Mono- and three-tailed sugar and iminosugar decorated benzenesulfonamide carbonic anhydrases inhibitors

Maria Giulia Davighi,[a] Camilla Matassini,[a] Andrea Goti,[a] Marta Ferraroni,[a] Andrea Angeli,[b] Claudio C. Supuran,[b]* and Francesca Cardona [a]*

[a] *Dipartimento di Chimica "Ugo Schiff" DICUS, Università degli Studi di Firenze, Via della Lastruccia 3-13, 50019 Sesto Fiorentino (FI), Italy.*

[b] *Dipartimento Neurofarba, Sezione di Scienze Farmaceutiche e Nutraceutiche, Università degli Studi di Firenze, 50019 Sesto Fiorentino (FI), Italy*

Electronic Supplementary Information (ESI)

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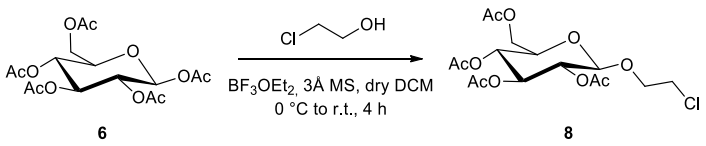
General methods: Commercial reagents were used as received. All reactions were carried out under magnetic stirring and monitored by TLC on 0.25 mm silica gel plates (Merck F254). Column chromatographies were carried out on Silica Gel 60 (32–63 µm) or on silica gel (230–400 mesh, Merck). Yields refer to spectroscopically and analytically pure compounds unless otherwise stated. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 MHz, a Varian Mercury 400 MHz or on a Varian INOVA 400 MHz instrument at 25 °C. Chemical shifts are reported relative to $CDCl_3$ (^{13}C: δ = 77.0 ppm, ^{1}H: 7.26 ppm), or to CD_3OD (^{13}C: δ = 49.0 ppm, ^{1}H: 3.31 ppm). Integrals are in accordance with assignments, coupling constants are given in Hz. For detailed peak assignments 2D spectra were measured (COSY, HSQC). Small scale microwave assisted syntheses were carried out in a microwave apparatus for synthesis (CEM Discover) with an open reaction vessel and external surface sensor. IR spectra were recorded with a IRAffinity-1S SHIMADZU system spectrophotometer. Optical rotation measurements were performed on a JASCO DIP-370 polarimeter. ESI-MS spectra were recorded with a Thermo Scientific™ LCQ fleet ion trap mass spectrometer. Elemental analyses were performed with a Thermoscientific FlashSmart Elemental Analyzer CHNS/O.

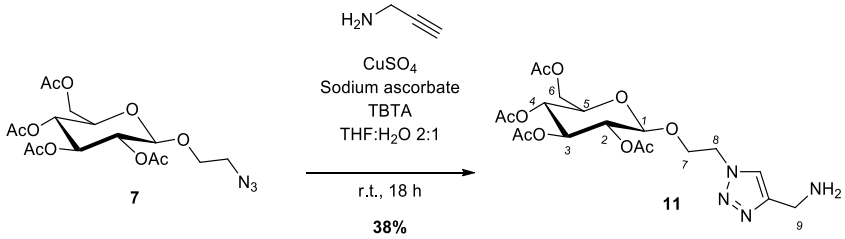
Alternative procedure for the synthesis of (2-chloroethyl)-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside 8 (Route II)



A suspension of acetylated glucose **6** (1.00 g, 2.56 mmol), 2-chloroethanol (258 µl, 3.84 mmol) and 3Å MS in dry DCM (10 ml) was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (2.25 ml, 17.9 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 4 hours until a ^{1}H-NMR spectrum attested the disappearance of **6**. The reaction mixture was neutralized at 0 °C by adding a $NaHCO_3$ saturated solution and then extracted with $NaHCO_3$, H_2O and brine. The organic layers were dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography on silica gel (gradient eluent from EtP:AcOEt 1.5:1 to 1:1) to give 635 mg of **8** (R_f = 0.26, EtP:AcOEt 1.5:1, 1.55 mmol, 60%) as a white solid.

The ^{1}H-NMR spectrum of **8** is in accordance with that reported in literature.[1]

Synthesis of compound 11



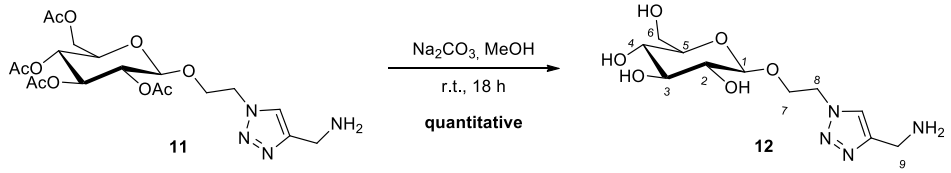
To a solution of azide **7**[1] (120 mg, 0.29 mmol) in THF (2 mL) and milliQ water (1 mL), propargylamine (16 µl, 0.26 mmol), TBTA (70 mg, 0.13 mmol) and sodium ascorbate (31 mg, 0.16 mmol) were added. The reaction was wrapped in a foil and $CuSO_4$ (13 mg, 0.08 mmol) was added and the reaction mixture was stirred at room temperature for 18 hours, until a TLC control attested the disappearance of propargylamine (R_f = 0.2, DCM:MeOH:NH_4OH (6%) 10:1:0.1). The mixture was filtered through Celite®, the solvent was removed under vacuum and subsequently the crude was treated with 'Quadrasil MP®' resin keeping the mixture under stirring at room temperature in the minimum amount of MeOH for 1 hour (1 g of resin for each mmol of copper). The crude was purified by flash column chromatography on silica gel (gradient eluent from DCM:MeOH:NH_4OH (6%) 15:1:0.1 to 10:1:0.1) to give 47 mg of **11** (R_f = 0.23, DCM:MeOH:NH_4OH (6%) 10:1:0.1, 0.10 mmol, 38%) as an orange oil.

11: $[\alpha]_D^{24}$ = − 13.53 (c = 0.85, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.51 (s, 1H, triazole), 5.16 (t, J = 9.5 Hz, 1H, H-3), 5.05 (t, J = 9.8 Hz, 1H, H-4), 4.98 (dd, J = 7.9, 9.5 Hz, 1H, H-2), 4.61-4.48 (m, 4H, H-8, H-9), 4.46 (d, J = 7.9 Hz, 1H, H-1), 4.26-4.16 (m, 2H, Ha-6, Ha-7), 4.11 (dd, J = 2.1, 12.3 Hz, 1H, Hb-6), 4.03-3.85 (m, 1H, Hb-7), 3.72-3.66 (m, 1H, H-5), 2.31-2.18 (br s, 2H, NH_2), 2.07 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.95 (s, 3H, OAc). ^{13}C-NMR (50 MHz, $CDCl_3$) δ ppm: 170.7 (s, 1C, C=O), 170.2 (s, 1C, C=O), 169.5 (s, 1C, C=O), 169.4 (s, 1C, C=O), 122.3 (d, 1C, triazole), 100.7 (d, 1C, C-1), 72.6 (d, 1C, C-3), 72.1 (d, 1C, C-5), 71.1 (d, 1C, C-

[1] P. Y. Chong, P. A. Petillo, *Org. Lett*., **2000**, *2*, 1093-1096.

2), 68.3 (d, 1C, C-4), 68.0 (t, 1C, C-7), 61.7 (t, 1C, C-6), 50.1 (t, 1C, C-8), 31.1 (t, 1C, C-9), 20.7 (q, 2C, CH_3) 20.6 (q, 2C, CH_3). IR ($CDCl_3$): ṽ = 3690, 3605, 2953, 2884, 2361, 2255, 1751, 1603, 1431, 1373, 1226, 1045 cm^{-1}. MS-ESI (m/z, %) = 473.08 (100) $[M+H]^+$, 495.08 (42) $[M+Na]^+$. $C_{19}H_{28}N_4O_{10}$ (472.45): calcd C, 48.30; H, 5.97; N, 11.86; found C, 48.08; H, 6.10; N, 11.90.

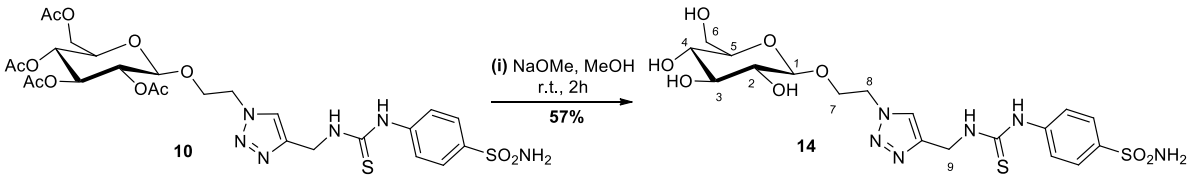
Synthesis of compound 12



Sodium carbonate (39 mg, 0.37 mmol) was added to a solution of **11** (35 mg, 0.07 mmol) in MeOH (6 mL) and the mixture was stirred at room temperature for 18 hours, until a TLC control attested the disappearance of the starting material **11** (R_f = 0.35, DCM:MeOH:NH_4OH (6%) 5:1:0.1). The mixture was neutralized with a HCl 1% in MeOH solution and then filtered. The solvent was removed under vacuum to obtain 23 mg of pure **12** (R_f = 0.00, DCM:MeOH:NH_4OH (6%) 5:1:0.1, 0.07 mmol, quantitative) as a waxy white solid.

12: $[\alpha]_D^{24}$ = – 5.82 (c = 0.55, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ ppm: 8.25 (s, 1H, triazole), 4.69 (t, J = 5.0 Hz, 2H, H-8), 4.31 (d, J = 7.8 Hz, 1H, H-1), 4.26 (br s, 2H, H-9), 4.25-4.20 (m, 1H, Ha-7), 4.06-3.99 (m, 1H, Hb-7), 3.86 (d, J = 12.3 Hz, 1H, Ha-6), 3.70-3.63 (m, 1H, Hb-6), 3.35-3.33 (m, 1H, H-3), 3.29-3.25 (m, 2H, H-4, H-5), 3.17 (t, J = Hz, 1H, H-2). ^{13}C-NMR (50 MHz, CD_3OD) δ ppm: 140.9 (s, 1C, triazole), 126.8 (d, 1C, triazole), 104.5 (d, 1C, C-1), 78.0, 77.9 (d, 2C, C-3, C-5), 74.9 (d, 1C, C-2), 71.5 (d, 1C, C-4), 69.1 (t, 1C, C-7), 62.6 (t, 1C, C-6), 51.8 (t, 1C, C-8), 35.5 (t, 1C, C-9). MS-ESI (m/z, %) = 305.11 (68) $[M+H]^+$, 327.16 (100) $[M+Na]^+$, 630.83 (49) $[2M+Na]^+$. $C_{11}H_{20}N_4O_6$ (304.30): calcd C, 43.42; H, 6.62; N, 18.41; found C, 43.22; H, 6.80; N, 18.50.

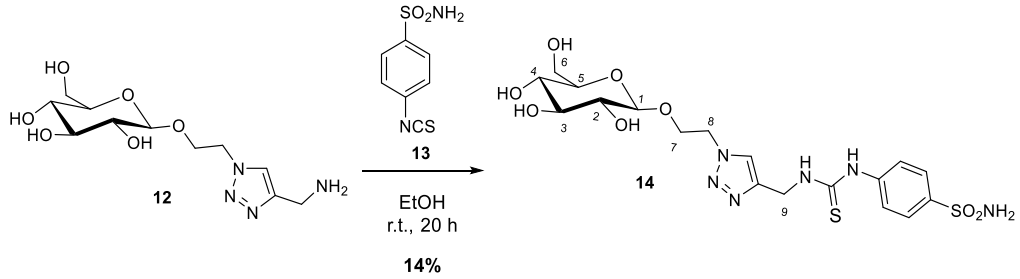
Synthesis of compound 14 – Procedure I



NaOMe (2 mg, 0.04 mmol) was added to a solution of **10** (28 mg, 0.04 mmol) in MeOH (2 ml), and the reaction mixture was left stirring for 2 hours until a TLC control attested the disappearance of the starting material (R_f = 0.37, DCM: MeOH 10:1). Then, a small amount of resin Amberlyst 15 was added to neutralize the reaction mixture. The mixture was filtered and concentrated under vacuum and the crude was purified by flash column chromatography on silica gel (DCM: MeOH 3:1) to give 12 mg of **14** (R_f = 0.13, DCM:MeOH 3:1, 0.02 mmol, 57%) as a pale yellow oil.

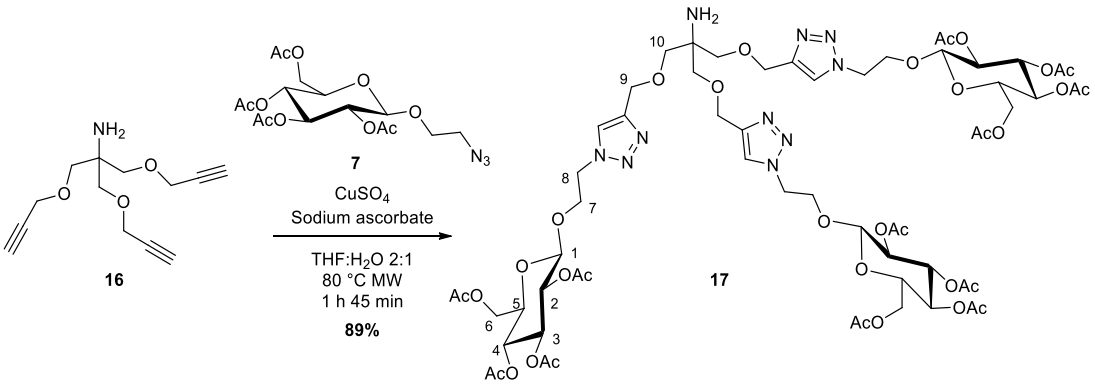
14: $[\alpha]_D^{24} = -2.67$ (c = 0.75, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ ppm: 8.13 (s, 1H, triazole), 7.84 (d, J = 8.8 Hz, AB system, 2H, Ar), 7.67 (d, J = 8.7 Hz, AB system, 2H, Ar), 4.88 (br s, 2H, H-9), 4.64 (t, J = 5.3 Hz, 2H, H-8), 4.30 (d, J = 7.8 Hz, 1H, H-1), 4.27-4.19 (m, 1H, Ha-7), 4.00 (quint, J = 4.8 Hz, 1H, Hb-7), 3.88-3.83 (m, 1H, Ha-6), 3.65 (dd, J = 5.4, 11.9 Hz, 1H, Hb-6), 3.35-3.33 (m, 1H, H-3), 3.28-3.24 (m, 2H, H-4, H-5), 3.18 (t, J = 7.9 Hz, 1H, H-2). ^{13}C-NMR (100 MHz, CD_3OD) δ ppm: 182.7 (s, 1C, C=S), 145.6 (s, 1C, triazole), 144.1 (s, 1C, Ar), 140.2 (s, 1C, Ar), 128.0 (d, 2C, Ar), 125.8 (d, 1C, triazole), 123.7 (d, 2C, Ar), 104.6 (d, 1C, C-1), 78.1, 77.9 (d, 2C, C-3, C-5), 74.9 (d, 1C, C-2), 71.5 (d, 1C, C-4), 69.1 (t, 1C, C-7), 62.7 (t, 1C, C-6), 51.7 (t, 1C, C-8), 40.5 (t, 1C, C-9). MS-ESI (m/z, %) = 541.00 (100) $[M+Na]^+$. $C_{18}H_{26}N_6O_8S_2$ (518.56): calcd C, 41.69; H, 5.05; N, 16.21; S, 12.37. found C, 41.39; H, 5.20; N, 16.30; S, 12.30.

Synthesis of compound 14 - Procedure II



Benzensulfonamide **13** (86 mg, 0.40 mmol) was added to a suspension of **12** (62 mg, 0.20 mmol) in EtOH (3 mL) and the mixture was stirred at room temperature for 20 hours. Then, the crude was evaporated under vacuum and purified by flash column chromatography on silica gel (DCM:MeOH from 10:1 to 5:1) to give 15 mg of **14** (R_f = 0.13, DCM:MeOH 3:1, 0.03 mmol, 14%) as a pale yellow oil.

Synthesis of compound 17

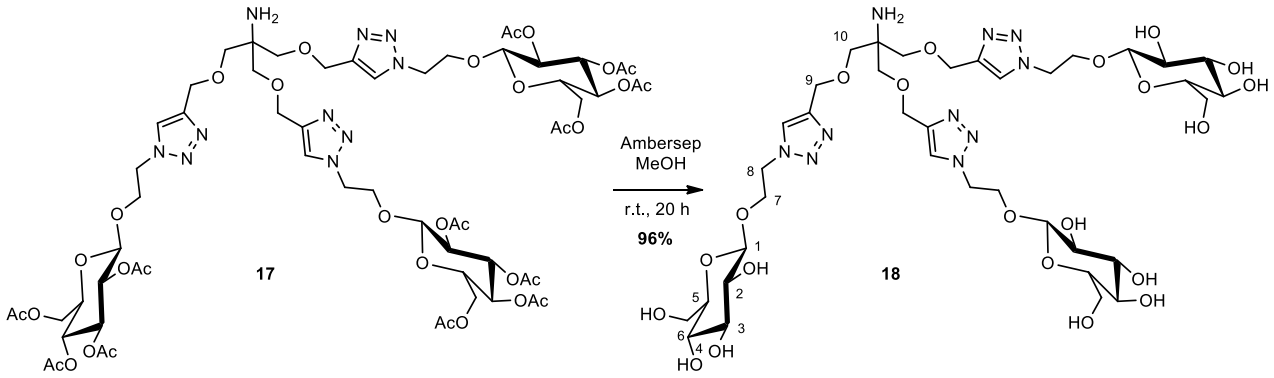


Azide **7** (247 mg, 0.59 mmol), $CuSO_4$ (10 mg, 0.06 mmol) and sodium ascorbate (23 mg, 0.12 mmol) were added to a solution of compound **16** (45 mg, 0.19 mmol) in THF (2 mL) and milliQ water (1 mL). The mixture was stirred under microwave irradiation at 80 °C for 1 h and 45 minutes, until a TLC control attested the disappearance of the starting material **16** (R_f = 0.47, DCM: MeOH 10:1). The mixture was filtered through Celite®, the solvent was removed under vacuum and subsequently the crude mixture was treated with 'Quadrasil MP®' resin keeping the mixture under stirring at room temperature in the minimum amount of MeOH for 1 hour (1 g of resin for each mmol of copper). The crude was purified by flash column

chromatography on silica gel (gradient eluent from DCM:MeOH 20:1 to DCM:MeOH:NH_4OH (6%) 10:1:0.1) to give 252 mg of **17** (R_f = 0.33, DCM:MeOH 10:1, 0.17 mmol, 89%) as a pale orange waxy solid.

17: $[\alpha]_D^{24}$ = − 11.38 (c = 0.8, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm = 7.58 (s, 3H, triazole), 5.13 (t, *J* = 9.5 Hz, 3H, H-3), 5.02 (t, *J* = 9.7 Hz, 3H, H-4), 4.94 (t, *J* = 9.5 Hz, 3H, H-2), 4.56-4.44 (m, 15H, H-1, H-8, H-9), 4.24-4.16 (m, 6H, Ha-6, Ha-7), 4.08 (dd, *J* = 1.9, 12.4 Hz, 3H, Hb-6), 3.93-3.84 (m, 3H, Hb-7), 3.70-3.63 (m, 3H, H-5), 3.40 (s, 6H, H-10), 2.04 (s, 9H, OAc), 1.97 (s, 9H, OAc), 1.95 (s, 9H, OAc), 1.89 (s, 9H, OAc). ^{13}C-NMR (100 MHz, $CDCl_3$): δ ppm = 170.6 (s, 3C, C=O), 170.1 (s, 3C, C=O), 169.4 (s, 3C, C=O), 169.3 (s, 3C, C=O), 144.9 (s, 3C, triazole), 123.9 (d, 3C, triazole), 110.1 (interference), 100.5 (d, 3C, C-1), 72.4 (d, 3C, C-3), 72.2 (t, 3C, C-10), 71.9 (d, 3C, C-5), 70.9 (d, 3C, C-2), 68.2 (d, 3C, C-4), 67.8 (t, 3C, C-7), 64.8 (t, 3C, C-9), 61.7 (t, 3C, C-6), 56.1 (s, 1C, HN<u>C</u>(CH_3O-), 49.9 (t, 3C, C-8), 20.8 (q, 3C, OAc), 20.6 (q, 9C, OAc). IR ($CDCl_3$): ν̃ = 3684, 2955, 2876, 2361, 2255, 1751, 1431, 1373, 1225, 1043, 931 cm^{-1}. MS-ESI (m/z, %) = 755.50 (100) $[M+H+Na]^{2+}$, 1487.01 (92) $[M+H]^+$. $C_{61}H_{86}N_{10}O_{33}$ (1487.38): calcd C, 49.26; H, 5.83; N, 9.42; found C, 45.99; H, 5.95; N, 9.55.

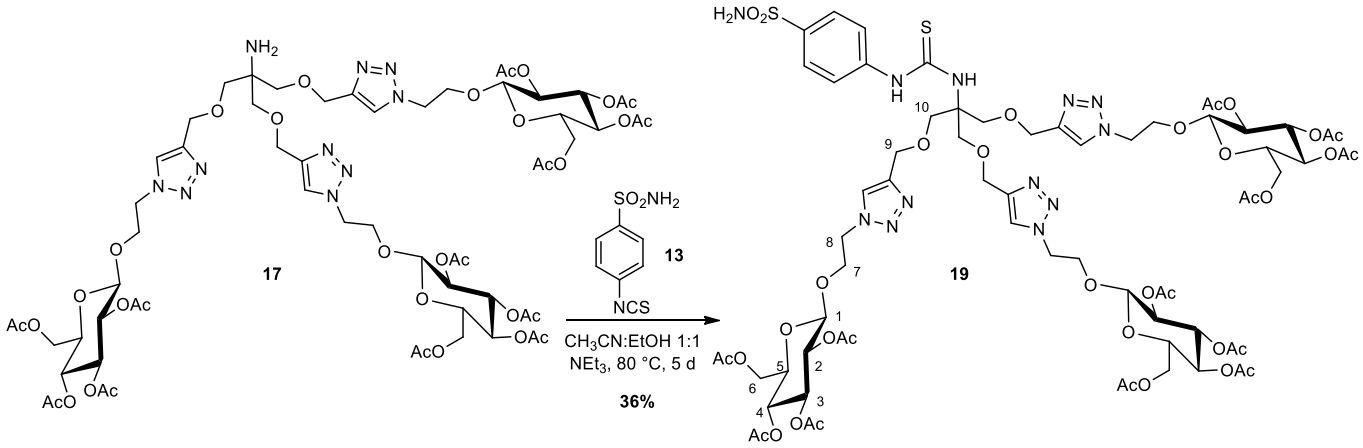
Synthesis of compound 18



A solution of compound **17** (82 mg, 0.06 mmol) in MeOH (11 mL) was left stirring at room temperature for 16 hours with the strongly basic resin Ambersep 900-OH. The reaction mixture was filtered and evaporated under vacuum to afford 52 mg of pure **18** (R_f = 0.00, DCM:MeOH 10:1, 0.05 mmol, 96%) as a white waxy solid.

18: $[\alpha]_D^{23}$ = − 7.80 (c = 0.65, MeOH). ^{1}H-NMR (400 MHz, CD_3OD): δ ppm = 8.10 (s, 3H, triazole), 4.64 (t, J = 4.9 Hz, 6H, H-8), 4.56 (s, 6H, H-9), 4.31 (d, J = 7.8 Hz, 3H, H-1), 4.27-4.20 (m, 3H, Ha-7), 4.03-3.97 (m, 3H, Hb-7), 3.86 (d, J = 11.7 Hz, 3H, Ha-6), 3.66 (dd, J = 4.2, 11.4 Hz, 3H, Hb-6), 3.41 (s, 6H, H-10), 3.36-3.33 (m, 3H, H-3), 3.30-3.23 (m, 6H, H-4, H-5), 3.19 (t, J = 8.4 Hz, 3H, H-2). ^{13}C-NMR (MHz, CD_3OD) δ ppm= 145.7 (s, 3C, triazole), 126.3 (d, 3C, triazole), 104.5 (s, 3C, C-1), 78.0, 77.9 (d, 6C, C-3, C-5), 74.9 (d, 3C, C-2), 72.5 (t, 3C, C-10), 71.5 (d, 3C, C-4), 69.1 (t, 3C, C-7), 65.3 (t, 3C, C-9), 62.6 (t, 3C, C-6), 57.0 (s, 1C, HN<u>C</u>(CH_2O)$_3$-), 51.6 (t, 3C, C-8). MS-ESI (m/z, %) = 503.14 (28) $[M+H+Na]^{2+}$, 983.21 (75) $[M+H]^+$, 1005.23 (100) $[M+Na]^+$. $C_{37}H_{62}N_{10}O_{21}$ (982.94): calcd C, 45.21; H, 6.36; N, 14.25; found C, 45.10; H, 6.66; N, 14.17.

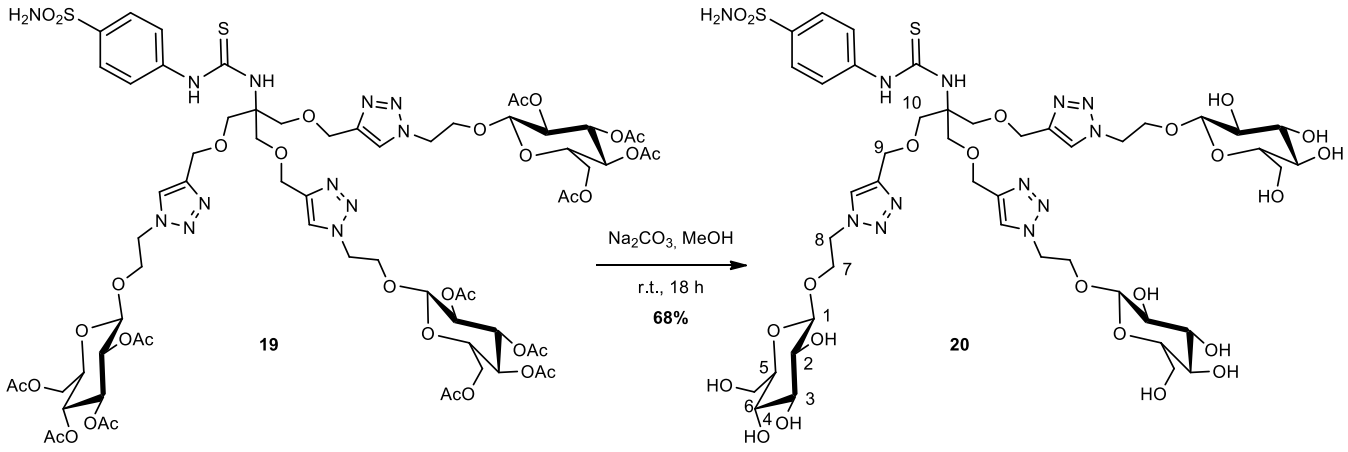
Synthesis of compound 19



Benzensulfonamide **13** (20 mg, 0.09 mmol) and NEt_3 (26 µl, 0.19 mmol) were added to a solution of **17** (140 mg, 0.09 mmol) in CH_3CN (1 ml) and EtOH (1 mL) and the mixture was stirred at 80 °C for 5 d until a TLC control attested the disappearance of the starting material **17** (R_f = 0.33, DCM: MeOH 10:1). Then, the crude was evaporated under vacuum and purified by flash column chromatography on silica gel (gradient eluent from DCM:MeOH 30:1 to 25:1) to give 58 mg of **19** (R_f = 0.43, DCM:MeOH 10:1, 0.03 mmol, 36%) as a yellow waxy solid.

19: $[\alpha]_D^{22}$ = − 31.70 (c = 0.6, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ ppm: 7.88 (s, 3H, triazole), 7.78 (d, J = 8.9 Hz, AB system, 2H, Ar), 7.50 (d, J = 8.8 Hz, AB system, 2H, Ar), 5.22 (t, J = 9.5 Hz, 3H, H-3), 5.01 (t, J = 9.6 Hz, 3H, H-4), 4.89-4.85 (m, 3H, H-2), 4.68 (d, J = 8.0 Hz, 3H, H-1), 4.63-4.56 (m, 12H, H-8, H-9), 4.28 (m, J = 4.8, 12.4 Hz, 3H, Ha-6), 4.24-4.17 (m, 3H, Ha-7), 4.13 (m, J = 2.3, 12.4 Hz, 3H, Hb-6), 4.04-3.96 (m, 3H, Hb-7), 3.90-3.80 (m, 9H, H-5, H-10), 2.05 (s, 9H, OAc), 2.00 (s, 9H, OAc), 1.96-1.94 (m, 9H, OAc), 1.93-1.91 (m, 9H, OAc). ^{13}C-NMR (50 MHz, CD_3OD) δ ppm: 172.3 (s, 3C, C=O), 171.6 (s, 3C, C=O), 171.3 (s, 3C, C=O), 171.1 (s, 3C, C=O), 156.4 (s, 1C, C-SH), 145.8 (s, 3C, triazole), 145.0 (s, 1C, Ar), 137.4 (s, 1C, Ar), 128.4 (d, 2C, Ar), 125.8 (d, 3C, triazole), 118.8 (d, 2C, Ar), 101.6 (d, 3C, C-1), 74.1 (d, 1C, C-3), 73.0 (d, 3C, C-5), 72.6 (d, 3C, C-2), 70.4 (t, 3C, C-10), 69.8 (d, 3C, C-4), 68.9 (t, 3C, C-7), 65.4 (t, 3C, C-9), 63.1 (t, 3C, C-6), 60.4 (s, 1C, HN<u>C</u>$(CH_2O)_3$-), 51.3 (t, 3C, C-8), 20.7 (q, 6C, OAc), 20.6 (q, 6C, OAc). IR ($CHCl_3$) ṽ = 3401, 3019, 2959, 2918, 1755, 1535, 1462, 1368, 1233, 1201, 1161, 1041 cm^{-1}. MS-ESI (m/z, %) = 865.42 (100) $[M-4H+8D+H+Na]^{2+}$. $C_{68}H_{92}N_{12}O_{35}S_2$ (1701.65): calcd C, 48.00; H, 5.45; N, 9.88; S, 3.77. found C, 47.88; H, 5.69; N, 9.65; S, 3.89.

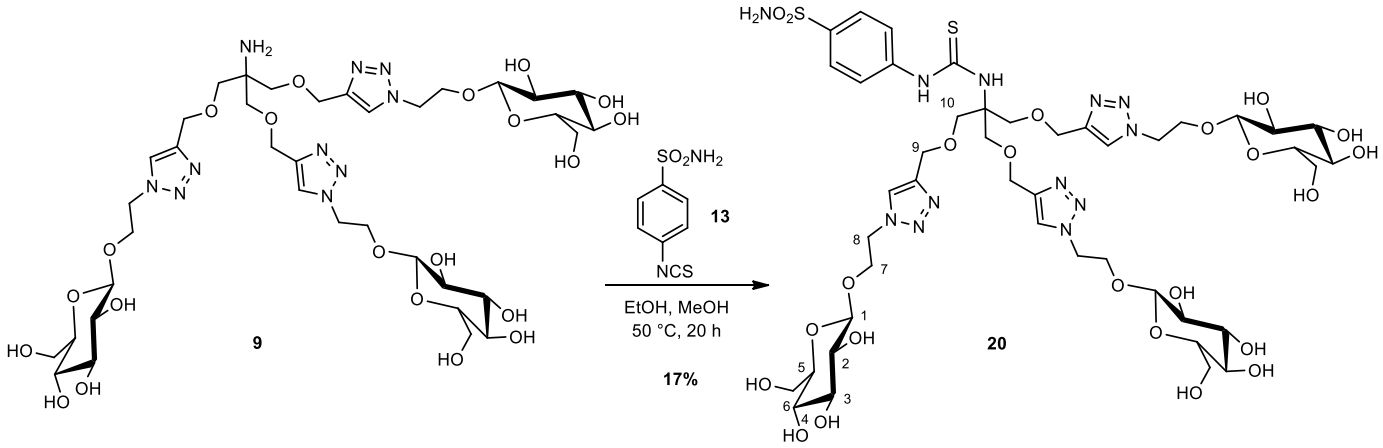
Synthesis of compound 20 – Procedure I



Na_2CO_3 (6 mg, 0.06 mmol) was added to a solution of **19** (20 mg, 0.01 mmol) in MeOH (1 ml) and the reaction mixture was left stirring for 18 hours at room temperature until a TLC control attested the disappearance of the starting material **19** (R_f = 0.43, DCM: MeOH 10:1). Then, the reaction mixture was filtered and concentrated under vacuum. The crude was purified by size exclusion chromatography, employing Sephadex LH-20® resin and eluting with MeOH to give 10 mg of **20** (R_f = 0.00, DCM:MeOH 10:1, 0.01 mmol, 68%) as a colourless oil.

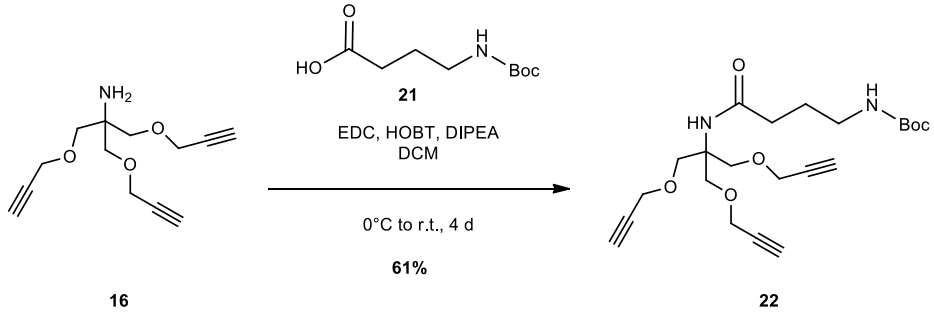
20: $[\alpha]_D^{22}$ = − 4.80 (c = 1, MeOH). ^{1}H-NMR (400 MHz, CD_3OD): δ ppm = 8.09 (s, 3H, triazole), 7.77 (d, J = 8.8 Hz, AB system, 2H, Ar), 7.48 (d, J = 8.8 Hz, AB system, 2H, Ar), 4.62 (t, J = 4.7 Hz, 6H, H-8), 4.59 (s, 6H, H-9), 4.30 (d, J = 7.8 Hz, 3H, H-1), 4.26-4.19 (m, 3H, Ha-7), 4.02-3.95 (m, 3H, Hb-7), 3.86 (d, J = 11.7 Hz, 3H, Ha-6), 3.78 (s, 6H, H-10), 3.65 (dd, J = 4.0, 11.4 Hz, 3H, Hb-6), 3.36-3.34 (m, 3H, H-3), 3.29-3.25 (m, 6H, H-4, H-5), 3.19 (t, J = 8.1 Hz, 3H, H-2). ^{13}C-NMR (100 MHz, CD_3OD) δ ppm= 156.5 (s, 1C, C-SH), 145.6 (s, 3C, triazole) 145.0 (s, 1C, Ar), 137.4 (s, 1C, Ar), 128.3 (d, 2C, Ar), 126.3 (d, 3C, triazole), 118.9 (d, 2C, Ar), 111.9, 111.4 (interferences), 104.5 (s, 3C, C-1), 78.0, 77.9 (d, 6C, C-3, C-4), 74.9 (d, 3C, C-2), 71.5 (d, 3C, C-5), 70.1 (t, 3C, C-10), 69.0 (t, 3C, C-7), 65.2 (t, 3C, C-9), 62.7 (t, 3C, C-6), 60.4 (s, 1C, HN<u>C</u>$(CH_2O)_3$-), 51.6 (t, 3C, C-8). MS-ESI (m/z, %) = 1203.08 (100), $[M-4H+8D+H]^+$, 613.25 (51) $[M-4H+8D+H+Na]^{2+}$. $C_{44}H_{68}N_{12}O_{23}S_2$ (1197.21): calcd C, 44.14; H, 5.72; N, 14.04; S, 5.36; found C, 43.95; H, 5.95; N, 14.15; S, 5.22.

Synthesis of compound 20 - Procedure II



Benzensulfonamide **13** (13 mg, 0.06 mmol) was added to a suspension of **9** (59 mg, 0.06 mmol) in EtOH (1 mL) and MeOH (0.6 mL) and the mixture was stirred at 50 °C for 20 hours. Then, the crude was evaporated under vacuum and purified by flash column chromatography on silica gel (gradient eluent from DCM:MeOH 10:1 to 2:1) to give 12 mg of **20** (R_f = 0.00, DCM:MeOH 10:1, 0.01 mmol, 17%) as a coulorless oil.

Synthesis of compound 22

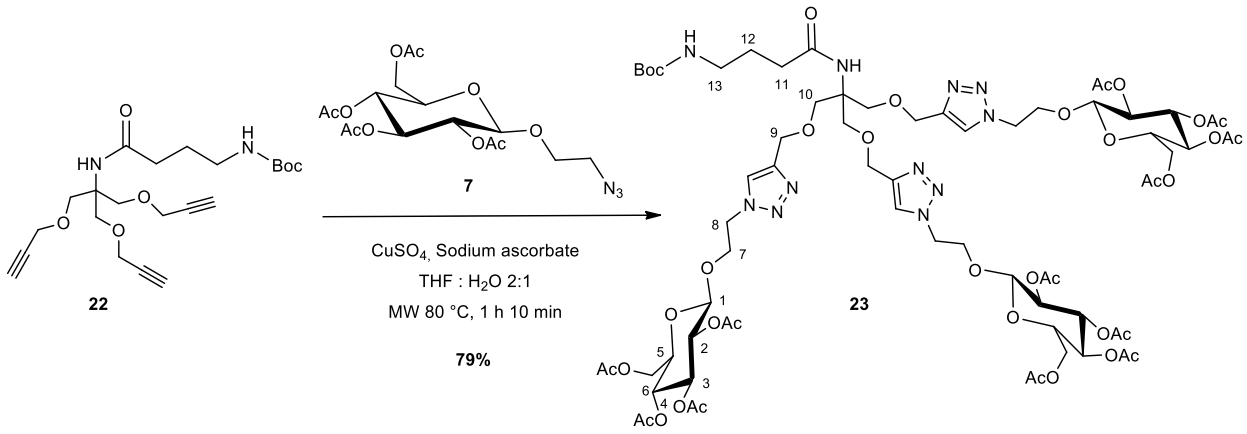


A solution of EDC·HCl (33 mg, 0.21 mmol), HOBt (28 mg, 0.21 mmol) and **21** (39 mg, 0.19 mmol) in DCM (19 mL) was left stirring for 1 hour and then added to a solution of **16** (45 mg, 0.19 mmol) and DIPEA (36 µL, 0.21 mmol). The reaction mixture was stirred at room temperature for 4 days until a TLC control attested the disappearance of the starting material **16** (R_f = 0.25, DCM:MeOH 20:1). Then, the reaction was diluted with DCM, washed with $KHSO_4$ (2x), $NaHCO_3$ (2x) and brine (2x) and finally concentrated after drying with Na_2SO_4. The crude residue was purified by flash column chromatography on silica gel (gradient eluent from DCM:Et_2O 8:1 to 4:1) to give 49 mg of **22** (R_f = 0.18, DCM:Et_2O 8:1, 0.12 mmol, 61%) as a colourless oil.

22: ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: = 5.94 (s, 1H, H-NC=O), 4.78 (s, 1H, HN-COO), 4.12 (d, J = 2.4 Hz, 6H, $CH_2C{\equiv}CH$), 3.82 (s, 6H, $C(CH_2O)_3$), 3.17-3.12 (m, 2H, CH_2NHBoc), 2.43 (t, J = 2.3 Hz, 3H, $-C{\equiv}CH$), 2.70 (t, J = 7.1 Hz, 2H, $CH_2C=O$), 1.76 (quint, J = 6.9 Hz, 2H, CH_2-CH_2-CH_2), 1.41 (s, 9H, $OC(CH_3)_3$). ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 172.8 (s, 1C, HN-C=O), 156.3 (s, 1C, HN-COO), 79.7 (s, 1C, $OC(CH_3)_3$), 79.3 (s, 3C, C≡C), 74.7 (d, 3C, C≡C), 68.7 (t, 3C, $C(CH_2O)_3$), 59.4 (s, 1C, $HNC(CH_2O)_3$-), 58.8 (t, 3C, $CH_2C{\equiv}CH$), 40.0 (t, 1C, CH_2NHBoc), 34.5 (t, 1C, $CH_2C=O$), 28.6 (q, 3C, $OC(CH_3)_3$), 26.2 (d, 1C, CH_2-CH_2-CH_2). IR ($CDCl_3$): ν̃ = 2429, 3306, 2936, 2253, 1703, 1508, 1470,

1364, 1256, 1219, 1167, 1098 cm^{-1}. MS (ESI) (*m/z,* %) = 443.20 (100) $[M+ Na]^+$. $C_{22}H_{32}N_2O_6$ (420.50): calcd C, 62.84; H, 7.67; N, 6.66; found C, 62.77; H, 7.88; N, 6.63.

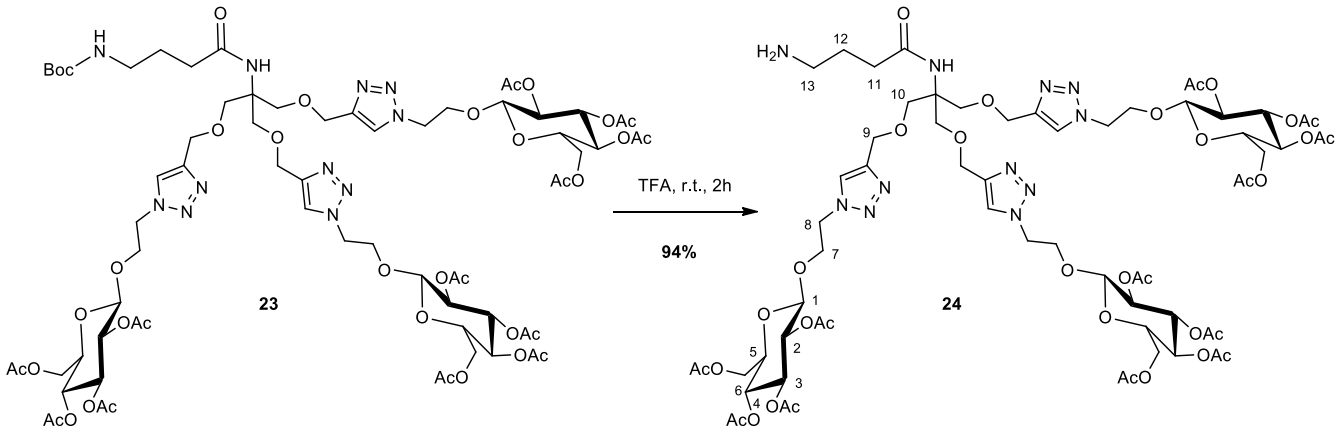
Synthesis of compound 23



Azide **7** (141 mg, 0.34 mmol), $CuSO_4$ (5 mg, 0.03 mmol) and sodium ascorbate (13 mg, 0.07 mmol) were added to a solution of compound **22** (46 mg, 0.11 mmol) in THF (2 mL) and milliQ water (1 mL). The mixture was stirred under microwave irradiation at 80 °C for 1 h and 10 minutes, until a TLC control attested the disappearance of the starting material **22** (R_f = 0.47, DCM:MeOH 10:1). The mixture was filtered through Celite®, the solvent was removed under vacuum and subsequently the crude mixture was treated with 'Quadrasil MP®' resin keeping the mixture under stirring at room temperature in the minimum amount of MeOH for 1 hour (1 g of resin for each mmol of copper). The crude was purified by flash column chromatography on silica gel (DCM:MeOH 20:1) to give 144 mg of **23** (R_f = 0.22, DCM:MeOH 20:1, 0.09 mmol, 79%) as a white waxy solid.

23: $[\alpha]_D^{21} = -$ 17.70 (c = 0.6, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.57 (s, 3H, triazole), 6.46 (br s, 1H, NH), 5.15 (t, J = 9.5 Hz, 3H, H-3), 5.03 (t, J = 9.9 Hz, 3H, H-4), 4.95 (t, J = 9.6 Hz, 3H, H-2), 4.60-4.44 (m, 15H, H-1, H-8, H-9), 4.26-4.17 (m, 6H, Ha-6, Ha-7), 4.09 (d, J = 12.2 Hz, 3H, Hb-6), 3.94-3.86 (m, 3H, Hb-7), 3.79 (s, 6H, H-10), 3.72-3.65 (m, 3H, H-5), 3.14-3.01 (m, 2H, H-13), 2.17 (t, J = 6.8 Hz, 2H, H-11), 2.06 (s, 9H, OAc), 1.99 (s, 9H, OAc), 1.96 (s, 9H, OAc), 1.90 (s, 9H, OAc), 1.72 (quint, J = 6.6 Hz, 2H, H-12), 1.39 (s, 9H, $OC(CH_3)_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 172.9 (s, 1C, HNC=O), 170.6 (s, 3C, O=CCH_3), 170.2 (s, 3C, O=CCH_3), 169.5 (s, 3C, O=CCH_3), 169.4 (s, 3C, O=CCH_3), 156.2 (s, 1C, HN-C=OO), 144.8 (s, 3C, triazole), 123.9 (d, 3C, triazole), 100.6 (d, 3C, C-1), 79.0 (s, 1C, -$OC(CH_3)_3$), 72.5 (d, 3C, C-3), 72.0 (d, 3C, C-5), 71.0 (d, 1C, C-2), 69.0 (t, 3C, C-10), 68.3 (d, 3C, C-4), 67.9 (t, 3C, C-7), 64.8 (t, 3C, C-8), 61.8 (t, 3C, C-6), 59.8 (s, 1C, $HNC(CH_2O)_3$-), 49.9 (t, 3C, C-9), 39.9 (t, 1C, C-13), 34.4 (t, 1C, C-11), 28.5 (q, 3C, $OC(CH_3)_3$), 26.1 (t, 1C, C-12), 20.8 (q, 6C, OAc), 20.6 (q, 6C, OAc). IR ($CDCl_3$) ν̃ = 3672, 3451, 3030, 3005, 2880, 1753, 1512, 1369, 1238, 1198, 1171, 1042, 959 cm^{-1}. MS-ESI (m/z, %) = 858.82 (100) $[M+H+Na]^{2+}$, 1693.92 (35) $[M+Na]^+$.$C_{70}H_{101}N_{11}O_{36}$ (1672.60): calcd C, 50.27; H, 6.09; N, 9.21; found C, 50.01; H, 6.38; N, 9.33.

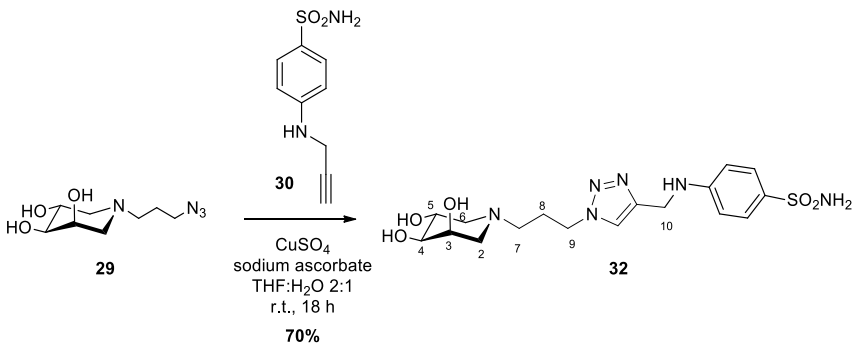
Synthesis of compound 24



A solution of **23** (77 mg, 0.05 mmol) in TFA (2 mL) was left stirring at room temperature for 2 h until a TLC control attested the disappearance of the starting material **23** (R_f = 0.45, DCM:MeOH 10:1). The reaction mixture was concentrated and then the crude was purified by flash column chromatography on silica gel (DCM:MeOH:NH_4OH (6%) 8:1:0.1) to give 68 mg of **24** (R_f = 0.29, DCM:MeOH:NH_4OH (6%) 8:1:0.1, 0.04 mmol, 94%) as a white waxy solid.

24: $[\alpha]_D^{22}$ = − 12.40 (c = 0.45, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.41 (br s, 1H, NH), 7.61 (s, 3H, triazole), 7.21 (br s, 1H, NH), 5.17 (t, J = 9.5 Hz, 3H, H-3), 5.06 (t, J = 9.8 Hz, 3H, H-4), 4.97 (t, J = 8.0 Hz, 3H, H-2), 4.65-4.47 (m, 15H, H-1, H-8, H-9), 4.29-4.18 (m, 6H, Ha-6, Ha-7), 4.12 (dd, J = 2.2, 12.4 Hz, 3H, Hb-6), 3.97-3.88 (m, 3H, Hb-7), 3.83-3.75 (m, 6H, H-10), 3.74-3.69 (m, 3H, H-5), 3.16 (br s, 2H, H-13), 2.42 (br s, 2H, H-11), 2.08 (s, 9H, OAc), 2.01 (s, 9H, OAc), 2.00-1.97 (m, 11H, OAc, H-12), 1.92 (s, 9H, OAc). ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 173.4 (s, 1C, HN-C=O), 170.8 (s, 3C, O=CCH$_3$), 170.2 (s, 3C, O=CCH$_3$), 169.6 (s, 6C, O=CCH$_3$), 144.5 (s, 3C, triazole), 124.2 (d, 3C, triazole), 100.7 (d, 3C, C-1), 72.6 (d, 3C, C-3), 72.1 (d, 3C, C-5), 71.1 (d, 1C, C-2), 69.0 (t, 3C, C-10), 68.4 (d, 3C, C-4), 67.9 (t, 3C, C-7), 64.4 (t, 3C, C-8), 61.9 (t, 3C, C-6), 60.1 (s, 1C, HNC(CH$_2$O)$_3$-), 50.2 (t, 3C, C-9), 39.7 (t, 1C, C-13), 34.7 (t, 1C, C-11), 23.3 (t, 1C, C-12), 20.8, 20.7 (q, 12C, O=CCH$_3$). IR ($CDCl_3$) ṽ = 3684, 3032, 3003, 2947, 2878, 1753, 1674, 1603, 1516, 1474, 1425, 1371, 1236, 1196, 1138, 1042 cm^{-1}. MS-ESI (m/z, %) = 1572.01 (100) $[M+H]^+$, 797.70 (31) $[M+H+Na]^{2+}$. $C_{65}H_{93}N_{11}O_{34}$ (1572.49): calcd C, 49.65; H, 5.96; N, 9.80; found C, 49.42; H, 6.15; N, 9.66.

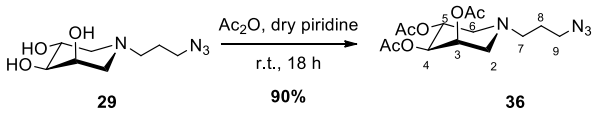
Synthesis of compound 32



Sulfonamide **30** (43 mg, 0.21 mmol), $CuSO_4$ (9 mg, 0,06 mmol) and sodium ascorbate (22 mg, 0.11 mmol) were added to a solution of azide **29** (40 mg, 0,19 mmol) in THF (2 mL) and milliQ water (1 mL). The reaction mixture was stirred at room temperature for 18 hours, until a TLC control attested the disappearance of the starting material **29** (R_f = 0.20, DCM:MeOH:NH_4OH (6%) 5:1:0.1). The mixture was filtered through Celite®, the solvent was removed under vacuum and subsequently the crude was treated with 'Quadrasil MP®' resin keeping the mixture under stirring at room temperature in the minimum amount of MeOH for 1 hour (1 g of resin for each mmol of copper). The crude was purified by flash column chromatography on silica gel (gradient eluent from DCM:MeOH:NH_4OH (6%) 2:1:0.1 to 1:1:0.1) to give 55 mg of **32** (R_f = 0.19, DCM:MeOH:NH_4OH (6%) 2:1:0.1, 0.13 mmol, 70%) as a white waxy solid.

32: $[\alpha]_D^{21}$ = − 8.50 (c = 1.00, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ ppm: 7.90 (s, 1H, H-triazole), 7.61 (d, J = 7.4 Hz, AB system, 2H, Ar), 6.69 (d, J = 7.6 Hz, AB system, 2H, Ar), 4.47-4.45 (m, 2H, H-10), 4.44-4.39 (m, 2H, H-9), 3.87 (br s, 1H, H-3), 3.79-3.73 (m, 1H, H-5), 3.43-3.36 (m, 1H, H-4), 2.80-2.70 (m, 1H, Ha-6), 2.70-2.59 (m, 1H, Ha-2), 2.36-2.18 (m, 3H, H-7, Hb-2), 2.10-1.97 (m, 3H, Hb-6, H-8). ^{13}C-NMR (100 MHz, CD_3OD) δ ppm: 152.7 (s, 1C, Ar), 146.9 (s, 1C, triazole), 131.4 (s, 1C, Ar), 128.9 (d, 2C, Ar), 124.6 (d, 1C, triazole), 112.7 (d, 2C, Ar), 75.2 (d, 1C, C-4), 69.5 (d, 1C, C-5), 69.1 (d, 1C, C-3), 57.8 (t, 1C, C-2), 57.4 (t, 1C, C-6), 55.0 (t, 1C, C-7), 49.1 (t, 1C, C-9), 39.4 (t, 1C, C-10), 28.1 (t, 1C, C-8). MS-ESI (m/z, %) = 425.12 (100) $[M-H]^-$. $C_{17}H_{26}N_6O_5S$ (426.49): calcd C, 47.87; H, 6.14; N, 19.71; S, 7.52; found C, 47.63; H, 6.28; N, 19.90; S, 7.55.

Synthesis of compound 36

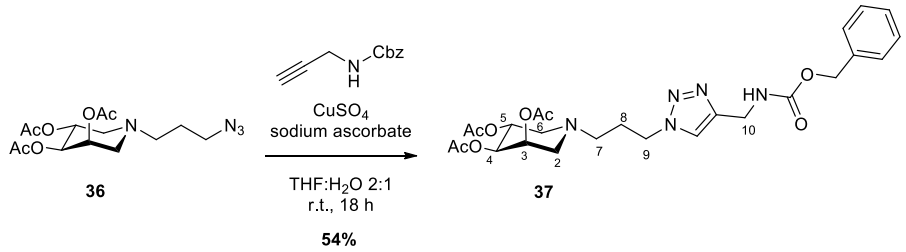


29 **36**

A solution of **29** (69 mg, 0.32 mmol) in dry pyridine (0.8 mL) was stirred with acetic anhydride (0.3 mL, 3.17 mmol) at room temperature for 18 h until a TLC control attested the disappearance of the starting material **29** (R_f = 0.14, DCM:MeOH 10:1). The crude mixture was diluted with toluene and then concentrated under vacuum. The crude was purified by gradient silica gel column chromatography (gradient eluent from Hexane:AcOEt 1.5:1 to 1:1) to give 98 mg of the acetylated compound **36** (R_f = 0.23, Hexane/AcOEt 1.5:1, 0.26 mmol, 90 %) as a colourless oil.

36: $[\alpha]_D^{21}$ = − 52.83 (c = 0.6, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 5.28-5.22 (m, 1H, H-3), 5.12 (ddd, J = 4.4, 8.3, 8.4 Hz, 1H, H-5), 4.97-4.89 (m, 1H, H-4), 3.38-3.25 (m, 2H, H-9), 2.96 (br d, J = 8.9 Hz, 1H, Ha-6), 2.86-2.77 (m, 1H, Ha-2), 2.46 (t, J = 6.7 Hz, 2H, H-7), 2.43-2.38 (m, 1H, Hb-2), 2.27-2.16 (m, 1H, Hb-6), 2.06 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.75-1.64 (m, 2H, H-8). ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 170.4 (s, 1C, C=O), 170.1 (s, 2C, C=O), 71.0 (d, 1C, C-4), 68.3 (d, 1C, C-5), 67.9 (d, 1C, C-3), 54.1 (t, 1C, C-6), 53.9 (t, 1C, C-7), 53.6 (t, 1C, C-2), 49.2 (t, 1C, C-9), 26.3 (t, 1C, C-8), 21.0 q, 2C, OAc), 20.9 (q, 1C, OAc). IR ($CDCl_3$) ν̃ = 3670, 3582, 2958, 2823, 2101, 1743, 1468, 1372, 1236, 1147, 1048, 938 cm^{-1}. MS-ESI (m/z, %) = 365.08 (99) $[M+Na]^+$, 706.42 $[2M+Na]^+$. $C_{14}H_{22}N_4O_6$ (342.35): calcd C, 49.12; H, 6.48; N, 16.37; found C, 48.99; H, 6.55; N, 16.45.

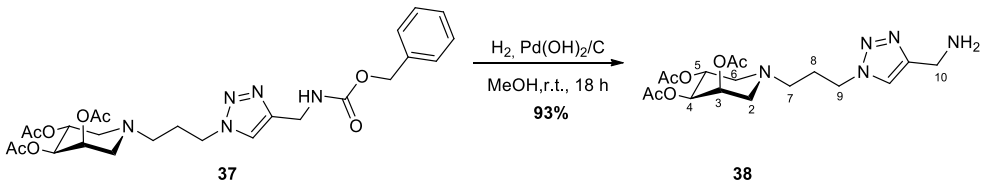
Synthesis of compound 37



Azide **36** (215 mg, 0.63 mmol), $CuSO_4$ (30 mg, 0.19 mmol) and sodium ascorbate (75 mg, 0.38 mmol) were added to a solution of protected propargylamine (130 mg, 0.69 mmol) in THF (2 mL) and milliQ water (1 mL). The reaction mixture was stirred at room temperature for 18 hours, until a TLC control attested the disappearance of the starting material **36** (R_f = 0.70, DCM: MeOH:NH_4OH (6%) 10:1:0.1). The mixture was filtered through Celite® and the crude was purified by flash column chromatography on silica gel (DCM: MeOH 25:1) to give 180 mg of **37** (R_f = 0.24, DCM:MeOH 25:1, 0.34 mmol, 54%) as a white waxy solid.

37: $[\alpha]_D^{24}$ = − 12.80 (c = 0.5, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.56 (s, 1H, triazole), 7.35-7.28 (m, 5H, Ar), 5.66 (t, J = 5.1 Hz, NH), 5.29-5.24 (m, 1H, H-3), 5.12-5.08 (m, 1H, H-5), 5.08-5.04 (m, 2H, CH_2Ph), 4.93 (dd, J = 3.3, 8.6 Hz, 1H, H-4), 4.42 (d, J = 6.0 Hz, 1H, H-10), 4.41-4.29 (m, 2H, H-9), 2.92 (br d, J = 9.2 Hz, 1H, Ha-6), 2.81-2.71 (m, 1H, Ha-2), 2.39 (br d, J = 12.1 Hz, 1H, Hb-2), 2.31 (t, J = 6.6 Hz, 2H, H-7), 2.17-2.14 (m, 1H, Hb-6), 2.08 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.01-1.96 (m, 5H, OAc, H-8). ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 170.4 (s, 1C, O=CCH_3), 170.3 (s, 1C, O=CCH_3), 170.1 (s, 1C, O=CCH_3), 156.5 (s, 1C, NHCOO), 145.0 (s, 1C, triazole), 136.5 (s, 1C, Ar), 128.5 (d, 2C, Ar), 128.2 (d, 1C, Ar), 128.0 (d, 2C, Ar), 122.7 (d, 1C, triazole), 70.9 (d, 1C, C-4), 68.2 (d, 1C, C-5), 67.9 (d, 1C, C-3), 66.8 (t, 1C, CH_2Ph), 53.9 (t, 1C, C-6), 53.6 (t, 1C, C-2), 53.0 (t, 1C, C-7), 47.8 (t, 1C, C-9), 36.5 (t, 1C, C-10), 27.2 (t, 1C, C-8), 21.1 (q, 1C, OAc), 21.0 (q, 1C, OAc), 20.8 (q, 1C, OAc). IR ($CHCl_3$) $\tilde{\nu}$ = 3687, 3451, 3027, 2962, 2825, 1747, 1511, 1468, 1435, 1372, 1253, 1207,1147 cm^{-1}. MS-ESI (m/z, %) = 554.17 (100) $[M+Na]^+$. $C_{25}H_{33}N_5O_8$ (531.56): calcd C, 58.24; H, 6.45; N, 13.58; found C, 58.20; H, 6.49; N, 13.67.

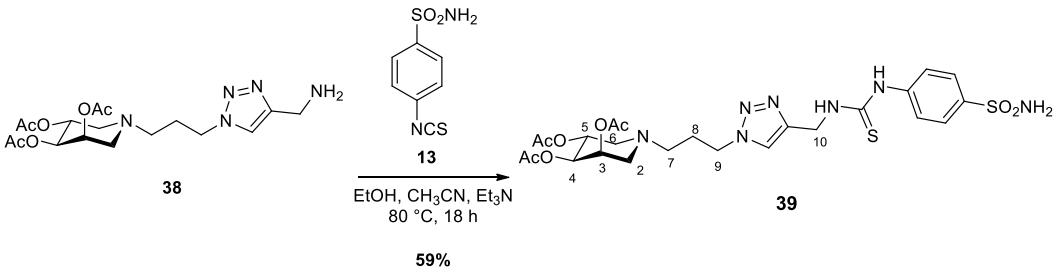
Synthesis of compound 38



To a solution of the protected amine **37** (38 mg, 0.07 mmol) in MeOH (2 ml), $Pd(OH)_2$/C (19 mg) was added under nitrogen atmosphere. Then nitrogen was replaced by hydrogen gas, bubbling hydrogen with a balloon and the reaction mixture was stirred at room temperature for 18 hours until ^{1}H-NMR analysis assessed the disappearance of benzyl and aromatic protons. The catalyst was removed by filtration on a short pad of Celite, washed several times with MeOH and the solvent was evaporated under vacuum. The crude product was purified by flash column chromatography on silica gel (DCM:MeOH:NH_4OH (6%) 8:1:0.1) to afford 26 mg of the corresponding amine **38** (R_f = 0.15, DCM:MeOH:NH_4OH (6%) 10:1:0.1, 0.07 mmol, 93%) as a colourless oil.

38: $[\alpha]_D^{24}$ = − 13.6 (c = 0.7, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.49 (s, 1H, triazole), 5.30-5.24 (m, 1H, H-3), 5.10 (td, J = 4.3, 8.4 Hz, 1H, H-5), 4.94 (dd, J = 3.3, 8.6 Hz, 1H, H-4), 4.48-4.30 (m, 2H, H-9), 4.13-3.84 (br s, 2H, NH_2), 2.93 (br d, J = 9.2 Hz, 1H, Ha-6), 2.80 (br d, J = 8.3 Hz, 1H, Ha-2), 2.51-2.38 (m, 3H, Hb-2, H-10), 2.34 (dt, J = 6.5, 11.2 Hz, 2H, H-7), 2.26-2.17 (m, 1H, Hb-6), 2.09 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.03-2.00 (m, 5H, OAc, H-8). ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 170.4 (s, 1C, O=C), 170.3 (s, 1C, O=C), 170.1 (s, 1C, O=C), 121.4 (d, 1C, triazole), 70.9 (d, 1C, C-4), 68.3 (d, 1C, C-5), 67.9 (d, 1C, C-3), 54.0 (t, 1C, C-6), 53.5 (t, 1C, C-2), 53.0 (t, 1C, C-7), 47.5 (t, 1C, C-9), 37.4 (t, 1C, C-10), 27.4 (t, 1C, C-8), 21.1 (q, 2C, OAc), (q, 1C, OAc), 20.9 (q, 1C, OAc). IR ($CHCl_3$) ṽ = 3705, 3674, 3019, 2963, 2929, 1742, 1373, 1228, 1206, 1049 cm^{-1}. MS-ESI (m/z, %) = 398.17 (51) $[M+H]^+$, 420.17 (100) $[M+Na]^+$. $C_{17}H_{27}N_5O_6$ (397.43): calcd C, 51.38; H, 6.85; N, 17.62; found C, 51.26; H, 6.89; N, 17.55.

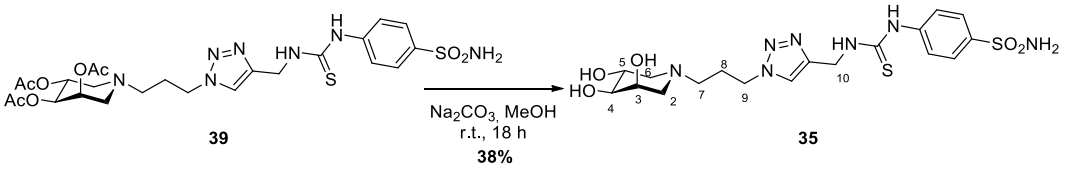
Synthesis of compound 39



Benzensulfonamide **13** (13 mg, 0.06 mmol) was added to a solution of **38** (24 mg, 0.06 mmol) and NEt_3 (3 µL, 0.02 mmol) in EtOH (1 mL) and CH_3CN (1.5 mL) and the mixture was stirred at 80 °C for 18 hours until a TLC control attested the disappearance of the starting material **38** (R_f = 0.23, DCM:MeOH:NH_4OH (6%) 8:1:0.1). Then, the reaction mixture was evaporated under vacuum. The crude was purified by flash column chromatography on silica gel (gradient eluent from DCM:MeOH 30:1 to 25:1) to afford 22 mg of **39** (R_f = 0.29, DCM:MeOH:NH_4OH (6%) 10:1:0.1, 0.04 mmol, 59%) as a colourless oil.

39: $[\alpha]_D^{25}$ = − 21.60 (c = 0.85, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ ppm: 8.00 (s, 1H, triazole), 7.83 (d, J = 8.7 Hz, AB system, 2H, Ar), 7.67 (d, J = 8.8 Hz, AB system, 2H, Ar), 5.30-5.26 (m, 1H, H-3), 5.11 (td, J = 4.3, 8.5 Hz, 1H, H-5), 4.96 (dd, J = 3.3, 8.6 Hz, 1H, H-4), 4.89-4.85 (br s, 2H, H-10), 4.54-4.40 (m, 1H, H-9), 2.97 (br d, J = 9.1 Hz, 1H, Ha-6), 2.85 (br d, J = 8.5 Hz, 1H, Ha-2), 2.48 (br d, J = 11.8 Hz, 1H, Hb-2), 2.37 (t, J = 6.8 Hz, 2H, H-7), 2.33-2.24 (m, 1H, Hb-6), 2.09 (s, 3H, OAc), 2.08-2.02 (m, 5H, OAc, H-8), 2.00 (s, 3H, OAc). ^{13}C-NMR (100 MHz, CD_3OD) δ ppm: 182.7 (s, 1C, C=S), 172.1 (s, 1C, O=C), 171.8 (s, 1C, O=C), 171.7(s, 1C, O=C), 145.8 (s, 1C, triazole), 144.1 (s, 1C, Ar), 140.2 (s, 1C, Ar), 128.0 (d, 2C, Ar), 125.2 (d, 1C, triazole), 123.6 (d, 2C, Ar), 72.4 (d, 1C, C-4), 69.4 (d, 1C, C-5), 69.3 (d, 1C, C-3), 54.8 (t, 1C, C-6), 54.4 (t, 1C, C-2), 54.0 (t, 1C, C-7), 48.8 (t, 1C, C-9), 40.4 (t, 1C, C-10), 28.1 (t, 1C, C-8), 21.0 (q, 1C, OAc), 20.9 (q, 1C, OAc), 20.7 (q, 1C, OAc). IR ($CHCl_3$) ṽ = 3653, 3342, 2930, 2850, 1744, 1533, 1372, 1334, 1235, 1162, 1050 cm^{-1}. MS-ESI (m/z, %) = 633.92 (100) $[M+Na]^+$. $C_{24}H_{33}N_7O_8S_2$ (611.69): calcd C, 47.12; H, 5.44; N, 16.03; S, 10.48; found C, 46.80; H, 5.73; N, 15.92; S, 10.10.

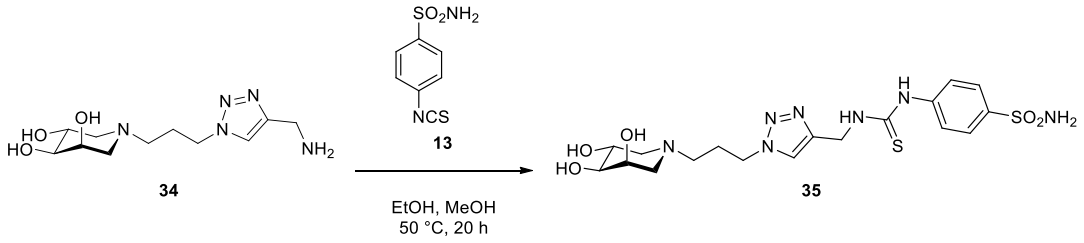
Synthesis of compound 35



Sodium carbonate (14 mg, 0.13 mmol) was added to a solution of **39** (16 mg, 0.03 mmol) in MeOH (2.5 mL) and the mixture was stirred at room temperature for 18 hours, until a TLC control attested the disappearance of the starting material **39** (R_f = 0.29, DCM:MeOH:NH_4OH (6%) 10:1:0.1). The mixture was filtered, and the solvent was removed under vacuum. A trituration with heated ethanol gave 6 mg of **35** (R_f = 0.14, DCM:MeOH 3:1, 0.01 mmol, 38%) as a white waxy solid.

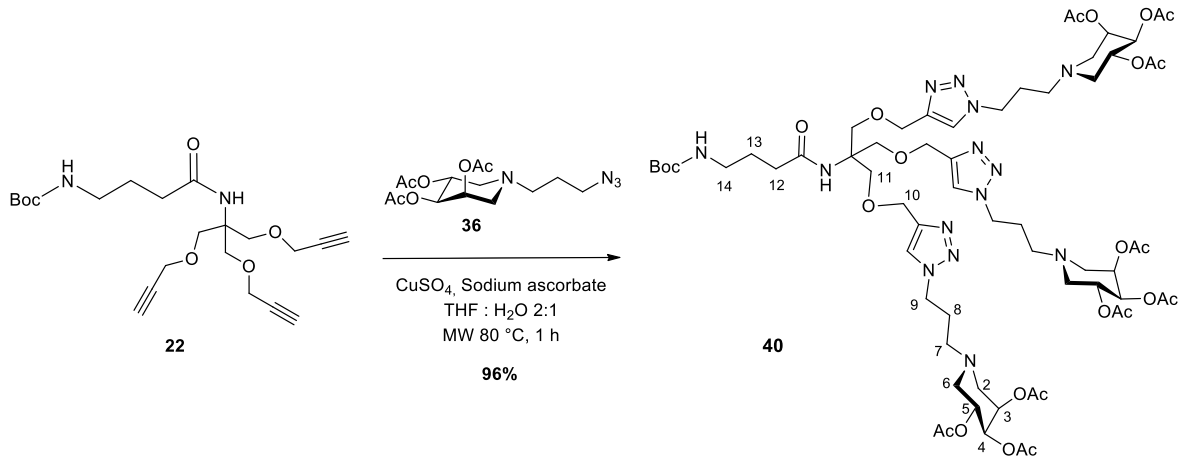
35: $[\alpha]_D^{20}$ = − 5.25 (c = 0.4, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ ppm: 8.02 (s, 1H, triazole), 7.82 (d, J = 8.7 Hz, AB system, 2H, Ar), 7.57 (d, J = 8.0 Hz, AB system, 2H, Ar), 4.85 (br s, 2H, H-10), 4.47 (m, J = 6.7 Hz, 2H, H-9), 3.91-3.86 (m, 1H, H-3), 3.76 (td, J = 4.1, 8.0 Hz, 1H, H-5), 3.41-3.36 (m, 1H, H-4), 2.78 (br d, J = 10.1 Hz, 1H, Ha-6), 2.75-2.66 (m, 1H, Ha-2), 2.38-2.29 (m , 2H, H-7), 2.25 (br d, J = 12.0, 1H, Hb-2), 2.12-2.00 (m, 3H, Hb-6, H-8). ^{13}C-NMR (100 MHz, CD_3OD) δ ppm: 182.7 7 (s, 1C, C=S), 145.8 (s, 1C, triazole), 144.3 (s, 1C, Ar), 140.2 (s, 1C, Ar), 127.9 (d, 2C, Ar), 125.1 (d, 2C, Ar), 123.6 (d, 1C, triazole), 75.4 (d, 1C, C-4), 69.6 (d, 1C, C-5), 69.3 (d, 1C, C-3), 58.2 (t, 1C, C-6), 57.7 (t, 1C, C-2), 55.1 (t, 1C, C-7), 40.5 (t, 1C, C-10), 28.3 (t, 1C, C-8). MS-ESI (m/z, %) = 508.17 (100) $[M+Na]^+$. $C_{18}H_{27}N_7O_5S_2$ (485.58): calcd C, 44.52; H, 5.60; N, 20.19; S, 13.21; found C, 44.31; H, 5.88; N, 20.10; S, 13.30.

Synthesis of compound 35 – Procedure 2



Benzensulfonamide **13** (17 mg, 0.08 mmol) was added to a suspension of **34** (23 mg, 0.08 mmol) in EtOH (1 mL) and MeOH (0.2 mL) and the mixture was stirred at 50 °C for 20 hours. Then, the crude was evaporated under vacuum and purified by flash column chromatography on silica gel (gradient eluent from DCM:MeOH 10:1 to 5:1) to give 6 mg of **35** (R_f = 0.14, DCM:MeOH 3:1, 0.01 mmol, 15%) as a white waxy solid.

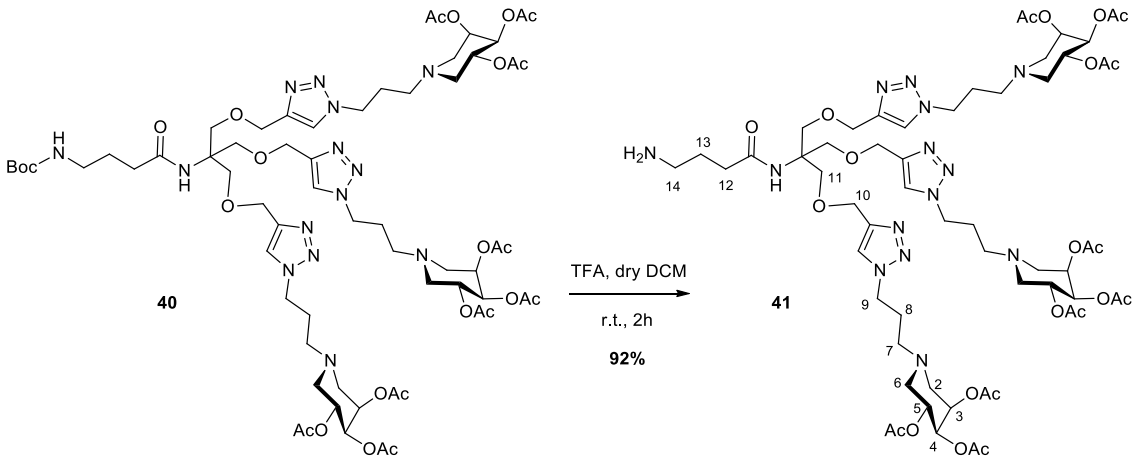
Synthesis of compound 40



Azide **36** (84 mg, 0.25 mmol), $CuSO_4$ (4 mg, 0.03 mmol) and sodium ascorbate (9 mg, 0.05 mmol) were added to a solution of compound **22** (33 mg, 0.08 mmol) in THF (2 mL) and milliQ water (1 mL). The mixture was stirred under microwave irradiation at 80 °C for 1 h, until a TLC control attested the disappearance of the starting material **22** (R_f = 0.47, DCM:MeOH 10:1). The mixture was filtered through Celite®, the solvent was removed under vacuum and subsequently the crude mixture was treated with 'Quadrasil MP®' resin keeping the mixture under stirring at room temperature in the minimum amount of MeOH for 1 hour (1 g of resin for each mmol of copper). The crude was purified by flash column chromatography on silica gel (DCM:MeOH:NH_4OH (6%) 15:1:0.1) to give 110 mg of **40** (R_f = 0.24, DCM:MeOH:NH_4OH (6%) 15:1:0.1, 0.08 mmol, 96%) as a white waxy solid.

40: $[\alpha]_D^{24}$ = − 23.30 (c = 0.33, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.59-7.56 (m, 3H, triazole), 6.43 (br s, 1H, N<u>H</u>), 5.28-5.22 (m, 3H, H-3), 5.13-5.03 (m, 3H, H-5), 4.96.4.88 (m, 3H, H-4), 4.57-4.52 (m, 6H, H-10), 4.46-4.32 (m, 6H, H-9), 3.81-3.71 (m, 6H, H-11), 3.11-3.02 (m, 2H, H-14), 2.99-2.89 (m, 3H, Ha-6), 2.84-2.73 (m, 3H, Ha-2), 2.44-2.32 (m, 9H, Hb-2, H-7), 2.26-2.18 (m, 3H, Hb-6), 2.17-2.11 (m, 2H, H-12), 2.10-1.95 (m, 33H, H-8, OAc), 1.75-1.65 (m, 2H, H-13), 1.41-1.35 (m, 9H, C(C<u>H</u>$_3$)$_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 172.9 (s, 1C, HN<u>C</u>O), 170.4 (s, 3C, OAc), 170.2 (s, 3C, OAc), 170.1 (s, 3C, OAc), 156.3 (s, 1C, HN<u>C</u>OO), 144.7 (s, 3C, triazole), 123.1 (d, 3C, triazole), 110.1 (interference), 79.0 (s, 1C, <u>C</u>(CH$_3$)$_3$), 70.9 (d, 3C, C-4), 68.9 (t, 3C, C-11), 68.2 (d, 3C, C-5), 67.9 (d, 3C, C-3), 64.7 (t, 3C, C-10), 59.8 (s, 1C, HN<u>C</u>(CH$_2$O)$_3$), 54.0 (t, 3C, C-6), 53.5 (t, 3C, C-2), 53.1 (t, 3C, C-7), 47.7 (t, 3C, C-9), 39.8 (t, 1C, C-14), 34.4 (t, 1C, C-12), 28.5 (q, 3C, C(<u>C</u>H$_3$)$_3$), 27.4 (t, 3C, C-8), 26.1 (t, 1C, C-13), 21.1 (q, 3C, OAc), 21.0 (q, 3C, OAc), 20.9 (q, 3C, OAc). IR ($CHCl_3$) ν̃ = 3690, 3449, 3029, 2964, 1744, 1510, 1371, 1259, 1236, 1198, 1094, 1049 cm^{-1}. MS-ESI (m/z, %) = 746.17 (100) $[M+2Na]^{2+}$. $C_{64}H_{98}N_{14}O_{24}$ (1447.54): calcd C, 53.10; H, 6.82; N, 13.55; found C, 52.88; H, 7.03; N, 13.38.

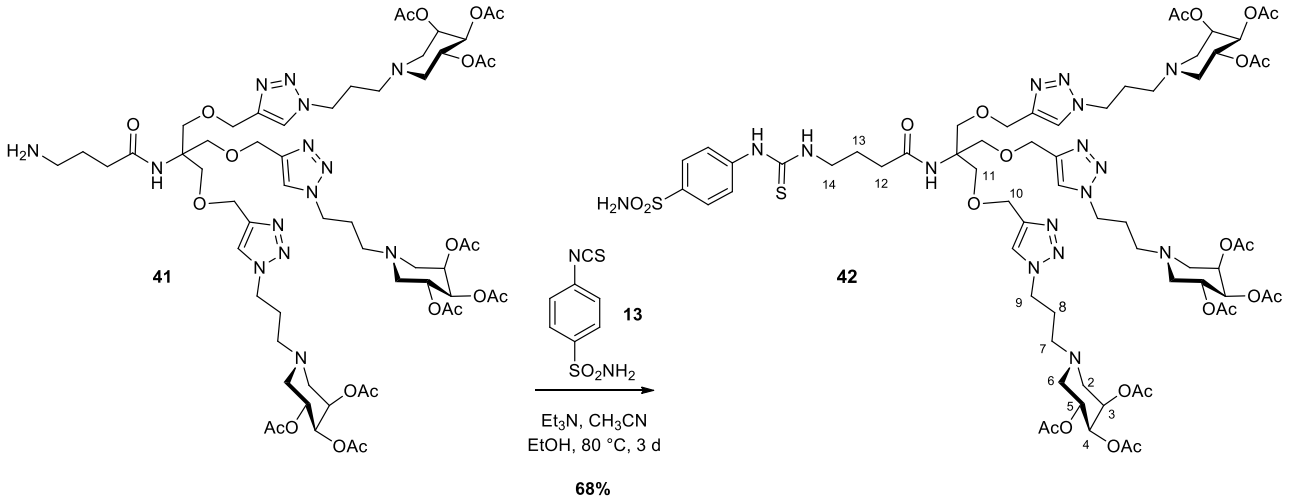
Synthesis of compound 41



A solution of **40** (80 mg, 0.06 mmol) in dry DCM (1 mL) was left stirring with TFA (93 µl, 1.21 mmol) at room temperature for 2 h until a TLC control attested the disappearance of the starting material **40** (R_f = 0.40, DCM:MeOH 10:1). The reaction mixture was concentrated and then the crude was purified by flash column chromatography on silica gel (gradient eluent from DCM:MeOH:NH_4OH (6%) 10:1:0.1 to 5:1:0.1) to give 68 mg of **41** (R_f = 0.42, DCM:MeOH:NH_4OH (6%) 5:1:0.1, 0.05 mmol, 92%) as a white waxy solid.

41: $[\alpha]_D^{24}$ = − 26.70 (c = 0.55, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.61 (s, 3H, triazole), 7.05 (br s, 1H, NH), 5.28-5.23 (m, 3H, H-3), 5.09 (td, J = 4.4, 8.2 Hz, 3H, H-5), 4.92 (m, 3H, H-4), 4.52 (s, 6H, H-10), 4.39 (m, 6H, H-9), 3.72 (s, 6H, H-11), 3.41 (br s, 1H, NH), 3.08 (t, J = 5.9 Hz, 2H, H-14), 3.00-2.88 (m, 3H, Ha-6), 2.85-2.74 (m, 3H, Ha-2), 2.44-2.33 (m, 5H, Hb-2, H-12), 2.36 (t, J = 6.6 Hz, 6H, H-7), 2.28-2.15 (m, 3H, Hb-6), 2.07 (s, 9H, OAc), 2.05-1.98 (m, 24H, H-8, OAc), 1.97 (m, 2H, H-13). ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 173.1 (s, 1C, HNCO), 170.4 (s, 3C, C=$OOCH_3$), 170.2 (s, 3C, C=$OOCH_3$), 170.1 (s, 3C, C=$OOCH_3$), 144.4 (s, 3C, triazole), 123.4 (d, 3C, triazole), 70.9 (d, 3C, C-4), 68.8 (t, 3C, C-11), 68.3 (d, 3C, C-5), 68.0 (d, 3C, C-3), 64.5 (t, 3C, C-10), 60.1 (s, 1C, HNC$(CH_2O)_3$), 54.0 (t, 3C, C-2), 53.5 (t, 3C, C-6), 53.1 (t, 3C, C-7), 47.8 (t, 3C, C-9), 39.4 (t, 1C, C-14), 34.3 (t, 1C, C-12), 27.4 (t, 3C, C-8), 23.4 (t, 1C, C-13), 21.1 (q, 3C, OAc), 21.0 (q, 3C, OAc), 20.9 (q, 3C, OAc). IR ($CHCl_3$) ṽ = 3673, 3025, 2963, 1744, 1674, 1372, 1236, 1198 1138, 1049 cm^{-1}. MS-ESI (m/z, %) = 685.33 (100) $[M+H+Na]^{2+}$. $C_{59}H_{90}N_{14}O_{22}$ (1347.43): calcd C, 52.59; H, 6.73; N, 14.55; found C, 52.38; H, 6.87; N, 14.90.

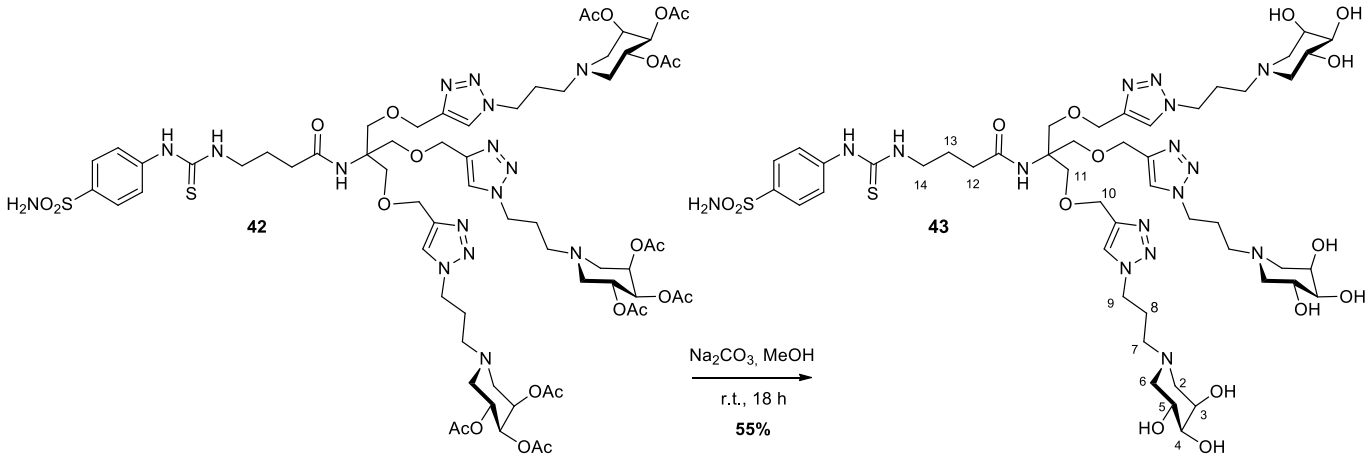
Synthesis of compound 42



Benzensulfonamide **13** (11 mg, 0.05 mmol) was added to a solution of **41** (63 mg, 0.05 mmol) and NEt_3 (2 µL, 0.01 mmol) in EtOH (1 mL) and CH_3CN (1.5 mL) and the mixture was stirred at 80 °C for 3 days until a TLC control attested the disappearance of the starting material **41** (R_f = 0.42, DCM:MeOH:NH_4OH (6%) 5:1:0.1). Then, the reaction mixture was evaporated under vacuum. The crude was purified by flash column chromatography on silica gel (gradient eluent from DCM:MeOH 20:1 to 10:1) to give 50 mg of **42** (R_f = 0.14, DCM:MeOH 15:1, 0.03 mmol, 68%) as a white waxy solid.

42: $[\alpha]_D^{24}$ = − 15.4 (c = 0.6, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ ppm: 7.95 (s, 3H, triazole), 7.84 (d, J = 8.7 Hz, AB system, 2H, Ar), 7.64 (br d, J = 7.8 Hz, AB system, 2H, Ar), 5.30-5.25 (m, 3H, H-3), 5.11 (td, J = 4.2, 8.4 Hz, 3H, H-5), 4.96 (dd, J = 3.4, 8.6 Hz, 3H, H-4), 4.54 (s, 6H, H-10), 4.46 (td, J = 7.0, 13.6 Hz, 6H, H-9), 3.73 (s, 6H, H-11), 3.63-3.51 (m, 2H, H-14), 3.02-2.93 (m, 3H, Ha-6), 2.88-2.79 (m, 3H, Ha-2), 2.48 (br d, J = 13.1 Hz, 3H, Hb-2), 2.39 (t, J = 6.7 Hz, 6H, H-7), 2.32-2.19 (m, 3H, Hb-6, H-12), 2.09 (s, 9H, OAc), 2.08-2.03 (m, 6H, H-8), 2.05 (s, 9H, OAc), 2.01 (s, 9H, OAc), 1.89-1.81 (m, 2H, H-13). ^{13}C-NMR (50 MHz, CD_3OD) δ ppm: 182.2 (s, 1C, C=S), 175.5 (s, 1C, HN<u>C</u>O), 172.0 (s, 3C, <u>C</u>=$OOCH_3$), 171.8 (s, 3C, <u>C</u>=$OOCH_3$), 171.7 (s, 3C, <u>C</u>=$OOCH_3$), 145.7 (s, 3C, triazole), 144.1 (s, 1C, Ar), 140.2 (s, 1C, Ar), 128.0 (d, 2C, Ar), 125.4 (d, 3C, triazole), 123.6 (d, 2C, Ar), 72.4 (d, 3C, C-4), 69.5 (d, 3C, C-5), 69.3 (d, 3C, C-3 and t, 3C, C-11), 65.2 (t, 3C, C-10), 61.3 (s, 1C, HN<u>C</u>$(CH_2O)_3$), 54.9 (t, 3C, C-6), 54.4 (t, 6C, C-2, C-7), 49.0 (t, 3C, C-9), 44.9 (t, 1C, C-14), 34.8 (t, 1C, C-12), 28.2 (t, 3C, C-8), 26.2 (t, 1C, C-13), 21.0 (q, 3C, OAc), 20.9 (q, 3C, OAc), 20.7 (q, 3C, OAc). IR (MeOH) ṽ = 3512, 3466, 3308, 3111, 2799, 2739, 1512, 1466, 1450, 1363, 1123, 1063, 1026 cm^{-1}. MS-ESI (m/z, %) = 782.17 (78) $[(M+2H)]^{2+}$, 803.17 (100) $[M+2Na]^{2+}$. $C_{66}H_{96}N_{16}O_{24}S_2$ (1561.69): calcd C, 50.76; H, 6.20; N, 14.35; S, 4.11; found C, 50.41; H, 6.42; N, 14.28; S, 4.41.

Synthesis of compound 43



Na_2CO_3 (14 mg, 0.05 mmol) was added to a solution of **42** (14 mg, 0.01 mmol) in MeOH (1 ml) and the reaction mixture was left stirring for 18 hours at room temperature until a TLC control attested the disappearance of the starting material (R_f = 0.45, DCM: MeOH 5:1). Then, the reaction mixture was filtered and concentrated under vacuum. The crude was purified by size exclusion chromatography, employing Bio-Beads_SX8 resin and eluting with MeOH to give 6 mg of **43** (R_f = 0.00, DCM:MeOH 10:1, 0.005 mmol, 55%) as a colourless oil.

43: $[\alpha]_D^{24}$ = − 3.80 (c = 0.5, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.99 (s, 3H, triazole), 7.84 (d, J = 8.8 Hz, AB system, 2H, Ar), 7.66 (d, J = 8.6 Hz, AB system, 2H, Ar), 4.55 (s, 6H, H-10), 4.47 (t, J = 6.8 Hz, 6H, H-9), 3.92-3.88 (m, 3H, H-3), 3.82-3.77 (m, 3H, H-5), 3.75 (s, 6H, H-11), 3.62-3.54 (m, 2H, H-14), 3.43-3.37 (m, 3H, H-4), 2.87-2.75 (m, 3H, Ha-6), 2.75-2.62 (m, 3H, Ha-2), 2.40-2.21 (m, 11H, Ha-2, H-7, H-12), 2.13-2.01 (m, 9H, Hb-6, H-8), 1.86 (t, J = 7.0 Hz, 2H, H-13). ^{13}C-NMR (50 MHz, $CDCl_3$) δ ppm: 182.3 (s, 1C, C=S), 175.6 (s, 1C, HN<u>C</u>O), 145.6 (s, 1C, triazole), 144.2 (s, 1C, Ar), 140.1 (s, 1C, Ar), 128.0 (d, 2C, Ar), 125.5 (d, 3C, triazole), 123.9 (d, 2C, Ar), 75.4 (d, 3C, C-4), 69.7 (d, 3C, C-5), 69.4, 69.3 (d, 3C, C-3 and t, 3C, C-11), 65.3 (t, 3C, C-10), 61.3 (s, 1C, HN<u>C</u>$(CH_2O)_3$), 58.0 (t, 3C, C-6), 57.6 (t, 3C, C-2), 55.1 (t, 3C, C-7), 49.3 (t, 3C, C-9), 44.9 (t, 1C, C-14), 34.9 (t, 1C, C-12), 28.3 (t, 3C, C-8), 26.2 (t, 1C, C-13). MS-ESI (m/z, %) = 603.17 (79) $[M+H+Na]^{2+}$, 1205.00 (100) $[M+Na]^+$. $C_{48}H_{78}N_{16}O_{15}S_2$ (1183.36): calcd C, 48.72; H, 6.64; N, 18.94; S, 5.42; found C, 48.45; H, 6.90; N, 19.05; S, 5.66.

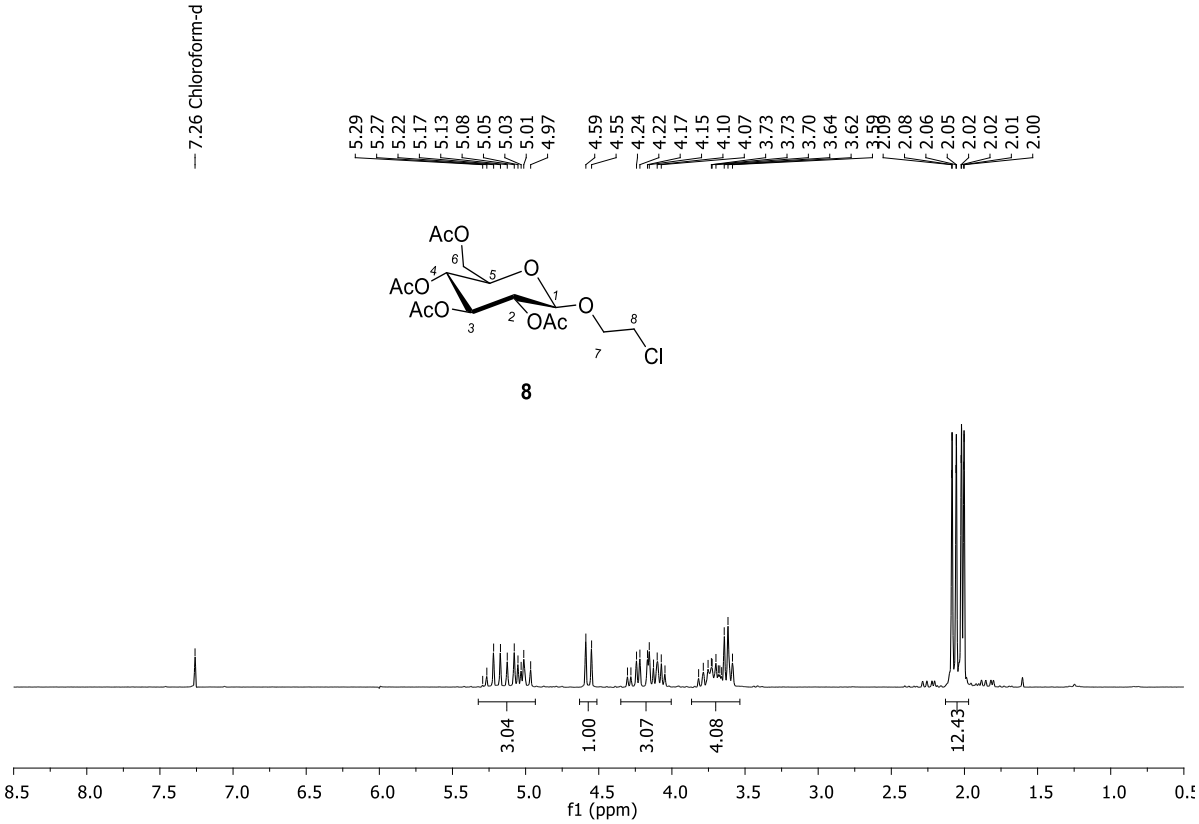


Figure S1: ^{1}H NMR spectrum of **8** (200 MHz, $CDCl_3$).

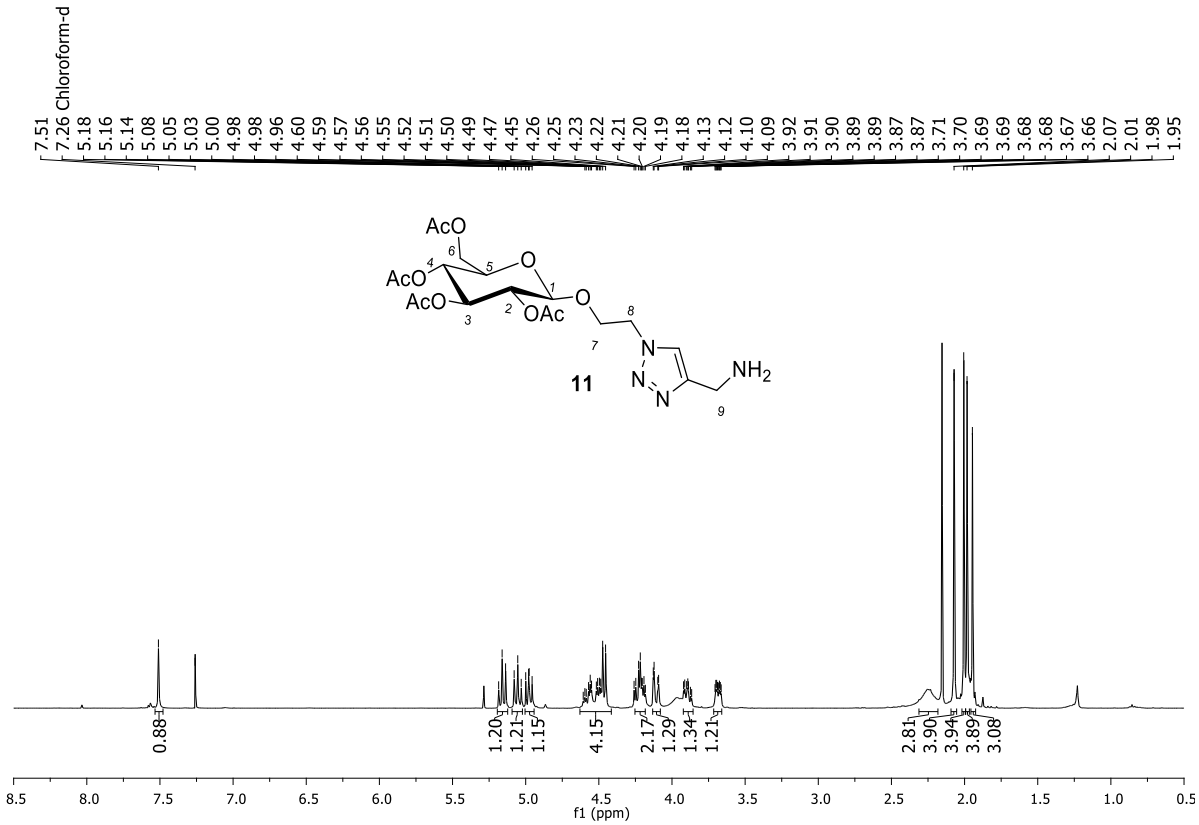


Figure S2: ^{1}H NMR spectrum of **11** (400 MHz, $CDCl_3$).

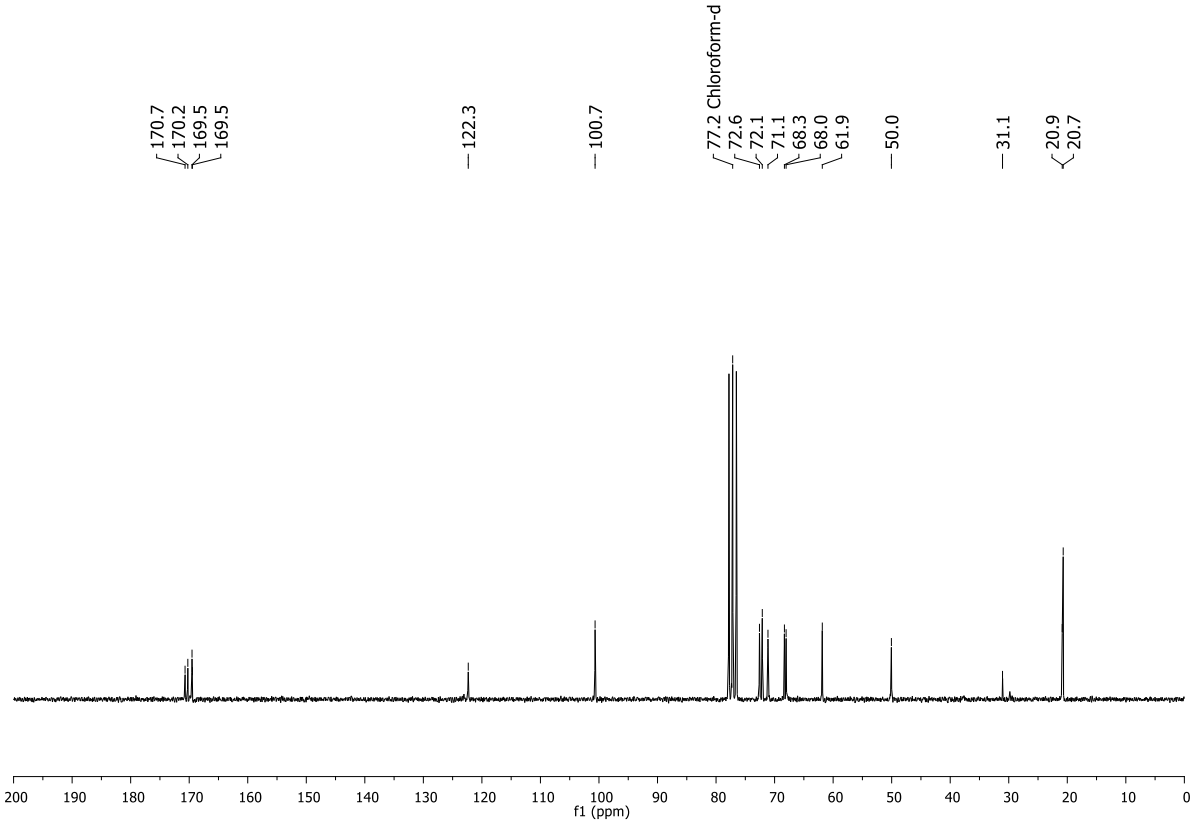


Figure S3: ^{13}C NMR spectrum of **11** (50 MHz, $CDCl_3$).

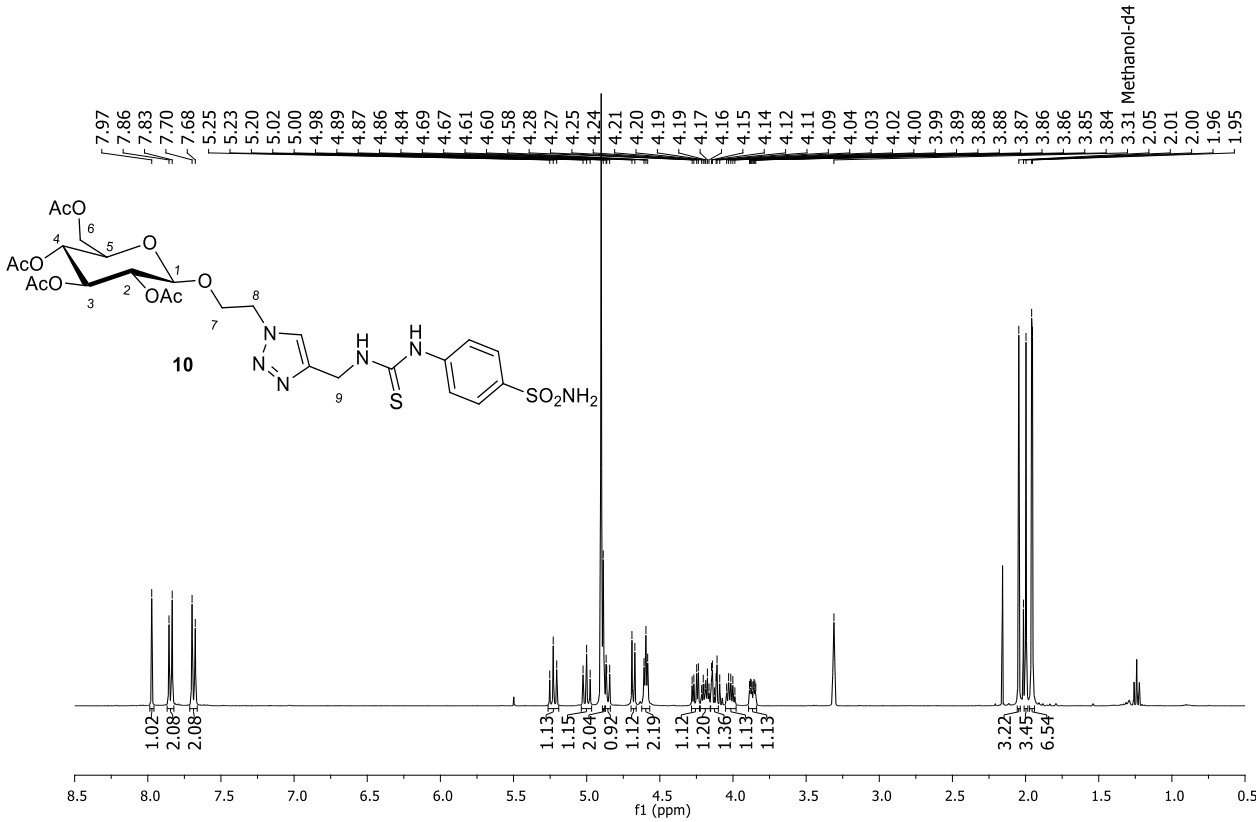


Figure S4: ^{1}H NMR spectrum of **10** (400 MHz, CD_3OD).

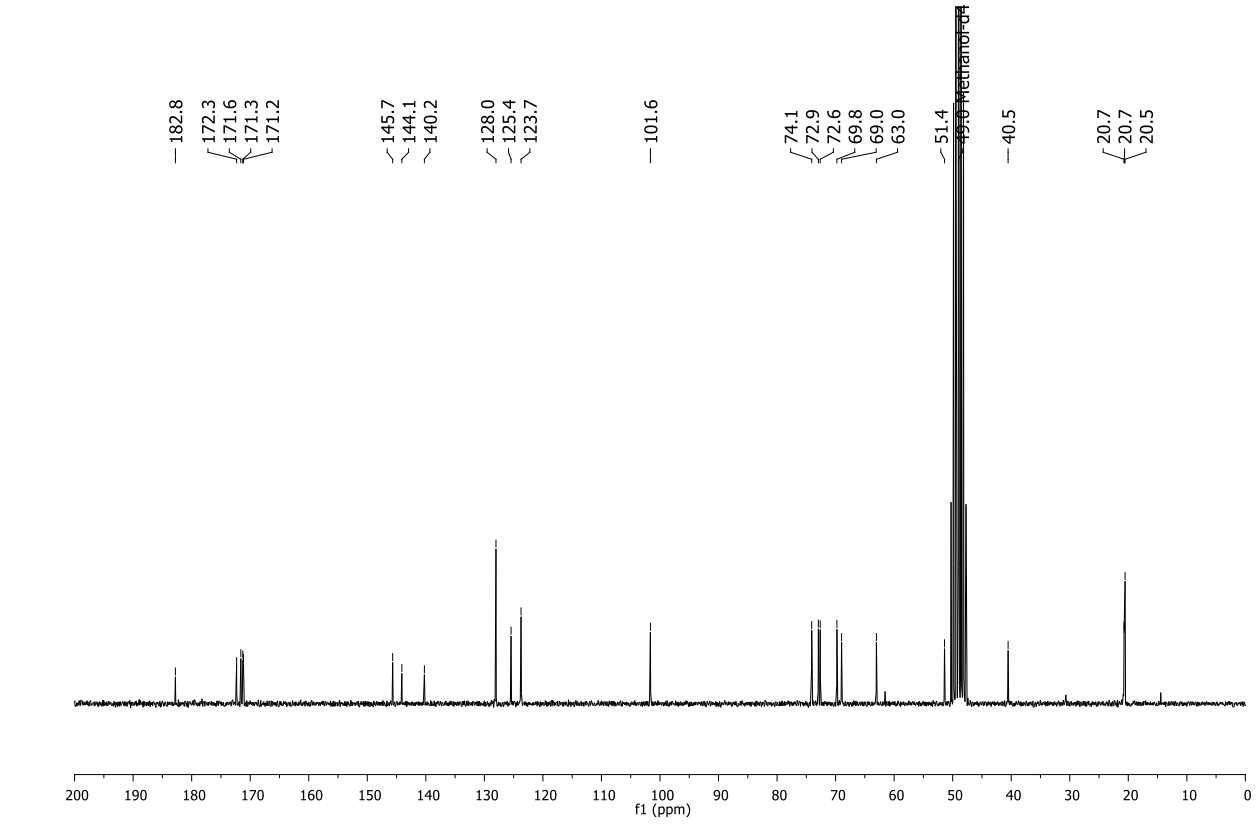


Figure S5: ^{13}C NMR spectrum of **10** (50 MHz, CD_3OD).

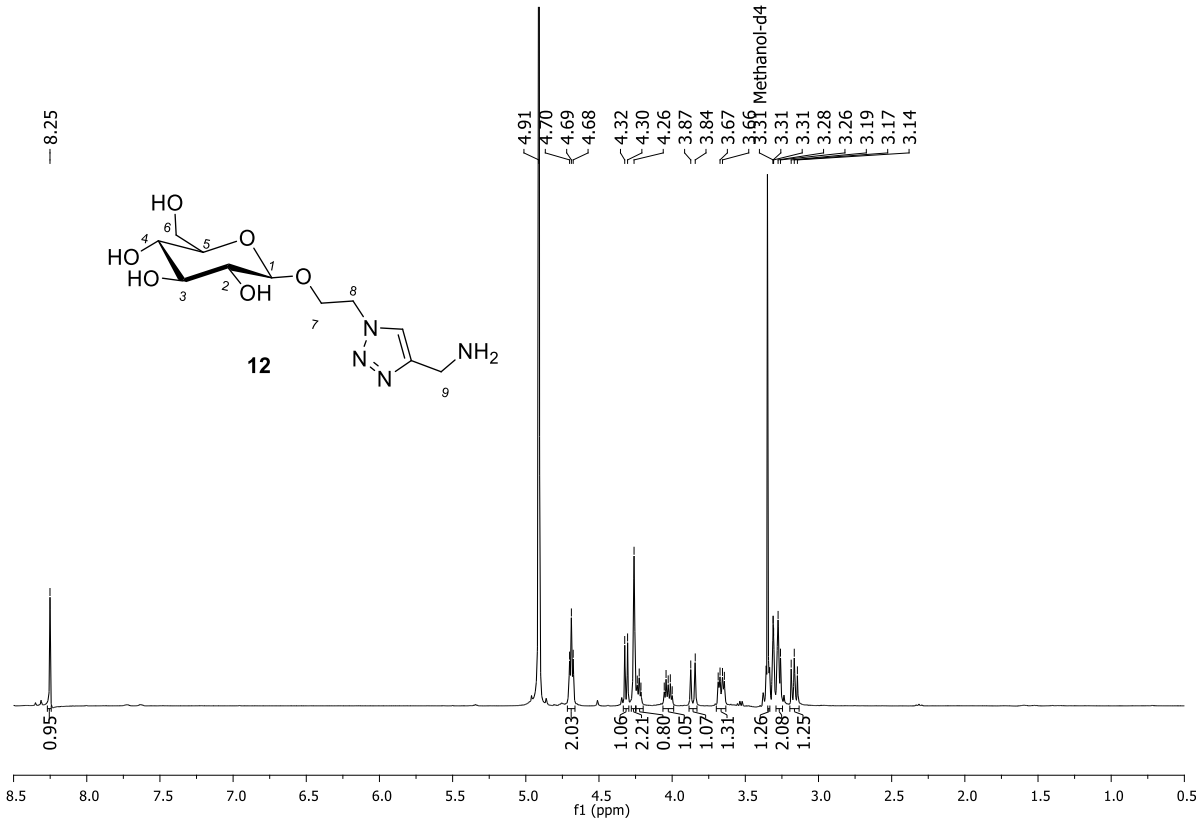


Figure S6: ^{1}H NMR spectrum of **12** (400 MHz, CD_3OD).

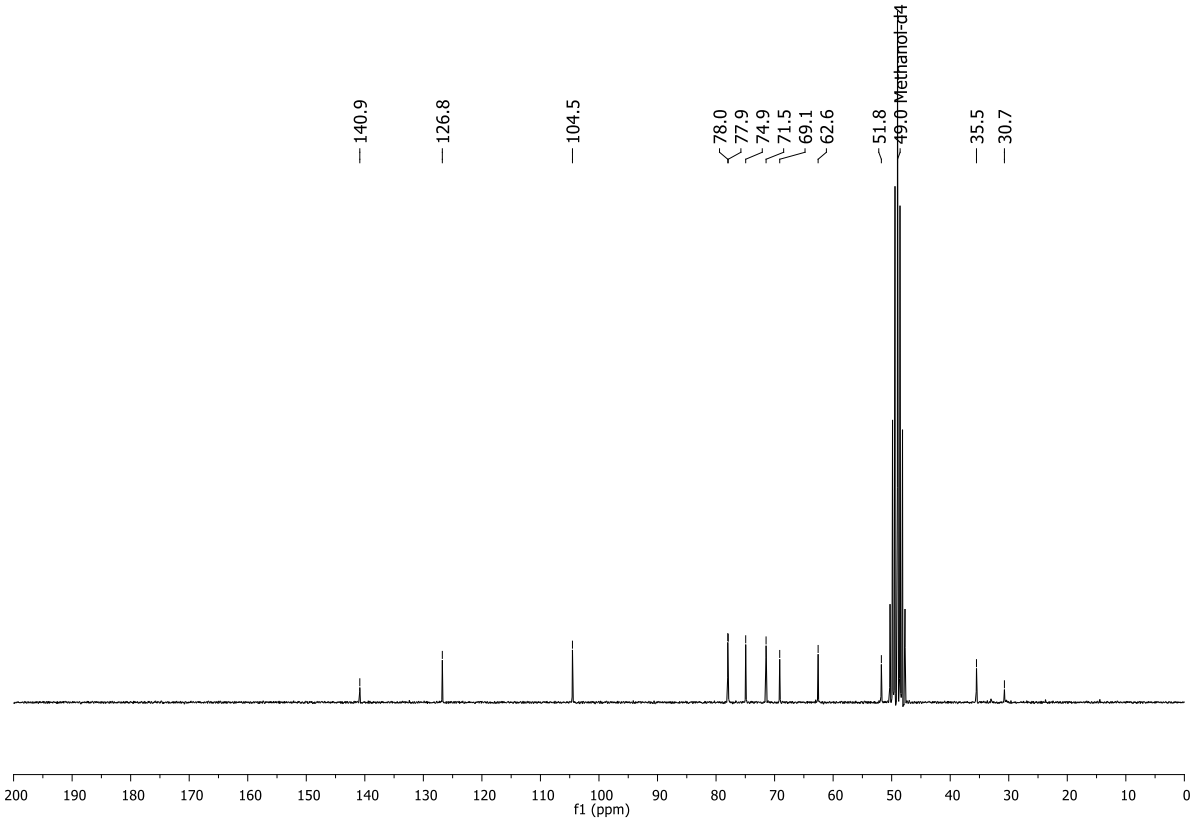


Figure S7: ^{13}C NMR spectrum of **12** (50 MHz, CD_3OD).

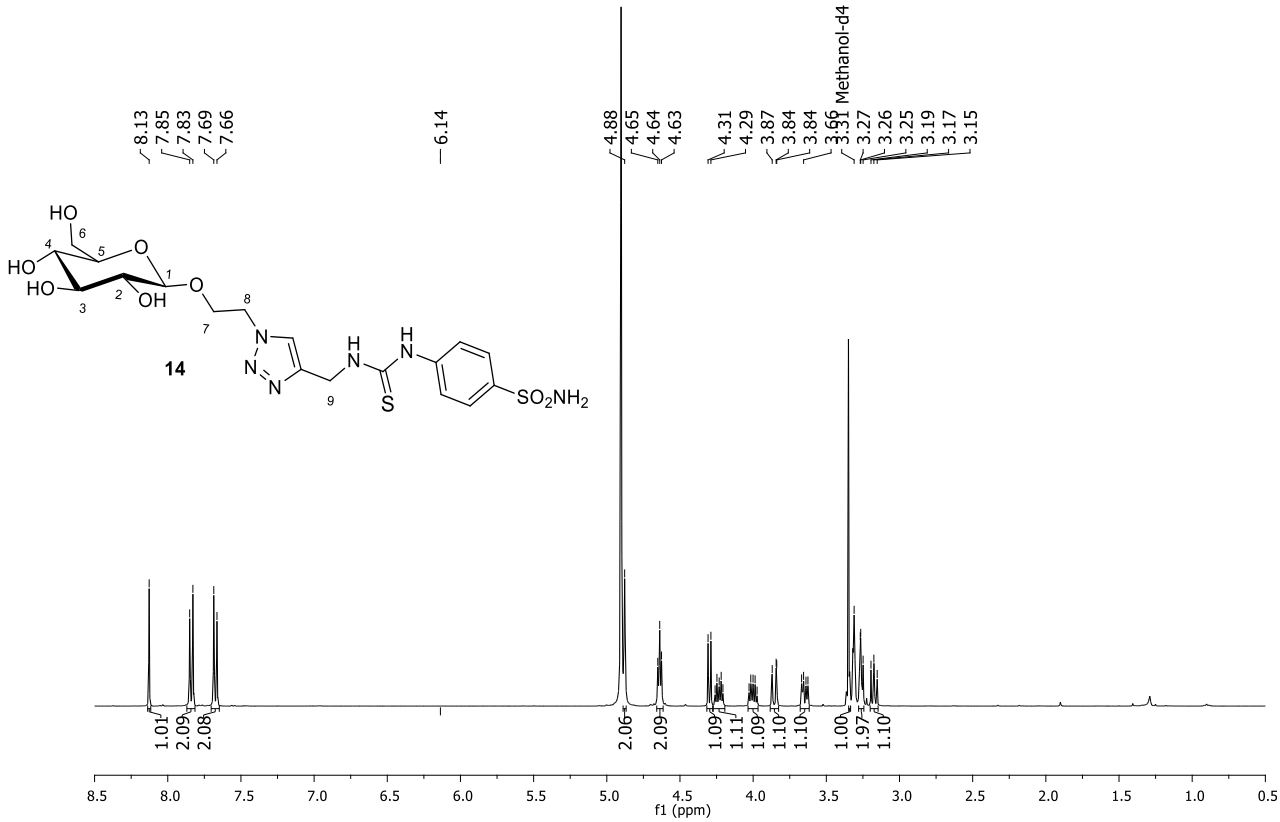


Figure S8: ^{1}H NMR spectrum of **14** (400 MHz, CD_3OD).

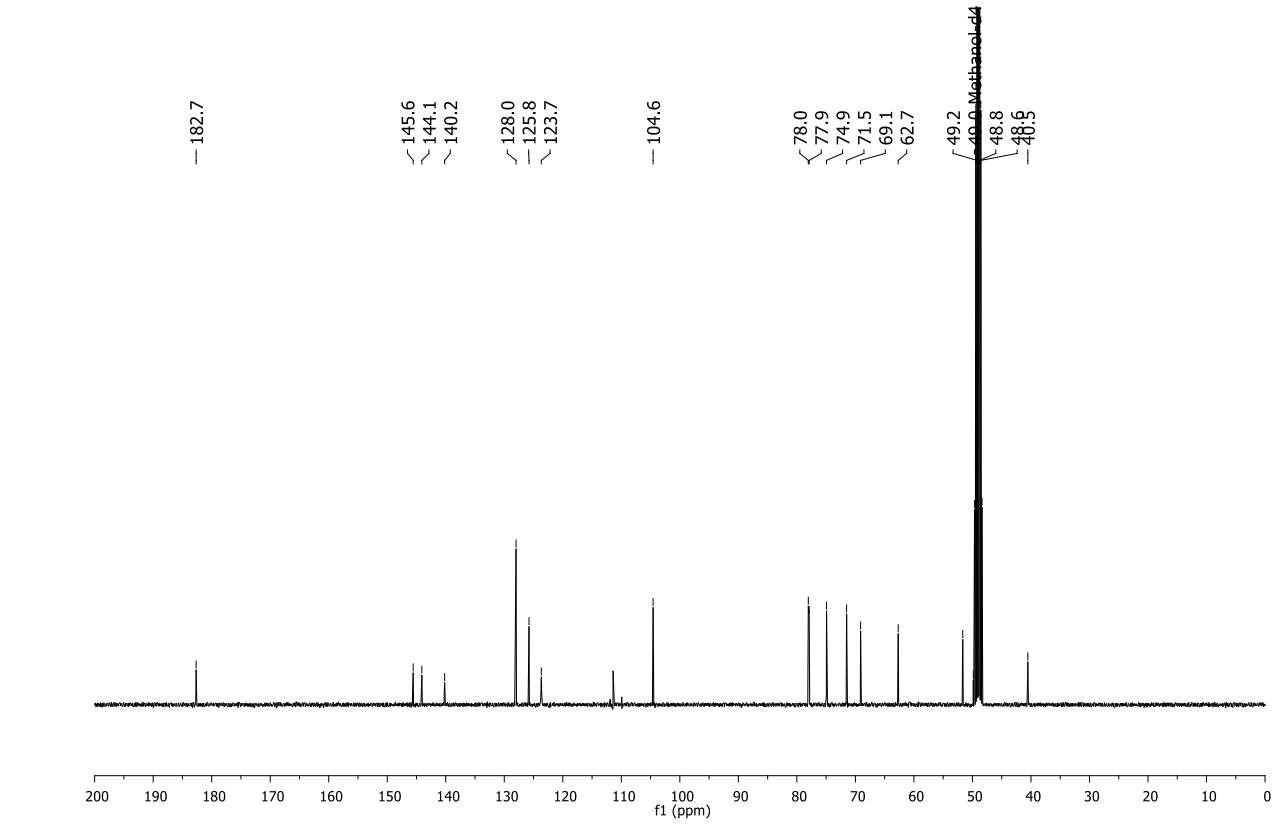


Figure S9: ^{13}C NMR spectrum of **14** (100 MHz, CD_3OD).

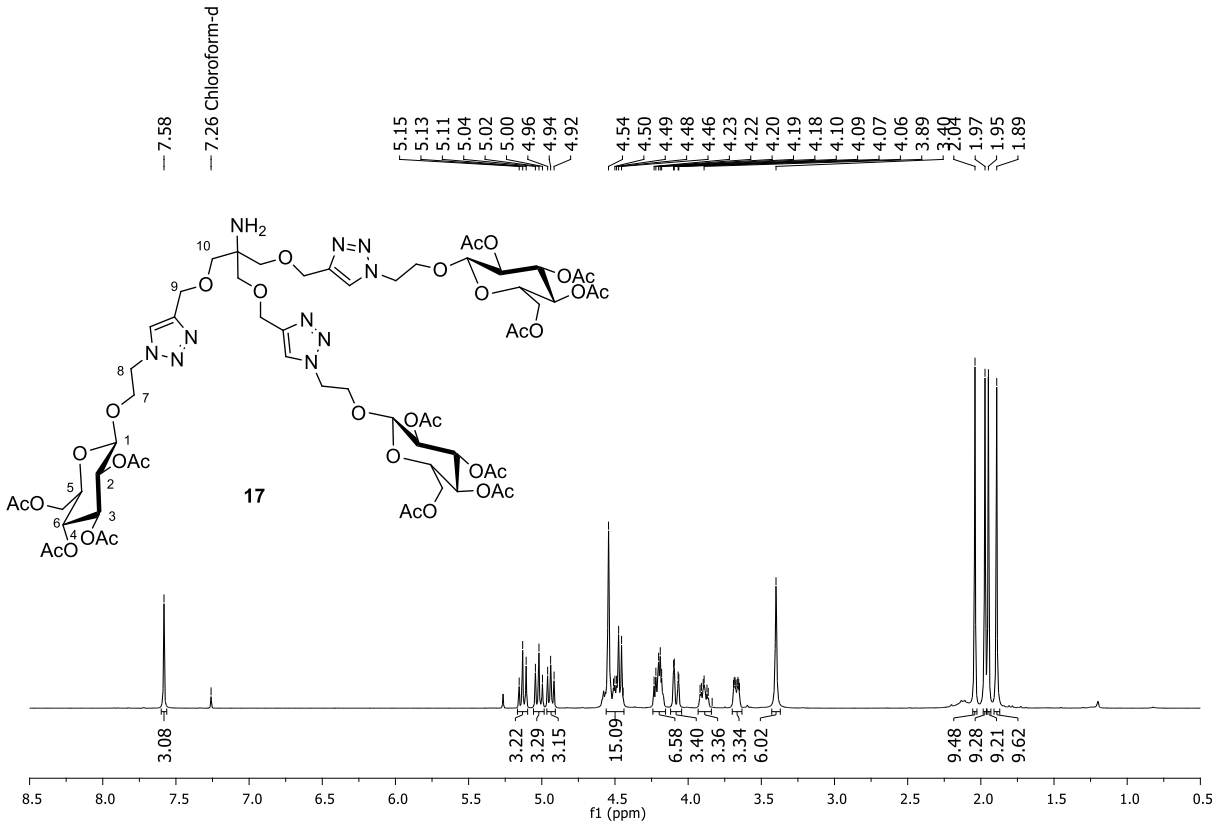


Figure S10: ^{1}H NMR spectrum of **17** (400 MHz, $CDCl_3$).

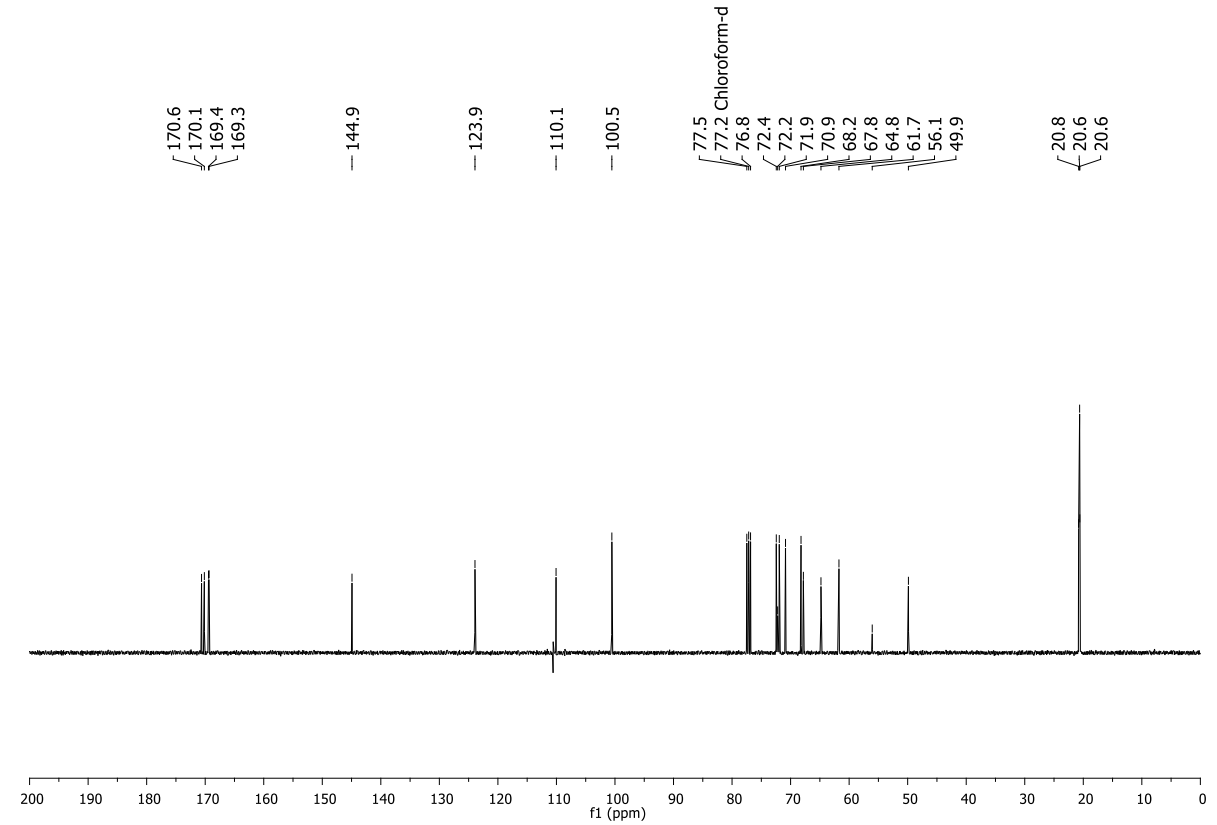


Figure S11: ^{13}C NMR spectrum of **17** (100 MHz, $CDCl_3$).

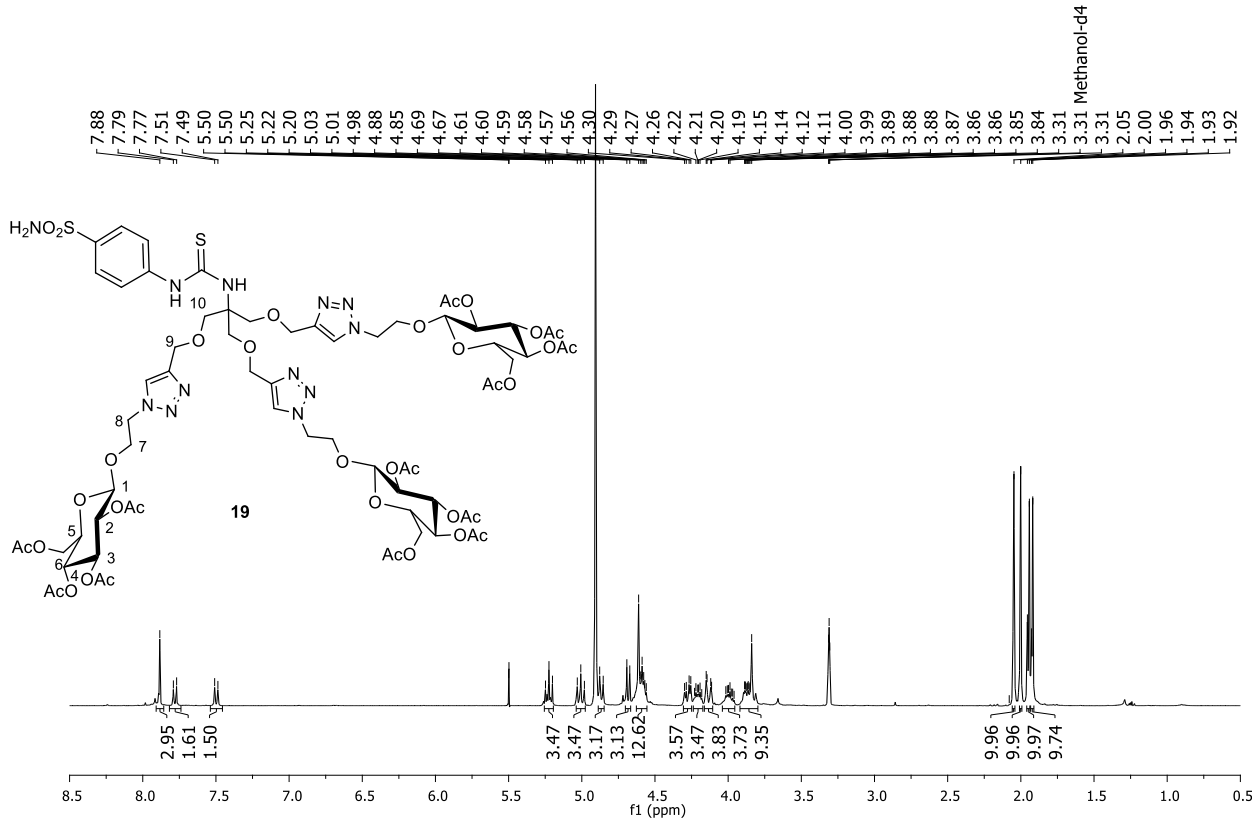


Figure S12: ^{1}H NMR spectrum of **19** (400 MHz, CD_3OD).

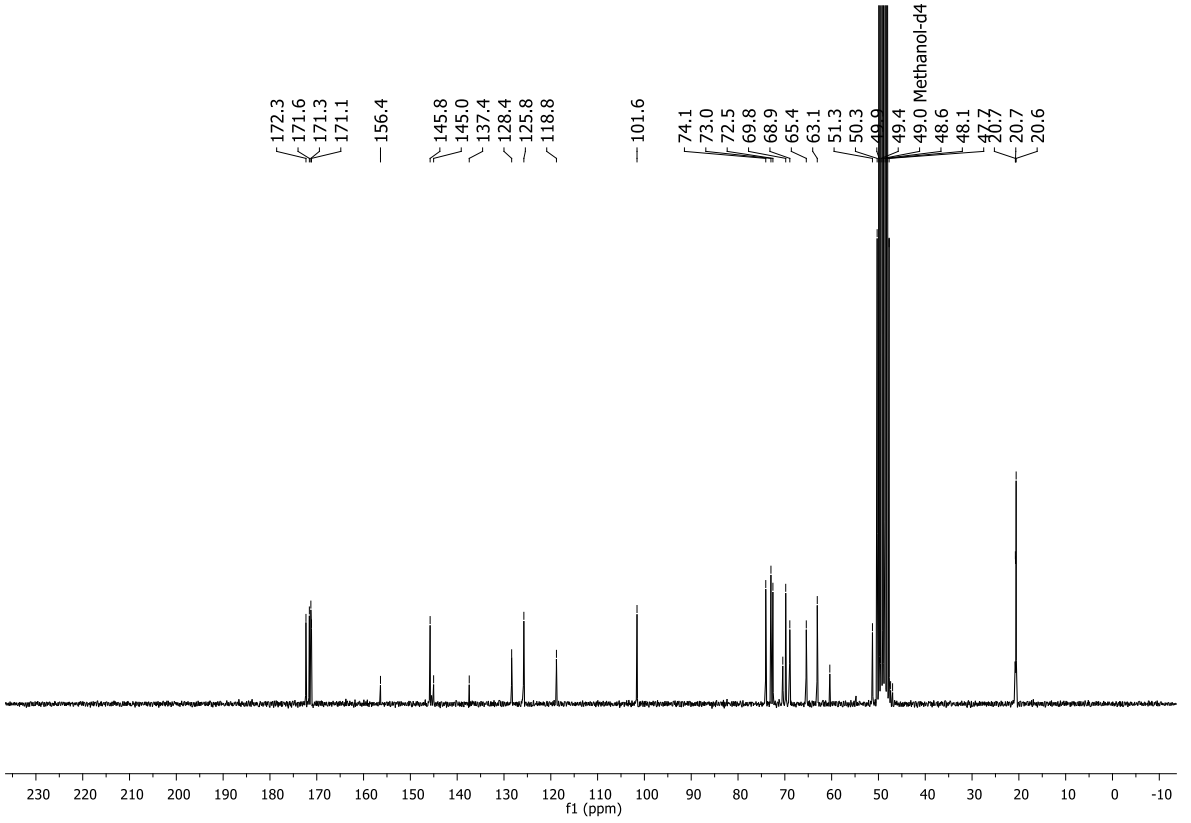


Figure S13: ^{13}C NMR spectrum of **19** (100 MHz, CD_3OD).

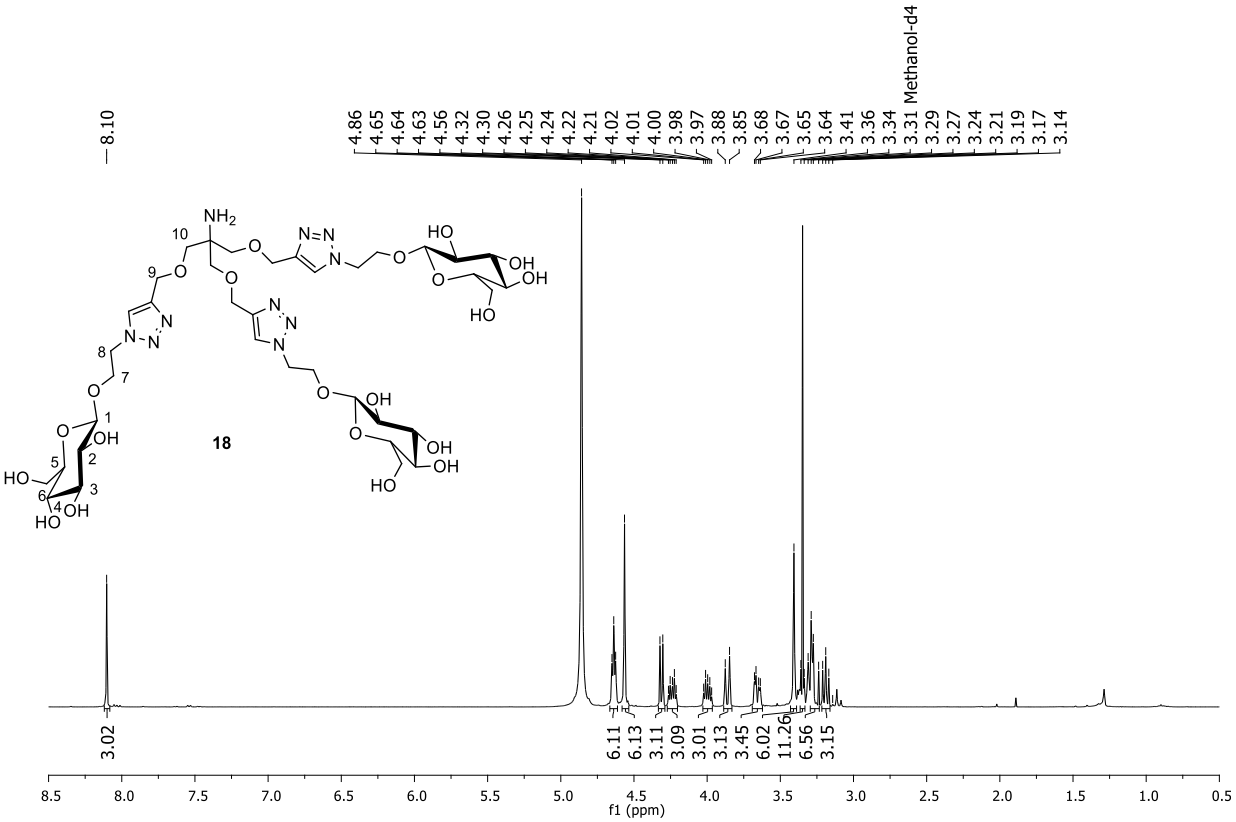


Figure S14: ^{1}H NMR spectrum of **18** (400 MHz, CD_3OD).

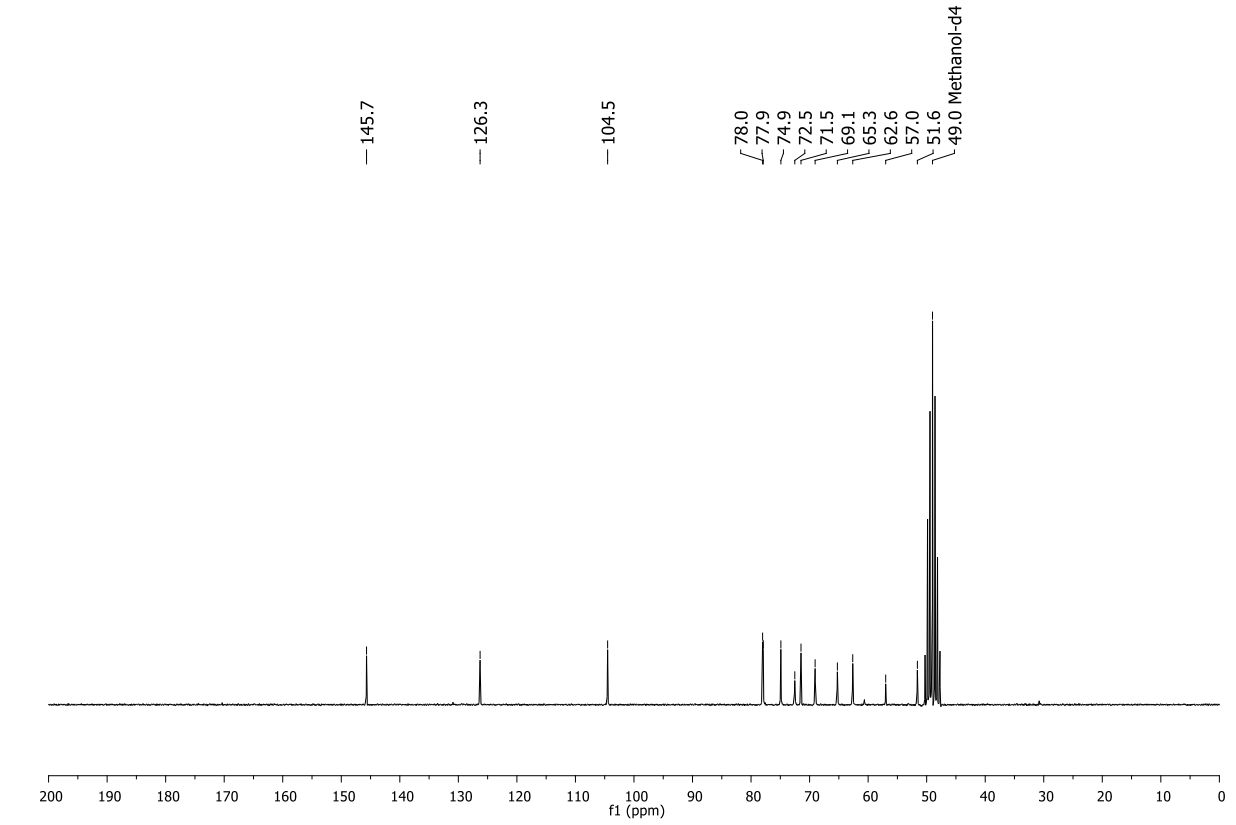


Figure S15: ^{13}C NMR spectrum of **18** (100 MHz, CD_3OD).

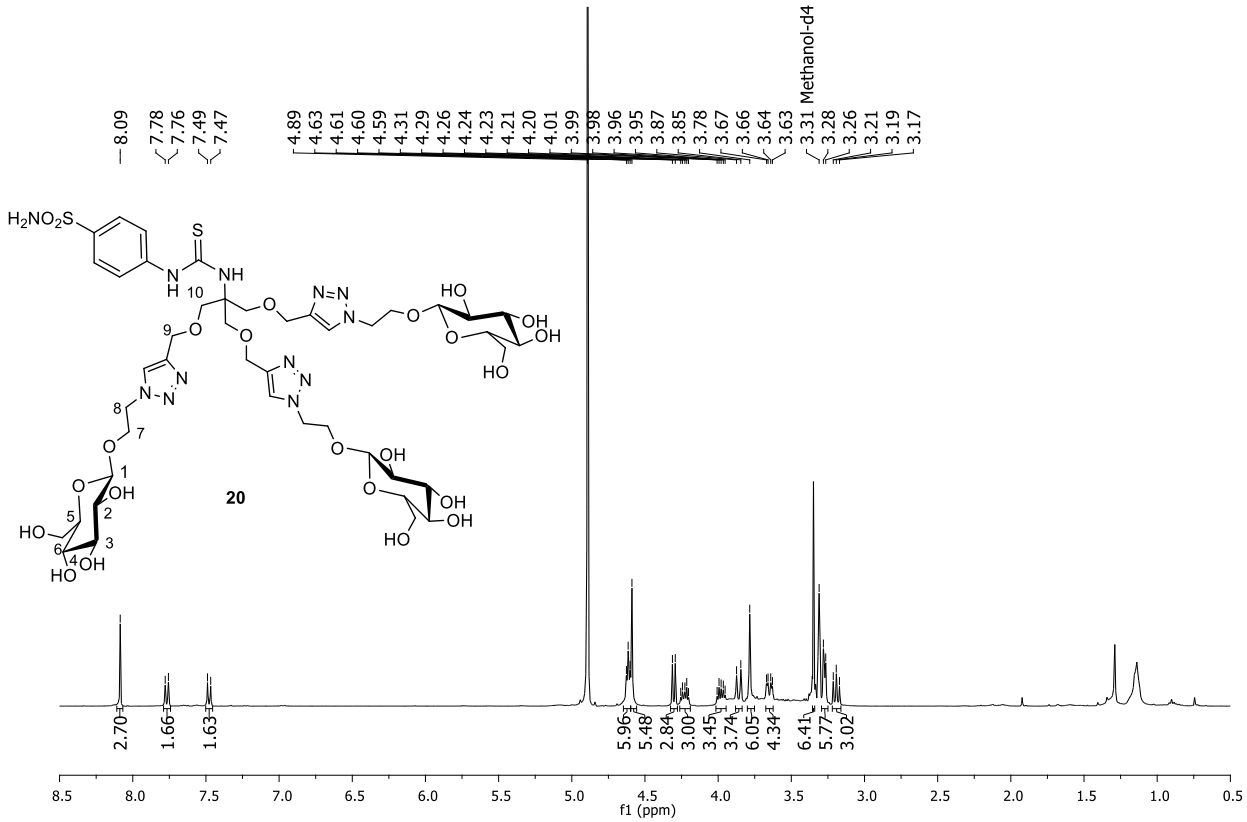


Figure S16: ^{1}H NMR spectrum of **20** (400 MHz, CD_3OD).

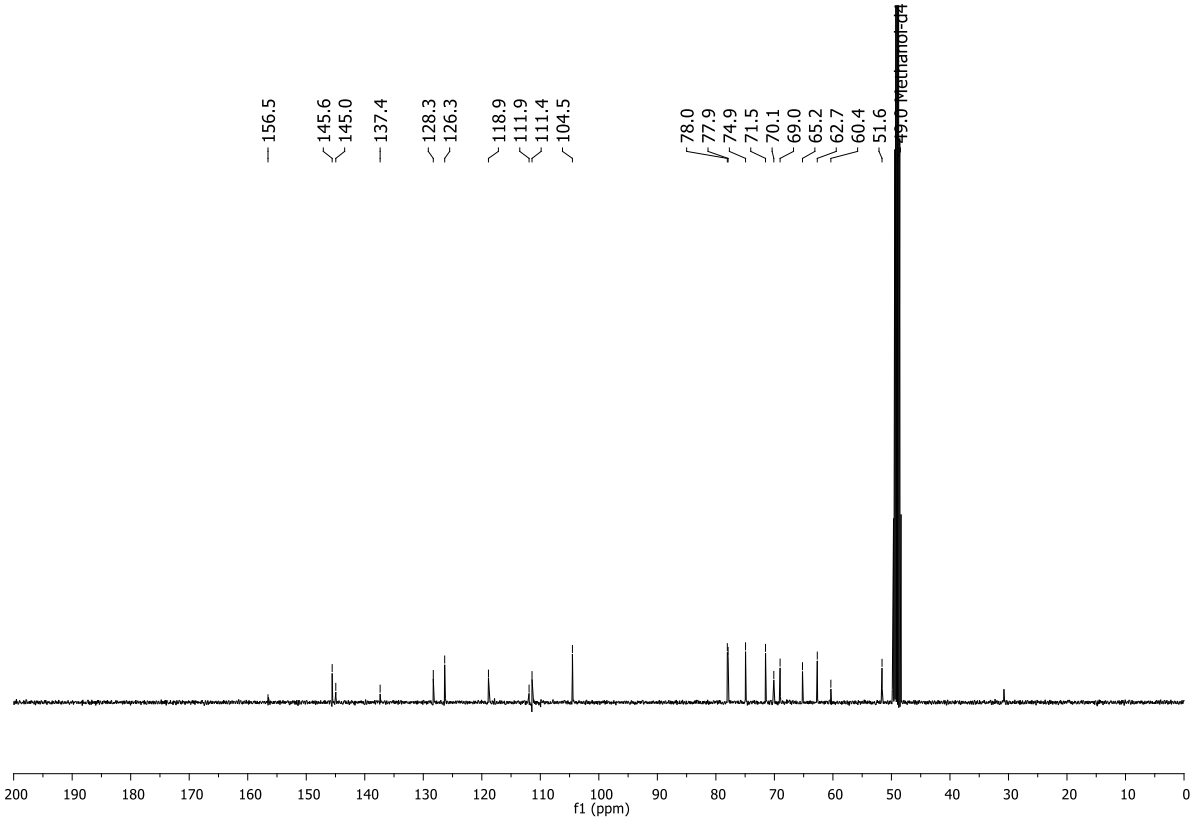


Figure S17: ^{13}C NMR spectrum of **20** (100 MHz, CD_3OD).

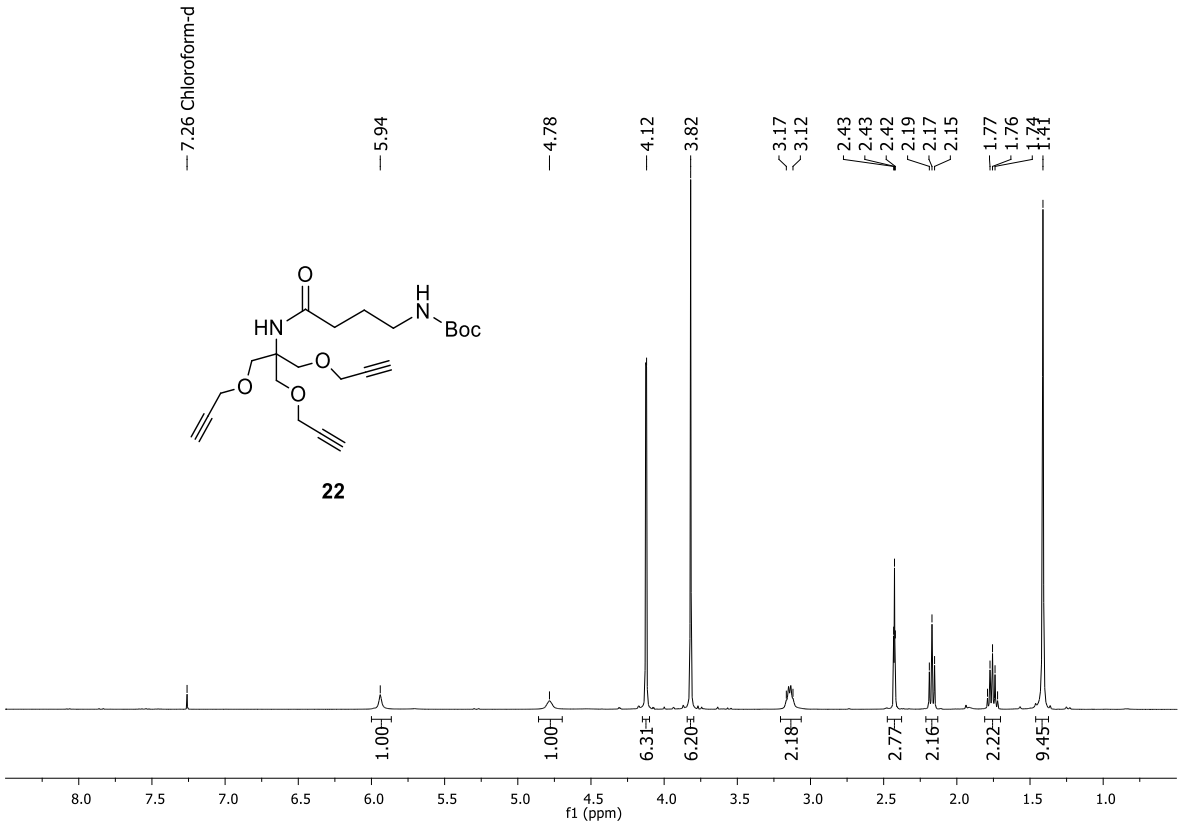


Figure S18: ^{1}H NMR spectrum of **22** (400 MHz, $CDCl_3$).

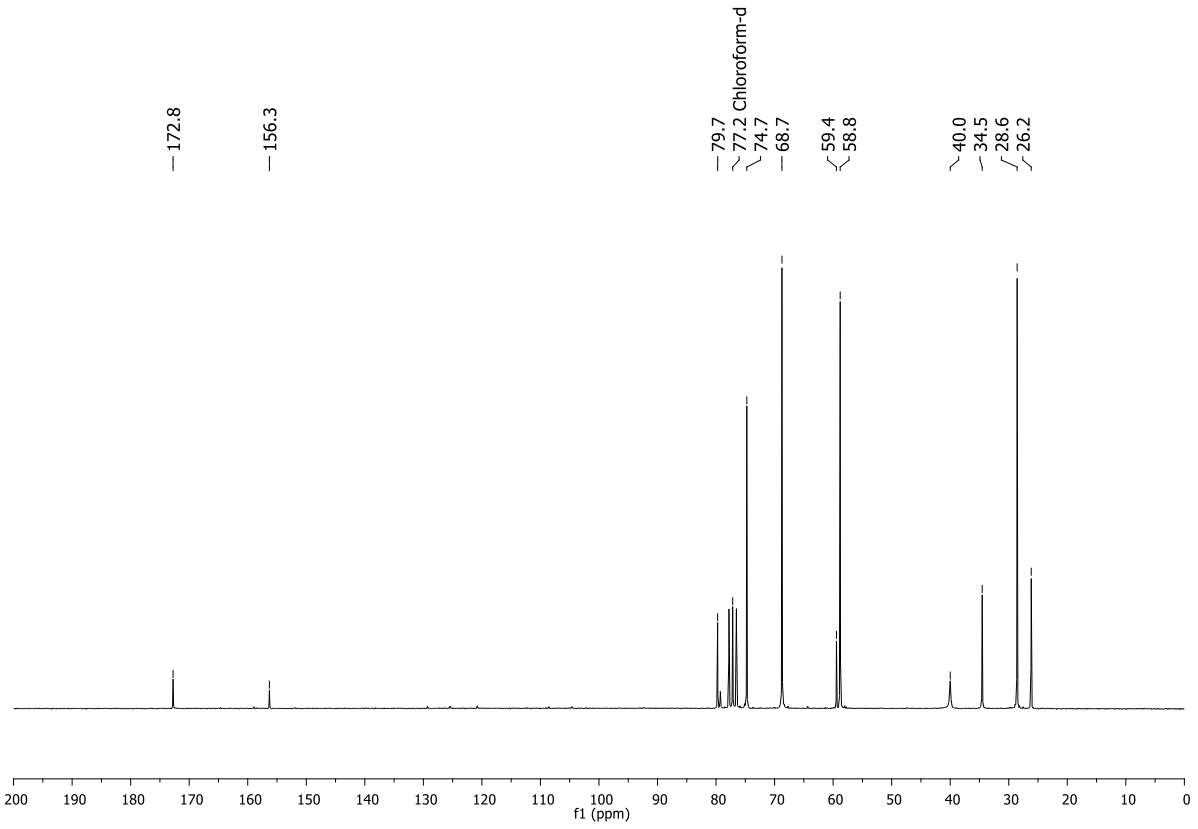


Figure S19: ^{13}C NMR spectrum of **22** (50 MHz, $CDCl_3$).

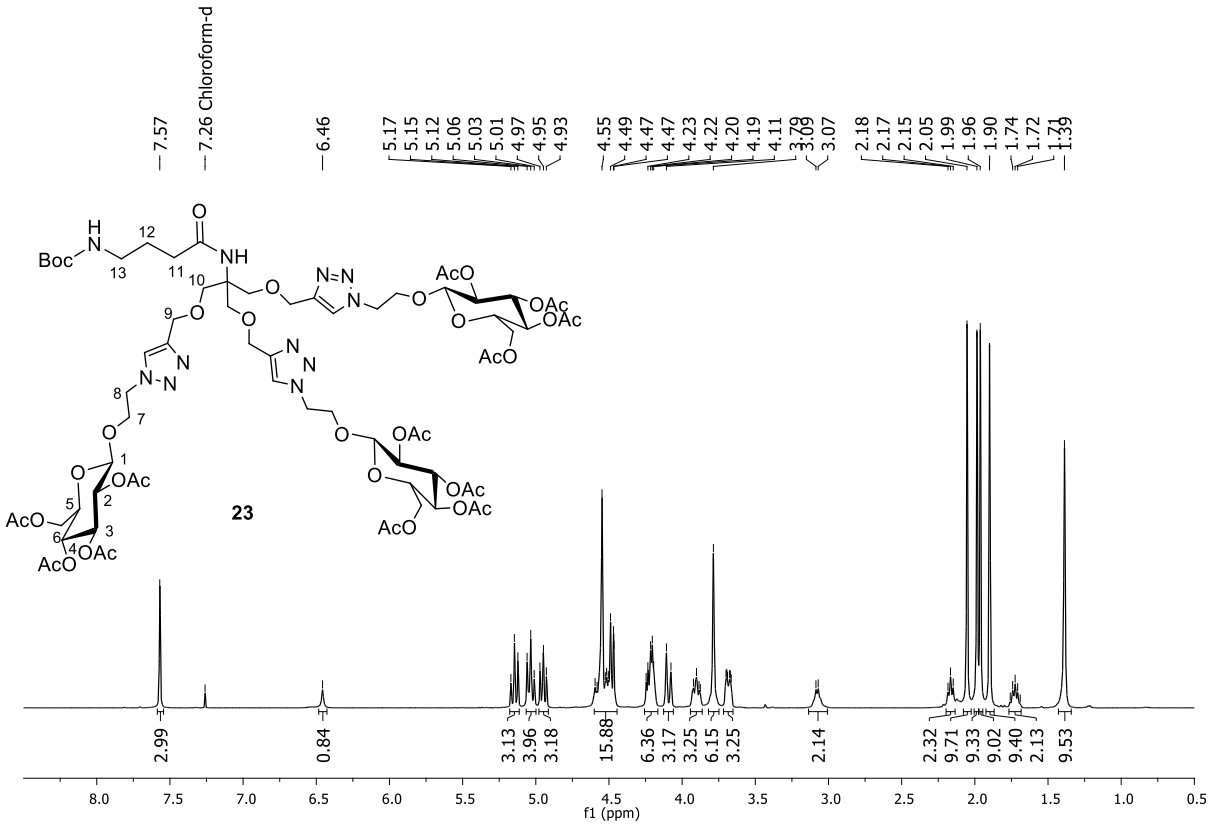


Figure S20: ^{1}H NMR spectrum of **23** (400 MHz, $CDCl_3$).

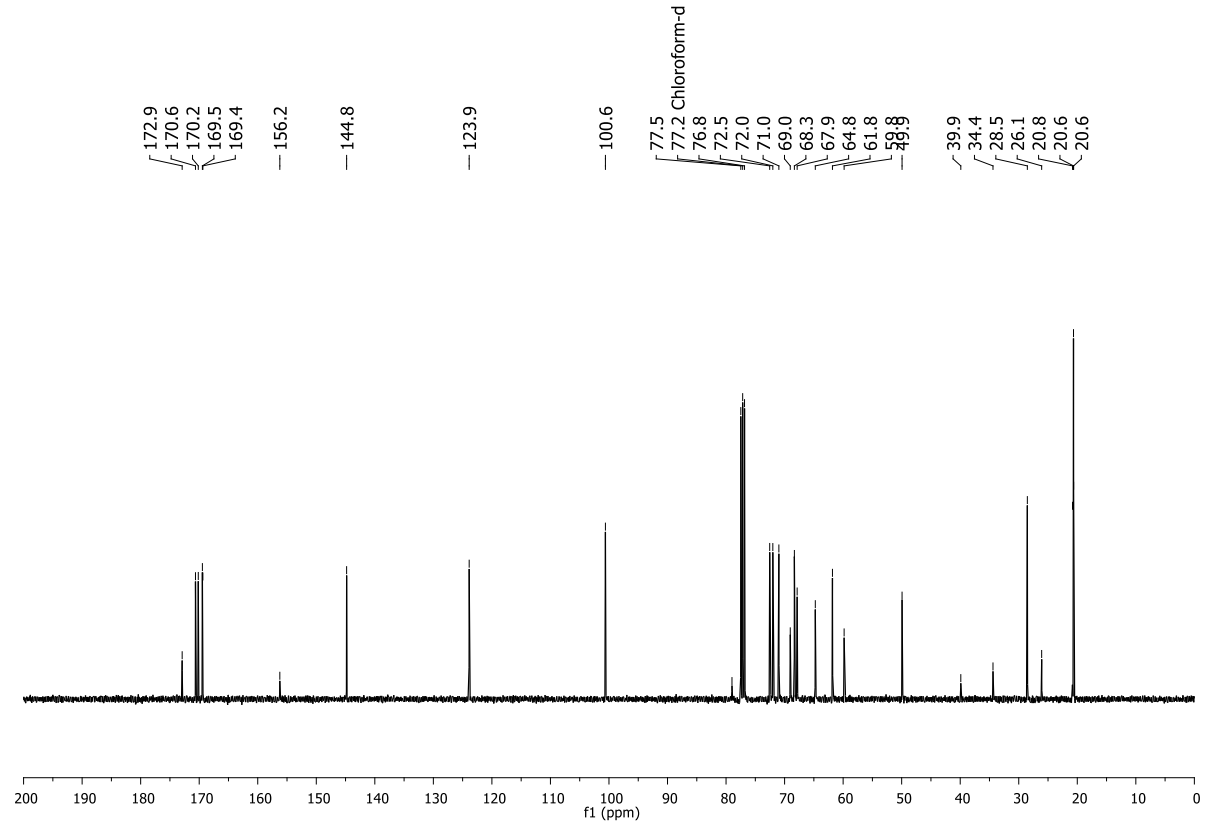


Figure S21: ^{13}C NMR spectrum of **23** (100 MHz, $CDCl_3$).

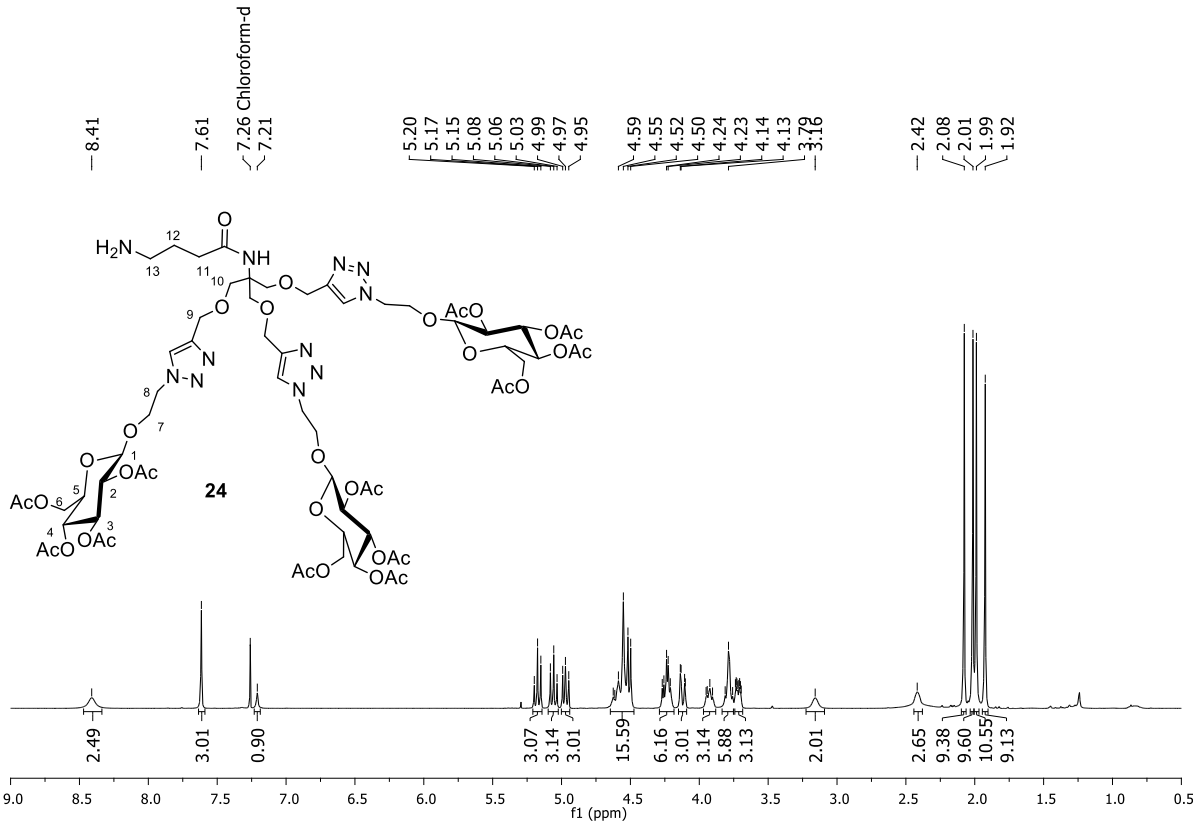


Figure S22: ^{1}H NMR spectrum of **24** (400 MHz, $CDCl_3$).

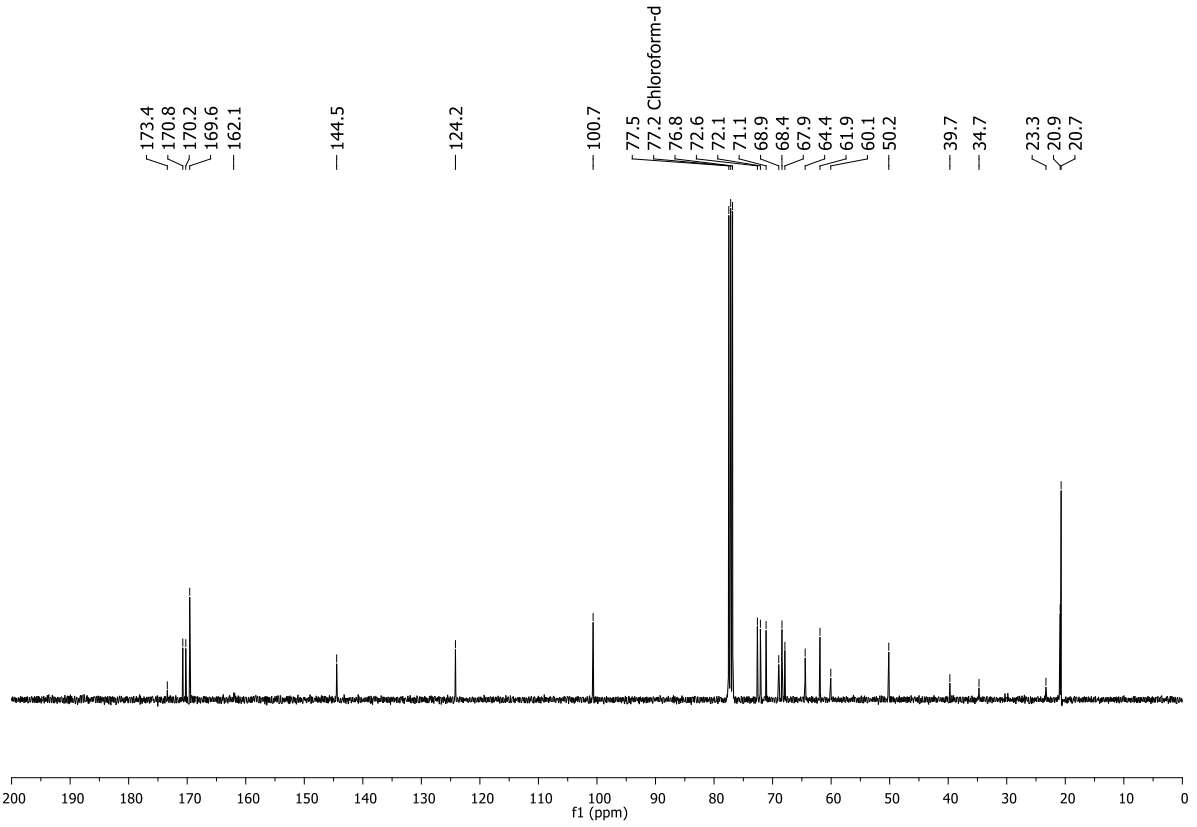


Figure S23: ^{13}C NMR spectrum of **24** (100 MHz, $CDCl_3$).

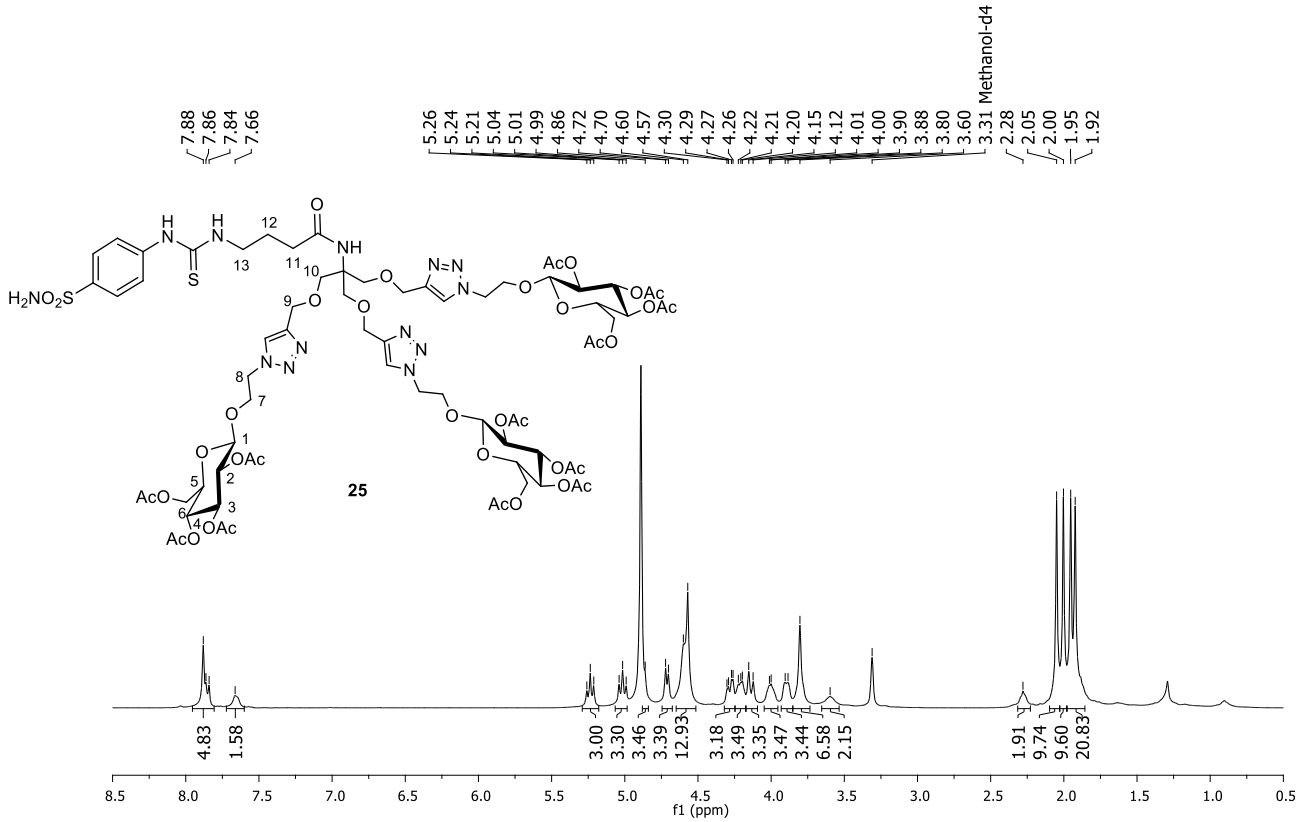


Figure S24: ^{1}H NMR spectrum of **25** (400 MHz, CD_3OD).

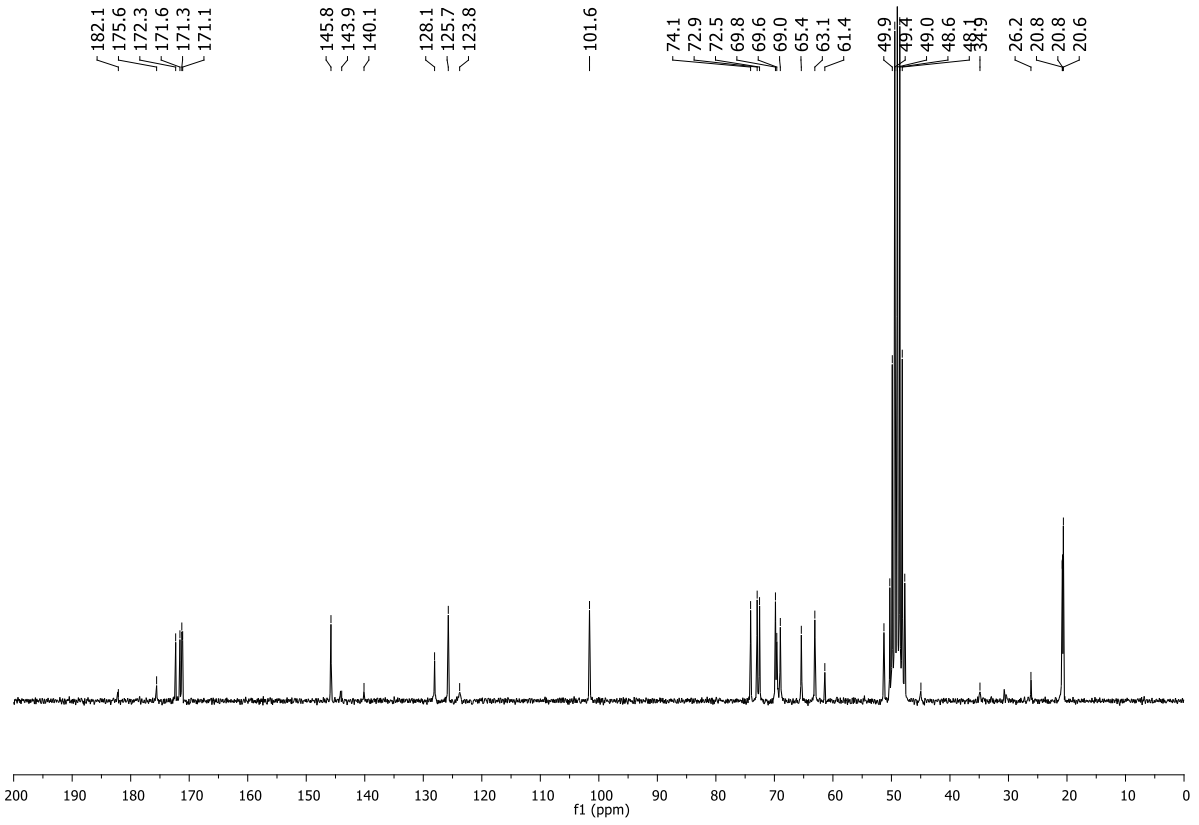


Figure S25: ^{13}C NMR spectrum of **25** (50 MHz, CD_3OD).

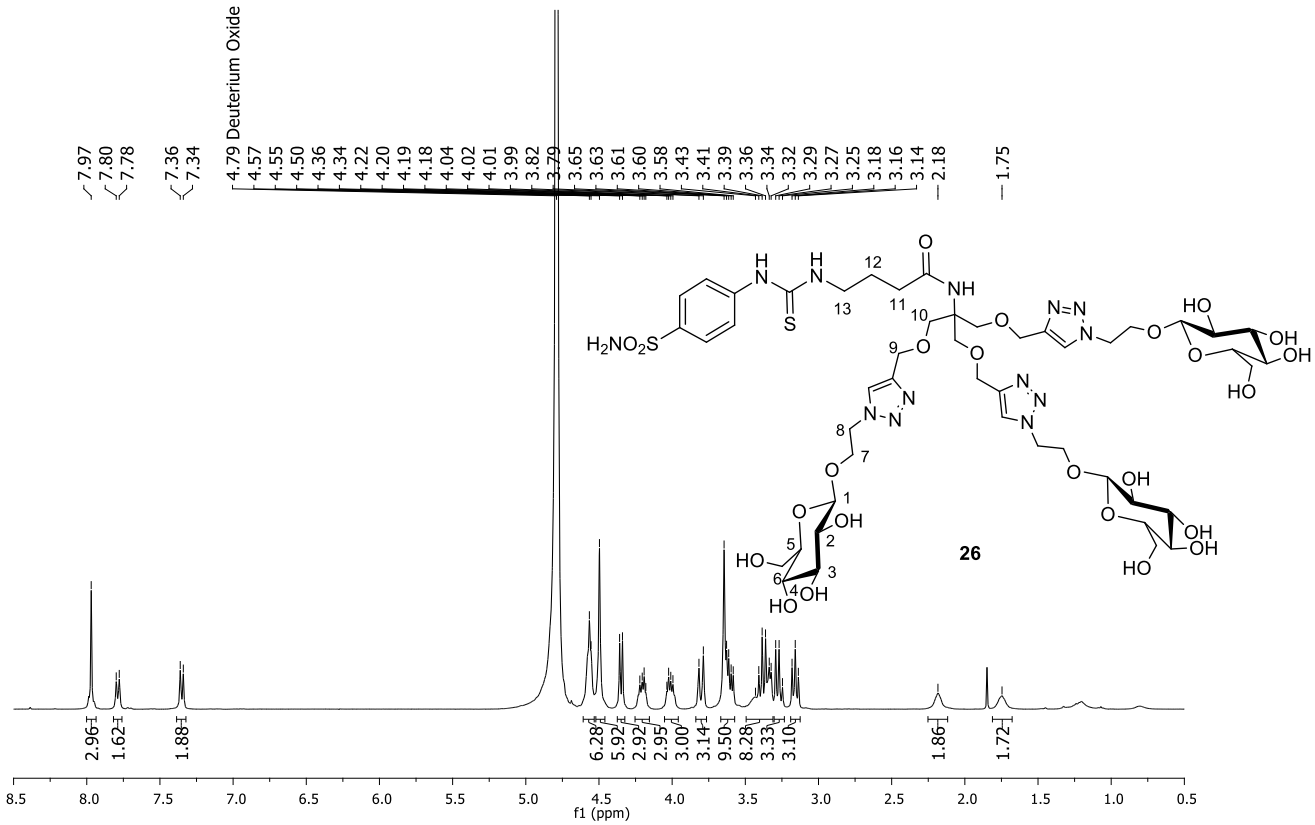


Figure S26: ^{1}H NMR spectrum of **26** (400 MHz, D_2O).

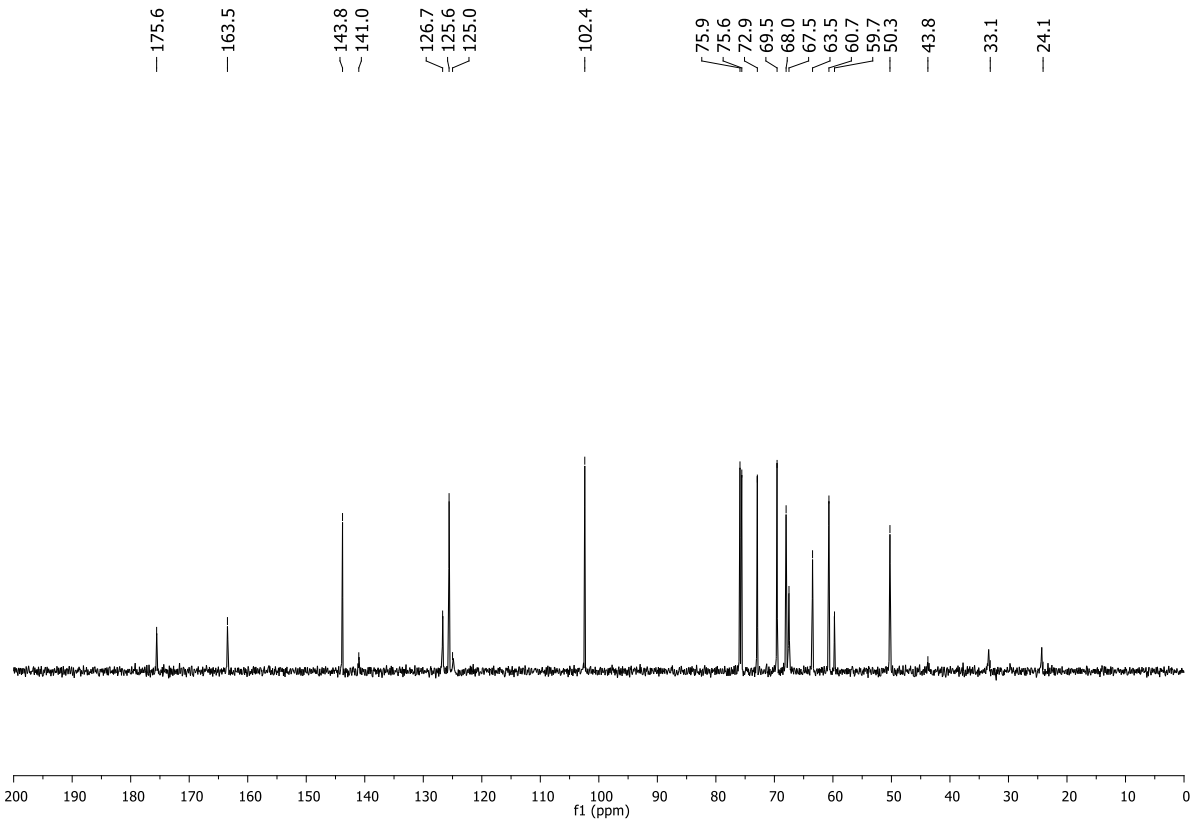


Figure S27: ^{13}C NMR spectrum of **26** (50 MHz, D_2O).

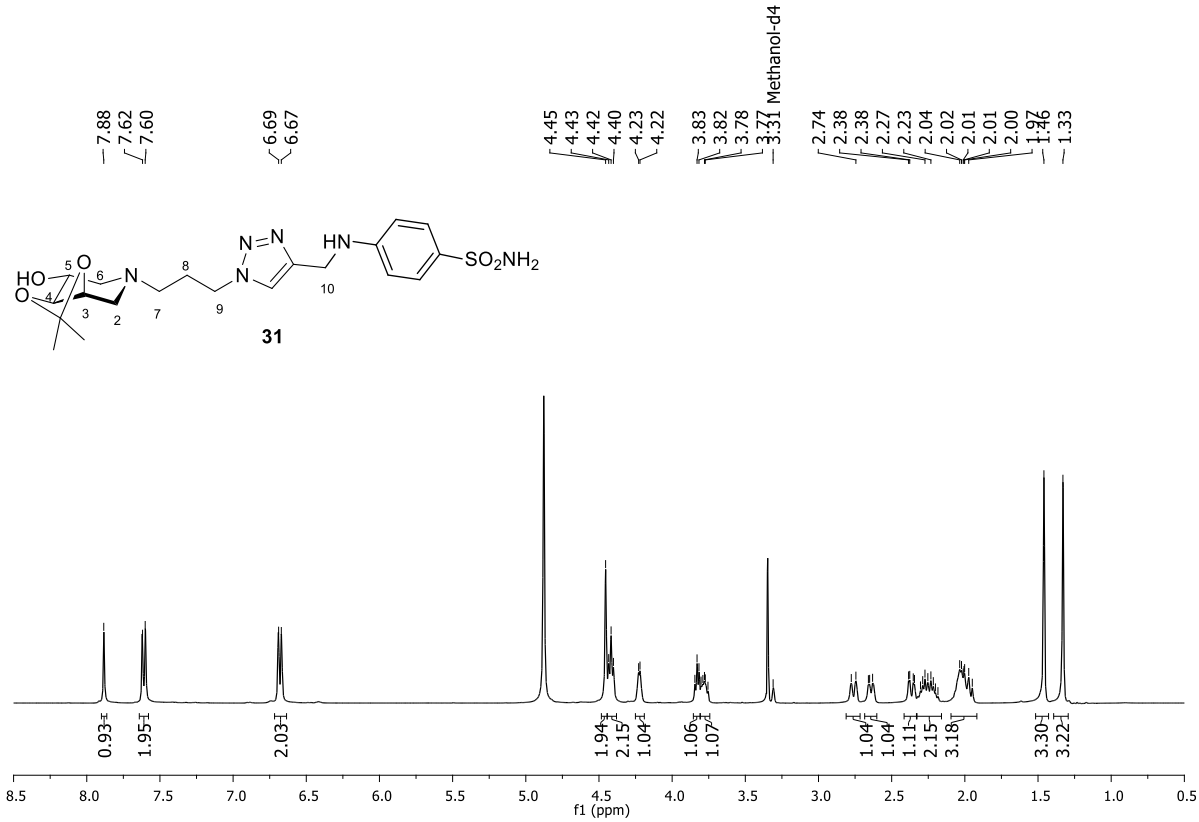


Figure S28: ^{1}H NMR spectrum of **31** (400 MHz, CD_3OD).

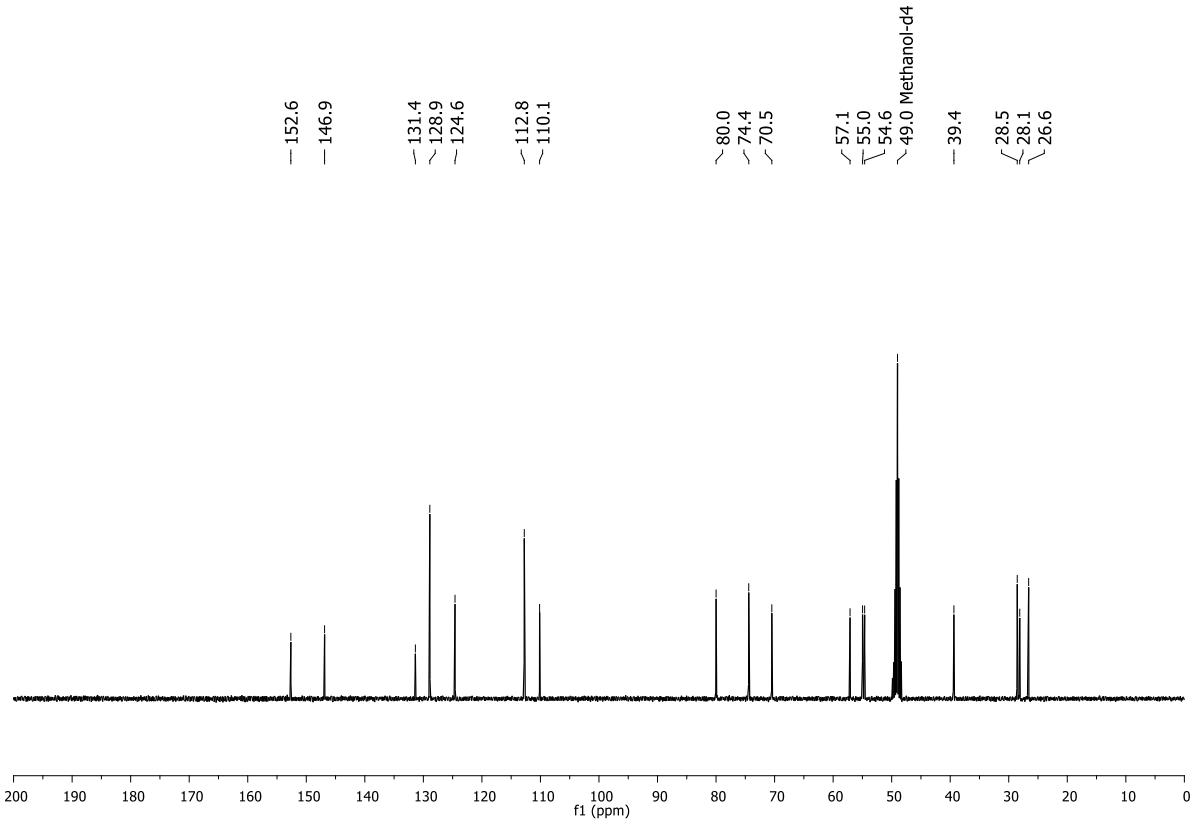


Figure S29: ^{13}C NMR spectrum of **31** (100 MHz, CD_3OD).

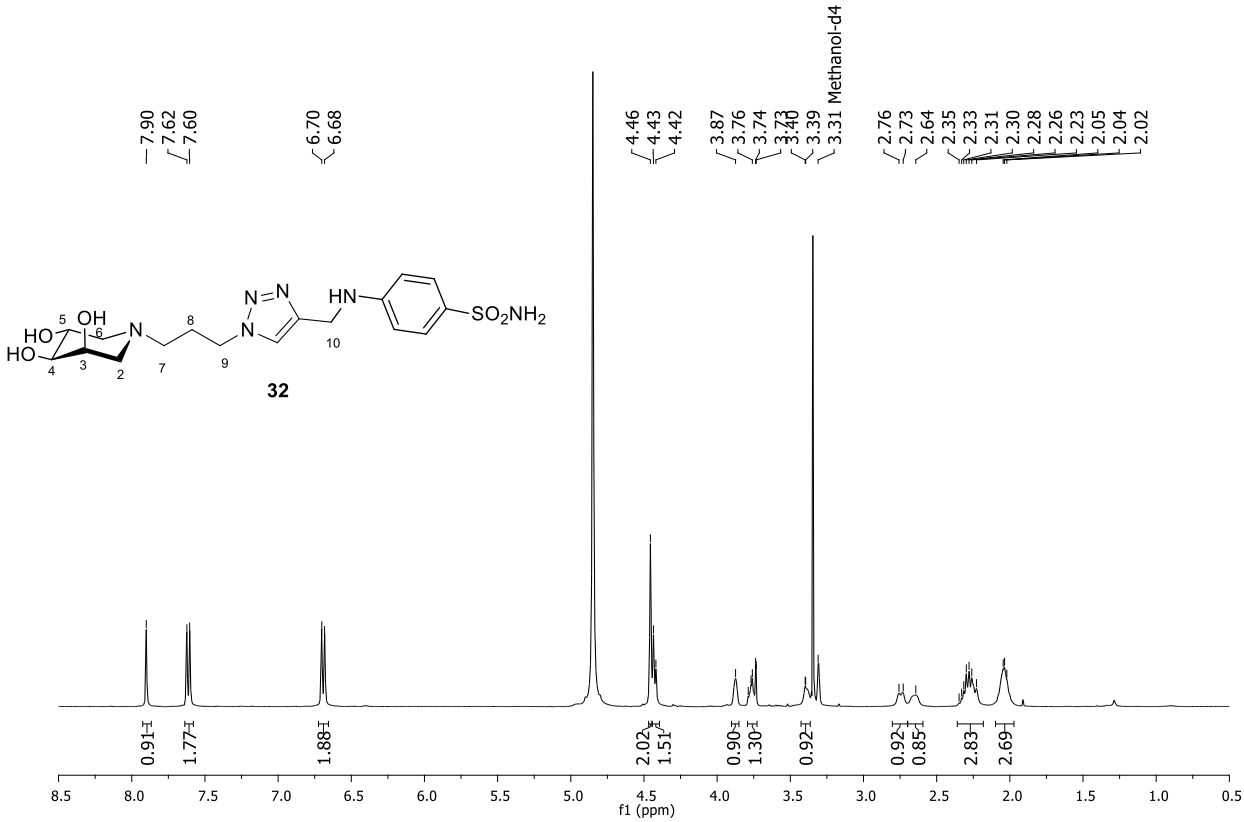


Figure S30: ^{1}H NMR spectrum of **32** (400 MHz, CD_3OD).

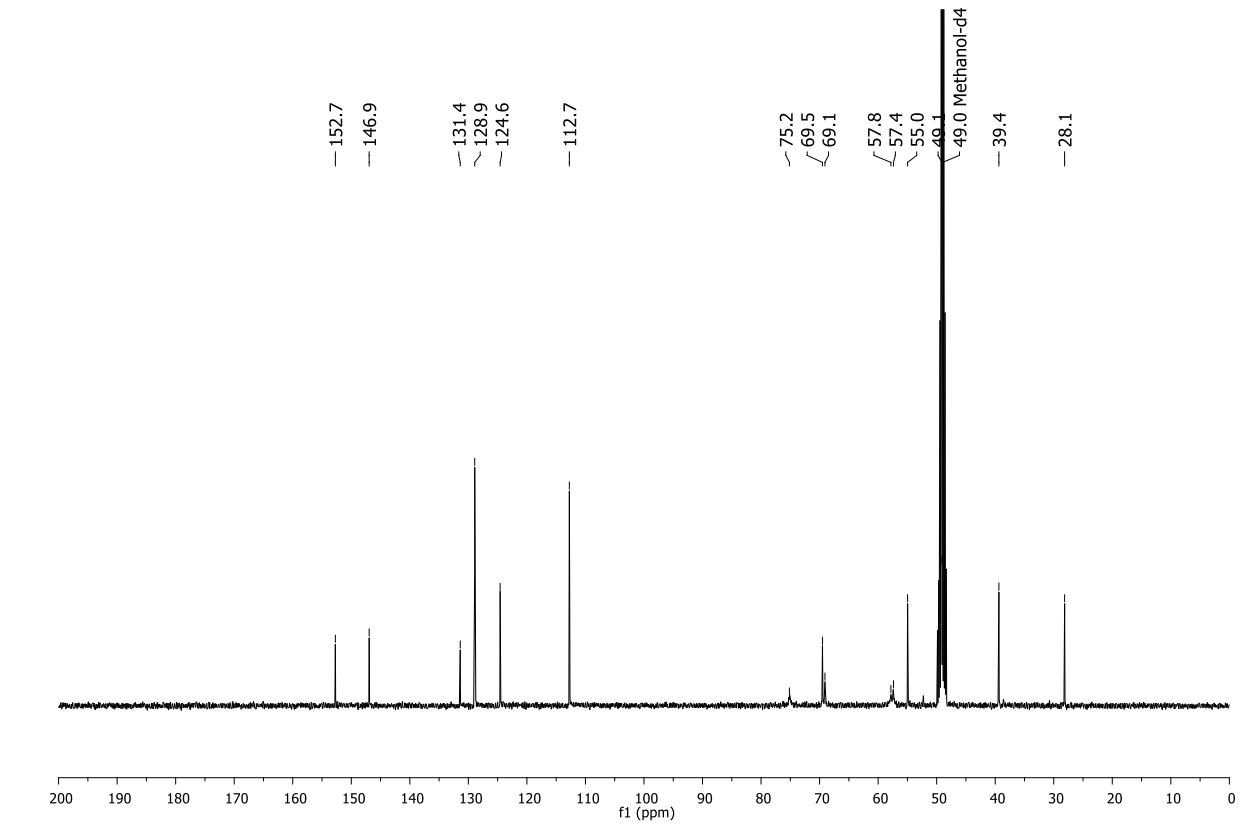


Figure S31: ^{13}C NMR spectrum of **32** (100 MHz, CD_3OD).

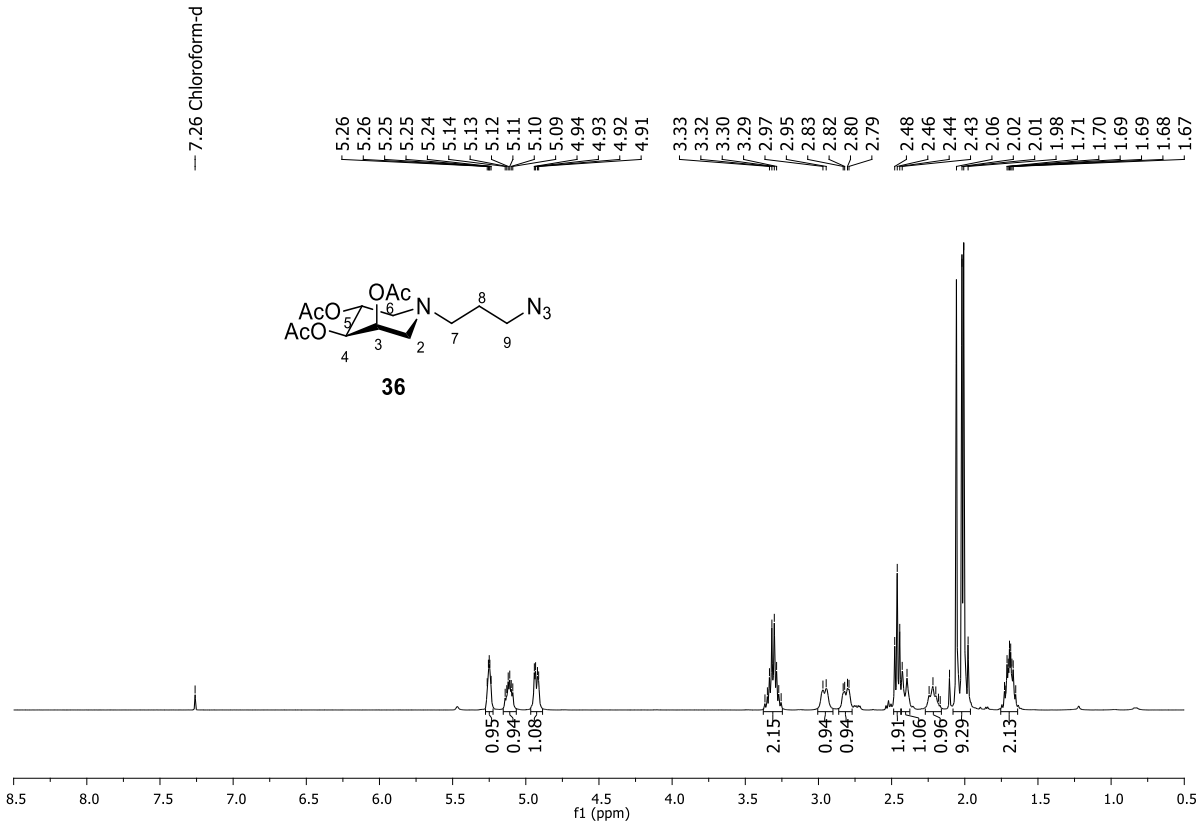


Figure S32: ^{1}H NMR spectrum of **36** (400 MHz, $CDCl_3$).

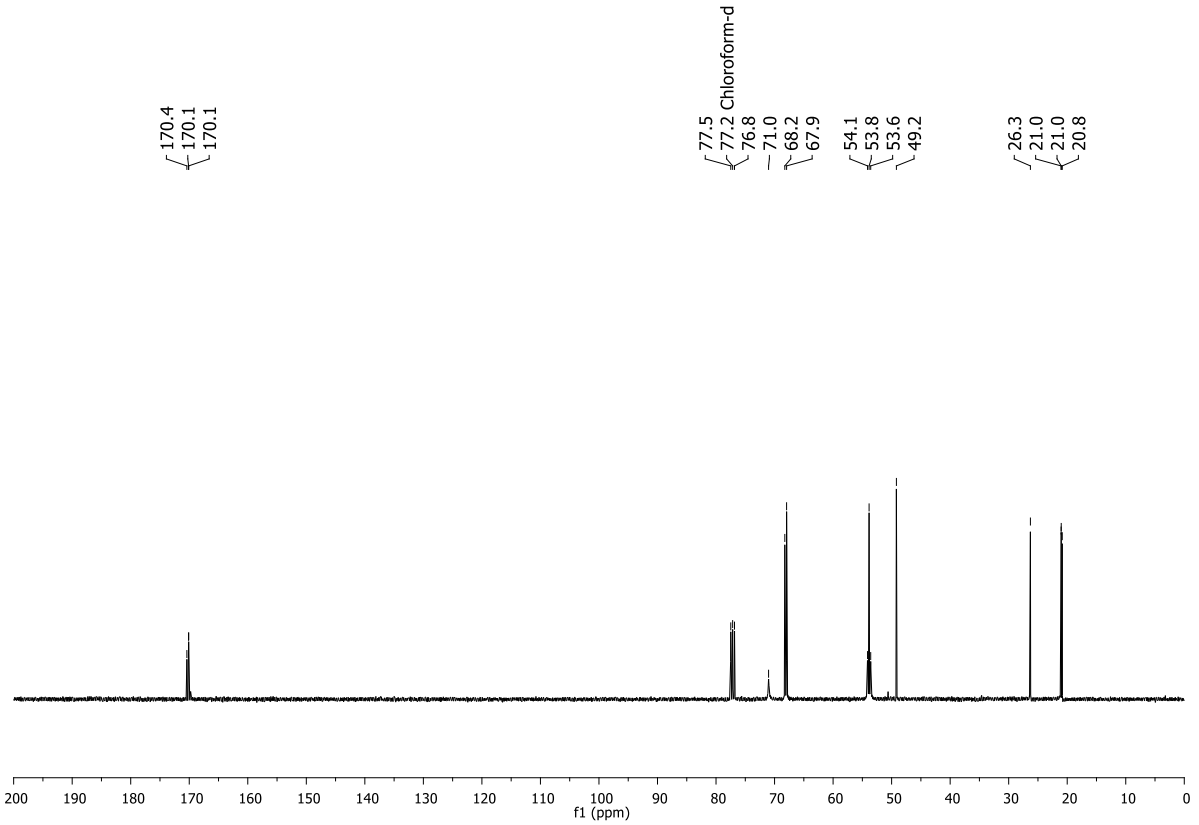


Figure S33: ^{13}C NMR spectrum of **36** (100 MHz, $CDCl_3$).

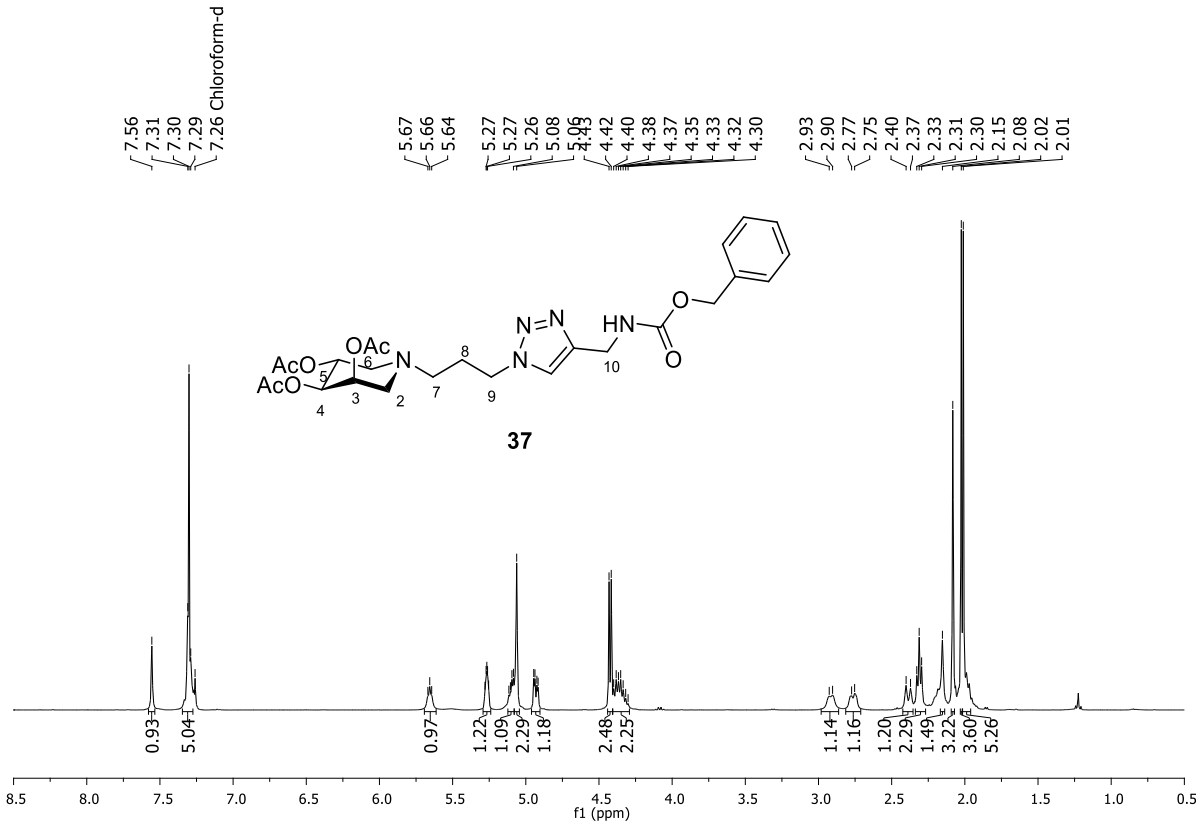


Figure S34: ^{1}H NMR spectrum of **37** (400 MHz, $CDCl_3$).

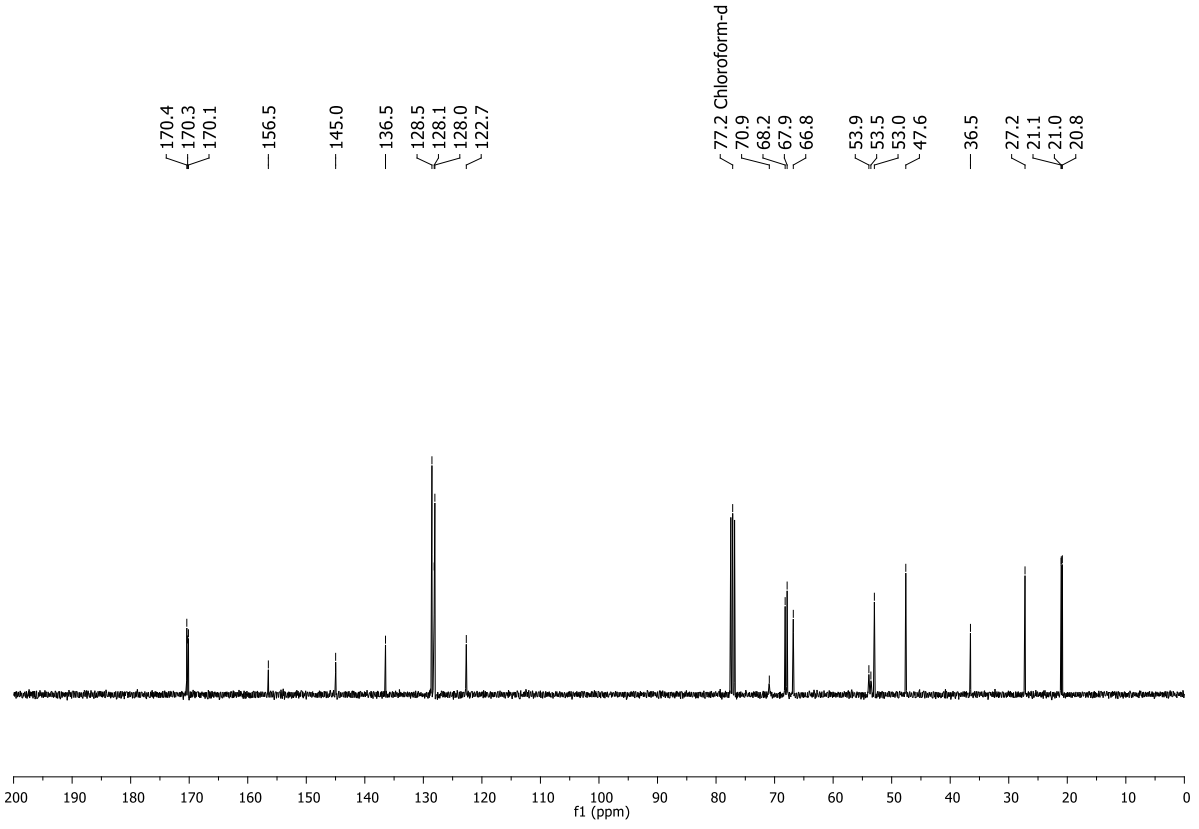


Figure S35: ^{13}C NMR spectrum of **37** (100 MHz, $CDCl_3$).

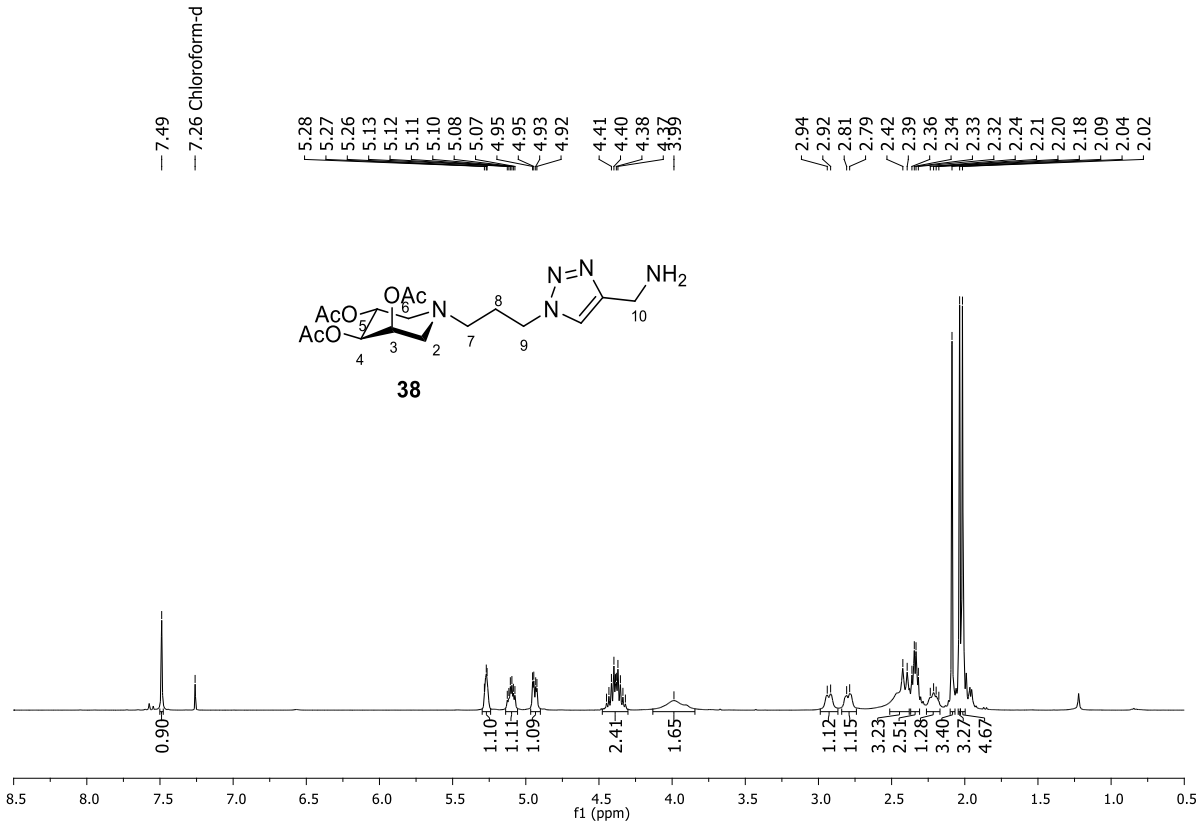


Figure S36: ^{1}H NMR spectrum of **38** (400 MHz, $CDCl_3$).

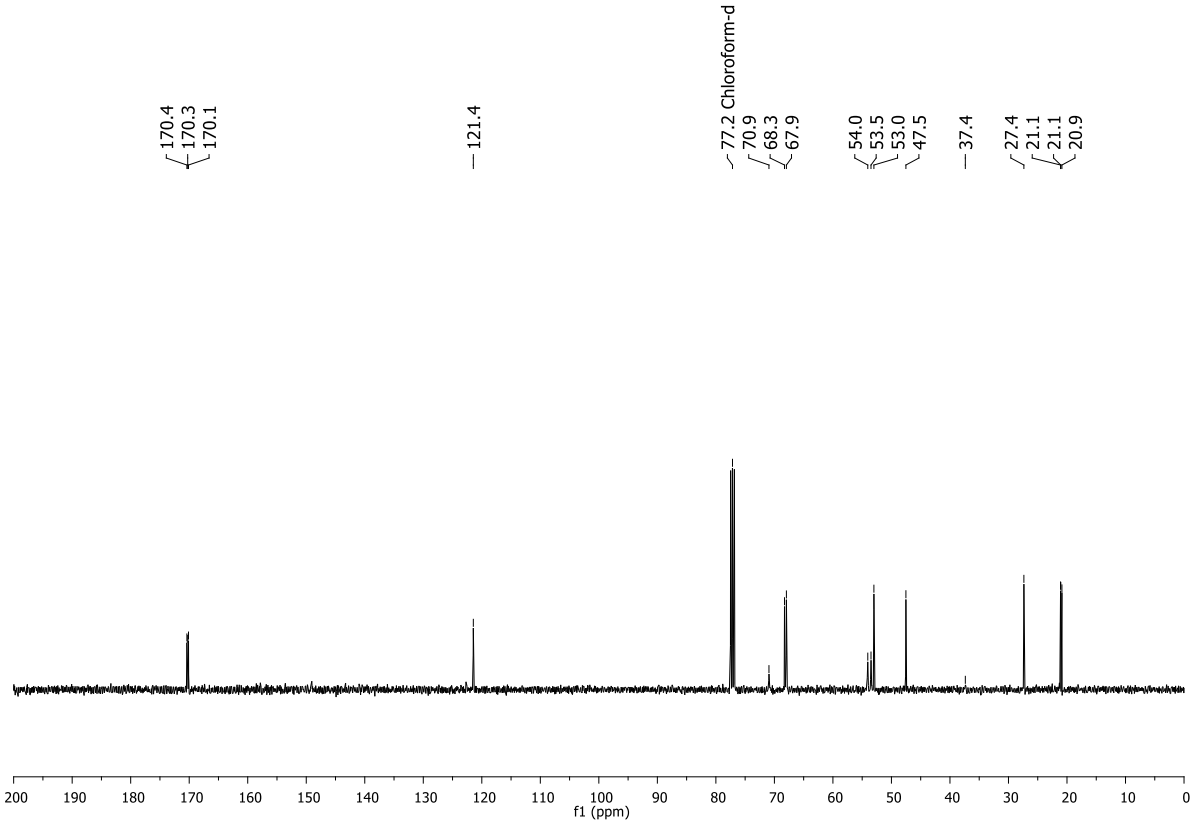


Figure S37: ^{13}C NMR spectrum of **38** (100 MHz, $CDCl_3$).

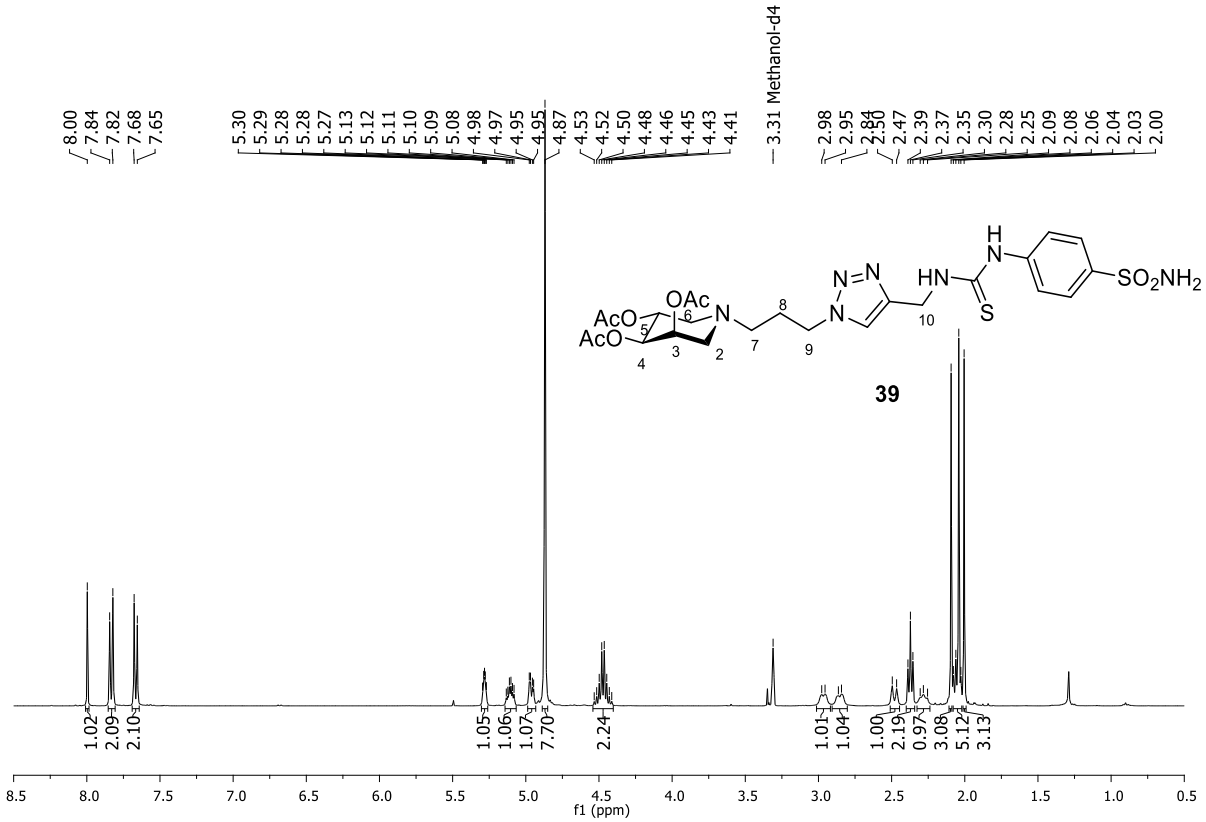


Figure S38: ^{1}H NMR spectrum of **39** (400 MHz, CD_3OD).

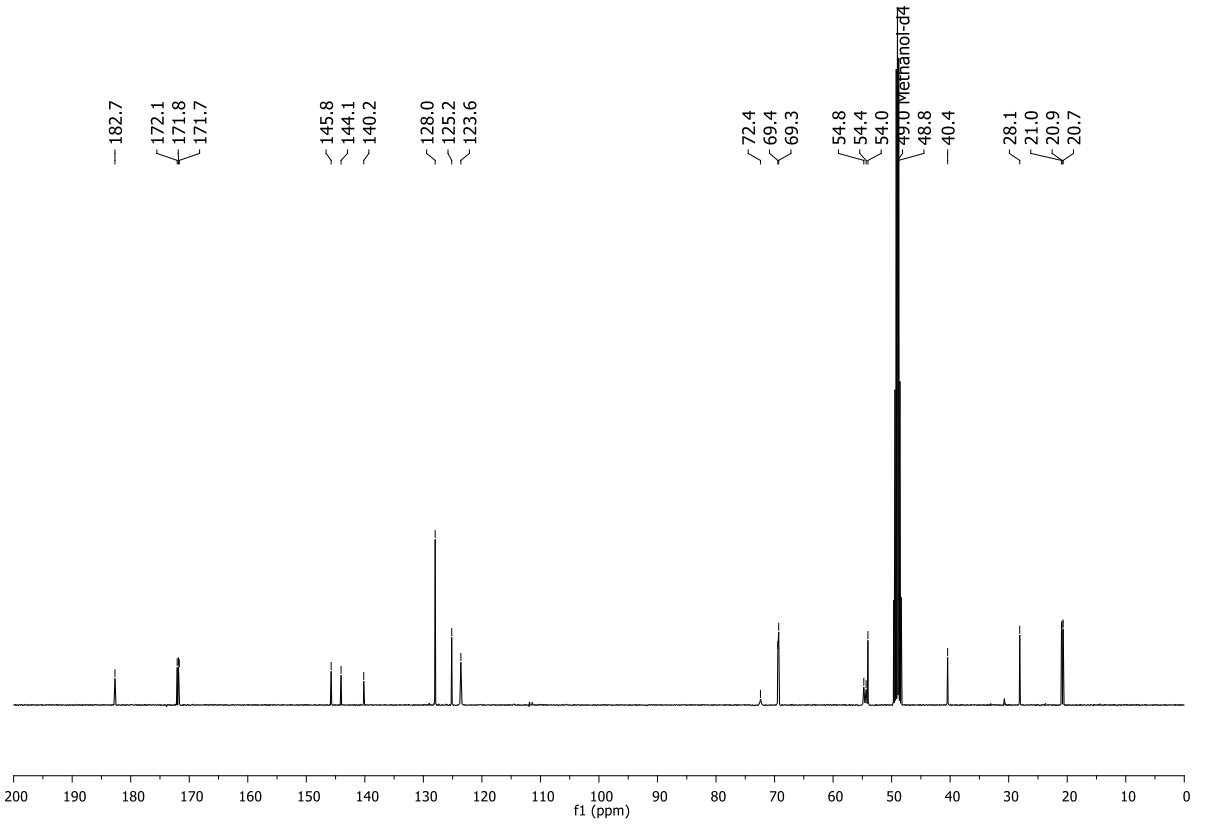
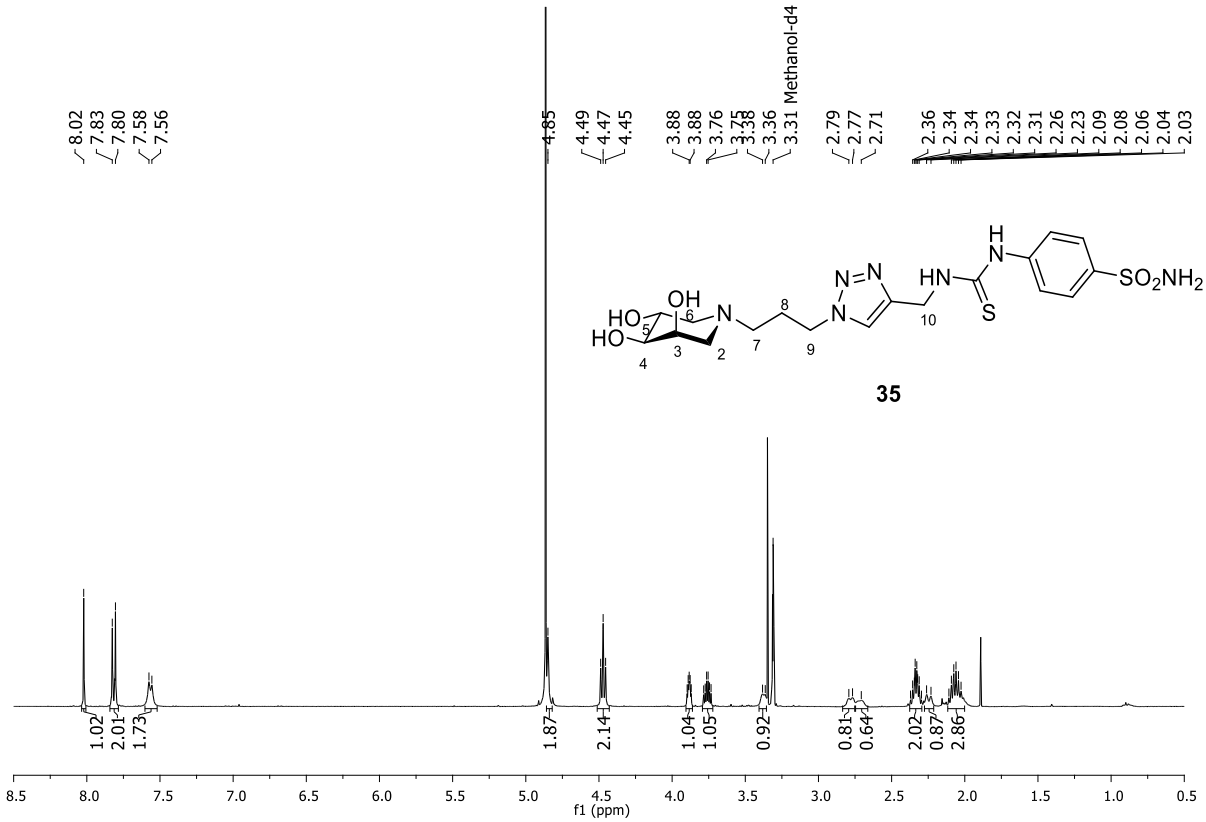


Figure S39: ^{13}C NMR spectrum of **39** (100 MHz, CD_3OD).



35

Figure S40: ^{1}H NMR spectrum of **35** (400 MHz, CD_3OD).

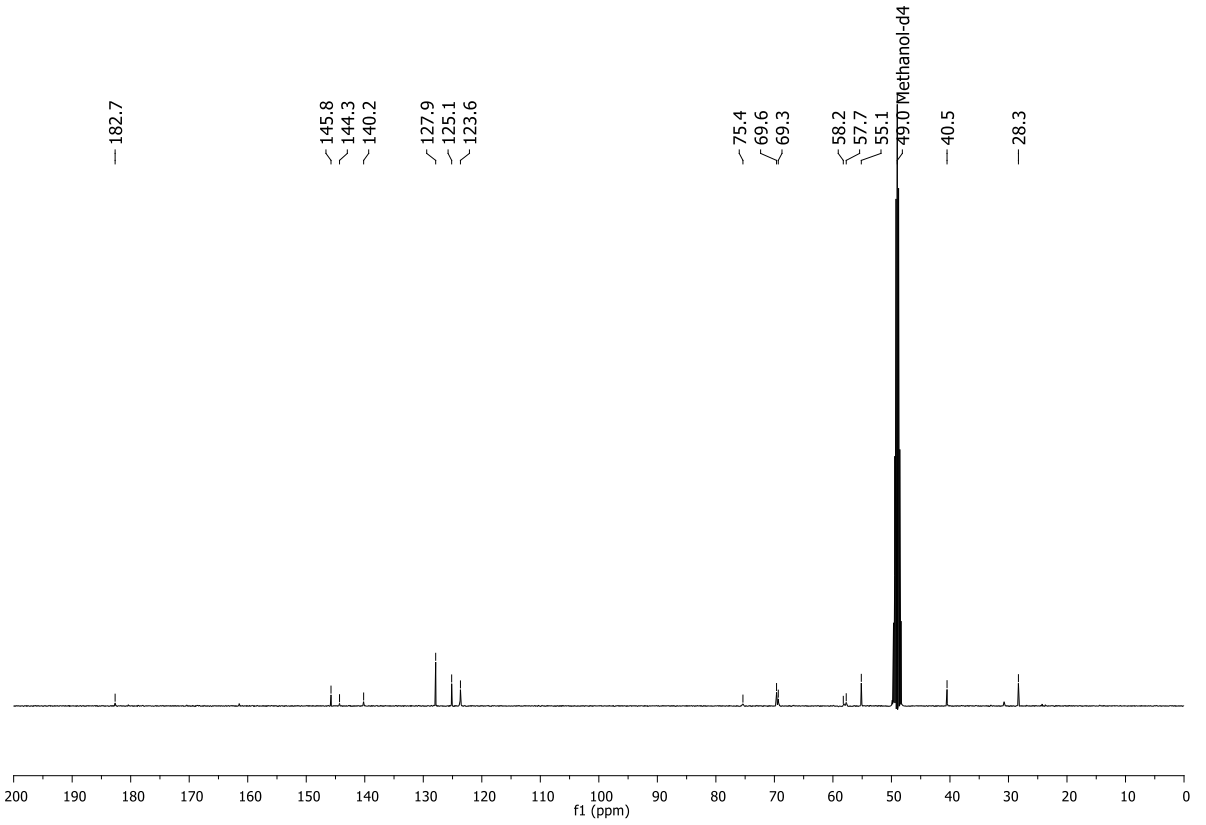


Figure S41: ^{13}C NMR spectrum of **35** (100 MHz, CD_3OD).

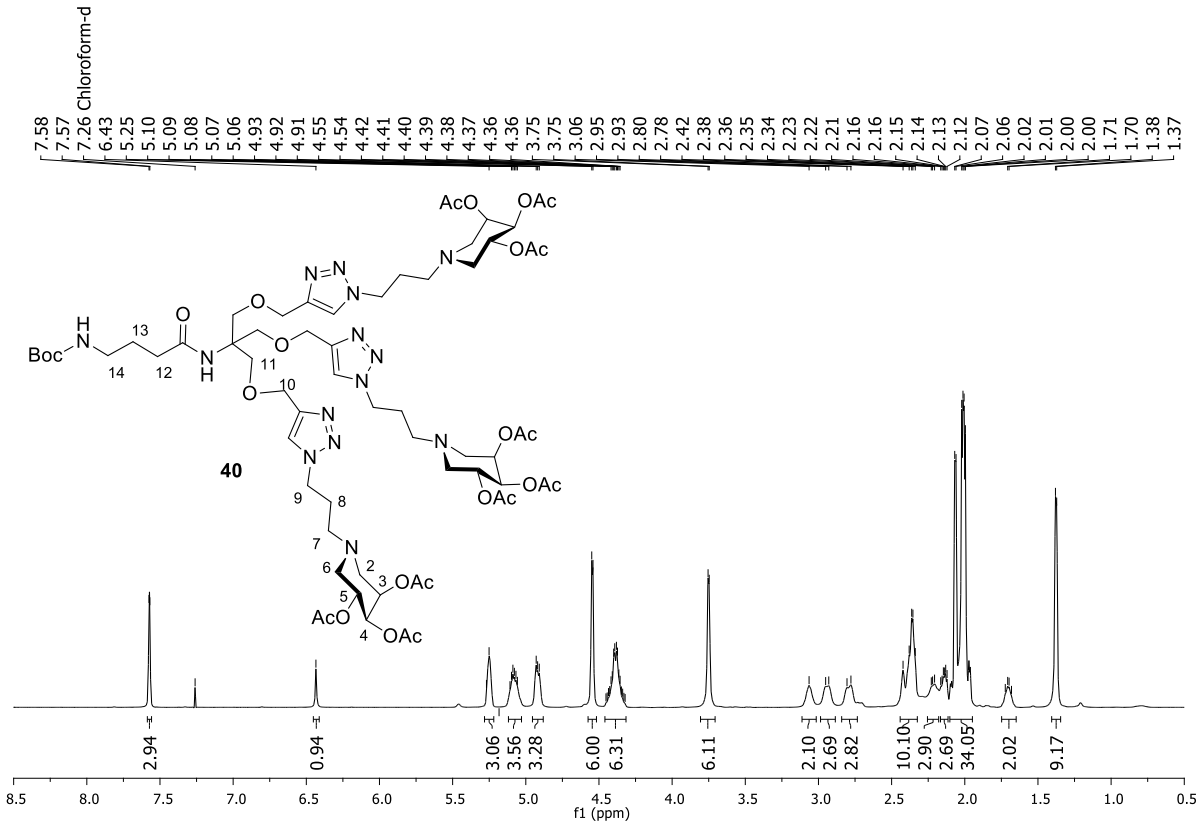


Figure S42: ^{1}H NMR spectrum of **40** (400 MHz, $CDCl_3$).

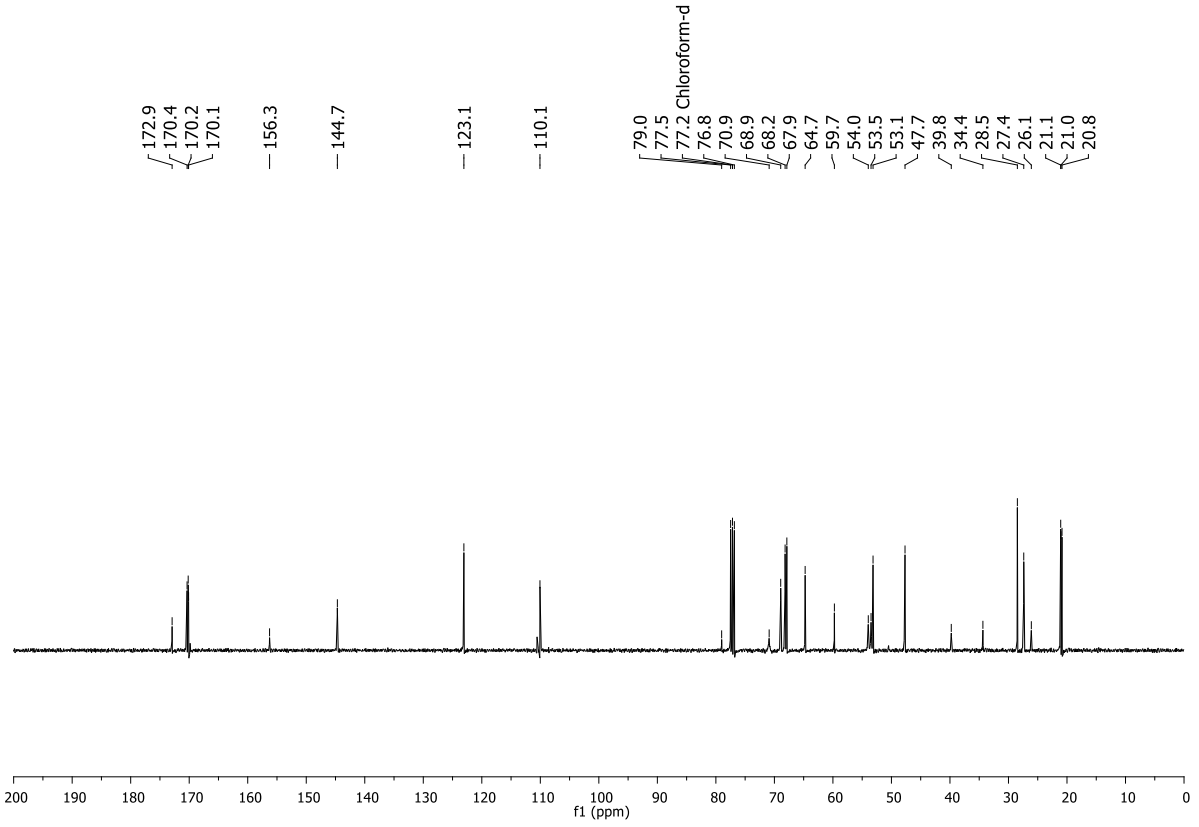


Figure S43: ^{13}C NMR spectrum of **40** (100 MHz, $CDCl_3$).

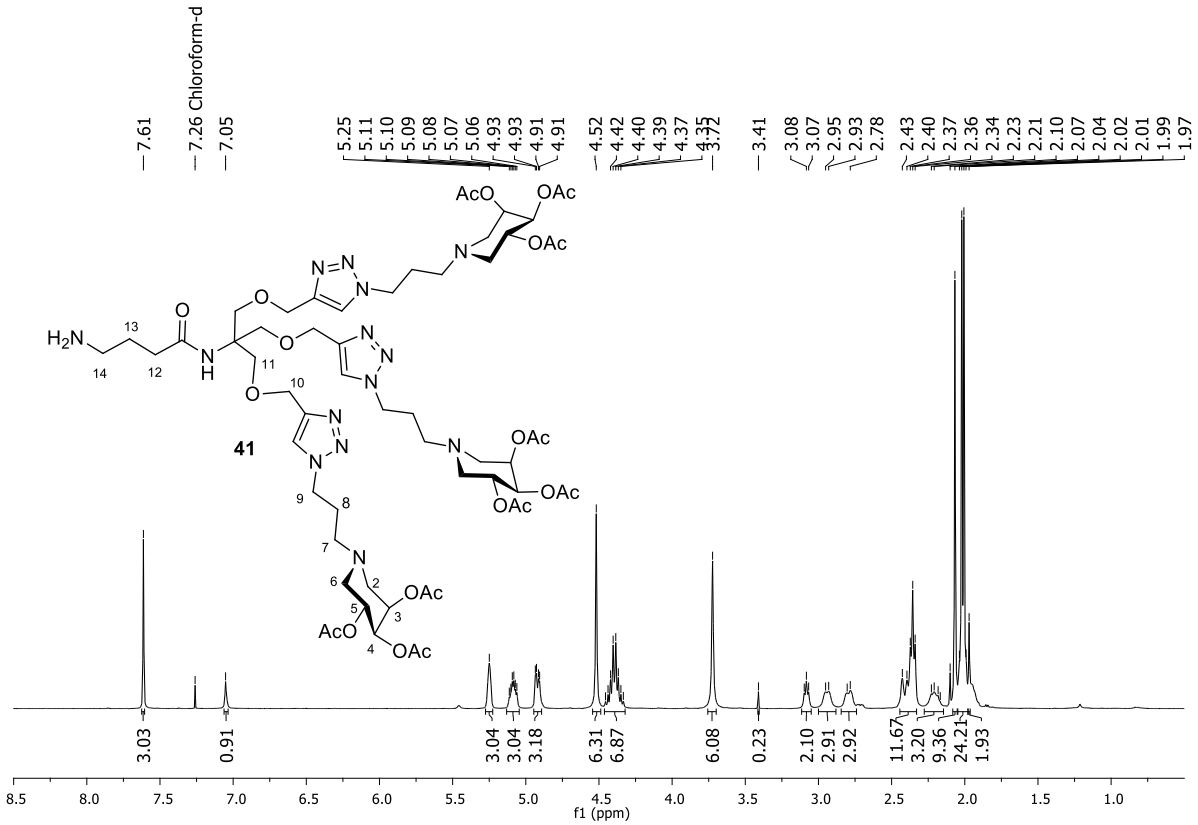


Figure S44: ^{1}H NMR spectrum of **41** (400 MHz, $CDCl_3$).

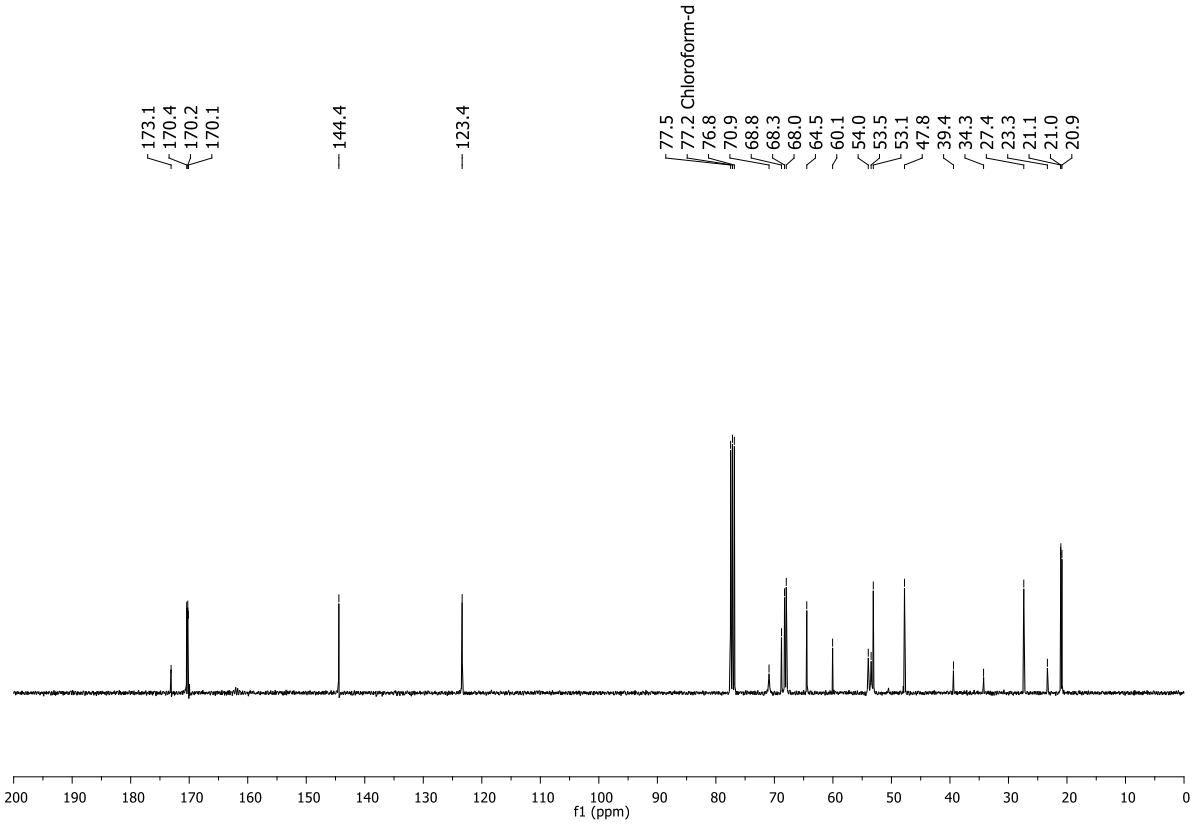


Figure S45: ^{13}C NMR spectrum of **41** (100 MHz, $CDCl_3$).

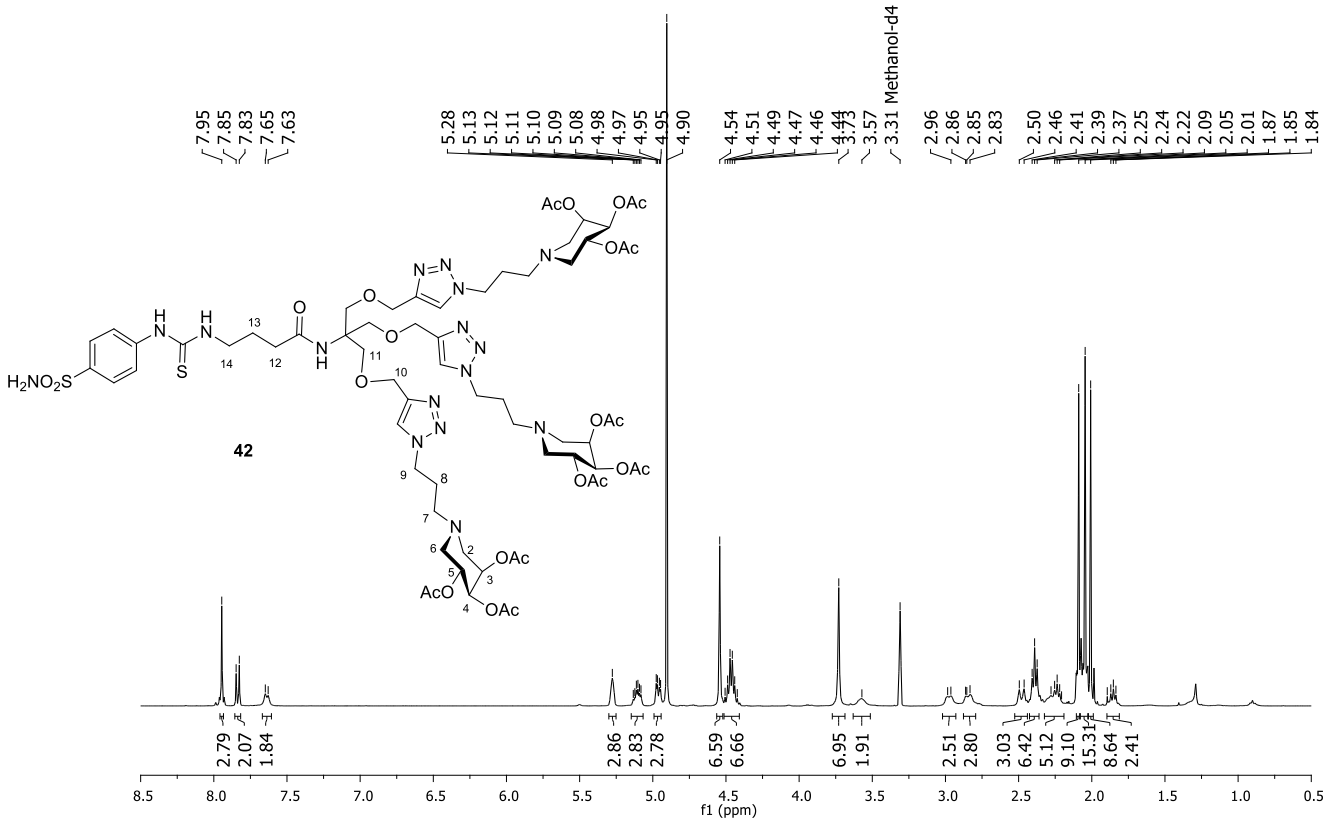


Figure S46: ^{1}H NMR spectrum of **42** (400 MHz, CD_3OD).

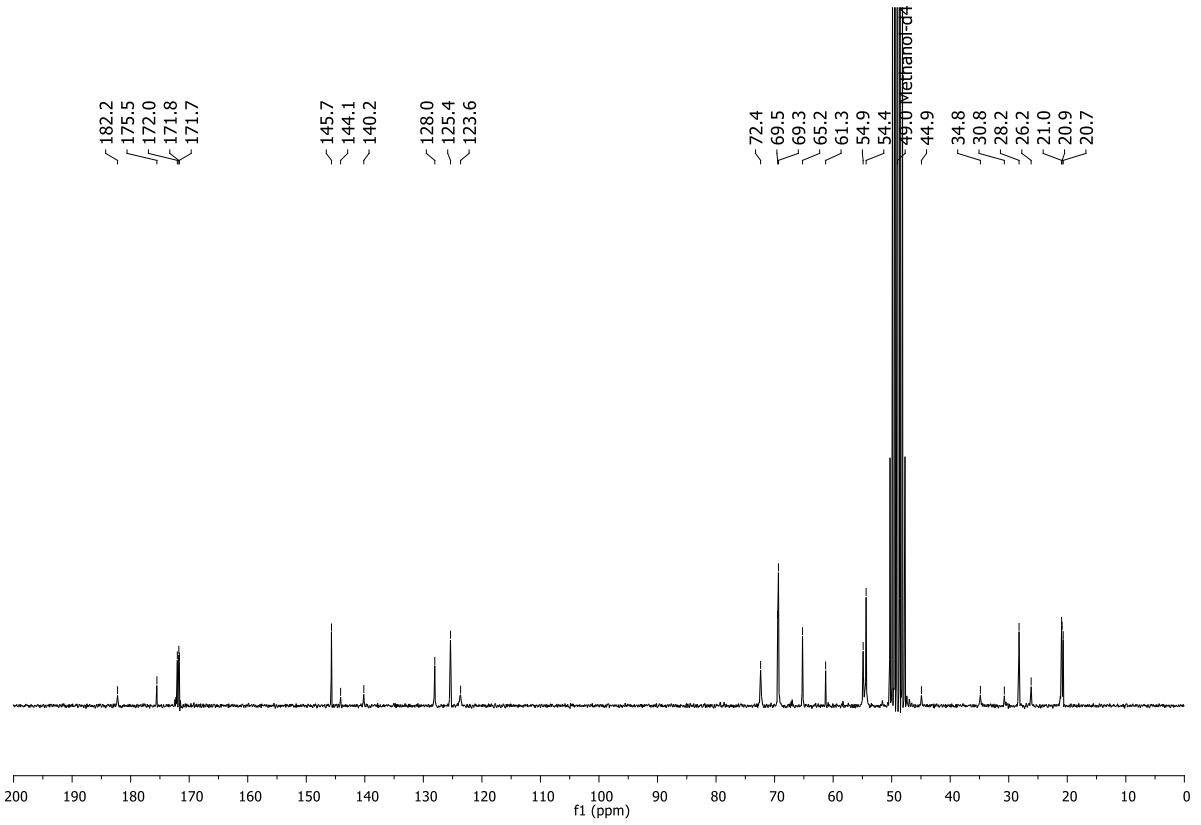


Figure S47: ^{13}C NMR spectrum of **42** (50 MHz, CD_3OD).

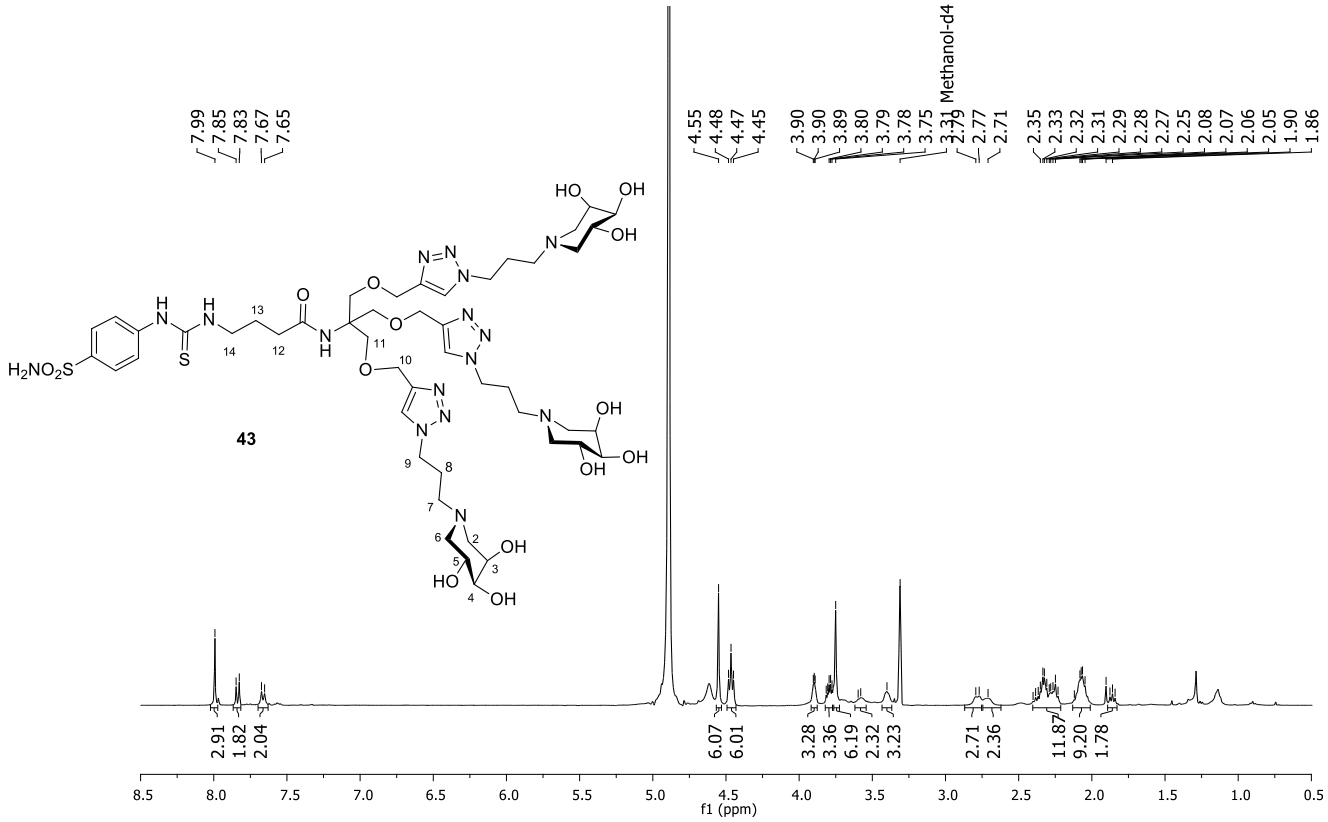


Figure S48: ^{1}H NMR spectrum of **43** (400 MHz, CD_3OD).

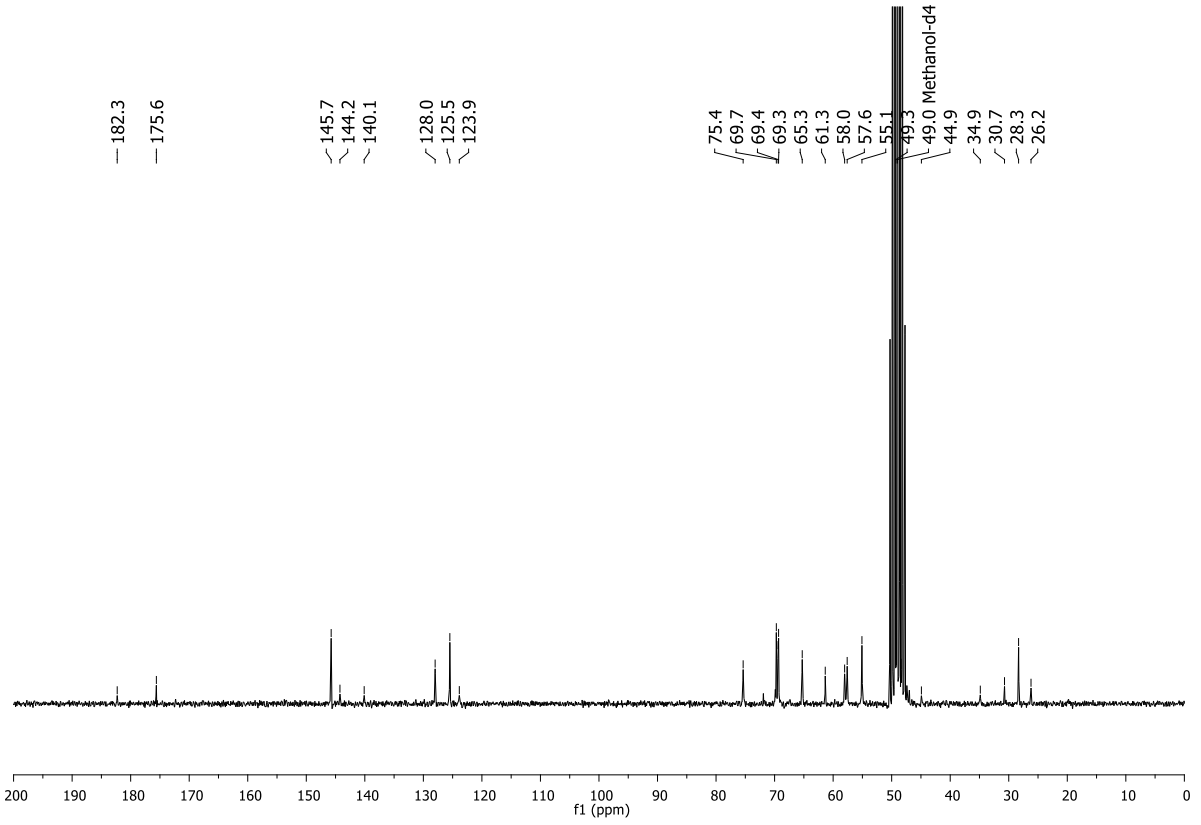
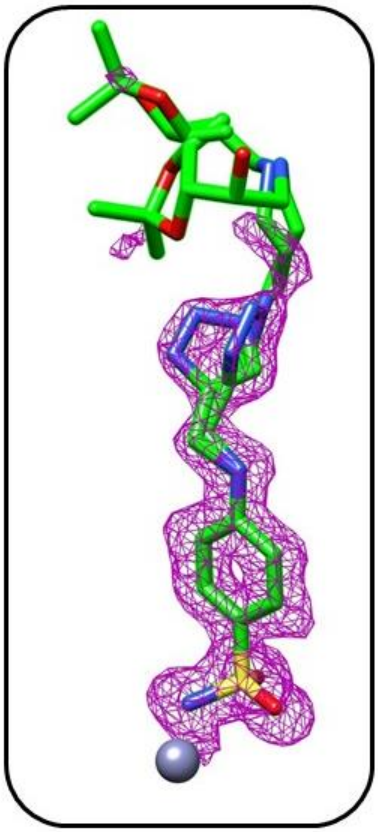


Figure S49: ^{13}C NMR spectrum of **43** (50 MHz, CD_3OD).

Summary of Data Collection and Atomic Model Refinement Statistics for hCAII

	hCAII + 31
PDB ID	8OGF
Wavelength (Å)	1.00
Space Group	P21
Unit cell (a, b, c, α, β, γ) (Å,°)	42.458 41.476 72.352 90.000 104.469 90.000
Limiting resolution (Å)	41.15-1.32 (1.32-1.36)
Unique reflections	53363 (2488)
Rmerge (%)	4.9 (48.8)
Rmeas (%)	5.3 (58.3)
Redundancy	5.79 (3.23)
Completeness overall (%)	93.0 (59.2)
<I/σ(I)>	20.25 (2.24)
CC (1/2)	99.9 (78.9)
Refinement statistics	
Resolution range (Å)	41.15-1.32
Rfactor (%)	11.73
Rfree(%)	15.59
r.m.s.d. bonds(Å)	0.01521
r.m.s.d. angles (°)	2.0125
Ramachandran statistics (%)	
Most favored	96.5
additionally allowed	3.5
outlier regions	0.0
Average B factor (Å^2)	
All atoms	19.062
inhibitors	50.041
solvent	29.679



31

Figure S50: Electron density of inhibitor **31** bound to zinc (grey) in hCA II active site. $2F_o$-F_c maps and contoured to the 1.0 σ level.