Supporting Information

Synthesis of some functionalized peptomers *via* Ugi four-component reaction

Eduardo H. B. Silva,[1] Flávio S. Emery,[2] Gino Del Ponte,[2] and Paulo M. Donate*[1]

[1] *Departamento de Química, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, Avenida Bandeirantes 3900, 14040-901, Ribeirão Preto, SP, Brazil*

[2] *Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Avenida do Café s/n°, 14040-903, Ribeirão Preto, SP, Brazil*

* Corresponding Author

E-mail: pmdonate@usp.br

1. General information

Unless noted otherwise, all the solvents and reagents were commercially available and used without further purification. Melting points were determined on a Reichert Kofler block apparatus and are uncorrected. Infrared spectra were measured with a Perkin Elmer Spectrum RX IFTIR System, and only the most intense or representative bands are reported. Mass spectra were acquired on an UltroTOF-Q mass spectrometer (Bruker Daltonics, Billerica, MA, USA) fitted with an ESI operating in the positive ion mode. ^{1}H NMR spectroscopy was performed on a Bruker DRX-400 instrument (Bruker, Fällanden, Switzerland) operating at 400 and 100 MHz for ^{1}H and ^{13}C, respectively. TMS was used as internal standard. The chemical shifts are reported in ppm (δ); the coupling constants (*J*) are given in Hertz (Hz). The following abbreviations were used to designate chemical shift multiplicities: d = doublet, m = multiplet, q = quadruplet, s = singlet, t = triplet. All the reactions were monitored by TLC using on pre-coated aluminum sheets (silica gel 60 F_{254}).

2. General Procedures for the Synthesis of Peptomers

2.1. General Procedure for the Ugi-4CR reaction:

In a round bottom flask of 5 ml was prepared a solution of *n*-butyl amine (0.5 mmol) and the corresponding aldehyde (0.5 mmol), dissolved in anhydrous methyl alcohol (1 mL). To this solution was added anhydrous $MgSO_4$ (0.05 g), the suspension was stirred at room temperature for 3 h and then was filtered. To the clear solution were added the Fmoc-protected amino acid (0.5 mmol) and the corresponding isocyanide (0.5 mmol). The reaction mixture was stirred at room temperature for 24 h. The solvent of the reaction mixture was removed under reduced pressure and the residue was purified by column chromatography through silica gel using as an eluent a mixture of dichloromethane and methanol (95:5 v/v) to give the peptomers **10**, **13a-f**, **15** (67-80% yields). All products were analyzed by HRMS, IR and NMR, and the spectra were consistent with the structures of the desired products.

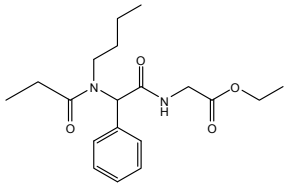
2.2. General Procedure for the Ugi 5C-4CR reaction:

In a round bottom flask of 25 ml was prepared a solution of α-amino acid (1 mmol) in anhydrous methyl alcohol (10 mL). The solution was cooled to –30 ºC and then was added benzaldehyde (1 mmol) and the corresponding isocyanide (1 mmol). The reaction mixture was stirred at –30 ºC for 3 h and after allowed to rise slowly to room temperature was stirred

for an additional 4 h. The solvent of the reaction mixture was removed under reduced pressure and the remaining/residual α-amino acid was extracted with a mixture of ethyl ether and water (1:1 v/v). The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography through silica gel using as an eluent a mixture of *n*-hexane and ethyl acetate (40:60 v/v) to give the peptomers **17a-c** (72-75% yields). All products were analyzed by HRMS, IR and NMR, and the spectra were consistent with the structures of the desired products.

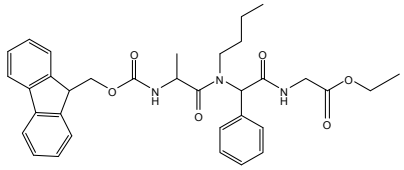
3. Characterization Data for Compounds

Compound 10:



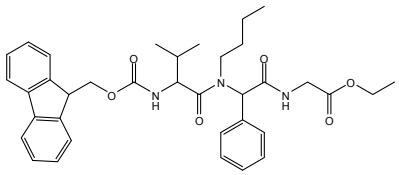
HRMS (ESI-TOF): calculated for $C_{19}H_{29}N_2O_4^+$ (MH^+): 349.2127, found: 349.2133.
IR (KBr) ν: 3298 (N–H), 1752 (C=O), 1686 (C=O), 1654 (C=O), 1196 (C–O).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.74 (t, *J* = 7.27 Hz, 3H), 1.19 (t, *J* = 7.40 Hz, 3H), 1.27 (t, *J* = 7.01 Hz, 3H), 1.41 (m, 4H), 2.31 (q, *J* = 7.40 Hz, 2H), 3.27 (m, 2H), 4.06 (m, 2H), 4.19 (q, *J* = 7.01 Hz, 2H), 6.45 (s, 1H), 7.35 (m, 4H), 7.41 (m, 1H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.52 (CONH), 169.06 (CON), 168.43 (COO), 130.80, 129.08, 127.74, 127.09, 65.51 (CHN), 61.50 (CH_2O), 49.52 (CH_2N), 41.25 (CH_2NH), 30.76 (CH_2), 26.32 (CH_2), 20.09 (CH_2), 14.11 (CH_3), 13.72 (CH_3), 12.64 (CH_3).

Compound 13a:



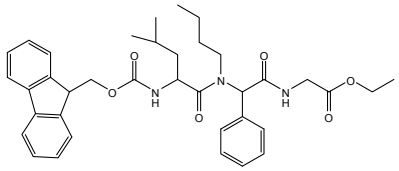
HRMS (ESI-TOF): calculated for $C_{34}H_{40}N_3O_6^+$ (MH^+): 586.2917, found: 586.2923.
IR (KBr) ν: 3296 (N–H), 1736 (C=O), 1718 (C=O), 1686 (C=O), 1654 (C=O).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.84 (t, *J* = 6.68 Hz, 3H), 1.30 (d, *J* = 6.84 Hz, 3H), 1.31 (t, *J* = 6.96 Hz, 3H), 1.43 (m, 4H), 3.04 (m, 2H), 3.58 (m, 2H), 3.75 (q, *J* = 6.96 Hz, 2H), 3.79 (t, *J* = 7.24 Hz, 1H), 4.21 (d, *J* = 7.24 Hz, 2H), 4.37 (q, *J* = 6.84 Hz, 1H), 6.32 (s, 1H), 7.33 (m, 9H), 7.60 (m, 2H), 7.73 (m, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.10 (CON), 169.29 (CONH), 168.82 (COO), 155.57 (COONH), 143.52, 141.01, 130.87, 129.16, 127.50, 127.45, 126.81, 124.86, 121.06, 119.72, 66.70 (CH_2O), 61.22 (CHN), 60.22 (CH_2O), 50.22 (CH_2N), 49.52 (CHNH), 46.84 (CH), 40.93 (CH_2NH), 30.56 (CH_2), 20.82 (CH_2), 18.42 (CH_3), 13.83 (CH_3), 13.47 (CH_3).

Compound 13b:



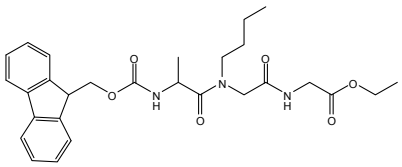
HRMS (ESI-TOF): calculated for $C_{36}H_{44}N_3O_6^+$ (MH^+): 614.3230, found: 614.3235.
IR (KBr) ν: 3352 (N–H), 1738 (C=O), 1732 (C=O), 1686 (C=O), 1640 (C=O), 1242 (C–O).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.84 (m, 3H), 0.93 (m, 6H), 1.25 (t, *J* = 7.10 Hz, 3H), 1.46 (m, 4H), 2.08 (m, 1H), 3.46 (m, 2H), 4.05 (m, 3H), 4.18 (m, 3H), 4.32 (d, *J* = 7.18 Hz, 2H), 6.07 (s, 1H), 7.30 (m, 2H), 7.36 (m, 6H), 7.43 (m, 1H), 7.60 (m, 2H), 7.75 (m, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.19 (CON), 173.70 (CONH), 169.53 (COO), 157.18 (COONH), 144.37, 141.75, 130.95, 129.25, 128.23, 128.17, 127.55, 126.68, 125.69, 120.46, 67.42 (CH_2O), 64.14 (CHN), 62.02 (CH_2O), 56.34 (CHNH), 50.86 (CH_2N), 47.65 (CH), 40.04 (CH_2NH), 31.58 (CH), 30.18 (CH_2), 20.08 (CH_2), 18.19 (CH_3), 14.58 (CH_3), 13.97 (CH_3).

Compound 13c:



HRMS (ESI-TOF): calculated for $C_{37}H_{46}N_3O_6^+$ (MH^+): 628.3387, found: 628.3393.
IR (KBr) ν: 3338 (N–H), 1744 (C=O), 1706 (C=O), 1688 (C=O), 1654 (C=O), 1246 (C–O).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.93 (m, 9H), 1.27 (t, *J* = 7.10 Hz, 3H), 1.55 (m, 6H), 1.68 (m, 1H), 3.53 (m, 2H), 4.06 (m, 3H), 4.19 (m, 3H), 4.37 (d, *J* = 5.77 Hz, 2H), 6.13 (s, 1H), 7.27 (m, 2H), 7.37 (m, 6H), 7.44 (m, 1H), 7.58 (m, 2H), 7.73 (m, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.46 (CON), 169.25 (CONH), 168.50 (COO), 155.97 (COONH), 143.34, 140.74, 130.09, 129.06, 127.24, 127.16, 126.60, 126.54, 124.68, 119.45, 66.61 (CH_2O), 62.52 (CHN), 60.93 (CH_2O), 50.03 (CH_2N), 48.79 (CHNH), 46.58 (CH), 41.39 (CH_2), 39.04 (CH_2NH), 30.26 (CH_2), 24.38 (CH_3), 22.96 (CH), 19.44 (CH_2), 13.59 (CH_3), 12.98 (CH_3).

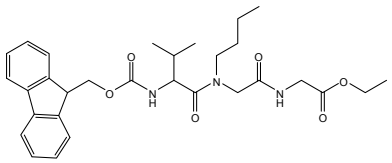
Compound 13d:



HRMS (ESI-TOF): calculated for $C_{28}H_{36}N_3O_6^+$ (MH^+): 510.2604, found: 510.2611.
IR (KBr) ν: 3382 (N–H), 1734 (C=O), 1718 (C=O), 1684 (C=O), 1654 (C=O), 1210 (C–O).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.93 (t, *J* = 7.58 Hz, 3H), 1.22 (m, 6H), 1.33 (m, 4H), 3.46 (m, 2H), 4.00 (m, 2H), 4.12 (m, 4H), 4.20 (t, *J* = 7.07 Hz, 1H), 4.36 (d, *J* = 7.07 Hz, 2H), 4.45 (q, *J* = 6.84 Hz, 1H), 7.29 (m, 2H), 7.39 (m, 2H), 7.58 (m, 2H), 7.75 (m, 2H).

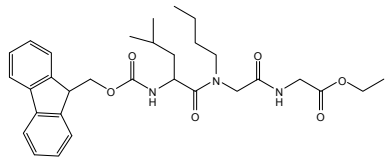
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.21 (CON), 169.47 (COO), 169.01 (CONH),156.50 (COONH), 143.76, 141.24, 127.67, 127.04, 125.07, 119.95, 67.09 (CH_2O), 61.45 (CH_2O), 55.80 (CH_2N), 50.40 (CH_2N), 47.13 (CHNH), 47.08 (CH), 41.20 (CH_2NH), 30.72 (CH_2), 19.86 (CH_2), 17.58 (CH_3), 14.06 (CH_3), 13.67 (CH_3).

Compound 13e:



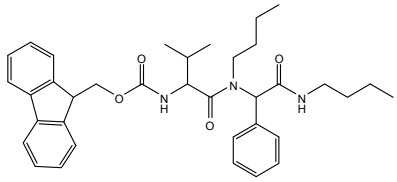
HRMS (ESI-TOF): calculated for $C_{30}H_{40}N_3O_6^+$ (MH^+): 538.2917, found: 538.2923.
IR (KBr) ν: 3322 (N–H), 1740 (C=O), 1706 (C=O), 1702 (C=O), 1654 (C=O), 1636 (C=O), 1244 (C–O).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.83 (t, *J* = 7.33 Hz, 3H), 0.93 (m, 6H), 1.20 (t, *J* = 7.20 Hz, 3H), 1.30 (m, 4H), 2.16 (m, 1H), 3.46 (m, 2H), 3.95 (m, 3H), 4.06 (q, *J* = 7.20 Hz, 2H), 4.20 (m, 2H), 4.29 (t, *J* = 6.82 Hz, 1H), 4.40 (d, *J* = 6.82 Hz, 2H), 7.29 (m, 2H), 7.36 (m, 2H), 7.58 (m, 2H), 7.73 (m, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.16 (COO), 169.83 (CON), 168.99 (CONH), 156.64 (COONH), 143.83, 141.21, 127.63, 127.01, 125.15, 119.92, 66.88 (CH_2O), 61.48 (CH_2O), 55.80 (CHNH), 50.32 (CH_2N), 49.52 (CH_2), 47.11 (CH), 39.50 (CH_2NH), 31.04 (CH), 29.64 (CH_2), 19.54 (CH_2), 17.65 (CH_3), 14.04 (CH_3), 13.43 (CH_3).

Compound 13f:



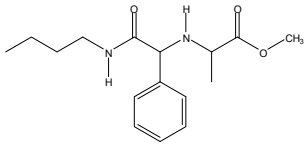
HRMS (ESI-TOF): calculated for $C_{31}H_{42}N_3O_6^+$ (MH^+): 552.3074, found: 552.3079.
IR (KBr) ν: 3348 (N–H), 1740 (C=O), 1706 (C=O), 1676 (C=O), 1654 (C=O), 1244 (C–O).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.92 (m, 9H), 1.20 (t, *J* = 7.20 Hz, 3H), 1.37 (m, 6H), 1.67 (m, 1H), 3.47 (m, 2H), 3.92 (m, 3H), 4.09 (q, *J* = 7.20 Hz, 2H), 4.19 (m, 2H), 4.25 (t, *J* = 6.75 Hz, 1H), 4.36 (d, *J* = 6.75 Hz, 2H), 7.28 (m, 2H), 7.37 (m, 2H), 7.57 (m, 2H), 7.74 (m, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.93 (CON), 169.72 (COO), 168.97 (CONH), 156.44 (COONH), 143.81, 141.21, 127.63, 127.01, 125.09, 119.92, 67.08 (CH_2O), 61.40 (CH_2O), 53.84 (CH_2N), 50.50 (CH_2N), 49.26 (CHNH), 47.10 (CH), 41.86 (CH_2), 39.51 (CH_2NH), 30.73 (CH_2), 24.85 (CH_3), 23.09 (CH), 19.91 (CH_2), 14.06 (CH_3), 13.68 (CH_3).

Compound 15:



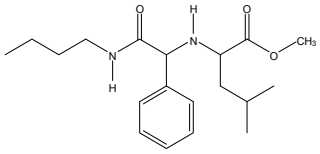
HRMS (ESI-TOF) calculated for $C_{36}H_{46}N_3O_4^+$ (MH^+): 584.3488, found: 584.3495.
IR (KBr) ν: 3284 (N–H), 1684 (C=O), 1676 (C=O), 1654 (C=O).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.93 (m, 12H), 1.28 (m, 4H), 1.51 (m, 4H), 2.00 (m, 1H), 3.21 (t, *J* = 6.54 Hz, 2H), 3.51 (t, *J* = 7.02 Hz, 2H), 3.98 (t, *J* = 8.30 Hz, 1H), 4.10 (t, *J* = 6.47 Hz, 1H), 4.33 (d, *J* = 6.47 Hz, 2H), 5.88 (s, 1H), 6.87 (m, 2H), 7.06 (m, 6H), 7.40 (m, 1H), 7.52 (m, 2H), 7.64 (m, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.15 (CON), 166.14 (CONH), 154.19 (COONH), 143.13, 141.39, 129.19, 128.85, 127.95, 127.82, 127.54, 126.60, 124.98, 119.48, 65.52 (CH_2O), 63.19 (CHN), 59.10 (CHNH), 53.40 (CH_2N), 44.95 (CH), 38.81 (CH_2NH), 31.57 (CH_2), 30.95 (CH), 29.12 (CH_2), 20.00 (CH_2), 18.79 (CH_2), 15.60 (CH_3), 13.52 (CH_3), 13.69 (CH_3).

Compound 17a:



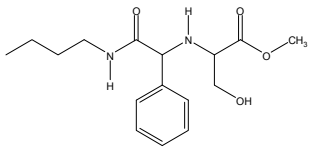
HRMS (ESI-TOF): calculated for $C_{16}H_{25}N_2O_3^+$ (MH^+): 293.1865, found: 293.1869.
IR (KBr) ν: 3330 (N–H), 1740 (C=O), 1666 (C=O), 1244 (C–O).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, *J* = 7;27 Hz, 3H). 1;30 (d, *J* = 6.92 Hz, 3H), 1.44 (m, 4H), 2.78 (q, *J* = 6.92 Hz, 1H), 3.21 (t, *J* = 6.75 Hz, 2H), 3.69 (s, 3H), 4.25 (s, 1H), 7.29 (m, 2H), 7.32 (m, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.07 (COO), 171.54 (CONH), 138.84, 128.86, 128.24, 127.66, 65.39 (CHNH), 54.34 (CHNH), 51.74 (CH_3O), 39.03 (CH_2NH), 31.56 (CH_2), 19.97 (CH_2), 18.77 (CH_3), 13.64 (CH_3).

Compound 17b:



HRMS (ESI-TOF): calculated for $C_{19}H_{31}N_2O_3^+$ (MH^+) 335.2335, found: 335.2339.
IR (KBr) ν: 3310 (N–H), 1738 (C=O), 1654 (C=O), 1198 (C–O).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.73 (d, *J* = 6.75 Hz, 6H), 0.86 (t, *J* = 6.48 Hz, 3H), 1.26 (m, 2H), 1.44 (m, 4H), 1.71 (m, 1H), 3.10 (m, 1H), 3.20 (t, *J* = 6.66 Hz, 2H), 3.68 (s, 3H), 4.20 (s, 1H), 7.29 (m, 2H), 7,32 (m, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.37 (COO), 171.51 (CONH), 138.64, 128.84, 128.32, 127.92, 65.71 (CHNH), 57.33 (CHNH), 51.72 (CH_3O), 42.57 (CH_2), 39.08 (CH_2NH), 31.54 (CH_2), 22.79 (CH), 21.91 (CH_3), 19.96 (CH_2), 13.64 (CH_3).

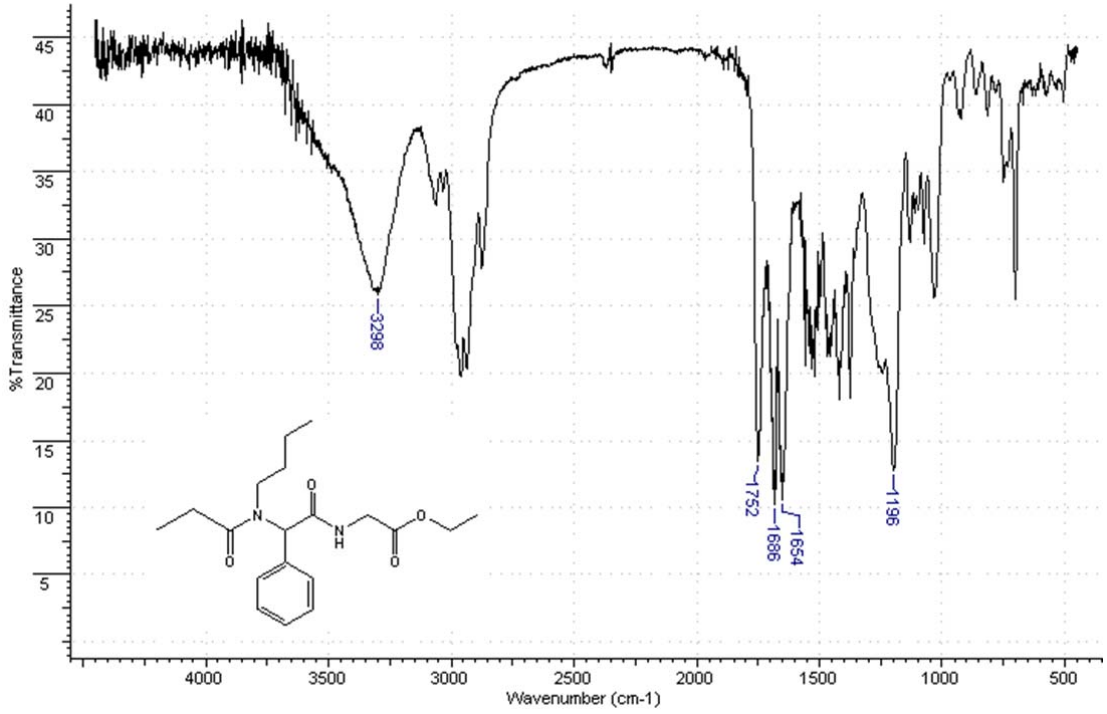
Compound 17c:



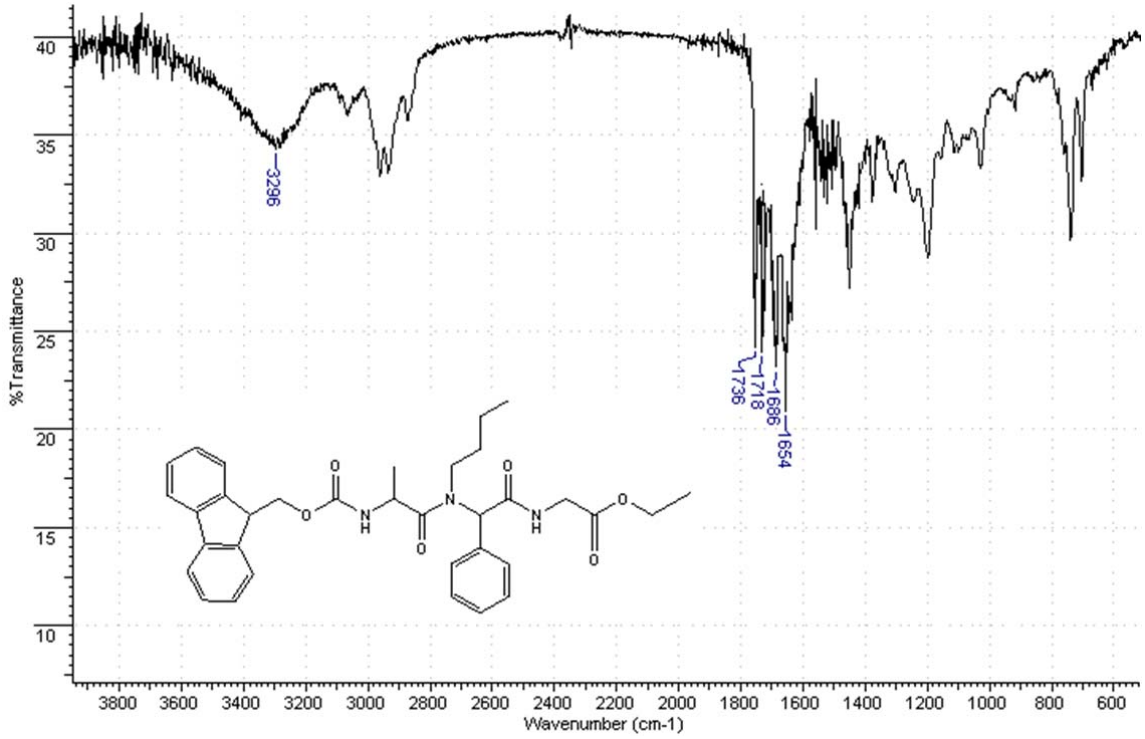
HRMS (ESI-TOF): calculated for $C_{16}H_{25}N_2O_4^+$ (MH^+): 309.1814, found: 309.1819.
IR (KBr) ν: 3310 (O–H), 1740 (C=O), 1652 (C=O), 1244 (C–O).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.95 (t, *J* = 7.27 Hz, 3H), 1.41 (m, 4H), 3.21 (m, 3H), 3.40 (m, 2H), 3.72 (s, 3H), 4.33 (s, 1H), 7.32 (m, 3H), 7.28 (m, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.77 (COO), 170.91 (CONH), 138.04, 128.24, 127.72, 127.32, 65.11 (CHNH), 61.43 (CH_2OH), 56.73 (CHNH), 51.12 (CH_3O), 38.48 (CH_2NH), 30.94 (CH_2), 19.36 (CH_2), 13.04 (CH_3).

4. Copies of IR spectra

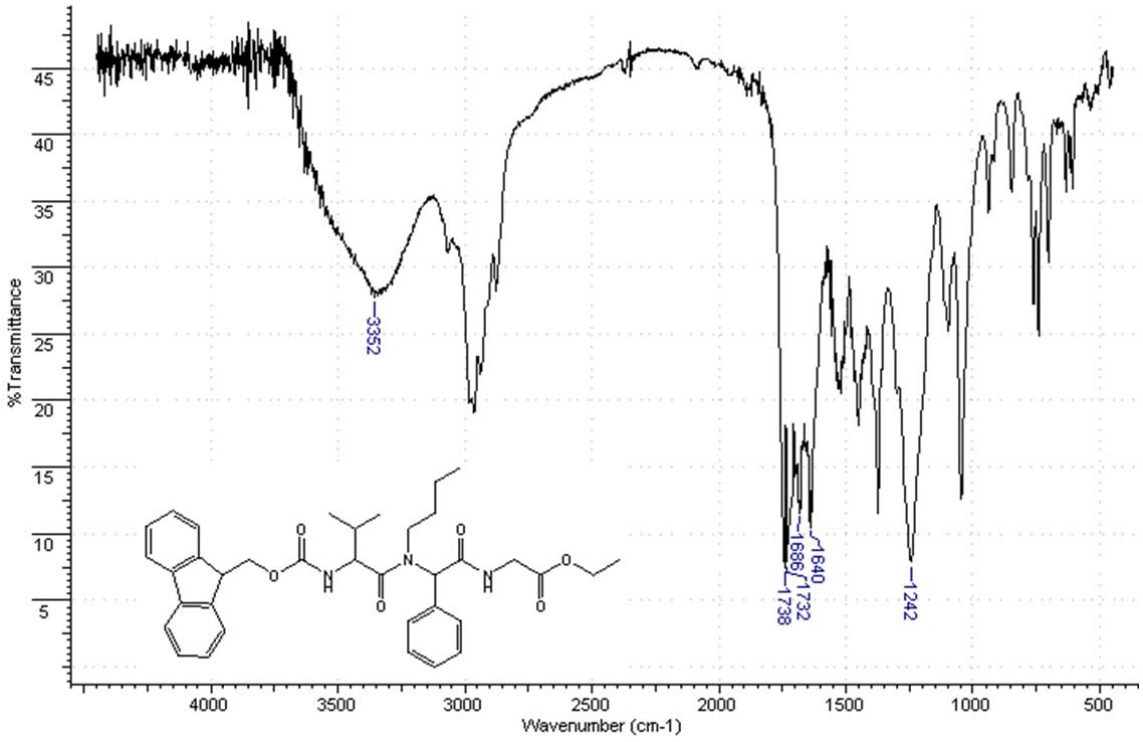
IR for compound 10:



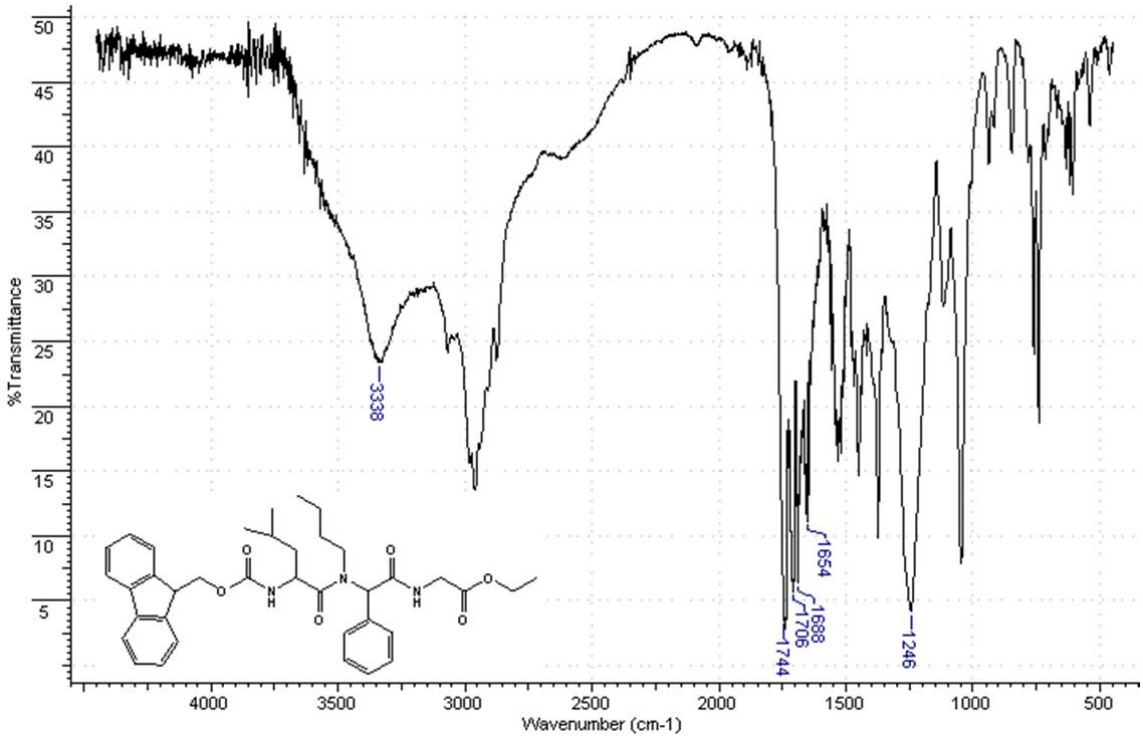
IR for compound 13a:



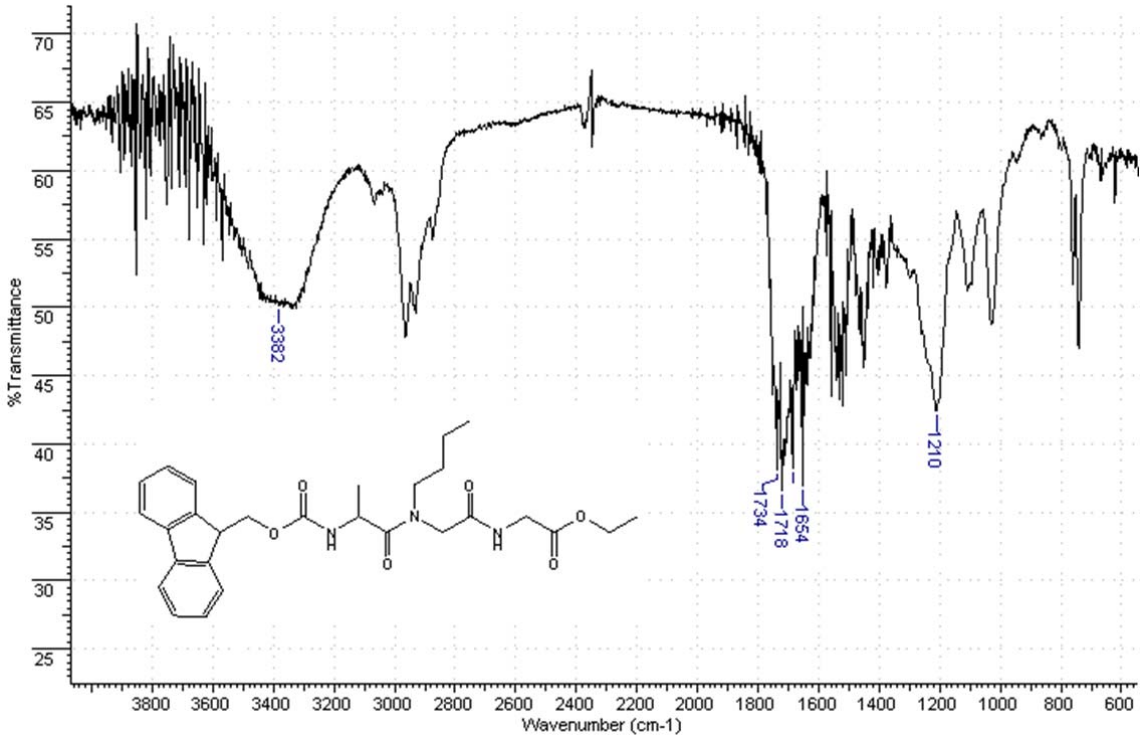
IR for compound 13b:



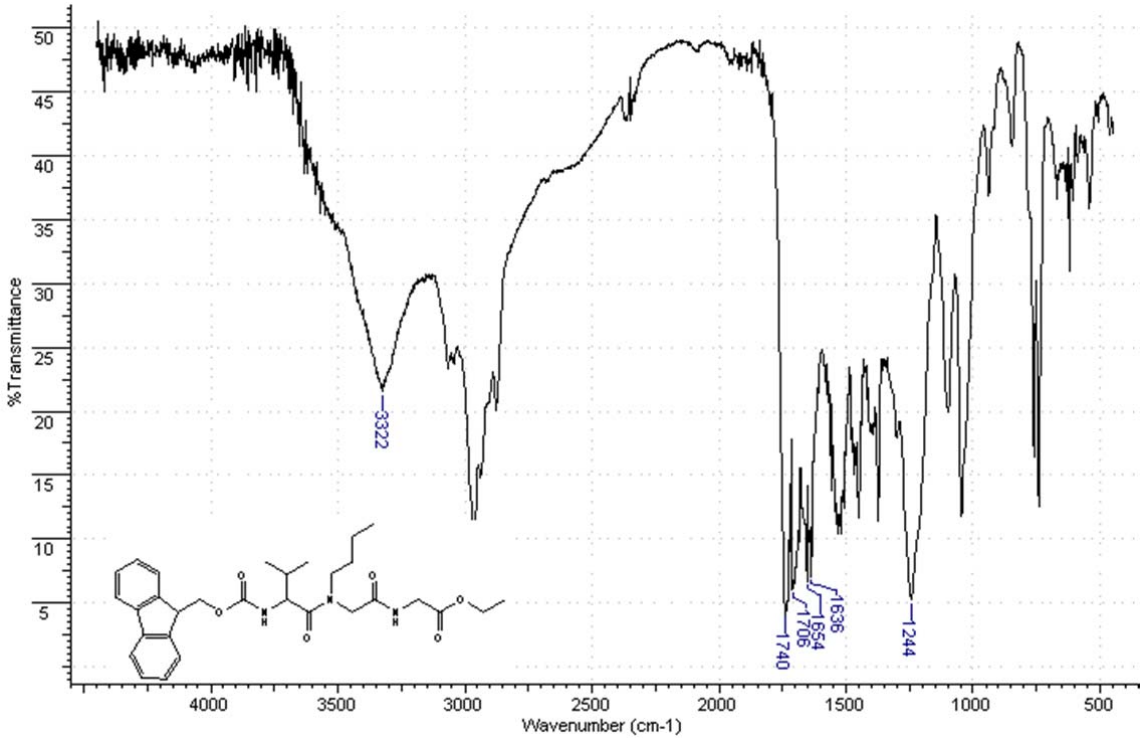
IR for compound 13c:



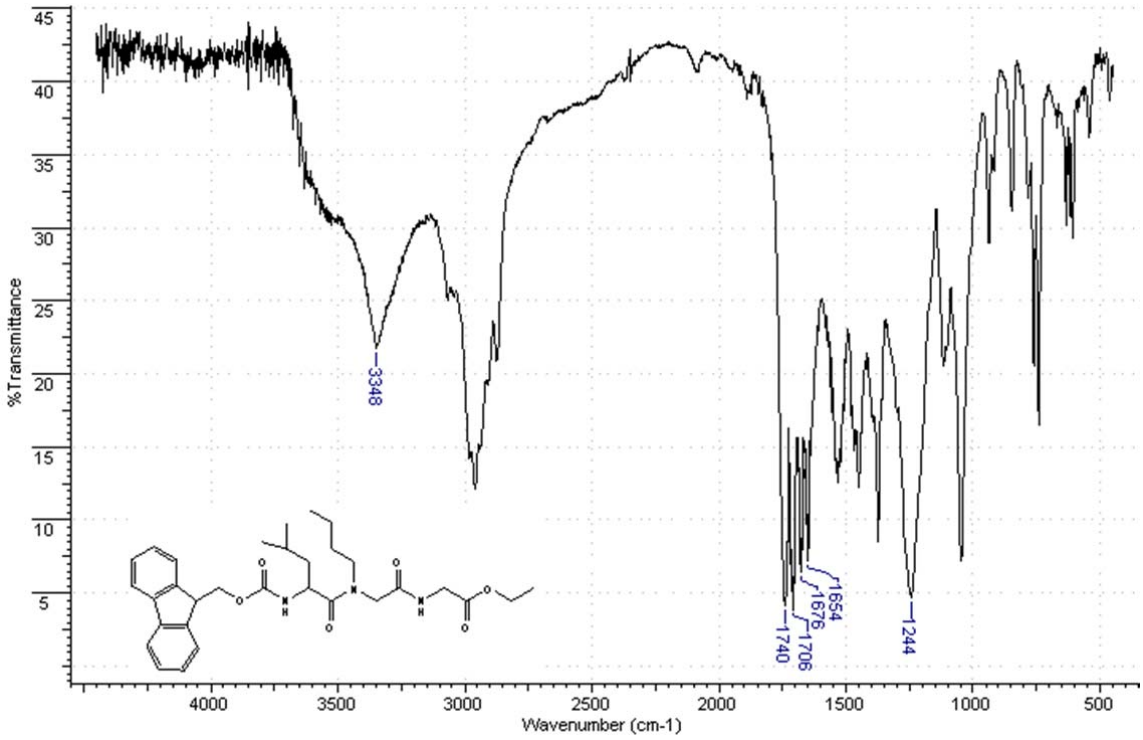
IR for compound 13d:



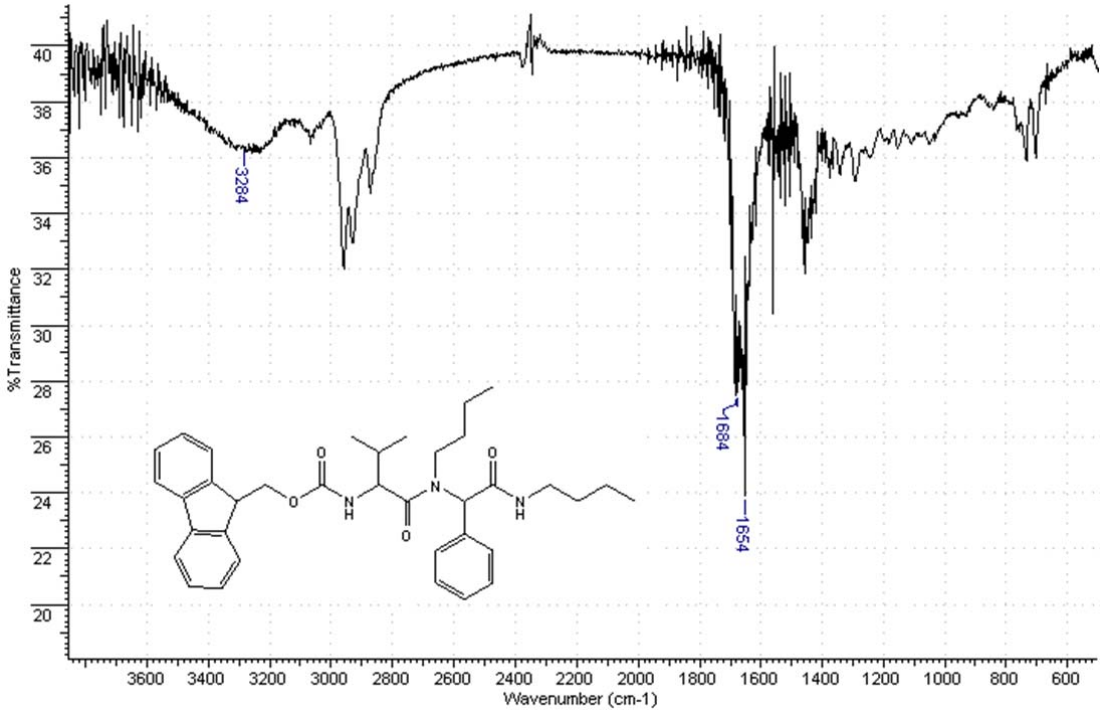
IR for compound 13e:



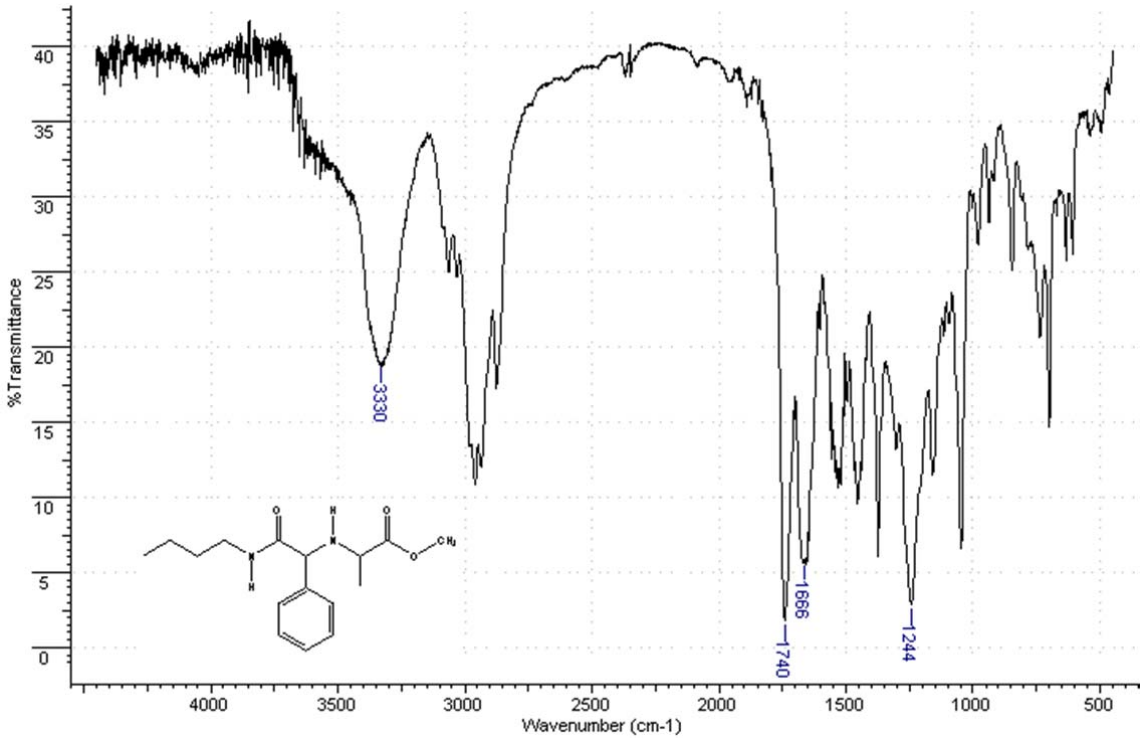
IR for compound 13f:



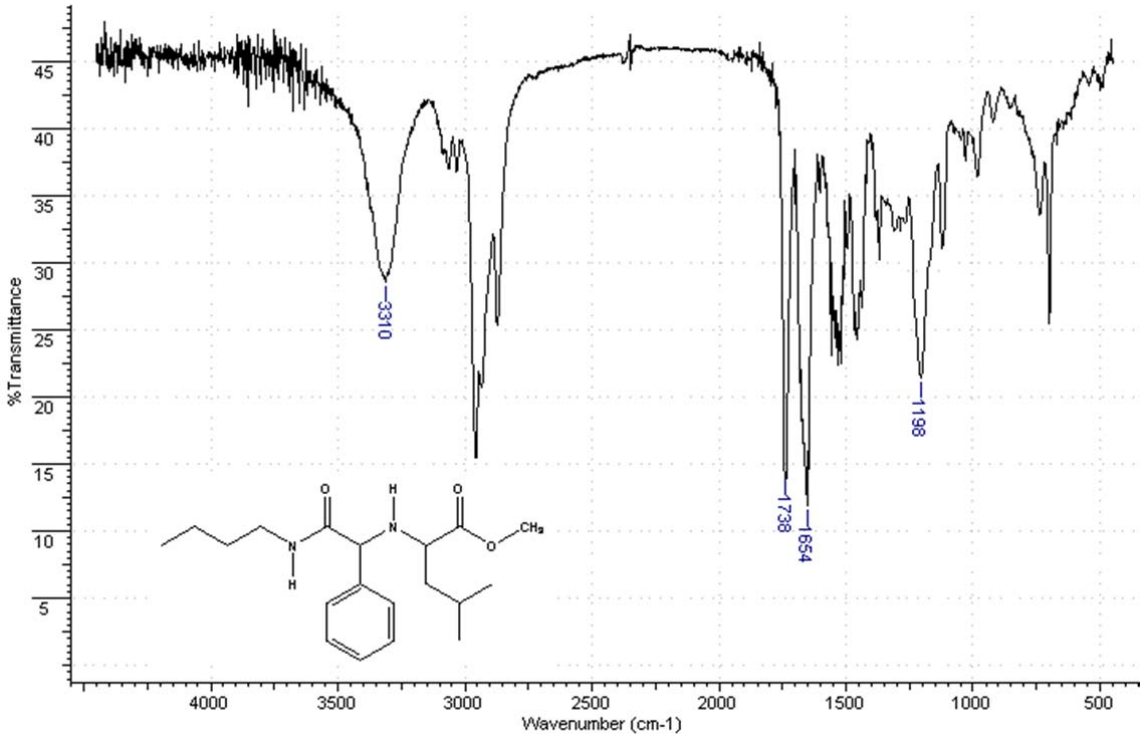
IR for compound 15:



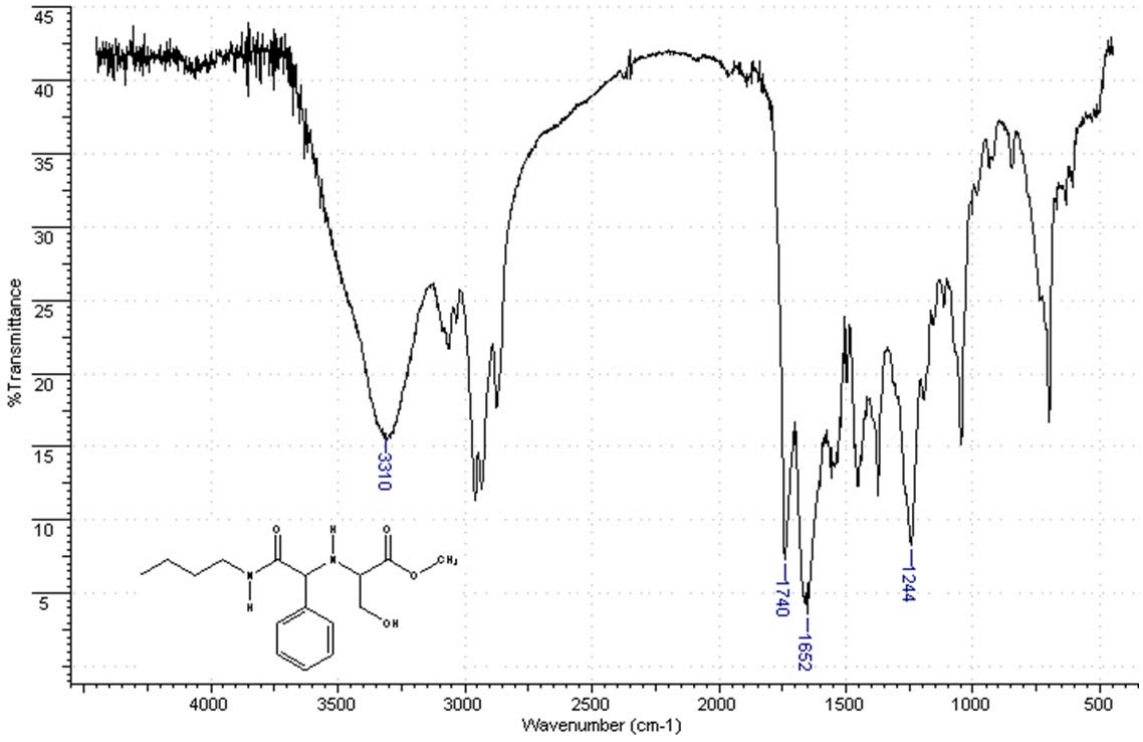
IR for compound 17a:



IR for compound 17b:

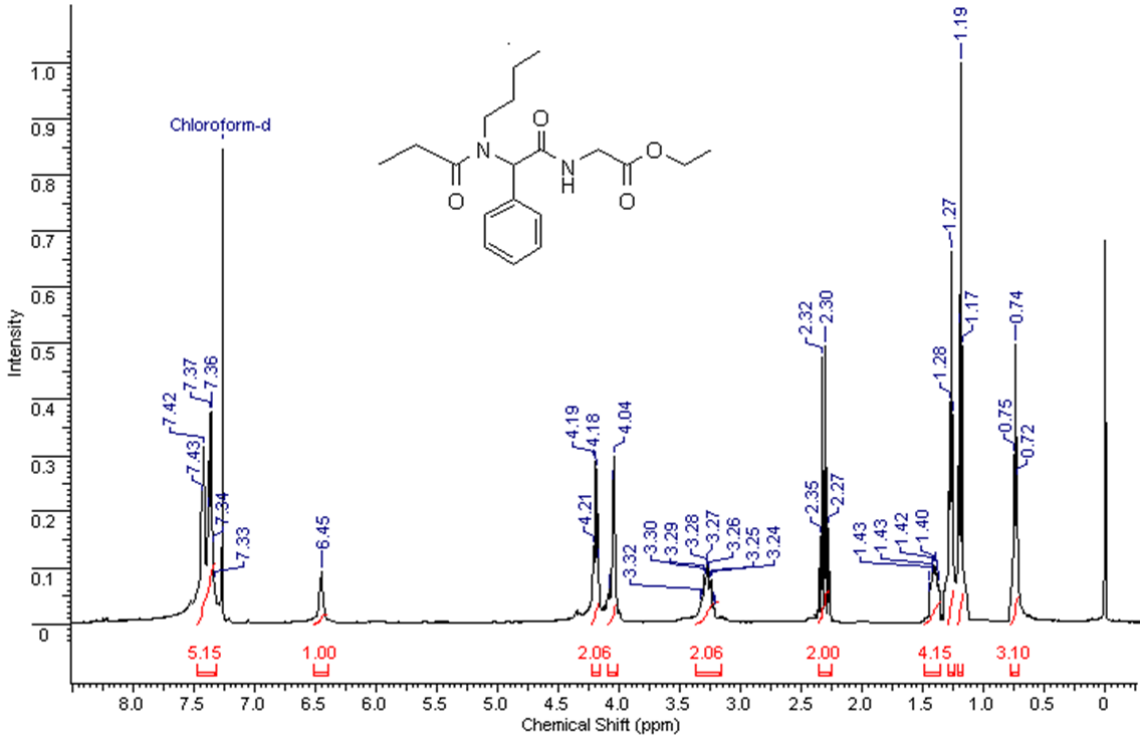


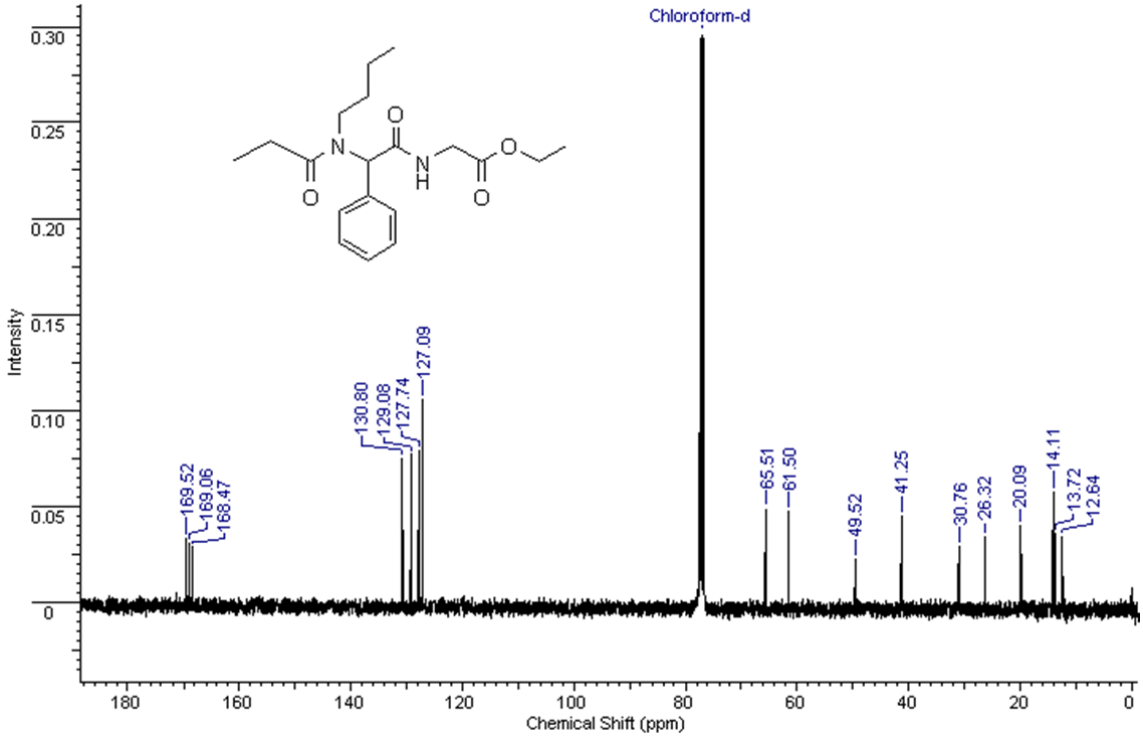
IR for compound 17c:



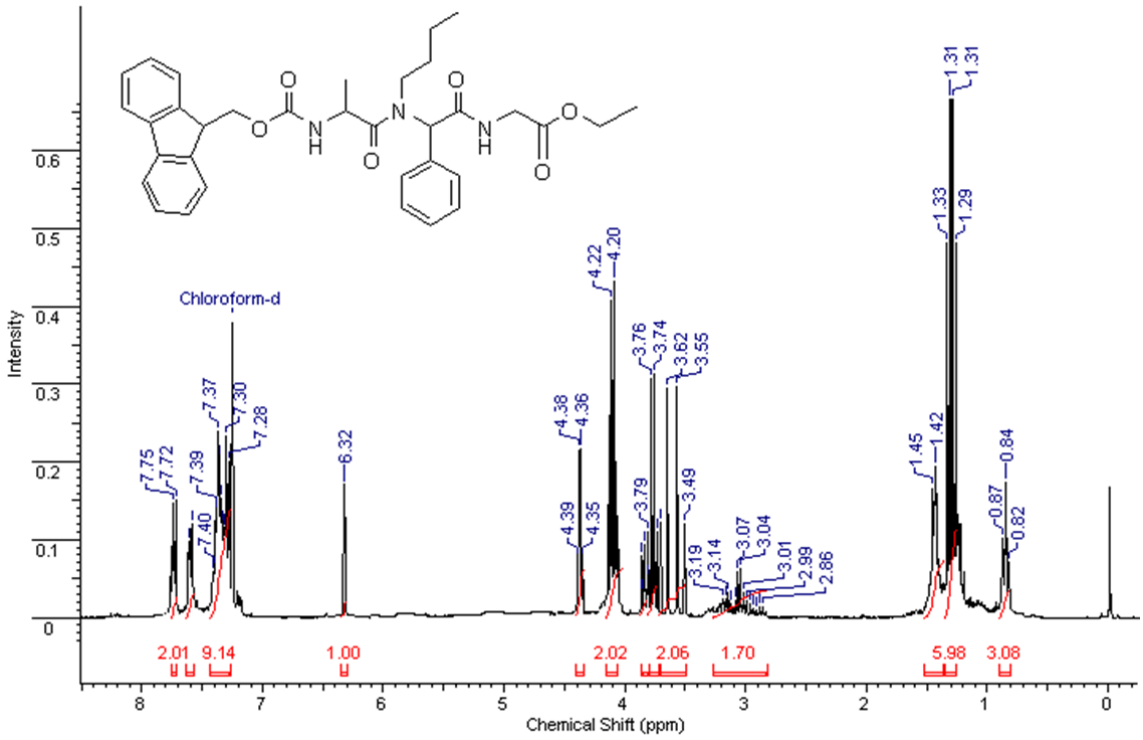
5. Copies of NMR spectra

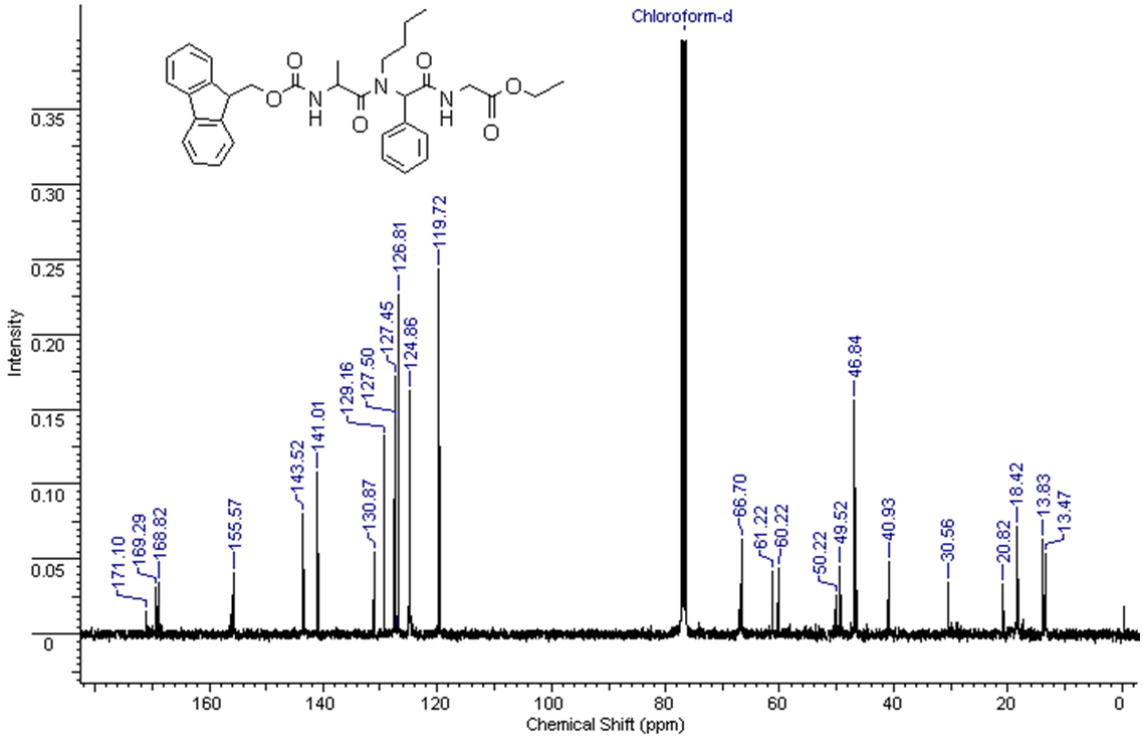
^{1}H NMR and ^{13}C NMR for compound 10:



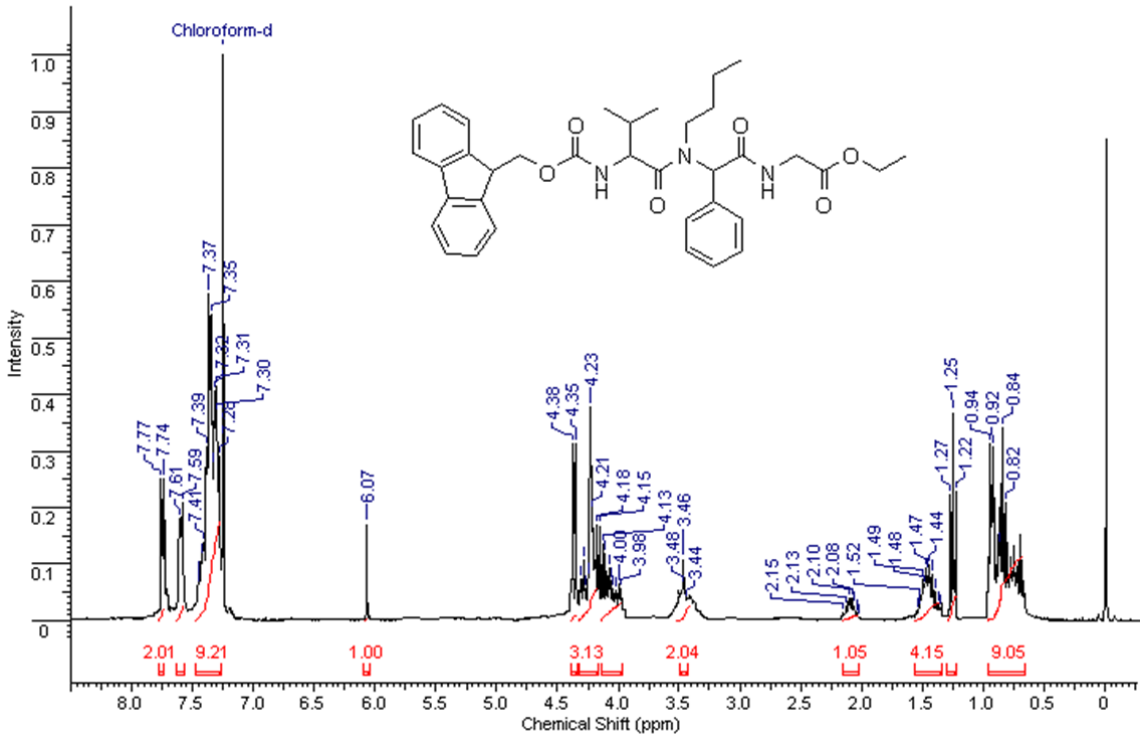


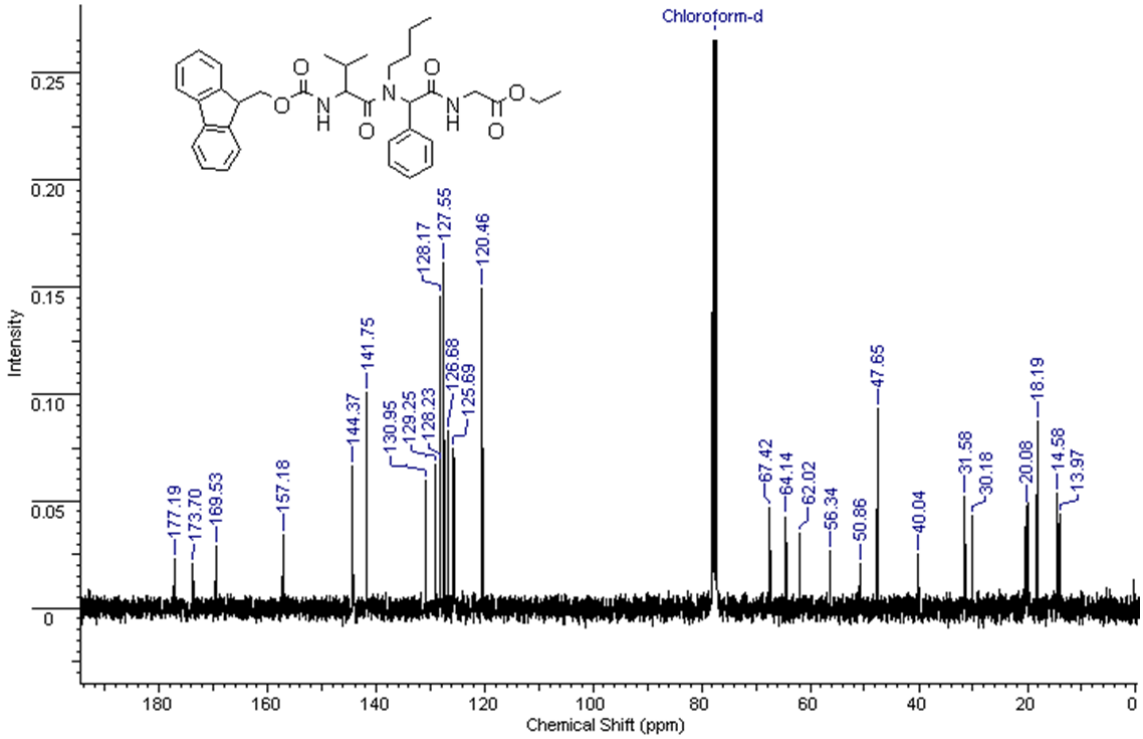
^{1}H NMR and ^{13}C NMR for compound 13a:



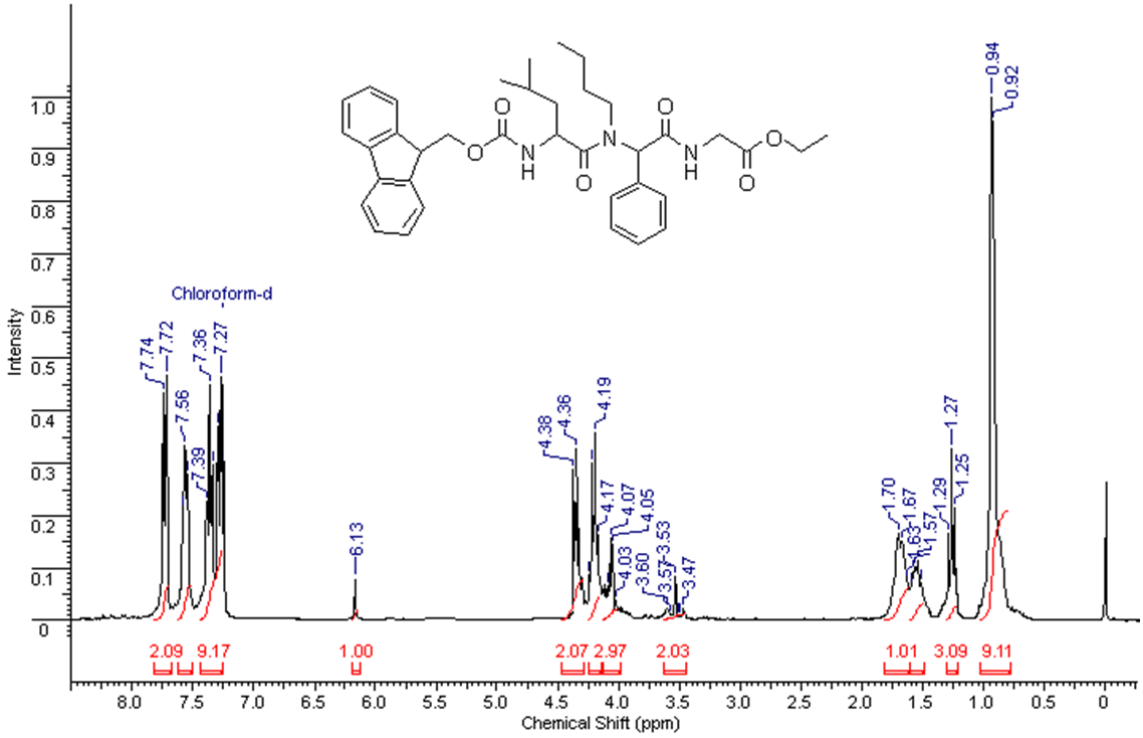


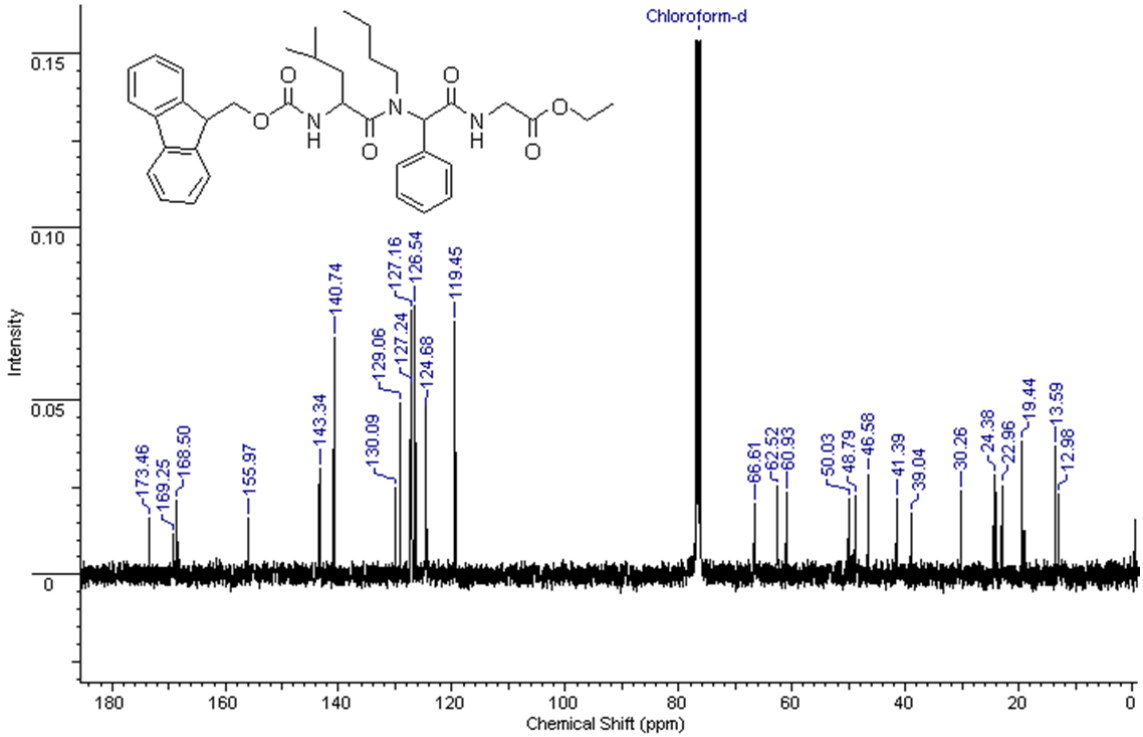
^{1}H NMR and ^{13}C NMR for compound 13b:



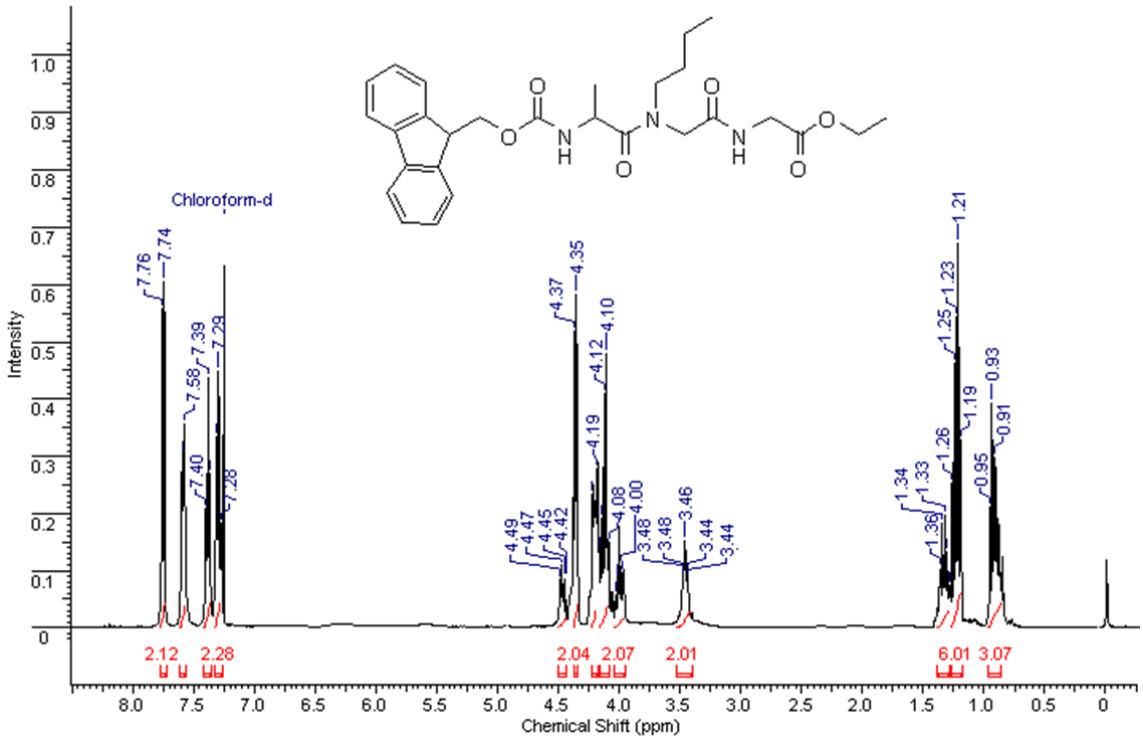


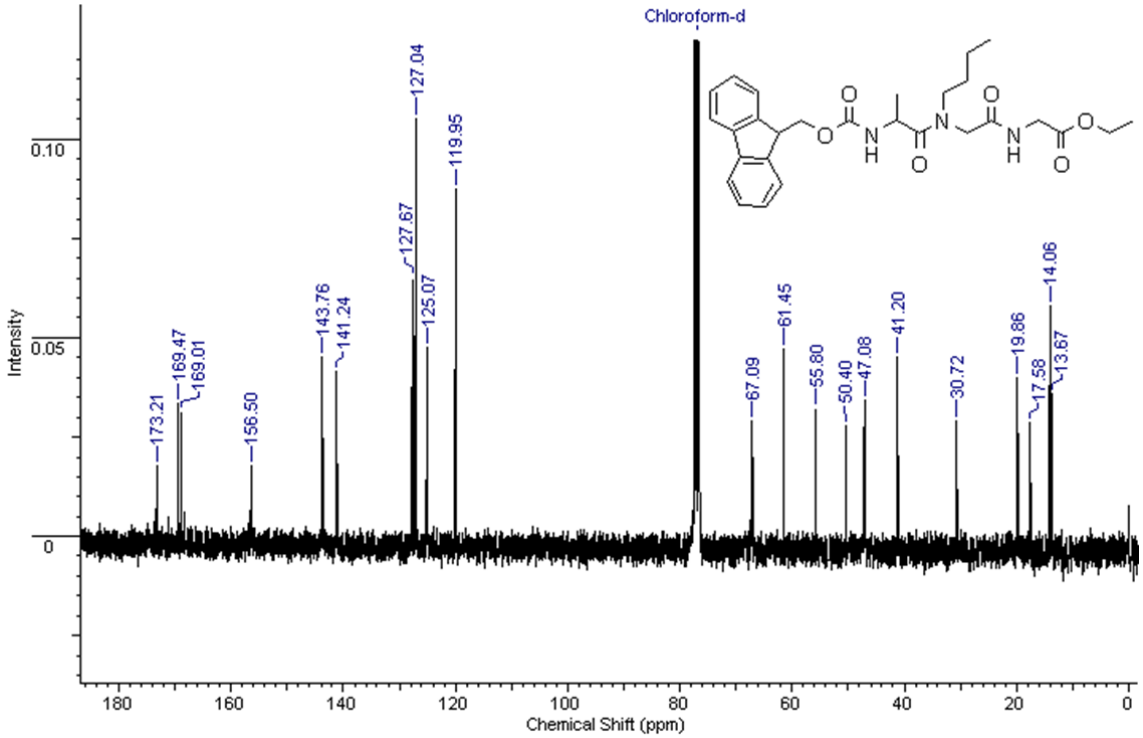
^{1}H NMR and ^{13}C NMR for compound 13c:



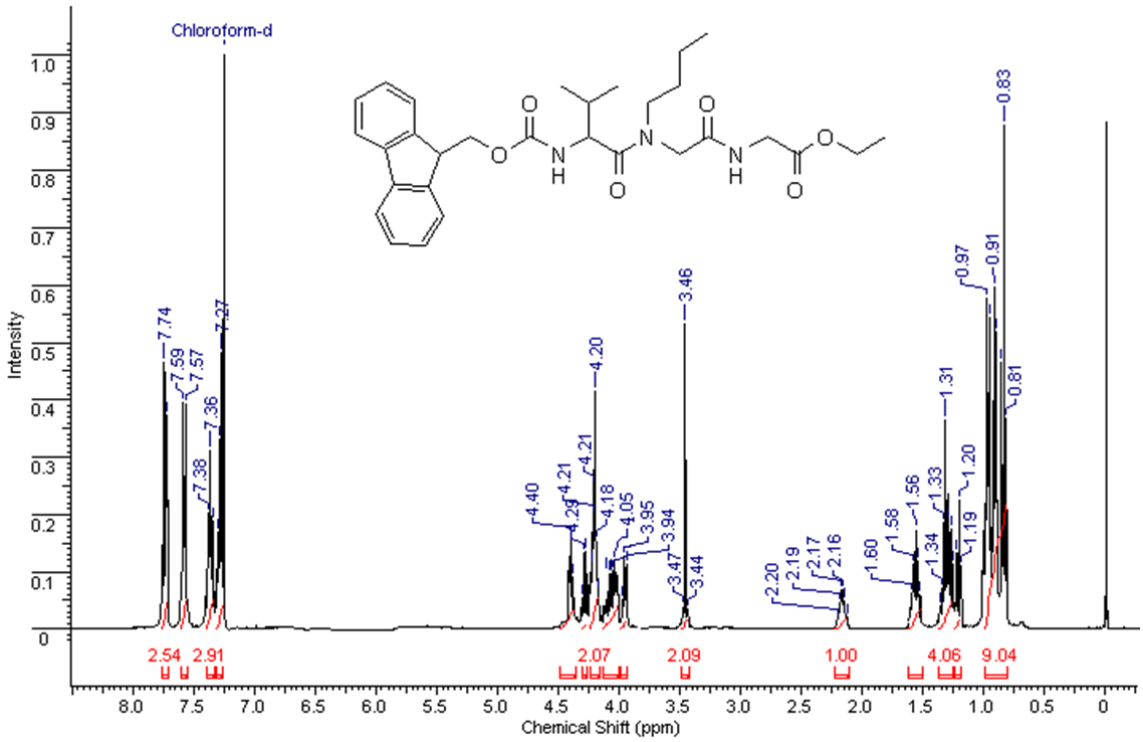


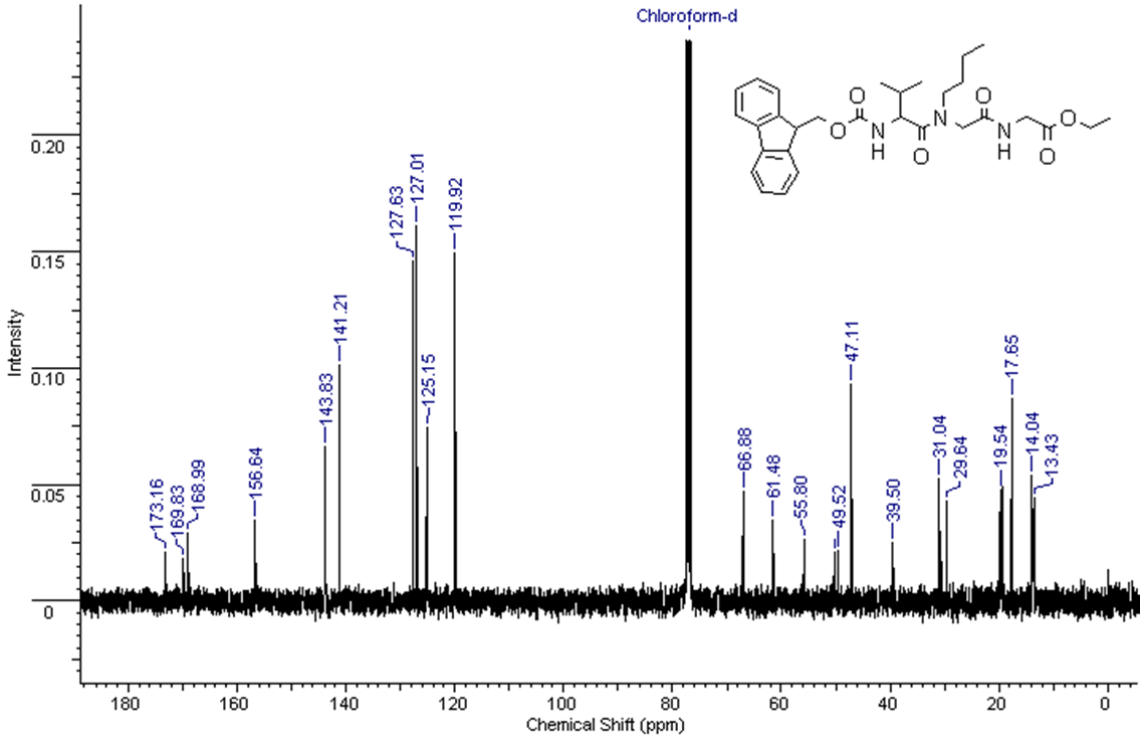
^{1}H NMR and ^{13}C NMR for compound 13d:



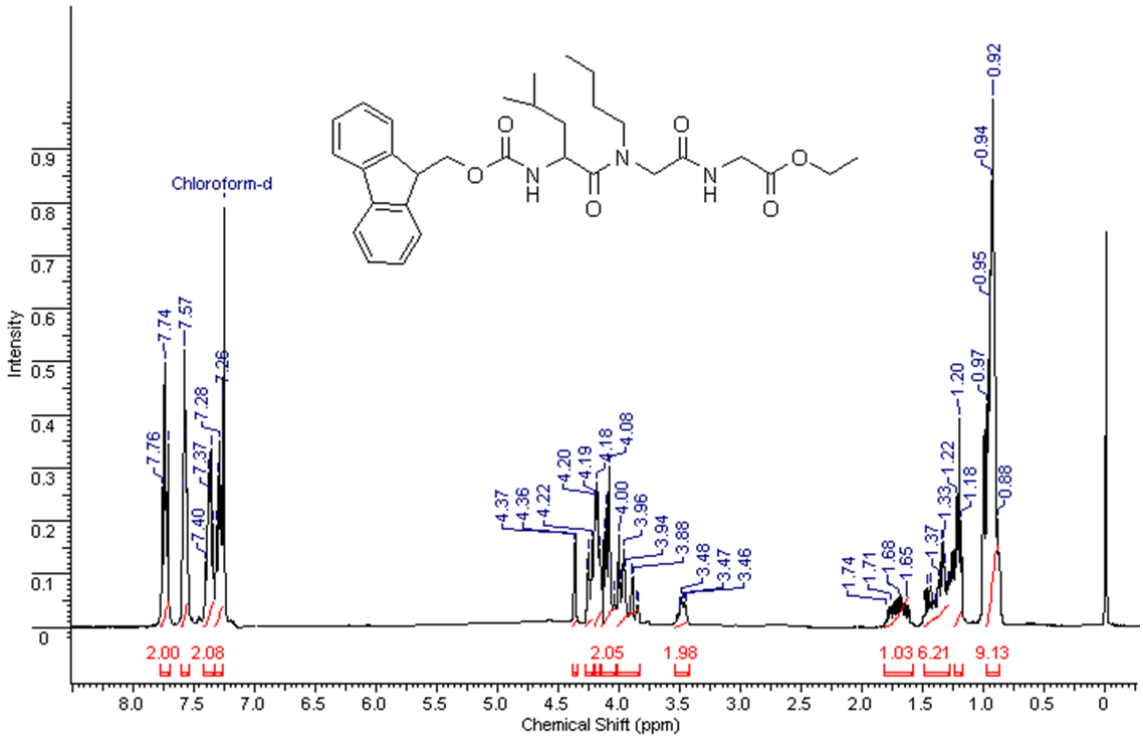


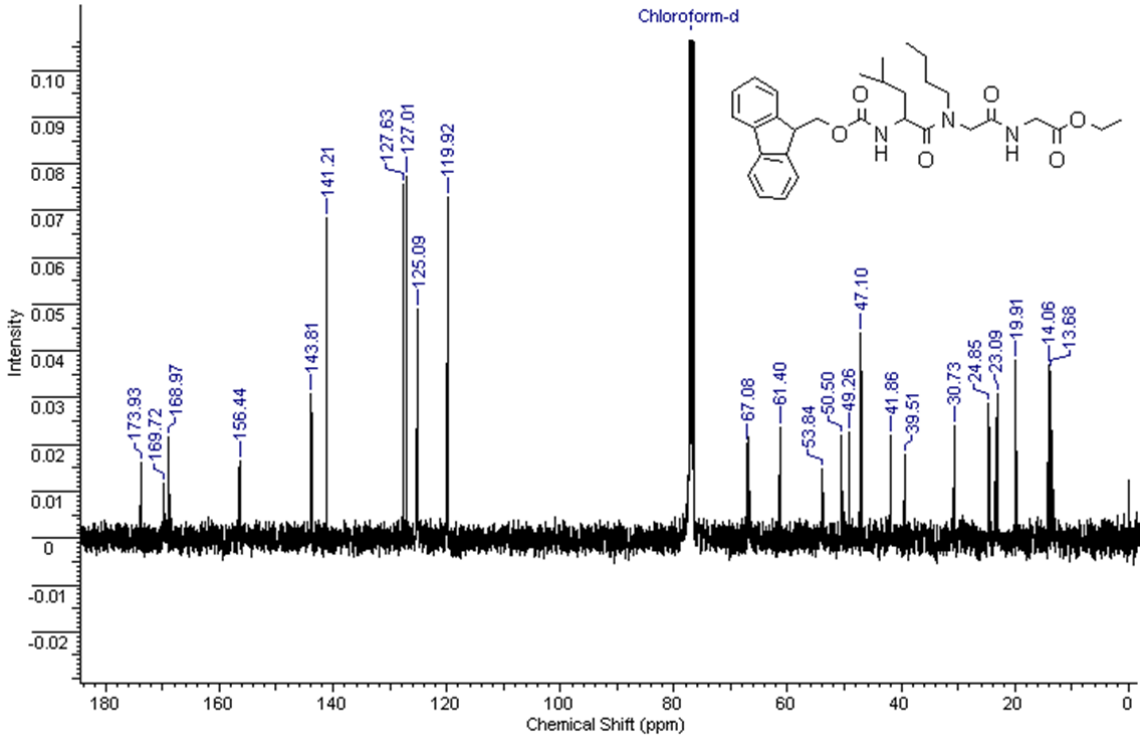
^{1}H NMR and ^{13}C NMR for compound 13e:



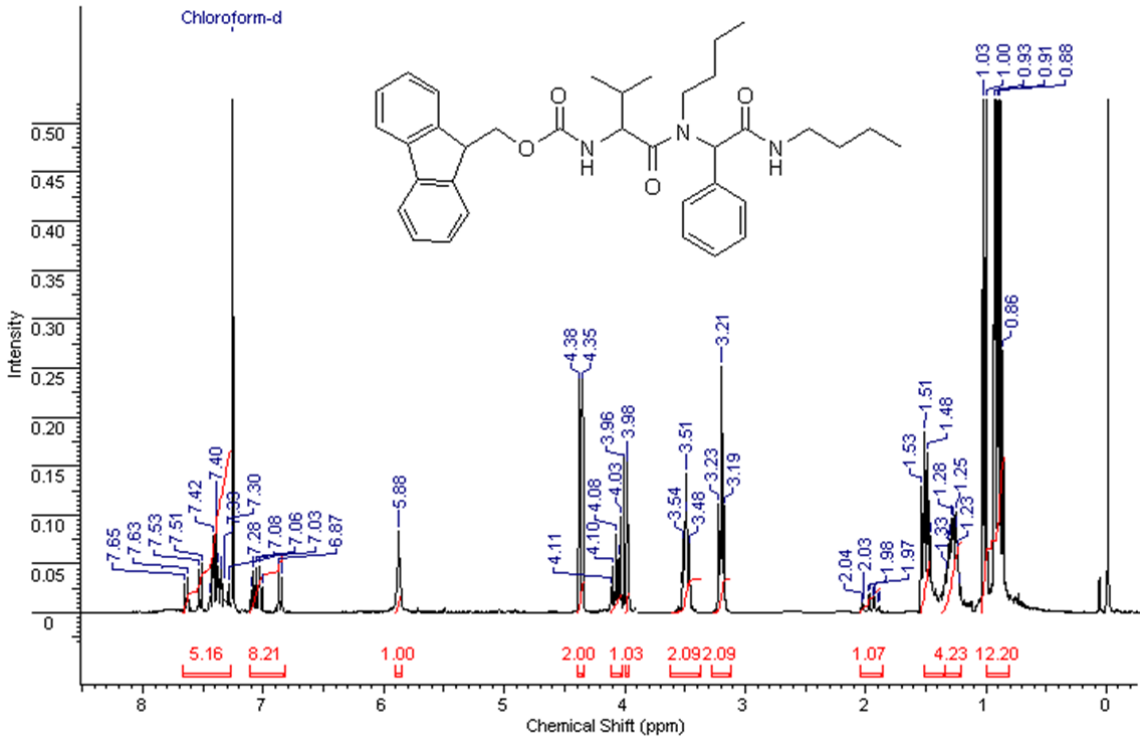


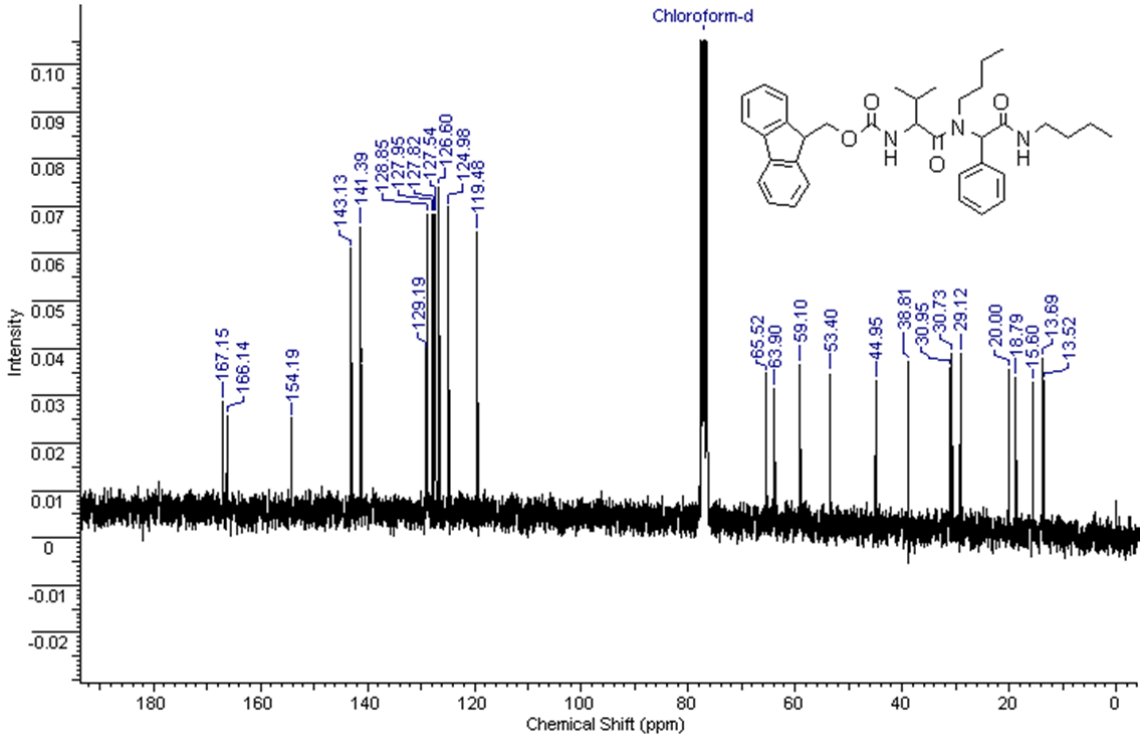
^{1}H NMR and ^{13}C NMR for compound 13f:



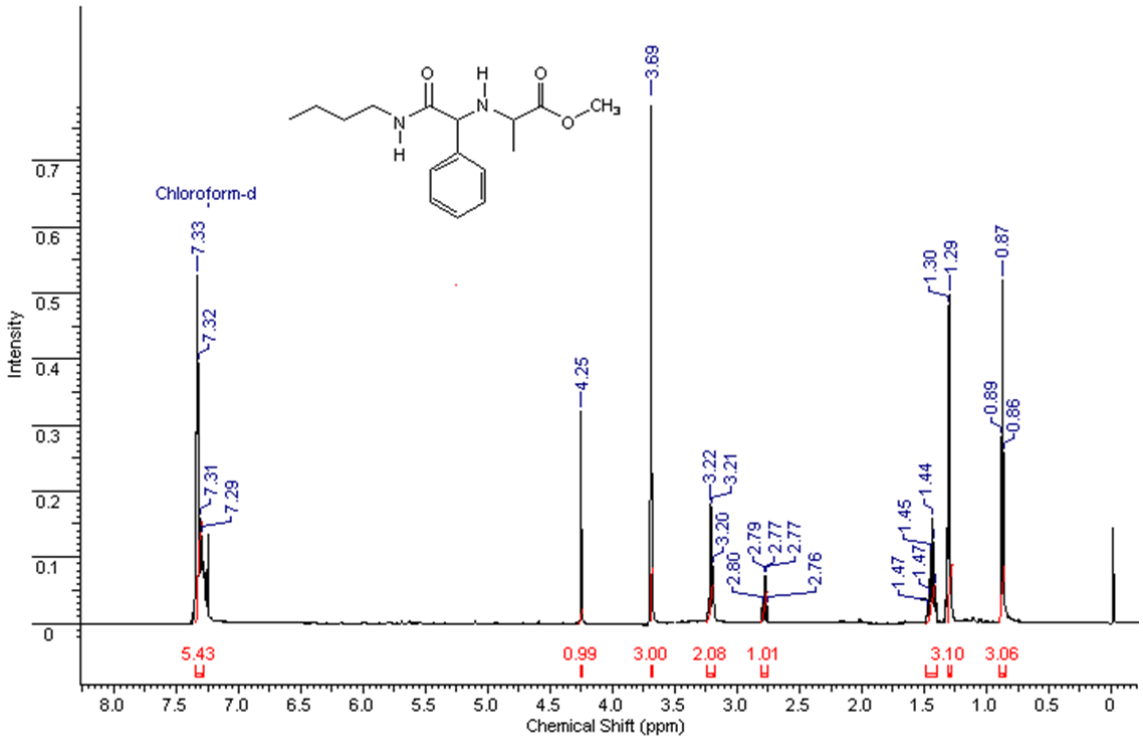


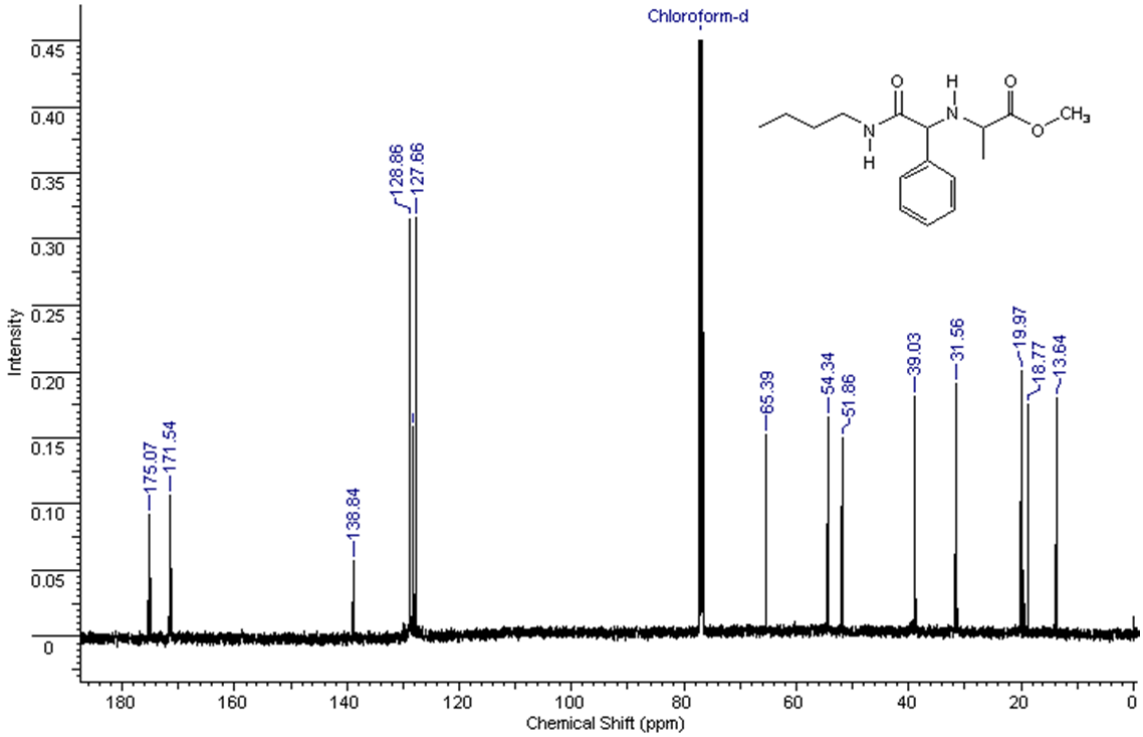
^{1}H NMR and ^{13}C NMR for compound 15:



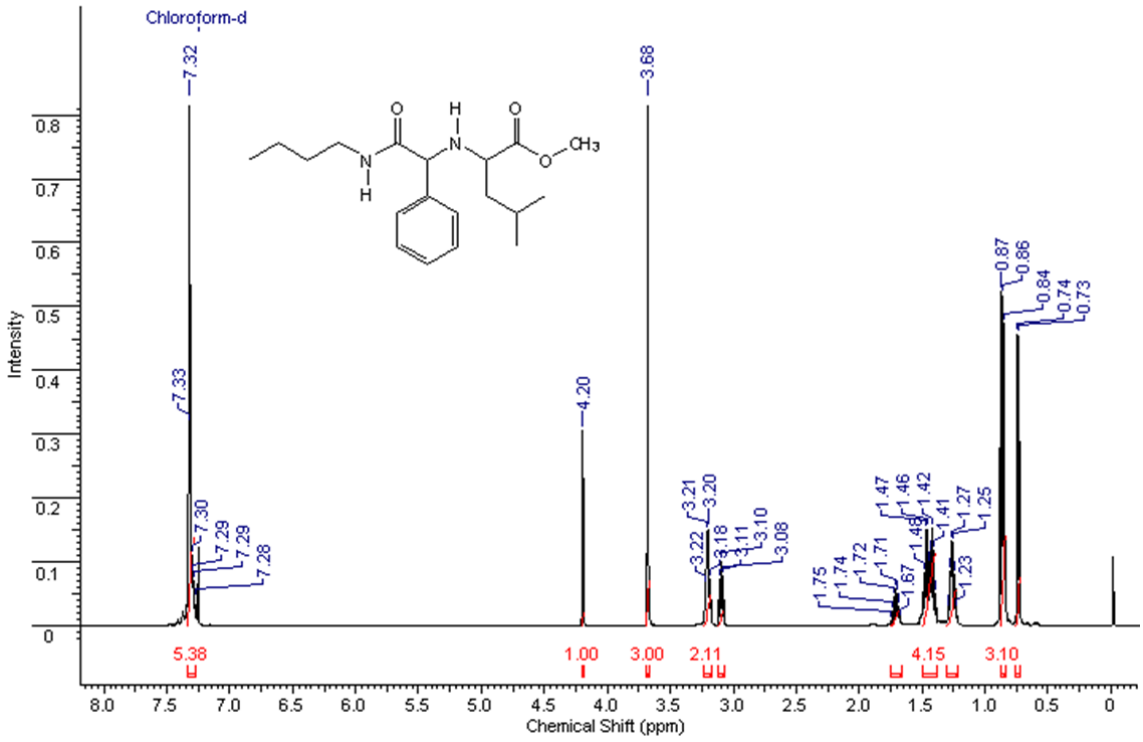


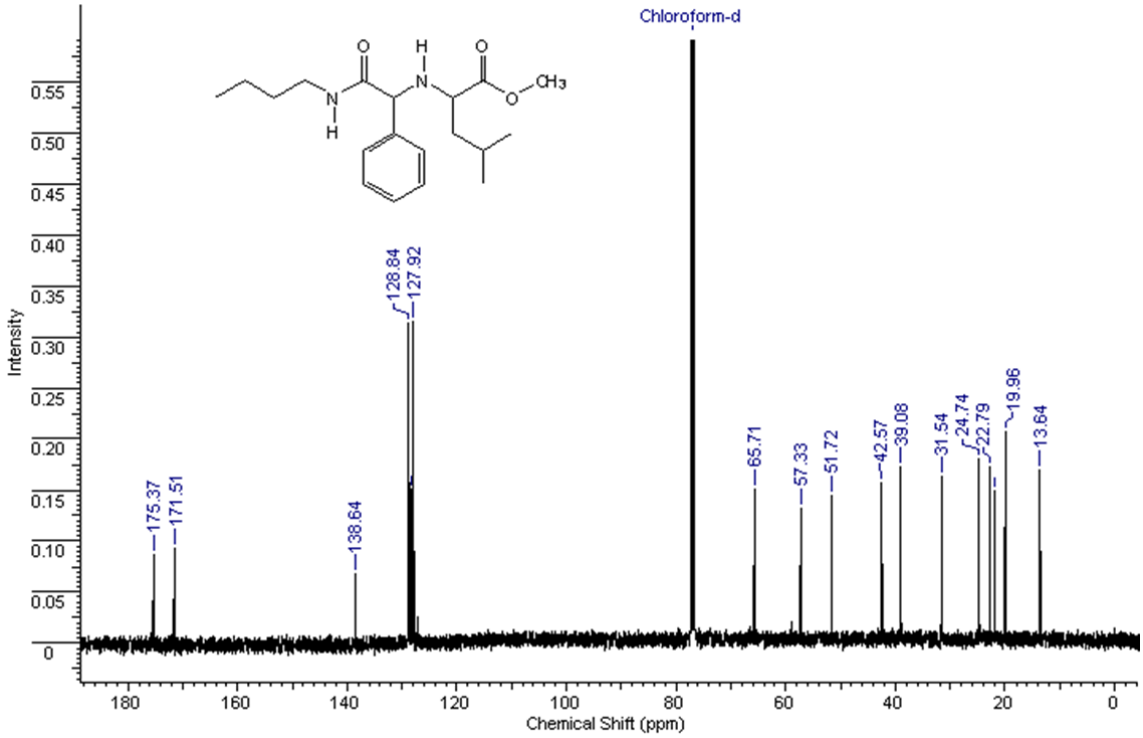
^{1}H NMR and ^{13}C NMR for compound 17a:





^{1}H NMR and ^{13}C NMR for compound 17b:





^{1}H NMR and ^{13}C NMR for compound 17c: