Selective Targeting of DC-SIGN by Controlling the Oligomannose Pattern on a Polyproline Tetra-Helix Macrocycle Scaffold

Electronic Supplementary Information

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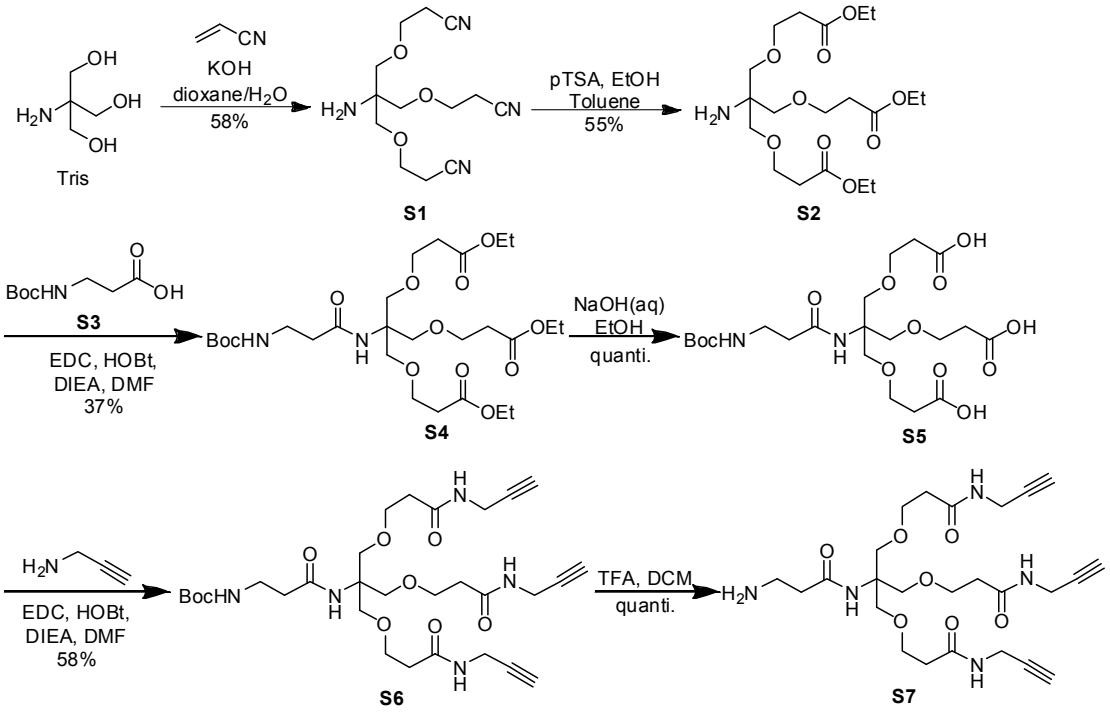
1. General Methods for Synthesis and Characterization

All reagents and solvents were purchased from Merck, Sigma-Aldrich and Acros. *N*-Fmoc-*trans*-(2*S*,4*R*)-4-(*N*-allyloxycarbonyl)amino-L-proline was synthesized according to the literature.[1] The composition of mixed solvents was given by volume ratio. Thin-layer chromatography was performed on Merck Glass Plate TLC Silica gel 60 F254. The spots were visualized by UV light, cerium ammonium molybdate, ninhydrin, $KMnO_4$, bromophenol blue and *p*-anisaldehyde staining. Column chromatography was performed on by Merck Geduran Si 60 Silica gel (40-63 um). ^{1}H- and ^{13}C- NMR spectra were recorded on Varian Mercury 400, Bruker AV-400 or Varian VNMRS-600 spectrometers. The signals are presented in parts per million (ppm, δ scale) unit. For ^{1}H NMR spectra, chemical shifts are expressed in ppm with residual proton signals in $CDCl_3$ (7.24 ppm), D_2O (4.80 ppm) or CD_3OD (3.31 ppm) as standards. For ^{13}C NMR spectra, chemical shifts are expressed in ppm with carbon signals in $CDCl_3$ (77.0 ppm) or CD_3OD (49.15 ppm) as standards. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad), coupling constant (*J*) in Hertz (Hz), and integration. A Bruker Impact HD instrument was used for electrospray ionization (ESI) mass spectrometry measurements. The products were confirmed by MALDI-TOF mass spectrometry (Bruker Daltonics, Autoflex III smartbeam LRF200-CID) by using 2,5-dihydroxybenzoic acid as matrix.

2. Synthesis of Glycodendrons



Scheme S1. Synthesis of **S7**.

Tris[(2-cyanoethoxy)methyl]aminomethane (S1)[2]

To a flask containing KOH (0.250 g, 4.46 mmol) in H_2O (1.25 mL) and dioxane (5 mL) was added tris(hydroxymethyl)aminomethane (5.0 g, 41 mmol) with stirring. Then acrylonitrile was dropwise added and the solution was stirred vigorously for 24 h. The dioxane was removed by reduced pressure and the residue was added DCM (70 mL), wash with H_2O (50 mL × 3) and brine, dried over Na_2SO_4, and concentrated under vacuum to give **S1** (6.75 g, 58%) without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (t, J = 5.8 Hz, 6H), 3.34 (s, 6H), 2.53 (t, J = 5.8 Hz, 6H); ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{20}N_4NaO_3$: 303.1428, found: 303.1429. Proton NMR was consistent with literature data.[2]

Tris[(2-ethylcarboxylethoxy)methyl]aminomethane (S2)[3]

To a flask containing **S1** (5.0 g, 17.84 mmol) in EtOH (6.4 mL) was added *p*-Toluenesulfonic acid monohydrate (20.0 g, 105.1 mmol) and toluene (5 mL), and the reaction was refluxed for 1 d. Then precipitate was removed by filtration. The filtrate was added DCM (80 mL), washed by $NaHCO_3$ (100 mL × 3) and brine, dried over Na_2SO_4, and concentrated under vacuum to give **S2** (4.148 g, 55%) without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (q, J = 7.1 Hz, 6H), 3.66 (t, J = 6.4 Hz, 6H), 3.30 (s, 6H), 2.51 (t, J = 6.4 Hz, 6H), 1.23 (t, J = 7.1 Hz, 9H); ESI-MS (m/z): $[M+H]^+$ calcd. for $C_{19}H_{36}NO_9$: 422.2385, found: 422.2391. Proton NMR was consistent with literature data.[3]

***tert*-butoxycarbonyl-3-{*N*-{tris[3-(ethylcarboxyl-ethoxy)methyl]}methylamide}-3-β-alanine (S4)[3]**

To a flask containing **S2** (1.50 g, 3.56 mmol) and **S3**[4] (0.81 g, 4.27 mmol) in DMF (12 mL) was added HOBt (0.72 g, 5.34 mmol) and DIEA (930 μL, 5.34 mmol) under argon protection in ice bath. Then EDC (1.23 g, 6.41 mmol) was added, and the reaction was stirred at room temperature for 14 h. The reaction solution was added ethyl acetate (200 mL), washed by H_2O (50 mL × 3) and brine, dried over Na_2SO_4, concentrated under vacuum and further purified by column chromatography (MeOH/$CHCl_3$ = 1:100 to 1:50) to give **S4** (0.7894 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (q, J = 7.1 Hz, 6H), 3.67 (s, 6H), 3.67 (t, J = 6.2 Hz, 6H), 3.71-3.68 (m, 12H), 3.34 (dt, J = 5.8, 5.8 Hz, 2H), 3.51 (t, J = 6.2 Hz, 6H), 2.32 (t, J = 5.8 Hz, 2H), 1.40 (s, 9H), 1.24 (t, J = 7.1 Hz, 6H). ESI-MS (m/z):

$[M+Na]^+$ calcd for $C_{27}H_{48}N_2NaO_{12}$: 615.3099, found: 615.3110. Proton NMR was consistent with literature data.[3]

***tert*-butoxycarbonyl-3-{*N*-{tris[3-(carboxyl-ethoxy)methyl]}methylamide}-3-β-alanine (S5)**

To a flask containing **S4** (0.4726 mg, 0.797 mmol) in EtOH (5 mL) was added 2 N NaOH(aq) (5 mL, 10 mmol) and stirred at room temperature for 2 h. The reaction solution was neutralized by adding AG® 50WX8 hydrogen form ion exchange resin, then filtered and concentrated under vacuum to give **S5** (0.4597 g, quanti.) without further purification. ^{1}H NMR (400 MHz, CD_3OD): δ 3.71 (s, 6H), 3.68 (t, *J* = 6.6 Hz, 6H), 3.28 (t, *J* = 6.9 Hz, 2H), 2.41 (t, *J* = 6.6 Hz, 6H), 2.39 (t, *J* = 6.9 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (100.7 MHz, CD_3OD): δ 180.41 (3C), 174.22, 158.41, 80.18, 70.84, 70.28, 61.49, 39.40, 38.18, 37.95, 28.96. ESI-MS (m/z): $[M+H]^+$ calcd for $C_{21}H_{37}N_2O_{12}$: 509.2341 found: 509.2342.

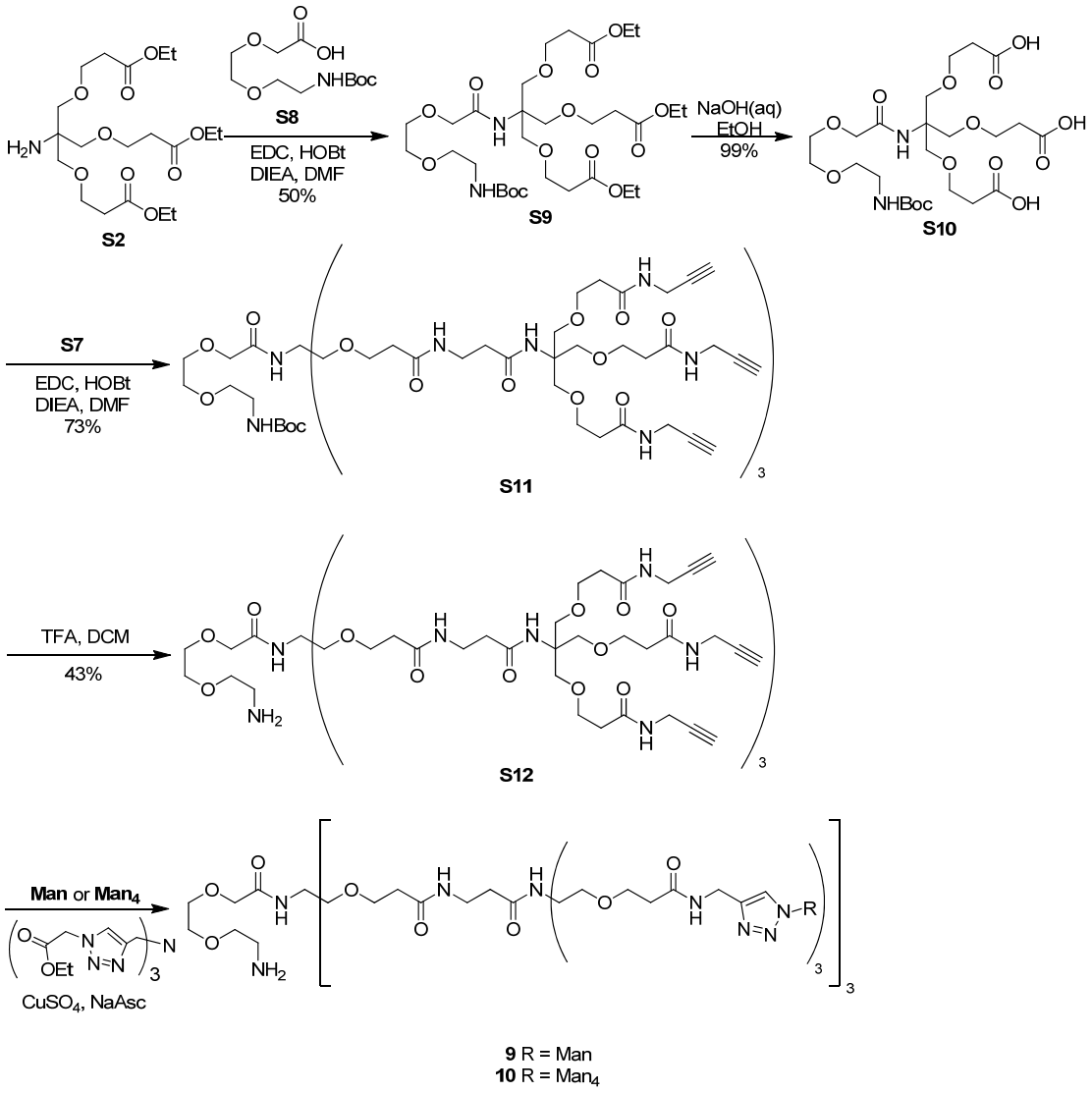
***tert*-Butoxycarbonyl-3-{*N*-{tris[3-[propargyl-methyl]}methylamide}-3-β-alanine (S6)[5]**

To a flask containing **S5** (180 mg, 0.354 mmol) and propargylamine (68 mg, 1.24 mmol) in DMF (3 mL) was added HOBt (220 mg, 1.42 mmol) and DIEA (250 μL, 1.42 mmol) under argon protection in ice bath. Then EDC (340 mg, 1.77 mmol) was added, and the reaction was stirred at room temperature for 14 h. The reaction solution was added ethyl acetate (50 mL), washed by H_2O (20 mL × 2) and brine, dried over Na_2SO_4, concentrated under vacuum and further purified by column chromatography to give **S6** (128.1 mg, 58.4%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (dd, *J* = 4.8, 2.5 Hz, 6H), 3.71 (t, *J* = 5.6 Hz, 6H), 3.67 (s, 6H), 3.37 (dt, *J* = 6.0, 6.0 Hz, 2H), 2.45-2.43 (m, 8H), 2.24 (t, *J* = 2.5 Hz, 3H), 1.42 (s, 9H).

ESI-MS (m/z): $[M+H]^+$ calcd for $C_{30}H_{46}N_5O_9$: 620.3290, found: 620.3302. Proton NMR was consistent with literature data.[5]

3-{*N*-{tris[3-[propargyl-methyl]}methylamide}-3-β-alanine (S7)[6]

To a flask containing **S6** (42.7 mg, 68.9 μmol) in DCM (2 mL) was added 50% TFA/DCM (2 mL) with stirring in ice bath, then reacted for 2 h. TFA and DCM was removed by reduced pressure to give **S7** (43.9 mg, quanti.) without further purification. ^{1}H NMR (400 MHz, CD_3OD): δ 3.98 (d, J = 2.5 Hz, 6H), 3.68 (t, J = 5.8 Hz, 6H), 3.68 (s, 6H), 3.17 (t, J = 6.4 Hz, 2H), 2.63 (t, J = 6.4 Hz, 2H), 2.62 (t, J = 2.5 Hz, 3H), 2.43 (t, J = 5.8 Hz, 6H). ESI-MS (m/z): $[M+Na]^+$ calcd for $C_{25}H_{37}N_5NaO_7$: 542.2585, found: 542.2604.



Scheme S2. Synthesis of **9** and **10**.

***N*-(tris[(2-ethylcarboxylethoxy)methyl]methyl)-8-*tert*-butyloxycarbonylamino-3,6-dioxaoctanamide (S9)**

To a flask containing **S2** (0.599 g, 1.42 mmol) and **S8**[7] (0.412 g, 1.56 mmol) in DMF (5 mL) was added HOBt (0.326 g, 2.13 mmol) and DIEA (0.371 mL, 2.13 mmol) under argon protection in ice bath. Then EDC (0.490 g, 2.56 mmol) was added, and the reaction was stirred at room temperature for 14 h. The reaction solution was added ethyl acetate (100 mL), washed by H_2O (30 mL × 3) and brine, dried

over Na_2SO_4, concentrated under vacuum and further purified by column chromatography (MeOH/$CHCl_3$ = 1:50) to give **S9** (0.4754 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (q, *J* = 7.1 Hz, 6H), 3.80 (s, 2H), 3.63 (s, 6H), 3.61 (t, *J* = 6.4 Hz, 6H), 3.57-3.54 (m, 4H), 3.46 (t, *J* = 5.0 Hz, 2H), 3.23 (m, 2H), 2.44 (t, *J* = 6.4 Hz, 6H), 1.35 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 9H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 171.2 (3C), 169.4, 155.8, 79.0, 70.8, 70.6, 70.2, 69.9, 68.9, 66.6, 60.3, 59.3, 40.2, 34.9, 28.2, 14.1; ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{30}H_{54}N_2NaO_{14}$: 689.3467, found: 689.3474.

_N_-(tris[(2-carboxylethoxy)methyl]methyl)-8-*tert*-butyloxycarbonylamino-3,6-dioxaoctanamide (S10)

To a flask containing **S9** (22.6 mg, 33.9 μmol) in EtOH (0.3 mL) was added 2 N NaOH(aq) (0.3 mL, 0.6 mmol) and stirred at room temperature for 2 h. The reaction solution was neutralized by adding AG® 50WX8 hydrogen form ion exchange resin, then filtered and concentrated under vacuum to give **S10** (19.45 mg, 99%) without further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 3.90 (s, 2H), 3.73 (s, 6H), 3.70 (t, *J* = 6.1 Hz, 6H), 3.66-3.63 (m, 4H), 3.54 (t, *J* = 5.6 Hz, 2H), 3.24 (t, *J* = 5.6 Hz, 2H), 2.53 (t, *J* = 6.1 Hz, 6H), 1.44 (s, 9H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 178.4 (3C), 172.3, 158.7, 80.2, 71.9, 71.6, 71.3, 71.2, 70.4, 69.4, 61.3, 41.2, 38.0, 29.0; ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{24}H_{42}N_2NaO_{14}$: 605.2528, found: 605.2541.

Boc-G2-alkyne (S11)

To a flask containing **S10** (9.6 mg, 16.5 μmol) and **S7** (43.9 mg, 84.5 μmol) in DMF (0.5 mL) was added HOBt (10 mg, 65.3 μmol) and DIEA (15 μL, 86.1 mmol) under argon protection in ice bath. Then EDC (19.2 mg, 10.0 μmol) was added, and the reaction was stirred at room temperature for 18 h. The reaction solution was added ethyl acetate (30 mL), washed by H_2O (10 mL × 2) and brine, dried over Na_2SO_4, concentrated under vacuum and further purified by column chromatography to give **S11** (25.1 mg, 73%). ^{1}H NMR (400 MHz, CD_3OD): δ 3.99 (d, *J* = 2.5 Hz, 18H), 3.93 (s, 2H), 3.72-3.68 (m, 54H), 3.54 (t, *J* = 5.7 Hz, 2H), 3.42 (t, *J* = 7.0 Hz, 6H), 3.25 (t, *J* = 5.7 Hz, 2H), 2.63 (t, *J* = 2.5 Hz, 9H), 2.46-2.41 (m, 30H), 1.45 (s, 9H); ^{13}C NMR (100.7 MHz, CD_3OD): δ 173.88 (3C), 173.82 (3C), 173.76 (9C), 172.28, 158.56, 81.05, 80.31, 72.60, 72.16, 71.69, 71.42, 71.33, 71.30, 70.37, 70.18, 68.88, 68.62, 61.66, 61.64, 61.32, 41.38, 37.78, 37.46, 37.39, 29.77, 29.64, 29.01. MALDI-TOF-MS (m/z): $[M+H]^+$ calcd for $C_{100}H_{149}N_{16}O_{32}$: 2086.052, found: 2087.647.

H_2N-G2-alkyne (S12)

To a flask containing **S11** (26.4 mg, 12.6 μmol) in DCM (0.5 mL) was added 50% TFA/DCM (0.5 mL) with stirring in ice bath, then reacted for 2 h. TFA and DCM was removed by reduced pressure to give **S12** (20.14 mg, 80%). ^{1}H NMR (400 MHz, CD_3OD): δ 3.99 (d, *J* = 2.5 Hz, 18H), 3.96 (s, 2H), 3.72-3.68 (m, 56H), 3.42 (t, *J* = 7.0 Hz, 6H), 3.20 (t, *J* = 5.0 Hz, 2H), 2.63 (t, *J* = 2.5 Hz, 9H), 2.46-2.42 (m, 30H); ^{13}C NMR (400 MHz, CD_3OD): 173.95 (3C), 173.86 (3C), 173.81 (9C), 172.24, 81.04, 72.58, 72.02,

71.42, 70.37, 70.18, 68.85, 68.63, 68.17, 61.76, 61.67, 61.39, 55.29, 40.83, 37.70, 37.44, 37.40, 29.78, 29.65. ESI-MS (m/z): $[M+2Na]^{2+}$ calcd for $C_{94}H_{139}N_{17}Na_2O_{30}$: 1015.9829, found: 1015.9729.

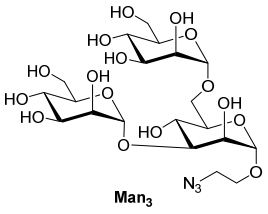
H_2N-G2-Man (9)

The solution of alkynyl dendrimer **S12** (2.5 mM) was added $CuSO_4$(aq) (30 equiv., 40 mM), tris(triazoly)amine ligand **5** (30 equiv., 40 mM in DMSO), sodium ascorbate (aq) (600 equiv., 800 mM), and 10 μL PBS buffer, and the glycan ligand **Man** (3 equiv./per alkyne, 25 mM) to react at room temperature for 1 h. The product was puridfied from crude reaction mixture by Microcon® 0.5 mL 3 kDa centrifugal filter. MS(MALDI): $[M+H]^+$ calcd. for $C_{166}H_{275}N_{44}O_{84}$: 4228.859, found: 4230.162.

H_2N-G2-Man_4 (10)

The solution of alkynyl dendrimer **S12** (2.5 mM) was added $CuSO_4$(aq) (30 equiv., 40 mM), tris(triazoly)amine ligand **5** (30 equiv., 40 mM in DMSO), sodium ascorbate (aq) (600 equiv., 800 mM), and 10 μL PBS buffer, and the glycan ligand **Man_4** (3 equiv./per alkyne, 25 mM) to react at room temperature for 1 h. The product was puridfied from crude reaction mixture by Microcon® 0.5 mL 3 kDa centrifugal filter. MS(MALDI): $[M+Cu]^+$ calcd. for $C_{355}H_{598}N_{44}CuO_{219}$: 9044.630, found: 9046.337.

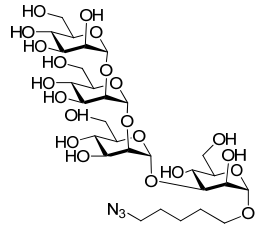
2-azidoethyl 3,6-di-*O*-(α-D-mannopyranosyl)-α-D-mannopyranoside (Man_3)



Man_3

Man$_3$ ^{1}H NMR (400 MHz, D_2O): δ 5.10 (s, 1H, H-1), 4.90 (d, $J_{1',2'}$ = 1.0 Hz, 1H, H-1'), 4.88 (d, $J_{1'',2''}$ = 1.2 Hz, 1H, H-1''), 4.12 (m, 1H, H-2), 4.06 (dd, $J_{2',1'}$ = 1.4 Hz, $J_{2',3'}$ = 3.1 Hz, 1H , H-2'), 3.98 (d, $J_{2'',1''}$ = 1.2 Hz, 1H, H-2''), 3.90-3.80 (m, 9H, H-3, H-3', H-3'', H-4*, H-4'*, H-5, H-6a,* H-6b*, H-6b'*), 3.77-3.70 (m , 5H, H-5', H-5'', H-6a'*, H-6''*, OC*H$_2$*CH$_2$N$_3$), 3.68-3.62 (m, 3H, H-4''*, H-6b''*), 3.56-3.48 (m, 2H, OCH$_2$C*H$_2$*N$_3$). Assignments indexed with * are interchangeable. Proton NMR was consistent with literature data.[8] ESI-MS(m/z): $[M+Na]^+$ calcd. for $C_{20}H_{35}N_3NaO_{16}$: 596.1910, found: 596.1923.

5-azidopentyl α-D-mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→3)-α-D-mannopyranoside (Man$_4$)



Man$_4$

Man$_4$ ^{1}H NMR (400 MHz, D_2O): δ 5.36 (s, 1H), 5.31 (s, 1H), 5.05 (s, 1H), 4.84 (s, 1H), 4.11 (s, 1H), 4.08 (s, 3H), 4.01−3.95 (m, 2H), 3.89−3.85 (m, 6H), 3.78−3.64 (m, 13H), 3.58−3.53 (m, 1H), 3.35 (t, J = 6.7 Hz, 2H), 1.68−1.63 (m, 4H), 1.48−1.43 (m, 2H). Proton NMR was consistent with literature data.[9]

3. Synthesis of Peptide and Glycoconjugates

General methods for peptide synthesis and analysis:

Peptide analysis:

^{1}H-NMR spectra were recorded on Varian VNMRS-600. The peptide products were confirmed by MALDI-TOF mass spectrometry (Bruker Daltonics, Autoflex III smartbeam LRF200-CID) by using 2,5-dihydroxybenzoic acid as matrix. Analytical HPLC (Agilent Technology, 1260 Infinity) was performed with a Vydac C18 column (218TP54 4.6 mm × 250 mm). 0.1% TFA in water (solvent A), Acetonitrile (solvent B) served as the mobile phase for compound purifications. Aviv Model 410 spectropolarimeter (Aviv Associates, Lakewood, NJ) was used for CD measurements. The solutions were measured in a quartz cell with a pathlength of 1.0 mm (Hellma 110-QS).

Solid phase peptide synthesis:

The peptides were prepared by manual solid phase peptide synthesis on 2-chlorotrityl chloride resin from Merck (Product No. 855017). A solution of Fmoc-Pro-OH (4.0 equiv.) and iPr_2NEt (6.0 equiv.) in 1:1 v/v DMF/DCM (final concentration 0.4 M) was added to the resins. The mixture was gently shaken for overnight and washed with DMF (3 × 3 mL), DCM (3 × 3 mL), and DMF (3 × 3 mL). A solution of DCM/MeOH/iPr_2NEt (17:2:1, 8 mL) was added and shaken for 1 h to block the unreacted sites on the resins. After washed with DMF (3 × 3 mL), DCM (3 × 3 mL), and DMF (3 × 3 mL), the amino acid loading was determined with a quantitative Fmoc test. The resins were further used in iterative peptide

synthesis. 10% piperidine in DMF (3 mL) was added to the resins to deprotect the Fmoc group. The vessel was shaken for 10 min and washed with DMF (3 × 3 mL), DCM (3 × 3 mL), and DMF (3 × 3 mL). The mixture of amino acids (4 equiv., Fmoc-Pro-OH or *N*-Fmoc-*trans*-(2*S*,4*R*)-4-(*N*-allyloxycarbonyl)amino-L-proline based on the designed sequence), PyBOP (4 equiv., for Fmoc-Pro-OH) or HATU (4 equiv., for *N*-Fmoc-*trans*-(2*S*,4*R*)-4-(*N*-allyloxycarbonyl)amino-L-proline) were dissolved in DMF, added NMM (4 equiv.) and react with the deprotect resins (final concentration 0.2 M). The mixture was gently shaken for 1 h then washed with DMF (3 × 3 mL), DCM (3 × 3 mL), and DMF (3 × 3 mL). After each coupling step, the resins were treated with Ac_2O/py. (1:9, 3mL) and shaken for 10 min to cap the unreacted amino groups. The resins were washed with DMF (3 × 3 mL), DCM (3 × 3 mL), and DMF (3 × 3 mL), and continued for the next round of synthesis. To cleave the peptide, the resins were washed with DCM (3 × 3 mL), then treated with DCM/TFA/TIS (90:5:5, 3 mL) and shaken for 1 h and repeated for a second time with shaking for 30 min. The filtrate was collected and all of the volatiles were removed under reduced pressure. Water (1-2 mL) was added to the resulting syrup-like residue and centrifuged before the supernatant was further purified by HPLC (Agilent Technology, 1260 Infinity) with a Vydac C18 column (218TP510 10 mm × 250 mm).

Polyproline N-terminus azido modification:

To a solution of azido connector **2** (4 equiv.) dissolved in DMF and iPr_2NEt (8 equiv.) was added to the resins carrying N-terminus deprotected peptide in DMF (final concentration of **2** at 0.2 M) and gently

shaken for 1 h. The resins were washed with DMF (3 × 3 mL), DCM (3 × 3 mL), and DMF (3 × 3 mL).

Polyproline C-terminus alkyne modification:

To the mixture of peptide acid, propargylamine (3 equiv.), and TEA (5 equiv.) dissolved in DMF/DCM (1:1, peptide concentration 10 mM) in a vial was added HATU (4 equiv.). After overnight stirring, DCM was removed from the reaction mixture under reduced pressure. The product was purified by HPLC with a Vydac C18 column.

Peptide assembly by CuAAC reaction on resins:

The azide-functionalized peptide on resins was treated in the solution of alkynyl peptide **4** (1.5 equiv.), $CuSO_4$ (aq) (0.13 equiv., 40 mM), tris(triazoly)amine ligand **5** (0.13 equiv., 40 mM in DMSO), sodium ascorbate (aq) (2.6 equiv., 800 mM), and iPr_2NEt (4.0 equiv.) in THF (final copper concentration is 3.6 mM) for 22 h. The resulted resins were washed with sodium diethyldithiocarbamate solution (25 mg in 5 mL DMF with 25 μL iPr_2NEt; 5 × 1 mL), DMF (5 × 1 mL), DCM (5 × 1 mL), and DMF (5 × 1 mL).

Peptide cyclization:

The linear peptide tetramer **7** was dissolved in water at 2 mM, and $CuSO_4$ (aq) (4.2 equiv., 40 mM), tris(triazoly)amine ligand **5** (4.2 equiv., 40 mM in DMSO), sodium ascorbate (aq) (84 equiv., 800 mM), and iPr_2NEt (144 equiv.) were added to react at room temperature for 1 h. The product was purified from crude reaction mixture by HPLC.

***N*-Alloc deprotection:**

To the solution of Alloc protected cyclic peptide **8c** and $Pd(PPh_3)_2Cl_2$ (3 equiv. for each Alloc group) in DCM/DMF (4:1, peptide concentration 40 mM) in a vial was added acetic acid (540 equiv.) and Bu_3SnH (240 equiv.) and stirred for 2 h before quenched by water. After removing DCM under reduced pressure, the deprotected peptide was purified by HPLC.

Alkyne group installation on scaffold:

To the solution of Alloc-deprotected amino peptide and 4-pentynoic acid OSu ester (30 equiv.) in DMF (peptide concentration 0.5 mM) in a vial was added iPr_2NEt (60 equiv.) and stirred for 2 h. The alkynyl peptide product was purified from crude reaction mixture by HPLC.

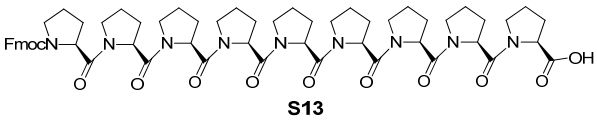
Glycan conjugation to scaffold:

The alkynyl scaffold peptide **11** dissolved in water at 1 mM was added $CuSO_4$ (aq) (30 equiv., 40 mM), tris(triazoly)amine ligand **5** (30 equiv., 40 mM in DMSO), sodium ascorbate (aq) (600 equiv., 800 mM), iPr_2NEt (200 equiv.), and the glycan ligand $\mathbf{Man_4}$ or $\mathbf{Man_3}$ (3 equiv. per alkyne) to react at room temperature for 1 h. The product was purified from crude reaction mixture by HPLC.

Synthesis of peptide monomers: peptide acids

Peptides **S13** and **S14** were prepared according to the method of solid phase peptide synthesis. Yields are based on quantitative Fmoc test and after lyophilization.

Peptide **S13**



S13

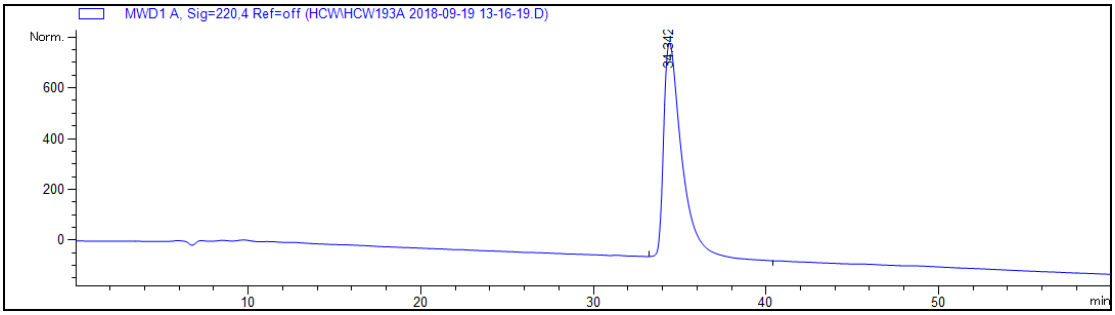


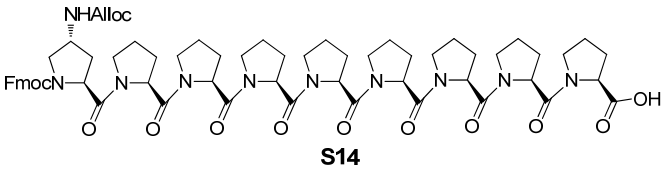
Figure S1. HPLC chromatogram of **S13**.

Yield: 49.1 mg, 49%.

Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 34.3 min.

MS(MALDI): $[M+Na]^+$ calcd. for $C_{60}H_{75}N_9NaO_{12}$: 1136.543, found: 1137.007.

Peptide **S14**



S14

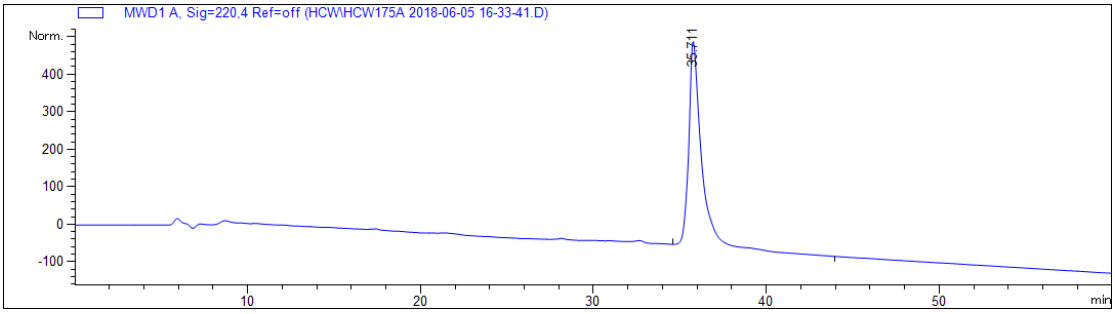


Figure S2. HPLC chromatogram of **S14**.

Yield: 309.1 mg, 50%.

Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 35.7 min.

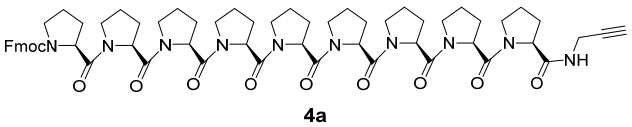
MS(MALDI): $[M+Na]^+$ calcd. for $C_{64}H_{80}N_{10}NaO_{14}$: 1235.575, found: 1234.312.

Synthesis of peptide monomers: peptide alkynes

Peptide **4a** and **4c** were prepared according to the method of polyproline C-terminus alkyne modification.

Yields are based on the isolated weight after lyophilization.

Peptide **4a**



4a

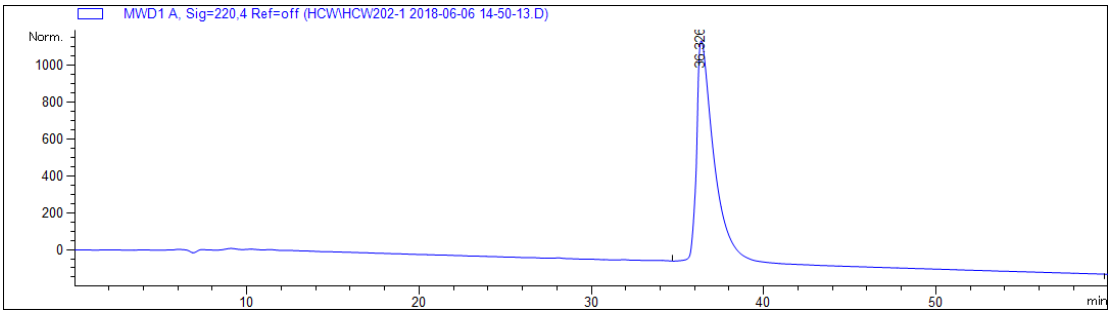


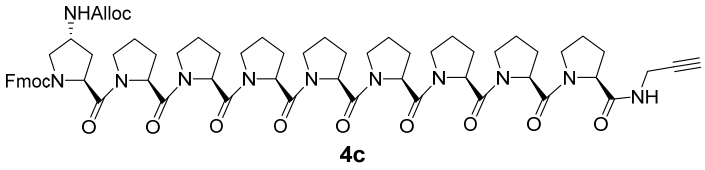
Figure S3. HPLC chromatogram of **4a**.

Yield: 110.5 mg, 82%.

Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 36.3 min.

MS(MALDI): $[M+H]^+$ calcd. for $C_{63}H_{79}N_{10}O_{11}$: 1151.592, found: 1151.102.

Peptide **4c**



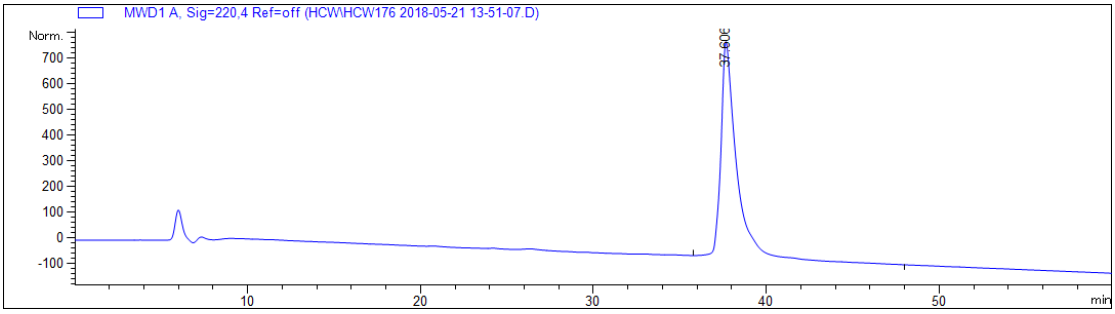


Figure S4. HPLC chromatogram of **4c**.

Yield: 141.6 mg, 91%.

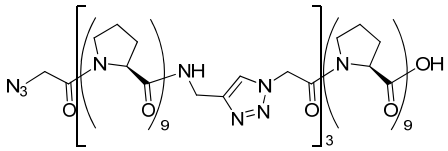
Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 37.6 min.

MS(MALDI): $[M+Na]^+$ calcd. for $C_{67}H_{83}N_{11}NaO_{13}$: 1272.606, found: 1272.023.

Synthesis of peptide oligomers: peptide acids

Peptide **S15–S17** were prepared according to the method of solid phase peptide synthesis, polyproline N-terminus azido modification, peptide assembly by CuAAC reaction on resins. Yields are based on the isolated weight after lyophilization.

Peptide tetramer S15



S15

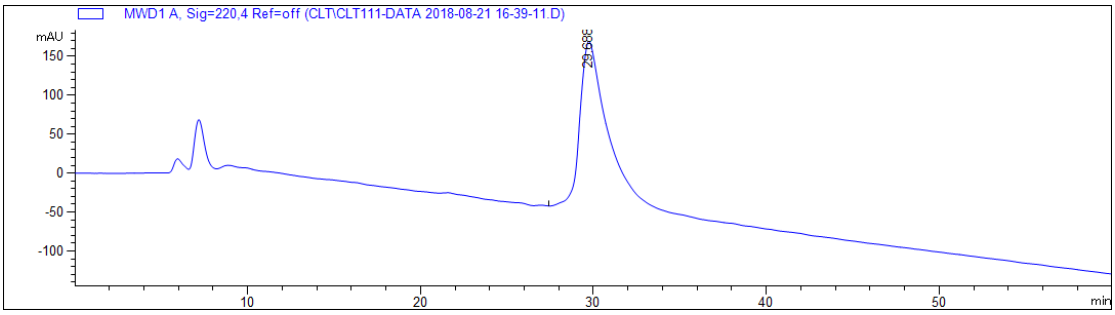


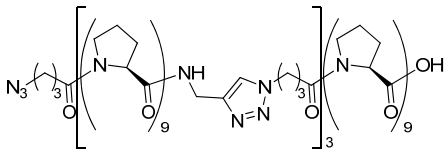
Figure S5. HPLC chromatogram of **S15**.

Yield: 4.04 mg, 34%.

Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R =29.7 min.

MS(MALDI): $[M+H]^+$ calcd. for $C_{197}H_{274}N_{51}O_{41}$: 4010.092, found: 4009.046.

Peptide tetramer S16



S16

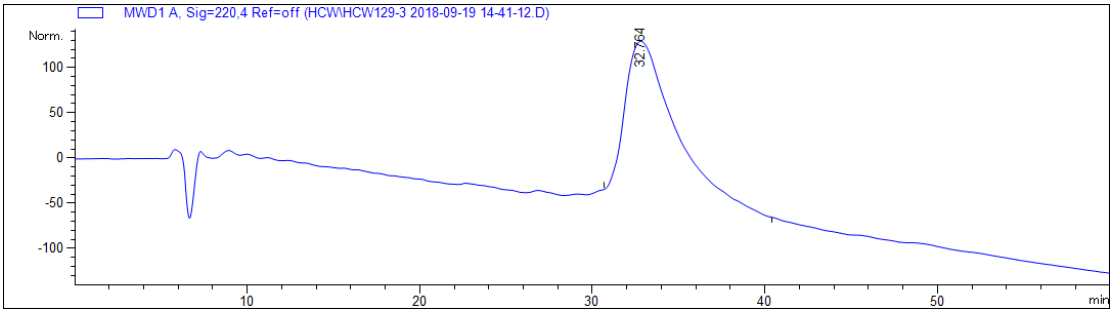


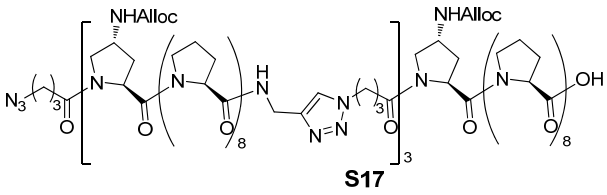
Figure S6. HPLC chromatogram of **S16**.

Yield: 9.03 mg, 52%.

Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 32.8 min.

MS(MALDI): $[M+K]^+$ calcd. for $C_{205}H_{289}N_{51}KO_{41}$: 4160.173, found: 4161.278.

Peptide tetramer S17



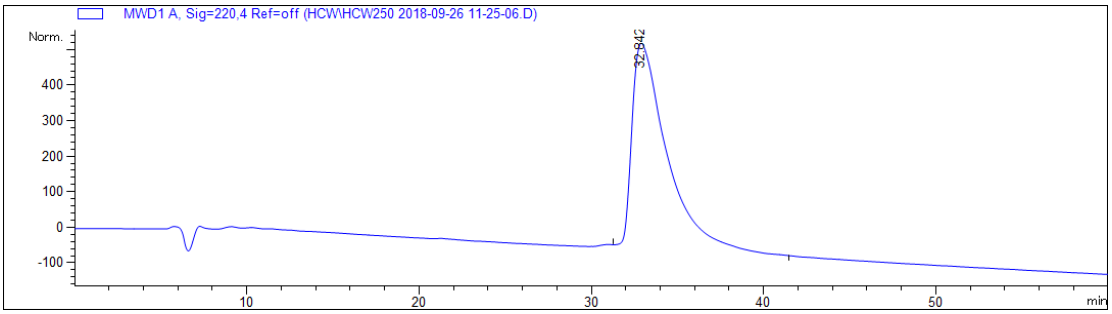


Figure S7. HPLC chromatogram of **S17**.

Yield: 23.06 mg, 45%.

Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 32.8 min.

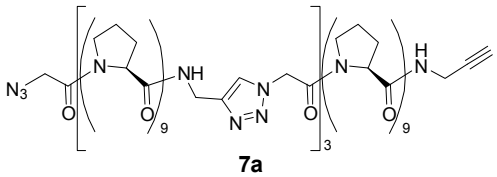
MS(MALDI): $[M+Na]^+$ calcd. for $C_{221}H_{309}N_{55}NaO_{49}$: 4540.327, found: 4538.916.

Synthesis of peptide oligomers: peptide alkynes

Peptide **7a**–**7c** were prepared according to the method of polyproline C-terminus alkyne modification.

Yields are based on the isolated weight after lyophilization.

Peptide tetramer 7a



7a

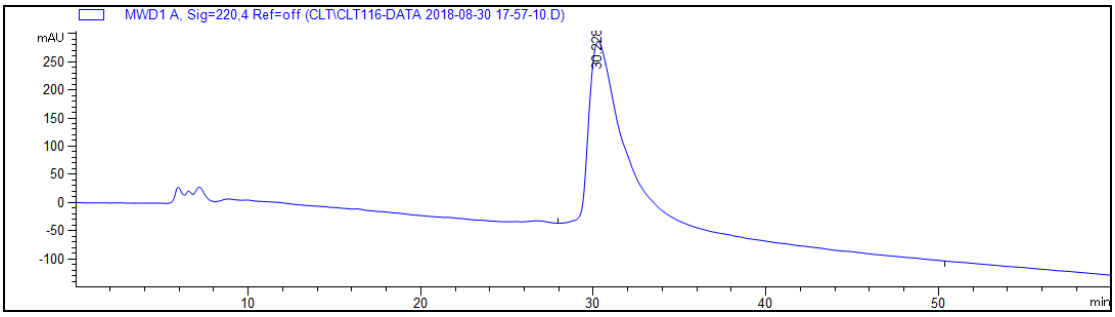


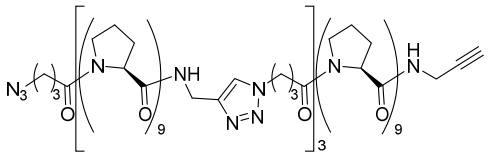
Figure S8. HPLC chromatogram of **7a**.

Yield: 3.26 mg, 80%.

Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 30.2 min.

MS(MALDI): $[M+H]^+$ calcd. for $C_{200}H_{277}N_{52}O_{40}$: 4047.123, found: 4046.195.

Peptide tetramer 7b



7b

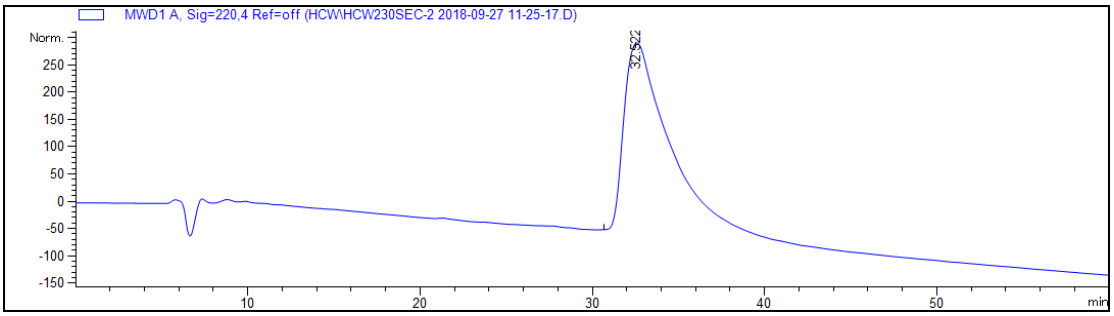


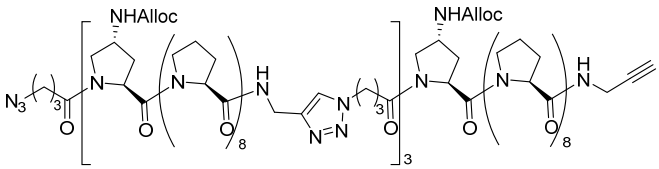
Figure S9. HPLC chromatogram of **7b**.

Yield: 2.33 mg, 91%.

Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 32.5 min.

MS(MALDI): $[M+K]^+$ calcd. for $C_{208}H_{292}N_{52}KO_{40}$: 4197.205, found: 4197.240.

Peptide tetramer 7c



7c

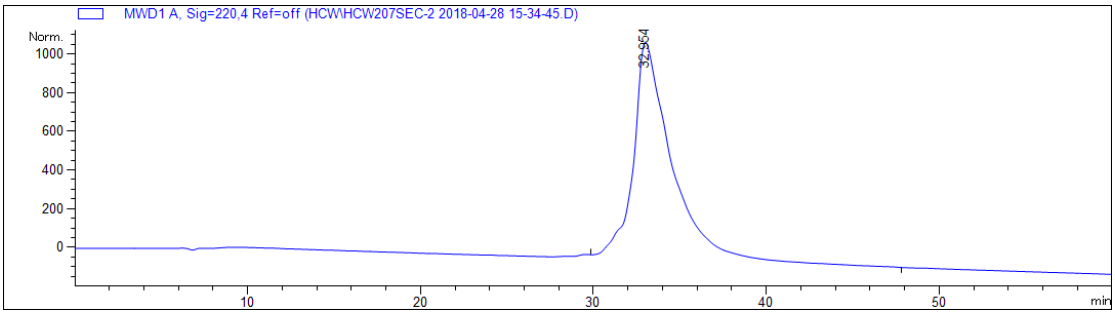


Figure S10. HPLC chromatogram of **7c**.

Yield: 14.26 mg, 61%.

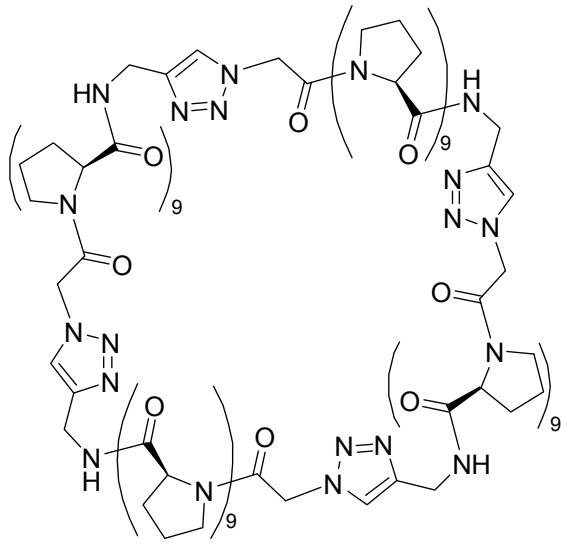
Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 33.0 min.

MS(MALDI): $[M+H]^+$ calcd. for $C_{224}H_{313}N_{56}O_{48}$: 4555.377, found: 4555.828.

Synthesis of peptide oligomers: cyclic peptides

Peptide **8a**–**8c** were prepared according to the method of peptide cyclization. Yields are based on the isolated weight after lyophilization.

Cyclic peptide tetramer 8a



8a

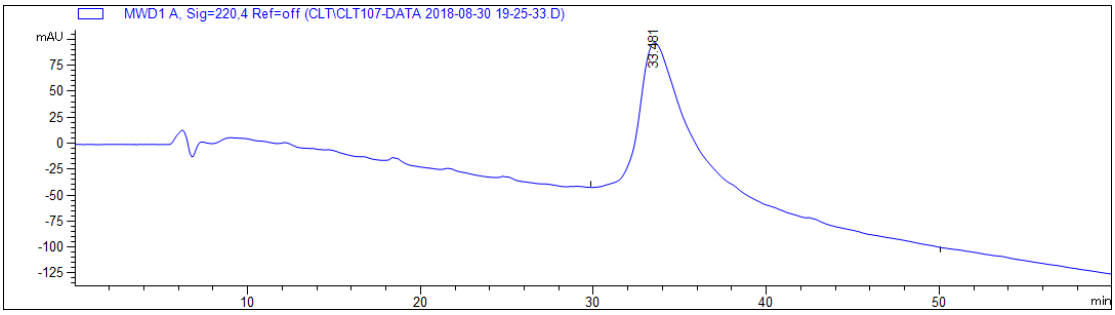


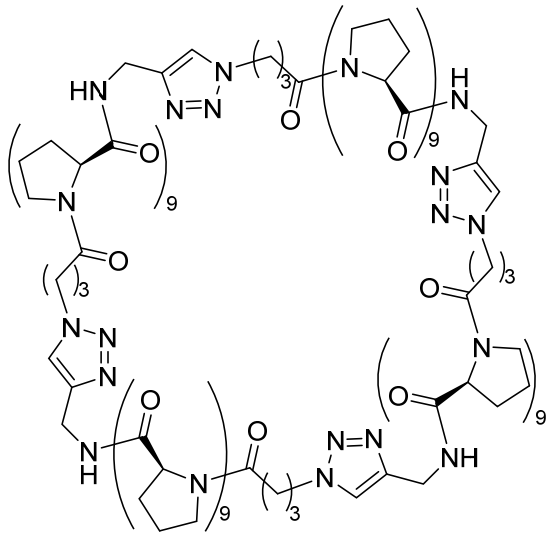
Figure S11. HPLC chromatogram of **8a**.

Yield: 0.65 mg, 43%.

Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 33.5 min.

MS(MALDI): $[M+H]^+$ calcd. for $C_{200}H_{277}N_{52}O_{40}$: 4047.123, found: 4047.898.

Cyclic peptide tetramer 8b



8b

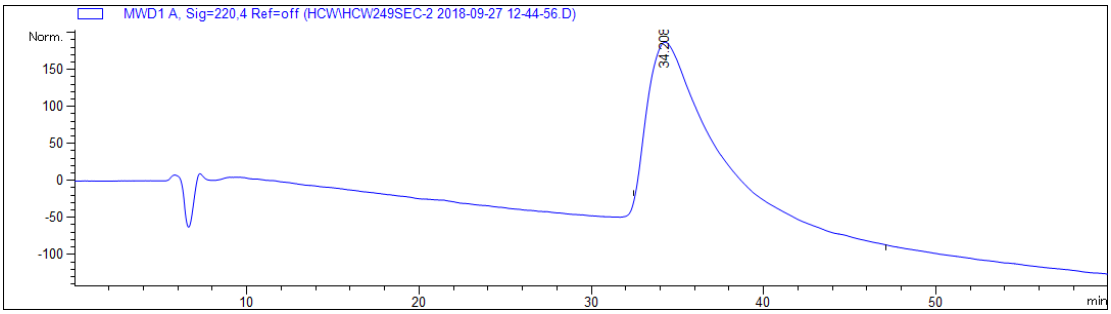


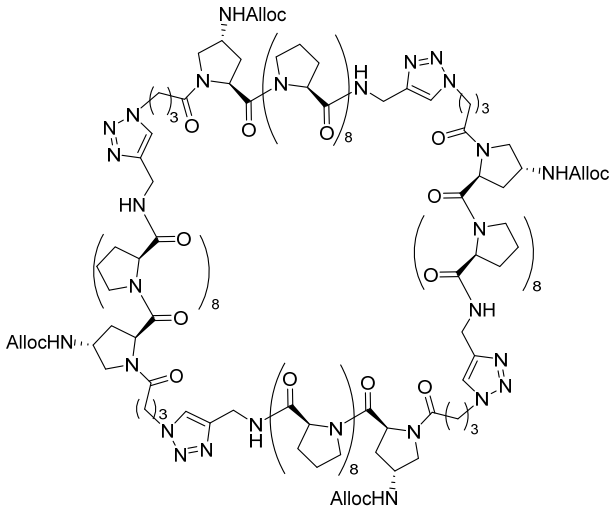
Figure S12. HPLC chromatogram of **8b**.

Yield: 1.25 mg, 29%.

Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 34.2 min.

MS(MALDI): $[M+H]^+$ calcd. for $C_{208}H_{293}N_{52}O_{40}$: 4159.249, found: 4158.433.

Cyclic peptide tetramer 8c



8c

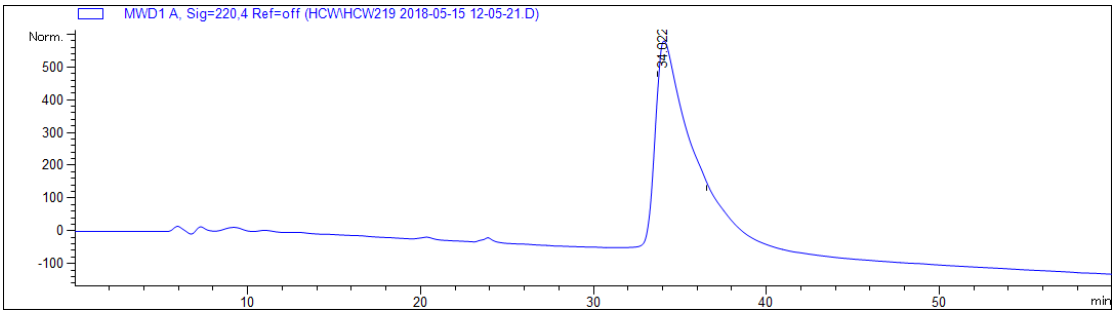


Figure S13. HPLC chromatogram of **8c**.

Yield: 2.44 mg, 48%.

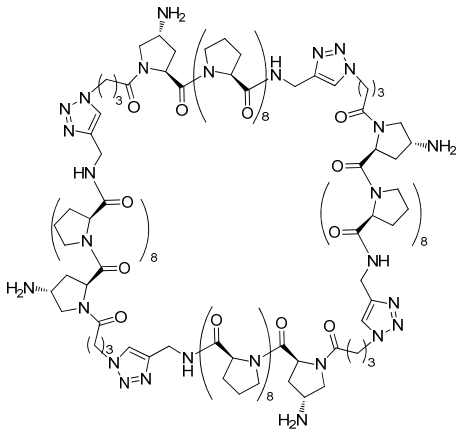
Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 34.0 min.

MS(MALDI): $[M+K]^+$ calcd. for $C_{224}H_{312}N_{56}KO_{48}$: 4593.333, found: 4593.893.

Synthesis of peptide oligomers: deprotected cyclic peptide

Peptide **S18** was prepared according to the method of *N*-Alloc deprotection. Yield is based on the isolated weight after lyophilization.

Deprotected cyclic peptide tetramer S18



S18

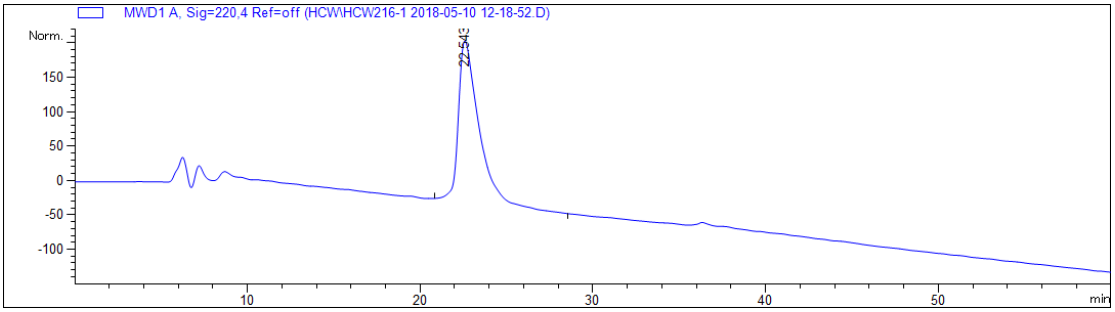


Figure S14. HPLC chromatogram of **S18**.

Yield: 2.01 mg, 48%.

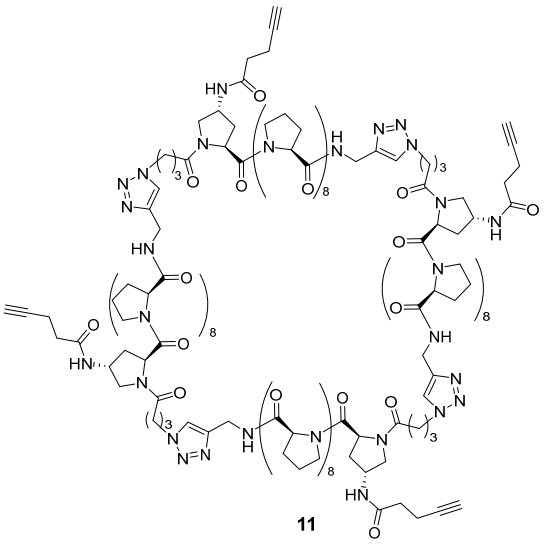
Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 22.5 min.

MS(MALDI): $[M+H]^+$ calcd. for $C_{208}H_{297}N_{56}O_{40}$: 4219.292, found: 4219.984.

Synthesis of peptide oligomers: alkynyl cyclic peptide

Peptide **11** was prepared according to the method of alkyne group installation on scaffold. Yield is based on the isolated weight after lyophilization.

Alkynyl cyclic peptide tetramer 11



11

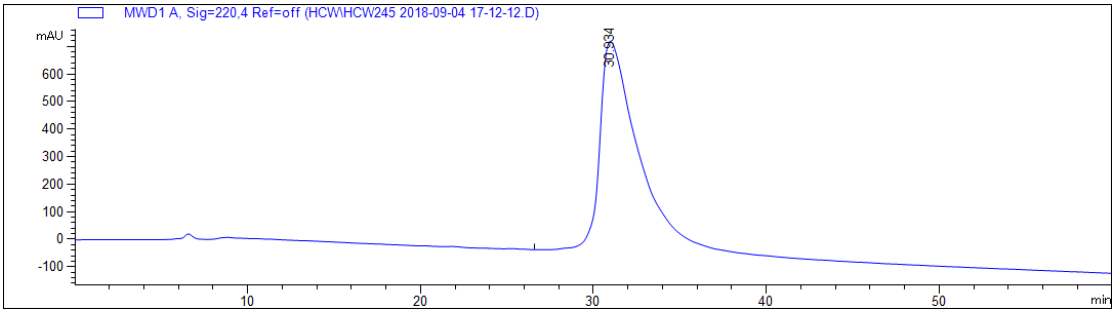


Figure S15. HPLC chromatogram of **11**.

Yield: 1.83 mg, 85%.

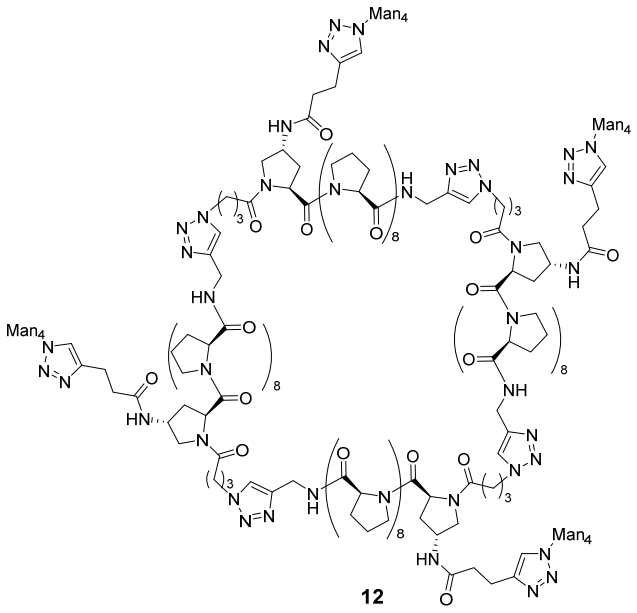
Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 30.9 min.

MS(MALDI): $[M+Na]^+$ calcd. for $C_{228}H_{312}N_{56}NaO_{44}$: 4561.379, found: 4562.115.

Synthesis of peptide oligomers: glycoconjugates

Glycoconjugate **12** and **13** were prepared according to the method of glycan conjugation to scaffold. Yields are based on the isolated weight after lyophilization.

Glycoconjugate 12



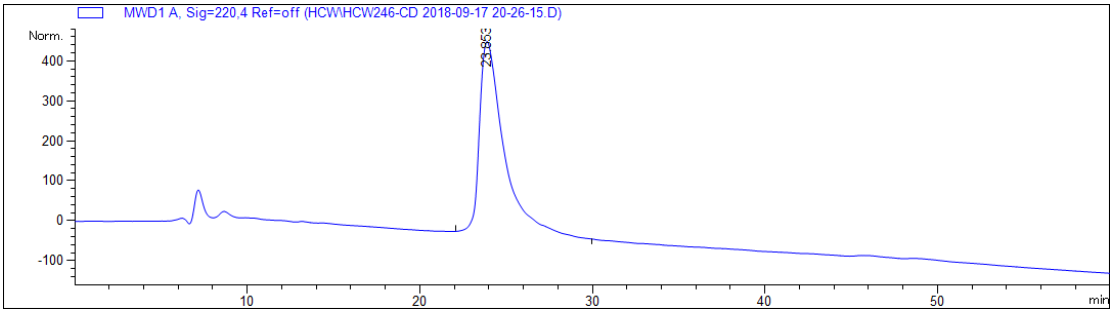


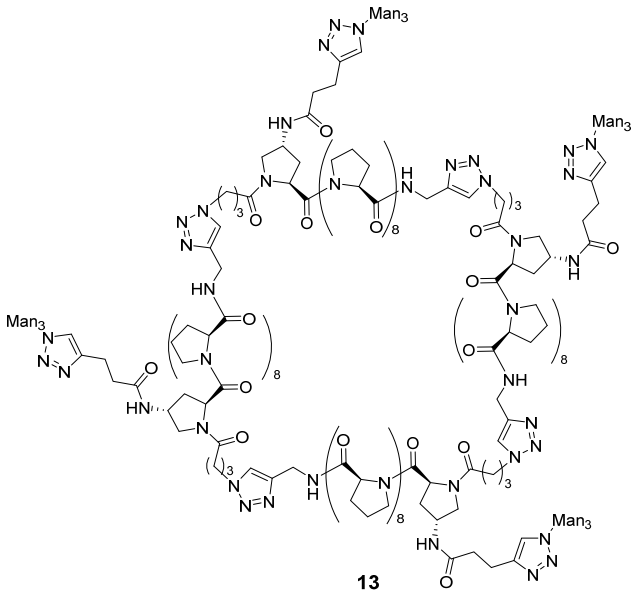
Figure S16. HPLC chromatogram of **12**.

Yield: 0.66 mg, 61%.

Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 23.9 min.

MS(MALDI): $[M+K]^+$ calcd. for $C_{344}H_{516}N_{68}KO_{128}$: 7686.559, found:7686.405.

Glycoconjugate 13



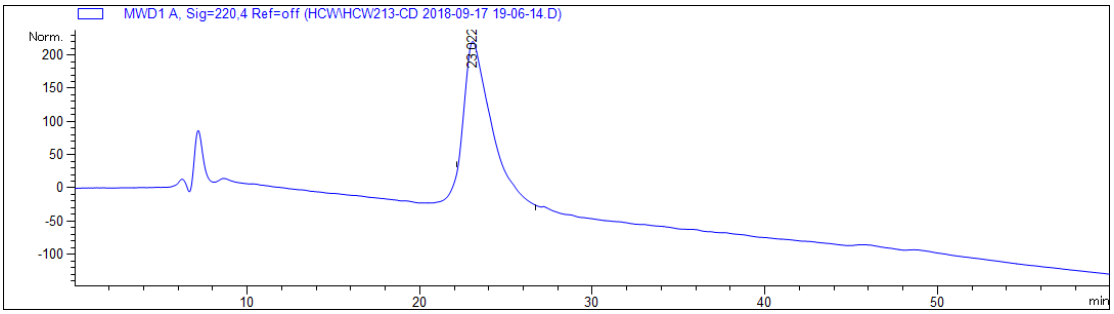


Figure S17. HPLC chromatogram of **13**.

Yield: 0.22 mg, 50%.

Analytical HPLC: 5% to 90% acetonitrile in water (0.1% TFA) over 60 min, 0.5 mL/min; t_R = 23.0 min.

MS(MALDI): $[M+K]^+$ calcd. for $C_{308}H_{452}N_{68}KO_{108}$: 6870.160, found: 6870.227.

^{1}H NMR spectra of 8b

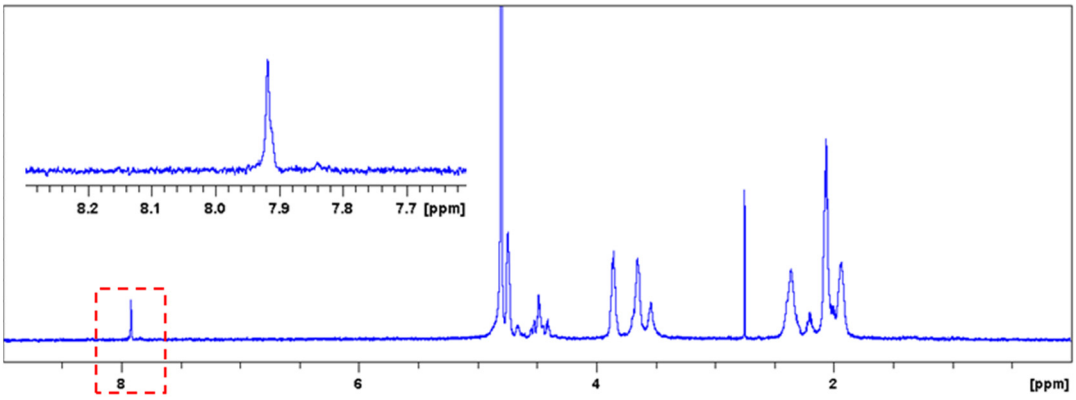


Figure S18. ^{1}H NMR of **8b** in D_2O; the inset shows the triazole proton signal as singlet.

Circular dichroism spectra of 7 and 8

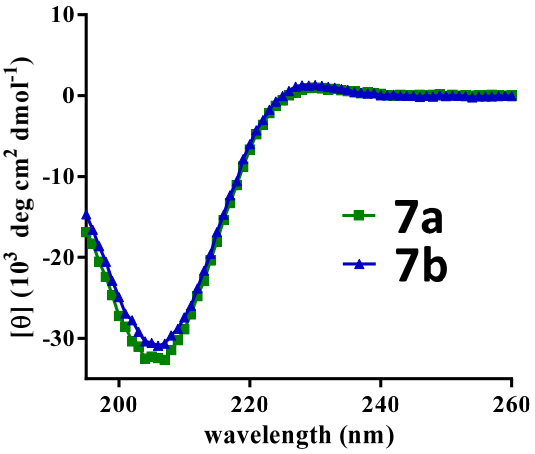


Figure S19. The circular dichroism spectra at far UV range of **7** in water.

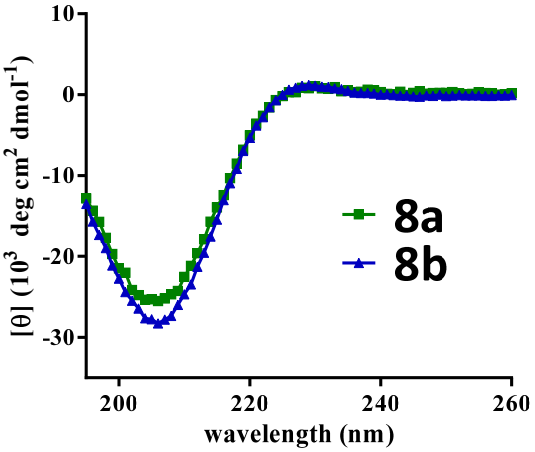


Figure S20. The circular dichroism spectra at far UV range of **8** in water.

4. Expression and Purification of Target Lectins

Langerin extracellular domain (Lg-ECD)[10]

DNA coding for langerin extracellular domain from residue 68 to 328 was synthesis and clone into NdeI and BamHI restriction sites of vector pET30b by Genomics. The plasmid of Lg-ECD in vector pET30b was transformed into *E. coli* BL21(DE3) competent cells. A 5 mL overnight culture of *E. coli* arrying the recombinant plasmid was grown in Luria-Bertani medium containing 50 μg/mL kanamycin at 37 °C. This culture was diluted into 1 L LB medium containing 100 μg/mL kanamycin and shake 220 rpm at 37 °C until the OD_{600} reached 0.7. Protein expression was induced by adding IPTG to a final concentration of 0.3 mM, and shaking vigorously at 37 °C for 3 h. The *E. coli* was harvested by centrifugation at 4 °C and 6000 × g for 20 min. The cell pellet was incubated in -20 °C overnight, then suspended in 15 mL buffer A (25 mM Tris, 150 mM NaCl, 4 mM $CaCl_2$, pH 7.8) containing 0.1 mM PMSF and sonicated at 5 s intervals under ice bath for 3 min. The lysate was centrifuged at 4 °C and 10000 × g for 20 min and the pellet was collected. The inclusion body dissolved under briefly sonication at 4 °C in 15 mL buffer B (6 N guanidine, 100 mM Tris, 0.01% β-mercaptoethanol, pH 7.0) for 30 min. The solution of denatured protein was centrifuged at 4 °C and 40000 × g for 1 h, and the supernatant was diluted 3-fold with buffer A by slow addition with stirring. The mixture was dialysis against buffer A with four buffer changes, and the precipitate was removed by centrifugation at 4 °C and 40000 × g for 2 h. The supernatant was loading into 3 mL mannose-Sepharose® column, which had been equilibrium

with buffer A. The column was washed by 20 mL buffer A, and the Lg-ECD was eluted by buffer C (25 mM Tris, 150 mM NaCl, 10 mM EDTA, pH 7.8) and analyzed by SDS-PAGE (10%). The protein was stored at 4 °C. The protein concentration was determined by UV 280 nm.

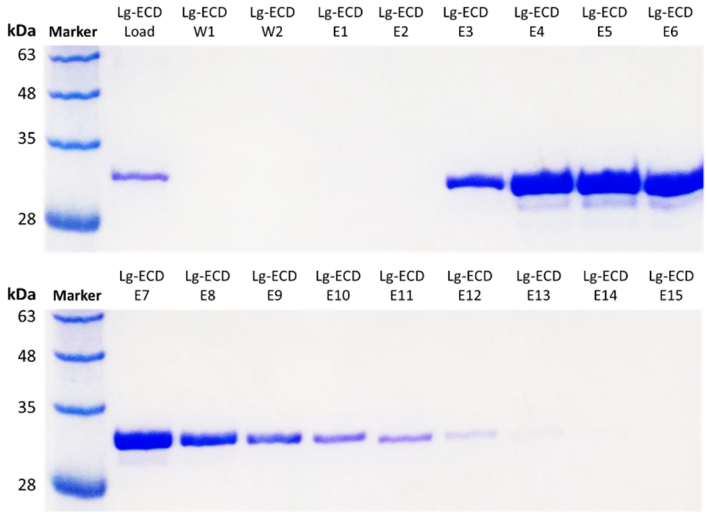


Figure S21. SDS-PAGE analysis of components during purification of LgECD by affinity column. Every washing and elution fraction is shown.

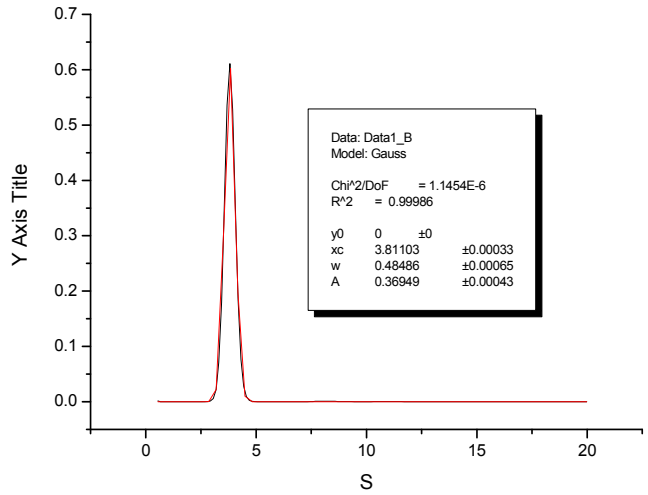


Figure S22. Analytical ultracentrifuge (AUC) result of trimeric LgECD. The original data (black line) and fitting data via the nonlinear least-squares fitting (NLSF) utility of Origin (red line) are shown.

DC-SIGN extracellular domain (DC-ECD)[11]

DNA coding for DC-SIGN extracellular domain from residue 62 to 404 was synthesis and clone into BamHI and XhoI restriction sites of vector pT5T by Genomics. The plasmid of DC-ECD in vector pT5T was transformed into *E. coli* BL21(DE3) competent cells. A 5 mL overnight culture of *E. coli* carrying the recombinant plasmid was grown in Luria-Bertani medium containing 100 μg/mL ampicillin at 37 °C. This culture was diluted into 1 L LB medium containing 100 μg/mL ampicillin and shake 220 rpm at 37 °C until the OD_{600} reached 0.7. Protein expression was induced by adding IPTG to a final concentration of 0.3 mM, and shaking vigorously at 37 °C for 3 h. The *E. coli* was harvested by centrifugation at 4 °C and 6000 × g for 20 min. The cell pellet was incubated in -20 °C overnight, then suspended in 15 mL buffer A (25 mM Tris, 150 mM NaCl, 4 mM $CaCl_2$, pH 7.8) containing 0.1 mM PMSF and sonicated at 5 s intervals under ice bath for 3 min. The lysate was centrifuged at 4 °C and 10000 × g for 20 min and the pellet was collected. The inclusion body dissolved by briefly sonication at 4 °C in 15 mL buffer C (6 N guanidine, 100 mM Tris, 0.01% β-mercaptoethanol, pH 7.0) for 30 min. The solution of denatured protein was centrifuged at 4 °C and 40000 × g for 1 h, and the supernatant was diluted 5-fold with buffer A by slow addition with stirring. The mixture was dialysis against buffer A with four buffer changes, and the precipitate was removed by centrifugation at 4 °C and 40000 × g for 2 h. The supernatant was loading into 1 mL mannose-Sepharose® column, which had been equilibrated with buffer A. The column was washed by 10 mL buffer A, and the DC-ECD was eluted by buffer C (25

mM Tris, 150 mM NaCl, 10 mM EDTA, pH 7.8) and analyzed by SDS-PAGE (10%). The protein was stored at 4 °C. The protein concentration was determined by UV 280 nm.

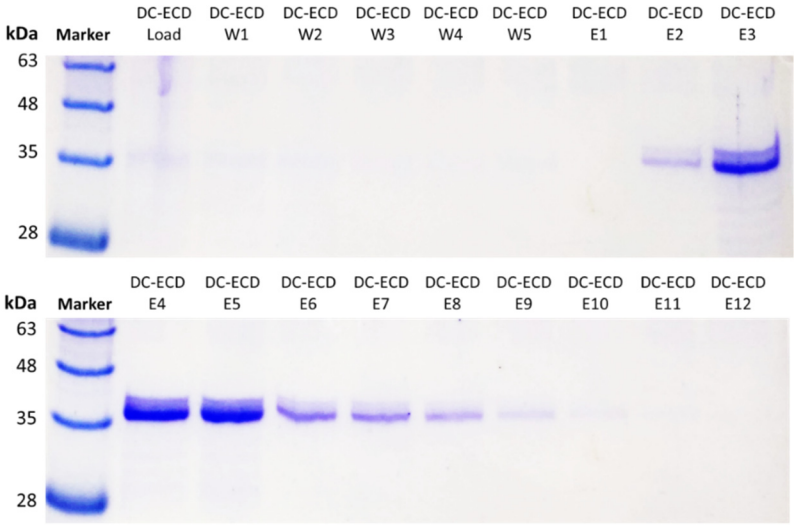


Figure S23. SDS-PAGE analysis of components during purification of DC-ECD by affinity column. Every washing and elution fraction is shown.

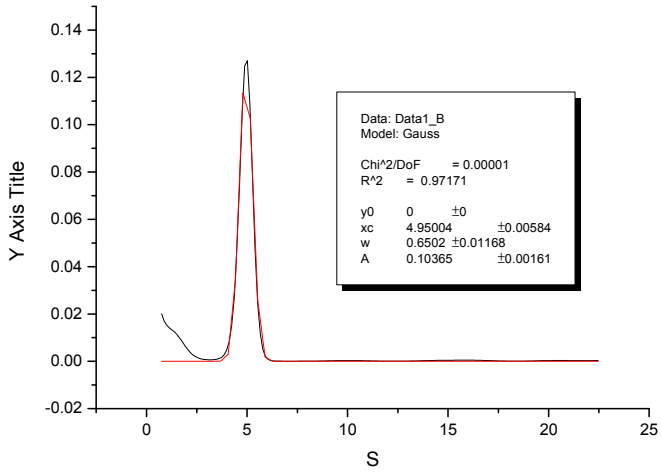


Figure S24. Analytical ultracentrifuge (AUC) result of tetrameric DC-SIGN. The original data (black line) and fitting data via the nonlinear least-squares fitting (NLSF) utility of Origin (red line) are shown.

5. Surface Plasmon Resonance Assay

Material

Sensor chip CM5 (Product Code BR100530) for surface plasmon resonance experiment was purchased from GE Healthcare.

Method

Surface plasmon resonance (SPR) experiments were performed on Biacore T100 or T200 at 25 °C using a functionalized CM5 sensor chip. Protein immobilization was performed according to the build-in wizard software template of the instrument. The CM5 sensor chip was activated with a solution containing *N*-ethyl-*N'*-(3-diethyl-aminopropyl)-carbodiimide (EDC) (0.2 M) and *N*-hydroxysuccinimide (NHS) (0.05 M). Then langerin ECD (10 μg/mL) in acetate buffer (pH 5.5, 10 mM) or DC-SIGN ECD (100 μg/mL) in acetate buffer (pH 3.5, 10 mM) was injected over the activated surface at a flow rate of 10 μL/min for 900 s. Then ethanolamine (pH 8.5, 1 M) was injected to block the remaining activated groups. Binding assays were performed with running buffer (25 mM Tris, 150 mM NaCl, 4 mM $CaCl_2$, 0.005% Tween 20, pH 7.8). Glycodendrimers **9**, **10** or glycoconjugates **12**, **13** were injected onto the surface, with several concentrations ranging from 400 nM to 6400 nM for **9**, 100 nM to 1600 nM for **10**, 4000 nM to 64000 nM for **12**, and 400 nM to 6400 nM for **13** langerin ECD or from 400 nM to 6400 nM for **9**, 0.625 nM to 10 nM for **10**, 6.25 nM to 100 nM for **12**, 400 nM to 6400 nM for **13**, 6.25 nM to 100 nM for **8b**, and 62500 nM to 1000000 nM for **Man_4** to DC-SIGN ECD at the rate of 10 μL/min diluted

in the running buffer. The surface was regenerated by 60 s injection of regeneration buffer (25 mM Tris, 150 mM NaCl, 10 mM EDTA, pH 7.8). The sensorgrams were reference subtracted, quality controlled and analyzed by Biacore T200 Evaluation Software, and the kinetic parameters were obtained by fitting curves to 1:1 Langmuir model.

Sensorgrams

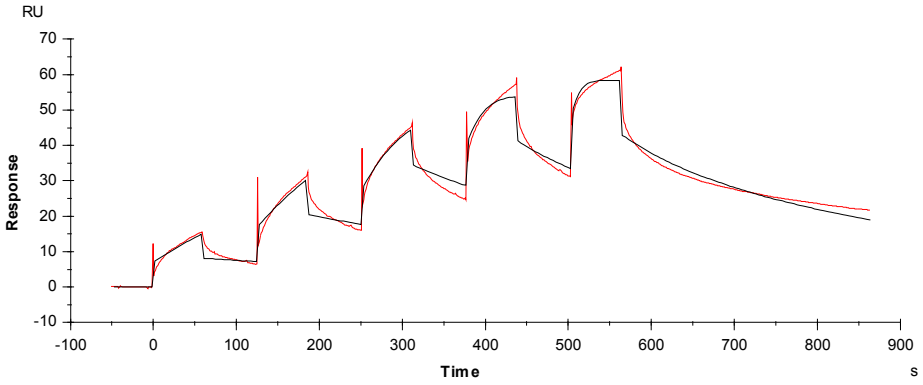


Figure S25. Sensorgram of **9** binding to a langerin sensorchip (Concentration = 400, 800, 1600, 3200 and 6400 nM).

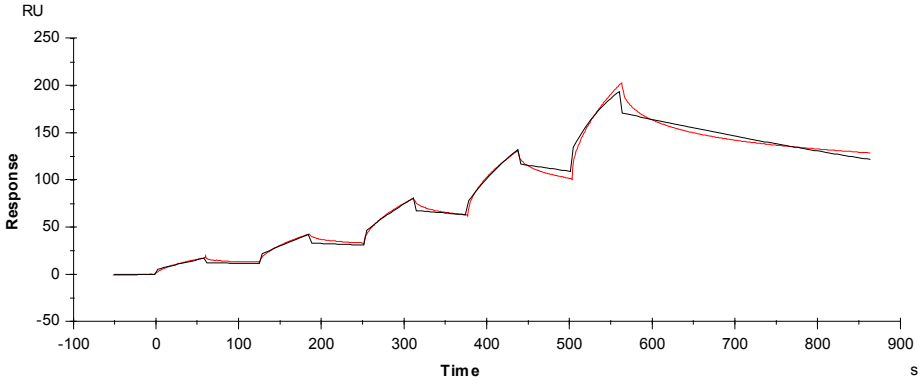


Figure S26. Sensorgram of **10** binding to a langerin sensorchip (Concentration = 100, 200, 400, 800 and 1600 nM).

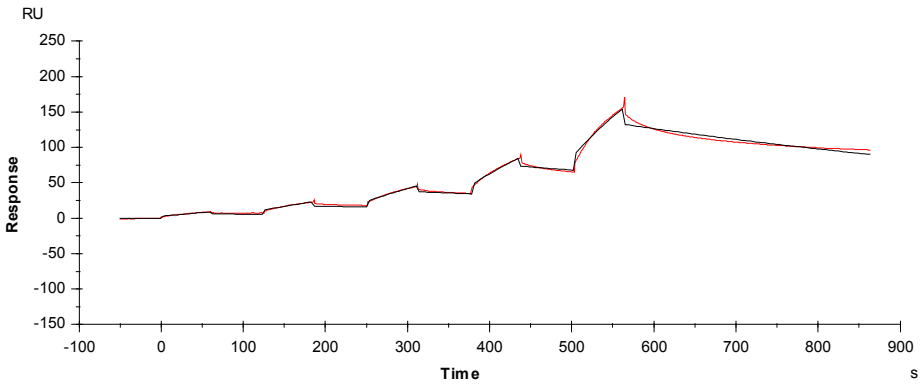


Figure S27. Sensorgram of **12** binding to a langerin sensorchip (Concentration = 4000, 8000, 16000, 32000 and 64000 nM).

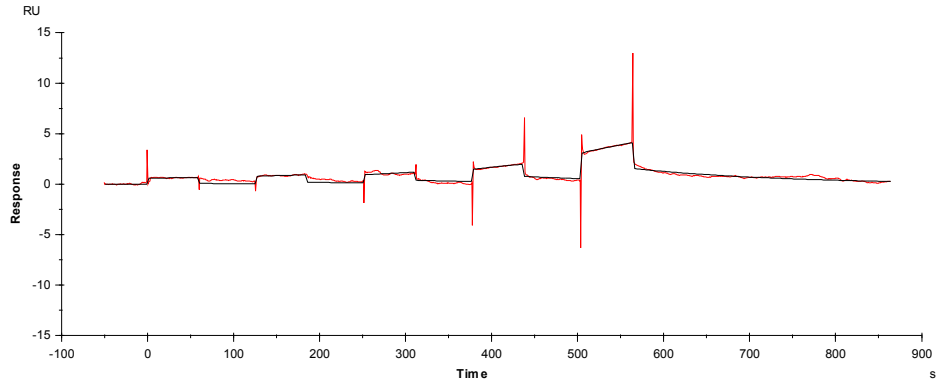


Figure S28. Sensorgram of **13** binding to a langerin sensorchip (Concentration = 400, 800, 1600, 3200 and 6400 nM).

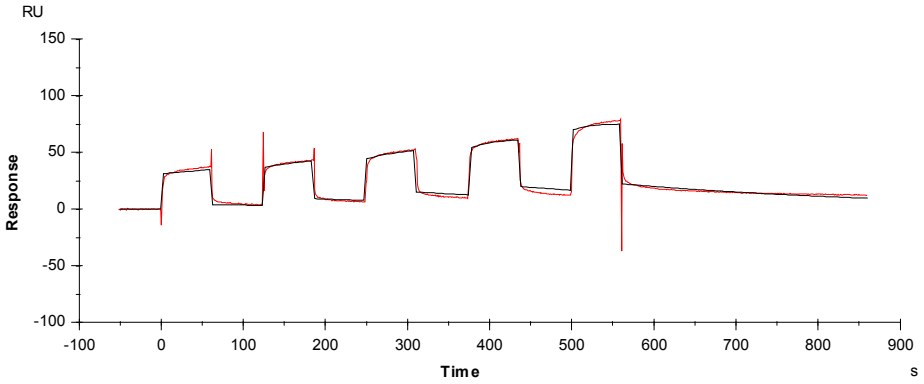


Figure S29. Sensorgram of **9** binding to a DC-SIGN sensorchip (Concentration = 400, 800, 1600, 3200 and 6400 nM).

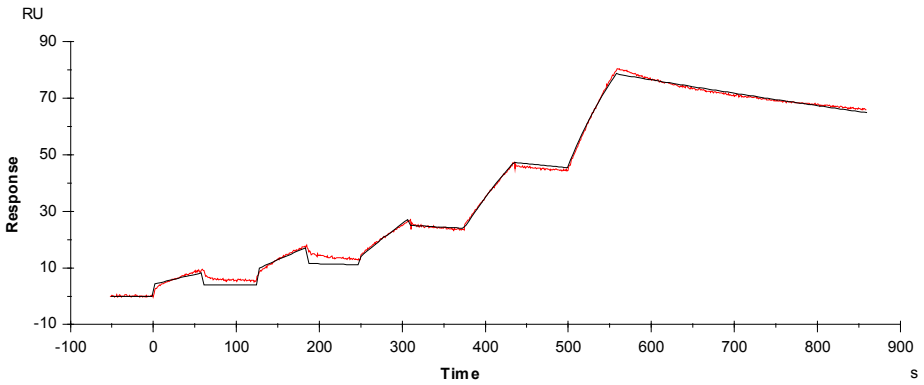


Figure S30. Sensorgram of **10** binding to a DC-SIGN sensorchip (Concentration = 0.625, 1.25, 2.5, 5 and 10 nM).

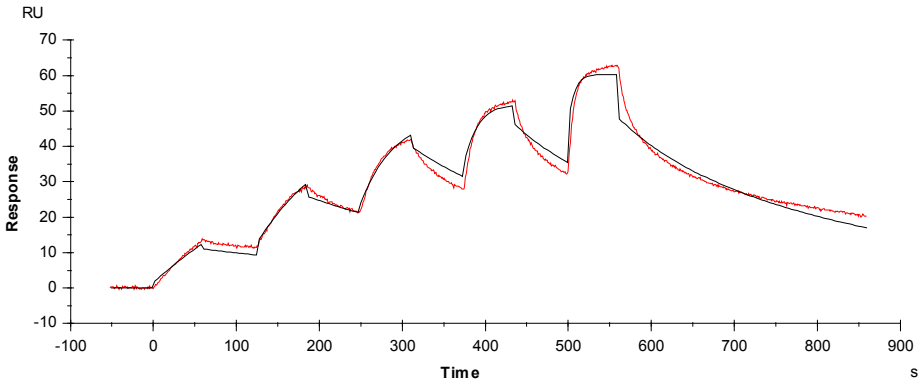


Figure S31. Sensorgram of **12** binding to a DC-SIGN sensorchip (Concentration = 6.25, 12.5, 25, 50 and 100 nM).

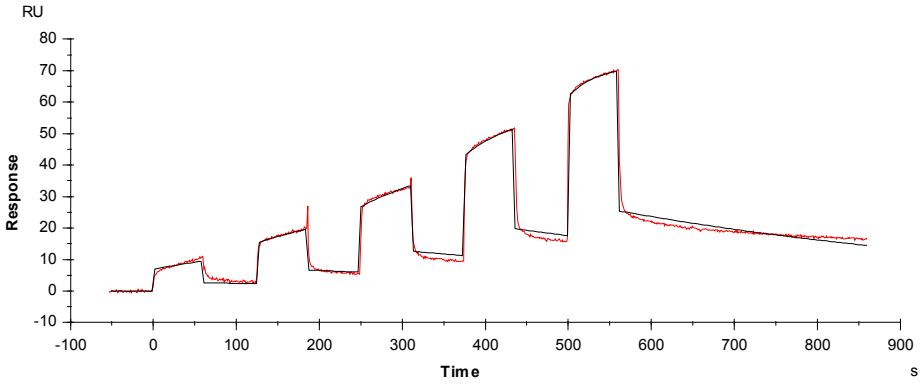


Figure S32. Sensorgram of **13** binding to a DC-SIGN sensorchip (Concentration = 400, 800, 1600, 3200 and 6400 nM).

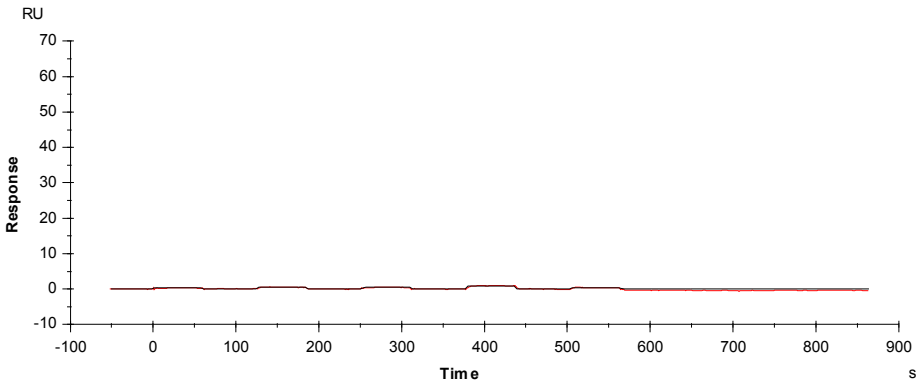


Figure S33. Sensorgram of **8b** binding to a DC-SIGN sensorchip showing no binding activity at the same concentrations for measurement of **12** (Concentration = 6.25, 12.5, 25, 50 and 100 nM).

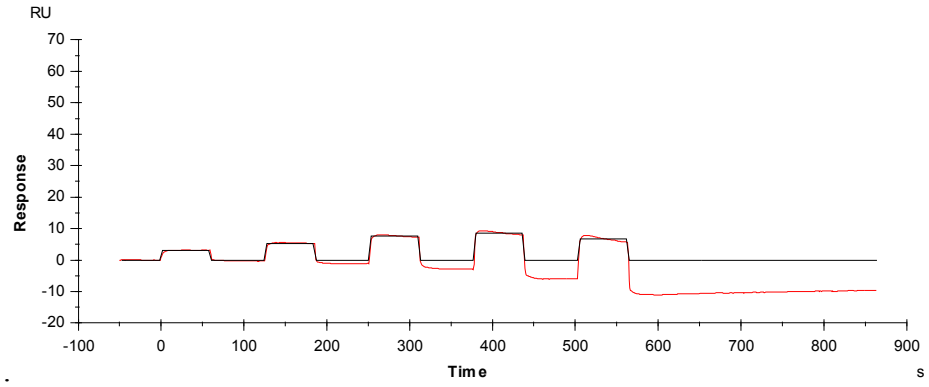


Figure S34. Sensorgram of **Man$_4$** binding to a DC-SIGN sensorchip showing very weak interaction that the K_D cannot be determined within instrument limitation (Concentration = 62500, 125000, 250000, 500000 and 1000000 nM).

References

1. C. H. Lin, H. C. Wen, C. C. Chiang, J. S. Huang, Y. Chen, S. K. Wang, *Small*, 2019, **15**, e1900561.

2. G. J. Miller, J. M. Gardiner, *Org. Lett.*, 2010, **12**, 5262–5265.

3. R. Kikkeri, L. H. Hossain, P. H. Seeberger, *Chem. Commun.*, 2008, 2127–2129.

4. C. Voshavar, R. C. Meka, S. Samanta, S. Marepally, A. Chaudhuri, *J. Med. Chem.*, 2017, **60**, 1605–1610.

5. R. Kikkeri, X. Liu, A. Adibekian, Y. H. Tsai, P. H. Seeberger, *Chem. Commun.*, 2010, **46**, 2197–2199.

6. S. K. Wang, P. H. Liang, R. D. Astronomo, T. L. Hsu, S. L. Hsieh, D. R. Burton, C. H. Wong, *Proc. Nat. Acad. Sci. U. S. A.*, 2008, **105**, 3690–3695.

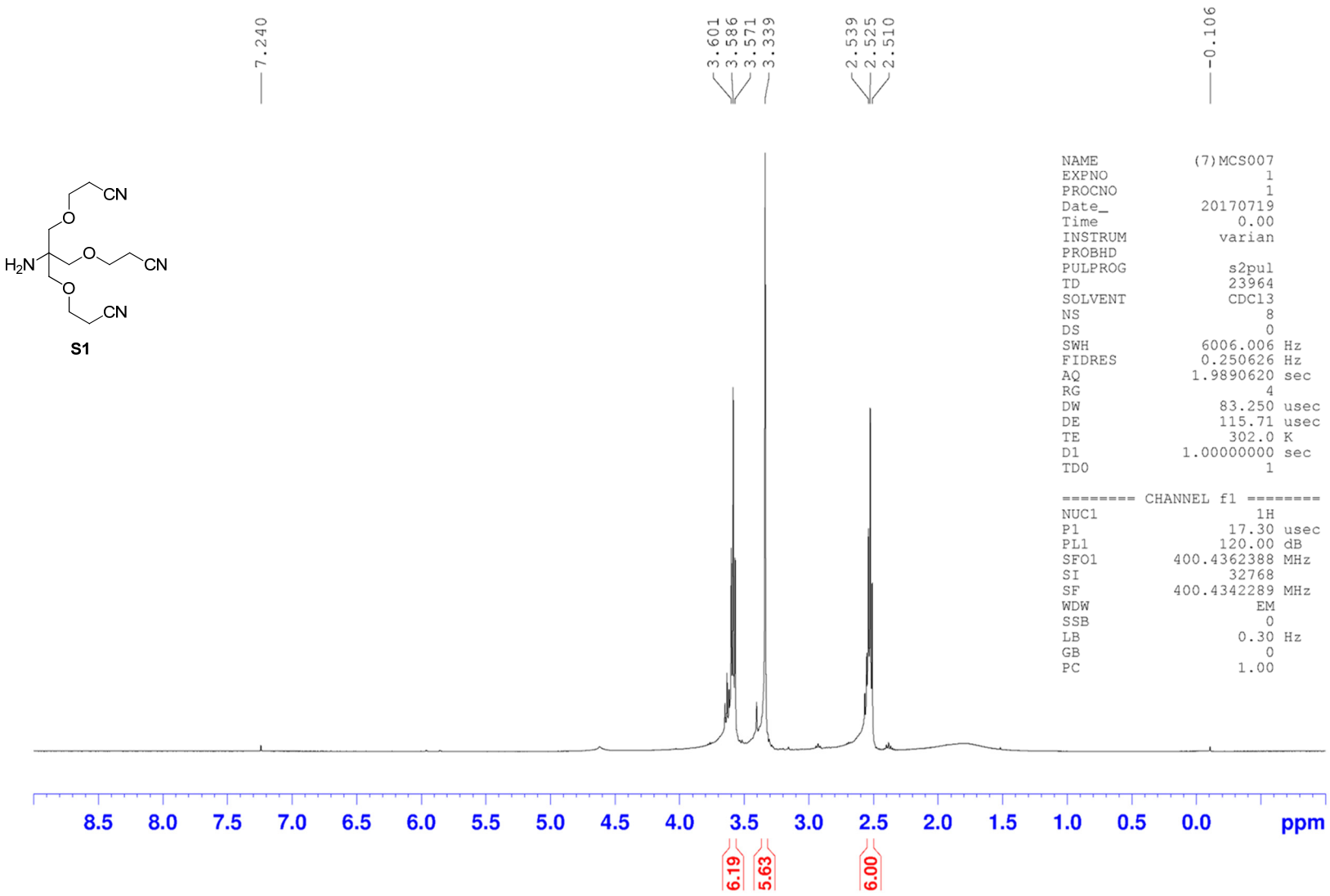
7. M. Adamczyk, J. R. Fishpaugh, M. Thiruvazhi, *Org. Prep. Proced. Int.*, 2002, **34**, 326–331.

8. T. K. Lindhorst, K. Bruegge, A. Fuchs, O. Sperling, *Beilstein J. Org. Chem.*, 2010, **6**, 801–809.

9. K. J. Doores, Z. Fulton, V. Hong, M. K. Patel, C. N. Scanlan, M. R. Wormald, M. G. Finn, D. R. Burton, I. A. Wilson, B. G. Davis, *Proc. Nat. Acad. Sci. U. S. A.*, 2010, **107**, 17107–17112.

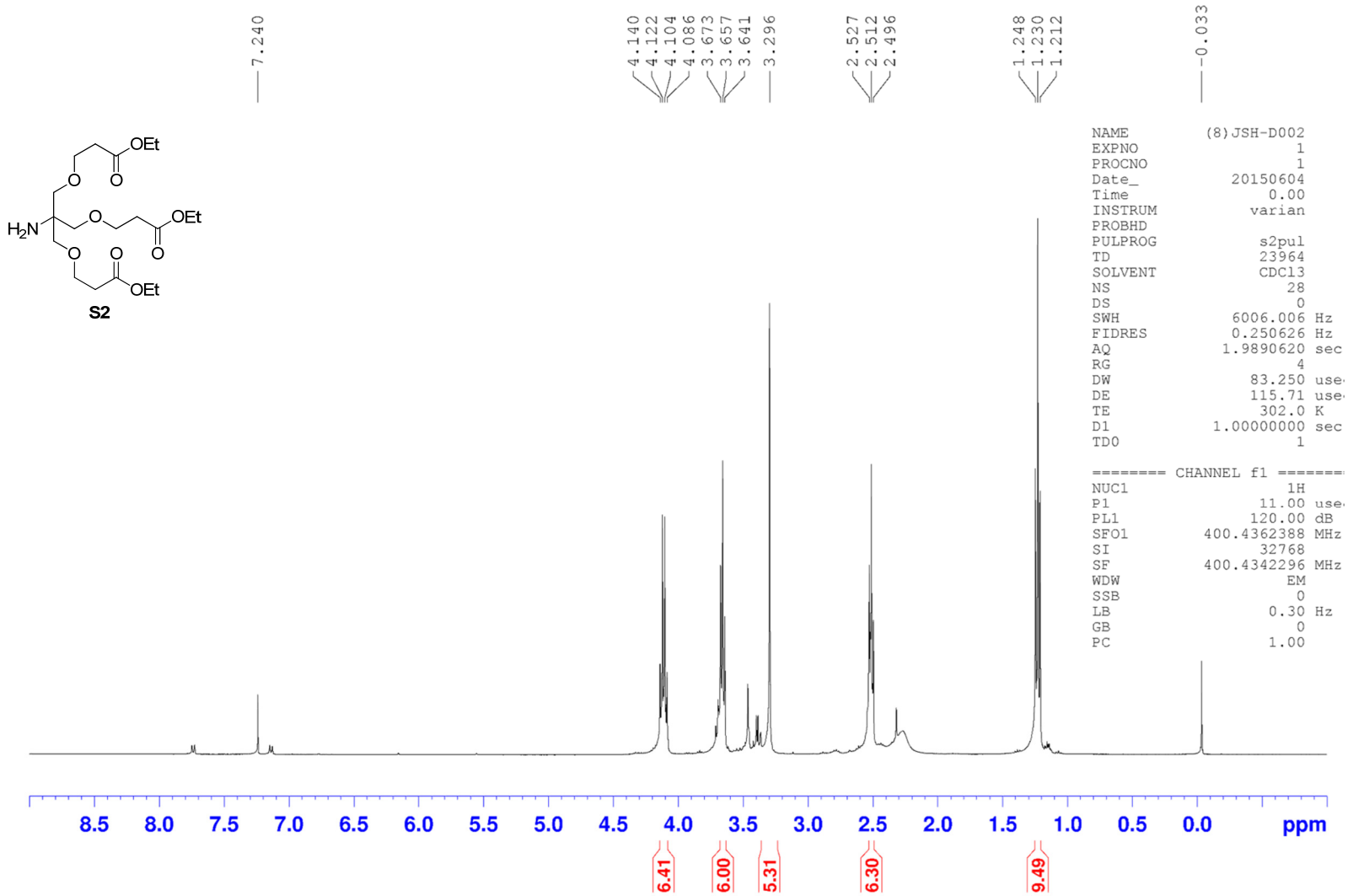
10. M. Thépaut, J. Valladeau, A. Nurisso, R. Kahn, B. Arnou, C. Vivès, S. Saeland, C. Ebel, C. Monnier, C. Dezutter-Dambuyant, A. Imberty, F. Fieschi, *Biochemistry*, 2009, **48**, 2684–2698.

11. D. A. Mitchell, A. J. Fadden, K. Drickamer, *J. Biol. Chem.*, 2001, **276**, 28939–28945.

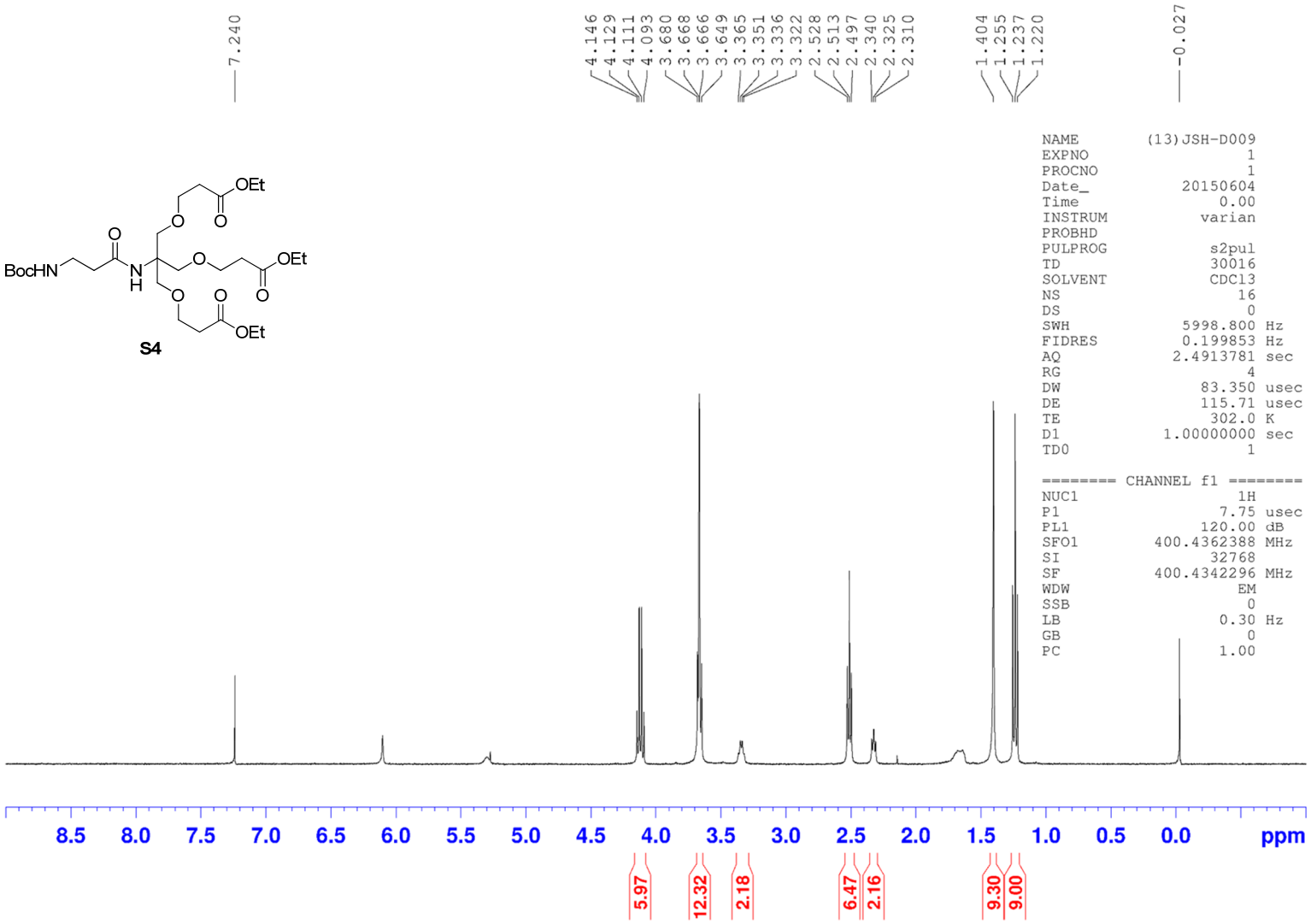


S1

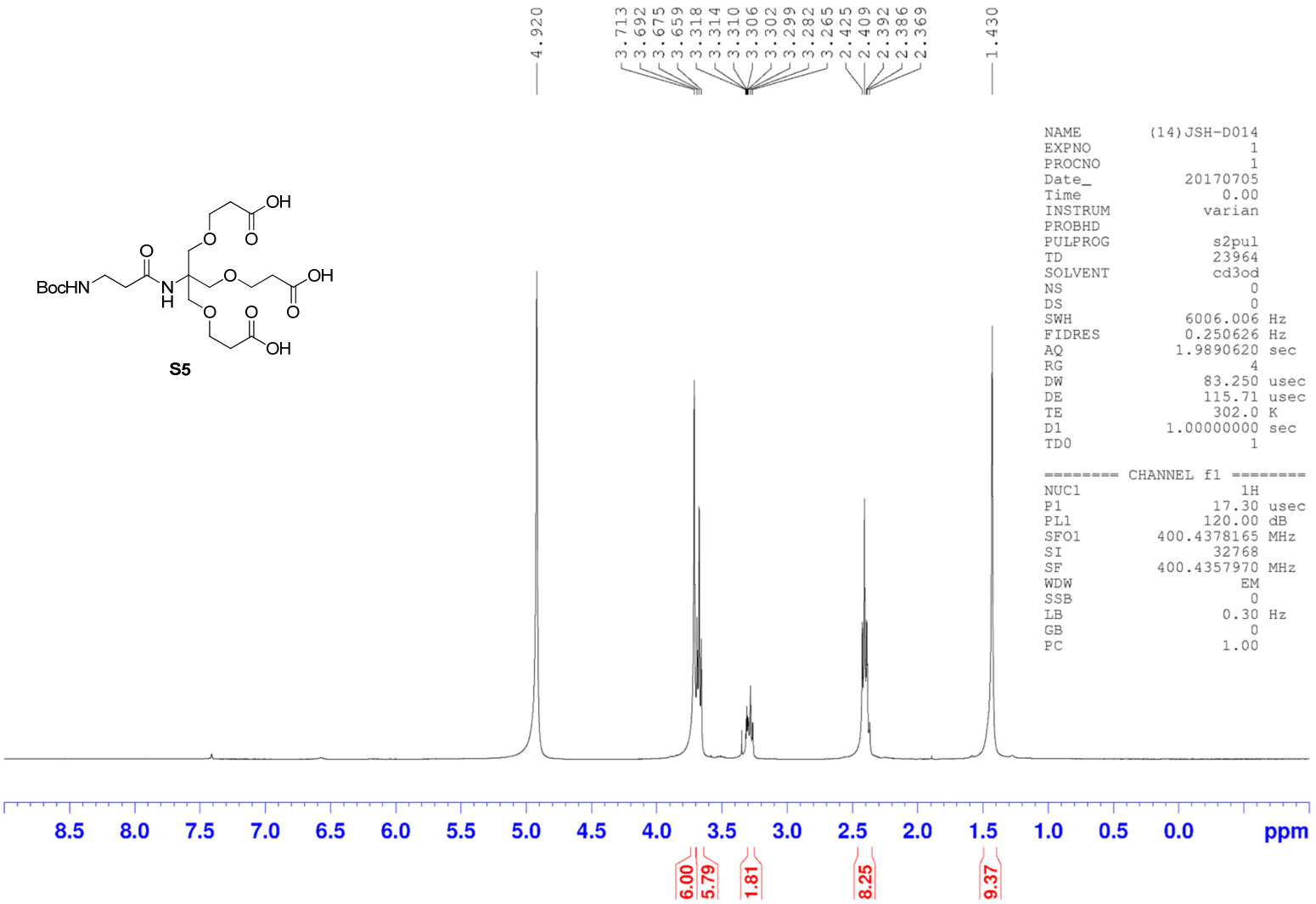
^{1}H NMR spectra of **S1** (400 MHz, $CDCl_3$)



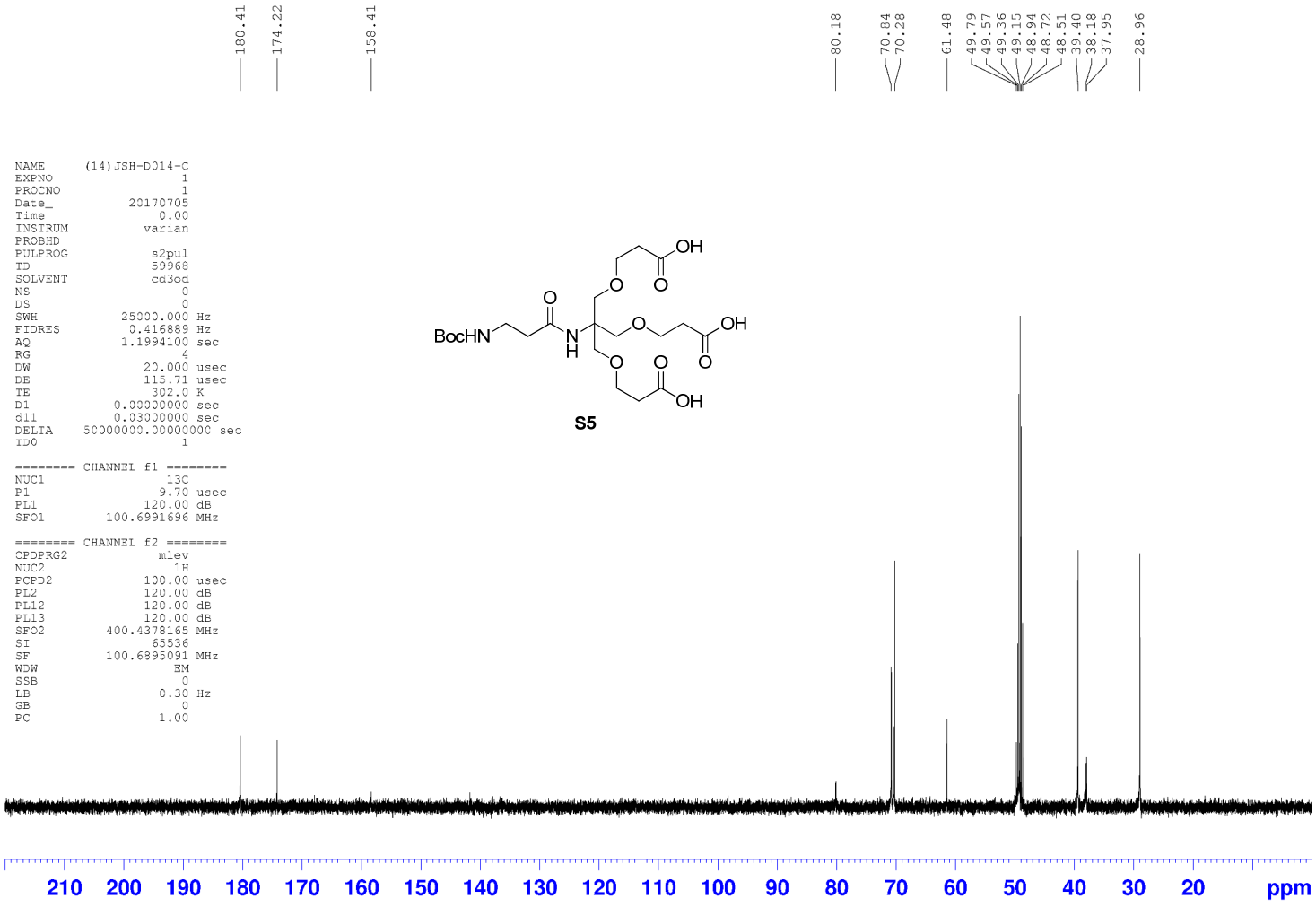
^{1}H NMR spectra of **S2** (400 MHz, $CDCl_3$)



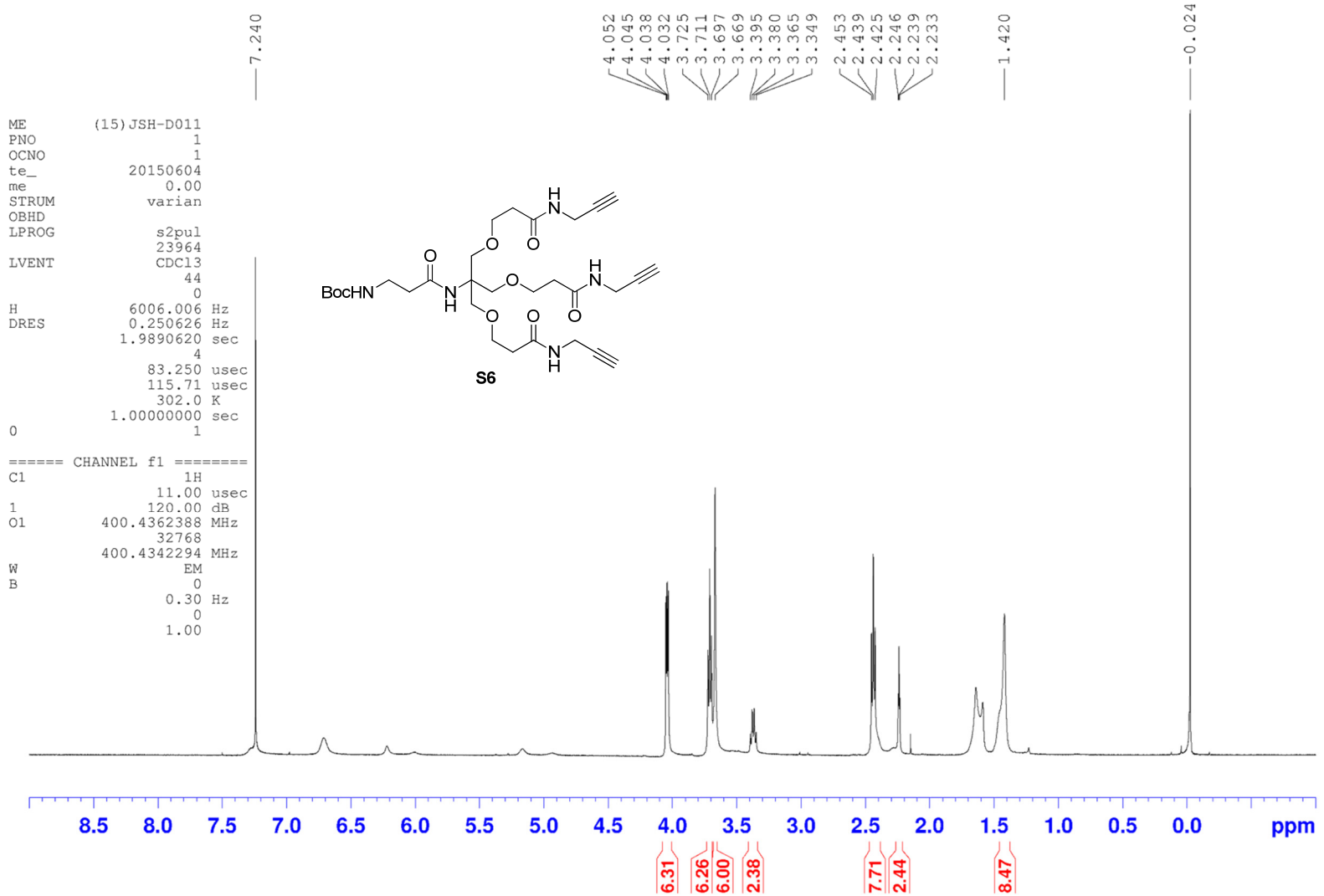
^{1}H NMR spectra of **S4** (400 MHz, $CDCl_3$)



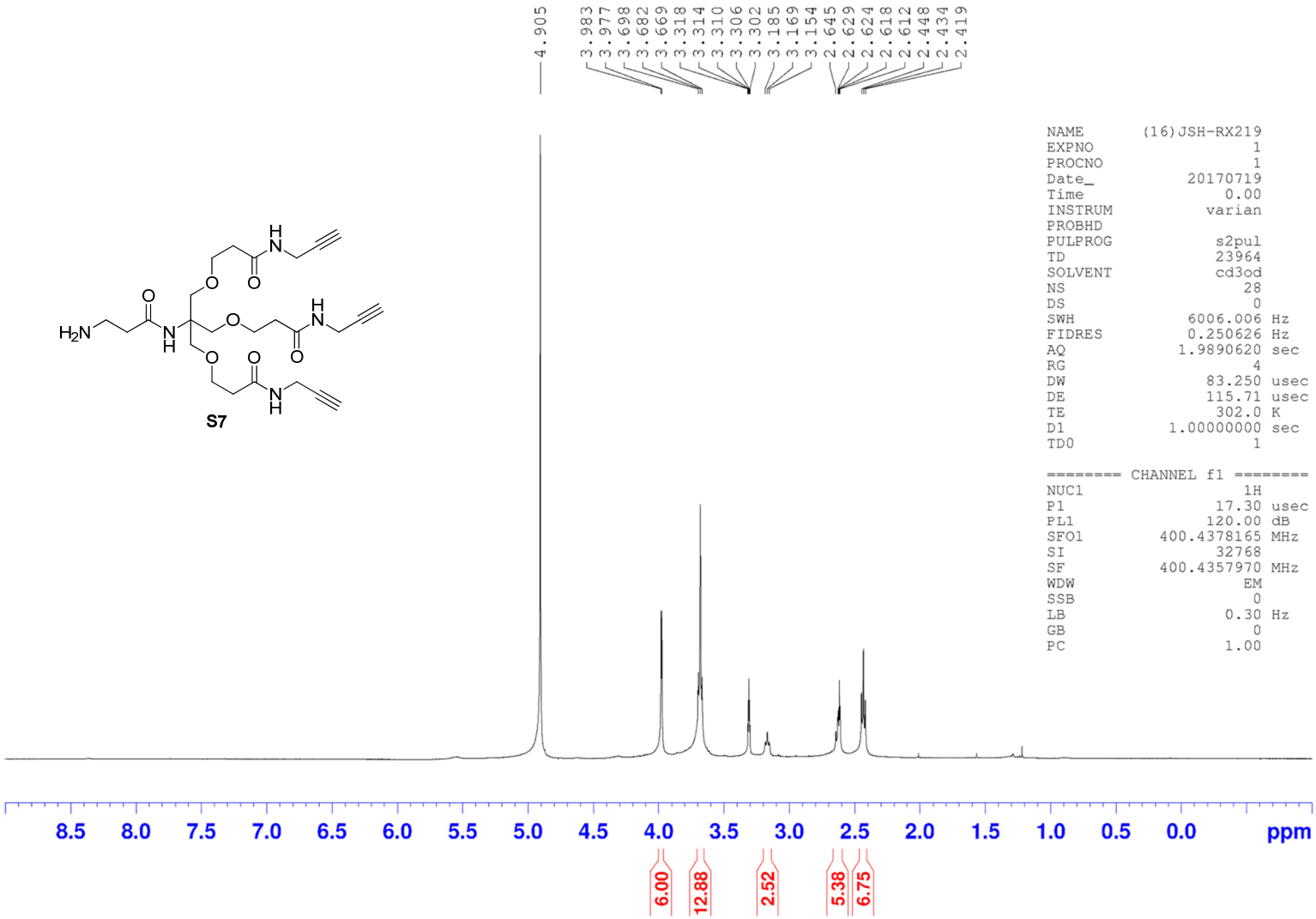
^{1}H NMR spectra of **S5** (400 MHz, CD_3OD)



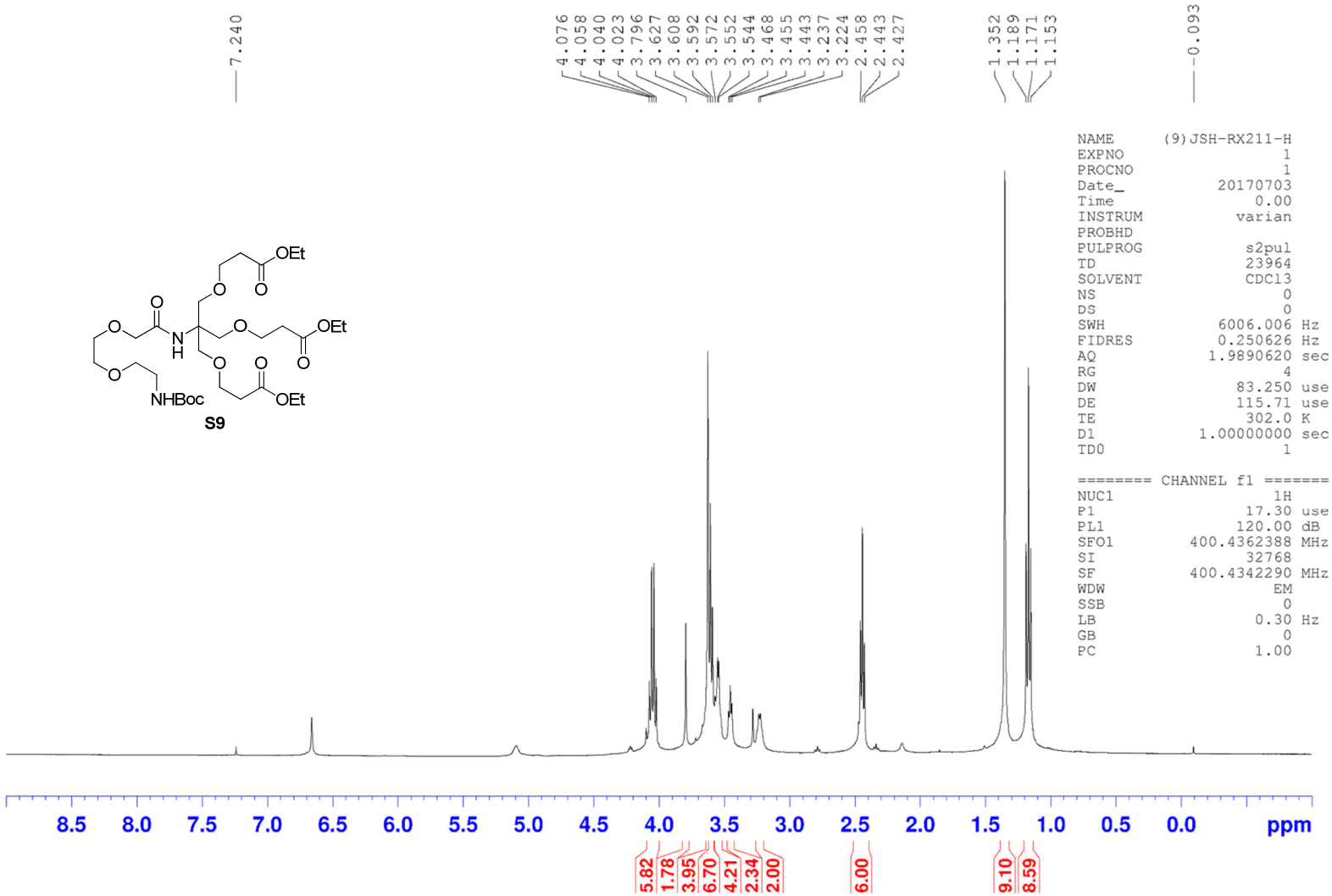
^{13}C NMR spectra of **S5** (100.7 MHz, CD_3OD)



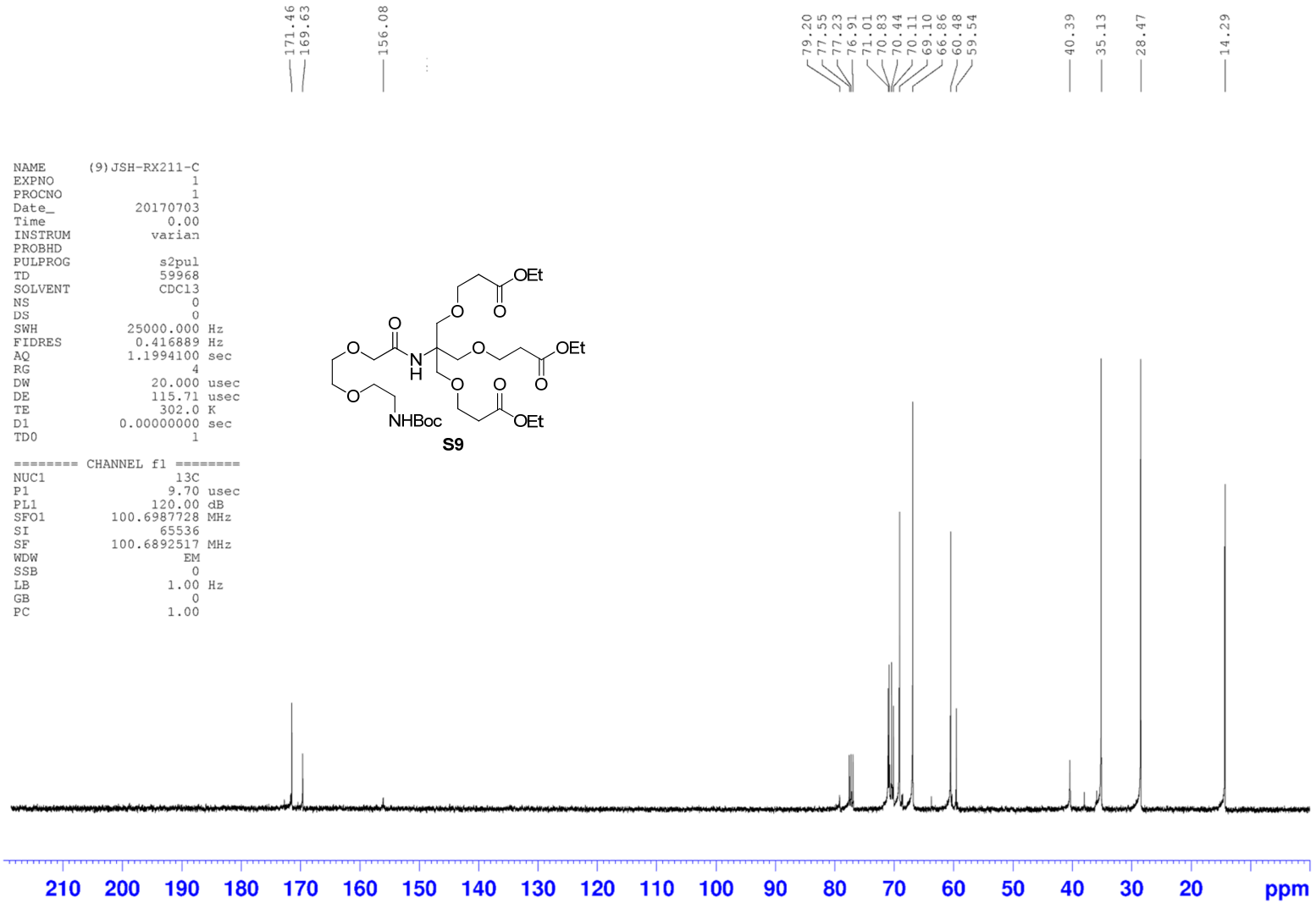
^{1}H NMR spectra of **S6** (400 MHz, $CDCl_3$)



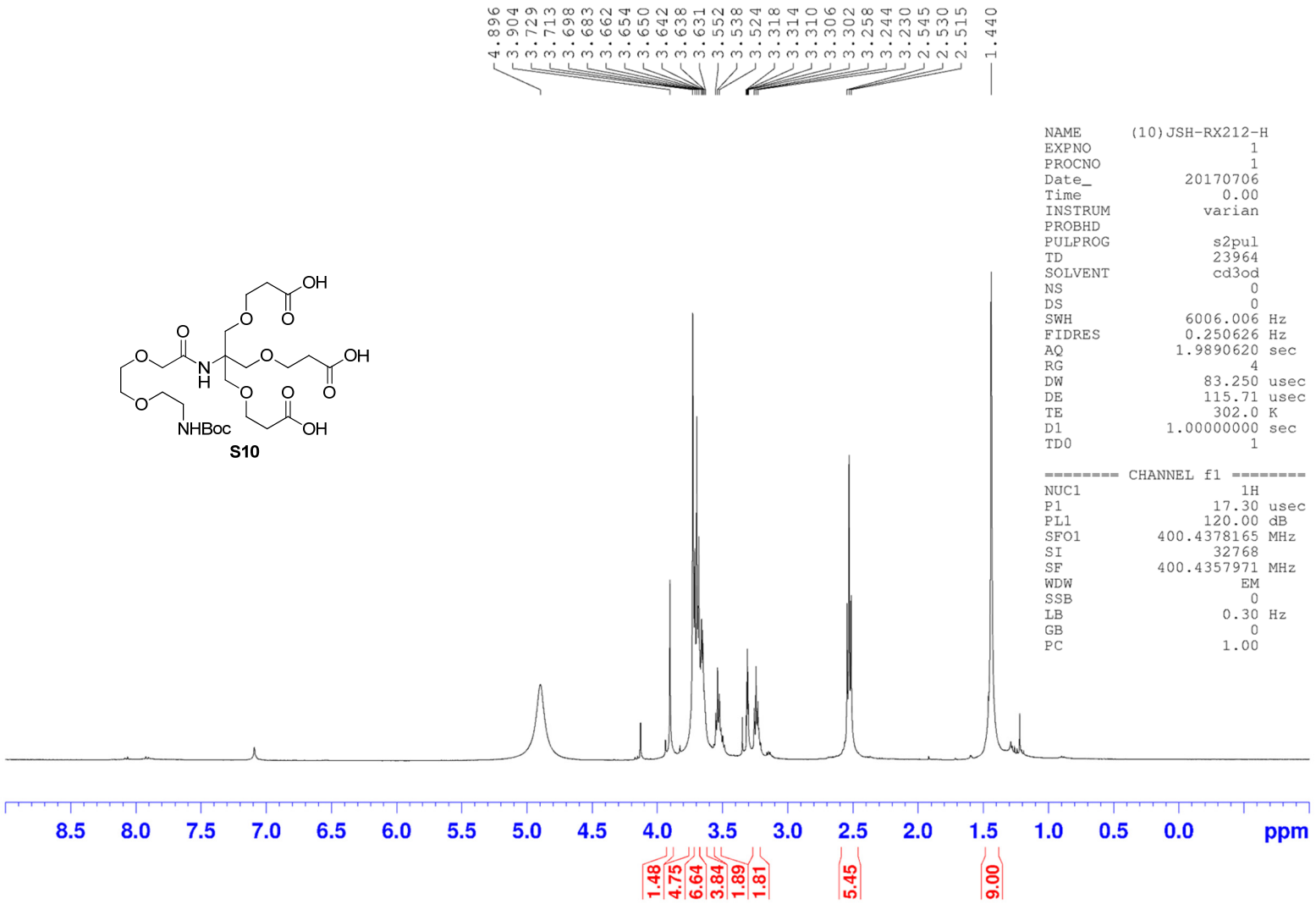
^{1}H NMR spectra of **S7** (400 MHz, CD_3OD)



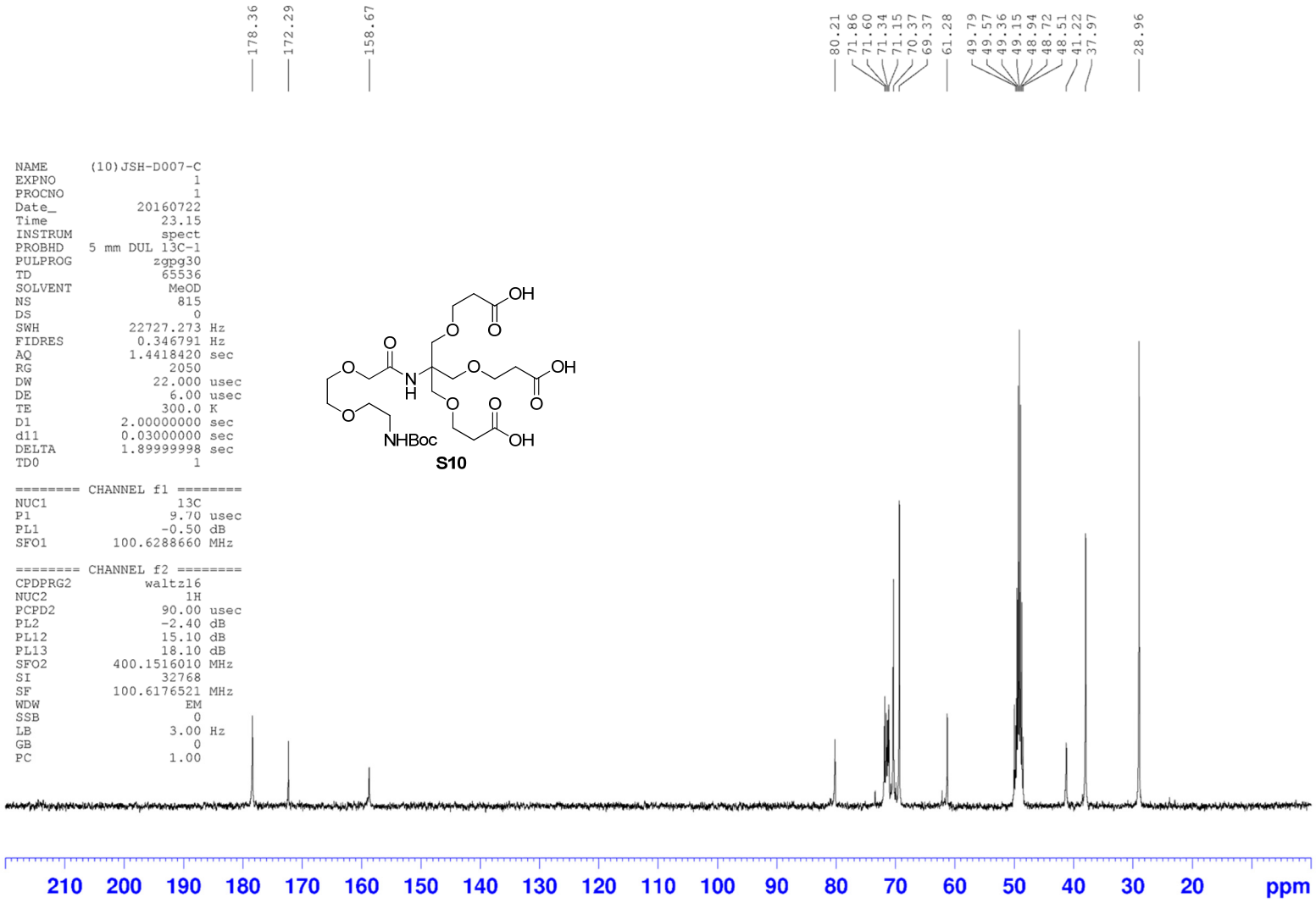
^{1}H NMR spectra of **S9** (400 MHz, $CDCl_3$)



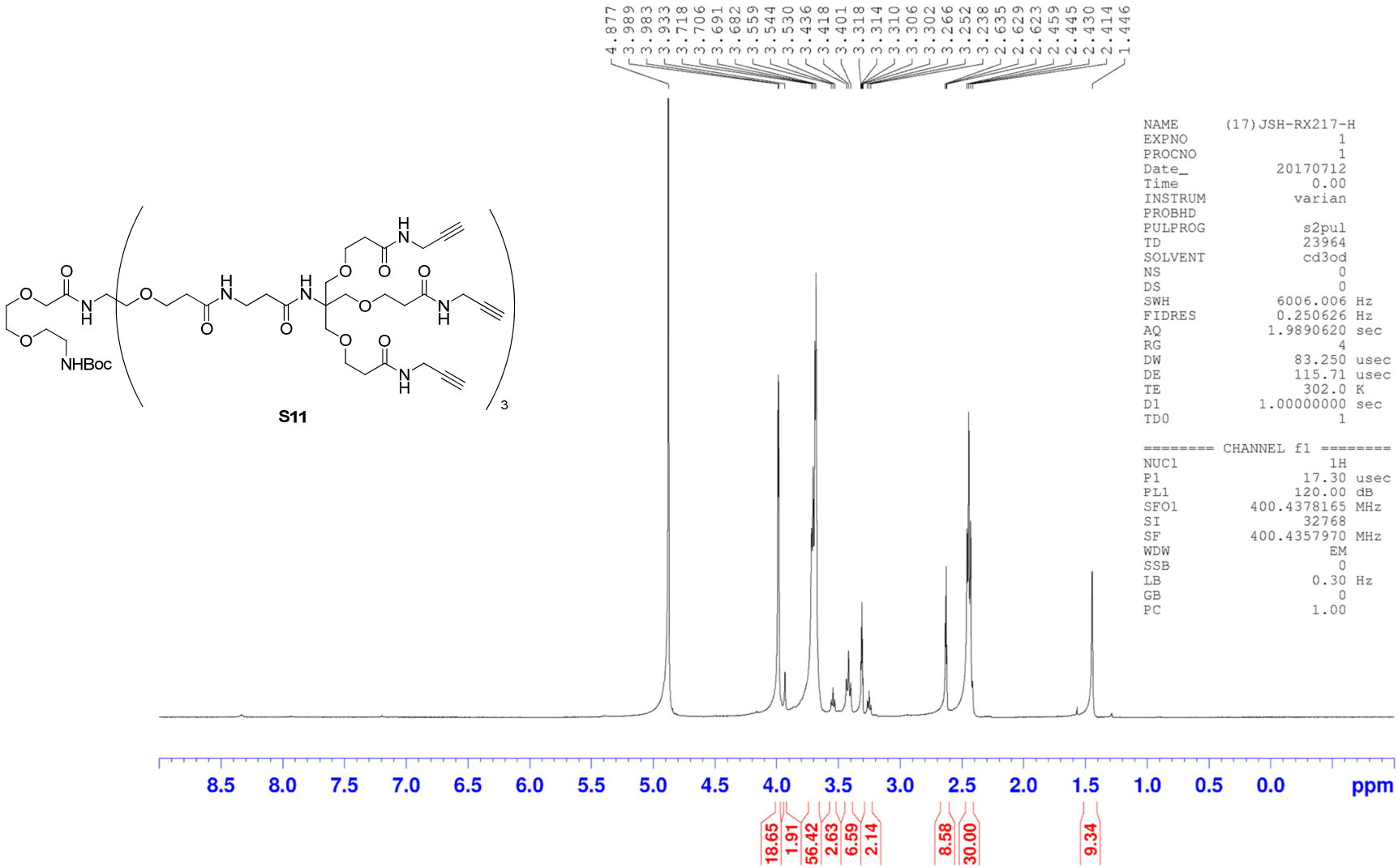
^{13}C NMR spectra of **S9** (100.7 MHz, $CDCl_3$)



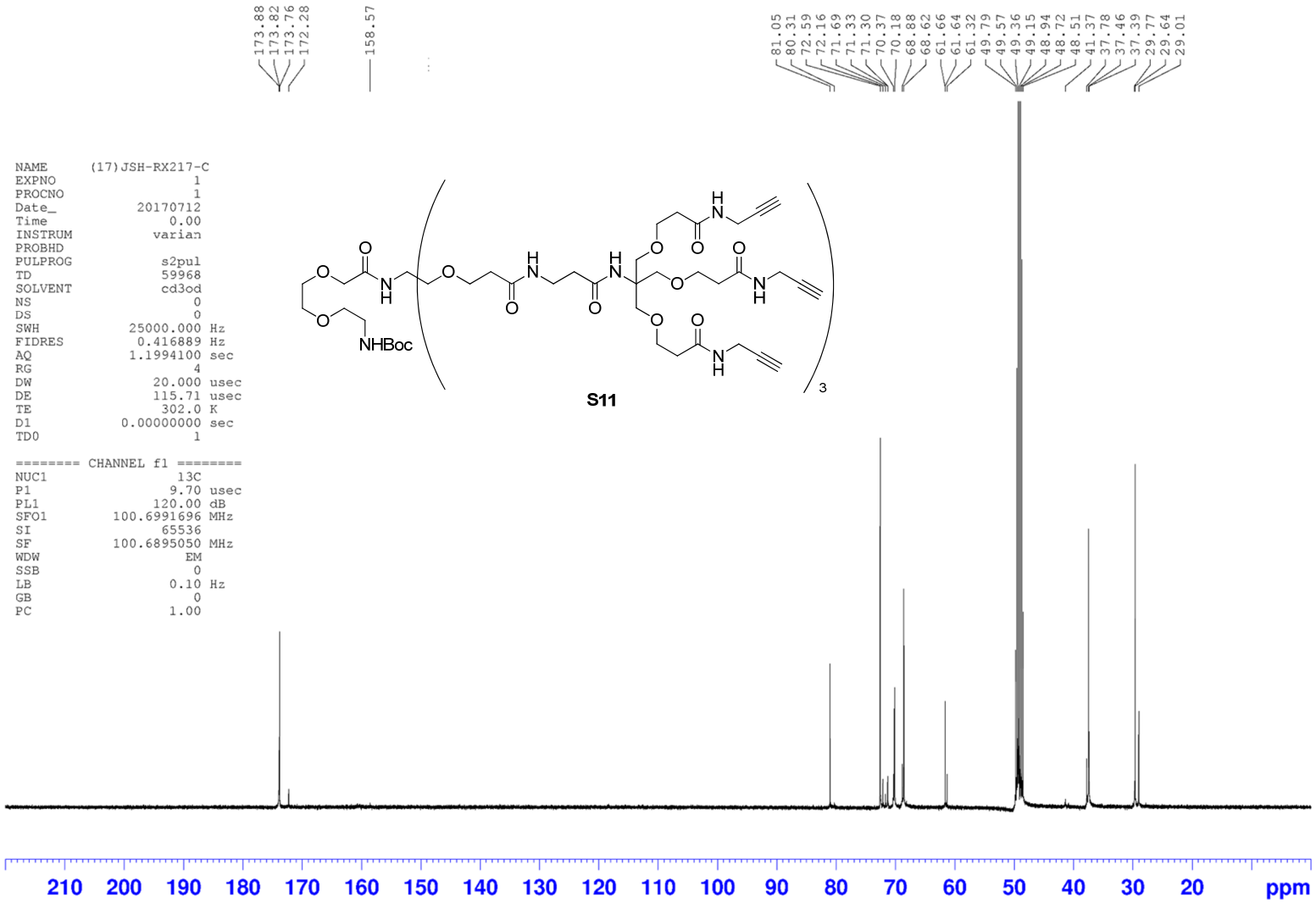
^{1}H NMR spectra of **S10** (400 MHz, CD_3OD)



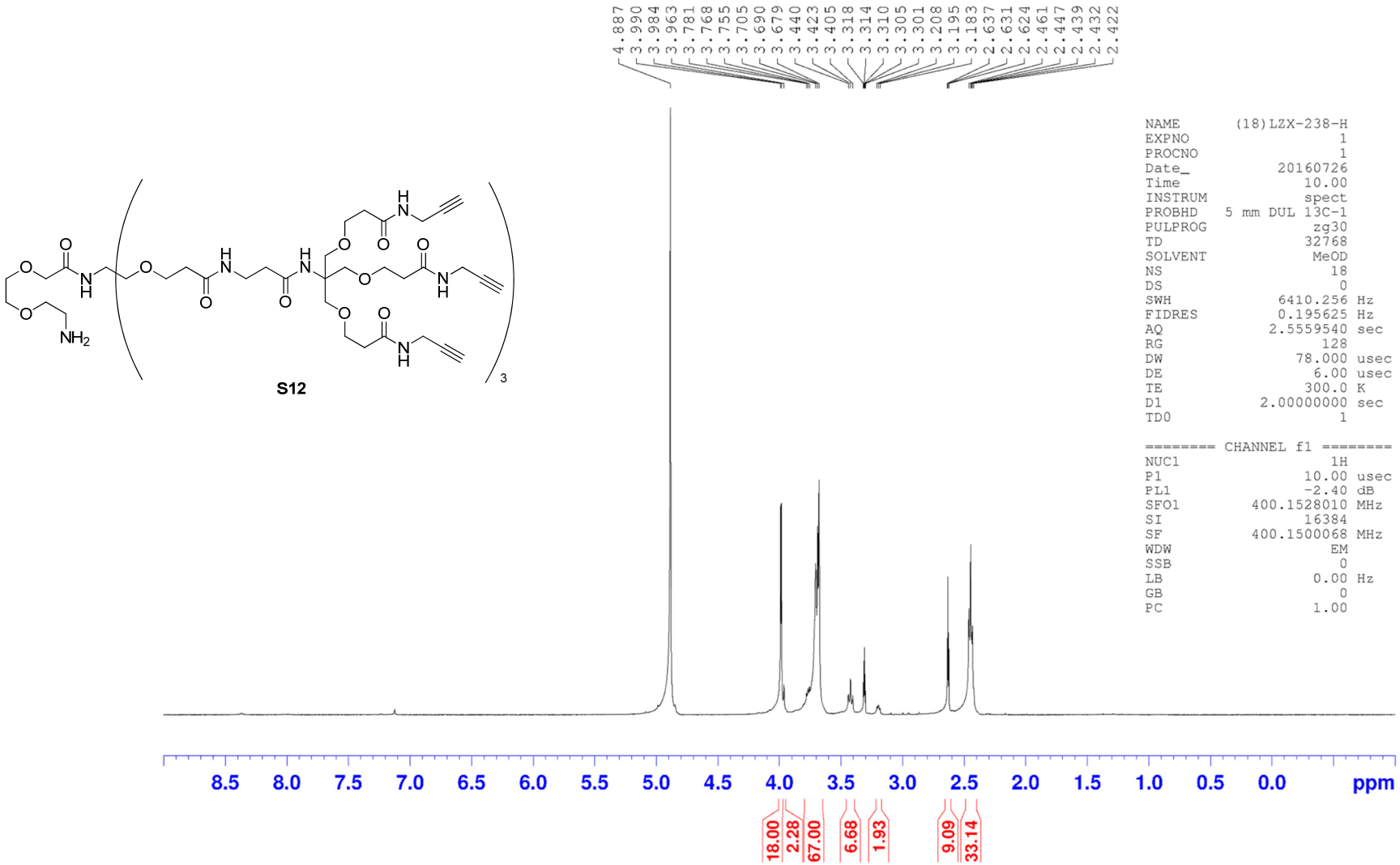
^{13}C NMR spectra of **S10** (100.7 MHz, CD_3OD)



^{1}H NMR spectra of **S11** (400 MHz, CD_3OD)

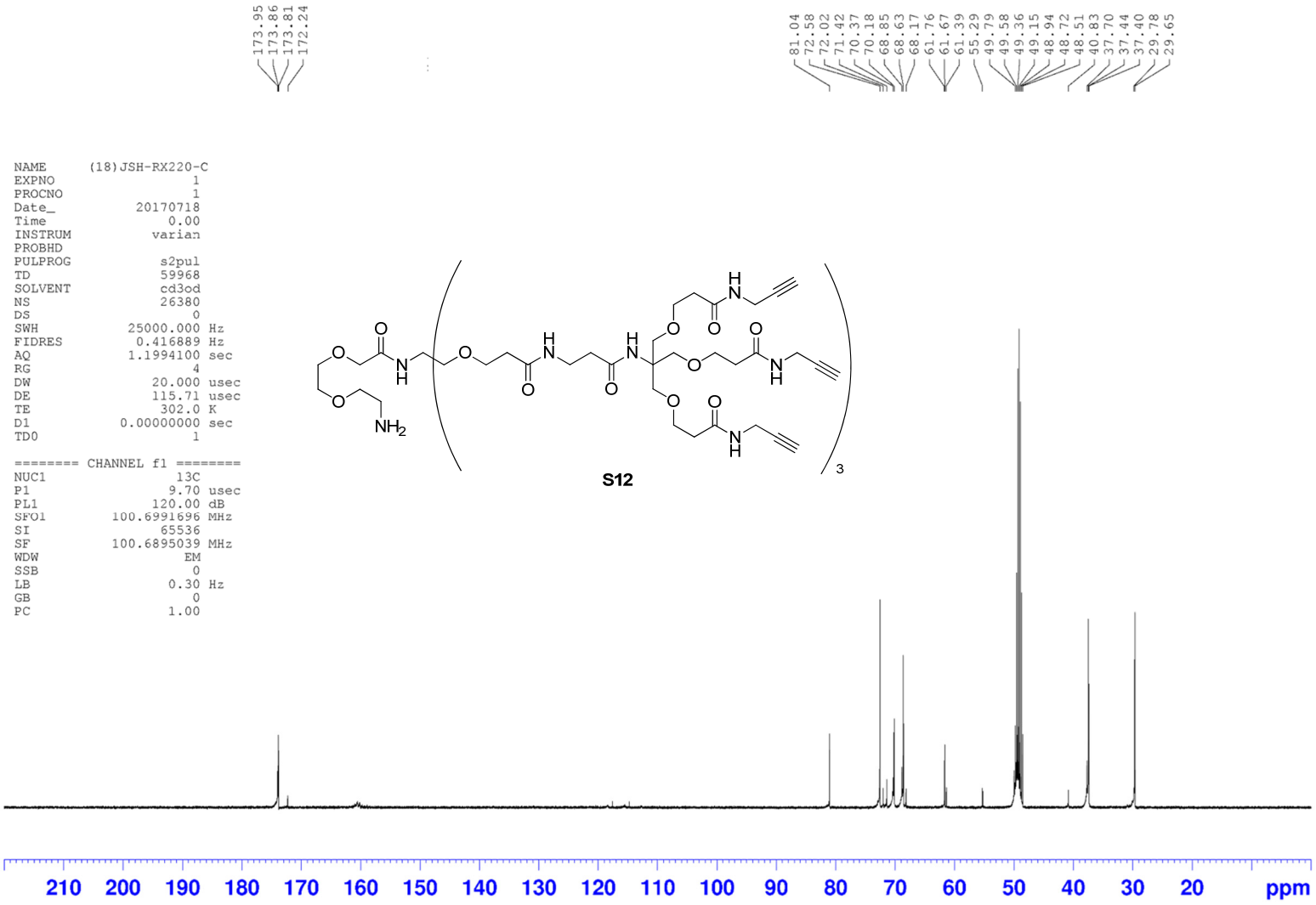


^{13}C NMR spectra of **S11** (100.7 MHz, CD_3OD)

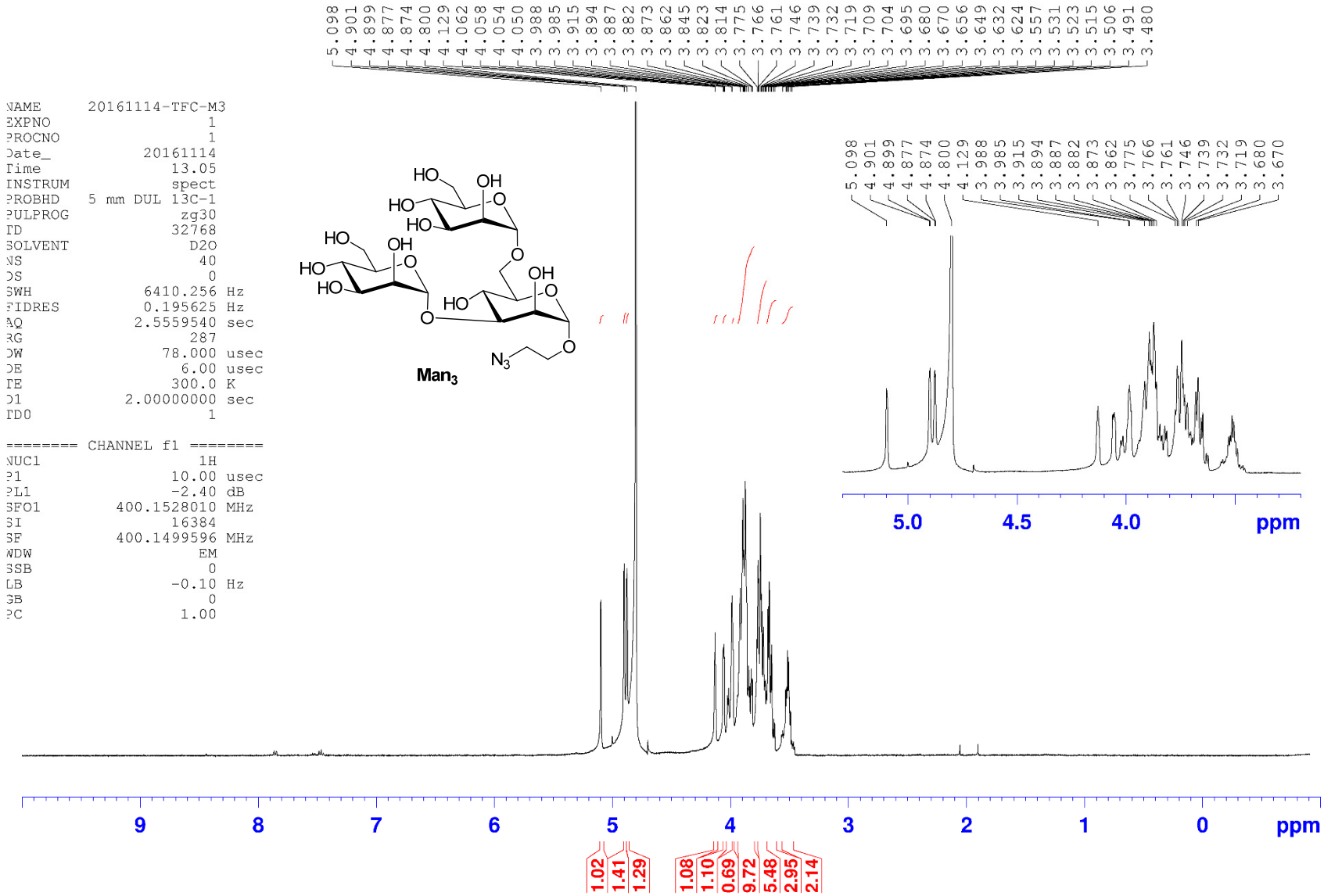


S12

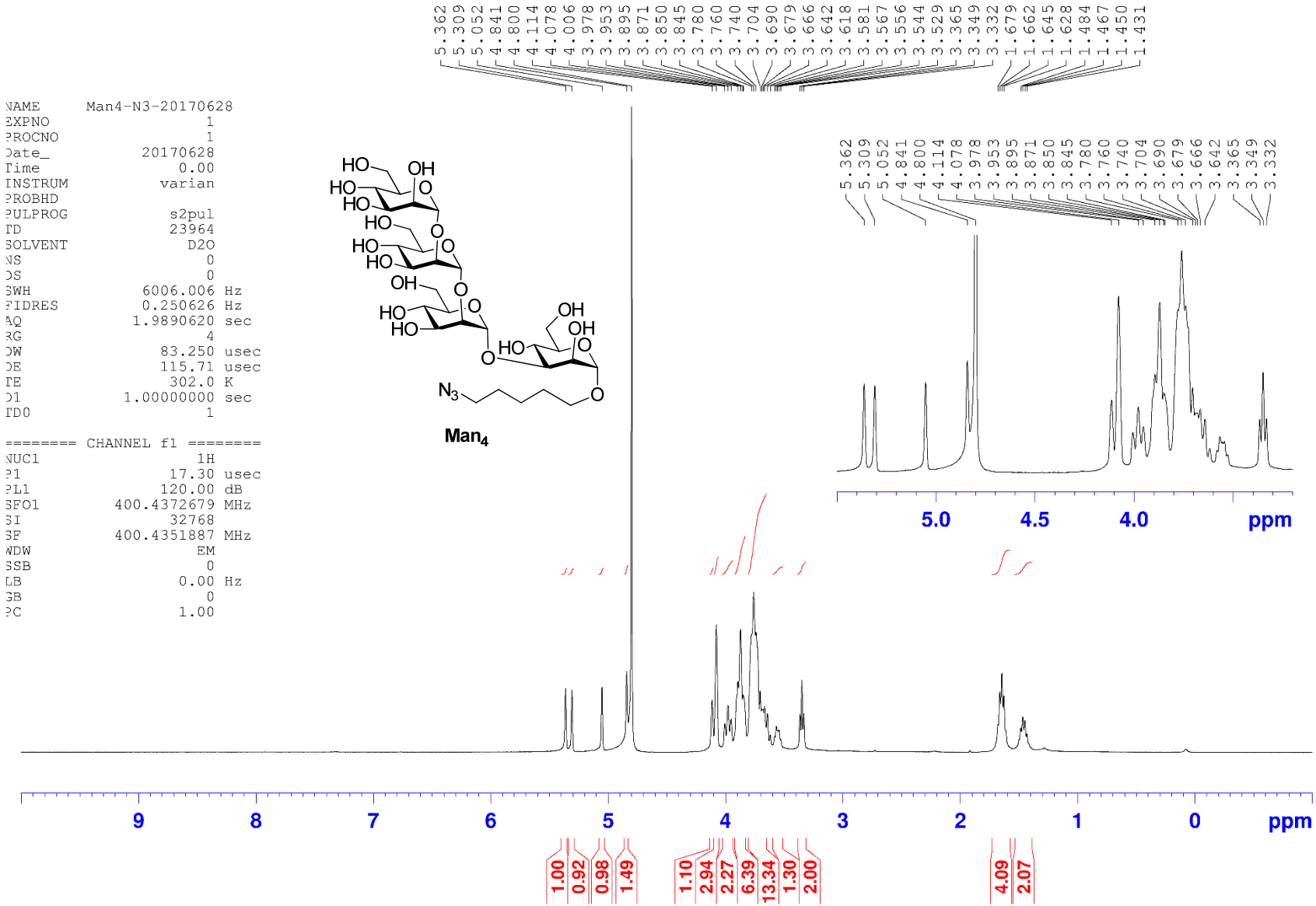
^{1}H NMR spectra of **S12** (400 MHz, CD_3OD)



^{13}C NMR spectra of **S12** (100.7 MHz, CD_3OD)



^{1}H NMR spectra of **Man$_3$** (400 MHz, D_2O)



^{1}H NMR spectra of **Man$_4$** (400 MHz, D_2O)