# Electronic Supplementary Information

## A "designer" surfactant engineered for peptide synthesis in water at room temperature

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## Table of Contents

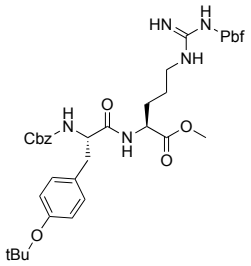
# 1. General information

A solution of 2 wt % surfactant/$H_2O$ was prepared by dissolving the surfactant in degassed HPLC grade water and was stored under argon. TPGS-750-M was made as previously described[1] and is available from Sigma-Aldrich (catalog #733857). Other surfactants were made according to the procedure described herein. All commercially available reagents were used without further purification. All experiments have been performed twice to confirm the results. Thin layer chromatography (TLC) was done using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). Flash chromatography was done in glass columns using Silica Gel 60 (EMD, 40-63 µm). $^{1}H$ and $^{13}C$ NMR were recorded at 25 °C either on a Varian Unity Inova 400 MHz, a Varian Unity Inova 500 MHz or on a Varian Unity Inova 600 MHz spectrometers in $CDCl_3$ or MeOD with residual $CHCl_3$ ($^{1}H$ = 7.27 ppm, $^{13}C$ = 77.16 ppm) or MeOH ($^{1}H$ = 4.78 ppm, $^{13}C$ = 49.0 ppm) as internal standards. Chemical shifts are reported in parts per million (ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, bd = broad doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constant (if applicable) and integration. Chiral HPLC data were collected using a Shimadzu LC-20AT Prominence liquid chromatograph coupled with Shimadzu SPD-M20A Prominence diode array detector. The HPLC method was run using HPLC grade isopropanol and hexanes through a Lux 5u Cellulose-2 (250 x 4.6 mm) column. HRMS data were recorded on a Waters Micromass LCT TOF ES+ Premier mass spectrometer using ESI ionization. Size distribution of particles was determined with a Malvern NanoSight NS300 equipped with a 488 nm laser and a syringe pump accessory to allow constant flow during analysis. The concentration used for these analyses was 1 mM to avoid aggregation and false results. For cryo-TEM images, samples were prepared by plunge-freezing in liquid ethane (FEI Vitrobot Mk IV). They were then kept under $LN_2$ before being transferred into a cryo transfer TEM holder (Gatan Single Tilt Cryo-Transfer Holder 626) and loaded into the microscope (FEI Tecnai G2 Sphera). The samples were imaged under low-dose conditions in order to minimize beam damage; images were acquired with a CCD camera (Gatan Ultrscan 1000 2k x 2k).

[1] B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, *J. Org. Chem*. **2011**, *76*, 4379.

## 2. Peptide scope

- Cbz-Tyr(tBu)-Arg(Pbf)-OMe (1)




To a 1 dr vial were added Cbz-Tyr(tBu)-OH* (92.9 mg, 0.25 mmol, 1.0 equiv) and HCl·Arg(Pbf)-OMe (119.3 mg, 0.25 mmol, 1.0 equiv). A 2 wt % surfactant/$H_2O$ solution (0.5 mL, [0.5 M]) and 10 % THF** (50 µL) were added. 2,6-lutidine (0.09 mL, 0.76 mmol, 3.05 equiv) was added. The solution was heated at 30 °C. After complete dissolution, COMU (112.4 mg, 0.26 mmol, 1.05 equiv) was added and the reaction was stirred at 30 °C for 24 h. After completion, the reaction mixture was extracted in flask with a 1:1 EtOAc/MTBE solution (3 x 2 mL). The organic layer was washed with a HCl 1 M solution (2 x 5 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 5 mL or until the aqueous layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica, and then concentrated under vacuum to yield a white powder.

* Cbz-Tyr(tBu)-OH is sold as a DCHA (dicyclohexylammonium) salt and was previously converted to the corresponding free acid following this procedure:

the DCHA or CHA salt was dissolved in dichloromethane (DCM). The organic layer was washed 3 x with an ice-cold aqueous $KHSO_4$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrate under vacuum to obtain the free acid.

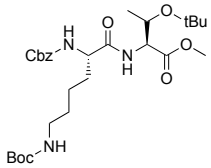
** THF is needed for all surfactants to help complete dissolution.

| medium | mass (mg) | yield (%) |
|---|---|---|
| water | 109.2 | 55 |
| TD-1000-M | 119.1 | 60 |
| PSD-2000-M | 117.2 | 59 |

| | | |
|---|---|---|
| PSD-1000-M = MC-1 | 162.7 | 82 |
| PSD-750-M | 134.1 | 68 |
| PSD-550-M | 127.2 | 64 |
| DSP-2000-M | 140.4 | 70 |
| DSP-1000-M | 133.8 | 67 |
| DSP-750-M | 99.5 | 50 |
| DSP-550-M | 129.0 | 65 |
| TPGS-750-M | 132.9 | 67 |

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 5H), 7.07 (d, *J* = 7.0 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.79 (bs, 1H), 6.09 (bs, 2H), 5.46 (bs, 1H), 5.03 (s, 2H), 4.59 – 4.35 (m, 2H), 3.71 (s, 3H), 3.14 (s, 2H), 3.08 – 2.97 (m, 2H), 2.95 (s, 2H), 2.58 (s, 3H), 2.52 (s, 3H), 2.09 (s, 2H), 2.09 – 2.03 (m, 1H), 1.90 – 1.74 (m, 1H), 1.74 – 1.60 (m, 1H), 1.46 (s, 6H), 1.40 (bs, 2H), 1.32 (d, *J* = 1.6 Hz, 9H); **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 172.2, 158.9, 156.7, 156.4, 154.2, 138.5, 136.2, 133.0, 132.4, 130.0, 128.6, 128.2, 127.8, 127.8, 124.8, 124.2, 117.7, 86.5, 67.0, 60.5, 56.3, 52.5, 43.4, 38.1, 29.2, 28.9, 28.8, 28.7, 25.1, 19.4, 18.1, 14.3, 12.6; **$R_f$** = 0.64 (100% AcOEt) UV + CAM blue spot; **HRMS (*m/z*): [M+Na]$^+$** calcd. for $C_{41}H_{55}N_5O_9SNa$, 816.3618; found, 816.3602.

- **Cbz-Lys(Boc)-Thr(tBu)-OMe (2)**



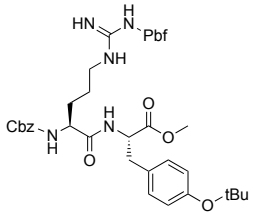

To a 2 dr vial were added Cbz-Lys(Boc)-OH (344.8 mg, 0.91 mmol, 1.0 equiv) and HCl·Thr(tBu)-OMe (204.6 mg, 0.91 mmol, 1.0 equiv). A 2 wt % surfactant/$H_2O$ solution (1.8 mL, [0.5 M]) was added, followed by 2,6-lutidine (0.32 mL, 2.8 mmol, 3.05 equiv). After complete dissolution, COMU (407.6 mg, 0.95 mmol, 1.05 equiv) was added and the reaction was stirred at rt (20-25 °C) for 1 h. After completion, the reaction mixture was extracted in flask with a 75:25 EtOAc/hexanes solution (3 x 3 mL). The organic layer was washed with a HCl 1 M solution (2 x 5 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 5 mL or until the aqueous

layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica, and concentrated under vacuum to yield a white powder.

| medium | mass (mg) | yield (%) |
|---|---|---|
| water | 301.2 | 60 |
| TD-1000-M | 401.6 | 80 |
| PSD-2000-M | 431.8 | 86 |
| PSD-1000-M = MC-1 | 466.9 | 93 |
| PSD-750-M | 451.8 | 90 |
| PSD-550-M | 456.8 | 91 |
| DSP-2000-M | 361.5 | 72 |
| DSP-1000-M | 469.8 | 94 |
| DSP-750-M | 451.7 | 90 |
| DSP-550-M | 391.6 | 78 |
| TPGS-750-M | 465.2 | 93 |

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 6.49 (d, *J* = 9.1, 1H), 5.55 (d, *J* = 7.8, 1H), 5.11 (s, 2H), 4.78 (s, 1H), 4.48 (dd, *J* = 9.2, 1.7, 1H), 4.34 – 4.18 (m, 2H), 3.71 (d, *J* = 2.2, 3H), 3.12 (qd, *J* = 15.0, 14.5, 7.4, 2H), 1.96 – 1.83 (m, 1H), 1.81 (d, *J* = 3.1, 1H), 1.71 (m, 1H), 1.50 (m, 2H), 1.43 (s, 12H), 1.17 (d, *J* = 6.4, 3H), 1.11 (d, *J* = 2.1, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 172.1, 171.2, 156.2, 156.1, 136.4, 128.6, 128.3, 128.2, 79.1, 74.4, 67.3, 67.1, 57.9, 54.8, 52.5, 40.1, 32.9, 29.7, 28.6, 28.4, 22.2, 21.1; **$R_f$** = 0.68 (75:25 EtOAc/hexanes) CAM stain.

- **Cbz-Arg(Pbf)-Tyr(tBu)-OMe (3)**




To a 2 dr vial were added Cbz-Arg(Pfb)-OH* (561.7 mg, 1.0 mmol, 1.0 equiv) and HCl·Tyr(*t*-Bu)-OMe (287.8 mg, 1.0 mmol, 1.0 equiv). A 2 wt % surfactant/$H_2O$ solution (2.0 mL, [0.5 M]) and 10 % THF** (200 µL) were added followed by 2,6-lutidine (0.4 mL, 3.05 mmol, 3.05 equiv). The

solution was heated at 40 °C. After complete dissolution, COMU (449.7 mg, 1.05 mmol, 1.05 equiv) was added and the reaction was stirred at 40 °C for 24 h. After completion, the reaction mixture was extracted in flask with a 75:25 EtOAc/hexanes solution (3 x 3 mL). The organic layer was washed with a HCl 1 M solution (2 x 5 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 5 mL or until the aqueous layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica, and concentrated under vacuum to yield a yellow powder.

* Cbz-Arg(Pfb)-OH is sold as a DCHA (dicyclohexylammonium) salt and was previously converted to the corresponding free acid following this procedure:

the DCHA or CHA salt was dissolved in dichloromethane (DCM). The organic layer was washed 3 x with an ice-cold aqueous $KHSO_4$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to obtain the free acid.

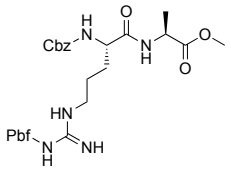
** THF is needed for all surfactants except for PSD-1000-M to help complete dissolution.

| medium | mass (mg) | yield (%) |
|---|---|---|
| water | 485.2 | 61 |
| TD-1000-M | 636.3 | 80 |
| PSD-2000-M | 466.2 | 59 |
| PSD-1000-M = MC-1 | 731.4 | 92 |
| PSD-750-M | 653.3 | 82 |
| PSD-550-M | 552.1 | 69 |
| DSP-2000-M | 662.5 | 83 |
| DSP-1000-M | 719.3 | 90 |
| DSP-750-M | 697.9 | 88 |
| DSP-550-M | 637.4 | 80 |
| TPGS-750-M | 667.1 | 84 |

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.11 (bs, 2H), 5.64 (bd, *J* = 7.5 Hz, 1H), 5.15 – 5.01 (m, 2H), 4.75 (td, *J* = 7.9, 5.9 Hz, 1H), 4.25 (d, *J* = 6.6 Hz, 1H), 3.67 (s, 3H), 3.27 – 2.97 (m, 4H), 2.95 (s, 2H), 2.59 (s, 3H), 2.52 (s, 3H), 2.10 (s, 3H), 1.81 (bs, 1H), 1.62 (bs, 4H), 1.46 (s, 6H), 1.31 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 172.2, 158.8, 156.4, 156.4, 154.1, 138.3, 136.2, 132.8, 132.2, 131.2, 129.7, 128.5, 128.0, 127.9, 124.6,

124.1, 117.5, 86.4, 78.4, 66.9, 66.6, 54.3, 53.9, 52.2, 47.3, 43.2, 38.4, 36.8, 29.7, 28.8, 28.8, 28.6, 25.3, 19.3, 18.0, 12.5; $R_f$ = 0.69 (100% EtOAc) UV and CAM stain.

- Cbz-Arg(Pbf)-Ala-OMe (4)




To a 2 dr vial were added Cbz-Arg(Pbf)-OH* (954.8 mg, 1.7 mmol, 1.0 equiv) and HCl·Ala-OMe (237.3 mg, 1.7 mmol, 1.0 equiv). A 2 wt % surfactant/$H_2O$ solution (3.4 mL, [0.5 M]) and 10 % THF** (340 µL) were added. 2,6-Lutidine (0.6 mL, 5.18 mmol, 3.05 equiv) was added. The solution was heated at 40 °C. After complete dissolution, COMU (764.5 mg, 1.8 mmol, 1.05 equiv) was added and the reaction was stirred at 40 °C for 24 h. After completion, the reaction mixture was extracted in flask with a 75:25 EtOAc/hexanes solution (3 x 3 mL). The organic layer was washed with a HCl 1 M solution (2 x 5 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 5 mL or until the aqueous layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica and concentrated under vacuum to yield a pale yellow oil.

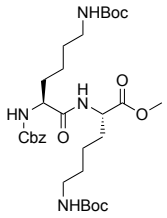
* Cbz-Arg(Pbf)-OH is sold as a DCHA (dicyclohexylammonium) salt and was previously converted to the corresponding free acid following this procedure:
the DCHA or CHA salt was dissolved in dichloromethane (DCM). The organic layer was washed 3 x with an ice-cold aqueous $KHSO_4$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrate under vacuum to obtain the free acid.
** THF is needed for all surfactants, to help complete dissolution. A goo is produced using all but PSD-1000-M.

| medium | mass (mg) | yield (%) |
|---|---|---|
| water | 566.1 | 51 |

| | | |
|---|---|---|
| TD-1000-M | 656.7 | 60 |
| PSD-2000-M | 592.1 | 54 |
| PSD-1000-M = MC-1 | 868.6 | 79 |
| PSD-750-M | 496.7 | 45 |
| PSD-550-M | 567.8 | 52 |
| DSP-2000-M | 286.0 | 26 |
| DSP-1000-M | 349.0 | 32 |
| DSP-750-M | 420.0 | 38 |
| DSP-550-M | 476.0 | 43 |
| TPGS-750-M | 528.0 | 48 |

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.31 (m, 5H), 6.28 (s, 2H), 6.12 – 5.82 (m, 2H), 5.07 (s, 2H), 4.54 – 4.35 (m, 2H), 3.69 (s, 3H), 3.33 (s, 1H), 3.26 – 3.11 (m, 1H), 2.94 (s, 2H), 2.58 (bs, 3H), 2.51 (s, 3H), 2.09 (s, 3H), 1.89 (bs, 2H), 1.63 (ddt, *J* = 36.9, 13.8, 6.9 Hz, 3H), 1.46 (s, 6H), 1.38 (d, *J* = 7.3 Hz, 3H); **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 173.8, 172.2, 158.9, 156.6, 138.5, 136.4, 132.8, 132.4, 128.6, 128.2, 128.1, 124.8, 117.7, 86.5, 67.1, 66.8, 53.9, 52.6, 48.5, 47.5, 43.4, 30.3, 28.7, 25.3, 19.4, 18.1, 17.3, 12.6; **$R_f$** = 0.52 (100% EtOAc) UV and CAM stain; **HRMS (*m/z*): [M+Na]$^+$** calcd. for $C_{31}H_{43}N_5O_8SNa$, 668.2730; found, 668.2738.

- **Cbz-Lys(Boc)-Lys(Boc)-OMe (5)**



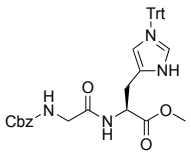

To a 2 dr vial were added Cbz-Lys(Boc)-OH (346.2 mg, 0.91 mmol, 1.0 equiv) and HCl·Lys(Boc)-OMe (270.1 mg, 0.91 mmol, 1.0 equiv). A 2 wt % surfactant/$H_2O$ solution (1.8 mL, [0.5 M]) was added followed by 2,6-lutidine (0.32 mL, 2.8 mmol, 3.05 equiv). After complete dissolution, COMU (409.2 mg, 0.95 mmol, 1.05 equiv) was added and the reaction was stirred at rt (20-25 °C) for 1 h. After completion, the reaction mixture was extracted in flask with a 75:25 EtOAc/hexanes solution (3 x 3 mL). The organic layer was washed with a HCl 1 M solution (2 x

5 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 5 mL or until the aqueous layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica, and concentrated under vacuum to yield a white powder.

| medium | mass (mg) | yield (%) |
|---|---|---|
| water | 385.4 | 68 |
| TD-1000-M | 453.4 | 80 |
| PSD-2000-M | 476.0 | 84 |
| PSD-1000-M = MC-1 | 521.4 | 92 |
| PSD-750-M | 515.7 | 91 |
| PSD-550-M | 385.4 | 68 |
| DSP-2000-M | 396.7 | 70 |
| DSP-1000-M | 487.4 | 86 |
| DSP-750-M | 467.1 | 82 |
| DSP-550-M | 481.7 | 85 |
| TPGS-750-M | 473.9 | 84 |

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 5H), 6.67 (d, *J* = 7.7 Hz, 1H), 5.58 (d, *J* = 7.7 Hz, 1H), 5.11 (s, 2H), 4.75 (s, 2H), 4.56 (s, 1H), 4.26 – 4.13 (m, 1H), 3.75 (s, 3H), 3.23 – 2.98 (m, 4H), 1.96 – 1.77 (m, 2H), 1.77 – 1.62 (m, 4H), 1.43 (d, *J* = 4.5 Hz, 24H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 172.7, 172.1, 156.4, 156.2, 136.2, 128.5, 128.5, 128.2, 128.2, 128.1, 79.1, 67.0, 54.6, 52.5, 52.1, 40.0, 39.9, 32.2, 31.6, 29.5, 29.4, 28.5, 22.5, 22.3; **$R_f$ =** 0.22 (1:1 hexanes/EtOAc) UV + CAM stain

- **Cbz-Gly-His(Trt)-OMe (6)**



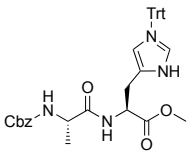

To a 1 dr vial were added Cbz-Gly-OH (105.1 mg, 0.5 mmol, 1.0 equiv) and HCl·His(Trt)-OMe (225.0 mg, 0.5 mmol, 1.0 equiv). A 2 wt % surfactant/$H_2O$ solution (1.0 mL, [0.5 M]) was added followed by 2,6-lutidine (0.18 mL, 1.53 mmol, 3.05 equiv). After complete dissolution, COMU (225.9 mg, 0.53 mmol, 1.05 equiv) was added and the reaction was stirred at rt (20-25 °C) for

1 h. After completion, the reaction mixture was extracted in flask with a 75:25 EtOAc/hexanes solution (3 x 1 mL). The organic layer was washed with a HCl 1 M solution (2 x 5 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 5 mL or until the aqueous layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica, and concentrated under vacuum to yield a yellow crystalline powder.

| medium | mass (mg) | yield (%) |
|---|---|---|
| water | 145.2 | 48 |
| TD-1000-M | 230.0 | 76 |
| PSD-2000-M | 150.4 | 50 |
| PSD-1000-M = MC-1 | 260.2 | 86 |
| PSD-750-M | 169.4 | 56 |
| PSD-550-M | 156.3 | 52 |
| DSP-2000-M | 164.2 | 54 |
| DSP-1000-M | 227.0 | 75 |
| DSP-750-M | 157.4 | 52 |
| DSP-550-M | 158.9 | 53 |
| TPGS-750-M | 154.3 | 51 |

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.29 (m, 15H), 7.11 (dt, *J* = 5.4, 3.9 Hz, 6H), 6.54 (s, 1H), 5.48 (s, 1H), 5.10 (s, 2H), 4.81 (dt, *J* = 7.7, 4.7 Hz, 1H), 3.95 (d, *J* = 5.4 Hz, 2H), 3.60 (s, 3H), 3.13 – 2.89 (m, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 171.6, 168.8, 156.4, 142.3, 138.8, 136.4, 129.8, 128.6, 128.3, 128.2, 128.2, 128.1, 119.8, 75.4, 67.1, 52.7, 52.4, 44.4, 29.6; **$R_f$** = 0.31 (EtOAc) – CAM stain.

- **Cbz-Ala-His(Trt)-OMe (7)**



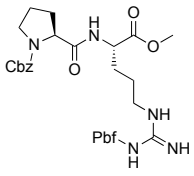

To a 1 dr vial were added Cbz-Ala-OH (111.6 mg, 0.5 mmol, 1.0 equiv) and HCl·His(Trt)-OMe (225.0 mg, 0.5 mmol, 1.0 equiv). A 2 wt % surfactant/$H_2O$ solution (1.0 mL, [0.5 M]) was added

followed by 2,6-lutidine (0.18 mL, 1.53 mmol, 3.05 equiv). After complete dissolution, COMU (225.9 mg, 0.53 mmol, 1.05 equiv) was added and the reaction was stirred at rt (20-25 °C) for 2.5 h. After completion, the reaction mixture was extracted in flask with a 75:25 EtOAc/hexanes solution (3 x 1 mL). The organic layer was washed with a HCl 1 M solution (2 x 5 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 5 mL or until the aqueous layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica, and concentrated under vacuum to yield a pale yellow powder.

| medium | mass (mg) | yield (%) |
|---|---|---|
| Water | 188.1 | 61 |
| TD-1000-M | 197.4 | 64 |
| PSD-2000-M | 212.8 | 69 |
| PSD-1000-M = MC-1 | 271.4 | 88 |
| PSD-750-M | 175.8 | 57 |
| PSD-550-M | 191.2 | 62 |
| DSP-2000-M | 222.1 | 72 |
| DSP-1000-M | 265.2 | 86 |
| DSP-750-M | 231.2 | 75 |
| DSP-550-M | 221.9 | 72 |
| TPGS-750-M | 222.0 | 72 |

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.42 – 7.28 (m, 22H), 7.10 (dt, *J* = 5.4, 3.9 Hz, 7H), 6.55 (s, 1H), 5.62 (d, *Jv* = 7.6 Hz, 1H), 5.16 – 5.00 (m, 2H), 4.78 (dt, *J* = 7.9, 4.7 Hz, 1H), 4.39 – 4.23 (m, 1H), 3.60 (s, 4H), 1.41 (d, *J* = 7.3 Hz, 5H); **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 172.2, 171.5, 142.3, 138.8, 136.4, 129.8, 128.8, 128.6, 128.6, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.3, 127.0, 119.8, 75.4, 67.2, 67.0, 66.8, 52.2, 50.6, 29.8, 29.6, 19.3; **$R_f$** = 0.41 (EtOAc) – CAM stain.

- **Cbz-Pro-Arg(Pbf)-OMe (8)**



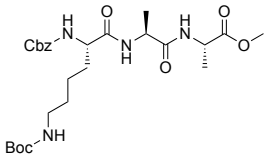

To a 2 dr vial were added Cbz-Pro-OH (249.3 mg, 1.0 mmol, 1.0 equiv) and HCl·Arg(Pbf)-OMe (477.0 mg, 1.0 mmol, 1.0 equiv). A 2 wt % surfactant/$H_2O$ solution (2.0 mL, [0.5 M]) was added followed by 2,6-lutidine (0.36 mL, 3.05 mmol, 3.05 equiv). After complete dissolution (0.5 h), COMU (449.7 mg, 1.05 mmol, 1.05 equiv) was added and the reaction was stirred at rt (20-25 °C) for 4 h. After completion, the reaction mixture was extracted in flask with a 75:25 EtOAc/hexanes solution (3 x 2 mL). The organic layer was washed with a HCl 1 M solution (2 x 5 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 5 mL or until the aqueous layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica, and concentrated under vacuum to yield a white powder.

| medium | mass (mg) | yield (%) |
|---|---|---|
| water | 443.4 | 66 |
| TD-1000-M | 403.1 | 60 |
| PSD-2000-M | 524.0 | 78 |
| PSD-1000-M = MC-1 | 564.3 | 84 |
| PSD-750-M | 544.2 | 81 |
| PSD-550-M | 476.9 | 71 |
| DSP-2000-M | 463.5 | 69 |
| DSP-1000-M | 557.6 | 83 |
| DSP-750-M | 483.7 | 72 |
| DSP-550-M | 490.4 | 73 |
| TPGS-750-M | 456.8 | 68 |

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.16 (s, 1H), 5.99 (d, *J* = 44.9 Hz, 1H), 5.09 (q, *J* = 13.0, 12.3 Hz, 2H), 4.53 (d, *J* = 37.5 Hz, 1H), 4.27 (t, *J* = 6.1 Hz, 1H), 3.75 (s, 3H), 3.69 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.61 (ddd, *J* = 10.4, 7.4, 4.9 Hz, 1H), 3.49 (q, *J* = 8.7, 8.3 Hz, 1H), 3.22 (d, *J* = 21.0 Hz, 1H), 2.95 (s, 2H), 2.59 (s, 3H), 2.53 (s, 3H), 2.18 (s, 1H), 2.09 (s, 3H), 2.03 (dd, *J* = 17.5, 9.1 Hz, 1H), 1.90 (dq, *J* = 12.0, 7.0, 5.9 Hz, 2H), 1.70 (q, *J* = 7.3 Hz, 1H),

1.65 (s, 3H), 1.57 (d, *J* = 12.5 Hz, 2H), 1.46 (s, 6H); **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 172.7, 172.5, 158.7, 156.4, 155.7, 138.4, 136.4, 133.3, 132.3, 128.6, 128.2, 127.7, 124.7, 117.5, 86.4, 67.4, 66.8, 60.5, 52.6, 47.4, 47.2, 43.4, 40.5, 38.5, 29.9, 29.3, 28.7, 25.4, 24.6, 19.4, 18.0, 12.6; **Rf** = 0.4 (100% EtOAc) UV + CAM stain; **HRMS (*m/z*): [M+Na]$^+$** calcd. for $C_{33}H_{45}N_5O_8SNa$, 694.2886; found, 694.2896.

- **Cbz-Lys(Boc)-Ala-Ala-OMe (9)**



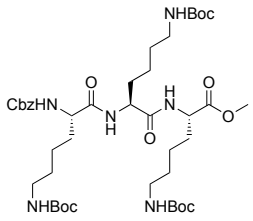

To a 1 dr vial were added Cbz-Ala-Ala-OH (200.0 mg, 0.43 mmol, 1.1 equiv) in 2 wt % surfactant/$H_2O$ solution (0.86 mL, [0.5 M]). Pd/$C_{10\%}$ (20.0 mg, 10 wt %) was added. The vial was capped with a septum and purged with argon for 1 min. A solution of HCl (12 M, 36.0 µL, 0.43 mmol, 1.1 equiv) was added. The vial was then purged with $H_2$ gas (balloon) and the reaction was stirred under $H_2$ atmosphere for 2 h. After complete deprotection, the vial was purged with argon for 30 min. Cbz-Lys(Boc)-OH (87.6 mg, 0.39 mmol, 1.0 equiv) and another volume of 2 wt % surfactant/$H_2O$ solution (0.86 mL, [0.25 M]) were added. After complete dissolution, COMU (176.4 mg, 0.41 mmol, 1.05 equiv) was added, followed by 2,6-lutidine (0.14 mL, 1.2 mmol, 3.05 equiv). The reaction was stirred at rt (20-25 °C) for 3 h. After completion, the reaction mixture was filtered through a pad of Celite® (rinsed with EtOAc). The organic layer washed with a HCl 1 M solution (2 x 10 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 10 mL or until the aqueous layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica and concentrated under vacuum to yield an off-white powder.

| medium | mass (mg) | yield (%) |
|---|---|---|
| water | 96.9 | 46 |
| TD-1000-M | 100.8 | 48 |
| PSD-2000-M | 74.5 | 35 |
| PSD-1000-M = MC-1 | 183.0 | 87 |

| | | |
|---|---|---|
| PSD-750-M | 162.0 | 77 |
| PSD-550-M | 178.4 | 85 |
| DSP-2000-M | 44.2 | 21 |
| DSP-1000-M | 149.4 | 71 |
| DSP-750-M | 164.1 | 78 |
| DSP-550-M | 104.0 | 49 |
| TPGS-750-M | 130.4 | 62 |

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 6.99 (dd, *J* = 37.4, 7.6 Hz, 2H), 5.86 (d, *J* = 7.4 Hz, 1H), 5.09 (s, 2H), 4.81 (s, 1H), 4.53 (p, *J* = 7.4 Hz, 2H), 4.20 (td, *J* = 10.3, 7.3, 3.4 Hz, 1H), 3.72 (s, 3H), 3.08 (p, *J* = 11.8, 9.0 Hz, 2H), 1.82 (h, *J* = 6.7 Hz, 1H), 1.67 (dt, *J* = 15.3, 8.2 Hz, 1H), 1.48 (p, *J* = 6.6 Hz, 3H), 1.42 (s, 9H), 1.37 (t, *J* = 6.8 Hz, 6H) ; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 173.3, 172.0, 171.9, 156.4, 136.3, 128.6, 128.3, 128.2, 79.3, 67.1, 55.0, 52.6, 48.9, 48.2, 39.8, 33.7, 32.2, 29.6, 28.5, 22.4, 18.4, 18.2 ; **$R_f$** = 0.55 (EtOAc) CAM stain ; **HRMS (*m/z*): [M+Na]$^+$** calcd. for $C_{26}H_{40}N_4O_8Na$, 559.2744; found, 559.2745.

- **Cbz-Lys(Boc)-Lys(Boc)-Lys(Boc)-OMe (10)**



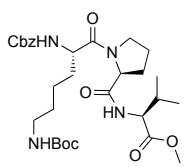

To a 1 dr vial were added Cbz-Lys(Boc)-Lys(Boc)-OMe (150 mg, 0.24 mmol, 1.1 equiv) in 2 wt % surfactant/$H_2O$ solution (0.48 mL, [0.5 M]). $Pd/C_{10\%}$ (15.0 mg, 10 wt %) was added. The vial was capped with a septum and purged with argon for 1 min. A solution of HCl (12 M, 20.0 µL, 0.24 mmol, 1.1 equiv) was added. The vial was then purged with $H_2$ gas (balloon) and the reaction was stirred under $H_2$ atmosphere for 2 h. After complete deprotection, the vial was purged with argon for 30 min. Cbz-Lys(Boc)-OH (83.3 mg, 0.22 mmol, 1.0 equiv) and another volume of 2 wt % surfactant/$H_2O$ solution (0.48 mL, [0.25 M]) were added. After complete dissolution, COMU (98.5 mg, 0.23 mmol, 1.05 equiv) was added, followed by 2,6-lutidine (80 µL, 0.67 mmol,

3.05 equiv). The reaction was stirred at rt (20-25 °C) for 7 h. After completion, the reaction mixture was filtered through a pad of Celite® (rinsed with EtOAc). The organic layer washed with a HCl 1 M solution (2 x 10 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 10 mL or until the aqueous layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica, and concentrated under vacuum to yield a white powder.

| medium | mass (mg) | yield (%) |
|---|---|---|
| water | 117.8 | 48 |
| TD-1000-M | 104.2 | 56 |
| PSD-2000-M | 86.7 | 47 |
| PSD-1000-M = MC-1 | 147.3 | 79 |
| PSD-750-M | 78.1 | 42 |
| PSD-550-M | 65.1 | 35 |
| DSP-2000-M | 93.2 | 50 |
| DSP-1000-M | 113.7 | 61 |
| DSP-750-M | 108.1 | 58 |
| DSP-550-M | 104.2 | 56 |
| TPGS-750-M | 95.1 | 51 |

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 6.88 (bs, 2H), 5.77 (bs, 1H), 5.10 (s, 2H), 4.90 (bd, *J* = 48.2 Hz, 2H), 4.53 (bs, 1H), 4.40 (bd, *J* = 7.2 Hz, 1H), 4.15 (bs, 1H), 3.73 (s, 3H), 3.07 (m, 6H), 1.84 (m, 4H), 1.76 – 1.58 (m, 3H), 1.42 (m, 40H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 172.7, 172.5, 171.7, 156.6, 156.4, 156.3, 136.2, 128.6, 128.2, 79.2, 67.1, 55.0, 53.3, 52.5, 52.2, 40.1, 39.8, 32.0, 31.6, 31.5, 29.5, 28.5, 22.6, 22.4; **$R_f$** = 0.77 (100% EtOAc – UV and CAM Stain); **HRMS (*m/z*):** **$[M+Na]^+$** calcd. for $C_{42}H_{70}N_6O_{12}Na$, 873.4949; found, 873.4932.

- Cbz-Lys(Boc)-Pro-Val-OMe (11)



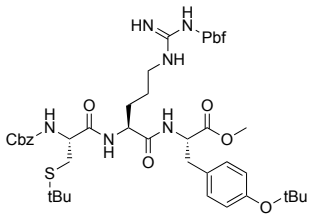
To a 1 dr vial were added Cbz-Pro-Val-OMe (90.0 mg, 0.34 mmol, 1.1 equiv) in 2 wt % surfactant/$H_2O$ solution (0.68 mL, [0.5 M]). $Pd/C_{10\%}$ (0.9 mg, 10 wt %) was added. The vial was capped with a septum and purged with argon for 1 min. A solution of HCl 12 M (28.0 µL, 0.34 mmol, 1.1 equiv) was added. The vial was then purged with $H_2$ gas (balloon) and the reaction was stirred under $H_2$ atmosphere for 2 h. After complete deprotection, the vial was purged with argon for 30 min. Cbz-Lys(Boc)-OH (117.6 mg, 0.31 mmol, 1.0 equiv) and another volume of 2 wt % surfactant/$H_2O$ solution (0.68 mL, [0.25 M]) were added. After complete dissolution, COMU (139.0 mg, 0.32 mmol, 1.05 equiv) was added, followed by 2,6-lutidine (110 µL, 0.94 mmol, 3.05 equiv). The reaction was stirred at rt (20-25 °C) for 24 h. After completion, the reaction mixture was filtered through a pad of Celite® (rinsed with EtOAc). The organic layer washed with a HCl 1 M solution (2 x 10 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 10 mL or until the aqueous layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica, and concentrated under vacuum to yield a colorless oil.

**$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 7.08 (dq, *J* = 15.1, 7.5, 6.6 Hz, 1H), 5.71 (d, *J* = 10.8 Hz, 1H), 5.32 – 5.28 (m, 1H), 5.13 – 5.04 (m, 2H), 4.88 (s, 1H), 4.58 (dd, *J* = 8.1, 3.2 Hz, 1H), 4.50 (ddd, *J* = 19.8, 8.8, 5.3 Hz, 2H), 3.75 – 3.72 (m, 3H), 3.72 – 3.67 (m, 1H), 3.58 (td, *J* = 9.2, 8.8, 3.6 Hz, 1H), 3.16 – 2.98 (m, 2H), 2.35 – 2.24 (m, 1H), 2.23 – 2.07 (m, 2H), 2.03 – 1.87 (m, 2H), 1.78 – 1.49 (m, 4H), 1.43 (s, 9H), 0.96 – 0.83 (m, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 172.4, 172.1, 171.0, 156.2, 156.2, 136.4, 128.6, 128.2, 128.1, 79.1, 67.0, 60.5, 60.1, 57.4, 53.6, 47.6, 40.1, 32.6, 31.3, 29.6, 28.5, 27.6, 25.3, 22.3, 19.1, 17.7; **$R_f$** = 0.71 (100% EtOAc) – CAM stain; **HRMS (*m/z*): [M+Na]$^+$** calcd. for $C_{30}H_{46}N_4O_8Na$, 613.3214; found, 613.3202.

| medium | mass (mg) | yield (%) |
|---|---|---|
| water | 92.4 | 46 |
| TD-1000-M | 157.9 | 79 |
| PSD-2000-M | 169.5 | 84 |
| PSD-1000-M = MC-1 | 184.1 | 92 |
| PSD-750-M | 162.5 | 81 |
| PSD-550-M | 174.1 | 87 |
| DSP-2000-M | 144.9 | 72 |

| | | |
|---|---|---|
| DSP-1000-M | 148.4 | 74 |
| DSP-750-M | 189.0 | 94 |
| DSP-550-M | 137.9 | 67 |
| TPGS-750-M | 102.4 | 51 |

- Cbz-Cys(*t*-Bu)-Arg(Pbf)-Tyr(*t*-Bu)-OMe (12)



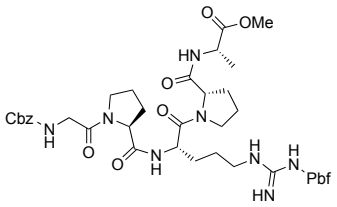

To a 1 dr vial were added Cbz-Arg(Pbf)-Tyr(*t*-Bu)-OMe (150.0 mg, 0.19 mmol, 1.0 equiv) in 2 wt % surfactant/$H_2O$ solution (0.38 mL, [0.5 M]). $Pd/C_{10\%}$ (15.0 mg, 10 wt %) was added. The vial was capped with a septum and purged with argon for 1 min. A solution of HCl (12 M, 28.0 µL, 0.34 mmol, 1.1 equiv) was added. The vial was then purged with $H_2$ gas (balloon) and the reaction was stirred under $H_2$ atmosphere for 2 h. After complete deprotection, the vial was purged with argon for 30 min. A solution of Cbz-Cys(tBu)-OH (64.6 mg, 0.21 mmol, 1.0 equiv) and 2,6-lutidine (60 µL, 0.52 mmol, 3.05 equiv) in 2 wt % surfactant/$H_2O$ solution (0.34 mL, [0.25 M]) was added. COMU (77.1 mg, 0.18 mmol, 1.05 equiv) was added and the reaction was stirred at rt (20-25 °C) for 24 h. After completion, the reaction mixture was filtered through a pad of Celite® (rinsed with EtOAc). The organic layer washed with a HCl 1 M solution (2 x 10 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 10 mL or until the aqueous layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica, and concentrated under vacuum to yield a pale yellow powder.

| medium | mass (mg) | yield (%) |
|---|---|---|
| water | 78.8 | 48 |
| TD-1000-M | 132.6 | 81 |
| PSD-2000-M | 131.8 | 80 |

| | | |
|---|---|---|
| PSD-1000-M = MC-1 | 146.7 | 89 |
| PSD-750-M | 135.9 | 83 |
| PSD-550-M | 132.1 | 80 |
| DSP-2000-M | 128.5 | 78 |
| DSP-1000-M | 137.4 | 84 |
| DSP-750-M | 145.9 | 89 |
| DSP-550-M | 164.1 | 92 |
| TPGS-750-M | 163.0 | 99 |

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 7.04 (t, *J* = 8.7 Hz, 2H), 6.87 (ddd, *J* = 7.4, 6.1, 1.2 Hz, 2H), 6.21 (s, 2H), 5.83 (dd, *J* = 48.4, 7.7 Hz, 1H), 5.07 (p, *J* = 11.9 Hz, 2H), 4.75 – 4.65 (m, 1H), 4.50 (q, *J* = 7.6 Hz, 0.5H), 4.39 (s, 0.5H), 4.28 (m, 0.5H), 3.67 – 3.57 (m, 3H), 3.17 (s, 2H), 3.05 (tq, *J* = 13.5, 8.2, 6.9 Hz, 2H), 2.94 (s, 2H), 2.91 – 2.83 (m, 1H), 2.59 (s, 3H), 2.52 (s, 3H), 2.09 (s, 3H), 1.80 (s, 2H), 1.89 – 1.57 (m, 2H), 1.46 (s, 6H), 1.37 – 1.21 (m, 18H); **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 172.5, 172.3, 170.9, 158.9, 158.9, 156.4, 154.3, 138.6, 138.5, 136.3, 136.2, 133.0, 132.5, 132.4, 129.8, 129.8, 128.7, 128.3, 128.3, 128.1, 128.1, 124.8, 124.4, 117.6, 86.5, 86.5, 78.7, 67.4, 67.2, 54.1, 52.5, 52.4, 43.4, 43.2, 37.1, 37.0, 31.0, 29.0, 29.0, 28.7, 25.1, 19.5, 18.1, 12.6; **$R_f$** = 0.70 (100% EtOAc) – CAM stain

- **Cbz-Gly-Pro-Arg(Pbf)-Pro-Ala-OMe•3$H_2O$ (13)**




To a 1 dr vial were added Cbz-Pro-Ala-OMe (131.4 mg, 0.29 mmol, 1.1 equiv) in 2 wt % PSD-1000-M/$H_2O$ solution (0.59 mL, [0.5 M]). Pd/$C_{10\%}$ (13.1 mg, 10 wt %) was added. The vial was capped with a septum and purged with argon for 1 min. A solution of HCl (12 M, 24.0 µL, 0.29 mmol, 1.1 equiv) was added. The vial was then purged with $H_2$ gas (balloon) and the reaction was stirred under $H_2$ atmosphere for 2 h. After complete deprotection, the vial was purged with argon for 30 min. A solution of Cbz-Gly-Pro-Arg(Pbf)-OH (190.2 mg, 0.27 mmol, 1.0 equiv) and 2,6-lutidine (90 µL, 0.81 mmol, 3.05 equiv) in 2 wt % PSD-1000-M/$H_2O$ solution (0.59 mL, [0.25

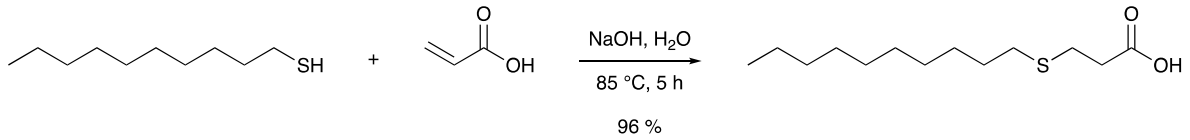
M]) was added. COMU (119.6 mg, 0.28 mmol, 1.05 equiv) was added and the reaction was stirred at rt (20-25 °C) for 24 h. After completion, the reaction mixture was filtered through a pad of Celite® (rinsed with EtOAc). The organic layer washed with a HCl 1 M solution (2 x 10 mL) and a 1:1 mixture of water and saturated $Na_2CO_3$ solution (3 x 10 mL or until the aqueous layer is colorless). The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica, and concentrated under vacuum to yield a white powder (181.1 mg, 76%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ δ 7.61 (bd, *J* = 7.7 Hz, 0.5H), 7.41 – 7.27 (m, 5H), 7.22 (bd, *J* = 7.1 Hz, 0.5H), 6.48 – 6.22 (m, 2H), 6.14 (bs, 0.5H), 5.98 (m, 1H), 5.07 (d, *J* = 2.9 Hz, 2H), 4.79 – 4.61 (m, 1H), 4.60 – 4.30 (m, 3H), 4.07 – 3.73 (m, 2H), 3.67 (d, *J* = 28.1 Hz, 3H), 3.61 – 3.31 (m, 4H), 3.29 – 3.05 (m, 2H), 2.93 (s, 2H), 2.57 (s, 3H), 2.50 (s, 3H), 2.35 (m, 2H), 2.07 (s, 3H), 2.05 – 1.48 (m, 12H), 1.35 (d, *J* = 7.2 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 173.9, 173.3, 171.7, 171.0, 168.5, 158.7, 158.7, 156.8, 156.6, 156.5, 138.4, 138.4, 136.5, 136.4, 132.3, 128.6, 128.6, 128.3, 128.2, 128.1, 124.6, 124.6, 117.5, 117.5, 86.4, 86.4, 67.1, 67.0, 60.8, 60.8, 60.5, 60.2, 52.5, 50.7, 48.4, 47.6, 46.7, 43.4, 29.0, 28.7, 25.2, 25.0, 19.4, 18.0, 17.9, 12.6; **R*f*** = 0.38 (9:1 DCM/MeOH) – CAM stain; **HRMS (*m/z*): [M+Na]$^+$** calcd. for $C_{43}H_{60}N_8O_{11}SNa$, 919.4000; found, 919.3986.

# 3. Surfactants synthesis

## 1.1. Sulfide synthesis

### 1.1.1. DSP series

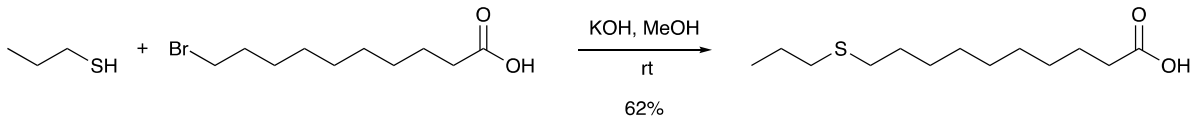



To a round-bottom flask was added NaOH (6.0 g, 0.15 mol, 2.5 equiv) in distilled water (30 mL). After dissolution (5 min), decanethiol (10.46 g, 60 mmol, 1 .0 equiv) and acrylic acid (4.1 mL, 60 mmol, 1.0 equiv) were added in succession. The reaction was stirred at 86 °C for 5 h. The mixture was transferred in a separatory funnel and washed with hexanes (2 x 10 mL). The

aqueous layer was collected and cooled to 0 °C with a dry-iced bath. The pH was lowered to 1-2 with a dropwise addition of HCl (12 M). The sulfide was extracted with EtOAc (3 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. A trituration in 3 mL of pentane followed by a filtration led to the desired product as a white powder (14.2 g, 96%).

**$^1$H NMR (500 MHz, $CDCl_3$) δ** 2.79 (t, *J* = 7.3 Hz, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.58 – 2.50 (m, 2H), 1.59 (p, *J* = 7.4 Hz, 2H), 1.38 (t, *J* = 7.5 Hz, 2H), 1.29 (dd, *J* = 13.4, 5.2 Hz, 12H), 0.89 (t, *J* = 6.8 Hz, 3H); **$^{13}$C NMR (151 MHz, $CDCl_3$) δ** 176.8, 34.6, 32.4, 32.0, 29.7, 29.7, 29.7, 29.5, 29.4, 29.0, 26.8, 22.8, 14.3; **$R_f$** = 0.45 (75:25 hexanes/EtOAc) – CAM stain; **mp** = 33-35 °C.

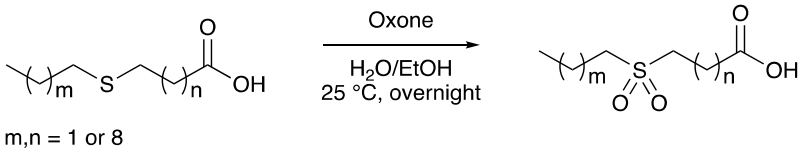
### 1.1.2. PSD series – sulfide **14**




To a 1000 mL round-bottom flask was added KOH (14.521 g, 258.8 mmol, 6.5 equiv) in MeOH (400 mL). After complete dissolution (10 min), propan-1-thiol (21.7 mL, 238.9 mmol, 6.0 equiv) was added. 10-Bromodecanoic acid (10.0 g, 39.8 mmol, 1.0 equiv) was added and the reaction was stirred at rt for 2 h. After completion, the reaction was quenched with HCl (1 M) to lower the pH to 1-2. The sulfide was extracted with DCM (2 x 300 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under high vacuum overnight. The crude was cooled in an iced-bath and precipitated in pentane (100 mL or more if necessary). The precipitate was filtered and the residue was collected as a white solid. The filtrate was concentrated and precipitated in pentane (50 mL) one more time. The solid fractions were combined (6.08 g, 62%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 11.32 (bs, 1H), 2.46 (m, 4H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.57 (m, 6H), 1.40 – 1.18 (m, 10H), 0.95 (t, *J* = 7.2 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 180.6, 34.2, 34.2, 32.1, 29.7, 29.3, 29.2, 29.0, 28.9, 24.7, 23.0, 13.6; **$R_f$** = 0.8 (EtOAc) – CAM stain ; **mp** = 37-39 °C.

## 1.2. Sulfone synthesis




To a 25 mL round bottom flask, the sulfide (0.30 mg, 1.2 mmol, 1.0 equiv) was dissolved in EtOH (7 mL). Oxone (1.11 g, 7.3 mmol, 6.0 equiv), dissolved in deionized water (14 mL), was added dropwise (the reaction is exothermic; temperature control with an ice-bath is required for scale-up). The reaction was stirred at 25 °C for 24 h. After completion, the reaction was diluted with HCl 1 M (10 mL). The sulfone was extracted with dichloromethane (20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*, leading to a white fluffy powder (PSD series) (98%) or a white powder (DSP series) (94%).

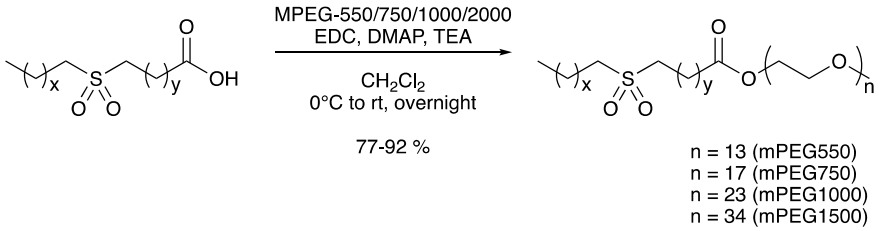
DSP series

**$^1$H NMR** (400 MHz, MeOD) δ 3.36 (t, *J* = 7.1 Hz, 2H), 3.30 (p, *J* = 1.6 Hz, 2H), 3.15 – 3.04 (m, 2H), 2.79 (t, *J* = 7.4 Hz, 2H), 1.79 (ddd, *J* = 11.8, 9.8, 6.4 Hz, 2H), 1.46 (p, *J* = 7.0 Hz, 2H), 1.41 – 1.21 (m, 12H), 0.90 (t, *J* = 6.6 Hz, 3H); **$^{13}$C NMR** (101 MHz, MeOD) δ 173.8, 53.7, 49.1, 33.1, 30.6, 30.5, 30.4, 30.2, 29.5, 27.7, 23.7, 22.8, 14.4; **Rf** = 0.43 (EtOAc) – CAM stain; **mp** = 80-83 °C.

PSD series – sulfone 15

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 2.95 (td, J = 7.8, 2.0 Hz, 4H), 2.37 (t, J = 7.4 Hz, 2H), 1.98 – 1.76 (m, 4H), 1.65 (p, J = 7.3 Hz, 2H), 1.45 (p, J = 6.9 Hz, 2H), 1.33 (bs, 8H), 1.11 (t, J = 7.4 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 179.7, 54.5, 52.8, 34.1, 29.2, 29.1, 29.1, 29.0, 28.6, 24.7, 22.0, 15.9, 13.3; **Rf** = 0.63 (EtOAc) – CAM stain; **mp** = 86-87 °C; **HRMS (*m/z*): [M+Na]$^+$** calcd. for C13H26O4sNa, 301.1450; found, 301.1447.

## 1.3. Esterification




To a round-bottom flask was added MPEG-550/750/1000/2000 (1 equiv), the sulfone (1.05 equiv), EDC (1.05 equiv) and DMAP (0.3 equiv) in dry DCM (0.1 mol/ L). TEA (3 equiv) was added and the reaction was stirred at rt overnight. The reaction was dissolved in DCM and washed with a 1 M HCl solution (2x), a 1 M $Na_2CO_3$ solution(2x) and water (the basic washings have to be done until the organic layers are clear). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum to yield:

- DSP-550-M

yellow oil

$^1$H NMR (500 MHz, $CDCl_3$) δ 4.31 – 4.26 (m, 2H), 3.76 – 3.69 (m, 2H), 3.69 – 3.60 (m, 47H), 3.58 – 3.53 (m, 3H), 3.39 (s, 3H), 3.30 (t, *J* = 7.5 Hz, 2H), 3.03 – 2.96 (m, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 1.90 – 1.80 (m, 1H), 1.44 (p, *J* = 7.4 Hz, 2H), 1.38 – 1.21 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.5, 72.6, 72.0, 70.7, 70.6, 70.6, 70.4, 68.9, 64.6, 61.8, 59.1, 53.5, 47.9, 31.9, 29.5, 29.3, 29.3, 29.1, 28.5, 26.9, 22.7, 22.0, 14.1; $R_f$ = 0.44 (9:1 DCM/MeOH) – CAM stain.

- DSP-750-M

white wax

$^1$H NMR (500 MHz, $CDCl_3$) δ 4.33 – 4.26 (m, 2H), 3.76 – 3.70 (m, 3H), 3.65 (d, *J* = 2.2 Hz, 62H), 3.58 – 3.53 (m, 2H), 3.38 (s, 3H), 3.30 (t, *J* = 7.5 Hz, 2H), 3.04 – 2.95 (m, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 1.90 – 1.80 (m, 4H), 1.44 (p, *J* = 7.3 Hz, 2H), 1.38 – 1.22 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.1, 72.3, 71.6, 70.2, 70.1, 70.0, 70.0, 68.5, 64.1, 61.2, 58.7, 58.6, 53.0, 47.6, 31.5, 29.1, 28.9, 28.9, 28.7, 28.1, 26.6, 22.3, 21.5, 13.8, 13.8; $R_f$ = 0.41 (9:1 DCM/MeOH) – CAM stain.

- DSP-1000-M

white wax

**$^1$H NMR** (600 MHz, $CDCl_3$) δ 4.23 – 4.18 (m, 2H), 3.87 – 3.38 (m, 76H), 3.30 (s, 3H), 3.22 (t, *J* = 7.5 Hz, 2H), 2.96 – 2.87 (m, 2H), 2.83 (t, *J* = 7.5 Hz, 2H), 1.76 (ddd, *J* = 11.7, 9.9, 6.6 Hz, 2H), 1.36 (p, *J* = 7.3 Hz, 2H), 1.32 – 1.11 (m, 11H), 0.80 (t, *J* = 7.0 Hz, 3H); **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 170.4, 71.8, 70.5, 70.5, 70.5, 70.5, 70.4, 68.7, 64.4, 58.9, 53.3, 47.8, 31.7, 29.3, 29.1, 29.1, 28.9, 28.3, 26.8, 22.5, 21.8, 14.0; **$R_f$** = 0.41 (9:1 DCM/MeOH) – CAM stain.

- **DSP-2000-M**

white solid

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.23 – 4.18 (m, 2H), 3.57 (d, *J* = 1.1 Hz, 225H), 3.31 (d, *J* = 1.1 Hz, 4H), 3.23 (t, *J* = 7.5 Hz, 2H), 2.95 – 2.88 (m, 2H), 2.84 (td, *J* = 7.5, 1.0 Hz, 2H), 1.96 – 1.55 (m, 10H), 1.36 (q, *J* = 7.4 Hz, 2H), 1.21 (d, *J* = 10.1 Hz, 12H), 0.85 – 0.75 (m, 3H) ; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 170.4, 72.5, 71.9, 71.9, 70.6, 70.5, 70.5, 70.5, 70.3, 68.8, 64.5, 61.6, 59.0, 59.0, 53.4, 47.9, 31.8, 31.8, 29.4, 29.4, 29.2, 29.2, 29.2, 29.0, 28.4, 26.8, 22.6, 21.9, 14.1; **$R_f$** = 0.38 (9:1 DCM/MeOH) – CAM stain.

- **PSD-550-M**

yellow oil

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.34 – 4.16 (m, 2H), 3.81 – 3.44 (m, 65H), 3.36 (s, 3H), 2.91 (ddd, *J* = 10.6, 5.3, 2.5 Hz, 4H), 2.30 (dd, *J* = 8.6, 6.5 Hz, 2H), 1.92 – 1.74 (m, 4H), 1.67 – 1.53 (m, 2H), 1.41 (t, *J* = 7.5 Hz, 2H), 1.36 – 1.19 (m, 8H), 1.12 – 1.02 (m, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 173.7, 77.5, 72.8, 71.9, 70.5, 70.5, 70.4, 70.4, 70.1, 69.1, 63.3, 61.5, 59.0, 54.4, 52.7, 34.1, 29.0, 29.0, 28.9, 28.4, 24.8, 21.9, 15.8, 13.2; **$R_f$** = 0.47 (9:1 DCM/MeOH) – CAM stain.

- **PSD-750-M**

white wax

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.21 (td, *J* = 5.1, 2.4 Hz, 2H), 3.64 (t, *J* = 2.3 Hz, 84H), 3.37 (d, *J* = 2.3 Hz, 3H), 2.92 (ddd, *J* = 10.4, 5.0, 2.0 Hz, 4H), 2.31 (td, *J* = 7.6, 2.3 Hz, 2H), 1.95 – 1.74 (m, 4H), 1.67 – 1.56 (m, 2H), 1.42 (dq, *J* = 13.6, 7.3 Hz, 2H), 1.29 (t, *J* = 4.4 Hz, 8H), 1.08 (td, *J* = 7.4, 2.2 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 173.7, 72.7, 71.9, 71.9, 70.6, 70.6, 70.5, 70.5, 70.5, 70.4, 70.2, 70.2, 69.2, 63.4, 61.6, 59.0, 59.0, 54.4, 52.7, 34.1, 29.1, 29.0, 29.0, 28.5, 24.8, 21.9, 15.8, 13.2; **$R_f$** = 0.44 (9:1 DCM/MeOH) – CAM stain.

- PSD-1000-M – MC-1

white wax

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.29 (td, *J* = 6.3, 5.4, 3.2 Hz, 2H), 4.23 – 4.11 (m, 2H), 3.62 (d, *J* = 2.1 Hz, 200H), 3.35 (s, 6H), 2.90 (ddd, *J* = 8.0, 6.5, 2.0 Hz, 4H), 2.30 (td, *J* = 7.4, 3.4 Hz, 2H), 2.22 (s, 1H), 1.94 – 1.72 (m, 5H), 1.58 (t, *J* = 7.7 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 2H), 1.35 – 1.20 (m, 9H), 1.07 (t, *J* = 7.4 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 161.0, 72.6, 72.0, 70.7, 70.6, 70.6, 70.5, 70.3, 68.9, 63.1, 61.7, 59.1, 54.4, 53.5, 52.8, 34.2, 29.1, 29.1, 29.0, 28.5, 24.9, 22.0, 15.8, 13.3; **$R_f$** = 0.44 (9:1 DCM/MeOH) – CAM stain.

- PSD-2000-M

white solid

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.15 (tt, *J* = 5.1, 1.6 Hz, 2H), 3.63 – 3.34 (m, 239H), 3.31 (d, *J* = 1.5 Hz, 4H), 2.90 – 2.81 (m, 4H), 2.25 (ddt, *J* = 9.3, 7.4, 1.5 Hz, 2H), 2.17 (q, *J* = 2.3, 1.6 Hz, 1H), 1.86 – 1.69 (m, 4H), 1.54 (p, *J* = 7.1 Hz, 2H), 1.36 (p, *J* = 7.1 Hz, 2H), 1.31 – 1.15 (m, 9H), 1.02 (tt, *J* = 7.5, 1.5 Hz, 3H); **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 173.6, 72.5, 71.8, 70.5, 70.5, 70.5, 70.4, 70.4, 70.2, 69.1, 63.3, 61.6, 58.9, 54.3, 52.7, 34.0, 29.0, 28.9, 28.9, 28.9, 28.4, 24.7, 21.8, 15.7, 13.1; **$R_f$** = 0.38 (9:1 DCM/MeOH) – CAM stain.

# 4. Determination of micellar diameter

## 1. Cryo-TEM images

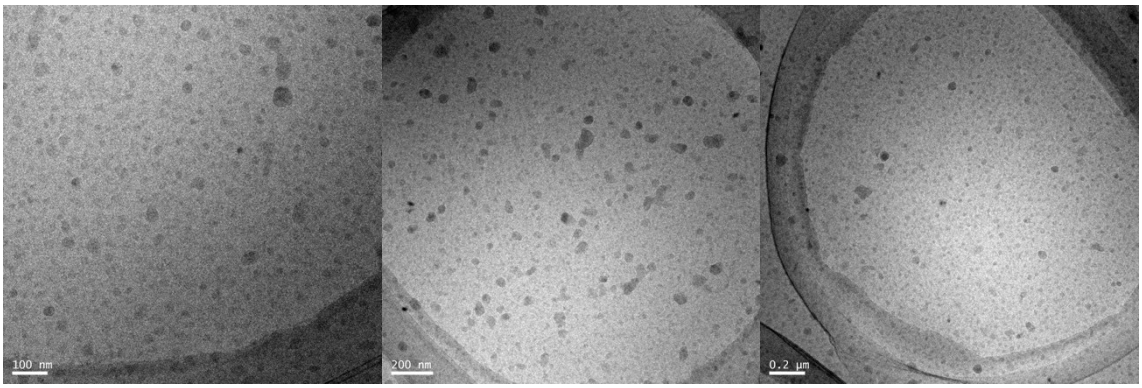



*Figure 1: Cryo-TEM images of TPGS-750-M/$H_2O$ – diameter ranges from 40 to 50 nm (magnification 19k, 11.5k and 5k)*

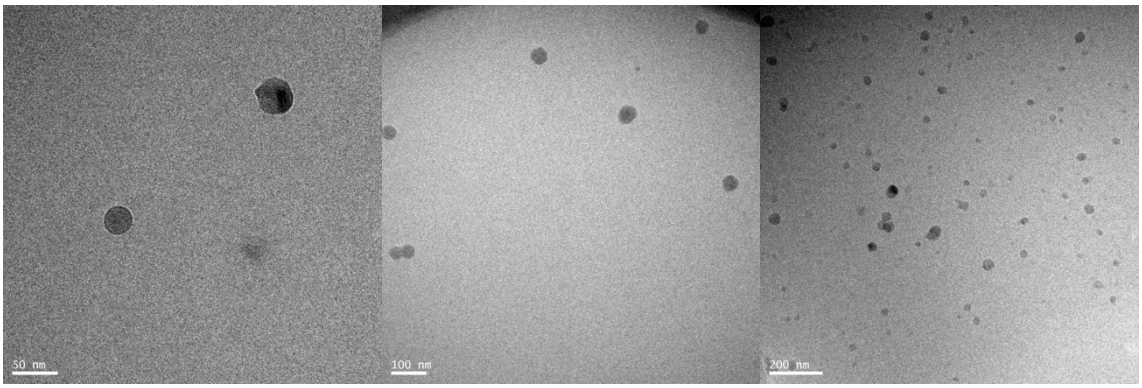



*Figure 2: Cryo-TEM images of DSP-1000-M/$H_2O$ – average diameter of 40 nm (magnification 50k, 19k and 14.5k)*

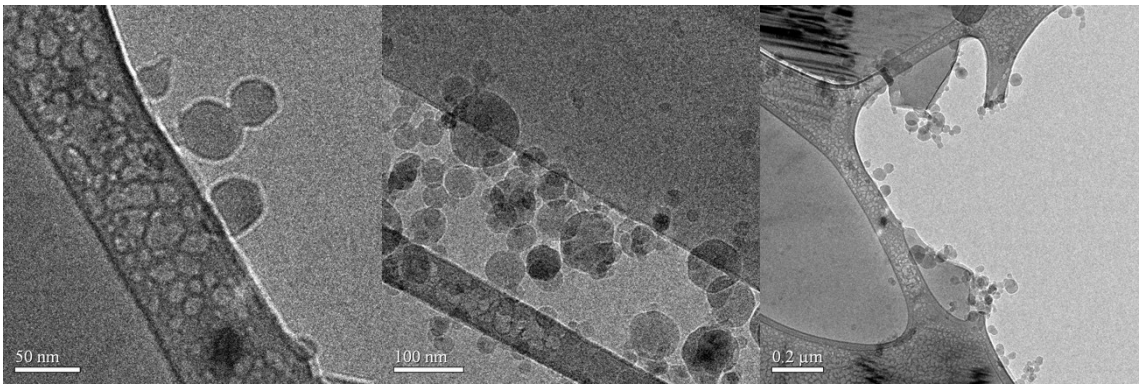



*Figure 3: Cryo-TEM images of MC-1/$H_2O$ – diameter ranges from 30 to 70 nm (magnification 71k, 29k and 15k)*

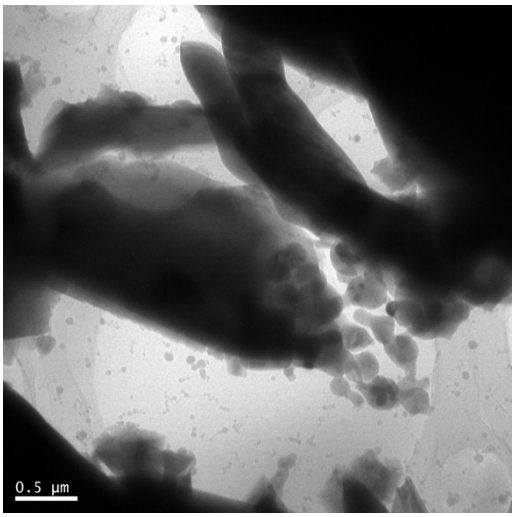



*Figure 4: Cryo-TEM images of Pd/C in MC-1/$H_2O$ – (magnification 5k)*

## 2. NanoSight

A solution of 2 wt % surfactant/$H_2O$ was diluted by 1000 (higher concentration showed clusters that led to false results).

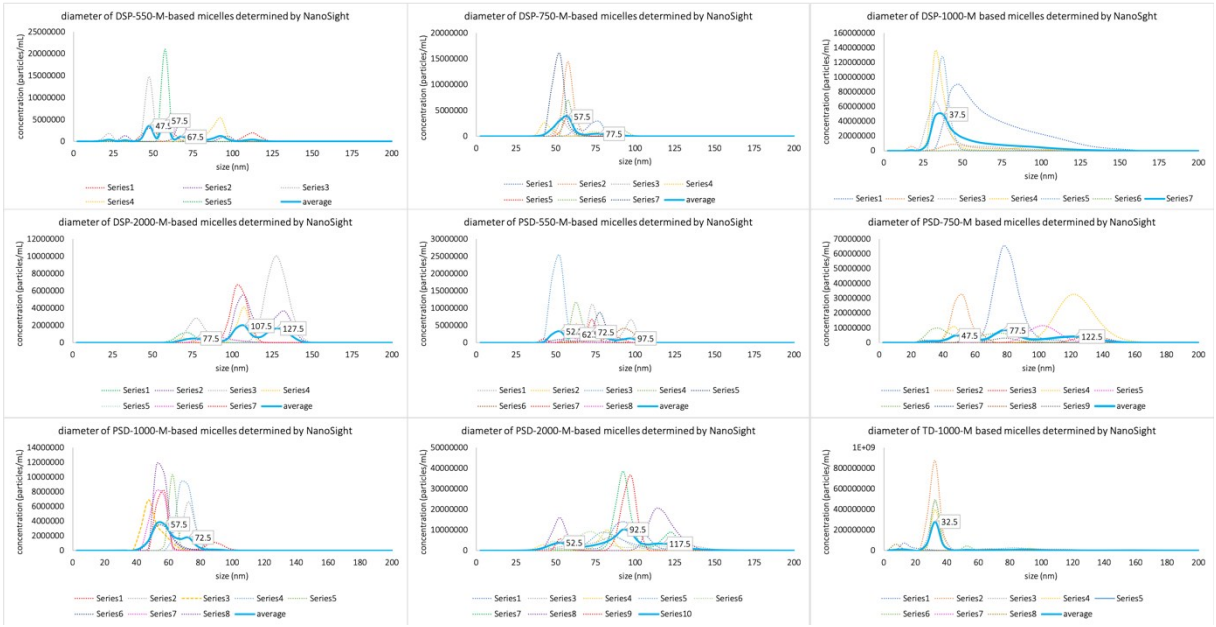



*Figure 5: Determination micellar diameter by NanoSight*

# 5. NMR Spectra

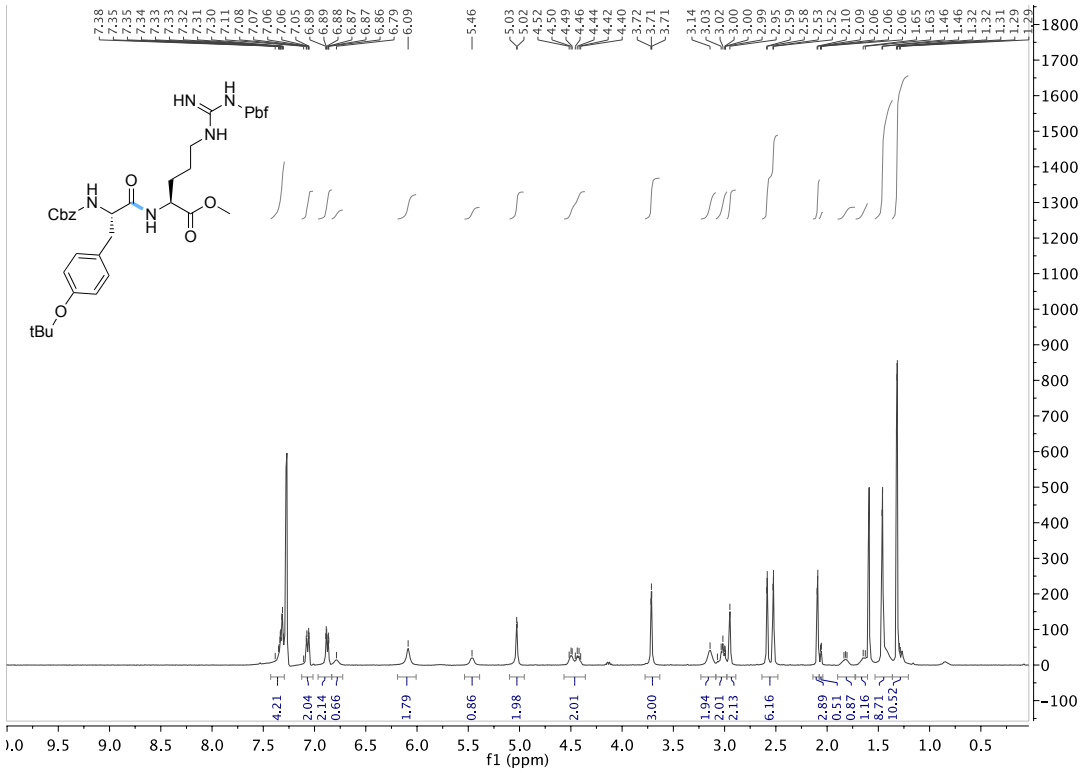



*Figure 6: $^{1}$H NMR spectra of Cbz-Tyr(tBu)-Arg(Pbf)-OMe (**1**)*

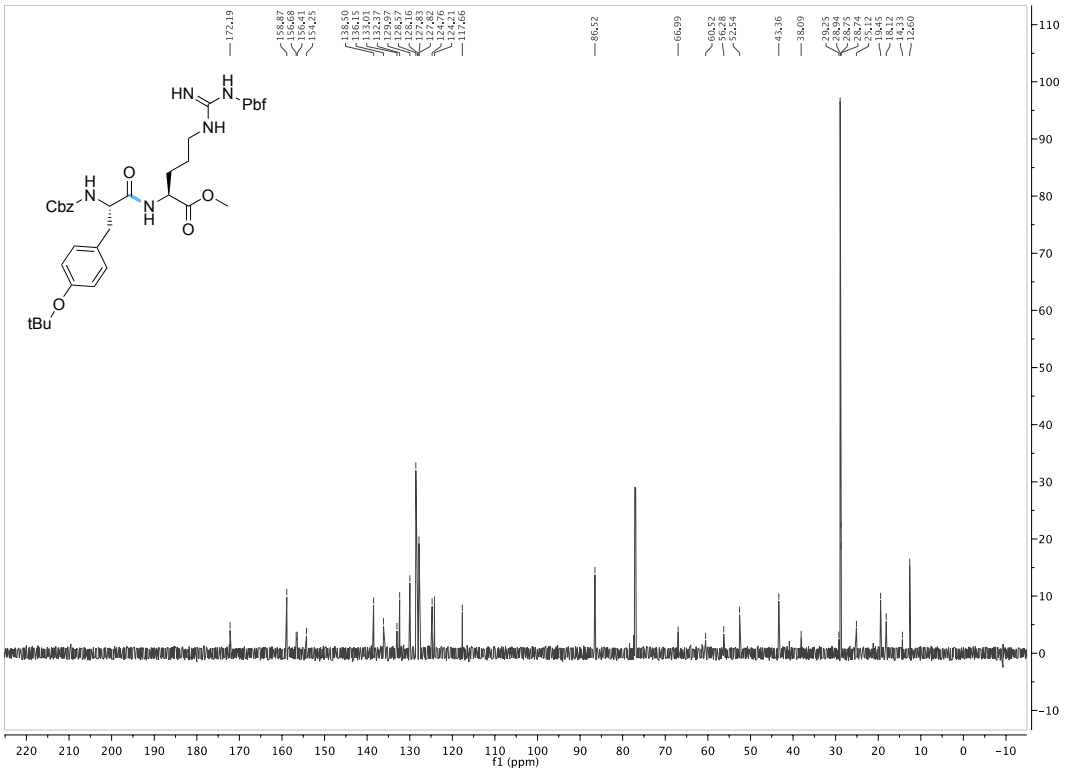



*Figure 7:[13]C NMR spectra of Cbz-Tyr(tBu)-Arg(Pbf)-OMe (**1**)*

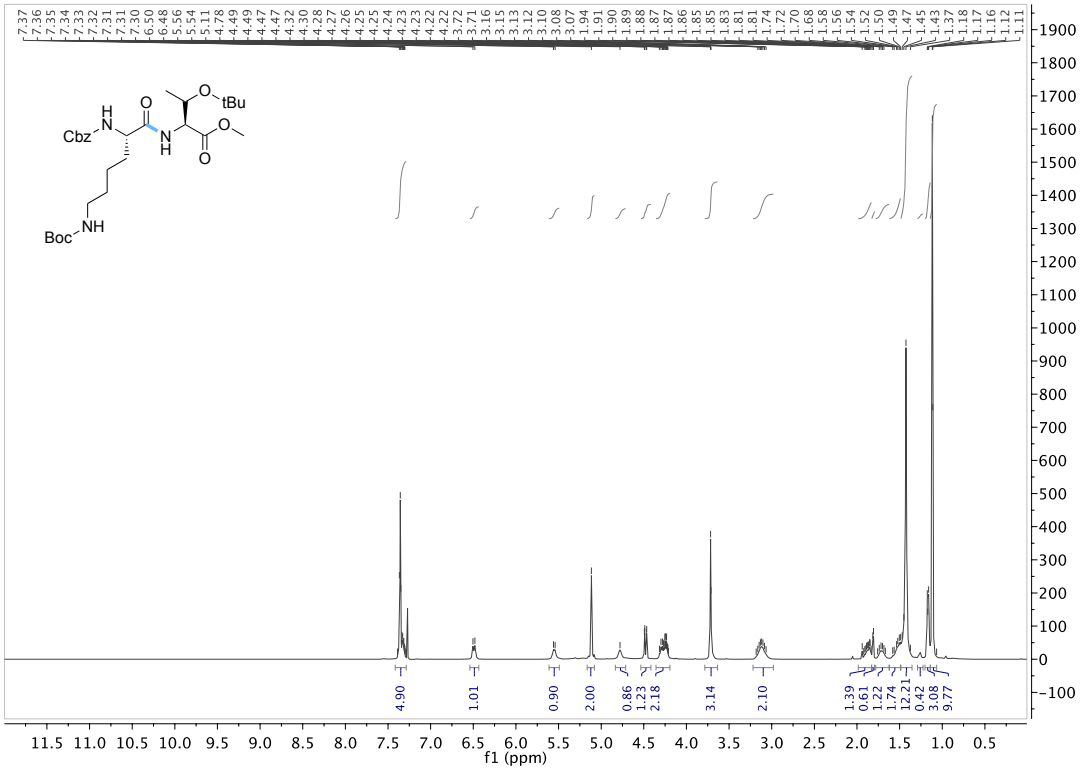



*Figure 8: [1]H NMR spectra of Cbz-Lys(Boc)-Thr(tBu)-OMe (**2**)*

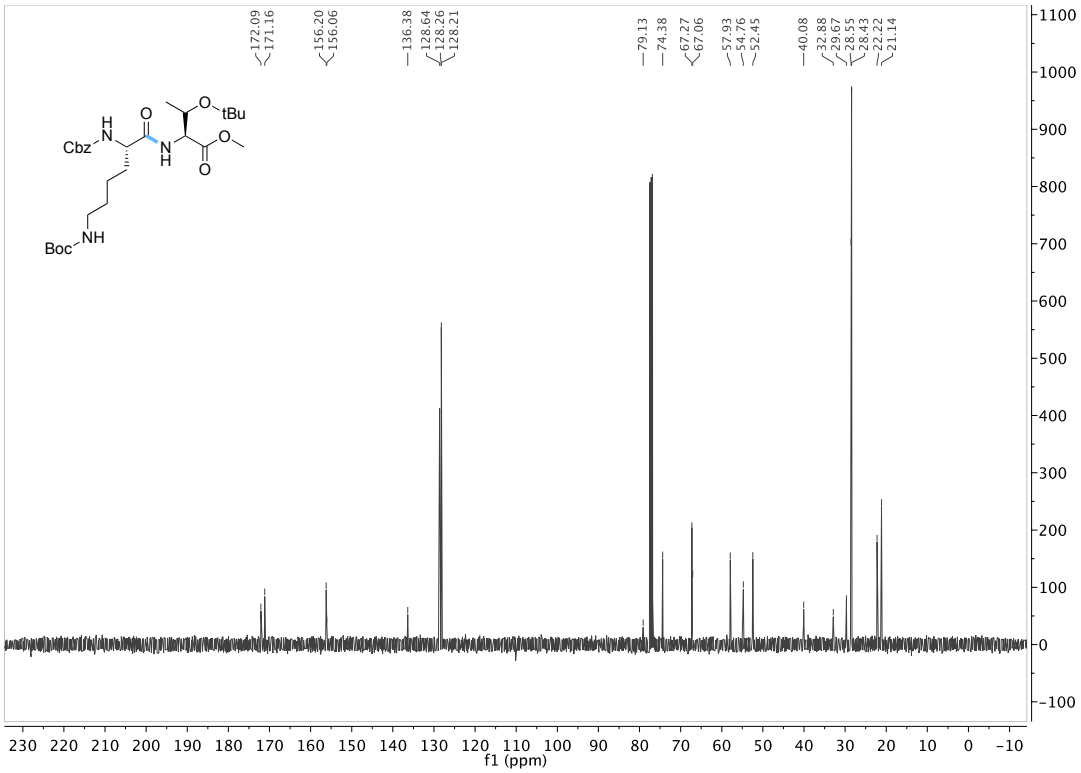



*Figure 9: $^{13}$C NMR spectra of Cbz-Lys(Boc)-Thr(tBu)-OMe (**2**)*

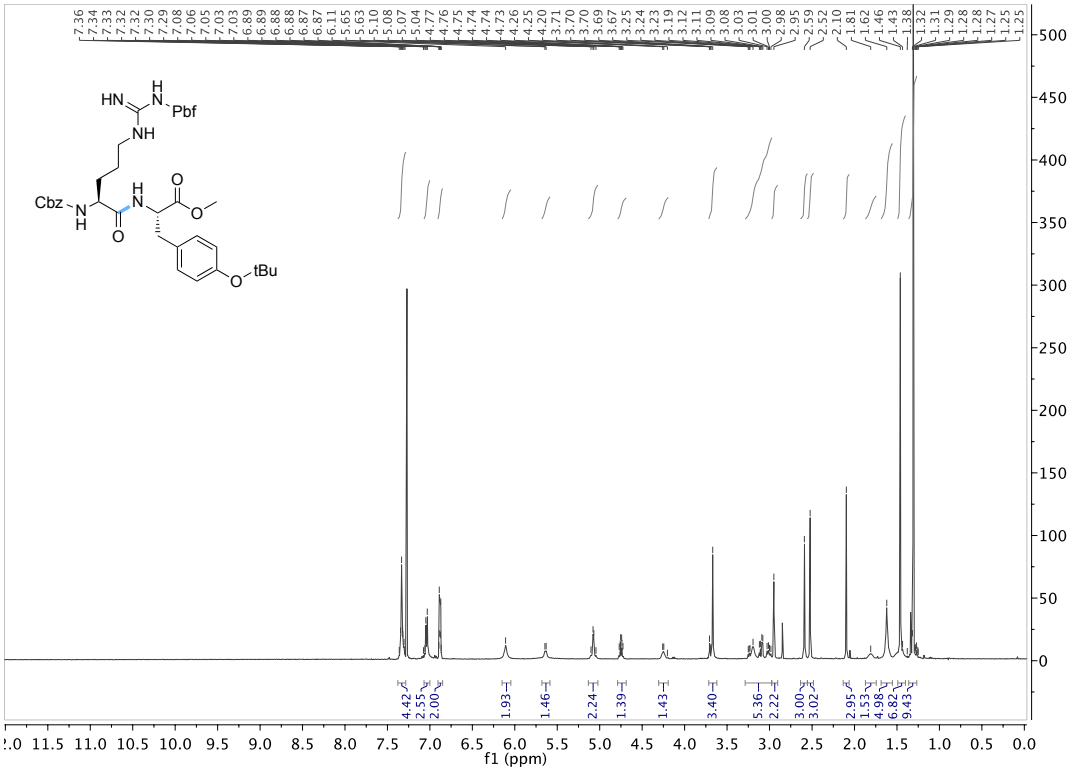



*Figure 10: $^{1}$H NMR spectra of Cbz-Arg(Pbf)-Tyr(tBu)-OMe (**3**)*

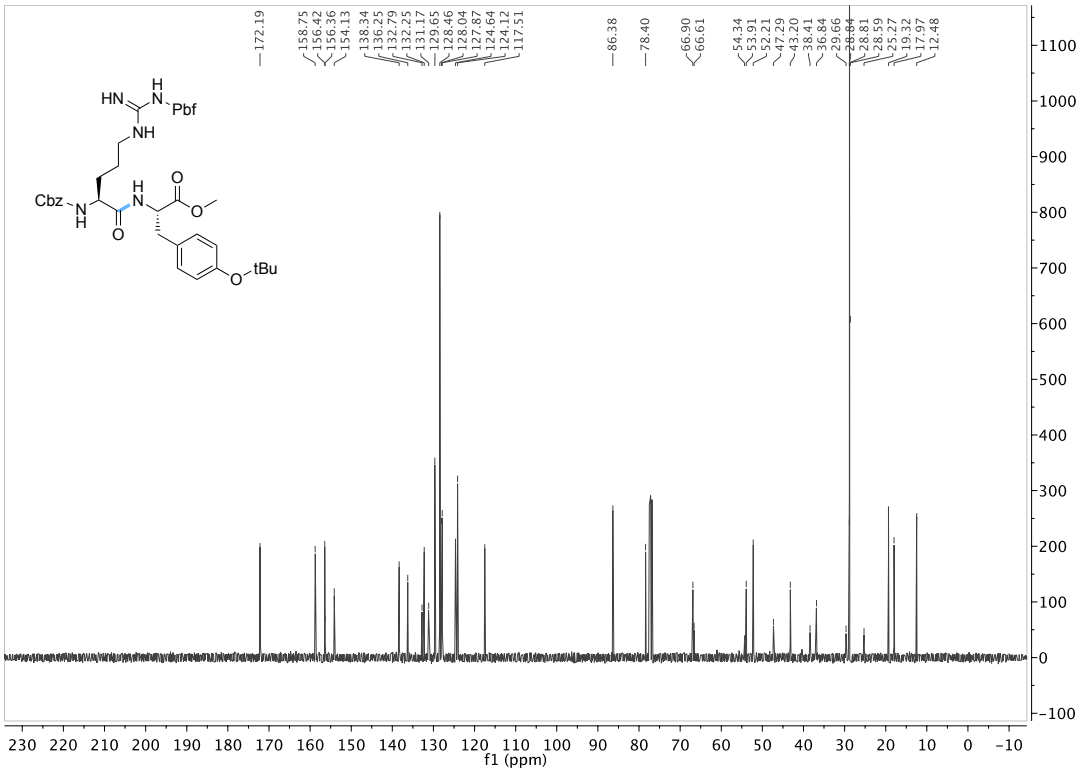



*Figure 11: $^{13}$C NMR spectra of Cbz-Arg(Pbf)-Tyr(tBu)-OMe (**3**)*

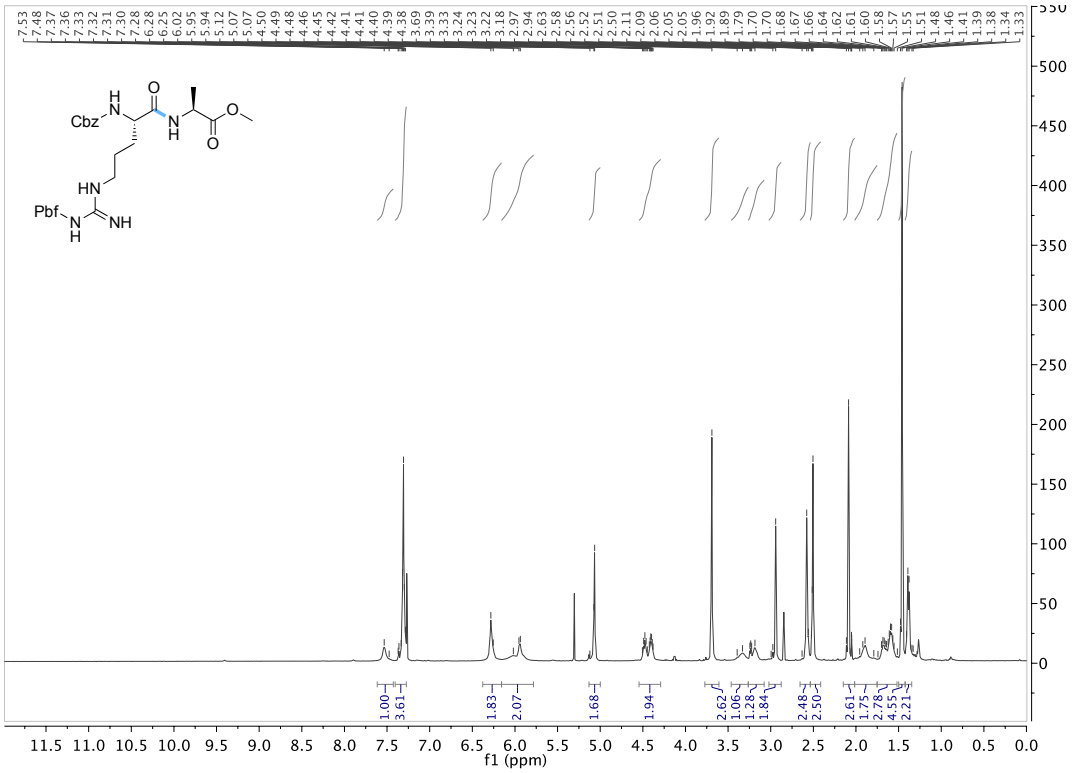



*Figure 12: $^{1}$H NMR spectra of Cbz-Arg(Pbf)-Ala-OMe (**4**)*

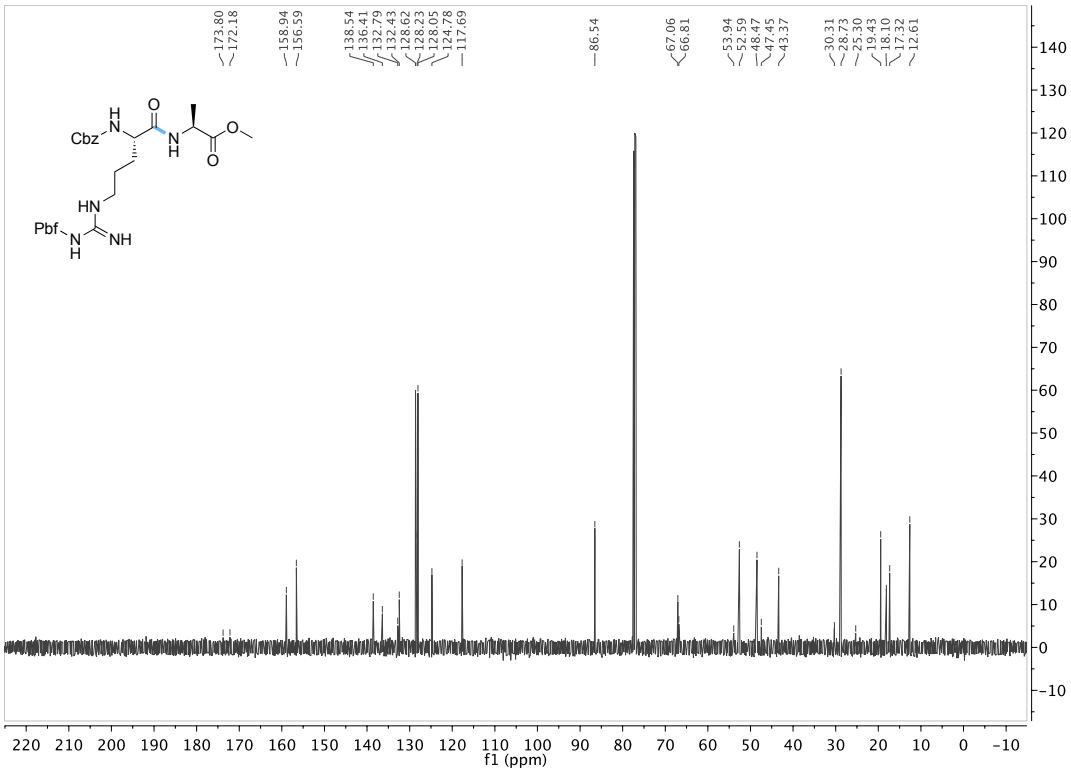



*Figure 13: $^{13}$C NMR spectra of Cbz-Arg(Pbf)-Ala-OMe (**4**)*

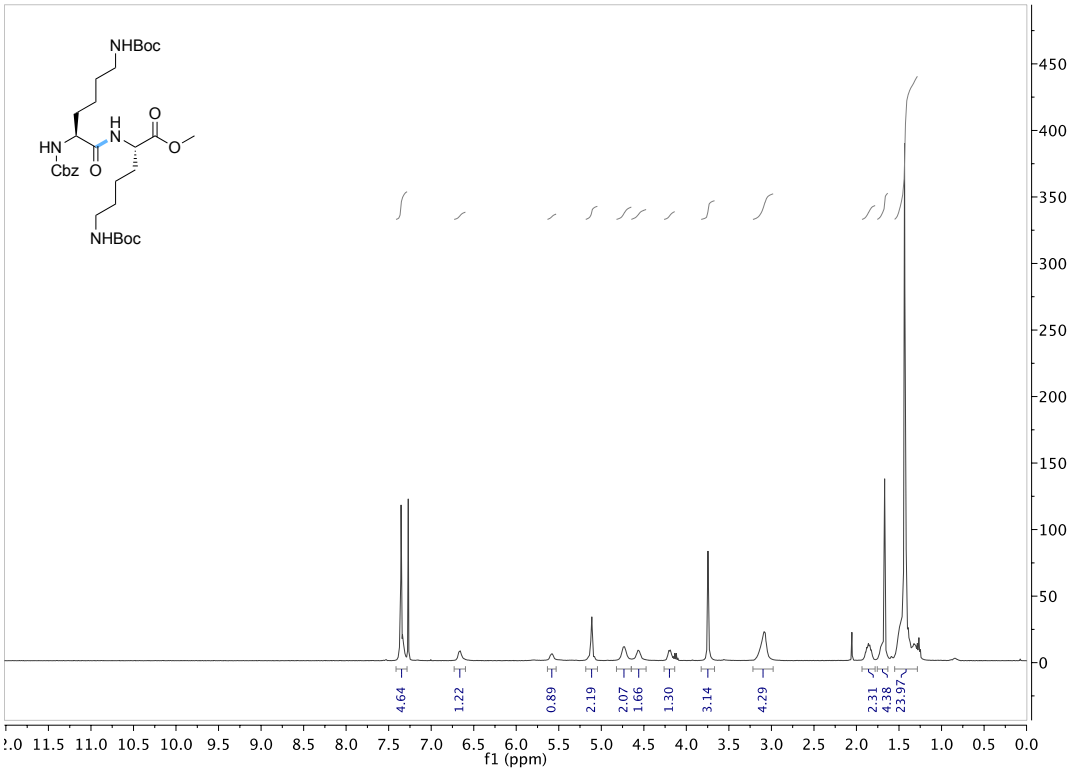



*Figure 14: $^{1}$H NMR spectra of Cbz-Lys(Boc)-Lys(Boc)-OMe (**5**)*

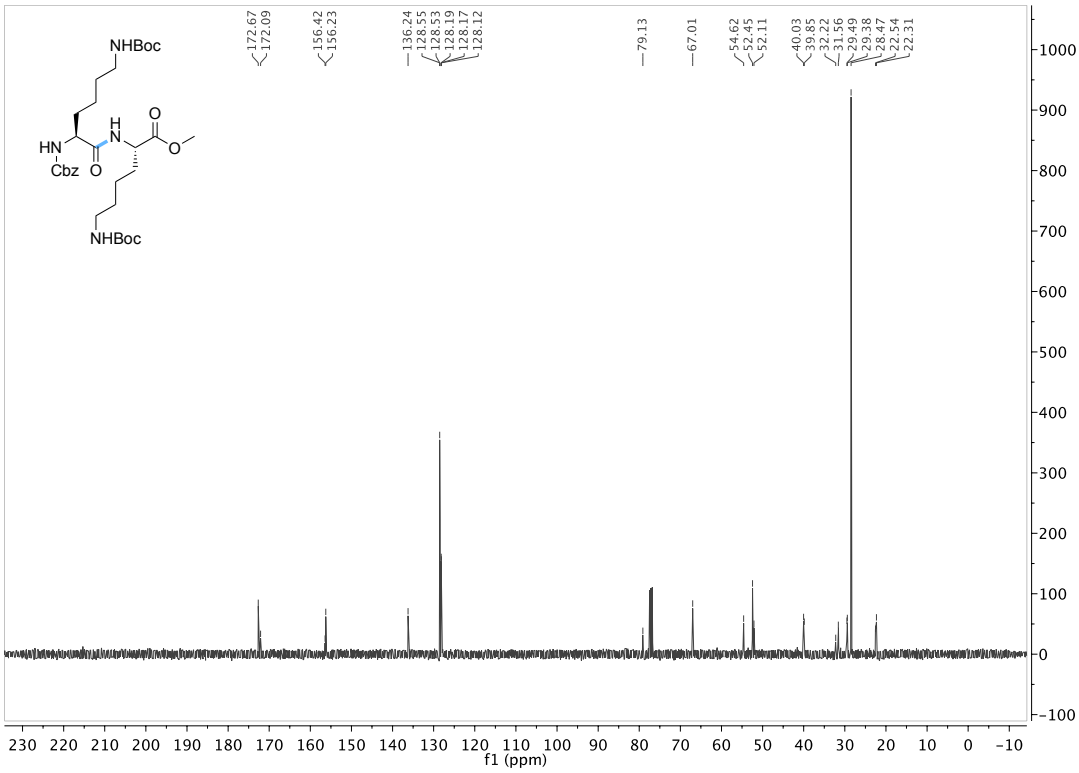



*Figure 15: $^{13}$C NMR spectra of Cbz-Lys(Boc)-Lys(Boc)-OMe (**5**)*

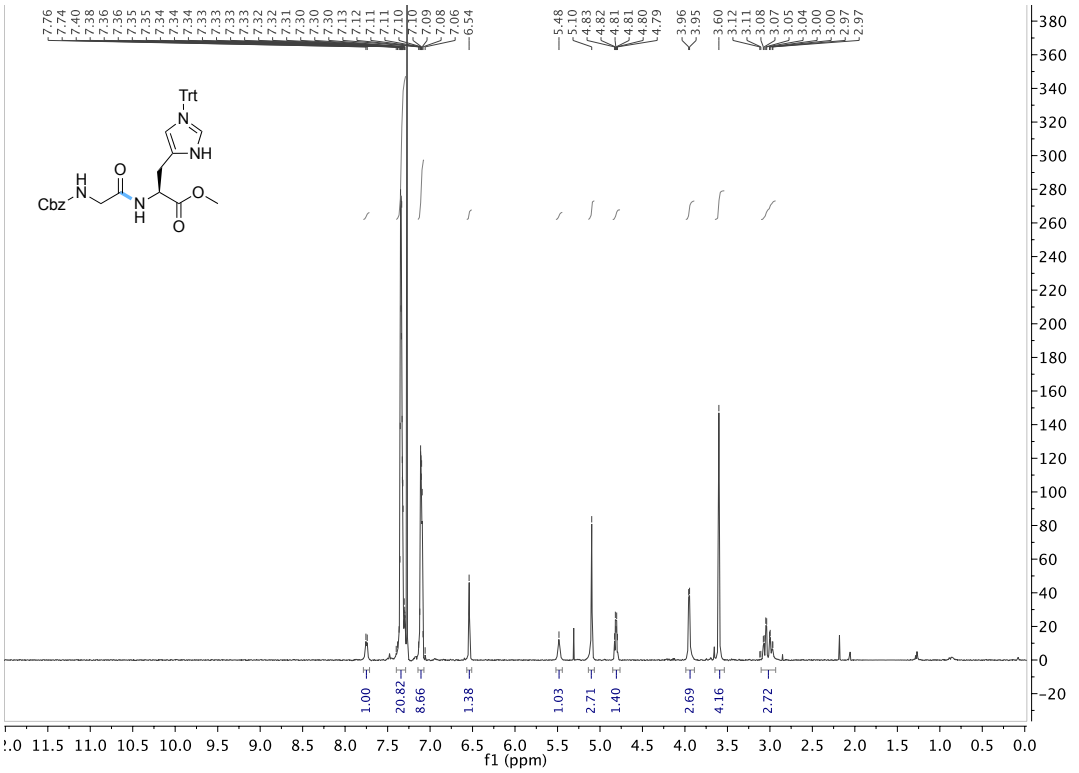



*Figure 16: $^{1}$H NMR spectra of Cbz-Gly-His(Trt)-OMe (**6**)*

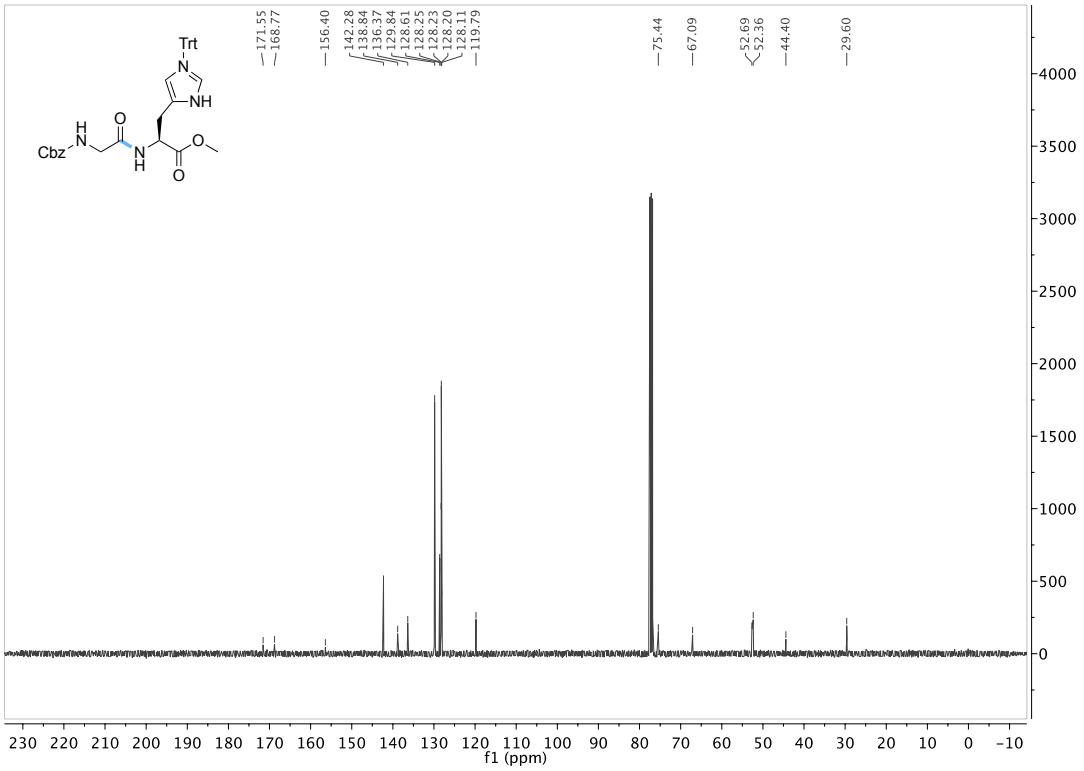



*Figure 17: $^{13}$C NMR spectra of Cbz-Gly-His(Trt)-OMe (**6**)*

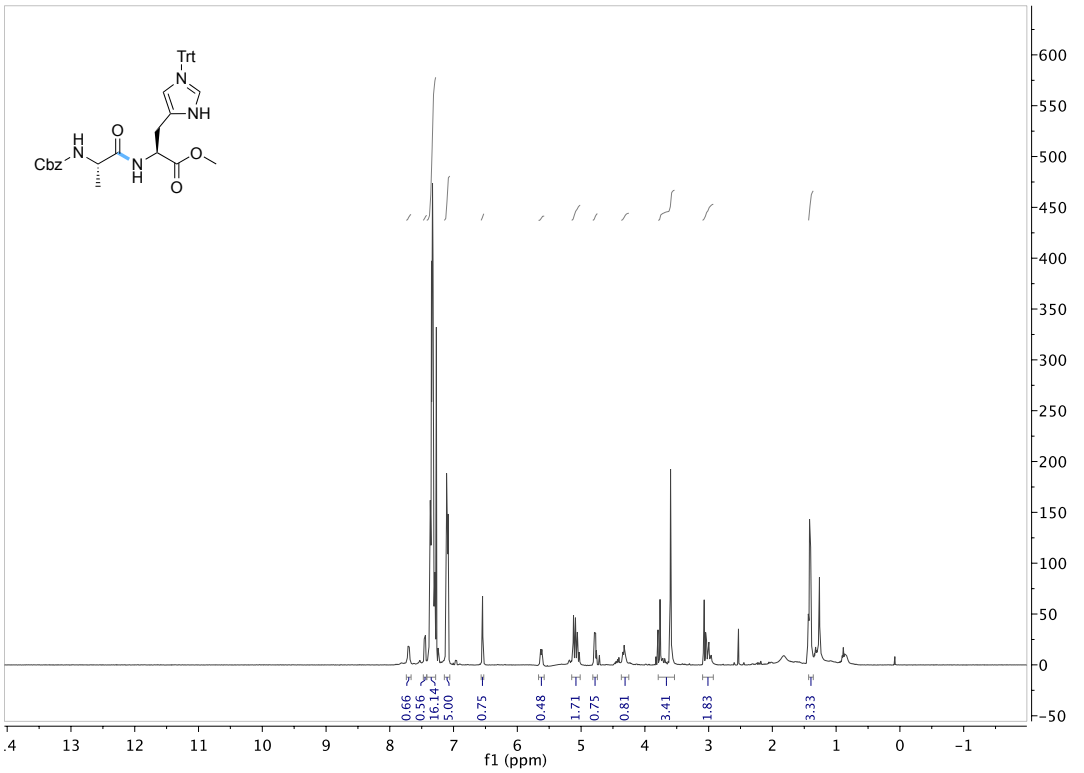



*Figure 18: $^{1}$H NMR spectra of Cbz-Ala-His(Trt)-OMe (**7**)*

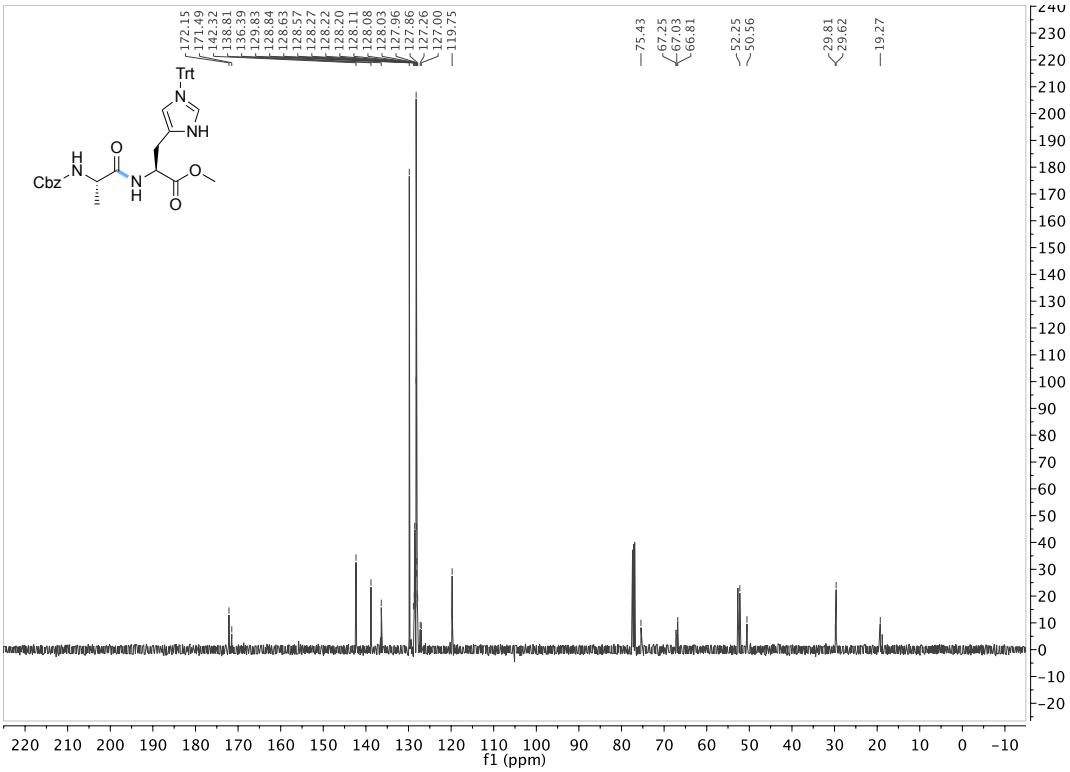



*Figure 19: $^{13}$C NMR spectra of Cbz-Ala-His(Trt)-OMe (**7**)*

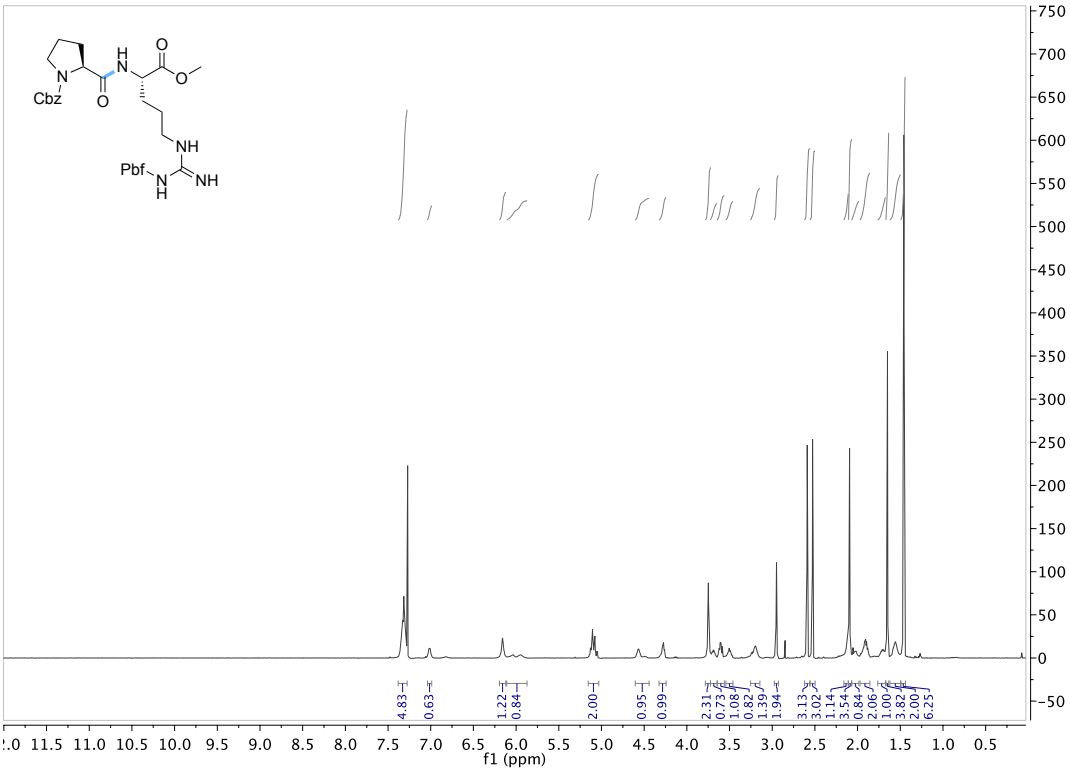



*Figure 20: 1H NMR spectra of Cbz-Pro-Arg(Pbf)-OMe (**8**)*

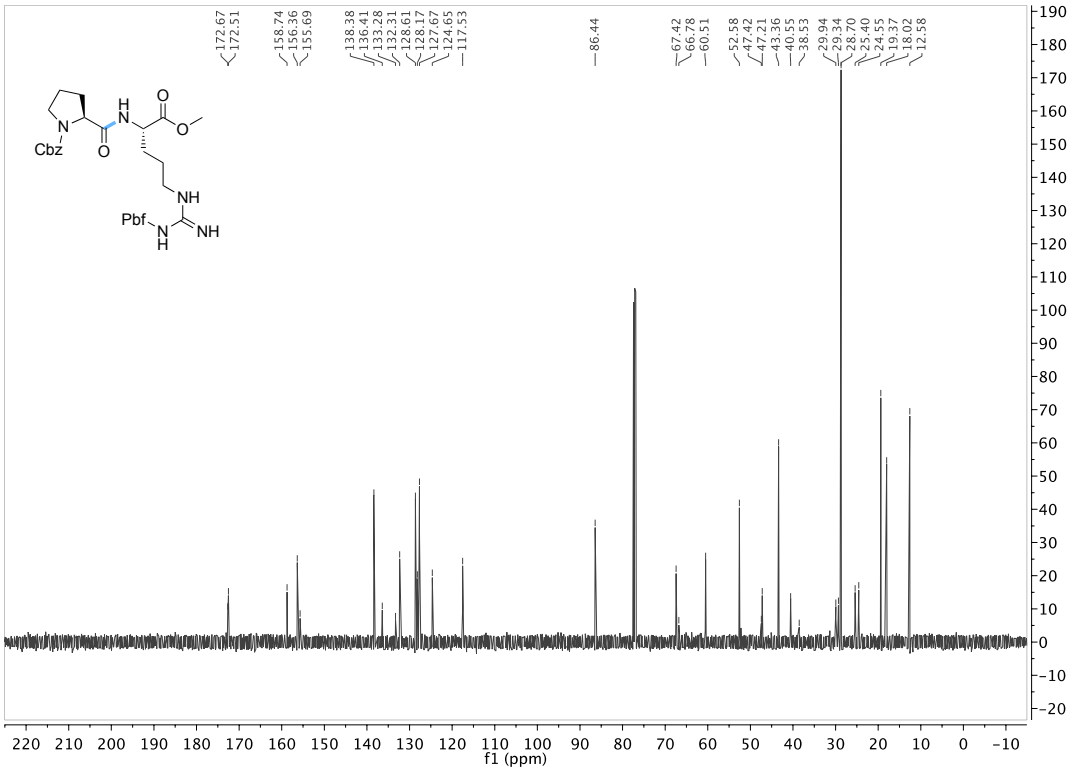



*Figure 21: $^{13}C$ NMR of Cbz-Pro-Arg(Pbf)-OMe (**8**)*

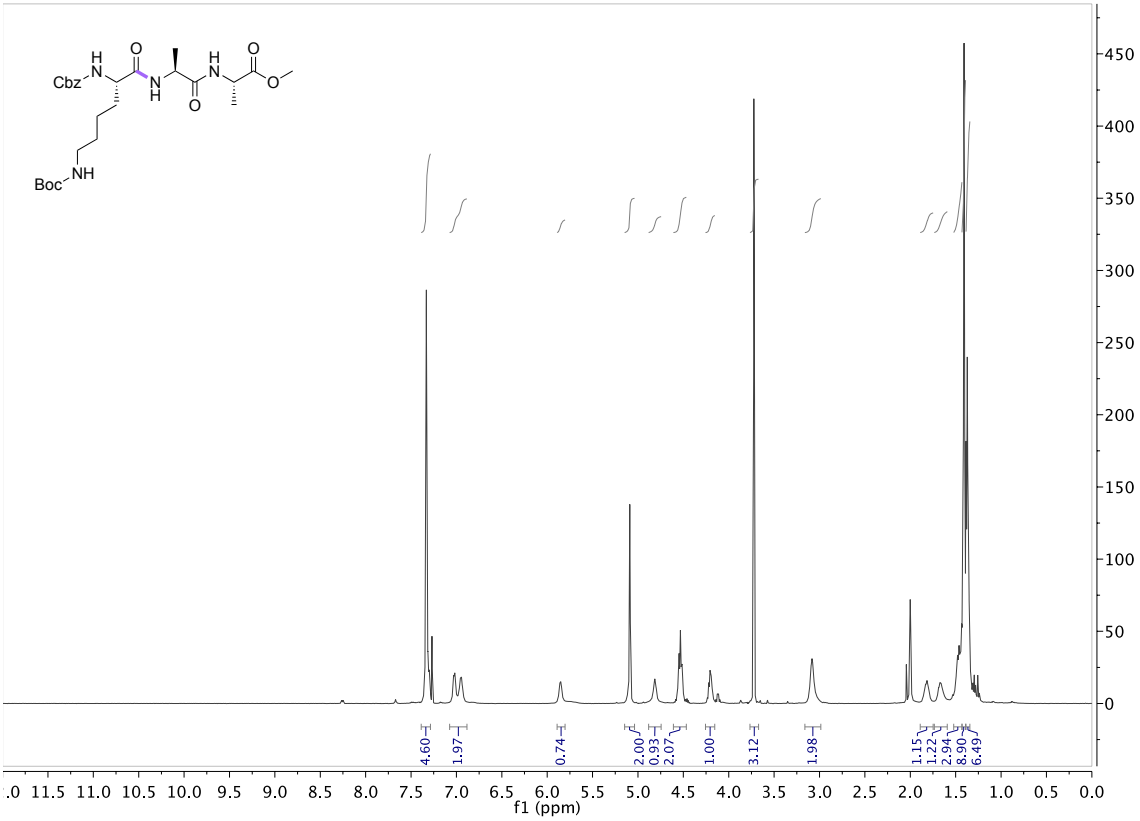



*Figure 22: 1H NMR spectra of Cbz-Lys(Boc)-Ala-Ala-OMe (**9**)*

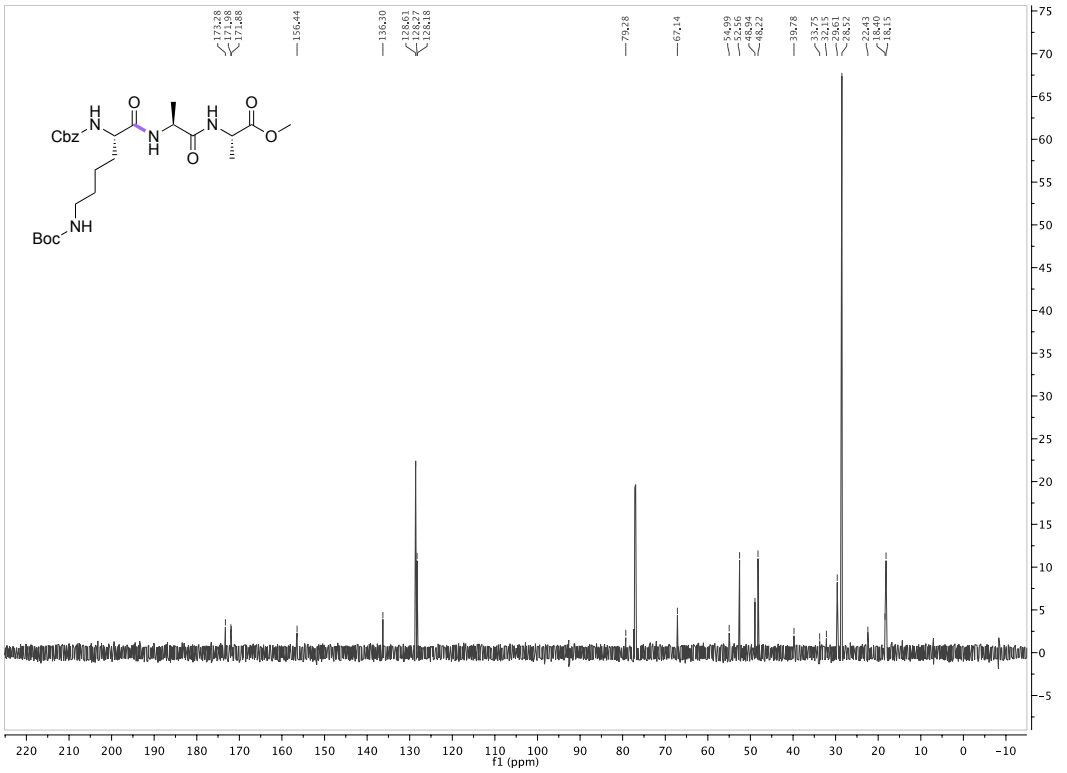



*Figure 23: $^{13}C$ NMR spectra of Cbz-Lys(Boc)-Ala-Ala-OMe (**9**)*

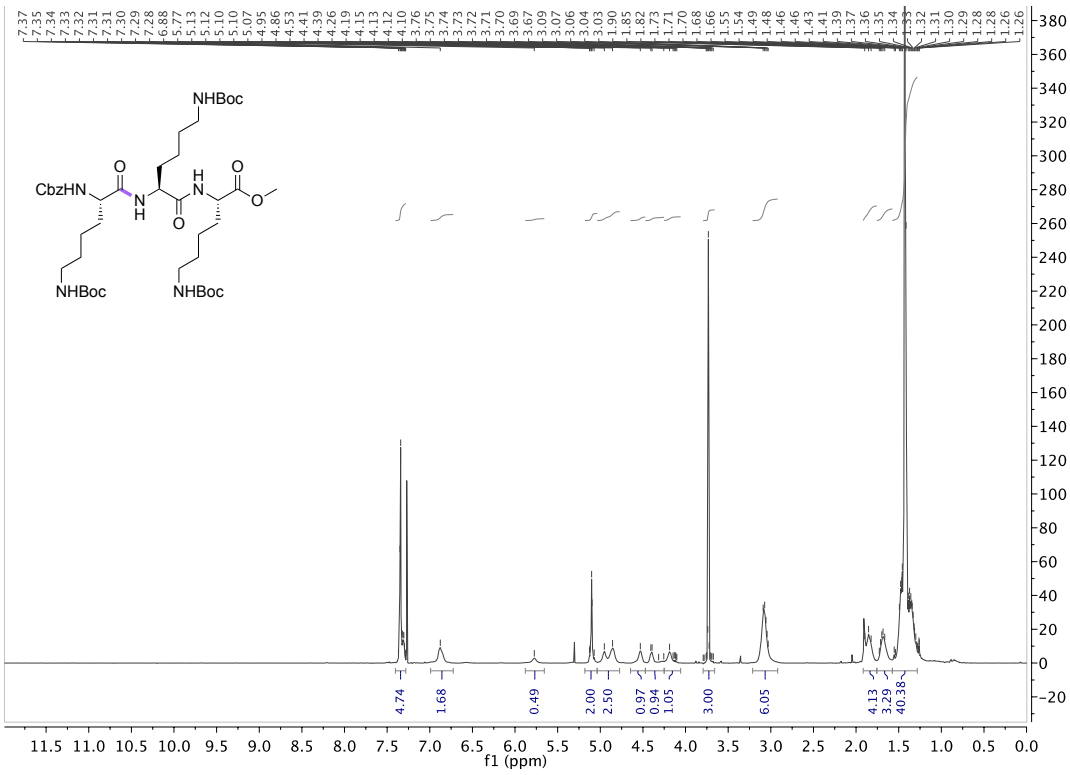



*Figure 24: $^{1}H$ NMR spectra of Cbz-Lys(Boc-Lys(Boc)-Lys(Boc)-OMe (**10**)*

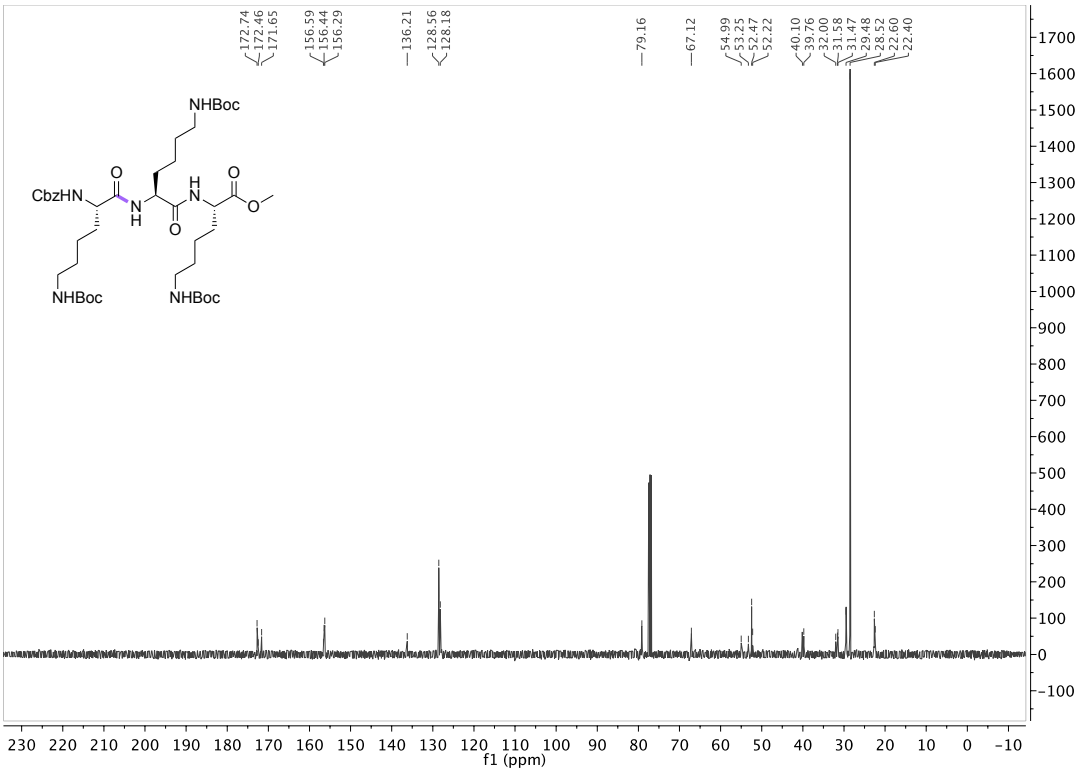



*Figure 25: [1]3C NMR spectra of Cbz-Lys(Boc)-Lys(Boc)Lys(Boc)-OMe (**10**)*

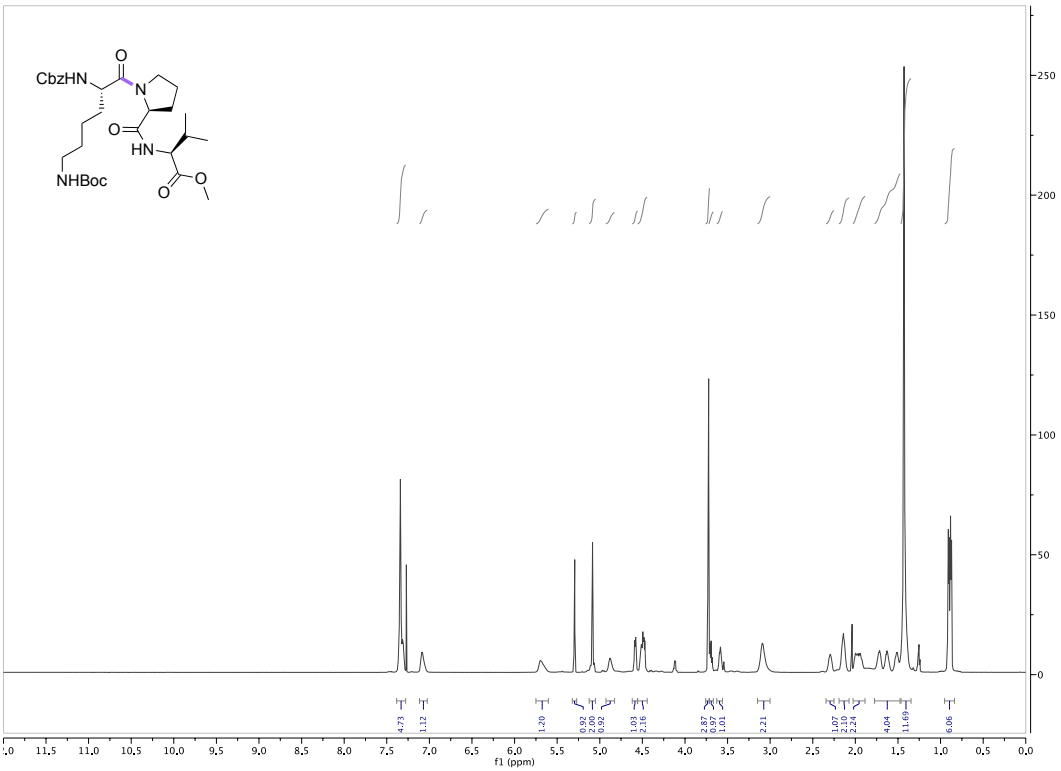



*Figure 26: [1]H NMR spectra of Cbz-Lys(Boc)-Pro-Val-OMe (**11**)*

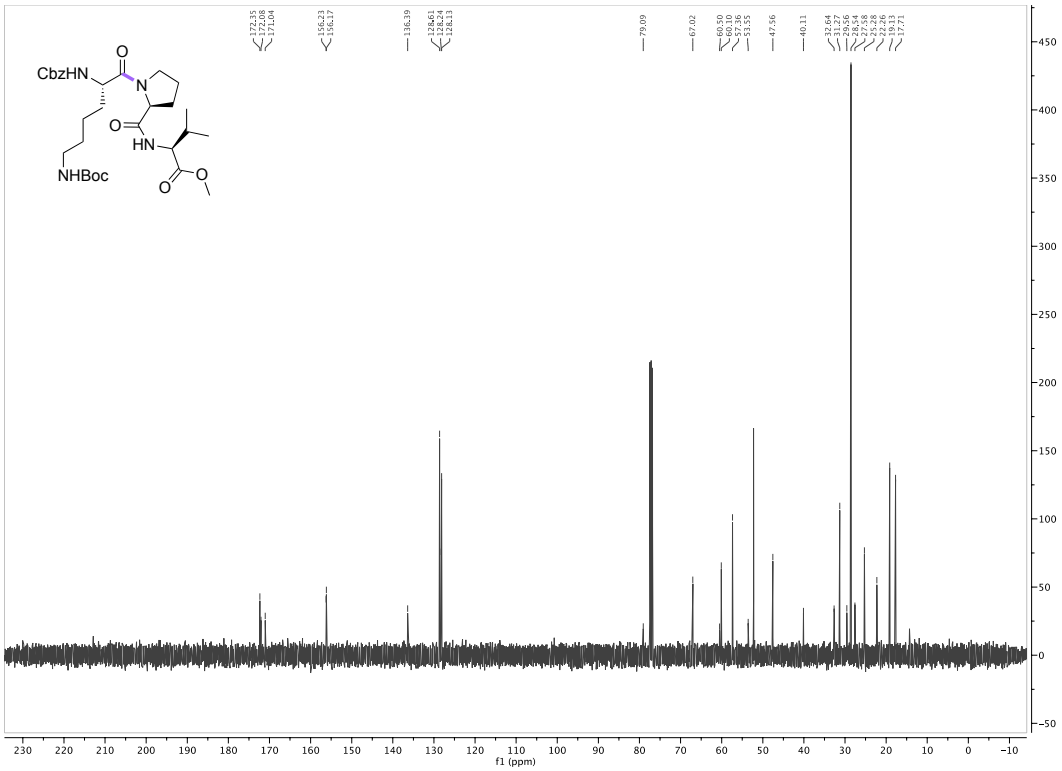



*Figure 27: $^{13}$C NMR spectra of Cbz-Lys(Boc)-Pro-Val-OMe (**11**)*

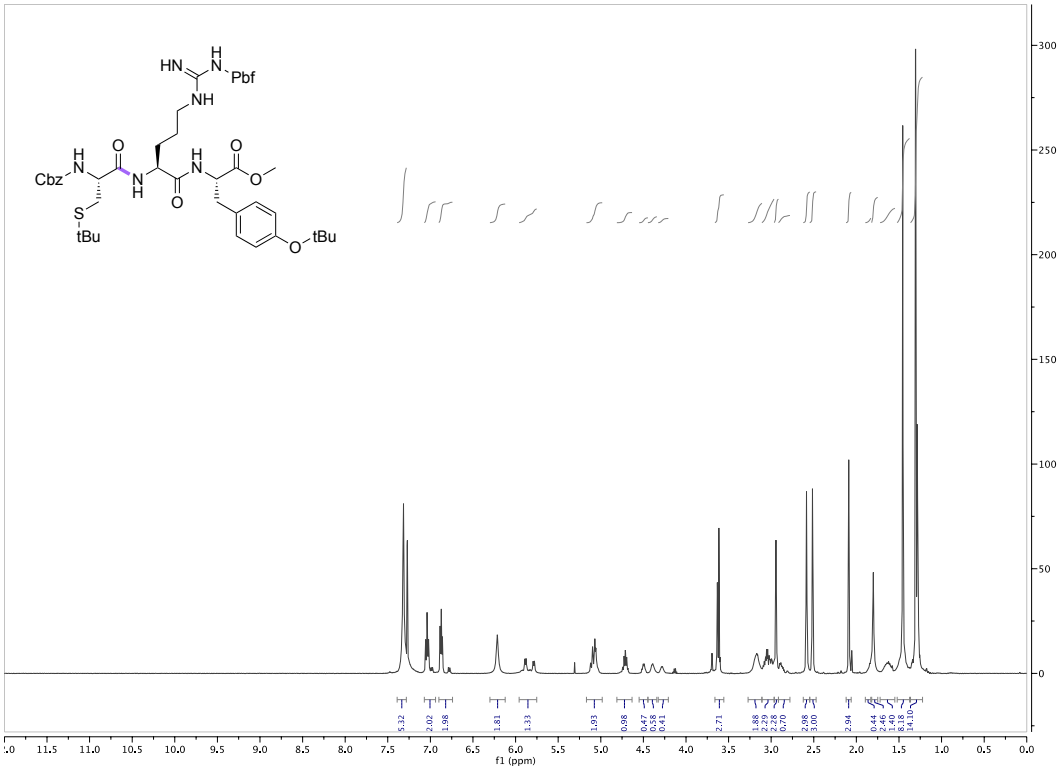



*Figure 28: $^{1}$H NMR spectra of Cbz-Cys(tBu)-Arg(Pbf)-Tyr(tBu)-OMe (**12**)*

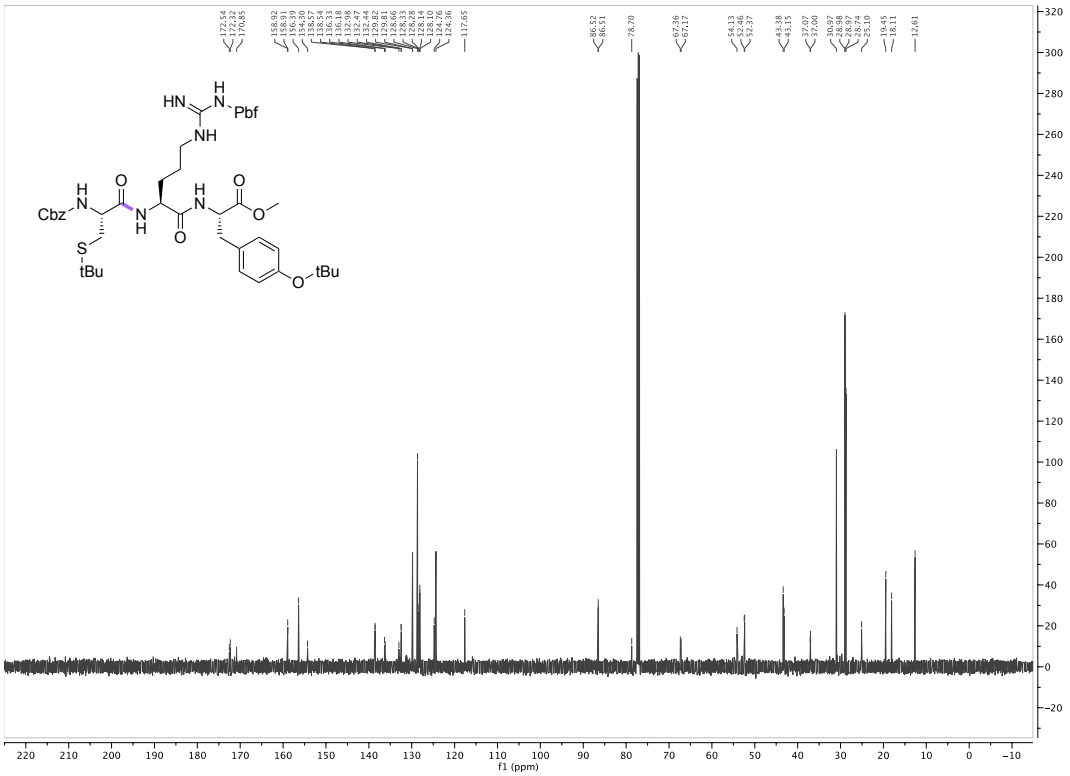


*Figure 29: $^{13}$C NMR spectra of Cbz-Cys(tBu)-Arg(Pbf)-Tyr(tBu)-OMe (**12**)*

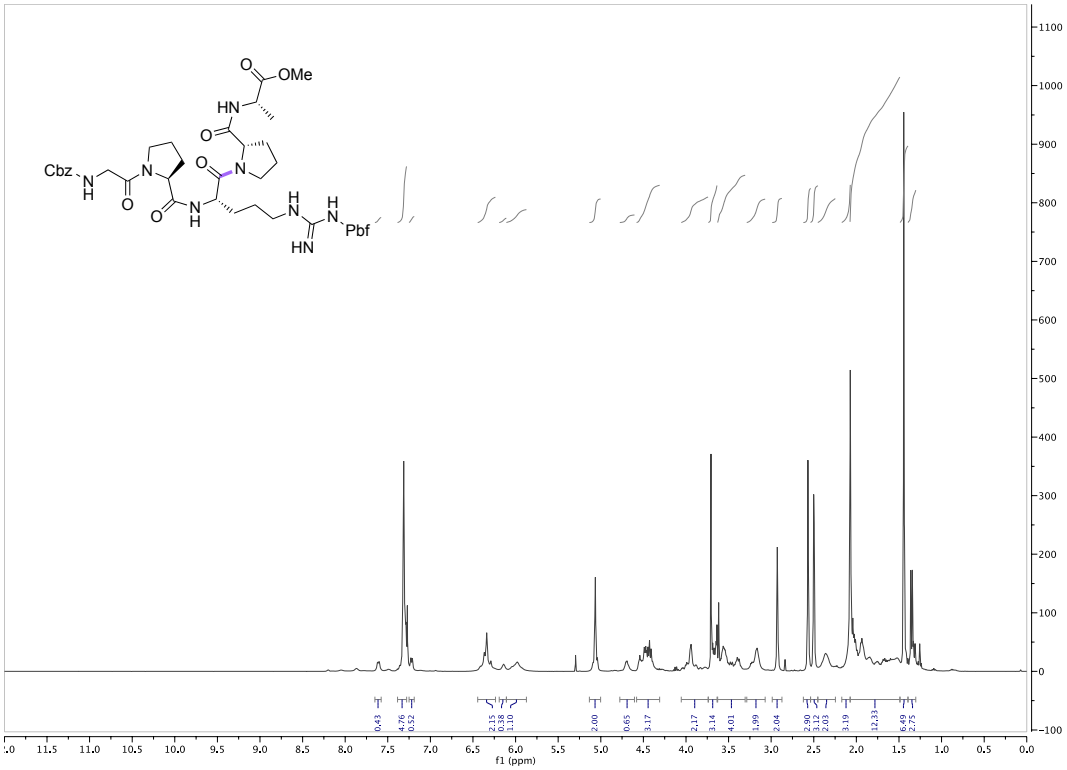


*Figure 30: $^{1}$H NMR spectra of Cbz-Gly-Pro-Arg(Pbf)-Pro-Ala-OMe (**13**)*

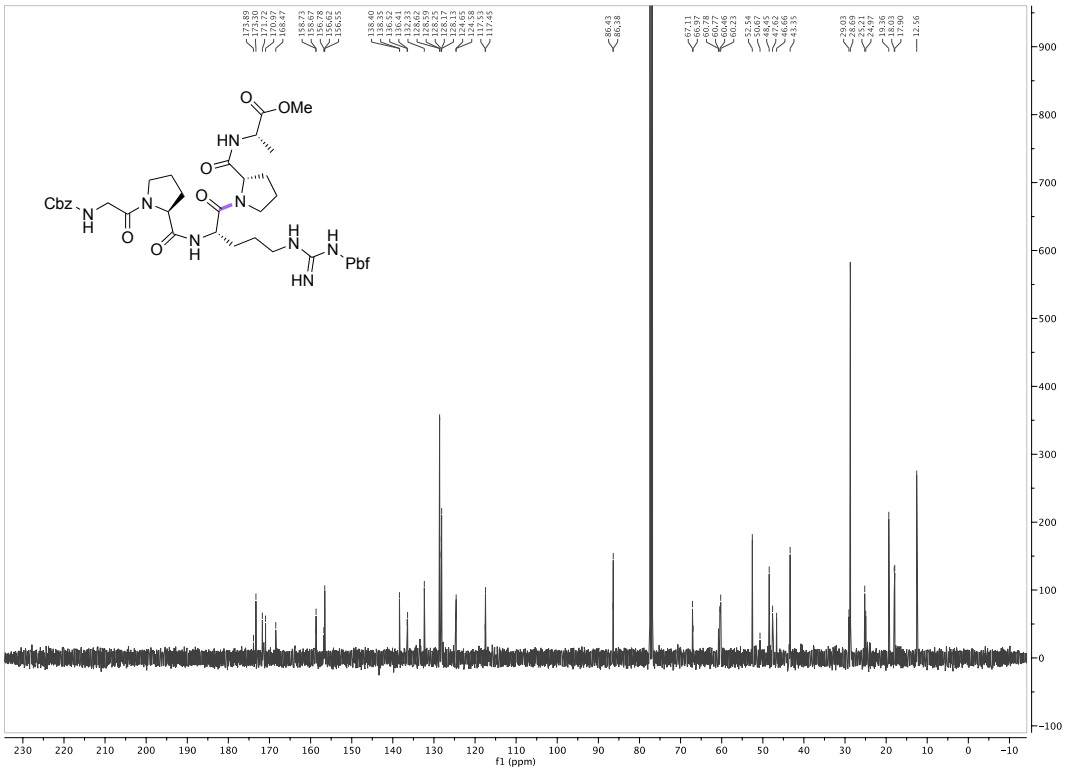



*Figure 31: $^{13}$C NMR spectra of Cbz-Gly-Pro-Arg(Pbf)-Pro-Ala-OMe (**13**)*

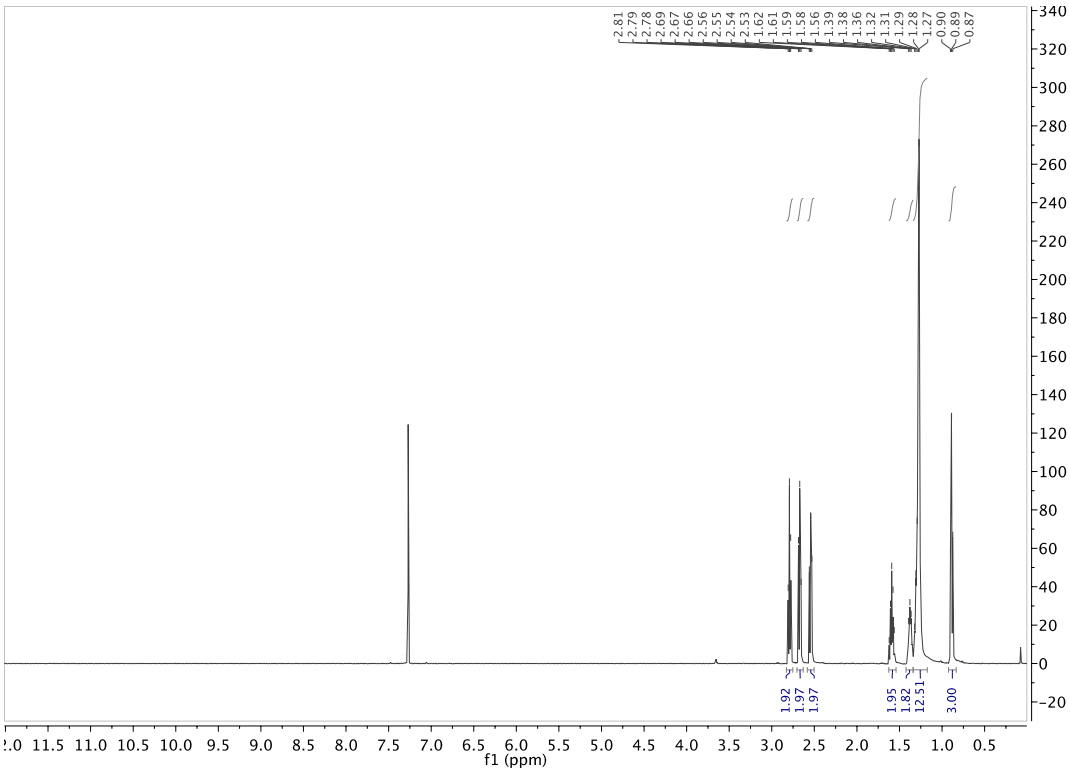



*Figure 32: $^{1}$H NMR spectra of 3-(decylthio)propanoic acid (DSP sulfide)*

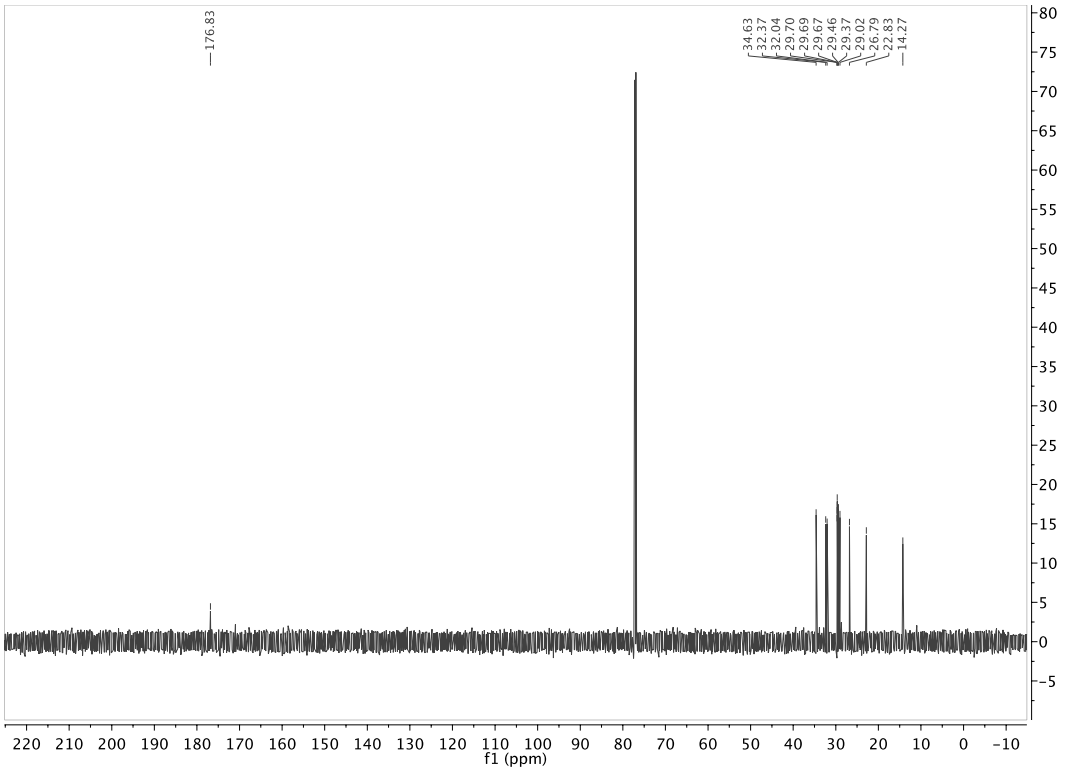



*Figure 33: [13]C NMR spectra of 3-(decylthio)propanoic acid (DSP sulfide)*

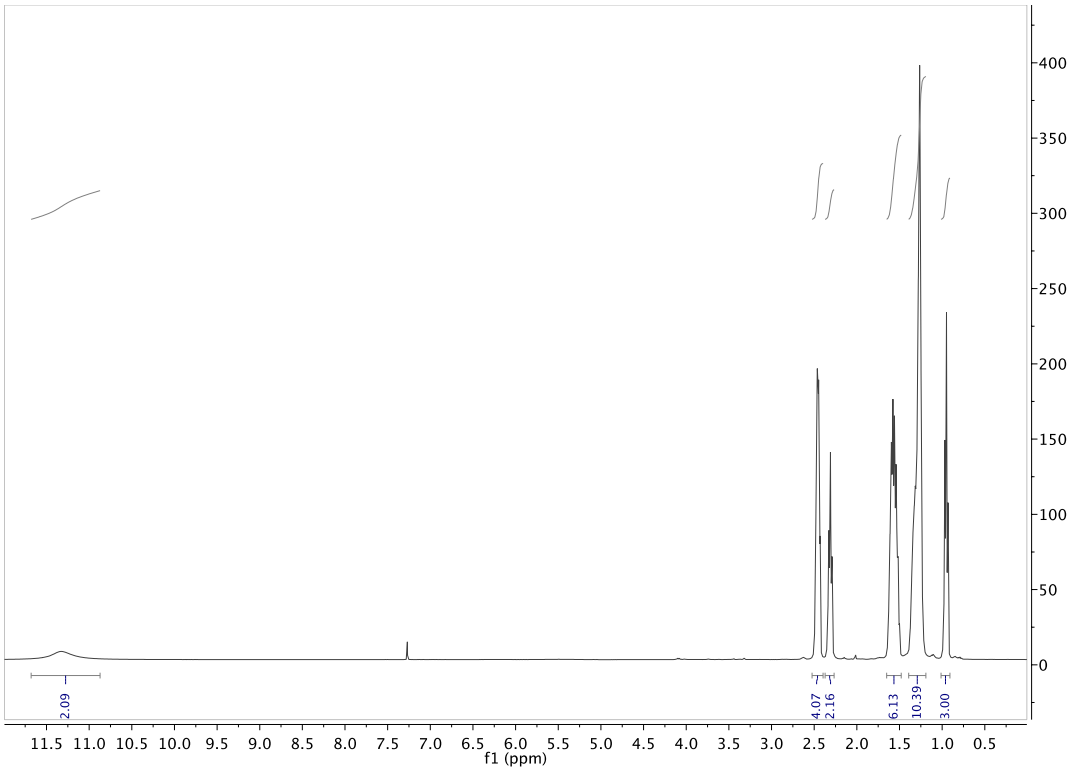



*Figure 34: [1]H NMR spectra of 10-(propylthio)decanoic acid (PSD sulfide **14**)*

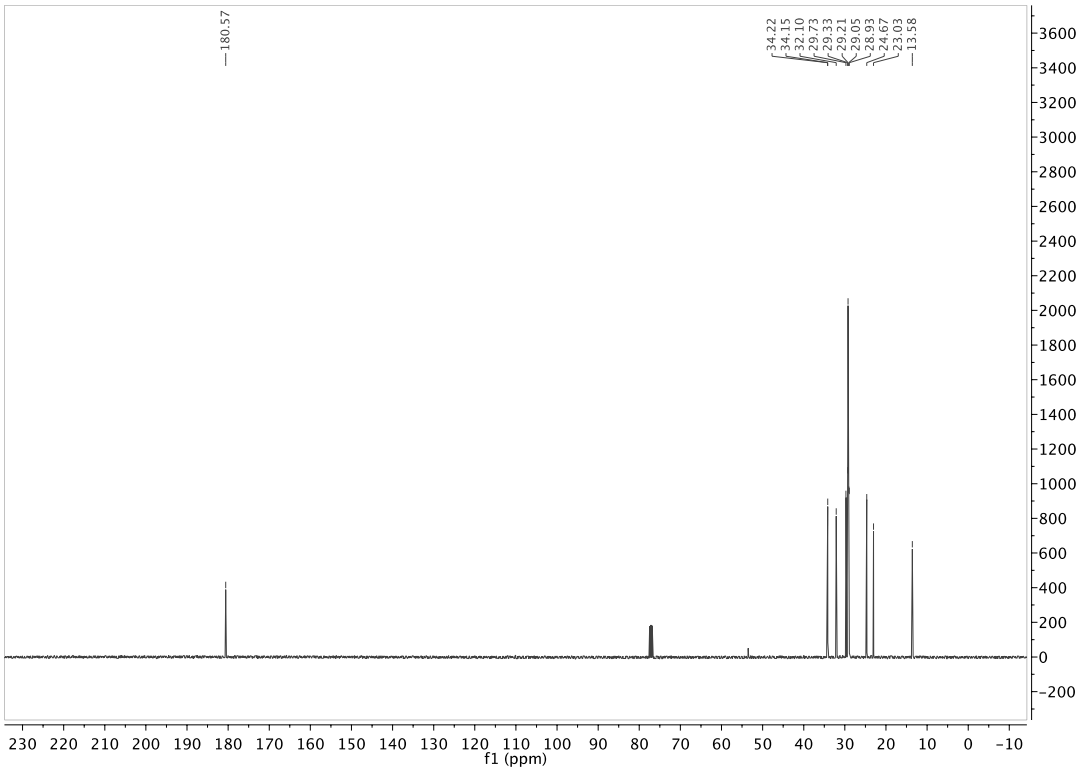



*Figure 35: $^{13}$C NMR spectra of 10-(propylthio)decanoic acid (PSD sulfide **14**)*

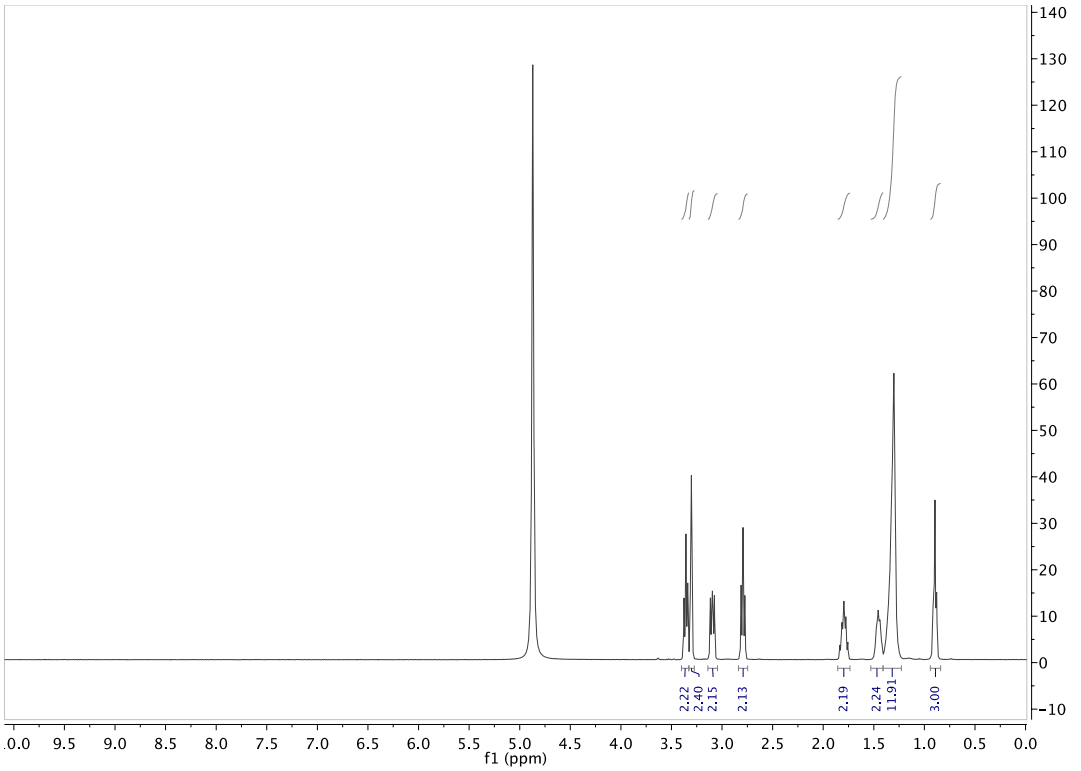



*Figure 36: $^{1}$H NMR spectra of 3-(decylsulfonyl)propanoic acid (DSP sulfone)*

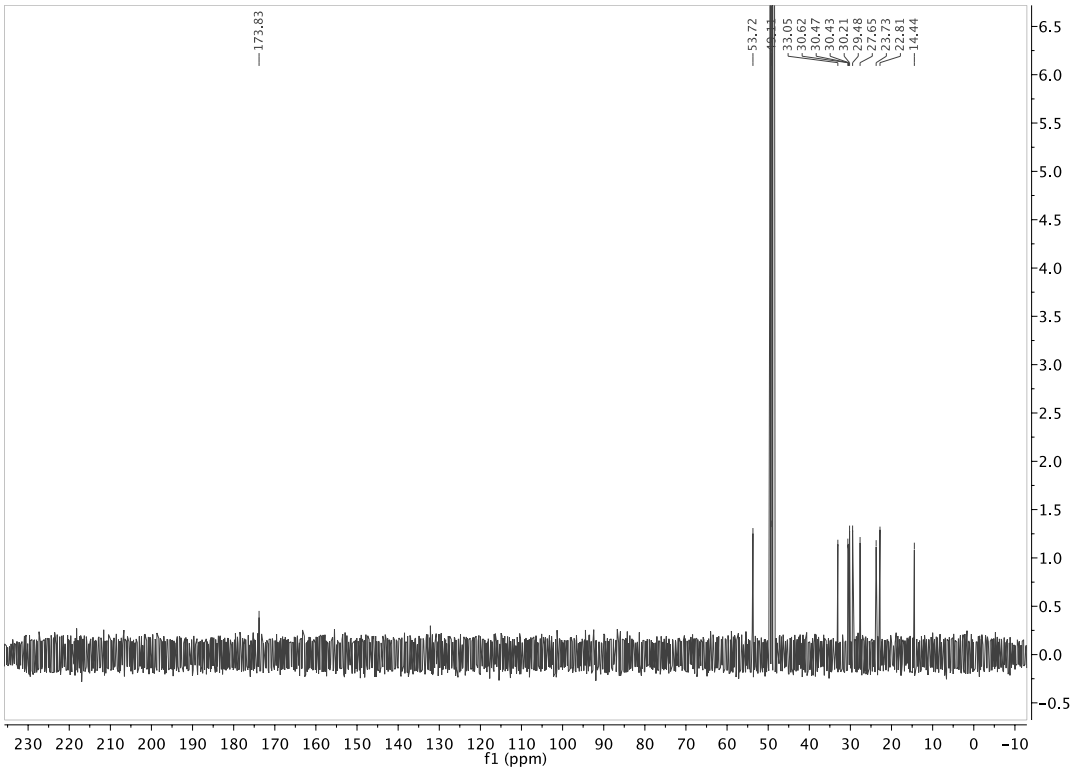



*Figure 37: $^{13}C$ NMR spectra of 3-(decylsulfonyl)propanoic acid (DSP sulfone)*

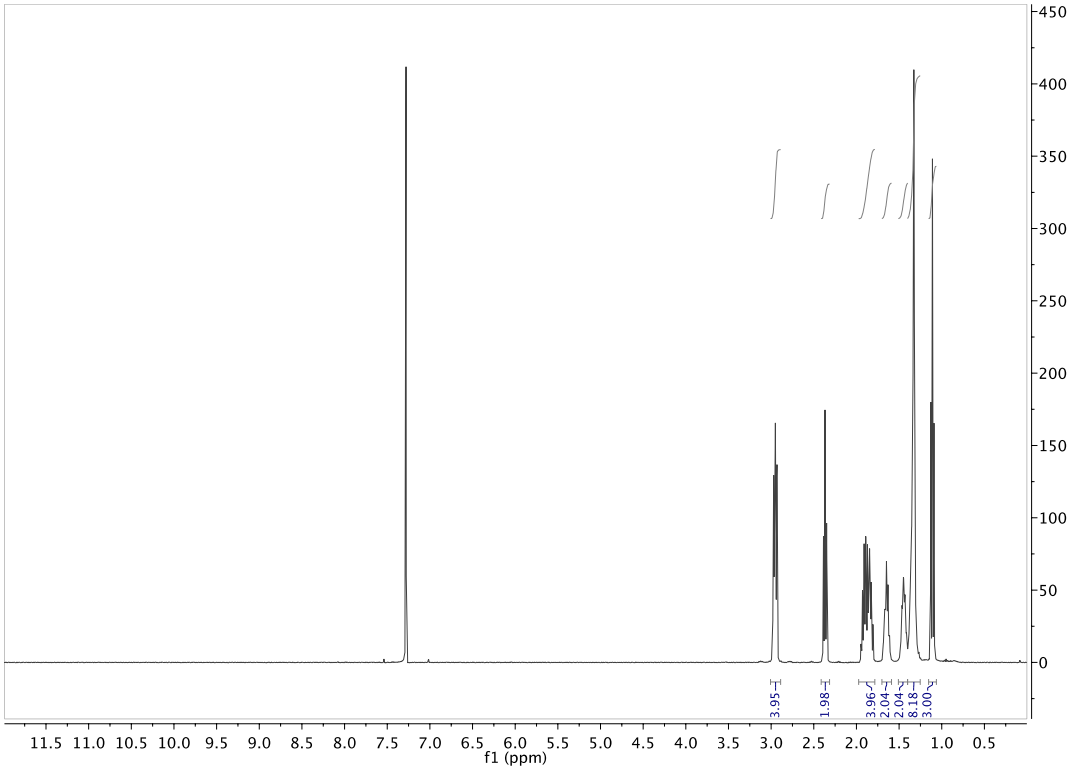



*Figure 38: $^{1}H$ NMR spectra of 10-(propylsulfonyl)decanoic acid (PSD sulfone **15**)*

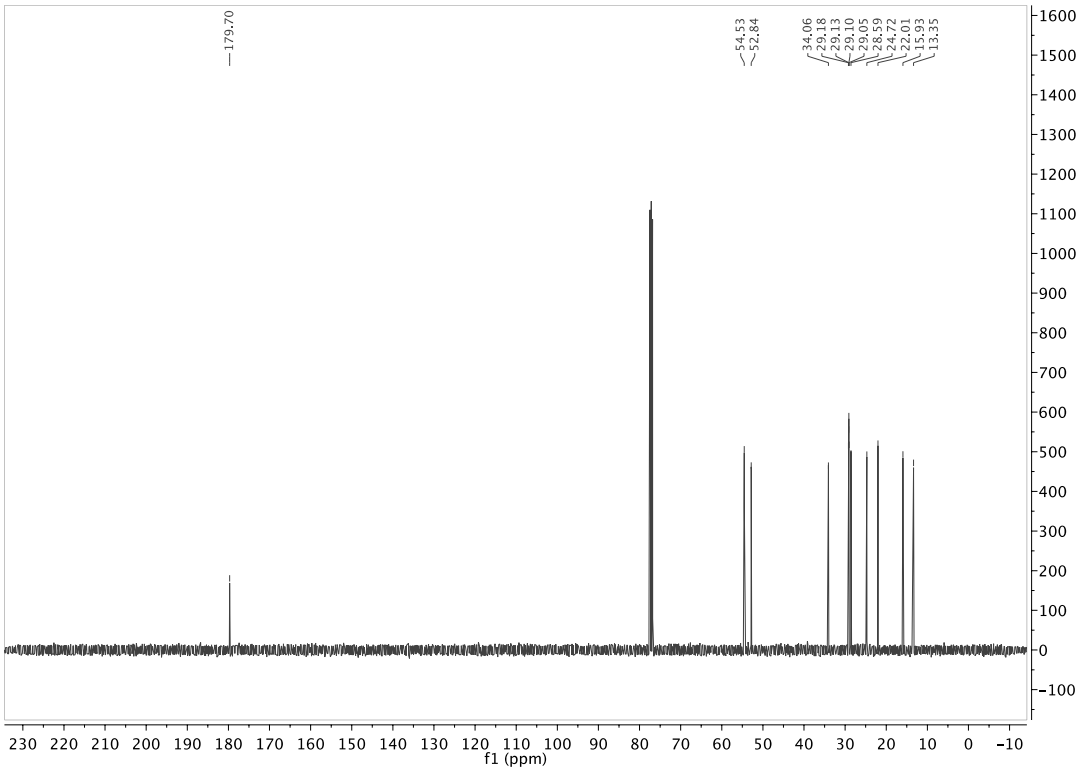



*Figure 39: $^{13}C$ NMR spectra of 10-(propylsulfonyl)decanoic acid (PSD sulfone **15**)*

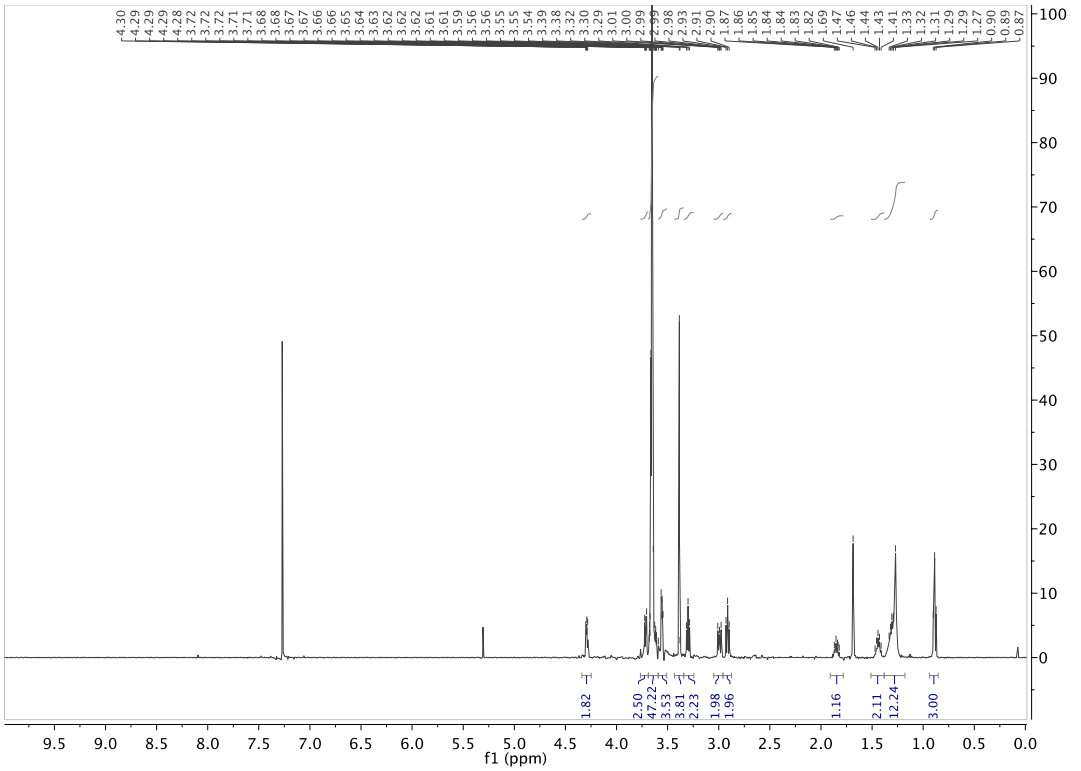



*Figure 40: $^{1}H$ NMR spectra of DSP-550-M*

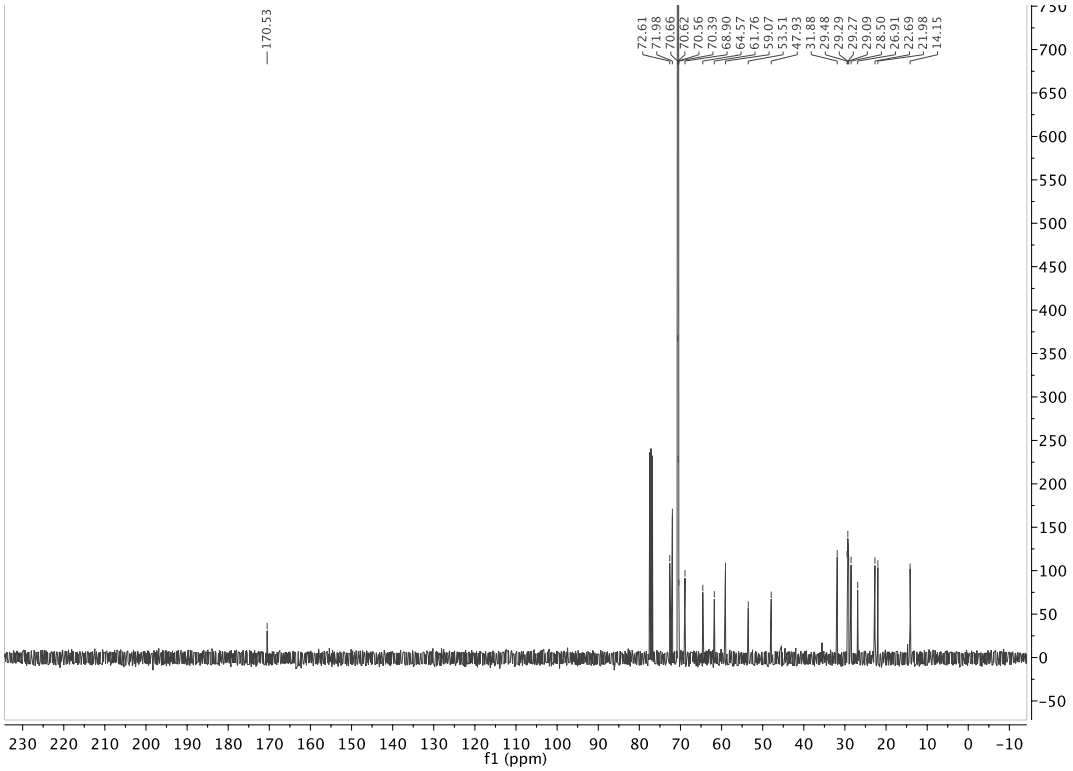



*Figure 41: $^{13}C$ NMR spectra of DSP-550-M*

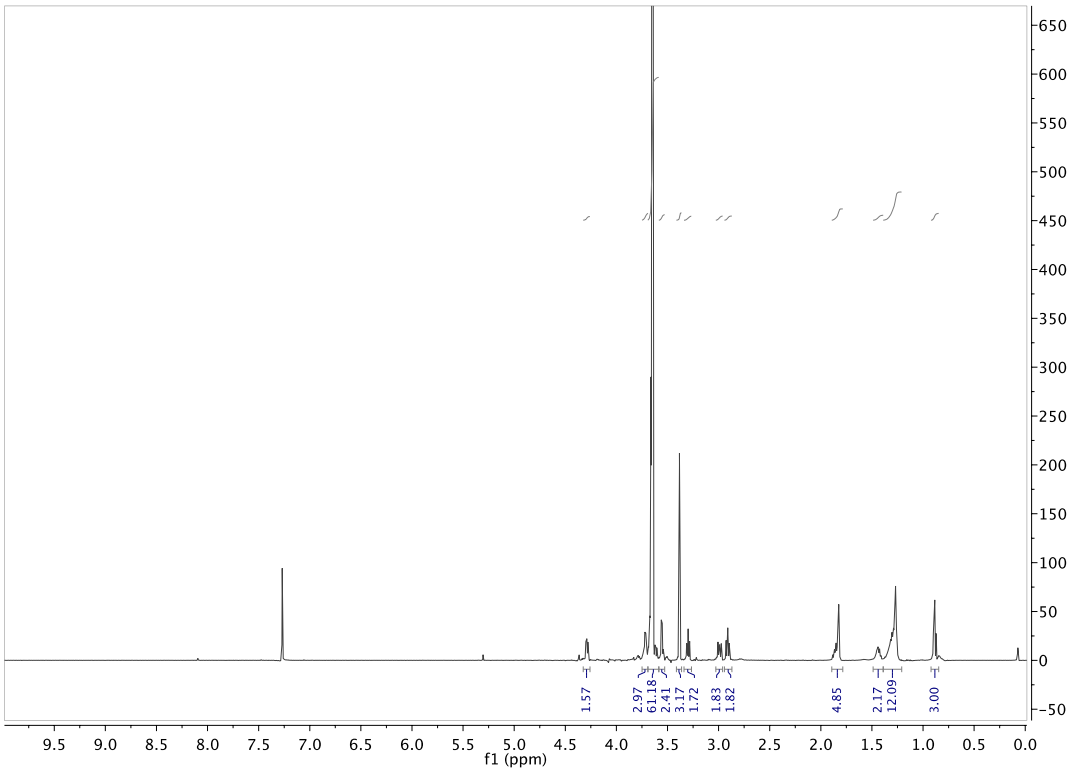



*Figure 42: $^{1}H$ NMR spectra of DSP-750-M*

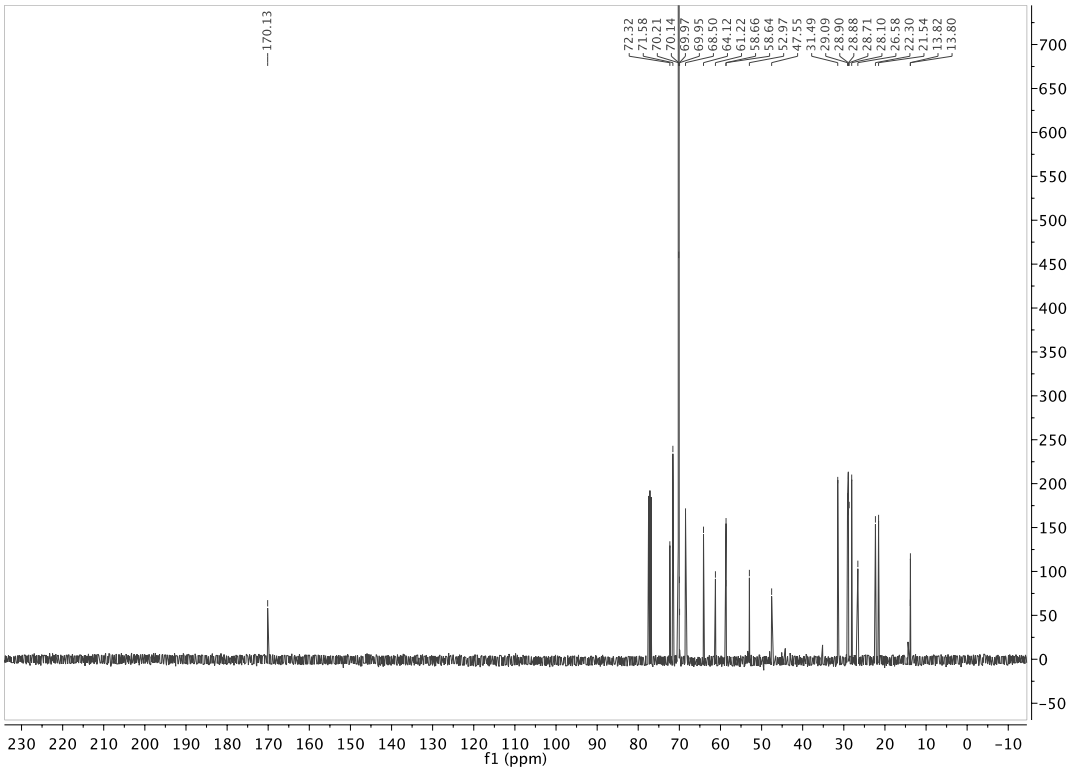



*Figure 43: [13]C NMR Spectra of DSP-750-M*

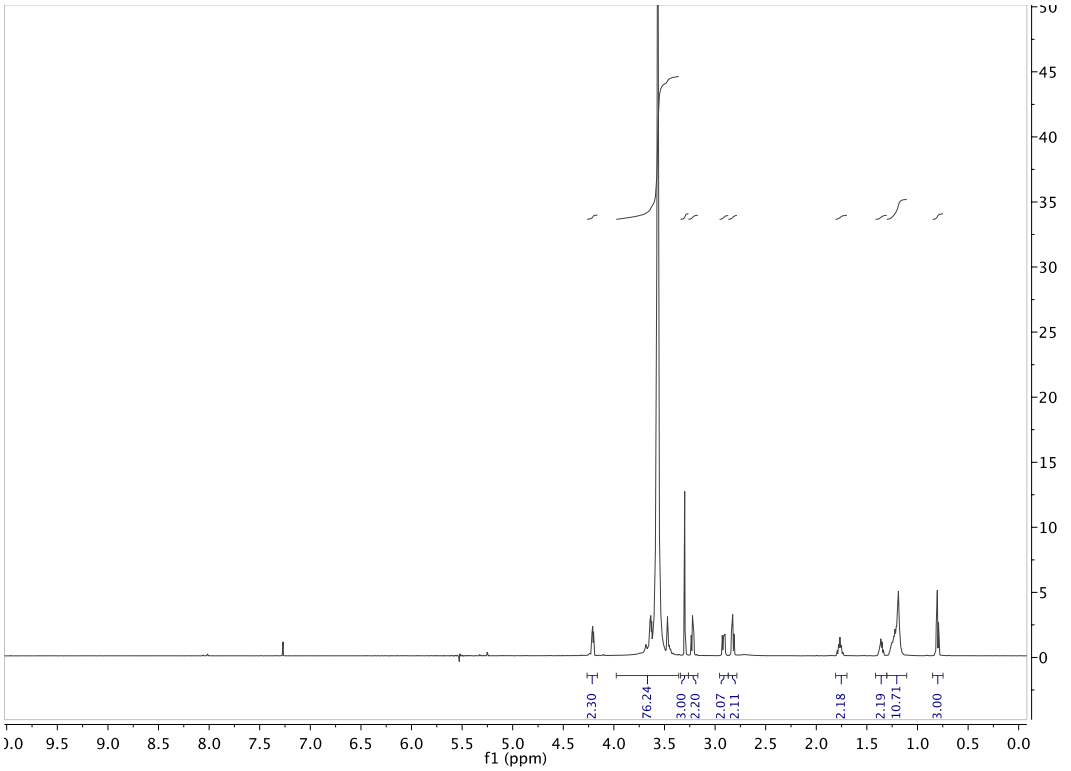



*Figure 44: [1]H NMR spectra of DSP-1000-M*

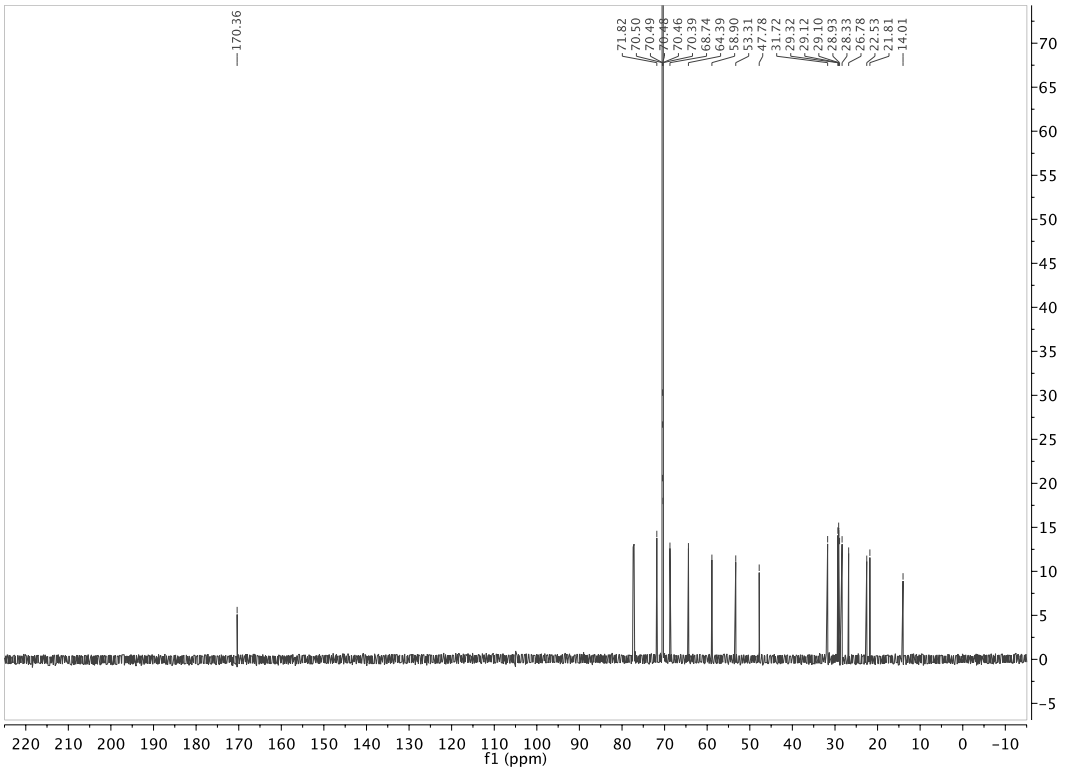



*Figure 45: $^{13}C$ NMR spectra of DSP-1000-M*

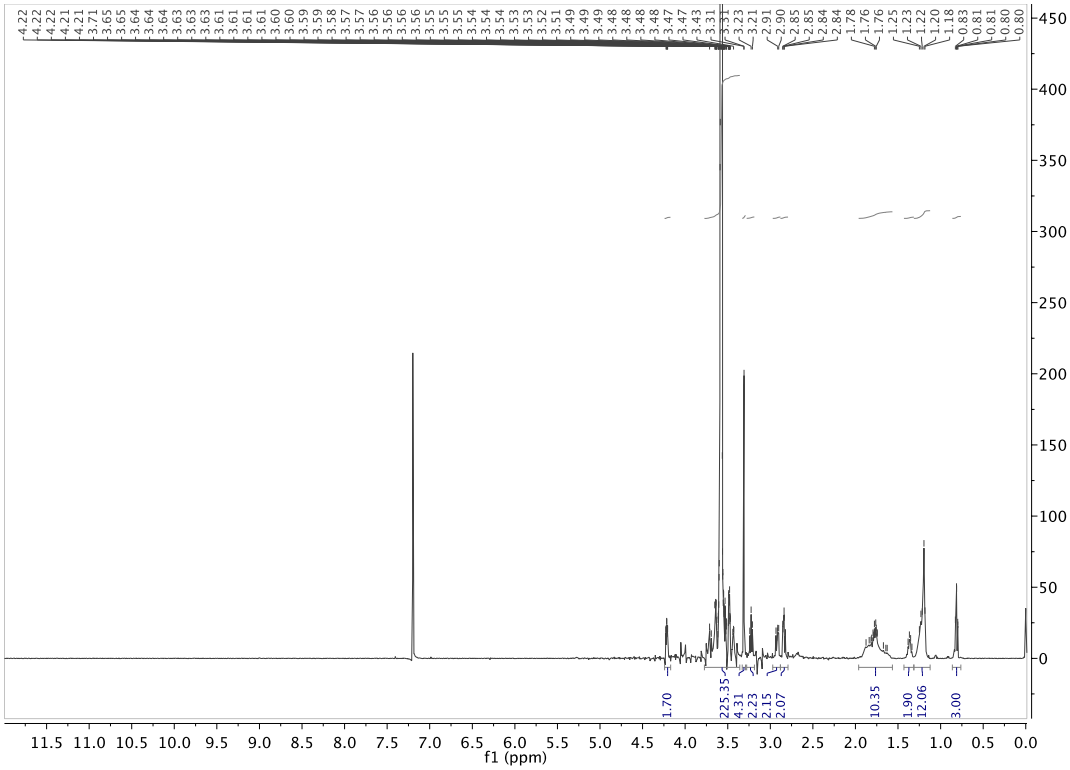



*Figure 46: $^{1}H$ NMR spectra of DSP-2000-M*

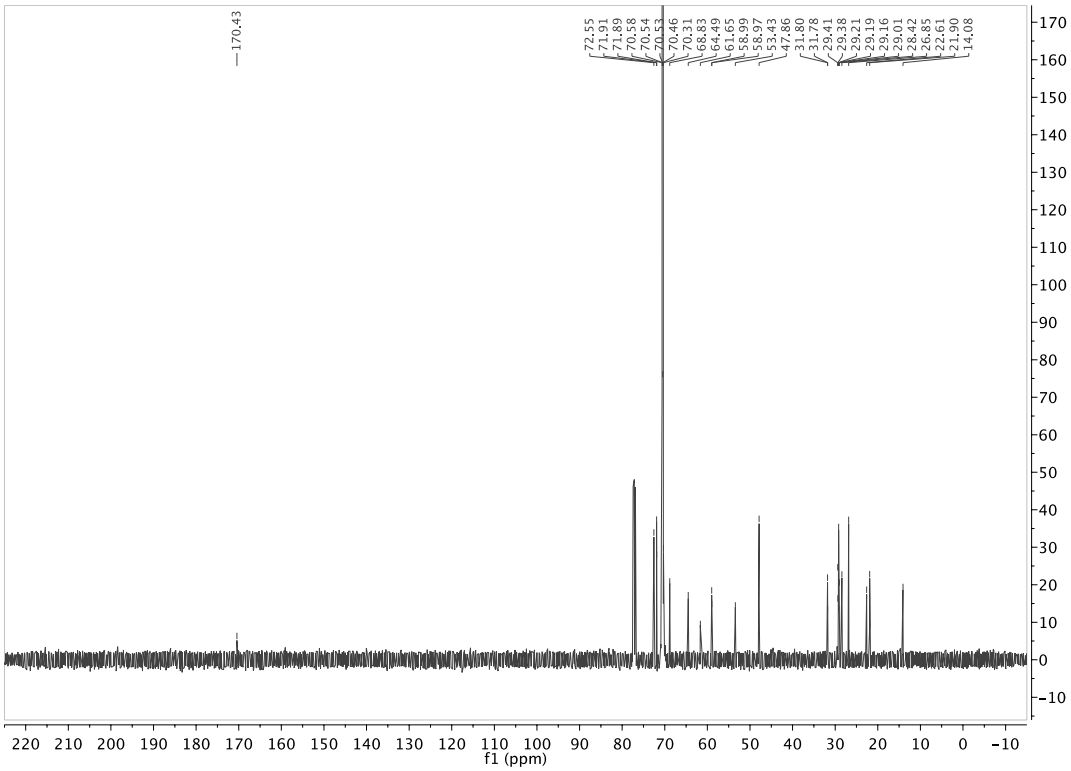



*Figure 47: $^{13}C$ NMR spectra of DSP-2000-M*

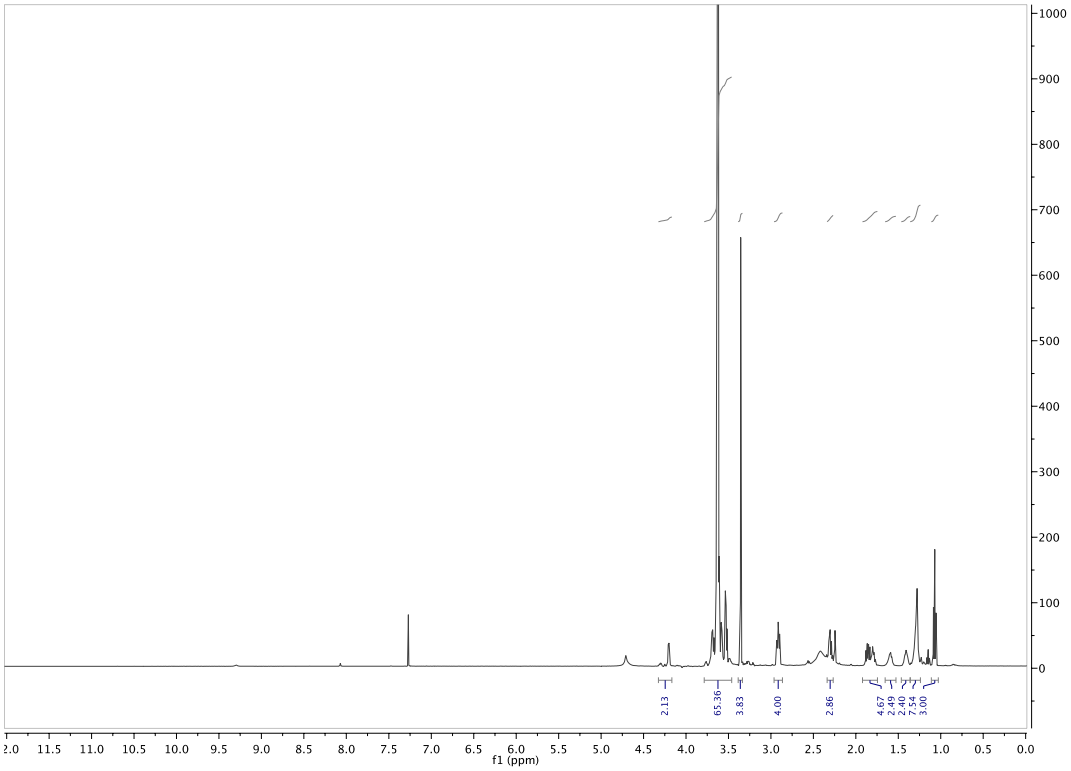



*Figure 48: $^{1}H$ NMR spectra of PSD-550-M*

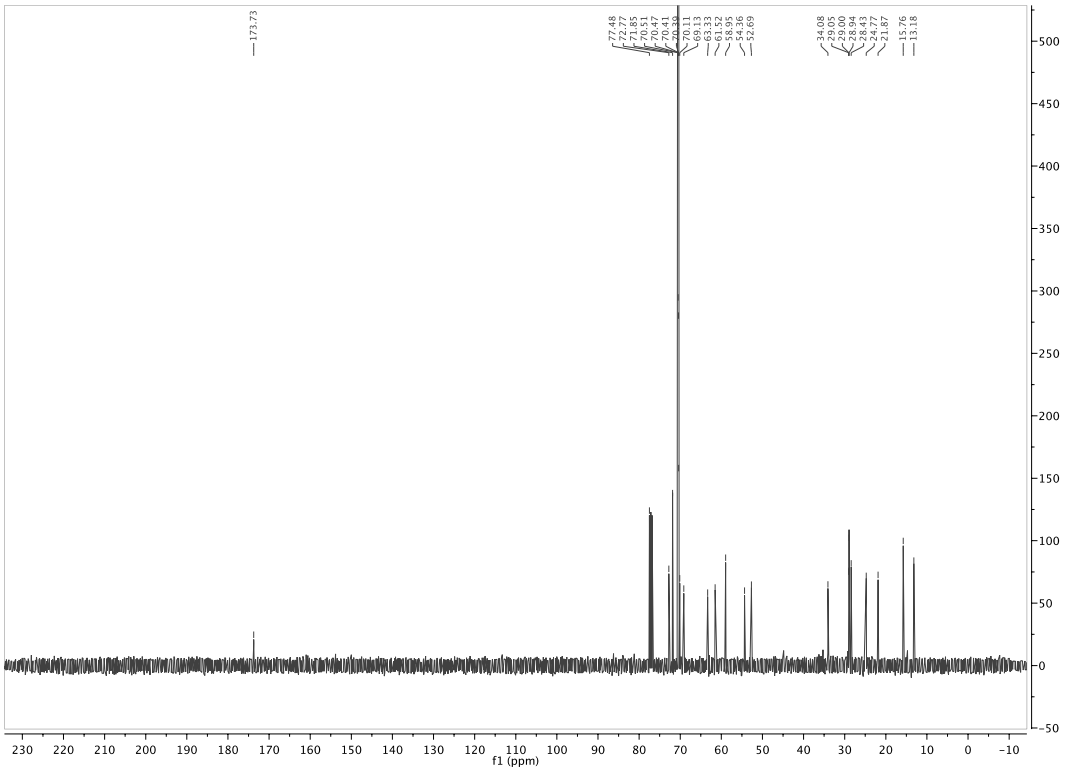



*Figure 49: $^{13}C$ NMR spectra of PSD-550-M*

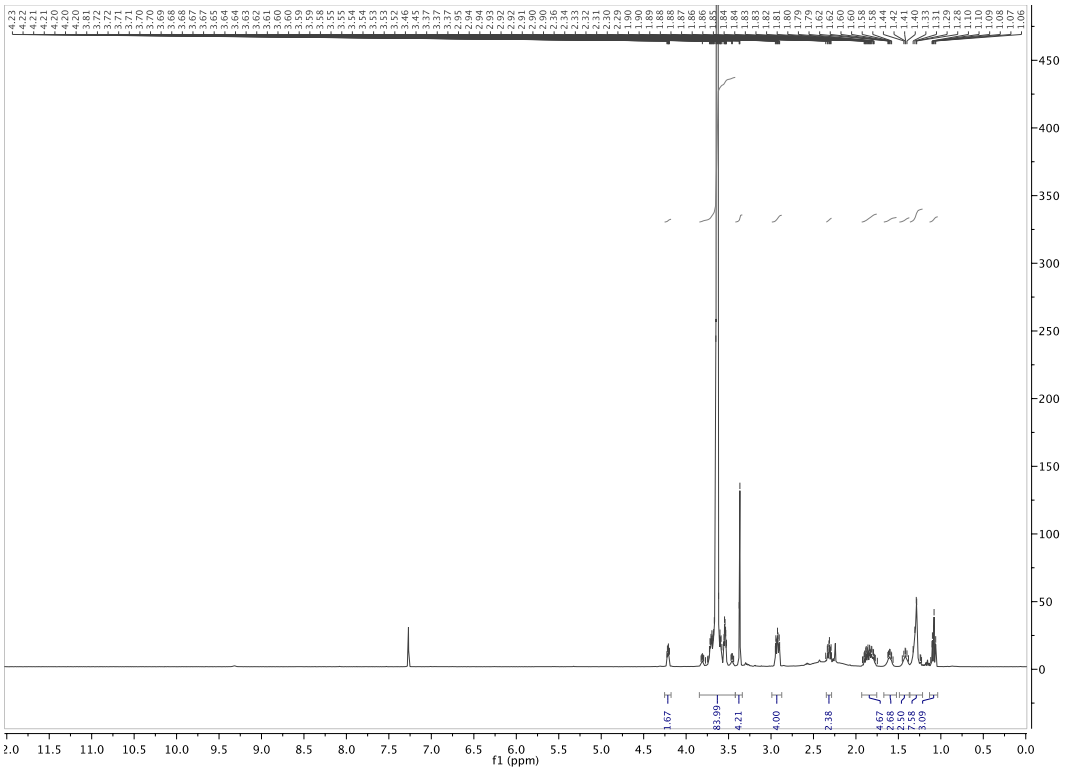



*Figure 50: $^{1}H$ NMR spectra of PSD-750-M*

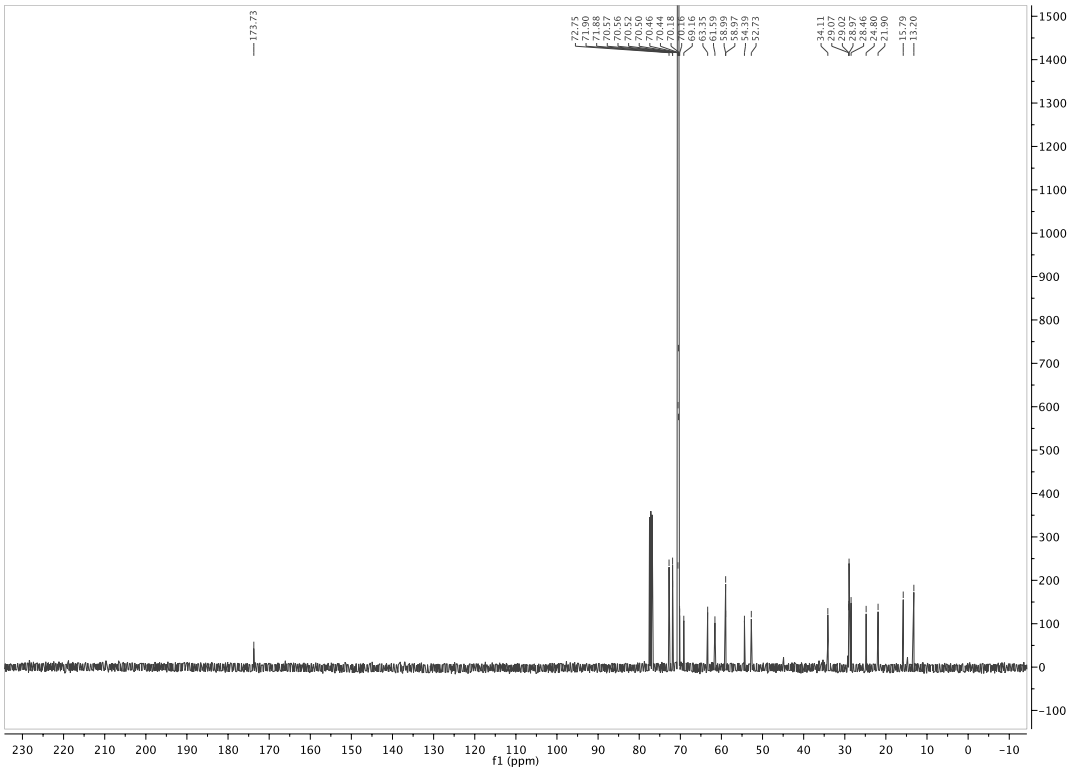



*Figure 51: $^{13}C$ NMR spectra of PSD-750-M*

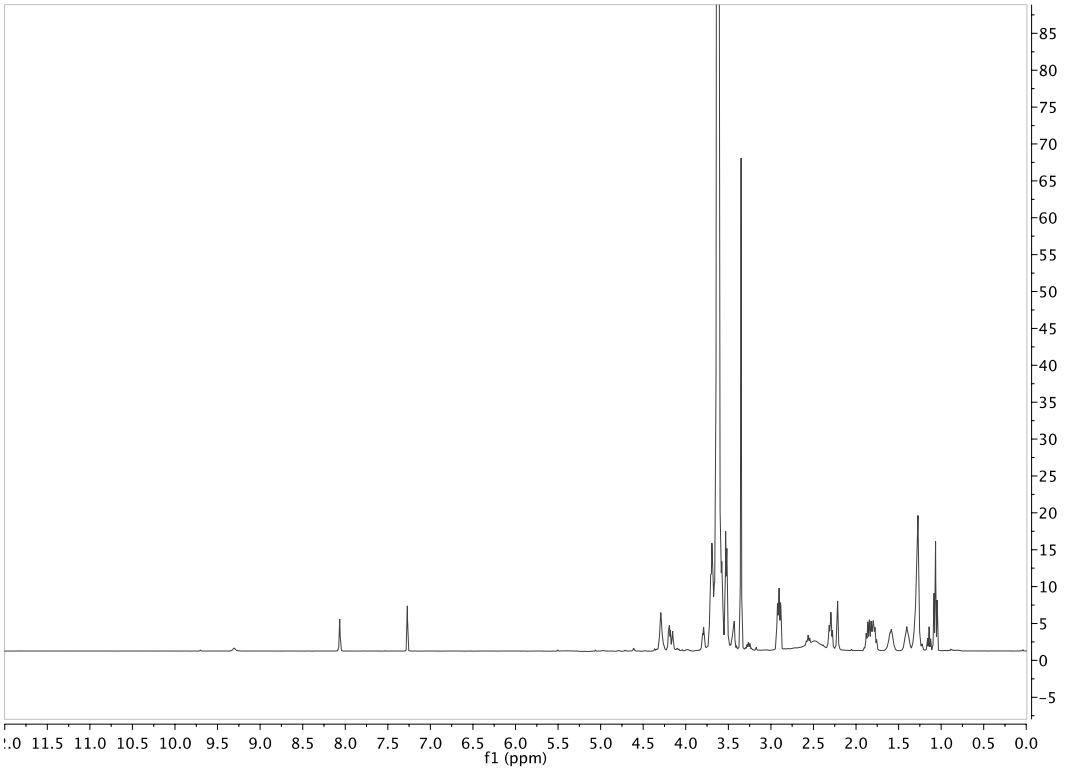



*Figure 52: 1H NMR spectra of PSD-1000-M – **MC-1***

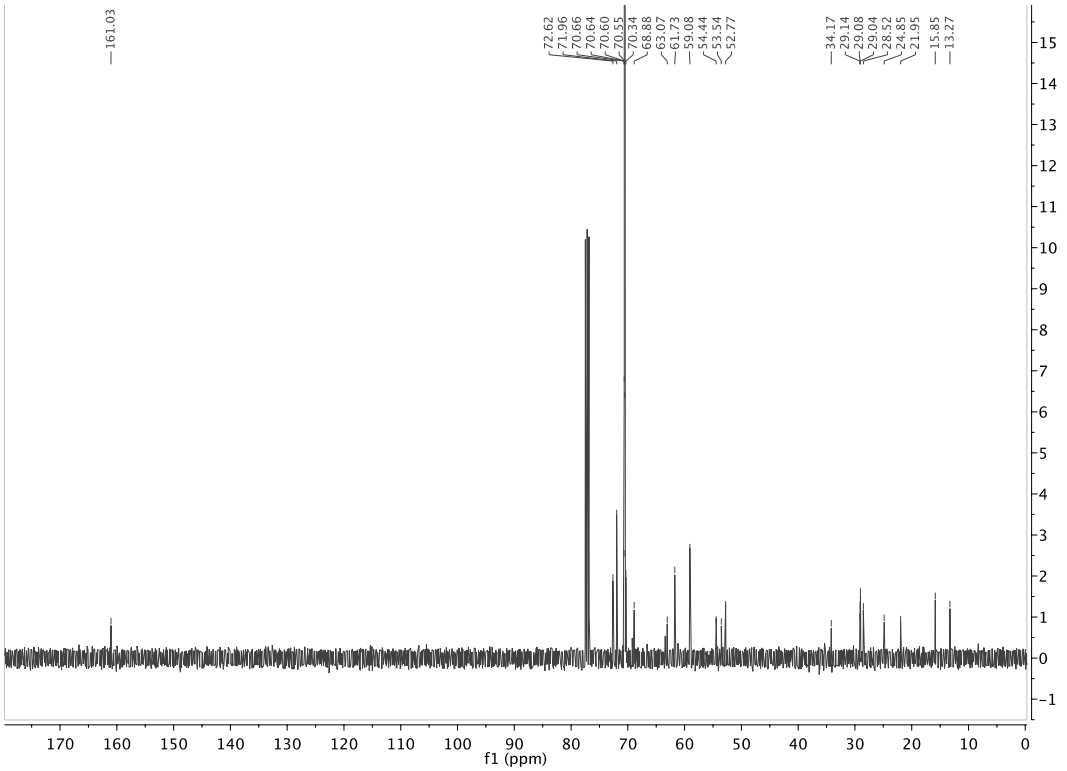



*Figure 53: 13C NMR spectra of PSD-1000-M – **MC-1***

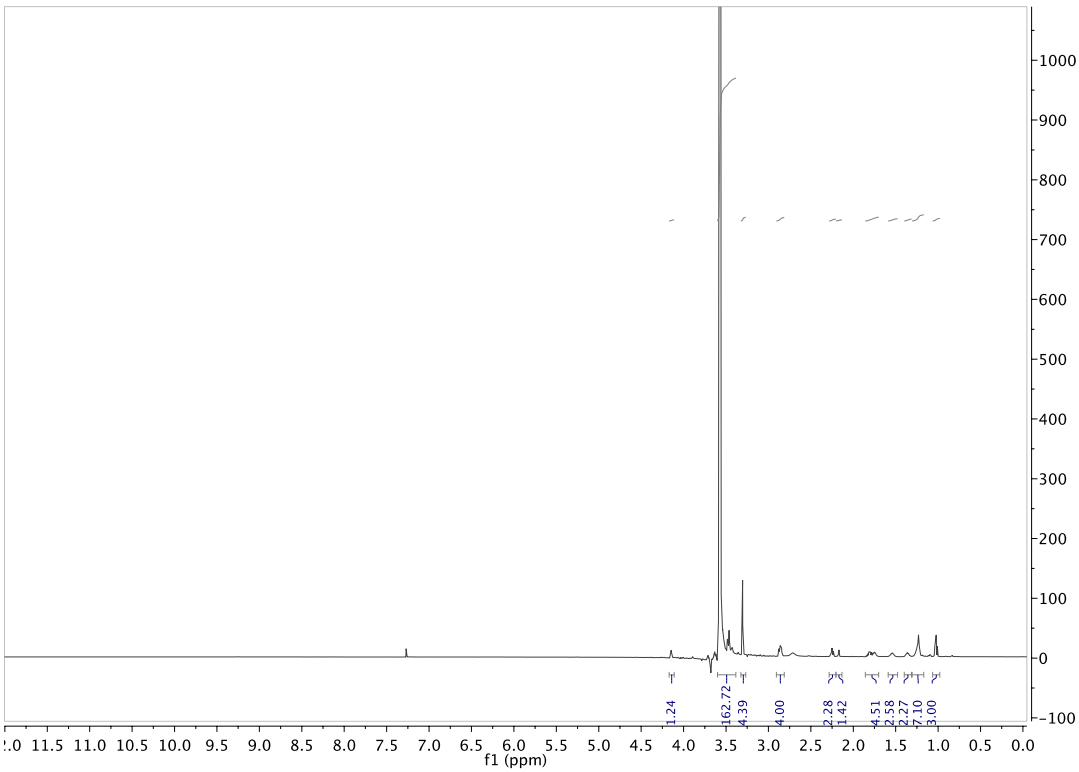



*Figure 54: [1]H NMR spectra of PSD-2000-M*

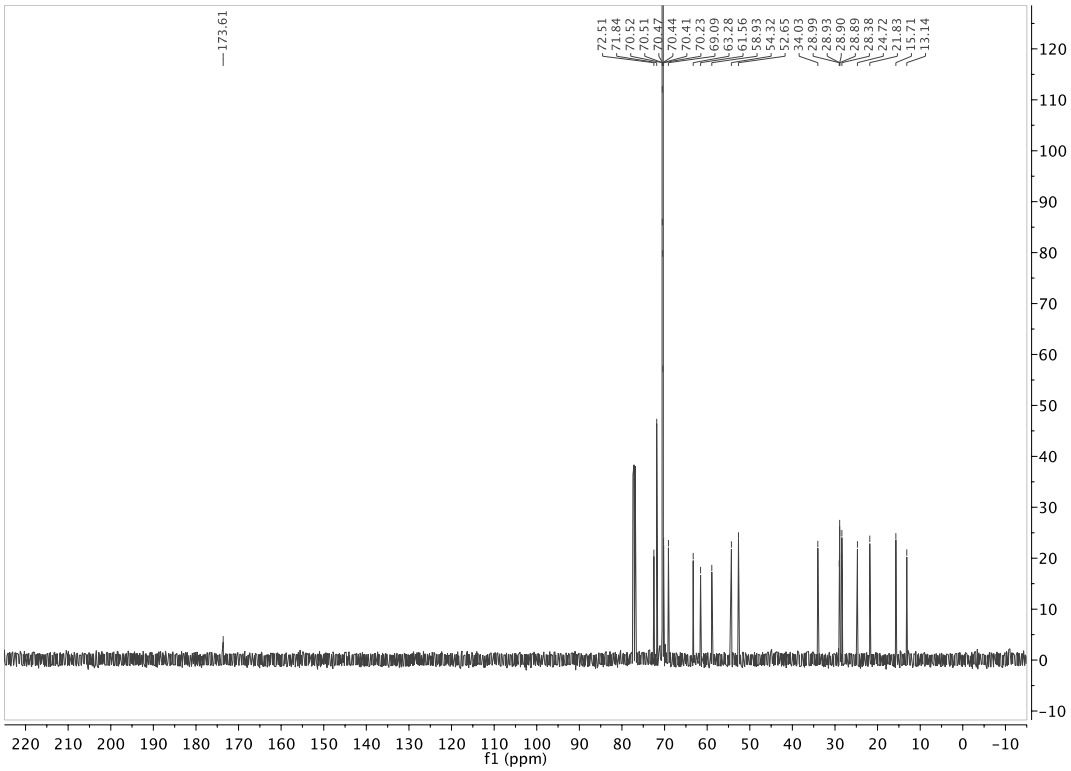



*Figure 55: $^{13}C$ NMR spectra of PSD-2000-M*