

Electronic Supporting Information

Active-Template CuAAC Enables High-Yield Synthesis of (2)Handcuff [2]Rotaxanes

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1. General Experimental Information	3
2. Synthesis of the bis-2,2'-bipyridine macrocycles 7a-c	4
Compound 3	5
Compound 4	9
Compound 5	13
Compound 6a	17
Compound 6b	21
Compound 6c	25
Compound 7a	29
Compound 7b	33
Compound 7c	37
3. Synthesis of the (2)handcuff [2]rotaxanes 10a-c	41
Compound 10a	41
Compound 10b	46
Compound 10c	51
4. Synthesis of the free axle S1	56
Compound S1	56
5. Effect of Reaction Concentration on (2)handcuff [2]rotaxanes Formation	60
6. Mass Spectrometry Analysis of Crude AT-CuAAC Reaction Mixtures	61
7. AT-CuAAC Reaction under Competitive Hydrogen-Bonding Conditions	62
8. References	63

1. General Experimental Information

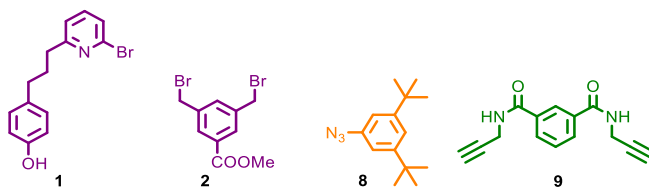
Unless otherwise stated, all reagents were purchased from commercial sources (Acros Organics, Alfa Aesar, Fisher Scientific, FluoroChem, Sigma Aldrich and VWR) and used without further purification. $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ was prepared as described by Pigorsch and Köckerling.¹ Anhydrous solvents were purchased from Acros Organics. THF refers to tetrahydrofuran. EDTA-NH₃ solution refers to an aqueous solution of NH₃ (17% w/w) saturated with sodium-ethylenediaminetetraacetate. CDCl_3 (without stabilising agent) was distilled over CaCl_2 and K_2CO_3 prior to use. Unless otherwise stated, all reaction mixtures were performed in oven dried glassware under an inert N₂ atmosphere with purchased anhydrous solvents. Unless otherwise stated experiments carried out in sealed vessels were performed in CEM microwave vials, with crimped aluminium caps, with PTFE septa.

Unless otherwise stated, flash column chromatography was performed using CombiFlash NextGen 300+ by Teledyne LABS using SiO_2 cartridges purchased from Bioanalytics (RediSep Silver Normal Phase Silica, 40–63 μm irregular silica; default flow rates). Analytical TLC was performed on precoated aluminium-backed silica gel plates (0.25 mm thick, 60F254, Merck, Germany) and observed under UV light (254 nm) or visualised with KMnO_4 .

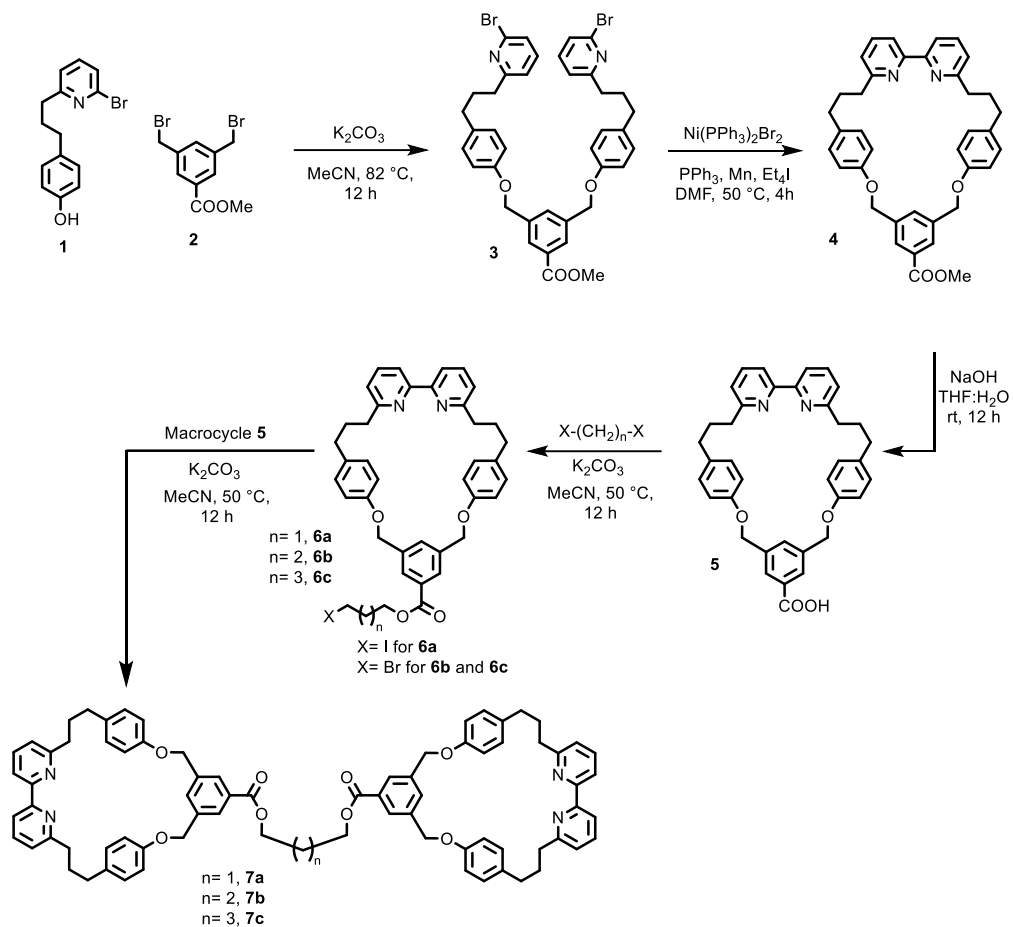
NMR analysis: NMR Spectra were recorded on Bruker Avance-300, Bruker Avance-400 and Bruker Avance-500 at 25 °C. Chemical shifts are reported in ppm units (δ) relative to TMS (δ_{H} and $\delta_{\text{C}} = 0$ ppm). The residual signals of under-deuterated solvents ($\delta_{\text{H}} = 7.26$ ppm in CDCl_3 , 4.79 ppm in D_2O and 2.50 ppm in $(\text{CD}_3)_2\text{SO}$) in ^1H NMR spectra, and the central peaks of CDCl_3 ($\delta_{\text{C}} = 77.16$ ppm), $(\text{CD}_3)_2\text{SO}$ ($\delta_{\text{C}} = 39.52$ ppm) or TMS in ^{13}C NMR spectra were used as internal standards. The coupling constants (J), calculated according to the first order NMR spectra, are reported in Hz. Standard abbreviations indicating multiplicity were used as follows: m = multiplet, quint = quintet, q = quartet, t = triplet, d = doublet, s = singlet, br = broad, sept = septet. ^1H signal assignment was carried out using 2D NMR methods (COSY, HMQC, HMBC) as appropriate. In some cases, complex multiplets with multiple contributing proton signals, exact assignment was not possible. In interlocked compounds, all proton signals corresponding to axle components are in lower case, and all proton signals corresponding to the macrocycle components are in upper case.

MS analysis: High-resolution mass spectra (HRMS) were obtained on an Agilent mass-spectrometer using electrospray ionization (ESI) at 100-250 eV in a positive mode or by atmospheric pressure chemical ionization (APCI) at 180-250 eV in either positive, unless otherwise stated, or negative mode. A quadrupole time-of-flight (Q-TOF) detector was applied for detection of the ions.

The following compounds were synthesized according to literature procedures: **1**,² **2**,³ **8**,⁴ and **9**.⁵

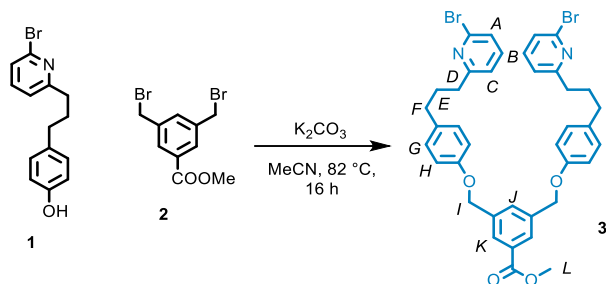


2. Synthesis of the bis-2,2'-bipyridine macrocycles **7a-c**



Scheme S1. Synthetic route to bis-macrocycles **7a-c**.

Compound 3



To a solution of **1** (500 mg, 1.71 mmol, 1.0 eq.) in CH_3CN (25.0 mL) were added K_2CO_3 (0.96 g, 6.84 mmol, 4.0 eq.) and **2** (273 mg, 0.85 mmol, 0.5 eq.), and the reaction mixture was stirred at reflux for 16 h. After cooling to ambient temperature, the reaction mixture was filtered through Celite[®], washing with CH_2Cl_2 , and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , *n*-Hexane-EtOAc 0→50%) to yield **3** (1.17 g, 1.57 mmol, 92%) as a yellow oil.

¹H NMR (400 MHz, $CDCl_3$) δ_H 8.06 (d, $J = 1.4$ Hz, 2H, H_K), 7.72 (t, $J = 1.4$ Hz, 1H, H_I), 7.43 (t, $J = 7.7$ Hz, 2H, H_B), 7.28 (d, $J = 7.7$ Hz, 2H, H_A), 7.11 (d, $J = 8.4$ Hz, 4H, H_G), 7.06 (d, $J = 7.7$ Hz, 2H, H_C), 6.90 (d, $J = 8.4$ Hz, 4H, H_H), 5.09 (s, 4H, H_I), 3.93 (s, 3H, H_L), 2.78 (t, $J = 8.4$ Hz, 4H, H_D), 2.62 (t, $J = 8.4$ Hz, 4H, H_F), 2.01 (m, 4H, H_E).

¹³C NMR (101 MHz, $CDCl_3$) δ_C 166.86, 163.91, 156.96, 141.74, 138.70, 138.37, 134.73, 131.00, 130.85, 129.61, 128.17, 125.44, 121.66, 114.97, 69.63, 52.38, 37.57, 34.70, 31.58.

HR-ESI-MS (+ve) $m/z = 745.1095$ [$M+H$]⁺ (calc. m/z for $C_{38}H_{37}N_2Br_2O_4$ 745.1093).

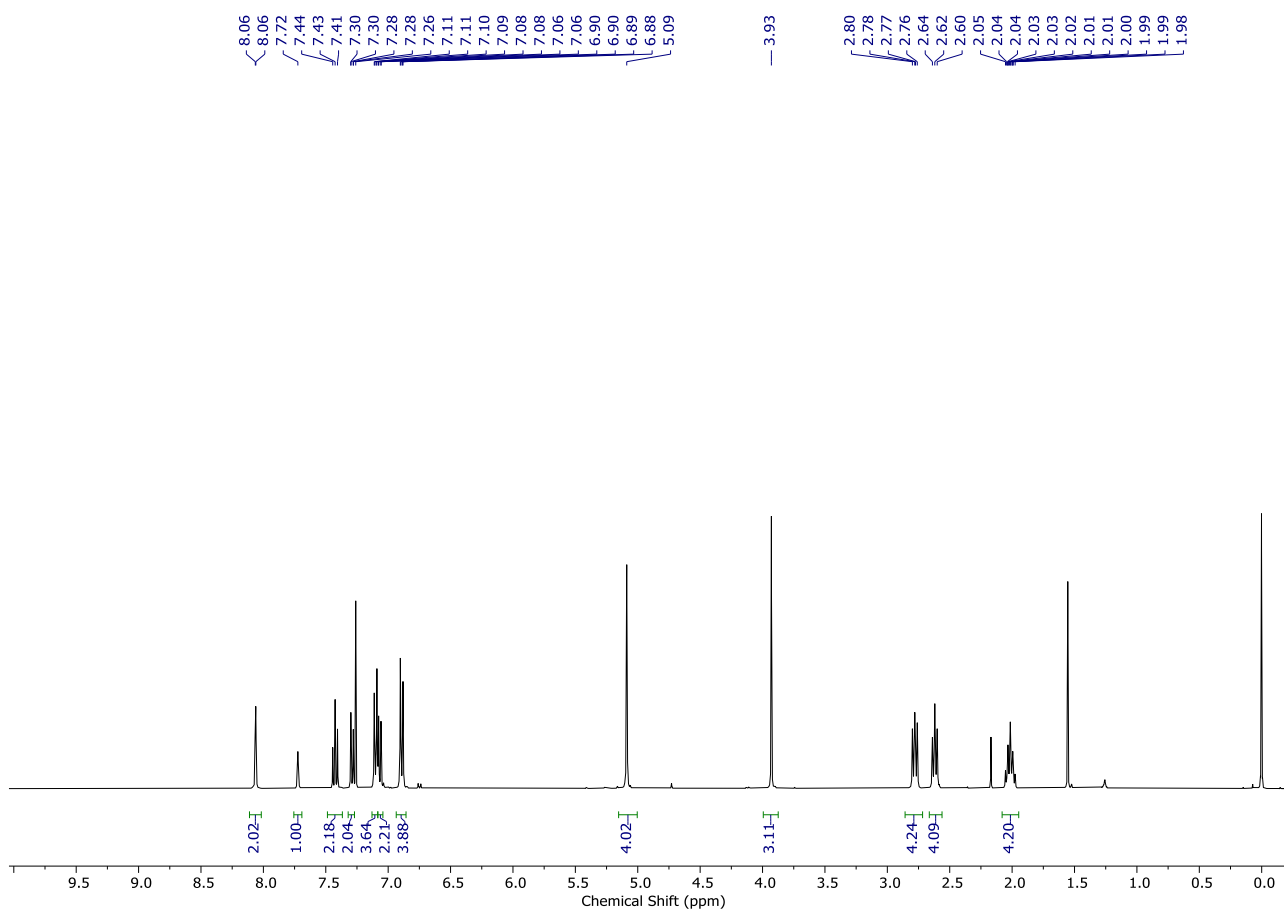


Figure S1. ^1H NMR (CDCl_3 , 400 MHz) of **3**.

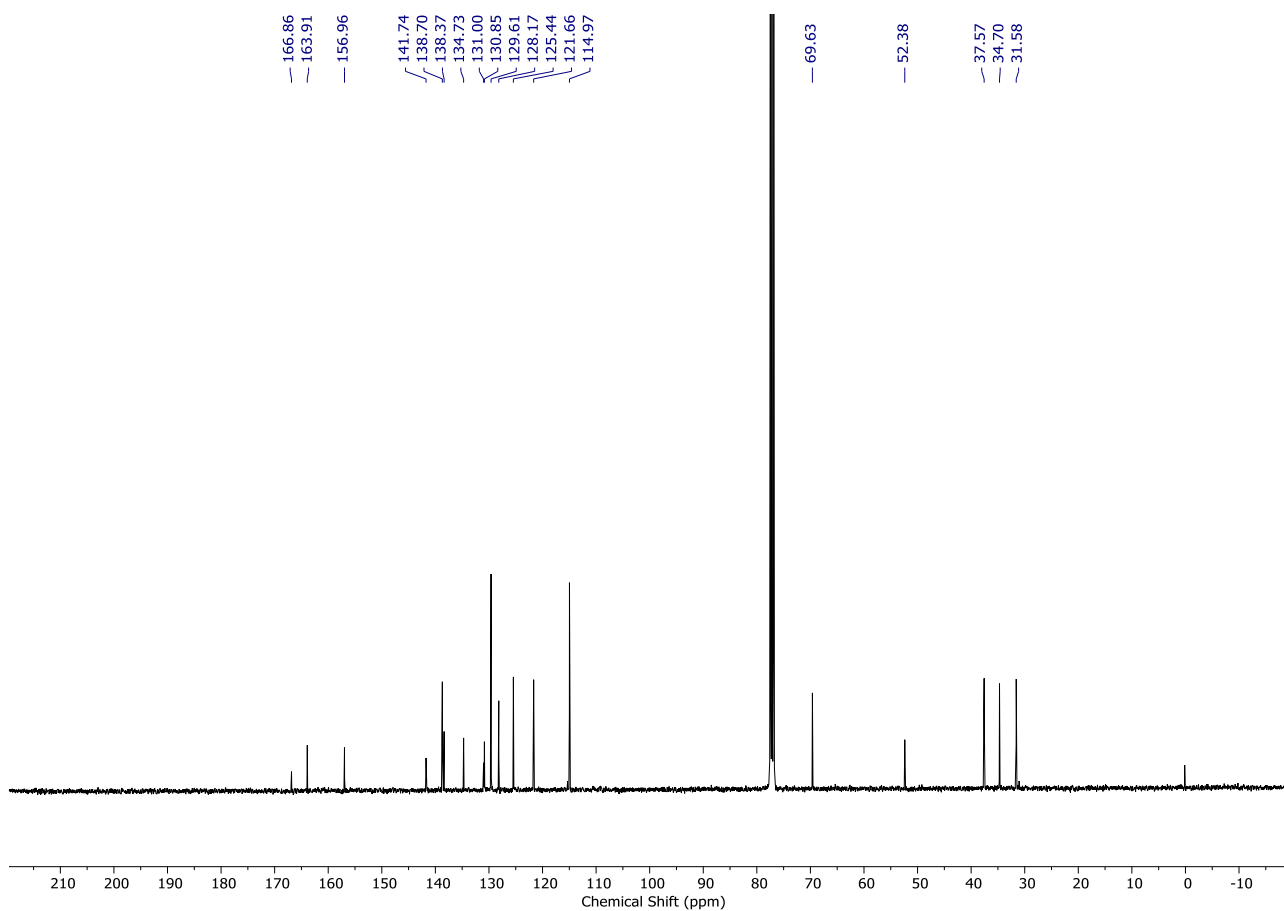


Figure S2. ^{13}C NMR (CDCl_3 , 101 MHz) of **3**.

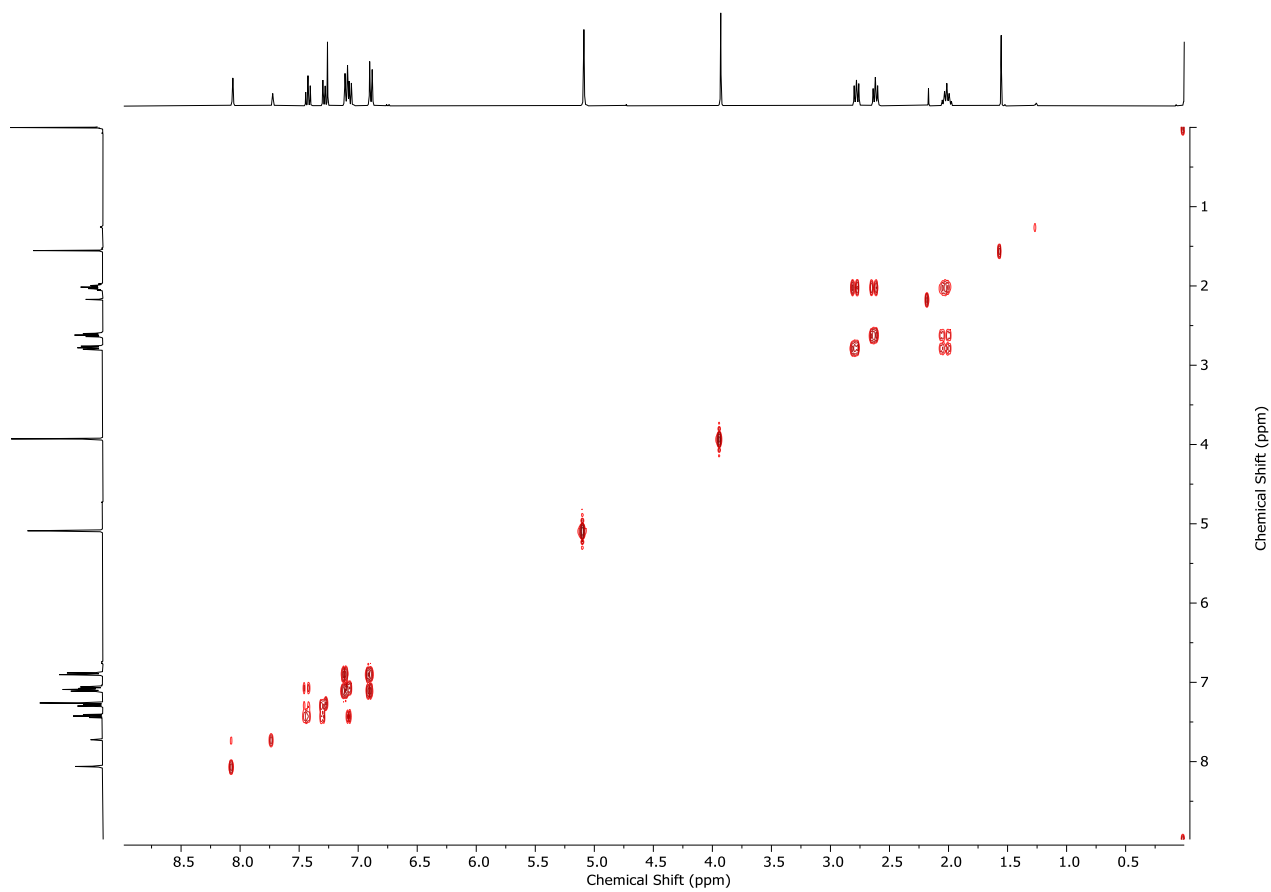


Figure S3. ^1H COSY NMR (CDCl_3) of **3**.

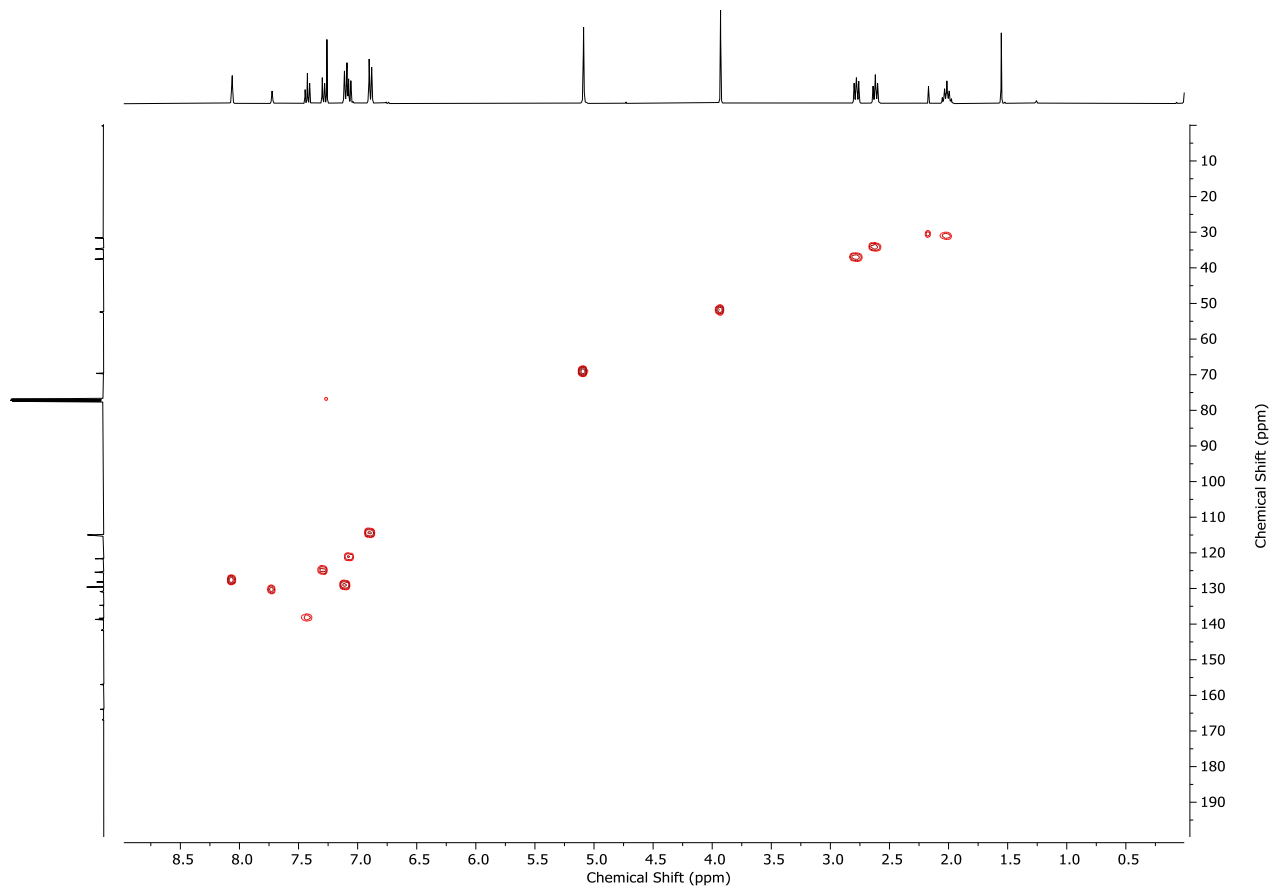


Figure S4. HMQC NMR (CDCl_3) of **3**.

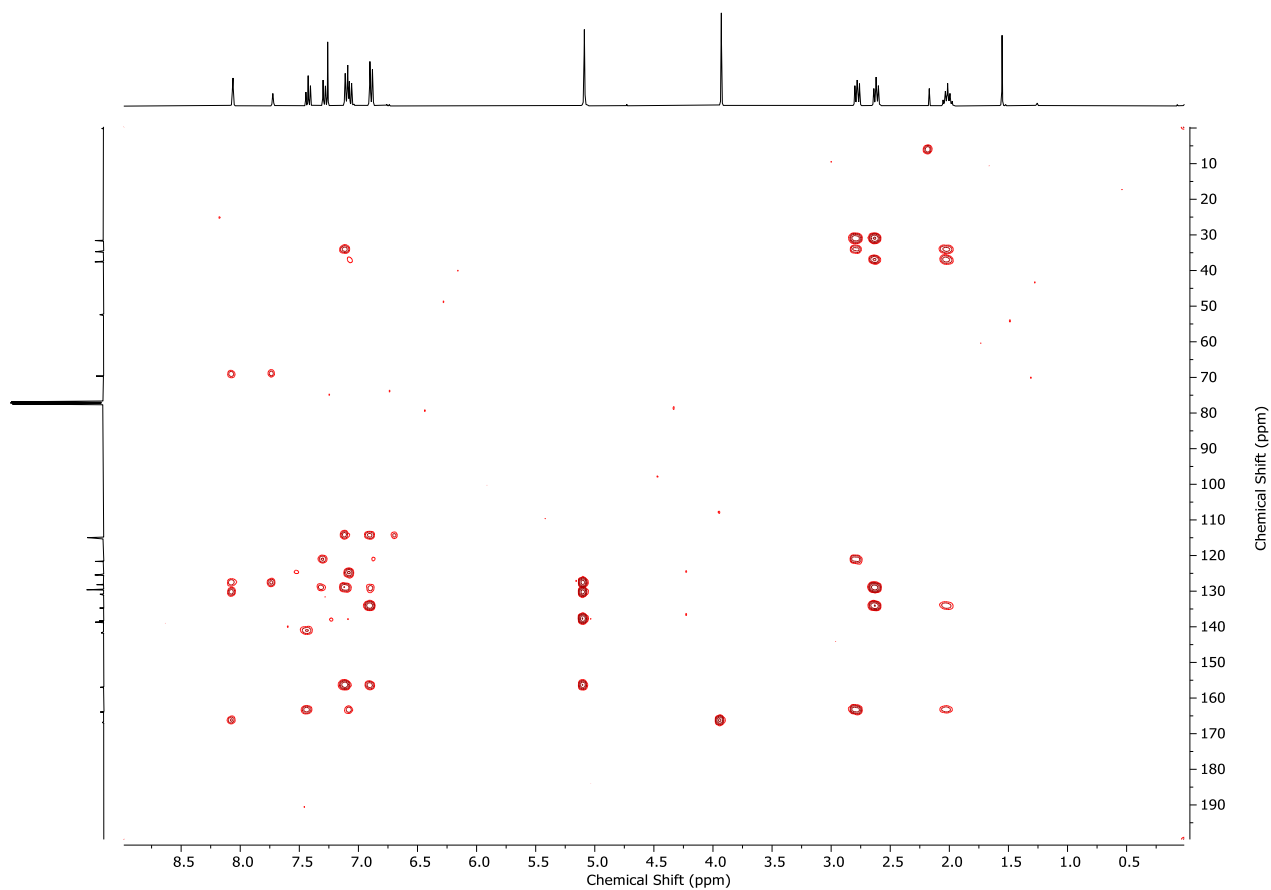


Figure S5. HMBC NMR (CDCl_3) of of **3**.

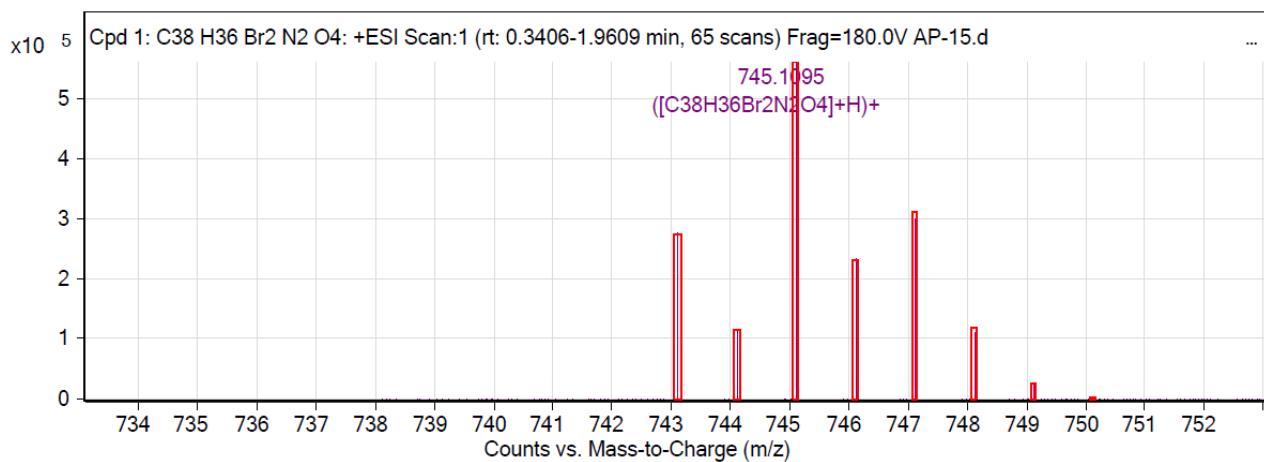
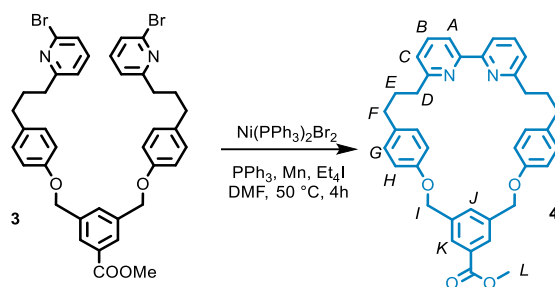


Figure S6. HRMS spectrum for **3**.

Compound 4



$\text{NiBr}_2(\text{PPh}_3)_2$ (1.17 g, 1.57 mmol, 1.0 eq.), PPh_3 (825.5 mg, 3.14 mmol, 2.0 eq.), Mn (863.5 mg, 15.7 mmol, 10.0 eq.), and NEt_4I (376.5 mg, 1.57 mmol, 1.0 eq.) dissolved in DMF (15 mL) and sonicated for 15 min, until a deep red colour developed. The activated catalyst mixture was then stirred at $50\text{ }^\circ\text{C}$ for 10 min, before a solution of **3** (1.17 g, 1.57 mmol, 1.0 eq.) in DMF (15 mL) was added *via* syringe pump over a 4 h period. After the addition was completed, the crude mixture was stirred at $50\text{ }^\circ\text{C}$ for an additional 30 min, before cooling to ambient temperature. The reaction mixture was diluted with EtOAc (100 mL) and washed with a sat. EDTA-NH_3 solution (30 mL), 5% LiCl ($3 \times 20\text{ mL}$), and brine (30 mL). All aqueous phases were extracted with EtOAc (20 mL), and the combined organics were dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , n -Hexane- EtOAc 0 \rightarrow 55%) to yield **4** (614.5 mg, 1.05 mmol, 67%) as a beige foam.

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.93 (d, $J = 1.4\text{ Hz}$, 2H, H_K), 7.75 (d, $J = 7.7\text{ Hz}$, 2H, H_A), 7.58 (t, $J = 7.7\text{ Hz}$, 2H, H_B), 7.48 (t, $J = 1.4\text{ Hz}$, 1H, H_I), 7.05 (d, $J = 7.7\text{ Hz}$, 2H, H_C), 6.92 (d, $J = 8.4\text{ Hz}$, 4H, H_G), 6.64 (d, $J = 7.7\text{ Hz}$, 4H, H_H), 5.08 (s, 4H, H_I), 3.90 (s, 3H, H_L), 2.89 (t, $J = 8.4\text{ Hz}$, 4H, H_D), 2.62 (t, $J = 8.4\text{ Hz}$, 4H, H_F), 2.11 (m, 4H, H_E).

^{13}C NMR (101 MHz, CDCl_3) δ_{C} 166.81, 161.89, 156.22, 138.74, 136.80, 135.20, 130.89, 130.08, 129.56, 127.28, 122.61, 119.17, 115.43, 69.63, 52.29, 37.79, 34.48, 31.26.

HR-ESI-MS (+ve) $m/z = 585.2769$ [$\text{M}+\text{H}$] $^+$ (calc. m/z for $\text{C}_{38}\text{H}_{37}\text{N}_2\text{O}_4$ 585.2771).

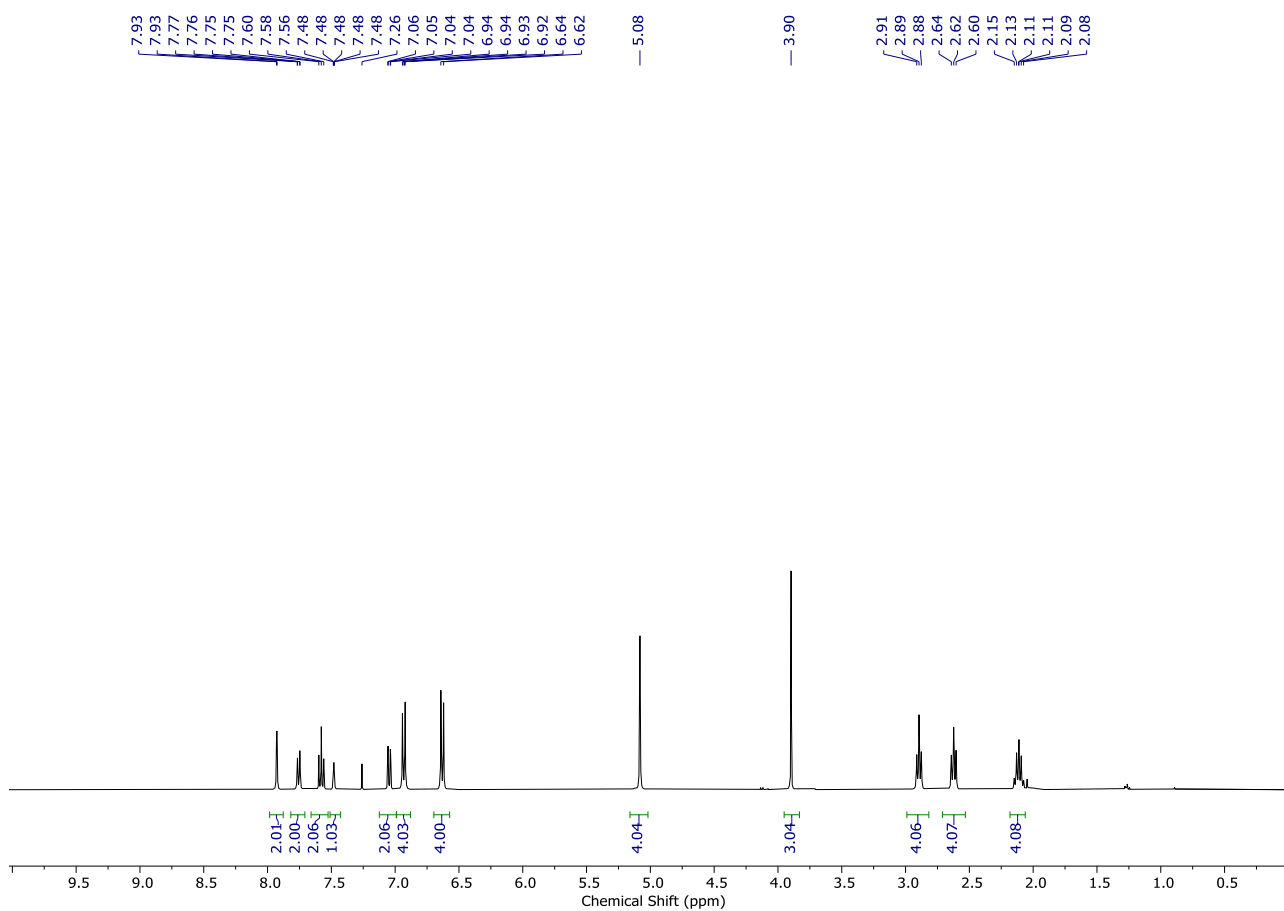


Figure S7. ^1H NMR (CDCl_3 , 400 MHz) of **4**.

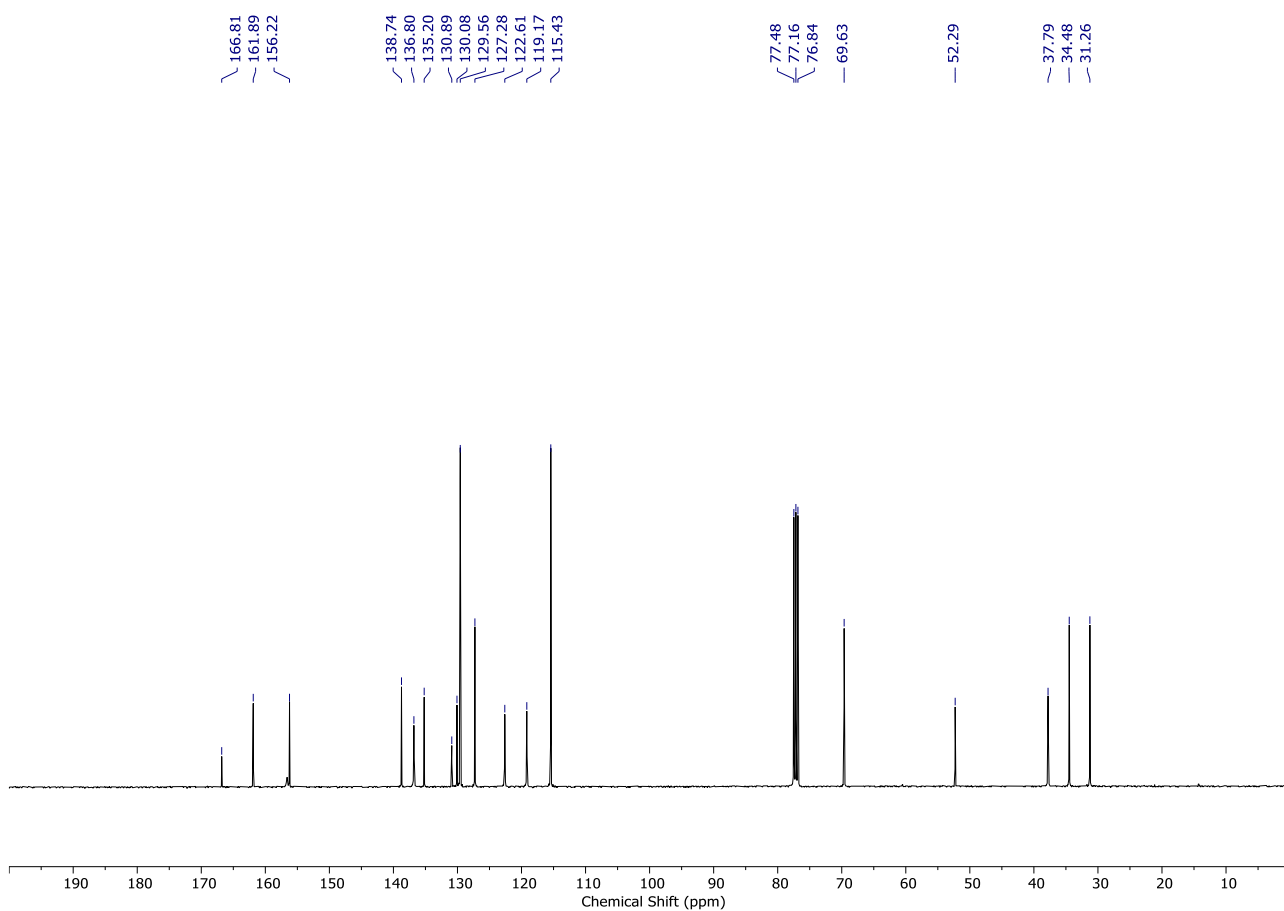


Figure S8. ^{13}C NMR (CDCl_3 , 101 MHz) of **4**.

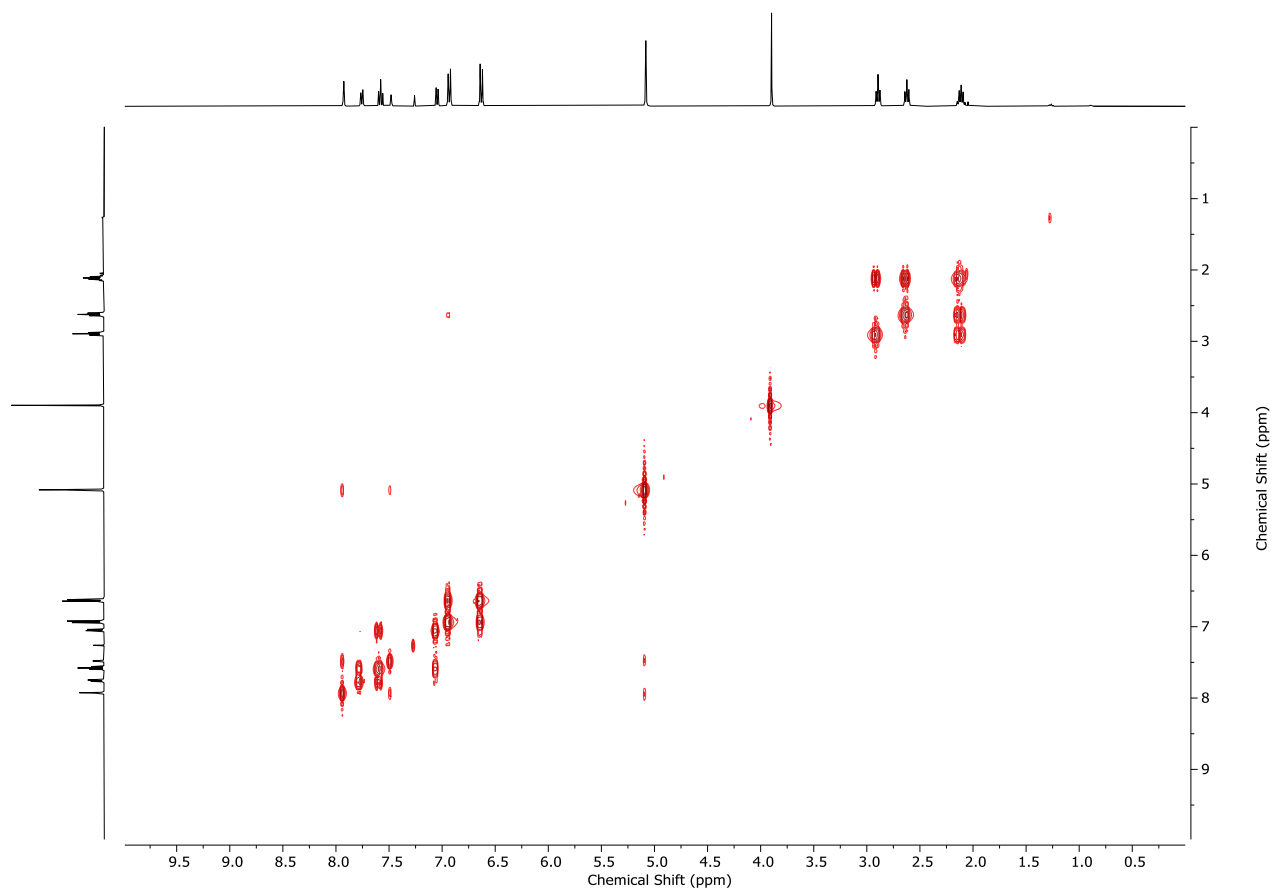


Figure S9. ^1H COSY NMR (CDCl_3) of **4**.

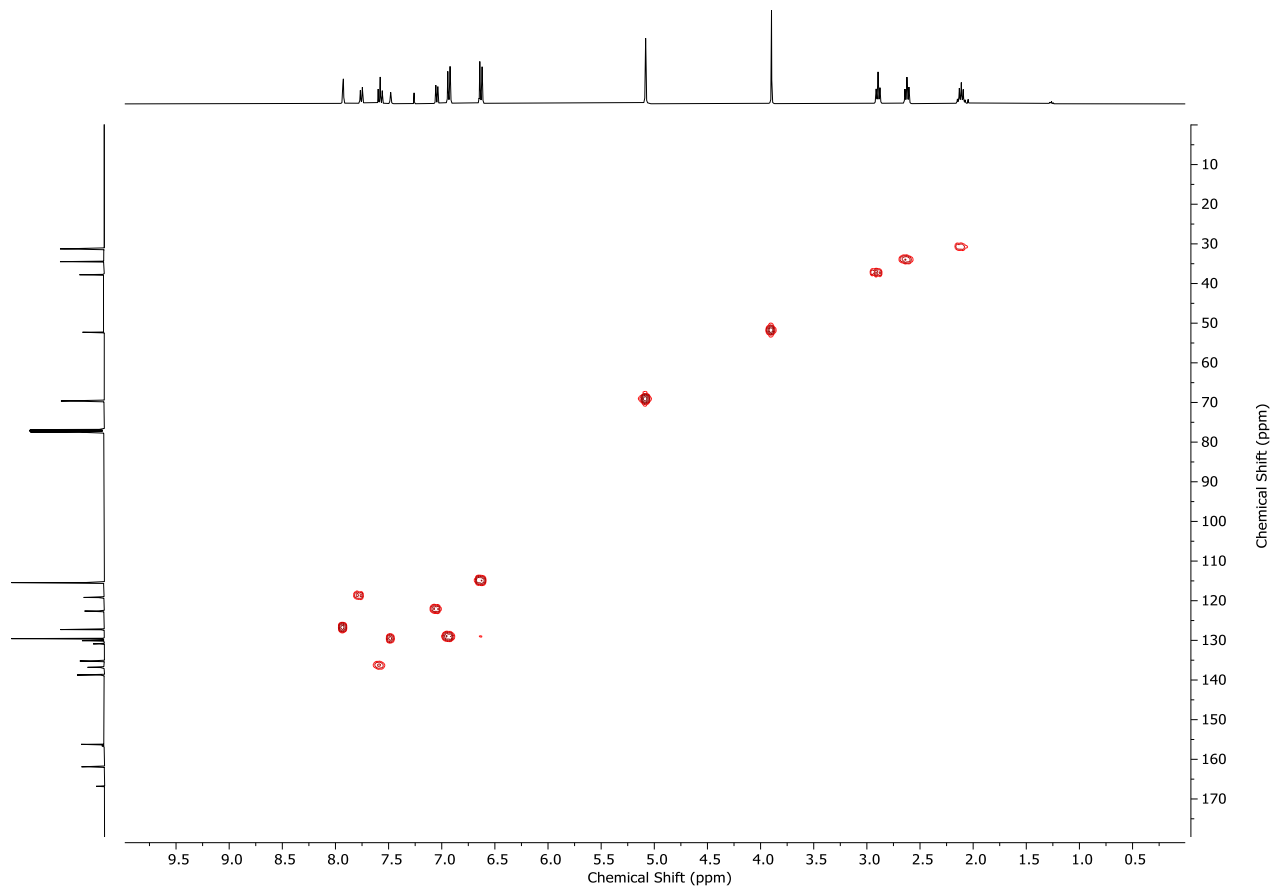


Figure S10. HMQC NMR (CDCl_3) of **4**.

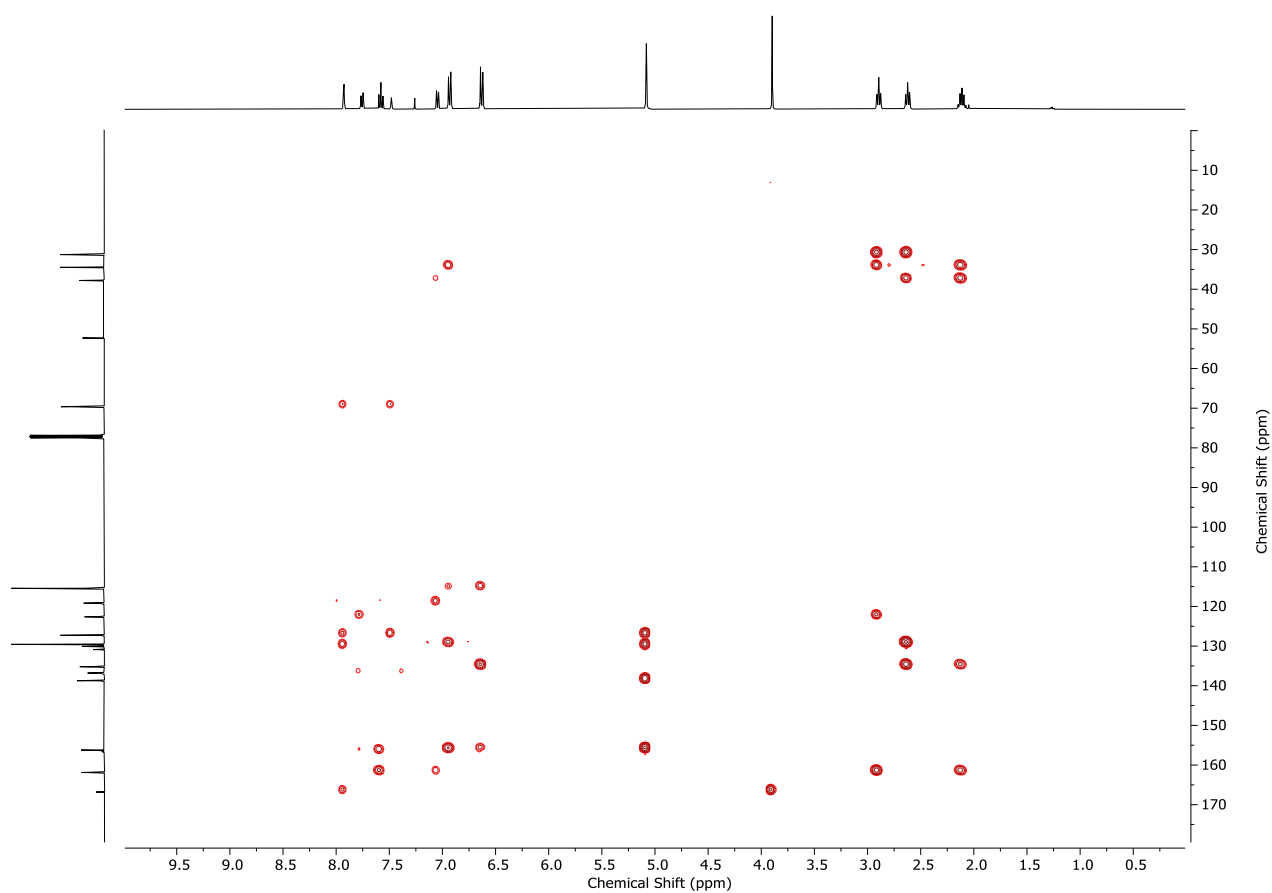


Figure S11. HMBC NMR (CDCl₃) of **4**.

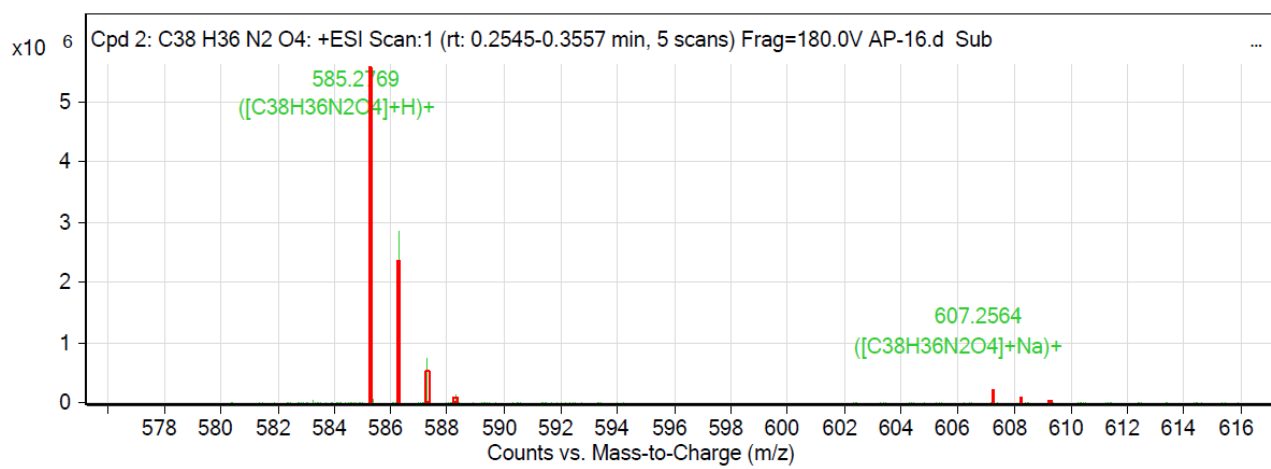
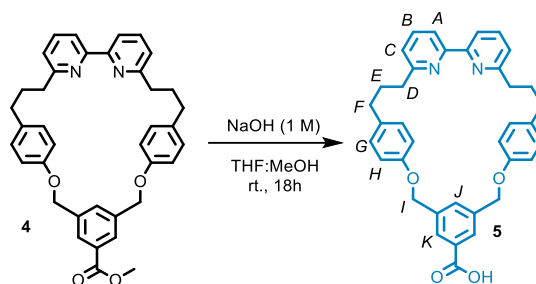


Figure S12. HRMS spectrum for **4**.

Compound 5



4 (610 mg, 1.04 mmol, 1.0 eq.) was dissolved in THF-MeOH (1 : 1, 10 mL), NaOH_(aq) (1 M, 5 mL) was added, and the reaction mixture stirred at rt for 18 h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc (20 mL) and H₂O (20 mL). HCl (1 M, 5 mL) was added to reach neutral pH and break the emulsion. The aqueous layer was extracted with EtOAc (3 × 20 mL), the combined organic layers were dried (MgSO₄) and the solvent removed *in vacuo*. **5** (595 mg, 1.04 mmol, qnt.) was obtained as a yellow foam and used without further purification.

¹H NMR (400 MHz, DMSO(d₆)) δ_H 7.81-7.79 (dd, *J* = 1.4, 7.7 Hz, 4H, H_K and H_A), 7.67 (t, *J* = 7.7 Hz, 2H, H_B), 7.48 (t, *J* = 2.5 Hz, 1H, H_I), 7.13 (d, *J* = 7.6 Hz, 2H, H_C), 6.86 (d, *J* = 8.6 Hz, 4H, H_G), 6.63 (d, *J* = 8.6 Hz, 4H, H_H), 5.11 (s, 4H, H_I), 2.77 (t, *J* = 7.2 Hz, 4H, H_D), 2.48 (t, *J* = 7.1 Hz, 4H, H_F), 1.98 (m, 4H, H_E).

¹³C NMR (101 MHz, DMSO(d₆)) δ_C 166.85, 160.99, 155.74, 155.59, 138.31, 136.81, 134.20, 131.18, 130.03, 129.07, 127.04, 122.60, 118.40, 114.84, 68.24, 36.70, 33.31, 30.51.

HR-ESI-MS (+ve) *m/z* = 571.2602 [M+H]⁺ (calc. *m/z* for C₃₇H₃₅N₂O₄ 571.2597).

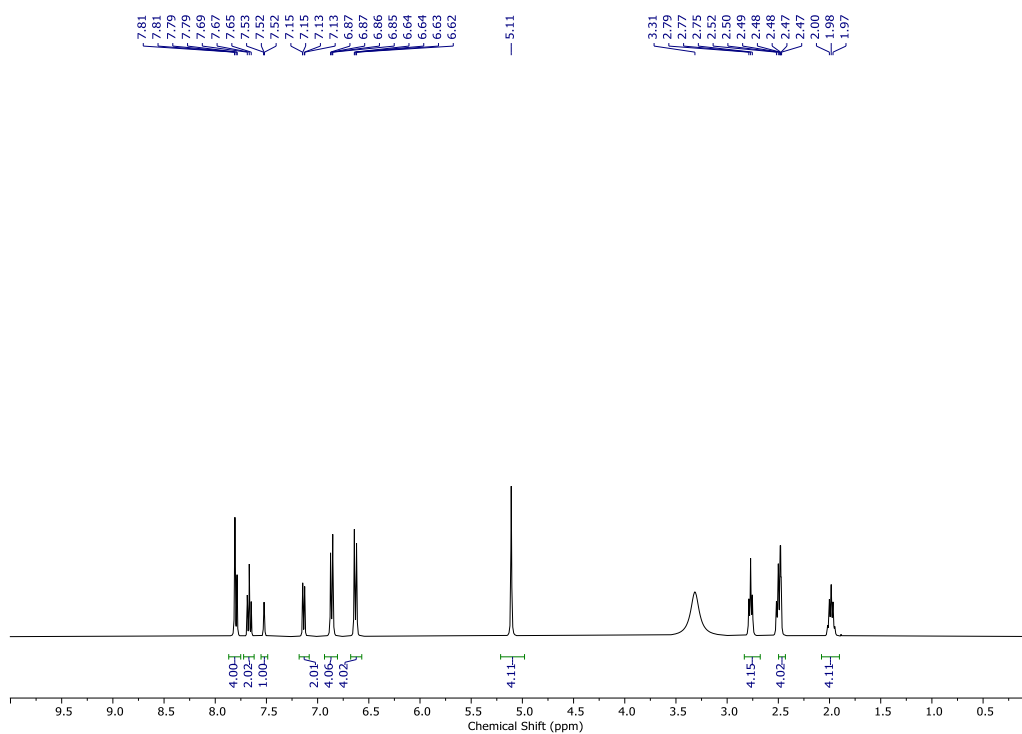


Figure S13. ^1H NMR ($\text{DMSO}(d_6)$, 400 MHz) of **5**.

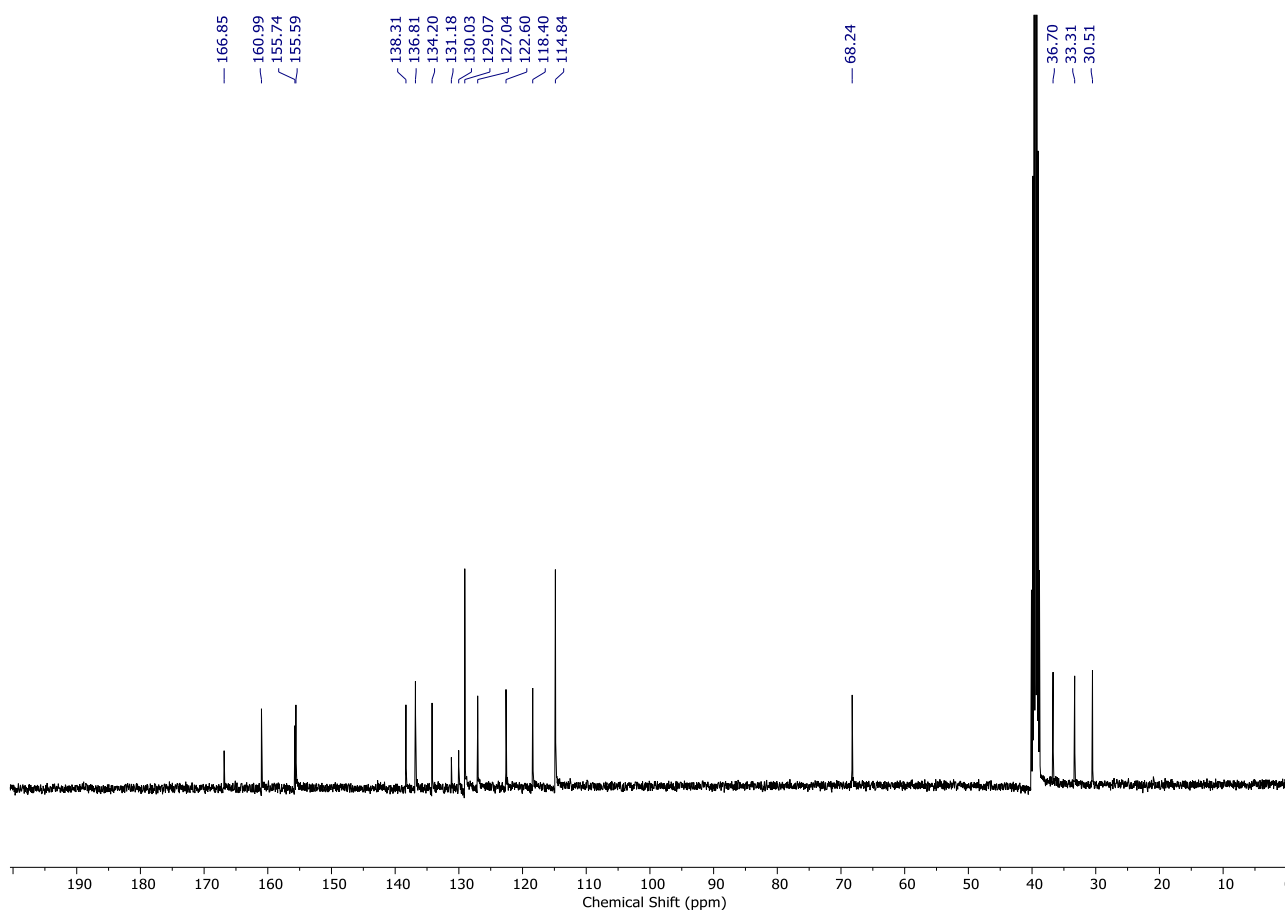


Figure S14. ^{13}C NMR ($\text{DMSO}(d_6)$, 101 MHz) of **5**.

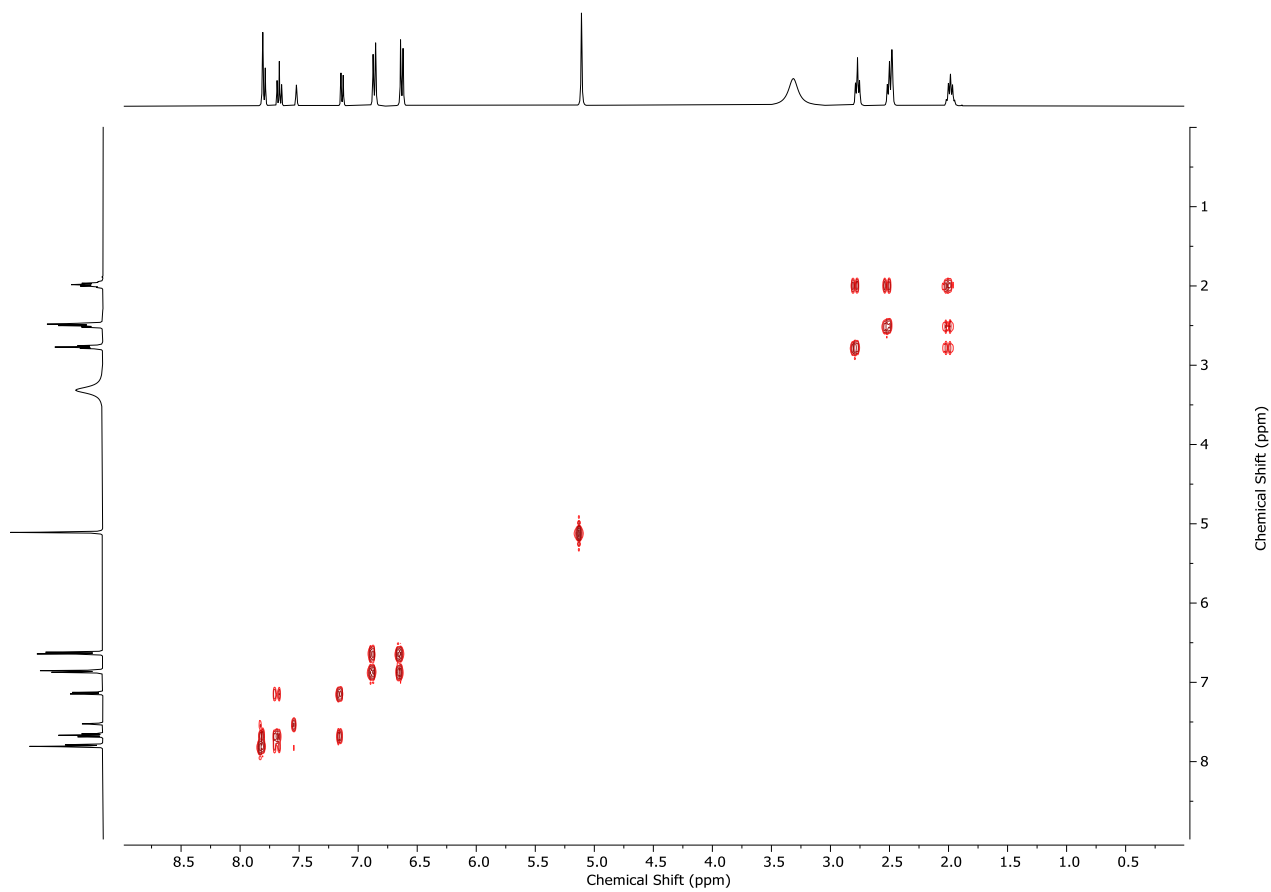


Figure S15. ^1H COSY NMR ($\text{DMSO}(d_6)$) of **5**.

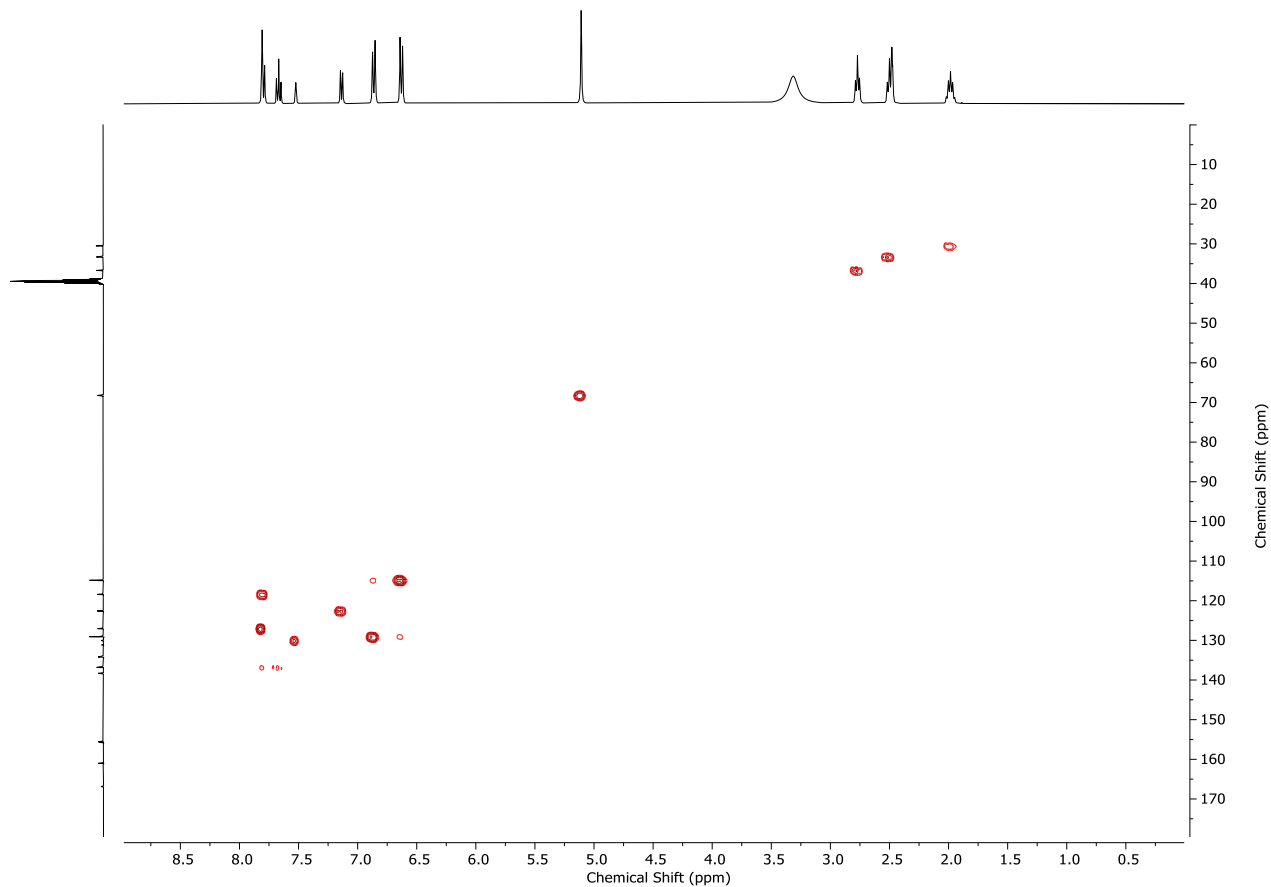


Figure S16. HMQC NMR ($\text{DMSO}(d_6)$) of **5**.

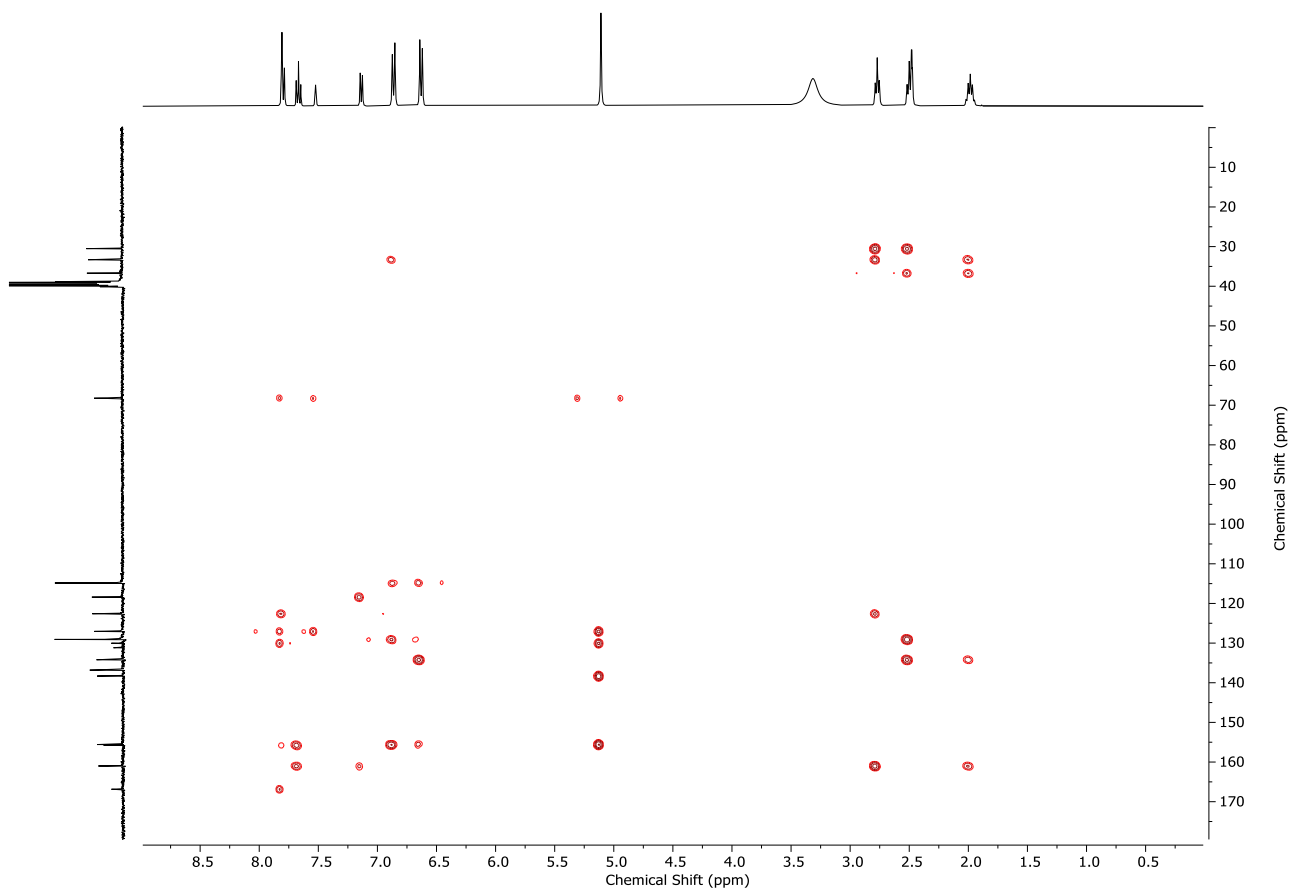


Figure S17. HMBC NMR (DMSO(d₆)) of 5.

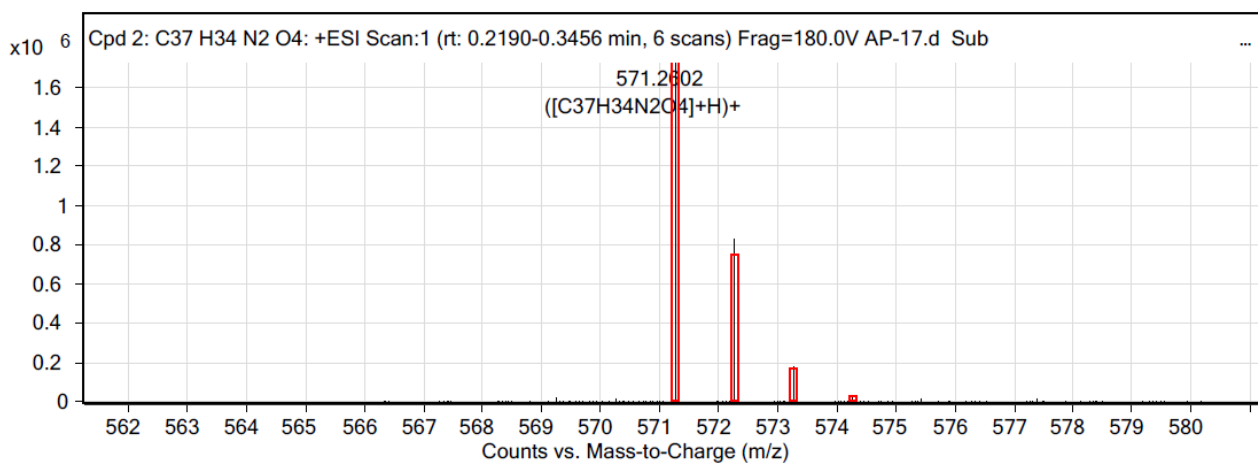
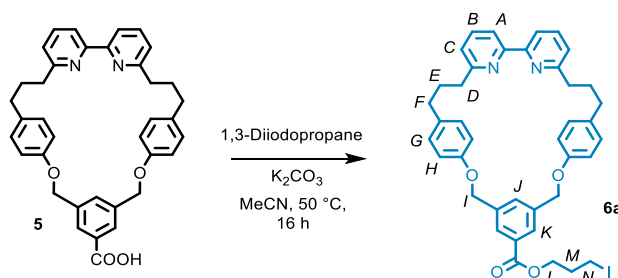


Figure S18. HRMS spectrum for 5.

Compound 6a



To a solution of **5** (50.0 mg, 0.08 mmol, 1.0 eq.) in CH_3CN (5.0 mL) were added K_2CO_3 (24.5 mg, 0.16 mmol, 2.0 eq.) and 1,3-diiodopropane (260 mg, 0.80 mmol, 10.0 eq.), and the reaction mixture was stirred at 50 °C for 16 h. After cooling to ambient temperature, the reaction mixture was filtered through Celite®, washing with CH_2Cl_2 , and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , $CHCl_3$ -MeOH 0→8%) to yield **6a** (64.4 mg, 0.08 mmol, 98%) as a yellow oil.

1H NMR (500 MHz, $CDCl_3$) δ_H 7.91 (d, $J = 1.4$ Hz, 2H, H_K), 7.74 (d, $J = 7.7$ Hz, 2H, H_A), 7.59 (t, $J = 7.7$ Hz, 2H, H_B), 7.49 (t, $J = 1.4$ Hz, 1H, H_I), 7.05 (d, $J = 7.5$ Hz, 2H, H_C), 6.93 (d, $J = 8.4$ Hz, 4H, H_G), 6.63 (d, $J = 8.4$ Hz, 4H, H_H), 5.09 (s, 4H, H_I), 4.38 (t, $J = 5.8$ Hz, 2H, H_L), 3.27 (t, $J = 7.1$ Hz, 2H, H_N), 2.90 (t, $J = 7.1$ Hz, 4H, H_D), 2.62 (t, $J = 7.1$ Hz, 4H, H_F), 2.27 (m, 2H, H_M), 2.10 (m, 4H, H_E).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 166.09, 161.90, 156.14, 138.79, 136.81, 135.20, 130.70, 130.21, 129.57, 127.25, 122.59, 119.21, 115.39, 69.52, 64.84, 37.78, 34.47, 32.61, 31.29.

HR-ESI-MS (+ve) $m/z = 739.2039$ [$M+H$]⁺ (calc. m/z for $C_{40}H_{39}IN_2O_4$ 739.2031).

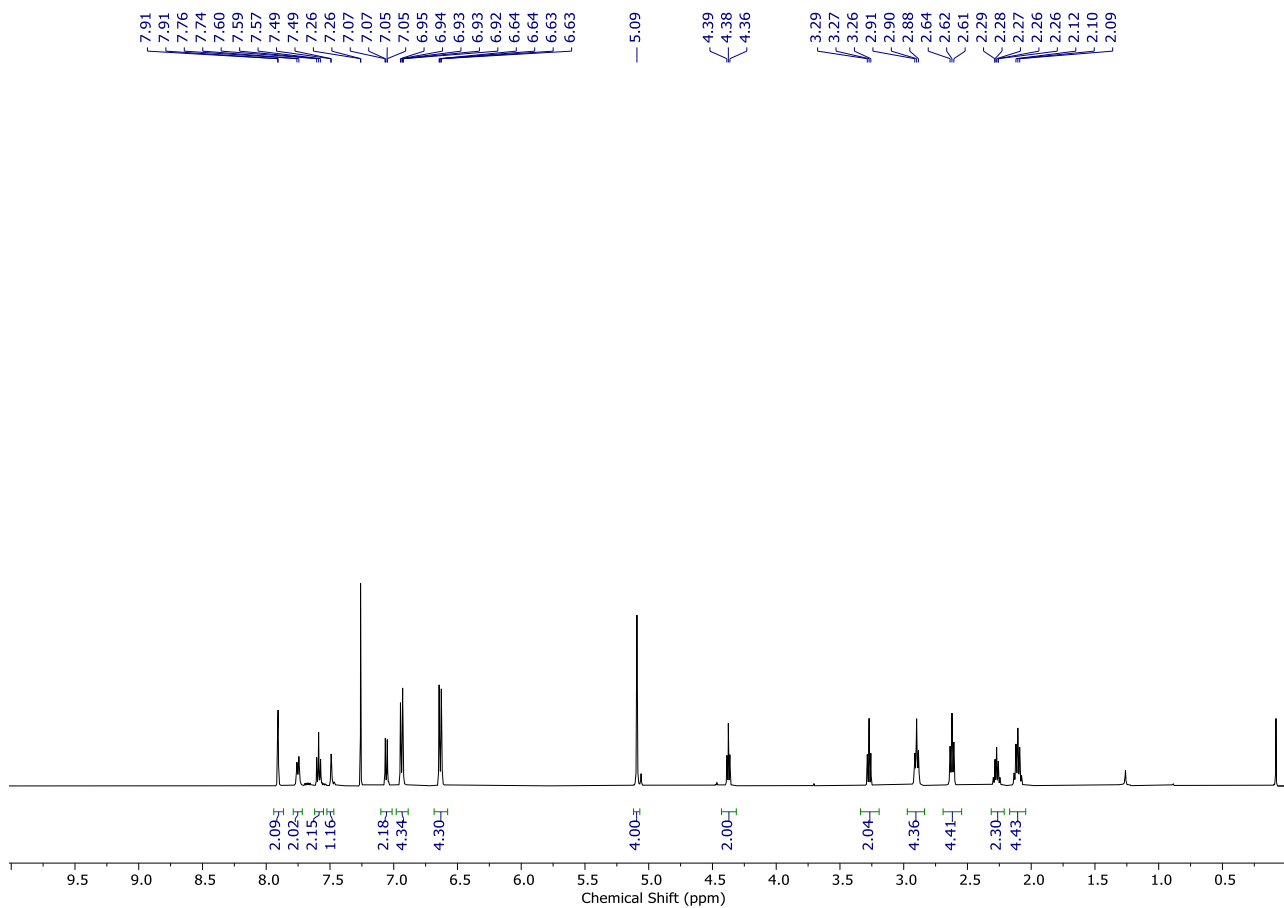


Figure S19. ^1H NMR (CDCl_3 , 500 MHz) of **6a**.

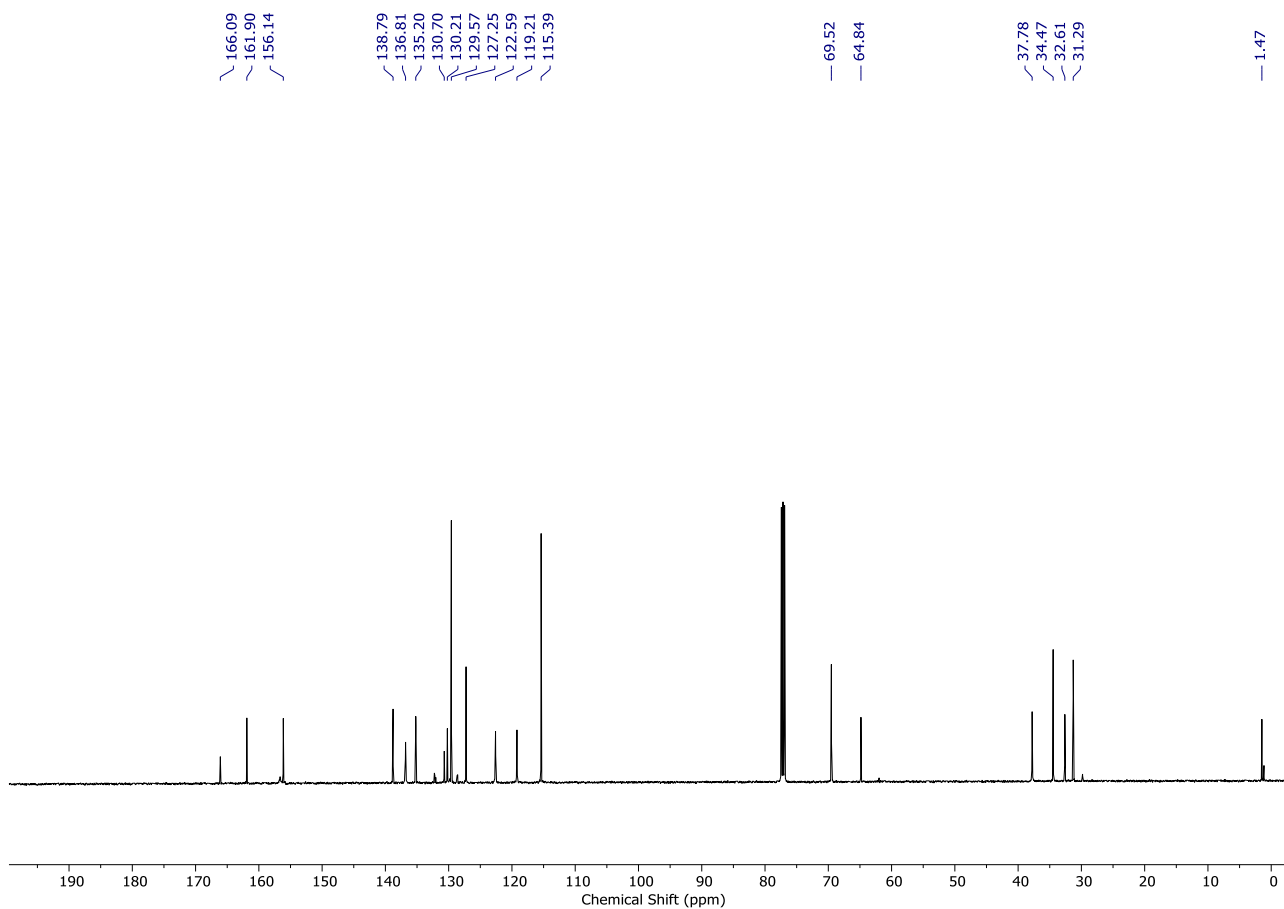


Figure S20. ^{13}C NMR (CDCl_3 , 126 MHz) of **6a**.

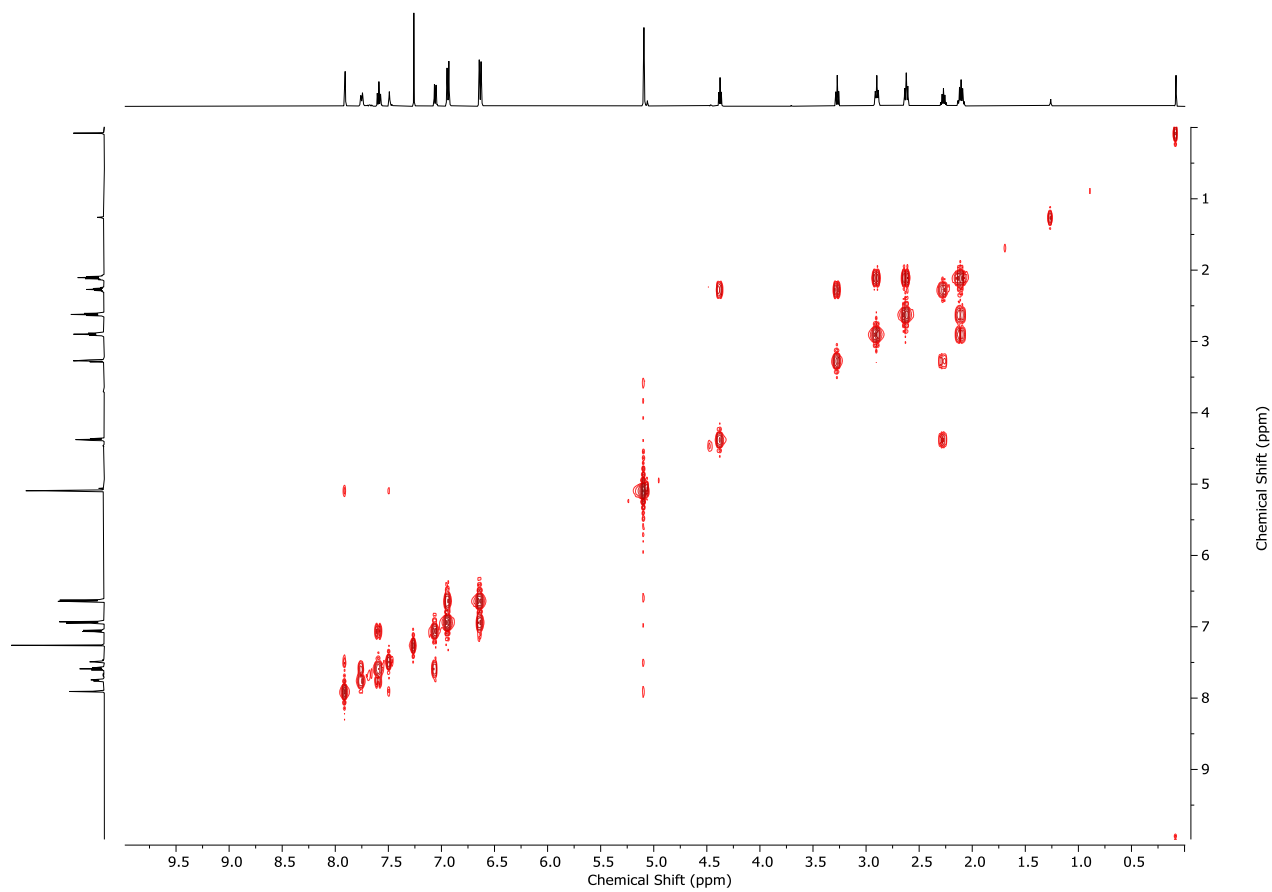


Figure S21. ¹H COSY NMR (CDCl₃) of **6a**.

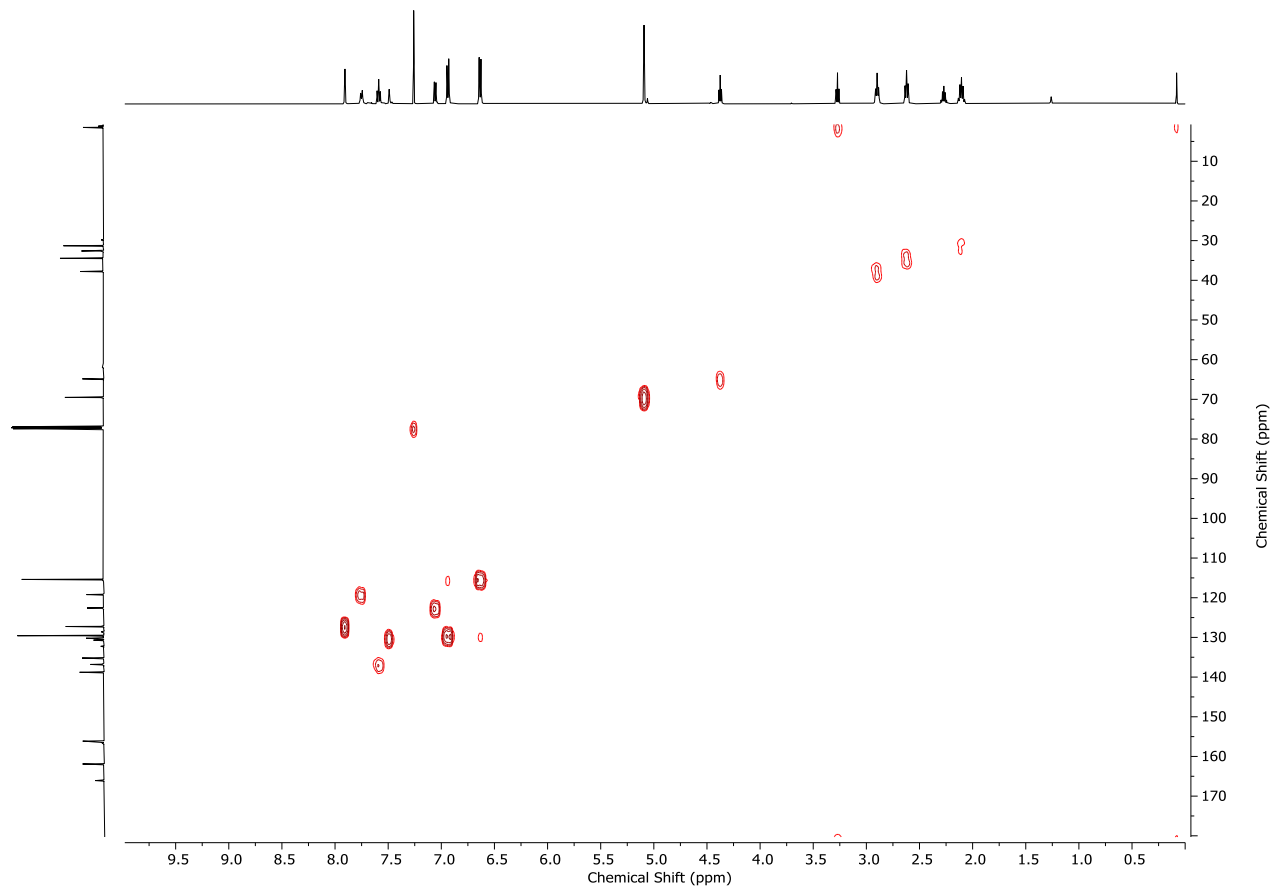


Figure S22. HMQC NMR (CDCl₃) of **6a**.

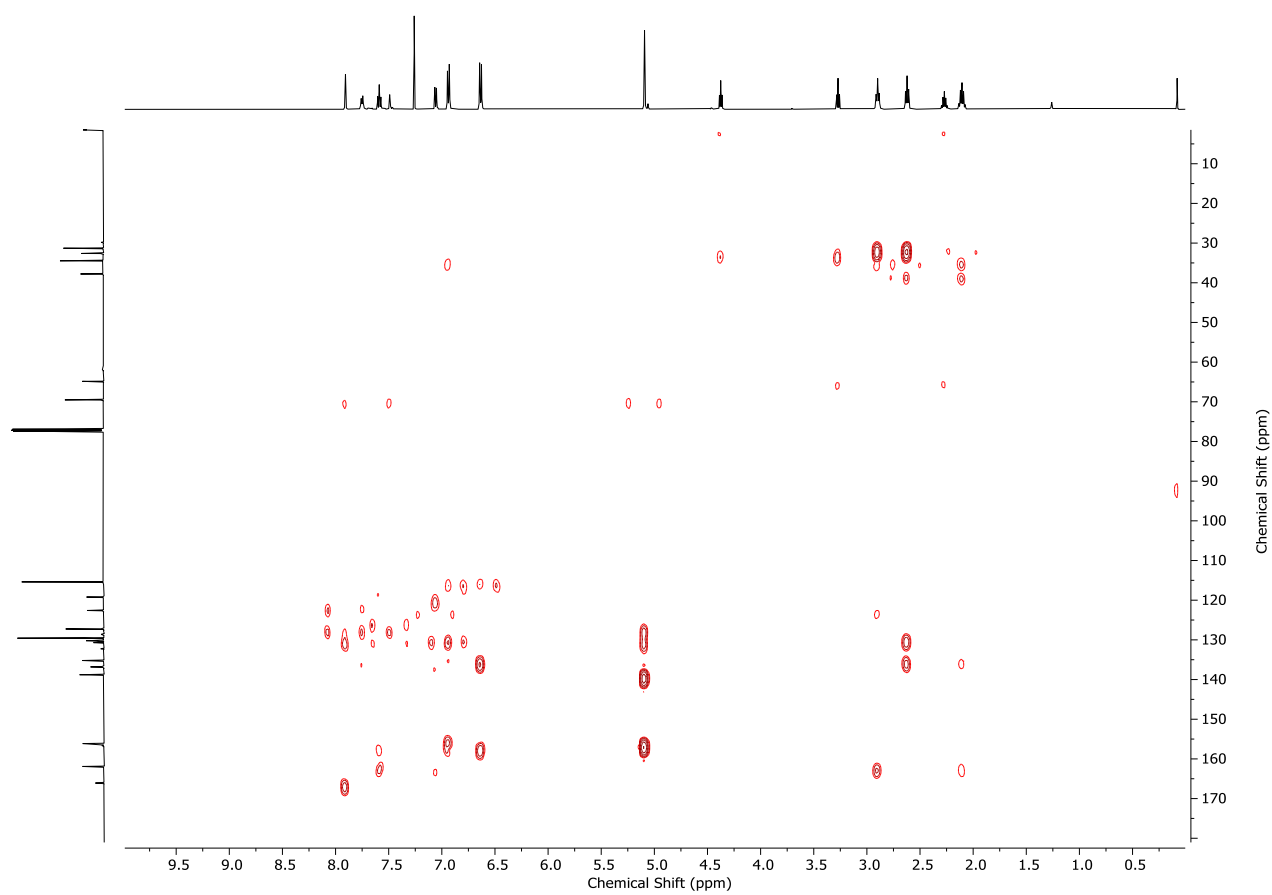


Figure S23. HMBC NMR (CDCl_3) of **6a**.

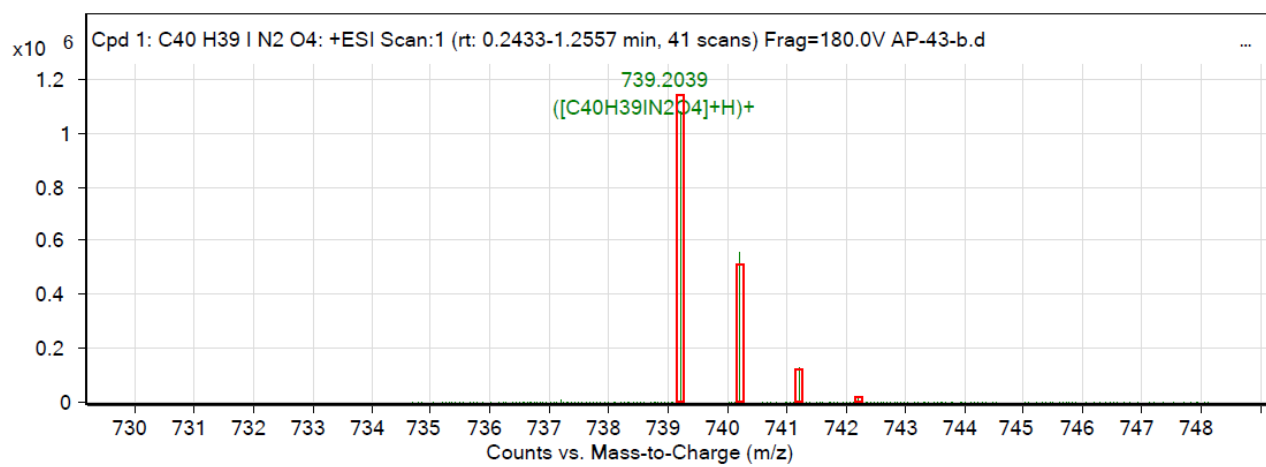
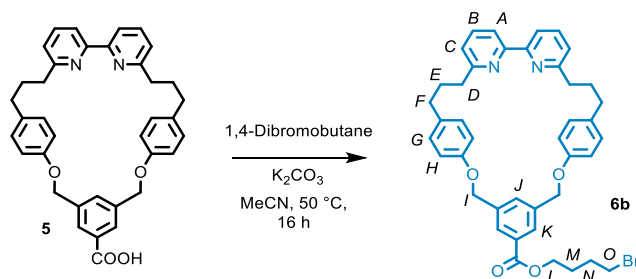


Figure S24. HRMS spectrum for **6a**.

Compound 6b



To a solution of **5** (50.0 mg, 0.08 mmol, 1.0 eq.) in CH_3CN (5.0 mL) were added K_2CO_3 (24.5 mg, 0.16 mmol, 2.0 eq.) and 1,4-dibromobutane (172 mg, 0.80 mmol, 10.0 eq.), and the reaction mixture was stirred at 50 °C for 16 h. After cooling to ambient temperature, the reaction mixture was filtered through Celite®, washing with CH_2Cl_2 , and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , $CHCl_3$ -MeOH 0→8%) to yield **6b** (57.7 mg, 0.07 mmol, 99%) as a yellow oil.

1H NMR (400 MHz, $CDCl_3$) δ_H 7.91 (d, $J = 1.4$ Hz, 2H, H_K), 7.76 (d, $J = 7.7$ Hz, 2H, H_A), 7.59 (t, $J = 7.7$ Hz, 2H, H_B), 7.48 (t, $J = 1.4$ Hz, 1H, H_I), 7.05 (d, $J = 7.5$ Hz, 2H, H_C), 6.93 (d, $J = 8.4$ Hz, 4H, H_G), 6.62 (d, $J = 8.4$ Hz, 4H, H_H), 5.09 (s, 4H, H_I), 4.34 (t, $J = 5.8$ Hz, 2H, H_L), 3.47 (t, $J = 7.1$ Hz, 2H, H_O), 2.91 (t, $J = 7.1$ Hz, 4H, H_D), 2.62 (t, $J = 7.1$ Hz, 4H, H_F), 2.18 (m, 4H, H_E), 2.00 (m, 2H, H_M), 1.94 (m, 2H, H_N).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 166.27, 161.90, 156.21, 138.78, 136.90, 135.22, 130.95, 130.20, 129.59, 127.28, 122.70, 119.27, 115.45, 69.61, 64.26, 37.75, 34.49, 33.19, 31.27, 29.51, 27.53.

HR-ESI-MS (+ve) $m/z = 707.2315$ [$M+H$]⁺ (calc. m/z for $C_{41}H_{41}BrN_2O_4$ 707.2311).

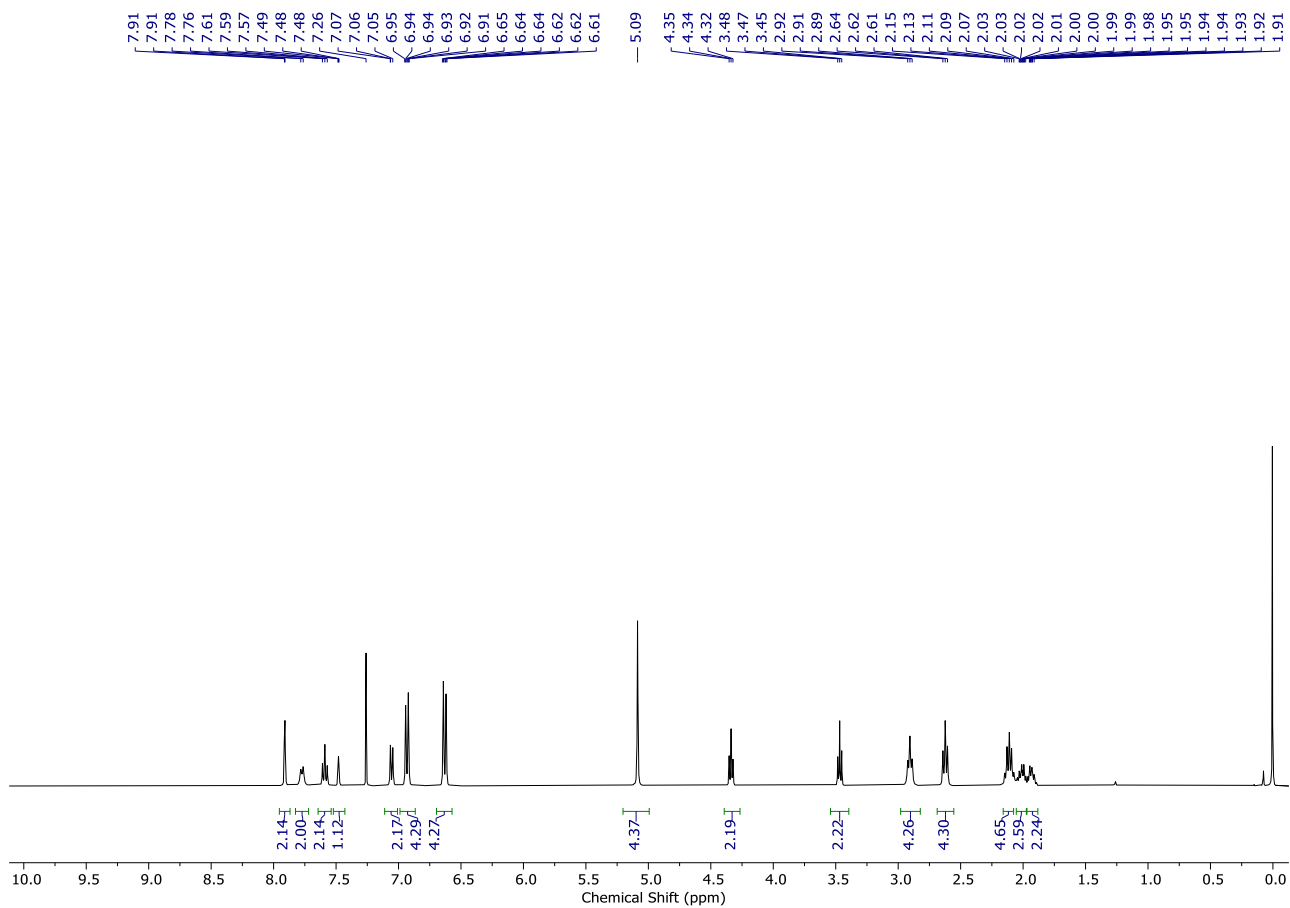


Figure S25. ^1H NMR (CDCl_3 , 400 MHz) of **6b**.

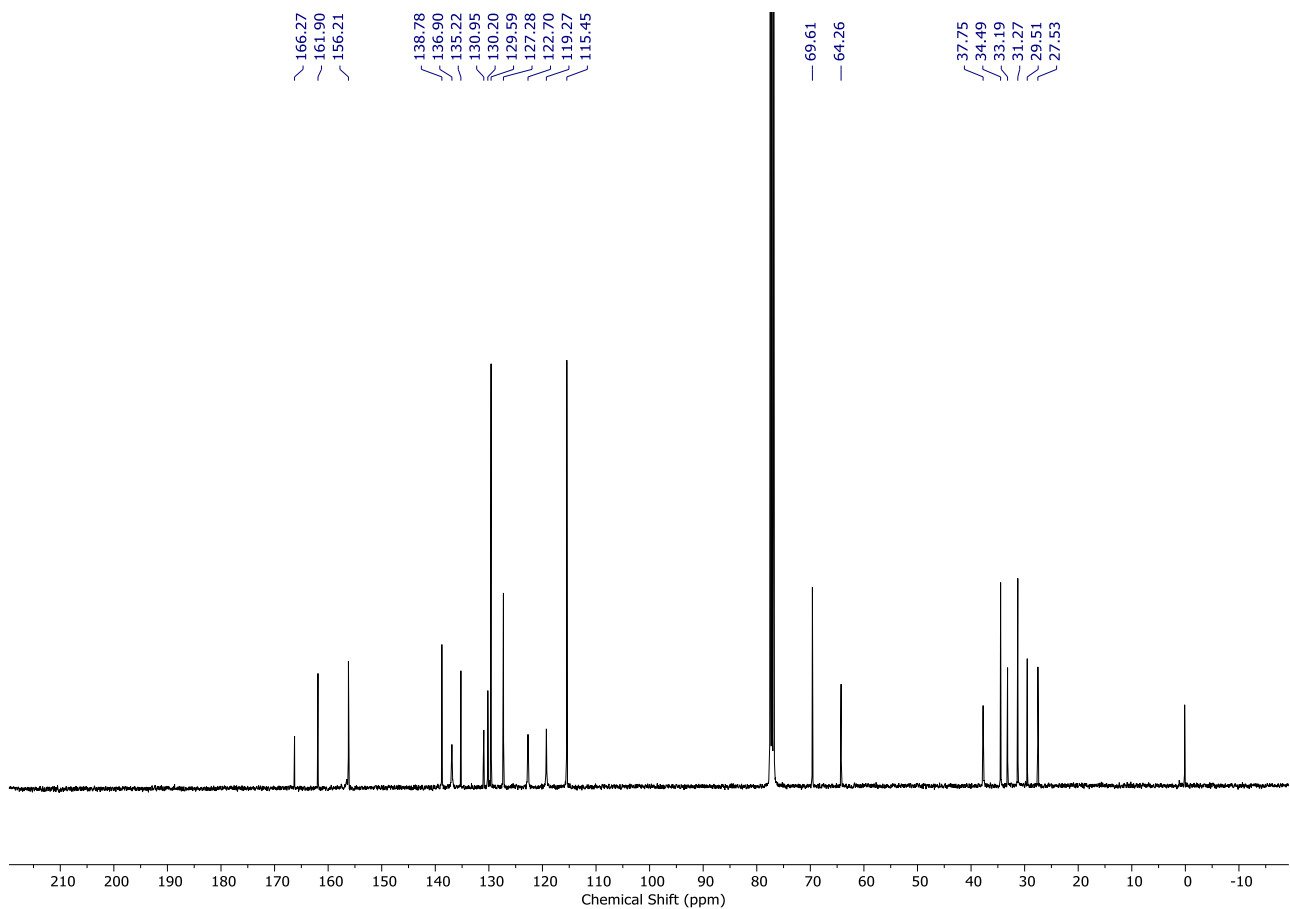


Figure S26. ^{13}C NMR (CDCl_3 , 101 MHz) of **6b**.

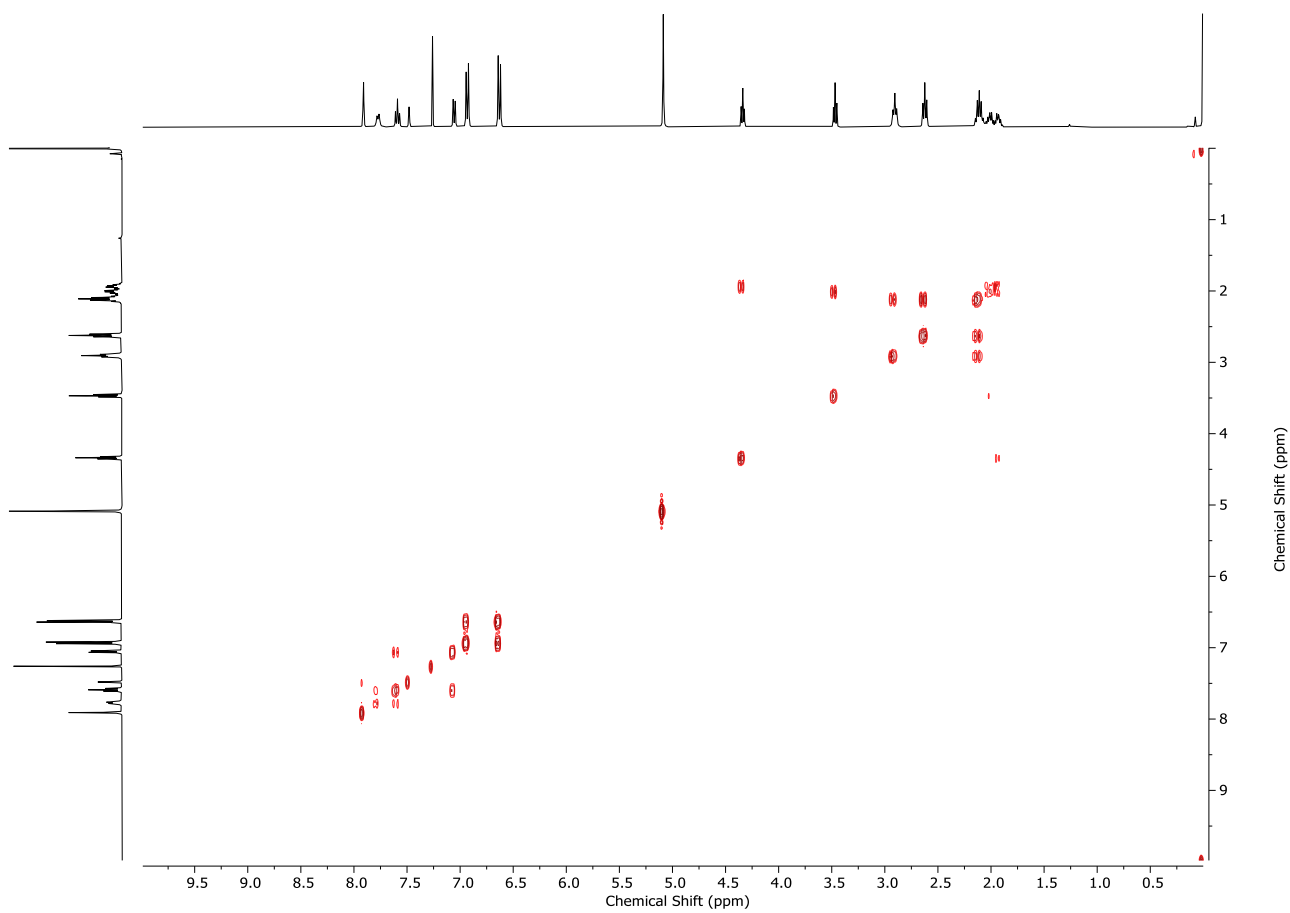


Figure S27. ^1H COSY NMR (CDCl_3) of **6b**.

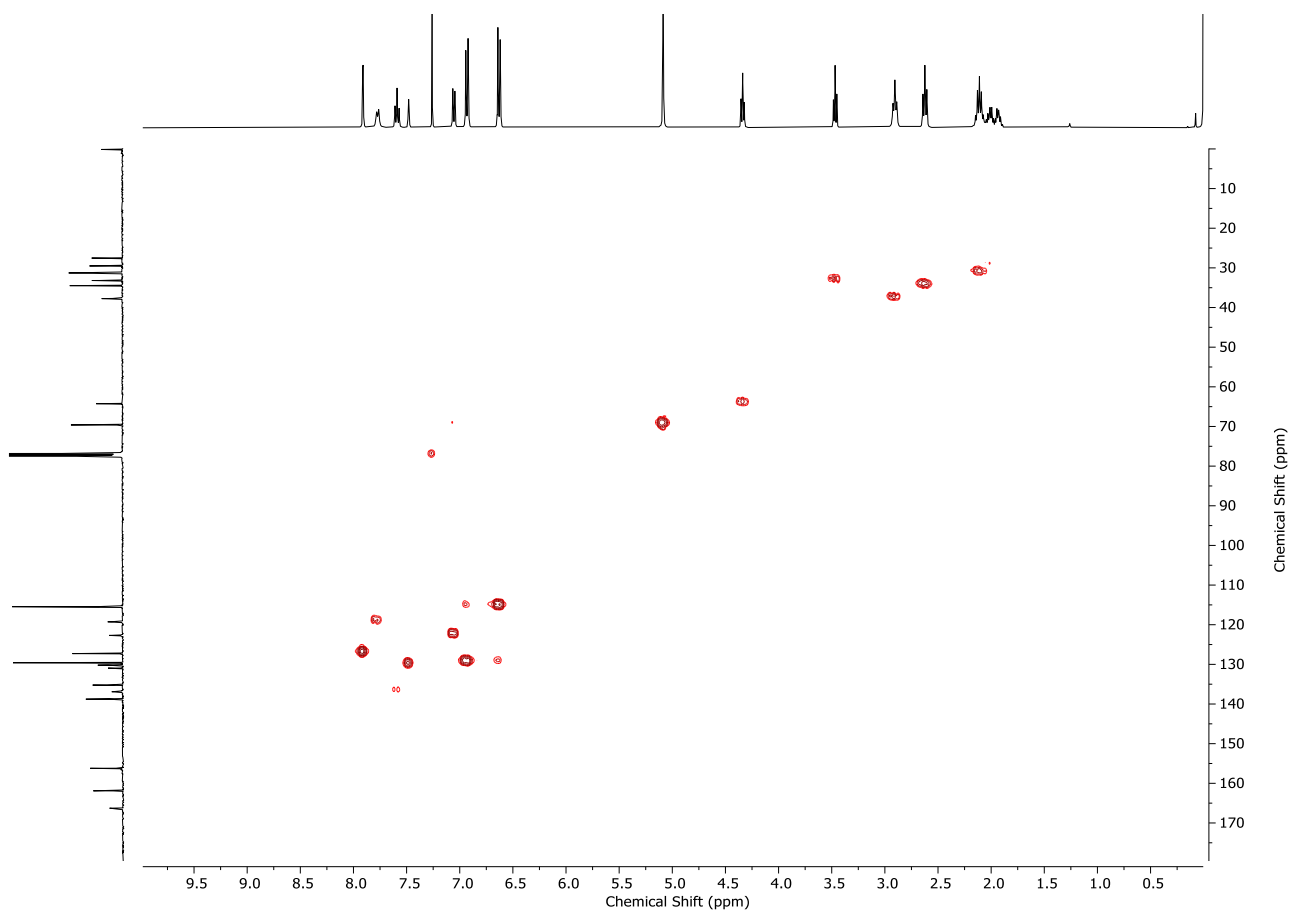


Figure S28. HMQC NMR (CDCl_3) of **6b**.

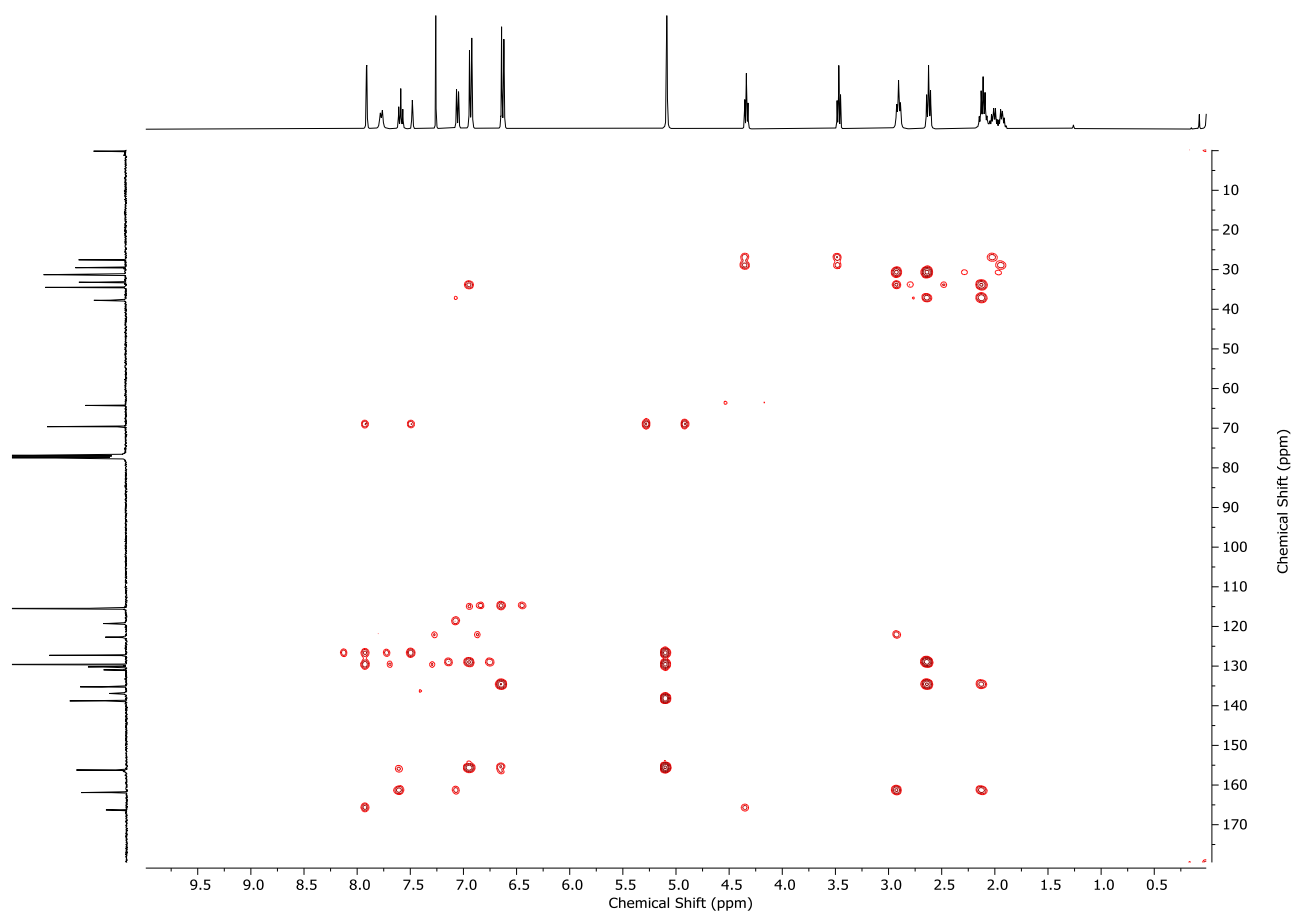


Figure S29. HMBC NMR (CDCl_3) of **6b**.

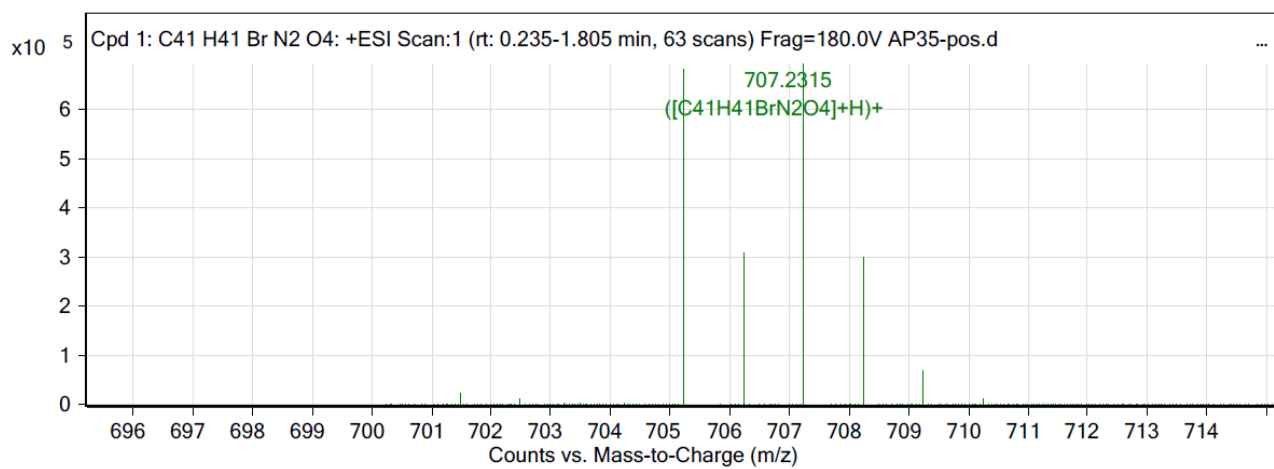
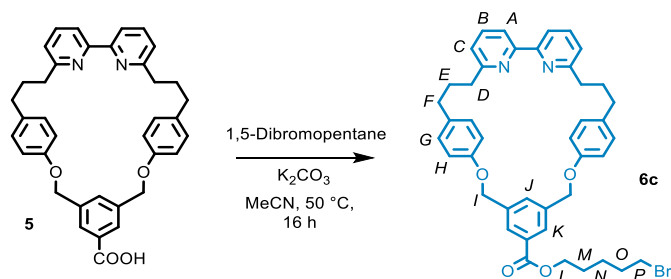


Figure S30. HRMS spectrum for **6b**.

Compound 6c



To a solution of **5** (50.0 mg, 0.08 mmol, 1.0 eq.) in CH_3CN (5.0 mL) were added K_2CO_3 (24.5 mg, 0.16 mmol, 2.0 eq.) and 1,5-dibromopentane (185 mg, 0.80 mmol, 10.0 eq.), and the reaction mixture was stirred at 50 °C for 16 h. After cooling to ambient temperature, the reaction mixture was filtered through Celite®, washing with CH_2Cl_2 , and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , $CHCl_3$ -MeOH 0→7%) to yield **6c** (53.6 mg, 0.07 mmol, 93%) as a yellow oil.

1H NMR (500 MHz, $CDCl_3$) δ_H 7.92 (d, $J = 1.4$ Hz, 2H, H_K), 7.75 (d, $J = 7.7$ Hz, 2H, H_A), 7.58 (t, $J = 7.7$ Hz, 2H, H_B), 7.48 (t, $J = 1.4$ Hz, 1H, H_I), 7.05 (d, $J = 7.5$ Hz, 2H, H_C), 6.94 (d, $J = 8.4$ Hz, 4H, H_G), 6.63 (d, $J = 8.4$ Hz, 4H, H_H), 5.09 (s, 4H, H_I), 4.31 (t, $J = 5.8$ Hz, 2H, H_L), 3.42 (t, $J = 7.1$ Hz, 2H, H_P), 2.90 (t, $J = 7.1$ Hz, 4H, H_D), 2.62 (t, $J = 7.1$ Hz, 4H, H_F), 2.11 (m, 4H, H_E), 1.92 (m, 2H, H_M), 1.79 (m, 2H, H_O), 1.61 (m, 2H, H_N).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 166.30, 161.88, 156.21, 138.73, 136.79, 135.20, 131.07, 130.09, 129.56, 127.25, 122.60, 119.16, 115.42, 69.62, 64.88, 37.79, 34.47, 33.52, 32.41, 31.46, 31.25, 29.81, 27.99, 24.83.

HR-ESI-MS (+ve) $m/z = 721.2473$ [$M+H$]⁺ (calc. m/z for $C_{42}H_{43}N_2O_4Br$ 721.2470).

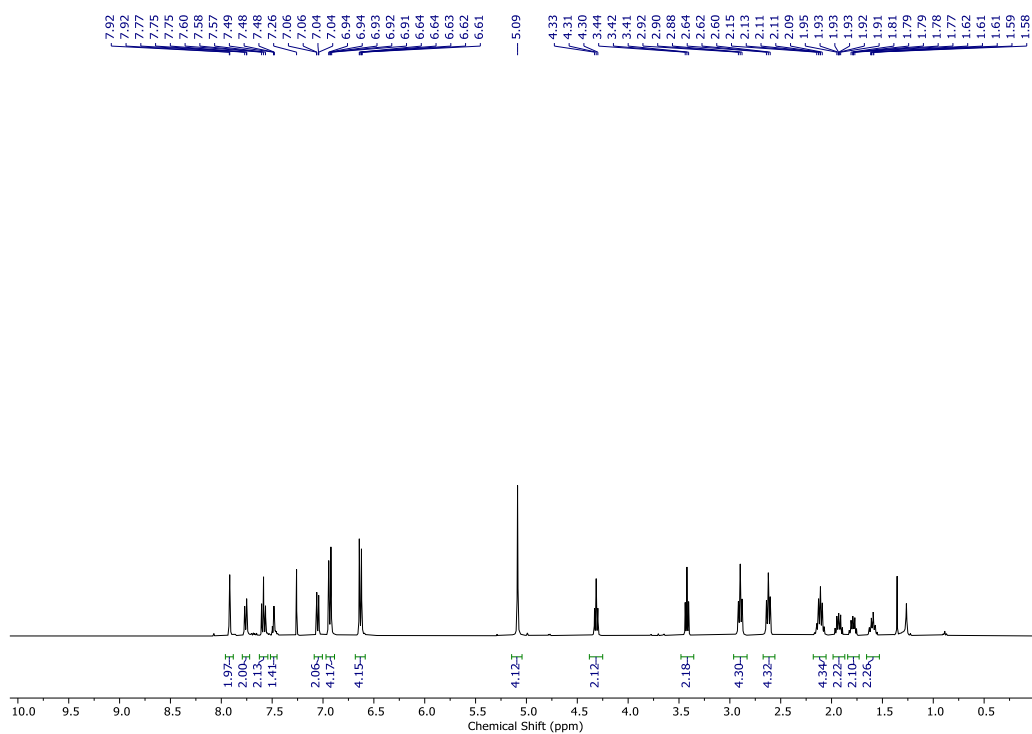


Figure S31. ^1H NMR (CDCl_3 , 400 MHz) of **6c**.

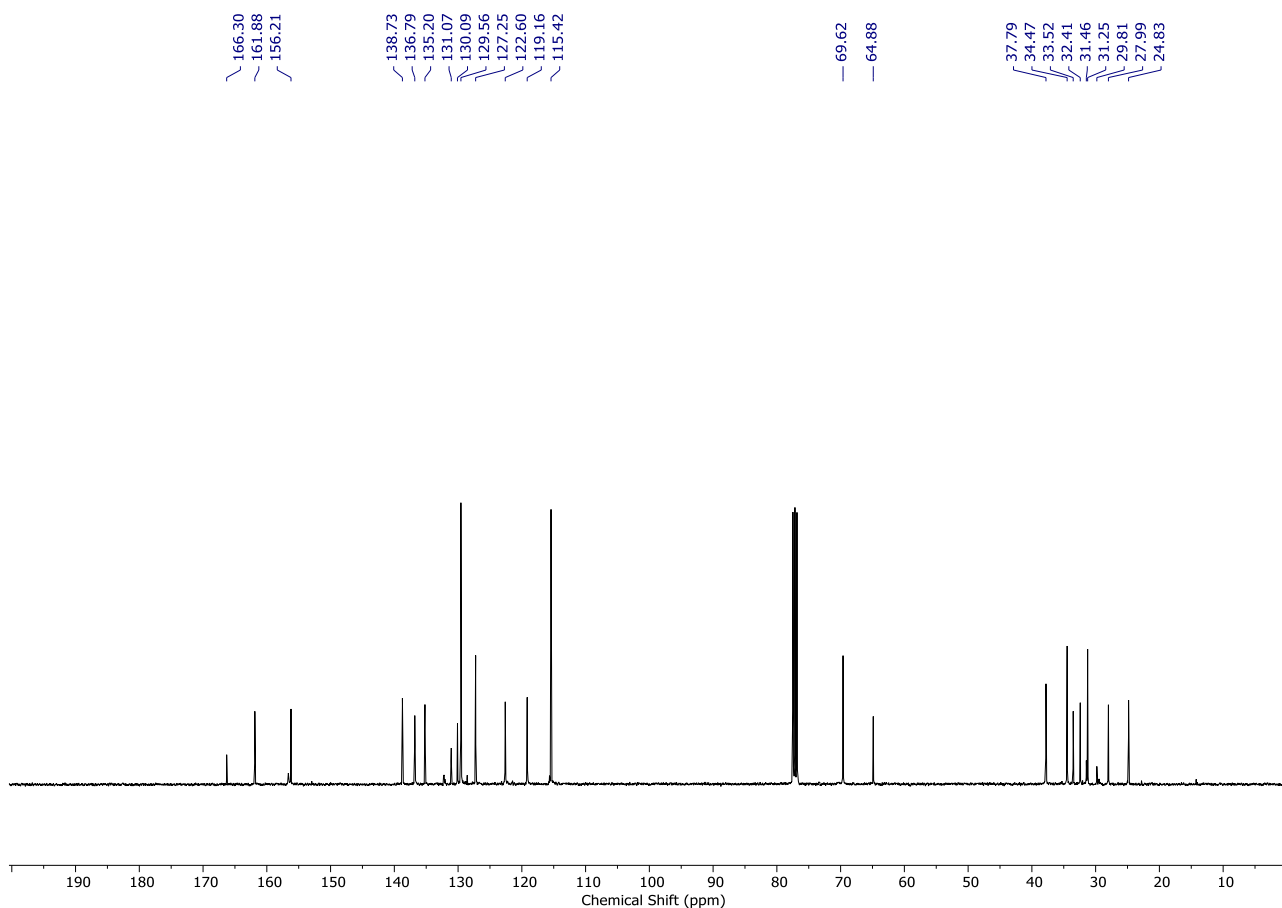


Figure S32. ^{13}C NMR (CDCl_3 , 101 MHz) of **6c**.

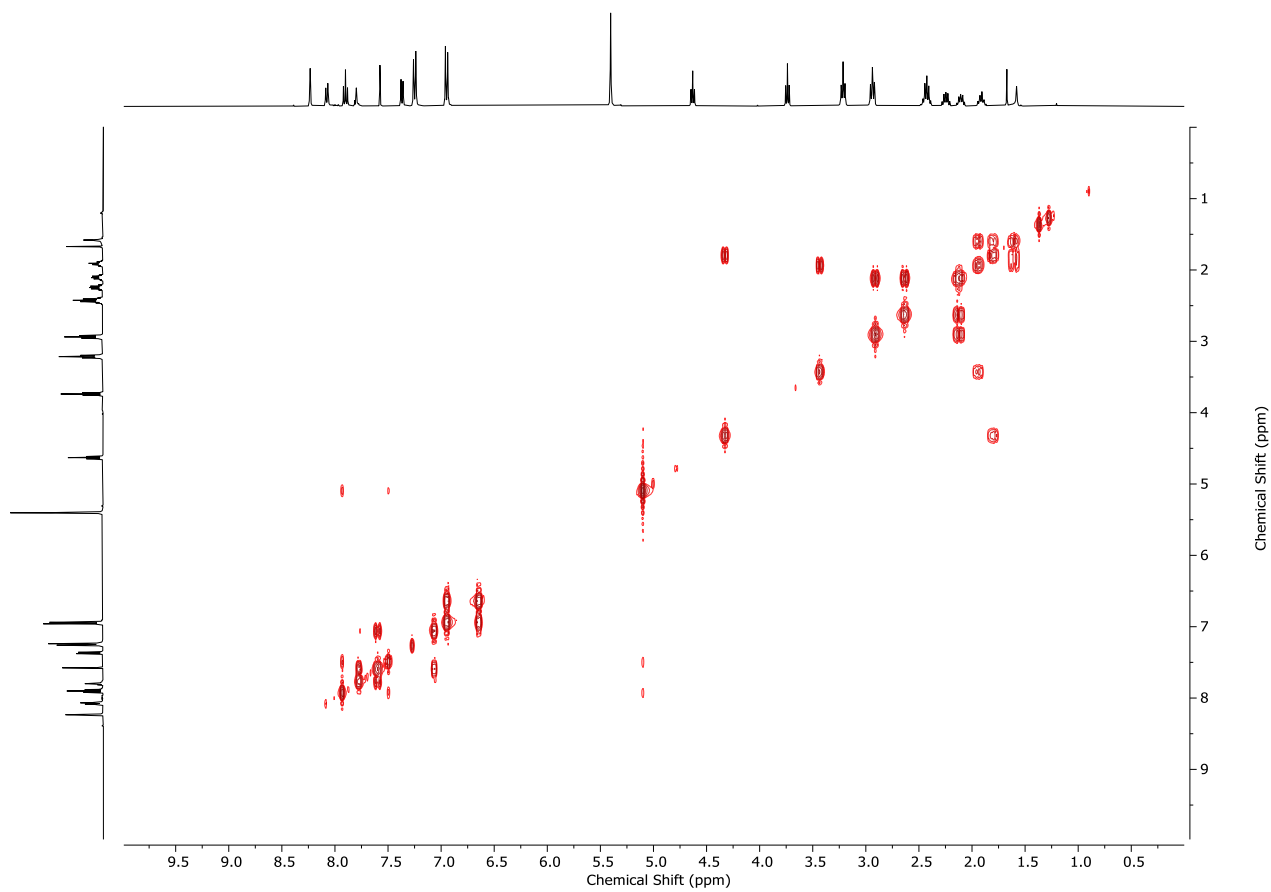


Figure S33. ^1H COSY NMR (CDCl_3) of **6c**.

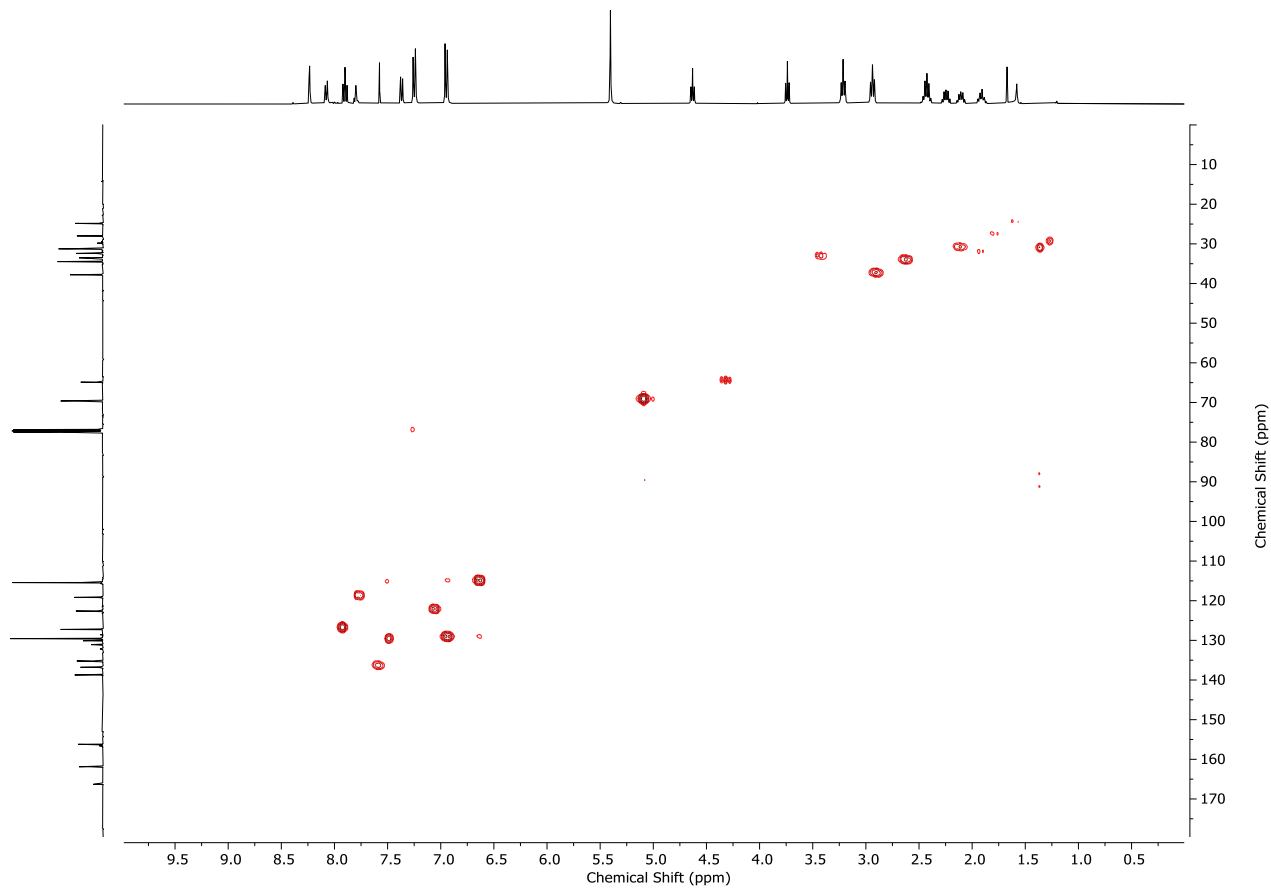


Figure S34. HMQC NMR (CDCl_3) of **6c**.

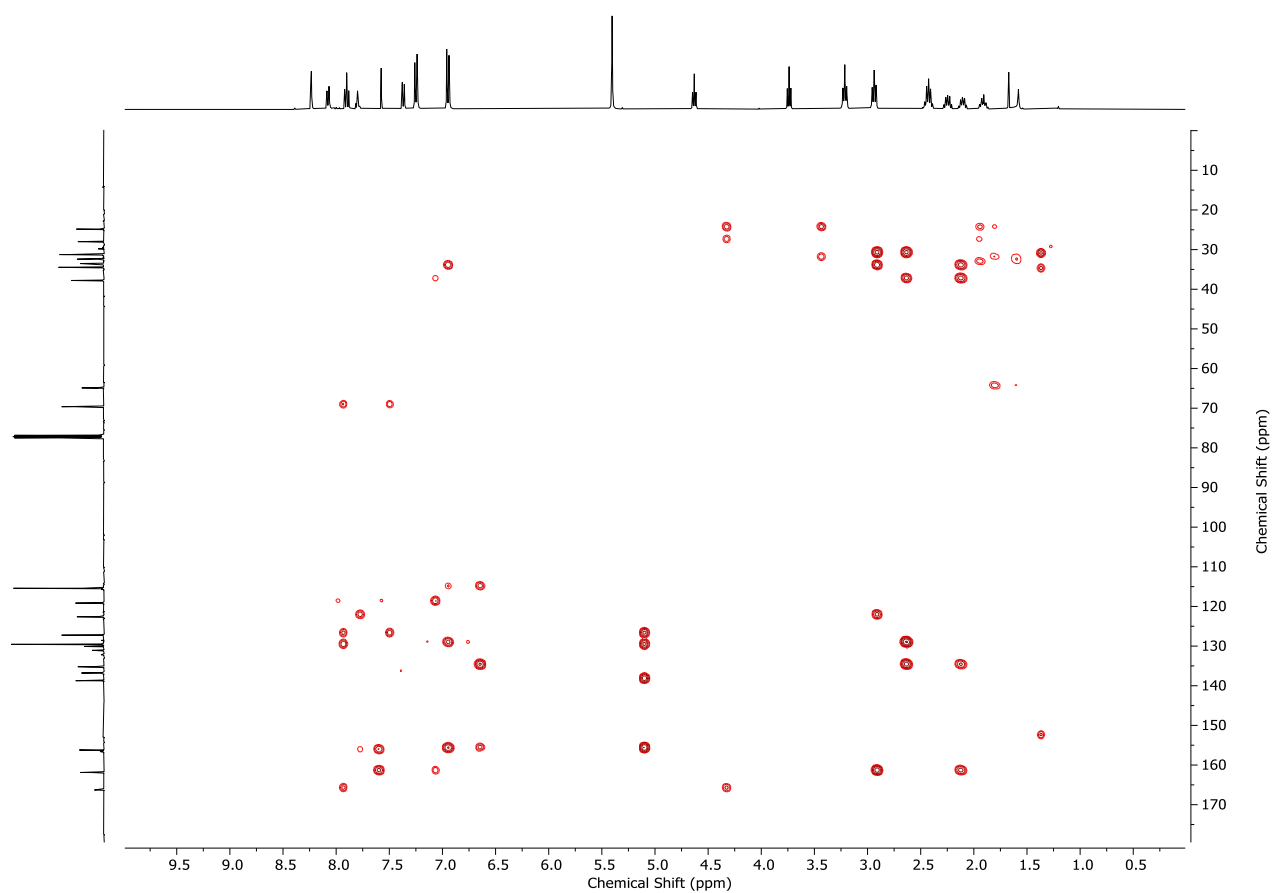


Figure S35. HMBC NMR (CDCl₃) of **6c**.

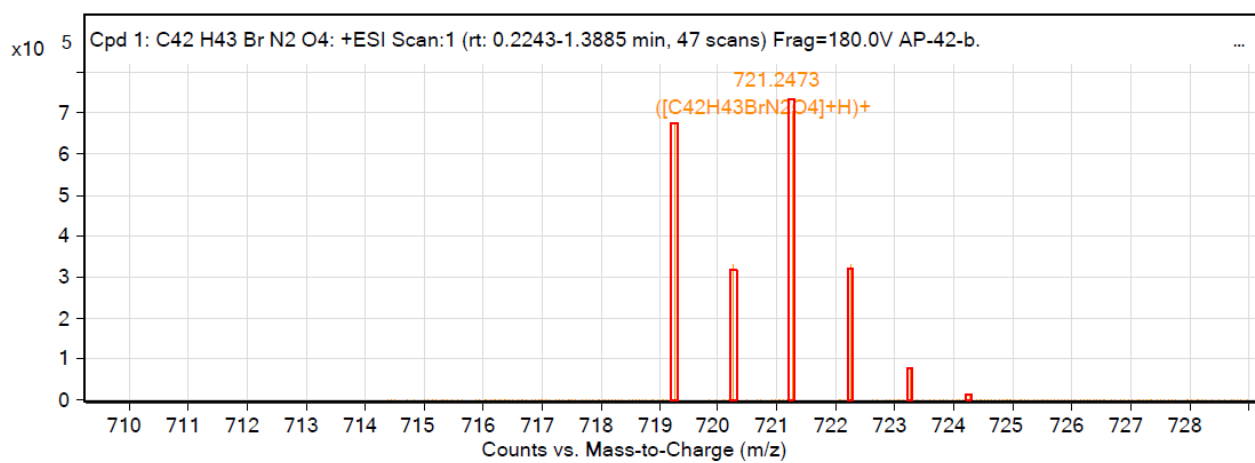
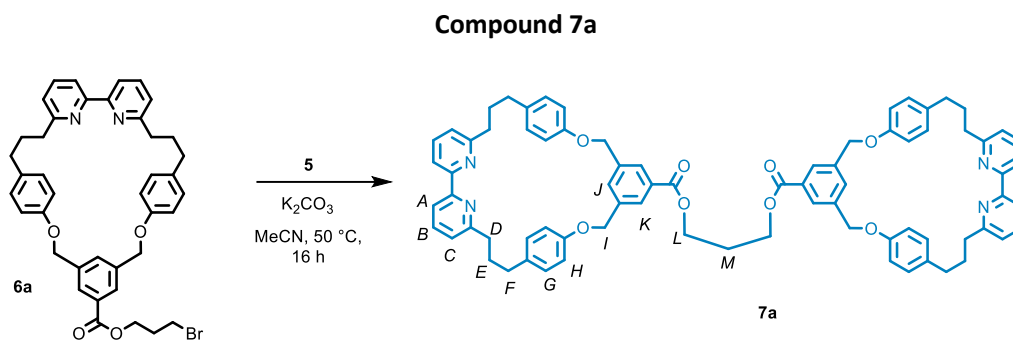


Figure S36. HRMS spectrum for **6c**.



To a solution of **6a** (30.0 mg, 0.04 mmol, 1.0 eq.) in CH_3CN (5.0 mL) were added K_2CO_3 (12.1 mg, 0.08 mmol, 2.0 eq.) and **5** (24.5 mg, 0.04 mmol, 1.0 eq.), and the reaction mixture was stirred at 50 °C for 16 h. After cooling to ambient temperature, the reaction mixture was filtered through Celite®, washing with CH_2Cl_2 , and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , n-Hexane-Acetone 0→35%) to yield **7a** (32.1 mg, 0.02 mmol, 68%) as a white foam.

1H NMR (500 MHz, $CDCl_3$) δ_H 7.91 (d, $J = 1.4$ Hz, 4H, H_K), 7.74 (d, $J = 7.7$ Hz, 4H, H_A), 7.59 (t, $J = 7.7$ Hz, 4H, H_B), 7.49 (t, $J = 1.4$ Hz, 2H, H_I), 7.04 (d, $J = 7.5$ Hz, 4H, H_C), 6.94 (d, $J = 8.4$ Hz, 8H, H_G), 6.62 (d, $J = 8.4$ Hz, 8H, H_H), 5.06 (s, 8H, H_L), 4.47 (t, $J = 5.8$ Hz, 4H, H_L), 2.90 (t, $J = 7.1$ Hz, 8H, H_D), 2.62 (t, $J = 7.1$ Hz, 8H, H_F), 2.24 (m, 2H, H_M), 2.11 (m, 8H, H_E).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 166.18, 161.90, 156.16, 138.74, 136.76, 135.16, 130.73, 130.18, 129.56, 127.24, 122.55, 119.16, 115.36, 69.50, 61.96, 37.79, 34.46, 31.26, 28.33.

HR-ESI-MS (+ve) $m/z = 1182.5441$ [$M+H$] $^+$ (calc. m/z for $C_{77}H_{72}N_4O_8$ 1182.5436).

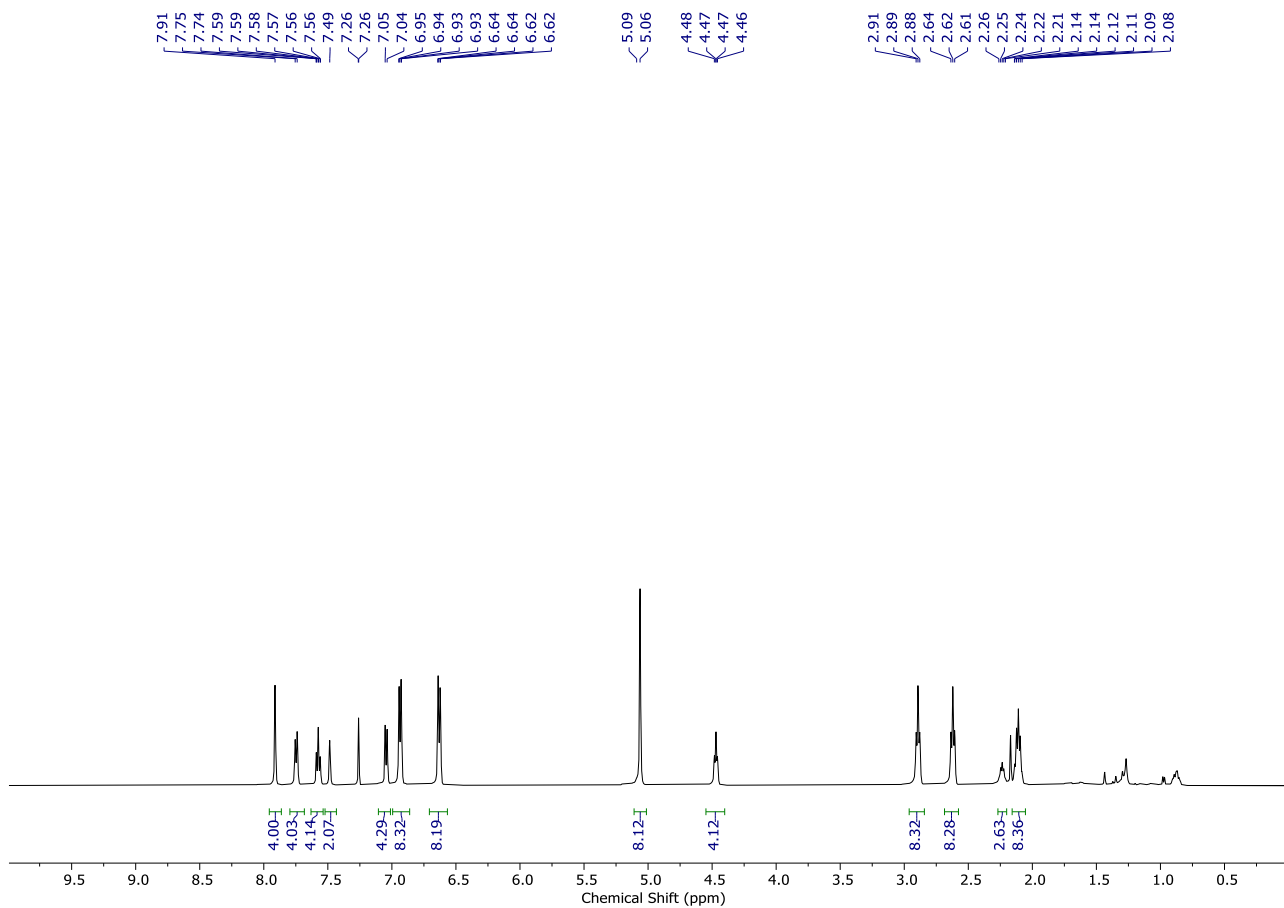


Figure S37. ^1H NMR (CDCl_3 , 500 MHz) of **7a**.

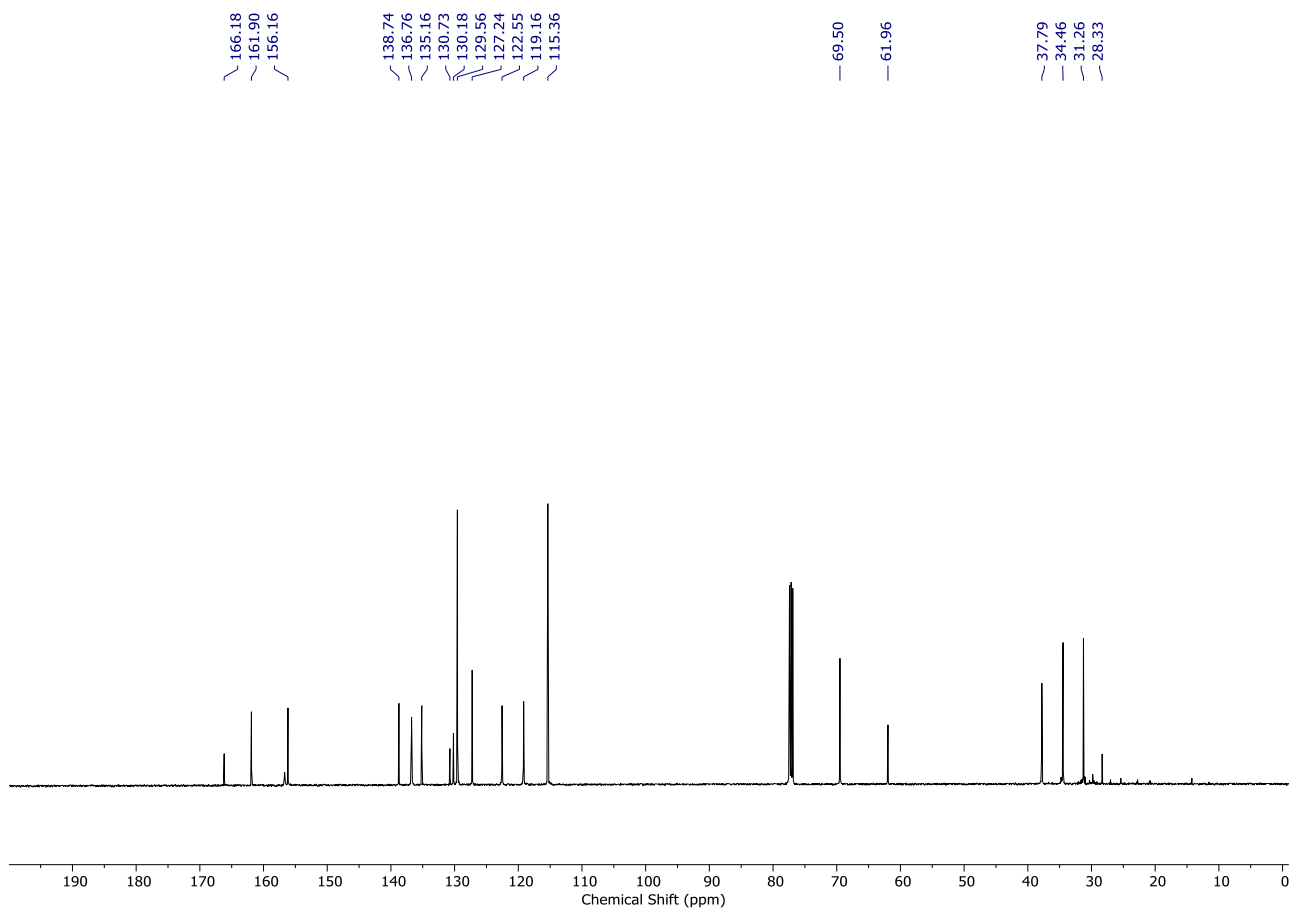


Figure S38. ^{13}C NMR (CDCl_3 , 126 MHz) of **7a**.

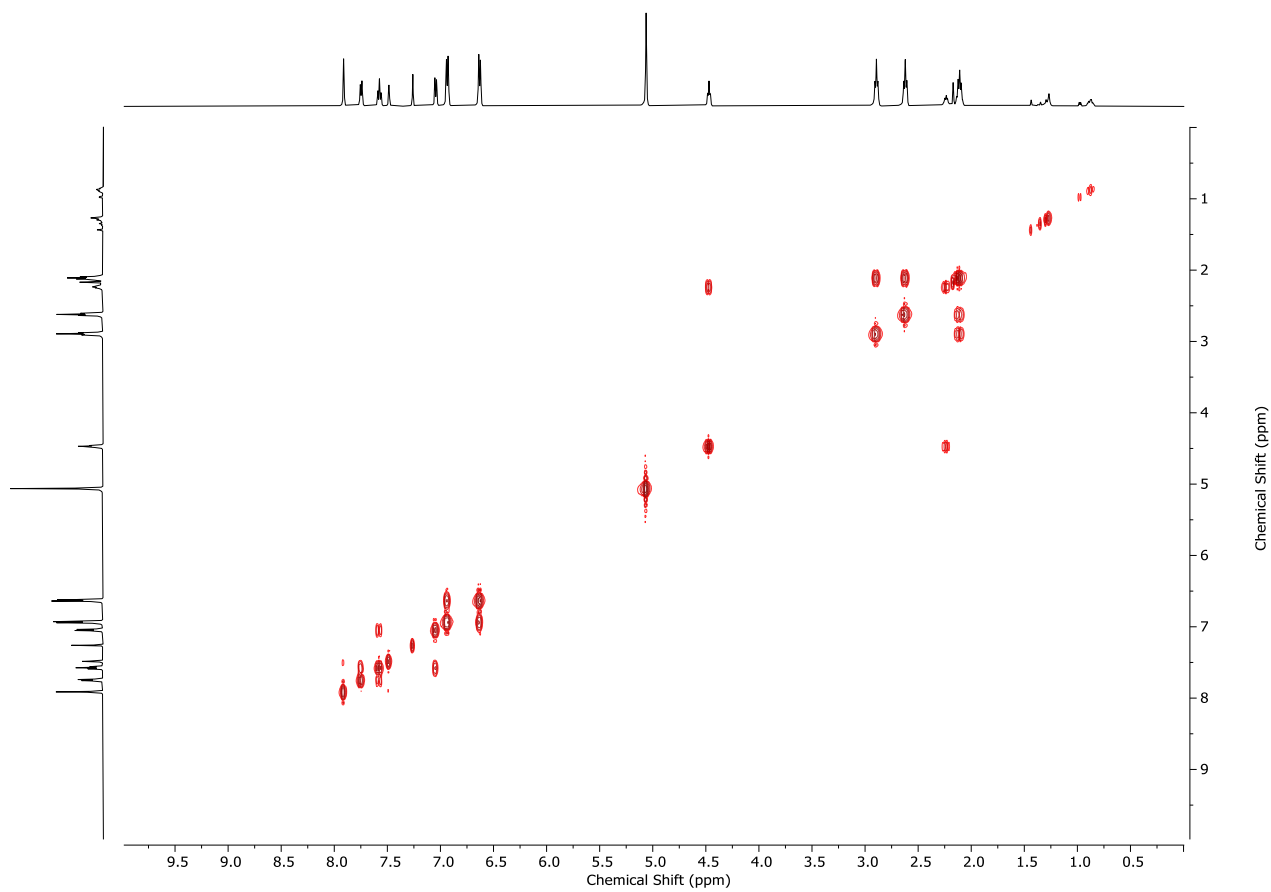


Figure S39. ^1H COSY NMR (CDCl_3) of **7a**.

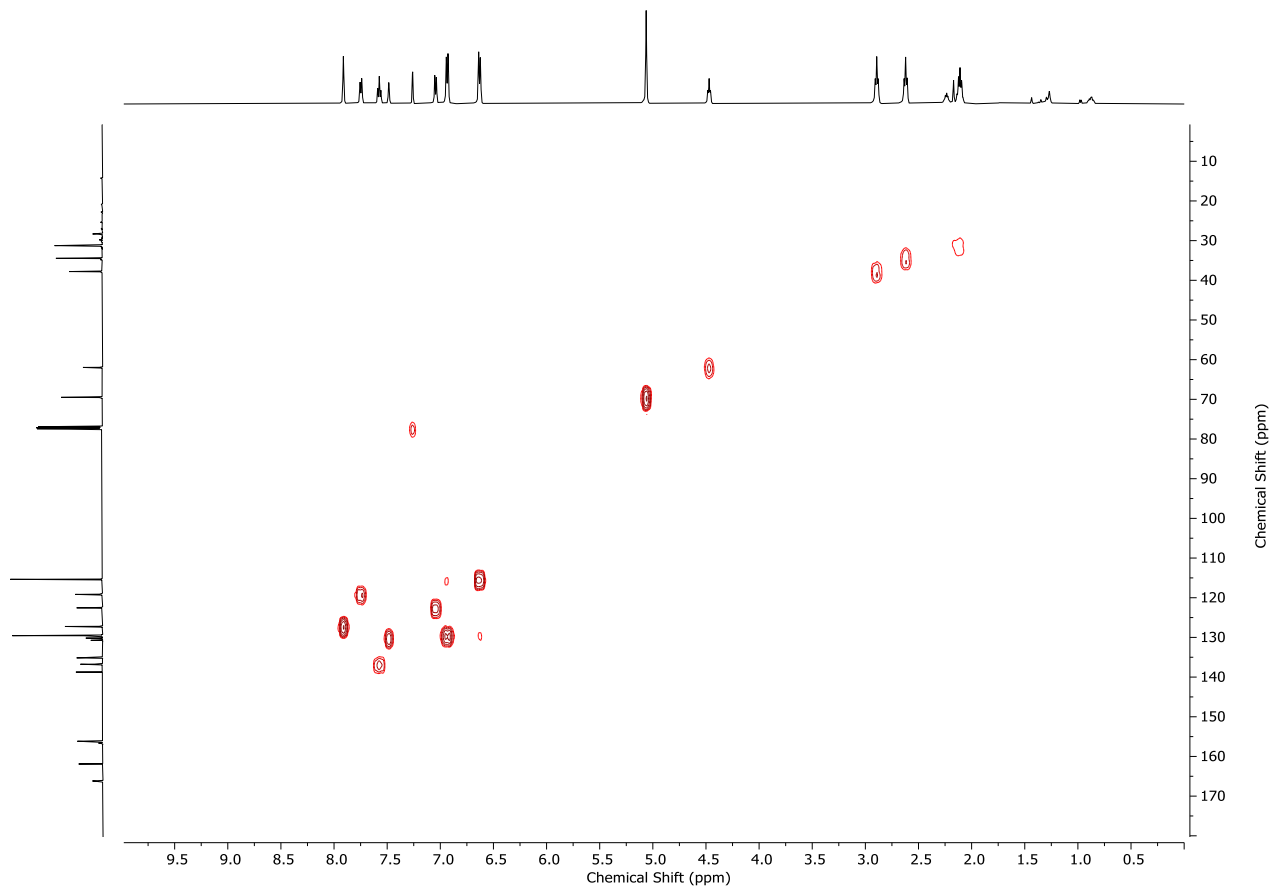


Figure S40. HMQC NMR (CDCl_3) of **7a**.

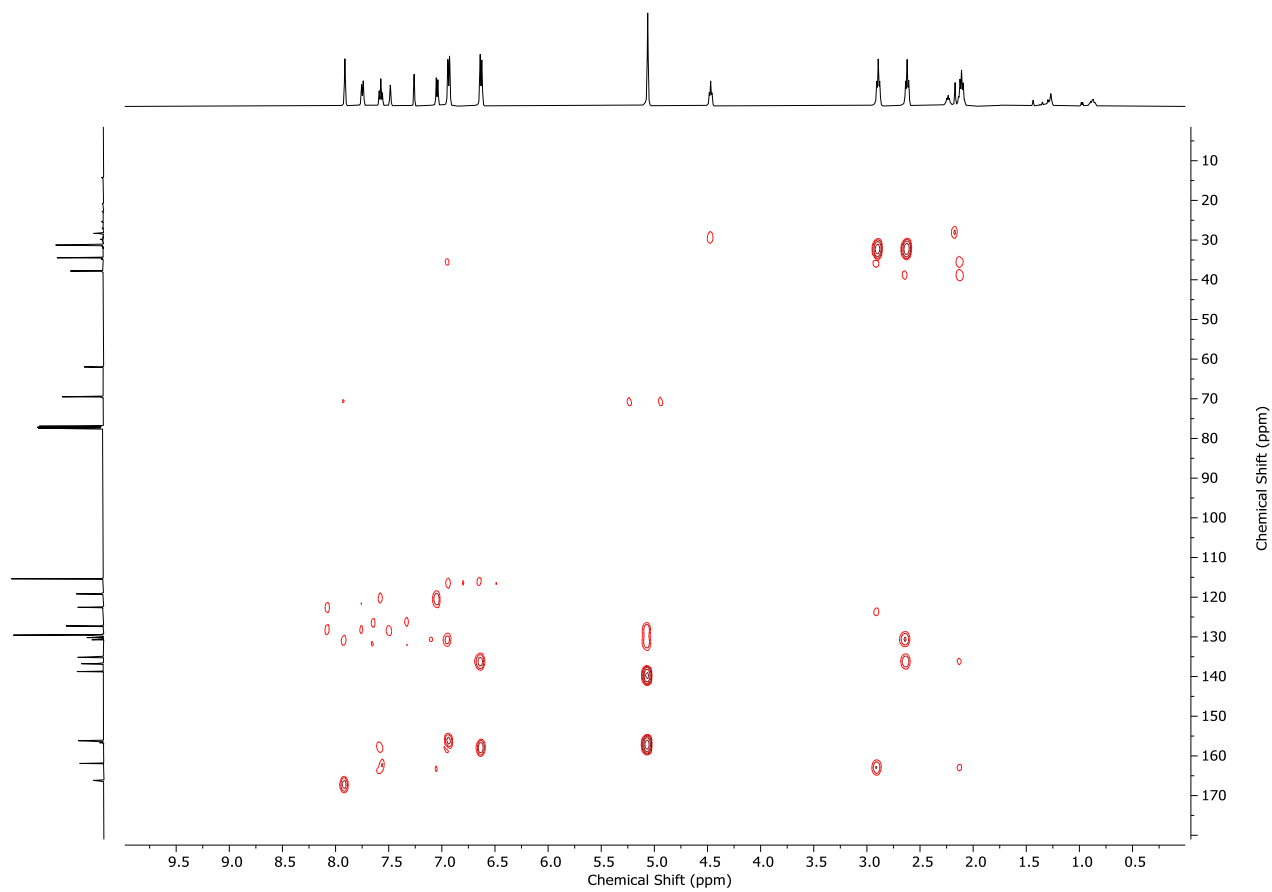


Figure S41. HMBC NMR (CDCl_3) of **7a**.

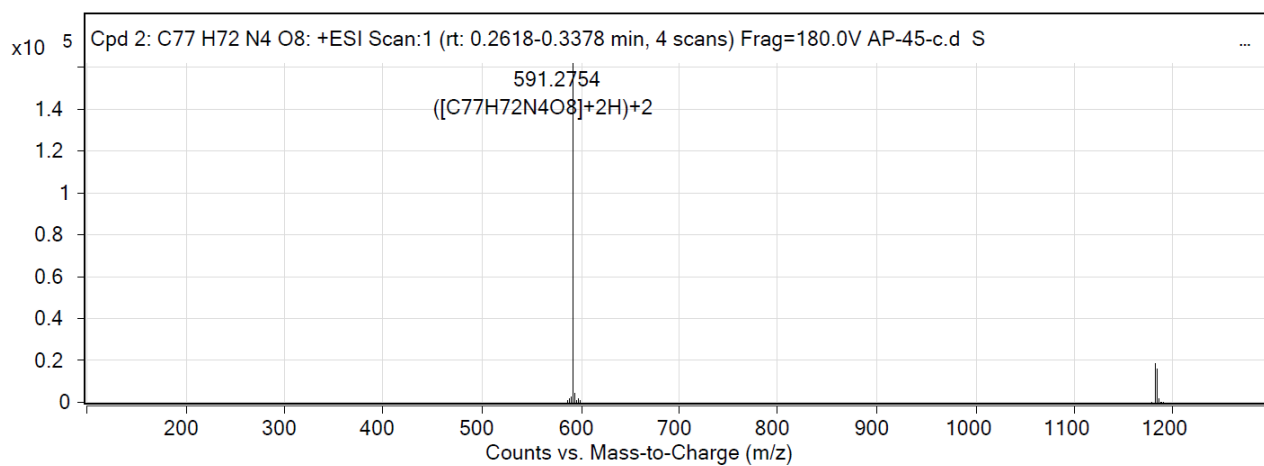
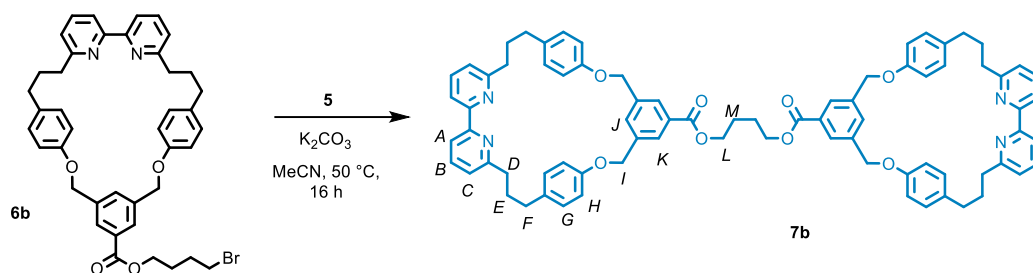


Figure S42. HRMS spectrum for **7a**.

Compound 7b



To a solution of **6b** (28.2 mg, 0.04 mmol, 1.0 eq.) in CH_3CN (5.0 mL) were added K_2CO_3 (12.1 mg, 0.08 mmol, 2.0 eq.) and **5** (24.5 mg, 0.04 mmol, 1.0 eq.), and the reaction mixture was stirred at 50 °C for 16 h. After cooling to ambient temperature, the reaction mixture was filtered through Celite®, washing with CH_2Cl_2 , and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , n-Hexane-Acetone 0→35%) to yield **7b** (36.3 mg, 0.03 mmol, 76%) as a yellow oil.

1H NMR (500 MHz, $CDCl_3$) δ_H 7.91 (d, $J = 1.4$ Hz, 4H, H_K), 7.75 (d, $J = 7.7$ Hz, 4H, H_A), 7.58 (t, $J = 7.7$ Hz, 4H, H_B), 7.49 (t, $J = 1.4$ Hz, 2H, H_J), 7.04 (d, $J = 7.5$ Hz, 4H, H_C), 6.93 (d, $J = 8.4$ Hz, 8H, H_G), 6.62 (d, $J = 8.4$ Hz, 8H, H_H), 5.07 (s, 8H, H_I), 4.38 (t, $J = 5.8$ Hz, 4H, H_L), 2.89 (t, $J = 7.1$ Hz, 8H, H_D), 2.61 (t, $J = 7.1$ Hz, 8H, H_F), 2.10 (m, 8H, H_E), 1.91 (t, $J = 5.8$ Hz, 4H, H_M).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 166.28, 161.91, 156.20, 138.74, 136.86, 135.17, 130.94, 130.13, 129.57, 127.25, 122.64, 119.25, 115.38, 69.55, 64.74, 37.75, 34.47, 31.27, 25.64.

HR-ESI-MS (+ve) $m/z = 1197.5625$ [$M+H$] $^+$ (calc. m/z for $C_{78}H_{74}N_4O_8$ 1197.5619).

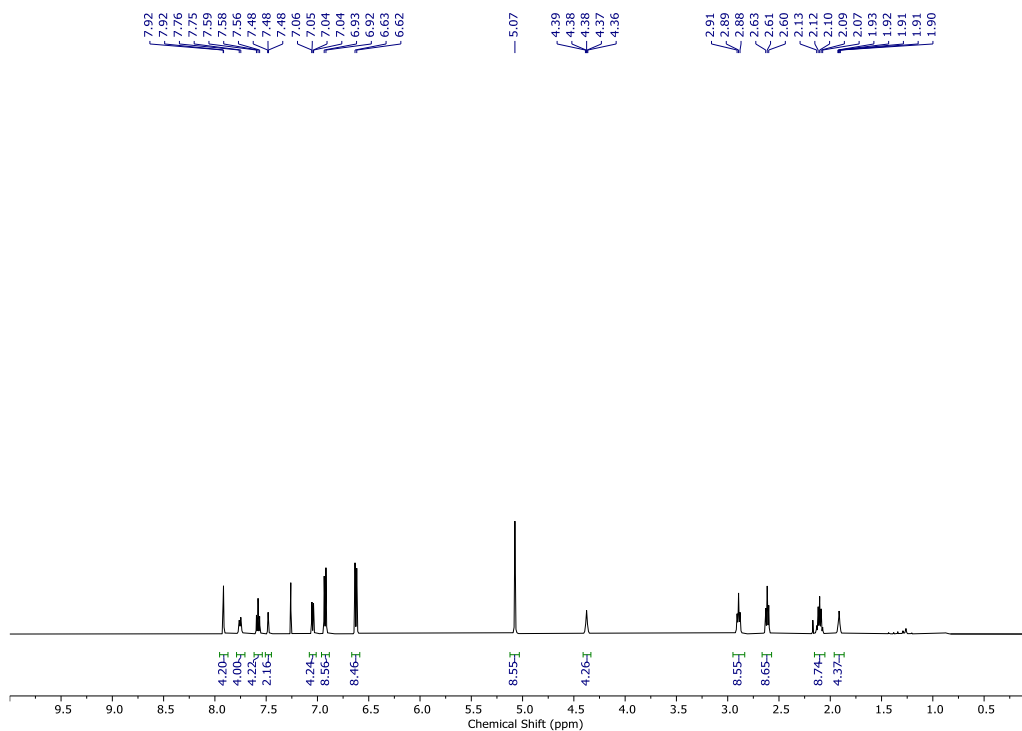


Figure S43. ^1H NMR (CDCl_3 , 500 MHz) of **10b**.

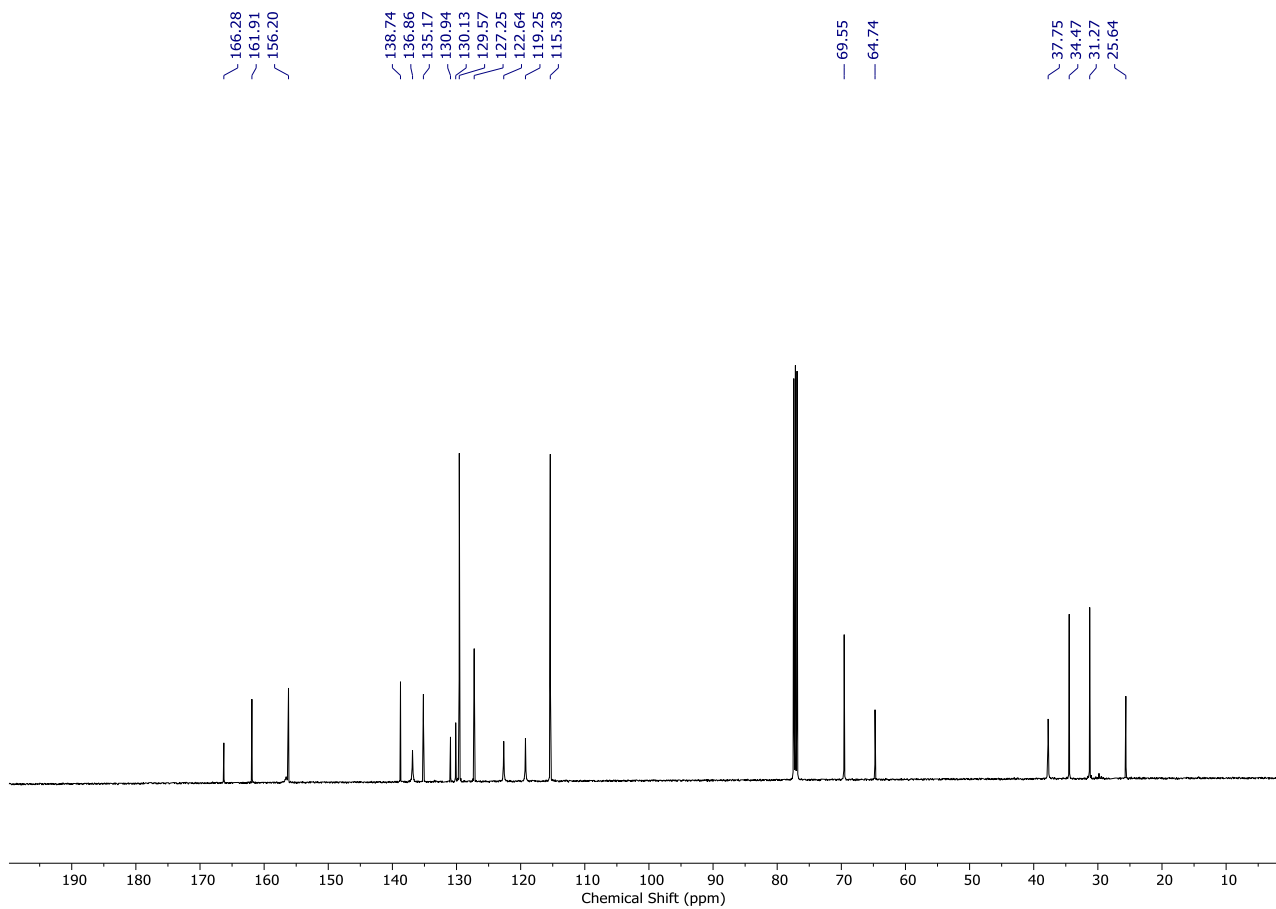


Figure S44. ^{13}C NMR NMR (CDCl_3 , 126 MHz) of **10b**.

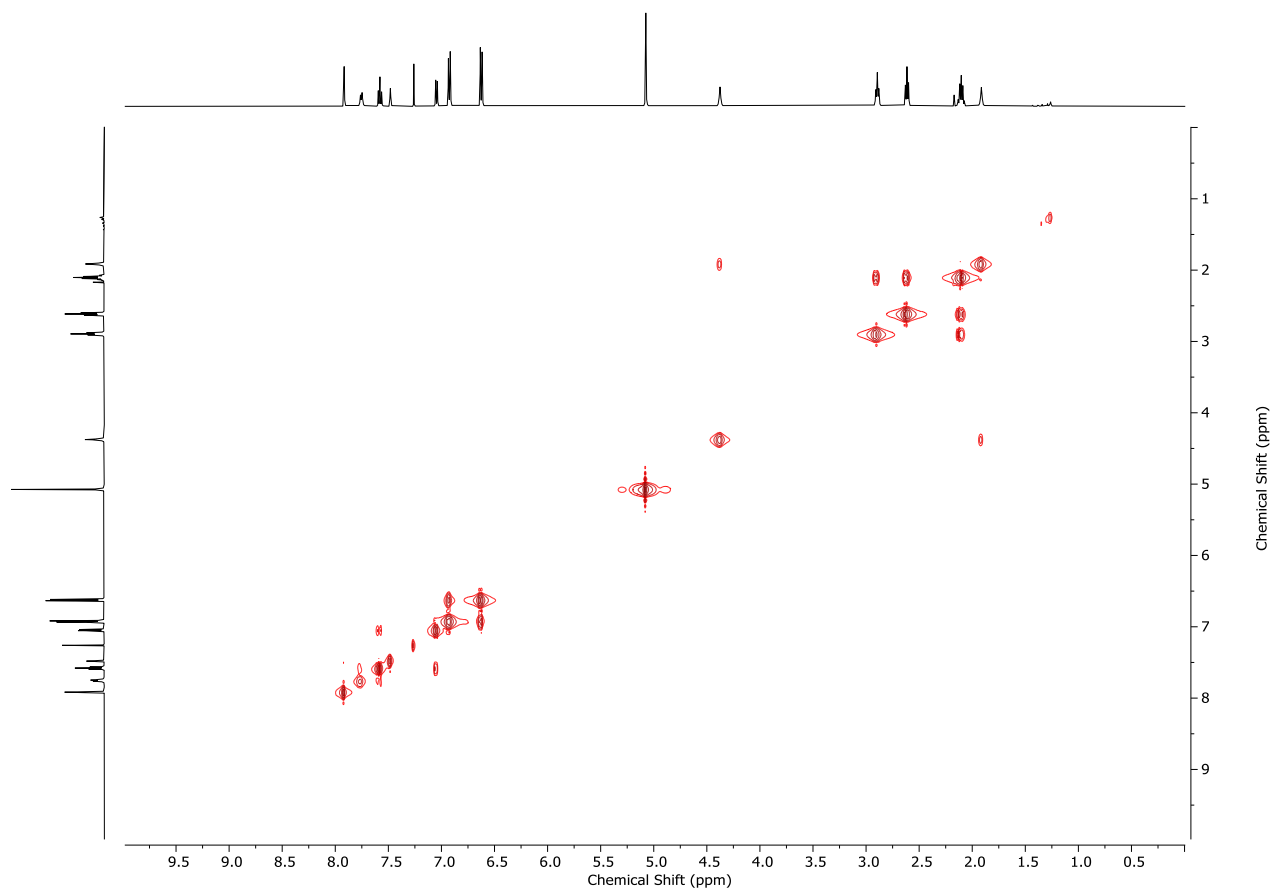


Figure S45. ^1H COSY NMR (CDCl_3) of **10b**.

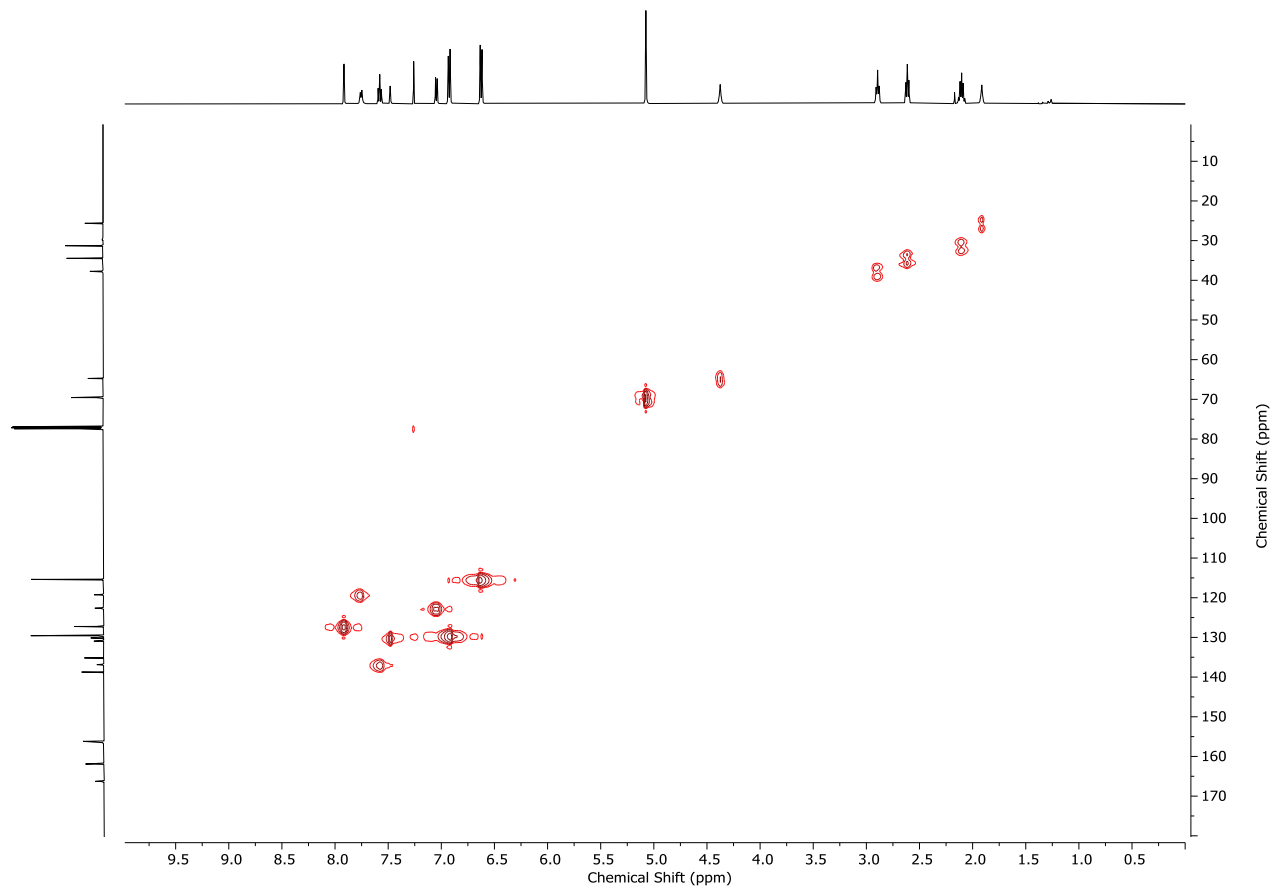


Figure S46. HMBC NMR (CDCl_3) of **10b**.

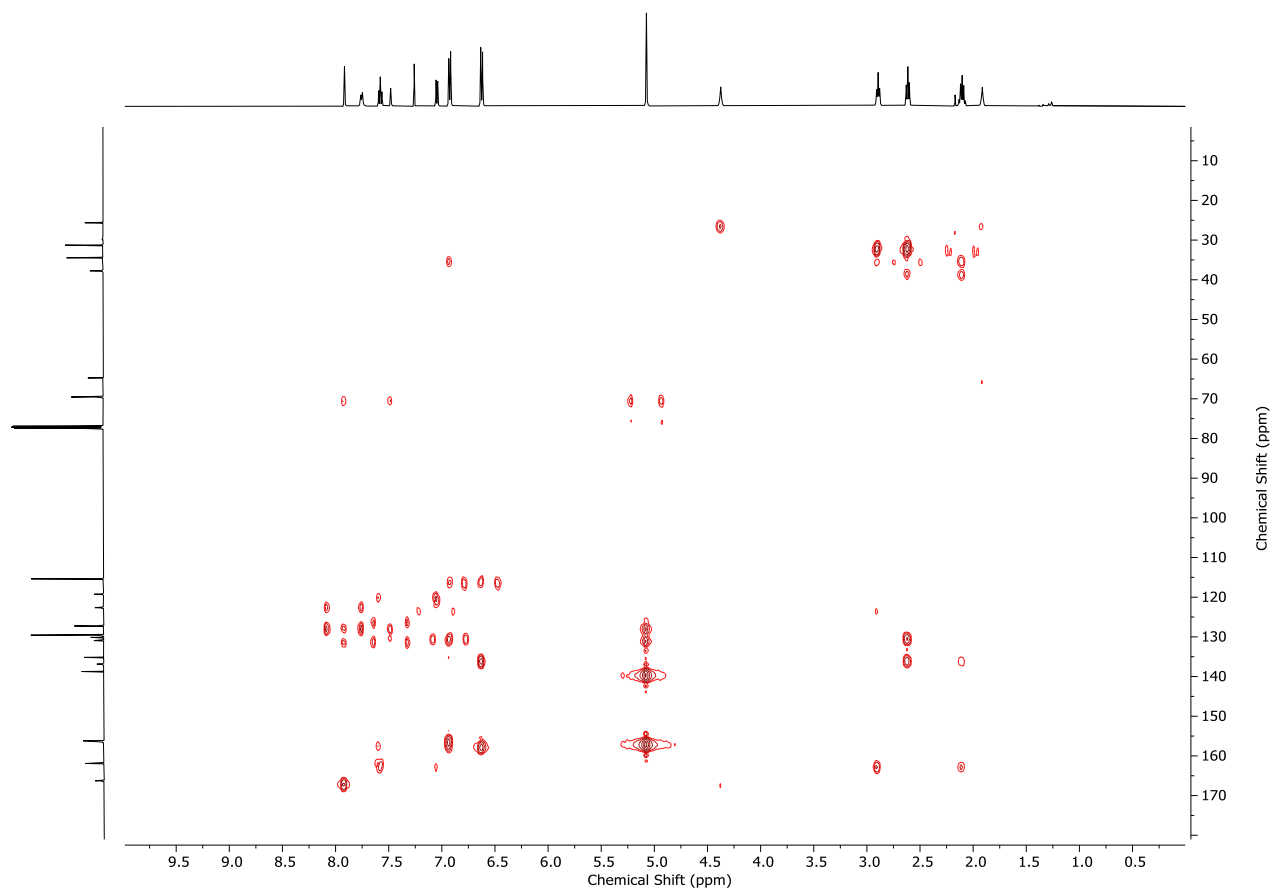


Figure S47. HMBC NMR (CDCl_3) of **10b**.

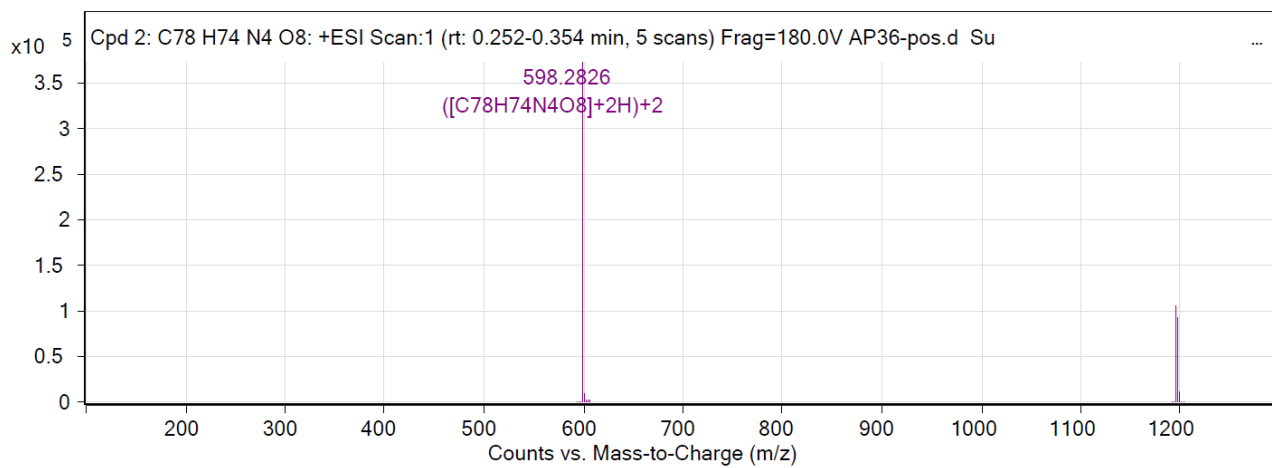
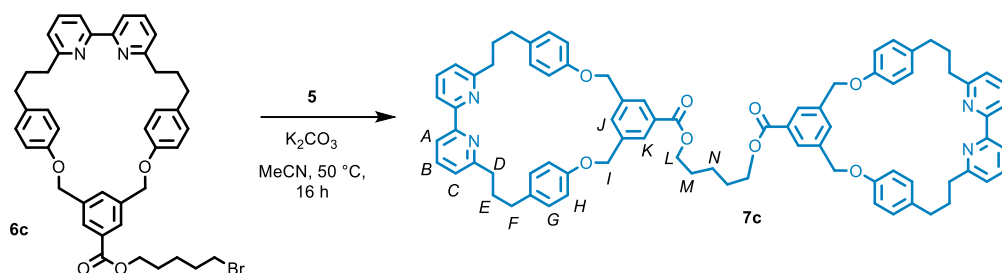


Figure S48. HRMS spectrum for **10b**.

Compound 7c



To a solution of **6c** (34.0 mg, 0.04 mmol, 1.0 eq.) in CH_3CN (5.0 mL) were added K_2CO_3 (12.1 mg, 0.08 mmol, 2.0 eq.) and **5** (24.5 mg, 0.04 mmol, 1.0 eq.), and the reaction mixture was stirred at 50 °C for 16 h. After cooling to ambient temperature, the reaction mixture was filtered through Celite®, washing with CH_2Cl_2 , and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , n-Hexane-Acetone 0→35%) to yield **7c** (31.4 mg, 0.02 mmol, 65%) as a white foam.

1H NMR (500 MHz, $CDCl_3$) δ_H 7.91 (d, $J = 1.4$ Hz, 4H, H_K), 7.73 (d, $J = 7.7$ Hz, 4H, H_A), 7.57 (t, $J = 7.7$ Hz, 4H, H_B), 7.48 (t, $J = 1.4$ Hz, 2H, H_J), 7.05 (d, $J = 7.5$ Hz, 4H, H_C), 6.92 (d, $J = 8.4$ Hz, 8H, H_G), 6.62 (d, $J = 8.4$ Hz, 8H, H_H), 5.07 (s, 8H, H_I), 4.33 (t, $J = 5.8$ Hz, 4H, H_L), 2.88 (t, $J = 7.1$ Hz, 8H, H_D), 2.62 (t, $J = 7.1$ Hz, 8H, H_F), 2.11 (m, 8H, H_E), 1.84 (m, 4H, H_M), 1.57 (m, 2H, H_N).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 166.34, 161.93, 156.86, 156.21, 138.73, 136.70, 135.18, 131.06, 130.06, 129.57, 127.21, 122.51, 119.12, 115.38, 69.57, 65.02, 37.87, 34.49, 31.29, 28.51, 22.75.

HR-ESI-MS (+ve) $m/z = 1209.5718$ $[M+H]^+$ (calc. m/z for $C_{79}H_{76}N_4O_8$ 1209.5711).

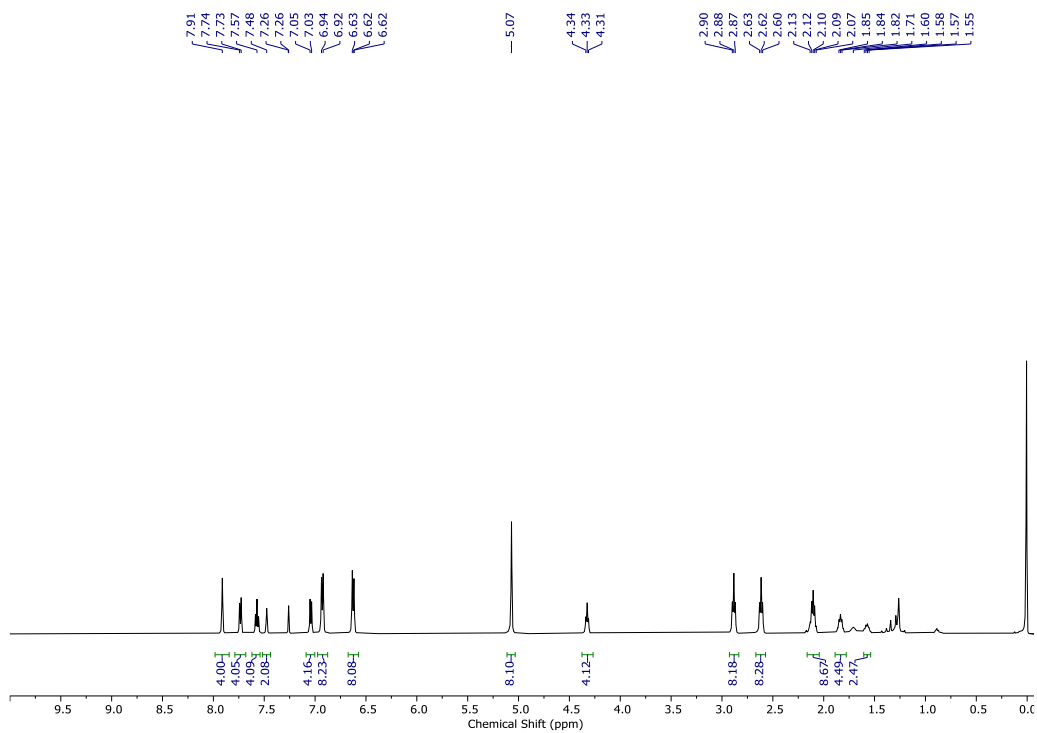


Figure S49. ^1H NMR (CDCl_3 , 500 MHz) of **7c**.

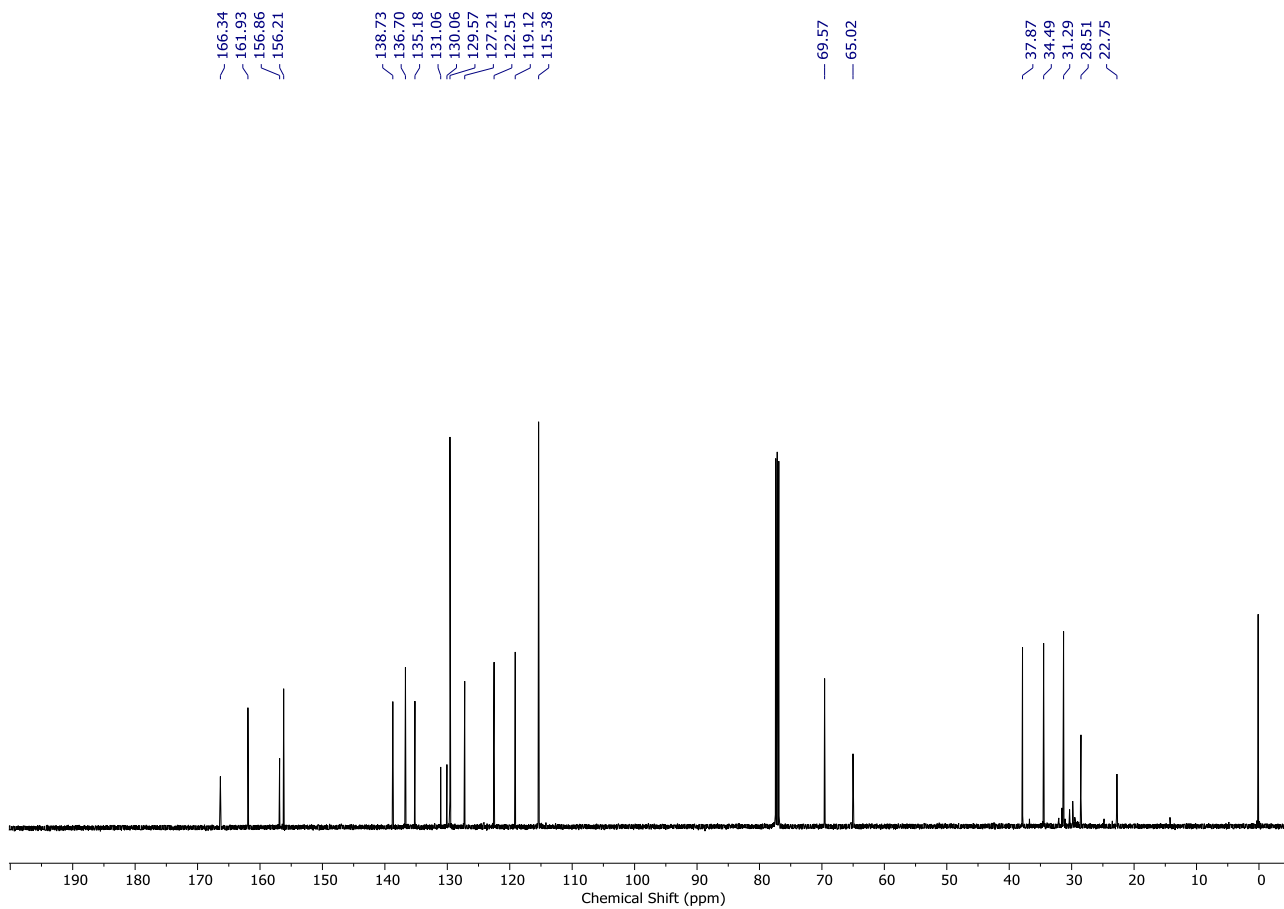


Figure S50. ^{13}C NMR (CDCl_3 , 126 MHz) of **7c**.

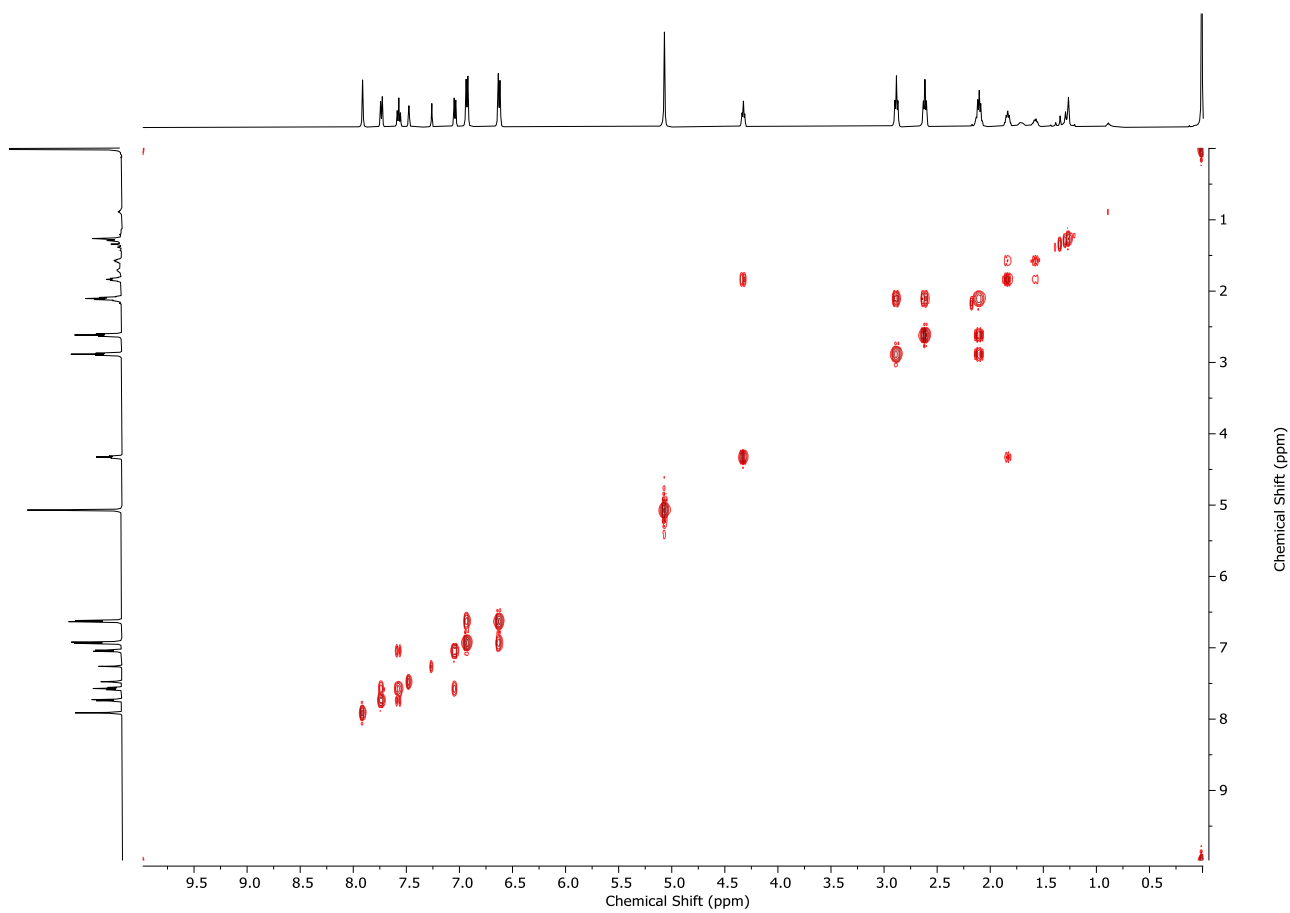


Figure S51. ^1H COSY NMR (CDCl_3) of **7c**.

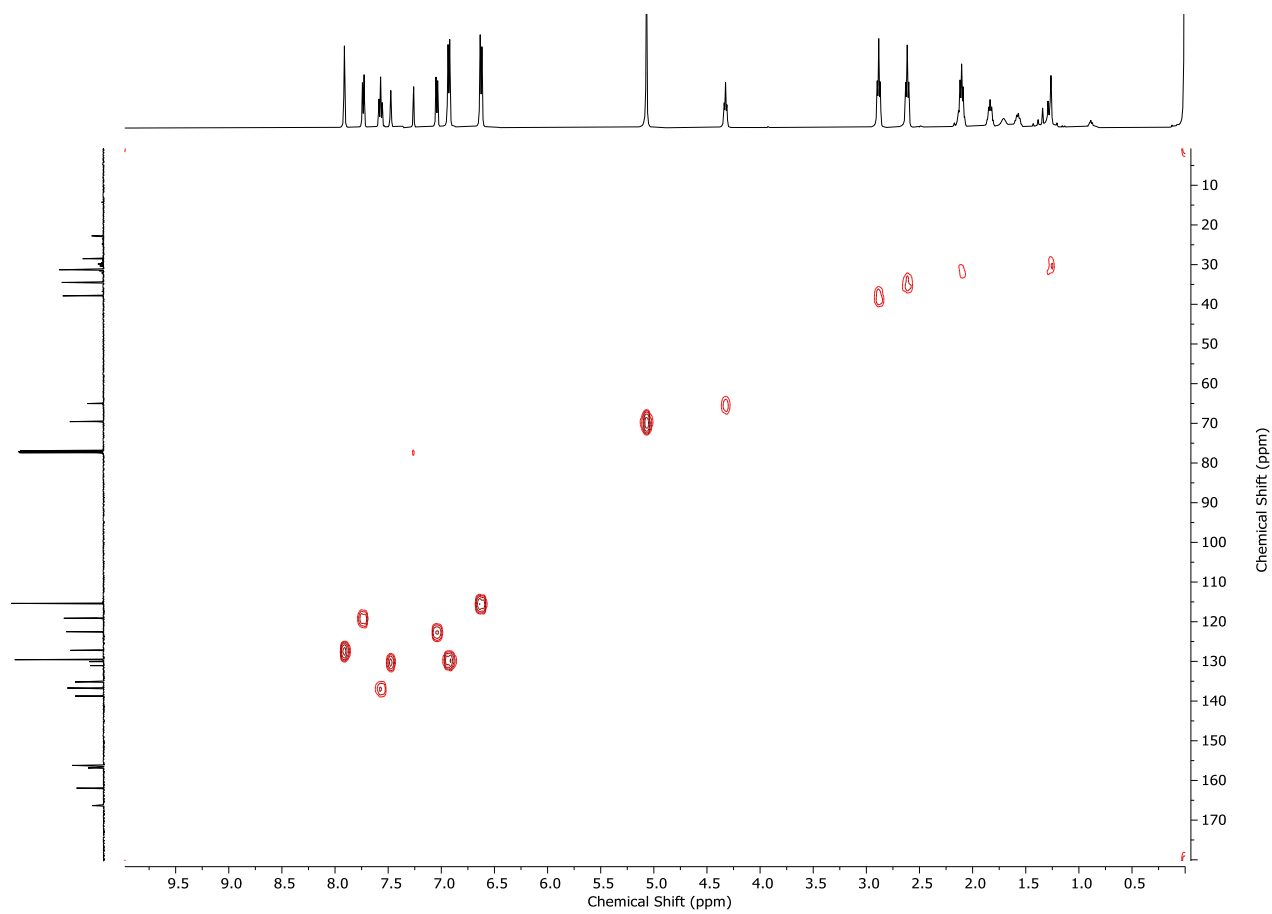


Figure S52. HMQC NMR (CDCl_3) of **7c**.

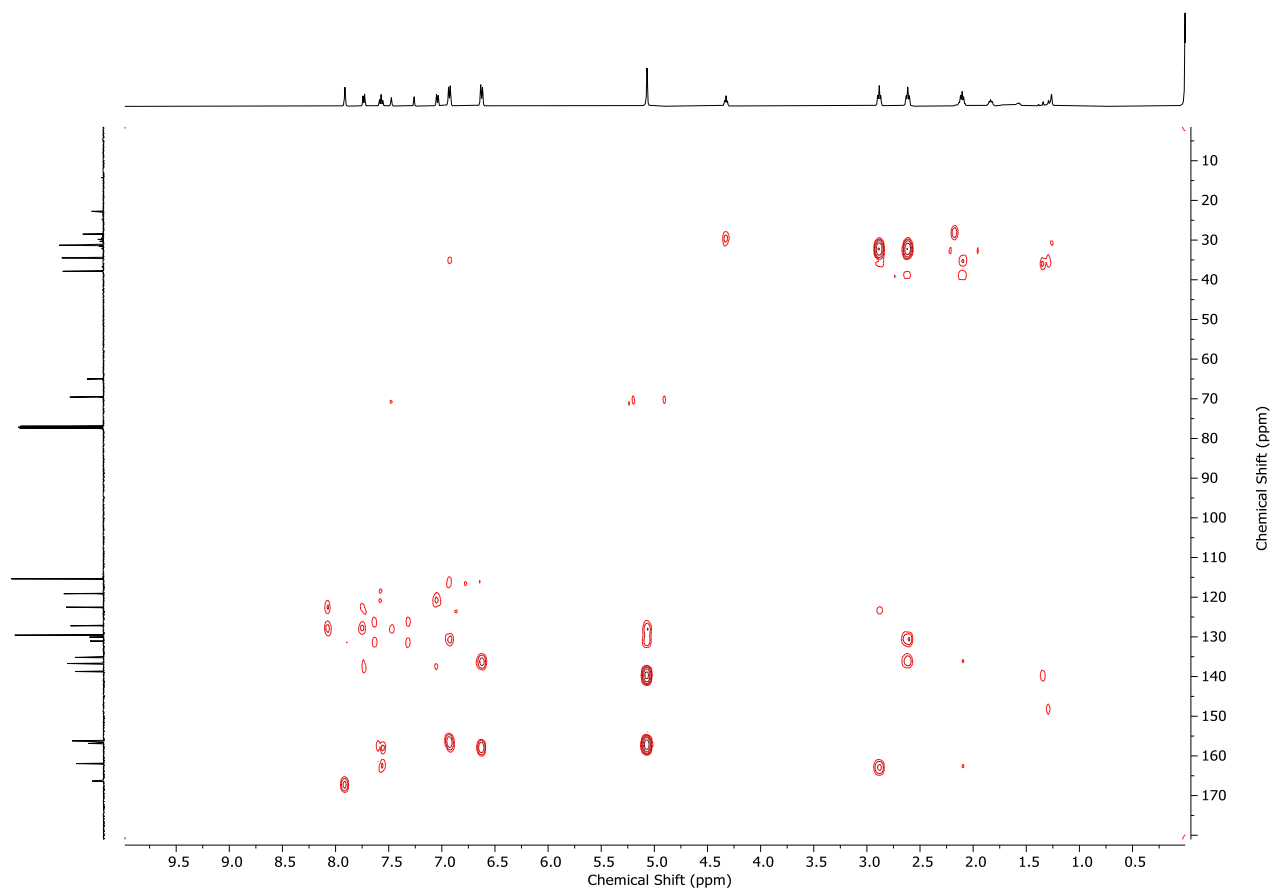


Figure S53. HMBC NMR (CDCl₃) of **7c**.

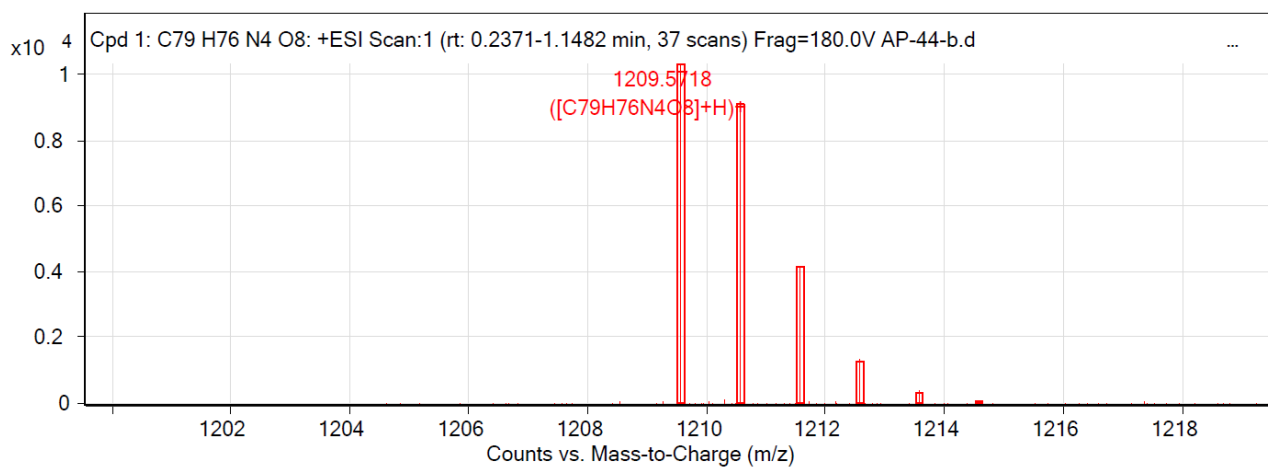
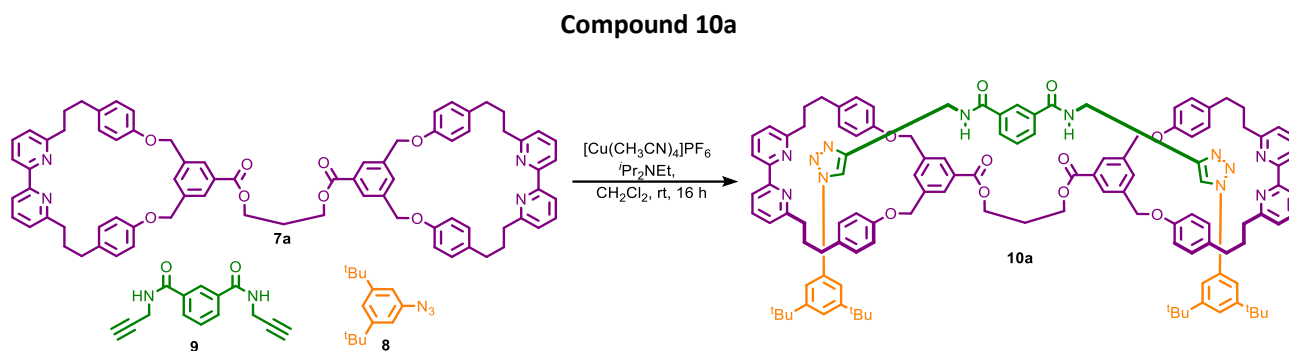
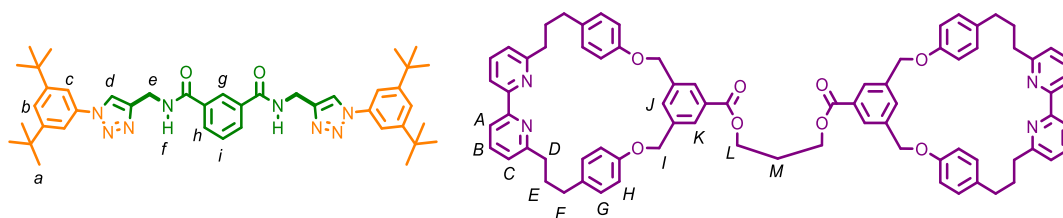


Figure S54. HRMS spectrum for **7c**.

3. Synthesis of the (2)handcuff [2]rotaxanes 10a-c



In a CEM vial were added **7a** (23.6 mg, 0.02 mmol, 1.0 eq.), **8** (9.21 mg, 0.04 mmol, 2.0 eq.), **9** (9.63 mg, 0.02 mmol, 1.0 eq.) and $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (14.8 mg, 0.04 mmol, 2.0 eq.). The vial was sealed and purged with N_2 , then CH_2Cl_2 was added (4.0 mL), followed by $i\text{Pr}_2\text{NEt}$ (14.2 μL , 0.08 mmol, 4.0 eq.). The solution was stirred at rt for 16 h. The crude mixture was diluted with CH_2Cl_2 (5 mL) and EDTA-NH_3 (10 mL) was added, and the resulting mixture was stirred vigorously for until colourless. The organic phase was separated, and the aqueous phase was then extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic extracts were washed with brine (10 mL), dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , CH_2Cl_2 - CH_3CN 0 \rightarrow 40%) to yield **10a** (22.9 mg, 0.012 mmol, 61%) as a yellow oil.



^1H NMR (500 MHz, CDCl_3) δ_{H} 9.00 (s, 1H, H_{g}), 8.69 (t, $J = 5.7$ Hz, 2H, H_{f}), 8.15 (s, 1H, H_{i}), 8.05 (s, 2H, H_{d}), 7.90 (dd, $J = 7.7, 1.7$ Hz, 2H, H_{h}), 7.73 (d, $J = 1.4$ Hz, 2H, H_{k}), 7.64 (d, $J = 1.4$ Hz, 2H, H_{k}), 7.57 (t, $J = 7.7$ Hz, 4H, H_{b}), 7.49-7.44 (m, 8H, H_{A} , H_{B} , $\text{H}_{\text{A}'}$, H_{C}), 7.36 (d, $J = 1.4$ Hz, 4H, H_{c}), 7.27 (s, 1H, H_{j}), 7.05 (d, $J = 1.4$ Hz, 2H, H_{b}), 6.93 (d, $J = 8.4$ Hz, 6H, H_{G} , H_{H}), 6.62 (m, $J = 8$ Hz, $\text{H}_{\text{H}'}$, $\text{H}_{\text{G}'}$), 6.55 (d, $J = 8.4$ Hz, 4H, H_{H}), 5.22 (s, 4H, $\text{H}_{\text{I}'}$), 5.06 (s, 4H, H_{I}), 4.46 (t, $J = 5.8$ Hz, 4H, H_{L}), 4.12 (d, $J = 5.3$ Hz, 4H, H_{E}), 2.88 (t, $J = 7.1$ Hz, 4H, H_{D}), 2.62 (t, $J = 7.1$ Hz, 4H, H_{F}), 2.29-2.21 (m, 14H, $\text{H}_{\text{E}'}$, H_{M} , $\text{H}_{\text{D}'}$, $\text{H}_{\text{F}'}$), 2.09 (m, 4H, H_{E}), 1.36 (s, 36H, H_{a}).

^{13}C NMR (126 MHz, CDCl_3) δ : 166.25, 162.81, 161.91, 156.59, 156.54, 156.19, 152.85, 145.62, 139.10, 138.76, 137.70, 136.87, 136.75, 135.16, 133.05, 132.67, 131.68, 131.42, 130.77, 130.19, 129.57, 129.19, 129.02, 128.24, 127.97, 127.27, 126.05, 122.80, 122.55, 122.35, 120.71, 120.68, 119.16, 115.38, 115.18, 114.82, 69.53, 69.18, 62.01, 37.81, 36.68, 35.29, 34.48, 31.49, 31.33, 31.27.

HR-ESI-MS (+ve) $m/z = 1884.9816$ $[\text{M}+\text{H}]^+$ (calc. m/z for $\text{C}_{119}\text{H}_{126}\text{N}_{12}\text{O}_{10}$ 1884.9811).

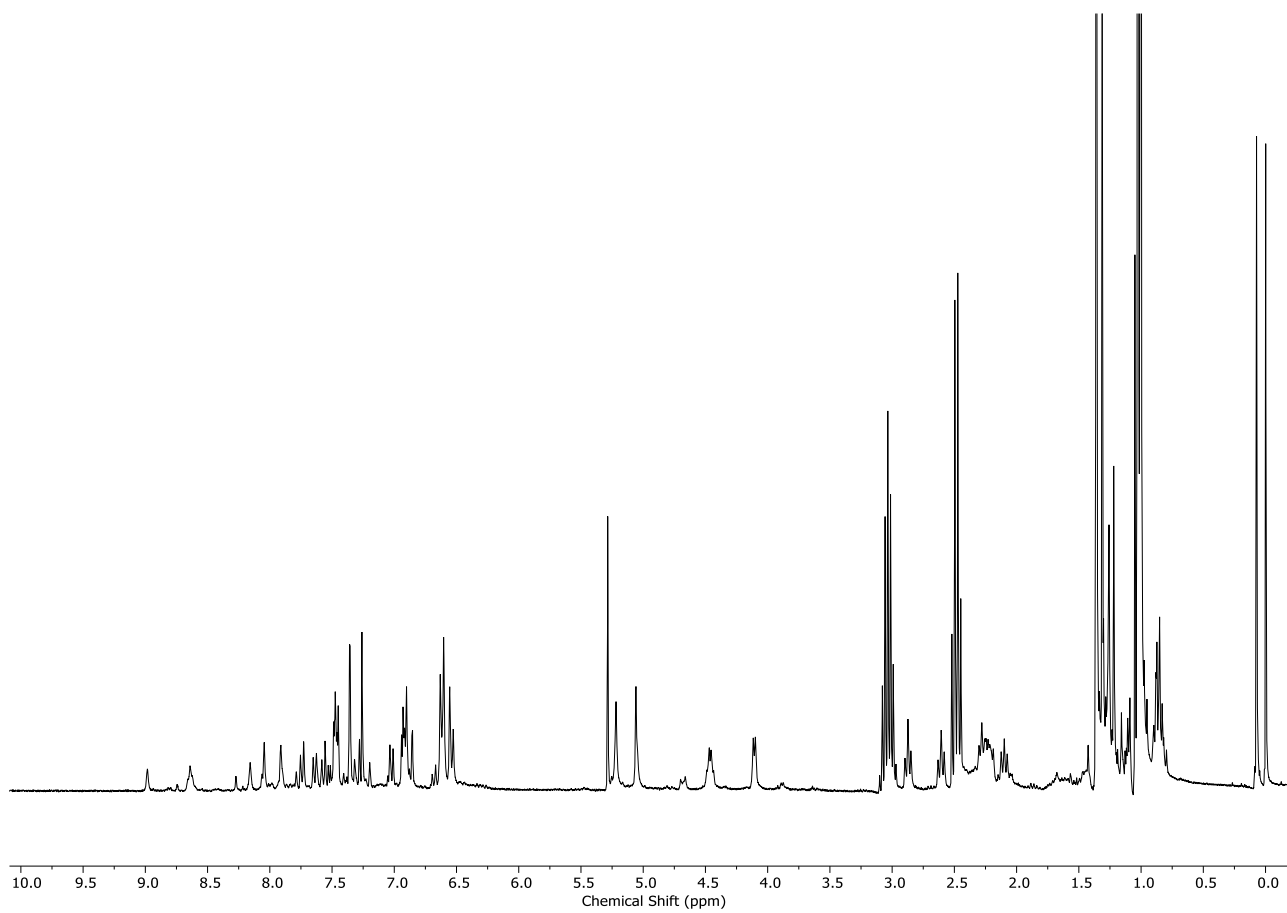


Figure S55. ^1H NMR (CDCl_3 , 400 MHz, 298 K) of **10a** prior to purification.

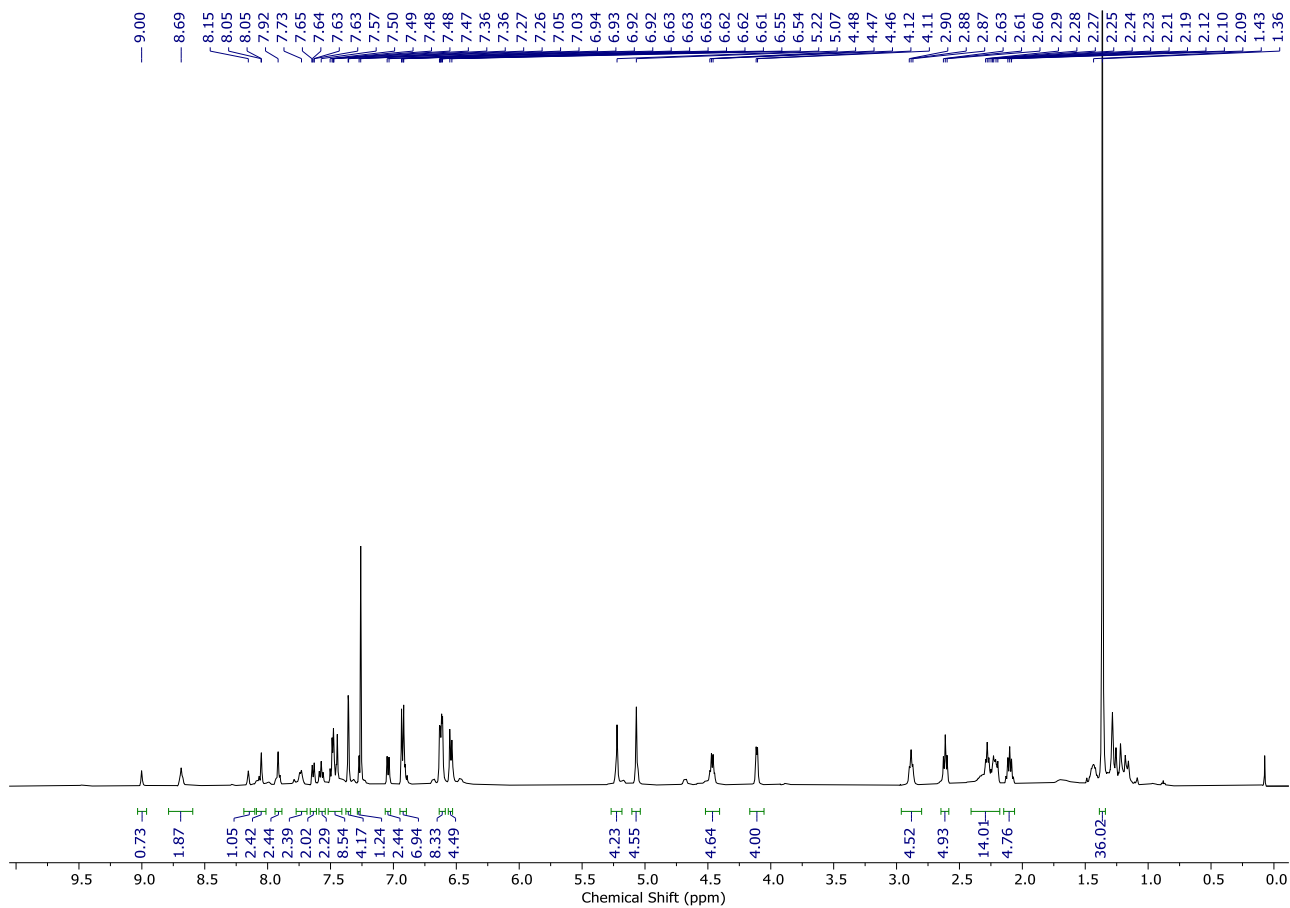


Figure S56. ^1H NMR (CDCl_3 , 500 MHz) of **10a**.

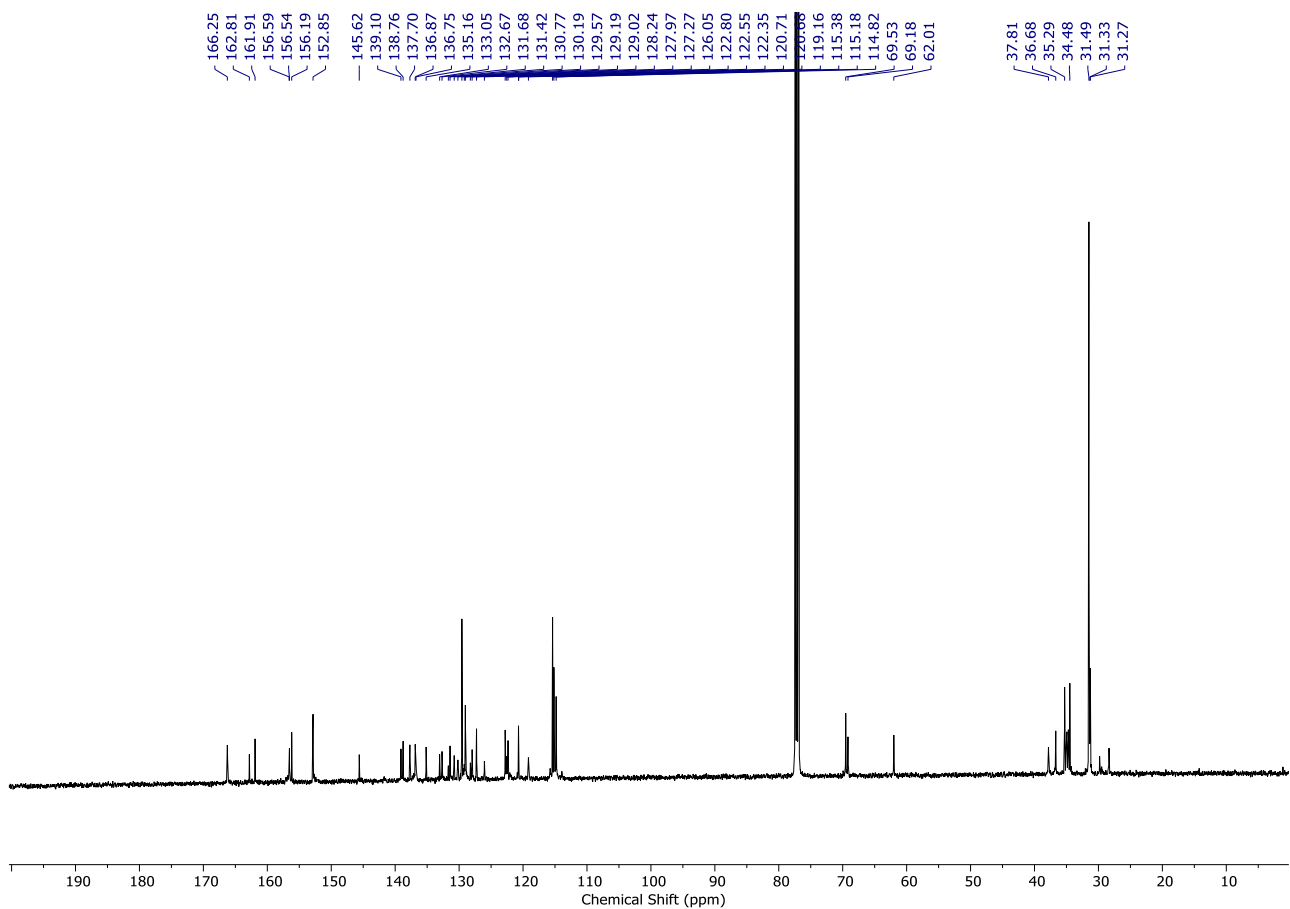


Figure S57. ^{13}C NMR (CDCl_3 , 126 MHz) of **10a**.

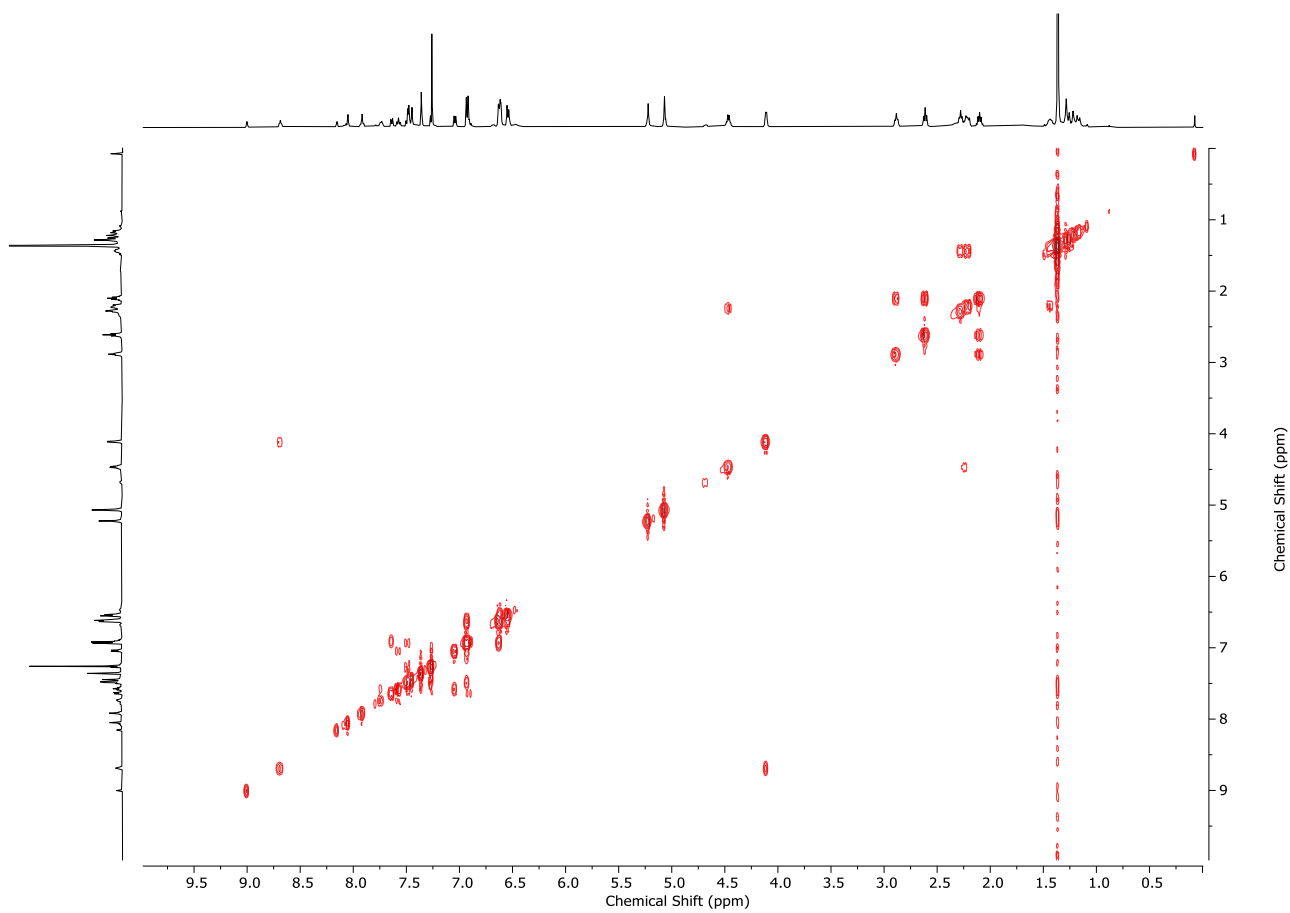


Figure S58. COSY NMR (CDCl₃) of **10a**.

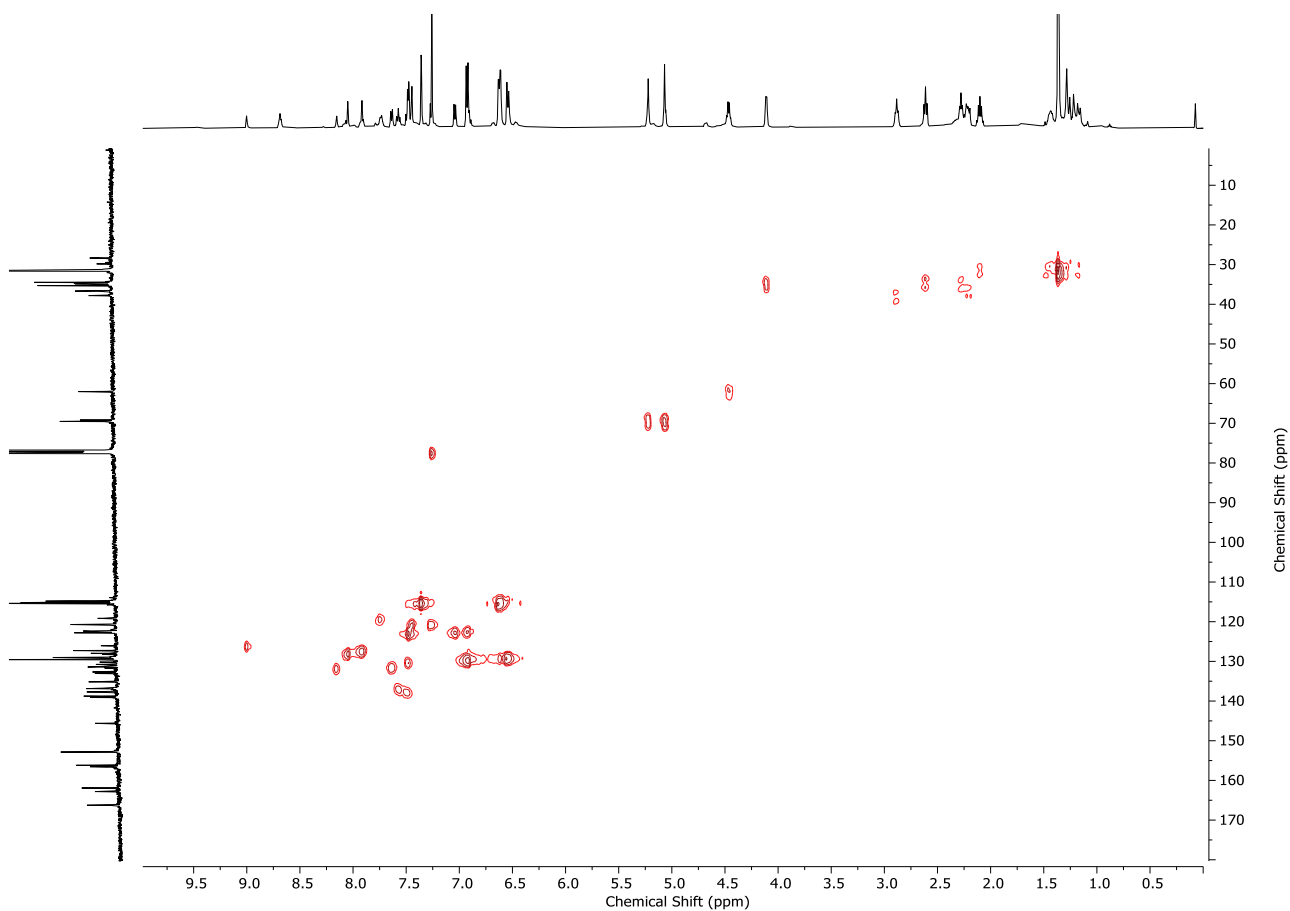


Figure S59. HMQC NMR (CDCl₃) of **10a**.

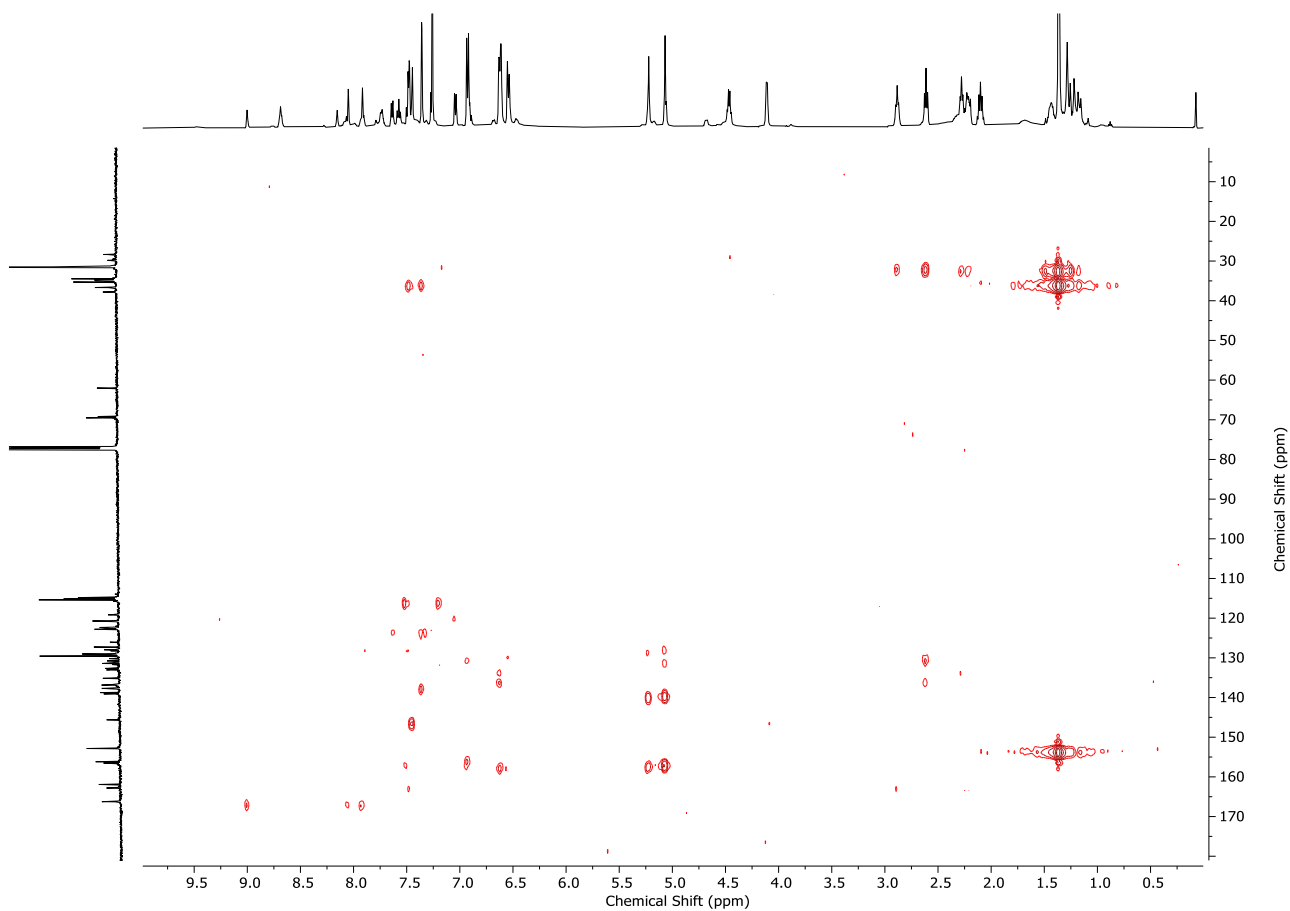


Figure S60. HMBC NMR (CDCl_3) of **10a**.

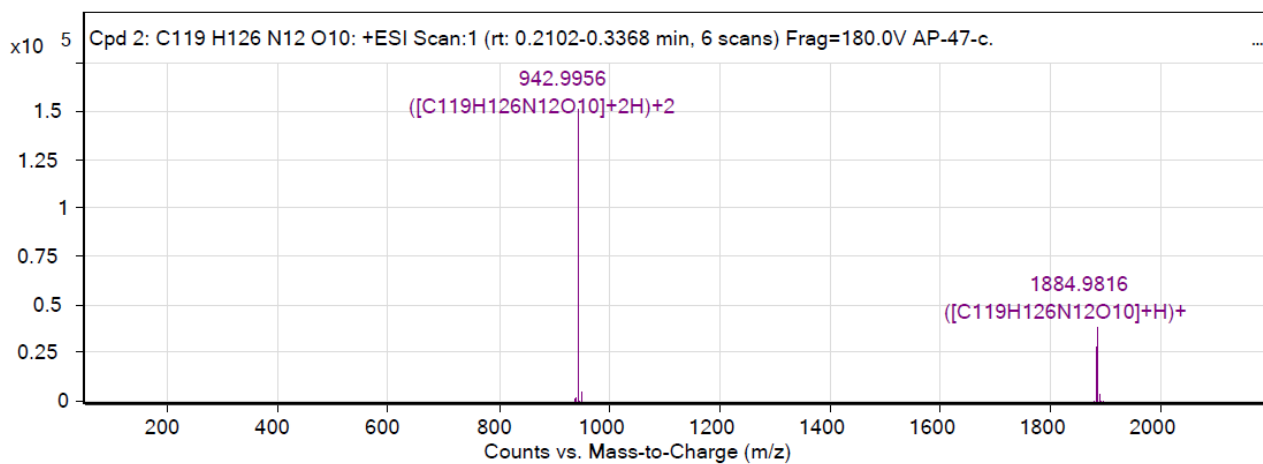
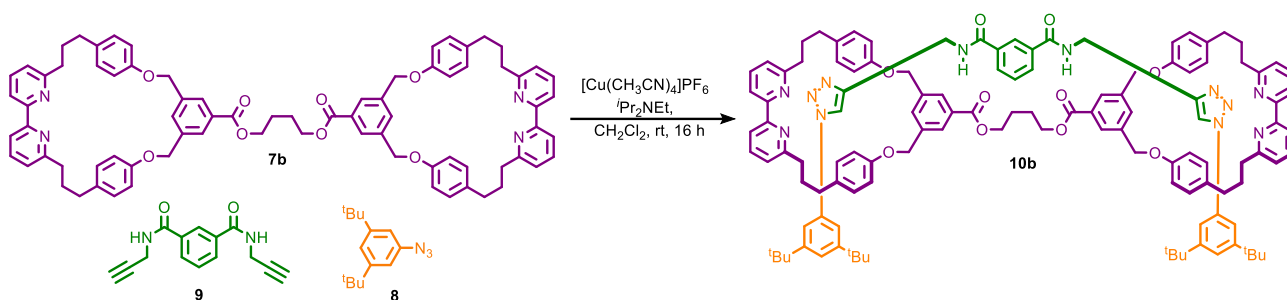
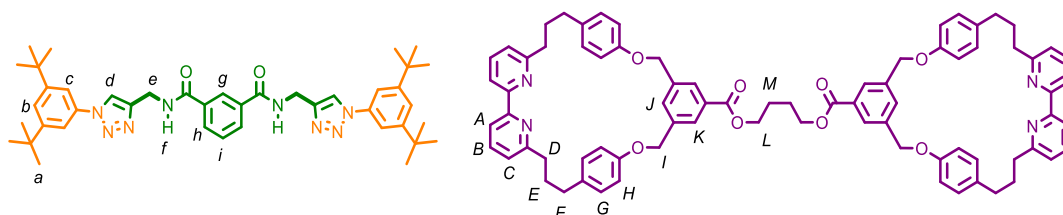


Figure S61. HRMS spectrum for **10a**.

Compound 10b



In a CEM vial were added **7b** (23.6 mg, 0.02 mmol, 1.0 eq.), **8** (9.21 mg, 0.04 mmol, 2.0 eq.), **9** (9.63 mg, 0.02 mmol, 1.0 eq.) and $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (14.8 mg, 0.04 mmol, 2.0 eq.). The vial was sealed and purged with N_2 , then CH_2Cl_2 was added (4.0 mL), followed by $i\text{Pr}_2\text{NEt}$ (14.2 μL , 0.08 mmol, 4.0 eq.). The solution was stirred at rt for 16 h. The crude mixture was diluted with CH_2Cl_2 (5 mL) and EDTA- NH_3 (10 mL) was added, and the resulting mixture was stirred vigorously for until colourless. The organic phase was separated, and the aqueous phase was then extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic extracts were washed with brine (10 mL), dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , CH_2Cl_2 - CH_3CN 0 \rightarrow 40%) to yield **10b** (27.7 mg, 0.014 mmol, 73%) as a yellow oil.



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 9.00 (s, 1H, H_g), 8.68 (t, $J = 5.7$ Hz, 2H, H_f), 8.15 (s, 1H, H_i), 8.05 (s, 2H, H_d), 7.92 (dd, $J = 7.7, 1.7$ Hz, 2H, H_h), 7.73 (d, $J = 1.4$ Hz, 2H, H_k), 7.63 (d, $J = 1.4$ Hz, 2H, H_k'), 7.57 (t, $J = 7.7$ Hz, 4H, H_b), 7.49-7.44 (m, 8H, $\text{H}_a, \text{H}_b', \text{H}_a', \text{H}_c$), 7.35 (d, $J = 1.4$ Hz, 4H, H_c), 7.28 (s, 1H, H_j), 7.05 (d, $J = 1.4$ Hz, 2H, H_b), 6.93 (d, $J = 8.4$ Hz, 6H, H_g, H_h), 6.62 (m, $J = 8\text{H}$, H_h', H_g'), 6.53 (d, $J = 8.4$ Hz, 4H, H_h), 5.23 (s, 4H, H_i'), 5.07 (s, 4H, H_i), 4.37 (t, $J = 5.8$ Hz, 4H, H_l), 4.11 (d, $J = 5.3$ Hz, 4H, H_e), 2.88 (t, $J = 7.1$ Hz, 4H, H_d), 2.61 (t, $J = 7.1$ Hz, 4H, H_f), 2.29-2.21 (m, 8H, $\text{H}_e', \text{H}_d', \text{H}_f'$), 2.10 (m, 4H, H_e), 1.91 (t, $J = 5.8$ Hz, 4H, H_m), 1.36 (s, 36H, H_a).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} 166.37, 166.30, 166.26, 162.85, 161.91, 156.66, 156.59, 156.24, 152.88, 145.63, 139.13, 138.76, 137.71, 136.92, 136.74, 135.20, 133.09, 132.74, 131.64, 131.44, 131.01, 130.17, 129.58, 129.05, 128.25, 127.96, 127.30, 126.07, 122.81, 122.57, 122.36, 120.74, 120.69, 119.14, 115.44, 115.21, 114.89, 69.62, 69.26, 64.77, 36.71, 35.31, 34.98, 34.73, 34.49, 31.51, 31.34, 31.25, 29.83, 29.79, 25.67.

HR-ESI-MS (+ve) $m/z = 1898.9970$ [$\text{M}+\text{H}$] $^+$ (calc. m/z for $\text{C}_{120}\text{H}_{128}\text{N}_{12}\text{O}_{10}$ 1898.9963).

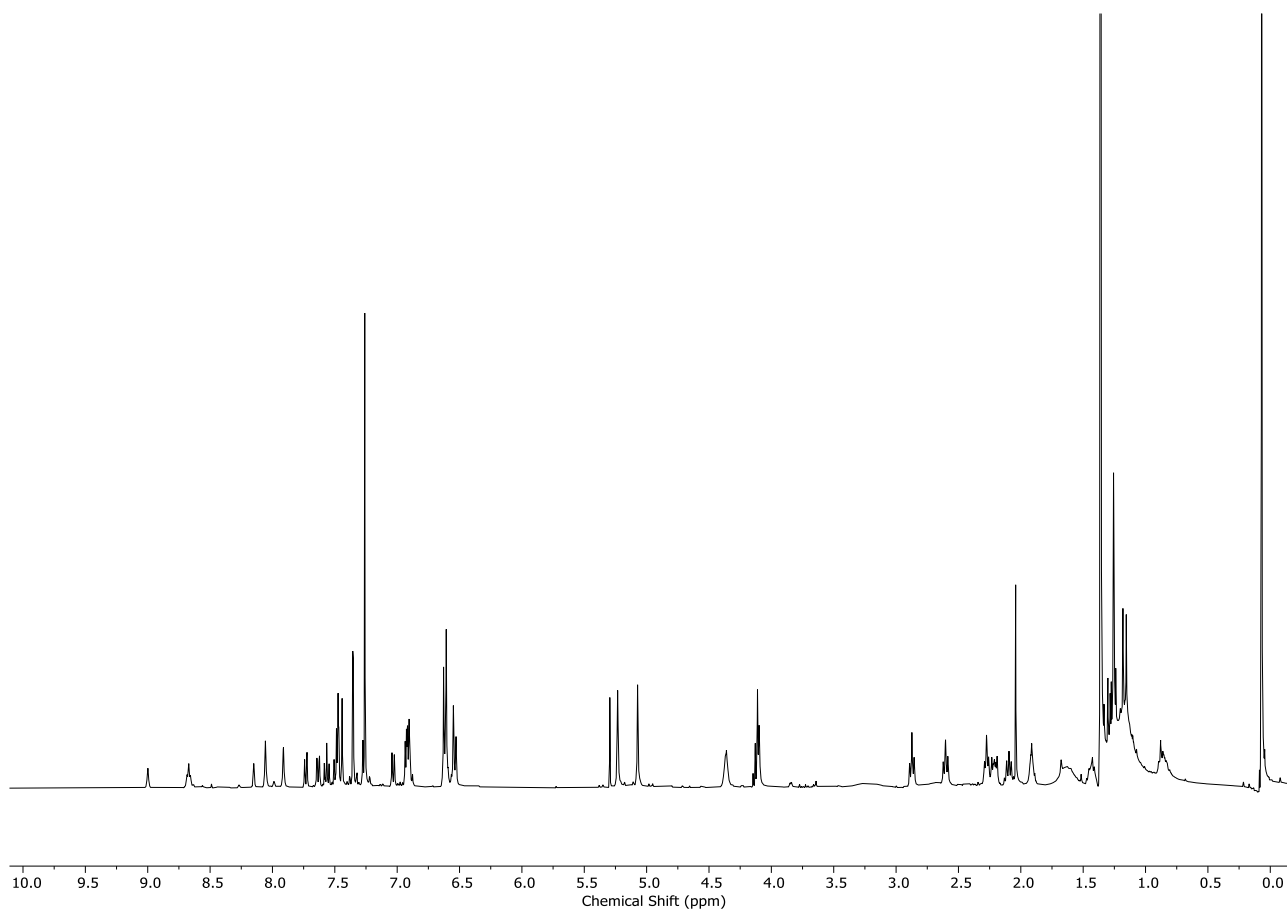


Figure S62. ^1H NMR (CDCl_3 , 400 MHz, 298 K) of **10b** prior to purification.

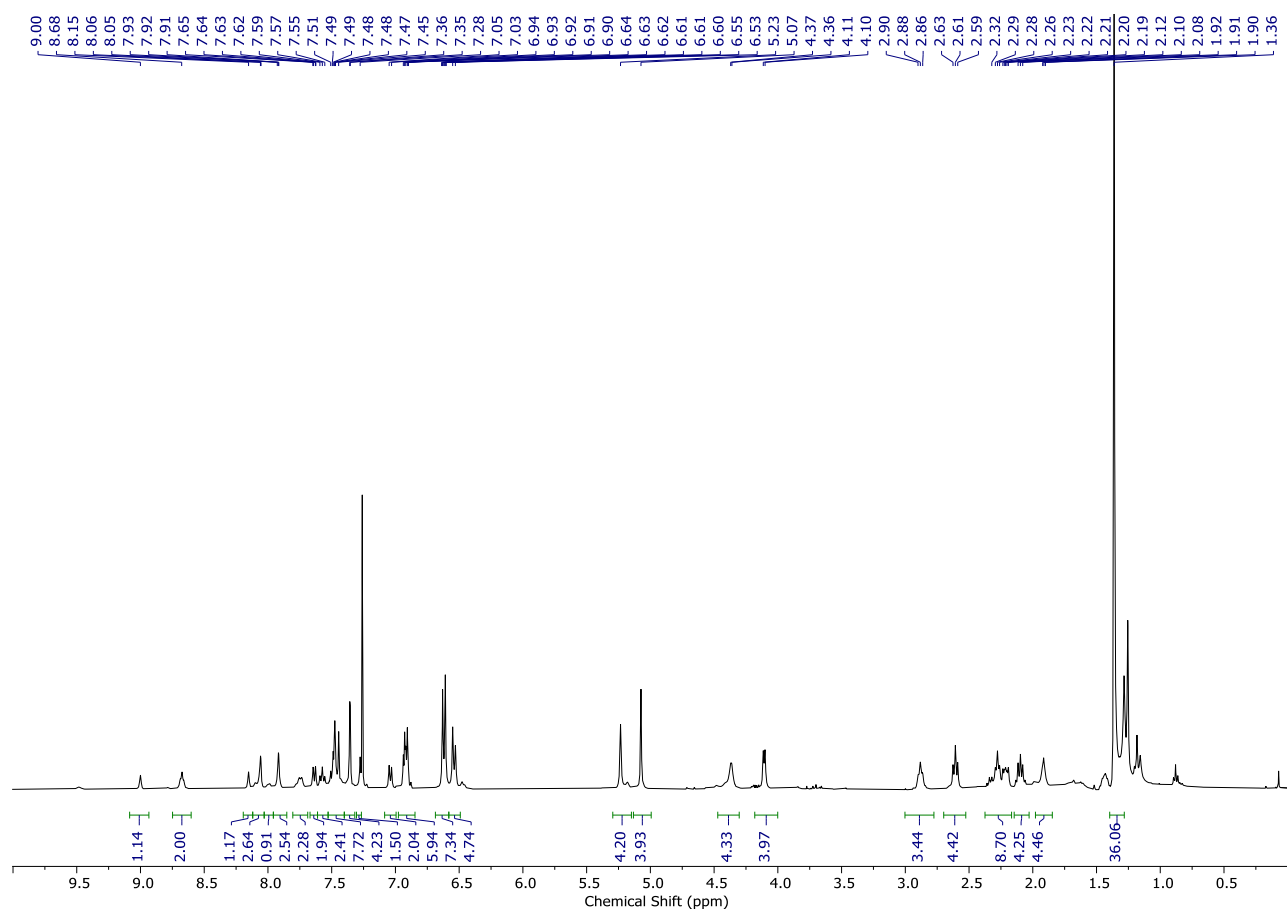


Figure S63. ^1H NMR (CDCl_3 , 400 MHz) of **10b**.

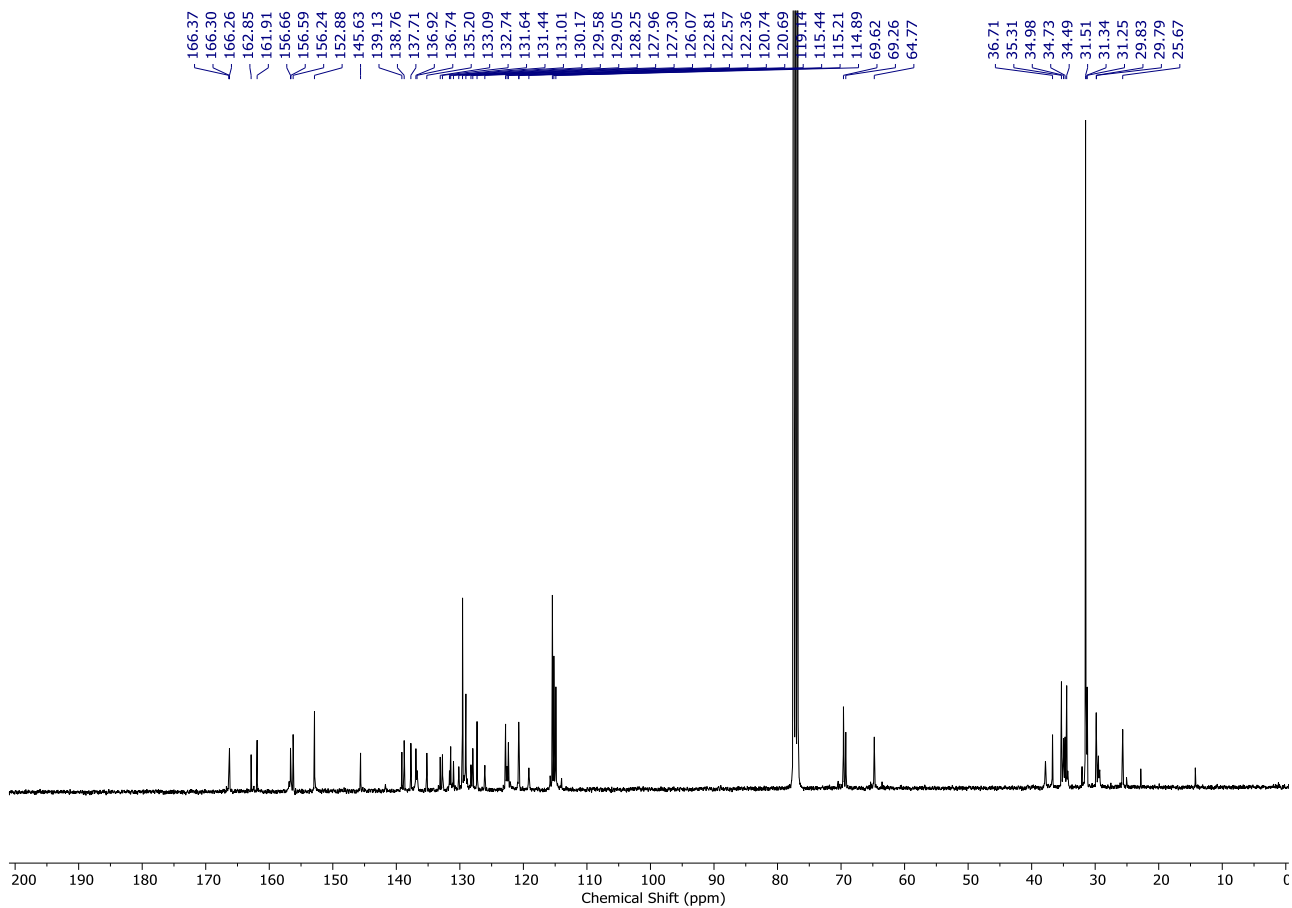


Figure S64. ^{13}C NMR (CDCl_3 , 101 MHz) of **10b**.

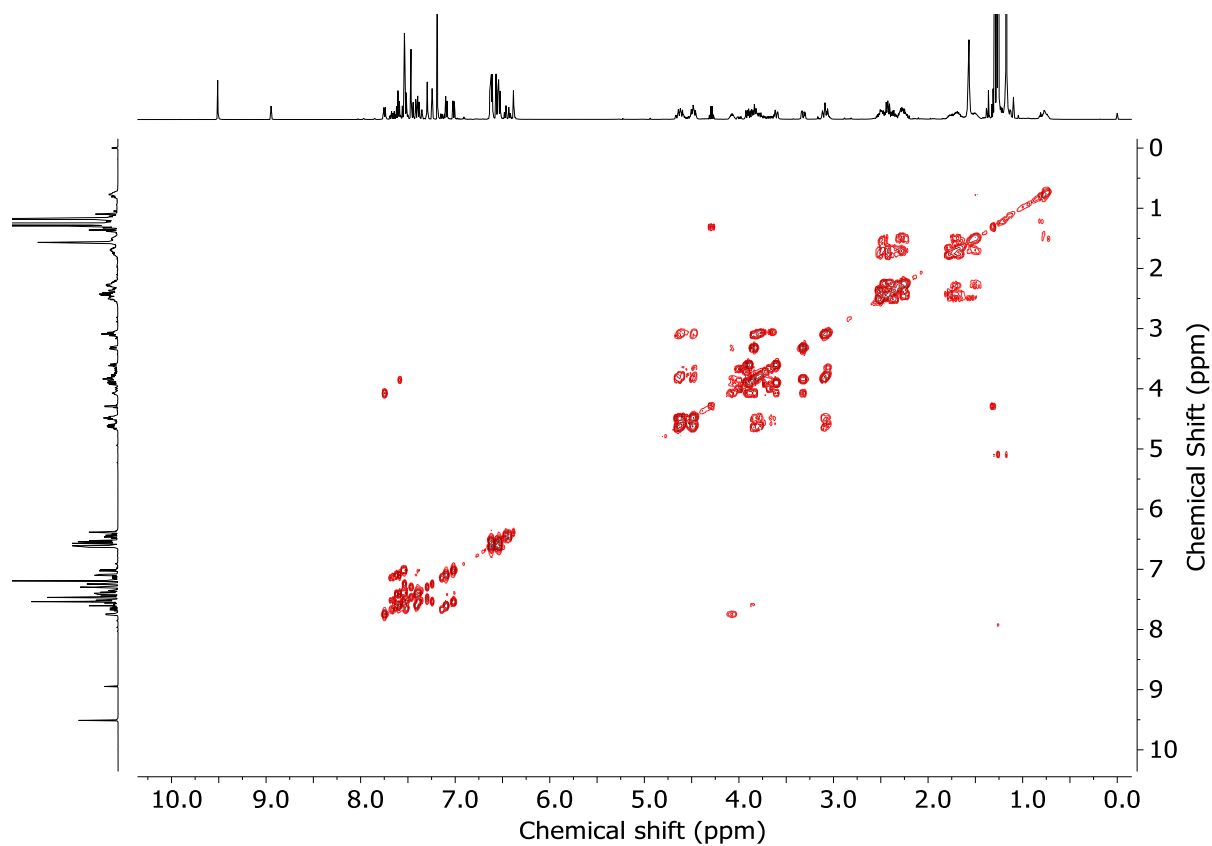


Figure S65. COSY NMR (CDCl_3) of **10b**.

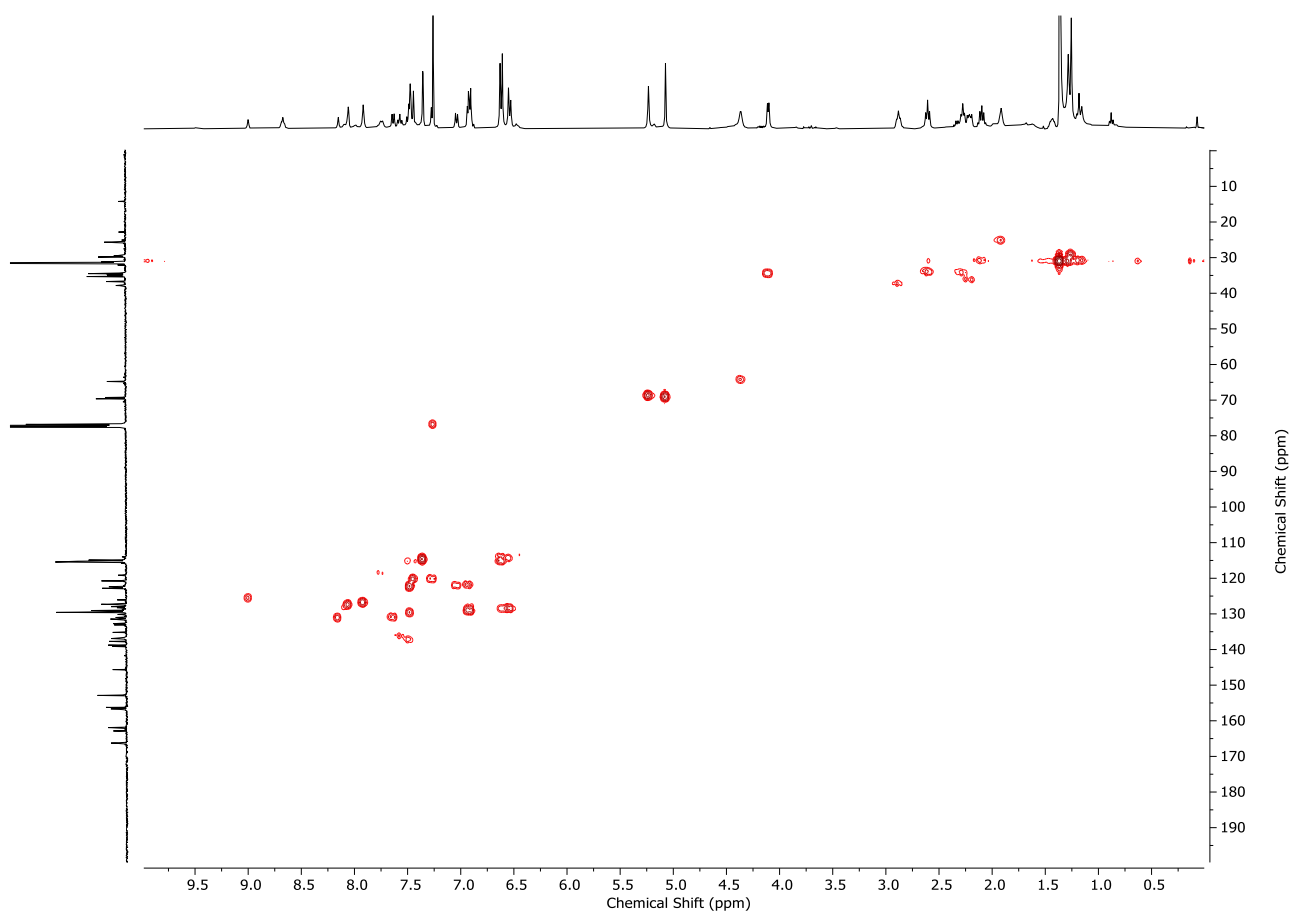


Figure S66. HMOC NMR (CDCl₃) of **10b**.

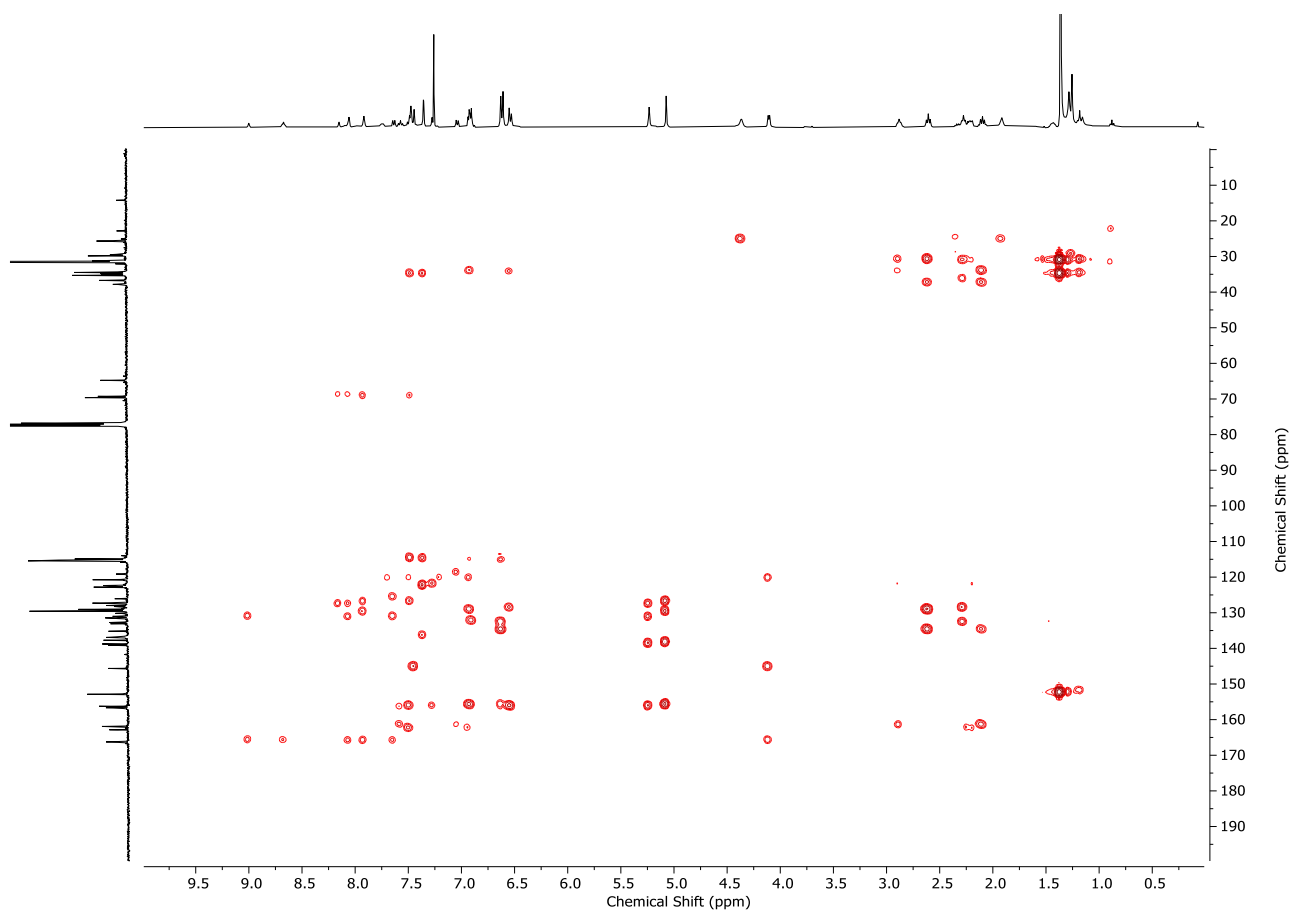


Figure S67. HMBC NMR (CDCl₃) of **10b**.

MS Spectrum

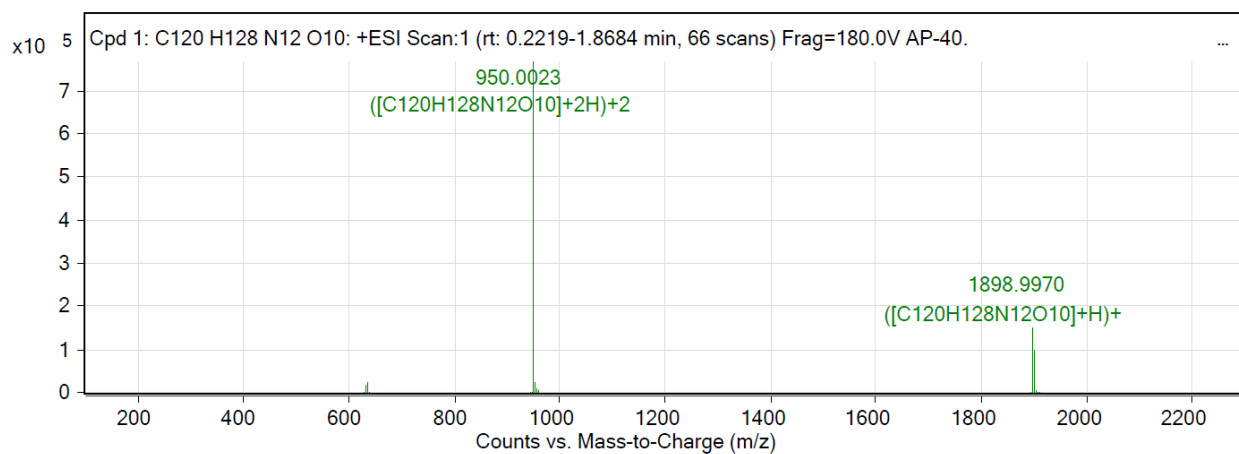
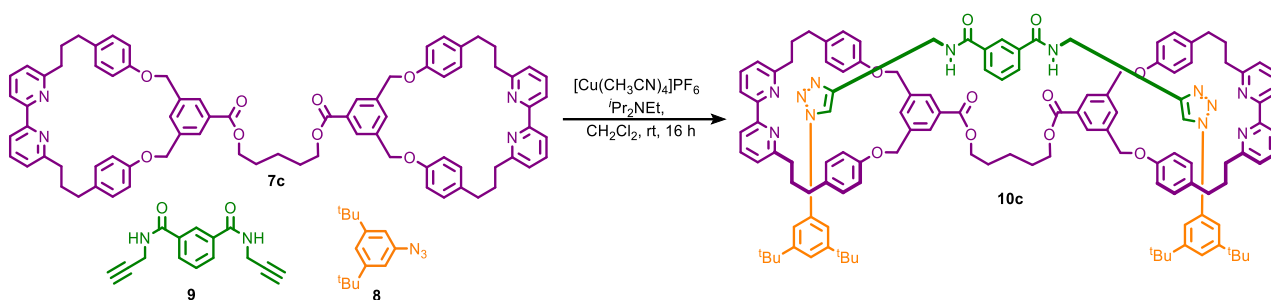
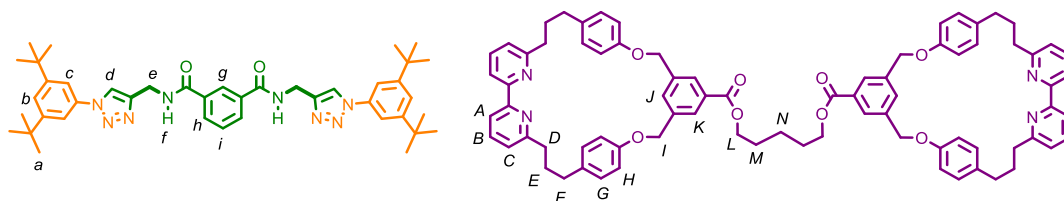


Figure S68. HRMS spectrum for **10b**.

Compound 10c



In a CEM vial were added **7c** (24.1 mg, 0.02 mmol, 1.0 eq.), **8** (9.21 mg, 0.04 mmol, 2.0 eq.), **9** (9.63 mg, 0.02 mmol, 1.0 eq.) and $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (14.8 mg, 0.04 mmol, 2.0 eq.). The vial was sealed and purged with N_2 , then CH_2Cl_2 was added (4.0 mL), followed by $i\text{Pr}_2\text{NEt}$ (14.2 μL , 0.08 mmol, 4.0 eq.). The solution was stirred at rt for 16 h. The crude mixture was diluted with CH_2Cl_2 (5 mL) and EDTA- NH_3 (10 mL) was added, and the resulting mixture was stirred vigorously for until colourless. The organic phase was separated, and the aqueous phase was then extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic extracts were washed with brine (10 mL), dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , CH_2Cl_2 - CH_3CN 0 \rightarrow 40%) to yield **10c** (24.8 mg, 0.013 mmol, 65%) as a yellow oil.



^1H NMR (500 MHz, CDCl_3) δ_{H} 9.01 (s, 1H, H_g), 8.70 (t, $J = 5.7$ Hz, 2H, H_f), 8.15 (s, 1H, H_i), 8.06 (s, 2H, H_d), 7.91 (dd, $J = 7.7, 1.7$ Hz, 2H, H_h), 7.72 (d, $J = 1.4$ Hz, 2H, H_k), 7.63 (d, $J = 1.4$ Hz, 2H, H_k'), 7.57 (t, $J = 7.7$ Hz, 4H, H_b), 7.49-7.45 (m, 10H, $\text{H}_A, \text{H}_B, \text{H}_A', \text{H}_C$), 7.36 (d, $J = 1.4$ Hz, 4H, H_c), 7.28 (s, 1H, H_j), 7.04 (d, $J = 1.4$ Hz, 2H, H_b), 6.92 (d, $J = 8.4$ Hz, 6H, H_G, H_H), 6.61 (m, $J = 8$ Hz, H_H', H_G'), 6.53 (d, $J = 8.4$ Hz, 4H, H_H), 5.23 (s, 4H, H_l'), 5.07 (s, 4H, H_l), 4.32 (t, $J = 5.8$ Hz, 4H, H_l), 4.11 (d, $J = 5.3$ Hz, 4H, H_e), 2.88 (t, $J = 7.1$ Hz, 4H, H_D), 2.61 (t, $J = 7.1$ Hz, 4H, H_F), 2.34-2.08 (m, 20H, $\text{H}_E', \text{H}_D', \text{H}_E, \text{H}_F', \text{H}_M, \text{H}_N$), 1.36 (s, 36H, H_a).

^{13}C NMR (126 MHz, CDCl_3) δ_{C} 166.25, 162.80, 161.92, 156.54, 156.19, 152.84, 145.61, 139.04, 138.70, 137.70, 136.86, 136.69, 135.15, 133.03, 132.66, 131.41, 131.08, 129.55, 129.01, 128.23, 127.91, 127.22, 126.04, 122.78, 122.49, 122.34, 120.70, 119.12, 115.36, 115.17, 114.82, 69.57, 69.21, 65.03, 37.85, 36.67, 35.28, 31.49, 29.80.

HR-ESI-MS (+ve) $m/z = 1913.0113$ [$\text{M}+\text{H}$] $^+$ (calc. m/z for $\text{C}_{121}\text{H}_{130}\text{N}_{12}\text{O}_{10}$ 1913.0111).

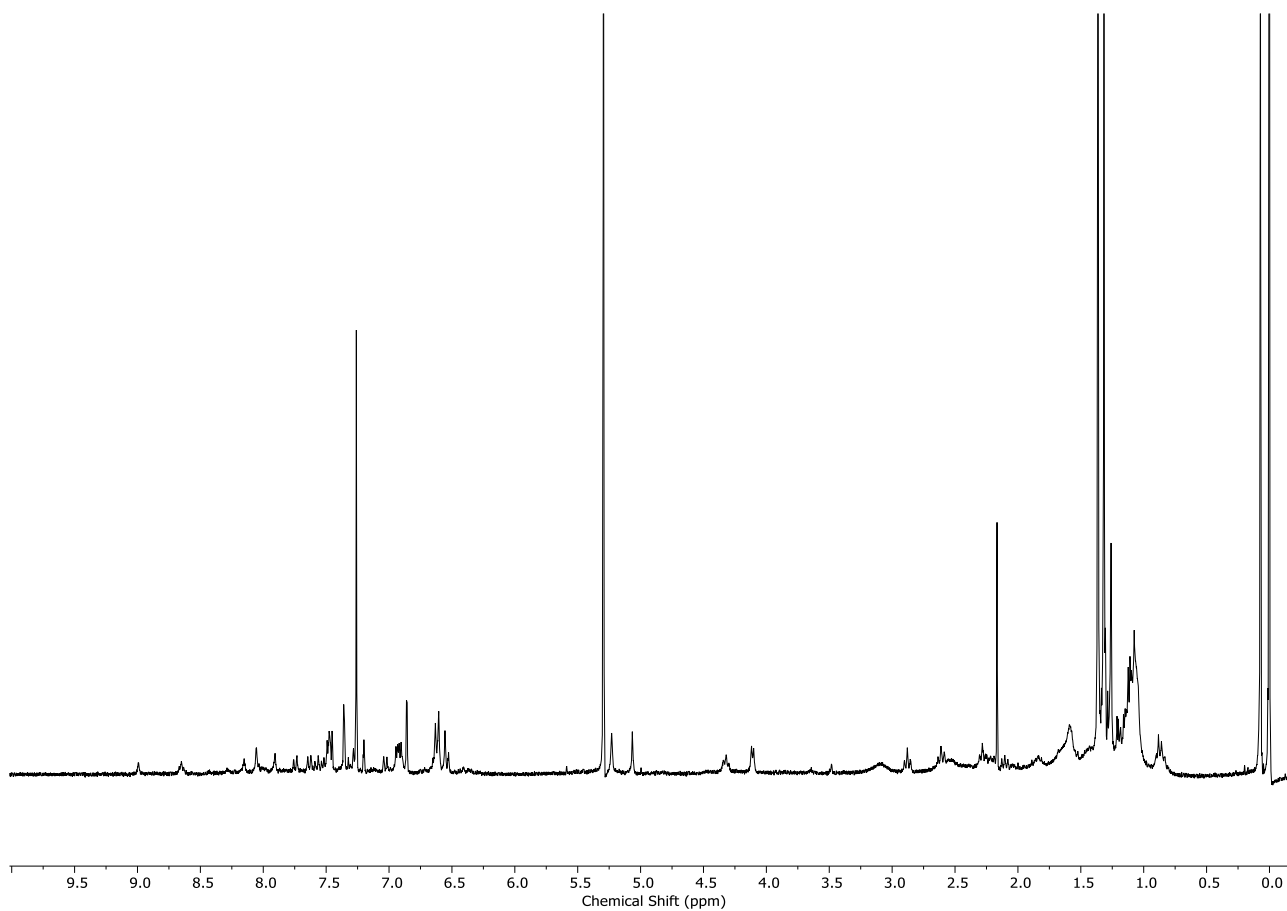


Figure S69. ^1H NMR (CDCl_3 , 300 MHz, 298 K) of **10c** prior to purification.

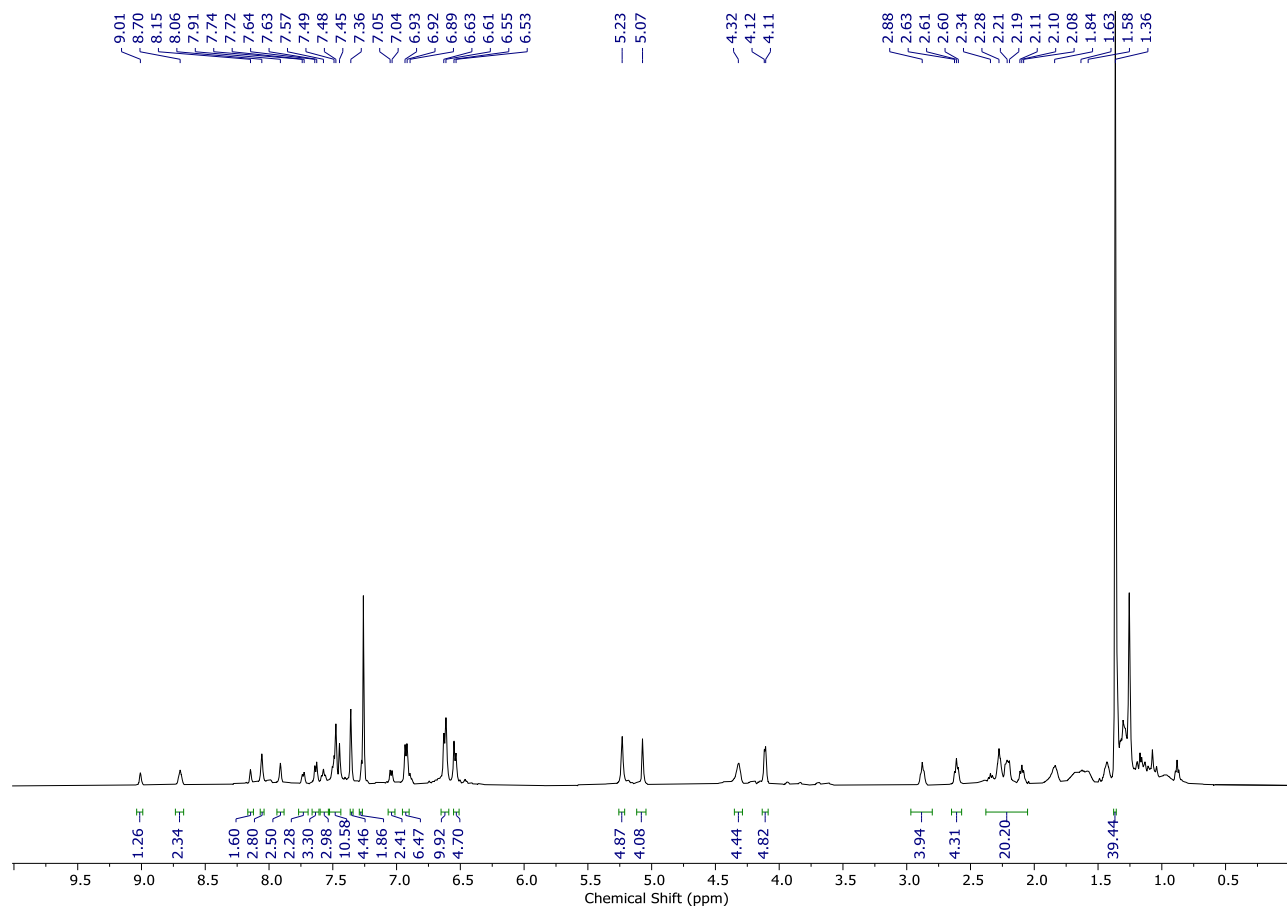


Figure S70. ^1H NMR (CDCl_3 , 500 MHz) of **10c**.

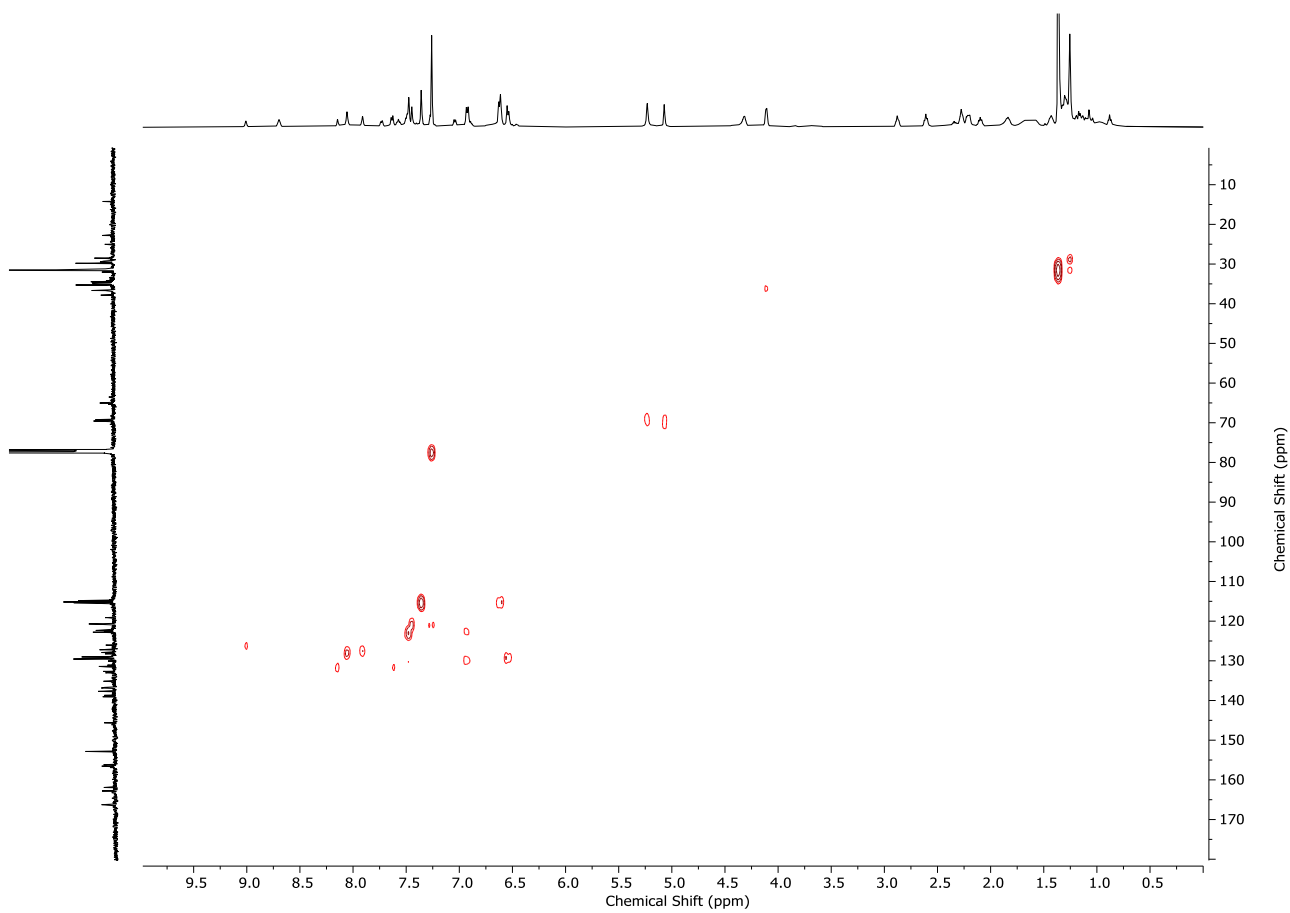


Figure S73. HMQC NMR (CDCl_3) of **10c**.

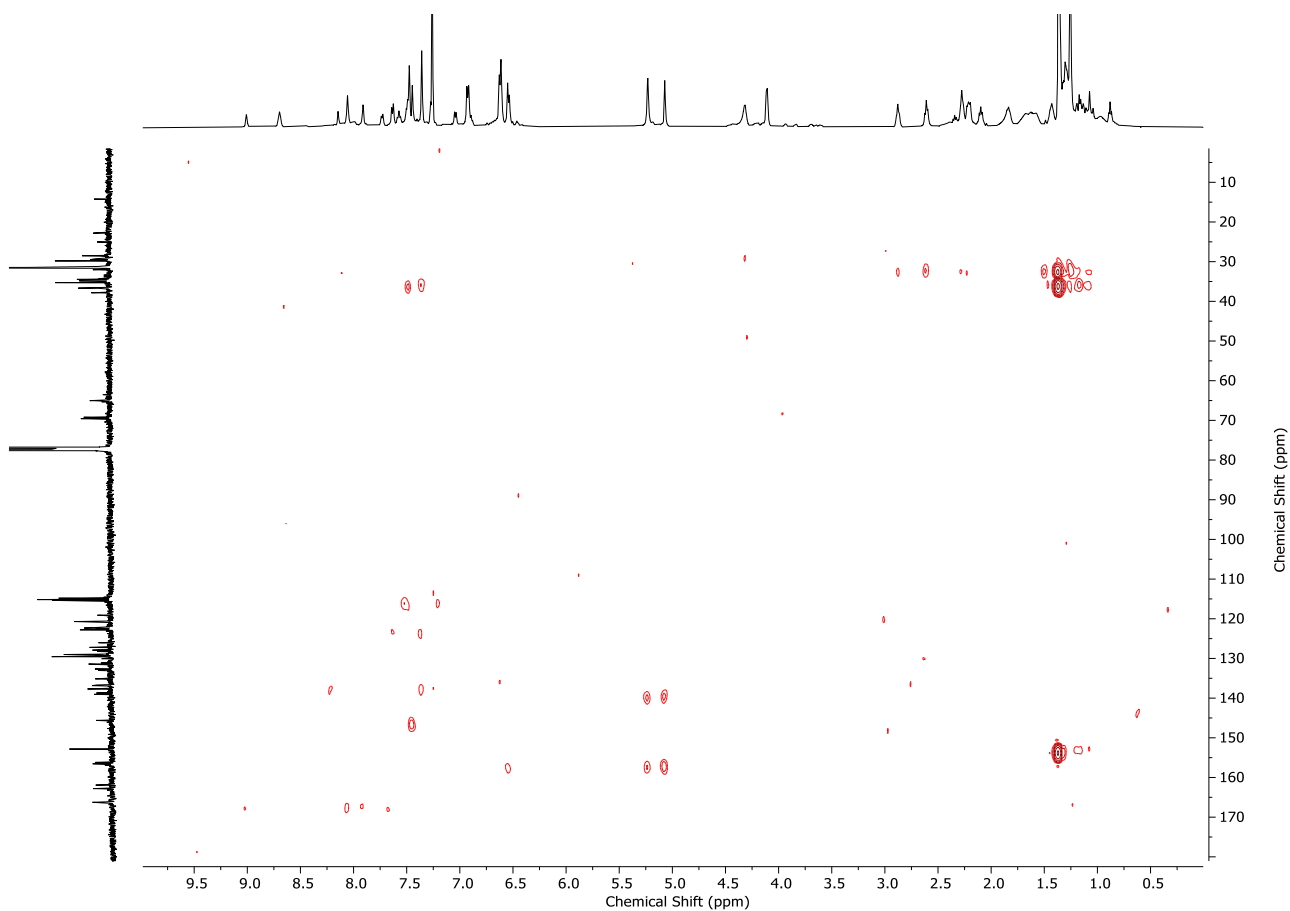


Figure S74. HMBC NMR (CDCl_3) of **10c**.

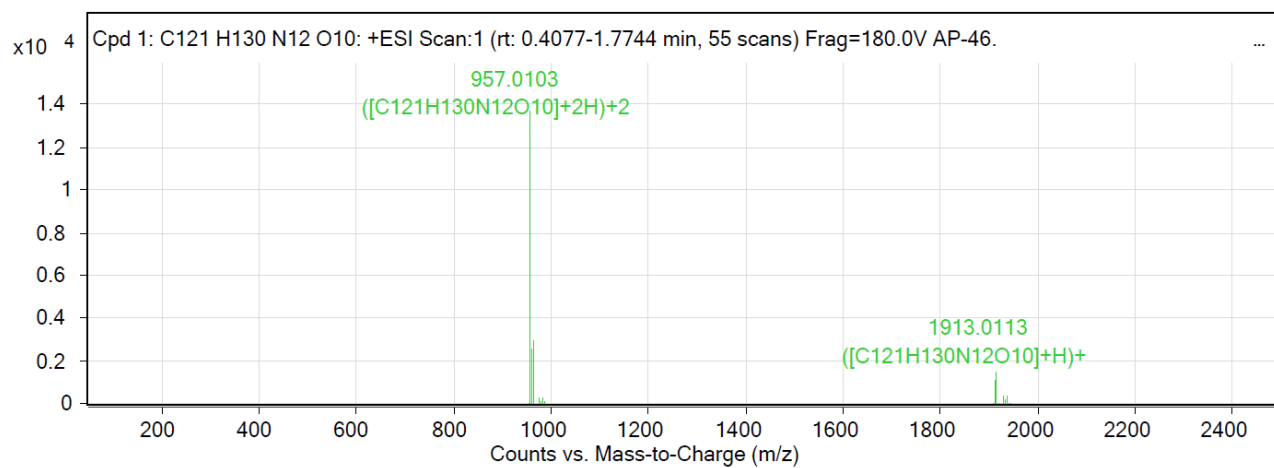
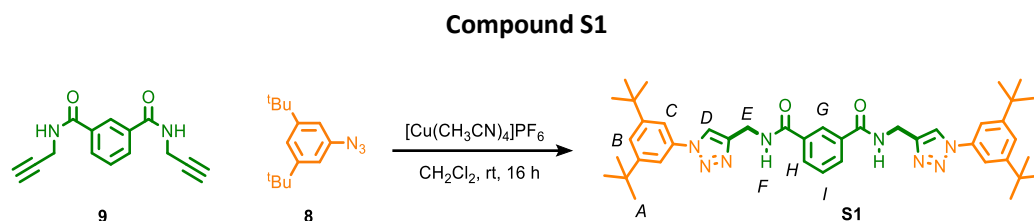


Figure S75. HRMS spectrum for **10c**.

4. Synthesis of the free axle S1



To a dry CEM vial, was added azide **8** (50.0 mg, 0.21 mmol), alkyne **9** (51.9 mg, 0.21 mmol) and $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (80.5 mg, 0.21 mmol). The vial was flushed with N_2 then anhydrous CH_2Cl_2 (5 mL) was added. The resulting mixture was stirred at rt for 16h. The mixture was diluted in CH_2Cl_2 (10 mL), washed with EDTA- NH_3 (10 mL) then brine (10 mL), dried over anhydrous MgSO_4 , filtered, then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , CH_2Cl_2 -MeOH 0 \rightarrow 7%) to yield **S1** (113.3 mg, 0.16 mmol, 77%) as a yellow oil.

^1H NMR (500 MHz, CDCl_3) δ_{H} 8.36 (d, $J = 1.7$ Hz, 1H, H_G), 8.18 (t, $J = 5.3$ Hz, 2H, H_F), 8.10 (s, 2H, H_D), 8.00 (dd, $J = 7.7, 1.7$ Hz, 2H, H_H), 7.48 (t, $J = 1.8$ Hz, 2H, H_B), 7.46 (d, $J = 1.8$ Hz, 4H, H_C), 7.43 (d, $J = 7.7$ Hz, 1H, H_I), 4.67 (d, $J = 5.3$ Hz, 4H, H_E), 1.33 (s, 36H, H_A).

^{13}C NMR (126 MHz, CDCl_3) δ_{C} 166.96, 152.97, 145.31, 136.71, 134.29, 130.94, 129.09, 125.39, 123.28, 121.87, 115.73, 35.27, 31.43.

HR-ESI-MS (+ve) $m/z = 703.4440$ $[\text{M}+\text{H}]^+$ (calc. m/z for $\text{C}_{42}\text{H}_{54}\text{N}_8\text{O}_2$ 703.4438).

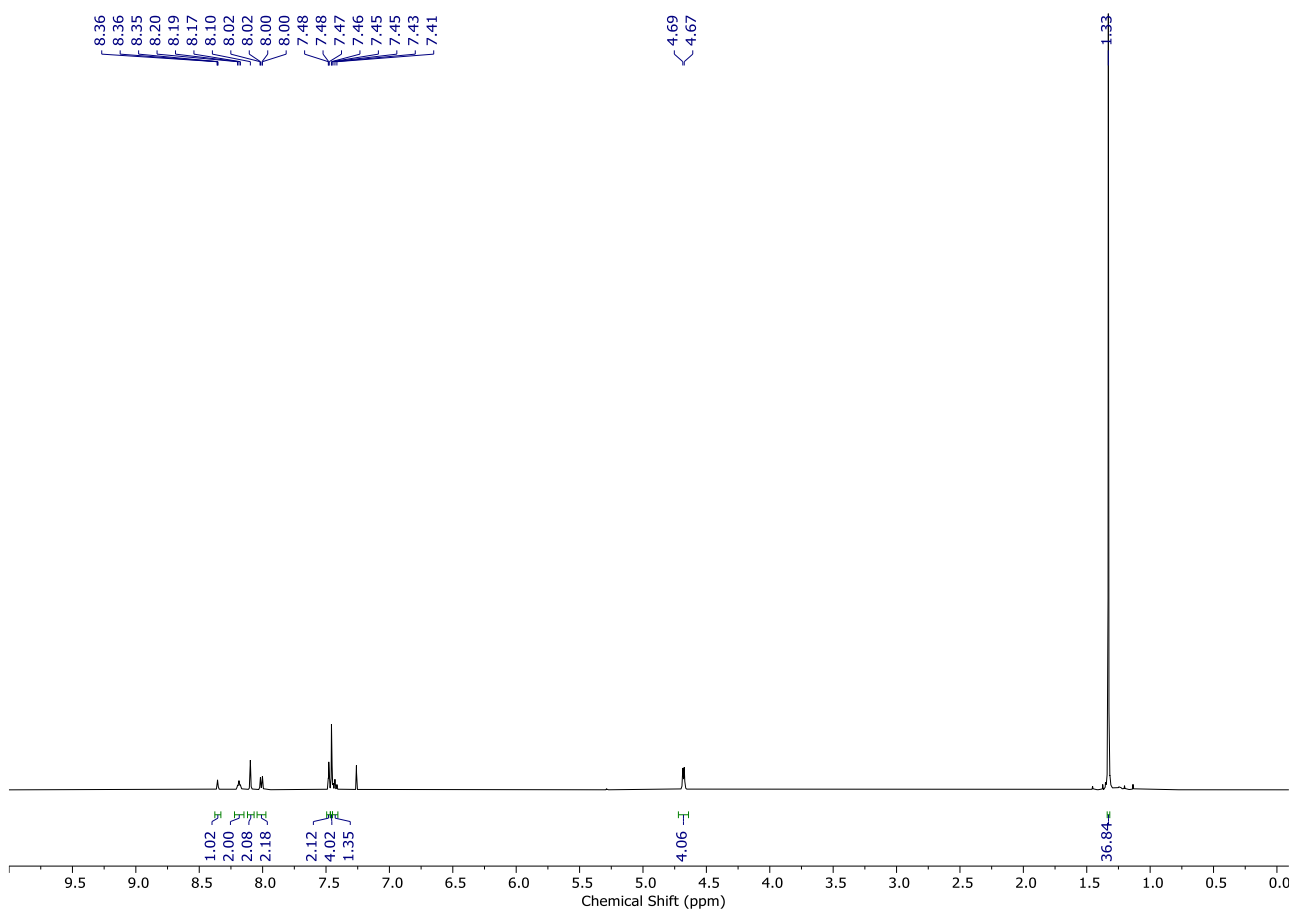


Figure S76. ^1H NMR (CDCl_3 , 500 MHz) of **S1**.

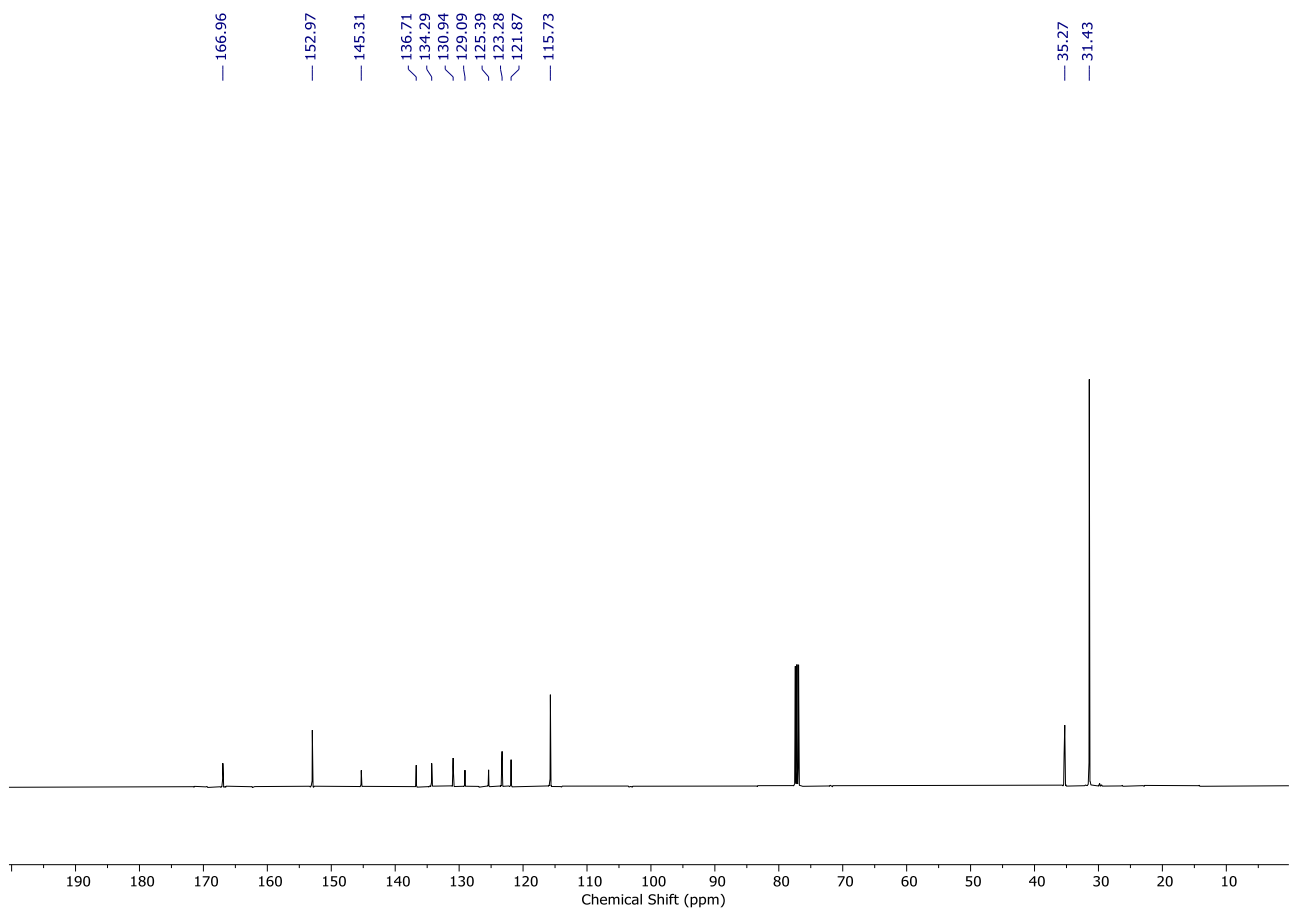


Figure S77. ^{13}C NMR (CDCl_3 , 126 MHz) of **S1**.

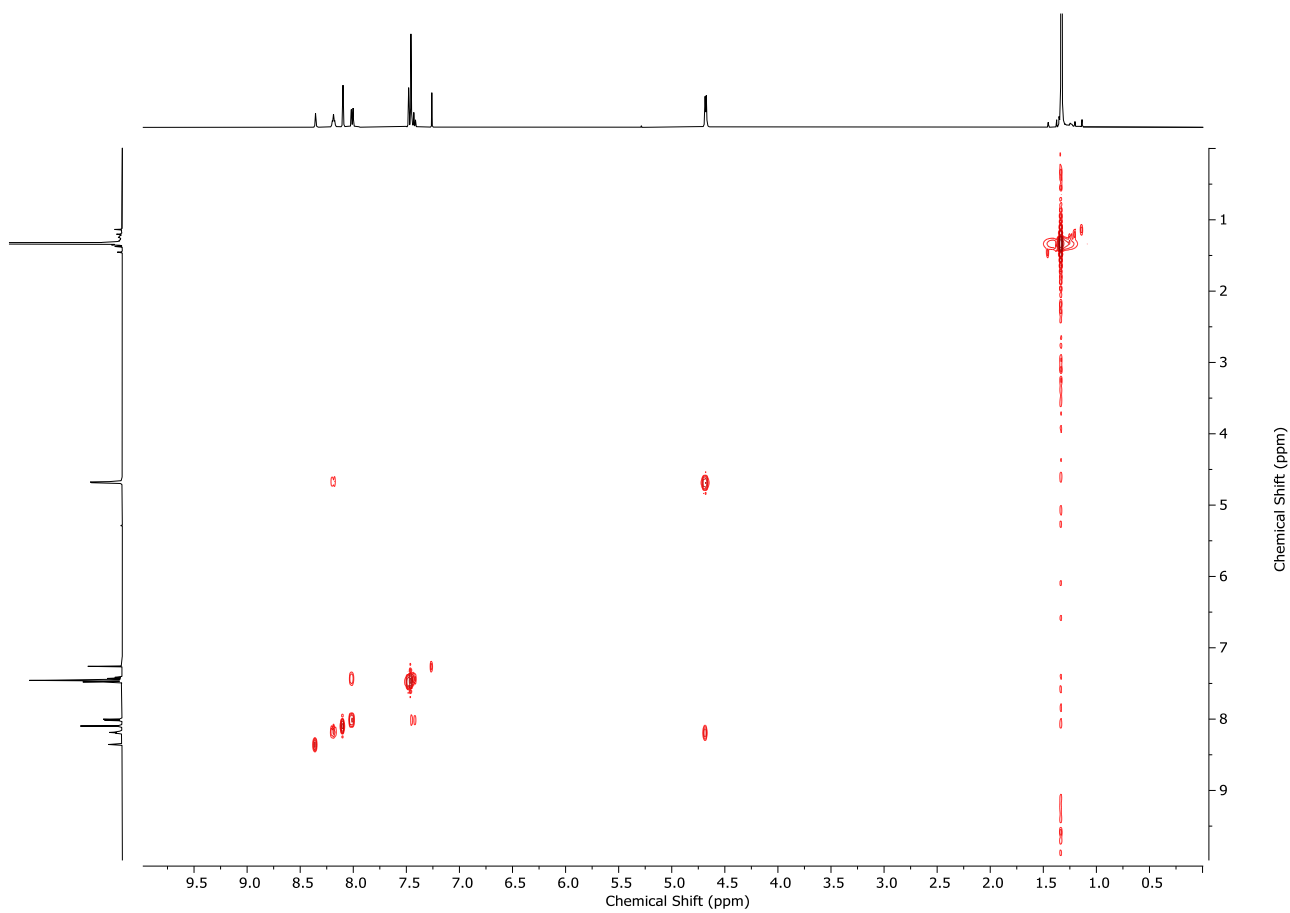


Figure S78. COSY NMR (CDCl_3) of **S1**.

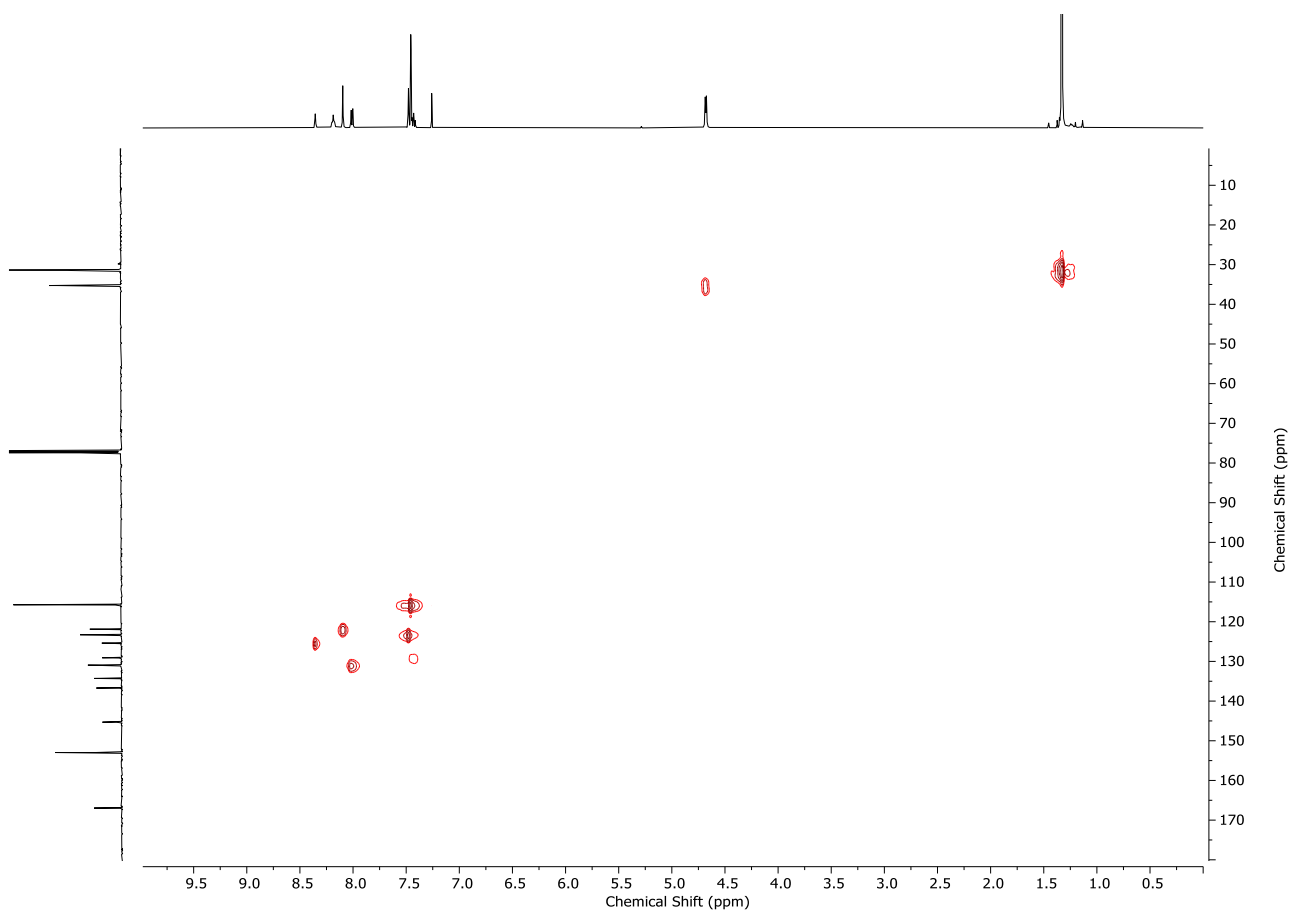


Figure S79. HMBC NMR (CDCl_3) of **S1**.

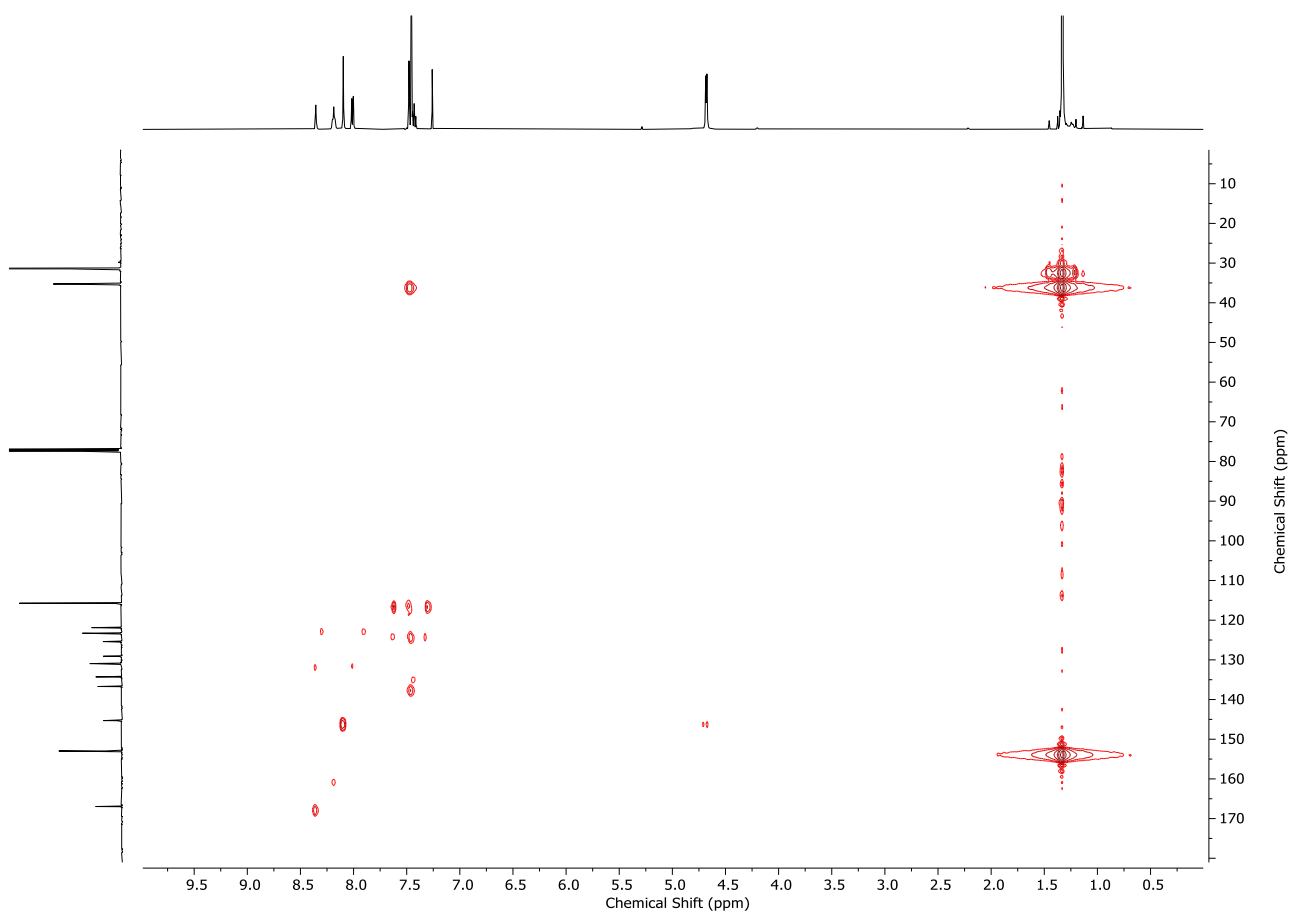


Figure S80. HMBC NMR (CDCl_3) of **S1**.

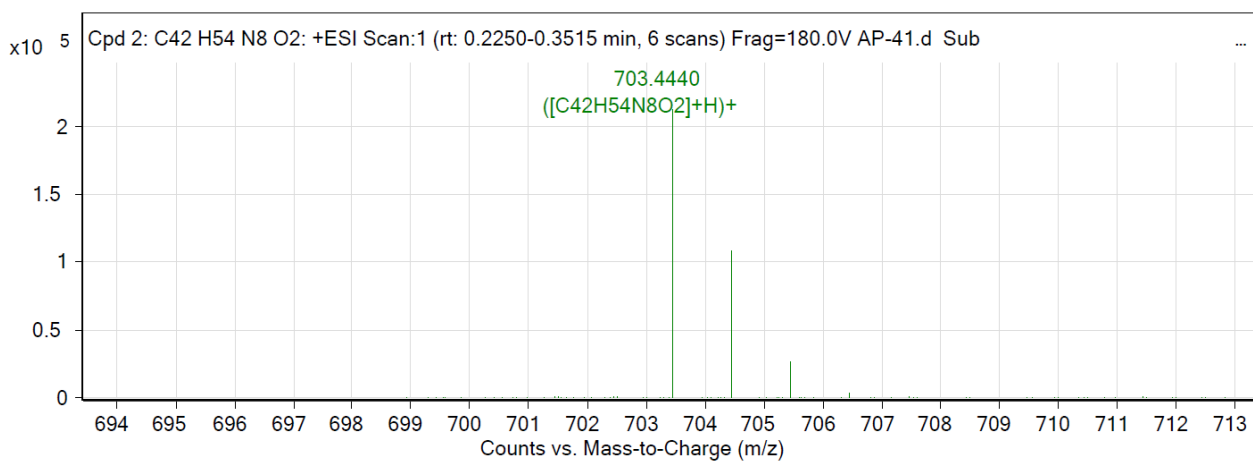


Figure S81. HRMS spectrum for **S1**.

5. Effect of Reaction Concentration on (2)handcuff [2]rotaxanes Formation

The influence of reaction concentration on the AT-CuAAC assembly of the (2)handcuff [2]rotaxane was examined using bis-macrocycle **7b**, which gave the highest isolated yield under the standard conditions. Reactions were conducted at concentrations of 0.001, 0.005, and 0.01 M with respect to **7b**, while all other reaction parameters were kept constant.

The crude reaction mixtures obtained at each concentration were analysed prior to purification, and the corresponding data are presented as a stack plot below. Across this concentration range, the isolated yields of the target (2)handcuff [2]rotaxane were essentially identical, differing by no more than $\pm 5\%$, and no significant changes in the overall product distribution were observed.

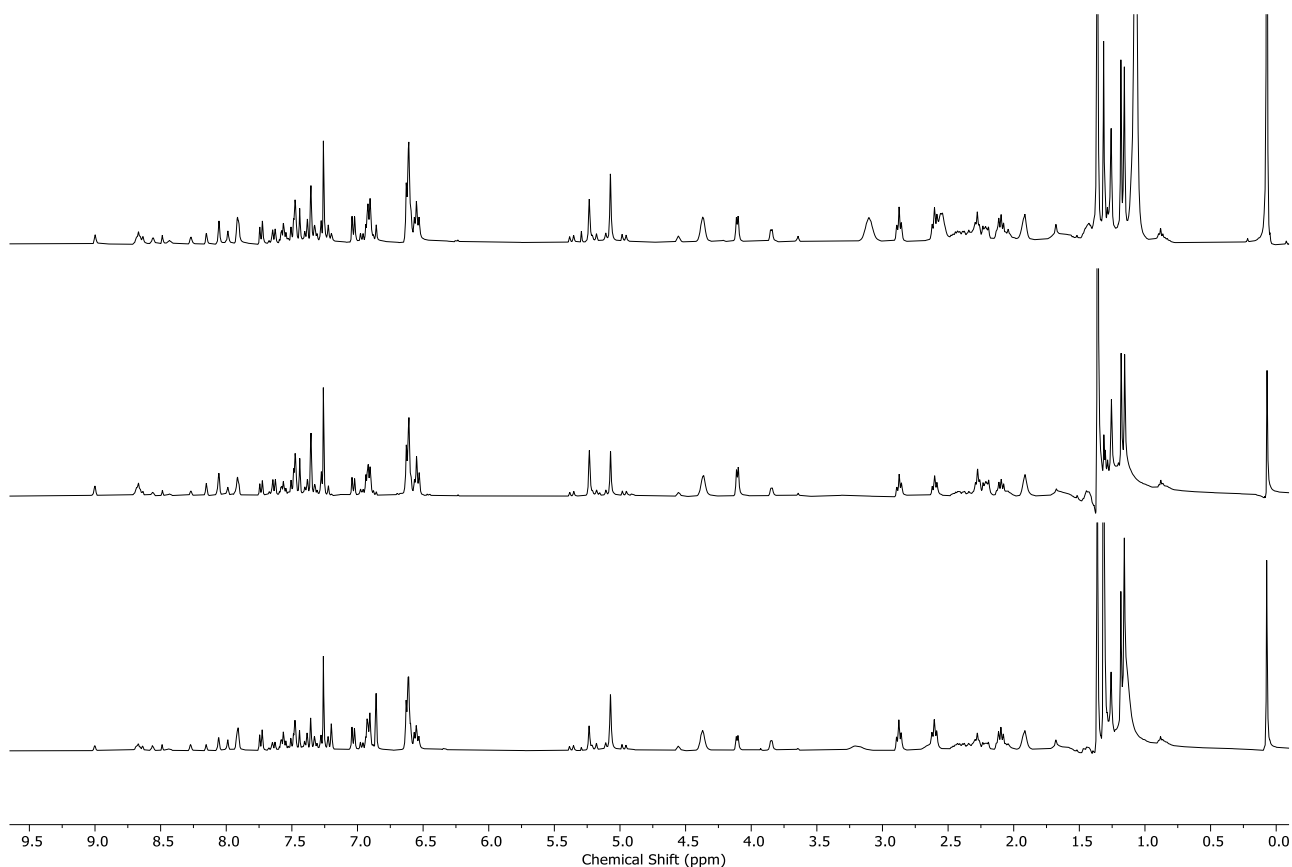
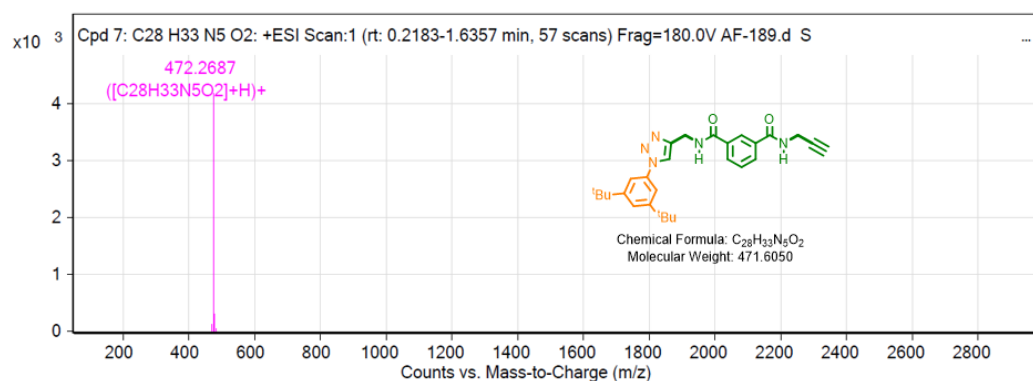
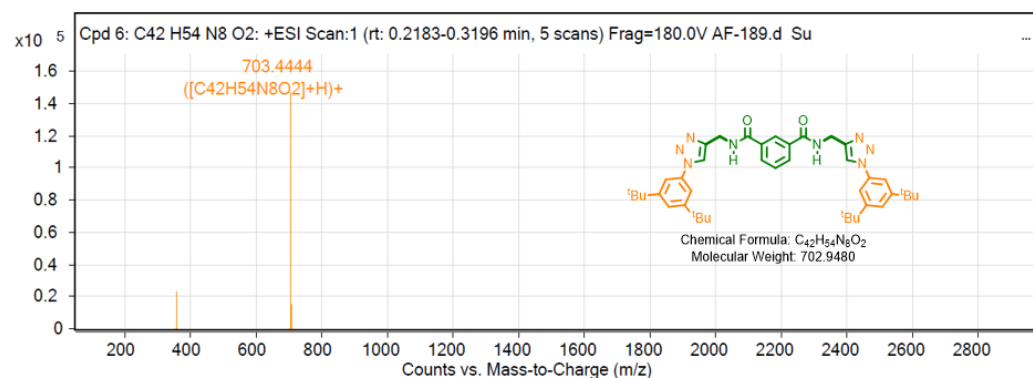
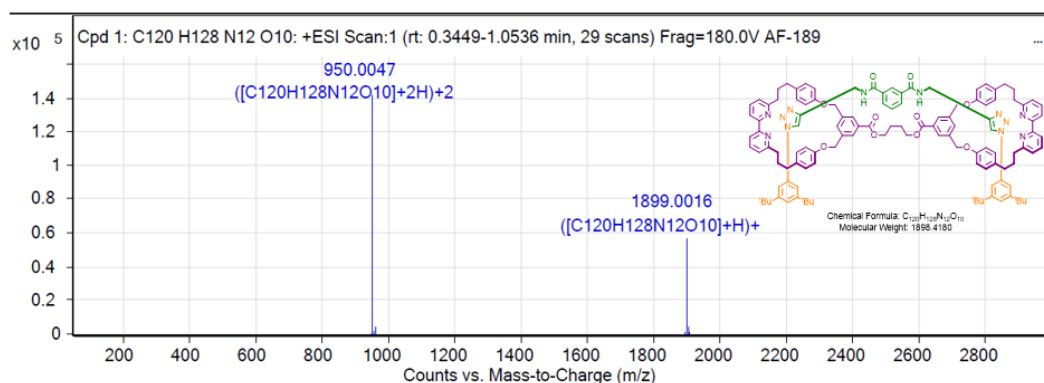
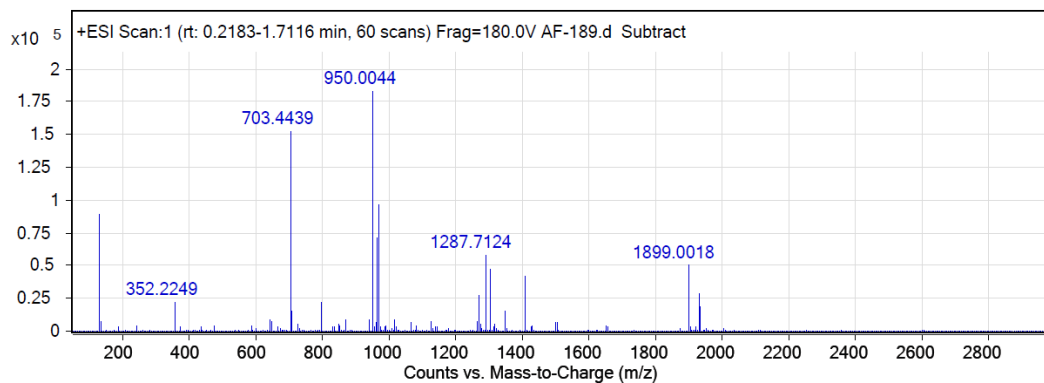


Figure S82. ^1H NMR (CDCl_3 , 400 MHz) Stack plot of the crude reaction mixtures obtained from the AT-CuAAC reaction of bis-macrocycle **7b** at different concentrations (0.001, 0.005, and 0.01 M, with respect to **7b**, from top to bottom respectively), recorded prior to purification.

6. Mass Spectrometry Analysis of Crude AT-CuAAC Reaction Mixtures

The crude reaction mixtures obtained from the AT-CuAAC reactions leading to compounds **10a–c** were analysed by electrospray ionisation mass spectrometry (ESI-MS) prior to purification. Representative data for compound **10b** are shown below; analogous mass spectral features were observed for reactions leading to **10a** and **10c**. In all cases, the (2)handcuff [2]rotaxane was identified as the dominant species, together with detectable amounts of the free axle, mono-clicked alkyne, and unreacted bis-macrocycle.



7. AT-CuAAC Reaction under Competitive Hydrogen-Bonding Conditions

This section describes AT-CuAAC reactions of bis-macrocycle **7b** performed in a CH₂Cl₂/MeOH (1:1) solvent mixture to assess the effect of competitive hydrogen-bonding conditions on handcuff rotaxane formation. Reaction outcomes were analysed by ¹H NMR spectroscopy and LCMS and compared with reactions conducted in CH₂Cl₂ alone.

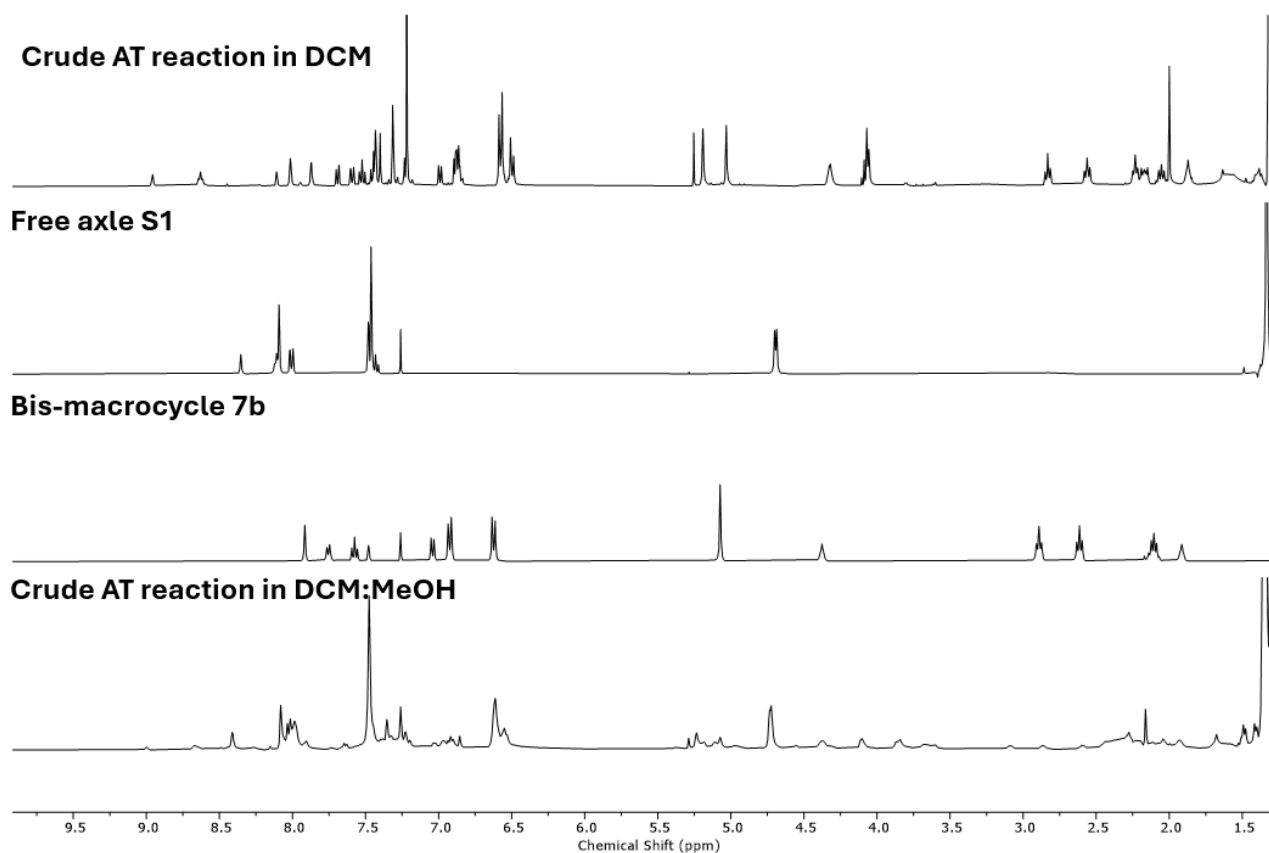


Figure S83. ¹H NMR (CDCl₃, 400 MHz) stack plot of (top to bottom): **10a** prior to purification, reaction in CH₂Cl₂, Free axle S1, bis-macrocycle **7b** and **10a** prior to purification, reaction in CH₂Cl₂/MeOH.

8. References

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