Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Ring closing metathesis of unprotected peptides

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General Experimental Information

General Considerations

Manipulation of organometallic compounds was performed using standard Schlenk techniques under an atmosphere of dry nitrogen or in a nitrogen-filled drybox.

Instrumentation

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on Bruker DRX400 or DRX600 spectrometers operating at 400 or 600 MHz respectively, as solutions in deuterated solvents as specified. Each resonance was assigned according to the following convention: chemical shift; multiplicity; observed coupling constants (*J* Hz); number of protons. Chemical shifts (δ), measured in parts per million (ppm), are reported relative to the residual proton peak in the solvent used as specified. Multiplicities are denoted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), septet (sept), multiplet (m) or prefixed broad (b), or a combination where necessary.

Low resolution electrospray ionisation (ESI) mass spectra were recorded on a Micromass Platform Electrospray mass spectrometer (QMS-quadrupole mass spectrometry) as solutions in specified solvents. Spectra were recorded in positive and negative modes (ESI^+ and ESI^-) as specified.

Reverse-phase high performance liquid chromatography (RP-HPLC) was performed on Agilent 1200 series instruments. For analytical experiments, the instrument was equipped with photodiode array (PDA) detection (controlled by ChemStation software) and an automated injector (100 μL loop volume). Experiments were carried out on a Vydac C18 analytical column (4.6 mm x 250 mm, 5 μm) at a flow rate of 1.5 mL min^{-1}. For preparative runs, the instrument used multivariable wavelength (MVW) detection (controlled by ChemStation software) and an Agilent unit injector (2 mL loop volume). Experiments were carried out on a Vydac C18 preparative column (22 mm x 250 mm, 10 μm) at a flow rate of 10 mL min^{-1}. The solvent systems were buffer A, 0.1% aqueous TFA; buffer B, 0.1% TFA in MeCN.

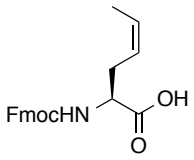
Solvents and Reagents

Dichloromethane (CH_2Cl_2) was supplied by Merck and distilled over CaH_2 prior to use. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were supplied by Merck and distilled over

potassium prior to use. Acetic acid (AcOH), acetone, acetonitrile (ACN), *tert*-butanol (^{t}BuOH), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), dimethylformamide (DMF), dioxane, ethyl acetate (EtOAc), hexane, methanol (CH_3OH) and *N*-methyl-2-pyrrolidone (NMP) were used as supplied by Merck. Dimethylacetamide (DMA), dimethylsulfoxide (DMSO), propylene carbonate, trifluoroacetic acid, (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium (**GII**) and (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium (**HGII**) were supplied by Sigma-Aldrich. D_2O, $(CD_3)_2SO$ and $CDCl_3$ were purchased from Cambridge Isotopes Laboratory.

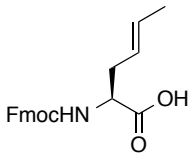
Experimental Section

(*S*,*Z*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)hex-4-enoic acid SI1



To a stirred solution of Fmoc-protected butynyl glycine (300 mg, 0.859 mmol) and quinolone (165 μL, 180 mg, 1.40 mmol) in EtOH (5 mL) was added Lindlar's catalyst (180 mg, 85.9 μmol). The reaction was charged with hydrogen through a balloon and stirred for 4 h at rt. The Lindlar's catalyst was removed *via* filtration through a celite plug and filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (50:50:1, hexane/EtOAc/AcOH) to provide the desired product **SI1** as an off-white solid (294 mg, 98%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.60-7.57 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 5.74-5.66 (m, 1H), 5.38-5.30 (m, 2H), 4.52-4.48 (m, 1H), 4.41 (d, *J* = 7.2 Hz, 2H), 4.22 (t, *J* = 7.2 Hz, 1H), 2.74-2.67 (m, 1H), 2.61-2.54 (m, 1H), 1.62 (d, *J* = 6.8 Hz, 3H), OH not observed. All data was consistent with that previously reported.[1]

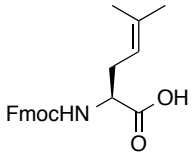
(*S*,*E*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)hex-4-enoic acid SI2



Butynyl glycine (300 mg, 2.36 mmol) was added to a three-neck flask with stir bar and the flask was cooled to -78 °C. A cold finger condenser with dry ice was added, and ammonia (3 mL) was distilled into the reaction vessel. Sodium metal (50 mg) was then added slowly to the reaction mixture until a deep blue colour was observed. The reaction was stirred for 4 h and allowed to slowly warm to rt. Once all ammonia had evaporated, the reaction vessel was cooled to 0 °C and placed under a positive nitrogen pressure before slow addition of H_2O (10 mL). $NaHCO_3$ (991 mg, 11.8 mmol) and acetone (5 mL) were then added to the stirred reaction mixture. A solution of Fmoc–OSu (795 mg, 2.36 mmol) in acetone (5 mL) was added at room temperature, and the reaction was stirred for 16 h. The mixture was acidified to pH 2 with aqueous 1 M HCl, and acetone was removed under reduced pressure. The resulting solution was extracted with EtOAc (40 mL), and the organic phase was washed with brine (40

mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by recrystallization from EtOAc to give titled compound **SI2** as a colorless solid (304 mg, 38%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.60-7.58 (m, 2H), 7.42-7.38 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 5.62-5.56 (m, 1H), 5.39-5.30 (m, 2H), 4.47-4.40 (m, 3H), 4.24 (t, *J* = 6.8 Hz, 1H), 2.57-2.51 (m, 2H), 1.68 (d, *J* = 6.0 Hz, 3H), OH not observed. All data was consistent with that previously reported.[1]

(*S*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-5-methylhex-4-enoic acid SI3



The Fmoc-protected prenyl glycine analogue **SI3** was synthesised by a modified procedure outlined by Robinson and coworkers.[2] A thick walled Schlenk vessel with stir bar was flushed with dry nitrogen. Allyl glycine (500 mg, 1.48 mmol) and dry CH_2Cl_2 (14 mL) were added to the vessel and lowered into a liquid nitrogen bath. **GII** (62 mg, 73.0 μmol) was added to the frozen substrate against the flow of nitrogen. The vessel was evacuated and backfilled with dry nitrogen three times before isobutylene (3 mL) was condensed into the vessel. The vessel was sealed and warmed to rt before being lowered into an oil bath at 40 °C. The reaction mixture was stirred for 12 h before the vessel was removed from the oil bath and cooled to rt. The excess isobutylene was carefully vented and the residue was purified by column chromatography (60:40:1, hexane/EtOAc/AcOH) to give **SI3** an off-white solid (438 mg, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.61-7.58 (m, 2H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 2H), 5.30 (d, *J* = 8.4 Hz, 1H), 5.09-5.03 (m, 1H), 4.50-4.45 (m, 1H), 4.41 (d, *J* = 6.8 Hz, 2H), 4.24 (t, *J* = 6.8 Hz, 1H), 2.69-2.62 (m, 1H), 2.56-2.49 (m, 1H), 1.73 (m, 3H), 1.63 (m, 3H), OH not observed. All data was consistent with that previously reported.[2]

General Procedure for Solid Phase Peptide Synthesis (SPPS)

Manual SPPS was performed in polypropylene Terumo syringes (5 mL) fitted with a porous (20 μm) polyethylene filter. Resin wash and filtering steps were aided by the use of a Visiprep SPE DL 24-port model vacuum manifold as supplied by Supelco. Capping reactions and cleavage mixtures were shaken on a KS125 basic KA elliptical shaker supplied by Labortechnik at 400 motions per minute.

Automated microwave-accelerated SPPS was carried out using a CEM Liberty-Discover synthesizer, involving the flow of dissolved reagents from external nitrogen pressurized bottles to a resin-containing microwave reactor vessel fitted with a porous filter. Coupling and deprotection reactions were carried out within this vessel and were aided by microwave energy. Each reagent delivery, wash, and evacuation step was carried out according to the automated protocols of the instrument (controlled by PepDriver software). In a 50 mL centrifuge tube, resin was swollen with DMF:CH_2Cl_2 (1:1; 10 mL, 1 x 60 min) and connected to the Liberty resin manifold. The Fmoc-amino acids (0.2 M in DMF), activators (0.5 M HATU: HOBt in DMF), activator base (2 M DIPEA in NMP), and deprotection agent (20% v/v piperidine in DMF) were solubilized in an appropriate volume of specified solvent as calculated by the PepDriver software program. The default microwave conditions used in the synthesis of each linear peptide included: initial deprotection (36 W, 37 °C, 2 min), deprotection (45 W, 75 °C, 10 min), preactivation (0 W, 25 °C, 2 min), and coupling (25 W, 75 °C, 10 min), or initial deprotection (40 W, 75 °C, 0.5 min), deprotection (40 W, 75 °C, 3 min), and coupling (20 W, 75 °C, 5 min). After sequence completion, the resin-bound peptides were automatically returned to the Liberty resin manifold as a suspension in DMF:DCM (1:1) and filtered through fritted plastic syringes (5 mL) for acid-mediated cleavage.

TFA Cleavage Procedure

A small aliquot of resin-bound peptide (approximately 3 mg) was suspended in cleavage solution (1 mL; 95:2.5:2.5; TFA:TIPS:water) and shaken gently for 2 h. The mixture was filtered through a fritted syringe and the beads rinsed with TFA (1 × 0.2 mL). The filtrate was concentrated under a constant stream of air, and the resultant oil was induced to precipitate in ice-cold Et_2O (1 mL). Cleaved peptides were collected by centrifugation (3 × 5 min) and dried for analysis by analytical RP-HPLC and mass spectrometry. For full-scale resin cleavages, 10 mL of cleavage solution was used, and after 4 h, the resin was rinsed with TFA (3 × 1 mL). The filtrate was concentrated under a constant stream of air, and the resultant oil was induced to precipitate in ice-cold Et_2O (30–35 mL). Collection by centrifugation was carried out over 5 × 6 min spin times. Cleaved peptides were collected by centrifugation at a speed of 6000 rpm on a Hermle Z200A centrifuge supplied by Medos, or at a speed of 6000 rpm on a TMC-1 mini centrifuge supplied by Thermoline.

General Procedure for Counter Ion Exchange of Peptides

Counter ion exchange was performed according to a modified procedure outlined by Alcalde and Dinarès.[3] In a sintered funnel, wet strongly basic ion exchange Amberlite IRA-400(OH)

(5 g) was washed with H_2O (50 mL) and H_2O:MeOH (1:1) (50 mL). A solution of 1% acid in 1:1 H_2O:MeOH was slowly passed through the resin until the eluent had the same pH value as the original selected acid solution. The resin was then transferred to a round-bottom flask and stirred in the 1% aqueous solution (50 mL) for a further 4 h at rt. The resin was filtered and washed generously with both H_2O:MeOH (1:1) (200 mL) and H_2O (500 mL) and allowed to air dry. In a separate round-bottom flask, the ion exchange resin was added to a stirred solution of peptide substrate in H_2O:MeOH (1:1) (5-10 mL) at rt. After 16 h, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The efficiency of the ion exchange was monitored by ^{19}F NMR spectroscopy.[3]

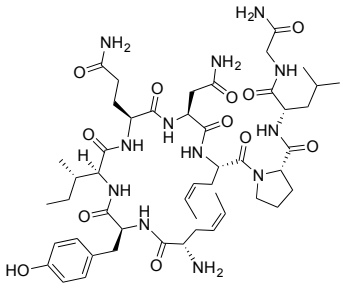
General Procedure for microwave accelerated solution phase RCM

RCM was carried out on a CEM Discover system fitted with the Benchmate option. Reactions were performed in 10 mL high pressure glass microwave vessels fitted with self-sealing Teflon septa as a pressure relief device. A microwave reactor vessel was loaded with substrate, deoxygenated solvent, deoxygenated chaotropic salt solution, and **GII** or **HGII** in an inert (nitrogen) environment. The system was sealed, and the reaction mixture irradiated with microwave energy while being stirred at a specified temperature for the specified period of time. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and then taken up in MeOH (0.1 mL) and precipitated with Et_2O (1 mL). Peptides were collected by centrifugation (1 × 5 min) and analysed by RP-HPLC and mass spectrometry.

General Procedure for solution phase RCM

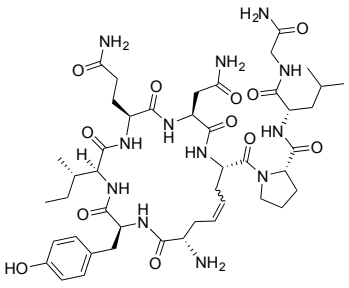
A Schlenk vessel was loaded with substrate, deoxygenated solvent, deoxygenated chaotropic salt solution, and **GII** in an inert (nitrogen) environment. The reaction mixture was stirred at a specified temperature for the specified period of time under a positive flow of nitrogen. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, taken up in a small amount of MeOH and precipitated with Et_2O. Peptides were collected by centrifugation (1 × 5 min) and analysed by RP-HPLC and mass spectrometry.

[1,6]-*Z*-Crt Oxytocin 6



Synthesis of the linear sequence **6** was performed according to the manual SPPS procedure described previously using Fmoc-Rink amide resin (50 μmol). Following synthesis, the peptide underwent acid-mediated cleavage to provide an off-white solid. The crude peptide was purified by RP-HPLC (Agilent Vydac C18 preparative column, 10-40% buffer B over 45 min, t_R = 20.0 min). Selected fractions were combined and lyophilized to give the desired peptide **6** (16.4 mg). Mass spectrum (ESI$^+$, MeCN:H_2O:HCOOH): *m/z* 1025.6 $[M + H]^+$, ($C_{49}H_{76}N_{11}O_{13}$) theoretical 1025.6. RP-HPLC (Agilent Vydac C18 analytical column, 15-50% buffer B over 35 min): t_R = 10.9 min. ^{1}H-NMR (600 MHz, D_2O): δ 7.13 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.83-5.77 (m, 1H), 5.73-5.67 (m, 1H), 5.39-5.35 (m, 1H), 5.32-5.28 (m, 1H), 4.71-4.66 (m, 1H), 4.63 (dd, *J* = 7.8, 6.0 Hz, 1H), 4.43 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.33 (dd, *J* = 9.6, 5.4 Hz, 1H), 4.22 (t, *J* = 7.2 Hz, 1H), 4.07-4.05 (m, 2H), 3.91 (q, *J* = 17.4 Hz, 2H), 3.79 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.68 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.02-2.95 (m, 2H), 2.81 (dd, *J* = 15.6, 5.4 Hz, 1H), 2.73 (dd, *J* = 15.6, 8.4 Hz, 1H), 2.70-2.62 (m, 2H), 2.60-2.55 (m, 1H), 2.48-2.43 (m, 1H), 2.25 (t, *J* = 7.8 Hz, 2H), 2.32-2.27 (m, 1H), 2.10-1.91 (m, 5H), 1.75-1.66 (m, 4H), 1.64 (d. *J* = 7.2 Hz, 3H), 1.60 (d. *J* = 6.0 Hz, 3H), 1.47-1.41 (m, 1H), 1.16-1.08 (m, 1H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.86-0.84 (m, 6H), 16 protons not observed.

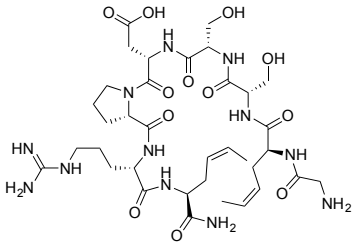
[1,6]-Dicarba Oxytocin 1



Linear peptide **6** was subjected to HBF_4 ion exchange conditions followed by the solution phase RCM procedure described previously under the following conditions: linear peptide **6** (65 mg, 59 μmol), DMF (6.5 mL), 0.4 M LiCl in DMF (0.6 mL), **GII** (15 mg, 17 μmol), 100

°C, 4 h. The crude reaction mixture was analysed (RP-HPLC (Agilent Vydac C18 analytical column, 15-50% buffer B over 35 min): t_R = 5.4 and 6.1 min.) and purified by RP-HPLC (Agilent Vydac C18 preparative column, 10-40% buffer B over 45 min, t_R = 20.8, 25.7 min). Selected fractions were combined and lyophilized to give the target peptide **1** as a colourless solid (31 mg). RP-HPLC and mass spectral analysis of the peptide supported formation of the required unsaturated carbocycle **1** in quantitative conversion (55:45; *cis*:*trans*). Mass spectrum (ESI$^+$, MeCN:H_2O:HCOOH): *m/z* 969.5 $[M + H]^+$, ($C_{45}H_{69}N_{12}O_{12}$) theoretical 969.5; 485.3 $[M + 2H]^{2+}$, ½ ($C_{45}H_{70}N_{12}O_{12}$) theoretical 485.3. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 9.9 and 10.7 min. ^{1}H-NMR (600 MHz, D_2O): δ 7.24-7.21 (m, 2H), 6.90-6.88 (m, 2H), 5.71-5.52 (m, 2H), 4.68-4.57 (m, 1H), 4.47-4.29 (m, 3H), 4.15-4.13 (m, 1H), 4.10-4.07 (m, 1H), 4.02 (d, *J* = 6.0 Hz, 1H), 3.95 (dd, *J* = 17.1, 4.2 Hz, 1H), 3.89 (d, *J* = 17.1 Hz, 1H), 3.76-3.71 (m, 1H), 3.67-3.61 (m, 1H), 3.21-3.14 (m, 1H), 3.06-3.02 (m, 1H), 3.01-3.86 (m, 1H), 2.84-2.74 (m, 2H), 2.66-2.51 (m, 2H), 2.48-2.28 (m, 4H), 2.15-1.87 (m, 7H), 1.74-1.60 (m, 3H), 1.44-1.23 (m, 1H), 1.17-1.00 (m, 1H), 0.96 (d, *J* = 5.4 Hz, 3H), 0.92-0.88 (m, 9H), 16 protons not observed. All data was consistent with that previously reported.[4,5]

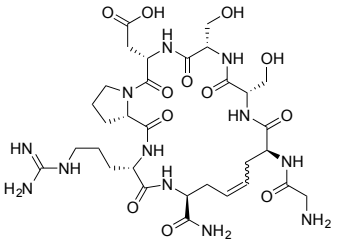
[2,8]-*Z*-Crt-[3]-Ser Conotoxin Vc1.1 (1-8) SI4



Synthesis of the linear sequence **SI4** was performed according to the microwave accelerated SPPS procedure described previously using Fmoc-Rink amide resin (100 μmol). Following synthesis, the peptide underwent acid-mediated cleavage to provide an off-white solid. The crude peptide was purified by RP-HPLC (Agilent Vydac C18 preparative column, 5-35% buffer B over 45 min, t_R = 16.2 min). Selected fractions were combined and lyophilized to give the target peptide **SI4** as a colourless solid (22.4 mg). Mass spectrum (ESI$^+$, MeCN, H_2O, HCOOH): *m/z* 839.4 $[M + H]^+$, ($C_{35}H_{59}N_{12}O_{12}$) theoretical 839.4; 420.3 $[M + 2H]^{2+}$, ½ ($C_{35}H_{60}N_{12}O_{12}$) theoretical 420.2. RP-HPLC (Agilent Vydac C18 analytical column, 0-30% buffer B over 30 min): t_R = 14.3 min. ^{1}H-NMR (600 MHz, D_2O): 5.75-5.69 (m, 2H), 5.42-5.36 (m, 2H), 4.99 (t, *J* = 7.2 Hz, 1H), 4.52 (t, *J* = 5.4 Hz, 1H), 4.48-4.43 (m, 3H), 4.33-4.30 (m, 2H), 3.93-3.76 (m, 8H), 3.25-3.21 (m, 2H), 2.94 (dd, *J* = 16.8, 7.2 Hz, 1H), 2.73 (dd, *J* = 16.8, 7.2 Hz, 1H), 2.65-2.60 (m, 2H), 2.58-2.50 (m, 2H), 2.34-2.28 (m, 1H), 2.07-2.01 (m,

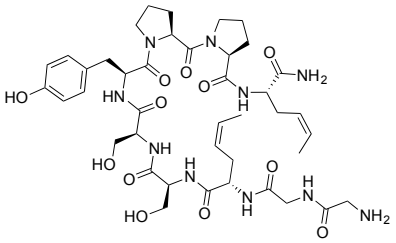
2H), 2.00-1.95 (m, 1H), 1.91-1.85 (m, 1H), 1.82-1.76 (m, 1H), 1.70-1.64 (m, 2H), 1.62 (dd, *J* = 6.6, 1.2 Hz, 3H), 1.60 (dd, *J* = 6.6, 1.2 Hz, 3H), 17 protons not observed.

[2,8]-Dicarba-[3]-Ser Conotoxin Vc1.1 (1-8) 2



Linear peptide **SI4** was subjected to HBF_4 ion exchange conditions followed by the solution phase RCM procedure described previously under the following conditions: linear peptide **SI4** (11.5 mg, 12.1 μmol), DMF (1 mL), 0.4 M LiCl in DMF (0.1 mL), **GII** (3.1 mg, 3.7 μmol), 100 °C, 4 h. RP-HPLC and mass spectral analysis of the peptide supported formation of the required unsaturated carbocycle **2** in quantitative conversion (isomers inseparable). Mass spectrum (ESI$^+$, MeCN:H_2O:HCOOH): *m/z* 783.4 $[M + H]^+$, ($C_{31}H_{51}N_{12}O_{12}$) theoretical 783.4; 392.3 $[M + 2H]^{2+}$, ½ ($C_{31}H_{52}N_{12}O_{12}$) theoretical 392.2. RP-HPLC (Agilent Vydac C18 analytical column, 0-30% buffer B over 30 min): t_R = 6.2 min.

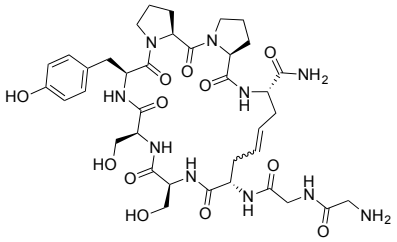
[3,9]-*Z*-Crt-[4]-Ser Conotoxin Pu1.2 (1-9) SI5



Synthesis of the linear sequence **SI5** was performed according to the microwave accelerated SPPS procedure described previously using Fmoc-Rink amide resin (100 μmol). Following synthesis, the peptide underwent acid-mediated cleavage to provide an off-white solid. The crude peptide was purified by RP-HPLC (Agilent Vydac C18 preparative column, 5-35% buffer B over 30 min, t_R = 20.8 min). Selected fractions were combined and lyophilized to give the target peptide **SI5** as a colourless solid (44.5 mg). Mass spectrum (ESI$^+$, MeCN, H_2O, HCOOH): *m/z* 885.5 $[M + H]^+$, ($C_{40}H_{61}N_{10}O_{12}$) theoretical 885.4. RP-HPLC (Agilent Vydac C18 analytical column, 5-35% buffer B over 30 min): t_R = 15.4 min. ^{1}H-NMR (600 MHz, D_2O): 7.17 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.75-5.66 (m, 2H), 5.43-5.35 (m, 2H), 4.49-4.38 (m, 4H), 4.05 (s, 2H), 3.90 (s, 2H), 3.89-3.78 (m, 5H), 3.75 (d, *J* = 5.4 Hz, 1H), 3.67-3.39 (m, 3H), 3.10 (dd, *J* = 14.4, 4.8 Hz, 1H), 2.92-2.90 (m, 1H), 2.81 (dd, *J* = 14.4,

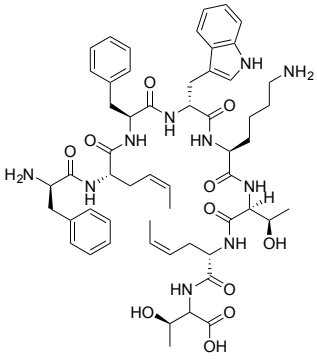
9.0 Hz, 1H), 2.64-2.48 (m, 4H), 2.39-2.28 (m, 2H), 2.10-2.00 (m, 4H), 1.98-1.92 (m, 2H), 1.89-1.73 (m, 1H), 1.65-1.57 (m, 6H), 13 protons not observed.

[3,9]-Dicarba-[4]-Ser Conotoxin Pu1.2 (1-9) 3



Linear peptide **SI5** was subjected to HBF_4 ion exchange conditions followed by the solution phase RCM procedure described previously under the following conditions: linear peptide **SI5** (12.5 mg, 12.5 μmol), DMF (1 mL), 0.4 M LiCl in DMF (0.1 mL), **GII** (3.2 mg, 3.8 μmol), 100 °C, 4 h. RP-HPLC and mass spectral analysis of the peptide supported formation of the required unsaturated carbocycle **3** in an 86% conversion (isomers inseparable). Mass spectrum (ESI^+, MeCN:H_2O:HCOOH): *m/z* 829.3 $[M + H]^+$, ($C_{37}H_{53}N_{10}O_{12}$) theoretical 829.4. RP-HPLC (Agilent Vydac C18 analytical column, 5-35% buffer B over 30 min): t_R = 11.0 min.

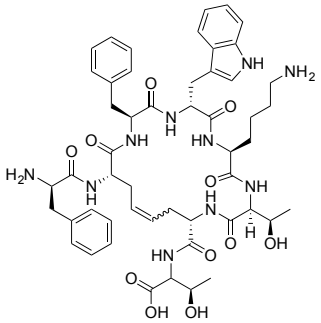
[2,7]-*Z*-Crt Octreotate SI6



Synthesis of the linear sequence **SI6** was performed according to the microwave accelerated SPPS procedure described previously using Fmoc-Rink amide resin (100 μmol). Following synthesis, the peptide underwent acid-mediated cleavage to provide an off-white solid. The crude peptide was purified by RP-HPLC (Agilent Vydac C18 preparative column, 15-45% buffer B over 40 min, t_R = 26.9 min). Selected fractions were combined and lyophilized to give the target peptide **SI6** as a colourless solid (35 mg). Mass spectrum (ESI^+, MeCN, H_2O, HCOOH): *m/z* 1051.6 $[M + H]^+$, ($C_{55}H_{75}N_{10}O_{11}$) theoretical 1051.6; 526.3 $[M + 2H]^{2+}$, ½ ($C_{55}H_{76}N_{10}O_{11}$) theoretical 526.3. RP-HPLC (Agilent Vydac C18 analytical column, 15-50% buffer B over 35 min): t_R = 19.5 min. ^{1}H-NMR (600 MHz, D_2O): 7.60-7.50 (m, 1H), 7.45-

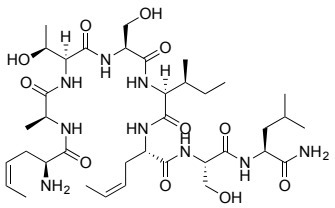
7.40 (m, 3H), 7.36-7.34 (m, 2H), 7.32-7.25 (m, 5H), 7.20-7.15 (m, 4H), 5.70-5.65 (m, 1H), 5.55-5.50 (m, 1H), 5.38-5.34 (m, 1H), 4.52-4.48 (m, 2H), 4.44 (d, *J* = 3.6 Hz, 1H), 4.39-4.35 (m, 1H), 4.30 (d. *J* = 6.0 Hz, 1H), 4.28-4.22 (m, 2H), 4.19-4.15 (m, 1H), 4.09 (dd, *J* = 9.0, 4.8 Hz, 1H), 3.26-3.23 (m, 1H), 3.15 (dd, *J* = 11.4, 9.0 Hz, 1H), 3.05 (t, *J* = 10.8 Hz, 1H), 2.98-2.94 (m, 3H), 2.79-2.70 (m, 2H), 2.64-2.60 (m, 1H), 2.52-2.47 (m, 1H), 2.26-2.21 (m, 1H), 2.16-2.12 (m, 1H), 1.63-1.62 (m, 1H), 1.59 (d, *J* = 6.0 Hz, 3H), 1.55-1.50 (m, 2H), 1.46 (d, *J* = 6.0 Hz, 3H), 1.40-1.39 (m, 3H), 1.26-1.23 (m, 2H), 1.20-1.18 (m, 6H), 15 protons not observed.

[2,7]-Dicarba Octreotate 4



Linear peptide **SI6** was subjected to HBF_4 ion exchange conditions followed by the solution phase RCM procedure described previously under the following conditions: linear peptide **SI6** (12.3 mg, 11.1 μmol), DMF (1 mL), 0.4 M LiCl in DMF (0.1 mL), **GII** (2.7 mg, 3.2 μmol), 100 °C, 4 h. RP-HPLC and mass spectral analysis of the peptide supported formation of the required unsaturated carbocycle **4** in an 96% conversion (isomers inseparable). Mass spectrum (ESI^+, MeCN:H_2O:HCOOH): *m/z* 995.6 $[M + H]^+$, ($C_{51}H_{67}N_{10}O_{11}$) theoretical 995.5; 498.5 $[M + 2H]^{2+}$, ½ ($C_{51}H_{68}N_{10}O_{11}$) theoretical 498.2. RP-HPLC (Agilent Vydac C18 analytical column, 15-50% buffer B over 35 min): t_R = 10.6 min.

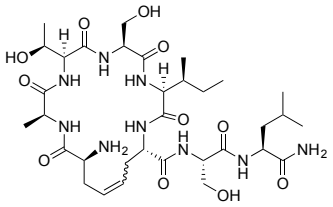
[1,6]-*Z*-Crt-[2]-Ala Human Insulin A Chain (6-13) SI7



Synthesis of the linear sequence **SI7** was performed according to the microwave accelerated SPPS procedure described previously using Fmoc-Rink amide resin (100 μmol). Following synthesis, the peptide underwent acid-mediated cleavage to provide an off-white solid. The crude peptide was purified by RP-HPLC (Agilent Vydac C18 preparative column, 10-40%

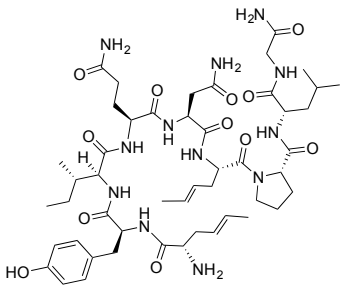
buffer B over 45 min, t_R = 27.1 min). Selected fractions were combined and lyophilized to give the target peptide **SI7** as a colourless solid (6.2 mg). Mass spectrum (ESI^+, MeCN, H_2O, HCOOH): *m/z* 812.4 $[M + H]^+$, ($C_{37}H_{66}N_9O_{11}$) theoretical 812.5. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 15.7 min. ^{1}H-NMR (600 MHz, D_2O): 5.86-5.81 (m, 1H), 5.73-5.67 (m, 1H), 5.40-5.34 (m, 2H), 4.54-4.45 (m, 3H), 4.38-4.33 (m, 3H), 4.25-4.23 (m, 1H), 4.22 (d, *J* = 7.8 Hz, 1H), 4.08 (t, *J* = 6.6 Hz, 1H), 3.91-3.82 (m, 4H), 2.75-2.65 (m, 2H), 2.63-2.53(m, 1H), 2.53-2.48 (m, 1H), 1.93-1.88 (m, 1H), 1.72-1.66 (m, 3H), 1.64 (dd, *J* = 7.2, 1.2 Hz, 3H), 1.60 (dd, *J* = 6.6, 1.2 Hz, 3H), 1.50-1.46 (m, 1H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.22-1.18 (m, 1H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 5.4 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H), 14 protons not observed.

[1,6]-Dicarba-[2]-Ala Human Insulin A Chain (6-13) 5



Linear peptide **SI7** was subjected to HBF_4 ion exchange conditions followed by the solution phase RCM procedure described previously under the following conditions: linear peptide **SI7** (5.4 mg, 5.8 μmol), DMF (1 mL), 0.4 M LiCl in DMF (0.1 mL), **GII** (1.5 mg, 1.8 μmol), 100 °C, 4 h. RP-HPLC and mass spectral analysis of the peptide supported formation of the required unsaturated carbocycle **5** in quantitative conversion (isomers inseparable). Mass spectrum (ESI^+, MeCN:H_2O:HCOOH): *m/z* 756.5 $[M + H]^+$, ($C_{33}H_{58}N_9O_{11}$) theoretical 756.4. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 10.0 min.

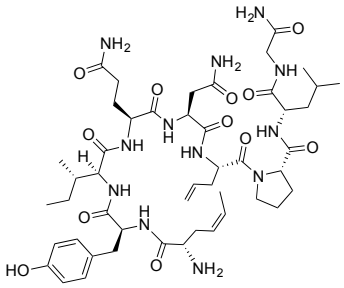
[1,6]-*E*-Crt Oxytocin 7



Synthesis of the linear sequence **7** was performed according to the manual SPPS procedure described previously using Fmoc-Rink amide resin (50 μmol). Following synthesis, the

peptide underwent acid-mediated cleavage to provide an off-white solid. The crude peptide was purified by RP-HPLC (Agilent Vydac C18 preparative column, 10-40% buffer B over 45 min, t_R = 21.4 min). Selected fractions were combined and lyophilized to give the desired peptide **7** (19.0 mg). Mass spectrum (ESI$^+$, MeCN:H_2O:HCOOH): *m/z* 1025.7 [M + H]$^+$, ($C_{49}H_{77}N_{11}O_{13}$) theoretical 1025.6; 513.5 [M + 2H]$^{2+}$, ½($C_{49}H_{78}N_{11}O_{13}$) theoretical 513.3. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 16.2 min. ^{1}H-NMR (600 MHz, D_2O): δ 7.13 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.74-5.63 (m, 2H), 5.42-5.37 (m, 1H), 5.33-5.28 (m, 1H), 4.71-4.65 (m, 1H), 4.59 (dd, *J* = 7.8, 5.4 Hz, 1H), 4.43 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.33 (dd, *J* = 9.6, 5.4 Hz, 1H), 4.23 (t, *J* = 7.2 Hz, 1H), 4.07 (d, *J* = 9.0 Hz, 1H), 4.03 (t, *J* = 6.6 Hz, 1H), 3.91 (q, *J* = 16.8 Hz, 2H), 3.77 (dt, *J* = 9.6, 7.2 Hz, 1H), 3.67 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.02-2.95 (m, 2H), 2.81 (dd, *J* = 15.6, 6.0 Hz, 1H), 2.73 (dd, *J* = 15.6, 7.8 Hz, 1H), 2.60-2.53 (m, 2H), 2.49-2.45 (m, 1H), 2.36 (t, *J* = 7.8 Hz, 3H), 2.32-2.26 (m, 1H), 2.10-1.92 (m, 6H), 1.77-1.69 (m, 3H), 1.67-1.65 (m, 6H), 1.64-1.60 (m, 1H), 1.48-1.42 (m, 1H), 1.17-1.10 (m, 1H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.87-0.84 (m, 6H), 16 protons not observed.

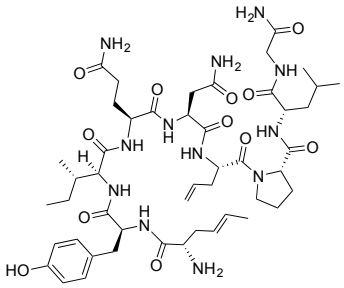
[1]-*Z*-Crt-[6]-Agl Oxytocin 8



Synthesis of the linear sequence **8** was performed according to the microwave accelerated SPPS procedure described previously using Fmoc-Rink amide resin (100 μmol). Following synthesis, the peptide underwent acid-mediated cleavage to provide an off-white solid. The crude peptide was purified by RP-HPLC (Agilent Vydac C18 preparative column, 10-30% buffer B over 40 min, t_R = 21.0 min). Selected fractions were combined and lyophilized to give the desired peptide **8**. (28.8 mg). Mass spectrum (ESI$^+$, MeCN:H_2O:HCOOH): *m/z* 1011.7 [M + H]$^+$, ($C_{48}H_{75}N_{12}O_{12}$) theoretical 1011.6; 506.6 [M + 2H]$^{2+}$, ½ ($C_{48}H_{76}N_{12}O_{12}$) theoretical 506.3. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 14.3 min. H-NMR (600 MHz, D_2O): δ 7.13 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.83-5.75 (m, 2H), 5.30 (qd, *J* = 7.2. 12.0 Hz, 1H), 5.22 (dd, *J* = 16.8, 1.2, 1H), 5.17 (d, *J* =10.2 Hz, 1H), 4.71-4.65 (m, 1H), 4.43 (dd, *J* = 8.4, 5.7 Hz, 1H), 4.33 (dd, *J* = 9.6, 5.7 Hz, 1H), 4.23 (t, *J* = 7.8 Hz, 1H), 4.07-4.048 (m, 2H), 3.91 (q, *J* = 16.8 Hz, 2H), 3.79 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.68 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.02-2.95 (m, 2H), 2.80 (dd, *J* = 15.6, 6.0

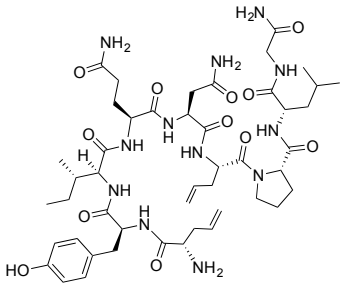
Hz, 1H), 2.73 (dd, *J* = 15.6, 8.4 Hz, 1H), 2.70-2.62 (m, 2H), 2.58-2.54 (m, 1H), 2.46-2.41 (m, 1H), 2.35 (t, *J* = 7.8 Hz, 2H), 2.32-2.26 (m, 1H), 2.10-1.90 (m, 6H), 1.76-1.61 (m, 5H), 1.60 (dd, *J* = 7.2, 1.2 Hz, 3H), 1.46-1.42 (m, 1H), 1.15-1.08 (m 1H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.86-0.84 (m, 6H), 16 protons not observed.

[1]-*E*-Crt-[6]-Agl Oxytocin 9



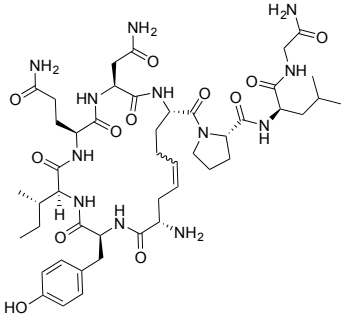
Synthesis of the linear sequence **9** was performed according to the microwave accelerated SPPS procedure described previously using Fmoc-Rink amide resin (100 μmol). Following synthesis, the peptide underwent acid-mediated cleavage to provide an off-white solid. The crude peptide was purified by RP-HPLC (Agilent Vydac C18 preparative column, 10-30% buffer B over 40 min, t_R = 21.7 min). Selected fractions were combined and lyophilized to give the desired peptide **9** (58.1 mg). Mass spectrum (ESI^+, MeCN:H_2O:HCOOH): *m/z* 1011.6 $[M + H]^+$, ($C_{48}H_{75}N_{12}O_{12}$) theoretical 1011.6. RP-HPLC (Agilent Vydac C18 analytical column, 10-30% buffer B over 40 min): t_R = 18.3 min. ^{1}H-NMR (600 MHz, D_2O): δ 7.13 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.82-5.75 (m, 1H), 5.74-5.68 (m, 1H), 5.30 (dtd, *J* = 16.2, 7.2, 1.8 Hz, 1H), 5.22 (dd, *J* = 16.2, 1.8 Hz, 1H), 5.17 (d, *J* = 10.8 Hz, 1H), 4.66 (t, *J* = 7.8 Hz, 1H), 4.42 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.33 (dd, *J* = 9.3, 5.4 Hz, 1H), 4.23 (dd, *J* = 7.8, 6.6 Hz, 1H), 4.07 (d, *J* = 9.3 Hz, 1H), 4.03 (t, *J* = 6.0 Hz, 1H), 3.91 (q, *J* = 16.8 Hz, 2H), 3.79 (dt, *J* = 10.2, 7.2 Hz, 1H), 3.68 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.02-2.95 (m, 2H), 2.80 (dd, *J* = 16.2, 6.0 Hz, 1H), 2.73 (dd, *J* = 16.2, 8.4 Hz, 1H), 2.58-2.54 (m, 3H), 2.47-2.41 (m, 1H), 2.35 (t, *J* = 7.8 Hz, 2H), 2.32-2.26 (m, 1H), 2.09-1.92 (m, 6H), 1.76-1.68 (m, 3H), 1.67 (d, *J* = 6.6 Hz, 3H), 1.64-1.60 (m, 2H), 1.47-1.43 (m, 1H), 1.16-1.11 (m, 1H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.87-0.84 (m, 6H), 16 protons not observed.

[1,6]-Agl Oxytocin 10



Synthesis of the linear sequence **10** was preformed according to the microwave accelerated SPPS procedure described previously using Fmoc-Rink amide resin (100 μmol). Following synthesis, the peptide underwent acid-mediated cleavage to provide an off-white solid. The solid was purified by RP-HPLC (Agilent Vydac C18 preparative column, 0-30% buffer B over 45 min, t_R = 17.3 min). Selected fractions were combined and lyophilized to give the desired peptide **10** (24 mg). Mass spectrum (ESI^+, MeCN:H_2O:HCOOH): *m/z* 997.5 $[M + H]^+$, ($C_{47}H_{73}N_{12}O_{12}$) theoretical 997.5; 499.4 $[M + 2H]^{2+}$, ½ ($C_{47}H_{74}N_{12}O_{12}$) theoretical 499.3. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 12.8 min. ^{1}H-NMR (600 MHz, D_2O): δ 7.13 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.82-5.67 (m, 2H), 5.29-5.16 (m, 4H), 4.70-4.65 (m, 2H), 4.43 (dd, *J* = 7.6, 6.3 Hz, 1H), 4.33 (dd, *J* = 9.0, 5.1 Hz, 1H), 4.22 (t, *J* = 7.2 Hz, 1H), 4.10-4.06 (m, 2H), 3.91 (q, *J* = 17.4 Hz, 2H), 3.78 (dt, *J* = 9.6, 7.2 Hz, 1H), 3.68 (dt, *J* = 9.6, 6.3 Hz, 1H), 3.02-2.95 (m, 2H), 2.80 (dd, *J* = 15.6, 5.1 Hz, 1H), 2.73 (dd, *J* = 15.6, 8.4 Hz, 1H), 2.66-2.63 (m, 2H), 2.57-2.54 (m, 1H), 2.45-2.40 (m, 1H), 2.35 (t, *J* = 7.8 Hz, 2H), 2.32-2.28 (m, 1H), 2.08-1.92 (m, 5H), 1.74-1.61 (m, 5H), 1.46-1.42 (m, 1H), 1.15-1.10 (m, 1H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.91 (d, *J* = 6.0 Hz, 3H), 0.86-0.84 (m, 6H), 16 protons not observed. All data was consistent with that previously reported.[4,5]

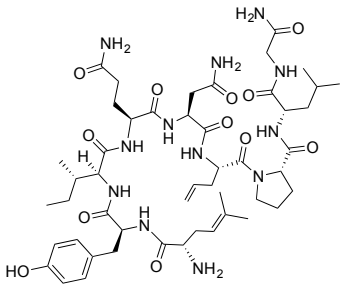
[1,6]-Homo-Dicarba Oxytocin 11



Linear peptide **10** was subjected to HBF_4 ion exchange conditions followed by the microwave accelerated solution phase RCM procedure described previously under the following conditions: linear peptide **10** (5.7 mg, 5.3 μmol), DMF (1 mL), 0.4 M LiCl in DMF (0.1 mL),

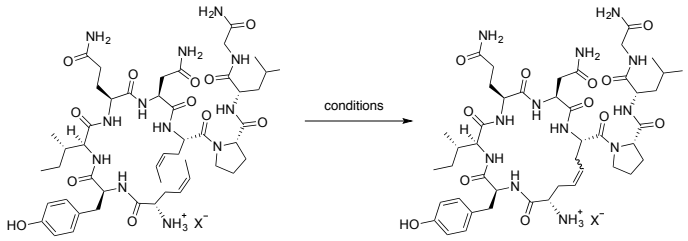
GII (4.3 mg, 5.1 μmol), 100 °C, 100 W, 2 h. Analysis of the crude reaction mixture by HPLC and MS showed both [1,6]-Dicarba oxytocin **1**, linear peptide **10** and by-product **11**. The crude solid was purified by RP-HPLC, and the major by-product peak was isolated (Agilent Vydac C18 preparative column, 10-30% buffer B over 40 min, t_R = 25.2 min). Selected fractions were combined and lyophilized to give a pure sample of the by-product, [1,6]-Homo-dicarba oxytocin **11** (0.5 mg). Mass spectrum (ESI$^+$, MeCN:H_2O:HCOOH): *m/z* 984.6 $[M + H]^+$, ($C_{46}H_{71}N_{12}O_{12}$) theoretical 984.5; 492.8 $[M + 2H]^{2+}$, ½ ($C_{46}H_{72}N_{12}O_{12}$) theoretical 492.7. RP-HPLC (Agilent Vydac C18 analytical column, 5-35% buffer B over 30 min): t_R = 15.2 min. ^{1}H-NMR (400 MHz, D_2O): δ 7.24 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 5.74 (dt, *J* = 10.4, 6.8 Hz, 1H), 5.56 (dt, *J* = 10.4, 7.4 Hz, 1H), 4.50-4.45 (m, 2H), 4.36-4.32 (m, 1H), 4.22-4.14 (m, 2H), 4.00-3.89 (m, 3H), 3.82-3.76 (m, 1H), 3.72-3.66 (m, 1H), 3.19-3.06 (m, 2H), 2.94 (dd, *J* = 16.0, 5.2 Hz, 1H), 2.84-2.77 (m, 2H), 2.47-2.29 (m, 5H), 2.12-1.82 (m, 8H), 1.82-1.61 (m, 4H), 1.20-1.13 (m, 1H), 0.99 (m, 3H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.92-0.86 (m, 6H), 16 protons not observed.

[1]-Pre-[6]-Agl Oxytocin SI8



Synthesis of the linear sequence **SI8** was performed according to the microwave accelerated SPPS procedure described previously using Fmoc-Rink amide resin (220 μmol). Following synthesis, the peptide underwent acid-mediated cleavage to provide an off-white solid. The crude peptide was purified by RP-HPLC (Agilent Vydac C18 preparative column, 15-45% buffer B over 40 min, t_R = 17.6 min). Selected fractions were combined and lyophilized to give the desired peptide **SI8** (62.1 mg). Mass spectrum (ESI$^+$, MeCN:H_2O:HCOOH): *m/z* 1025.7 $[M + H]^+$, ($C_{49}H_{77}N_{12}O_{12}$) theoretical 1025.6. RP-HPLC (Agilent Vydac C18 analytical column, 10-40% buffer B over 30 min): t_R = 15.7 min. ^{1}H-NMR (600 MHz, D_2O): δ 7.12 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 5.82-5.75 (m, 1H), 5.22 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.17 (d, *J* = 10.8 Hz, 1H), 5.04 (t, *J* = 7.2 Hz, 1H), 4.71-4.65 (m, 1H), 4.43 (dd, *J* = 8.4, 5.4 Hz, 1H), 4.33 (dd, *J* = 9.3, 4.8 Hz, 1H), 4.24 (dd, *J* = 7.8, 7.2 Hz, 1H), 4.08-4.06 (m, 1H), 4.01 (t, *J* = 6.6 Hz, 1H), 3.91 (q, *J* = 17.4 Hz, 2H), 3.79 (dt, *J* = 9.3, 7.2 Hz, 1H), 3.68 (dt, *J* = 9.6, 7.2 Hz, 1H), 3.21 (q, *J* = 7.2 Hz, 1H), 2.98 (dd, *J* = 7.2, 2.4 Hz, 2H), 2.81 (dd, *J* = 15.6,

5.4 Hz, 1H), 2.73 (dd, *J* = 15.6, 8.4 Hz, 1H), 2.64-2.54 (m, 3H), 2.46-2.41 (m, 1H), 2.36 (d, *J* = 7.8 Hz, 2H), 2.32-2.26 (m, 1H), 2.10-1.91 (m, 5H), 1.77-1.74 (m, 1H), 1.73 (s, 3H), 1.72-1.62 (m, 2H), 1.61 (s, 3H), 1.48-1.42 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 2H), 1.16-1.11 (m, 1H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.87-0.85 (m, 6H), 16 protons not observed.

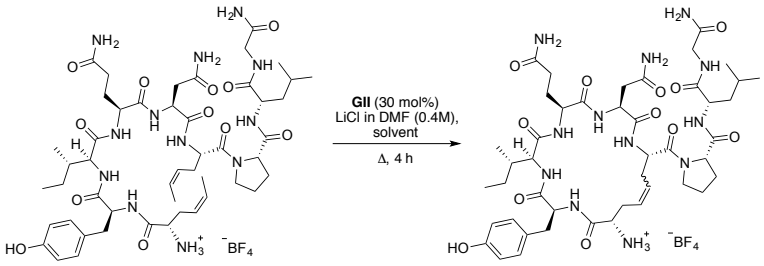


6 **1**

Table SI1. Additional optimisation studies for RCM of linear oxytocin **6**

Entry	Solvent	Additive	Catalyst	Cat. Loading (mol %)	Counter ion X^-	Temp. (°C)	Time (h)	Conv. (%)
1	DMF	-	**GII**	20	BF_4^-	100[a]	2	35
2	NMP	-	**GII**	20	BF_4^-	100[a]	2	33
3	Dioxane	-	**GII**	20	BF_4^-	100[a]	2	0
4	DMSO	-	**GII**	20	BF_4^-	100[a]	2	0
5	DMA	-	**GII**	20	BF_4^-	100[a]	2	0
6	H_2O/^{t}BuOH	-	**GII**	20	BF_4^-	100[a]	2	0
7	DMF	$MgCl_2$[b]	**GII**	20	BF_4^-	100[a]	2	27
8	DMF	Bmim Cl[c]	**GII**	20	BF_4^-	100[a]	2	26
9	DMF	Bmim BF_4[c]	**GII**	20	BF_4^-	100[a]	2	8
10	DMF	LiCl[b]	**GII**	20	TFA^-	100[a]	2	4
11	DMF	LiCl[b]	**GII**	20	Cl^-	100[a]	2	7
12	DMF	LiCl[b]	**GII**	20	TsO^-	100[a]	2	6
13	DMF	LiCl[b]	**HGII**	20	BF_4^-	100[a]	2	0
14	DMF	LiCl[b]	**GII**	2 x 10	BF_4^-	100[a]	2	10
15	DMF	LiCl[b]	**GII**	20	BF_4^-	rt	2	7
16	DMF	LiCl[b]	**GII**	20	BF_4^-	40	2	8
17	DMF	LiCl[b]	**GII**	20	BF_4^-	60	2	32
18	DMF	LiCl[b]	**GII**	20	BF_4^-	80	2	31
19	DMF	LiCl[b]	**GII**	20	BF_4^-	100	2	50
20	DMF	LiCl[b]	**GII**	20	BF_4^-	100	4	56
21	DMF	LiCl[b]	**GII**	20	BF_4^-	100	16	55
22	DMF	LiCl[b]	**GII**	30	BF_4^-	100	4	100

[a]μW irradiation, [b]0.4 M, [c]15%

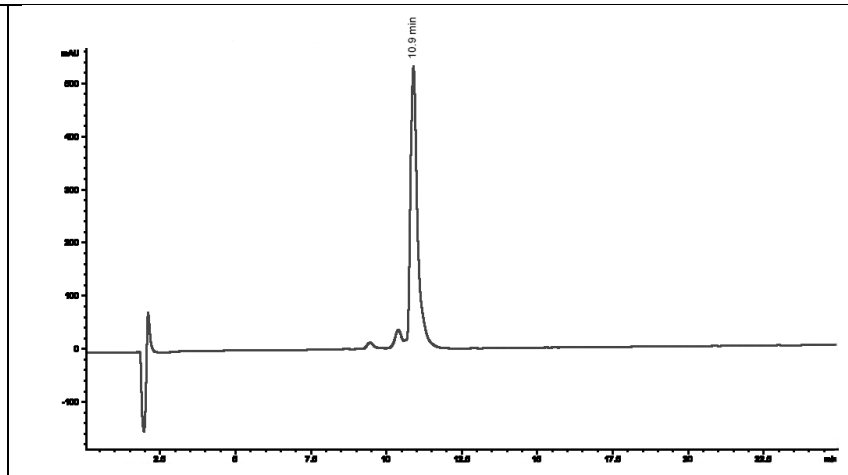
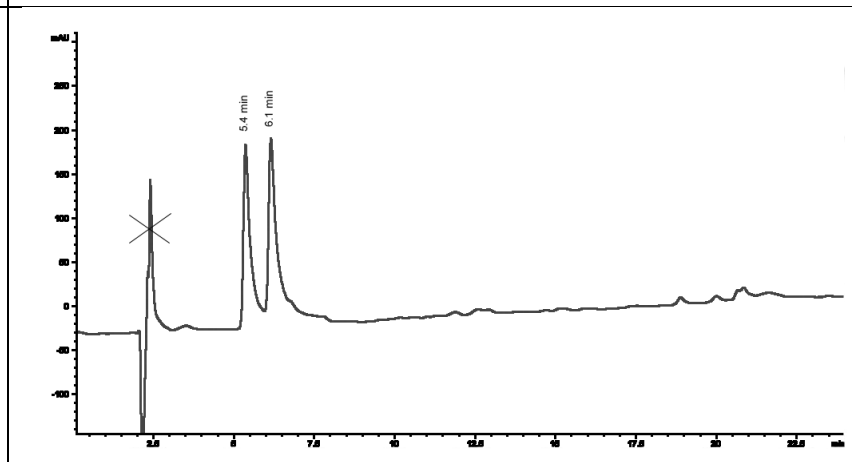


6 **1**

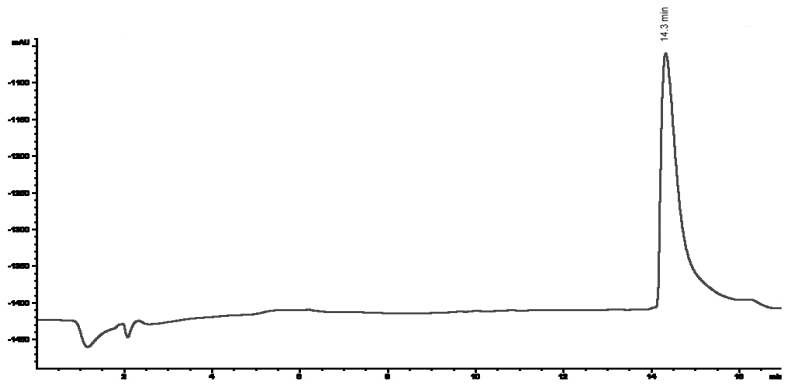
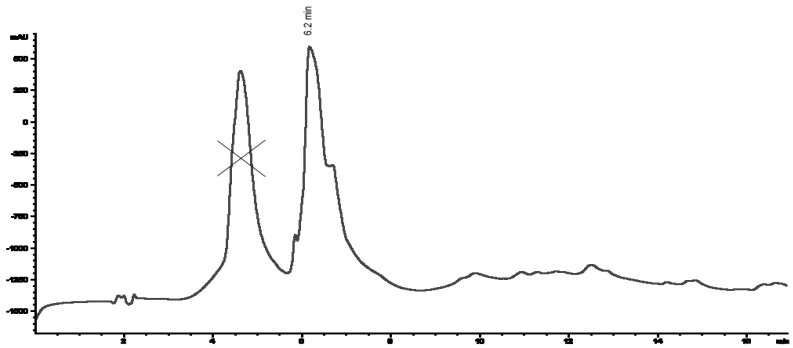
Table SI2. RCM of linear oxytocin **6** under varying solvent conditions

Entry	Solvent	Temp. (°C)	Conv. to **1** (%)
1	DMF	100	Quant.
2	MeOH	reflux	84
3	EtOH	reflux	66
4	*N*-Butylpyrrolidinone	100	trace
5	Propylene carbonate	100	0
6	ACN	reflux	0
7	1:1 DMF/H_2O	100	0
8	2:1 MeOH/H_2O	reflux	0

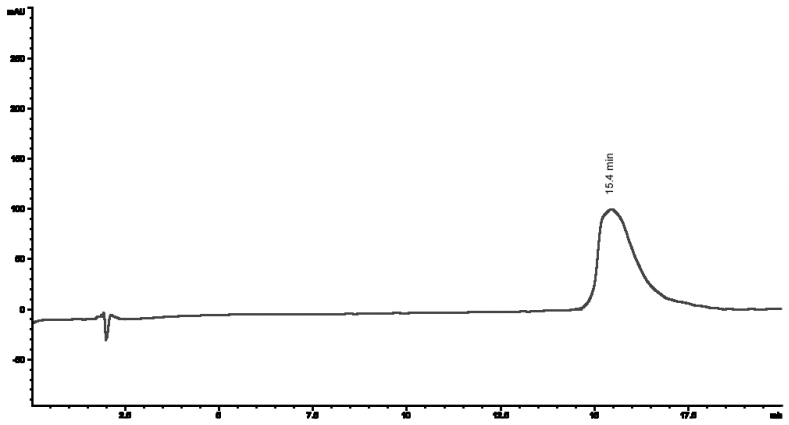
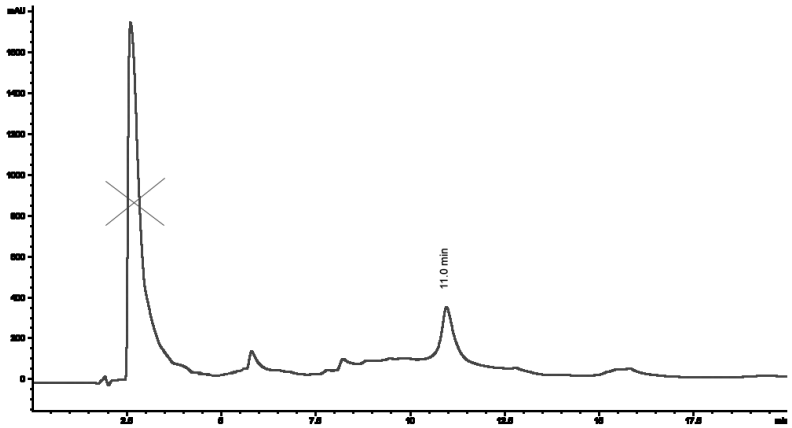
Supporting Spectra

Target: [1,6]-Dicarba Oxytocin **1**		
6		Pre-metathesis (crude) 15-50% Buffer B over 35 min
[1,6]-Dicarba Oxytocin **1**		Post-metathesis (crude) 15-50% Buffer B over 35 min X = DMF

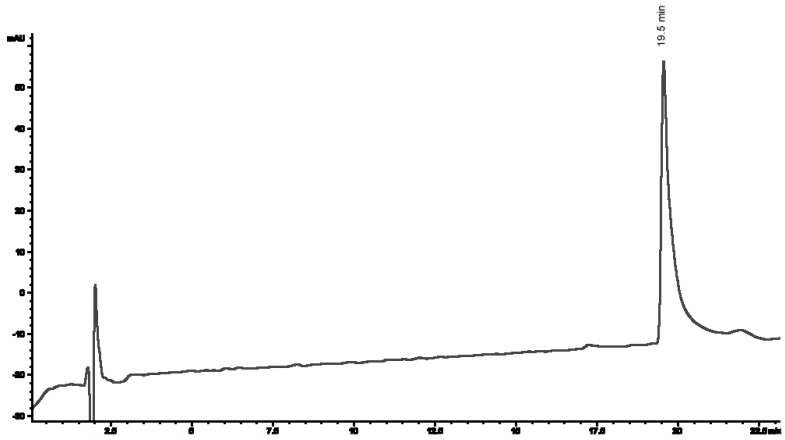
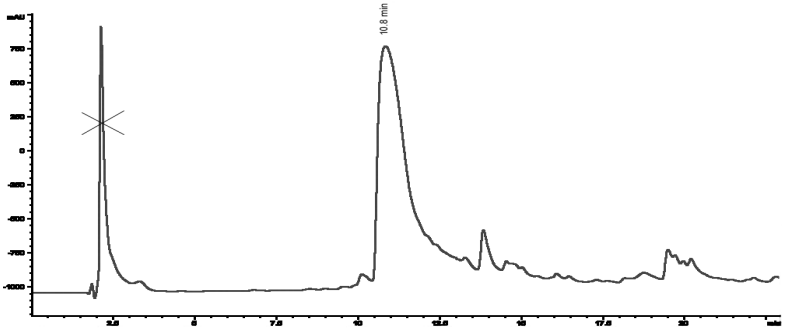
Target: [2,8-Dicarba-[3]-Ser Conotoxin Vc1.1 (1-8) **2**

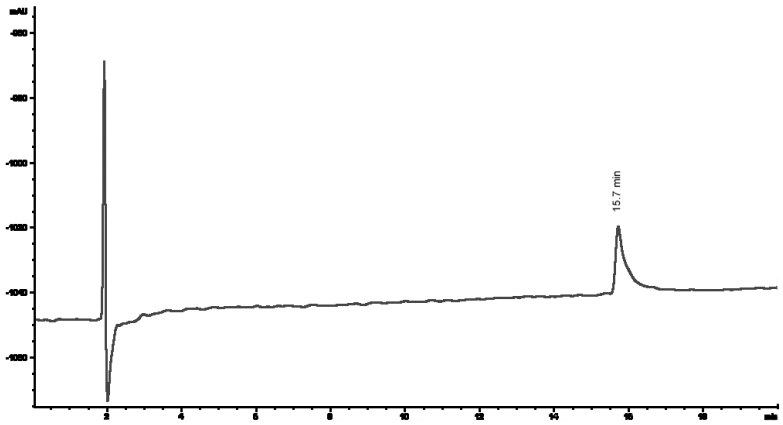
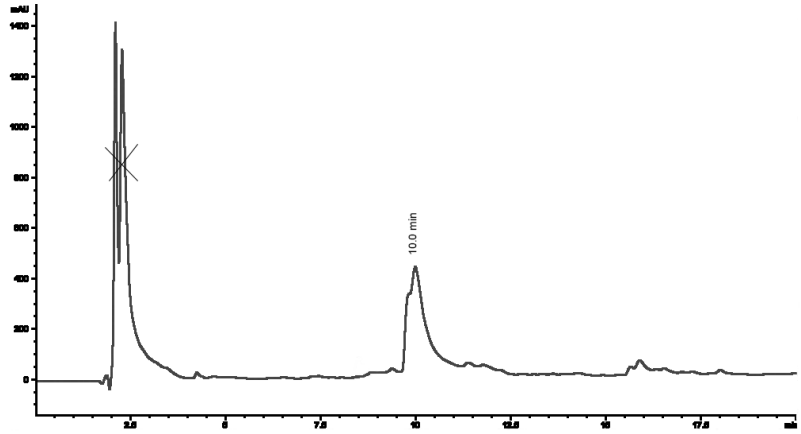
SI4		Pre-metathesis (crude) 0-30% Buffer B over 30 min
[2,8-Dicarba-[3]-Ser Conotoxin Vc1.1 (1-8) **2**		Post-metathesis (crude) 0-30% Buffer B over 30 min X = DMF

Target: [3,9]-Dicarba-[4]-Ser Conotoxin Pu1.2 (1-9) **3**

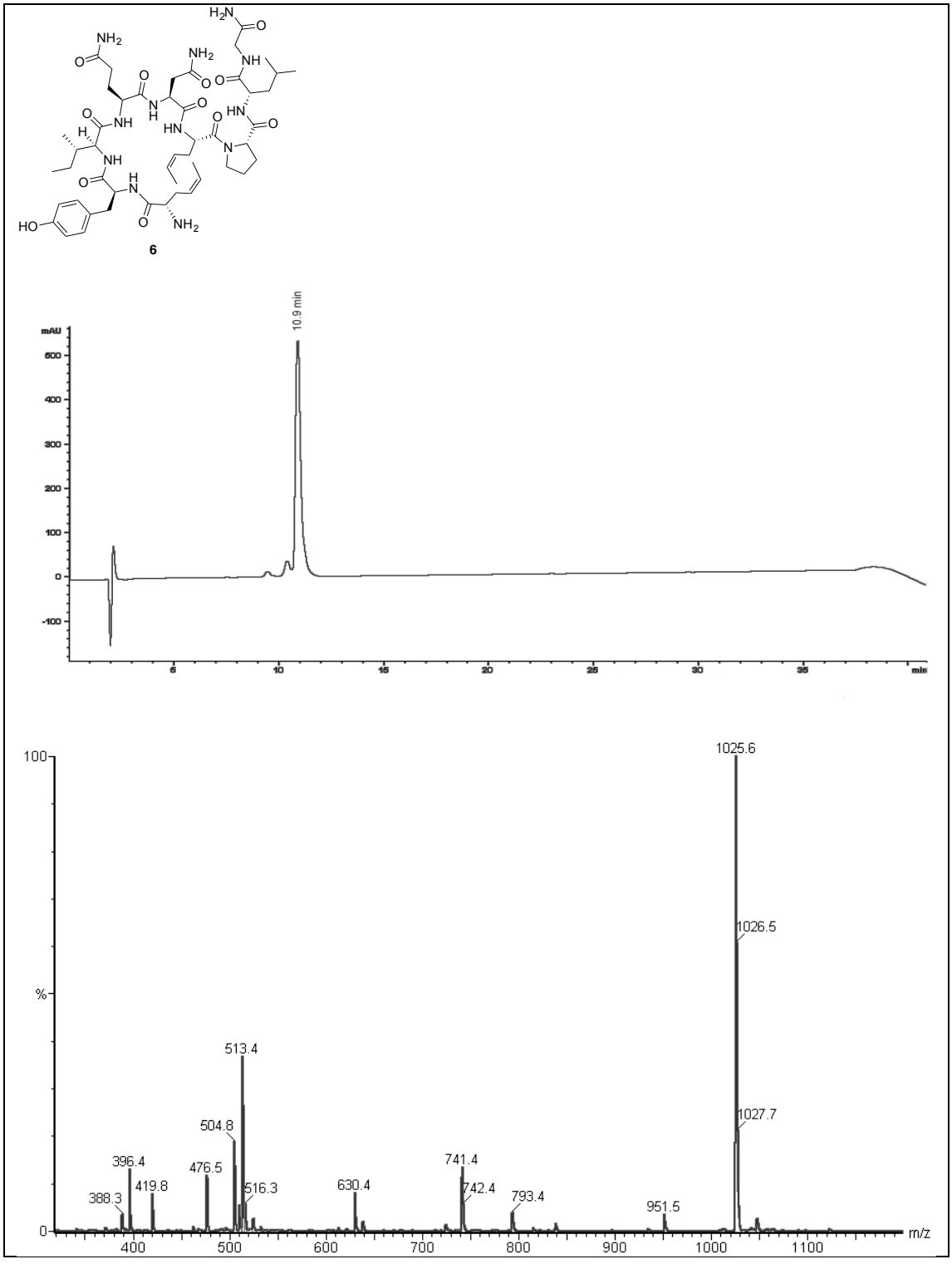
SI5		Pre-metathesis (crude) 5-35% Buffer B over 30 mins
[3,9]-Dicarba-[4]-Ser Conotoxin Pu1.2 (1-9) **3**		Post-metathesis (crude) 5-35% Buffer B over 30 mins X = DMF

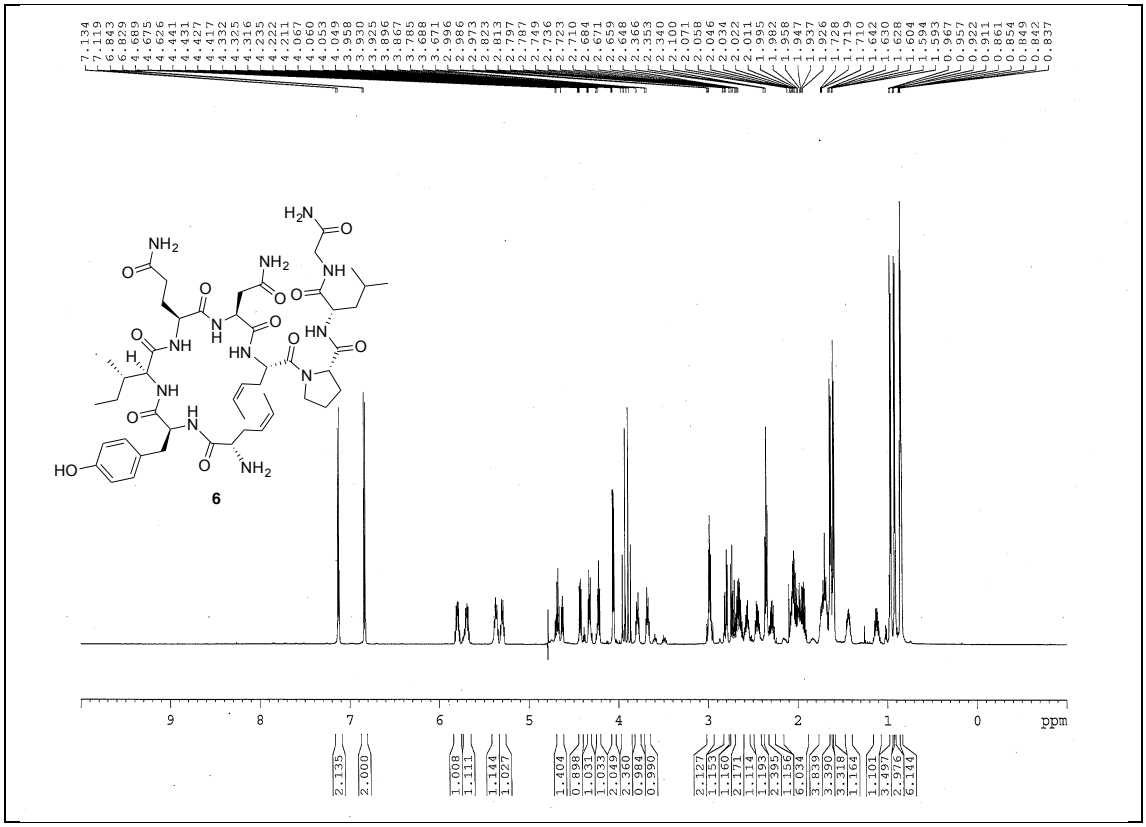
Target: [2,7]-Dicarba Octreotate **4**

SI6		Pre-metathesis (crude) 15-50% Buffer B over 35 mins
[2,7]-Dicarba Octreotate **4**		Post-metathesis (crude) 15-50% Buffer B over 35 mins X = DMF

Target: [1,6]-Dicarba-[2]-Ala Human Insulin A Chain (6-13) **5**		
SI7		Pre-metathesis (crude) 10-40% Buffer B over 30 mins
[1,6]-Dicarba-[2]-Ala Human Insulin A Chain (6-13) **5**		Post-metathesis (crude) 10-40% Buffer B over 30 mins X = DMF

[1,6]-*Z*-Crt Oxytocin 6

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4.427
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4.325
4.316
4.235
4.222
4.211
4.067
4.060
4.053
4.049
3.958
3.930
3.925
3.896
3.867
3.785
3.768
3.671
2.996
2.986
2.973
2.823
2.813
2.797
2.749
2.736
2.723
2.710
2.684
2.671
2.659
2.648
2.366
2.353
2.340
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1.926
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1.710
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1.628
1.604
1.594
1.593
0.967
0.957
0.922
0.911
0.851
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0.842
0.837
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9
8
7
6
5
4
3
2
1
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2.000
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1.111
1.144
1.027
1.404
0.898
1.031
1.033
2.049
2.360
0.984
0.990
2.127
1.153
1.160
2.171
1.114
1.193
2.395
1.156
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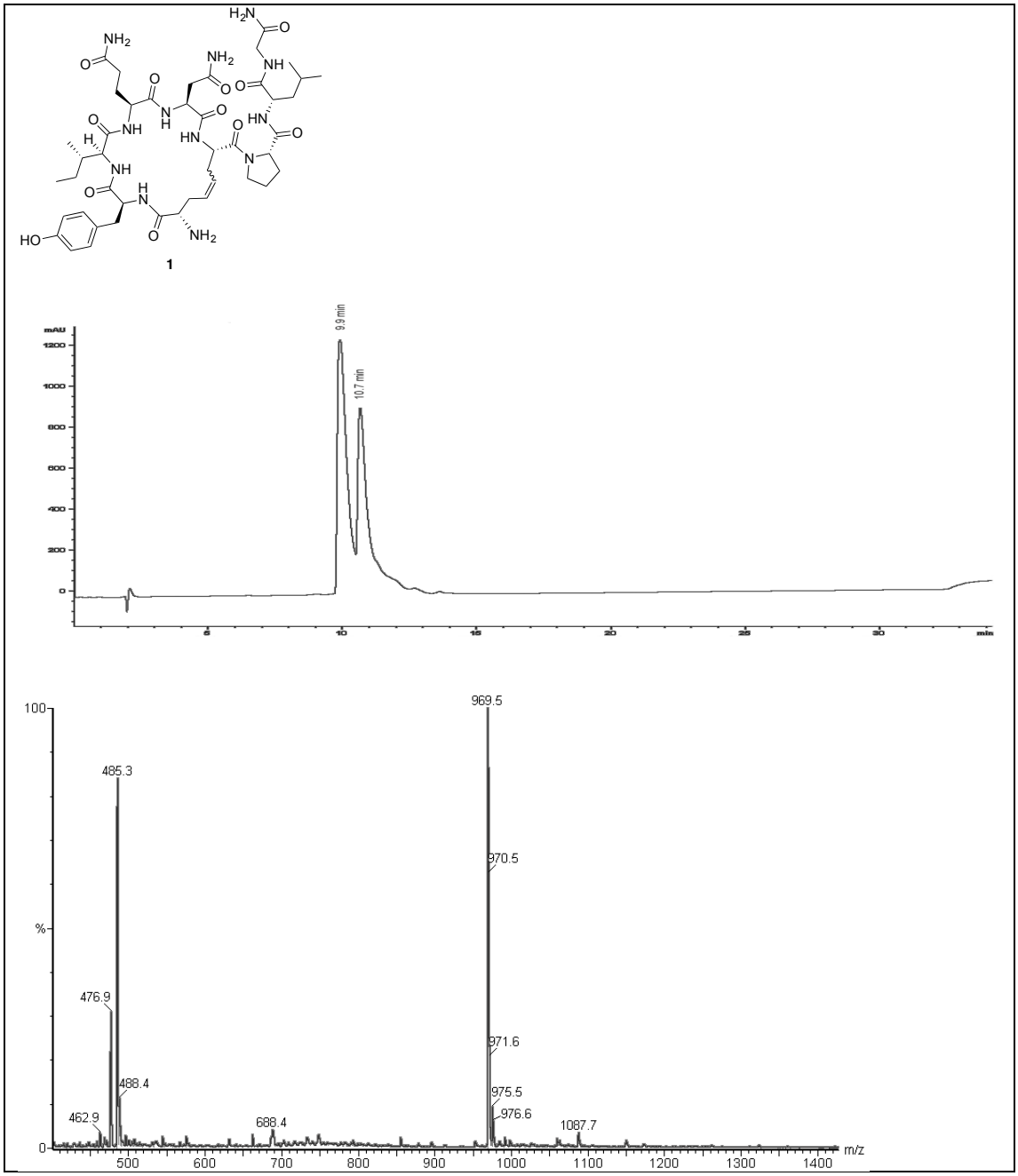
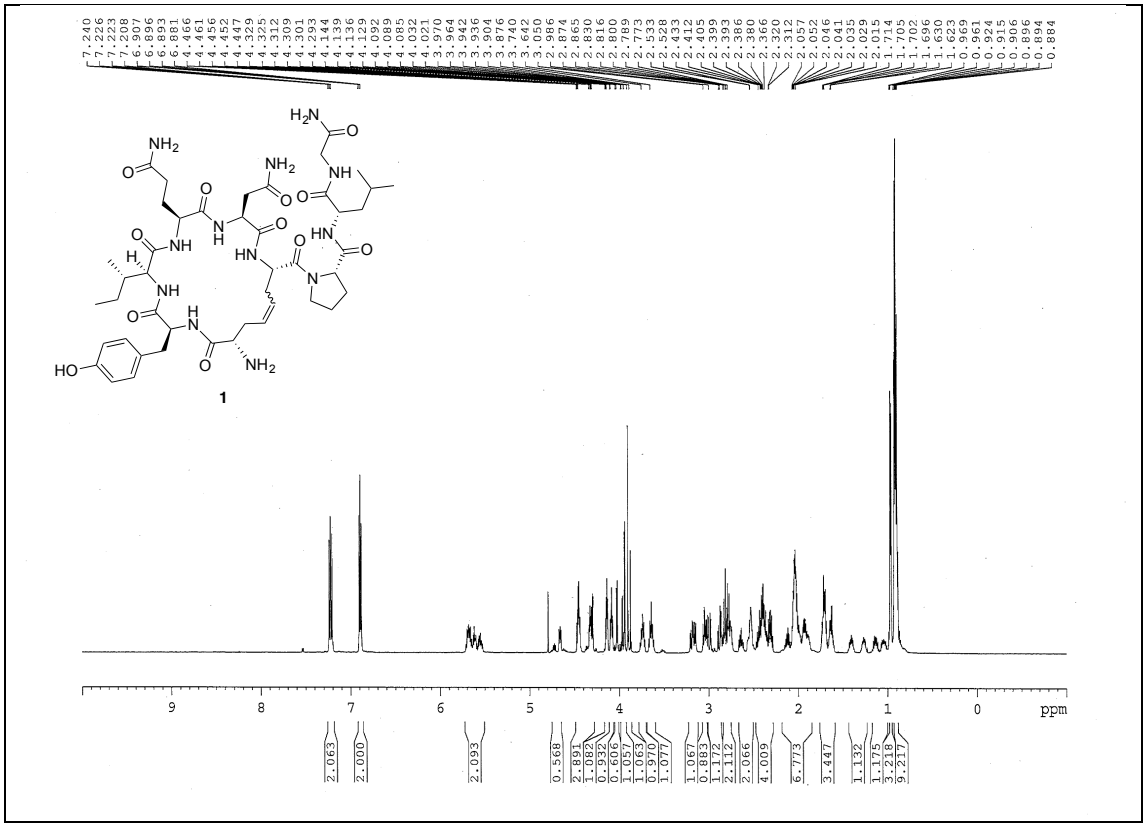
3.390
3.318
1.164
1.101
3.497
2.976
6.144

[1,6]-Dicarba Oxytocin 1

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7.223
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6.907
6.896
6.893
6.881
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4.461
4.456
4.452
4.447
4.329
4.325
4.312
4.309
4.301
4.243
4.244
4.139
4.136
4.129
4.092
4.089
4.085
4.032
4.021
3.970
3.964
3.942
3.936
3.904
3.876
3.740
3.642
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2.896
2.876
2.865
2.830
2.816
2.800
2.789
2.773
2.533
2.528
2.433
2.413
2.405
2.399
2.393
2.386
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2.366
2.320
2.312
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2.046
2.041
2.035
2.029
2.015
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1.702
1.696
1.630
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0.961
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0.906
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0.894
0.884
1
9
8
7
6
5
4
3
2
1
0
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1.082
0.932
0.606
1.057
1.063
0.970
1.077
1.067
0.983
1.172
2.112
2.066
4.009
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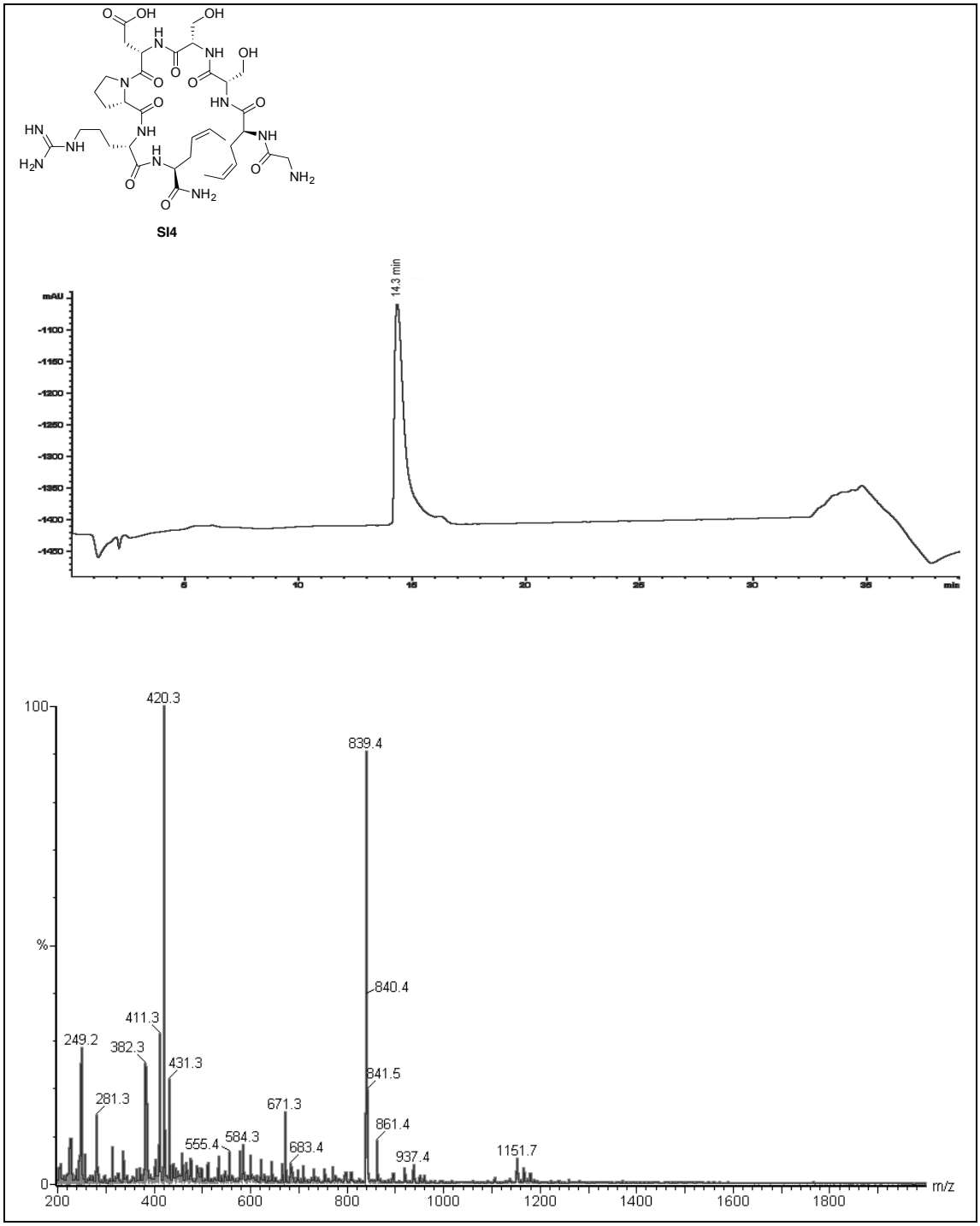
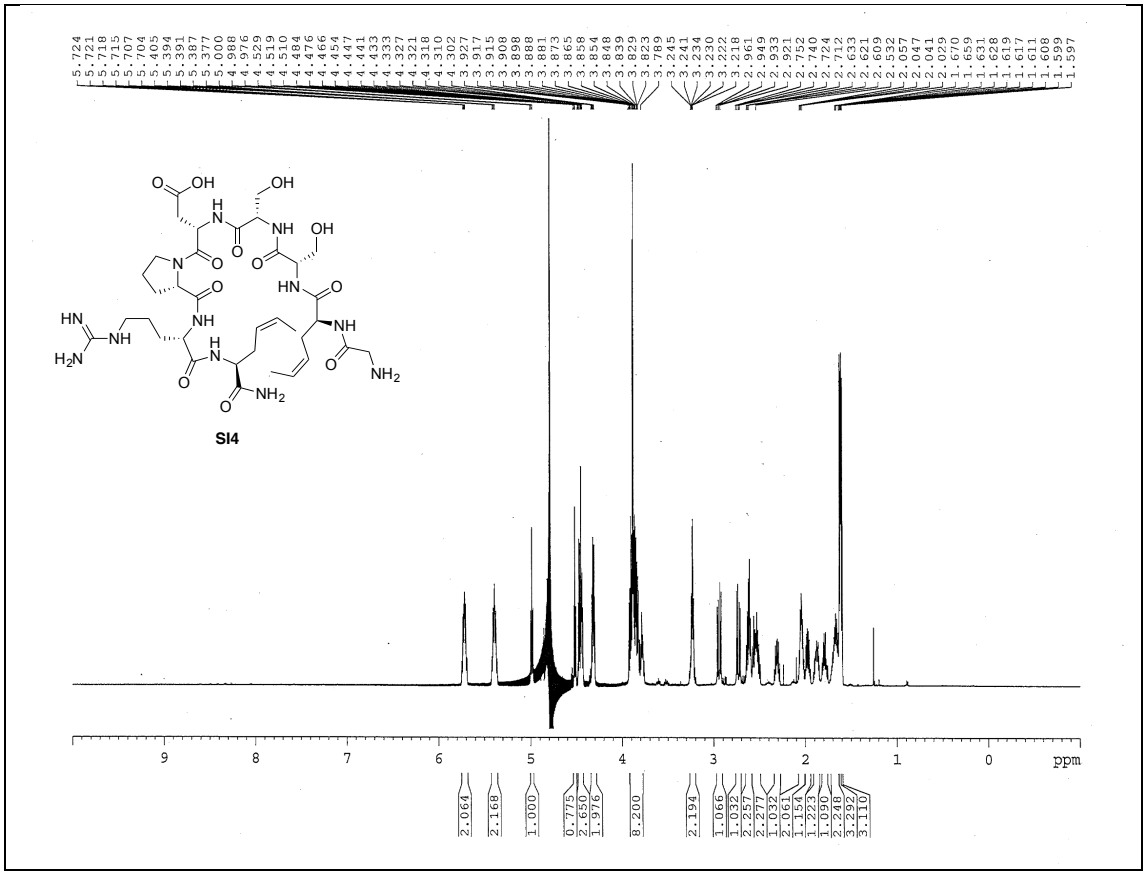
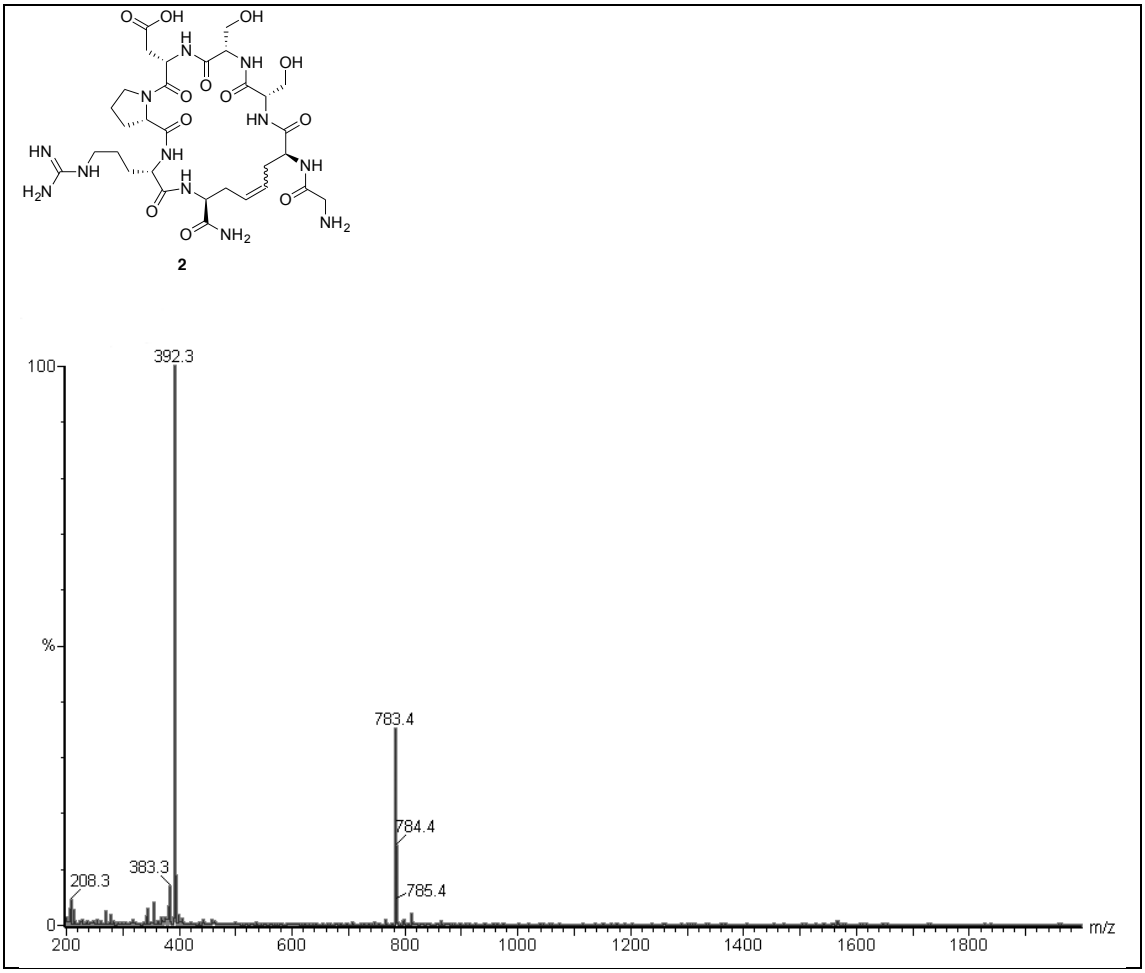
1.175
3.218
9.217

[2,8]-*Z*-Crt-[3]-Ser Conotoxin Vc1.1 (1-8) SI4

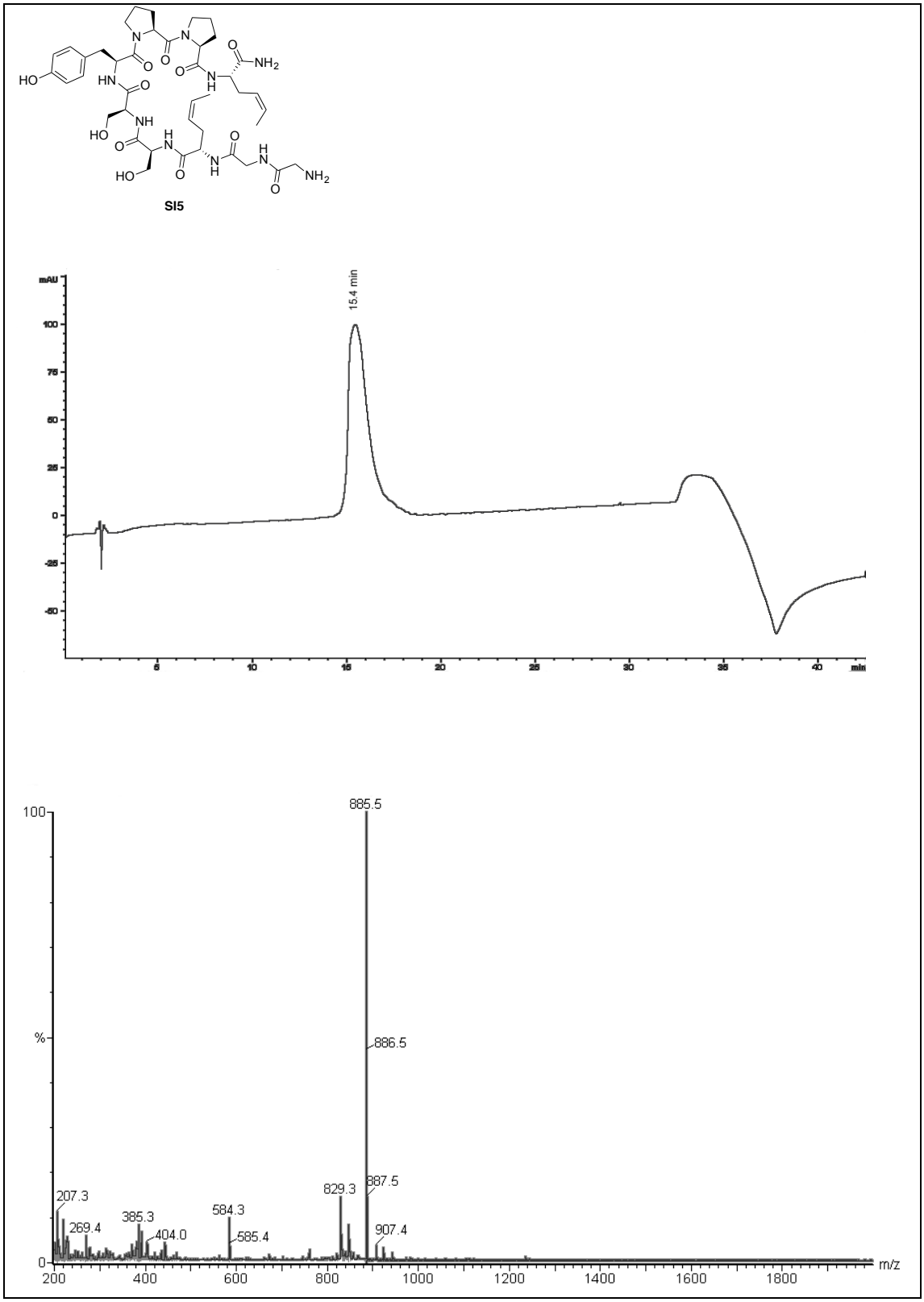


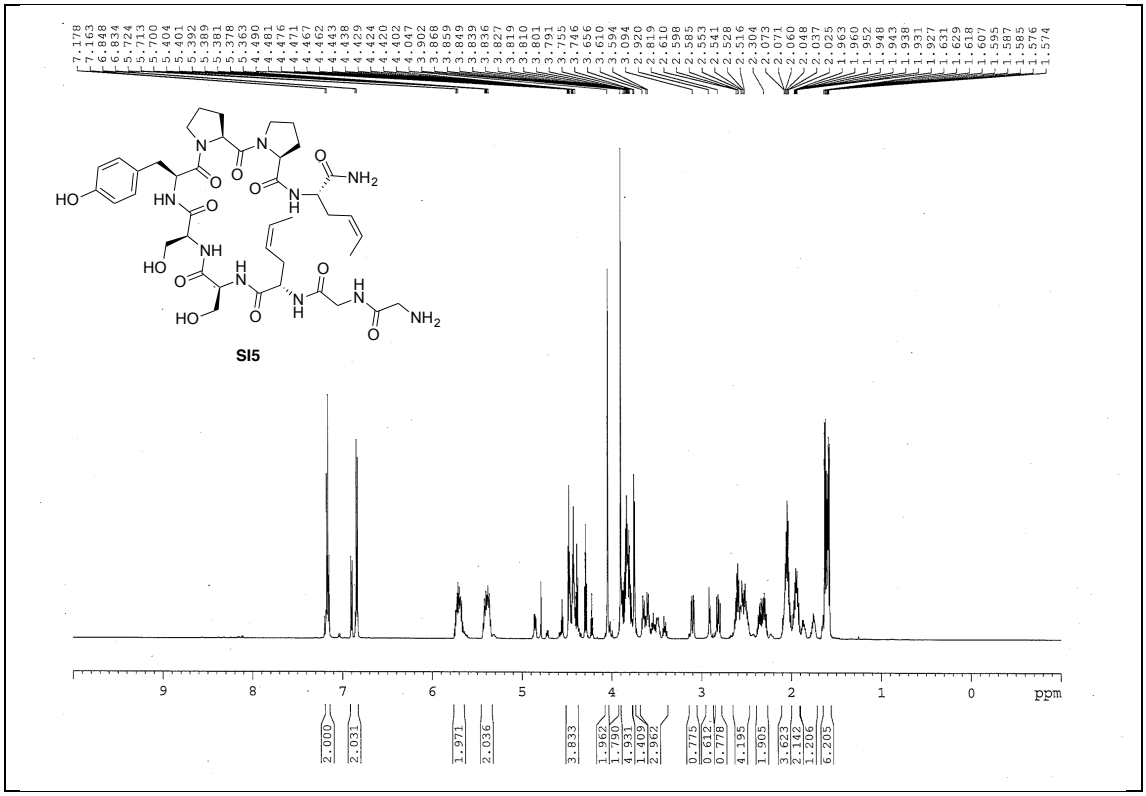

SI4
ppm

[2,8]-Dicarba-[3]-Ser Conotoxin Vc1.1 (1-8) 2



[3,9]-*Z*-Crt-[4]-Ser Conotoxin Pu1.2 (1-9) SI5

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4.476
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4.462
4.443
4.438
4.429
4.424
4.420
4.402
4.007
3.902
3.868
3.859
3.849
3.839
3.836
3.827
3.819
3.810
3.801
3.791
3.755
3.746
3.656
3.610
3.594
3.094
2.920
2.819
2.610
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2.071
2.060
2.048
2.037
2.025
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1.960
1.952
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1.927
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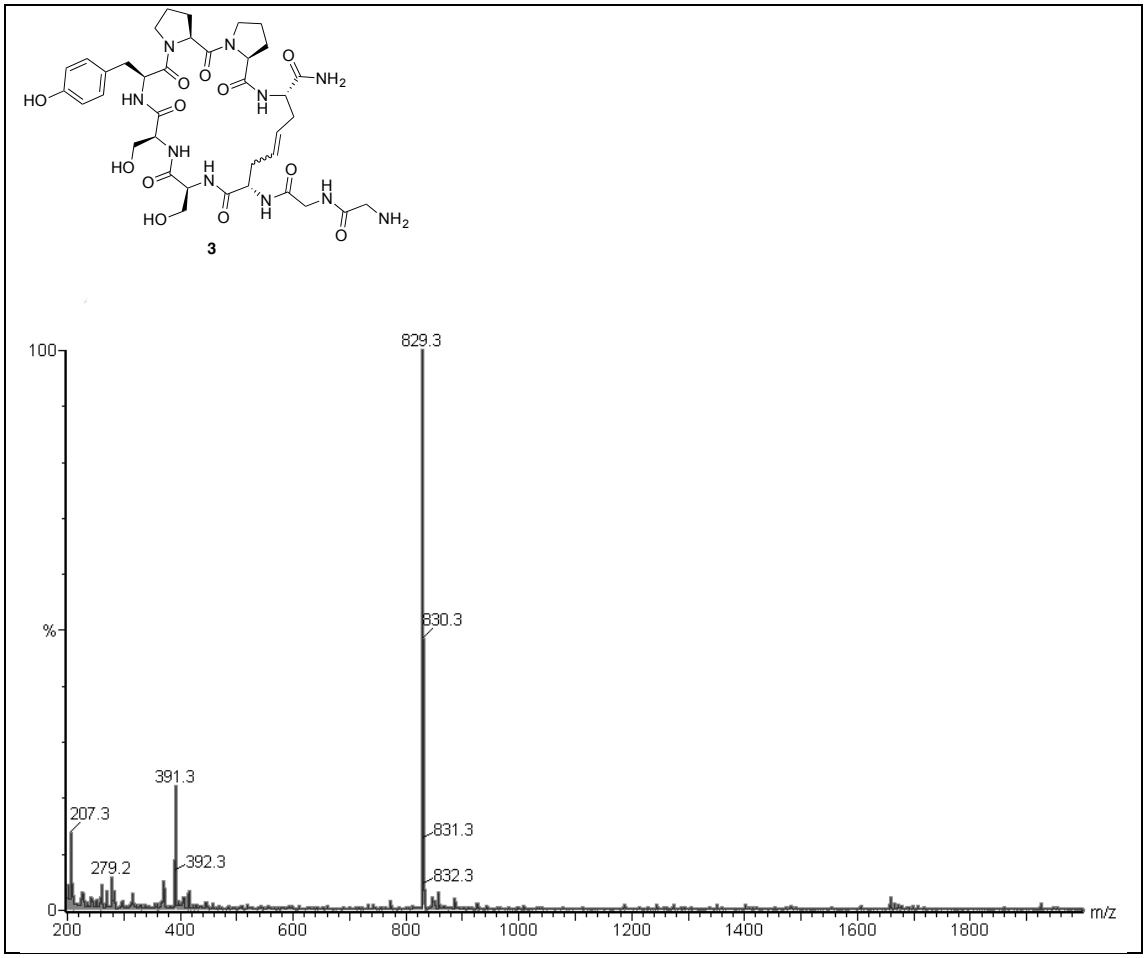
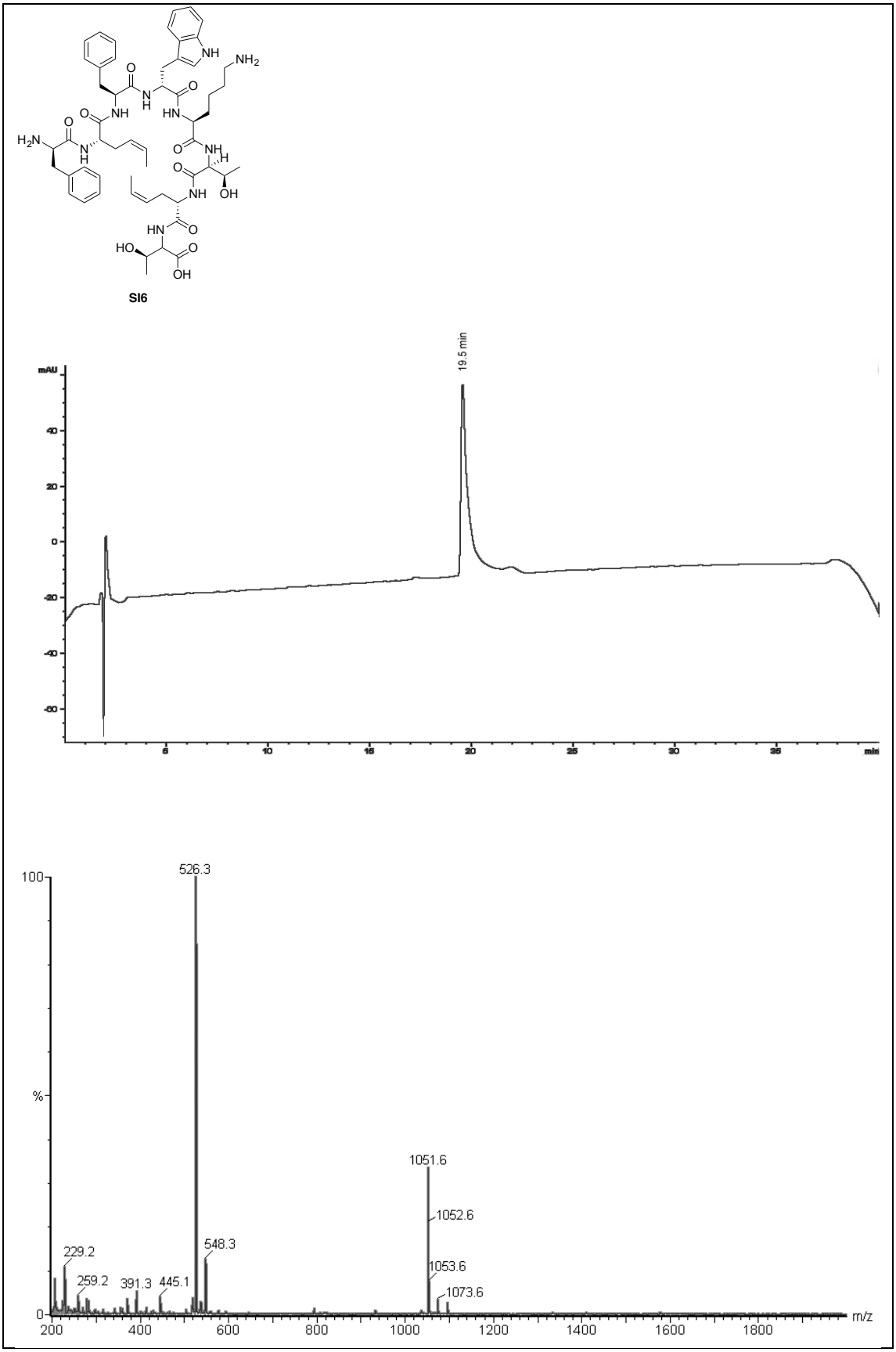
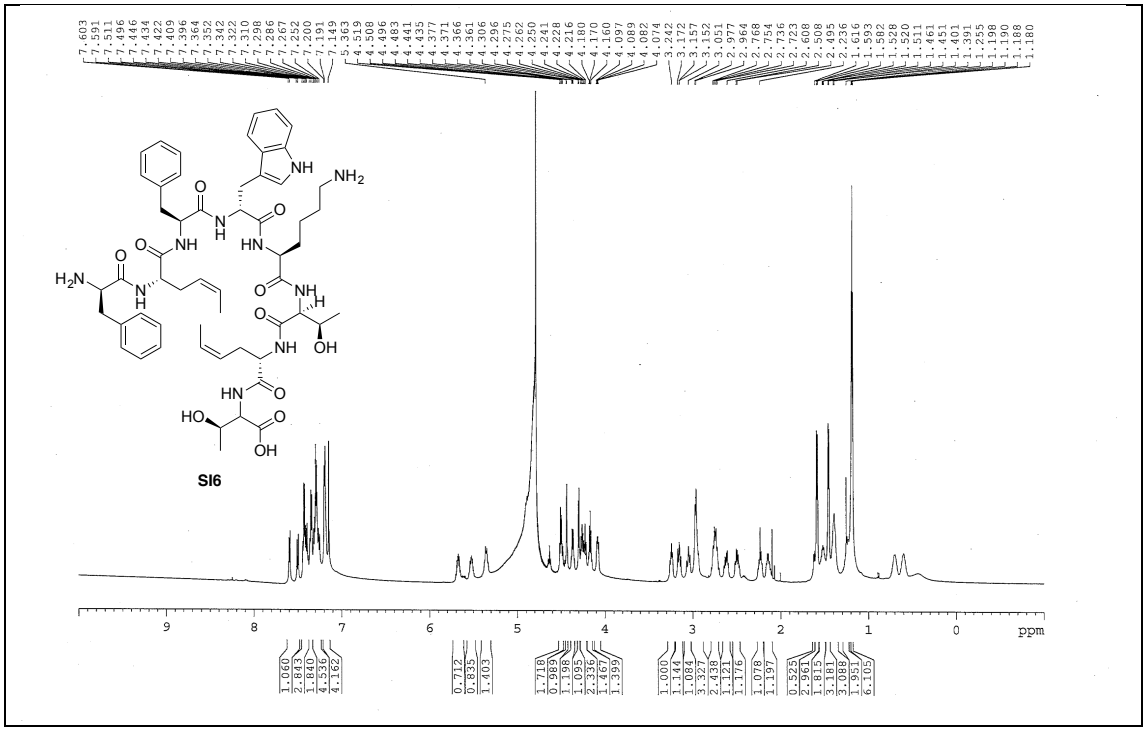
1.618
1.607
1.595
1.587
1.585
1.576
1.574
HO
HN
NH
HO
HO
NH2
NH2
SI5
9
8
7
6
5
4
3
2
1
0
ppm
2.000
2.031
1.971
2.036
3.833
1.962
1.790
4.931
1.409
2.962
0.775
0.612
0.778
4.195
1.905
3.623
2.142
1.206
6.205

[3,9]-Dicarba-[4]-Ser Conotoxin Pu1.2 (1-9) 3

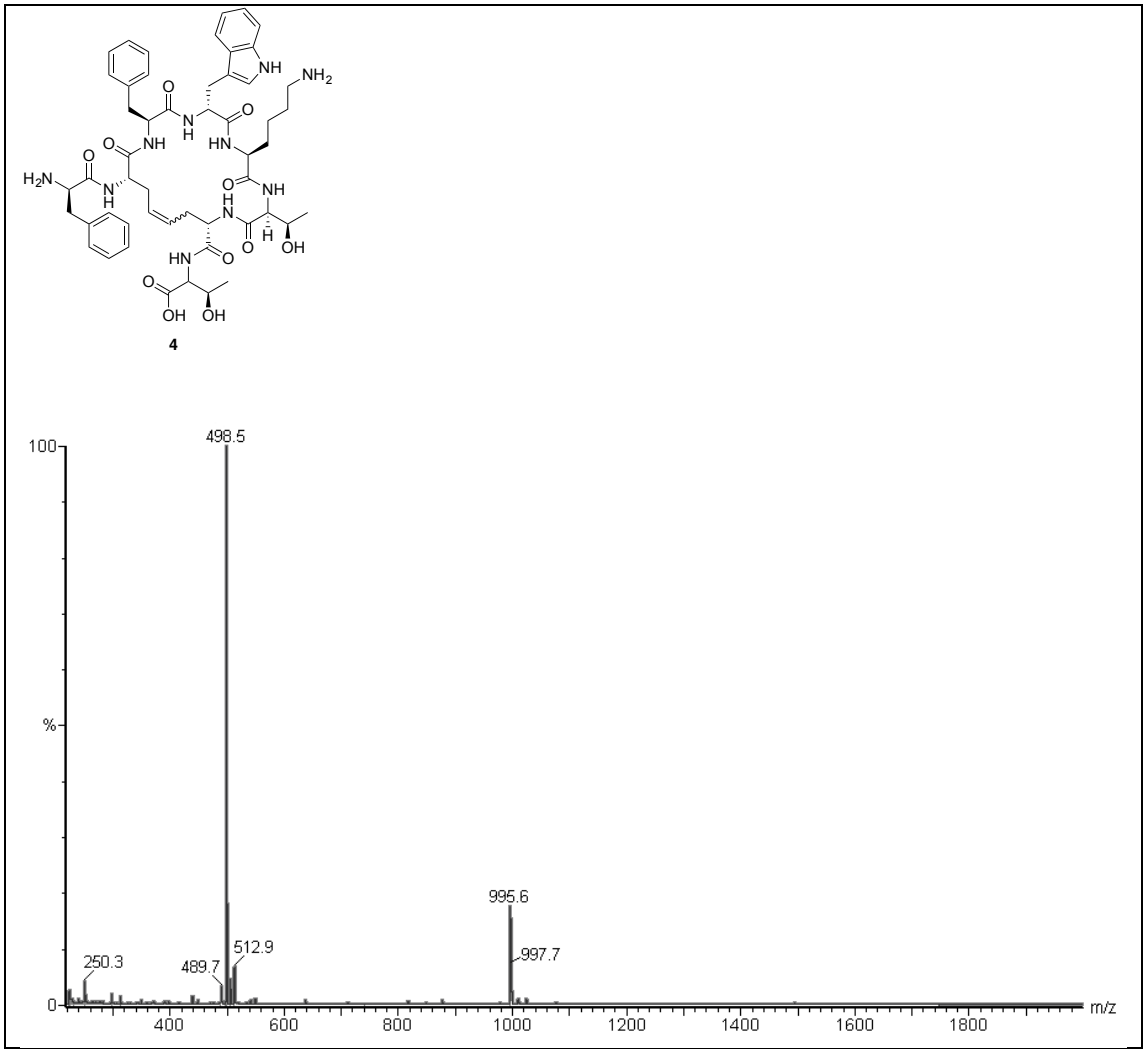


[2,7]-*Z*-Crt Octreotate SI6

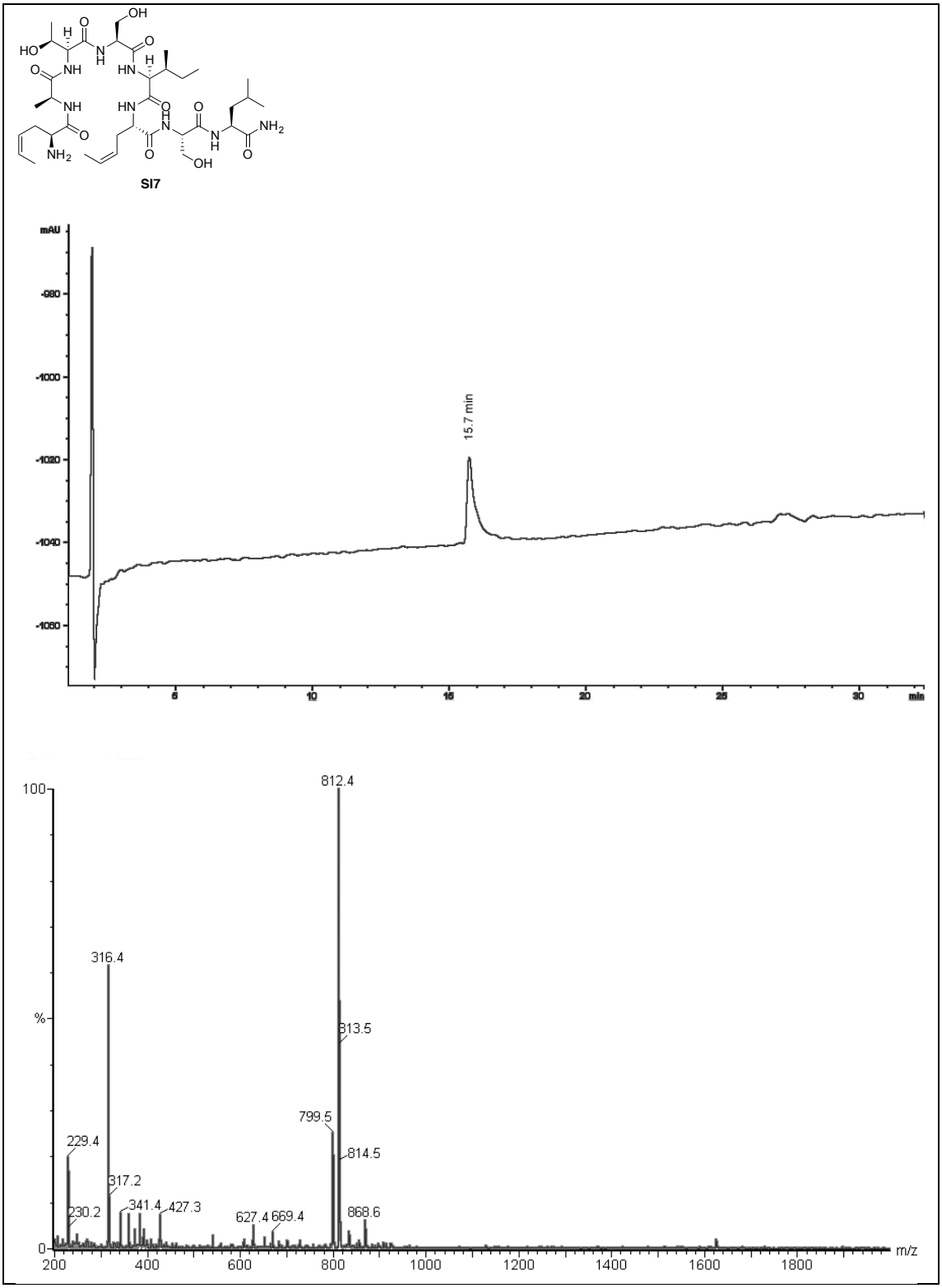


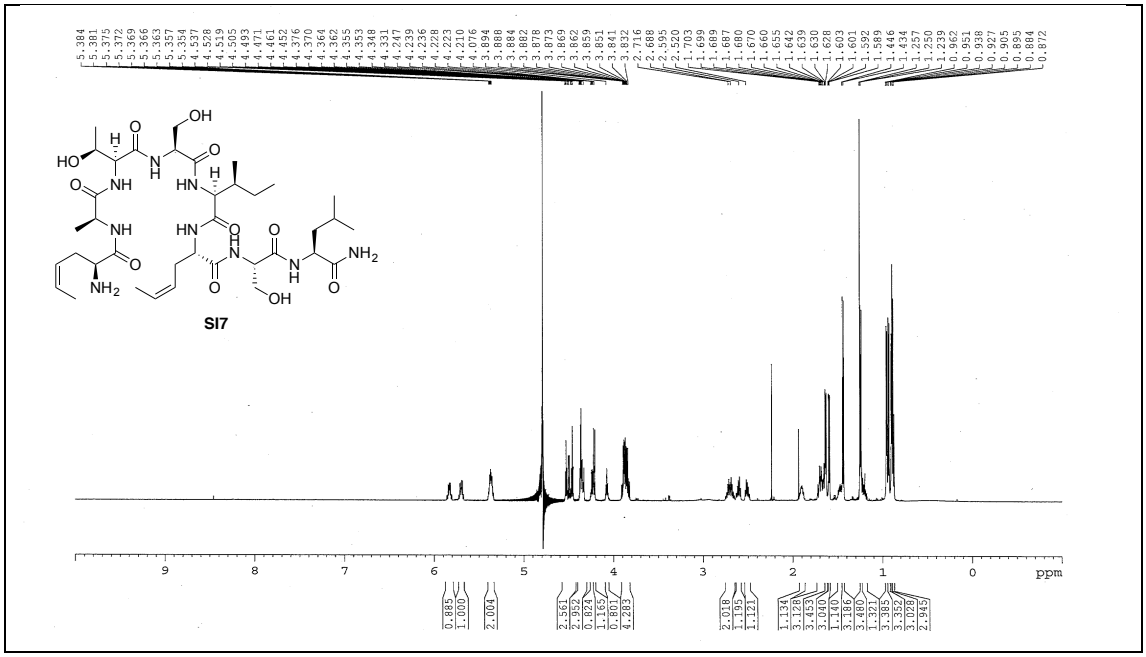

SI6
ppm

[2,7]-Dicarba Octreotate 4

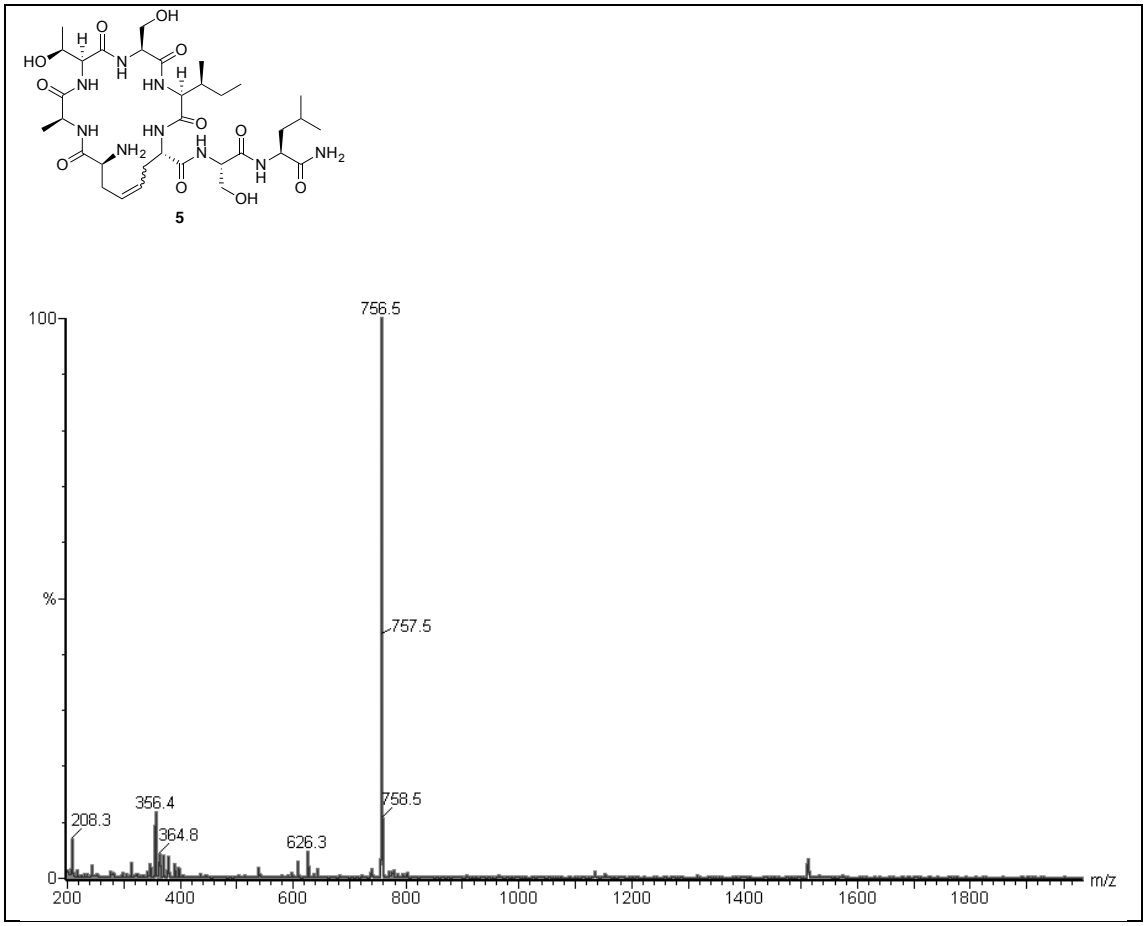


[1,6]-*Z*-Crt-[2]-Ala Human insulin A chain (6-13) SI7

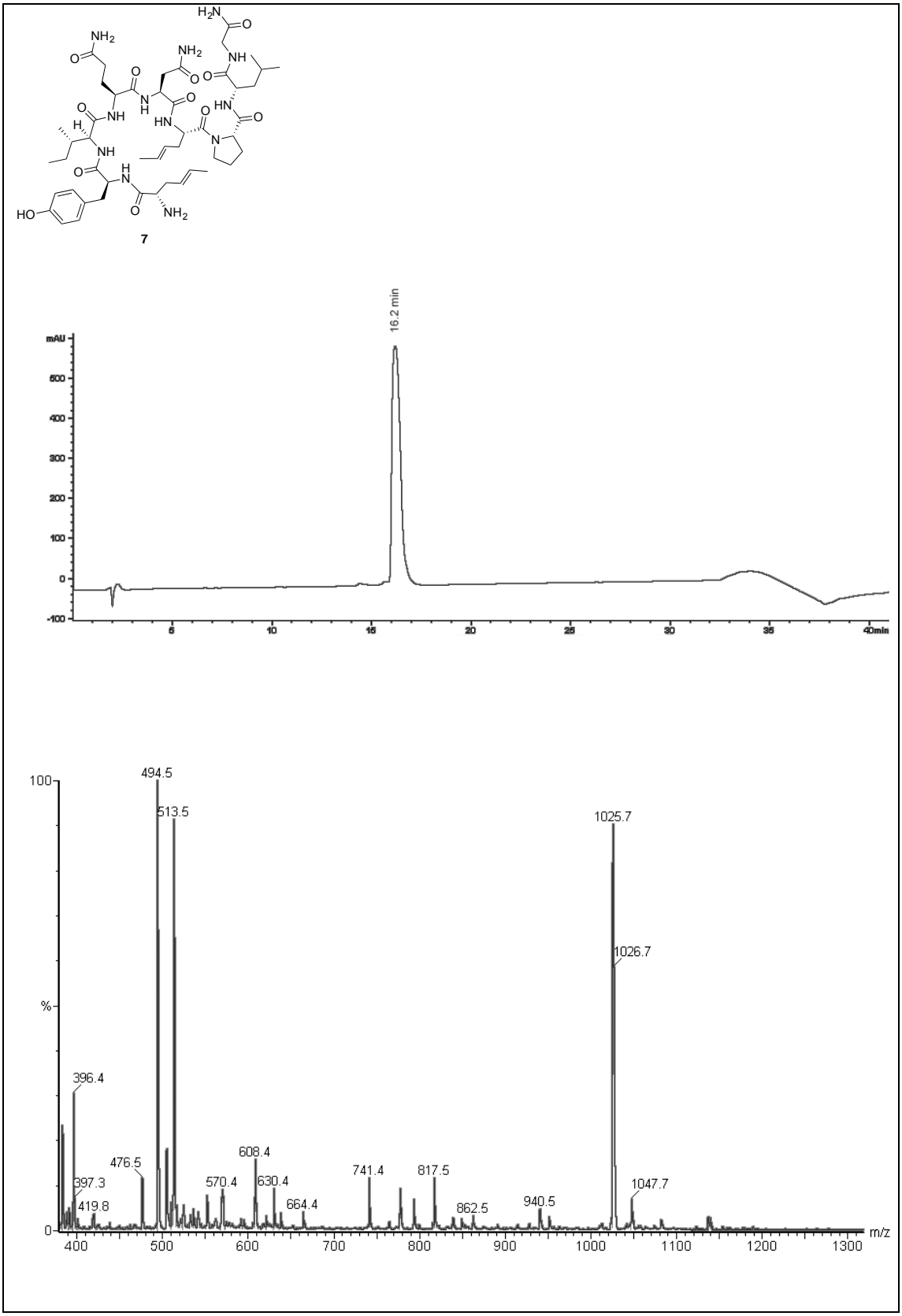


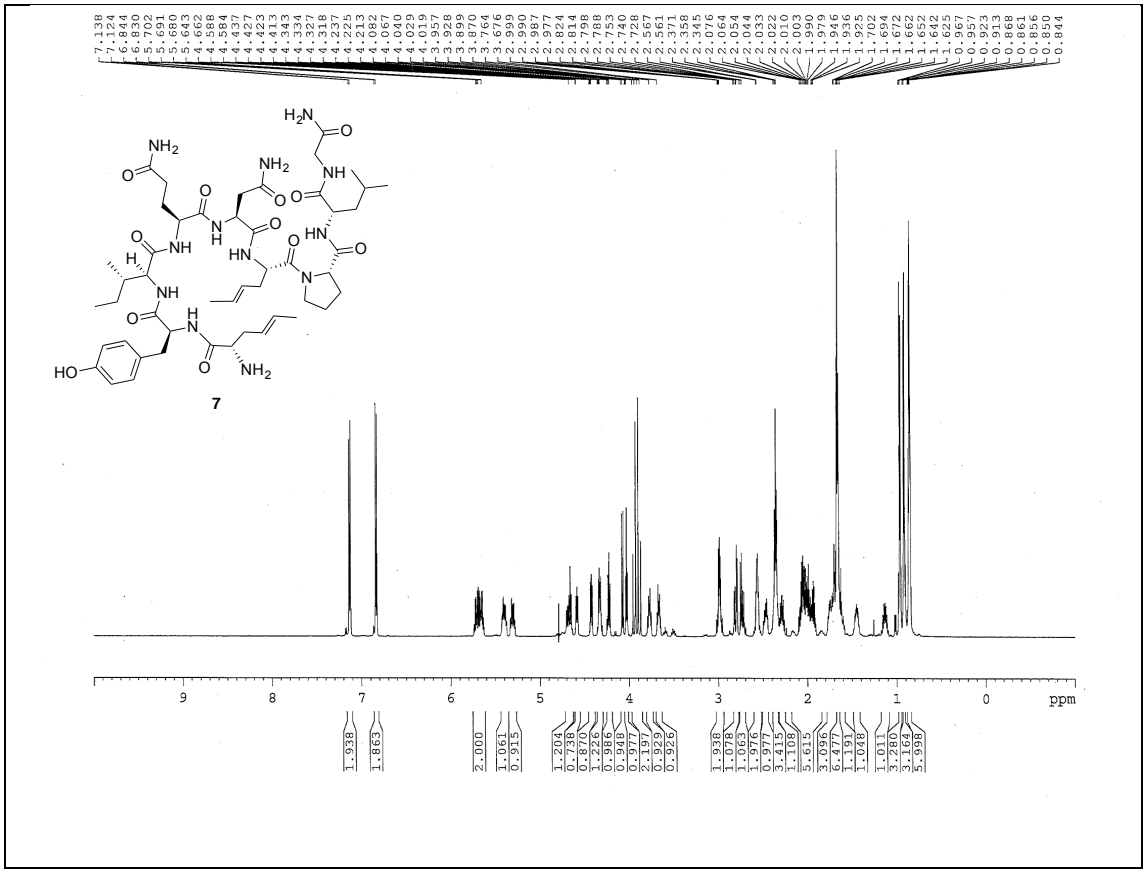

SI7
ppm

[1,6]-Dicarba-[2]-Ala Human insulin A chain (6-13) 5



[1,6]-*E*-Crt Oxytocin 7

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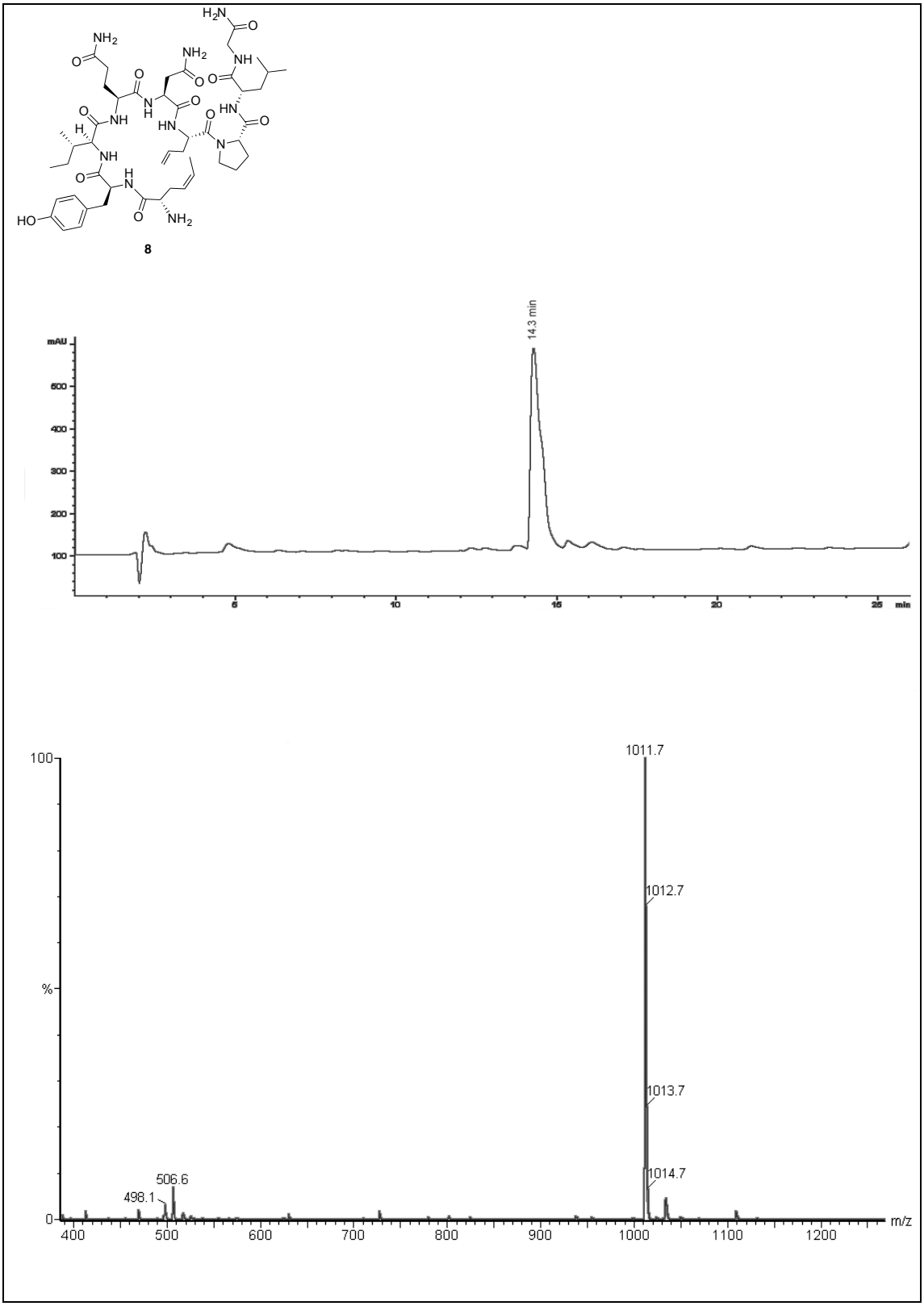
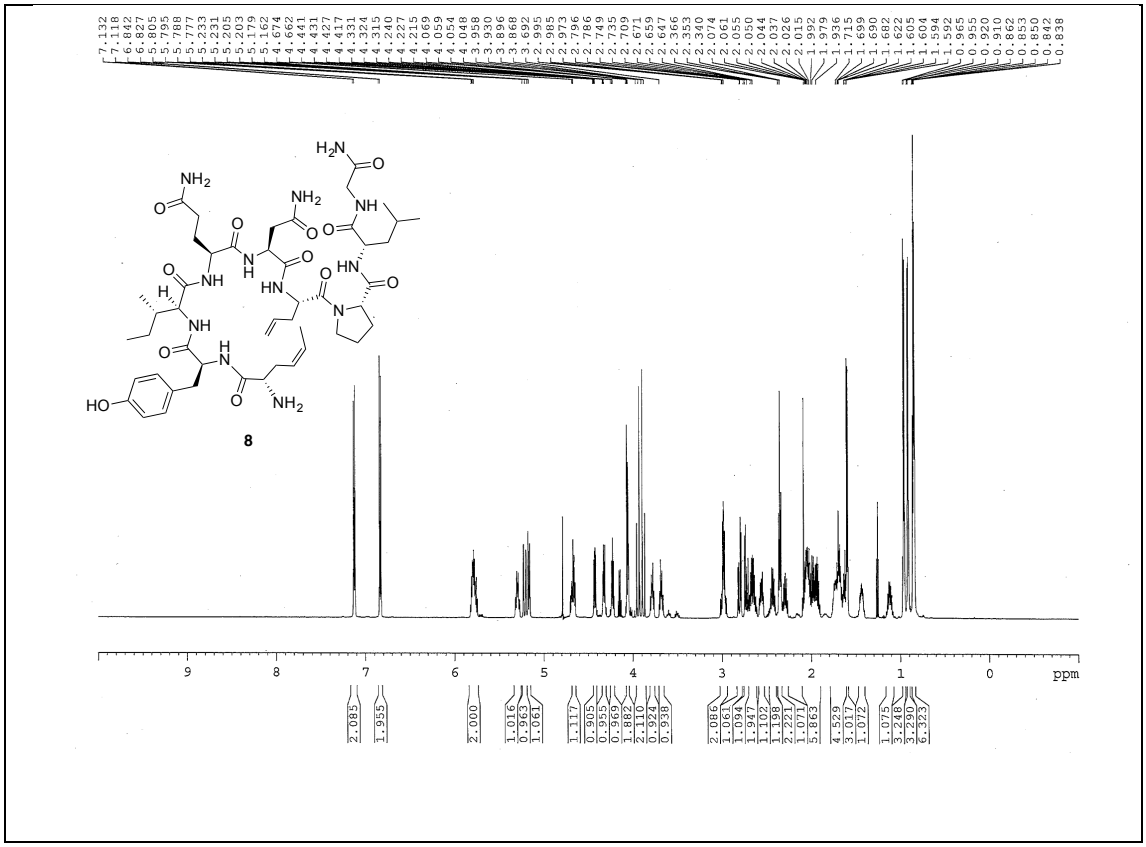
5.702
5.691
5.680
5.643
4.662
4.588
4.584
4.437
4.427
4.423
4.413
4.343
4.334
4.327
4.318
4.237
4.225
4.213
4.082
4.067
4.040
4.029
4.019
3.957
3.928
3.899
3.870
3.764
3.676
2.999
2.990
2.987
2.977
2.824
2.814
2.798
2.788
2.753
2.740
2.728
2.567
2.561
2.371
2.358
2.345
2.076
2.064
2.054
2.044
2.033
2.022
2.010
2.003
1.990
1.979
1.946
1.936
1.925
1.702
1.694
1.672
1.662
1.652
1.642
1.625
0.967
0.957
0.923
0.913
0.868
0.861
0.856
0.850
0.844
7
9
8
7
6
5
4
3
2
1
0
ppm
1.938
1.863
2.000
1.061
0.915
1.204
0.738
0.870
1.226
0.986
0.949
0.977
2.197
0.929
0.926
1.938
1.078
1.063
1.976
0.977
3.415
1.108
5.615
3.096
6.477
1.191
1.048
1.011
3.280
3.164
5.998

[1]-*Z*-Crt-[6]-Agl Oxytocin 8




8
ppm

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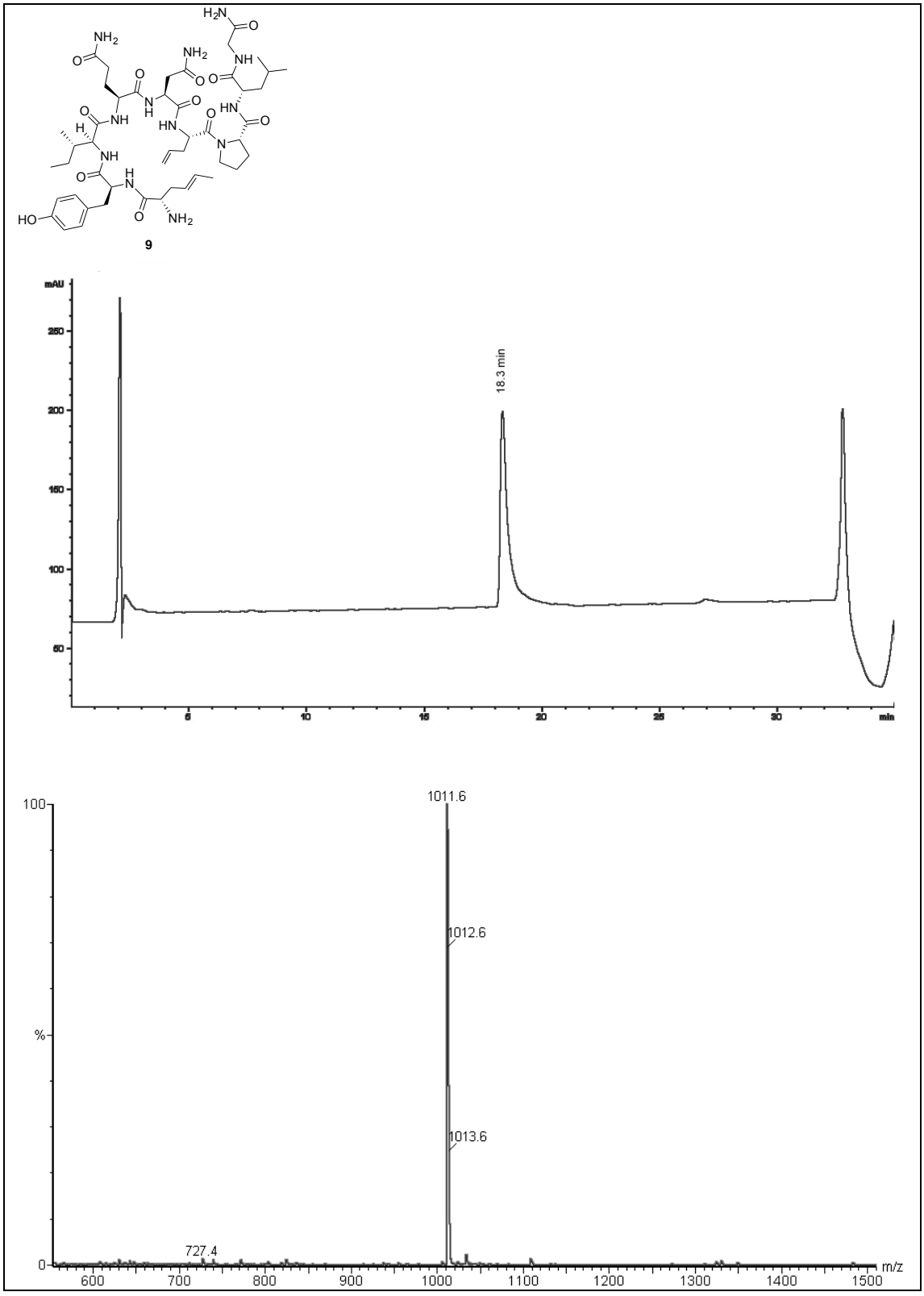
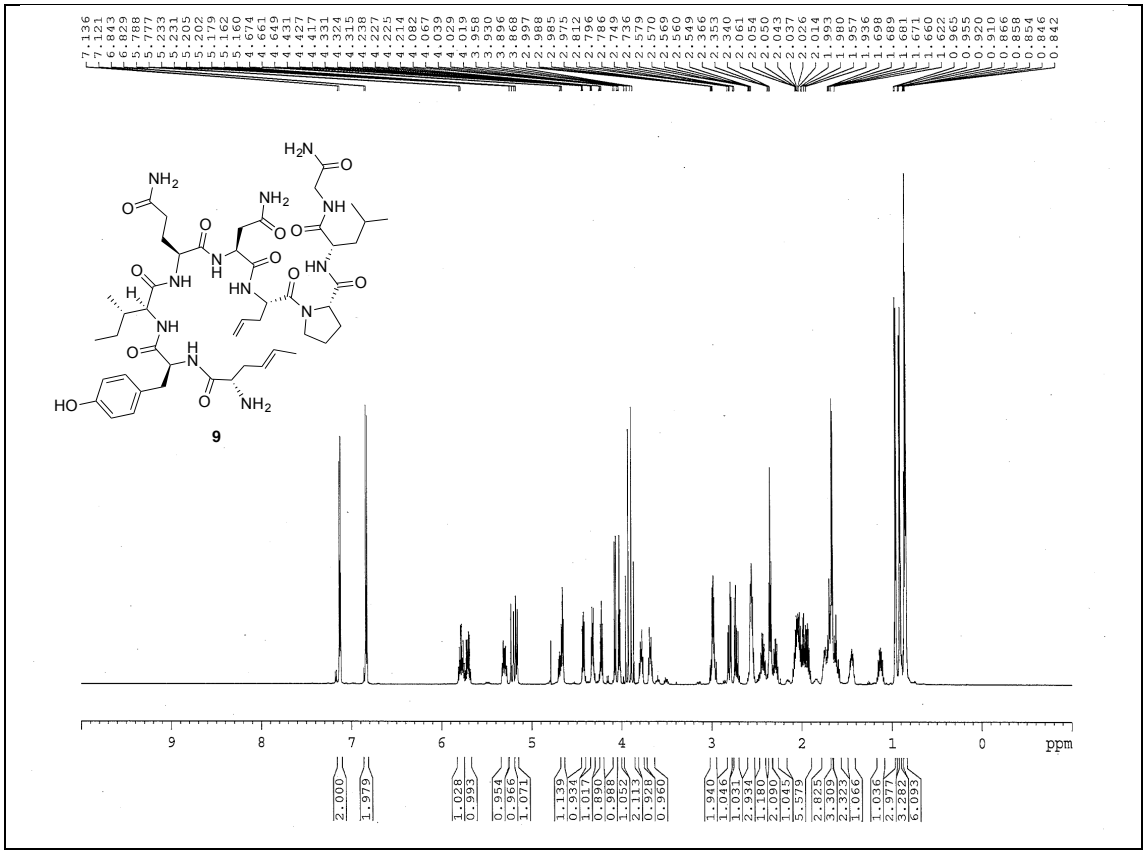
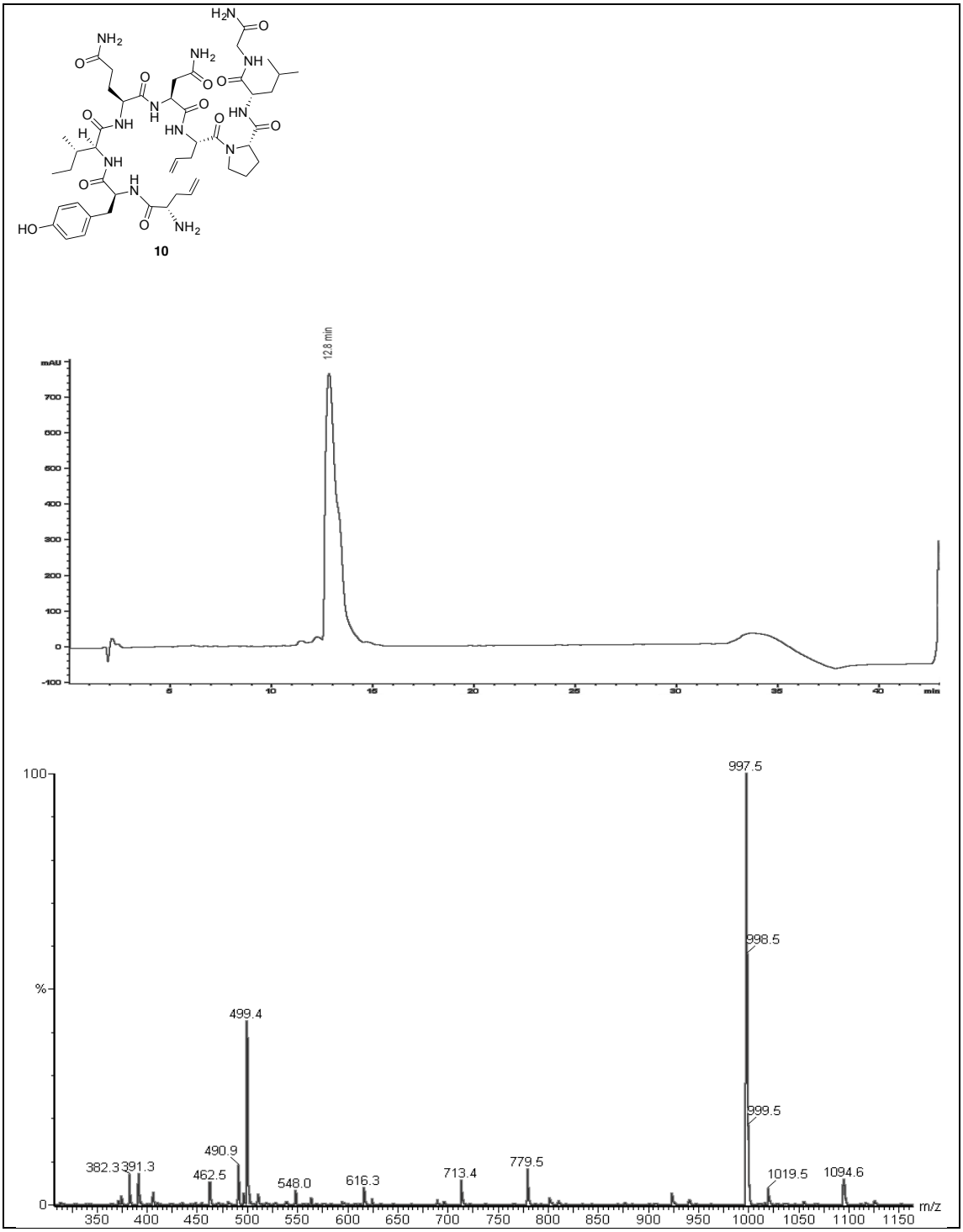
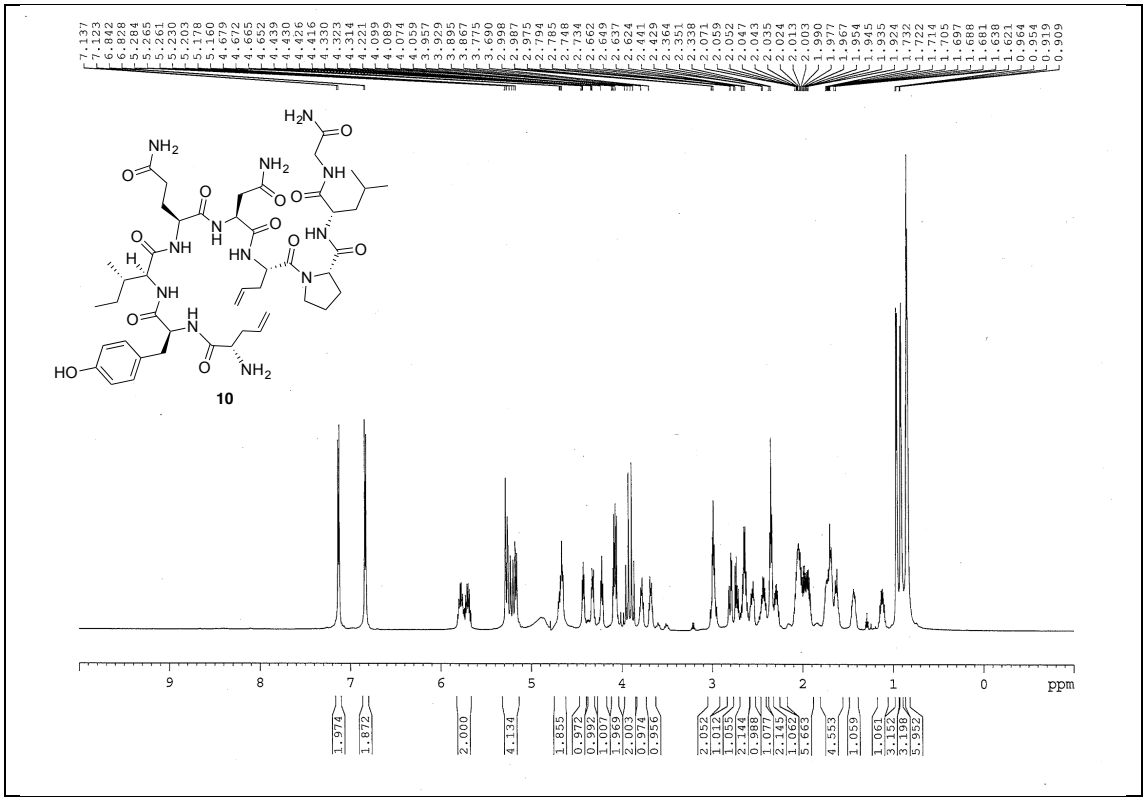



9
ppm

[1,6]-Agl Oxytocin 10

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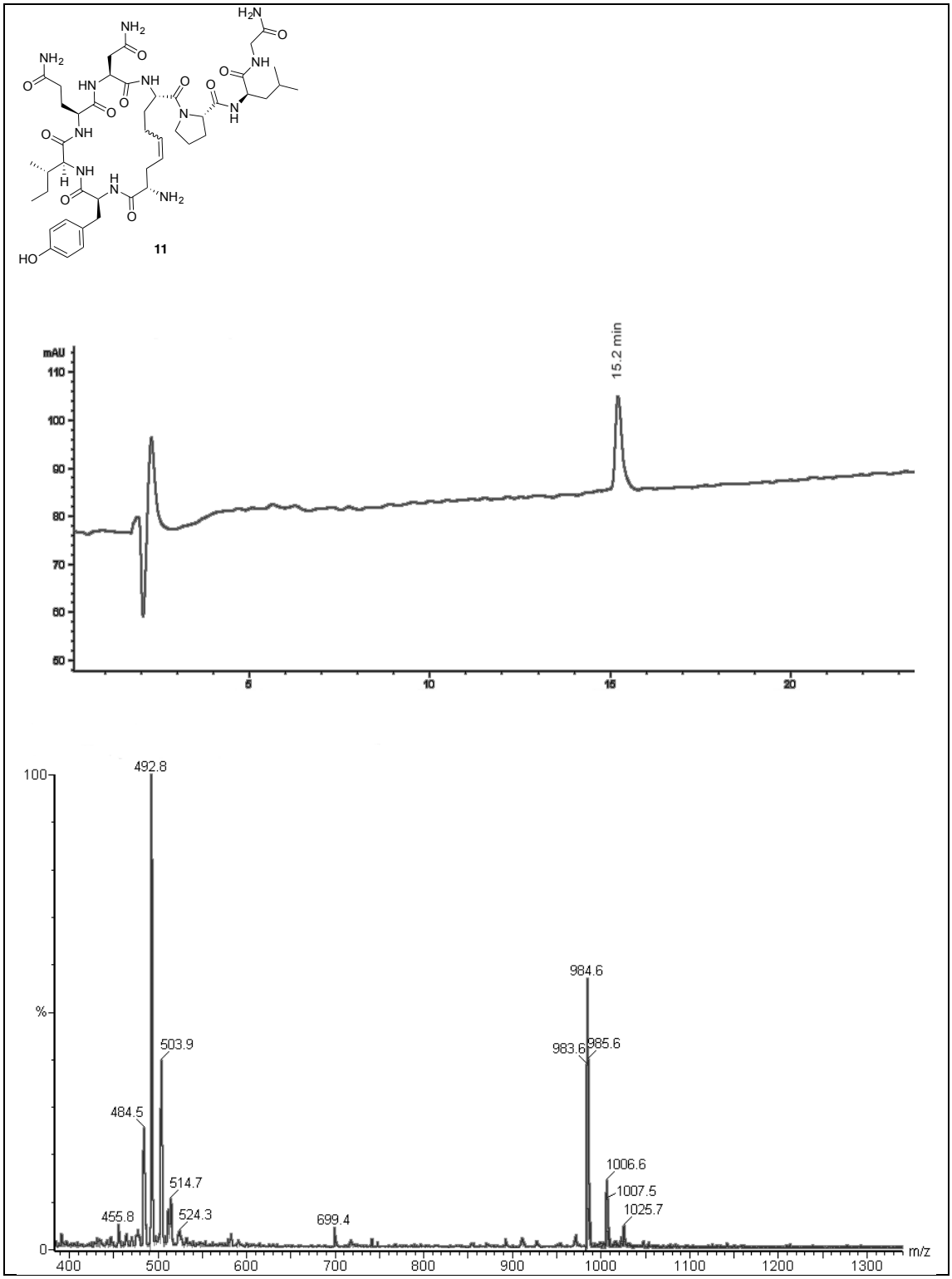
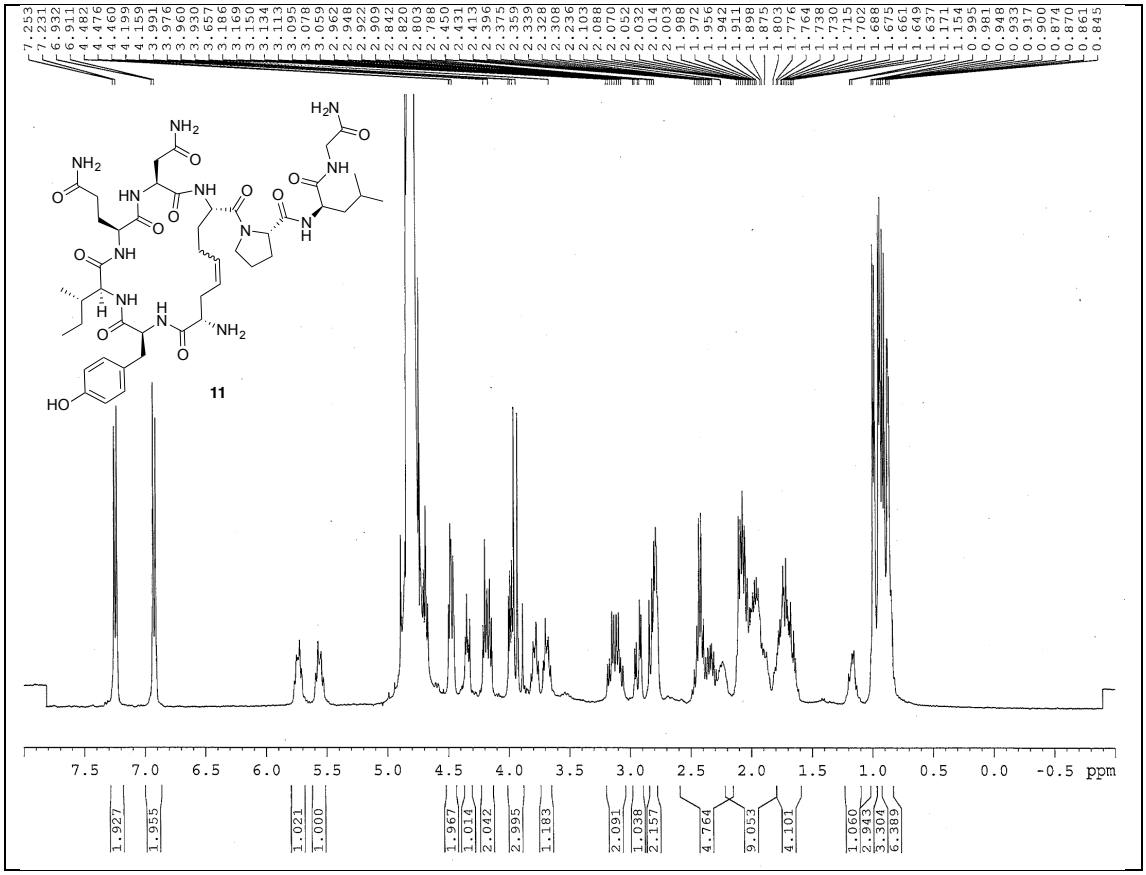
ppm

[1,6]-Homo-Dicarba Oxytocin 11




11
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6.0
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5.0
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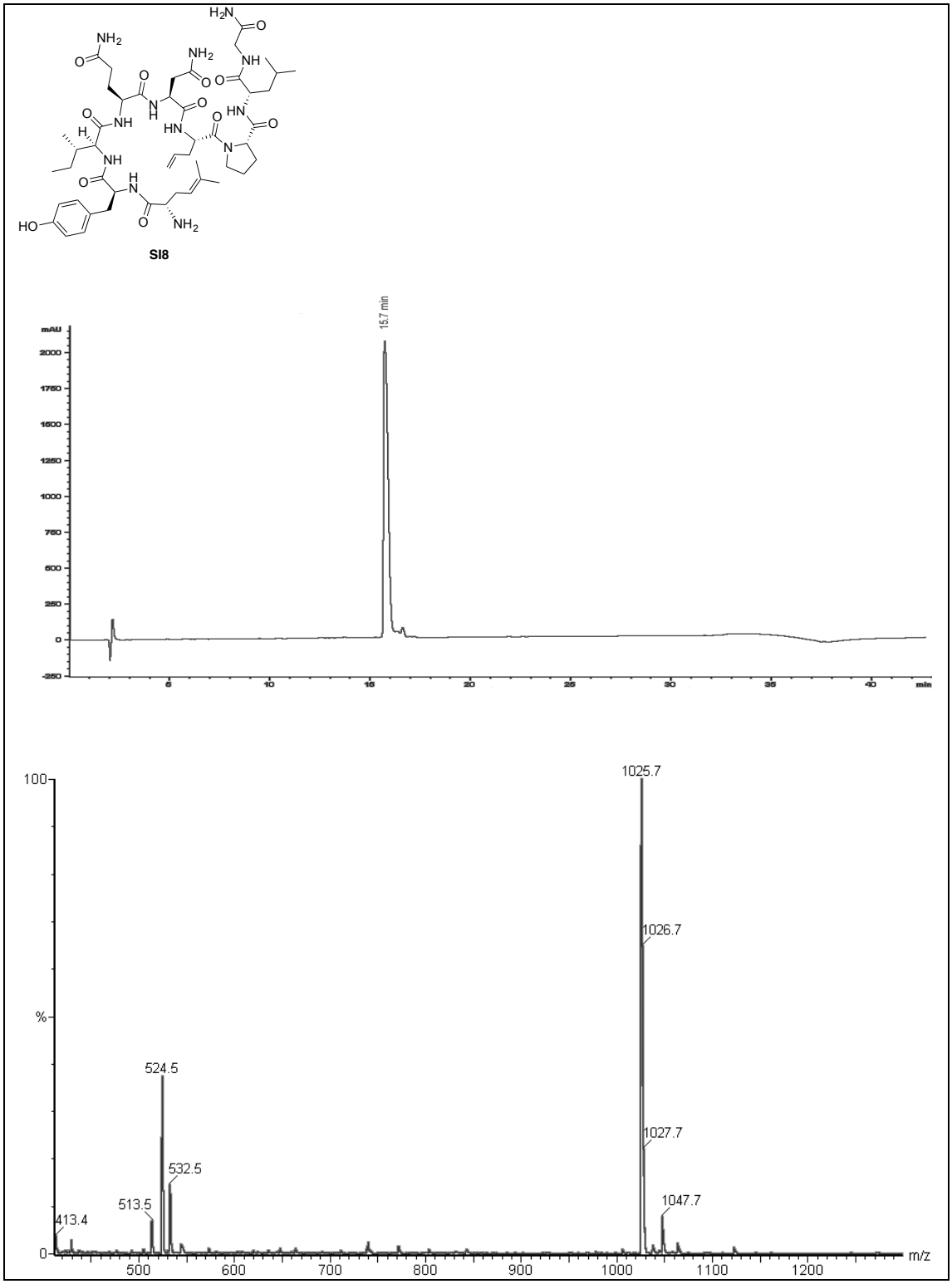
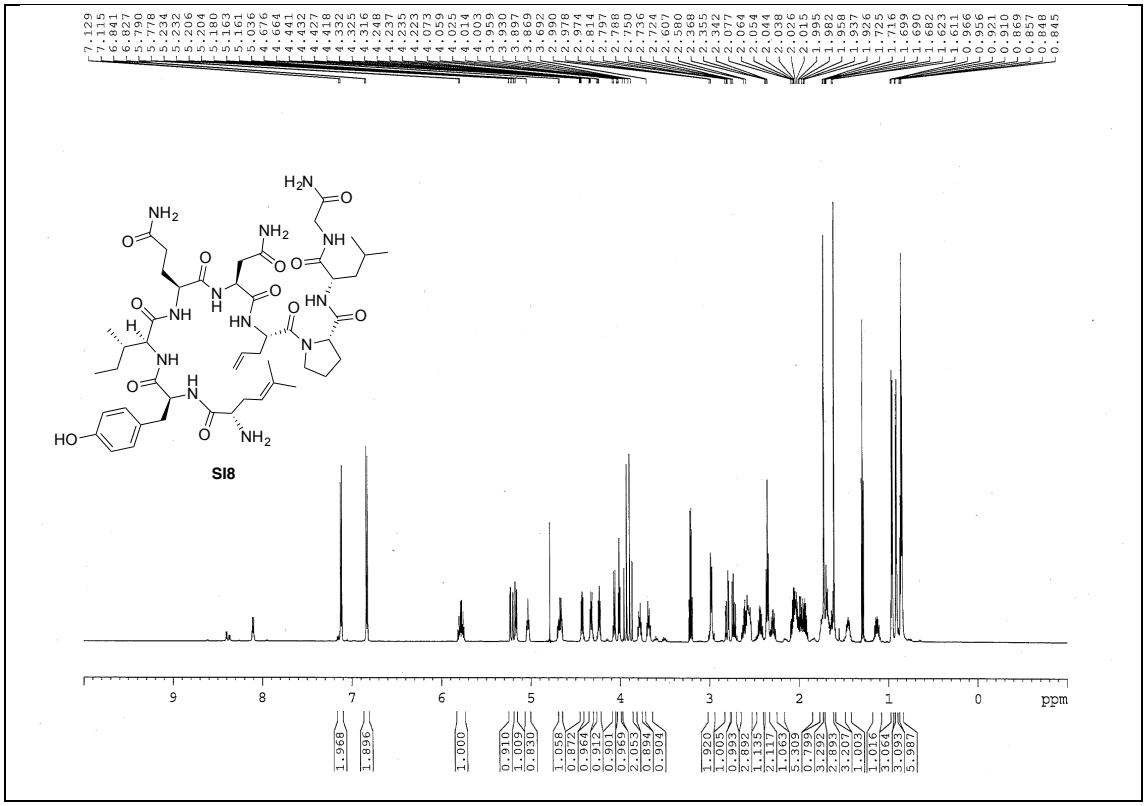
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

[1]-Pre-[6]-Agl Oxytocin SI8





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