Electronic Supplementary Material (ESI) for Chemical Science.
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Construction of diverse peptide structural architectures via chemoselective peptide ligation

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1. General remarks on materials and methods

All commercially available amino acids and coupling reagents (purchased from Aldrich and GL Biochem) were used without further purification. All solvents in reagent grade (RCI) or HPLC grade (DUKSAN) were used without purification. Anhydrous dichloromethane (DCM) was freshly distilled from calcium hydride (CaH_2) before use. Analytical HPLC was performed on a Waters system equipped with a photodiode array detector (Waters 2996), using a Vydac 218TPTM C18 column (5 μm, 4.6 × 250 mm) at a flow rate of 0.6 mL/min. Waters UPLC H-class system equipped with an ACQUITY UPLC photodiode array detector and a Waters SQ Detector 2 mass spectrometer using a Waters ACQUITY BEH C18 column (1.7 μm, 130 Å, 2.1 × 50 mm) at a flow rate of 0.4 mL/min. Preparative HPLC was performed on a Waters system, using a Vydac 218TPTM C18 column (10 μm, 22 × 250 mm) at a flow rate of 10 mL/min or a Vydac 218TPTM C18 column (10 μm, 30 × 250 mm) at a flow rate of 20 mL/min. Mobile phases of HPLC used are as followed: Solvent A: 0.1% TFA (v/v) in acetonitrile; Solvent B: 0.1% TFA (v/v) in water. Mass analysis were performed with a Waters 3100 mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DRX 400 FT-NMR spectrometer at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR and Bruker Avance DRX 500 FT-NMR spectrometer at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR at 298K. The spectra were processed using TopSpin software.

2. General experimental procedures

2.1 Fmoc-based Solid Phase Peptide Synthesis (SPPS)

For Rink amide-AM resin

Rink amide-AM resin (100 mg) was swollen in anhydrous CH_2Cl_2 (3 mL) for 15 minutes then washed with CH_2Cl_2 (6 × 3 mL). The removal of Fmoc group was executed using a deblock solution of 20% piperidine in DMF at room temperature for 20 min. The resin was then washed with DMF (5 × 3 mL), CH_2Cl_2 (5 × 3 mL), and DMF (5 × 3 mL) and subsequently submitted to iterative peptide assembly (Fmoc-SPPS). The following Fmoc amino acids were employed: Fmoc-Ala-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gly-OH, Fmoc-His(Boc)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Phe-OH, Fmoc-Pro-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Tyr(tBu)-OH and Fmoc-Val-OH. Fmoc-AspBenzofuran-OH, Fmoc-GluBenzofuran-OH, Fmoc-Dap-Ser-OH dipeptide and Fmoc-Lys-Ser-OH were obtained by synthesis (Supporting information). For the coupling step, a solution of Fmoc-AA-OH (4 equiv. according to the resin capacity), HATU (4 eq. relative to resin capacity) and DIEA (8 eq.

relative to resin capacity) in DMF was added and the resin was shaken at room temperature for 1 hour. After each coupling cycle, the resin was washed with DMF (5 × 3 mL) and CH_2Cl_2 (5 × 3 mL).

For 2-chlorotrityl chloride resin

2-chloro-trityl resin (100 mg) was swollen in anhydrous CH_2Cl_2 (3 mL) for 15 minutes then washed with CH_2Cl_2 (6 × 3 mL). After that, a solution of Fmoc-Xaa-COOH (4.0 equiv. relative to resin loading capacity) and DIEA (8.0 equiv. relative to resin capacity) in anhydrous CH_2Cl_2 was added and the resin was shaken at room temperature for 2 h to load the first amino acid. Then the resin was washed with DMF (5 x 3mL) and CH_2Cl_2 (5 x 3mL) and subsequently treated with a solution of CH_2Cl_2/CH_3OH/DIEA (17:2:1, v/v/v, 5 mL) for 1 h. The resin was then washed with DMF (5 mL × 3), CH_2Cl_2 (5 mL × 3), and DMF (5 mL × 3). Finally, it was submitted to iterative peptide assembly (Fmoc-SPPS) following the procedures listed above.

2.2 Global deprotection to obtain free peptide

A mixture solution of TFA/H_2O/TIPS (95%/2.5%/2.5%, cocktail A) was added to the resin-bound peptide obtained according to General Procedure 2.1, and the mixture was gently agitated for 2 h at room temperature. The resin was then washed with CH_2Cl_2 (5 mL × 6). TFA was then blown off and the oily residue was triturated with cold diethyl ether to give a white suspension. After centrifugation, the precipitate was pelleted and the resulting peptide residue was ready for HPLC purification with the separation yield of 30-48%.

2.3 Mild acidic cleavage to obtain side-chain protected peptide

The 2-chlorotrityl chloride resin-bound fully protected peptide with C-terminal Gly obtained according to General Procedure 2.1 was subjected to mild acidic cleavage cocktail (5-10 mL) of CH_2Cl_2/AcOH/trifluoroethanol (8/1/1, v/v/v), 2 times for 60 min each. Followed by filtration, the resulting cleavage solutions were combined and concentrated to give crude side-chain protected peptide with a free carboxylic acid at the C-terminus.

2.4 Ozonolysis of the peptide to form SAL ester

The peptide obtained from General Procedure 2.2 was dissolved in the mixture solvent of H_2O/ACN = 1:1 with 0.7% TFA under ice bath. The solution was treated with O_3, which was produced from ozone generator, for 1 min.

2.5 Direct coupling to form C-terminal Gly peptide SAL ester

The fully protected peptidyl acid obtained from General Procedure 2.3 (1.0 equiv.) was dissolved in CH_2Cl_2 at a concentration of 10 mM, then N, N'-Dicyclohexylcarbodiimide (DCC) (5.0 equiv.), 4-Dimethylaminopyridine (DMAP) (0.5 equiv.) and α, α-dimethoxy-salicylaldehyde (30 equiv.) were added. The resulting reaction mixture was stirred at room temperature for overnight. After that, the reaction mixture was concentrated under *vacuo* and the resulting residue was treated with TFA/H_2O (95:5, v/v) for 2h. TFA was then blown off and the oily residue was triturated with cold diethyl ether to give a white suspension. After centrifugation, the precipitate was pelleted and the resulting peptide residue was ready for HPLC purification.

2.6 Intramolecular STL to form side chain-to-side chain cyclic peptide, Class II and III peptide architecture

The peptide obtained from General Procedure 2.4 or General Procedure 2.5 was dissolved in the solvent of pyridine/AcOH 1:1, 1:2, 1:6 or 1:12 mol/mol, the ratio used for each ligation were specified in the reaction schemes below per entry. The final peptide concentration was 0.5 mM. The resulting solution was stirred at room temperature for about 6 h and was monitored by UPLC-MS. No dimer was formed but the product. After the reaction has completed, the solvent was blown off under a stream of condensed air. The resulting residue was treated with a cocktail of TFA/H_2O/TIPS (95:2.5:2.5, v/v) for 15 min. TFA was then blown off and the oily residue was triturated with cold diethyl ether to give a white suspension. After centrifugation, the precipitate was pelleted and the resulting peptide residue was ready for HPLC purification with the separation yield of 33.5-48.0%.

2.7 Intermolecular STL to form Class I, II and III peptide architecture

The peptide obtained from General Procedure 2.4 (1.0 equiv.) and peptide with free N-terminal Ser/Thr obtained according to General Procedure 2.1 (1.2 to 1.5 equiv.) were dissolved in the solvent of pyridine/AcOH 1:1, 1:2, 1:6 or 1:12 mol/mol. The final peptide concentration was 5 or 10 mM depending on the solubility of the peptides. The equivalent, solvent ratio and concentration used for each ligation were specified in the reaction schemes below per entry. The resulting solution was stirred at room temperature for about 4 h and was monitored by UPLC-MS. After the reaction has completed, the solvent was blown off under a stream of condensed air. The resulting residue was treated with a cocktail of TFA/H_2O/TIPS (95:2.5:2.5, v/v) for 15 min. TFA was then blown off and the oily residue

was triturated with cold diethyl ether to give a white suspension. After centrifugation, the precipitate was pelleted and the resulting peptide residue was ready for HPLC purification with the separation yield of 31.1-53.3%.

2.8 One-pot Thz deprotection to form free N-terminal Cys

The crude intramolecular STL product obtained from General Procedure 2.6 was lyophilized to yield white solid. The dried peptide was then dissolved in Thz (thiazolidine)-opening buffer (0.2 M PB solution, pH = 4, containing 50 mM TCEP·HCl 6 M Gn·HCl, and 300 mM $MeONH_2$·HCl) and stirred at room temperature for overnight. The resulting peptide with free N-terminal Cys was ready for HPLC purification. The separation yield over two steps was 35.4-37.2%.

2.9 One-pot Fmoc deprotection to form free N-terminal Ser

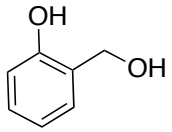
The crude intramolecular STL product obtained from General Procedure 2.6 was lyophilized to yield white solid. The dried peptide was then dissolved in ACN/H_2O solution with 10% diethylamine. The final peptide concentration was 2.5mM. The reaction mixture was stirred at room temperature for 2h and was monitored by UPLC-MS. The resulting reaction mixture was ready for HPLC purification. The separation yield over two steps was 32.6%.

2.10 Intermolecular CPL to form class III peptide architecture

The peptides obtained from General Procedure 2.4 (1.0 equiv.) and General Procedure 2.8 (1.2 equiv.) were dissolved in the solvent of pyridine/formic acid (1:12, mol/mol). The peptide concentration was 5mM to 10 mM depending on the solubility of the peptides. The solvent ratio and concentration used for each ligation were specified in the reaction schemes below per entry. The resulting solution was stirred at 0^oC to room temperature for about 4 h and monitored by UPLC-MS. After the reaction has completed, the solvent was blown off under a stream of condensed air. The resulting residue was treated with a cocktail of TFA/H_2O/EDT (95:2.5:2.5, v/v) for 4 h. TFA was then blown off and the oily residue was triturated with cold diethyl ether to give a white suspension. After centrifugation, the precipitate was pelleted and the resulting peptide residue was ready for HPLC purification with the separation yield of 45.8-50.4%.

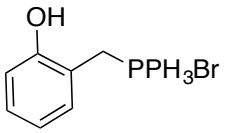
3. Synthesis of building blocks

3.1 Compound 1



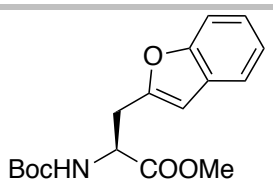
Salicylaldehyde (8.0 g, 65.51 mmol) was dissolved in EtOH (30 mL) and $NaBH_4$ (2.0 g, 52.40 mmol) was added portion-wise under ice bath. The resulting mixture was stirred for 2 hours under ice bath, then quenched with 1N HCl (30 mL). The mixture was extracted with EtOAc (100 mL × 3) and the combined organic phase was washed with brine (100 mL × 1), dried over Na_2SO_4 and concentrated under *vacuo*. Purification by silica gel chromatography (n-hexane/EtOAc = 2:1) gave the white solid (7.5 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.29 (1H, s), 7.18-7.23 (1H, dt, *J* = 1.4 Hz, 7.7 Hz), 7.02-7.04 (1H, dd, *J* = 1.1 Hz, 7.0 Hz), 6.87-6.89 (1H, d, *J* = 8.4 Hz), 6.83-6.85 (1H, dd, *J* = 0.9 Hz, 7.4 Hz), 4.85-4.86 (2H, d, *J* = 3.4 Hz), 2.34 (1H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), δ 156.2, 129.6, 127.9, 124.7, 120.2, 116.7, 64.8 ppm.

3.2 Compound 2



Compound **1** (7.5 g, 60.42 mmol) and triphenylphosphine hydrobromide (20.7 g, 60.42 mmol) were dissolved in anhydrous ACN under the protection of argon. The resulting mixture was refluxed overnight and concentrated under *vacuo*. Purification by silica gel chromatography (CH_2Cl_2/MeOH = 10:1) gave the white solid (23.5 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 9.00 (1H, s), 7.68-7.79 (3H, m), 7.44-7.63 (m, 12H), 7.27 (1H, m), 6.95-7.02 (1H, m), 6.90-6.95 (1H, m), 6.59 (1H, t, *J* = 7.4 Hz), 4.55 (2H, d, *J* = 13.5 Hz) ppm.

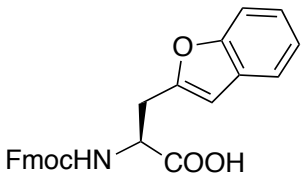
3.3 Compound 3



Boc-Asp-OMe (2.80 g, 8.78 mmol) and compound **2** (3.28g, 7.31 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) under the protection of argon in ice bath. N,N′-Diisopropylcarbodiimide (1.70 ml, 10.96 mmol) was added in dropwise to the above solution. The resulting mixture was stirred for overnight. After the reaction was complete, the mixture was concentrated under *vacuo* to give an activated ester intermediate, which was then dissolved in anhydrous toluene (30 mL) under the protection of argon. Triethylamine (1.12 ml, 8.04 mmol) was added to the reaction mixture and refluxed overnight.

The reaction mixture was then concentrated under *vacuo* and diluted with EtOAc (300 mL), washed with 1N HCl (100 mL × 1) and brine (100 mL × 1). The organic phase was dried over Na_2SO_4, concentrated under *vacuo* and purified by silica gel chromatography (n-hexane/EtOAc = 6:1) to give the yellowish oil (1.0 g, 26%). ^{1}H NMR (400 MHz, $CDCl_3$), δ7.48-7.50 (1H, dd, *J* = 1.3 Hz, 6.8 Hz), 7.39-7.41 (1H, dd, *J* = 0.9 Hz, 7.3 Hz), 7.16-7.25 (2H, m), 5.20-5.22 (1H, d, *J* = 7.7 Hz), 4.67-4.69 (1H, d, *J* = 7.8 Hz), 3.76 (3H, s), 3.30-3.31 (2H, d, *J* = 5.41 Hz), 1.42 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), δ 171.9, 155.3, 155.1, 153.6, 128.5, 123.9, 122.8, 120.7, 111.1, 105.0, 80.3, 52.7, 52.5, 31.6, 28.4 ppm. HRMS (ESI$^+$) calcd. for $C_{17}H_{21}NNaO_5$ (+) $[M+Na]^+$ 342.1312, found 342.1310

3.4 Compound 4 - Fmoc-AspBenzofuran-OH

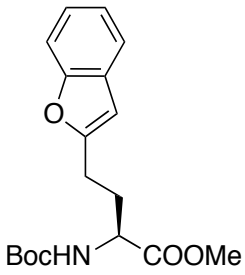


The compound **3** (1.0 g, 3.13 mmol) was dissolved in THF/H_2O = 3:1 (12 mL) at room temperature. To the above solution was added LiOH.H_2O (394.38 mg, 9.39 mmol), the reaction mixture was stirred at room temperature for around 2 hours, followed by quenching with 1N HCl (20 mL). The resulting mixture was extracted with EtOAc (40 mL × 3), the combined organic phase was washed with brine (30 mL × 1), dried over Na_2SO_4 and concentrated under *vacuo*. The obtained white solid **3.1** was devoted to the next step without further purification.

Crude compound **3.1** was dissolved in solution of 4N HCl in dioxane (3 mL). The resulting solution was stirred at room temperature for about 2 hours and the white solid was precipitated out. The solvent was blow away by a stream of air and the resulting crude solid **3.2** was devoted to the next step without further purification.

Crude compound **3.2** (754.5 mg, 3.13 mmol) and Na_2CO_3 (1.20 g, 10.95 mmol) were dissolved in H_2O (6 mL) under ice bath. To the above solution was slowly added the solution of Fmoc-Cl (2.0 g, 7.82 mmol) in dioxane (12 mL). The temperature was allowed to rise to room temperature and stirred for overnight, followed by diluting the mixture with EtOAc (150 mL), washed by 1N HCl (30 mL × 2), brine (30 mL × 1) dried over Na_2SO_4 and concentrated under *vacuo*. Purified by silica gel chromatography (n-hexane/EtOAc = 2:1 with 0.5% AcOH) to give the white solid (870.0 mg, 65% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.72-7.74 (2H, d, *J* = 7.5 Hz), 7.53-7.54 (2H, d, *J* = 7.2 Hz), 7.47-7.49 (1H, d, *J* = 6.9 Hz), 7.35-7.40 (3H, m), 7.17-7.26 (4H, m), 6.50 (1H, s), 5.51-5.53 (1H, d, *J* = 6.9 Hz), 4.76-4.77 (1H, m), 4.43-4.44 (2H, m), 4.18-4.21 (1H, m), 3.32-3.35 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), δ 174.5, 156.0, 155.1, 153.2, 143.8, 143.7, 141.4, 128.4, 127.9, 127.2, 125.2, 124.2, 122.9, 120.8, 120.1, 111.2, 105.4, 67.4, 52.8, 47.2, 31.0 ppm. HRMS (ESI^+) calcd. for $C_{26}H_{21}NNaO_5$ (+) $[M+H]^+$ 334.1576, found 334.1642.

3.5 Compound 5

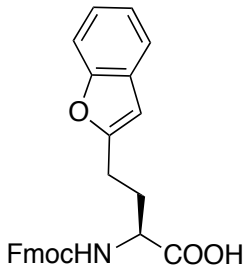


Boc-Glu-OMe (2.88 g, 8.64 mmol) and compound **2** (3.24g, 7.20 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) under the protection of argon in ice bath. N,N′-Diisopropylcarbodiimide (1.67 ml, 10.79 mmol) was added in dropwise to the above solution. The resulting mixture was stirred for overnight. After the reaction was complete, the mixture was concentrated under *vacuo* to give an activated ester intermediate, which was then dissolved in anhydrous toluene (30 mL) under the

protection of argon. Triethylamine (1.10 ml, 7.92 mmol) was added to the reaction mixture and refluxed overnight.

After the reaction was completed, the mixture was concentrated under *vacuo* and diluted with EtOAc (300 mL), washed with 1N HCl (100 mL × 1) and brine (100 mL × 1). The organic phase was dried over Na_2SO_4, concentrated under *vacuo* and purified by silica gel chromatography (n-hexane/EtOAc = 8:1) to give the yellowish oil (1.44 g, 62.50 %) ^{1}H NMR (500 MHz, $CDCl_3$), δ7.46-7.48 (1H, dd, *J* = 1.2 Hz, 7.0 Hz), 7.39-7.40 (1H, dd, *J* = 0.9 Hz, 7.3 Hz), 7.17-7.21 (2H, m), 6.42 (1H, d, J=0.78 Hz), 5.14-5.16 (1H, d, *J* = 7.8 Hz), 4.42-4.43 (1H, d, *J* = 5.1 Hz), 3.71 (3H, s), 2.82-2.89 (2H,m), 2.26-2.33 (1H, m), 2.03-2.11 (1H,m), 1.42 (9H, s) ppm; ^{13}C NMR (125 MHz, $CDCl_3$), δ 172.9, 157.6, 155.5, 154.8, 128.9, 123.5, 122.6, 120.5, 110.8, 102.7, 80.1, 53.1, 52.5, 30.9, 28.4, 24.7 ppm. HRMS (ESI$^+$) calcd. for $C_{18}H_{23}NO_5$ (+) $[M+H]^+$ 334.1576, found 334.1642.

3.6 Compound 6 - Fmoc-GluBenzofuran-OH



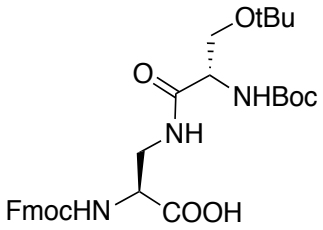
The compound **5** (1.44g, 4.30 mmol) was dissolved in THF/H_2O = 3:1 (20 mL) at room temperature. To the above solution was added LiOH.H_2O (540.30 mg, 12.86 mmol), the resulting mixture was stirred at room temperature for about 2 hours, followed by quenching with 1N HCl (28 mL). The resulting mixture was extracted with EtOAc (60 mL × 3), the combined organic phase was washed with brine (50 mL × 1), dried over Na_2SO_4 and concentrated under *vacuo*. The obtained white solid **5.1** was devoted to the next step without further purification.

Crude compound **5.2** was dissolved in solution of 4N HCl in dioxane (7 mL). The resulting solution was stirred at room temperature for about 2 hours and the white solid was precipitated out. The solvent was blown away by a stream of air and the resulting crude solid **5.3** was devoted to the next step without further purification.

Crude compound **5.3** obtained (941.7mg, 4.30 mmol) and Na_2CO_3 (1.64 g, 15 mmol) were

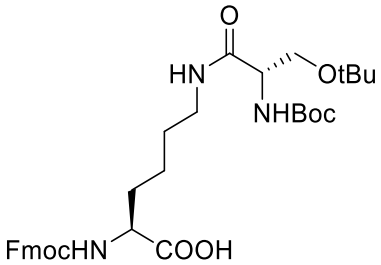
dissolved in H_2O (6 mL) under ice bath. To the above solution was slowly added the solution of Fmoc-Cl (2.74 g, 10.71 mmol) in dioxane (20 mL). The temperature was allowed to rise to room temperature and stirred for 6 hours, followed by diluting the mixture with EtOAc (150 mL), washed by 1N HCl (40mL × 2), brine (40 mL × 1) dried over Na_2SO_4 , concentrated under *vacuo* and purified by silica gel chromatography (n-hexane/EtOAc = 2:1 with 0.5% AcOH) to give the white solid (606.08mg, 53% over three steps). ^{1}H NMR (500 MHz, $CDCl_3$), δ7.75-7.76 (2H, d, *J* = 7.3 Hz), 7.56-7.59 (2H, t, *J* = 7.2 Hz), 7.47-7.48 (1H, d, *J* = 7.5 Hz),7.37-7.41 (3H, m), 7.28-7.32 (2H, m), 7.15-7.22 (3H, m), 6.43(1H, s), 5.37-5.39 (1H, d, *J* = 8.1 Hz), 4.48-4.52 (1H, m), 4.42-4.44 (2H, d, J= 6.6 Hz), 4.18-4.21 (1H, t), 2.87 (2H, m), 2.37-2.40 (1H, m), 2.11-2.18 (1H, m) ppm; ^{13}C NMR (125 MHz,$CDCl_3$), δ 176.7, 157.3, 156.4, 154.9, 143.8, 141.5, 128.8, 127.9, 127.3, 125.2, 123.6, 122.7, 120.6, 120.2, 110.9, 103.0, 69.3, 53.5, 47.3, 30.5, 24.7 ppm. HRMS (ESI^+) calcd. for $C_{27}H_{23}NO_5$ (+) $[M+H]^+$ 442.1576, found 442.1636.

3.7 Compound 7a - Fmoc-Dap-Ser-OH dipeptide



Boc-Ser(tBu)-OH (827.0mg, 3.83mmol) was dissolved in anhydrous CH_2Cl_2 (60ml) under argon protection, in ice bath. Isobutylchloroformate (0.55ml, 4.21mmol) was add slowly to the solution, followed by DIEA (3ml, 17.2mmol) added dropwise. The reaction mixture was stirred for 2 hours and Fmoc-Dap-OH (1.5g, 4.59mmol) was added and reacted for 2 hours. After the reaction was completed, the mixture was diluted with EtOAc (100ml), washed with 1N HCl (30ml x1) and brine (100ml x2). The organic phase was dried over Na_2SO_4, concentrated under *vacuo* and purified by silica gel chromatography (n-hexane/EtOAc = 1:1, 0.5% AcOH) to give a white solid (1.44 g, 66.1 %). ^{1}H NMR (500 MHz, $CDCl_3$), δ7.75-7.77 (2H, d, *J* = 7.5 Hz), 7.60-7.61 (2H, d, *J* = 6.3 Hz), 7.33-7.41 (2H, t, *J* = 7.4 Hz), 7.30-7.33 (2H, t, J= 7.4 Hz), 6.22 (1H, s) , 5.48 (1H, s), 4.33-4.42 (3H, m), 4.21-4.24 (2H, t, J= 6.96 Hz), 3.86 (1H, s), 3.70-3.72 (2H, m), 3.46-3.49(1H, t, J=7.5), 1.46 (9H, s), 1.17 (9H, s) ppm; ^{13}C NMR (125 MHz,$CDCl_3$), δ172.8, 156.5, 156.0, 143.9, 141.4, 127.8, 127.2, 125.4, 120.0, 80.2, 73.8, 67.7, 62.0, 54.5, 47.0, 41.0, 28.2, 27.4 ppm. HRMS (ESI^+) calcd. for $C_{30}H_{39}N_3O_8$ (+) $[M+H]^+$ 570.2737, found 570.2799.

Compound 7b - Fmoc-Lys-Ser-OH dipeptide

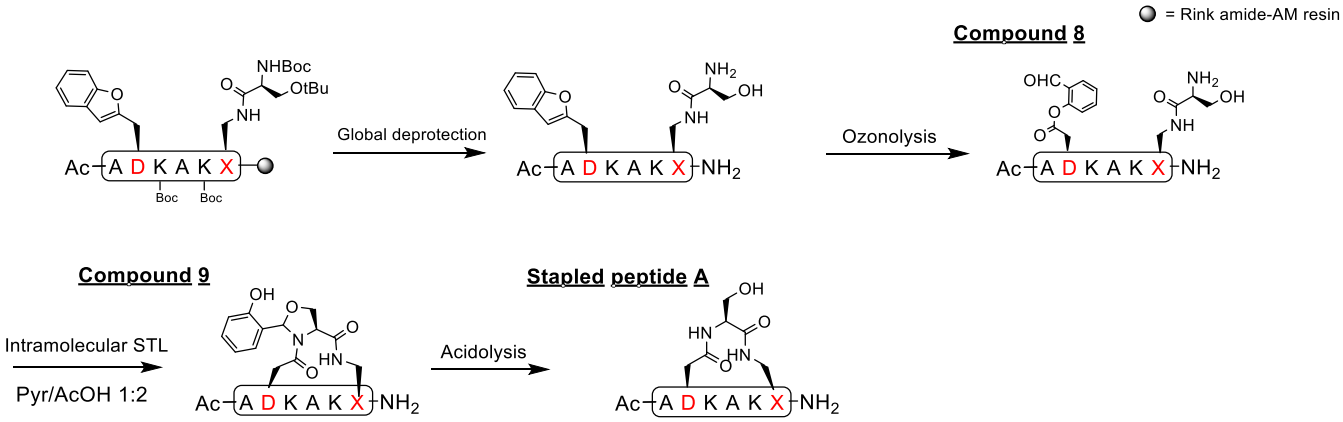


Boc-Ser(tBu)-OH (827.0mg, 3.83mmol) was dissolved in anhydrous CH_2Cl_2 (60ml) under argon protection, in ice bath. Isobutylchloroformate (0.55ml, 4.21mmol) was add slowly to the solution, followed by DIEA (3ml, 17.2mmol) added dropwise. The reaction mixture was stirred for 2 hours and Fmoc-Lys-OH (1.69g, 4.59mmol) was added and reacted for 2 hours. After the reaction was completed, the mixture was diluted with EtOAc (100ml), washed with 1N HCl (30ml x1) and brine (100ml x2). The organic phase was dried over Na_2SO_4, concentrated under *vacuo* and purified by silica gel chromatography (n-hexane/EtOAc = 1:1, 0.5% AcOH) to give a white solid (1.59 g, 68.0 %). ^{1}H NMR (500 MHz, $CDCl_3$), δ7.75-7.77 (2H, d, *J* = 7.8 Hz), 7.60-7.61 (2H, d, *J* = 6.3 Hz), 7.33-7.41 (2H, t, *J* = 7.5 Hz), 7.30-7.33 (2H, t, J= 7.8 Hz), 6.79 (1H, s), 5.84 (1H, s), 5.60 (1H, s), 4.33-4.42 (3H, m), 4.21-4.24 (2H, t, J= 7.1 Hz), 3.72-3.76 (1H, dd, J= 8.6, 3.7 Hz), 3.37-3.47 (1H, m), 3.20-3.36 (2H, m), 1.86-1.98 (1H, m), 1.73-1.85 (1H, m), 1.51-1.58 (2H, m), 1.46 (9H, s), 1.17 (9H, s) ppm; ^{13}C NMR (125 MHz,$CDCl_3$), δ175.0, 171.3, 156.3, 155.8, 143.8, 141.3, 127.7, 127.1, 125.2, 120.0, 80.3, 74.0, 67.0, 61.8, 54.5, 53.6, 47.1, 39.0, 31.8, 29.0, 28.3, 27.4, 22.2 ppm.

4. UPLC-Chromatogram and MS-Spectra

4.1 Synthesis of side chain-to-side chain cyclic peptide (Stapled peptide A-F)

Stapled peptide A



Ozonolysis of the purified peptide (10.00 mg, 12.24 µmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 8 as white solid.

The ligation of crude Compound 8 (4.8 mg, 5.65 µmol) was performed as described in general procedure 2.6. Reverse phase HPLC purification followed by lyophilization afforded the product Stapled peptide A (1.58 mg, 38.4 % yield) as white solid.

Compound 8

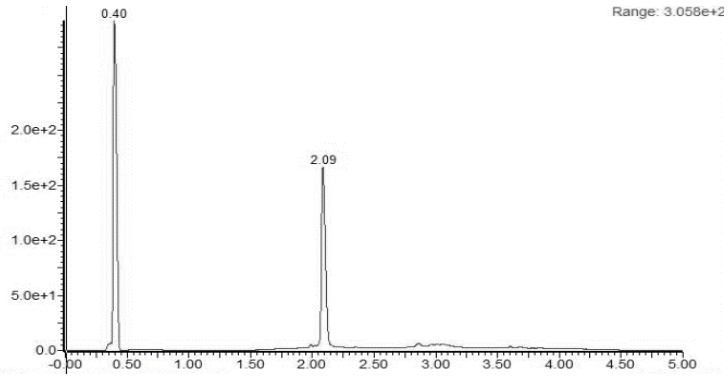


Figure S1: UV trace from analytical UPLC-MS analysis for crude **Compound 8**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

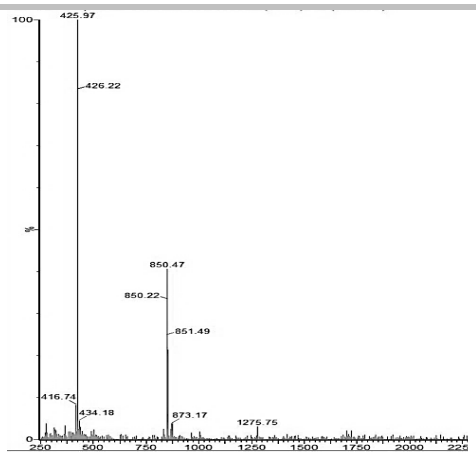


Figure S2: ESI-MS calcd. for $C_{37}H_{59}N_{11}O_{12}$ = 849.43; $[M+H]^+$ *m/z* =850.43, found 850.47; $[M+2H]^{2+}$ *m/z* = 425.72, found 425.97.

Compound 9

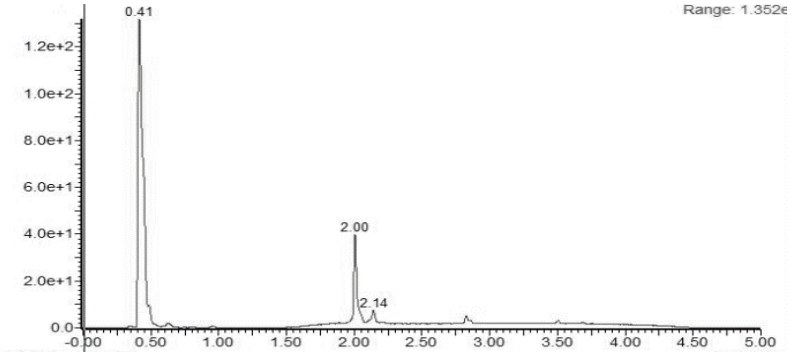


Figure S3: UV trace from analytical UPLC-MS analysis for crude **Compound 9**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

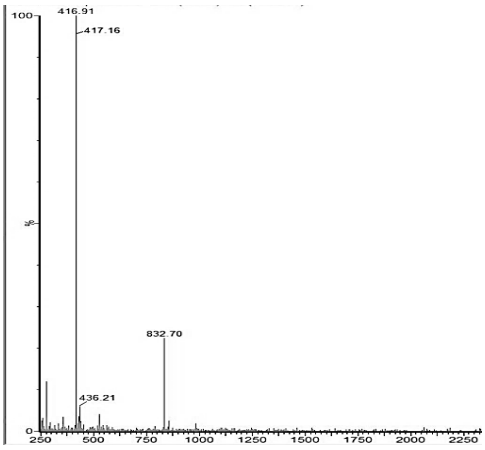


Figure S4: ESI-MS calcd. for $C_{37}H_{57}N_{11}O_{11}$ = 831.42; $[M+H]^+$ *m/z* =832.42, found 832.70; $[M+2H]^{2+}$ *m/z* = 416.71, found 416.91.

Stapled A

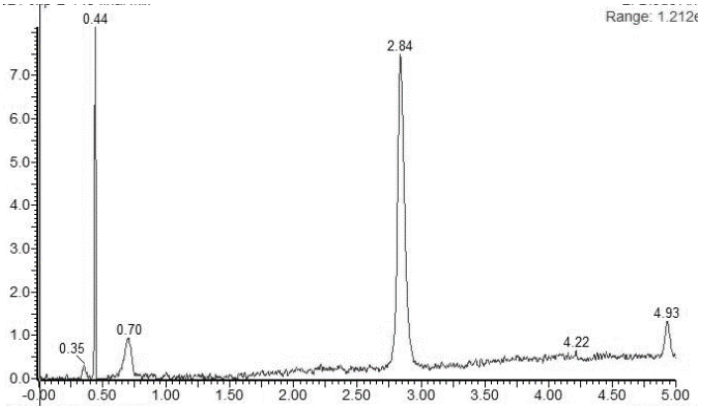


Figure S5: UV trace from analytical UPLC-MS analysis for purified **Stapled A**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

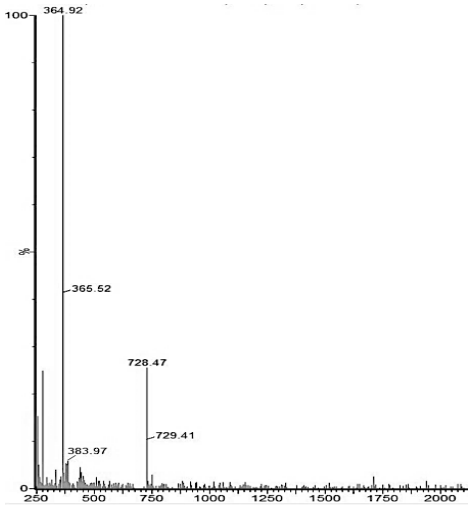
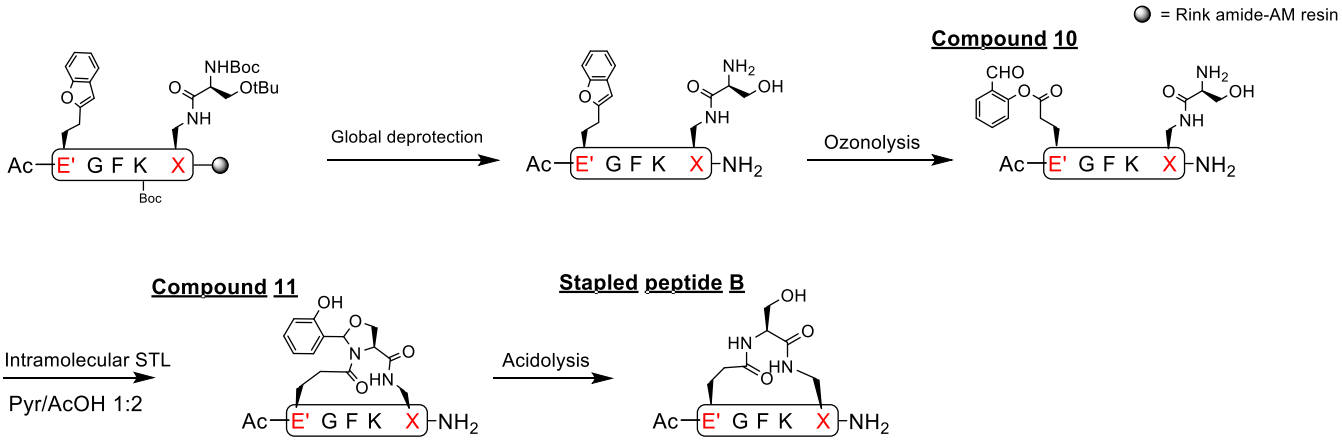


Figure S6: ESI-MS calcd. for $C_{29}H_{50}N_{11}O_{10}$ = 727.40 ; $[M+H]^+$ *m/z* =728.40, found 728.47; $[M+2H]^{2+}$ *m/z* = 364.70, found 364.92.

Stapled peptide B



Ozonolysis of the purified peptide (10.00 mg, 13.07 µmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 10 as white solid.

The ligation of crude Compound 10 (3.88 mg, 4.87 µmol) was performed as described in general procedure 2.6. Reverse phase HPLC purification followed by lyophilization afforded the product Stapled peptide B (1.10 mg, 33.5 % yield) as white solid.

Compound 10

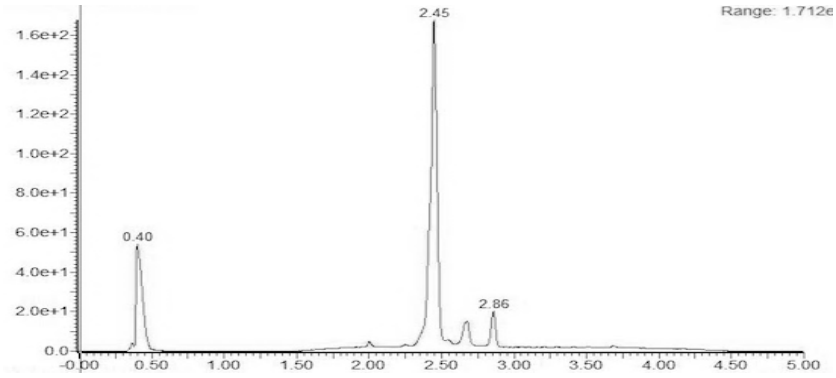


Figure S7: UV trace from analytical UPLC-MS analysis for crude **Compound 10**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

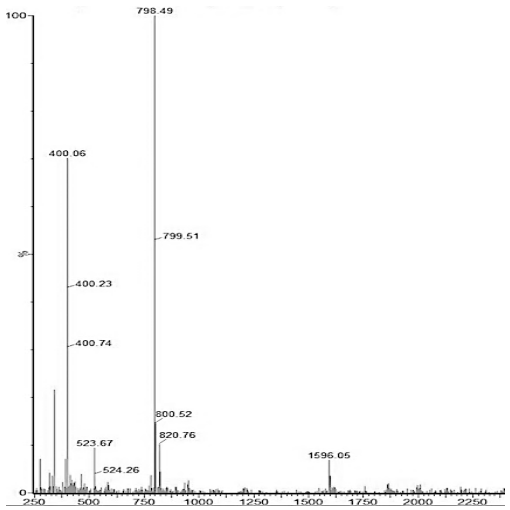


Figure S8: ESI-MS calcd. for $C_{37}H_{51}N_9O_{11}$ = 797.37; $[M+H]^+$ *m/z* = 798.37, found 798.49; $[M+2H]^{2+}$ *m/z* = 399.69, found 400.06; $[2M+H]^+$ *m/z* = 1595.74, found 1596.05.

Compound 11

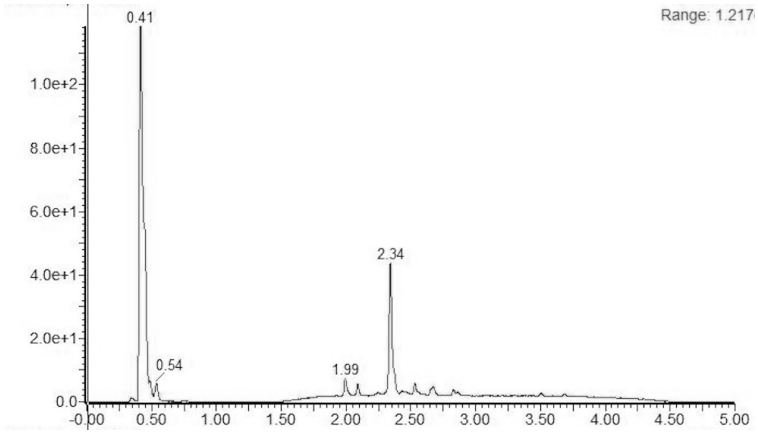


Figure S9: UV trace from analytical LC-MS analysis for crude **Compound 11**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 15 min at a flow rate of 0.6 mL/min.

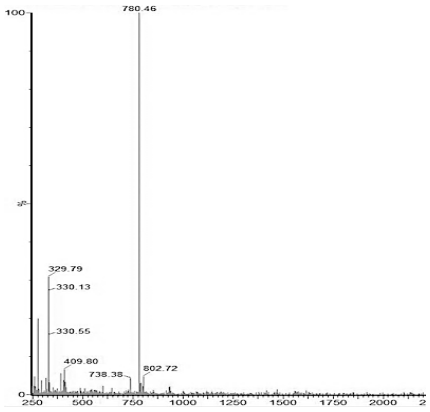


Figure S10: ESI-MS calcd. for $C_{37}H_{49}N_9O_{10}$ = 779.36, $[M+H]^+$ *m/z* = 780.36, found 780.46.

Stapled peptide B

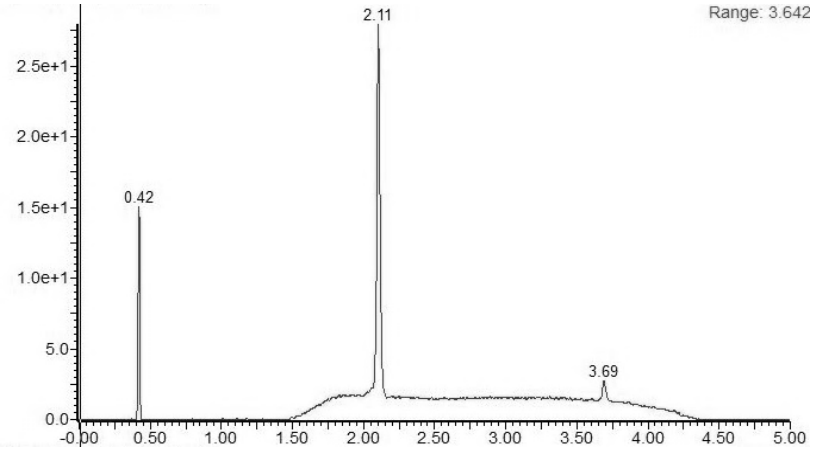


Figure S11: UV trace from analytical UPLC-MS analysis for purified **Stapled peptide B**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

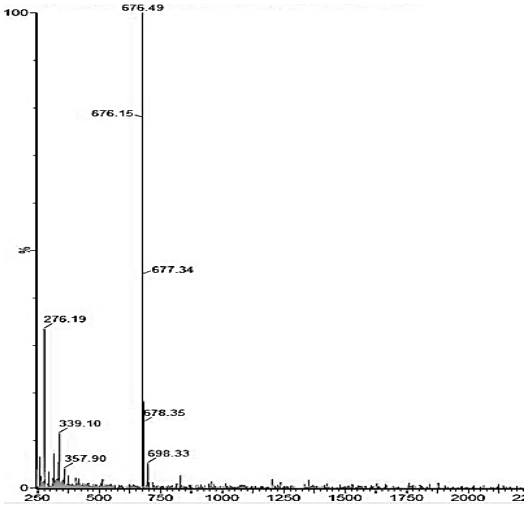
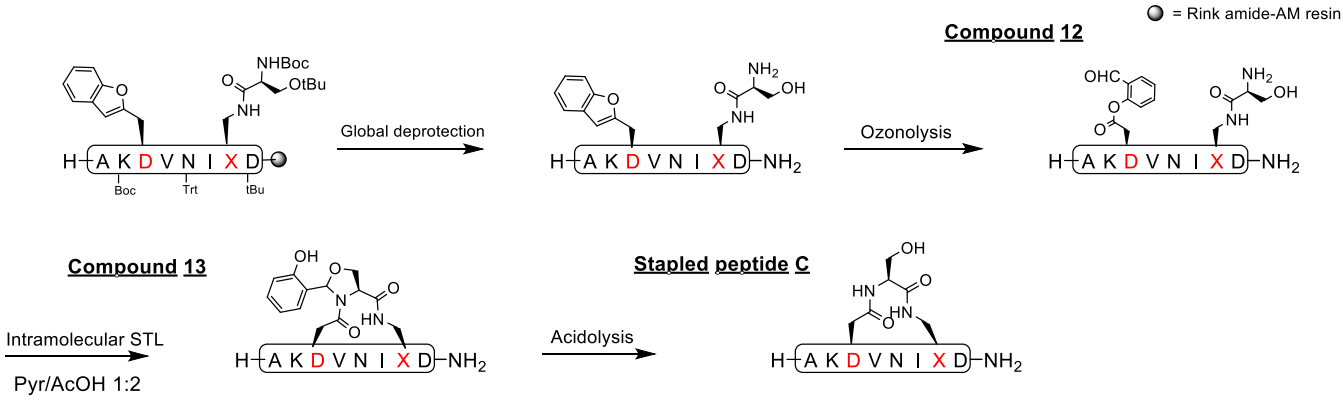


Figure S12: ESI-MS calcd. for $C_{30}H_{45}N_9O_9$ = 675.33; $[M+H]^+$ *m/z* = 676.33, found 676.49; $[M+2H]^{2+}$ *m/z* = 338.67, found 339.10.

Stapled peptide C



Ozonolysis of the purified peptide (10.00 mg, 9.82 µmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 12 as white solid.

The ligation of crude Compound 12 (4.02 mg, 3.83 µmol) was performed as described in general procedure 2.6. Reverse phase HPLC purification followed by lyophilization afforded the product Stapled peptide C (1.24 mg, 34.9 % yield) as white solid.

Compound 12

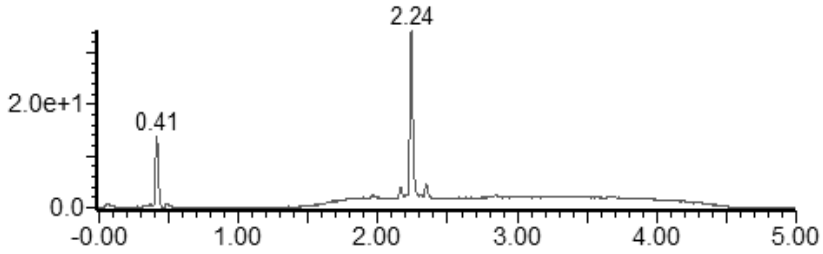


Figure S13: UV trace from analytical UPLC-MS analysis for crude **Compound 12**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

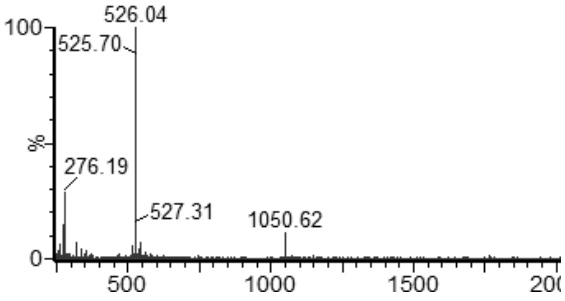


Figure S14: ESI-MS calcd. for $C_{45}H_{70}N_{12}O_{17}$ = 1050.50 ; $[M+H]^+$ *m/z* = 1051.50, found 1050.62; $[M+2H]^{2+}$ *m/z* =526.25, found 526.04.

Compound 13

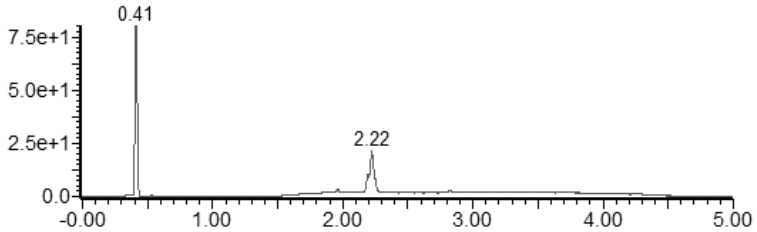


Figure S15: UV trace from analytical UPLC-MS analysis for crude **Compound 13**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

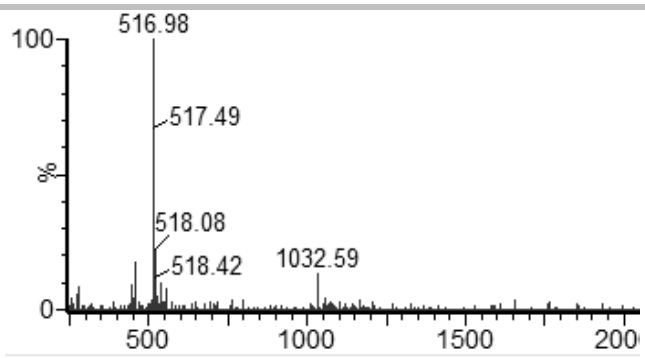


Figure S16: ESI-MS calcd. for $C_{45}H_{68}N_{12}O_{16}$ = 1032.49; $[M+H]^+$ *m/z* =1033.49, found 1032.59; $[M+2H]^{2+}$ *m/z* = 517.24, found 516.98.

Stapled peptide C

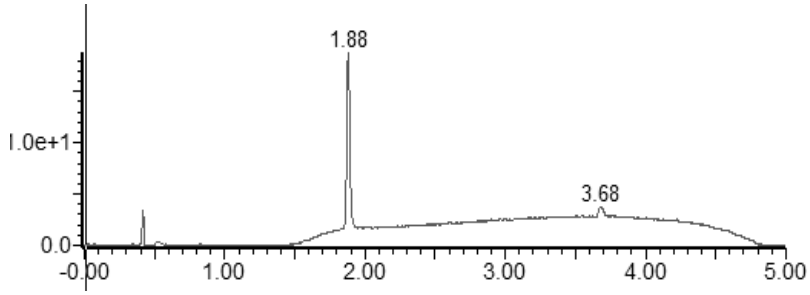


Figure S17: UV trace from analytical UPLC-MS analysis for purified **Stapled peptide C**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

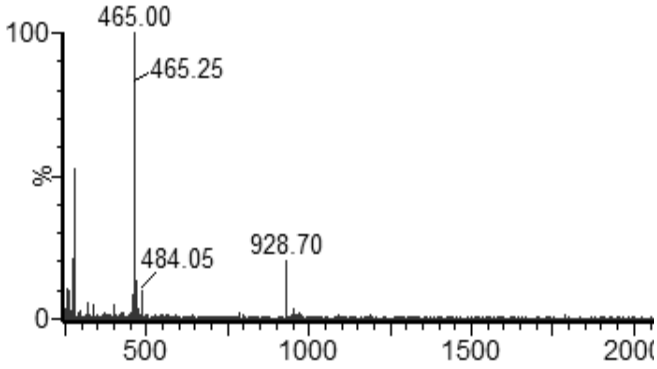
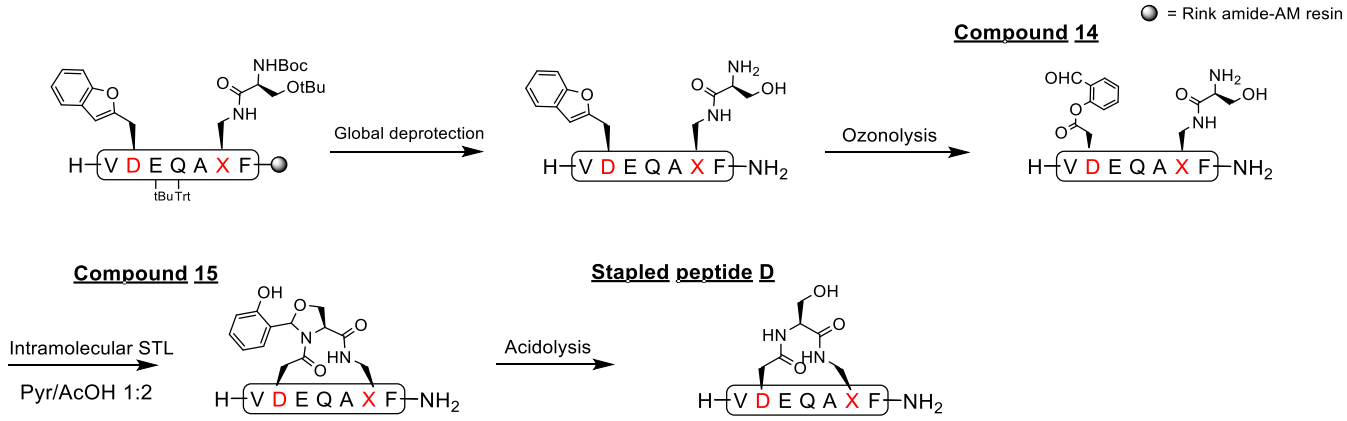


Figure S18: ESI-MS calcd. for $C_{38}H_{64}N_{12}O_{15}$ = 928.46; $[M+H]^+$ *m/z* = 929.46, found 928.70; $[M+2H]^{2+}$ *m/z* = 465.23, found 465.00.

Stapled peptide D



Ozonolysis of the purified peptide (10.00 mg, 10.50 µmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 14 as white solid.

The ligation of crude Compound 14 (4.21 mg, 4.28 µmol) was performed as described in general procedure 2.6. Reverse phase HPLC purification followed by lyophilization afforded the product Stapled peptide D (1.36 mg, 37.0 % yield) as white solid.

Compound 14

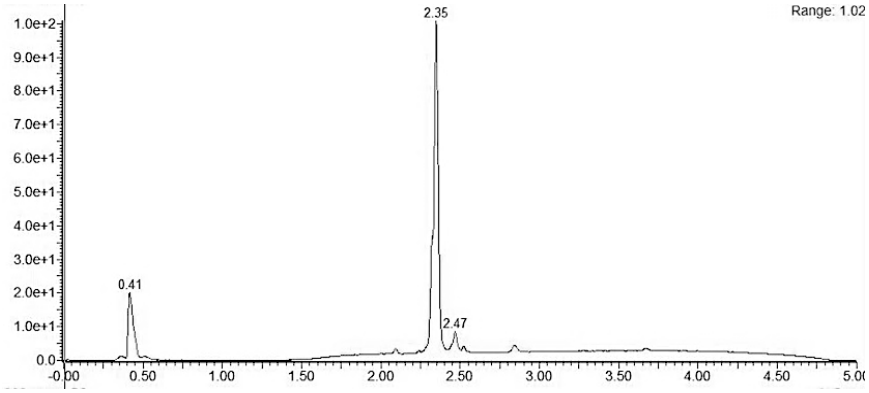


Figure S19: UV trace from analytical UPLC-MS analysis for crude **Compound 14**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

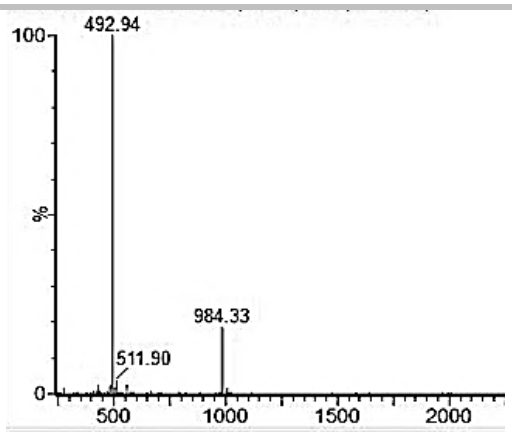


Figure S20: ESI-MS calcd. for $C_{43}H_{60}N_{12}O_{15}$ = 983.43; $[M+H]^+$ *m/z* =984.43, found 1032.76; $[M+2H]^{2+}$ *m/z* = 492.71, found 492.94.

Compound 15

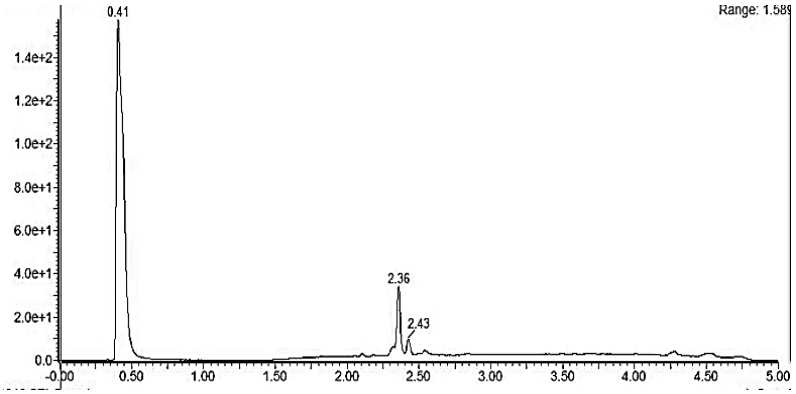


Figure S21: UV trace from analytical UPLC-MS analysis for crude **Compound 15**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

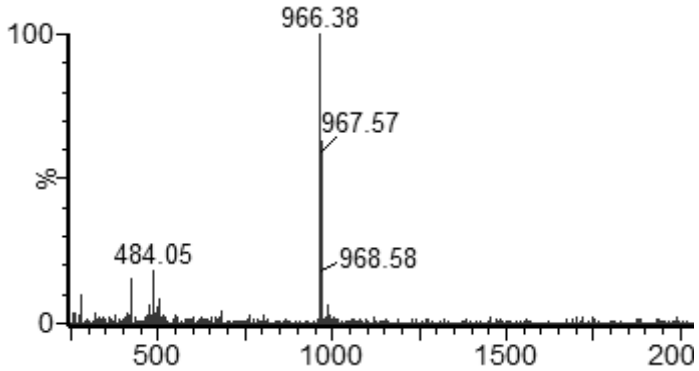


Figure S22: ESI-MS calcd. for $C_{45}H_{68}N_{12}O_{16}$ = 965.42; $[M+H]^+$ *m/z* =966.42, found 966.38; $[M+2H]^{2+}$ *m/z* = 483.71, found 484.05.

Stapled peptide D

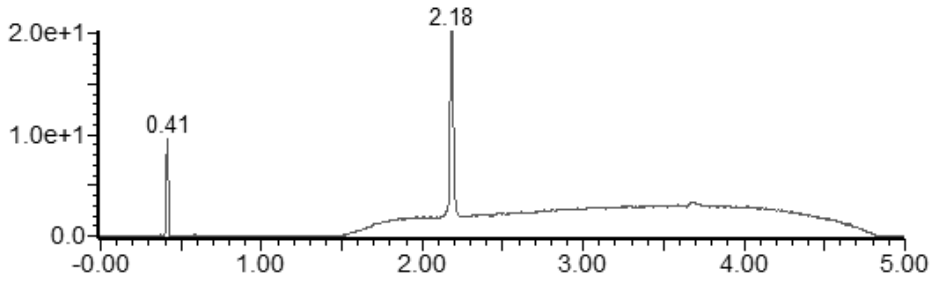


Figure S23: UV trace from analytical UPLC-MS analysis for purified **Stapled peptide D**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

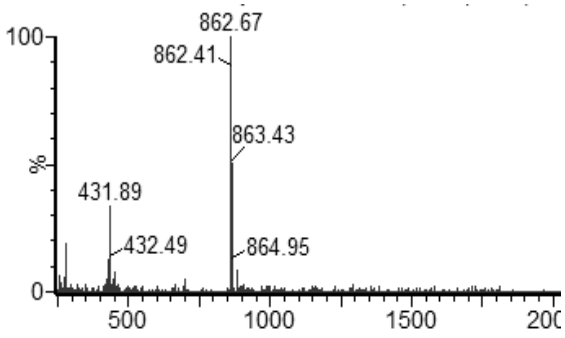
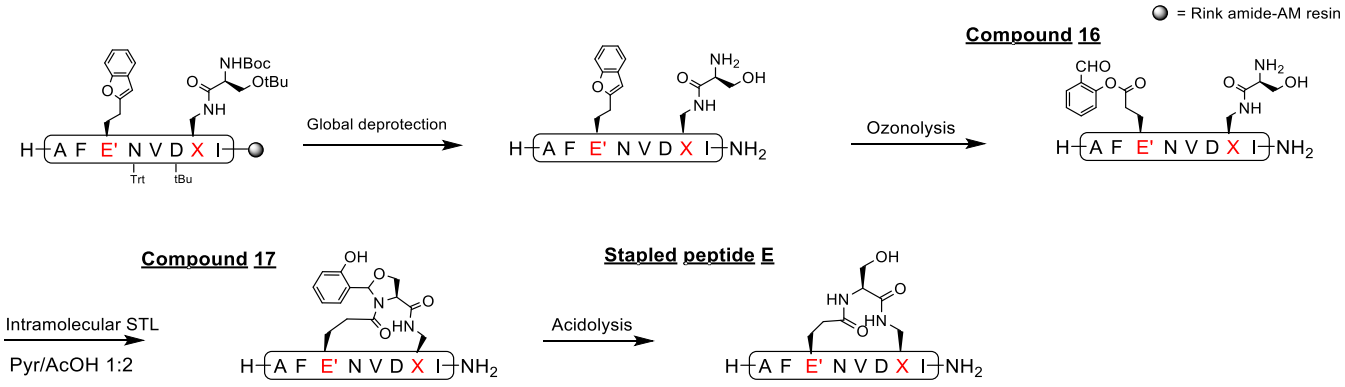


Figure S24: ESI-MS calcd. for $C_{37}H_{55}N_{11}O_{13}$ = 861.40; $[M+H]^+$ *m/z* = 862.40, found 862.67$[M+2H]^{2+}$ *m/z* = 431.70, found 431.89.

Stapled peptide E



Ozonolysis of the purified peptide (10.00 mg, 9.52 µmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 16 as white solid.

The ligation of crude Compound 16 (3.79 mg, 3.50 µmol) was performed as described in general

procedure 2.6. Reverse phase HPLC purification followed by lyophilization afforded the product Stapled peptide E (1.19 mg, 35.2 % yield) as white solid.

Compound 16

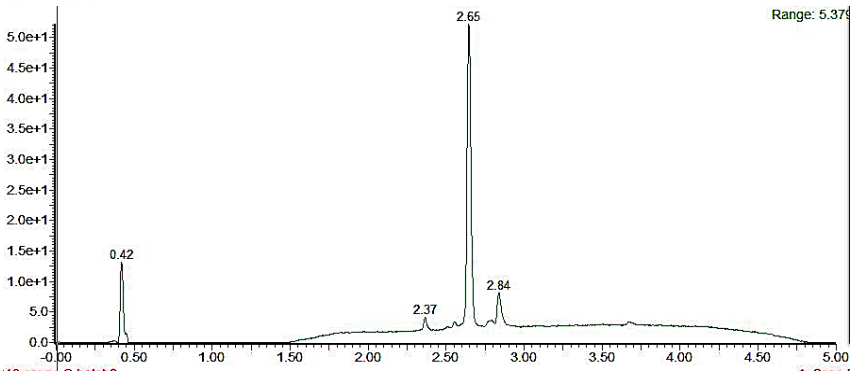


Figure S25: UV trace from analytical UPLC-MS analysis for crude **Compound 16**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

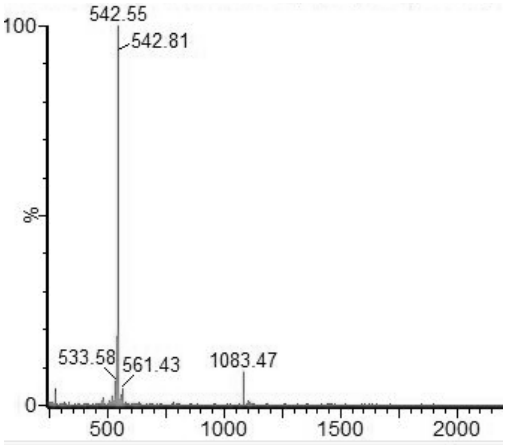


Figure S26: ESI-MS calcd. for $C_{49}H_{70}N_{12}O_{16}$ =1082.50; $[M+H]^+$ *m/z* =1083.50, found 1083.47; $[M+2H]^{2+}$ *m/z* = 542.25, found 542.55.

Compound 17

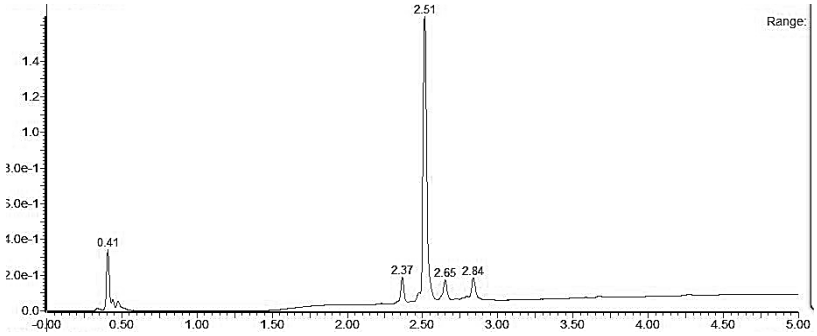


Figure S27: UV trace from analytical UPLC-MS analysis for crude **Compound 17**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

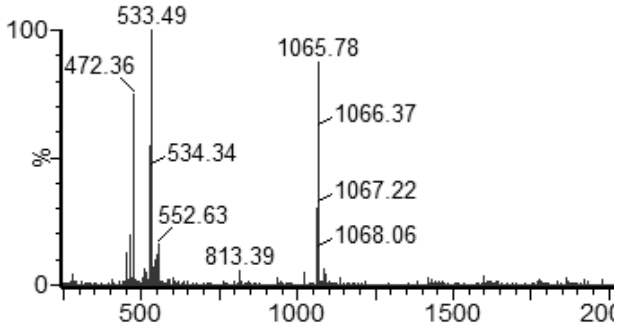


Figure S28: ESI-MS calcd. for $C_{96}H_{160}N_{32}O_{23}$ = 1064.49; $[M+H]^+$ *m/z* =1065.49, found 1065.78$[M+2H]^{2+}$ *m/z* = 533.25, found 533.49.

Stapled peptide E

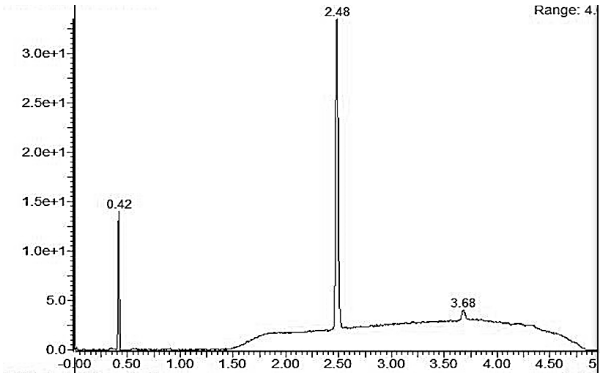


Figure S29: UV trace from analytical UPLC-MS analysis for purified **Stapled peptide E**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

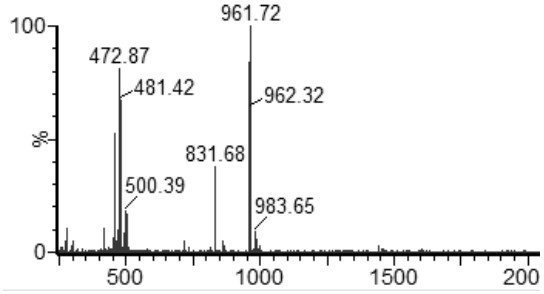
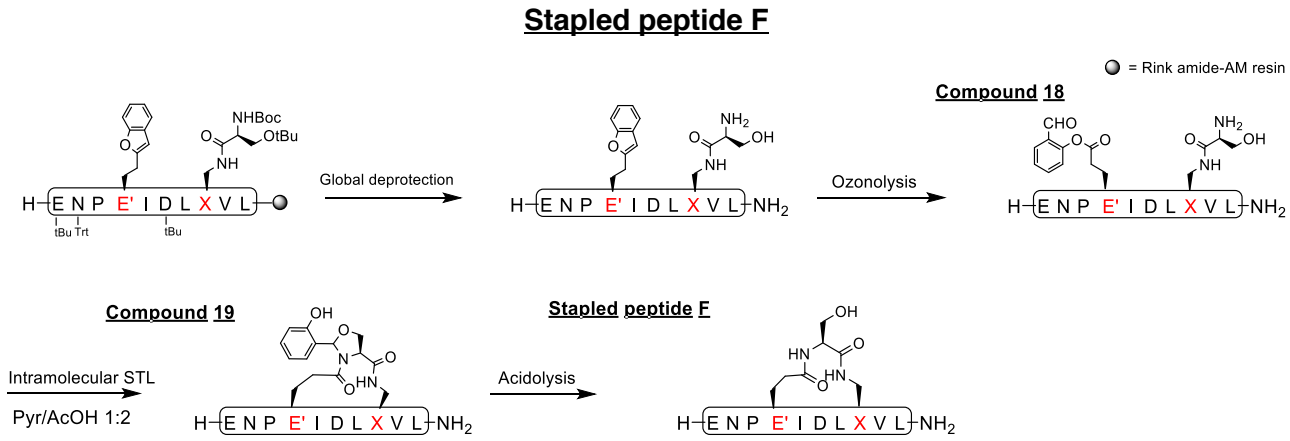


Figure S30: ESI-MS calcd. For $C_{37}H_{55}N_{11}O_{13}$ =960.47; $[M+H]^+$ *m/z* = 961.47, found 961.72; $[M+2H]^{2+}$ *m/z* = 481.24, found 481.42.



Ozonolysis of the purified peptide (10.00 mg, 10.16 μmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 18 as white solid.

The ligation of crude Compound 18 (4.11 mg, 4.04 μmol) was performed as described in general procedure 2.6. Reverse phase HPLC purification followed by lyophilization afforded the product Stapled peptide F (1.80 mg, 37.3 % yield) as white solid.

Compound 18

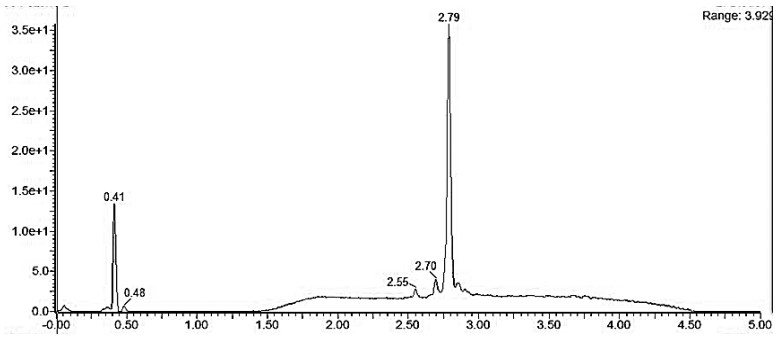


Figure S31: UV trace from analytical UPLC-MS analysis for crude **Compound 18**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

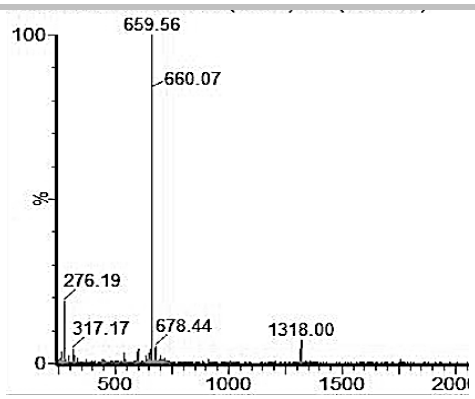


Figure S32: ESI-MS calcd. for $C_{59}H_{92}N_{14}O_{20}$ =1016.66; $[M+H]^+$ *m/z* =1017.66, found 1018.00; $[M+2H]^{2+}$ *m/z* = 659.33, found 659.56.

Compound 19

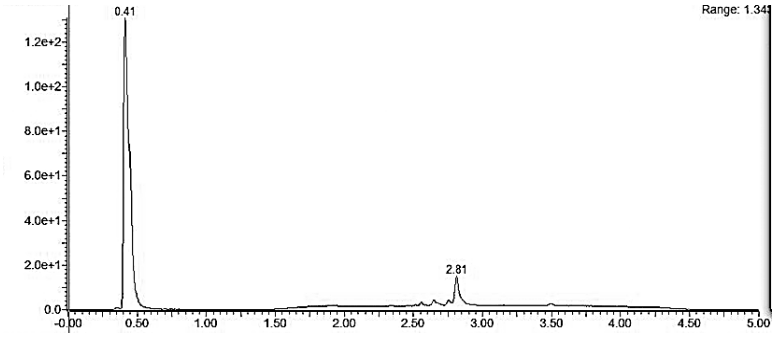


Figure S33: UV trace from analytical UPLC-MS analysis for crude **Compound 19**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

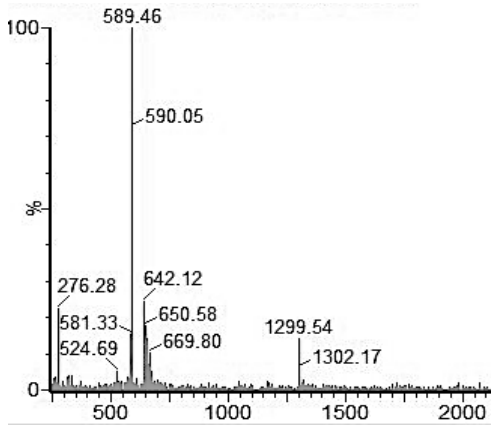


Figure S34: ESI-MS calcd. for $C_{59}H_{90}N_{14}O_{19}$ = 1298.65; $[M+H]^+$ *m/z* =1299.65, found 1299.54; $[M+2H]^{2+}$ *m/z* = 650.33, found 650.58.

Stapled peptide F

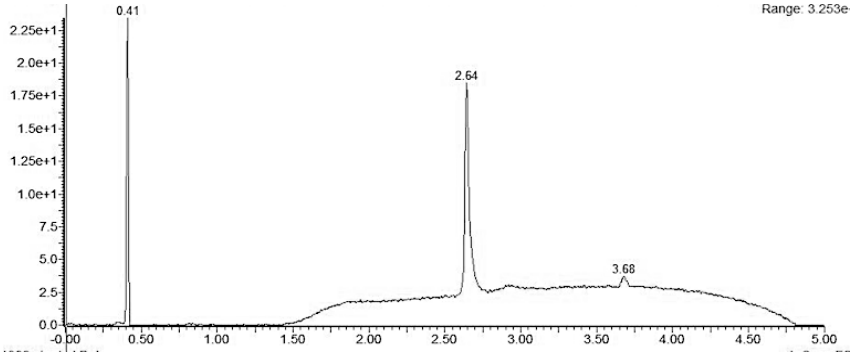


Figure S35: UV trace from analytical UPLC-MS analysis for purified **Stapled peptide F**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

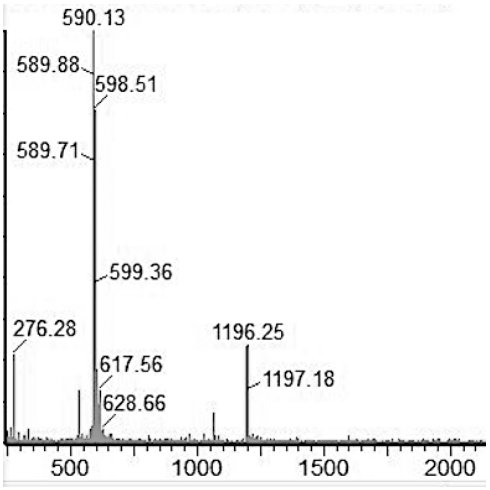
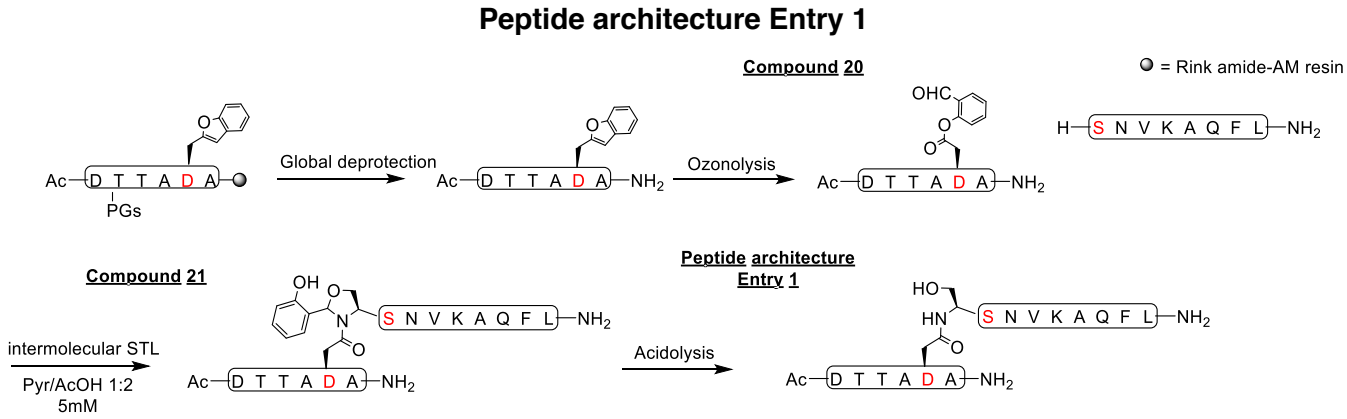


Figure S36: ESI-MS calcd. for $C_{52}H_{86}N_{14}O_{18}$ =1194.62; $[M+H]^+$ *m/z* = 1195.62, found 1196.25; $[M+2H]^{2+}$ *m/z* = 598.31, found 598.51.

4.2 Synthesis of Class I: bridge peptides and branched peptides (Entry 1-11)



The synthesis of Compound 20 started from 200 mg rink amide resin. Ozonolysis of the crude side-chain unprotected peptide was performed as described in general procedure 2.4. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 20 (30.08 mg, 40.8% yield based on the resin loading) as white solid.

The ligation between Compound 20 (2.38 mg, 3.22 μmol) and H-SNVKAQFL-NH_2 (3.21 mg, 3.54 μmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 1 (1.8 mg, 36.6% yield) as white solid.

Compound 20

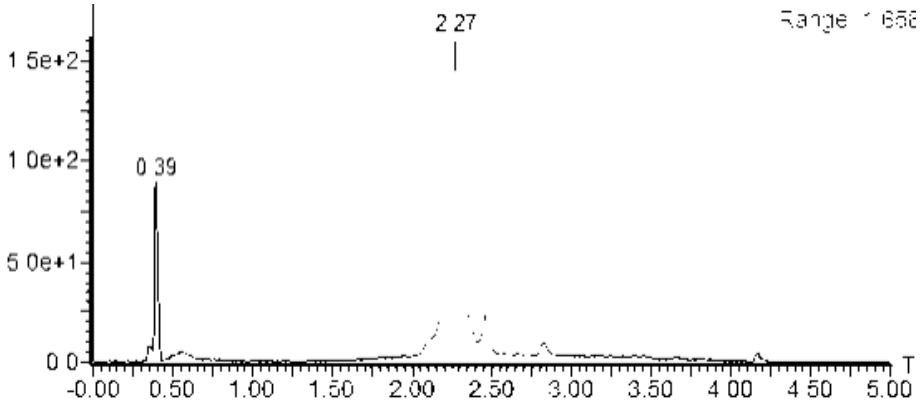


Figure S37: UV trace from analytical UPLC-MS analysis for crude **Compound 20**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

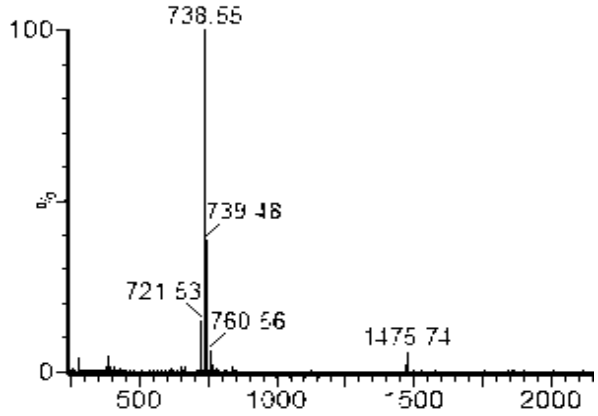


Figure S38: ESI-MS calcd. for $C_{31}H_{43}N_7O_{14}$ =737.29; $[M+H]^+$ *m/z* =738.29, found 738.55; $2[M+H]^+$ *m/z* = 1475.58, found 1475.74.

Compound 21

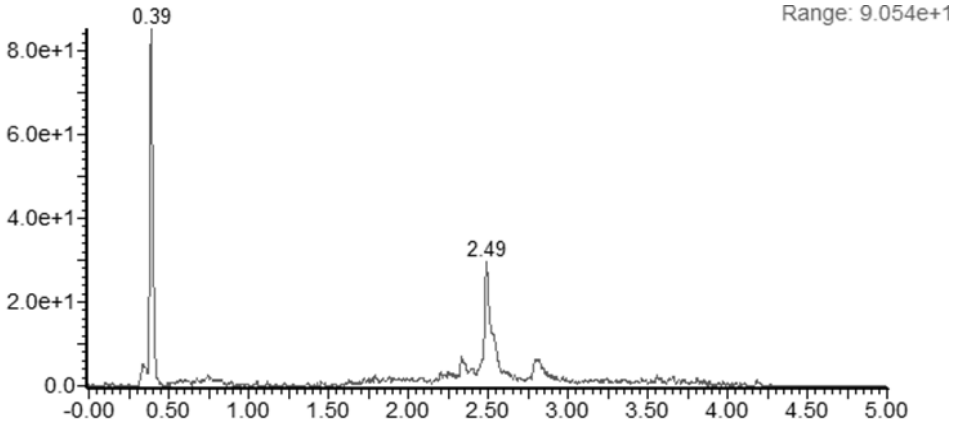


Figure S39: UV trace from analytical UPLC-MS analysis for crude **Compound 21**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

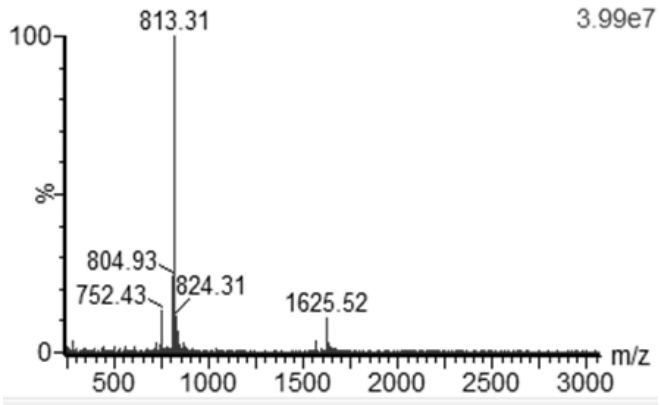


Figure S40: ESI-MS calcd. for $C_{72}H_{109}N_{19}O_{24}$ = 1624.77; $[M+H]^+$ *m/z* =1625.77, found 1625.52; $[M+2H]^{2+}$ *m/z* = 813.38, found 813.31.

Peptide architecture entry 1

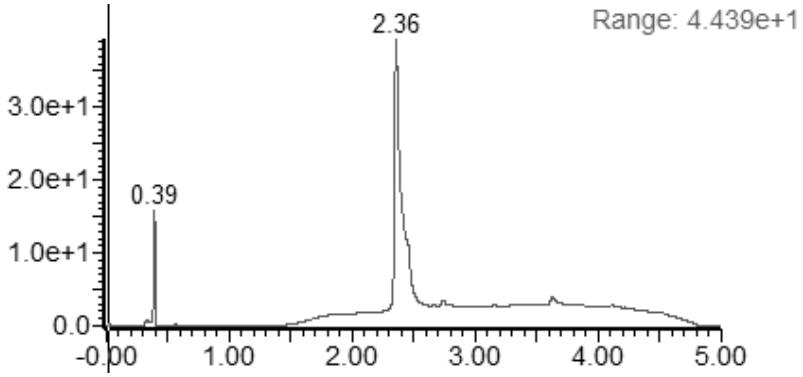


Figure S41: UV trace from analytical UPLC-MS analysis for purified **Stapled peptide F**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

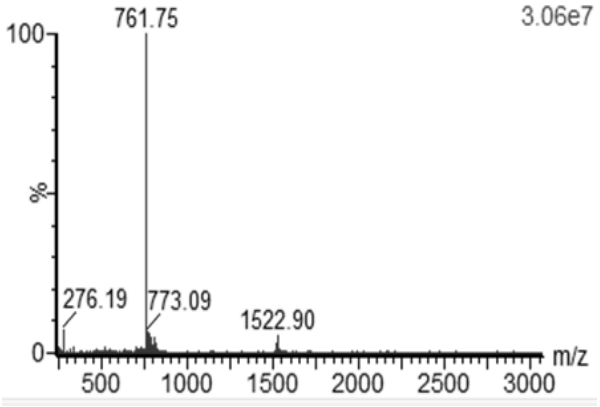
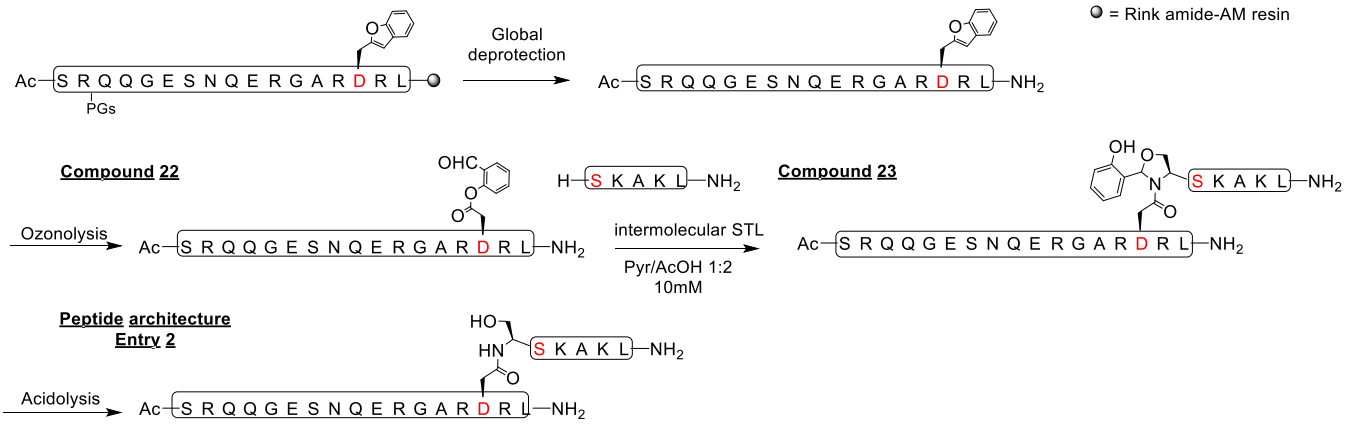


Figure S42: ESI-MS calcd. for $C_{65}H_{105}N_{19}O_{23}$ = 1520.67; $[M+H]^+$ *m/z* = 1521.67, found 1522.90; $[M+2H]^{2+}$ *m/z* = 761.33, found 761.75.

Peptide architecture Entry 2



The synthesis of Compound 22 started from 200 mg rink amide resin. Ozonolysis of the crude side-chain unprotected peptide was performed as described in general procedure 2.4. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 22 (88.91 mg, 41.7% yield based on the resin loading) as white solid.

The ligation between Compound 22 (3.39 mg, 1.59 μmol) and H-SKAKL-NH_2 (0.95 mg, 1.74 μmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 2 (1.6 mg, 39.4% yield) as white solid.

Compound 22

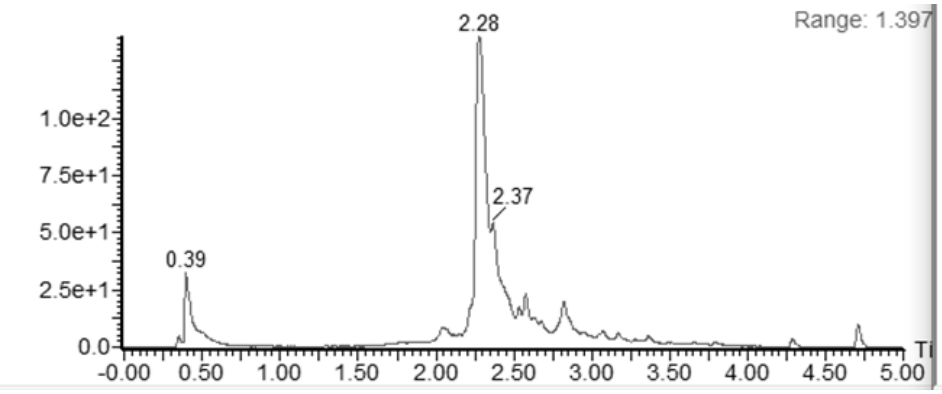


Figure S43: UV trace from analytical UPLC-MS analysis for crude **Compound 22**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

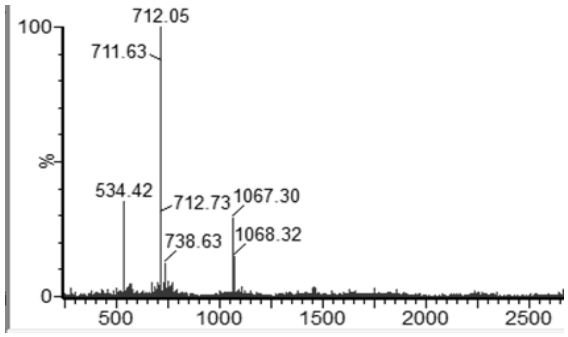


Figure S44: ESI-MS calcd. for $C_{85}H_{138}N_{34}O_{31}$ =2132.25; $[M+2H]^{2+}$ *m/z* =1067.12, found 1067.30; $[M+3H]^{3+}$ *m/z* =711.75, found 712.05; $[M+4H]^{4+}$ *m/z* =534.06, found 534.42.

Compound 23

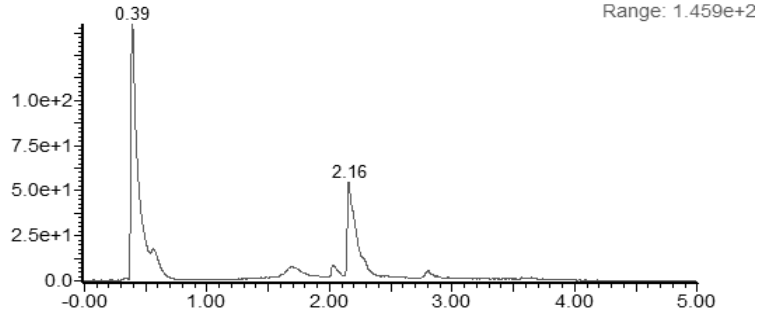


Figure S45: UV trace from analytical UPLC-MS analysis for crude **Compound 23**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

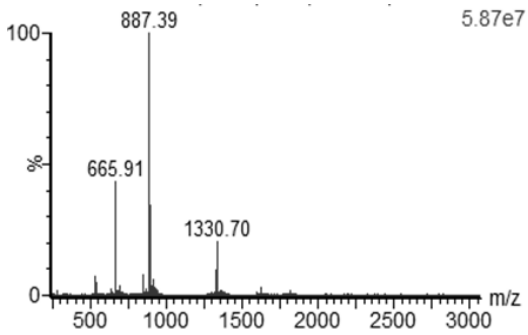


Figure S46: ESI-MS calcd. for $C_{109}H_{184}N_{42}O_{36}$ = 2658.93; $[M+2H]^{2+}$ *m/z* =1330.46, found 1330.70; $[M+3H]^{3+}$ *m/z* =887.31, found 887.39; $[M+4H]^{4+}$ *m/z* =665.73, found 665.91.

Peptide architecture entry 2

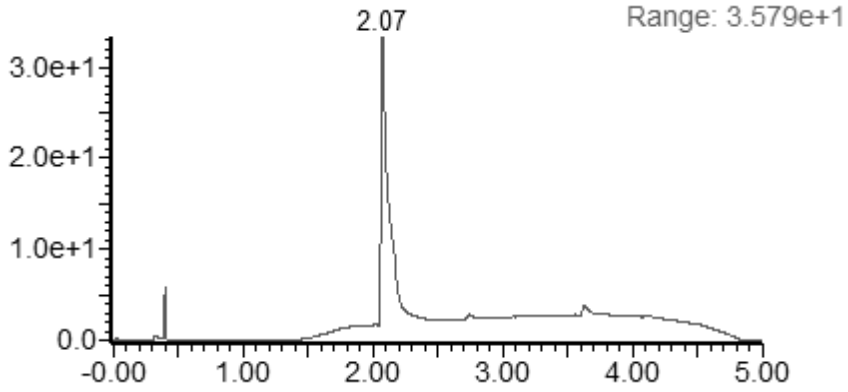


Figure S47: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 2**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

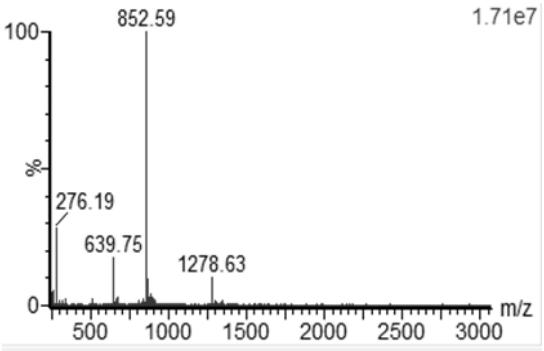
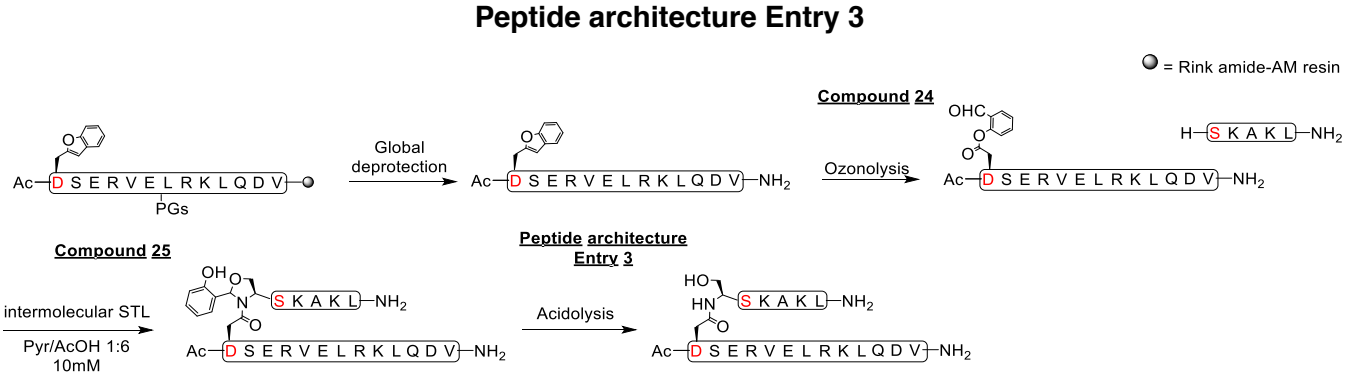


Figure S48: ESI-MS calcd. for $C_{102}H_{180}N_{42}O_{35}$ = 2554.82; $[M+2H]^{2+}$ *m/z* =1278.41, found 1278.63; $[M+3H]^{3+}$ *m/z* =852.60, found 852.59; $[M+4H]^{4+}$ *m/z* =639.70, found 639.75.



Ozonolysis of the purified peptide (30.82 mg, 18.12 µmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 24 as white solid.

The ligation between crude Compound 24 (3.7 mg, 2.13 µmol) and H-SKAKL-NH_2 (1.28 mg, 2.34 µmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture 3 (1.81 mg, 39.1% yield) as white solid.

Compound 24

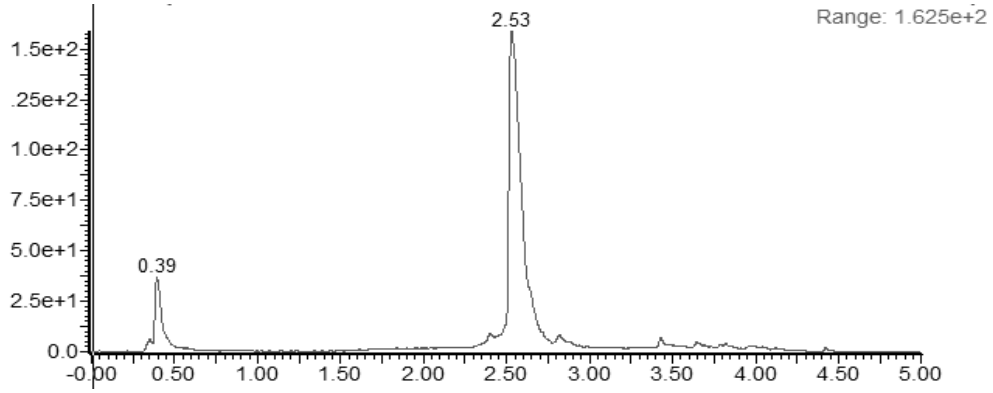


Figure S49: UV trace from analytical UPLC-MS analysis for crude **Compound 24**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

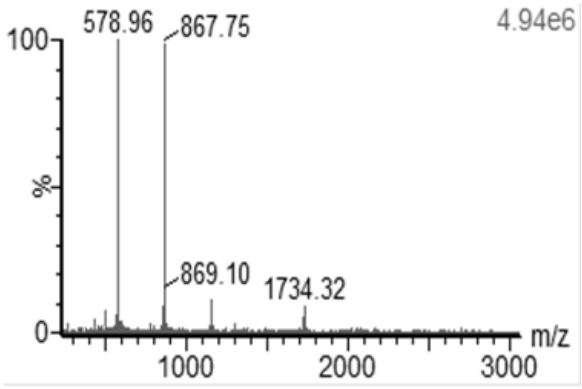


Figure S50: ESI-MS calcd. for $C_{75}H_{121}N_{21}O_{26}$ =1732.91; $[M+H]^+$ *m/z* =1733.91, found 1734.32; $[M+2H]^{2+}$ *m/z* =867.45, found 867.75; $[M+3H]^{3+}$ *m/z* =578.63, found 578.96.

Compound 25

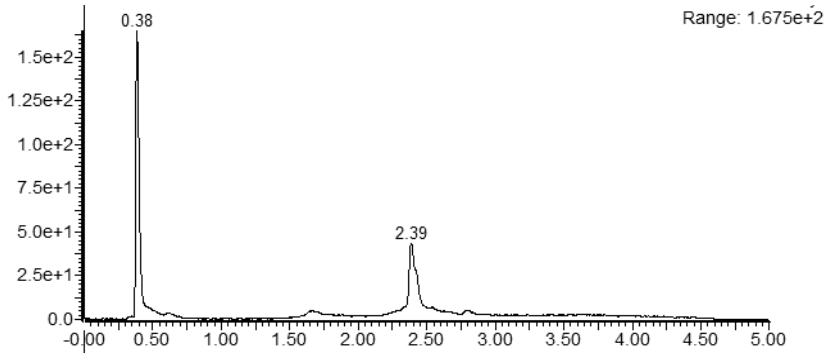


Figure S51: UV trace from analytical UPLC-MS analysis for crude **Compound 25**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

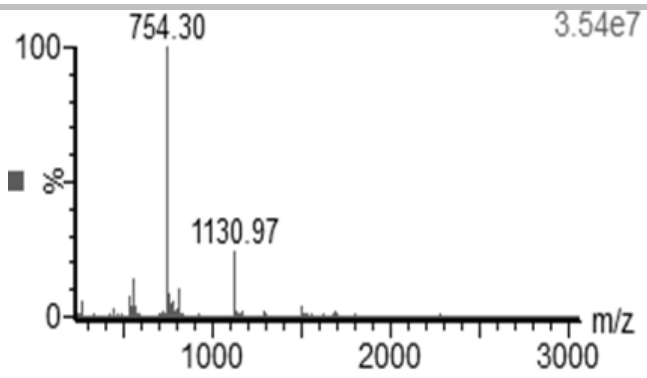


Figure S52: ESI-MS calcd. for $C_{99}H_{157}N_{29}O_{31}$ = 2259.60; $[M+2H]^{2+}$ *m/z* =1130.80, found 1130.97; $[M+3H]^{3+}$ *m/z* =754.20, found 754.30.

Peptide architecture entry 3

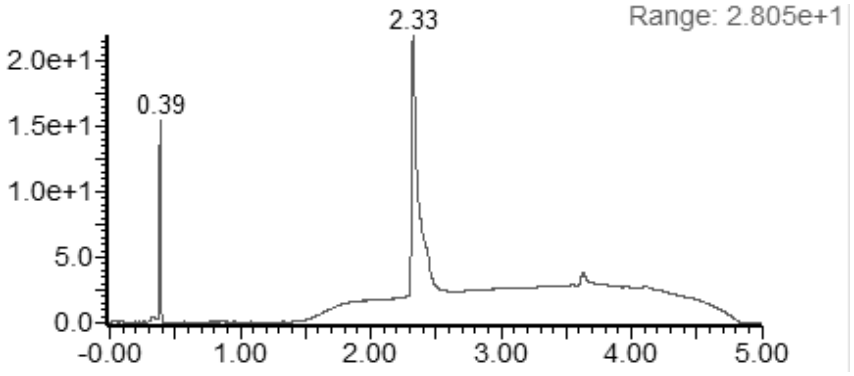


Figure S53: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 3** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

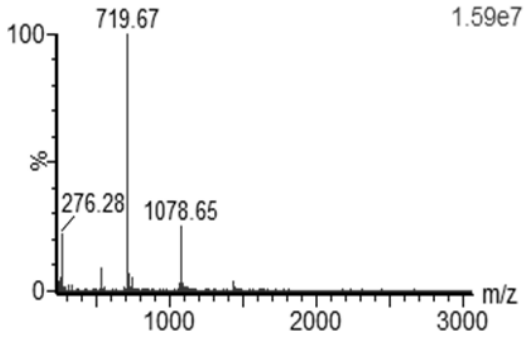
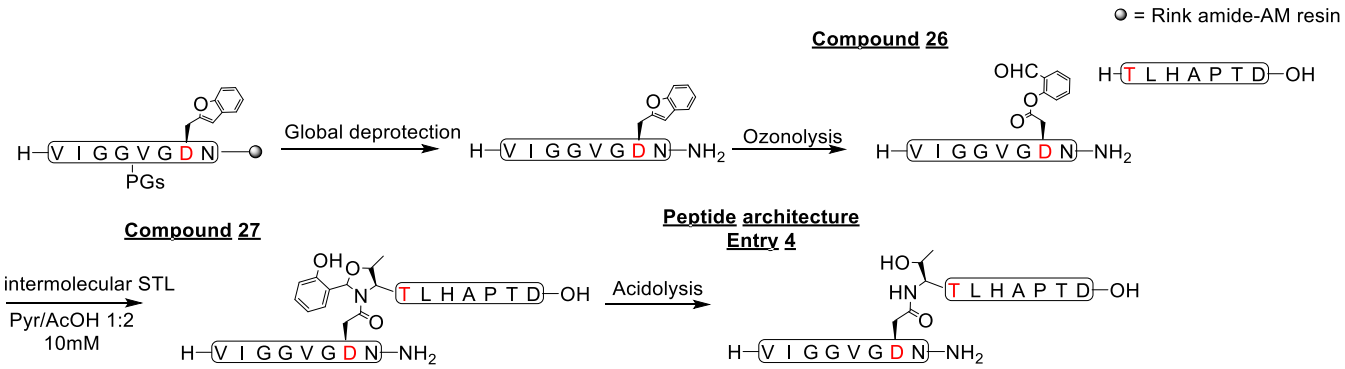


Figure S54: ESI-MS calcd. for $C_{92}H_{163}N_{29}O_{30}$ = 2155.49; $[M+2H]^{2+}$ *m/z* =1078.74, found 1078.65; $[M+3H]^{3+}$ *m/z* =719.49, found 719.67

Peptide architecture Entry 4



Ozonolysis of the purified peptide (18.48 mg, 23.07 μmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 26 as white solid.

The ligation between crude Compound 26 (3.50 mg, 4.20 μmol) and H-TLHAPTD-NH_2 (3.80 mg, 5.04 μmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 4 (2.02 mg, 32.8% yield) as white solid.

Compound 26

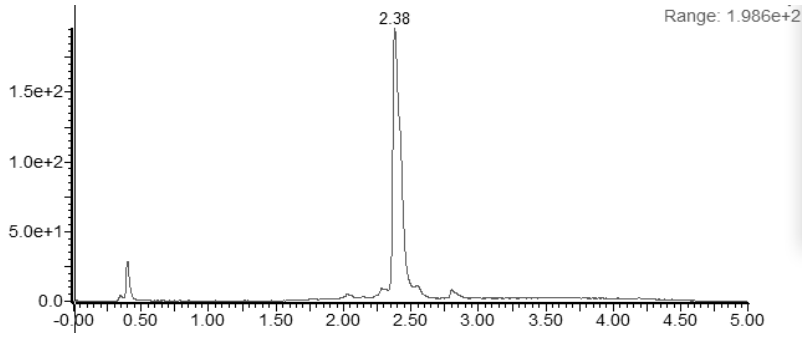


Figure S55: UV trace from analytical UPLC-MS analysis for crude **Compound 26**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

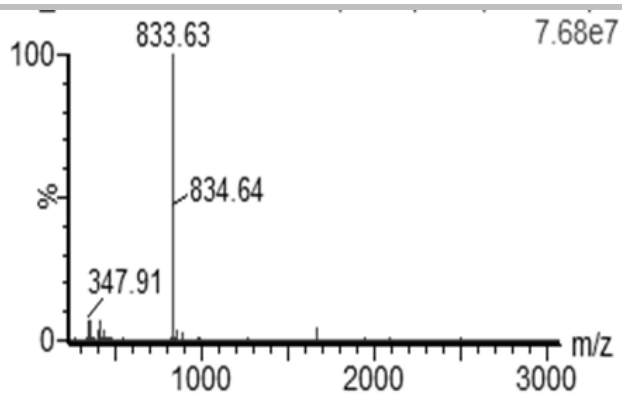


Figure S56: ESI-MS calcd. for $C_{37}H_{56}N_{10}O_{12}$ =832.91; $[M+H]^+$ *m/z* =833.91, found 833.63.

Compound 27

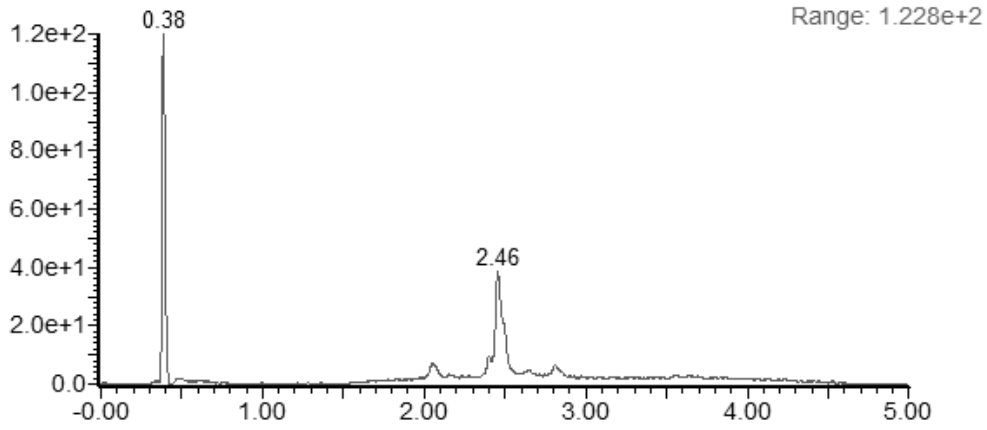


Figure S57: UV trace from analytical UPLC-MS analysis for crude **Compound 27**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

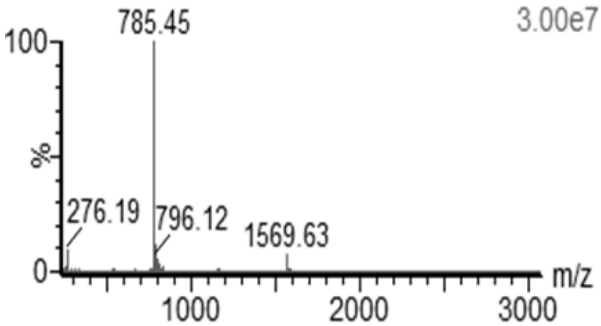


Figure S58: ESI-MS calcd. for $C_{69}H_{105}N_{19}O_{23}$ =1568.71; $[M+H]^+$ *m/z* =1569.71, found1569.63; $[M+2H]^{2+}$ *m/z* =785.36, found 785.45.

Peptide architecture entry 4

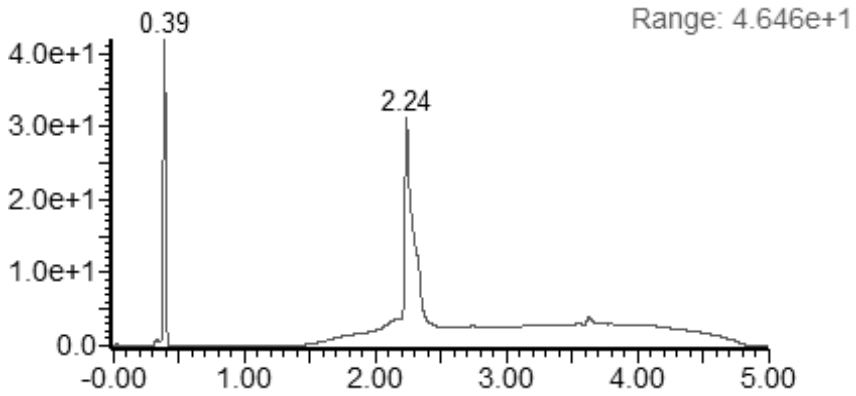


Figure S59: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 4** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

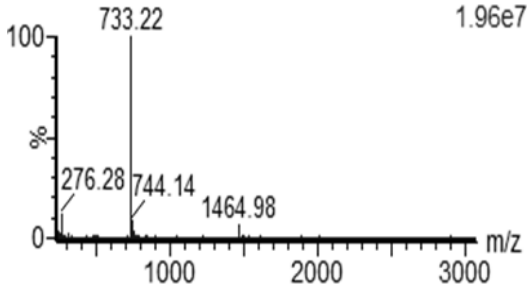
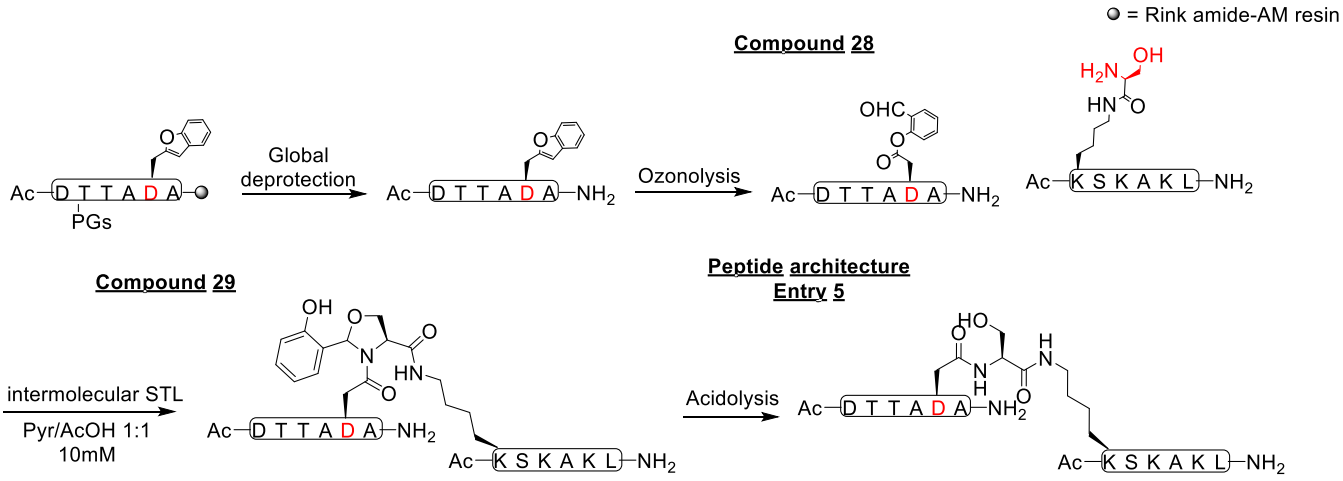


Figure S60: ESI-MS calcd. for $C_{62}H_{101}N_{19}O_{22}$ = 1464.60; $[M+H]^+$ *m/z* =1465.60, found 1464.98; $[M+2H]^{2+}$ *m/z* =733.30, found 733.22.

Peptide architecture Entry 5



The synthesis of Compound 28 started from 200 mg rink amide resin. Ozonolysis of the crude side-chain unprotected peptide was performed as described in general procedure 2.4. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 28 (30.08 mg, 40.8% yield based on the resin loading) as white solid.

The ligation between Compound 28 (2.57 mg, 3.48 µmol) and Ac-(K-S)SKAKL-NH_2 (3.07 mg, 3.83 µmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 5 (2.39 mg, 48.5% yield) as white solid.

Compound 28

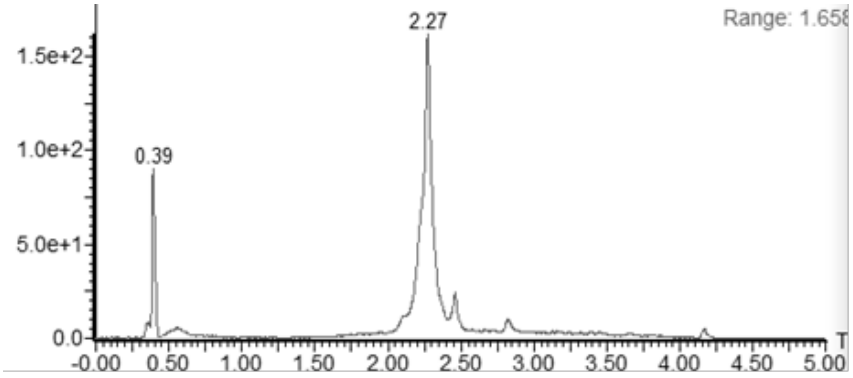


Figure S61: UV trace from analytical UPLC-MS analysis for crude **Compound 28**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

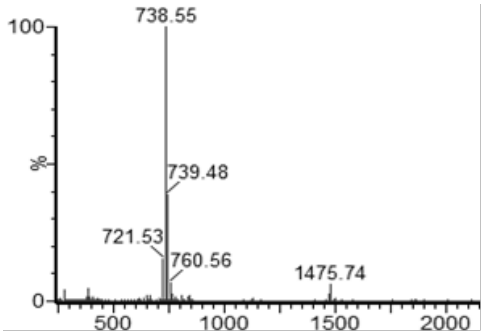


Figure S62: ESI-MS calcd. for $C_{31}H_{43}N_7O_{14}$ =737.29; $[M+H]^+$ *m/z* =738.29, found 738.55; $2[M+H]^+$ *m/z* = 1475.58, found 1475.74.

Compound 29

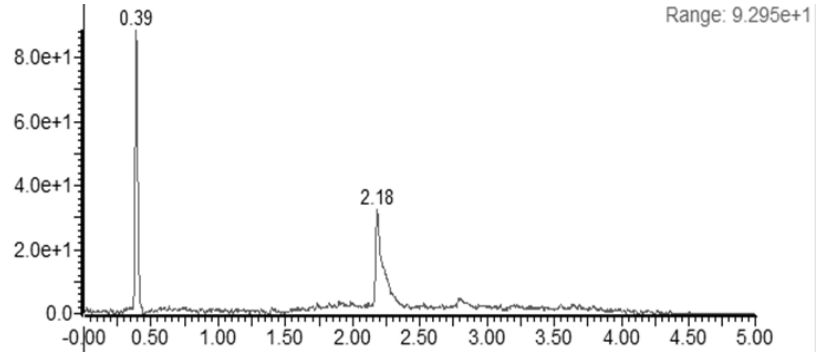


Figure S63: UV trace from analytical UPLC-MS analysis for crude **Compound 29**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

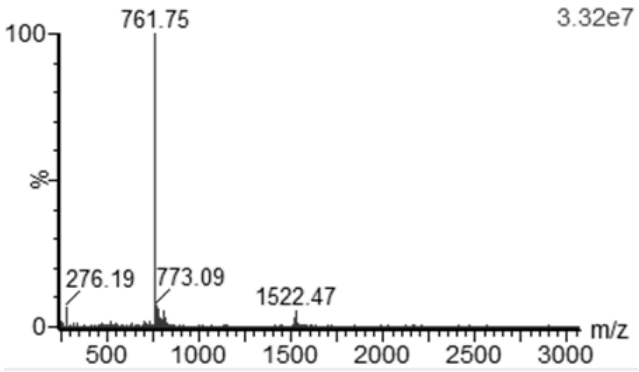


Figure S64: ESI-MS calcd. for $C_{66}H_{108}N_{18}O_{23}$ =1521.69; $[M+H]^+$ *m/z* =1522.69, found 1522.47; $[M+2H]^{2+}$ *m/z* =761.84, found 761.75.

Peptide architecture entry 5

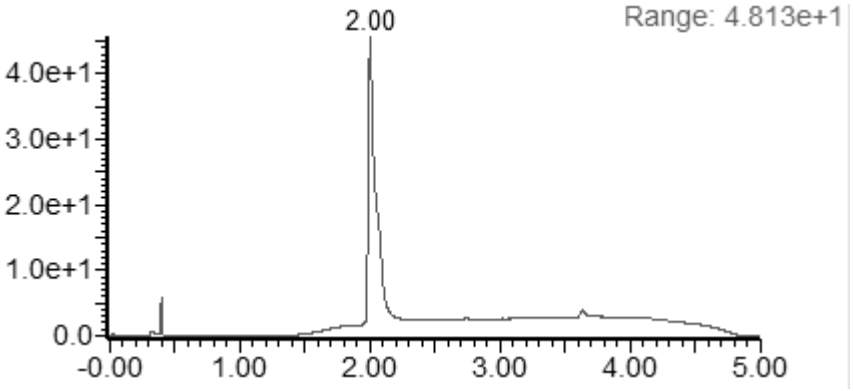


Figure S65: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 5** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

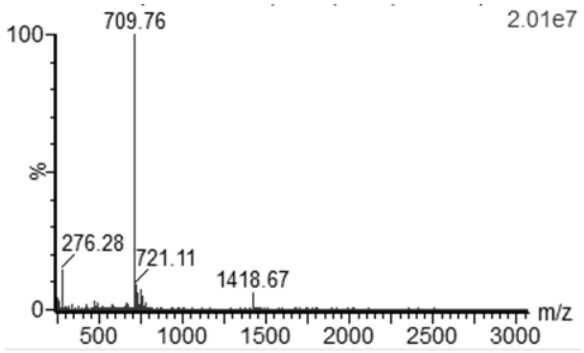
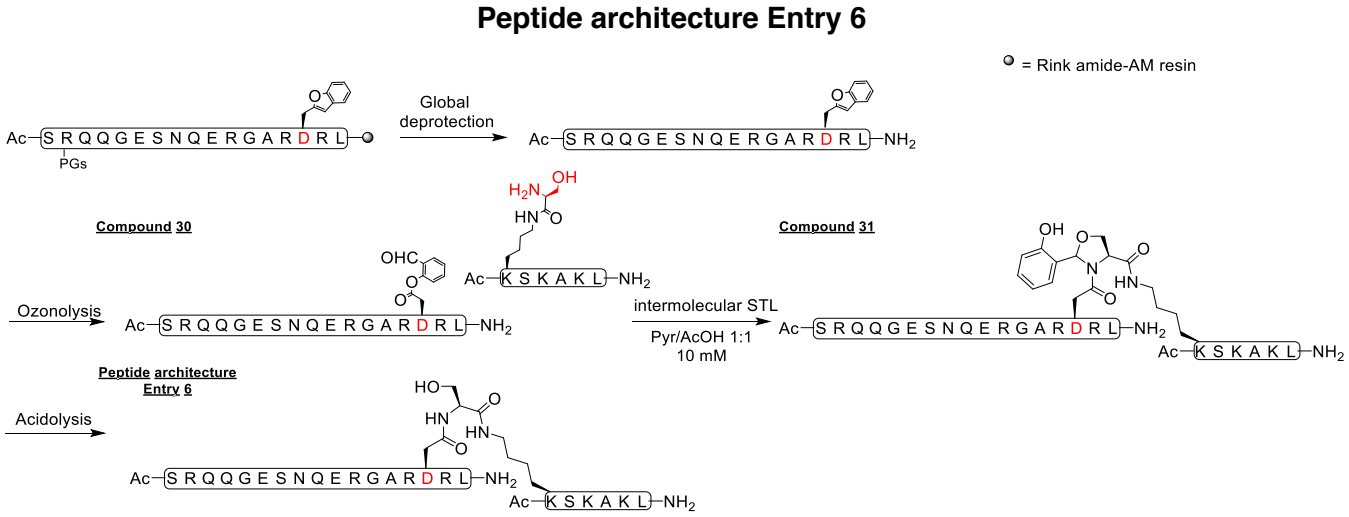


Figure S66: ESI-MS calcd. for $C_{59}H_{104}N_{18}O_{22}$ = 1417.59; $[M+H]^+$ *m/z* =1418.59, found 1418.67; $[M+2H]^{2+}$ *m/z* =709.79, found 709.76.



The synthesis of Compound 30 started from 200 mg rink amide resin. Ozonolysis of the crude side-chain unprotected peptide was performed as described in general procedure 2.4. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 30 (88.91 mg, 41.7% yield based on the resin loading) as white solid.

The ligation between Compound 30 (2.74 mg, 1.28 µmol) and Ac-(K-S)SKAKL-NH_2 (1.13 mg, 1.41 µmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 6 (1.92 mg, 53.0% yield) as white solid.

Compound 30

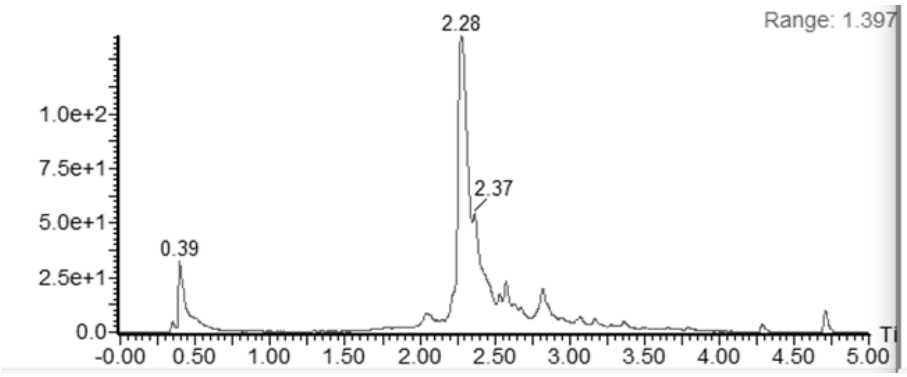


Figure S67: UV trace from analytical UPLC-MS analysis for crude **Compound 30**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

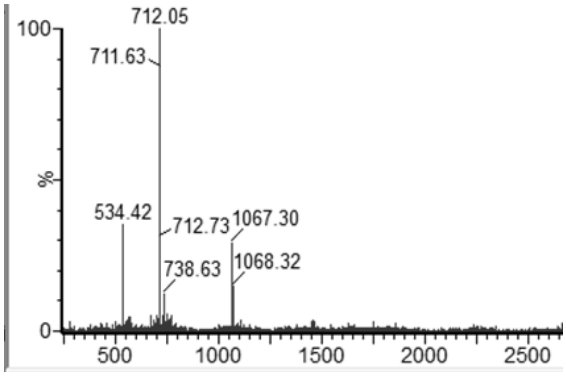


Figure S68: ESI-MS calcd. for $C_{85}H_{138}N_{34}O_{31}$ =2132.25; $[M+2H]^{2+}$ *m/z* =1067.12, found 1067.30; $[M+3H]^{3+}$ *m/z* =711.75, found 712.05; $[M+4H]^{4+}$ *m/z* =534.06, found 534.42.

Compound 31

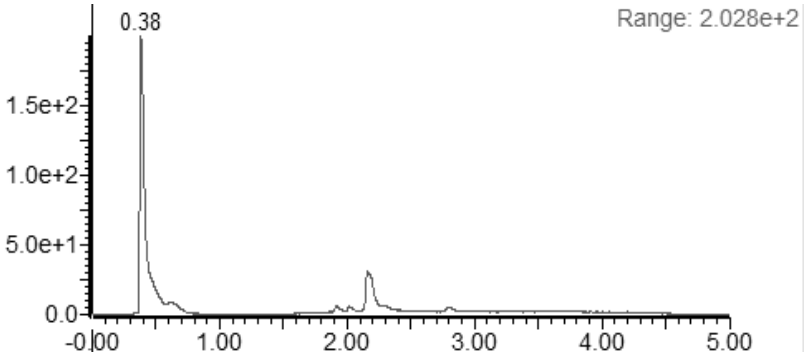


Figure S69: UV trace from analytical UPLC-MS analysis for crude **Compound 31**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

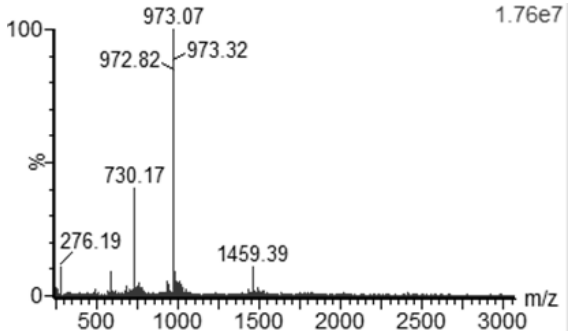


Figure S70: ESI-MS calcd. for $C_{120}H_{203}N_{45}O_{40}$ =2916.22; $[M+2H]^{2+}$ *m/z* =1459.11, found 1459.39; $[M+3H]^{3+}$ *m/z* =973.07, found 973.07; $[M+4H]^{4+}$ *m/z* =730.06, found 730.17.

Peptide architecture entry 6

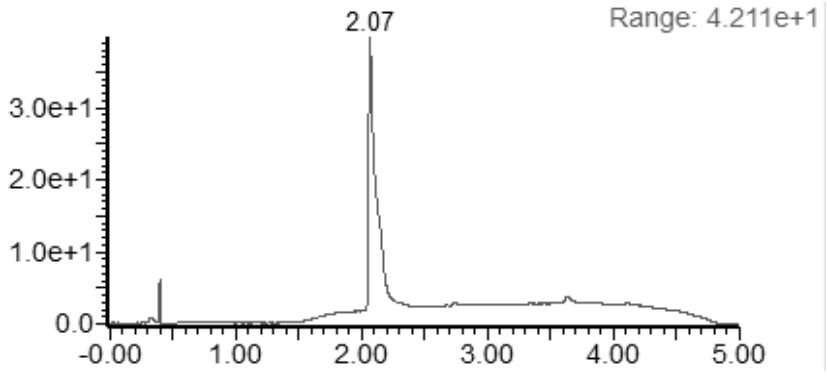


Figure S71: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 6** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

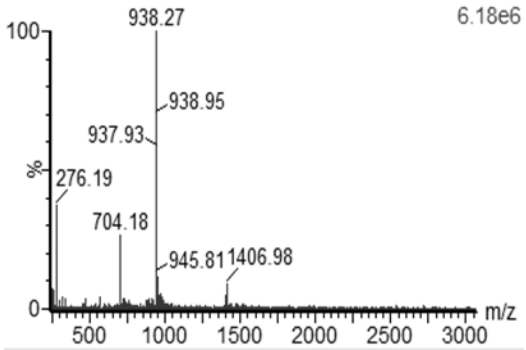
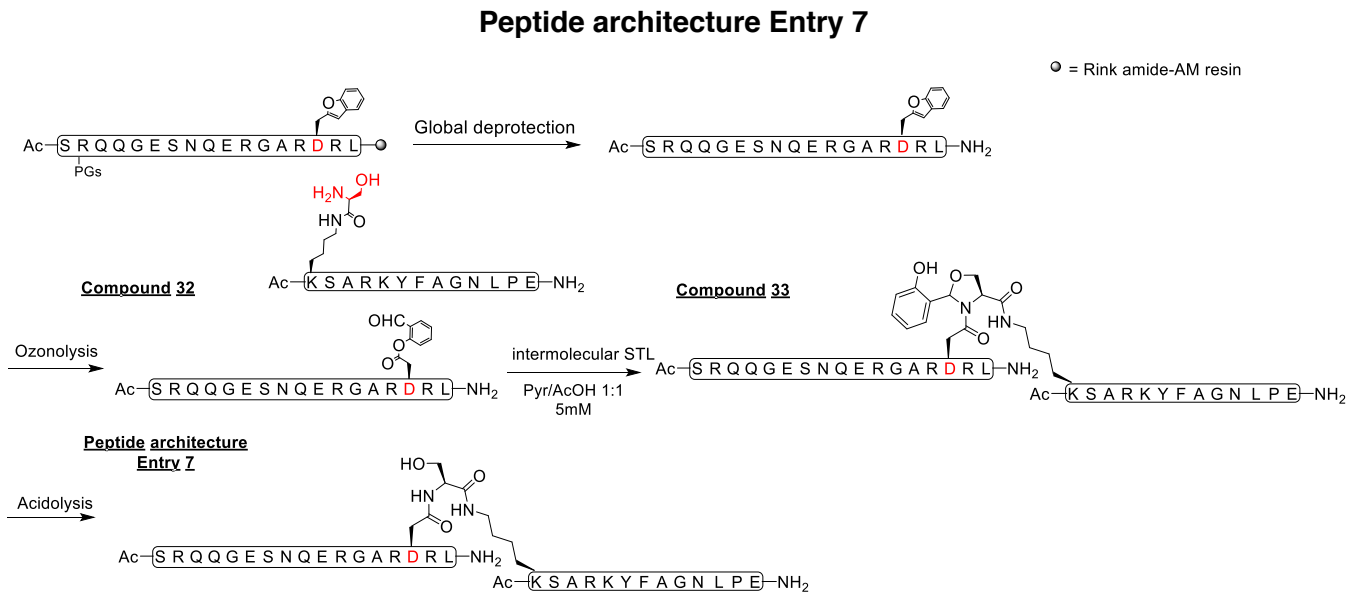


Figure S72: ESI-MS calcd. for $C_{113}H_{199}N_{45}O_{39}$ = 2812.11; $[M+2H]^{2+}$ *m/z* =1407.06, found 1406.98; $[M+3H]^{3+}$ *m/z* =938.37, found 938.27; $[M+4H]^{4+}$ *m/z* =704.03, found 704.18.



The synthesis of Compound 32 started from 200 mg rink amide resin. Ozonolysis of the crude side-chain unprotected peptide was performed as described in general procedure 2.4. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 32 (88.91 mg, 41.7% yield based on the resin loading) as white solid.

The ligation between Compound 32 (3.3 mg, 1.55 µmol) and Ac-(K-S)SARKYFAGNLPE-NH_2 (2.74 mg, 1.70 µmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 7 (2.10 mg, 37.4% yield) as white solid.

Compound 32

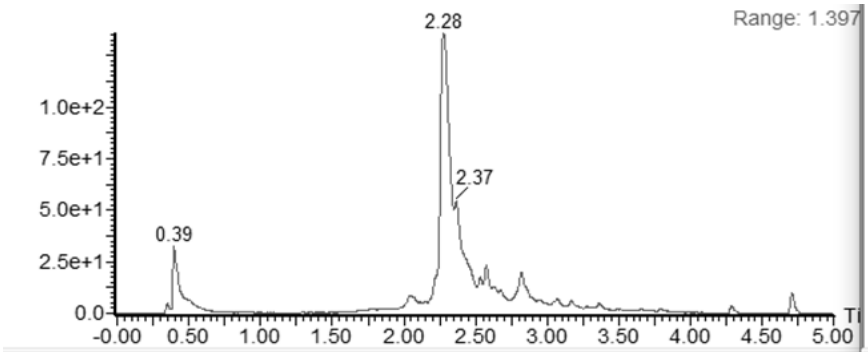


Figure S73: UV trace from analytical UPLC-MS analysis for crude **Compound 32**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

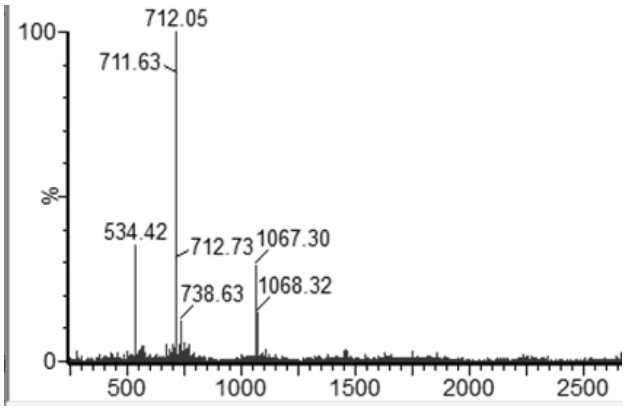


Figure S74: ESI-MS calcd. for $C_{85}H_{138}N_{34}O_{31}$ =2132.25; $[M+2H]^{2+}$ *m/z* =1067.12, found 1067.30; $[M+3H]^{3+}$ *m/z* =711.75, found 712.05; $[M+4H]^{4+}$ *m/z* =534.06, found 534.42.

Compound 33

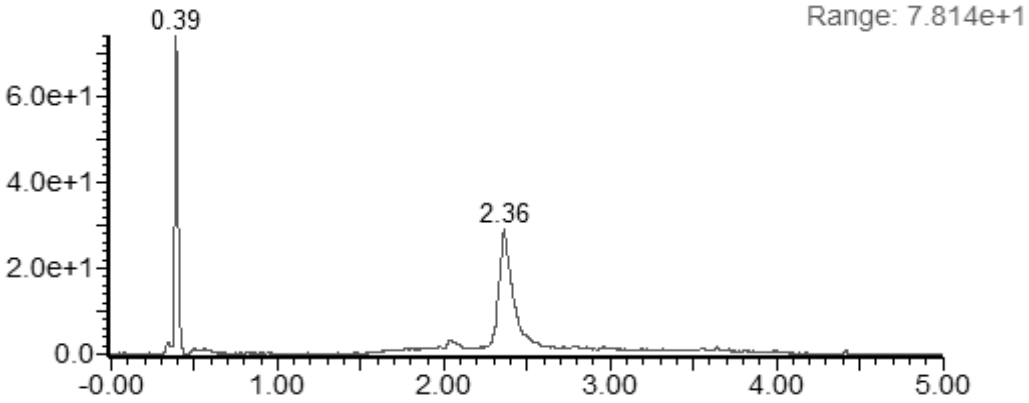


Figure S75: UV trace from analytical UPLC-MS analysis for crude **Compound 33**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

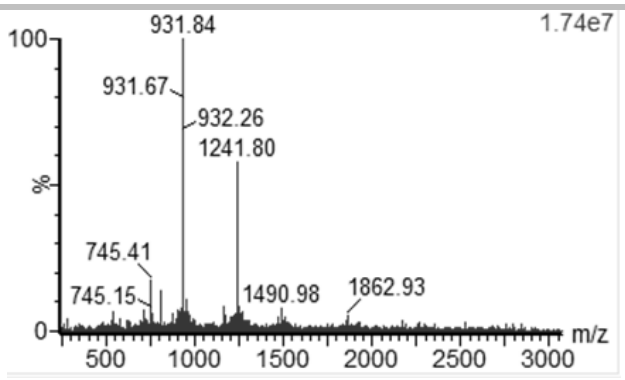


Figure S76: ESI-MS calcd. for $C_{157}H_{249}N_{55}O_{51}$ =3723.05; $[M+2H]^{2+}$ *m/z* =1862.53, found 1862.93; $[M+3H]^{3+}$ *m/z* =1242.02, found 1241.80; $[M+4H]^{4+}$ *m/z* =931.76, found 931.84; $[M+5H]^{5+}$ *m/z* =745.61, found 745.41.

Peptide architecture entry 7

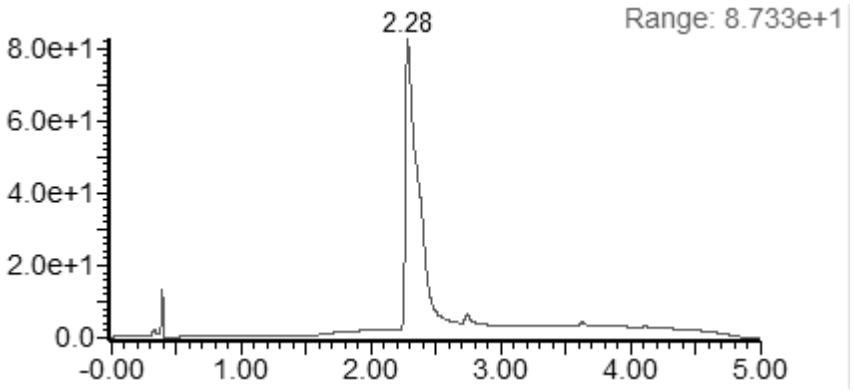


Figure S77: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 7** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

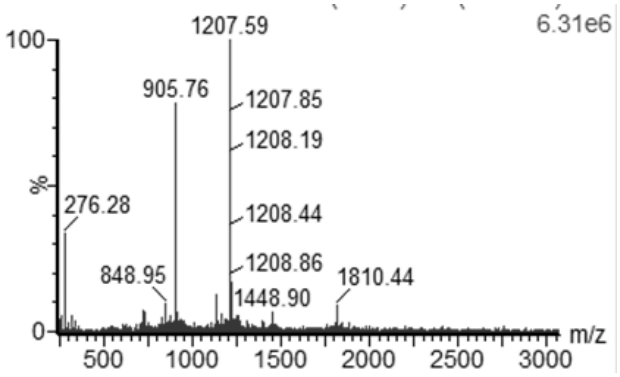
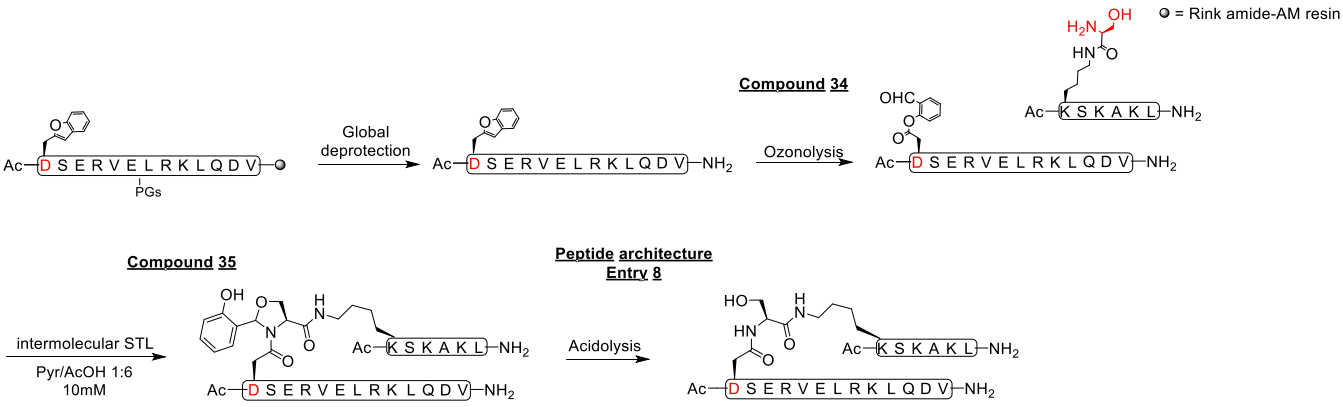


Figure S78: ESI-MS calcd. for $C_{150}H_{245}N_{55}O_{50}$ =3618.95; $[M+2H]^{2+}$ *m/z* =1810.48, found 1810.44; $[M+3H]^{3+}$ *m/z* =1207.32, found 1207.59; $[M+4H]^{4+}$ *m/z* =905.74, found 905.76.

Peptide architecture Entry 8



Ozonolysis of the purified peptide (30.82 mg, 18.12 µmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 34 as white solid.

The ligation between crude Compound 34 (3.1 mg, 1.79 µmol) and Ac-(K-S)SKAKL-NH_2 (1.58 mg, 1.97 µmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 8 (1.43 mg, 33.3% yield) as white solid.

Compound 34

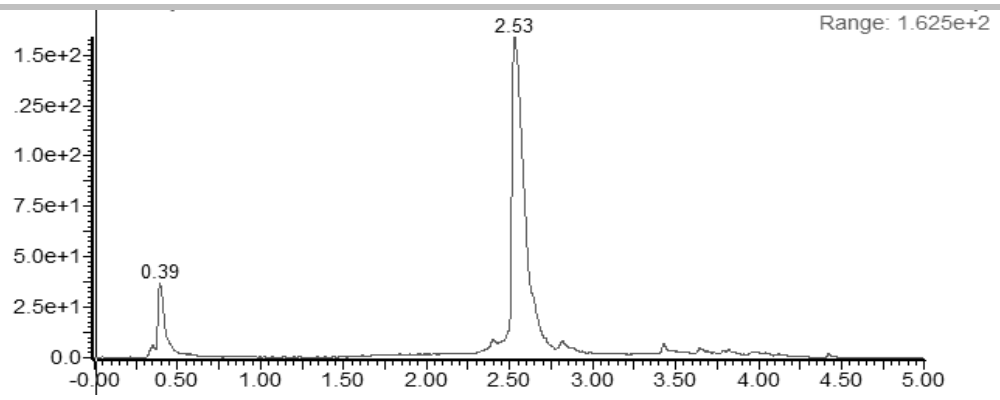


Figure S79: UV trace from analytical UPLC-MS analysis for crude **Compound 34**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

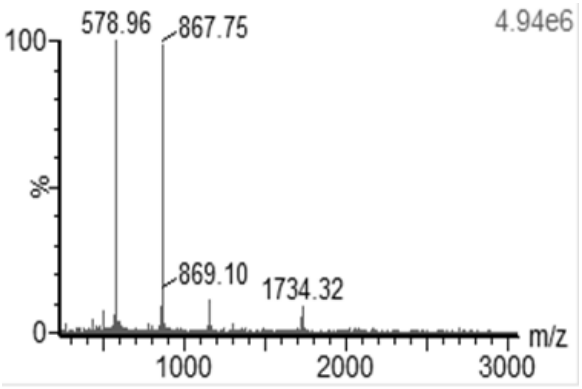


Figure S80: ESI-MS calcd. for $C_{75}H_{121}N_{21}O_{26}$ =1732.91; $[M+H]^+$ *m/z* =1733.91, found 1734.32; $[M+2H]^{2+}$ *m/z* =867.45, found 867.75; $[M+3H]^{3+}$ *m/z* =578.63, found 578.96.

Compound 35

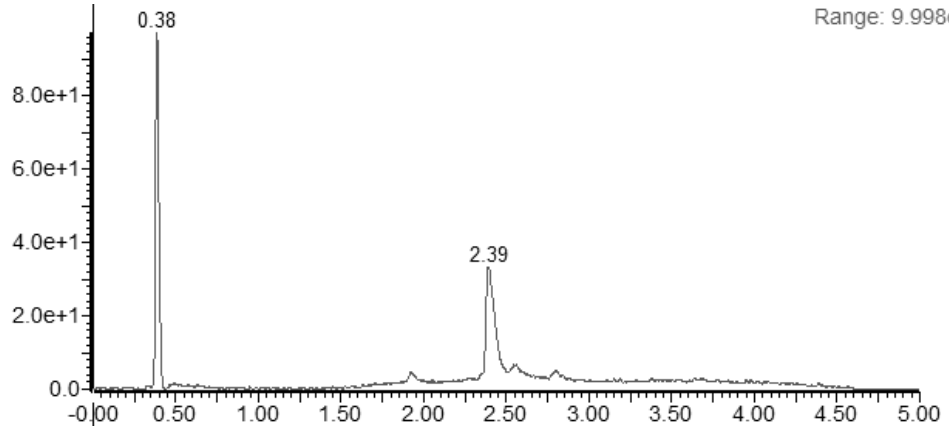


Figure S81: UV trace from analytical UPLC-MS analysis for crude **Compound 35**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

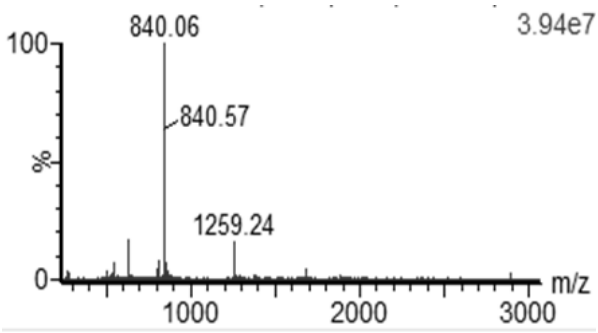


Figure S82: ESI-MS calcd. for $C_{110}H_{186}N_{32}O_{35}$ =2516.89; $[M+2H]^{2+}$ *m/z* =1259.45, found 1259.24; $[M+3H]^{3+}$ *m/z* =839.96, found 840.06.

Peptide architecture entry 8

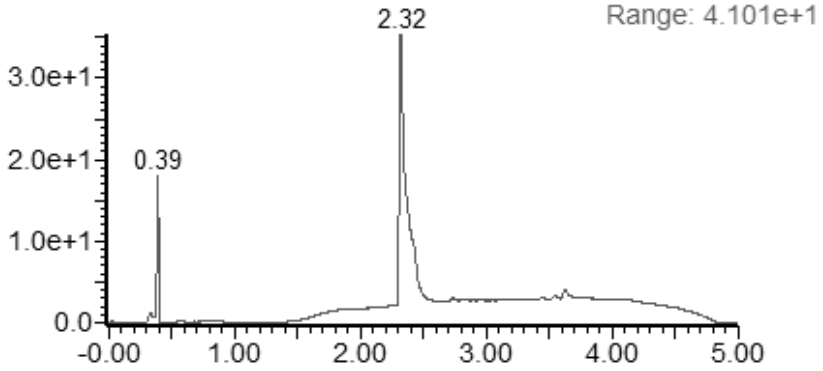


Figure S83: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 8** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

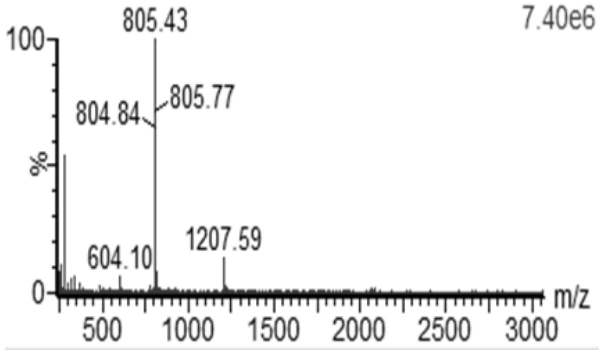
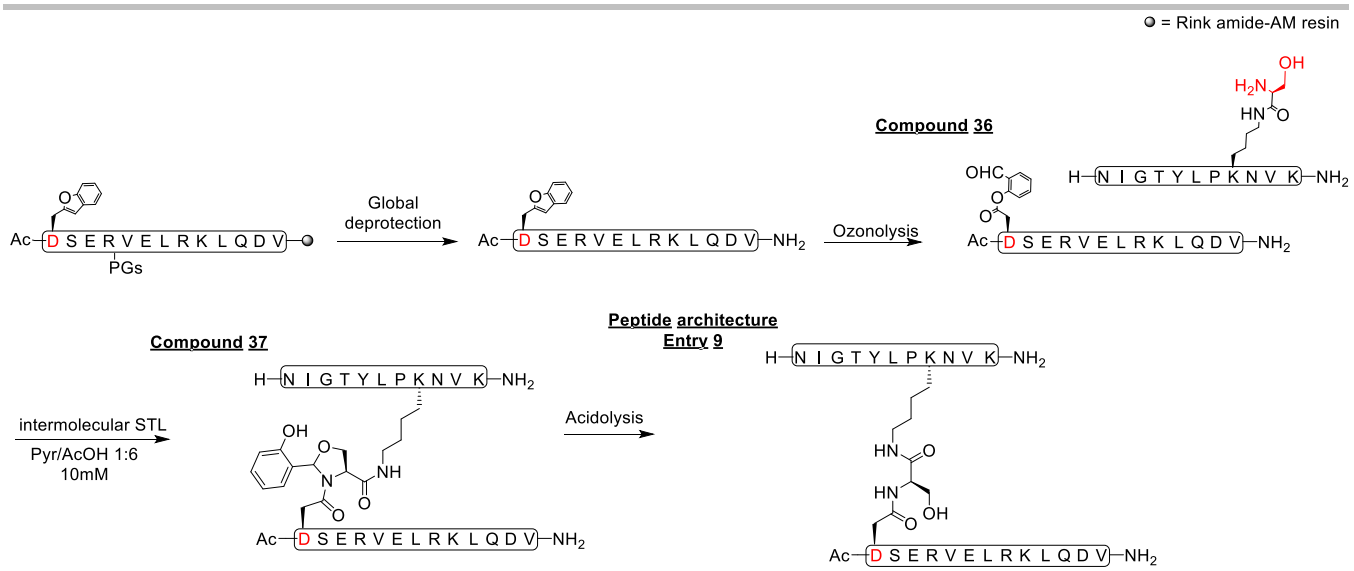


Figure S84: ESI-MS calcd. for $C_{103}H_{182}N_{32}O_{34}$ =2412.78; $[M+2H]^{2+}$ *m/z* =1207.39, found 1207.59; $[M+3H]^{3+}$ *m/z* =805.26, found 805.43; $[M+4H]^{4+}$ *m/z* =604.19, found 604.10.

Peptide architecture Entry 9



Ozonolysis of the purified peptide (30.82 mg, 18.12 µmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 36 as white solid.

The ligation between crude Compound 36 (2.27 mg, 1.31 µmol) and H-NIGTYLP(K-S)NVK-NH_2 (2.44mg, 1.83 µmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 9 (1.20 mg, 31.1% yield) as white solid.

Compound 36

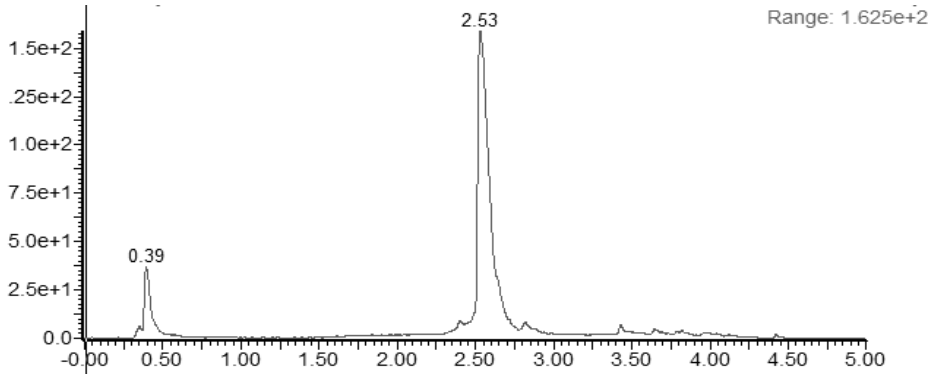


Figure S85: UV trace from analytical UPLC-MS analysis for crude **Compound 36**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

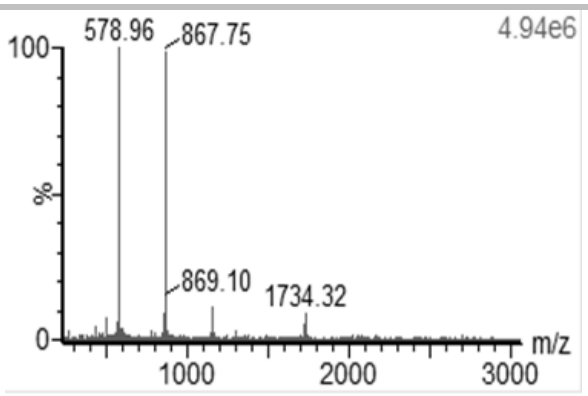


Figure S86: ESI-MS calcd. for $C_{75}H_{121}N_{21}O_{26}$ =1732.91; $[M+H]^+$ *m/z* =1733.91, found 1734.32; $[M+2H]^{2+}$ *m/z* =867.45, found 867.75; $[M+3H]^{3+}$ *m/z* =578.63, found 578.96.

Compound 37

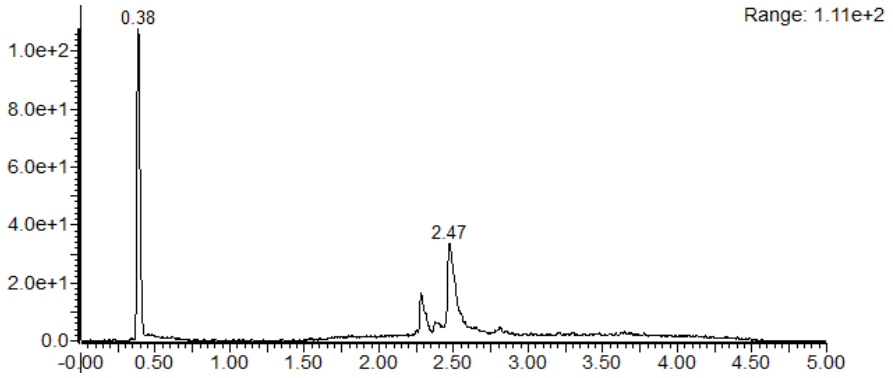


Figure S87: UV trace from analytical UPLC-MS analysis for crude **Compound 37**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

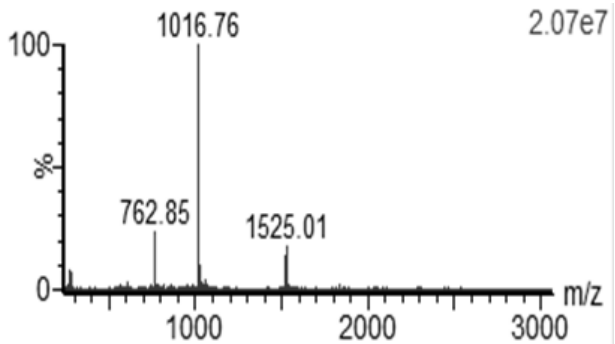


Figure S88: ESI-MS calcd. for $C_{135}H_{220}N_{38}O_{42}$ =3047.47; $[M+2H]^{2+}$ *m/z* =1524.73, found 1525.01; $[M+3H]^{3+}$ *m/z* =1016.82, found 1016.76; $[M+4H]^{4+}$ *m/z* =762.87, found 762.85.

Peptide architecture entry 9

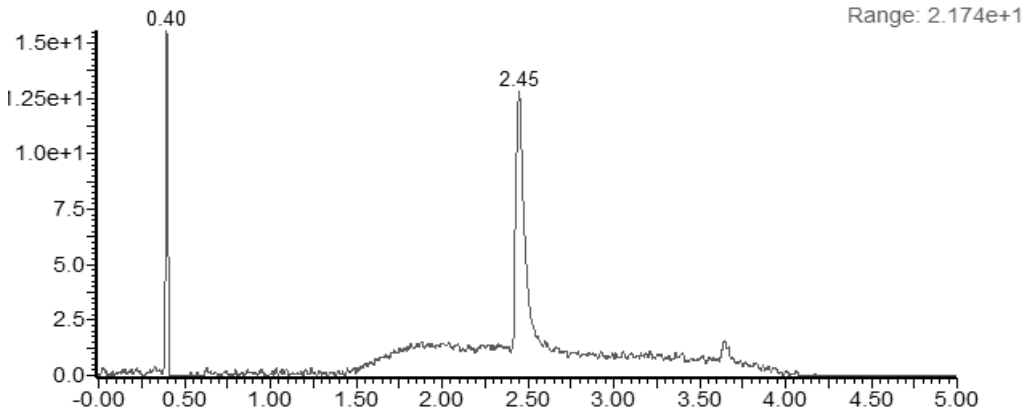


Figure S89: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 9** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

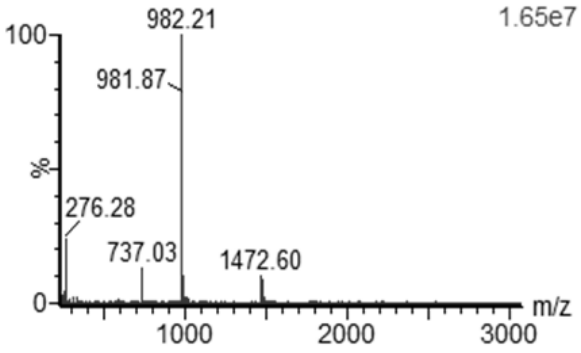
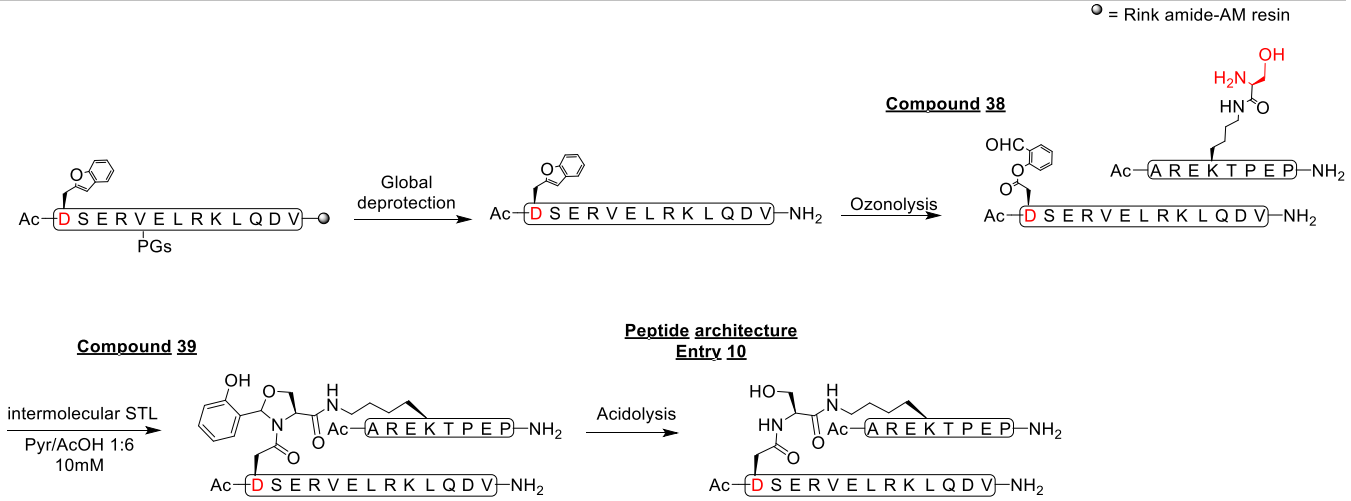


Figure S90: ESI-MS calcd. for $C_{128}H_{216}N_{38}O_{41}$ = 2943.36; $[M+2H]^{2+}$ *m/z* =1472.68, found 1472.60; $[M+3H]^{3+}$ *m/z* =982.12, found 982.21; $[M+4H]^{4+}$ *m/z* =736.84, found 737.03.

Peptide architecture Entry 10



Ozonolysis of the purified peptide (30.82 mg, 18.12 μmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 38 as white solid.

The ligation between crude Compound 38 (2.37 mg, 1.37 μmol) and Ac-ARE(K-S)TPEP-NH_2 (1.59 mg, 1.50 μmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 10 (1.40 mg, 38.4% yield) as white solid.

Compound 38

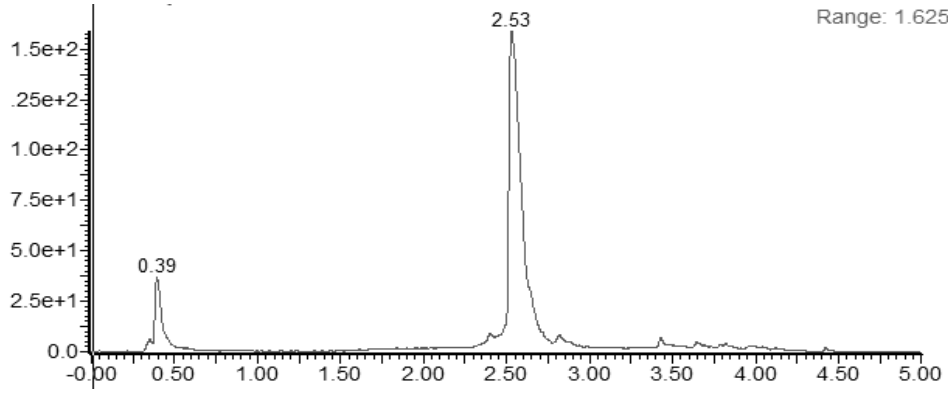


Figure S91: UV trace from analytical UPLC-MS analysis for crude **Compound 38**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

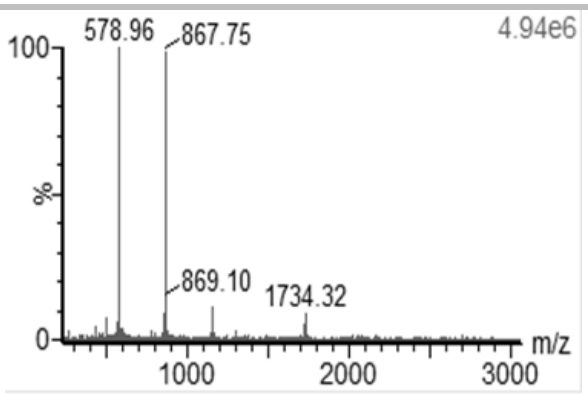


Figure S92: ESI-MS calcd. for $C_{75}H_{121}N_{21}O_{26}$ =1732.91; $[M+H]^{+}$ *m/z* =1733.91, found 1734.32; $[M+2H]^{2+}$ *m/z* =867.45, found 867.75; $[M+3H]^{3+}$ *m/z* =578.63, found 578.96.

Compound 39

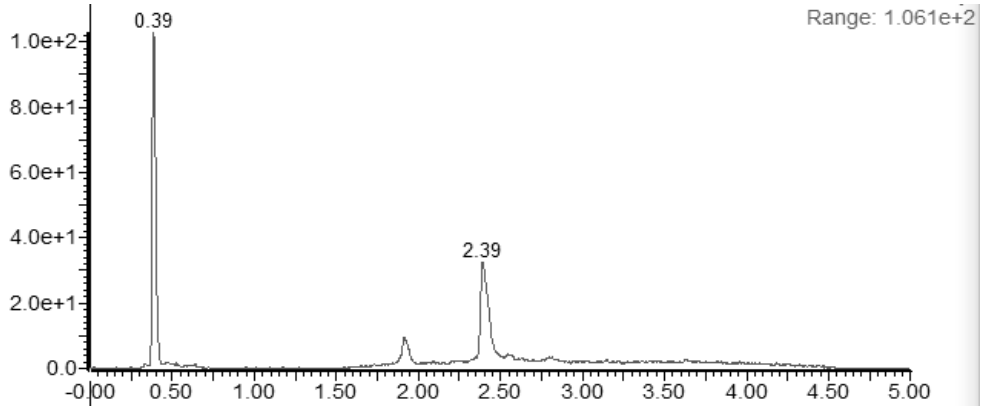


Figure S93: UV trace from analytical UPLC-MS analysis for crude **Compound 39**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

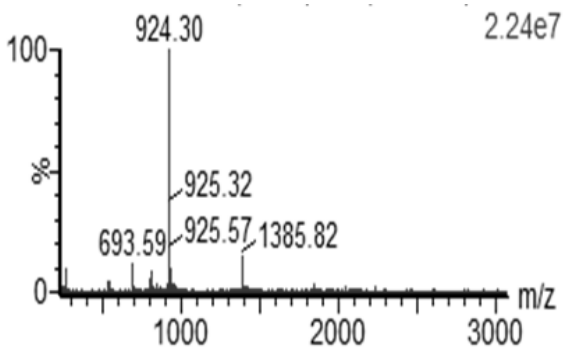


Figure S94: ESI-MS calcd. for $C_{112}H_{189}N_{35}O_{40}$ =2770.06; $[M+2H]^{2+}$ *m/z* =1386.03, found 1385.82; $[M+3H]^{3+}$ *m/z* =924.35, found 924.30; $[M+4H]^{4+}$ *m/z* =693.51, found 693.59.

Peptide architecture entry 10

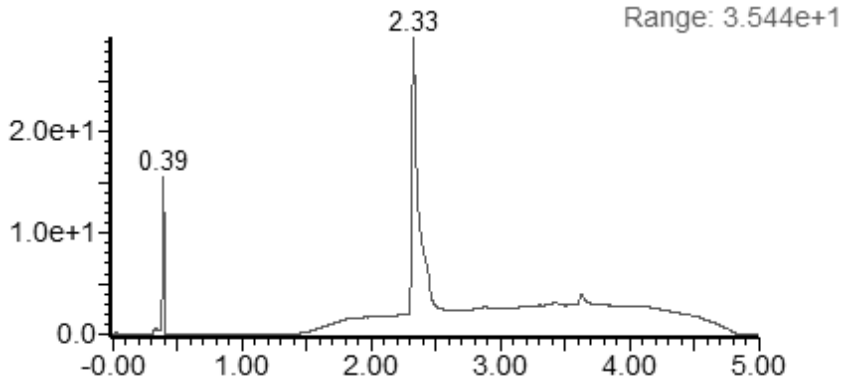


Figure S95: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 10** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

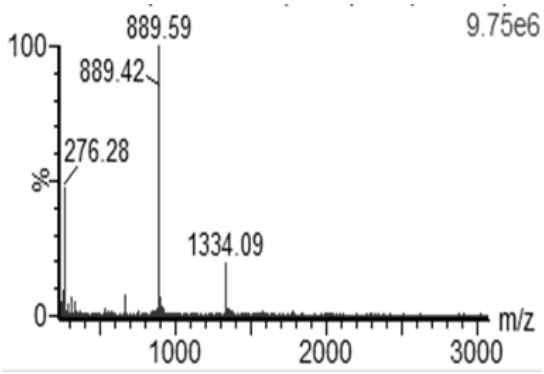
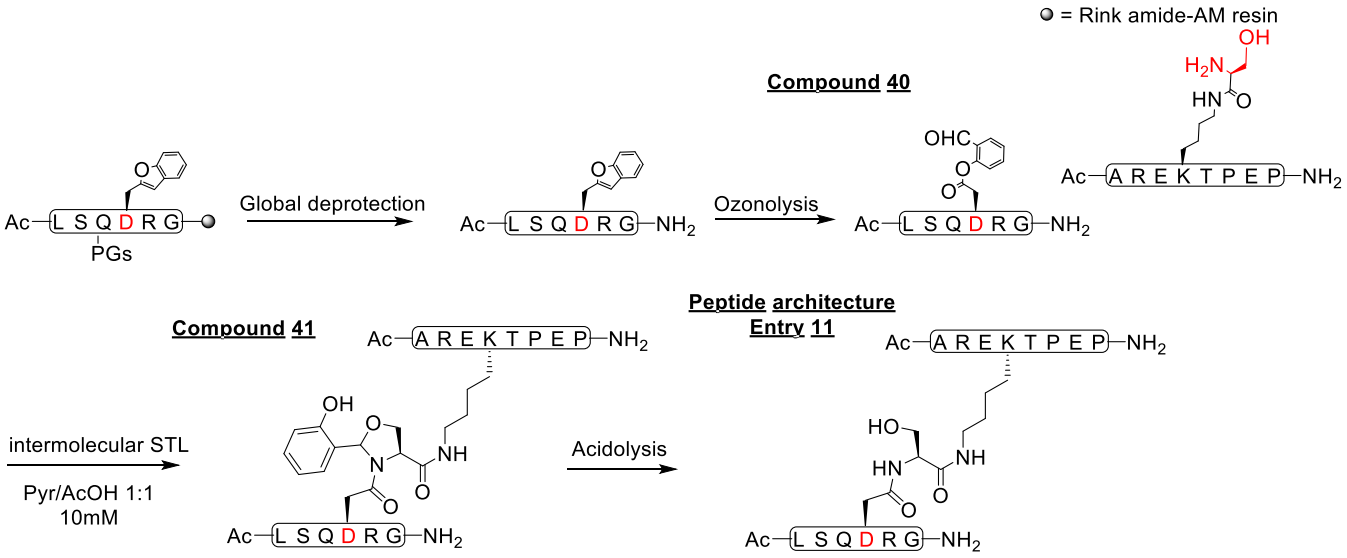


Figure S96: ESI-MS calcd. for $C_{75}H_{121}N_{21}O_{26}$ =2666.91; $[M+2H]^{2+}$ *m/z* =1334.45, found 1334.09; $[M+3H]^{3+}$ *m/z* =889.97, found 889.59.

Peptide architecture Entry 11



Ozonolysis of the purified peptide (20.03 mg, 23.07 µmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 40 as white solid.

The ligation between crude Compound 40 (2.17 mg, 2.65 µmol) and Ac-ARE(K-S)TPEP-NH_2 (3.07 mg, 3.07 µmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 11 (1.61 mg, 34.7% yield) as white solid.

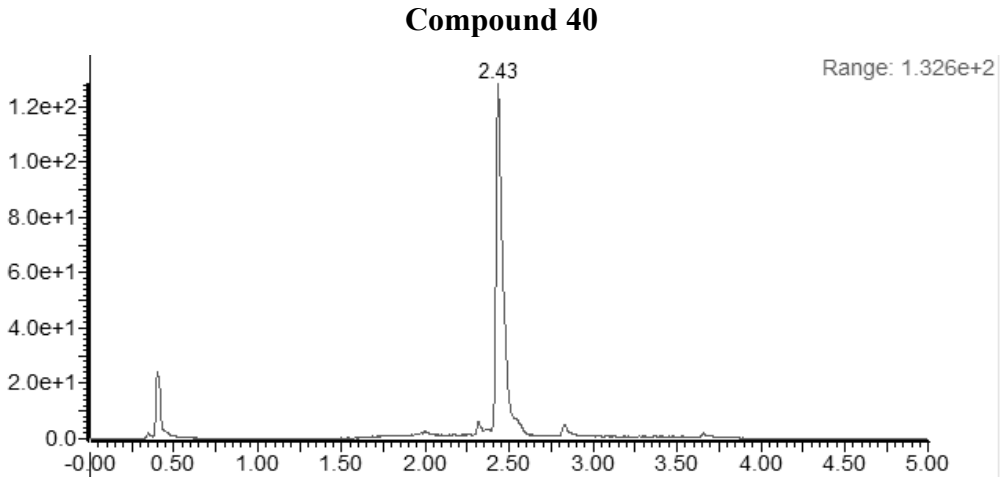


Figure S97: UV trace from analytical UPLC-MS analysis for crude **Compound 40**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

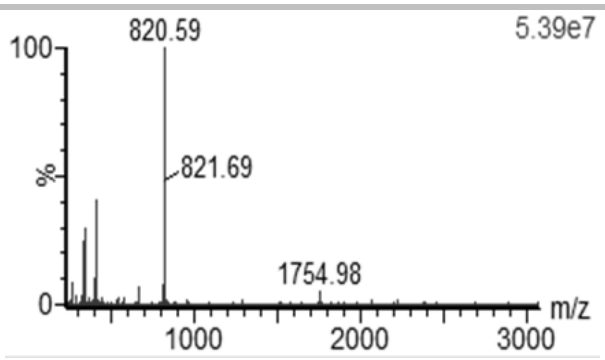


Figure S98: ESI-MS calcd. for $C_{35}H_{53}N_{11}O_{12}$ =819.87; $[M+H]^+$ *m/z* =820.87, found 820.59.

Compound 41

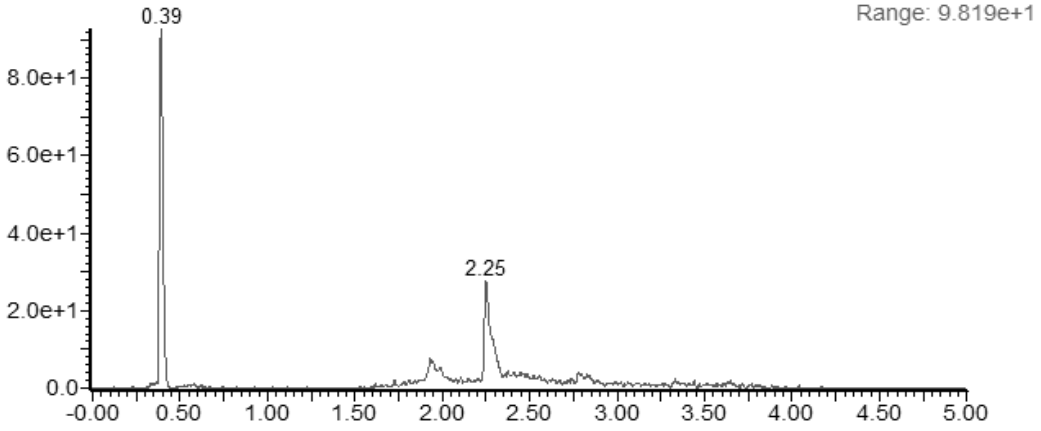


Figure S99: UV trace from analytical UPLC-MS analysis for crude **Compound 41**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

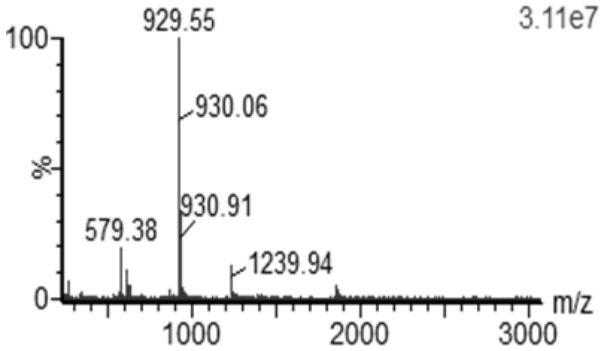


Figure S100: ESI-MS calcd. for $C_{79}H_{125}N_{26}O_{27}$ =1857.02; $[M+2H]^{2+}$ *m/z* =929.51, found 929.55; $2[M+3H]^{3+}$ *m/z* =1240.01, found 1239.94.

Peptide architecture entry 11

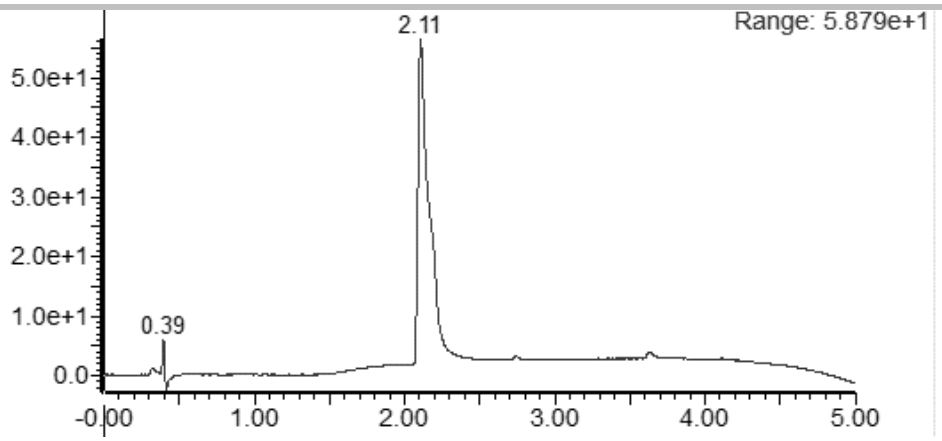


Figure S101: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 11** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

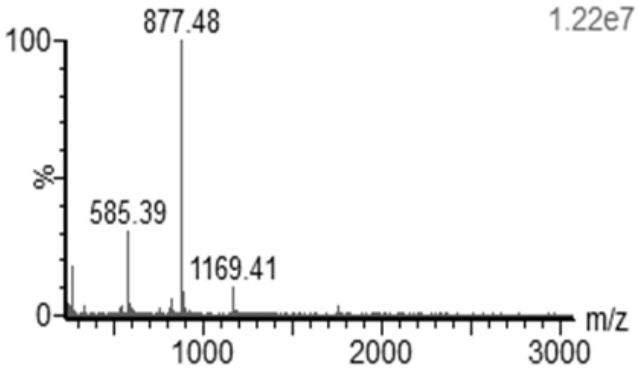
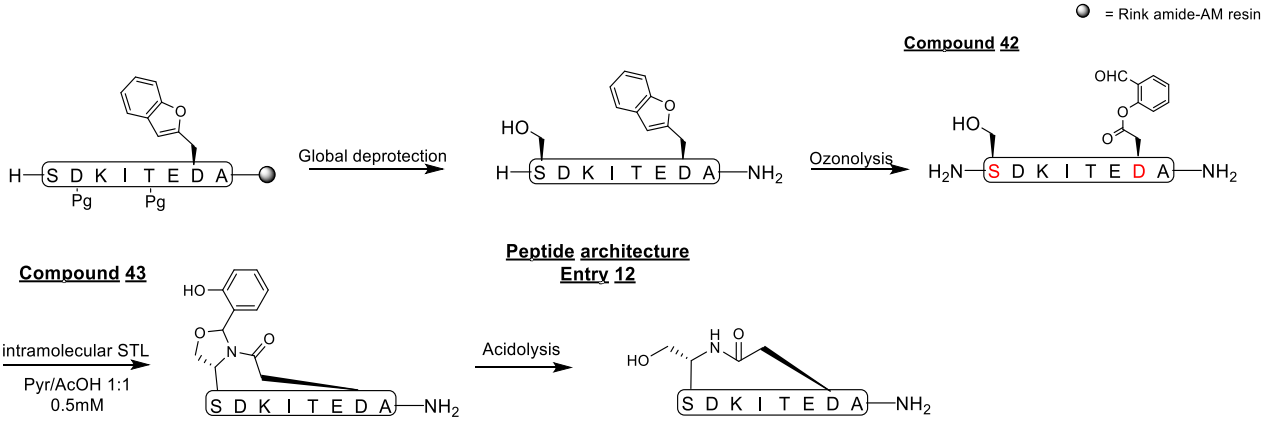


Figure S102: ESI-MS calcd. for $C_{72}H_{121}N_{26}O_{26}$ = 1752.91; [$[M+2H]^{2+}$ *m/z* =877.46, found 877.48; $[M+3H]^{3+}$ *m/z* =585.30, found 585.39; $2[M+3H]^{3+}$ *m/z* =1170.61, found1169.41.

Synthesis of* Class II: cyclic peptides with tails *(Entry 12-19)

Peptide architecture entry 12



Ozonolysis of the crude side-chain unprotected peptide (25.08 mg, 26.4 μmol) was performed as described in general procedure 2.4. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 42 (11.33 mg, 43.7% yield based on the resin loading) as white solid.

The ligation of Compound 42 (3.89 mg, 3.97 μmol) was performed as described in general procedure 2.6. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 12 (1.44 mg, 42.3 % yield) as white solid.

Compound 42

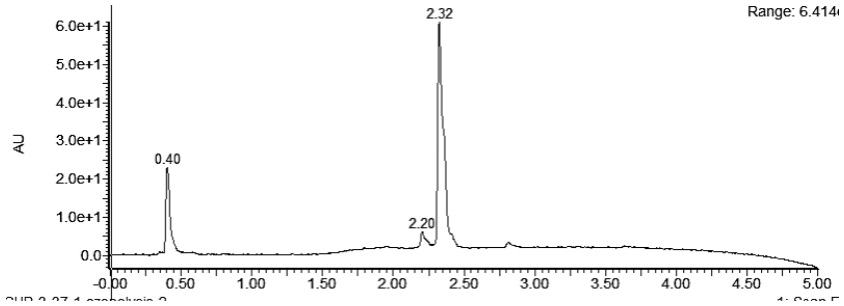


Figure S103: UV trace from analytical UPLC-MS analysis for crude **Compound 42**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

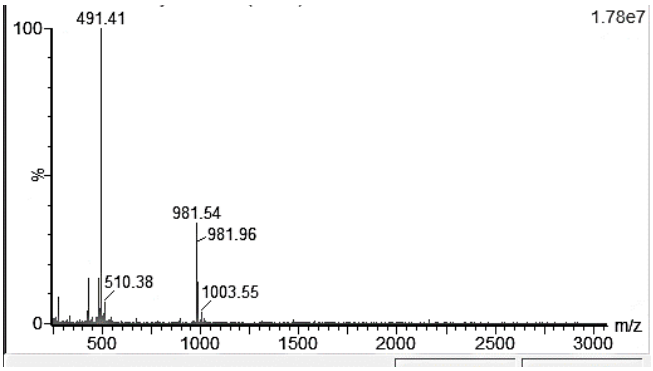


Figure S104: ESI-MS calcd. for $C_{42}H_{64}N_{10}O_{17}$ = 980.45; $[M+H]^+$ *m/z* = 981.45, found 981.54; $[M+2H]^{2+}$ *m/z* =491.22, found 491.41.

Compound 43

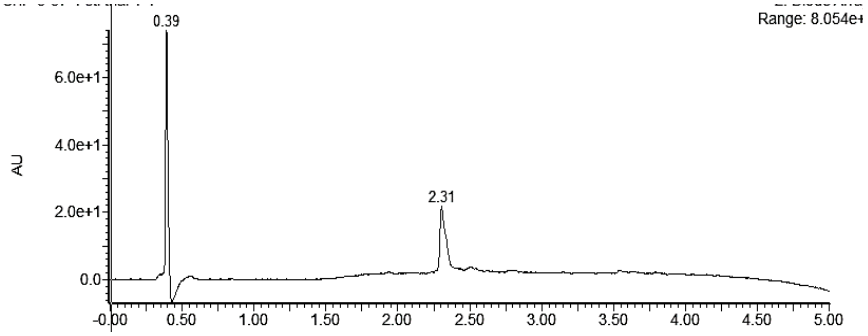


Figure S105: UV trace from analytical UPLC-MS analysis for crude **Compound 43**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

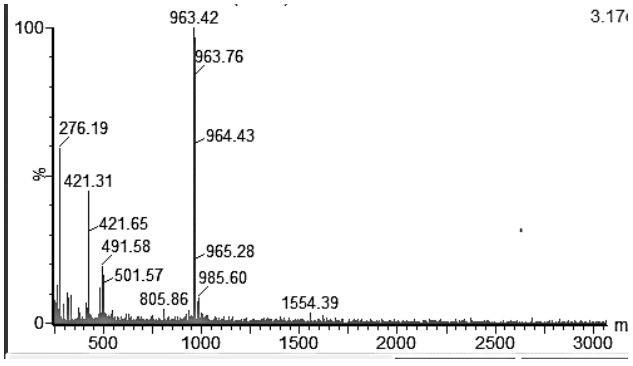


Figure S106: ESI-MS calcd. for $C_{42}H_{62}N_{10}O_{16}$= 962.43; $[M+H]^+$ *m/z*= 963.43, found 963.42.

Peptide architecture entry 12

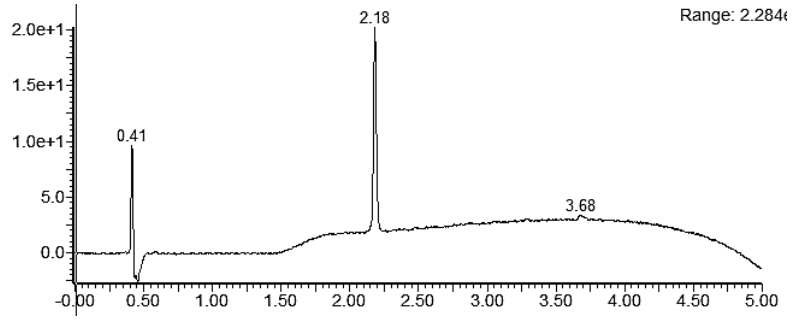


Figure S107: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 12**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

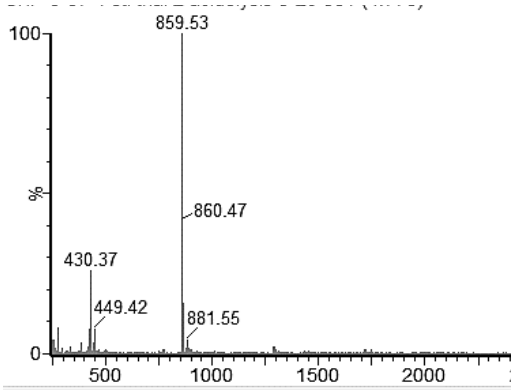
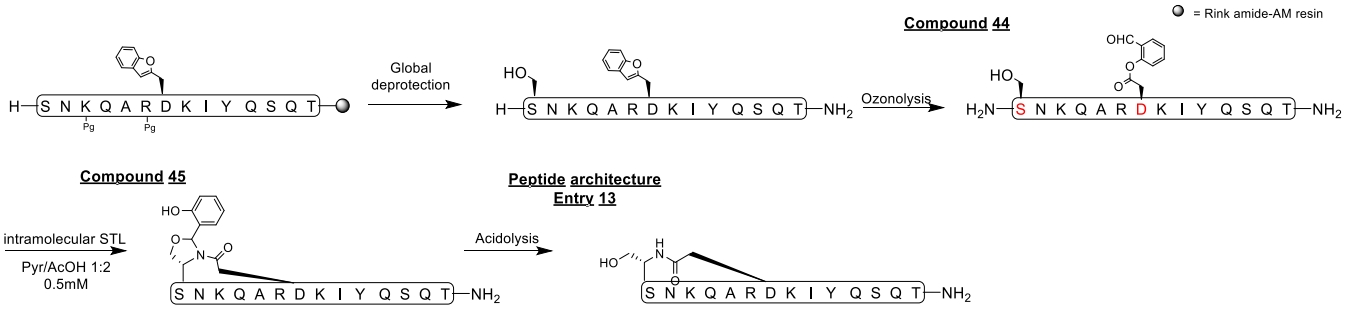


Figure S108: ESI-MS calcd. for $C_{35}H_{58}N_{10}O_{15}$= 858.41, $[M+H]^+$ *m/z*=859.41, found 859.53; $[M+2H]^{2+}$ *m/z* = 430.20, found 430.37.

Peptide architecture entry 13



Ozonolysis of the purified peptide (20.38 mg, 11.73 µmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 44 as white solid.

The ligation of crude Compound 44 (4.05 mg, 2.29 µmol) was performed as described in general

procedure 2.6. Reverse phase HPLC purification followed by lyophilization afforded the product (1.74 mg, 46.1% yield) as white solid.

Compound 44

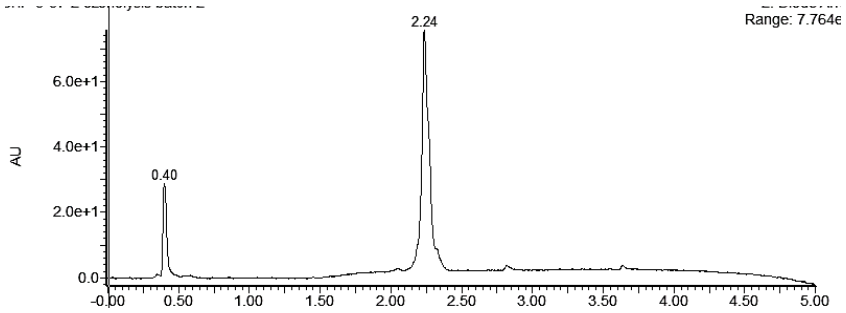


Figure S109: UV trace from analytical UPLC-MS analysis for crude **Compound 44**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

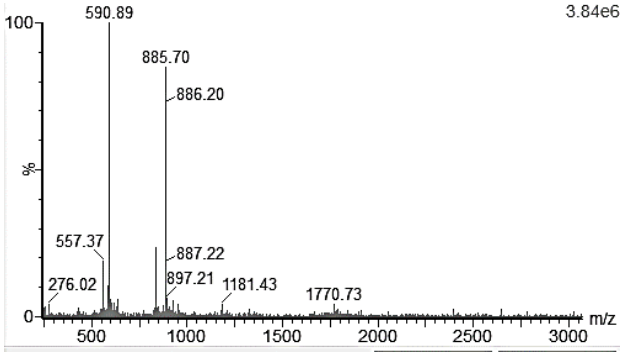


Figure S110: ESI-MS calcd. for $C_{76}H_{120}N_{24}O_{25}$=1769.94; $[M+2H]^{2+}$ *m/z* = 885.97, found 885.70; $[M+3H]^{3+}$ *m/z* = 590.98, found 590.89.

Compound 45

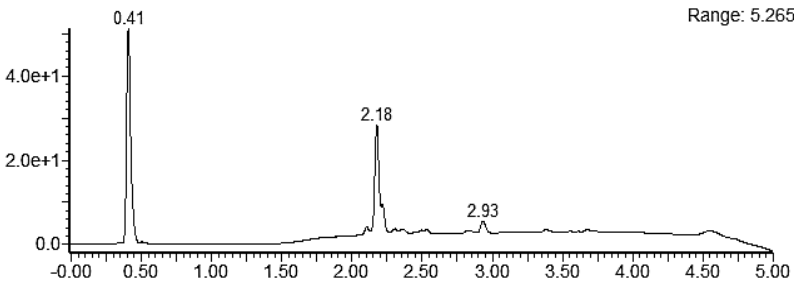


Figure S111: UV trace from analytical UPLC-MS analysis for crude **Compound 45**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

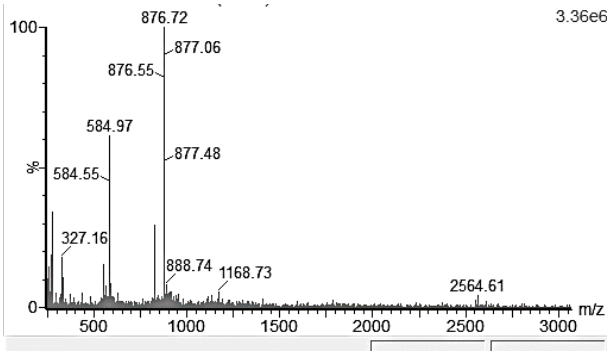


Figure S112: ESI-MS calcd. for $C_{76}H_{119}N_{24}O_{24}$=1750.90; $[M+2H]^{2+}$ *m/z* = 876.45, found 876.42; $[M+3H]^{3+}$ *m/z* = 584.30, found 584.97.

Peptide architecture entry 13

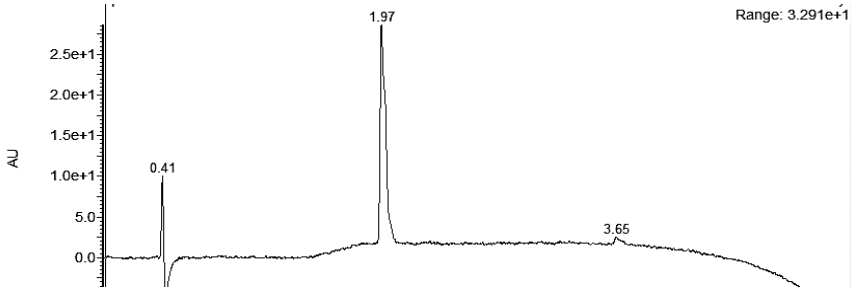


Figure S113: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 13**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

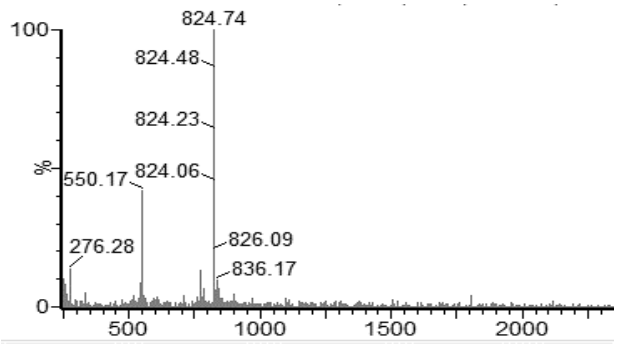
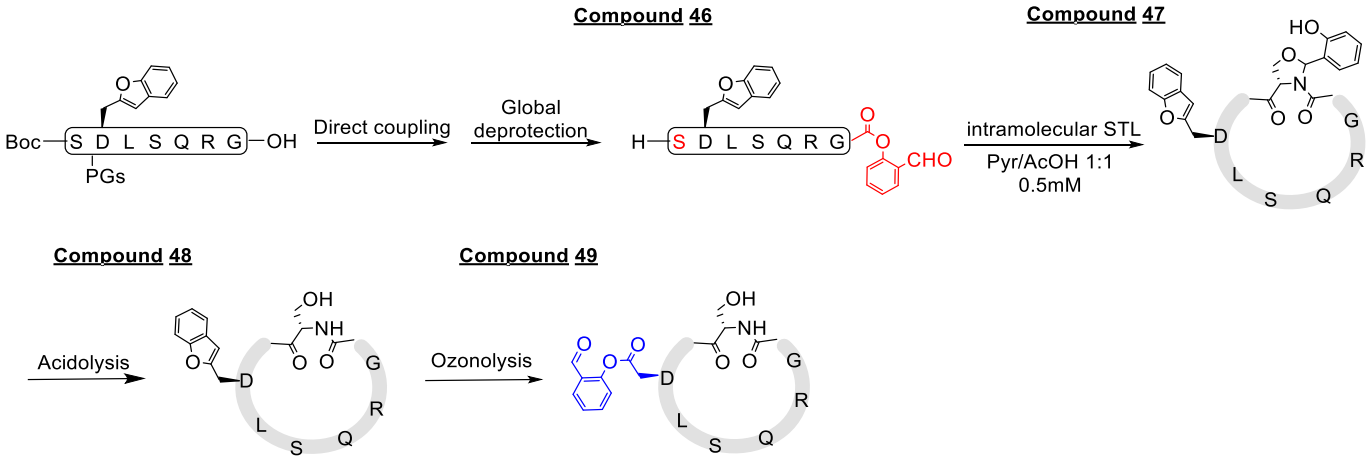


Figure S114: ESI-MS calcd. for $C_{70}H_{118}N_{24}O_{22}$=1647.86; $[M+2H]^{2+}$ *m/z* = 824.93, found 824.74. $[M+3H]^{3+}$ *m/z* = 550.29, found 550.17.

Preparation of Compound 49 for tailed cyclic peptides and bicyclic peptides: (Entry 14-21)



Direct coupling was performed on the side-chain protected crude peptide (203.39 mg, 132.07 μmol) as described in general procedure 2.5. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 46 (69.45 mg, 56% yield) as white solid.

The ligation of Compound 46 (69.45 mg, 74.05 μmol) was performed as described in general procedure 2.6. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 48 (29.00 mg, 48.0% yield) as white solid.

Ozonolysis of Compound 48 (35.35 mg, 43.37 μmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 49 as white solid.

Compound 46

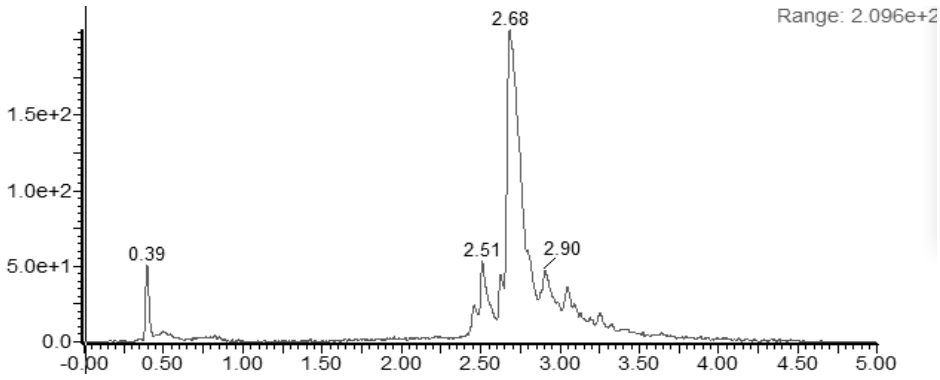


Figure S115: UV trace from analytical UPLC-MS analysis for crude **Compound 46**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

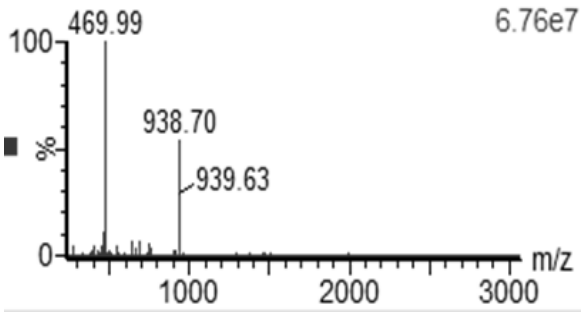


Figure S116: ESI-MS calcd. for $C_{43}H_{59}N_{11}O_{13}$ =938.01; $[M+H]^+$ *m/z* =939.01, found938.7; $[M+2H]^{2+}$ *m/z* =470.00, found 469.99.

Compound 47

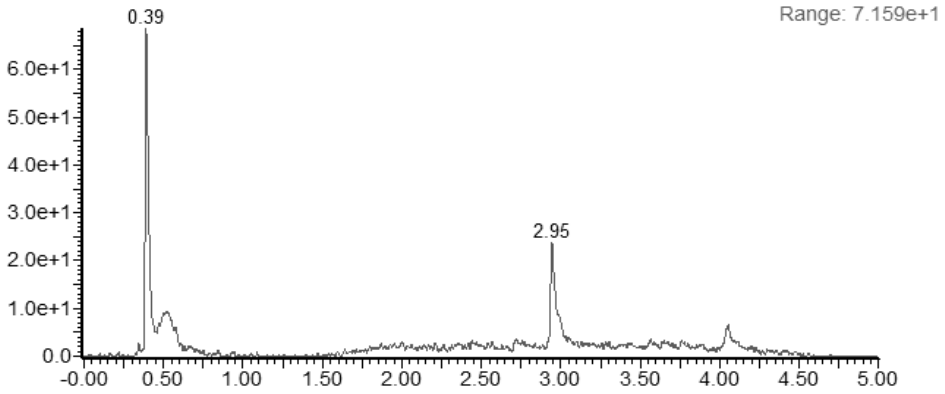


Figure S117: UV trace from analytical UPLC-MS analysis for crude **Compound 47**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

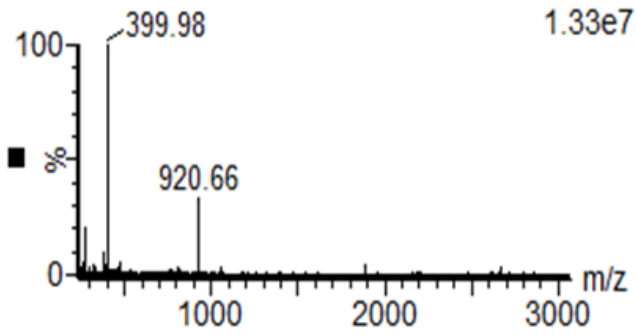


Figure S118: ESI-MS calcd. for $C_{43}H_{57}N_{11}O_{12}$ =919.99; $[M+H]^+$ *m/z* =920.99, found 920.66.

Compound 48

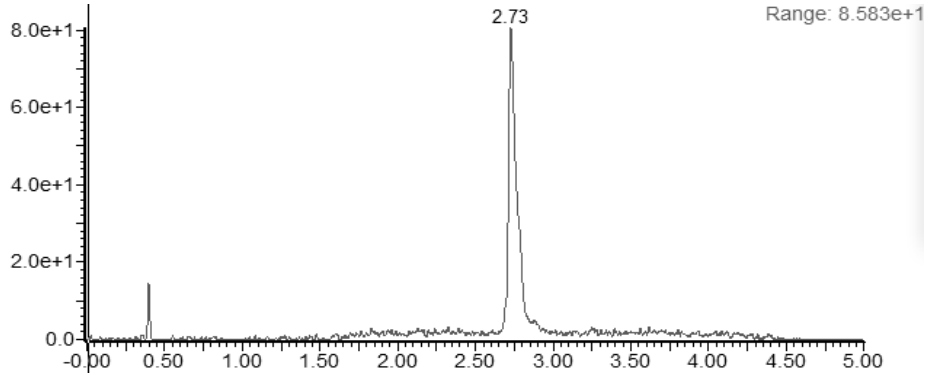


Figure S119: UV trace from analytical UPLC-MS analysis for purified **Compound 48**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

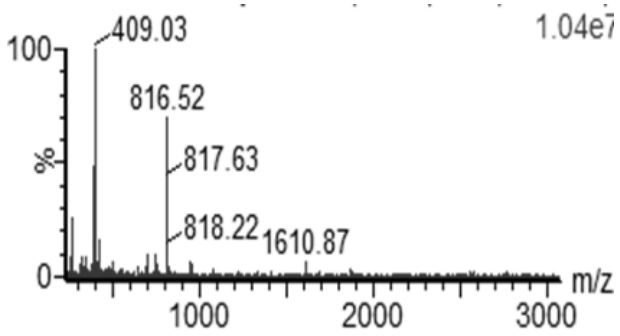


Figure S120: ESI-MS calcd. for $C_{36}H_{53}N_{11}O_{11}$ =815.89; $[M+H]^+$ *m/z* =816.90, found 816.52; $[M+2H]^{2+}$ *m/z* =408.95, found 409.03.

Compound 49

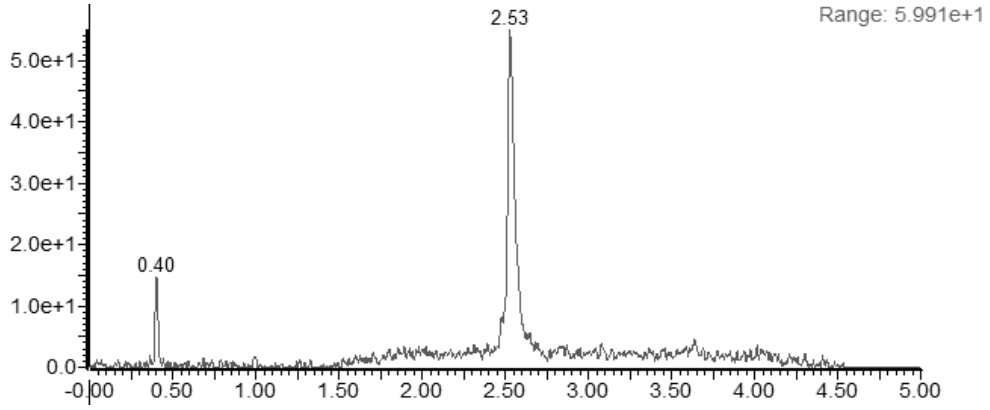


Figure S121: UV trace from analytical UPLC-MS analysis for crude **Compound 49**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

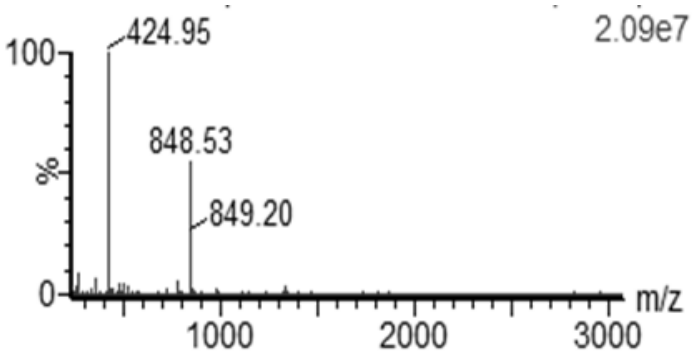
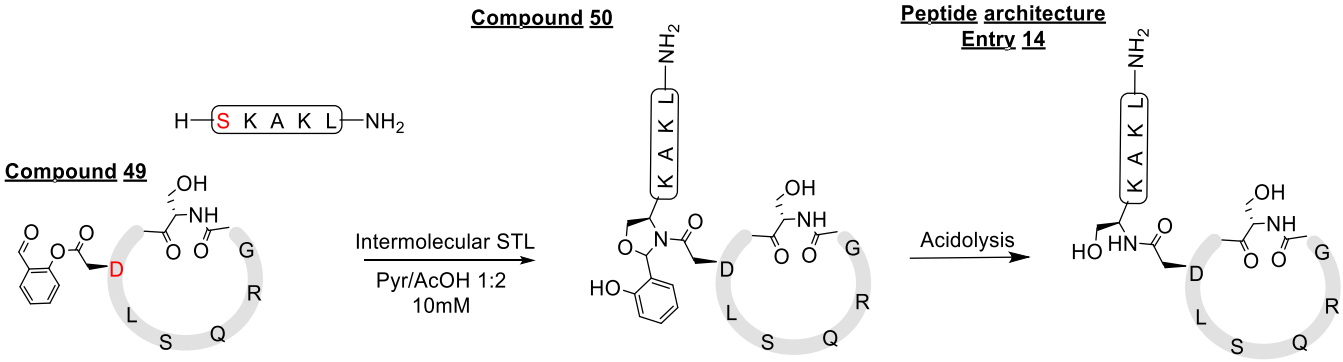


Figure S122: ESI-MS calcd. for $C_{36}H_{53}N_{11}O_{13}$ = 847.88; $[M+H]^+$ *m/z* = 848.88, found 848.53; $[M+2H]^{2+}$ *m/z* = 424.94, found 424.95.

Peptide architecture Entry 14



The ligation between crude Compound 49 (1.86 mg, 2.19 µmol) and H-SKAKL-NH_2 (1.31 mg, 2.41 µmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 14 (1.10 mg, 39.5% yield) as white solid.

Compound 50

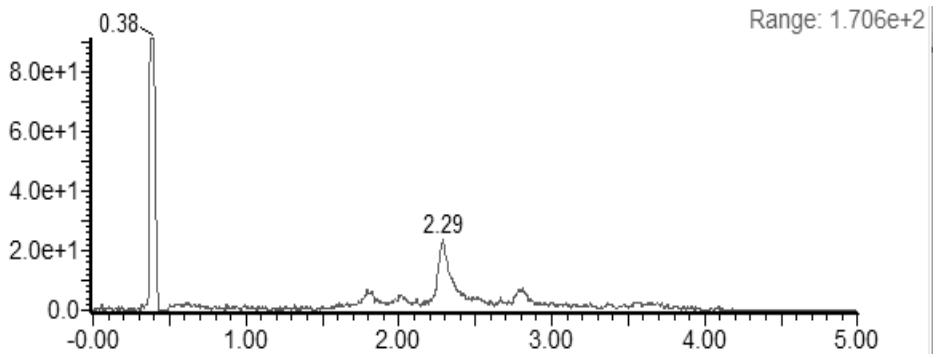


Figure S123: UV trace from analytical UPLC-MS analysis for crude **Compound 50**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

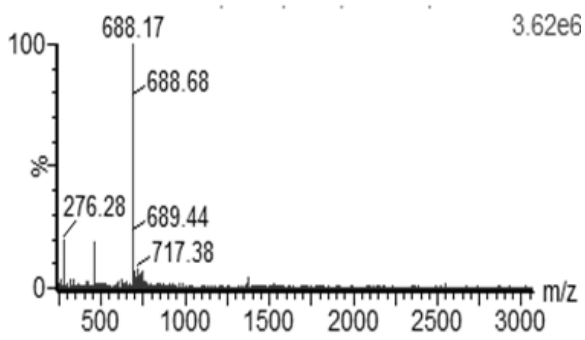


Figure S124: ESI-MS calcd. for $C_{60}H_{99}N_{19}O_{18}$ = 1374.57, $[M+2H]^{2+}$ *m/z* =688.29, found 688.17.

Peptide architecture entry 14

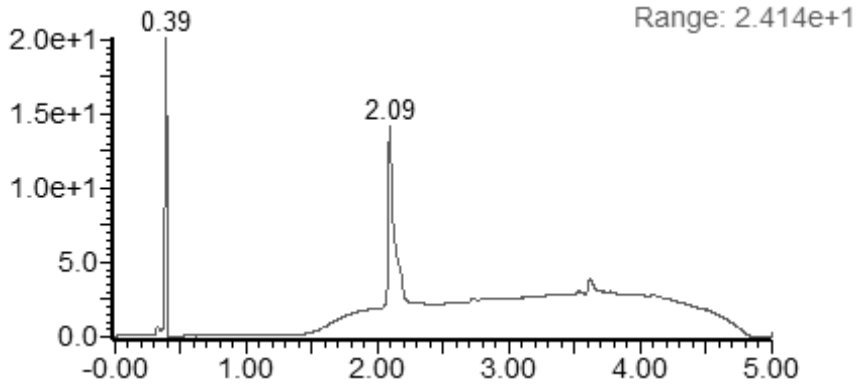


Figure S125: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 14**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

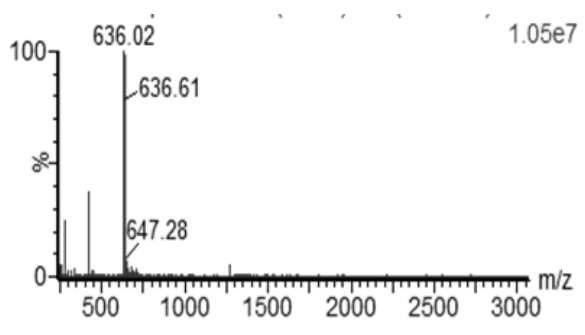
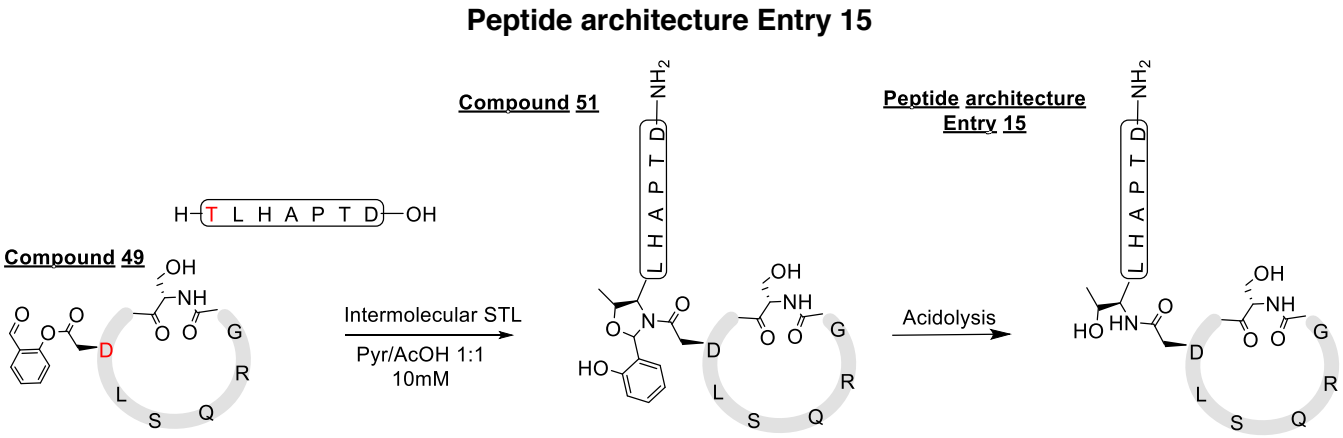


Figure S126: ESI-MS calcd. for $C_{53}H_{95}N_{19}O_{17}$ =1270.46; $[M+2H]^{2+}$ *m/z* =636.23, found 636.02.



The ligation between crude Compound 49 (1.50 mg, 1.84 µmol) and H-TLHAPTD-NH_2 (1.46 mg, 2.02 µmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 15 (1.08 mg, 41.2% yield) as white solid.

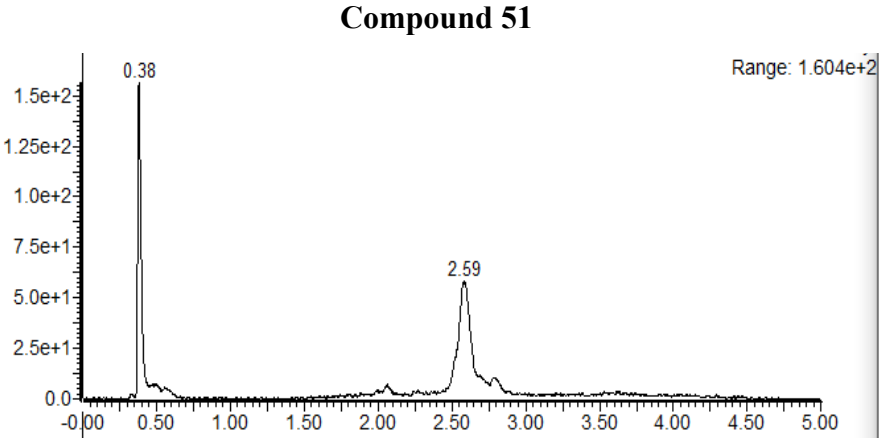


Figure S127: UV trace from analytical UPLC-MS analysis for crude **Compound 51**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

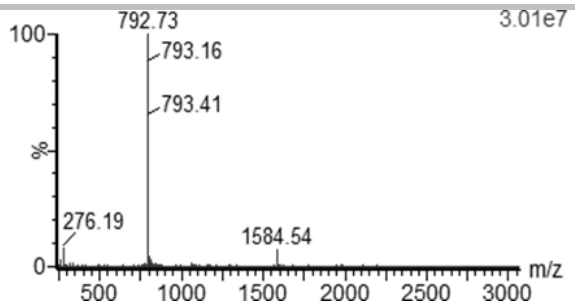


Figure S128: ESI-MS calcd. for $C_{68}H_{102}N_{20}O_{24}$ = 1583.68, $[M+H]^+$ *m/z* =1584.68, found 1584.54. $[M+2H]^{2+}$ *m/z* =792.84, found 792.73.

Peptide architecture entry 15

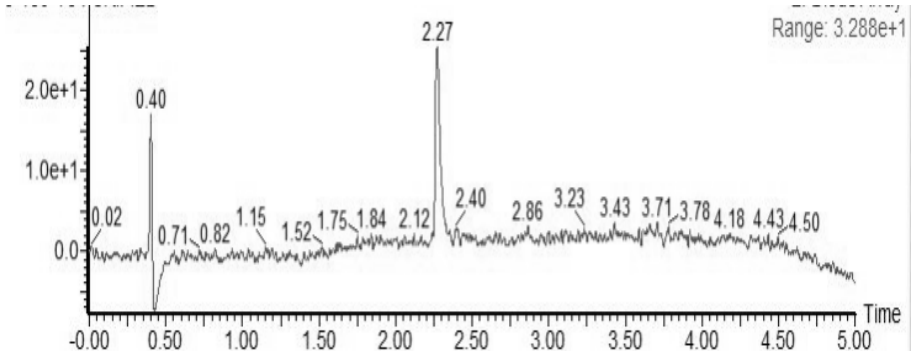


Figure S129: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 15**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

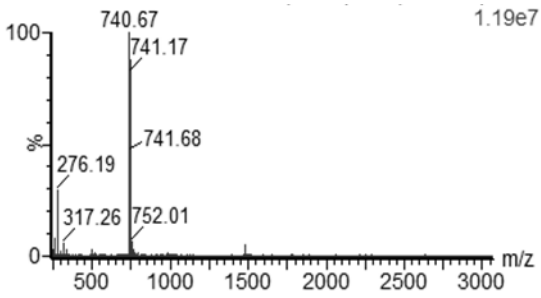
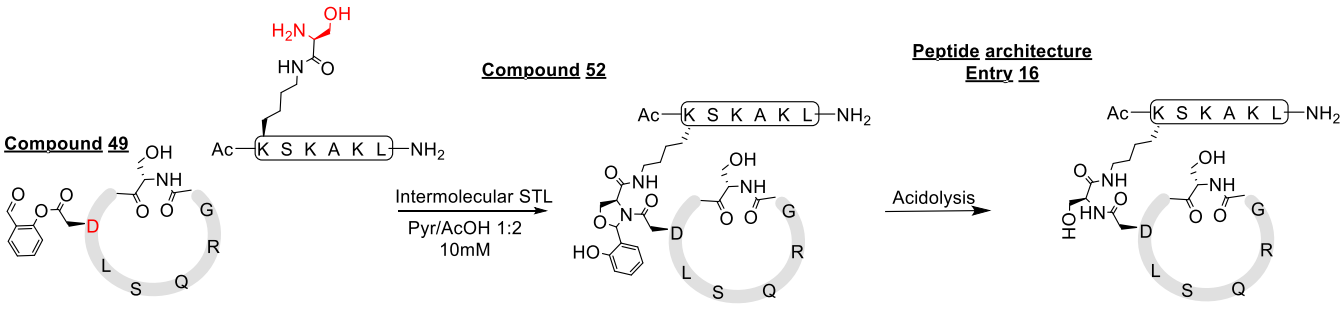


Figure S130: ESI-MS calcd. for $C_{61}H_{98}N_{20}O_{23}$ = 1479.57; $[M+2H]^{2+}$ *m/z* =740.5, found 740.67.

Peptide architecture Entry 16



The ligation between crude Compound 49 (1.56 mg, 1.84 µmol) and Ac-(K-S)SKAKL-NH_2 (1.62 mg, 2.02 µmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 16 (1.49 mg, 53.3% yield) as white solid.

Compound 52

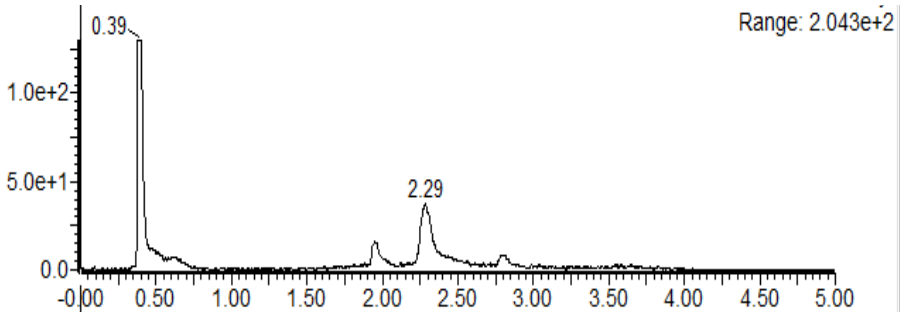


Figure S131: UV trace from analytical UPLC-MS analysis for crude **Compound 52**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

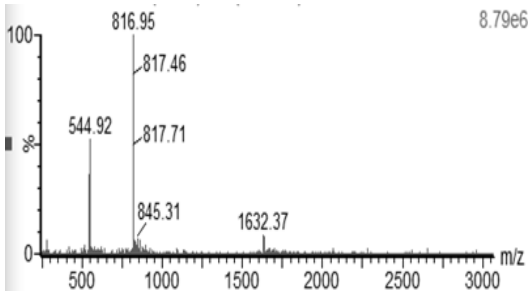


Figure S132: ESI-MS calcd. for $C_{71}H_{118}N_{22}O_{22}$ =1631.86, $[M+H]^+$ *m/z* =1632.86, found 1632.37; $[M+2H]^{2+}$ *m/z* =816.93, found 816.95; $[M+3H]^{3+}$ *m/z* = 544.95, found 544.92.

Peptide architecture entry 16

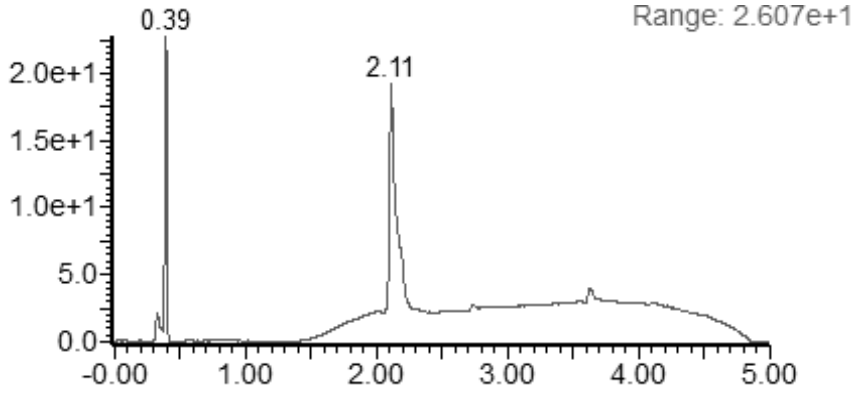


Figure S133: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 16** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

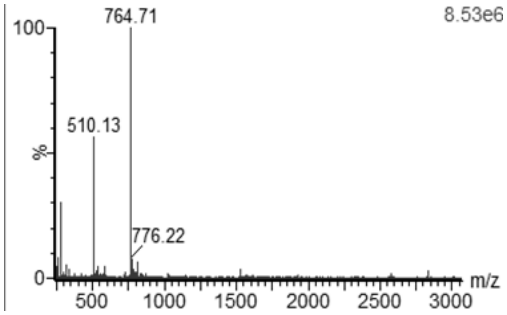
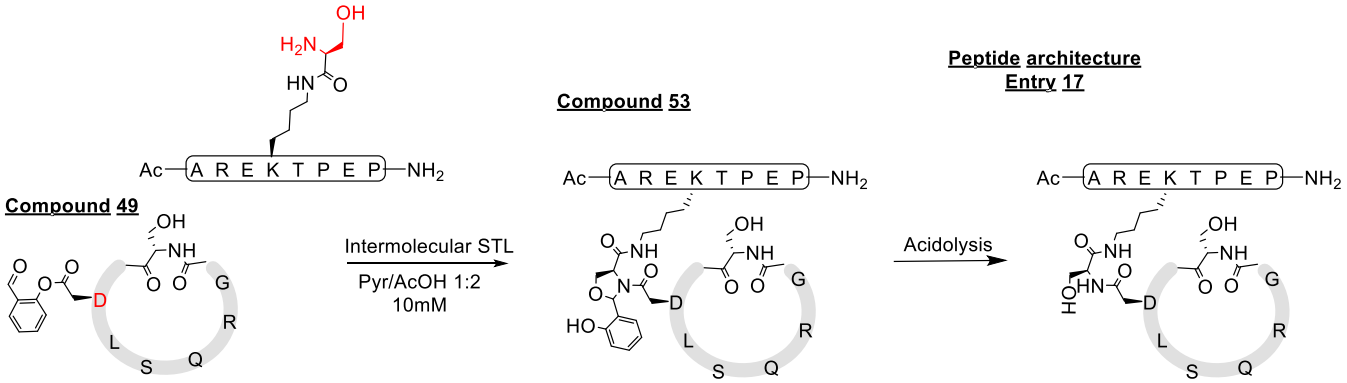


Figure S134: ESI-MS calcd. for $C_{64}H_{114}N_{22}O_{21}$ =1527.75; $[M+2H]^{2+}$ *m/z* =764.88, found 764.71; $[M+3H]^{3+}$ *m/z* =510.25, found 510.13.

Peptide architecture Entry 17



The ligation between crude Compound 49 (1.06 mg, 1.25 μmol) and Ac-ARE(K-S)TPEP- NH_2 (2.21 mg, 1.38 μmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 17 (1.40 mg, 52.5% yield) as white solid.

Compound 53

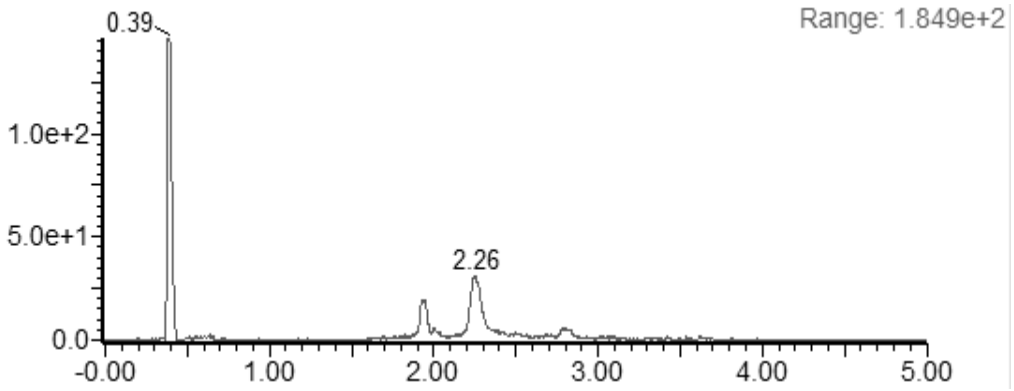


Figure S135: UV trace from analytical UPLC-MS analysis for crude **Compound 53**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

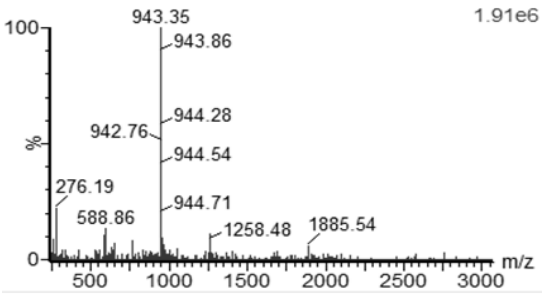


Figure S136: ESI-MS calcd. for $C_{80}H_{125}N_{25}O_{28}$ = 1885.03, $[M+H]^+$ *m/z* =1886.03, found 1885.54; $[M+2H]^{2+}$ *m/z* =943.52, found 943.35; $2[M+2H]^{2+}$ *m/z* = 1258.69, found 1258.48.

Peptide architecture entry 17

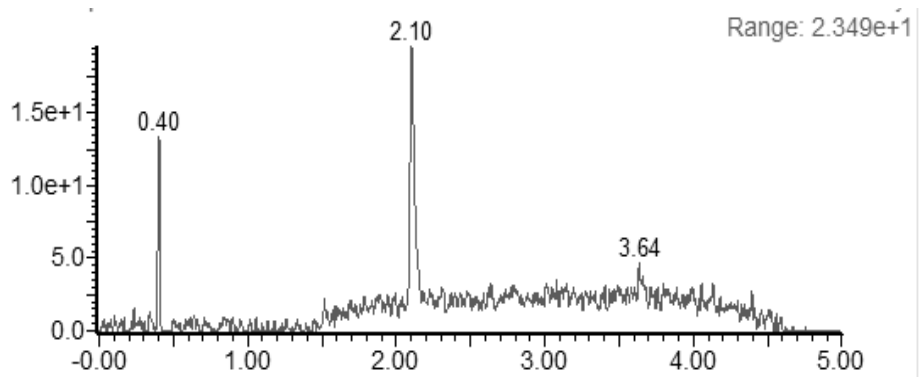


Figure S137: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 17**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

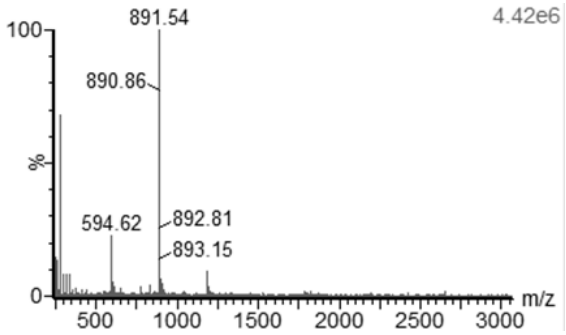
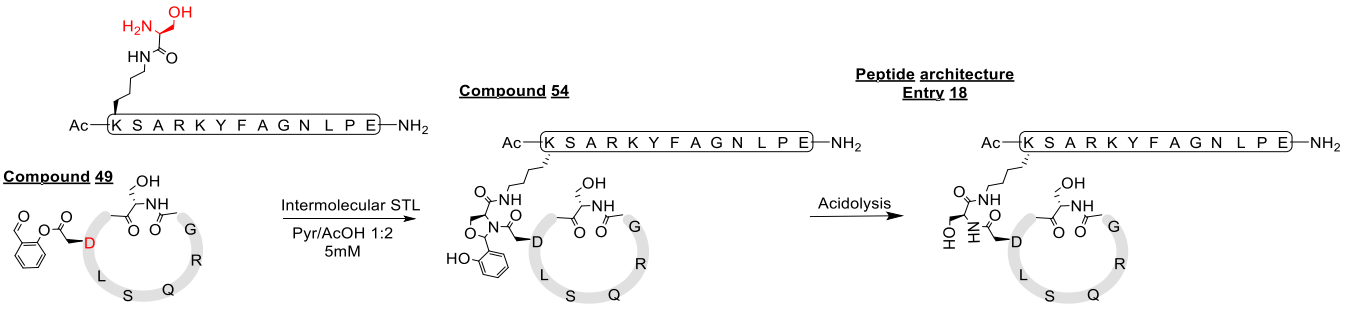


Figure S138: ESI-MS calcd. for $C_{73}H_{121}N_{25}O_{27}$ =1780.92; $[M+2H]^{2+}$ *m/z* =891.46, found 891.54; $[M+3H]^{3+}$ *m/z* = 594.64, found 594.62.

Peptide architecture Entry 18



The ligation between crude Compound 49 (1.06 mg, 1.25 µmol) and Ac-(K-S)SARKYFAGNLPE-NH_2 (2.21 mg, 1.38 µmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 18 (1.43 mg, 49.0% yield) as white solid.

Compound 54

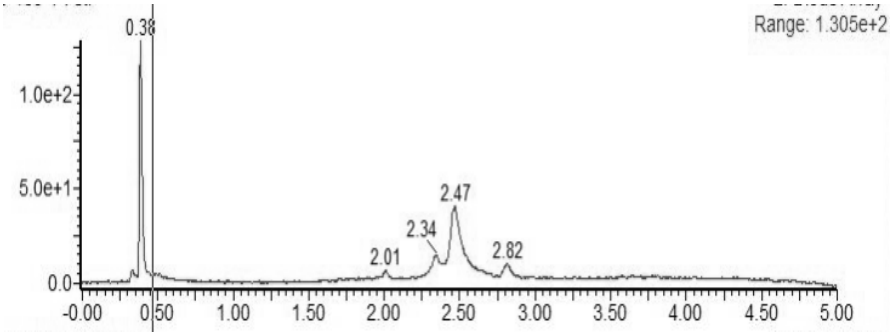


Figure S139: UV trace from analytical UPLC-MS analysis for crude **Compound 54**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

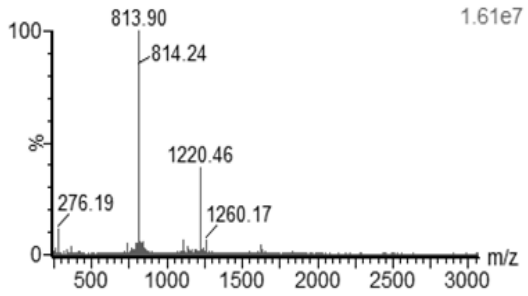


Figure S140: ESI-MS calcd. for $C_{108}H_{164}N_{32}O_{33}$ = 2438.69, $[M+2H]^{2+}$ *m/z* = 1220.35, found 1220.46; $[M+3H]^{3+}$ *m/z* = 813.90, found 813.90.

Peptide architecture entry 18

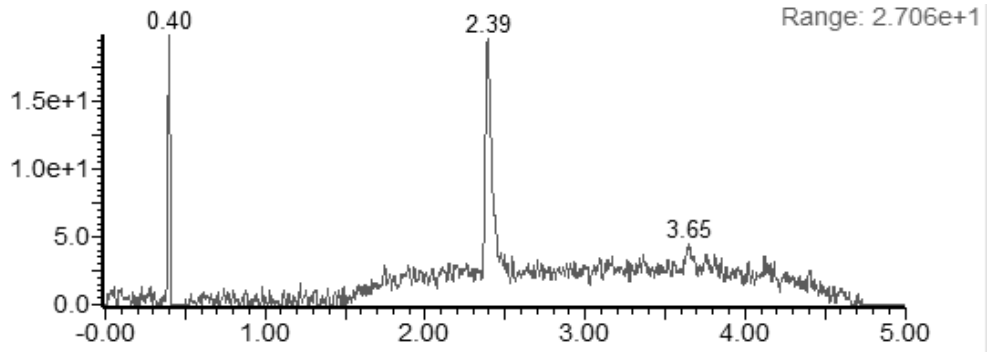


Figure S141: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 18** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

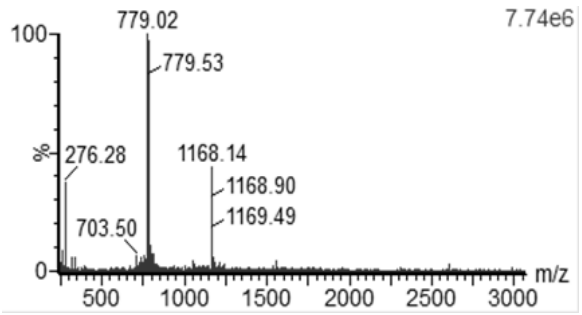
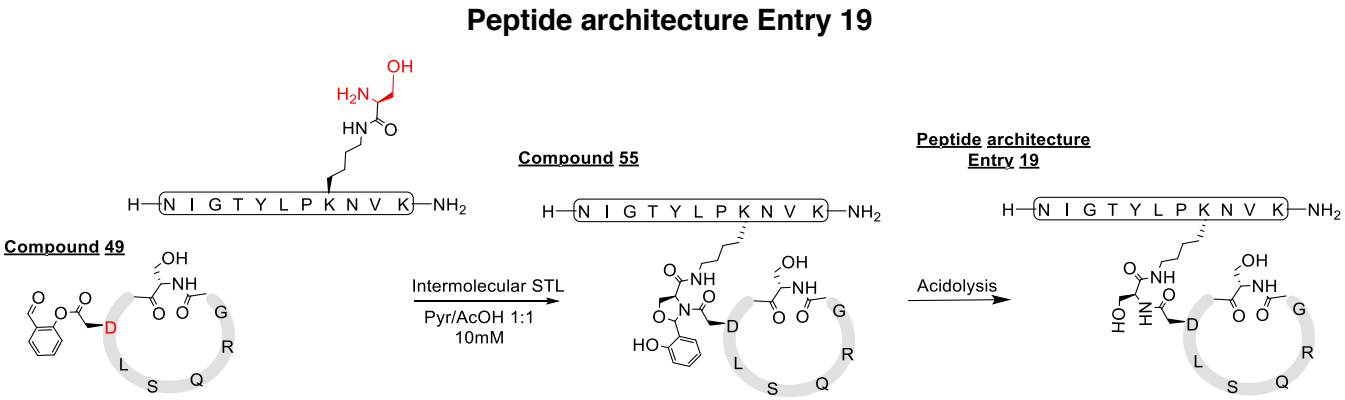


Figure S142: ESI-MS calcd. for $C_{101}H_{160}N_{32}O_{32}$ =2334.58; $[M+2H]^{2+}$ *m/z* = 1168.29, found 1168.14; $[M+3H]^{3+}$ *m/z* = 779.19, found 779.02.



The ligation between crude Compound 49 (1.20 mg, 1.42 µmol) and H-NIGTYLP(K-S)NVK-NH_2 (2.07 mg, 1.56 µmol) was performed as described in general procedure 2.7. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 19 (1.52 mg, 52.3% yield) as white solid.

Compound 55

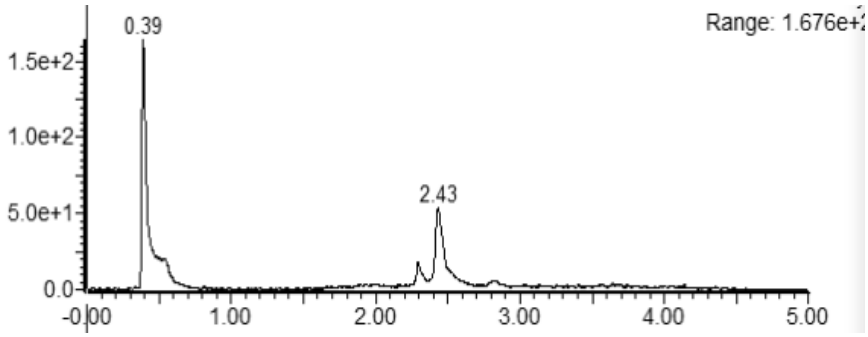


Figure S143: UV trace from analytical UPLC-MS analysis for crude **Compound 55**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

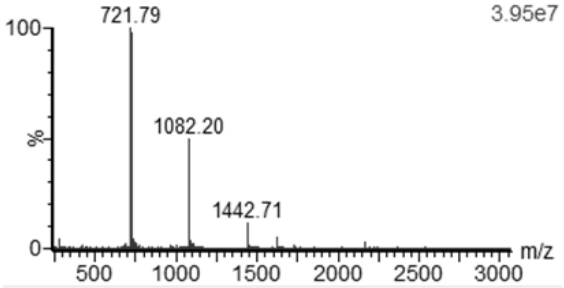


Figure S144: ESI-MS calcd. for $C_{96}H_{152}N_{28}O_{29}$ = 2162.44, $[M+2H]^{2+}$ *m/z* = 1082.22, found 1082.20; $[M+3H]^{3+}$ *m/z* = 721.81, found 721.79; $2[M+3H]^{3+}$ *m/z* = 1443.62, found 1442.71.

Peptide architecture entry 19

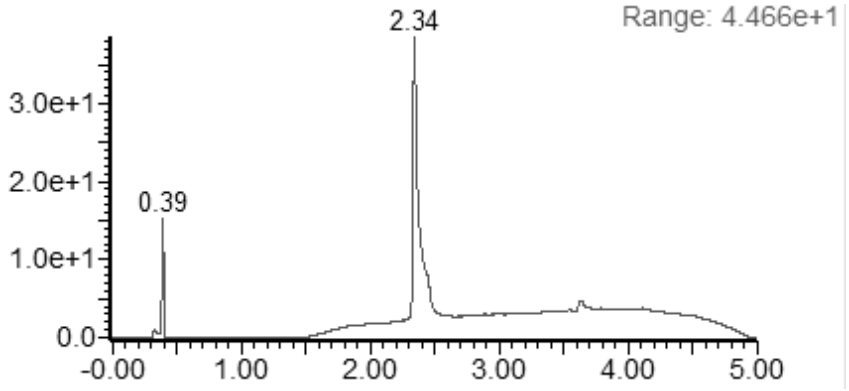


Figure S145: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture entry 19** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

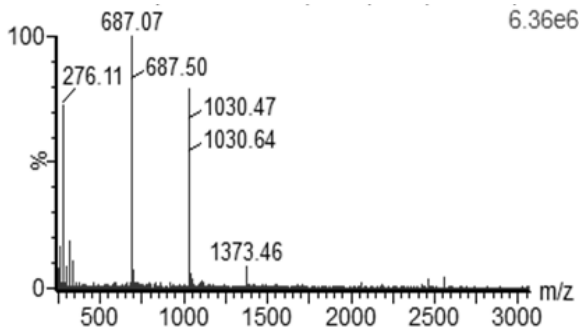
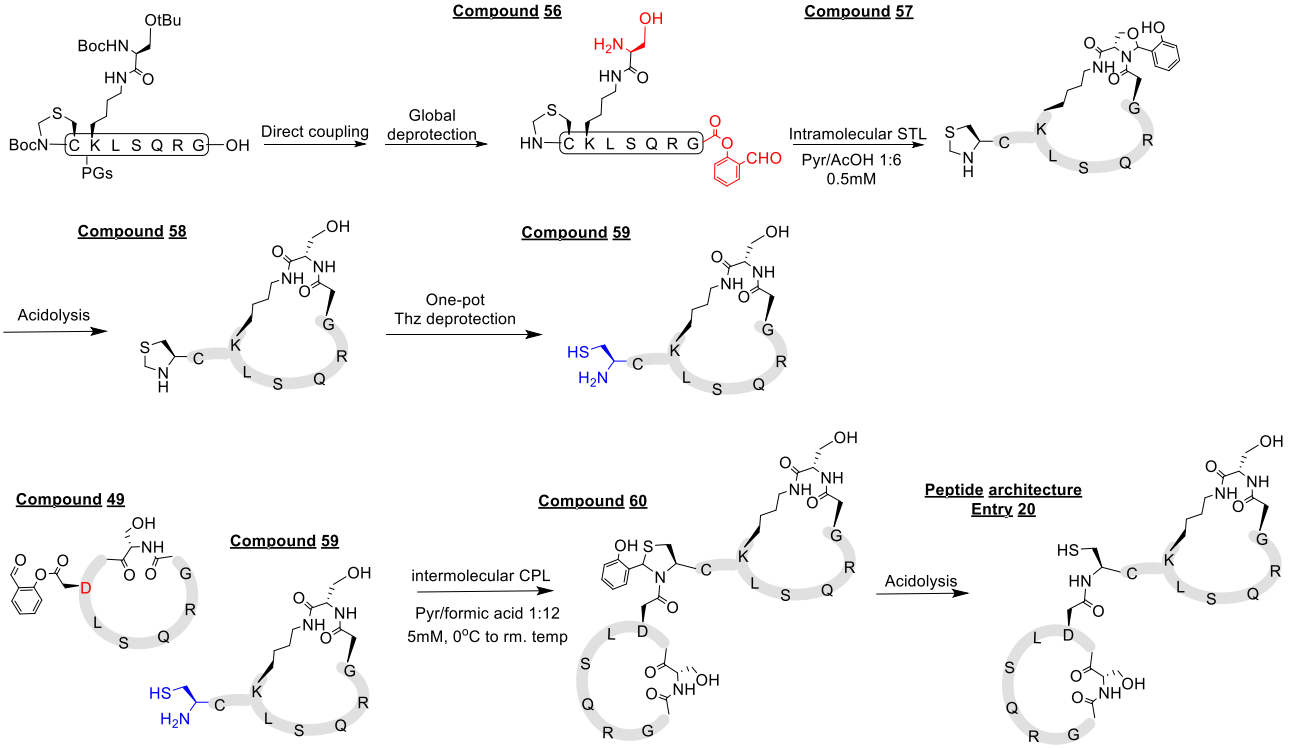


Figure S146: ESI-MS calcd. for $C_{89}H_{148}N_{28}O_{28}$ = 2058.33; $[M+2H]^{2+}$ *m/z* = 1030.17, found1030.47; $[M+3H]^{3+}$ *m/z* = 687.11, found 687.07; $2[M+3H]^{3+}$ *m/z* = 1374.22, found 1373.46.

4.4 Synthesis of Class III: bicyclic peptides *(Entry 20-22)*

Peptide architecture Entry 20



Direct coupling was performed on the side-chain protected crude peptide (282.20 mg, 176.71 µmol) as described in general procedure 2.5. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 56 (59.66 mg, 34.0% yield) as white solid.

The ligation of Compound 56 (59.66 mg, 60.00 µmol) was performed as described in general procedure 2.6, followed by one-pot Thz deprotection as described in general procedure 2.8. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 59 (19.20 mg, 37.2 % yield) as white solid.

The ligation between crude Compound 49 (1.38 mg, 1.63 µmol) and Compound 59 (1.54 mg, 1.79 µmol) was performed as described in general procedure 2.10. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture Entry 20 (1.30 mg, 50.4% yield) as white solid.

Compound 56

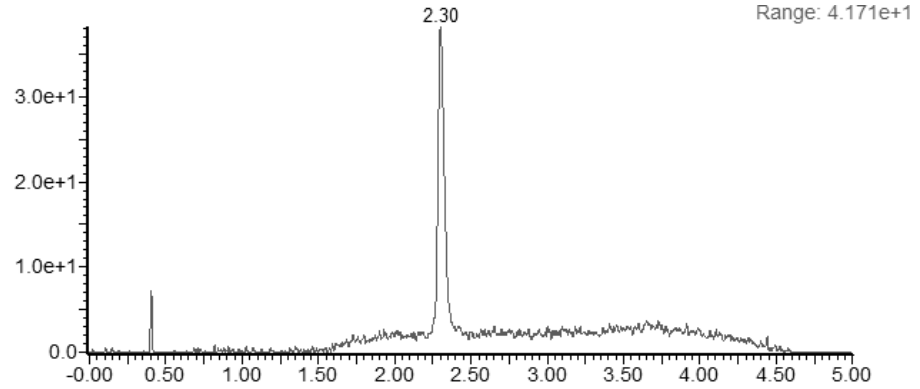


Figure S147: UV trace from analytical UPLC-MS analysis for purified **Compound 56**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

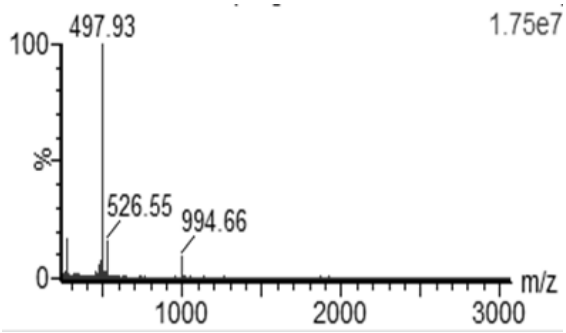


Figure S148: ESI-MS calcd. for $C_{42}H_{67}N_{13}O_{13}S$ = 993.47, $[M+H]^+$ *m/z* = 994.47, found 994.66; $[M+2H]^{2+}$ *m/z* = 497.74.

Compound 57

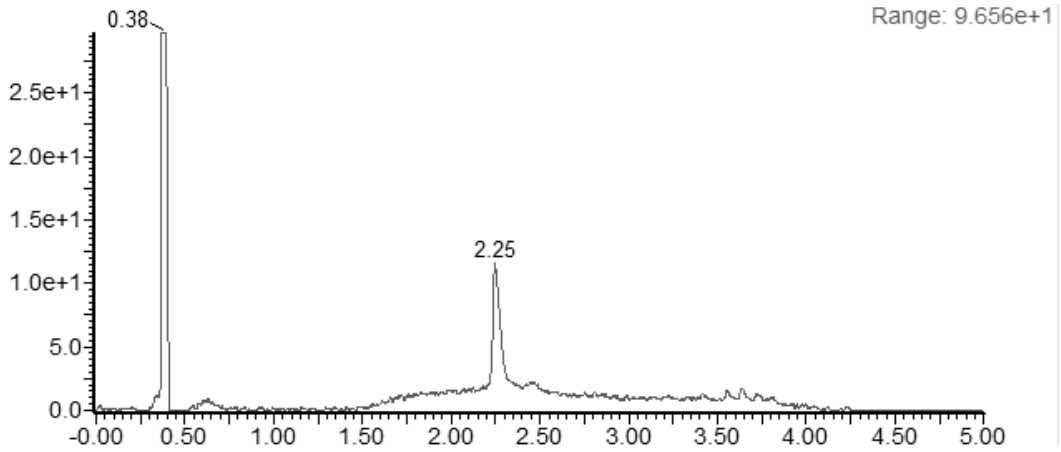


Figure S149: UV trace from analytical UPLC-MS analysis for crude **Compound 57**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

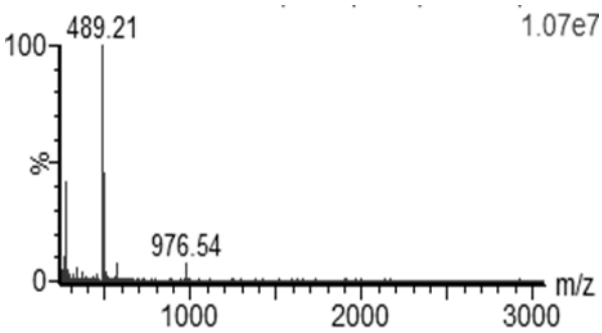


Figure S150: ESI-MS calcd. for $C_{42}H_{65}N_{13}O_{12}S$ = 975.46, $[M+H]^+$ *m/z* = 976.46, found 976.54; $[M+2H]^{2+}$ *m/z* = 489.23, found 489.21.

Compound 58

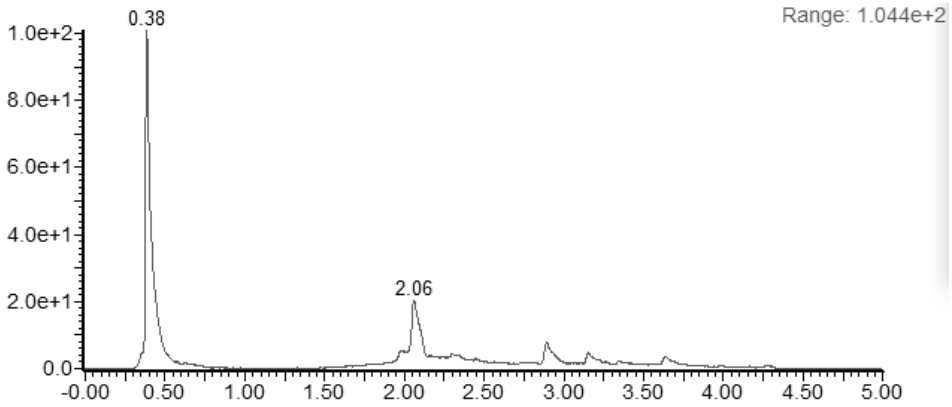


Figure S151: UV trace from analytical UPLC-MS analysis for crude **Compound 58**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

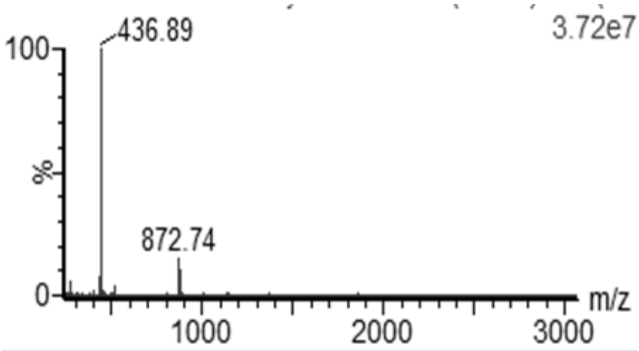


Figure S152: ESI-MS calcd. for $C_{35}H_{61}N_{13}O_{11}S$ = 871.43, $[M+H]^+$ *m/z* = 872.73, found 872.71; $[M+2H]^{2+}$ *m/z* = 436.72, found 436.89.

Compound 59

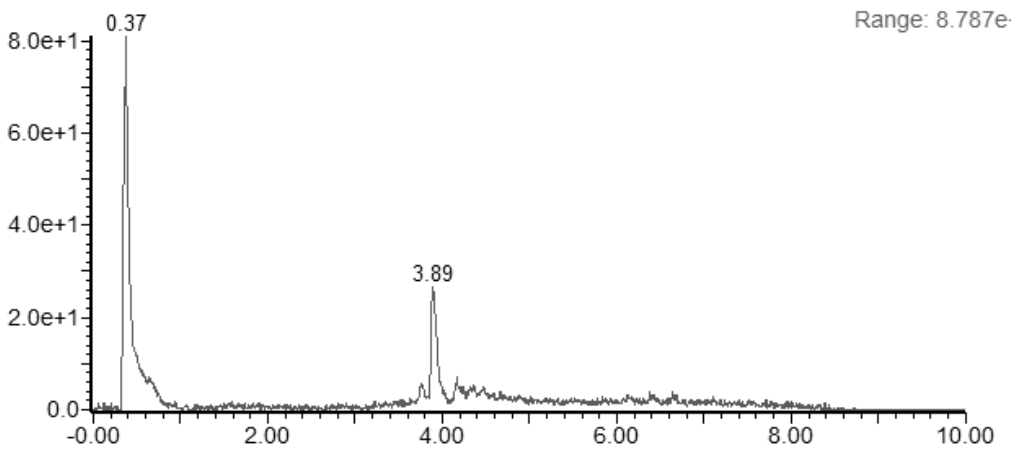


Figure S153: UV trace from analytical UPLC-MS analysis for crude **Compound 59**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

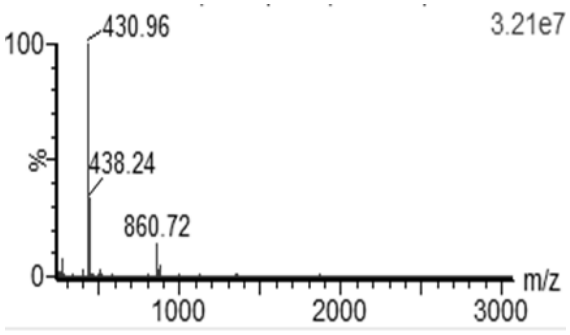


Figure S154: ESI-MS calcd. for $C_{34}H_{61}N_{13}O_{11}S$ = 859.43, $[M+H]^+$ *m/z* = 860.43, found 860.72; $[M+2H]^{2+}$ *m/z* = 430.72, found 430.96.

Compound 60

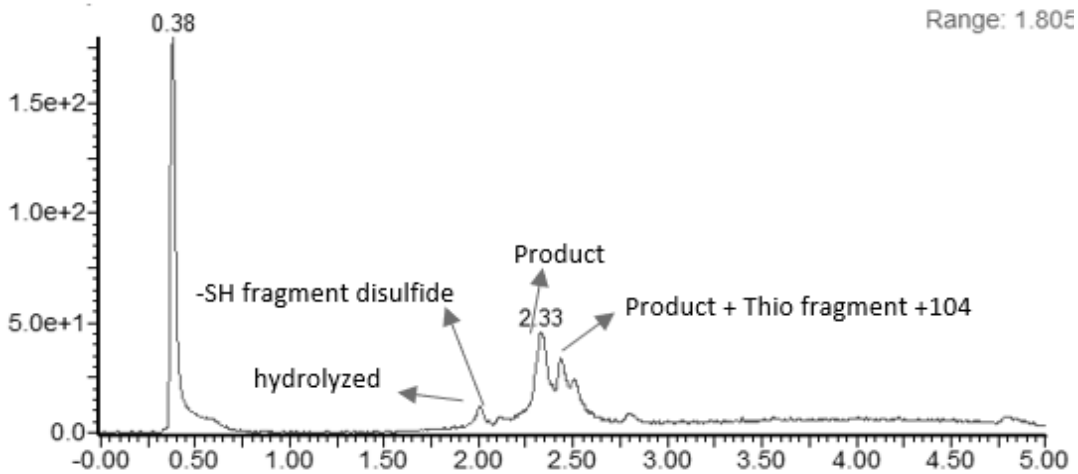


Figure S155: UV trace from analytical UPLC-MS analysis for crude **Compound 60**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

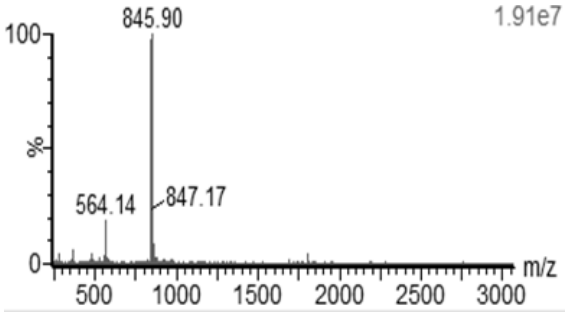


Figure S156: ESI-MS calcd. for $C_{70}H_{112}N_{24}O_{23}S$ = 1689.87, $[M+2H]^{2+}$ *m/z* = 845.94, found 845.90; $[M+3H]^{3+}$ *m/z* = 564.29, found 564.14.

Peptide architecture Entry 20

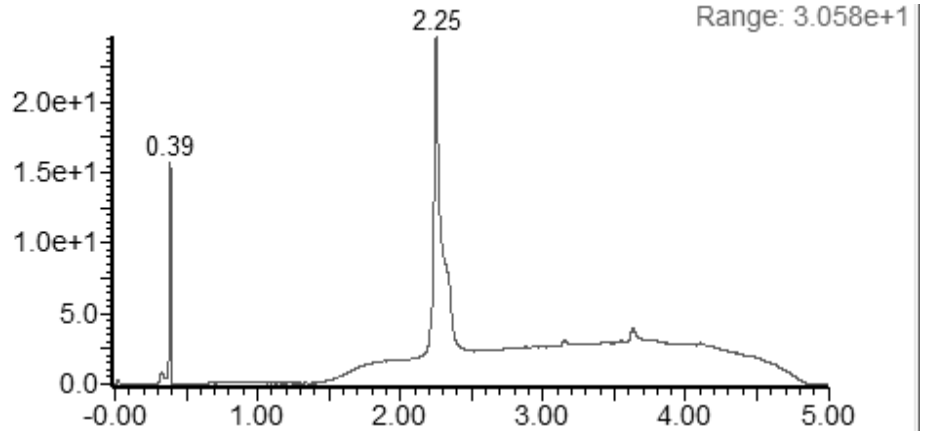


Figure S157: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture Entry 20**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

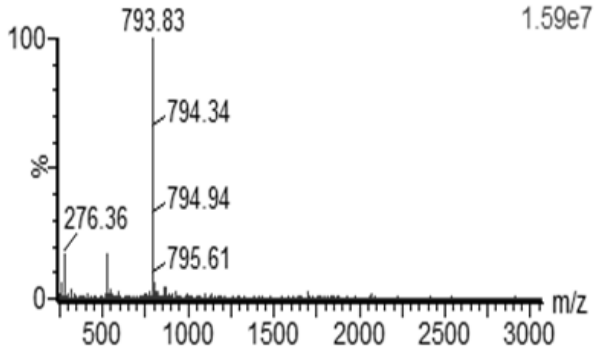
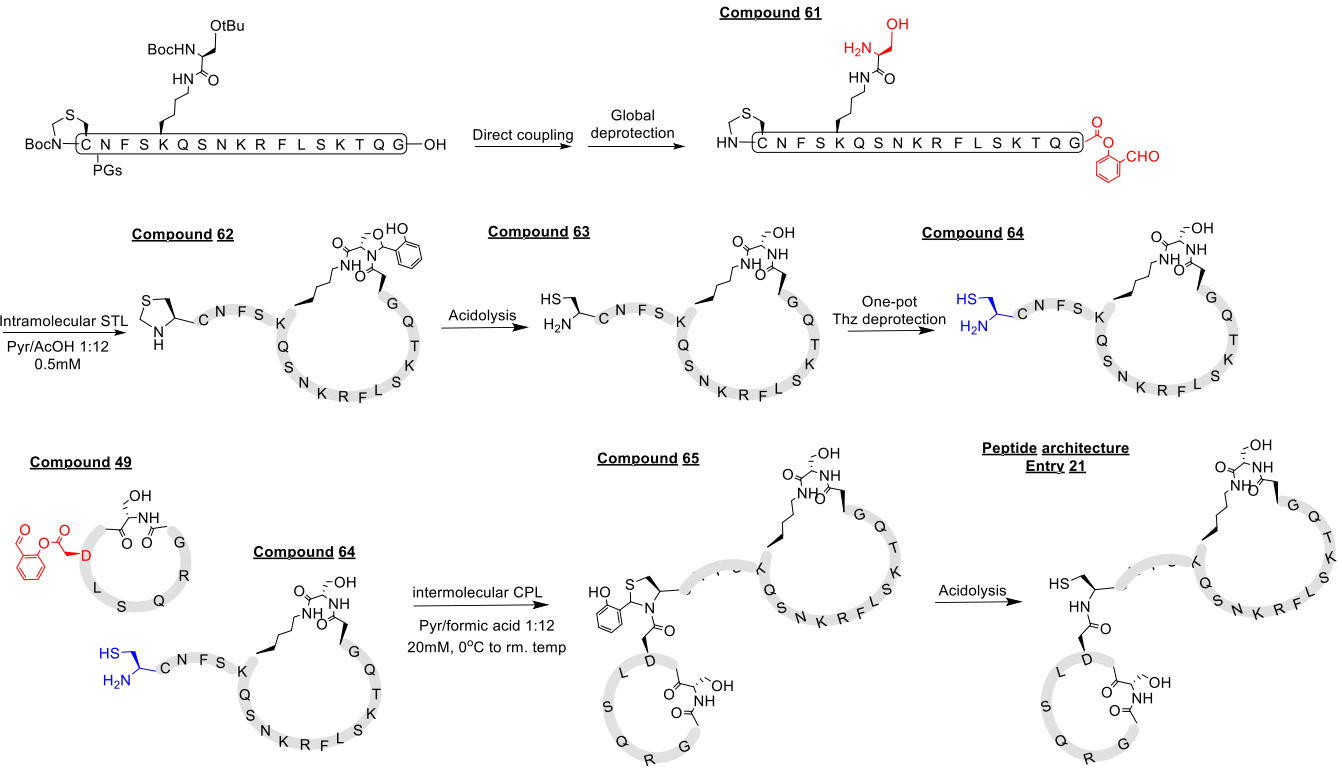


Figure S158: ESI-MS calcd. for $C_{63}H_{108}N_{24}O_{22}S$ = 1585.76, $[M+2H]^{2+}$ *m/z* = 793.88, found 793.83; $[M+3H]^{3+}$ *m/z* = 529.59, found 529.55.

Peptide architecture Entry 21



Direct coupling was performed on the side-chain protected crude peptide (150.68 mg, 38.90 µmol) as described in general procedure 2.5. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 61 (24.38 mg, 28.8% yield) as white solid.

The ligation of Compound 61 (24.38 mg, 11.2 µmol) was performed as described in general procedure 2.6, followed by one-pot Thz deprotection as described in general procedure 2.8. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 64 (8.10 mg, 35.4% yield) as white solid.

The ligation between crude Compound 49 (1.29 mg, 1.52 µmol) and Compound 64 (3.73 mg, 1.83 µmol) was performed as described in general procedure 2.10. Reverse phase HPLC purification followed by lyophilization afforded the product Peptide architecture entry 21 (1.93 mg, 45.8% yield) as white solid.

Compound 61

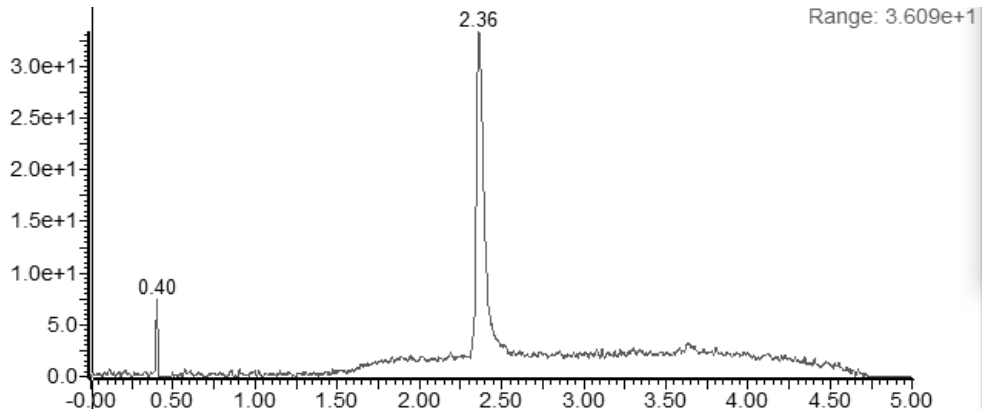


Figure S159: UV trace from analytical UPLC-MS analysis for purified **Compound 61**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

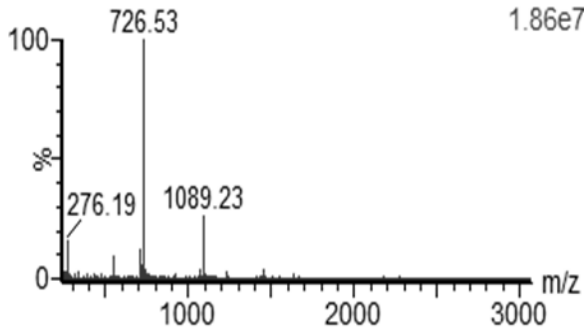


Figure S160: ESI-MS calcd. for $C_{95}H_{146}N_{28}O_{29}S$ = 2176.44, $[M+2H]^{2+}$ *m/z* = 1089.22, found 1089.23; $[M+3H]^{3+}$ *m/z* = 726.48, found 726.53.

Compound 62

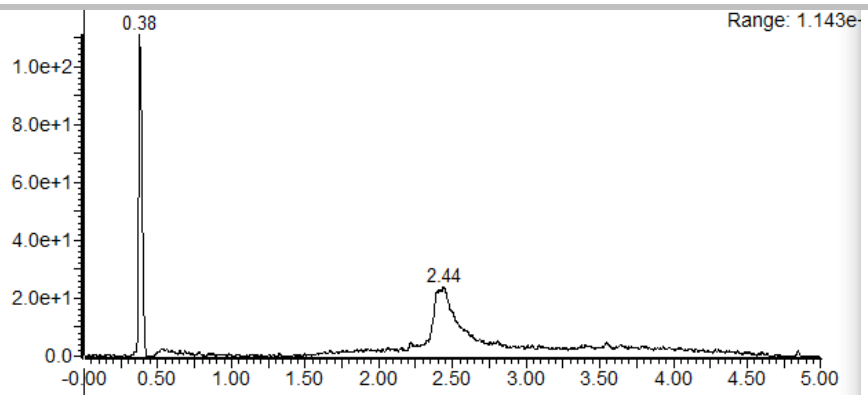


Figure S161: UV trace from analytical UPLC-MS analysis for crude **Compound 62**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

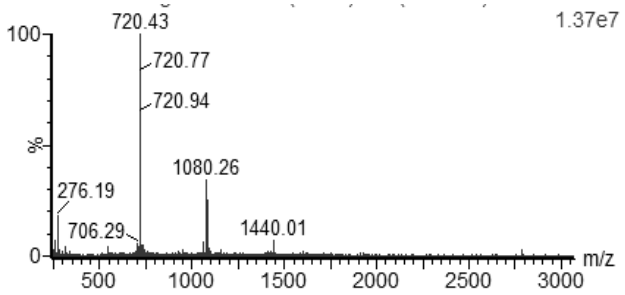


Figure S162: ESI-MS calcd. for $C_{95}H_{144}N_{28}O_{28}S$ =2157.04, $[M+2H]^{2+}$ *m/z* = 1079.52, found 1080.26; $[M+3H]^{3+}$ *m/z* = 720.01, found 720.43; $2[M+3H]^{3+}$ *m/z* = 1440.02, found 1440.01.

Compound 63

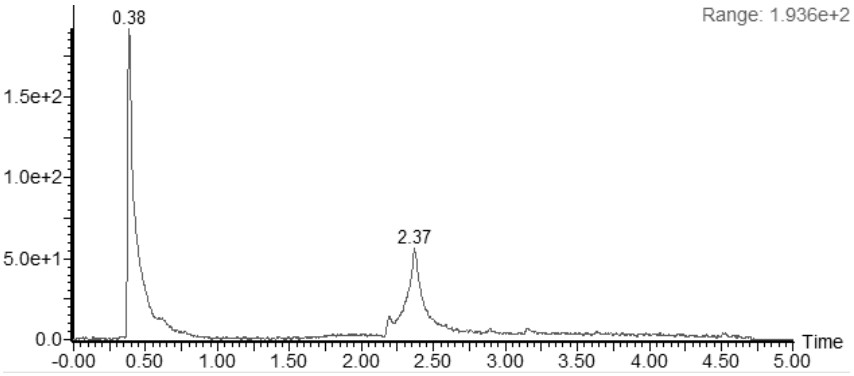


Figure S163: UV trace from analytical UPLC-MS analysis for crude **Compound 63**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

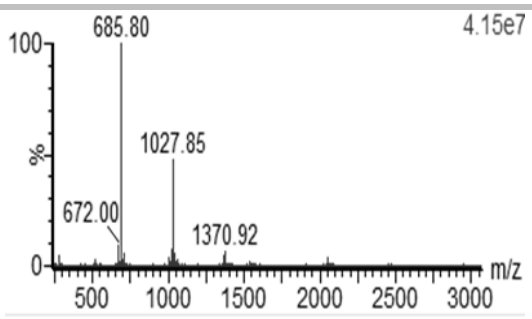


Figure S164: ESI-MS calcd. for $C_{88}H_{140}N_{28}O_{27}S$ = 2053.02, $[M+2H]^{2+}$ *m/z* = 1027.51, found 1027.85; $[M+3H]^{3+}$ *m/z* = 685.34, found 685.80; $2[M+3H]^{3+}$ *m/z* = 1370.68, found 1370.92.

Compound 64

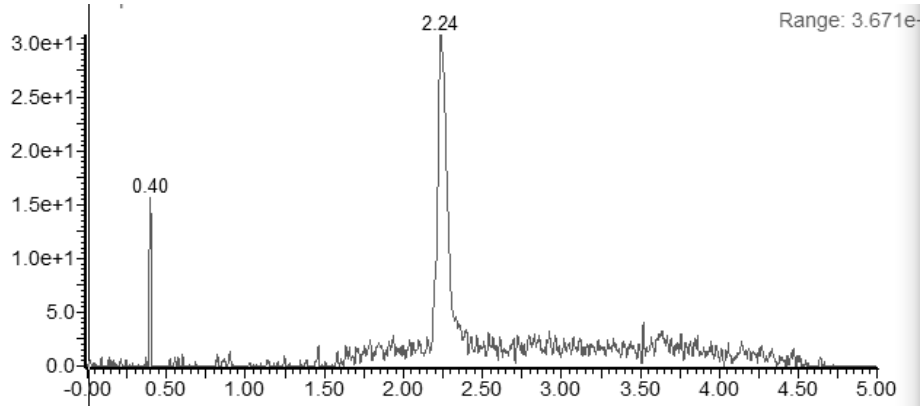


Figure S165: UV trace from analytical UPLC-MS analysis for crude **Compound 64**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

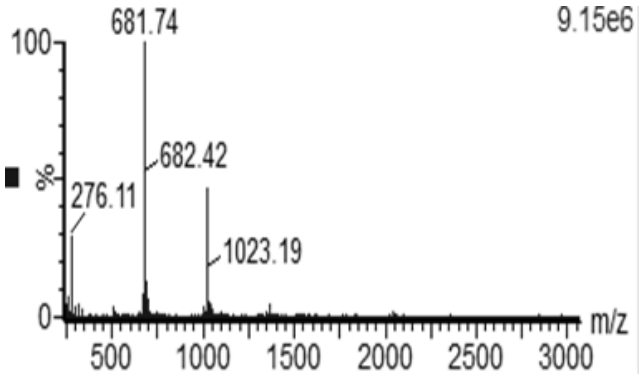


Figure S166: ESI-MS calcd. for $C_{87}H_{142}N_{28}O_{26}S$ = 2042.31, $[M+2H]^{2+}$ *m/z* = 1022.16, found 1023.19; $[M+3H]^{3+}$ *m/z* = 681.77, found 681.74.

Compound 65

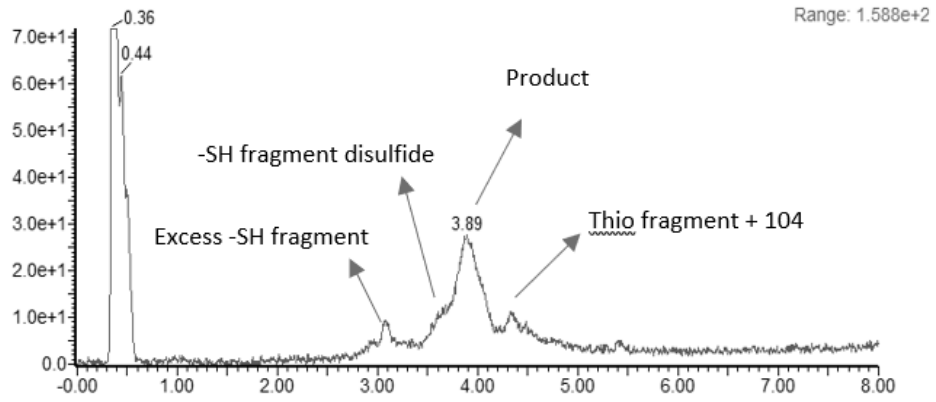


Figure S167: UV trace from analytical UPLC-MS analysis for crude **Compound 65**. Gradient: 10-40% ACN/H_2O containing 0.1% TFA over 8 min at a flow rate of 0.4 mL/min.

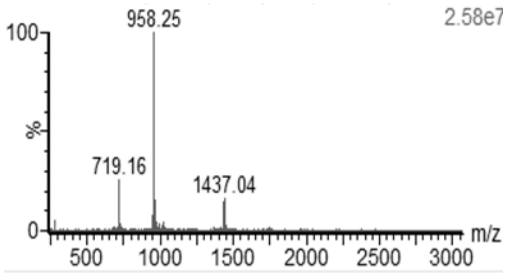


Figure S168: ESI-MS calcd. for $C_{123}H_{191}N_{39}O_{39}S$ = 2872.18, $[M+2H]^{2+}$ *m/z* = 1437.09, found 1437.04; $[M+3H]^{3+}$ *m/z* = 958.39, found 958.25; $[M+4H]^{4+}$ *m/z* = 719.05, found 719.16.

Peptide architecture Entry 21

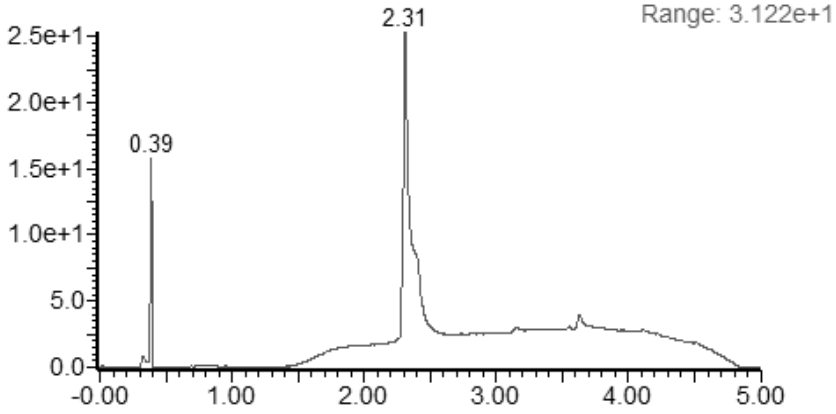


Figure S169: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture Entry 21** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

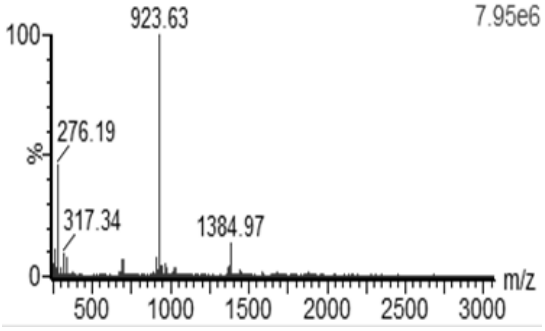
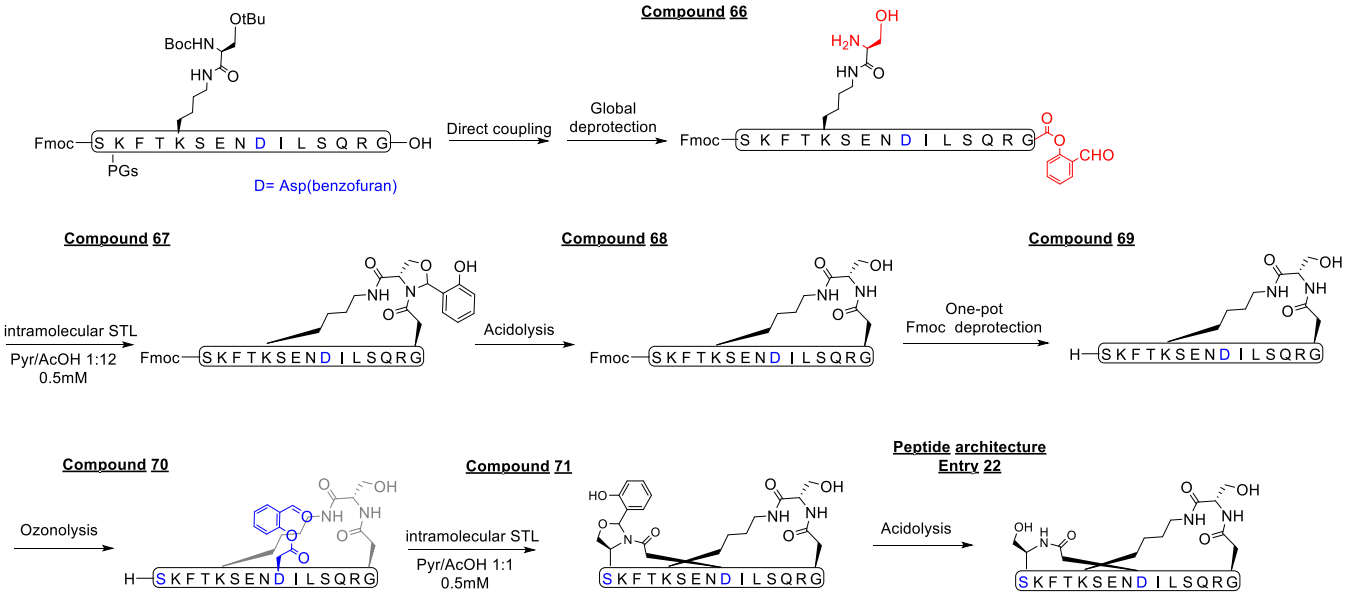


Figure S170: ESI-MS calcd. for $C_{116}H_{187}N_{39}O_{38}S$ = 2766.36, $[M+2H]^{2+}$ *m/z* = 1384.18, found 1384.97; $[M+3H]^{3+}$ *m/z* = 923.12, found 923.63.

Peptide architecture Entry 22



Direct coupling was performed on the side-chain protected crude peptide (428 mg, 11.79 µmol) as described in general procedure 2.5. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 66 (26.50 mg, 10.2 % yield) as white solid. The low isolated yield is due to the poor solubility of the peptide.

The ligation of Compound 66 (17.13 mg, 7.80 µmol) was performed as described in general procedure 2.6, followed by one-pot Fmoc deprotection as described in general procedure 2.9. Reverse phase HPLC purification followed by lyophilization afforded the product Compound 69 (4.71 mg, 32.6% yield) as white solid.

Ozonolysis of purified Compound 69 (4.71 mg, 2.50 µmol) was performed as described in general procedure 2.4. Lyophilization afforded the crude product Compound 70 as white solid.

The ligation of Compound 70 (4.71 mg, 2.50 µmol) was performed as described in general procedure 2.6. Reverse phase HPLC purification followed by lyophilization afforded the product (1.30 mg, 29.5% yield) as white solid.

Compound 66

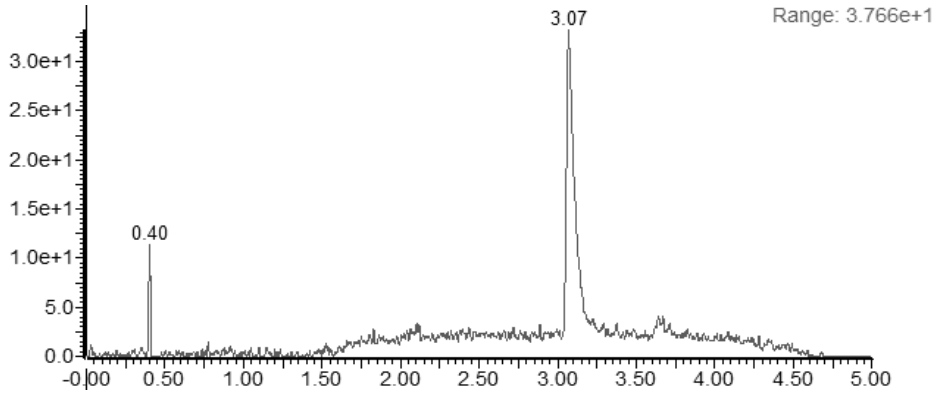


Figure S171: UV trace from analytical UPLC-MS analysis for purified **Compound 66**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

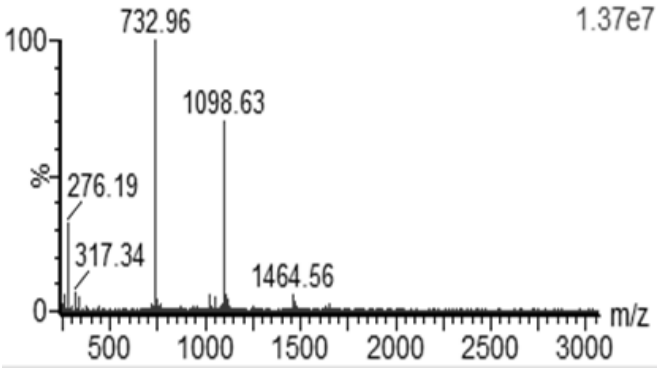


Figure S172: ESI-MS calcd. for $C_{104}H_{143}N_{23}O_{30}$ = 2195.42, $[M+2H]^{2+}$ *m/z* =1098.5, found 1098.63; $[M+3H]^{3+}$ *m/z* = 732.81, found 732.96; $2[M+3H]^{3+}$ *m/z* = 1465.61, found 1464.56.

Compound 67

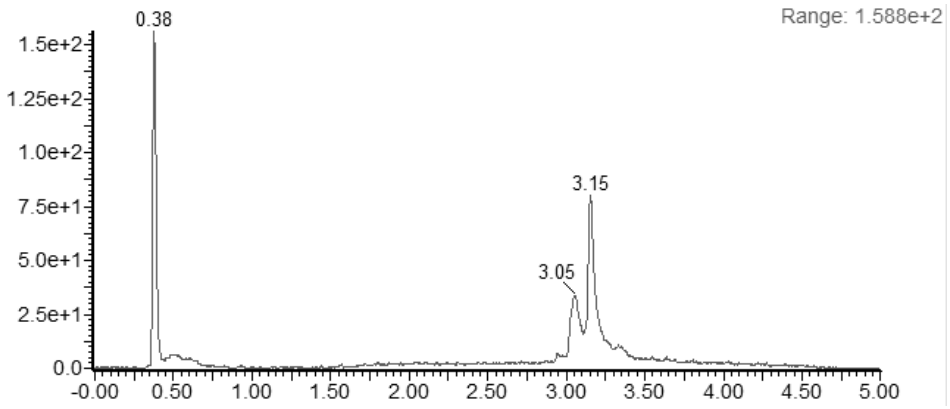


Figure S173: UV trace from analytical UPLC-MS analysis for crude **Compound 67**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

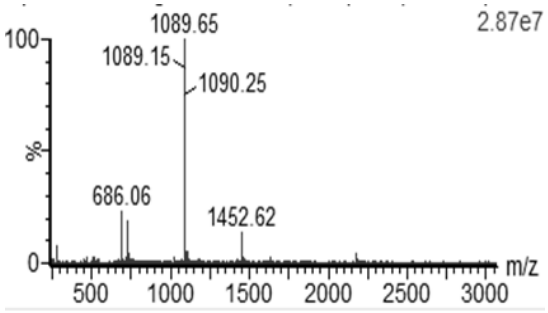


Figure S174: ESI-MS calcd. for $C_{104}H_{141}N_{23}O_{29}$ = 2177.40, $[M+2H]^{2+}$ *m/z* = 1089.70, found 1089.65; $2[M+3H]^{3+}$ *m/z* = 1453.6, found 1452.62.

Compound 68

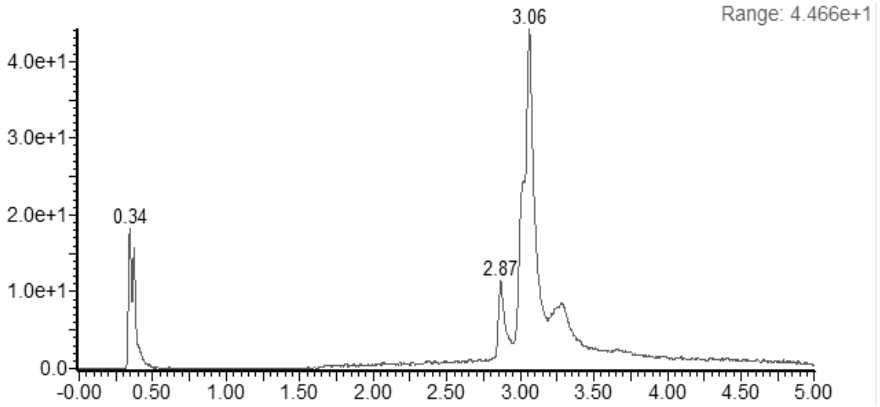


Figure S175: UV trace from analytical UPLC-MS analysis for crude **Compound 68**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

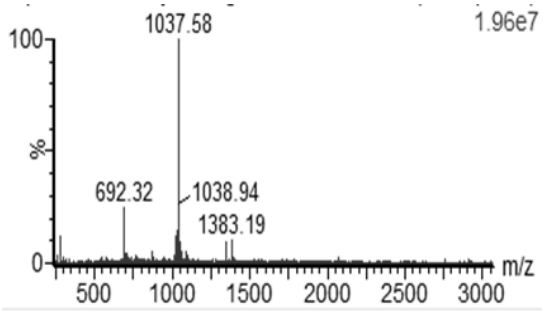


Figure S176: ESI-MS calcd. for $C_{97}H_{137}N_{23}O_{28}$ =2073.30, $[M+2H]^{2+}$ *m/z* = 1037.65, found 1037.58; $[M+3H]^{3+}$ *m/z* = 692.10, found 692.32; $2[M+3H]^{3+}$ *m/z* = 1384.20, found 1383.19.

Compound 69

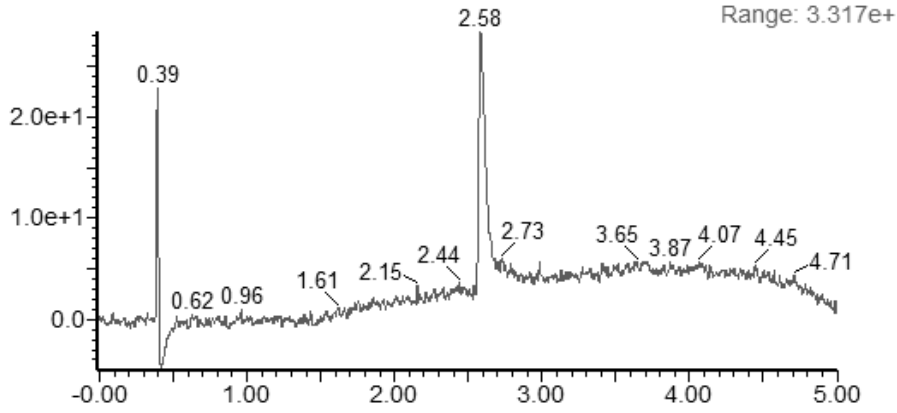


Figure S177: UV trace from analytical UPLC-MS analysis for purified **Compound 69**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

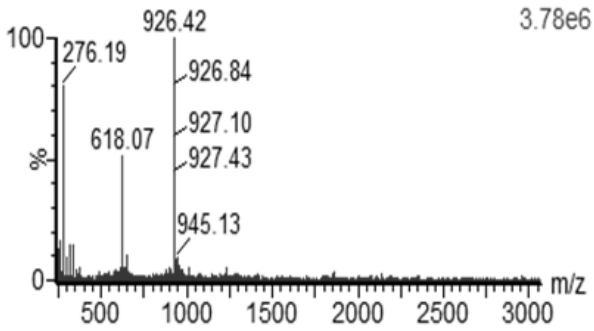


Figure S178: ESI-MS calcd. for $C_{82}H_{127}N_{23}O_{26}$ = 1851.05, $[M+2H]^{2+}$ *m/z* = 926.53, found 926.42; $[M+3H]^{3+}$ *m/z* = 618.02, found 618.07.

Compound 70

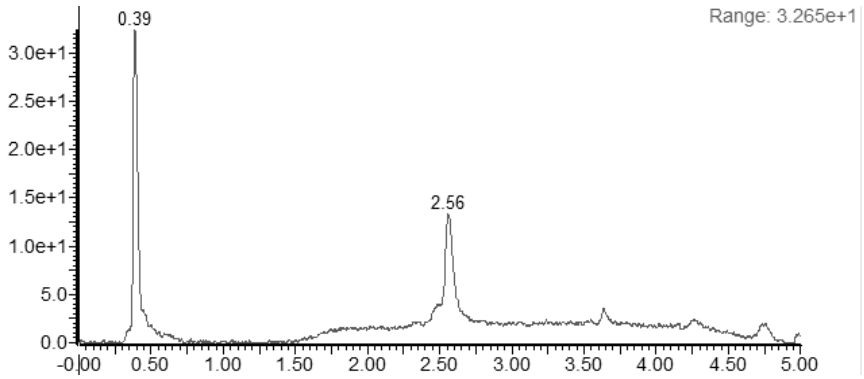


Figure S179: UV trace from analytical UPLC-MS analysis for crude **Compound 70**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

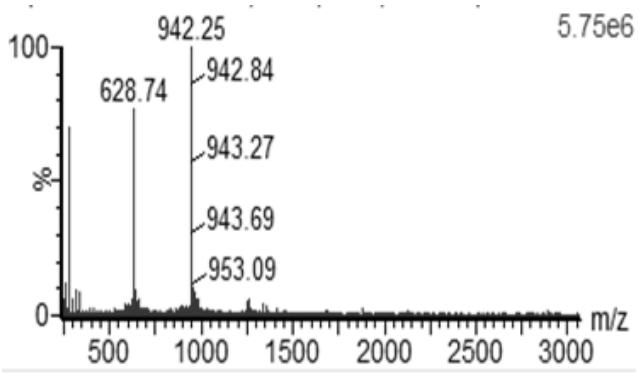


Figure S180: ESI-MS calcd. for $C_{82}H_{127}N_{23}O_{28}$ = 1883.05, $[M+2H]^{2+}$ *m/z* = 942.53, found 942.25; $[M+3H]^{3+}$ *m/z* = 628.68, found 628.74.

Compound 71

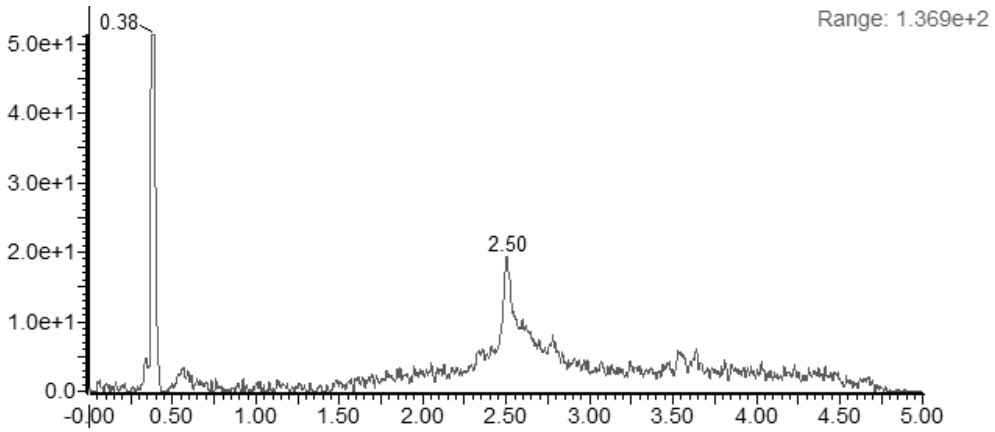


Figure S181: UV trace from analytical UPLC-MS analysis for crude **Compound 71**. Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

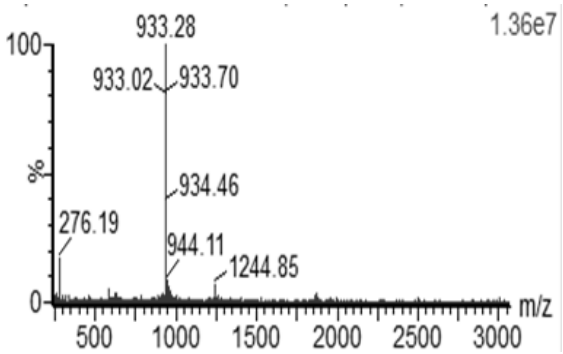


Figure S182: ESI-MS calcd. for $C_{82}H_{125}N_{23}O_{27}$ = 1865.04, $[M+2H]^{2+}$ *m/z* = 933.50, found 933.58; $2[M+3H]^{3+}$ *m/z* =1245.33, found 1244.85.

Peptide architecture Entry 22

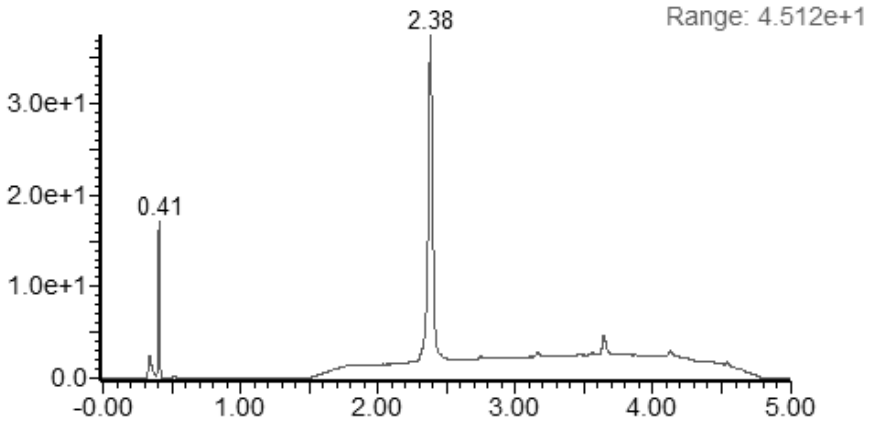


Figure S183: UV trace from analytical UPLC-MS analysis for purified **Peptide architecture Entry 22** . Gradient: 5-95% ACN/H_2O containing 0.1% TFA over 5 min at a flow rate of 0.4 mL/min.

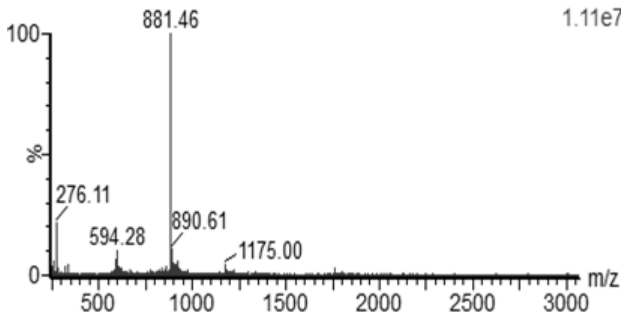
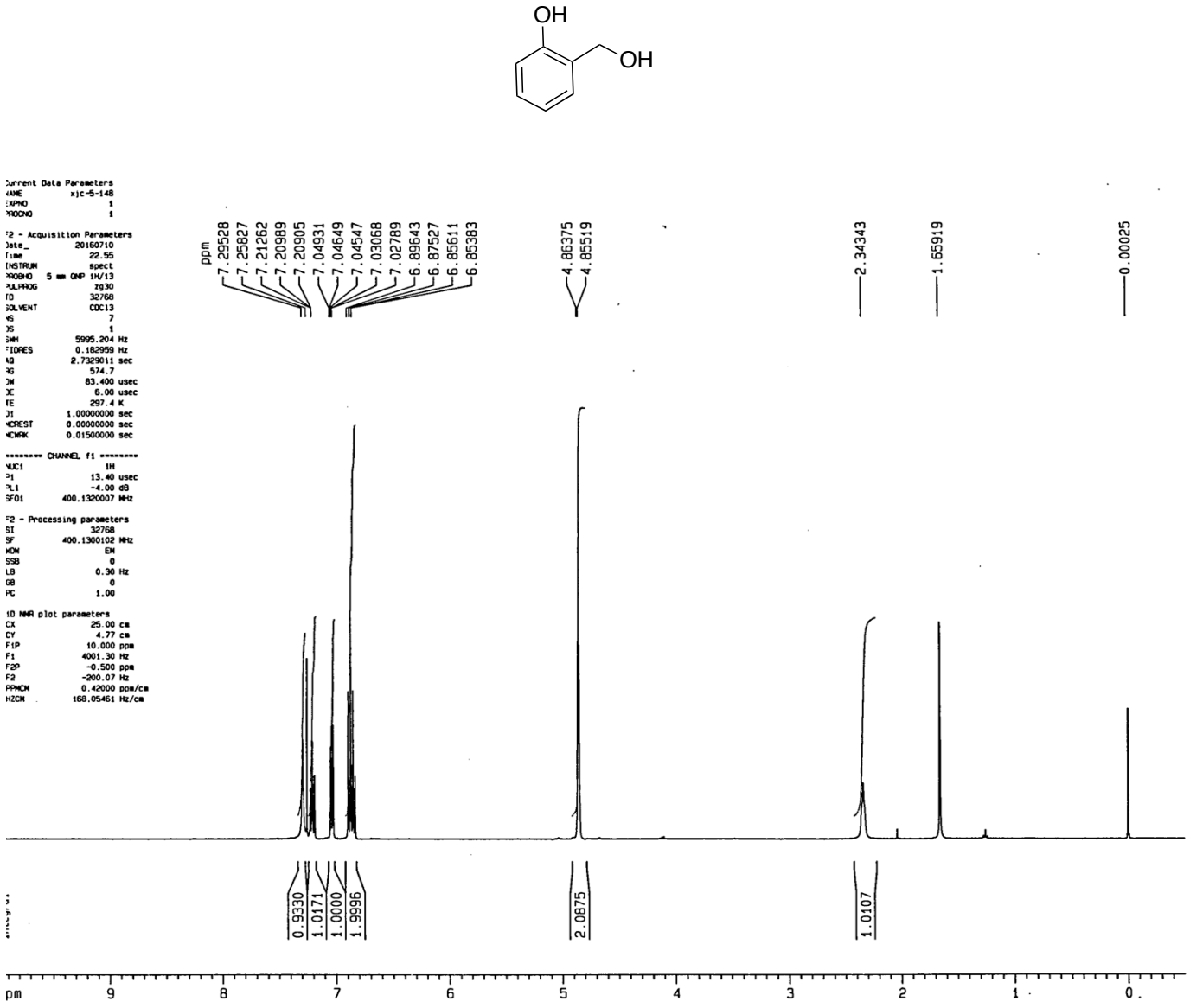


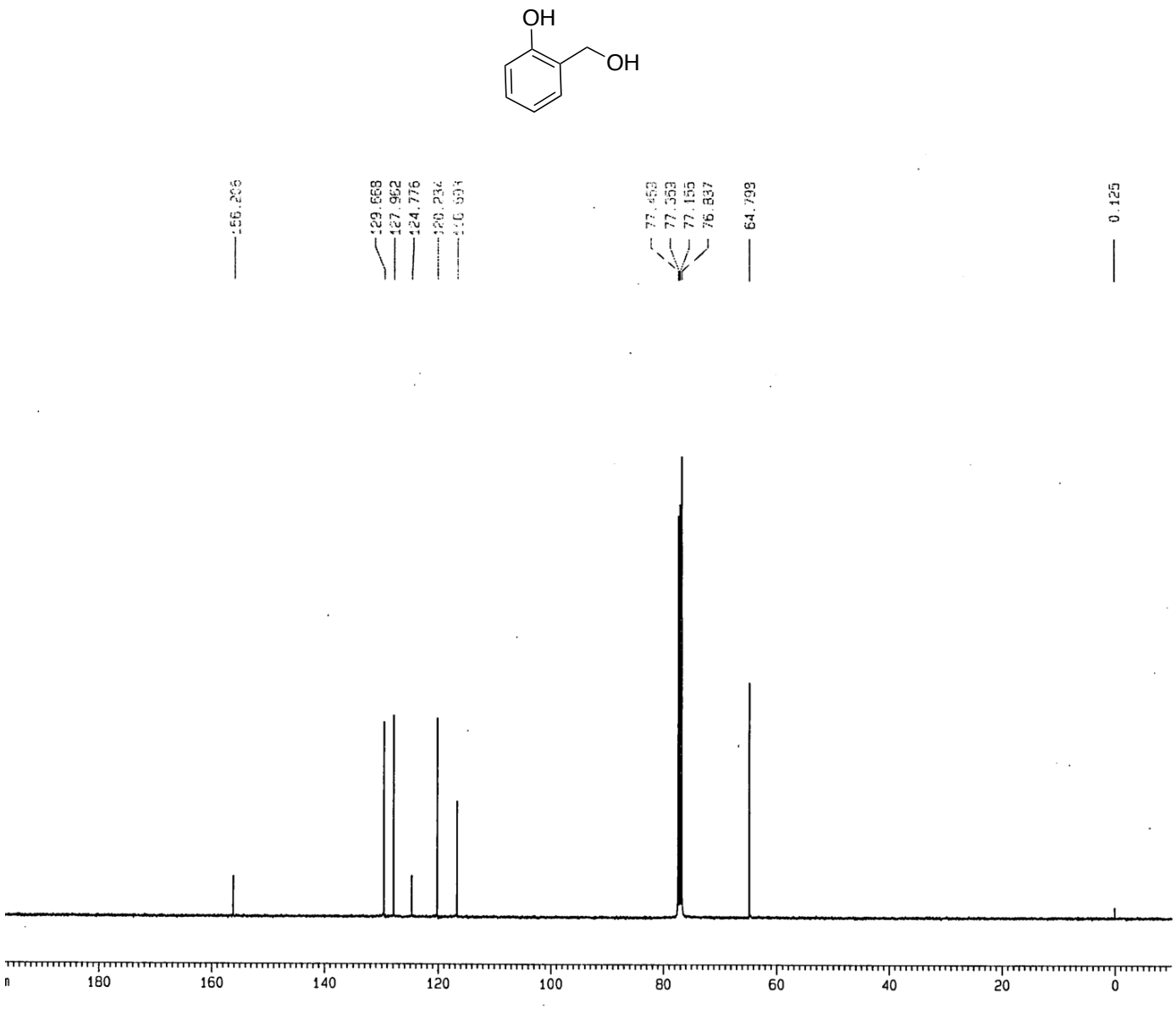
Figure S184: ESI-MS calcd. for $C_{75}H_{121}N_{23}O_{26}$ = 1760.93, $[M+2H]^{2+}$ *m/z* = 881.47, found 881.46; $2[M+3H]^{3+}$ *m/z* = 1175.33, found 1175.00.

5. NMR spectra

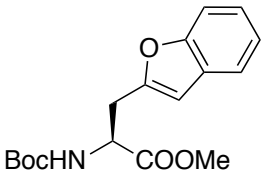
[1]H spectrum of Compound 1

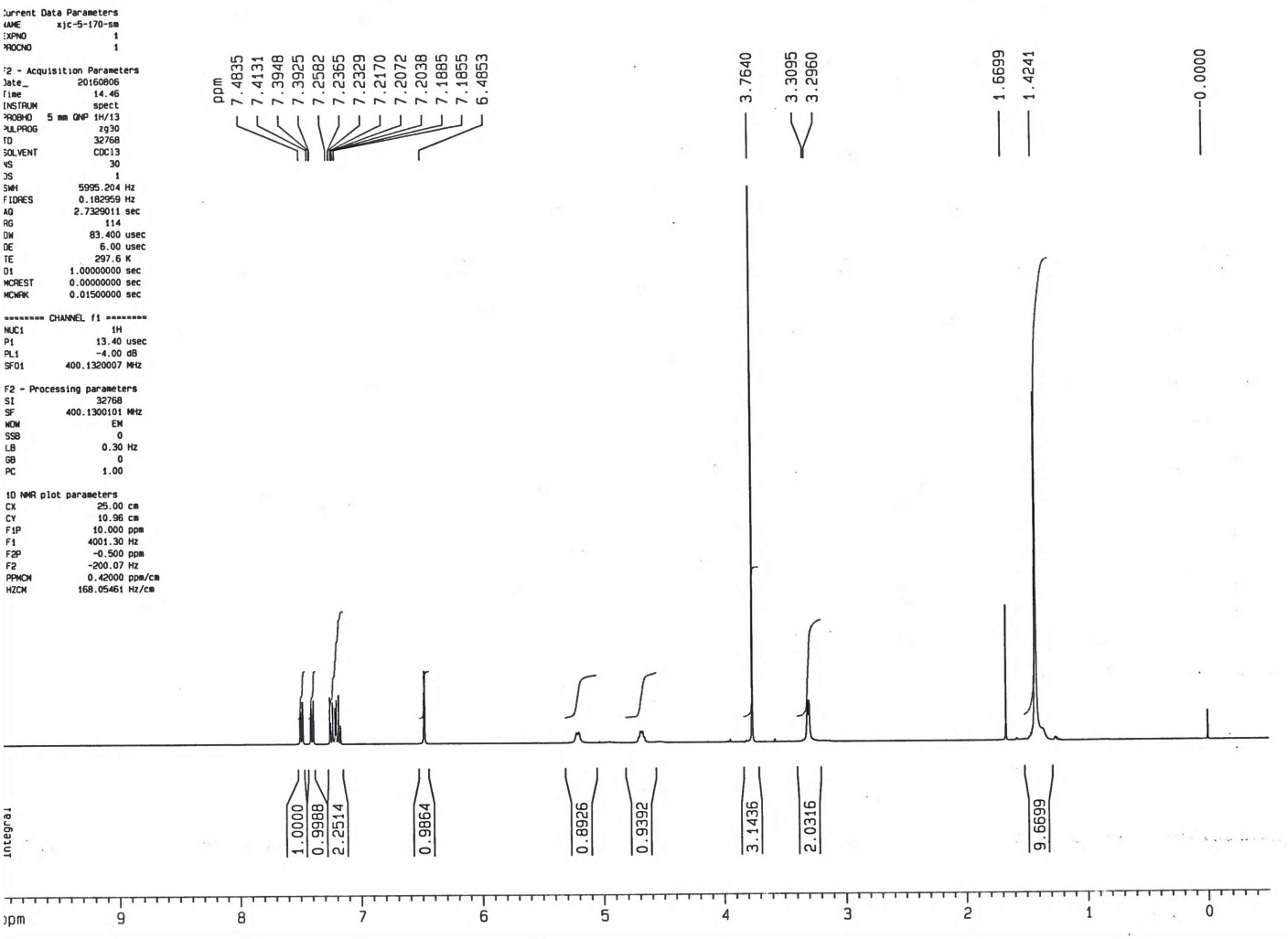


^{13}C spectrum of Compound 1

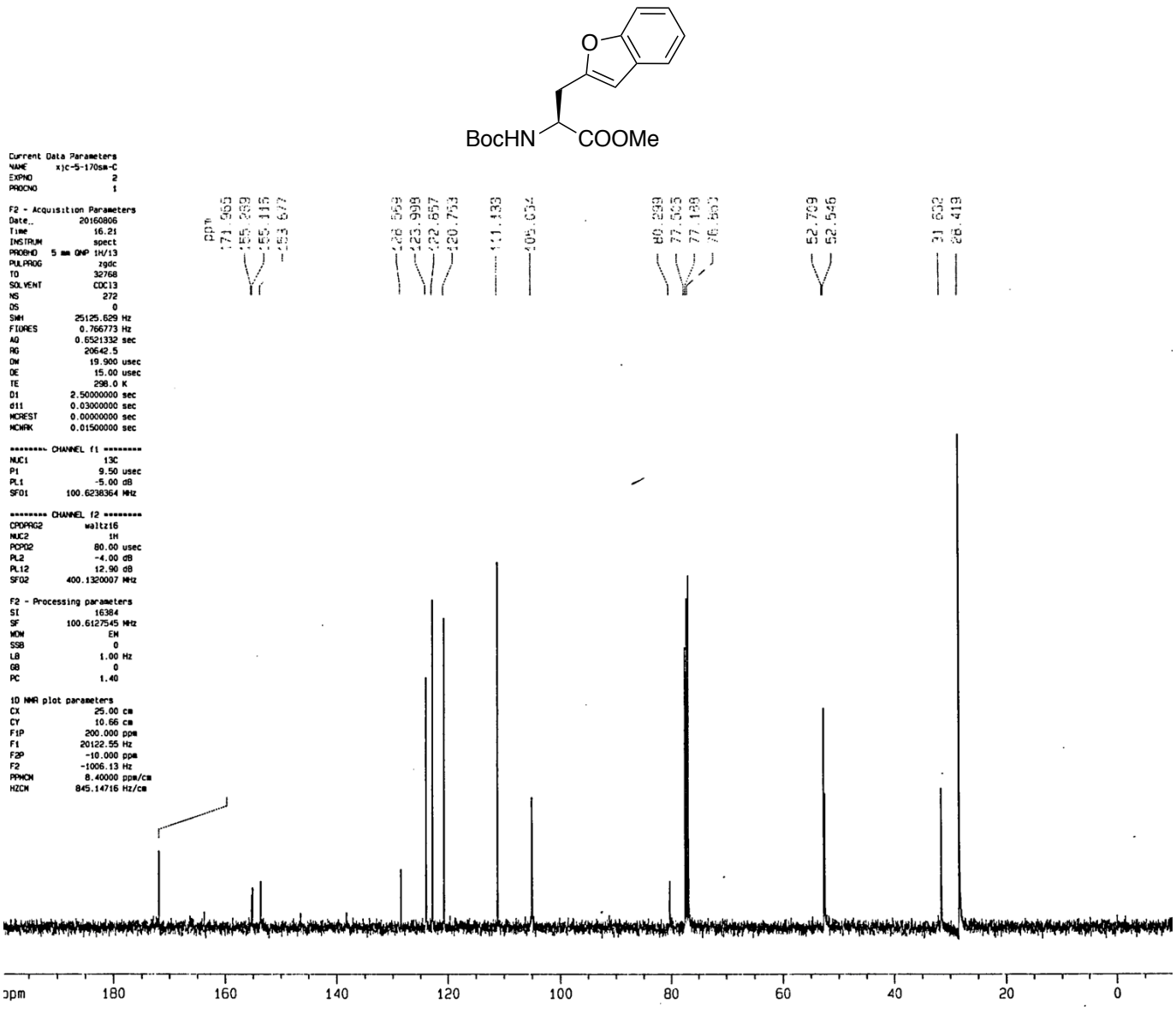


^{1}H spectrum of Compound 3





^{13}C spectrum of Compound 3



Current Data Parameters
NAME xjc-5-170sm-C
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160806
Time 16.21
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgdc
TD 32768
SOLVENT CDCl3
NS 272
DS 0
SWH 25125.629 Hz
FIDRES 0.766773 Hz
AQ 0.6521332 sec
RG 20642.5
DW 19.900 usec
DE 15.00 usec
TE 298.0 K
D1 2.50000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

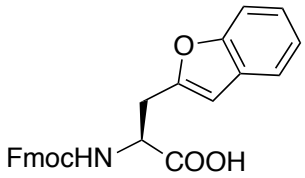
======== CHANNEL f1 ========
NUC1 13C
P1 9.50 usec
PL1 -5.00 dB
SFO1 100.6238364 MHz

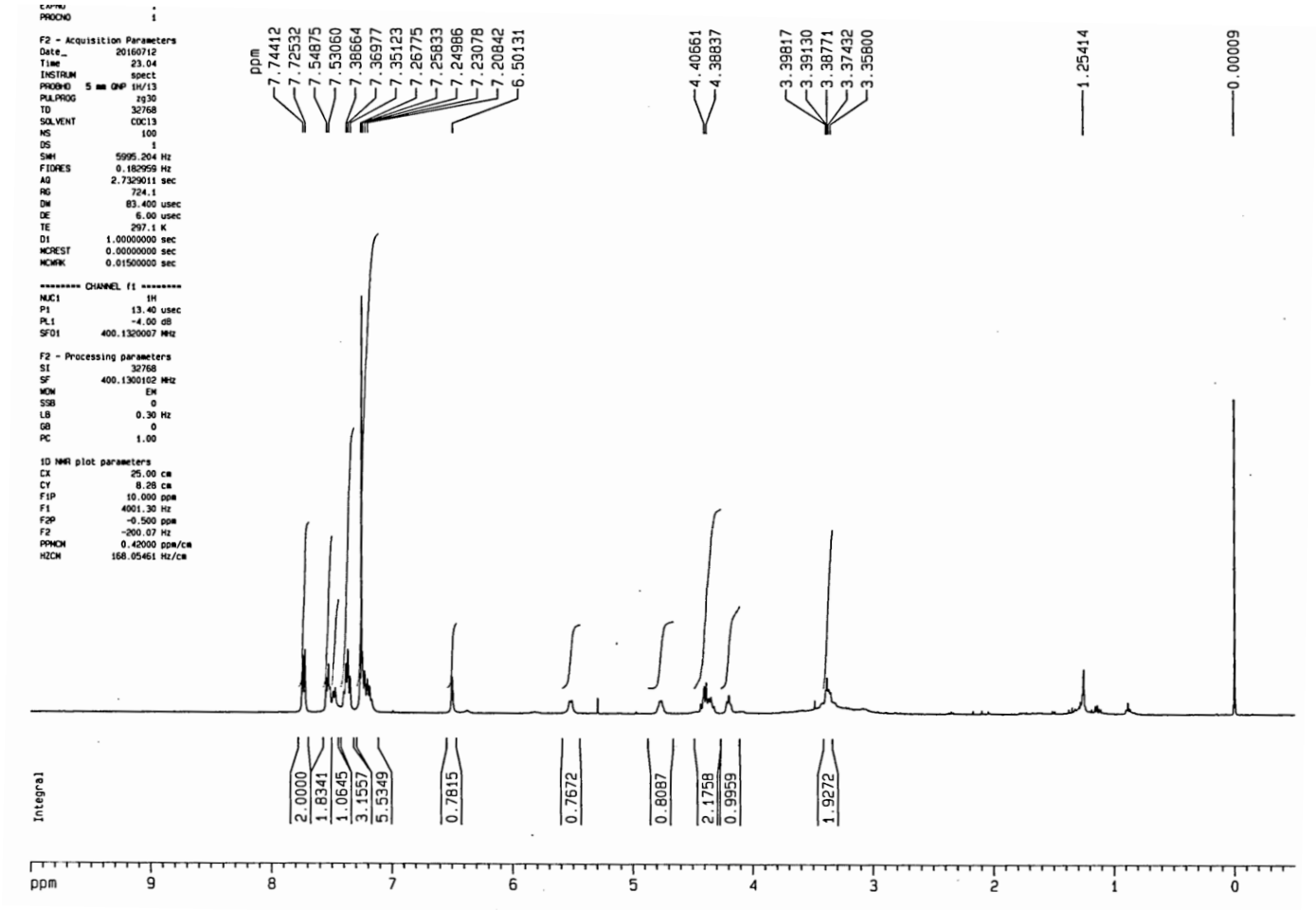
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -4.00 dB
PL12 12.90 dB
SFO2 400.1320007 MHz

F2 - Processing parameters
SI 16384
SF 100.6127545 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

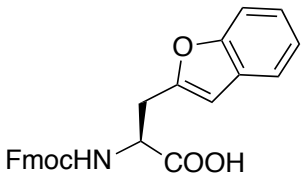
1D NMR plot parameters
CX 25.00 cm
CY 10.66 cm
F1P 200.000 ppm
F1 20122.55 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 8.40000 ppm/cm
HZCM 845.14716 Hz/cm

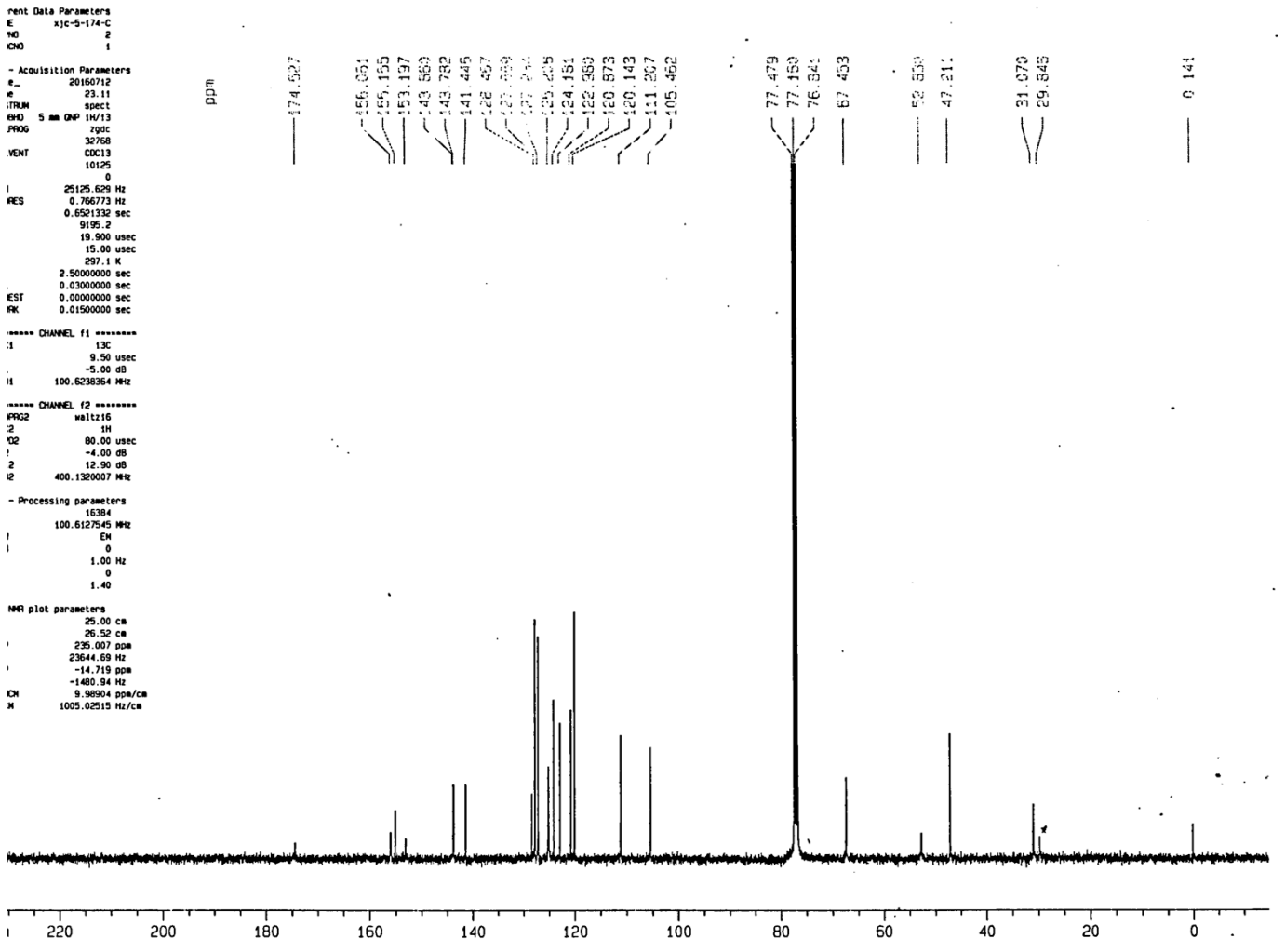
[1]H spectrum of Compound 4



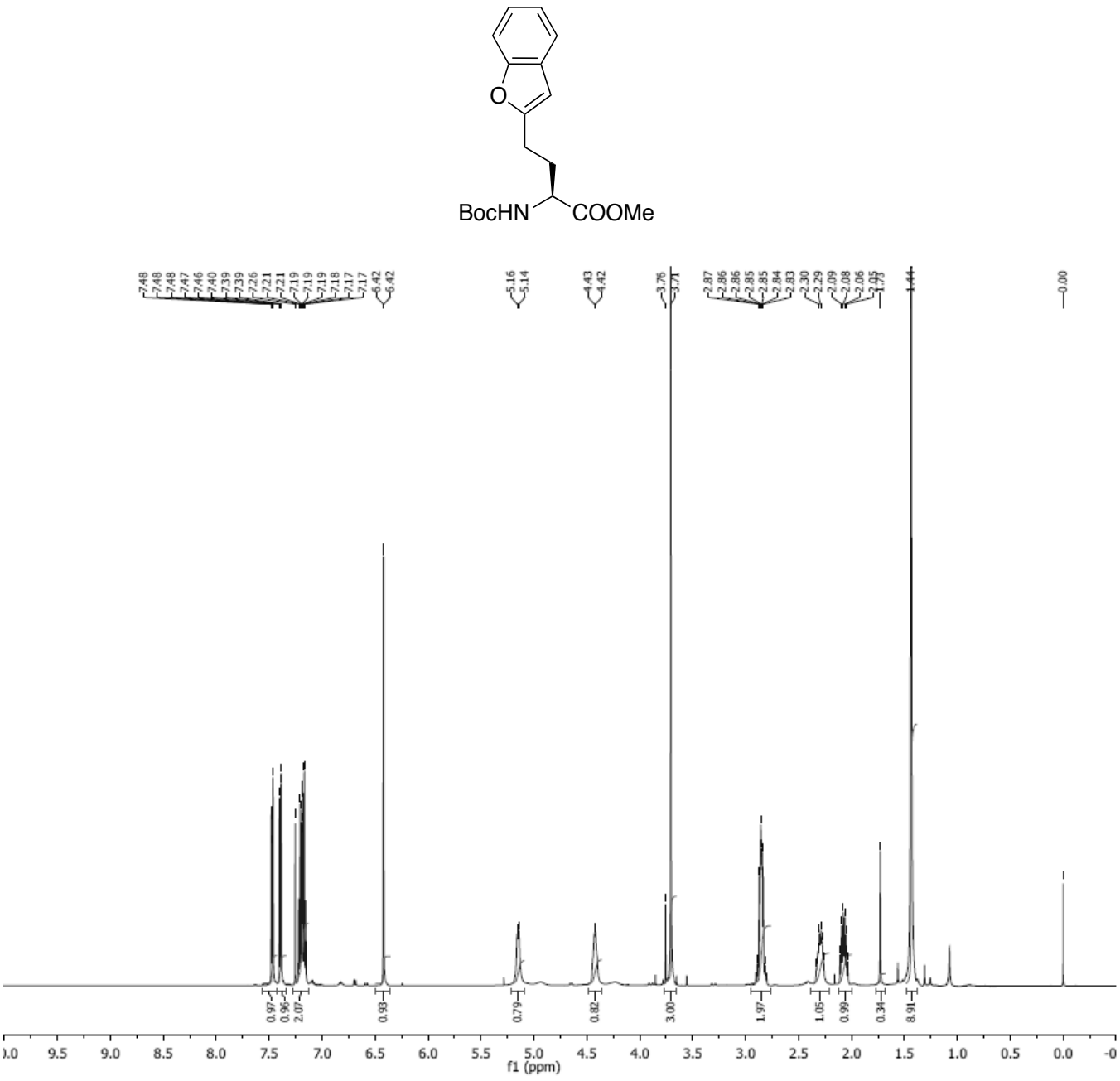


^{13}C spectrum of Compound 4

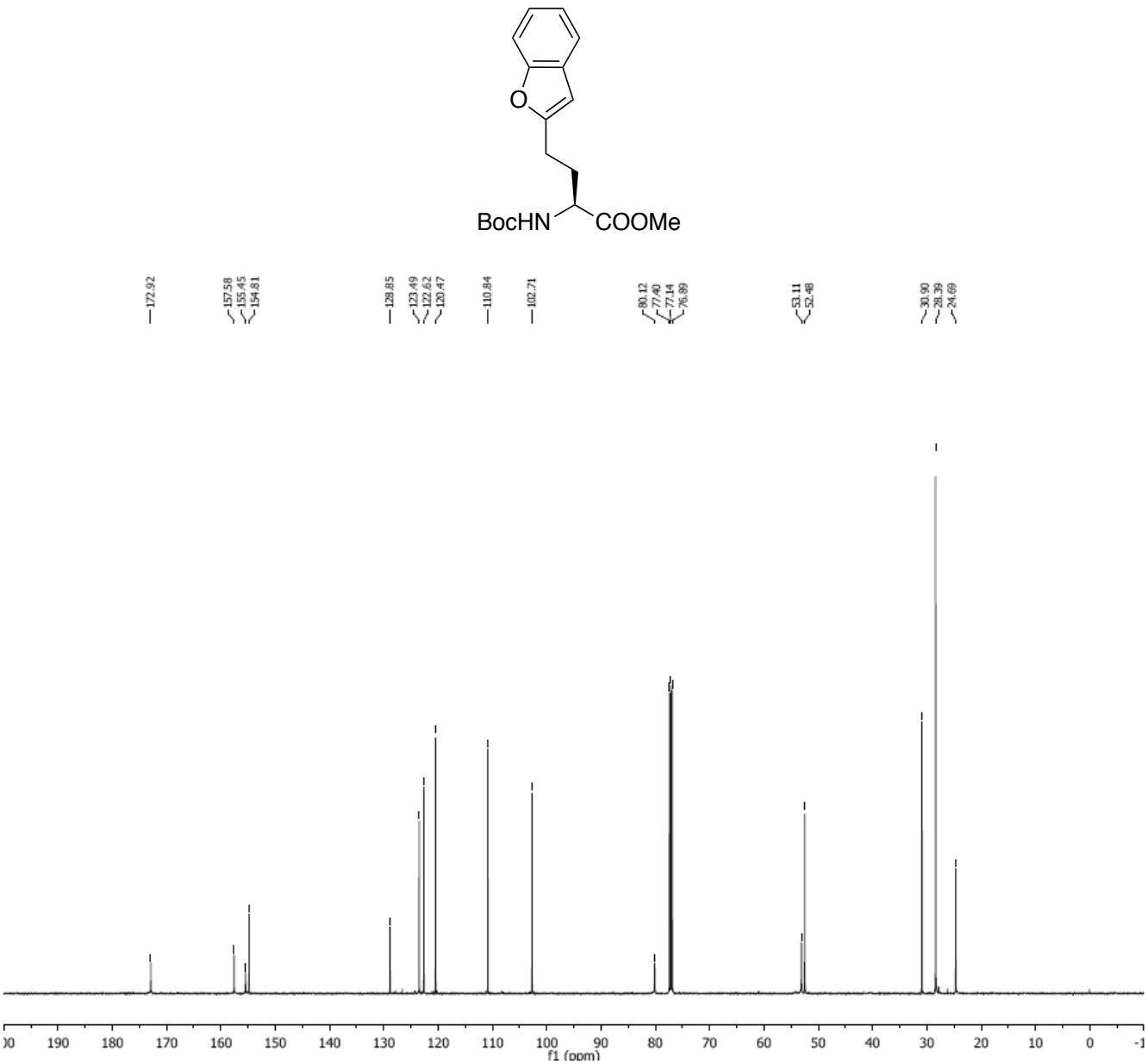




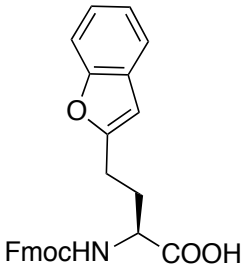
^{1}H spectrum of Compound 5

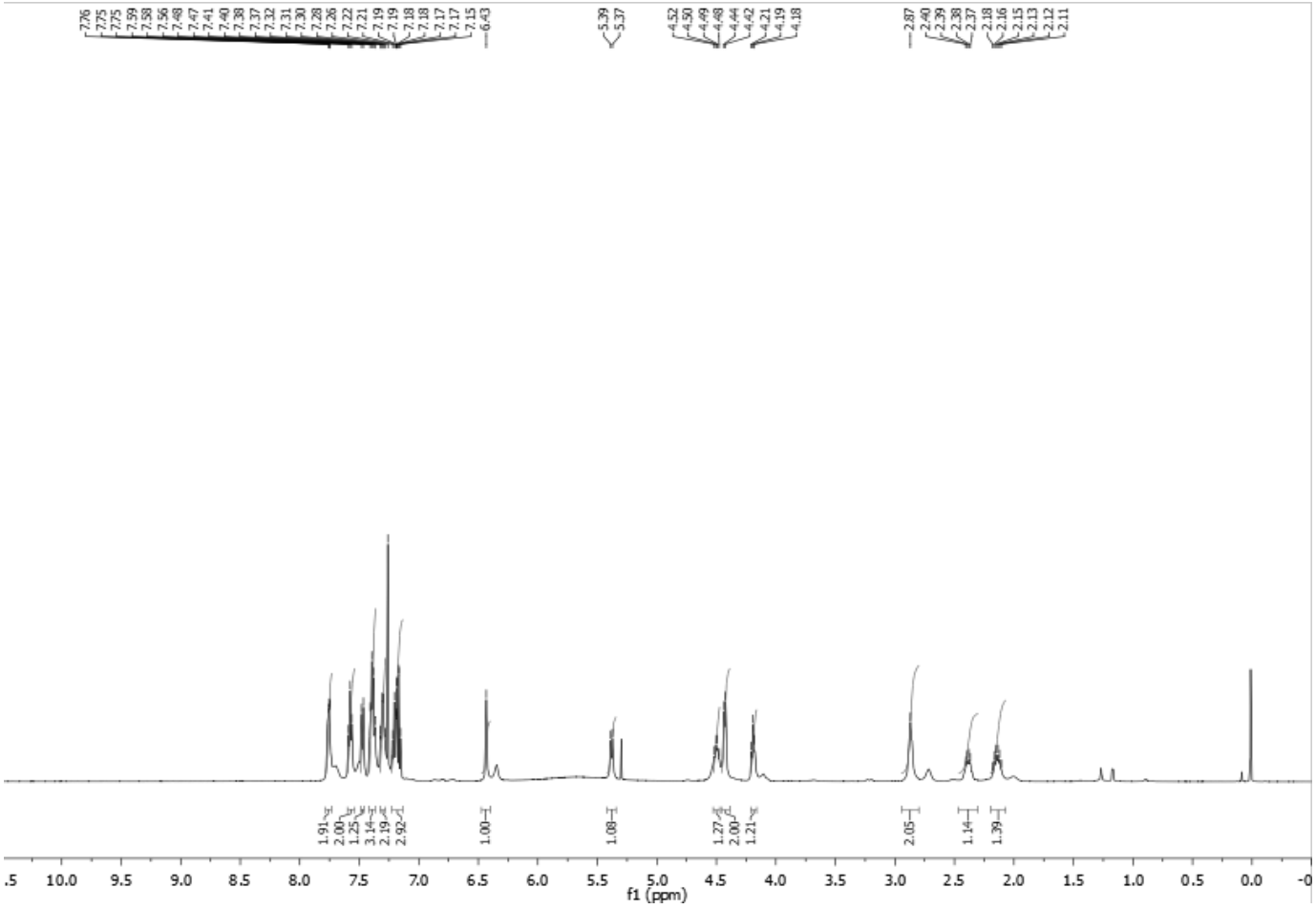


^{13}C spectrum of Compound 5

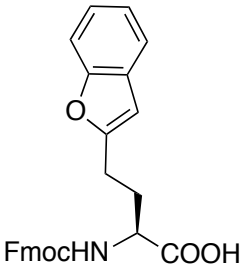


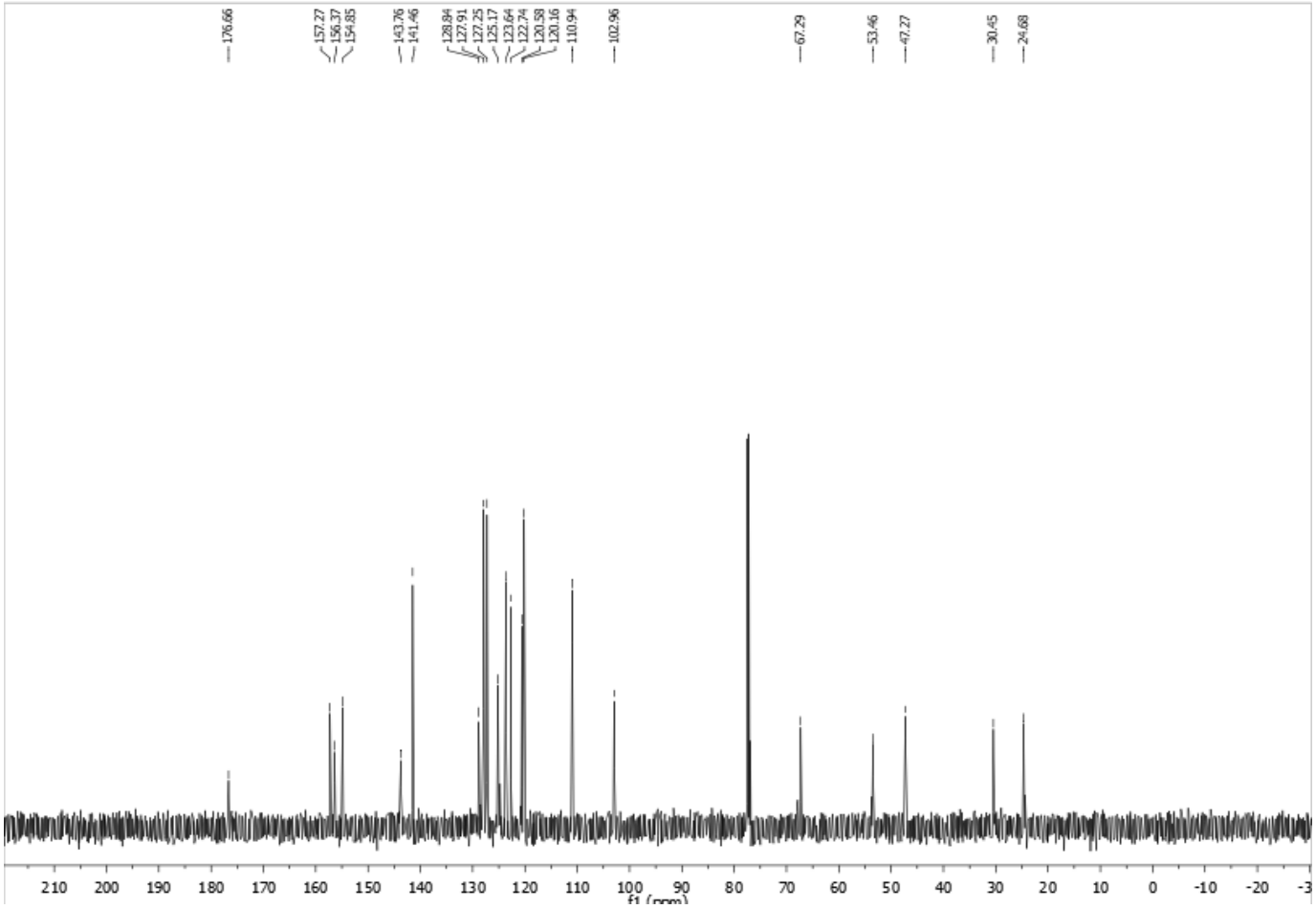
^{1}H spectrum of Compound 6



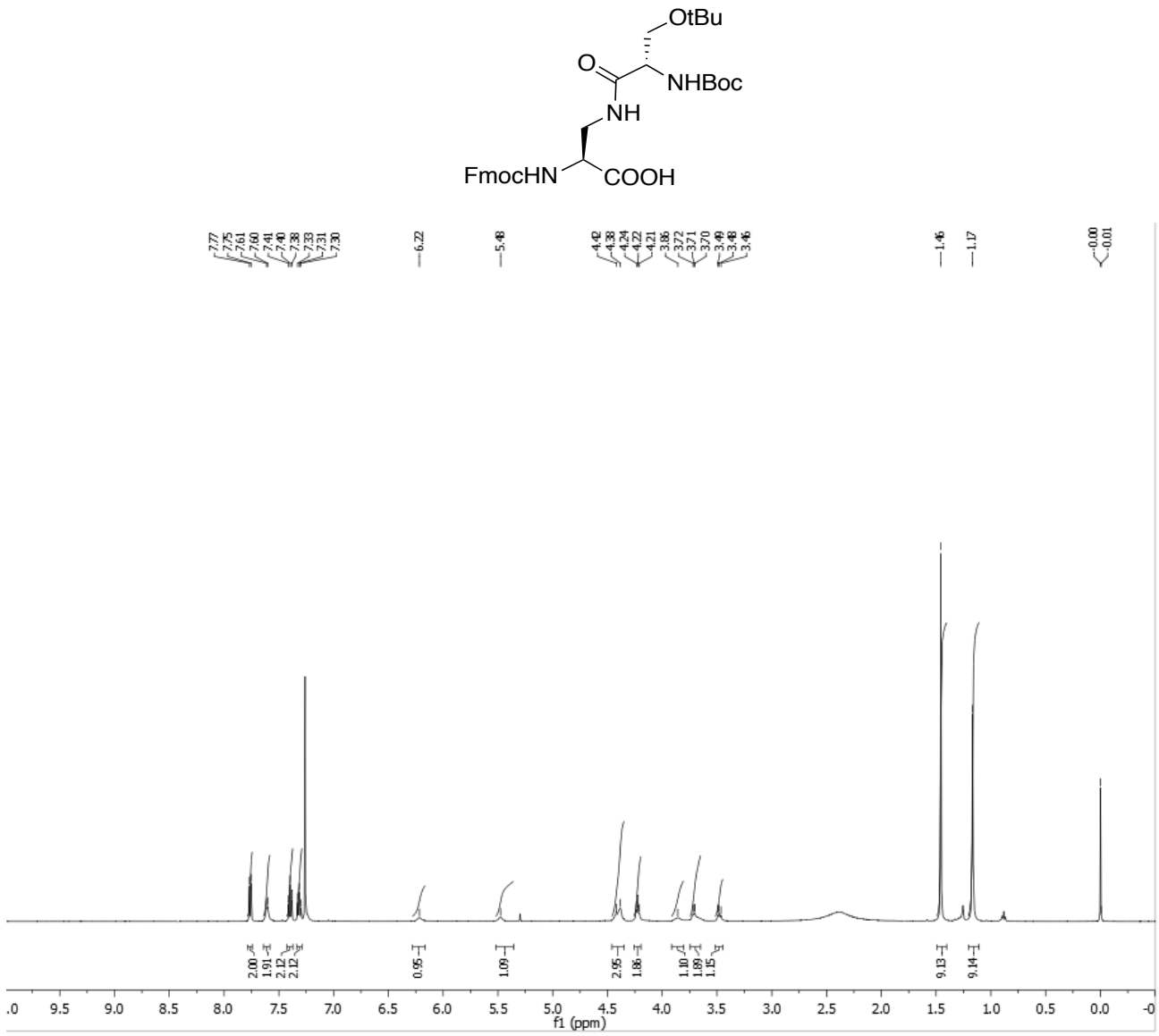


^{13}C spectrum of Compound 6

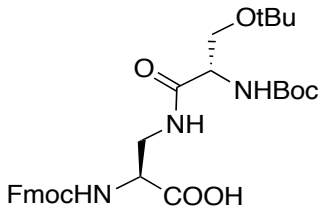


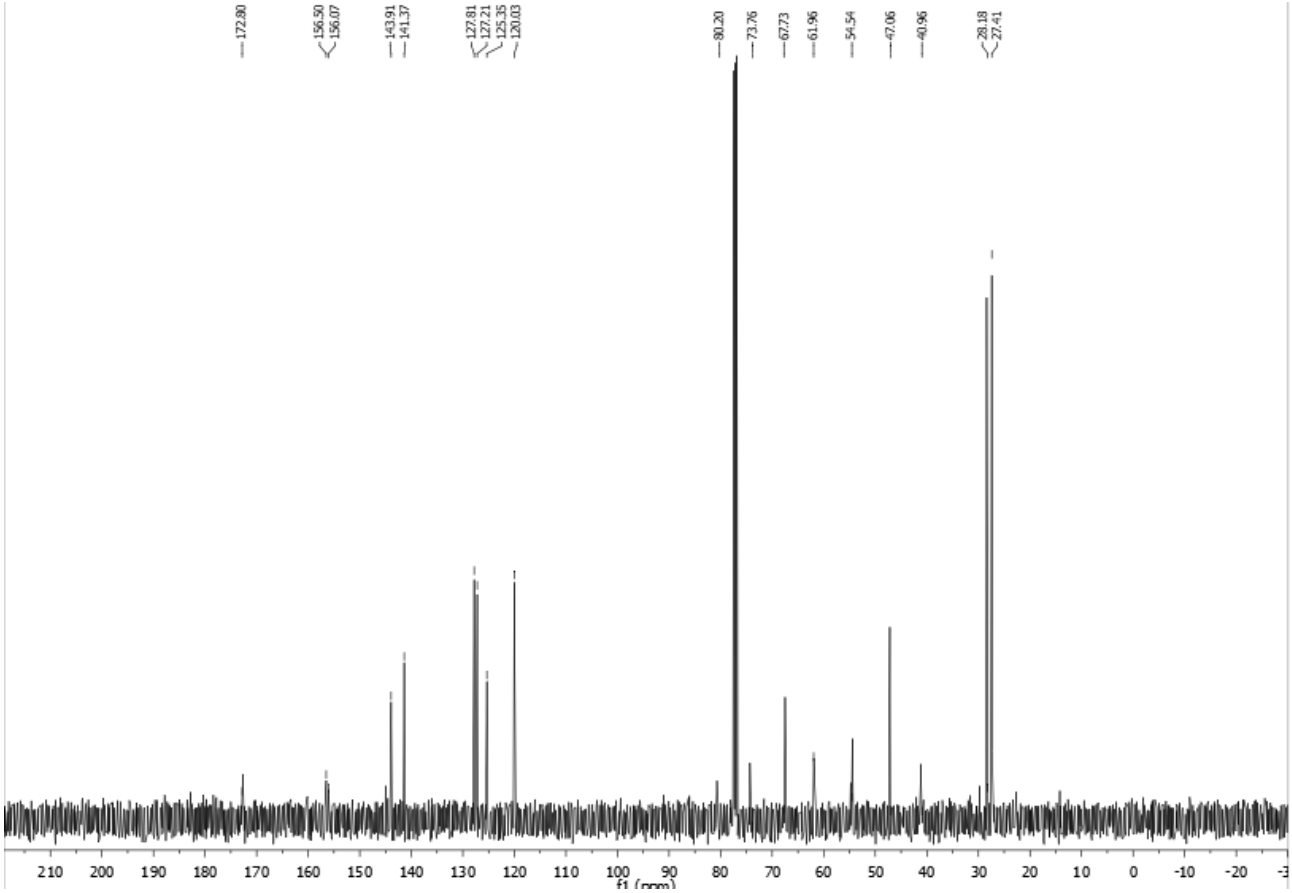


^{1}H spectrum of Compound 7a

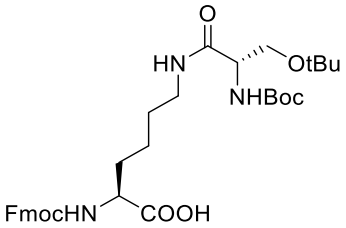


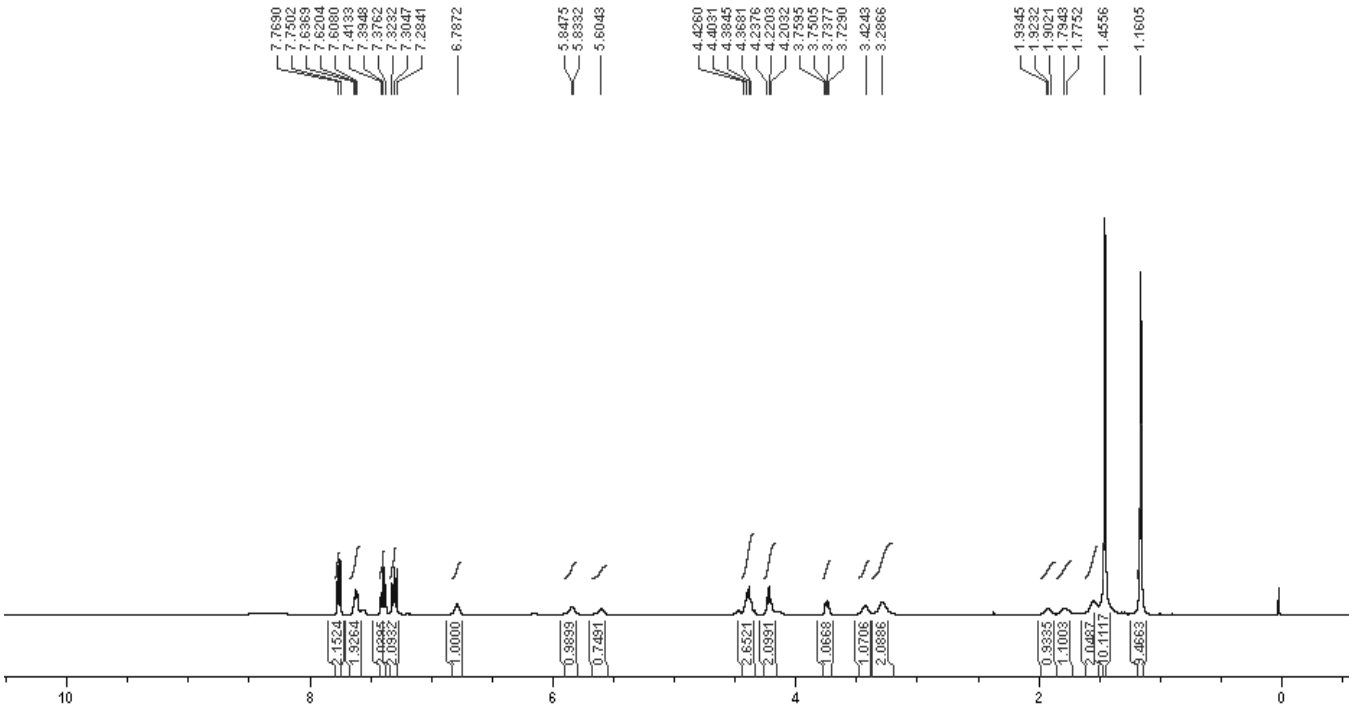
^{13}C spectrum of Compound 7a





[1]H spectrum of Compound 7b





^{13}C spectrum of Compound 7