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Supporting Information

Aromatic Oligoamide Macrocycles from Biomolecular Coupling of Folded Oligomeric Precursors

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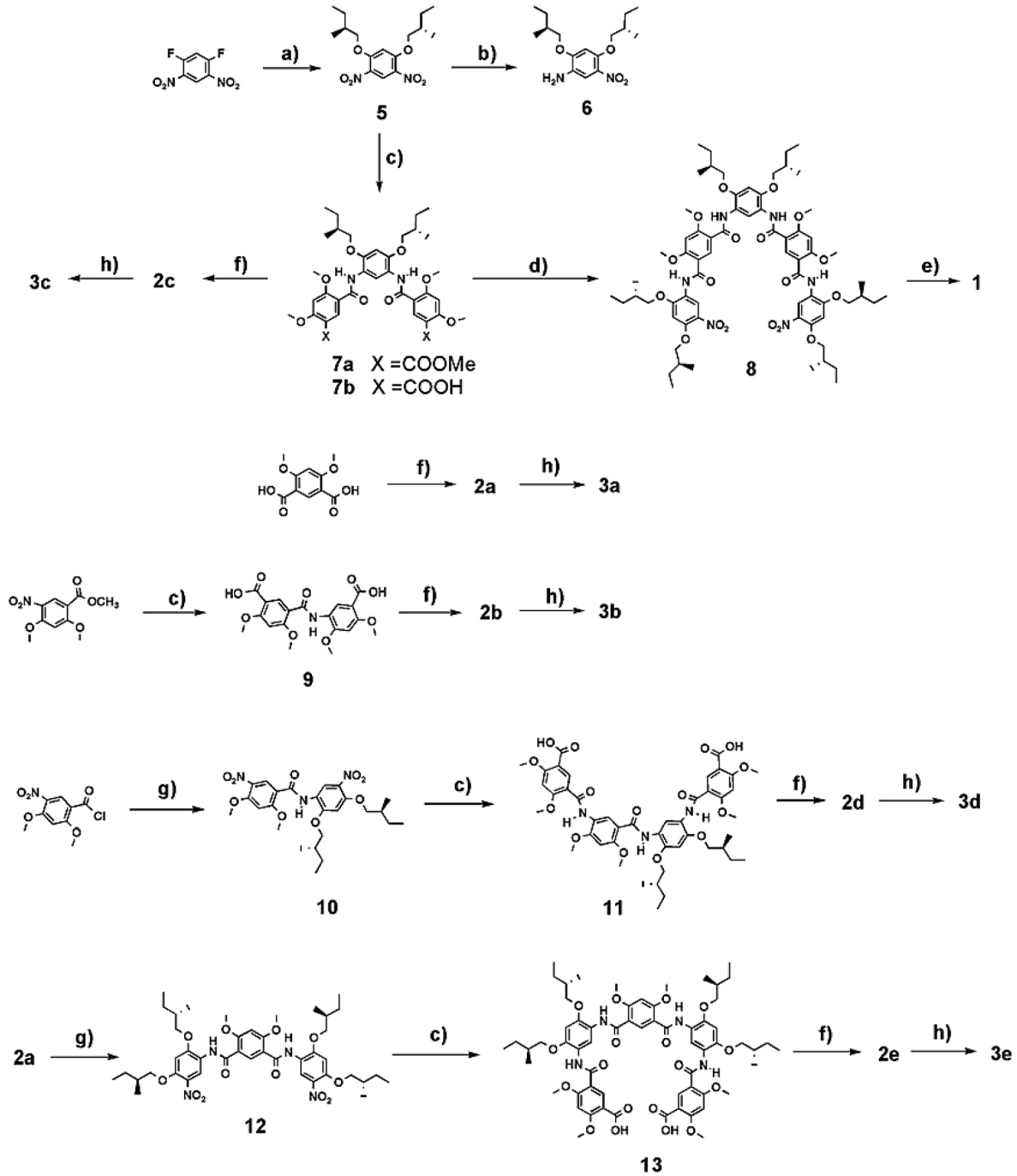
Contents:

Synthesis



Scheme S1. Reagents and conditions: a) S(-)-2-Methyl-1-butanol, Et_3N, K_2CO_3, r.t. 10 h; **b)** $Na_2S{\cdot}9H_2O$, EtOH, 80 ^{0}C, 15min. **c)** (i) H_2, 10% Pd/C; (ii) 5-Chlorocarbonyl-2,4-dimethoxy-benzoic acid methyl ester, DIEA, CH_2Cl_2, rt., 3 h; (iii) KOH, EtOH, reflux, 5h; **d) 6**, EDCI, HOBt, CH_2Cl_2, r.t. 48 h; **e)** H_2, 10% Pd/C, $CHCl_3$/ MeOH, 52 ^{0}C, 10 h, HCl; **f)** $(COCl)_2$, DMF (cat.), CH_2Cl_2, r.t. 5h; **g) 6**, DIEA, CH_2Cl_2, r.t. 3 h; **h) 1**, DIEA, CH_2Cl_2, 0 ^{0}C, 3 h.

General: All chemicals were obtained from commercial suppliers and were used as received unless otherwise noted. CH_2Cl_2 was dried over CaH_2. Unless otherwise specified, all solvents were removed with a rotary vacuum evaporator. Analytical thin layer chromatography (TLC) was conducted on Analtech Uniplate silica gel plates with

detection by UV light. 4,6-Dimethoxy-isophthalic acid monomethyl ester, 2,4-dimethoxy-5-nitro-benzoic acid and 4,6-dimethoxy-isophthalic acid were synthesised according to literature procedures.

NMR analyses were carried out on Bruker AV II-400 MHz, VarianUNITY INOVA400 (400MHz) or Bruker AV II-600 MHz (600MHz) spectrometer. Tetramethylsilane (TMS) was used as the internal standard for ^{1}H NMR and ^{13}C NMR. Chemical shifts are reported in ppm values downfield from tetramethylsilane and *J* values are reported in Hz. The yield of the macrocycle is calculated using p-xylene as internal standard. MALDI-TOF MS spectra were recorded on a Bruker Biflex IV MS spectrometer with dithranol as a matrix. All high-resolution (HR) electrospray ionisation (ESI) mass spectra were recorded on Waters Q-Tof Premier .

1,5-Bis-(2-methyl-butoxy)-2,4-dinitro-benzene (5): A mixture of s(-)-2-methyl-1-butanol (5.00 g, 56.7mmol), Et_3N (8.61g, 85.1mmol) and 1,5-difluoro-2, 4-dinitro-benzene (5.28g, 25.8 mmol) was stirred at room temperature for 2h, and then K_2CO_3 (1.00g, 7.2mmol) was added. The mixture was stirred at room temperature for 8h. The mixture was dissolved in EtOAc and washed with water, dried over Na_2SO_4. The yellow solid after removal of the solvent was subjected to chromatography ($CHCl_3$/EtOAc, 60:1) to provide the product as a yellow solid (7.74g, 88.1%). ^{1}H NMR (500 MHz, $CDCl_3$) □ 8.76 (s, 1H), 6.55 (s, 1H), 4.03 (m, 2H), 3.97 (m, 2H), 1.99 (m, 2H), 1.62 (m, 2H), 1.36 (m, 2H), 1.10 (d, J = 7.0 Hz), 0.98 (t, J = 7.5 Hz, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) □ 158.3, 125.9, 98.6, 75.2, 34.7, 25.9, 16.5, 11.4. MS (ESI) m/z, calcd. for $C_{16}H_{25}N_2O_6$ ($M+H^+$) 341.2, Found 341.0 ($M+H^+$).

2,4-Bis-(2-methyl-butoxy)-5-nitro-phenylamine (6): $Na_2S{\cdot}9H_2O$ (145.7mg, 0.59mmol) was added to a stirred solution of **5** (100.0mg, 0.29mmol) in EtOH (10mL) at 50 ^{0}C. The mixture was refluxed for 15 min at 80 ^{0}C. The mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water 3 times till pH=8, and then was dried with Na_2SO_4. The mixture was subjected to column chromatography (EtOAc/$CHCl_3$, 1:20) to give a yellow oil (54.9mg, 61.0%). ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.39 (s, 1H), 6.44 (s, 1H), 3.93~3.70 (m, 4H), 3.70 (s, 2H), 1.94 (m, 2H), 1.59 (m, 2H), 1.32 (m, 2H), 1.06 (t, 6H), 1.01~0.94 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) □ 152.13, 148.26, 132.14, 129.89, 111.18, 99.06, 75.51, 73.70, 34.97, 34.72, 26.19, 26.01, 16.63, 16.53, 11.37. MS (ESI) m/z, calcd. for $C_{16}H_{27}N_2O_4$ 311.2 ($M+H^+$), found 311.2 ($M+H^+$).

Trimer (7b): 1,5-Bis-(2-methyl-butoxy)-2,4-dinitro-benzene **5** (4.07g, 12.0 mmol) was hydrogenated in the presence of 10% Pd/C (0.8g) at 0.3MPa for 8h at room temperature. The solution was filtered in darkness as fast as possible followed by immediate removal of the solvent. The reduced diamine was used for the immediate coupling reaction. The acid chloride, prepared from 4,6-dimethoxy-isophthalic acid monomethyl ester (6.32g, 26.3mmol), was dissolved in CH_2Cl_2 (10 mL) and added dropwise to a mixture of the above diamine and Et_3N (2.93g, 29.0mmol) in CH_2Cl_2 (40 mL). The solution was stirred at room temperature under N_2 for 7h. The organic layer was washed with water. Removal of CH_2Cl_2 and trituration with MeOH afforded the product as a white solid **7a** (8.00g, 92.8%). A mixture of the white solid **7a** (5.80g, 8.3mmol) in EtOH 150ml, KOH (6.40g, 114.1mmol) in water (20mL) was refluxed for 10 h. The mixture was acidified followed by removing most of the organic solvent, and the residue was filtered to give a white solid **7b** (5.46g, 94.4%). ^{1}H NMR (400 MHz, DMSO-d_6) □ 12.54(s, 2H), 9.91 (s, 2H), 9.38 (s, 1H), 8.53 (s, 2H), 6.85 (s, 3H), 4.14 (s, 6H), 4.02 (m, 2H), 3.94 (s, 6H), 3.91 (s, 2H), 1.93 (m, 2H), 1.58 (m, 2H), 1.28 (m, 2H), 1.02(d, J = 6.8 Hz, 6H), 0.95 (t, J = 7.2 Hz, 6H). ^{13}C NMR (150MHz, 90%$CDCl_3$-10%CD_3OD) □ 167.5, 164.2, 162.8, 162.6, 146.4, 137.1, 120.4, 115.5, 114.5, 113.0, 97.6, 96.4, 74.6, 57.2, 56.8, 35.3, 26.4, 16.7, 11.4. ESI-HRMS (*m/z*) calcd. for $C_{36}H_{44}N_2O_{12}$ (M^+) 696.2894; Found 696.2880 (M^+).

Pentamer (8): A mixture of the acid *7***a** (1.00g, 1.4mmol) and **6** (0.90g, 2.9mmol) in CH_2Cl_2 (70 mL), EDCI.HCl

(0.57g, 3.0mmol) and HOBt (0.42g, 3.1mmol) was stirred at room temperature for 48h. After removing solvent, the solid was triturated with MeOH and $CHCl_3$ several times. Filtration gave a yellow solid **8** (1.00g, 55.7%). ^{1}H NMR (400 MHz, 90%$CDCl_3$-10%CD_3OD) □ 10.15 (s, 4H), 9.63 (s, 1H), 9.28 (s, 2H), 9.01 (s, 2H), 6.82 (s, 2H), 6.64 (s, 3H), 4.45 (s, 6H), 4.23 (s, 6H), 3.90~4.15 (m, 12H), 2.05 (m, 6H), 1.67 (m, 6H), 1.30 (m, 6H), 1.15(m, 18H), 1.02 (m, 18H)**.** MALDI TOF MS (*m/z*) calcd. for $C_{68}H_{92}N_6O_{18}Na$ ($M+Na^+$) 1303.6; Found 1303.2 ($M+Na^+$).

Pentamer (1): A mixture of pentamer **8** (222.0mg, 0.17mmol) and 10% Pd/C (44mg) in $CHCl_3$ (40ml) and CH_3OH (20ml) was stirred under H_2 atmosphere 0.3 (MPa) at 52 ^{0}C for 10h. The solution was acidified with HCl and filtered in darkness. The solvent was removed immediately, followed by drying in vacuum for 5h to afford a green solid **1** in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) □ 9.81 (s, 2H), 9.60 (s, 2H), 9.39 (s, 1H), 9.13 (s, 2H), 8.20 (s, 2H), 6.52 (s, 2H), 6.39 (s, 2H), 6.24 (s, 1H), 4.11 (s, 6H), 4.03 (s, 6H), 3.80~3.59 (m, 12H), 1.88 (m, 6H), 1.56 (m, 6H), 1.22 (m, 6H), 1.06~0.89 (m, 32H). Diamine of **1**: ESI-HRMS (*m/z*) calcd. for $C_{68}H_{97}N_6O_{14}$ ($M+H^+$) 1221.7063; Found 1221.7139 ($M+H^+$).

Dimer (9): Prepared according to the same method as for **(7b)**. Yield 93.6%; ^{1}H NMR (400MHz, DMSO-d_6) □ 10.24 (s, 1H), 8.83 (s, 1H), 8.51 (s, 1H), 6.83 (s, 1H), 6.80 (s, 1H), 4.17 (s, 3H), 4.05 (s, 3H), 3.96 (s, 3H), 3.87 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) □ 166.3, 163.0, 161.0, 161.9, 156.3, 152.3, 135.5, 122.4, 120.6, 112.9, 111.5, 96.9, 96.8, 57.0, 56.6, 56.3, 56.2. ESI-HRMS (*m/z*) calcd. for $C_{19}H_{19}NO_9$ (M^+) 405.1060; Found 405.1055 (M^+).

Dimer (10): 2,4-Dimethoxy-5-nitro-benzoyl chloride, prepared from 2,4-dimethoxy-5-nitro-benzoic acid (220.4mg, 0.97mmol), was dissolved in CH_2Cl_2 (5 mL) and added dropwise to a mixture of **6** (200.0mg, 0.64mmol) and DIEA (166.5mg, 1.29mmol) in CH_2Cl_2 (20 mL). The solution was stirred at room temperature under N_2 for 7h. Removal of solvent and trituration with MeOH provided the product as a yellow solid (332.0mg, 99.8%). ^{1}H NMR (400MHz, $CDCl_3$) □ 9.69 (s, 1H), 9.12 (s, 1H), 8.75 (s, 1H), 6.40 (s, 1H), 6.33 (s, 1H), 4.14 (s, 3H), 3.95 (s, 3H), 4.00-3.77 (m, 4H), 2.05 (m, 1H), 1.91 (m, 1H), 1.69-1.56 (m, 2H), 1.42-1.25 (m, 2H), 1.16 (d, J=6.7, 3H), 1.08-1.03 (m, 6H), 0.98 (t, J=7.4, 3H). ^{13}C NMR (150MHz, $CDCl_3$) □ 161.4, 160.2, 157.2, 152.8, 150.9, 132.8, 131.2, 131.1, 120.4, 117.7, 113.7, 97.0, 96.3, 74.6, 74.5, 57.1, 56.7, 34.8, 34.7, 26.0, 25.9, 16.6, 16.4, 11.3, 11.2. ESI-HRMS (*m/z*) calcd. for $C_{25}H_{34}N_3O_9$ ($M+H^+$) 520.2295; Found 520.2304 ($M+H^+$).

Tetramer (11): A mixture of **10** (100.0mg, 0.19mmol) and 10% Pd/C (20mg) in $CHCl_3$ (30ml) and CH_3OH(15ml) was stirred under H_2 atmosphere 0.3MPa at 52 ^{0}C for 10h. The solution was filtered in darkness as fast as possible followed by immediate removal of the solvent, followed by drying in vacuum for 5h to afford a white solid. The reduced diamine was used for the immediate coupling reaction. The acid chloride, prepared from 4,6-dimethoxy-isophthalic acid monomethyl ester (110.9mg, 0.46mmol), was dissolved in CH_2Cl_2 (5 mL) and added dropwise to a mixture of the above diamine and DIEA (121.3mg, 0.94mmol) in CH_2Cl_2 (20 mL). The solution was stirred at room temperature under N_2 for 7h. The solution was washed with water. After removing the solvent and triturating with MeOH the product was obtained as a white solid (160mg, 93.2%), which was directed used for the next step. A mixture of the white solid (160.0mg, 0.17mmol) in EtOH (60ml) and KOH (190.4mg, 3.4mmol) in water (5mL) was refluxed for 10 h. The mixture was acidified followed by removing most of the organic solvent, and the residue was filtered and washed with water to give **11** as a white solid (141.4mg, 95.0%). ^{1}H NMR (400MHz, DMSO-d_6) □ 10.27 (s, 1H), 10.07 (s, 1H), 9.90 (s, 1H), 9.40(s, 1H), 9.10 (s, 1H), 6.94 (s, 1H), 6.85 (s, 3H), 4.18 (s, 3H), 4.14 (s, 3H), 4.09 (s, 3H), 4.08 (s, 3H), 4.02 (m, 2H), 3.96 (s, 6H), 3.92 (m, 2H), 1.94 (m, 2H), 1.59 (m, 2H), 1.28 (m, 2H), 1.03 (dd, 6H), 0.94 (t, J=7.3, 6H) ^{13}C NMR (100MHz, 90%$CDCl_3$-10%CD_3OD)

□ 166.9, 163.9, 163.3, 162.3, 158.4, 156.8, 155.3, 145.7, 137.6, 123.4, 122.1, 120.2, 119.3, 115.8, 114.6, 113.6, 112.6, 97.3, 96.2, 95.6, 74.5, 57.0, 35.1, 26.4, 17.0, 11.3. ESI-HRMS (*m/z*) calcd. for $C_{45}H_{54}N_3O_{15}$ ($M+H^+$) 876.3555; found 876.3544 ($M+H^+$)

Trimer (12): Prepared according to the same method as for **(10)**. Yield 92.2%; ^{1}H NMR (400MHz, $CDCl_3$) □ 9.88 (s, 2H), 9.25 (s, 2H), 8.57 (s, 1H), 6.53 (s, 1H), 6.21 (s, 2H), 4.22 (s, 6H), 3.84-3.73 (m, 6H), 3.67 (t, J=7.9, 2H), 1.99~1.88 (m, 4H), 1.63~1.54 (m,4H), 1.33~1.24 (m,4H), 1.06 (dd, 12H), 0.97 (m, 12H). ^{13}C NMR (100MHz, $CDCl_3$) □ 161.3, 160.7, 152.8, 150.4, 136.6, 130.9, 121.4, 117.0, 113.9, 96.9, 95.1, 74.6, 74.5, 56.7, 34.7, 34.5, 25.9, 25.8, 16.3, 16.2, 11.2, 11.0. ESI-HRMS (*m/z*) calcd. for $C_{42}H_{58}N_4O_{12}$ (M^+) 810.4051; Found 810.3982 (M^+).

Pentamer (13): Prepared according to the same method as for **(11)**. Yield 72.1%; ^{1}H NMR (400MHz, DMSO-d_6) □ 9.95 (s, 2H), 9.93 (s, 2H), 9.37 (s, 2H), 8.84 (s, 1H), 8.54 (s, 2H), 6.99 (s, 1H), 6.86 (s, 4H), 4.18 (s, 3H), 4.18 (s, 6H), 4.14 (s, 6H), 4.03 (m, 4H), 3.97 (s, 6H), 3.93 (s, 4H), 1.96 (m, 4H), 1.61 (m, 4H), 1.30 (m, 4H), 1.03 (d, J=6.8, 6H), 0.95 (t, J=7.8, 6H). ^{13}C NMR (100MHz, 90%$CDCl_3$-10%CD_3OD) □ 163.6, 162.4, 161.9, 161.5, 145.7, 137.4, 120.5, 115.2, 114.4, 97.2, 96.0, 74.4, 57.1, 56.9, 56.7, 35.1, 26.2, 16.6, 11.3. ESI-HRMS (*m/z*) calcd. for $C_{62}H_{79}N_4O_{18}$ ($M+H^+$) 1167.5389; Found 1167.5343 ($M+H^+$).

General synthetic procedure for macrocycles

A mixture of diacid (1 equiv), dry CH_2Cl_2 (20ml), oxalyl chloride (3 equiv) and 4□L DMF was stirred 5h at room temperature. The solvent was then removed. The resulting diacid chloride **2(a, b, c, d or e)** was dissolved in CH_2Cl_2. This solution was then added immediately to a precold solution of diamine salt **1** (1equiv) in CH_2Cl_2 containing DIEA (5 equiv) at 0 ^{0}C. The final concentration of **1** was 0.5mM. The reaction mixture was stirred at 0 ^{0}C for 3h and at room tempearture for 8h, followed by refluxing for 1h. After quenching with CH_3OH and removing the solvent, the residue was triturated with CH_3OH and EtOAc. Filtration provided the crude product. Furhter recrystallization with $CHCl_3$/CH_3OH and/or purification with PTLC ($CHCl_3$/EtOAc/CH_3OH, 10:1:1.5) provided the pure product.

Six-residue macrocycle (3a): Prepared according to the general synthetic procedure for macrocycles. 4,6-Dimethoxy-isophthalic acid (17.5mg, 0.077mmol) and oxalyl chloride (29.3mg, 0.23mmol) were used to prepare **2a**. Diamine salt **1** (100.0mg, 0.077mmol), DIEA (50.0mg, 0.39mmol) and CH_2Cl_2 (150ml) were used for the macrocyclization. Yield 84.5%; ^{1}H NMR (400 MHz, 90%$CDCl_3$-10%CD_3OD) □ 9.52 (s, 6H), 9.43 (s, 3H),9.12 (s, 3H), 6.46 (s, 3H), 6.23 (s, 3H), 4.04 (s, 18H), 3.93 (m, 6H), 3.83 (m, 6H), 1.93 (m, 6H), 1.49 (m, 6H), 1.37 (m, 6H), 1.14 (d, J = 6.5 Hz, 18H), 1.08 (t, J = 7.3 Hz, 18H). ^{13}C NMR (100 MHz, 90%$CDCl_3$-10%CD_3OD) □ 162.2, 160.5, 144.4, 138.8, 120.6, 116.0, 114.7, 96.1, 94.2, 74.1, 56.4, 35.1, 25.9, 16.6, 11.2. MALDI TOF MS (*m/z*) calcd. for $C_{68}H_{92}N_6O_{18}Na$ ($M+Na^+$) 1433.7; Found 1434.1 ($M+Na^+$). ESI-HRMS (*m/z*) calcd. for $C_{68}H_{93}N_6O_{18}$ ($M+H^+$) 1411.7329; Found 1411.7405 ($M+H^+$).

Seven-residue macrocycle (3b): Prepared according to the general synthetic procedure for macrocycles. Diacid **9** (31.3mg, 0.077mmol) and oxalyl chloride (29.3mg, 0.23mmol) were used to prepare **2b**. Diamine salt **1** (100.0mg, 0.077mmol), DIEA (50.0mg, 0.39mmol) and CH_2Cl_2 (150ml) were used for the macrocyclization.Yield 49.7%; ^{1}H NMR (400 MHz, 90%$CDCl_3$-10%CD_3OD) □ 10.25 (s, 2H), 10.20 (s, 1H), 10.15 (s, 1H), 10.09 (s, 1H), 9.94 (s, 2H), 9.36 (s, 1H), 9.16 (s, 1H), 9.09 (s, 2H), 8.97 (s, 3H), 6.56~6.31 (m, 7H), 4.17~3.86 (s, 36H), 1.98 (m, 6H), 1.64 (m, 6H), 1.35 (m, 6H), 1.10 (m, 18H), 1.01 (m, 18H). ^{13}C NMR (100 MHz, 90%$CDCl_3$-10%CD_3OD) □ 162.4, 161.6, 161.4, 160.9, 154.2, 152.0, 144.1, 137.0, 122.1, 121.3, 121.0, 120.9, 120.5, 114.3, 114.1, 113.1, 112.6, 97.1,

96.4, 95.4, 95.1, 94.3, 74.7, 74.4, 57.1, 56.8, 56.7, 56.3, 35.2, 25.9, 16.5, 16.4, 11.1. MALDI TOF MS (*m/z*) calcd. for $C_{87}H_{111}N_7O_{21}Na$ (M+Na$^+$) 1612.8; Found 1613.3 (M+Na$^+$). ESI-HRMS (*m/z*) calcd. for $C_{87}H_{112}N_7O_{21}$ (M+H$^+$) 1590.7911; Found 1590.7941 (M+H$^+$). Anal. Calcd. (%) for $C_{87}H_{111}N_7O_{21}$: C, 65.68; H, 7.03; N, 6.16; found: C, 65.58; H, 7.07; N, 6.36.

Eight-residue macrocycle (3c): Prepared according to the general synthetic procedure for macrocycles. Diacid **7b** (26.9mg, 0.039mmol) and oxalyl chloride (14.7mg, 0.12mmol) were used to prepare **2c**. Diamine salt **1** (50.0mg, 0.039mmol), DIEA (25.0mg, 0.19mmol) and CH_2Cl_2 (75ml) were used for the macrocyclization. Yield 13.8%; ^{1}H NMR (400 MHz, 90%$CDCl_3$-10%CD_3OD) □ 10.18 (s, 8H), 9.33 (s, 4H), 8.99 (s, 4H), 6.78 (s, 4H), 6.64 (s, 4H), 4.20(s, 24H), 4.00 (m, 8H), 3.88 (m, 8H), 1.98 (m, 8H), 1.64 (m, 8H), 1.37 (m, 8H), 1.34 (m, 8H), 1.10 (d, 24H), 1.08 (t, 24H). ^{13}C NMR (100 MHz, 90%$CDCl_3$-10%CD_3OD) □ 162.1, 161.5, 145.8, 136.7, 122.9, 120.7, 115.3, 99.1, 96.4, 74.8, 57.1, 35.1, 26.2, 16.7, 11.3. MALDI TOF MS (*m/z*) calcd. for $C_{104}H_{136}N_8O_{24}Na$ (M+Na$^+$) 1905.0; Found 1905.8 (M+Na$^+$). ESI-HRMS (*m/z*) calcd. for $C_{104}H_{137}N_8O_{24}$ (M+H$^+$) 1882.9779; Found 1882.9792 (M+H$^+$).

Nine-residue macrocycle (3d): Prepared according to the general synthetic procedure for macrocycles. **11** (20.4mg, 0.023mmol) and oxalyl chloride (8.82mg, 0.070mmol) were used to prepare **2d**. Diamine salt **1** (30.0mg, 0.023mmol), DIEA (15.0mg, 0.12mmol) and CH_2Cl_2 (45ml) were used for the macrocyclization. Yield 10.0%; ^{1}H NMR (400 MHz, 90%$CDCl_3$-10%CD_3OD) □ 10.14~9.80 (m, 9H), 9.25~8.92 (m, 9H), 6.74~6.58 (m, 9H), 4.23~4.10 (m, 30H), 3.97~3.85 (m, 16H), 1.97 (m, 8H), 1.61 (m, 8H), 1.37 (m, 8H), 1.08 (m, 24H), 0.99 (m, 24H). MALDI TOF MS (*m/z*) calcd. for $C_{113}H_{145}N_9O_{27}Na$ (M+Na$^+$) 2084.0; Found 2083.3 (M+Na$^+$). ESI-HRMS (*m/z*) calcd. for $C_{113}H_{146}N_9O_{27}$ (M+H$^+$) 2062.0362; Found 2062.0374 (M+H$^+$). Anal. Calcd. (%) for $C_{113}H_{145}N_9O_{27}$: C, 65.84; H, 7.09; N, 6.12; found: 65.85; H, 7.12; N, 6.32.

Ten-residue macrocycle (3e): Prepared according to the general synthetic procedure for macrocycles. **13** (27.5mg, 0.023mmol) and oxalyl chloride (8.82mg, 0.070mmol) were used to prepare **2e**. Diamine salt **1** (30.0mg, 0.023mmol), DIEA (15.0mg, 0.12mmol) and CH_2Cl_2 (45ml) were used for the macrocyclization. Yield 6.2%; ^{1}H NMR (400 MHz, 90%$CDCl_3$-10%CD_3OD) □ 10.27~9.80 (m, 10H), 8.95 (m, 10H), 6.72~6.04 (m, 10H), 4.17~4.05 (m, 30H), 3.95~3.85 (m, 20H), 1.97 (m, 10H), 1.61 (m, 10H), 1.37 (m, 10H), 1.09 (m, 30H), 0.97 (m, 30H). MALDI TOF MS (*m/z*) calcd for $C_{130}H_{170}N_{10}O_{30}Na$ (M+Na$^+$) 2375.2; Found 2374.4 (M+Na$^+$). ESI-HRMS (*m/z*) calcd. for $C_{130}H_{171}N_{10}O_{30}$ (M+H$^+$) 2353.2196; Found 2353.2183 (M+H$^+$). Anal. Calcd. (%) for $C_{130}H_{170}N_{10}O_{30}$: C, 66.36; H, 7.28; N, 5.95; found: C, 66.56; H, 7.21; N, 5.75.

Experimental procedure of competition reaction

A mixture of 4,6-Dimethoxy-isophthalic acid (8.7mg, 0.039mmol), diacid **9** (15.6mg, 0.039mmol), dry CH_2Cl_2 (20ml), oxalyl chloride (39.2mg, 0.309mmol) and 4□L DMF was stirred 5h at room temperature. The solvent and excess oxalyl chloride were then removed. The resulting diacid chloride was dissolved in CH_2Cl_2 (5ml). This solution was then added concurrently to a precold solution of diamine salt **1** (50.0mg, 0.039mmol) in CH_2Cl_2 (70ml) containing DIEA (54.9mg, 0.42mmol) at 0 ^{0}C. The reaction was stirred at ice bath for 2h. followed by warming up to room temperature and stirring for overnight, and then heated under reflux for 2 hrs. After quenching with CH_3OH and removing the solvent, the residue was triturated with CH_3OH and EtOAc. Filtration provided the crude product.

NMR Data

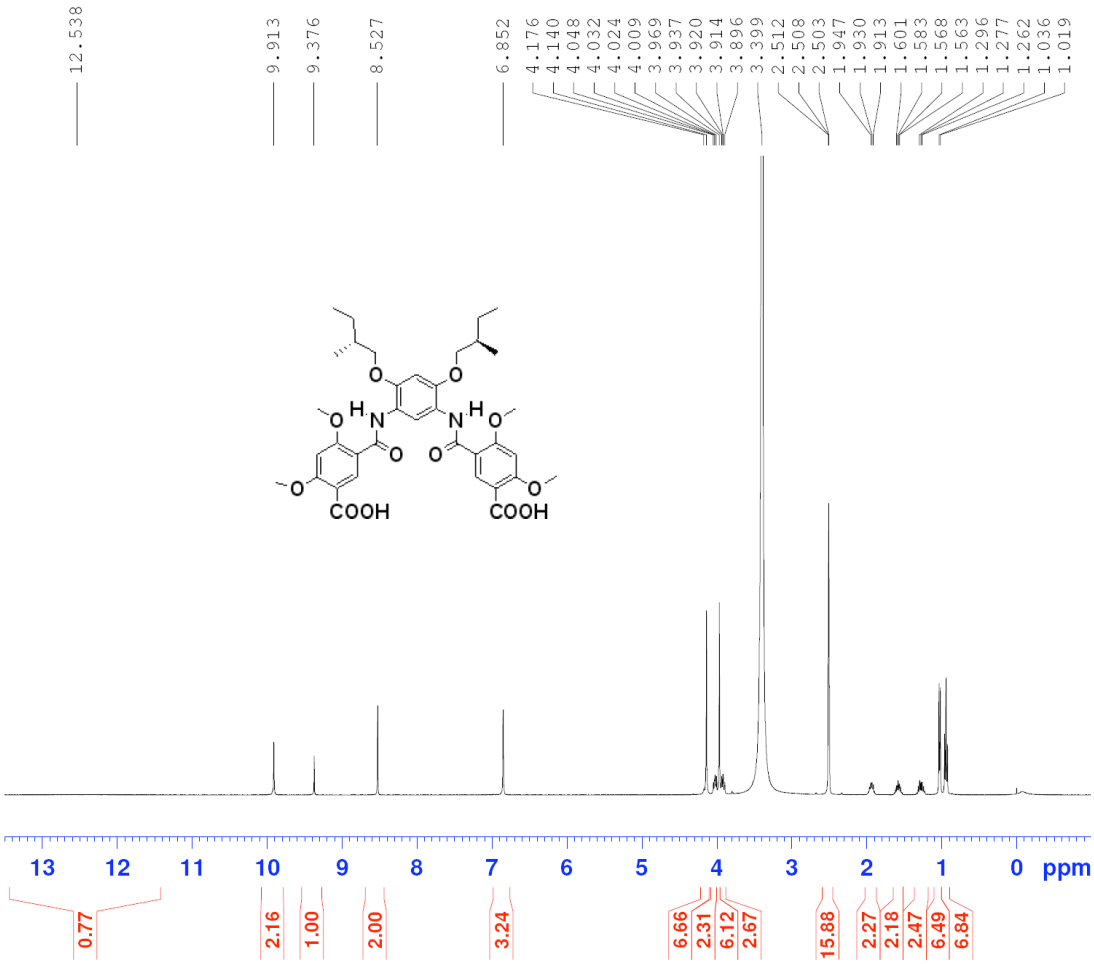


Figure S1. ^{1}H NMR spectrum of ***7b*** in DMSO-d_6.

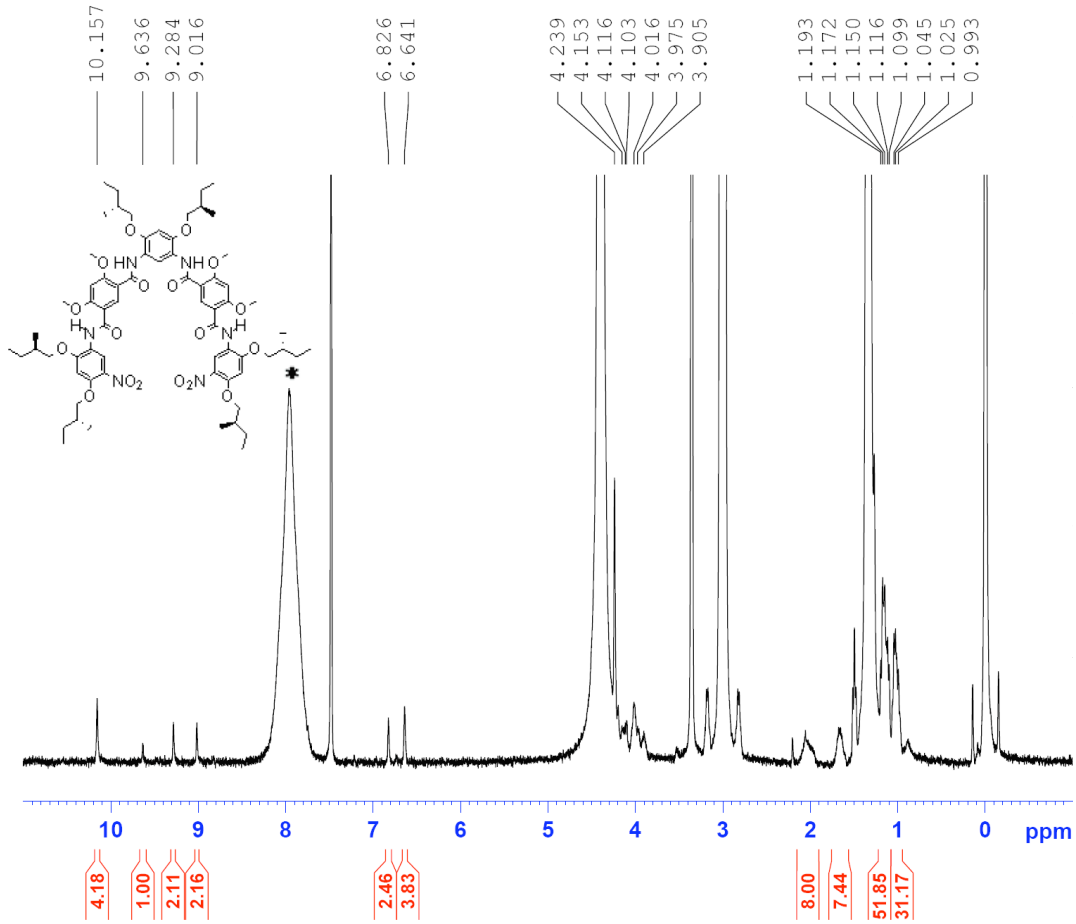


Figure S2. ^{1}H NMR spectrum of ***8*** in 90%$CDCl_3$-10%CD_3OD. ✱ $EtNH_3Cl$

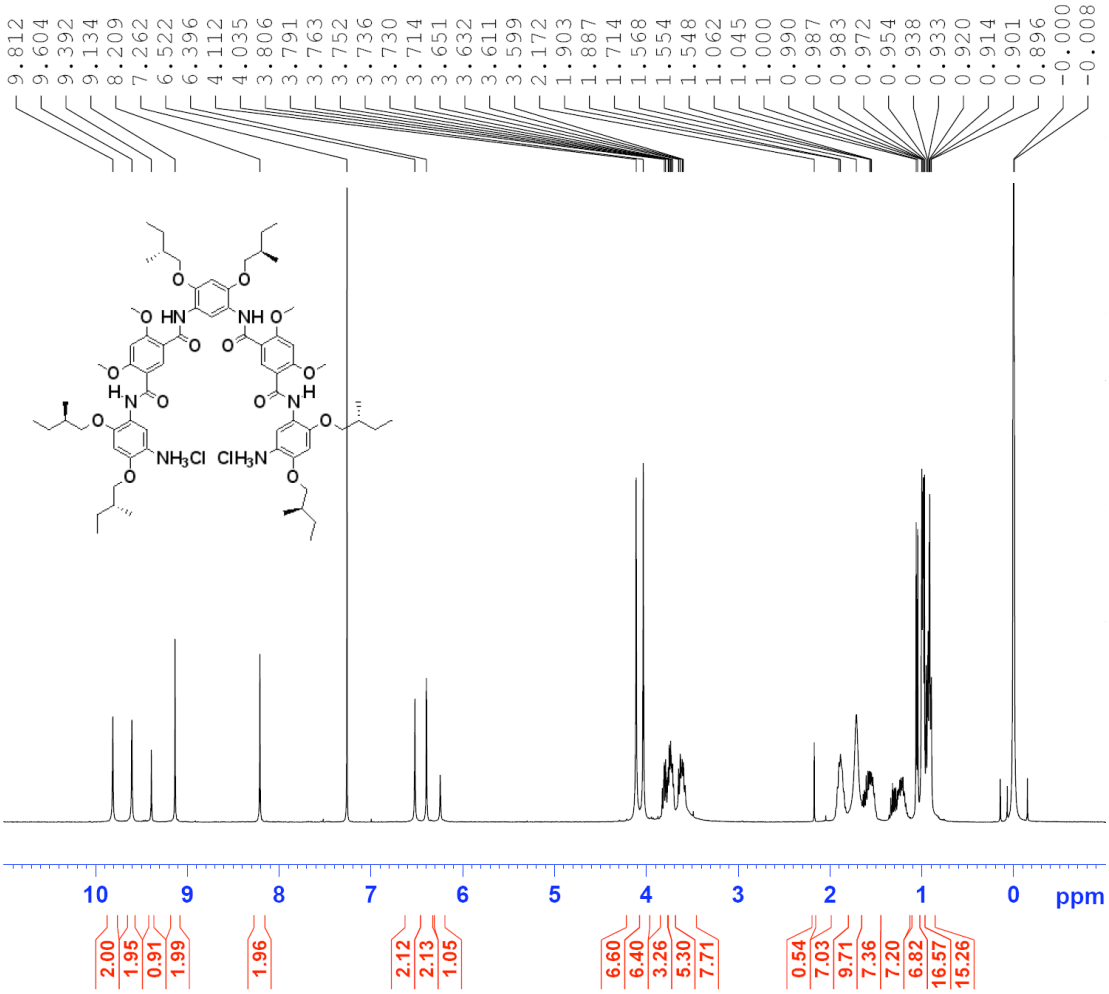


Figure S3. ^{1}H NMR spectrum of ***1*** in $CDCl_3$.

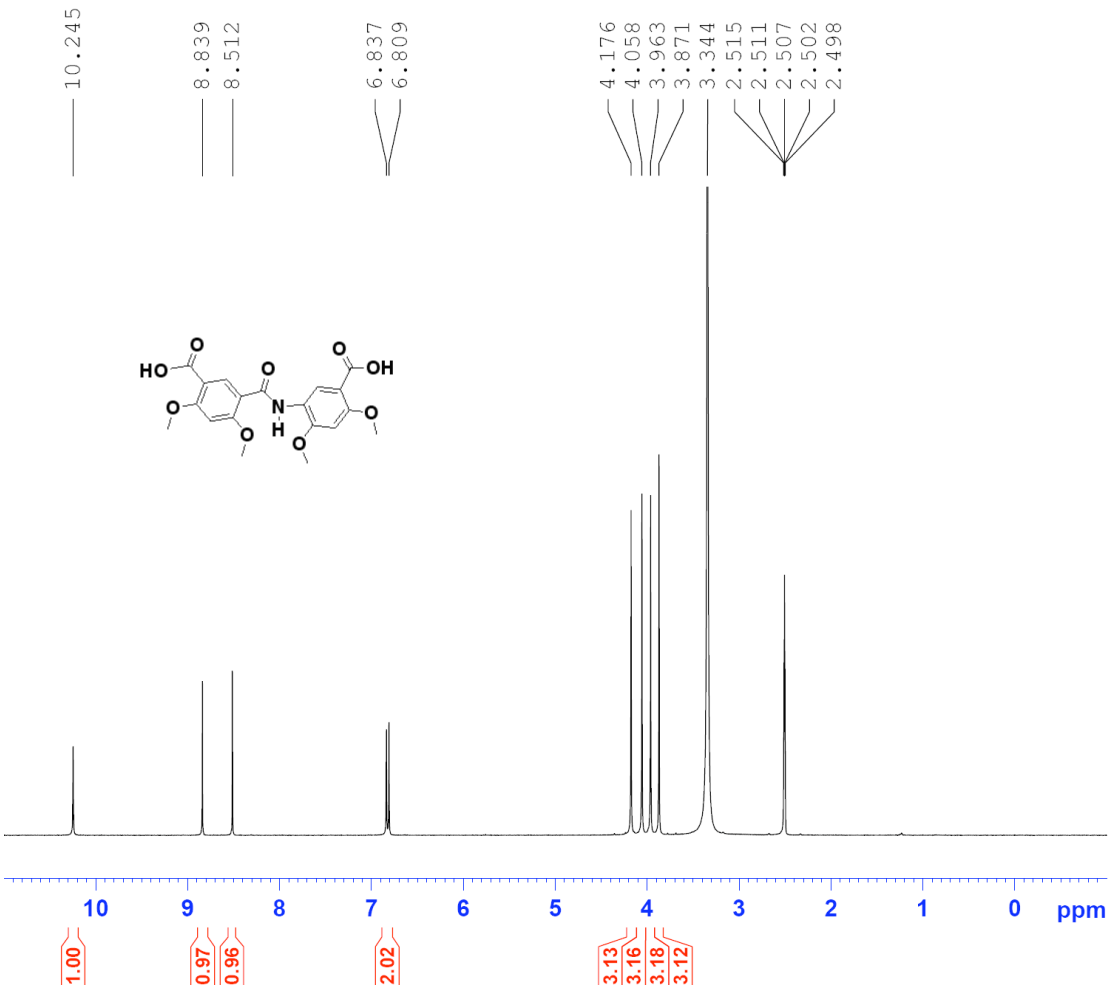


Figure S4. ^{1}H NMR spectrum of ***9*** in DMSO-d_6.

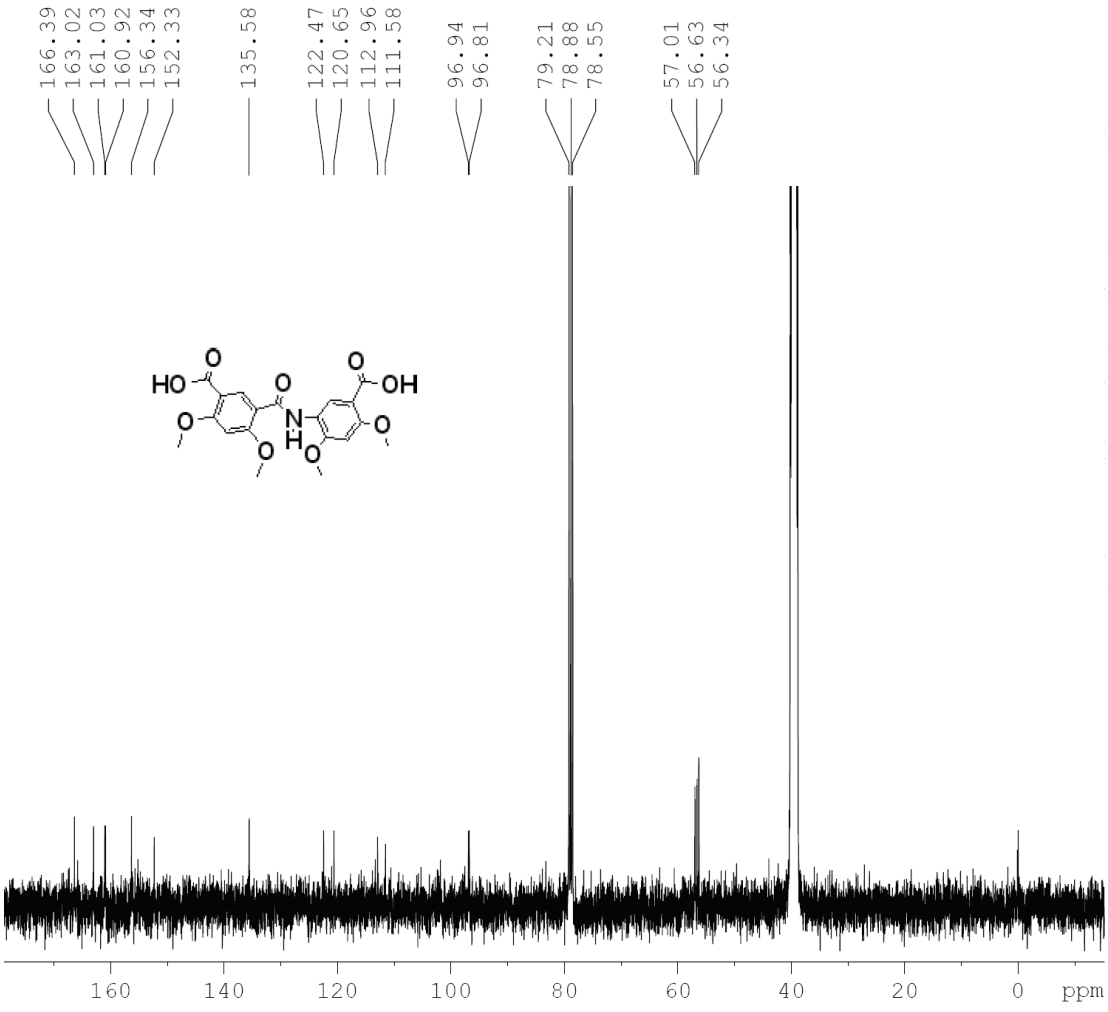


Figure S5. ^{13}C NMR spectrum of ***9*** in DMSO-d_6.

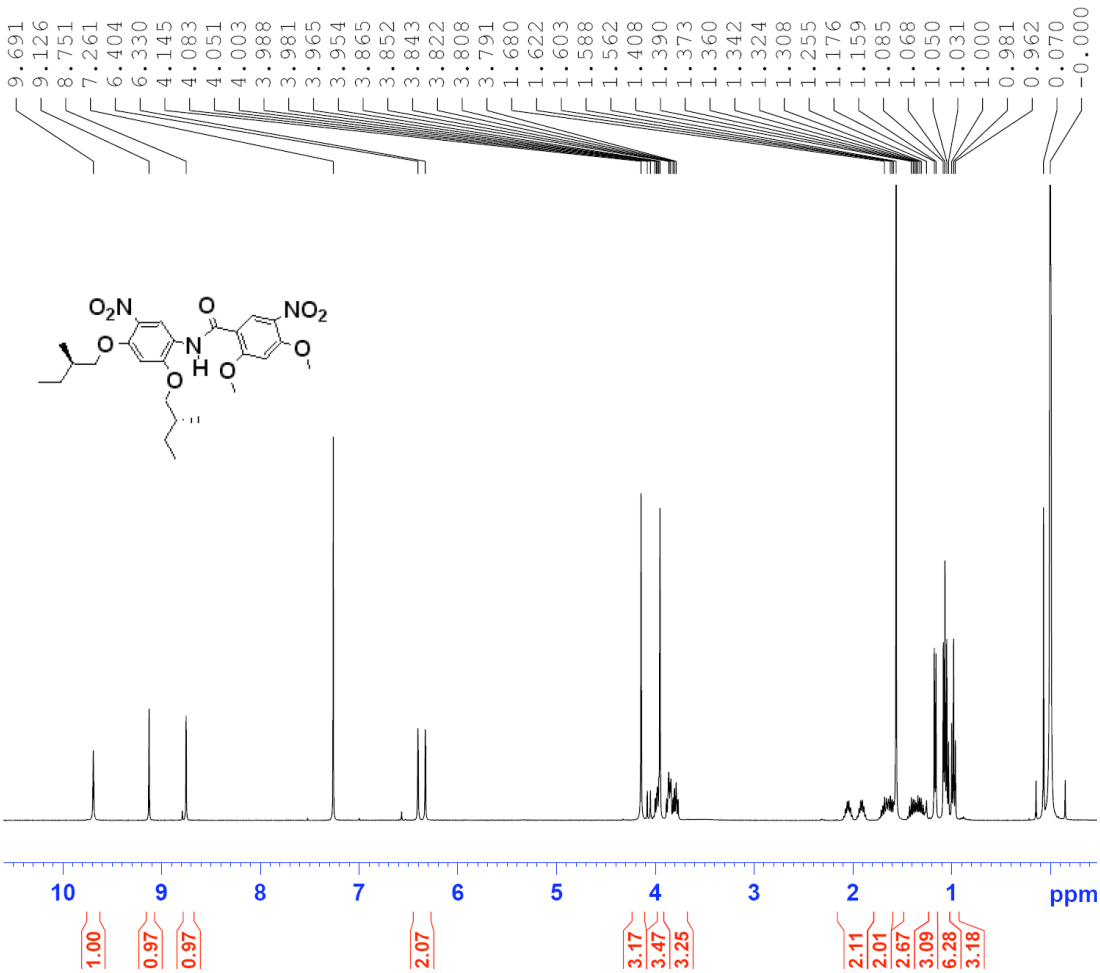


Figure S6. ^{1}H NMR spectrum of ***10*** in $CDCl_3$.

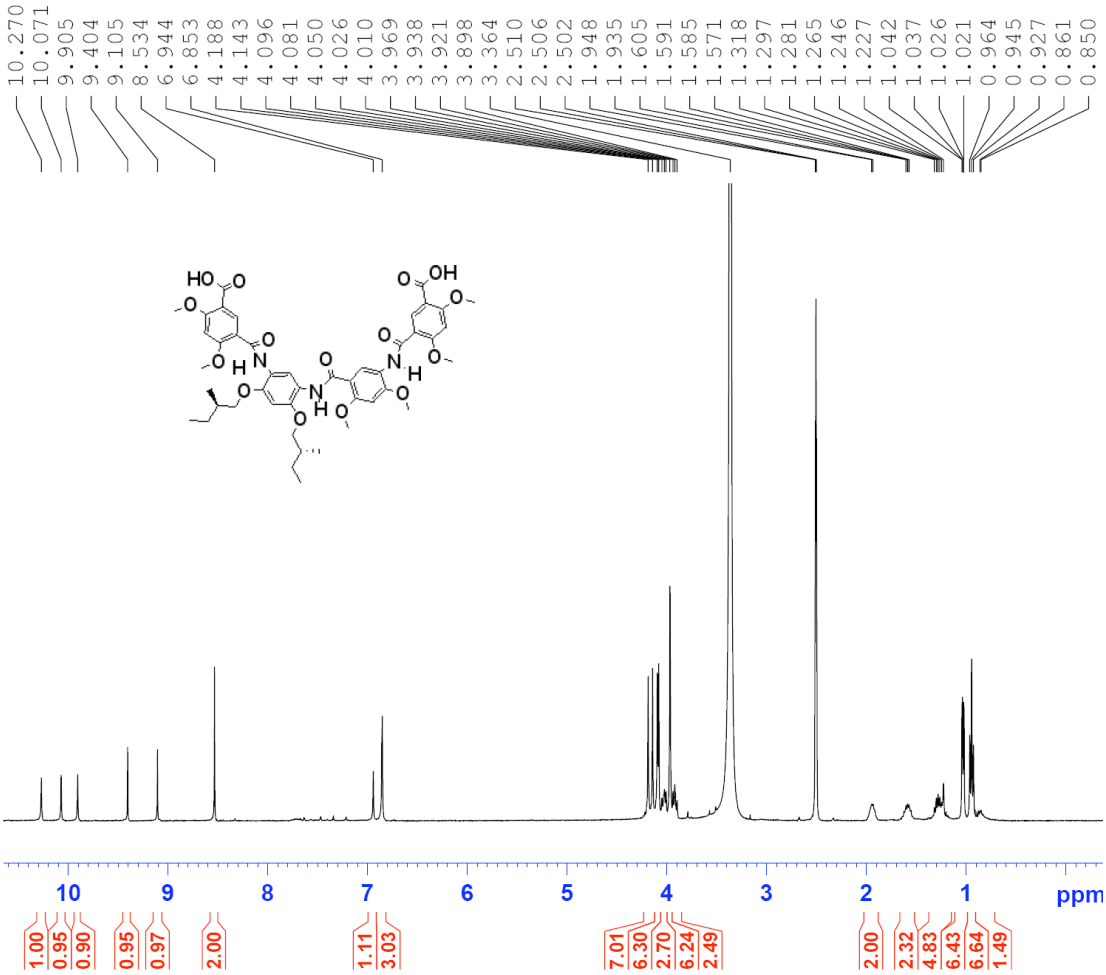


Figure S7. ^{1}H NMR spectrum of ***11*** in DMSO-d_6.

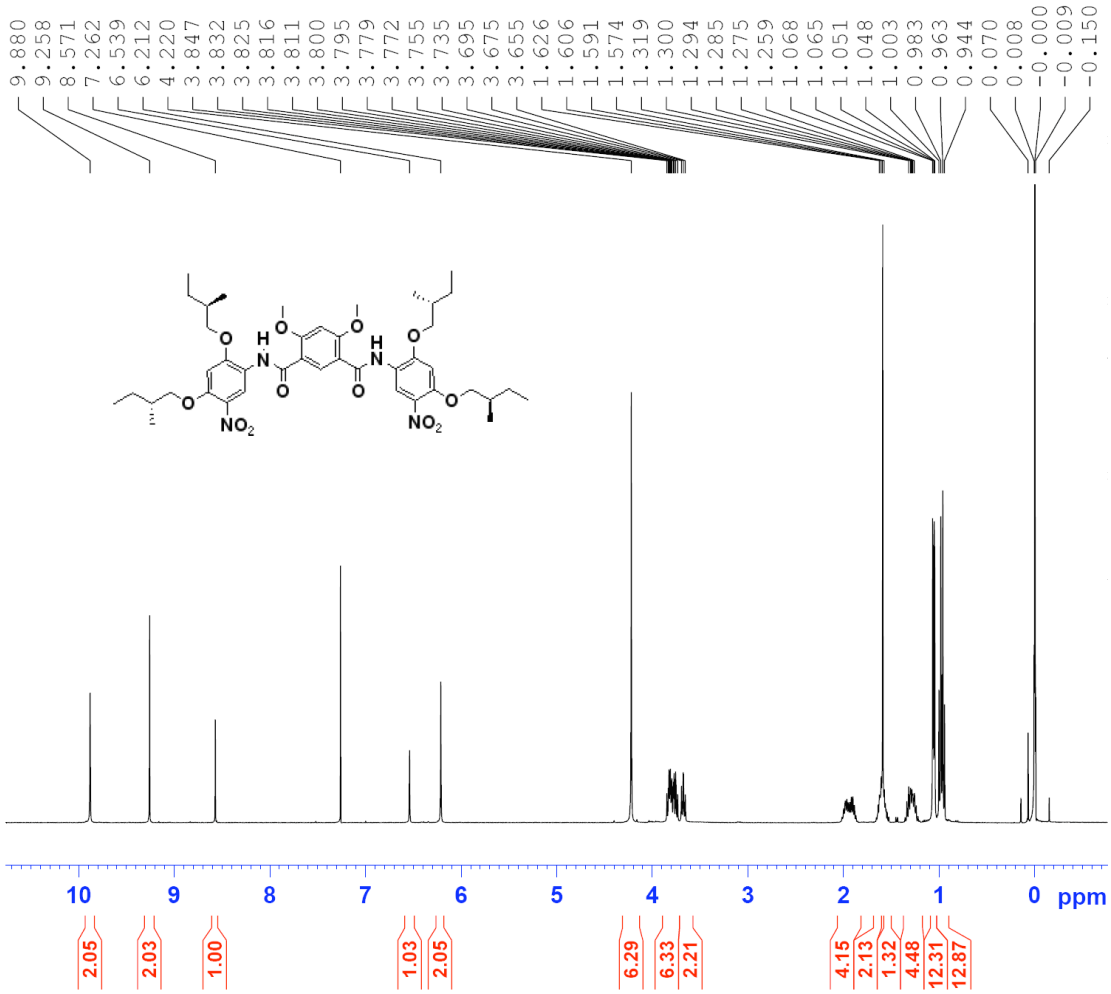


Figure S8. ^{1}H NMR spectrum of ***12*** in $CDCl_3$.

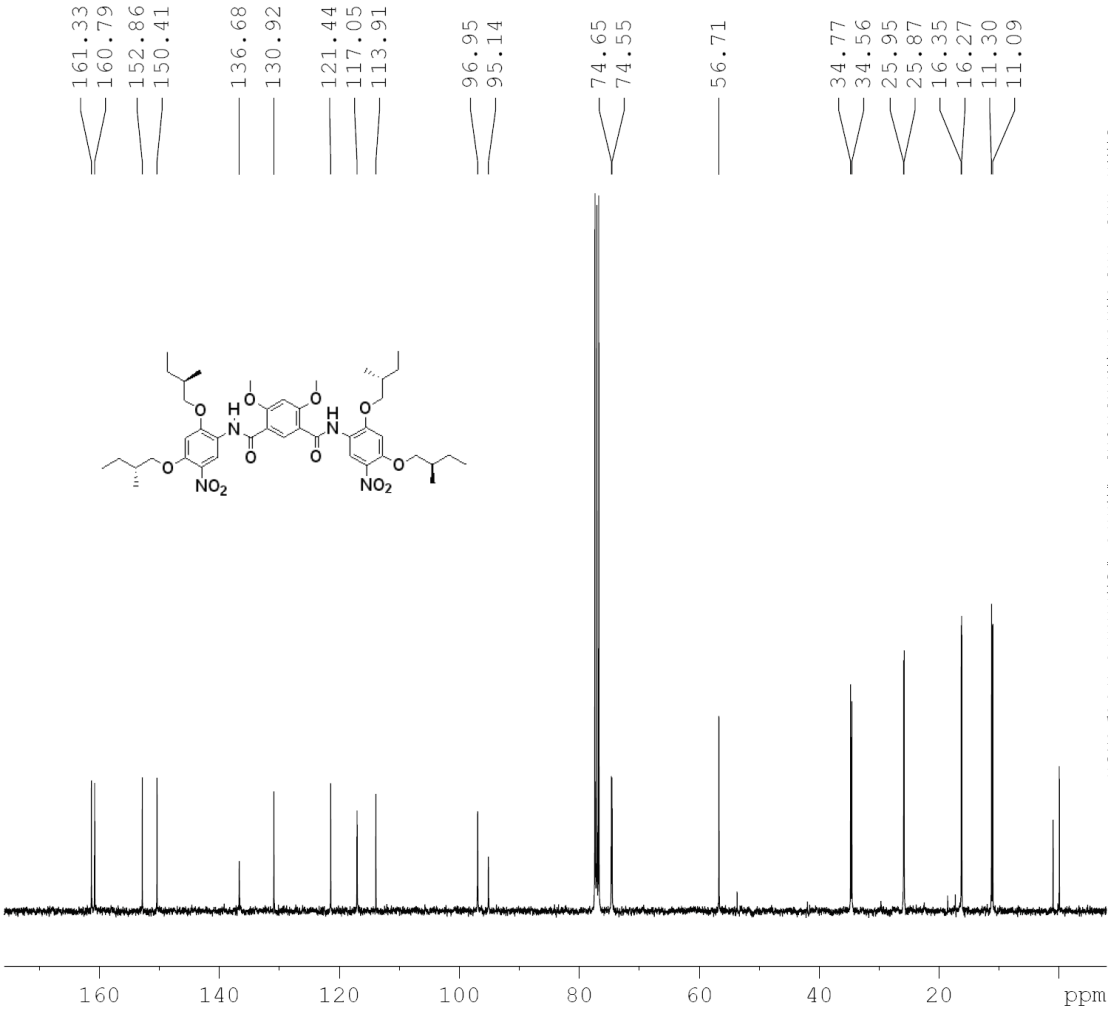


Figure S9. ^{13}C NMR spectrum of ***12*** in $CDCl_3$.

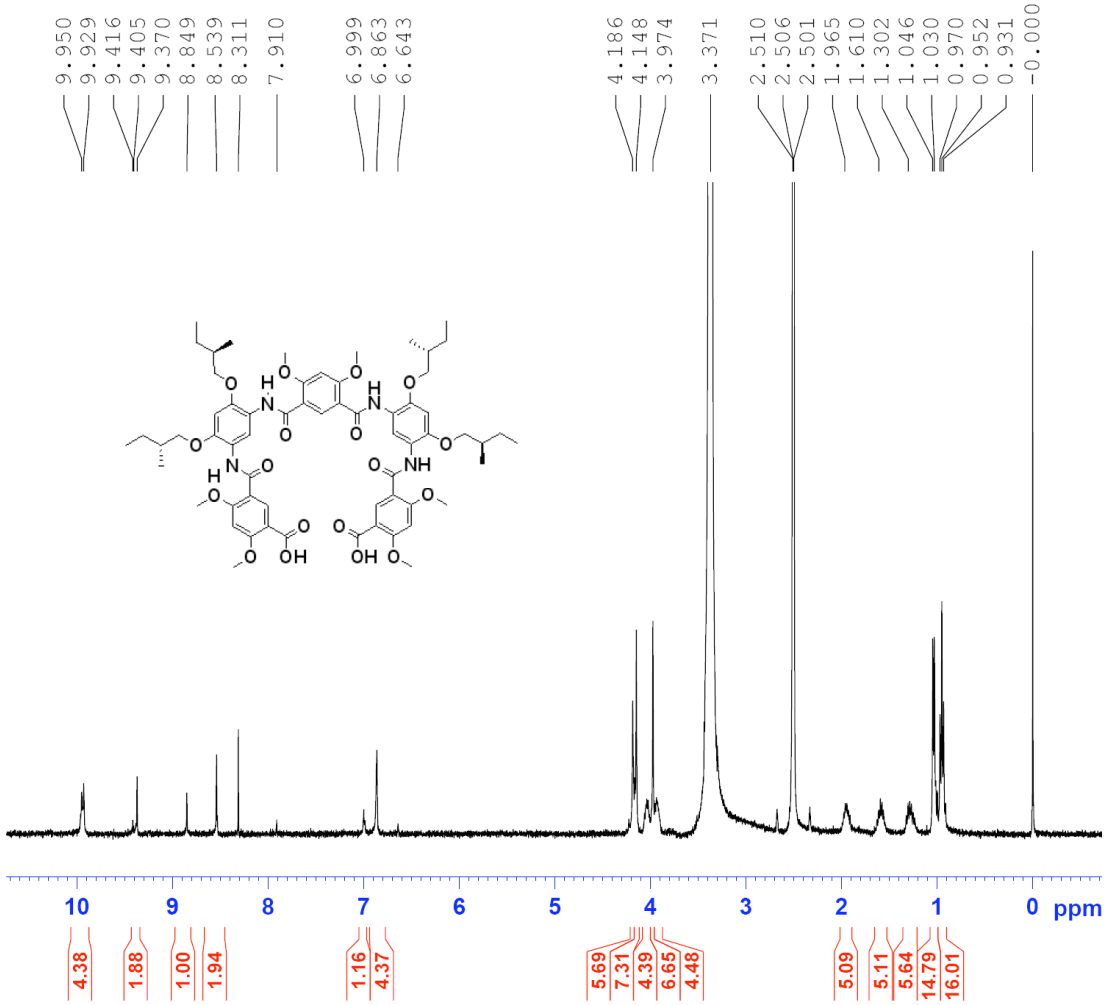


Figure S10. ^{1}H NMR spectrum of ***13*** in DMSO-d_6.

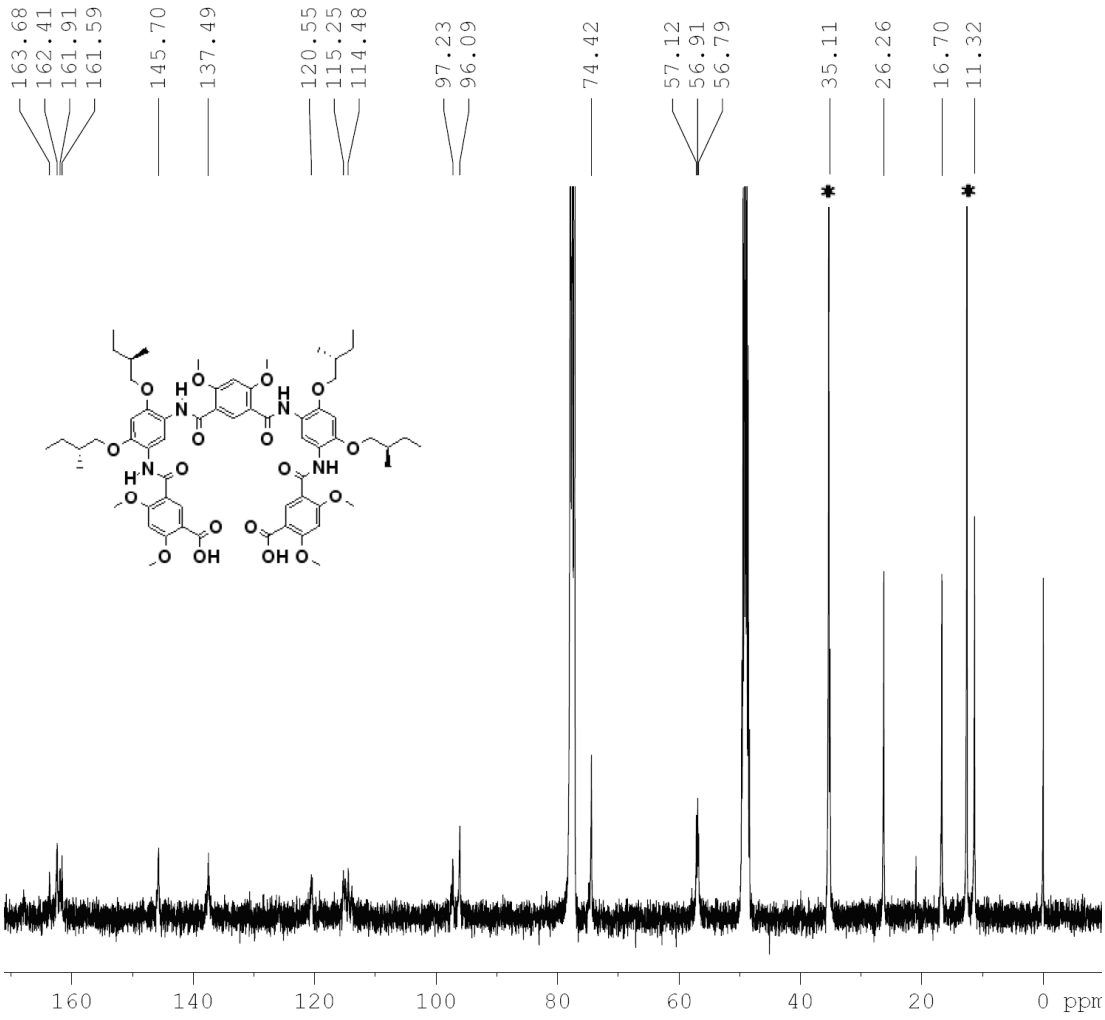


Figure S11. ^{13}C NMR spectrum of ***13*** in 90%$CDCl_3$-10%CD_3OD. ● $EtNH_3Cl$

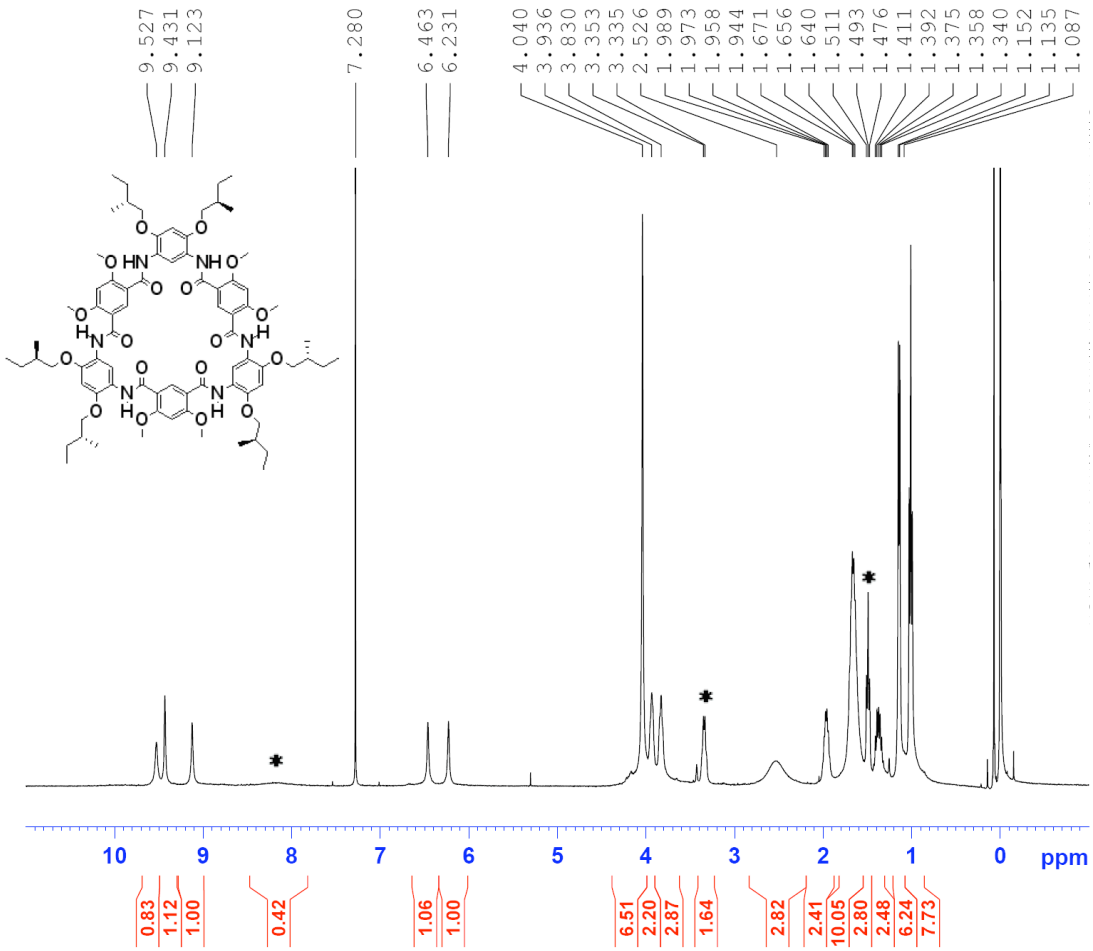


Figure S12. ^{1}H NMR spectrum of ***3a*** in 99%$CDCl_3$-1%CD_3OD. * $EtNH_3Cl$

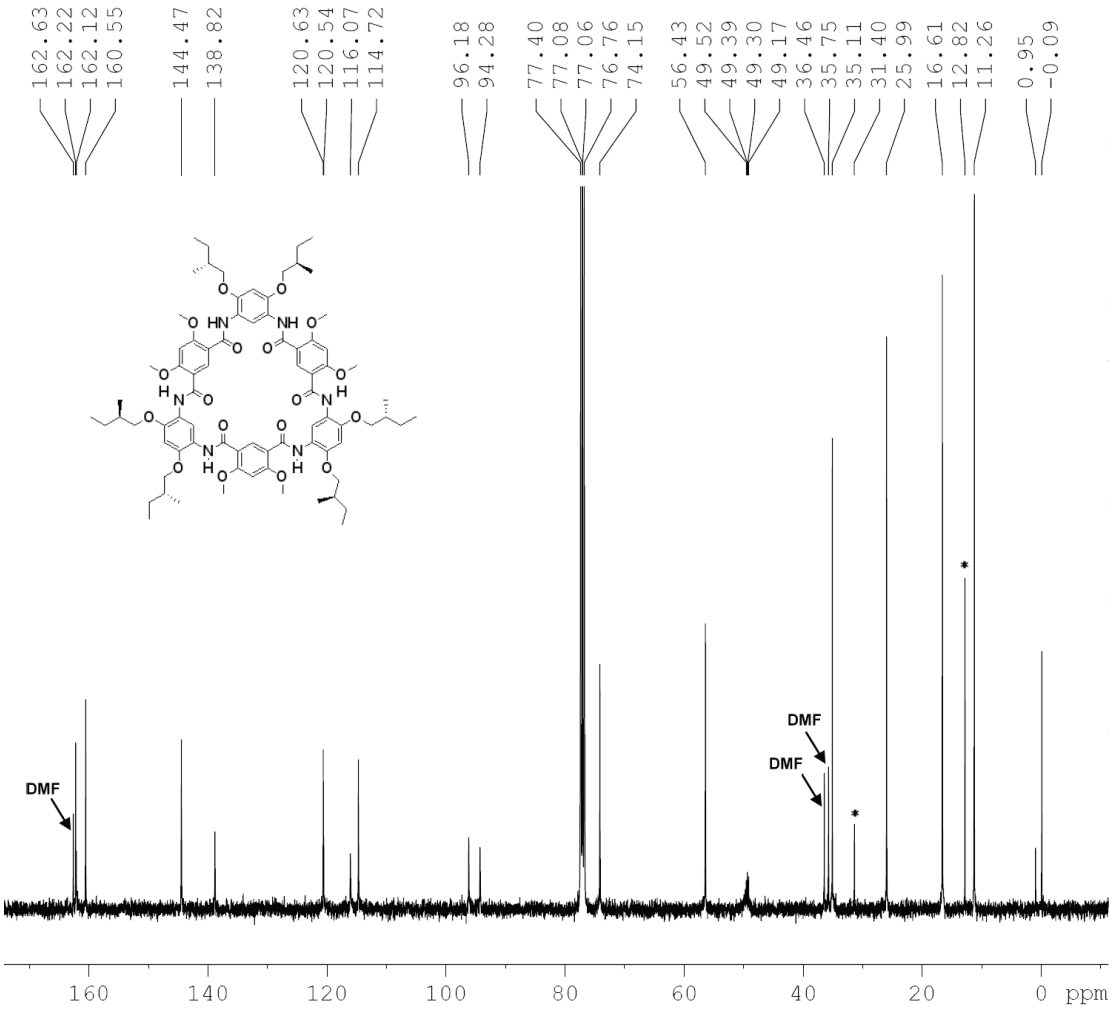


Figure S13. ^{13}C NMR spectrum of ***3a*** in 99%$CDCl_3$-1%CD_3OD. ● $EtNH_3Cl$

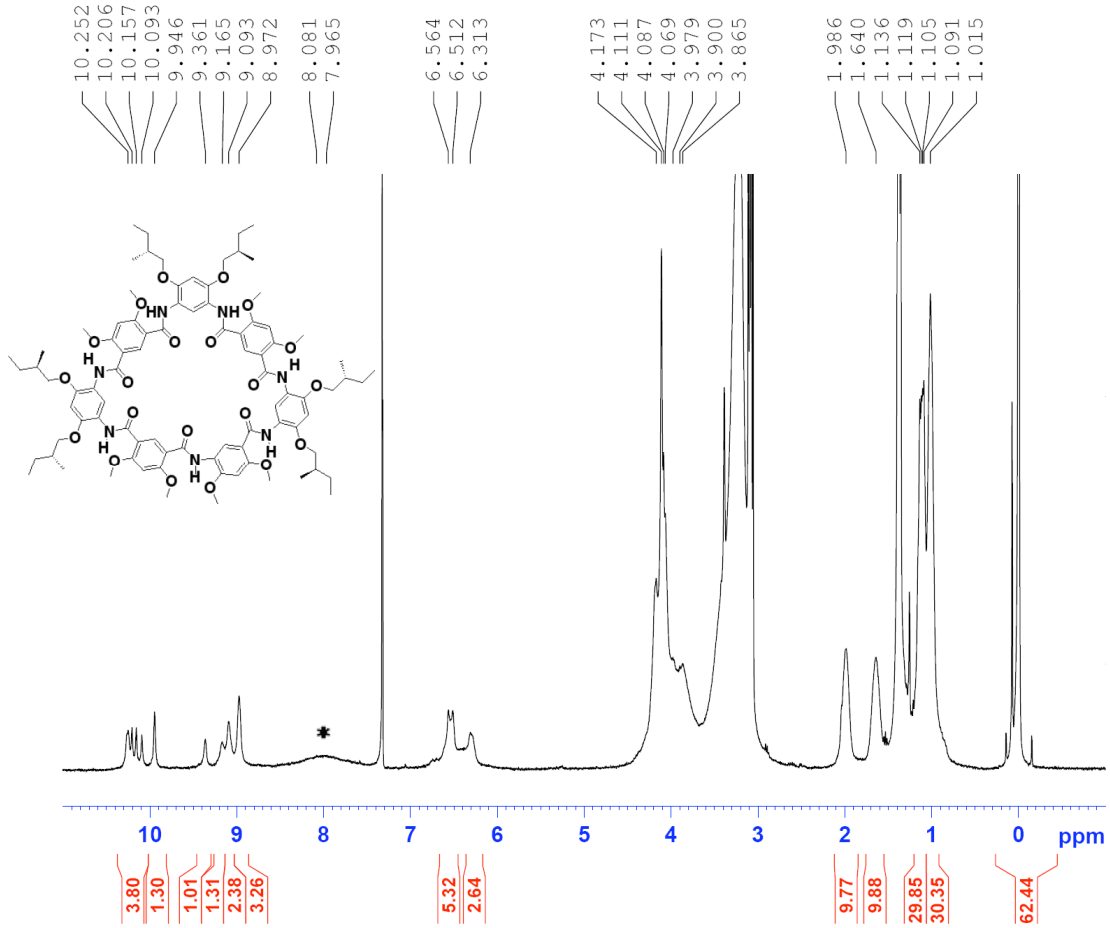


Figure S14. ^{1}H NMR spectrum of ***3b*** in 90%$CDCl_3$-10%CD_3OD. * $EtNH_3Cl$

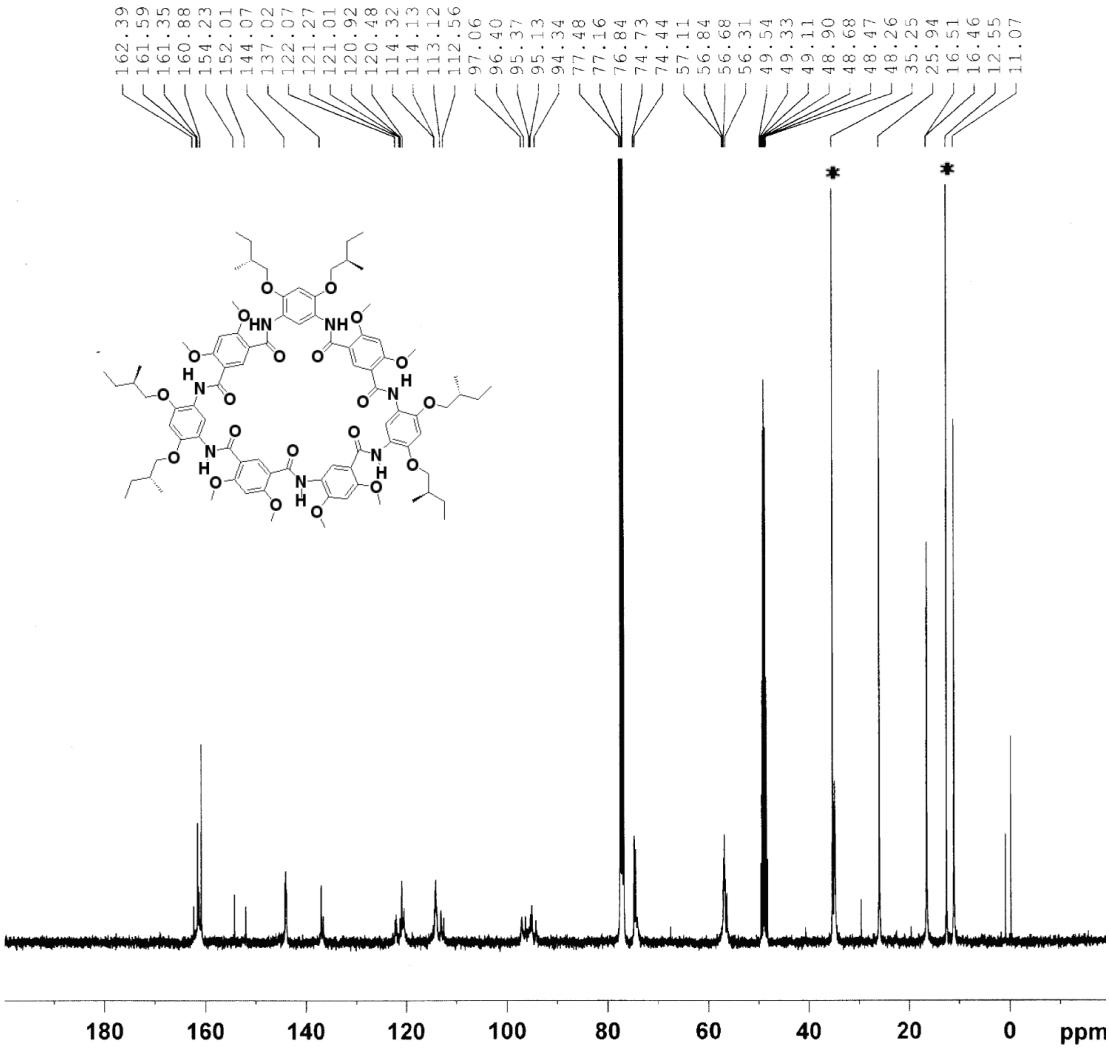


Figure S15. ^{13}C NMR spectrum of ***3b*** in 99%$CDCl_3$-1%CD_3OD. * $EtNH_3Cl$

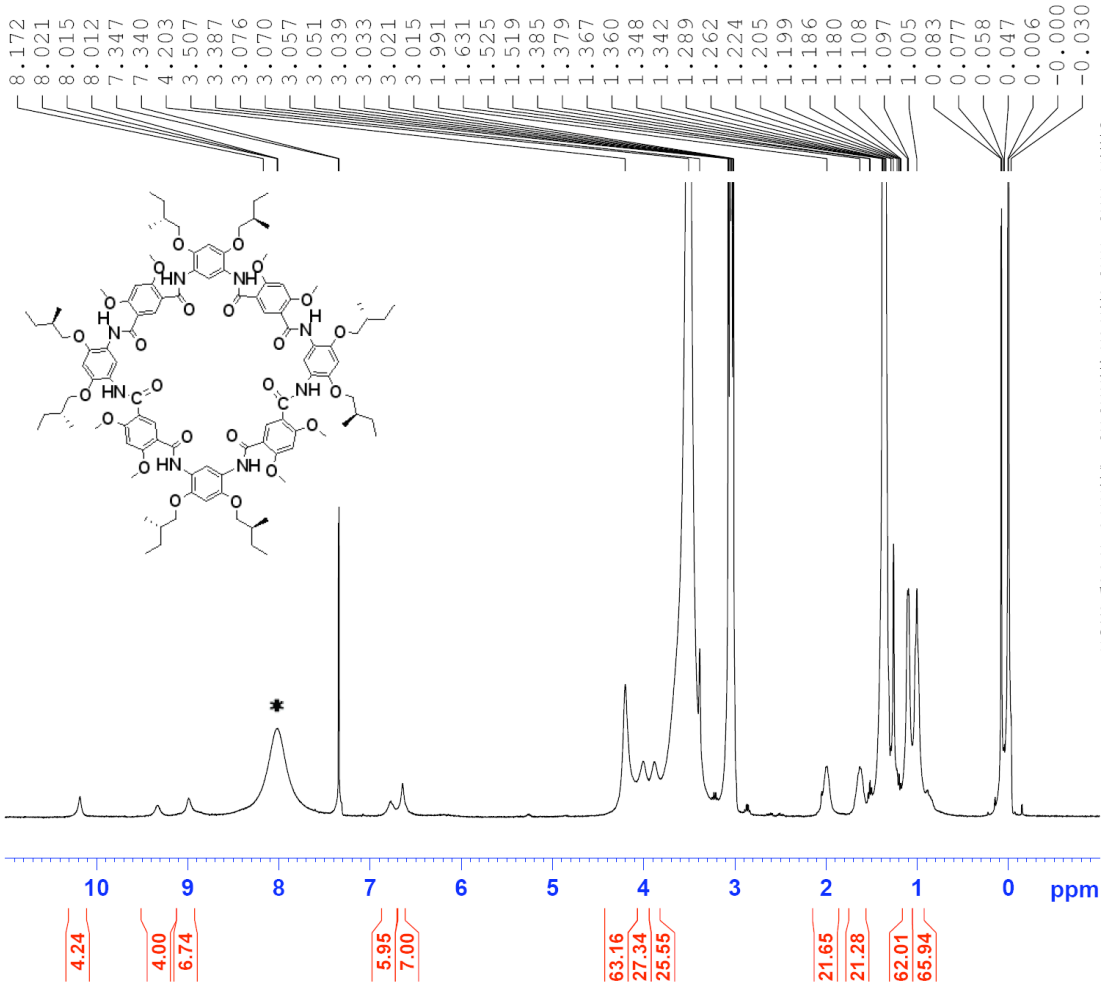


Figure S16. ^{1}H NMR spectrum of ***3c*** in 90%$CDCl_3$-10%CD_3OD. ✱ $EtNH_3Cl$

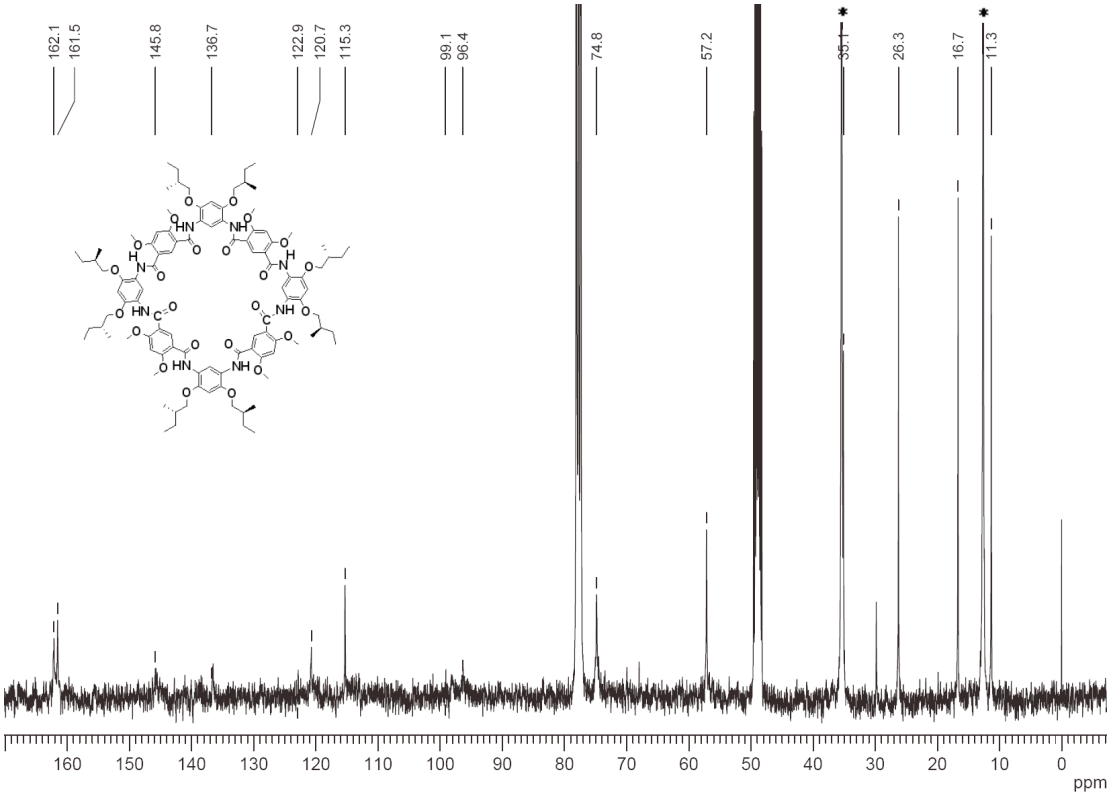


Figure S17. ^{13}C NMR spectrum of ***3c*** in 99%$CDCl_3$-1%CD_3OD. ✱ $EtNH_3Cl$

Figure S18. ^{1}H NMR spectrum of ***3d*** in 90%$CDCl_3$-10%CD_3OD.

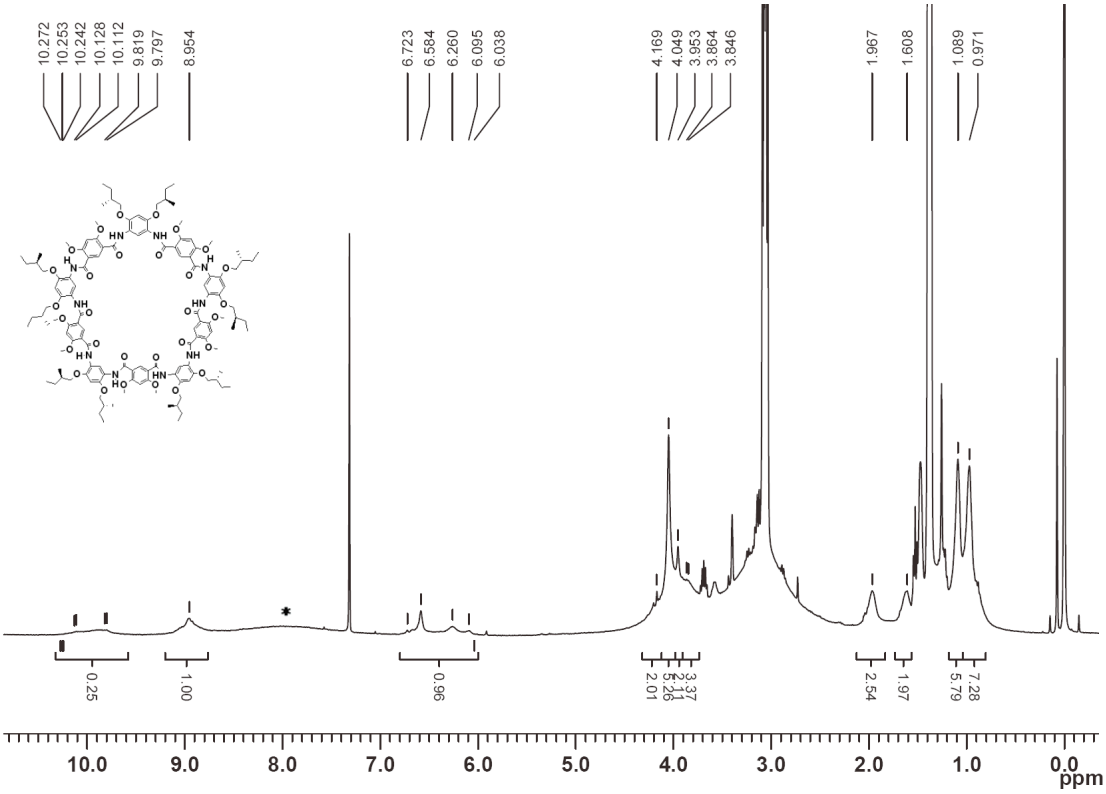


Figure S19. ^{1}H NMR spectrum of ***3e*** in 90%$CDCl_3$-10%CD_3OD. ✱ $EtNH_3Cl$

MASS spectra

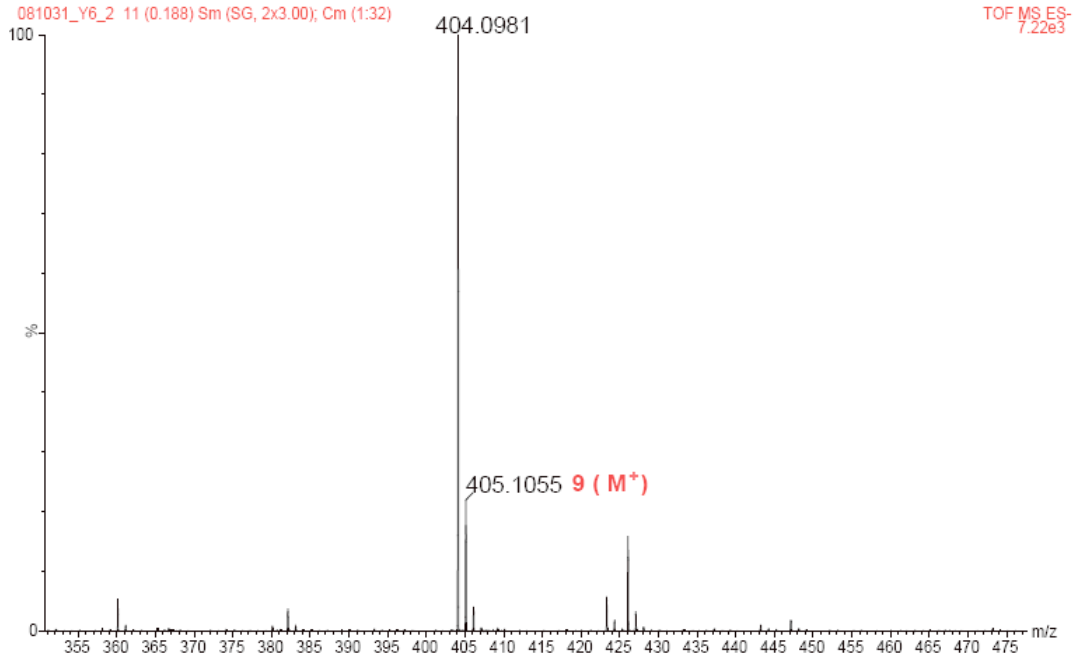


Figure S20. ESI-HRMS Spectrum of ***9***

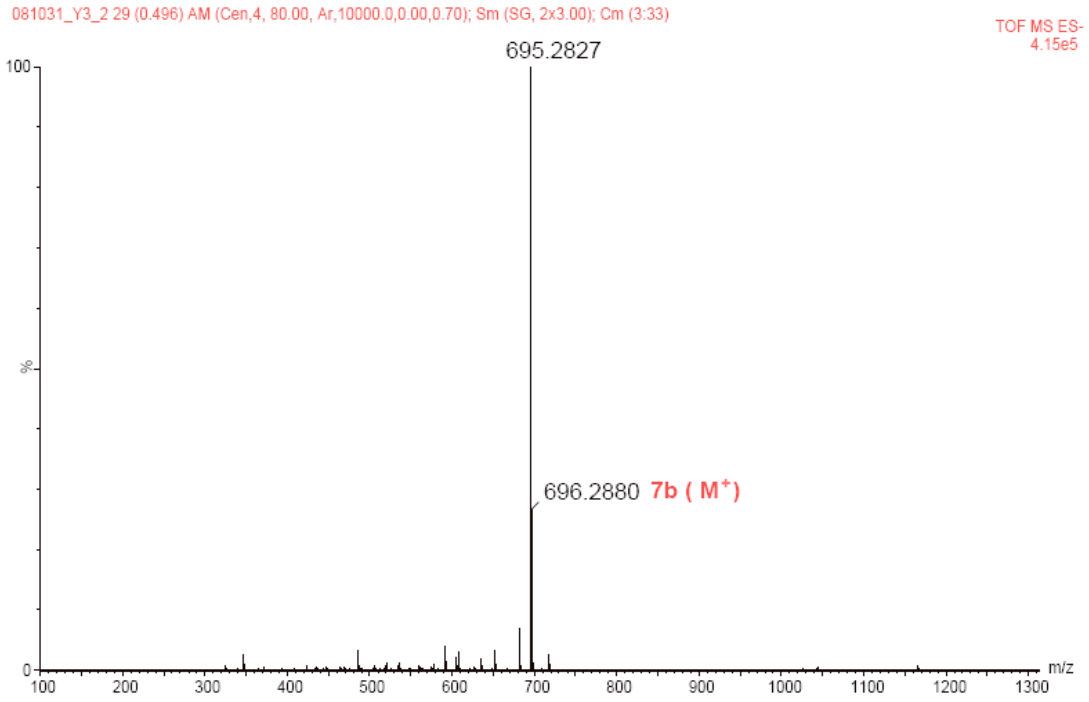


Figure S21. ESI-HRMS Spectrum of ***7b***

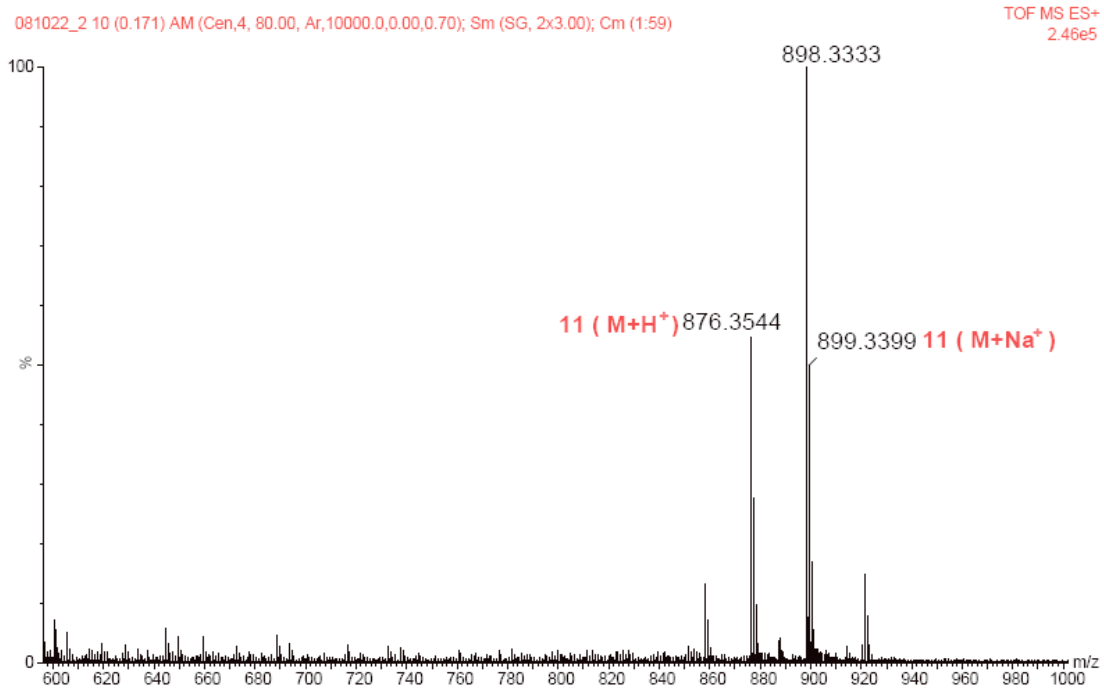


Figure S22. ESI-HRMS Spectrum of ***11***

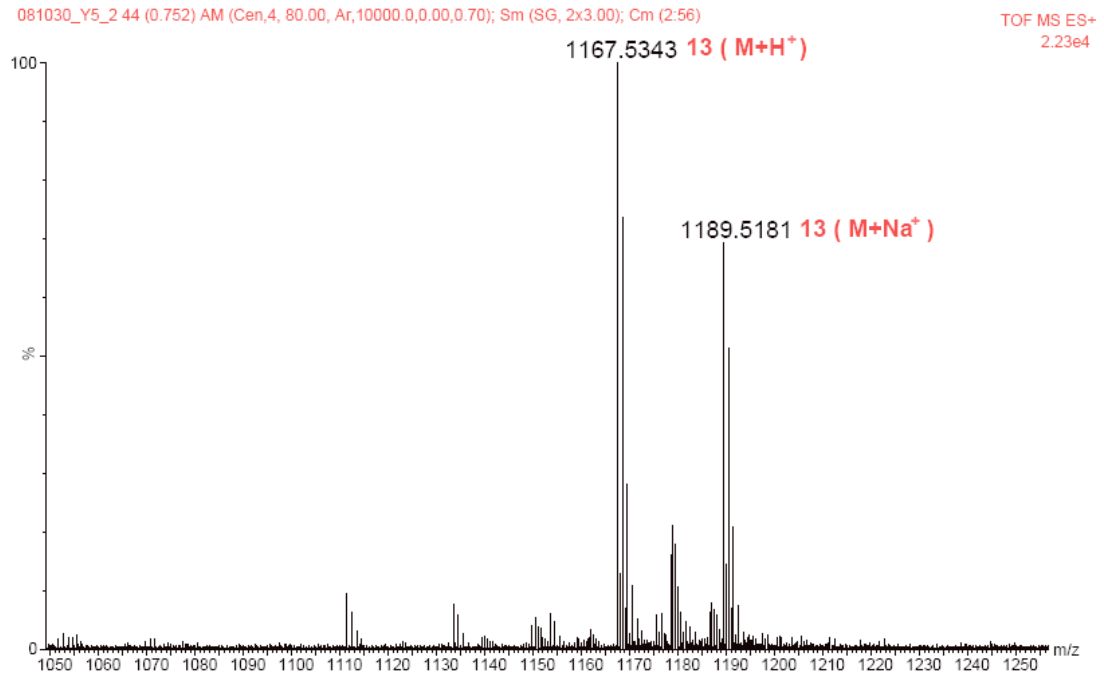


Figure S23. ESI-HRMS Spectrum of ***13***

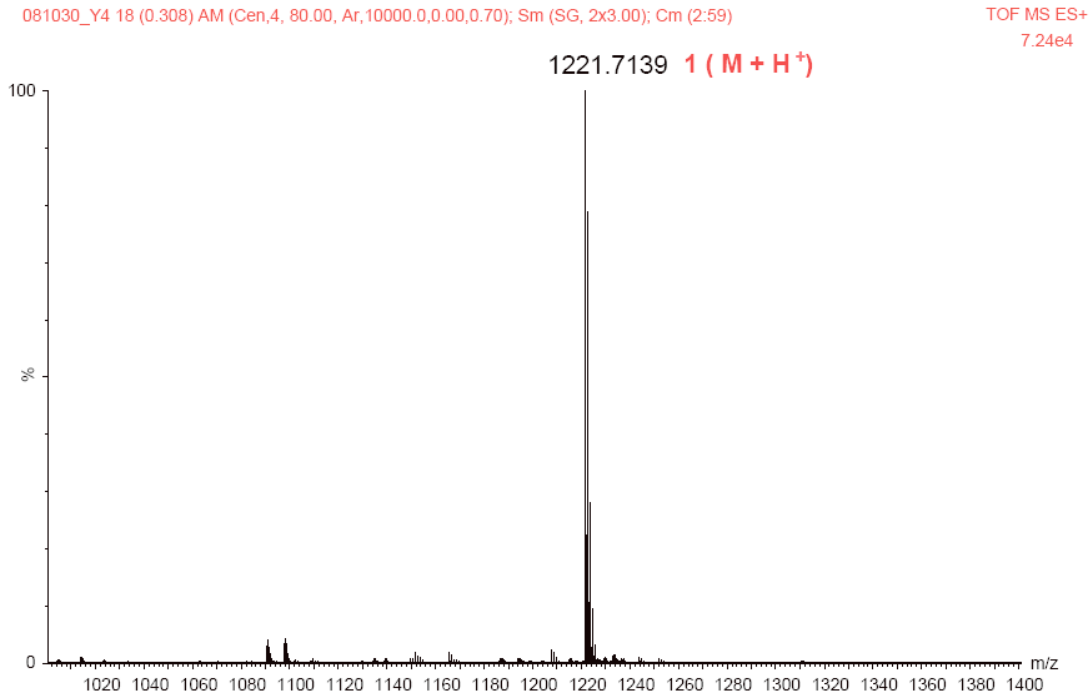


Figure S24. ESI-HRMS Spectrum of ***1***

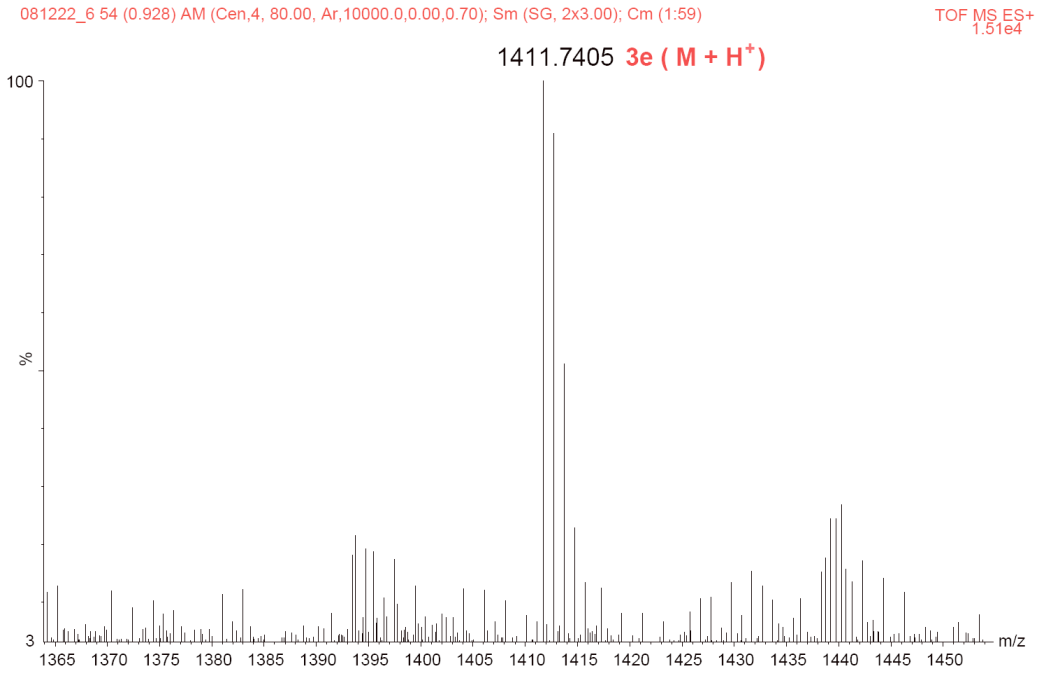


Figure S25. ESI-HRMS Spectrum of ***3a***

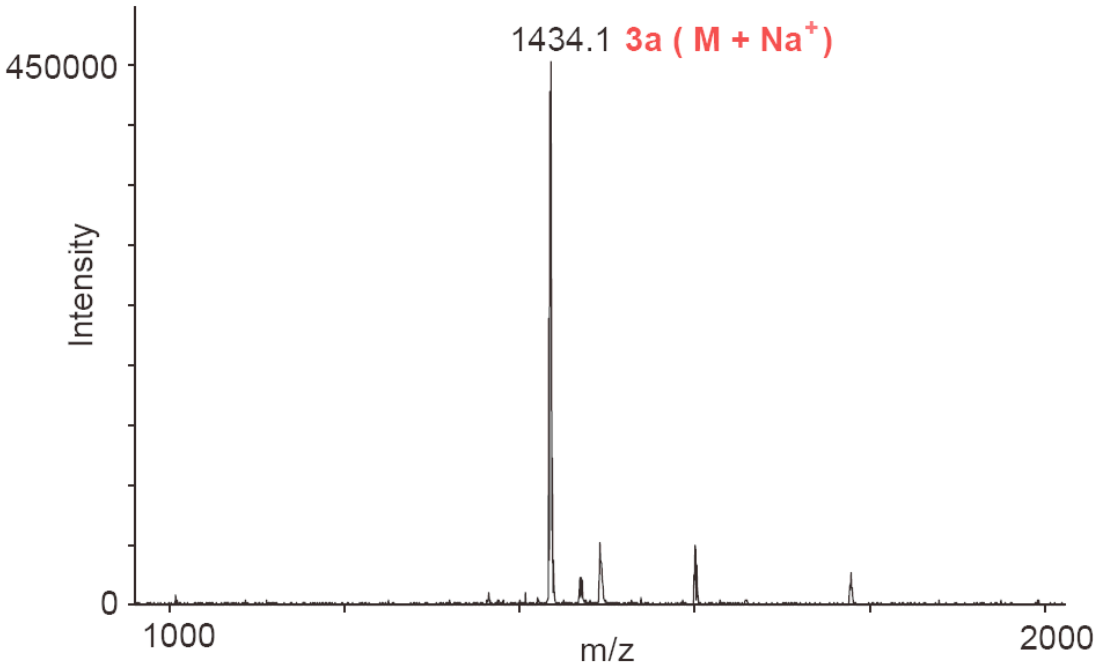


Figure S26. MALDI TOF MS Spectrum of ***3a***

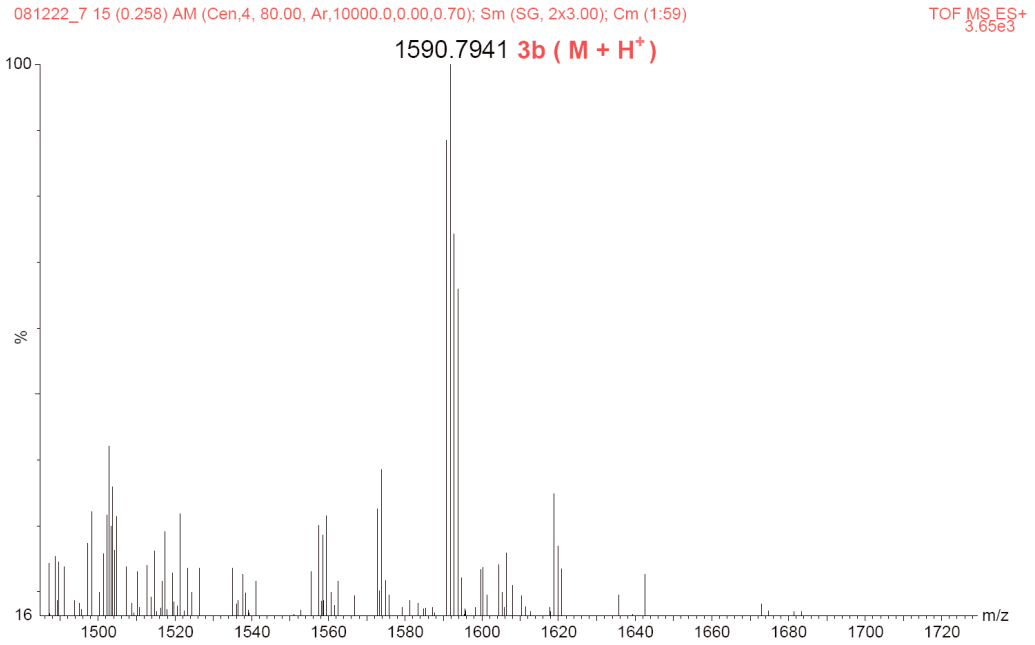


Figure S27. ESI-HRMS Spectrum of ***3b***

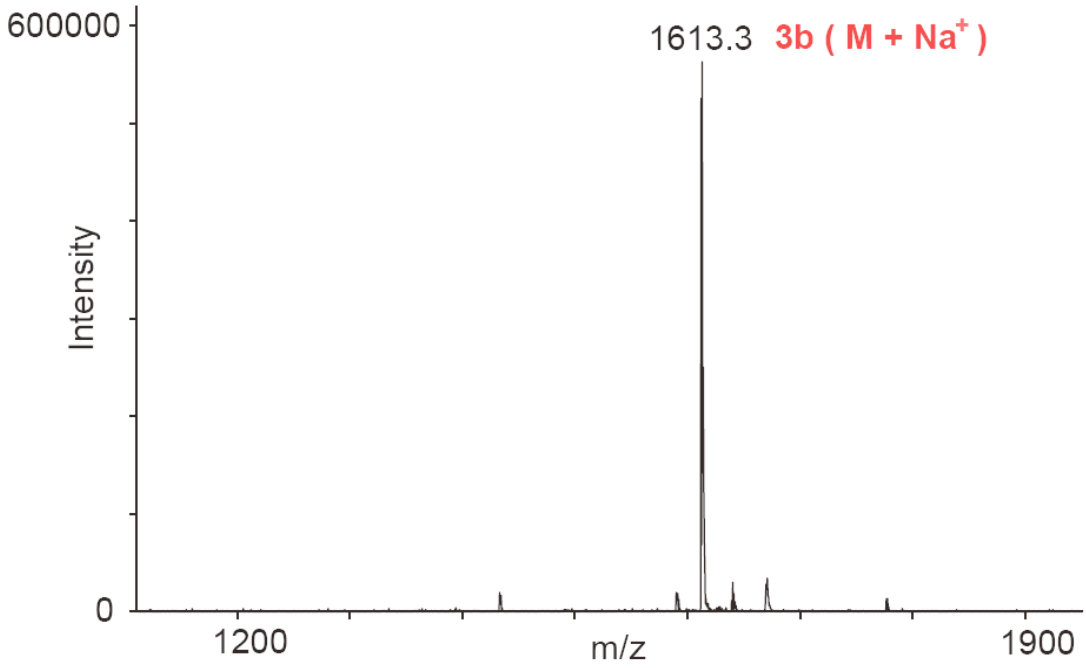


Figure S28. MALDI TOF MS Spectrum of ***3b***

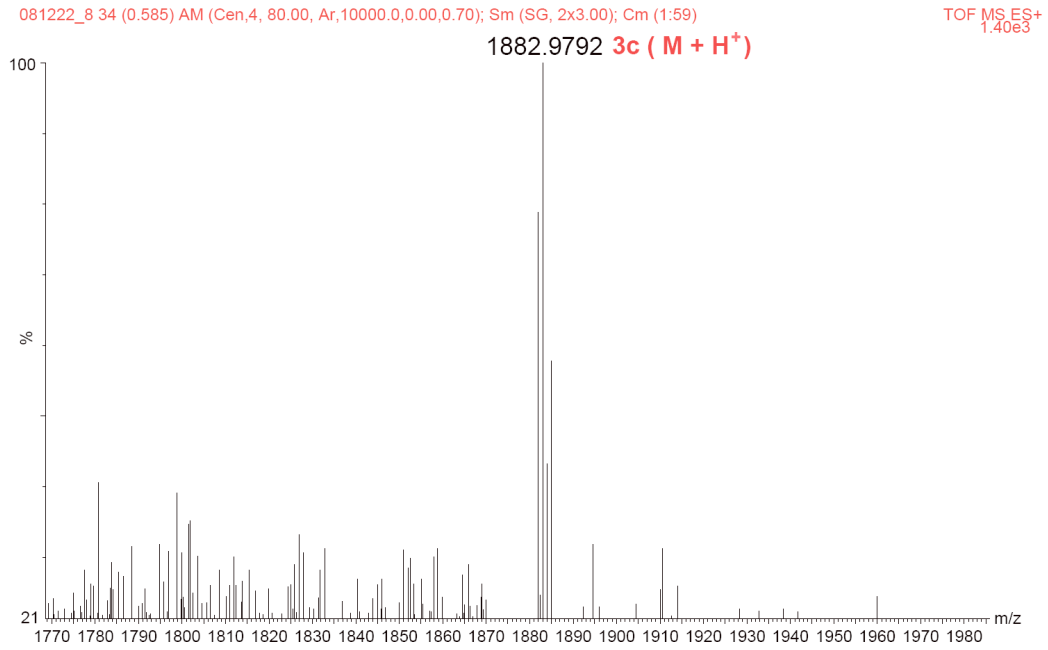


Figure S29. ESI-HRMS Spectrum of ***3c***

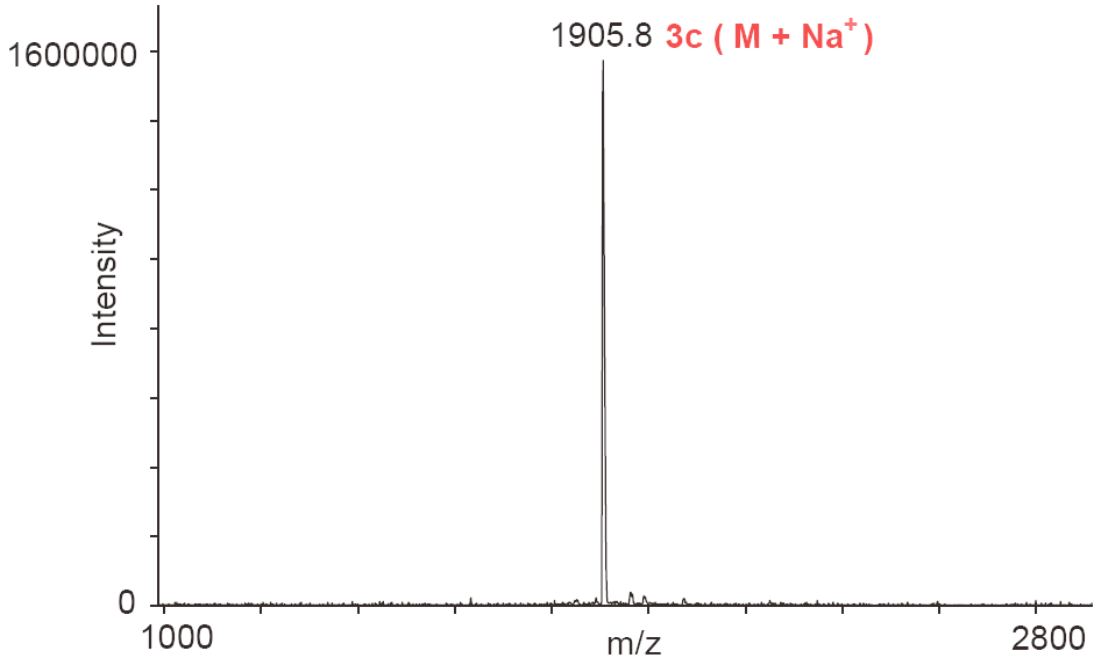


Figure S30. MALDI TOF MS Spectrum of ***3c***

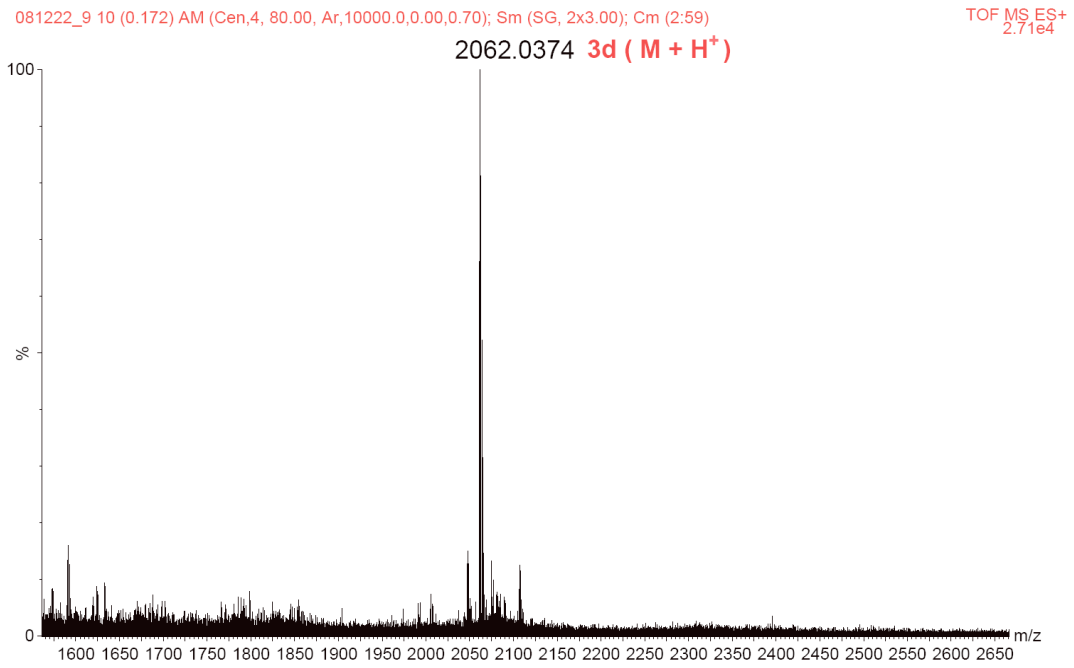


Figure S31. ESI-HRMS Spectrum of ***3d***

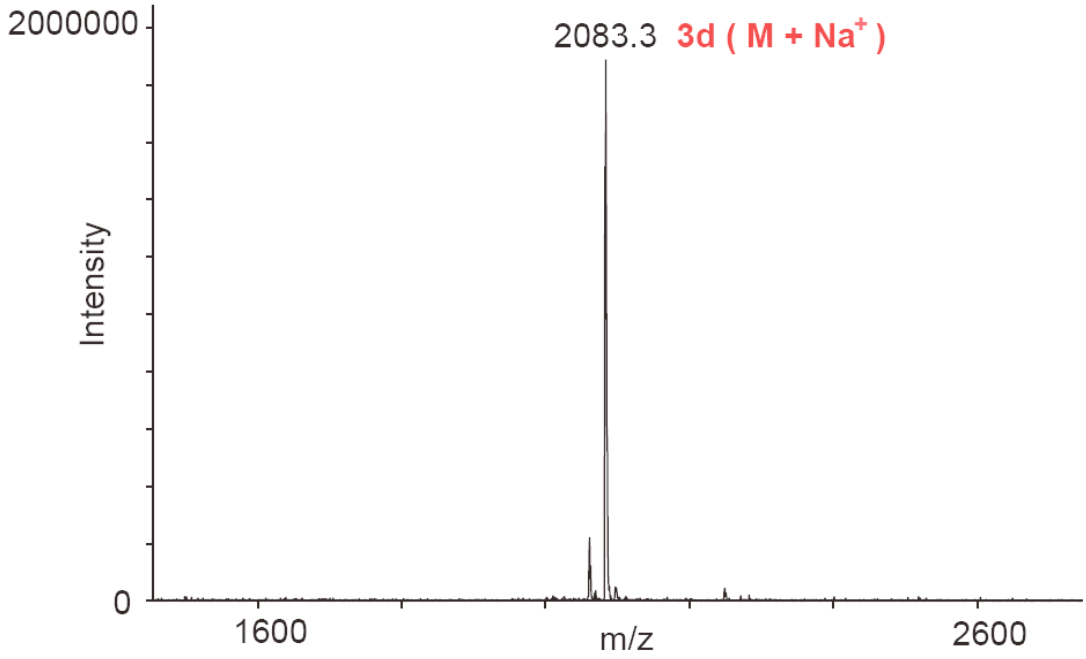


Figure S32. MALDI TOF MS Spectrum of ***3d***

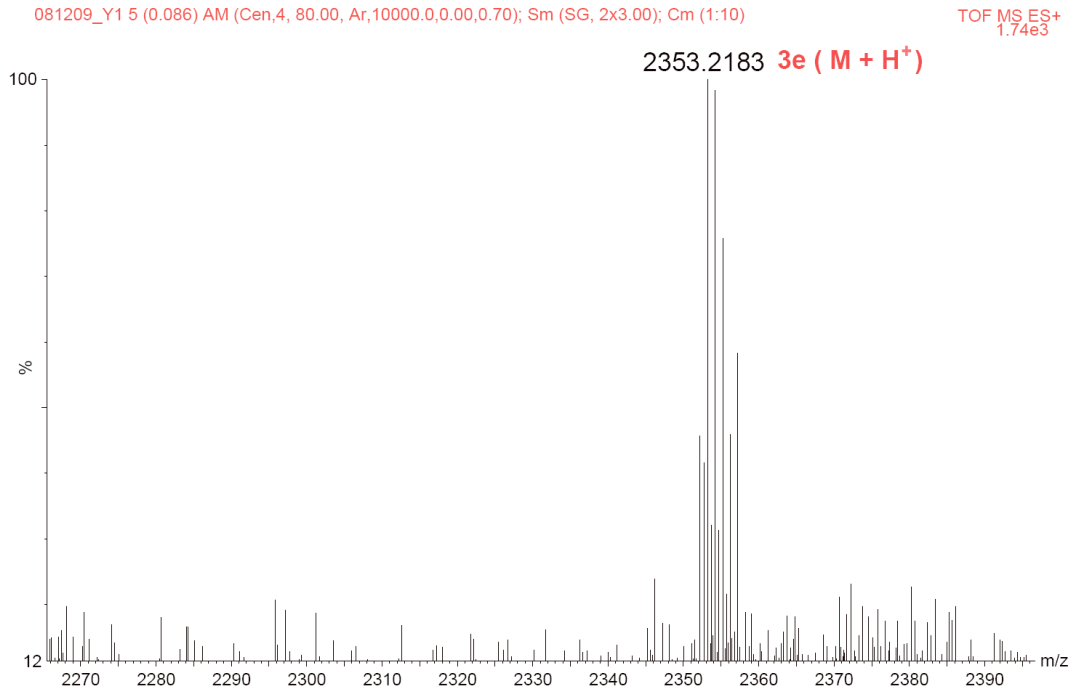


Figure S33. ESI-HRMS Spectrum of ***3e***

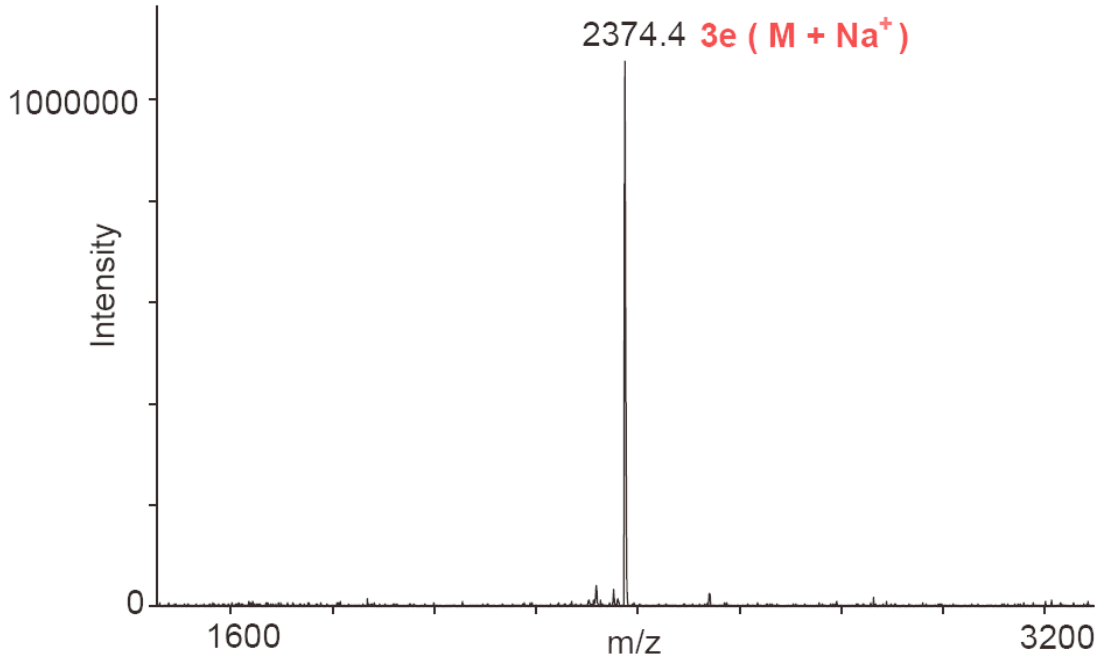


Figure S34. MALDI TOF MS Spectrum of ***3e***