Synthesis and Structural Characterization of Sialic Acid-Glutamic Acid Hybrid Foldamers as Conformational Surrogates of α-2,8-Linked Polysialic Acid

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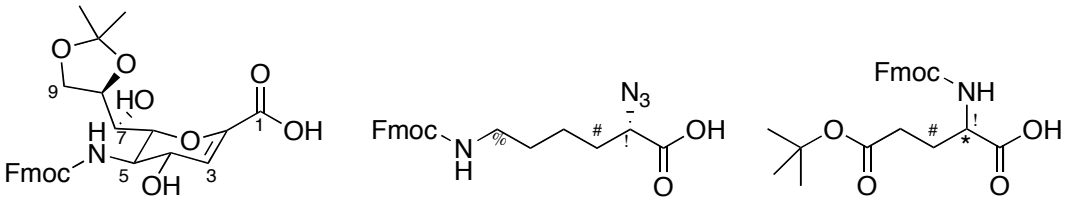
Supporting Information

General Experimental Section. NMR spectra were recorded on 400 and 600 MHz NMR spectrometers. Chemical shifts were referenced to residual $CHCl_3$ (δ_H = 7.26), CHD_2OD (δ_H = 3.30), $(CHD_2)_2CO$ (δ_H = 2. 05), $CDCl_3$ (δ_C = 77.1), CD_3OD, (δ_C = 49.0) or $(CD_3)_2CO$ (δ_C = 39.0). Solutions in D_2O were referenced to dioxane calibrated to TSP. Low-resolution mass spectra were obtained using a QTRAP mass spectrometer. High Resolution mass spectra were recorded at the UC Davis Molecular Structure Facility using MALDI-TOF with internal calibration. Infrared spectra were recorded on an ATR-FTIR spectrometer. Microwave-assisted SPPS was done using a commercial microwave reactor. Rink amide resin, *N*-acetylneuraminic acid, and Fmoc-Glu(OBut)-OH, and *N*-acetylneuraminic acid were obtained from commercial sources. Reagents were used as received unless otherwise indicated. Solution phase reactions were monitored by TLC using Si gel 60 F254 or RP-C_{18} glass-backed plate.

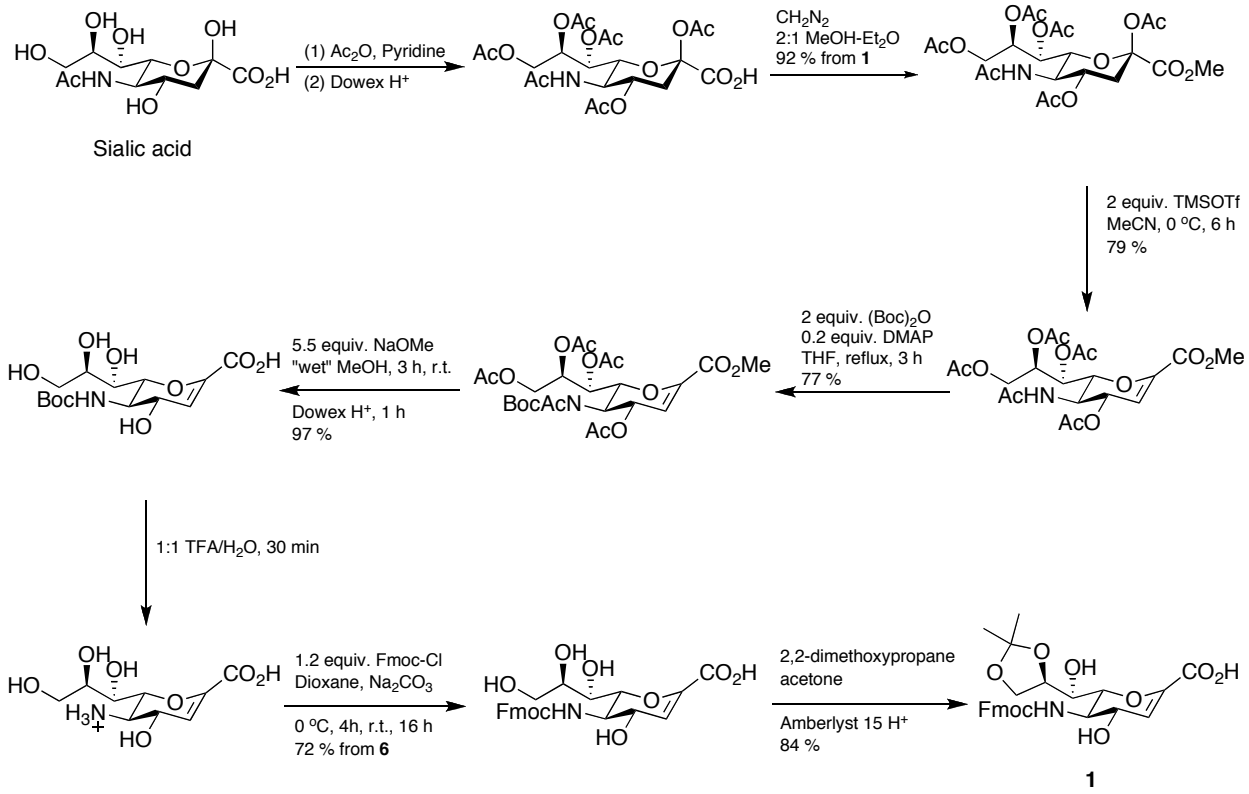
Amino acids used for constructing the α/δ hybrid peptides



Neu2en N_3Lys Glu

Synthesis of Sialic Acid Derivative Fmoc-Neu2en (1)

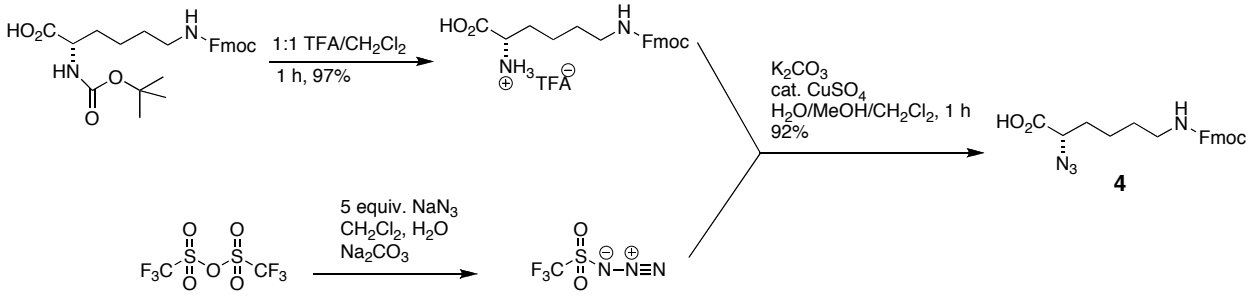
N-(9-fluorenylmethoxycarbonyl)-2,3-dehydro-8,9-isopropylidene neuraminic acid **1** (Fmoc-Neu2en) was synthesized following our previous method[1] with slight modification to furnish an overall yield of 32% in eight steps Scheme 1.



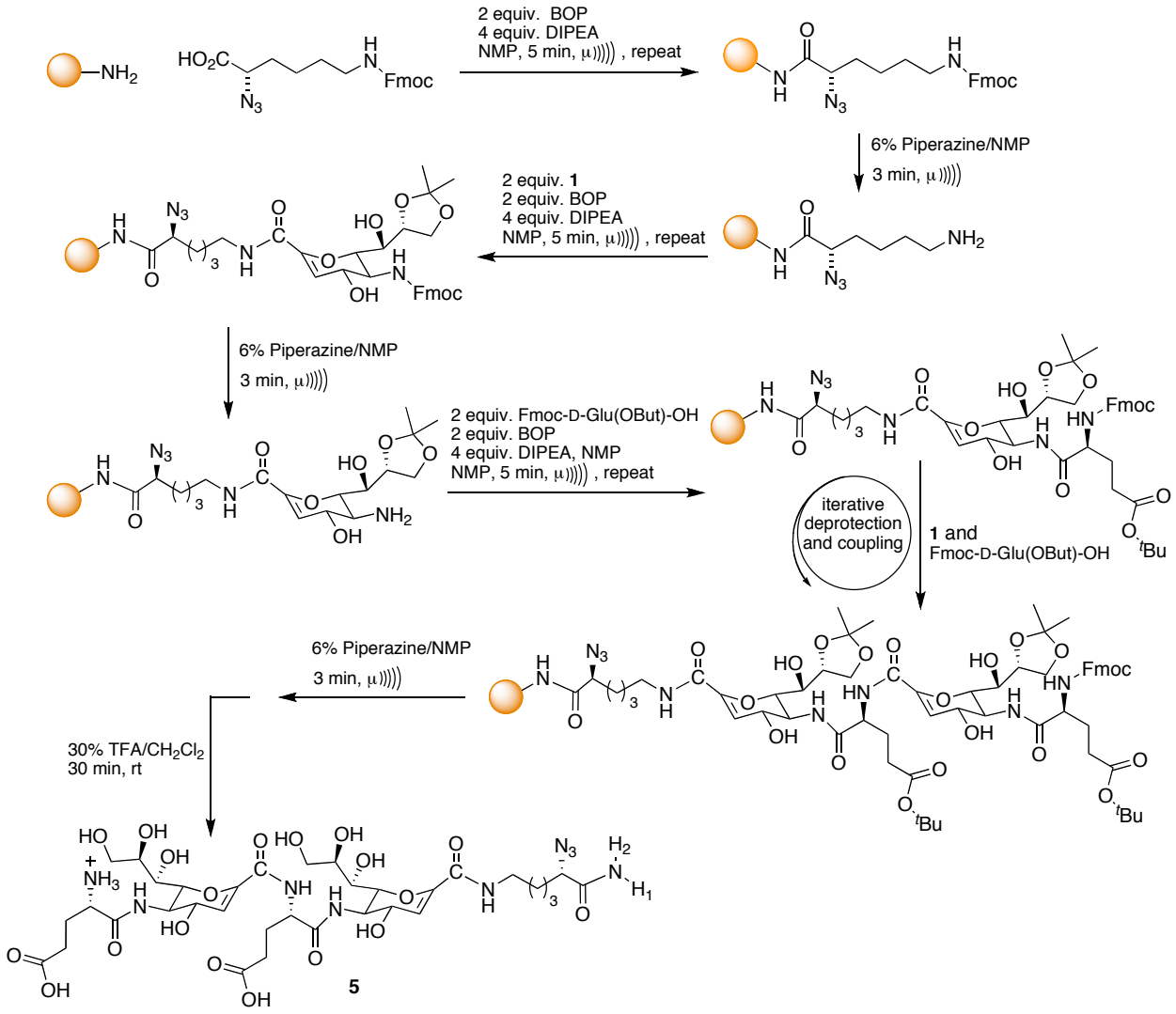
Scheme S1. Synthetic scheme for **1.**

Synthesis of Azidolysine Linker (4)

Compound **4** (N_3Lys) was prepared following the method developed by Wong,[2] and adopted by others.[3] The cude product was concentrated to dryness, and chromatographed through a column of silica gel using 85:15 CH_2Cl_2-MeOH to yield **4** (2.07 g, 92%) as shown in Scheme 2.

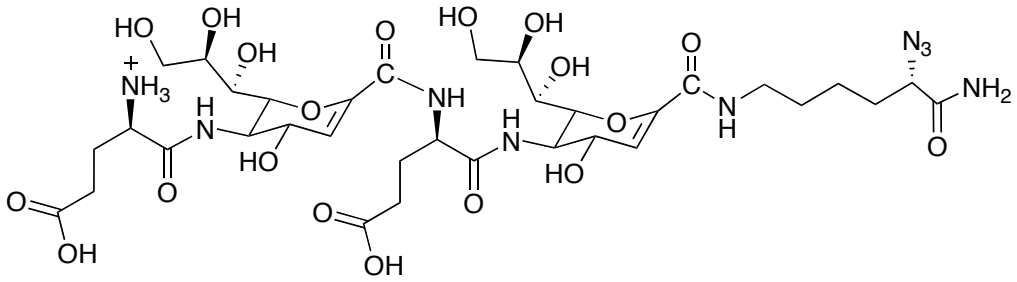


Scheme S2. Synthetic scheme for **4.**

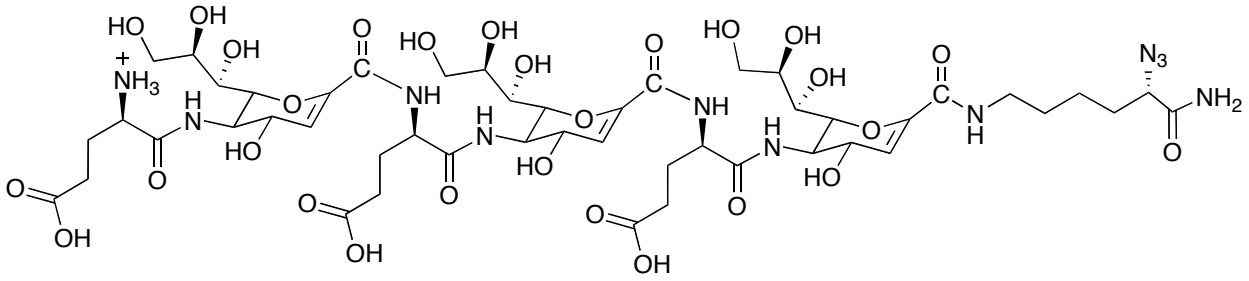


Scheme S3. Representative microwave-assisted solid phase peptide synthesis.

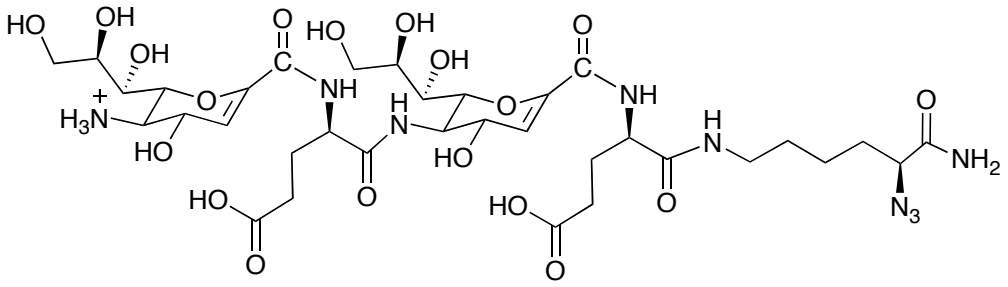
Assignments of H for each oligomer are based upon the following sytem: **HX-Y**, which refers to **H** in position **X** at residue number **Y** counting from the *N*-terminus.



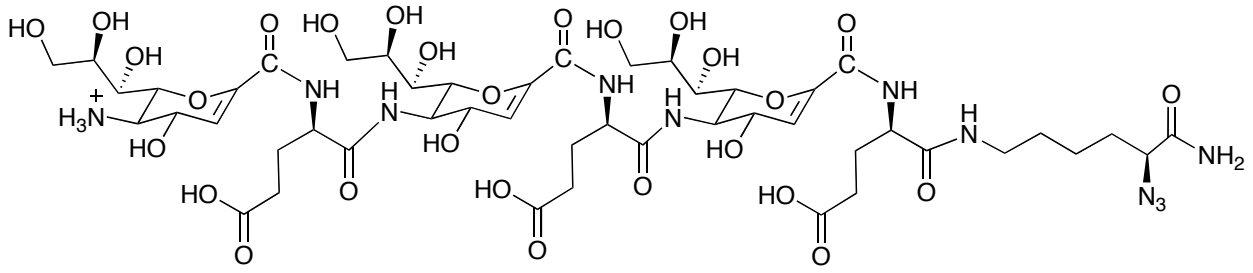
Neu2en/D-Glu-4 (5): obtained in 27% purified yield. ^{1}H NMR (D_2O, 600 MHz): d 5.91 (d, 1H, *J* = 3.0 Hz, H3-2), 5.82 (d, 1H, *J* = 3.0 Hz, H3-4), 4.57 (dd, 1H, *J* = 7.2, 2.4 Hz, H4-2), 4.55 (dd, 1H, *J* = 7.2, 2.4 Hz, H3-4), 4.54 (dd, 1H, *J* = 7.2, 4.8 Hz, Hα-3), 4.48 (dd, 1H, *J* = 10.8, 0.6 Hz, H6-2), 4.39 (dd, 1H, *J* = 10.8, 0.6 Hz, H6-4), 4.24 (dd, 1H, *J* = 10.8, 9.0 Hz, H5-2), 4.16 (dd, 1H, *J* = 10.8, 8.4 Hz, H5-2), 4.15 (dd, 1H, *J* = 4.8, 2.4 Hz, Hα-5), 4.14 (dd, 1H, *J* = 4.8, 2.4 Hz, Hα-2), 4.00 (ddd, 1H, *J* = 9.6, 5.4, 2.4 Hz, H8-2), 3.92-3.88 (m, 3H, H8-4, H9/9'-2), 3.71 (dd, 1H, *J* = 6.0, 6.0 Hz, H9'-4), 3.69 (dd, 1H, *J* = 3.0, 3.0 Hz, H7-2), 3.67 (dd, 1H, *J* = 6.0, 6.0 Hz, H9-4), 3.62 (d, 1H, *J* = 9.0 Hz, H7-4), 3.37-3.28 (m, 2H, Hε-5), 2.62-2.49 (m, 4H, Hγ-1/3), 2.28-2.09 (m, 4H, Hβ-1/3), 1.90-1.78 (m, 2H, Hβ-5), 1.66-1.58 (m, 2H, Hδ-5), 1.44 (p, 2H, *J* = 7.8 Hz, Hγ-5). ^{13}C NMR (D_2O, 150 MHz): d 180.2, 179.3, 178.3, 176.2, 172.8, 166.4, 148.7, 148.0, 111.7, 110.9, 78.8, 72.7, 70.7, 70.2, 69.8, 65.8, 65.7, 56.5, 55.9, 55.8, 52.8 42.0, 33.6, 33.1, 32.6, 30.6, 29.1, 24.8. MALDI-TOFMS: [M + Na^+] calcd for $C_{34}H_{53}N_9O_{19}Na^+$, 914.3350; found, 914.3400.



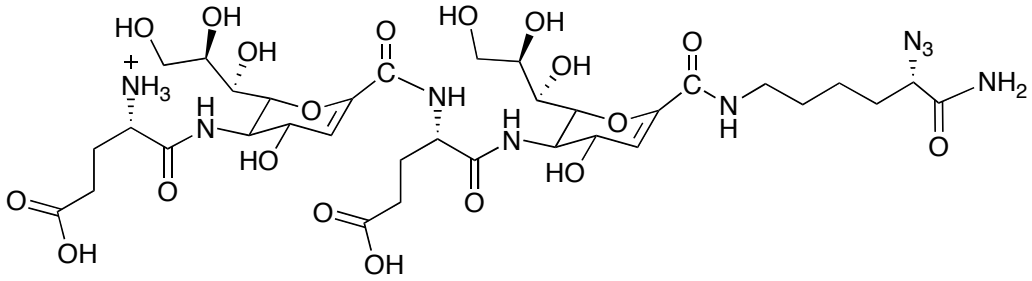
Neu2en/D-Glu-6 (6): obtained in 39% purified yield. ^{1}H NMR (D_2O, 600 MHz): d 5.91 (d, 1H, *J* = 2.4 Hz, H3-2), 5.89 (d, 1H, *J* = 2.4 Hz, H3-4), 5.82 (d, 1H, *J* = 1.8 Hz, H3-6), 4.57-4.51 (m, 5H, H4-6, Hα-5, H4-4, Hα-3, H4-2), 4.48 (dd, 1H, *J* = 10.8, 1.2 Hz, H6-2), 4.43 (dd, 1H, *J* = 10.8, 1.2 Hz, H6-4), 4.38 (dd, 1H, *J* = 10.8, 1.2 Hz, H6-6), 4.24 (dd, 1H, *J* = 10.8, 9.0 Hz, H5-2), 4.20-4.18 (m, 1H, H5-4), 4.15 (dd, 1H, *J* = 9.0, 1.8 Hz, H5-6), 4.14 (t, 1H, *J* = 5.4 Hz, Hα-7), 4.14-4.12 (m, 1H, Hα-1), 4.01-3.96 (m, 3H, H8-2/4), 3.91-3.85 (m, 5H, H8-6, H9-2/4), 3.72-3.61 (m, 5H, H7-6, H9-6, H7-4, H7-2), 3.37-3.28 (m, 2H, Hε-7), 2.58-2.47 (m, 6H, Hγ-1/3/5), 2.27-2.09 (m, 6H, Hβ-1/3/5), 1.88-1.78 (m, 2H, Hβ-7), 1.61 (p, 2H, *J* = 6.6 Hz, Hδ-7), 1.44 (p, 2H, *J* = 7.8 Hz, Hγ-7). ^{13}C NMR (D_2O, 150 MHz): d 180.7, 180.4, 179.9, 178.4, 176.5, 172.7, 166.6, 166.0, 148.6, 148.0, 111.9, 111.7, 110.9, 79.0, 78.9, 72.9, 72.8, 70.8, 70.7, 69.7, 69.6, 65.9, 65.8, 65.7, 56.6, 55.8, 52.9, 52.8, 41.9, 33.8, 33.4, 33.0, 30.7, 29.4, 29.3, 24.8. MALDI-TOFMS: [M + Na^+] calcd for $C_{48}H_{73}N_{11}O_{28}Na^+$, 1274.4518; found, 1274.452.



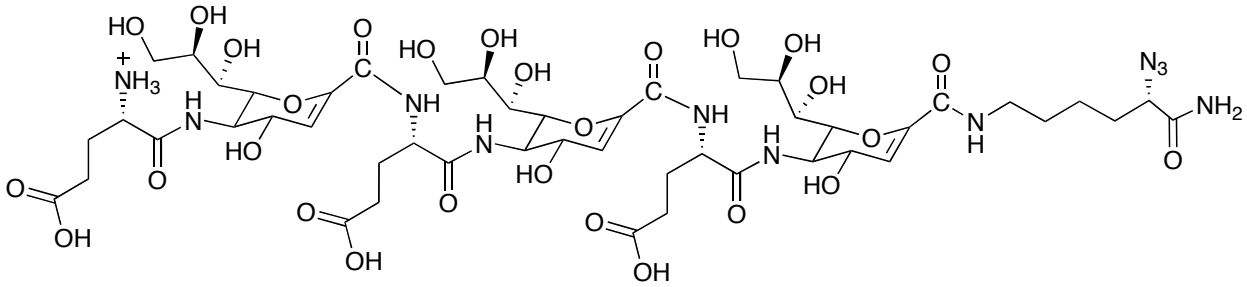
D-Glu/Neu2en-4 (7): obtained in 39% purified yield. ^{1}H NMR (D_2O, 600 MHz): d 5.97 (d, 1H, *J* = 2.4 Hz, H3-1), 5.90 (d, 1H, *J* = 2.4 Hz, H3-3), 4.66 (dd, 1H, *J* = 8.4, 3.0 Hz, H4-1), 4.65 (dd, 1H, *J* = 10.2, 1.8 Hz, H6-1), 4.58 (dd, 2H, *J* = 9.0, 2.4 Hz, H4-3, Hα-2), 4.45 (dd, 1H, *J* = 10.8, 0.6 Hz, H6-3), 4.43 (dd, 1H, *J* = 9.0, 5.4 Hz, Hα-4), 4.20 (dd, 1H, *J* = 10.8, 9.0 Hz, H5-3), 4.15 (dd, 1H, *J* = 7.2, 5.4 Hz, Hα-5), 4.08 (ddd, 1H, *J* = 9.0, 5.4, 2.4 Hz, H8-1), 4.00 (ddd, 1H, *J* = 9.6, 6.0, 2.4 Hz, H8-3), 3.94 (dd, 1H, *J* = 12.0, 2.4 Hz, H9'-1), 3.92 (dd, 1H, *J* = 10.8, 2.4 Hz, H7-1), 3.91 (dd, 1H, *J* = 9.0, 1.8 Hz, H9-3), 3.71 (dd, 1H, *J* = 12.0, 6.0 Hz, H9'-3), 3.66 (dd, 1H, *J* = 9.6, 1.2 Hz, H7-3), 3.65 (dd, 1H, *J* = 10.2, 8.4 Hz, H5-1), 3.31-3.22 (m, 2H, Hε-5), 2.60-2.48 (m, 4H, Hγ-2/4), 2.30-2.06 (m, 4H, Hβ-2/4), 1.91-1.77 (m, 2H, Hβ-5), 1.64-1.52 (m, 2H, Hδ-5), 1.44 (p, 2H, *J* = 7.2 Hz, Hγ-5). ^{13}C NMR (D_2O, 150 MHz): d 180.3, 180.2, 178.4, 176.3, 175.7, 166.4, 166.0, 145.0, 111.8, 111.0, 79.0, 77.9, 72.9, 72.8, 70.8, 70.6, 69.7, 67.6, 66.0, 65.8, 65.5, 56.6, 56.4, 53.7, 52.9, 41.8, 33.8, 33.1, 30.8, 29.2, 24.8. MALDI-TOFMS: [M + Na^+] calcd for $C_{34}H_{53}N_9O_{19}Na^+$, 914.3350; found, 914.3410.



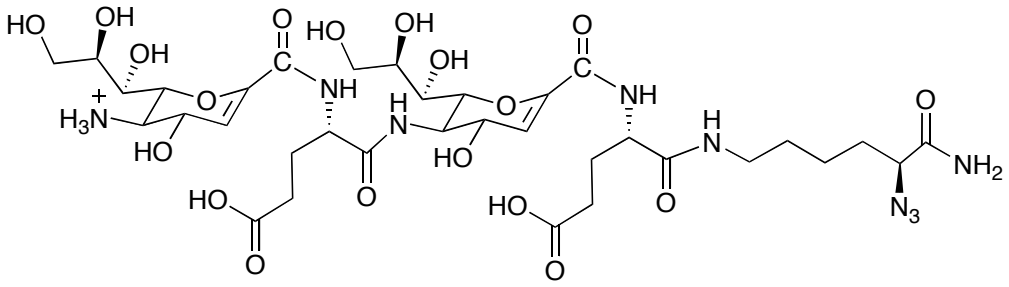
D-Glu/Neu2en-6 (8): obtained in 24% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 5.98 (d, 1H, *J* = 2.4 Hz, H3-1), 5.92 (d, 1H, *J* = 2.4 Hz, H3-3), 5.90 (d, 1H, *J* = 2.4 Hz, H3-5), 4.67 (dd, 1H, *J* = 6.6, 2.4 Hz, H4-1), 4.66 (dd, 1H, *J* = 7.8, 2.4 Hz, H6-1), 4.59 (dd, 2H, *J* = 9.0, 2.4 Hz, H4-3/5), 4.58 (dd, 1H, *J* = 9.0, 4.8 Hz, Hα-2), 4.56 (dd, 1H, *J* = 8.4, 4.2 Hz, Hα-4), 4.47 (dd, 1H, *J* = 7.2, 1.2 Hz, H6-3), 4.45 (dd, 1H, *J* = 7.2, 1.2 Hz, H6-5), 4.42 (dd, 1H, *J* = 9.0, 5.4 Hz, Hα-6), 4.22 (dd, 1H, *J* = 9.0, 4.8 Hz, H5-3), 4.20 (dd, 1H, *J* = 8.4, 4.2 Hz, H5-5), 4.16 (dd, 1H, *J* = 7.8, 5.4 Hz, Hα-7), 4.07 (ddd, 1H, *J* = 9.0, 5.4, 3.0 Hz, H8-1), 4.03-3.99 (m, 2H, H8-3/5), 3.95 (dd, 1H, *J* = 12.0, 3.0 Hz, H9'-1), 3.93 (dd, 2H, *J* = 11.4, 2.4 Hz, H9'-3/5),), 3.92 (dd, 1H, *J* = 8.4, 1.8 Hz, H7-1),), 3.80 (dd, 1H, *J* = 12.6, 6.0 Hz, H9-1), 3.73 (dd, 1H, *J* = 6.6, 1.8 Hz, H9-3), 3.71 (dd, 1H, *J* = 7.8, 1.8 Hz, H9-5), 3.67 (dd, 1H, *J* = 9.0, 1.2 Hz, H7-3), 3.66 (dd, 1H, *J* = 9.0, 1.2 Hz, H5-5), 3.32-3.22 (m, 2H, Hε-7), 2.60-2.49 (m, 6H, Hγ-2/4/6), 2.31-2.07 (m, 6H, Hβ- 2/4/6), 1.91-1.78 (m, 2H, Hβ-7), 1.63-1.56 (m, 2H, Hδ-7), 1.44 (p, 2H, *J* = 7.8 Hz, Hγ-7). ^{13}C NMR (D_2O, 150 MHz): δ 180.3, 178.3, 176.2, 175.6, 166.2, 166.1, 165.8, 148.1, 148.0, 111.8, 110.9, 79.0, 77.8, 72.9, 72.6, 70.7, 70.5, 69.6, 67.5, 65.9, 65.8, 65.4, 56.5, 53.7, 52.7, 41.8, 33.7, 33.3, 30.7, 29.3, 24.8. MALDI-TOFMS: [M + Na^+] calcd for $C_{48}H_{73}N_{11}O_{28}Na^+$, 1274.4518; found, 1274.452.



Neu2en/L-Glu-4 (9): obtained in 28% purified yield. ^{1}H NMR (D_2O, 600 MHz): d 5.89 (d, 1H, *J* = 2.4 Hz, H3-2), 5.83 (d, 1H, *J* = 1.8 Hz, H3-4), 4.53 (dd, 1H, *J* = 9.0, 2.4 Hz, H4-2), 4.52 (dd, 1H, *J* = 9.0, 2.4 Hz, H4-4), 4.49 (dd, 1H, *J* = 9.0, 5.4 Hz, Hα-1), 4.42 (d, 1H, *J* = 10.8 Hz, H6-2), 4.39 (d, 1H, *J* = 10.8 Hz, H6-4), 4.22 (dd, 1H, *J* = 10.8, 9.0 Hz, H5-2), 4.16-4.12 (m, 2H, Hα-5, H5-4), 4.11 (m, 1H, Hα-3), 4.00 (ddd, 1H, *J* = 9.6, 5.4, 2.4 Hz, H8-2), 3.96-3.86 (m, 2H, H8-4, H9'-2), 3.72 (d, 1H, *J* = 10.2 Hz, H7-2), 3.70-3.69 (m, 2H, H9-2/4), 3.68 (d, 1H, *J* = 10.8 Hz, H7-4), 3.38-3.28 (m, 2H, Hε-5), 2.66-2.51 (m, 4H, Hγ-1/3), 2.35-2.10 (m, 4H, Hβ-1/3), 1.89-1.77 (m, 2H, Hβ-5), 1.65-1.57 (m, 2H, Hδ-5), 1.44 (p, 2H, *J* = 7.8 Hz, Hγ-5). ^{13}C NMR (D_2O, 150 MHz): d 180.0, 179.0, 178.1, 176.2, 172.4, 166.3, 166.1, 148.2, 147.6, 111.8, 110.8, 78.9, 72.7, 72.5, 70.6, 70.5, 69.7, 65.8, 65.7, 56.4, 55.6, 52.9, 41.9, 33.7, 32.8, 32.0, 30.6, 28.9, 24.8. MALDI-TOFMS: [M + Na^+] calcd for $C_{34}H_{53}N_9O_{19}Na^+$, 914.3350; found, 914.3320.

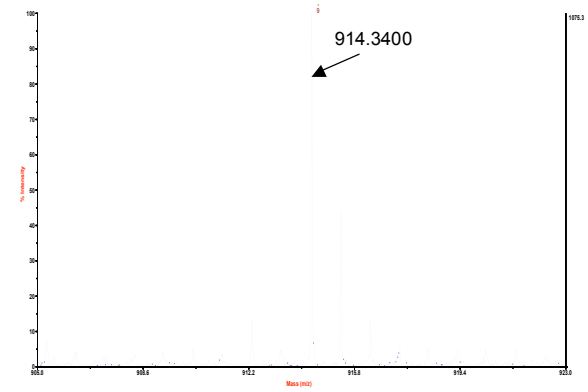


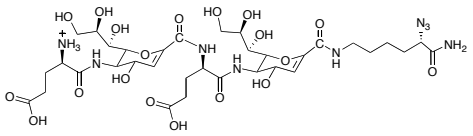
Neu2en/L-Glu-6 (10): obtained in 15% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 5.88 (d, 1H, *J* = 2.4 Hz, H3-2), 5.87 (d, 1H, *J* = 2.4 Hz, H3-4), 5.82 (d, 1H, *J* = 2.4 Hz, H3-6), 4.54 (dd, 3H, 9.0, 3.0 Hz, H4-2/4/6), 4.43-4.37 (m, 5H, H6-6, Hα-5, H6-4, Hα-3, H6-2), 4.22 (dd, 1H, *J* = 10.2, 8.4 Hz, H5-2), 4.17-4.11 (m, 3H, Hα-7, H5-4/6), 4.08 (t, 1H, *J* = 6.6 Hz, Hα-1), 4.01 (ddd, 1H, *J* = 9.0, 5.4, 2.4 Hz, H8-2), 3.97 (ddd, 1H, *J* = 12.0, 6.0, 2.4 Hz, H8-4), 3.92-3.86 (m, 3H, H8-C_a, H9'-2/4), 3.91-3.85 (m, 7H, H7-2/4/6, H9-2/4/6, H9'-6), 3.36-3.28 (m, 2H, Hε-7), 2.45-2.35 (m, 6H, Hγ-1/3/5), 2.18-2.07 (m, 6H, Hβ-1/3/5), 1.78-1.88 (m, 2H, Hβ-7), 1.65-159 (m, 2H, Hδ-7), 1.44 (p, 2H, *J* = 7.8 Hz, Hγ-7). ^{13}C NMR (D_2O, 150 MHz): δ 179.9, 179.8, 178.7, 177.9, 176.0, 172.4, 166.2, 166.1, 166.0, 148.1, 147.4, 111.7, 111.5, 111.0, 78.8, 72.7, 72.5, 70.5, 69.5. 66.5, 65.8, 65.6, 57.1, 56.0, 52.8, 52.7, 41.8, 35.6, 33.7, 30.7, 30.1, 24.8. MALDI-TOFMS: [M + Na^+] calcd for $C_{48}H_{73}N_{11}O_{28}Na^+$, 1274.4518; found, 1274.456.



L-Glu/Neu2en-4 (11): obtained in 24% purified yield. ^{1}H NMR (D_2O, 600 MHz): d 5.96 (d, 1H, *J* = 2.4 Hz, H3-1), 5.91 (d, 1H, *J* = 2.4 Hz, H3-3), 4.67 (dd, 1H, *J* = 8.4, 3.0 Hz, H4-1), 4.64 (dd, 1H, *J* = 9.6, 2.4 Hz, H6-1), 4.57 (dd, 1H, *J* = 9.0, 2.4 Hz, H4-3), 4.52 (dd, 1H, *J* = 8.4, 5.4 Hz, Hα-2), 4.44 (dd, 1H, *J* = 7.2, 4.2 Hz, Hα-4), 4.44 (dd, 1H, *J* = 10.8, 1.2 Hz, H6-3), 4.19 (dd, 1H, *J* = 10.8, 9.0 Hz, H5-3), 4.15 (dd, 1H, *J* = 7.2, 5.4 Hz, Hα-5), 4.08 (ddd, 1H, *J* = 9.0, 6.0, 3.0 Hz, H8-1), 4.00 (ddd, 1H, *J* = 9.0, 6.0, 3.0 Hz, H8-3), 3.94 (dd, 1H, *J* = 12.0, 3.0 Hz, H9'-1), 3.92 (dd, 1H, *J* = 8.4, 1.2 Hz, H7-1), 3.91 (dd, 1H, *J* = 12.0, 3.0 Hz, H9'-3), 3.80 (dd, 1H, *J* = 12.0, 5.4 Hz, H9-1), 3.72 (dd, 1H, *J* = 9.6, 1.2 Hz, H7-3), 3.71 (dd, 1H, *J* = 12.0, 6.0 Hz, H9-3), 3.66 (dd, 1H, *J* = 9.6, 8.4 Hz, H5-1), 3.31-3.22 (m, 2H, Hε-5), 2.57 (dd, 4H, *J* = 7.2, 7.2 Hz, Hγ'-2/4), 2.53 (dd, 4H, *J* = 7.2, 7.2 Hz, Hγ-2/4), 2.28-2.07 (m, 4H, Hβ-2/4), 1.90-1.78 (m, 2H, Hβ-5), 1.64-1.55 (m, 2H, Hδ-5), 1.44 (p, 2H, *J* = 7.8 Hz, Hγ-5). ^{13}C NMR (D_2O, 150 MHz): d 180.3, 180.2, 178.4, 176.5, 175.6, 166.3, 165.9, 148.1, 148.0, 112, 110.9, 79.1, 77.9, 72.8, 72.7, 70.7, 70.5, 69.7, 67.6, 66.0, 65.8, 65.4, 56.4, 56.3, 53.7, 52.8, 41.9, 33.7, 33.0, 30.6, 29.2, 29.0, 24.8. MALDI-TOFMS: [M + Na^+] calcd for $C_{34}H_{53}N_9O_{19}Na^+$, 914.3350; found, 914.3330.

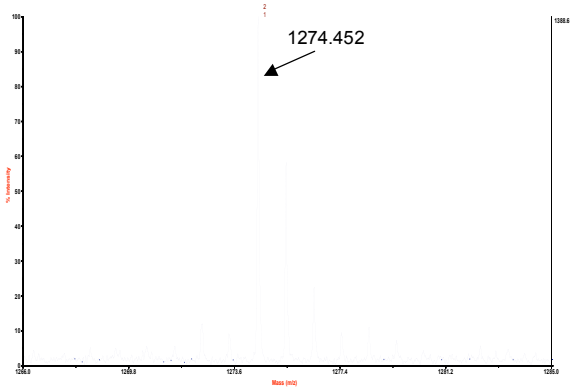
Figure S1. Mass spectra of α/δ-hybrid peptides (**5-12**).

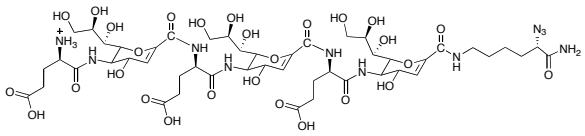




5

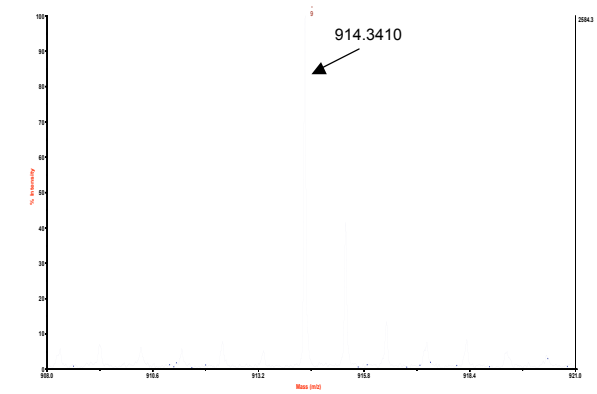
$C_{34}H_{53}N_9O_{19}Na^+$
Found = 914.3400
Theor. = 914.3350

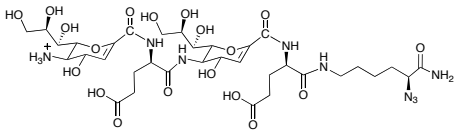




6

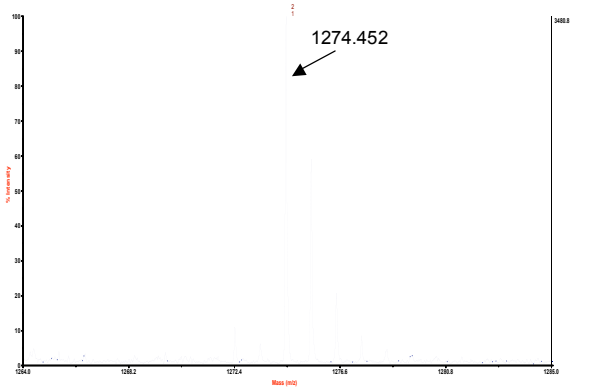
$C_{48}H_{73}N_{11}O_{28}Na^+$
Found = 1274.452
Theor. = 1274.4518

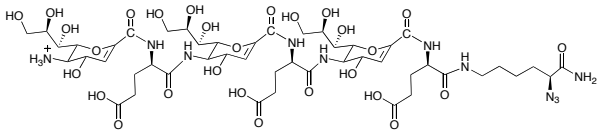




7

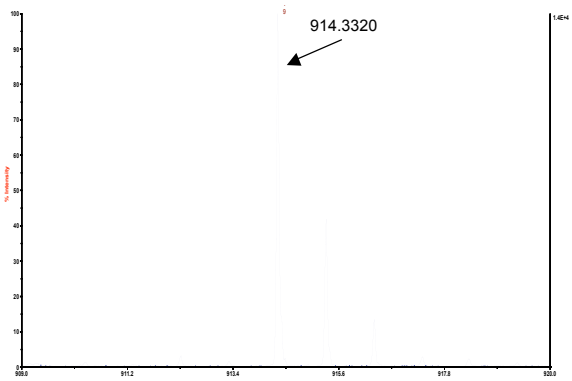
$C_{34}H_{53}N_9O_{19}Na^+$
Found = 914.3410
Theor. = 914.3350

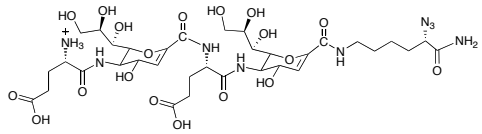




8

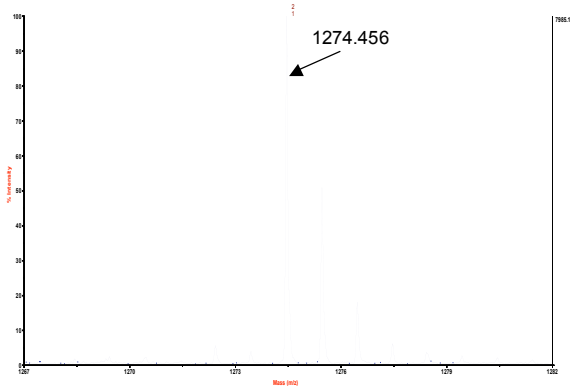
$C_{48}H_{73}N_{11}O_{28}Na^+$
Found = 1274.452
Theor. = 1274.4518

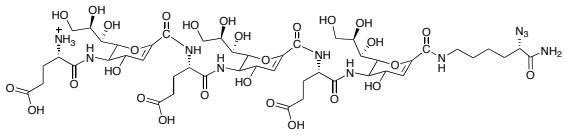




9

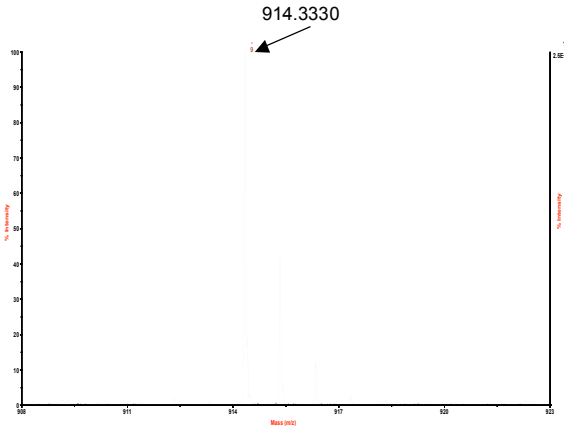
$C_{34}H_{53}N_9O_{19}Na^+$
Found = 914.3320
Theor. = 914.3350

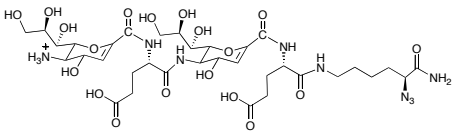




10

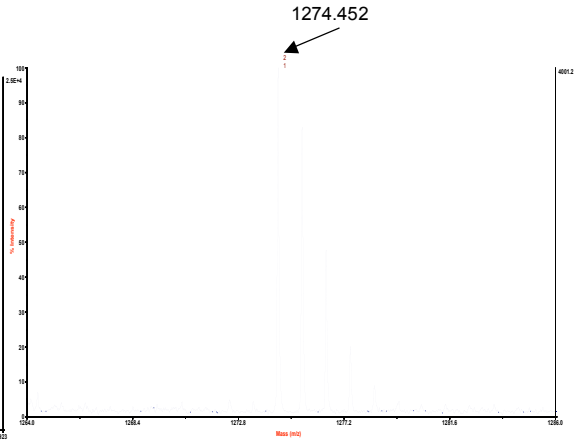
$C_{48}H_{73}N_{11}O_{28}Na^+$
Found = 1274.456
Theor. = 1274.4518

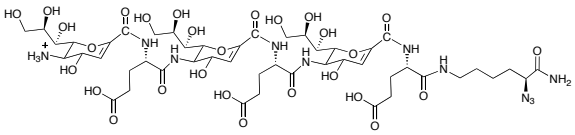




11

$C_{34}H_{53}N_9O_{19}Na^+$
Found = 914.3330
Theor. = 914.3350





12

$C_{48}H_{73}N_{11}O_{28}Na^+$
Found = 1274.452
Theor. = 1274.4518

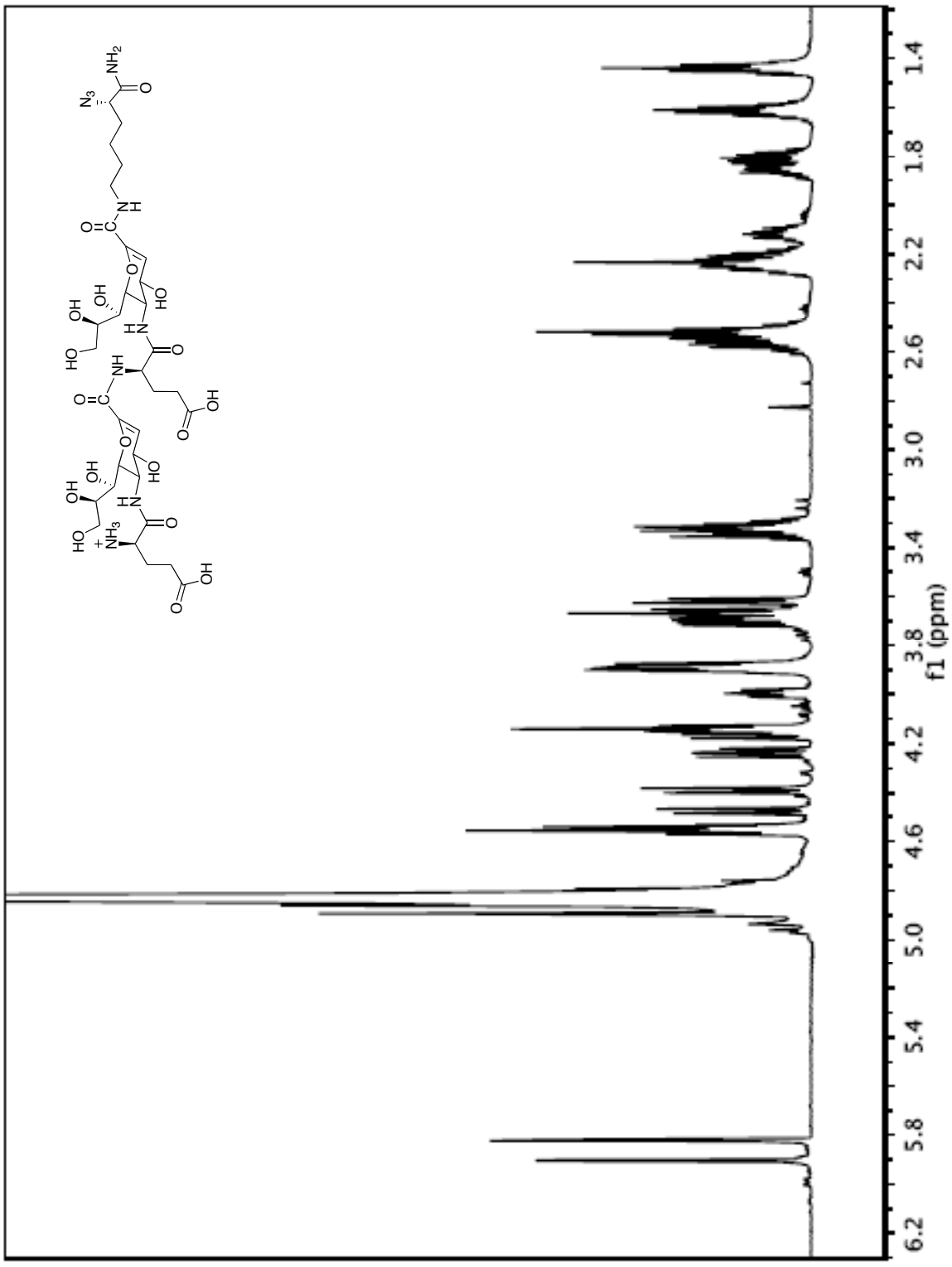


Figure S2. ^{1}H NMR spectrum of α/δ-hybrid peptide **5**.

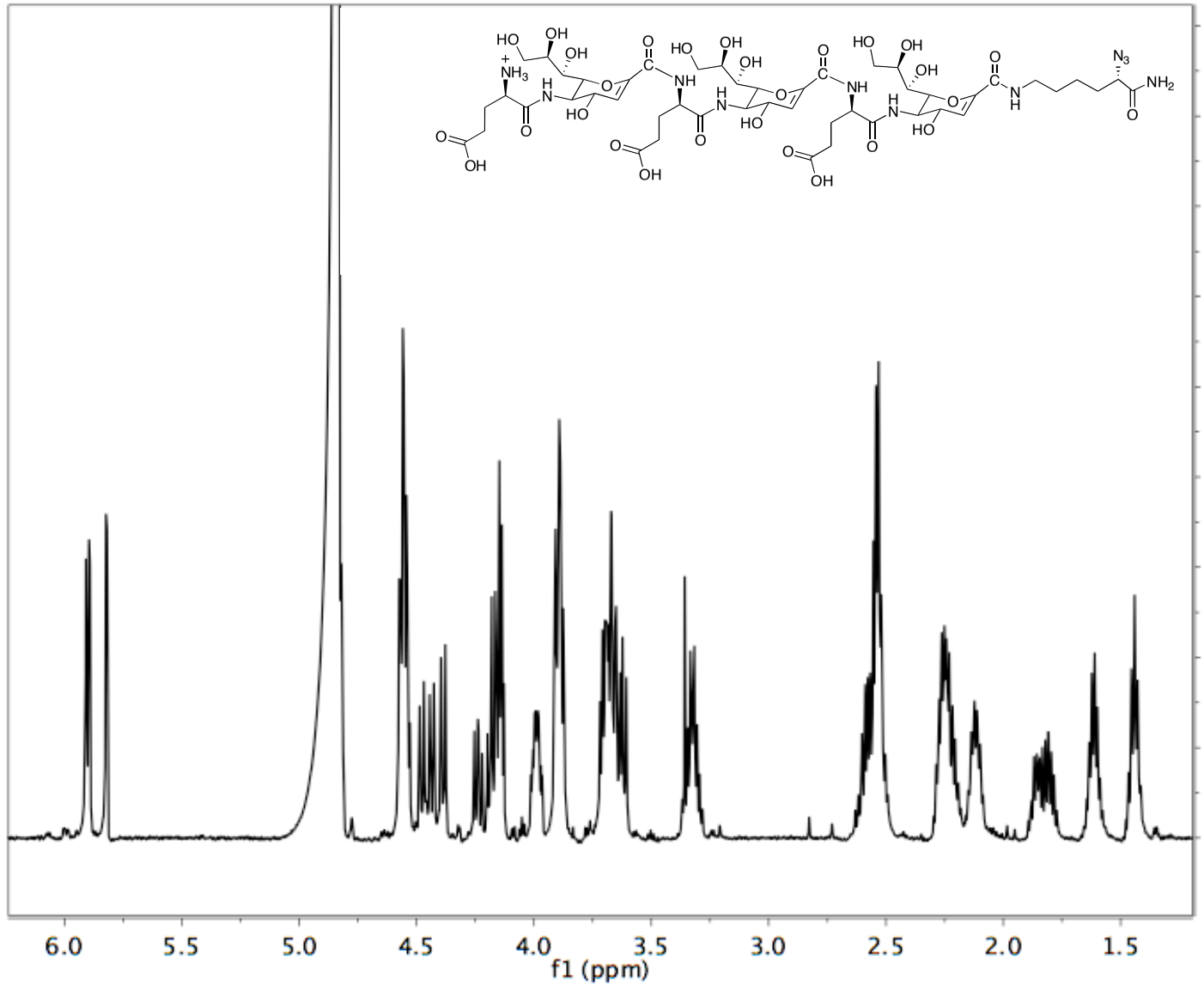


Figure S3. ^{1}H NMR spectrum of α/δ-hybrid peptide **6**.

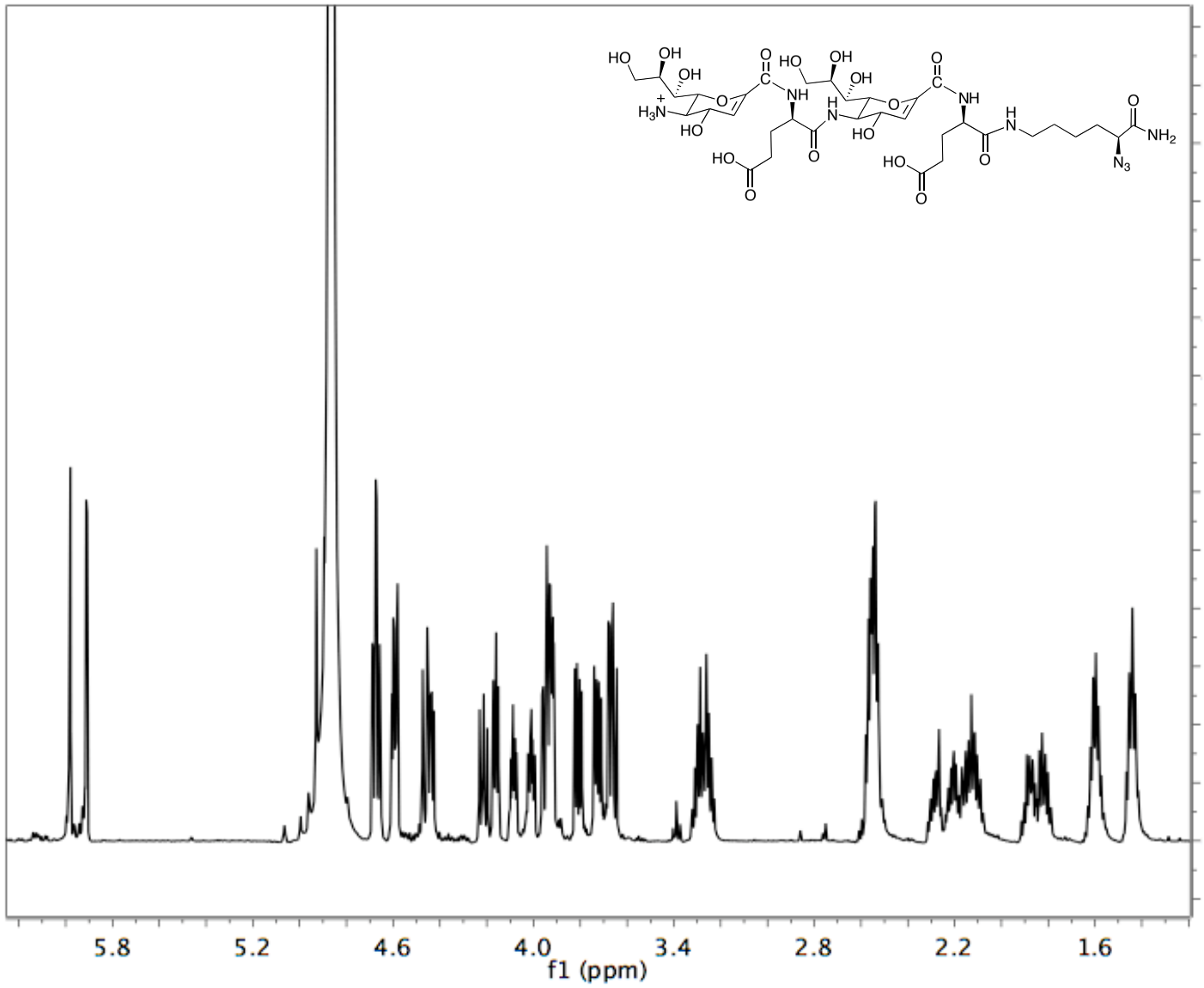


Figure S4. ^{1}H NMR spectrum of α/δ-hybrid peptide **7**.

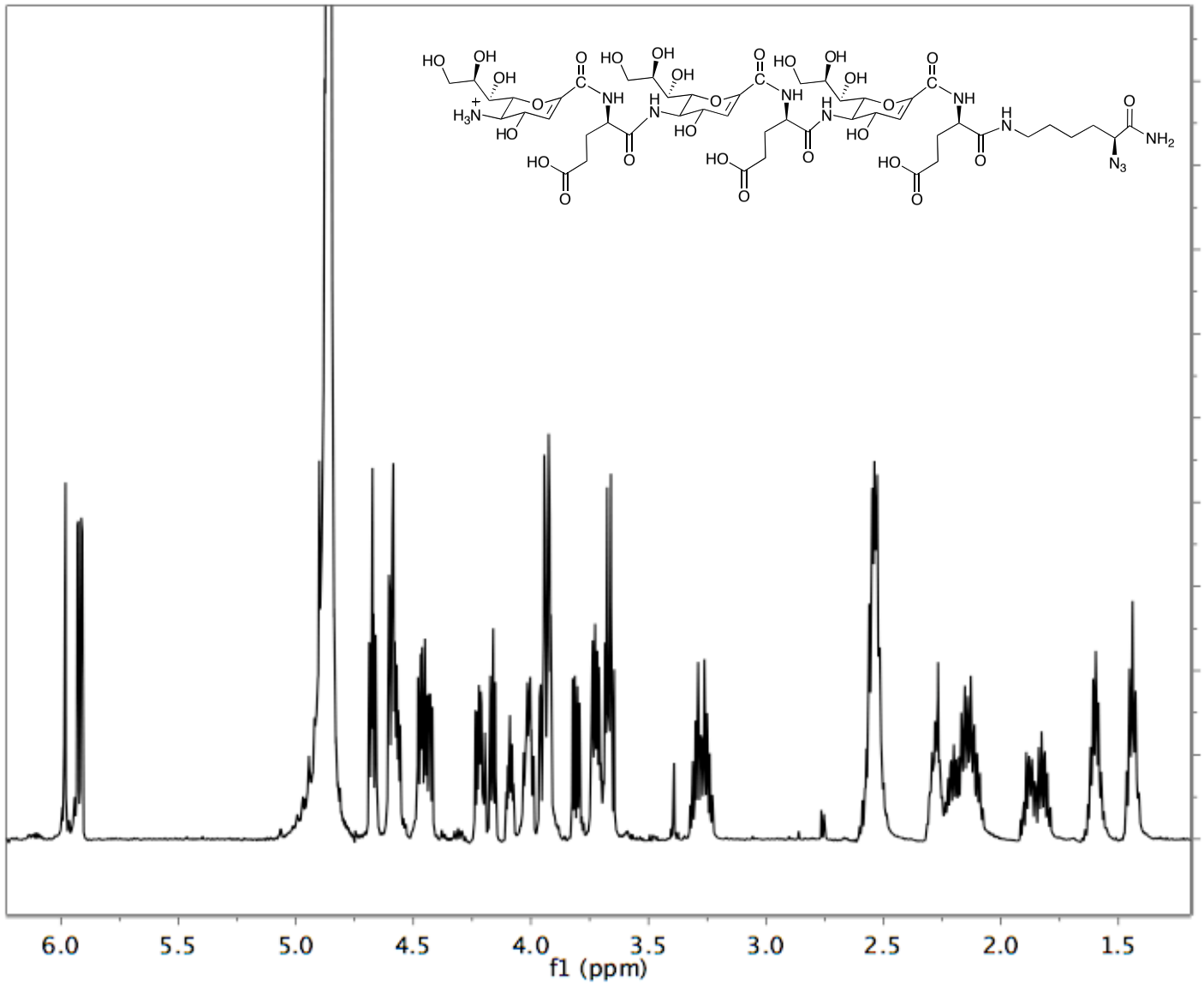


Figure S5. ^{1}H NMR spectrum of α/δ-hybrid peptide **8**.

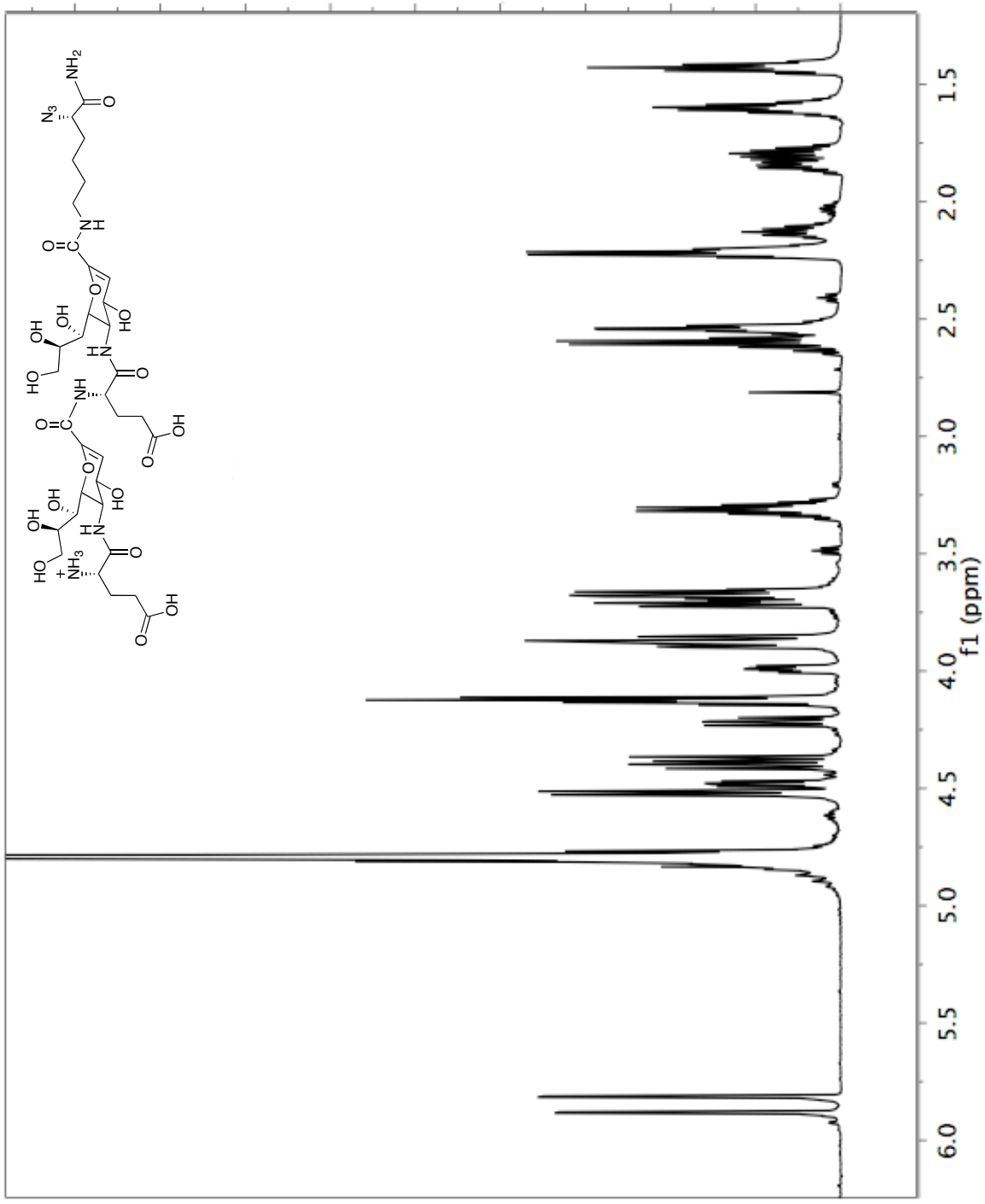


Figure S6. ^{1}H NMR spectrum of α/δ-hybrid peptide **9**.

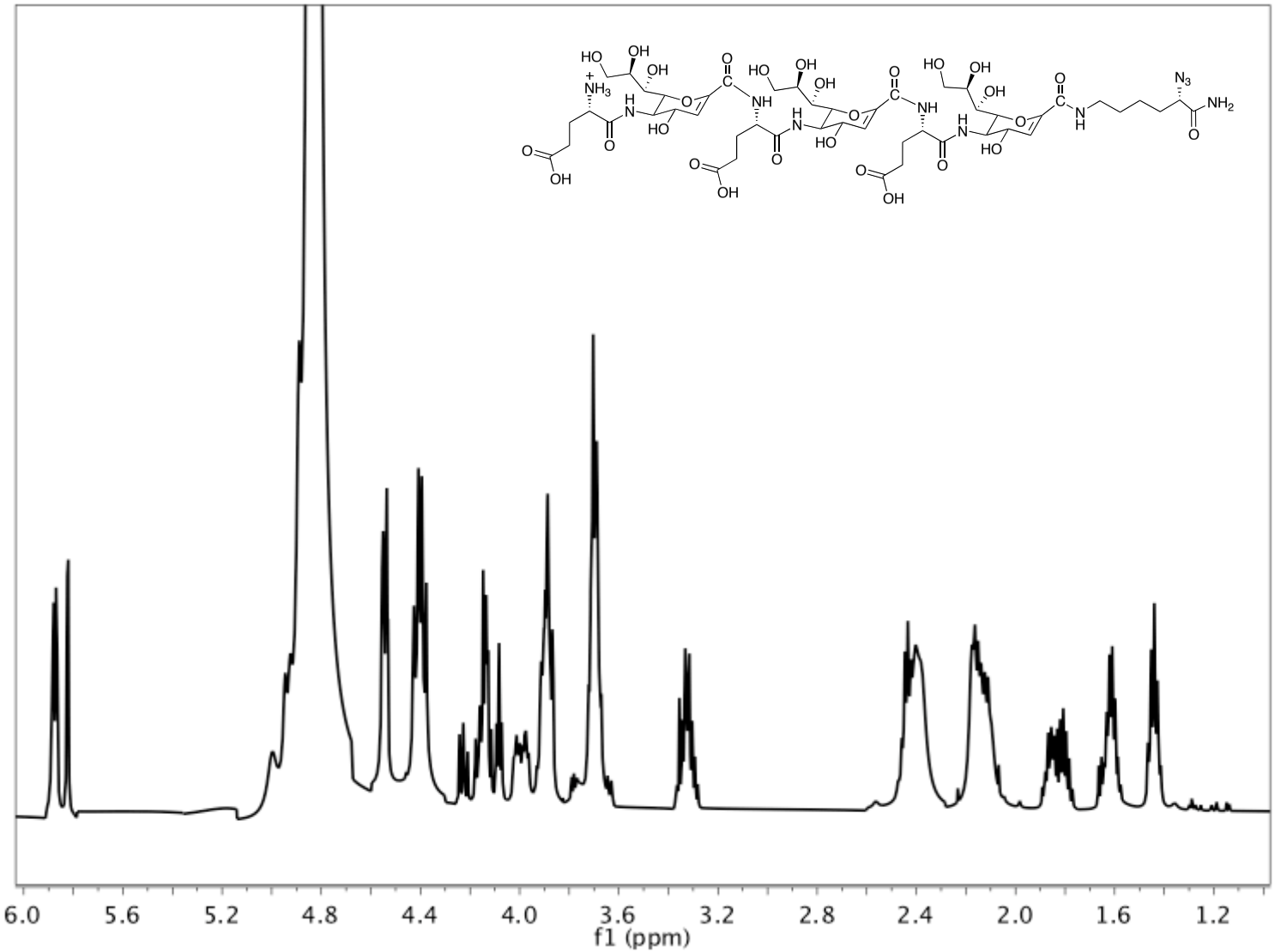


Figure S7. ^{1}H NMR spectrum of α/δ-hybrid peptide **10**.

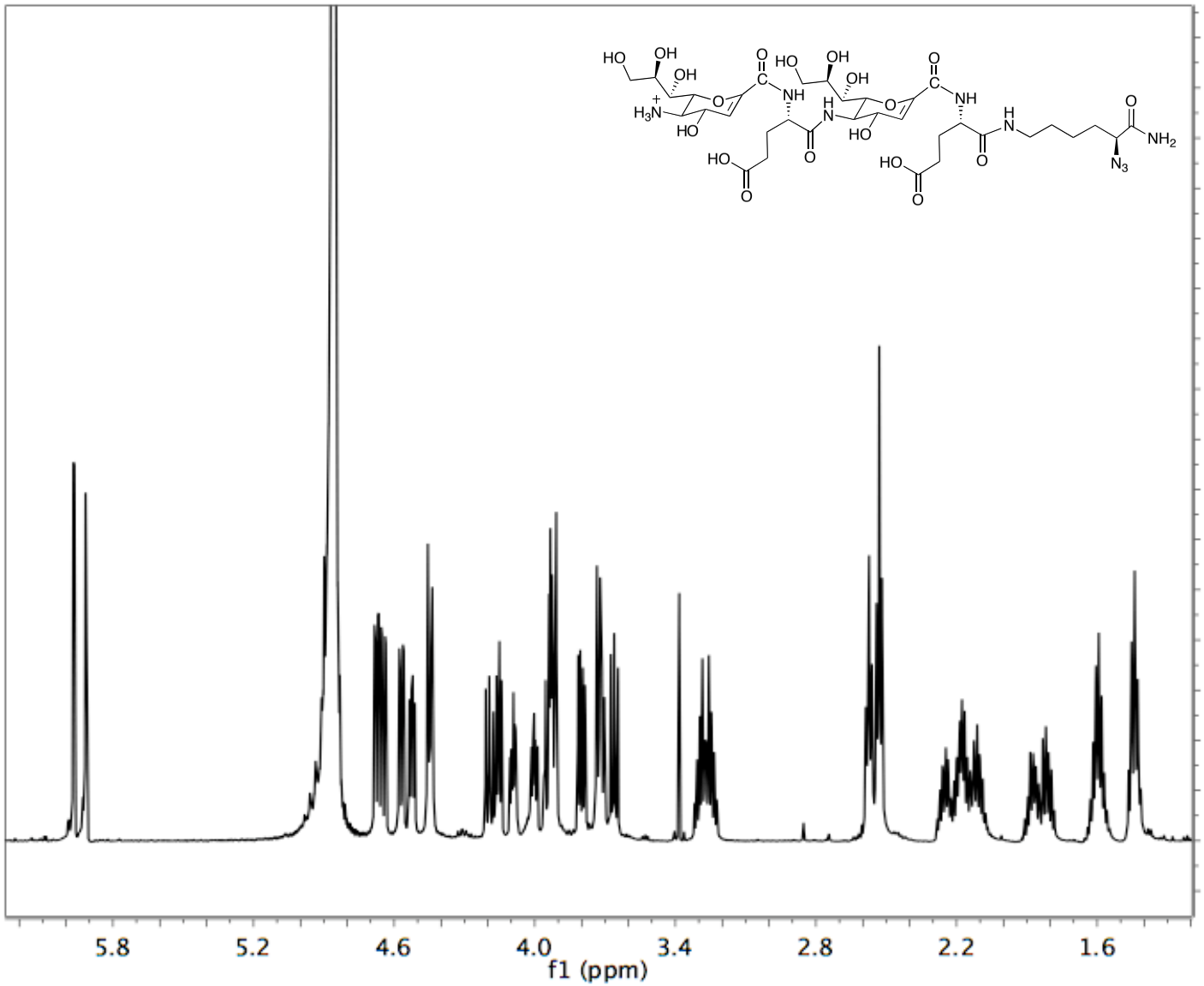


Figure S8. ^{1}H NMR spectrum of α/δ-hybrid peptide **11**.

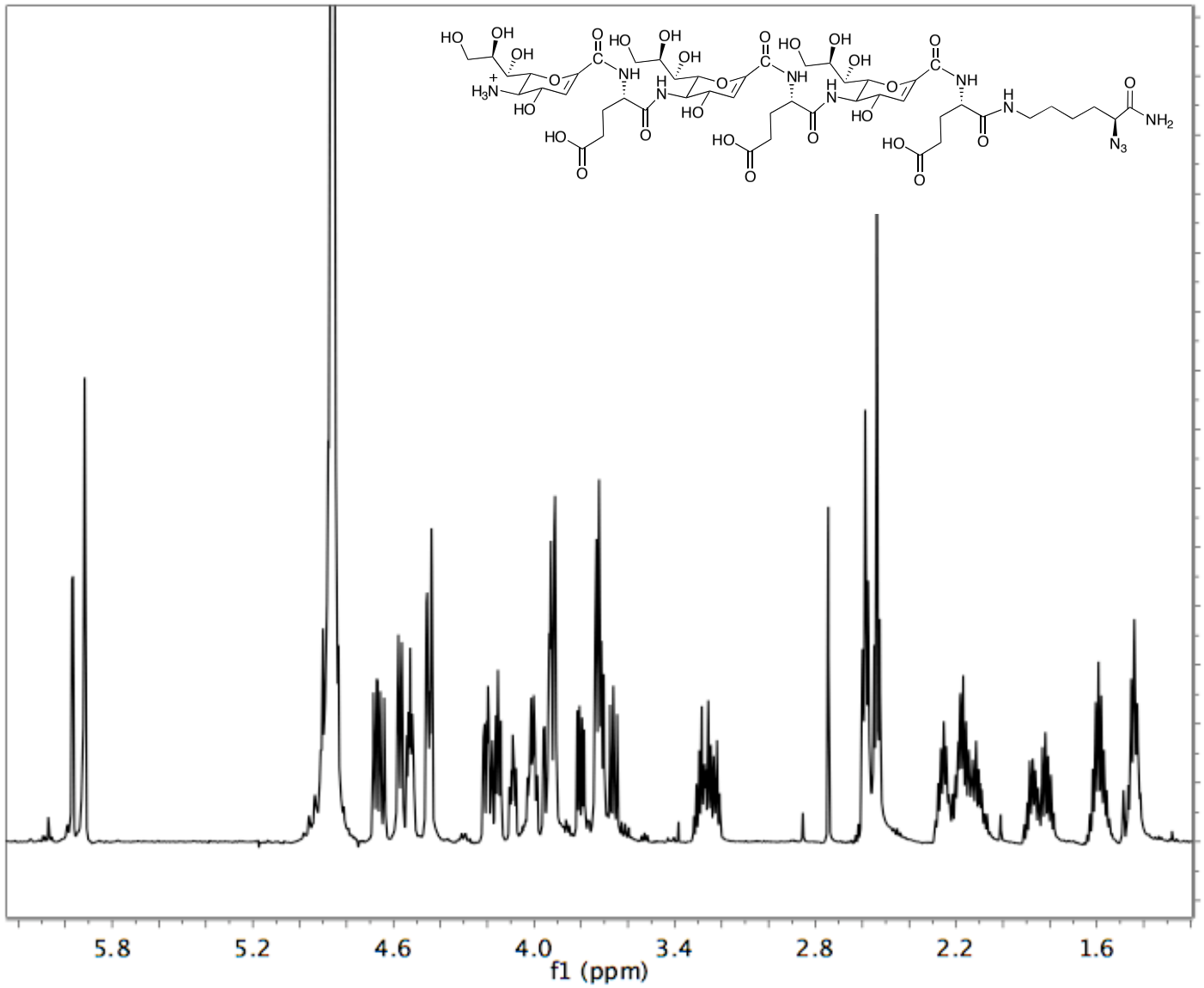


Figure S9. ^{1}H NMR spectrum of α/δ-hybrid peptide **12**.

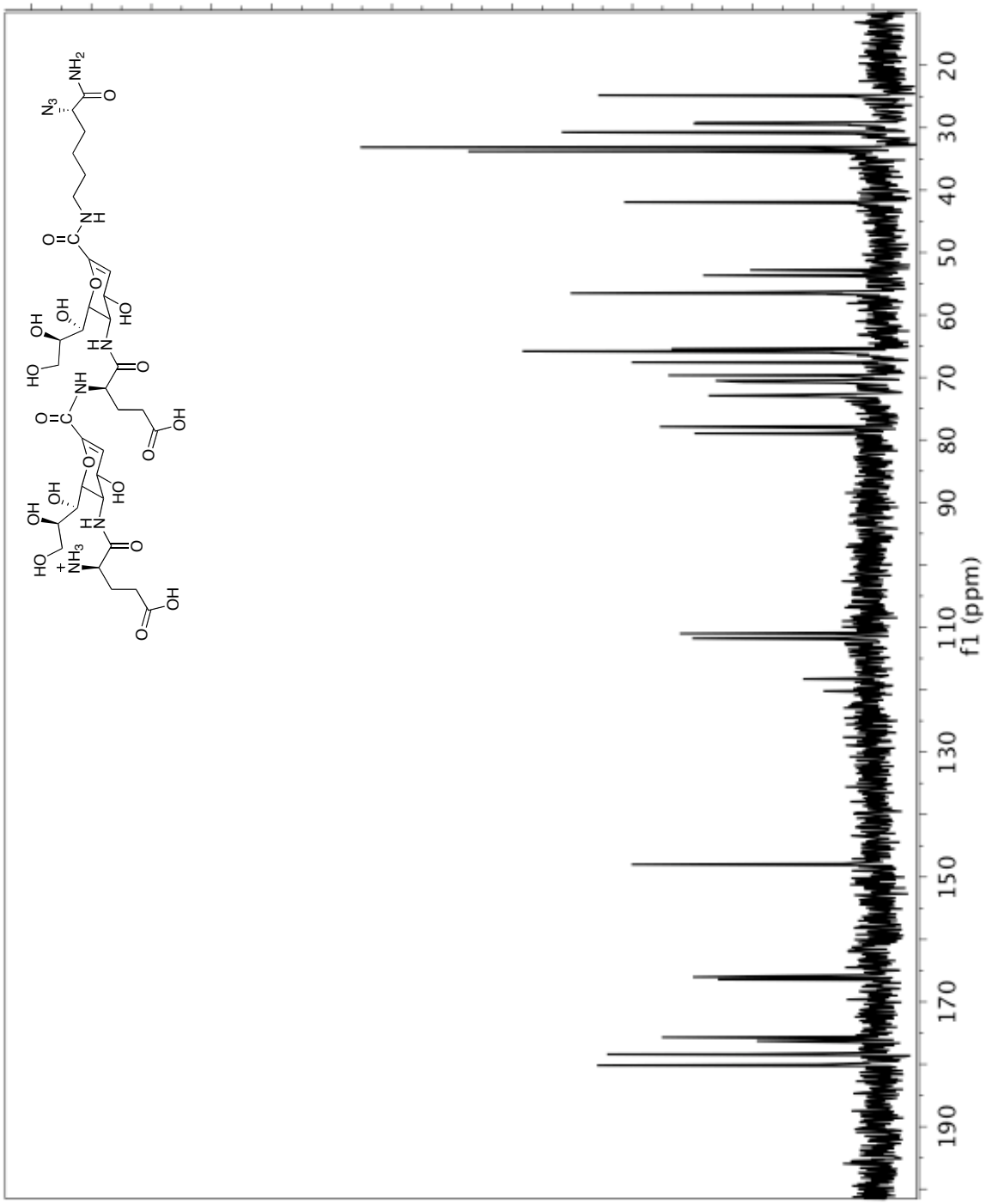


Figure S10. ^{13}C NMR spectrum of α/δ-hybrid peptide **5**.

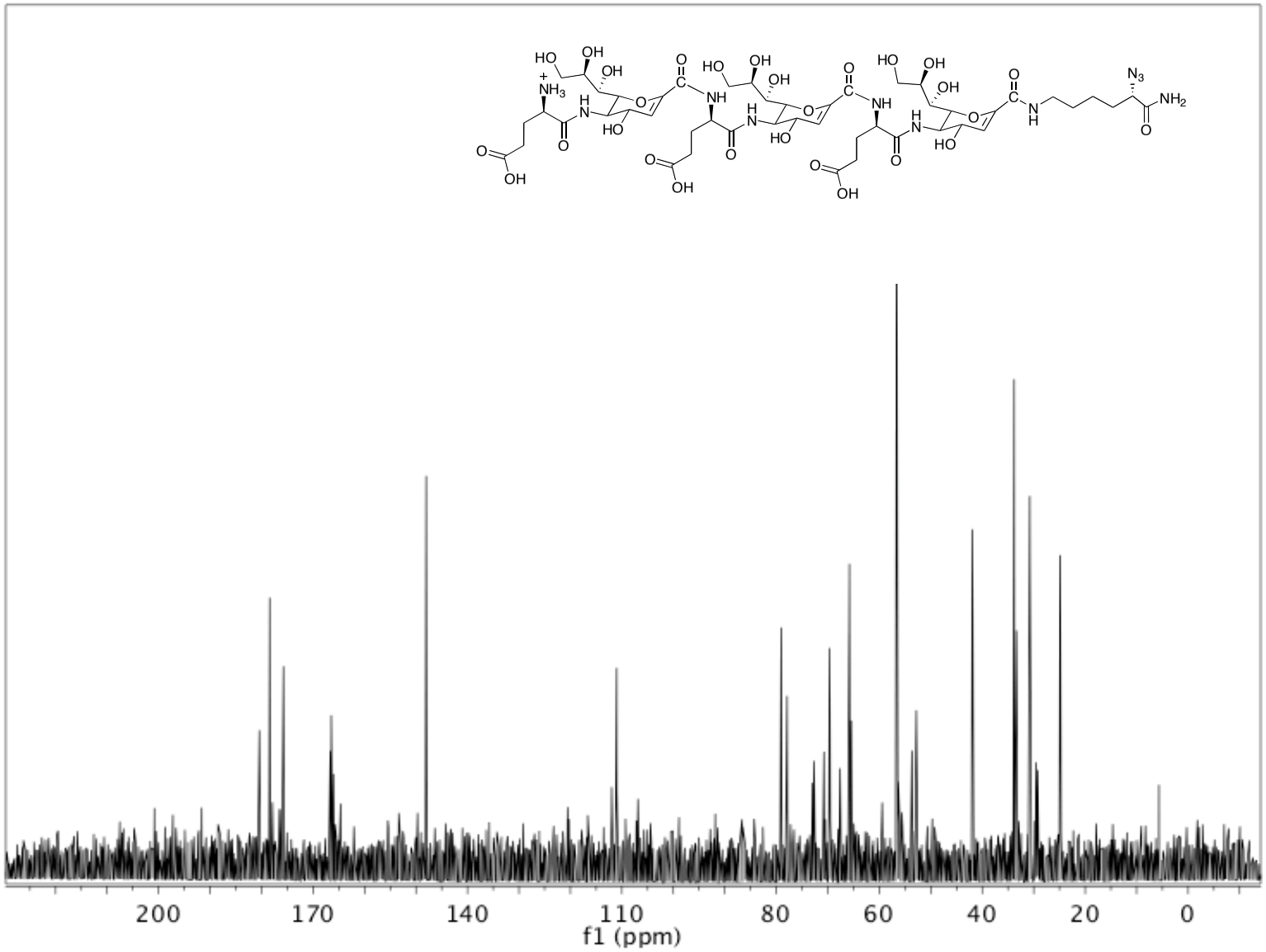


Figure S11. ^{13}C NMR spectrum of α/δ-hybrid peptide **6**.

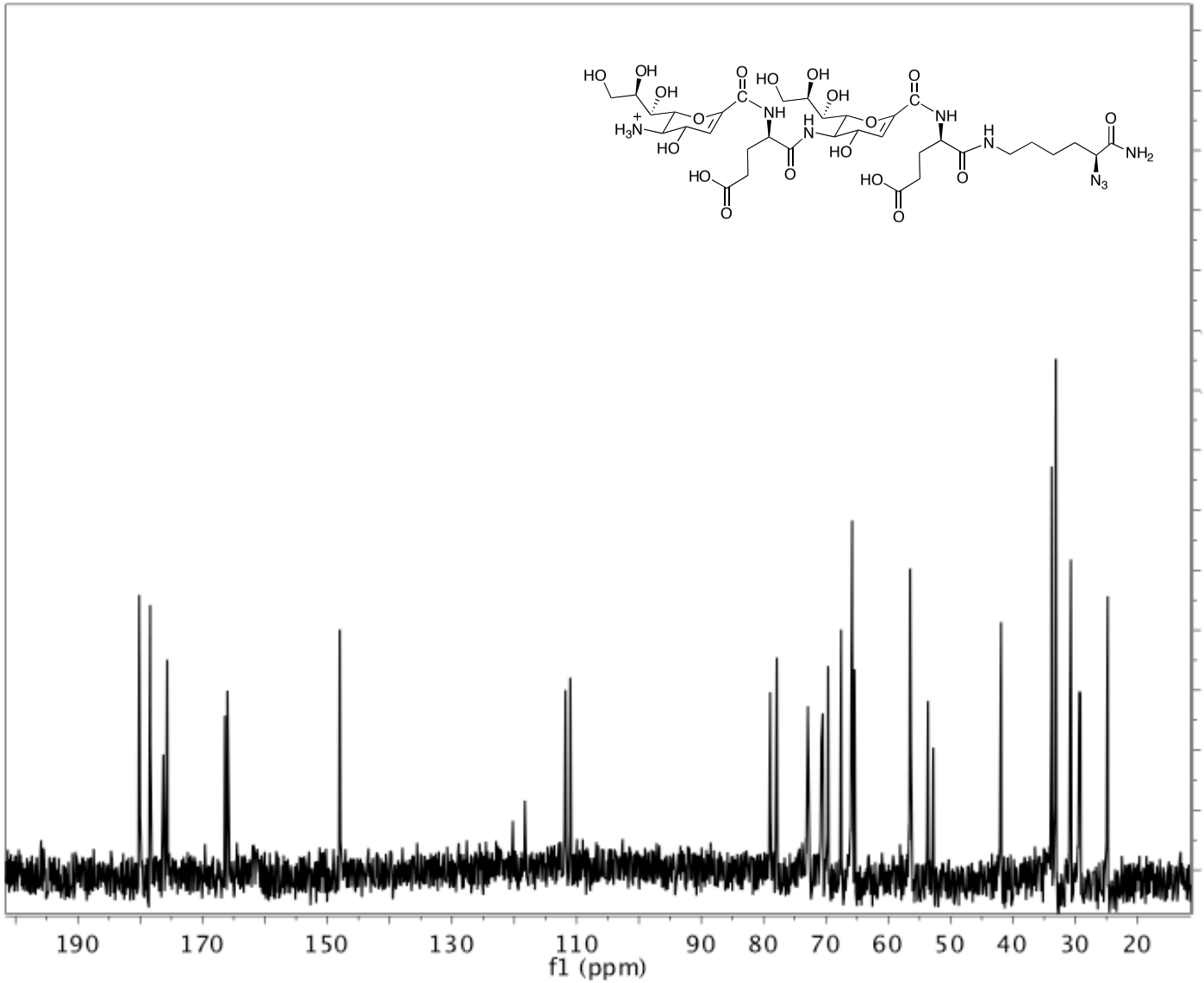


Figure S12. ^{13}C NMR spectrum of α/δ-hybrid peptide **7**.

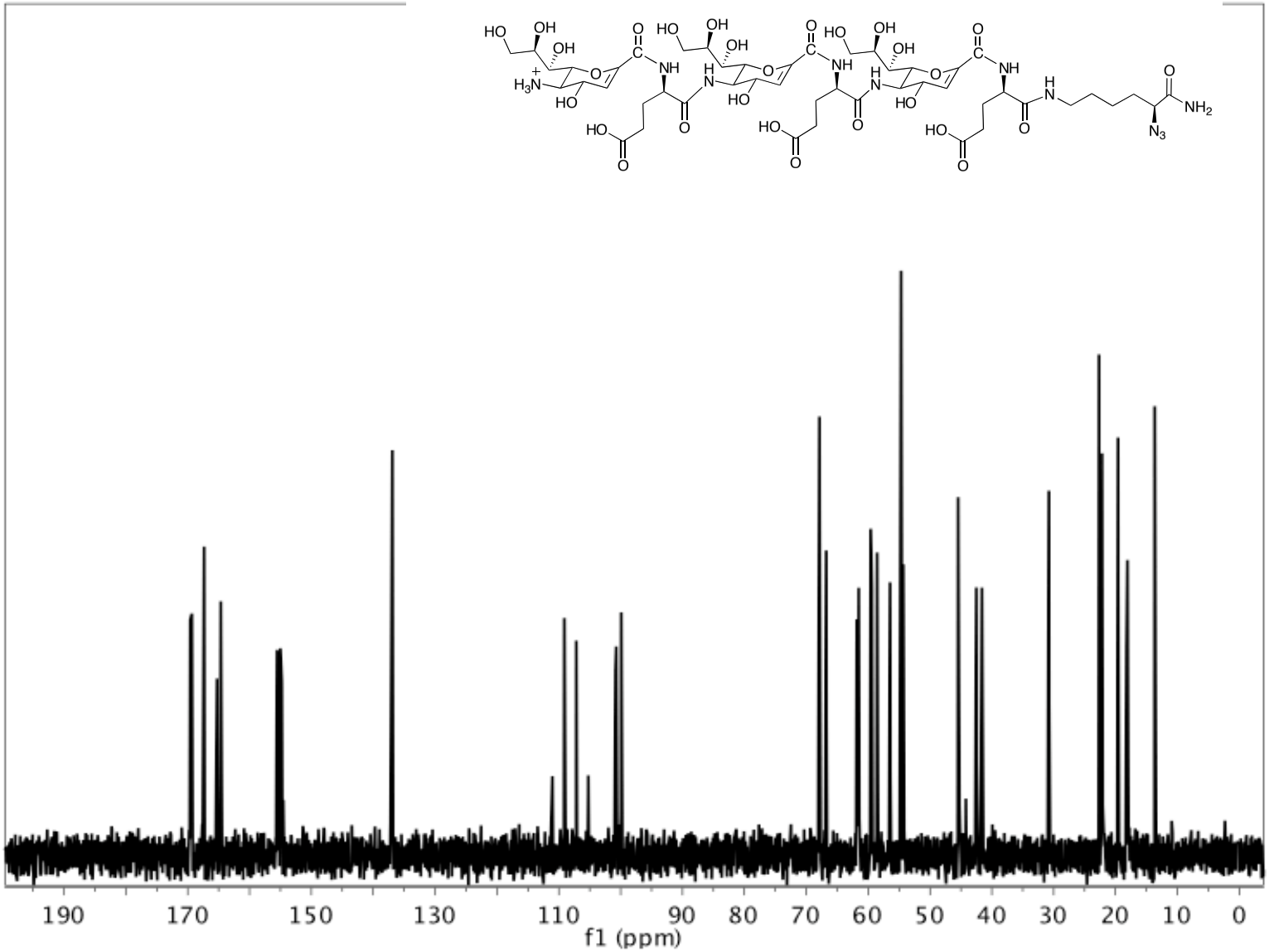


Figure S13. ^{13}C NMR spectrum of α/δ-hybrid peptide **8**.

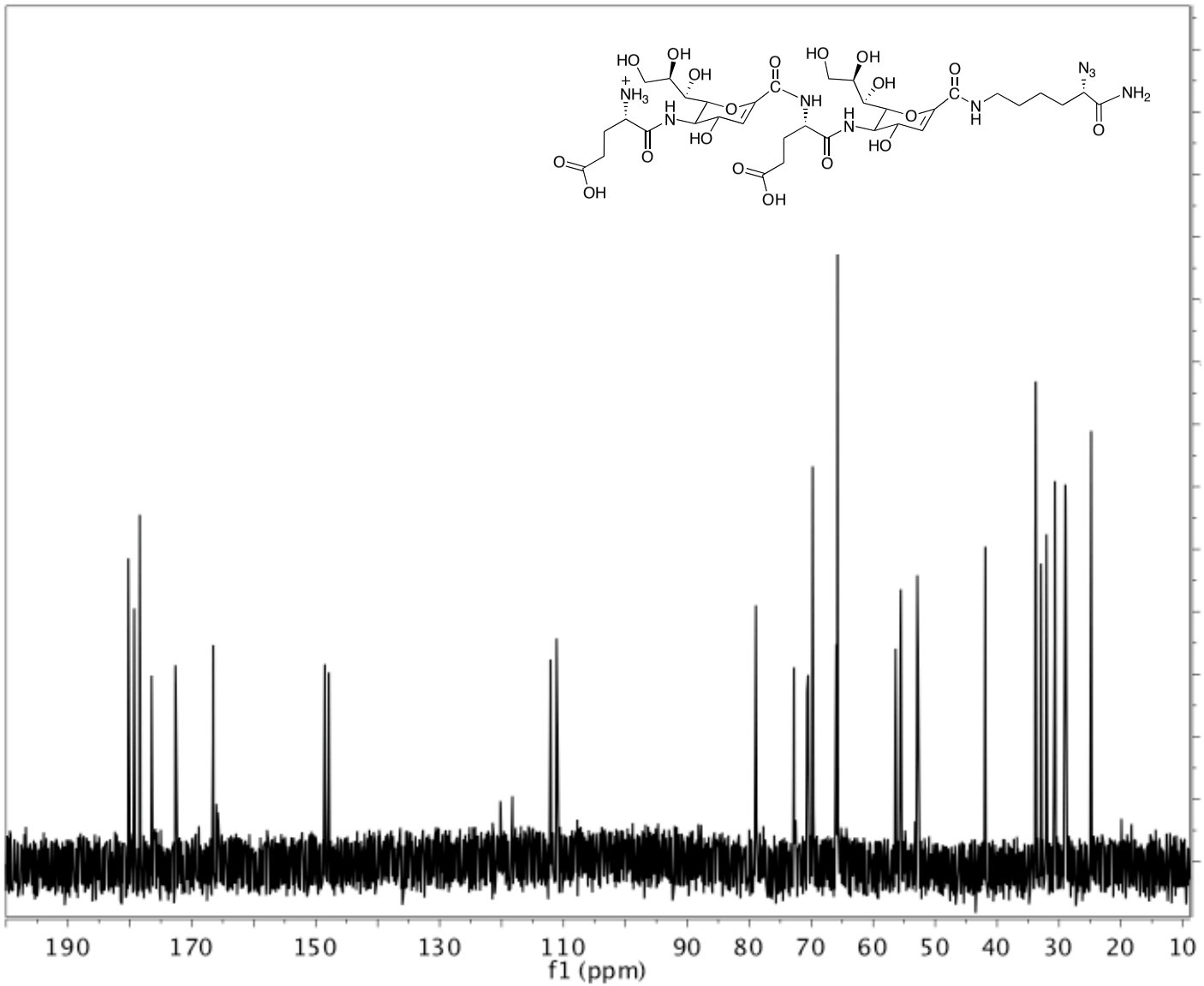


Figure S14. ^{13}C NMR spectrum of α/δ-hybrid peptide **9**.

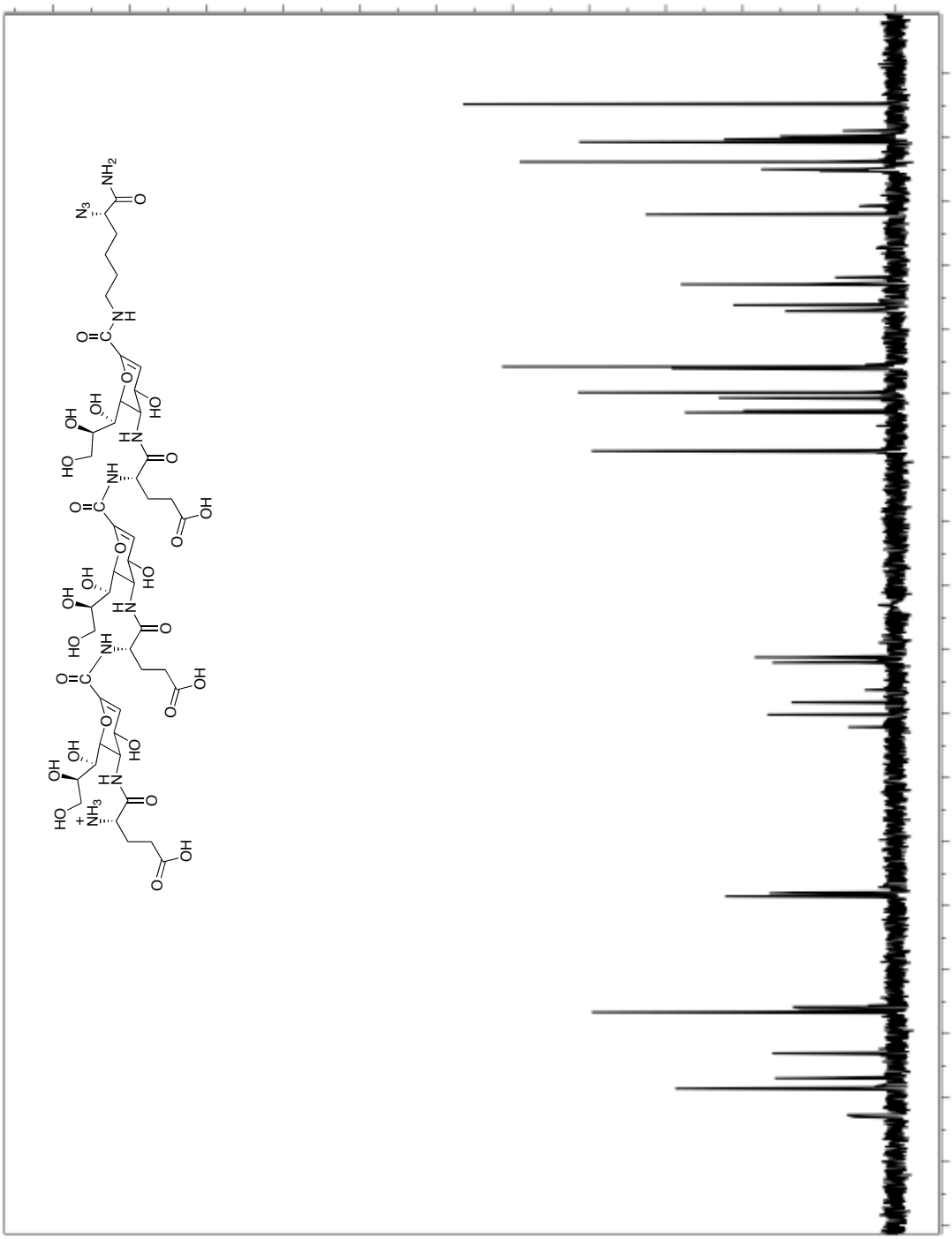


Figure S15. ^{13}C NMR spectrum of α/δ-hybrid peptide **10**.

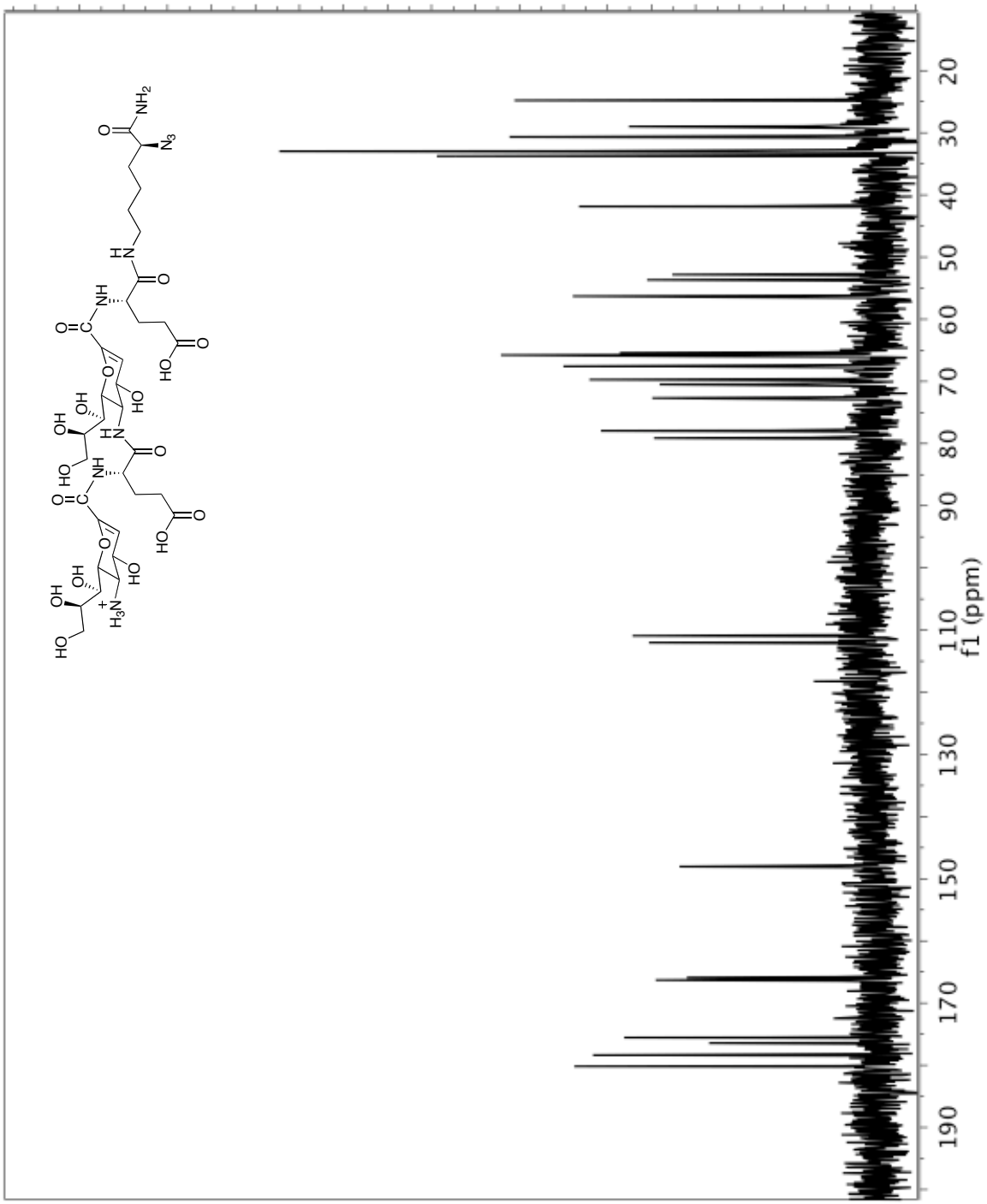


Figure S16. ^{13}C NMR spectrum of α/δ-hybrid peptide **11**.

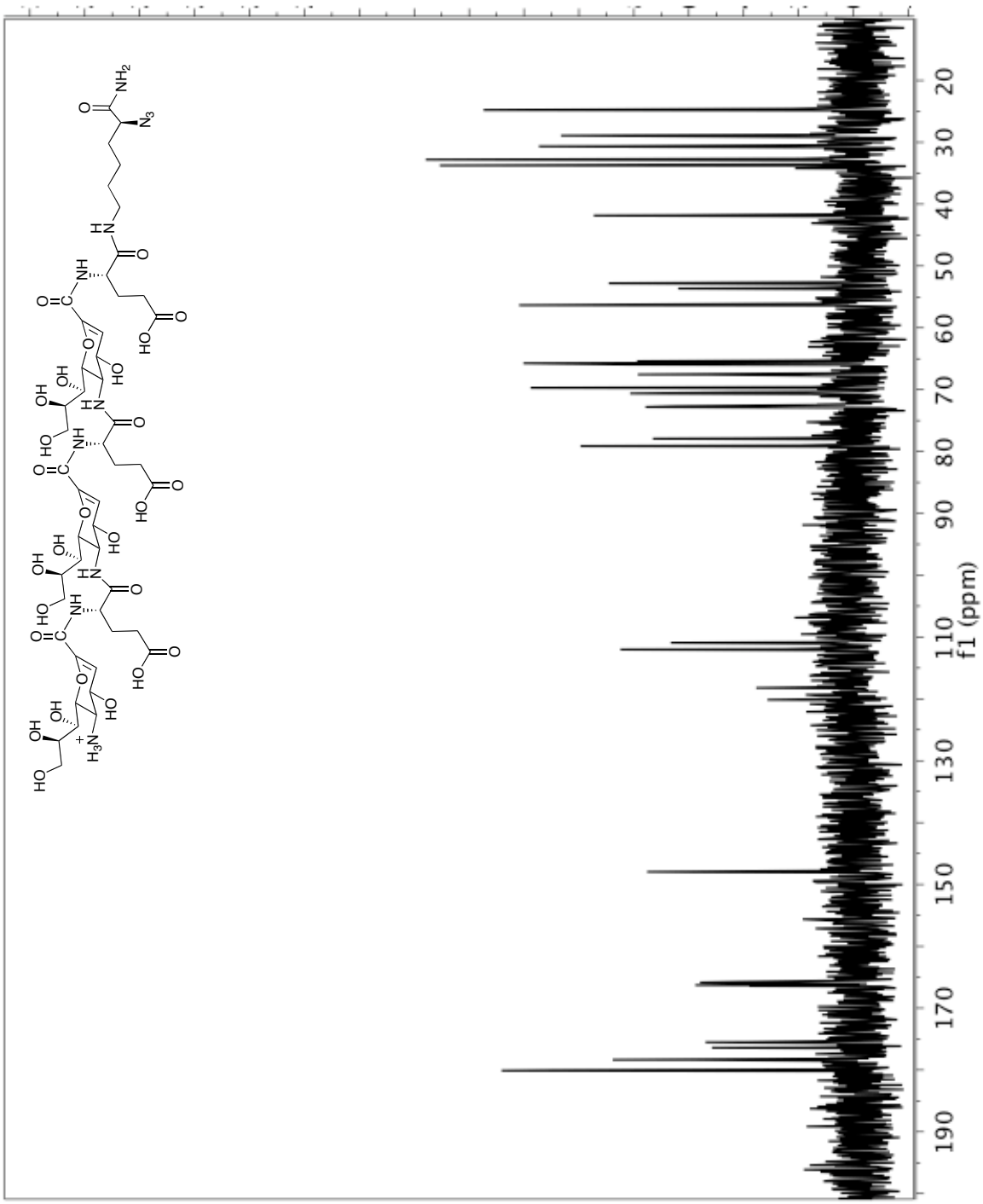


Figure S17. ^{13}C NMR spectrum of α/δ-hybrid peptide **12**.

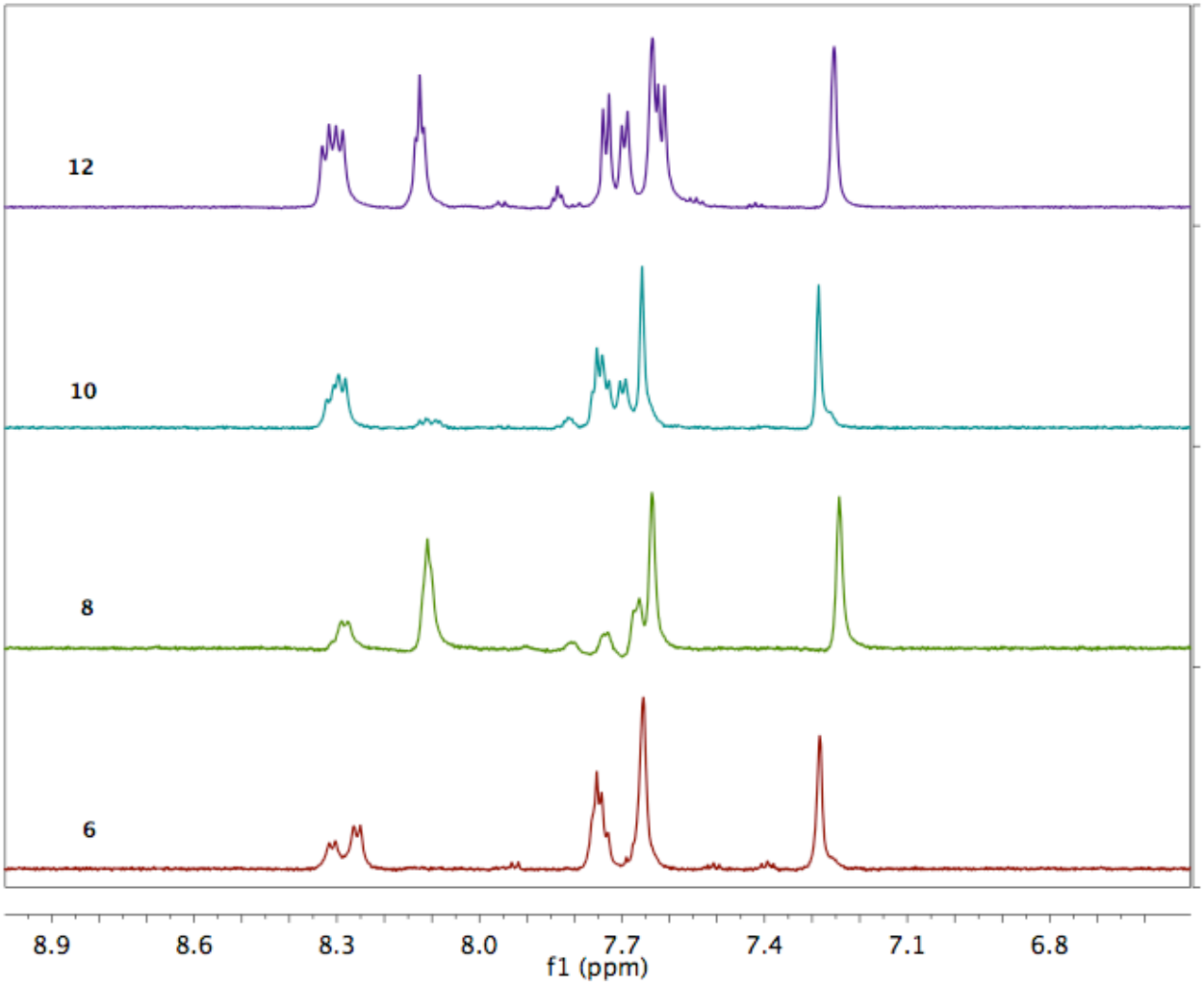


Figure S18. Stack plot of the amide regions from ^{1}H NMR spectra (DMSO-d_6 at 298 K, 600 MHz) showing that the amide H of **12** are more dispersed and distinct from each other compared to **6**, **8**, and **10**.

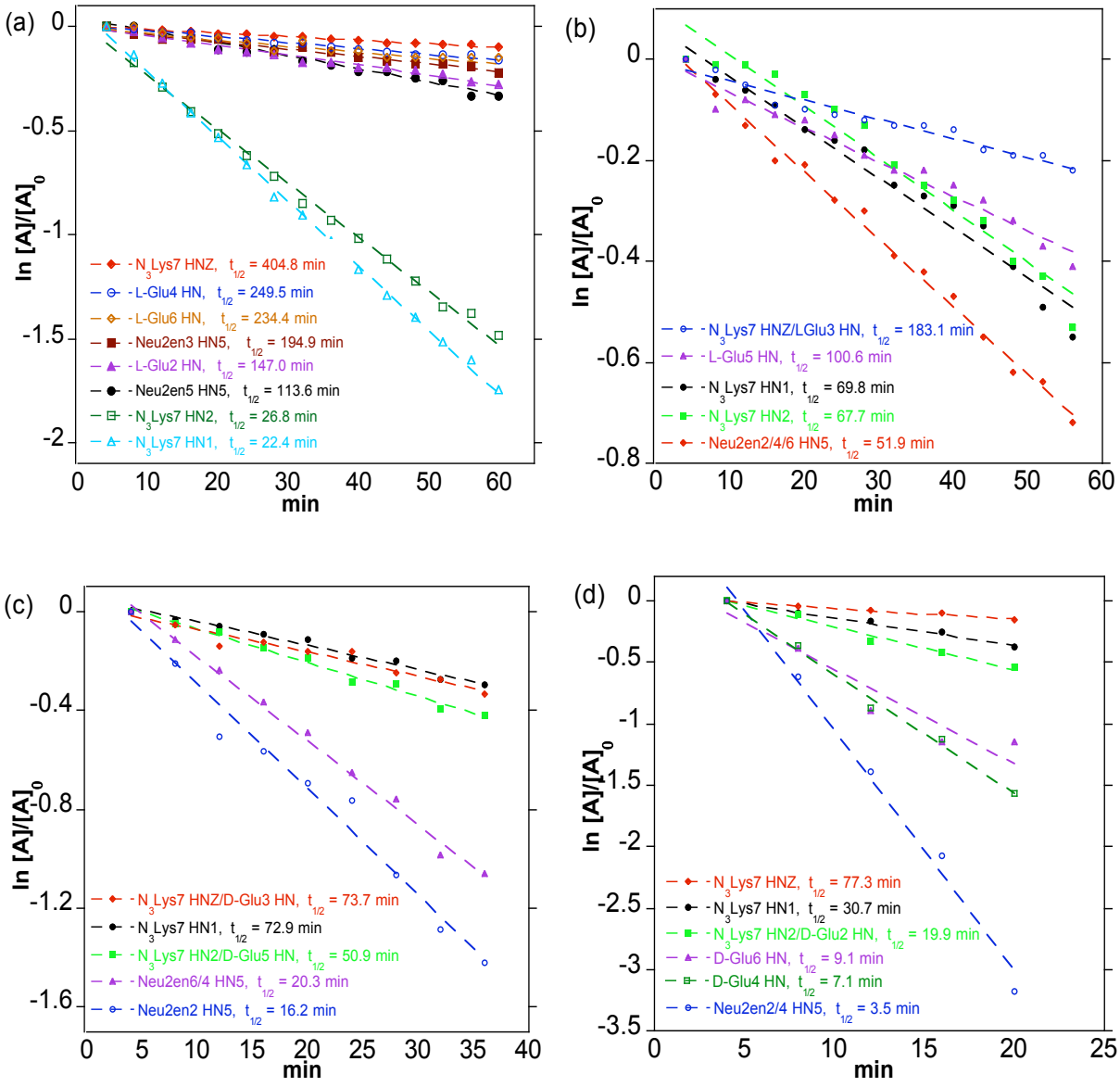


Figure S19. NH/ND exchange study for **6**, **8**, **10**, **and 12** in DMSO-d_6 at 298 K, 600 MHz. Pseudo first order rate plots showing the long $t_{1/2}$ of H-bonded amide protons of **12** (a) indicating a 2° structure stabilized by intramolecular amide H-bonds. The amide H of **6** (c) and **8** (d) have relatively shorter $t_{1/2}$ of 3-20 min indicating unfolded peptide chain while those of **10** (b) have $t_{1/2}$ of 52-100 min that are equivalent to about double the NH/ND exchange rate of **12.**

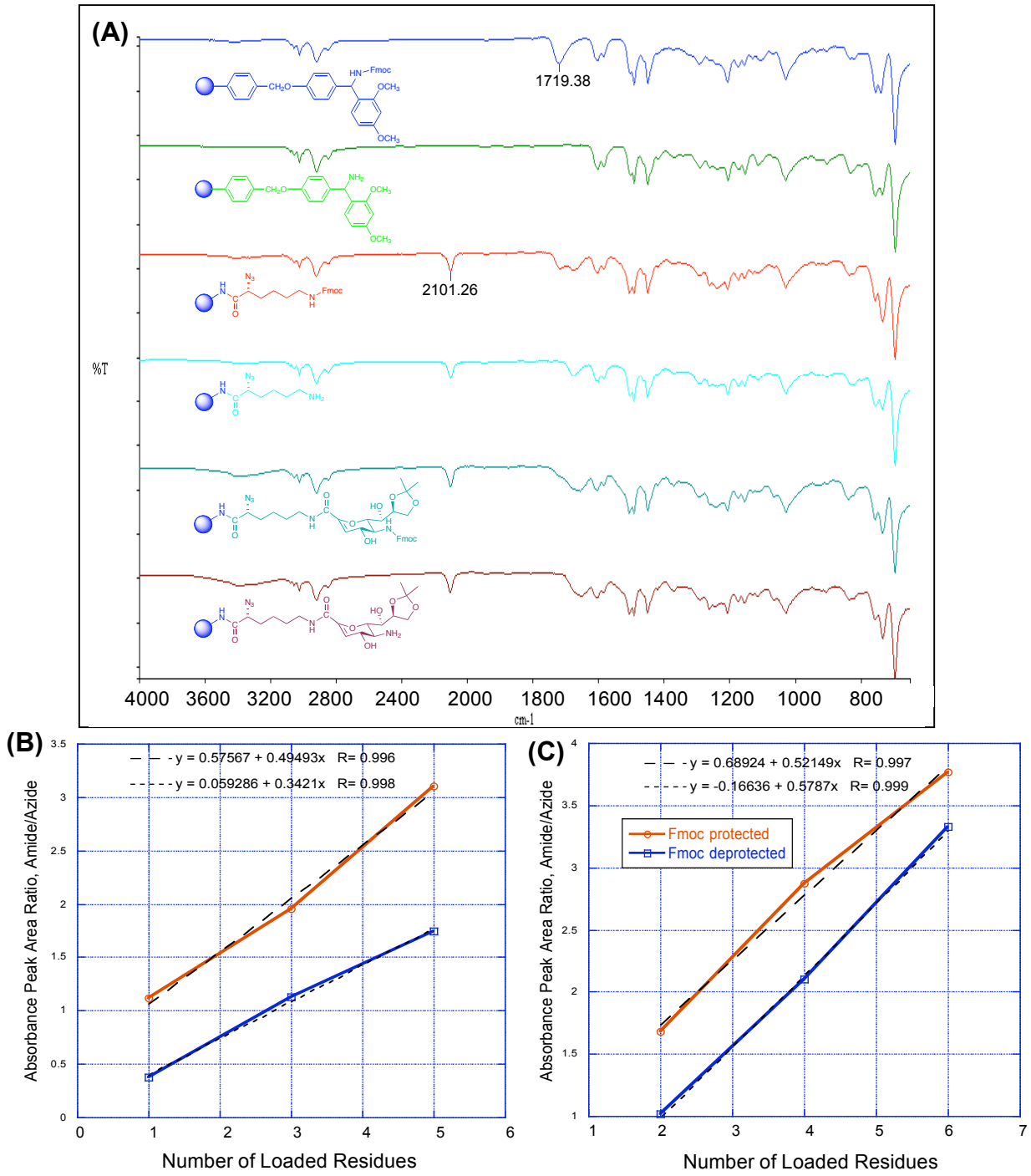
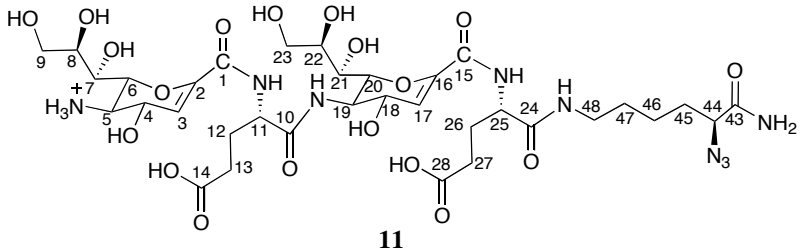
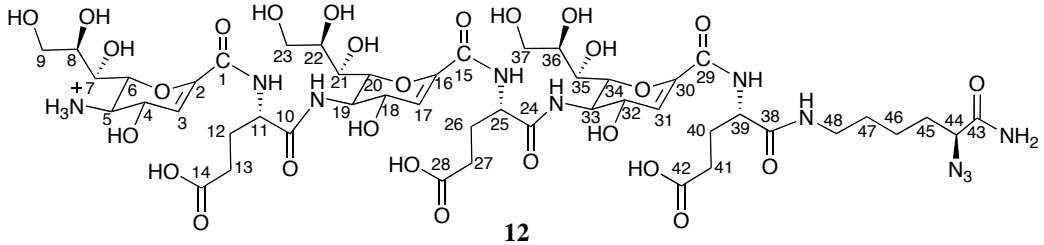


Figure S20. (A) Stack plot of IR spectra for on-bead monitoring of SPPS using the synthesis of **8** as an example. Absorption bands at 1719 cm^{-1} due to C=O of Fmoc, 2101 cm^{-1} due to N_3. (B) and (C) Plots of amide/azide IR band peak area integration showing the linear correlation as a function of peptide length: (B) Odd numbered* residues, (C) even numbered* residues. red plot: oligomer with Fmoc protected *N*-terminus; blue plot: oligomer with deprotected *N*-terminus. **N.B*. Number system is based on the growing peptide chain bound to N_3Lys on the bead, *i.e.* Glu6 is loaded residue number 1.

Assignment strategy for the NMR chemical shifts of 11 and 12. NMR characterization of **12** proved to be challenging because of very close and overlapping peaks in its ^{1}H NMR spectra. Our previous report on amide-linked Neu2en polymers[1] made it possible to distinguish between the downfield H3 proton of *N*-terminal from internal Neu2en residue. This distinction proved to be crucial in our strategy for **12.** We began the characterization with Hε (δ 3.22-3.31) of N_3Lys-7 of **11** because it is an unambiguous aminomethylene, and walked through the residue to completely assign the protons using homonuclear COSY. Next, we used Neu2en H3 as a reporter atom that distinguished Neu2en-1 (δ 5.96) from Neu2en-3 (δ 5.91). Assignment of proton resonances was accomplished by separately walking through intraresidue connectivities of terminal and internal Neu2en residues using homonuclear COSY, while one-bond C→H connectivities were accomplished using HSQC. Another approach was used to connect the amino acid residues and differentiate the two LGlu residues since their Hα's have different chemical shifts: L-Glu-2 (Hα, δ 4.52) and L-Glu-4 (Hα, δ 4.44). L-Glu-4 Hα was assigned using HMBC since we found strong correlations that allowed us to unambiguously identify L-Glu-4: L-Glu-4 C=O→Hα of L-Glu-4 and L-Glu-4 C=O→Hε of N_3Lys. By deduction, we assigned the other Hα to L-Glu-2. Following the same approach that we used for **11**, we assigned the proton resonances of **12** using Neu2en H3 as reporter atom. Neu2en-1 has a unique set of ^{1}H NMR resonance peaks. Overlapping peaks were found for H4, H6, H7, H9, and H9' of Neu2en-3 and -5 and these resonances were assigned to both, while their H5 and H8 were very distinct. Neu2en-5 and L-Glu-6 were identified using the following HMBC correlations: L-Glu-6 C=O→Hε of N_3Lys, L-Glu-6 C=O→Hα of L-Glu-6 and Neu2en-5 C=O→Hα of L-Glu-6. We also found another HMBC correlations for the following: Neu2en-3 C=O→Hα of L-Glu-4 and Neu2en-1 C=O→Hα of L-Glu-2. Furthermore, Hβ and Hγ of all L-Glu residues are overlapped for both **11** and **12** and we were not able to differentiate them, so all L-Glu Hβ and Hγ were assigned the same chemical shifts. The table for **11** and **12** below summarizes our approach, which is the same strategy that we applied for **7**, **8**, **9**, and **10**.



11



12

	#	**11**, H-H COSY[a]	**11**, HMBC[a,b]	**12**, H-H COSY[a]	**12**, HMBC[a,b]
Neu2en-1					
	1	-	3	-	3, 11
	2	-	3	-	3 ,4
	3	4	4	4	4
	4	3, 5	5, 6	3, 5	5, 6
	5	4, 6	3, 4	4, 6	4, 6
	6	5, 7	5, 7	5, 7	5, 7
	7	6, 8	-	6, 8	-
	8	7, 9 ,9’	7	7, 9, 9’	-
	9	8, 9’	-	8, 9’	-
	9’	8, 9		8, 9	
L-Glu-2					
	10	-	11, 19	-	11, 12
	11	12	12, 13	12	12, 13
	12	11, 13	11, 13	11, 13	11, 13
	13	12	11, 12	12	11, 12
	14	-	13	-	13
Neu2en-3					
	15	-	17	-	17, 25
	16	-	17	-	17, 18
	17	18	18	18	18
	18	17, 19	19	17, 19	19, 20
	19	18, 20	17, 18, 20	18, 20	17, 18, 20
	20	19, 21	19	19, 21	19
	21	20, 22	-	20, 22	19, 20
	22	21, 23, 23’	21, 23	21, 23, 23’	21, 23, 23’
	23	22, 23’	-	22, 23’	21
	23’	22, 23	-	22, 23	

L-Glu-4				
24	-	25, 48	-	25, 26
25	26	26, 27	26	26, 27
26	25, 27	25, 27	25, 27	25, 27
27	26	25, 26	26	25, 26
28	-	27	-	26, 27
Neu2en-5				
29	-	-	-	31, 39
30	-	-	-	31
31	-	-	32	32
32	-	-	31, 33	33, 34
33	-	-	32, 34	31, 32, 34
34	-	-	33, 35	33
35	-	-	34, 36	33, 34
36			35, 37, 37’	35, 37
37	-	-	36, 37’	35
37’	-	-	36, 37	
L-Glu-6				
38	-	-	-	39, 40, 48
39	-	-	40	40, 41
40	-	-	39, 41	39, 41
41	-	-	40	39,40
42	-	-	-	40, 41
N_3Lys-5 (7)				
43	-	44	-	44, 45
44	45	45, 46	45	45, 46
45	44, 46	44, 46	44, 46	44, 46
46	45, 47	44, 45, 48	45, 47	45, 47
47	46, 48	45, 46, 48	46, 48	45, 46, 48
48	47	46, 47	47	46, 47

[a] D_2O, 600 MHz

[b] HMBC correlations are from carbon atom #(s) in column 1 to the indicated proton; $J_{C,H}$ at 8 Hz.

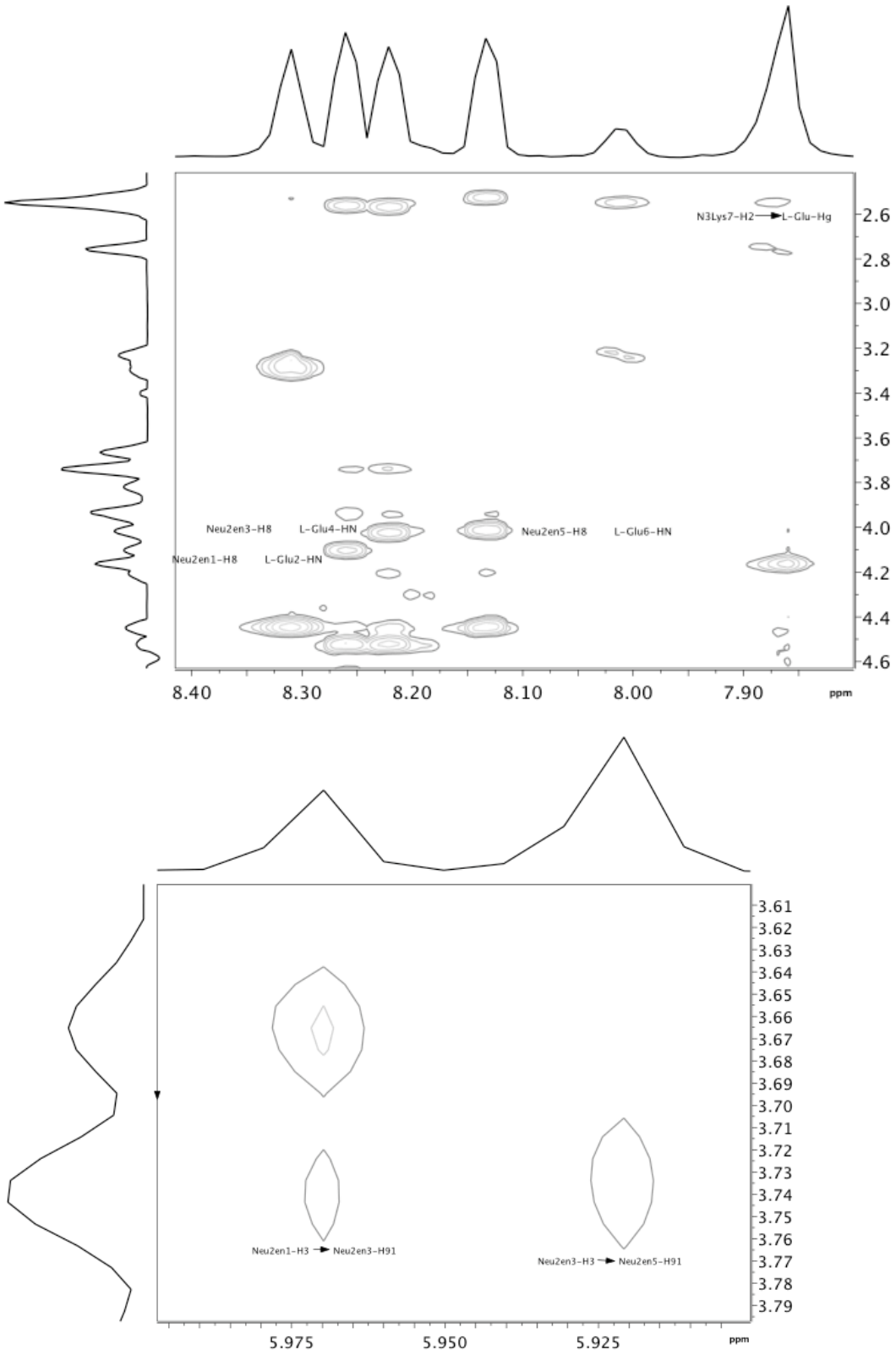


Figure S21. Prominent long range ROE's for **12**.

Figure S22. The effect of solvent and solvent screening of electrostatic charges in the X-PLOR structure calculation was implemented using the 1/R dielectric option for the electrostatic energy function in XPLOR by setting the dielectric constant equal to $!_0 R$. The electrostatic energy function ($f_{ELEC}(R)$) is given by:

$$f_{ELEC}(R) = Q_i Q_j \frac{C}{!_0 R^2} SW(R, R_{on}, R_{off})$$

where $SW(R, R_{on}, R_{off}) = 0$ or 1 if $R > R_{off}$ (7.5 Å) or $R < R_{on}$ (6.5 Å) respectively, and

$$SW(R, R_{on}, R_{off}) = \frac{(R^2 ! R_{off}^2)\ \ (R^2 ! R_{off}^2 ! 3(R^2 ! R_{on}^2)}{R_{off}^2 ! R_{on}^2}$$ if $R_{off} > R > R_{on}$.

Table 1. Strong (s)[a], medium (m)[a] and weak (w)[a] ROEs observed in the 500 ms ROESY spectrum of **10** in 9:1 H_2O/D_2O at 600 MHz, 298 K.

Atom	Residue	Atom	Residue	ROE	Atom	Residue	Atom	Residue	ROE
α	1	γ	1	w	NH	4	5	4	w
α	1	β	1	w	NH	4	6	4	s
γ	1	β	1	w	NH	4	9	4	w
3	2	4	2	m	α	5	γ	5	w
3	2	α	3	w	γ	5	β	5	w
3	2	5	2	w	NH	5	α	3	w
4	2	5	2	w	NH	5	α	5	w
5	2	7	2	w	NH	5	β	5	w
6	2	β	1	w	NH	5	γ	5	w
6	2	9	4	w	NH	5	6	4[b]	w
8	2	9	2	s	NH	5	7	4	w
9’	2	7	2	s	NH	5	9	4	w
NH	2	α	1[b]	s	3	6	α	7	w
NH	2	α	3	w	3	6	4	6	m
NH	2	β	1	w	3	6	5	6	w
NH	2	4	2	w	5	6	9	6	w
NH	2	5	2	w	5	6	9’	6	w
NH	2	6	4	w	6	6	6	9	w
NH	2	9	2	w	8	6	9	6	s
α	3	γ	3	w	NH	6	α	5[b]	s
α	3	9’	4	w	NH	6	4	6	m
γ	3	β	3	w	NH	6	5	6	w
NH	3	α	3	w	NH	6	6	6	s
NH	3	β	3	w	α	7	γ	7	w
NH	3	γ	3	w	α	7	8	6	w
NH	3	3	4	w	α	7	9’	6	w
NH	3	6	2[b]	w	β	7	α	7	w
NH	3	7	2	w	β	7	δ	7	w
NH	3	8	2	w	δ	7	5	6	w
NH	3	9’	2	w	ε	7	δ	7	w
3	4	4	4	m	ε	7	γ	7	w
3	4	5	4	w	NH	7	α	7	w
3	4	9	6	w	NH	7	δ	7	w
3	4	9’	6	w	NH	7	γ	7	w
4	4	6	4	w	NH	7	ε	7	w
6	4	9	4	w	NH	7	3	6	w
8	4	α	3	w	NH	7	6	6	w
8	4	9	4	w	NH	7	7	6	w
9b	4	7	4	s	NH	7	8	6	w
NH	4	α	3[b]	s	NH	7	9	6	w
NH	4	4	4	m	NH	7	9’	6	w

[a]Distance were categorized s (2.9 Å), m (3.3 Å), and w (5.0 Å) as upper bond distance limits.
[b]Interresidue ROE assignment consistent with calculations but ambiguous due to overlap.

Table 2. Strong (s)[a], medium (m)[a] and weak (w)[a] ROEs observed in the 500 ms ROESY spectrum of **12** in 9:1 H_2O/D_2O at 600 MHz, 298 K.

Atom	Residue	Atom	Residue	ROE	Atom	Residue	Atom	Residue	ROE
3	1	4	1	s	NH	4	γ	4	w
3	1	5	1	w	NH	4	3	3	w
3	1	9	3[b]	w	NH	4	5	3	w
4	1	5	1	w	NH	4	6	3	w
6	1	8	1	w	NH	4	8	3	w
8	1	9	1	w	NH	4	9	5	w
9a	1	9’	1	m	NH	4	9’	5	w
9b	1	7	3	m	3	5	α	6	w
α	2	γ	2	w	3	5	4	5	s
α	2	β	2	w	3	5	5	5	w
NH	2	β	2	w	4	5	6	5	w
NH	2	γ	2	w	5	5	7	5	w
NH	2	3	1	w	6	5	7	5	w
NH	2	6	1	w	7	5	9’	5	s
NH	2	6	3	w	8	5	7	5	w
NH	2	8	1	w	NH	5	α	4[b]	s
NH	2	9	3	w	NH	5	β	6[b]	w
NH	2	9’	3	w	NH	5	4	5	m
3	3	4	3	s	NH	5	6	5	w
3	3	5	3	w	NH	5	7	5	w
3	3	5	5	w	α	6	β	6	w
3	3	6	5	w	α	6	γ	6	w
3	3	9	5[b]	w	NH	6	β	6	w
4	3	6	3	w	NH	6	γ	6	w
6	3	7	5	w	NH	6	3	5	w
6	3	8	3	w	NH	6	5	5	w
7	3	9’	3	s	NH	6	6	5	w
NH	3	α	2[b]	s	NH	6	8	5	w
NH	3	β	4[b]	w	α	7	β	7	w
NH	3	4	3	m	α	7	γ	7	w
NH	3	6	3	w	α	7	δ	7	w
NH	3	7	3	w	β	7	γ	7	w
NH	3	9	5	w	γ	7	δ	7	w
α	4	β	4	w	NH	7	α	6	w
α	4	γ	4	w	NH	7	ε	7	w
NH	4	α	2	w	NH	7	NH	6	w
NH	4	α	4	w	NH_2	7	α	7	w
NH	4	β	4	w	NH_2	7	γ	4	w

[a]Distance were categorized s (2.9 Å), m (3.3 Å), and w (5.0 Å) as upper bond distance limits.
[b]Interresidue ROE assignment consistent with calculations but ambiguous due to overlap.

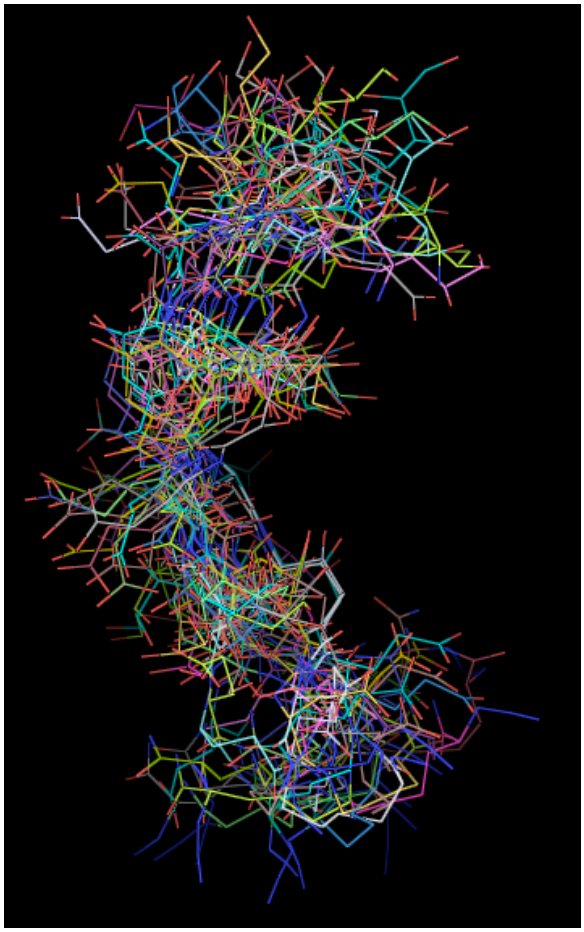


Figure S23. Overlay of 25 low energy structures of **8** showing non-convergence to a single-preferred structure; all H have been omitted for clarity (backbone atom rmsd: 2.080 ±0.750; non-hydrogen atom rmsd: 3.325 ±1.013).

Sample Name	: Cpd **6**	Function	: Absorbance
Solvent Name	: D2O	Wavelength Range	: 194 to 600 nm
Concentration	: 0.36	Integration Time	: 5.0 s
Unit	: mM		

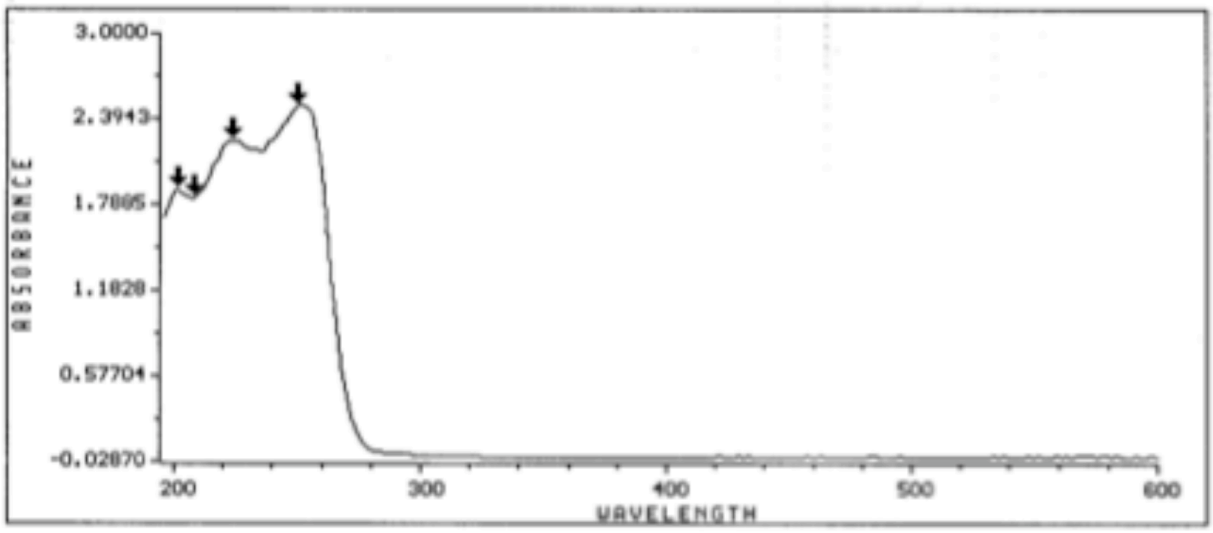


Figure S24. UV spectrum of **6** in D_2O.

Sample Name	: Cpd **8**	Function	: Absorbance
Solvent Name	: D2O	Wavelength Range	: 194 to 600 nm
Concentration	: 0.36	Integration Time	: 5.0 s
Unit	: mM		

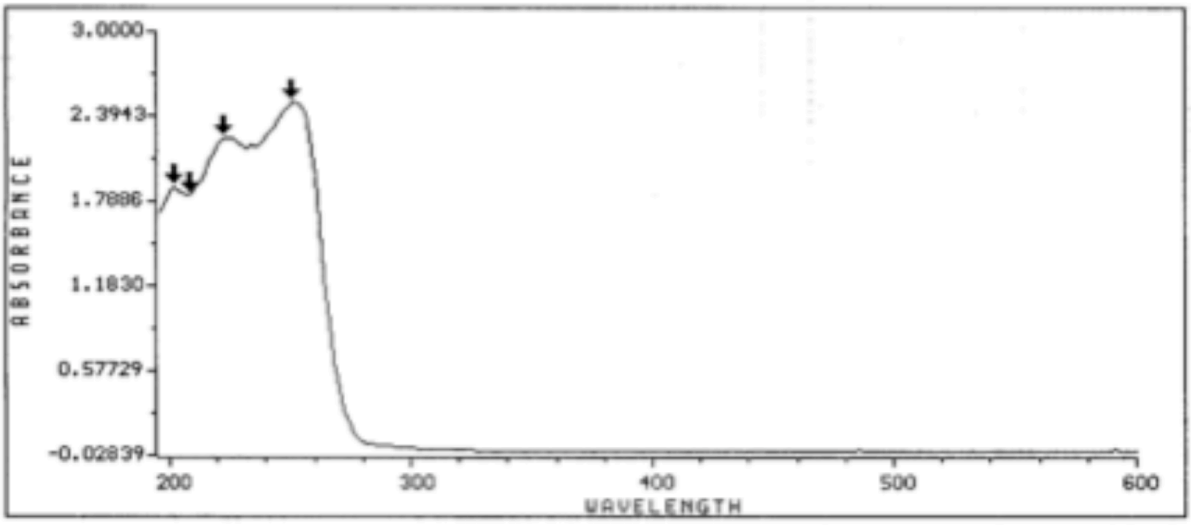


Figure S25. UV spectrum of **8** in D_2O.

Sample Name	: Cpd **10**	Function	: Absorbance
Solvent Name	: D2O	Wavelength Range	: 194 to 600 nm
Concentration	: 0.36	Integration Time	: 5.0 s
Unit	: mM		

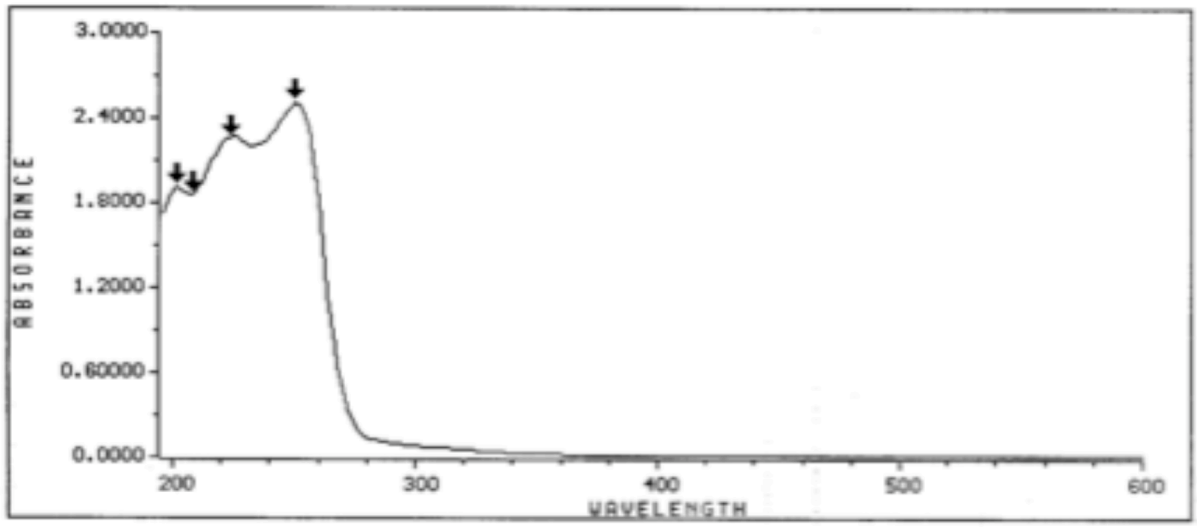


Figure S26. UV spectrum of **10** in D_2O.

Sample Name	: Cpd **12**	Function	: Absorbance
Solvent Name	: D2O	Wavelength Range	: 194 to 600 nm
Concentration	: 0.36	Integration Time	: 5.0 s
Unit	: mM		

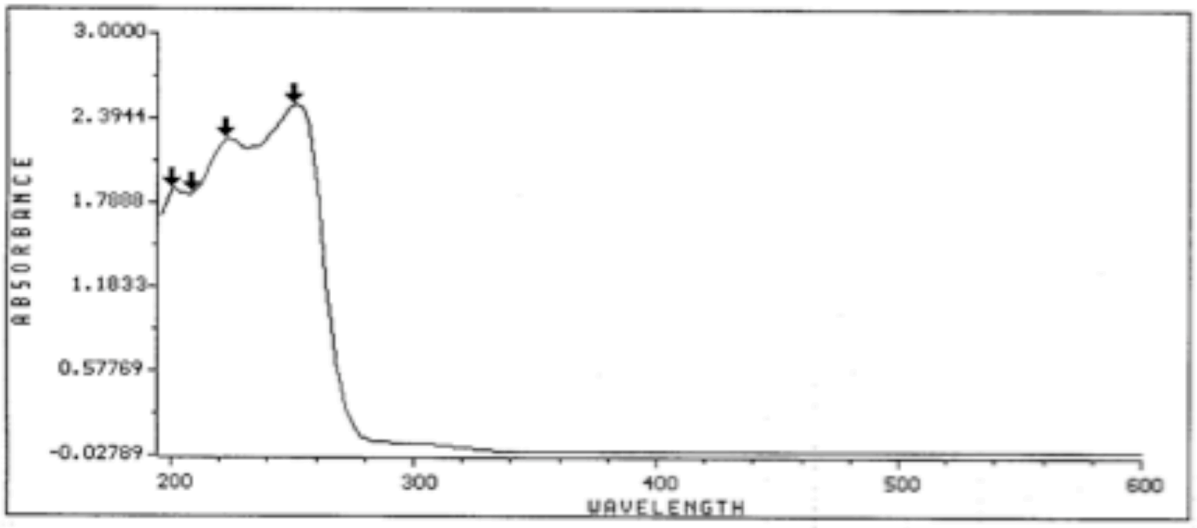


Figure S27. UV spectrum of **12** in D_2O.

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(3) Lundquist, J. T.; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781-783.