Supporting Informations

A titanium tetrachloride-based effective methodology for the synthesis of dipeptides

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***N*-Boc-L-Asp(OtBu)-Phe-OMe (1)** Oil (0.133 g), 84 % yield; *Rf* = 0.90; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 – 7.21 (m, 3H, ArH), 7.18 – 7.07 (m, 2H, ArH), 7.01 (d, *J* = 6.9 Hz, 1H, CONH), 5.66 (d, *J* = 8.2 Hz, 1H, OCONH), 4.80 (m, 1H, C<u>H</u>$COOCH_3$), 4.46 (m, 1H, C<u>H</u>CONH), 3.68 (s, 3H, OCH_3), 3.12-3.07 (m, 2H, CH_2Ph), 2.86 (dd, *J* = 16.9, 4.5 Hz, 1H, $CH_2COOtBu$), 2.58 (dd, *J* = 16.9, 6.5 Hz, 1H, $CH_2COOtBu$), 1.43 (s, 18H, $(CH_3)_3C$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.59, 171.39, 170.61, 157.14, 135.82, 129.29, 128.53, 127.05, 81.64, 80.19, 53.51, 52.13, 50.68, 37.91, 37.28, 28.25, 28.00; GC/MS (EI, 70eV) m/z (% rel.): 281 (6), 276 (10), 262 (4), 207 (19), 162 (24), 131 (16), 91 (55), 86 (49), 71 (69), 57 (100). Found: C, 61.53; H, 7.63; N, 6.27. $C_{23}H_{34}N_2O_7$ requires C, 61.32; H, 7.61; N, 6.22 %.

***N*-Boc-L-Ala-L-Ala-OMe (3)** White solid (0.167 g), 87 % yield; mp = 110-111 °C; Rf = 0,70; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.94 (s_{broad}, 1H, CONH), 5.28 (d, *J* = 6.7 Hz, 1H, OCONH), 4.53 (p, *J* = 7.2 Hz, 1H, C<u>H</u>$COOCH_3$), 4.18 (m, 1H, C<u>H</u>CONH), 3.71 (s, 3H, OCH_3), 1.40 (s, 9H, $(CH_3)_3C$), 1.36 (d, *J* = 7.2 Hz, 3H, C<u>H</u>$_3$CH); 1.33 (d, *J* = 7.1 Hz, 3H, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.14, 172.37, 155.44, 79.91, 52.32, 52.31, 47.96, 28.25, 18.30, 18.13; GC/MS (EI, 70eV) m/z (% rel.): 218 (2), 201 (23), 187 (6), 172 (3), 159 (5), 144 (60), 102 (40), 88 (48), 57 (100). Found: C, 52.68; H, 8.05; N, 10.16. $C_{12}H_{22}N_2O_5$ requires C, 52.54; H, 8.08; N, 10.21 %.

***N*-Boc-D-Ala-L-Ala-OMe (4)** White solid (0.176 g), 87 % yield; mp = 67-68 °C; Rf = 0.80; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.93 (s_{broad}, 1H, CONH), 5.15 (d, *J* = 6.8 Hz, 1H, OCONH), 4.55 (p, *J* = 7.2 Hz, 1H, C<u>H</u>$COOCH_3$), 4.20 (m, 1H, C<u>H</u>CONH), 3.72 (s, 3H, OCH_3), 1.51 – 1.27 (m, 15H, $(CH_3)_3C$, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.22, 172.27, 155.24, 80.19, 52.34, 52.33, 47.98, 28.27, 18.17, 18.16. GC/MS (EI, 70eV) m/z (% rel.): 218 (2), 201 (23), 187 (6), 172 (3), 159 (5), 144 (60), 102 (40), 88 (48), 57 (100). Found: C, 52.65; H, 8.03; N, 10.18. $C_{12}H_{22}N_2O_5$ requires C, 52.54; H, 8.08; N, 10.21 %.

***N*-Boc-L-Ala-L-Cys(Bzl)-OMe (5)** Oil (0.250 g), 80 % yield; Rf = 0.76; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 – 7.21 (m, 5H, ArH), 6.89 (d, *J* = 6.5 Hz, 1H, CONH), 5.06 (d, *J* = 7.1 Hz, 1H, OCONH), 4.77 (m, 1H, C<u>H</u>$COOCH_3$), 4.18 (m, 1H, C<u>H</u>CONH), 3.73 (s, 3H, OCH_3), 3.70 (s, 2H, CH_2Ph), 2.95-2.78 (m, 2H, CH_2S), 1.44 (s, 9H, $(CH_3)_3C$), 1.36 (d, J = 7.1 Hz, 3H, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.56, 171.02, 155.45, 137.69, 128.96, 128.61, 127.27, 80.34, 52.67, 51.31, 49.81, 36.55, 32.84, 28.32, 18.12. GC/MS (EI, 70eV) m/z (% rel.): 322 (4), 296 (1), 281 (3), 231 (11), 208 (31), 175 (9), 124 (5), 101 (2), 91 (100), 73 (5). Found: C, 57.76; H, 7.09; N, 7.03; S, 8.06. $C_{19}H_{28}N_2O_5S$ requieres C, 57.55; H, 7.12; N,7.07; S, 8.09 %.

***N*-Boc-L-Ala-L-Lys(Boc)-OMe (6)** Oil (0.176 g), 80 % yield; Rf = 0.85; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78 (d, J = 7.3 Hz, 1H, CONH), 5.15 (m, 1H, OCONH), 4.75 (m, 1H, $CH_2N\underline{H}COO$), 4.58 (m, 1H, $C\underline{H}COOCH_3$), 4.19 (m, 1H, $C\underline{H}CONH$), 3.73 (s, 3H, OCH_3), 3.15 – 3.02 (m, 2H, $C\underline{H}_2NHCOO$), 1.96 – 1.78 (m, 2H, $CHC\underline{H}_2$), 1.68 (m, 1H, $CHCH_2C\underline{H}_2$), 1.56 – 1.39 (m, 21H, $CHCH_2C\underline{H}_2C\underline{H}_2$, $(CH_3)_3C$)), 1.36 (d, J = 7.1 Hz, 3H, , $C\underline{H}_3CH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.71, 172.61, 156.17, 155.52, 80.00, 79.00, 52.38, 51.77, 49.81, 39.97, 31.88, 29.68, 29.19, 28.43, 28.29, 22.29, 17.93. GC/MS (EI, 70eV) m/z (% rel.): 331 (3), 321 (8), 258 (18), 187 (25), 158 (24), 145 (100), 128 (36), 84 (98), 73 (26), 57 (70). Found: C, 55.58; H, 8.62; N, 9.72. $C_{20}H_{37}N_3O_7$ requires C, 55.67; H, 8.64; N, 9.74 %.

***N*-Fmoc-L-Asp(tBu)-L-Phe-OMe (7)** Oil (0.245 g), 84 % yield; *Rf* = 0.80; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 7.4 Hz, 2H, Ar$\underline{H}$), 7.59 (d, *J* = 7.3 Hz, 2H, Ar$\underline{H}$), 7.42 (t, *J* = 7.4 Hz, 2H, Ar$\underline{H}$), 7.36-7.11 (m, 7H, Ar$\underline{H}$), 7.06 (d, J=7.3 Hz, 1H, CO$\underline{NH}$), 5.97 (d, *J* = 8.0 Hz, 1H, OCO$\underline{NH}$), 4.83 (m, 1H, $C\underline{H}COOCH_3$), 4.55 (m, 1H, $\underline{CH}CONH$), 4.38 (m, 2H, $\underline{CH_2}$-Fmoc), 4.22 (m, 1H, $\underline{CH}$-Fmoc), 3.70 (s, 3H, $OC\underline{H}_3$), 3.22-2.99 (m, 2 H, $C\underline{H}_2Ph$), 2.90 (dd, *J* = 17.1, *J* = 4.1 Hz, 1H, $C\underline{H}_2COOtBu$), 2.62 (dd, *J* = 17.1, *J* = 6.6 Hz, 1H, $C\underline{H}_2COOtBu$), 1.45 (s, 9H, $(\underline{CH}_3)_3CH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.38, 170.20, 170.14, 160.17, 143.73, 141.32, 135.75, 129.25, 128.59, 127.77, 127.11, 125.05, 120.01, 81.90, 67.18, 53.57, 52.18, 49.95, 47.13, 37.18, 31.57, 28.03. Found: C, 69.47; H, 6.36; N, 4.91. $C_{33}H_{36}N_2O_7$ requires C, 69.21; H, 6.34; N, 4.89 %.

***N*-Fmoc-L-Ala-L-Ala-OMe (8)** White solid (0.285 g), 71 % yield; mp = 192-194 °C; Rf = 0.54; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 7.5 Hz, 2H, ArH), 7.50 (d, *J* = 7.3 Hz, 2H, ArH), 7.31 (t, *J* = 7.5 Hz, 2H, ArH), 7.27 – 7.16 (m, 2H, ArH), 6.73 (d, *J* = 7.1 Hz, 1H, CONH), 5.55 (d, *J* = 7.5 Hz, 1H, OCONH), 4.50 (p, *J* = 7.1 Hz, 1H, $C\underline{H}COOCH_3$), 4.37-4.17 (m, 3H, CH_2-Fmoc, $\underline{CH}CONH$), 4.13 (t, *J* = 7.0 Hz, 1H, CH-Fmoc), 3.65 (s, 1H, OCH_3), 1.41-1.22 (m, 6H, $C\underline{H}_3CH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.13, 171.96, 156.11, 143.74, 141.31, 127.74, 127.09, 125.08, 120.00, 67.14, 52.48, 50.46, 48.12, 47.14, 18.87, 18.22. Found: C, 66.41; H, 6.07; N, 7.04. $C_{22}H_{24}N_2O_5$ requires C, 66.65; H, 6.10; N, 7.07 %.

***N*-Fmoc-L-Leu-L-Ala-OMe (9)** White solid (0.256 g), 80 % yield; mp = 162-163 °C; Rf = 0,65; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.81 – 7.71 (m, 2H, ArH), 7.64 – 7.52 (m, 2H, ArH), 7.45-7.35 (m, 2H, ArH), 7.34 – 7.22 (m, 2H, ArH), 6.91 (d, *J* = 7.2 Hz, 1H, CONH), 5.65 (d, *J* = 8.7 Hz, 1H, OCONH), 4.57 (p, *J* = 7.2 Hz, 1H, $C\underline{H}COOCH_3$), 4.46 – 4.26 (m, 3H, CH_2-Fmoc, $\underline{CH}CONH$), 4.20 (m, 1H, CH-Fmoc), 3.72 (s, 3H, OCH_3), 1.79 – 1.51 (m, 3H, $C\underline{H}_2C\underline{H}(CH_3)_2$), 1.39 (d, J = 7.2 Hz, 3H, $C\underline{H}_3CH$),

1.02-0.83 (m, 6H, CH(C<u>H</u>$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.11, 171.93, 156.17, 143.84, 141.31, 127.70, 127.07, 125.04, 119.97, 67.10, 53.44, 52.40, 48.07, 47.18, 41.65, 24.64, 22.88, 18.14. Found: C, 68.21; H, 6.85; N, 6.37. $C_{25}H_{30}N_2O_5$ requires C, 68.47; H, 6.90; N, 6.39 %.

***N*-Fmoc-D-Leu-L-Ala-OMe (10)** White solid (0.326 g), 80 % yield; mp = 141-144 °C; *Rf* = 0.66; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.79-7.72 (m, 2H, ArH), 7.65 – 7.53 (m, 2H, ArH), 7.44-7.35 (m, 2H, ArH), 7.34 – 7.25 (m, 2H, ArH), 6.78 (d, *J* = 7.1 Hz, 1H, CONH), 5.39 (d, *J* = 8.5 Hz, 1H, OCONH), 4.58 (p, *J* = 7.2 Hz, 1H, C<u>H</u>COOCH$_3$), 4.50 – 4.34 (m, 2H, CH$_2$-Fmoc), 4.33-4.16 (m, 2H, <u>CH</u>CONH, CH-Fmoc), 3.71 (s, 3H, OCH$_3$), 1.75 – 1.49 (m, 3H, C<u>H</u>$_2$C<u>H</u>(CH$_3$)$_2$), 1.40 (d, J = 7.1 Hz, 3H, C<u>H</u>$_3$CH), 0.99-0.85 (m, 6H, CH(C<u>H</u>$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.11, 171.75, 158.44, 143.74, 141.32, 127.71, 127.06, 125.02, 119.98, 66.71, 53.37, 52.44, 48.07, 47.21, 41.47, 24.73, 22.94, 18.22. Found: C, 68.23; H, 6.84; N, 6.35. $C_{25}H_{30}N_2O_5$ requires C, 68.47; H, 6.90; N, 6.39 %.

***N*-Fmoc-Gly-L-Ala-OMe (11)** Oil (0.191 g), 80 % yield; Rf = 0.80; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76 (d, J = 7.4 Hz, 2H, ArH), 7.60 (d, *J* = 7.3 Hz, 2H, ArH), 7.40 (t, *J* = 7.3 Hz, 2H, ArH), 7.35-7.28 (m, 2H, ArH), 6.78 (d, *J* = 6.1 Hz, 1H, CONH), 5.70 (s$_{broad}$, 1H, OCONH), 4.59 (m, 1H, C<u>H</u>COOCH$_3$), 4.41 (d, *J* = 7.0 Hz, 2H, CH$_2$-Fmoc), 4.22 (t, *J* = 7.0 Hz, 1H, CH-Fmoc), 3.88 (s$_{broad}$, 2H, C<u>H</u>$_2$CONH), 3.73 (s, 3H, OCH$_3$), 1.41 (d, *J* = 7.1 Hz, 3H, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.27, 168.65, 155.64, 143.74, 141.30, 127.76, 127.10, 125.07, 120.02, 67.28, 52.59, 48.12, 47.07, 44.34, 18.24. Found: C, 66.22; H, 5.77; N, 7.29. $C_{21}H_{22}N_2O_5$ requires C, 65.96; H, 5.80; N, 7.33 %.

***N*-Fmoc-L-Leu-L-Ile-OMe (12)** Oil (0.120 g), 87 % yield; Rf = 0.80; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77 (d, J = 7.5 Hz, 2H, ArH), 7.59 (d, *J* = 7.3 Hz, 2H, ArH), 7.40 (t, *J* = 7.4 Hz, 2H, ArH), 7.34 – 7.28 (m, 2H, ArH), 6.58 (d, *J* = 8.4 Hz, 1H, CONH), 5.36 (d, *J* = 8.4 Hz, 1H, OCONH), 4.58 (dd, *J* = 8.4, J = 4.9 Hz, 1H, C<u>H</u>COOCH$_3$), 4.47-4.35 (m, 2H, CH$_2$-Fmoc), 4.31-4.17 (m, 2H, CH-Fmoc, C<u>H</u>CONH), 3.73 (s, 3H, OCH$_3$), 1.98-1.74 (m, 2H, CH$_3$C<u>H</u>, (CH$_3$)$_2$C<u>H</u>), 1.73-1.61 (m, 2H, (CH$_3$)$_2$CHC<u>H</u>$_2$,), 1.41 (m, 1H, CH$_3$C<u>H</u>$_2$), 1.15 (m, 1H, CH$_3$C<u>H</u>$_2$), 1.02 – 0.83 (m, 12H, (C<u>H</u>$_3$)$_2$CH, C<u>H</u>$_3$CH, C<u>H</u>$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.05, 171.93, 156.16, 143.73, 141.31, 127.71, 127.06, 125.02, 119.97, 67.10, 56.46, 53.53, 52.02, 47.19, 41.32, 37.86, 25.14, 24.67, 22.86, 22.01, 15.40, 11.48. Found: C, 69.77; H, 7.51; N, 5.79. $C_{28}H_{36}N_2O_5$ requires C, 69.98; H, 7.55; N, 5.83 %.

***N*-Fmoc-L-Ser(tBu)-L-Ala-OMe (13)** White solid (0.114 g), 76 % yield; mp = 86-87 °C; Rf = 0.83; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 7.4 Hz, 2H, ArH), 7.65 – 7.58 (m, 2H, ArH), 7.51 (d, *J* =

6.9 Hz, 1H, CONH), 7.41 (t, *J* = 7.2 Hz, 2H, ArH), 7.37 – 7.29 (m, 2H, ArH), 5.84 (d, J = 6.0 Hz, 1H, OCONH), 4.60 (m, 1H, C<u>H</u>COOCH$_3$), 4.40 (d, *J* = 7.1 Hz, 2H, CH$_2$-Fmoc), 4.32 – 4.19 (m, 2H, CH-Fmoc, <u>CH</u>CONH), 3.83 (dd, *J* = 8.5, *J* = 4.1 Hz, 1H, C<u>H</u>$_2$OtBu), 3.77 (s, 3H, OCH$_3$), 3.41 (t, *J* = 8.5Hz, 1H, C<u>H</u>$_2$OtBu), 1.44 (d, *J* = 7.2 Hz, 3H, C<u>H</u>$_3$CH), 1.25 (s, 9H, (CH$_3$)$_3$C); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 172.99, 170.04, 160.96, 143.90, 141.30, 127.71, 127.07, 125.14, 119.98, 80.89, 67.01, 61.87, 52.02, 50.66, 48.03, 47.16, 27.35, 18.15. Found: C, 66.88; H, 6.86; N, 5.95. $C_{26}H_{32}N_2O_6$ requires C, 66.65; H, 6.88; N, 5.98 %.

***N*-Fmoc-L-Ala-L-Cys(Bzl)-OMe (14)** Oil (0.170 g), 78 % yield; Rf = 0.76 ; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.77 (d, *J* = 7.5 Hz, 2H, ArH), 7.67-7.54 (m, 2H, ArH), 7.41 (t, *J* = 7.3 Hz, 2H, ArH), 7.36 – 7.21 (m, 7H, ArH), 6.82 (s$_{broad}$, 1H, CONH), 5.50 (s$_{broad}$, 1H, OCONH), 4.78 (m, 1H, C<u>H</u>COOCH$_3$), 4.40 (d, *J* = 7.0 Hz, 2H, CH$_2$-Fmoc), 4.31 (m, 1H, <u>CH</u>CONH), 4.22 (t, *J* = 7.0 Hz, 1H, CH-Fmoc), 3.73 (s, 3H, OCH$_3$), 3.66 (s, 2H, CH$_2$Ph), 2.89 (d, *J* = 4.9 Hz, 2H, CHC<u>H</u>$_2$S), 1.40 (d, *J* = 6.8 Hz, 3H, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 172.15, 170.89, 156,01, 143.99, 141.31, 137.67, 128.90, 128.62, 127.72, 127.30, 127.09, 125.08, 119.98, 67.00, 52.64, 51.81, 50.40, 47.16, 36.65, 33.34, 18.57. Found: C, 66.98; H, 5.80; N, 5.36; S, 6.16. $C_{29}H_{30}N_2O_5S$ requieres C, 67.16; H, 5.83; N, 5.4; S, 6.18%.

***N*-Fmoc-L-Ala-L-Lys(Boc)-OMe (15)** Yellow solid (0.227 g), 74 % yield; mp = 140-143 °C; Rf = 0.66; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.81-7.71 (m, 2H, ArH), 7.65-7.52 (m, 2H, ArH), 7.40 (t, J = 7.0 Hz, 2H, ArH), 7.35-7.27 (m, 2H, ArH), 6.86 (d, J = 7.6 Hz, 1H, CONH), 5.73 (d, J = 7.3 Hz, 1H, OCONH), 5.29 (s, 1H, N<u>H</u>CH$_2$), 4.77 (m, 1H, C<u>H</u>COOCH$_3$), 4.57 (m, 1H, <u>CH</u>CONH), 4.37 (d, J = 7.1 Hz, 2H, CH$_2$-Fmoc), 4.21 (t, J = 7.1 Hz, 1H, CH-Fmoc), 3.73 (s, 3H, OCH$_3$), 3.18-2.95 (m, 2H, NHC<u>H</u>$_2$CH$_2$), 1.83 (m, 1H, CHC<u>H</u>$_2$), 1.66 (m, 1H, CHC<u>H</u>$_2$), 1.49 – 1.19 (m, 16H, C<u>H</u>$_3$CH, (CH$_3$)$_3$C, CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$ CH$_2$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 172.56, 172.36, 161.52, 157.67, 143.69, 141.28, 127.73, 127.10, 125.10, 119.98, 79.28, 67.22, 56.70, 52.24, 50.46, 47.05, 41.54, 29.37, 28.42, 22.22, 16.03. Found: C, 64.87; H, 7.06; N, 7.55. $C_{30}H_{39}N_3O_7$ requires C, 65.08; H, 7.10; N, 7.59 %.

***N*-Fmoc-L-Cys(Bzl)-L-Ala-OMe (16)** Yellow solid (0.296 g), 78 % yield; mp = 155-157 °C; Rf = 0.86; ^{1}H NMR (300 MHz, CDCl$_3$) two diastereoisomers (90*:10) δ 7.80 (d, J = 7.5 Hz, 2H, ArH), 7.63 (d, J = 7.3 Hz, 2H, ArH), 7.44 (t, J = 7.4 Hz, 2H, ArH), 7.40-7.20 (m, 7H, ArH), 6.89* and 6.81 (2s$_{broad}$, 1H, CONH), 5.72 (s$_{broad}$, 1H, OCONH), 4.59 (p, J = 7.2 Hz, 1H, C<u>H</u>COOCH$_3$), 4.53 – 4.39 (m, 2H, CH$_2$-Fmoc), 4.39-4.15 (m 2H, <u>CH</u>CONH, CH-Fmoc), 3.92-3.63 (m, 5H, SCH$_2$Ph, OCH$_3$), 2.92 (dd, J = 13.5 Hz, J = 5.4 Hz, 1H, CHC<u>H</u>$_2$S), 2.79 (dd, J = 13.5 Hz, J = 6.9 Hz, 1H, CHC<u>H</u>$_2$S),

1.44 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.96, 169.88, 156.01, 143.72, 141.32, 137.94, 129.78, 128.78, 128.19, 126.26, 124.06, 121.09, 119.03, 67.09, 54.90, 51.67, 49.07, 47.90, 36.56, 34.23, 17.28. Found: C, 66.89; H, 5.81; N, 5.35; S, 6.17. $C_{29}H_{30}N_2O_5S$ requieres C, 67.16; H, 5.83; N, 5.4; S, 6.18%.

***N*-Fmoc-D-Cys(Bzl)-L-Ala-OMe (17)** Yellow solid (0.310 g), 74 % yield; mp = 147-148 °C; Rf = 0.86; ^{1}H NMR (300 MHz, $CDCl_3$) two diastereoisomers (90*:10) δ 7.80 (d, J = 7.5 Hz, 2H, ArH), 7.63 (d, J = 7.3 Hz, 2H, ArH), 7.44 (t, J = 7.4 Hz, 2H, ArH), 7.40-7.23 (m, 7H, ArH), 6.91 and 6.82* (2 s_{broad}, 1H, CONH), 5.73 (s_{broad}, 1H, OCONH), 4.61 (p, J = 7.1 Hz, 1H, C<u>H</u>$COOCH_3$), 4.53 – 4.30 (m, 3H, CH_2-Fmoc, <u>CH</u>CONH), 4.26 (t, J = 7.0 Hz, 1H, CH-Fmoc), 3.89-3.61 (m, 5H, SCH_2Ph, OCH_3), 2.92 (dd, J = 13.4 Hz, J = 4.7 Hz, 1H, CHC<u>H</u>$_2$S), 2.81 (dd, J = 13.4 Hz, J = 7.1 Hz, 1H, CHC<u>H</u>$_2$S), 1.44 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.96, 169.77, 156.03, 143.68, 141.30, 137.89, 129.76, 128.68, 128.18, 126.28, 124.05, 121.07, 119.03, 67.19, 54.91, 51.66, 49.06, 47.95, 36.52, 34.33, 17.26. Found: C, 66.87; H, 5.78; N, 5.38; S, 6.16. $C_{29}H_{30}N_2O_5S$ requieres C, 67.16; H, 5.83; N, 5.4; S, 6.18%.

***N*-Cbz-L-Ala-L-Ala-OMe (18)** White solid (0.243 g), 74 % yield; mp = 104-106 °C; Rf = 0.84; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 – 7.20 (m, 5H, ArH), 6.78 (d, *J* = 7.2 Hz, 1H, CONH), 5.54 (d, *J* = 7.5 Hz, 1H, OCONH), 5.10 (s, 2H, CH_2Ph), 4.55 (p, 1H, *J* = 7.2 Hz, C<u>H</u>$COOCH_3$), 4.30 (m, 1H, 173.12, 171.86, 155.67, 136.26, 128.50, 128.14, 128.00, 66.99, 52.39, 50.36, 48.07, 18.61, 18.17. GC/MS (EI, 70eV) m/z (% rel.): 308 [$M^{\bullet+}$] (2), 249 (2), 206 (3), 178 (9), 134 (16), 102 (9), 91 (100), 88 (13), 70 (6), 59 (2). Found: C, 58.51; H, 6.53; N, 9.07. $C_{15}H_{20}N_2O_5$ requires C, 58.43; H, 6.54; N, 9.09 %.

***N*-Cbz-D-Ala-L-Ala-OMe (19)** White solid (0.197 g), 75 % yield; mp = 136-137 °C; Rf = 0.85; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 – 7.18 (m, 5H, ArH), 7.01 (d, J = 7.1 Hz, 1H, CONH), 5.71 (d, J = 7.6 Hz, 1H, OCONH), 5.09 (s, 2H, CH_2Ph), 4.55 (p, J = 7.1 Hz, 1H, C<u>H</u>$COOCH_3$), 4.33 (m, 1H, <u>CH</u>CONH), 3.70 (s, 3H, OCH_3), 1.37 (d, J = 7.0 Hz, 6H, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.35, 172.01, 155.96, 136.19, 128.54, 128.20, 128.06, 67.01, 52.52, 50.74, 48.01, 18.66, 18.08. GC/MS (EI, 70eV) m/z (% rel.): 308 [$M^{\bullet+}$] (2), 249 (2), 206 (3), 178 (9), 134 (16), 102 (9), 91 (100), 88 (13), 70 (6), 59 (2). Found: C, 58.53; H, 6.51; N, 9.07. $C_{15}H_{20}N_2O_5$ requires C, 58.43; H, 6.54; N, 9.09 %.

***N*-Ns-L-Phe-L-Ala-OMe (20)** Yellow solid (0.169 g), 48 % yield; mp = 168-172 °C; Rf = 0.85; ^{1}H NMR (300 MHz, $CDCl_3$), two diastereoisomers (74*:26) δ: 8.14 (d, *J* = 8.2 Hz, 2H, ArH), 7.77 (d, *J* = 8.2 Hz, 2H, ArH), 7.20-7.07 (m, 3H, ArH), 7.07-6.94 (m, 3H, ArH), 6.89* and 6.66 (2d, *J* = 6.8 Hz, 1H, $ArSO_2NH$), 6.19 (d, *J* = 7.6 Hz, 1H, CONH), 4.44 (m, 1H, $C\underline{H}COOCH_3$), 4.03 (m, 1H, $\underline{CH}CONH$), 3.73* and 3.72 (2s, 3H, OCH_3), 3.09 (dd, *J* = 13.5, *J* = 4.5 Hz, 1H, $C\underline{H}_2Ph$), 2.91 (dd, *J* = 13.5, 8.8 Hz, 1H, $C\underline{H}_2Ph$), 1.32* and 1.26 (2d, *J* = 7.0 Hz, 3H, $C\underline{H}_3CH$); ^{13}C NMR (75 MHz, $CDCl_3$) two diastereoisomers (74*:26) δ: 172.64, 169.65, 149.93, 145.21, 135.45, 129.27, 128.78, 128.19, 127.28, 124.17, 58.48, 53.30 and 52.36*, 48.41, 38.92, 19.29 and 18.01*. GC/MS (EI, 70eV) m/z (% rel.): 376 (7), 344 (8), 305 (100), 233 (43), 186 (23), 174 (63), 156 (10), 130 (32), 122 (36), 118 (45), 91 (63), 76 (14), 59 (9). Found: C, 52.32; H, 4.87; N, 9.67; S, 7.35. $C_{19}H_{21}N_3O_7S$ requieres C, 52.41; H, 4.86; N, 9.65; S, 7.36%.

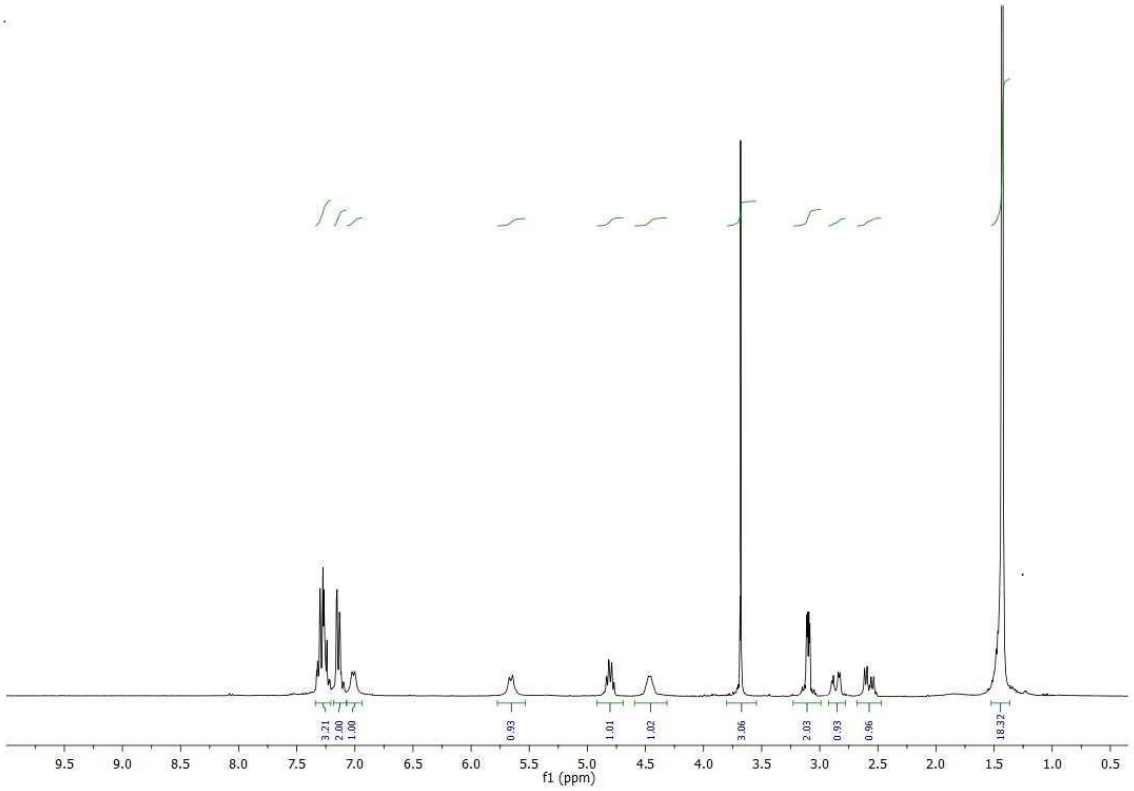
Synthesis of L-Asp-L-Phe-OMe (1a)

To a solution of *N*-Boc-Asp-(OtBu)-Phe-OMe (**1**) (0.1 g, 0.22 mmol), in dry CH_2Cl_2 (1,5 mL), trifluoroacetic acid (TFA) (1,5 mL) was added and stirred for 2 h at room temperature. The progress of the reaction was followed by TLC analysis with chloroform–methanol 80 : 20, (v/v) as eluent and visualization with 0.2% ninhydrin in ethanol. Then excess reagent and solvent were removed under vacuum. The resulting oil was stirred in cold diethyl ether (15 mL) and L-Asp-L-Phe-OMe (**1a**) was recovered by filtration as a white solid (0.086 g) in 95 % yield.

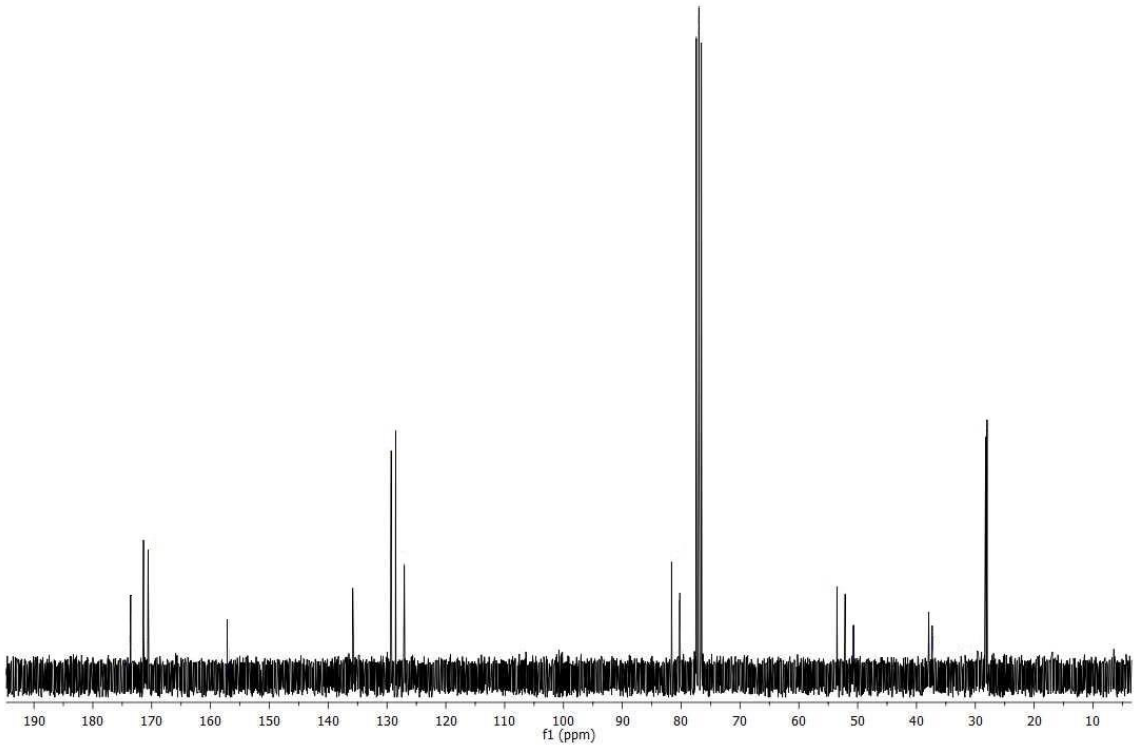
mp = 244-245 °C; *Rf* = 0.20; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.86 (d, J = 6.9 Hz, 1H, CONH), 7.39 – 7.09 (m, 5H, ArH), 4.52 (m, 1H, C<u>H</u>COOCH$_3$), 4.01 (m, 1H, C<u>H</u>CONH), 3.61 (s, 3H, OCH$_3$), 3.07 (dd, *J* = 13.9, 5.3 Hz, 1H, CH_2Ph), 2.93 (dd, *J* = 13.9, 9.1 Hz, 1H, CH_2Ph), 2.78 (dd, *J* = 17.5, 3.4 Hz, 1H, C<u>H$_2$</u>COOH), 2.65 (dd, *J* = 17.5, 8.4 Hz, 1H, C<u>H$_2$</u>COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.74, 171.50, 168.84, 137.28, 129.50, 128.82, 127.17, 54.52, 52.50, 50.63, 38.14, 36.82. Found: C, 56.98; H, 6.14; N, 9.49. $C_{14}H_{18}N_2O_5$ requires C, 57.13; H, 6.16; N, 9.52 %.

N-Boc-L-Asp(OtBu)-Phe-OMe (1)

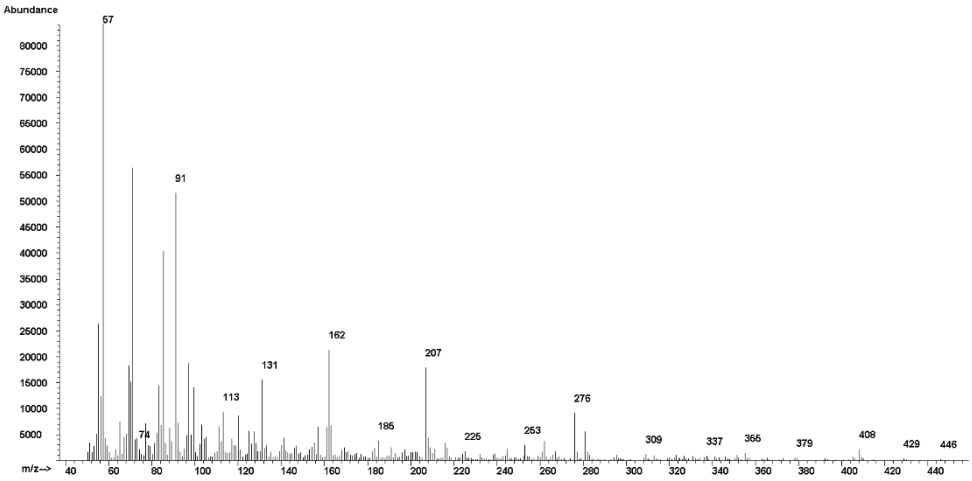
^{1}H NMR



^{13}C NMR



MS (EI)


Abundance
m/z-->
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185
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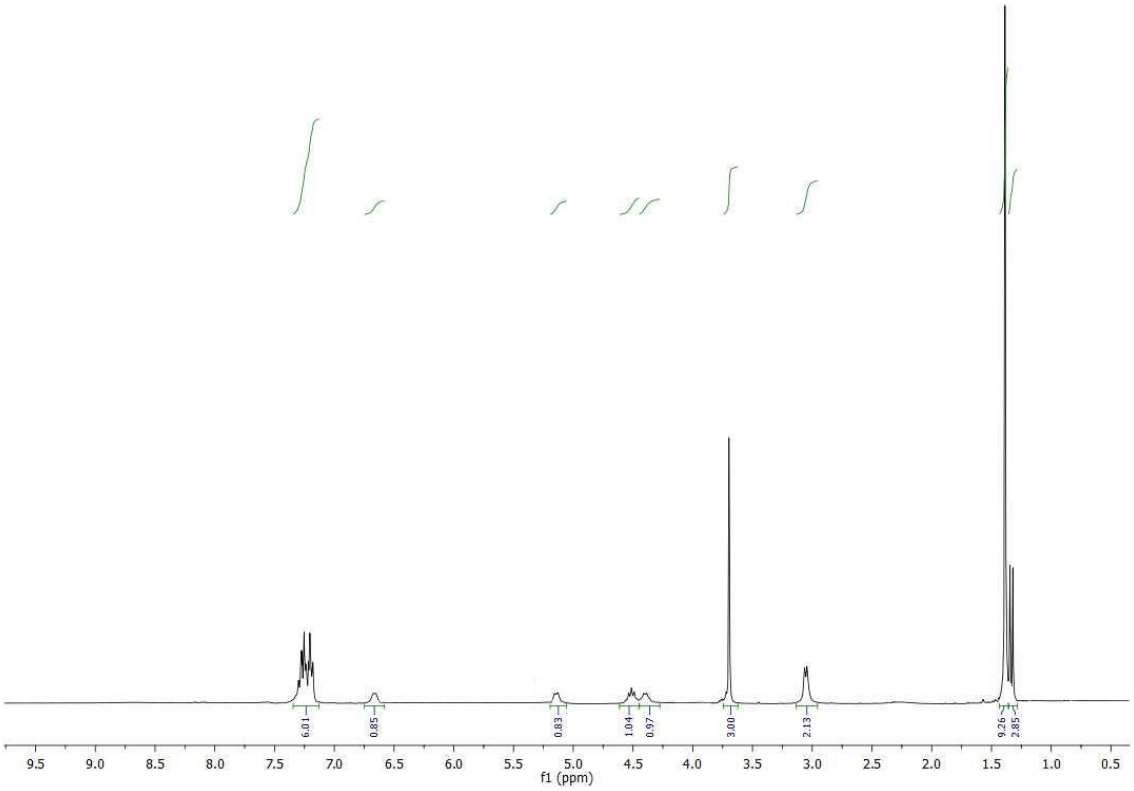
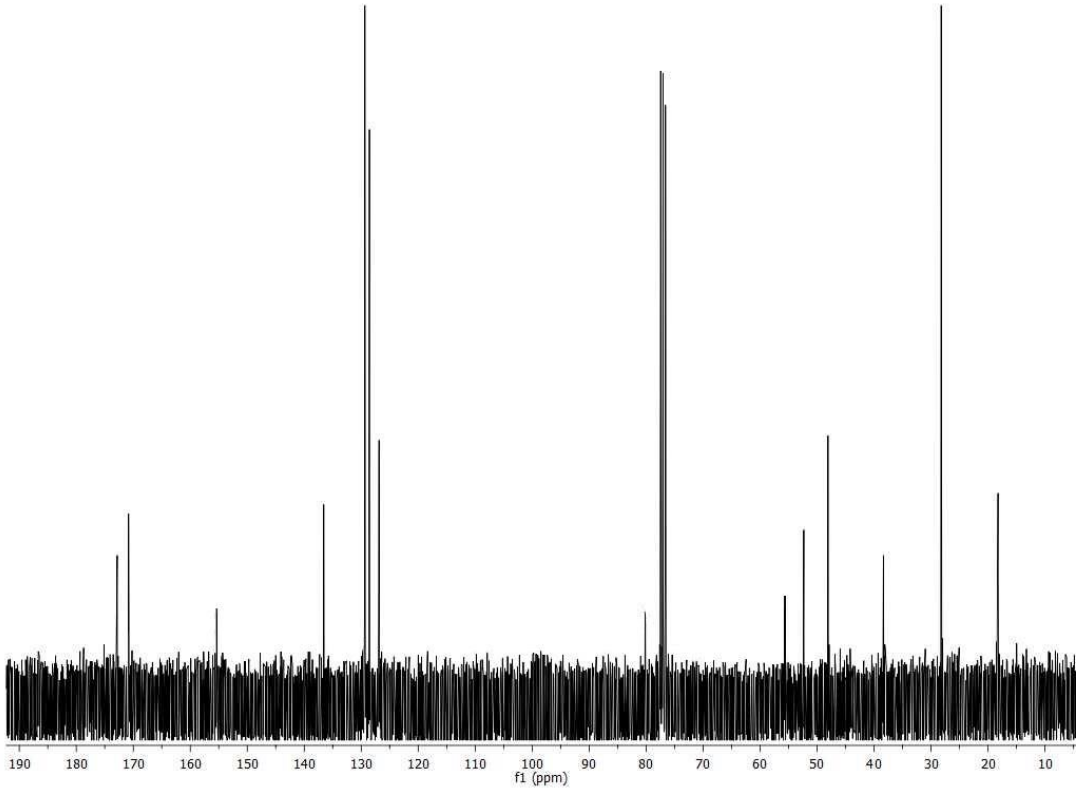
408
429
446

N-Boc-L-Phe-L-Ala-OMe (2)

^{1}H NMR



^{13}C NMR



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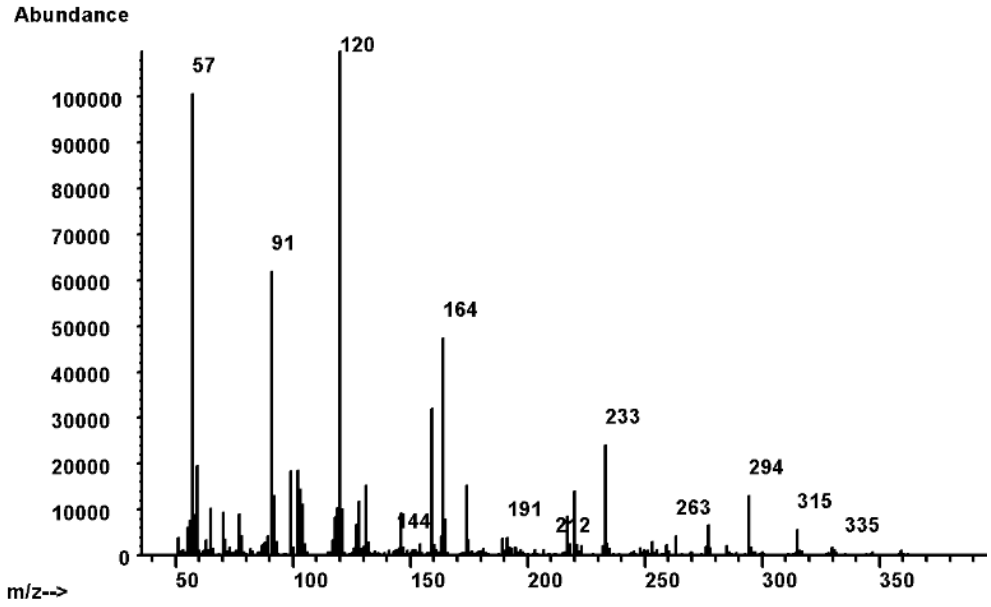
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m/z-->
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300
350
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315
335
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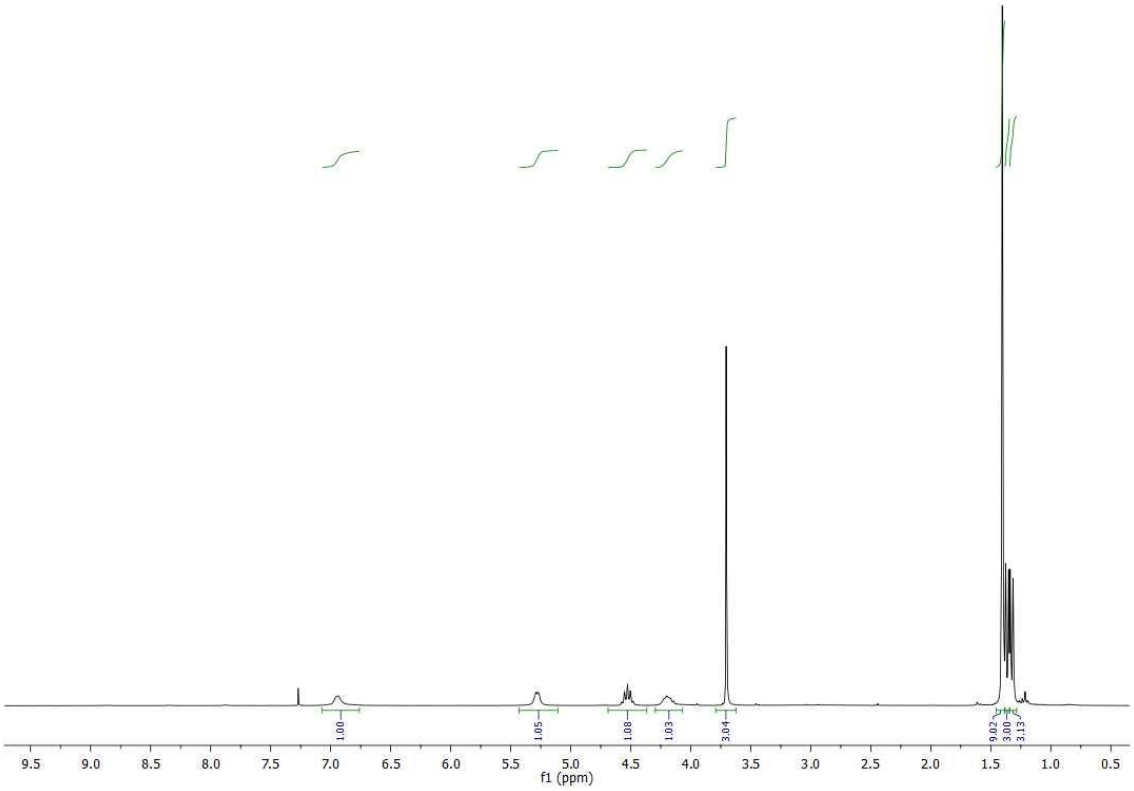
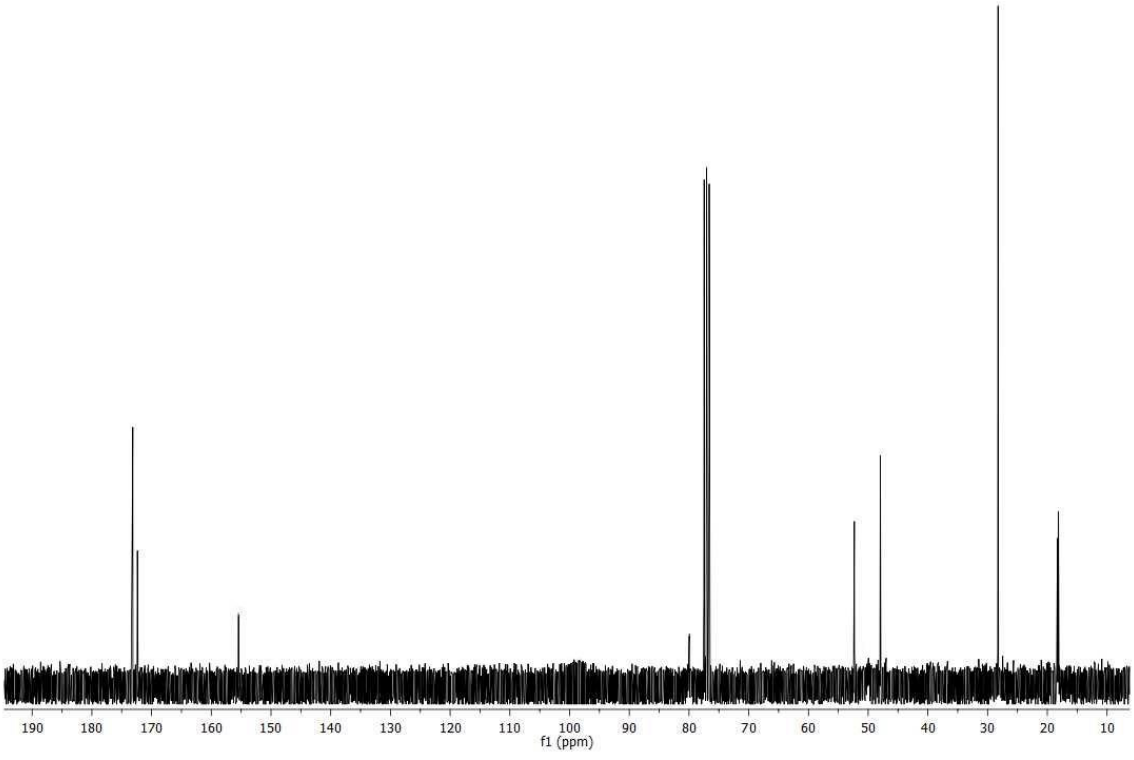
191
212
144

N-Boc-L-Ala-L-Ala-OMe (3)

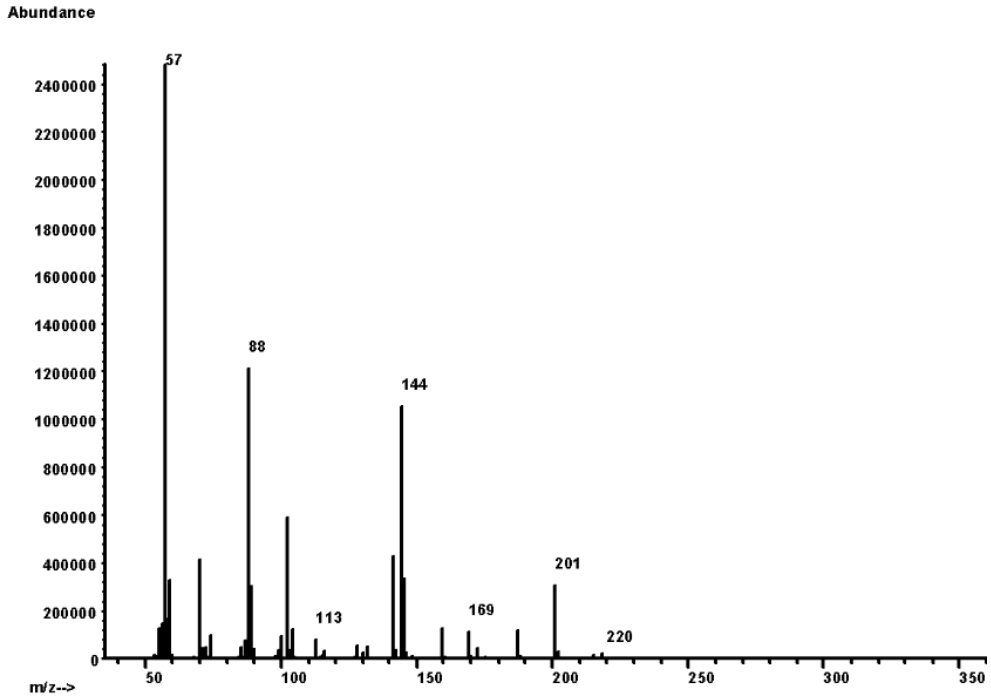
^{1}H NMR



^{13}C NMR



MS (EI)


Abundance
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113
169
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1400000
1200000
1000000
800000
600000
400000
200000
0
m/z-->
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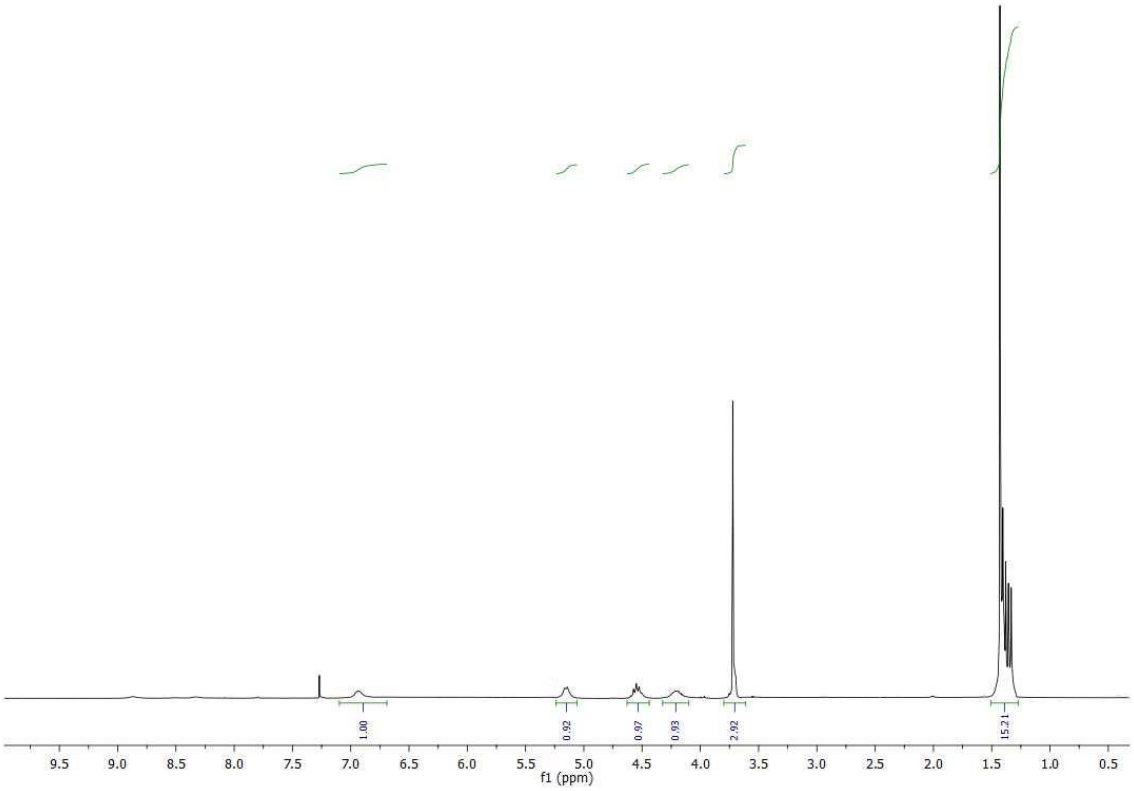
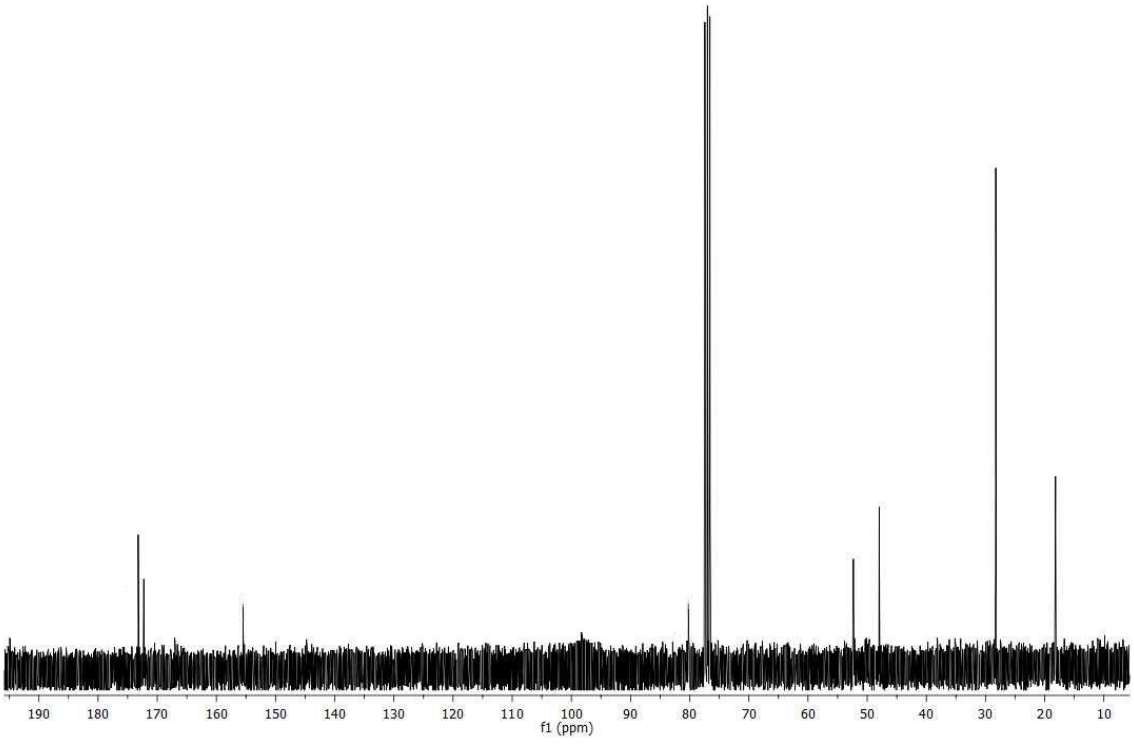
100
150
200
250
300
350

N-Boc-D-Ala-L-Ala-OMe (4)

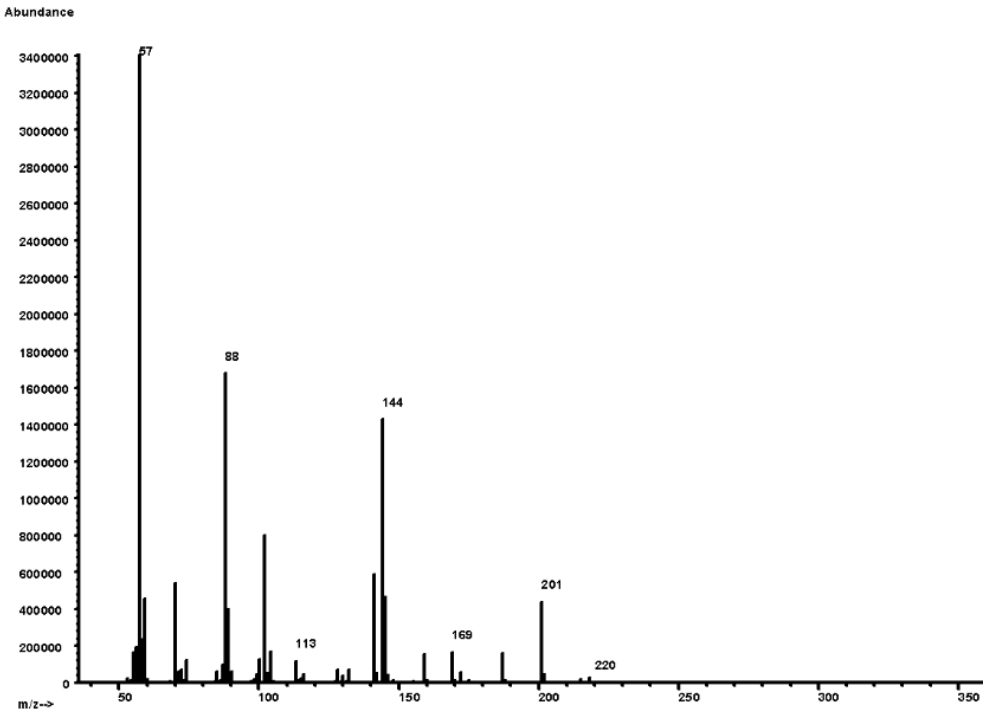
^{1}H NMR



^{13}C NMR



MS (EI)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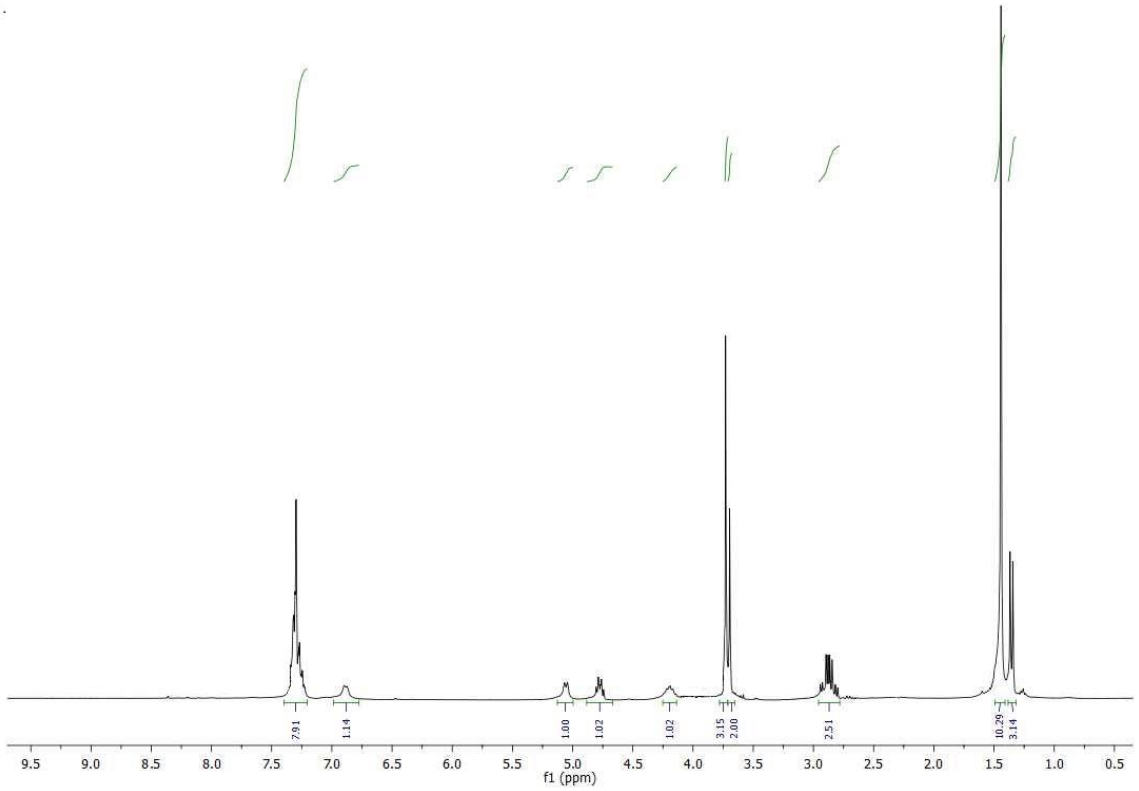
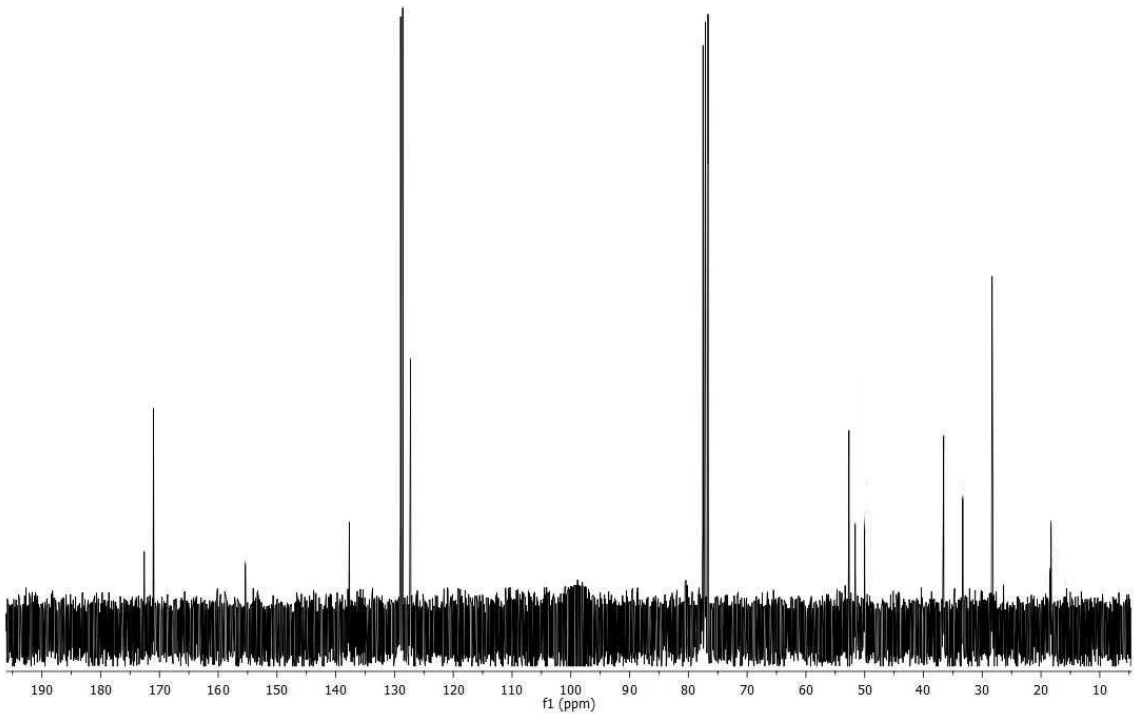
600000
400000
200000
0
m/z-->
50
100
150
200
250
300
350
57
88
113
144
169
201
220

N-Boc-L-Ala-L-Cys(Bzl)-OMe (5)

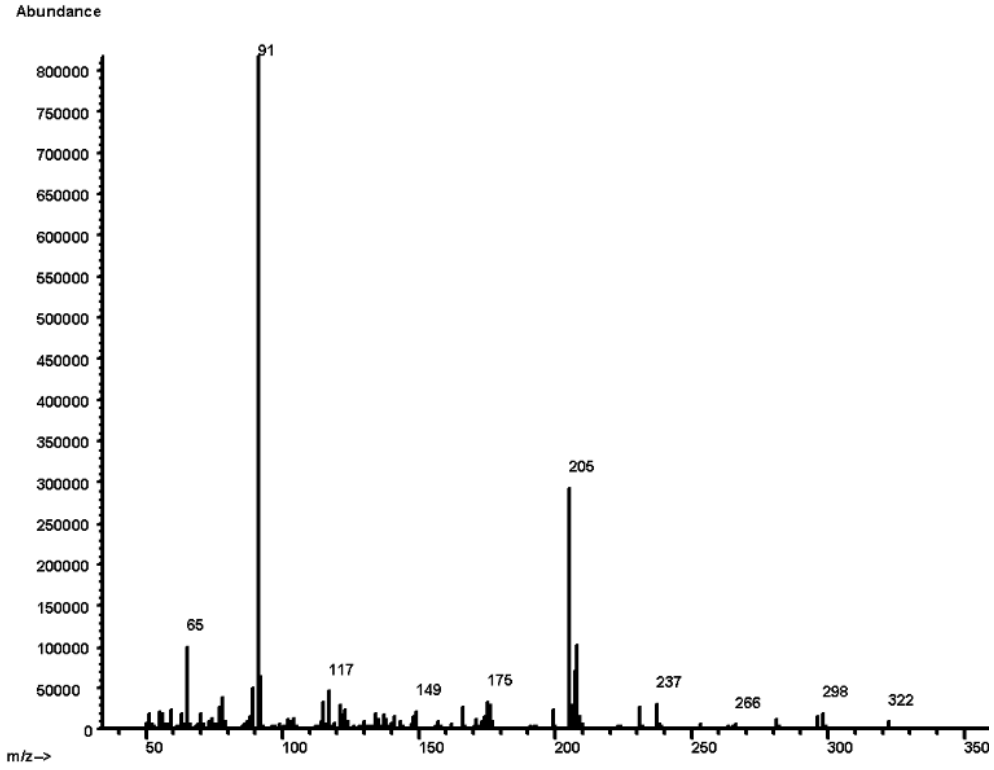
^{1}H NMR



^{13}C NMR



MS (EI)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0
m/z-->
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100
150
200
250
300
350
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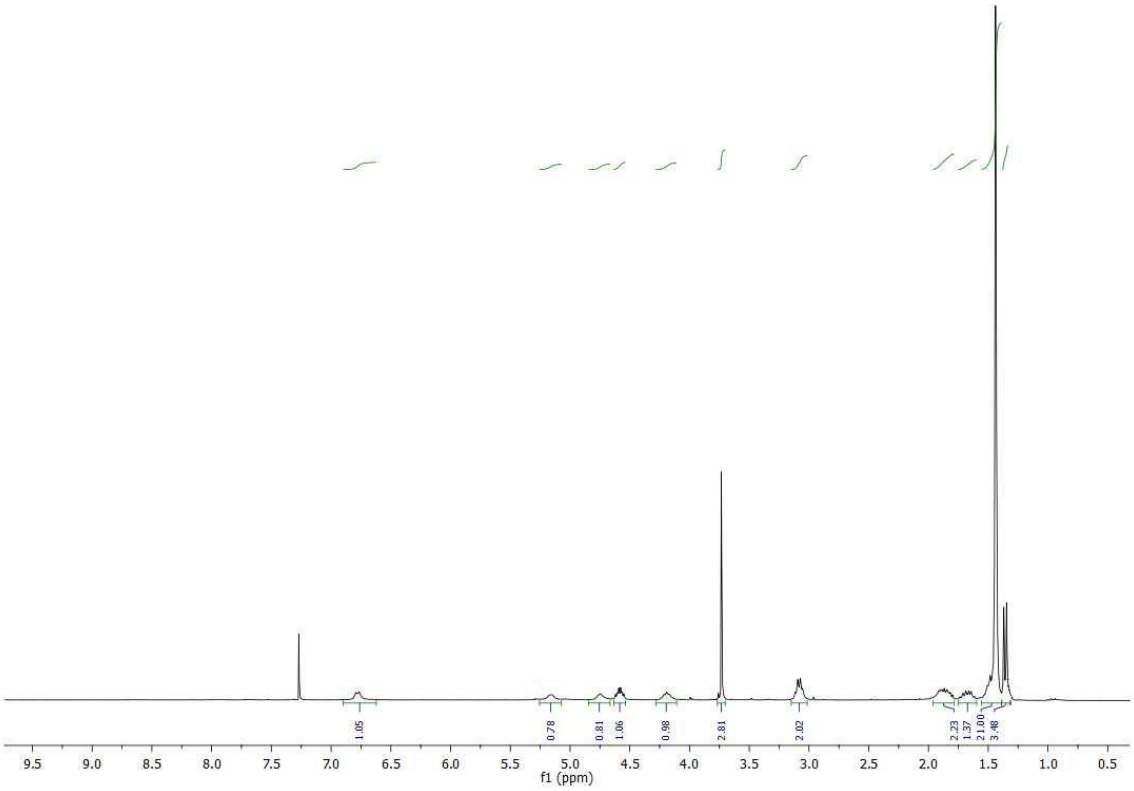
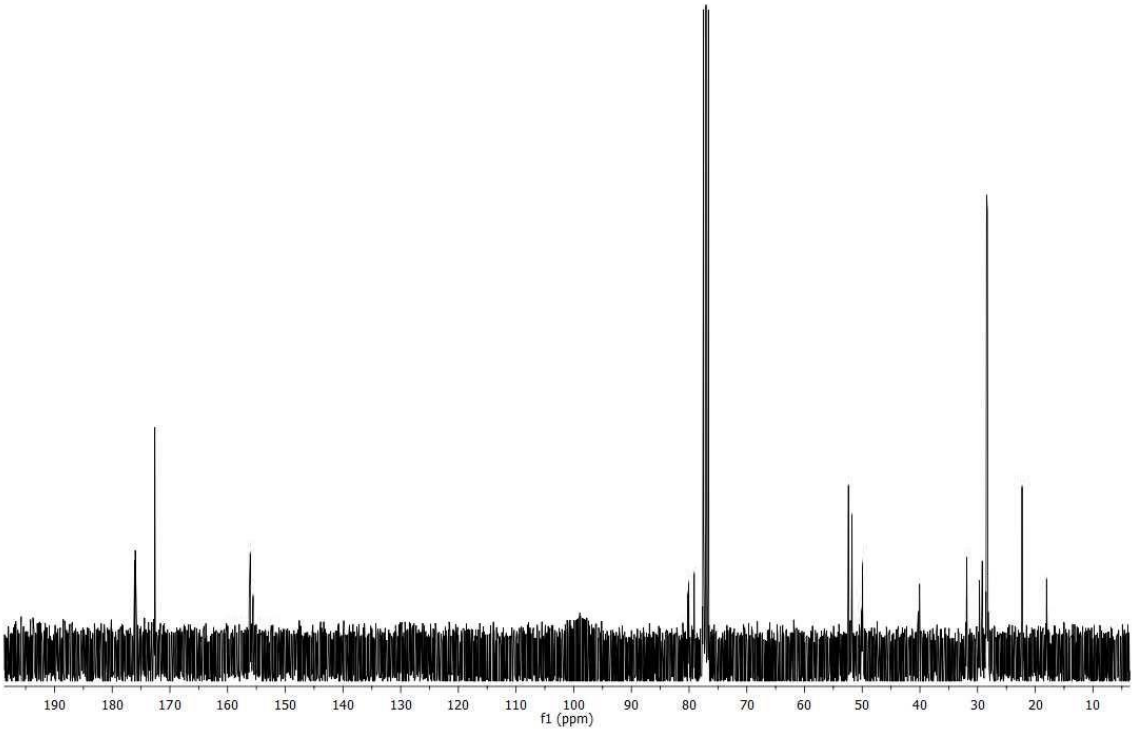
149
175
237
266
298
322

N-Boc-L-Ala-L-Lys(Boc)-OMe (6)

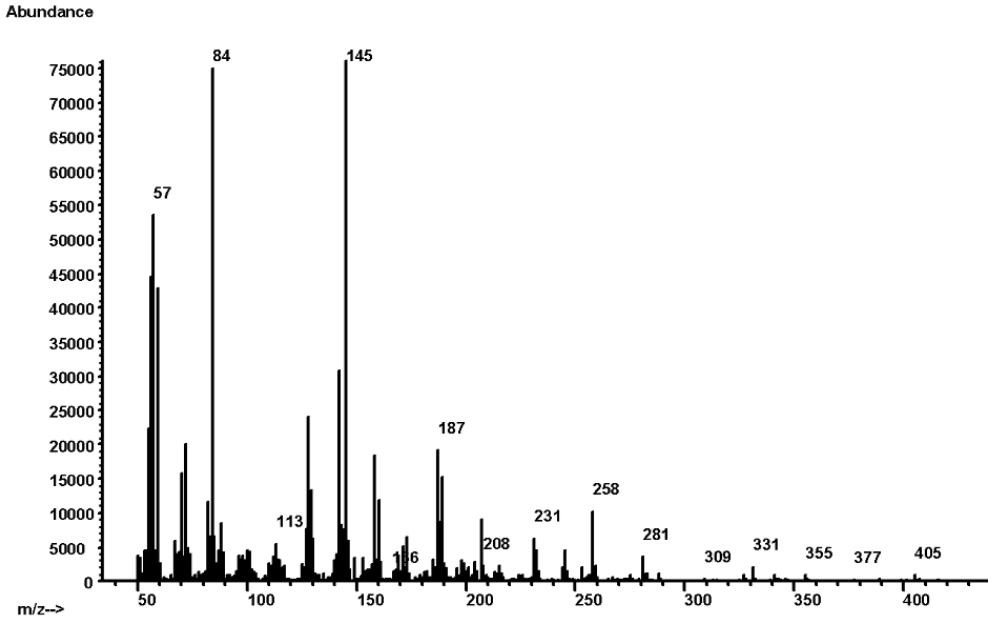
^{1}H NMR



^{13}C NMR



MS (EI)


Abundance
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m/z-->
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100
150
200
250
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350
400
57
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309
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355
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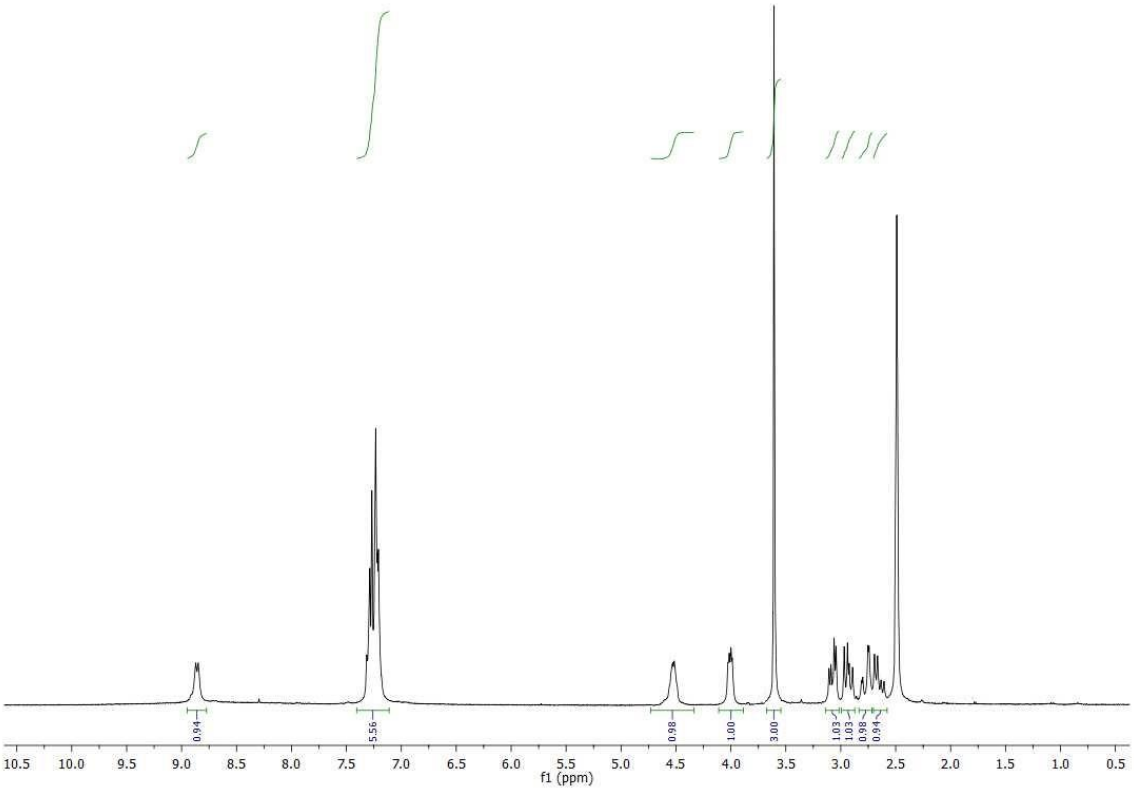
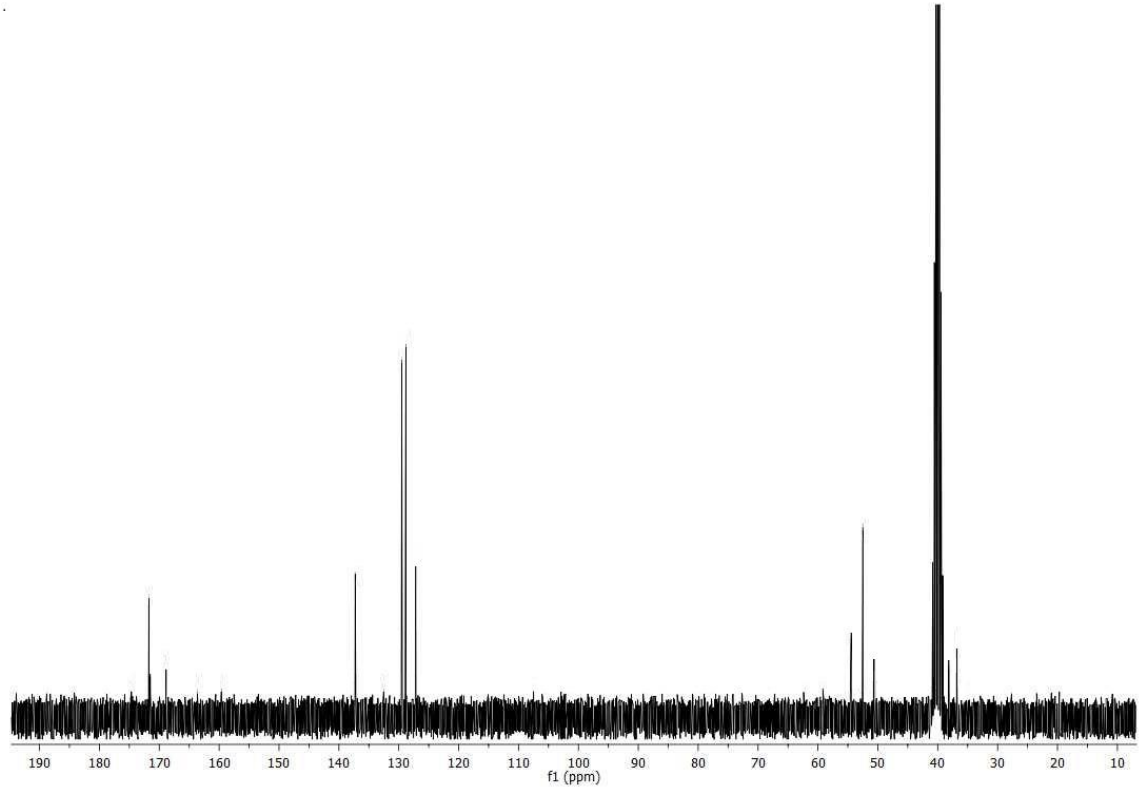
405

L-Asp-Phe-OMe (1a)

^{1}H NMR

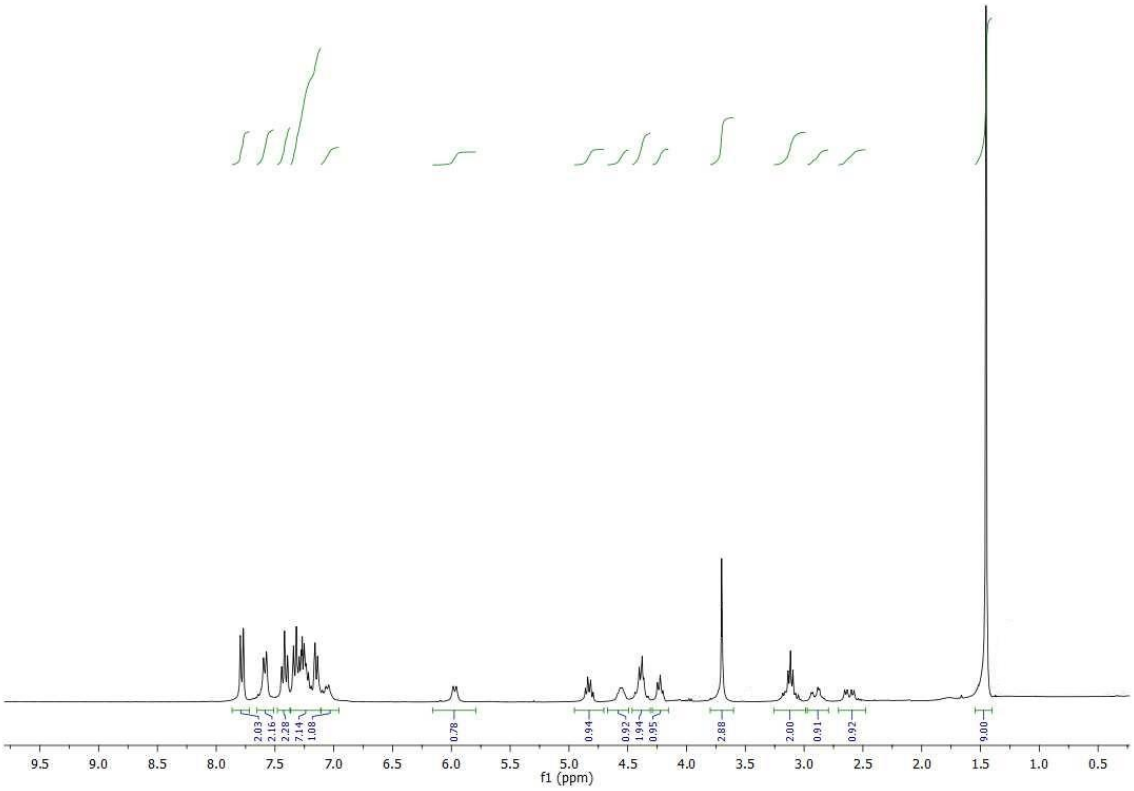


^{13}C NMR

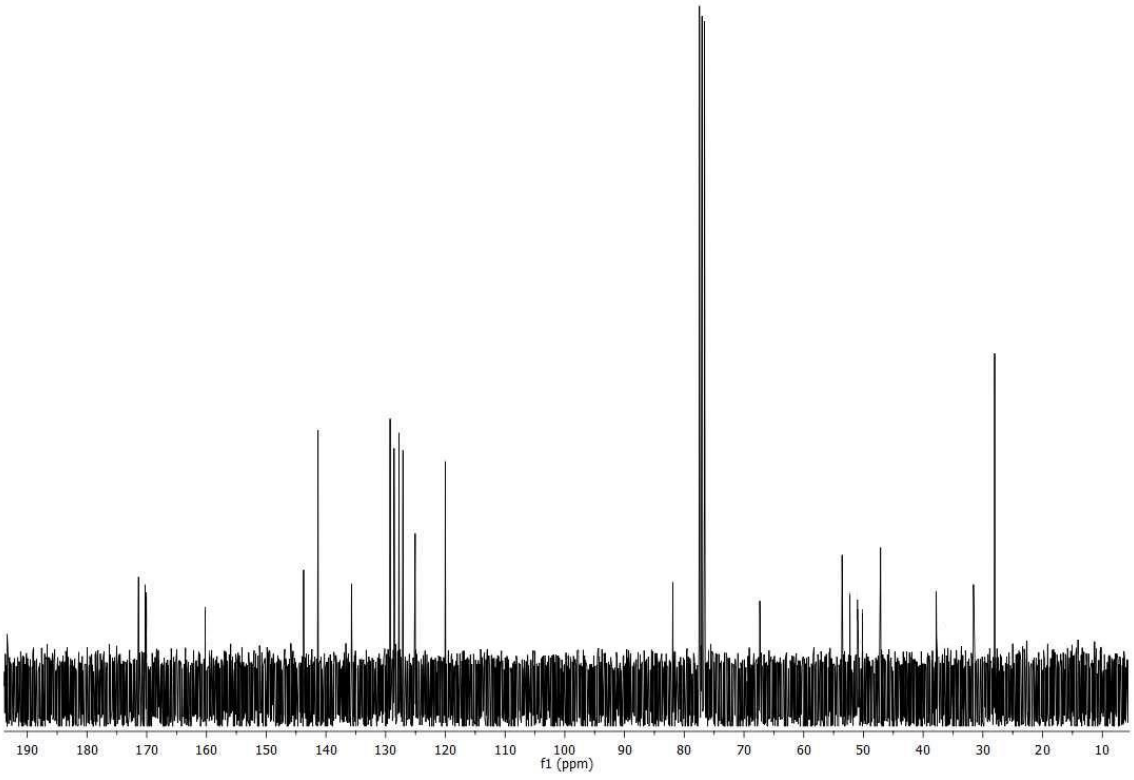


N-Fmoc-L-Asp-L-Phe-OMe (7)

^{1}H NMR

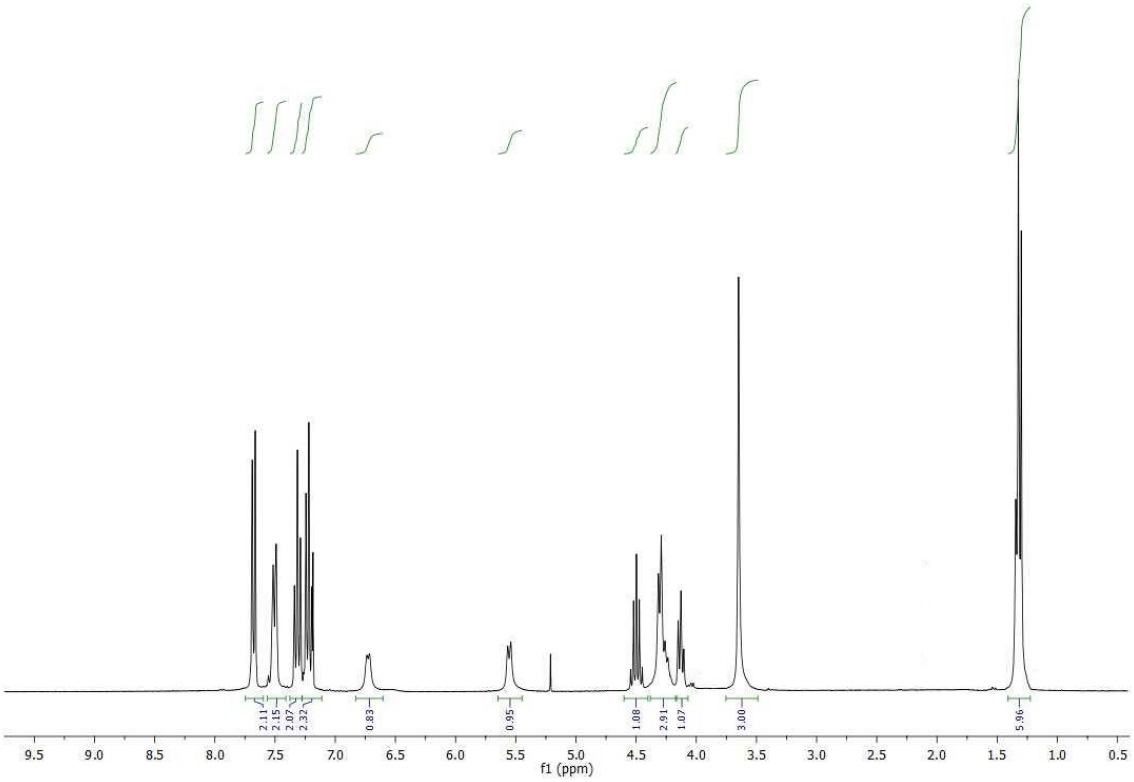


^{13}C NMR

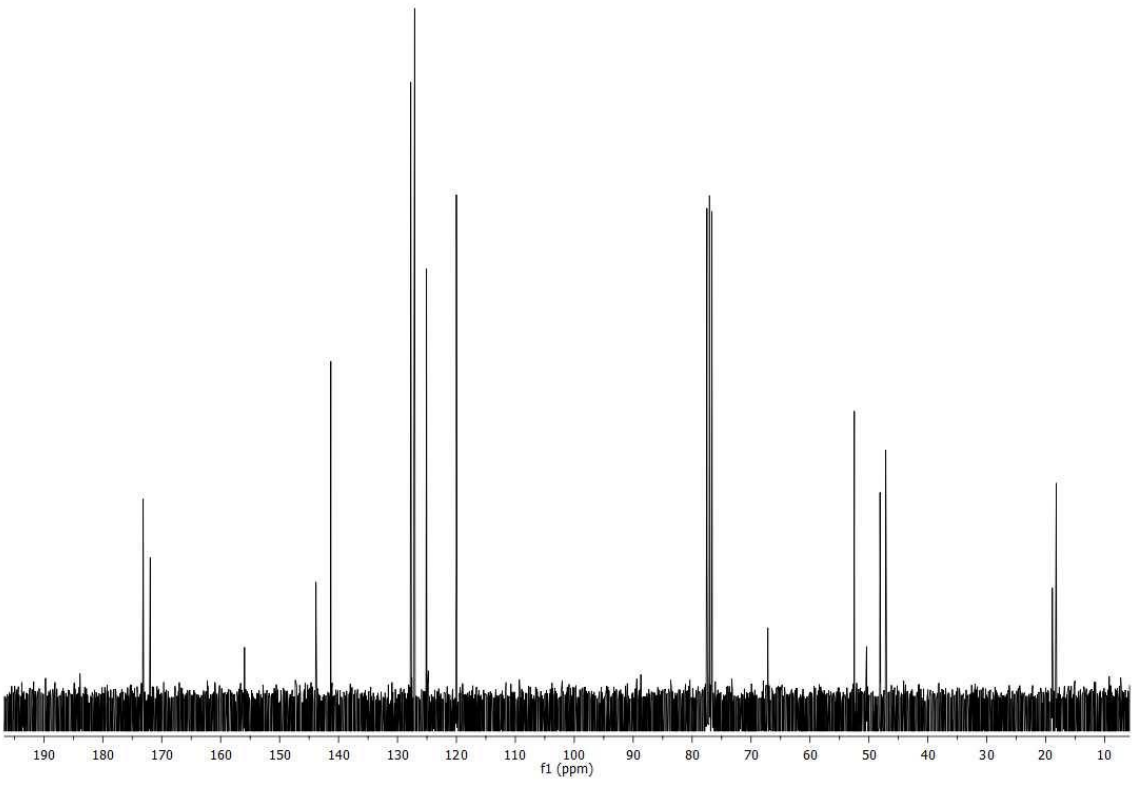


N-Fmoc-L-Ala-L-Ala-OMe (8)

^{1}H NMR

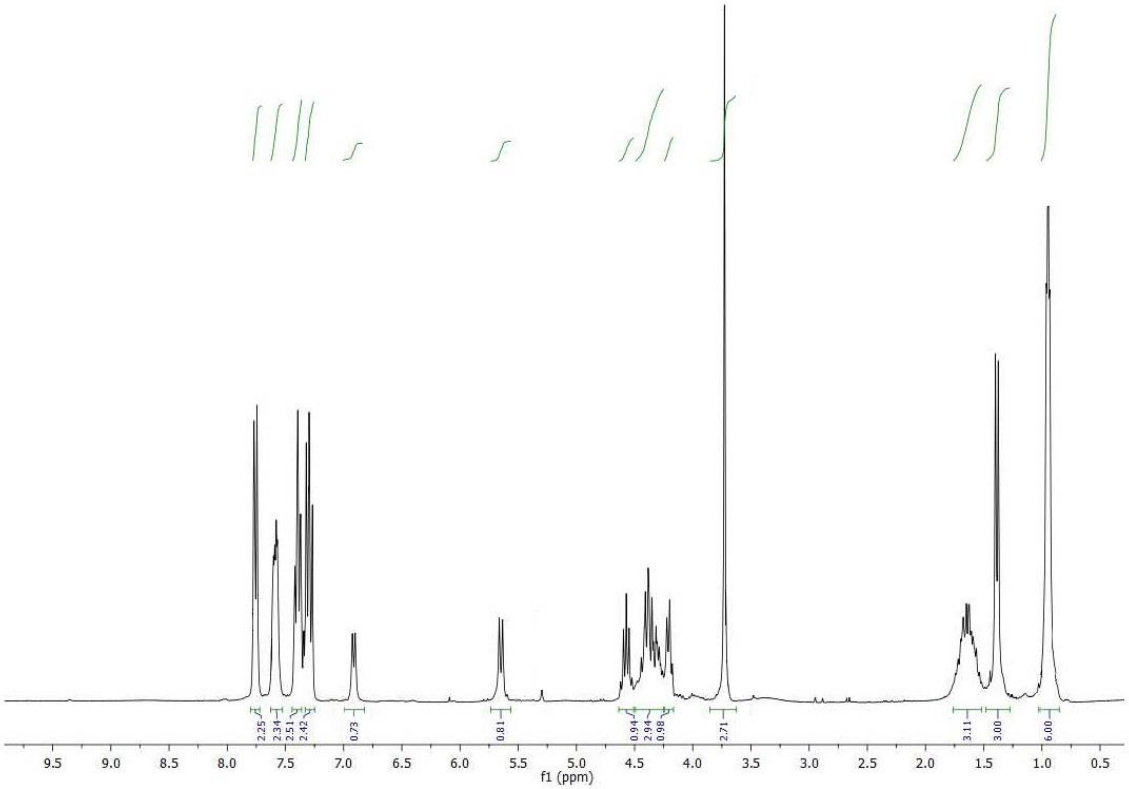


^{13}C NMR

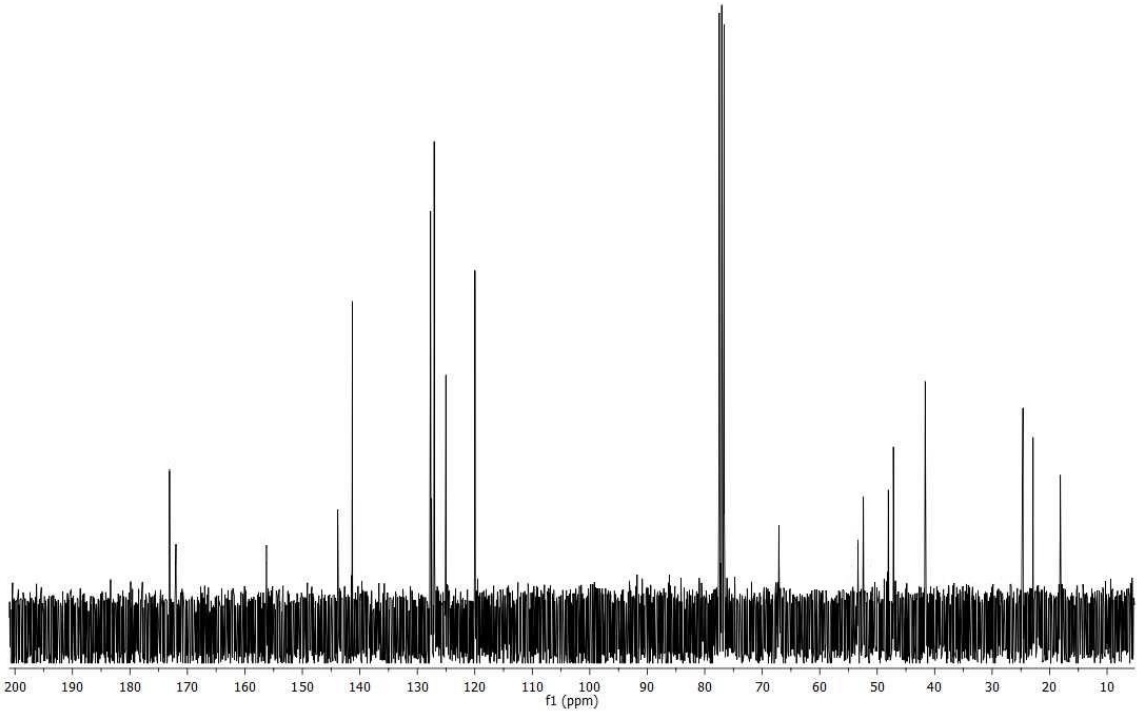


N-Fmoc-L-Leu-L-Ala-OMe (9)

^{1}H NMR

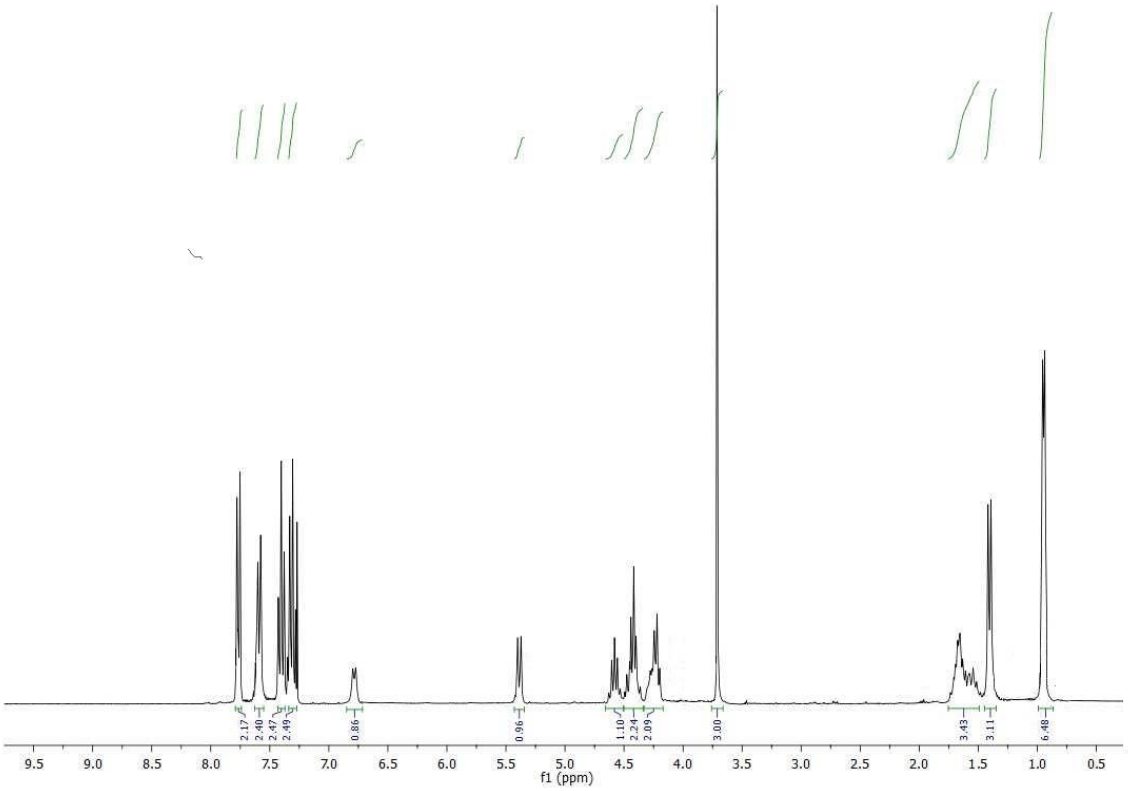


^{13}C NMR

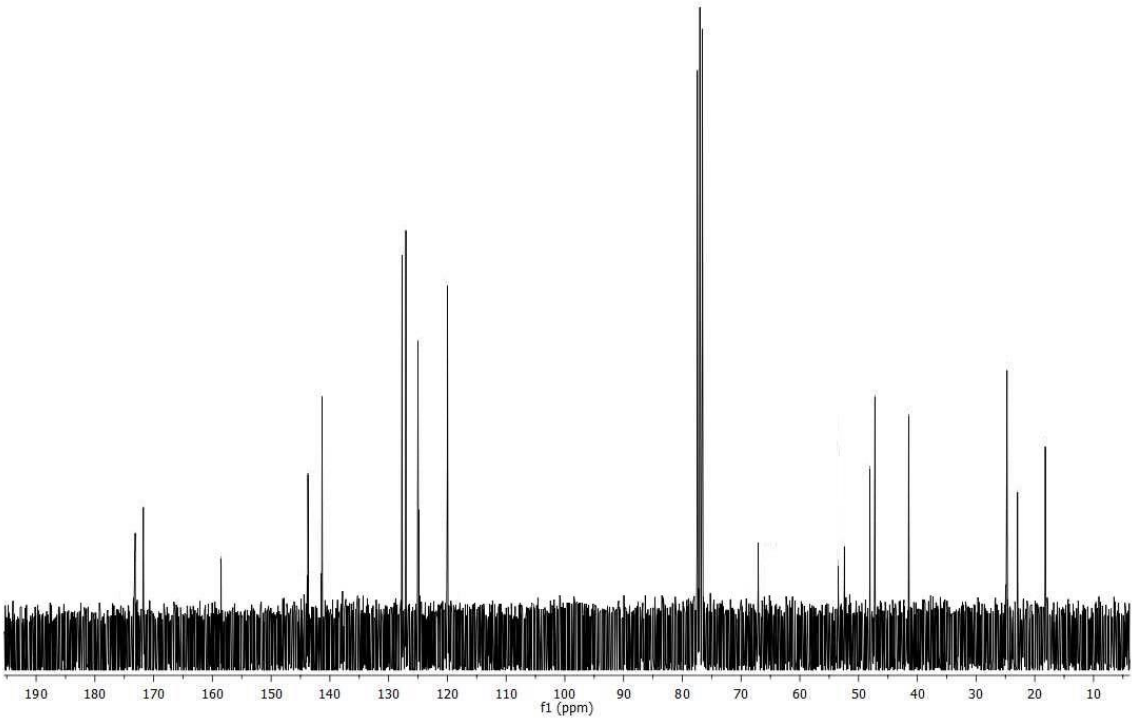


N-Fmoc-D-Leu-D-Ala-OMe (10)

^{1}H NMR

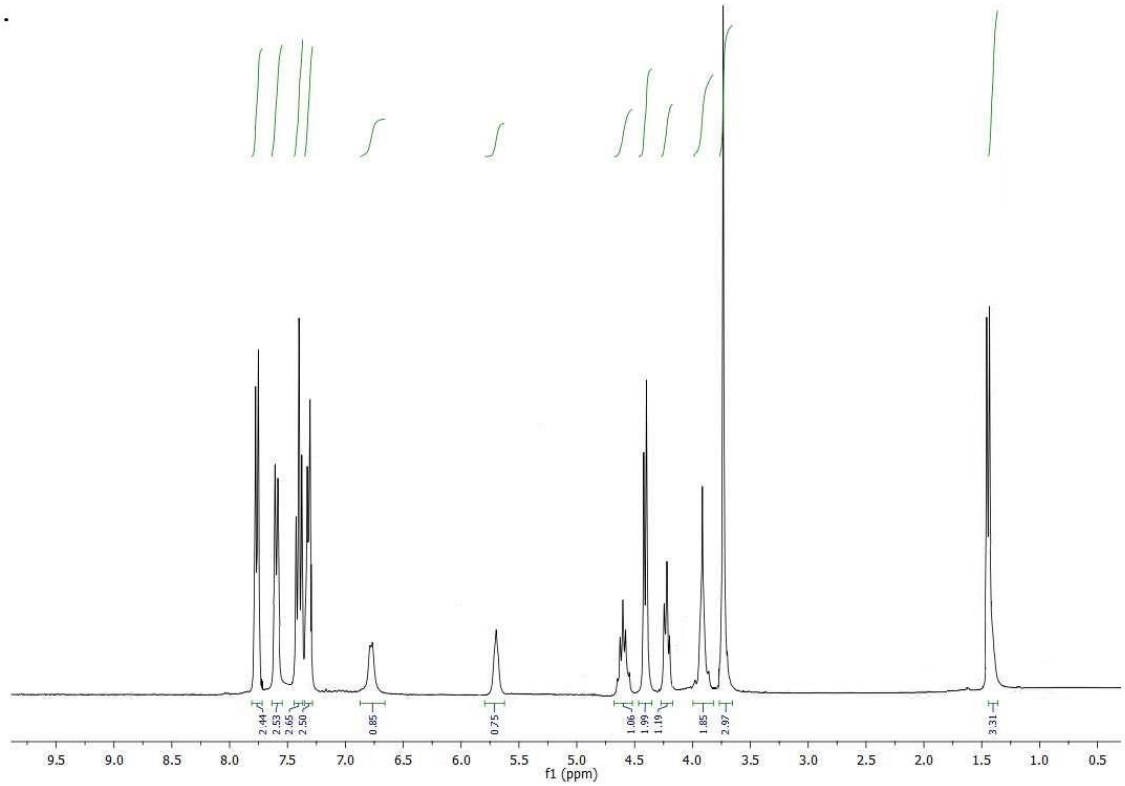


^{13}C NMR

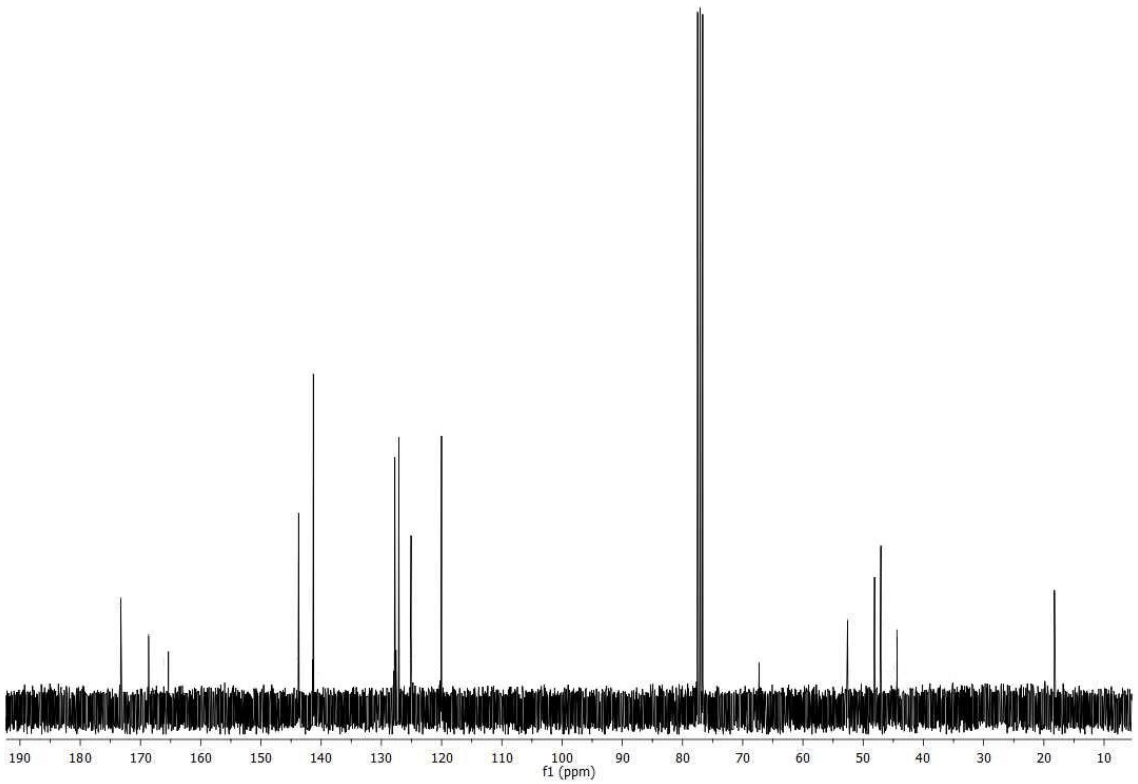


N-Fmoc-Gly-L-Ala-OMe (11)

^{1}H NMR

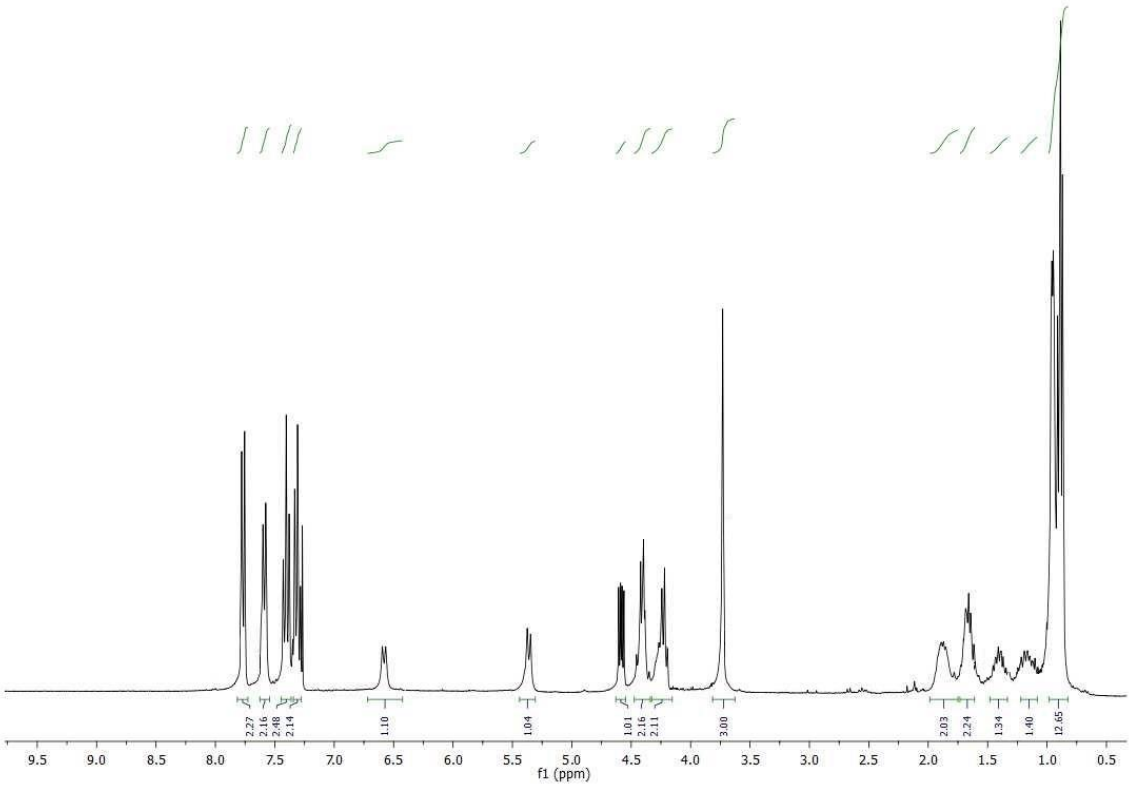


^{13}C NMR

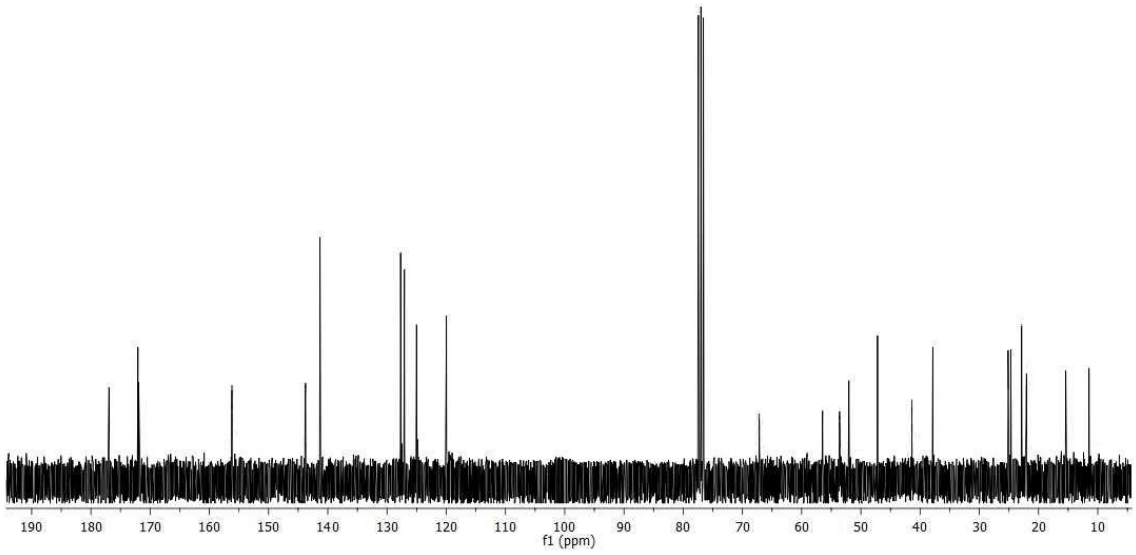


N-Fmoc-L-Leu-L-Ile-OMe (12)

^{1}H NMR

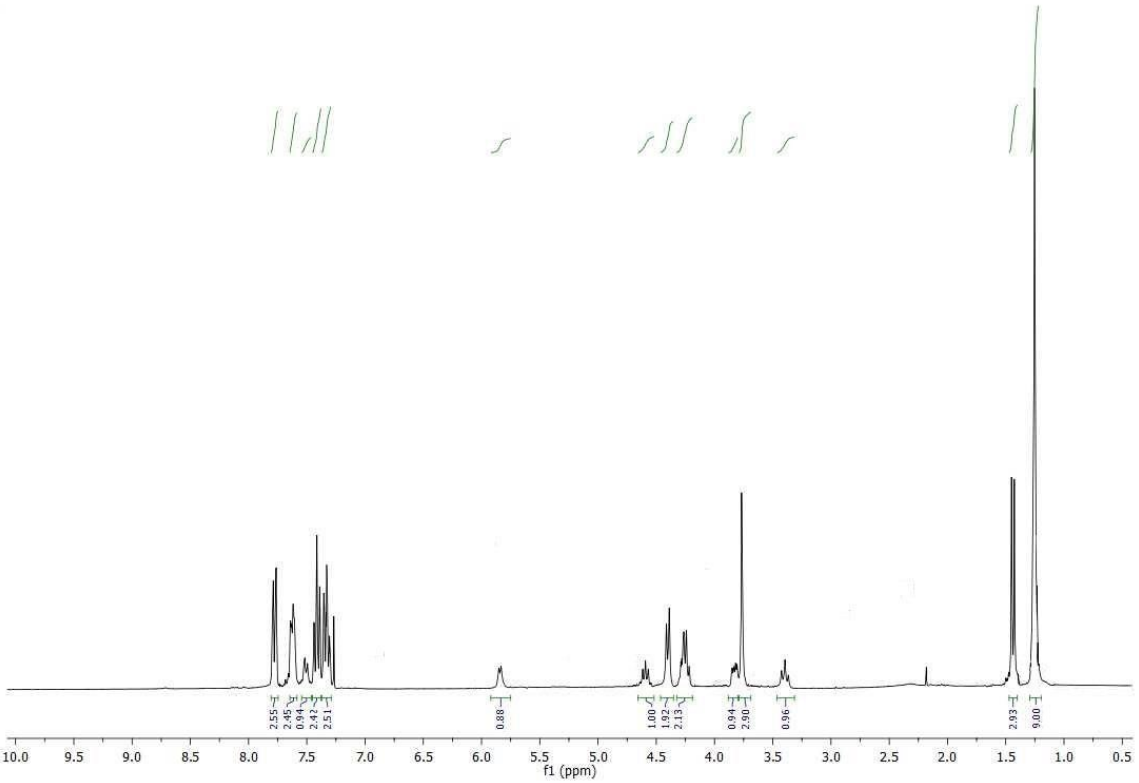


^{13}C NMR

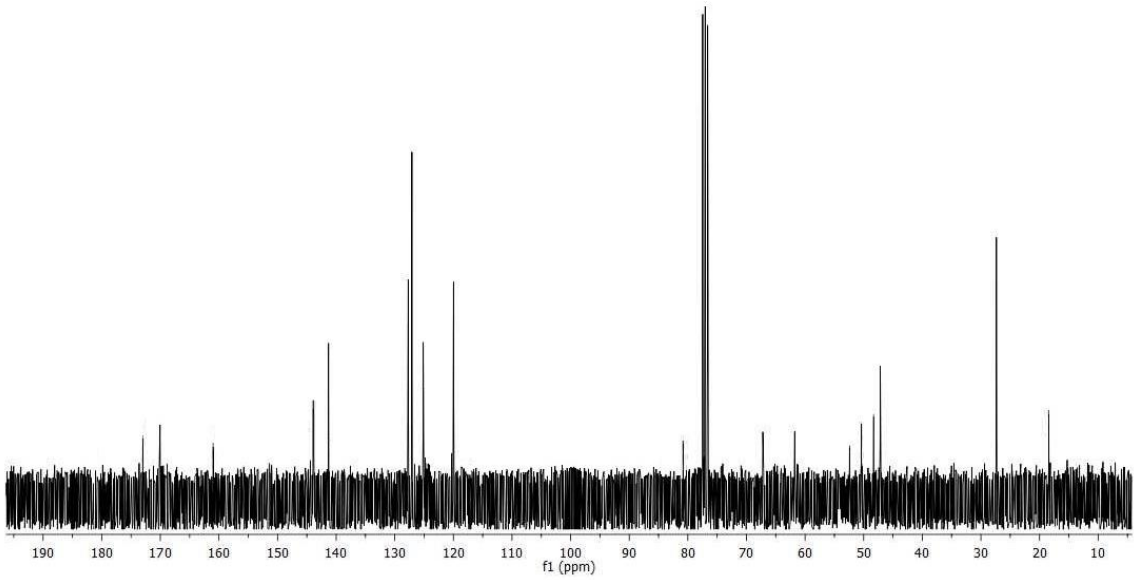


N-Fmoc-L-Ser(tBu)-L-Ala-OMe (13)

^{1}H NMR

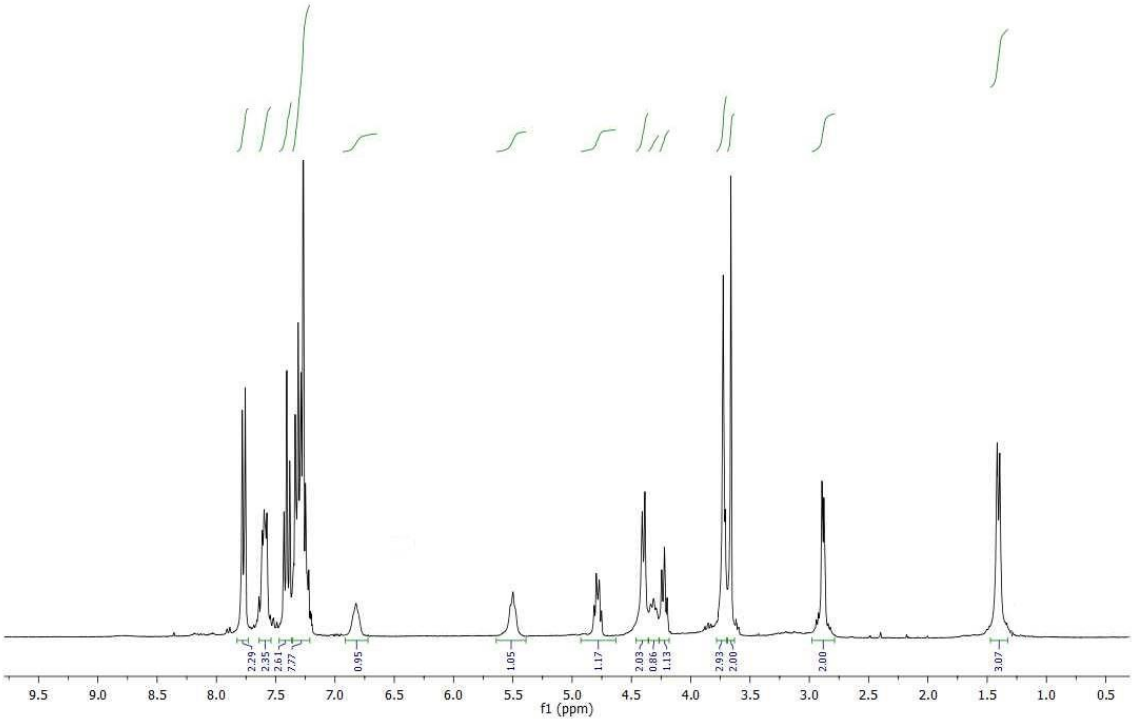


^{13}C NMR

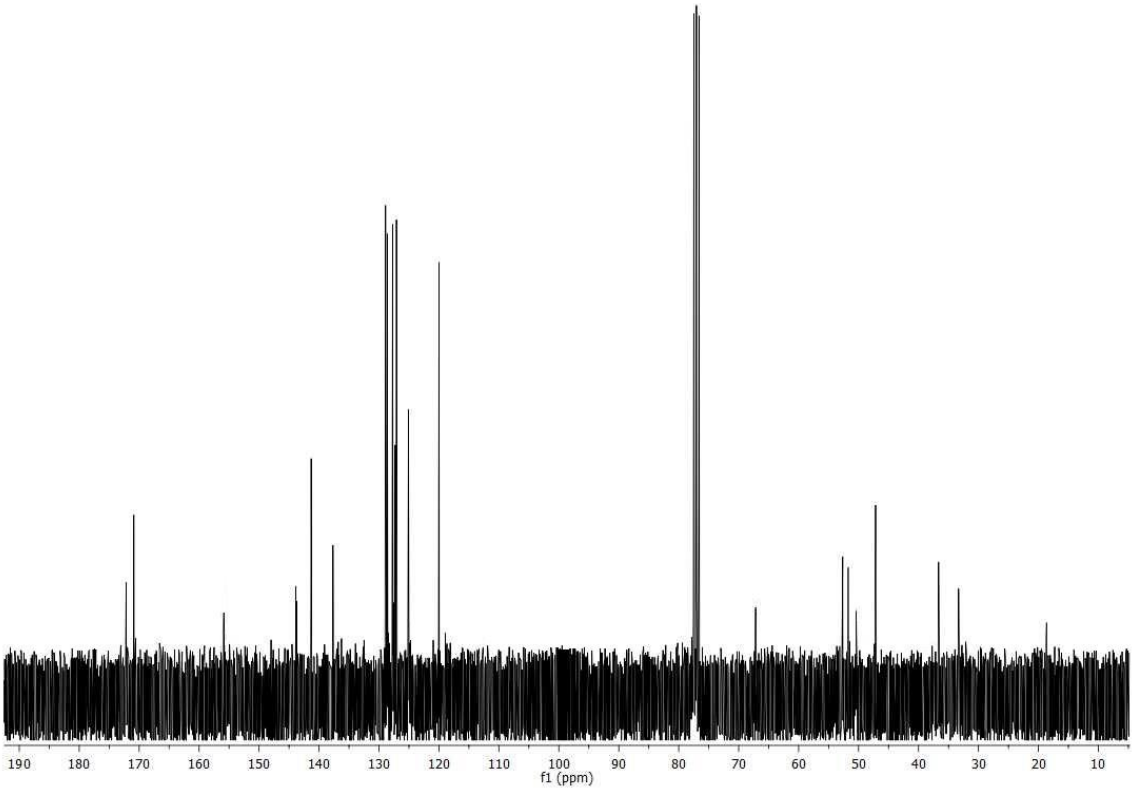


N-Fmoc-L-Ala-L-Cys(Bzl)-OMe (14)

^{1}H NMR

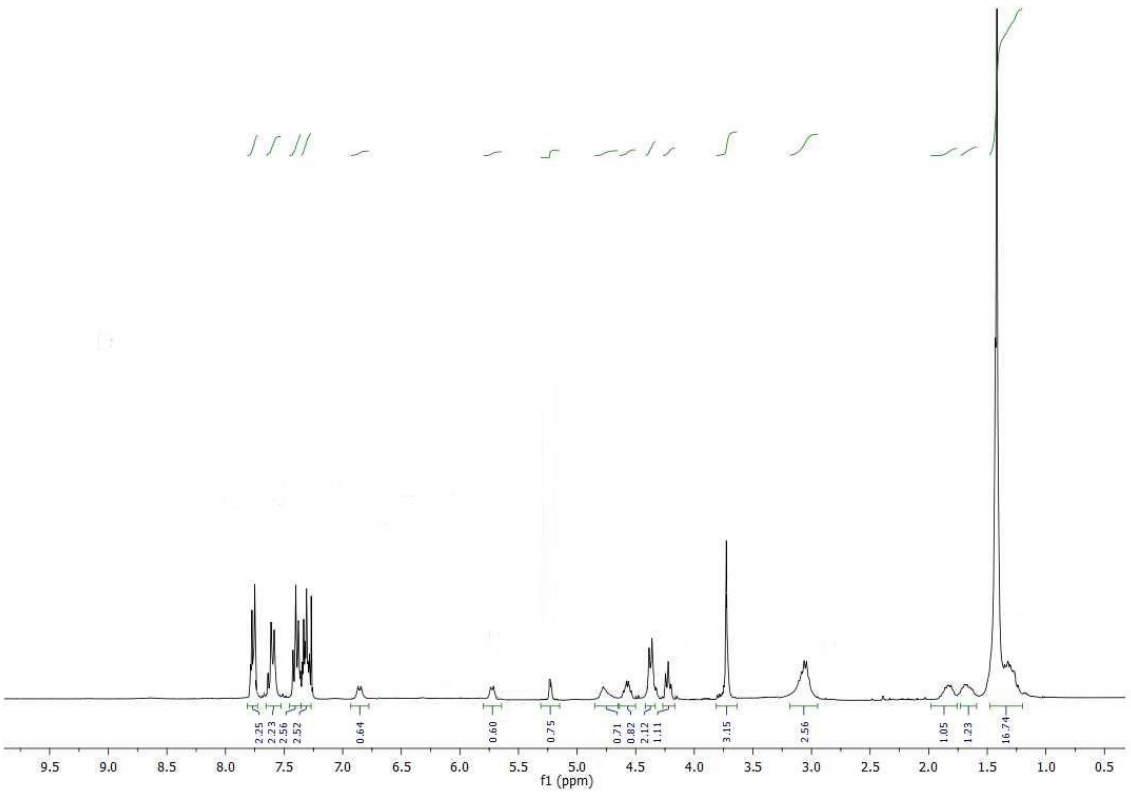


^{13}C NMR

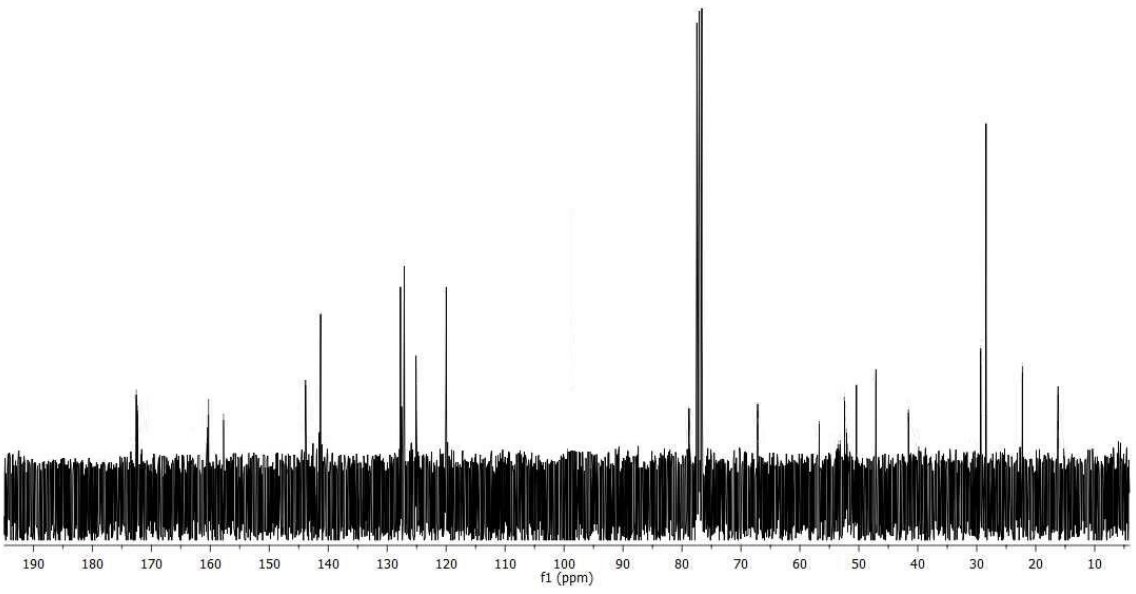


N-Fmoc-L-Ala-L-Lys(Boc)-OMe (15)

^{1}H NMR

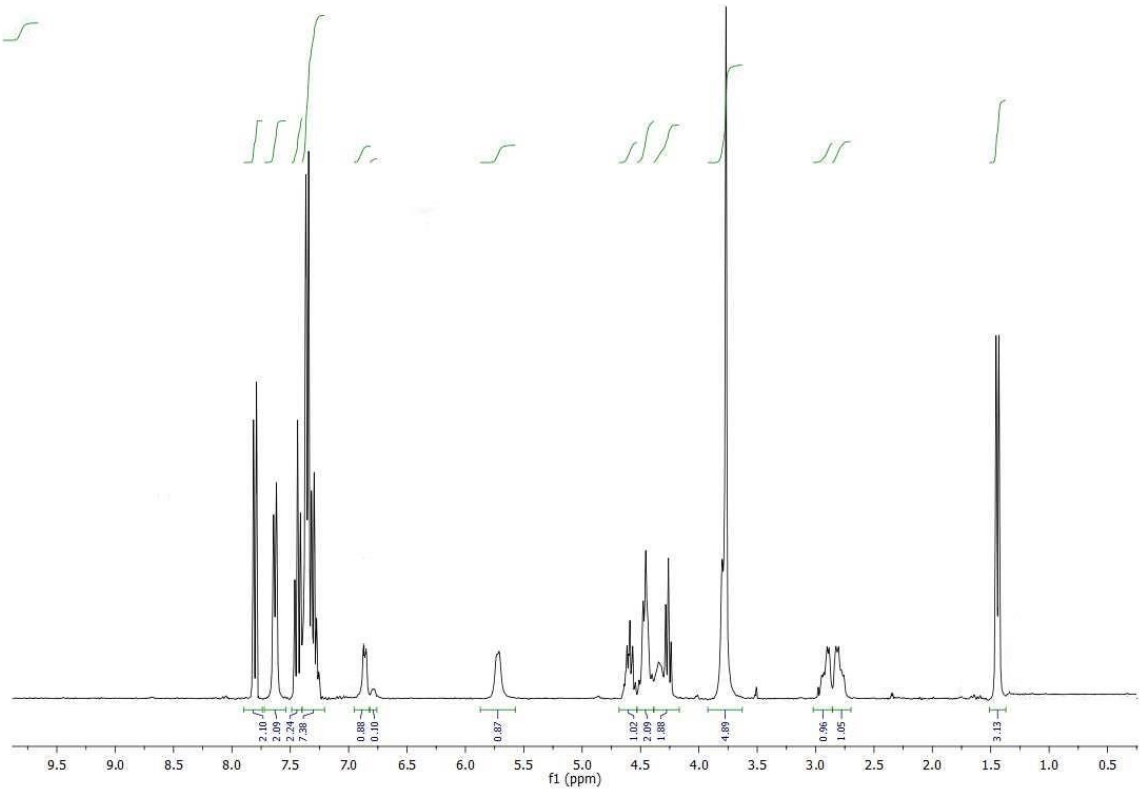


^{13}C NMR

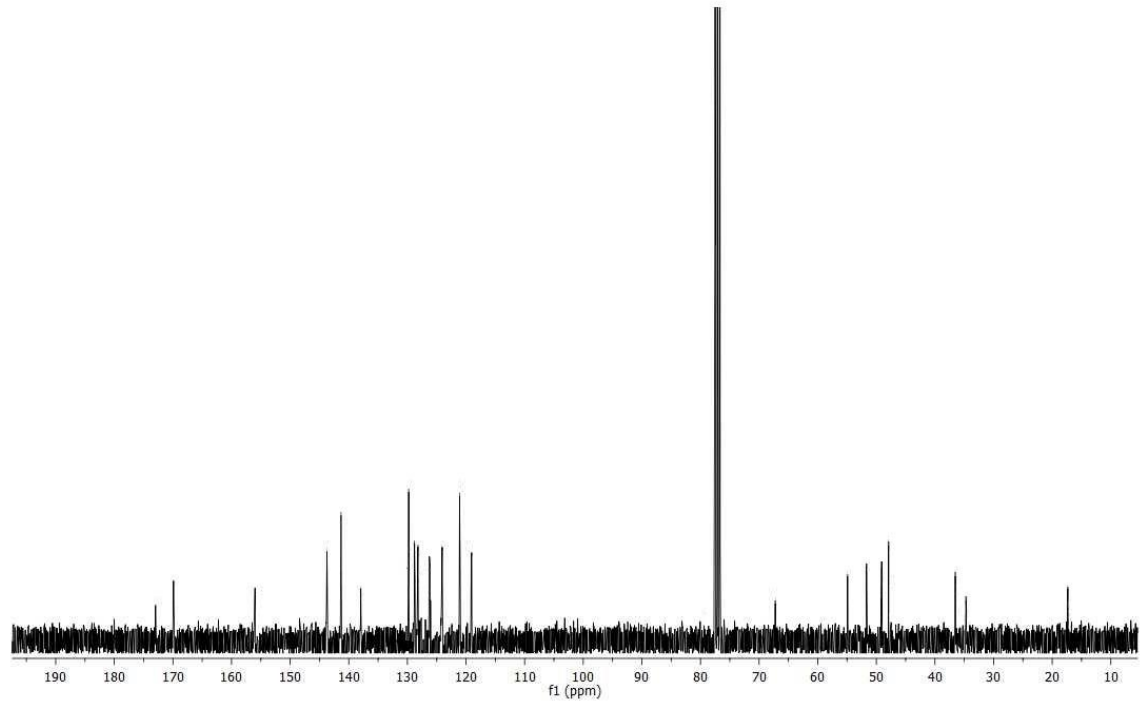


***N*-Fmoc-L-Cys(Bzl)-L-Ala-OMe (16)**

^{1}H NMR

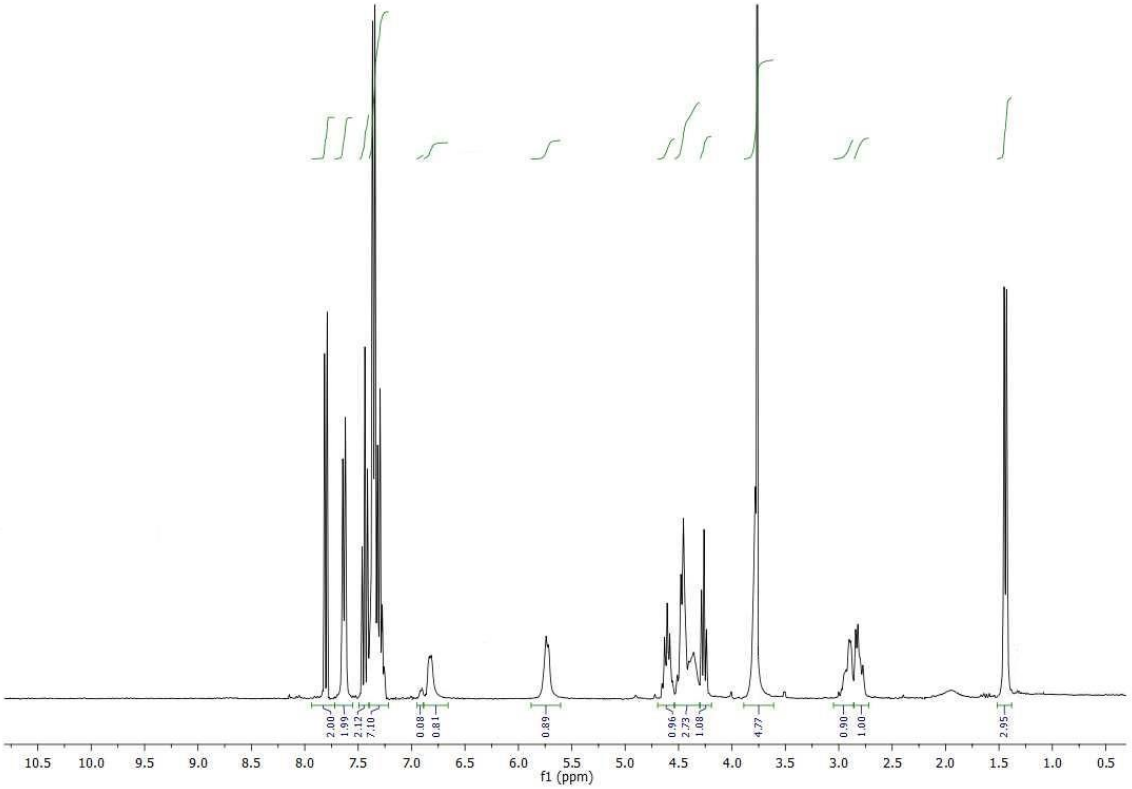


^{13}C NMR

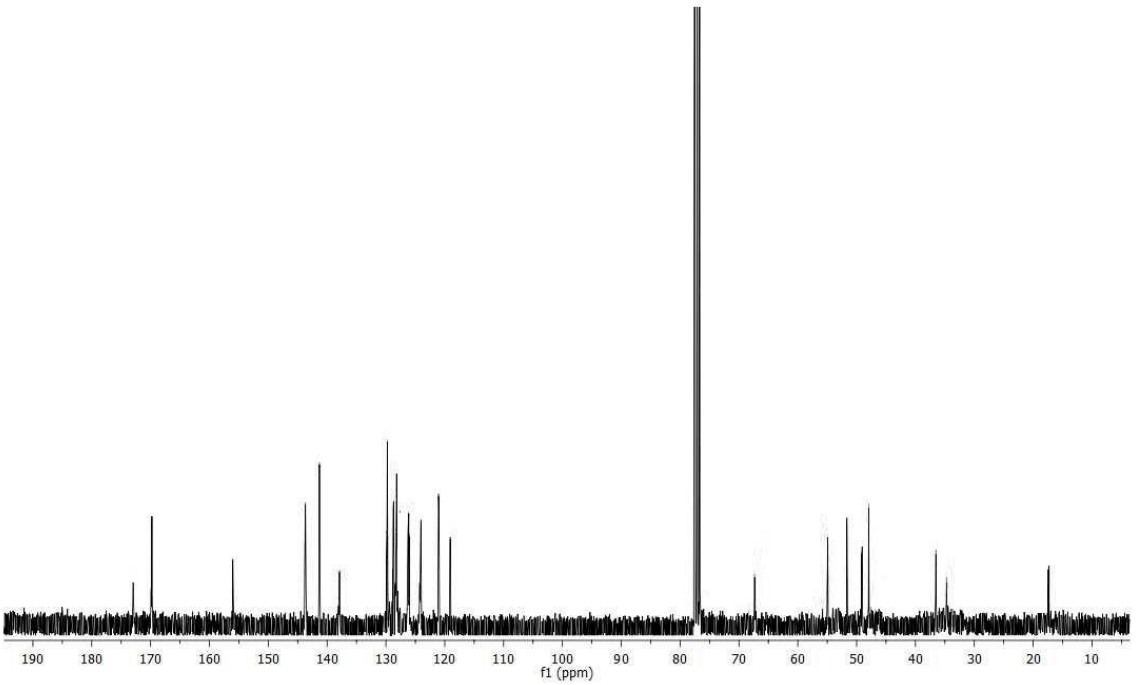


***N*-Fmoc-D-Cys(Bzl)-L-Ala-OMe (17)**

^{1}H NMR

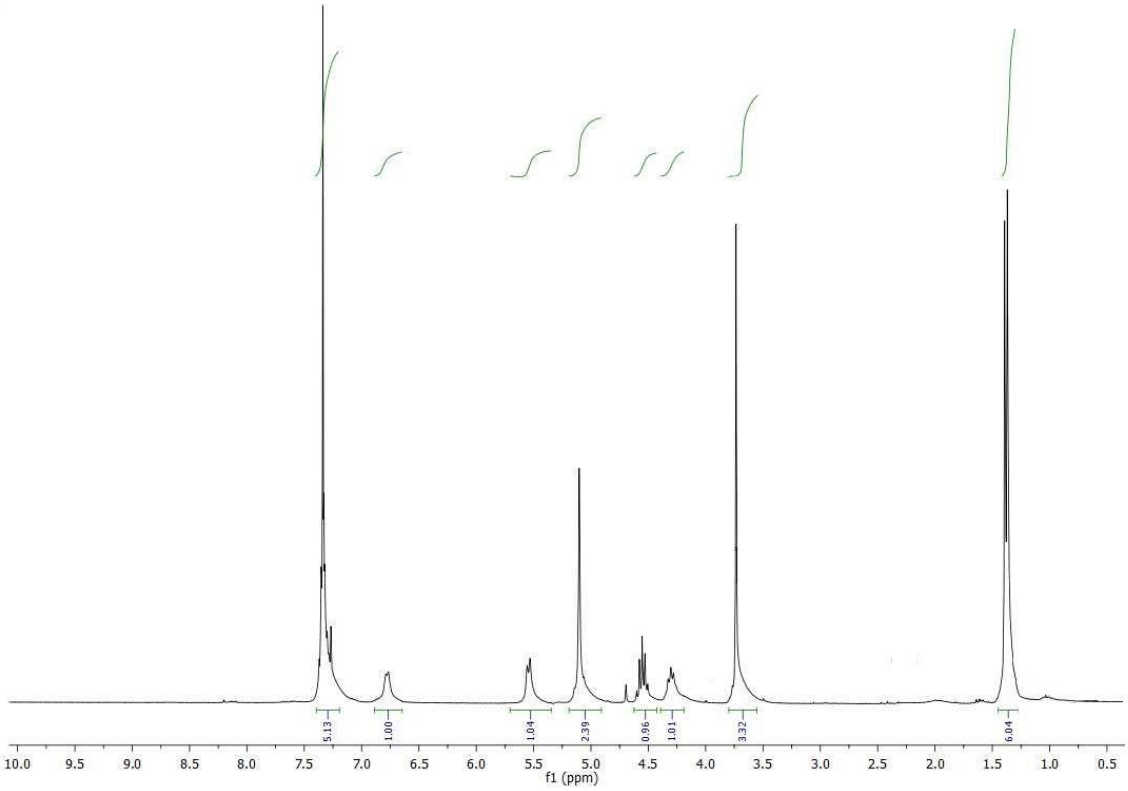


^{13}C NMR

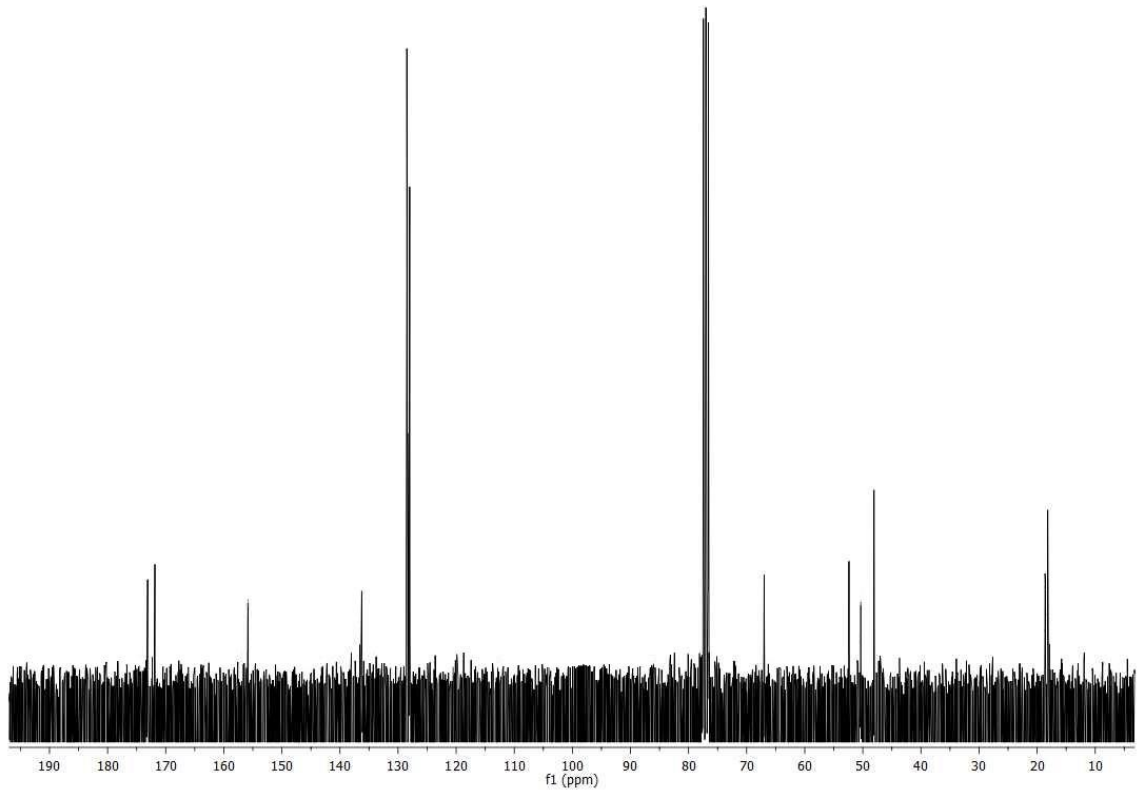


N-Cbz-L-Ala-L-Ala-OMe (18)

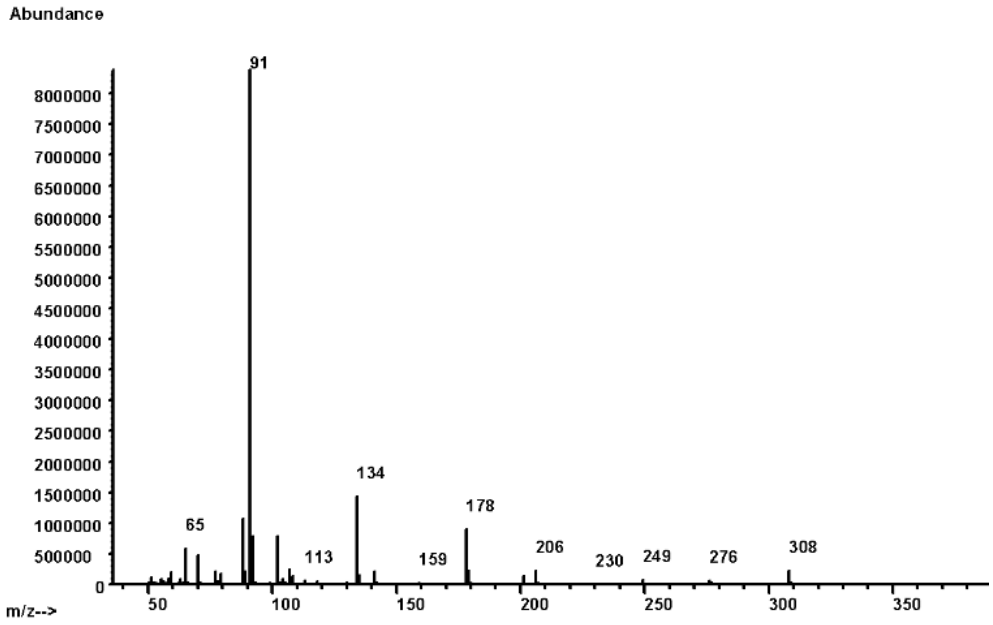
^{1}H NMR



^{13}C NMR



MS (EI)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6000000
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5000000
4500000
4000000
3500000
3000000
2500000
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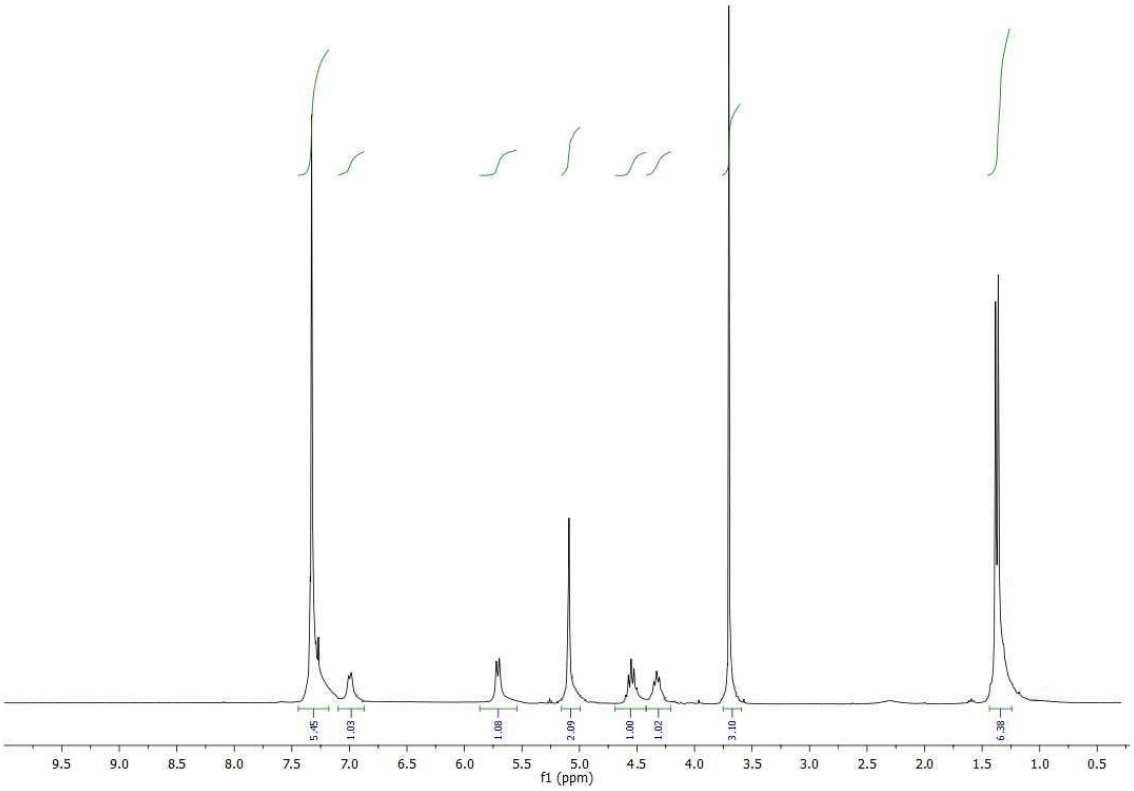
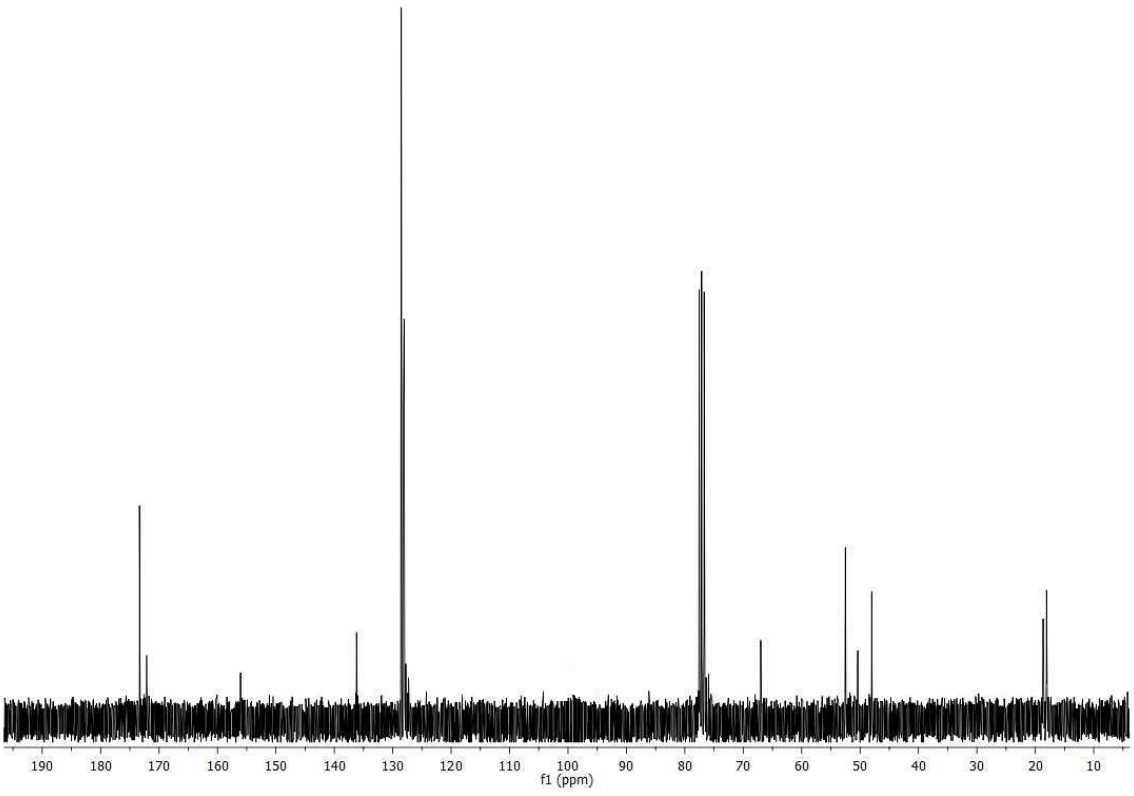
1000000
500000
0
134
178
65
113
159
206
230
249
276
308
m/z-->
50
100
150
200
250
300
350

N-Cbz-D-Ala-L-Ala-OMe (19)

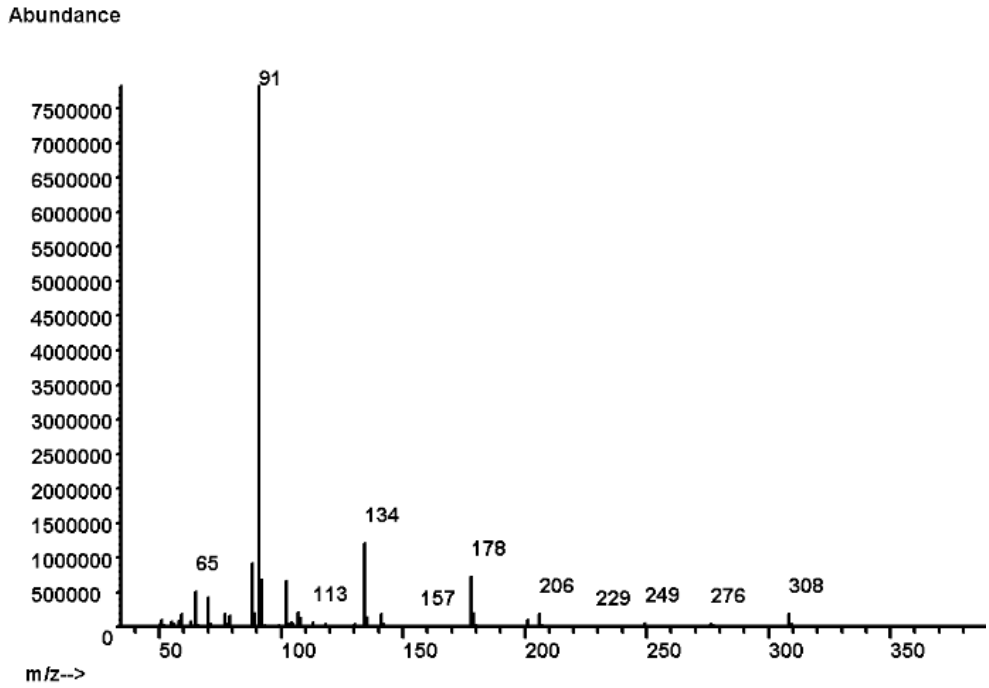
^{1}H NMR



^{13}C NMR



MS (EI)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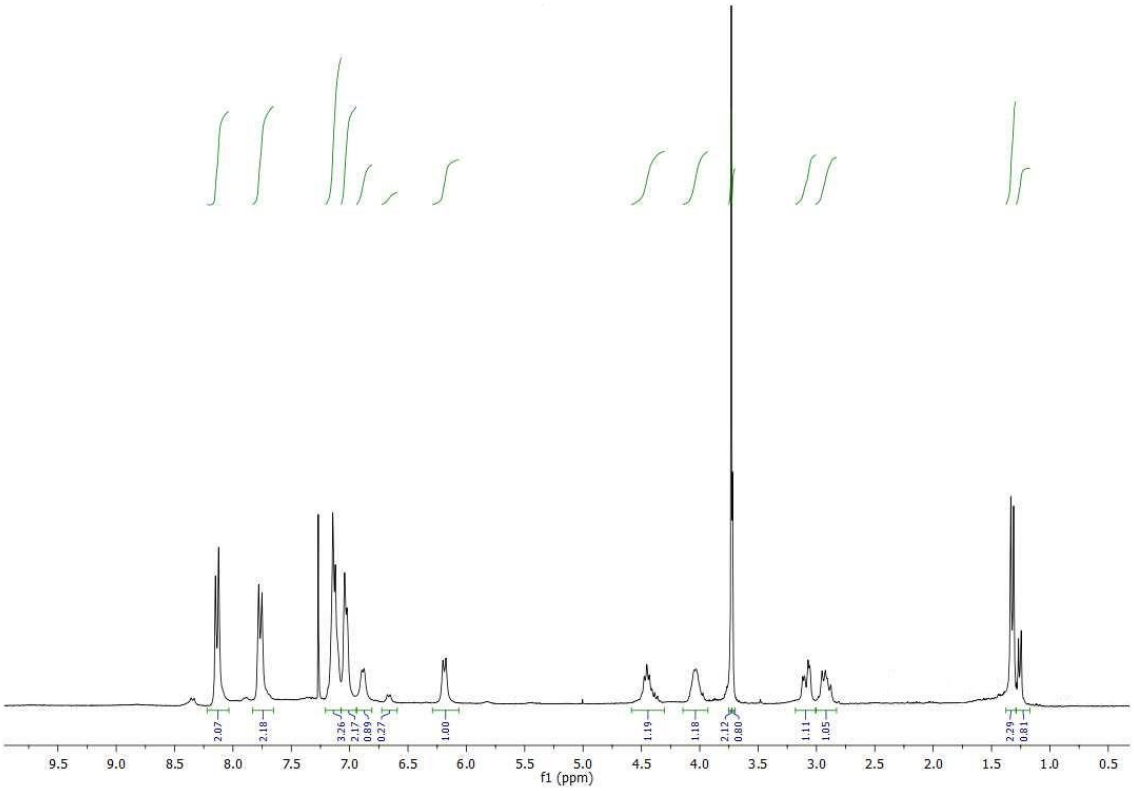
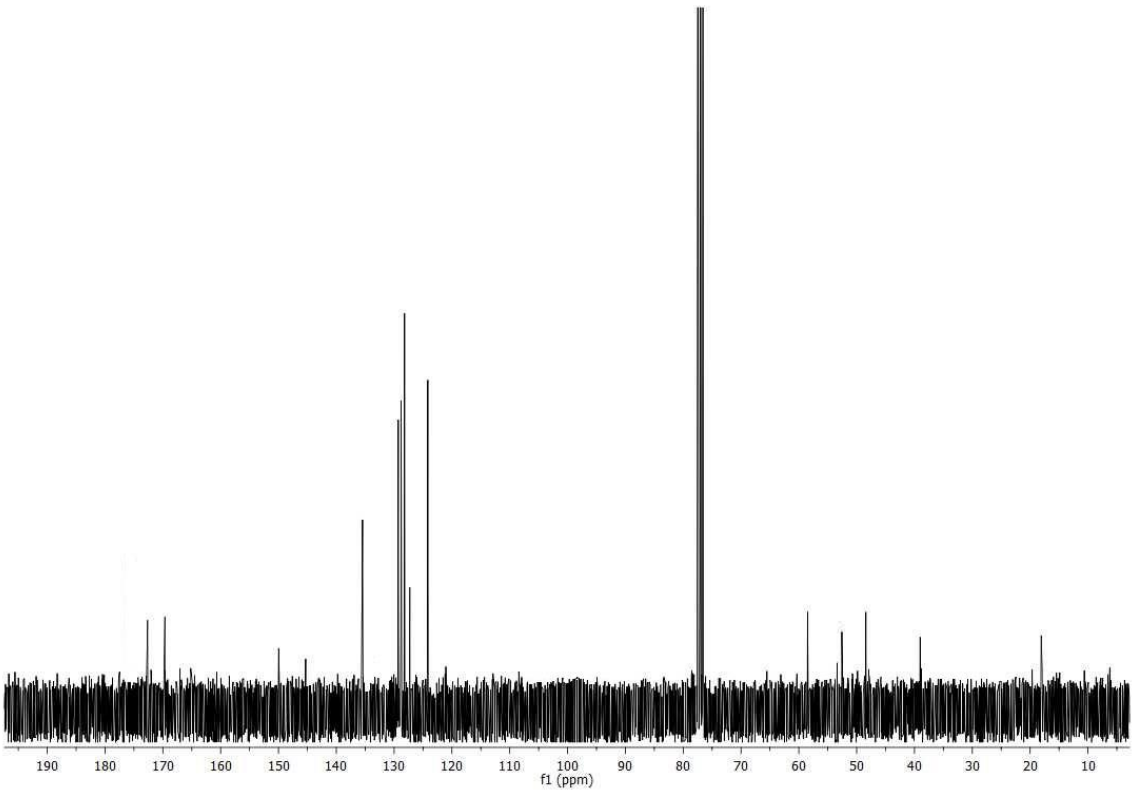
500000
0
65
113
134
157
178
206
229
249
276
308
50
100
150
200
250
300
350
m/z-->

N-Ns-L-Phe-L-Ala-OMe (20)

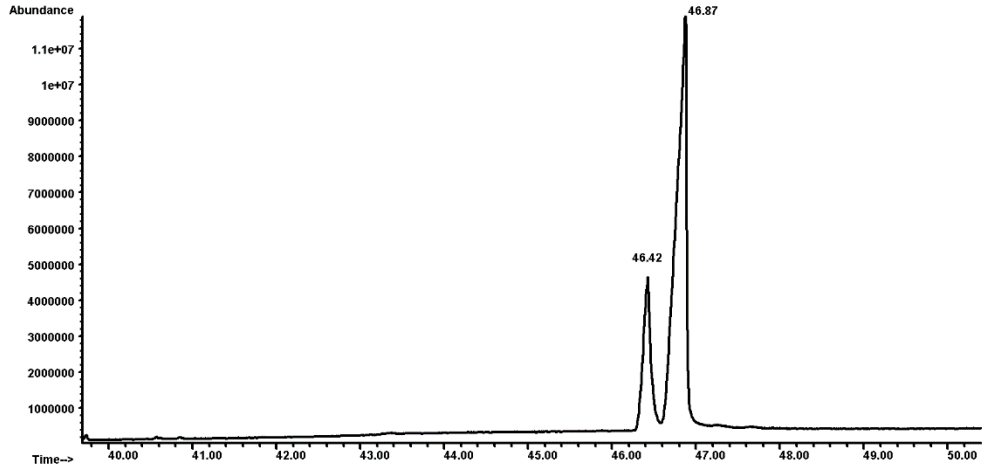
^{1}H NMR



^{13}C NMR



GC/MS (EI)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Time-->
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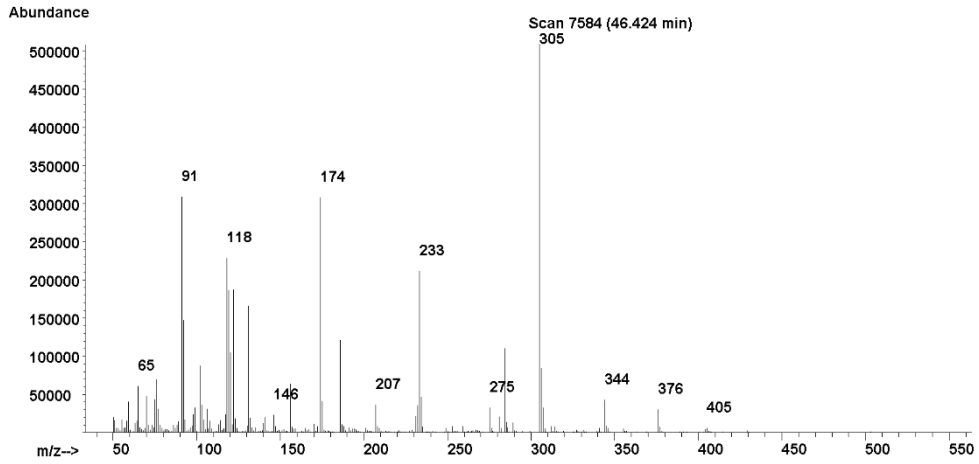
49.00
50.00
46.42
46.87

MS (EI)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300000
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200000
150000
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50000
91
174
118
233
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146
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344
376
405
m/z-->
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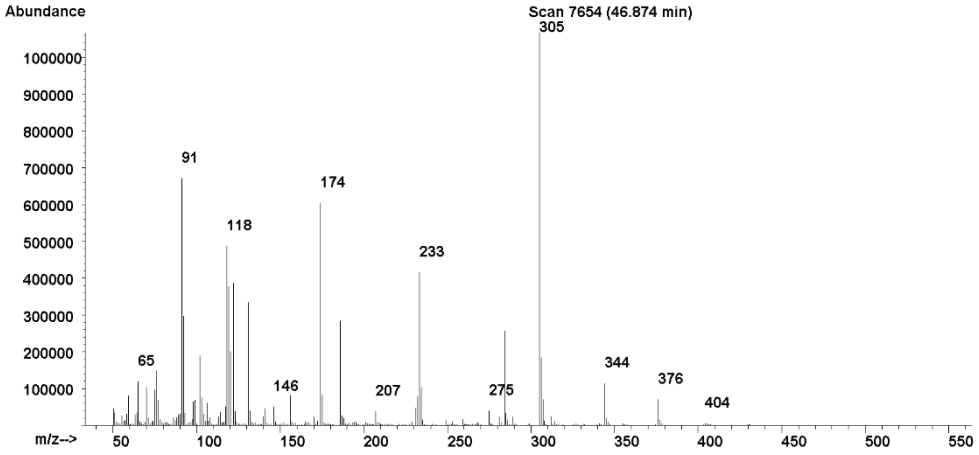
100
150
200
250
300
350
400
450
500
550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200000
100000
91
174
118
233
65
146
207
275
344
376
404
m/z-->
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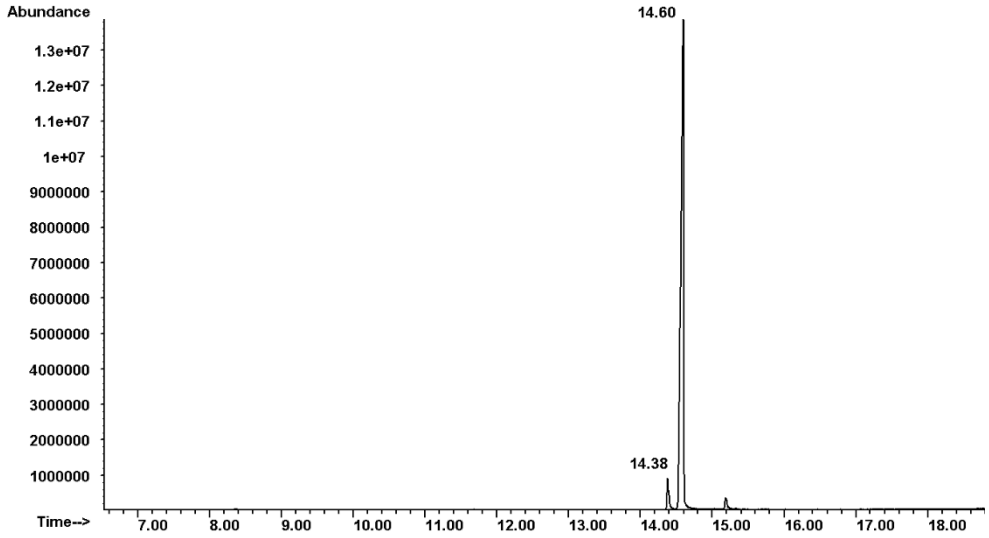
100
150
200
250
300
350
400
450
500
550

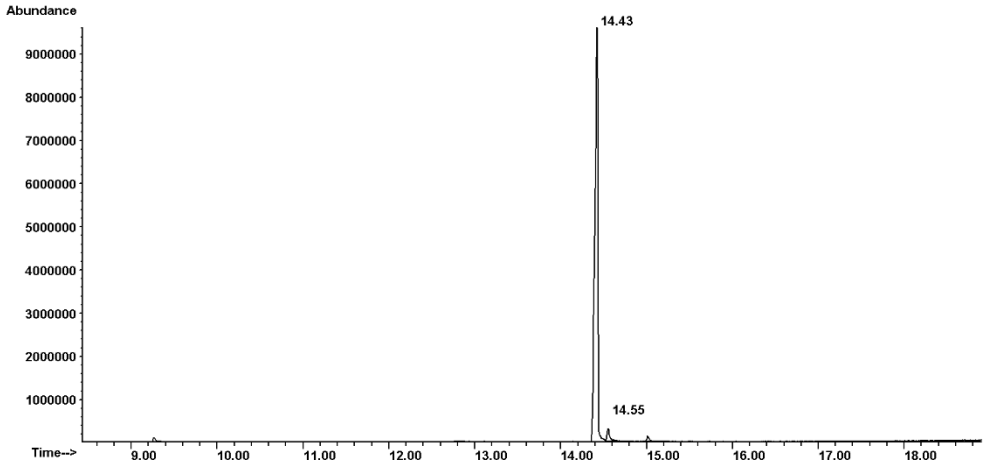
N-Boc-L-Ala-L-Ala-OMe (3)

GC/MS (EI)



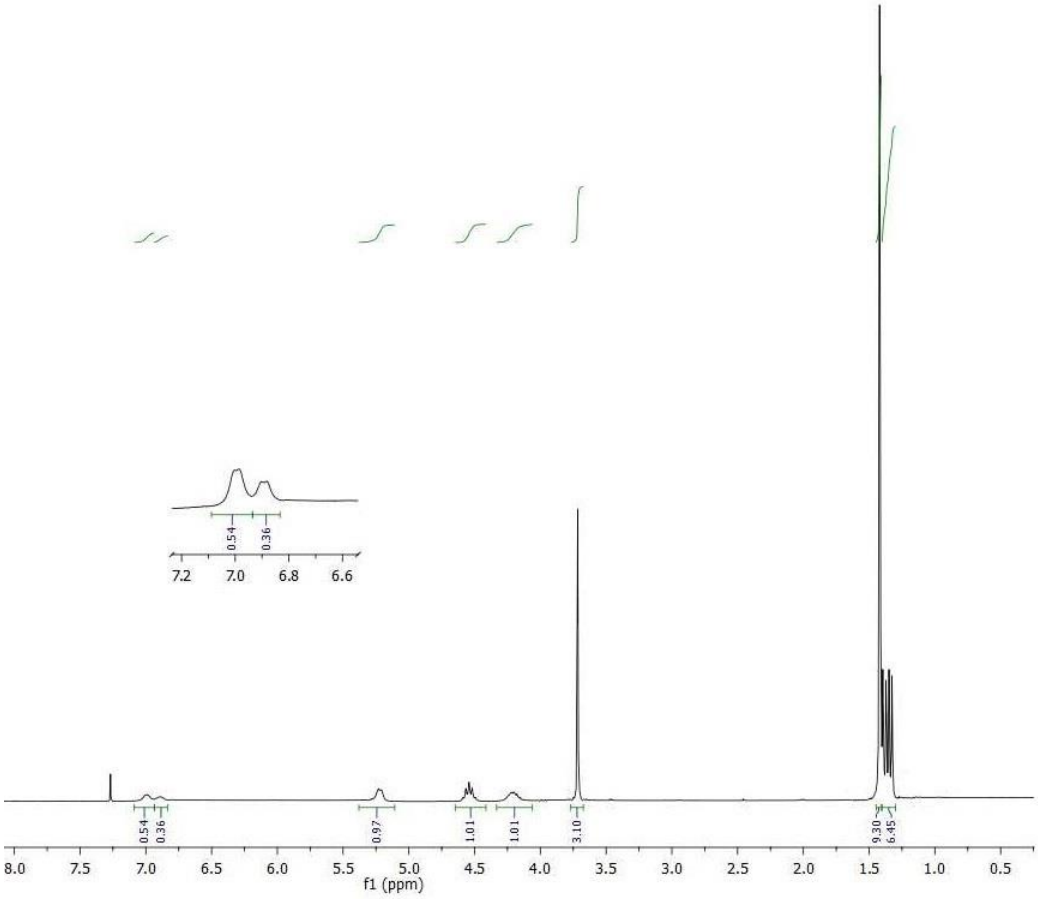
N-Boc-D-Ala-L-Ala-OMe (4)

GC/MS (EI)



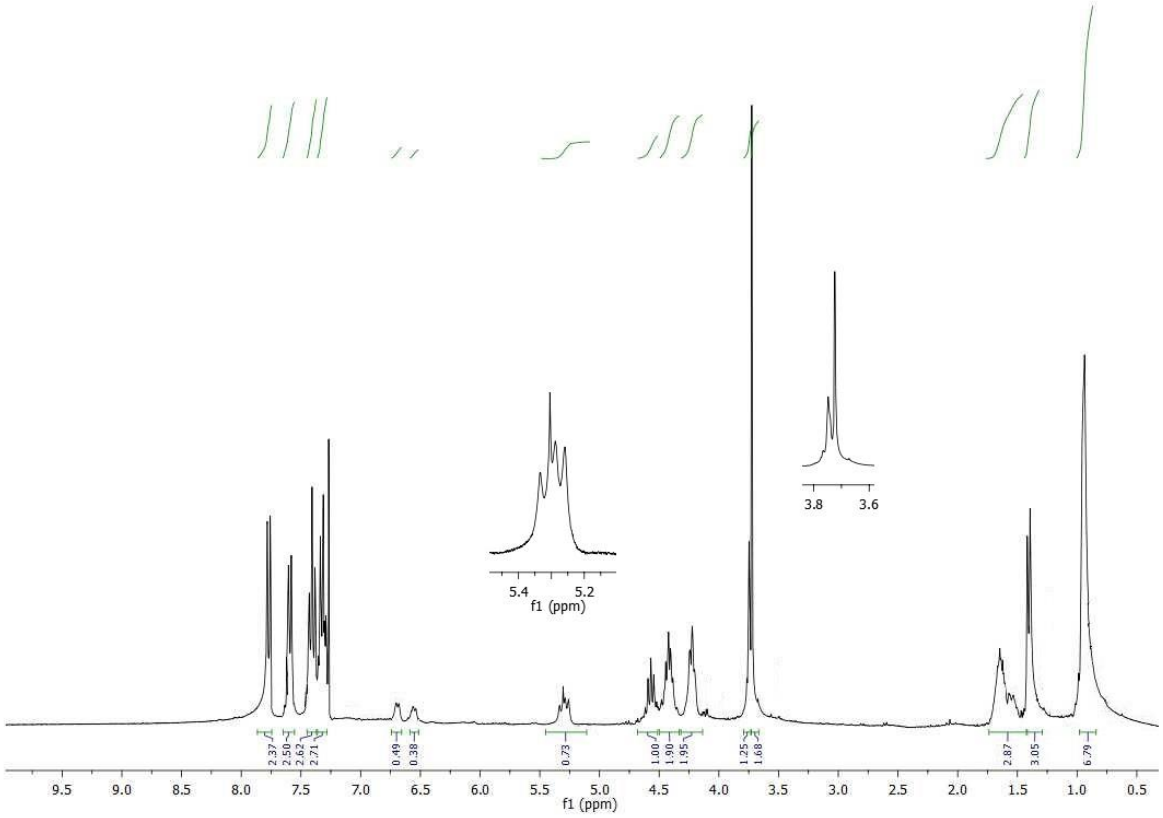
_N_-Boc-L-Ala-L-Ala-OMe (3) and _N_-Boc-D-Ala-L-Ala-OMe (4) (4 : 6)

^{1}H NMR



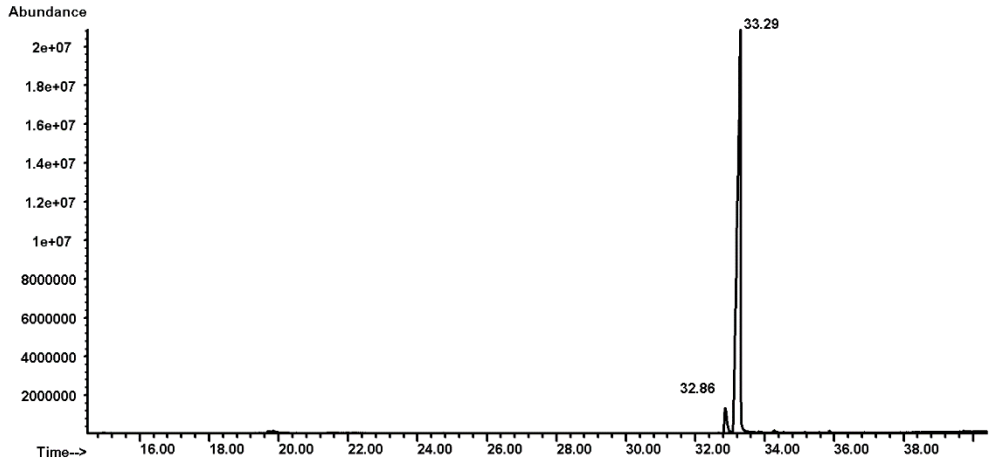
***N*-Fmoc-L-Leu-L-Ala-OMe (9) and *N*-Fmoc-D-Leu-L-Ala-OMe (10) (5.8 : 4.2)**

^{1}H NMR



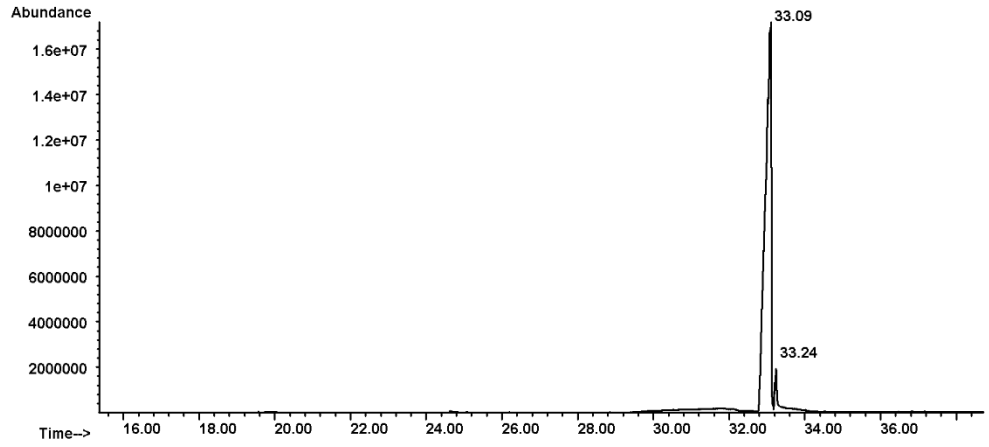
N-Cbz-L-Ala-L-Ala-OMe (16)

GC/MS (EI)



N-Cbz-D-Ala-L-Ala-OMe (17)

GC/MS (EI)



N-Cbz-L-Ala-L-Ala-OMe (16) and *N*-Cbz-D-Ala-L-Ala-OMe (17) (5.8 : 4.2)

^{1}H NMR