Electronic Supplementary Material (ESI) for Chemical Communications


# Chemical communication: conductors and insulators of screw-sense preference between helical oligo(aminoisobutyric acid) domains

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**Supporting Information**

## 1. General Experimental

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Brucker Ultrashield 400 or 500 spectrometer. $^{1}H$ and $^{13}C$ spectra were referenced relative to the solvent residual peaks and the chiemical shits ($\delta$) reported in ppm downfield of trimethylsilane ($\delta_H$: $CDCl_3$ 7.26 ppm; $\delta_C$ $CDCl_3$ 77.0 ppm; $\delta_H$: $CD_3OD$ 3.31 ppm; $\delta_C$ $CD_3OD$ 49.05 ppm). Coupling constants (*J*) are reported in hertz and rounded to 0.5 Hz. Splitting patters are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) apparent (ap) or a combination of these. Carbon multiplicities have been assigned by gradient heteronuclear single quantum correlation (gHSQC) or by distortionless enhancement by polarization transfer (DEPT) experiments.

Low and high resolution mass spectra were recorded by staff in the University of Manchester. Electrospray (ES) spectra were recorded on a Waters Platform II and high resolution mass spectra (HRMS) were recorded on a Thermo Finnigan MAT95XP and accurate to ± 0.001. Infrared spectra were recorded as on an Ati Mason Genesis Series FTIR spectrometer as film on a sodium chloride plate or as a soli deposit. Melting points were determined on a GallenKamp apparatus and are uncorrected. Circular dicroism spectra (CD) were recorded on a Jasco J-815 spectrometer using 1 mm cell length at 20 $^{o}C$. Optical rotation measurements were taken on a AA-100 polarimeter at 20 $^{o}C$ with the solvent and concentration stated.

Thin layer chromatography (TLC) was performed using commercially available pre-coated plates (Macherey-Nagel alugram. Sil G/$UV_{254}$) and visualised with UV light at 254 nm; paranisaldehyde, ninhydrin or phosphomolibdic acid dips were used to reveal the products. Flash column chromatography was carried out using Fluorochem Davisil 40-63u 60Å.

All reactions were conducted under a nitrogen atmosphere unless otherwise stated and oven flamed glassware was used. THF was distilled under nitrogen from sodium using a benzophenone indicator. $CH_2Cl_2$ and toluene were obtained by distillation over calcium hydride under a nitrogen atmosphere. Anhydrous acetonitrile and dimethylformamide were purchased from Sigma-Aldrich. Acetonitrile was further dried over 4 Å oven-activated molecular sieves for 1h previous use. Triethylamine was distilled over calcium hydride under nitrogen atmosphere. Petrol refers to the fraction of light petroleum ether boiling between 40 and 65 $^{o}C$. All other solvents and commercially available reagents were used as received.

The procedures for the synthesis of $HAib_4OtBu$, $N_3Aib_4OH$, $HAib_4GlyNH_2$, Cbz-L-$PheAib_4OH$, and Cbz-L-$PheAib_8OH$ have been described previously.[1]

## 2. Supplementary methods: Detailed synthetic procedures

**General procedure A for the coupling reaction between the Cbz-linkerOH Cbz-2 and $HAib_4GlyNH_2$ 5 using EDC in the presence of HOBt.**

A round-bottomed flask was charged with a solution of 1.5 equiv of Cbz-linkerOH **Cbz-2** and 2.25 equiv of HOBt in dry $CH_2Cl_2$ (10 mL/mmol). This mixture was cooled down to 0 ºC and 2.25 equiv of EDC were added dropwise. After completed dissolution or at least 1 h, 1.0 equiv of $HAib_4GlyNH_2$ **5** was added and the mixture was allowed to warm up to room temperature. After 2 days, the reaction was concentrated under reduced pressure to give a crude product Cbz-linker-$Aib_4GlyNH_2$ **8** that was purified by column chromatography using the appropriate mixture of eluents.

**General procedure B for the coupling reaction between the Cbz-linkerOH 2 and $HAib_4GlyNH_2$ 5 using HBTU in the presence of HOBt.**

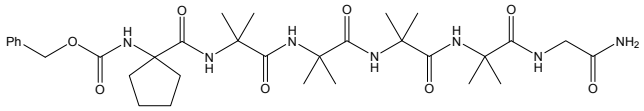
A round-bottomed flask was charged with a solution of 1.0 equiv of Cbz-linkerOH **Cbz-2** in dry $CH_2Cl_2$ (10 mL/mmol). This mixture was cooled down to 0 ºC, then 1.0 equiv of HBTU, 1.0 equiv of HOBt and 2.0 equiv of DIPEA were added dropwise. After 1 h at 0 °C, 1.0 equiv of $HAib_4GlyNH_2$ **5** was added and the mixture was allowed to warm up to room temperature. After 4 days, the reaction was concentrated under reduced pressure to give a crude product Cbz-linker-$Aib_4GlyNH_2$ **8** that was purified by column chromatography using the appropriate mixture of eluents.[2]

**General procedure C for the coupling reaction between the Cbz-linkerOH Cbz-2 and $HAib_4GlyNH_2$ 5 *via* the acyl fluoride.**

A round-bottomed flask was charged with a solution of 1.0 equiv of Cbz-linkerOH **Cbz-2** in dry $CH_2Cl_2$ (5 mL/mmol). This mixture was cooled down to 0 ºC, 2.0 or 10.0 equiv of cyanuric fluoride and 1.0 or 2.0 equiv of pyridine were added. The mixture was stirred at 0 ºC for 1 h, allowed to warm up to room temperature and stirred for additional 1 h. The mixture was then diluted with $CH_2Cl_2$ (80 mL/mmol) and the mixture was washed with cold water (3 times, 20 mL/mmol), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give the corresponding acyl fluoride that required no further purification and directly engaged to the following step.

A round-bottomed flask was charged with a solution of 3.0 or 2.0 equiv of Cbz-linker-F and 1 equiv of $HAib_4GlyNH_2$ **5** in dry acetonitrile (10 mL/mmol). Then 1.1 equiv of DIPEA was added and the mixture was stirred at room temperature for 4 days. The mixture was then diluted with EtOAc (70 mL/mmol) and the mixture was washed with 5% solution of $KHSO_4$ (2 times, 5 mL/mmol), saturated solution of $NaHCO_3$ (2 times, 5 mL/mmol) and brine (1 time, 5 mL/mmol). The organic phase was dried over $Na_2SO_4$ and concentrated under reduced pressure to give a crude product Cbz-linker-$Aib_4GlyNH_2$ **8** that was purified by column chromatography using the appropriate mixture of eluents.[3]

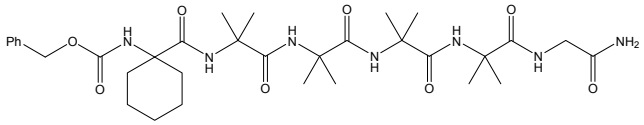
**Synthesis of CbzAc$_5$cAib$_4$GlyNH$_2$ 8b**



From a solution of Cbz-Ac$_5$cOH[4] (95 mg, 0.36 mmol), HOBt (73 mg, 0.54 mmol), EDC (0.10 mL, 84 mg, 0.54 mmol) and HAib$_4$GlyNH$_2$ **5** (100 mg, 0.24 mmol) in $CH_2Cl_2$ (2 mL) following the general procedure A and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-Ac$_5$cAib$_4$GlyNH$_2$ **8b** was obtained as a white solid (110 mg, 70 %).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.20. **mp:** 235-237 ºC. **IR**: (solid): $\nu_{max}$= 3285, 2983, 2938, 1655, 1650, 1643, 1536, 1530, 1519, 1382, 1360, 1262, 1227 cm$^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.32 (s, 6H), 1.35 (s, 6H), 1.46 (s, 6H), 1.50 (s, 6H), 1.69-1.86 (m, 6H), 2.13-2.25 (m, 2H), 3.82 (brs, 1H), 5.14 (s, 1H), 7.29-7.43 (m, 5H), 7.61 (brs, 1H), 7.88 (brs, 1H), 8.02 (brs, 1H), 8.04 (brs, 1H), 8.10 (brs, 1H). **$^{13}$C-NMR** (125 MHz, $CD_3OD$): $\delta$ 25.1 (2$CH_3$), 25.3 (2$CH_3$), 25.3 (2$CH_2$), 25.4 (2$CH_3$), 25.7 (2$CH_3$), 37.6 (2$CH_2$), 43.8 ($CH_2$), 57.7 (C), 58.0 (C), 58.2 (C), 58.3 (C), 67.7 ($CH_2$), 68.1 (C), 128.5 (2CH), 129.1 (CH), 129.7 (2CH), 138.8 (C), 158.3 (CO), 175.4 (CO), 176.8 (CO), 177.0 (CO), 178.0 (CO), 178.1 (CO), 178.2 (CO) ppm. **MS** (ES$^+$, MeOH) *m/e*= 682 ([M +Na]$^+$, 100%). **HRMS** (ES$^+$, MeOH): Calcd for $C_{32}H_{49}N_7O_8$+Na: 682.3535, found 682.3545.

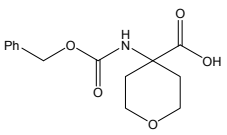
**Synthesis of CbzAc$_6$cAib$_4$GlyNH$_2$ 8c**



From a solution of Cbz-Ac$_6$cOH[4] (100 mg, 0.36 mmol), HOBt (73 mg, 0.54 mmol), EDC (0.10 mL, 84 mg, 0.54 mmol) and HAib$_4$GlyNH$_2$ **5** (100 mg, 0.24 mmol) in $CH_2Cl_2$ (2 mL) following the general procedure A and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-Ac$_6$cAib$_4$GlyNH$_2$ **8c** was obtained as a white solid (124 mg, 77 %).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.27. **mp:** 223-225 ºC. **IR**: (solid): $\nu_{max}$= 3292, 2983, 2935, 1654, 1529, 1453, 1382, 1359, 1247, 1226 cm$^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.31 (s, 6H), 1.34 (s, 6H), 1.46 (s, 6H), 1.50 (s, 6H), 1.50-1.70 (m, 6H), 1.83-1.89 (m, 4H), 3.83 (brs, 1H), 5.15 (s, 1H), 7.29-7.43 (m, 5H), 7.61 (brs, 1H), 7.96 (brs, 1H), 8.01 (brs, 1H), 8.10 (brs, 1H). **$^{13}$C-NMR** (125 MHz, $CD_3OD$): $\delta$ 22.5 (2$CH_2$), 25.2 (2$CH_3$), 25.2 (2$CH_3$), 25.4 (2$CH_3$), 25.7 (2$CH_3$), 26.4 ($CH_2$), 33.4 (2$CH_2$), 43.8 ($CH_2$), 57.5 (C), 57.9 (C), 58.2 (C), 58.3 (C), 60.3 (C), 67.7 ($CH_2$), 128.5 (2CH), 129.1 (CH), 129.7 (2CH), 138.8 (C), 157.8 (CO), 175.4 (CO), 177.0 (CO), 177.5 (CO), 178.1 (2CO), 178.3 (CO) ppm. **MS** (ES$^+$, MeOH) *m/e*= 696 ([M +Na]$^+$, 100%). **HRMS** (ES$^+$, MeOH): Calcd for $C_{33}H_{51}N_7O_8$+Na: 696.3691, found 696.3692.

**Synthesis of CbzThpOH Cbz-2d**



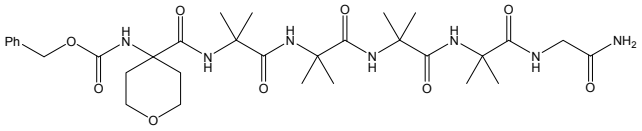
A round-bottomed flask was charged with a solution of 4-pyrone (2.86 g, 28.6 mmol), KCN (3.72 g, 57.2 mmol), $(NH_4)_2CO_3$ (11.0 g, 114.4 mmol) in a 1:1 mixture of water/ethanol (34 mL/34 mL). The mixture was heated under reflux (60 ºC) for 6 h. The solvents were removed under reduced pressure and the residue was

stirred in cold water, filtered and dried under high vaccum to give the hydantoin (2.86 g, 59 %), as a white solid that required no further purification.[5]

A round-bottomed flask was charged with the resulting hydantoin (2.76 g, 16.2 mmol), KOH (13.6 g, 243.6 mmol) in water (135 mL). The mixture was heated under reflux (130 ºC) for 16 h. The mixture was cooled down to 0 ºC and diluted with acetone (110 mL), then a solution of Cbz-Cl (11.6 mL, 13.85 g, 81.2 mmol) in acetone (36 mL) was added dropwise in 1 h. The mixture was stirred at room temperature for 6 h, an additional solution of Cbz-Cl (5.8 mL, 6.9 g, 40.6 mmol) in acetone (18 mL) was added dropwise. The mixture was stirred at room temperature for 3 days. Acetone was removed under reduced pressure, the unreacted Cbz-Cl was extracted with EtOAc (2 times, 50 mL). The aqueous phase was acidified to pH=1 with HCl (6N) and the product was extracted with EtOAc (4 times, 50 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give the expected product Cbz-Thp **Cbz-2d** (3.69 g, 81 %), as a white solid that required no further purification. The product was recrystallised ($MeOH/CH_2Cl_2$) for analysis.[5]

**Rf**: $SiO_2/CH_2Cl_2$:MeOH 90:10 = 0.25. **mp:** 129-131 ºC. **IR**: (solid): $\nu_{max}$= 3332, 3032, 2974, 2853, 1718, 1654, 1532, 1279, 1249, 1103 $cm^{-1}$. **$^1$H-NMR** (400 MHz, $CD_3OD$): $\delta$ 1.93-2.03 (m, 2H), 2.07-2.17 (m, 2H), 3.62-3.71 (m, 2H), 3.74-3.81 (m, 2H), 5.07 (s, 2H), 7.26-7.40 (m, 5H) ppm. **$^{13}$C-NMR** (100 MHz, $CD_3OD$): $\delta$ 33.6 ($2CH_2$), 57.8 (C), 64.4 ($2CH_2$), 67.3 ($CH_2$), 128.8 (2CH), 129.0 (CH), 129.5 (2CH), 138.3 (C), 157.9 (CO), 177.2 (CO) ppm. **MS** ($ES^+$, MeOH) *m/e*= 302 ($[M+Na]^+$, 100%). **HRMS** ($ES^+$, MeOH): Calcd for $C_{14}H_{17}N_1O_5$+Na: 302.0999, found 302.0997.

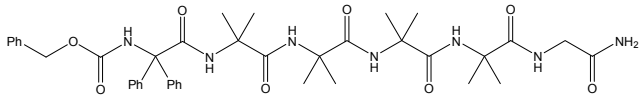
**Synthesis of CbzThpAib$_4$GlyNH$_2$ 8d**



From a solution of Cbz-ThpOH **Cbz-2d** (67 mg, 0.24 mmol), HOBt (32 mg, 0.24 mmol), HBTU (91 mg, 0.24 mmol), DIPEA (84 µL, 62 mg, 0.48 mmol) and $NH_2Aib_4GlyNH_2$ **5** (100 mg, 0.24 mmol) in $CH_2Cl_2$ (2 mL) following the general procedure B and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-ThpAib$_4$GlyNH$_2$ **8d** was obtained as a white solid (107 mg, 66 %).

**Rf**: $SiO_2/CH_2Cl_2$:MeOH 90:10 = 0.35. **mp:** 129-131 ºC. **IR**: (solid): $\nu_{max}$= 3285, 2982, 1651, 1527, 1454, 1382, 1361, 1262, 1225 $cm^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.32 (s, 6H), 1.34 (s, 6H), 1.46 (s, 6H), 1.50 (s, 6H), 1.78-1.85 (m, 2H), 2.09-2.18 (m, 2H), 3.67-3.74 (m, 2H), 3.77-3.85 (m, 4H), 5.16 (s, 2H), 7.28-7.43 (m, 5H), 7.46-7.51 (m, 1H), 7.53-7.57 (m, 1H), 7.72-7.76 (m, 2H), 7.86-7.90 (m, 1H), 8.00 (brs, 1H), 8.09-8.12 (m, 1H), 8.14 (brs, 1H) ppm. **$^{13}$C-NMR** (100 MHz, $CD_3OD$): $\delta$ 25.1 ($2CH_3$), 25.2 ($2CH_3$), 25.4 ($2CH_3$), 25.7 ($2CH_3$), 33.6 ($2CH_2$), 43.8 ($CH_2$), 54.9 (C), 57.6 (C), 57.8 (C), 58.2 (C), 58.3 (C), 64.5 ($2CH_2$), 67.8 ($CH_2$), 128.5 (2CH), 129.2 (CH), 129.7 (2CH), 138.7 (C), 157.9 (CO), 175.4 (CO), 176.4 (CO), 176.8 (CO), 176.8 (CO), 178.1 (CO), 178.2 (CO) ppm. **MS** ($ES^+$, MeOH) *m/e*= 698 ($[M+Na]^+$, 100%). **HRMS** ($ES^+$, MeOH): Calcd for $C_{32}H_{49}N_7O_8$+Na: 698.3484, found 698.3477.

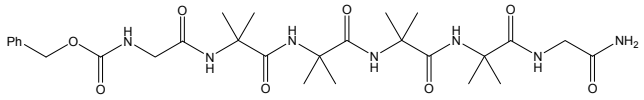
**Synthesis of Cbz-DpgAib$_4$GlyNH$_2$ 8e**



From a solution of Cbz-DpgOH[3] (181 mg, 0.50 mmol), cyanuric fluoride (86 µL, 135 mg, 1.0 mmol), pyridine (41 µL, 40 mg, 0.50 mmol), DIPEA (32 µL, 24 mg, 0.18 mmol) and NH$_2$Aib$_4$GlyNH$_2$ **5** (69 mg, 0.17 mmol) following the general procedure C and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-DpgAib$_4$GlyNH$_2$ **8e** was obtained as a white solid (110 mg, 87 %).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.38. **mp:** 216-218 ºC. **IR**: (solid): $\nu_{max}$= 3310, 2986, 2935, 1655, 1650, 1523, 1518, 1382, 1359, 1248, 1225, 1214 cm$^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.30 (s, 6H), 1.33 (s, 6H), 1.34 (s, 6H), 1.50 (s, 6H), 3.82 (s, 2H), 5.20 (s, 2H), 7.25-7.42 (m, 15H), 7.84 (m, 2H), 7.92 (brs, 1H), 8.42 (brs, 1H) ppm. **$^{13}$C-NMR** (125 MHz, $CD_3OD$): $\delta$ 24.9 ($2CH_3$), 25.2 ($2CH_3$), 25.3 ($2CH_3$), 25.7 ($2CH_3$), 43.7 ($CH_2$), 57.8 (C), 58.1 (C), 58.3 (C), 58.4 (C), 68.3 ($CH_2$), 70.6 (C), 128.7 (2CH), 128.8 (2CH), 128.9 (4CH), 129.2 (CH), 129.2 (4CH), 129.7 (2CH), 138.5 (C), 142.9 (2C), 158.7 (CO), 173.2 (CO), 175.4 (CO), 177.0 (CO), 178.1 (3CO) ppm. **MS** (ES$^+$, MeOH) *m/e*= 780 ([M +Na]$^+$, 100%). **HRMS** (ES$^+$, MeOH): Calcd for $C_{40}H_{51}N_7O_8$+Na: 780.3691, found 780.3690.

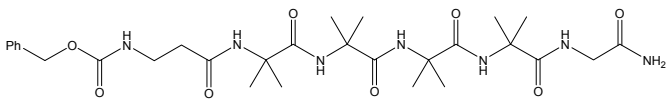
**Synthesis of CbzGlyAib$_4$GlyNH$_2$ 8g**



From a solution of Cbz-GlyOH (75 mg, 0.36 mmol), HOBt (73 mg, 0.54 mmol), EDC (0.10 mL, 84 mg, 0.54 mmol) and HAib$_4$GlyNH$_2$ **5** (100 mg, 0.24 mmol) in $CH_2Cl_2$ (2 mL) following the general procedure A and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-GlyAib$_4$GlyNH$_2$ **8g** was obtained as a white solid (110 mg, 76 %).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.33. **mp:** 261-263 ºC. **IR**: (solid): $\nu_{max}$= 3312, 2984, 2933, 2459, 2391, 1650, 1646, 1634, 1521, 1436, 1415, 1361, 1168 cm$^{-1}$. **$^1$H-NMR** (400 MHz, $CD_3OD$): $\delta$ 1.40 (s, 6H), 1.41 (s, 12H), 1.50 (s, 6H), 3.73 (s, 2H), 3.82 (s, 2H), 5.11 (s, 2H), 7.27-7.40 (m, 5H) ppm. **$^{13}$C-NMR** (100 MHz, $CD_3OD$): $\delta$ 25.2 ($4CH_3$), 25.4 ($2CH_3$), 25.6 ($2CH_3$), 43.8 ($CH_2$), 45.2 ($CH_2$), 57.6 (C), 57.8 (C), 58.0 (C), 58.2 (C), 67.9 ($CH_2$), 128.8 (2CH), 129.2 (CH), 129.6 (2CH), 138.2 (C), 159.5 (CO), 172.3 (CO), 175.4 (CO), 176.7 (CO), 177.8 (CO), 178.0 (CO), 178.1 (CO) ppm. **MS** (ES$^+$, MeOH) *m/e*= 628 ([M +Na]$^+$, 100%). **HRMS** (ES$^+$, MeOH): Calcd for $C_{28}H_{43}N_7O_8$+Na: 628.3065, found 628.3058.

**Synthesis of CbzβAlaAib$_4$GlyNH$_2$ 8h**

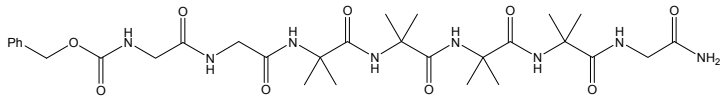


From a solution of Cbz-βAlaOH (80 mg, 0.36 mmol), HOBt (73 mg, 0.54 mmol), EDC (0.10 mL, 84 mg, 0.54 mmol) and HAib$_4$GlyNH$_2$ **5** (100 mg, 0.24 mmol) in $CH_2Cl_2$ (2 mL) following the general procedure A and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-βAlaAib$_4$GlyNH$_2$ **8h** was obtained as a white solid (117 mg, 79 %).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.30. **mp:** 247-249 ºC. **IR**: (solid): $\nu_{max}$= 3297, 3270, 2994, 2982, 2919, 1650, 1536, 1529, 1383, 1360, 1271 cm$^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.38 (s, 12H), 1.45 (s, 6H), 1.50 (s,

6H), 2.45 ($t_{ap}$, $J_{ap}$=6.3 Hz, 2H), 3.41 ($t_{ap}$, $J_{ap}$=6.3 Hz, 2H), 3.82 (s, 2H), 5.07 (s, 2H), 7.27-7.36 (m, 5H). **$^{13}$C-NMR** (100 MHz, $CD_3OD$): $\delta$ 25.3 ($4CH_3$), 25.3 ($2CH_3$), 25.7 ($2CH_3$), 37.3 ($CH_2$), 38.3 ($CH_2$), 43.8 ($CH_2$), 57.5 (C), 57.8 (C), 58.1 (C), 58.2 (C), 67.6 ($CH_2$), 128.9 (2CH), 129.1 (CH), 129.6 (2CH), 138.3 (brC), 158.9 (brCO), 173.9 (CO), 175.4 (CO), 176.6 (CO), 177.9 (CO), 178.1 (2CO) ppm. **MS** ($ES^+$, MeOH) *m/e*= 642 ([M +Na]$^+$, 100%). **HRMS** ($ES^+$, MeOH): Calcd for $C_{29}H_{45}N_7O_8$+Na: 642.3222, found 642.3226.

**Synthesis of Cbz-GlyGlyAib$_4$GlyNH$_2$ 8i**



From a solution of Cbz-GlyGlyOH (96 mg, 0.36 mmol), HOBt (73 mg, 0.54 mmol), EDC (0.10 mL, 84 mg, 0.54 mmol) and HAib$_4$GlyNH$_2$ **5** (100 mg, 0.24 mmol) in $CH_2Cl_2$ (2 mL) following the general procedure A and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide CbzGlyGlyAib$_4$GlyNH$_2$ **8i** was obtained as a white solid (127 mg, 80 %).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.20. **mp:** 230-232 ºC. **IR**: (solid): $\nu_{max}$= 3278, 2983, 2935, 1655, 1650, 1536, 1530, 1223 cm$^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.41 (s, 6H), 1.43 (s, 6H), 1.45 (s, 6H), 1.50 (s, 6H), 3.80-3.84 (m, 6H), 5.12 (s, 2H), 7.28-7.38 (m, 5H), 7.44-7.56 (m, 2H), 7.71-7.78 (m, 2H), 7.83-7.92 (m, 3H), 8.12 (brs, 1H), 8.18 (brs, 1H). **$^{13}$C-NMR** (100 MHz, $CD_3OD$): $\delta$ 25.3 ($6CH_3$), 25.7 ($2CH_3$), 43.7 ($CH_2$), 44.4 ($CH_2$), 45.2 ($CH_2$), 57.7 (C), 57.9 (C), 58.2 (C), 58.3 (C), 68.0 ($CH_2$), 128.9 (2CH), 129.2 (CH), 129.6 (2CH), 138.1 (C), 159.3 (CO), 171.7 (CO), 173.5 (CO), 175.4 (CO), 176.6 (CO), 176.7 (CO), 178.2 (CO), 178.3 (CO) ppm. **MS** ($ES^+$, MeOH) *m/e*= 685 ([M +Na]$^+$, 100%). **HRMS** ($ES^+$, MeOH): Calcd for $C_{30}H_{46}N_8O_9$+H: 663.3461, found 663.3481.

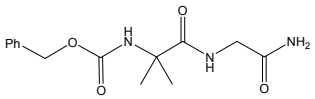
**General procedure D for cleavage of the Cbz protecting group from 8.**

A round-bottomed flask was charged with a solution of 1.0 equiv of Cbz-linker-Aib$_4$GlyNH$_2$ **8** in MeOH (5 mL/mmol) and 5-10% of Pd/C was added carefully. The mixture was stirred under $H_2$ atmosphere (balloon) until completion (TLC monitoring). Upon completion, the mixture was filtered through a celite pad washing with EtOAc. The mixture was then concentrated under reduced pressure to give the expected amine NH$_2$-linker-Aib$_4$GlyNH$_2$ **9** that required no further purification.

**General procedure E for the coupling of Cbz-L-PheAib$_4$OH 7 and NH$_2$-linker-Aib$_4$GlyNH$_2$ 9 *via* azlactone opening.**

A round-bottomed flask was charged with a solution of 1.0 equiv. of Cbz-L-PheAib$_4$-OH **7** in acetic anhydride (10 mL/mmol). The mixture was heated at 120 ºC for 2h. The solvent was removed in vacuo and last traces of acetic anhydride were removed by coevaporation with dry toluene (3 times). The resulting azlactone was directly dissolved in dry acetonitrile (20 mL/mmol), 1.0 equiv of NH$_2$-linker-Aib$_4$GlyNH$_2$ **9** (obtained by the cleavage of the Cbz protecting group from Cbz-linker-Aib$_4$GlyNH$_2$ **8** following the general procedure D) was added. The mixture was heated under reflux (90 °C) for 3 days. The mixture was cooled down to 0 ºC and the precipitate collected by filtration and washed with cold acetonitrile and cold ether (mother liquor contains oftentimes some product). The precipitate (eventually mother liquid) was further purified by column chromatography, using the appropriate mixture of eluents, to give the expected product Cbz-L-PheAib$_4$-linker-Aib$_4$GlyNH$_2$ **1**.

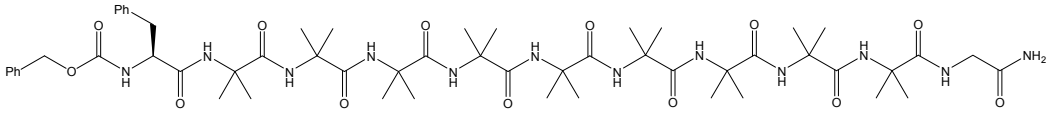
**Synthesis of CbzAibGlyNH$_2$**



A round-bottomed flask was charged with a solution of Cbz-AibOH (400 mg, 1.68 mmol), HOBt (340 mg, 2.52 mmol) in dry $CH_2Cl_2$ (5 mL). This mixture was cooled down to 0 ºC and EDC (0.46 mL, 84 mg, 2.52 mmol) were added dropwise. After completed dissolution or at least 1 h, glycinamide hydrochloride (242 mg, 2.20 mmol) was then added followed by $NEt_3$ (0.48 mL, 3.30 mmol). The mixture was allowed to warm up to room temperature for 24 h. Then the mixture was diluted with $CH_2Cl_2$ (100 mL), which was washed with $NaHCO_3$ saturated solution (3 times, 5 mL) and brine (1 times, 5 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a crude product that was purified by column chromatography (2% EtOH-$CH_2Cl_2$), peptide Cbz-AibGlyNH$_2$ (310 mg, 63%) was obtained as a white solid.

**Rf:** $SiO_2$/$CH_2Cl_2$:EtOH 95:5 = 0.30. **mp:** 148-150 °C. **IR** (film): $\nu_{max}$= 3327, 1699, 1651, 1519, 1259, 1079 cm$^{-1}$. **$^1$H NMR** (400 MHz, $CD_3OD$): $\delta$ 1.43 (s, 6H), 3.77 (s, 2H), 5.08 (s, 2H), 7.29–7.36 (m, 5H) ppm. **$^{13}$C NMR** (100 MHz, $CD_3OD$): $\delta$ 25.6 ($2CH_3$), 43.8 ($CH_2$), 57.8 (C), 67.8 ($CH_2$), 129.1 (2CH), 129.2 (CH), 129.5 (2CH), 138.1 (C), 158.2 (CO), 175.3 (CO), 177.9 (CO) ppm. **MS** ($ES^+$, MeOH): 316 ($[M+Na]^+$, 100%), 294 ($[M+H]^+$, 5%). **HRMS** ($ES^+$, MeOH): Calcd for $C_{14}H_{19}N_3O_4$ + Na: 316.1268, found 316.1279

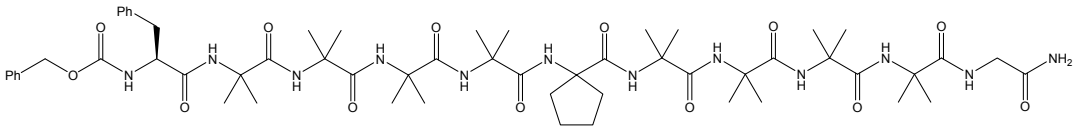
**Synthesis of Cbz-L-PheAib$_9$GlyNH$_2$ 1a**



A round-bottomed flask was charged with a solution of Cbz-L-PheAib$_8$OH **12** (210 mg, 0.21 mmol) in acetic anhydride (4 mL). The mixture was heated at 120 ºC for 2h. The solvent was removed in vacuo and last traces of acetic anhydride were removed by coevaporation with dry toluene (3 times). The resulting azlactone was directly dissolved in dry acetonitrile (4 mL), $NH_2$AibGlyNH$_2$ (37 mg, 0.24 mmol) (obtained by the cleavage of the Cbz protecting group from Cbz-$NH_2$AibGlyNH$_2$ following the general procedure B) was added. The mixture was heated under reflux (90 °C) for 3 days. The mixture was cooled to 0 ºC and the precipitate collected by filtration and washed with cold acetonitrile and cold ether. The precipitate was further purified by column chromatography (10 % EtOH-$CH_2Cl_2$) the peptide Cbz-L-PheAib$_9$GlyNH$_2$ **1a** was obtained as a white solid (70 mg, 29%).

**Rf:** $SiO_2$/$CH_2Cl_2$:EtOH 90:10 = 0.33. **mp:** 242-244 °C. **IR** (film): $\nu_{max}$= 3289, 2985, 1649, 1526, 1382, 1361, 1226, 1168 cm$^{-1}$. **$^1$H NMR** (400 MHz, $CD_3OD$): $\delta$ 1.25 (s, 3H), 1.30 (s, 3H), 1.37 (s, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 1.48 (m, 33 H), 1.53 (s, 6H), 2.96–3.05 (m, 2H), 3.77 (d of A of AB quartet, $J$=17.0, 4.1 Hz, 1H), 3.91 (d of B of AB quartet, $J$=17.0, 5.0 Hz, 1H), 4.23 ($t_{ap}$, $J_{ap}$=7.5 Hz, 1H), 5.07 (A of AB quartet, $J$=12.5 Hz, 1H), 5.11 (B of AB quartet, $J$=12.5 Hz, 1H), 7.22–7.33 (m, 11H), 7.58 (brs, 1H), 7.73 (brs, 1H), 7.78 (brs, 1H), 7.88 (brs, 1H), 7.89 (brs, 1H), 7.91 (brs, 1H), 7.92 (brs, 1H), 8.00 (brs, 1H), 8.14 (t, $J$=6.0 Hz, 1H), 8.36 (brs, 1H) ppm. **$^{13}$C NMR** (125 MHz, $CD_3OD$): $\delta$ 24.0–25.1 (overlapping signals, $CH_3$), 26.0–26.4 (overlapping signals, $CH_3$), 38.3 ($CH_2$), 43.9 ($CH_2$), 57.6–58.3 (overlapping signals 9 C + 1 CH), 67.7 ($CH_2$), 128.0 (CH), 128.6 (2CH), 129.1 (CH), 129.6 (2CH), 129.6 (2CH), 130.6 (2CH), 138.0 (C), 138.2 (C), 158.6 (CO), 174.3 (CO), 175.5 (CO), 176.7 (CO), 177.3 (CO), 177.6 (CO), 177.7 (CO), 177.7 (2CO), 178.1 (CO), 178.2 (CO), 178.4 (CO) ppm. **MS** ($ES^+$, MeOH): 1143 ($[M+Na]^+$, 100%).

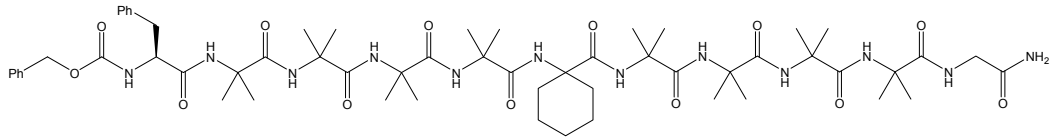
**Synthesis of Cbz-L-PheAib$_4$Ac$_5$cAib$_4$GlyNH$_2$ 1b**



From a solution of Cbz-L-PheAib$_4$OH azlactone (97 mg, 0.16 mmol, obtained quantitatively from Cbz-L-PheAib$_4$OH **7**), HAc$_5$cAib$_4$GlyNH$_2$ **9b** (82 mg, 0.16 mmol, obtained quantitatively from CbzAc$_5$cAib$_4$GlyNH$_2$ **8b** by procedure D) in dry acetonitrile (3 mL) following the general procedure E and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-L-PheAib$_4$Ac$_5$cAib$_4$GlyNH$_2$ **1b** was obtained as a white solid (117 mg, 65%).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.54. **mp:** 249-251 °C. **IR**: (solid): $\nu_{max}$= 3290, 1653, 1526, 1465, 1382, 1361, 1081 cm$^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.25 (s, 3H), 1.30 (s, 3H), 1.37 (s, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 1.47 (s, 6H), 1.48 (s, 6H), 1.49 (s, 9H), 1.50 (s, 6H), 1.53 (s, 6H), 1.68-1.86 (m, 4H), 1.92-2.08 (m, 2H), 2.18-2.38 (m, 2H), 2.94-3.07 (m, 2H), 3.67 (d of A of AB quartet, *J*=16.7, 4.0 Hz, 1H), 3.82 (d of B of AB quartet, *J*=16.7, 5.0 Hz, 1H), 4.23 ($t_{ap}$, $J_{ap}$= 7.9 Hz, 1H), 5.08 (A of AB quartet, *J*=12.6 Hz, 1H), 5.11 (B of AB quartet, *J*=12.6 Hz, 1H), 7.22-7.36 (m, 10H), 7.59 (brs, 1H), 7.79-7.83 (m, 2H), 7.89-7.93 (m, 3H), 8.00 (brs, 1H), 8.12-8.15 (m, 1H) ppm. **$^{13}$C-NMR** (125 MHz, $CDCl_3$): $\delta$ 23.6-24.4 (overlapping signals, 8$CH_3$), 24.8-25.8 (overlapping signals, 8$CH_3$), 24.4 (2$CH_2$), 29.7 (2$CH_2$), 36.9 ($CH_2$), 43.4 ($CH_2$), 57.04-56.52 (overlapping signals, 8C + 1CH), 66.8 (C), 67.3 ($CH_2$), 127.3 (CH), 128.0 (2CH), 128.5 (CH), 128.7 (2CH), 128.8 (2CH), 129.2 (2CH), 135.9 (C), 135.9 (C), 156.8 (CO), 172.0 (CO), 173.7 (CO), 174.4 (CO), 175.5 (CO), 175.5 (CO), 175.8 (CO), 176.2 (CO), 176.3 (CO), 176.4 (CO), 176.6 (CO), 176.8 (CO) ppm. **MS** (ES$^+$, MeOH) *m/e*= 1169 ([M +Na]$^+$, 100%).

**Synthesis of Cbz-L-PheAib$_4$Ac$_6$cAib$_4$GlyNH$_2$ 1c**

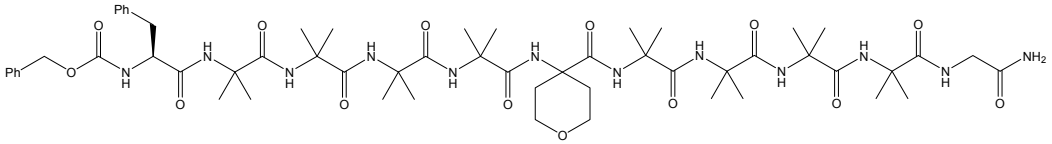


From a solution of Cbz-L-PheAib$_4$OH azlactone (62 mg, 0.10 mmol, obtained quantitatively from Cbz-L-PheAib$_4$OH **7**), HAc$_6$cAib$_4$GlyNH$_2$ **9c** (54 mg, 0.10 mmol, obtained quantitatively from Cbz-Ac$_6$cAib$_4$GlyNH$_2$ **8c**) in dry acetonitrile (2 mL) following the general procedure E and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-L-PheAib$_4$Ac$_6$cAib$_4$GlyNH$_2$ **1c** was obtained as a white solid (90 mg, 69%).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.50. **mp:** 253-255 °C. **IR**: (solid): $\nu_{max}$= 3290, 1655, 1520, 1465, 1382, 1361, 1081 cm$^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.27 (s, 3H), 1.31 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 1.47 (s, 6H), 1.48 (s, 15H), 1.49 (s, 3H), 1.51 (s, 3H), 1.53 (s, 6H), 1.45-1.55 (m, 2H), 1.58-1.67 (m, 3H), 1.68-1.78 (m, 2H), 1.79-1.90 (m, 1H), 2.08-2.17 (m, 1H), 2.23-2.30 (m, 1H), 2.95-3.07 (m, 2H), 3.67 (A of AB quartet, *J*=17.3 Hz, 1H), 3.82 (B of AB quartet, *J*=17.3 Hz, 1H), 4.23 ($t_{ap}$, $J_{ap}$= 7.9 Hz, 1H), 5.08 (A of AB quartet, *J*=12.6 Hz, 1H), 5.11 (B of AB quartet, *J*=12.6 Hz, 1H), 7.22-7.36 (m, 10H), 7.51 (brs, 1H), 7.75 (brs, 1H), 7.80 (brs, 1H), 7.90-7.97 (m, 4H), 8.11-8.16 (m, 1H) ppm. **$^{13}$C-NMR** (125 MHz, $CDCl_3$): $\delta$ 23.6-24.9 (overlapping signals, 8$CH_3$), 25.6-26.5 (overlapping signals, 8$CH_3$), 21.7 (2$CH_2$), 25.5 ($CH_2$), 36.8 (2$CH_2$), 36.8 ($CH_2$), 43.4 ($CH_2$), 57.1-56.4 (overlapping signals, 8C + 1CH), 59.4 (C), 67.4 ($CH_2$), 127.4 (CH), 128.0

(2CH), 128.5 (CH), 128.7 (2CH), 128.9 (2CH), 129.2 (2CH), 135.9 (C), 135.9 (C), 156.8 (CO), 171.9 (CO), 173.6 (CO), 174.3 (CO), 175.2 (CO), 175.2 (CO), 175.8 (CO), 176.1 (CO), 176.3 (CO), 176.5 (CO), 176.6 (CO), 176.8 (CO) ppm. **MS** ($ES^+$, MeOH) *m/e*= 1183 ($[M+Na]^+$, 100%).

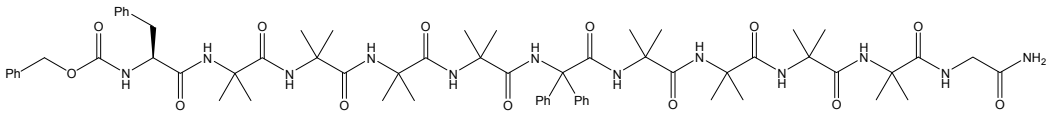
**Synthesis of Cbz-L-PheAib$_4$ThpAib$_4$GlyNH$_2$ 1d**



From a solution of Cbz-L-PheAib$_4$OH azalactone (87 mg, 0.14 mmol, obtained quantitatively from Cbz-L-PheAib$_4$OH **7**), HThpAib$_4$GlyNH$_2$ **9d** (76 mg, 0.14 mmol, obtained quantitatively from Cbz-ThpAib$_4$GlyNH$_2$ **8d**) in dry acetonitrile (3 mL) following the general procedure E and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-L-PheAib$_4$ThpAib$_4$GlyNH$_2$ **1d** was obtained as a white solid (49 mg, 30%).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.60. **mp:**. 223-225 °C. **IR**: (solid): $\nu_{max}$= 3298, 2981, 1646, 1521, 1382, 1361, 1168 $cm^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.27 (s, 3H), 1.32 (s, 3H), 1.36 (s, 3H), 1.40 (s, 3H), 1.42 (s, 3H), 1.47 (s, 3H), 1.49 (s, 6H), 1.49 (s, 9H), 1.51 (s, 3H), 1.52 (s, 3H), 1.53 (s, 3H), 1.54 (s, 6H), 2.01-2.16 (m, 3H), 2.18-2.28 (m, 1H), 2.95-3.07 (m, 2H), 3.56-3.68 (brs, 1H), 3.74-3.96 (m, 5H), 4.23 ($t_{ap}$, $J_{ap}$= 7.9 Hz, 1H), 5.08 (A of AB quartet, *J*=12.6 Hz, 1H), 5.12 (B of AB quartet, *J*=12.6 Hz, 1H), 7.24-7.37 (m, 10H), ppm. **MS** ($ES^+$, MeOH) *m/e*= 1185 ($[M+Na]^+$, 100%).

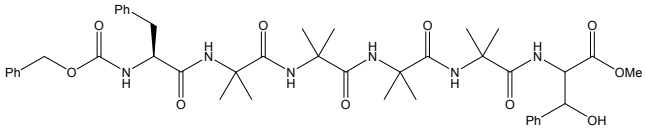
**Synthesis of Cbz-L-PheAib$_4$DpgAib$_4$GlyNH$_2$ 1e**



From a solution of Cbz-L-PheAib$_4$OH azlactone (42 mg, 0.07 mmol, obtained quantitatively from Cbz-L-PheAib$_4$OH **7**), $NH_2$DpgAib$_4$GlyNH$_2$ **9e** (42 mg, 0.07 mmol, obtained quantitatively from Cbz-DpgAib$_4$GlyNH$_2$ **8e**) in dry acetonitrile (2 mL) following the general procedure E and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-L-PheAib$_4$DpgAib$_4$GlyNH$_2$ **1e** was obtained as a white solid (43 mg, 52%).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.50. **mp:** 228-230 °C. **IR**: (solid): $\nu_{max}$= 3299, 2984, 1650, 1524, 1454, 1383, 1361, 1224, 1169 $cm^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.11 (s, 6H), 1.24 (s, 3H), 1.28 (s, 3H), 1.32 (s, 6H), 1.34 (s, 3H), 1.38 (s, 3H), 1.42 (s, 3H), 1.45 (s, 6H), 1.47 (s, 3H), 1.49 (s, 12H), 2.92-3.05 (m, 2H), 3.77-3.83 (m, 2H), 4.21 ($t_{ap}$, $J_{ap}$= 7.6 Hz, 1H), 5.05 (A of AB quartet, *J*=12.6 Hz, 1H), 5.09 (B of AB quartet, *J*=12.6 Hz, 1H), 6.92 (brs, 1H), 7.22-7.38 (m, 16H), 7.43 (d, *J*= 7.6 Hz, 4H), 7.52 (brs, 1H), 7.64 (brs, 1H), 7.66 (brs, 1H), 7.67 (brs, 1H), 7.81 (brs, 1H), 8.04-8.10 (m, 1H), 8.31 (brs, 1H) ppm. **$^{13}$C-NMR** (125 MHz, $CDCl_3$): $\delta$ 24.3-24.4 (overlapping signals, 8$CH_3$), 24.7-25.1 (overlapping signals, 8$CH_3$), 36.8 ($CH_2$), 43.1 ($CH_2$), 56.0 (C), 56.3 (C), 56.7 (C), 56.8 (C), 56.8 (C), 56.9 (C), 57.0 (C), 57.1 (CH), 57.2 (C), 67.2 (C), 72.8 (C), 127.1 (CH), 127.8 (2CH), 127.9 (2CH), 128.2 (4CH), 128.3 (CH), 128.4 (4CH), 128.6 (2CH), 128.7 (2CH), 129.2 (2CH), 136.1 (C), 136.2 (C), 141.9 (C), 141.9 (C), 156.8 (CO), 172.0 (CO), 173.2 (CO), 173.3 (CO), 173.6 (CO), 174.3 (CO), 174.8 (CO), 175.6 (CO), 175.6 (CO), 175.7 (CO), 175.9 (CO), 176.3 (CO) ppm. **MS** ($ES^+$, MeOH) *m/e*= 1267 ($[M+Na]^+$, 100%).

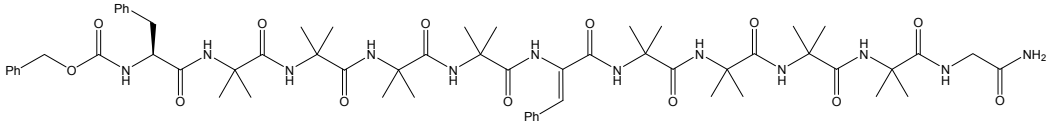
**Synthesis of Cbz-L-PheAib$_4$PhSerOMe 10**



A round-bottomed flask was charged with a solution of Cbz-L-PheAib$_4$OH **7** (200 mg, 0.31 mmol), HOBt (64 mg, 0.47 mmol), HBTU (142 mg, 0.38 mmol), DIPEA (0.164 ml, 121 mg, 0.94 mmol) in dry $CH_2Cl_2$ (5 mL). After 2 h, (±)-phenylserine methyl ester hydrochloride (88 mg, 0.38) was added and the mixture was stirred at room temperature for 24 h. $CH_2Cl_2$ was removed under reduced pressure, the residue was diluted in EtOAc (100 mL), which was washed with HCl (1N) (2 times, 20 mL), $NaHCO_3$ saturated solution (2 times, 20 mL), brine (1 time, 20 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a crude product that was purified by column chromatography (5-10% MeOH-$CH_2Cl_2$), the two diastereomers (dr = 1:1) of the peptide Cbz-L-PheAib$_4$PhSerOMe **10** (230 mg, 91%) was obtained as a white solid.

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.50. **mp:** 84-86 °C. **IR**: (solid): $\nu_{max}$= 3297, 2983, 2938, 1677, 1672, 1665, 1657, 1644, 1633, 1536, 1530, 1519, 1514, 1504, 1383, 1361, 1229, 1169 cm$^{-1}$. **$^1$H-NMR** (400 MHz, $CD_3OD$): two diastereomers: $\delta$ 1.25 (s, 3H), 1.26 (s, 3H), 1.29 (s, 3H), 1.32 (s, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 1.44 (s, 3H), 1.45 (s, 6H), 1.46 (s, 3H), 1.48 (s, 3H), 1.50 (s, 3H), 2.93-3.09 (m, 4H), 3.56 (s, 3H), 3.61 (s, 3H), 4.23 ($t_{ap}$, $J_{ap}$= 7.6 Hz, 1H), 4.24 ($t_{ap}$, $J_{ap}$= 7.6 Hz, 1H), 4.71-4.78 (m, 2H), 5.01-5.13 (m, 4H), 5.15 (d, $J$= 5.5 Hz, 1H), 5.18 (d, $J$= 5.0 Hz, 1H), 7.21-7.36 (m, 26H), 7.37-7.43 (m, 4H), 7.60 (brs, 1H), 7.61 (brs, 1H), 7.74 (brs, 1H), 7.76 (brs, 1H), 7.78 (brs, 1H), 7.85 (brs, 1H), 7.87 (brs, 1H), 7.96 (brs, 1H) ppm. **$^{13}$C-NMR** (100 MHz, $CD_3OD$): two diastereomers: $\delta$ 23.7–27.2 (overlapping signals, 16$CH_3$), 38.2 ($CH_2$), 38.2 ($CH_2$), 52.5 ($CH_3$), 52.6 ($CH_3$), 57.5 (C), 57.5 (C), 57.8 (C), 57.8 (C), 58.1 (2C), 58.2 (2C), 58.3 (2CH), 60.5 (CH), 60.8 (CH), 67.6 ($CH_2$), 67.6 ($CH_2$), 74.9 (CH), 75.1 (CH), 127.7 (2CH), 127.8 (2CH), 127.9 (2CH), 128.6 (2CH), 128.8 (CH), 128.9 (CH), 129.1 (2CH), 129.2 (2CH), 129.2 (2CH), 129.4 (CH), 129.5 (4CH), 129.6 (5CH), 130.5 (2CH), 130.6 (2CH), 138.0 (C), 138.0 (C), 138.1 (C), 138.2 (C), 141.2 (C), 141.6 (C), 158.5 (CO), 158.5 (CO), 171.8 (CO), 171.9 (CO), 174.2 (CO), 174.3 (CO), 176.4 (CO), 176.5 (CO), 176.6 (CO), 176.9 (CO), 177.4 (CO), 177.6 (CO), 177.7 (CO), 177.7 (CO) ppm. **MS** (ES$^+$, MeOH) *m/e*= 839 ([M +Na]$^+$, 100%). **HRMS** (ES$^+$, MeOH): Calcd for $C_{43}H_{56}N_6O_{10}$+Na: 839.3950, found 839.3952.

**Synthesis of Cbz-L-PheAib$_4^{\Delta}$PheAib$_4$GlyNH$_2$ 1f**



A round-bottomed flask was charged with a solution of Cbz-L-PheAib$_4$PhSerOMe **10** (230 mg, 0.28 mmol) in THF (2 mL). A solution of LiOH (~8 mg, ~0.34 mmol) in water (2mL) was added slowly. The mixture was stirred at room temperature for 3 h. Then the mixture was diluted with EtOAc (40 mL) and HCl(1N) (60 mL). The aqueous phase was extracted with EtOAc (5 times, 40 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to give the expected acid Cbz-L-PheAib$_4$PhSerOH (223 mg, 98%) as a white solid that required no further purification.[6]

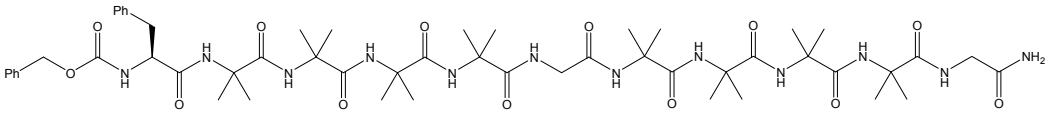
A round-bottomed flask was charged with a solution of the resulting Cbz-L-PheAib$_4$PhSerOH (276 mg, 0.34 mmol), NaOAc (36 mg, 0.52 mmol) in acetic anhydride (3 mL). The mixture was stirred at room temperature for 60 h. Then the mixture was diluted with $CH_2Cl_2$ (70 mL) and the mixture was washed with $KHSO_4$ (2

times, 10 mL), $Na_2CO_3$ saturated solution (2 times, 10 mL), brine (1 time, 10 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure and last traces of acetic anhydride were removed by coevaporation with dry toluene (3 times) to give the corresponding azlactone (259 mg, 98%) as a white solid that required no further purification and directly engaged to the following step.

A round-bottomed flask was charged with a solution of the resulting azlactone (150 mg, 0.20 mmol) in dry acetonitrile (4 mL). The $HAib_4GlyNH_2$ **5** (81 mg, 0.20 mmol) was added and the mixture was heated under reflux (90 °C) for 1 day. The mixture was cooled down to 0 ºC and the precipitate collected by filtration and washed with cold acetonitrile and cold ether. The precipitate was further purified by column chromatography (5-10% MeOH-$CH_2Cl_2$), peptide Cbz-L-$PheAib_4{}^{\Delta}PheAib_4GlyNH_2$ **1f** (151 mg, 65%) was obtained as a white solid.

**Rf**: $SiO_2/CH_2Cl_2$:MeOH 90:10 = 0.34. **mp:** 261-263 °C. **IR**: (solid): $\nu_{max}$= 3285, 2983, 2934, 1653, 1647, 1527, 1382, 1361, 1225, 1170 $cm^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.05 (s, 3H), 1.14 (s, 3H), 1.24 (s, 3H), 1.27 (s, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 1.50 (s, 9H), 1.52 (s, 3H), 1.54 (s, 6H), 1.57 (s, 6H), 1.59 (s, 3H), 1.61 (s, 3H), 2.93-3.05 (m, 2H), 3.78 (A of AB quartet, *J*=16.7 Hz, 1H), 3.91 (B of AB quartet, *J*=16.7 Hz, 1H), 4.21 ($t_{ap}$, $J_{ap}$= 7.9 Hz, 1H), 5.05 (A of AB quartet, *J*=12.6 Hz, 1H), 5.08 (B of AB quartet, *J*=12.6 Hz, 1H), 7.23-7.35 (m, 14H), 752-7.56 (m, 2H), 7.85 (brs, 1H), 7.92 (brs, 1H), 8.01 (brs, 1H), 8.06 (brs, 1H) ppm. **$^{13}$C-NMR** (125 MHz, $CDCl_3$): $\delta$ 22.3-23.9 (overlapping signals, $8CH_3$), 25.9-27.2 (overlapping signals, $8CH_3$), 36.8 ($CH_2$), 43.4 ($CH_2$), 56.5-57.1 (overlapping signals, 8C + 1CH), 67.4 ($CH_2$), 130.6-127.2 (overlapping signals, 20CH + 1C), 133.8 (C), 135.8 (2C), 165.9 (CO), 171.9 (CO), 173.6 (CO), 174.2 (CO), 174.4 (CO), 175.8 (CO), 175.9 (CO), 176.0 (CO), 176.3 (CO), 176.5 (CO), 176.6 (CO), 176.8 (CO) ppm. **MS** ($ES^+$, MeOH) *m/e*= 1203 ($[M+Na]^+$, 100%).

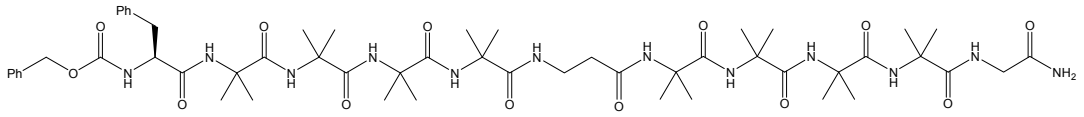
**Synthesis of Cbz-L-$PheAib_4GlyAib_4GlyNH_2$ 1g**



From a solution of Cbz-L-$PheAib_4OH$ azlactone (87 mg, 0.14 mmol, obtained quantitatively from Cbz-L-$PheAib_4OH$ **7**), $NH_2GlyAib_4GlyNH_2$ **9g** (66 mg, 0.14 mmol, obtained quantitatively from Cbz-$GlyAib_4GlyNH_2$ **8g**) in dry acetonitrile (3 mL) following the general procedure E and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-L-$PheAib_4GlyAib_4GlyNH_2$ **1g** was obtained as a white solid (76 mg, 50%).

**Rf**: $SiO_2/CH_2Cl_2$:MeOH 90:10 = 0.35. **mp:** >300 ºC. **IR**: (solid): $\nu_{max}$= 3300, 1651, 1532, 1452, 1380, 1362, 1076 $cm^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.25 (s, 3H), 1.29 (s, 3H), 1.36 (s, 3H), 1.40 (s, 3H), 1.43 (s, 3H), 1.45 (s, 6H), 1.46 (s, 6H), 1.50 (s, 9H), 1.52 (s, 12H), 2.95-3.06 (m, 2H), 3.70-3.91 (m, 4H), 4.23 ($t_{ap}$, $J_{ap}$= 7.6 Hz, 1H), 5.09 (A of AB quartet, *J*=12.6 Hz, 1H), 5.11 (B of AB quartet, *J*=12.6 Hz, 1H), 7.20-7.36 (m, 10H), 7.61 (brs, 1H), 7.73 (brs, 1H), 7.81 (brs, 1H), 7.89 (brs, 1H), 7.94-8.01 (m, 4H), 8.09-8.18 (m, 4H), 8.37 (brs, 1H) ppm. **$^{13}$C-NMR** (125 MHz, $CDCl_3$): $\delta$ 24.7-24.1 (overlapping signals, $8CH_3$), 24.9-25.5 (overlapping signals, $8CH_3$), 36.9 ($CH_2$), 43.4 ($CH_2$), 45.3 ($CH_2$), 57.0-56.5 (overlapping signals, 8C + 1CH), 67.2 ($CH_2$), 127.2 (CH), 127.9 (2CH), 128.4 (CH), 128.6 (2CH), 128.7 (2CH), 129.2 (2CH), 136.0 (C), 136.1 (C), 156.8 (CO), 171.0 (CO), 172.2 (CO), 173.9 (CO), 174.6 (CO), 175.6 (CO), 176.1 (CO), 176.3 (CO), 176.3 (CO), 176.4 (CO), 176.4 (CO), 177.6 (CO) ppm. **MS** ($ES^+$, MeOH) *m/e*= 1115 ($[M+Na]^+$, 100%).

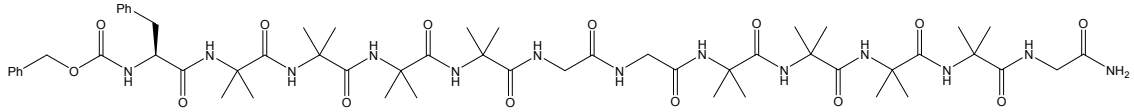
**Synthesis of Cbz-L-PheAib$_4$βAlaAib$_4$GlyNH$_2$ 1h**



From a solution of Cbz-L-PheAib$_4$OH azlactone (71 mg, 0.12 mmol, obtained quantitatively from Cbz-L-PheAib$_4$OH **7**), HβAlaAib$_4$GlyNH$_2$ **9h** (56 mg, 0.12 mmol, obtained quantitatively from Cbz-βAlaAib$_4$GlyNH$_2$ **8h**) in dry acetonitrile (3 mL) following the general procedure E and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-L-PheAib$_4$βAlaAib$_4$GlyNH$_2$ **1h** was obtained as a white solid (102 mg, 74%).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.30. **mp:** >300 ºC. **IR**: (solid): $\nu_{max}$= 3285, 1652, 1538, 1455, 1382, 1361, 1081 cm$^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.24 (s, 3H), 1.28 (s, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.42 (s, 3H), 1.43 (s, 6H), 1.44 (s, 3H), 1.45 (s, 3H), 1.47 (s, 3H), 1.48 (s, 6H), 1.49 (s, 3H), 1.50 (s, 3H), 1.51 (s, 6H), 2.38-2.51 (m, 2H), 2.92-3.05 (m, 2H), 3.35-3.45 (m, 1H), 3.54-3.64 (m, 1H), 3.70 (d of A of AB quartet, *J*=17.3, 6.0 Hz, 1H), 3.77 (d of B of AB quartet, *J*=17.3, 6.4 Hz, 1H), 4.19-4.25 (m, 1H), 5.04-5.12 (m, 2H), 7.22-7.36 (m, 10H), 7.51 (brs, 1H), 7.60 (brs, 1H), 7.61 (brs, 1H), 7.66 (brs, 1H), 7.72 (brs, 1H), 7.76-7.79 (m, 1H), 7.87 (brs, 1H), 8.04 (brs, 1H), 8.12 (m, 1H), 8.15 (t, *J*= 6.0 Hz, 1H), 8.36 (brs, 1H) ppm. **$^{13}$C-NMR** (125 MHz, $CDCl_3$): $\delta$ 23.4-25.8 (overlapping signals, 16$CH_3$), 36.8 ($CH_2$), 40.3 ($CH_2$), 43.3 ($CH_2$), 43.4 ($CH_2$), 56.5-57.2 (overlapping signals, 8C + 1CH), 67.3 ($CH_2$), 127.3 (CH), 128.0 (2CH), 128.4 (CH), 128.6 (2CH), 128.8 (2CH), 129.2 (2CH), 136.0 (C), 136.0 (C), 156.8 (CO), 172.0 (CO), 172.8 (CO), 173.7 (CO), 174.3 (CO), 175.0 (CO), 175.1 (CO), 176.3 (CO), 176.4 (CO), 176.6 (CO), 176.7 (CO), 176.8 (CO) ppm. **MS** (ES$^+$, MeOH) *m/e*= 1129 ([M +Na]$^+$, 100%).

**Synthesis of Cbz-L-PheAib$_4$GlyGlyAib$_4$GlyNH$_2$ 1i**

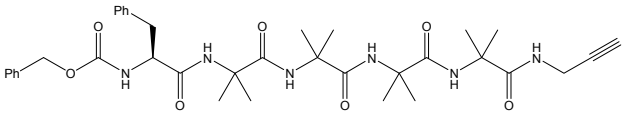


From a solution of Cbz-L-PheAib$_4$OH azlactone (104 mg, 0.17 mmol, obtained quantitatively from Cbz-L-PheAib$_4$OH **7**), HGlyGlyAib$_4$GlyNH$_2$ **9i** (88 mg, 0.17 mmol, obtained quantitatively from Cbz-GlyGlyAib$_4$GlyNH$_2$ **8i**) in dry acetonitrile (4 mL) following the general procedure E and after purification by column chromatography (5-10 % MeOH-$CH_2Cl_2$) the peptide Cbz-L-PheAib$_4$GlyGlyAib$_4$GlyNH$_2$ **1i** was obtained as a white solid (141 mg, 73%).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.30. **mp:** >300 ºC. **IR**: (solid): $\nu_{max}$= 3310, 1650, 1530, 1454, 1384, 1362, 1076 cm$^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.24 (s, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 1.41 (s, 3H), 1.44 (s, 3H), 1.44 (s, 3H), 1.46 (s, 6H), 1.47 (s, 6H), 1.49 (s, 3H), 1.51 (s, 6H), 1.51 (s, 6H), 2.94-3.06 (m, 2H), 3.75-3.98 (m, 6H), 4.23 ($t_{ap}$, $J_{ap}$= 7.6 Hz, 1H), 5.07 (A of AB quartet, *J*=12.9 Hz, 1H), 5.10 (B of AB quartet, *J*=12.9 Hz, 1H), 7.22-7.35 (m, 10H), 7.45-7.55 (m, 1H), 7.63 (brs, 1H), 7.73 (brs, 1H), 7.75 (brs, 1H), 7.76 (brs, 1H), 7.85-7.88 (m, 1H), 7.90 (brs, 1H), 7.96 (brs, 1H), 7.98 (brs, 2H), 8.11-8.17 (m, 2H), 8.27 (t, *J*= 5.7 Hz, 1H), 8.40 (brs, 1H) ppm. **$^{13}$C-NMR** (100 MHz, $CDCl_3$): $\delta$ 24.3-24.6 (overlapping signals, 8$CH_3$), 24.7-25.3 (overlapping signals, 8$CH_3$), 36.9 ($CH_2$), 43.4 ($CH_2$), 44.6 ($CH_2$), 44.6 ($CH_2$), 56.5 (C), 56.6 (C), 56.6 (CH), 56.6 (C), 56.7 (C), 56.7 (C), 56.7 (C), 56.8 (C), 57.0 (C), 67.2 ($CH_2$), 127.2 (CH), 127.8 (2CH), 128.4 (CH), 128.6 (2CH), 128.7 (2CH), 129.2 (2CH), 136.0 (C), 136.0 (C), 156.8 (CO), 170.6 (CO), 172.0 (CO),

172.2 (CO), 173.9 (CO), 174.8 (CO), 175.1 (CO), 176.1 (CO), 176.4 (CO), 176.5 (CO), 176.9 (CO), 177.6 (CO), 177.7 (CO) ppm. **MS** ($ES^+$, MeOH) *m/e*= 1172 ($[M+Na]^+$, 100%).

**Synthesis of Cbz-L-PheAib$_4$NHCH$_2$C≡CH 11**



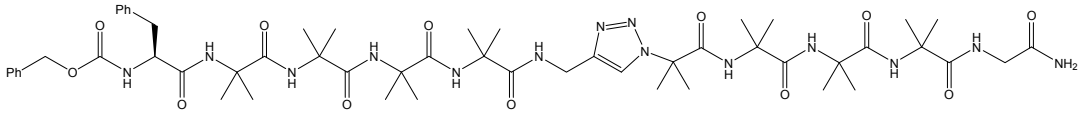
A round-bottomed flask was charged with a solution of Cbz-L-PheAib$_4$OH **7** (200 mg, 0.31 mmol), HOBt (93 mg, 0.69 mmol), HBTU (237 mg, 0.63 mmol), DIPEA (0.218 ml, 162 mg, 1.25 mmol) in dry $CH_2Cl_2$ (5 mL). After 1 h, distilled propargylamine (43 µl, 34 mg, 0.63) was added and the mixture was stirred at room temperature for 4 days. Then the mixture was diluted with $CH_2Cl_2$ (100 mL), which was washed with HCl (1N) (2 times, 20 mL), $NaHCO_3$ saturated solution (2 times, 20 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a crude product that was purified by column chromatography (5-10% MeOH-$CH_2Cl_2$), peptide Cbz-L-PheAib$_4$NHCH$_2$C≡CH **11** (164 mg, 78%) was obtained as a white solid.[7]

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.55. **mp:** 179-182 °C. **IR**: (solid): $\nu_{max}$= 3355, 3318, 2987, 2932, 2479, 2425, 1676, 1666, 1655, 1650, 1643, 1530, 1523, 1519, 1514, 1434, 1421, 1417, 1361, 1225 $cm^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.24 (s, 3H), 1.29 (s, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 1.41 (s, 3H), 1.46 (s, 3H), 1.48 (s, 3H), 1.51 (s, 3H), 2.48 (s, 1H), 2.93-3.07 (m, 2H), 3.90 (A of AB quartet, *J*=17.0 Hz, 1H), 4.03 (B of AB quartet, *J*=17.0 Hz, 1H), 4.23 ($t_{ap}$, $J_{ap}$= 7.6 Hz, 1H), 5.06 (A of AB quartet, *J*=12.6 Hz, 1H), 5.09 (B of AB quartet, *J*=12.6 Hz, 1H), 7.20-7.35 (m, 10H), 7.54 (brs, 1H), 7.67 (brs, 1H), 7.86 (brs, 1H), 7.87 (brs, 1H), 7.88 (brs, 1H), 7.89 (brs, 1H) ppm. **$^{13}$C-NMR** (125 MHz, $CD_3OD$): $\delta$ 24.0 ($CH_3$), 24.3 ($CH_3$), 24.5 ($CH_3$), 24.9 ($CH_3$), 26.1 ($CH_3$), 26.3 ($CH_3$), 26.5 ($CH_3$), 26.8 ($CH_3$), 29.7 ($CH_2$), 38.2 ($CH_2$), 57.5 (C), 57.8 (C), 58.0 (C), 58.1 (C), 58.2 (CH), 67.6 ($CH_2$), 71.8 (CH), 80.8 (C), 127.9 (CH), 128.6 (2CH), 129.1 (CH), 129.5 (2CH), 129.6 (2CH), 129.6 (2CH), 138.0 (C), 138.1 (C), 158.5 (CO), 174.3 (CO), 176.5 (CO), 177.0 (CO), 177.4 (CO), 177.6 (CO) ppm. **MS** ($ES^+$, MeOH) *m/e*= 699 ($[M+Na]^+$, 100%). **HRMS** ($ES^+$, MeOH): Calcd for $C_{36}H_{48}N_6O_7$+Na: 699.3477, found 699.3475.

**General procedure F for the "click" reaction between Cbz-L-PheAib$_4$NHCH$_2$C≡CH 11 and N$_3$Aib$_4$GlyNH$_2$ 4 or N$_3$GlyOH.**

A microwave sealed tube was charged with a solution of 1.0 equiv. of Cbz-L-PheAib$_4$NHCH$_2$C≡CH **11**, 1.0 equiv. of the azide, 10 mol% of CuOAc in dry DMF (7 mL/mmol). The tube was sealed and the mixture mixture was heated at 80 ºC for 30 min. Most of the DMF was removed in vacuo and diluted with ether (30 mL/mmol). The mixture was cooled down to 0 ºC and the precipitate collected by filtration and washed with cold ether. The precipitate was further purified by column chromatography, using the appropriate mixture of eluents, to give the triazole.[8]

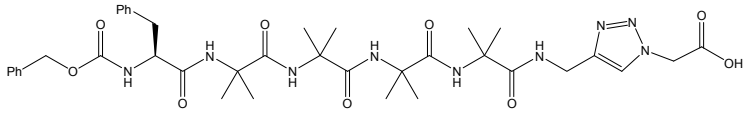
**Synthesis of Cbz-L-PheAib$_4$TrzAib$_4$GlyNH$_2$ 1j**



From a solution of Cbz-L-PheAib$_4$NHCH$_2$C≡CH **11** (50 mg, 0.07 mmol), N$_3$Aib$_4$GlyNH$_2$ **4** (33 mg, 0.07 mmol) in dry DMF (0.5 mL) following the general procedure F and after purification by column chromatography (5-10% MeOH-$CH_2Cl_2$) the peptide Cbz-L-PheAib$_4$CH$_2$-Triazol-Aib$_4$GlyNH$_2$ **1j** was obtained as a white solid (65 mg, 79%).

**Rf**: $SiO_2$/$CH_2Cl_2$:MeOH 90:10 = 0.30. **mp:** 126-128 °C. **IR**: (solid): $\nu_{max}$= 3299, 2983, 2933, 1655, 1650, 1524, 1519, 1383, 1361, 1224, 1170 cm$^{-1}$. **$^1$H-NMR** (500 MHz, $CD_3OD$): $\delta$ 1.24 (s, 3H), 1.28 (s, 3H), 1.31 (s, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 1.43 (s, 6H), 1.46 (s, 6H), 1.47 (s, 3H), 1.51 (s, 3H), 1.53 (s, 3H), 1.86 (s, 3H), 1.88 (s, 3H), 2.93-3.05 (m, 2H), 3.80 (A of AB quartet, *J*=17.3 Hz, 1H), 3.84 (B of AB quartet, *J*=17.3 Hz, 1H), 4.22 ($t_{ap}$, $J_{ap}$= 7.6 Hz, 1H), 4.42 (A of AB quartet, *J*=15.5 Hz, 1H), 4.46 (B of AB quartet, *J*=15.5 Hz, 1H), 5.06 (A of AB quartet, *J*=12.6 Hz, 1H), 5.09 (B of AB quartet, *J*=12.6 Hz, 1H), 7.22-7.35 (m, 11H), 7.60 (brs, 1H), 7.75 (brs, 1H), 7.75 (brs, 1H), 7.87 (brs, 1H), 8.20 (brs, 1H) ppm. **$^{13}$C-NMR** (125 MHz, $CD_3OD$): $\delta$ 24.0–27.0 (overlapping signals, 16$CH_3$), 36.5 ($CH_2$), 38.3 ($CH_2$), 43.8 ($CH_2$), 57.6 (C), 57.7 (C), 58.0 (C), 58.1 (C), 58.2 (C), 58.3 (C), 58.3 (C), 58.5 (CH), 66.5 (C), 67.7 ($CH_2$), 123.3 (CH), 128.0 (CH), 128.6 (2CH), 129.1 (CH), 129.6 (2CH), 129.6 (2CH), 130.6 (2CH), 138.0 (C), 138.2 (C), 147.5 (C), 158.6 (CO), 173.4 (CO), 174.3 (CO), 175.4 (CO), 176.6 (CO), 177.0 (CO), 177.1 (CO), 177.5 (CO), 177.6 (CO), 178.0 (CO), 178.3 (CO) ppm. **MS** ($ES^+$, MeOH) *m/e*= 1139 ([M +Na]$^+$, 100%).

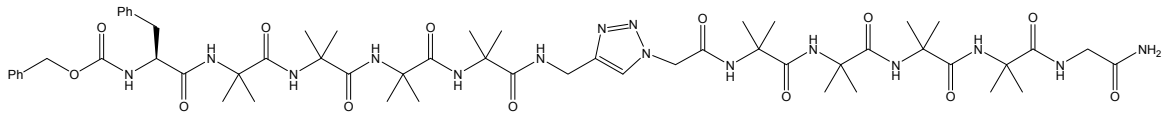
**Synthesis of Cbz-L-PheAib$_4$TrzGlyOH**



From a solution of Cbz-L-PheAib$_4$NHCH$_2$C≡CH **11** (50 mg, 0.07 mmol), N$_3$GlyOH[9] (8 mg, 0.07 mmol) in dry DMF (0.5 mL) following the general procedure F and after purification by column chromatography (10-30% MeOH-$CH_2Cl_2$) the peptide Cbz-L-PheAib$_4$CH$_2$-Triazol-GlyOH was obtained as a white solid (38 mg, 65%).

**Rf**: $SiO_2$/ $CH_2Cl_2$:MeOH 90:10 = 0.10. **mp:** 103-105 °C. **IR**: (solid): $\nu_{max}$= 3300, 2940, 1652, 1651, 1530, 1385, 1370, cm$^{-1}$. **$^1$H-NMR** (400 MHz, $CD_3OD$): $\delta$ 1.23 (s, 3H), 1.27 (s, 3H), 1.29 (s, 3H), 1.31 (s, 3H), 1.38 (s, 3H), 1.45 (s, 3H), 1.50 (s, 3H), 1.52 (s, 3H), 2.92-3.06 (m, 2H), 4.22 ($t_{ap}$, $J_{ap}$= 7.6 Hz, 1H), 4.51 (brs, 2H), 4.94 (brs, 2H), 5.05 (A of AB quartet, *J*=12.6 Hz, 1H), 5.09 (B of AB quartet, *J*=12.6 Hz, 1H), 7.21-7.35 (m, 11H), 7.60 (brs, 1H), 7.56 (brs, 1H), 7.71 (brs, 1H), 7.81 (brs, 1H) ppm. **$^{13}$C-NMR** (100 MHz, $CD_3OD$): $\delta$ 24.0 ($CH_3$), 24.2 ($CH_3$), 24.5 ($CH_3$), 25.0 ($CH_3$), 26.1 ($CH_3$), 26.3 ($CH_3$), 26.5 ($CH_3$), 26.9 ($CH_3$), 38.3 ($CH_2$), 43.4 (br$CH_2$), 57.6 ($CH_2$), 57.7 (C), 57.8 (C), 58.0 (C), 58.1 (C), 58.2 (CH), 67.7 ($CH_2$), 124.5 (br CH), 127.9 (CH), 128.6 (2CH), 129.1 (CH), 129.5 (2CH), 129.6 (2CH), 130.6 (2CH), 138.1 (C), 138.2 (C), 148.8 (br C), 158.6 (CO), 174.3 (CO), 176.5 (CO), 177.1 (CO), 177.2 (CO), 177.4 (CO), 177.5 (CO) ppm. **MS** ($ES^-$, MeOH) *m/e*= 776 ([M-H]$^-$, 100%). **HRMS** ($ES^-$, MeOH): Calcd for $C_{38}H_{51}N_9O_9$-H: 776.3736, found 776.3728.

**Synthesis of Cbz-L-PheAib$_4$TrzGlyAib$_4$GlyNH$_2$ 1k**

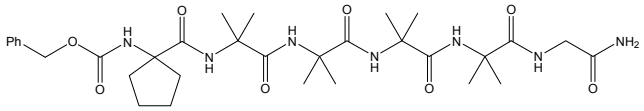


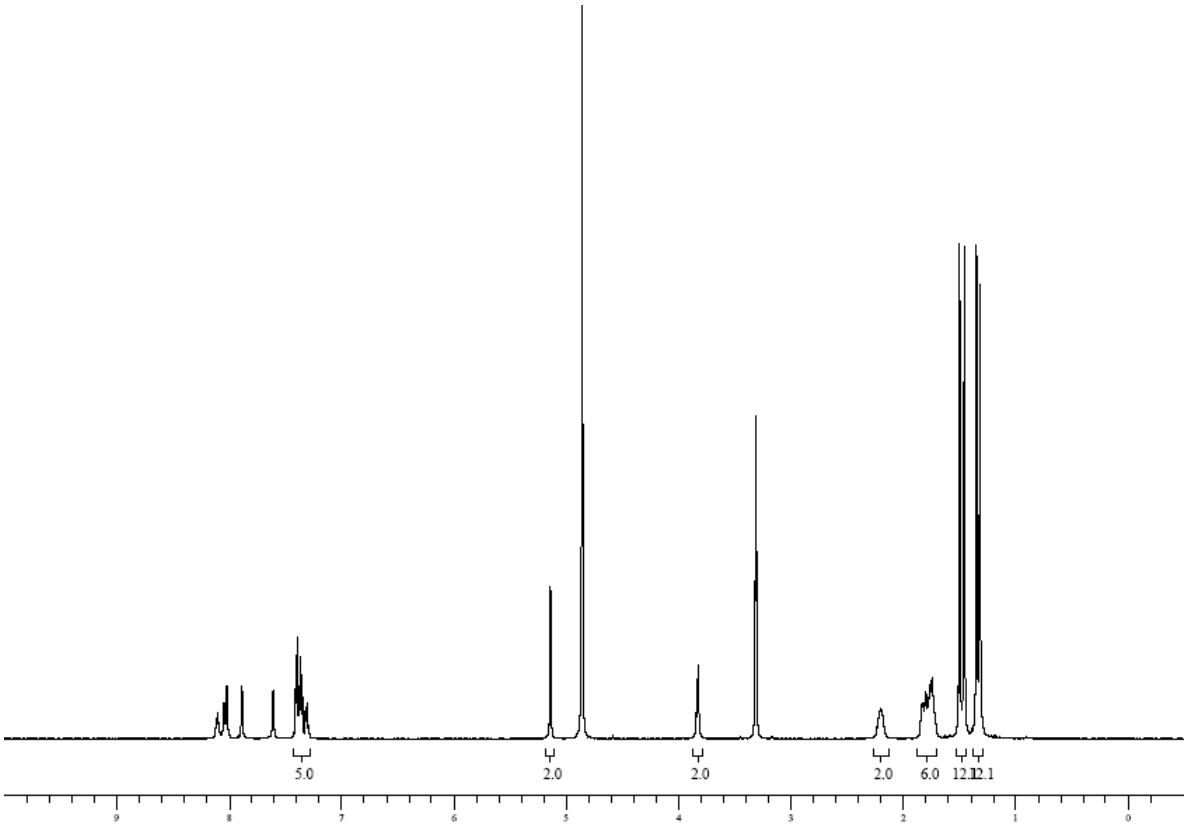
A round-bottomed flask was charged with a solution of Cbz-L-PheAib$_4$TrzGlyOH (35 mg, 0.05 mmol), HOBt (14 mg, 0.10 mmol) in dry DMF (1 mL). This mixture was cooled down to 0 ºC and EDC (0.18 mL, 16 mg, 0.10 mmol) were added dropwise. After completed dissolution or at least 1 h, HAib$_4$GlyNH$_2$ **5** (19 mg, 0.05 mmol) was then added. The mixture was allowed to warm to room temperature for 7 d. Then the mixture was concentrated under reduced pressure and diluted with $CH_2Cl_2$ (30 mL), which was washed with water (1 time, 5 mL). The organic phase was concentrated under reduced pressure to give a crude product that was purified by column chromatography (5-10% MeOH-$CH_2Cl_2$), peptide Cbz-L-PheAib$_4$TrzGlyAib$_4$GlyNH$_2$ **1k.** (33 mg, 63%) was obtained as a white solid.

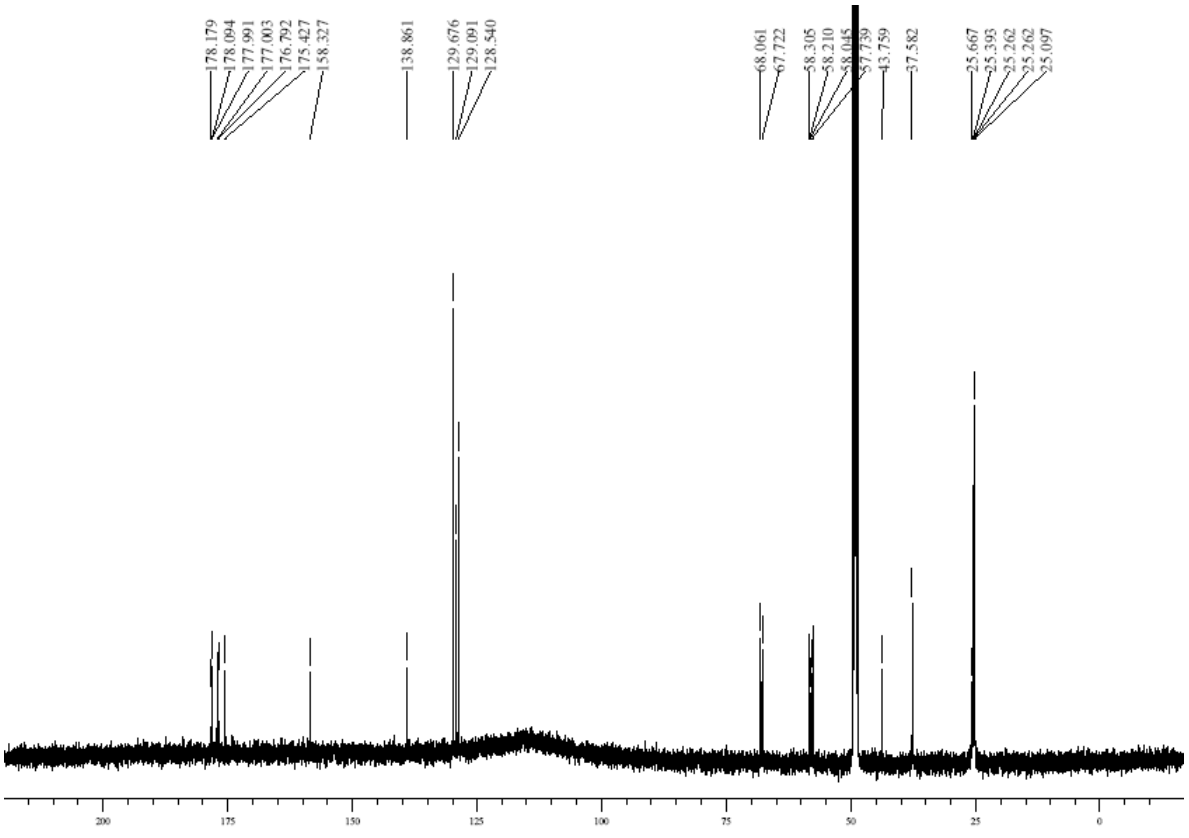
**Rf**: $SiO_2$/ $CH_2Cl_2$:EtOH 90:10 = 0.45. **mp:**. 130–135 $^oC$. **IR**: (solid): $\nu_{max}$= 3310, 2989, 2935, 1655, 1652, 1522 1365, 1230, 1175 $cm^{-1}$. **$^1$H-NMR** (400 MHz, $CD_3OD$): $\delta$ 1.23 (s, 3H), 1.24 (s, 3H), 1.25 (s, 3H), 1.27 (s, 3H), 1.30 (s, 3H), 1.33 (s, 3H), 1.37 (s, 3H), 1.40 (s, 6H), 1.42 (s, 3H), 1.46 (s, 6H), 1.46 (s, 6H), 1.49 (s, 3H), 1.52 (s, 3H), 2.93-3.05 (m, 2H), 3.79-3.85 (m, 2H), 4.22 ($t_{ap}$, $J_{ap}$= 7.8 Hz, 1H), 4.43 (d of A of AB quartet, *J*=15.5, 6.3 Hz, 1H), 4.55 (d of B of AB quartet, *J*=15.5, 6.3 Hz, 1H), 4.70 (brs, 2H), 5.05 (A of AB quartet, *J*=12.6 Hz, 1H), 5.09 (B of AB quartet, *J*=12.6 Hz, 1H), 5.16 (brs, 2H), 7.21-7.36 (m, 11H), 7.58 (brs, 1H), 7.74 (brs, 1H), 7.76 (brs, 1H), 7.84 (brs, 1H), 7.93 (brs, 1H) 8.02-8.18 (m, 2H) ppm. **$^{13}$C-NMR** (100 MHz, $CD_3OD$): $\delta$ 23.8–27.2 (overlapping signals, 16$CH_3$), 36.3 ($CH_2$), 38.3 ($CH_2$), 43.7 ($CH_2$), 53.2 ($CH_2$), 57.6 (C), 57.7 (C), 57.7 (C), 57.8 (C), 58.0 (CH), 58.1 (C), 58.2 (C), 58.2 (C), 58.3 (C), 67.7 ($CH_2$), 126.2 (CH), 128.0 (CH), 128.6 (2CH), 129.1 (CH), 129.5 (2CH), 129.6 (2CH), 130.6 (2CH), 138.0 (C), 138.2 (C), 147.4 (C), 158.6 (CO), 167.9 (CO), 174.3 (CO), 175.4 (CO), 176.3 (CO), 176.6 (CO), 177.2 (CO), 177.5 (CO), 177.7 (CO), 178.0 (CO), 178.1 (CO), 178.1 (CO) ppm. **MS** ($ES^+$, MeOH) *m/e*= 1196 ($[M+Na]^+$, 100%).

## 3. Supplementary figures: $^{1}H$ and $^{13}C$ NMR spectra

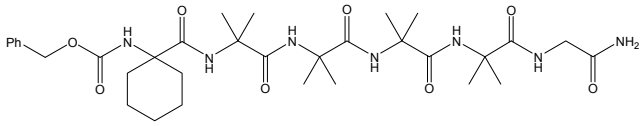
**Cbz-Ac$_5$cAib$_4$GlyNH$_2$ 8b**

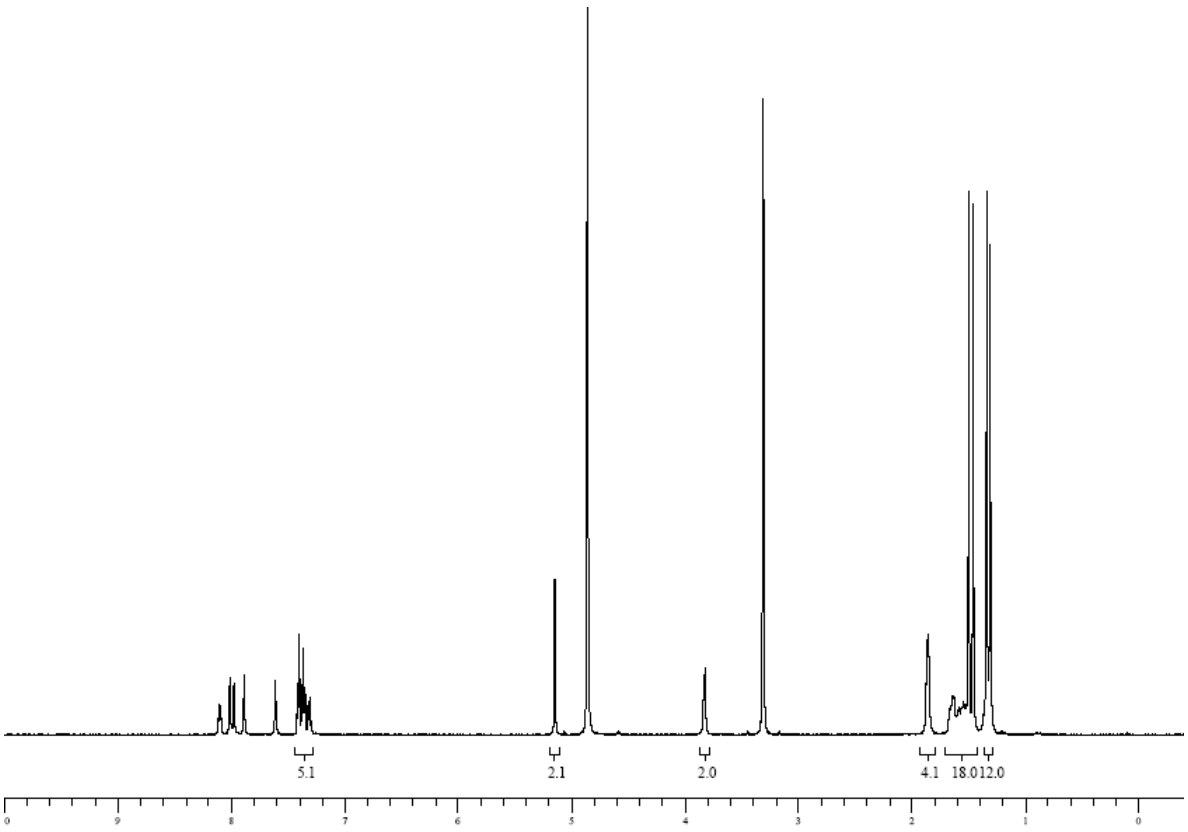


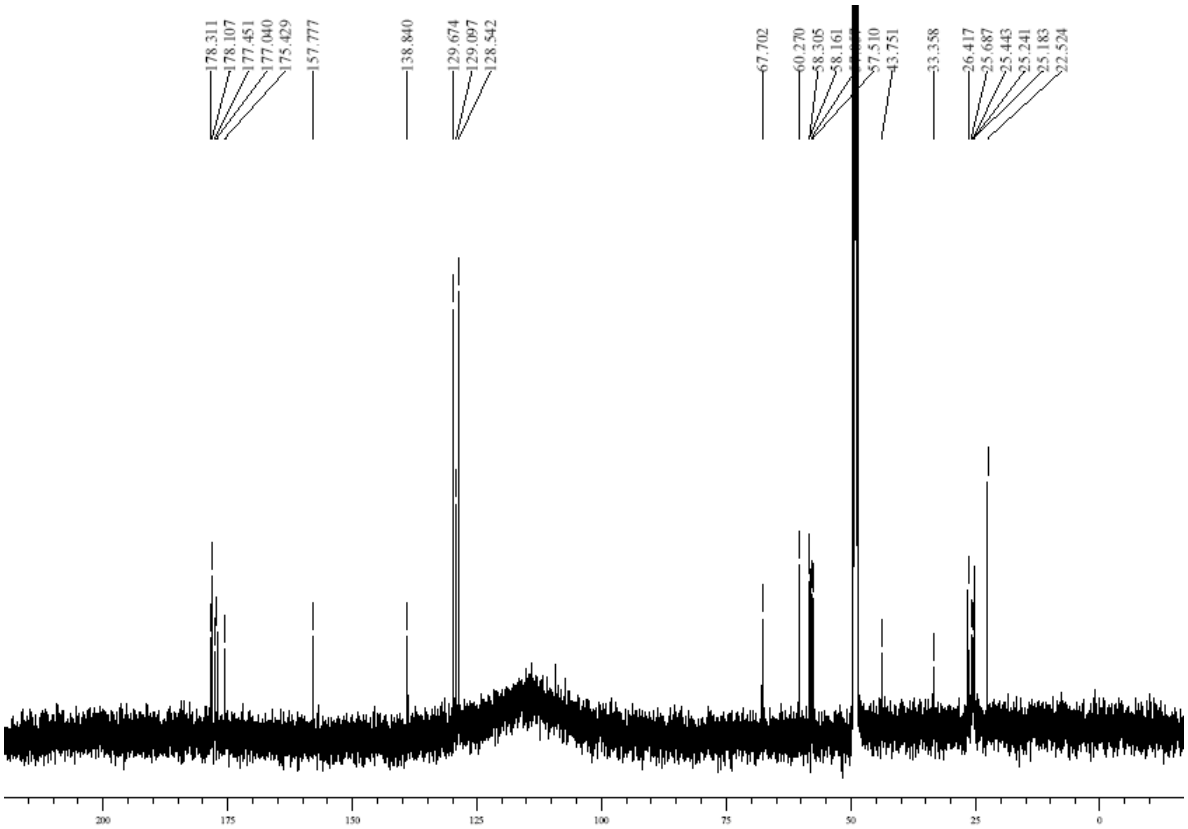



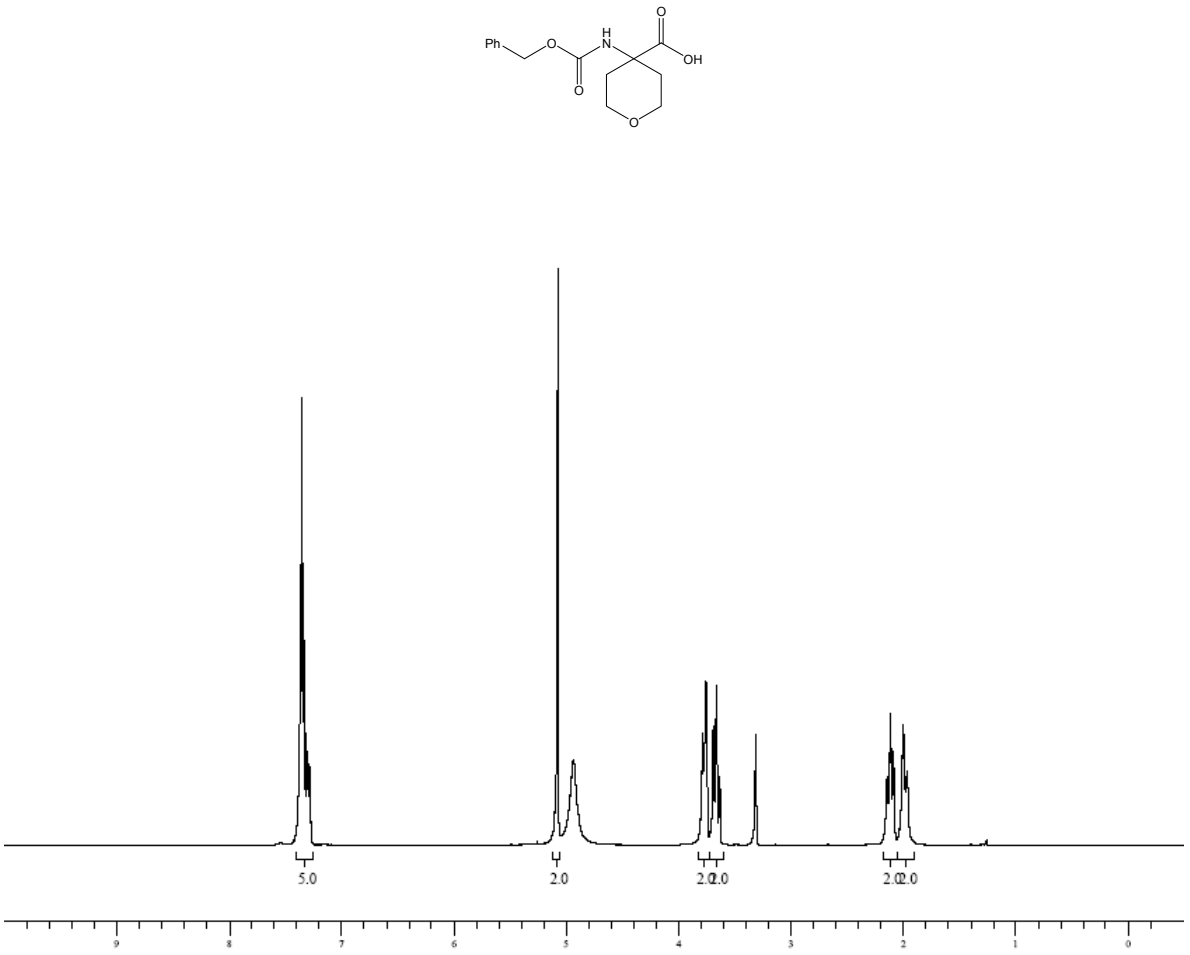
**Cbz-Ac$_6$cAib$_4$GlyNH$_2$ 8c**

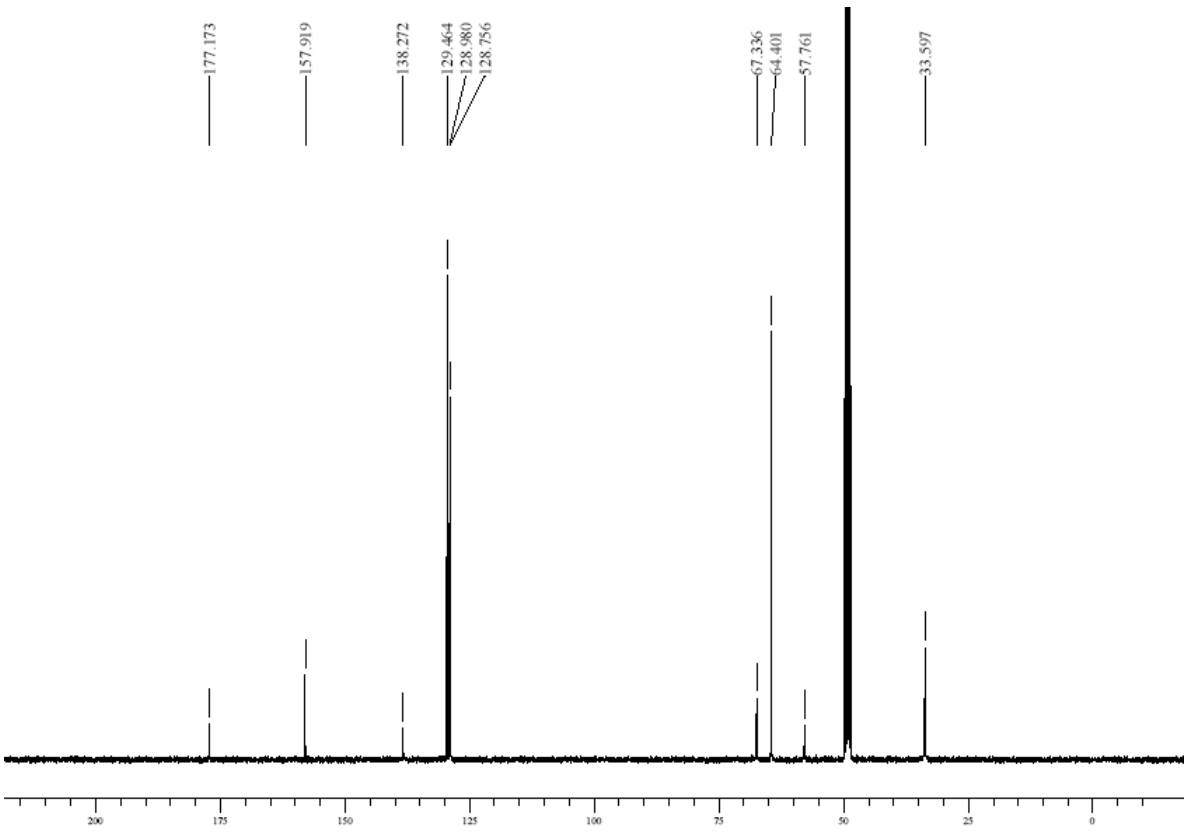


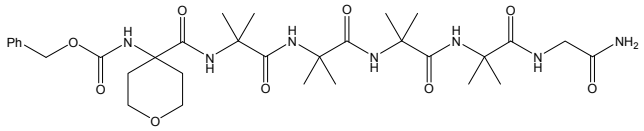



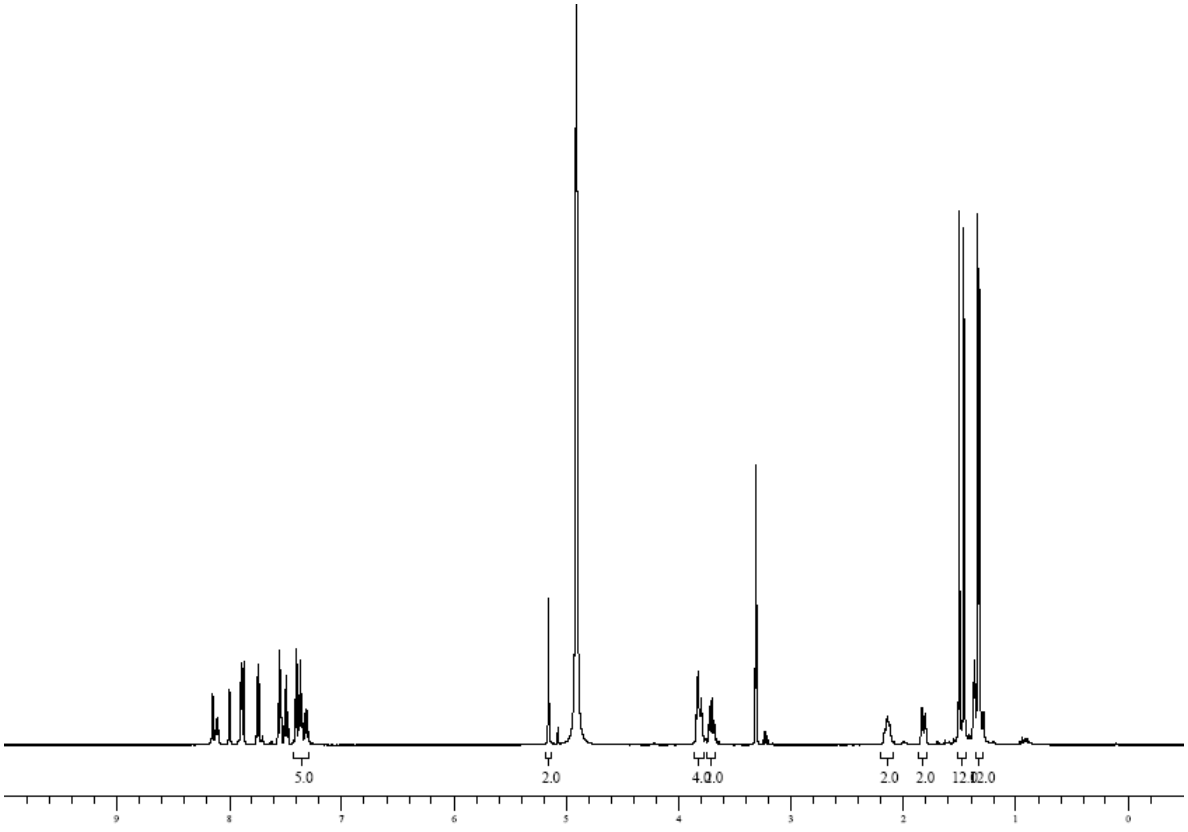
**Cbz-ThpOH Cbz-2d**

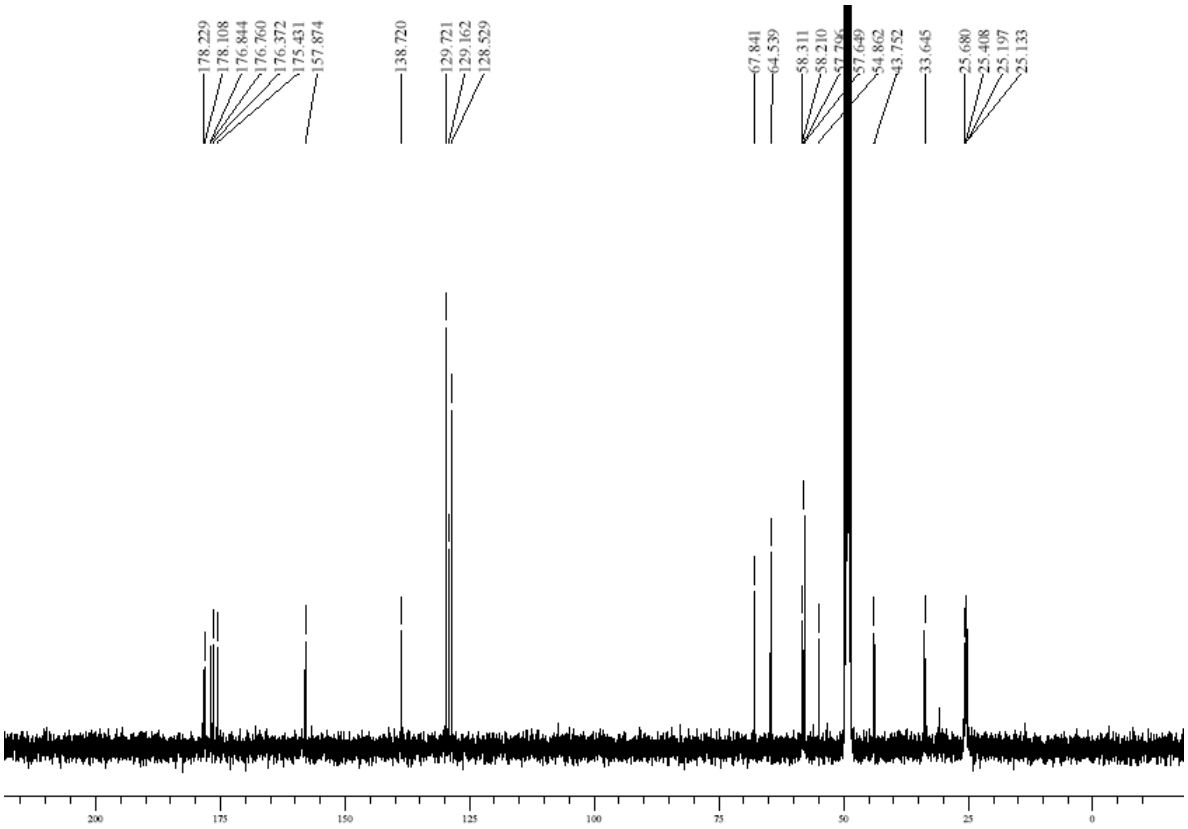


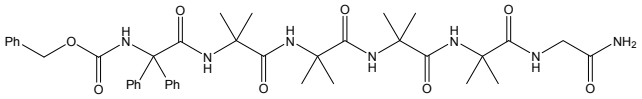
**Cbz-ThpAib$_4$GlyNH$_2$ 8d**

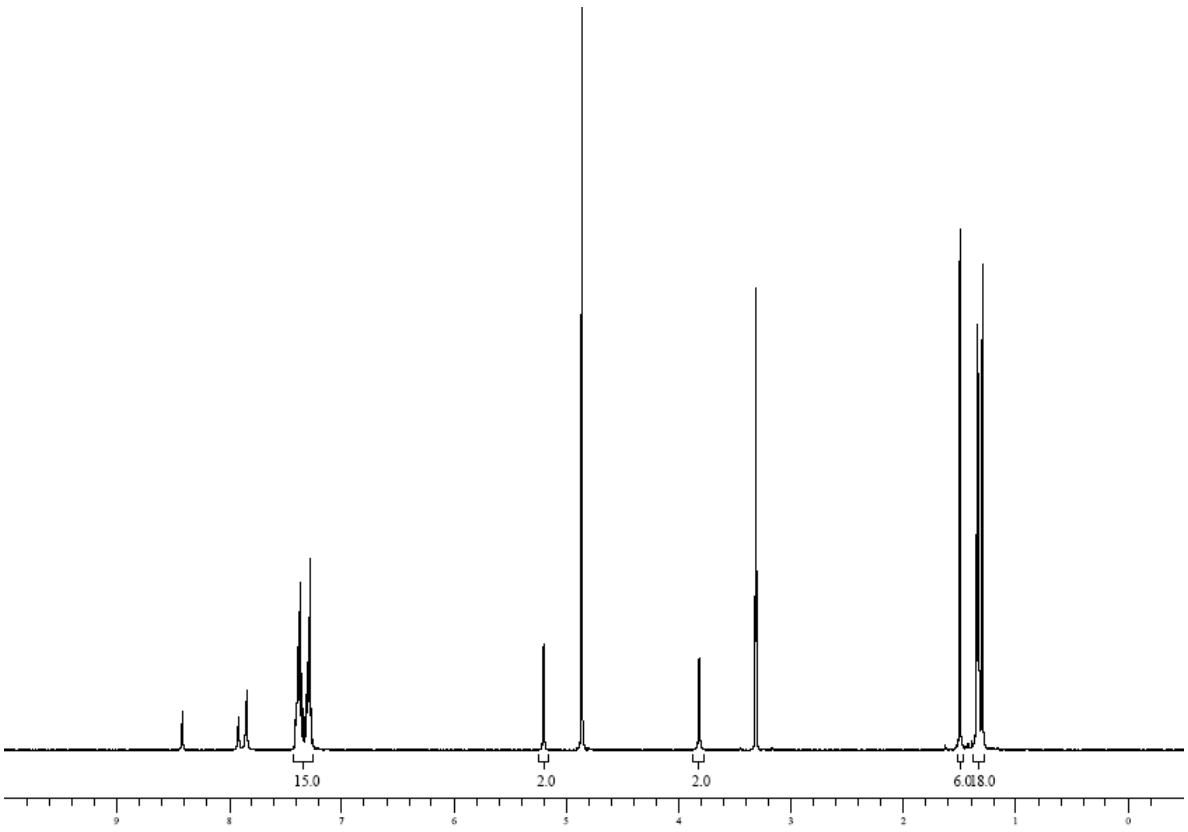


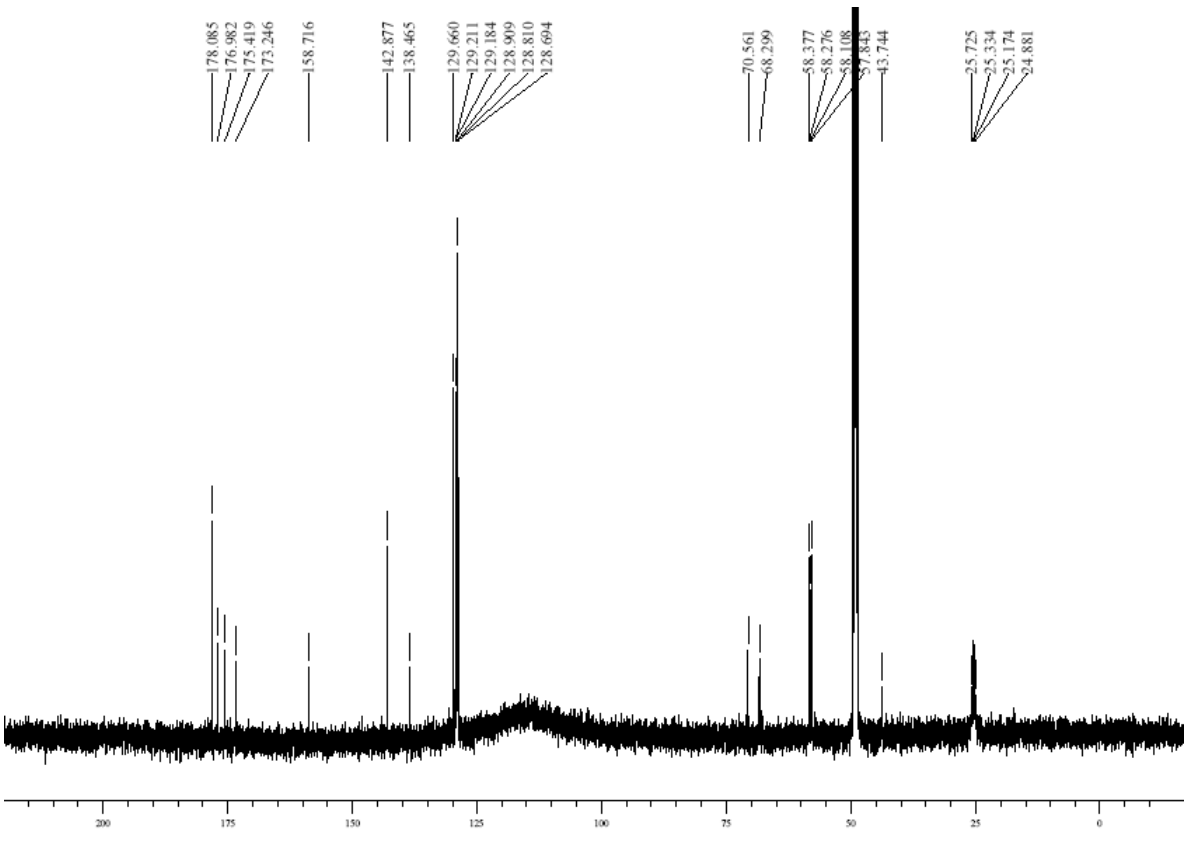



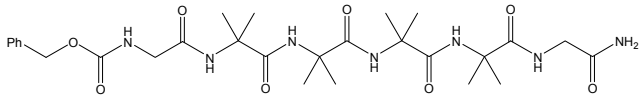
**Cbz-DpgAib$_4$GlyNH$_2$ 8e**

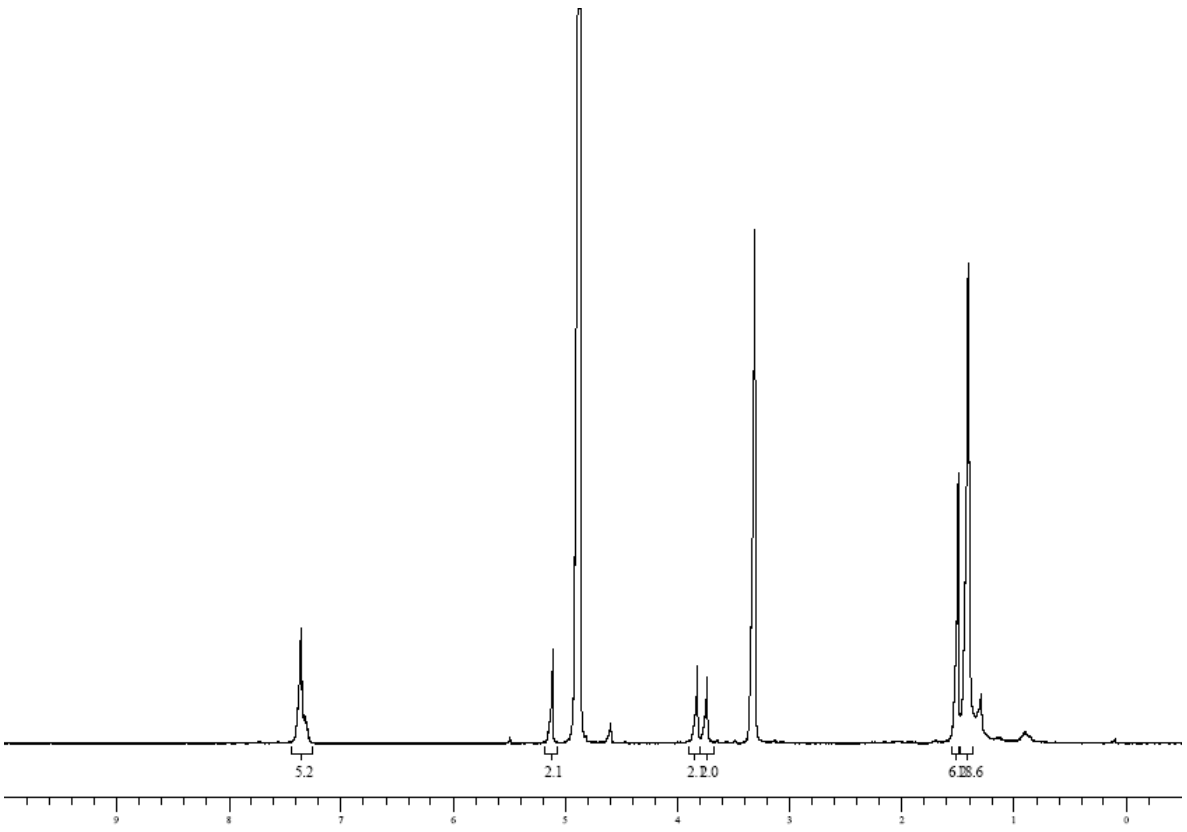


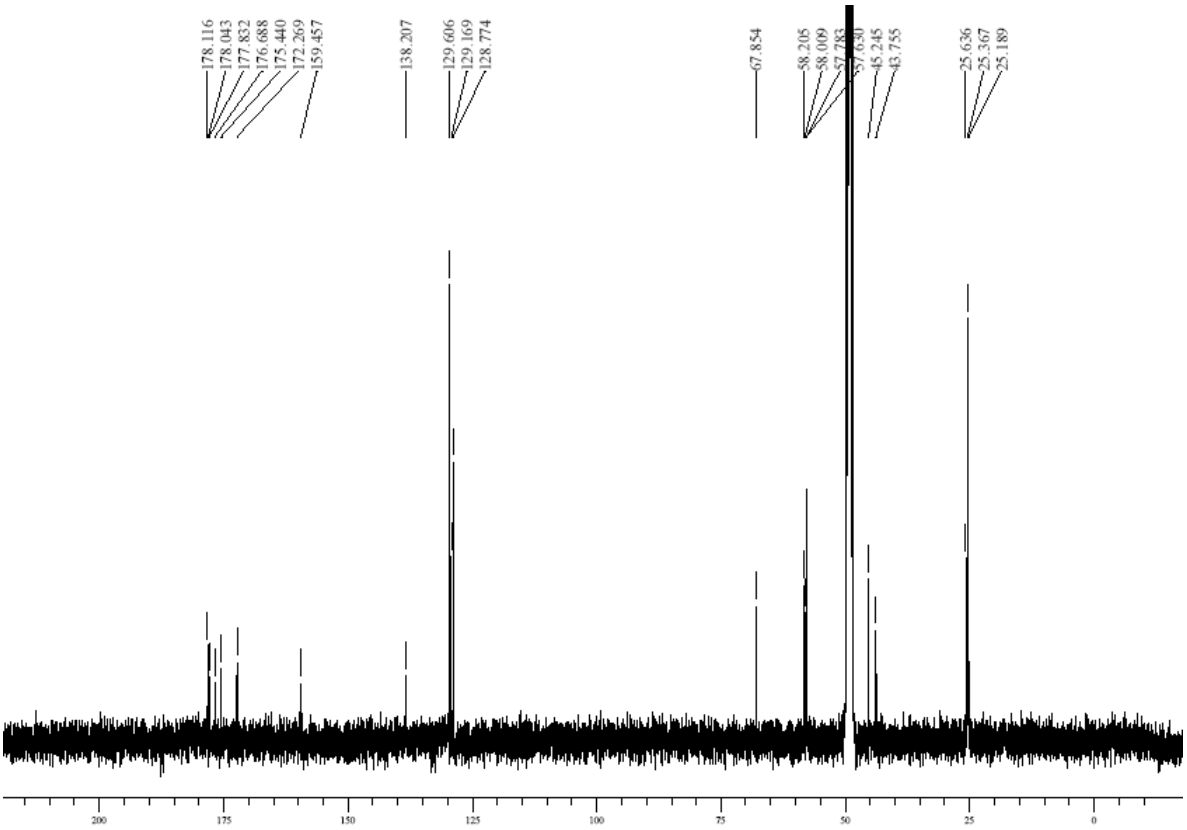



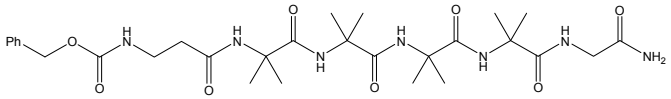
**Cbz-GlyAib$_4$GlyNH$_2$ 8g**

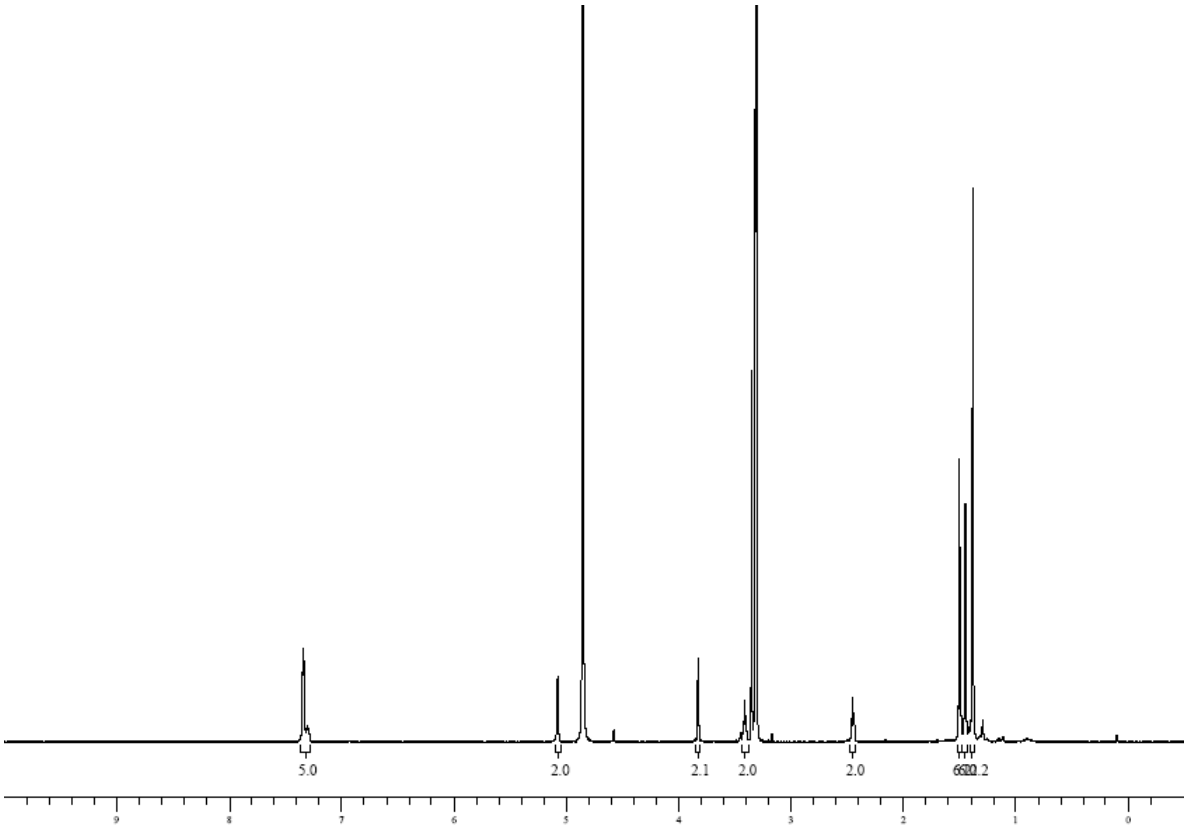


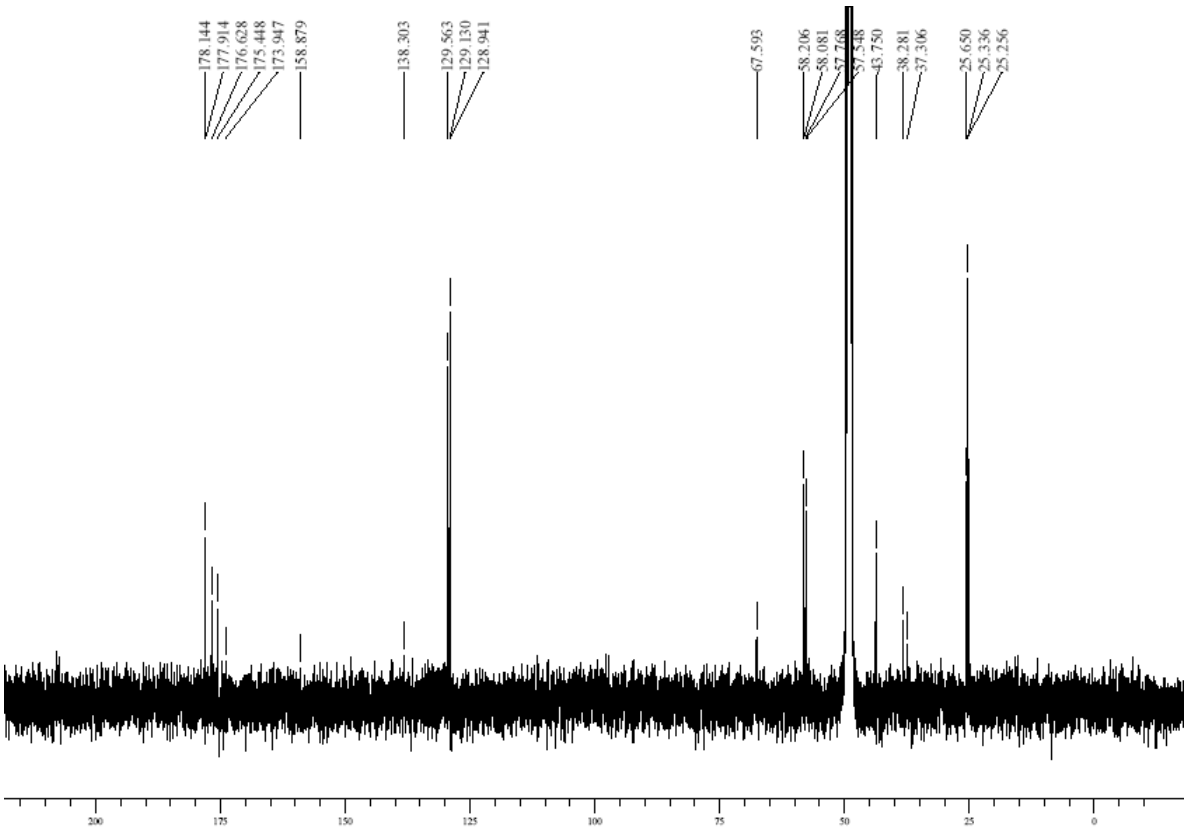



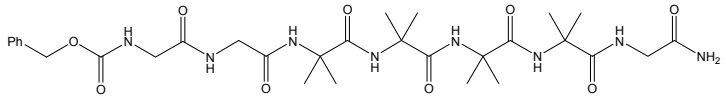
**Cbz-βAlaAib$_4$GlyNH$_2$ 8h**

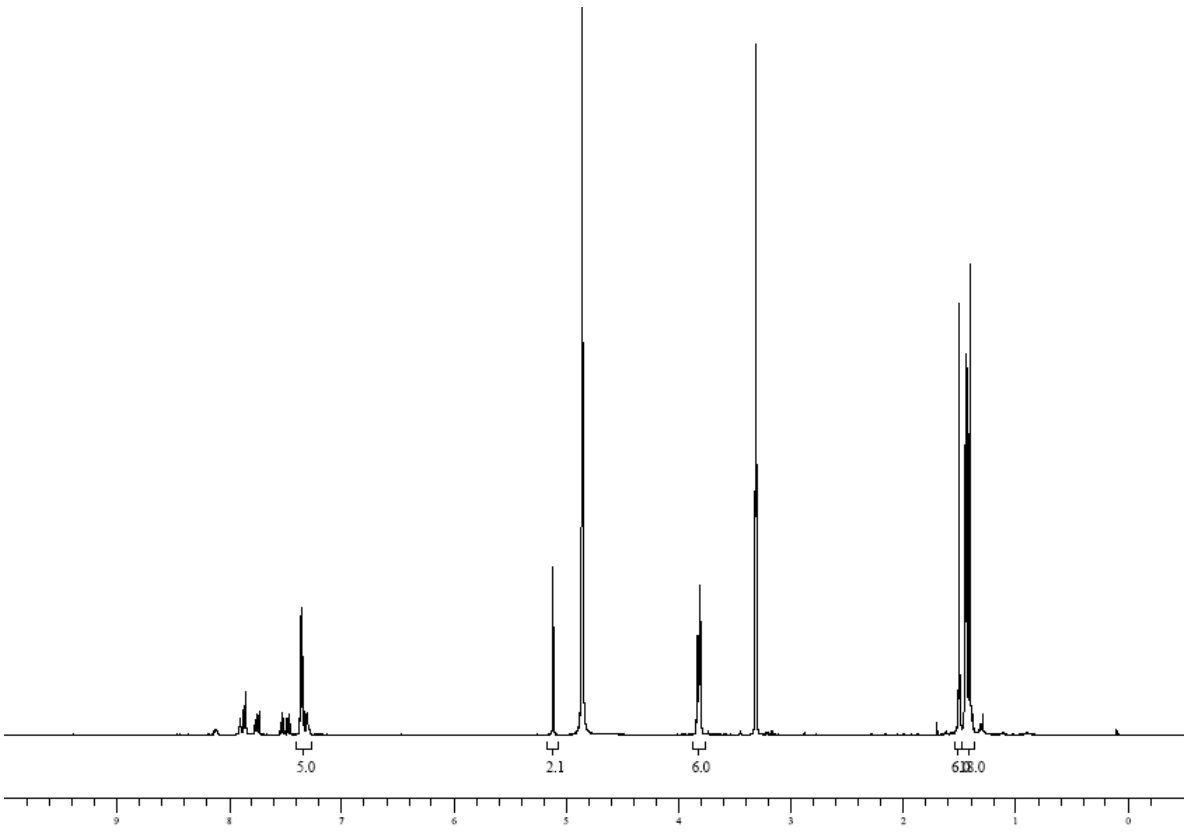


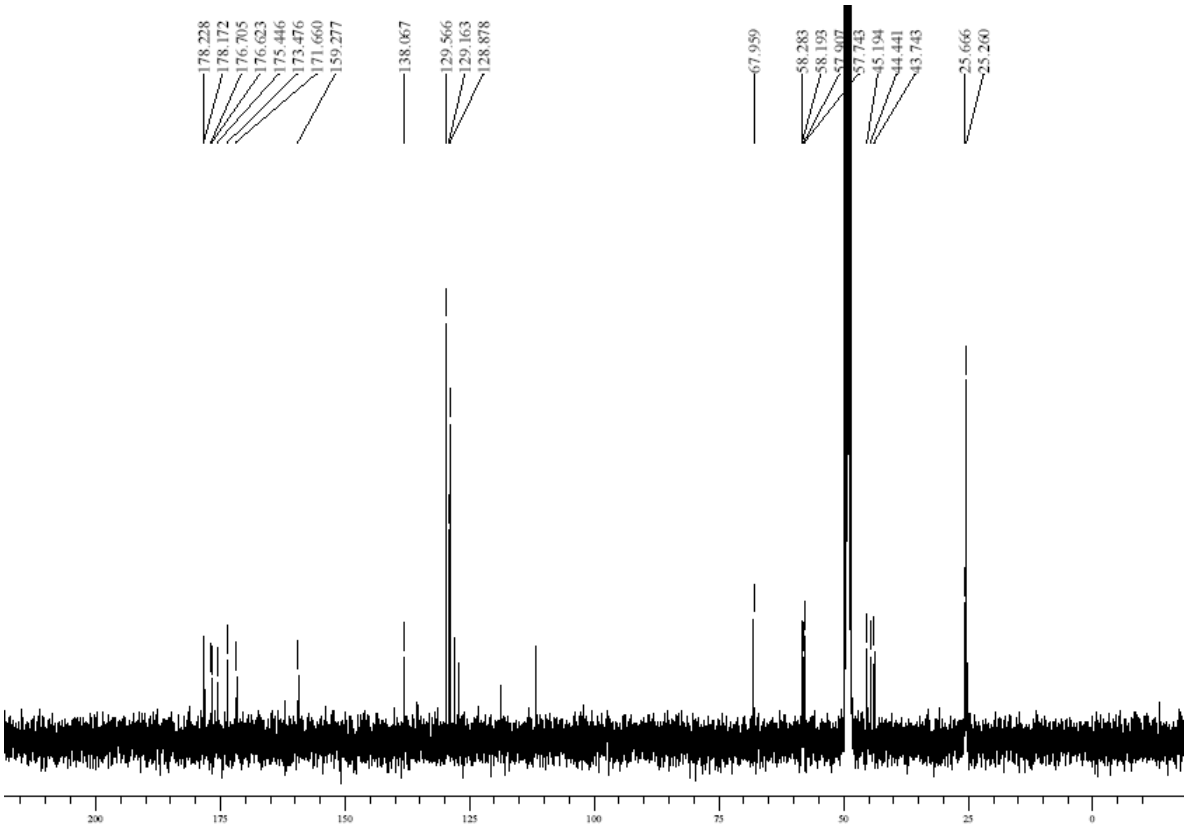



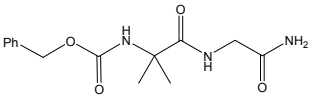
**Cbz-GlyGlyAib$_4$GlyNH$_2$ 8i**

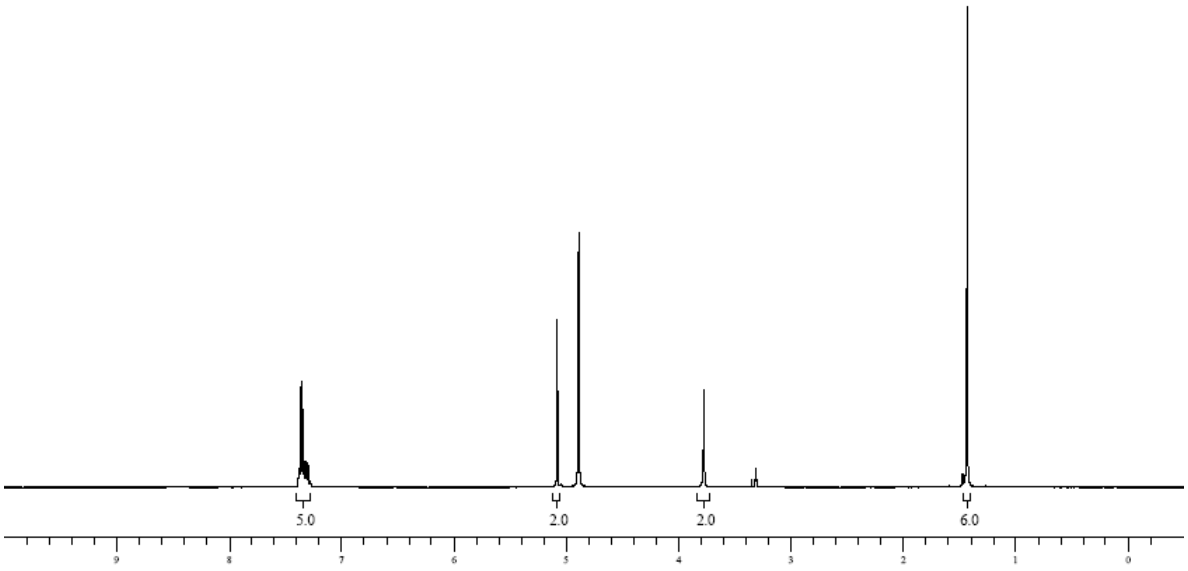


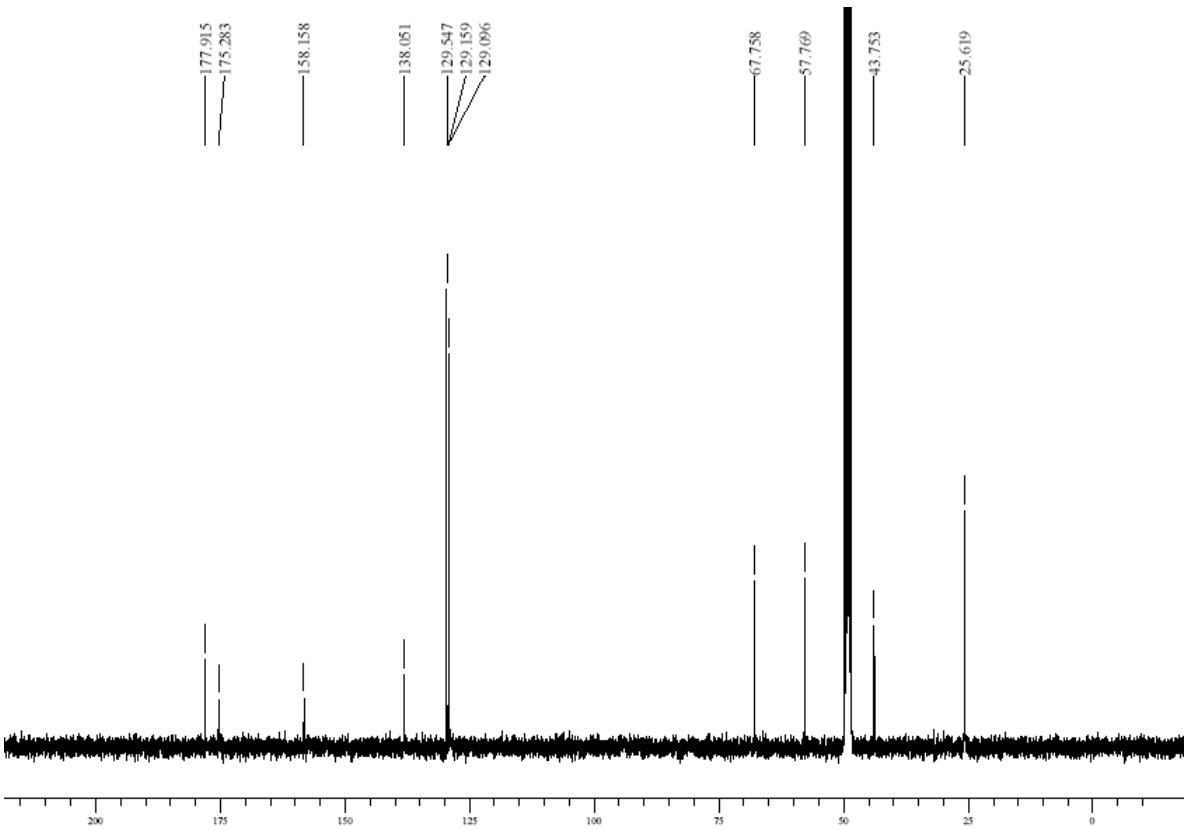



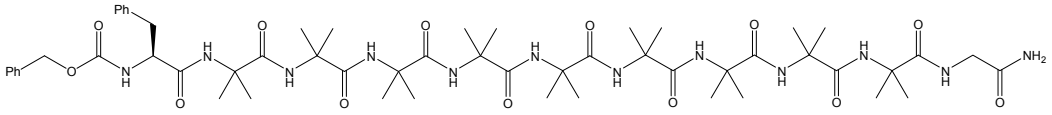
**Cbz-AibGlyNH$_2$**

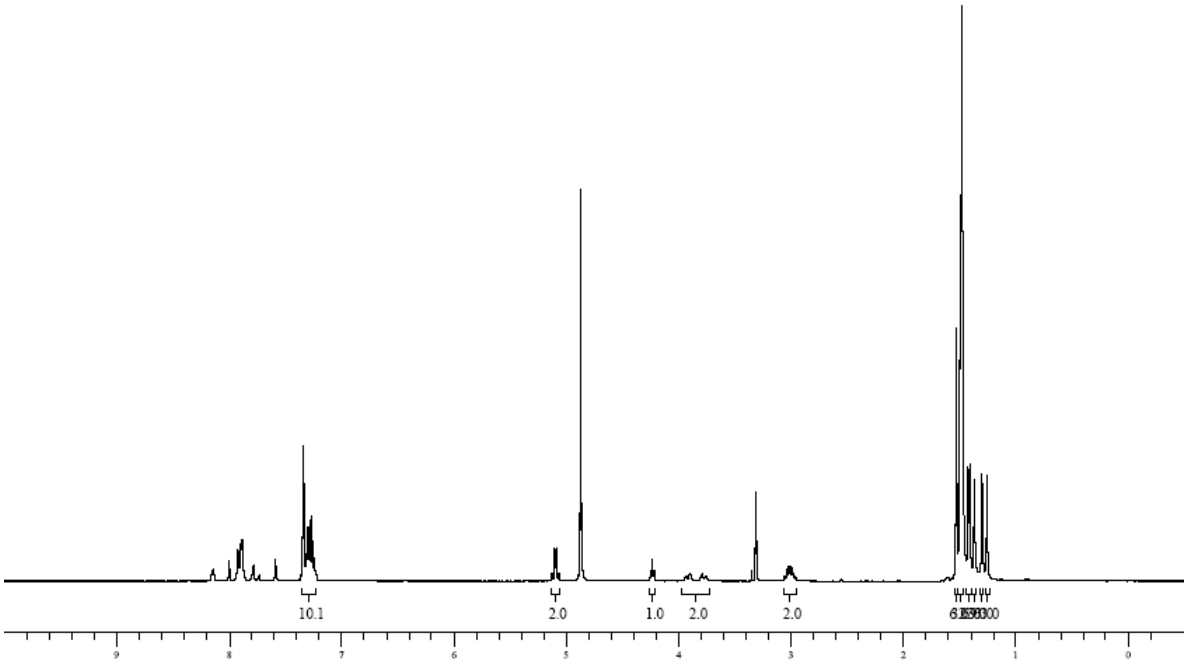


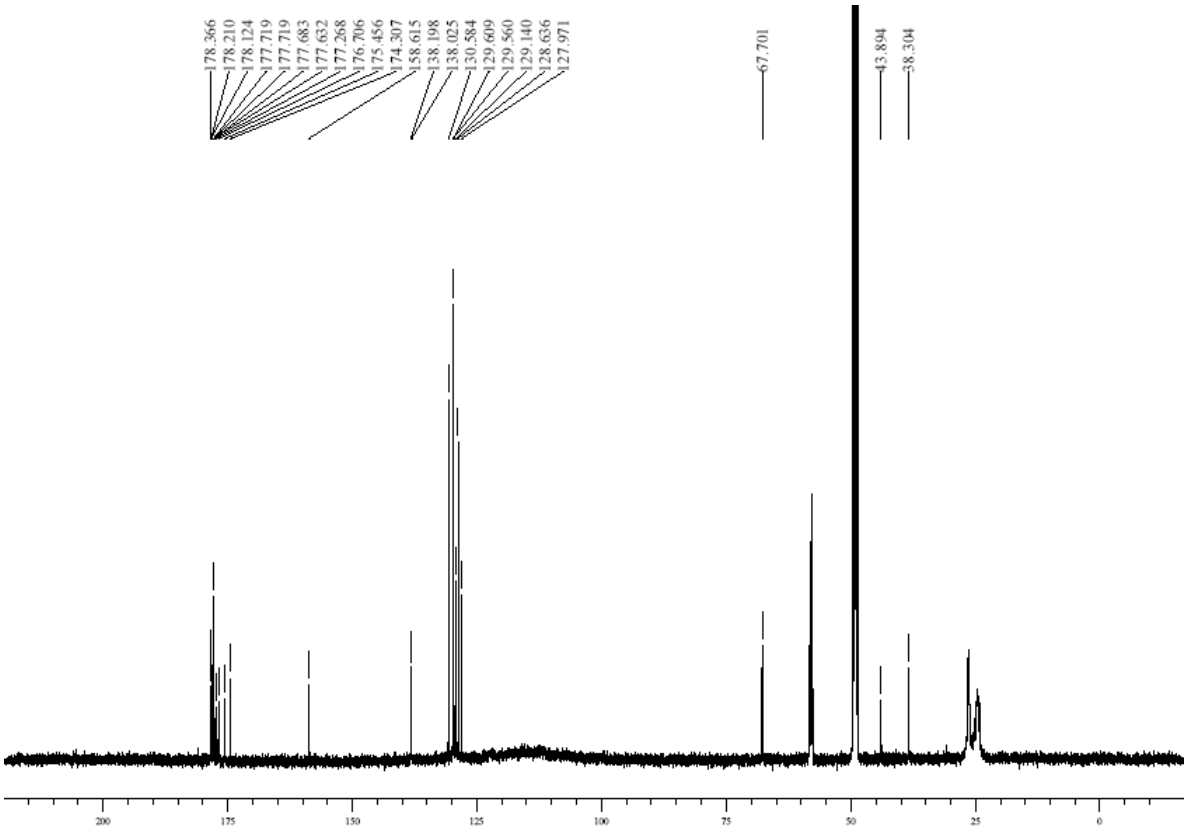



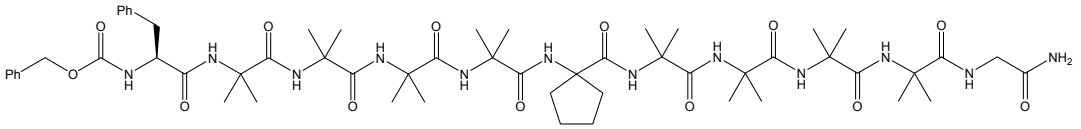
**Cbz-L-PheAib$_9$GlyNH$_2$ 1a**

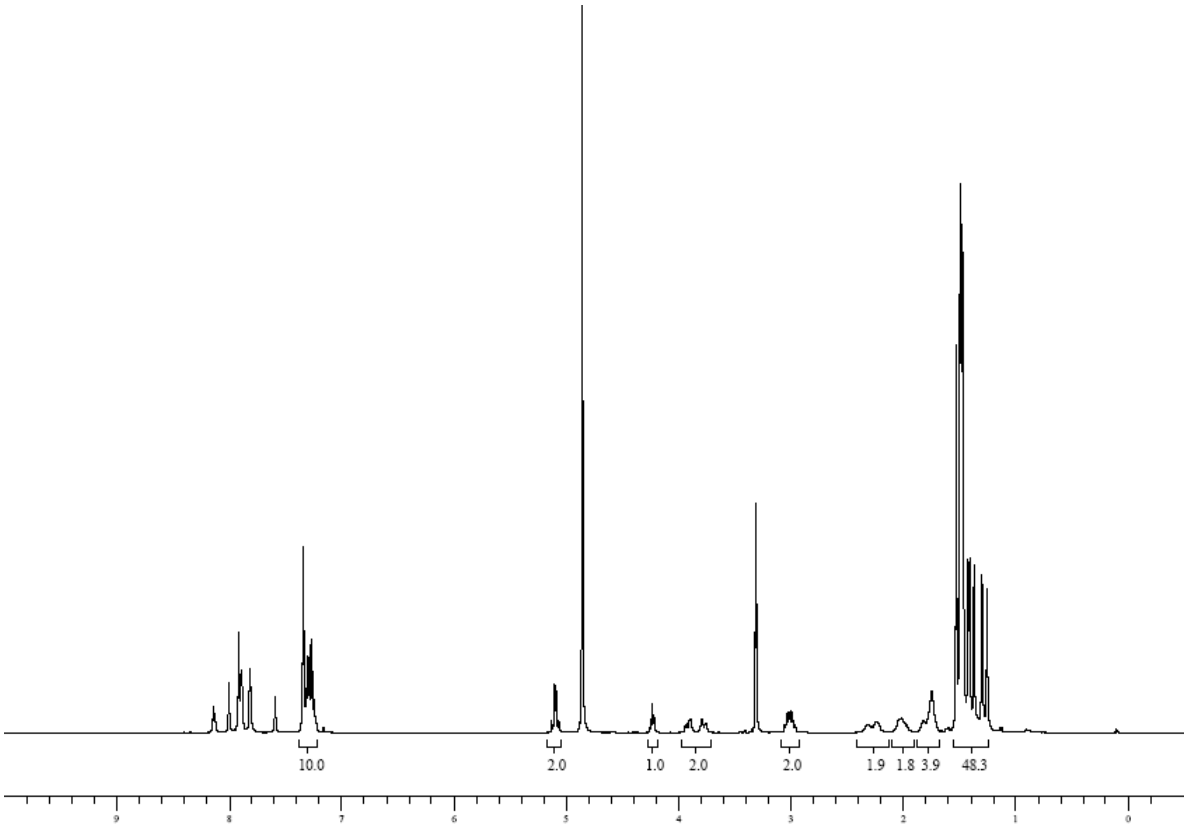


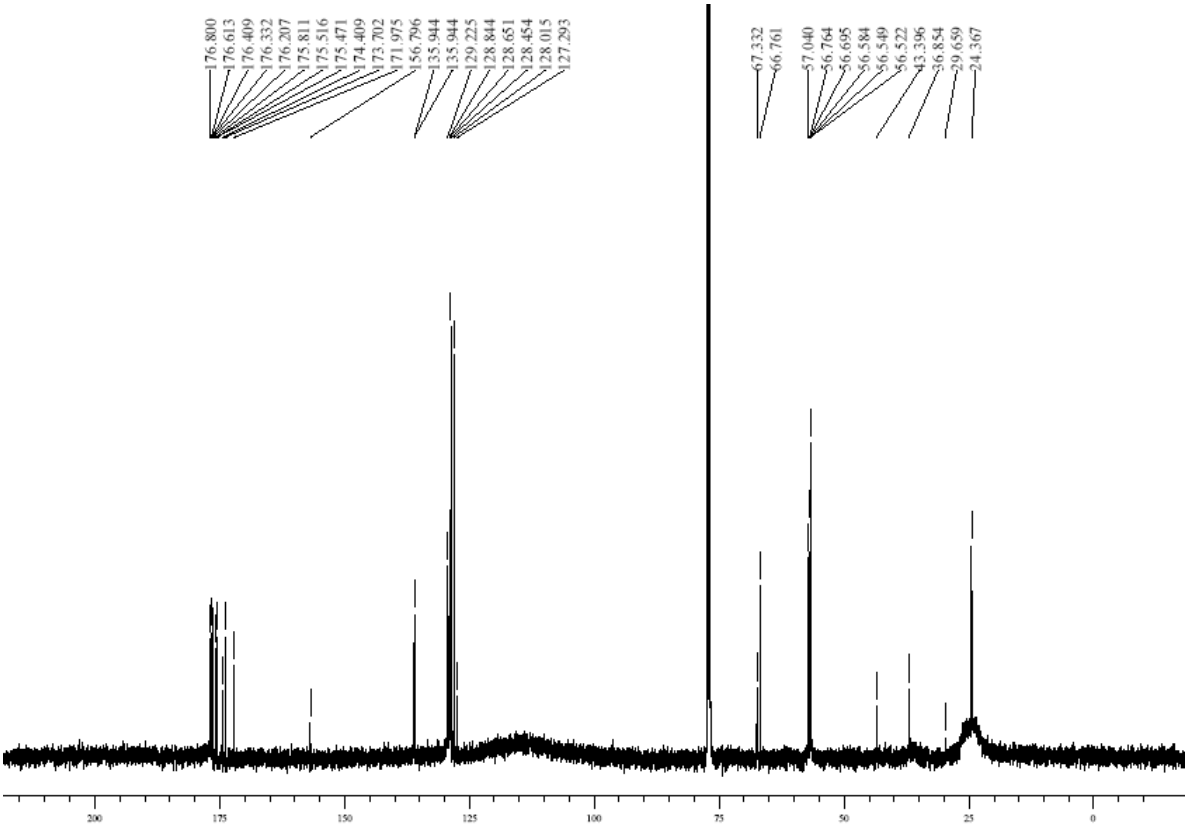


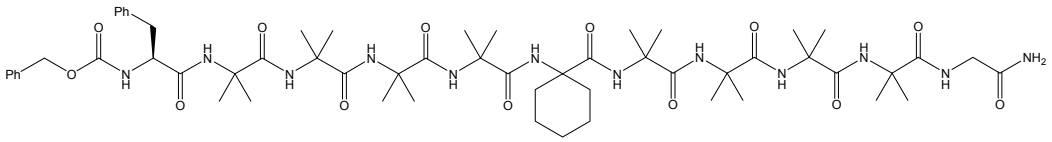
**Cbz-L-PheAib$_4$Ac$_5$cAib$_4$GlyNH$_2$ 1b**

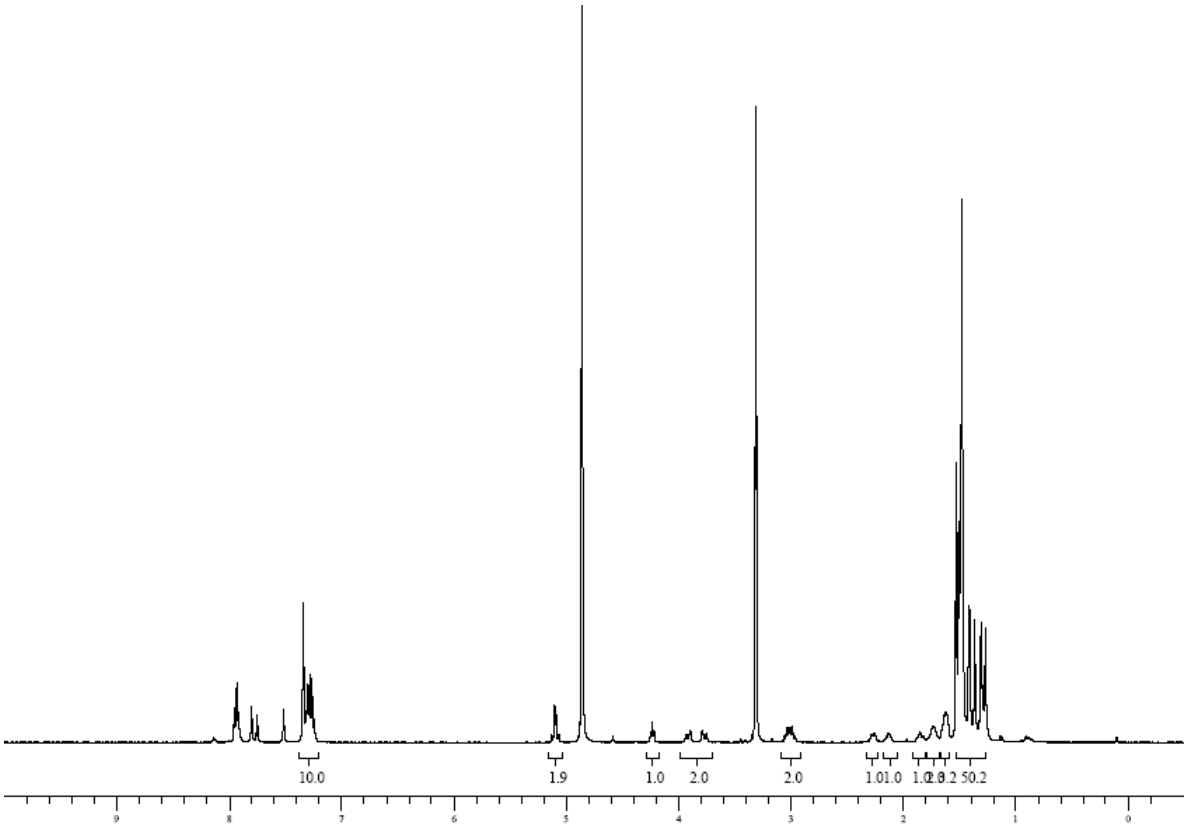


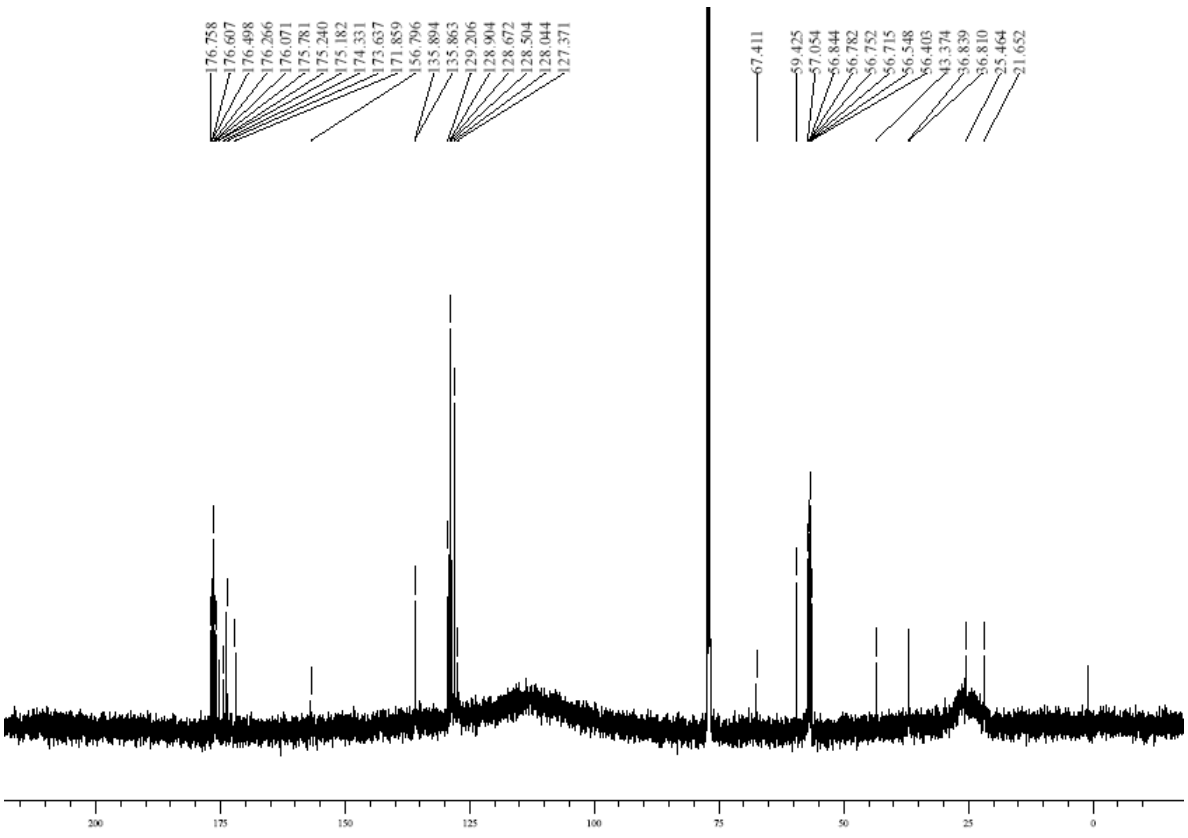


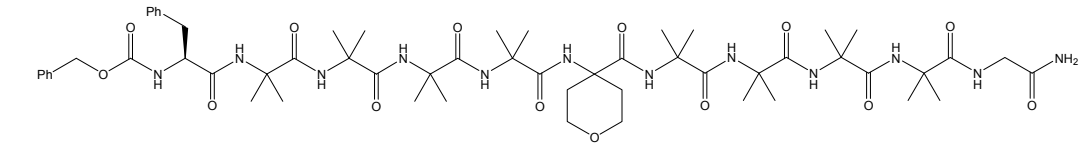
**Cbz-L-PheAib$_4$Ac$_6$cAib$_4$GlyNH$_2$ 1c**

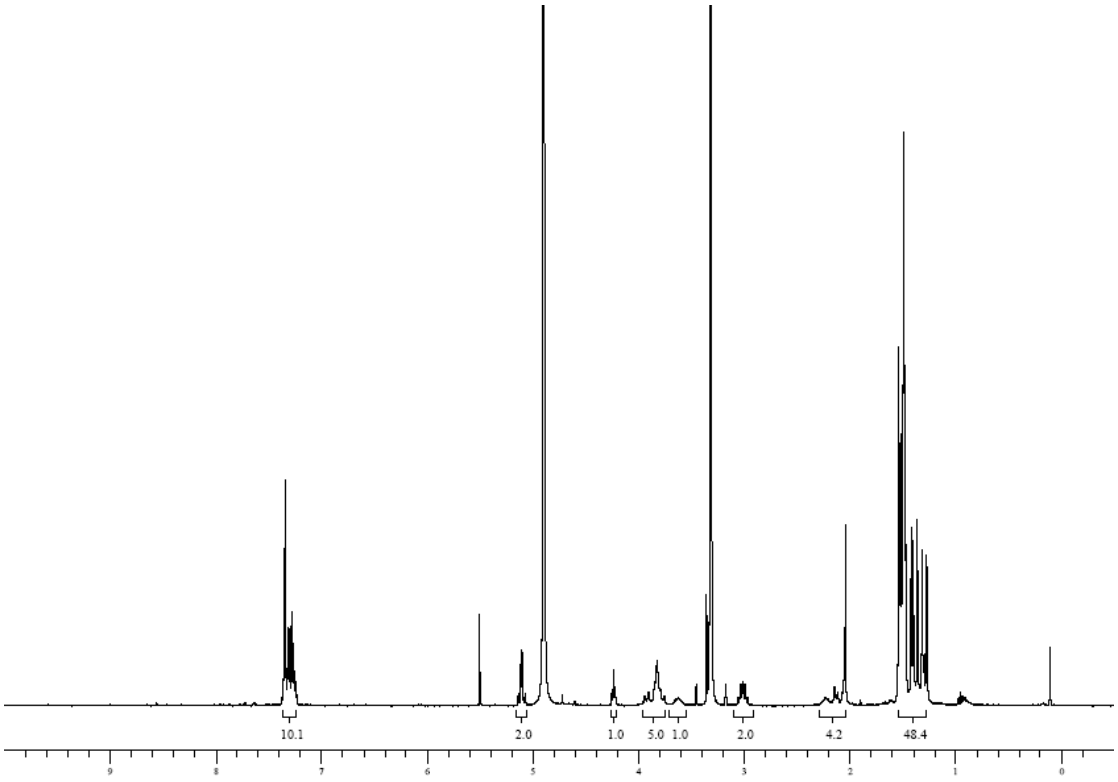




**Cbz-L-PheAib$_4$ThpAib$_4$GlyNH$_2$ 1d**



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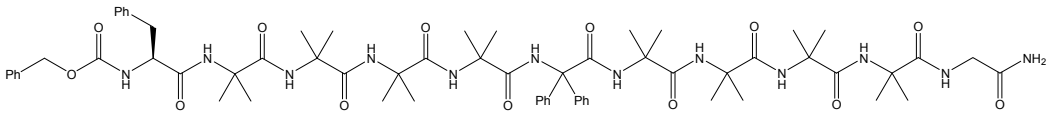
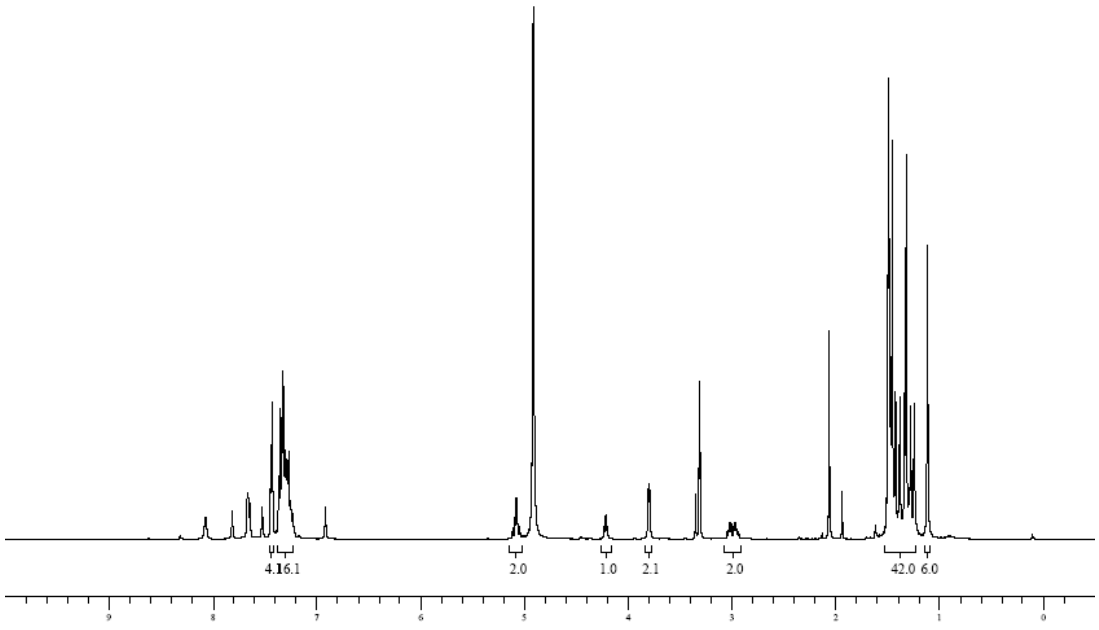
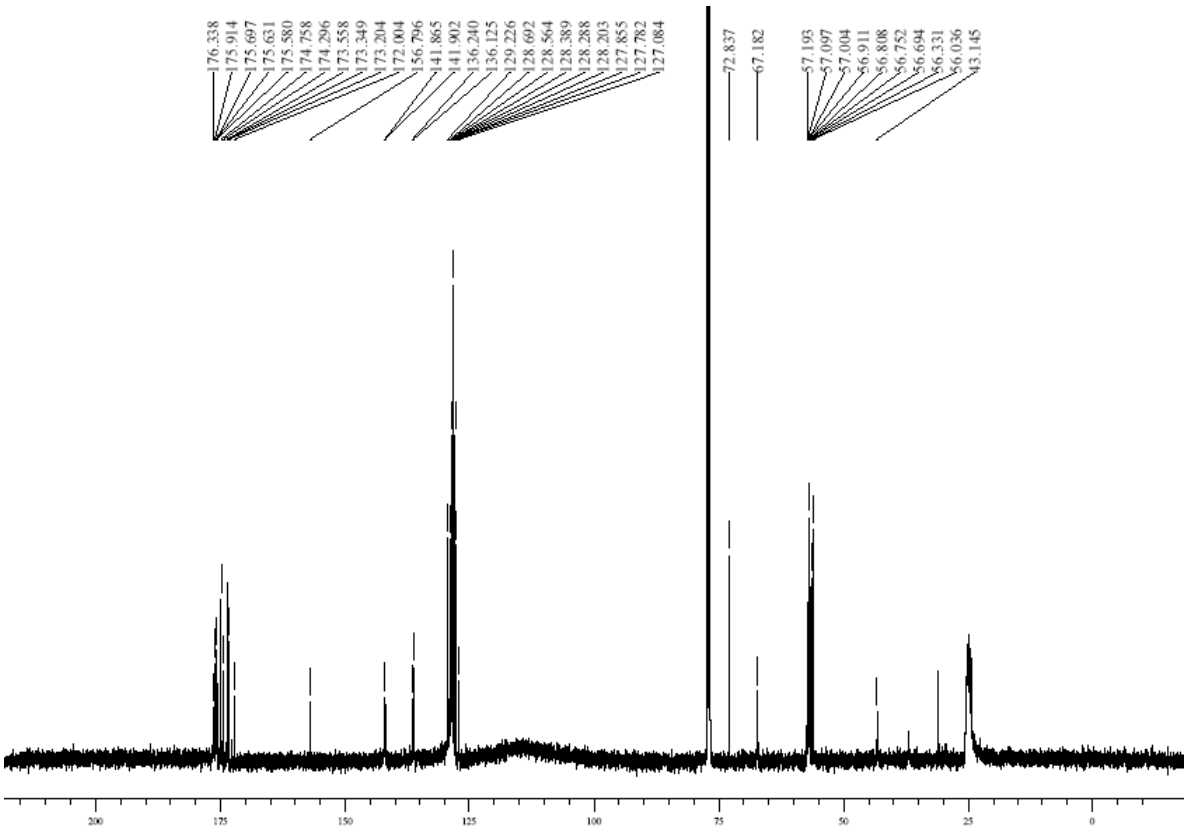
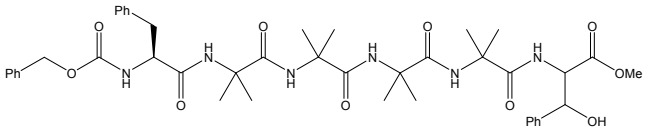
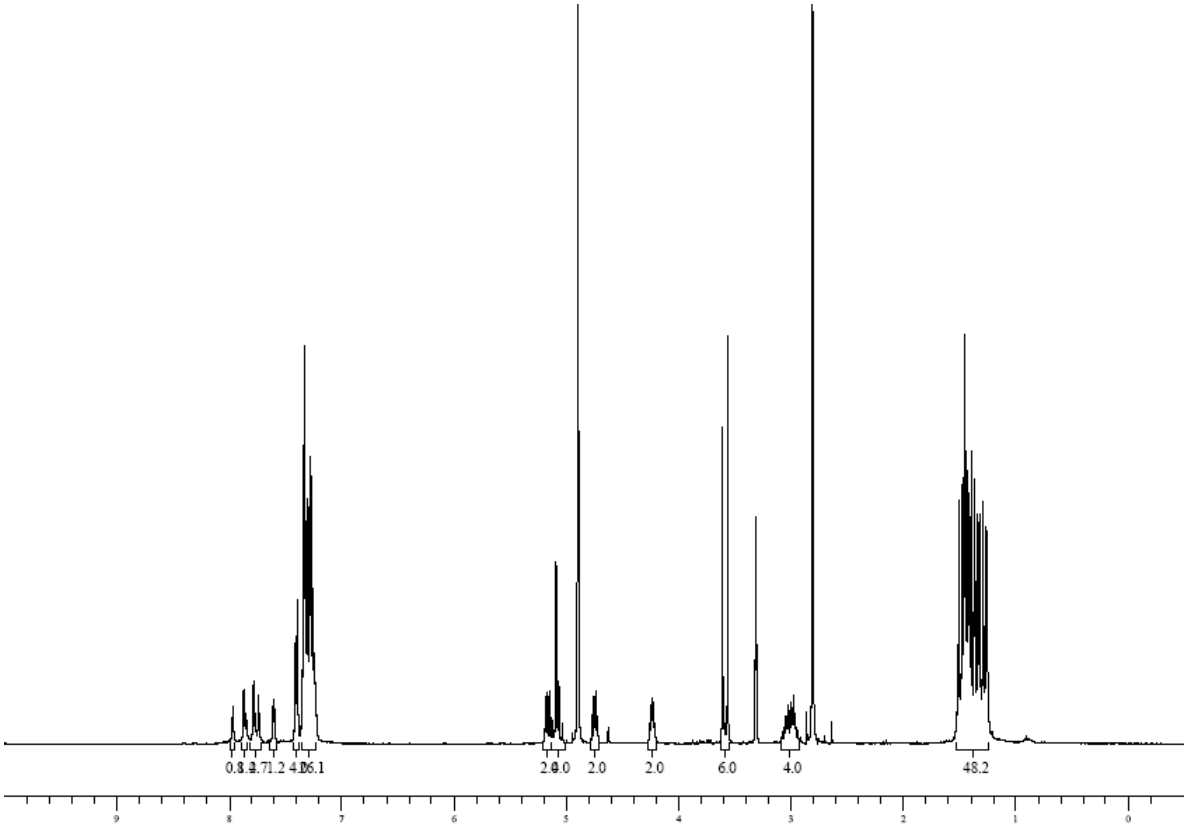


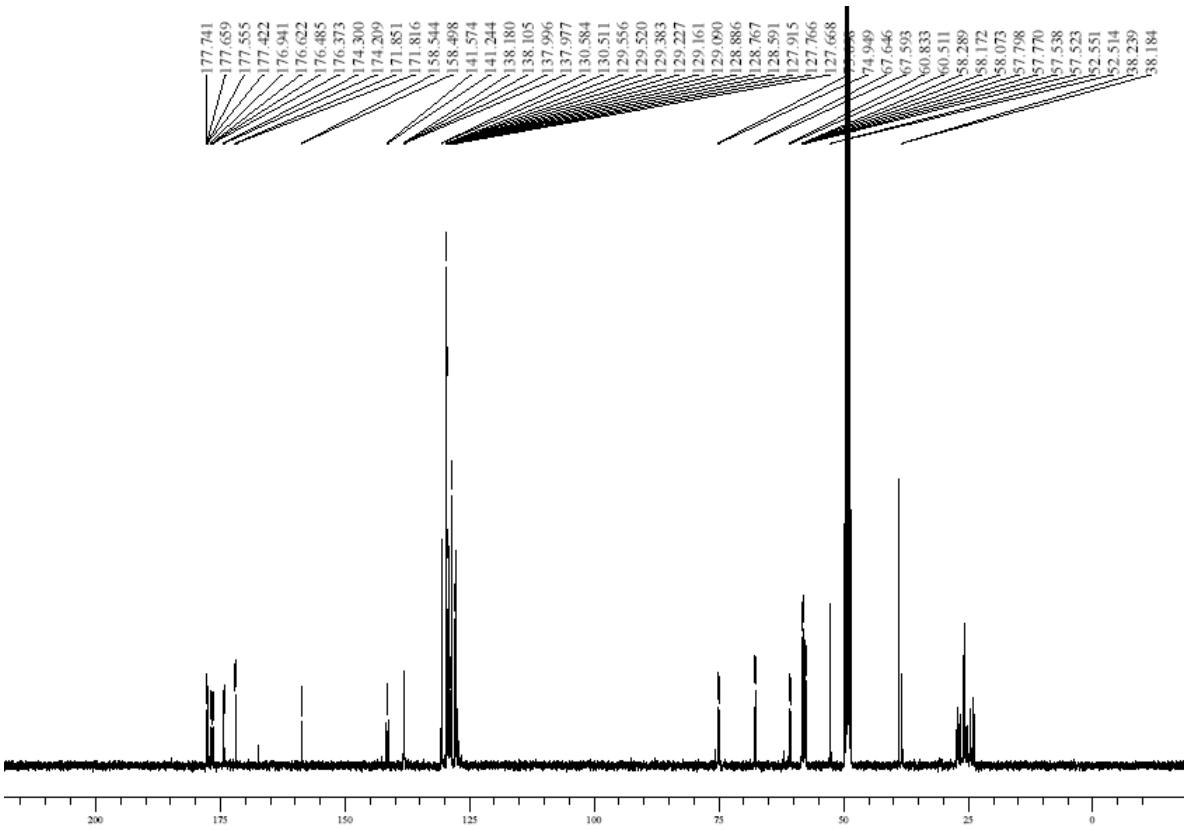




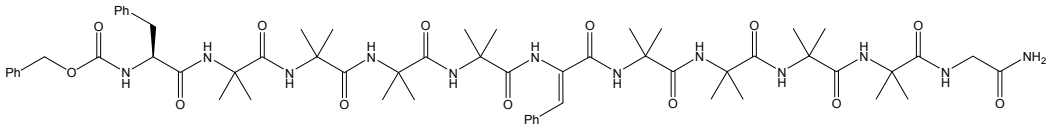

**Cbz-L-PheAib$_4$PhSerOMe 10**

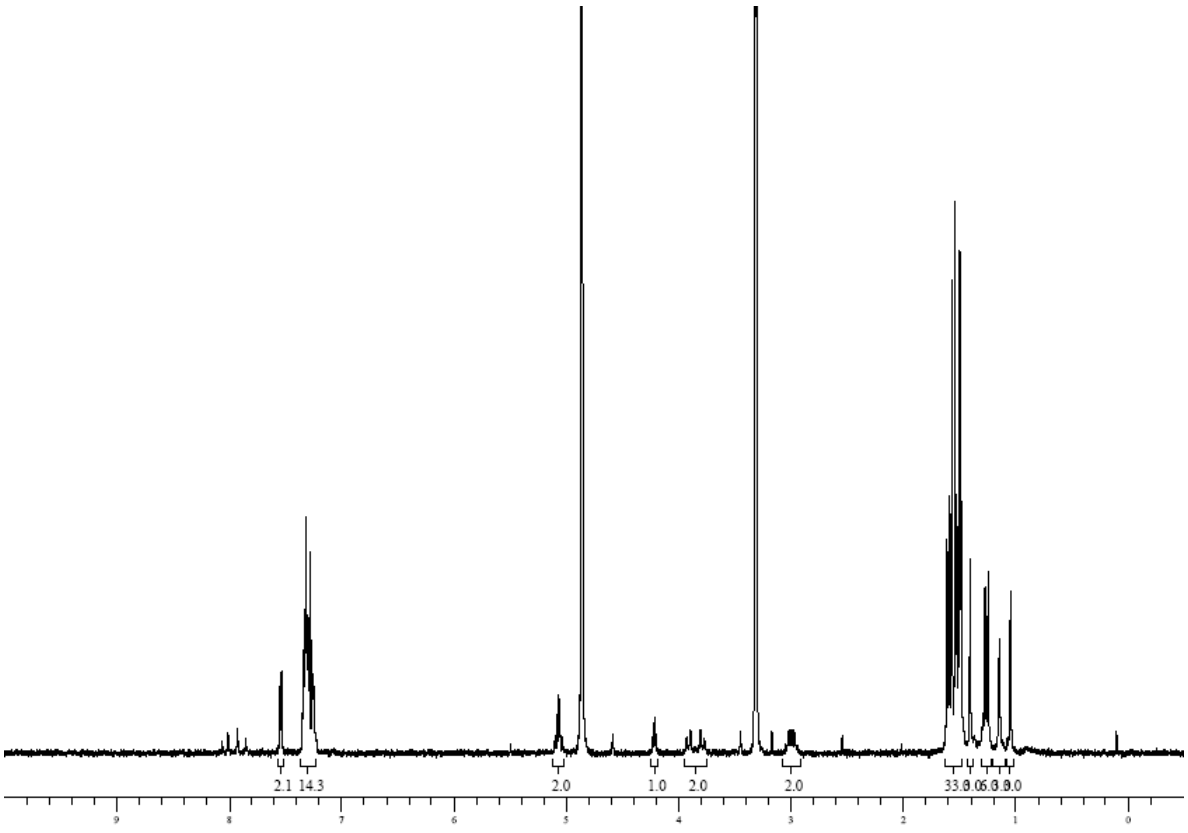


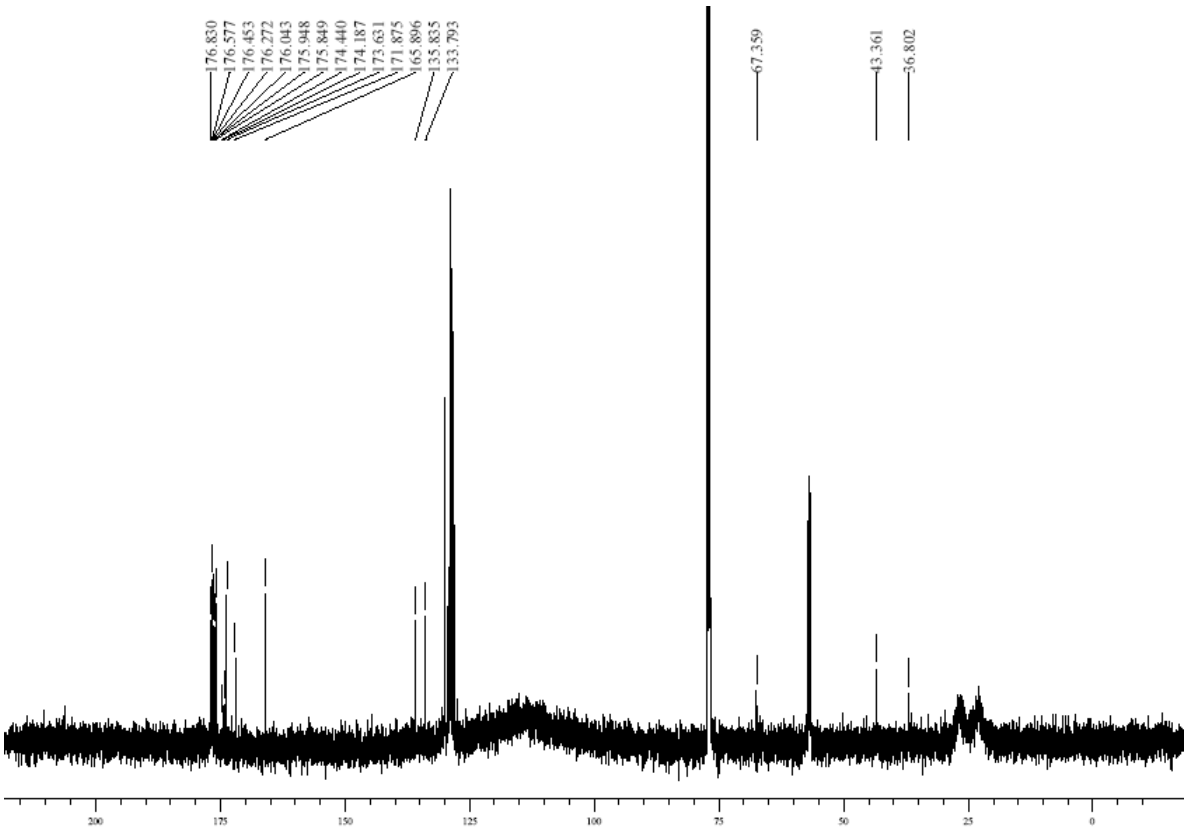





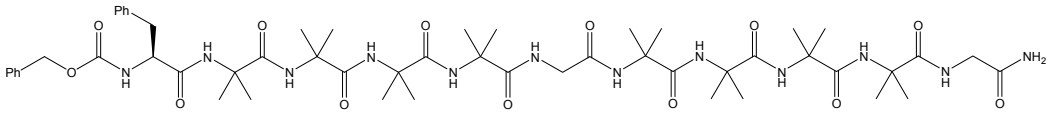

**Cbz-L-PheAib$_4$$^{\Delta}$PheAib$_4$GlyNH$_2$ 1f**

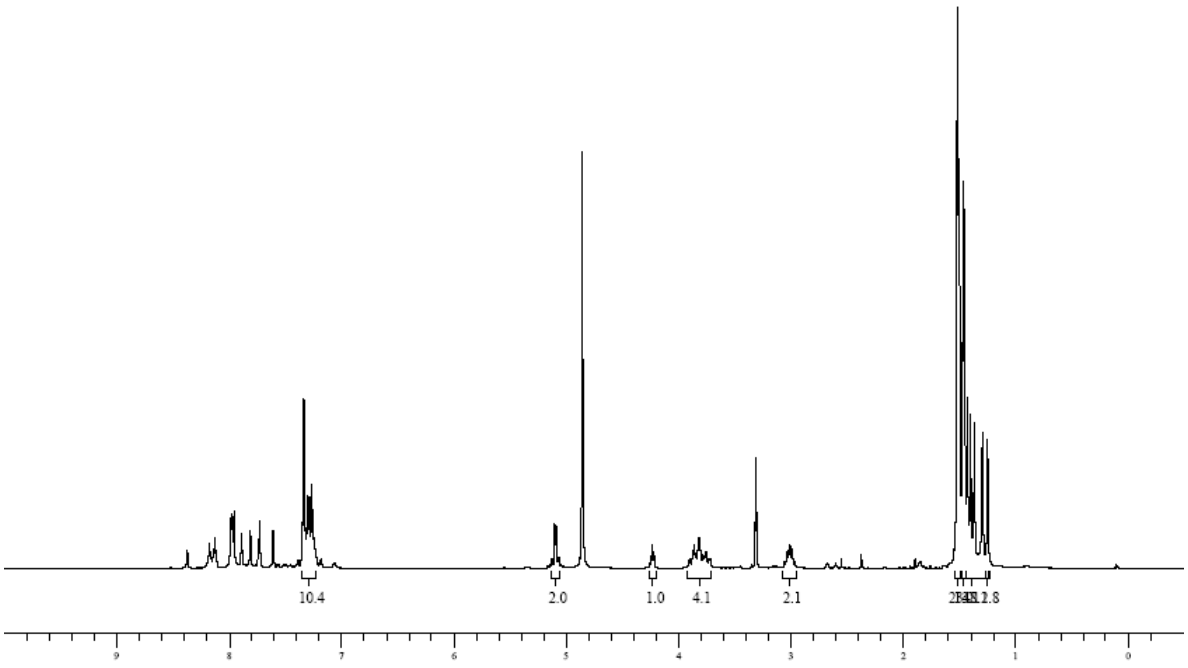


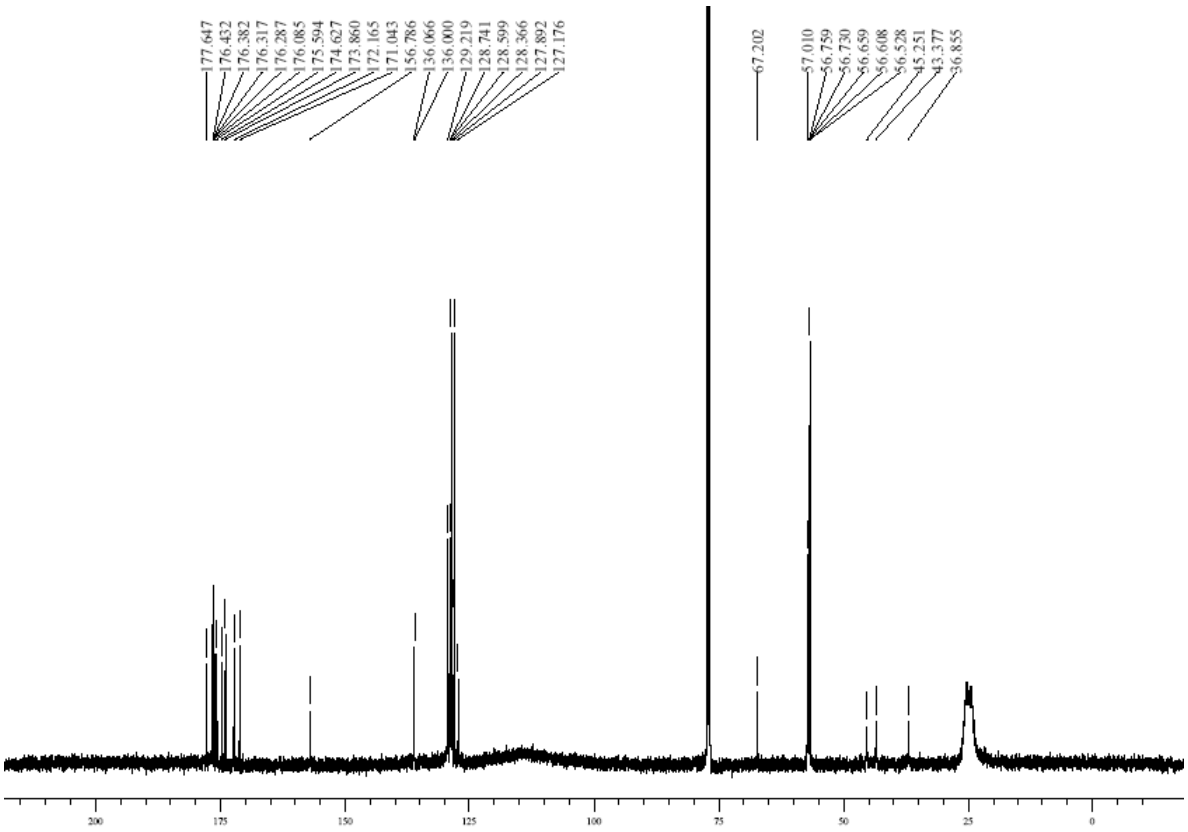





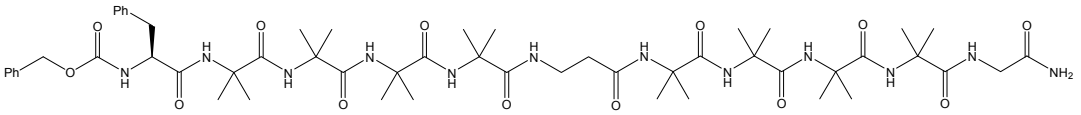

**Cbz-L-PheAib$_4$GlyAib$_4$GlyNH$_2$ 1g**

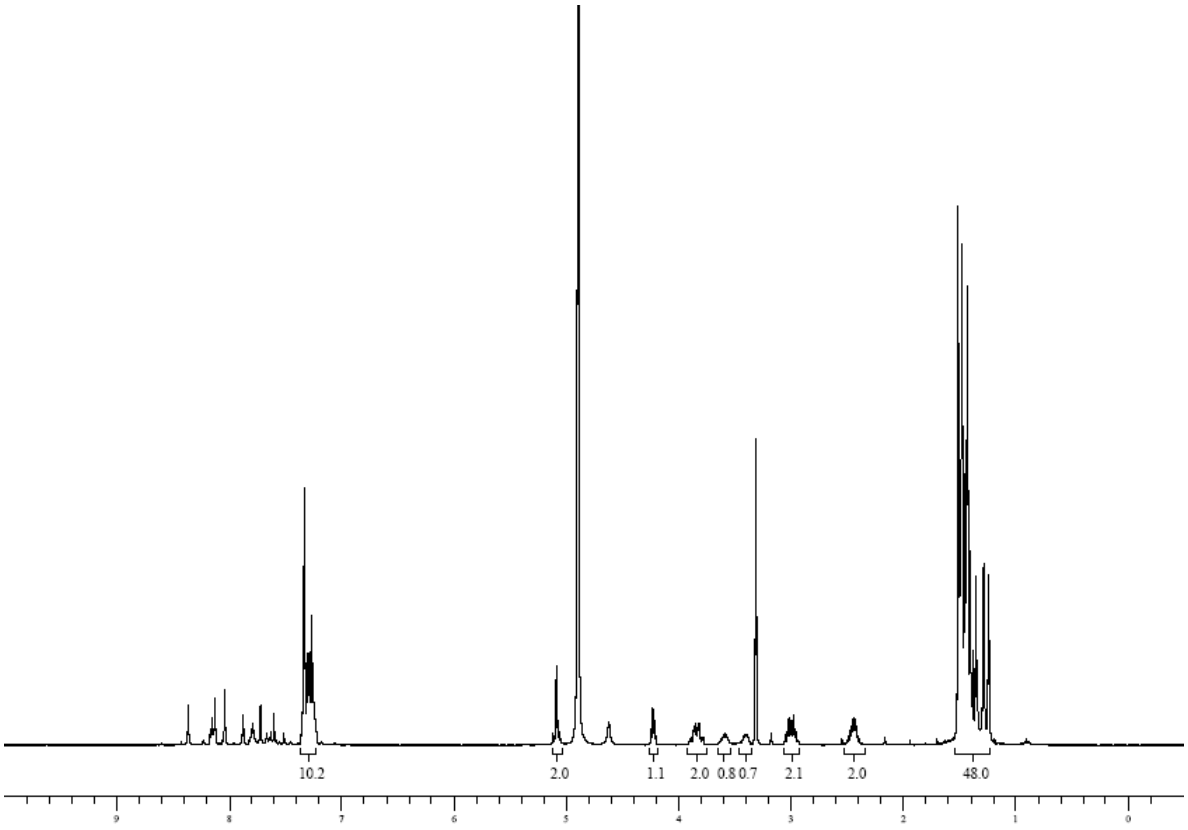


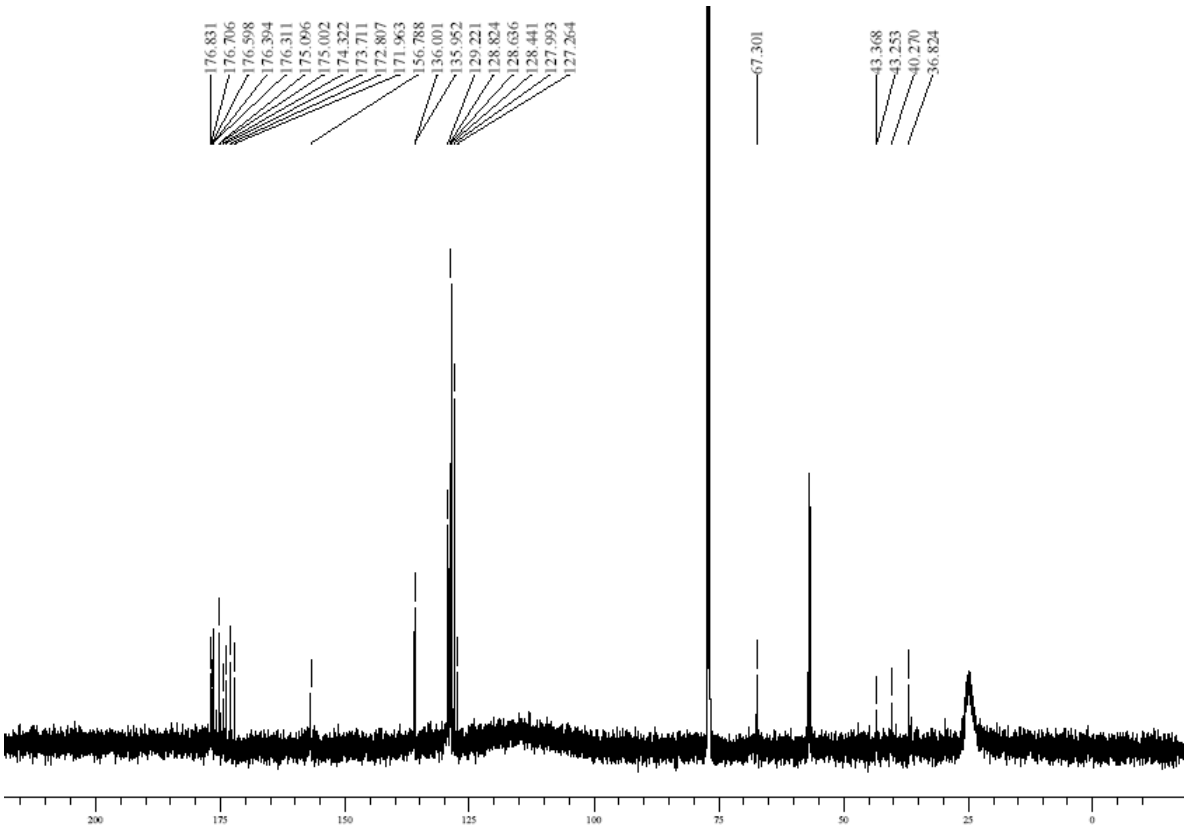






**Cbz-L-PheAib$_4$βAlaAib$_4$GlyNH$_2$ 1h**



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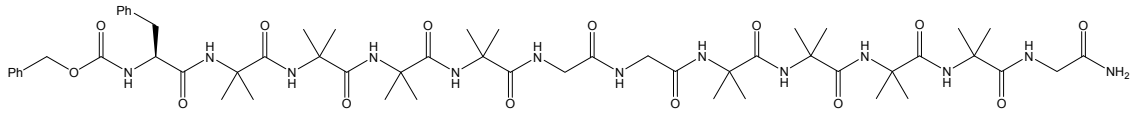
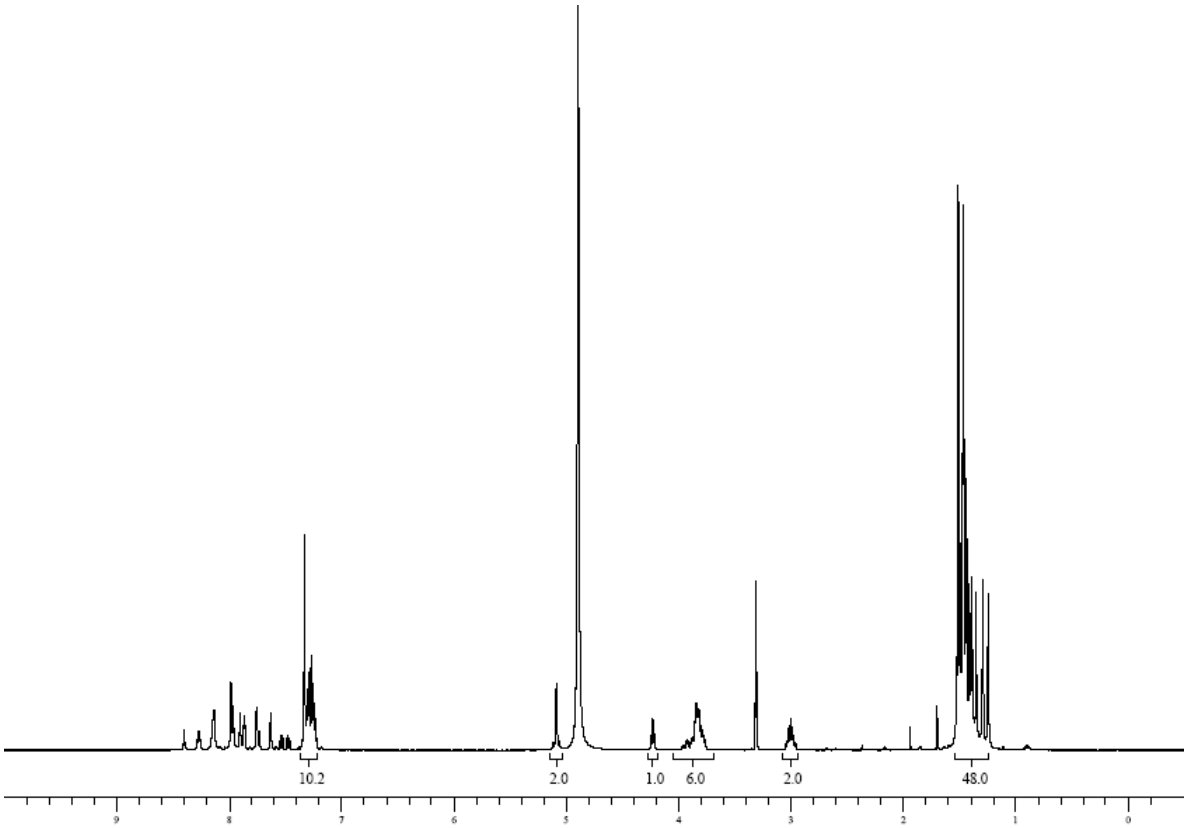
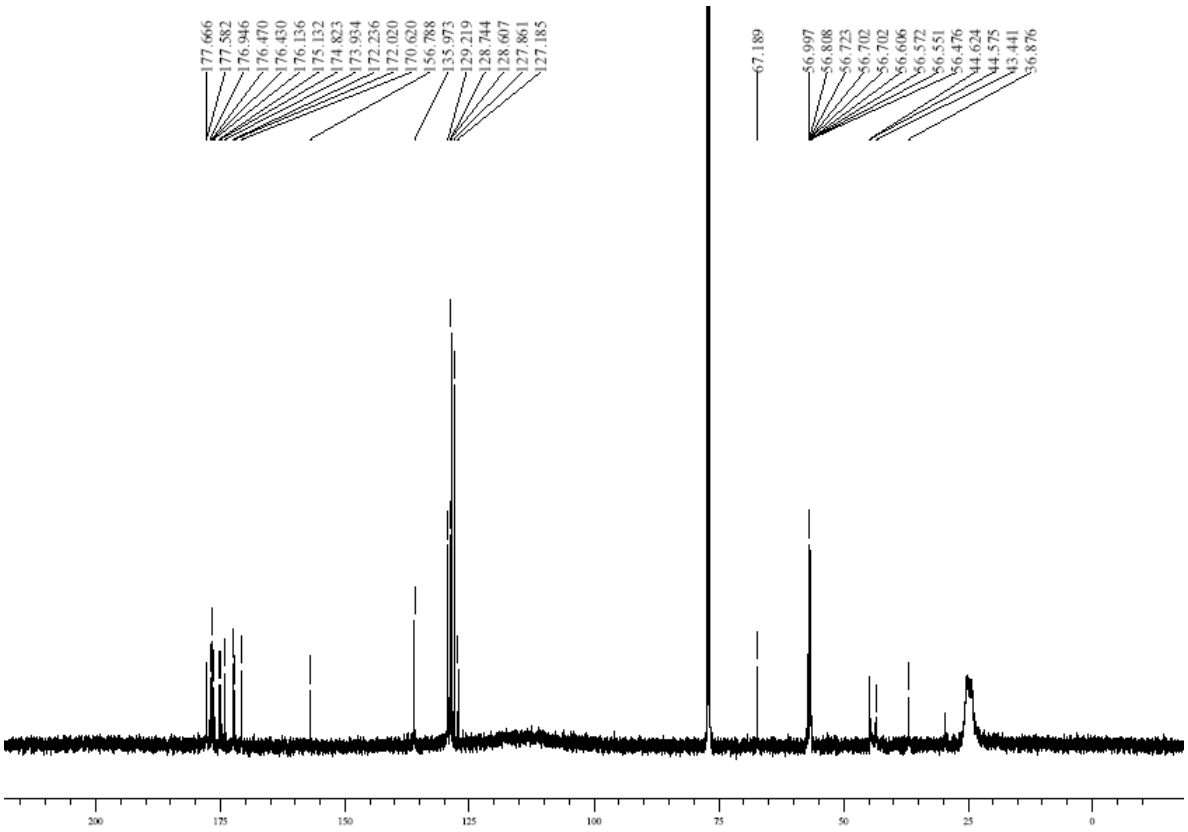
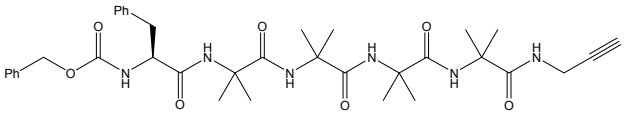
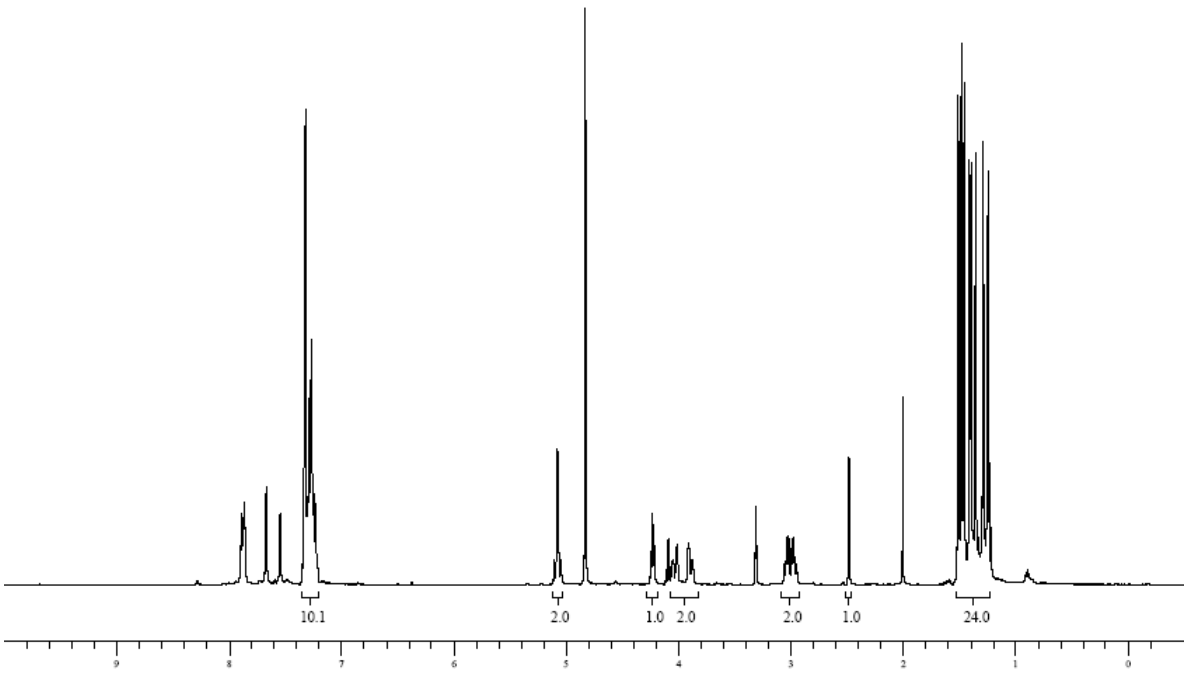


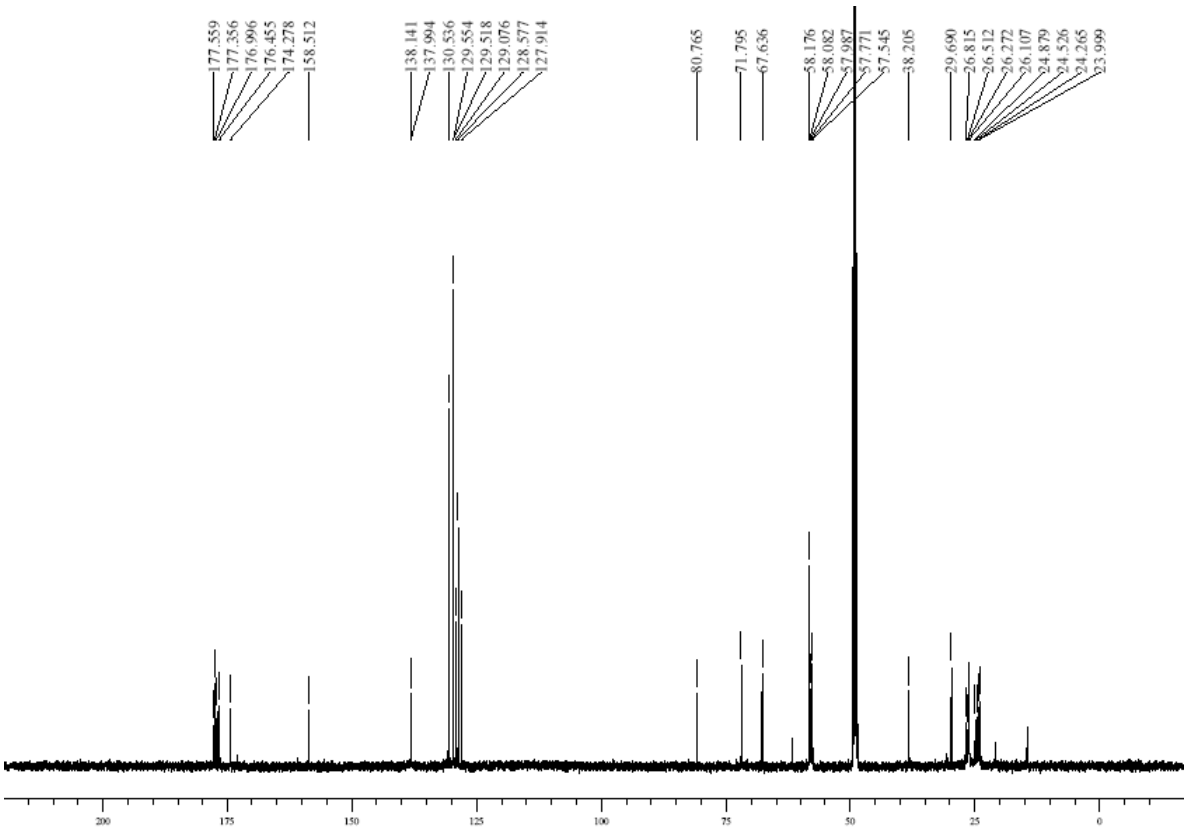





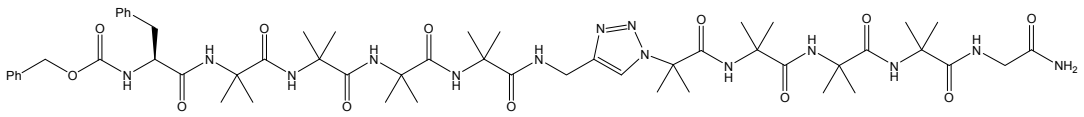

**Cbz-L-PheAib$_4$NHCH$_2$C≡CH 11**

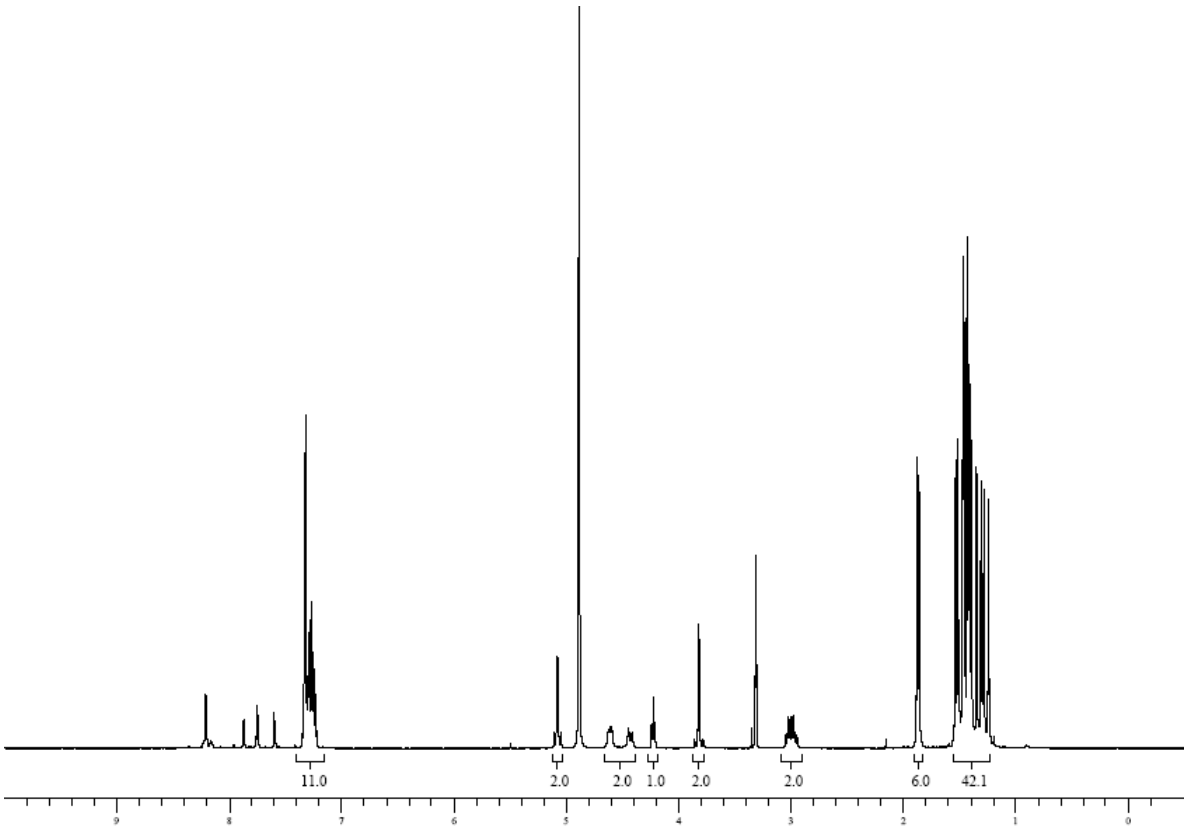


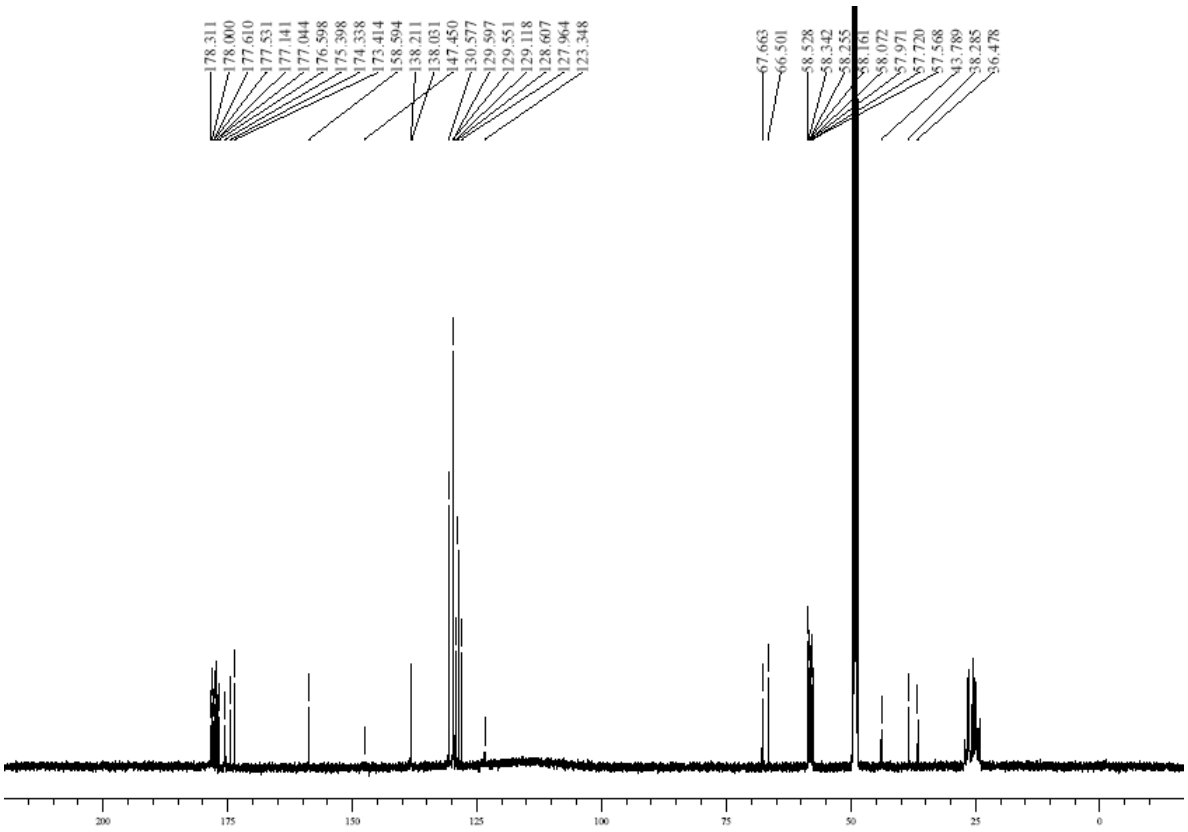





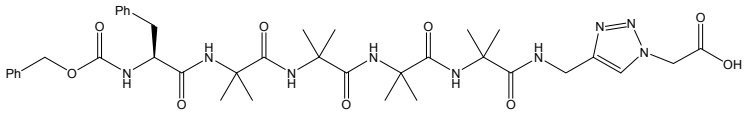

**Cbz-L-PheAib$_4$TrzAib$_4$GlyNH$_2$ 1j**

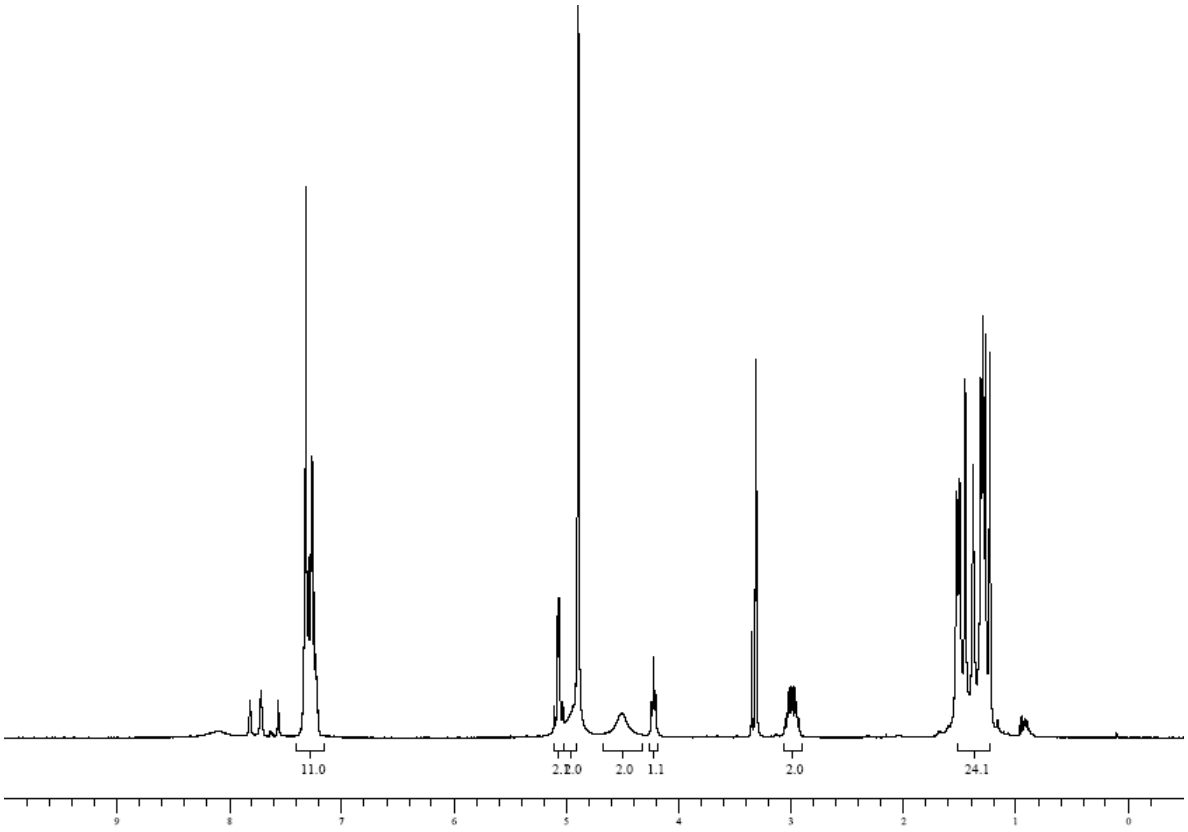


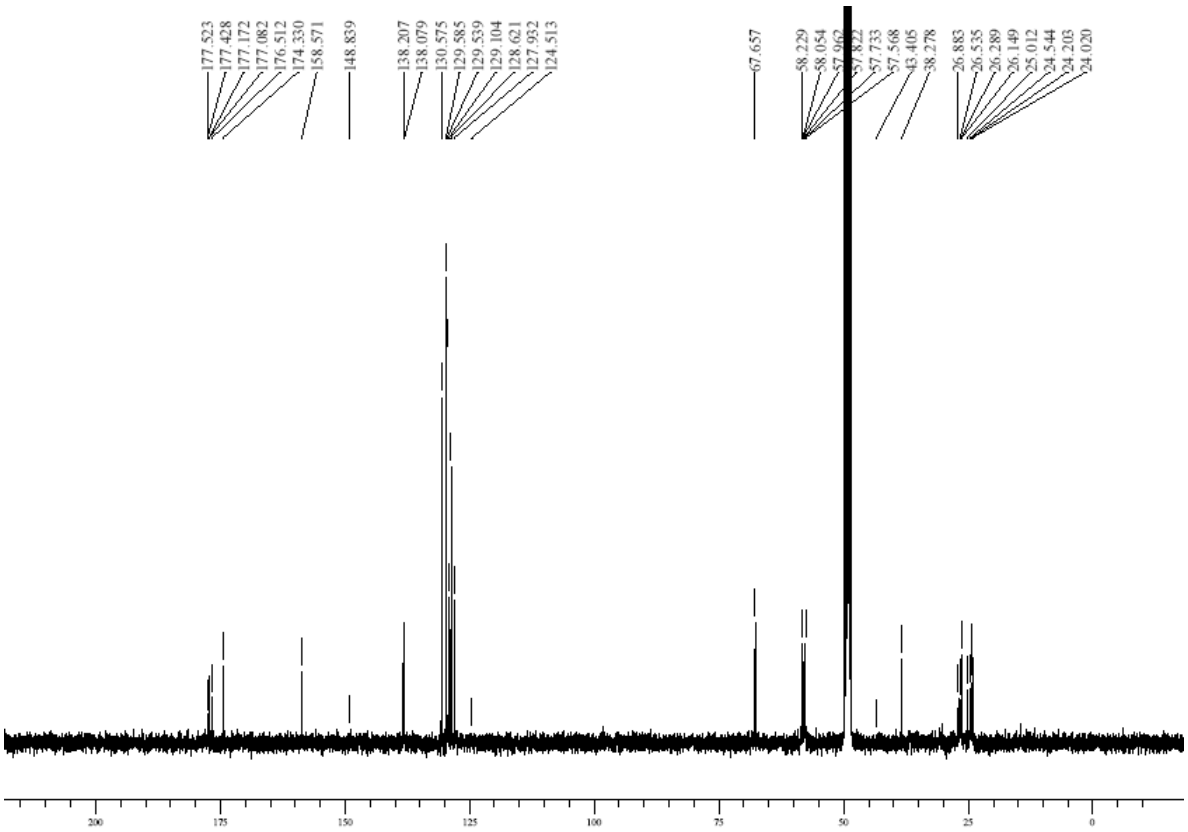





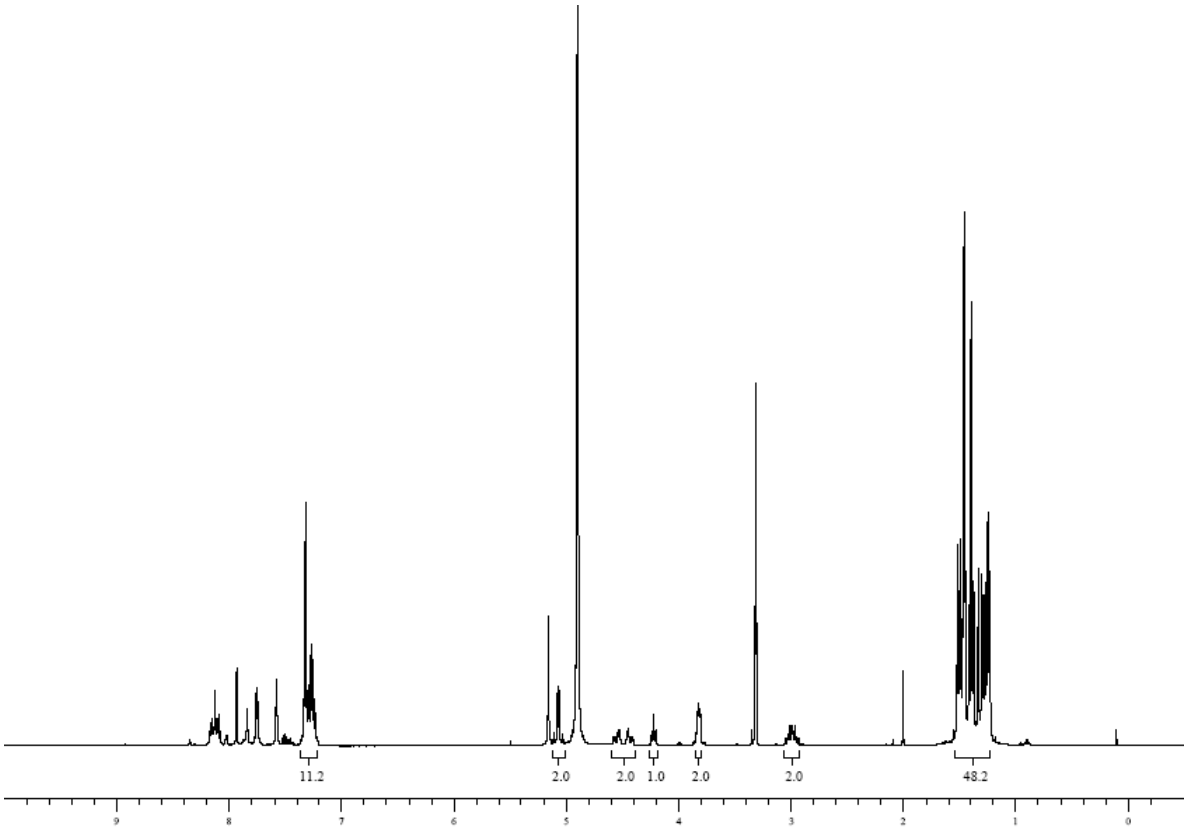

**Cbz-L-PheAib$_4$TrzGlyOH**

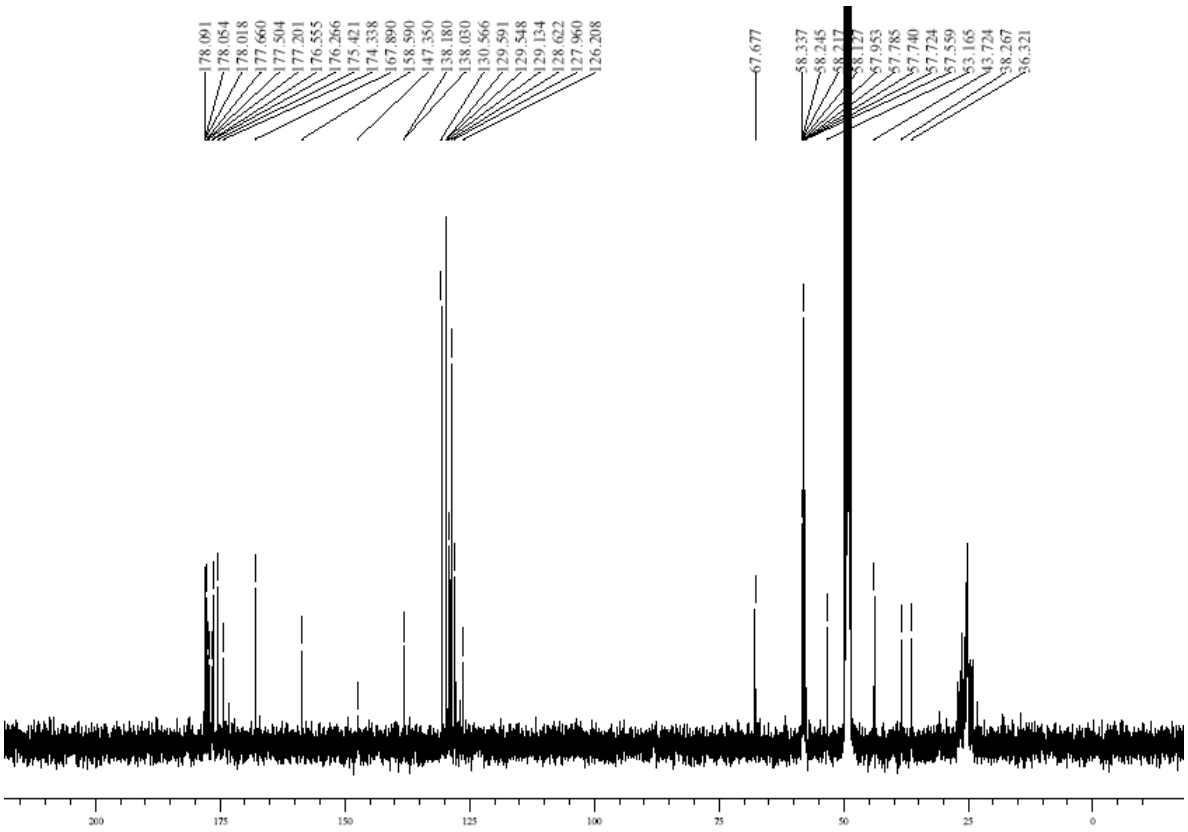





**Cbz-L-PheAib$_4$TrzGlyAib$_4$GlyNH$_2$ 1k**

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58.217
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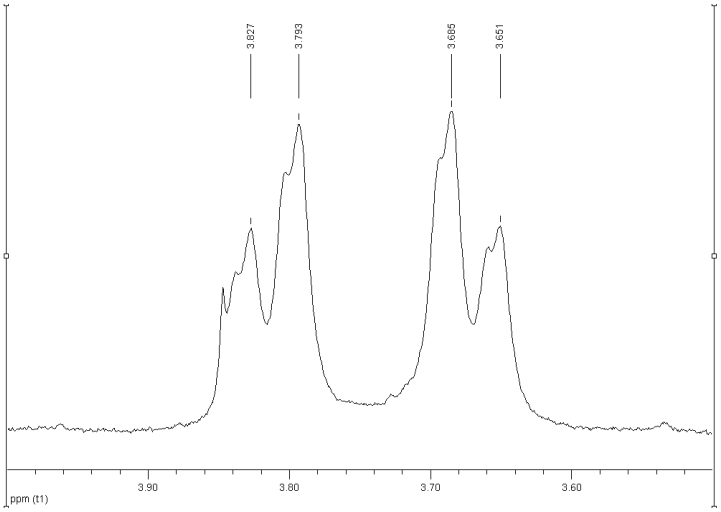
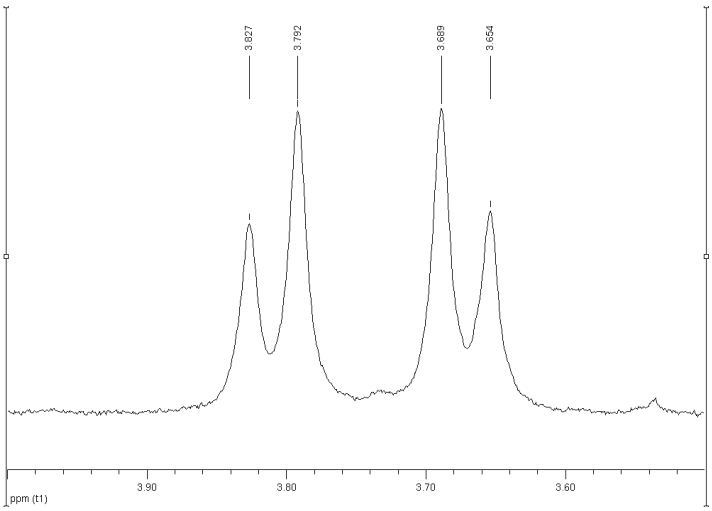
57.953
57.785
57.740
57.724
57.559
53.165
43.724
38.267
36.321
200
175
150
125
100
75
50
25
0

## 4. Supplementary figures: Expanded $^{1}H$ NMR $CH_2$ ($GlyNH_2$) region for peptides 1

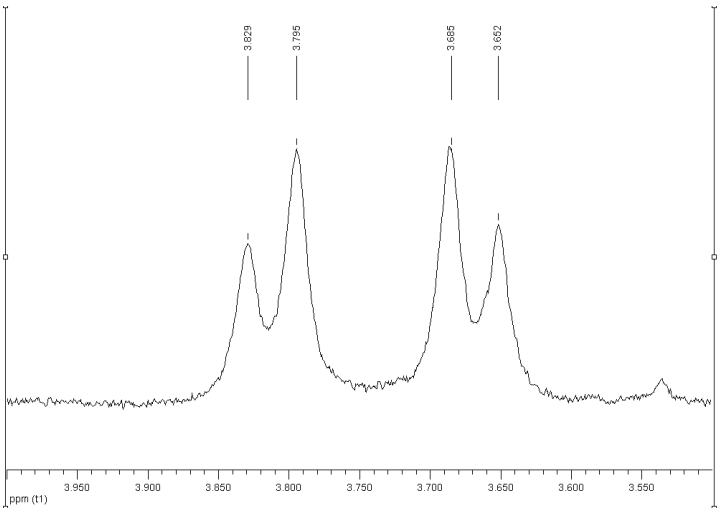
**Cbz-L-PheAib$_9$GlyNH$_2$ 1a** (500 MHz, $CD_3OD$)



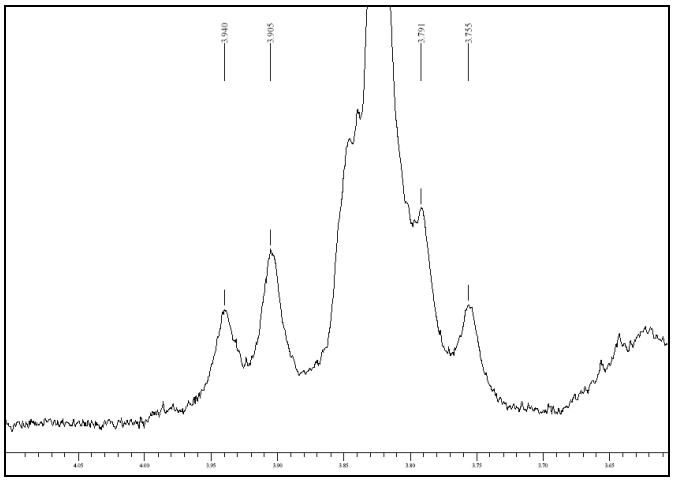

**Cbz-L-PheAib$_4$Ac$_5$cAib$_4$GlyNH$_2$ 1b** (500 MHz, $CD_3OD$)



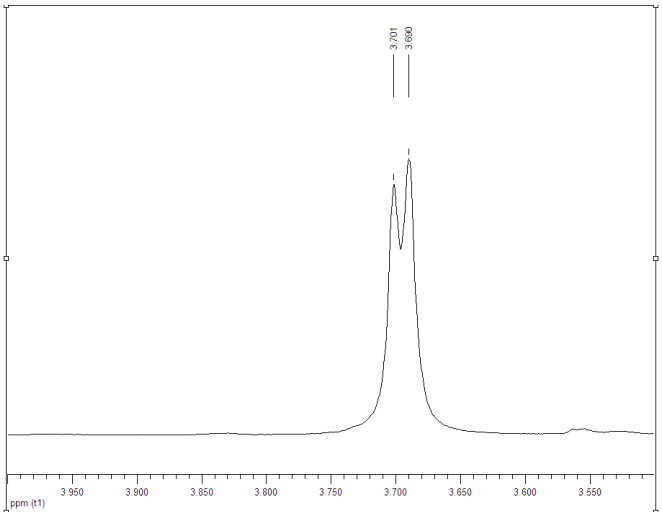

**Cbz-L-PheAib$_4$Ac$_6$cAib$_4$GlyNH$_2$ 1c** (500 MHz, $CD_3OD$)



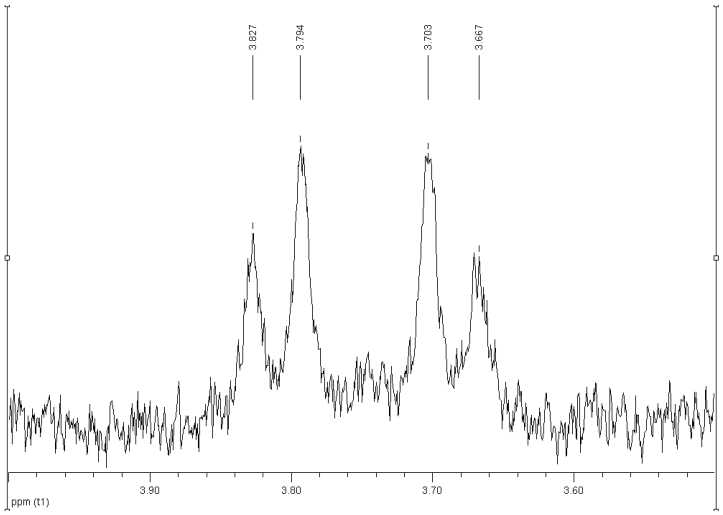
**Cbz-L-PheAib$_4$ThpAib$_4$GlyNH$_2$ 1d** (500 MHz, $CD_3OD$)



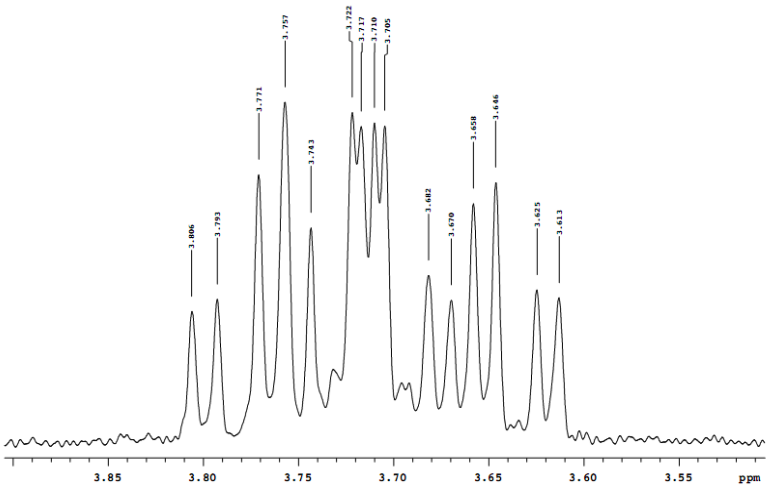

**Cbz-L-PheAib$_4$DpgAib$_4$GlyNH$_2$ 1e** (500 MHz, $CD_3OD$)



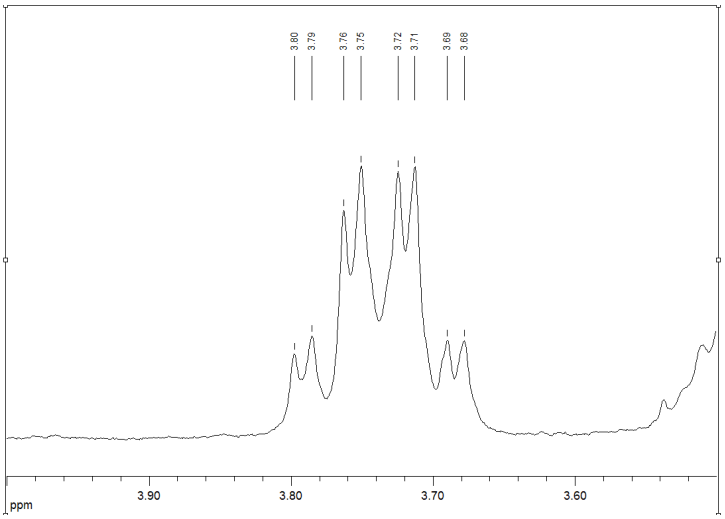

**Cbz-L-PheAib$_4^{\Delta}$PheAib$_4$GlyNH$_2$ 1f** (500 MHz, $CD_3OD$)



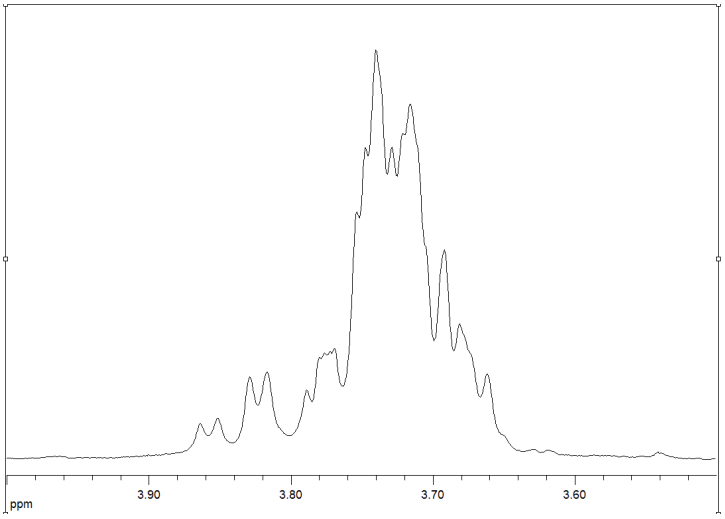
**Cbz-L-PheAib$_4$GlyAib$_4$GlyNH$_2$ 1g.** (500 MHz, $CD_3OD$) *(After deconvolution to 2 Hz Gaussian)*



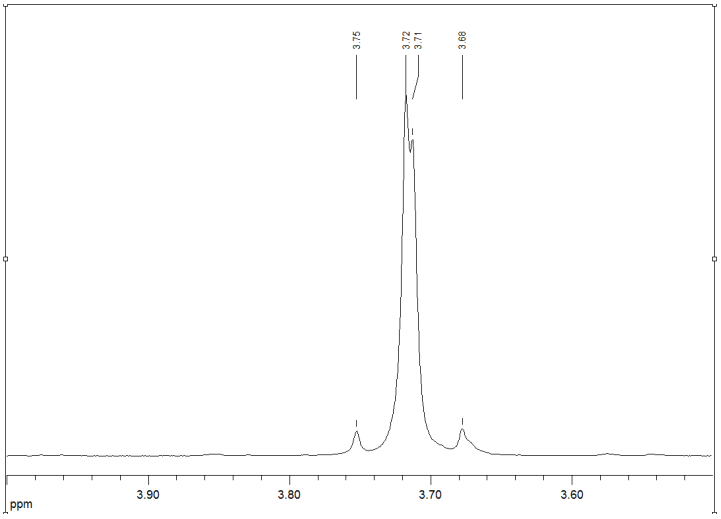

**Cbz-L-PheAib$_4$βAlaAib$_4$GlyNH$_2$ 1h** (500 MHz, $CD_3OD$)



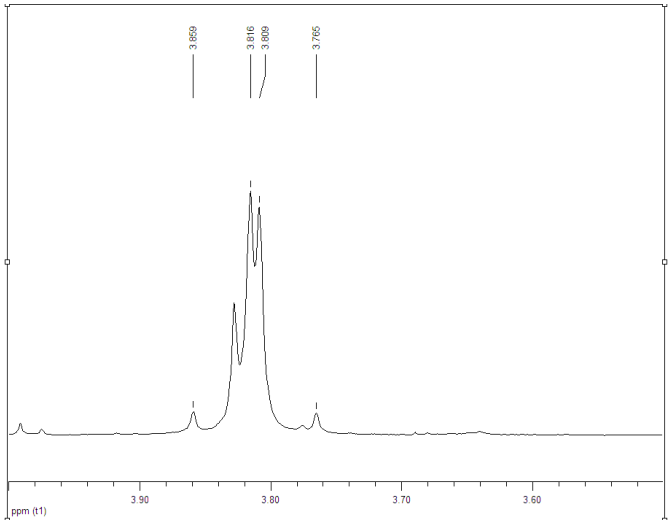

**Cbz-L-PheAib$_4$GlyGlyAib$_4$GlyNH$_2$ 1i** (500 MHz, $CD_3OD$)



**Cbz-L-PheAib$_4$CH$_2$TrzAib$_4$GlyNH$_2$ 1j** (500 MHz, CD$_3$OD)




**Cbz-L-PheAib$_4$TrzGlyAib$_4$GlyNH$_2$ 1k** (500 MHz, CD$_3$OD)



## 5. Supplementary figures: Circular Dichroism spectra for peptides 1

QuickTime™ and a
decompressor
are needed to see this picture.

QuickTime™ and a
decompressor
are needed to see this picture.

1 a) J. Clayden, A. Castellanos, J. Sola, G. A. Morris, *Angew. Chem. Int. Ed.* **2009**, *48*, 5962-5965. b) J. Sola, M. Helliwell, J. Clayden, *J. Am. Chem. Soc.* **2010**, *132*, 4548-4549. c) R. A. Brown, T. Marcelli, M. De Poli, J. Solà, J. Clayden, *Angew Chemie Int. Ed.* in press [doi: 10.1002/anie.201107583]

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