Supporting Information

Modular synthesis and modification of novel bifunctional dendrons

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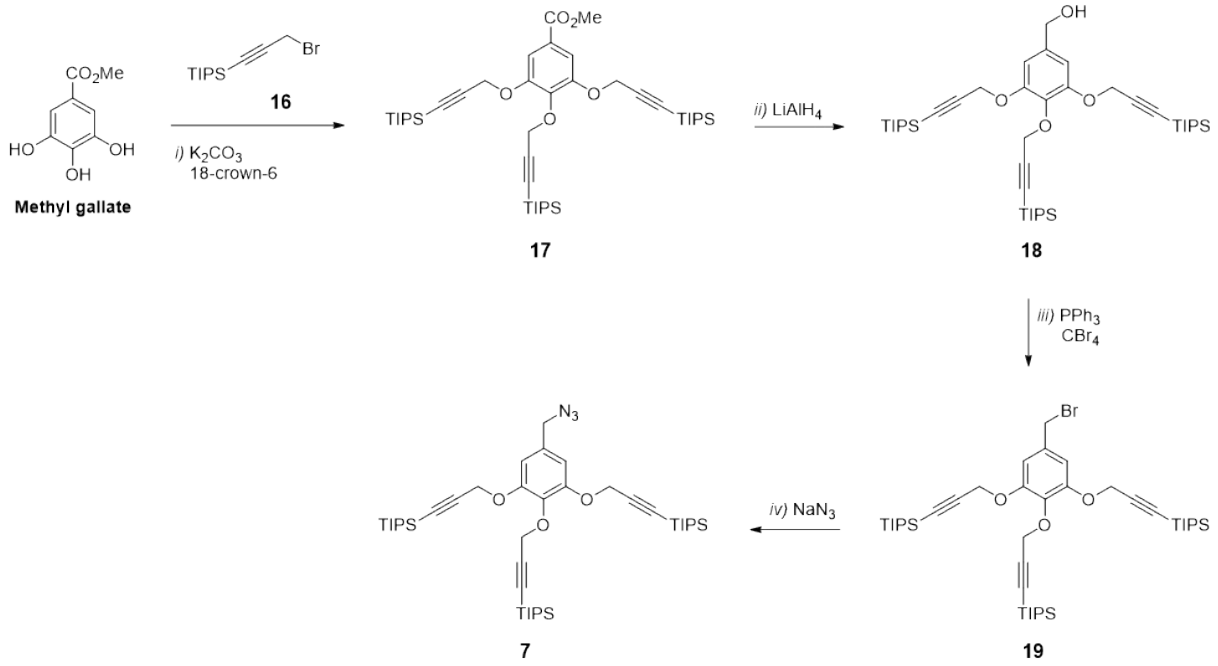
Synthesis of the building block 7



Scheme S1. Synthesis of the building block **7**. Reagents and conditions: *i*) **16**, K_2CO_3, 18-crown-6, acetone, reflux, 12 h, 90%; *ii*) $LiAlH_4$ (1 M in THF), THF dry, RT, 1 h, 88%; *iii*) PPh_3, CBr_4, DMF dry, RT, 30 min, 72%; *iv*) NaN_3, DMF dry, RT, 12 h, 96%.

Synthesis of 3-bromo-1-(triisopropylmethylsilyl)-1-propyne (16)

Compound **16** was synthesized as described in the literature.[1]

Synthesis of methyl 3,4,5-tris((3-(triisopropylsilyl)prop-2-yn-1-yl)oxy)benzoate (17)

Methyl gallate (848 mg, 4.61 mmol) and 3-bromo-1-(triisopropylmethylsilyl)-1-propyne **16** (4.56 g, 16.58 mmol) were dissolved in acetone (20 mL). K_2CO_3 (761 mg, 3.84 mmol) and 18-crown-6 (10 mg, 0.038 mmol) were added to the solution. The resulting mixture was stirred at RT for 12 h and the solvent evaporated to dryness. DCM and H_2O were added and the product was extracted once with DCM. The organic solvent was dried over Na_2SO_4, filtered and the reaction mixture absorbed onto Isolute. Purification by flash chromatography eluting with heptane/ethyl acetate gave **17** (3.35 g, 90% yield, 98% pure) as a yellow oil. UPLC R_t = 1.61 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 2H), 4.91 (s, 2H), 4.81 (s, 4H), 3.86 (s, 3H), 1.01-0.98 (m, 63H). ^{13}C NMR (101

MHz, $CDCl_3$): δ 166.3, 151.2, 141.3, 125.1, 110.4, 102.2, 101.5, 89.9, 88.7, 61.0, 58.0, 52.0, 18.4, 11.0. HRMS calcd for $C_{44}H_{74}O_5Si_3$ $[M+H]^+$ 767.4917, found 767.4907.

Synthesis of (3,4,5-tris((3-(triisopropylsilyl)prop-2-yn-1-yl)oxy)phenyl)methanol (18)

To a stirred solution of **17** (3.00 g, 3.91 mmol) in anhydrous THF (50 mL) under inert atmosphere, $LiAlH_4$ (1 M in THF, 9 mL, 9.00 mmol) was added dropwise. The reaction mixture was stirred at RT for 1 h. The reaction mixture was cooled to 0 °C and quenched with a saturated solution of ammonium chloride (3 mL). The solution was acidified with a 0.1 M HCl solution and the solvent evaporated. DCM and H_2O were added and the product was extracted twice with DCM. The organic solvent was dried over Na_2SO_4, filtered and evaporated to yield the crude product **18** (2.53 g, 88% yield, 94% pure). ^1H NMR (400 MHz, $CDCl_3$): δ 6.81 (s, 2H), 4.82 (s, 2H), 4.78 (s, 4H), 4.56 (s, 2H), 1.02-1.00 (m, 63H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.9, 137.0, 136.5, 107.9, 102.8, 102.3, 89.5, 88.3, 65.6, 61.1, 58.1, 18.6, 11.2. HRMS calcd for $C_{43}H_{74}O_4Si_3$ $[M+H]^+$ 739.4968, found 739.4960.

Synthesis of (((5-(bromomethyl)benzene-1,2,3-triyl)tris(oxy))tris(prop-1-yne-3,1-diyl))tris(triisopropylsilane) (19)

To a stirred solution of **18** (2.52 g, 3.41 mmol) in anhydrous DMF (70 mL) was added PPh_3 (1.79 g, 6.82 mmol) and CBr_4 (2.26 g, 6.82 mmol). The reaction mixture was stirred at RT for 30 min. The reaction mixture was concentrated *in-vacuo* and absorbed onto Isolute. Purification by flash chromatography eluting with heptane/ethyl acetate gave **19** as a pale yellow oil (2.03 g, 72% yield, 97% pure). UPLC R_t = 1.61 min. ^1H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 2H), 4.84 (s, 2H), 4.78 (s, 4H), 4.37 (s, 2H), 1.04-1.00 (m, 63H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.8, 137.6, 133.0, 110.1, 102.6, 102.0, 89.8, 88.6, 61.1, 58.1, 33.7, 18.7, 11.2. HRMS calcd for $C_{43}H_{73}BrO_3Si_3$ $[M+H]^+$ 801.4124, found 801.4116.

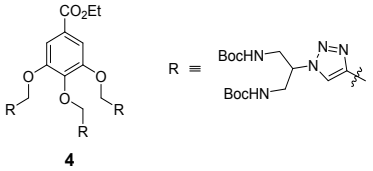
Synthesis of (((5-(azidomethyl)benzene-1,2,3-triyl)tris(oxy))tris(prop-1-yne-3,1-diyl))tris(triisopropylsilane) (7)

To a stirred solution of **19** (1.07 g, 1.33 mmol) in anhydrous DMF (40 mL) was added NaN_3 (173 mg, 2.67 mmol). The reaction mixture was stirred at RT for 12 h. The solvent was evaporated, DCM and H_2O were added to the mixture and the product extracted once with DCM. After extraction, the organics were washed once with brine, dried over Na_2SO_4, filtered and concentrated

in-vacuo to yield **7** as a yellow oil (1.00 g, 96% yield, 98% pure). UPLC R_t = 1.61 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (s, 2H), 4.83 (s, 2H), 4.79 (s, 4H), 4.22 (s, 2H), 1.03-1.00 (m, 63H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.0, 137.3, 131.0, 109.0, 102.7, 102.0, 89.7, 88.4, 61.0, 58.1, 55.0, 18.6, 11.2. HRMS calcd for $C_{43}H_{73}N_3O_3Si_3$ $[M+H]^+$ 764.5032, found 764.5047.

Synthesis of the dendrons 6 and 12

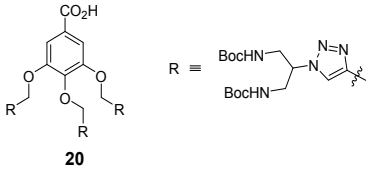
Synthesis of ethyl 3,4,5-tris((1-(2,2,12,12-tetramethyl-4,10-dioxo-3,11-dioxa-5,9-diazatridecan-7-yl)-1H-1,2,3-triazol-4-yl)methoxy)benzoate (4)



4

Compounds **1** (400 mg, 1.28 mmol) and **2** (1.33 g, 4.23 mmol) were dissolved in THF (20 mL). Sodium ascorbate (761 mg, 3.84 mmol) was dissolved in H_2O (5 mL) and added to the mixture. Subsequently, $CuSO_4 \bullet 5H_2O$ (480 mg, 1.92 mmol) was dissolved in H_2O (5 mL) and added to the mixture. The mixture was stirred at RT for 3 h. The reaction mixture was concentrated *in-vacuo*, DCM and an ammonium citrate buffer (pH = 7.1) were added and the mixture let under vigorous stirring for 15 min. After extraction, the organics were washed once with brine, dried over Na_2SO_4, filtered and absorbed onto Isolute. Purification by flash chromatography eluting with heptane/ethyl acetate gave **4** as a white solid (1.32 g, 81% yield, 98% pure). UPLC-MS $[M+2H]^{2+}$ = 630.0, R_t = 1.37 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.67 (m, 3H), 7.46 (s, 2H), 5.65-5.59 (m, 6H), 5.30-5.17 (m, 6H), 4.75 (m, 3H), 4.38 (q, J = 7.1 Hz, 2H), 3.75-3.58 (m, 12H), 1.44-1.39 (m, 54H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.9, 159.0, 156.5, 152.1, 143.9, 143.3, 141.9, 126.4, 124.2, 123.6, 109.8, 80.1, 79.9, 75.9, 66.3, 63.4, 61.5, 60.8, 43.4, 42.9, 41.5, 28.5, 14.5. HRMS calcd for $C_{57}H_{91}N_{15}O_{17}$ $[M+H]^+$ 1258.6790, found 1258.6791.

Synthesis of 3,4,5-tris((1-(2,2,12,12-tetramethyl-4,10-dioxo-3,11-dioxa-5,9-diazatridecan-7-yl)-1H-1,2,3-triazol-4-yl)methoxy)benzoic acid (20)

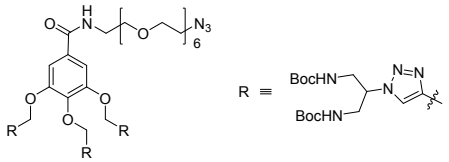


20

Compound **4** (1.3 g, 1.03 mmol) was dissolved in THF (20 mL). LiOH • H_2O (130 mg, 3.10 mmol) was dissolved in H_2O (10 mL) and subsequently added to THF solution. The reaction mixture was stirred under reflux for 17 h. The reaction mixture was neutralized (pH = 7) with a 0.1 M HCl

solution. H_2O was added and the product extracted with DCM. After extraction, the organics were dried over Na_2SO_4, filtered and concentrated *in-vacuo* to afford **20** as a transparent viscous oil (1.24 g, 93% yield, 95% pure). UPLC-MS $[M+2H]^{2+}$ = 616.0, R_t = 1.27 min. ^1H NMR (400 MHz, CD_3OD): δ 8.17 (s, 2H), 8.03 (s, 1H), 7.51 (s, 2H), 6.79-6.70 (m, 6H), 5.22-5.18 (m, 6H), 3.60-3.57 (m, 12H), 1.38 (m, 54H). A peak containing 3H falls under the peak of the solvent. ^{13}C NMR (101 MHz, CD_3OD): δ 157.9, 157.1, 153.3, 144.3, 141.8, 125.5, 125.1, 110.5, 81.2, 80.2, 76.8, 66.9, 63.6, 63.0, 62.6, 62.3, 44.5, 44.1, 43.9, 43.0, 42.9, 28.6. HRMS calcd for $C_{55}H_{87}N_{15}O_{17}$ $[M+H]^+$ 1230.6477, found 1230.6428.

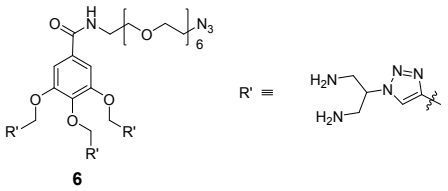
Synthesis of hexa-tert-butyl (((((5-((2-(2-azidoethoxy)ethyl)carbamoyl)benzene-1,2,3-triyl)tris(oxy))tris(methylene))tris(1H-1,2,3-triazole-4,1-diyl))tris(propane-2,1,3-triyl))hexacarbamate (5)



5

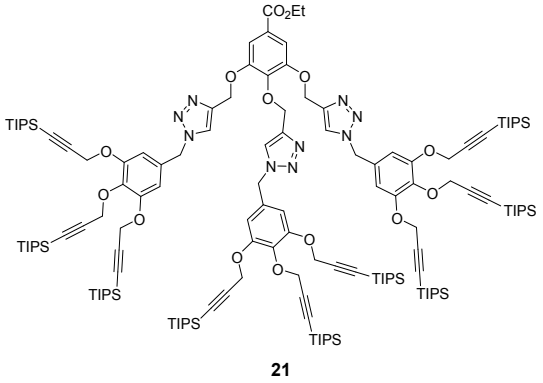
To a solution of **20** (700 mg, 0.57 mmol) and O-(2-Aminoethyl)-O'-(2-azidoethyl)pentaethylene glycol **3** (299 mg, 0.85 mmol) in anhydrous DMF (30 mL) was added DIPEA (221 mg, 1.71 mmol) and HATU (433 mg, 1.14 mmol). The reaction mixture was stirred at RT for 1 h, concentrated *in-vacuo,* and DCM and H_2O added. The product was extracted with DCM. After extraction, the organics were washed once with brine, dried over Na_2SO_4, filtered and absorbed onto Isolute. Purification by flash chromatography eluting with heptane/ethyl acetate afforded **5** as a white solid (1.32 g, 81% yield, 98% pure). UPLC-MS $[M+2H]^{2+}$ = 782.3, R_t = 1.35 min. ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (bs, 3H), 5.58 (bs, 6H), 5.24-5.17 (m, 6H), 4.75 (m, 3H), 3.70-3.65 (m, 38H), 3.39 (t, J = 4.9 Hz, 2H), 1.40 (m, 54H). A peak containing 2H falls under the peak of the solvent. ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 156.5, 152.1, 150.8, 143.3, 124.1, 123.8, 120.5, 108.2, 107.9, 80.0, 79.9, 70.7, 70.6, 70.5, 70.4, 70.3, 70.2, 70.0, 69.9, 69.4, 66.3, 63.3, 60.8, 55.2, 50.8, 50.7, 45.1, 43.2, 41.5, 40.1, 40.0, 28.4. HRMS calcd for $C_{69}H_{115}N_{19}O_{22}$ $[M+2H]^{2+}$ 781.9304, found 781.9304.

Synthesis of 2,2',2''-((((5-((2-(2-azidoethoxy)ethyl)carbamoyl)benzene-1,2,3-triyl)tris(oxy))tris(methylene))tris(1H-1,2,3-triazole-4,1-diyl))tris(propane-1,3-diaminium) (6)



Hydrogen chloride solution 4 M in dioxane (10 mL, 40.0 mmol) was added to **5** (400 mg, 0.26 mmol). The reaction mixture was stirred at RT for 20 min, concentrated *in-vacuo* and the product purified by reversed-phase HPLC eluting with ACN/H_2O to afford **6** as a white solid (278 mg, 66% yield, 98% pure, TFA salt). UPLC-MS $[M+2H]^{2+}$ = 481.0, R_t = 7.47 min. ^1H NMR (400 MHz, CD_3OD): δ 8.41-8.34 (m, 3H), 7.39 (s, 2H), 5.48-5.39 (m, 3H), 5.30 (s, 4H), 5.18 (s, 2H), 3.82-3.58 (m, 38H), 3.38 (t, *J* = 4.9 Hz, 2H). ^{13}C NMR (101 MHz, D_2O): δ 169.5, 162.9 (q, *J* = 40 Hz), 151.5, 144.2, 143.9, 138.6, 130.6, 126.2, 125.9, 116.4 (q, *J* = 293 Hz), 107.4, 69.5, 69.4, 69.2, 68.8, 65.0, 61.9, 57.0, 56.8, 50.1, 40.8, 39.6. HRMS calcd for $C_{39}H_{67}N_{19}O_{10}$ $[M+2H]^{2+}$ 481.7732, found 481.7734.

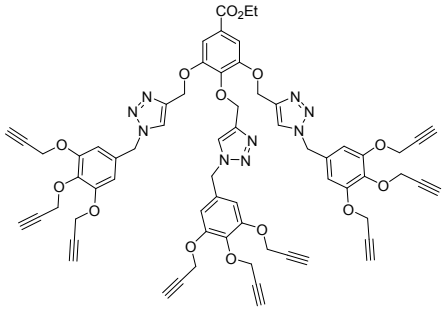
Synthesis of 21



Compounds **7** (115 mg, 0.37 mmol) and **1** (929 mg, 1.22 mmol) were dissolved in THF (16 mL). Sodium ascorbate (219 mg, 1.11 mmol) was dissolved in H_2O (2 mL) and added to the mixture. Subsequently, $CuSO_4 \cdot 5H_2O$ (138 mg, 0.55 mmol) was dissolved in H_2O (2 mL) and added to the mixture. The reaction mixture was stirred at RT for 3 h. The reaction mixture was concentrated *in-vacuo*, DCM and an ammonium citrate buffer (pH = 7.1) were added and the mixture let under

vigorous stirring for 15 min. The organic layer was washed once with brine, dried over Na_2SO_4, filtered and absorbed onto Isolute. Purification by flash chromatography eluting with heptane/ethyl acetate gave **21** as a yellow oil (768 mg, 78% yield, 98% pure). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.68 (s, 2H), 7.40 (s, 2H), 6.79-6.75 (m, 6H), 5.39 (s, 6H), 5.22-5.16 (m, 6H), 4.83-4.77 (m, 18H), 4.36-4.32 (m, 2H), 1.39-1.36 (m, 3H), 1.02-0.98 (m, 189H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.9, 152.2, 152.1, 152.0, 144.6, 143.7, 141.8, 138.2, 138.1, 130.2, 129.7, 126.2, 124.0, 123.2, 109.7, 109.6, 109.5, 102.6, 102.5, 102.4, 101.9, 101.8, 101.7, 89.7, 89.5, 88.5, 88.4, 66.6, 63.2, 61.3, 61.1, 58.3, 54.4, 54.1, 18.6, 14.5, 11.2. HRMS calcd for $C_{147}H_{235}N_9O_{14}Si_9$ $[M+H]^+$ 2603.5950, found 2603.6086.

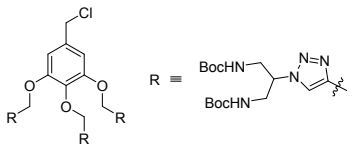
Synthesis of ethyl 3,4,5-tris((1-(3,4,5-tris(prop-2-yn-1-yloxy)benzyl)-1H-1,2,3-triazol-4-yl)methoxy)benzoate (8)



8

To a solution of **21** (700 mg, 0.27 mmol) in anhydrous THF (80 mL) was added TBAF • $3H_2O$ (932 mg, 2.96 mmol) and the reaction mixture was stirred at RT for 1 h. The reaction mixture was quenched with H_2O and DCM was added. After extraction, the organics were washed once with brine, dried over Na_2SO_4, filtered and absorbed onto Isolute. Purification by flash chromatography eluting with heptane/ethyl acetate gave **8** as a yellow solid (250 mg, 74% yield, 96% pure). UPLC-MS $[M+H]^+$ = 1198.4, R_t = 1.21 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.80 (m, 3H), 7.38 (s, 2H), 6.75-6.73 (m, 6H), 5.48-5.43 (m, 6H), 5.19-5.16 (m, 6H), 4.73-4.71 (m, 18H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.54-2.45 (m, 9H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.4, 151.6, 151.5, 144.0, 143.4, 140.9, 136.8, 136.7, 130.8, 130.5, 125.9, 124.0, 123.3, 108.7, 108.3, 108.2, 78.8, 78.7, 78.0, 77.8, 76.4, 76.3, 75.4, 65.9, 62.8, 61.0, 60.0, 56.7, 53.8, 14.1. HRMS calcd for $C_{66}H_{55}N_9O_{14}$ $[M+H]^+$ 1198.3941, found 1198.3967.

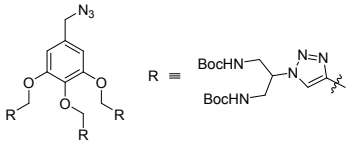
Synthesis of hexa-tert-butyl (((((5-(chloromethyl)benzene-1,2,3-triyl)tris(oxy))tris(methylene))tris(1H-1,2,3-triazole-4,1-diyl))tris(propane-2,1,3-triyl))hexacarbamate (22)



22

To a solution of compound **9** (450 mg, 1.56 mmol), **2** (1.62 g, 5.14 mmol) and TBTA (1.24 g, 2.34 mmol) in THF (24 mL) was added a solution of sodium ascorbate (926 mg, 4.68 mmol) in H_2O (6 mL). Subsequently, $CuSO_4 \bullet 5H_2O$ (584 mg, 2.34 mmol) was dissolved in H_2O (6 mL) and added to the mixture. The mixture was allowed to stir at RT for 12 h. The reaction mixture was concentrated *in-vacuo*, DCM and an ammonium citrate buffer (pH = 7.1) were added and the mixture let under vigorous stirring for 15 min. The organic layer was washed once with brine, dried over Na_2SO_4, filtered and the reaction mixture absorbed onto Isolute. Purification by flash chromatography eluting with heptane/ethyl acetate gave **22** as a white solid (1.58 g, 82% yield, 97% pure). UPLC-MS $[M+H]^+$ = 1234.2, R_t = 1.37 min. ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (bs, 2H), 7.67 (bs, 1H), 6.78 (s, 2H), 5.57 (m, 6H), 5.18 (s, 4H), 5.10 (s, 2H), 4.75-4.68 (m, 3H), 4.53 (s, 2H), 3.79-3.52 (m, 12H), 1.44-1.40 (m, 54H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.5, 152.4, 143.5, 133.8, 124.1, 123.6, 109.0, 80.1, 80.0, 77.4, 75.8, 66.3, 63.4, 60.8, 60.5, 46.4, 42.9, 41.6, 41.5, 28.5. HRMS calcd for $C_{55}H_{88}ClN_{15}O_{15}$ $[M+H]^+$ 1234.6346, found 1234.6349.

Synthesis of hexa-tert-butyl (((((5-(azidomethyl)benzene-1,2,3-triyl)tris(oxy))tris(methylene))tris(1H-1,2,3-triazole-4,1-diyl))tris(propane-2,1,3-triyl))hexacarbamate (10)

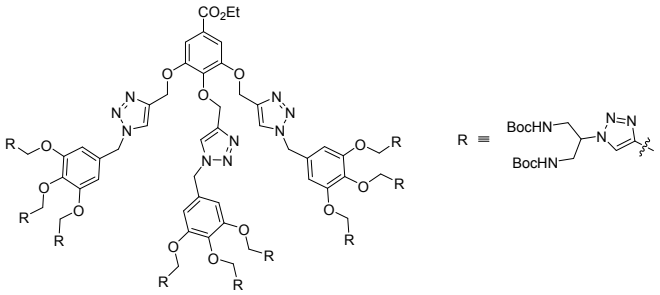


10

To a stirred solution of **22** (1.29 g, 1.05 mmol) in DMF dry (25 mL), NaN_3 (126 mg, 2.10 mmol) was added. The reaction mixture was stirred at RT for 12 h, concentrated *in-vacuo*, DCM and H_2O were added, and the product extracted once with DCM. After extraction, the organics were washed

once with brine, dried over Na_2SO_4, filtered and absorbed onto Isolute. Purification by flash chromatography eluting with heptane/ethyl acetate gave **10** as a white solid (1.27 g, 96% yield, 98% pure). UPLC-MS $[M+2H]^{2+}$ = 621.6, R_t = 1.37 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (bs, 2H), 7.66 (bs, 1H), 6.70 (s, 2H), 5.58 (m, 6H), 5.19 (s, 4H), 5.11 (s, 2H), 4.74-4.67 (m, 3H), 4.29 (s, 2H), 3.78-3.55 (m, 12H), 1.44-1.40 (m, 54H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.5, 152.6, 144.0, 143.5, 131.8, 124.1, 123.6, 108.5, 80.0, 79.9, 75.8, 66.2, 63.4, 60.8, 60.7, 54.8, 43.4, 42.9, 41.6, 41.5, 28.4. HRMS calcd for $C_{55}H_{88}N_{18}O_{15}$ $[M+H]^+$ 1241.6749, found 1241.6754.

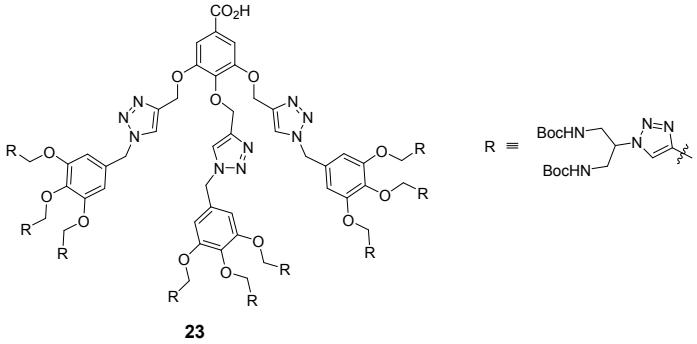
Synthesis of 11



11

To a solution of compound **1** (80 mg, 0.26 mmol), **10** (1.05 g, 0.85 mmol) and TBTA (204 mg, 0.38 mmol) in THF (10 mL) was added a solution of sodium ascorbate (152 mg, 0.77 mmol) in H_2O (2.5 mL). Subsequently, $CuSO_4 \bullet 5H_2O$ (96 mg, 0.38 mmol) was dissolved in H_2O (2.5 mL) and added to the reaction mixture. The reaction mixture was stirred at RT for 12 h, concentrated *in-vacuo*, DCM and an ammonium citrate buffer (pH = 7.1) were added and the mixture let under vigorous stirring for 15 min. The organic layer was washed once with brine, dried over Na_2SO_4, filtered and absorbed onto Isolute. Purification by flash chromatography eluting with DCM/MeOH gave **11** as a pale yellow solid (716 mg, 63% yield, 92% pure). UPLC-MS $[M+3H]^{3+}$ = 1346.2, R_t = 1.65 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99-7.70 (m, 12H), 7.40 (s, 2H), 6.77 (s, 2H), 6.69 (s, 4H), 5.84-5.78 (m, 18H), 5.47 (s, 4H), 5.42 (s, 2H), 5.29-5.20 (m, 6H), 5.08-4.98 (m, 18H), 4.78-4.66 (m, 9H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.74-3.51 (m, 36H), 1.38-1.26 (m, 165H). ^{13}C NMR (101 MHz, CD_3OD): δ 167.2, 158.1, 157.3, 154.0, 153.4, 145.6, 145.2, 144.9, 144.4, 143.0, 138.9, 133.0, 127.4, 126.1, 125.9, 125.6, 125.2, 110.7, 109.3, 81.0, 80.4, 67.0, 63.9, 63.1, 62.7, 62.5, 62.4, 54.9, 44.6, 43.1, 30.9, 28.8, 14.7. HRMS calcd for $C_{183}H_{280}N_{54}O_{50}$ $[M+2H]^{2+}$ 2018.0585, found 2018.0635.

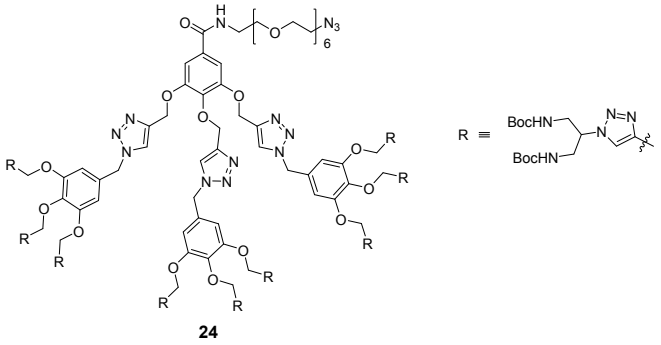
Synthesis of 23



23

To a solution of **11** (490 mg, 1.03 mmol) in THF (15 mL) was added a solution of LiOH • H_2O (51 mg, 1.21 mmol) in H_2O (7.5 mL). The reaction mixture was stirred at reflux for 17 h and neutralized (pH = 7) with a 0.1 M HCl solution. H_2O was added and the product extracted with DCM. After extraction, the organics were dried over Na_2SO_4, filtered and absorbed onto Isolute. Purification by flash chromatography eluting with DCM/MeOH yielded **23** as a pale yellow solid (492 mg, 91% yield, 95% pure). UPLC-MS $[M+3H]^{3+}$ = 1336.3, R_t = 1.62 min. ^{1}H NMR (400 MHz, CD_3OD): δ 8.16-8.00 (m, 12H), 7.44 (s, 2H), 6.92-6.67 (m, 24H), 5.56-5.41 (m, 6H), 5.19-5.12 (m, 24H), 3.65-3.50 (m, 36H), 1.40-1.35 (m, 162H). A peak containing 9H falls under the peak of the solvent. ^{13}C NMR (101 MHz, CD_3OD): δ 157.9, 157.0, 153.9, 153.3, 153.4, 145.7, 145.2, 144.9, 144.3, 138.8, 132.9, 126.2, 126.1, 125.9, 125.5, 125.1, 110.7, 110.5, 109.3, 81.0, 80.2, 67.2, 67.1, 63.8, 63.7, 62.7, 62.6, 62.3, 54.9, 44.6, 43.2, 31.1, 28.9. HRMS calcd for $C_{181}H_{276}N_{54}O_{50}$ $[M+2H]^{2+}$ 2004.0461, found 2004.0430.

Synthesis of 24

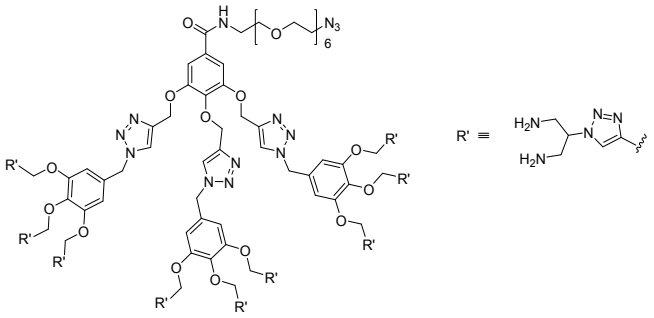


24

To a solution of **23** (260 mg, 0.07 mmol) and O-(2-Aminoethyl)-O'-(2-azidoethyl)pentaethylene glycol **3** (34 mg, 0.10 mmol) in DMF (10 mL) was added DIPEA (25 mg, 0.2 mmol) and HATU

(49 mg, 1.13 mmol). The reaction mixture was stirred at RT for 1 h, concentrated *in-vacuo* and DCM and H_2O were added. The product was extracted with DCM. After extraction, the organics were washed once with brine, dried over Na_2SO_4, filtered and absorbed onto Isolute. Purification by flash chromatography eluting with DCM/MeOH afforded **24** as a white solid (184 mg, 64% yield, 98% pure). UPLC-MS $[M+3H]^{3+}$ = 1447.0, R_t = 1.69 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.66 (m, 12H), 6.69 (s, 6H), 5.90-5.82 (m, 18H), 5.45-5.41 (m, 6H), 5.20 (m, 6H), 5.04-4.96 (m, 20H), 4.78-4.76 (m, 10H), 3.73-3.57 (m, 62H), 3.37 (m, 2H), 1.39-1.37 (m, 162H). ^{13}C NMR (101 MHz, CD_3OD): δ 156.5, 155.6, 152.6, 152.5, 152.0, 144.3, 143.9, 143.2, 137.9, 137.7, 131.3, 131.1, 124.9, 124.2, 123.7, 108.1, 107.9, 80.5, 79.9, 70.4, 70.3, 70.2, 70.0, 69.9, 66.2, 66.1, 65.9, 63.2, 63.1, 61.0, 60.7, 54.1, 50.7, 41.6, 40.1, 29.8, 28.5. HRMS calcd for $C_{195}H_{304}N_{58}O_{55}$ $[M+2H]^{2+}$ 2170.1498, found 2170.1460.

Synthesis of 12

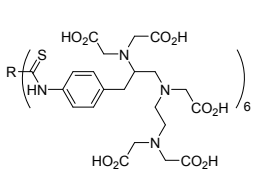


12

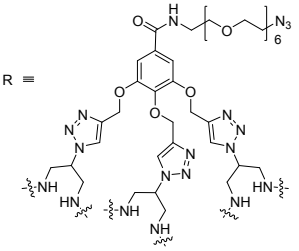
Hydrogen chloride solution 4 M in dioxane (5 mL) was added to **24** (250 mg, 0.26 mmol). The reaction mixture was stirred at RT for 20 min, concentrated *in-vacuo* and the product purified by reversed-phase HPLC eluting with ACN/H_2O to afford **12** as a white solid (99 mg, 61% yield, 98% pure, TFA salt). UPLC-MS $[M+3H]^{3+}$ = 845.7, R_t = 13.59 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (s, 6H), 8.31-8.24 (s, 5H), 7.97 (s, 1H), 7.28 (s, 2H), 6.95 (s, 4H), 6.84 (s, 2H), 5.65 (s, 4H), 5.52-5.42 (m, 12H), 5.26-5.13 (m, 24H) 3.86-3.33 (m, 64H). ^{13}C NMR (101 MHz, D_2O): δ 170.2, 164.2 (q, J = 30 Hz), 153.5, 153.4, 153.3, 145.8, 145.4, 145.0, 144.7, 139.9, 137.5, 133.8, 131.7, 130.2, 127.7, 127.4, 127.2, 118.0 (q, J = 293 Hz), 109.6, 109.5, 108.6, 71.1, 71.0, 70.7, 70.4, 66.7, 66.6, 63.5, 58.6, 58.5, 55.4, 55.2, 51.6, 42.4, 41.3. HRMS calcd for $C_{105}H_{160}N_{58}O_{19} \cdot 18C_2HF_3O_2$ $[M+3H]^{3+}$ 846.7852, found 846.7857.

Synthesis of the metal-loaded dendron 15

Synthesis of 14

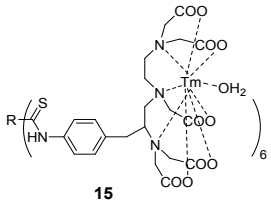


14

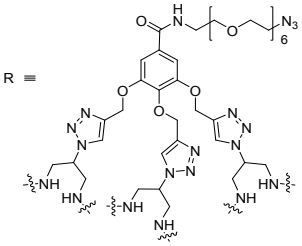


To a solution of **6** (40 mg, 24.30 µmol) in anhydrous DMF (Volume: 8 mL) was added Et_3N (0.34 mL, 2.43 mmol) and **13** (284 mg, 0.44 mmol). The reaction mixture was stirred at RT for 24 h, concentrated *in-vacuo* and an aq. $NaHCO_3/Na_2CO_3$ solution (pH = 9.1) was added to reach a final pH of 7. The product was purified by SEC, desalted and lyophilized to afford **14** as a white solid (57 mg, 53% yield, 95% pure). ^1H NMR (400 MHz, D_2O): δ 8.29 (s, 2H), 8.03 (s, 1H), 7.34-7.09 (m, 26H), 5.34-5.26 (m, 9H), 4.17-2.84 (m, 154H). HRMS calcd for $C_{171}H_{235}N_{43}O_{70}S_6$ $[M-3H]^{3-}$ 1399.8075, found 1399.8109.

Synthesis of 15



15



To as solution of compound **14** (40 mg, 9.51 µmol) in 8 mL of a citrate buffer (pH = 6.2) was slowly added a solution of $TmCl_3 \bullet H_2O$ (88 mg, 0.23 mmol) in H_2O (4 mL). The reaction mixture was stirred at RT for 12 h. The product was desalted and lyophilized to afford **15** as a white solid (49 mg, 84% yield, 95% pure). ICP-MS showed that **15** contains 5.8 Tm ions indicating full metal complexation.

Synthesis of the antibody-dendron conjugate Ab-15

Synthesis of DBCO-modified RPA-T4

A solution of DBCO-PEG4-NHS ester in DMSO (10 mg/mL, 1.95 µL) was added to a solution of RPA-T4 in PBS (1 mg/mL, 500 µL). 50 µL of aq. $NaHCO_3$ 1M solution was added to the solution containing RPA-T4. The solution was incubated at 37 °C for 4 h. Excess of DBCO-PEG4-NHS ester was removed by ultrafiltration (4 times, molecular weight cutoff: 50 kDa). The DBCO-antibody ratio of 5.3:1 was determined by UV-Vis.

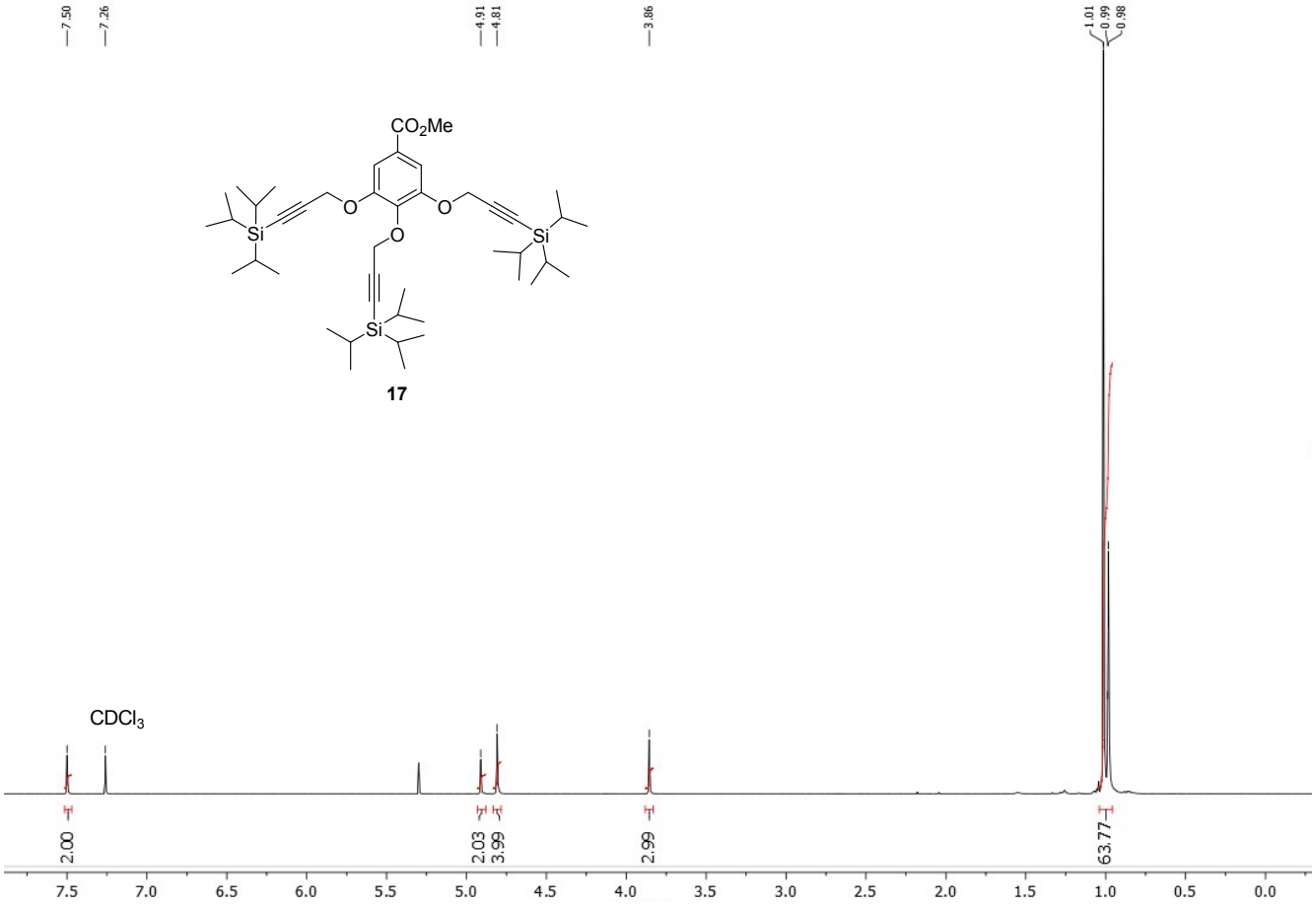
Synthesis of Ab-15

To a solution of DBCO-modified RPA-T4 in PBS (250 µL, 0.0015 µmol), 40 equivalents of the dendron **15** dissolved in PBS (1 mg/mL, 285 µL) were added. The solution was incubated at 37 °C for 4 h and at 4 °C for 44 h. Excess of **15** was removed by ultrafiltration (4 times, molecular weight cutoff: 50 kDa).

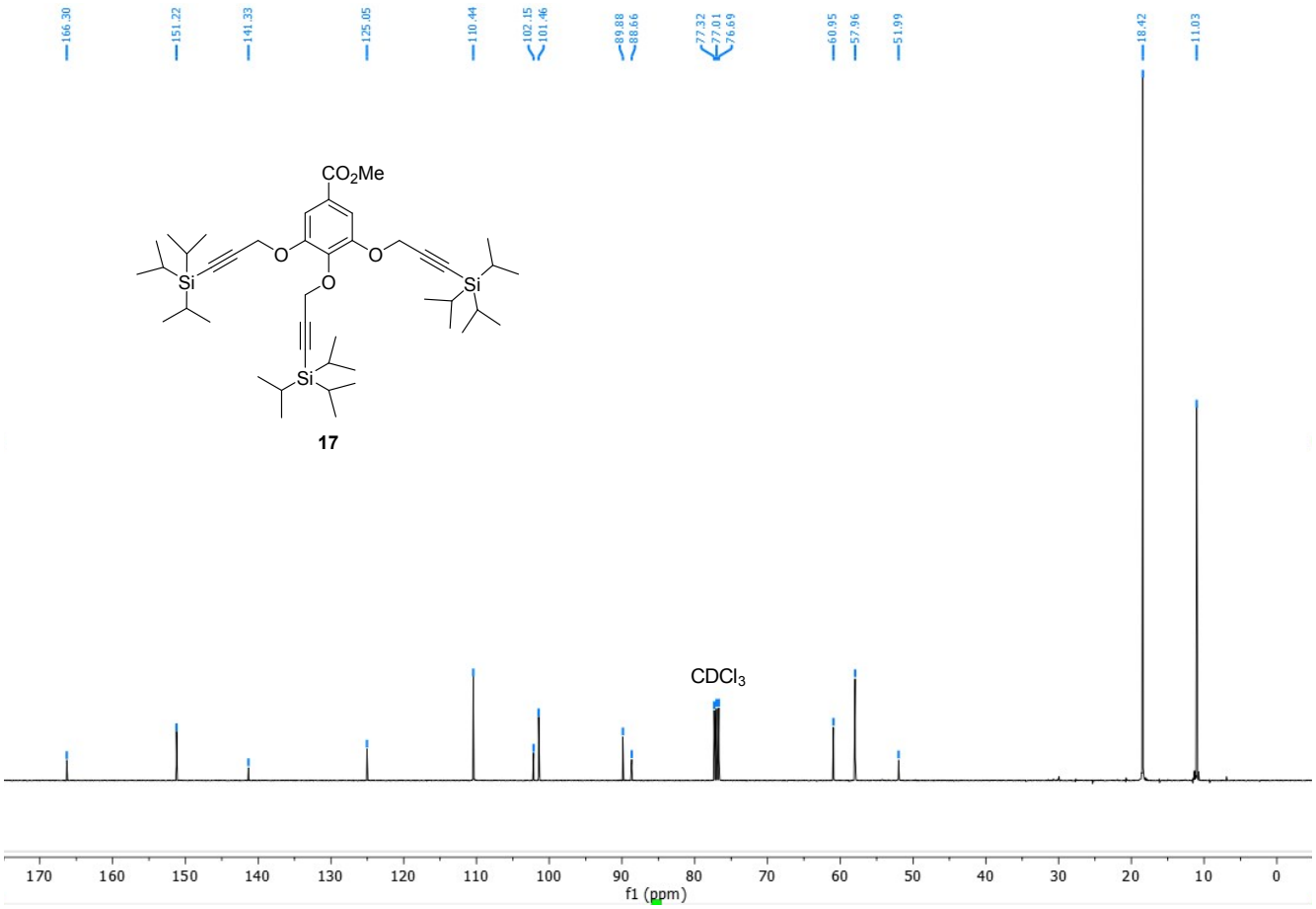
Synthesis of Ab-Tm

The bifunctional chelator **13** dissolved in aq. NaHCO3 1M (0.023 µmol, 10 mg/mL) was added to a solution of 100 µL of RPA-T4 in PBS (1 mg/mL). 10 µL of aq. $NaHCO_3$ 1M solution was added to the solution containing RPA-T4. The solution was incubated at 37 °C for 3 h. Excess of **15** was removed by ultrafiltration (4 times, molecular weight cutoff: 50 kDa). 0.2 µL of a freshly prepared 50 mM solution of $TmCl_3 \bullet H_2O$ in the MaxPar L-buffer (Fluidigm) was added to the solution of the **13**-modified antibody (90 µL, 0.44 mg/mL). The solution was incubated at 37 °C for 4 h. Excess of Tm ions were removed by desalting. ICP-MS showed that 2.3 Tm ions are bound to the antibody.

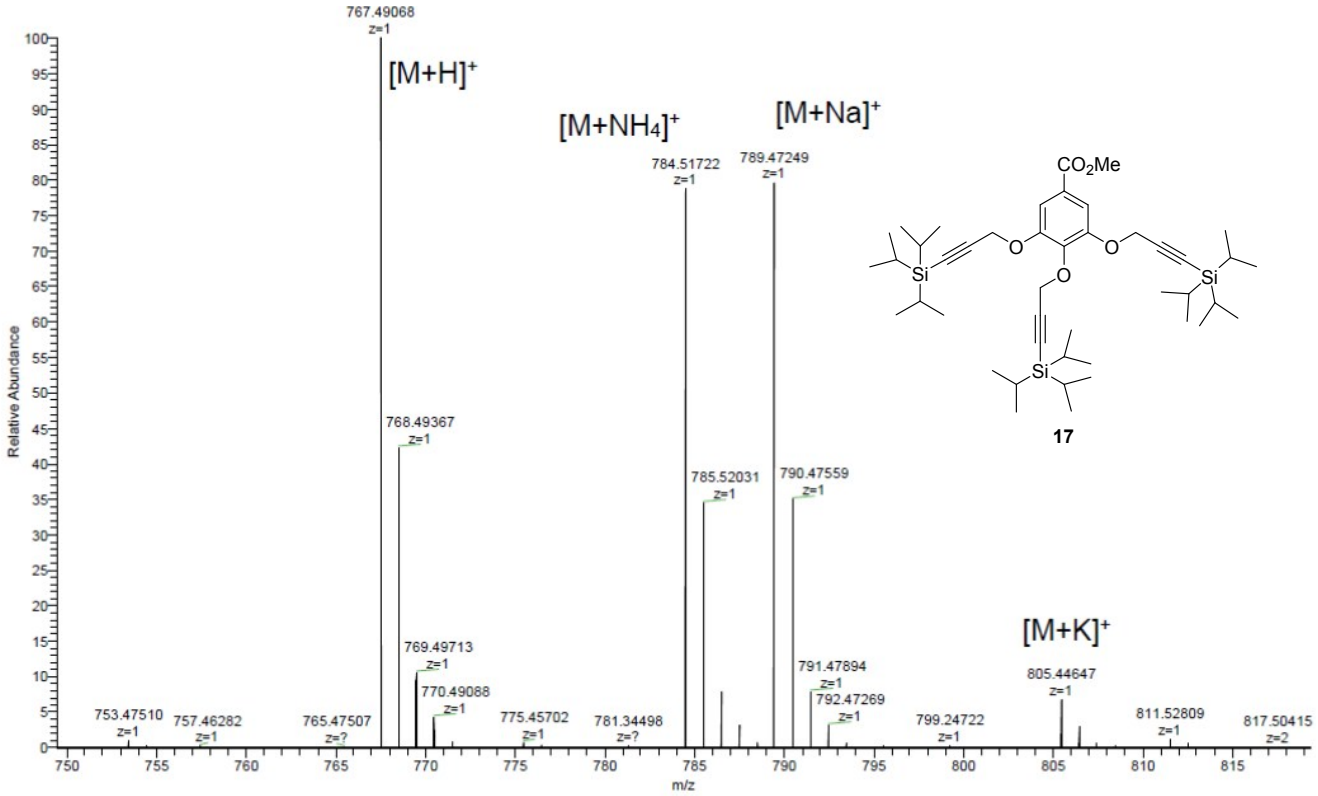
^{1}H, ^{13}C NMR and HRMS spectra



^{1}H NMR of **17** in $CDCl_3$. The peak falling at 5.3 belongs to residual DCM



^{13}C NMR of **17** in $CDCl_3$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[M+NH4]+
[M+Na]+
784.51722
z=1
789.47249
z=1
CO2Me
O
O
O
Si
Si
Si
17
768.49367
z=1
785.52031
z=1
790.47559
z=1
[M+K]+
769.49713
z=1
770.49088
z=1
791.47894
z=1
792.47269
z=1
805.44647
z=1
753.47510
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757.46282
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765.47507
z=?
775.45702
z=1
781.34498
z=?
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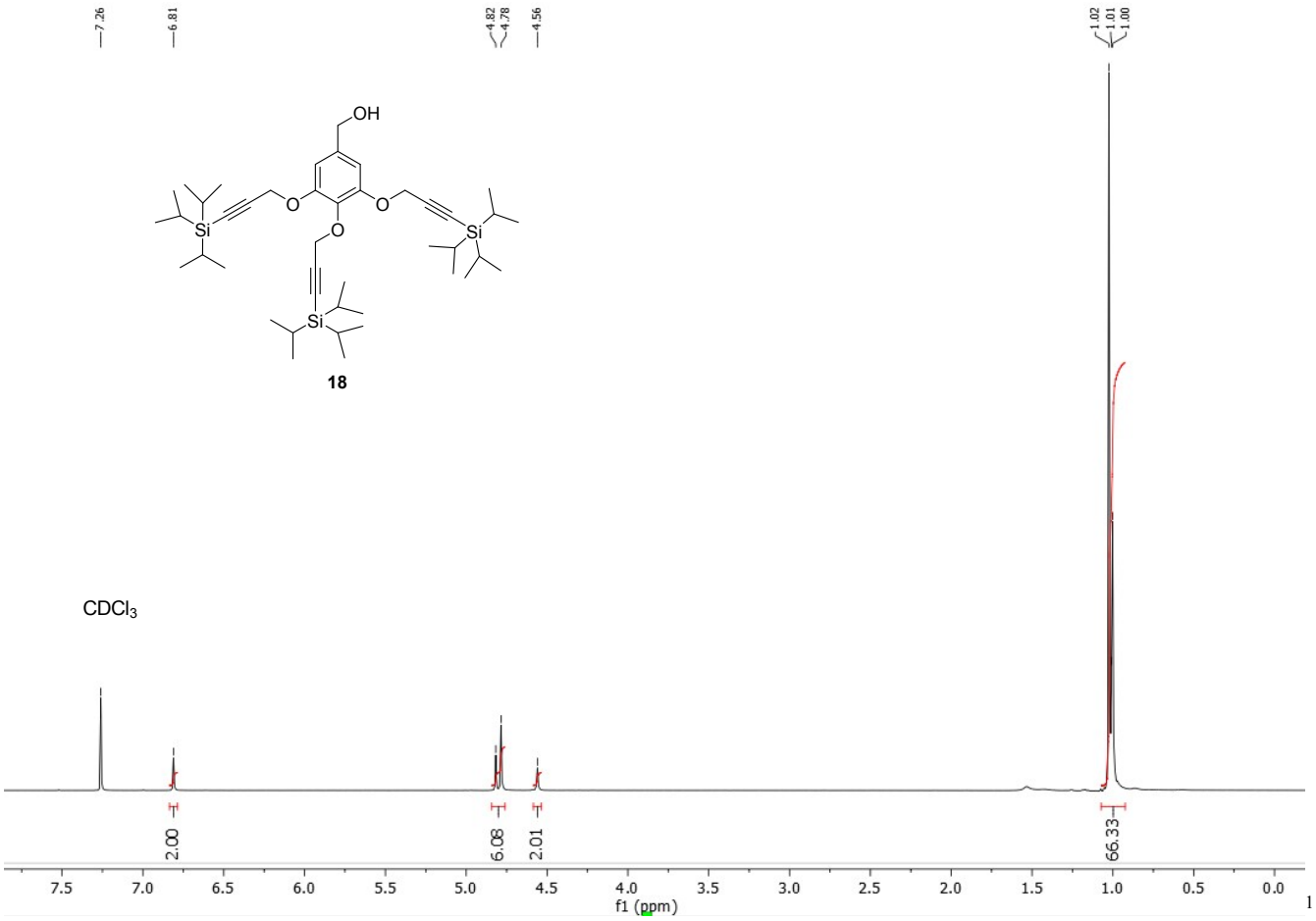
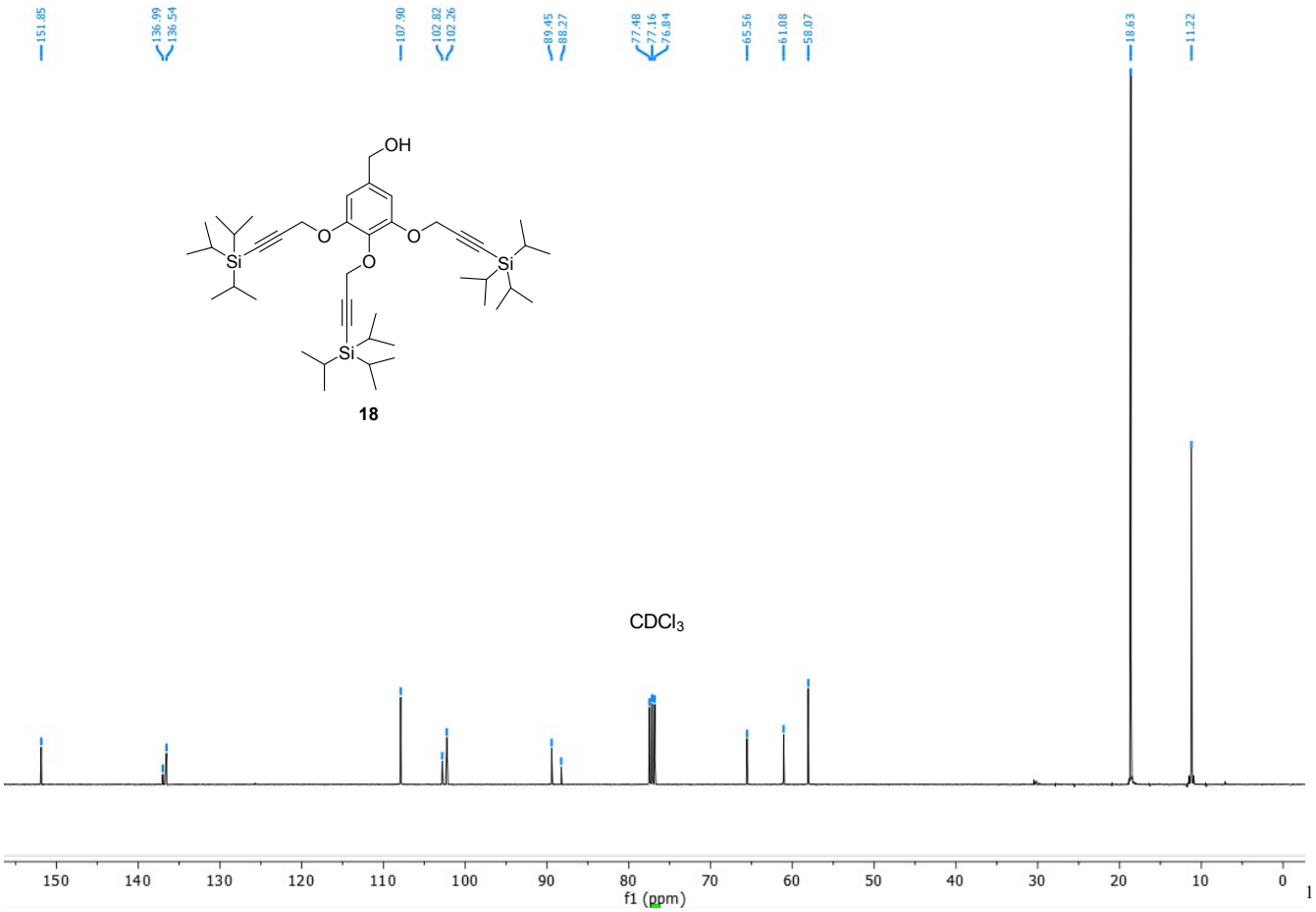
z=1
811.52809
z=1
817.50415
z=2
Relative Abundance
m/z

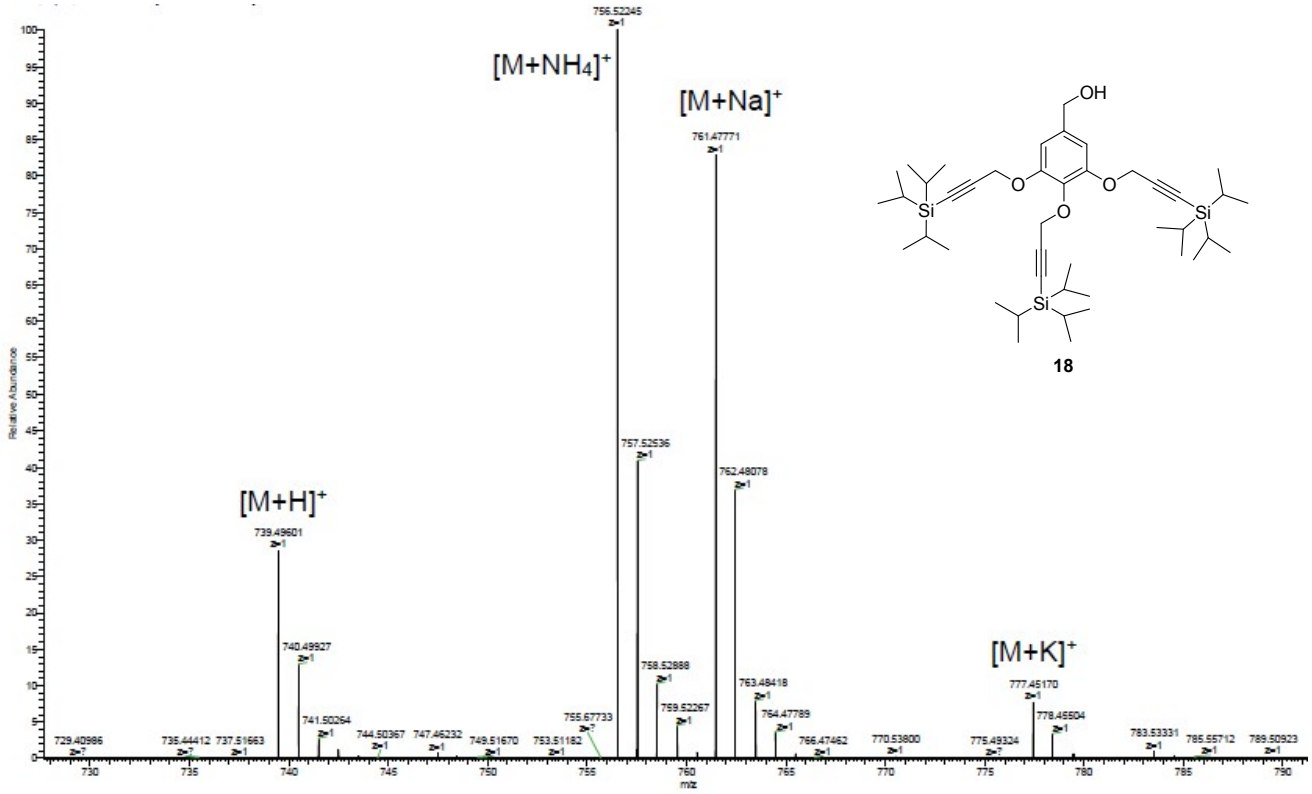
HRMS of **17**



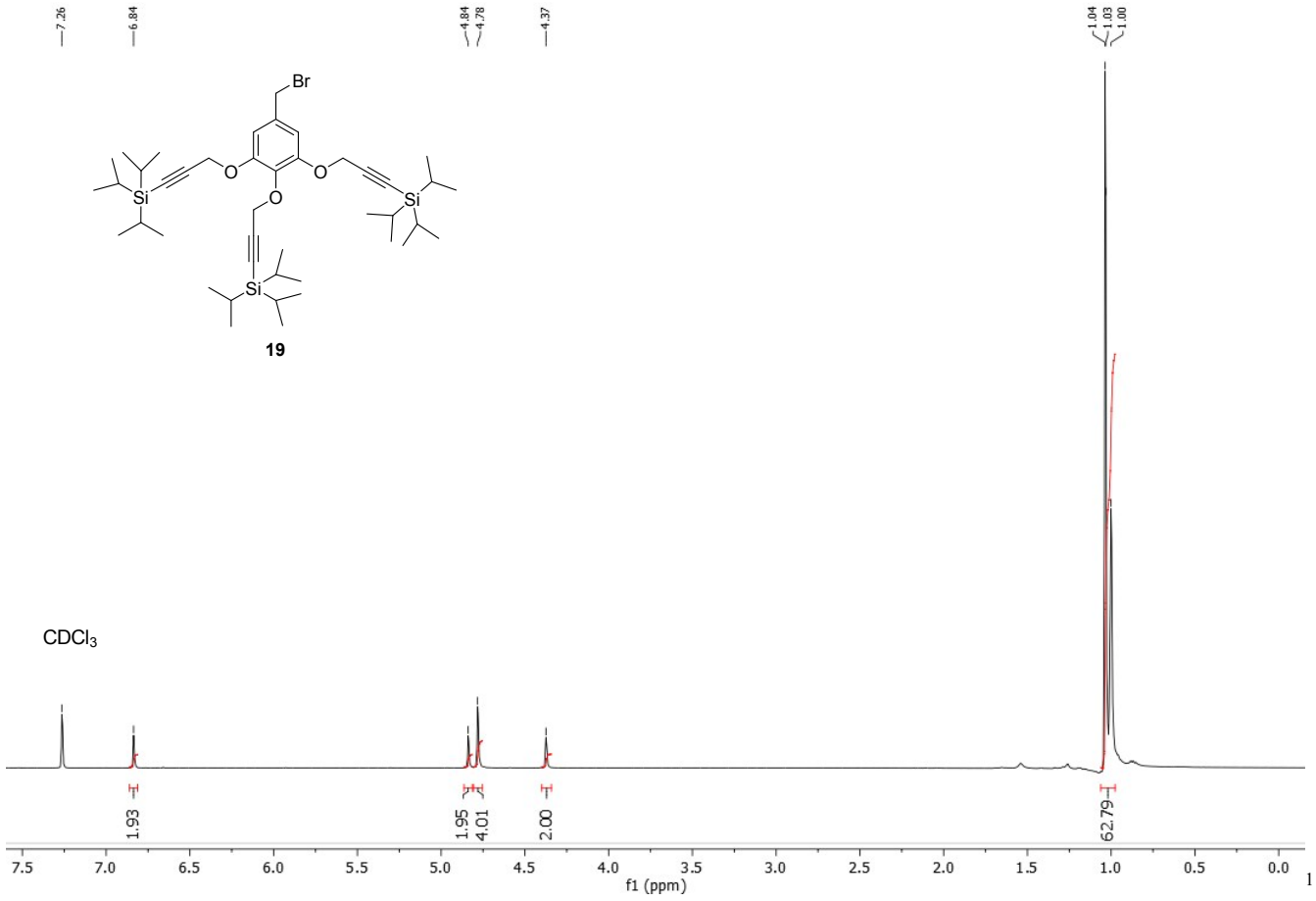
H NMR of **18** in $CDCl_3$



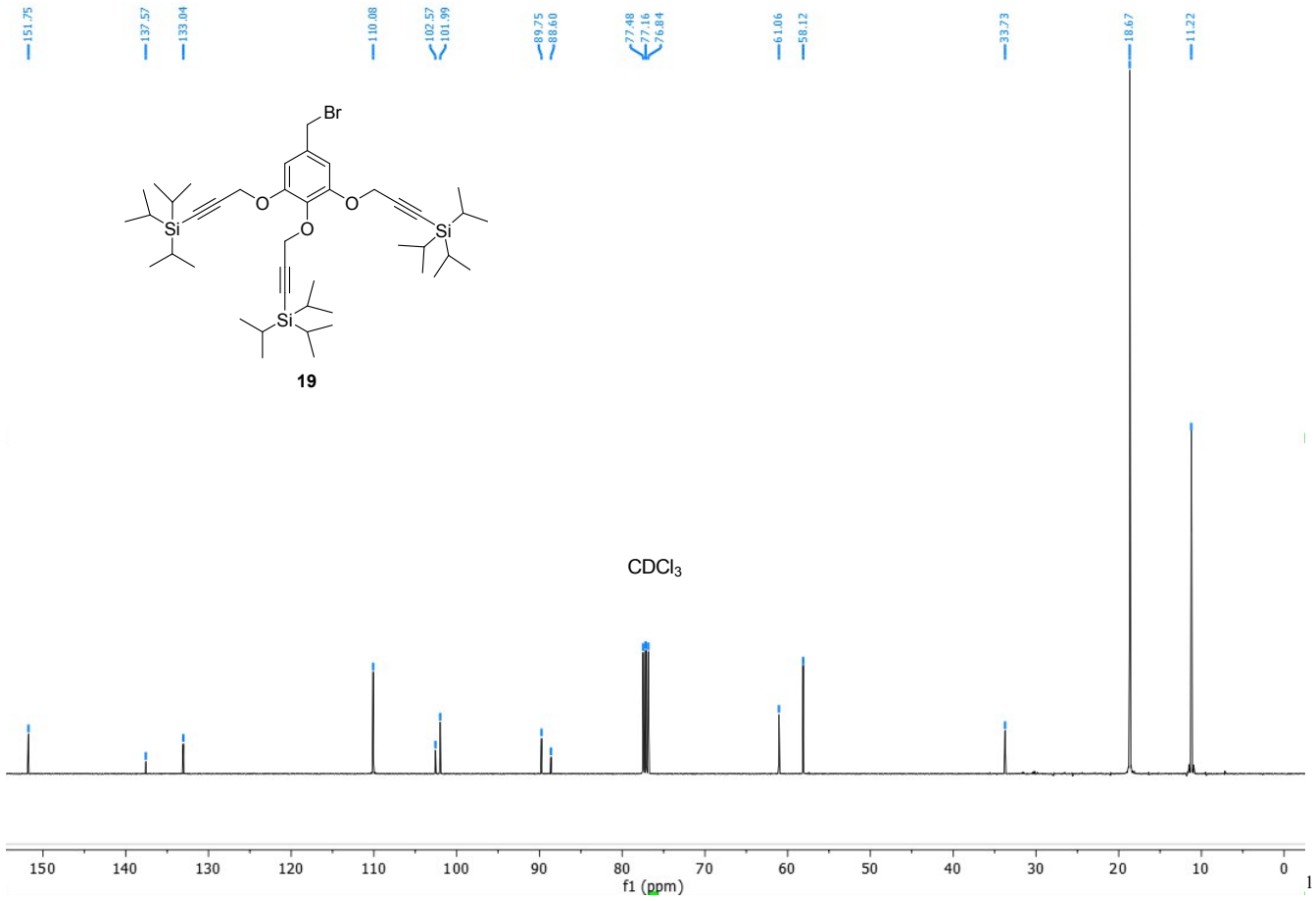
^{3}C NMR of **18** in $CDCl_3$



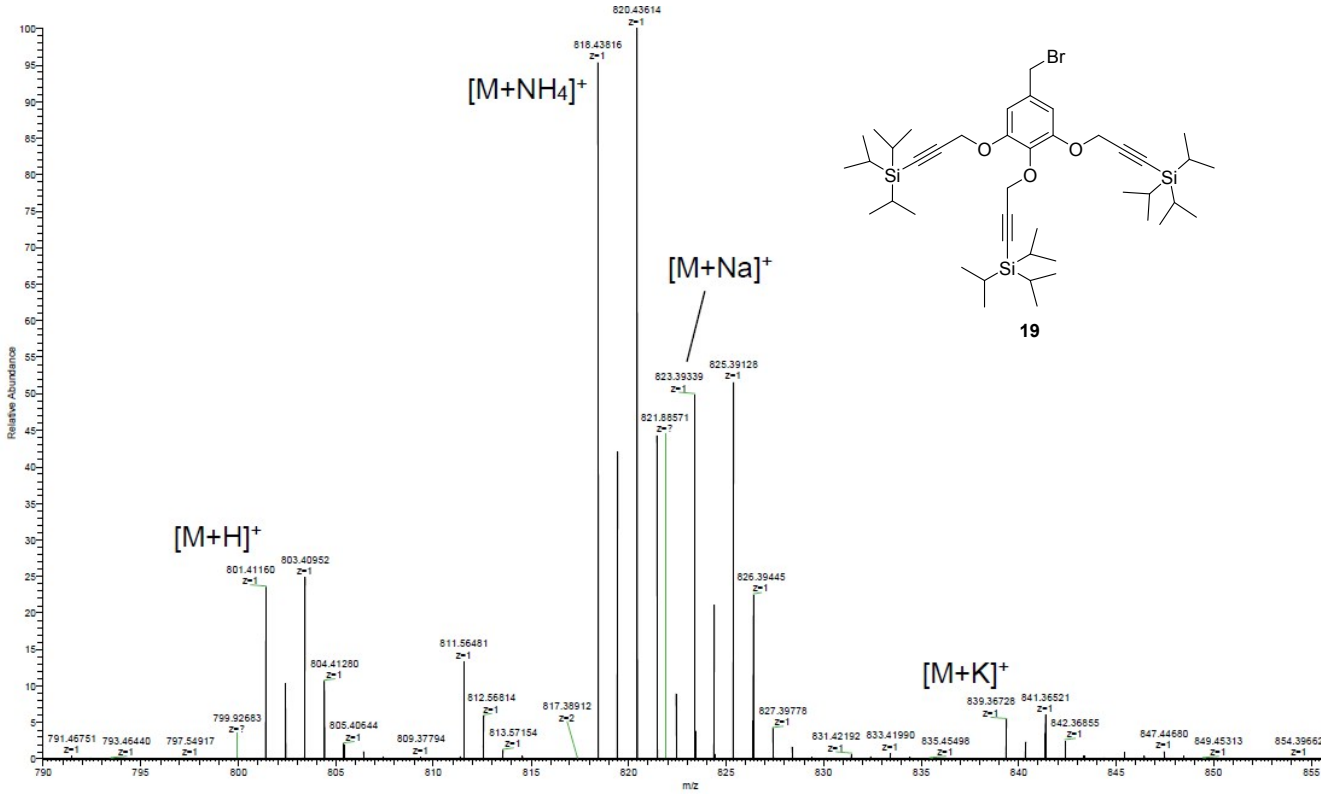
HRMS of **18**



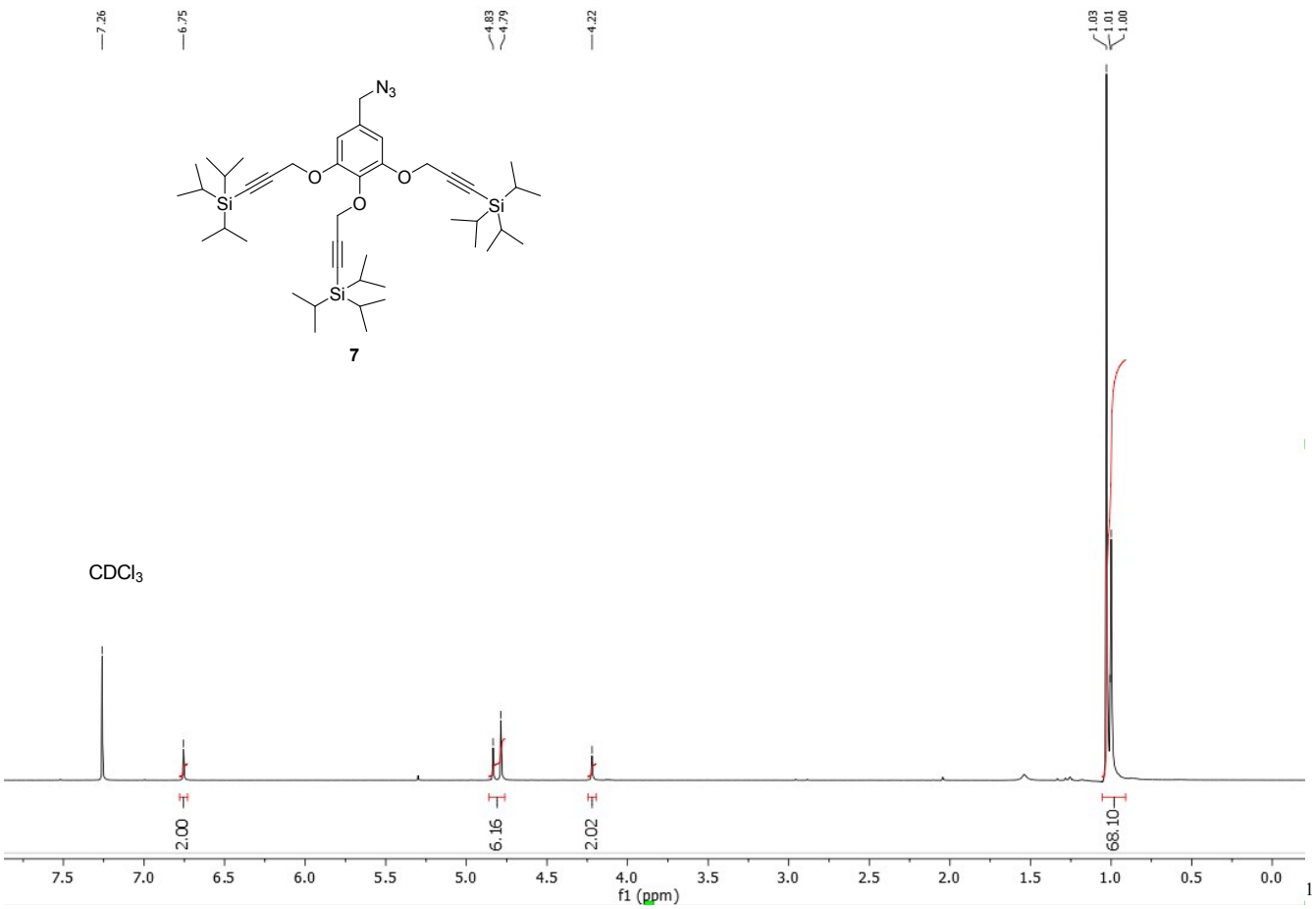
H NMR of **19** in $CDCl_3$



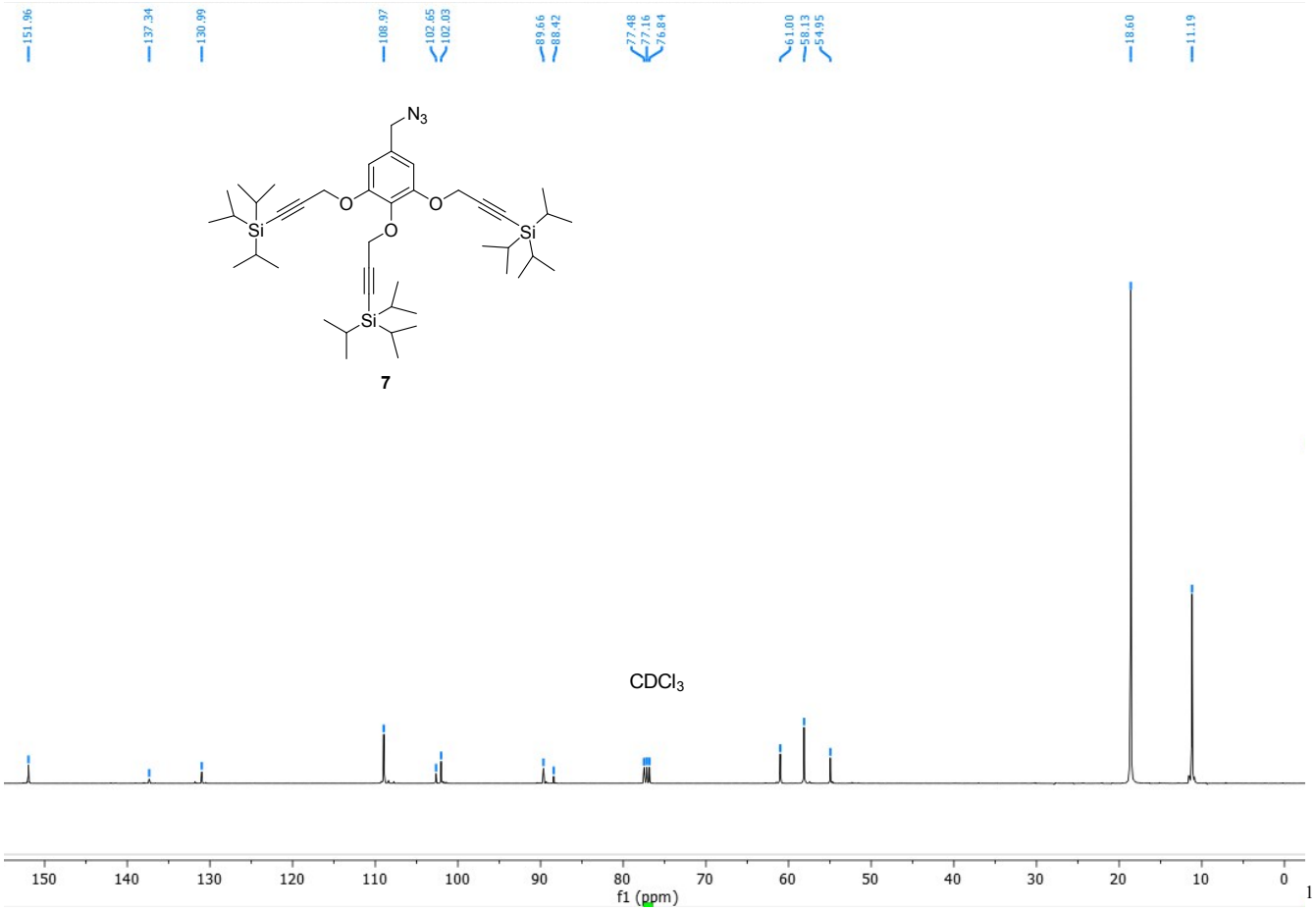
^{3}C NMR of **19** in $CDCl_3$



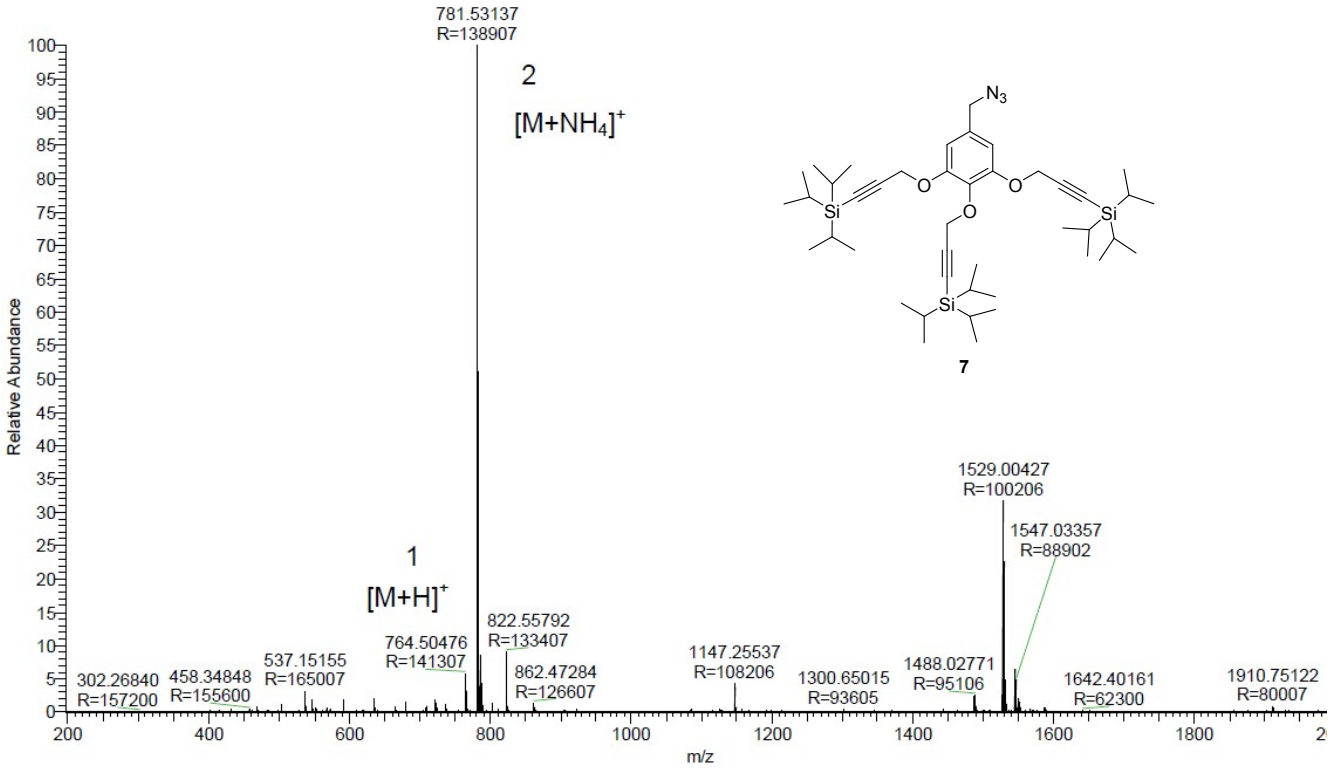
HRMS of **19**



H NMR of **7** in $CDCl_3$



^{3}C NMR of **7** in $CDCl_3$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2
[M+NH4]+
1
[M+H]+
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1547.03357
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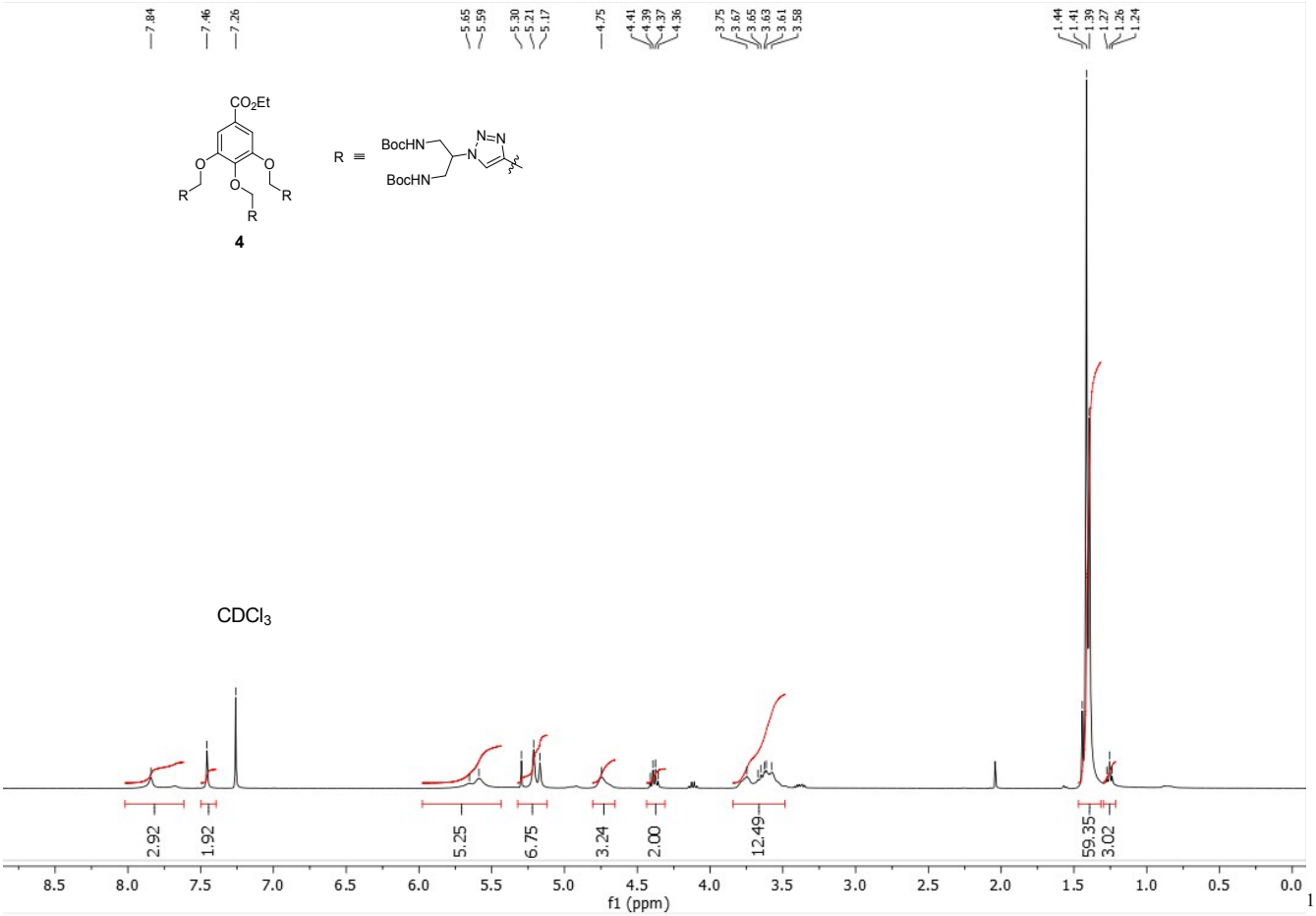
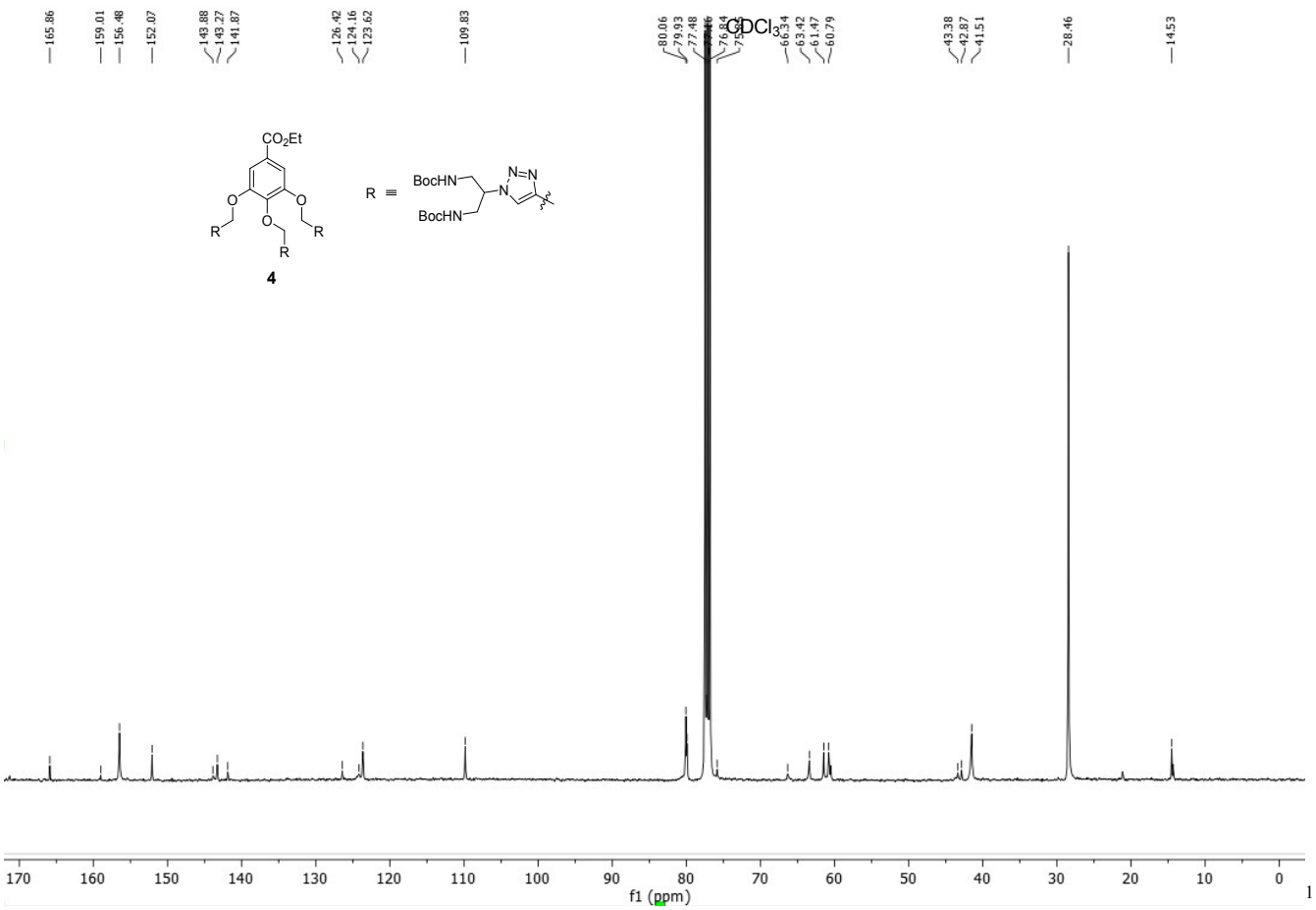
822.55792
R=133407
764.50476
R=141307
537.15155
R=165007
458.34848
R=155600
302.26840
R=157200
862.47284
R=126607
1147.25537
R=108206
1300.65015
R=93605
1488.02771
R=95106
1642.40161
R=62300
1910.75122
R=80007
Relative Abundance
m/z
N3
O
O
O
Si
Si
Si
7

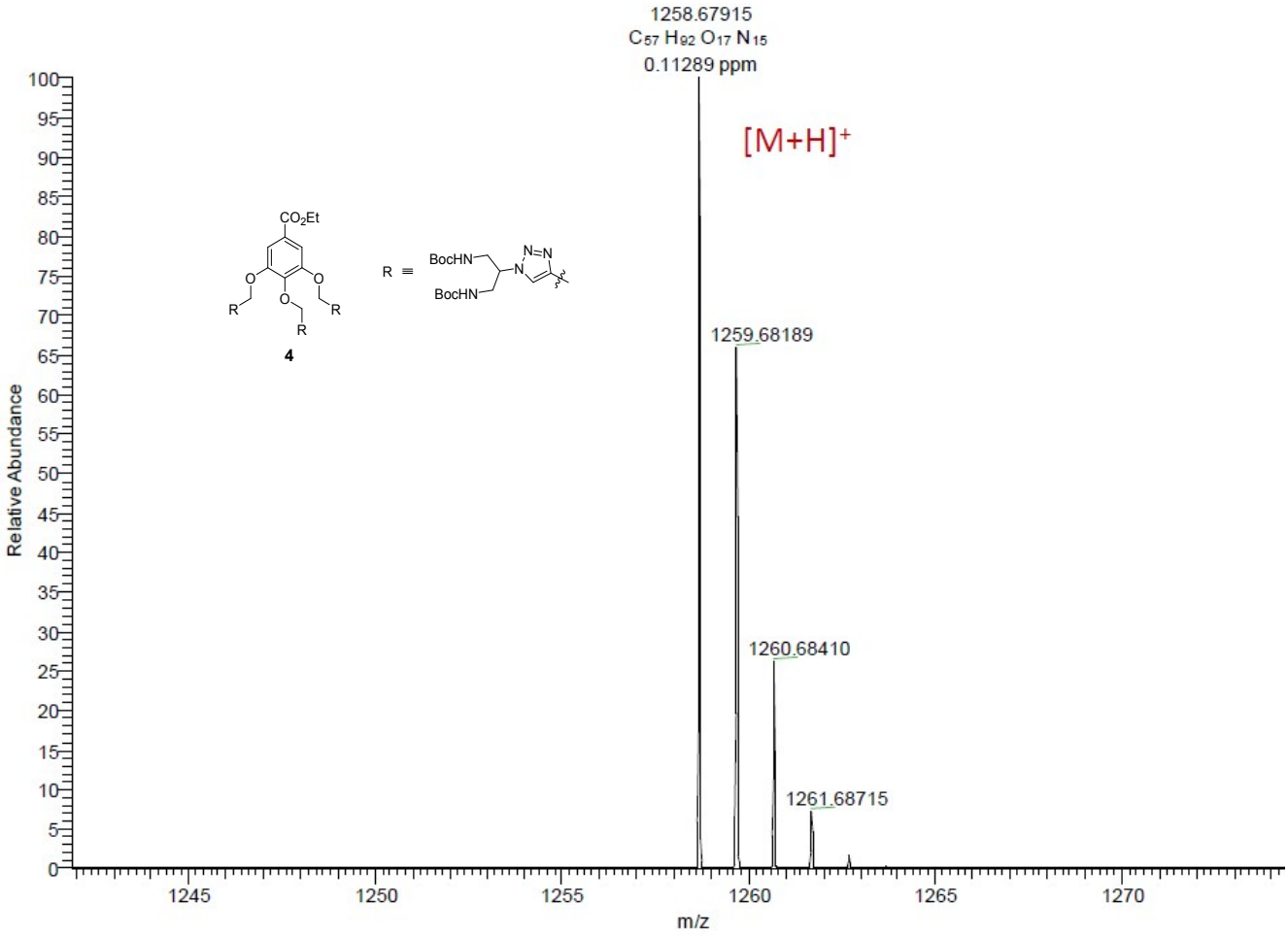
HRMS of **7**



H NMR of **4** in $CDCl_3$. The peaks falling at 4.1 and 2.0 belong to residual ethyl acetate



^{3}C NMR of **4** in $CDCl_3$


1258.67915
C57 H92 O17 N15
0.11289 ppm
[M+H]+
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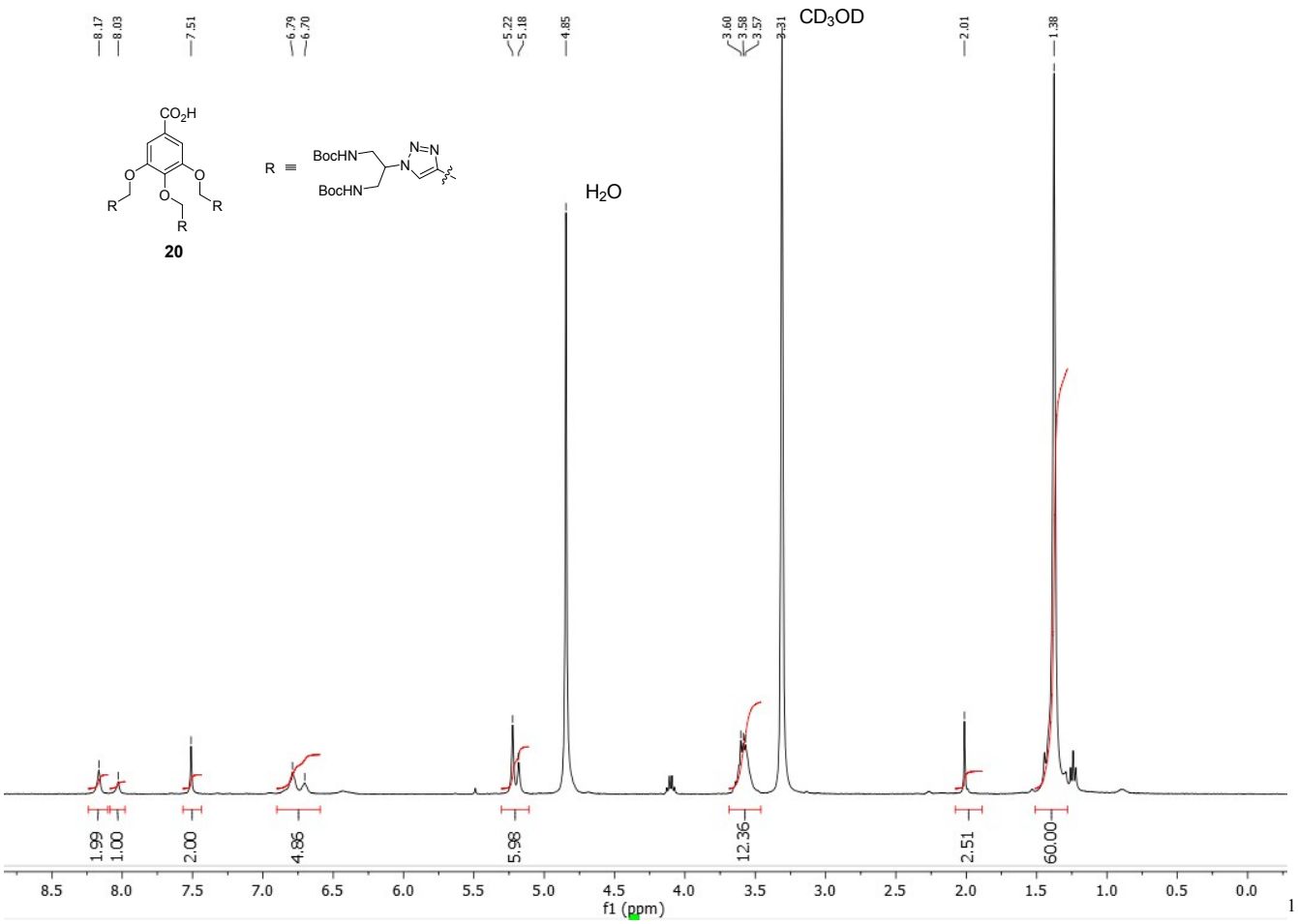
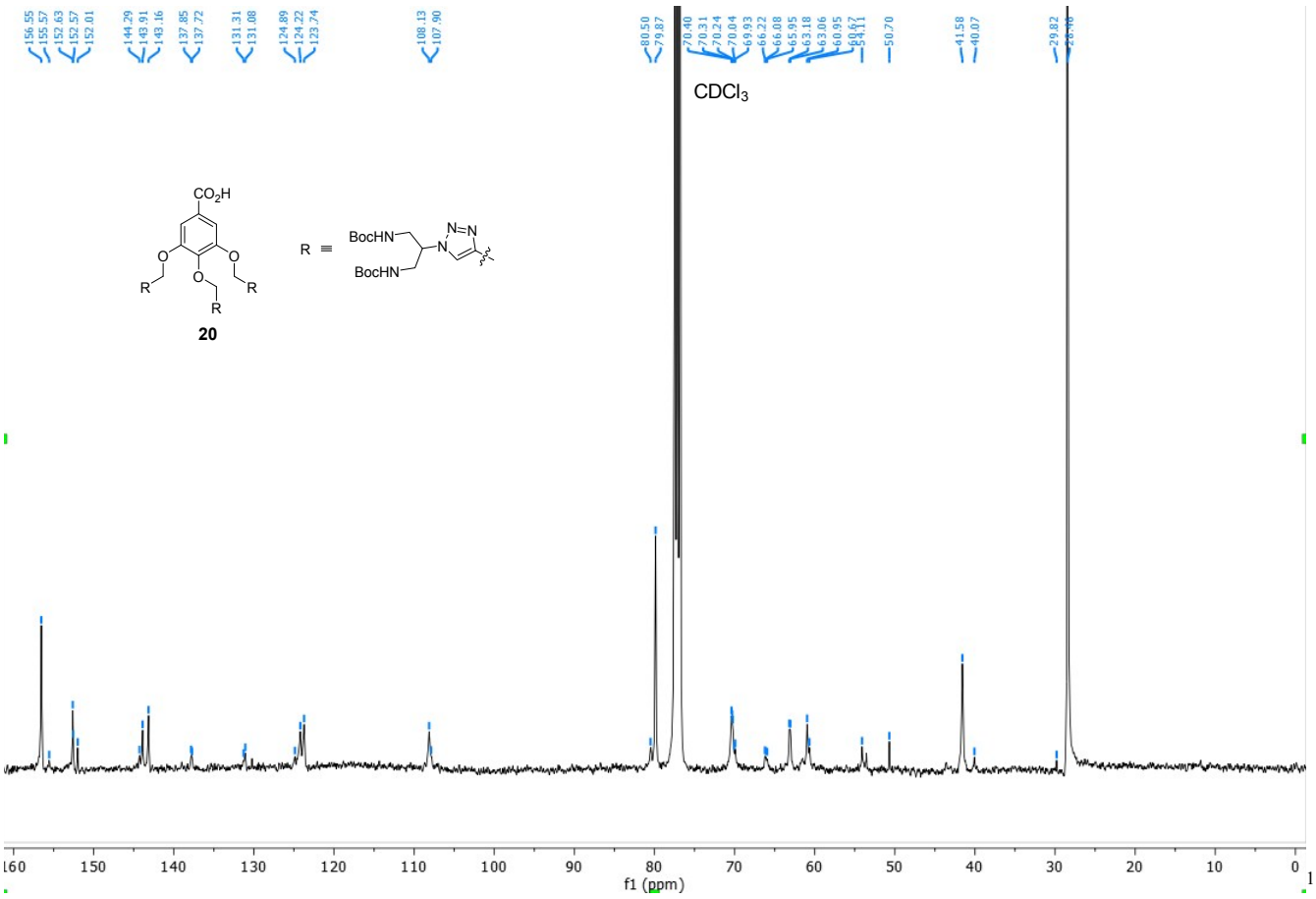
1260.68410
1261.68715
Relative Abundance
m/z
CO2Et
R ≡
BocHN
BocHN
4

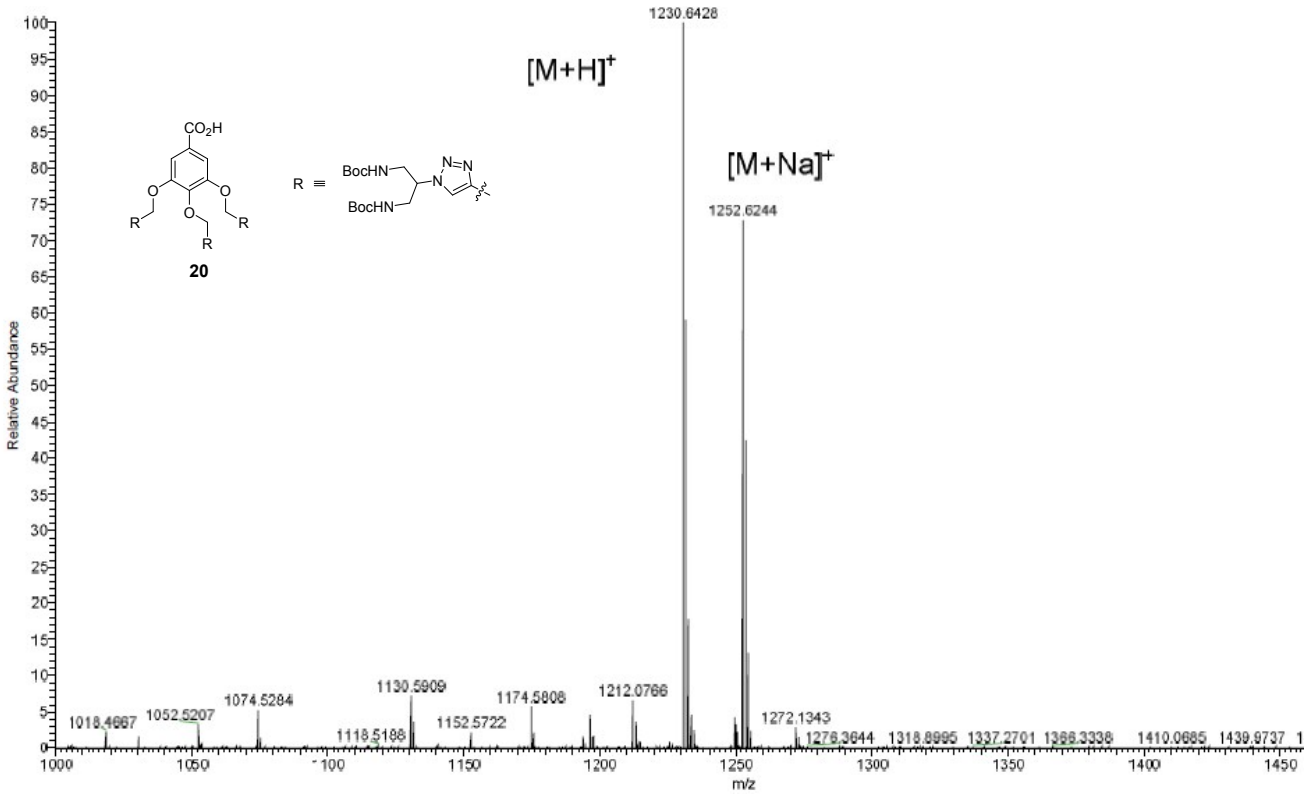
HRMS of **4**



H NMR of **20** in CD_3OD. The peaks falling at 4.1 and 1.2 belong to residual ethyl acetate



^{3}C NMR of **20** in $CDCl_3$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[M+Na]+
1252.6244
CO2H
R =
BocHN
BocHN
20
Relative Abundance
m/z
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1118.5188
1130.5909
1152.5722
1174.5808
1212.0766
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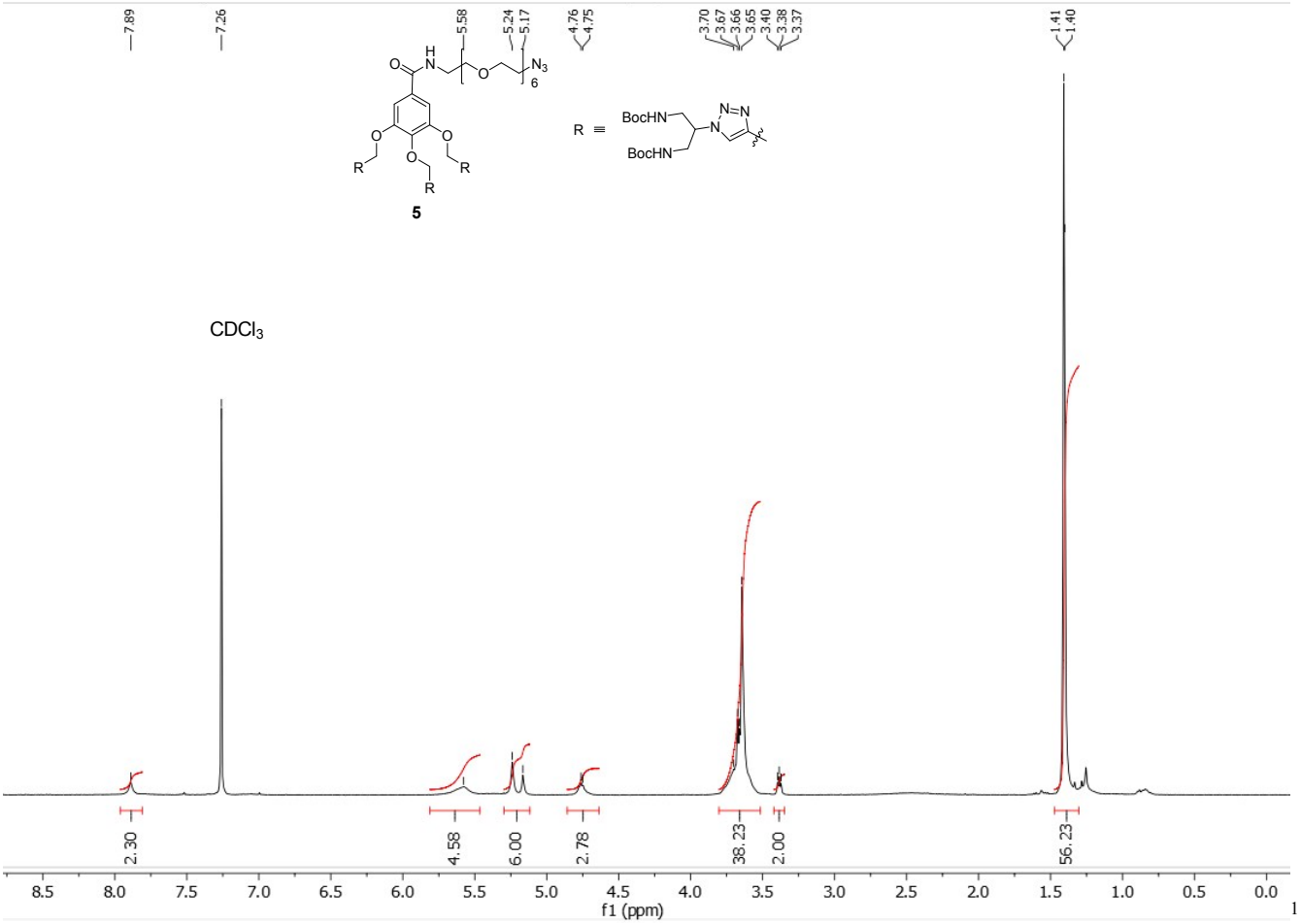
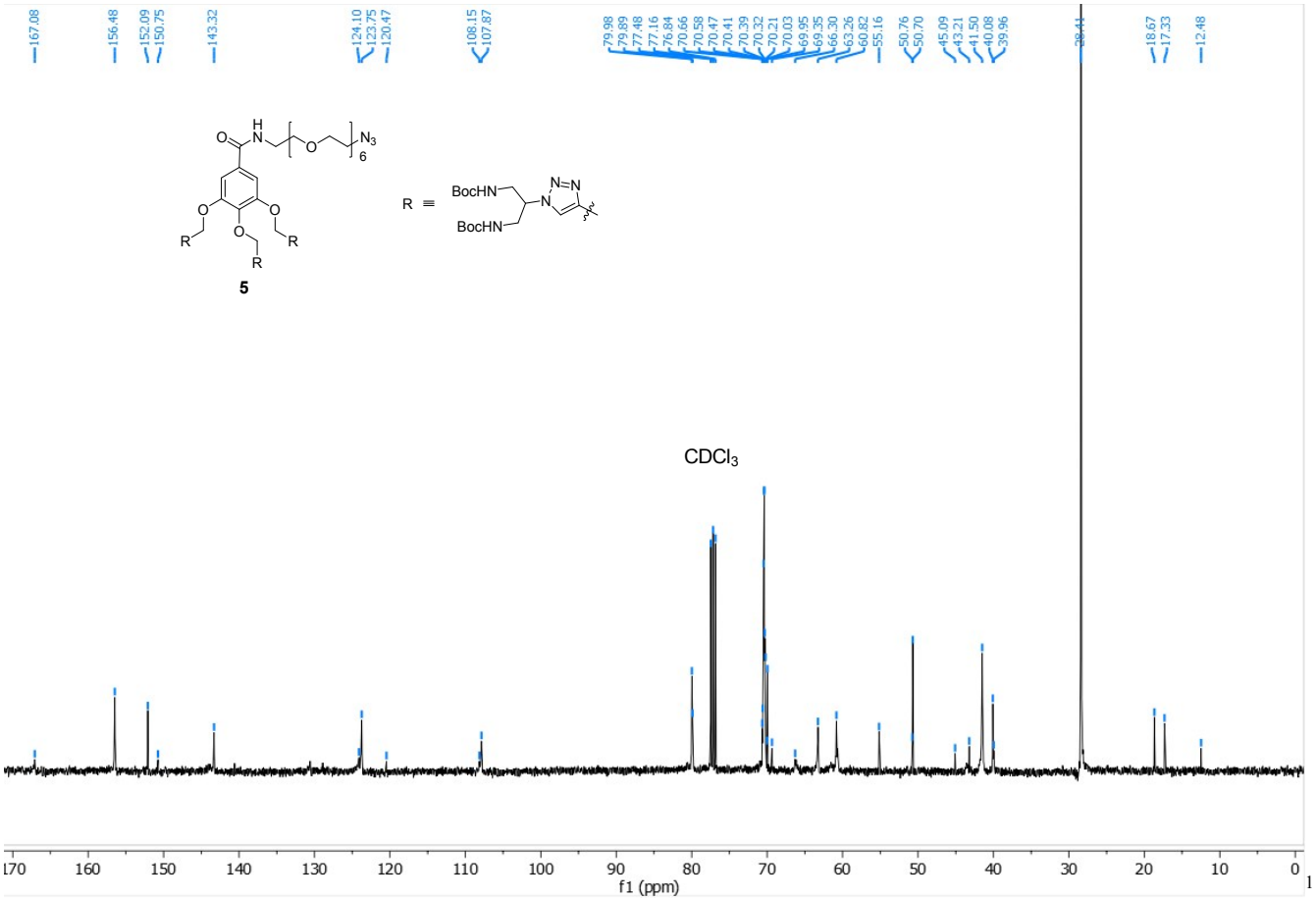
1388.3338
1410.0685
1439.9737

HRMS of **20**



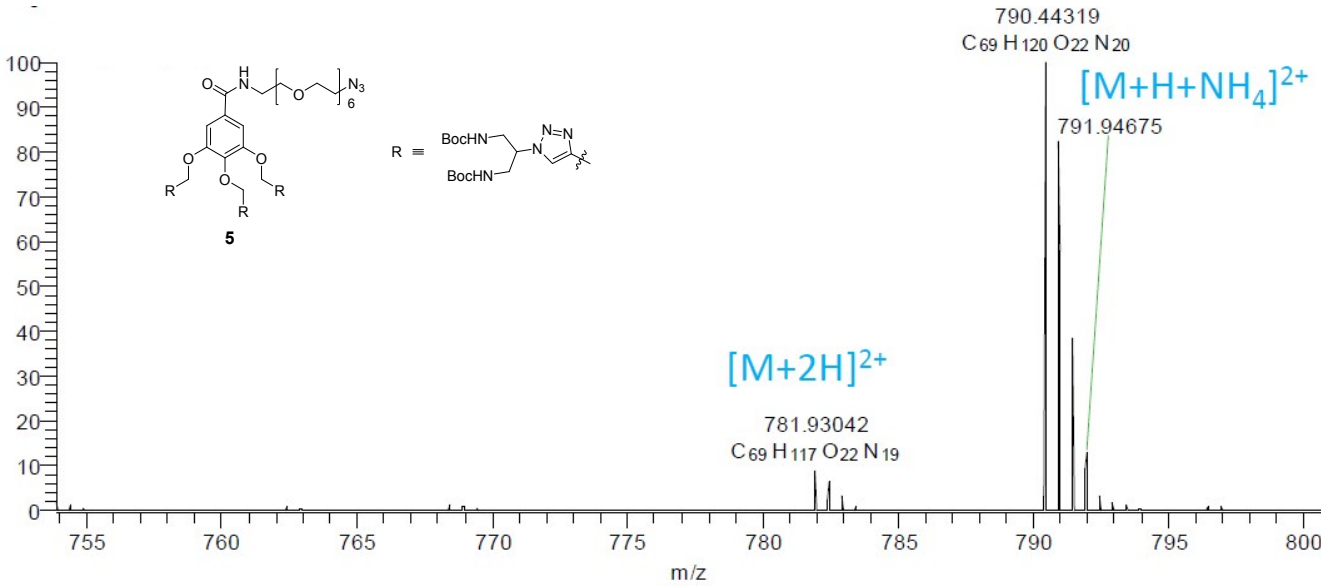
H NMR of **5** in $CDCl_3$



5

R ≡ BocHN, BocHN

^{3}C NMR of **5** in $CDCl_3$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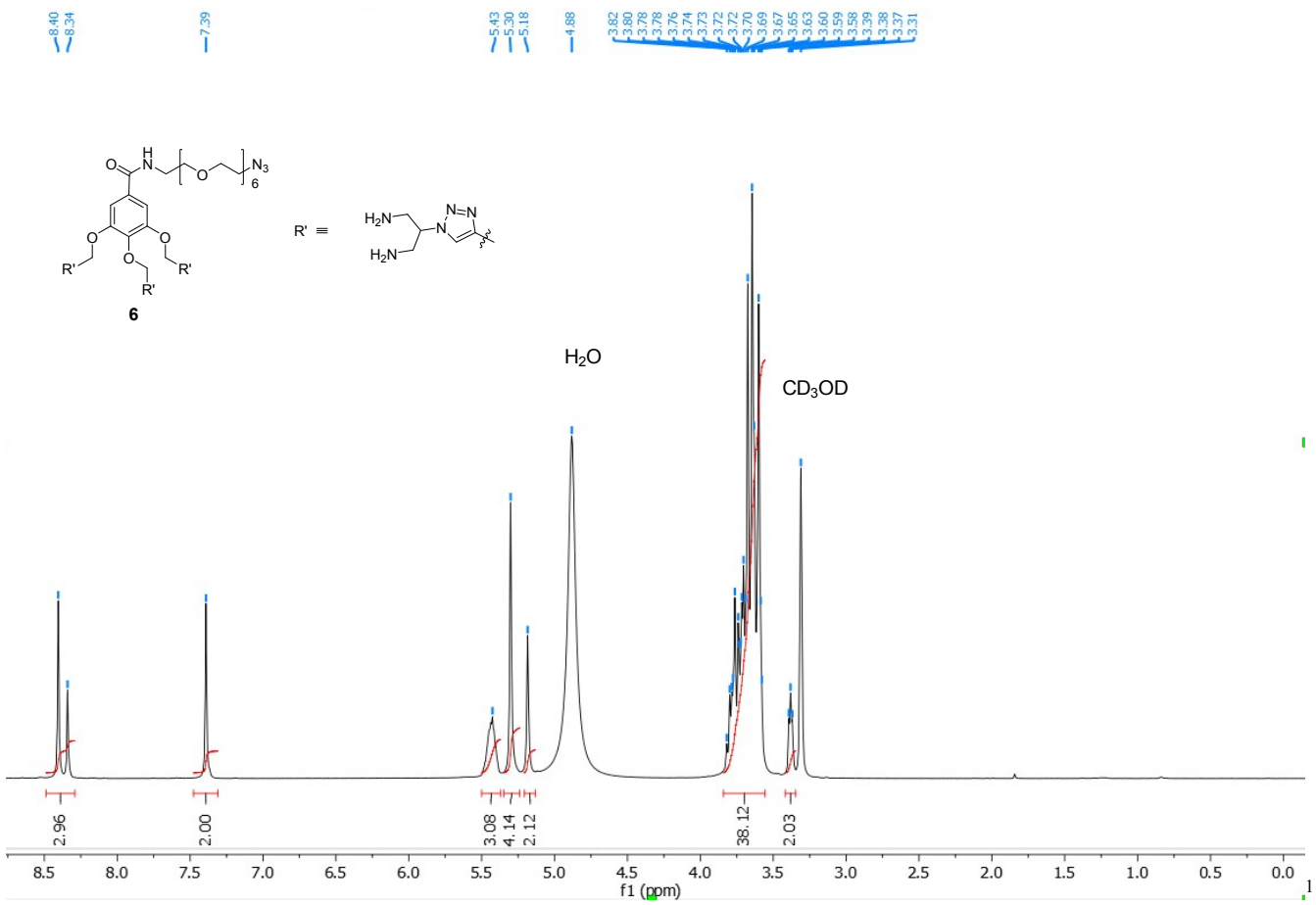
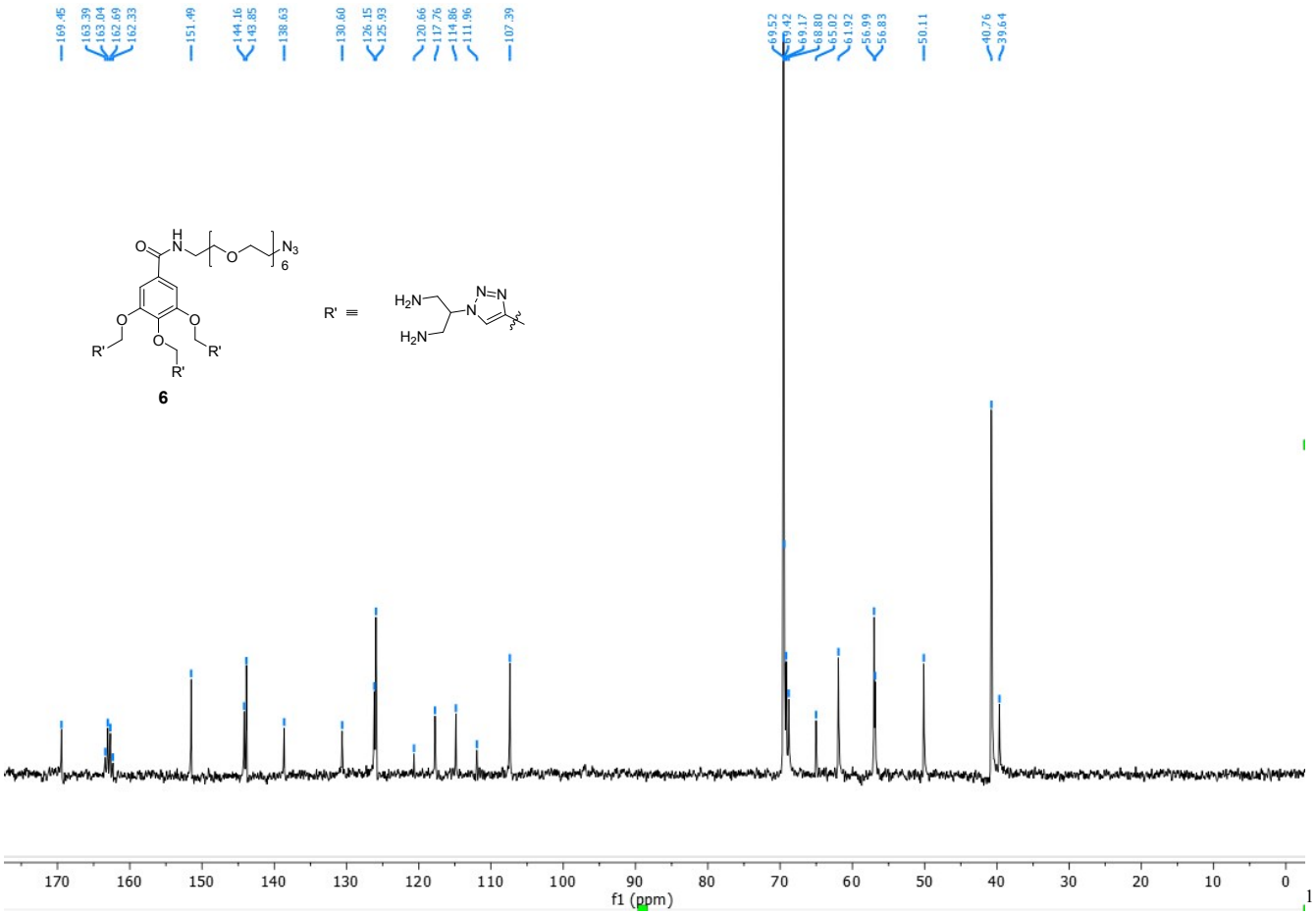
791.94675
[M+2H]2+
781.93042
C69 H117 O22 N19
5
R =
BocHN
BocHN
100
90
80
70
60
50
40
30
20
10
0
755
760
765
770
775
780
785
790
795
800
m/z

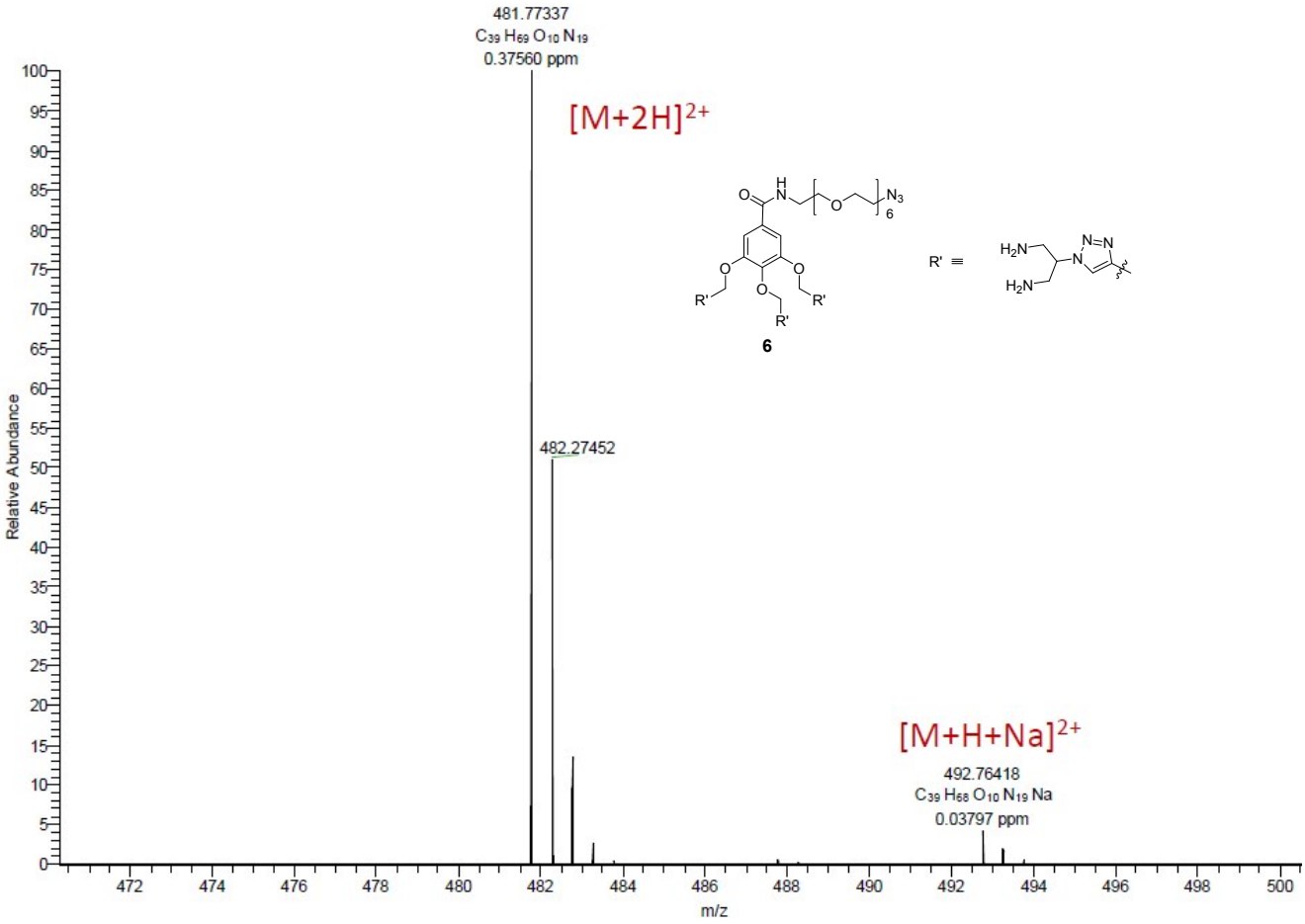
HRMS of **5**



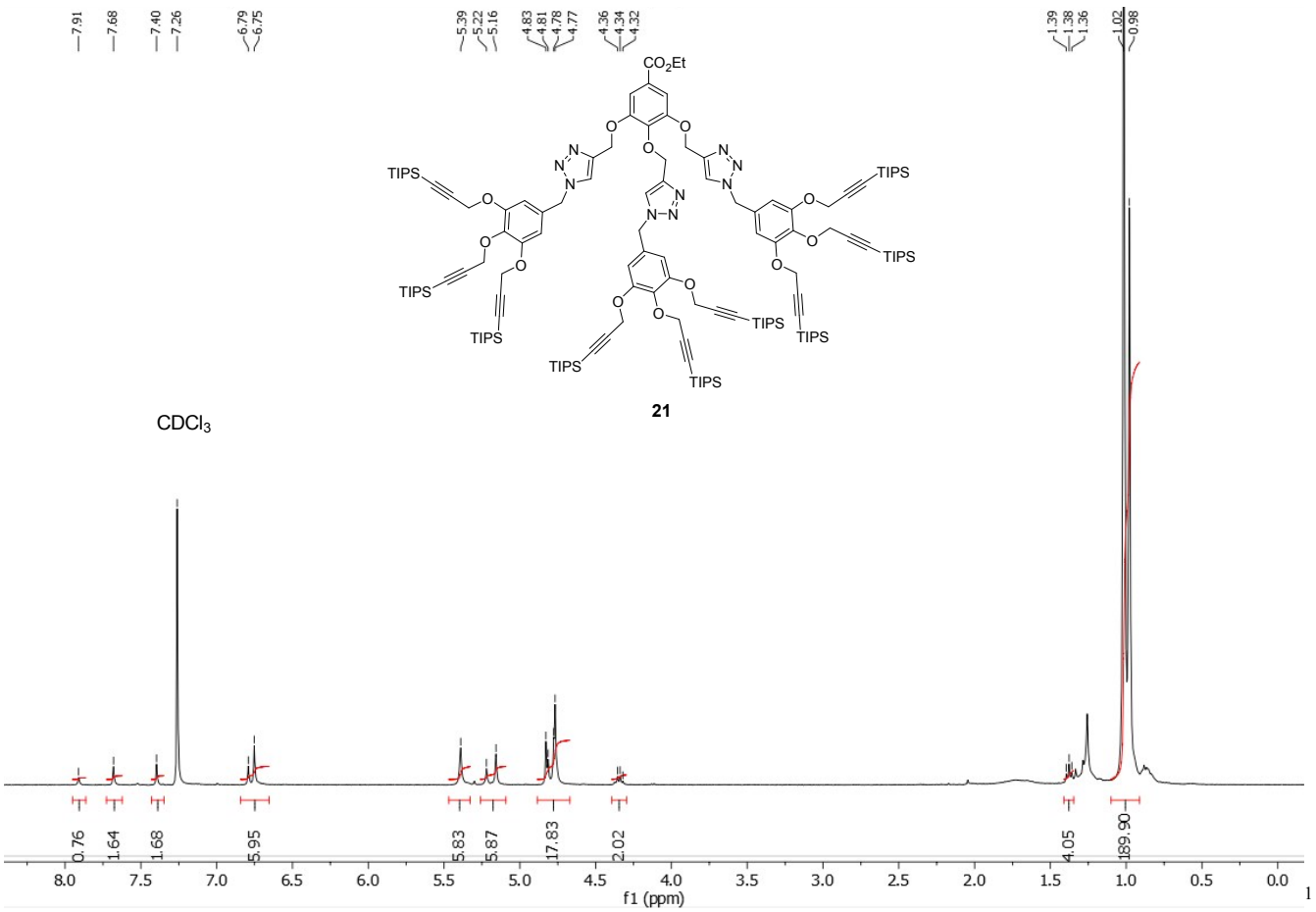
H NMR of **6** in CD_3OD



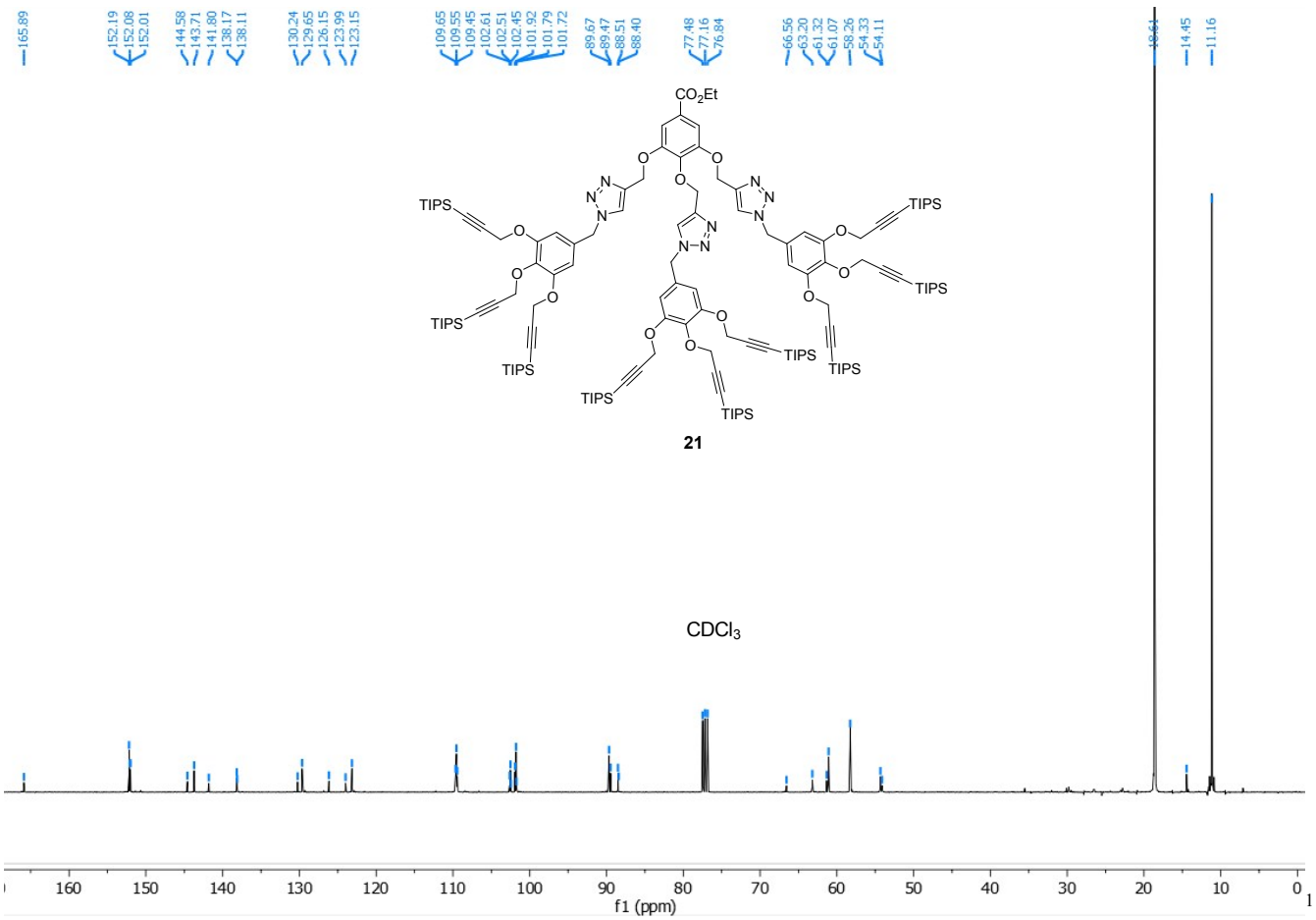
^{3}C NMR of **6** in D_2O


481.77337
C39 H69 O10 N19
0.37560 ppm
[M+2H]2+
482.27452
[M+H+Na]2+
492.76418
C39 H68 O10 N19 Na
0.03797 ppm
Relative Abundance
m/z
R' ≡
6

HRMS of **6**

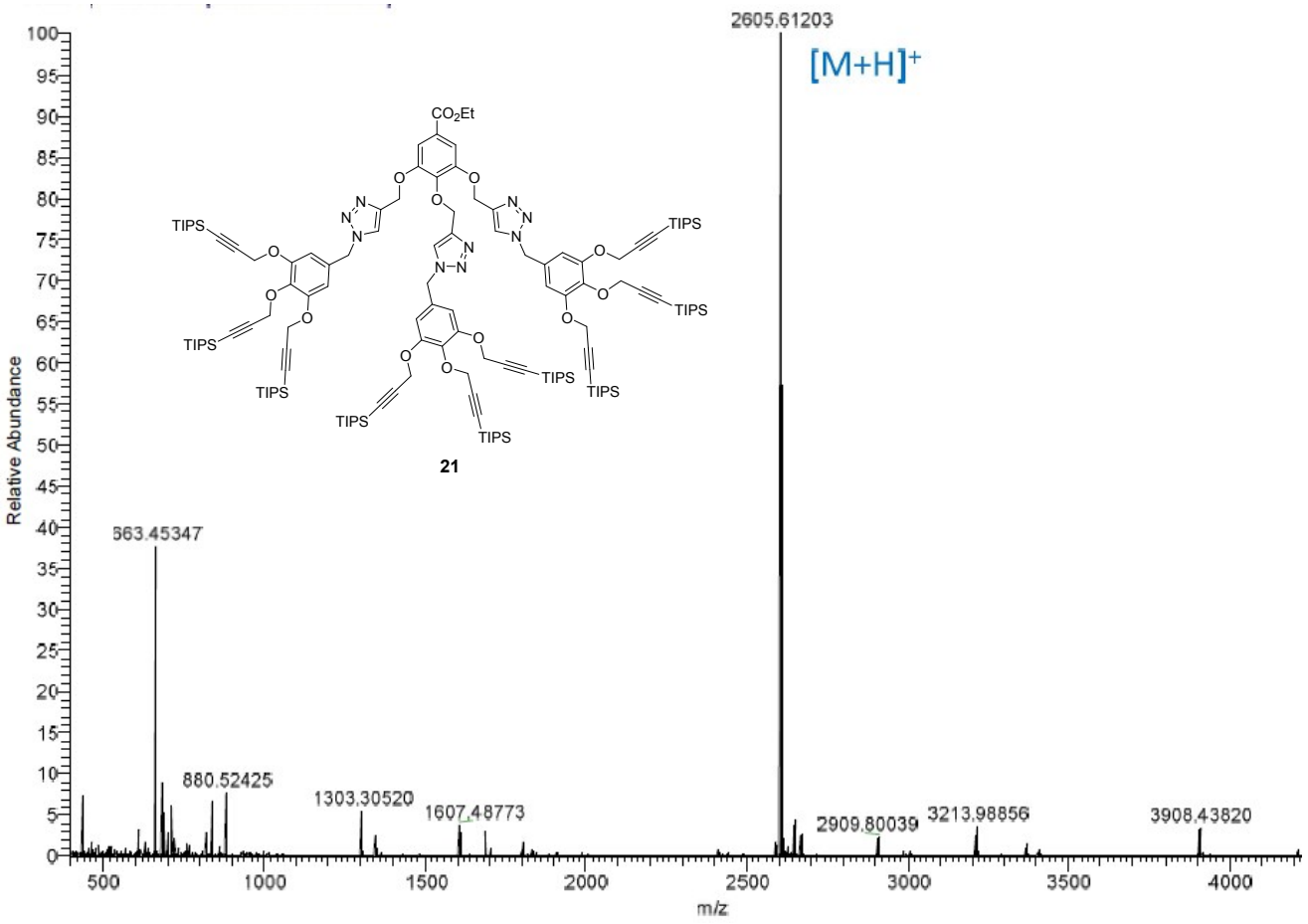


H NMR of **21** in $CDCl_3$. The peaks falling at 1.3 and 0.9 belong to residual heptane

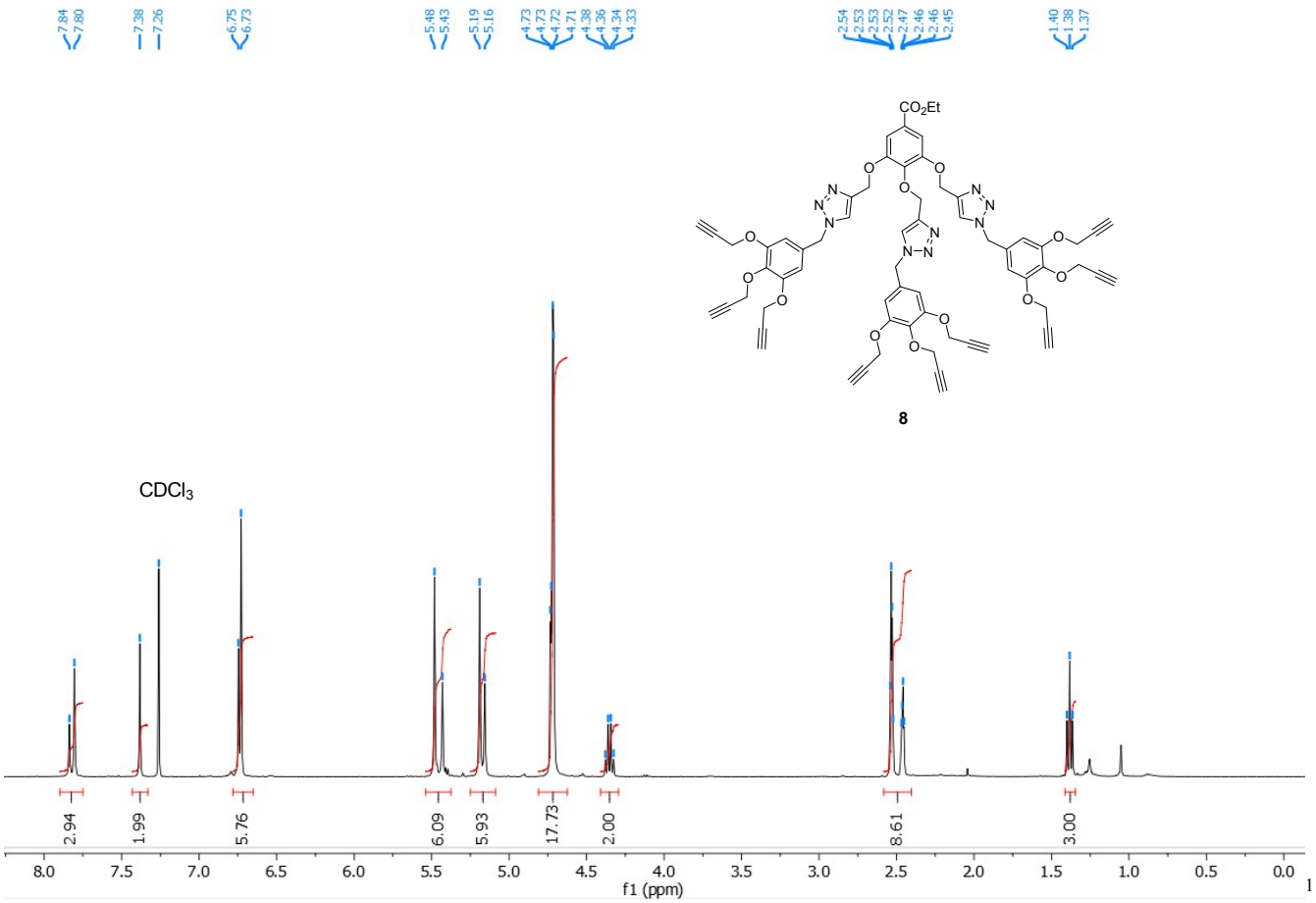


21

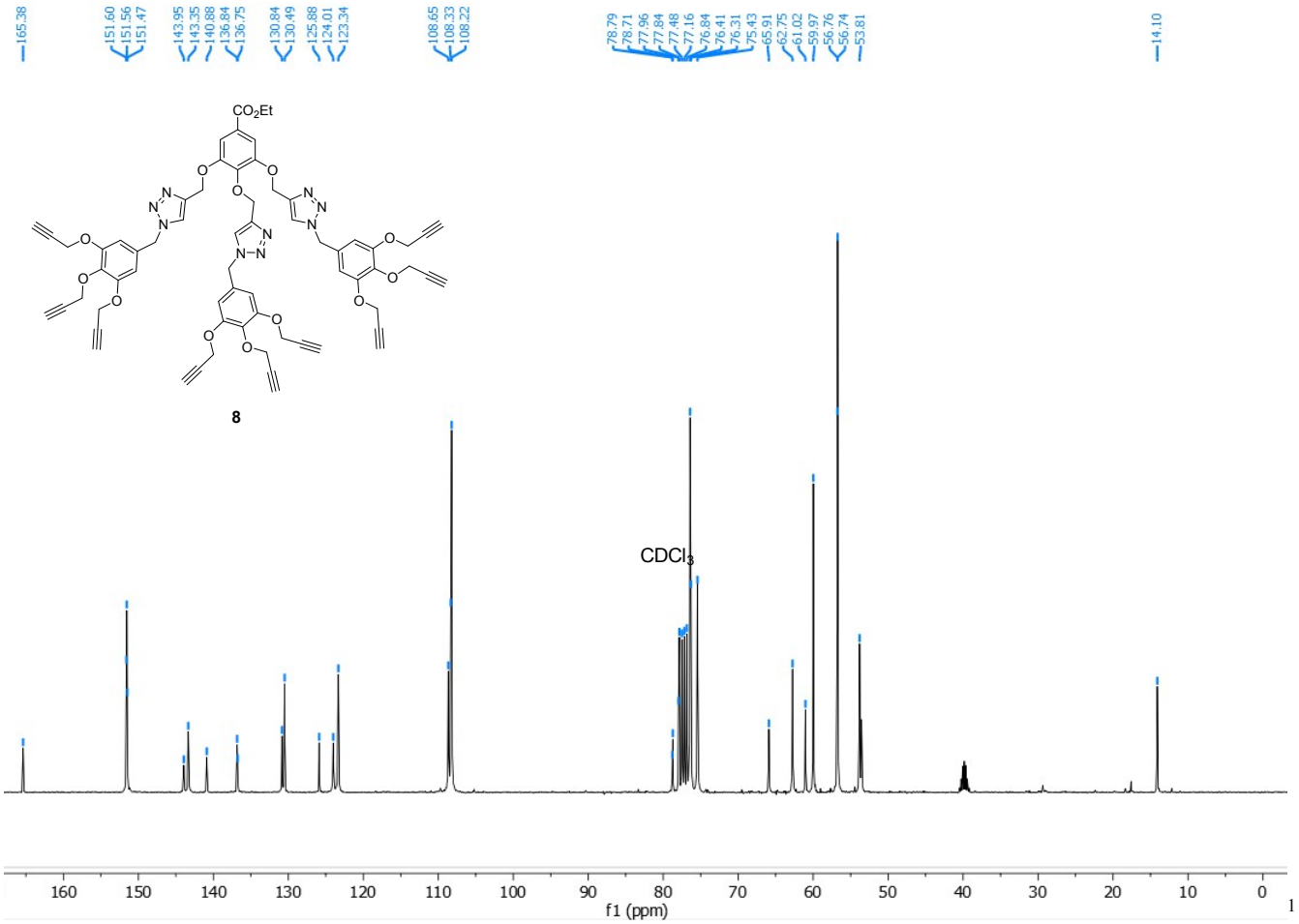
H NMR of **21** in $CDCl_3$


2605.61203
[M+H]+
CO2Et
TIPS
21
563.45347
880.52425
1303.30520
1607.48773
2909.80039
3213.98856
3908.43820
Relative Abundance
m/z

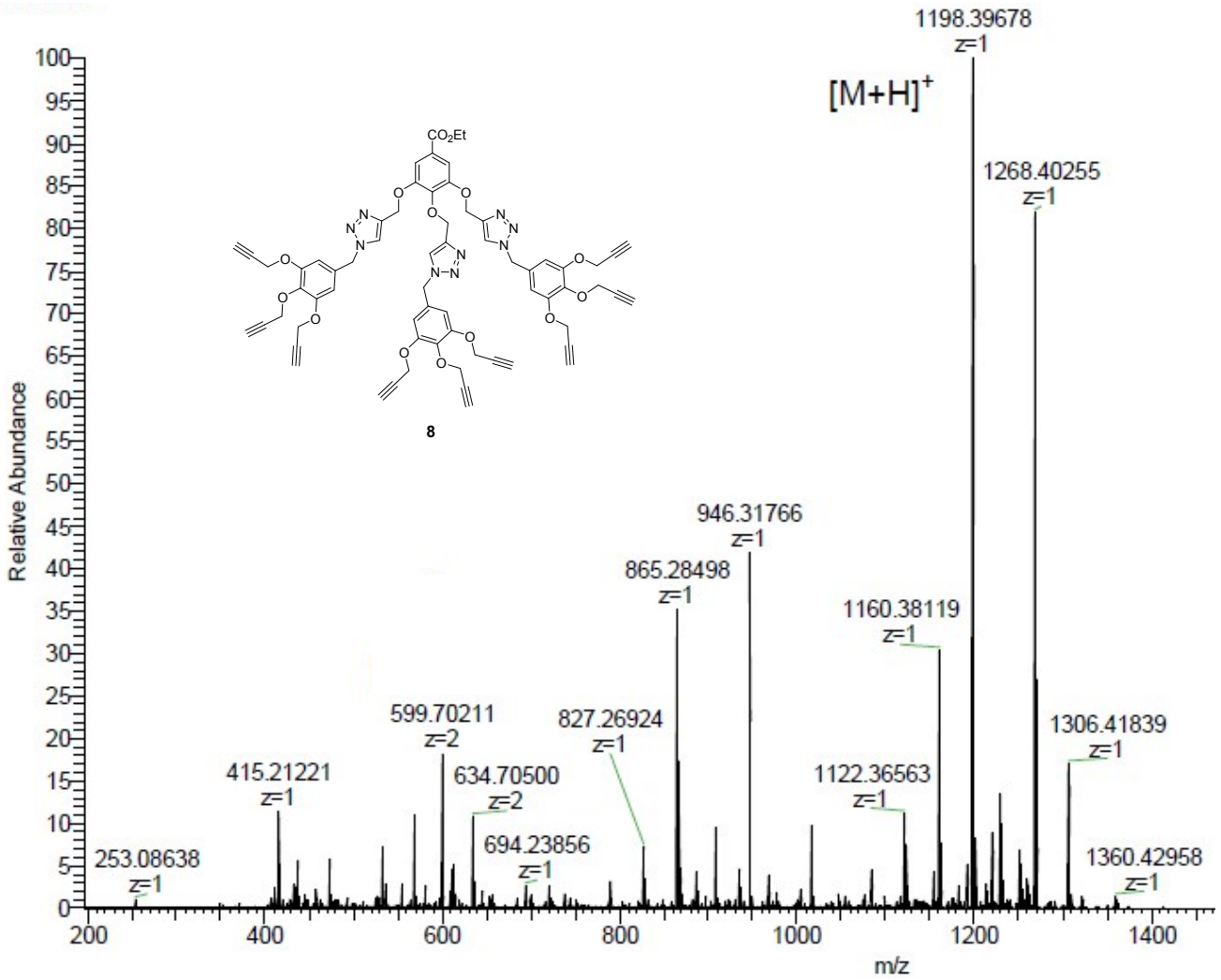
HRMS of **21**



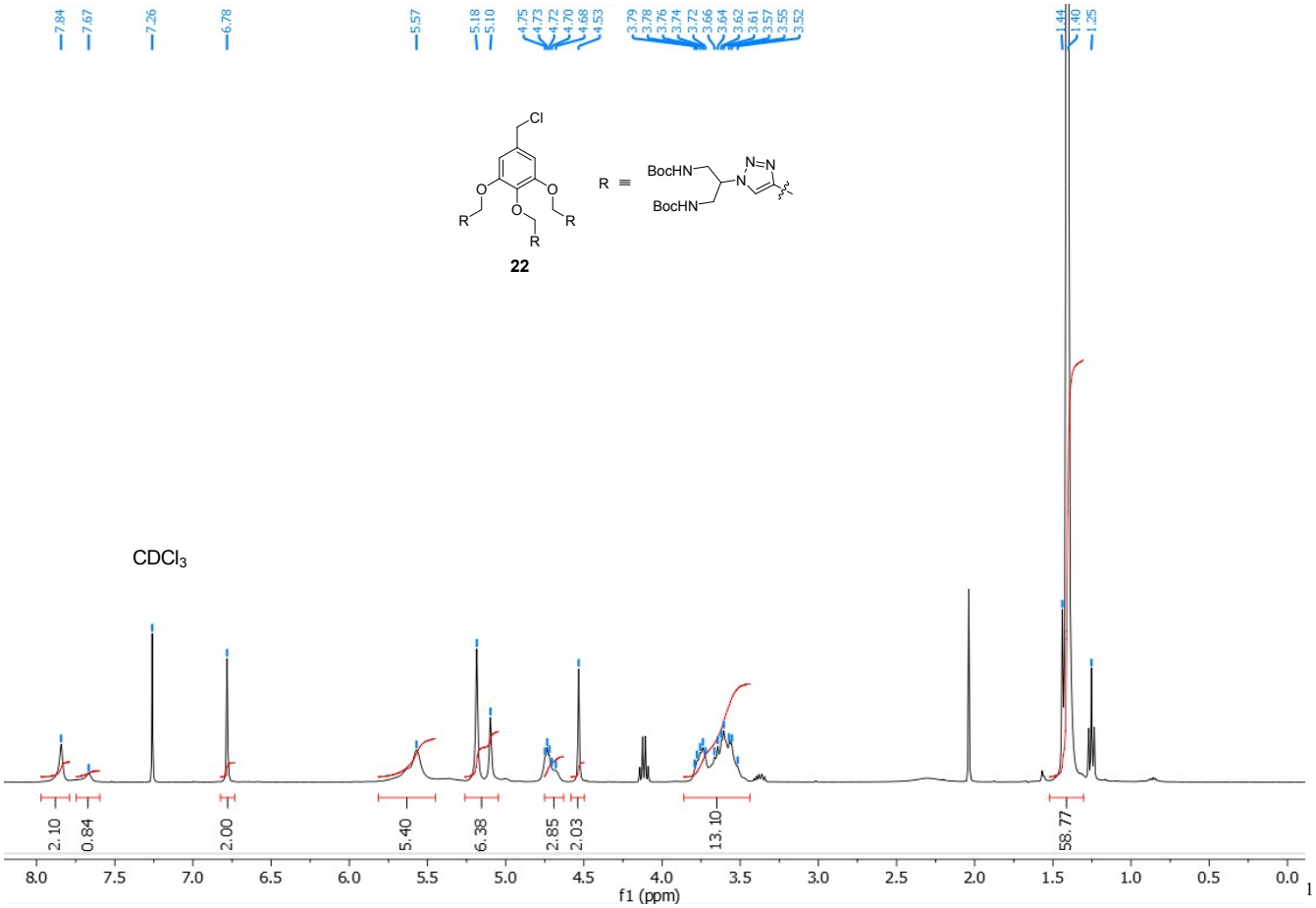
H NMR of **8** in $CDCl_3$. The peak falling at 1.3 belongs to residual heptane



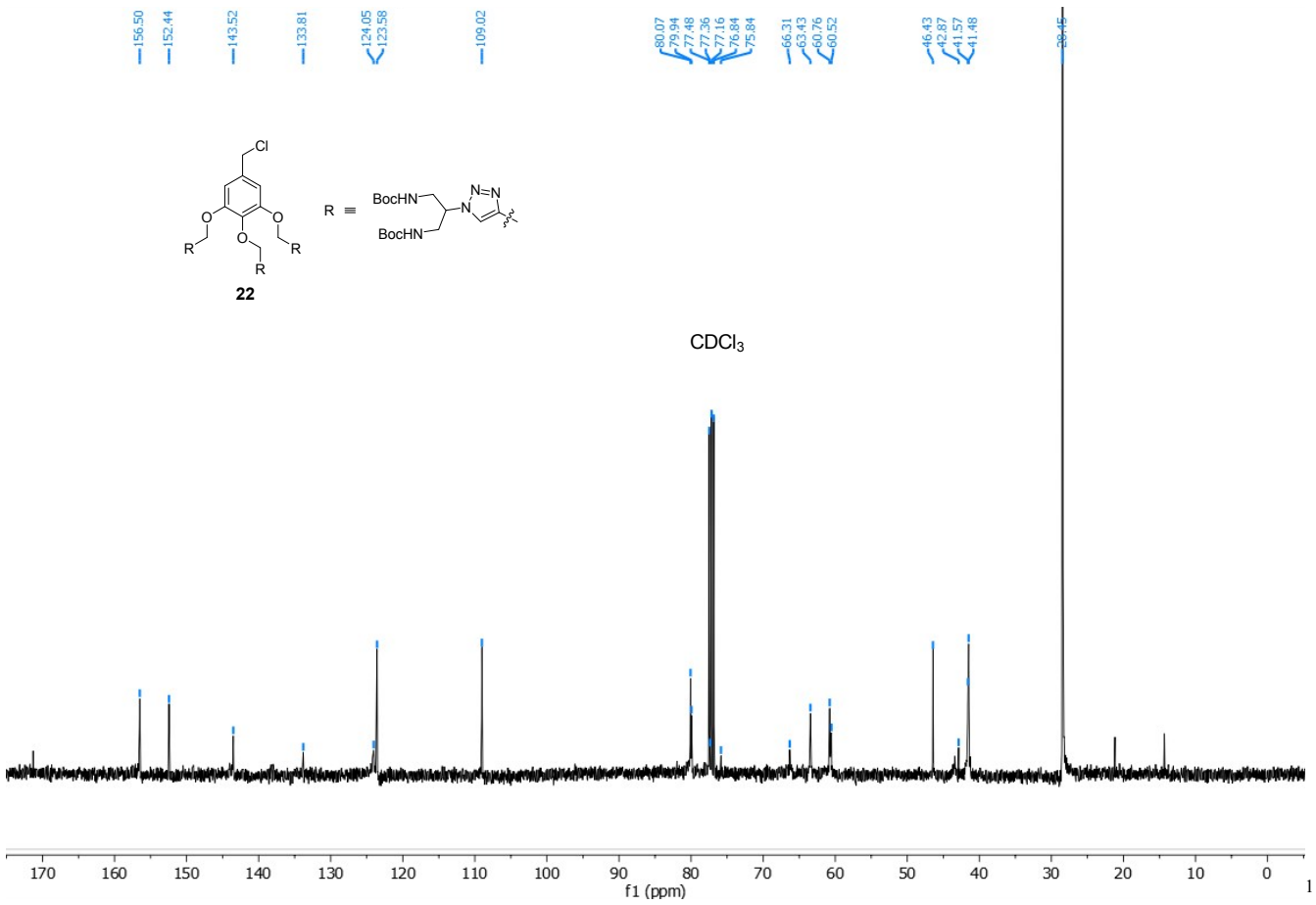
^{3}C NMR of **8** in $CDCl_3$


1198.39678
z=1
[M+H]+
1268.40255
z=1
946.31766
z=1
865.28498
z=1
1160.38119
z=1
599.70211
z=2
827.26924
z=1
1306.41839
z=1
415.21221
z=1
634.70500
z=2
1122.36563
z=1
694.23856
z=1
253.08638
z=1
1360.42958
z=1
Relative Abundance
m/z
8

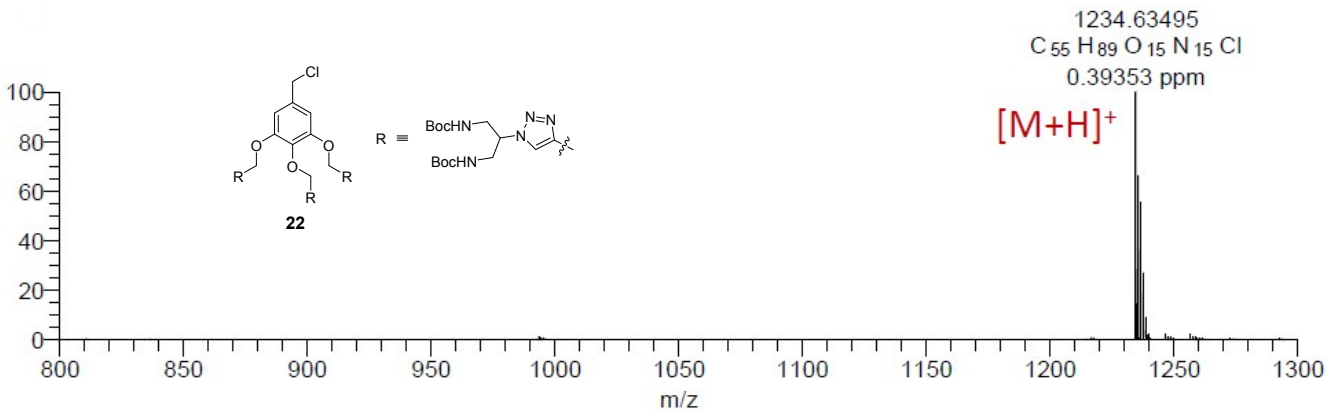
HRMS of **8**



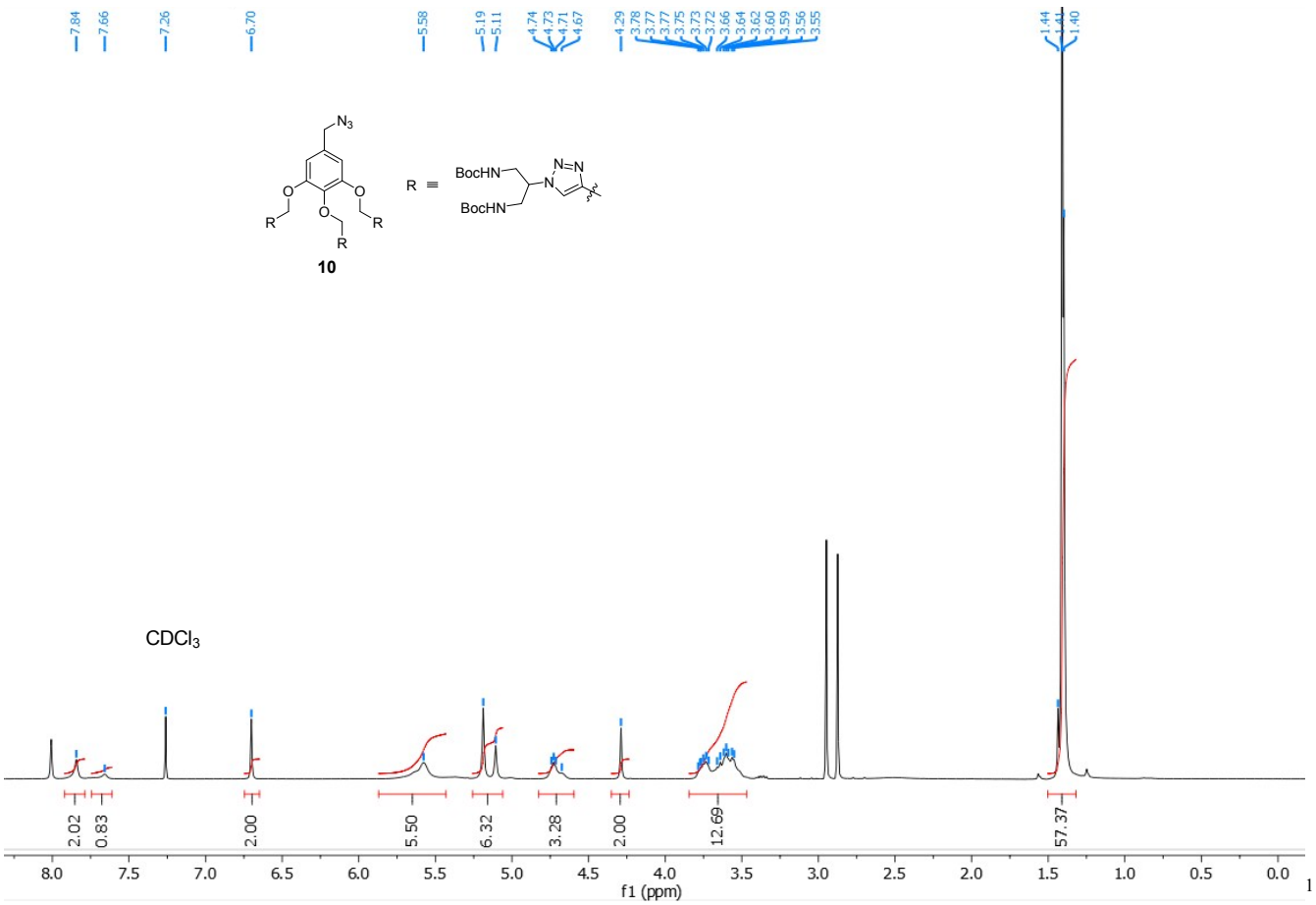
H NMR of **22** in $CDCl_3$. The peaks falling at 1.3, 2.0 and 4.1 belong to residual ethyl acetate



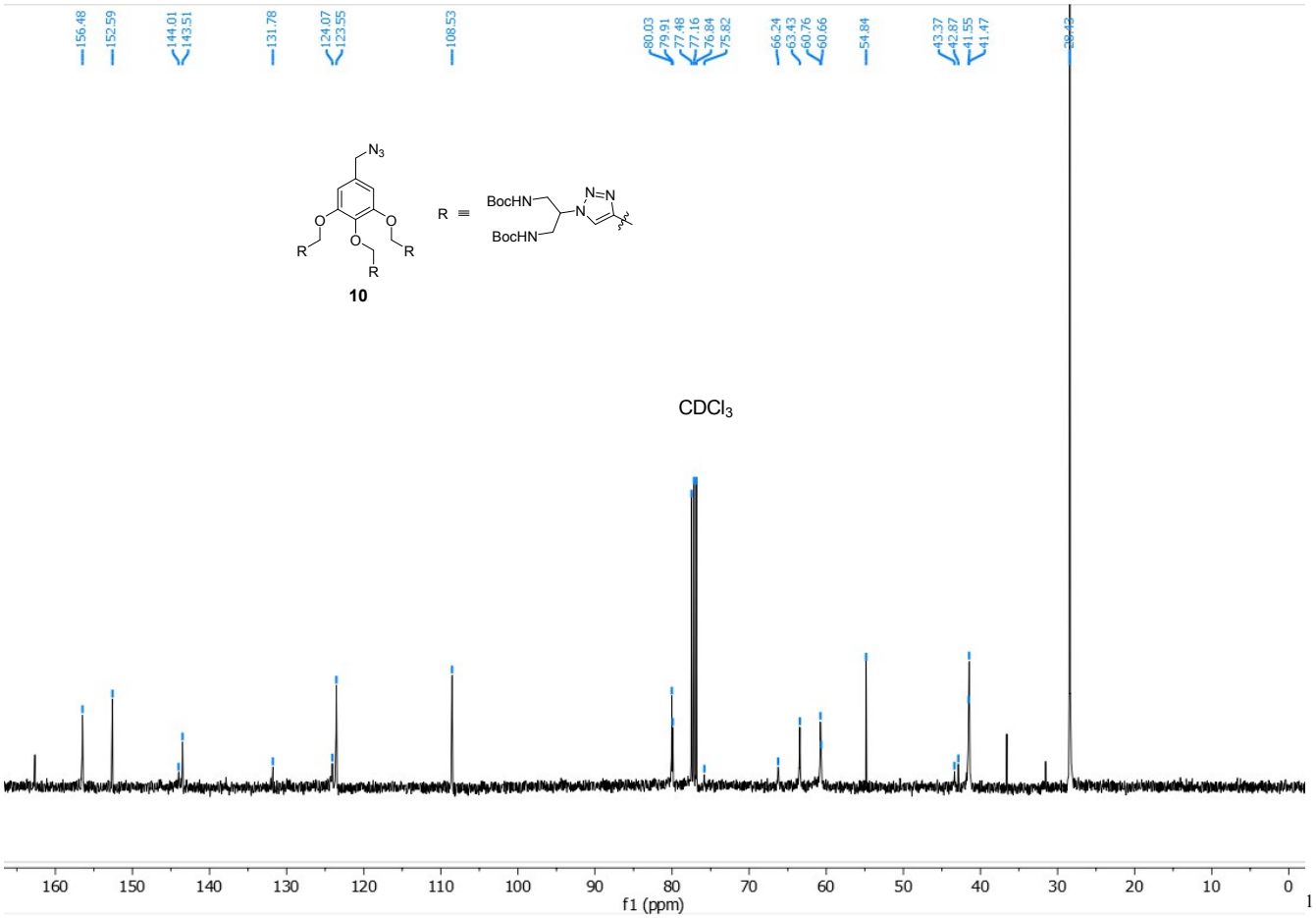
^{3}C NMR of **22** in $CDCl_3$. The peaks falling at 14.3, 21.2, 60.6 and 171.3 belong to residual ethyl acetate


1234.63495
C 55 H 89 O 15 N 15 Cl
0.39353 ppm
[M+H]+
22
R ≡
BocHN
BocHN
100
80
60
40
20
0
800
850
900
950
1000
1050
1100
1150
1200
1250
1300
m/z

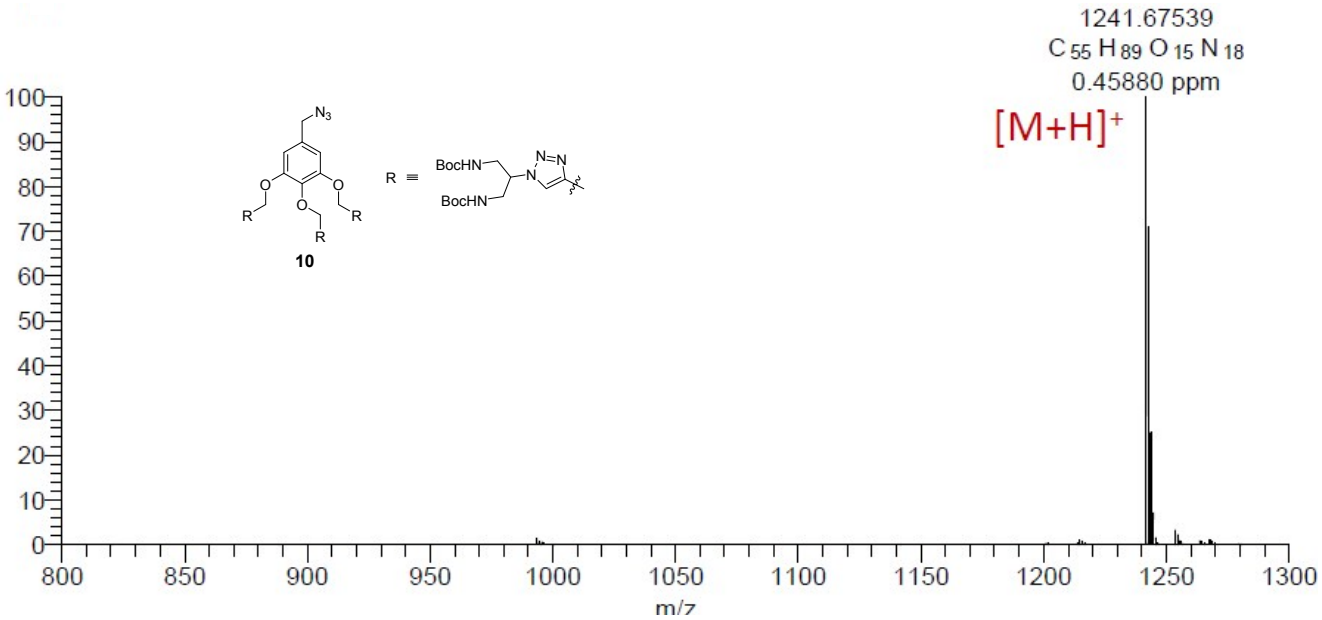
HRMS of **22**



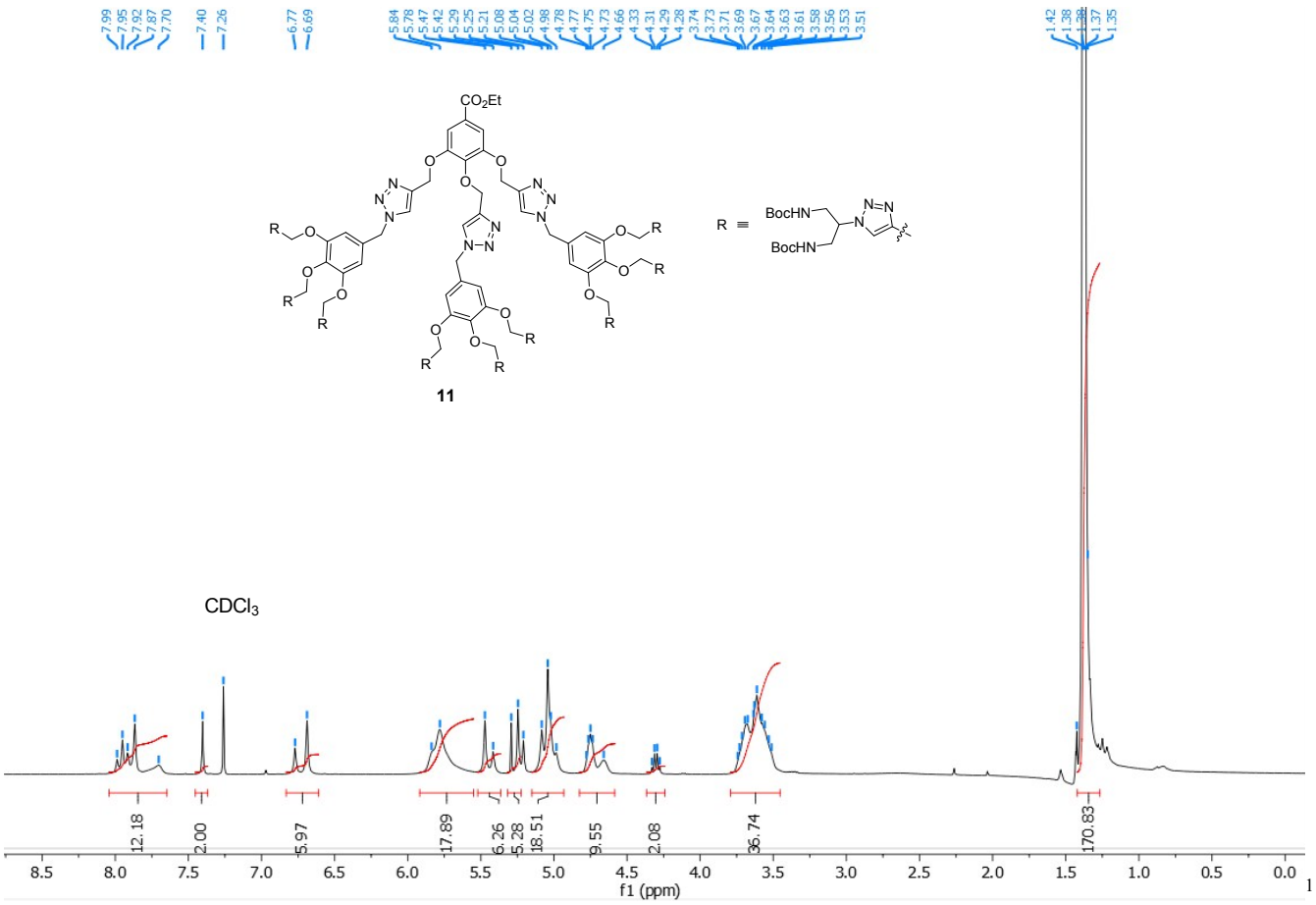
H NMR of **10** in $CDCl_3$. The peaks falling at 2.8, 2.9 and 8.0 belong to residual DMF



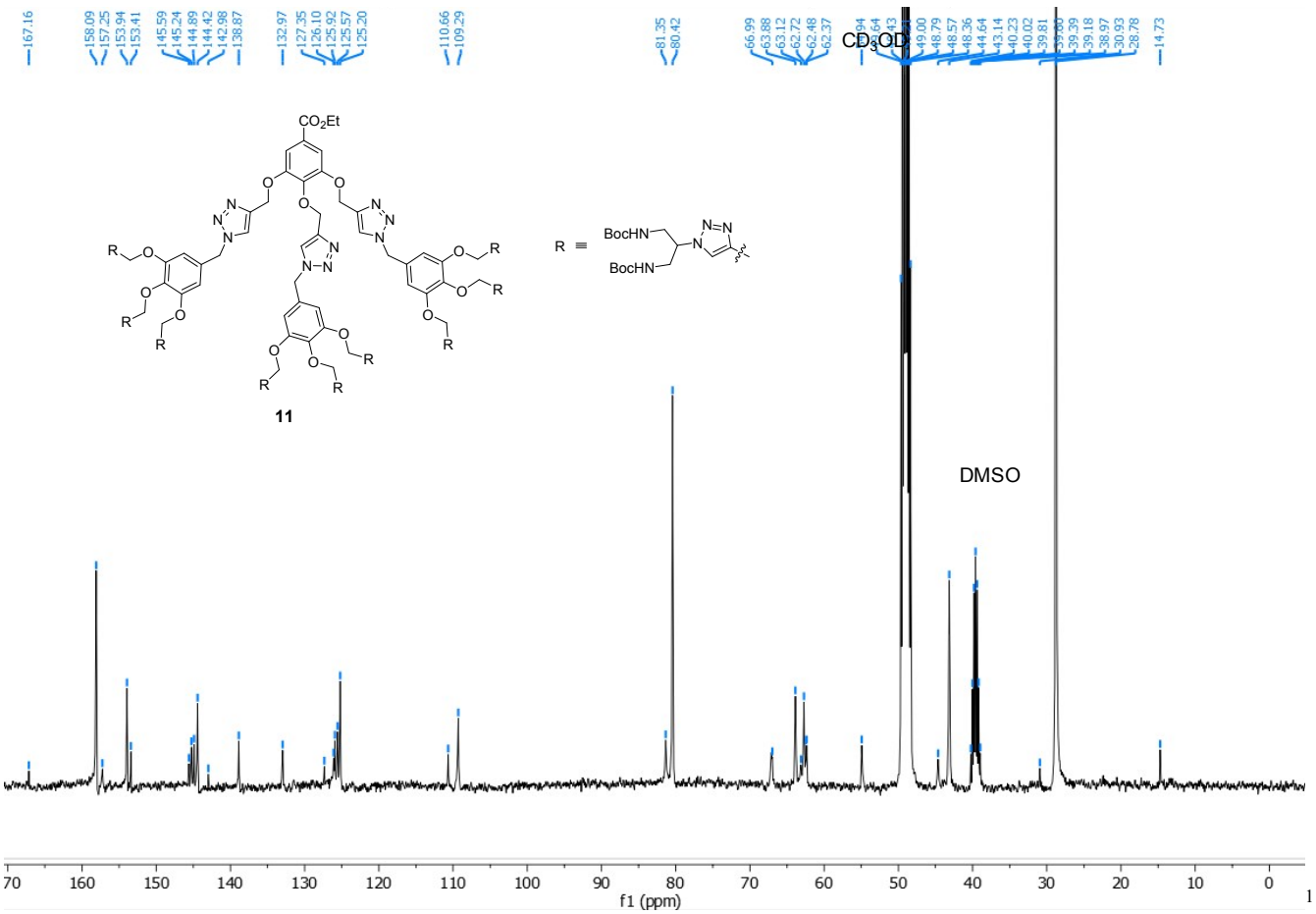
^{3}C NMR of **10** in $CDCl_3$. The peaks falling at 31.6, 36.6 and 162.6 belong to residual DMF


1241.67539
C 55 H 89 O 15 N 18
0.45880 ppm
[M+H]+
100
90
80
70
60
50
40
30
20
10
0
800
850
900
950
1000
1050
1100
1150
1200
1250
1300
m/z
N3
O
R
BocHN
N=N
N
10

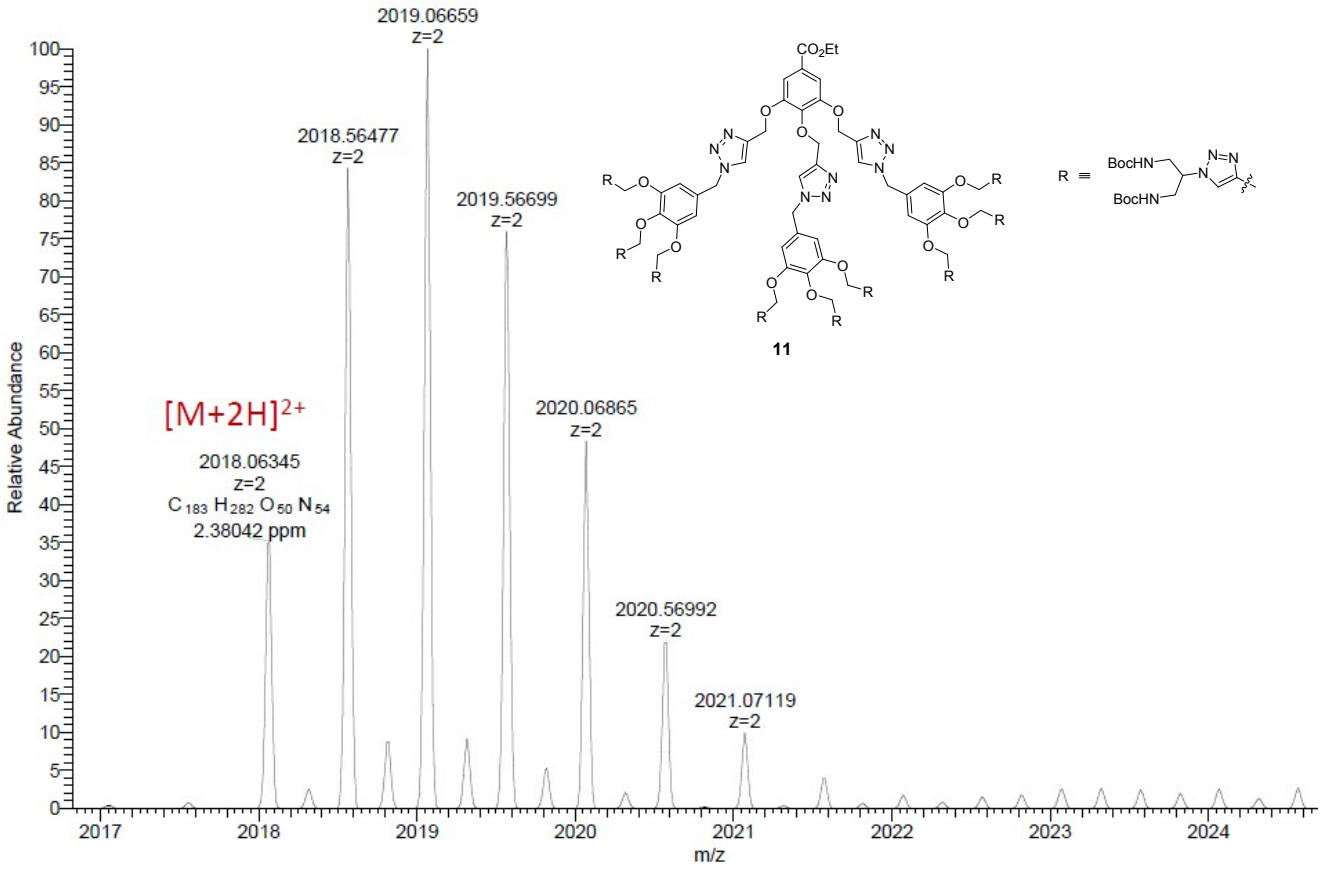
HRMS of **10**



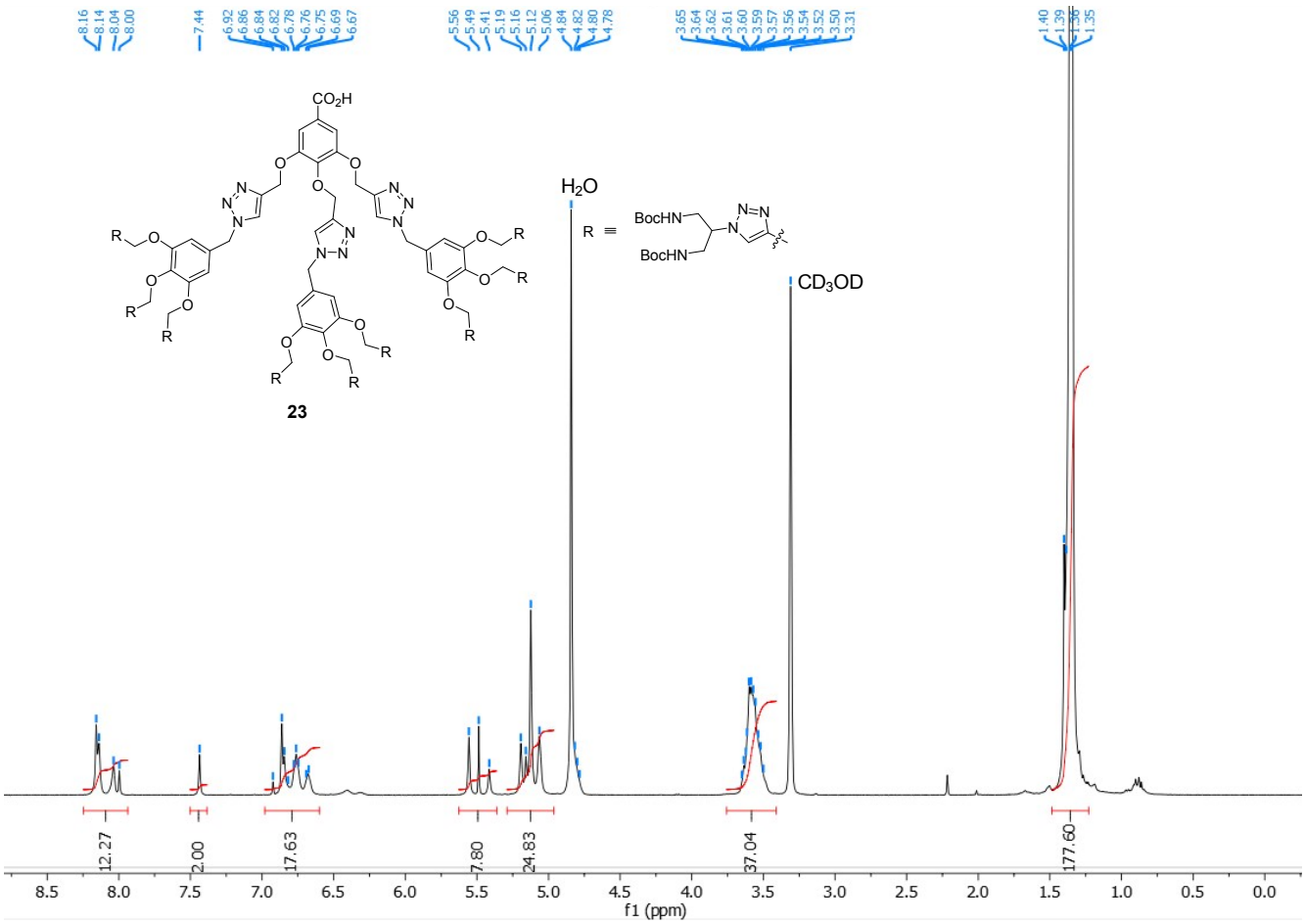
H NMR of **11** in $CDCl_3$



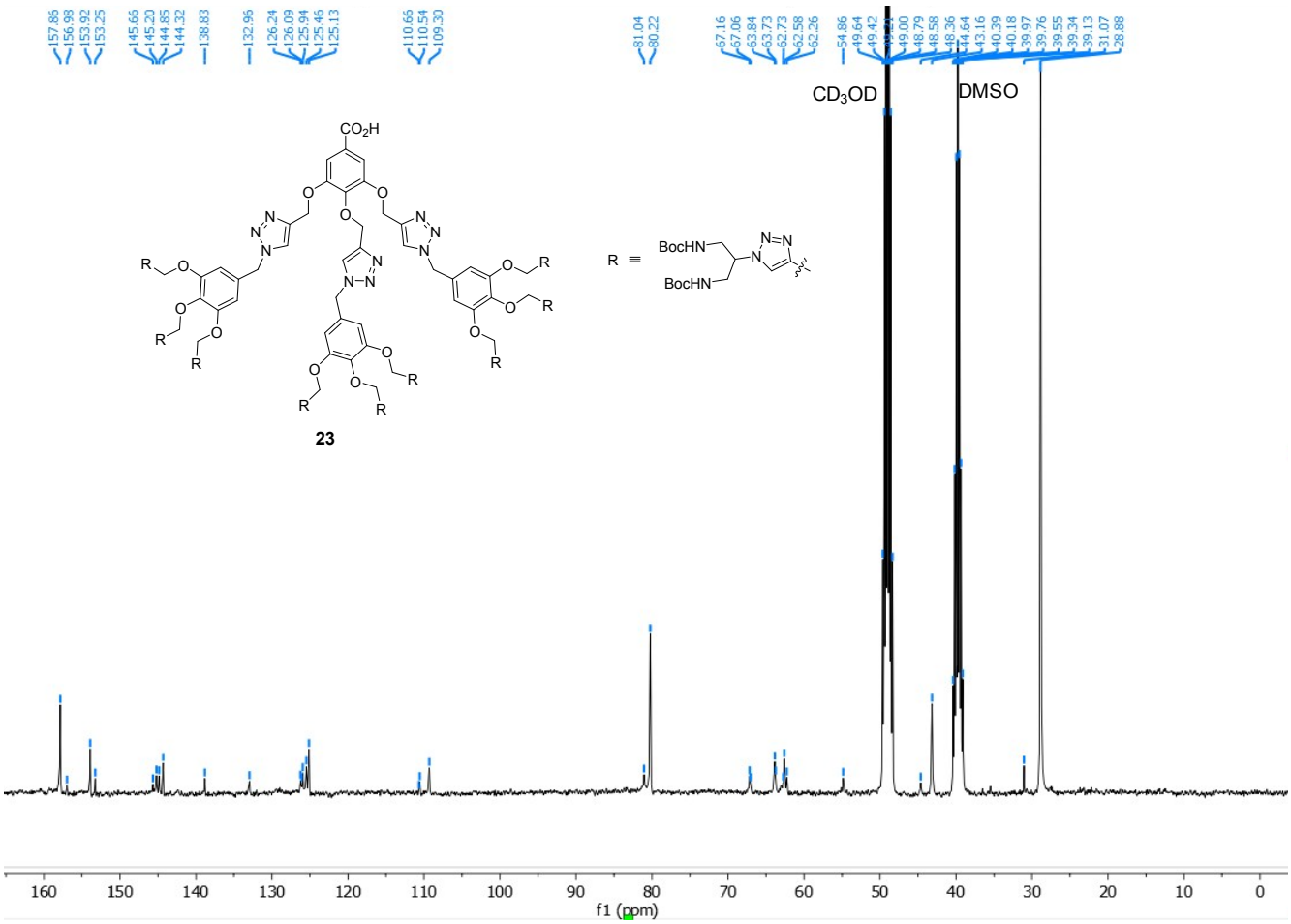
^{3}C NMR of **11** in CD_3OD/DMSO-d_6


2019.06659
z=2
2018.56477
z=2
2019.56699
z=2
2020.06865
z=2
2020.56992
z=2
2021.07119
z=2
[M+2H]2+
2018.06345
z=2
C183 H282 O50 N54
2.38042 ppm
Relative Abundance
m/z
11
R =
BocHN
BocHN

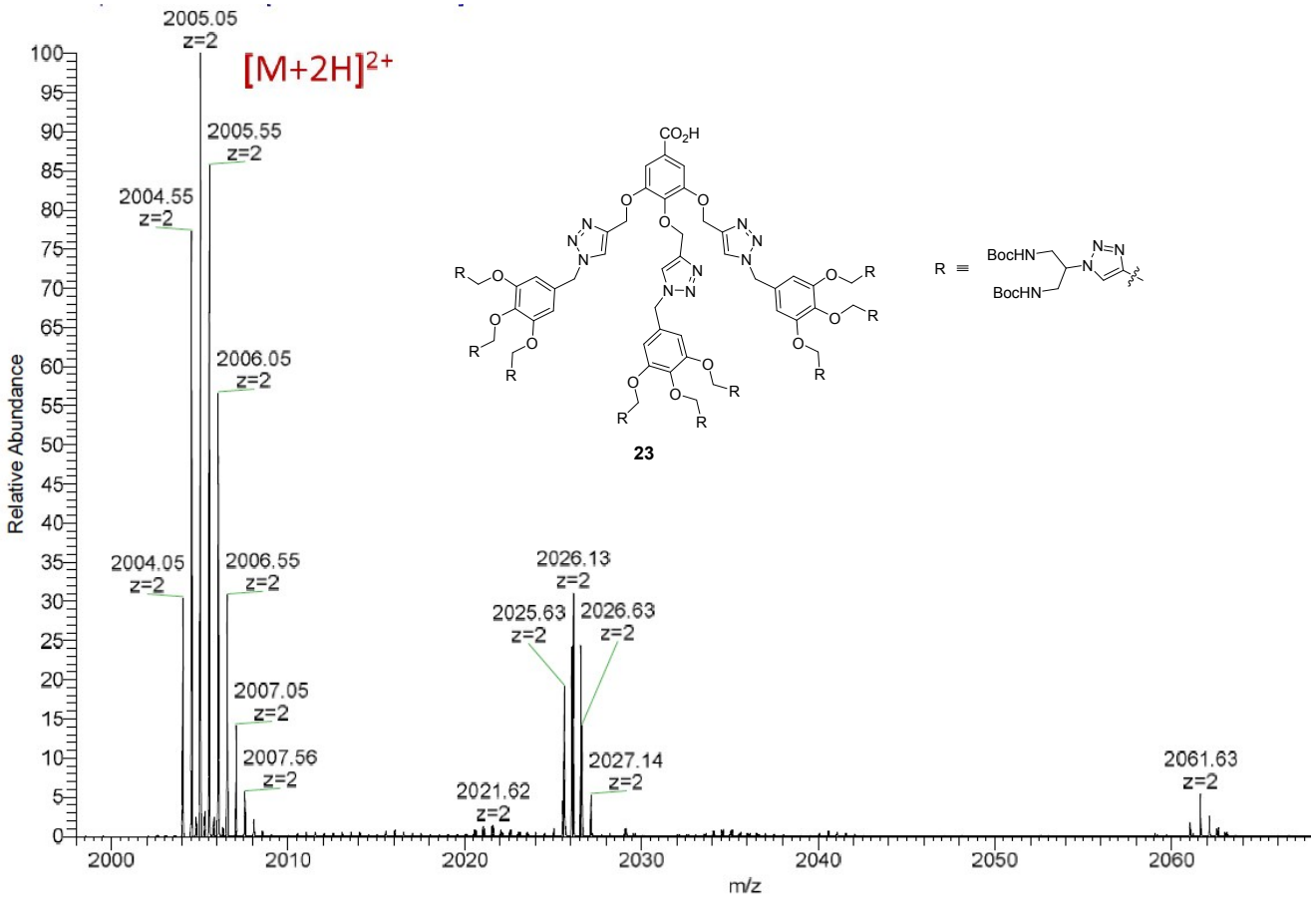
HRMS of **11**



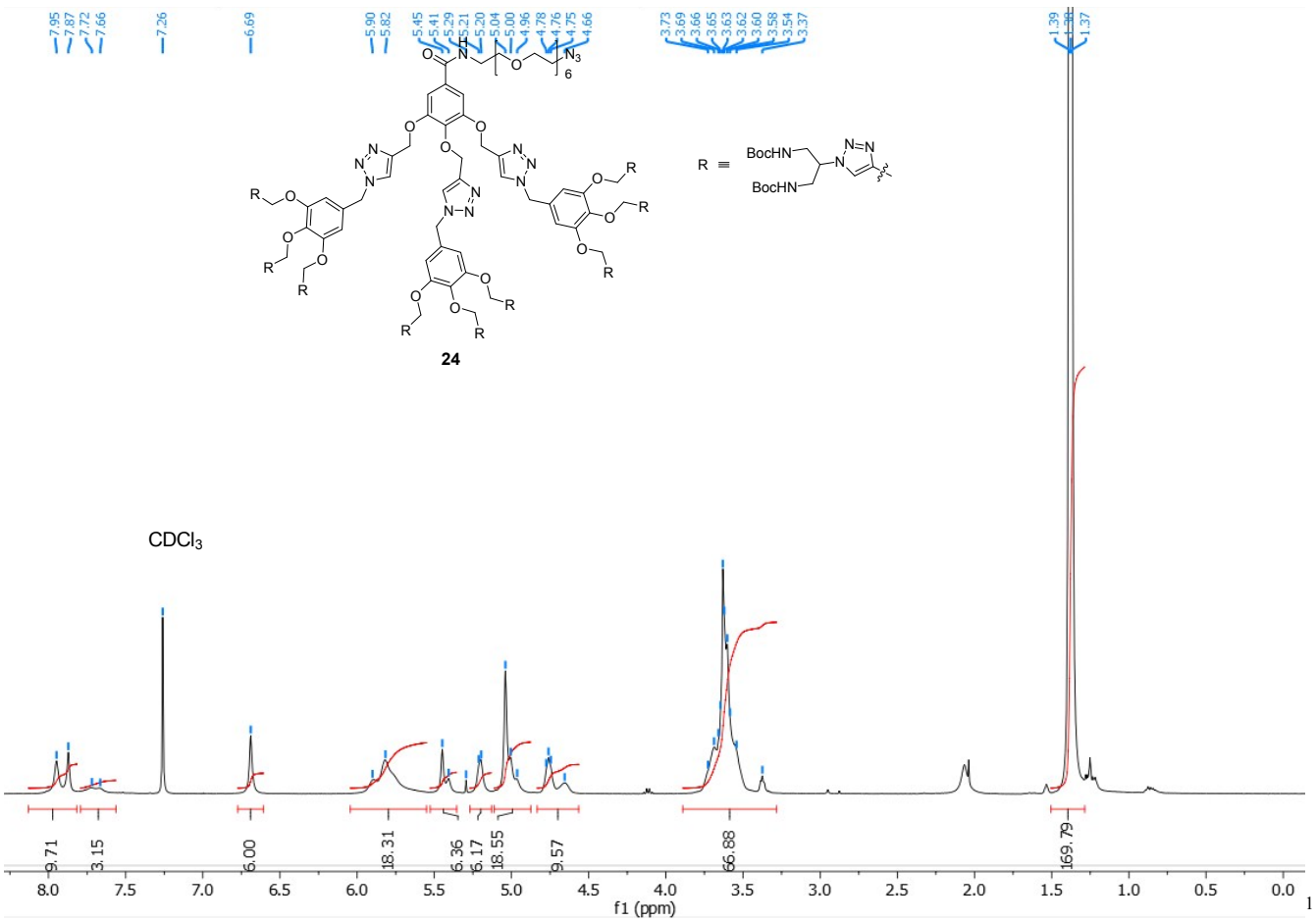
^{1}H NMR of **23** in CD_3OD



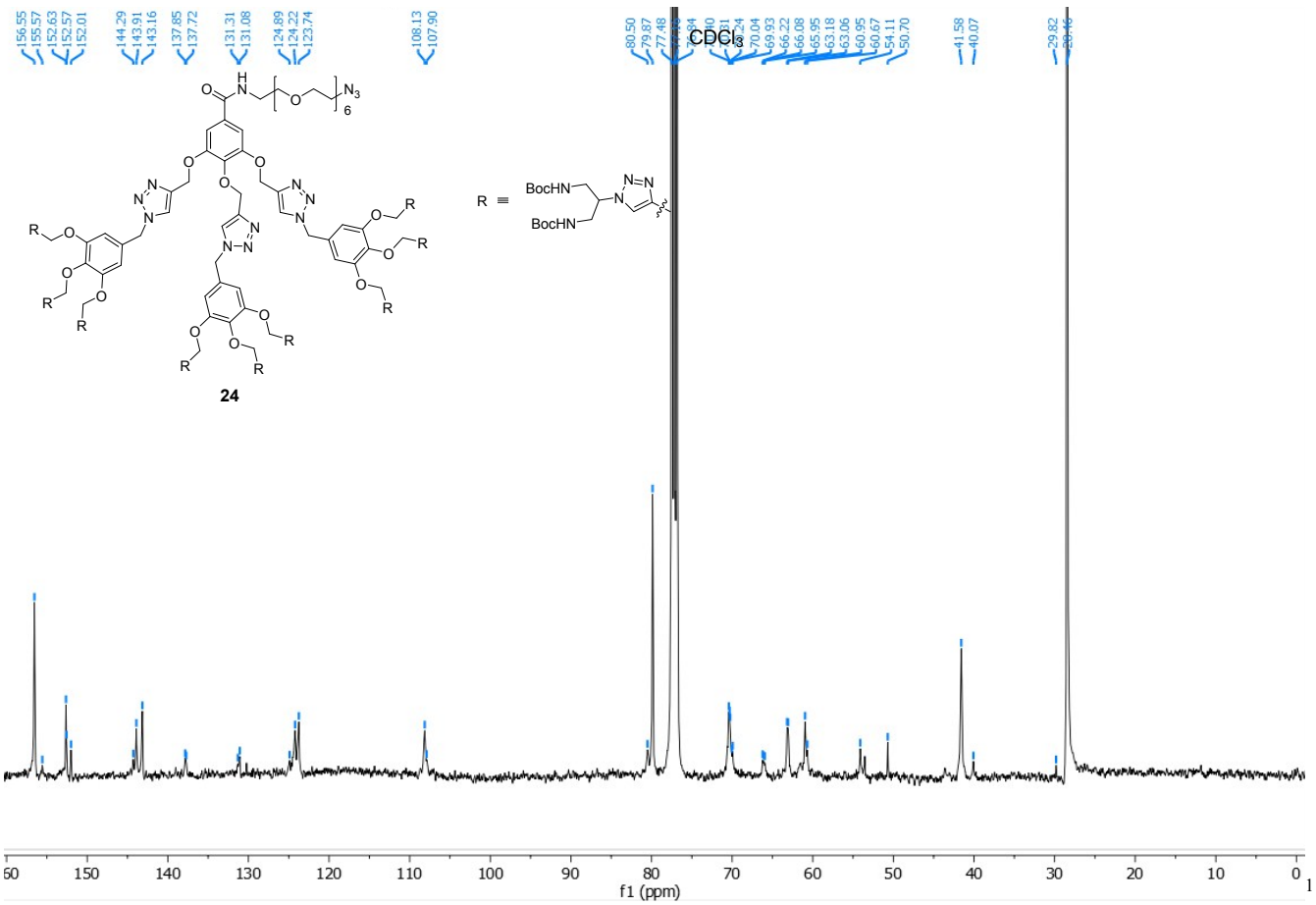
^{13}C NMR of **23** in CD_3OD/DMSO-d_6


2005.05
z=2
[M+2H]2+
2005.55
z=2
2004.55
z=2
2006.05
z=2
2004.05
z=2
2006.55
z=2
2007.05
z=2
2007.56
z=2
2021.62
z=2
2026.13
z=2
2025.63
z=2
2026.63
z=2
2027.14
z=2
2061.63
z=2
Relative Abundance
m/z
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
2000
2010
2020
2030
2040
2050
2060
CO2H
R ≡
BocHN
BocHN
23

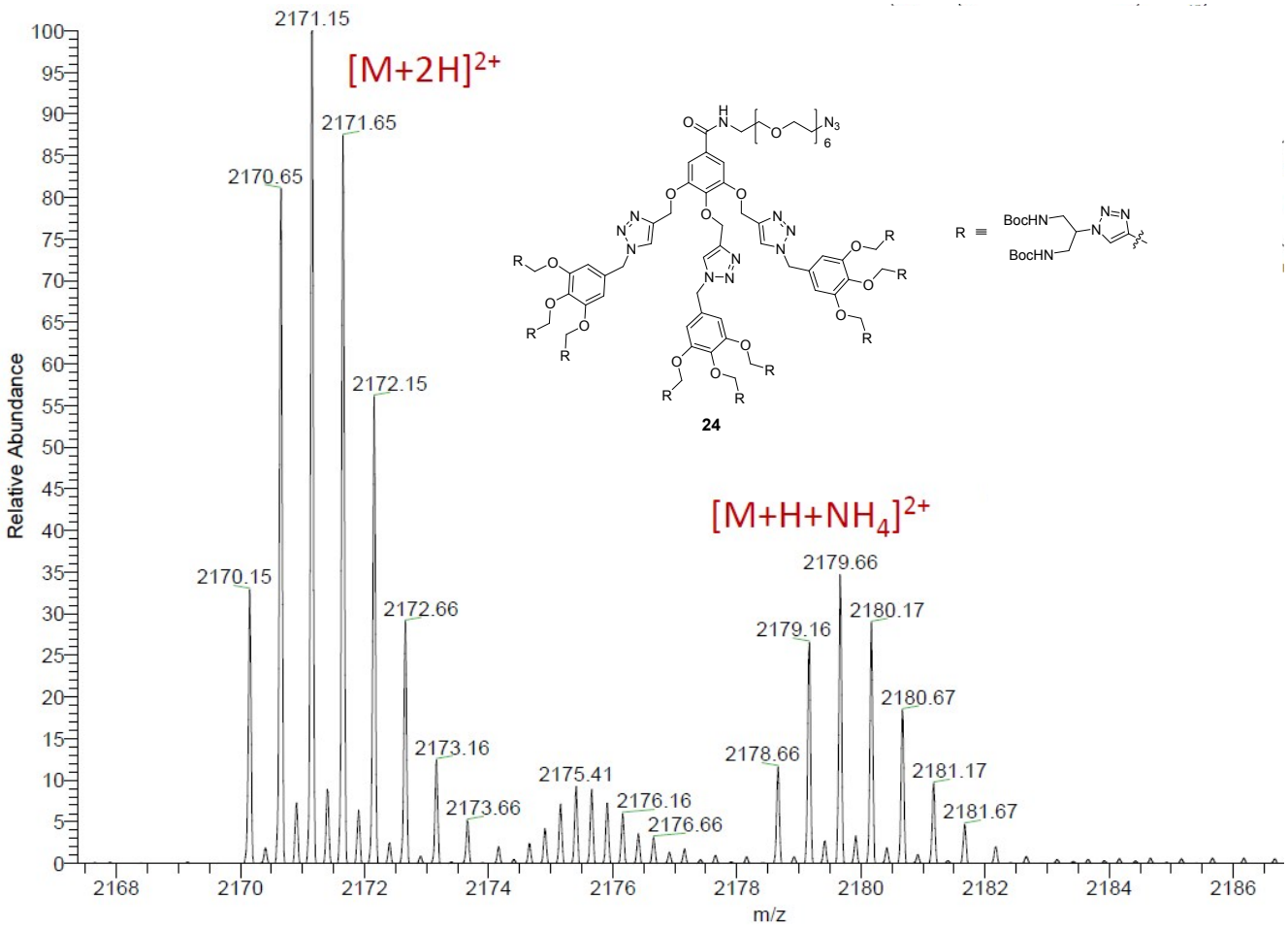
HRMS of **23**



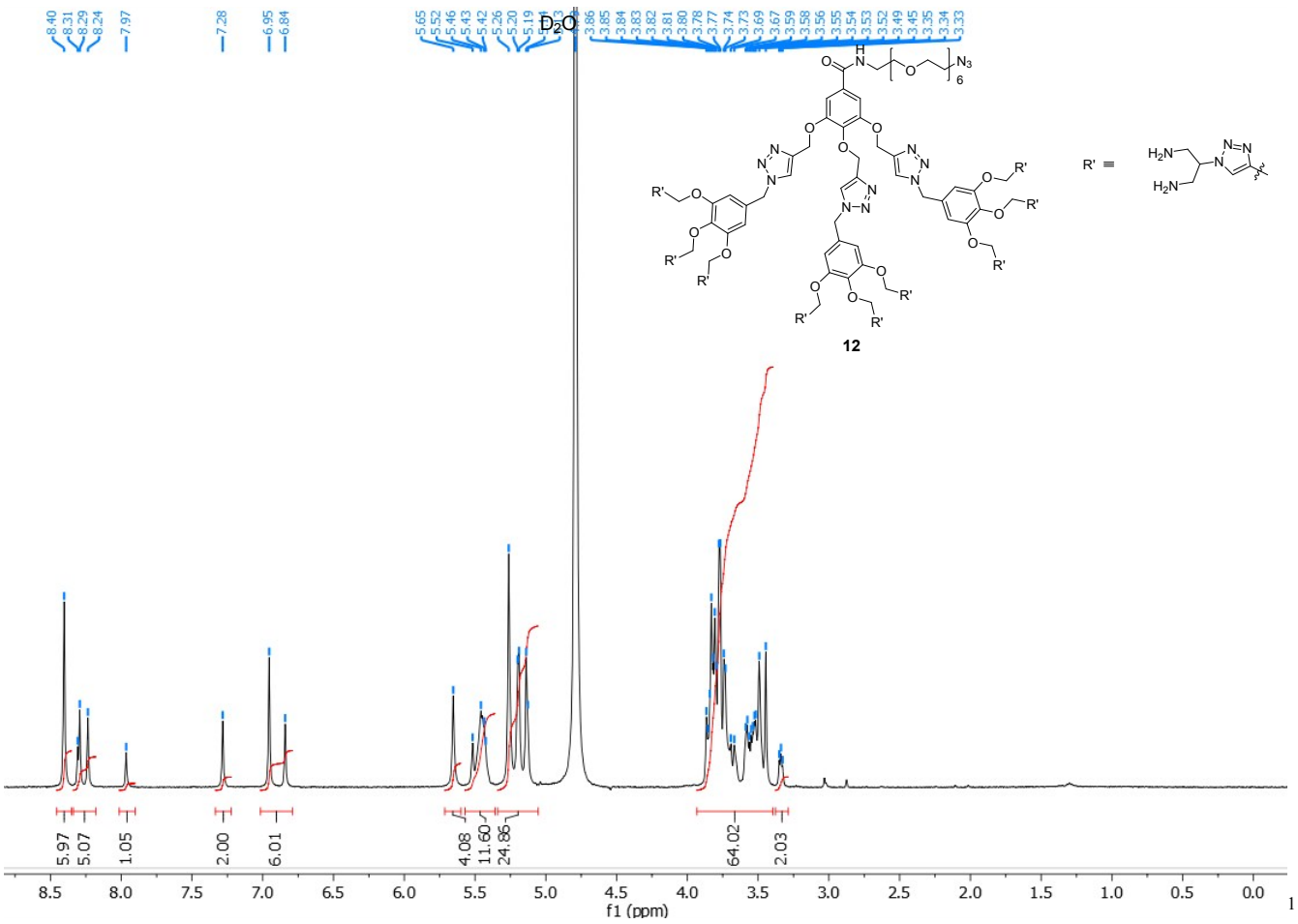
H NMR of **24** in $CDCl_3$. The peaks falling at 1.3 and 2.1 belong to residual ethyl acetate



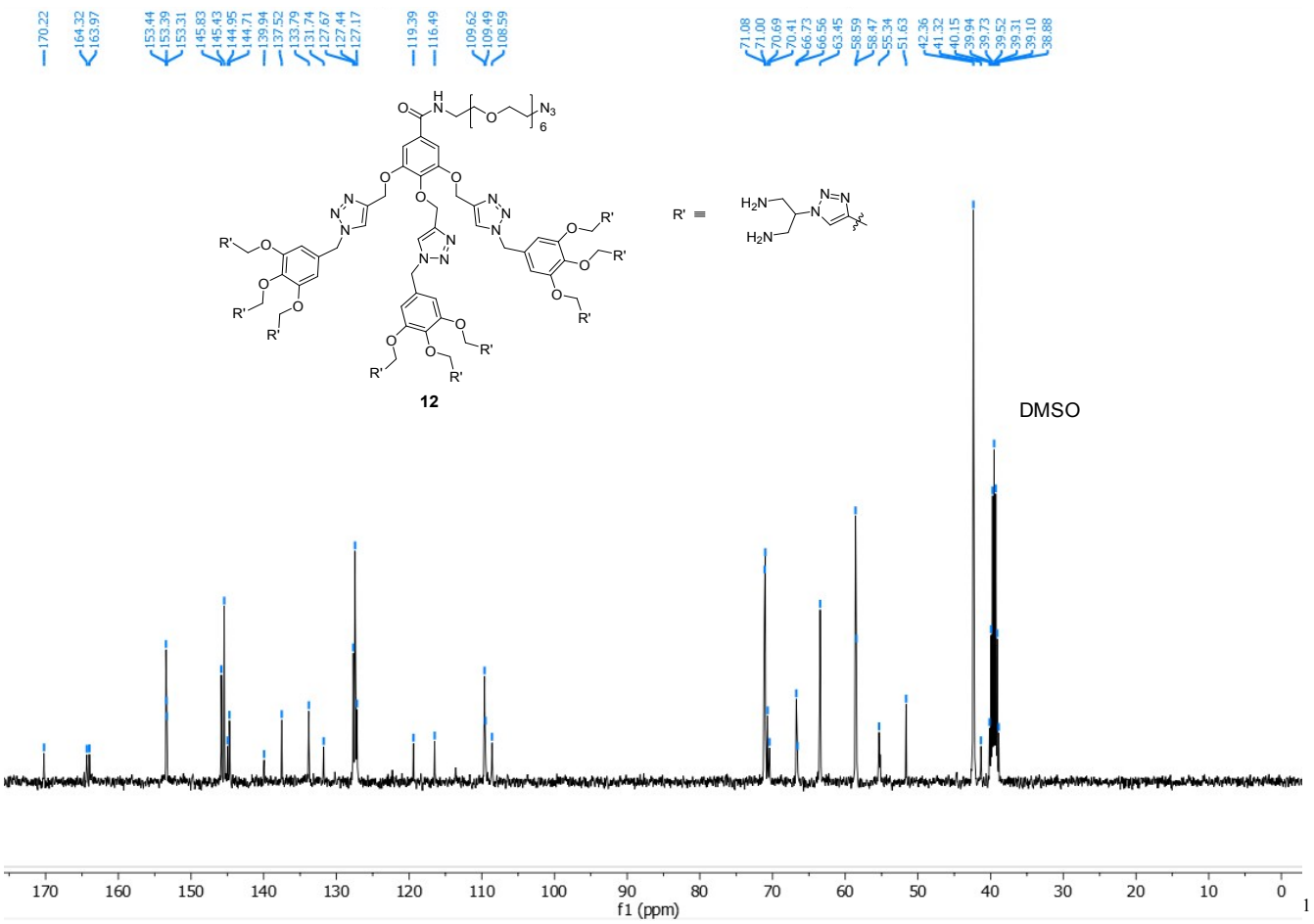
^{3}C NMR of **24** in $CDCl_3$


[M+2H]2+
2171.15
2171.65
2170.65
2172.15
2170.15
2172.66
2173.16
2173.66
2175.41
2176.16
2176.66
[M+H+NH4]2+
2179.66
2180.17
2179.16
2180.67
2178.66
2181.17
2181.67
Relative Abundance
m/z
24
R ≡ BocHN BocHN

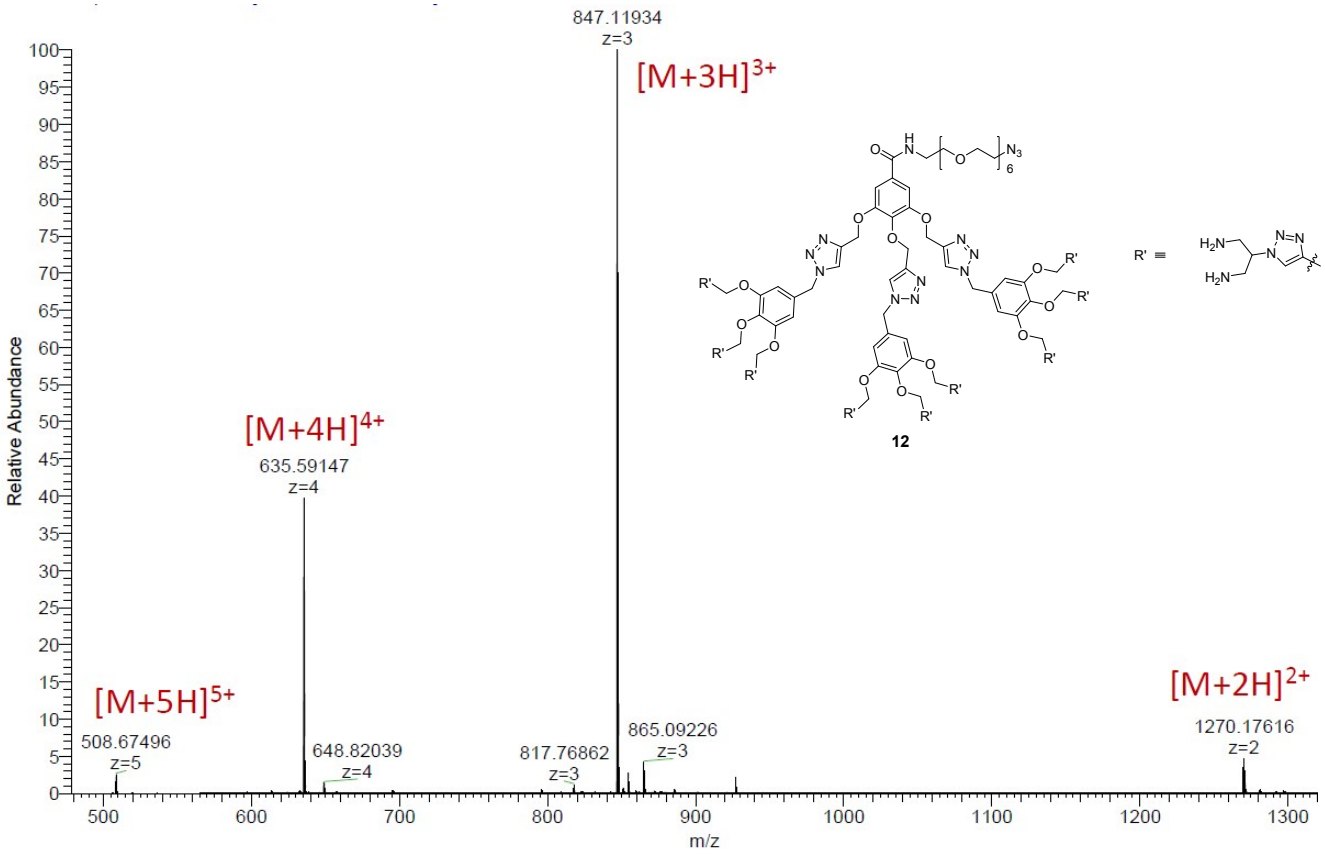
HRMS of **24**



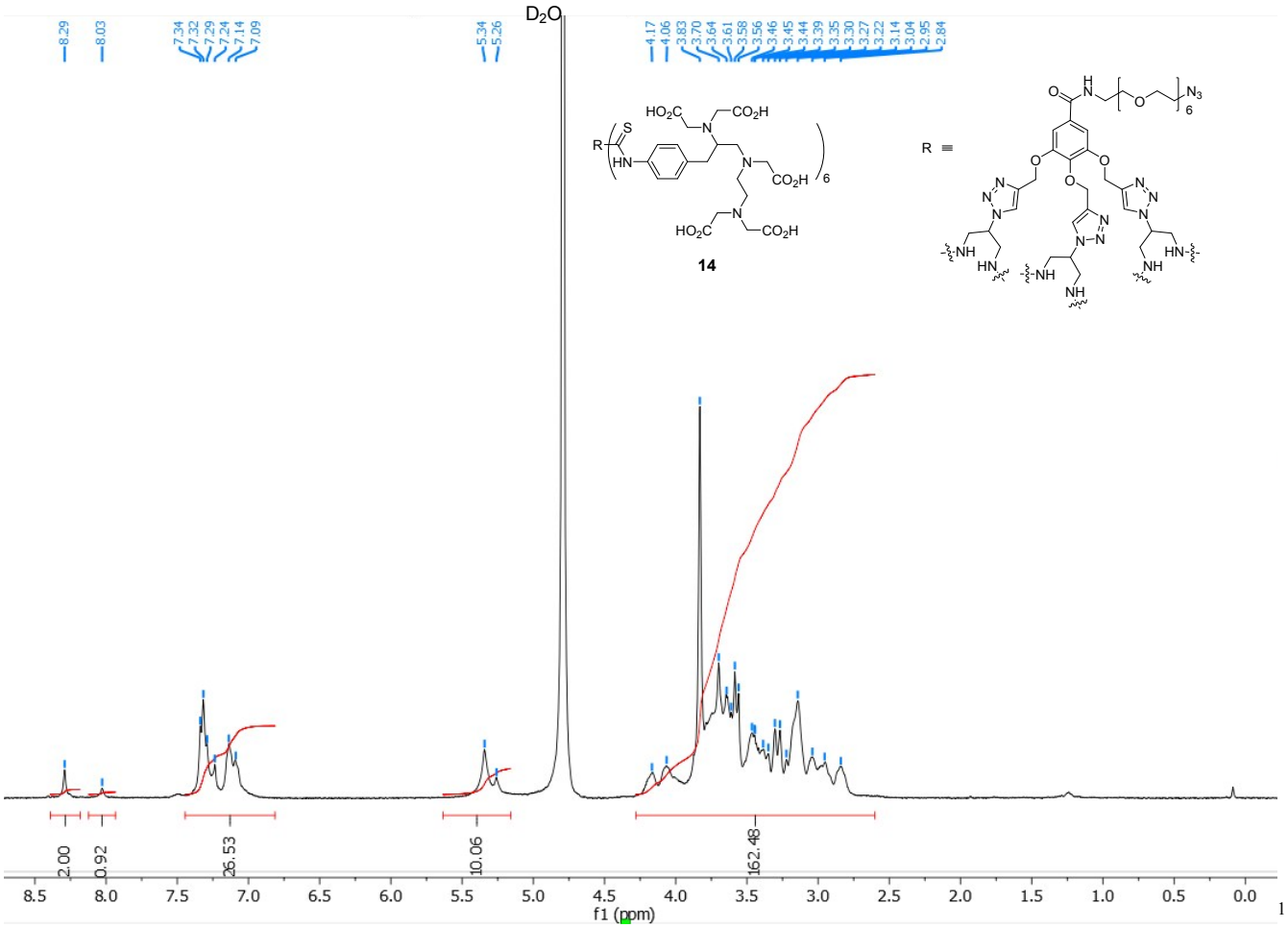
H NMR of **12** in D_2O



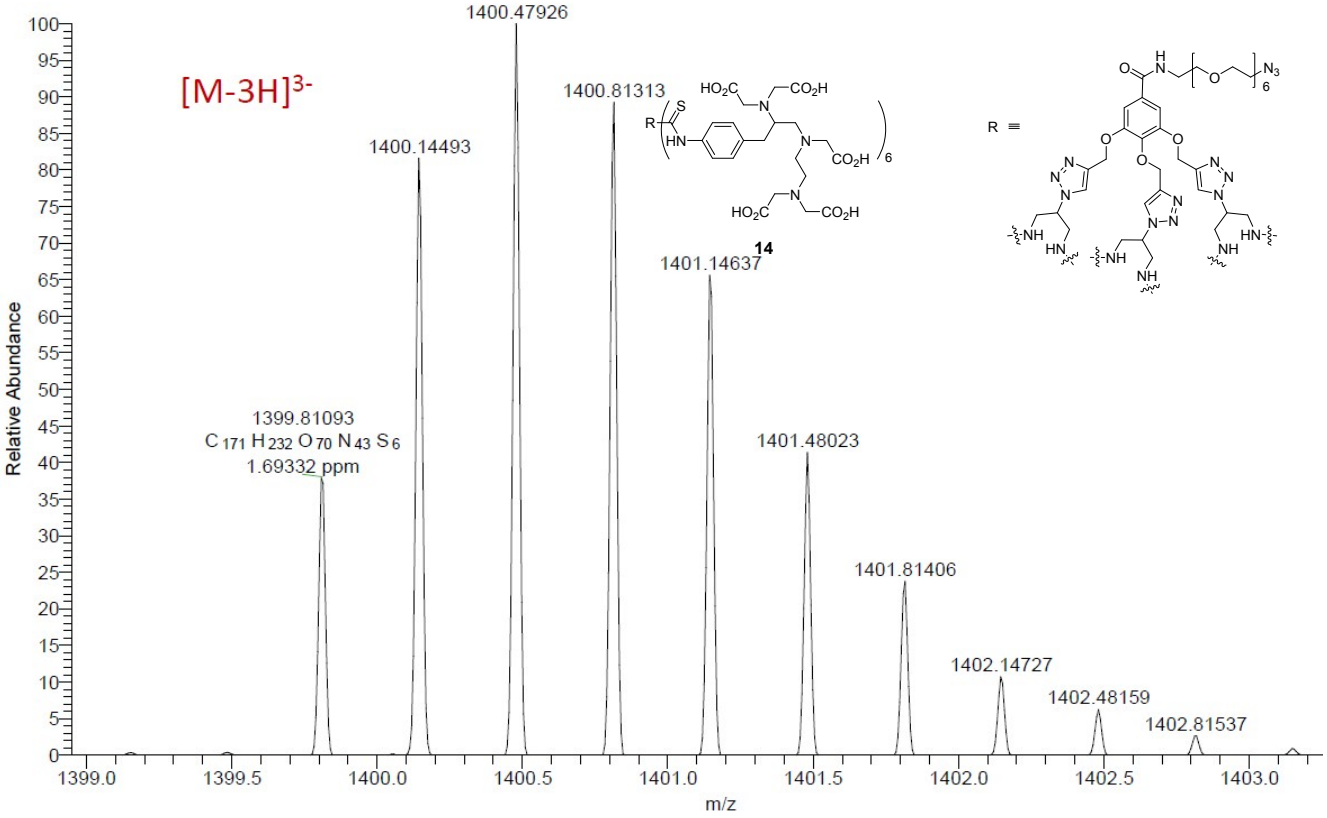
^{3}C NMR of **12** in D2O/DMSO-d_6


847.11934
z=3
[M+3H]3+
[M+4H]4+
635.59147
z=4
[M+5H]5+
508.67496
z=5
648.82039
z=4
817.76862
z=3
865.09226
z=3
[M+2H]2+
1270.17616
z=2
Relative Abundance
m/z
12
R' ≡

HRMS of **12**



H NMR of **14** in D_2O


[M-3H]3-
1400.47926
1400.81313
1400.14493
1401.14637
1399.81093
C 171 H 232 O 70 N 43 S 6
1.69332 ppm
1401.48023
1401.81406
1402.14727
1402.48159
1402.81537
Relative Abundance
m/z
14
R =

HRMS of **14**

Supplementary figures

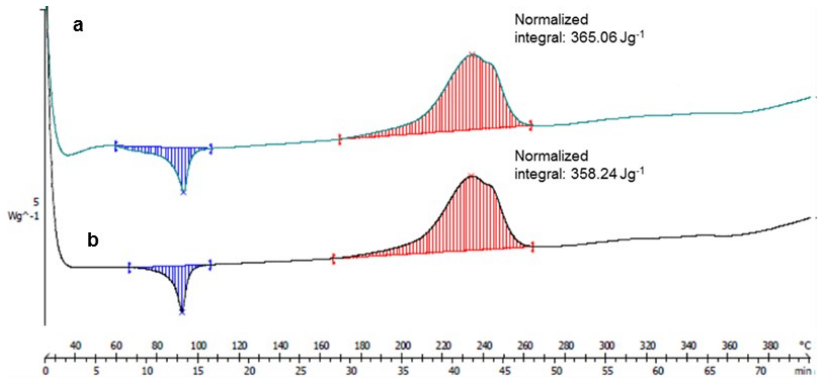


Figure S1. DSC analysis of the building block **2**. Dynamic measurements from 25 to 400 °C before (**a**) and after (**b**) the isothermic measurement (12 h at 90 °C). The normalized integral of **a** and **b** are highly similar indicating that **2** is stable at 90 °C for 12 h.

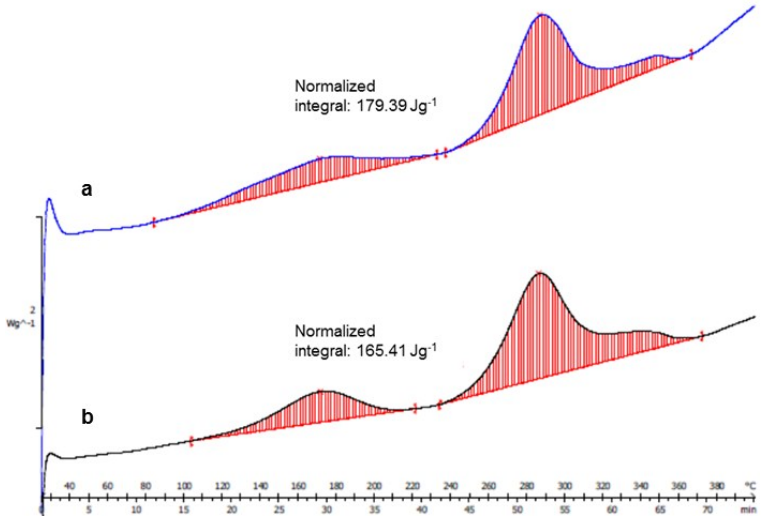


Figure S2. DSC analysis of the building block **7**. Dynamic measurements from 25 to 400 °C before (**a**) and after (**b**) the isothermic measurement (12 h at 50 °C). The normalized integral of **a** and **b** are highly similar indicating that **7** is stable at 50 °C for 12 h.

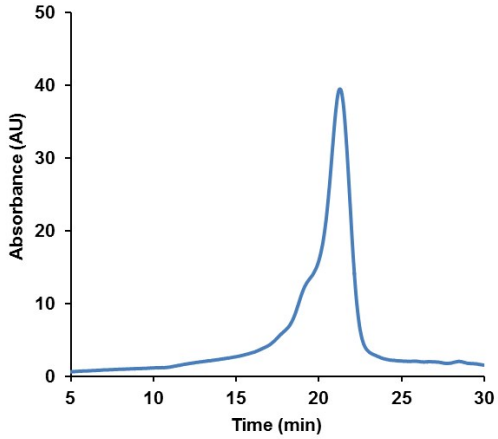


Figure S3. SEC of the G2 dendron fully loaded with the bifunctional chelator **13**. The presence of a shoulder at higher MW indicates the formation of aggregates.

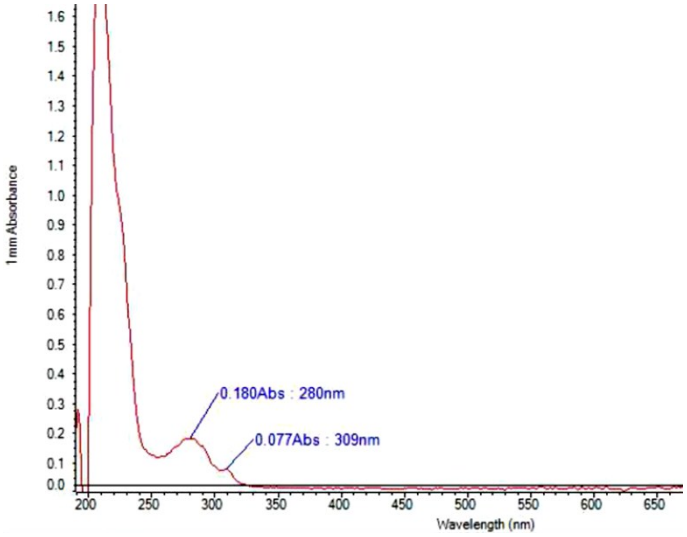


Figure S4. UV-Vis spectrum of the DBCO-modified RPA-T4. The different absorption maxima of RPA-T4 and DBCO-PEG_4-NHS ester, *i.e.* 280 and 309 nm respectively, along with the knowledge of their extinction coefficients, allow the determination of the average DBCO-to-antibody ratio.

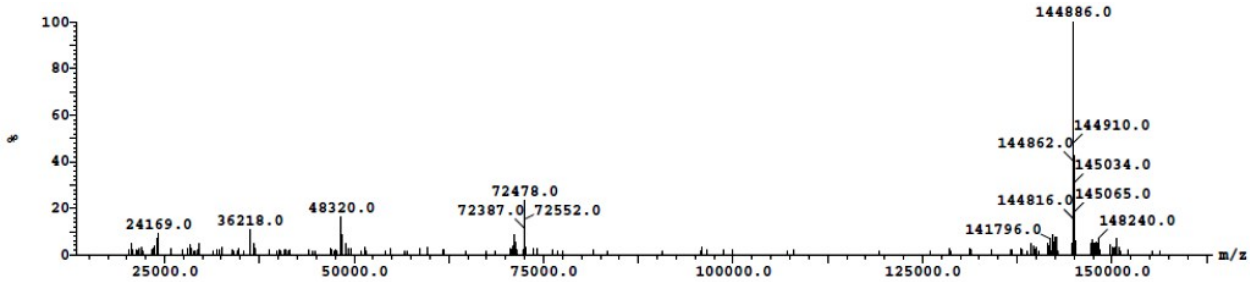


Figure S5. Mass spectrum of the intact deglycosylated monoclonal antibody RPA-T4.

References

(1) Le, C. M., Menzies, P. J. C., Petrone, D. A., Lautens, M. (2015) Synergistic Steric Effects in the Development of a Palladium-Catalyzed Alkyne Carbohalogenation: Stereodivergent Synthesis of Vinyl Halides. *Angew. Chem., Int. Ed. 54*, 254-2