Supporting information

Solid-phase synthesis of macrocyclic peptides by backbone anchoring using a traceless Ugi multicomponent approach

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Materials and equipment

All the chemical reagents and solvents from commercial sources were used without further purification. Coupling reagents and amino acid derivatives were purchased from Matrix Innovation Inc. (Québec, QC, Canada). Aminomethyl ChemMatrix® resin (0.55 mmol/g) and HMBA ChemMatrix® (0.46 mmol/g) were purchased from PCAS Biomatrix (St-Jean-sur-Richelieu, QC, Canada). All other reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA). Reactions on solid support were performed in filter columns (2 and 10 mL) from Roland Vetter Laborbedarf OHG (Ammerbuch, Germany). RP-HPLC analyses were achieved on a Shimadzu Prominence instrument (Columbian, MD, USA) using a Phenomenex Kinetex column (4.6 mm x 100 mm, 2.6 µm XB-C18, 100 Å, 1.5 mL/min) with a 10.5 min gradient from water (0.1% TFA) and MeCN (0.1% TFA) (MeCN 10-100%) and detection at 220 nm and 254 nm. LC-MS analyses were performed on a Shimadzu Prominence LCMS-2020 equipped with an ESI and APCI ion source. Microwave experiments were conducted on a Biotage Initiator microwave instrument (Charlotte, NC, USA) with 0.2-0.5 and 0.5-2 mL microwave vials. Peptides were synthetized on a Prelude peptide synthetizer from Protein Technologies (Tucson, AZ, USA). High-resolution mass spectrometry was performed on a Waters Synapt G2-Si (Quadrupole/TOF) with a Waters UPLC binary pump and FTN injector. The mass spectrometer was operated in High resolution mode and calibration done with a sodium formate solution and lock-mass correction using a Leucine-enkephaline solution (Waters).

General procedure for solid phase peptide synthesis

Peptides were synthesized by standard Fmoc solid phase synthesis. Briefly, amino acid couplings were performed with a solution of Fmoc-Xaa-OH (3 equiv), HATU (3 equiv) and NMM (6 equiv) in DMF for 20 min. The coupling step was repeated once and the resin washed with DMF (5 $\times$ 30 s). The Fmoc protecting group was removed by treating the resin twice with a solution of 20% piperidine in DMF (v/v) for 8 min followed by washing with DMF (5 $\times$ 30 s).

Synthesis of C-terminal fragment

Synthesis of C-terminal peptide fragments bearing a free amine was carried out on hydroxymethylbenzoic acid (HMBA) resin. The first amino acid (3 equiv) was attached to the resin in presence of diisopropylcarbodiimide (DIC) (3 equiv) in DMF for 30 min. Then, the peptide was assembled by standard Fmoc solid-phase synthesis and the resin washed thoroughly with DMF (5×) and DCM (5×). The fully protected peptide was released from the resin with a solution of propylamine (1M) for 1h. The resin was filtered and the solvent removed under reduced pressure. The resulting mixture was analyzed by HPLC and ESI-MS. The peptides were used without further purification in Ugi-4CR ligation.

H-Gly-Phe-Gly-Lys(Boc)-Leu-Gly-CONPr : 99 % purity; RP-HPLC t_R = 7.93 min; ESI-MS *m/z*: 619.45 $[M-H]^-$; calcd for $C_{30}H_{50}N_8O_6$: 619.39.

Synthesis of N-terminal fragment

Synthesis of N-terminal peptide fragments bearing a free carboxylic acid was carried out on 2-chlorotrityl chloride (CTC) resin. The first amino acid (3 equiv) was attached to the resin in presence of diisopropylethylamine (DIPEA) (7 equiv) DCM for 3h. After filtration the remaining trityl chloride groups were capped by a solution of DCM, MeOH, DIPEA (17:2:1; v:v:v) for 15 min. Then, the peptide was assembled by standard Fmoc solid-phase synthesis and the resin washed thoroughly with DMF (5×) and DCM (5×). The fully protected peptide was released from the resin with a solution of 20% HFIP in DCM (v/v) for 30 min. The resin was filtered and the solvent removed under reduced pressure and the resulting mixture precipitated with cold diethyl ether. The solid was washed twice with diethyl ether and dried under vacuum to be analyzed by HPLC and ESI-MS. The peptides were used without further purification in Ugi-4CR ligation.

Fmoc-Gly-Phe-Gly-Tyr(tBu)-Leu-Gly-OH : 99 % purity; RP-HPLC t_R = 11.12 min; ESI-MS *m/z*: 889.55 $[M-H]^-$; calcd for $C_{49}H_{57}N_6O_{10}$: 889.41.

Fmoc-Gly-Phe-Gly-Tyr(tBu)-Leu-Phe-OH : 92 % crude purity; RP-HPLC t_R = 11.65 min; ESI-MS *m/z*: 979.45 $[M-H]^-$; calcd for $C_{56}H_{63}N_6O_{10}$: 979.46.

Preparation of backbone anchoring linker (BAL resin)

Aminomethyl ChemMatrix® was swollen in DMF before the addition of Fmoc-Ile-OH (3 equiv), HATU (3 equiv) and NMM (6 equiv) and stired for 2x30 min. The resin was then washed with DMF (5x) and DCM (5x) before being dried under reduced pressure. Once the resin was dry, Fmoc dosage according to the method of Gude *et Al.* was performed and loading was estimated to 0.297 mmol/g. The resin was then treated with a 20% piperidine in DMF solution, washed with DMF and stirred with 4-(4-formyl-3,5-dimethoxyphenoxy)butanoic acid (3 equiv), HATU (3 equiv), DIPEA (6 equiv), in DMF for 3h. The resin was once again washed with DMF and DCM before being dried in vaccuo. The resin BAL is then ready to use.

Reductive amination protocol

BAL resin was swelled in DMF for 10 minutes and a solution of $NaBH_3CN$ (10 equiv.) and glycine *tert*-butyl ester hydrochloride (10 equiv) was added to the resin and stirred at room temperature for 3h. The resin was washed with DMF (5x) and the subsequent acylation was performed using Fmoc-Xaa-OH (3 equiv), HATU (3 equiv) and NMM (6 equiv) for 3h. The resin was then washed with DMF (5x) and DCM (5x) and dried under reduced pressure. Classic Fmoc SPPS was then performed with the backbone anchored peptide. Following removal of the Fmoc group on the last amino acid, the peptide was cleaved from the resin with a solution of TFA/H_2O/TIPS (95:2.5:2.5) for 30 min at room temperature. After filtration and washing with TFA, the filtrate was evaporated under reduced pressure and the resulting mixture precipitated with cold diethyl ether. The solid was washed twice with diethyl ether and dried under vacuum to be analyzed by HPLC and ESI-HRMS.

H-Gly-Tyr-Lys-Leu-Gly-Gly-OH (**1**) (White powder, 3.2 mg, 53% isolated yield): 85% crude purity; RP-HPLC t_R = 5.49 min; HRMS (ESI-TOF) *m/z*: 594.3260 $[M+H]^+$; calcd for $C_{27}H_{44}N_7O_8$ 594.3246.

Synthesis of phenylisopropyl ester C-terminal protected amino acids (PhiPr)

1. Sodium hydride 60% in mineral oil (80 mg, 1.5 mmol) was first dissolved in diethyl ether (2 mL) and a solution of 2-phenyl-2-propanol in diethyl ether (2.0 g, 14.8 mmol in 2 mL) was slowly added dropwise. The mixture was allowed to react at room temperature for 20 minutes before being cold in an ice bath. Trichloroacetonitrile (1.65 mL, 16.3 mmol) was added over 15 minutes and the reaction mixture allowed returning at room temperature for 1h. Diethyl ether was then removed under vacuum. Pentane was added to form a brown precipitate that was removed from the product by filtration. Pentane was evaporated under reduced pressure and the product was analyzed and used without further purification.

2-phenylpropan-2-yl 2,2,2-trichloroacetimidate, pale yellow oil, (3.14 g, 11.2 mmol, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (broad, s, 1H), 7.47 – 7.42 (m, 2H), 7.38 – 7.34 (m, 2H), 7.30 – 7.27 (m, 1H), 1.89 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.36 (Cq), 145.01 (Cq), 129.37 (CH), 128.24 (CH), 127.14 (CH), 125.45 (CH), 124.27 (CH), 112.38 (Cq), 84.99 (Cq), 28.08 (CH_3).

2. Fmoc-Gly-OH (670 mg, 2.30 mmol) was dissolved in DCM and another solution of DCM containing trichloroacetimidate (1.47 g, 4.6 mmol) added dropwise. The reaction was stirred at room temperature overnight and DCM removed under reduced pressure. Crude product was purified by flash chromatography with a gradient from 100% hexanes to 90:10 and then 80:20 hexanes : ethyl acetate.

2-phenylpropan-2-yl(((9H-fluoren-9-yl)methoxy)carbonyl) glycinate, white oil, (933 mg, 2.25 mmol, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 4.7 Hz, 2H), 7.57 (d, J = 4.7 Hz, 2H), 7.41 – 7.27 (m, 9H), 5.24 (broad, t, J = 3.0 Hz, 1H), 4.37 (d, J = 4.7 Hz, 2H), 4.20 (t, J = 4.4 Hz, 1H), 4.00 (d, J = 3.4 Hz, 2H), 3.49 (s, 1H), 1.81 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.70 (Cq), 156.17 (Cq), 144.92 (Cq), 143.73 (Cq), 141.20 (Cq), 128.35 (CH), 127.63 (CH), 127.29 (CH), 127.00 (CH), 125.04 (CH), 124.21 (CH), 119.90 (CH), 83.36 (Cq), 67.09 (CH_2), 47.01 (CH), 43.35 (CH_2), 28.47 (CH_3).

3. Fmoc-Gly-OPhiPr (933 mg, 2.25 mmol) was dissolved in DCM (10 mL). Excess of diethylamine (10 mL) was added to the mixture and allowed to react at room temperature for 1h. Solvent was removed under vacuum and product purified by flash chromatography with a gradient from 100% DCM to 99:1 (DCM:TEA) to 97:2:1 (DCM:MeOH:TEA).

2-phenylpropan-2-yl glycinate, yellow oil (384 mg, 1.99 mmol, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 4H), 7.28-7.23 (m, 1H), 3.41 (s, 2H), 1.79 (s, 6H), 1.40 (broad s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.82 (Cq), 145.31 (Cq), 128.16 (CH), 126.97 (CH), 124.07 (CH), 81.97 (Cq), 44.50 (CH_2), 28.44 (CH_3).

General procedure for Ugi backbone anchoring and cleavage from the solid support

The supported aldehyde (BAL resin) was first swelled in a minimum of MeCN/MeOH (1:1) (≈15 µL/mg of resin) in a microwave vial with the previously isolated amine (2.5 equiv). After stirring for 15 min, the carboxylic acid (5 equiv) was added and the mixture stirred for 5 min. Finally, *tert*-butyl isocyanide (10 equiv) was added, the microwave vial sealed and the reaction mixture heated for 30 min at 60°C under microwave irradiations. The resin was filtered and washed with MeCN/MeOH (1:1) (3x), DMF (3x) and DCM (3x). Classic Fmoc SPPS was then performed with the backbone anchored dipeptide. Following removal of the Fmoc group on the last amino acid, the peptide was cleaved from the resin with a solution of TFA/H_2O/TIPS (95:2.5:2.5) for 45 min under microwave irradiations at 60°C. After filtration and washing with TFA, the filtrate was evaporated under reduced pressure and the resulting mixture precipitated with cold diethyl ether. The solid was washed twice with diethyl ether and dried under vacuum to be analyzed by HPLC, purified by preparative HPLC and analyzed by HPLC and ESI-HRMS.

H-Gly-Tyr-Lys-Leu-Gly-Gly-OH (**1**) (White powder, 5.0 mg, 72% isolated yield): 92% crude purity; RP-HPLC t_R = 5.54 min; HRMS (ESI-TOF) *m/z*: 594.3228 $[M+H]^+$; calcd for $C_{27}H_{44}N_7O_8$ 594.3246.

H-Gly-Tyr-Lys-Leu-Ala-Gly-OH (**2**) (White powder, 2.4 mg, 36% isolated yield): 92% crude purity; RP-HPLC t_R = 5.65 min; HRMS (ESI-TOF) *m/z*: 608.3382 $[M+H]^+$; calcd for $C_{28}H_{46}N_7O_8$ 608.3402.

H-Gly-Tyr-Lys-Leu-Phe-Gly-OH (**3**) (White powder, 3.6 mg, 51% isolated yield): 93% crude purity; RP-HPLC t_R = 6.78 min; HRMS (ESI-TOF) *m/z*: 684.3702 $[M+H]^+$; calcd for $C_{34}H_{50}N_7O_8$ 684.3715.

H-Gly-Phe-Gly-Tyr-Leu-Gly-Gly-OH (**4**) (White powder, 4.3 mg, 60% isolated yield): 95% crude purity; RP-HPLC t_R = 6.82 min; HRMS (ESI-TOF) *m/z*: 670.3240 $[M+H]^+$; calcd for $C_{32}H_{44}N_7O_9$ 670.3195.

H-Gly-Phe-Gly-Tyr-Leu-Phe-Gly-OH (**5**) (White powder, 4.9 mg, 58% isolated yield): 82% crude purity; RP-HPLC t_R = 7.60 min; HRMS (ESI-TOF) *m/z*: 760.3700 $[M+H]^+$; calcd for $C_{39}H_{50}N_7O_9$ 760.3665.

H-Gly-Phe-Gly-Tyr-Leu-Gly-Gly-Phe-Gly-Lys-Leu-Gly-OH (**6**) (White powder, 0.5 mg, 5% isolated yield): 72% crude purity; RP-HPLC t_R = 7.53 min; HRMS (ESI-TOF) *m/z*: 1213.6790 $[M+H]^+$; calcd for $C_{60}H_{89}N_{14}O_{13}$ 1213.6728.

H-Gly-Tyr-Lys-Leu-Gly-Gly-OH (**7a**) (White powder, 4.3 mg, 66% isolated yield*):* 92% crude purity; RP-HPLC t_R = 5.49 min; HRMS (ESI-TOF) *m/z:* 594.3260 $[M+H]^+$; calcd for $C_{27}H_{44}N_7O_8$ 594.3246.

H-Gly-Phe-Gly-Tyr-Leu-Gly-Gly-OH (**8a**) (White powder, 3.4 mg, 48% isolated yield): 95% crude purity; RP-HPLC t_R = 6.86 min; HRMS (ESI-TOF) *m/z*: 670.3198 $[M+H]^+$; calcd for $C_{32}H_{44}N_7O_9$ 670.3195.

H-Gly-Leu-Lys-Pro-Tyr-Lys-Glu*-Gly-Gly-OH* (**9a**) (White powder, 4.0 mg, 53% isolated yield): 76% crude purity; RP-HPLC t_R = 7.05 min; HRMS (ESI-TOF) *m/z*: 1072.5720 $[M+H]^+$; calcd for $C_{50}H_{78}N_{11}O_{15}$ 1072.5673.

H-Gly-Leu-Ala-Lys-Tyr-Pro-Ala-Lys-Gly-Glu*-Gly-Gly-OH* (**10a**) (White powder, 4.2 mg, 51% isolated yield): 73% crude purity; RP-HPLC t_R = 6.96 min; HRMS (ESI-TOF) *m/z*: 1271.6691 $[M+H]^+$; calcd for $C_{58}H_{91}N_{14}O_{18}$ 1271.6630.

H-Gly-Leu-Lys-Pro-Tyr-Gly-Lys-Gly-Glu*-Gly-OH* (**11a**) (White powder, 5.5 mg, 85% isolated yield): 77% crude purity; RP-HPLC t_R = 7.10 min; HRMS (ESI-TOF) *m/z*: 1086.5856 $[M+H]^+$; calcd for $C_{51}H_{80}N_{11}O_{15}$ 1086.5830.

H-Gly-Ala-Lys-Tyr-Leu-Lys-Gly-Glu*-Gly-Gly-OH* (**12a**) (White powder, 3.1 mg, 41% isolated yield): 79% crude purity; RP-HPLC t_R = 7.02 min; HRMS (ESI-TOF) *m/z*: 1046.5510 $[M+H]^+$; calcd for $C_{48}H_{76}N_{11}O_{15}$ 1046.5517.

H-Lys-Gly-Ala-Tyr-Leu-Lys-Gly-Glu*-Gly-Gly-OH* (**13a**) (White powder, 3.1 mg, 40% isolated yield): 79% crude purity; RP-HPLC t_R = 6.72 min; HRMS (ESI-TOF) *m/z*: 1101.5592 $[M+H]^+$; calcd for $C_{50}H_{77}N_{12}O_{16}$ 1101.5575.

Allyl ester deprotection on solid support

The resin was swollen in DCM for 15 min before the introduction of a mixture of $Pd(PPh_3)_4$ (0.5 equiv) and phenylsilane (15 equiv) in DCM and stirred for 40 minutes. The step was repeated once and the resin washed with DCM (3 × 30 s), with a solution of 0.5% DIPEA in DMF (3 × 30 s), with a solution of 0.5% sodium diethyldithiocarbamate trihydrate in DMF (3 × 30s) and another time with DCM (3 × 30 s).

PhiPr ester deprotection on solid support

The resin was swollen in DCM for 15 min before the introduction of a mixture of 1% TFA in DCM and stirred for 5 min. The step was repeated once and the resin washed with DCM (3 × 30 s) and DMF (3 x 30 s).

On resin peptide cyclization protocol

The resin bearing the free carboxylic acid and the free amine was swollen in DMF for 15 min. Then a solution of PyAOP (5 equiv), HOAt (5 equiv), and DIPEA (10 equiv) in DMF was added to the resin and the resulting mixture was stirred for 3 h. Finally, the resin was washed with DMF (5 × 30 s), DCM (5 x 30 s) and dried under vacuum. The peptide was then cleaved from the resin as described above, with a

solution of TFA/H_2O/TIPS (95:2.5:2.5) for 45 min under microwave irradiations at 60°C. After filtration and washing with TFA, the filtrate was evaporated under reduced pressure and the resulting mixture precipitated with cold diethyl ether. The solid was washed twice with diethyl ether and dried under vacuum to be analyzed by HPLC, purified by preparative HPLC and analyzed by HPLC and ESI-HRMS.

Cyclo [Gly-Tyr-Lys-Leu-Gly-Gly] (**7b**) (White powder, 2.5 mg, 36% isolated yield): 66% crude purity; RP-HPLC t_R = 6.01 min; HRMS (ESI-TOF) *m/z*: 576.3144 $[M+H]^+$; calcd for $C_{27}H_{42}N_7O_7$ 576.3140.

Cyclo [Gly-Phe-Gly-Tyr-Leu-Gly-Gly] (**8b**) (White powder, 1.9 mg, 29% isolated yield): 71% crude purity; RP-HPLC t_R = 6.86 min; HRMS (ESI-TOF) *m/z*: 652.3072 $[M+H]^+$; calcd for $C_{32}H_{42}N_7O_8$ 652.3089.

Cyclo [Gly-Leu-Lys-Pro-Tyr-Lys-Glu*-Gly-Gly]* (**9b**) (White powder, 2.3 mg, 31% isolated yield): 74% crude purity; RP-HPLC t_R = 7.64 min; HRMS (ESI-TOF) *m/z*: 1054.5603 $[M+H]^+$; calcd for $C_{50}H_{76}N_{11}O_{14}$ 1054.5568.

Cyclo [Gly-Leu-Ala-Lys-Tyr-Pro-Ala-Lys-Gly-Glu*-Gly-Gly]* (**10b**) (White powder, 2.0 mg, 25% isolated yield): 57% crude purity; RP-HPLC t_R = 7.45 min; HRMS (ESI-TOF) *m/z*: 1253.6576 $[M+H]^+$; calcd for $C_{58}H_{89}N_{14}O_{17}$ 1253.6525.

Cyclo [Gly-Leu-Lys-Pro-Tyr-Gly-Lys-Gly-Glu*-Gly]* (**11b**) (White powder, 3.0 mg, 42% isolated yield): 79% crude purity; RP-HPLC t_R = 7.73 min; HRMS (ESI-TOF) *m/z*: 1068.5767 $[M+H]^+$; calcd for $C_{51}H_{78}N_{11}O_{14}$ 1068.5724.

Cyclo [Gly-Ala-Lys-Tyr-Leu-Lys-Gly-Glu*-Gly-Gly]* (**12b**) (White powder, 1.6 mg, 21% isolated yield): 70% crude purity; RP-HPLC t_R = 7.49 min; HRMS (ESI-TOF) *m/z*: 1028.5421 $[M+H]^+$; calcd for $C_{48}H_{74}N_{11}O_{14}$ 1028.5411.

Cyclo [Lys-Gly-Ala-Tyr-Leu-Lys-Gly-Glu*-Gly-Gly]* (**13b**) (White powder, 2.3 mg, 32% isolated yield): 66% crude purity; RP-HPLC t_R = 7.16 min; HRMS (ESI-TOF) *m/z* 1083.5485 $[M+H]^+$; calcd for $C_{50}H_{75}N_{12}O_{15}$ 1083.5469.

Cyclo [Gly-Leu- Cyclo [Lys-Pro-Tyr-Lys-Glu] -Gly-Gly] (**9c**) (White powder, 1.5 mg, 31% isolated yield): 74% crude purity; RP-HPLC t_R = 6.50 min; HRMS (ESI-TOF) *m/z*: 912.4963 $[M+H]^+$; calcd for $C_{43}H_{66}N_{11}O_{11}$ 912.4938.

Cyclo [Gly-Leu-Ala- Cyclo [Lys-Tyr-Pro-Ala-Lys-Gly-Glu] -Gly-Gly] (**10c**) (White powder, 1.8 mg, 22% isolated yield): 82% crude purity; RP-HPLC t_R = 6.45 min; HRMS (ESI-TOF) *m/z*: 1111.5909 $[M+H]^+$; calcd for $C_{51}H_{79}N_{14}O_{14}$ 1111.5895.

Cyclo [Gly-Leu- Cyclo [Lys-Pro-Tyr-Gly-Lys-Gly-Glu] -Gly] (**11c**) (White powder, 1.6 mg, 24% isolated yield): 75% crude purity; RP-HPLC t_R = 6.73 min; HRMS (ESI-TOF) *m/z*: 926.5120 $[M+H]^+$; calcd for $C_{44}H_{68}N_{11}O_{11}$ 926.5094.

Cyclo [Gly-Ala- Cyclo [Lys-Tyr-Leu-Lys-Gly-Glu] -Gly-Gly] (**12c**) (White powder, 0.8 mg, 11% isolated yield): 55% crude purity; RP-HPLC t_R = 6.41 min; HRMS (ESI-TOF) *m/z*: 886.4810 $[M+H]^+$; calcd for $C_{41}H_{64}N_{11}O_{11}$ 886.4781.

Cyclo [Cyclo [Lys-Gly-Ala-Tyr-Leu-Lys-Gly-Glu] -Gly-Gly] (**13c**) (White powder, 1.0 mg, 12% isolated yield): 97% crude purity; RP-HPLC t_R = 5.83 and 6.25 min; HRMS (ESI-TOF) *m/z*: 941.4851 $[M+H]^+$; calcd for $C_{43}H_{65}N_{12}O_{12}$ 941.4839.

Figures

Figure S1. HPLC profiles (λ = 220 nm) and ESI-HRMS spectras.

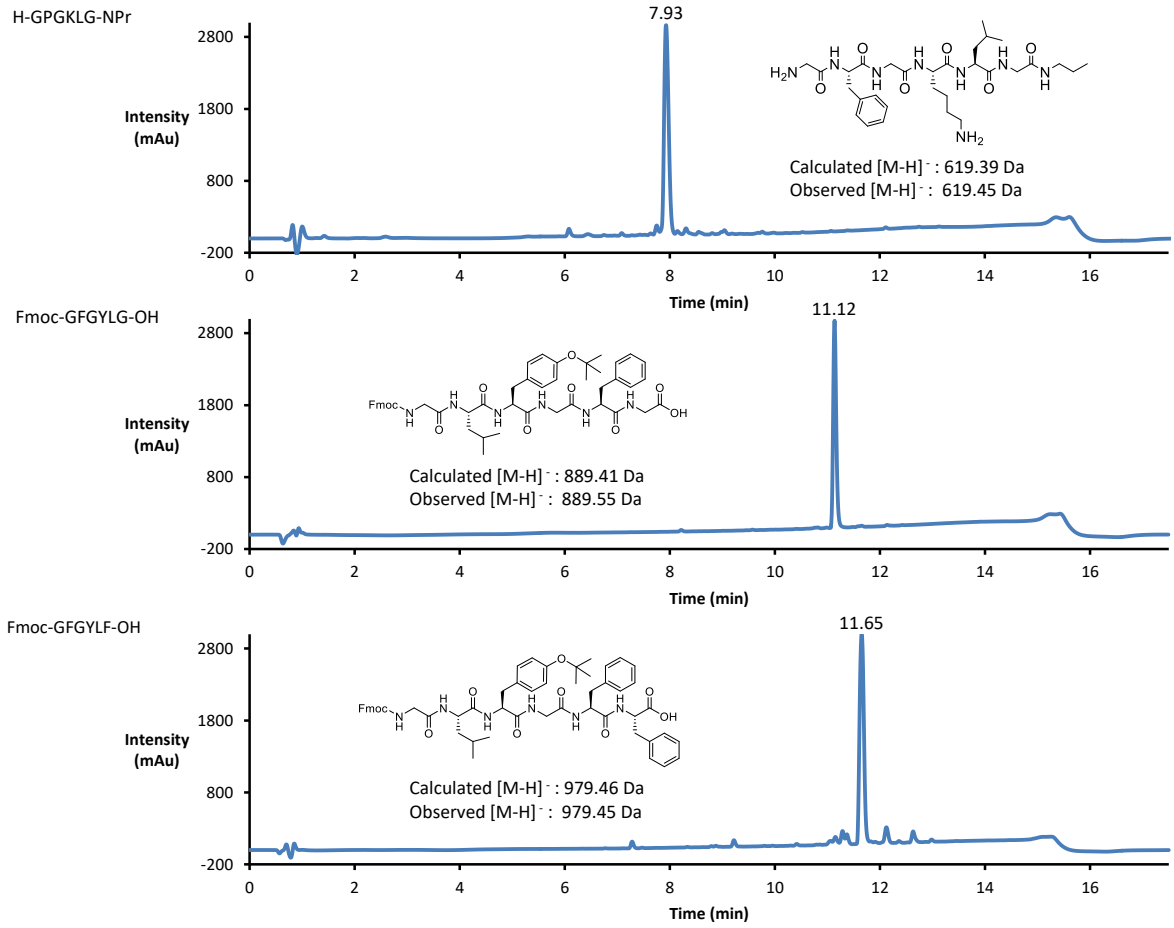
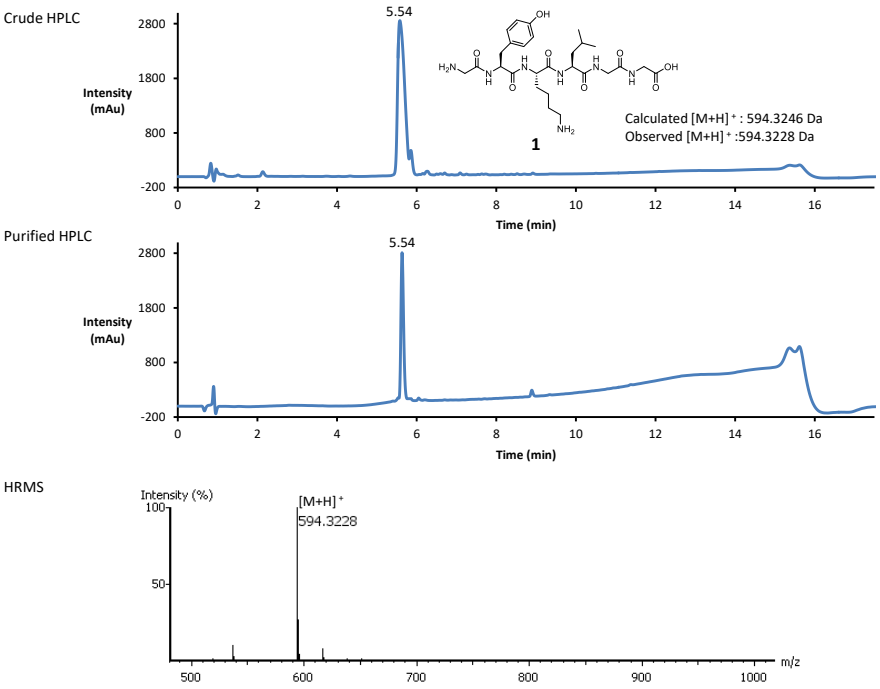


Figure S1. (Continued)

H-Gly-Tyr-Lys-Leu-Gly-Gly-OH (**1**)

Ugi procedure



Reductive amination procedure

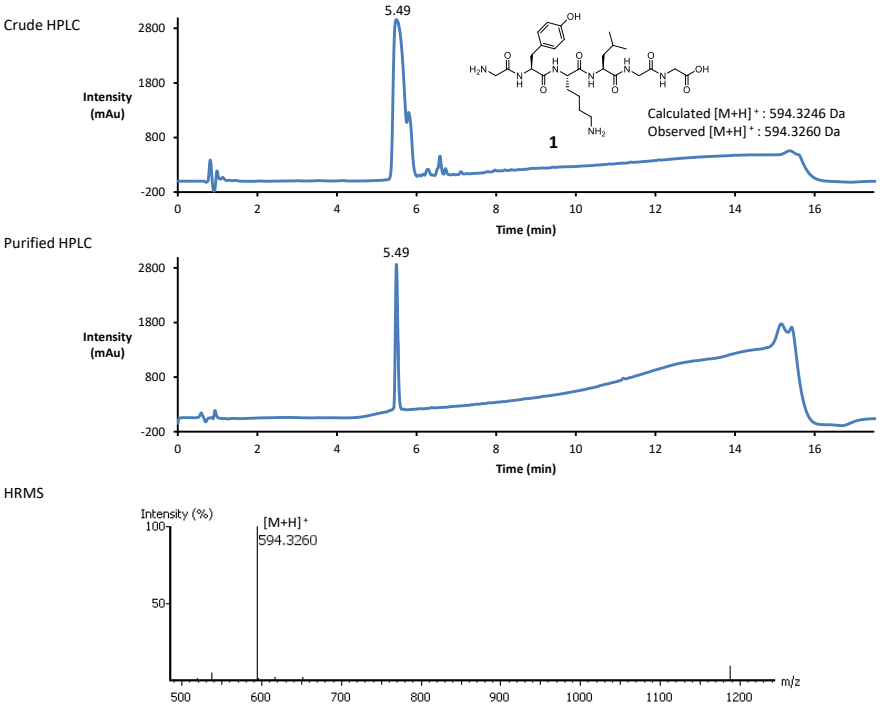
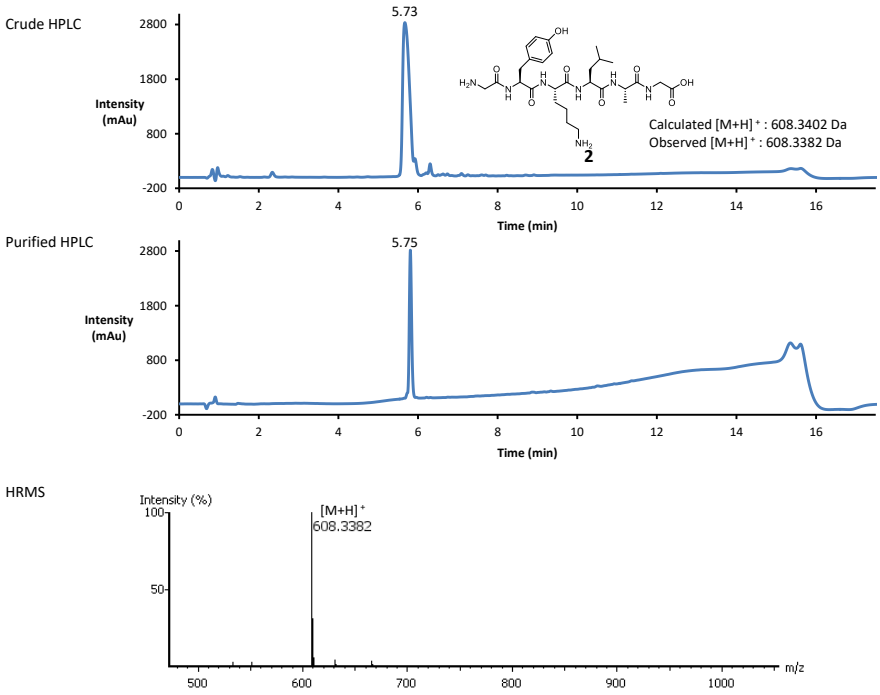


Figure S1. (Continued)

H-Gly-Tyr-Lys-Leu-Ala-Gly-OH (**2**)



H-Gly-Tyr-Lys-Leu-Phe-Gly-OH (**3**)

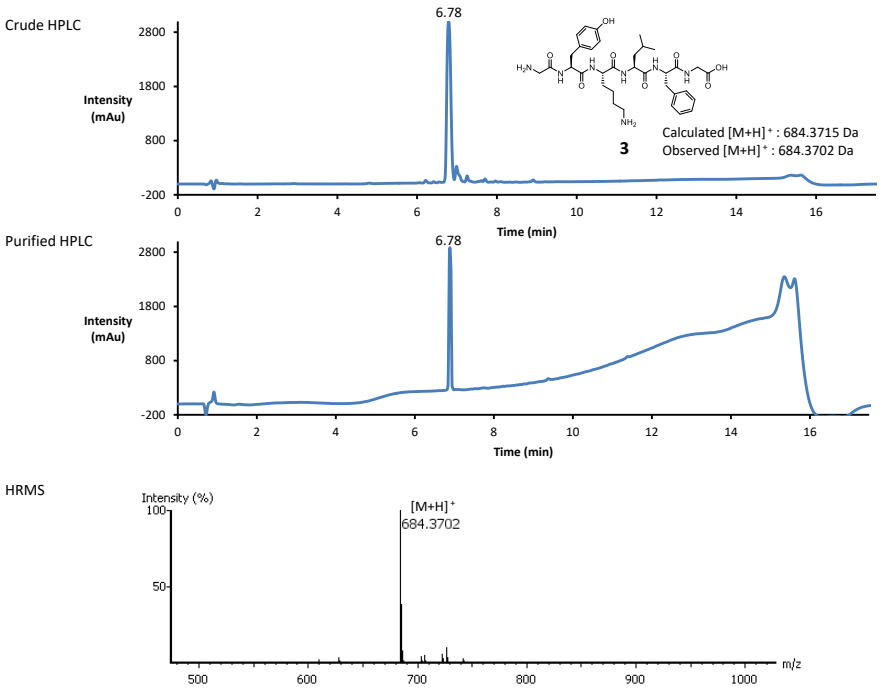
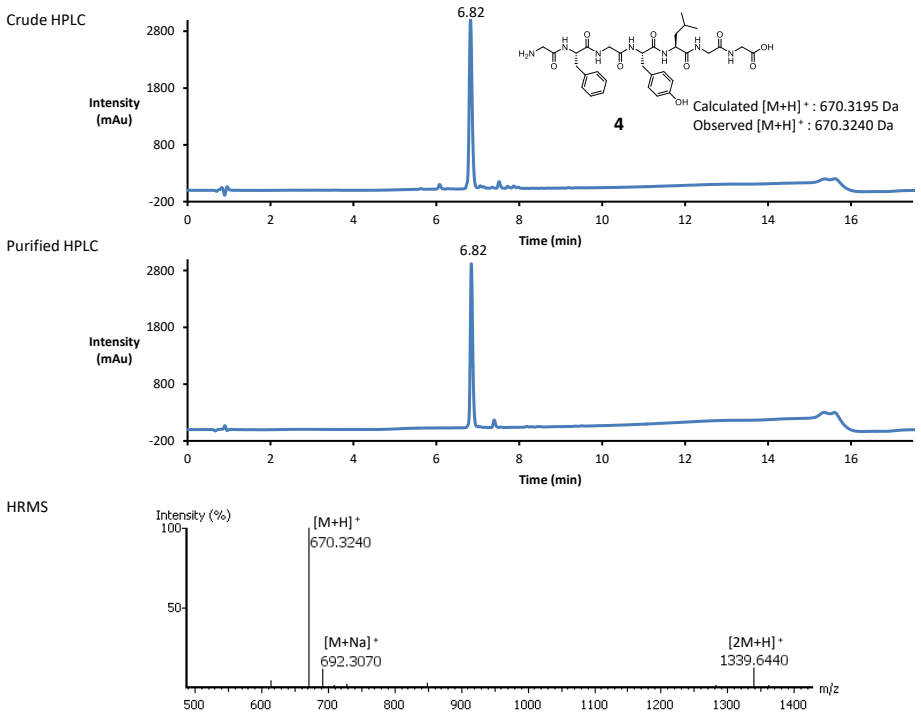


Figure S1. (Continued)

H-Gly-Phe-Gly-Tyr-Leu-Gly-Gly-OH (**4**)



H-Gly-Phe-Gly-Tyr-Leu-Phe-Gly-OH (**5**)

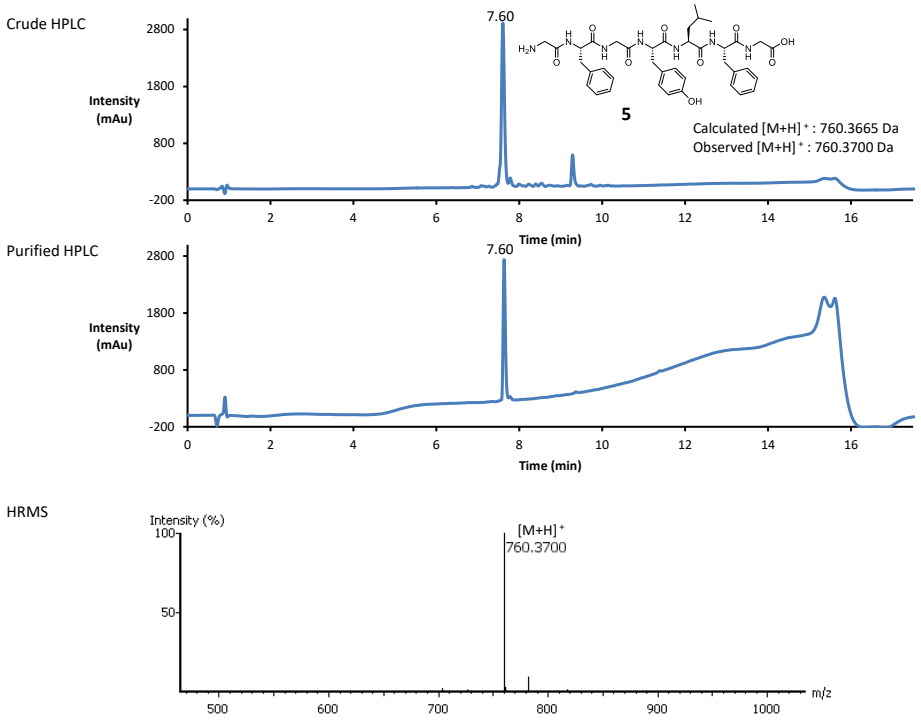
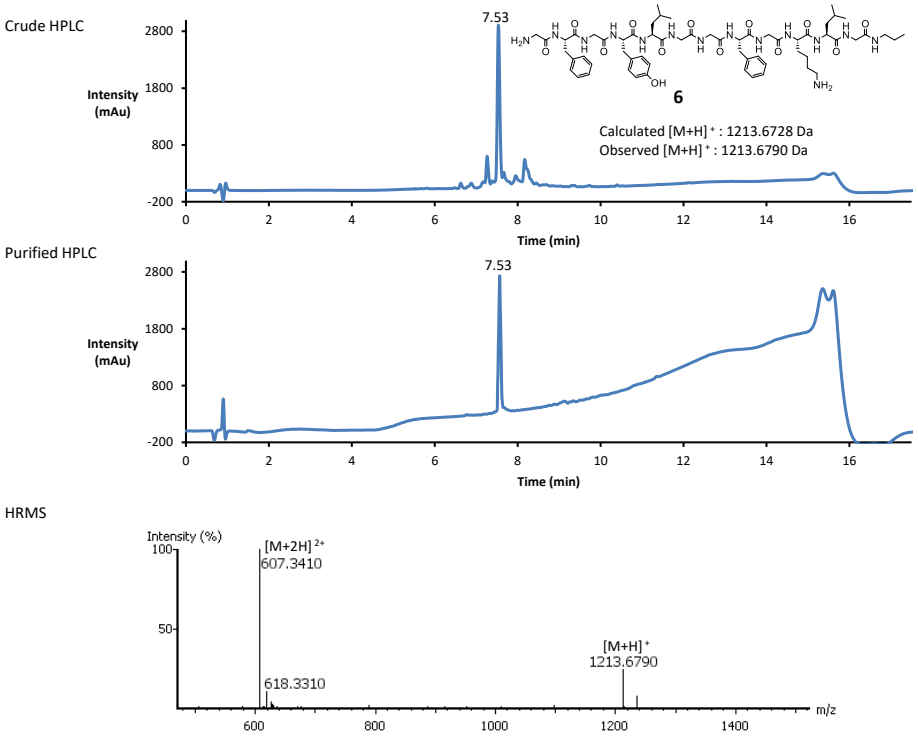


Figure S1. (Continued)

H-Gly-Phe-Gly-Tyr-Leu-Gly-Gly-Phe-Gly-Lys-Leu-Gly-OH (**6**)



H-Gly-Tyr-Lys-Leu-Gly-Gly-OH (**7a**)

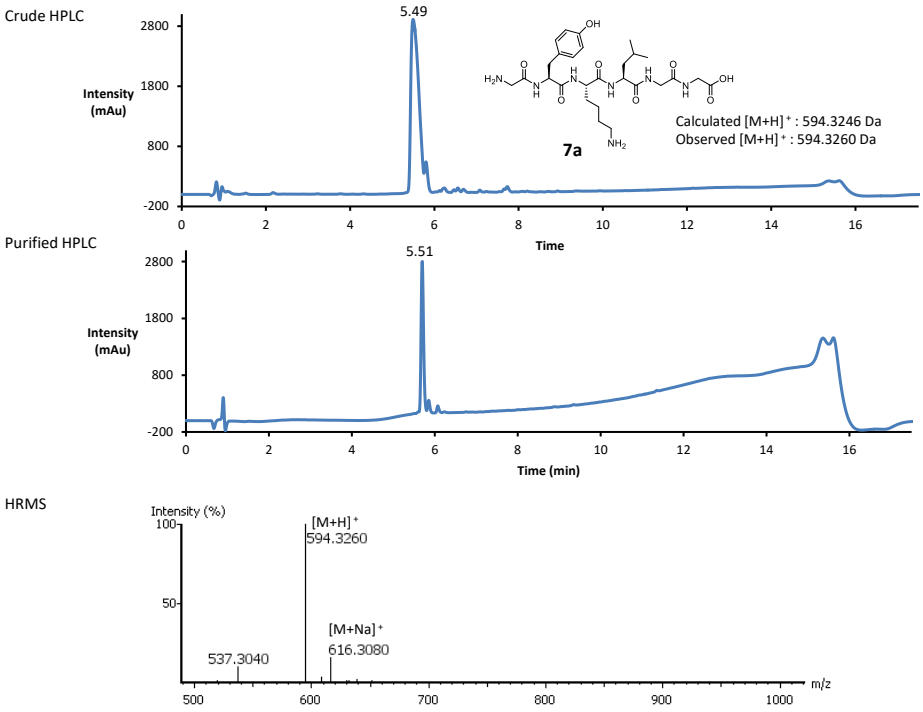
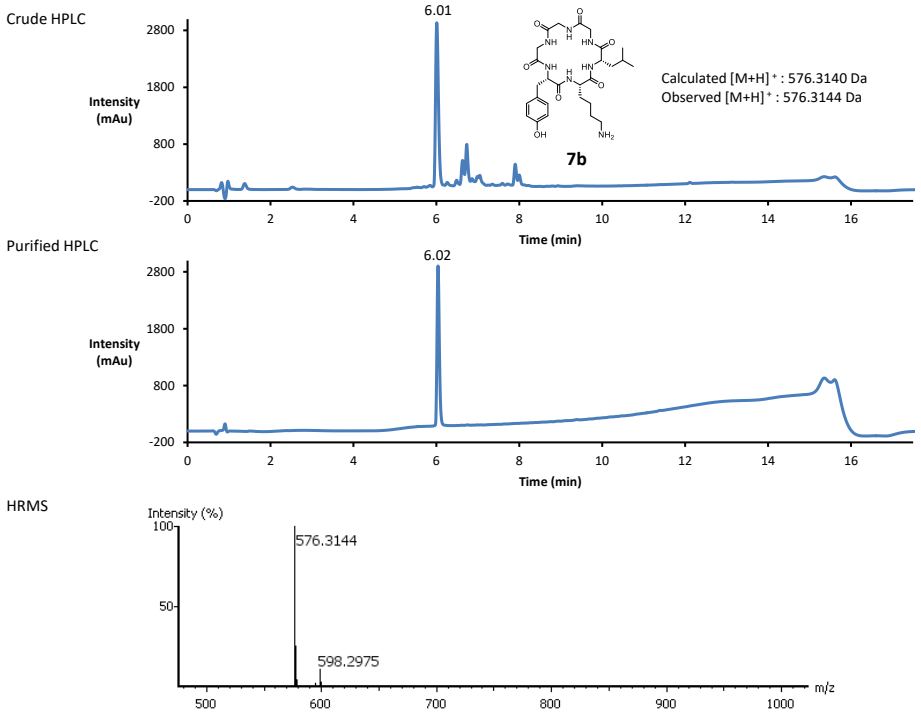


Figure S1. (Continued)

Cyclo [Gly-Tyr-Lys-Leu-Gly-Gly] (**7b**)



H-Gly-Phe-Gly-Tyr-Leu-Gly-Gly-OH (**8a**)

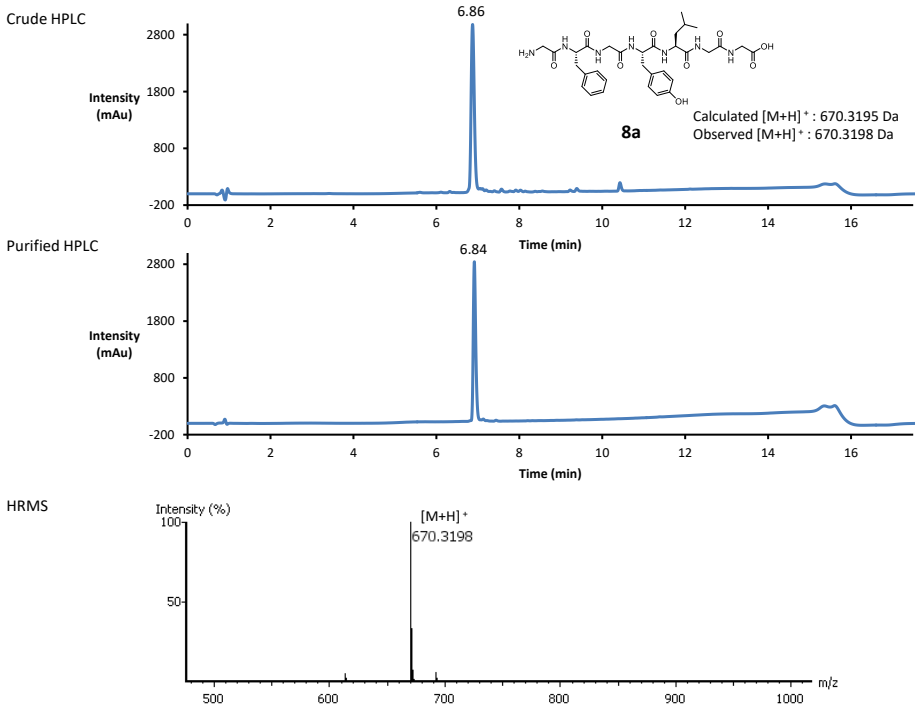
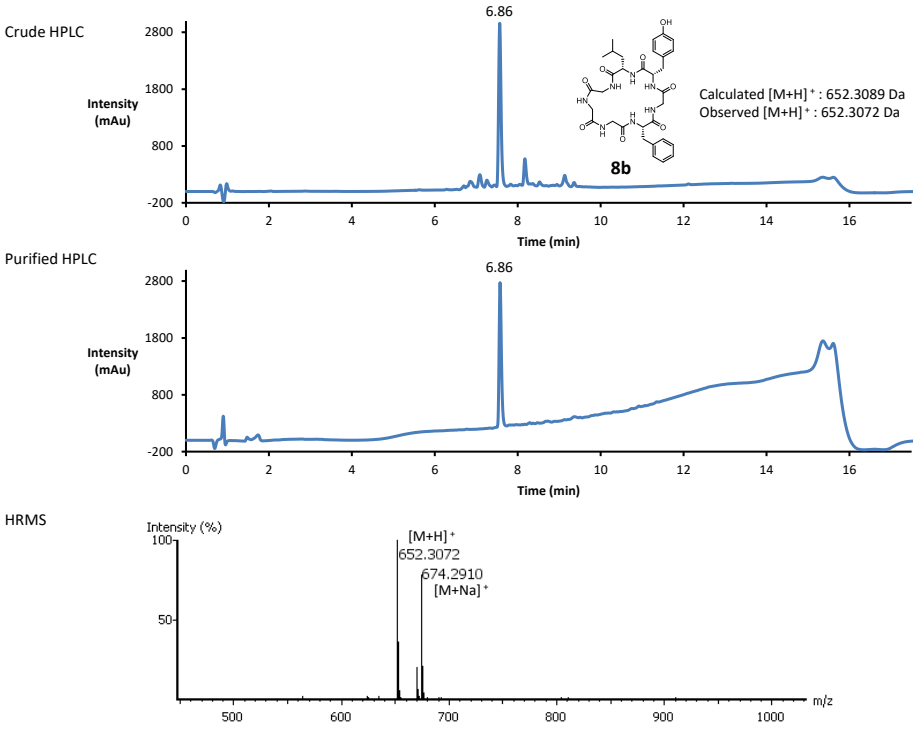


Figure S1. (Continued)

Cyclo [Gly-Phe-Gly-Tyr-Leu-Gly-Gly] (**8b**)



H-Gly-Leu-Lys-Pro-Tyr-Lys-Glu*-Gly-Gly-OH* (**9a**)

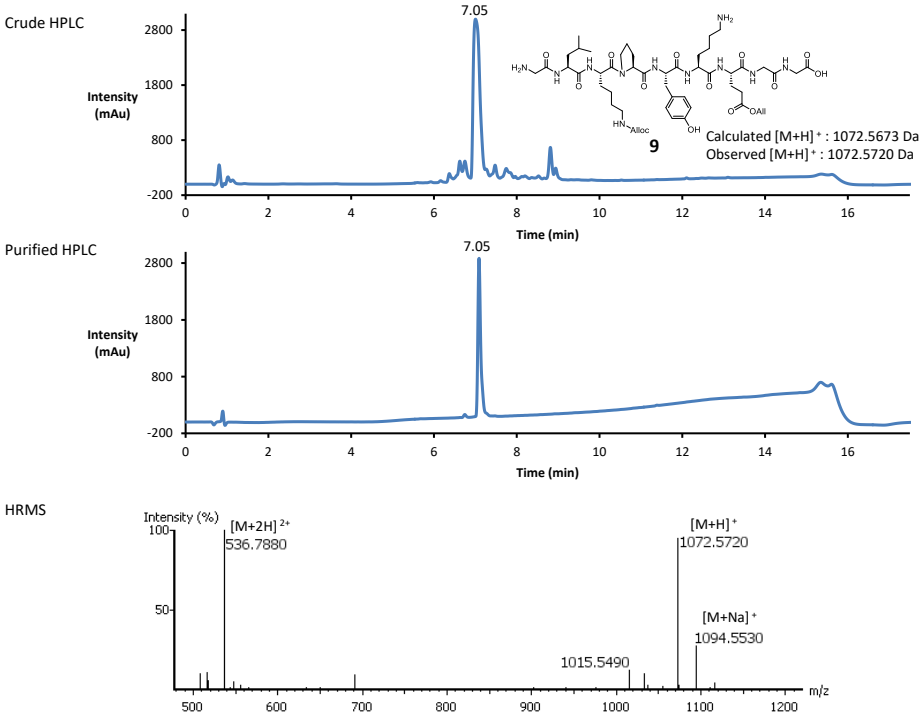
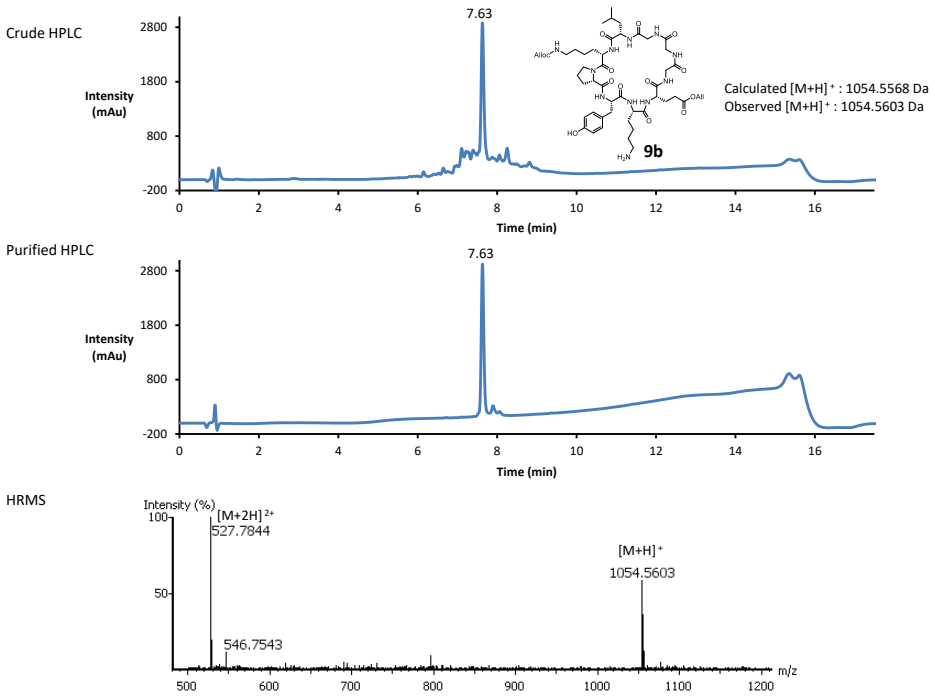


Figure S1. (Continued)

Cyclo [Gly-Leu-Lys-Pro-Tyr-Lys-Glu*-Gly-Gly]* (**9b**)



Cyclo [Gly-Leu- Cyclo [Lys-Pro-Tyr-Lys-Glu] -Gly-Gly] (**9c**)

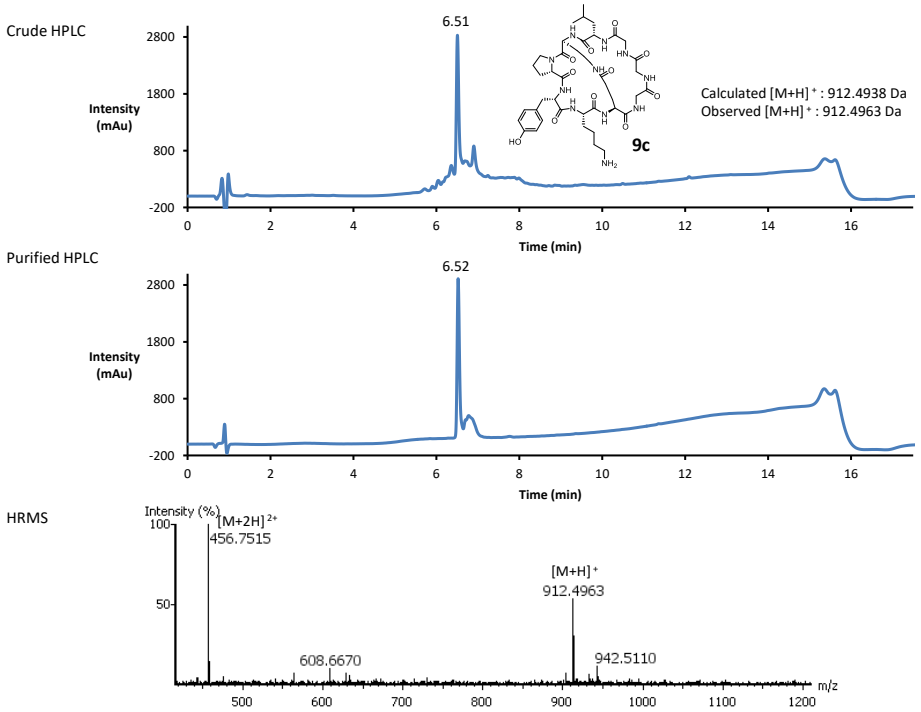
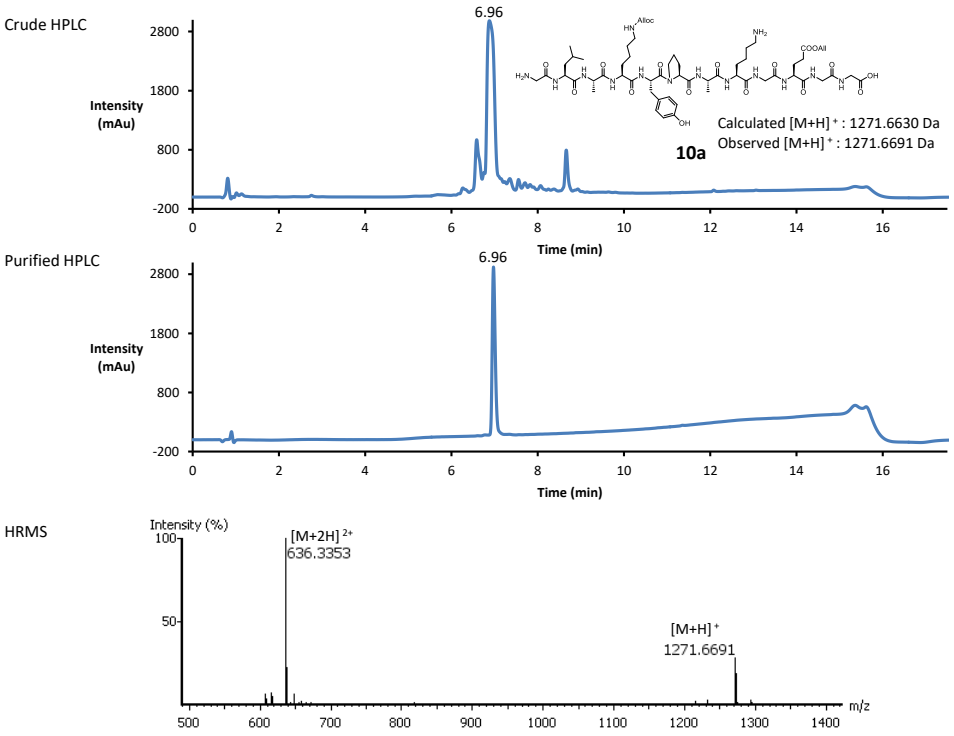


Figure S1. (Continued)

H-Gly-Leu-Ala-Lys-Tyr-Pro-Ala-Lys-Gly-Glu*-Gly-Gly-OH* (**10a**)



Cyclo [Gly-Leu-Ala-Lys-Tyr-Pro-Ala-Lys-Gly-Glu*-Gly-Gly]* (**10b**)

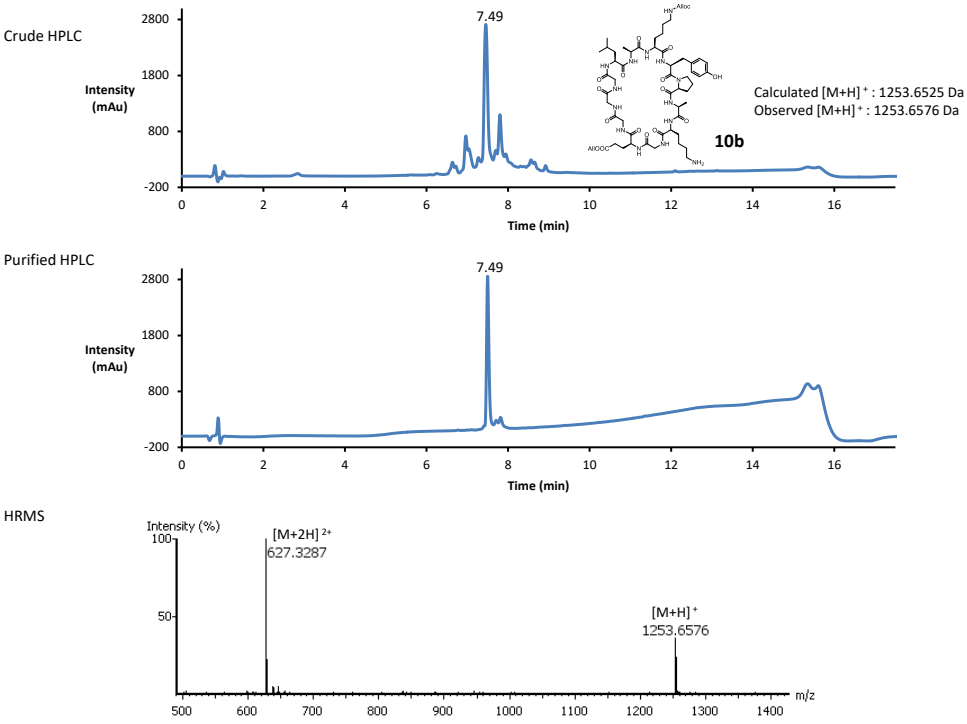
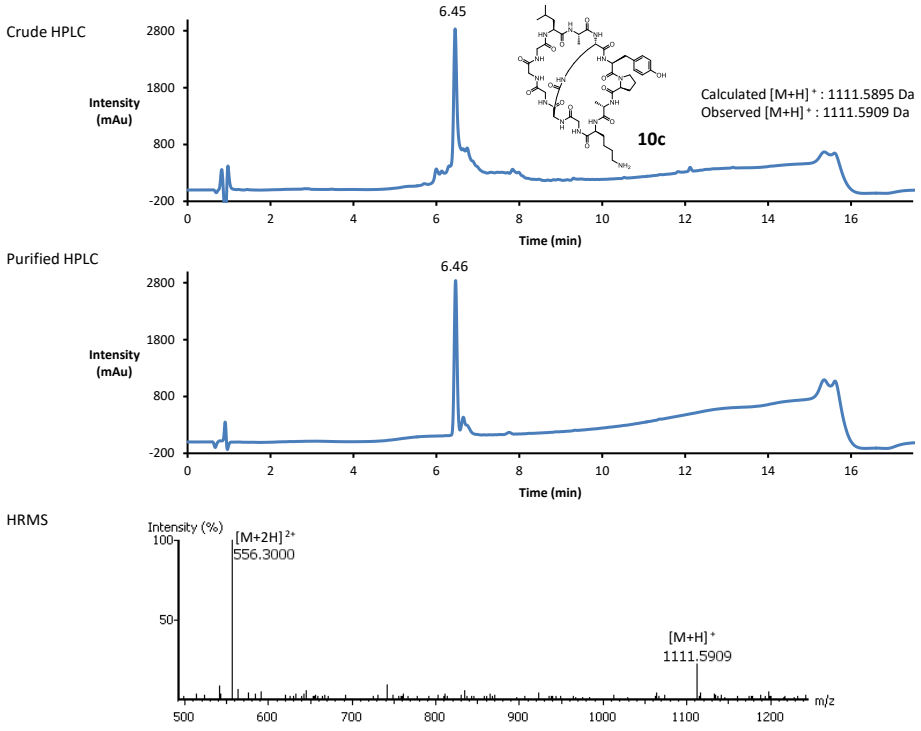


Figure S1. (Continued)

Cyclo [Gly-Leu-Ala- Cyclo [Lys-Tyr-Pro-Ala-Lys-Gly-Glu] -Gly-Gly] (**10c**)



H-Gly-Leu-Lys-Pro-Tyr-Gly-Lys-Gly-Glu*-Gly-OH* (**11a**)

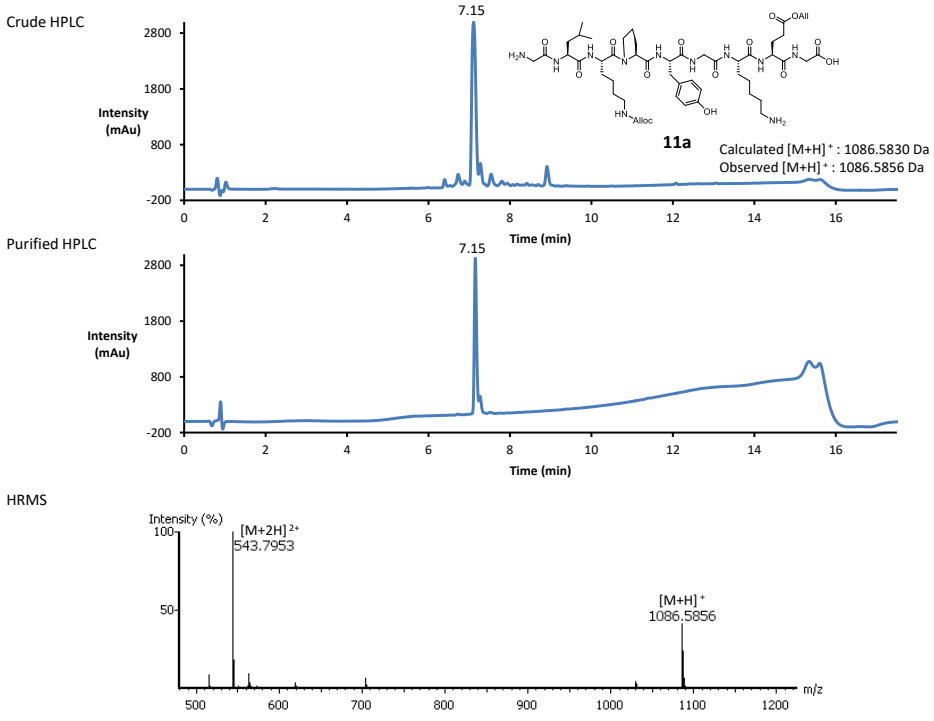
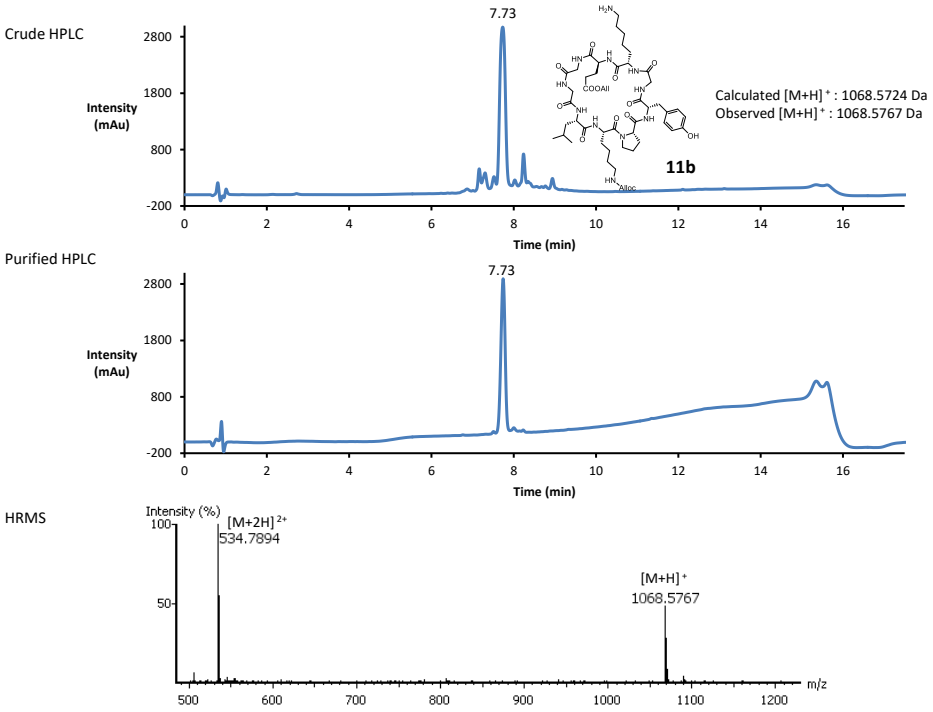


Figure S1. (Continued)

Cyclo [Gly-Leu-Lys-Pro-Tyr-Gly-Lys-Gly-Glu*-Gly]* (**11b**)



Cyclo [Gly-Leu- Cyclo [Lys-Pro-Tyr-Gly-Lys-Gly-Glu] -Gly] (**11c**)

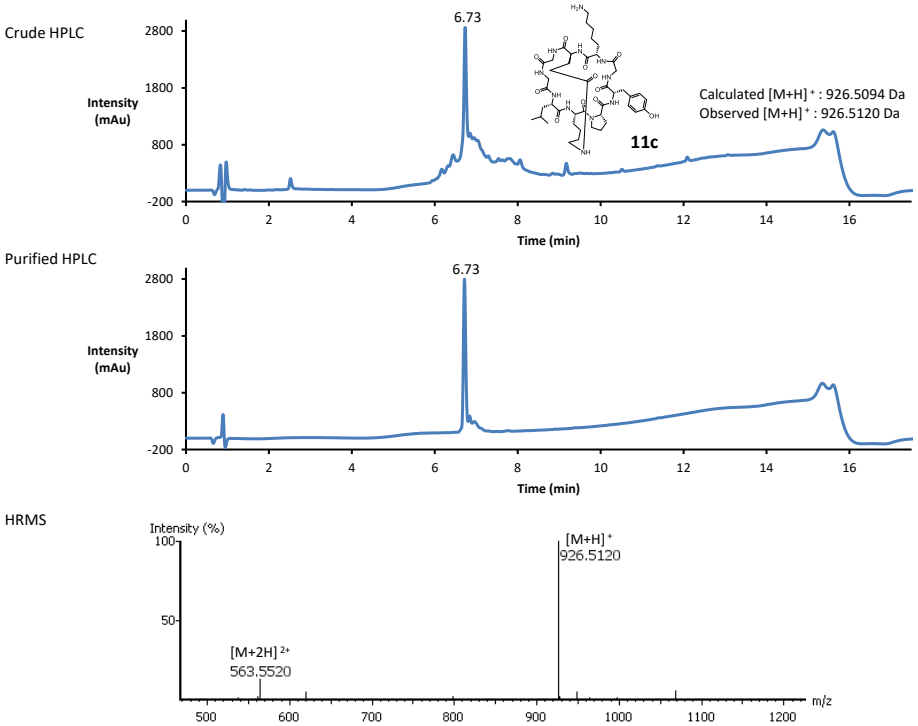
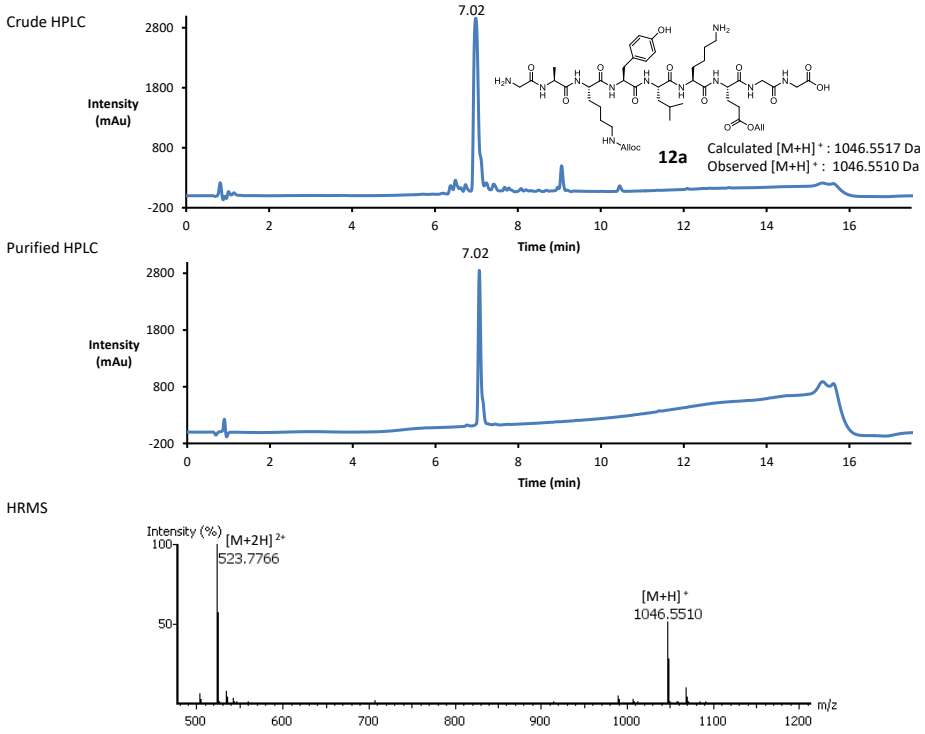


Figure S1. (Continued)

H-Gly-Ala-Lys-Tyr-Leu-Lys-Gly-Glu*-Gly-Gly-OH* (**12a**)



Cyclo [Gly-Ala-Lys-Tyr-Leu-Lys-Gly-Glu*-Gly-Gly]* (**12b**)

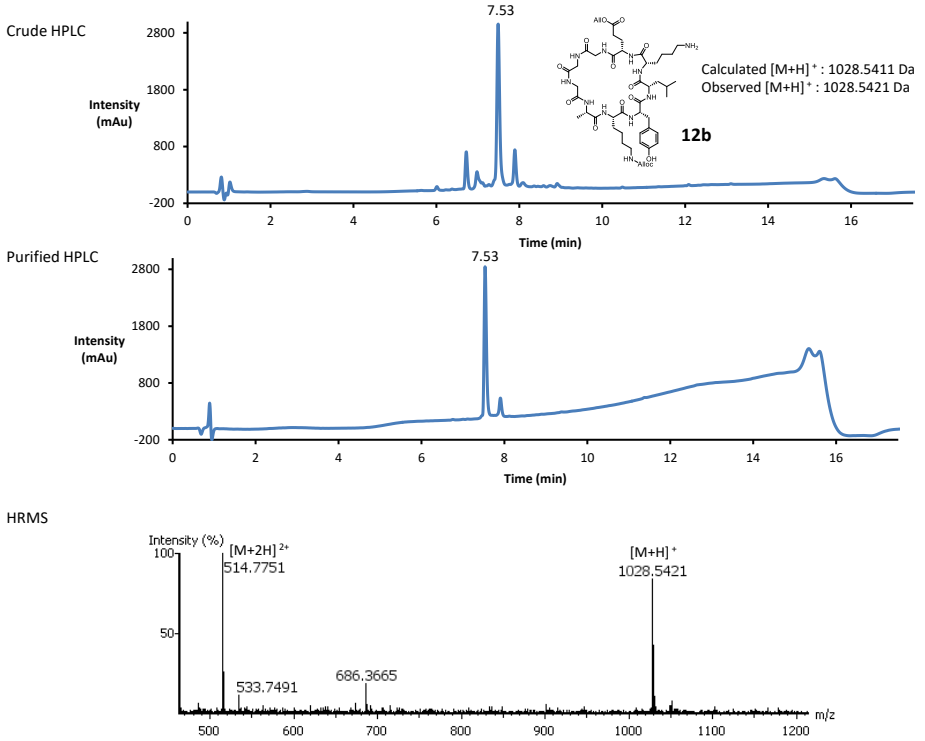
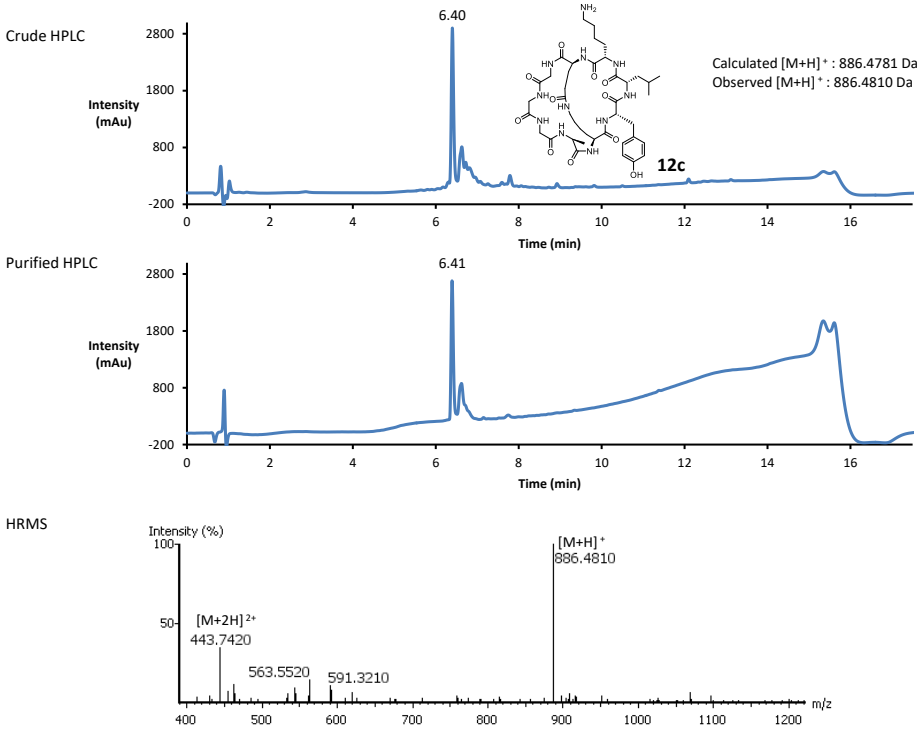


Figure S1. (Continued)

Cyclo [Gly-Ala- Cyclo [Lys-Tyr-Leu-Lys-Gly-Glu] -Gly-Gly] (**12c**)



H-Lys-Gly-Ala-Tyr-Leu-Lys-Gly-Glu*-Gly-Gly-OH* (**13a**)

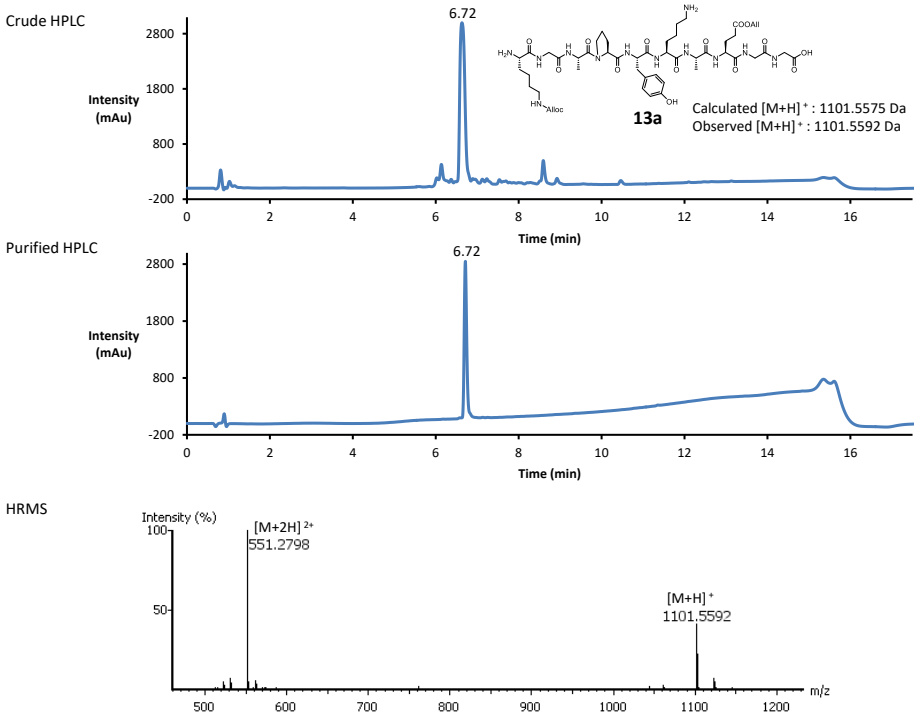
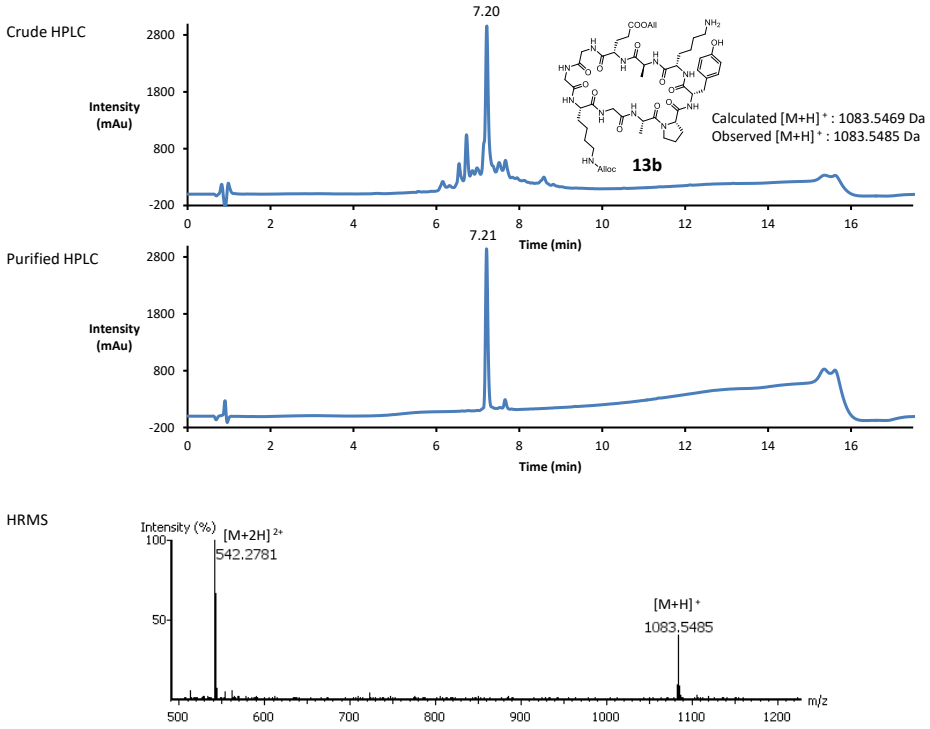


Figure S1. (Continued)

Cyclo [Lys-Gly-Ala-Tyr-Leu-Lys-Gly-Glu*-Gly-Gly]* (**13b**)



Cyclo [Cyclo [Lys-Gly-Ala-Tyr-Leu-Lys-Gly-Glu] -Gly-Gly] (**13c**)

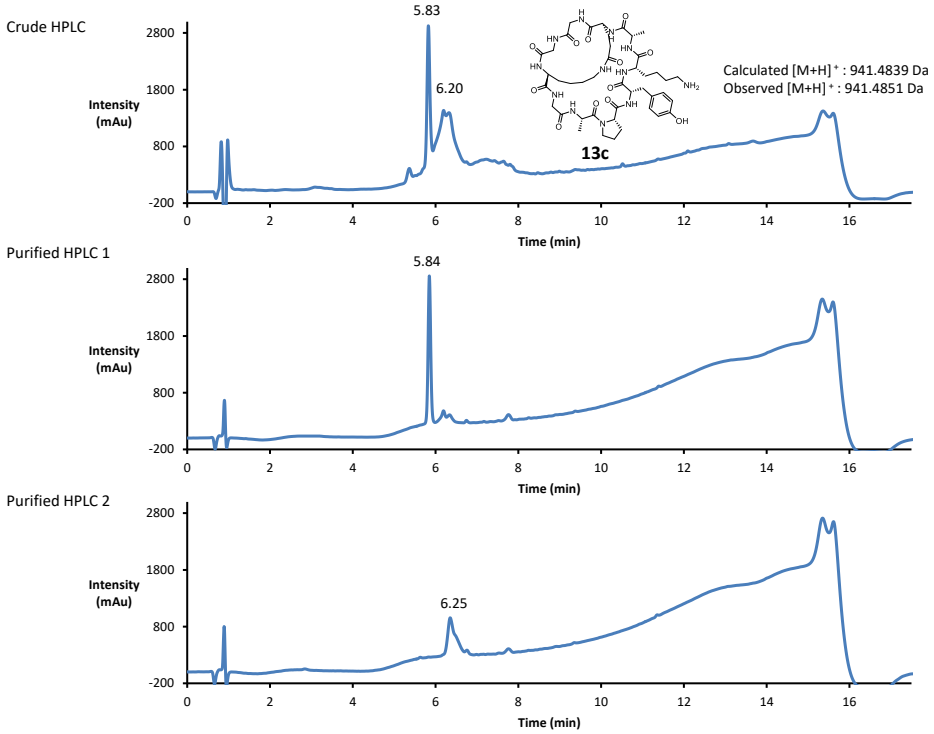
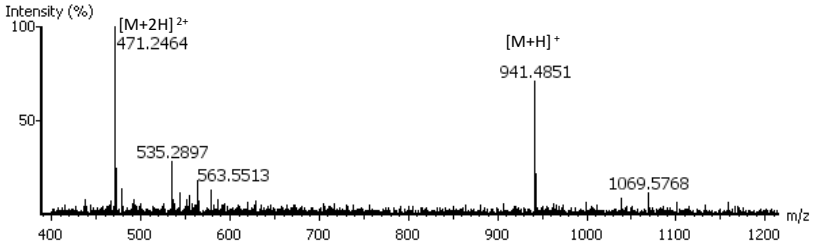


Figure S1. (Continued)

HRMS 1



HRMS 2

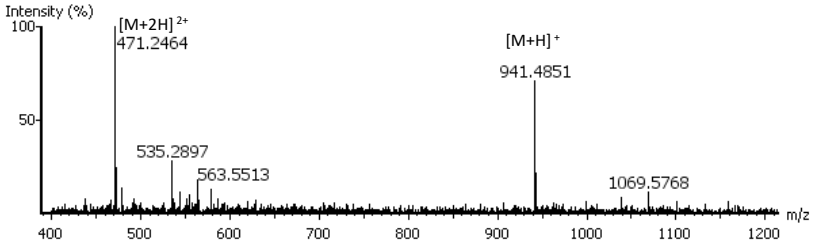


Figure S2. NMR ^{1}H and ^{13}C spectras.

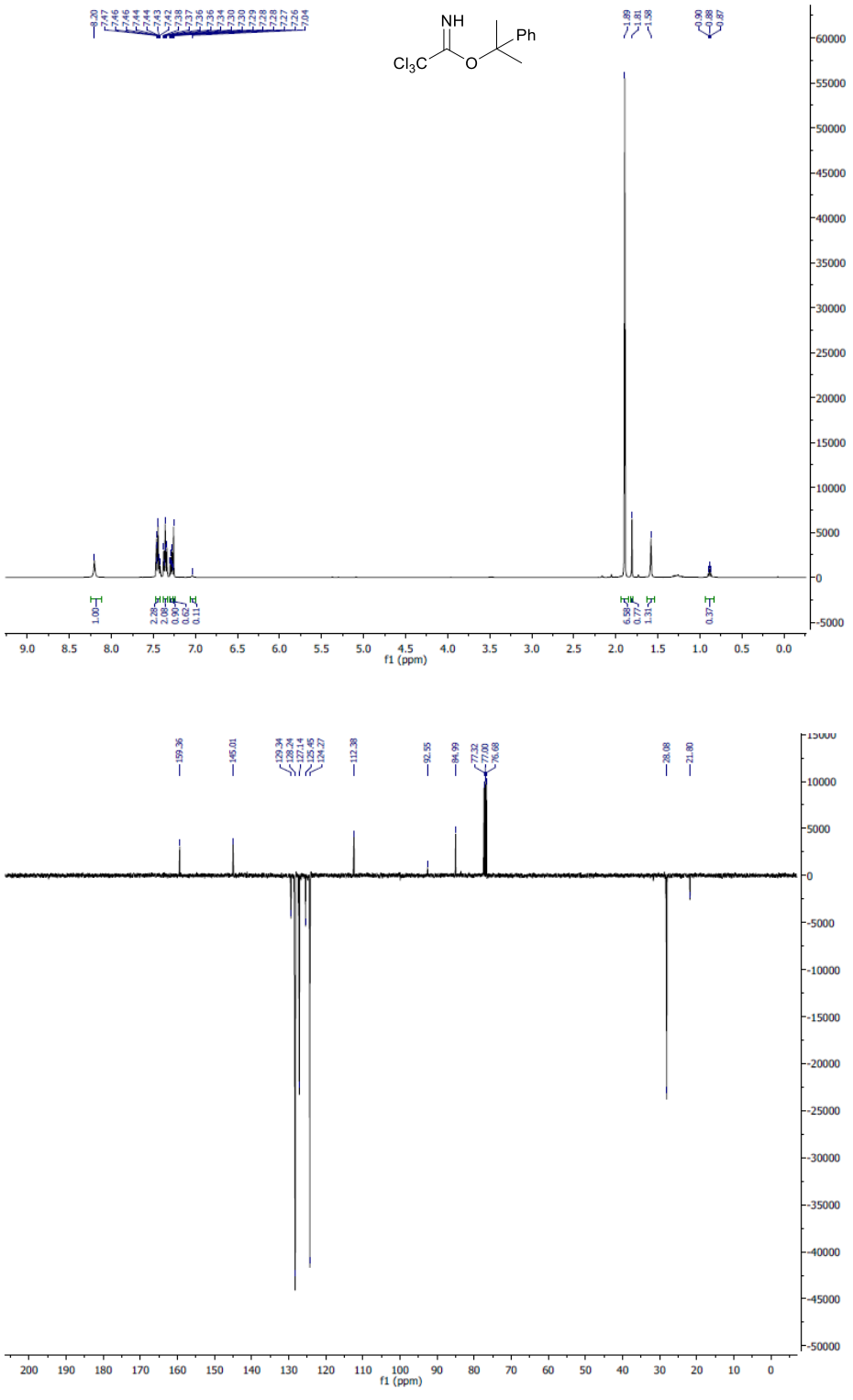


Figure S2. (Continued)

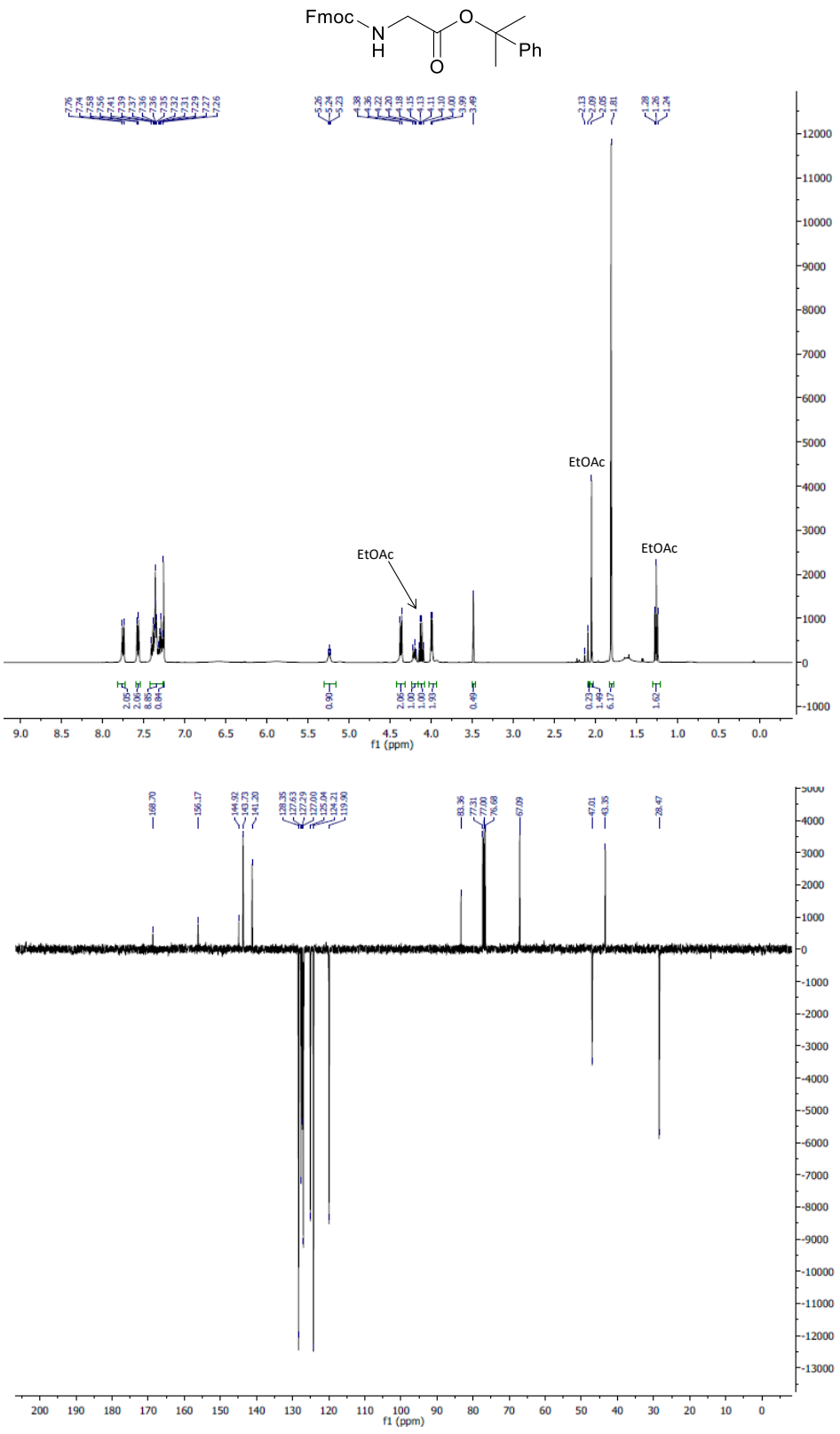


Figure S2. (Continued)