Supplementary Material (ESI) for New Journal of Chemistry

Supporting Information for:

γ-AApeptides: Design, Synthesis and Evaluation

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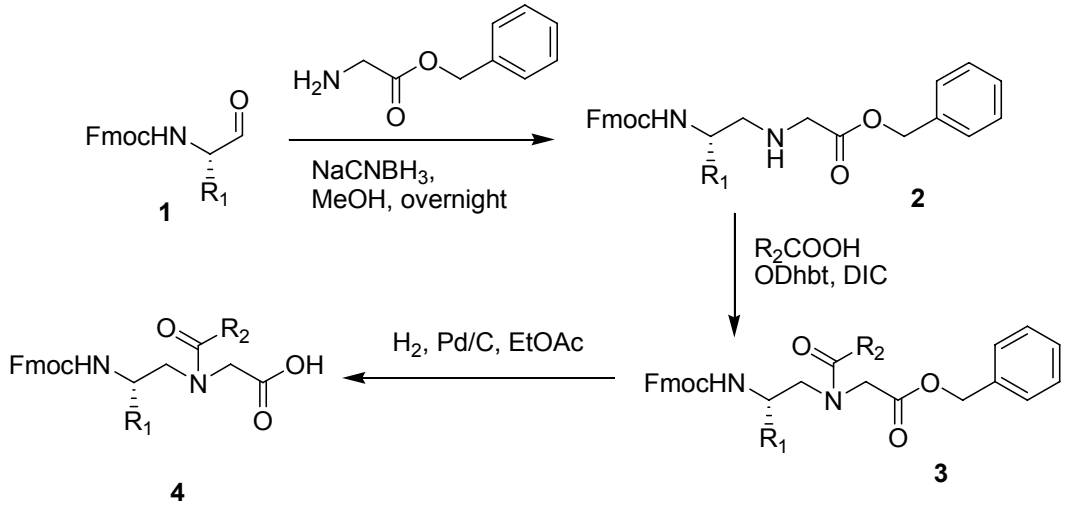
Table of Contents

1. General experimental methods. Fmoc protected α-amino acids and Knorr resin were obtained from Chem-Impex International, Inc. All other reagents and solvents were provided by either Sigma-Aldrich or Fisher Scientific. NMR spectra of intermediates and γ-AApeptide building blocks were obtained on either a Varian Inova 400 or a Brucker 250. γ-AApeptide sequences were prepared on a Knorr resin in peptide synthesis vessels on a Burrell Wrist-Action shaker. The γ-AApeptides were analyzed and purified on an analytical and a preparative Dionex HPLC systems, respectively, and then lyophilized using a Labcono lyophilizer. Molecular weights of γ-AApeptides were identified on a Bruker AutoFlex MALDI-TOF mass spectrometer. Circular Dichroism (CD) experiments were carried out on an Aviv 215 circular dichroism spectrometer.

2. Synthesis of γ-AApeptide building blocks



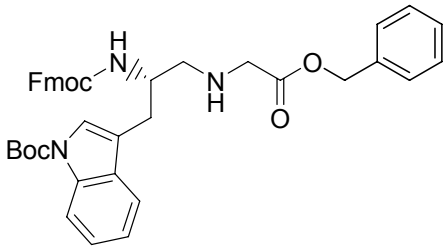
General procedure.

Typical synthesis of 2. An glycine benzyl ester hydrochloride in 15 ml methanol in a 100 ml round bottom flask was added 1.1 equiv. of triethylamine and stirred at 0 ^{o}C for 15 min. Stoichiometric amount of a Fmoc protected amino acid aldehyde [1, 2] was added and the solution mixture was stirred for another 30 min. Catalytic amount of acetic acid was then added, followed by 2 equiv. of $NaBH_3CN$. The solution was allowed to stir at 0 ^{o}C for 1 h and continue at room temperature overnight. The solvent was evaporated and 100 ml ethyl acetate and 100 ml saturated sodium bicarbonate solution were added to the residue. The organic layer was separated and washed with 100 ml brine, dried over anhydrous sodium sulfate, and removed in vacuo. Flash chromatography using ethyl acetate/hexane 1:1 gave **2** (R_f = 0.2) as a colorless oil.

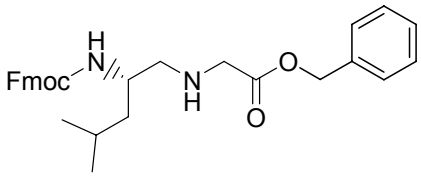
Typical synthesis of 3. Compound **2,** 1.2 equiv. of DIC, Oxohydroxybenzotriazole, and R_2COOH were stirred in 20 ml DMF overnight. The solution was then partitioned in 100 ml ethyl acetate and 100 ml water. The organic layer was separated and washed with water (3 ×100 ml) and Brine (2 ×100 ml), dried over anhydrous sodium sulfate, and then

concentrated in vacuo. Flash chromatography using ethyl acetate/hexane 1:3 gave **3** (R_f = 0.1) as a colorless oil.

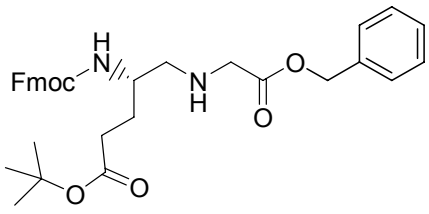
Typical synthesis of 4.
3 in 20 ml ethyl acetate was added 10% Pd/C and hydrogenated at atmospheric pressure and room temperature overnight. The solution was evaporated and the residue was purified by flash chromatography 5-7% MeOH/CH_2Cl_2 to give **4** (R_f = 0.2 in 7% MeOH/CH_2Cl_2) as a white foam solid.



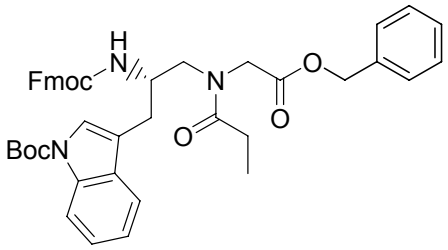
Compound (2a). Yield 81.5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.11 (m, 1H), 7.75-7.52 (m, 4H), 7.43-7.23 (m, 14H), 5.32-5.11 (m, 3H), 4.44-4.38 (m, 2H), 4.21-4.06 (m, 2H), 3.49-3.36(m, 2H), 3.06-2.71(m, 4H), 1.64 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 156.2, 149.6, 143.9, 143.8, 141.3, 135.5, 128.6, 128.4, 128.3, 127.65, 127.6, 127.0, 125.1, 124.4, 123.8, 122.6, 119.9, 119.1, 116.6, 115.3, 115.2, 83.5, 66.62, 66.60, 63.7, 52.7, 51.5, 50.8, 47.3, 28.2. HRMS (ESI) Calc for $[C_{40}H_{42}N_3O_6]^+$, 660.3068; found, 660.3060.



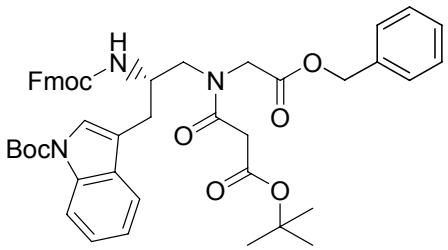
Compound (**2b**). Yield 76.6%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.60-7.58(m, 2H), 7.39-7.27 (m, 9H), 5.16 (d, J = 12 Hz, 1H), 5. 14 (d, J = 12 Hz, 1H), 4.87 (d, J = 8.0 Hz, 1H), 4.41 (m, 2H), 4.22-4.19 (m, 1H), 3.78 (br.s, 1H), 3.44 (m, 2H), 2.64 (br.s, 2H), 1.62 (br.s, 1H), 1.35-1.25 (m, 2H), 0.91-0.81 (m, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 156.2, 144.0, 141.3, 135.6, 128.6, 128.4, 128.3, 127.6, 127.0, 125.1, 125.0, 119.9, 66.5, 66.3, 53.4, 51.0, 49.2, 47.4, 42.3, 24.8, 23.0, 22.2. HRMS (ESI): Calc for $[C_{30}H_{35}N_2O_4]^+$, 487.2591; found, 487.2588.



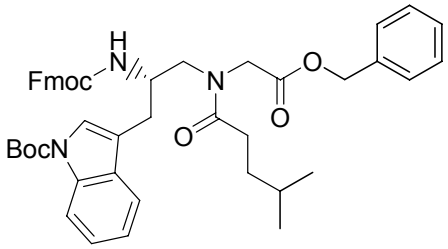
Compound (**2c**). Yield 70.3%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.73(d, J = 8.0 Hz, 2H), 7.60-7.55(m, 2H), 7.39-7.27(m, 9H), 5.25-5.11 (m, 3H), 4.44-4.31(m, 2H), 4.21-4.18 (m, 1H), 3.69-2.61(m, 5H), 2.30-2.25 (m, 2H), 1.87-1.74 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.3, 156.3, 144.0, 143.9, 141.3, 135.5, 128.6, 128.4, 128.3, 127.64, 127.6, 127.0, 125.0, 119.9, 80.5, 66.6, 66.4, 64.6, 52.9, 50.9, 47.3, 32.1, 31.9, 28.1. HRMS (ESI): Calc for $[C_{33}H_{39}N_2O_6]^+$, 559.2803; found, 559.2786.



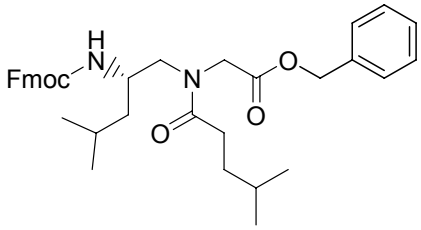
Compound **3a-1** .Yield 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 8.13-8.12 (m, 2H), 7.74-7.21 (m, 17H), 5.68(d, J = 8.0 Hz, 1H), 5.14 (d, J = 12 Hz, 1H), 5.08 (d, J = 12 Hz, 1H), 4.30-3.94 (m, 6H), 3.89-3.62 (m, 1H), 3.12-2.82 (m, 3H), 2.30-2.13 (m, 2H), 1.64 (s, 9H), 1.08 (t, J = 8.0 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (two rotamers) 175.9, 168.9, 156.4, 149.6, 143.9, 141.2, 134.9,130.5, 128.6, 128.55, 128.4, 128.3, 127.7, 127.6, 127.0, 126.98, 125.2, 124.7, 124.5, 123.9, 122.8, 122.7, 120.0, 119.9, 118.7, 116.2, 115.4, 115.2, 83.6, 67.4, 67.0, 66.7, 52.0, 51.0, 50.7, 50.1, 50.08, 49.3, 47.2, 47.1, 28.9, 28.2, 28.1, 26.3, 25.9, 9.22, 9.12. HRMS (ESI): Calc for $[C_{43}H_{46}N_3O_7]^+$, 716.3330; found, 716.3323.



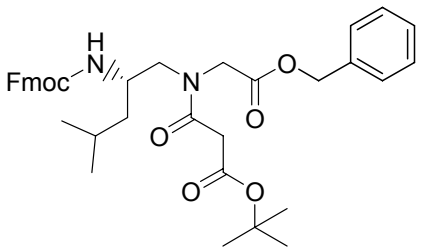
Compound **3a-2**. Yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 8.12 (d, J = 8.0 Hz, 1H), 7.74-7.66 (m, 2H), 7.52-7.20 (m, 15H), 5.70-5.52 (m, 1H, rotamers), 5.15-5.07 (m, 2H), 4.35-4.28 (m, 2H), 4.20-4.17 (m, 2H), 4.16-3.99 (m, 2H), 3.63-3.50 (m, 1H), 3.42-3.38 (m, 1H), 3.26-2.23 (m, 2H), 3.10-2.89 (m, 2H), 1.63&1.61 (2s, 9H), 1.42&1.41 (2s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (two rotamers) 169.1, 168.7, 167.2, 166.0, 156.3, 149.6, 144.0, 143.8, 143.7, 141.2, 135.5, 135.2, 14.8, 128.7, 128.6, 128.5, 128.4, 128.2, 127.7, 127.6, 127.0, 125.2, 125.2, 124.7, 124.5, 124.0, 122.8, 122.7, 119.9, 119.2, 118.8, 116.2, 115.7, 115.4, 115.2, 83.6, 82.2, 67.6, 67.0, 66.8, 51.9, 50.6, 50.5, 50.2, 47.9, 47.2, 47.1, 28.6, 28.1, 27.9. HRMS (ESI): Calc for $[C_{47}H_{51}N_3O_9Na]^+$, 824.3518; found, 824.3518.



Compound **3a-3**. Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 8.12 (d, J = 8.0 Hz, 1H), 7.74-7.23 (m, 17H), 5.69 (d, J = 4.0 Hz, 1H), 5.14 (d, J = 12.0 Hz, 1H), 5.07 (d, J = 12.0Hz, 1H), 4.32-4.26 (m, 2H), 4.19-4.07 (m, 2H), 4.04-3.90 (m, 2H), 3.60-3.50 (m, 1H), 3.12-2.82 (m, 3H), 2.19-2.09 (m, 2H), 1.63&1.61 (2s, 9H), 1.67-1.61 (m, 1H), 1.46-1.45 (m, 2H), 0.80-0.75 (m, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ (two rotamers) 175.4, 168.97, 156.4, 149.6, 143.9, 143.86, 141.22, 141.19, 135.5, 134.9, 128.64, 128.6, 128.56, 128.4, 128.34,128.26, 127.7, 127.6, 127.1, 127.0, 125.2, 124.7, 124.5, 123.9, 122.8, 122.7, 119.92, 119.86, 119.2, 118.6, 116.2, 115.4, 115.2, 83.6, 67.4, 67.0, 66.8, 50.7, 50.2, 50.1, 49.3, 47.2, 33.8, 33.7, 31.0, 30.7, 28.7, 28.2, 27.7, 27.6, 22.3, 22.2. HRMS (ESI): Calc for $[C_{46}H_{52}N_3O_7]^+$, 758.3800; found, 758.3811.

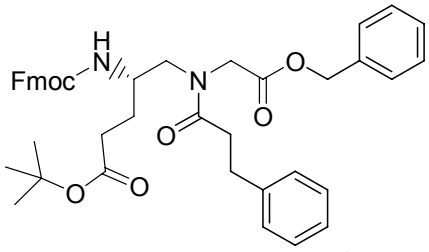


Compound **3b-1**. Yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 7.73 (d, J = 8.0 Hz, 2H), 7.57-7.53 (m, 2H), 7.39-7.24 (m, 9H), 5.20-5.14 (m, 2H), 5.04-4.81 (m, 1H), 4.42-4.28 (m, 2H), 4.17-4.04 (m, 3H), 3.91-3.86 (m, 1H), 3.47-3.00 (m, 2H), 2.35-2.08 (m, 2H), 1.66-1.41 (m, 5H), 1.27-1.23 (m, 1H), 0.92-0.74 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (two rotamers) 174.8, 169.2, 156.4, 155.8, 143.92, 143.86, 143.74, 141.3, 141.2, 135.4, 135.0, 130.0, 128.7, 128.6, 128.5, 128.4, 128.36, 128.3, 128.2, 127.7, 127.6, 127.04, 127.02, 125.1, 124.9, 119.94, 119.87, 67.3, 66.9, 66.5, 66.4, 53.4, 53.3, 50.6, 49.9, 49.3, 49.0, 48.3, 47.3, 42.2, 41.3, 33.9, 33.7, 31.0, 30.7, 27.7, 27.6, 24.8, 24.7, 23.3, 23.1, 22.3, 21.2, 21.19, 21.15. HRMS (ESI): Calc for $[C_{36}H_{44}N_2O_5Na]^+$, 607.3142; found, 607.3131.

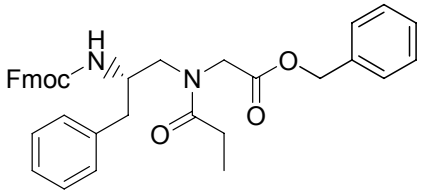


Compound **3b-2**. Yield 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 7.73 (d, J = 8.0 Hz, 2H), 7.57-7.53 (m, 2H), 7.37-7.26 (m, 9H), 5.19-4.95(m, 3H), 4.39-4.33 (m, 2H), 4.20-4.12 (m, 2H), 3.97-3.77 (m, 2H), 3.45-3.13 (m, 4H), 1.65-1.56 (m, 1H), 1.45&1.40

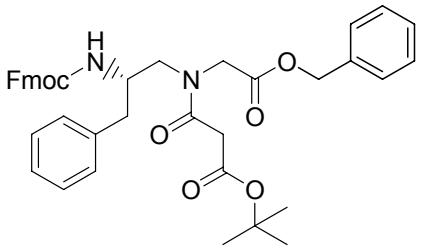
(2s, 9H), 1.45-1.37 (m, 1H), 1.27-1.24 (m, 1H), 0.91-0.86 (m, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ (two rotamers) 167.98, 167.2, 166.7, 166.1, 156.3, 156.0, 144.0, 143.8, 143.7, 141.2, 135.3, 134.9, 128.6, 128.57, 128.3, 128.27, 128.2, 127.6, 127.5, 127.0, 126.99, 126.96, 125.1, 125.0, 124.94,124.88, 119.88, 119.82, 82.3, 82.0, 67.4, 66.9, 66.7, 53.3, 50.7, 50.3, 48.1, 47.2, 42.6, 42.34, 42.29, 42.0, 41.94, 41.6, 27.9, 27.8, 24.72, 24.69, 23.2, 23.1, 22.0, 21.64, 21.57, 20.8. HRMS (ESI): Calc for $[C_{37}H_{45}N_2O_7]^+$, 629.3221; found, 629.3203.



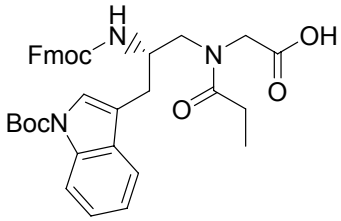
Compound **3c**. Yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 7.75 (d, J = 8.0 Hz, 2H), 7.60-7.55 (m, 2H), 7.40-7.04 (m, 14H), 5.35-5.13 (m, 3H), 4.40-4.29 (m, 2H), 4.18-4.00 (m, 3H), 3.88-3.77 (m, 1H), 3.62-3.18 (m, 2H), 2.96-2.67 (m, 2H), 2.67-2.63 (m, 1H), 2.45-2.23 (m, 3H), 1.73-1.67 (m, 2H), 1.44&1.42 (2s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (two rotamers) 173.7, 173.0, 172.55, 169.6, 168.9, 156.4, 155.9, 143.8, 143.7, 143.6, 141.2, 141.15, 140.9, 140.8, 135.3, 134.9, 128.6, 128.5, 128.33,128.31, 128.24, 128.17, 128.15, 127.6, 127.0, 126.0, 125.0, 124.84, 124.81, 119.9, 119.82, 80.7, 80.4, 67.3, 66.9, 66.4, 52.8, 50.7, 50.5, 50.1, 49.9, 49.1, 47.2, 47.1, 34.8, 34.5, 31.9, 31.82, 31.1, 30.96, 28.0. HRMS (ESI): Calc for $[C_{42}H_{46}N_2O_7Na]^+$, 713.3197; found, 713.3190.



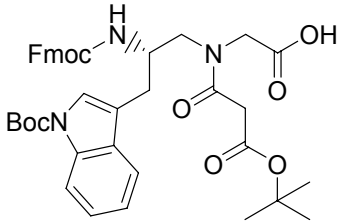
Compound **3d-1** . Yield 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 7.73(d, J = 8.0 Hz, 2H), 7.53-7.13 (m, 16H), 5.42-4.95 (m, 1H), 5.15-5.09 (m, 2H), 4.30-4.26 (m, 2H), 4.16-3.91 (m, 4H), 3.55-3.47 (m, 1H), 3.08-2.79 (m, 3H), 2.29-2.12 (m, 2H), 1.06 (t, J = 8.0 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (two rotamers) 175.6, 169.0, 156.2, 143.9, 141.3, 141.2, 137.4, 135.4, 135.0, 129.2, 129.0, 128.8, 128.7, 128.6, 128.57, 128.4, 127.7, 127.6, 127.0, 126.9, 126.6, 125.2, 124.9, 67.4, 67.0, 66.6, 51.9, 51.7, 50.0, 47.0, 39.2, 26.2, 25.9, 9.3, 9.1. HRMS (ESI): Calc for $[C_{36}H_{36}N_2O_5K]^+$, 615.2256; found, 615.2267.



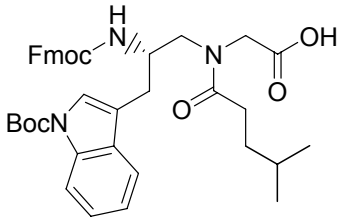
Compound **3d-2** . Yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 7.73 (d, J = 8.0 Hz, 2H), 7.54-7.47 (m, 2H), 7.33-7.14 (m, 14H), 5.45-5.30 (m, 1H),, 5.16 (d, J = 12.0 Hz, 1H), 5.12 (d, J = 12.0 Hz, 1H), 4.31-4.24 (m, 2H), 4.16-4.14 (m, 1H), 4.05-3.91 (m, 3H), 3.60-3.21 (m, 4H), 2.91-2.78 (m, 2H), 1.44&1.41 (2s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ (two rotamers) 169.1, 168.7, 167.2, 166.1, 156.1, 143.96, 143.88, 143.76, 141.25, 141.22, 137.3, 136.9, 135.3, 134.9, 129.2, 129.1, 128.7, 128.68, 128.64, 128.57, 128.4, 128.3, 128.2, 127.7, 127.6, 127.0, 126.9, 126.6, 1225.2, 125.0, 119.9, 119.87, 82.2, 67.5, 67.0, 66.6, 51.97, 51.6, 50.5, 50.1, 48.1, 47.2, 42.2, 41.8, 38.99, 38.5, 27.93, 27.89. HRMS (ESI): Calc for $[C_{40}H_{43}N_2O_7]^+$, 663.3065; found, 663.3052.



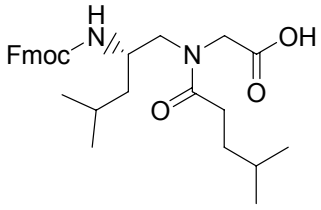
Compound **4a-1**. Yield 86%. $[\alpha]_D^{22}$=-3.34^{o}. ^{1}H NMR (400 MHz, CD_3OD) δ (two rotamers) 8.01 (d, J = 8.0 Hz, 1H), 7.68-7.57 (m, 3H), 7.46-7.09 (m, 6H), 4.23-4.19 (m, 2H), 4.08-3.86 (m, 4H), 3.63-3.52 (m, 2H), 2.89-2.80 (m, 2H), 2.39-2.22 (m, 2H), 1.48&1.47 (2s, 9H), 1.02 (t, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ (two rotamers) 176.3, 175.3, 157.1, 149.5, 143.8, 143.76, 143.6, 141.1, 141.0, 135.4, 130.6, 130.3, 127.3, 127.2, 126.7, 124.8, 124.7, 124.0, 123.9, 123.3, 123.2, 122.3, 122.2, 119.45, 119.4, 118.8, 118.6, 117.2, 116.9, 114.8, 114.7, 83.2, 83.1, 52.6, 52.3, 51.1, 50.0, 49.8, 46.8, 27.8, 26.9, 26.0, 25.5, 8.6, 8.5. HRMS (ESI): Calc for $[C_{36}H_{39}N_3O_7Na]^+$, 648.2680; found, 648.2678.



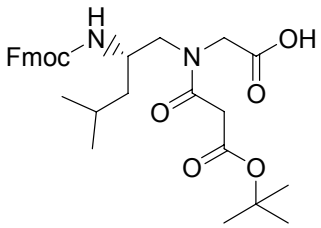
Compound **4a-2**. Yield 99%. ^{1}H NMR (400 MHz, CD_3OD) δ (two rotamers) 8.06-8.02 (m, 1H), 7.73-7.64(m, 3H), 7.48-7.15 (m, 9H), 4.13-3.93 (m, 6H), 3.75-3.44 (m, 3H), 3.30-3.22 (m, 1H), 2.96-2.80 (m, 2H), 1.51&1.50 (2s, 9H), 1.40 (s, 9H).^{13}C NMR (100 MHz, CD_3OD) δ (two rotamers) 173.3, 169.15, 169.13, 167.1, 156.7, 156.3, 149.6, 149.5, 143.9, 143.8, 143.7, 141.1, 135.4, 135.3, 130.8, 130.4, 127.5, 127.0, 125.3, 125.1, 124.6, 124.3, 124.0, 122.8, 122.6, 119.8, 119.2, 115.3, 115.2, 83.5, 82.1, 67.0, 66.8, 52.5, 50.6, 47.0, 42.3, 42.2, 41.4, 42.3, 29.7, 28.1, 27.9, 27.8. HRMS (ESI): Calc for $[C_{40}H_{45}N_3O_9Na]^+$, 734.3048; found, 734.3040.



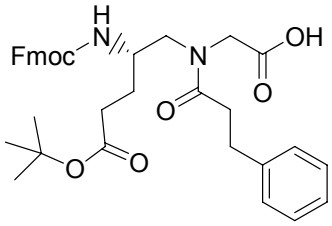
Compound **4a-3**. Yield 93%. $[\alpha]_D^{22}$=-0.93°. ^{1}H NMR (400 MHz, CD_3OD) δ (two rotamers) 8.07-8.03 (m, 1H), 7.74-7.60 (m, 3H), 7.50-7.16 (m, 9H), 4.34-4.05 (m, 6H), 3.67-3.58 (m, 1H), 3.46-3.40 (m, 1H), 2.93-2.77 (m, 2H), 2.23-2.18 (m, 2H), 1.62-1.34 (m, 12H), 0.84-0.74 (m, 6H) ^{13}C NMR (100 MHz, CD_3OD) δ (two rotamers) 175.8, 172.2, 156.9, 156.8, 149.6, 149.5, 143.8, 143.76, 143.6, 141.2, 141.14, 141.1, 135.41, 135.38, 130.6, 127.6, 127.58, 127.0, 125.3, 125.2, 124.98, 124.7, 124.4, 123.9, 122.8, 122.6, 119.9, 119.8, 119.1, 118.8, 118.7, 116.2, 116.07, 116.04, 115.2, 83.8, 83.6, 67.0, 66.8, 52.0, 50.5, 50.3, 47.0, 33.7, 33.66, 31.0, 30.9, 28.1, 27.6, 22.3, 22.1, 22.0. HRMS (ESI): Calc for $[C_{39}H_{45}N_3O_7Na]^+$, 690.3150; found, 690.3161.



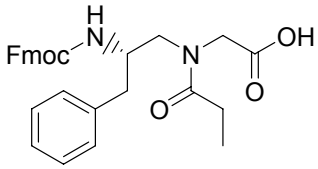
Compound **4b-1**. Yield 97%. $[\alpha]_D^{22}$=-3.92°. ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 7.69-7.65 (m, 2H), 7.52-7.49 (m, 2H), 7.32-7.22 (m, 4H), 5.53 (br.s, 1H), 4.39-3.77 (m, 6H), 3.40-2.97 (m, 2H), 2.30-2.16 (m, 2H), 1.58-1.1 (m, 6H), 0.84-0.72 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (two rotamers) 175.7, 156.8, 156.2, 144.0, 143.8, 143.84, 143.76, 141.2, 141.1, 127.6, 127.0, 125.2, 125.1, 119.8, 110.0, 66.7, 66.5, 53.7, 50.9, 49.2, 48.5, 47.1, 42.3, 41.4, 33.9, 31.1, 30.7, 27.8, 27.6, 24.7, 23.4, 23.3, 22.3, 22.1, 21.6. HRMS (ESI): Calc for $[C_{29}H_{38}N_2O_5K]^+$, 533.2412; found, 533.2411.



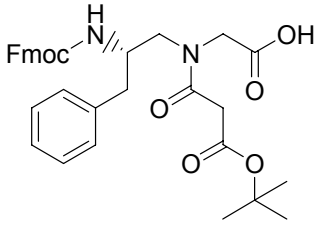
Compound **4b-2**. Yield 100%. $[\alpha]_D^{22}$=-1.4°. ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 7.77-7.70 (m, 2H), 7.57-7.52 (m, 2H), 7.37-7.27 (m, 4H), 5.22 (br.s 1H), 4.55-3.69 (m, 7H), 3.46-3.40 (m, 1H), 3.32-3.11 (m, 2H), 1.61-1.53 (m, 1H), 1.42-1.38 (m, 10H), 1.23-1.17 (m, 1H), 0.88-0.68 (m, ,6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (two rotamers) 168.7, 168.1, 167.1, 166.8, 156.7, 156.2, 144.1, 143.8, 143.7, 141.2, 141.1, 127.6, 127.5, 127.0, 125.2, 125.1, 125.0, 119.9, 119.8, 82.6, 82.1, 66.7, 66.5, 53.6, 51.0, 50.9, r48.4, 47.1, 42.2, 42.1, 41.7, 41.4, 27.9, 27.8, 24.7, 23.3, 23.2, 22.0, 21.6. HRMS (ESI): Calc for $[C_{30}H_{39}N_2O_7]^+$, 539.2752; found, 539.2736.



Compound **4c**. Yield 95%. $[\alpha]_D^{22}$=-0.80°. ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 7.71-7.69 (d, J = 8.0 Hz, 2H), 7.55-7.49 (m, 2H), 7.33-7.03 (m, 10H), 5.66-5.39 (m, 1H), 4.31-4.24 (m, 2H), 4.14-3.80 (m, 4H), 3.60-3.00 (m, 2H), 2.86-2.82 (m, 2H), 2.62-2.44 (m, 2H), 2.28-2.19 (m, 2H), 1.74-1.58 (m, 2H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (two rotamers) 174.5, 174.2, 172.9, 172.8, 157.1, 156.1, 143.9, 143.8, 143.7, 141.24, 141.1, 140.8, 140.7, 128.41, 128.38, 128.37, 128.3, 127.7, 127.1, 126.1, 126.06, 125.2, 124.96, 119.92, 119.89, 80.66, 66.9, 66.6, 53.1, 50.8, 50.3, 47.1, 34.8, 34.5, 32.0, 31.8, 31.2, 31.1, 28.2, 28.03, 28.01. HRMS (ESI): Calc for $[C_{35}H_{41}N_2O_7]^+$, 601.2908; found, 601.2890.



Compound **4d-1**. Yield 83%. $[\alpha]_D^{22}$=-6.6°. ^{1}H NMR (400 MHz, CD_3OD) δ (two rotamers) 7.2 (d, J = 8.0 Hz, 2H), 7.50-7.46 (m, 2H), 7.34-7.10 (m, 10H), 4.21-4.00 (m, 4H), 3.89-3.84 (m, 2H), 3.54-3.43 (m, 2H), 2.81-2.77 (m, 2H), 2.39-2.19 (m, 2H), 1.00 (t, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ (two rotamers) 176.3, 175.7, 175.3, 156.97, 143.82, 143.79, 141.1, 138.2, 137.97, 128.9 128.8, 128.0, 127.9, 127.3, 126.7, 126.1, 125.9, 124.9, 124.8, 124.75, 124.6, 66.4, 66.3, 52.5, 52.2, 51.9, 51.3, 51.0, 46.95, 46.92, 38.3, 38.2, 26.0, 25.5, 8.4, 8.3. HRMS (ESI): Calc for $[C_{29}H_{30}N_2O_5Na]^+$, 509.2047; found, 509.2036.



Compound **4d-2**. Yield 96%. $[\alpha]_D^{22}$=-3.26°. ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 7.73-7.72 (m. 2H),, 7.52-7.48 (m, 2H), 7.36-7.16 (m, 9H), 5.58 (br.s, 1H), 4.31-3.79 (m, 7H), 3.40-3.22 (m, 3H), 2.85-2.80 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (two rotamers) 174.3, 169.1, 168.3, 167.5, 167.3, 156.5, 156.2, 144.0, 143.9, 143.8, 141.2, 137.4, 129.4, 129.2, 128.6, 128.4, 127.7, 127.0, 126.7, 126.5, 125.3, 125.2, 119.8, 82.6, 82.1, 66.8, 66.6, 52.3, 51.6, 50.5, 47.0, 42.2, 41.4, 39.0, 38.4, 27.9. HRMS (ESI): Calc for $[C_{33}H_{36}N_2O_7Na]^+$, 595.2415; found, 595.2393.

3. Solid phase synthesis, purification and characterization of γ-AApeptides.

γ-AApeptides were prepared on a Knorr resin in peptide synthesis vessels on a Burrell Wrist-Action shaker following the standard Fmoc chemistry of solid phase peptide synthesis protocol. Each coupling cycle included an Fmoc deprotection using 20% Piperidine in DMF, and 4 h coupling of 1.5 equiv of γ-AApeptide building blocks onto resin in the presence 2 equiv of DIC (diisopropylcarbodiimide) / Oxohydroxybenzotriazole in DMF. After desired sequences were assembled, they were transferred into a 4 ml vial and cleaved from solid support in 74:24:2 TFA/CH_2Cl_2/triisopropylsilane for 2 h. Then solvent was evaporated and the residues were analyzed and purified on an analytical (1 ml/min) and a preparative Dionex (20 ml/min) HPLC systems, respectively. Both HPLC had same methods which were using 5% to 100% linear gradient of solvent B (0.1% TFA in acetonitrile) in A (0.1% TFA in water) over 40 min, followed by 100% solvent B over 10 min. The desired fractions were generally over 80% in crude (determined by HPLC) and eluted as single peaks at > 95% purity. They were collected and lyophilized. The molecular weights of γ-AApeptides were obtained on Bruker AutoFlex MALDI-TOF mass spectrometer using α–cyano-4-hydroxy-cinnamic acid as the matrix.

Table S1. MALDI-TOF MS analysis of AApeptides.

AApeptides	Formula	Mass calcd.	Mass found
1	$C_{57}H_{86}N_{10}O_{12}$	1103.35	1104.79 $(M + H)^+$
2	$C_{76}H_{104}N_{12}O_{16}$	1441.71	1442.96 $(M + H)^+$
3	$C_{79}H_{110}N_{12}O_{16}$	1483.79	1484.87 $(M+H)^+$

4. ELISA assay.

GST-MDM2-1-150 and full-length His6-p53 were expressed in *E. coli* and affinity purified under non-denaturing conditions. ELISA plates were incubated with 2.5 μg/ml His6-p53 in phosphate buffered saline (PBS) for 16 hrs. After washing with PBS+0.1% Tween 20 (PBST), the plates were blocked with PBS+5% non-fat dry milk+0.1% Tween 20 (PBSMT) for 0.5 hr. GST-HDM2 was mixed with inhibitors in PBSMT+10% glycerol+10 mM DTT and added to the wells. The plates were washed with PBST after incubating for 1 hr at room temperature, incubated with MDM2 antibody 4B2 in PBSMT for 1 hr, followed by washing and incubation with HRP-rabbit-anti-mouse Ig antibody for

1 hr. The plates were developed by incubation with TMB peroxidase substrate (KPL) and measured by absorbance at 450 nm.

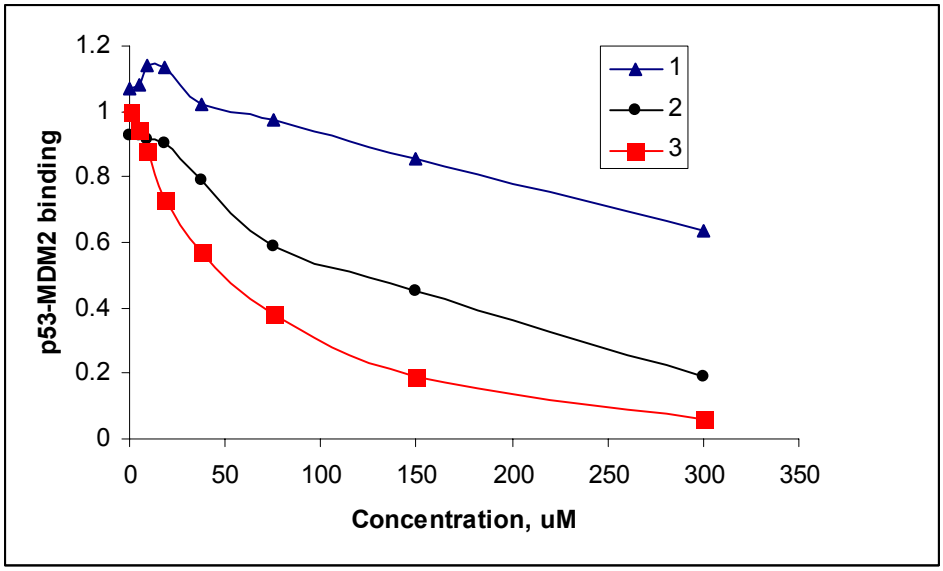


Figure S1. Inhibition of p53-MDM2 interaction by γ-AApeptides with ELISA assay.

5. Assay for enzymatic hydrolysis

γ-AApeptide **3** (1 mg/ml) was incubated with 0.1 mg/ml chymotrypsin (room temperature), thermolysin (37 ^{o}C), and pronase (37 ^{o}C) in 100 mM pH 7.8 ammonium bicarbonate buffer for 24 h, respectively. Then the reaction mixtures were analyzed by HPLC by comparing their retention time and integration to those of the starting material. A tiny shoulder (less that 5%) was observed at 37 ^{o}C even without enzyme incubation. This is due to the syn/anti isomerization of tertiary amide bond on the backbone. [3]

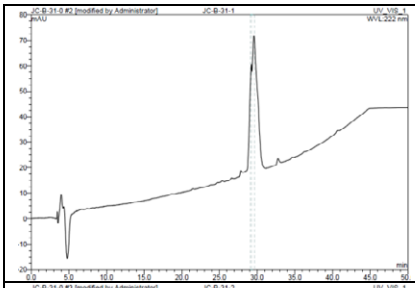
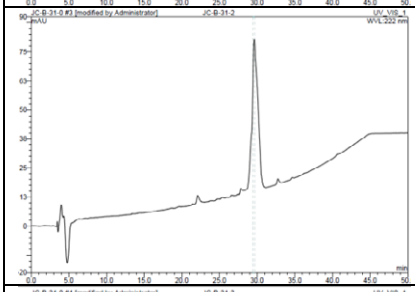
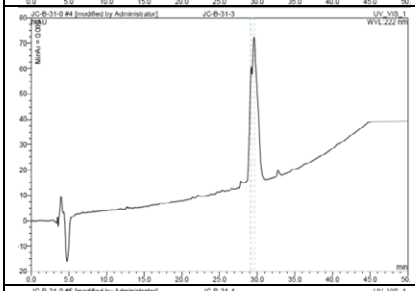
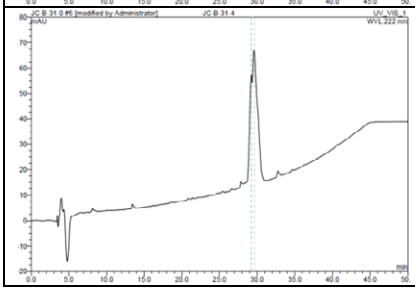
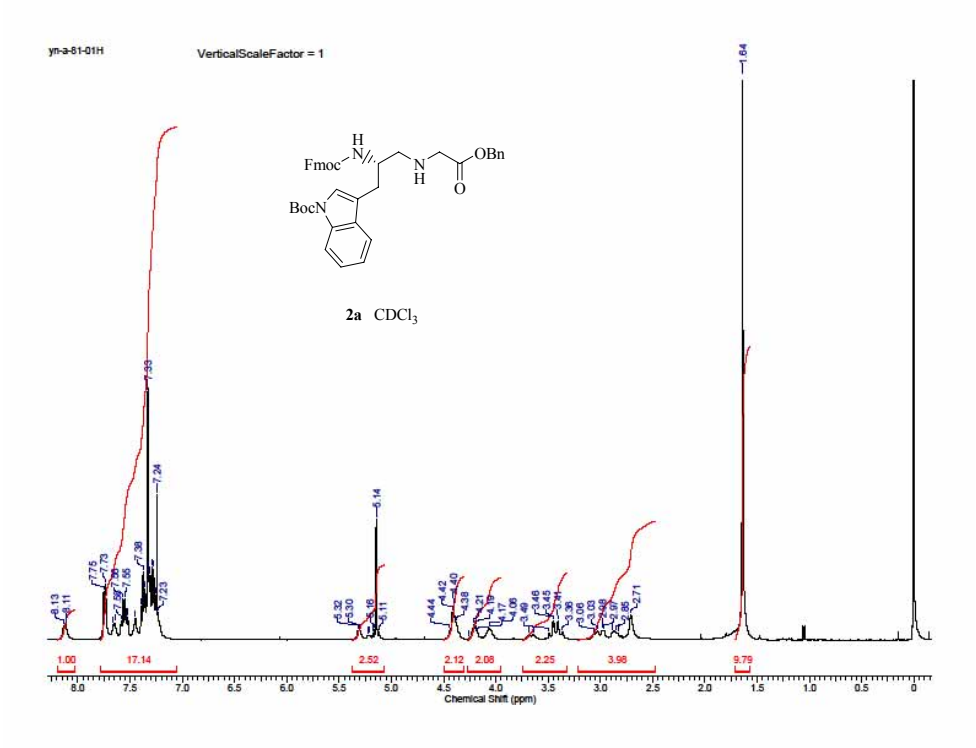
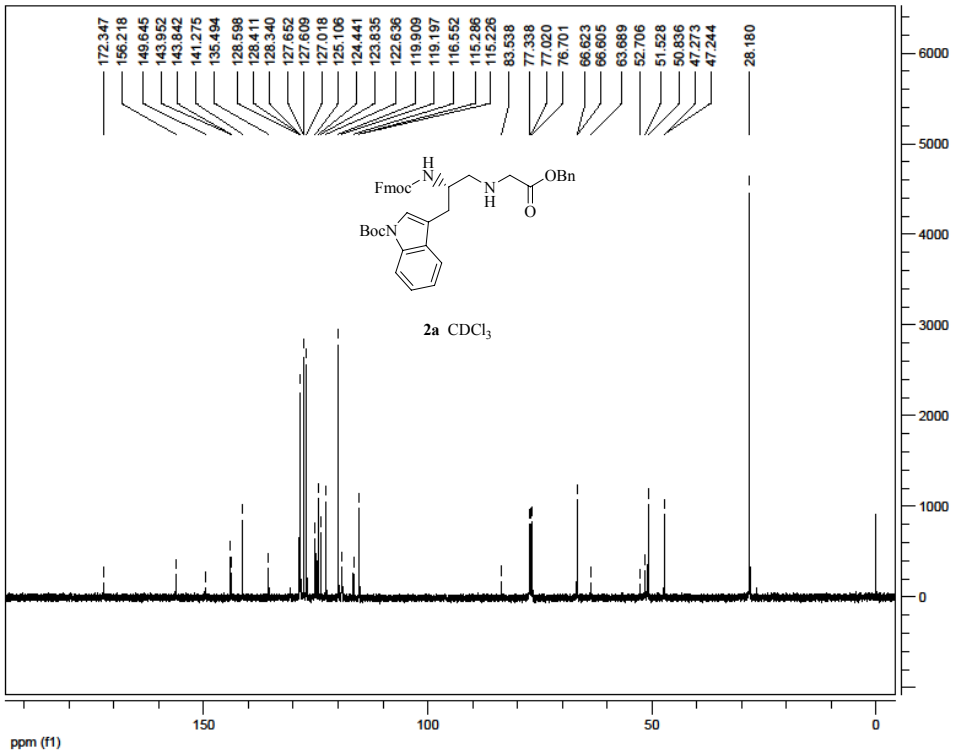
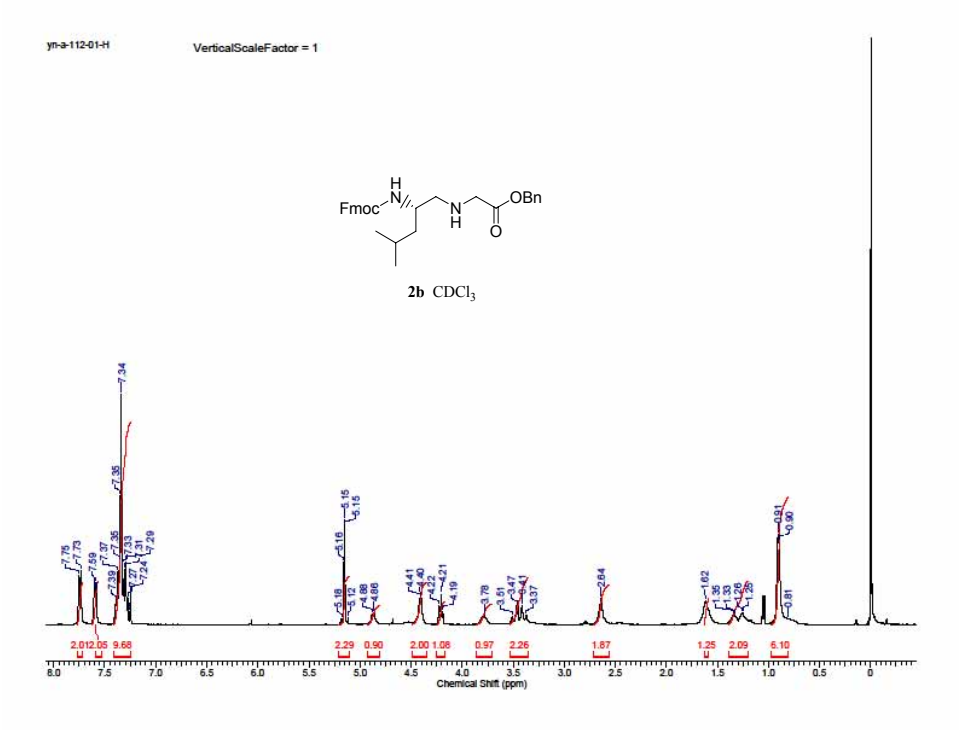
	γ-AApeptide **3** (37 ^{o}C)
	γ-AApeptide **3** + **chymotrypsin at RT**
	γ-AApeptide **3** + thermolysin (37 ^{o}C)
	γ-AApeptide **3** + pronase (37 ^{o}C)

Figure S2. Incubation of γ-AApeptides with different enzymes.

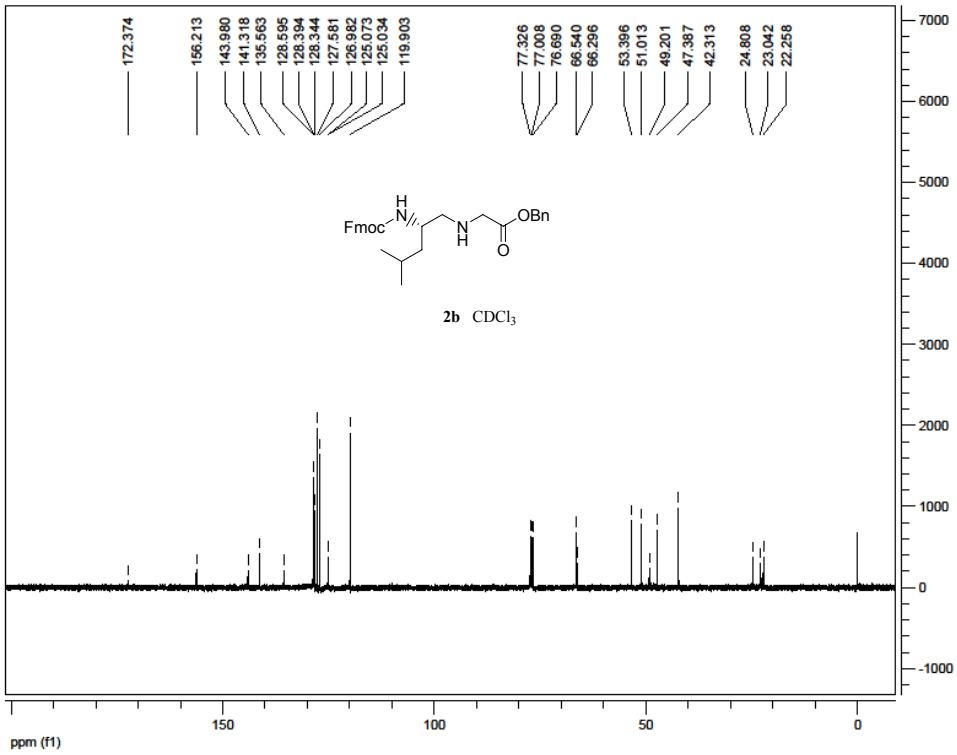
[1] F. Debaene, J. A. Da Silva, Z. Pianowski, F. J. Duran, N. Winssinger, *Tetrahedron* **2007**, *63*, 6577.
[2] F. Debaene, L. Mejias, J. L. Harris, N. Winssinger, *Tetrahedron* **2004**, *60*, 8677.
[3] A. S. Norgren, S. Zhang, P. I. Arvidsson, *Organic Letters* **2006**, *8*, 4533.



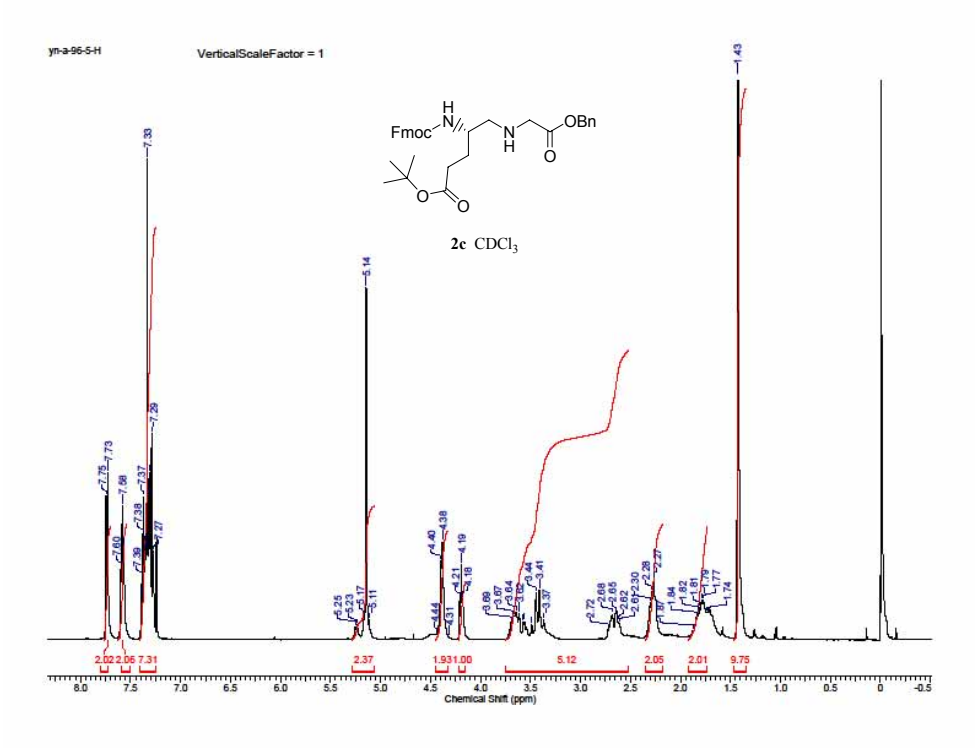


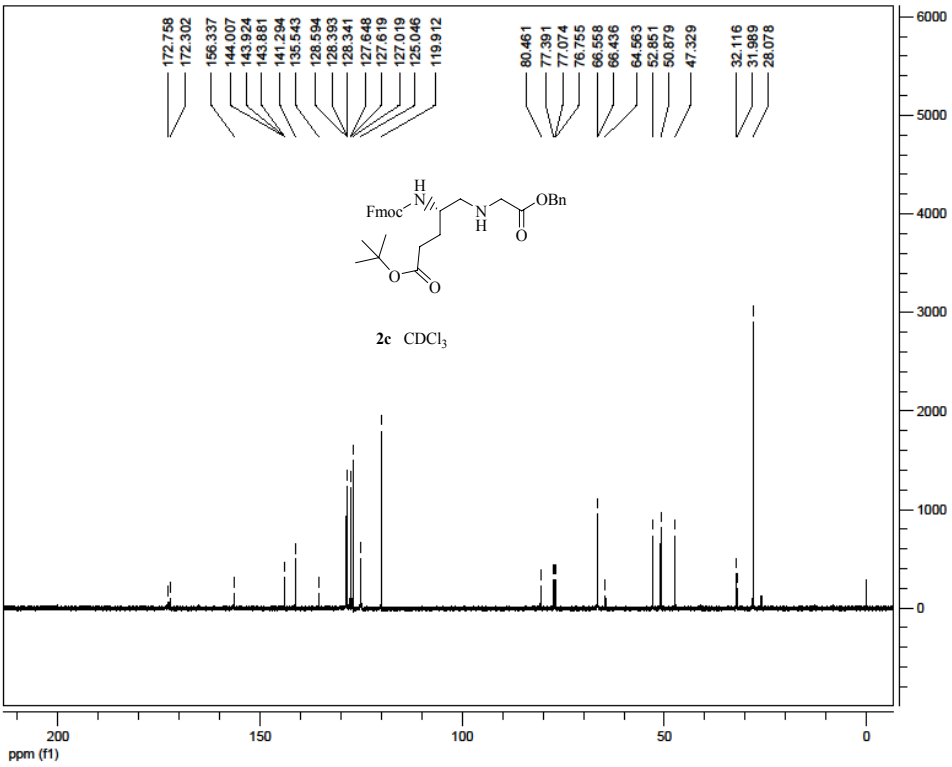


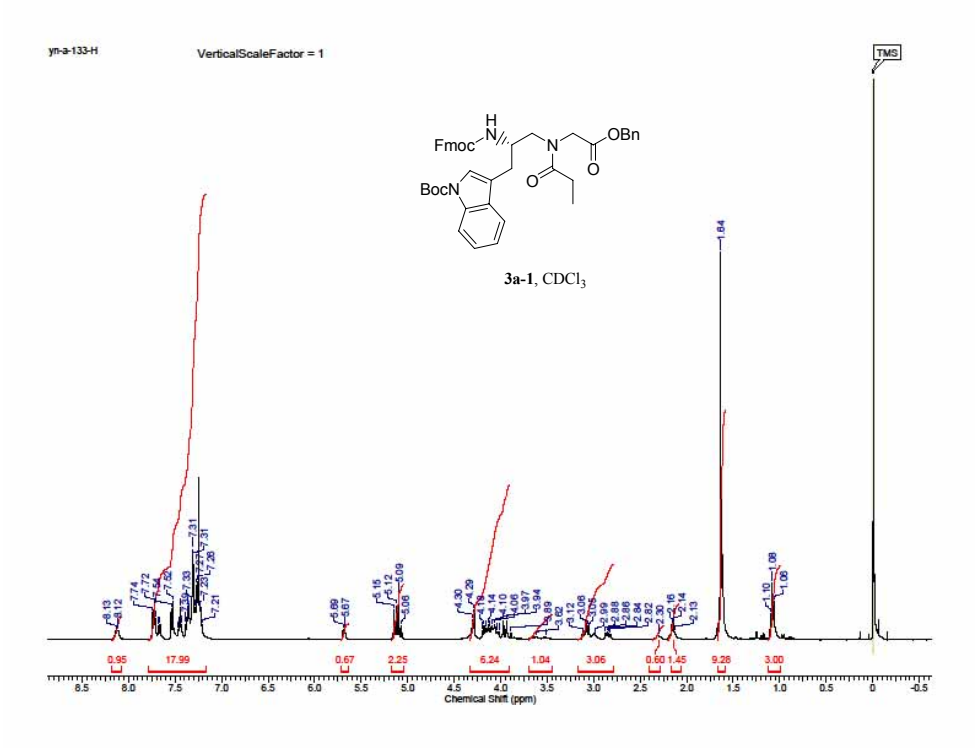
2b $CDCl_3$



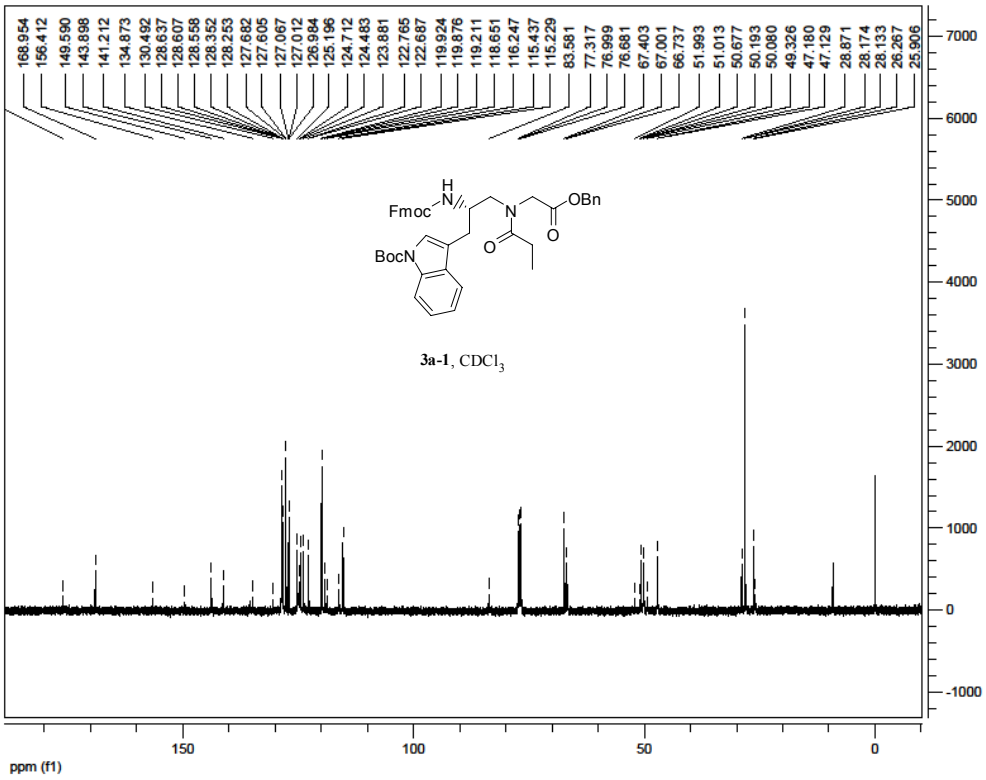
2b $CDCl_3$

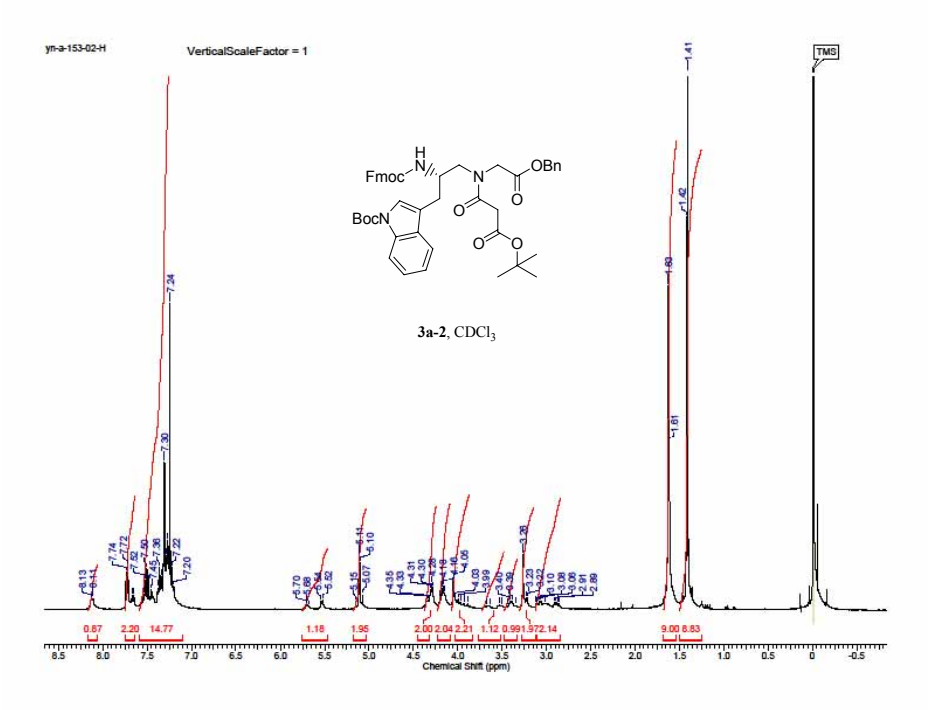






3a-1, $CDCl_3$





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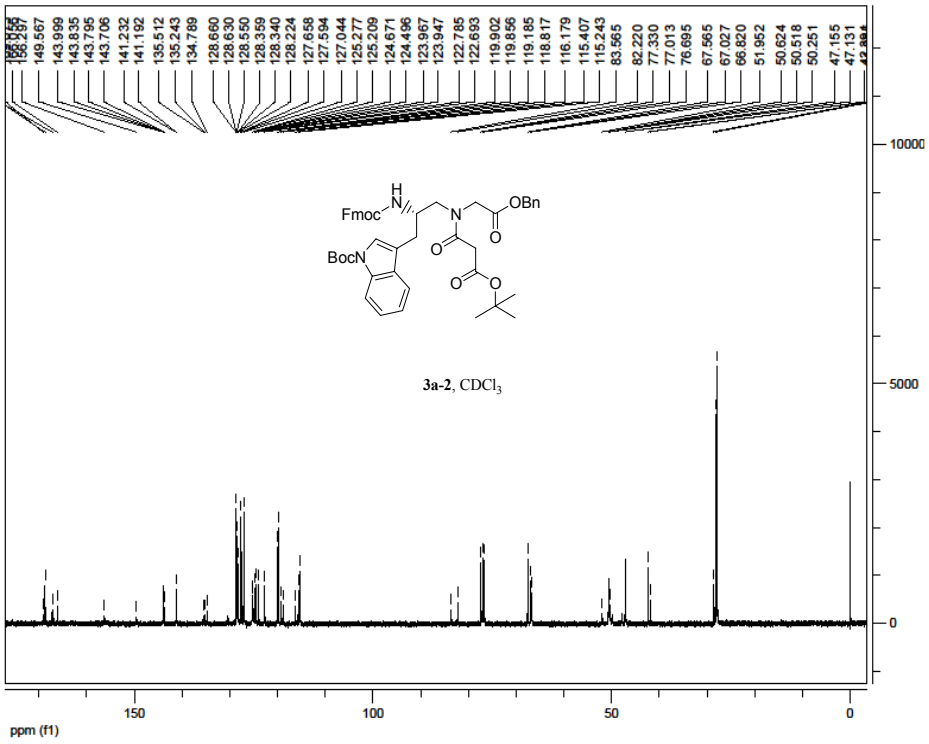

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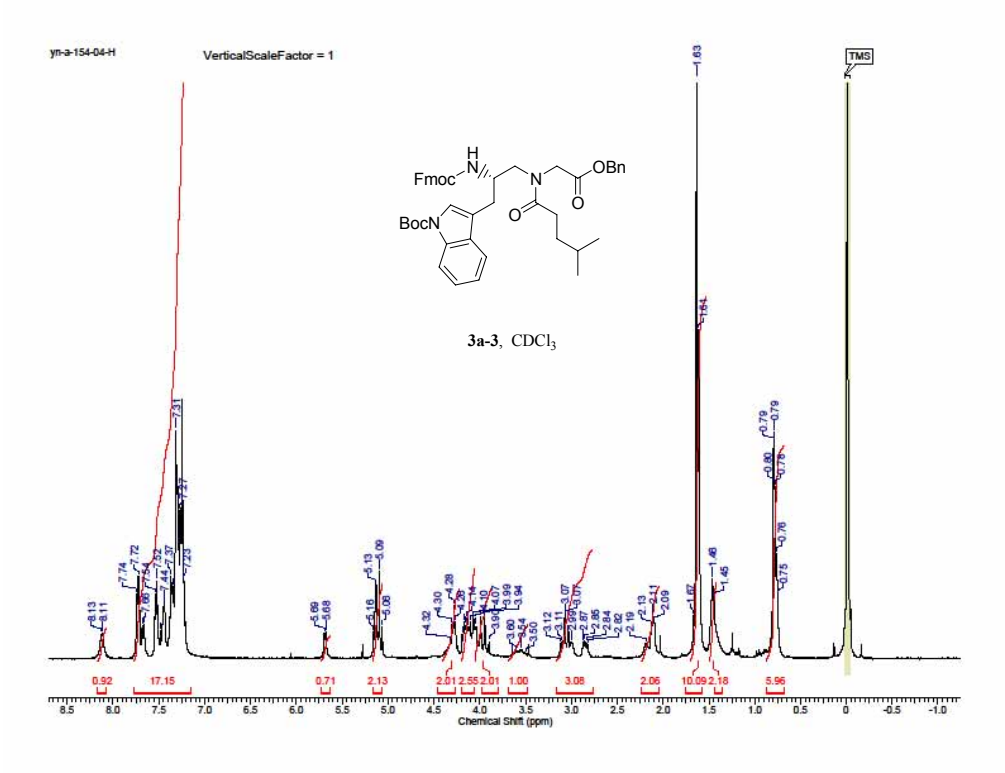

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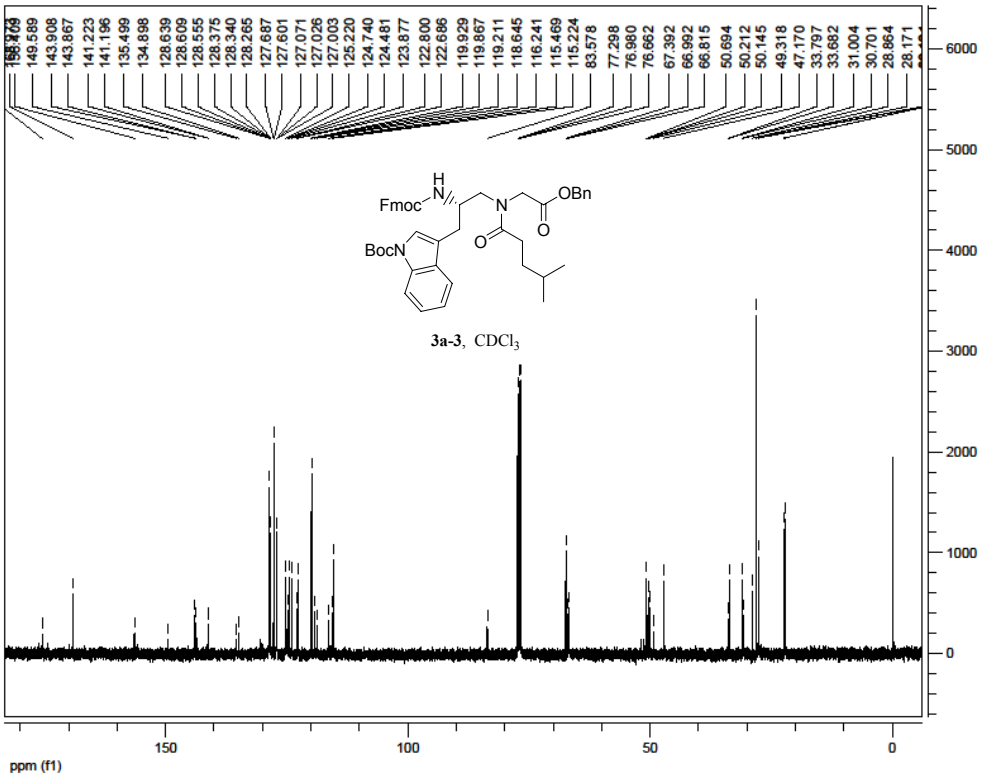
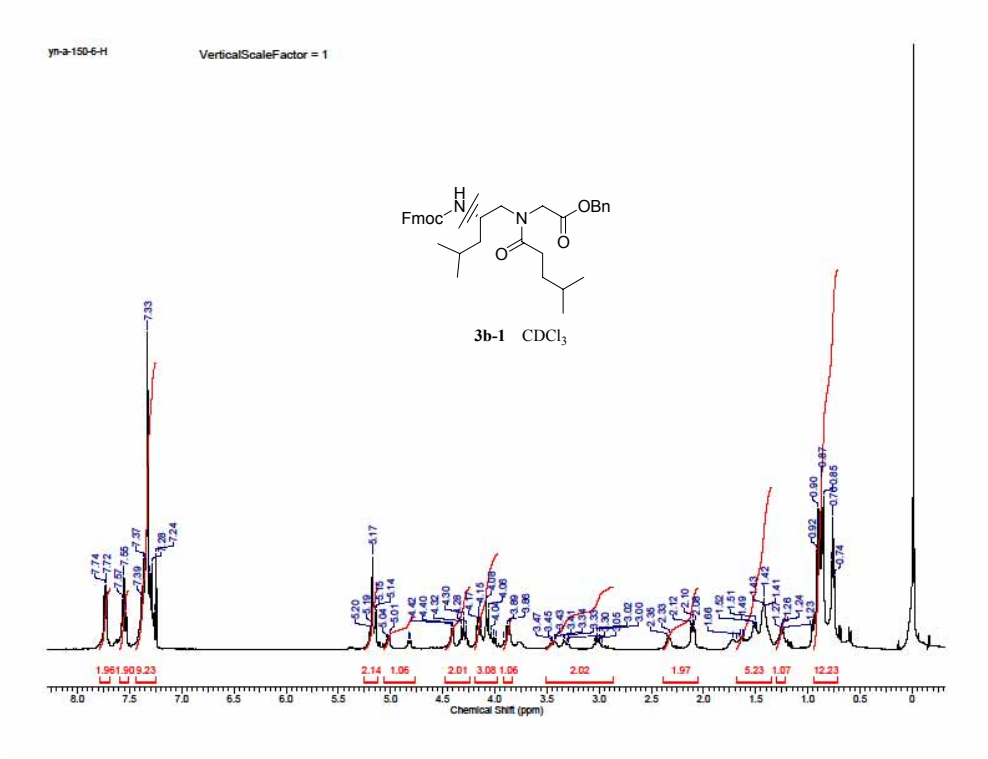
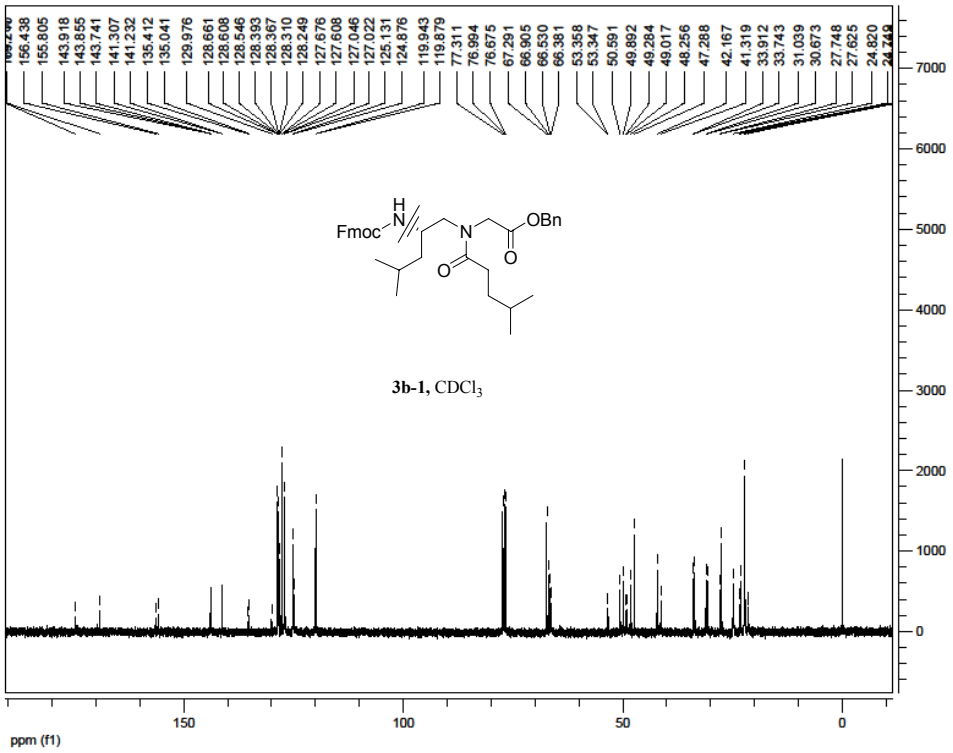
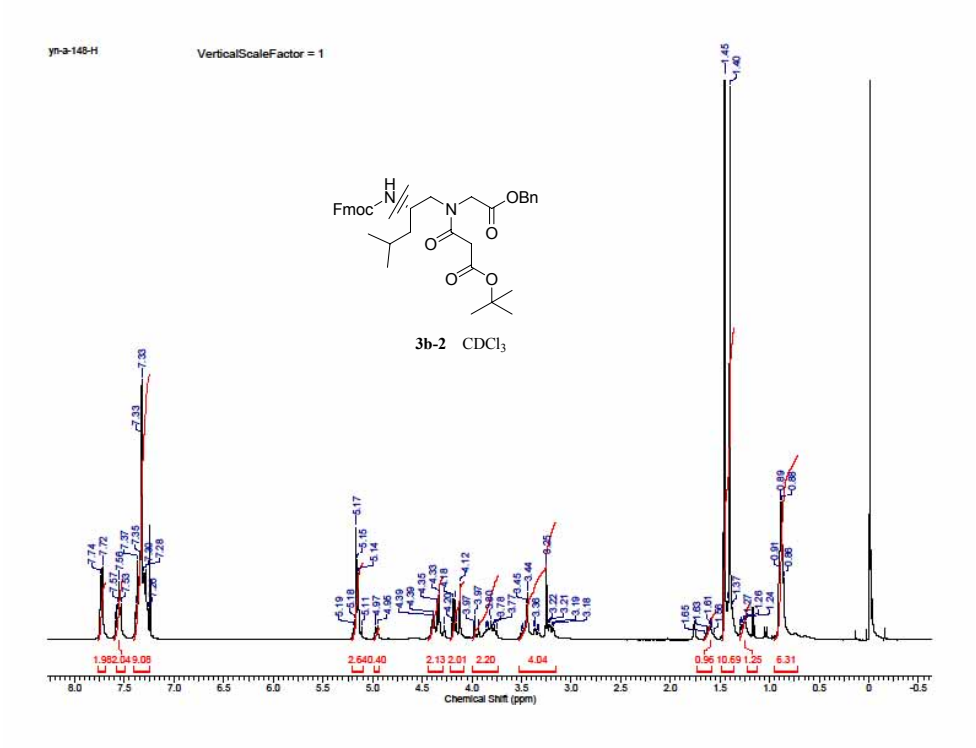
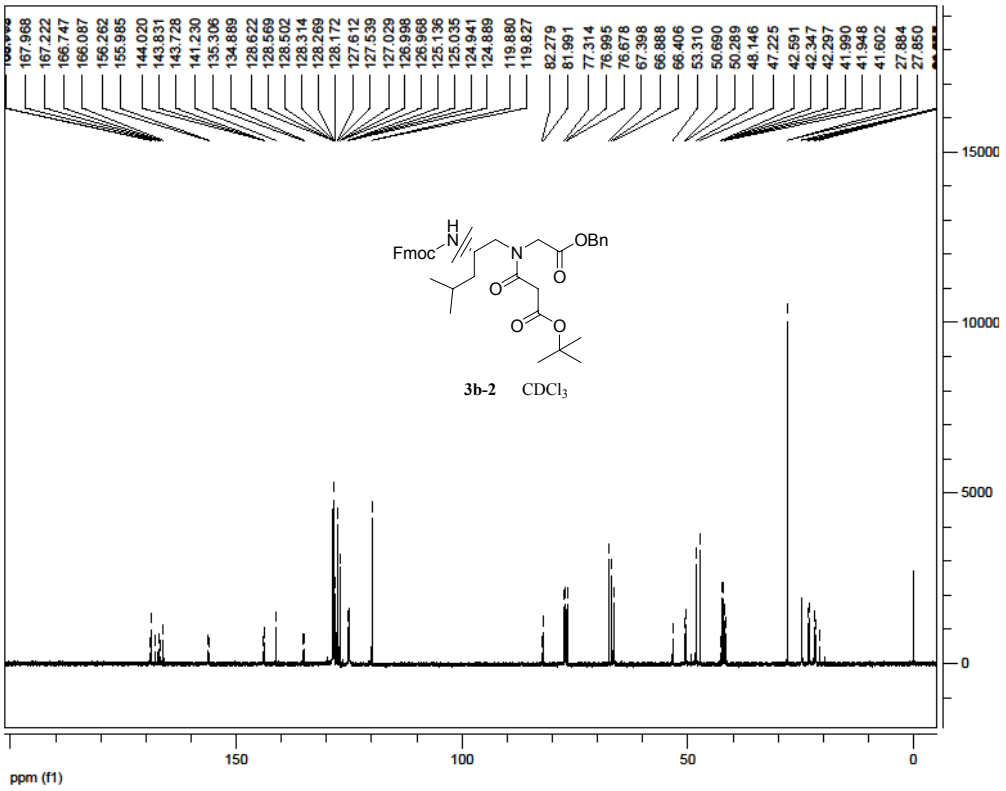






3b-1, $CDCl_3$





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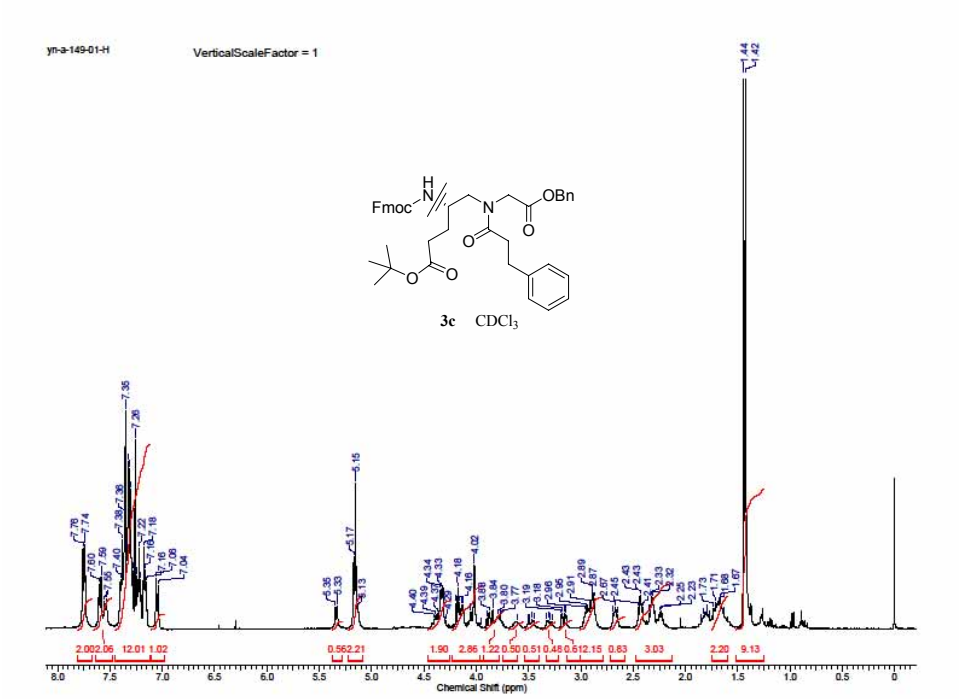
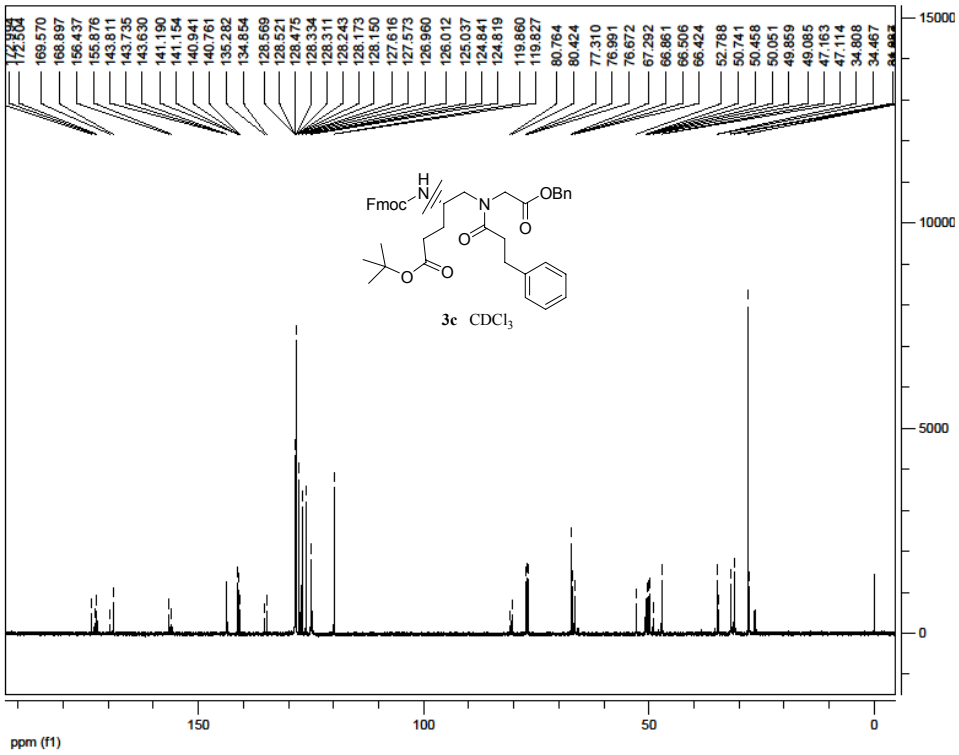
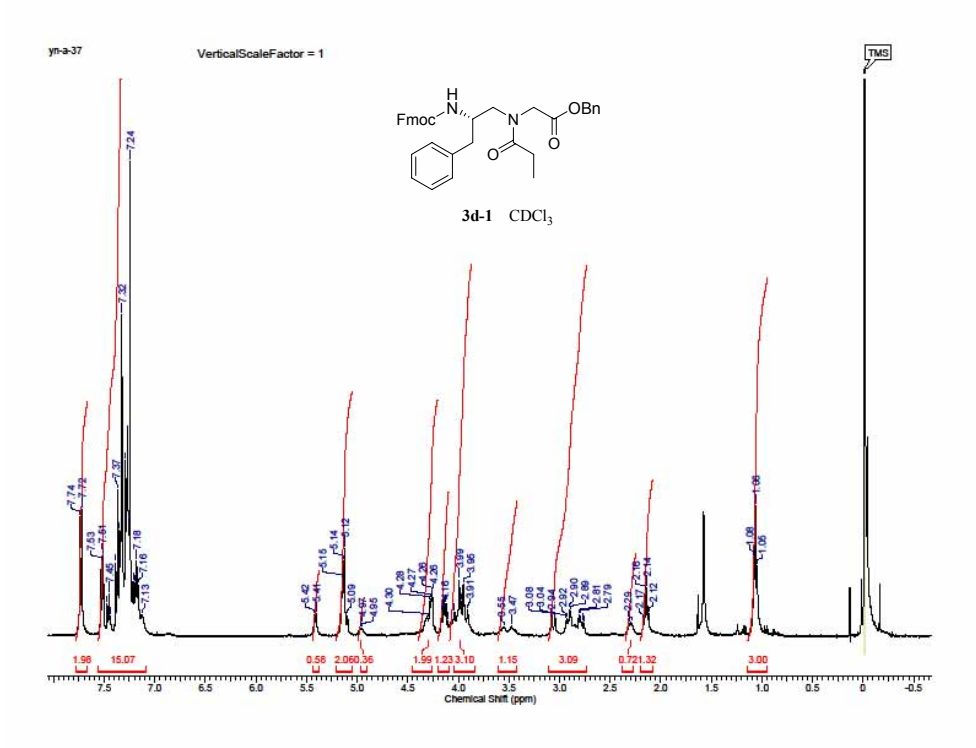
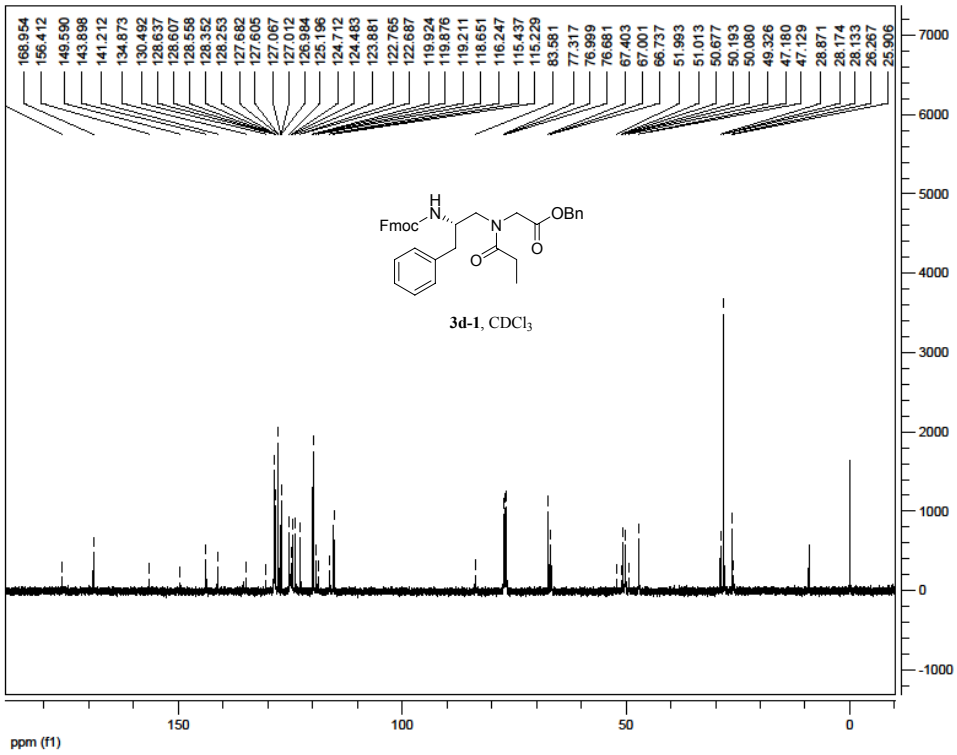
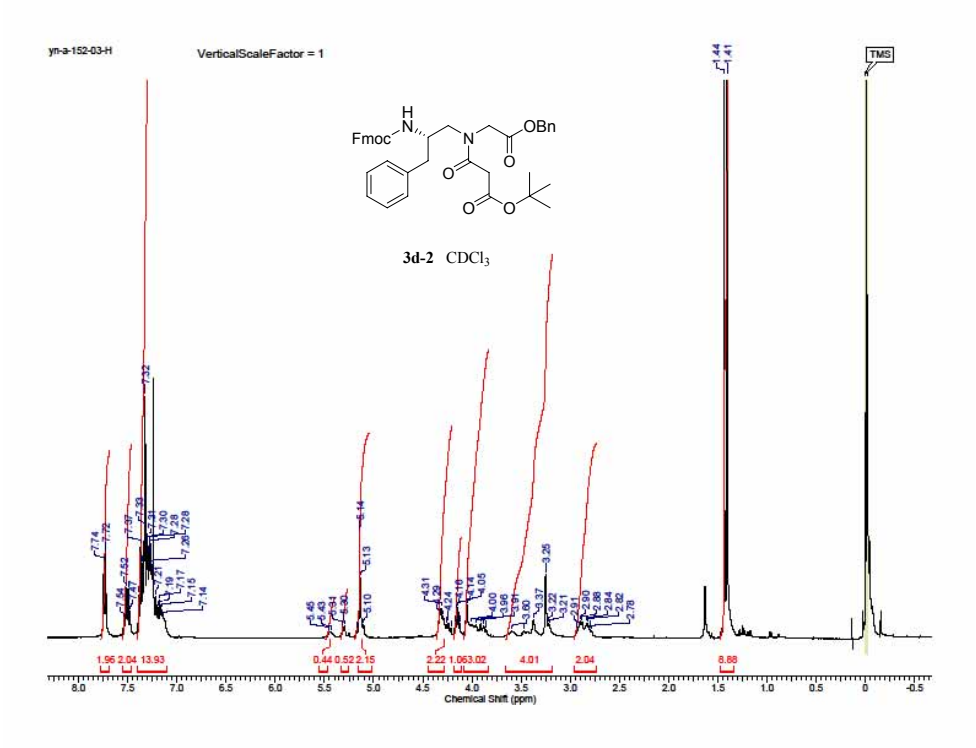


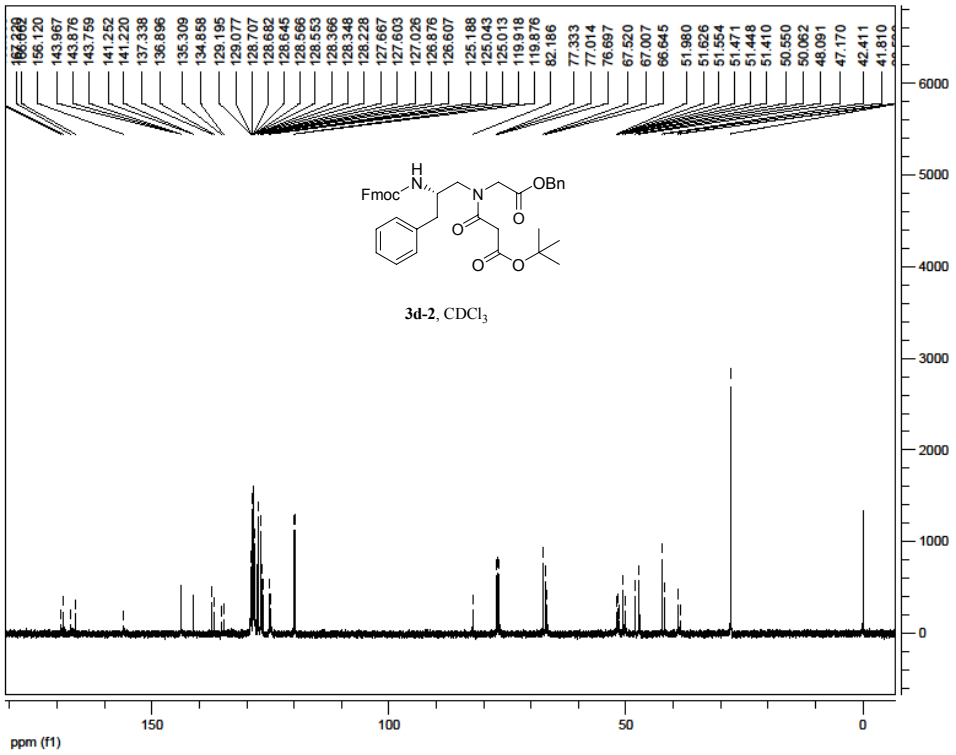




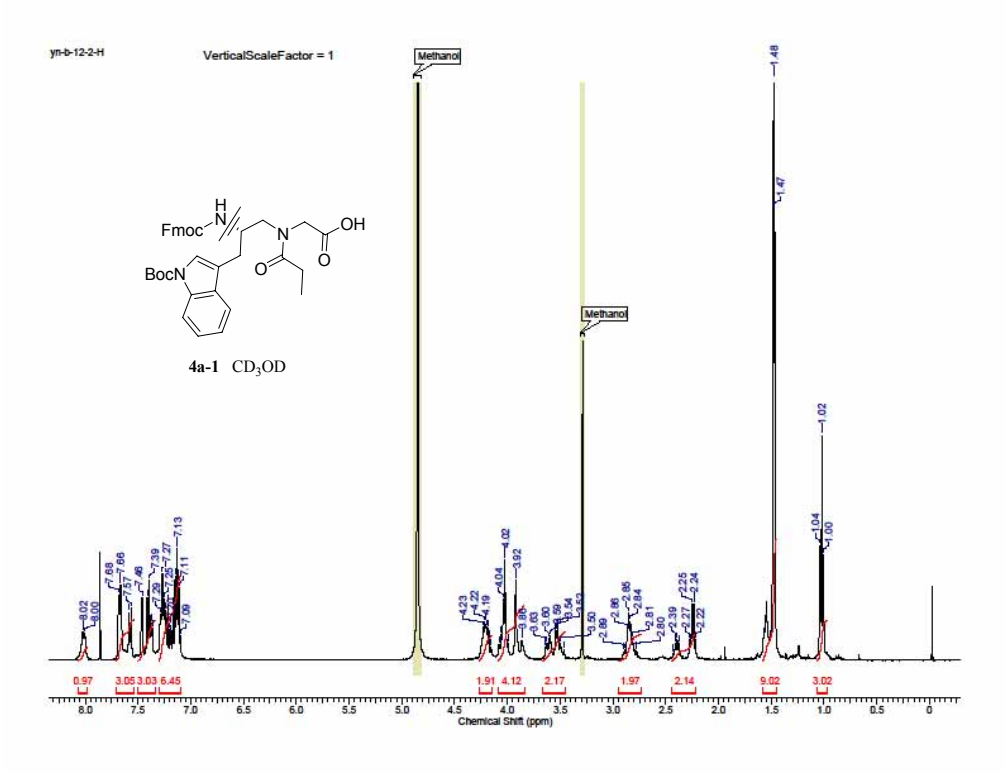


3d-1, $CDCl_3$

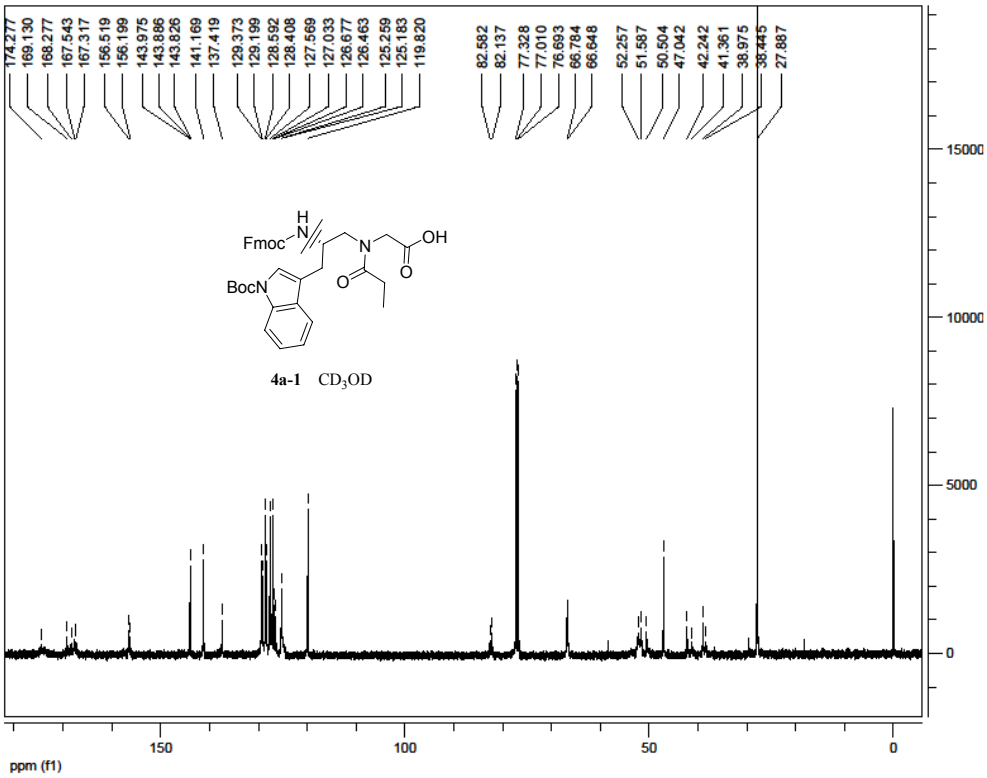


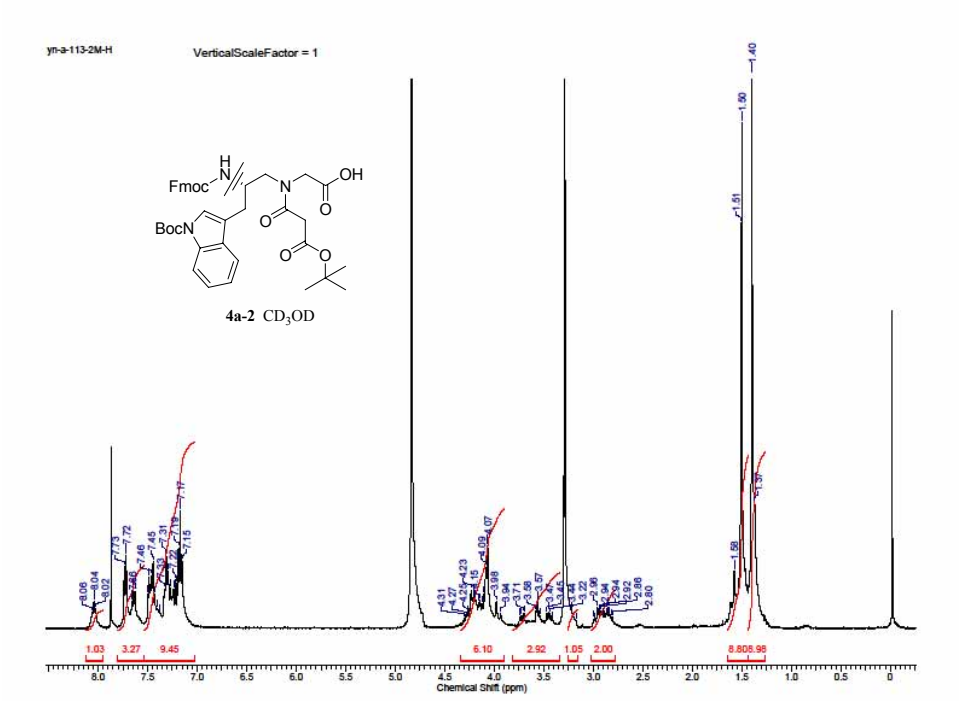


3d-2, $CDCl_3$



4a-1 CD_3OD





4a-2 CD_3OD

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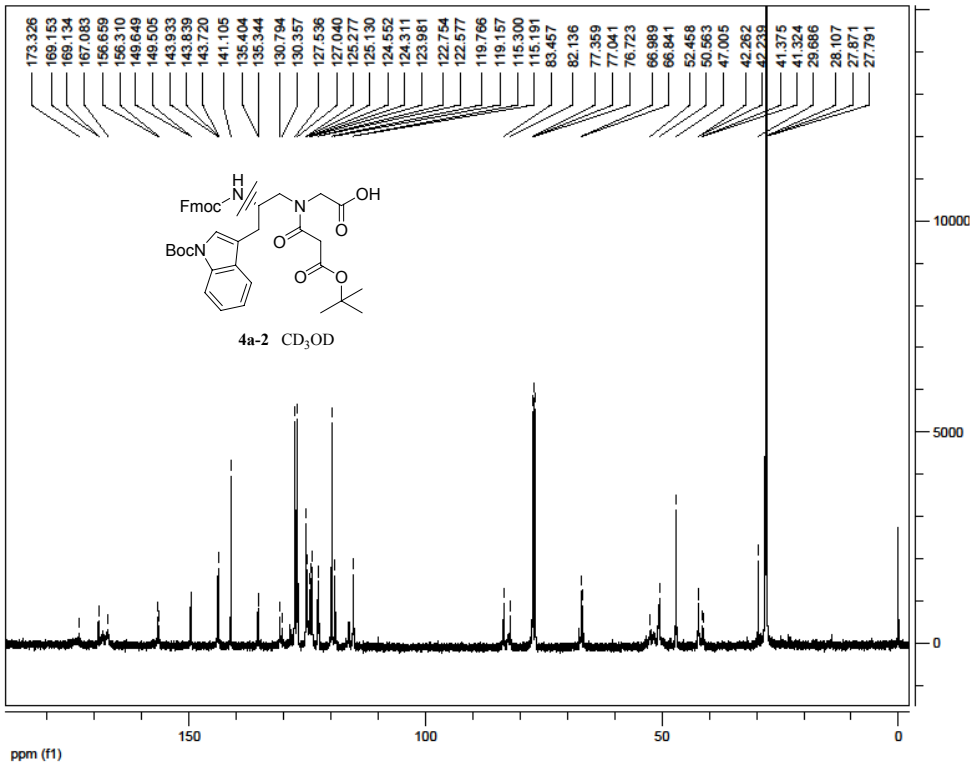
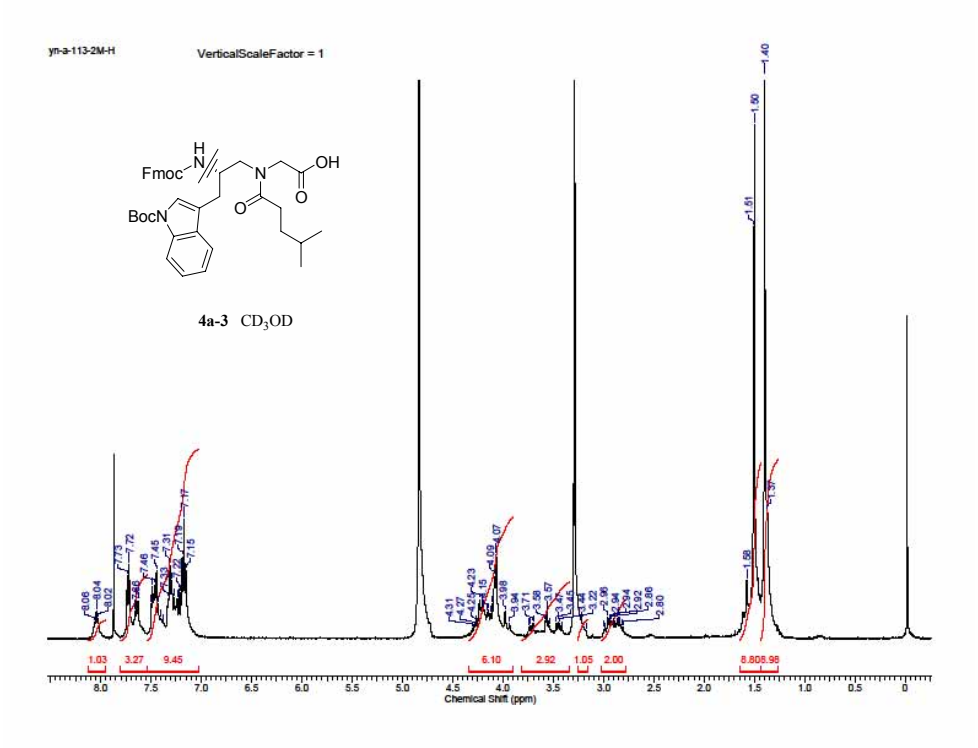
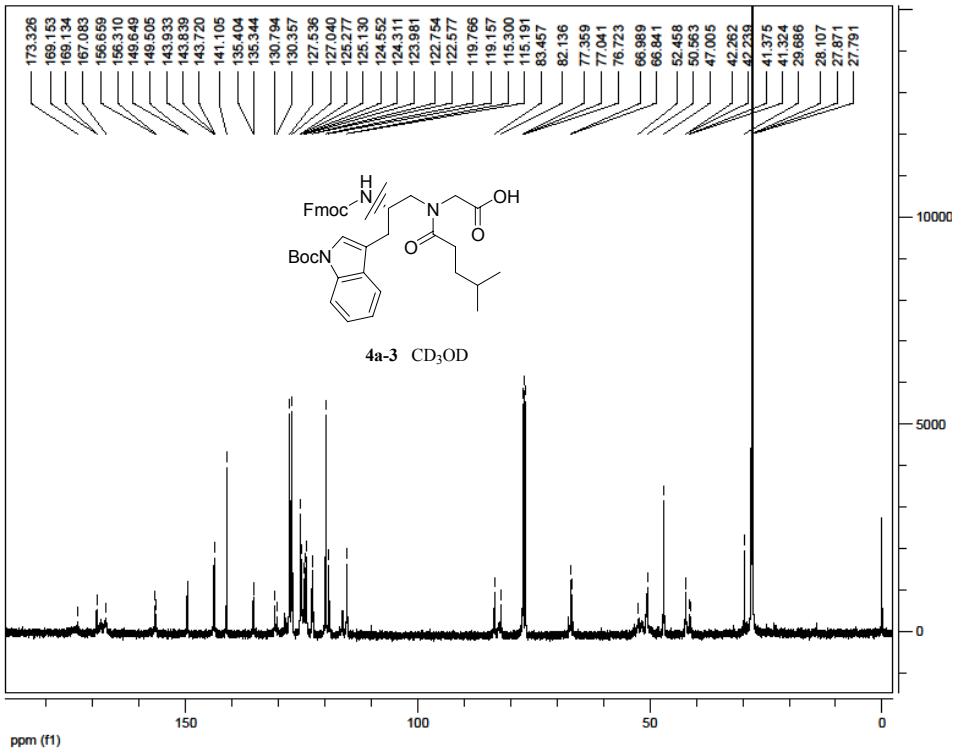
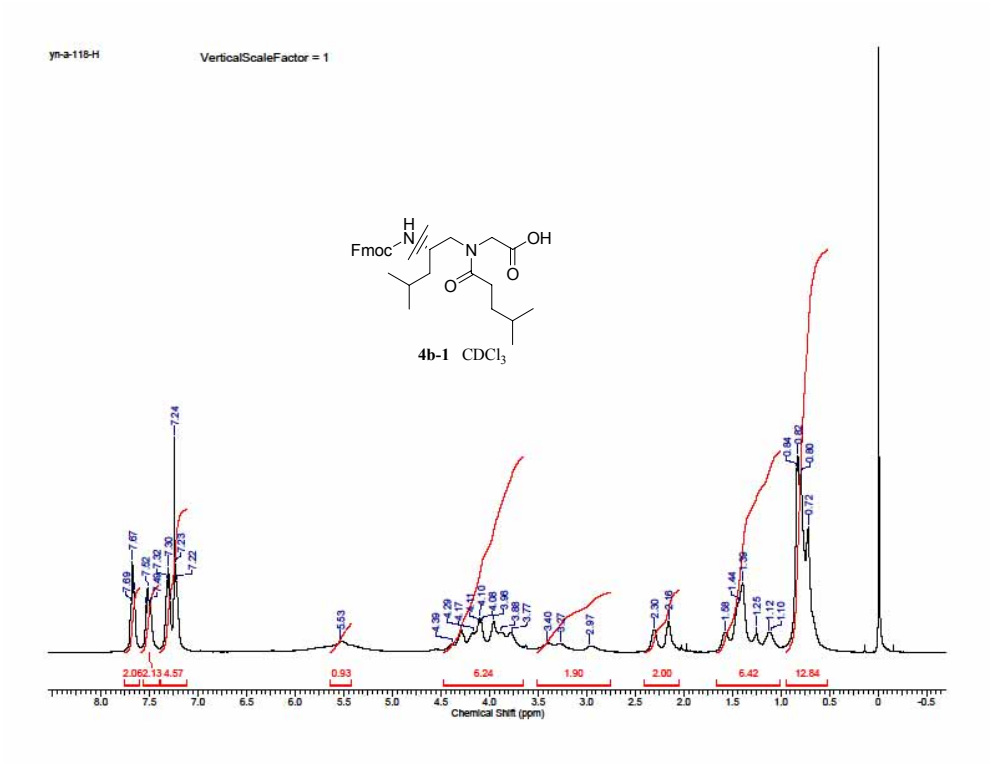
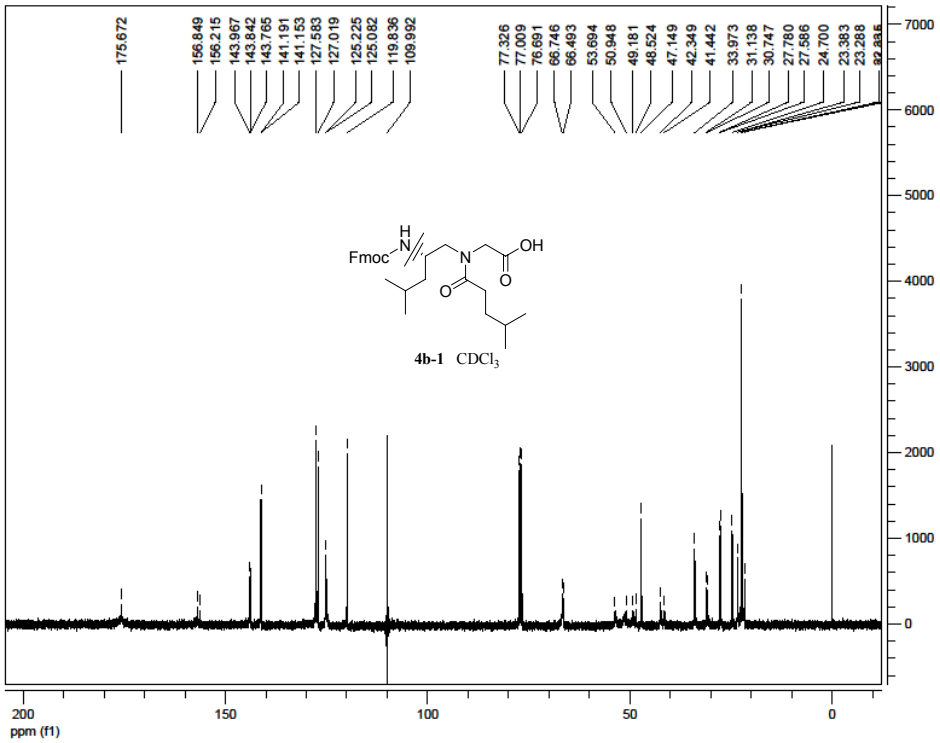


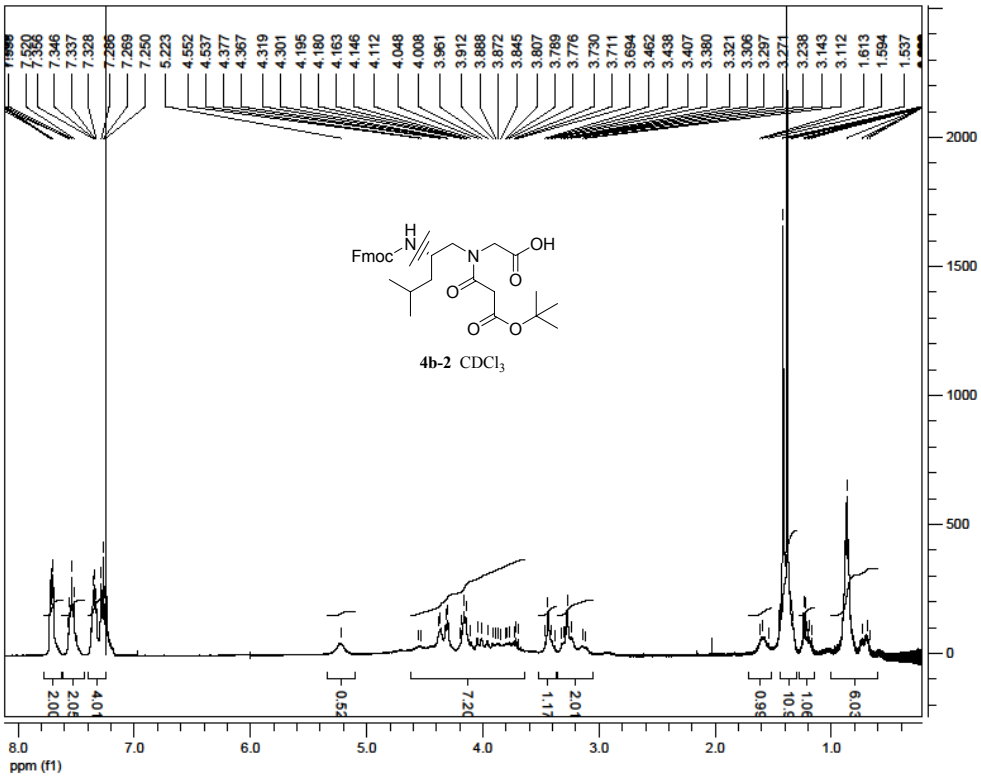




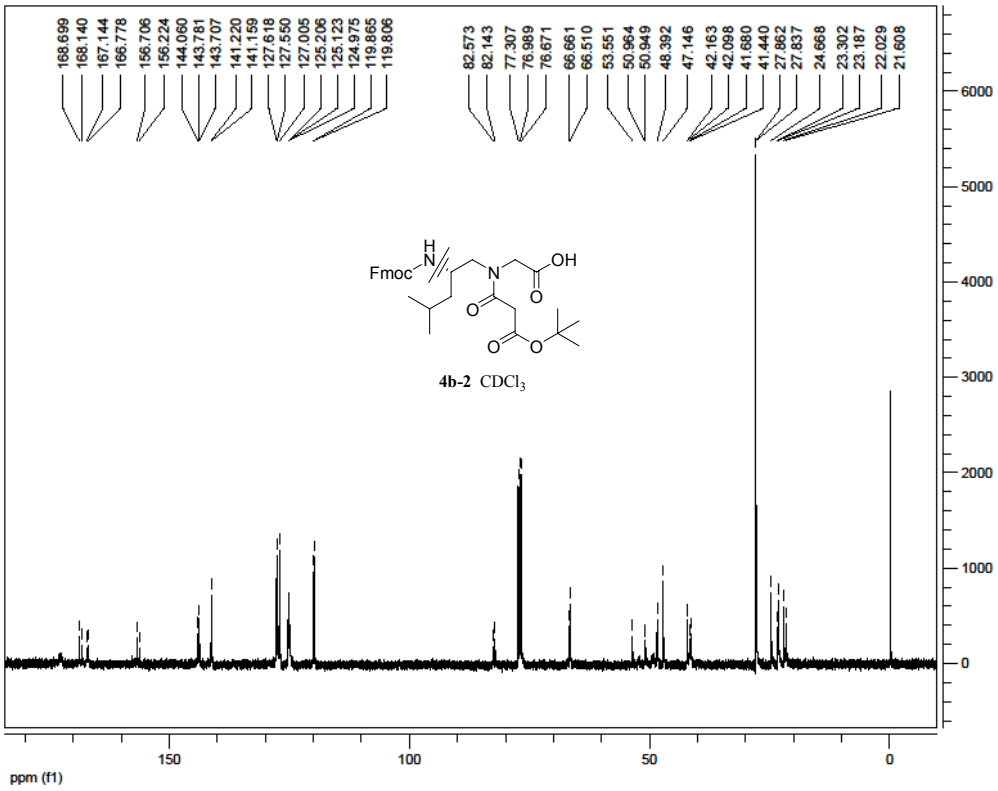
4a-3 CD_3OD







4b-2 $CDCl_3$



4b-2 $CDCl_3$