Supporting Information
Chemical Communications

β-Strand mimics based on tetrahydropyridazinedione (tpd) peptide stitching

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SYNTHETIC PROCEDURES

General notes. Unless stated otherwise, reactions were performed in flame-dried glassware under a positive pressure of argon or nitrogen gas using dry solvents. Commercial grade reagents and solvents were used without further purification except where noted. Diethyl ether, toluene, dimethylformamide dichloromethane, and tetrahydrofuran were purified by a Glass Contour column-based solvent purification system. Other anhydrous solvents were purchased directly from chemical suppliers. Thin-layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed using silica gel (60 μm particle size). The purity of all compounds was judged by TLC analysis (single spot/two solvent systems) using a UV lamp, CAM (ceric ammonium molybdate), ninhydrin, or basic $KMnO_4$ stain(s) for detection purposes. NMR spectra were recorded on a 400 MHz spectrometer. Proton chemical shifts are reported as δ values relative to residual signals from deuterated solvents ($CDCl_3$ or DMSO-d_6).

Solution-phase synthesis of acyclic dipeptide amides. Hydrazino acid derivative **5** or **6**[1] was dissolved in neat *i*$BuNH_2$ or 7N NH_3/MeOH and stirred in a sealed tube at 50 °C. After TLC indicated completion of the reaction (24 - 48 h), the solution was concentrated to dryness under vacuum. The intermediate hydrazino amide (0.386 mmol) was then directly treated with 2,4,6-collidine (2.31 mmol) and Fmoc-D-Asp(Me)-Cl[1] (0.771 mmol) in 10 mL of THF at rt. After stirring for 18 h, the reaction was diluted with EtOAc and washed with 1 M aq. HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel flash chromatography (EtOAc/hexanes) to give the product as a white solid.

Synthesis of Fmoc-(D)Asp(Me)-(*N*-NHBoc)Ala-NH_2 (7). Yield over 2 steps = 23%; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.25 (bs, 0.4H), 7.79 (s, 1H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 7.4 Hz, 2H), 7.40 (t, J=7.4 Hz, 2H), 7.30 (t, J=7.4 Hz, 2H), 6.98 (bs, 0.6H), 6.05 (s, 0.5H), 5.71 (m, 1.5H), 5.05 (m, 1H), 4.82 (m, 0.6H), 4.62 (m, 0.4H), 4.30 (m, 2H), 4.17 (t, J = 7.1 Hz, 1H), 3.73-3.61 (m, 3H), 3.03-2.55 (m, 2H), 1.48 (s, 9H), 1.40 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 174.3, 173.8, 173.1, 172.2, 170.8, 156.6, 155.5, 155.3, 144.0, 143.7, 141.4, 127.9, 127.2, 125.2, 120.1, 83.7, 82.7, 67.6, 67.3, 58.7, 57.3, 52.3, 52.2 48.1, 47.2, 47.1, 46.8, 38.2, 36.1, 28.2, 14.3, 13.1; HRMS (ESI-TOF) *m/z* $[M + H]^+$cald for $C_{28}H_{35}N_4O_8$ 555.2449, found 555.2469.

Fmoc-(D)Asp(Me)-(*N*-NHBoc)Phe-NH*i*Bu (8). Yield over 2 steps = 63%; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.26 (s, 0.2H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.57 (dd, *J* = 7.4, 2.9 Hz, 2H), 7.40 (dd, *J* = 9.7, 5.0 Hz, 2H), 7.35 – 7.17 (m, 7H), 6.99 (s, 0.7H), 6.79 (s, 0.7H), 5.78 (d, *J* = 8.8 Hz, 0.7H), 5.46 (d, *J* = 8.3 Hz, 0.3H), 5.25 (d, *J* = 9.3 Hz, 0.3H), 5.01 (m, 0.7H), 4.89 (m, 0.3H), 4.44 – 4.13 (m, 4H), 3.69 (s, 2H), 3.51 (s, 1H), 3.28 (m, 1.5H), 3.13 – 2.76 (m, 3.5H), 2.57 (dd, *J* = 15.5, 7.9 Hz, 1H), 1.65 (m, 1H), 1.49 (s, 3H), 1.44 (s, 6H), 0.88 (d, *J* = 6.4 Hz, 2H), 0.83 – 0.74 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 173.0, 170.6, 168.3, 155.7, 155.6, 143.8, 143.6, 141.2, 137.6, 137.2, 129.2, 128.9, 127.8, 127.1, 127.1, 125.1, 120.0, 83.2, 67.4, 67.2, 67.0, 52.1, 48.2, 47.0, 38.1, 36.5, 34.7, 33.5, 28.3, 28.0, 20.0, 20.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$cald for $C_{38}H_{47}N_4O_8$ 687.3388, found 687.3409.

[1] Kang, C.; Ranatunga, S.; Sarnowski M. P.; Del Valle J. R. *Org. Lett.* **2014**, *16*, 5434.

Fmoc-(D)Asp(Me)-(*N*-NHBoc)Ala-NH*i*Bu (9). Yield over 2 steps = 66%; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.19 (bs, 0.3H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 6.61 (bs, 0.3H), 5.85 and 5.42 (2m, 1H), 5.12 – 5.01 (m, 1H), 4.87 (d, *J* = 7.4 Hz, 0.6H), 4.69 (d, *J* = 7.5 Hz, 0.4H), 4.33 (d, *J* = 7.9 Hz, 2H), 4.21 (m, 1H), 3.70 and 3.68 (2s, 3H), 3.11 – 2.67 (m, 4H), 1.74 (m, 1H), 1.48 (s, 9H), 1.41 (d, *J* = 7.2 Hz, 3H), 0.84 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 173.7, 172.0, 171.1, 170.7, 170.3, 156.2, 155.4, 155.0, 143.6, 141.2, 127.81, 127.66, 127.1, 125.1, 125.0, 120.0, 120.0, 83.4, 82.5, 67.5, 67.2, 58.9, 58.8, 52.3, 52.1, 52.0, 48.2, 48.0, 47.0, 38.4, 36.2, 28.3, 28.0, 20.1, 20.0,f 14.6, 13.3; HRMS (ESI-TOF) *m/z* $[M + H]^+$cald for $C_{32}H_{43}N_4O_8$ 611.3075, found 611.3076.

Solution-phase synthesis of tpd dipeptide amides. The dipeptide amides above were treated with 2-5 mL of 4N HCl/dioxane and stirred at rt for 5 h. After removing volatiles under vacuum, the residue was taken up in 5 mL of toluene and heated at 100 °C for 3 h. The reaction was cooled to rt and stirred for 12 h. The volatiles were removed under vacuum and the residue purified by silica gel flash chromatography ($CHCl_3$/MeOH) to give the product as an off white solid.

Fmoc-tpd-Ala-NH$_2$ (10). Yield over 2 steps = 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 6.0 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.31 – 7.24 (m, 4H), 6.47 (d, *J* = 35.0 Hz, 2H), 5.90 (d, *J* = 5.8 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 4.61 (s, 1H), 4.37 (s, 2H), 4.22 – 4.12 (m, 1H), 2.94 (m, 1H), 2.52 (m, 1H), 1.44 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 168.0, 166.6, 155.9, 143.7, 143.5, 141.2, 127.8, 127.1, 125.0, 120.0, 67.3, 52.7, 48.0, 47.0, 34.5, 15.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$cald for $C_{22}H_{23}N_4O_5$ 423.1663, found 423.1663.

Fmoc-tpd-Phe-NH*i*Bu (11). Yield over 2 steps = 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.23 (m, 5H), 7.20 (d, *J* = 7.3 Hz, 2H), 6.18 (t, *J* = 5.7 Hz, 1H), 5.53 (m, 2H), 4.46 (m, 1H), 4.37 (d, *J* = 7.3 Hz, 2H), 4.17 (t, *J* = 6.9 Hz, 1H), 3.30 – 3.15 (m, 2H), 3.10 (dt, *J* = 13.4, 6.6 Hz, 1H), 3.06 – 2.95 (m, 1H), 2.73 (dd, *J* = 15.4, 4.6 Hz, 1H), 1.80 – 1.65 (m, 1H), 1.35 – 1.22 (m, 1H), 0.89 – 0.84 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 167.2, 166.4, 155.6, 143.6, 141.3, 134.6, 129.2, 128.9, 127.8, 127.6, 127.1, 125.0, 120.0, 67.2, 56.7, 48.0, 47.0, 47.0, 35.9, 34.4, 28.3, 20.0, 19.9; HRMS (ESI-TOF) *m/z* $[M + H]^+$cald for $C_{32}H_{35}N_4O_5$ 555.2602, found 555.2589.

Fmoc-tpd-Ala-NH*i*Bu (12). Yield over 2 steps = 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 6.4 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.31 (td, *J* = 7.5, 0.9 Hz, 2H), 6.14 (t, *J* = 5.9 Hz, 1H), 5.79 (d, *J* = 5.4 Hz, 1H), 5.25 (m, 1H), 4.59 (d, *J* = 13.9 Hz, 1H), 4.42 (d, *J* = 4.8 Hz, 2H), 4.22 (t, *J* = 6.9 Hz, 1H), 3.17 – 2.95 (m, 3H), 2.57 – 2.40 (m, 1H), 1.83 – 1.70 (m, 1H), 1.48 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 167.0, 165.9, 155.7, 143.7, 143.6, 141.3, 127.8, 127.1, 125.1, 120.2, 67.3, 67.1, 52.3, 48.0, 47.1, 46.9, 34.9, 29.7, 28.3, 20.0, 19.9 15.8; HRMS (ESI-TOF) *m/z* $[M + H]^+$cald for $C_{26}H_{31}N_4O_5$ 479.2289, found 479.2284.

Solid-phase synthesis of tpd-constrained β-strand mimics. Solid-phase peptide synthesis was carried out on Fmoc-capped polystyrene rink amide MBHA resin (59 μmol/g loading, 100-200 mesh, 0.1 mmol scale). The following side-chain protected amino acid derivatives suitable for Fmoc SPPS were used: Fmoc-Tyr(tBu)-OH, Fmoc-Ala-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Trp(Boc)-OH. Dry resin was washed with DMF 3x and

allowed to swell in DMF for 2 h prior to use. All reactions were carried out using gentle agitation. Fmoc deprotection steps were carried out by treating the resin with a solution of 20% piperidine/DMF at 50 °C (15 min x 2). Coupling of Fmoc-protected amino acids as well as (*N*'-Boc)-hydrazino acids was effected using 5 equiv. HATU (0.5 M in DMF), 10 equiv. DIEA (1.0 M in DMF), and 5 equiv. of the carboxylic acid in 5:1 DMF:DCM at 50 °C (1 h x 2). Coupling of the D-Asp subunit to the resin-bound Boc-hydrazine was carried out with 9 equiv. collidine and 3 equiv. of Fmoc-D-Asp(Me)-Cl[1] in THF at 50 °C (1 h x 3). Acetylation of the peptide N-terminus was carried out using 10 equiv. of Ac_2O and 20 equiv. of pyridine in DCM at rt (1 h x 2). After each reaction the resin was washed with DMF 3x, DCM 2x, then DMF 1x. Prior to cleavage, the resin was washed with MeOH 5x and dried thoroughly under vacuum. Compounds were cleaved by incubating the dried resin in 2 mL of 95:5 TFA:H_2O at rt for 4 h. The cleavage mixture was filtered and the resin was rinsed with an additional 1 mL of cleavage solution. The filtrate was concentrated to remove the bulk of the TFA and the remaining residue was treated with 8 mL of cold Et_2O to induce precipitation. The mixture was centrifuged and the supernatant was removed. The remaining solid was washed 2 more times with Et_2O and dried under vacuum. The crude peptides were purified by RP-HPLC on a C8 semi-preparative column using linear gradients of MeCN in 0.1% aq. formic acid, then lyophilized to afford white powders. All peptides were characterized by LCMS (ESI), HRMS (ESI-TOF), and ^{1}H NMR.

Ac-tpd-Ala-tpd-Phe-Tyr-NH_2 (13). Overall yield = 14%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (bs, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 7.6 Hz, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.36 (s, 1H), 7.25 – 7.09 (m, 5H), 7.02 (s, 1H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.58 (d, *J* = 8.5 Hz, 2H), 5.39 (dd, *J* = 11.9, 4.6 Hz, 1H), 4.96 (q, *J* = 7.1 Hz, 1H), 4.59 (ddd, *J* = 13.9, 7.9, 4.8 Hz, 1H), 4.46 (ddd, *J* = 14.5, 7.7, 4.7 Hz, 1H), 4.30 (dd, *J* = 14.1, 8.0 Hz, 1H), 3.20 (dd, *J* = 14.5, 4.4 Hz, 1H), 3.03 (dd, *J* = 14.2, 12.3 Hz, 1H), 2.85 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.74 – 2.54 (m, 2H), 2.37 (dd, *J* = 15.3, 4.8 Hz, 1H), 2.07 (dd, *J* = 15.1, 4.6 Hz, 1H), 1.82 (s, 3H), 1.34 (t, *J* = 14.8 Hz, 1H), 1.22 (d, *J* = 7.1 Hz, 3H); HRMS (ESI-TOF) m/z [M + H]+ calcd for $C_{31}H_{37}N_8O_9$ 665.2678, found 665.2661.

Ac-tpd-Ala-tpd-Ala-Tyr-NH_2 (14). Overall yield = 21%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, *J* = 7.8 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 2H), 7.35 (s, 1H), 7.04 (s, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 5.06 (q, *J* = 7.1 Hz, 1H), 4.97 (q, *J* = 7.1 Hz, 1H), 4.79 – 4.47 (m, 2H), 4.28 (dd, *J* = 14.0, 8.1 Hz, 1H), 2.97 – 2.61 (m, 4H), 2.46 – 2.37 (m, 2H), 1.87 (s, 3H), 1.34 (d, *J* = 7.4 Hz, 3H), 1.32 (d, *J* = 7.2 Hz, 3H); HRMS (ESI-TOF) m/z [M + H]+ calcd for $C_{25}H_{33}N_8O_9$ 589.2365, found 589.2356.

H-Leu-tpd-Phe-tpd-Leu-Asn-NH_2 (15). Overall yield = 16%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, *J* = 7.8 Hz, 1H), 8.44 – 8.38 (m, 2H), 8.18 (s, 1H), 7.42 (s, 1H),), 7.29 – 7.16 (m, 5H), 7.07 (s, 1H), 6.95 (s, 1H), 5.58 (dd, *J* = 11.8, 4.9 Hz, 1H), 5.08 (dd, *J* = 11.1, 4.1 Hz, 1H), 4.86 – 4.70 (m, 1H), 4.60 – 4.49 (m, 1H), 4.44 (dd, *J* = 13.5, 7.9 Hz, 1H), 3.61 (d, *J* = 3.2 Hz, 1H), 3.51 (dd, *J* = 13.8, 8.0 Hz, 1H), 3.31 (dd, *J* = 14.4, 4.6 Hz, 1H), 3.10 (dd, *J* = 14.0, 12.2 Hz, 1H), 2.73 (m, 1H), 2.66 (dd, *J* = 35.1, 5.7 Hz, 1H), 2.55 (dd, *J* = 24.7, 5.2 Hz, 1H), 2.54 – 2.49 (m, 1H), 2.36 (dd, *J* = 15.2, 8.0 Hz, 1H), 2.17 (dd, *J* = 14.9, 4.5 Hz, 1H), 1.83 – 1.74 (m, 1H), 1.70 – 1.55 (m, 2H), 1.47 – 1.20 (m, 3H), 0.90 – 0.79 (m, 12H); HRMS (ESI-TOF) m/z [M + H]+ calcd for $C_{33}H_{49}N_{10}O_9$ 729.3679, found 729.3680.

H-Leu-tpd-Ile-tpd-Leu-Asp-NH_2 (16). Overall yield = 15%; ^{1}H NMR (400 MHz, DMSO- d_6) δ 9.13 (d, *J* = 7.8 Hz, 1H), 8.52 (d, *J* = 6.9 Hz, 1H), 8.42 (d, *J* = 7.6 Hz, 1H), 8.24 (s, 1H), 7.22 (s, 1H), 7.06 (s, 1H), 5.04 – 4.96 (m, 1H), 4.96 (d, *J* = 10.4 Hz, 1H), 4.85 – 4.74 (m, 1H), 4.71 – 4.58 (m, 1H), 4.41 (dd, *J* = 13.5, 6.7 Hz, 1H), 3.43 (dd, *J* = 8.7, 5.2 Hz, 1H), 2.86 – 2.56 (m, 3H), 2.55 – 2.37 (m, 2H), 2.12 – 2.00 (m, 1H), 1.86 – 1.75 (m, 1H), 1.74 – 1.61 (m, 2H), 1.51 – 1.27 (m, 4H), 1.09 – 0.98 (m, 1H), 0.91 – 0.75 (m, 18H); HRMS (ESI-TOF) m/z [M + H]+ calcd for $C_{30}H_{50}N_9O_{10}$ 696.3675, found 696.3680.

H-Leu-tpd-Leu-tpd-Leu-Glu-NH_2 (17). Overall yield = 13%; ^{1}H NMR (400 MHz, DMSO- d_6) δ 8.65 (d, *J* = 7.9 Hz, 1H), 8.57 (d, *J* = 7.2 Hz, 1H), 8.32 (d, *J* = 7.3 Hz, 1H), 8.22 (s, 1H), 7.27 (s, 1H), 7.04 (s, 1H), 5.10 (dd, *J* = 11.1, 3.9 Hz, 1H), 4.98 (d, *J* = 10.9 Hz, 1H), 4.81 – 4.65 (m, 2H), 4.14 – 4.03 (m, 1H), 3.52 – 3.43 (m, 1H), 2.83 – 2.62 (m, 2H), 2.46 – 2.35 (m, 2H), 2.26 – 2.08 (m, 2H), 1.92 – 1.80 (m, 3H), 1.79 – 1.65 (m, 2H), 1.64 – 1.54 (m, 2H), 1.52 – 1.29 (m, 4H), 0.90 – 0.80 (m, 18H); HRMS (ESI-TOF) m/z [M + H]+ calcd for $C_{31}H_{52}N_9O_{10}$ 710.3831, found 710.3831.

H-Leu-tpd-Val-tpd-Val-Gln-NH_2 (18). Overall yield = 11%; ^{1}H NMR (400 MHz, DMSO- d_6) δ 9.05 (d, *J* = 7.8 Hz, 1H), 8.70 (d, *J* = 7.1 Hz, 1H), 8.63 (d, *J* = 7.2 Hz, 1H), 8.19 (s, 1H), 7.39 (s, 1H), 7.29 (s, 1H), 7.03 (s, 1H), 6.77 (s, 1H), 4.88 – 4.77 (m, 2H), 4.76 – 4.66 (m, 1H), 4.13 (dd, *J* = 13.6, 7.7 Hz, 1H), 3.52 (dd, *J* = 14.2, 8.5 Hz, 1H), 2.83 (dt, *J* = 23.9, 14.7 Hz, 2H), 2.54 – 2.48 (m, 2H), 2.27 – 2.11 (m, 2H), 2.06 (dd, *J* = 8.4, 7.5 Hz, 2H), 1.90 – 1.78 (m, 1H), 1.77 – 1.63 (m, 2H), 1.54 – 1.44 (m, 1H), 1.43 – 1.32 (m, 1H), 0.95 (d, *J* = 6.2 Hz, 3H), 0.94 (d, *J* = 5.5 Hz, 3H), 0.89 – 0.79 (m, 12H); HRMS (ESI-TOF) m/z [M + H]+ calcd for $C_{29}H_{49}N_{10}O_9$ 681.3679, found 681.3670.

H-tpd-Ala-tpd-Ala-tpd-Ala-Trp-NH_2 (19). Overall yield = 11%; ^{1}H NMR (400 MHz, DMSO- d_6) δ 10.76 (s, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 8.28 (d, *J* = 8.1 Hz, 1H), 8.24 (s, 1H), 8.19 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.34 (s, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 1.4 Hz, 1H), 7.01 (d, *J* = 1.2 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 5.04 (q, *J* = 7.0 Hz, 1H), 5.04 (q, *J* = 7.0 Hz, 1H), 4.95 (q, *J* = 7.8 Hz, 1H), 4.70 – 4.62 (m, 1H), 4.62 – 4.54 (m, 1H), 4.36 (dd, *J* = 13.8, 7.5 Hz, 1H), 3.58 (dd, *J* = 12.6, 5.2 Hz, 1H), 3.52 – 3.46 (m, 1H), 3.08 (dd, *J* = 14.6, 5.8 Hz, 1H), 2.92 (dd, *J* = 14.9, 8.3 Hz, 1H), 2.74 (dd, *J* = 30.6, 15.4 Hz, 2H), 2.48 – 2.34 (m, 3H), 1.30 (d, *J* = 7.3 Hz, 3H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.25 (d, *J* = 7.1 Hz, 3H); HRMS (ESI-TOF) m/z [M + H]+ calcd for $C_{32}H_{41}N_{12}O_{10}$ 753.3063, found 753.3072.

QUANTUM MECHANICS CALUCULATIONS

All quantum calculations were performed with the Jaguar[2,3] quantum chemistry program from Schrödinger, Inc. Ramachandran-type energy surfaces of ϕ_2 vs ψ_2 dihedral angles were generated by combinatorialy fixing ϕ and ψ angles (Figure 2) at every 15° from 0° to 360°. No other constraints were imposed. The ω angle for all molecules was constructed in a trans configuration for all simulations. A relaxed coordinate scan was performed with geometry optimization and energy calculations determined at the M06-2X-D3/6-31G* level[4] with the SM6 implicit solvent model[5].

X-RAY DIFFRACTION ANALYSIS

[2] Bochevarov, A.D.; Harder, E.; Hughes, T.F.; Greenwood, J.R.; Braden, D.A.; Philipp, D.M.; Rinaldo, D.; Halls, M.D.; Zhang, J.; Friesner, R.A *Int. J. Quantum Chem.*, **2013**, *113*, 2110.
[3] Jaguar, version 8.3, Schrödinger, LLC, New York, NY, 2014.
[4] Zhao; Yan; Schultz, N.E.; Truhlar, D.G.; *J. Chem. Theory Comput*. *2*, **2006,** 2, 364.
[5] Kelly, C.P.; Cramer, C.J.; Truhlar, D.G. *J. Chem. Theory Comput*. *1,* **2005,** *6***,** 1133.

The X-ray diffraction data for **10** and **11** were measured on a Bruker D8 Venture PHOTON 100 CMOS system equipped with a Cu Kα INCOATEC Imus micro-focus source (λ = 1.54178 Å). Indexing was performed using *APEX2*[6] (Difference Vectors method). Data integration and reduction were performed using SaintPlus 6.01.[7] Absorption correction was performed by multi-scan method implemented in SADABS[8]. Space groups were determined using XPREP implemented in APEX2[6]. The structure was solved using SHELXS-97 (direct methods) and refined using SHELXL-2013[9] (full-matrix least-squares on F2) contained in APEX2[6,9], WinGX v1.70.01[9,10,11,12] and OLEX2[9,13]. Part of the molecule is disordered over two positions with 0.84:0.16 occupancy ratio (refined as FVAR 2/-2). Non-disordered atoms and those in major part of the disorder were refined anisotropically and atoms with low occupancy were refined isotropically and with geometry and isotropic displacement parameters restraints. Hydrogen atoms of –NH groups have been found from difference Fourier map and were refined freely or with Uiso(H) = 1.2Ueq(-NH). Hydrogen atoms of –CH, -CH2 and -CH3 groups were placed in geometrically calculated positions and included in the refinement process using riding model with isotropic thermal parameters: Uiso(H) = 1.2(1.5)Ueq(-CH,-CH2(-CH3)). The contents of asymmetric units (with the exception of minor part of disorder) has been shown on Figs.1 and 2. Crystal data and refinement conditions are shown in Tables 1 and 2.

Table 1. Crystal data and structure refinement for **10.**

[6] Bruker (2013). *APEX2* (Version 2013.6-2). Bruker AXS Inc., Madison, Wisconsin, USA.
[7] Bruker (2013). SAINT-V8.32A. Data Reduction Software.
[8] Sheldrick, G. M. (1996). *SADABS. Program for Empirical Absorption Correction.* University of Gottingen, Germany.
[9] Sheldrick, G. M. *Acta Cryst*. 2008, *A64*, 112.
[10] Farrugia L. *J. Appl. Cryst.* **1999**, *32*, 837.
[11] Sheldrick, G.M. (1997) SHELXL-97. Program for the Refinement of Crystal
[12] Sheldrick, G.M. *Acta Cryst.* **1990,** *A46*, 467.
[13] Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. *J. Appl. Cryst.*, **2009**, *42*, 339.

Identification code	**10**
Empirical formula	$C_{24}H_{28}N_4O_6$
Moiety Formula	$C_{22}H_{22}N_4O_5$, C_2H_6O
Formula weight	468.50
Temperature/K	100
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.1328(2)
b/Å	16.7206(4)
c/Å	22.9284(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2351.17(11)
Z	4
ρ_{calc}g/cm^3	1.324
μ/mm^{-1}	0.798
F(000)	992.0
Crystal size/mm^3	0.11 × 0.09 × 0.01
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.542 to 134.8
Index ranges	$-7 \leq h \leq 6$, $-19 \leq k \leq 19$, $-27 \leq l \leq 27$
Reflections collected	19352
Independent reflections	4184 [R_{int} = 0.0419, R_{sigma} = 0.0307]
Data/restraints/parameters	4184/70/378
Goodness-of-fit on F^2	1.051
Final R indexes [I>=2σ (I)]	R_1 = 0.0395, wR_2 = 0.0932
Final R indexes [all data]	R_1 = 0.0449, wR_2 = 0.0963
Largest diff. peak/hole / e Å^{-3}	0.20/-0.17
Flack parameter	-0.15(11)

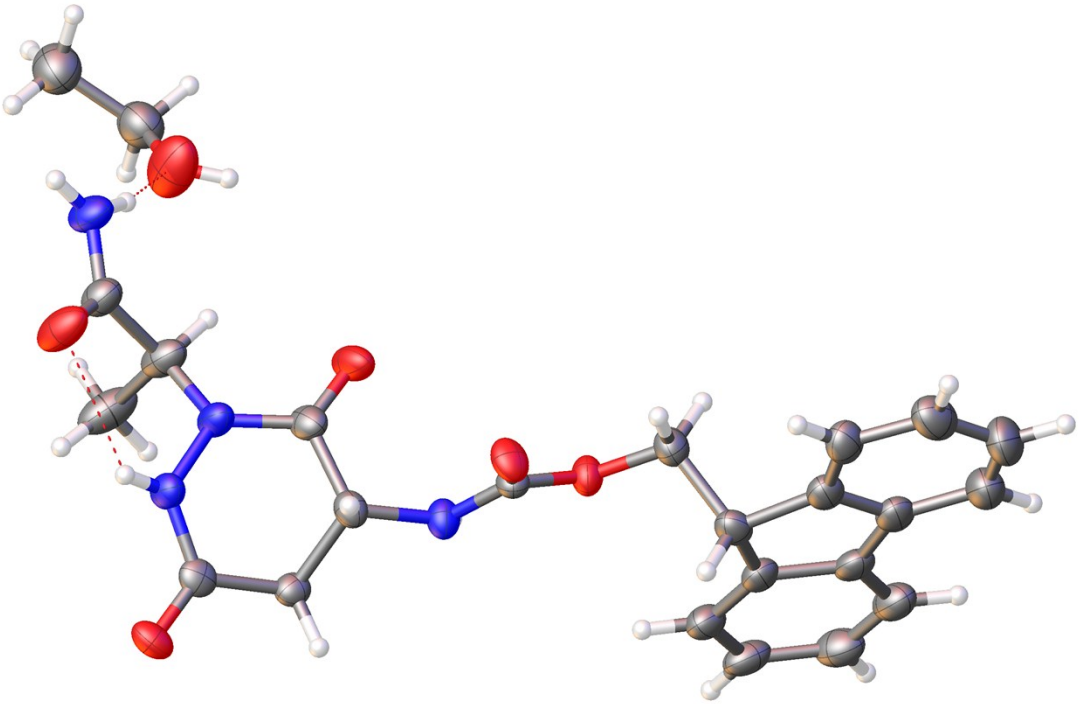


Figure 1. Asymmetric unit of **10.** Thermal ellipsoids have been drawn at 50% probability level. Color scheme: Gray – C, Red – O, Blue – N, White – H. The minor part of disorder has been omitted for clarity.

Table 2. Crystal data and structure refinement for **11**.	
Identification code	**11**
Empirical formula	C32H34N4O5
Formula weight	554.63
Temperature/K	100.0
Crystal system	orthorhombic
Space group	P212121
a/Å	11.0349(3)
b/Å	14.8582(3)
c/Å	17.2323(4)
α/°	90
β/°	90
γ/°	90
Volume/Å3	2825.39(12)
Z	4
ρcalcg/cm3	1.304
μ/mm-1	0.724
F(000)	1176.0
Crystal size/mm3	0.14 × 0.06 × 0.04
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.856 to 149.374
Index ranges	-13 ≤ h ≤ 12, -18 ≤ k ≤ 18, -21 ≤ l ≤ 21
Reflections collected	42988
Independent reflections	5797 [Rint = 0.0395, Rsigma = 0.0196]
Data/restraints/parameters	5797/0/384
Goodness-of-fit on F2	1.085
Final R indexes [I>=2σ (I)]	R1 = 0.0294, wR2 = 0.0697
Final R indexes [all data]	R1 = 0.0312, wR2 = 0.0707
Largest diff. peak/hole / e Å-3	0.23/-0.22
Flack parameter	0.07(5)

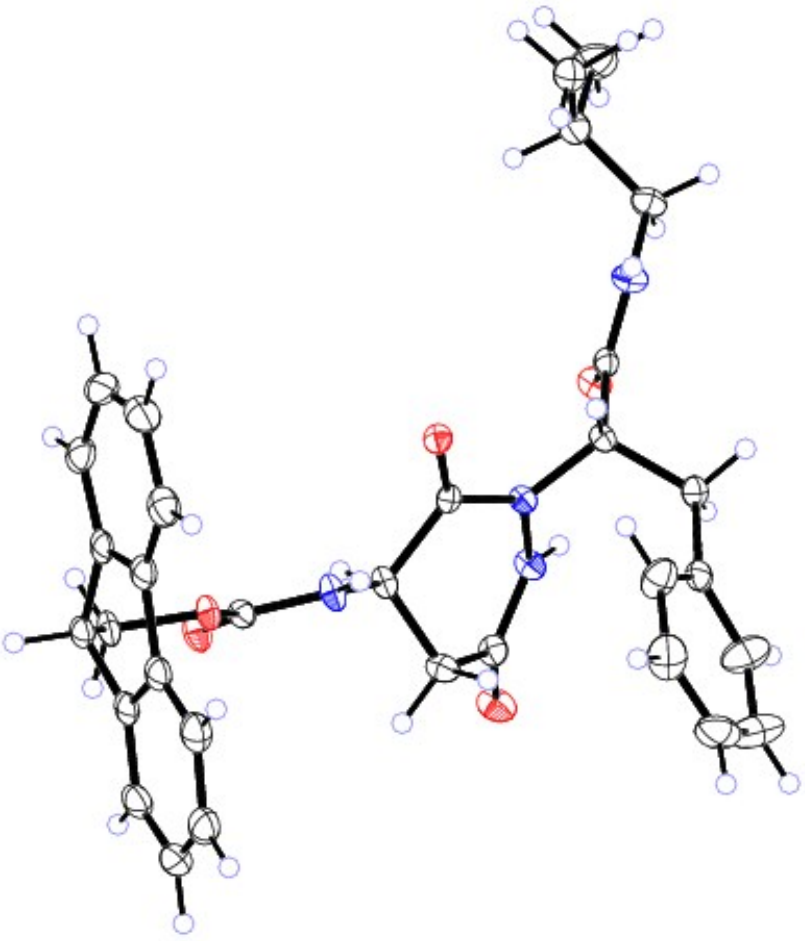
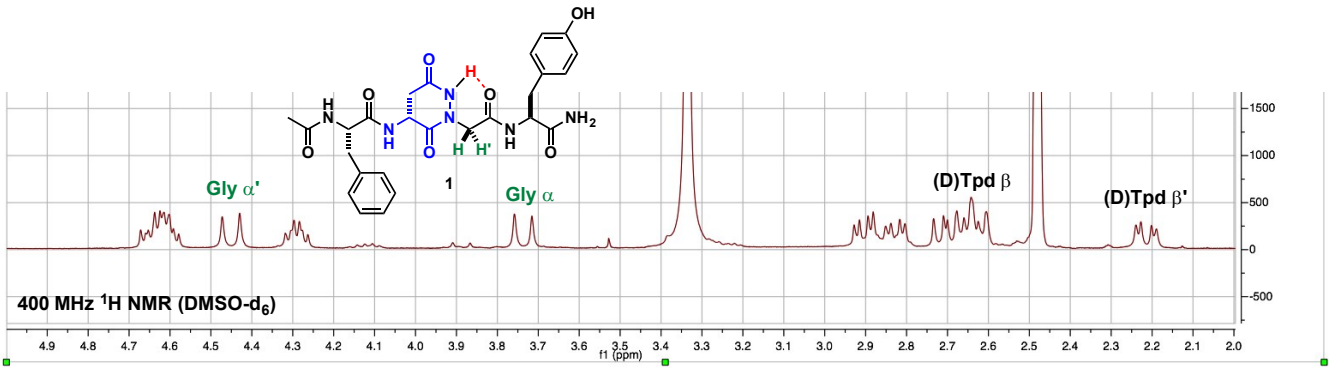
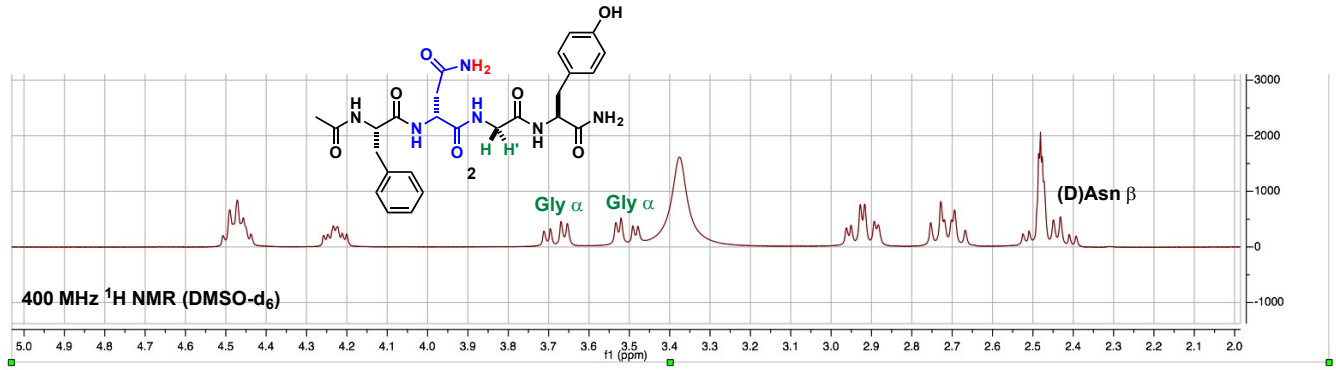
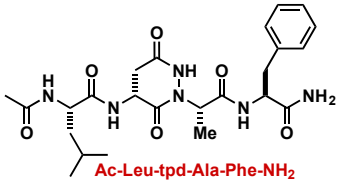


Figure 2. Asymmetric unit of **11**. Thermal ellipsoids have been drawn at 50% probability level.

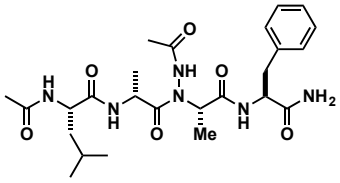
^{1}H NMR OVERLAYS for 1-4



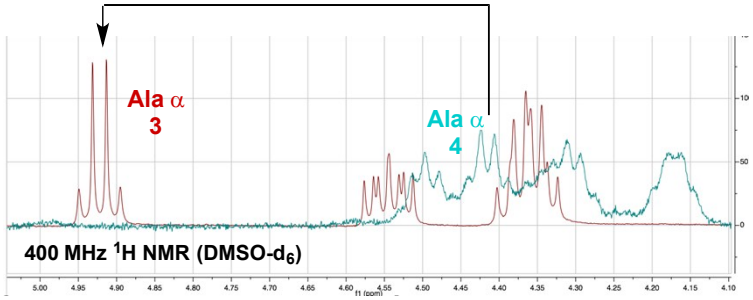




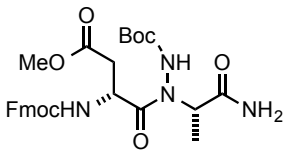
Ac-Leu-tpd-Ala-Phe-NH$_2$
3



Ac-Leu-ala-(*N*-NHBoc)Ala-Phe-NH$_2$
4

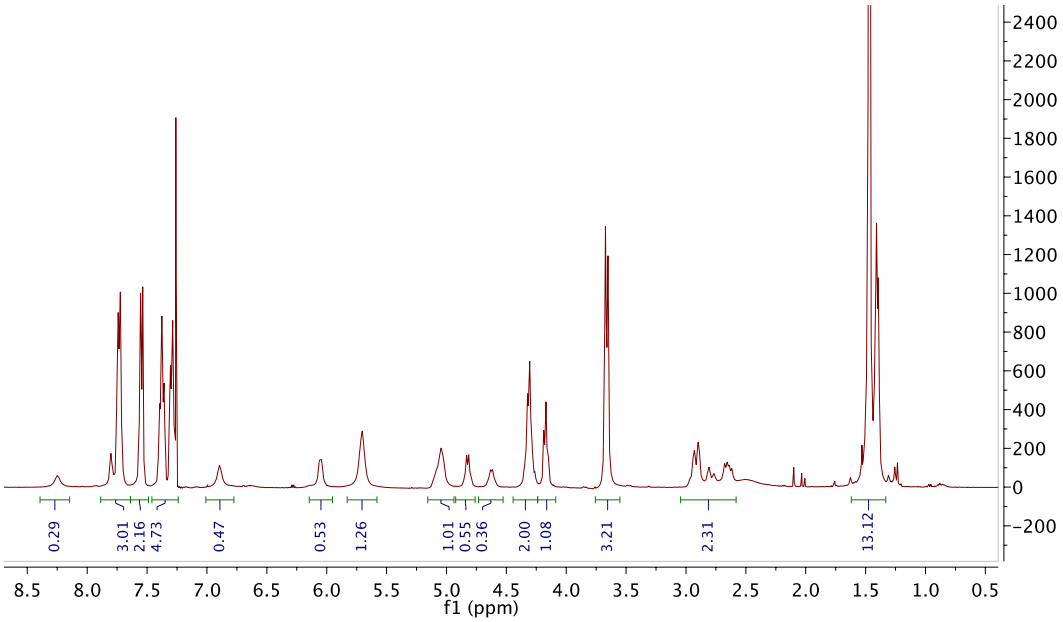


^{1}H and ^{13}C NMR SPECTRA for 7-12

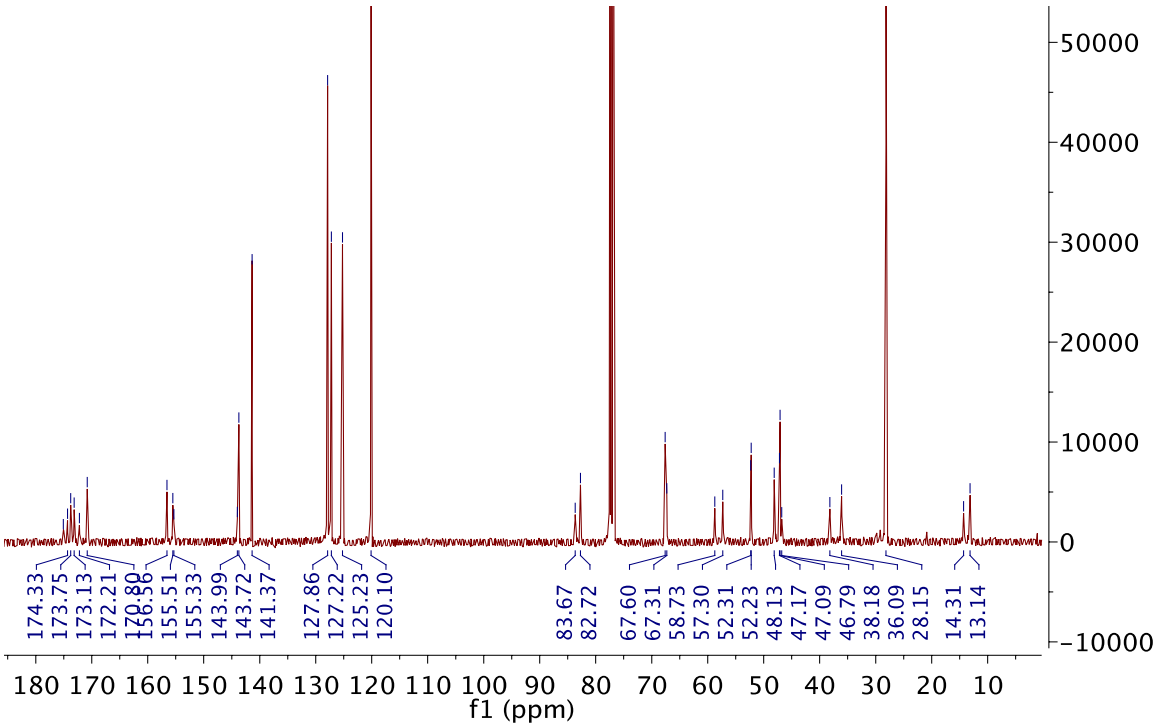


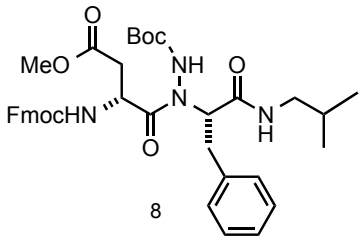
7

^{1}H NMR 400 MHz ($CDCl_3$)

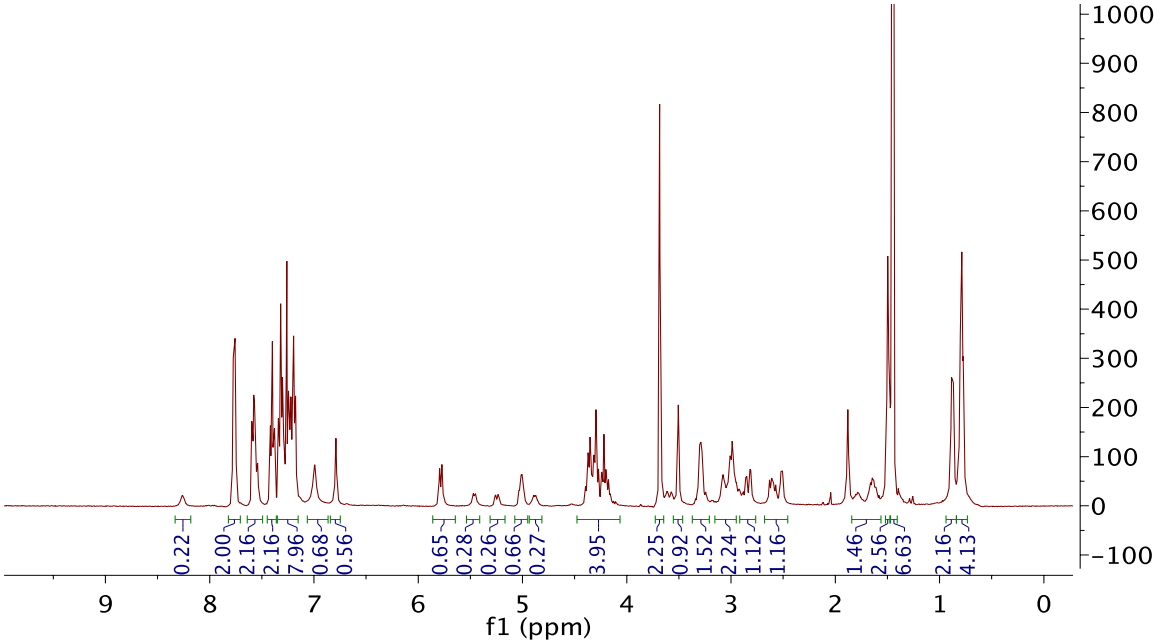


^{13}C NMR 101 MHz ($CDCl_3$)

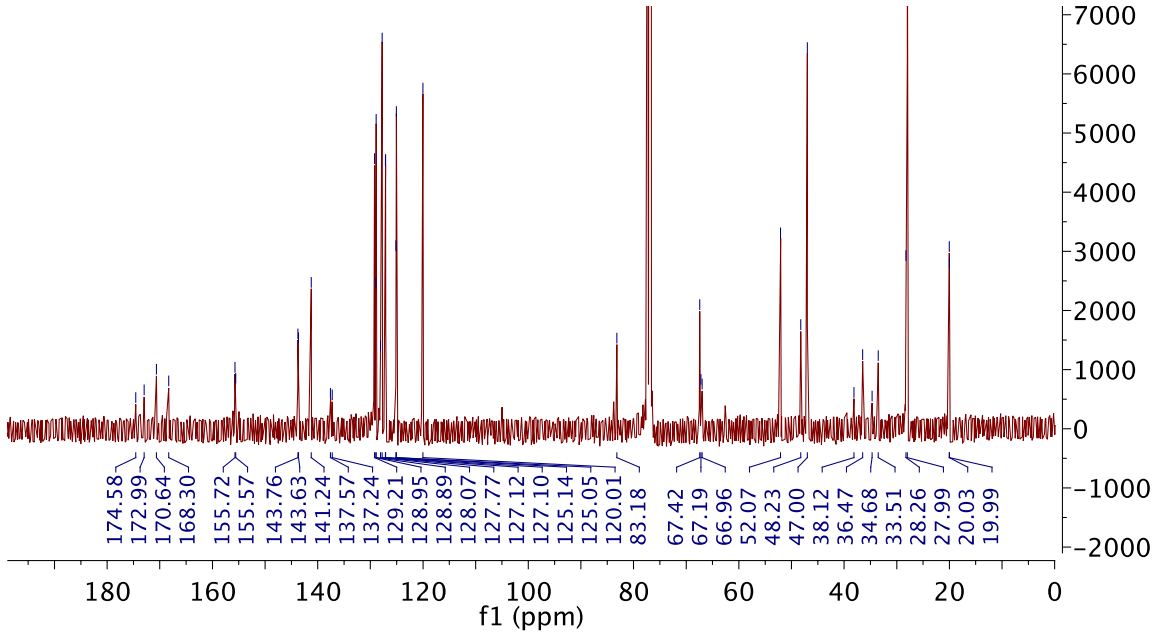


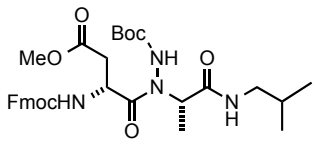


^{1}H NMR 400 MHz ($CDCl_3$)



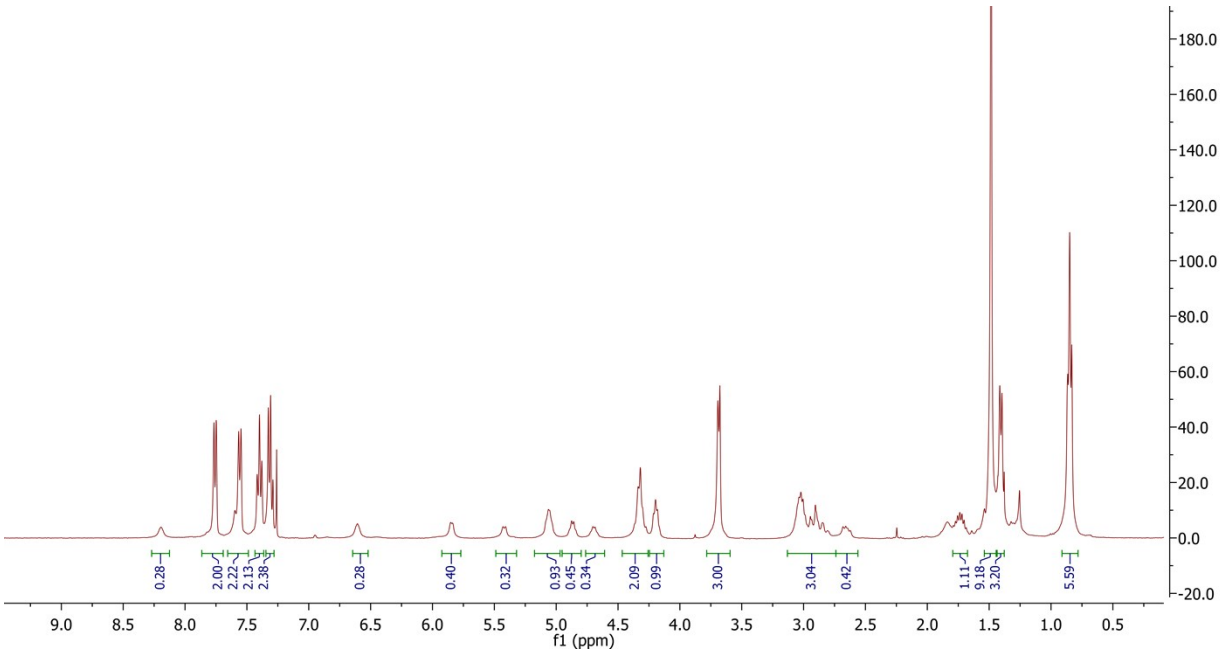
^{13}C NMR 101 MHz ($CDCl_3$)



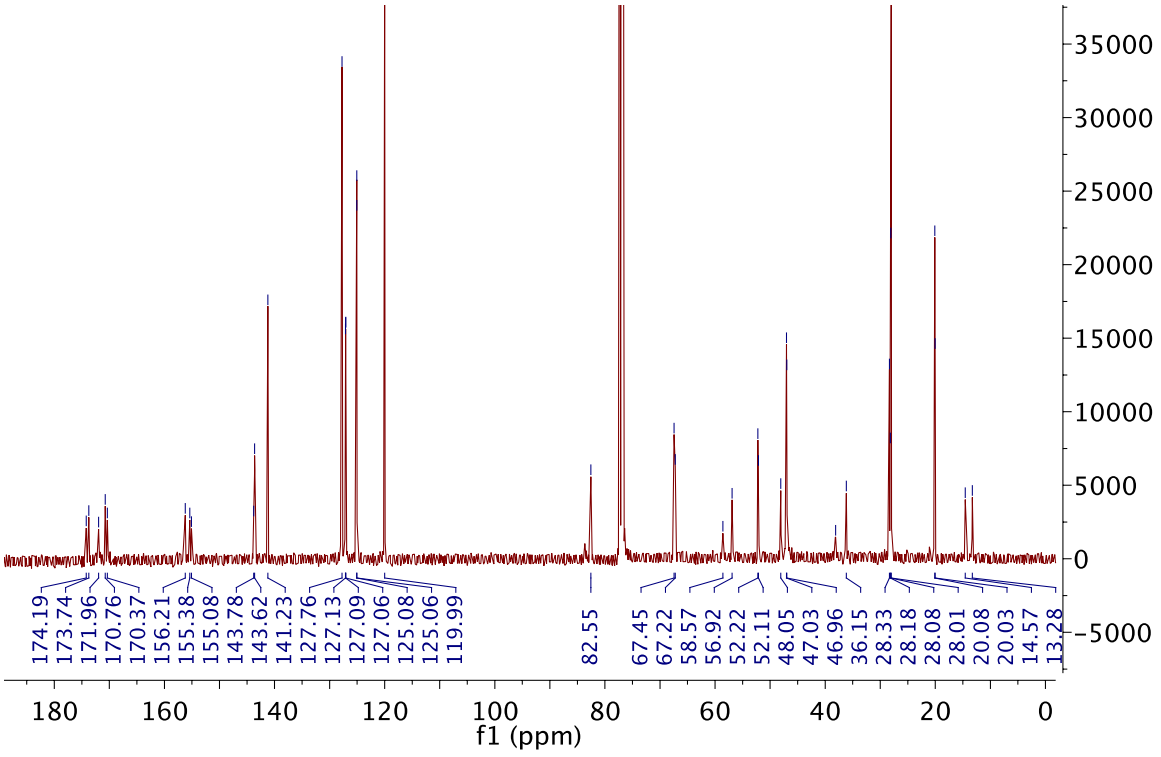


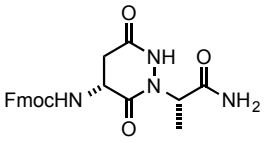
9

^{1}H NMR 400 MHz ($CDCl_3$)



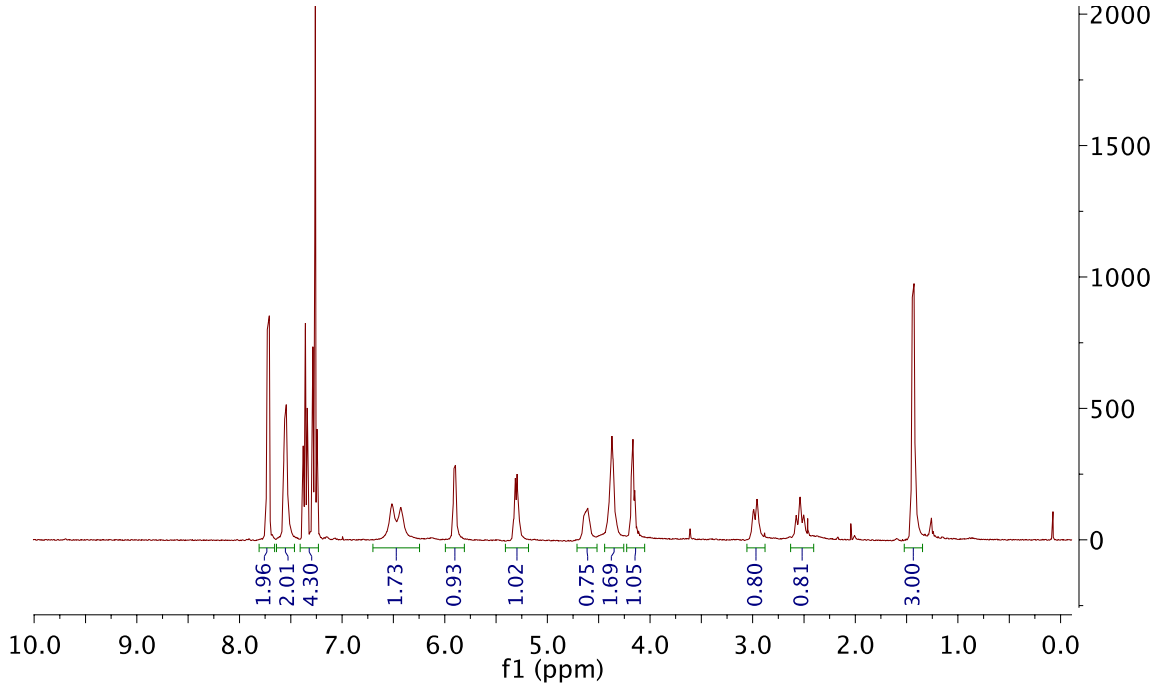
^{13}C NMR 101 MHz ($CDCl_3$)



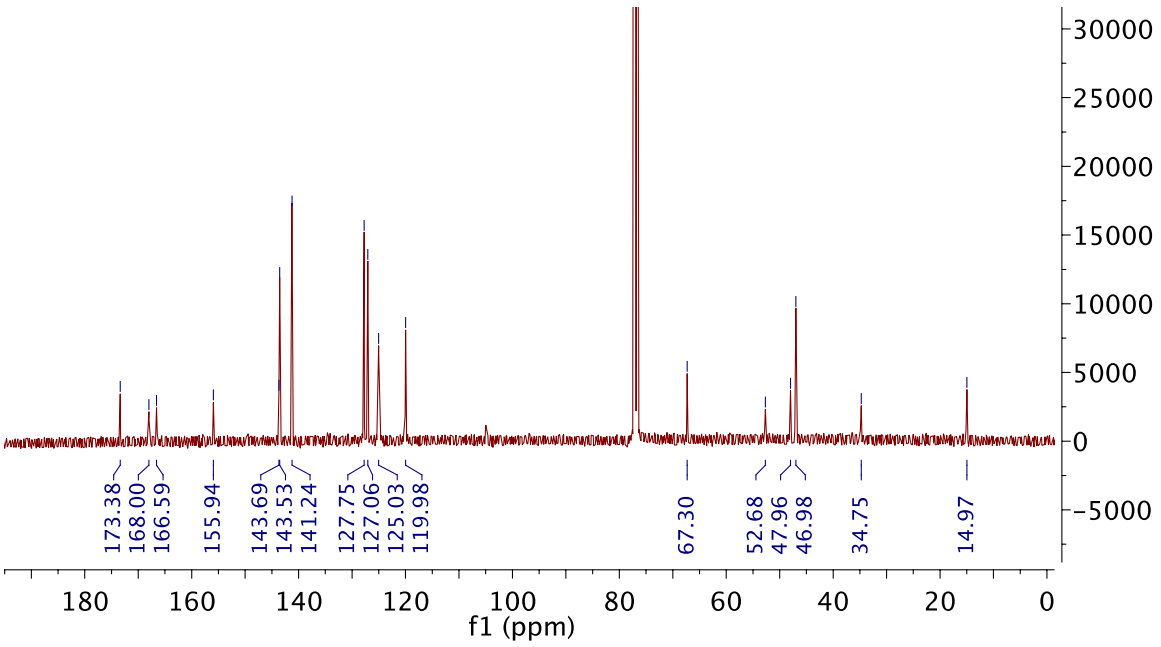


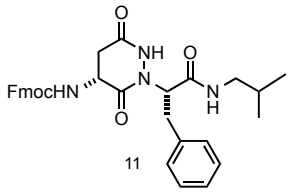
10

^{1}H NMR 400 MHz ($CDCl_3$)

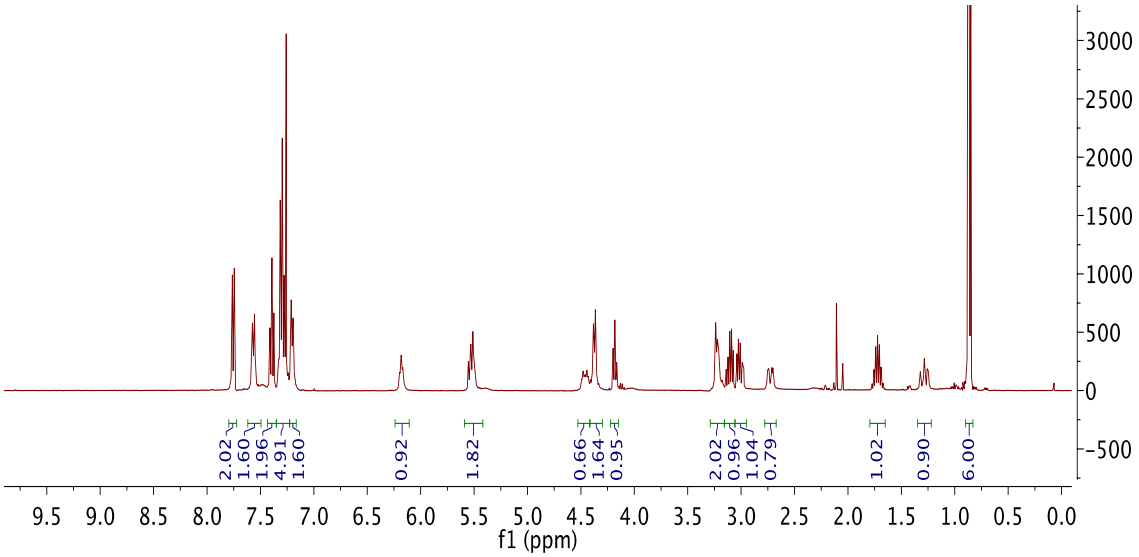


^{13}C NMR 101 MHz ($CDCl_3$)

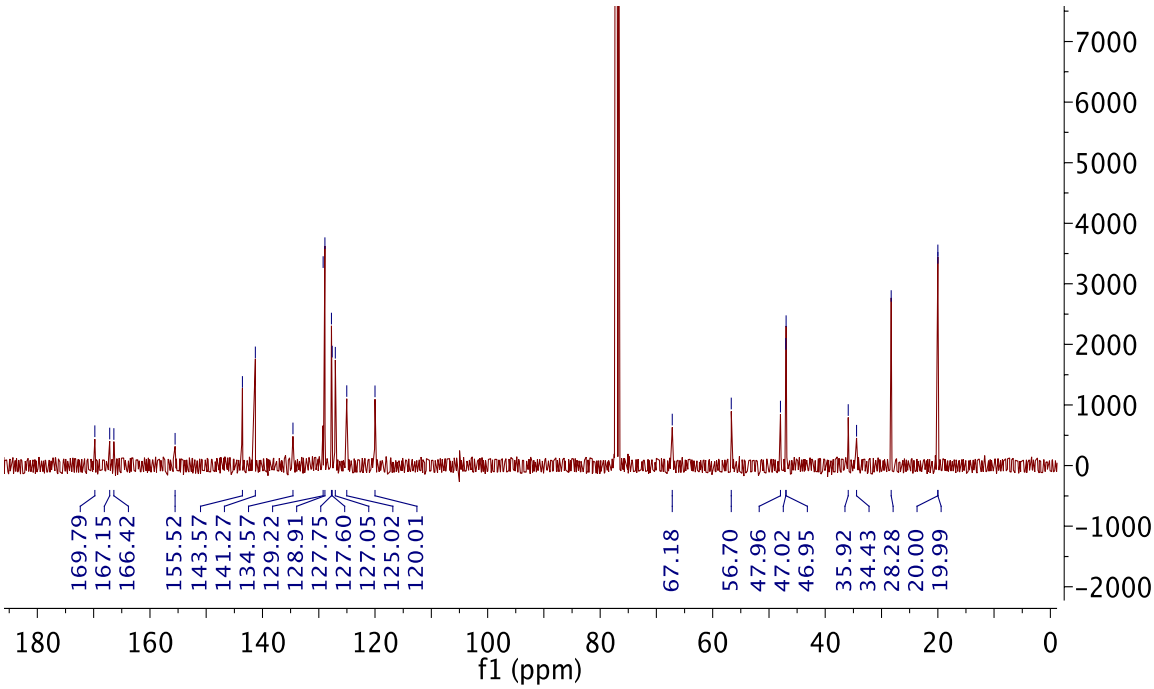


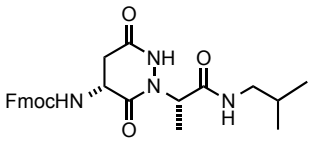


^{1}H NMR 400 MHz ($CDCl_3$)



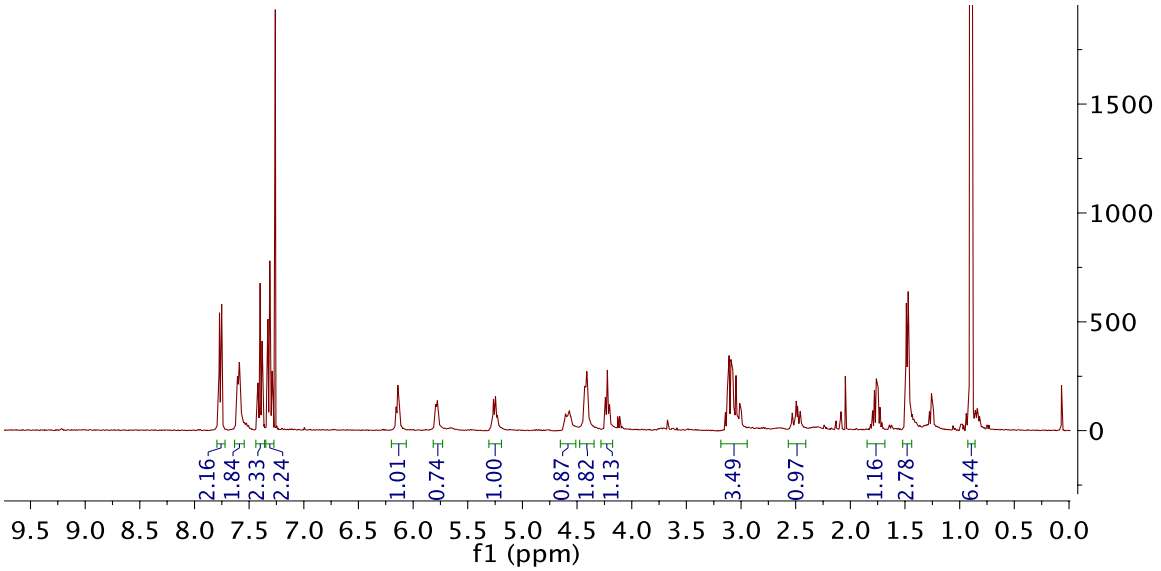
^{13}C NMR 101 MHz ($CDCl_3$)



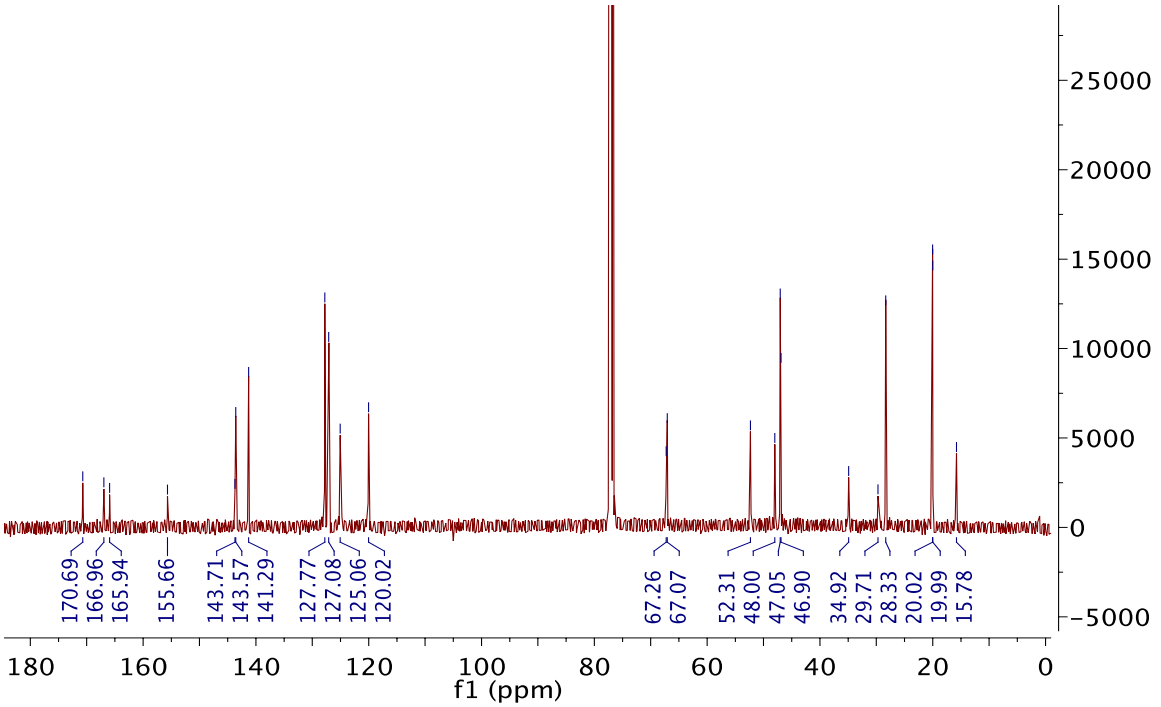


12

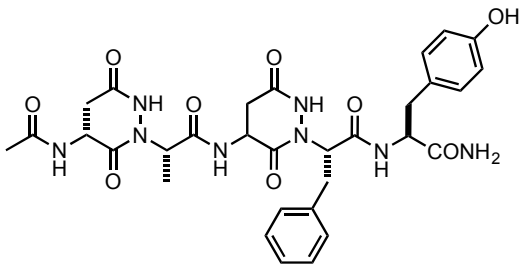
^{1}H NMR 400 MHz ($CDCl_3$)



^{13}C NMR 101 MHz ($CDCl_3$)

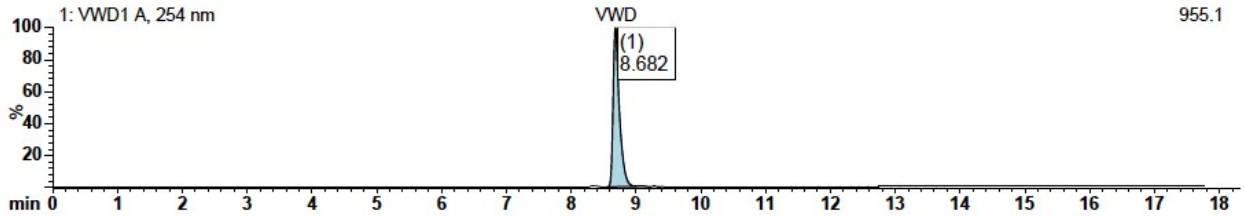


LCMS and ^{1}H NMR SPECTRA for 13-19

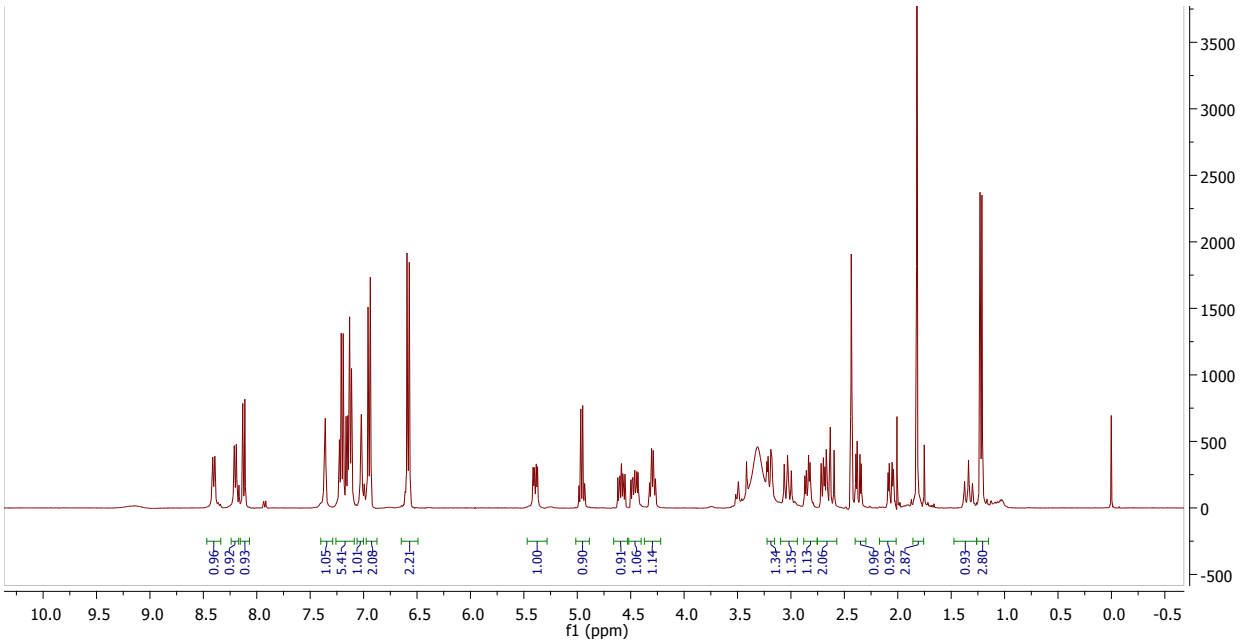


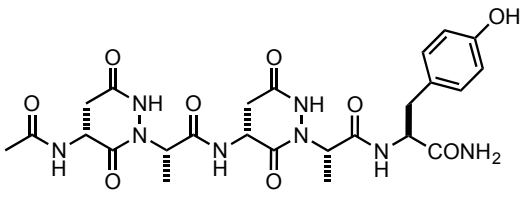
Ac-tpd-Ala-tpd-Phe-Tyr-NH$_2$
13

RP-LC/MS (C_{18} column, 5-95% MeOH in 0.1M aq. HCO_2H linear gradient):



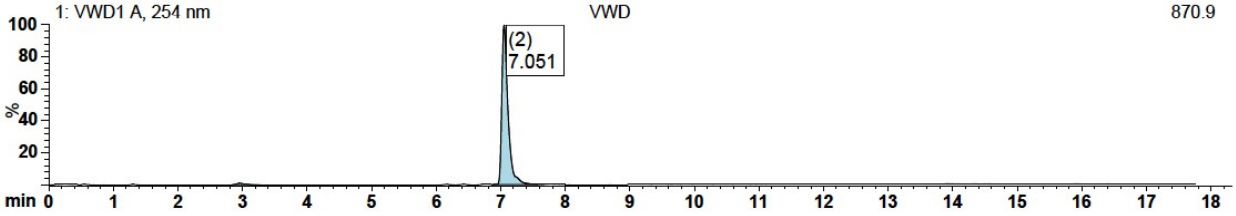
^{1}H NMR 400 MHz (DMSO-d_6):



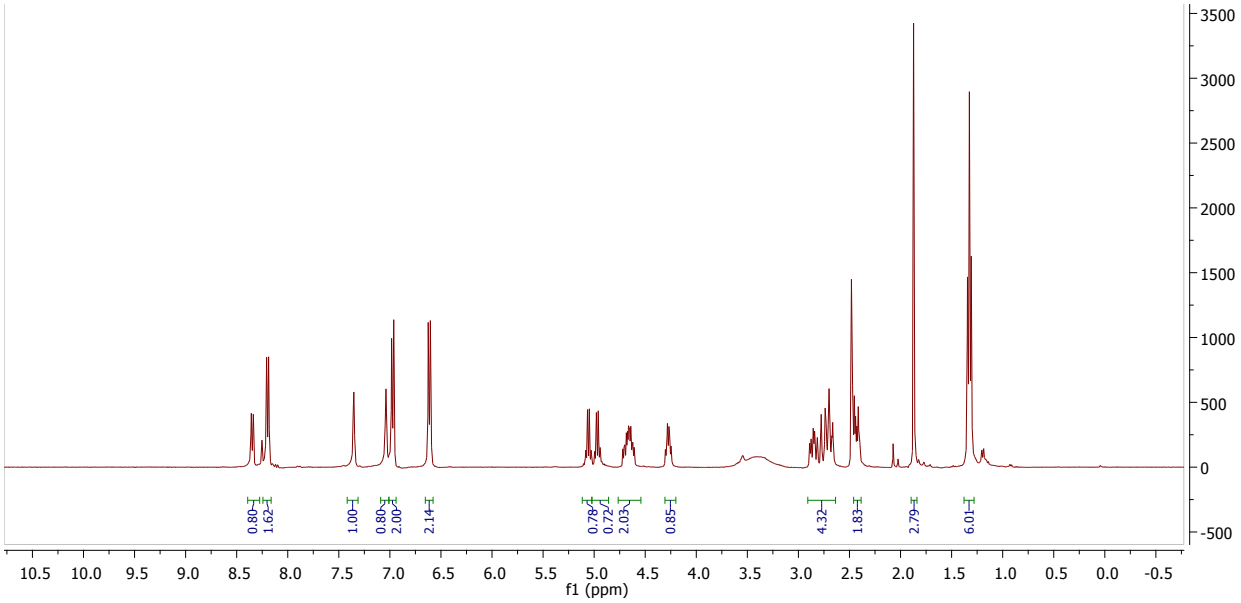


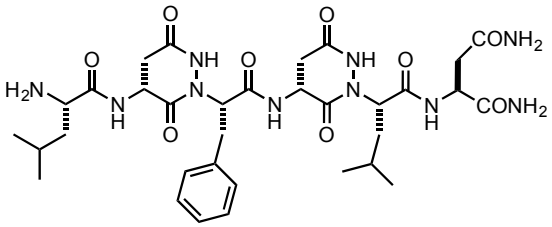
Ac-tpd-Ala-tpd-Ala-Tyr-NH_2
14

RP-LC/MS (C_{18} column, 5-95% MeOH in 0.1M aq. HCO_2H linear gradient):



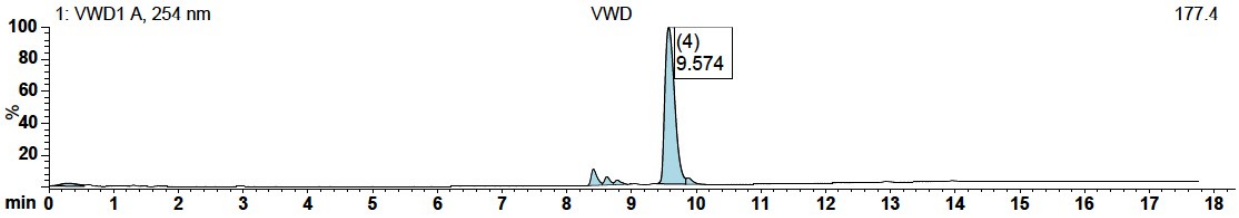
^{1}H NMR 400 MHz (DMSO-d_6):



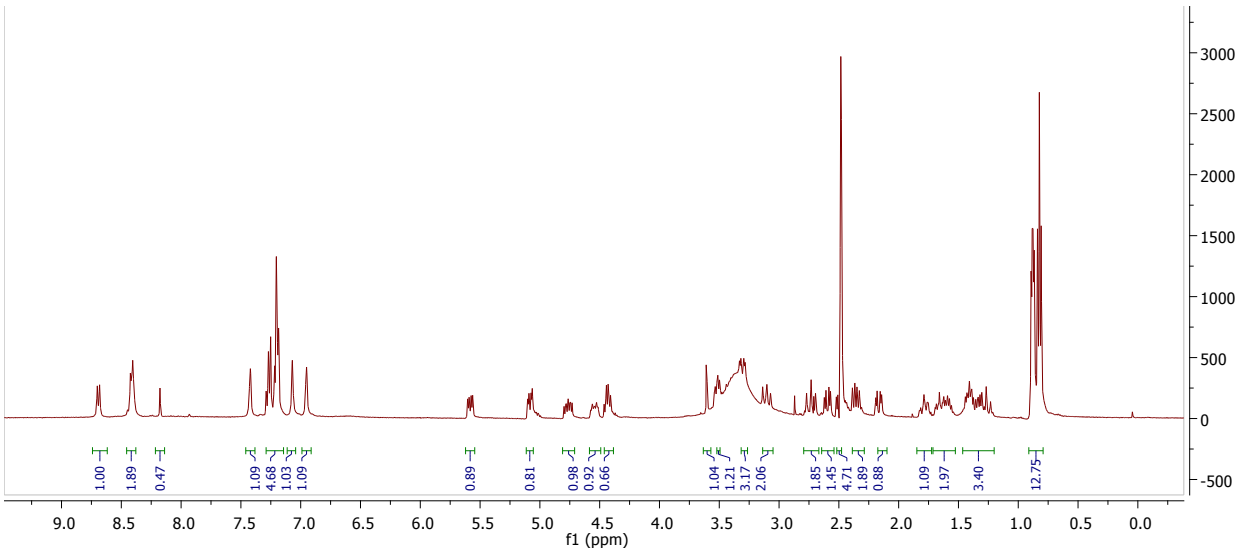


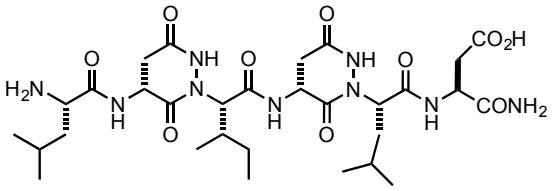
H-Leu-tpd-Phe-tpd-Leu-Asn-NH_2
15

RP-LC/MS (C_{18} column, 5-95% MeOH in 0.1M aq. HCO_2H linear gradient):



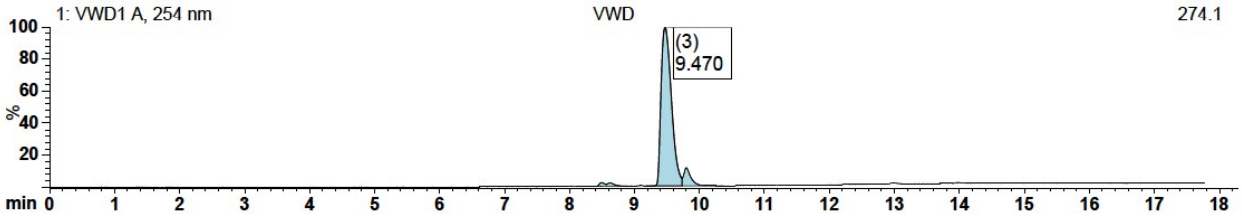
^{1}H NMR 400 MHz (DMSO-d_6):



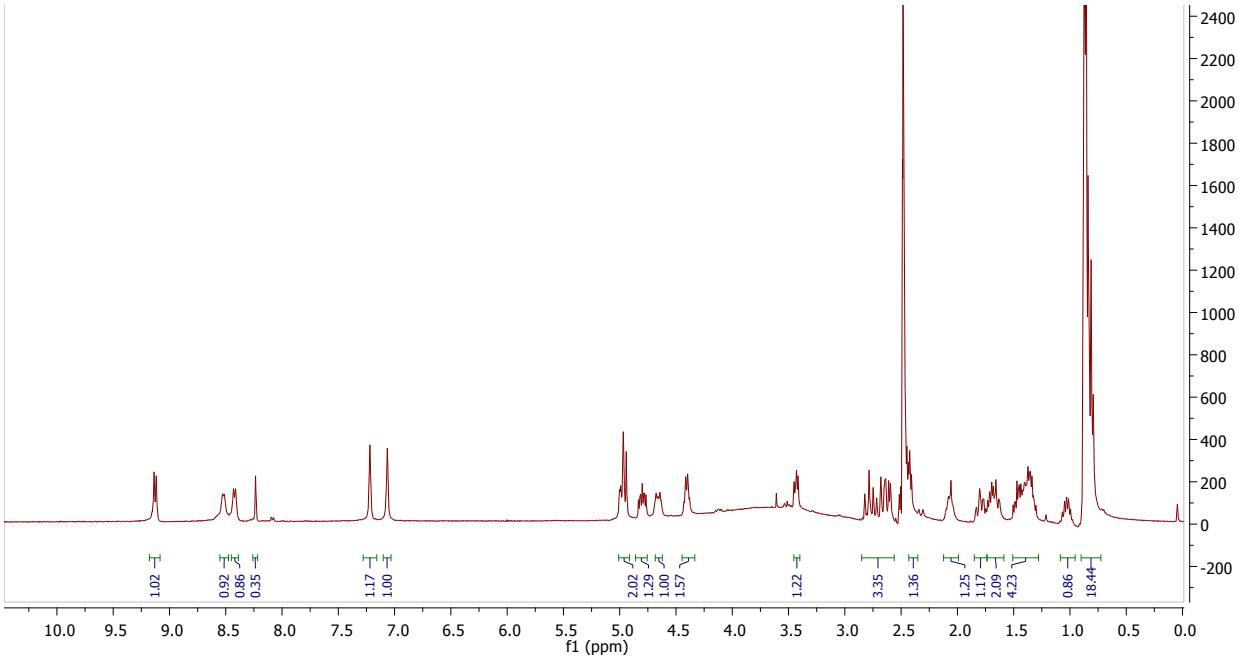


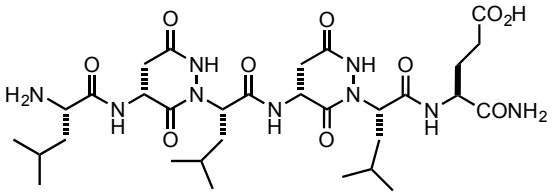
H-Leu-tpd-Ile-tpd-Leu-Asp-NH_2
16

RP-LC/MS (C_{18} column, 5-95% MeOH in 0.1M aq. HCO_2H linear gradient):



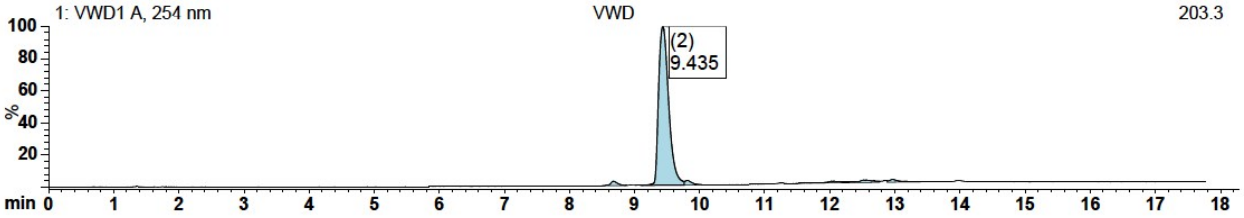
^{1}H NMR 400 MHz (DMSO-d_6):



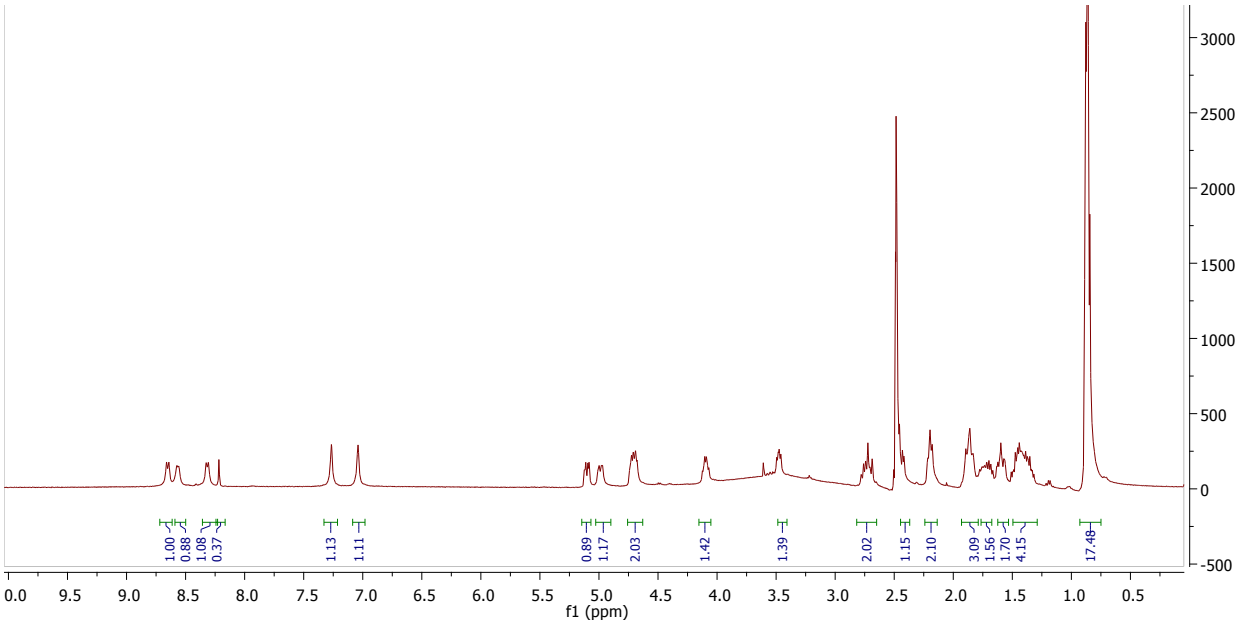


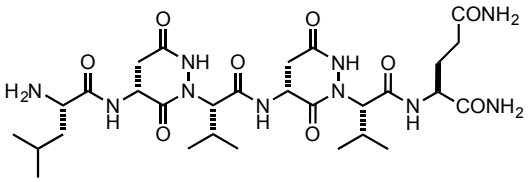
H-Leu-tpd-Leu-tpd-Leu-Glu-NH_2
17

RP-LC/MS (C_{18} column, 5-95% MeOH in 0.1M aq. HCO_2H linear gradient):



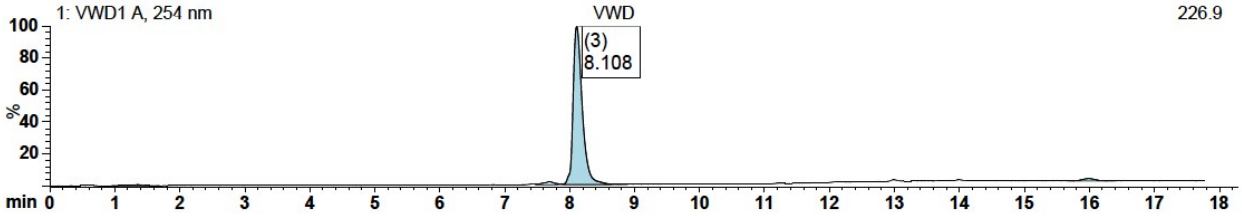
^{1}H NMR 400 MHz (DMSO-d_6):



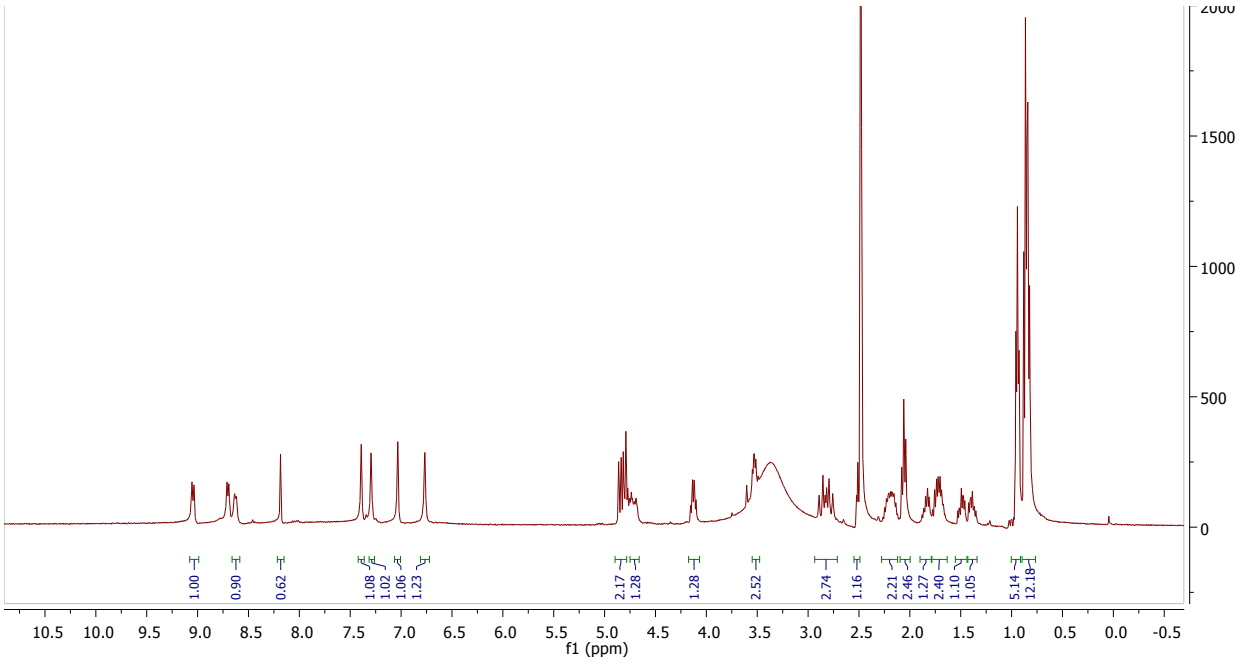


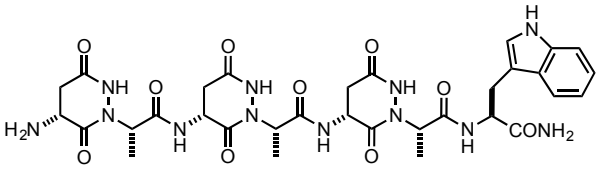
H-Leu-tpd-Val-tpd-Val-Gln-NH$_2$
18

RP-LC/MS (C_{18} column, 5-95% MeOH in 0.1M aq. HCO_2H linear gradient):



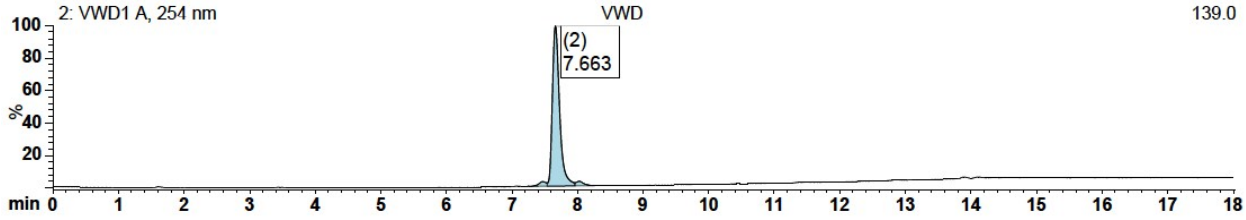
^{1}H NMR 400 MHz (DMSO-d_6):





H-tpd-Ala-tpd-Ala-tpd-Phe-Trp-NH$_2$
19

RP-LC/MS (C_{18} column, 5-95% MeOH in 0.1M aq. HCO_2H linear gradient):



^{1}H NMR 400 MHz (DMSO-d_6):