Supplementary Information for

# Shapeshifting Bullvalene Linked Vancomycin Dimers as Effective Antibiotics Against Multidrug-Resistant Gram-Positive Bacteria

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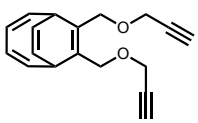
# 1 Synthesis

## 1.1 General Methods

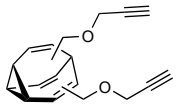
Vancomycin was purchased from SavMart pharmacy and used without further purification. All other reagents were purchased from Sigma Aldrich and used without further purification. Tetrahydrofuran (THF) was purified by a Pure SolvTM Micro solvent purification system and stored over 4 Å molecular sieves under an atmosphere of nitrogen. Yields refer to chromatographically pure and/or HPLC pure isolated compounds. NMR spectra were recorded on Bruker Avance III 600, DRX-500, DRX-400, or Avance III-HD 300 instruments and calibrated using the residual as an internal standard. The following abbreviations, or combinations thereof, were used to describe $^{1}$H NMR multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, appt. = apparent, br. = broad). Unless otherwise indicated, NMR spectra were recorded at room temperature (25 °C). Low temperature spectra were recorded at –60 °C using a Bruker Avance III 600 instrument. IR spectra were recorded neat on a Perkin Elmer spectrum 100 FT-IR Spectrometer with an ATR. ESI-HRMS measurements (electrospray ionization - ESI) were recorded on an Agilent 6230 or 6530 time-of-flight LC/MS system. Analytical thin-layer chromatography was conducted with commercial aluminium sheets coated with 0.25 mm silica gel (E. Merck, silica gel 60 F254). Compounds were either visualized under UV-light at 254 nm, or by dipping the plates in aqueous potassium permanganate or cerium ammonium molybdenite solution followed by heating. Flash column chromatography was performed using a Biotage IsoleraTM One Flash Chromatography System using iLOKTM Empty Solid Load Cartridges, and Carl Roth silica gel 60 (230–400 mesh grade). Hexanes and ethyl acetate (EtOAc) were distilled prior to use in chromatography. Preparative HPLC was performed on an Agilent 10 Prep -C18 150 mm x 21.2 mm with flow rate 20 mL/min. The $t_R$ were calculated on an Agilent prepshell 120 EC -C18 2.7 µm 4.6 x 100 mm, flow rate 1 mL / min, 10 to 90% $CH_3CN$ (0.1% TFA) in H2O (0.1% TFA) over 10 minutes.

1.2 Synthesis of (2*Z*,4*Z*)-7,8-bis((prop-2-yn-1-yloxy)methyl)bicyclo[4.2.2]deca-2,4,7,9-tetraene **2**



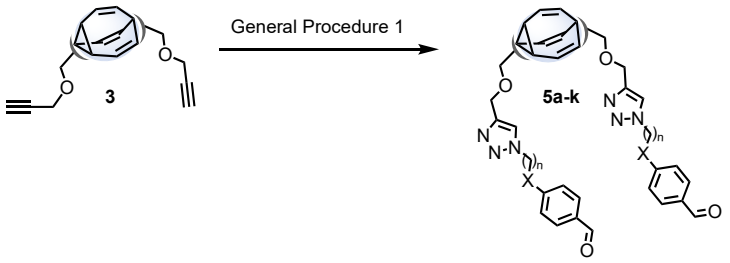
Under argon atmosphere an oven-dried 250 mL round bottom flask was charged with bis(methylenehydroxy)bicyclo[4.2.2]decatetraene, prepared according to the published procedure(1) (4.50 g, 23.6 mmol, 1.00 equiv) and tetrahydrofuran (100 mL). The solution was cooled to 0 ºC in an ice bath, and sodium hydride (3.41 g, 141 mmol, 60 wt% in mineral oil) was added slowly. After 30 min, propargyl bromide (15.6 mL, 166 mmol, 80 wt% in toluene) was added, and the reaction was stirred overnight. The reaction was quenched with distilled water and extracted with dichloromethane. The organic layer was washed three times with a saturated sodium chloride solution, dried over $MgSO_4$, and the solvent was evaporated under vacuum. The crude product was purified by flash column chromatography using hexane/ethyl acetate (9:1 v/v) as eluents ($R_f$ = 0.23). The desired product was obtained as an orange oil (5.5 g, 87%). **$^1$H NMR** (300 MHz, $CDCl_3$): δ= 6.35 – 6.11 (2H, td, *J* = 8.8, 3.4 Hz), 5.92 – 5.38 (4H, m), 4.30 – 4.23 (2.8H, m) 4.15 – 4.08 (2.7H, m), 4.14 – 3.97 (3.5H, d, *J* = 2.4 Hz), 3.56 – 3.27 (2H, dd, *J* = 8.8, 2.6 Hz), 2.70 – 2.10 (2H, s). **$^{13}$C NMR** (75 MHz, $CDCl_3$): δ= 141.6 (CH), 131.7 (C), 124.6 (CH), 121 (CH), 80 (C), 74.5 (CH), 65.9 ($CH_2$), 56.5 ($CH_2$), 37.63 (CH). **HRMS** (EI): *m/z* calcd for $C_{18}H_{18}O_2$ 266.1307 found 266.1291. **IR (ATR)**: v/cm$^{-1}$ = 3287, 3015, 2930, 2855, 1711, 1676, 1636, 1438, 1392, 1381, 1358, 1255, 1218, 1126, 1064, 1000, 978, 917, 885, 842, 832, 827, 812, 735.

1.3 Synthesis of bis-propargyl-bullvalene **3**



A 20 mL pyrex sealed tube was charged with compound **2** (400 mg, 1.50 mmol) in acetone (20 mL). The solution was flushed with argon and was placed in a water bath 2.5 cm from a 150W high-pressure mercury emission lamp (Osram SUPRATEC HTT 150-211). The tube was irradiated for 2 days. After the reaction was completed, the solvent was evaporated, and the desired product was purified by flash column chromatography (phosphate buffered silica pH 7) using hexane /ethyl acetate (9:1) as eluents. The desired product was obtained as yellow oil (200 mg, 50%). **$^1$H NMR** (600 MHz, $CDCl_3$, -60 °C): δ= 5.93 – 5.75 (6H, m), 4.19 – 4.18 (0.5H, m), 4.08 (4H, brs), 4.06 (1H, m), 4.05 (0.5H, m), 4.01 – 3.99 (1H, m), 3.97 – 3.90 (4H, m), 2.61 – 2.58 (1H, m), 2.51 (0.2H, m), 2.48 (H, m), 2.46 (1H, m), 2.42 – 2.38 (1H, m), 2.29 – 2.25 (3H, m), 2.20 – 2.15 (0.5H, m). **$^{13}$C NMR** (150 MHz, $CDCl_3$, -60 °C): δ= 137.8, 136.9, 135.9, 135.8, 134.4, 134.1, 133.3, 128.7, 128.6, 128.5, 128.3, 128.1, 128.1, 127.9, 127.6, 127.4, 127.2, 127.0, 126.8, 126.6, 126.5, 126.3, 126.2, 125.9, 125.8, 125.3, 82.1, 79.8, 79.8, 79.8, 79.6, 78.7, 77.7, 77.6, 77.6, 77.4, 77.2, 76.2, 76.1, 75.7, 75.3, 75.2, 75.0, 75.0, 74.9, 74.9, 74.9, 74.8, 74.8, 57.8, 57.7, 56.8, 56.6, 56.3, 56.1, 56.0, 56.0, 55.8, 55.7, 34.0A, 32.0C/E, 31.7B, 30.1, 29.8D, 29.1F, 28.3, 28.1, 26.3F, 25.6E, 25.5C, 24.8F, 24.6C, 21.6B, 20.9D, 20.8A, 20.2B, 20.1A, 19.5D, 19.2B. **HRMS** (EI): *m/z* calcd for $C_{18}H_{18}O_2$ $[M+H]^+$: 266.1307 found 266.1315. **IR (ATR):** v/cm-1 = 3287, 3027, 2850, 1440, 1349, 1100, 928, 864, 748.

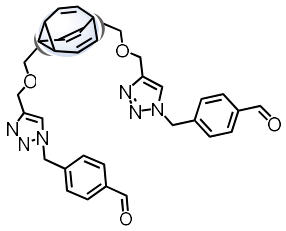
1.4 Synthesis of bis-aldehyde intermediates **5a**–**k**



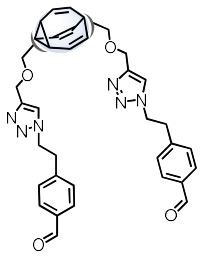

*General procedure 1:* To a solution of bis-propargyl bullvalene **3** (10 mg, 0.038 mmol, 1 equiv) and the corresponding azide (0.083 mmol, 2.2 equiv) in $^{t}$BuOH:$H_2O$ (0.3 mL: 0.3 mL) was added sodium ascorbate (3.72 mg, 0.019 mmol, 0.50 equiv), followed by $CuSO_4 \cdot 5H_2O$ (2.34 mg, 0.009 mmol, 0.25 equiv). The mixture was stirred at 85 °C for 16 hours. The mixture was concentrated, dissolved in 1 mL of $H_2O$, and extracted with EtOAc (3 x 1 mL). The organic layer was washed with $H_2O$ and brine. After drying with $MgSO_4$, the solvent was removed, and the crude was purified by flash column chromatography using DCM/MeOH (9:1) as eluents ($R_f$ = 0.23). (MeOH 0% to 10% in DCM).

*Azide preparation:* The azides employed in the synthesis of bis-aldehyde intermediates **5a**–**k** were prepared using literature procedures(2–8).

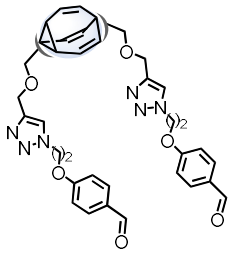
*Comments on characterization:* Due to the fluxional nature of the bis-aldehyde intermediates **5a–k**, $^{13}$C NMR spectroscopy did not reveal signals for all carbon environments, specifically those associated with the shapeshifting bullvalene core. To aid full structural determination, copies of the high-resolution mass spectra obtained for compounds **5a–k** have been included in **Section 6**.



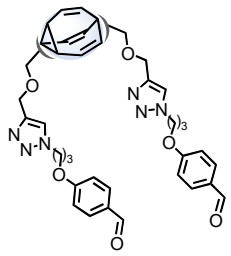
**Compound 5a:** Using general procedure 1 and employing the known azide **4a**(6), the product was isolated as an orange oil after flash column chromatography (10 mg, 45%). **$^1$H NMR** (400 MHz, $CDCl_3$, RT): δ= 10.01 (s, 2H), 7.87 (appt. d, *J* = 8.0 Hz, 4H), 7.53 (s, 2H), 7.40 (appt. d, *J* = 8.1 Hz, 4H), 5.84 (s, 2H), 5.60 (s, 4H), 4.54 (s, 2H), 3.87 (s, 2H). **$^1$H NMR** (600 MHz, $CDCl_3$, -60 °C): δ= 10.03 – 9.98 (m, 2H), 7.93 – 7.85 (m, 4H), 7.62 – 7.56 (m, 2H), 7.43 – 7.36 (m, 4H), 5.94 – 5.82 (m, 2H), 5.80 – 5.73 (m, 1H), 5.64 (s, 4H), 4.54 – 4.50 (m, 2H), 4.47 (appt. d, *J* = 8.1 Hz, 1H), 3.97 – 3.89 (m,2H), 3.85 (appt. d, *J* = 7.6 Hz,1H), 2.61 – 2.51 (m, 1H), 2.42 – 2.34 (m,1H), 2.25 (s,2H).**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ= 191.5, 146.3, 141.3, 136.6, 130.5, 128.57, 122.8, 53.7. **HRMS** (EI): *m/z* calcd for $C_{34}H_{32}N_6O_4$ $[M+H]^+$: 589.2563, found 589.2575. **IR (ATR)**: v/cm$^{-1}$: 2988, 2926, 1697, 1265, 1215, 1049**.**



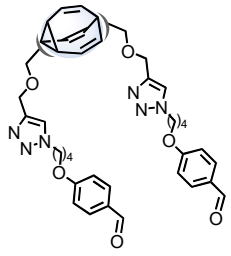
**Compound 5b:** Using general procedure 1 and employing the azide **4b**, the product was isolated as an orange oil after flash column chromatography (15 mg, 65%). **$^1$H NMR** (400 MHz, $CDCl_3$, RT): δ= 9.96 (s, 2H), 7.79 (appt. d, *J* = 8.2 Hz, 4H), 7.34 (s, 2H), 7.30 – 7.25 (m, 4H), 5.84 (s, 2H), 4.62 (t, *J* = 7.2 Hz, 4H), 4.51 (s, 2H), 3.85 (s, 2H), 3.31 (t, *J* = 7.2 Hz, 4H). **$^1$H NMR** (600 MHz, $CDCl_3$, -60 °C): δ= 10.05 – 9.86 (m, 2H), 7.80 (m, 4H), 7.37 (m, 2H), 7.28 – 7.24 (m, 6H), 5.94 – 5.71 (m, 5H), 4.66 – 4.58 (m, 5H), 4.53 – 4.42 (m, 3H), 3.96 – 3.77 (m, 4H), 3.29 (appt. dd, *J* = 9.2, 4.6 Hz, 4H), 2.61 – 2.33 (m, 3H), 2.29 – 2.19 (m, 2H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ= 191.8, 145.4, 144.2, 135.6, 130.3, 129.6, 122.9, 51.0, 36.9. **HRMS** (EI): *m/z* calcd for $C_{36}H_{36}N_6O_4$ $[M+H]^+$: 617.2876, found 617.2876. **IR (ATR)**: v/cm$^{-1}$: 2924, 2852, 1697, 1170, 1051.



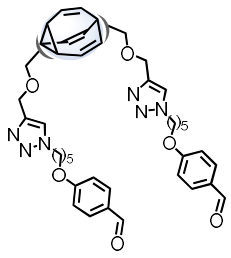
**Compound 5c:** Following a modification to general procedure 1 and employing the known azide **4c**(9), bis-propargyl bullvalene **3** (30 mg, 0.113 mmol, 1 equiv) was used. The product was isolated as an orange oil after flash column chromatography (31 mg, 42%). **$^1$H NMR** (400 MHz, $CDCl_3$, RT): δ= 9.88 (s, 2H), 7.82 (appt. d, *J* = 8.7 Hz, 4H), 7.72 (s, 2H), 6.97 (appt. d, *J* = 8.8 Hz, 4H), 5.86 (s, 2H), 4.79 (t, *J* = 5.1 Hz, 4H), 4.56 (s, 2H), 4.45 (t, *J* = 5.0 Hz, 4H), 3.89 (s, 2H). **$^1$H NMR** (600 MHz, $CDCl_3$, -60 °C): δ= 9.87 (appt. d, *J* = 3.2 Hz, 2H), 7.86 – 7.82 (m, *J* = 5.1 Hz, 4H), 7.80 (s, 2H), 6.97 (appt. d , *J* = 5.3 Hz, 4H), 5.98 – 5.76 (m, 4H), 4.89 – 4.79 (m, 4H), 4.58 – 4.48 (m, 3H), 4.45 – 4.37 (m, 4H) 3.99 – 3.83 (m, 3H), 2.64 (d, *J* = 5.7 Hz, 0.5H), 2.60 (t, *J* = 5.8 Hz, 0.25H), 2.57 – 2.52 (m, 0.2H), 2.41 – 2.36 (m, 0.5H), 2.25 (s, 2H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ= 190.8, 162.8, 145.8, 132.2, 130.9, 123.7, 114.9, 66.7, 49.6. **HRMS** (EI): *m/z* calcd for $C_{36}H_{36}N_6O_6$ $[M+H]^+$: 649.2775, found 649.2784. **IR (ATR)**: v/cm$^{-1}$: 2926, 2359, 2340, 1703, 1697, 1604, 1518, 1165.



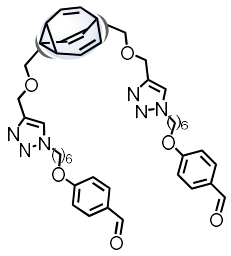
**Compound 5d:** Following a modification to general procedure 1 and employing the known azide **4d**(10), bis-propargyl bullvalene **3** (50 mg, 188 mmol, 1 equiv) was used. The product was isolated as an orange oil after flash column chromatography (90 mg, 71%). **$^1$H NMR** (500 MHz, $CDCl_3$, RT): δ= 9.87 (s, 2H), 7.82 (appt. d, *J* = 8.8 Hz, 4H), 7.55 (s, 2H), 6.96 (appt. d, *J* = 8.7 Hz, 4H), 5.84 (s, 2H), 4.58 (t, *J* = 6.8 Hz, 4H), 4.54 (s, 2H), 4.05 (t, *J* = 5.7 Hz, 4H), 3.89 (s, 2H), 2.47 – 2.38 (m, 4H). **$^1$H NMR** (600 MHz, $CDCl_3$, -60 °C): δ= 9.86 (s, 2H), 7.84 (appt. d, *J* = 4.6 Hz, 4H), 7.65 – 7.58 (m, 2H), 6.97 (appt. d, *J* = 5.4 Hz, 2H), 5.90 – 5.72 (m, 4H), 4.66 – 4.59 (m, 5H), 4.55 – 4.45 (m, 4H), 4.04 – 3.98 (m, 4H), 3.96 – 3.82 (m, 3H), 2.61 (d, *J* = 5.8 Hz, 0.5H), 2.56 (t, *J* = 5.9 Hz, 0.5H), 2.53 – 2.49 (m, 0.5H), 2.48 – 2.39 (m, 5H), 2.24 (appt. s, 2H). **$^{13}$C NMR** (126 MHz, $CDCl_3$): δ= 190.9, 163.5, 145.6, 132.2, 130.4, 123.0, 114.9, 64.7, 47.0, 29.9. **HRMS** (EI): *m/z* calcd for $C_{38}H_{40}N_6O_6$ $[M+H]^+$: 677.3088, found 677.3064. **IR (ATR)**: v/cm$^{-1}$: 2924, 1686, 1599, 1508, 1256, 1161, 1047.



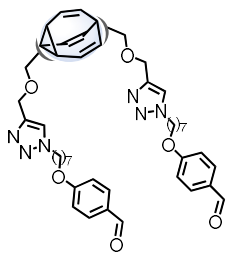
**Compound 5e:** Using general procedure 1 and employing the known azide **4e**(11), the product was isolated as an orange oil after flash column chromatography (18 mg, 68%). **$^1$H NMR** (400 MHz, $CDCl_3$, RT): δ= 9.87 (s, 2H), 7.82 (appt. d, *J* = 8.9 Hz, 4H), 7.57 (s, 2H), 6.96 (appt. d, *J* = 8.6 Hz, 4H), 5.88 (s, 2H), 4.56 (s, 2H), 4.44 (t, *J* = 7.0 Hz, 4H), 4.06 (t, *J* = 6.0 Hz, 4H), 3.92 (s, 2H), 2.17 – 2.07 (m, *J* = 14.8, 7.4 Hz, 4H), 1.89 – 1.80 (m, 4H). **$^1$H NMR** (600 MHz, $CDCl_3$, -60 °C): δ= 9.86 (s, 2H), 7.84 (appt. d, *J* = 4.1 Hz, 4H), 7.66 – 7.61 (m, 2H), 6.96 (appt. d, *J* = 5.5 Hz, 4H), 5.95 – 5.77 (m, 3H), 4.57 – 4.45 (m, 7H), 4.07 – 3.86 (m, 8H), 2.66 (d, *J* = 6.2 Hz, 0.5H), 2.64 – 2.59 (m, 0.25H), 2.45 – 2.38 (m, 1H), 2.30 – 2.24 (m, 2H), 2.17 – 2.07 (m, 5H), 1.87 – 1.77 (m, 5H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ= 190.9, 163.9, 145.7, 132.2, 130.2, 122.5, 114.8, 67.4, 49.9, 27.2, 26.2. **HRMS** (EI): *m/z* calcd for $C_{40}H_{44}N_6O_6$ $[M+H]^+$: 705.3401, found 705.3391. **IR (ATR)**: v/cm$^{-1}$: 2949, 2857, 1686, 1601, 1508, 1253, 1161.



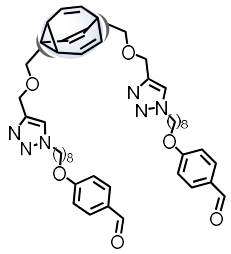
**Compound 5f:** Using general procedure 1 and employing the known azide **4f**(12), the product was isolated as an orange oil after flash column chromatography (11 mg, 40%). **$^1$H NMR** (400 MHz, $CDCl_3$, RT): δ= 9.87 (s, 2H), 7.81 (appt. d, *J* = 8.7 Hz, 4H), 7.53 (s, 2H), 6.96 (appt. d, *J* = 8.7 Hz, 4H), 5.87 (s, 2H), 4.56 (s, 3H), 4.38 (t, *J* = 7.1 Hz, 3H), 4.02 (t, *J* = 6.3 Hz, 4H), 3.92 (s, 2H), 2.08 – 1.91 (m, 4H), 1.90 – 1.80 (m, 4H), 1.59 – 1.47 (m, 4H). **$^1$H NMR** (600 MHz, $CDCl_3$, -60 °C): δ= 9.86 (s, 2H), 7.83 (appt. d, *J* = 5.1 Hz, 4H), 7.63 – 7.57 (m, 2H), 6.95 (appt. d, *J* = 5.6 Hz, 4H), 5.94 – 5.76 (m, 3H), 4.58 – 4.48 (m, 3H), 4.44 – 4.38 (m, 4H), 4.03 – 3.86 (m, 8H), 2.65 (d, *J* = 6.0 Hz, 0.5H), 2.61 (t, *J* = 6.1 Hz, 0.25), 2.45 – 2.37 (m, 0.5H), 2.26 (s, 2H), 2.01 – 1.93 (m, 4H), 1.88 – 1.81 (m, 5H), 1.60 – 1.35 (m, 5H). **$^{13}$C NMR** (126 MHz, $CDCl_3$): δ= 190.9, 164.1, 145.6, 132.1, 130.1, 122.5, 114.9, 67.9, 50.2, 30.1, 28.6, 23.3. **HRMS** (EI): *m/z* calcd for $C_{42}H_{48}N_6O_6$ $[M+H]^+$: 733.3714, found 733.3711. **IR (ATR)**: v/cm$^{-1}$: 2941, 2862, 1684, 1599, 1576, 1508, 1256, 1159.



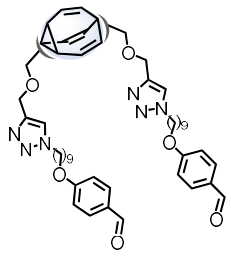
**Compound 5g:** Using general procedure 1 and employing the known azide **4g**(13), the product was isolated as an orange oil after flash column chromatography (14.1 mg, 50%). **$^1$H NMR** (400 MHz, $CDCl_3$, RT): δ= 9.87 (s, 2H), 7.82 (appt. d, *J* = 8.8 Hz, 4H), 7.52 (s, 2H), 6.97 (appt. d, *J* = 8.7 Hz, 4H), 5.87 (s, 2H), 4.56 (s, 2H), 4.35 (t, *J* = 7.1 Hz, 4H), 4.02 (t, *J* = 6.3 Hz, 4H), 3.91 (s, 2H), 2.04 – 1.87 (m, 4H), 1.82 – 1.71 (m, 4H), 1.56 – 1.47 (m, 4H), 1.44 – 1.35 (m, 4H). **$^1$H NMR** (600 MHz, $CDCl_3$, -60 °C): δ= 9.86 (s, 2H), 7.83 (appt. d, *J* = 5.3 Hz, 4H), 7.62 – 7.56 (m, 2H), 6.97 (appt. d, *J* = 5.6 Hz, 4H), 5.95 – 5.76 (m, 3H), 4.58 – 4.48 (m, 3H), 4.42 – 4.34 (m, 4H), 4.04 – 3.85 (m, 8H), 2.66 (d, *J* = 5.8 Hz, 0.5H), 2.62 (t, 0.3H), 2.45 – 2.37 (m, 0.5H), 2.26 (s, 2H), 1.96 – 1.88 (m, 5H), 1.82 – 1.74 (m, 5H), 1.54 – 1.45 (m, 5H), 1.40 – 1.32 (m, 5H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ= 190.9, 164.2, 145.5, 132.1, 130.0, 122.4, 114.9, 68.2, 50.3, 30.3, 28.9, 26.4, 25.6. **HRMS** (EI): *m/z* calcd for $C_{44}H_{52}N_6O_6$ $[M+H]^+$: 761.4027, found 761.4021. **IR (ATR)**: v/cm$^{-1}$: 2940, 2860, 1686, 1601, 1576, 1508, 1258, 1159.



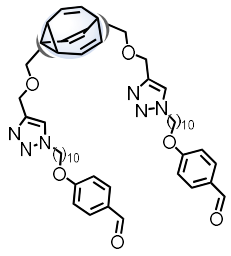
**Compound 5h:** Using general procedure 1 and employing the azide **4h**, the product was isolated as an orange oil after flash column chromatography (16.3 mg, 55%). **$^1$H NMR** (400 MHz, $CDCl_3$, RT): δ= 9.85 (s, 2H), 7.80 (appt. d, *J* = 8.7 Hz, 4H), 7.51 (s, 1H), 6.96 (appt. d, *J* = 8.7 Hz, 4H), 5.86 (s, 2H), 4.55 (s, 2H), 4.33 (t, *J* = 7.2 Hz, 4H), 4.00 (t, *J* = 6.4 Hz, 4H), 3.91 (s, 2H), 1.94 – 1.85 (m, 4H), 1.83 – 1.74 (m, 4H), 1.47 – 1.29 (m, 12H). **$^1$H NMR** (600 MHz, $CDCl_3$, -60 °C): δ= 9.86 (s, 2H), 7.83 (appt. d, *J* = 4.8 Hz, 4H), 7.65 – 7.52 (m, 2H), 6.97 (appt. d, *J* = 5.3 Hz, 4H), 5.95 – 5.76 (m, 3H), 4.80 – 4.49 (m, 6H), 4.42 – 4.32 (m, 5H), 4.02 – 3.87 (m, 8H), 2.70 – 2.54 (m, 1H), 2.45 – 2.36 (m, 1H), 2.26 (s, 2H), 1.95 – 1.83 (m, 5H), 1.83 – 1.71 (m, 6H), 1.48 – 1.21 (m, 19H). **$^{13}$C NMR** (126 MHz, $CDCl_3$): δ= 190.9, 164.2, 145.4, 132.1, 129.9, 122.4, 114.8, 68.3, 50.3, 30.3, 29.0, 28.8, 26.5, 25.9. **HRMS** (EI): *m/z* calcd for $C_{46}H_{57}N_6O_6$ $[M+H]^+$: 789.4334, found 789.4326. **IR (ATR)**: v/cm$^{-1}$: 2936, 2857, 1686, 1601, 1576, 1508, 1256, 1159.



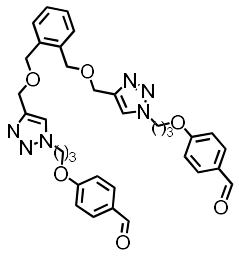
**Compound 5i:** Using general procedure 1 and employing the azide **4i**, the product was isolated as an orange oil after flash column chromatography (15 mg, 49%). **$^1$H NMR** (500 MHz, $CDCl_3$, RT): δ= 9.87 (s, 2H), 7.82 (appt. d, *J* = 8.8 Hz, 4H), 7.52 (s, 2H), 6.97 (appt. d, *J* = 8.7 Hz, 4H), 5.88 (s, 2H), 4.56 (s, 2H), 4.33 (t, *J* = 7.2 Hz, 4H), 4.02 (t, *J* = 6.5 Hz, 4H), 3.92 (s, 2H), 1.94 – 1.84 (m, 4H), 1.82 – 1.75 (m, 4H), 1.48 – 1.39 (m, 4H), 1.37 – 1.30 (m, 12H). **$^1$H NMR** (600 MHz, $CDCl_3$, -60 °C): δ= 9.85 (s, 2H), 7.83 (appt. d, *J* = 5.2 Hz, 4H), 7.61 – 7.52 (m, 2H), 6.97 (appt. d, *J* = 5.7 Hz, 4H), 5.95 – 5.74 (m, 3H), 4.58 – 4.47 (m, 3H), 4.39 – 4.29 (m, 4H), 4.03 – 3.84 (m, 8H), 2.65 (d, *J* = 5.9 Hz, 0.25H), 2.61 (t, 0.25H), 2.46 – 2.36 (m, 0.5H), 2.25 (s, 1H), 1.91 – 1.81 (m, 4H), 1.81 – 1.70 (m, 5H), 1.45 – 1.36 (m, 4H), 1.35 – 1.21 (m, 15H). **$^{13}$C NMR** (126 MHz, $CDCl_3$): δ= 190.9, 164.3, 145.5, 132.1, 129.9, 122.4, 114.9, 68.4, 50.4, 30.4, 29.2, 29.1, 29.0, 26.5, 26.0. **HRMS** (EI): *m/z* calcd for $C_{48}H_{60}N_6O_6$ $[M+H]^+$: 817.4653, found 817.4646. **IR (ATR)**: v/$cm^{-1}$: 2936, 2859, 1684, 1601, 1260, 1215, 1159.



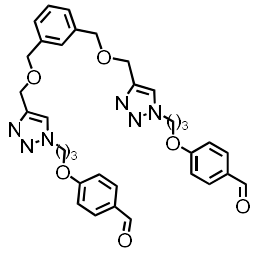
**Compound 5j:** Following a modification to general procedure 1 and employing the azide **5j**, bis-propargyl bullvalene **3** (20 mg, 0.075 mmol, 1 equiv) was used. The product was isolated as an orange oil after flash column chromatography (45 mg, 71%). **$^1$H NMR** (400 MHz, $CDCl_3$): δ= 9.85 (s, 2H), 7.80 (appt. d, *J* = 8.7 Hz, 4H), 7.51 (s, 2H), 6.97 (appt. d, *J* = 8.7 Hz, 4H), 5.86 (s, 2H), 4.55 (s, 2H), 4.31 (t, *J* = 7.2 Hz, 4H), 4.01 (t, *J* = 6.5 Hz, 4H), 3.91 (s, 2H), 1.91 – 1.82 (m, 4H), 1.82 – 1.72 (m, 4H), 1.47 – 1.38 (m, 4H), 1.36 – 1.26 (m, *J* = 21.3 Hz, 16H).**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ= 190.9, 164.3, 145.4, 132.1, 129.9, 122.3, 114.9, 68.4, 50.4, 30.4, 29.4, 29.3, 29.1, 29.0, 26.5, 26.0. **HRMS** (EI): *m/z* calcd for $C_{50}H_{64}N_6O_6$ $[M+H]^+$: 845.4966, found 845.4958. **IR (ATR)**: v/$cm^{-1}$: 3019, 2932, 2857, 1686, 1601, 1216, 1159.



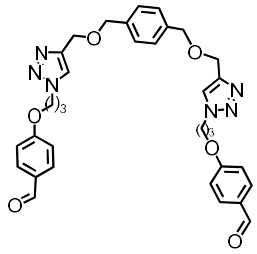
**Compound 5k:** Using general procedure 1 and employing the known azide **4k**(14), the product was isolated as an orange oil after flash column chromatography (23 mg, 70%). **$^1$H NMR** (400 MHz, $CDCl_3$): δ= 9.86 (s, 2H), 7.81 (appt. d, *J* = 8.7 Hz, 4H), 7.51 (s, 2H), 6.97 (appt. d, *J* = 8.8 Hz, 4H), 5.87 (s, 2H), 4.56 (s, 2H), 4.32 (t, *J* = 7.2 Hz, 4H), 4.02 (t, *J* = 6.5 Hz, 4H), 3.91 (s, 2H), 1.93 – 1.84 (m, 4H), 1.83 – 1.72 (m, 4H), 1.48 – 1.39 (m, 4H), 1.38 – 1.19 (m, *J* = 22.3 Hz, 20H). **$^1$H NMR** (600 MHz, $CDCl_3$, -60 °C): δ= 9.86 (s, 2H), 7.83 (appt. d, *J* = 4.6 Hz, 4H), 7.63 – 7.56 (m, 2H), 6.98 (appt. d, *J* = 5.2 Hz, 4H), 5.96 – 5.75 (m, 3H), 4.61 – 4.46 (m, 3H), 4.40 – 4.27 (m, 6H), 4.05 – 3.83 (m, 10H), 2.65 (d, *J* = 5.8 Hz, 0.3H), 2.61 (t, 0.25H), 2.47 – 2.35 (m, 1H), 2.25 (s, 1H), 1.94 – 1.67 (m, 14H), 1.45 – 1.33 (m, 8H), 1.31 – 1.04 (m, 40H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ= 190.9, 164.4, 145.4, 132.1, 129.9, 122.3, 114.9, 68.5, 50.4, 30.4, 29.5, 29.4, 29.4, 29.1, 29.1, 26.6, 26.0. **HRMS** (EI): *m/z* calcd for $C_{52}H_{68}N_6O_6$ $[M+H]^+$: 873.5279, found 873.5243. **IR (ATR)**: v/$cm^{-1}$: 3019, 2930, 2857, 1647, 1215.



**Compound *o*-5:** Following a modification to general procedure 1, 1,2-bis((prop-2-yn-1-yloxy)methyl)benzene (10 mg, 0,047mmol, 1 equiv) was used. The product was isolated as an orange oil after flash column chromatography (21 mg, 72%). **$^{1}$H NMR** (400 MHz, $CDCl_3$): δ= 9.86 (s, 2H), 7.80 (appt. d, *J* = 8.8 Hz, 4H), 7.60 (s, 2H), 7.39 – 7.32 (m, 2H), 7.29 – 7.25 (m, 2H), 6.96 (appt. d, *J* = 8.7 Hz, 4H), 4.63 (d, *J* = 2.8 Hz, 8H), 4.59 (t, *J* = 6.8 Hz, 4H), 4.05 (t, *J* = 5.8 Hz, 4H), 2.47 – 2.39 (m, *J* = 6.4 Hz, 4H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ= 190.8, 163.4, 145.2, 136.2, 132.1, 130.3, 129.1, 128.1, 123.2, 114.8, 70.2, 64.7, 63.8, 47.0, 29.8. **HRMS** (EI): *m/z* calcd for $C_{34}H_{36}N_6O_6$ $[M+H]^+$: 625.2769, found 625.2790. **IR (ATR)**: v/$cm^{-1}$: 3018, 1690, 1601, 1258, 1215.

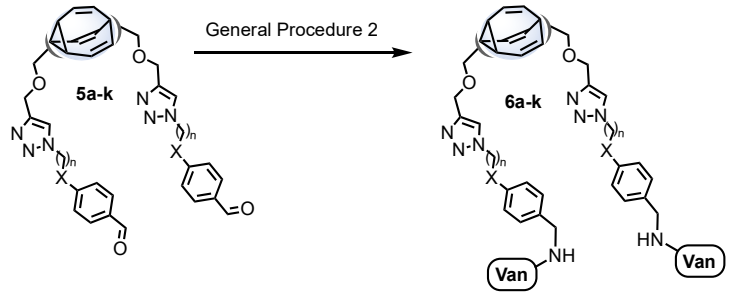


**Compound *m*-5:** Following a modification to general procedure 1, 1,3-bis((prop-2-yn-1-yloxy)methyl)benzene (10 mg, 0.047mmol, 1 equiv) was used. The product was isolated as an orange oil after flash column chromatography (20 mg, 69%). **$^{1}$H NMR** (500 MHz, $CDCl_3$): δ= 9.86 (s, 2H), 7.80 (appt.d, *J* = 8.7 Hz, 4H), 7.64 (s, 2H), 7.38 – 7.20 (m, 5H), 6.95 (appt.d, *J* = 8.7 Hz, 4H), 4.67 (s, 4H), 4.62 – 4.55 (m, 8H), 4.06 (t, *J* = 5.8 Hz, 4H), 2.47 – 2.40 (m, 4H). **$^{13}$C NMR** (126 MHz, $CDCl_3$): δ= 190.9, 163.4, 145.0, 138.1, 132.1, 130.4, 128.7, 127.5, 127.4, 123.5, 114.8, 72.6, 64.6, 63.5, 47.4, 29.8. **HRMS** (EI): *m/z* calcd for $C_{34}H_{36}N_6O_6$ $[M+H]^+$: 625.2769, found 625.2822. **IR (ATR)**: v/$cm^{-1}$: 2957, 1686, 1601, 1256, 1217, 1161.



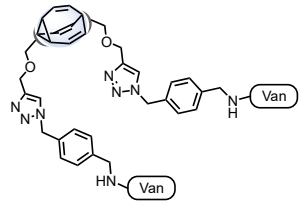
**Compound *p*-5:** Following a modification to general procedure 1, 1,4-bis((prop-2-yn-1-yloxy)methyl)benzene (10 mg, 0.047mmol, 1 equiv) was used. The product was isolated as an orange oil after flash column chromatography (20 mg, 69%). **$^{1}$H NMR** (400 MHz, $CDCl_3$): δ= 9.86 (s, 2H), 7.80 (appt. d, *J* = 8.8 Hz, 4H), 7.56 (s, 2H), 7.29 (s, 4H), 6.96 (appt. d, *J* = 8.6 Hz, 4H), 4.65 (s, 4H), 4.61 – 4.55 (m, 8H), 4.05 (t, *J* = 5.8 Hz, 4H), 2.47 – 2.40 (m, 4H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ= 190.8, 163.5, 145.4, 137.5, 132.2, 130.4, 128.1, 123.1, 114.8, 72.4, 64.6, 63.8, 47.1, 29.8. **HRMS** (EI): *m/z* calcd for $C_{34}H_{36}N_6O_6$ $[M+H]^+$: 625.2769, found 625.2788. **IR (ATR)**: v/$cm^{-1}$: 2932, 2857, 1686, 1599, 1508, 1256, 1159.

1.5 Synthesis of vancomycin dimers **6a**–**k**

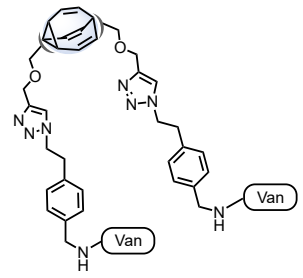



*General procedure 2:* To a solution of vancomycin hydrochloride (22.3 mg, 0.015 mmol, 2.5 equiv) in MeOH (0.25 mL) and DMF (0.25 mL) were added DIPEA (0.024 mmol, 4.0 equiv) and corresponding bullvalene derivate (0.006 mmol, 1 equiv). The mixture was stirred at 70 °C for 2 hours and cooled to room temperature, at which time $NaCNBH_3$ (0.060 mmol, 10.0 equiv) was added. The solution was heated to 70 °C and stirred overnight (16 hours) then, concentrated to remove the solvent. The crude was redissolved in 0.25 mL $H_2O$ and 0.25 mL DMSO and directly purified by HPLC to afford the desired product.

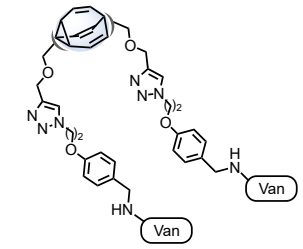
*Comments on characterization:* Due to the fluxional nature and large molecular weight of the vancomycin dimers **6a–k**, characterization using NMR spectroscopy was found to be inappropriate (See figure S2-S4 below). Vancomycin has been demonstrated to be stable to reductive amination conditions using $NaCNBH_3$(15). Therefore, we have characterized the shapeshifting vancomycin dimers primarily using high-resolution mass spectrometry, and copies of the spectra obtained for compounds **6a–k** have been included in **Section 6**.




**Compound 6a:** Following a modification to general procedure 2, vancomycin hydrochloride (53.6 mg, 0.036 mmol, 2.5 equiv) was used. The product was purified by HPLC (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 4 min, 20 to 40% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 10 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 5 min) and isolated as a white solid (10 mg, 20%). $\mathbf{t_R}$: 5.3 min. **HRMS** (EI): *m/z* calcd for $C_{166}H_{182}Cl_4N_{24}O_{50}$ $[M+3H]^+$: 1151.3809, found 1151.3824; $[M+4H]^+$: 863.7876, found 863.7872. $\mathbf{[\alpha]_D^{26}}$ +44.44 (*c* = 0.9, MeOH).

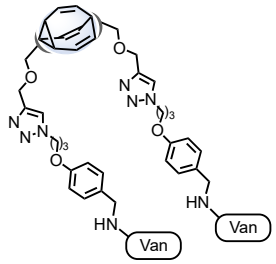



**Compound 6b:** Following a modification to general procedure 2, vancomycin hydrochloride (78.3 mg, 0.053 mmol, 2.5 equiv) was used. The product was purified by HPLC (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 4 min, 10 to 60% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 10 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 2 min) and isolated as a white solid (6 mg, 8%). $\mathbf{t_R}$: 4.9 min. **HRMS** (EI): *m/z* calcd for $C_{168}H_{186}Cl_4N_{24}O_{50}$ $[M+3H]^+$: 1160.7168, found 1160.7206; $[M+4H]^+$: 870.7876, found 870.7919. $\mathbf{[\alpha]_D^{26}}$ +40.00 (*c* = 1.00, MeOH).



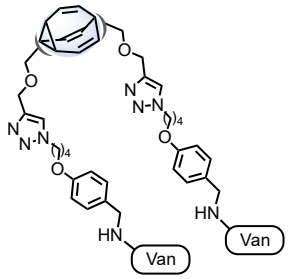

**Compound 6c:** Following a modification to general procedure 2, vancomycin hydrochloride (71.6 mg, 0.048 mmol, 2.5 equiv) was used. The product was purified by HPLC (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 4 min, 10 to 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 12 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 1 min) and isolated as a white solid (9 mg, 19%). $\mathbf{t_R}$:5.2 min. **HRMS** (EI): *m/z* calcd for

$C_{168}H_{186}Cl_4N_{24}O_{52}$ [M+3H]$^+$: 1171.3873, found 1171.3857; [M+4H]$^+$: 878.7923, found 878.7919. **[α]$_D^{26}$** +88.89 (*c* = 0.9, MeOH).

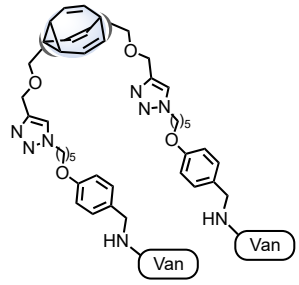


**Compound 6d:** Following a modification to general procedure 2, vancomycin hydrochloride (504.9 mg, 0.340 mmol, 2.5 equiv) was used. The product was purified by HPLC (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 4 min, 10 to 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 10 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 2 min) and isolated a white solid (112 mg, 23%). **$t_R$**: 5.3 min. **HRMS** (EI): *m/z* calcd for $C_{170}H_{190}Cl_4N_{24}O_{52}$ [M+3H]$^+$: 1180.7311, found 1180.7270; [M+4H]$^+$: 885.8002, found 885.7996. **[α]$_D^{26}$** +40.00 (*c* = 0.9, MeOH).

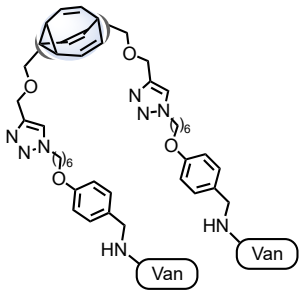
*Scaled-up procedure:* To a solution of vancomycin hydrochloride (851 mg, 0.587 mmol, 2.50 equiv.) in MeOH (30 mL) and DMF (30 mL) was added DIPEA (160 µL, 0.919 mmol, 4.00 equiv.) and **5d** (155 mg, 0.229 mmol 1.00 equiv.). The solution was heated to 80 °C and, after 2 hours, cooled to room temperature. $NaCNBH_3$ (144.5 mg, 2.30 mmol, 10.0 equiv.) was added, and the solution was then heated to 80 °C for 22 hours. The mixture was cooled to room temperature, concentrated to remove the solvent, and purified by HPLC (Phenomenex, Luna 5u C18(2), 100 Å, 21.2 X 250mm, 5 µm, flow rate 25 mL/min, Mobile Phase A: 0.1% formic acid in $H_2O$, Mobile Phase B: 0.1% formic acid in $CH_3CN$, 10% B for 3 minutes, 10–90% B over 4.5 minutes, 90% B for 1 minute, 90–10% B over 1.5 minutes, 10% B for 2 minutes) and isolated as a white solid (244 mg, 30%) **$t_R$**: 6.7 min. **HRMS** (EI): *m/z* calcd for $C_{170}H_{190}Cl_4N_{24}O_{52}$ [M+4H]$^+$: 885.8002, found 885.8009.



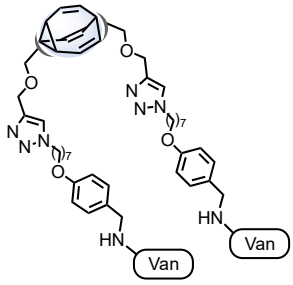
**Compound 6e:** Following a modification to general procedure 2, vancomycin hydrochloride (68.5 mg, 0.046 mmol, 2.5 equiv) was used. The product was isolated a white solid after HPLC purification (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 4 min, 20 to 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 12 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 3 min, 13 mg, 20%). **$t_R$**: 5.7 min. **HRMS** (EI): *m/z* calcd for $C_{172}H_{194}Cl_4N_{24}O_{52}$ [M+3H]$^+$: 1190.0749, found 1190.0750; [M+4H]$^+$: 892.8080, found 892.8081. **[α]$_D^{26}$** +57.14 (*c* = 1.4, MeOH).



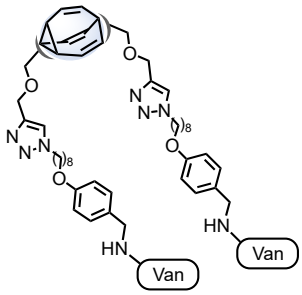
**Compound 6f:** Following general procedure 2, the product was purified by HPLC (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 1 min, 20 to 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 10 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 5 min) and isolated as a white solid (2.1 mg, 10%). **$t_R$**: 5.9 min. **HRMS** (EI): *m/z* calcd for $C_{174}H_{198}Cl_4N_{24}O_{52}$ [M+3H]$^+$: 1199.4186, found 1199.4143; [M+4H]$^+$: 899.8158, found 899.8186. **[α]$_D^{26}$** +40.00 (*c* = 1.00, MeOH).



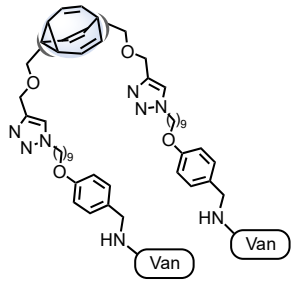
**Compound 6g:** Following a modification to general procedure 2, vancomycin hydrochloride (17.1 mg, 0.012 mmol, 2.5 equiv) were used. The product was purified by HPLC as TFA salt (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 1 min, 20 to 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 10 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 5 min) and isolated as a white solid (2.5 mg, 15%). $\mathbf{t_R}$: 5.8 min. **HRMS** (EI): *m/z* calcd for $C_{176}H_{202}Cl_4N_{24}O_{52}$ $[M+3H]^+$: 1208.7624, found 1208.7603; $[M+4H]^+$: 906.8236, found 906.8234. $\mathbf{[\alpha]_D^{26}}$ +61.54 (*c* = 1.3, MeOH).



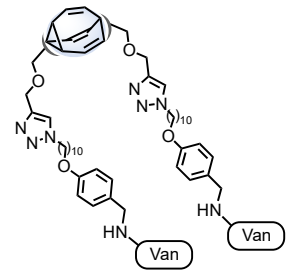
**Compound 6h:** Following a modification to general procedure 2, vancomycin hydrochloride (56.5 mg, 0.038mmol, 2.5 equiv) was used. The product was purified by HPLC as TFA salt (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 4 min, 20 to 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 12 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 3 min) and isolated as a white solid (6 mg, 11%). $\mathbf{t_R}$: 6.2 min. **HRMS** (EI): *m/z* calcd for $C_{178}H_{206}Cl_4N_{24}O_{52}$ $[M+3H]^+$: 1218.1062, found 1218.0998; $[M+4H]^+$: 913.8315, found 913.8287. $\mathbf{[\alpha]_D^{26}}$ +88.89 (*c* = 0.9, MeOH).



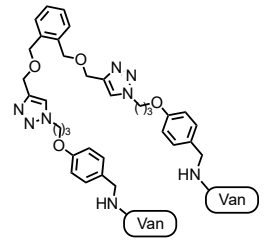
**Compound 6i:** Following a modification to general procedure 2, vancomycin hydrochloride (20.5 mg, 0.014 mmol, 2.5 equiv) was used. The product was purified by HPLC as TFA salt (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 4 min, 20 to 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 10 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 2 min) and isolated as a white solid (3 mg, 15%). $\mathbf{t_R}$: 6.7 min. **HRMS** (EI): *m/z* calcd for $C_{180}H_{210}Cl_4N_{24}O_{52}$ $[M+3H]^+$: 1227.4499, found 1227.6791; $[M+4H]^+$: 920.8393, found 921.0120. $\mathbf{[\alpha]_D^{26}}$ +100.00 (*c* = 0.8, MeOH).



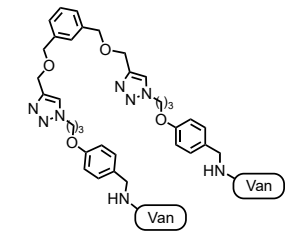
**Compound 6j:** Following a modification to general procedure 2, vancomycin hydrochloride (74.7 mg, 0.050 mmol, 2.5 equiv) was used. The product was purified by HPLC as TFA salt (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 4 min, 20 to 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 10 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 2 min) and isolated as a white solid (6 mg, 10%). $\mathbf{t_R}$: 6.8 min. **HRMS** (EI): *m/z* calcd for $C_{182}H_{214}Cl_4N_{24}O_{52}$ $[M+3H]^+$: 1235.4604, found 1236.7936; $[M+4H]^+$: 926.8453, found 927.8480. $\mathbf{[\alpha]_D^{27}}$ +44.44 (*c* = 0.9, MeOH).



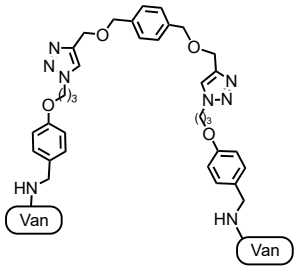
**Compound 6k:** Following general procedure 2, the product was purified by HPLC (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 1 min, 20 to 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 10 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 5 min) and isolated as a white solid (2 mg, 9%). $\mathbf{t_R}$: 7.2 min. **HRMS** (EI): *m/z* calcd for $C_{184}H_{218}Cl_4N_{24}O_{52}$ $[M+3H]^+$: 1246.1375, found 1246.3540; $[M+4H]^+$: 934.8549, found 935.0183. $\mathbf{[\alpha]_D^{27}}$ +114.29 (*c* = 0.7, MeOH).



**Compound 7a:** Following a modification to general procedure 2, vancomycin hydrochloride (59.5 mg, 0.040 mmol, 2.5 equiv) was used. The product was purified by HPLC as TFA salt (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 4 min, 10 to 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 10 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 2 min) and isolated as a white solid (12 mg, 21%). $\mathbf{t_R}$: 5.15 min**. HRMS** (EI): *m/z* calcd for $C_{166}H_{186}Cl_4N_{24}O_{52}$ $[M+3H]^+$: 1163.3873, found 1163.6029; $[M+4H]^+$: 872.7923, found 872.7964. $\mathbf{[\alpha]_D^{26}}$ +44.44 (*c* = 0.9, MeOH).



**Compound 7b:** Following a modification to general procedure 2, vancomycin hydrochloride (71.4 mg 0.048 mmol, 2.5 equiv) was used. The product was purified by HPLC as TFA salt (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 4 min, 10 to 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 10 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 2 min) and isolated as a white solid (17 mg, 25%). $\mathbf{t_R}$: 5.16 min. **HRMS** (EI): *m/z* calcd for $C_{166}H_{186}Cl_4N_{24}O_{52}$ $[M+3H]^+$: 1163.3873, found 1163.3880; $[M+4H]^+$: 872.7923, found 872.7964. $\mathbf{[\alpha]_D^{26}}$ +66.67 (*c* = 1.2, MeOH).



**Compound 7c:** Following a modification to general procedure 2, vancomycin hydrochloride (59.5 mg 0.040 mmol, 2.5 equiv) was used. The product was purified by HPLC as TFA salt (Agilent C18 150 mm x 21.2 mm, flow rate 20 mL / min, 5% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 4 min, 10 to 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) over 10 minutes, 90% $CH_3CN$ (0.1% TFA) in $H_2O$ (0.1% TFA) for 2 min) and isolated as a white solid (13.5 mg, 24%). $\mathbf{t_R}$: 5.11 min. **HRMS** (EI): *m/z* calcd for $C_{166}H_{186}Cl_4N_{24}O_{52}$ $[M+3H]^+$: 1163.3873, found 1163.3881; $[M+4H]^+$: 872.7923, found 872.7955. $\mathbf{[\alpha]_D^{26}}$ +44.44 (*c* = 0.9, MeOH).

## 1.6 Purification and characterization of vancomycin dimers **6a–k**

SVDs **6a–k** were purified using reverse-phase HPLC. Figure S1 shows a representative example of the HPLC trace of the crude reaction mixture and the purified product **6d**. Figure S2 shows the full spectrum $^{1}$H NMR of **6d** in methanol-$d_4$. Figure S3 compares the $^{1}$H NMR spectra of vancomycin, bis-aldehyde bullvalene **5d**, and shape-shifting vancomycin dimer **6d** at room temperature. Identification of the bullvalene linker within the sample is obscured due to its low relative signal intensity, amplified by signal broadening. The pair of doublets at 7.56 ppm (Y) and 7.29 ppm (E) most likely arise from the *para*-substituted benzylamine fragment of the tether. The alkenic signals from the bullvalene are most likely buried in the baseline, and other methylene signals from the tether appear to be obscured by low intensity and/or signal overlap.

***Note:*** SVDs **6a–k** were found to be unstable in methanol-$d_4$ and rapidly decomposed. NMR analyses were done immediately after sample preparation.

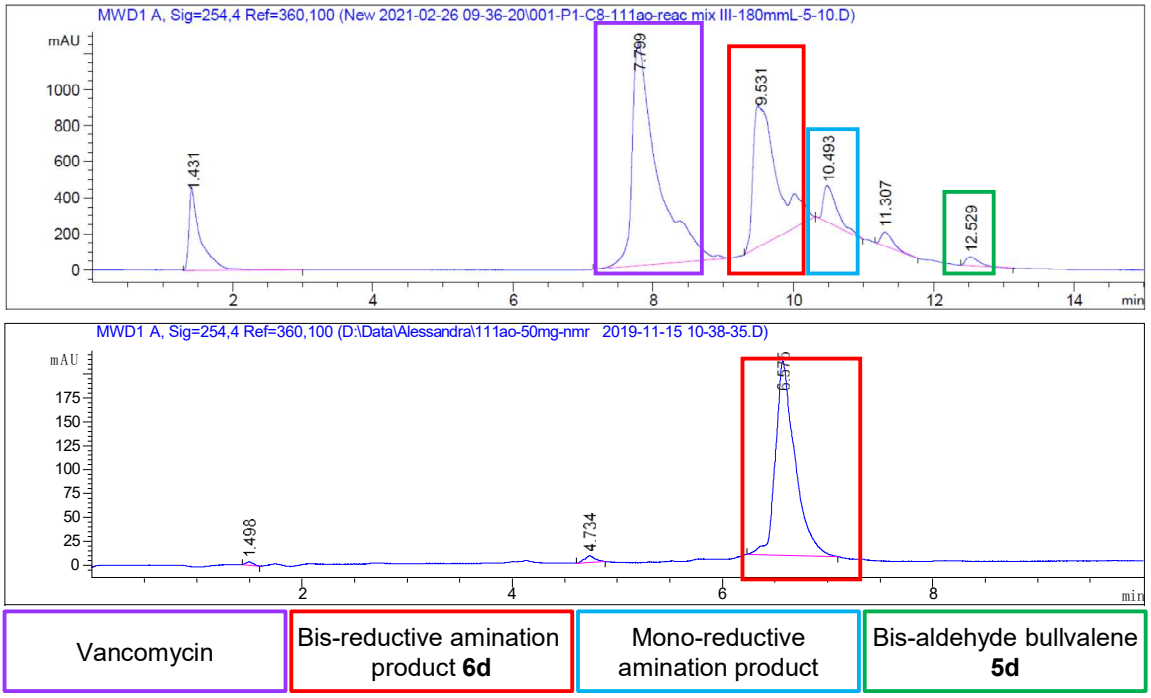



**Figure S1:** A) HPLC trace of the crude reaction mixture of the synthesis of **6d**. B) HPLC trace of compound **6d** after purification. This purified sample was used for subsequent NMR and HRMS characterization.

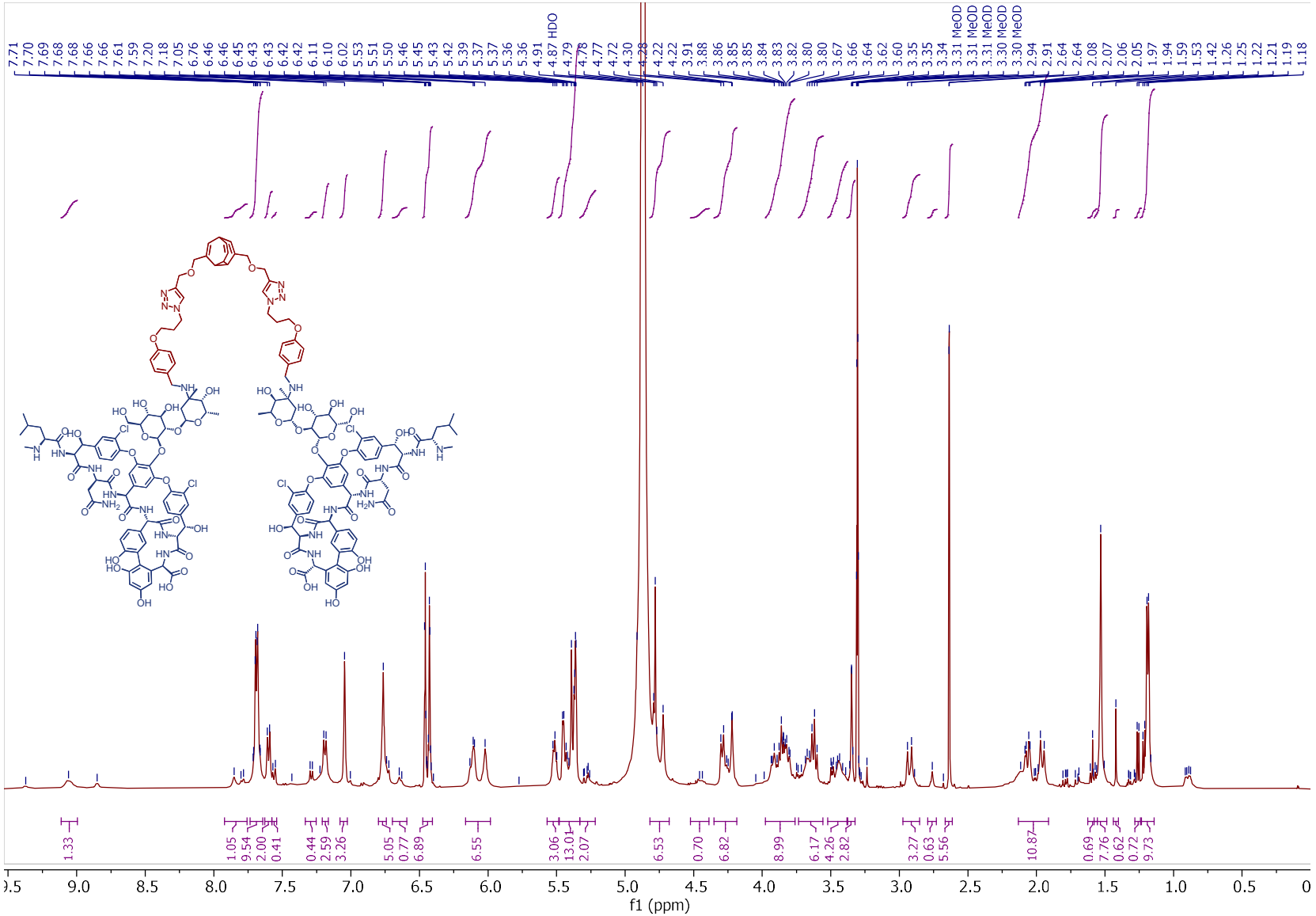



**Figure S2:** $^{1}H$ NMR Spectrum for SVD **6d** in methanol-$d_4$. NMR taken at room temperature.

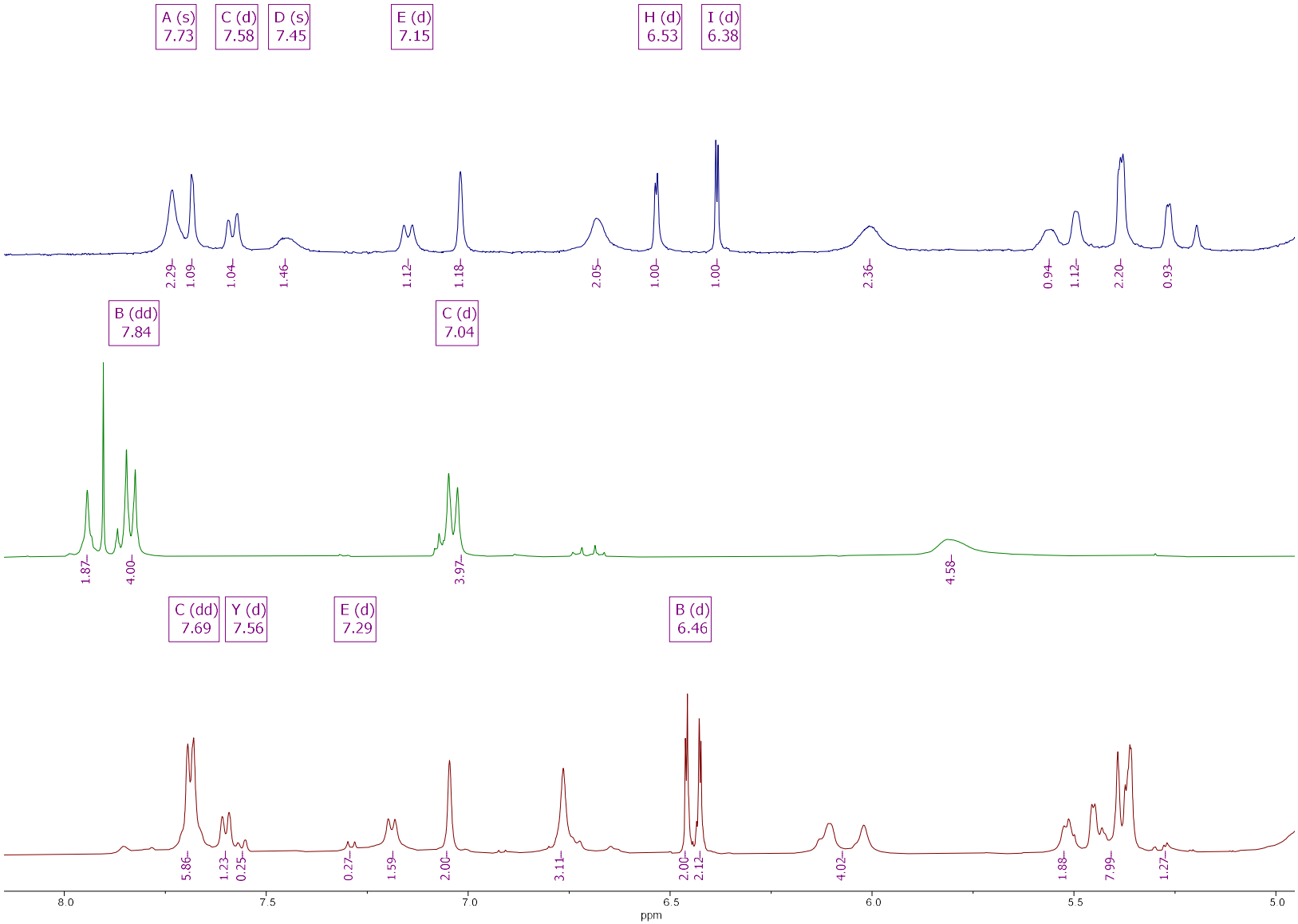



**Figure S3:** Comparison of the $^{1}$H NMR spectra of vancomycin (top), bis-aldehyde bullvalene **5d** (middle), and SVD **6d** (bottom) from 8.0–5.0 ppm in methanol-$d_4$. NMR taken at room temperature.

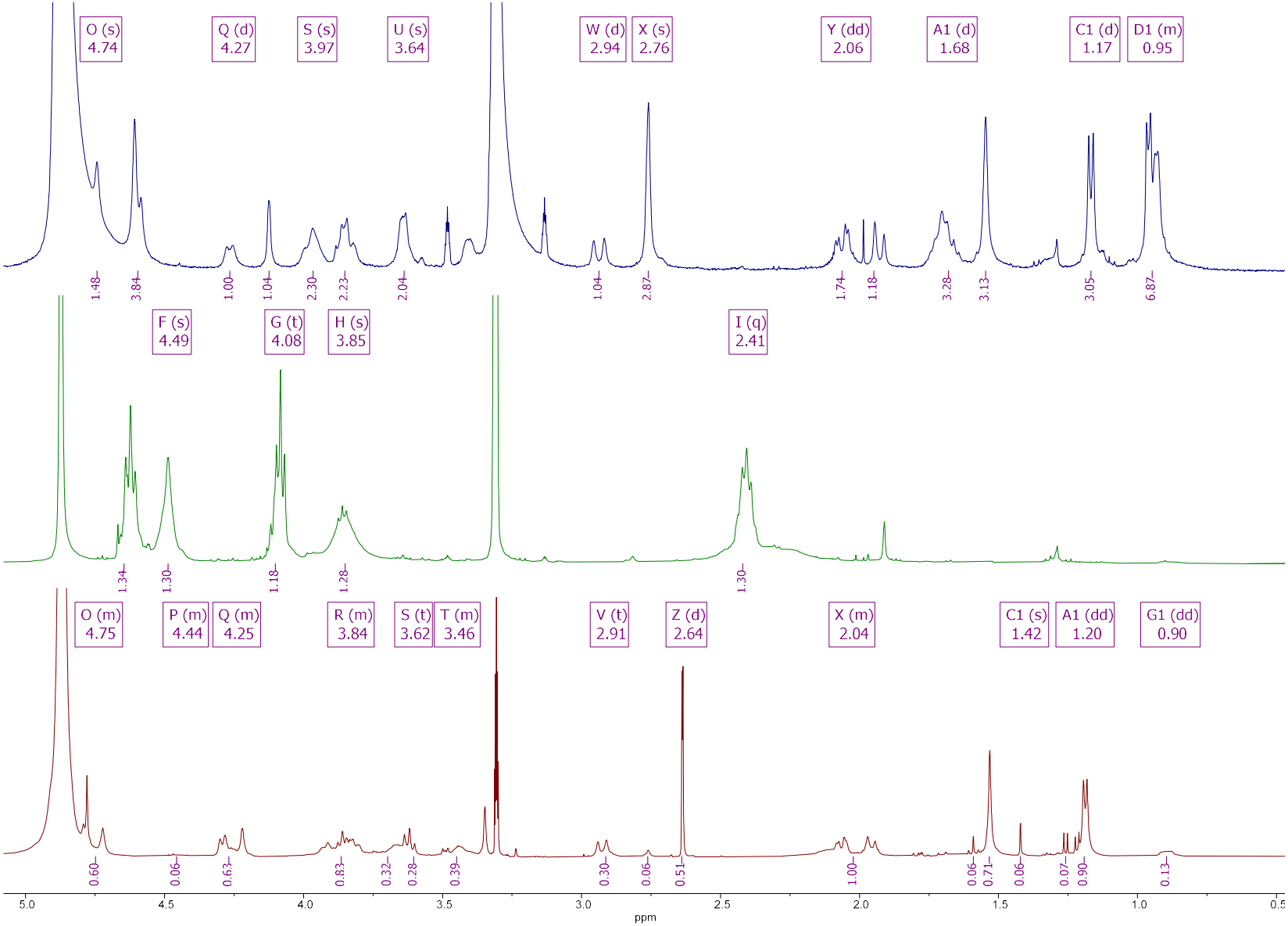



**Figure S4:** Comparison of the $^{1}H$ NMR spectra of vancomycin (top), bis-aldehyde bullvalene **5d** (middle), and SVD **6d** (bottom) from 5.0–0.5 ppm in methanol-$d_4$. NMR taken at room temperature.

## 2 Structural Analysis

The isomer distribution of bullvalene **3** was determined by analogy to *bis*(methylenehydroxy)bullvalene (R=$CH_2OH$), which has been subject to extensive NMR structural elucidation and computational studies.(1) For disubstituted bullvalenes of this type there are six isomers (A-F) whereby substituents are non-adjacent and not substituted at the apical bridgehead position - both structural features that will incur a significant energetic penalty. This is illustrated in the isomer network diagram below (Figure S5). Our previous studies showed that for *bis*(methylenehydroxy)bullvalene all six of these isomers are indeed populated and revealed their characteristic patterns of signals in the aliphatic region of the $^{13}C$ spectrum. From a careful examination of the $^{13}C$ spectrum of dipropargyl bullvalene **3** (Figure S6), these same patterns are apparent and can be assigned in analogy. We can estimate the population distribution from the relative integrals of selected $^{13}C$ signals as A/B/C/D/E/F ~42:36:8:6:4:4. This relatively broad isomer distribution is likely to be characteristic of the derivatives **6a–k**.

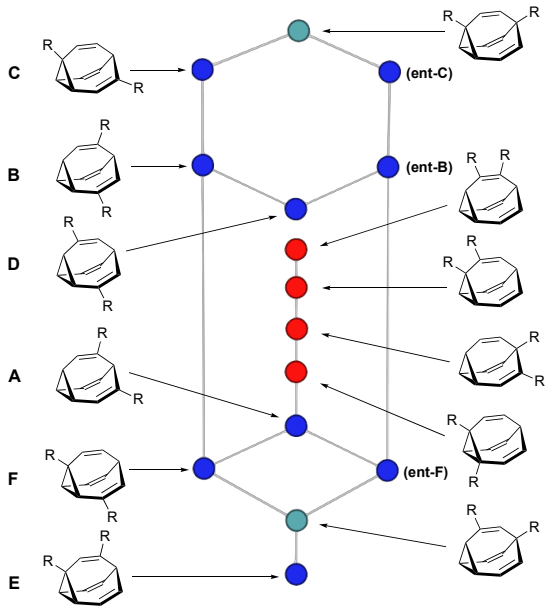



**Figure S5.** *Network diagram of disubstituted bullvalenes.*

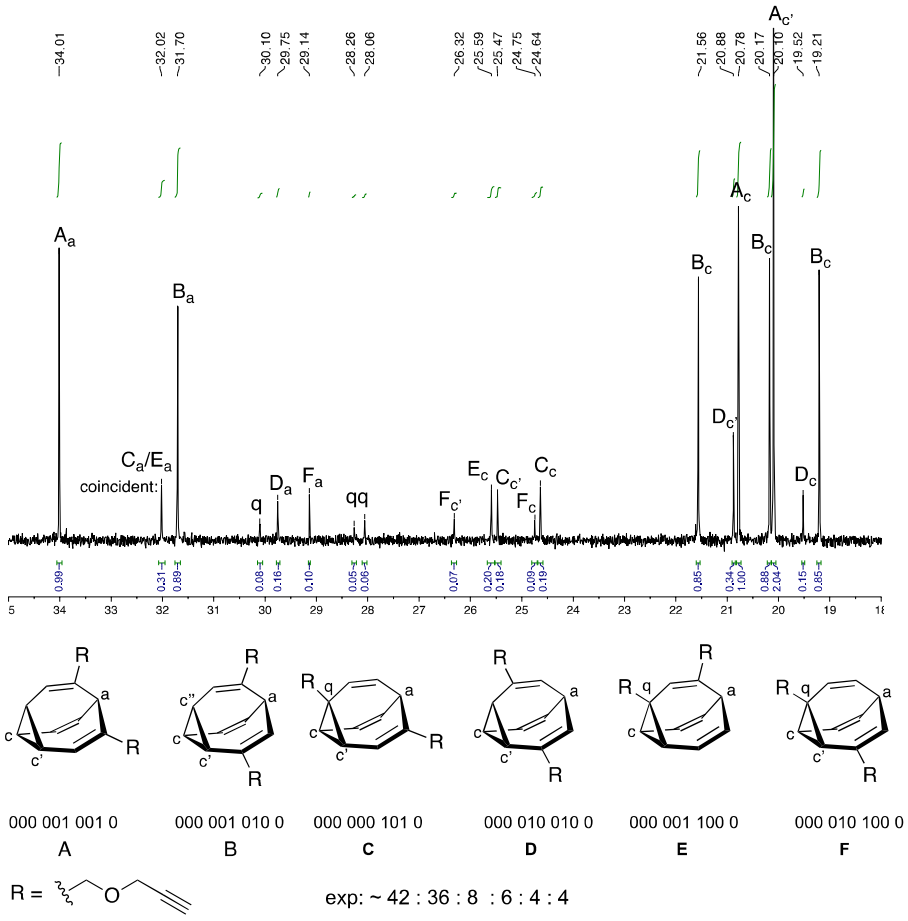



**Figure S6.** NMR analysis of the aliphatic region of the $^{13}C$ spectrum of dipropargyl bullvalene **3**.

The nature and magnitude of the dynamic distance and shape constraints imparted by the bullvalene unit can be appreciated through simple molecular modelling of dimethylbullvalene isomers A-F. Figure S7 presents the predicted methyl-methyl distances which ranges from 4.4 Å (isomer A) to 6.1 Å (isomer C). The methyl-methyl angle ranges from 73° (isomer A) to 142° (isomers C and F). Naturally, the geometric constraints of the bullvalene unit will be coupled with the conformational flexibility of the tether.

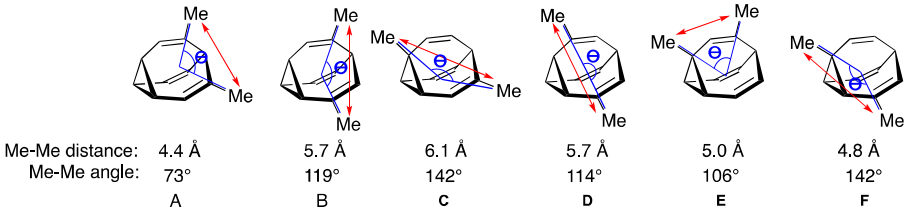



**Figure S7.** Distance and angle constraints of dimethylbullvalene.

The isomer distribution analysis of the *bis*-aldehyde intermediates **5a–k** was assessed by $^{1}H$ and $^{13}C$ NMR spectra, at room temperature and -60 °C ($^{1}H$ NMR only). The analysis of **5f** is presented as an exemplar (Figure S8). In the room temperature proton and carbon spectra, the signals within or nearby to the bullvalene unit appear broad. In the proton spectrum, the triazole proton **Hc** is a broad singlet at room temperature but resolves into a set of overlapping singlets at -60 °C. The bullvalene alkene signals **He** appear as a broad signal at RT, but resolve into a complex set of signals at -60 °C. The same is true for **Hf**, **Hi**, and **Hj**. The aliphatic bullvalene protons **Hj** are

particularly informative, as the low-temperature proton spectrum reveals a doublet and a doublet of doublets characteristic of the apical bridgehead proton signals of isomers **A** and **B**, respectively, in a ~1:1 integral ratio. Indicating that these are the major isomers. The room temperature $^{13}C$ spectrum shows signals distant from the bullvalene core, with the limit being **Cf**. However, very broad signals in the alkenic region are likely due to the bullvalene alkene carbons. The other compounds in this series **5a–k** all show similar diagnostic characteristics.

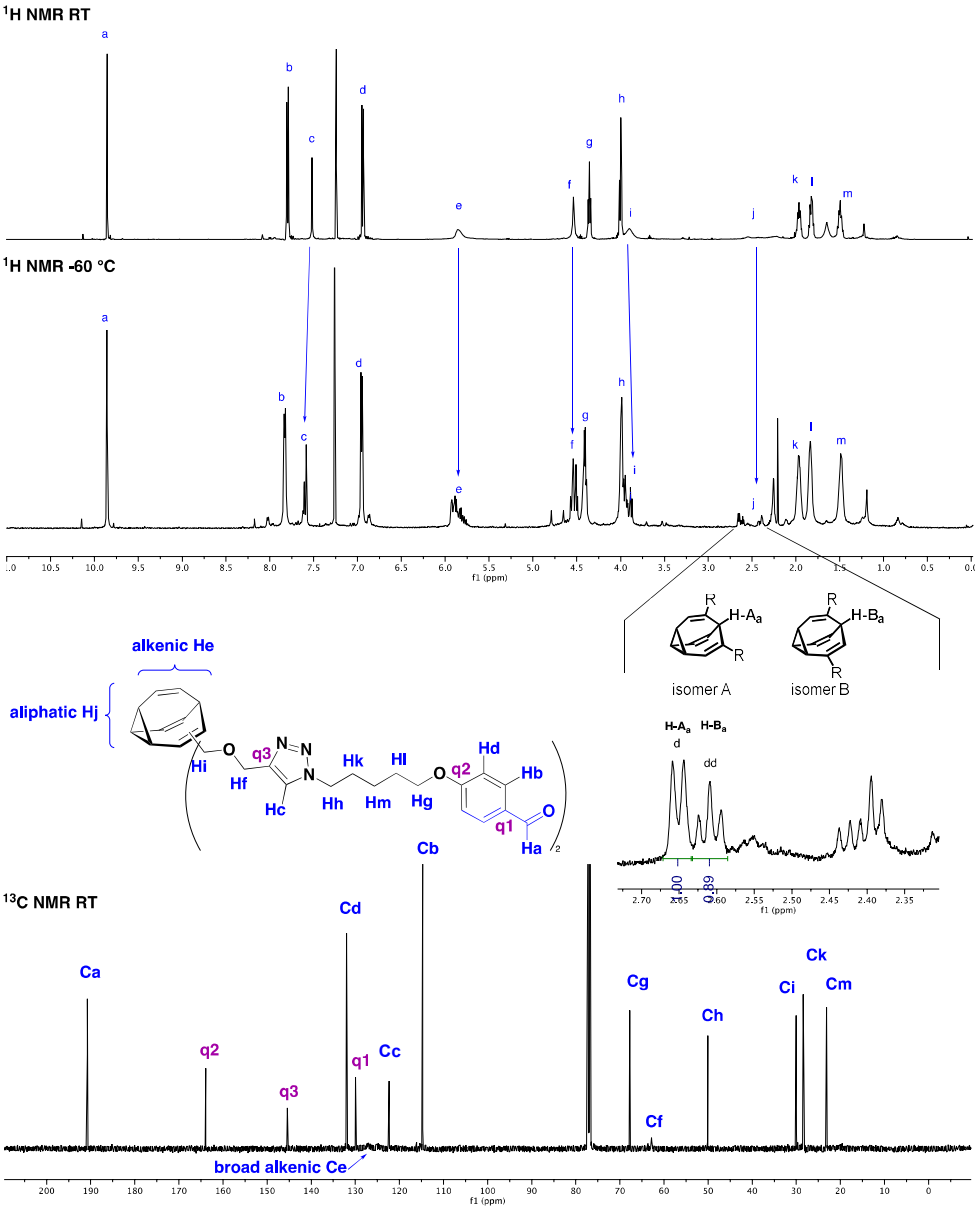



**Figure S8.** NMR analysis of **5f**.

## 3 Biological Screening Methods

### 3.1 Bacterial Strains and Growth Conditions

The methicillin sensitive *Staphylococcus aureus* strain (ATCC® 9144™), Methicillin-Resistant *S. aureus* Panel (ATCC® MP-3™) (Table S1) and the Vancomycin-Resistant Enterococci Panel (ATCC® MP-1™) (Table S2) were sourced from the American Type Culture Collection (ATCC). All bacterial strains were cultured in tryptic soy broth (TSB) or on tryptic soy agar (TSA) plates at 37 °C. Vancomycin sensitive *S. aureus* strain SH1000 was obtained from S. Foster (Horsburgh et al 2002(16)) and vancomycin-resistant *S. aureus* (VRSA) strain VRS1 was from BEI Resources (https://www.beiresources.org/Catalog/bacteria/NR-46410.aspx).

**Table S1.** ATCC Methicillin-Resistant *Staphylococcus aureus* (MRSA) panel, MP-3. The susceptibility profile of strains to the antibiotics methicillin (Met) and vancomycin (Van) are described as R = resistant or S = sensitive.

| ATCC No. | Susceptibility | |
|---|---|---|
| | Met | Van |
| BAA-1761 | R | S |
| BAA-1720 | R | S |
| BAA-1717 | R | S |
| BAA-1707 | R | S |
| BAA-1763 | R | S |
| BAA-1754 | R | S |
| BAA-1766 | R | S |
| BAA-1768 | R | S |
| BAA-1747 | R | S |
| BAA-1764 | R | S |

**Table S2.** ATCC Vancomycin-Resistant Enterococci (VRE) panel, MP-1. The susceptibility profile of strains to the antibiotic vancomycin (Van) are described as R = resistant, I = intermediate or S = sensitive.

| ATCC No. | *Enterococcus* species | Susceptibility | |
|---|---|---|---|
| | | Van | Resistance Type |
| 700221 | *Enterococcus faecium* | R | VanA |
| BAA-2316 | *Enterococcus faecium* | R | VanA |
| BAA-2317 | *Enterococcus faecium* | R | VanA |
| BAA-2318 | *Enterococcus faecium* | R | VanA |
| BAA-2319 | *Enterococcus faecium* | R | VanA |
| BAA-2320 | *Enterococcus faecium* | R | VanA |
| 51299 | *Enterococcus faecalis* | R | VanB |
| 51575 | *Enterococcus faecalis* | R | VanB |
| 51858 | *Enterococcus faecium* | R | VanB |
| BAA-2365 | *Enterococcus faecalis* | R | VanB |
| 49608 | *Enterococcus gallinarum* | I | VanC |
| 49609 | *Enterococcus gallinarum* | I | VanC |
| 49610 | *Enterococcus gallinarum* | I | VanC |
| 700425 | *Enterococcus gallinarum* | I | VanC |
| 700668 | *Enterococcus casseliflavus* | I | VanC |
| 49532 | *Enterococcus faecalis* | S | None |
| 49533 | *Enterococcus faecalis* | S | None |
| BAA-2127 | *Enterococcus faecium* | S | None |
| BAA-2128 | *Enterococcus faecalis* | S | None |

### 3.2 Cell Lines

The human embryonic kidney (HEK293) and human liver (HepG2) cells were maintained through tri-weekly passaging. The cells were cultured in Dulbecco's Modified Eagle Media (DMEM), supplemented with 10% (v/v) fetal bovine serum, 1% (v/v) penicillin/streptomycin, and glucose at a final concentration of 4.5 g/L for the HEK293 cells and 1 g/L for the HepG2 cells. The cell lines were incubated at 37 °C and 5% $CO_2$.

### 3.3 Antibacterial Activity

The minimum inhibitory concentration (MIC) was determined using a broth microdilution method according to guidelines defined by the Clinical Laboratory Standards Institute(17, 18). The assay was conducted using tryptic soy broth (except for VRSA where LB broth was used) in 96-well plates and a bacterial inoculum of $1 \times 10^5$ colony forming units per mL as described previously(19, 20). Plates were incubated at 37 °C for 20 h and growth was assessed by measuring the absorbance at 600 nm. The MIC value was defined as the lowest concentration of compound where no bacterial growth was observed. Experiments were repeated with 3 biological replicates.

### 3.4 Cytotoxicity Screening

The toxicity assays using human cell lines HEK293 and HepG2 was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) viability assay(21, 22). Briefly, cells were seeded in 96-well plates and incubated overnight at 37 °C (5% $CO_2$). The compounds were tested in a 2-fold dilution series in DMEM, with a top concentration of 500 µg/mL in 1% (v/v) DMSO. Compounds were then added to the 96-well plate containing the cells, and the plates incubated at 37 °C (5% $CO_2$) for 48 h. To determine the viability of the cells, MTT is serum-free media and 1 × phosphate buffered saline (PBS) was added to each well at a final concentration of 0.5 mg/mL and plates were incubated for 3 h. Subsequently, the MTT/media solution was removed, and the purple formazan crystals were solubilised in 100% (v/v) DMSO. The absorbance at 570 nm was measured and the percentage viability remaining relative to the DMSO vehicle control determined. Experiments were performed with three technical replicates with the cytotoxic peptide NaD1, at 50 µM, employed as a positive control and 1% (v/v) DMSO as the vehicle control. Unpaired two-tailed Student's *t*-tests were performed using GraphPad Prism software (version 8.0.2).

### 3.5 *Galleria mellonella* Infection Model

Bacteria from an overnight culture of VRE (ATCC© 51575™) was adjusted to a known concentration in 1 × PBS and a microfluidic syringe pump was used to inject 20 µL of suspension into *Galleria mellonella* larvae. Injections were performed into the haemolymph of 20 larvae per treatment via the foremost left proleg. Control larvae were injected with 20 µL of 1 × PBS to measure any potential lethal effects of the injection procedure as well as to measure the tolerance of the larvae to the treatments. After a 30 min recovery, larvae were injected with their respective treatment, vancomycin at 20 mg/kg, SVD **6d** at 20 mg/kg or 5% (v/v) DMSO. Larvae were then incubated statically at 37 °C and observed daily for 7 days post-injection.

### 3.6 Resistance Studies

To determine the propensity for bacteria to develop resistance, VSE (ATCC® BAA-2127™) was continuously exposed to the analogues using the extended gradient MIC method from 0.25 × MIC up to 4 × MIC(23). After a 48 h incubation with the compounds at 4 × MIC, aliquots of the cultures were streaked onto drug-free TSA plates. The MIC values were then determined using the broth microdilution method described above to determine if changes in susceptibility to the analogues were observed relative to the vehicle-treated cultures. Vehicle used was 1% (v/v) DMSO and experiments were carried out in biological duplicate.

### 3.7 Microscale Thermophoresis

The binding affinities between the compounds and the tripeptides acetyl-Lys-D-Ala-D-Ala or acetyl-Lys-D-Ala-D-Lac was investigated by microscale thermophoresis (MST) employing the Monolith NT.115 instrument (NanoTemper Technologies) as described previously(24, 25). The tripeptides

were labelled with an amine reactive dye using the Monolith Protein Labeling Kit RED-NHS 2nd Generation (NanoTemper Technologies) following the manufacturer‘s instructions. Aqueous solutions of the compounds (final concentration of 200 µM – 6.1 nM) were mixed 1:1 with the labelled tripeptides. Reactions were incubated at 25 °C for 5 min prior to loading into Monolith NT.115 Capillaries (NanoTemper Technologies). Measurements were performed at 25 °C using 20% LED power and 20 % IR-laser power (30 s ON time, 5 s OFF time). Data from three independent measurements were fitted to the single binding model (equation below) using the signal from Thermophoresis + T-jump within the NT Analysis software, version 1.5.41 (NanoTemper Technologies(26, 27).

Where: f(c) = fraction bound at a given inhibitor concentration
c = inhibitor concentration
Unbound = normalized fluorescence signal ($F_{norm}$)
Bound = $F_{norm}$ of inhibitor-protein complex
c(target) = protein concentration
$K_D$ = dissociation constant

### 3.8 Native Mass Spectrometry

MurJ protein used in mass spectrometry experiments has been prepared by following the procedure described before(28). Prior to mass spectrometry analysis, purified MurJ was buffer exchanged into 200 mM ammonium acetate pH 8.0 and 2×critical micelle concentration of LDAO using Biospin-6 (BioRad) column and introduced directly into the mass spectrometer using gold-coated capillary needles (prepared in-house). Data were collected on a Q-Exactive UHMR mass spectrometer (ThermoFisher). The instrument parameters were as follows: capillary voltage 1.1 kV, quadrupole selection from 1,000 to 20,000 m/z range, S-lens RF 100%, collisional activation in the HCD cell 200 V, trapping gas pressure setting 7.5, temperature 200 °C, and resolution of the instrument 12,500. The noise level was set at 3 rather than the default value of 4.64. No in-source dissociation was applied. Data were analyzed using Xcalibur 4.2 (Thermo Scientific) software package.

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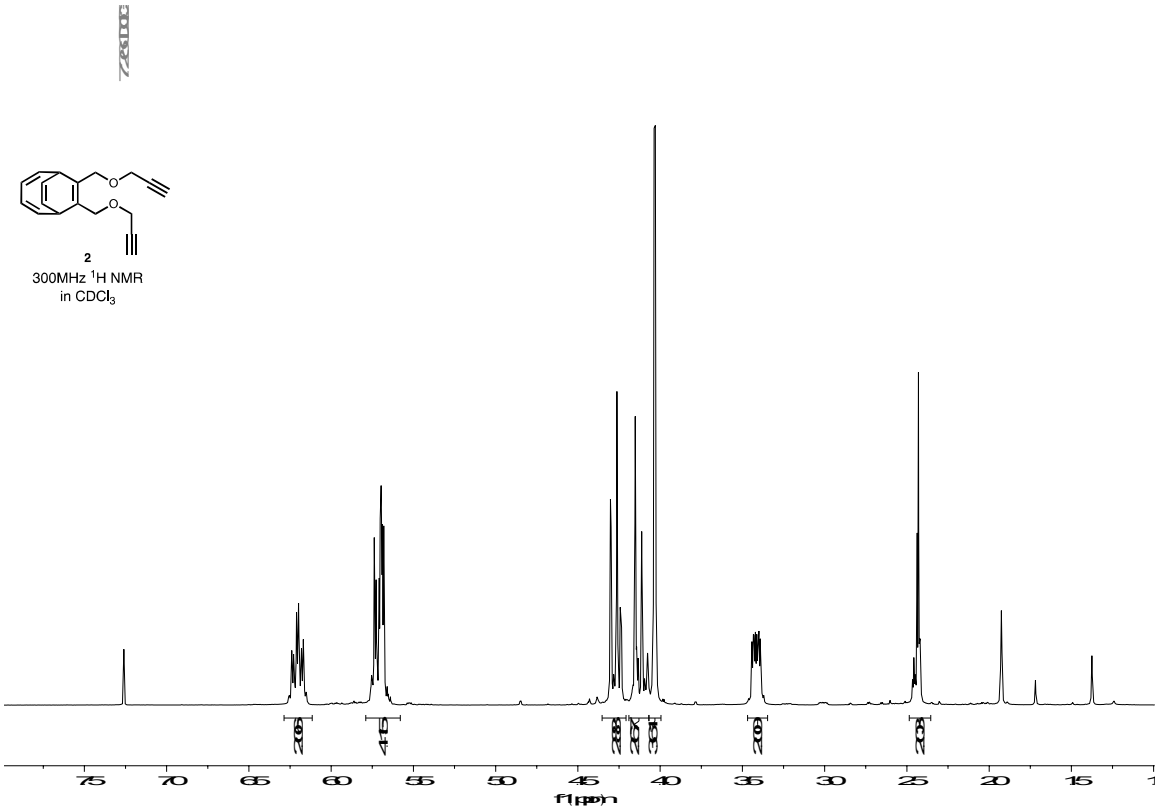
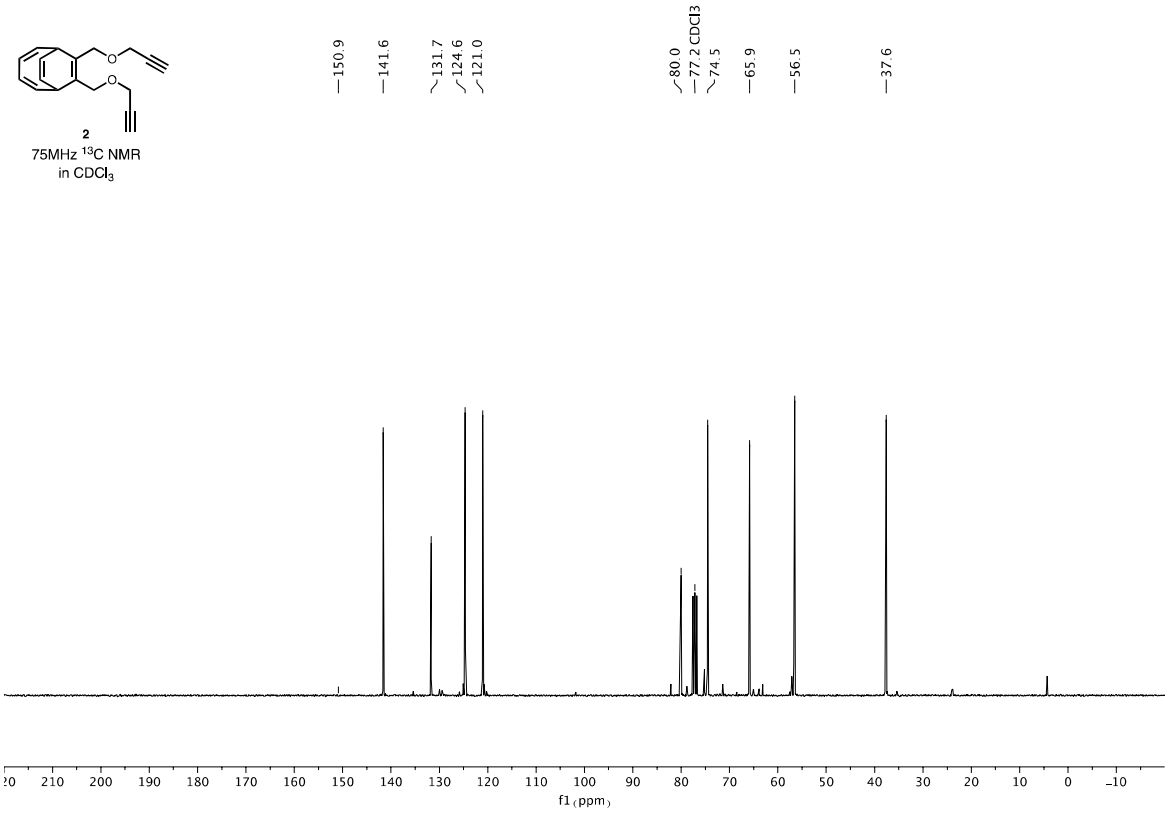
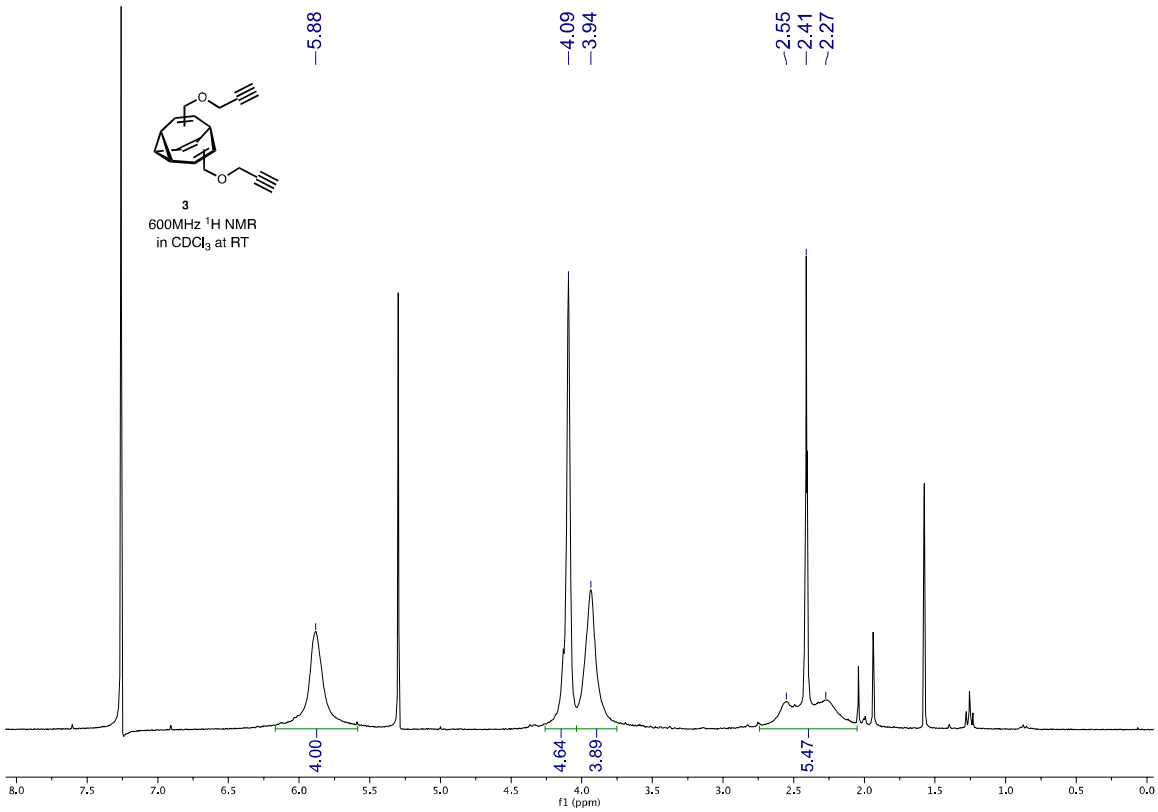
## 5 NMR Spectra

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4.09
3.94
2.55
2.41
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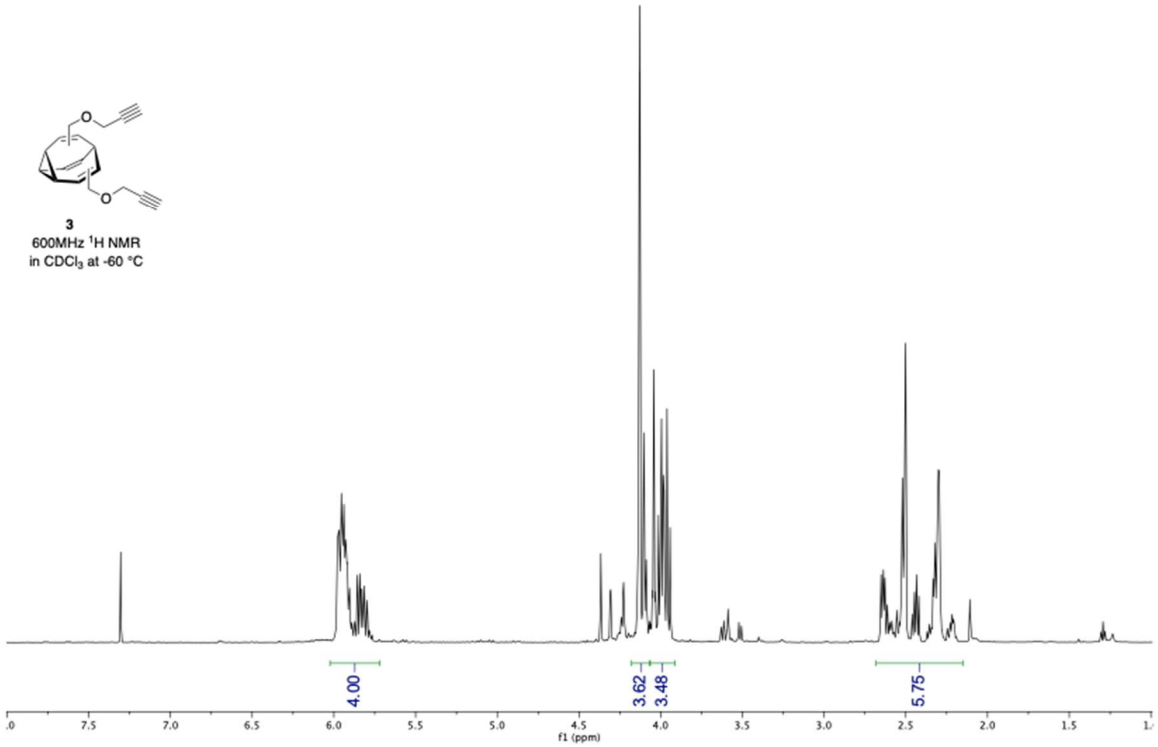
4.64
3.89
5.47
f1 (ppm)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3.62
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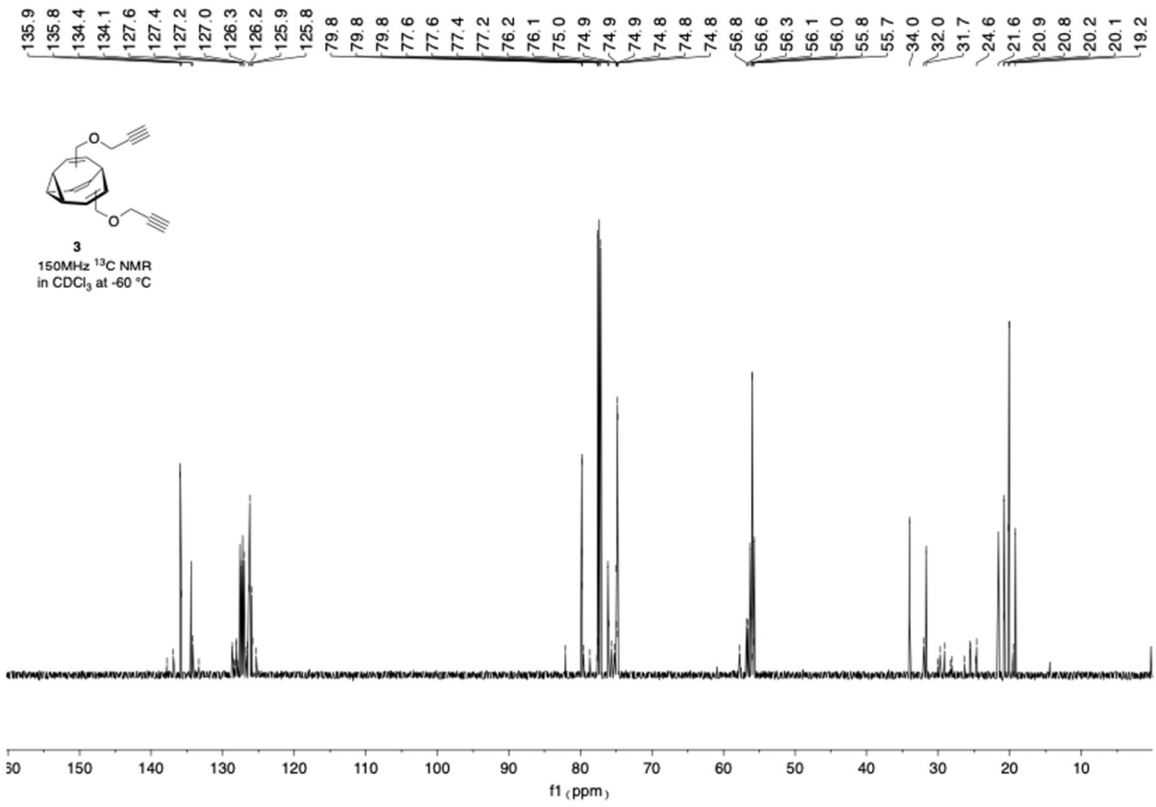
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127.4
127.2
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126.2
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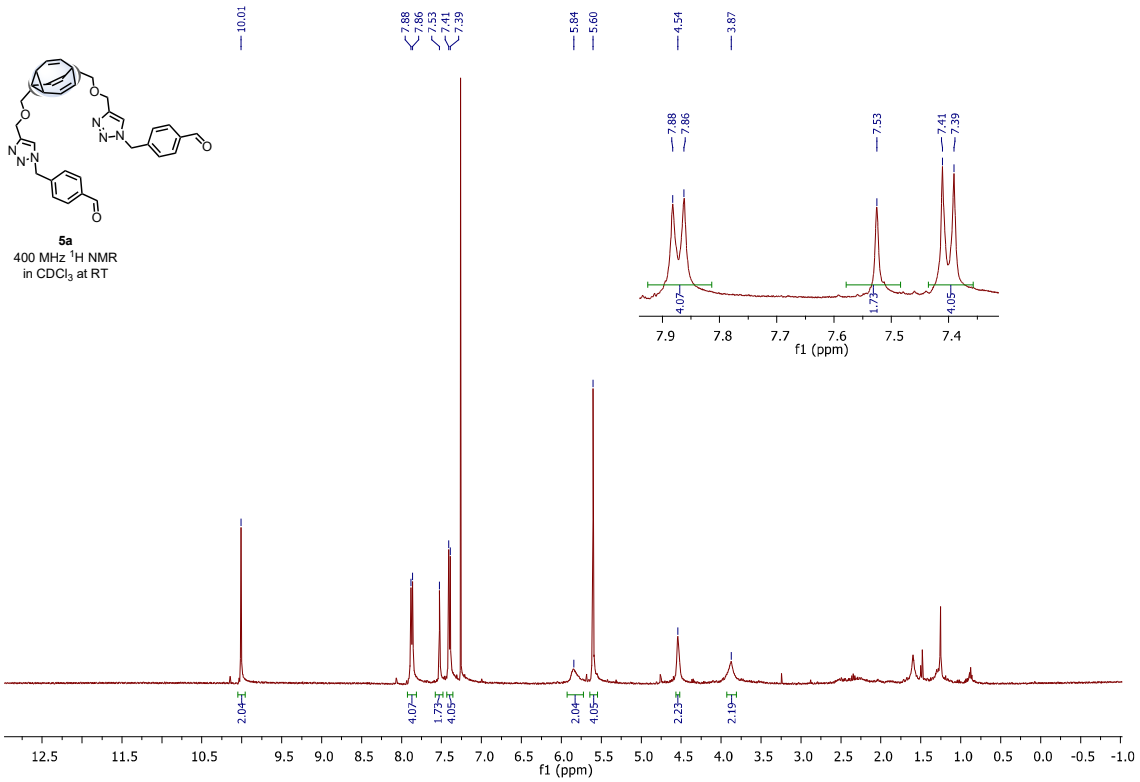
125.8
79.8
79.8
79.8
77.6
77.6
77.4
77.2
76.2
76.1
75.0
74.9
74.9
74.9
74.8
74.8
74.8
56.8
56.6
56.3
56.1
56.0
55.8
55.7
34.0
32.0
31.7
24.6
21.6
20.9
20.8
20.2
20.1
19.2
O
O
3
150MHz 13C NMR
in CDCl3 at -60 °C
30
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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7.88
7.86
7.53
7.41
7.39
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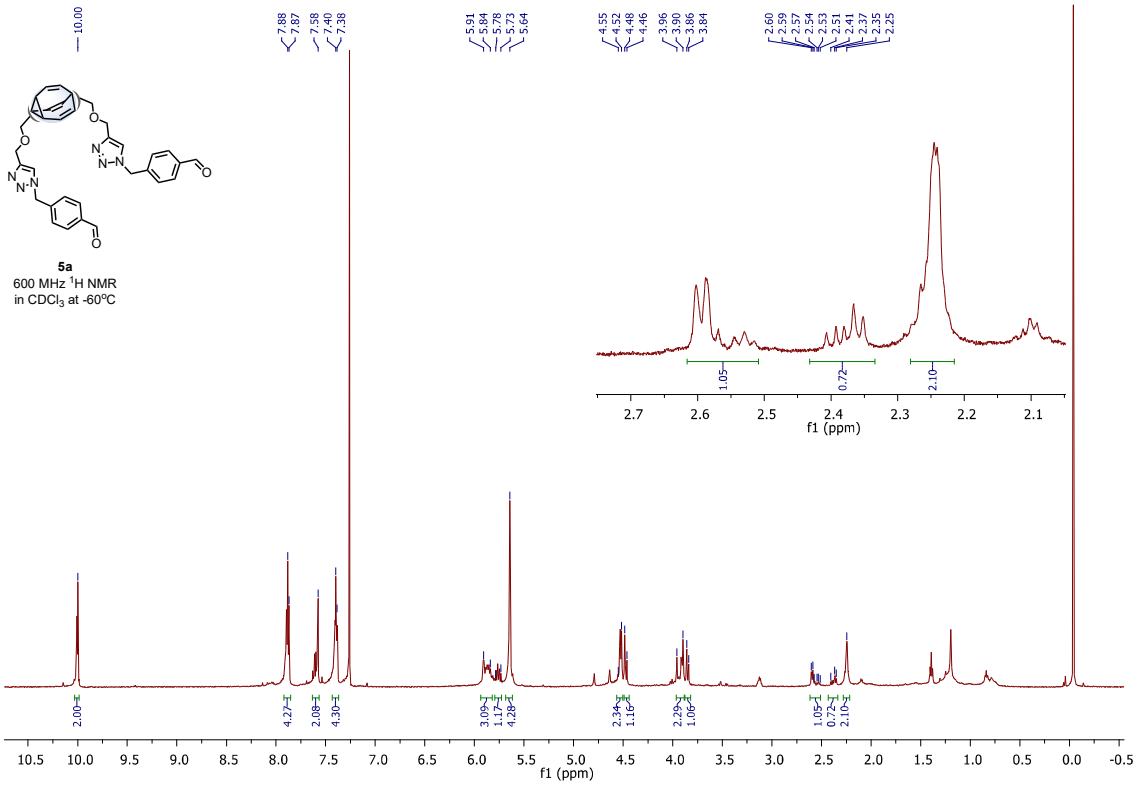
5.60
4.54
3.87
5a
400 MHz ¹H NMR
in CDCl₃ at RT
f1 (ppm)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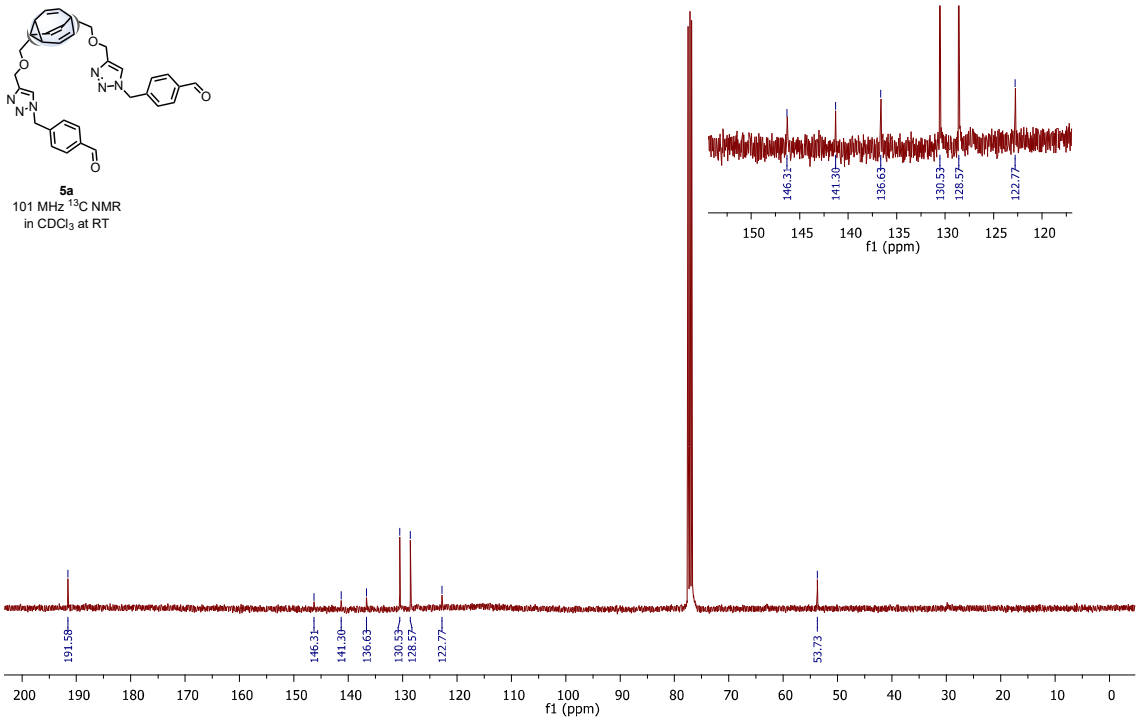
4.48
4.46
3.96
3.90
3.86
3.84
2.60
2.59
2.57
2.54
2.53
2.51
2.41
2.37
2.35
2.25
5a
600 MHz ¹H NMR
in CDCl₃ at -60°C
f1 (ppm)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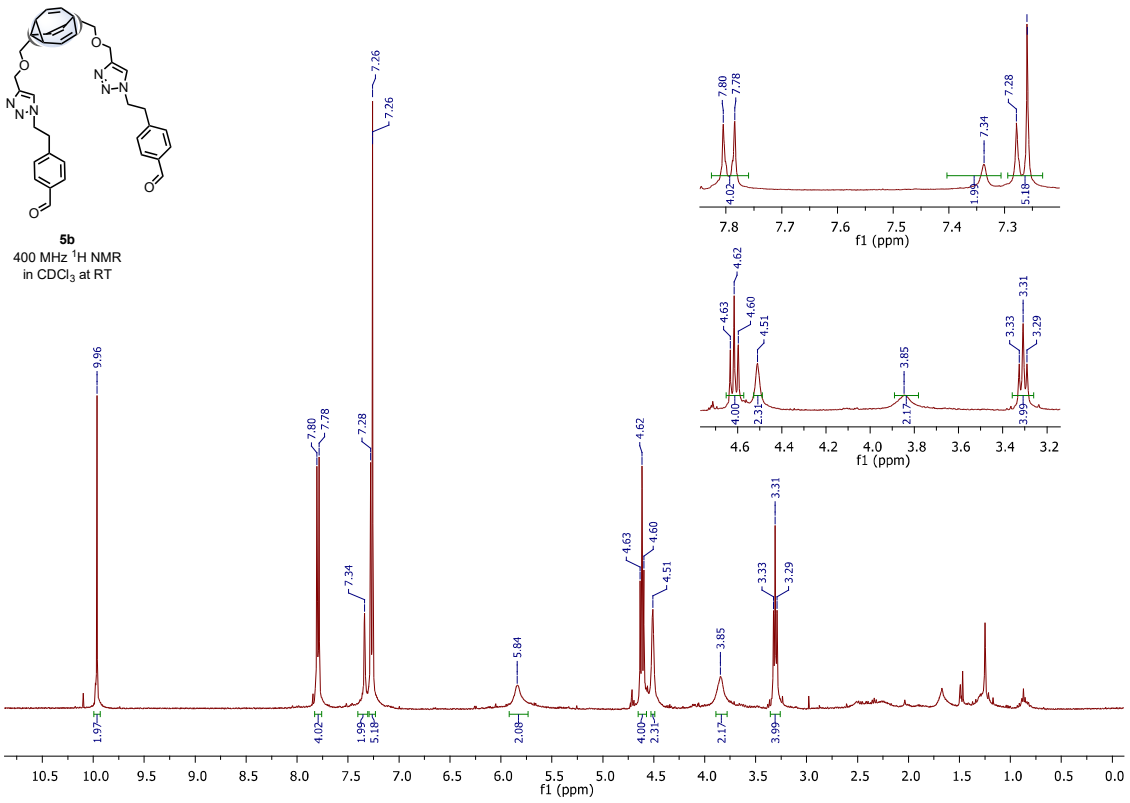
128.57
122.77
53.73
f1 (ppm)



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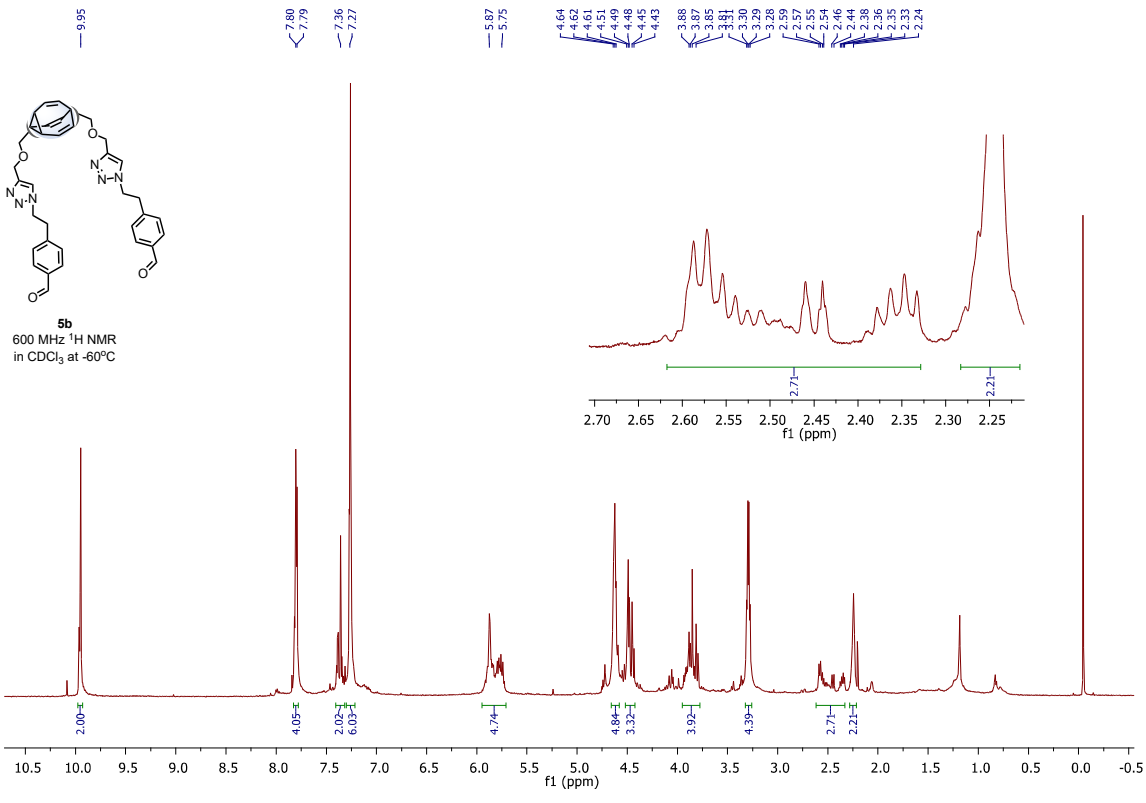

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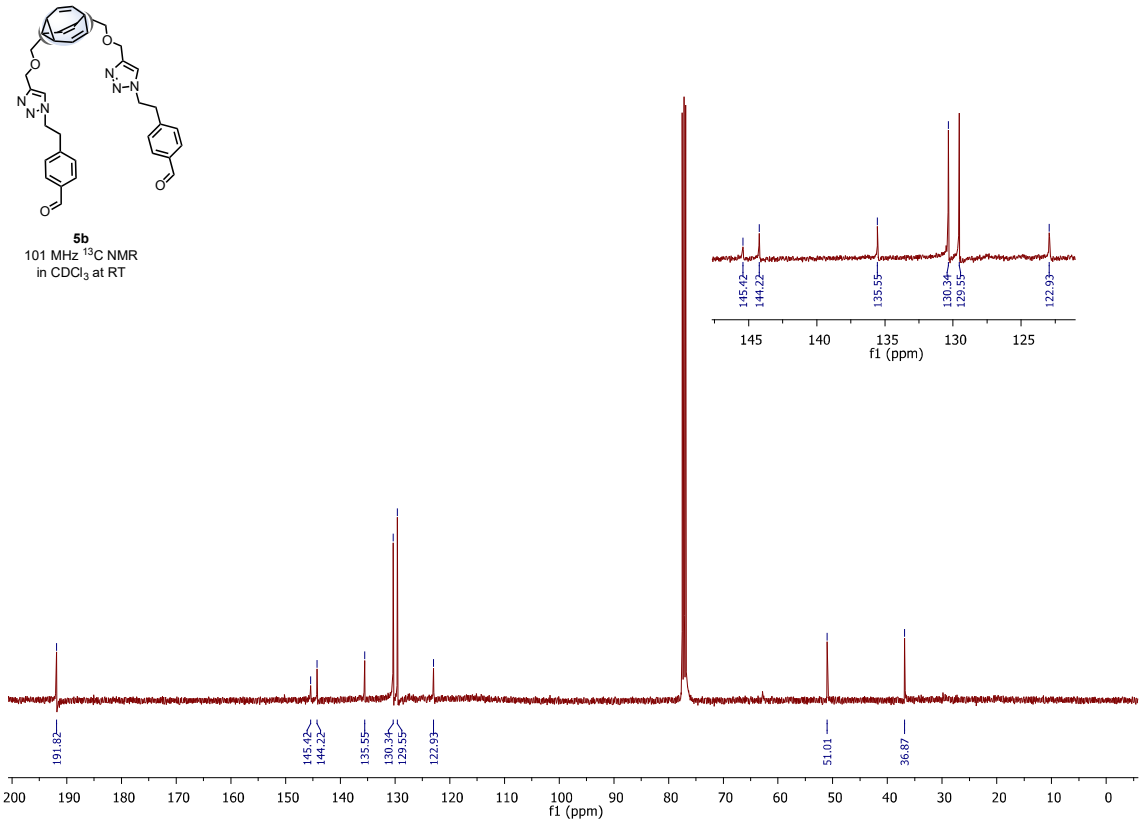
in $CDCl_3$ at -60°C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129.55
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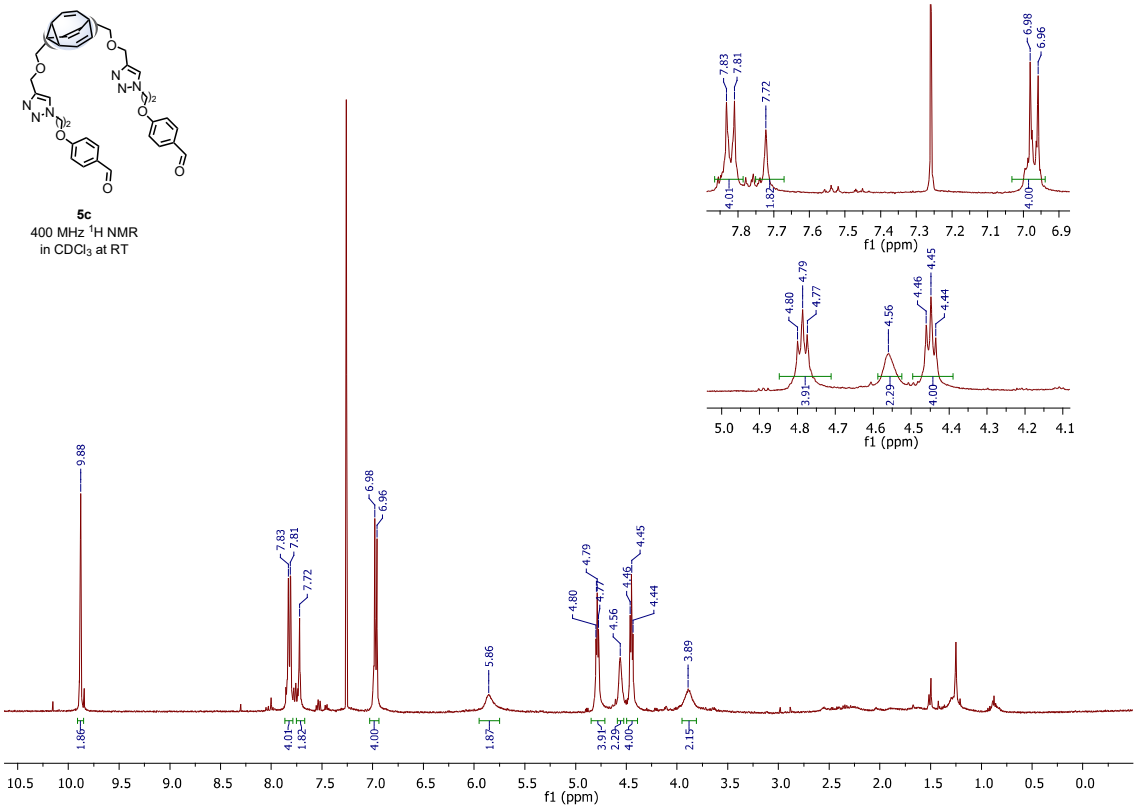
36.87
f1 (ppm)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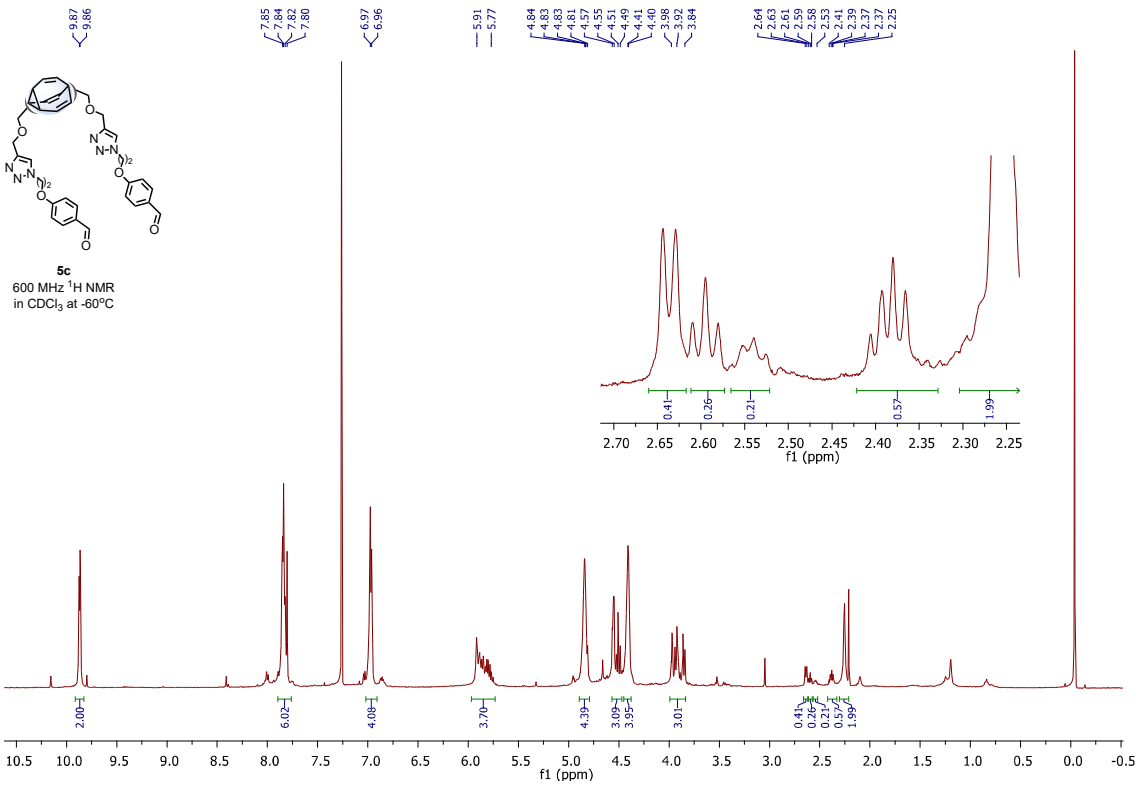
in $CDCl_3$ at RT
f1 (ppm)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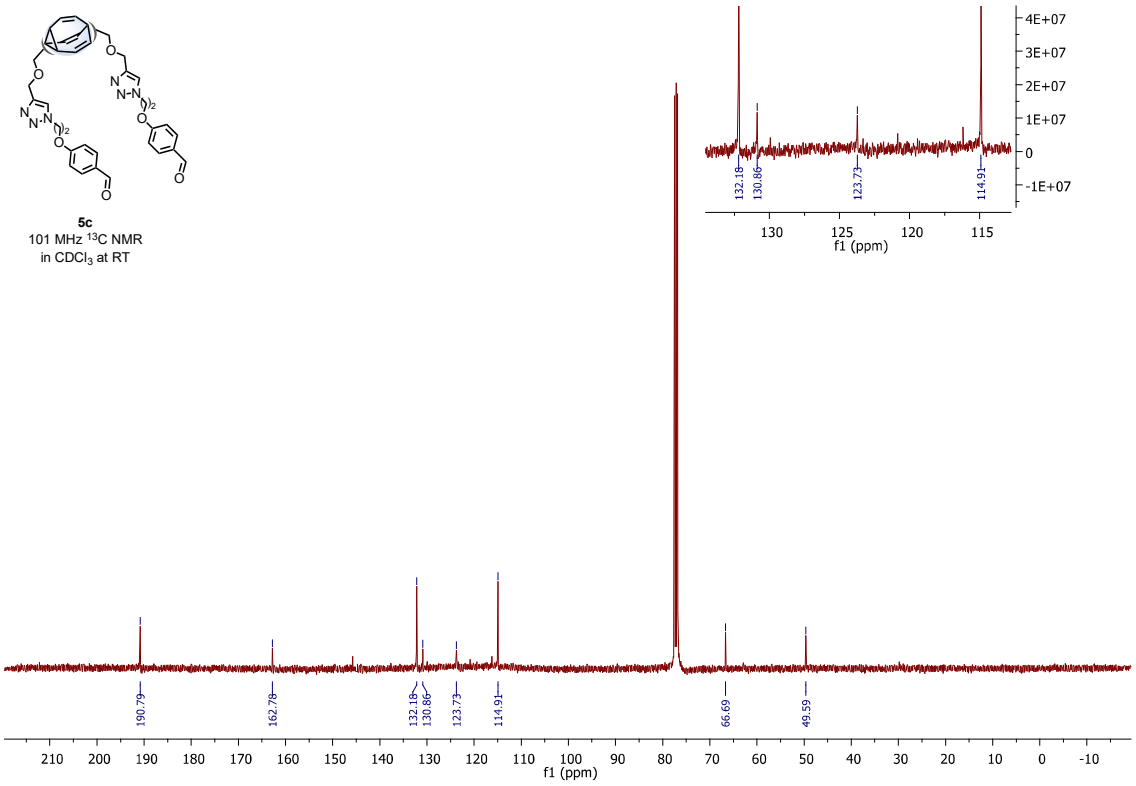
f1 (ppm)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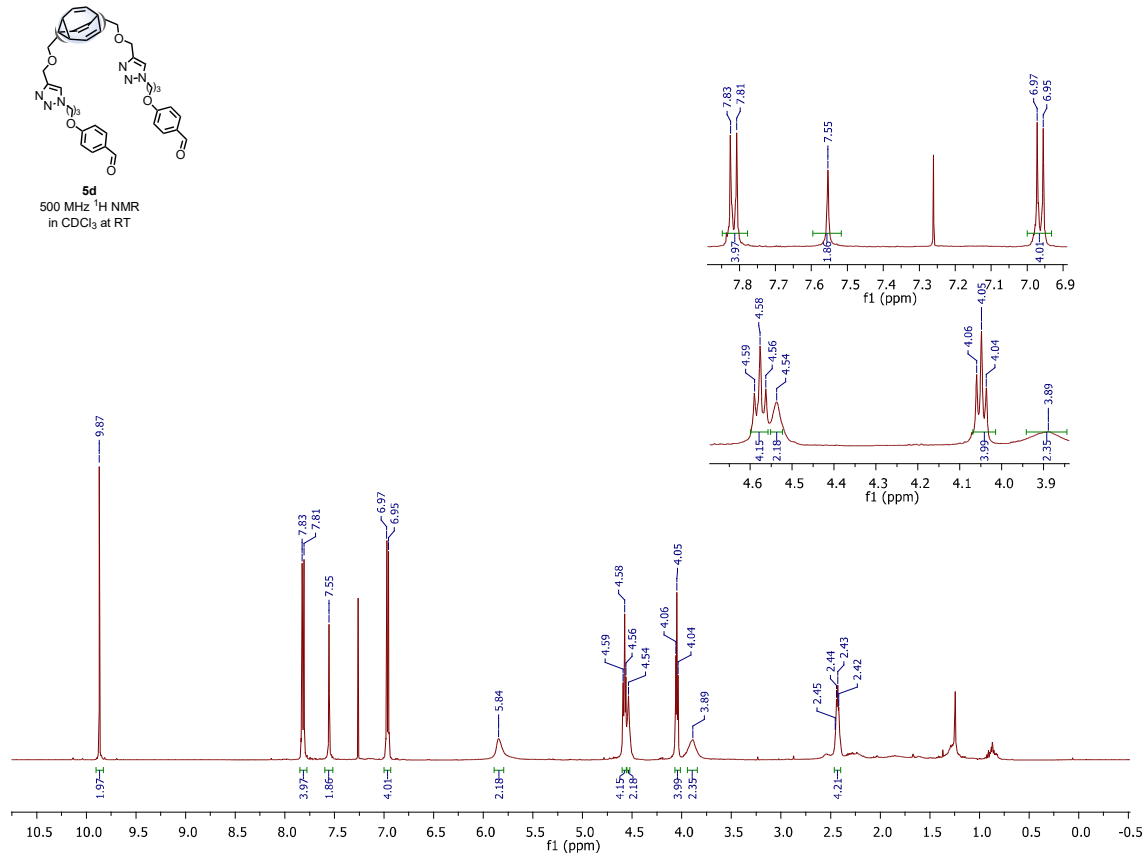
49.59
f1 (ppm)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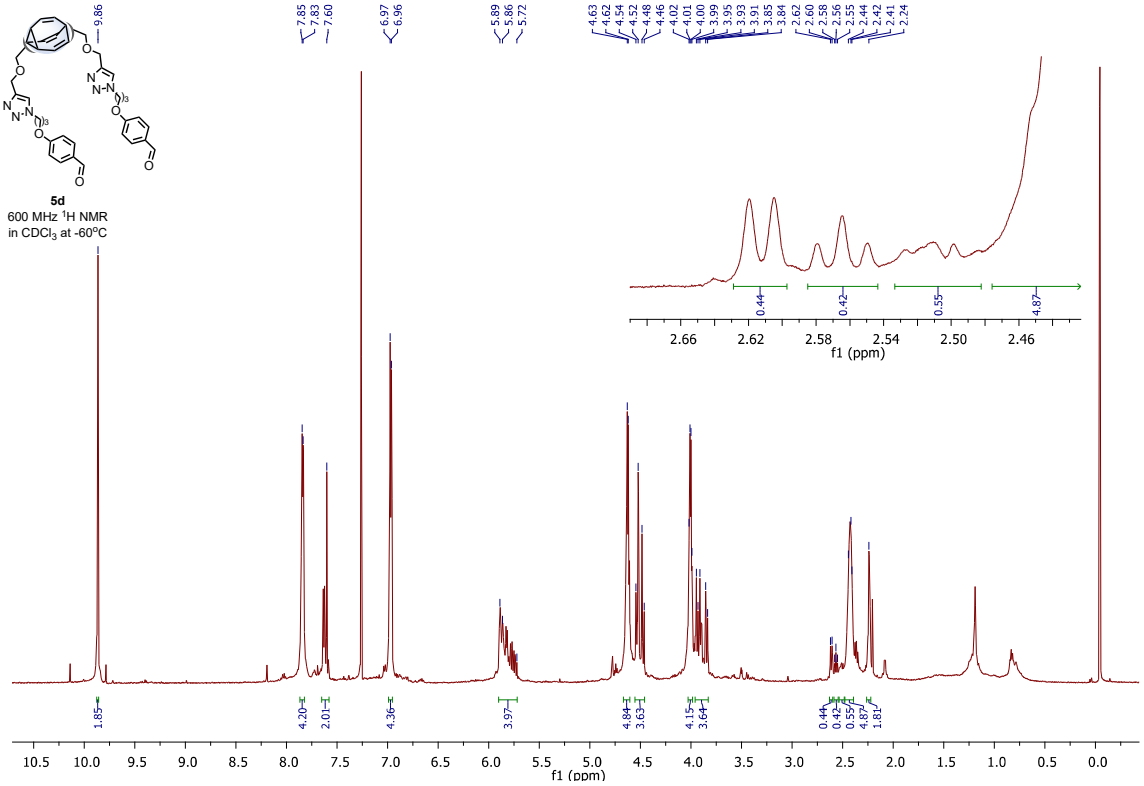
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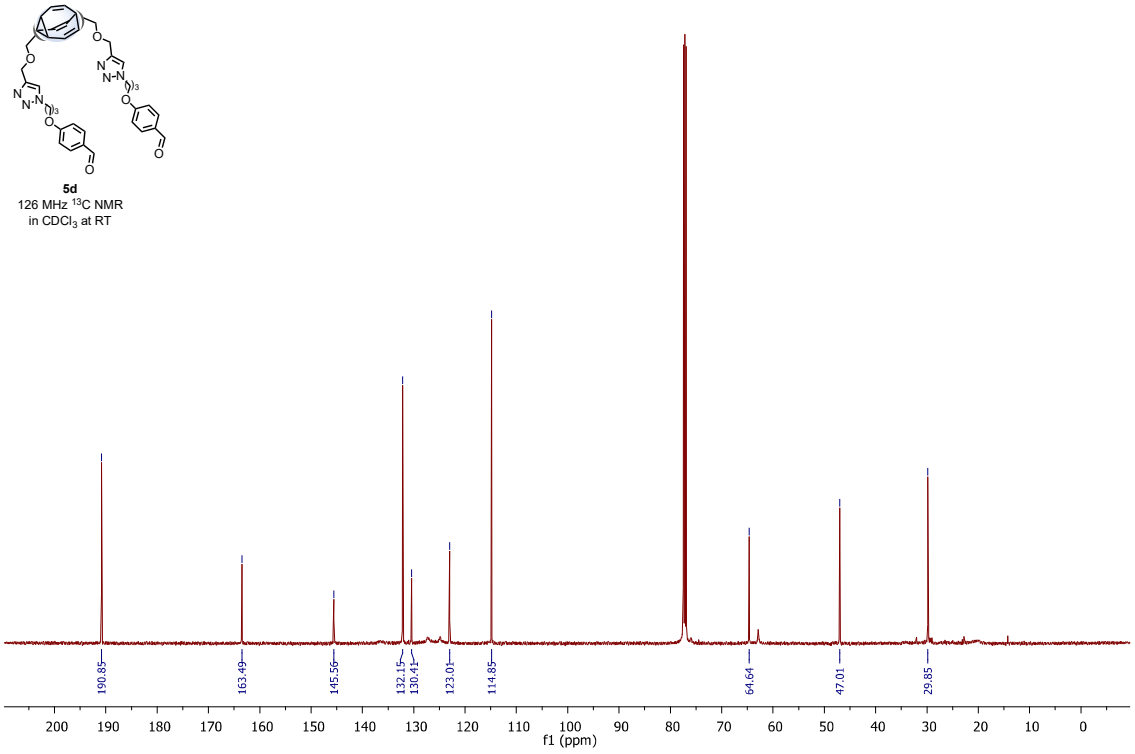
in CDCl3 at -60°C
f1 (ppm)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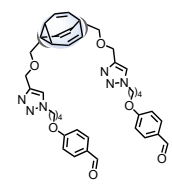
f1 (ppm)



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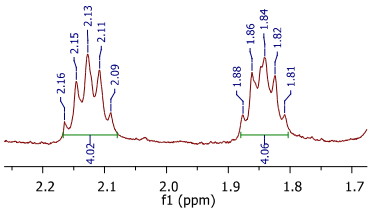


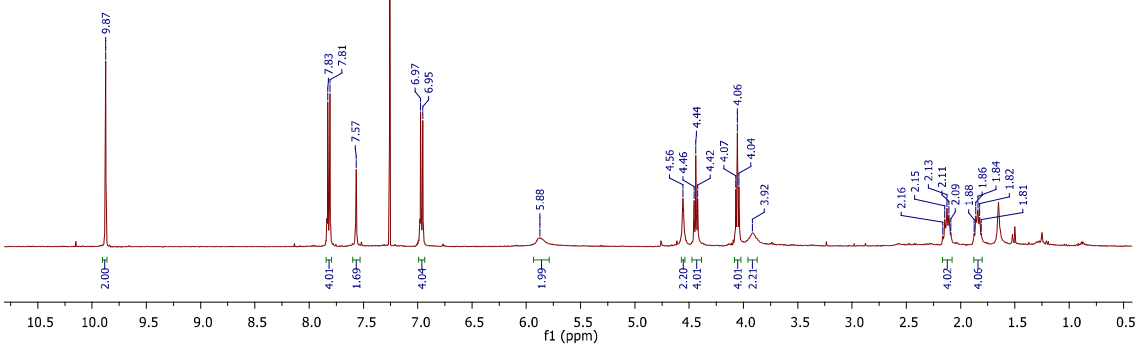


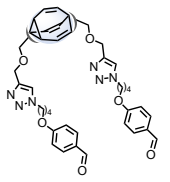

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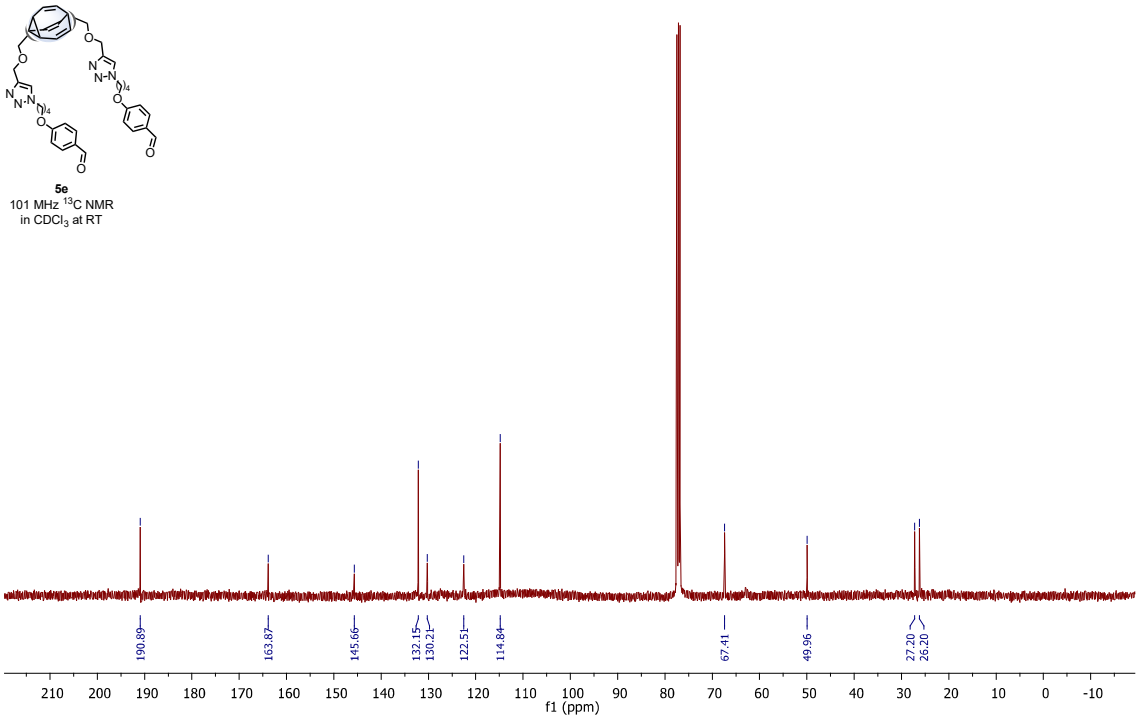
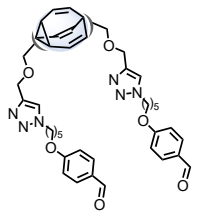
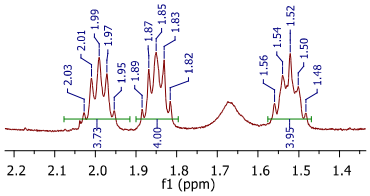
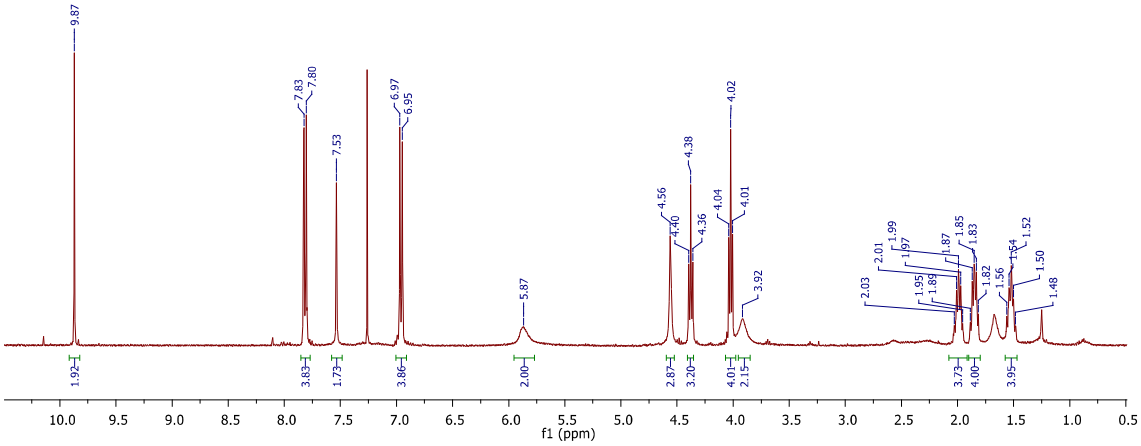
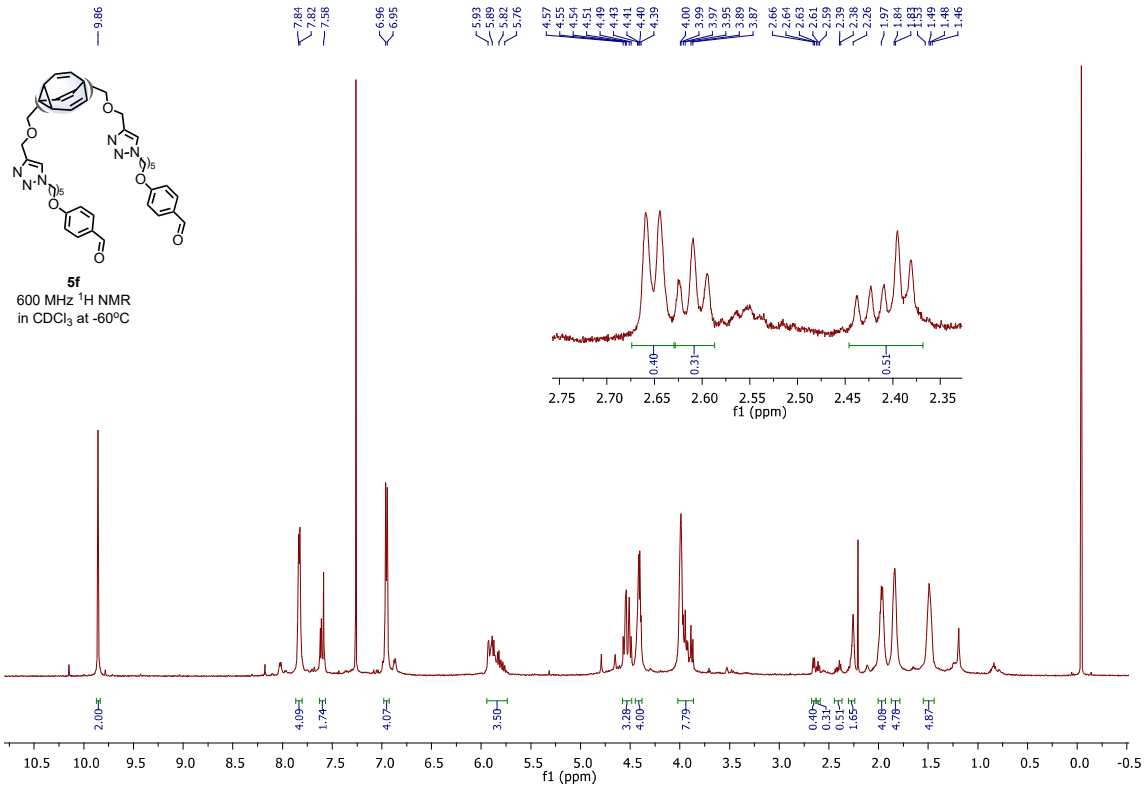

5e
101 MHz 13C NMR
in CDCl3 at RT
190.89
163.87
145.66
132.15
130.21
122.51
114.84
67.41
49.96
27.20
26.20
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



**5f**
400 MHz $^1$H NMR
in $CDCl_3$ at RT

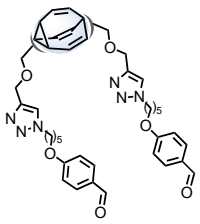


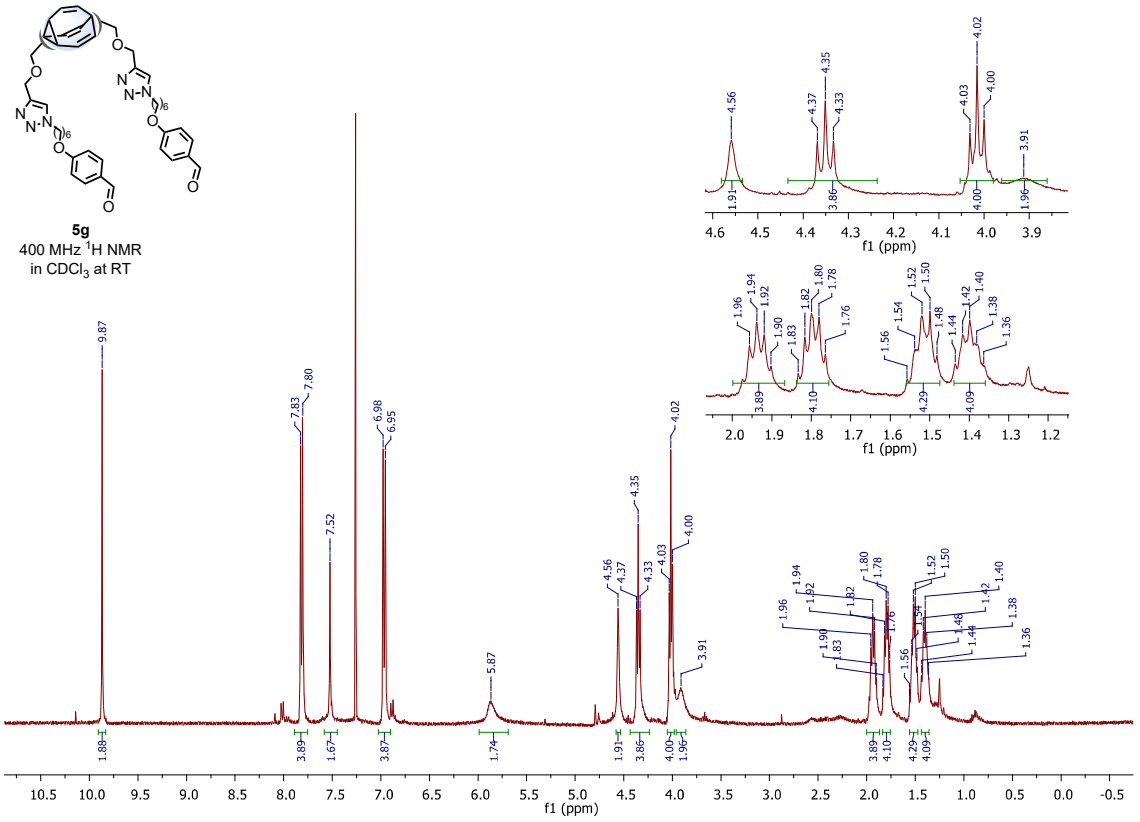





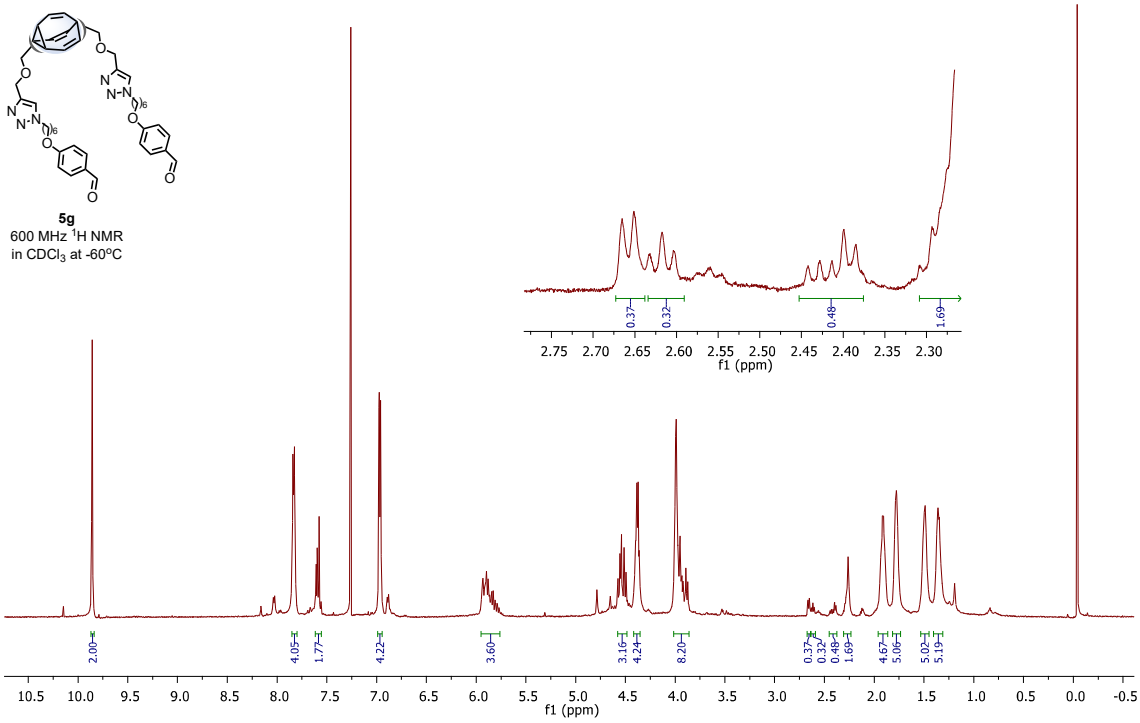

**5f**
600 MHz $^1$H NMR
in $CDCl_3$ at -60°C



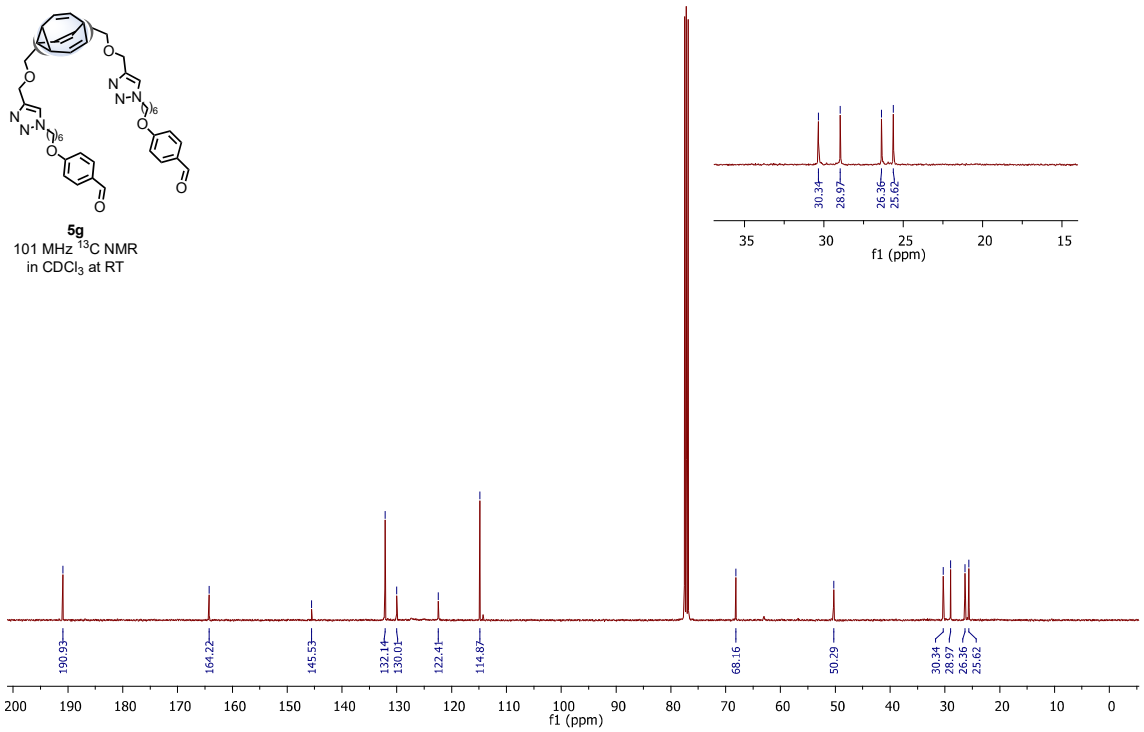
**5f**
126 MHz $^{13}$C NMR
in $CDCl_3$ at RT

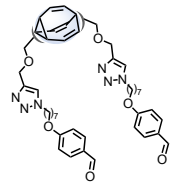


**5g**
400 MHz $^1$H NMR
in $CDCl_3$ at RT

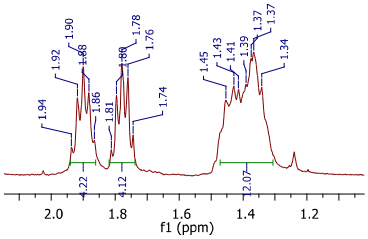


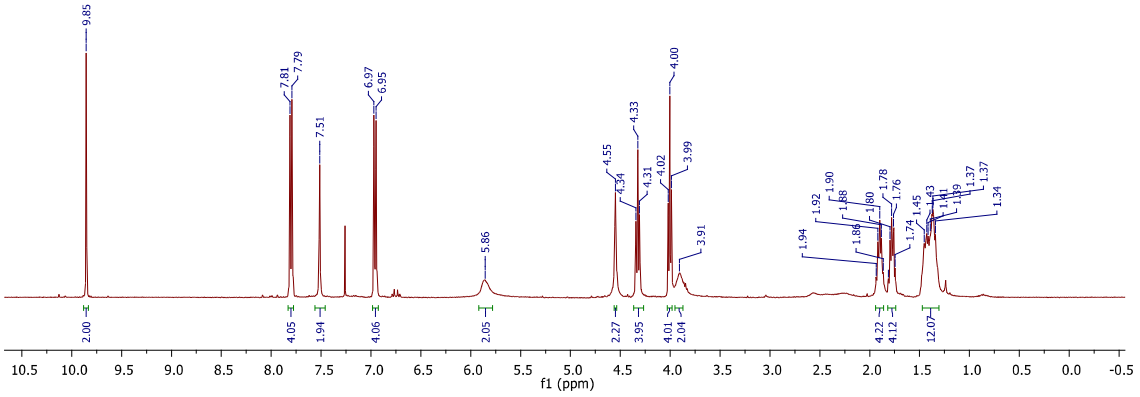
**5g**
600 MHz $^1$H NMR
in $CDCl_3$ at -60°C

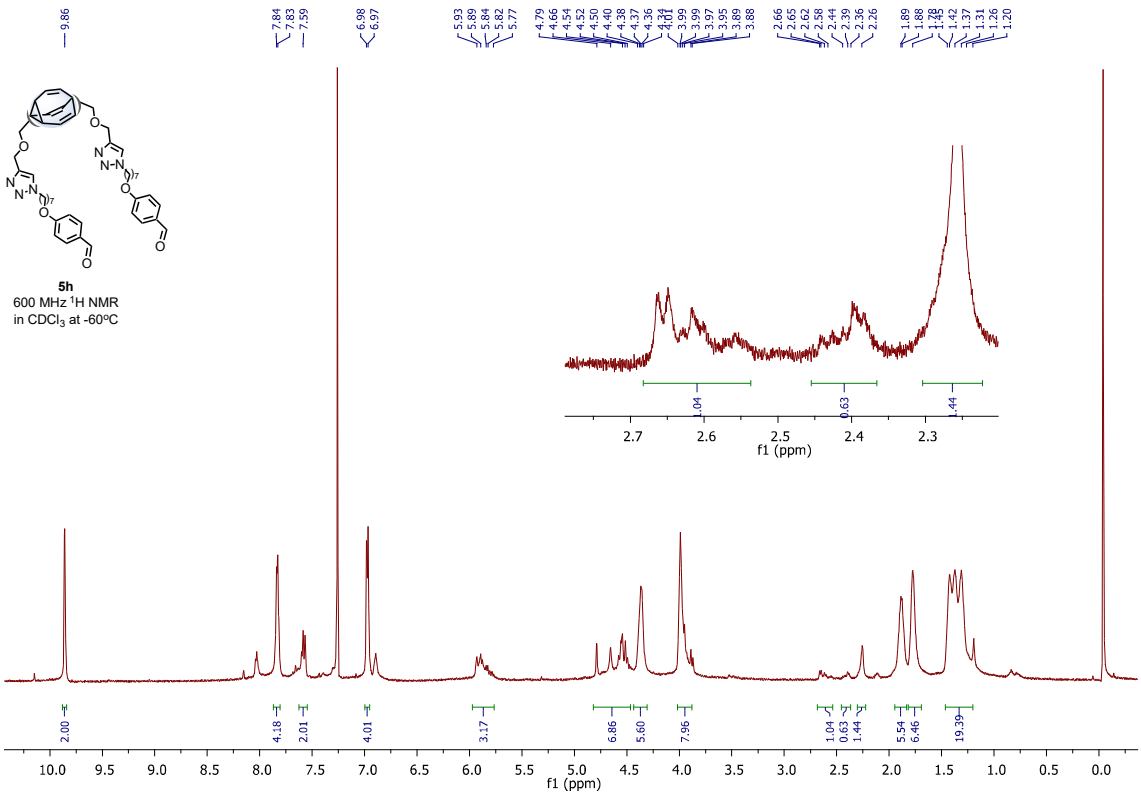

5g
101 MHz 13C NMR
in CDCl3 at RT
30.34
28.97
26.36
25.62
35
30
25
20
15
f1 (ppm)
190.93
164.22
145.53
132.14
130.01
122.41
114.87
68.16
50.29
30.34
28.97
26.36
25.62
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



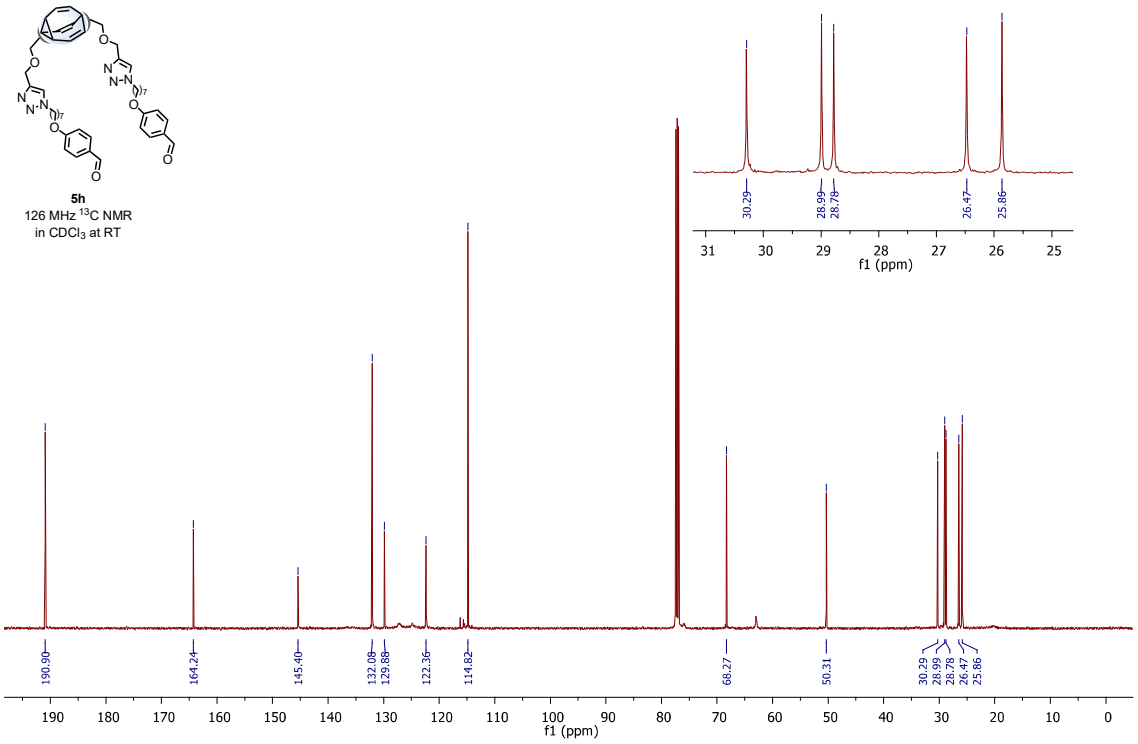
**5h**
400 MHz $^1$H NMR
in $CDCl_3$ at RT

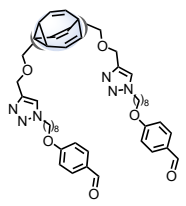


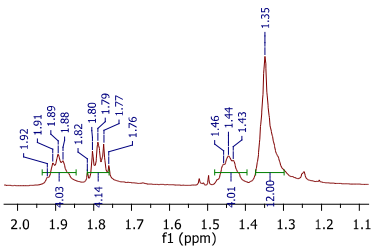



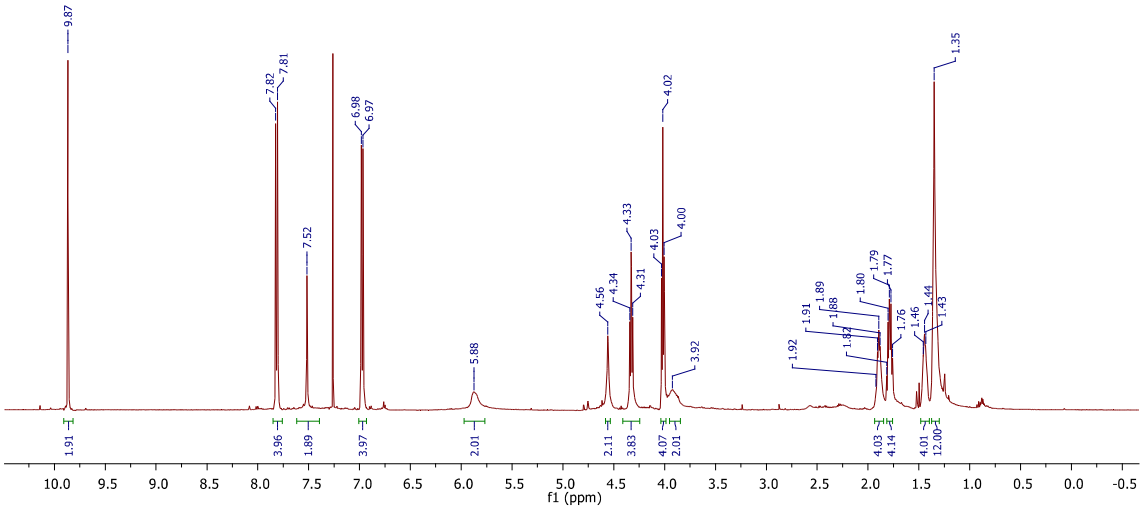

**5h**
600 MHz $^1$H NMR
in $CDCl_3$ at -60°C

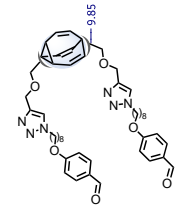

5h
126 MHz $^{13}$C NMR
in $CDCl_3$ at RT
190.90
164.24
145.40
132.08
129.88
122.36
114.82
68.27
50.31
30.29
28.99
28.78
26.47
25.86
f1 (ppm)



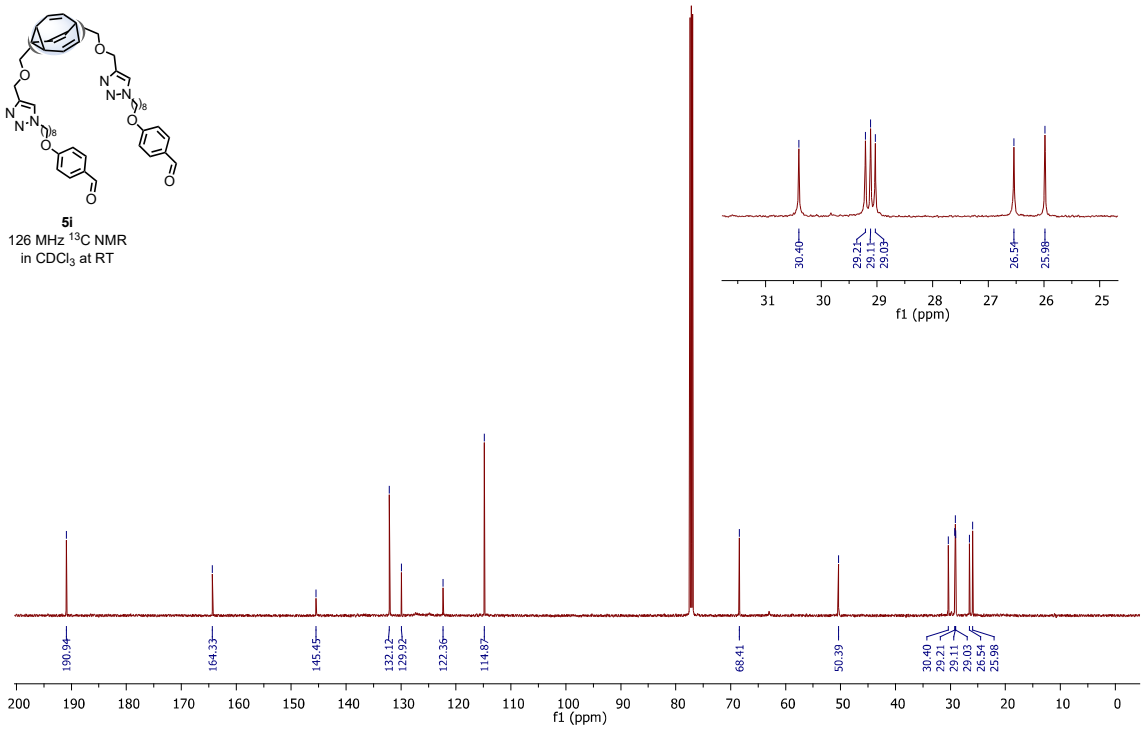
**5i**
400 MHz $^1$H NMR
in $CDCl_3$ at RT

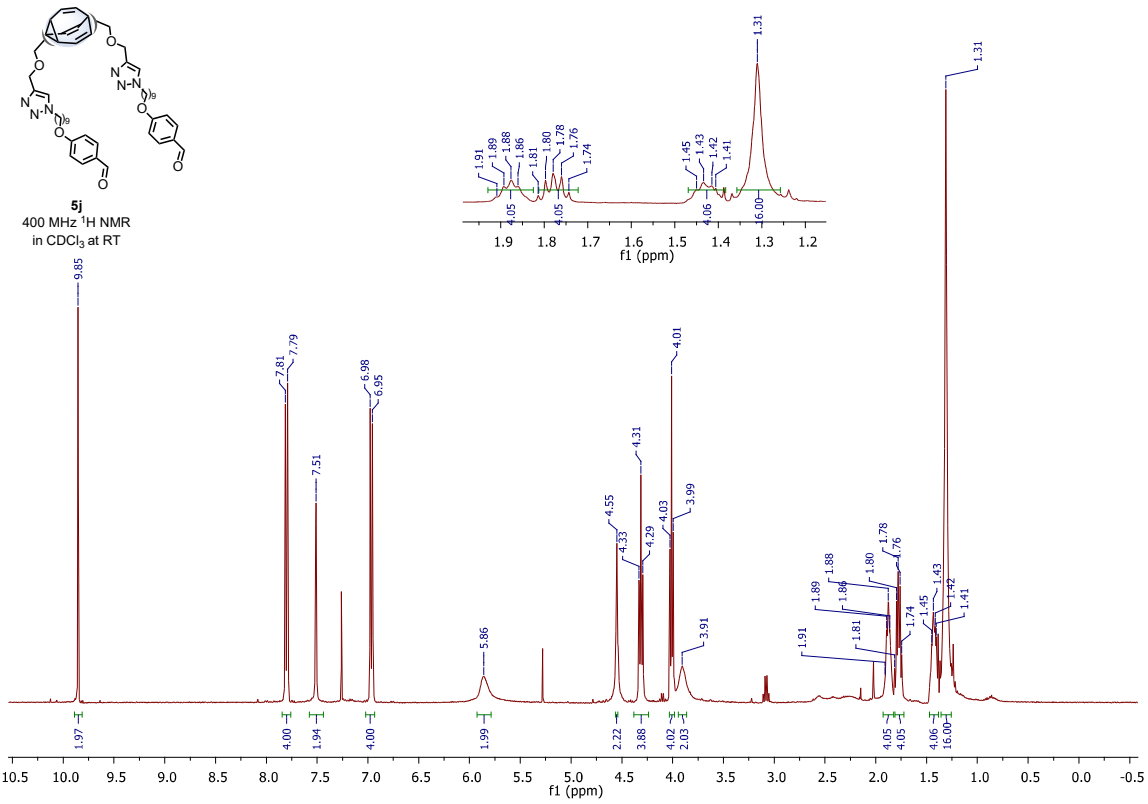


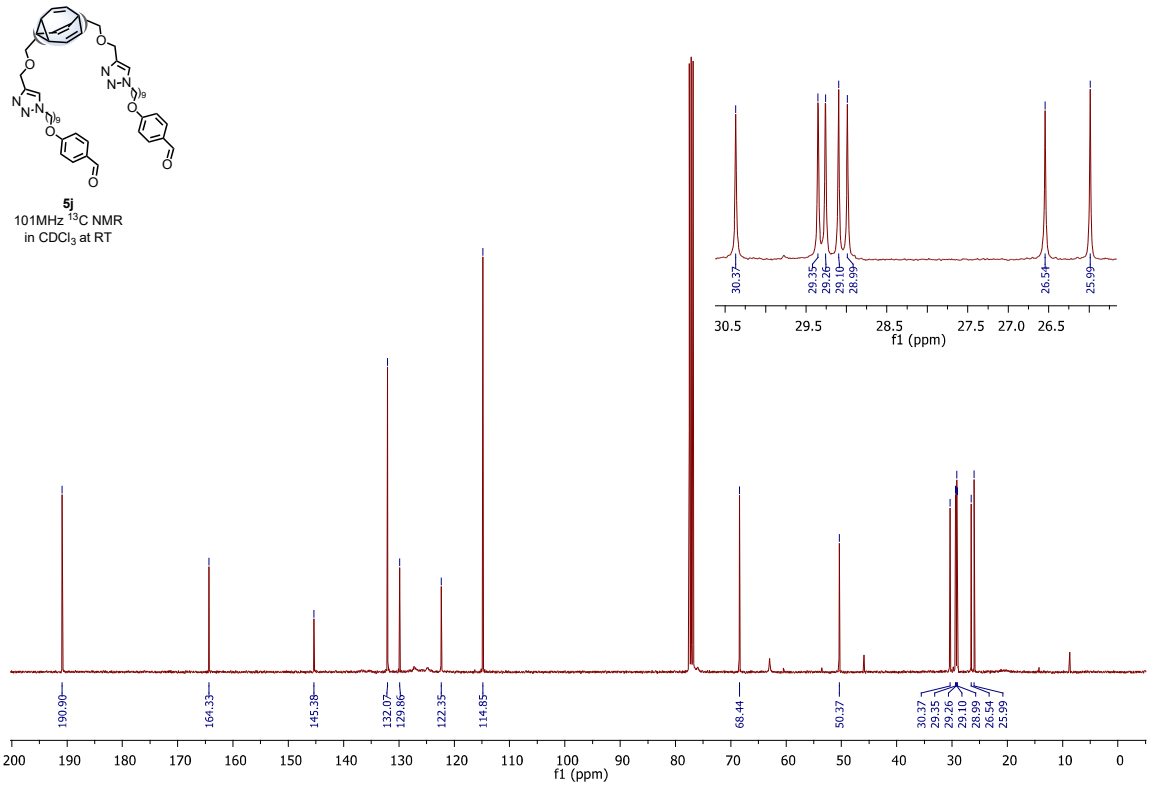



**5i**
600 MHz $^1$H NMR
in $CDCl_3$ at -60°C

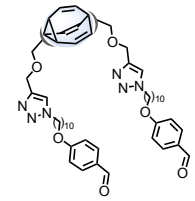

5i
126 MHz 13C NMR
in CDCl3 at RT
190.94
164.33
145.45
132.12
129.92
122.36
114.87
68.41
50.39
30.40
29.21
29.11
29.03
26.54
25.98
f1 (ppm)



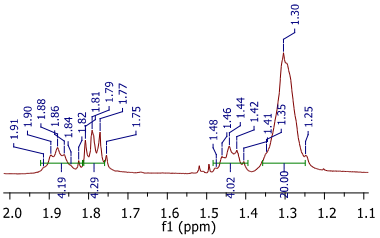
**5j**
400 MHz $^{1}$H NMR
in $CDCl_3$ at RT

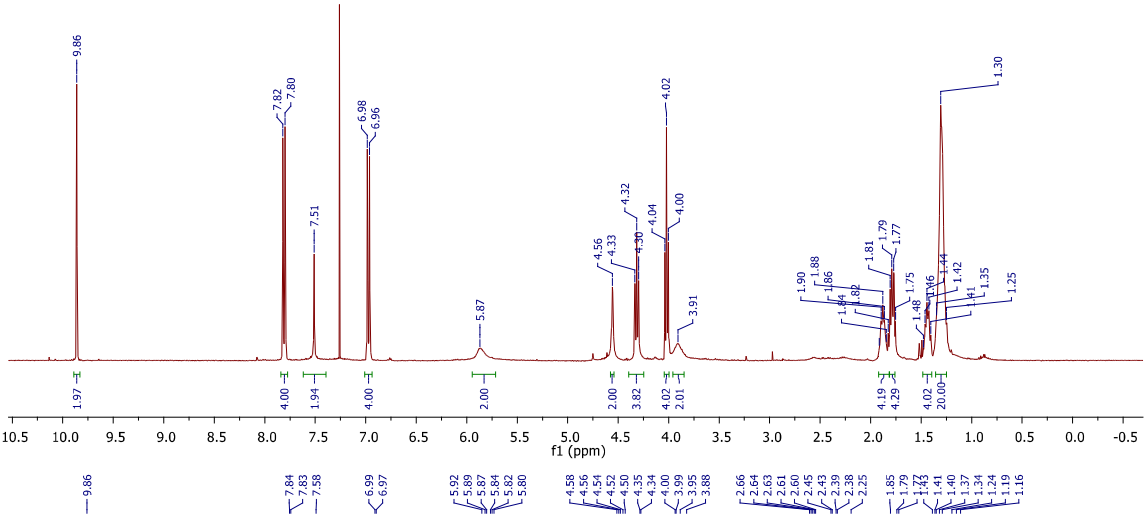


**5j**
101MHz $^{13}$C NMR
in $CDCl_3$ at RT



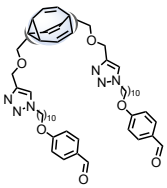
**5k**
400 MHz $^1$H NMR
in $CDCl_3$ at RT



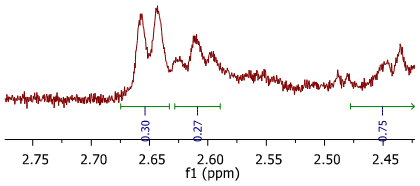



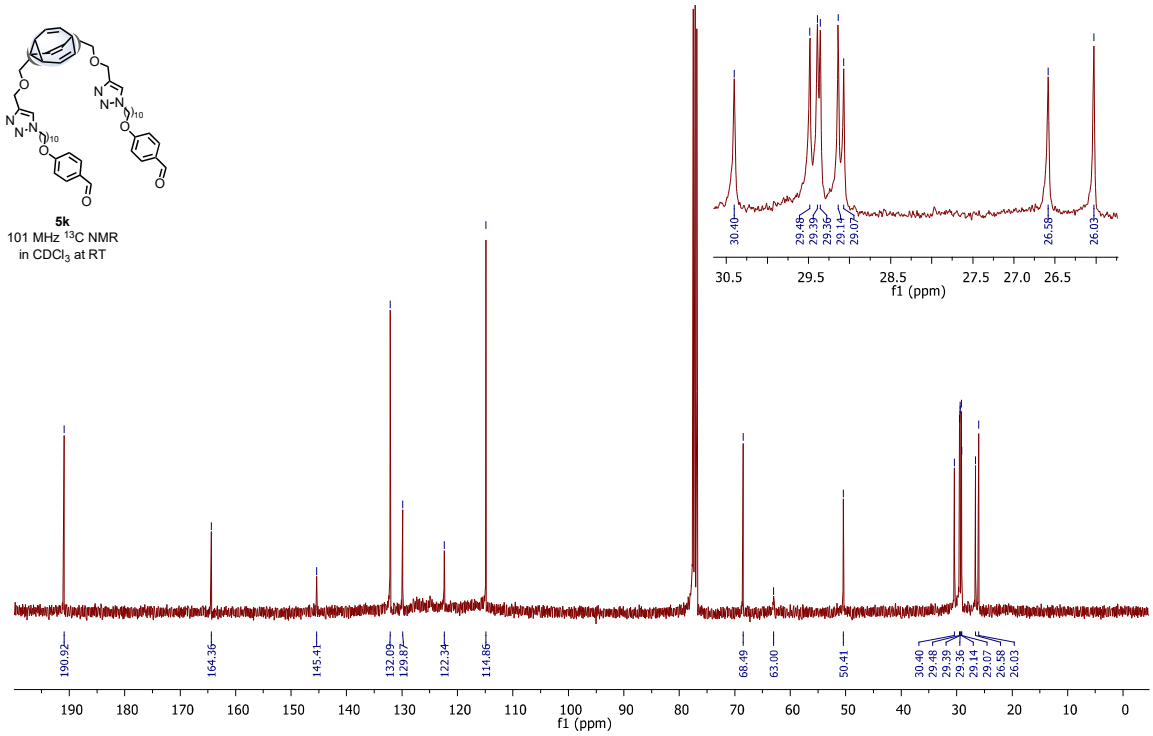


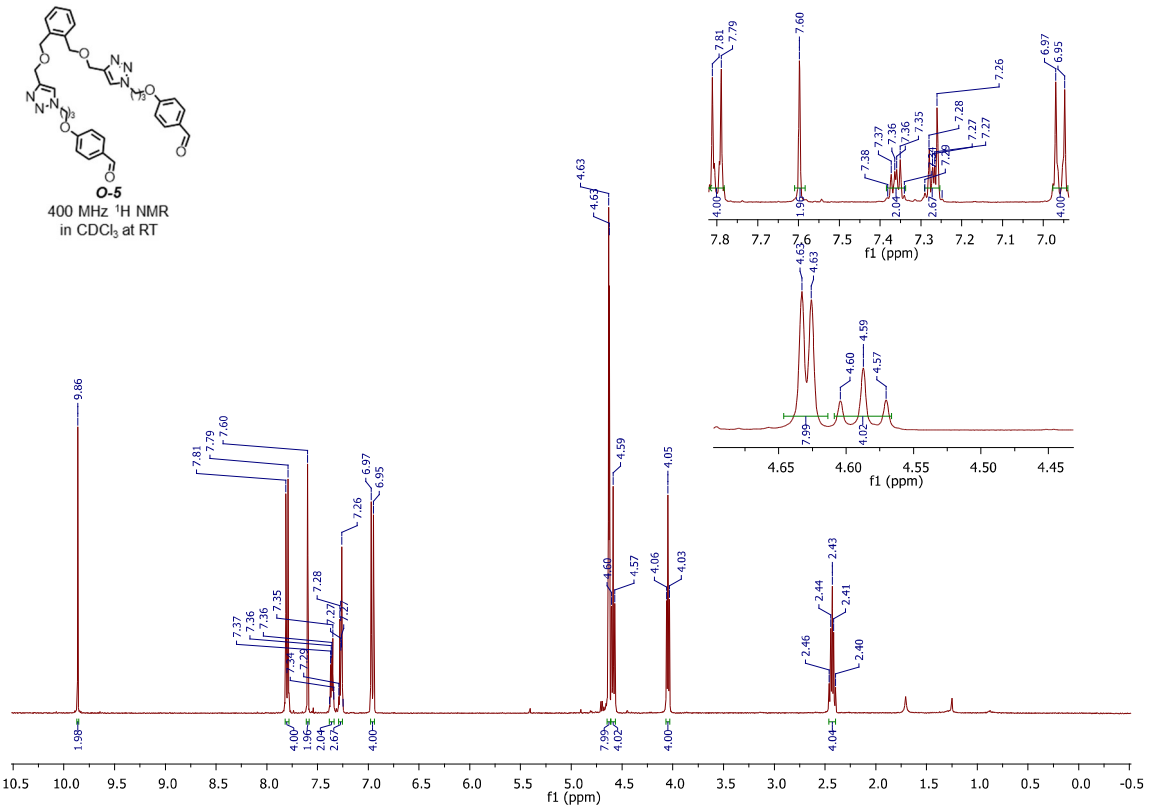


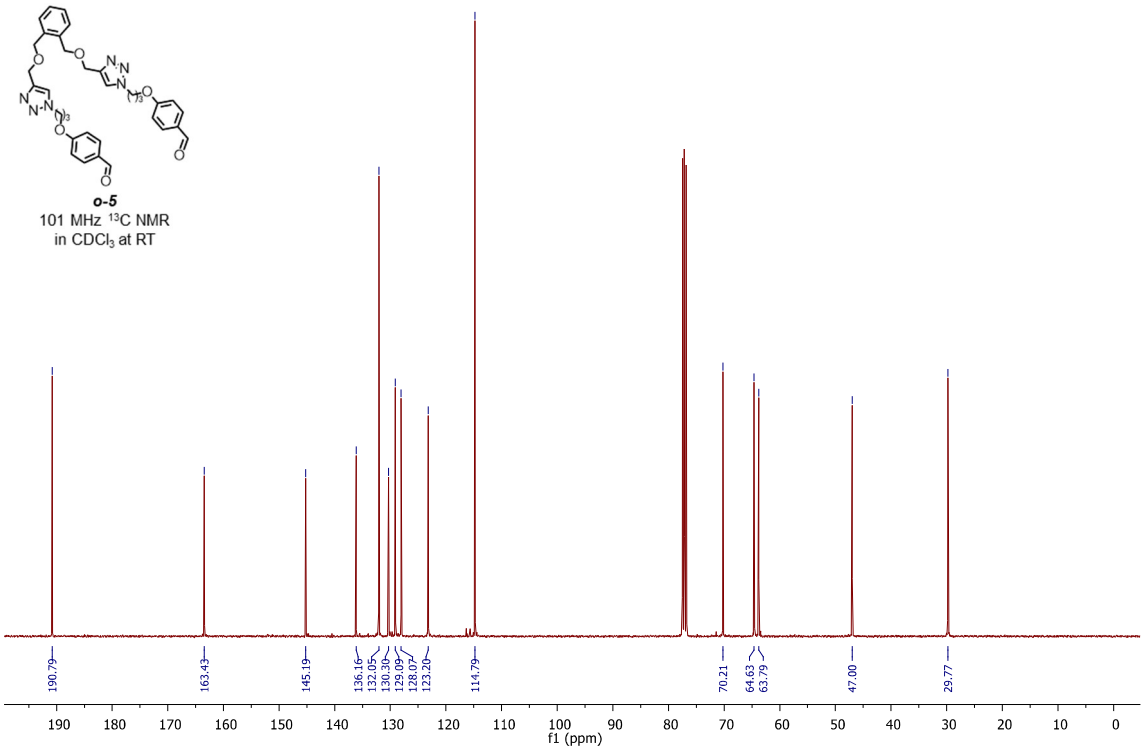


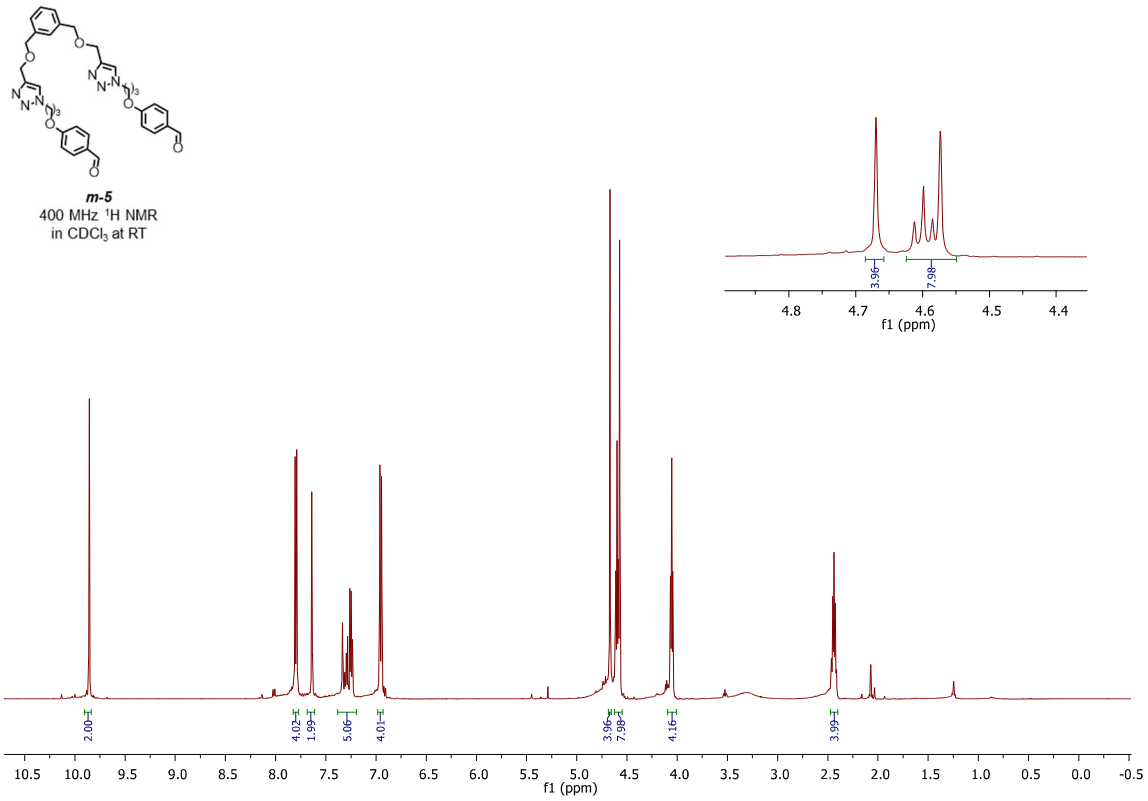
**5k**
600 MHz $^1$H NMR
in $CDCl_3$ at -60°C

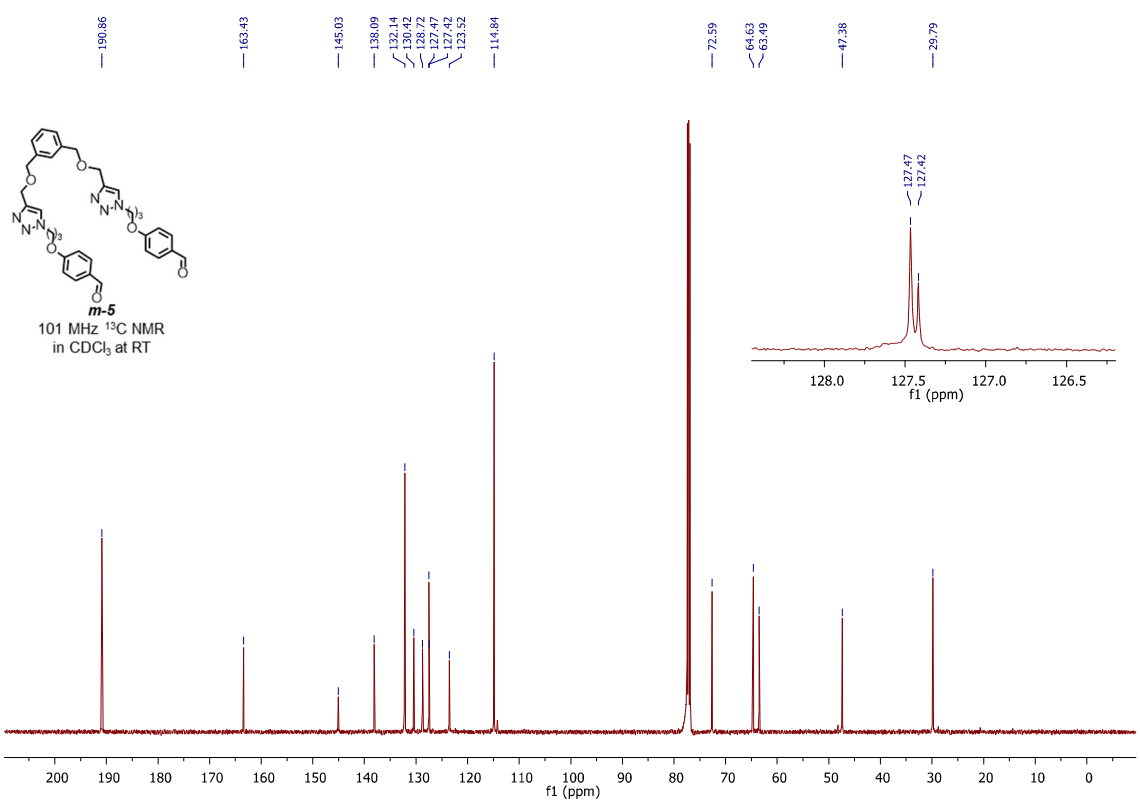


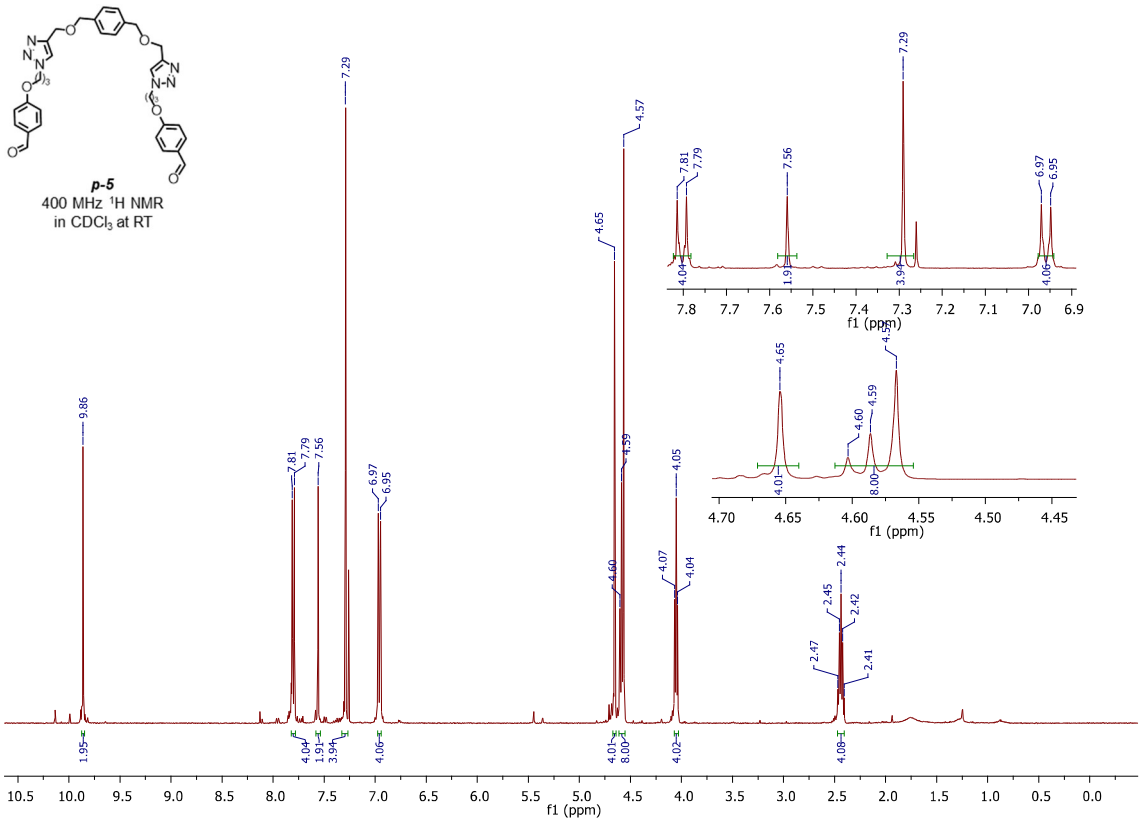

5k
101 MHz $^{13}$C NMR
in $CDCl_3$ at RT
190.92
164.36
145.41
132.09
129.87
122.34
114.86
68.49
63.00
50.41
30.40
29.48
29.39
29.36
29.14
29.07
26.58
26.03
f1 (ppm)

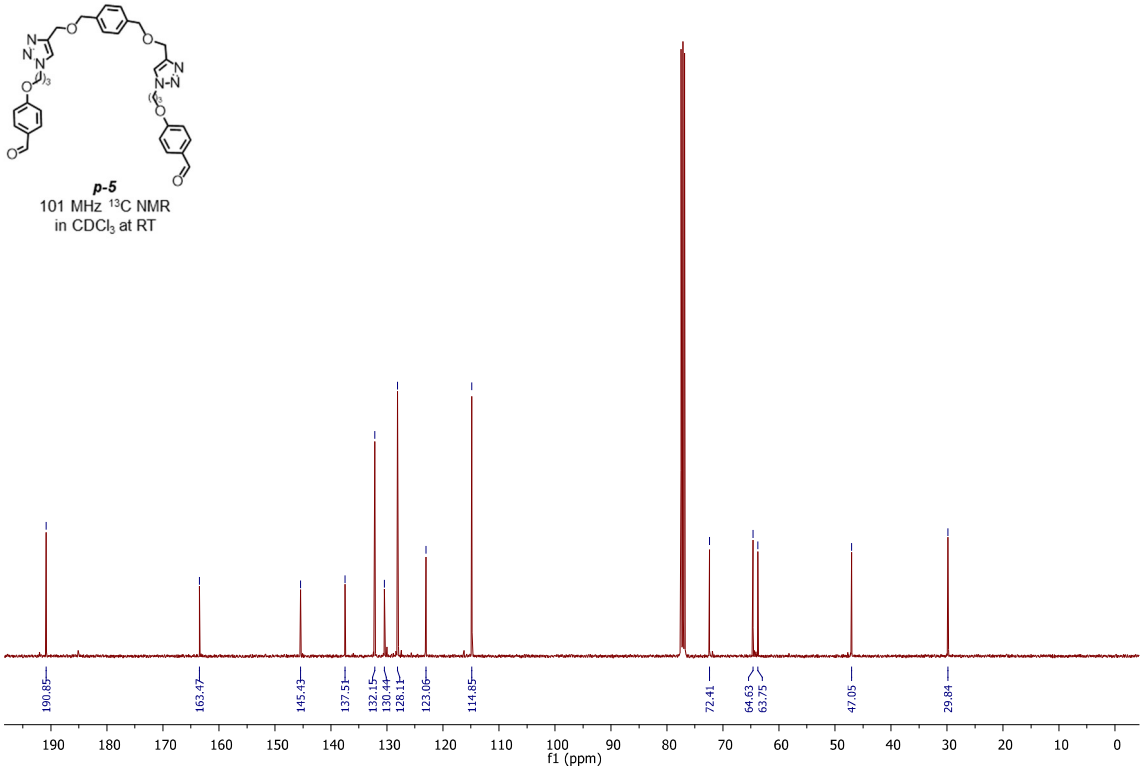

O-5
400 MHz ¹H NMR
in CDCl3 at RT
f1 (ppm)


o-5
101 MHz ¹³C NMR
in CDCl3 at RT
f1 (ppm)

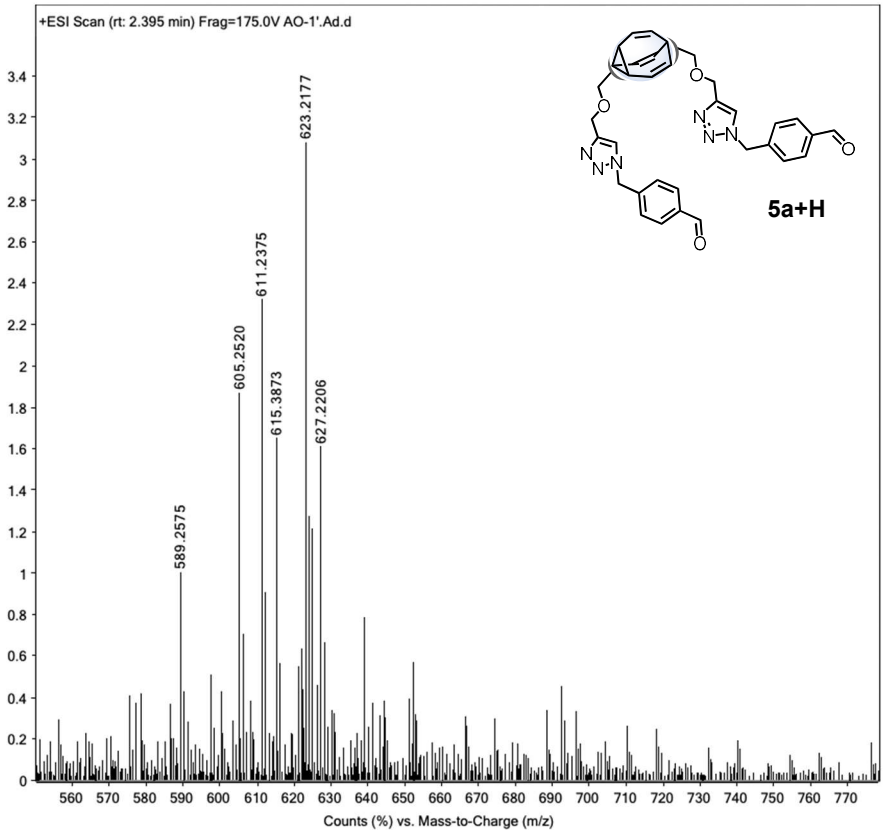

m-5
400 MHz ¹H NMR
in CDCl₃ at RT
2.00
4.02
1.99
5.06
4.01
3.96
7.98
4.16
3.99
3.96
7.98
f1 (ppm)

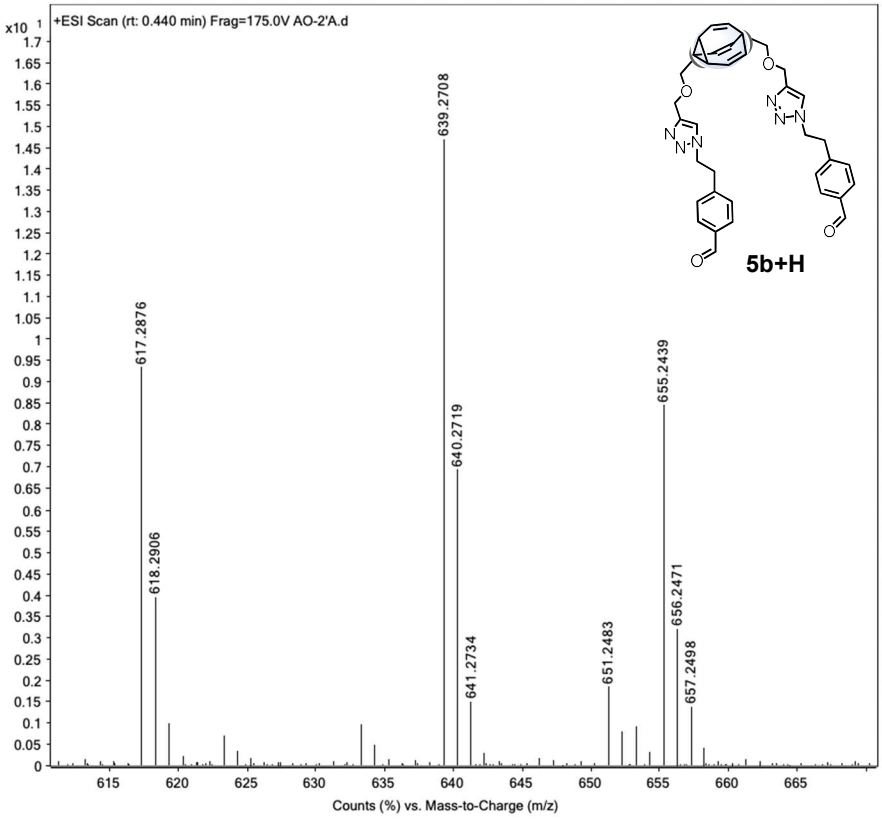

m-5
101 MHz ¹³C NMR
in CDCl₃ at RT
190.86
163.43
145.03
138.09
132.14
130.42
128.72
127.47
127.42
123.52
114.84
72.59
64.63
63.49
47.38
29.79
127.47
127.42
f1 (ppm)

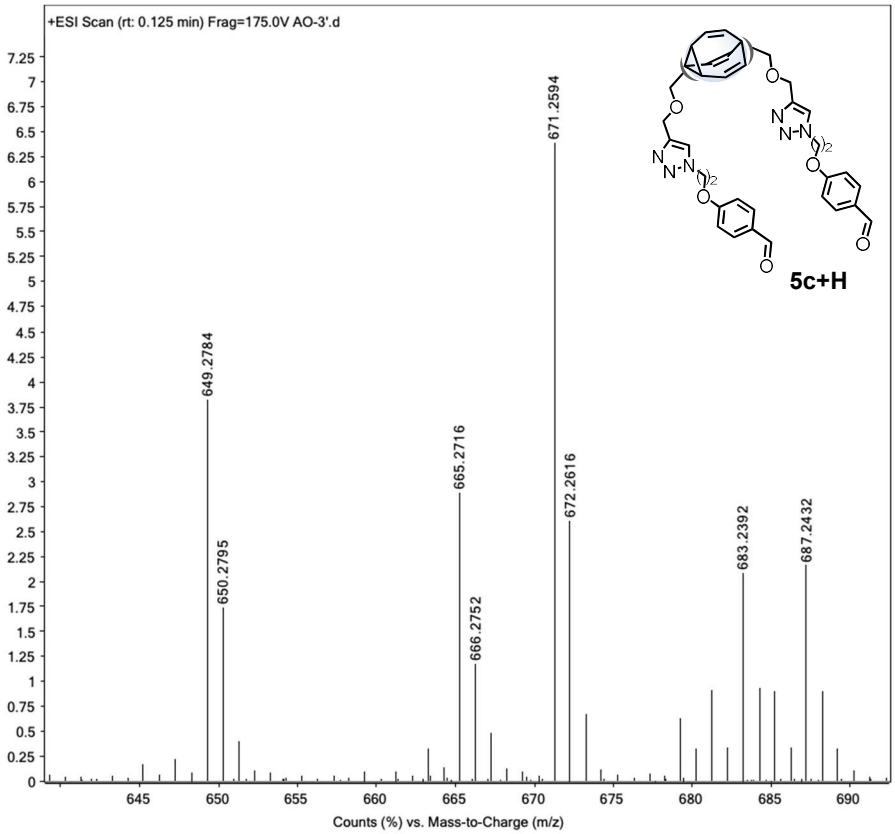

p-5
400 MHz ¹H NMR
in CDCl3 at RT
f1 (ppm)

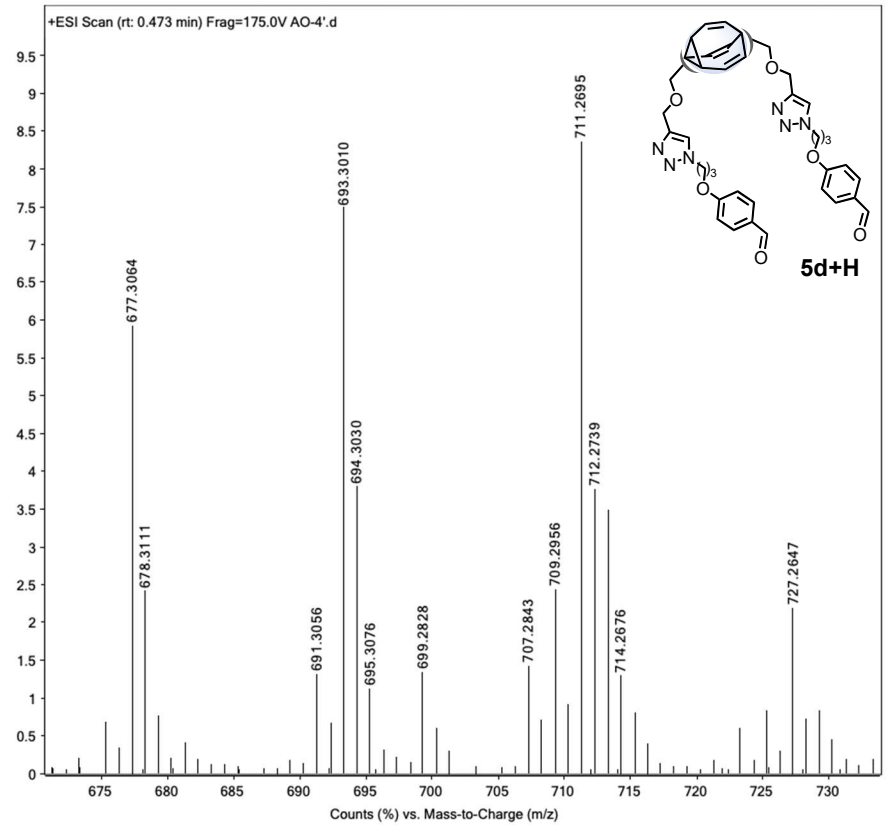

p-5
101 MHz ¹³C NMR
in CDCl3 at RT
f1 (ppm)

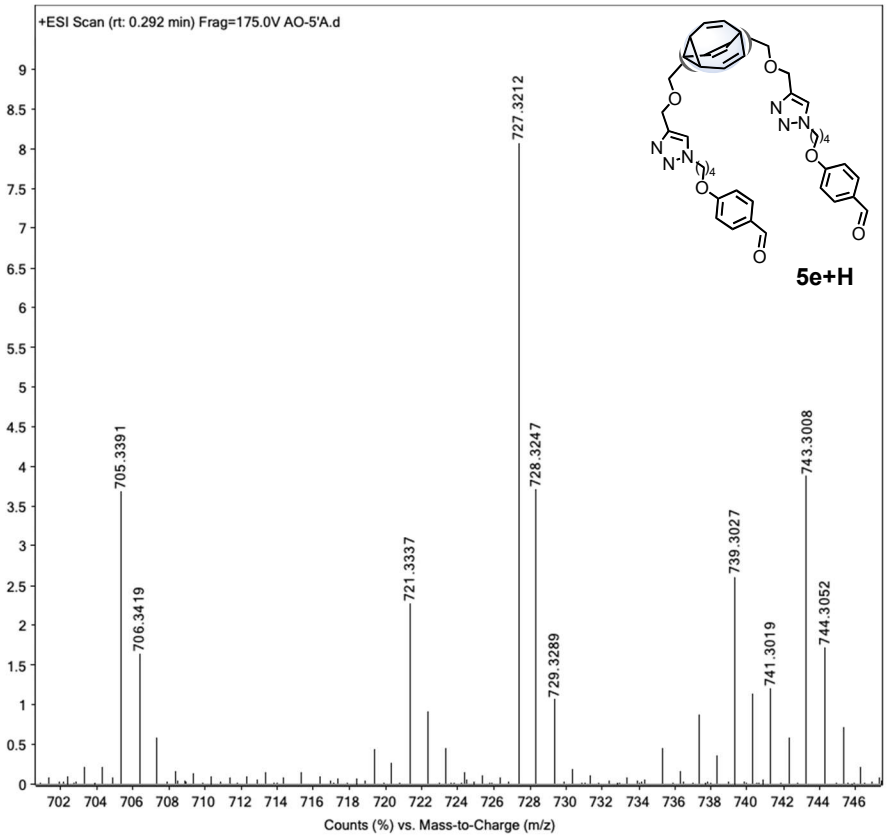
## 6 Mass Spectra

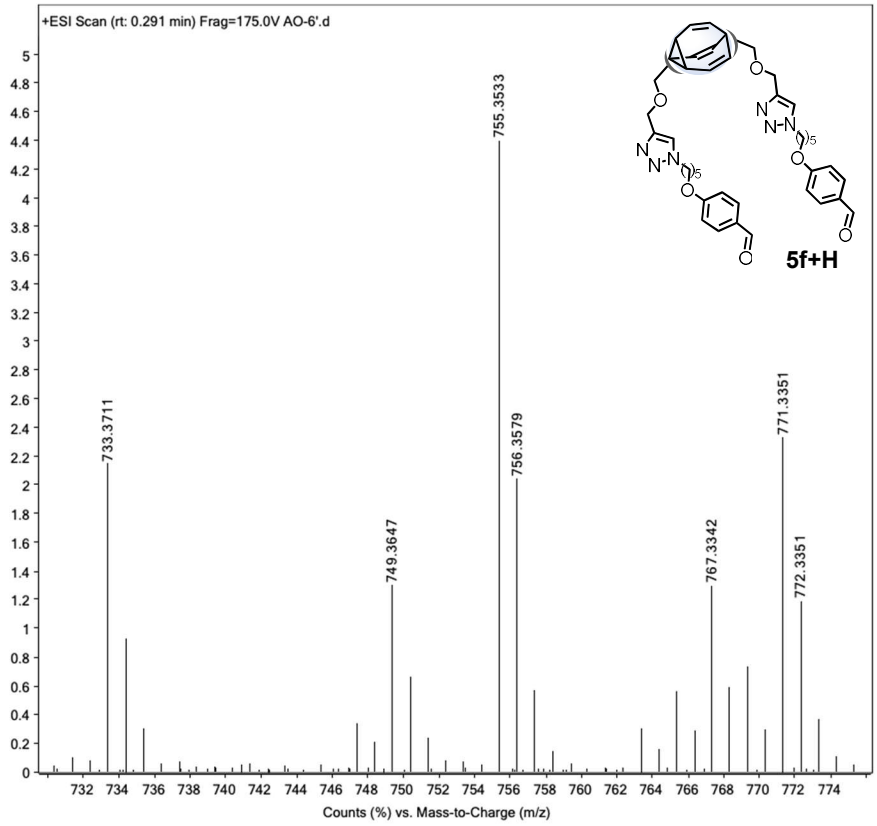


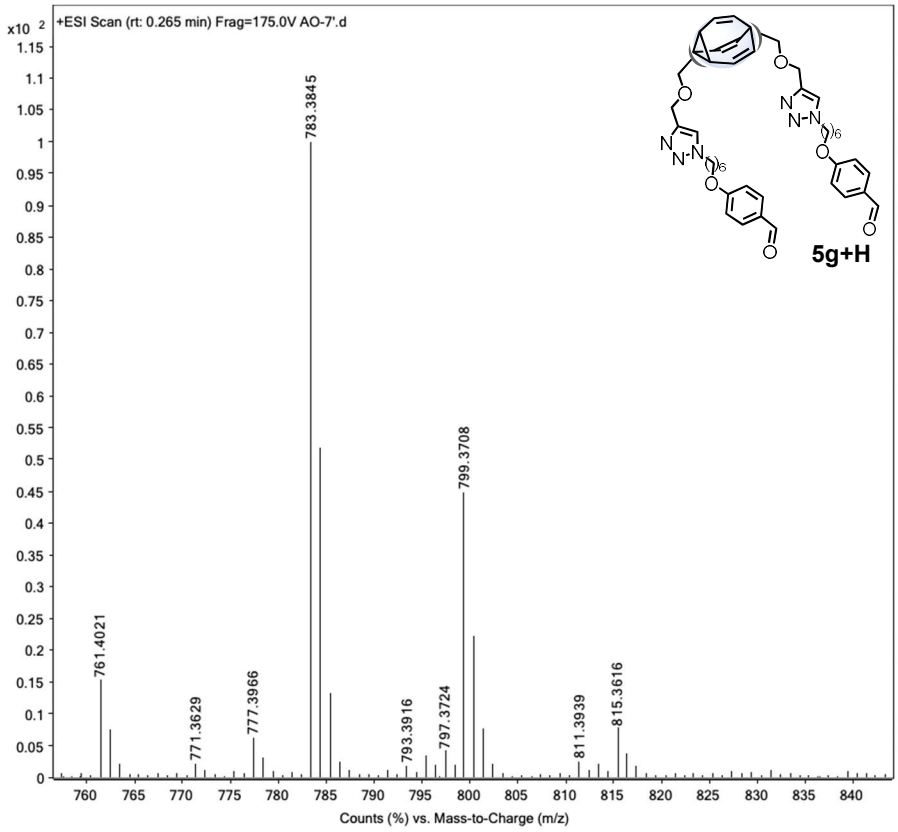



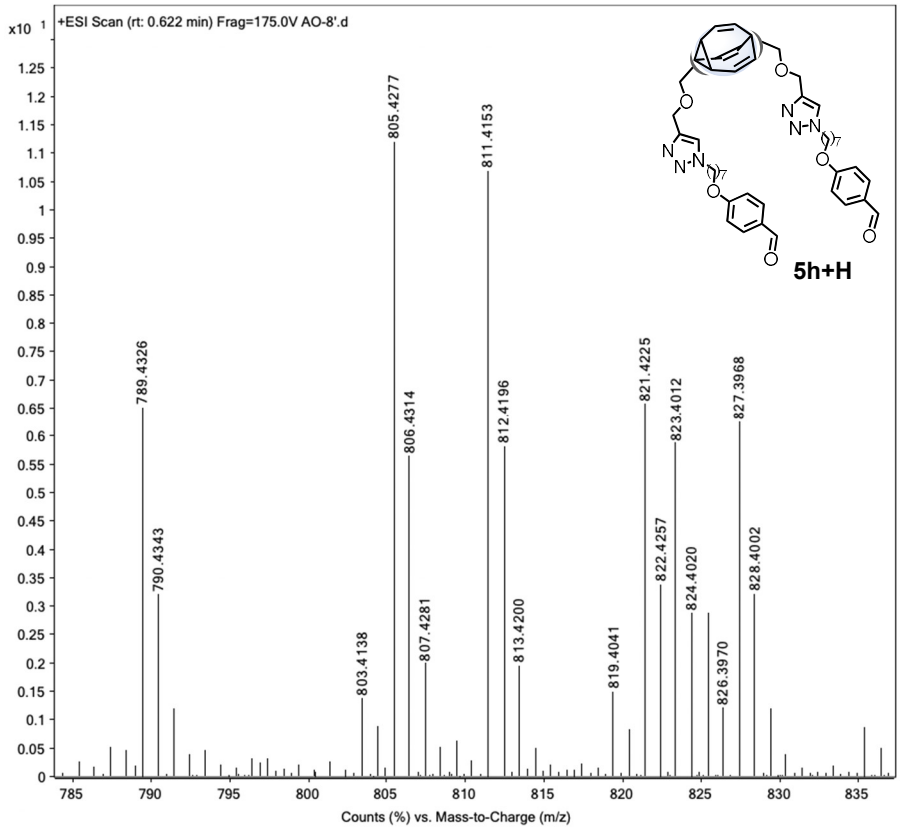

+ESI Scan (rt: 0.125 min) Frag=175.0V AO-3'.d
649.2784
650.2795
665.2716
666.2752
671.2594
672.2616
683.2392
687.2432
5c+H
Counts (%) vs. Mass-to-Charge (m/z)

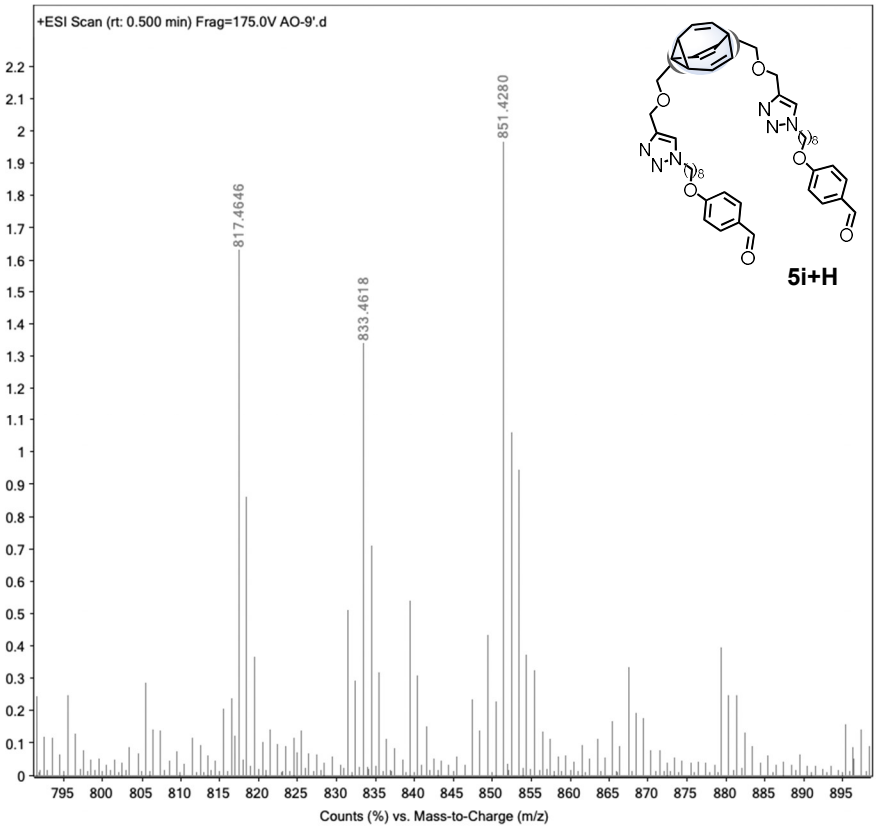

+ESI Scan (rt: 0.473 min) Frag=175.0V AO-4'.d
677.3064
678.3111
691.3056
693.3010
694.3030
695.3076
699.2828
707.2843
709.2956
711.2695
712.2739
714.2676
727.2647
5d+H
Counts (%) vs. Mass-to-Charge (m/z)

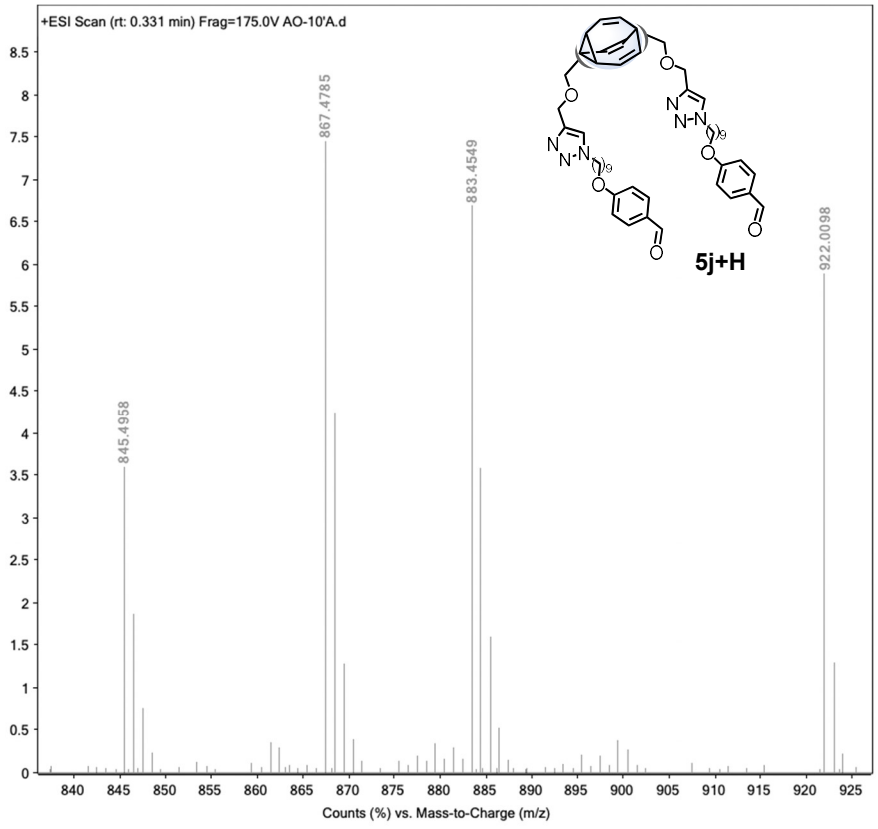

+ESI Scan (rt: 0.292 min) Frag=175.0V AO-5'A.d
5e+H
705.3391
706.3419
721.3337
727.3212
728.3247
729.3289
739.3027
741.3019
743.3008
744.3052
Counts (%) vs. Mass-to-Charge (m/z)

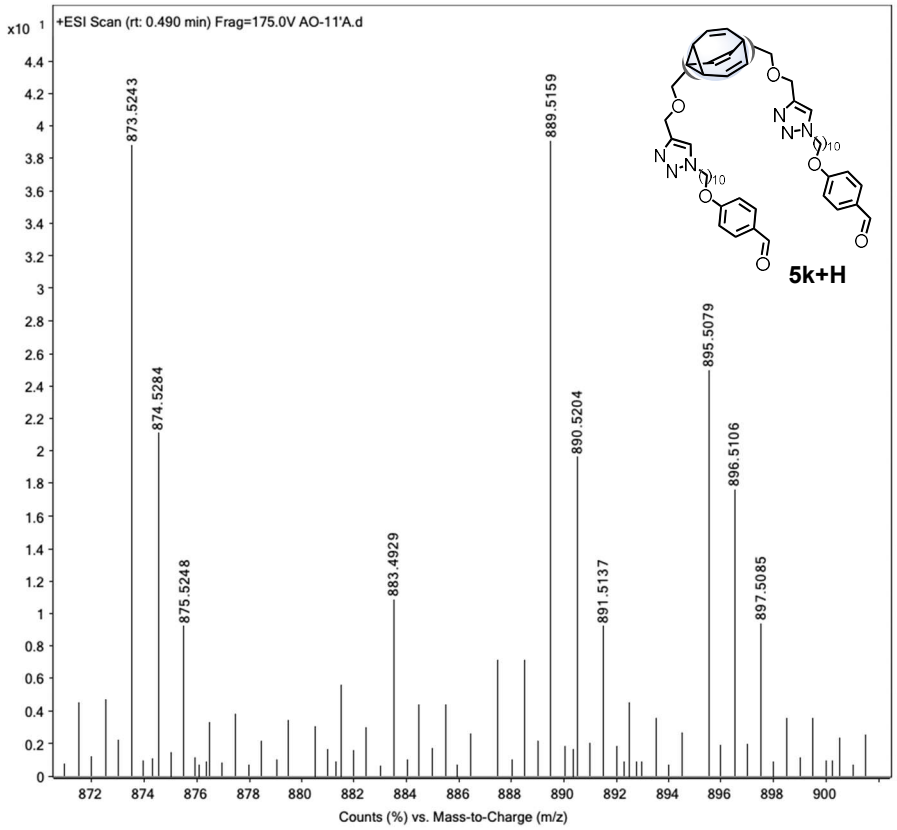

+ESI Scan (rt: 0.291 min) Frag=175.0V AO-6'.d
5f+H
733.3711
749.3647
755.3533
756.3579
767.3342
771.3351
772.3351
Counts (%) vs. Mass-to-Charge (m/z)

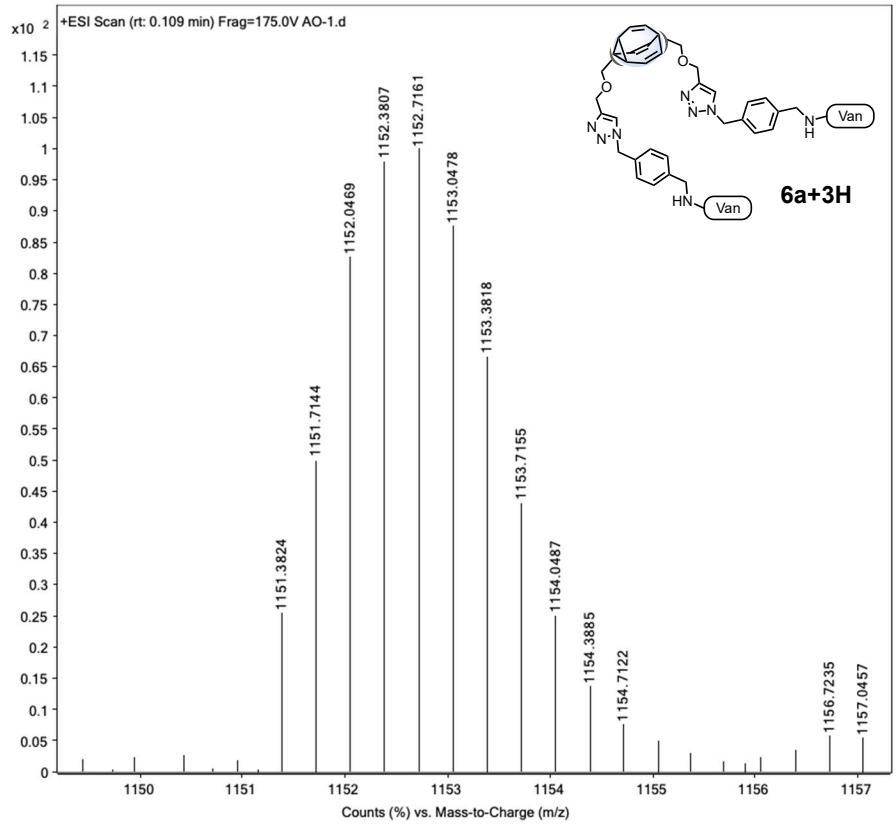

+ESI Scan (rt: 0.265 min) Frag=175.0V AO-7'.d
x10 2
783.3845
799.3708
761.4021
777.3966
771.3629
793.3916
797.3724
811.3939
815.3616
5g+H
Counts (%) vs. Mass-to-Charge (m/z)

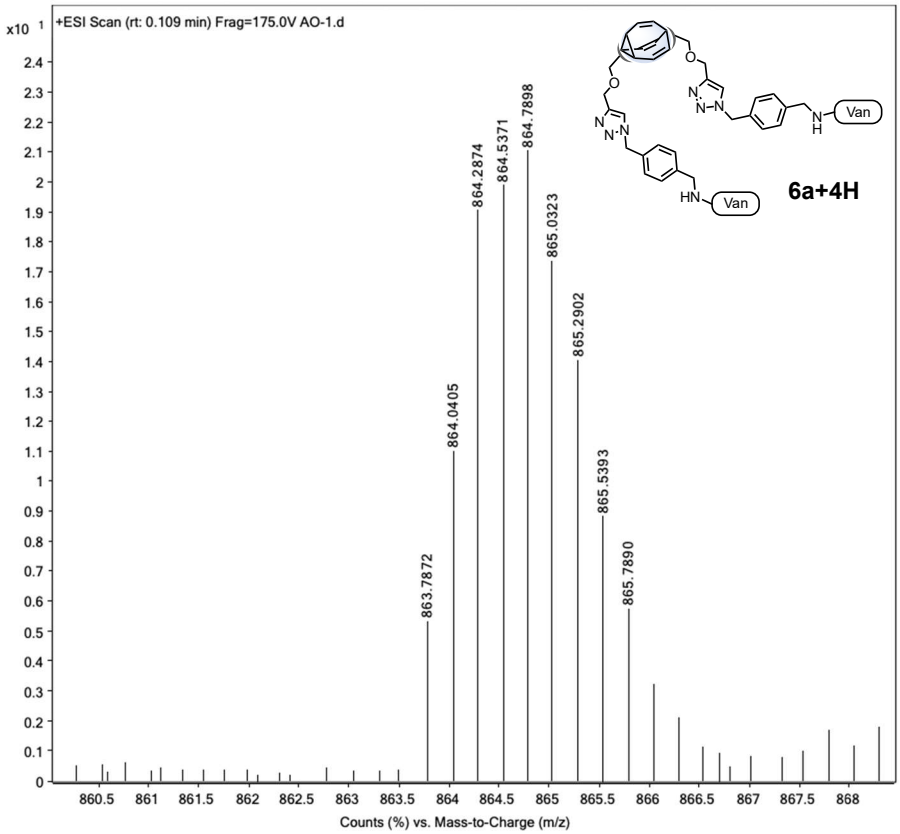

+ESI Scan (rt: 0.622 min) Frag=175.0V AO-8'.d
x10 1
805.4277
811.4153
789.4326
806.4314
812.4196
821.4225
823.4012
827.3968
790.4343
822.4257
824.4020
828.4002
807.4281
813.4200
803.4138
819.4041
826.3970
5h+H
Counts (%) vs. Mass-to-Charge (m/z)

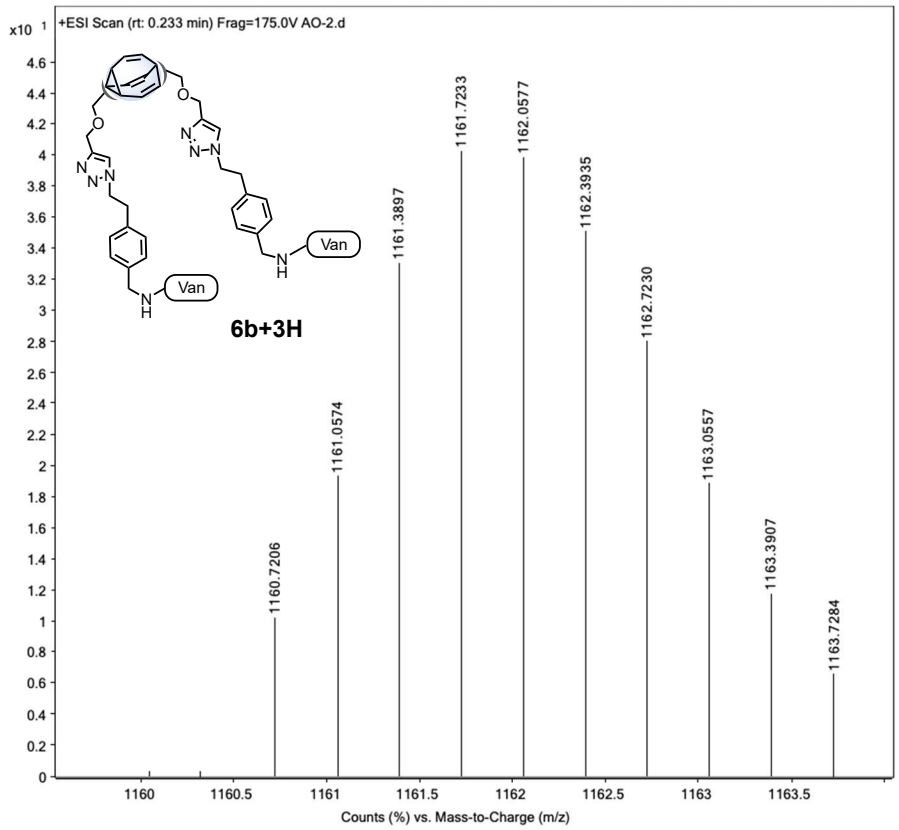

+ESI Scan (rt: 0.500 min) Frag=175.0V AO-9'.d
817.4646
833.4618
851.4280
5i+H
Counts (%) vs. Mass-to-Charge (m/z)

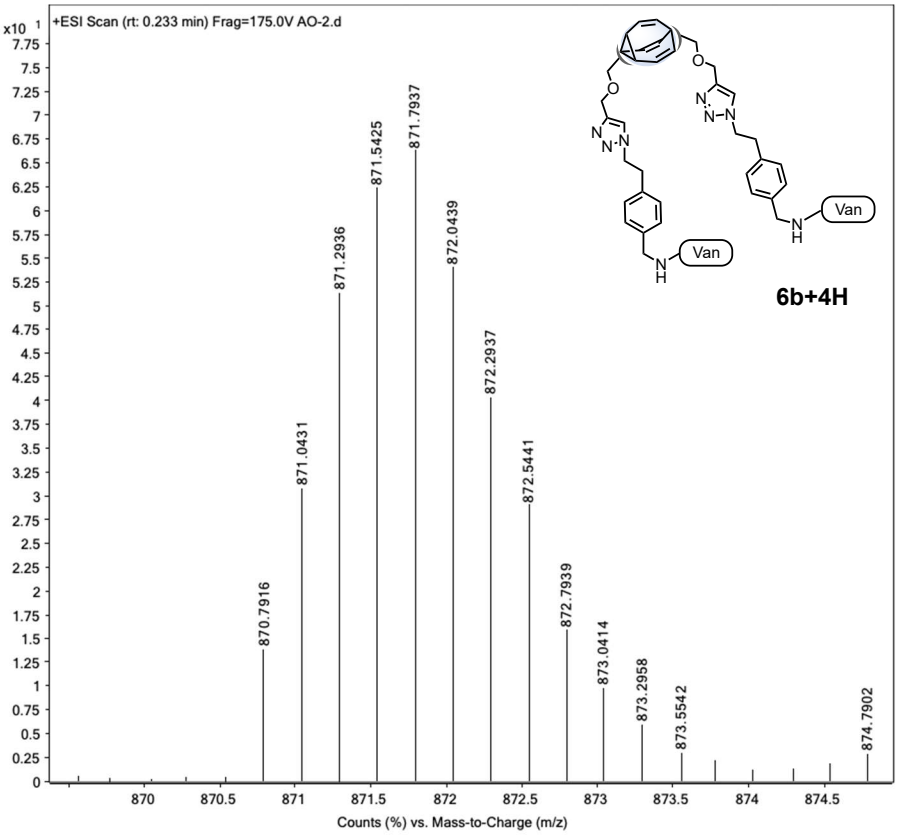

+ESI Scan (rt: 0.331 min) Frag=175.0V AO-10'A.d
845.4958
867.4785
883.4549
922.0098
5j+H
Counts (%) vs. Mass-to-Charge (m/z)

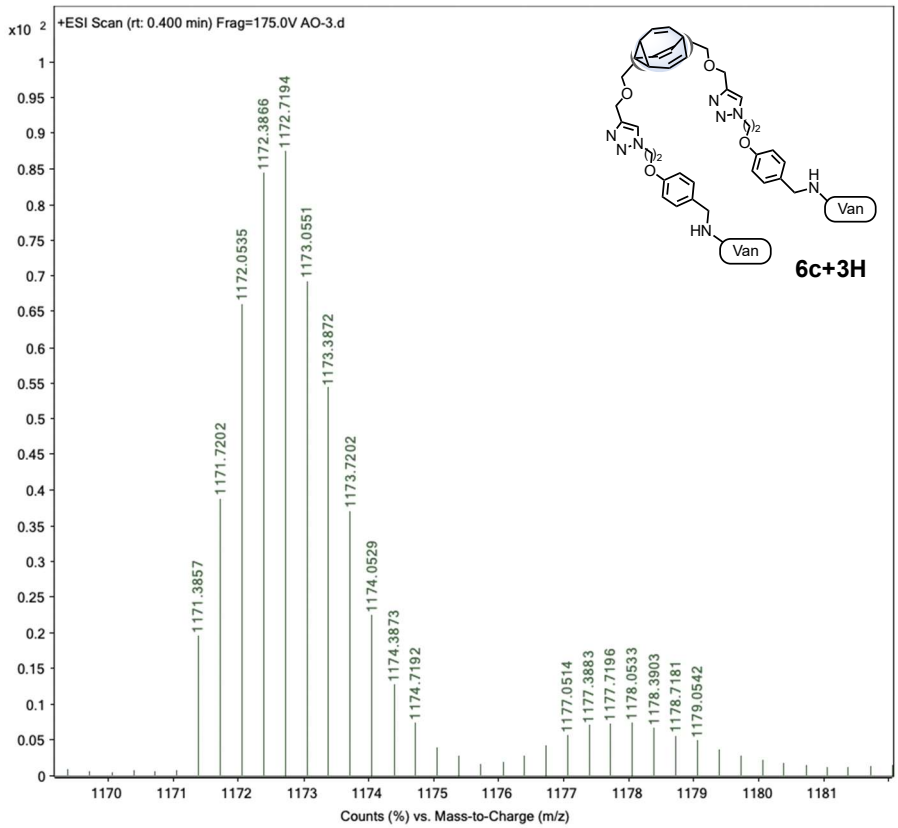

+ESI Scan (rt: 0.490 min) Frag=175.0V AO-11'A.d
x10 1
873.5243
874.5284
875.5248
883.4929
889.5159
890.5204
891.5137
895.5079
896.5106
897.5085
5k+H
Counts (%) vs. Mass-to-Charge (m/z)

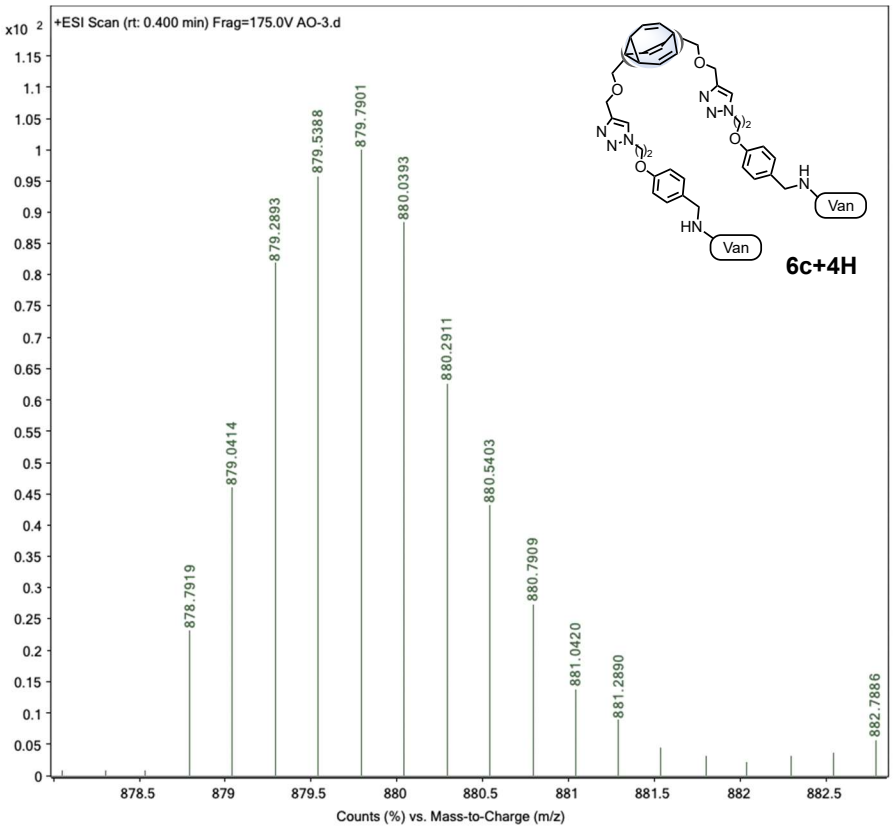

+ESI Scan (rt: 0.109 min) Frag=175.0V AO-1.d
x10 2
1151.3824
1151.7144
1152.0469
1152.3807
1152.7161
1153.0478
1153.3818
1153.7155
1154.0487
1154.3885
1154.7122
1156.7235
1157.0457
Counts (%) vs. Mass-to-Charge (m/z)
Van
6a+3H

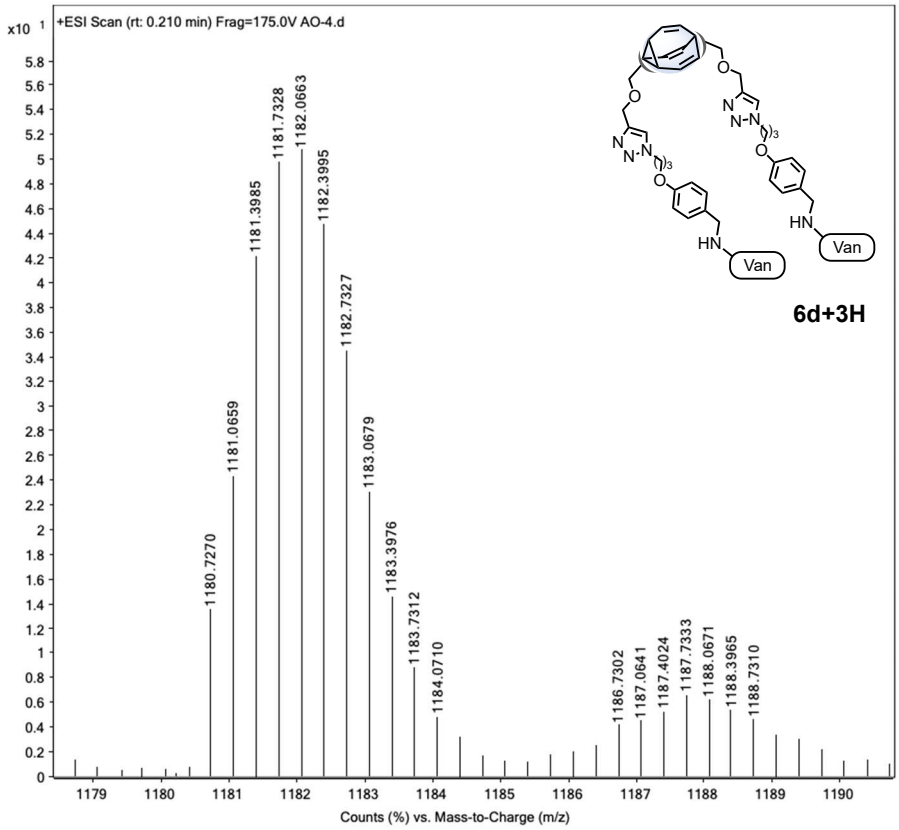

+ESI Scan (rt: 0.109 min) Frag=175.0V AO-1.d
x10 1
863.7872
864.0405
864.2874
864.5371
864.7898
865.0323
865.2902
865.5393
865.7890
Counts (%) vs. Mass-to-Charge (m/z)
Van
6a+4H

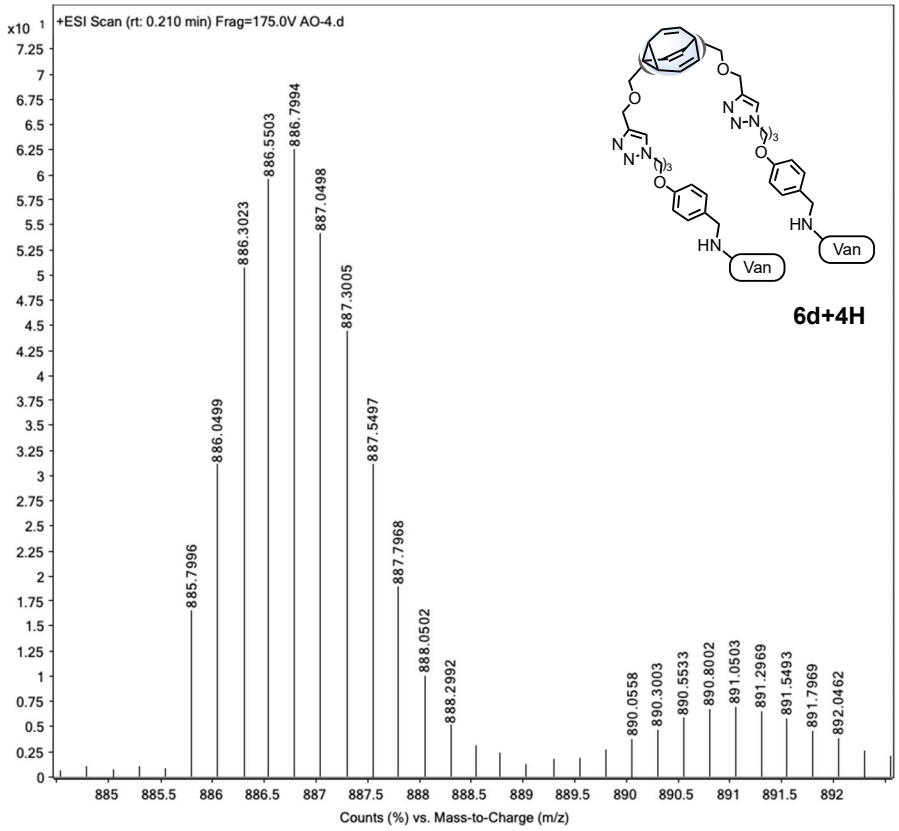

+ESI Scan (rt: 0.233 min) Frag=175.0V AO-2.d
x10 1
Van
Van
6b+3H
1160.7206
1161.0574
1161.3897
1161.7233
1162.0577
1162.3935
1162.7230
1163.0557
1163.3907
1163.7284
Counts (%) vs. Mass-to-Charge (m/z)

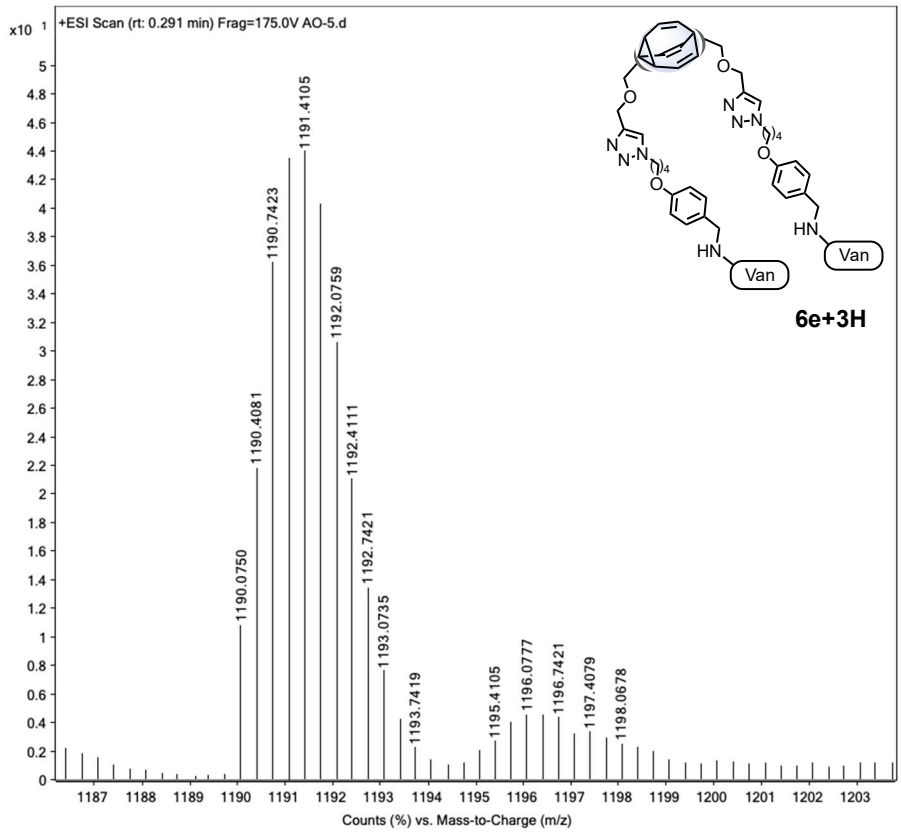

+ESI Scan (rt: 0.233 min) Frag=175.0V AO-2.d
x10 1
Van
Van
6b+4H
870.7916
871.0431
871.2936
871.5425
871.7937
872.0439
872.2937
872.5441
872.7939
873.0414
873.2958
873.5542
874.7902
Counts (%) vs. Mass-to-Charge (m/z)

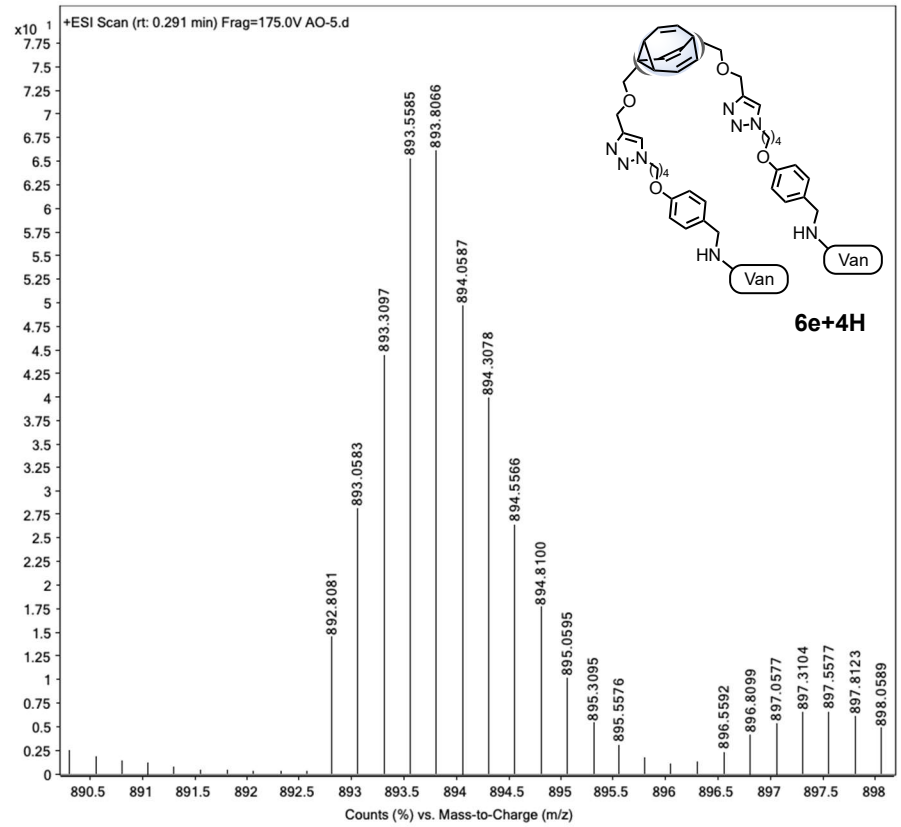

+ESI Scan (rt: 0.400 min) Frag=175.0V AO-3.d
x10 2
1171.3857
1171.7202
1172.0535
1172.3866
1172.7194
1173.0551
1173.3872
1173.7202
1174.0529
1174.3873
1174.7192
1177.0514
1177.3883
1177.7196
1178.0533
1178.3903
1178.7181
1179.0542
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6c+3H

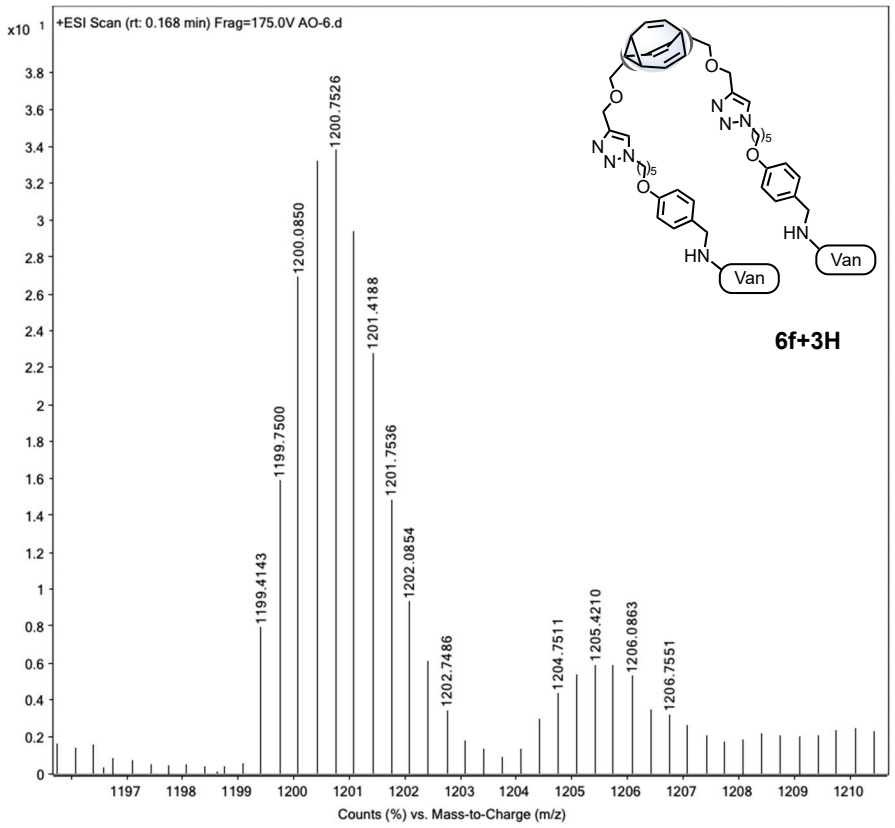

+ESI Scan (rt: 0.400 min) Frag=175.0V AO-3.d
x10 2
878.7919
879.0414
879.2893
879.5388
879.7901
880.0393
880.2911
880.5403
880.7909
881.0420
881.2890
882.7886
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6c+4H

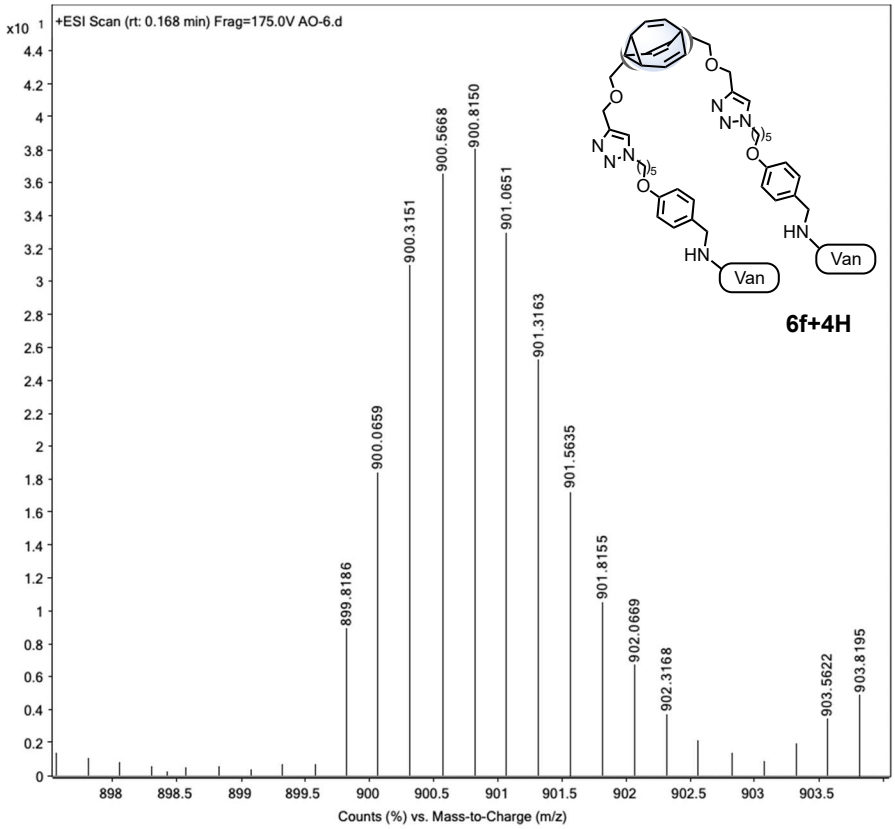

+ESI Scan (rt: 0.210 min) Frag=175.0V AO-4.d
x10 1
1180.7270
1181.0659
1181.3985
1181.7328
1182.0663
1182.3995
1182.7327
1183.0679
1183.3976
1183.7312
1184.0710
1186.7302
1187.0641
1187.4024
1187.7333
1188.0671
1188.3965
1188.7310
Counts (%) vs. Mass-to-Charge (m/z)
Van
6d+3H

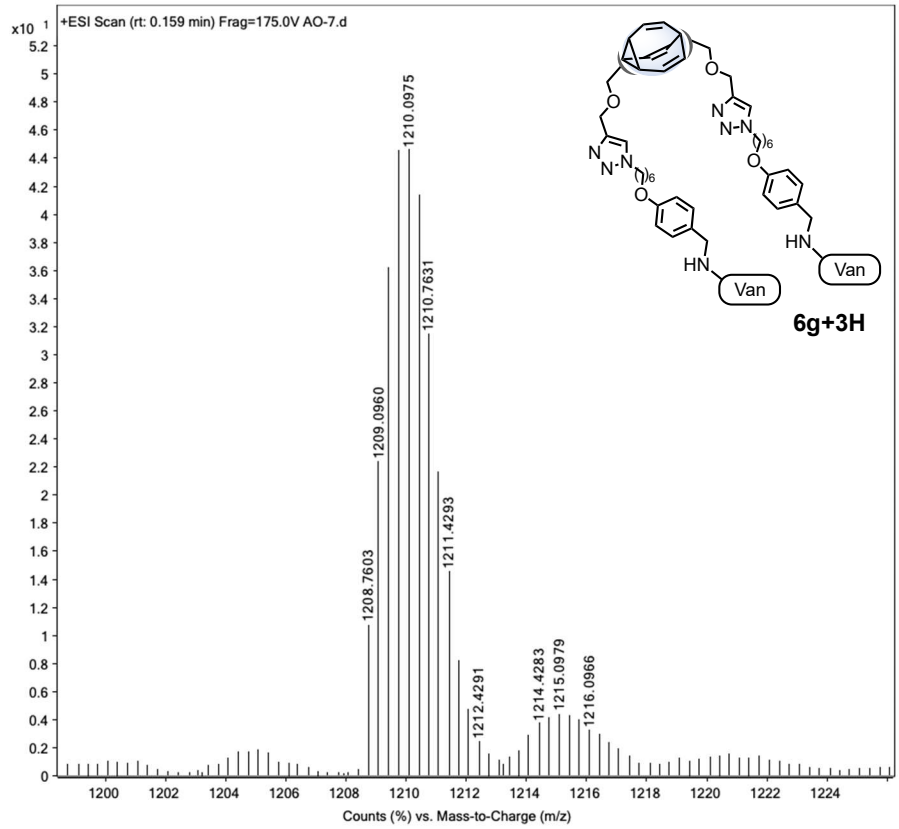

+ESI Scan (rt: 0.210 min) Frag=175.0V AO-4.d
x10 1
885.7996
886.0499
886.3023
886.5503
886.7994
887.0498
887.3005
887.5497
887.7968
888.0502
888.2992
890.0558
890.3003
890.5533
890.8002
891.0503
891.2969
891.5493
891.7969
892.0462
Counts (%) vs. Mass-to-Charge (m/z)
Van
6d+4H

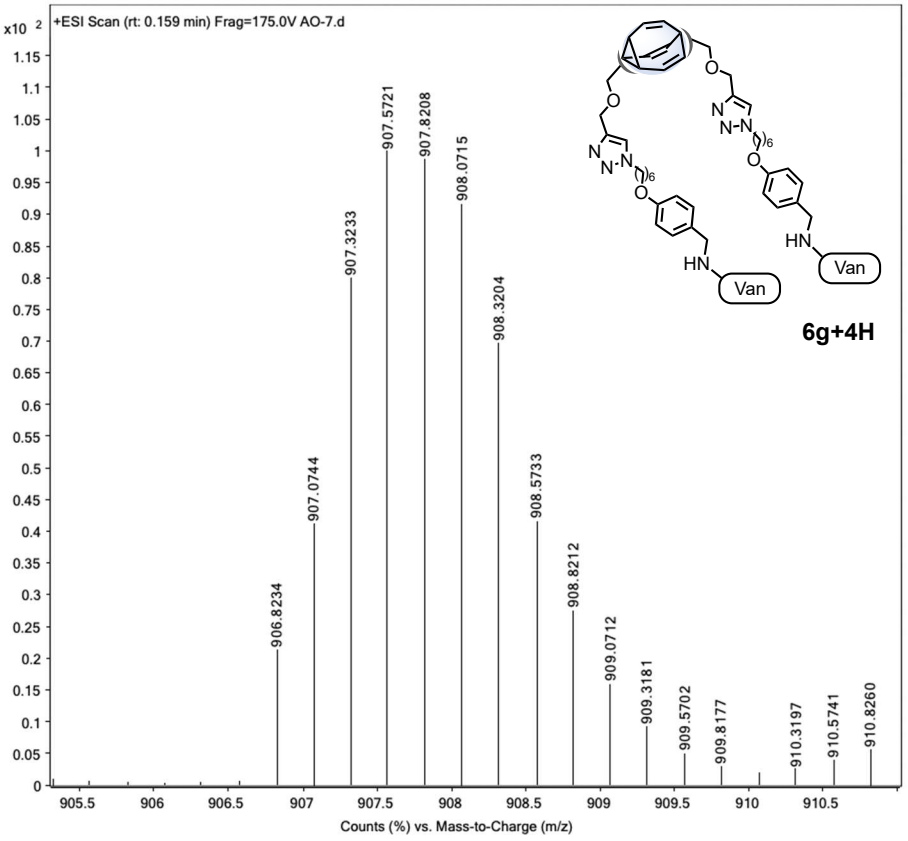

+ESI Scan (rt: 0.291 min) Frag=175.0V AO-5.d
x10 1
1190.0750
1190.4081
1190.7423
1191.4105
1192.0759
1192.4111
1192.7421
1193.0735
1193.7419
1195.4105
1196.0777
1196.7421
1197.4079
1198.0678
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6e+3H

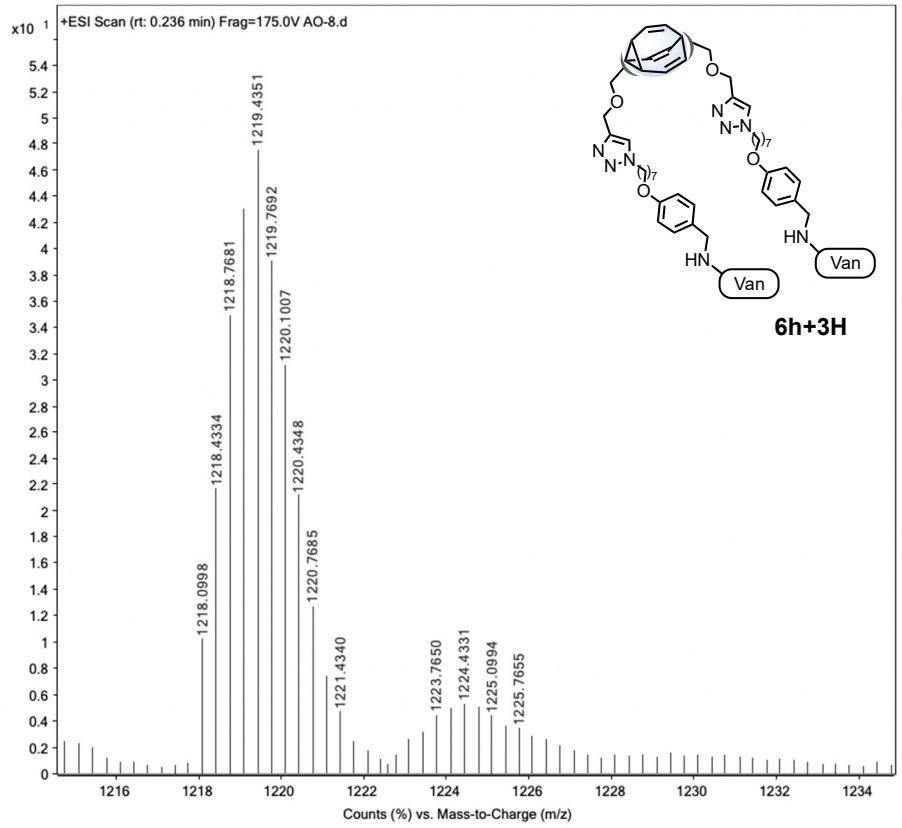

+ESI Scan (rt: 0.291 min) Frag=175.0V AO-5.d
x10 1
892.8081
893.0583
893.3097
893.5585
893.8066
894.0587
894.3078
894.5566
894.8100
895.0595
895.3095
895.5576
896.5592
896.8099
897.0577
897.3104
897.5577
897.8123
898.0589
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6e+4H

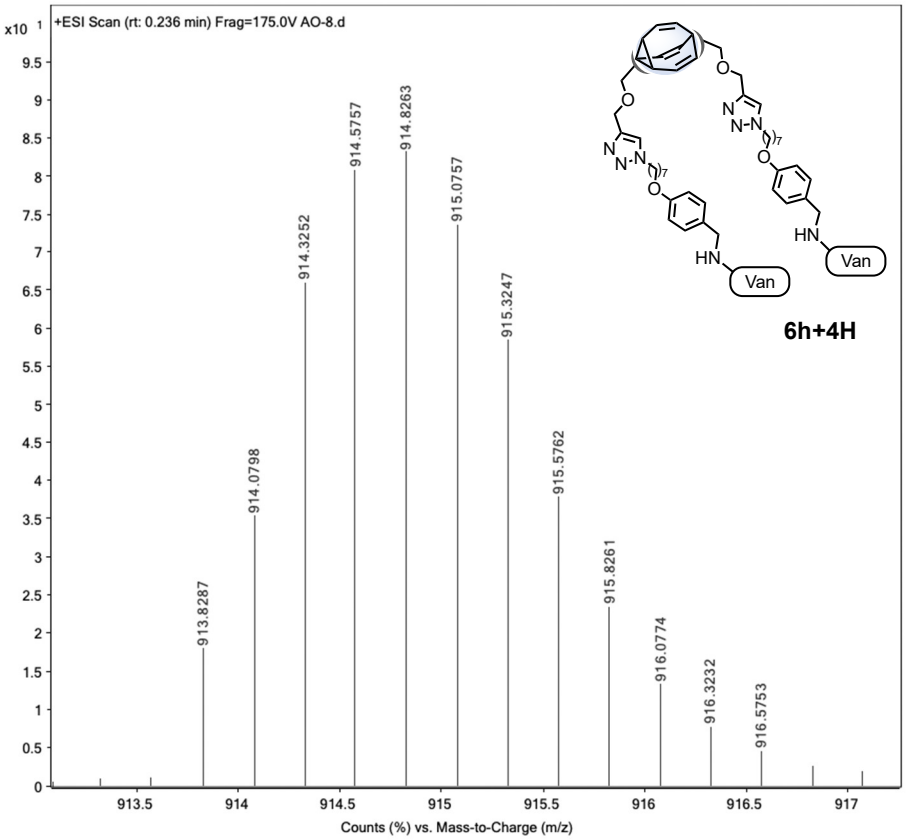

+ESI Scan (rt: 0.168 min) Frag=175.0V AO-6.d
x10 1
1199.4143
1199.7500
1200.0850
1200.7526
1201.4188
1201.7536
1202.0854
1202.7486
1204.7511
1205.4210
1206.0863
1206.7551
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6f+3H

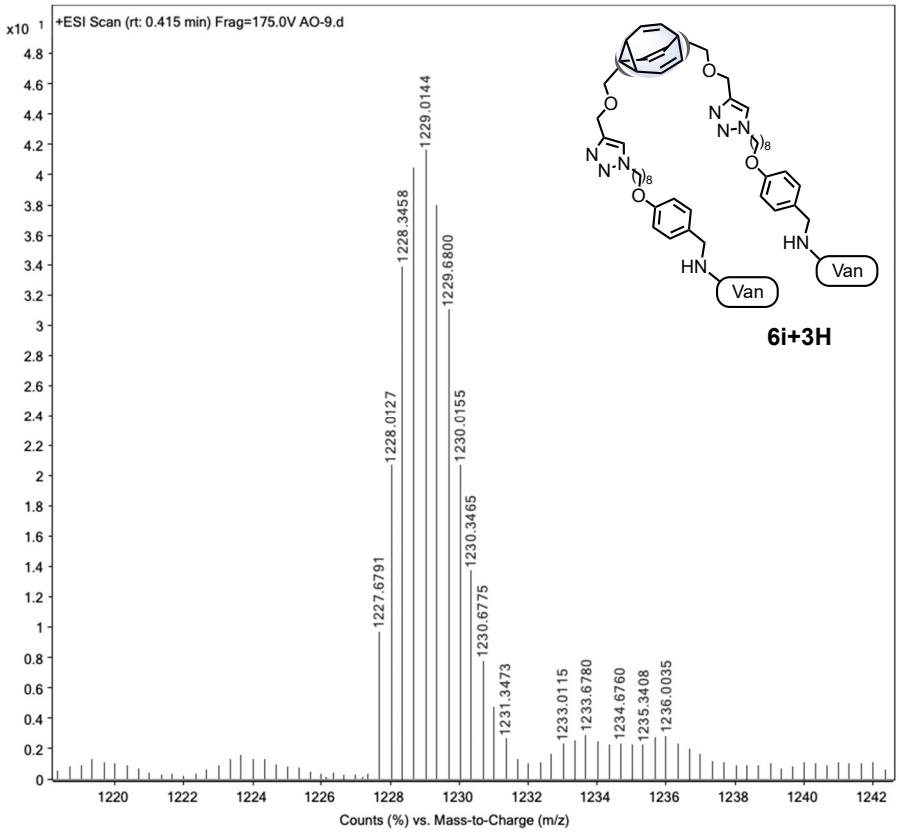

+ESI Scan (rt: 0.168 min) Frag=175.0V AO-6.d
x10 1
899.8186
900.0659
900.3151
900.5668
900.8150
901.0651
901.3163
901.5635
901.8155
902.0669
902.3168
903.5622
903.8195
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6f+4H

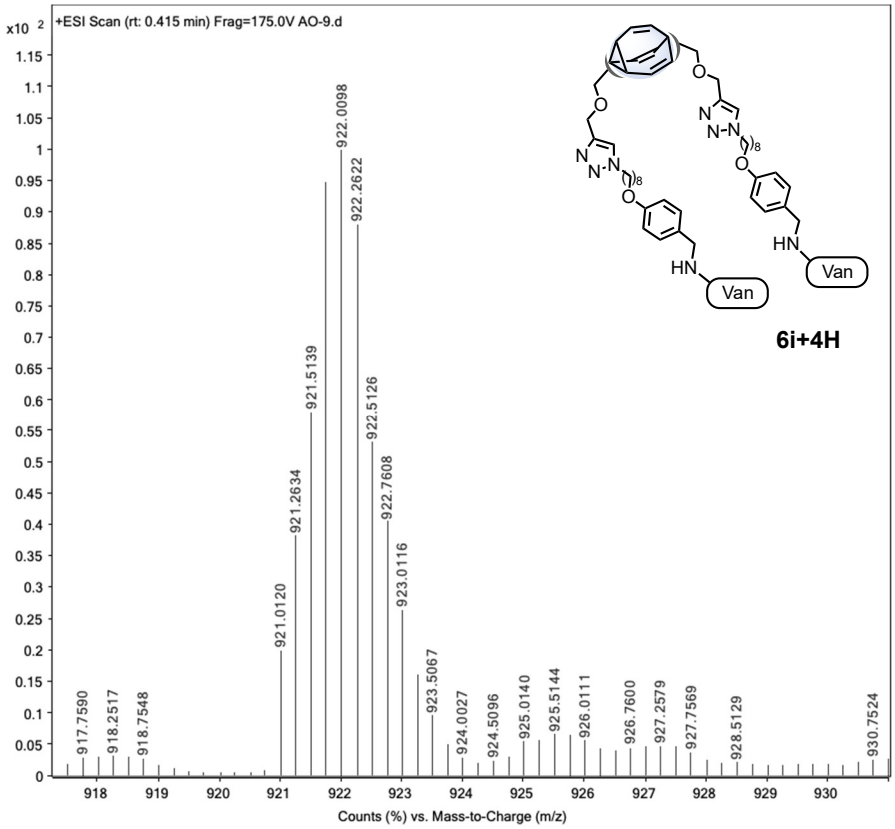

+ESI Scan (rt: 0.159 min) Frag=175.0V AO-7.d
x10 1
1208.7603
1209.0960
1210.0975
1210.7631
1211.4293
1212.4291
1214.4283
1215.0979
1216.0966
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6g+3H

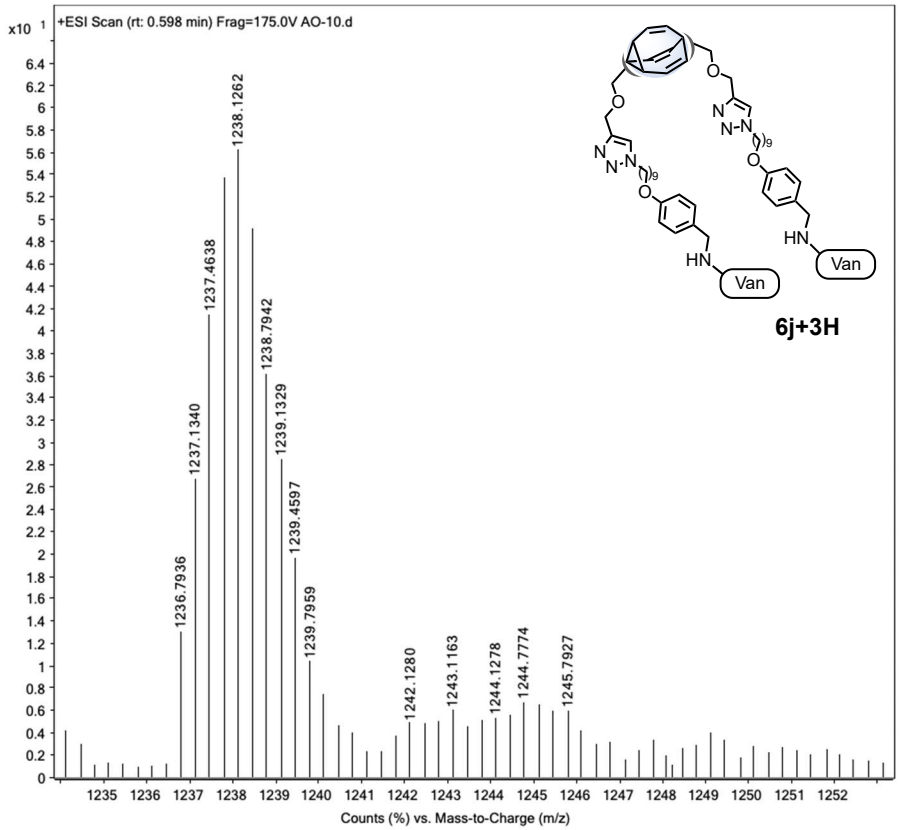

+ESI Scan (rt: 0.159 min) Frag=175.0V AO-7.d
x10 2
906.8234
907.0744
907.3233
907.5721
907.8208
908.0715
908.3204
908.5733
908.8212
909.0712
909.3181
909.5702
909.8177
910.3197
910.5741
910.8260
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6g+4H

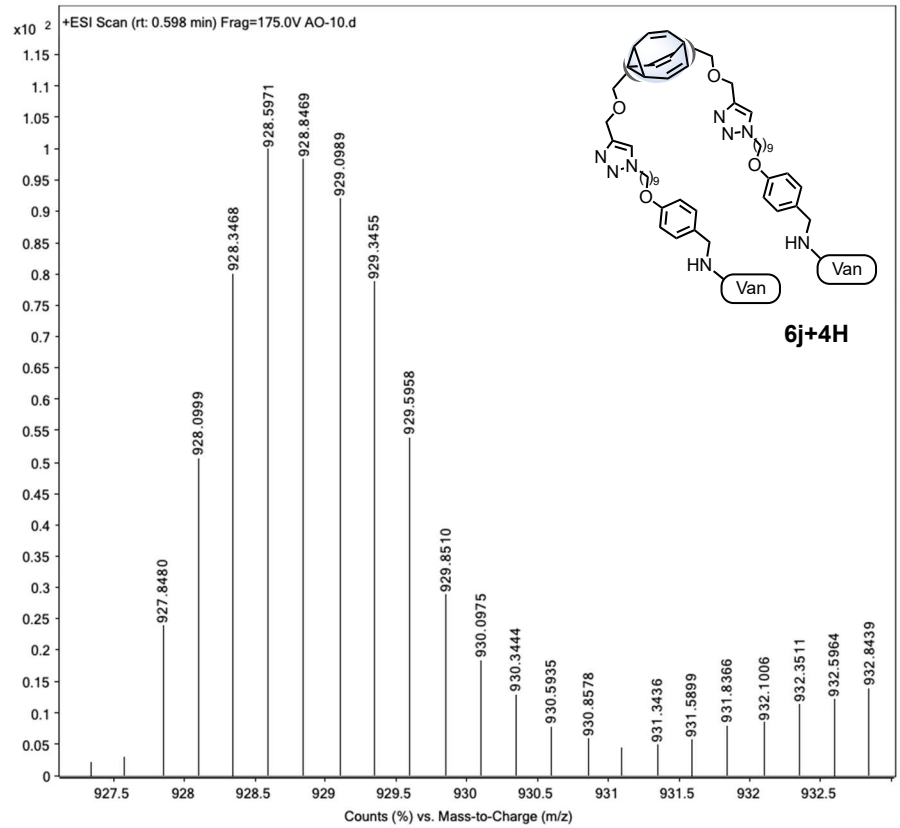

+ESI Scan (rt: 0.236 min) Frag=175.0V AO-8.d
x10 1
1218.0998
1218.4334
1218.7681
1219.4351
1219.7692
1220.1007
1220.4348
1220.7685
1221.4340
1223.7650
1224.4331
1225.0994
1225.7655
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6h+3H

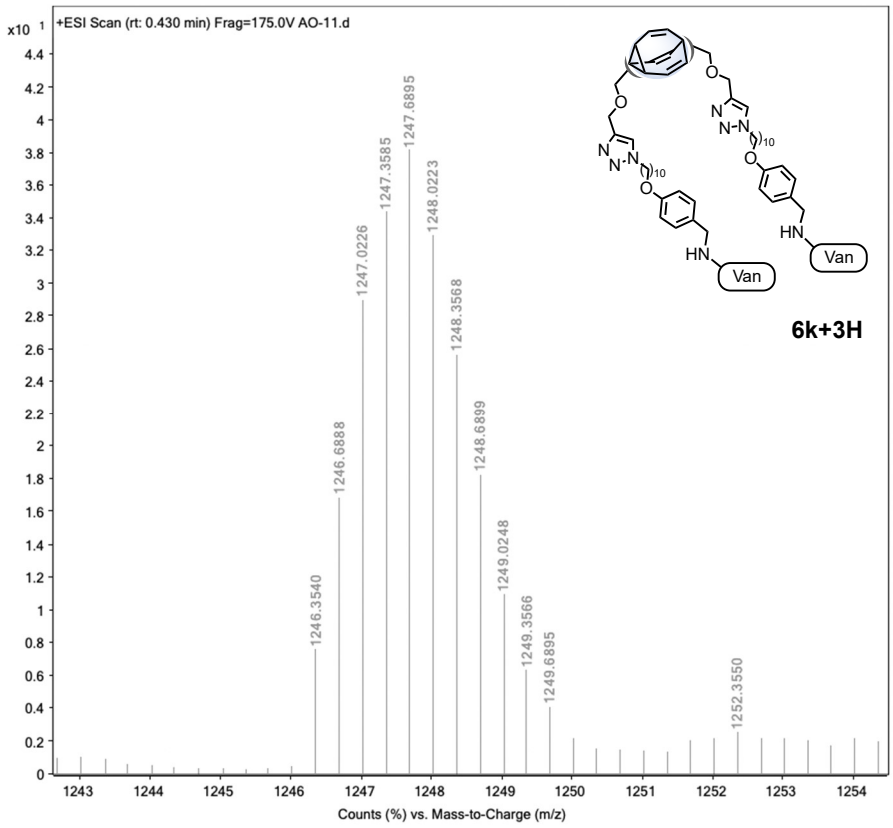

+ESI Scan (rt: 0.236 min) Frag=175.0V AO-8.d
x10 1
913.8287
914.0798
914.3252
914.5757
914.8263
915.0757
915.3247
915.5762
915.8261
916.0774
916.3232
916.5753
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6h+4H

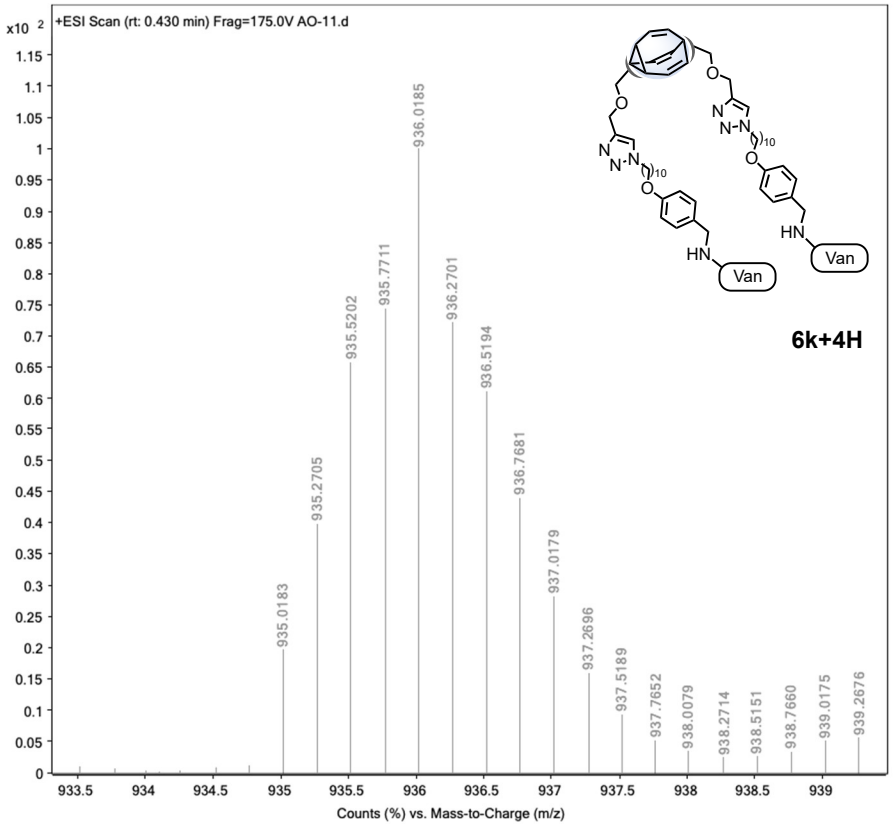

+ESI Scan (rt: 0.415 min) Frag=175.0V AO-9.d
x10 1
1227.6791
1228.0127
1228.3458
1229.0144
1229.6800
1230.0155
1230.3465
1230.6775
1231.3473
1233.0115
1233.6780
1234.6760
1235.3408
1236.0035
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6i+3H


+ESI Scan (rt: 0.415 min) Frag=175.0V AO-9.d
x10 2
917.7590
918.2517
918.7548
921.0120
921.2634
921.5139
922.0098
922.2622
922.5126
922.7608
923.0116
923.5067
924.0027
924.5096
925.0140
925.5144
926.0111
926.7600
927.2579
927.7569
928.5129
930.7524
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6i+4H


+ESI Scan (rt: 0.598 min) Frag=175.0V AO-10.d
x10 1
1238.1262
1237.4638
1237.1340
1238.7942
1239.1329
1239.4597
1236.7936
1239.7959
1242.1280
1243.1163
1244.1278
1244.7774
1245.7927
Van
Van
6j+3H
Counts (%) vs. Mass-to-Charge (m/z)


+ESI Scan (rt: 0.598 min) Frag=175.0V AO-10.d
x10 2
928.5971
928.8469
928.3468
929.0989
929.3455
928.0999
929.5958
927.8480
929.8510
930.0975
930.3444
930.5935
930.8578
931.3436
931.5899
931.8366
932.1006
932.3511
932.5964
932.8439
Van
Van
6j+4H
Counts (%) vs. Mass-to-Charge (m/z)


x10 1
+ESI Scan (rt: 0.430 min) Frag=175.0V AO-11.d
1246.3540
1246.6888
1247.0226
1247.3585
1247.6895
1248.0223
1248.3568
1248.6899
1249.0248
1249.3566
1249.6895
1252.3550
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6k+3H


x10 2
+ESI Scan (rt: 0.430 min) Frag=175.0V AO-11.d
935.0183
935.2705
935.5202
935.7711
936.0185
936.2701
936.5194
936.7681
937.0179
937.2696
937.5189
937.7652
938.0079
938.2714
938.5151
938.7660
939.0175
939.2676
Counts (%) vs. Mass-to-Charge (m/z)
Van
Van
6k+4H