



Supporting Information

for

Synthesis of a novel category of pseudo-peptides using an Ugi three-component reaction of levulinic acid as bifunctional substrate, amines, and amino acid-based isocyanides

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Experimental procedures, characterization data and copies of ^1H and ^{13}C NMR spectra of all compounds

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General experimental procedure and characterization data for all compounds

General. All reagents and solvents were analytically pure and were used as received. Column chromatographic purification was carried out using SiO₂ (0.040-0.060 mm, type KG 60). TLC was performed on Macherey-Nagel SiO₂ F254 plates on aluminum sheets. Melting points were determined with a Branstead Electrothermal 9200 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT RX1 spectrophotometer over the range 400–4000 cm⁻¹. ¹H and ¹³C NMR spectra of isolated products were recorded on a Bruker AMX R500 (measuring frequency: ¹H NMR = 500.1 MHz, ¹³C NMR = 125.8 MHz) or a Bruker Avance III 500 (measuring frequency: ¹H NMR = 499.9 MHz, ¹³C NMR = 125.7 MHz) in CDCl₃ solution. HRMS (high-resolution mass spectra) were measured on a THERMO SCIENTIFIC Advantage and a THERMO SCIENTIFIC Exactive instrument. Elemental analyses were conducted with a Perkin-Elmer 2004 (II) CHN analyzer.

General procedure for the synthesis of amino acid-based isocyanides 3a–c

(a) *General procedure for the preparation of DL-amino acid methyl ester hydrochlorides:* DL-amino acid (50 mmol) was dissolved in MeOH (550 mL) and the solution was cooled in an ice/salt bath. Then, thionyl chloride (50 mmol) was added dropwise for 1 hour. The reaction temperature was maintained between –5–0 °C during the addition. Then, the reaction mixture was stirred for 24 h at room temperature. Finally, the reaction mixture was concentrated on a rotary evaporator to give the crude product. The crude product was washed with DCM (two times) to give the corresponding pure racemic amino acid ester hydrochloride.

(b) *General procedure for the formylation of DL-amino acid methyl ester hydrochlorides:* DL-amino acid methyl ester hydrochloride (20 mmol) was dissolved in ethyl formate (100 mL)/EtOH (30 mL) mixture. Then, sodium bicarbonate (20 mmol) was added to the flask. The reaction mixture was stirred at 50 °C for 2 days. After the completion of the reaction, the mixture was filtered for removing the excess amount of sodium bicarbonate. Then, the filtrate was concentrated on a rotary evaporator to give the product.

(c) *General procedure for the transformation of DL-formamide to DL-isocyanide:* DL-formylated amino acid methyl ester (20 mmol) was dissolved in DCM (200 mL) and TEA (100 mmol) was added to the solution at room temperature. Then the reaction mixture was cooled in an ice/salt bath to maintain the temperature between –10 and –5 °C. Then, phosphorus oxychloride (20 mmol) was added dropwise to the reaction mixture and was stirred for 2 h. The reaction mixture was quenched by aqueous NaHCO₃ and the organic phase was separated, dried over Na₂SO₄, and evaporated under reduced pressure to give a precipitate. The precipitate was purified by column chromatography using DCM as solvent.

General procedure for the synthesis of Ugi adducts:

A solution of levulinic acid (**1**, 1 mmol) and an amine **2** (1 mmol) in MeOH (5 mL) was stirred for 0.5 h at room temperature. Then, *DL*-amino acid-based isocyanide **3** (1 mmol) was added to the reaction mixture at the same temperature. The reaction progress was monitored by TLC. After 24 h, the solvent was removed under reduced pressure and the precipitate purified by column chromatography using petroleum ether and ethyl acetate mixture as eluent (SiO₂, PE/EtOAc; 2:1 v/v). All products were obtained as 1:1 mixture of diastereomers after column chromatography as determined by ¹H NMR spectroscopy. All compounds were characterized using IR, ¹H NMR, ¹³C NMR and HRMS or CHN analyses.

Methyl (2-methyl-5-oxo-1-phenylpyrrolidine-2-carbonyl)tryptophanate (**4a**): White crystalline solid (yield, 318 mg, 72%); mp: 158 – 159 °C; ¹H NMR (500 MHz, Chloroform-*d*) δ 1.35 (s, 3H), 2.00 (m, 1H), 2.42 – 2.54 (m, 2H), 2.72 (m, 1H), 3.26 (dd, *J* = 14.9 and 7.9 Hz, 1H), 3.41 (m, 1H), 3.77 (s, 3H), 4.90 (m, 1H), 6.52 (d, *J* = 7.1 Hz, 1H), 6.84 (d, *J* = 2.5 Hz, 1H), 6.91 – 6.94 (m, 2H), 7.08 – 7.18 (m, 4H), 7.21 – 7.25 (m, 1H), 7.32 (m, 1H), 7.55 (dd, *J* = 8.0 and 1.0 Hz, 1H), 8.13 (brs, 1H) ppm; ¹³C NMR (126 MHz, Chloroform-*d*) δ 22.3, 27.2, 30.3, 34.1, 52.4, 52.5, 68.3, 109.4, 111.5, 118.3, 119.8, 122.6, 122.7, 122.8, 125.6, 126.9, 128.9, 135.9, 136.4, 172.0, 173.4, 175.4 ppm; IR (KBr): ν 3328, 1736, 1690, 1659, 1595, 1381, 1229, 748 cm⁻¹; Anal. calcd for C₂₄H₂₅N₃O₄ (419.47) C, 68.72; H, 6.01; N, 10.02; Found: C, 68.42; H, 6.04; N, 9.88%.

The (*R**,*S**)-diastereomer (*R**,*S**)-**4a** was obtained from **4a** (a mixture of two racemic diastereomers) as a pure compound after several recrystallization steps from MeOH.

Methyl (1-(4-chlorophenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)tryptophanate (**4b**): White crystalline solid (yield, 240 mg, 53%); mp: 155 – 156 °C; ¹H NMR (500 MHz, Chloroform-*d*) δ 1.33 (s, 3H), 1.89 (m, 1H), 2.13 (m, 1H), 2.31 (m, 1H), 2.51 (m, 1H), 3.20 (m, 1H), 2.37 (m, 1H), 3.80 (s, 3H), 4.91 (dd, *J* = 7.3 and 5.3 Hz, 1H), 6.79 – 6.85 (m, 2H), 6.86 (s, 1H), 6.96 – 7.04 (m, 2H), 7.14 (m, 1H), 7.27 (m, 1H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 7.9 Hz, 1H), 8.11 (brs, 1H) ppm; ¹³C NMR (126 MHz, Chloroform-*d*) δ 22.6, 27.1, 29.7, 30.2, 33.8, 52.5, 68.4, 109.4, 111.5, 118.3, 122.6, 122.8, 126.6, 126.9, 127.6, 129.1, 132.6, 134.4, 136.3, 172.05, 172.9, 175.6 ppm; IR (KBr): ν 3259, 1746, 1691, 1644, 1358, 1221, 822, 739 cm⁻¹; HRMS calcd for C₂₄H₂₄ClN₃O₄ [M + Na]⁺ 476.1353; Found . 476.1351.

Methyl (1-(2-chlorobenzyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)tryptophanate (**4c**): Yellow crystalline solid (yield, 320 mg, 68%); mp 150 – 154 °C; ¹H NMR (500 MHz, Chloroform-*d*) δ 1.28 (s, 3H), 1.86 (m, 1H), 2.17 (m, 1H), 2.32 (m, 1H), 2.47 (m, 1H), 3.18 (m, 1H), 3.31 (m, 1H), 3.74 (s, 3H), 4.03 (d, *J* = 16.3 Hz, 1H), 4.62 (d, *J* = 16.4 Hz, 1H), 4.79 (m, 1H), 6.99 (d, *J* = 2.3 Hz, 1H), 7.10–7.45 (m, 8H), 7.53 (m, 1H), 8.34 (brs, 1H) ppm; ¹³C NMR (126 MHz, Chloroform-*d*) δ 22.4, 27.1, 29.3, 32.9, 41.4, 41.7, 52.6, 67.5, 109.5, 111.5, 118.3, 119.8, 122.5, 127.0, 127.1, 128.2, 128.5, 128.8, 129.3, 129.4, 134.7, 136.2, 171.8, 173.0, 176.3

ppm; IR (KBr): ν 3261, 1749, 1683, 1656, 1539, 1202, 740 cm^{-1} ; Anal. calcd for $\text{C}_{25}\text{H}_{26}\text{ClN}_3\text{O}_4$ (467.1612) C, 64.17; H, 5.60; N, 8.98; Found: C, 64.12; H, 5.72; N, 8.58%.

Methyl (1-(4-fluorophenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)tryptophanate (**4d**): Cream solid (yield, 385 mg, 88%); mp: 114 – 115 $^{\circ}\text{C}$; ^1H NMR (500 MHz, Chloroform-*d*) δ 1.31 (s, 3H), 1.96 (m, 1H), 2.34 (m, 1H), 2.45 (m, 1H), 2.74 (m, 1H), 3.24 (m, 1H), 3.40 (m, 1H), 3.81 (s, 3H), 4.89 (m, 1H), 6.45 (d, $J = 6.2$ Hz, 1H), 6.75 – 7.24 (m, 7H), 7.35 (m, 1H), 7.55 (dd, $J = 7.9$ and 1.0 Hz, 1H), 8.16 (brs, 1H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 22.5, 27.2, 29.8, 33.9, 52.5, 52.6, 68.3, 109.5, 111.4, 115.9 (d, $^2J_{\text{C-F}} = 25$ Hz), 118.3, 119.9, 122.6, 126.9, 127.7, 128.5, 131.6, 136.3, 160.3 (d, $^1J_{\text{C-F}} = 246$ Hz), 172.0, 173.0, 175.6 ppm; IR (KBr): ν 3302, 1743, 1694, 1657, 1372, 1218, 839, 744 cm^{-1} ; HRMS calcd for $\text{C}_{24}\text{H}_{24}\text{FN}_3\text{O}_4$ [$\text{M} + \text{Na}$] $^{+}$ 460.1649; Found: 460.1643.

Methyl (1-(3-methoxyphenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)tryptophanate (**4e**): Viscous oil (yield, 224 mg, 51%); ^1H NMR (500 MHz, Chloroform-*d*) δ 1.38 (s, 3H), 1.96 (m, 1H), 2.17 (m, 1H), 2.42 (m, 1H), 2.70 (m, 1H), 3.28 (m, 1H), 3.37 (m, 1H), 3.68 (s, 3H), 3.76 (s, 3H), 4.87 (m, 1H), 6.46 (m, 1H), 6.54 (m, 1H), 6.70 – 7.05 (m, 3H), 7.11 (m, 1H), 7.17 – 7.25 (m, 2H), 7.33 (dd, $J = 7.9$ and 1.0 Hz, 1H), 7.53 (dd, $J = 8.0$ and 1.0 Hz, 1H), 8.18 (brs, 1H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 22.4, 22.6, 27.2, 29.9, 34.0, 52.4, 55.25, 68.6, 109.4, 111.5, 111.8, 112.4, 118.4, 118.9, 119.8, 122.5, 122.8, 122.9, 129.6, 136.3, 137.0, 159.9, 172.0, 173.2, 175.5 ppm; IR (KBr): ν 3327, 1741, 1658, 1602, 1363, 1211, 745 cm^{-1} ; HRMS calcd for $\text{C}_{25}\text{H}_{27}\text{N}_3\text{O}_5$ [$\text{M} + \text{Na}$] $^{+}$ 472.1848; Found: 472.1840.

Methyl (2-methyl-5-oxo-1-(*p*-tolyl)pyrrolidine-2-carbonyl)tryptophanate (**4f**): Cream viscous oil (yield, 260 mg, 60%); ^1H NMR (500 MHz, Chloroform-*d*) δ 1.34 (s, 3H), 1.86 – 2.20 (m, 2H), 2.29 (s, 3H), 2.48 (m, 1H), 2.70 (m, 1H), 3.28 (m, 1H), 3.38 (m, 1H), 3.77 (s, 3H), 4.88 (m, 1H), 6.52 (brs, 1H), 6.79 – 6.93 (m, 3H), 7.07 – 7.15 (m, 3H), 7.24 (m, 1H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 8.18 (brs, 1H) ppm; ^{13}C NMR (75 MHz, Chloroform-*d*) δ 20.7, 22.2, 26.9, 27.4, 29.6, 33.7, 52.1, 68.2, 109.1, 111.2, 118.2, 119.5, 122.2, 122.6, 125.4, 126.6, 129.3, 132.8, 136.1, 136.5, 171.82, 173.2, 175.4 ppm; IR (KBr): ν 3270, 1734, 1692, 1648, 1513, 1374, 1201, 819, 741 cm^{-1} ; HRMS calcd for $\text{C}_{25}\text{H}_{27}\text{N}_3\text{O}_4$ [$\text{M} + \text{Na}$] $^{+}$ 456.1899; Found: 456.1894.

Methyl (2-methyl-5-oxo-1-phenylpyrrolidine-2-carbonyl)leucinate (**4g**): Cream solid (yield, 218 mg, 63%); mp: 107 – 108 $^{\circ}\text{C}$; ^1H NMR (500 MHz, Chloroform-*d*) δ 0.92 – 0.97 (m, 6H), 1.50 (s, 3H), 1.54 (m, 1H), 1.69 (m, 1H), 2.10 (m, 1H), 2.52 (m, 1H), 2.56 – 2.76 (m, 2H), 2.88 (m, 1H), 3.76 (s, 3H), 4.65 (m, 1H), 6.37 (d, $J = 8.2$ Hz, 1H), 7.25 – 7.45 (m, 5H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.45, 22.8, 23.0, 25.0, 30.3, 34.3, 40.8, 51.1, 52.4, 68.6, 125.4, 127.1, 129.0, 136.0, 173.0, 173.6, 175.5 ppm; IR (KBr): ν 3308, 1755, 1739, 1694, 1597, 1534, 1381, 1222, 1020, 764, 697 cm^{-1} ; Anal. calcd for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4$ (346.1893) C, 65.87; H, 7.56; N, 8.09; Found: C, 65.52; H, 8.0; N, 7.71%.

Methyl (1-(4-chlorophenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)leucinate (**4h**): Creamy viscous oil (yield, 140 mg, 37%); ^1H NMR (500 MHz, Chloroform-*d*) δ 0.91 – 0.94 (m, 6H), 1.48 (s, 3H), 1.61 (m, 1H), 1.67 (m, 1H), 2.10 (m, 1H), 2.47 (m, 1H), 2.61 (m, 1H), 2.67 (m, 1H), 2.73 (m, 1H), 3.75 (s, 3H), 4.63 (m, 1H), 6.69 (d, J = 8.4 Hz, 1H), 7.24 – 7.39 (m, 4H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.4, 22.7, 25.0, 27.5, 30.30, 34.1, 40.5, 51.1, 52.4, 68.4, 126.7, 129.1, 132.3, 134.6, 173.0, 173.3, 175.6 ppm; IR (KBr): ν 3327, 1743, 1700, 1671, 1526, 1495, 1367, 1199, 828 cm^{-1} ; HRMS calcd for $\text{C}_{19}\text{H}_{25}\text{ClN}_2\text{O}_4$ $[\text{M} + \text{Na}]^+$ 403.1401; Found: 403.1395.

Methyl (2-methyl-5-oxo-1-(*p*-tolyl)pyrrolidine-2-carbonyl)leucinate (**4i**): Cream solid (yield, 234 mg, 65%); mp: 108 – 110 $^\circ\text{C}$; ^1H NMR (500 MHz, Chloroform-*d*) δ 0.90 – 0.98 (m, 6H), 1.48 (s, 3H), 1.57 (m, 1H), 1.69 (m, 1H), 2.09 (m, 1H), 2.36 (s, 3H), 2.48 – 2.61 (m, 2H), 2.69 (m, 1H), 2.87 (m, 1H), 3.75 (s, 3H), 4.63 (m, 1H), 6.49 (d, J = 8.2 Hz, 1H), 7.16 – 7.30 (m, 4H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.0, 21.5, 22.8, 22.9, 24.9, 30.3, 34.3, 40.7, 51.1, 52.3, 68.5, 126.4, 129.7, 133.5, 137.1, 173.05, 173.7, 175.7 ppm; IR (KBr): ν 3289, 1748, 1674, 1609, 1537, 1387, 1221, 817 cm^{-1} ; HRMS calcd for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_4$ $[\text{M} + \text{Na}]^+$ 383.1947; Found: 383.1942.

Methyl (1-(2-(1H-indol-3-yl)ethyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)leucinate (**4j**): Creamy viscous oil (yield, 120 mg, 29%); ^1H NMR (500 MHz, Chloroform-*d*) δ 0.89 (d, J = 6.1 Hz, 6H), 1.23 – 1.34 (m, 2H), 1.56 (s, 3H), 1.98 (m, 1H), 2.37 (m, 1H), 2.46 – 2.51 (m, 2H), 3.06 (m, 1H), 3.13–3.23 (m, 2H), 3.39 (m, 1H), 3.67 (s, 3H), 3.79 (m, 1H), 4.47 (m, 1H), 6.08 (d, J = 8.0 Hz, 1H), 7.12 – 7.24 (m, 3H), 7.38 (m, 1H), 7.69 (d, J = 7.9 Hz, 1H), 8.03 (brs, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 21.5, 22.6, 22.7, 24.5, 24.9, 29.6, 33.2, 40.3, 42.3, 50.9, 52.2, 67.6, 111.1, 112.7, 118.7, 119.3, 121.9, 122.08, 127.2, 136.2, 173.0, 174.1, 176.3 ppm; IR (KBr): ν 3297, 1743, 1672, 1654, 1555, 1407, 1339, 1227, 760 cm^{-1} ; HRMS calcd for $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_4$ $[\text{M} + \text{Na}]^+$ 436.2212; Found . 436.2207; Anal. calcd for $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_4$ (413.2315) C, 66.81; H, 7.56; N, 10.16; Found: C, 67.05; H, 7.63; N, 9.75%.

Methyl (1-(4-fluorophenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)leucinate (**4k**): Viscous oil (yield, 255 mg, 70%); ^1H NMR (500 MHz, Chloroform-*d*) δ 0.90 – 0.96 (m, 6H), 1.47 (s, 3H), 1.53 – 1.63 (m, 2H), 1.65 – 1.71 (m, 1H), 2.08 (m, 1H), 2.46 – 2.59 (m, 2H), 2.65 – 2.76 (m, 1H), 3.75 (s, 3H), 4.63 (m, 1H), 6.56 (d, J = 8.2 Hz, 1H), 7.04 – 7.12 (m, 2H), 7.26 (m, 1H), 7.38 (m, 1H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.4, 22.8, 25.04, 27.6, 30.2, 34.1, 40.6, 51.1, 52.4, 68.4, 115.8 ($^2J_{\text{C-F}}$ = 22 Hz), 127.7 ($^3J_{\text{C-F}}$ = 8.2 Hz), 131.9, 160.1 ($^2J_{\text{C-F}}$ = 247 Hz), 173.0, 173.2, 175.8 ppm; IR (KBr): ν 3331, 1745, 1698, 1670, 1511, 1369, 1219, 838 cm^{-1} ; HRMS calcd for $\text{C}_{19}\text{H}_{25}\text{FN}_2\text{O}_4$ $[\text{M} + \text{Na}]^+$ 387.1696; Found: 387.1693.

Methyl (1-(3-methoxyphenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)leucinate (**4l**): Cream solid (yield 218 mg, 58%); mp: 98 – 99 $^\circ\text{C}$; ^1H NMR (500 MHz, Chloroform-*d*) δ 0.91 – 0.96 (m, 6H), 1.51 (s, 3H), 1.60 – 1.71 (m, 3H), 2.11 (m, 1H), 2.48 – 2.61 (m, 2H), 2.71 (m, 1H), 3.75 (s, 3H), 3.80 (s, 3H), 4.64 (m, 1H), 6.45 (d, J = 8.3 Hz, 1H), 6.80 – 6.97 (m, 3H), 7.27 (m,

1H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.4, 21.5, 22.9, 24.9, 30.4, 34.4, 40.6, 51.2, 52.3, 55.4, 68.6, 111.7, 112.4, 117.5, 129.6, 137.1, 160.1, 172.9, 173.5, 175.5 ppm; IR (KBr): ν 3295, 1746, 1673, 1537, 1392, 1213, 1037, 699 cm^{-1} ; Anal. calcd for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_5$ (376.1998) C, 63.81; H, 7.50; N, 7.44; Found: C, 63.68; H, 7.91; N, 7.10%.

Methyl (1-(4-hydroxyphenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)leucinate (**4m**): Cream solid (yield, 220 mg, 61%); mp: 165 – 169 °C; ^1H NMR (500 MHz, Chloroform-*d*) δ 0.90 – 0.96 (m, 6H), 1.48 (s, 3H), 1.52 – 1.72 (m, 3H), 2.07 (m, 1H), 2.50 – 2.62 (m, 2H), 2.78 (m, 1H), 3.75 (s, 3H), 4.66 (m, 1H), 6.31 (d, J = 8.1 Hz, 1H), 6.63 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.5, 21.7, 22.8, 24.9, 30.3, 33.7, 41.0, 51.2, 51.3, 68.7, 116.3, 127.4, 155.8, 173.0, 173.2, 176.7 ppm; IR (KBr): ν 3600 – 2600 (–OH and –NH), 1746, 1681, 1644, 1517, 1391, 1275, 1228, 833 cm^{-1} ; HRMS calcd for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_5$ $[\text{M} + \text{Na}]^+$ 385.1739; Found: 385.1739.

Methyl (2-methyl-5-oxo-1-phenylpyrrolidine-2-carbonyl)phenylalaninate (**4n**): White crystalline solid (yield, 230 mg, 60%); mp: 129 – 130 °C; ^1H NMR (500 MHz, Chloroform-*d*) δ 1.34 (s, 3H), 1.92 (m, 1H), 2.27 (m, 1H), 2.43 (m, 1H), 2.52 (m, 1H), 3.00 (m, 1H), 3.29 (m, 1H), 3.78 (s, 3H), 4.93 (m, 1H), 6.99 (brs, 1H), 7.00 – 7.13 (m, 2H), 7.20 – 7.38 (m, 8H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 22.7, 23.0, 30.0, 34.3, 36.7, 53.2, 68.4, 126.0, 126.1, 126.7, 127.1, 128.7, 128.9, 136.0, 136.2, 171.9, 173.8, 175.7 ppm; IR (KBr): ν 3304, 1741, 1692, 1678, 1530, 1381, 1233, 1029, 700 cm^{-1} ; Anal. calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4$ (380.1736) C, 69.46; H, 6.36; N, 7.36; Found: C, 69.69; H, 6.50; N, 7.30%.

Methyl (1-(4-chlorophenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)phenylalaninate (**4o**): Viscous Oil (yield, 224 mg, 54%); ^1H NMR (500 MHz, Chloroform-*d*) δ 1.38 (s, 3H), 2.38 (m, 1H), 2.62 (m, 1H), 2.69 (m, 1H), , 2.75 (m, 1H), 3.02 (m, 1H), 3.30 (m, 1H), 3.82 (s, 3H), 4.93 (m, 1H), 6.61 (d, J = 7.9 Hz, 1H, –NH), 6.95 (d, J = 7.8 Hz, 1H), 7.02– 7.12 (m, 2H), 7.17 – 7.42 (m, 6H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 22.5, 27.6, 29.7, 34.2, 37.7, 53.1, 68.40, 127.18, 127.3, 127.7, 128.8, 129.2, 132.7, 134.4, 135.88, 173.3, 175.7, 176.6 ppm; IR (KBr): ν 3272, 1740, 1652, 1654, 1396, 1223, 704 cm^{-1} ; Anal. calcd for $\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_4$ (414.1346) C, 63.69; H, 5.59; N, 6.75; Found: C, 63.30; H, 5.72; N, 6.40%.

Methyl (1-(4-hydroxyphenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)phenylalaninate (**4p**): Cream solid (yield, 218 mg, 55%); mp: 144 – 147 °C; ^1H NMR (500 MHz, Chloroform-*d*) δ 1.36 (s, 3H), 1.99 (m, 1H), 2.10 (m, 1H), 2.34 – 2.55 (m, 2H), 3.05 (m, 1H), 3.23 (m, 1H), 3.77 (s, 3H), 4.87 (m, 1H), 6.36 (d, J = 7.7 Hz, 1H), 6.77 (m, 2H), 6.82 – 7.20 (m, 5H), 7.23 – 7.32 (m, 3H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 22.8, 30.0, 33.6, 37.2, 52.5, 53.2, 68.6, 116.4, 127.4, 128.4, 128.6, 128.8, 128.9, 135.5, 155.7, 171.7, 173.0, 176.6 ppm; IR (KBr): ν 3600 – 2500 (OH and NH), 1742, 1685, 1650, 1515, 1387, 1221, 837, 700 cm^{-1} ; HRMS calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5$ $[\text{M} + \text{Na}]^+$ 419.1583; Found: 419.1577.

CC1(C)CC(=O)N1C(=O)C2C=C3C(=C2)C(=C4C(=C3)C(=C5C(=C4)C(=C6C(=C5)C(=C7C(=C6)C(=C8C(=C7)C(=C9C(=C8)C(=C10C(=C9)C(=C11C(=C10)C(=C12C(=C11)C(=C13C(=C12)C(=C14C(=C13)C(=C15C(=C14)C(=C16C(=C15)C(=C17C(=C16)C(=C18C(=C17)C(=C19C(=C18)C(=C20C(=C19)C(=C21C(=C20)C(=C22C(=C21)C(=C23C(=C22)C(=C24C(=C23)C(=C25C(=C24)C(=C26C(=C25)C(=C27C(=C26)C(=C28C(=C27)C(=C29C(=C28)C(=C30C(=C29)C(=C31C(=C30)C(=C32C(=C31)C(=C33C(=C32)C(=C34C(=C33)C(=C35C(=C34)C(=C36C(=C35)C(=C37C(=C36)C(=C38C(=C37)C(=C39C(=C38)C(=C40C(=C39)C(=C41C(=C40)C(=C42C(=C41)C(=C43C(=C42)C(=C44C(=C43)C(=C45C(=C44)C(=C46C(=C45)C(=C47C(=C46)C(=C48C(=C47)C(=C49C(=C48)C(=C50C(=C49)C(=C51C(=C50)C(=C52C(=C51)C(=C53C(=C52)C(=C54C(=C53)C(=C55C(=C54)C(=C56C(=C55)C(=C57C(=C56)C(=C58C(=C57)C(=C59C(=C58)C(=C60C(=C59)C(=C61C(=C60)C(=C62C(=C61)C(=C63C(=C62)C(=C64C(=C63)C(=C65C(=C64)C(=C66C(=C65)C(=C67C(=C66)C(=C68C(=C67)C(=C69C(=C68)C(=C70C(=C69)C(=C71C(=C70)C(=C72C(=C71)C(=C73C(=C72)C(=C74C(=C73)C(=C75C(=C74)C(=C76C(=C75)C(=C77C(=C76)C(=C78C(=C77)C(=C79C(=C78)C(=C80C(=C79)C(=C81C(=C80)C(=C82C(=C81)C(=C83C(=C82)C(=C84C(=C83)C(=C85C(=C84)C(=C86C(=C85)C(=C87C(=C86)C(=C88C(=C87)C(=C89C(=C88)C(=C90C(=C89)C(=C91C(=C90)C(=C92C(=C91)C(=C93C(=C92)C(=C94C(=C93)C(=C95C(=C94)C(=C96C(=C95)C(=C97C(=C96)C(=C98C(=C97)C(=C99C(=C98)C(=C100C(=C99)C(=C101C(=C100)C(=C102C(=C101)C(=C103C(=C102)C(=C104C(=C103)C(=C105C(=C104)C(=C106C(=C105)C(=C107C(=C106)C(=C108C(=C107)C(=C109C(=C108)C(=C110C(=C109)C(=C111C(=C110)C(=C112C(=C111)C(=C113C(=C112)C(=C114C(=C113)C(=C115C(=C114)C(=C116C(=C115)C(=C117C(=C116)C(=C118C(=C117)C(=C119C(=C118)C(=C120C(=C119)C(=C121C(=C120)C(=C122C(=C121)C(=C123C(=C122)C(=C124C(=C123)C(=C125C(=C124)C(=C126C(=C125)C(=C127C(=C126)C(=C128C(=C127)C(=C129C(=C128)C(=C130C(=C129)C(=C131C(=C130)C(=C132C(=C131)C(=C133C(=C132)C(=C134C(=C133)C(=C135C(=C134)C(=C136C(=C135)C(=C137C(=C136)C(=C138C(=C137)C(=C139C(=C138)C(=C140C(=C139)C(=C141C(=C140)C(=C142C(=C141)C(=C143C(=C142)C(=C144C(=C143)C(=C145C(=C144)C(=C146C(=C145)C(=C147C(=C146)C(=C148C(=C147)C(=C149C(=C148)C(=C150C(=C149)C(=C151C(=C150)C(=C152C(=C151)C(=C153C(=C152)C(=C154C(=C153)C(=C155C(=C154)C(=C156C(=C155)C(=C157C(=C156)C(=C158C(=C157)C(=C159C(=C158)C(=C160C(=C159)C(=C161C(=C160)C(=C162C(=C161)C(=C163C(=C162)C(=C164C(=C163)C(=C165C(=C164)C(=C166C(=C165)C(=C167C(=C166)C(=C168C(=C167)C(=C169C(=C168)C(=C170C(=C169)C(=C171C(=C170)C(=C172C(=C171)C(=C173C(=C172)C(=C174C(=C173)C(=C175C(=C174)C(=C176C(=C175)C(=C177C(=C176)C(=C178C(=C177)C(=C179C(=C178)C(=C180C(=C179)C(=C181C(=C180)C(=C182C(=C181)C(=C183C(=C182)C(=C184C(=C183)C(=C185C(=C184)C(=C186C(=C185)C(=C187C(=C186)C(=C188C(=C187)C(=C189C(=C188)C(=C190C(=C189)C(=C191C(=C190)C(=C192C(=C191)C(=C193C(=C192)C(=C194C(=C193)C(=C195C(=C194)C(=C196C(=C195)C(=C197C(=C196)C(=C198C(=C197)C(=C199C(=C198)C(=C200C(=C199)C(=C201C(=C200)C(=C202C(=C201)C(=C203C(=C202)C(=C204C(=C203)C(=C205C(=C204)C(=C206C(=C205)C(=C207C(=C206)C(=C208C(=C207)C(=C209C(=C208)C(=C210C(=C209)C(=C211C(=C210)C(=C212C(=C211)C(=C213C(=C212)C(=C214C(=C213)C(=C215C(=C214)C(=C216C(=C215)C(=C217C(=C216)C(=C218C(=C217)C(=C219C(=C218)C(=C220C(=C219)C(=C221C(=C220)C(=C222C(=C221)C(=C223C(=C222)C(=C224C(=C223)C(=C225C(=C224)C(=C226C(=C225)C(=C227C(=C226)C(=C228C(=C227)C(=C229C(=C228)C(=C230C(=C229)C(=C231C(=C230)C(=C232C(=C231)C(=C233C(=C232)C(=C234C(=C233)C(=C235C(=C234)C(=C236C(=C235)C(=C237C(=C236)C(=C238C(=C237)C(=C239C(=C238)C(=C240C(=C239)C(=C241C(=C240)C(=C242C(=C241)C(=C243C(=C242)C(=C244C(=C243)C(=C245C(=C244)C(=C246C(=C245)C(=C247C(=C246)C(=C248C(=C247)C(=C249C(=C248)C(=C250C(=C249)C(=C251C(=C250)C(=C252C(=C251)C(=C253C(=C252)C(=C254C(=C253)C(=C255C(=C254)C(=C256C(=C255)C(=C257C(=C256)C(=C258C(=C257)C(=C259C(=C258)C(=C260C(=C259)C(=C261C(=C260)C(=C262C(=C261)C(=C263C(=C262)C(=C264C(=C263)C(=C265C(=C264)C(=C266C(=C265)C(=C267C(=C266)C(=C268C(=C267)C(=C269C(=C268)C(=C270C(=C269)C(=C271C(=C270)C(=C272C(=C271)C(=C273C(=C272)C(=C274C(=C273)C(=C275C(=C274)C(=C276C(=C275)C(=C277C(=C276)C(=C278C(=C277)C(=C279C(=C278)C(=C280C(=C279)C(=C281C(=C280)C(=C282C(=C281)C(=C283C(=C282)C(=C284C(=C283)C(=C285C(=C284)C(=C286C(=C285)C(=C287C(=C286)C(=C288C(

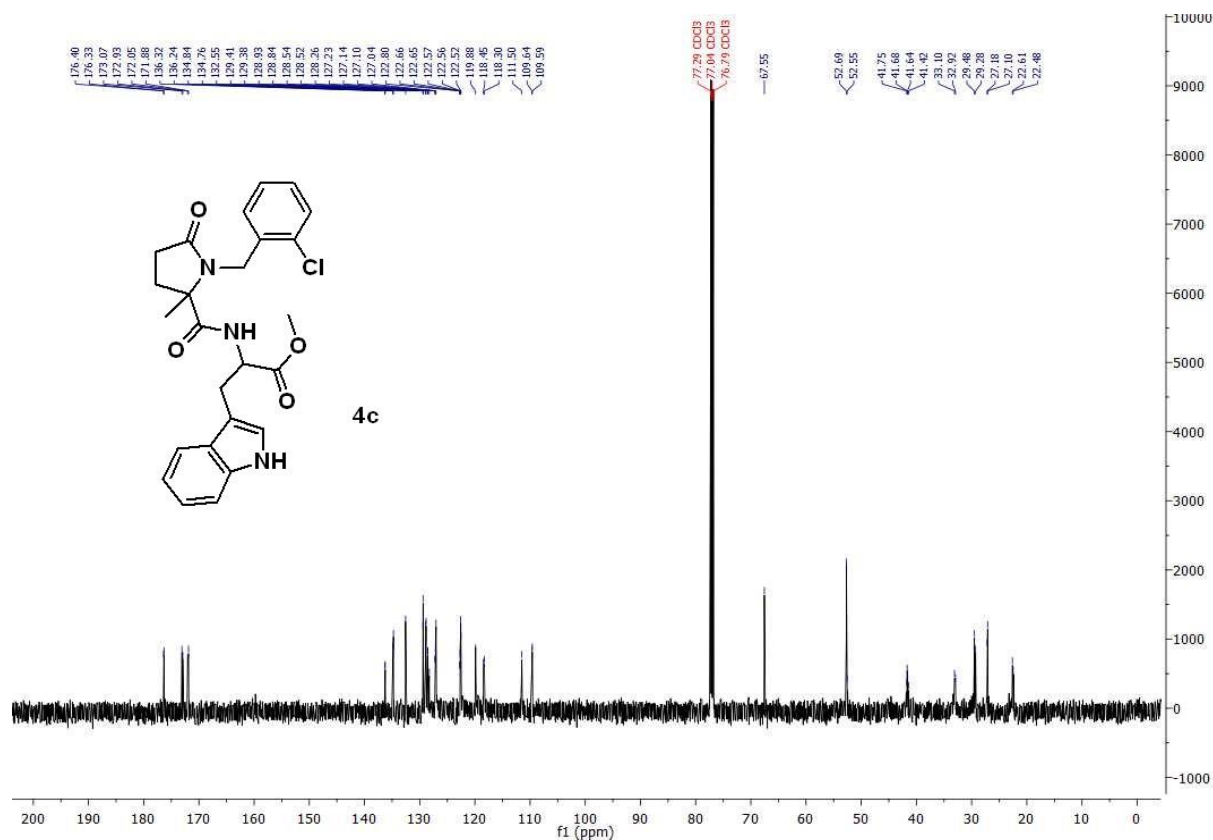
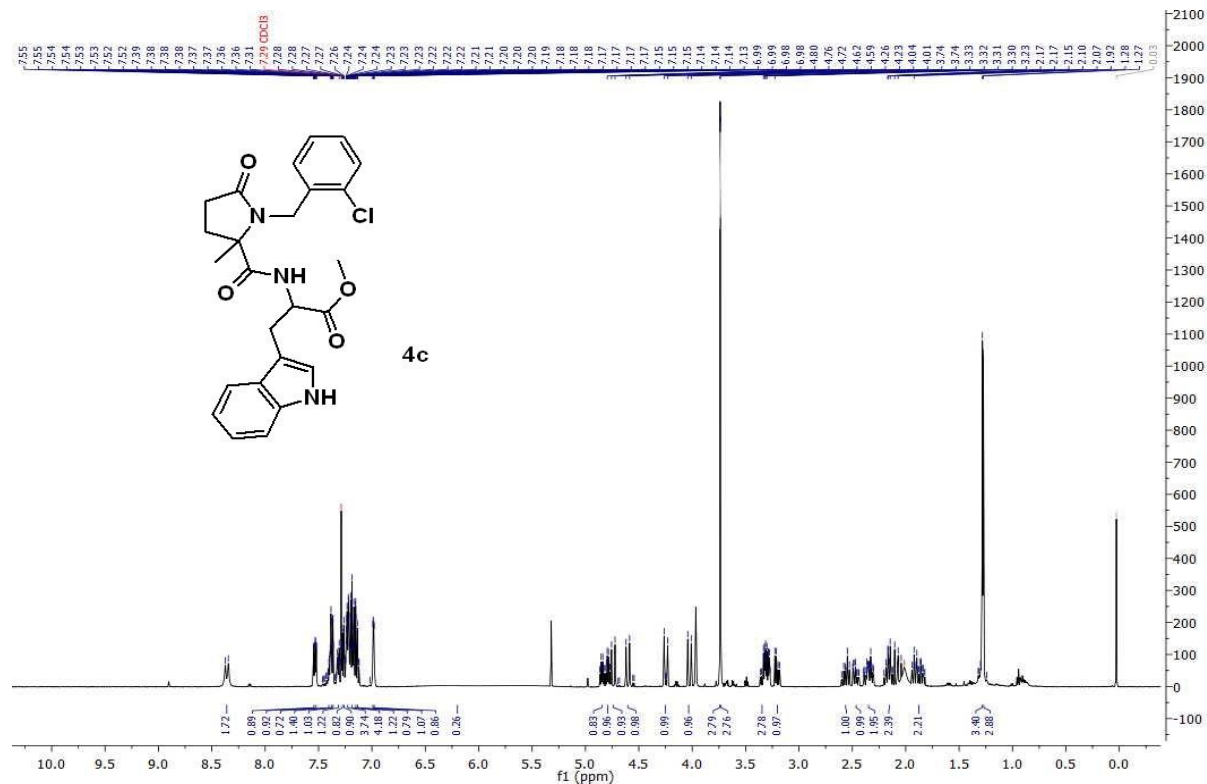


CC1(C)CC(=O)N(C1)c2ccc(Cl)cc2C(=O)NCCc3c[nH]c4ccccc34 **4b**

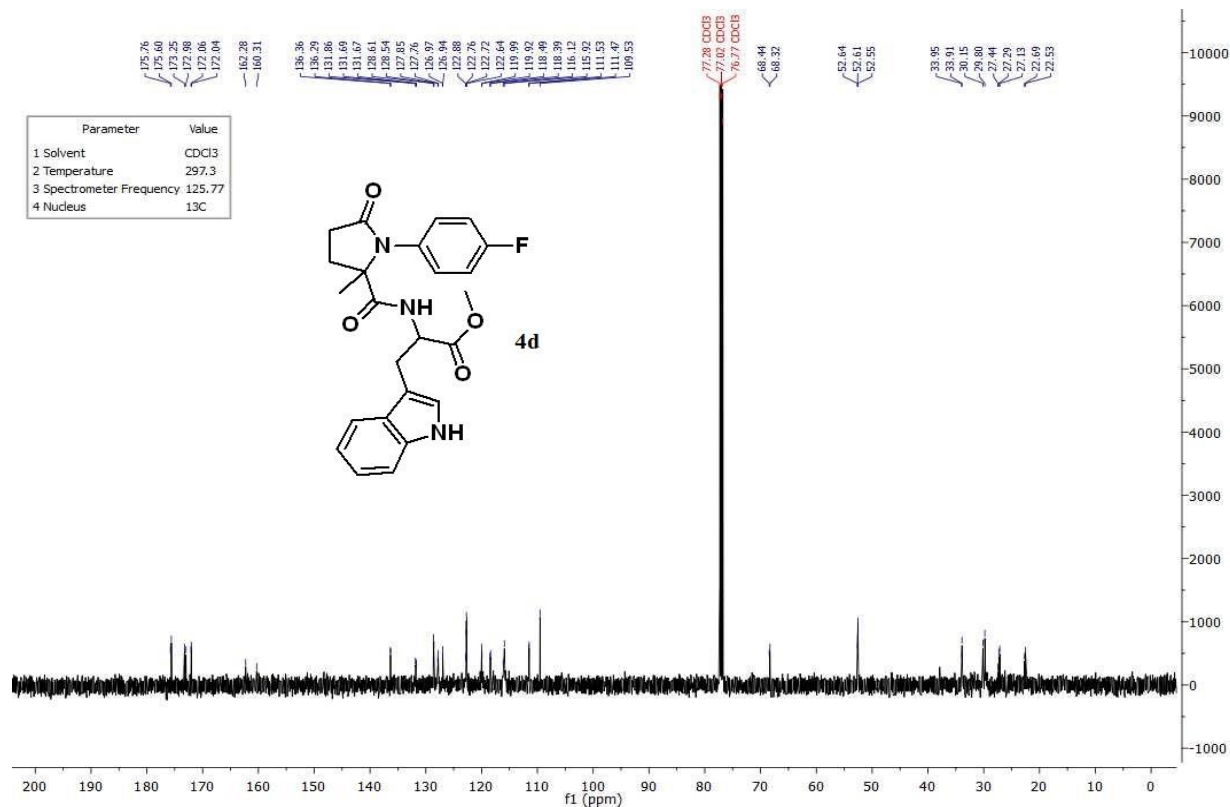
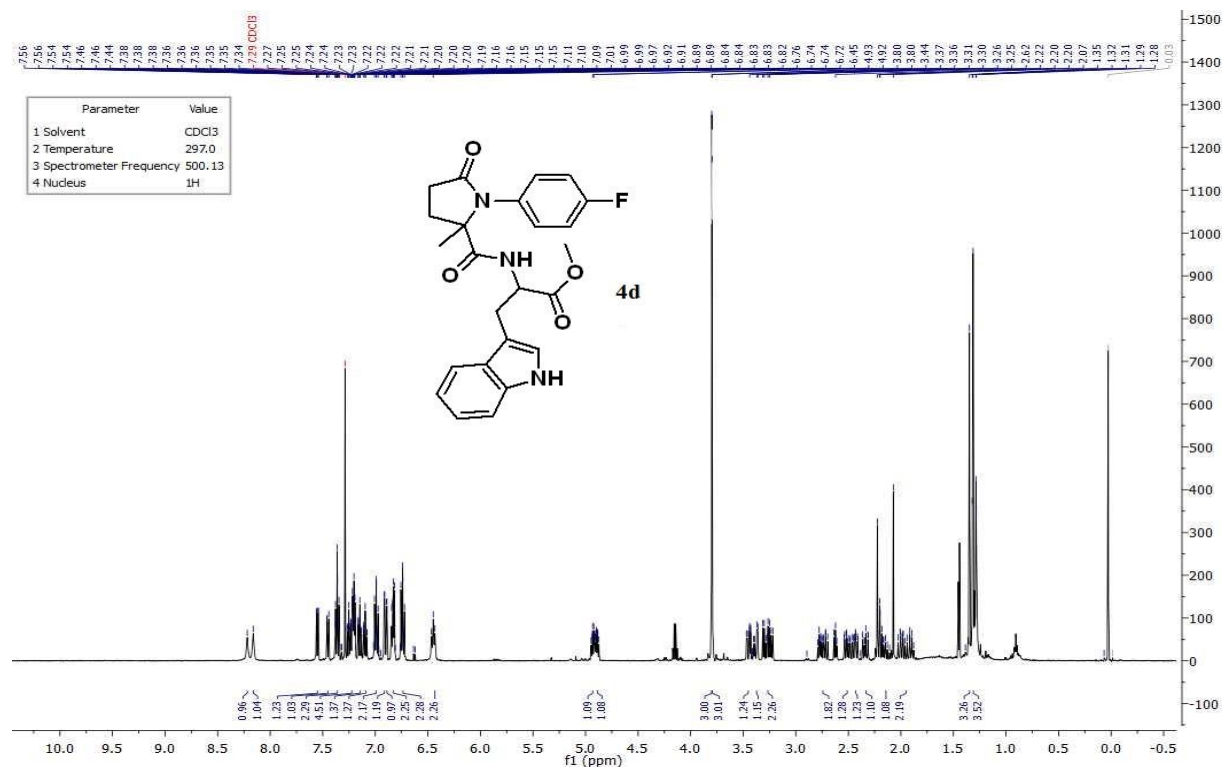
¹H NMR spectrum (CDCl₃) of compound **4b**. The x-axis represents the chemical shift in ppm (f1), ranging from 10.0 to -0.5. The y-axis represents the intensity in arbitrary units (PROTON, CDCl₃), ranging from -200 to 1400. The spectrum shows several peaks, with integration values provided below the baseline: 0.77, 1.09, 2.20, 8.34, 2.20, 2.09, 1.96, 2.02, 0.97, 1.00, 5.96, 2.11, 2.01, 0.99, 1.12, 1.06, 2.44, 2.44, 2.22, 7.25.



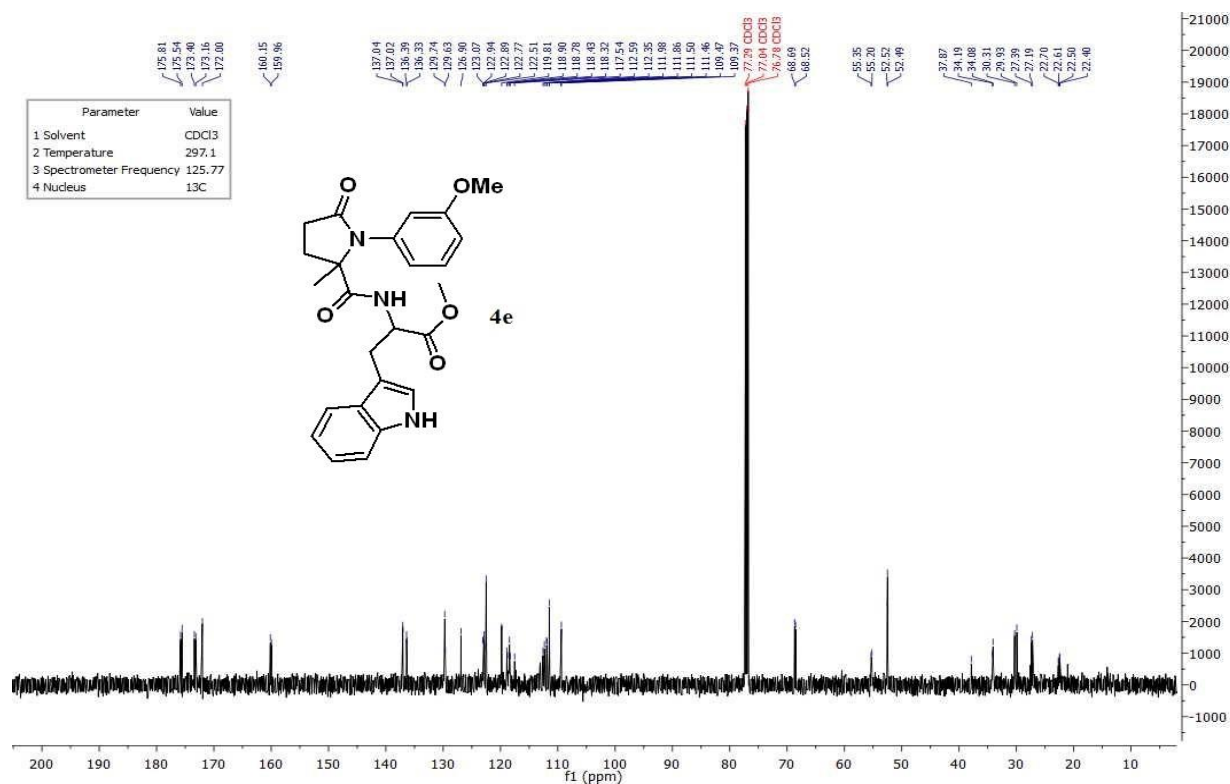
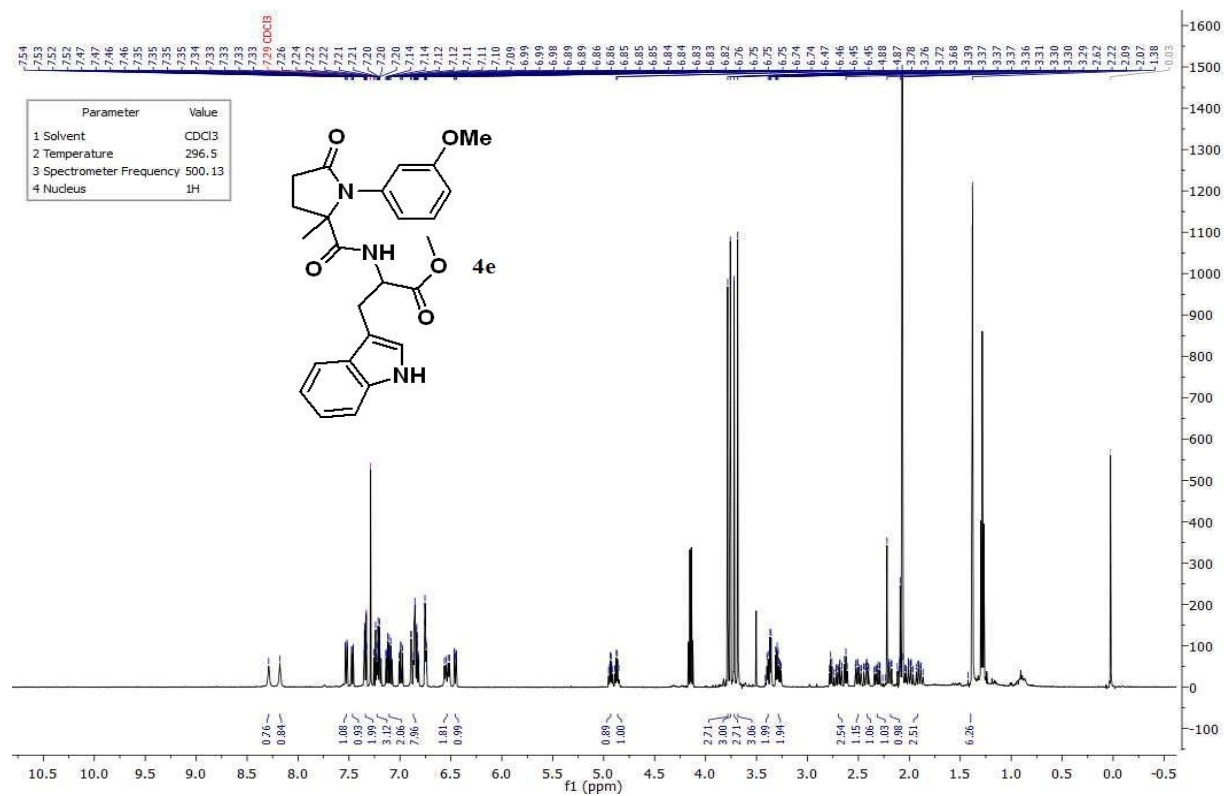
4c: Methyl (1-(2-chlorobenzyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)tryptophanate



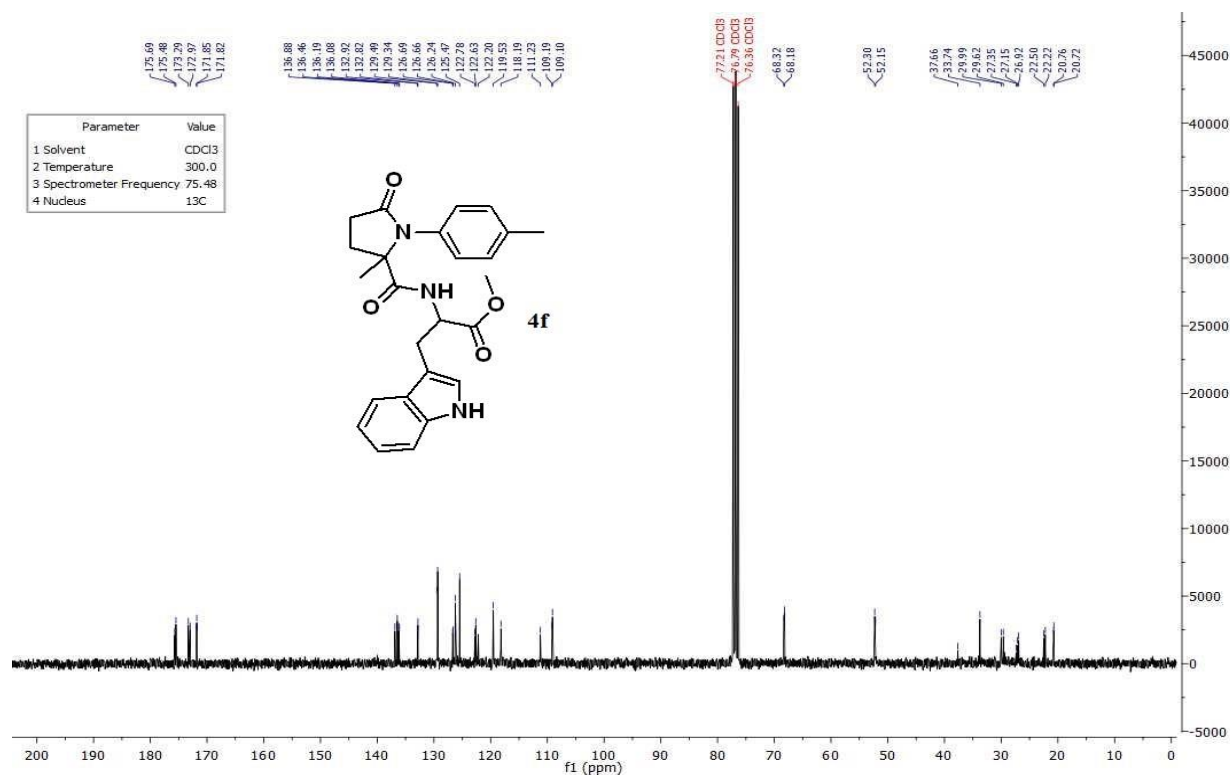
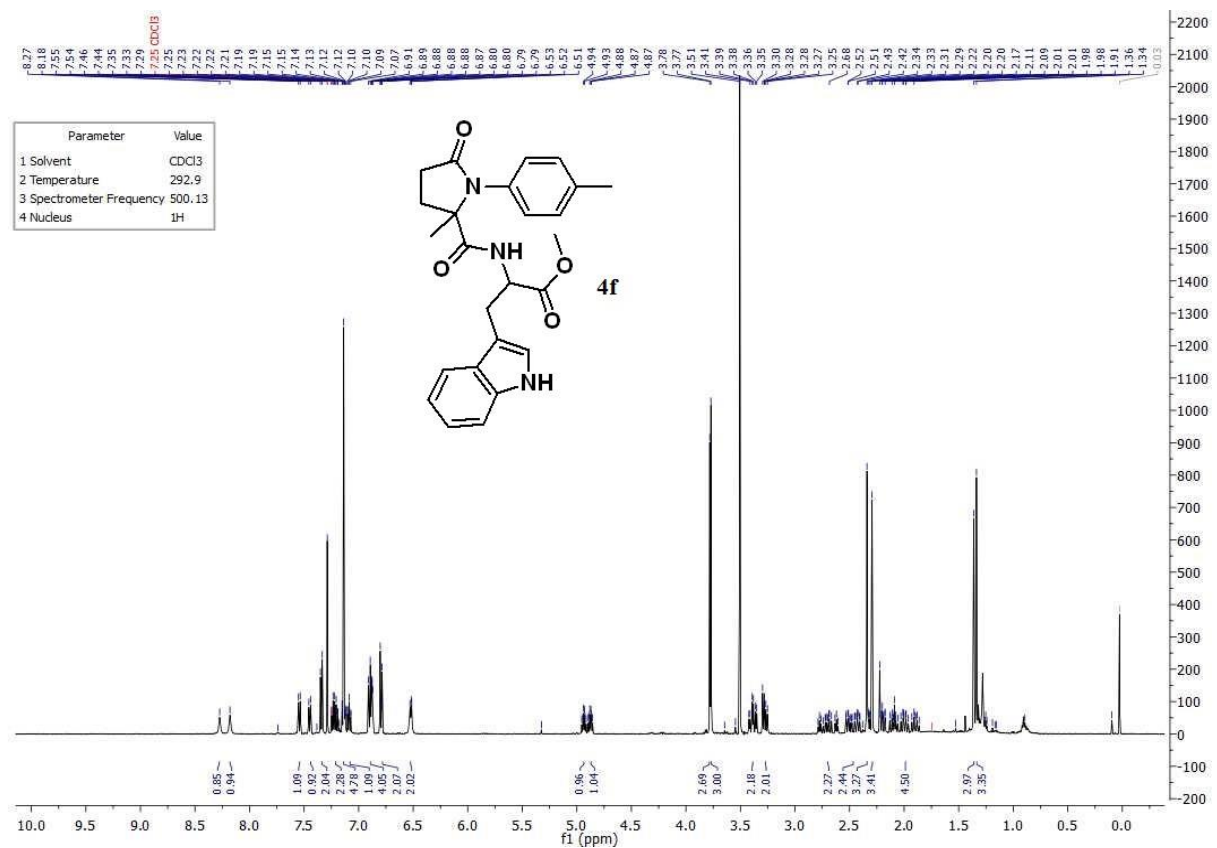
4d: Methyl (1-(4-fluorophenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)tryptophan



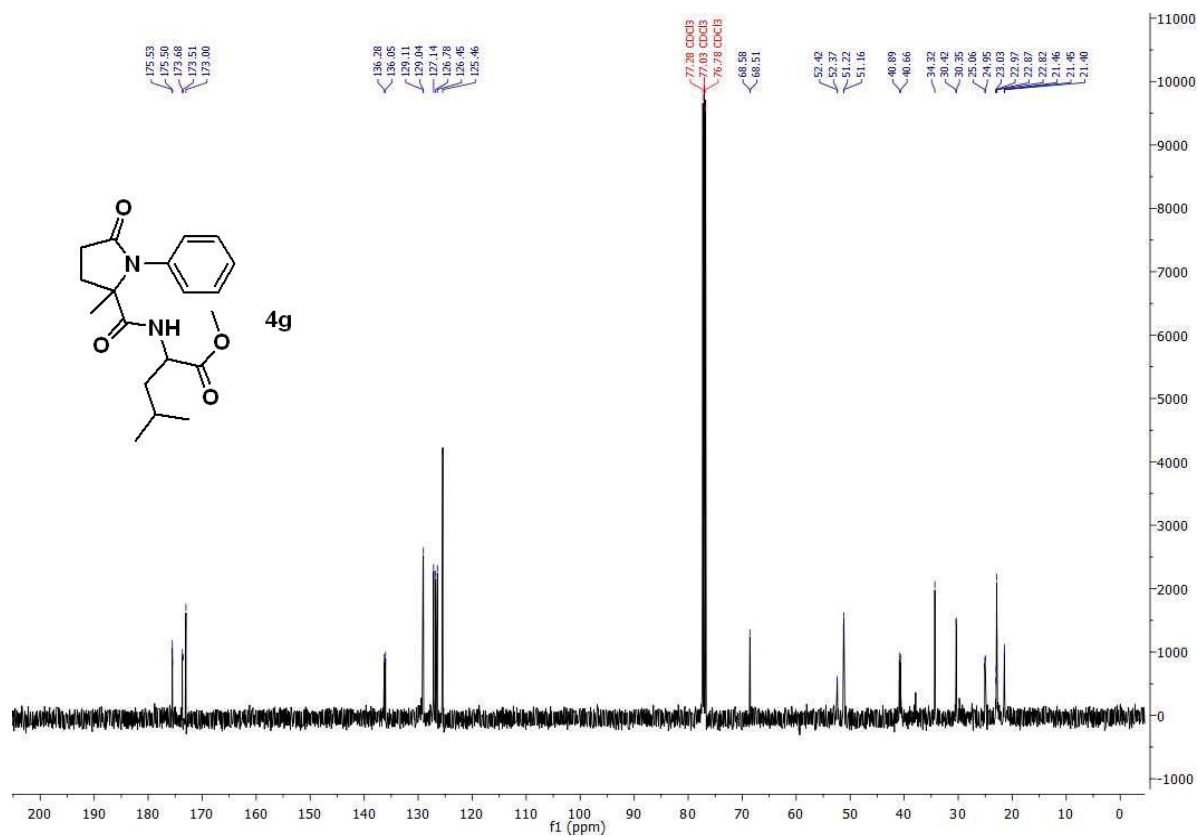
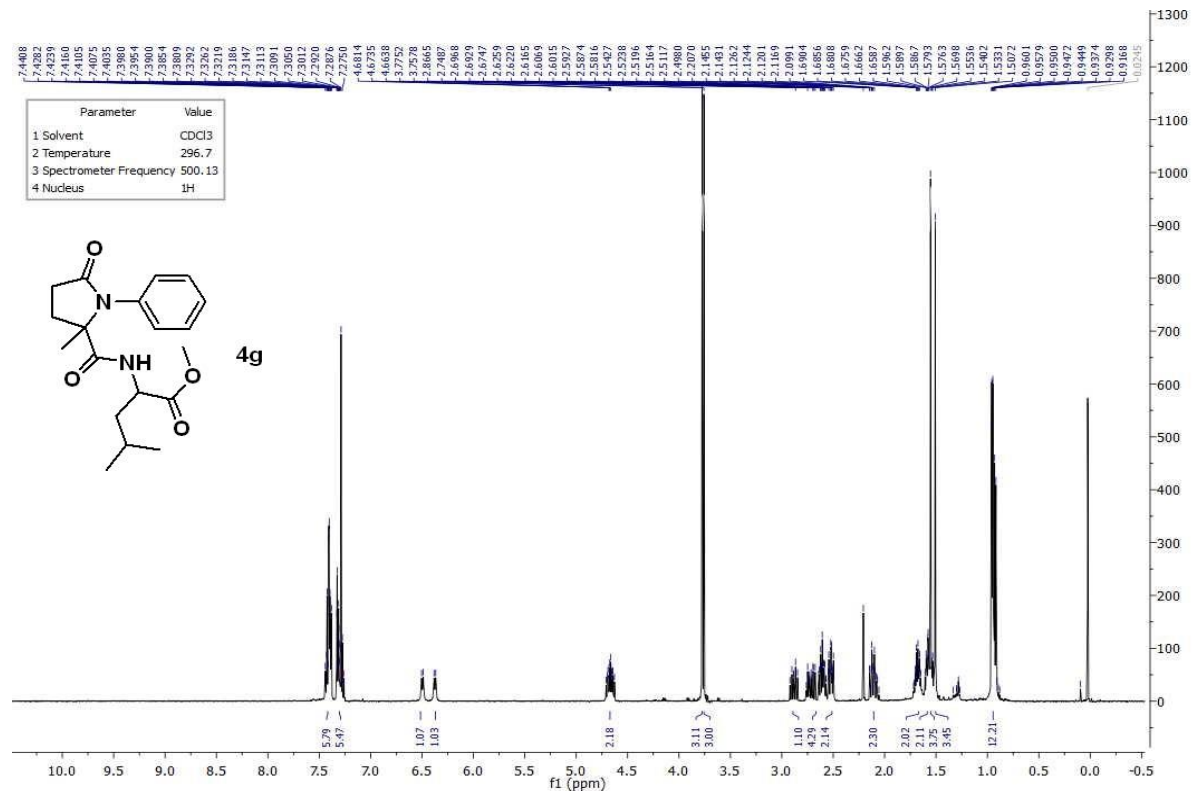
4e: Methyl (1-(3-methoxyphenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)tryptophanate



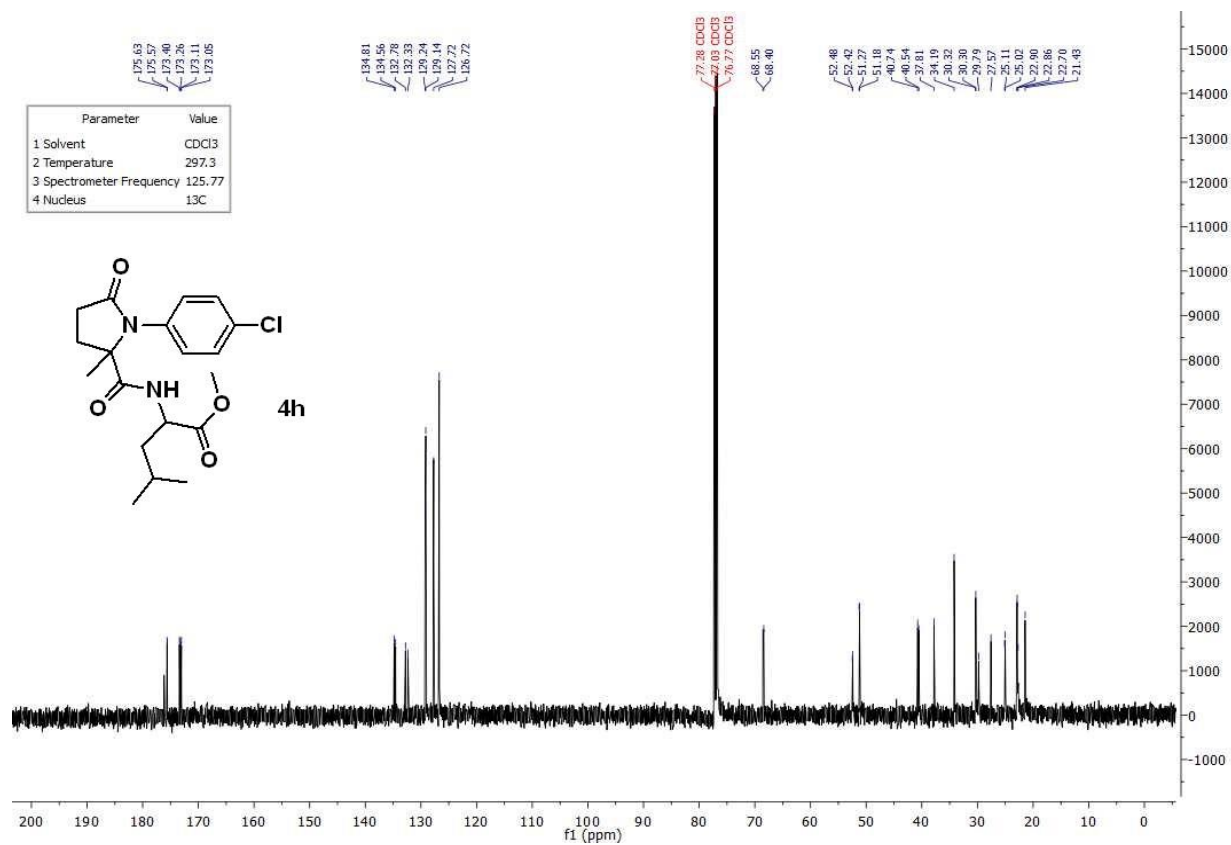
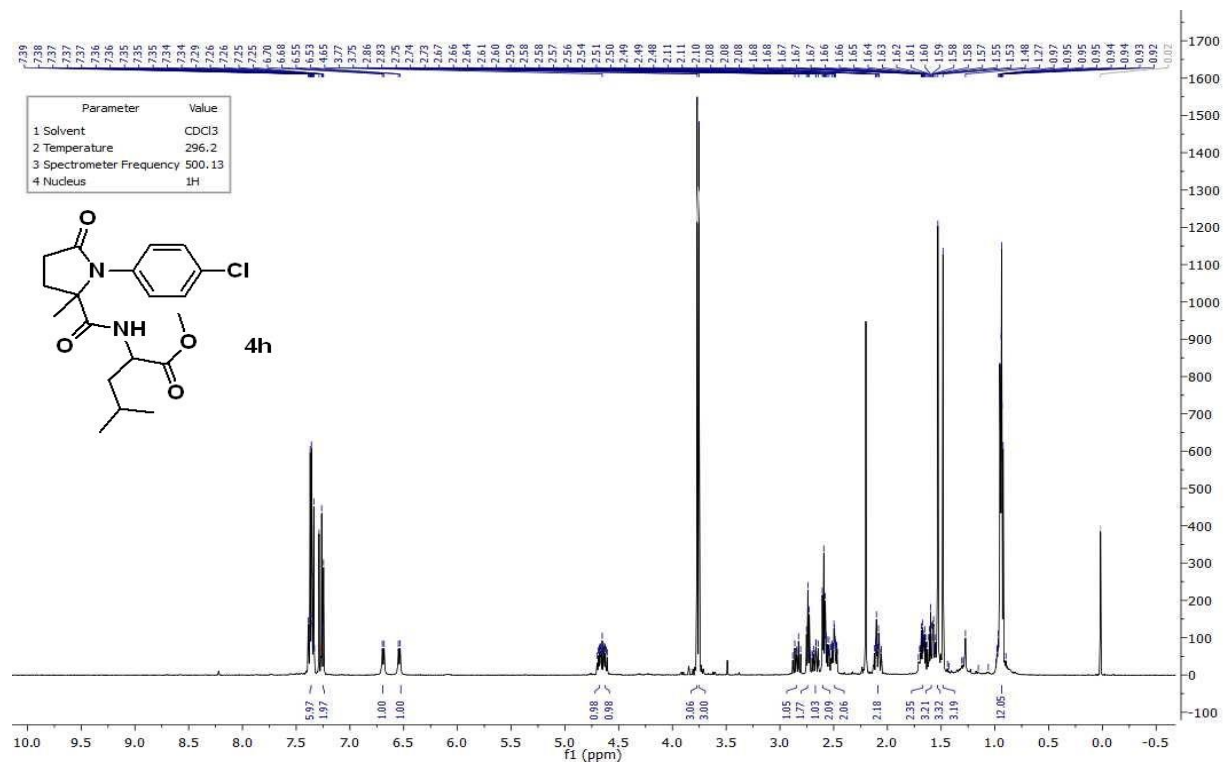
4f: Methyl (2-methyl-5-oxo-1-(*p*-tolyl)pyrrolidine-2-carbonyl)tryptophanate



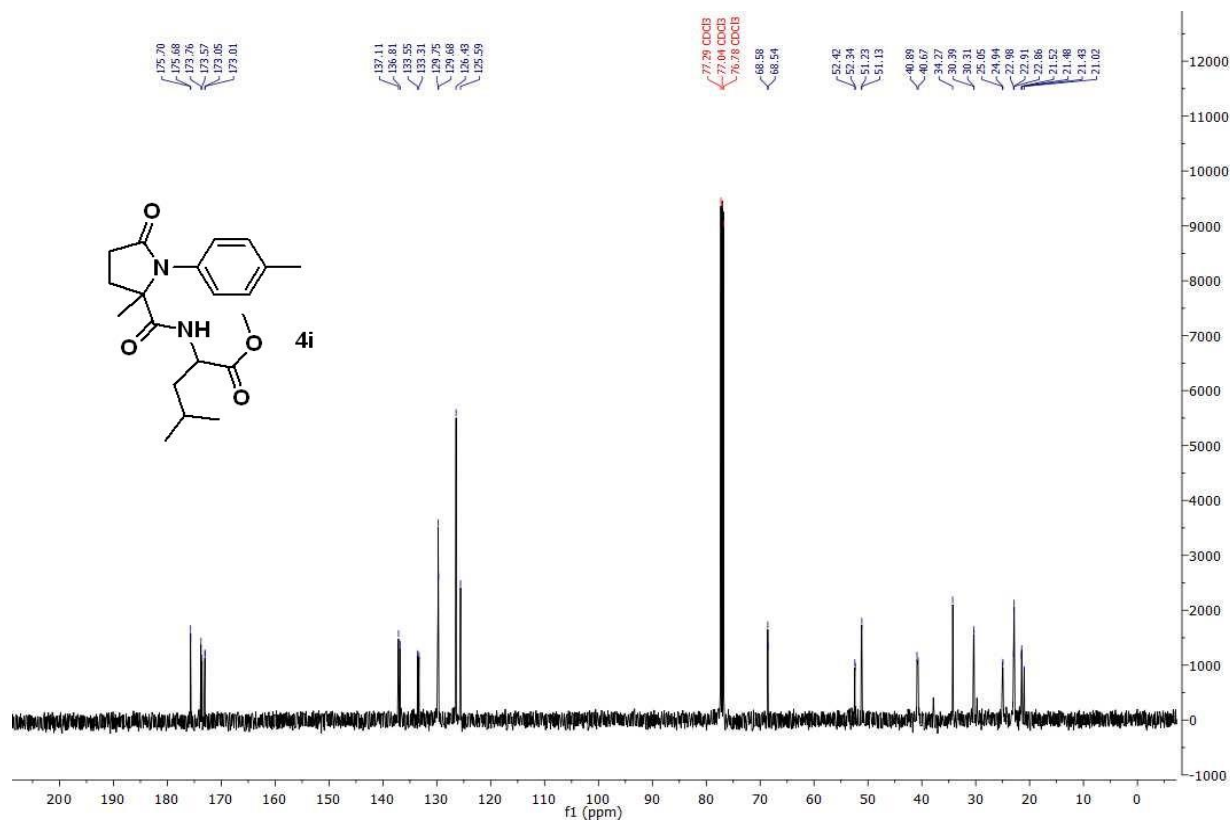
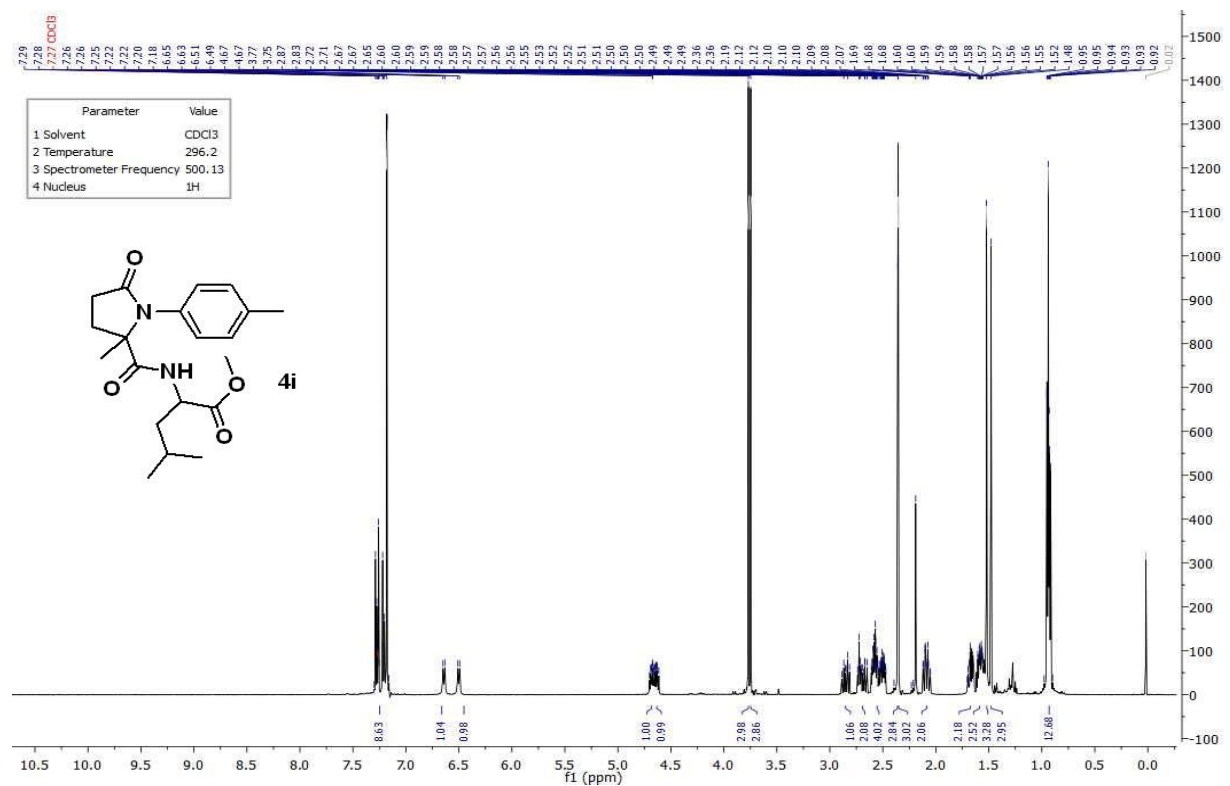
4g: Methyl (2-methyl-5-oxo-1-phenylpyrrolidine-2-carbonyl)leucinate



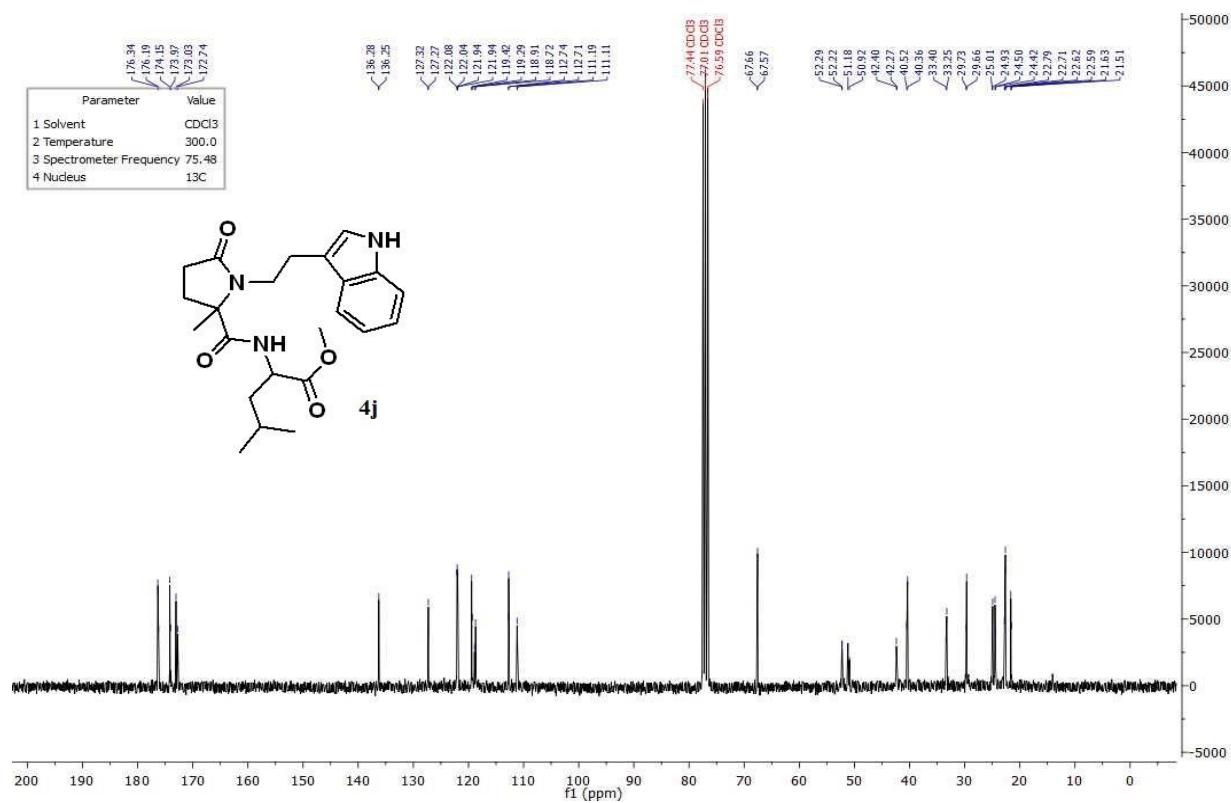
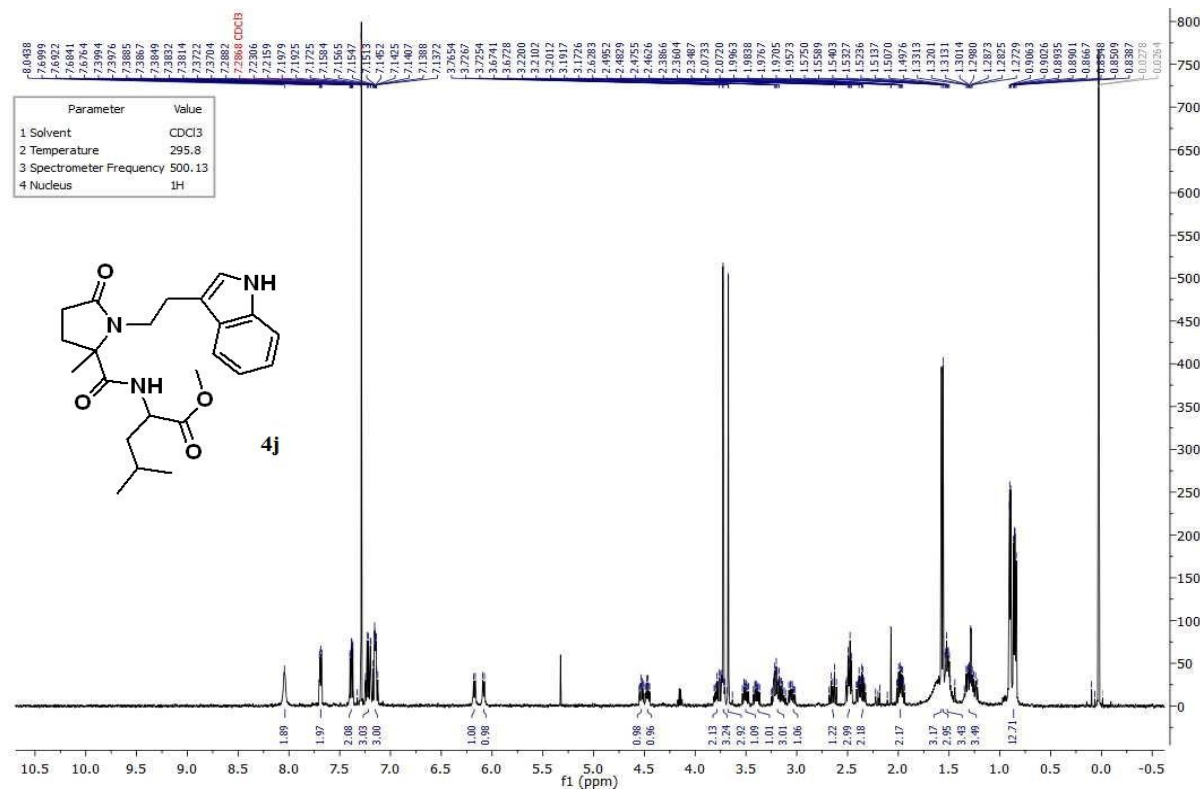
4h: Methyl (1-(4-chlorophenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)leucinate



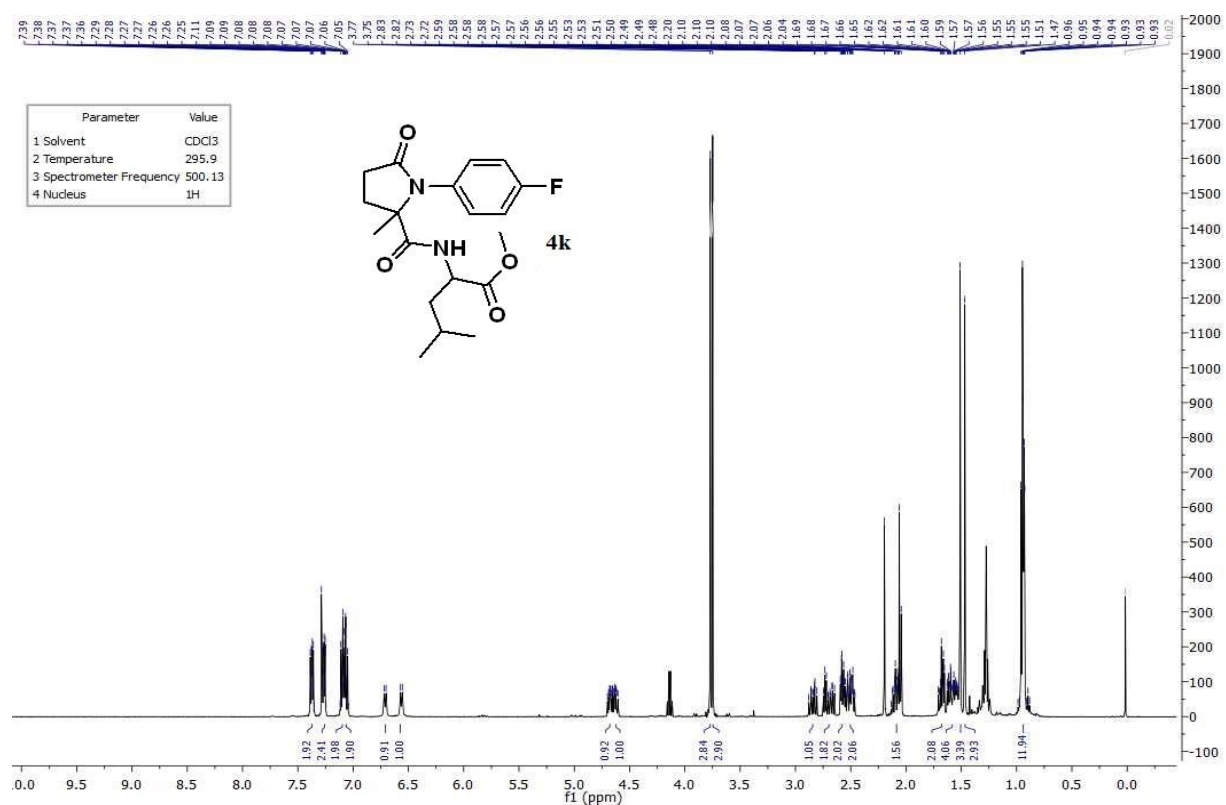
4i: Methyl (2-methyl-5-oxo-1-(p-tolyl)pyrrolidine-2-carbonyl)leucinate



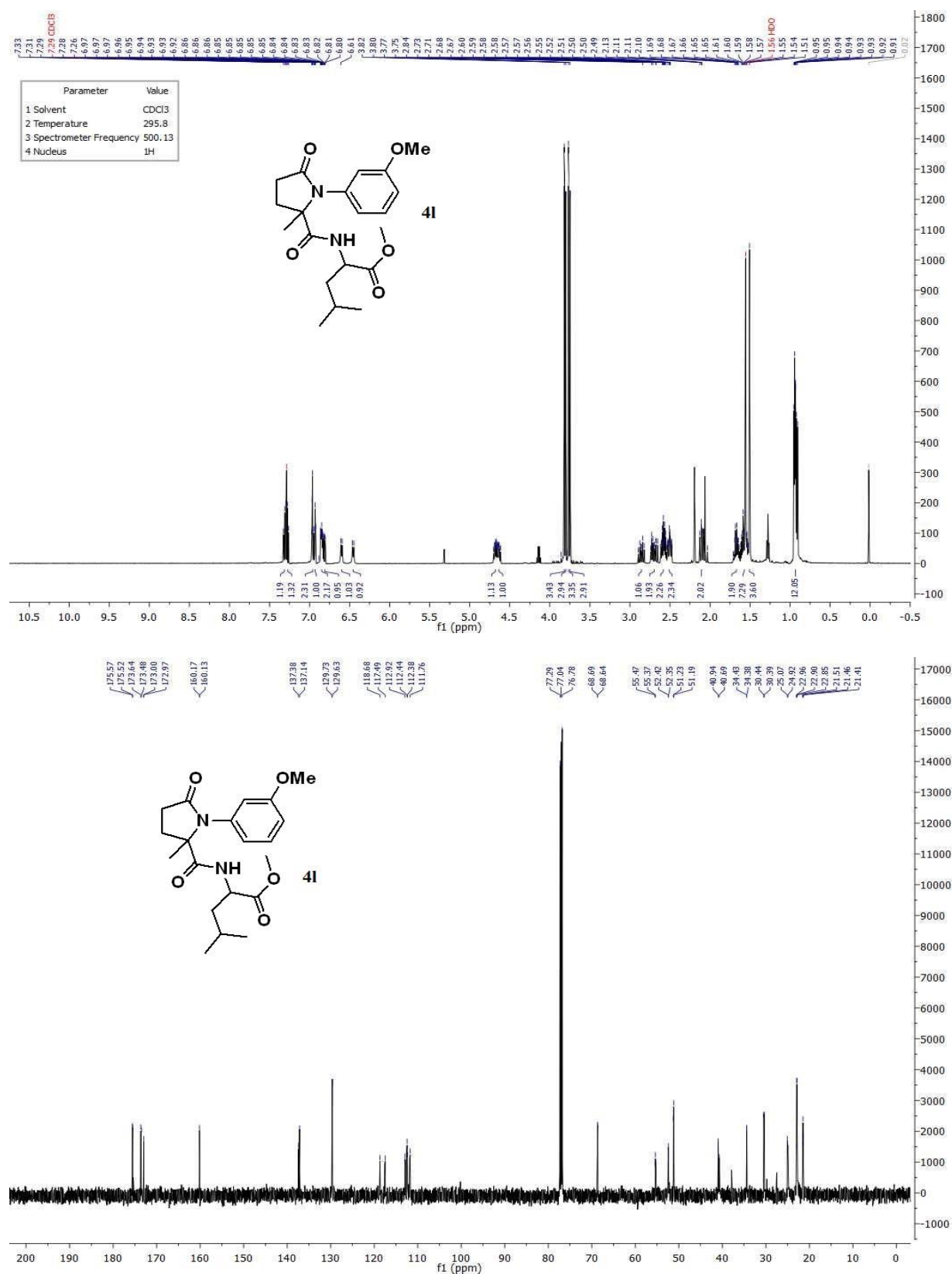
4j: Methyl (1-(2-(1H-indol-3-yl)ethyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)leucinate



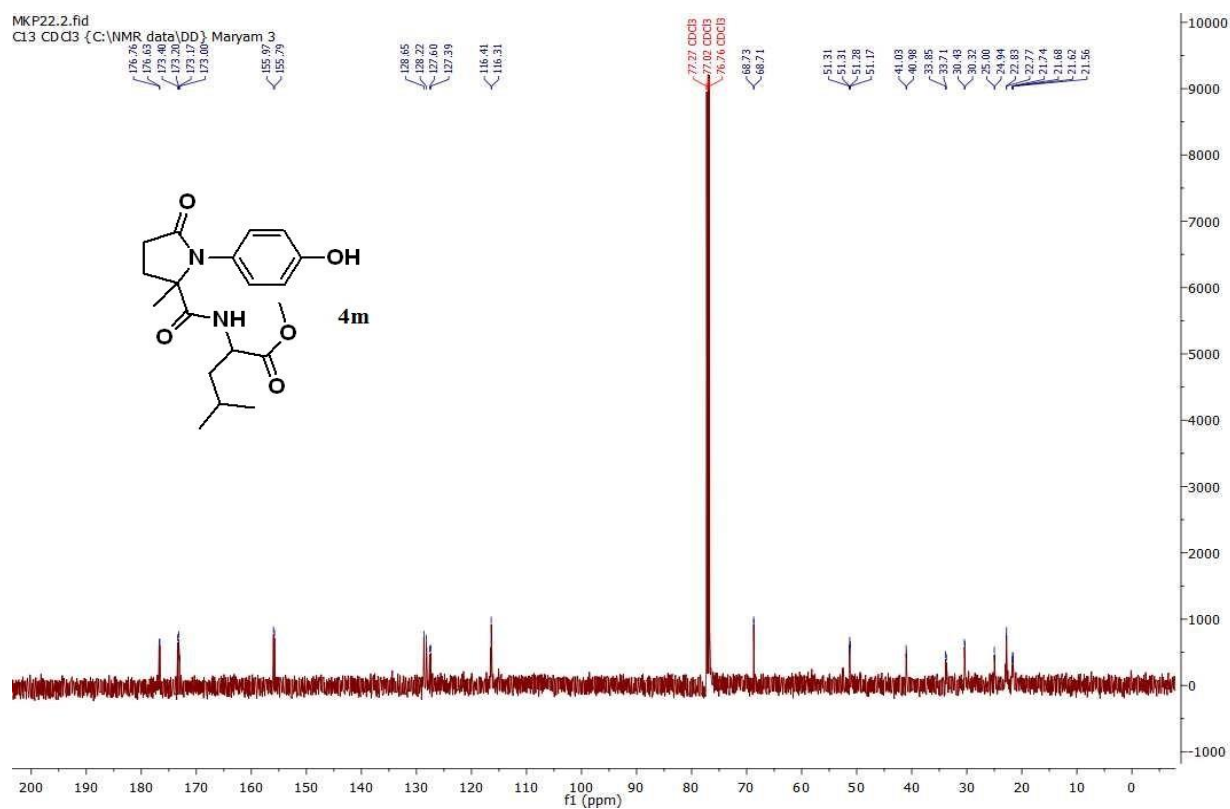
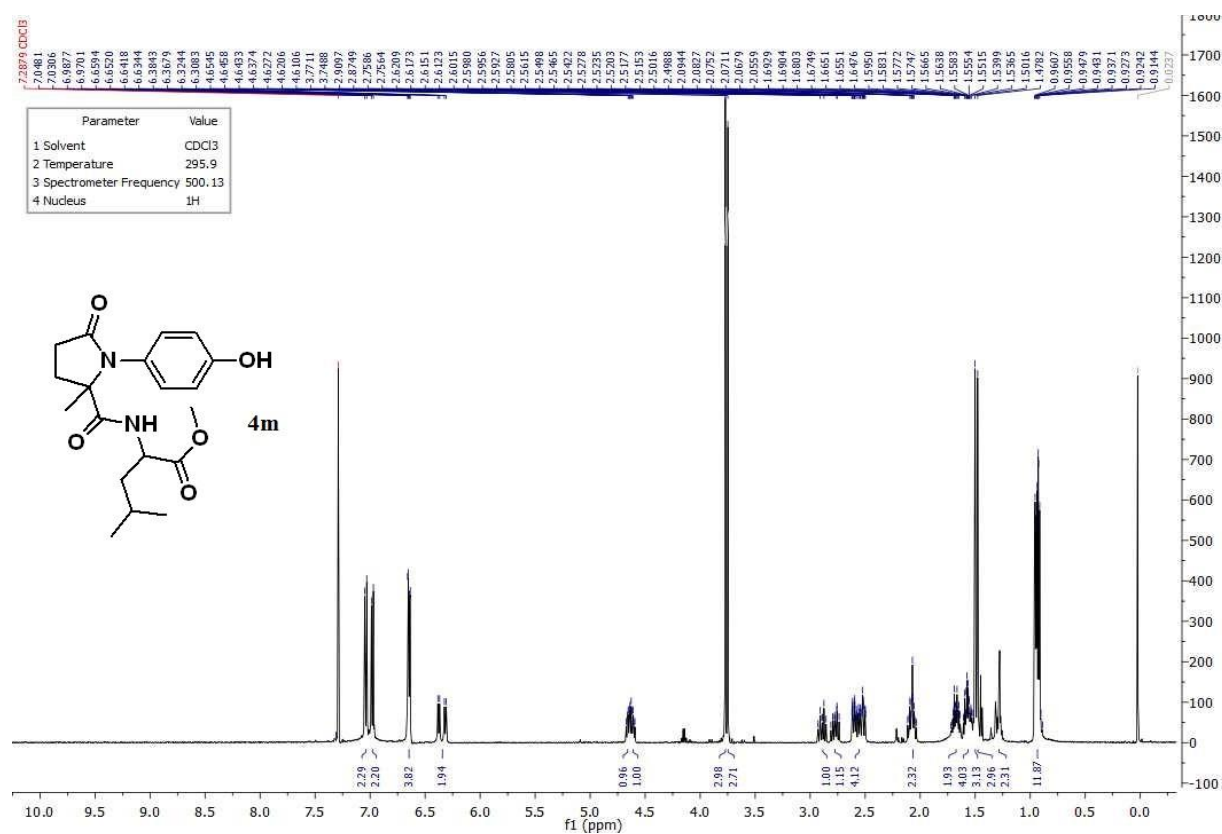
4k: Methyl (1-(4-fluorophenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)leucinate



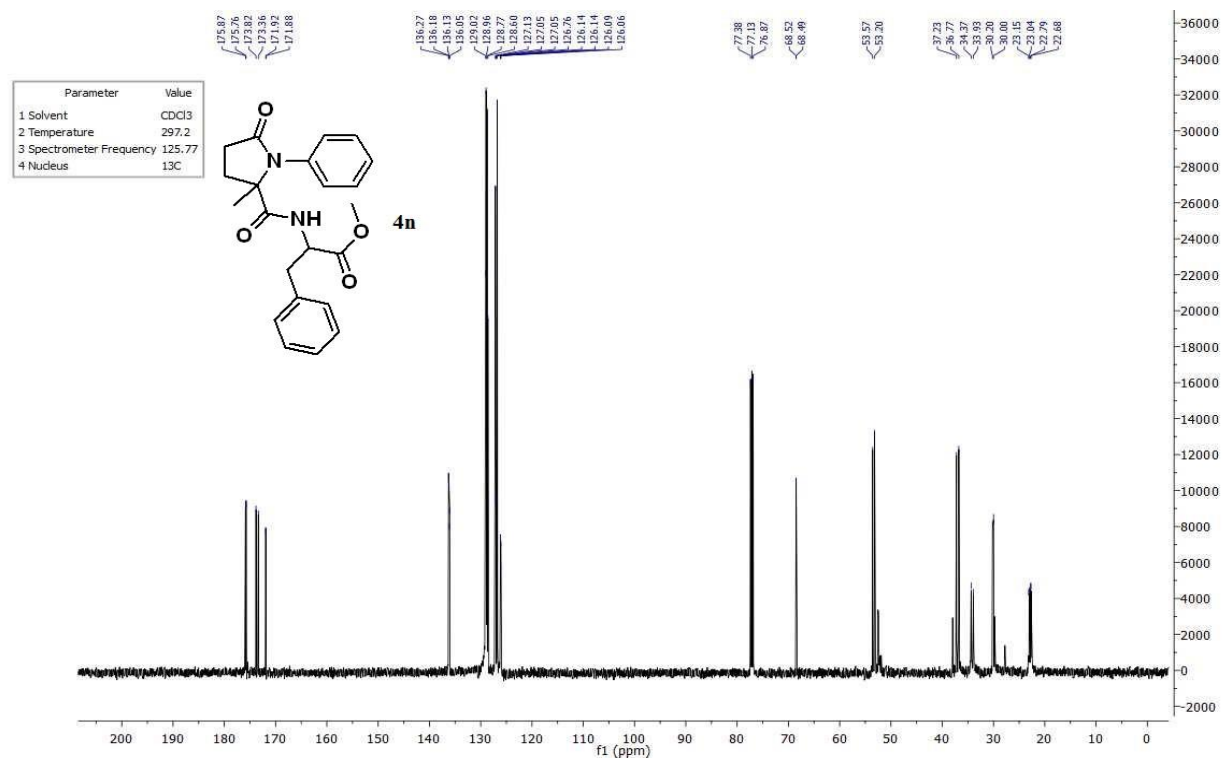
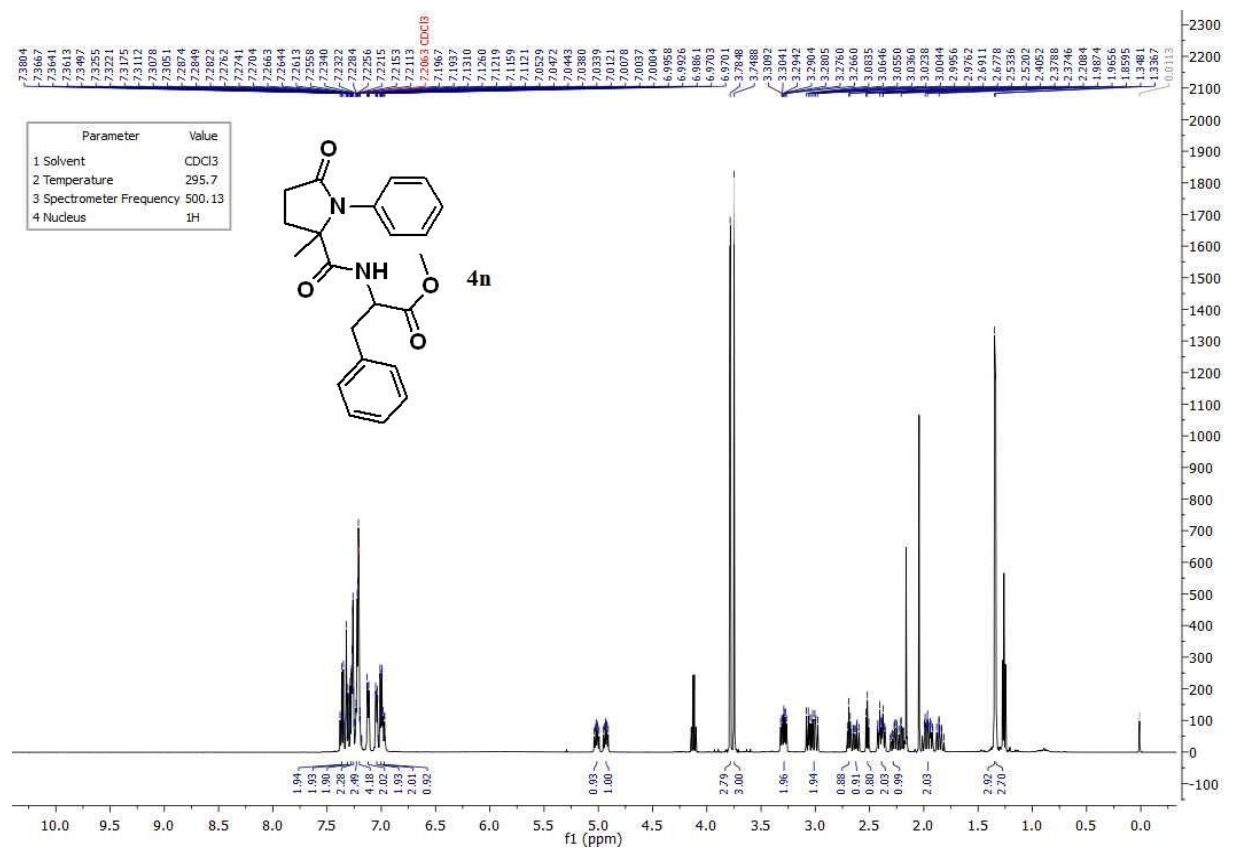
4l: Methyl (1-(3-methoxyphenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)leucinate



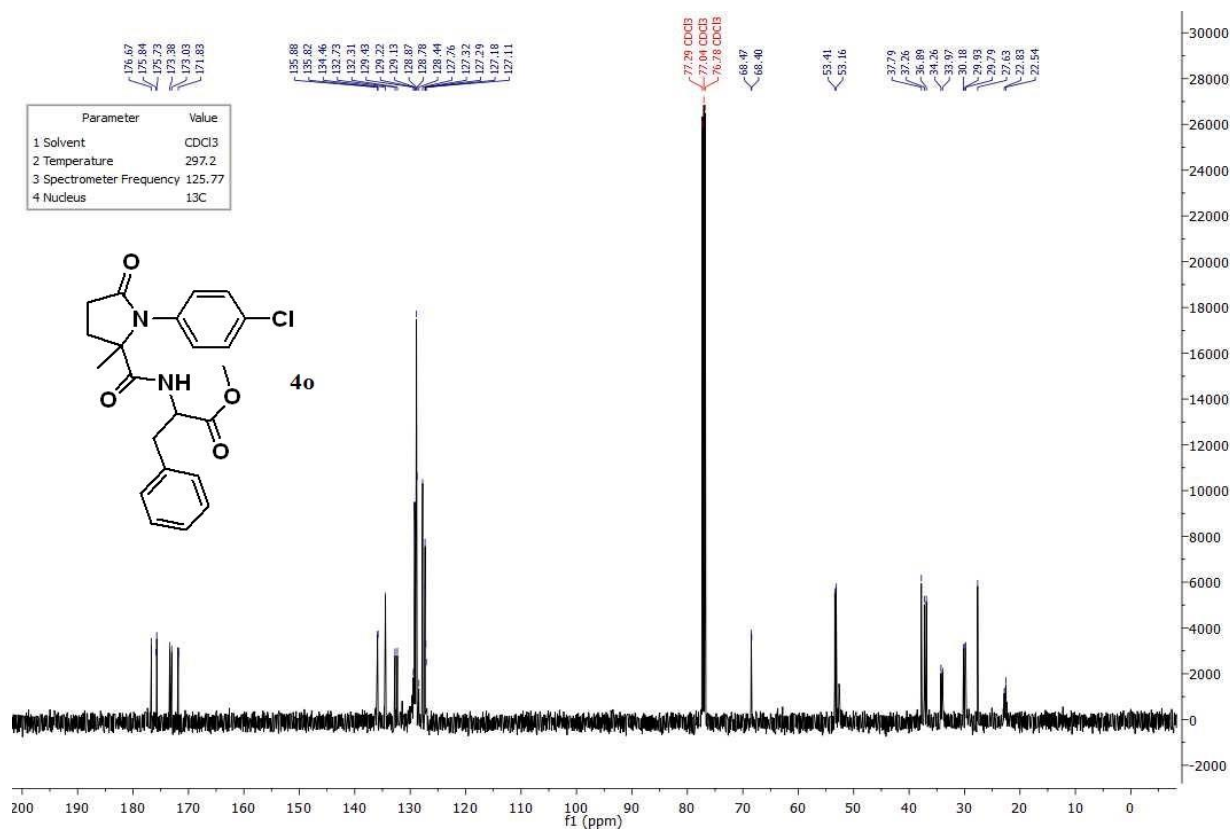
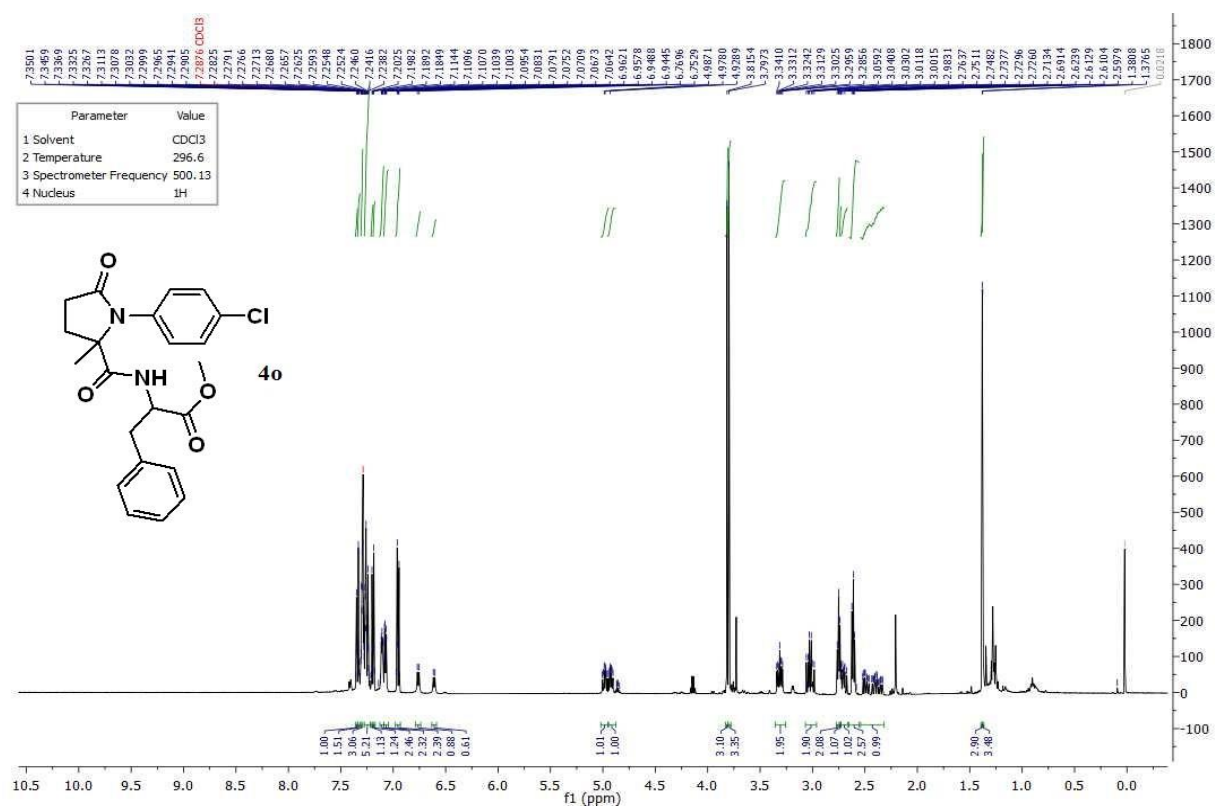
4m: Methyl (1-(4-hydroxyphenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)leucinate



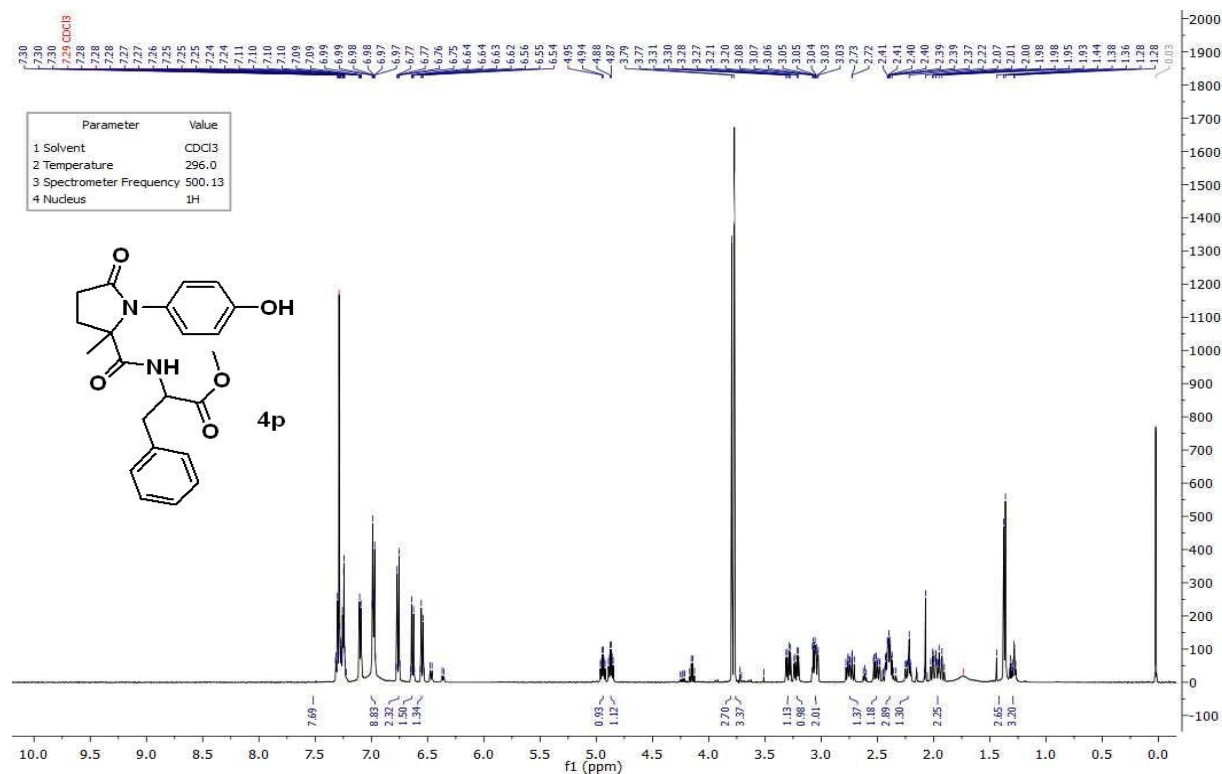
4n: Methyl (2-methyl-5-oxo-1-phenylpyrrolidine-2-carbonyl)phenylalaninate



4o: Methyl (1-(4-chlorophenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)phenylalaninate



4p: Methyl (1-(4-hydroxyphenyl)-2-methyl-5-oxopyrrolidine-2-carbonyl)phenylalaninate



X-ray crystallographyCrystal data of compound (*R**,*S**)-**4a** (CCDC- 1896942)

Empirical formula	C ₂₄ H ₂₅ N ₃ O ₄		
Formula weight	419.47		
Temperature	298 (2)		
Wavelength	0.71073		
Crystal system	triclinic		
Space group	<i>P</i> -1		
Unit cell dimensions	<i>a</i> = 9.6897(19) Å	<i>α</i> = 117.44(3) °	
	<i>b</i> = 12.831(3) Å	<i>β</i> = 98.57(3) °	
	<i>c</i> = 12.984(3) Å	<i>γ</i> = 103.49(3)°	
Volume	1330.2(8)		
Z	2		
Calculated density	1.047 Mg/m ³		
Absorption coefficient	0.072 mm ⁻¹		
F(000)	444		
Crystal size	0.500 x 0.400 x 0.200 mm ³		
Theta range for data collection	1.85 to 25.00 °		
Index ranges	-11<= <i>h</i> <=11, -15<= <i>k</i> <=13, 0<= <i>l</i> <=15		
Reflections collected	4648		
Independent reflections	4648 [R(int) = 0.0000]		
Data / restraints / parameters	4648/2/288		
Goodness-of-fit on F ²	0.936		
Final R indices [I>2σ(I)]	R1 = 0.1018, ωR2 = 0.2673		
R indices (all data)	R1 = 0.1717, ωR2 = 0.3041		
Largest diff. peak and hole	0.433 and -0.282 e×Å ³		