173.4, 173.9 (fourteen carbon signals overlapping or obscured). **MS** (ESI) *m/z* 447.3 ($[M\text{-}4TFA+2H]^{2+}$, 56%), 893.6 ($[M\text{-}4TFA+H]^+$, 100%). **HRMS** (ESI) 893.59554 ($[M\text{-}4TFA+H]^+$); calcd. for $C_{47}H_{77}N_{10}O_7$ ($[M\text{-}4TFA+H]^+$) 893.59712. **Anal.** Calcd. for $C_{55}H_{80}F_{12}N_{10}O_{15}\cdot H_2O$: C 48.31, H 6.04, N 10.24; Found: C 48.40, H 6.07, N 10.42.

10-((7*S*,10*S*,13*S*,16*S*,19*S*)-7-(4-Ammoniobutyl)-16-benzyl-19-carboxy-10-isobutyl-13-isopropyl-2,5,8,11,14,17-hexaoxo-20-phenyl-3,6,9,12,15,18-hexaazaicosyl)-10-aza-1,4,7-triazoniacyclododecane-1,4,7-triium 2,2,2-trifluoroacetate (3).

Wang resin (100-200 mesh, loading 1.1 mmol/g, 227 mg, 0.250 mmol) was pre-loaded with Fmoc-Phe-OH (**S1**) and cyclen-hexapeptide conjugate **3** was assembled using general synthetic procedure A. The combined cleavage solution and TFA washings were concentrated under reduced pressure, and the residue was purified by preparative RP-HPLC (gradient 0% to 50% B over 45 min) to give **3** as a white solid (179 mg, 52%). **m.p.** 216-217 °C. **$[\alpha]_D^{20}$** -41.0 (*c* 0.50, H_2O). **IR** ν_{max}/cm^{-1} 3270, 3075, 2962, 2874, 1674, 1627, 1531, 1423, 1363, 1185, 1131, 834, 796, 717. **^{1}H NMR** (400 MHz, D_2O) δ 0.72 (d, 3H, *J* 6.8, CH_3), 0.80 (d, 3H, *J* 6.8, CH_3), 0.83 (d, 3H, *J* 6.4, CH_3), 0.90 (d, 3H, *J* 6.0, CH_3), 1.28-1.48 (m, 3H), 1.48-1.59 (m, 2H), 1.59-1.69 (m, 2H), 1.69-1.81 (m, 2H), 1.81-1.93 (m, 1H) (total 10H, $CH_2CH_2CH_2CH_2NH_3^+$ & $CH_2CH(CH_3)_2$ & $CHCH(CH_3)_2$), 2.70-3.30 (br m, 22H, 2 × CH_2Ph & $CH_2NH_3^+$ & 3 × $CH_2NH_2^+CH_2$ & $CH_2N(CH_2CONH)CH_2$), 3.50 (s, 2H,

NCH_2CONH), 3.93-4.03 (m, 3H, NHCHCO & CONHCH_2CONH), 4.25 (t, 1H, J 6.8, NHCHCO), 4.28-4.32 (m, 1H, NHCHCO), 4.58 (t, 1H, J 9.2, NHCHCO), 4.59 (t, 1H, J 8.8, NHCHCO), 7.17 (d, 2H, J 6.8, Ph-H), 7.21 (d, 2H, J 7.2, Ph-H), 7.25-7.35 (m, 6H, Ph-H) (nine ammonium proton signals (3 × NH_2^+ & NH_3^+), six amide proton signals (6 × CONH) and one carboxylic acid proton signal (COOH) not observed due to H/D exchange). **^{13}C NMR** (75 MHz, D_2O) δ 17.9, 18.6, 21.6, 22.0, 22.2, 24.4, 26.4, 31.1, 31.3, 36.9, 38.0, 39.1, 40.5, 42.1, 42.6, 44.3, 49.6, 51.8, 53.2, 53.8, 54.1, 55.3, 58.6, 116.3 (q, $J_{C\text{-}F}$ 292.5, 4 × CF_3), 126.9, 128.4, 129.1, 136.1, 136.2, 162.5 (q, $J_{C\text{-}F}$ 37.5, 4 × $CF_3$$C$OOH), 170.3, 171.7, 172.0, 172.5, 173.0, 173.6, 173.8 (twelve carbon signals overlapping or obscured). **MS** (ESI) m/z 461.8 ([M-4TFA+2H]$^{2+}$, 100%), 922.6 ([M-4TFA+H]$^+$, 85%). **HRMS** (ESI) 922.58649 ([M-4TFA+H]$^+$); calcd. for $C_{47}H_{76}N_{11}O_8$ ([M-4TFA+H]$^+$) 922.58728. **Anal.** Calcd. for $C_{55}H_{79}F_{12}N_{11}O_{16}$: C 47.93, H 5.78, N 11.18; Found: C 47.90, H 6.05, N 11.33.

11-((7*S*,10*S*,13*S*,16*S*,19*S*)-7-(4-Ammoniobutyl)-16-benzyl-19-carboxy-10-isobutyl-13-isopropyl-2,5,8,11,14,17-hexaoxo-20-phenyl-3,6,9,12,15,18-hexaazaicosyl)-11-aza-1,4,8-triazoniacyclotetradecane-1,4,8-triium 2,2,2-trifluoroacetate (4).

Wang resin (100-200 mesh, loading 1.1 mmol/g, 227 mg, 0.250 mmol) was pre-loaded with Fmoc-Phe-OH (**S1**) and cyclam-hexapeptide conjugate **4** was assembled using general synthetic procedure A. The combined cleavage solution and TFA washings were concentrated under reduced pressure, and the residue was purified by preparative RP-HPLC (gradient 0% to 50% B over 45 min) to give **4** as a white solid (211 mg, 60%). **m.p.** 156-157 °C. **[α]$_D^{20}$** -40.4 (c 1.0, H_2O). **IR** ν_{max}/cm^{-1} 3272, 3074, 3033, 2960, 2866, 1672, 1628, 1535, 1430, 1364, 1187, 1130, 835, 798, 717. **^{1}H NMR** (400 MHz, D_2O) δ 0.72 (d, 3H, J 6.8, CH_3), 0.80 (d, 3H, J 6.8, CH_3), 0.83 (d, 3H, J 6.0, CH_3), 0.90 (d, 3H, J 6.0, CH_3), 1.28-1.47 (m, 3H), 1.47-1.59 (m, 2H), 1.59-1.80 (m, 4H), 1.80-2.00 (m, 5H) (total 14H, 2 × NCH$_2$CH_2CH$_2$N & CH_2CH_2CH_2CH$_2$NH$_3^+$ & CH_2CH(CH$_3$)$_2$ & CHCH(CH$_3$)$_2$), 2.70-3.26 (br m, 22H, 2 × CH_2Ph & CH_2NH$_3^+$ & 3 × CH_2NH$_2^+$CH_2 & CH_2N(CH$_2$CONH)CH_2), 3.34 (br s, 2H, NCH_2CONH), 3.95-4.06 (m, 1H, NHCHCO), 3.99 (s, 2H, CONHCH_2CONH), 4.23-4.30 (m, 2H, 2 × NHCHCO), 4.58 (t, 1H, J 9.2, NHCHCO), 4.59 (t, 1H, J 8.8, NHCHCO), 7.16 (d, 2H, J 6.8, Ph-H), 7.20 (d, 2H, J 7.2, Ph-H), 7.25-7.34 (m, 6H, Ph-H) (nine ammonium proton signals (3 × NH_2^+ & NH_3^+), six amide proton signals (6 × CONH) and one

carboxylic acid proton signal (COOH) not observed due to H/D exchange). **^{13}C NMR** (75 MHz, D_2O) δ 17.7, 18.4, 21.0, 22.0, 22.6, 24.0, 24.3, 26.4, 30.5, 30.8, 36.7, 37.5, 39.1, 39.7, 41.9, 43.3, 44.8, 46.0, 46.9, 47.3, 52.3, 53.6, 53.9, 54.4, 54.8, 59.0, 116.3 (q, $J_{C\text{-}F}$ 292.5, 4 × CF_3), 127.2, 128.6, 128.7, 129.1, 129.2, 136.1, 136.3, 162.8 (q, $J_{C\text{-}F}$ 37.5, 4 × CF_3*C*OOH), 170.9, 172.0, 172.2, 173.4, 173.7, 174.1 (ten carbon signals overlapping or obscured). **MS** (ESI) *m/z* 475.8 ([M-4TFA+2H]$^{2+}$, 100%), 950.6 ([M-4TFA+H]$^+$, 65%). **HRMS** (ESI) 950.61653 ([M-4TFA+H]$^+$); calcd. for $C_{49}H_{80}N_{11}O_8$ ([M-4TFA+H]$^+$) 950.61859. **Anal.** Calcd. for $C_{57}H_{83}F_{12}N_{11}O_{16}$: C 48.68, H 5.95, N 10.96; Found: C 48.47, H 6.19, N 11.05.

10-((1-((4*S*,7*S*,10*S*,13*S*,16*S*)-4-(4-Ammoniobutyl)-13-benzyl-16-carboxy-7-isobutyl-10-isopropyl-2,5,8,11,14-pentaoxo-17-phenyl-3,6,9,12,15-pentaazaheptadecyl)-1*H*-1,2,3-triazol-4-yl)methyl)-10-aza-1,4,7-triazoniacyclododecane-1,4,7-triium 2,2,2-trifluoroacetate (5).

Wang resin (100-200 mesh, loading 1.1 mmol/g, 227 mg, 0.250 mmol) was pre-loaded with Fmoc-Phe-OH (**S1**) and cyclen-pentapeptide conjugate **5** was assembled using general synthetic procedure A. The combined cleavage solution and TFA washings were concentrated under reduced pressure, and the residue was purified by preparative RP-HPLC (gradient 0% to 40% B over 45 min) to give **5** as a white solid (209 mg, 60%). **m.p.** 217-218 °C. **$[\alpha]_D^{20}$** -44.6 (*c* 1.0, H_2O). **IR** ν_{max}/cm^{-1} 3274, 3078, 2961, 2869, 1672, 1630, 1546, 1421, 1363, 1186, 1131, 833, 798, 706. **^{1}H NMR** (400 MHz, D_2O) δ 0.73 (d, 3H, *J* 6.4, CH_3), 0.80 (d, 3H, *J* 6.8, CH_3), 0.82 (d, 3H, *J* 6.0, CH_3), 0.89 (d, 3H, *J* 6.0, CH_3), 1.33-1.49 (m, 3H), 1.49-1.62 (m, 2H), 1.62-1.74 (m, 2H), 1.74-1.93 (m, 3H) (total 10H, C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$NH$_3^+$ & C*H*$_2$C*H*(CH$_3$)$_2$ & CHC*H*(CH$_3$)$_2$), 2.70-3.50 (br m, 22H, 2 × C*H*$_2$Ph & C*H*$_2$NH$_3^+$ & 3 × C*H*$_2$NH$_2^+$C*H*$_2$ & C*H*$_2$N(CH$_2$-triazole)C*H*$_2$), 3.95 (s, 2H, CH$_2$N(C*H*$_2$-triazole)CH$_2$), 4.02 (d, 1H, *J* 8.0, NHC*H*CO), 4.29-4.34 (m, 2H, 2 × NHC*H*CO), 4.57-4.65 (m, 2H, 2 × NHC*H*CO), 5.32 (s, 2H, triazole-C*H*$_2$CONH), 7.19 (d, 2H, *J* 6.8, Ph-H), 7.24 (d, 2H, *J* 7.2, Ph-H), 7.27-7.37 (m, 6H, Ph-H), 8.02 (s, 1H, triazole-H) (nine ammonium proton signals (3 × NH_2^+ & NH_3^+), five amide proton signals (5 × CONH) and one carboxylic acid proton signal (COOH) not observed due to H/D exchange). **^{13}C NMR** (75 MHz, D_2O) δ 17.7, 18.4, 20.8, 22.1, 24.3, 26.3, 30.4, 36.7, 37.4, 39.1, 39.6, 41.7, 42.0, 44.3, 46.3, 47.6, 51.7, 52.3, 53.9, 54.4, 59.0, 116.3 (q, $J_{C\text{-}F}$ 292.5, 4 × CF_3), 126.6, 127.2, 128.7, 129.1, 129.2, 136.2, 136.3, 142.4, 162.8 (q, $J_{C\text{-}F}$ 37.5, 4 × CF_3*C*OOH), 167.6, 172.1, 172.2, 173.2, 173.8,

174.1 (thirteen carbon signals overlapping or obscured). **MS** (ESI) *m/z* 473.5 ([M-4TFA+2H]$^{2+}$, 100%), 946.5 ([M-4TFA+H]$^{+}$, 5%). **HRMS** (ESI) 946.59841 ([M-4TFA+H]$^{+}$); calcd. for $C_{48}H_{76}N_{13}O_7$ ([M-4TFA+H]$^{+}$) 946.59852. **Anal.** Calcd. for $C_{56}H_{79}F_{12}N_{13}O_{15}$: C 47.96, H 5.68, N 12.99; Found: C 47.95, H 5.99, N 13.26.

11-((1-((4*S*,7*S*,10*S*,13*S*,16*S*)-4-(4-Ammoniobutyl)-13-benzyl-16-carboxy-7-isobutyl-10-isopropyl-2,5,8,11,14-pentaoxo-17-phenyl-3,6,9,12,15-pentaazaheptadecyl)-1*H*-1,2,3-triazol-4-yl)methyl)-11-aza-1,4,8-triazoniacyclotetradecane-1,4,8-triium 2,2,2-trifluoroacetate (6).

Wang resin (100-200 mesh, loading 1.1 mmol/g, 182 mg, 0.200 mmol) was pre-loaded with Fmoc-Phe-OH (**S1**) and cyclam-pentapeptide conjugate **6** was assembled using general synthetic procedure A. The combined cleavage solution and TFA washings were concentrated under reduced pressure, and the residue was purified by preparative RP-HPLC (gradient 0% to 40% B over 45 min) to give **6** as a white solid (165 mg, 58%). **m.p.** 150-151 °C. **[α]$_D^{20}$** -42.3 (*c* 1.0, H_2O). **IR** ν_{max}/cm^{-1} 3273, 3076, 2961, 2868, 1672, 1630, 1547, 1430, 1366, 1187, 1131, 836, 799, 717. **^{1}H NMR** (400 MHz, D_2O) δ 0.73 (d, 3H, *J* 6.4, CH_3), 0.81 (d, 3H, *J* 7.6, CH_3), 0.82 (d, 3H, *J* 6.8, CH_3), 0.90 (d, 3H, *J* 5.6, CH_3), 1.33-1.50 (m, 3H), 1.50-1.63 (m, 2H), 1.63-1.75 (m, 2H), 1.75-1.96 (m, 5H), 2.00-2.15 (m, 2H) (total 14H, 2 × $NCH_2CH_2CH_2N$ & $CH_2CH_2CH_2CH_2NH_3^+$ & $CH_2CH(CH_3)_2$ & $CHCH(CH_3)_2$), 2.70-3.40 (br m, 22H, 2 × CH_2Ph & $CH_2NH_3^+$ & 3 × $CH_2NH_2^+CH_2$ & $CH_2N(CH_2\text{-triazole})CH_2$), 3.82 (br s, 2H, $CH_2N(CH_2\text{-triazole})CH_2$), 4.02 (d, 1H, *J* 8.0, NHC*H*CO), 4.28-4.33 (m, 2H, 2 × NHC*H*CO), 4.57-4.65 (m, 2H, 2 × NHC*H*CO), 5.33 (s, 2H, triazole-CH_2CONH), 7.19 (d, 2H, *J* 7.2, Ph-H), 7.24 (d, 2H, *J* 7.2, Ph-H), 7.27-7.37 (m, 6H, Ph-H), 7.97 (s, 1H, triazole-H) (nine ammonium proton signals (3 × NH_2^+ & NH_3^+), five amide proton signals (5 × CONH) and one carboxylic acid proton signal (COOH) not observed due to H/D exchange). **^{13}C NMR** (75 MHz, D_2O) δ 17.5, 18.2, 20.7, 21.9, 24.1, 26.2, 30.3, 36.6, 37.3, 39.0, 39.4, 39.6, 41.2, 41.5, 43.3, 43.6, 46.6, 48.0, 50.5, 51.6, 52.1, 53.7, 54.3, 58.9, 115.8 (q, $J_{C\text{-}F}$ 360.0, 4 × CF_3), 127.0, 128.5, 129.0, 136.0, 136.2, 141.0, 161.7 (q, $J_{C\text{-}F}$ 60.0, 4 × CF_3COOH), 167.3, 171.9, 172.0, 173.0, 173.6, 174.0 (fourteen carbon signals overlapping or obscured). **MS** (ESI) *m/z* 487.5 ([M-4TFA+2H]$^{2+}$, 100%), 974.6 ([M-4TFA+H]$^{+}$, 10%). **HRMS** (ESI) 974.63091 ([M-4TFA+H]$^{+}$); calcd. for

$C_{50}H_{80}N_{13}O_7$ ([M-4TFA+H]$^+$) 974.62982. **Anal.** Calcd. for $C_{58}H_{83}F_{12}N_{13}O_{15}\cdot 2H_2O$: C 47.51, H 5.98, N 12.42; Found: C 47.43, H 5.76, N 12.50.

[Cu(1-4TFA)]Cl_2 complex (19).

Compound **1** (119 mg, 0.0900 mmol) and $CuCl_2\cdot 2H_2O$ (15.3 mg, 0.0897 mmol) were complexed according to general synthetic procedure B to give **19** as a blue powder (85.1 mg, 94%). **m.p.** 170-175 °C. **$[\alpha]_D^{20}$** -53.0 (*c* 0.10, H_2O). **UV-Vis** (H_2O) λ_{max}/nm 586, ε 211. **IR** ν_{max}/cm^{-1} 3411, 3269, 3082, 2957, 1632, 1546, 1456, 1396, 1199, 1136, 1080, 700. **HRMS** (ESI) 463.74372, 464.24552, 464.74318, 465.24474, 465.74642, 466.24827 ([M-2Cl]$^{2+}$); calcd. for $C_{45}H_{72}CuN_{10}O_7$ ([M-2Cl]$^{2+}$) 463.74352, 464.24516, 464.74284, 465.24432, 465.74597, 466.24765. **Anal.** Calcd. for $C_{45}H_{72}Cl_2CuN_{10}O_7\cdot CF_3COOH\cdot 2H_2O$: C 49.10, H 6.75, N 12.18; Found: C 49.01, H 6.61, N 12.19.

[Cu(2-4TFA)]Cl_2 complex (20).

Compound **2** (135 mg, 0.100 mmol) and $CuCl_2\cdot 2H_2O$ (17.1 mg, 0.100 mmol) were complexed according to general synthetic procedure B. The reaction mixture was concentrated under reduced pressure. The residue was triturated with Et_2O (10 mL), washed with CH_3CN (3 × 10 mL) and Et_2O (3 × 10 mL), and dried *in vacuo* to give **20** as a purple powder (83.3 mg, 81%). **m.p.** 160-165 °C. **$[\alpha]_D^{20}$** -66.5 (*c* 0.20, H_2O). **UV-Vis** (H_2O) λ_{max}/nm 555, ε 138. **IR** ν_{max}/cm^{-1} 3272, 3076, 2934, 2879, 1633, 1540, 1452, 1395, 1192, 1132, 1040, 699. **HRMS** (ESI) 477.75911, 478.26068, 478.75802, 479.25963, 479.76098 ([M-2Cl]$^{2+}$); calcd. for $C_{47}H_{76}CuN_{10}O_7$ ([M-2Cl]$^{2+}$) 477.75917, 478.26081, 478.75850, 479.25998, 479.76162. **Anal.** Calcd. for $C_{47}H_{76}Cl_2CuN_{10}O_7\cdot CF_3COOH\cdot 3H_2O$: C 49.22, H 7.00, N 11.71; Found: C 48.98, H 6.95, N 11.68.

[Zn(2-4TFA)]Cl_2 complex (21).

Compound **2** (41 mg, 0.030 mmol) and $ZnCl_2$ (4.1 mg, 0.030 mmol) were complexed according to general synthetic procedure B. The reaction mixture was concentrated under reduced pressure. The residue was triturated with Et_2O (5 mL), washed with CH_3CN (3 × 5 mL) and Et_2O (3 × 5 mL), and dried *in vacuo* to give **21** as a white powder

(17 mg, 54%). **m.p.** 230-235 °C. **$[\alpha]_D^{20}$** -68.5 (*c* 0.20, H_2O). **IR** ν_{max}/cm^{-1} 3230, 3079, 2936, 2862, 1633, 1524, 1197, 1140, 999, 950, 870, 702. **HRMS** (ESI) 478.25962, 478.76159, 479.25780, 479.75968, 480.25720, 480.75922, 481.26122 ($[M-2Cl]^{2+}$); calcd. for $C_{47}H_{76}N_{10}O_7Zn$ ($[M-2Cl]^{2+}$) 478.25895, 478.76060, 479.25758, 479.75906, 480.25691, 480.75849, 481.26014. **Anal.** Calcd. for $C_{47}H_{76}Cl_2N_{10}O_7Zn{\cdot}4CF_3COOH{\cdot}3CH_3CN{\cdot}4H_2O$: C 43.59, H 5.82, N 10.83; Found: C 43.51, H 6.22, N 10.53.

[Cu(3-4TFA)]Cl_2 complex (22).

Compound **3** (110 mg, 0.0798 mmol) and $CuCl_2{\cdot}2H_2O$ (13.6 mg, 0.0798 mmol) were complexed according to general synthetic procedure B. The reaction mixture was concentrated under reduced pressure. The residue was triturated with Et_2O (10 mL), washed with 1% EtOH in CH_3CN (3 × 10 mL) and Et_2O (3 × 10 mL), and dried *in vacuo* to give **22** as a blue powder (71.4 mg, 85%). **m.p.** 185-190 °C. **$[\alpha]_D^{20}$** -52.0 (*c* 0.10, H_2O). **UV-Vis** (H_2O) λ_{max}/nm 582, ε 220. **IR** ν_{max}/cm^{-1} 3267, 3086, 2957, 2928, 1627, 1535, 1452, 1399, 1198, 1134, 1078, 698. **HRMS** (ESI) 492.25531, 492.75700, 493.25507, 493.75641, 494.25801, 494.75905 ($[M-2Cl]^{2+}$); calcd. for $C_{47}H_{75}CuN_{11}O_8$ ($[M-2Cl]^{2+}$) 492.25426, 492.75589, 493.25359, 493.75506, 494.25670, 494.75838. **Anal.** Calcd. for $C_{47}H_{75}Cl_2CuN_{11}O_8{\cdot}CF_3COOH{\cdot}2H_2O$: C 48.77, H 6.68, N 12.77; Found: C 48.70, H 6.77, N 12.95.

[Cu(4-4TFA)]Cl_2 complex (23).

Compound **4** (141 mg, 0.100 mmol) and $CuCl_2{\cdot}2H_2O$ (17.1 mg, 0.100 mmol) were complexed according to general synthetic procedure B. The reaction mixture was concentrated under reduced pressure. The residue was triturated with Et_2O (10 mL), washed with CH_3CN (3 × 10 mL) and Et_2O (3 × 10 mL), and dried *in vacuo* to give **23** as a purple powder (96.2 mg, 88%). **m.p.** 175-180 °C. **$[\alpha]_D^{20}$** -42.5 (*c* 0.20, H_2O). **UV-Vis** (H_2O) λ_{max}/nm 552, ε 110. **IR** ν_{max}/cm^{-1} 3273, 3085, 2956, 2878, 1628, 1539, 1444, 1400, 1191, 1131, 1031, 695. **HRMS** (ESI) 506.27045, 506.77217, 507.27029, 507.77175, 508.27302, 508.77454 ($[M-2Cl]^{2+}$); calcd. for $C_{49}H_{79}CuN_{11}O_8$ ($[M-2Cl]^{2+}$) 506.26991, 506.77154, 507.26925, 507.77071, 508.27235, 508.77403. **Anal.** Calcd. for

$C_{49}H_{79}Cl_2CuN_{11}O_8 \cdot CF_3COOH \cdot 3H_2O$: C 48.90, H 6.92, N 12.30; Found: C 48.59, H 6.86, N 12.30.

[Cu(5-4TFA)]Cl_2 complex (24).

Compound **5** (112 mg, 0.0799 mmol) and $CuCl_2 \cdot 2H_2O$ (13.7 mg, 0.0804 mmol) were complexed according to general synthetic procedure B. The reaction mixture was concentrated under reduced pressure. The residue was triturated with Et_2O (10 mL), washed with 1% H_2O in CH_3CN (3 × 10 mL) and Et_2O (3 × 10 mL), and dried *in vacuo* to give **24** as a blue powder (57.9 mg, 67%). **m.p.** 214-215 °C. **$[\alpha]_D^{20}$** -62.5 (*c* 0.080, H_2O). **UV-Vis** (H_2O) λ_{max}/nm 591, ε 258. **IR** ν_{max}/cm^{-1} 3384, 3267, 3080, 2957, 1630, 1545, 1440, 1391, 1203, 1134, 1076, 699. **HRMS** (ESI) 504.26051, 504.76231, 505.26029, 505.76171, 506.26307, 506.76428 ($[M-2Cl]^{2+}$); calcd. for $C_{48}H_{75}CuN_{13}O_7$ ($[M-2Cl]^{2+}$) 504.25987, 504.76150, 505.25921, 505.76067, 506.26232, 506.76400. **Anal.** Calcd. for $C_{48}H_{75}Cl_2CuN_{13}O_7 \cdot 3H_2O$: C 50.81, H 7.20, N 16.05; Found: C 50.65, H 7.12, N 15.93.

[Cu(6-4TFA)]Cl_2 complex (25).

Compound **6** (124 mg, 0.0867 mmol) and $CuCl_2 \cdot 2H_2O$ (14.8 mg, 0.0868 mmol) were complexed according to general synthetic procedure B. The reaction mixture was concentrated under reduced pressure. The residue was triturated with Et_2O (10 mL), washed with 1% H_2O in CH_3CN (3 × 10 mL) and Et_2O (3 × 10 mL), and dried *in vacuo* to give **25** as a purple powder (51.3 mg, 53%). **m.p.** 193-194 °C. **$[\alpha]_D^{20}$** -51.9 (*c* 0.212, H_2O). **UV-Vis** (H_2O) λ_{max}/nm 553, ε 115. **IR** ν_{max}/cm^{-1} 3272, 3082, 2954, 2877, 1668, 1631, 1545, 1455, 1398, 1193, 1138, 1063, 699. **HRMS** (ESI) 518.27644, 518.77816, 519.27609, 519.77749, 520.27905, 520.78054 ($[M-2Cl]^{2+}$); calcd. for $C_{50}H_{79}CuN_{13}O_7$ ($[M-2Cl]^{2+}$) 518.27552, 518.77715, 519.27486, 519.77632, 520.27797, 520.77965. **Anal.** Calcd. for $C_{50}H_{79}Cl_2CuN_{13}O_7 \cdot 5H_2O$: C 50.10, H 7.48, N 15.19; Found: C 50.33, H 7.24, N 15.22.

[Zn(6-4TFA)]Cl_2 complex (26).

Compound **6** (80 mg, 0.056 mmol) and $ZnCl_2$ (7.7 mg, 0.056 mmol) were complexed according to general synthetic procedure B. The reaction mixture was concentrated

under reduced pressure. The residue was triturated with Et_2O (5 mL), washed with CH_3CN (3 × 5 mL) and Et_2O (3 × 5 mL), and dried *in vacuo* to give **26** as a white powder (43 mg, 69%). **m.p.** 230-235 °C. **$[\alpha]_D^{20}$** -52.5 (*c* 0.2, H_2O). **IR** ν_{max}/cm^{-1} 3260, 2944, 1633, 1530, 1192, 1142, 1089, 698, 563. **HRMS** (ESI) 518.77545, 519.27716, 519.77391, 520.27578, 520.77317, 521.27480, 521.77656, 522.27844 ($[M-2Cl]^{2+}$); calcd. for $C_{50}H_{79}N_{13}O_7Zn$ ($[M-2Cl]^{2+}$) 518.77530, 519.27694, 519.77394, 520.27542, 520.77327, 521.27484, 521.77648, 522.27817. **Anal.** Calcd. For $C_{50}H_{79}Cl_2N_{13}O_7Zn{\cdot}4CF_3COOH{\cdot}4CH_3CN{\cdot}4H_2O$: C 43.97, H 5.76, N 13.21; Found: C 44.12, H 6.19, N 13.11.

6. Colors of Copper(II)-Tetraazamacrocycle Complexes 19 and 20

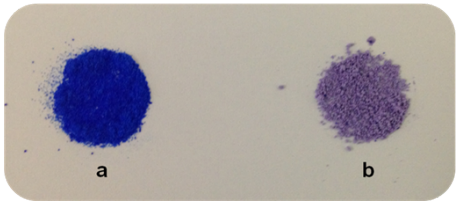
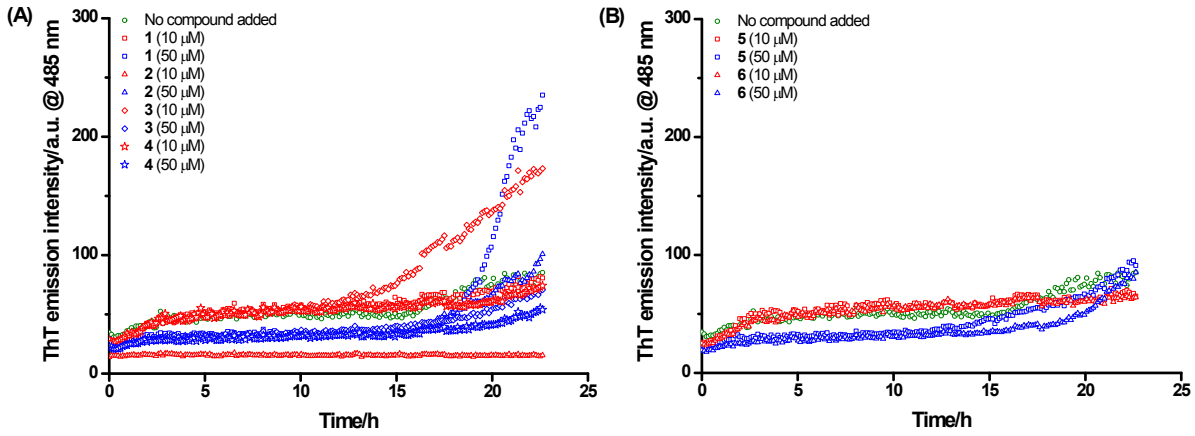


Figure S1. (a) Copper(II)-cyclen-KLVFF complex **19** – a blue powder; (b) Copper(II)-cyclam-KLVFF complex **20** – a purple powder.

7. ThT Extrinsic Fluorescence Assay



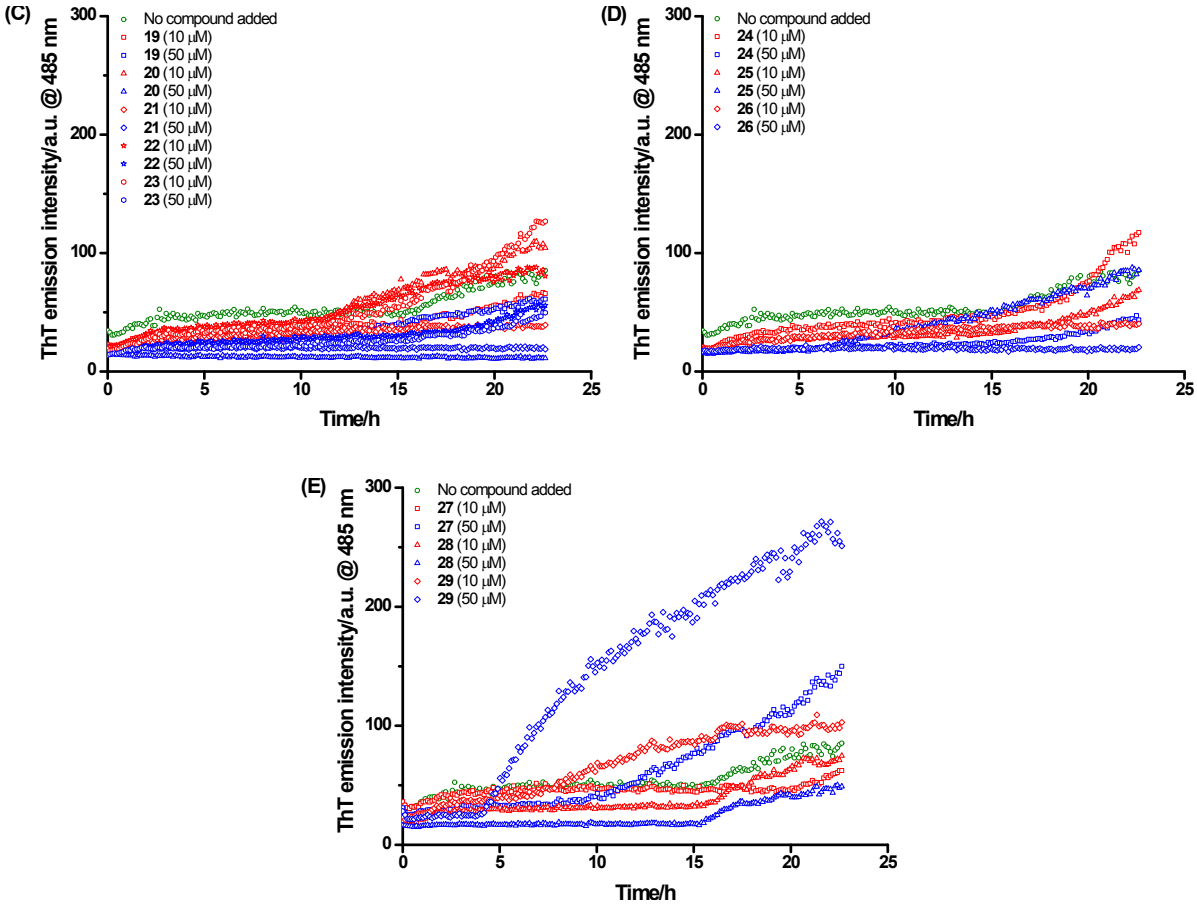


Figure S2. Effects of compounds **1**-**6** and **19**-**29** on Aβ fibril formation. ThT fluorescence over time for Aβ in the absence (green hollow circle) and presence of the amide-tethered hybrids **1**-**4** (A), the triazole-linked hybrids **5** and **6** (B), the amide-tethered metal complexes **19**-**23** (C), the triazole-linked metal complexes **24**-**26** (D) and the control compounds **27**-**29** (E).

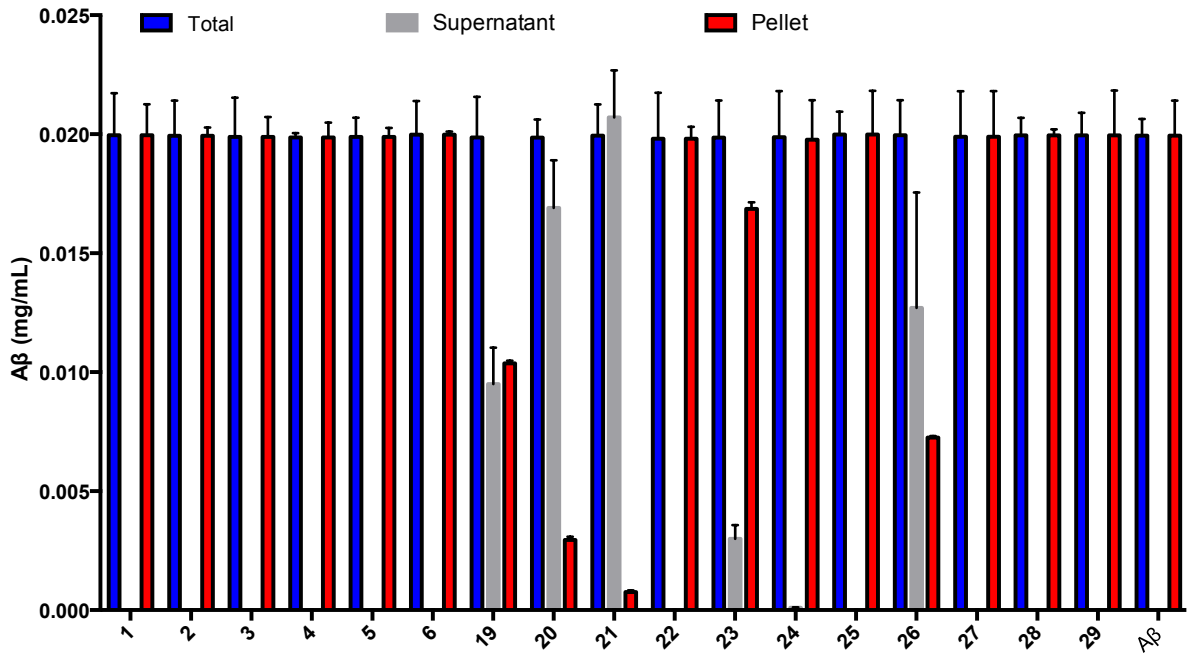


Figure S3. Pelleting assay of $A\beta_{42}$ aggregation. Aβ solutions, incubated for 24 h at 37 °C in the presence and absence of the test compound (50 μM), were centrifuged at 100,000 × *g*. The protein concentration of the sample prior to centrifugation, and of the pellet and supernatant fractions after centrifugation was determined using a microBCA assay, and confirmed using the Direct Detect protein quantitation instrument from Millipore.

8. MALDI-TOF-MS

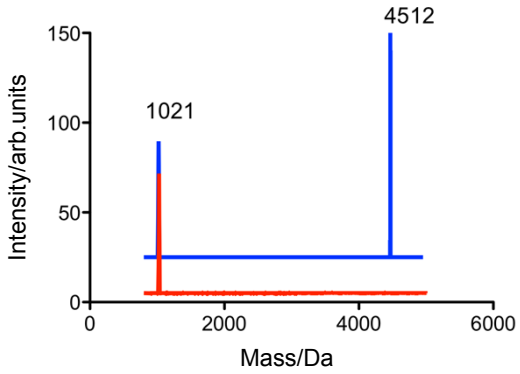
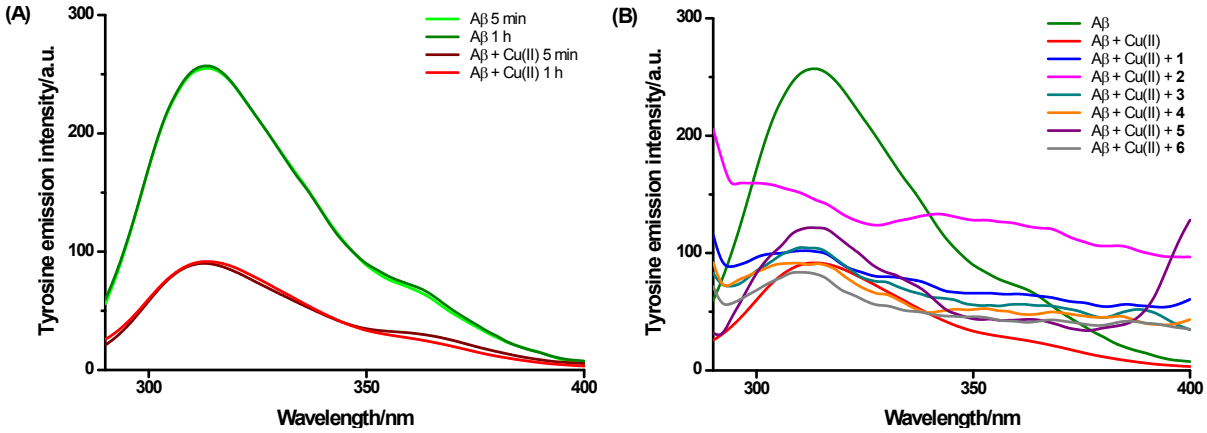
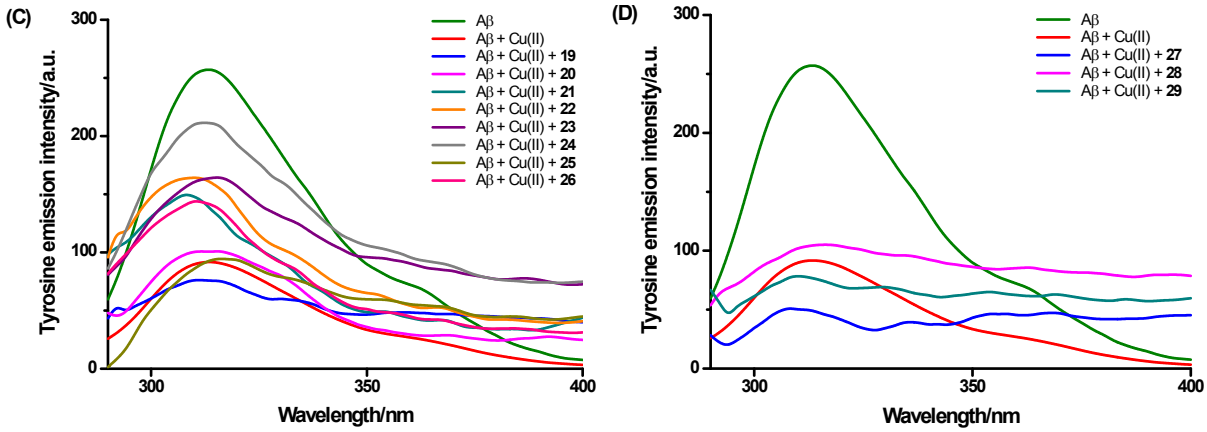
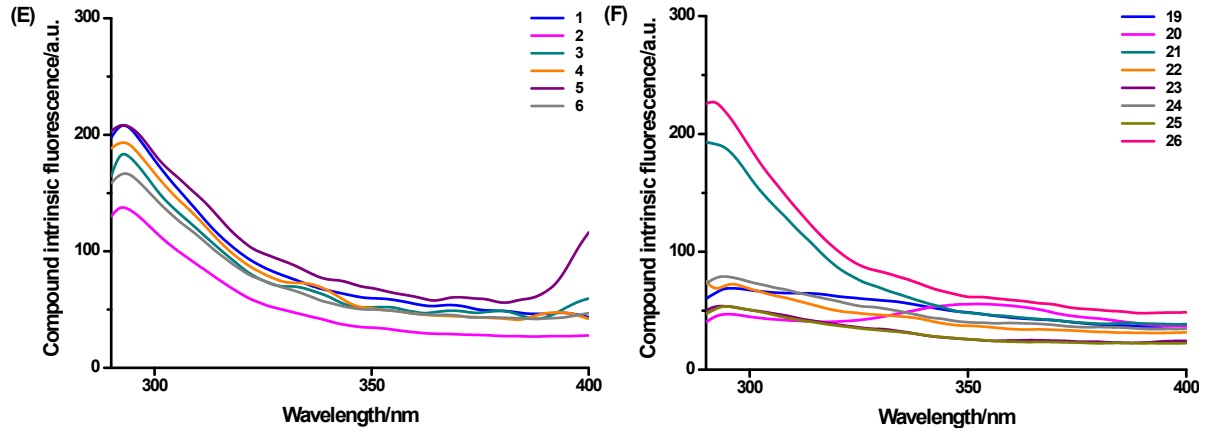


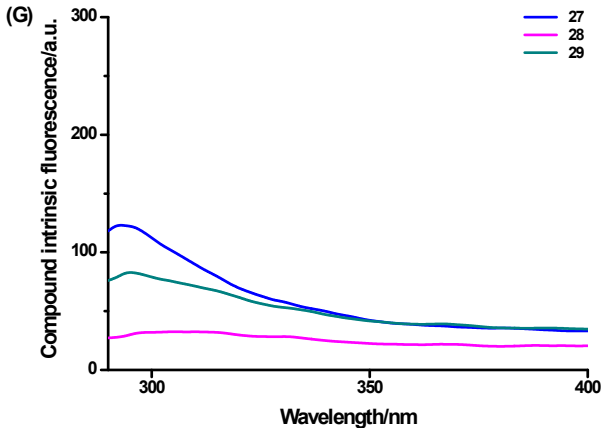
Figure S4. Selected data from MALDI-TOF-MS analysis. MALDI-TOF-MS spectra were recorded from a 7-day incubated solution of compound **22** (50 μM) in PBS buffer (pH 7.4) in the presence (blue signals) or absence (a red signal) of Aβ (10 μM). The signals at *m/z* = 1021 and 4512 indicate the presence of compound **22** and $A\beta_{42}$ respectively.

9. Tyrosine Intrinsic Fluorescence Assay







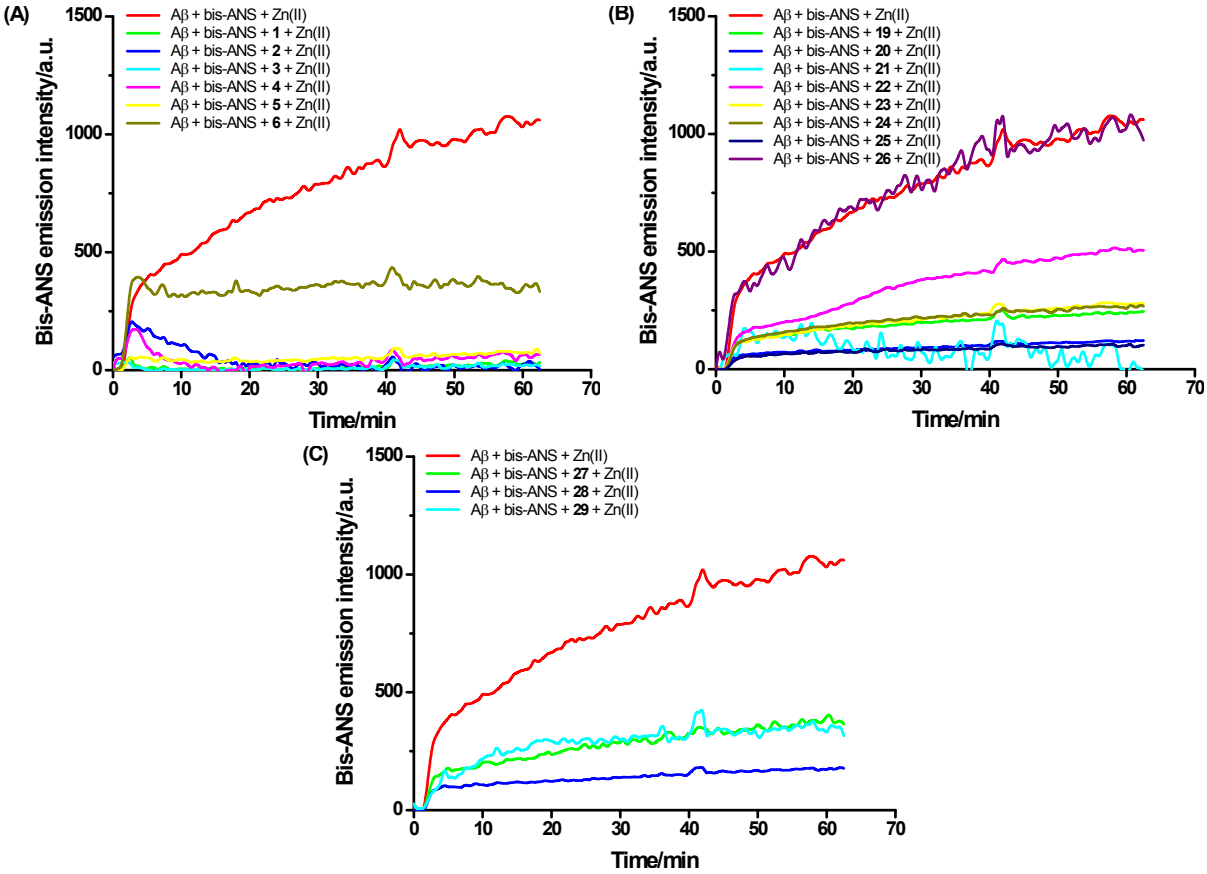


621

622 **Figure S5.** (A) Aβ tyrosine fluorescence over time in the absence and presence of copper (II); (B)-(D)
623 Effects of compounds **1**-**6** and **19**-**29** on the copper(II)-induced quenching of Aβ tyrosine fluorescence. (E)-
624 (G) Intrinsic fluorescence ofcompounds **1**-**6** and **19**-**29**.

625

626 ## 10. Bis-ANS Extrinsic Fluorescence Assay



627

628

629 **Figure S6.** Effects of compounds **1**-**6** and **19**-**29** on the bis-ANS fluorescence intensity in the presence of
630 Aβ and zinc(II).

11. Neurotoxicity Assay

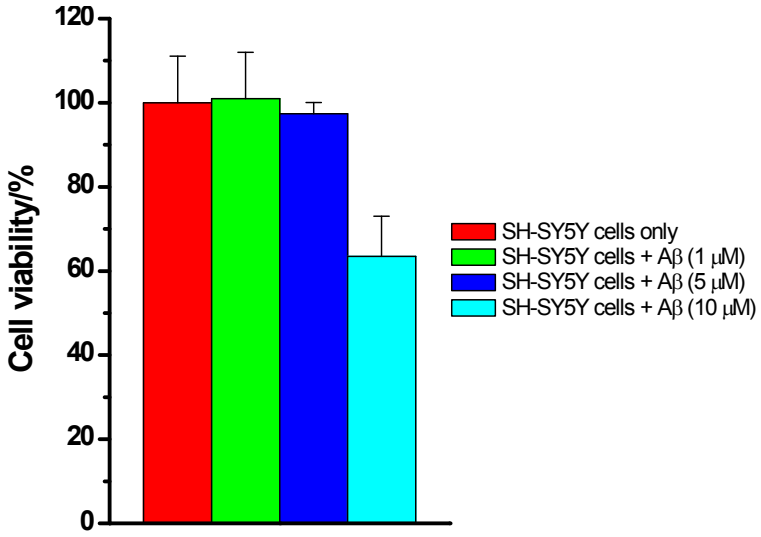


Figure S7. Neurotoxicity of Aβ (0, 1, 5 and 10 μM) against SH-SY5Y cells.

12. ^{1}H & ^{13}C NMR Spectra for Novel Compounds

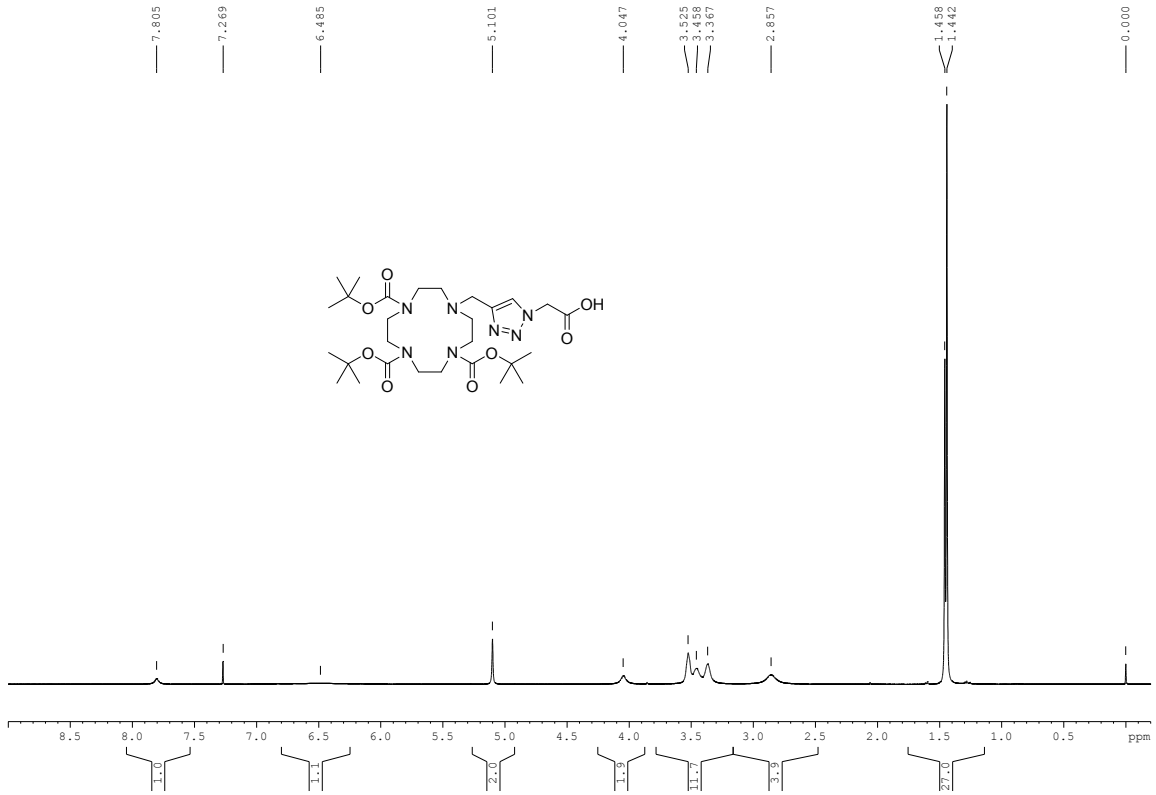


Figure S8. ^{1}H NMR spectrum (400 MHz) of **11** in $CDCl_3$.

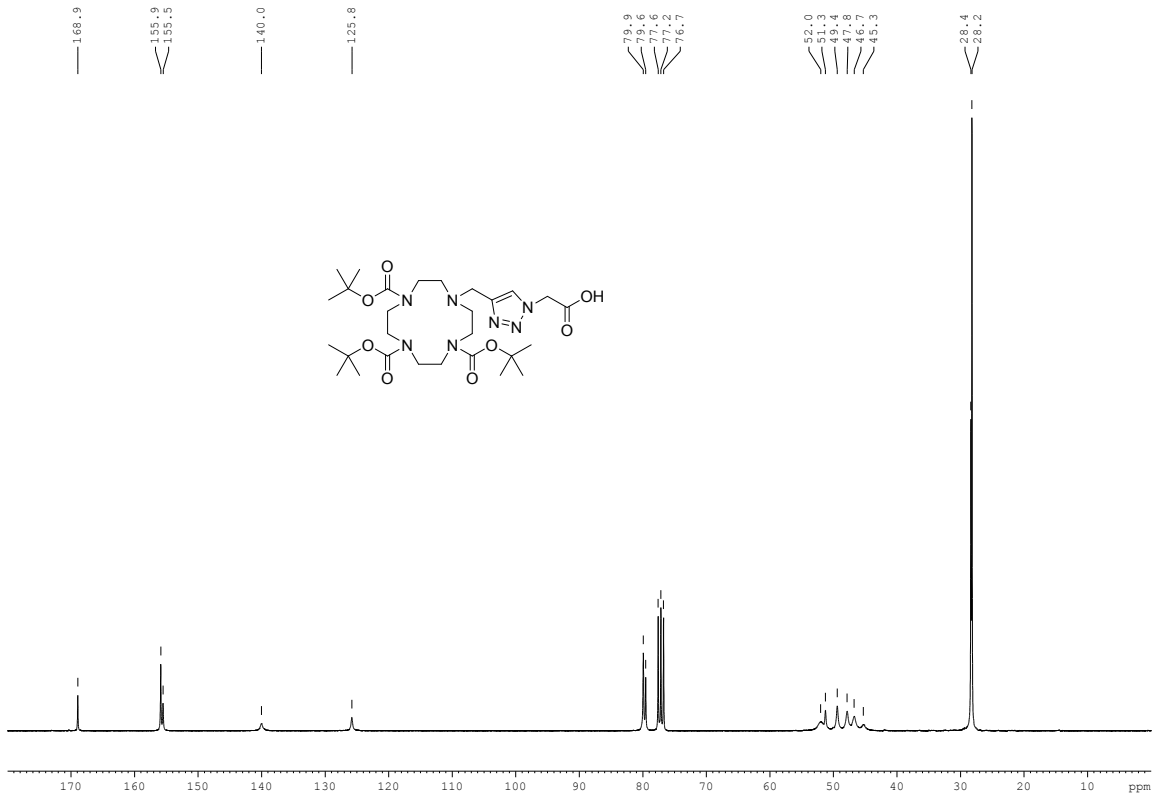
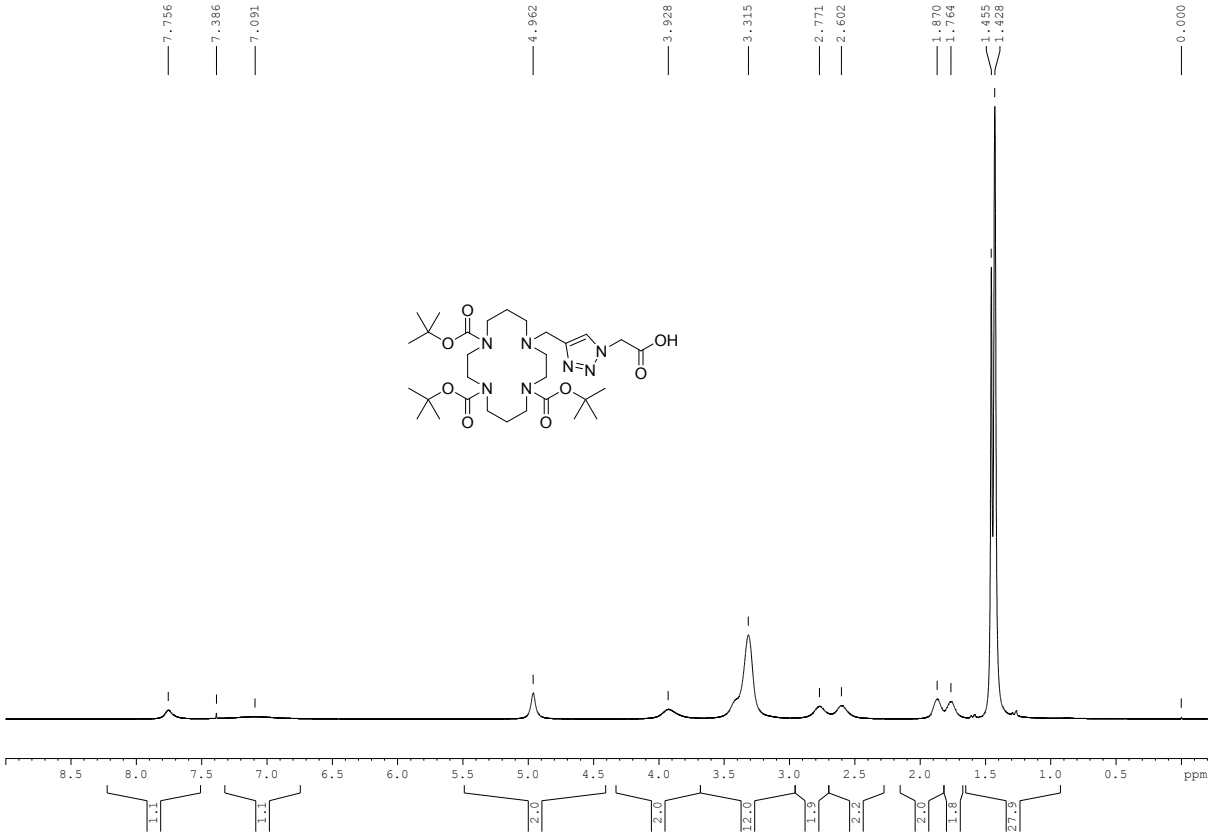


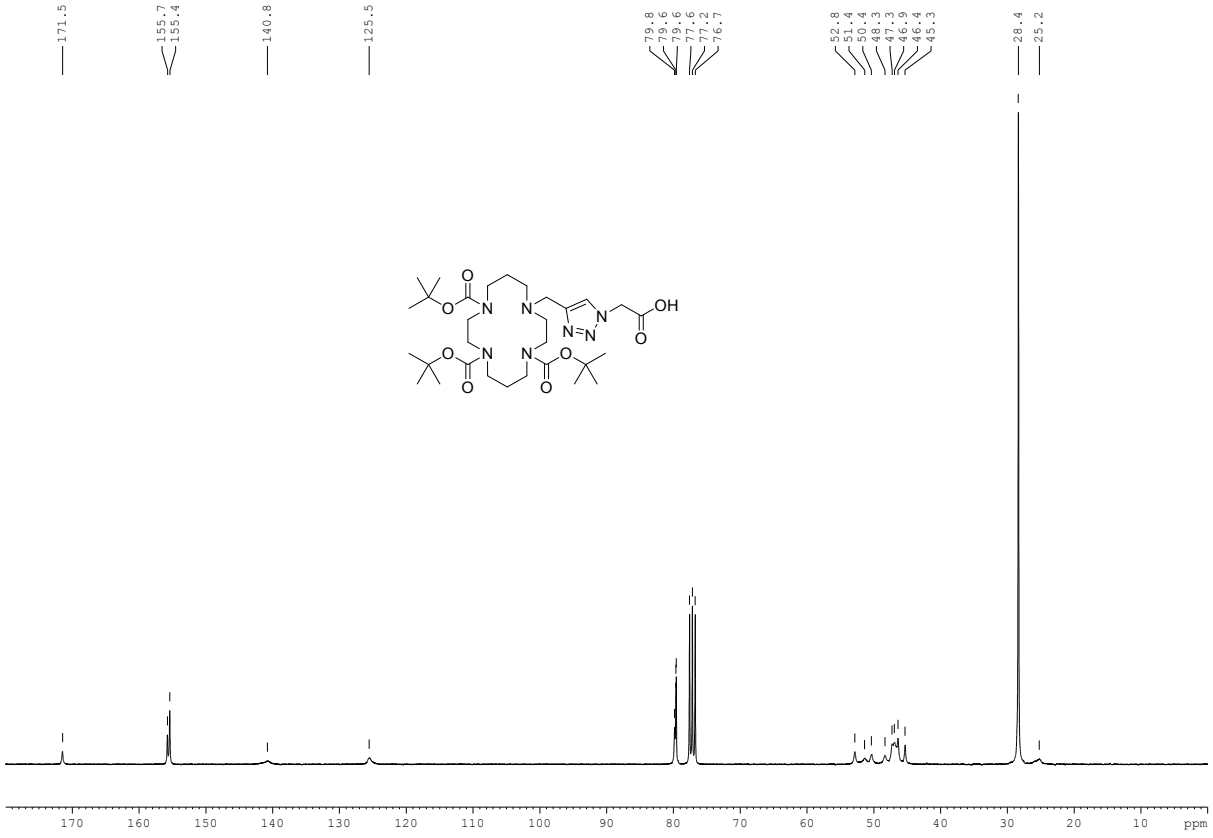
Figure S9. ^{13}C NMR spectrum (75 MHz) of **11** in $CDCl_3$.



641

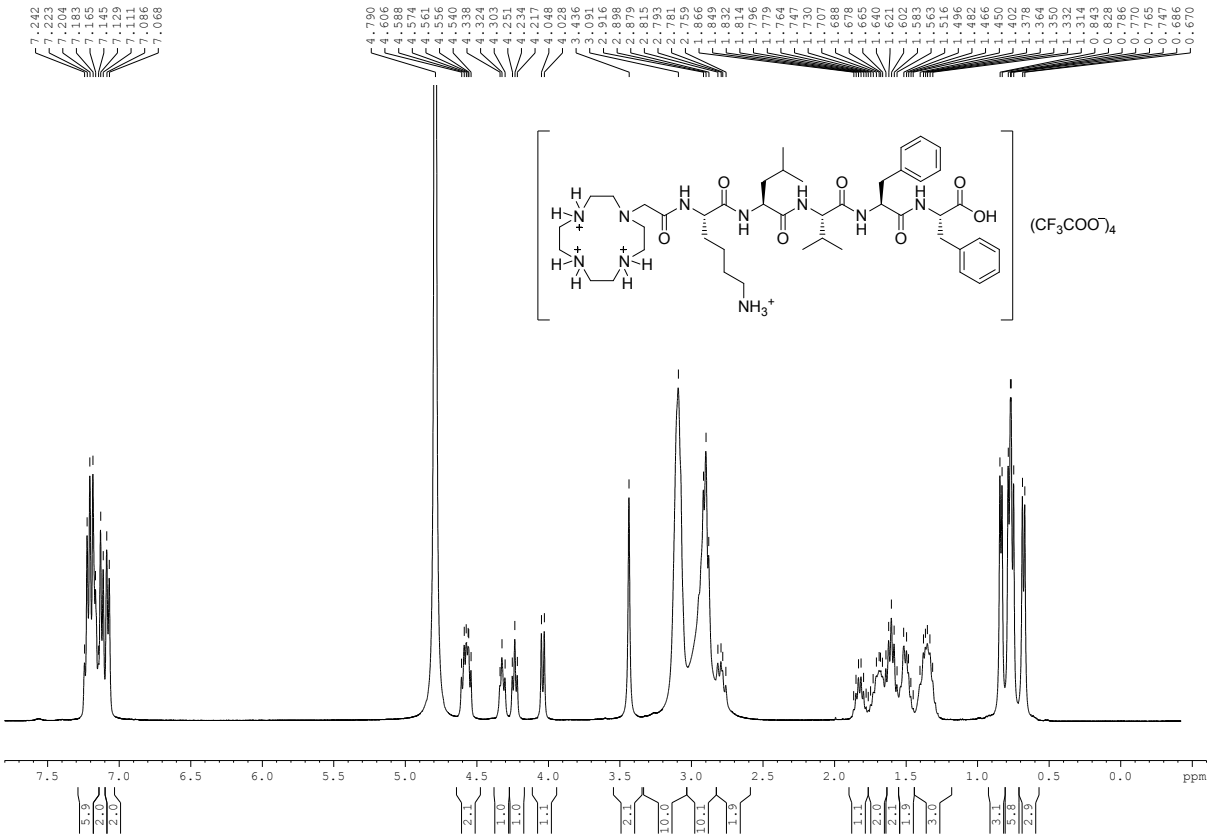
642 **Figure S10.** ^{1}H NMR spectrum (400 MHz) of **12** in $CDCl_3$.

643



644

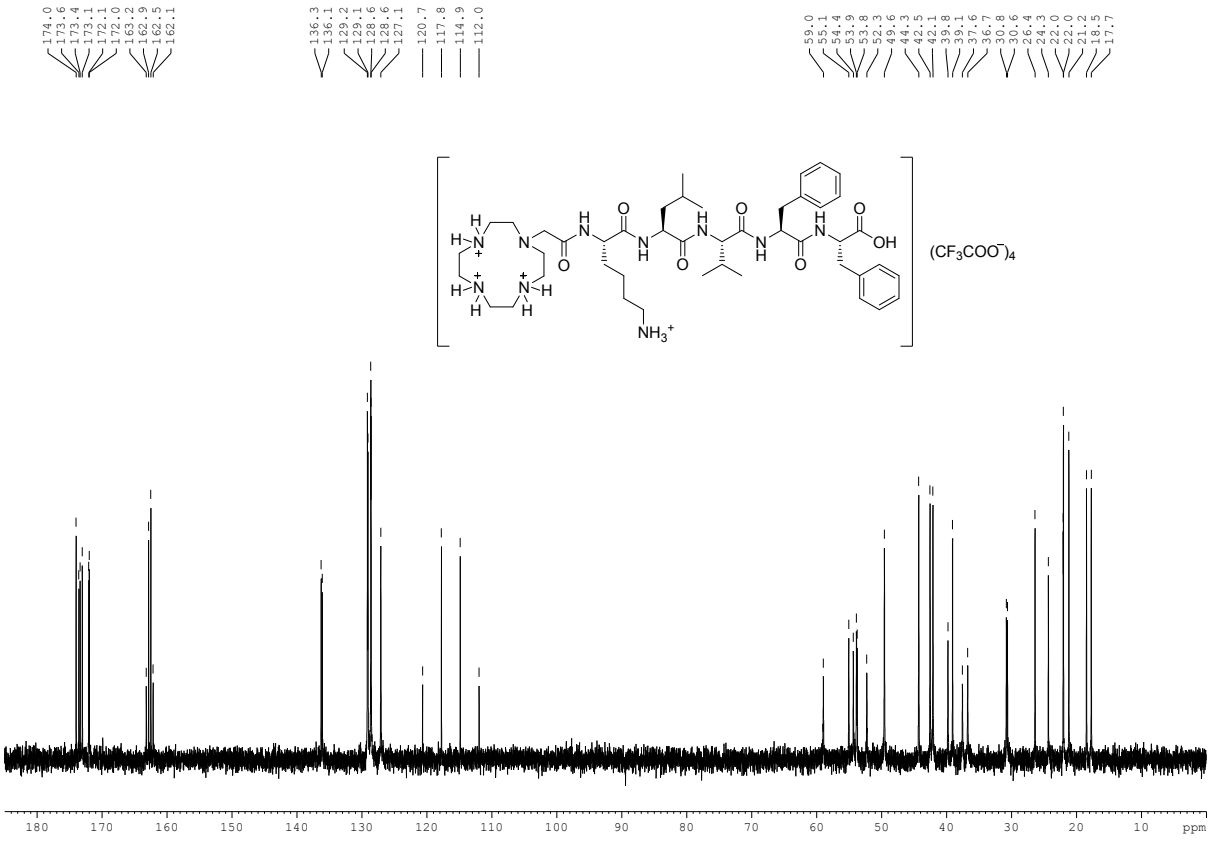
645 **Figure S11.** ^{13}C NMR spectrum (75 MHz) of **12** in $CDCl_3$.



647

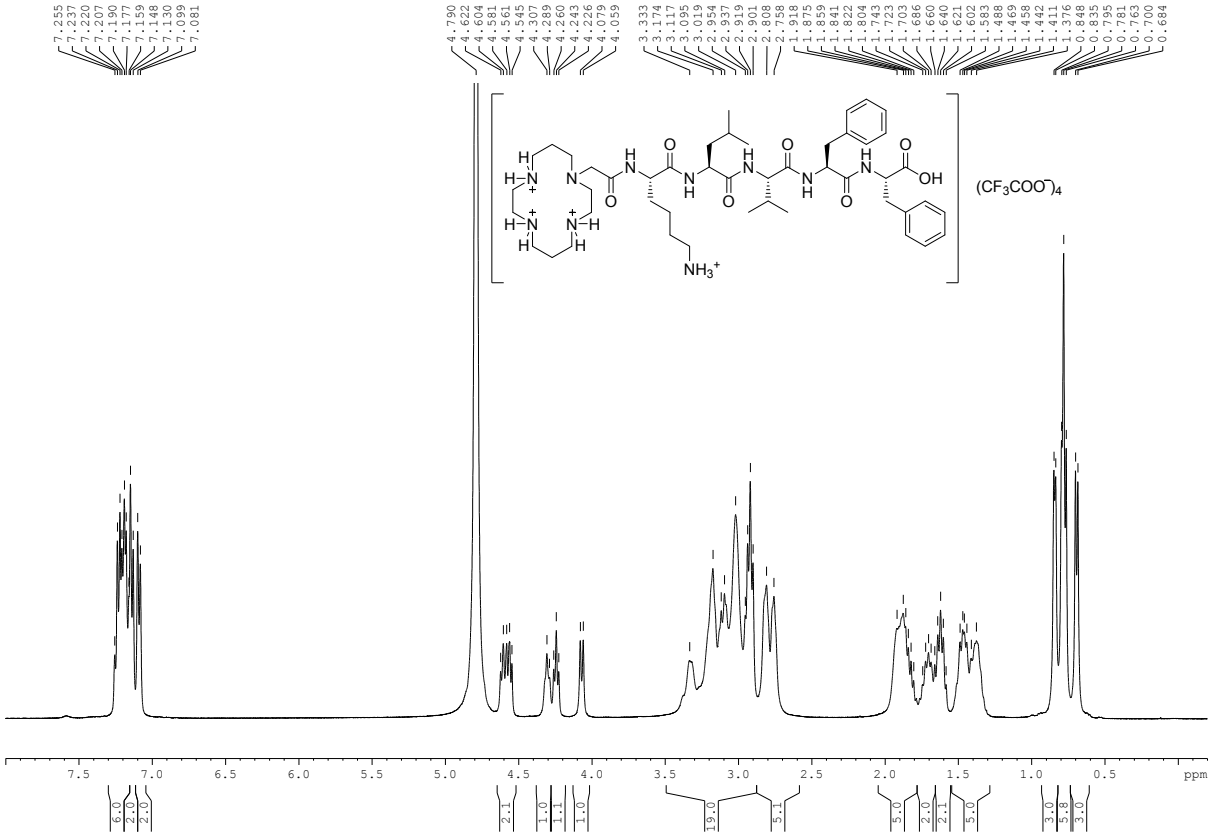
648 **Figure S12.** ^{1}H NMR spectrum (400 MHz) of **1** in D_2O.

649



650

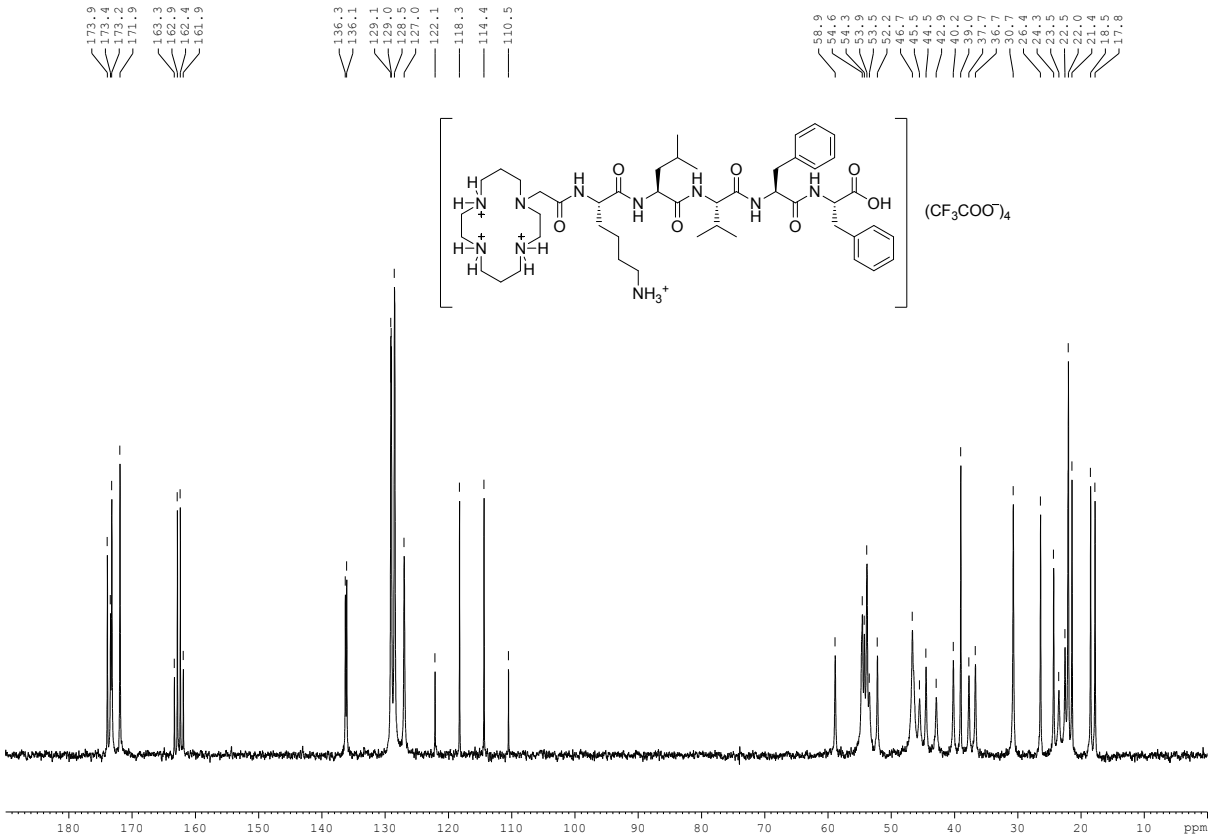
651 **Figure S13.** ^{13}C NMR spectrum (100 MHz) of **1** in D_2O.



653

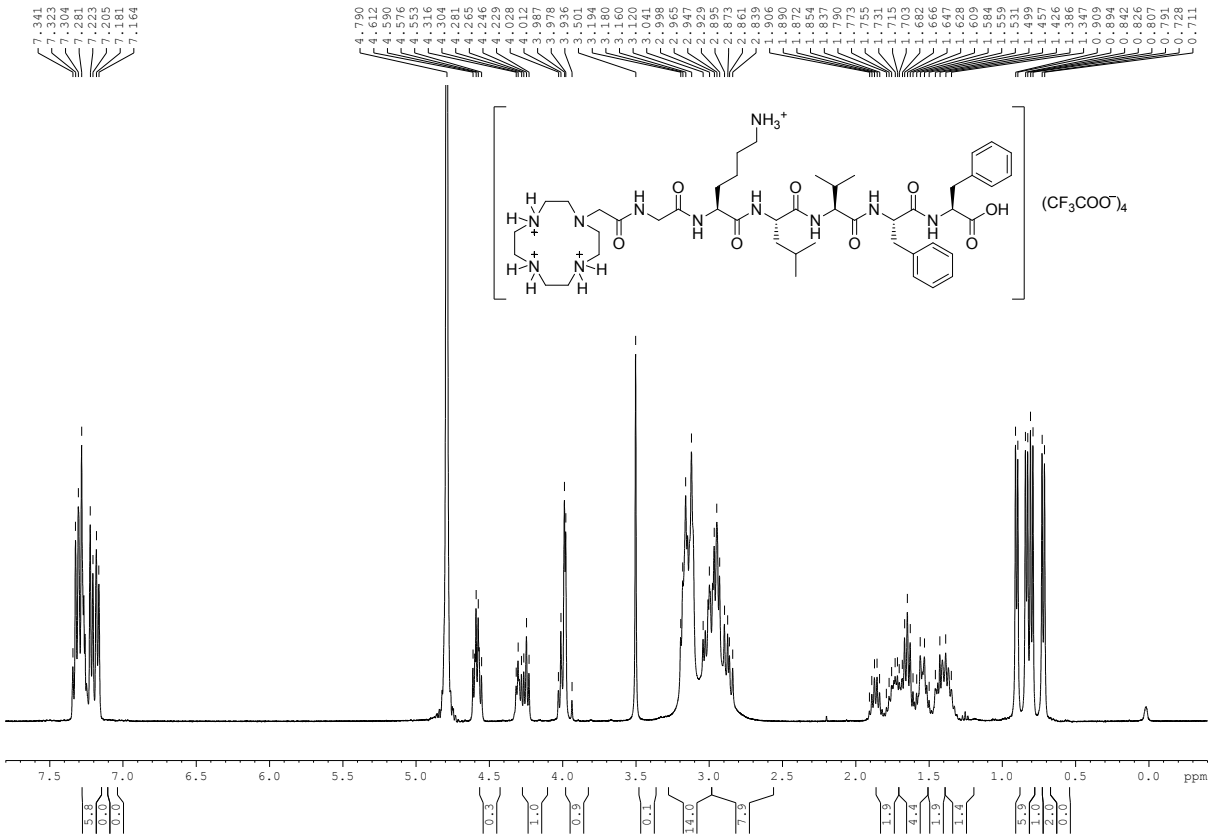
654 **Figure S14.** ^{1}H NMR spectrum (400 MHz) of **2** in D_2O.

655



656

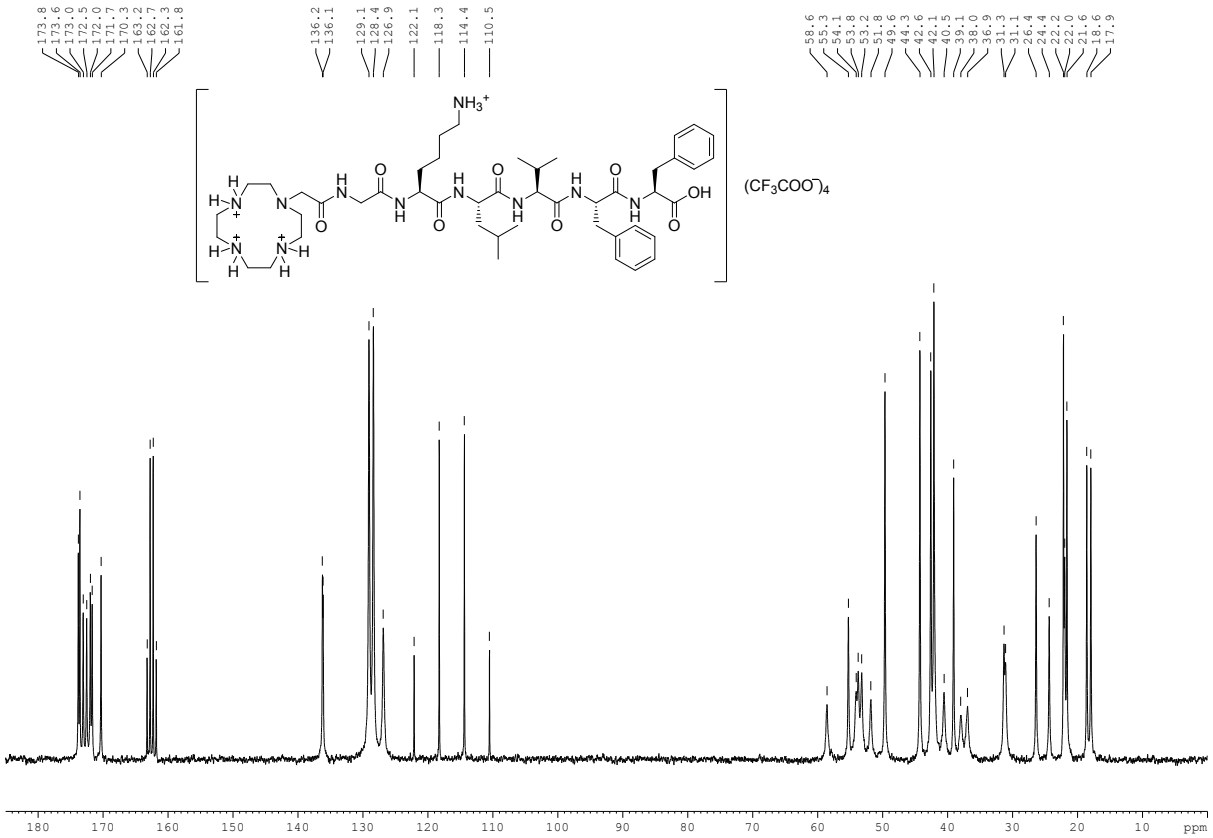
657 **Figure S15.** ^{13}C NMR spectrum (75 MHz) of **2** in D_2O.



659

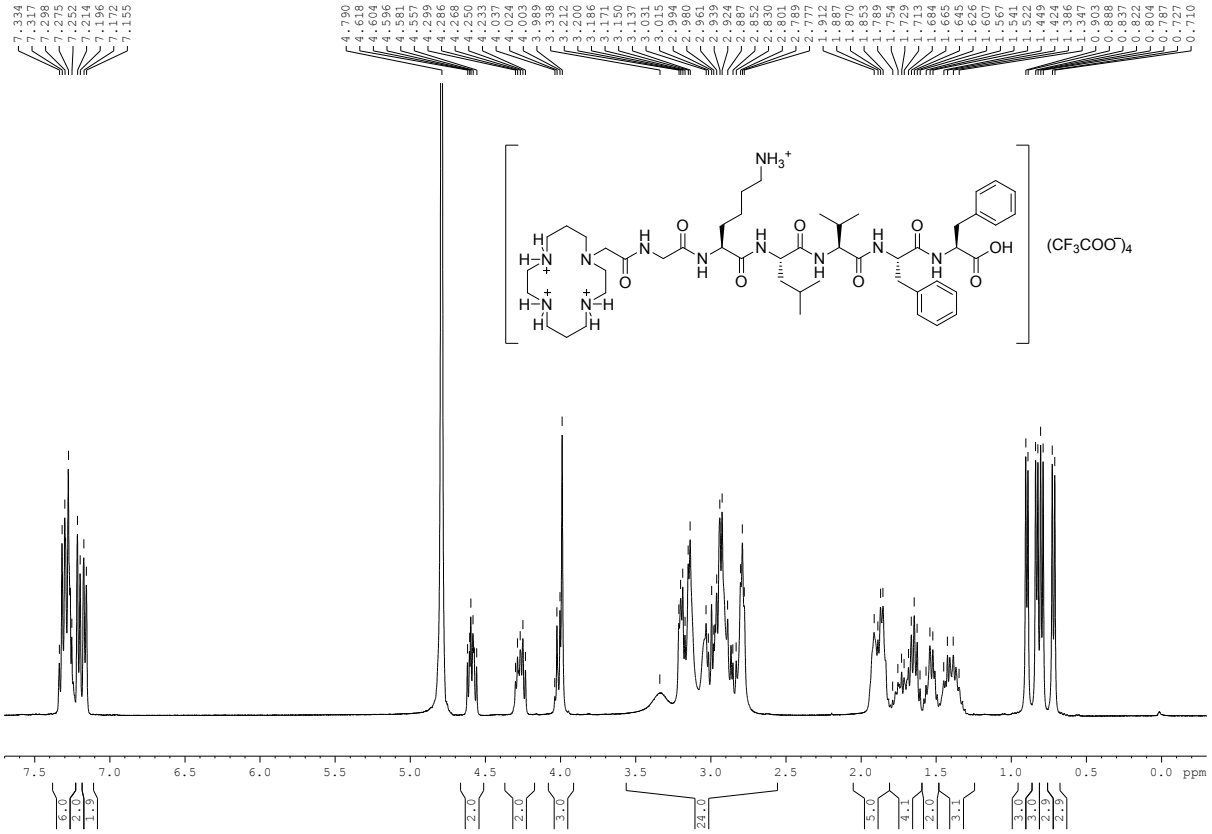
660 **Figure S16.** ^{1}H NMR spectrum (400 MHz) of **3** in D_2O.

661



662

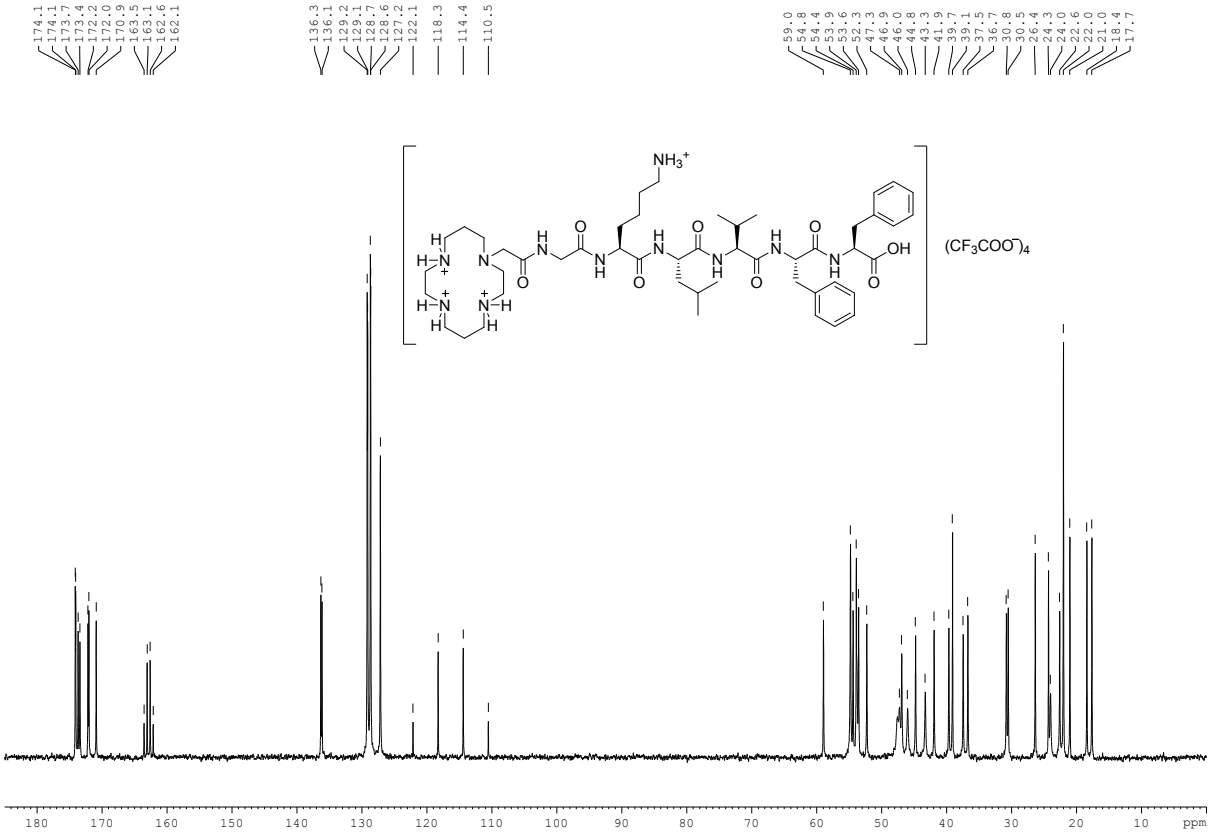
663 **Figure S17.** ^{13}C NMR spectrum (75 MHz) of **3** in D_2O.



665

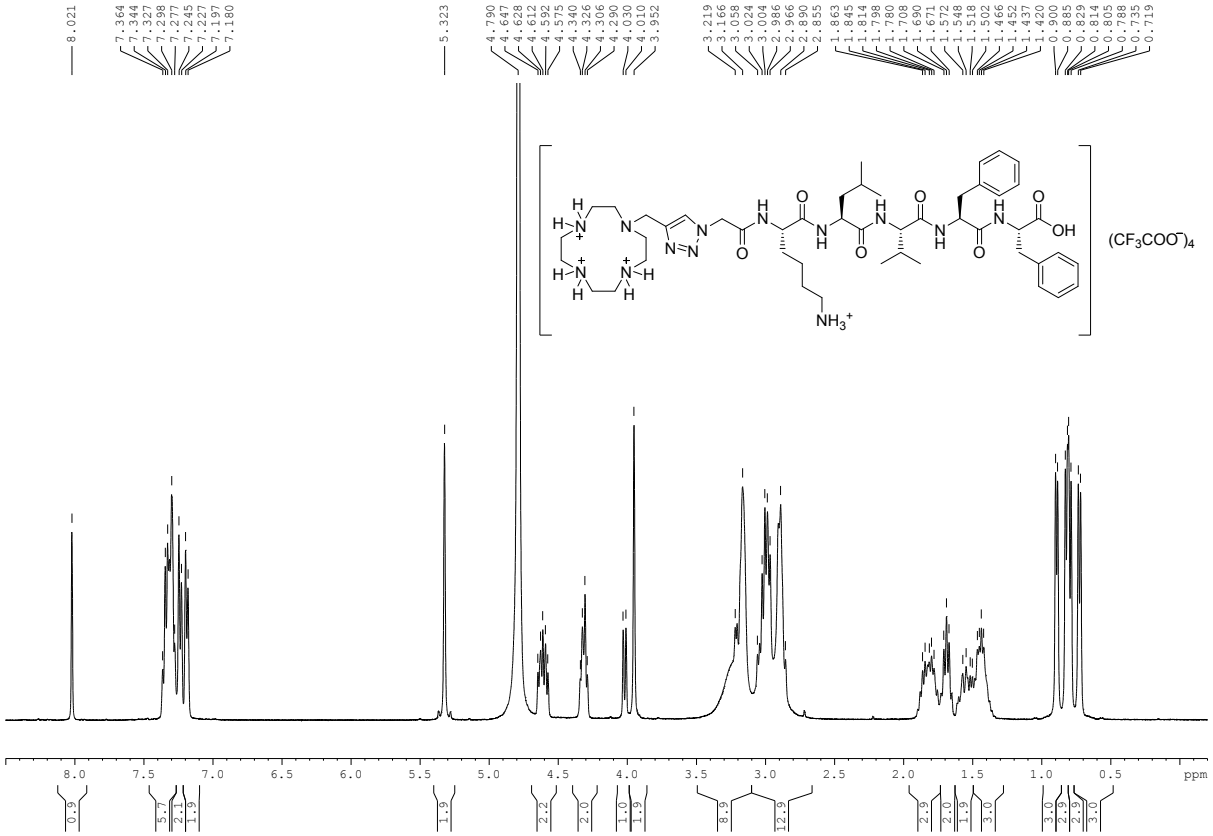
666 **Figure S18.** ^{1}H NMR spectrum (400 MHz) of **4** in D_2O.

667



668

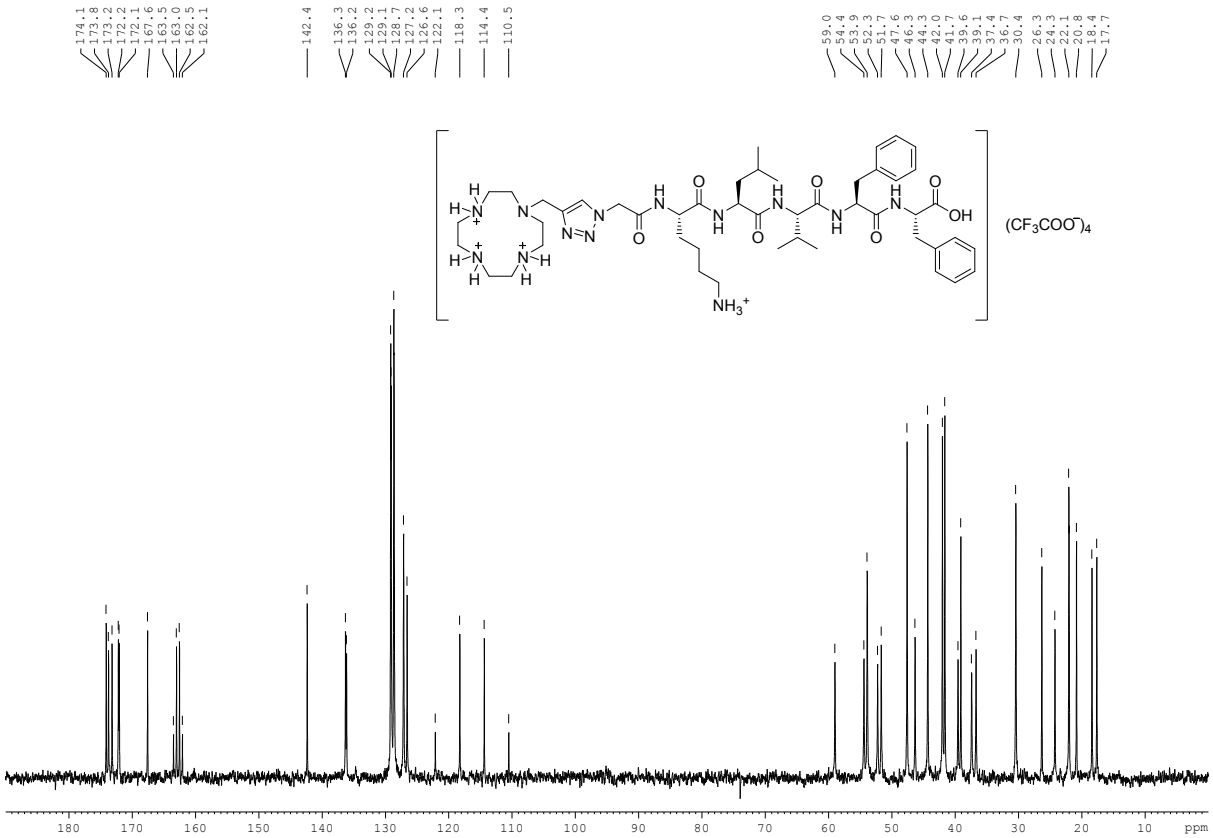
669 **Figure S19.** ^{13}C NMR spectrum (75 MHz) of **4** in D_2O.



671

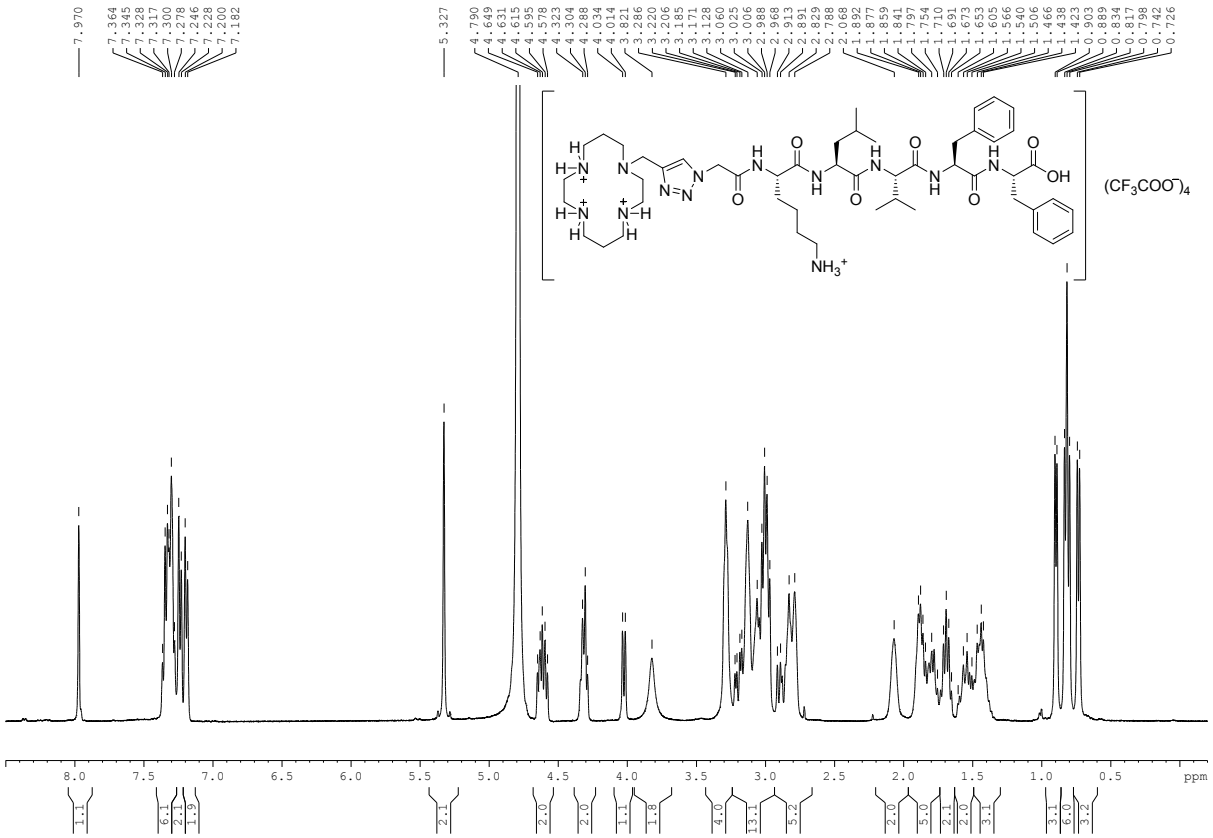
672 **Figure S20.** ^{1}H NMR spectrum (400 MHz) of **5** in D_2O.

673



674

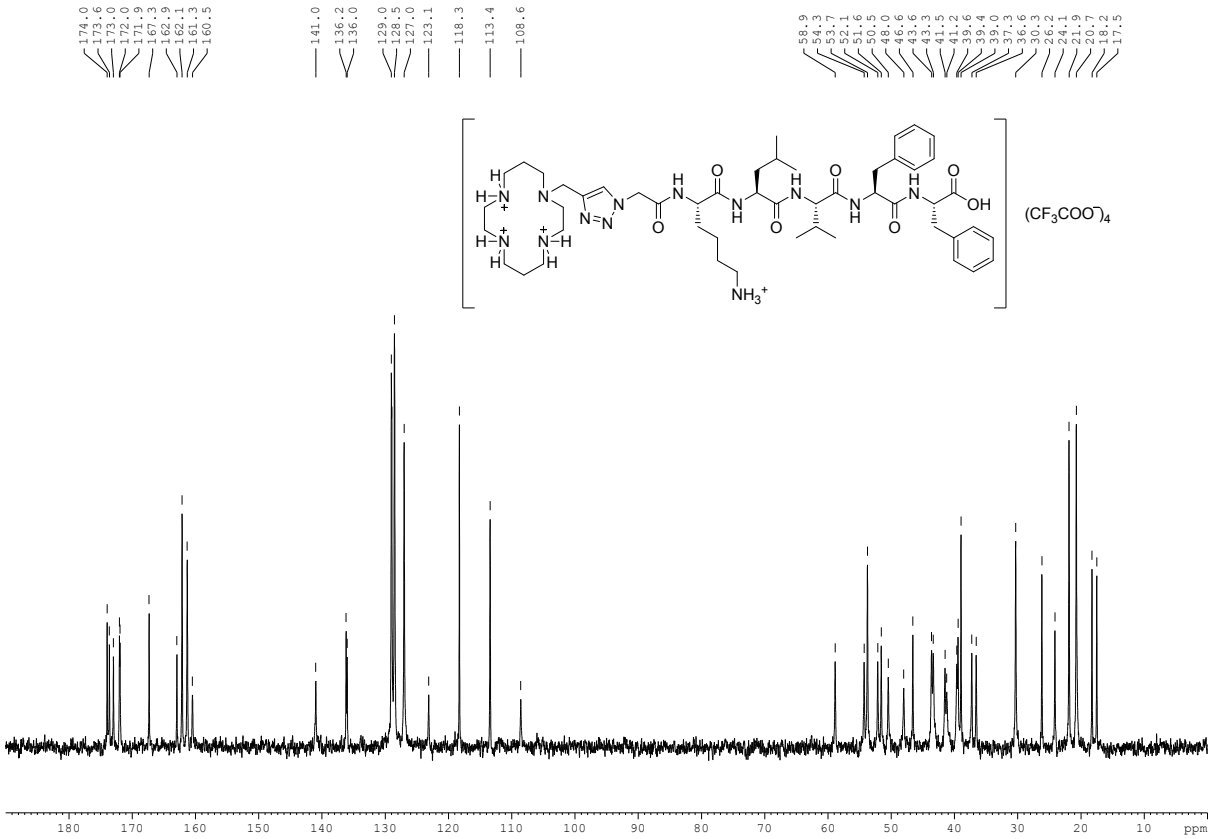
675 **Figure S21.** ^{13}C NMR spectrum (75 MHz) of **5** in D_2O.



677

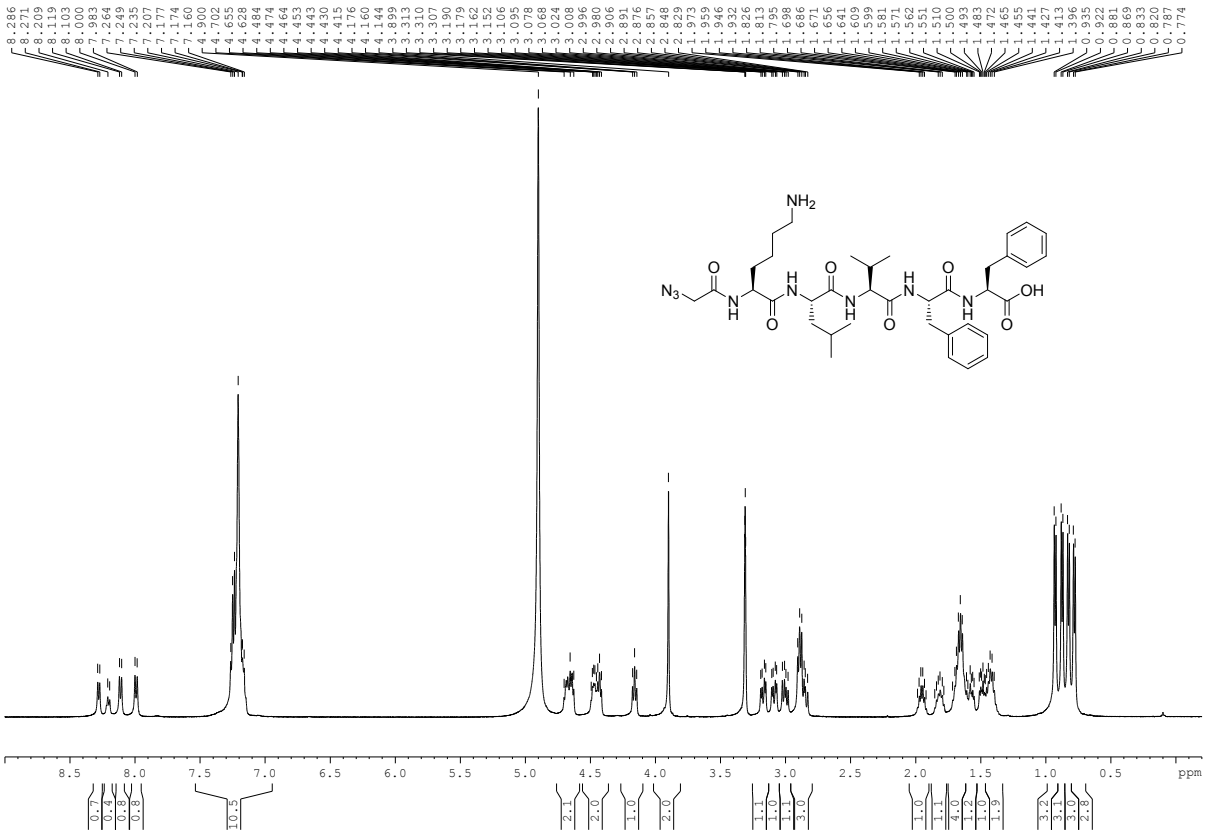
678 **Figure S22.** ^{1}H NMR spectrum (400 MHz) of **6** in D_2O.

679



680

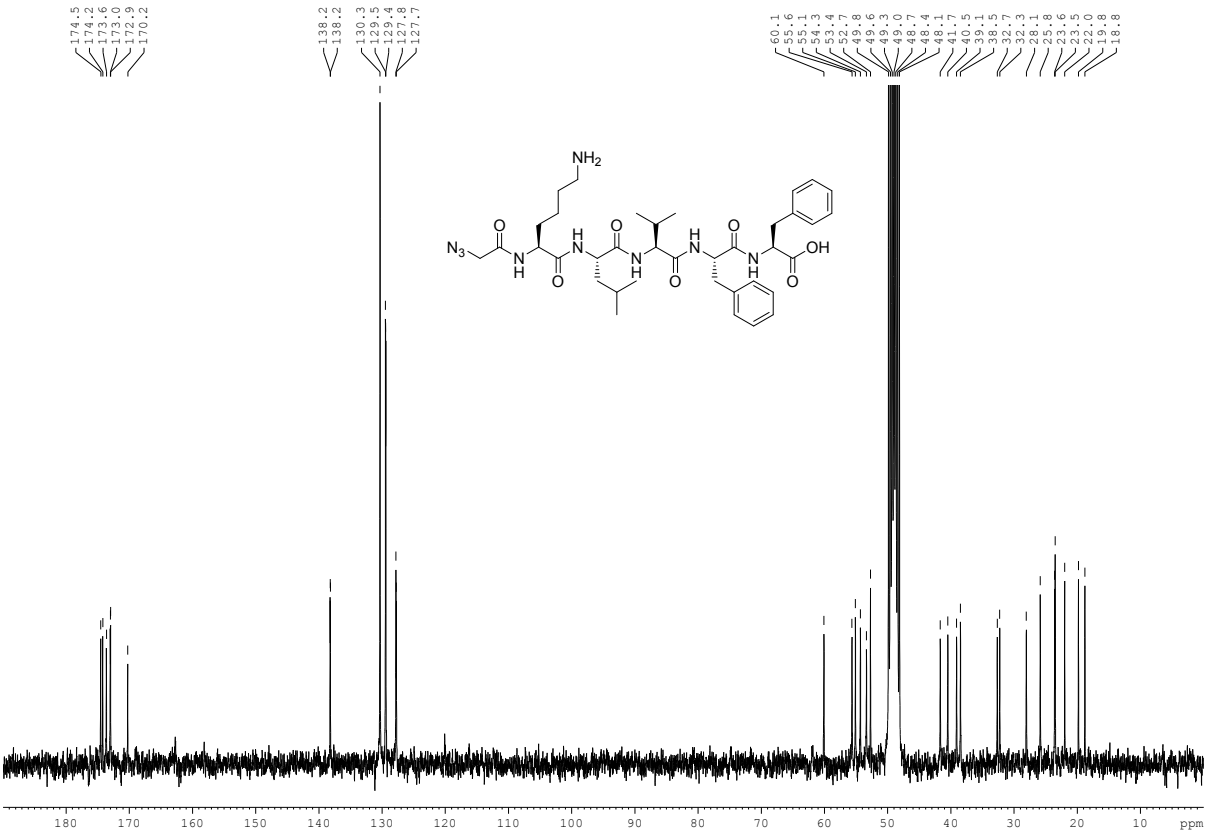
681 **Figure S23.** ^{13}C NMR spectrum (75 MHz) of **6** in D_2O.



683

684 **Figure S24.** ^{1}H NMR spectrum (500 MHz) of **27** in CD_3OD.

685



686

687 **Figure S25.** ^{13}C NMR spectrum (75 MHz) of **27** in CD_3OD.

688 59. S. Ficht, R. J. Payne, R. T. Guy and C. H. Wong, Chem. Eur. J., 2008, 14, 3620-3629.

689 60. C. K. Y. Chun and R. J. Payne, Aust. J. Chem., 2009, 62, 1339-1343.

690 61. S. Hwang, W. Cha and M. E. Meyerhoff, Angew. Chem. Int. Ed., 2006, 45, 2745-2748.

691 62. A. C. Benniston, P. Gunning and R. D. Peacock, J. Org. Chem., 2005, 70, 115-123.

692 63. E. Kimura, S. Aoki, T. Koike and M. Shiro, J. Am. Chem. Soc., 1997, 119, 3068-3076.

693 64. L. Fabbrizzi, F. Foti, M. Licchelli, P. M. Maccarini, D. Sacchi and M. Zema, Chem. Eur. J., 2002, 8,
694 4965-4972.

695 65. J. W. Jeon, S. J. Son, C. E. Yoo, I. S. Hong, J. B. Song and J. Suh, Org. Lett., 2002, 4, 4155-4158.

696 66. A. V. Ramana, M. Watkinson and M. H. Todd, Bioorg. Med. Chem. Lett., 2008, 18, 3007-3010.

697 67. S. J. Krivickas, E. Tamanini, M. H. Todd and M. Watkinson, J. Org. Chem., 2007, 72, 8280-8289.

698 68. F. Schmidt, I. C. Rosnizeck, M. Spoerner, H. R. Kalbitzer and B. König, Inorg. Chim. Acta, 2011, 365,
699 38-48.

700 69. K. Michaelis and M. Kalesse, Angew. Chem. Int. Ed., 1999, 38, 2243-2245.

701 70. E. Tamanini, S. E. J. Rigby, M. Motevalli, M. H. Todd and M. Watkinson, Chem. Eur. J., 2009, 15,
702 3720-3728.