

## SUPPORTING INFORMATION

### **An efficient microwave-assisted synthesis of cotinine and iso-cotinine analogs from an Ugi-4CR approach**

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## Experimental

### General Information

All reagents and solvents were obtained from Sigma-Aldrich and were used without further purification. CH<sub>3</sub>CN and DMF were dried with CaH<sub>2</sub> and stored over 4 Å molecular sieves; THF was dried over sodium benzophenone ketyl under N<sub>2</sub> atmosphere prior to use. Methanol was dried over magnesium/iodide and stored over 4 Å molecular sieves. The progress of the reactions was monitored by TLC using precoated silica gel Kieselgel 60 F254 plates; the spots were visualized under UV light (254 nm), or with phosphomolibdic acid and vanillin. Flash column chromatography (FCC) was performed using Macherey-Nagel silica gel 60 (230-400 mesh). NMR spectra were collected on an Agilent MR (400 MHz) and Agilent Unity Inova (300 MHz) spectrometer, using tetramethylsilane (TMS) as internal standard. The <sup>1</sup>H NMR chemical shifts and coupling constants were determined assuming first order behavior. Multiplicity is indicated by one or more of the following: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Microwave-assisted reactions were performed using a CEM Discover Synthesis™ unit (CEM corp., Matthews, NC) with monomodal open-vessel system. Melting points (mp) were determined on a Fisher-Johns instrument and are uncorrected. High-resolution mass spectra were recorded on a Jeol SX-102A instrument. IR spectra were measured on a Perkin-Elmer Spectrum 400 FT-IR/FIR spectrometer with ATR.

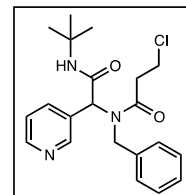
### SPECTROSCOPIC DATA OF UGI ADDUCTS

#### General procedure: Synthesis of the Ugi adducts 11a-r.

A solution of 3-chloropropionic acid **7** (1.0 eq.), 3-pyridinecarboxaldehyde **9** (1.0 eq.), amine (1.0 eq.), isocyanide (1.0 eq.) and indium (III) chloride (2 mol %) in anhydrous MeOH (0.33 M) was heated in a vial to 50 °C under microwave irradiation (100 W) for 2 hours. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography.

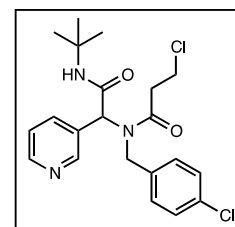
***N*-benzyl-*N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloropropanamide**

(11a). Using the general procedure, this compound was obtained as a white solid in 73% yield (1.0 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.40 (EtOAc), mp: 136-138 °C.  $^1\text{H}$



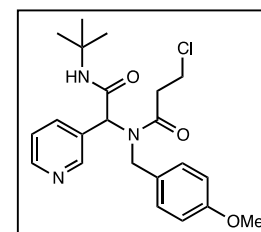
**NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.52 (s, 1H), 8.44 (d,  $J = 3.9$  Hz, 1H), 7.74 (d,  $J = 8.1$  Hz, 1H), 7.23-7.10 (m, 4H), 6.96 (d,  $J = 6.9$  Hz, 2H), 5.96 (s, 1H), 5.86 (s, 1H), 4.80 (d,  $J = 17.9$  Hz, 1H), 4.61 (d,  $J = 17.9$  Hz, 1H), 3.87-3.81 (m, 2H), 2.90-2.83 (m, 1H), 2.79-2.72 (m, 1H), 1.34 (s, 9H).  $^{13}\text{C}$  **NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 171.9, 167.8, 151.0, 149.7, 137.2, 136.6, 130.9, 128.8, 127.5, 126.0, 123.4, 60.8, 52.1, 49.9, 40.2, 36.9, 28.7. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3278, 2967, 1669, 1628, 1547, 1146, 1422, 1407, 1360, 1218, 940, 796, 711, 693, 597. **LRMS (EI)**: 252 (28), 251 (32), 197 (52), 192 (16), 161 (34), 107 (38), 91 (100). **HRMS (FAB $^+$ , M $^+$ )** calcd for  $\text{C}_{21}\text{H}_{27}\text{ClN}_3\text{O}_2$ :  $[\text{M}+1]$  388.1792, found 388.1798.

***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-(4-chlorobenzyl)-propanamide (11b).** Using the general procedure, this compound was



obtained as a white solid in 75% yield (1.0 mmol scale) after purification by flash column chromatography (50% EtOAc-hexanes),  $R_f$  0.30 (50% EtOAc-hexanes), mp: 124-126 °C.  $^1\text{H}$  **NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.55 (s, 1H), 8.47 (s, 1H), 7.73 (d,  $J = 7.8$  Hz, 1H), 7.18-7.16 (m, 3H), 6.90 (d,  $J = 8.4$  Hz, 2H), 6.01 (s, 1H), 5.86 (s, 1H), 4.77 (d,  $J = 18.1$  Hz, 1H), 4.58 (d,  $J = 18.1$  Hz, 1H), 3.89-3.78 (m, 2H), 2.86-2.78 (m, 1H), 2.75-2.67 (m, 1H), 1.34 (s, 9H).  $^{13}\text{C}$  **NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 171.8, 167.7, 150.8, 149.8, 137.2, 135.3, 133.3, 130.9, 128.9, 127.3, 123.5, 60.4, 52.2, 49.2, 40.1, 36.9, 28.7. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3224, 3052, 2964, 1677, 1646, 1555, 1424, 1364, 1222, 1197, 1090, 1014, 798, 714. **HRMS (FAB $^+$ , M $^+$ )** calcd for  $\text{C}_{21}\text{H}_{26}\text{Cl}_2\text{N}_3\text{O}_2$ :  $[\text{M}+1]$  422.1402, found 422.1396.

***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-(4-methoxybenzyl)-propanamide (11c).** Using the general procedure, this compound was

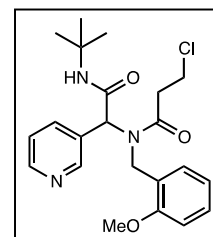


obtained as a pale yellow solid in 68% yield (1.0 mmol scale) after purification by flash column chromatography (80% EtOAc-hexanes),  $R_f$  0.35 (EtOAc), mp: 122-124 °C.  $^1\text{H}$  **NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.51 (s, 1H), 8.46 (br s, 1H), 7.74 (d,  $J = 7.9$  Hz, 1H), 7.16 (dd,  $J = 7.9, 4.7$  Hz, 1H), 6.88 (d,  $J = 8.2$  Hz, 2H), 6.73 (d,  $J = 8.5$  Hz, 2H), 5.86

(br s, 2H), 4.71 (d,  $J = 17.5$  Hz, 1H), 4.53 (d,  $J = 17.5$  Hz, 1H), 3.86-3.80 (m, 2H), 3.74 (s, 3H), 2.89-2.82 (m, 1H), 2.80-2.73 (m, 1H), 1.32 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 171.8, 167.8, 159.0, 150.8, 149.5, 137.3, 131.2, 128.4, 127.4, 123.4, 114.3, 61.1, 55.4, 52.0, 49.7, 40.2, 37.0, 28.7. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3249, 3225, 3055, 2962, 1674, 1643, 1611, 1563, 1514, 1423, 1255, 1199, 1174, 1029, 821, 719, 547. LRMS (EI): 227 (6), 192 (24), 190 (20), 161 (10), 136 (23), 121 (100), 107 (17). HRMS ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{21}\text{H}_{29}\text{ClN}_3\text{O}_3$ :  $[\text{M}+1]$  418.1897, found 418.1887.

***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-(2-methoxybenzyl)propanamide (11d).**

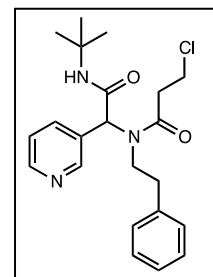
Using the general procedure, this compound was obtained as a pale yellow solid in 59% yield (1.0 mmol scale) after purification by flash column chromatography (60% EtOAc-hexanes),  $R_f$  0.30 (60% EtOAc-hexanes), mp: 120-122 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.45 (s, 1H), 8.42 (d,  $J = 3.9$  Hz, 1H), 7.75 (d,  $J = 8.0$



Hz, 1H), 7.19 (td,  $J = 8.0, 1.7$  Hz, 1H), 7.13 (dd,  $J = 8.0, 4.8$  Hz, 1H), 7.00 (dd,  $J = 7.5, 1.8$  Hz, 1H), 6.84 (td,  $J = 7.5, 1.1$  Hz, 1H), 6.76 (d,  $J = 8.1$  Hz, 1H), 5.92 (s, 1H), 5.61 (s, 1H), 4.69 (d,  $J = 17.5$  Hz, 1H), 4.60 (d,  $J = 17.5$  Hz, 1H), 3.92-3.80 (m, 2H), 3.77 (s, 3H), 2.91 (td,  $J = 6.4, 1.5$  Hz, 2H), 1.30 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 171.5, 167.7, 156.7, 150.7, 149.4, 137.2, 131.2, 129.1, 128.1, 124.1, 123.2, 120.7, 110.3, 61.9, 55.3, 51.8, 46.6, 40.2, 36.7, 28.7. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3253, 3227, 3052, 2965, 1648, 1641, 1554, 1466, 1418, 1364, 1281, 1247, 1193, 1106, 1029, 943, 801, 752, 714, 549. HRMS ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{22}\text{H}_{29}\text{ClN}_3\text{O}_3$ :  $[\text{M}+1]$  418.1897, found 418.1902.

***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-phenethylpropanamide (11e).**

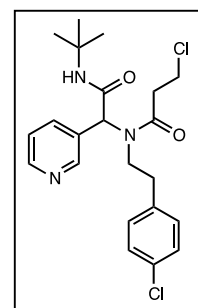
Using the general procedure, this compound was obtained as a white solid in 40% yield (1.0 mmol scale) after purification by flash column chromatography (50% EtOAc- $\text{CH}_2\text{Cl}_2$ ),  $R_f$  0.55 (50% EtOAc- $\text{CH}_2\text{Cl}_2$ ), mp: 118-120 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.65 (br s, 1H), 8.62 (d,  $J = 6.3$  Hz, 1H), 7.88 (d,  $J = 8.0$  Hz, 1H), 7.35 (dd,  $J = 8.0, 4.8$  Hz, 1H), 7.27-7.17 (m, 3H), 6.96 (d,  $J = 6.9$  Hz, 2H), 6.03 (br s, 1H), 5.93 (s, 1H), 3.86 (td,  $J = 6.4, 2.4$  Hz, 2H), 3.56 (ddd,  $J = 10.2, 6.4, 3.6$  Hz, 2H), 2.90 (dt,  $J = 16.0, 6.5$  Hz, 1H), 2.84-2.70 (m, 2H), 2.33 (ddd,  $J = 13.4, 9.8, 6.4$  Hz, 1H), 1.36 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 171.1, 167.9, 150.9, 149.8, 137.6,



137.1, 131.5, 128.9, 128.6, 127.0, 123.7, 60.8, 52.0, 48.5, 40.4, 36.4, 36.4, 28.7. **IR**  $\nu$  (cm<sup>-1</sup>): 3310, 3064, 2967, 1682, 1652, 1639, 1549, 1422, 1363, 1295, 1259, 1218, 1164, 1027, 959, 755, 709, 699, 550, 502. **LRMS (EI)**: 401 (2), 302 (14), 265 (40), 220 (28), 211 (100), 175 (74), 121 (24), 105 (54), 92 (18), 55 (30). **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>22</sub>H<sub>29</sub>ClN<sub>3</sub>O<sub>2</sub>: [M+1] 402.1948, found 402.1940.

***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-(4-chlorophenethyl)-**

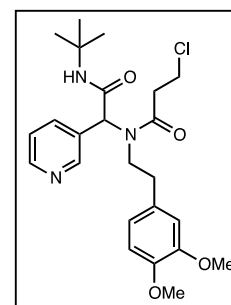
**propanamide (11f)**. Using the general procedure, this compound was obtained as a white solid in 52% yield (1.0 mmol scale) after purification by flash column chromatography (60% EtOAc-hexanes), *R<sub>f</sub>* 0.35 (60% EtOAc-hexanes), mp: 154-156 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 8.65 (d, *J* = 2.1 Hz, 1H), 8.63 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.86 (dt, *J* = 8.1, 2.0 Hz, 1H), 7.35 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.21 (d, *J* = 8.3



Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.00 (s, 1H), 5.95 (s, 1H), 3.88 (t, *J* = 6.4 Hz, 2H), 3.57-3.44 (m, 2H), 2.98-2.66 (m, 3H), 2.38-2.24 (m, 1H), 1.36 (s, 9H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 171.0, 167.9, 150.9, 149.9, 137.0, 136.1, 132.8, 131.4, 130.0, 129.0, 123.7, 60.6, 52.1, 48.2, 40.3, 36.4, 35.8, 28.7. **IR**  $\nu$  (cm<sup>-1</sup>): 3311, 2965, 1652, 1638, 1547, 1478, 1454, 1423, 1367, 1254, 1225, 1163, 1027, 847, 810, 711, 517, 425. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>22</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>: [M+1] 436.1559, found 436.1560.

***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-(3,4-dimethoxyphenethyl)-propanamide (11g)**. Using the general

procedure, this compound was obtained as a white solid in 63% yield (1.0 mmol scale) after purification by flash column chromatography (80% EtOAc-hexanes), *R<sub>f</sub>* 0.30 (60% EtOAc-hexanes), mp: 121-123 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 8.66 (s, 1H), 8.62 (d, *J* = 4.5 Hz, 1H), 7.87 (dt, *J* = 8.4, 2.0 Hz, 1H), 7.35 (ddd, *J* = 8.1, 4.8, 0.9 Hz,

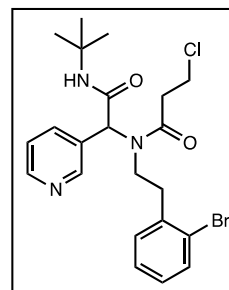


1H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.53 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.47 (d, *J* = 2.0 Hz, 1H), 6.01 (s, 1H), 5.90 (s, 1H), 3.86 (td, *J* = 6.5, 2.1 Hz, 2H), 3.83 (s, 6H), 3.61-3.47 (m, 2H), 2.93-2.65 (m, 3H), 2.31 (ddd, *J* = 13.7, 9.7, 6.2 Hz, 1H), 1.36 (s, 9H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 171.1, 168.0, 150.9, 149.8, 149.2, 148.0, 137.1, 131.5, 130.2, 123.6, 120.6, 112.0, 111.6, 61.0, 56.1, 52.0, 48.7, 40.4, 36.4, 36.0, 28.7. **IR**  $\nu$  (cm<sup>-1</sup>): 3320, 2966,

2936, 1647, 1635, 1545, 1516, 1422, 1259, 1233, 1158, 1139, 1028, 941, 802, 713, 623, 550. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>24</sub>H<sub>33</sub>ClN<sub>3</sub>O<sub>4</sub>: [M+1] 462.2160, found 462.2155.

***N*-(2-bromophenethyl)-*N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-**

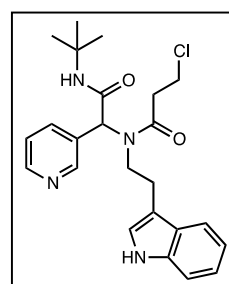
**chloropropanamide (11h).** Using the general procedure, this compound was obtained as a pale orange solid in 55% yield (1.0 mmol scale) after purification by flash column chromatography (40% EtOAc-hexanes), *R<sub>f</sub>* 0.30 (40% EtOAc-hexanes), mp: 114-116 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ (ppm): 8.68 (d, *J* = 2.1 Hz, 1H), 8.63 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.3



Hz, 1H), 7.36 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 7.19 (td, *J* = 7.5, 1.3 Hz, 1H), 7.07 (td, *J* = 7.7, 1.8 Hz, 1H), 6.91 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.04 (s, 1H), 5.97 (s, 1H), 3.92-3.85 (m, 2H), 3.65-3.47 (m, 2H), 3.09-2.87 (m, 3H), 2.52 (ddd, *J* = 13.2, 10.7, 5.7 Hz, 1H), 1.37 (s, 9H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ (ppm): 171.4, 168.0, 150.8, 149.7, 137.3, 137.2, 133.0, 131.5, 131.1, 128.8, 128.1, 124.2, 123.7, 60.8, 52.0, 46.6, 40.4, 36.7, 36.4, 28.7. **IR** ν (cm<sup>-1</sup>): 3299, 2970, 1654, 1643, 1555, 1471, 1421, 1364, 1261, 1220, 1166, 1027, 959, 755, 709, 659, 552, 444. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>22</sub>H<sub>28</sub>BrClN<sub>3</sub>O<sub>2</sub>: [M+1] 480.1053, found 480.1049.

***N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-**

**chloropropanamide (11i).** Using the general procedure, this compound was obtained as a white solid in 57% yield (1.0 mmol scale) after purification by flash column chromatography (85% EtOAc-hexanes), *R<sub>f</sub>* 0.30 (80% EtOAc-hexanes), mp: 174-176 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ (ppm): 8.66 (s, 1H), 8.60 (d, *J* = 4.7 Hz, 1H), 8.07 (br s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H),

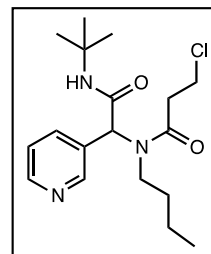


7.36-7.29 (m, 2H), 7.18 (dd, *J* = 8.3, 6.9 Hz, 1H), 7.11 (td, *J* = 7.4, 6.8, 1.1 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 6.00 (br s, 1H), 5.88 (s, 1H), 3.86 (td, *J* = 6.4, 2.7 Hz, 2H), 3.74-3.59 (m, 2H), 2.97-2.78 (m, 3H), 2.59 (ddd, *J* = 15.1, 10.1, 5.8 Hz, 1H), 1.36 (s, 9H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ (ppm): 171.3, 168.1, 150.9, 149.7, 137.1, 136.3, 131.6, 127.0, 123.7, 122.5, 122.2, 119.8, 118.4, 112.0, 111.5, 61.4, 52.0, 47.8, 40.5, 36.4, 28.8, 26.0. **IR** ν (cm<sup>-1</sup>): 3309, 2216, 2966, 1651, 1637, 1550, 1452, 1425, 1359, 1259, 1224, 1167, 1126, 1029,

819, 736, 708, 668, 567. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>24</sub>H<sub>30</sub>ClN<sub>4</sub>O<sub>2</sub>: [M+1] 441.2057, found 441.2054.

***N*-butyl-*N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloropropanamide**

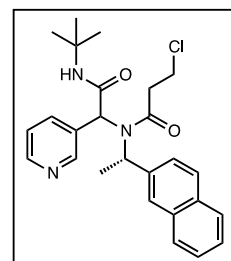
**(11j)**. Using the general procedure, this compound was obtained as a white solid in 85% yield (1.0 mmol scale) after purification by flash column chromatography (70% EtOAc-hexanes), *R<sub>f</sub>* 0.30 (70% EtOAc-hexanes), mp: 95-97 °C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.59 (br s, 2H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.32 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.13 (br s, 1H), 5.82 (s, 1H), 3.89 (t, *J* = 6.5 Hz, 2H), 3.34 (ddd, *J* = 9.7, 6.1, 3.0 Hz, 2H), 3.01-2.78



(m, 2H), 1.60-1.40 (m, 1H), 1.35 (s, 9H), 1.26-0.96 (m, 3H), 0.79 (t, *J* = 7.2 Hz, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ (ppm): 171.0, 168.1, 150.5, 149.5, 137.0, 131.6, 123.6, 61.2, 51.9, 47.1, 40.4, 36.4, 32.0, 28.7, 20.1, 13.6. **IR** ν (cm<sup>-1</sup>): 3296, 2961, 2932, 1647, 1625, 1549, 1460, 1417, 1222, 1123, 723, 713, 656, 609. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>18</sub>H<sub>29</sub>ClN<sub>3</sub>O<sub>2</sub>: [M+1] 354.1948, found 354.1939.

***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-((*S*)-1-(naphthalen-2-yl)ethyl)propanamide (11k)**. Using the general procedure, this

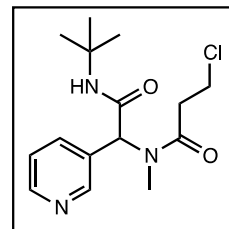
compound was obtained as a white solid in 40% yield (1.0 mmol scale) after purification by flash column chromatography (50% EtOAc-hexanes), *R<sub>f</sub>* 0.25 (50% EtOAc-hexanes), mp: 72-74 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ (ppm): 7.97 (d, *J* = 5.1 Hz, 1H), 7.76-7.61 (m, 4H), 7.53-7.28 (m, 4H), 7.20 (dt, *J* = 8.2, 2.0 Hz, 1H), 6.61 (dd, *J*



= 7.9, 4.7 Hz, 1H), 5.89 (q, *J* = 6.9 Hz, 1H), 5.24 (s, 1H), 4.39 (s, 1H), 4.15 (ddd, *J* = 16.2, 10.2, 7.0 Hz, 1H), 3.98 (dt, *J* = 11.4, 5.9 Hz, 1H), 3.50 (dt, *J* = 16.3, 7.0 Hz, 1H), 3.23 (dt, *J* = 16.4, 6.0 Hz, 1H), 1.98 (d, *J* = 6.8 Hz, 3H), 1.41-1.32 (m, 3H), 1.22 (s, 9H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ (ppm): 170.0, 168.1, 149.3, 148.4, 135.9, 133.7, 133.6, 132.0, 131.6, 130.0, 129.0, 126.7, 126.0, 125.7, 125.0, 122.7, 122.5, 62.6, 53.6, 51.7, 40.2, 36.8, 28.6, 18.1. **IR** ν (cm<sup>-1</sup>): 3426, 3212, 3049, 2969, 1677, 1634, 1509, 1450, 1423, 1364, 1221, 1150, 803, 780, 708. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>26</sub>H<sub>31</sub>ClN<sub>3</sub>O<sub>2</sub>: [M+1] 452.2105, found 452.2114.

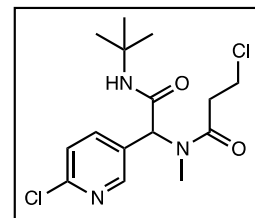
***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-methylpropanamide**

(11l). Using the general procedure, this compound was obtained as a pale yellow solid in 62% yield (1.0 mmol scale) after purification by flash column chromatography (60% EtOAc-hexanes),  $R_f$  0.30 (60% EtOAc-hexanes), mp: 119-121 °C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.59 (dd,  $J = 4.8, 1.6$  Hz, 1H), 8.56 (d,  $J = 2.3$  Hz, 1H), 7.74 (dddd,  $J = 8.0, 2.4, 1.7, 0.7$  Hz, 1H), 7.33 (ddd,  $J = 8.0, 4.8, 0.9$  Hz, 1H), 6.24 (s, 1H), 5.83 (br s, 1H), 3.87 (t,  $J = 6.8$  Hz, 2H), 2.99-2.80 (m, 2H), 2.92 (s, 3H), 1.37 (s, 9H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 171.1, 167.7, 150.5, 149.7, 136.9, 131.2, 123.6, 58.5, 52.1, 40.0, 36.5, 32.6, 28.8. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3213, 3042, 2962, 1685, 1629, 1561, 1478, 1424, 1405, 1361, 1317, 1223, 1121, 800, 711, 644, 593, 555. **HRMS** ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{15}\text{H}_{23}\text{ClN}_3\text{O}_2$ :  $[\text{M}+1]$  312.1479, found 312.1482.



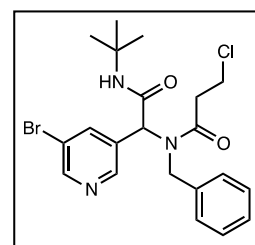
***N*-(2-(*tert*-butylamino)-1-(6-chloropyridin-3-yl)-2-oxoethyl)-3-chloro-*N*-methylpropanamide (11m).**

Using the general procedure, this compound was obtained as a white solid in 36% yield (1.0 mmol scale) after purification by flash column chromatography (40% EtOAc-hexanes),  $R_f$  0.30 (40% EtOAc-hexanes), mp: 114-116 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.35 (d,  $J = 2.4$  Hz, 1H), 7.73 (ddd,  $J = 8.4, 2.7, 0.7$  Hz, 1H), 7.35 (dd,  $J = 8.4, 0.8$  Hz, 1H), 6.21 (s, 1H), 5.84 (br s, 1H), 3.87 (td,  $J = 6.6, 1.6$  Hz, 2H), 2.98-2.81 (m, 2H), 2.92 (s, 3H), 1.37 (s, 9H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 171.3, 167.3, 151.6, 150.4, 139.8, 130.1, 124.4, 57.8, 52.2, 40.1, 36.5, 32.6, 28.8. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3300, 2975, 2952, 1687, 1627, 1585, 1548, 1459, 1418, 1402, 1386, 1361, 1329, 1268, 1221, 1103, 956, 941, 808, 672, 630. **HRMS** ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{15}\text{H}_{22}\text{Cl}_2\text{N}_3\text{O}_2$ :  $[\text{M}+1]$  346.1089, found 346.1083.



***N*-benzyl-*N*-(1-(5-bromopyridin-3-yl)-2-(*tert*-butylamino)-2-oxoethyl)-3-chloro-**

**propanamide (11n).** Using the general procedure, this compound was obtained as a white solid in 50% yield (1.0 mmol scale) after purification by flash column chromatography (80% EtOAc-hexanes),  $R_f$  0.40 (80% EtOAc-hexanes), mp: 172-173 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.48 (d,  $J = 2.2$  Hz, 1H), 8.44 (d,  $J = 2.0$  Hz, 1H), 7.87 (t,  $J = 2.1$  Hz, 1H), 7.27-7.17 (m, 3H), 6.99 (d,  $J = 6.6$  Hz, 2H), 5.91 (br s, 1H),

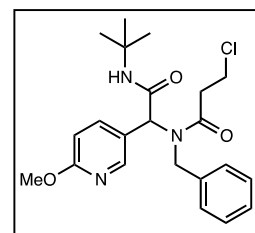




5.89 (s, 1H), 4.82 (d,  $J = 17.8$  Hz, 1H), 4.61 (d,  $J = 17.7$  Hz, 1H), 3.93-3.80 (m, 2H), 2.93-2.77 (m, 2H), 1.34 (s, 9H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 171.8, 167.1, 150.7, 148.8, 139.9, 136.3, 132.6, 128.9, 127.8, 126.1, 120.6, 60.3, 52.2, 50.1, 40.3, 36.8, 28.7. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3287, 3053, 2964, 1670, 1627, 1549, 1449, 1433, 1413, 1359, 1235, 1216, 1102, 1019, 745, 736, 723, 695, 651, 630, 516. **LRMS (EI)**: 368 (6), 367 (5), 277 (46), 275 (44), 272 (12), 241 (26), 239 (27), 187 (18), 185 (20), 91 (100). **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for  $\text{C}_{21}\text{H}_{26}\text{BrClN}_3\text{O}_2$ :  $[\text{M}+1]$  466.0897, found 466.0903.

***N*-benzyl-*N*-(2-(*tert*-butylamino)-1-(6-methoxypyridin-3-yl)-2-oxoethyl)-3-chloro-propanamide (11o)**. Using the general procedure, this compound

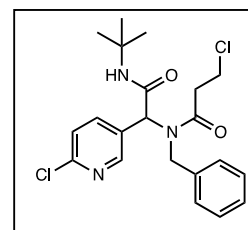
was obtained as a white solid in 67% yield (1.0 mmol scale) after purification by flash column chromatography (50% EtOAc-hexanes),  $R_f$  0.30 (50% EtOAc-hexanes), mp: 146-147 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.07 (d,  $J = 2.5$  Hz, 1H), 7.59 (dd,  $J = 8.6$ ,



2.6 Hz, 1H), 7.25-7.11 (m, 3H), 6.97 (d,  $J = 7.1$  Hz, 2H), 6.57 (d,  $J = 8.6$  Hz, 1H), 5.88 (s, 1H), 5.71 (br s, 1H), 4.77 (d,  $J = 17.9$  Hz, 1H), 4.55 (d,  $J = 17.9$  Hz, 1H), 3.90-3.77 (m, 2H), 3.86 (s, 3H), 2.89-2.81 (m, 1H), 2.76-2.69 (m, 1H), 1.33 (s, 9H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 171.8, 168.3, 164.2, 148.5, 140.0, 137.0, 128.7, 127.4, 126.1, 123.5, 110.9, 60.4, 53.7, 52.0, 49.7, 40.2, 37.0, 28.7. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3283, 3061, 2959, 2972, 1667, 1632, 1607, 1546, 1496, 1448, 1393, 1358, 1280, 1234, 1165, 1018, 537, 826, 727, 694, 591, 524. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for  $\text{C}_{22}\text{H}_{29}\text{ClN}_3\text{O}_3$ :  $[\text{M}+1]$  418.1897, found 418.1891.

***N*-benzyl-*N*-(2-(*tert*-butylamino)-1-(6-chloropyridin-3-yl)-2-oxoethyl)-3-chloro**

**propanamide (11p)**. Using the general procedure, this compound was obtained as a white solid in 57% yield (1.0 mmol scale) after purification by flash column chromatography (30% EtOAc-hexanes),  $R_f$  0.45 (30% EtOAc-hexanes), mp: 140-142 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.29 (d,  $J = 2.5$  Hz, 1H), 7.71 (dd,  $J = 8.3$ ,

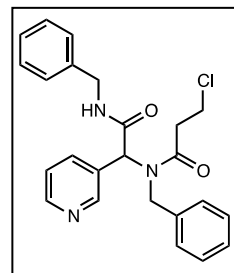


2.6 Hz, 1H), 7.26-7.20 (m, 3H), 7.15 (d,  $J = 8.3$  Hz, 1H), 6.98 (dd,  $J = 7.0, 2.2$  Hz, 2H), 5.88 (br s, 1H), 5.86 (s, 1H), 4.79 (d,  $J = 17.6$  Hz, 1H), 4.59 (d,  $J = 17.7$  Hz, 1H), 3.92-3.79 (m, 2H), 2.92-2.74 (m, 2H), 1.33 (s, 9H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 171.7, 167.2, 151.4, 150.7, 139.9, 136.2, 129.8, 128.8, 127.7, 126.0, 123.9, 60.1, 52.0, 50.0, 40.1, 36.7, 28.5. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3273, 3066, 2968, 2968, 2919, 1671, 1632, 1554, 1447, 1434, 1414,

1221, 1232, 1105, 720, 695. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>21</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>: [M+1] 422,1402, found 422.1403.

***N*-benzyl-*N*-(2-(benzylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloropropanamide**

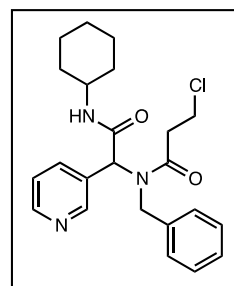
**(11q)**. Using the general procedure, this compound was obtained as a white solid in 66% yield (1.0 mmol scale) after purification by flash column chromatography (60% EtOAc-hexanes), *R<sub>f</sub>* 0.30 (60% EtOAc-hexanes), mp: 80-82 °C. (Due to dynamic effects <sup>1</sup>H NMR spectra for this compound was obtained as a mixture of rotamers. Eventhough NMR experiments at variable temperature were conducted;



unsatisfactory results were obtained and the chemical shifts for the different signals are reported as intervals). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C) δ (ppm): 9.51-8.32 (m, 3H) 8.13-6.24 (m, 11H), 6.07-5.49 (m, 1H), 5.08-4.19 (m, 5H), 3.86-2.68 (m, 4H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 171.9, 168.5, 150.9, 149.6, 137.7, 137.5, 136.3, 130.7, 128.8, 128.6, 128.1, 127.9, 127.6, 126.1, 123.5, 60.7, 50.2, 43.9, 40.1, 36.9. **IR** ν (cm<sup>-1</sup>): 3210, 3029, 2927, 1645, 1527, 1496, 1452, 1423, 1359, 1234, 1200, 1081, 1028, 730, 696, 624, 604. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>24</sub>H<sub>25</sub>ClN<sub>3</sub>O<sub>2</sub>: [M+1] 422.1635, found 422.1645.

***N*-benzyl-3-chloro-*N*-(2-(cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl)propanamide**

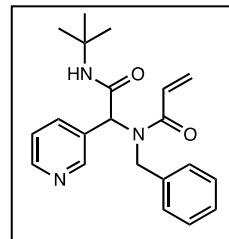
**(11r)**. Using the general procedure, this compound was obtained as a white solid in 78% yield (1.0 mmol scale) after purification by flash column chromatography (70% EtOAc-hexanes), *R<sub>f</sub>* 0.40 (70% EtOAc-hexanes), mp: 108-110 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 8.51 (s, 1H), 8.44 (d, *J* = 3.9 Hz, 1H), 7.76 (s, 1H), 7.25-7.11 (m, 4H), 6.98 (d, *J* = 6.9 Hz, 2H), 5.96 (s, 1H), 5.93 (br s, 1H), 4.78 (d, *J* = 17.8 Hz,



1H), 4.60 (d, *J* = 17.8 Hz, 1H), 3.83 (t, *J* = 6.5 Hz, 2H), 3.80-3.72 (m, 1H), 2.92-2.67 (m, 2H), 1.94-1.80 (m, 2H), 1.70-1.57 (m, 3H), 1.38-1.27 (m, 2H), 1.18-1.03 (m, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 171.7, 167.3, 150.7, 149.4, 137.3, 136.3, 130.8, 128.7, 127.4, 125.9, 123.3, 60.6, 50.0, 48.8, 40.1, 36.8, 32.8, 32.7, 25.4, 24.7, 24.7. **IR** ν (cm<sup>-1</sup>): 3269, 3085, 2963, 2853, 1639, 1560, 1419, 1363, 1196, 947, 715, 567, 536. **LRMS (EI)**: 251 (32), 218 (24), 197 (42), 161 (24), 107 (28), 91 (100), 55 (25). **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>23</sub>H<sub>29</sub>ClN<sub>3</sub>O<sub>2</sub>: [M+1] 414.1948, found 414.1960.

***N*-benzyl-*N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)acrylamide (16).** A

solution of acrylic acid **17** (1.0 eq.), 3-pyridinecarboxaldehyde **9** (1.0 eq.), benzylamine **10** (1.0 eq.), *tert*-butylisocyanide **8** (1.0 eq.) and indium(III) chloride (2 mol %) in anhydrous MeOH (0.33 M) was



heated in a vial to 50 °C under microwave irradiation (100 W) for 2 hours. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography to give a pale yellow solid in 49% yield (1.0 mmol scale) (80% EtOAc-Hexanes),  $R_f$  0.16 (80% EtOAc-Hexanes), mp: 55-57 °C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 8.52 (d,  $J$  = 2.4 Hz, 1H), 8.43 (d,  $J$  = 4.7 Hz, 1H), 7.73 (d,  $J$  = 8.0 Hz, 1H), 7.25-7.07 (m, 4H), 6.96 (d,  $J$  = 7.0 Hz, 2H), 6.47 (d,  $J$  = 4.9 Hz, 1H), 6.46 (br s, 1H), 6.03 (br s, 2H), 5.76-5.67 (m, 1H), 4.86 (d,  $J$  = 17.9 Hz, 1H), 4.68 (d,  $J$  = 17.2 Hz, 1H), 1.32 (s, 9H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 168.0, 150.9, 149.5, 137.3, 137.1, 131.1, 130.2, 128.7, 127.9, 127.4, 126.1, 123.3, 60.6, 52.0, 49.8, 28.7. **IR**  $\nu$  (cm<sup>-1</sup>): 3315, 3060, 2966, 2919, 1680, 1644, 1604, 1546, 1452, 1420, 1362, 1256, 1220, 1196, 1028, 977, 943, 797, 729, 712, 695, 624, 570, 458. **HRMS** (FAB<sup>+</sup>, M<sup>+</sup>) calcd for C<sub>21</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub>: [M+1] 352.2025, found 352.2025.

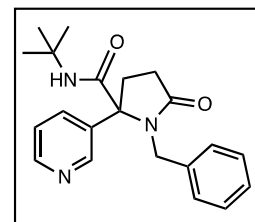
### SPECTROSCOPY DATA OF COTININE ANALOGS

#### General procedure: Synthesis of the cotinine analogs 12a-r.

To a solution of the corresponding Ugi adduct **11a-r** (1.0 equiv) in anhydrous CH<sub>3</sub>CN (0.1 M) was added potassium *tert*-butoxide at once (2.0 equiv). The resulting mixture was heated in a vial to 110 °C under microwave irradiation (100 W) for 2 hours. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography.

#### **1-benzyl-*N*-(*tert*-butyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12a).** Using

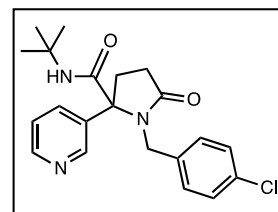
the general procedure, this compound was obtained as a white solid in 78% yield (0.1 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.16 (EtOAc), mp: 130-132 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 8.62 (d,  $J$  = 2.0 Hz, 1H), 8.59 (d,  $J$  = 4.7 Hz, 1H), 7.67 (ddd,  $J$  = 8.2, 2.5, 1.6 Hz, 1H), 7.29 (dd,  $J$  =



8.3, 4.6 Hz, 1H), 7.27-7.24 (m, 3H), 7.14 (dd,  $J = 6.8, 2.9$  Hz, 2H), 5.53 (br s, 1H), 4.71 (d,  $J = 15.2$  Hz, 1H), 3.78 (d,  $J = 15.1$  Hz, 1H), 2.90-2.76 (m, 1H), 2.66-2.47 (m, 3H), 1.06 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 176.6, 169.9, 150.0, 149.7, 137.5, 136.1, 134.6, 129.3, 128.8, 128.2, 123.4, 73.6, 51.9, 45.8, 35.6, 29.5, 28.1. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3299, 3039, 2967, 1669, 1528, 1435, 1406, 1275, 1218, 1153, 1087, 970, 836, 781, 713, 698, 668. HRMS ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_2$ :  $[\text{M}+1]$  352.2025, found 352.2034.

***N*-(*tert*-butyl)-1-(4-chlorobenzyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide**

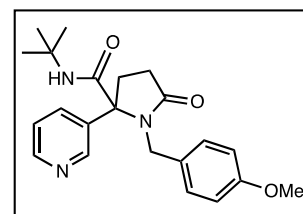
(12b). Using the general procedure, this compound was obtained as a pale yellow solid in 82% yield (0.1 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.30 (EtOAc), mp: 144-146 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.61-8.56 (m, 2H), 7.61 (ddd,  $J = 8.1, 2.5, 1.6$  Hz, 1H), 7.30-7.23



(m, 1H), 7.20 (d,  $J = 8.6$  Hz, 2H), 7.03 (d,  $J = 8.6$  Hz, 2H), 5.47 (br s, 1H), 4.54 (d,  $J = 15.3$  Hz, 1H), 4.00 (d,  $J = 15.3$  Hz, 1H), 2.85-2.77 (m, 1H), 2.64-2.50 (m, 3H), 1.16 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 176.4, 169.7, 149.8, 149.8, 135.9, 134.4, 133.8, 129.9, 129.1, 123.5, 73.3, 52.2, 45.2, 34.9, 29.4, 28.3. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3340, 2959, 2924, 1687, 1667, 1519, 1492, 1389, 1277, 1227, 1148, 1088, 1016, 965, 889, 836, 810, 797, 711, 616. HRMS ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{21}\text{H}_{25}\text{ClN}_3\text{O}_2$ :  $[\text{M}+1]$  386.1635, found 386.1634.

***N*-(*tert*-butyl)-1-(4-methoxybenzyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide**

(12c). Using the general procedure, this compound was obtained as a white solid in 77% yield (0.1 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.20 (EtOAc), mp: 108-110 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.61 (br s, 1H), 8.58 (d,  $J = 4.6$  Hz, 1H), 7.66 (ddd,  $J = 8.1, 2.5, 1.6$  Hz,

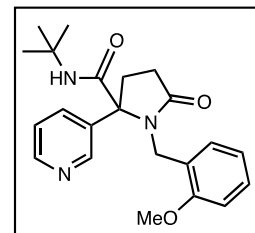


1H), 7.30 (ddd,  $J = 8.2, 4.7, 0.8$  Hz, 1H), 7.06 (d,  $J = 8.6$  Hz, 2H), 6.77 (d,  $J = 8.7$  Hz, 2H), 5.58 (br s, 1H), 4.65 (d,  $J = 15.0$  Hz, 1H), 3.75 (s, 3H), 3.64 (d,  $J = 15.0$  Hz, 1H), 2.84-2.76 (m, 1H), 2.61-2.49 (m, 3H), 1.07 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 176.6, 170.0, 159.6, 150.0, 149.6, 136.2, 134.6, 130.3, 129.5, 123.5, 114.6, 73.6, 55.5, 51.8, 45.1, 35.8, 29.6, 28.2. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3397, 3321, 2967, 2837, 1670, 1511, 1455, 1391, 1244, 1175,

1028, 834, 812, 749, 712, 665, 514. **LRMS (EI)**: 381 (2), 281 (30), 121 (100). **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>22</sub>H<sub>28</sub>N<sub>3</sub>O<sub>3</sub>: [M+1] 382.2131, found 382.2122.

***N*-(*tert*-butyl)-1-(2-methoxybenzyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide**

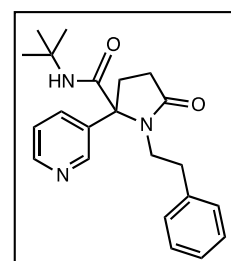
**(12d)**. Using the general procedure (Reaction time of cyclization: 10 minutes), this compound was obtained as a pale yellow solid in 90% yield (0.2 mmol scale) after purification by flash column chromatography (EtOAc), *R<sub>f</sub>* 0.25 (EtOAc), mp: 74-76 °C. **<sup>1</sup>H NMR**



(300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.65 (dd, *J* = 2.6, 0.9 Hz, 1H), 8.57 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.71 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1H), 7.43 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.32-7.26 (m, 1H), 7.25-7.20 (m, 1H), 6.92 (td, *J* = 7.5, 1.1 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 5.66 (br s, 1H), 4.67 (d, *J* = 15.3 Hz, 1H), 3.96 (d, *J* = 15.3 Hz, 1H), 3.66 (s, 3H), 2.96-2.79 (m, 1H), 2.71-2.38 (m, 3H), 1.02 (s, 9H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ (ppm): 176.9, 169.7, 157.0, 150.0, 149.3, 136.1, 135.1, 130.9, 129.5, 125.3, 123.0, 121.4, 110.5, 73.6, 55.0, 51.6, 39.3, 36.2, 29.6, 28.0. **IR** ν (cm<sup>-1</sup>): 3306, 2972, 2928, 1688, 1523, 1493, 1462, 1420, 1387, 1361, 1280, 1242, 1218, 1170, 1113, 1027, 808, 753, 722, 580. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>22</sub>H<sub>28</sub>N<sub>3</sub>O<sub>3</sub>: [M+1] 382.2131, found 382.2127.

***N*-(*tert*-butyl)-5-oxo-1-phenethyl-2-(pyridin-3-yl)pyrrolidine-2-carboxamide** (12e).

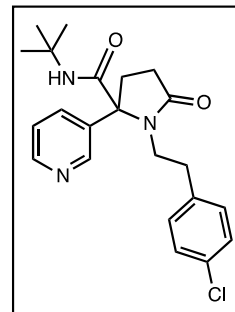
Using the general procedure, this compound was obtained as a pale yellow solid in 75% yield (0.1 mmol scale) after purification by flash column chromatography (EtOAc), *R<sub>f</sub>* 0.25 (EtOAc), mp: 68-70 °C. **<sup>1</sup>H NMR**



(400 MHz, CDCl<sub>3</sub>) δ (ppm): δ 8.66 (br s, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.37 (br s, 1H), 7.26-7.13 (m, 3H), 6.98 (d, *J* = 6.8 Hz, 2H), 5.60 (br s, 1H), 3.41 (ddd, *J* = 13.3, 11.8, 5.1 Hz, 1H), 3.24 (ddd, *J* = 13.5, 11.8, 5.2 Hz, 1H), 2.88-2.77 (m, 2H), 2.60-2.46 (m, 3H), 2.38 (td, *J* = 12.2, 5.2 Hz, 1H), 1.40 (s, 9H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ (ppm): 175.5, 170.1, 149.7, 149.5, 138.4, 135.7, 135.4, 128.8, 128.7, 126.7, 123.7, 73.2, 52.6, 45.0, 34.5, 33.8, 29.7, 28.8. **IR** ν (cm<sup>-1</sup>): 3325, 3159, 2973, 1686, 1652, 1516, 1392, 1357, 1222, 1150, 1001, 758, 715, 704, 645, 581, 464. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>22</sub>H<sub>28</sub>N<sub>3</sub>O<sub>2</sub>: [M+1] 366.2182, found 366.2181.

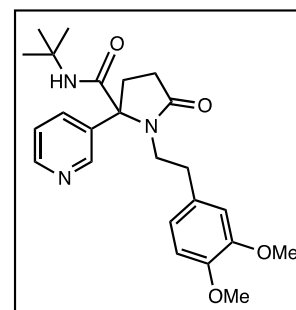
***N*-(*tert*-butyl)-1-(4-chlorophenethyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide**

(12f). Using the general procedure (Reaction time for cyclization: 10 minutes), this compound was obtained as a white solid in 87% yield (0.2 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.20 (EtOAc), mp: 159-161 °C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.67-8.62 (m, 2H), 7.64 (ddd,  $J = 8.1, 2.5, 1.6$  Hz, 1H), 7.36 (ddd,  $J = 8.0, 4.8, 0.8$  Hz, 1H), 7.18 (d,  $J = 8.4$  Hz, 2H), 6.91 (d,  $J = 8.4$  Hz, 2H), 5.55 (br s, 1H), 3.40 (ddd,  $J = 13.5, 11.4, 5.1$  Hz, 1H), 3.21 (ddd,  $J = 13.5, 11.3, 5.5$  Hz, 1H), 2.89-2.67 (m, 2H), 2.62-2.44 (m, 3H), 2.43-2.27 (m, 1H), 1.40 (s, 9H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 175.5, 170.0, 150.0, 149.5, 136.8, 135.4, 135.2, 132.4, 130.1, 128.8, 123.7, 73.0, 52.6, 44.7, 33.8, 33.6, 29.6, 28.8. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3354, 2972, 2934, 1685, 1656, 1492, 1508, 1389, 1366, 1359, 1329, 1222, 1151, 1091, 1017, 850, 812, 727, 717, 621, 516. **HRMS** ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{22}\text{H}_{27}\text{ClN}_3\text{O}_2$ :  $[\text{M}+1]$  400.1792, found 400.1795.



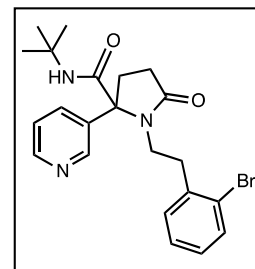
***N*-(*tert*-butyl)-1-(3,4-dimethoxyphenethyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12g).**

Using the general procedure (Reaction time of cyclization: 10 minutes), this compound was obtained as a pale yellow solid in 58% yield (0.2 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.20 (EtOAc), mp: 86-88 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.68-8.65 (m, 1H), 8.64 (dd,  $J = 4.8, 1.6$  Hz, 1H), 7.67 (ddd,  $J = 8.1, 2.6, 1.6$  Hz, 1H), 7.35 (ddd,  $J = 8.1, 4.8, 0.8$  Hz, 1H), 6.72 (d,  $J = 7.8$  Hz, 1H), 6.50 (s, 1H), 6.49 (d,  $J = 7.5$  Hz, 1H), 5.62 (br s, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.41 (ddd,  $J = 13.5, 11.4, 5.2$  Hz, 1H), 3.21 (ddd,  $J = 13.6, 11.5, 5.3$  Hz, 1H), 2.89-2.71 (m, 2H), 2.63-2.46 (m, 3H), 2.39-2.27 (m, 1H), 1.40 (s, 9H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 175.5, 170.1, 149.8, 149.7, 149.1, 147.8, 135.6, 135.2, 131.0, 123.6, 120.6, 112.0, 111.4, 73.2, 56.0, 56.0, 52.5, 45.1, 34.1, 33.7, 29.7, 28.8. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3412, 3316, 3103, 2998, 2979, 1688, 1654, 1538, 1515, 1456, 1389, 1349, 1259, 1234, 1147, 1022, 858, 827, 712, 634, 620, 565, 456. **HRMS** ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_4$ :  $[\text{M}+1]$  426.2393, found 426.2397.



**1-(2-bromophenethyl)-*N*-(*tert*-butyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide**

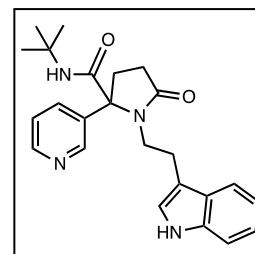
(**12h**). Using the general procedure (Reaction time of cyclization: 10 minutes), this compound was obtained as a pale yellow solid in 85% yield (0.1 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.25 (EtOAc), mp: 151-153 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.66 (dd,  $J = 2.6, 0.8$  Hz, 1H), 8.62 (dd,  $J = 4.8, 1.6$  Hz, 1H), 7.68 (ddd,  $J = 8.1, 2.6, 1.6$  Hz, 1H),



7.41 (dd,  $J = 7.9, 1.2$  Hz, 1H), 7.33 (ddd,  $J = 8.1, 4.8, 0.8$  Hz, 1H), 7.23-7.11 (m, 2H), 7.04 (ddd,  $J = 7.9, 7.0, 2.1$  Hz, 1H), 5.63 (br s, 1H), 3.45 (ddd,  $J = 13.3, 11.0, 4.7$  Hz, 1H), 3.20 (ddd,  $J = 13.2, 10.9, 5.8$  Hz, 1H), 2.98 (ddd,  $J = 12.7, 10.9, 4.7$  Hz, 1H), 2.83-2.69 (m, 1H), 2.69-2.50 (m, 4H), 1.41 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 175.7, 170.3, 149.8, 138.0, 135.9, 134.8, 132.9, 131.1, 128.5, 127.8, 124.4, 123.7, 73.2, 52.6, 42.9, 34.6, 34.2, 29.8, 28.8. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3565, 3320, 2971, 2934, 1688, 1644, 1520, 1452, 1396, 1357, 1219, 1151, 1122, 1025, 819, 760, 712, 639, 448. HRMS ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{22}\text{H}_{27}\text{BrN}_3\text{O}_2$ :  $[\text{M}+1]$  444.1287, found 444.1293.

**1-(2-(1*H*-indol-3-yl)ethyl)-*N*-(*tert*-butyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide**

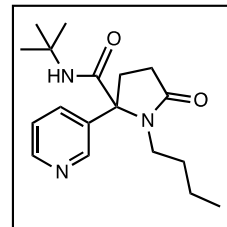
(**12i**). Using the general procedure (Reaction time of cyclization: 10 minutes), this compound was obtained as a pale yellow solid in 86% yield (0.1 mmol scale) after purification by flash column chromatography (5% MeOH-EtOAc),  $R_f$  0.35 (5% MeOH-EtOAc), mp: 214-216 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm):



8.71-8.68 (m, 1H), 8.62 (dd,  $J = 4.8, 1.6$  Hz, 1H), 8.19 (br s, 1H), 7.68 (ddd,  $J = 8.1, 2.6, 1.6$  Hz, 1H), 7.37-7.28 (m, 3H), 7.15 (ddd,  $J = 8.3, 7.0, 1.2$  Hz, 1H), 7.06 (ddd,  $J = 7.9, 7.0, 1.1$  Hz, 1H), 6.91 (d,  $J = 2.4$  Hz, 1H), 5.71 (br s, 1H), 3.51-3.32 (m, 2H), 3.04-2.92 (m, 1H), 2.85-2.74 (m, 1H), 2.66-2.50 (m, 4H), 1.33 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 175.8, 170.4, 149.8, 149.7, 136.3, 135.8, 135.1, 127.2, 123.5, 122.3, 122.0, 119.6, 118.9, 112.6, 111.2, 73.3, 52.4, 43.7, 34.2, 29.8, 28.7, 24.2. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3308, 2964, 2927, 1689, 1649, 1523, 1450, 1391, 1361, 1222, 1232, 1152, 1143, 1096, 1009, 835, 757, 748, 712, 638, 611, 557, 427. HRMS ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{24}\text{H}_{29}\text{N}_4\text{O}_2$ :  $[\text{M}+1]$  405.2291, found 405.2290.

***N*-(*tert*-butyl)-1-butyl-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12j).** Using

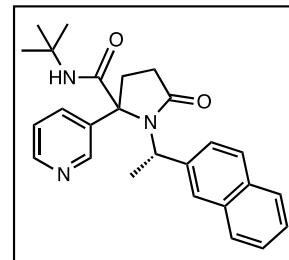
the general procedure (Reaction time of cyclization: 10 minutes), this compound was obtained as a pale yellow solid in 79% yield (0.2 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.20 (EtOAc), mp: 54-56 °C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.63-8.59 (m, 2H), 7.66 (ddd,  $J = 8.1, 2.5, 1.6$  Hz, 1H), 7.35 (ddd,  $J =$



8.1, 4.8, 0.9 Hz, 1H), 5.62 (br s, 1H), 3.23-3.01 (m, 2H), 2.90-2.78 (m, 1H), 2.58-2.33 (m, 3H), 1.47-1.32 (m, 2H), 1.40 (s, 9H), 1.20-1.10 (m, 2H), 0.82-0.72 (m, 3H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 175.6, 170.0, 149.8, 149.5, 135.5, 123.5, 73.2, 52.5, 43.1, 34.0, 30.5, 29.6, 28.7, 20.5, 13.7. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3299, 3323, 2964, 2933, 1661, 1534, 1454, 1393, 1365, 1276, 1219, 1132, 1025, 714, 682, 625, 565, 493. **HRMS** ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{18}\text{H}_{28}\text{N}_3\text{O}_2$ :  $[\text{M}+1]$  318.2182, found 318.2184.

***N*-(*tert*-butyl)-1-((*S*)-1-(naphthalen-2-yl)ethyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12k).** Using the general procedure, this compound

was obtained as a pale yellow oil in 36% yield (0.2 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.30 (EtOAc),  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): (Diastereoisomeric mixture) 8.85 (dd,  $J = 2.7, 0.8$  Hz, 1H), 8.71



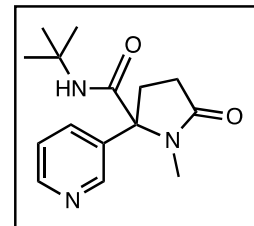
(dd,  $J = 4.8, 1.6$  Hz, 1H), 8.44 (dd,  $J = 2.7, 0.9$  Hz, 1H), 8.39 (dd,  $J = 7.3, 1.2$  Hz, 1H), 7.94 (dd,  $J = 4.8, 1.6$  Hz, 1H), 7.88 (tdd,  $J = 5.9, 2.8, 1.3$  Hz, 2H), 7.83-7.78 (m, 12H), 7.76-7.72 (m, 1H), 7.66 (ddd,  $J = 7.5, 4.2, 1.1$  Hz, 1H), 7.62-7.55 (m, 6H), 7.52-7.44 (m, 15H), 7.36 (dddd,  $J = 9.2, 6.8, 5.1, 2.2$  Hz, 2H), 7.30 (ddd,  $J = 8.1, 2.6, 1.6$  Hz, 1H), 6.56 (ddd,  $J = 8.2, 4.8, 0.9$  Hz, 1H), 5.86 (br s, 1H), 5.80 (br s, 1H), 5.26 (q,  $J = 7.2$  Hz, 1H), 4.83 (q,  $J = 7.1$  Hz, 1H), 2.89 (d,  $J = 6.9$  Hz, 1H), 2.84-2.60 (m, 7H), 1.88 (d,  $J = 7.2$  Hz, 2H), 1.60 (d,  $J = 7.1$  Hz, 3H), 1.34 (s, 6H), 0.56 (s, 9H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 196.9, 177.5, 176.6, 170.5, 170.1, 150.2, 150.0, 149.8, 148.8, 139.0, 138.6, 137.8, 136.5, 136.4, 135.9, 134.1, 133.4, 132.5, 130.3, 130.2, 129.7, 129.5, 129.1, 128.9, 128.4, 128.0, 127.1, 126.8, 126.6, 126.5, 126.1, 125.6, 125.5, 125.4, 123.5, 122.0, 121.7, 121.6, 77.4, 75.8, 74.8, 52.4, 51.8, 51.2, 36.5, 35.6, 35.0, 31.4, 31.2, 28.7, 27.5, 23.4, 21.0, 20.2. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3566, 3391, 3058, 2969, 1967, 1655, 1655, 1597, 1577, 1511, 1446, 1317, 1275, 1175, 1150, 941,



919, 778, 763, 696, 637. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>26</sub>H<sub>30</sub>N<sub>3</sub>O<sub>2</sub>: [M+1] 416.2338, found 416.2345.

***N*-(*tert*-butyl)-1-methyl-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12l).** Using

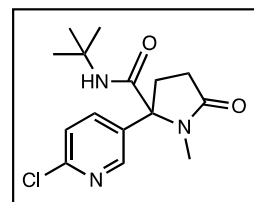
the general procedure (Reaction time of cyclization: 10 minutes), this compound was obtained as a white solid in 76% yield (0.2 mmol scale) after purification by flash column chromatography (EtOAc), *R<sub>f</sub>* 0.20 (EtOAc), mp: 92-94 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ (ppm): 8.65-8.56 (m, 2H), 7.67 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1H), 7.36



(ddd, *J* = 8.1, 4.8, 0.8 Hz, 1H), 5.59 (br s, 1H), 2.82 (ddd, *J* = 12.8, 8.9, 6.3 Hz, 1H), 2.76 (s, 3H), 2.53 (dddd, *J* = 11.8, 8.8, 6.7, 0.8 Hz, 2H), 2.45-2.29 (m, 1H), 1.40 (s, 9H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ (ppm): 175.7, 169.5, 149.7, 148.9, 135.2, 134.9, 123.6, 72.7, 52.4, 34.2, 29.6, 28.8, 28.2. **IR** ν (cm<sup>-1</sup>): 3297, 2965, 2997, 9663, 1535, 1452, 1420, 1384, 1360, 1277, 1255, 1218, 1160, 1120, 1025, 930, 834, 780, 714, 650, 650, 618, 551, 463. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>15</sub>H<sub>22</sub>N<sub>3</sub>O<sub>2</sub>: [M+1] 276.1712, found 276.1714.

***N*-(*tert*-butyl)-2-(6-chloropyridin-3-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (12m).** Using the general procedure, this compound was obtained as

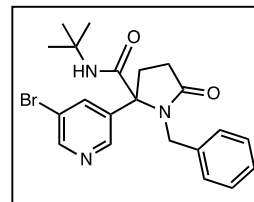
a white solid in 67% yield (0.2 mmol scale) after purification by flash column chromatography (50% EtOAc-hexanes), *R<sub>f</sub>* 0.15 (50% EtOAc-hexanes), mp: 145-147 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ (ppm): 8.35 (dd, *J* = 2.8, 0.8 Hz, 1H), 7.68 (dd, *J* = 8.4, 2.7 Hz, 1H),



7.38 (dd, *J* = 8.4, 0.7 Hz, 1H), 5.63 (br s, 1H), 2.83-2.76 (m, 1H), 2.75 (s, 3H), 2.61-2.43 (m, 2H), 2.31 (ddd, *J* = 13.1, 9.0, 7.0 Hz, 1H), 1.40 (s, 9H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ (ppm): 175.6, 169.2, 151.6, 148.9, 138.3, 133.9, 124.4, 72.1, 52.5, 34.7, 29.5, 28.8, 28.2. **IR** ν (cm<sup>-1</sup>): 3285, 3057, 2967, 2928, 2928, 1693, 1665, 1537, 1384, 1363, 1282, 1219, 1155, 1119, 1103, 1014, 951, 840, 821, 764, 668, 573, 455. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>15</sub>H<sub>21</sub>ClN<sub>3</sub>O<sub>2</sub>: [M+1] 310.1322, found 310.1319.

**1-benzyl-2-(6-bromopyridin-3-yl)-*N*-(*tert*-butyl)-5-oxopyrrolidine-2-carboxamide (12n).** Using the general procedure, this compound was obtained as a

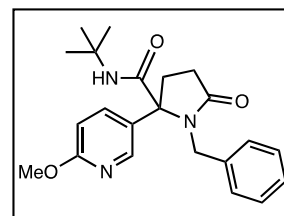
white solid in 62% yield (0.1 mmol scale) after purification by flash column chromatography (80% EtOAc-hexanes), *R<sub>f</sub>* 0.40 (80% EtOAc-hexanes), mp: 182-184 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ



(ppm): 8.62 (br s, 1H), 8.52 (br s, 1H), 7.79 (br s, 1H), 7.32-7.24 (m, 3H), 7.13 (dd,  $J = 6.8$ , 2.8 Hz, 2H), 5.56 (br s, 1H), 4.64 (d,  $J = 15.1$  Hz, 1H), 3.92 (d,  $J = 15.1$  Hz, 1H), 2.83-2.73 (m, 1H), 2.65-2.56 (m, 2H), 2.56-2.45 (m, 1H), 1.09 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 176.4, 169.3, 150.7, 147.9, 138.9, 137.3, 129.3, 128.7, 128.3, 120.9, 73.0, 52.1, 46.0, 35.7, 29.4, 28.2. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3312, 3035, 2975, 2965, 2918, 1671, 1523, 1405, 1366, 1348, 1348, 1269, 1215, 1154, 1115, 973, 887, 792, 774, 739, 702, 642, 593, 463. HRMS ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{21}\text{H}_{25}\text{BrN}_3\text{O}_2$ :  $[\text{M}+1]$  430.1130, found 430.1139.

### 1-benzyl-*N*-(*tert*-butyl)-2-(6-methoxypyridin-3-yl)-5-oxopyrrolidine-2-carboxamide

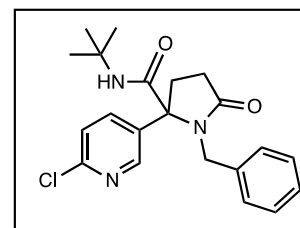
(12o). Using the general procedure, this compound was obtained as a pale yellow solid in 46% yield (0.1 mmol scale) after purification by flash column chromatography (50% EtOAc-hexanes),  $R_f$  0.15 (50% EtOAc-hexanes), mp: 114-116 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.15 (dd,  $J = 2.8$ , 0.7 Hz, 1H), 7.50 (dd,  $J = 8.8$ ,



2.7 Hz, 1H), 7.27-7.22 (m, 3H), 7.19-7.14 (m, 2H), 6.71 (dd,  $J = 8.7$ , 0.7 Hz, 1H), 5.52 (br s, 1H), 4.66 (d,  $J = 15.1$  Hz, 1H), 3.96 (s, 3H), 3.83 (d,  $J = 15.1$  Hz, 1H), 2.81-2.73 (m, 1H), 2.60-2.46 (m, 3H), 1.06 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 176.5, 170.2, 164.0, 147.2, 138.8, 137.7, 129.2, 128.8, 128.0, 127.0, 111.1, 73.3, 53.8, 51.8, 45.6, 35.3, 29.6, 28.2. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3419, 2970, 2936, 1691, 1660, 1604, 1515, 1493, 1455, 1377, 1364, 1327, 1291, 1233, 1218, 1137, 1023, 847, 704, 680, 533. HRMS ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{21}\text{H}_{28}\text{N}_3\text{O}_3$ :  $[\text{M}+1]$  382.2131, found 382.2127.

### 1-benzyl-*N*-(*tert*-butyl)-2-(6-chloropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide

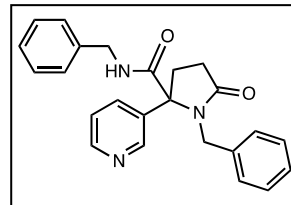
(12p). Using the general procedure, this compound was obtained as a pale yellow solid in 96% yield (0.1 mmol scale) after purification by flash column chromatography (80% EtOAc-hexanes),  $R_f$  0.15 (70% EtOAc-hexanes), mp: 118-120 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.38 (dd,  $J = 2.7$ , 0.7 Hz,



1H), 7.62 (dd,  $J = 8.4$ , 2.7 Hz, 1H), 7.30-7.25 (m, 4H), 7.16-7.11 (m, 2H), 5.55 (br s, 1H), 4.67 (d,  $J = 15.1$  Hz, 1H), 3.84 (d,  $J = 15.1$  Hz, 1H), 2.84-2.73 (m, 1H), 2.63-2.46 (m, 3H), 1.06 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 176.5, 169.5, 151.6, 150.0, 139.0, 137.4, 133.6, 129.3, 128.7, 128.3, 124.1, 72.9, 52.0, 45.9, 35.8, 29.4, 28.1. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3313, 3032, 2972, 2923, 1668, 1528, 1454, 1403, 1366, 1342, 1277, 1217, 1150, 1108, 786,

693, 669, 628, 491, 477, 507. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>21</sub>H<sub>25</sub>ClN<sub>3</sub>O<sub>2</sub>: [M+1] 386.1635, found 386.1645.

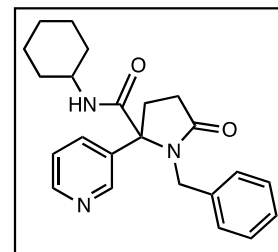
**N,1-dibenzyl-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12q)**. Using the general procedure (Reaction time of cyclization: 10 minutes), this compound was obtained as a white solid in 64% yield (0.1 mmol scale) after purification by flash column chromatography (EtOAc), *R<sub>f</sub>* 0.25 (EtOAc), mp: 168-170 °C.



**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.56 (dd, *J* = 2.6, 0.8 Hz, 1H), 8.54 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.59 (ddd, *J* = 8.1, 2.6, 1.6 Hz, 1H), 7.33-7.26 (m, 3H), 7.23 (ddd, *J* = 8.1, 4.8, 0.9 Hz, 1H), 7.17-7.12 (m, 3H), 7.06-6.98 (m, 4H), 6.09 (t, *J* = 5.7 Hz, 1H), 4.67 (d, *J* = 15.2 Hz, 1H), 4.23 (dd, *J* = 14.5, 6.0 Hz, 1H), 4.05 (dd, *J* = 14.5, 5.5 Hz, 1H), 3.97 (d, *J* = 15.2 Hz, 1H), 2.88 (ddd, *J* = 11.7, 7.3, 4.3 Hz, 1H), 2.61-2.46 (m, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ (ppm): 176.3, 170.5, 149.7, 149.7, 137.2, 137.1, 135.8, 134.2, 129.0, 128.9, 128.2, 128.0, 127.9, 127.9, 123.4, 73.2, 45.8, 44.2, 35.1, 29.4. **IR** ν (cm<sup>-1</sup>): 3296, 3067, 3029, 2914, 1675, 1654, 1547, 1396, 1347, 1279, 1266, 1150, 1023, 771, 731, 699, 668. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>24</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub>: [M+1] 386.1869, found 386.1866.

**1-benzyl-N-cyclohexyl-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12r)**. Using

the general procedure, this compound was obtained as a white solid in 78% yield (0.1 mmol scale) after purification by flash column chromatography (10% MeOH-EtOAc), *R<sub>f</sub>* 0.325 (10% MeOH-EtOAc), mp: 146-148 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ (ppm): 8.52-8.50 (m, 2H), 7.56 (ddd, *J* = 8.1, 2.6, 1.6 Hz, 1H), 7.24-7.16 (m, 4H), 7.07-7.01 (m, 2H), 5.53 (d, *J* = 8.0 Hz, 1H),



4.64 (d, *J* = 15.1 Hz, 1H), 3.72 (d, *J* = 15.1 Hz, 1H), 3.58-3.48 (m, 1H), 2.80 (ddd, *J* = 10.8, 7.1, 3.2 Hz, 1H), 2.59-2.41 (m, 3H), 1.63-1.42 (m, 5H), 1.25-1.06 (m, 2H), 0.99-0.83 (m, 1H), 0.67-0.47 (m, 1H), 0.52-0.38 (m, 1H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ (ppm): 176.6, 169.7, 149.9, 149.7, 137.5, 136.0, 134.4, 129.3, 128.7, 128.1, 123.5, 73.5, 49.0, 45.7, 35.5, 32.4, 29.5, 25.4, 25.0, 24.9. **IR** ν (cm<sup>-1</sup>): 3360, 2941, 2919, 2853, 1698, 1654, 1510, 1495, 1447, 1392, 1361, 1255, 1237, 1114, 1059, 1018, 884, 816, 746, 708, 583. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>23</sub>H<sub>28</sub>N<sub>3</sub>O<sub>2</sub>: [M+1] 378.2182, found 378.2184.

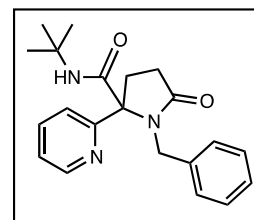
## SPECTROSCOPIC DATA OF ISO-COTININE ANALOGS

### General procedure: Synthesis of the iso-cotinine analogs 15a-l

A solution of 3-chloropropionic acid (**7**) (1.0 eq.), pyridinecarboxaldehyde (1.0 eq.), amine (1.0 eq.), isocyanide (1.0 eq.) and indium (III) chloride (2 mol %) in anhydrous MeOH (0.33 M) was heated in a vial at 70 °C under microwave irradiation (100 W) for 2 hours. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography.

### 1-benzyl-*N*-(*tert*-butyl)-5-oxo-2-(pyridin-2-yl)pyrrolidine-2-carboxamide (**15a**). Using

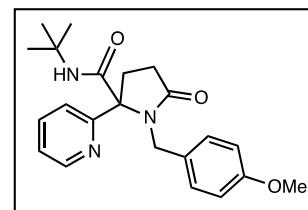
the general procedure, this compound was obtained as a pale yellow solid in 54% yield (1.0 mmol scale) after purification by flash column chromatography (50% EtOAc-hexanes),  $R_f$  0.22 (50% EtOAc-hexanes), mp: 113-115 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.53 (ddd,  $J = 4.8, 1.9, 0.9$  Hz, 1H), 7.56 (ddd,  $J = 8.0, 7.6,$



1.9 Hz, 1H), 7.47 (br s, 1H), 7.31 (dt,  $J = 8.0, 1.0$  Hz, 1H), 7.21-7.14 (m, 6H), 4.46 (d,  $J = 15.2$  Hz, 1H), 4.10 (d,  $J = 15.2$  Hz, 1H), 2.65-2.55 (m, 4H), 1.19 (s, 9H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 178.0, 170.3, 159.2, 148.6, 137.9, 136.8, 129.0, 128.7, 127.5, 123.7, 122.9, 75.1, 51.4, 46.7, 34.6, 29.8, 28.4.  $\text{IR } \nu$  ( $\text{cm}^{-1}$ ): 3285, 3065, 3045, 2959, 2971, 1666, 1539, 1402, 1349, 1278, 1217, 1152, 996, 840, 750, 767, 695, 670, 492.  $\text{HRMS (FAB}^+, \text{M}^+)$  calcd for  $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_2$ :  $[\text{M}+1]$  352.2025, found 352.2030.

### *N*-(*tert*-butyl)-1-(4-methoxybenzyl)-5-oxo-2-(pyridin-2-yl)pyrrolidine-2-carboxamide

(**15b**). Using the general procedure, this compound was obtained as a pale yellow oil in 66% yield (1.0 mmol scale) after purification by flash column chromatography (50% EtOAc-hexanes),  $R_f$  0.10 (50% EtOAc-hexanes).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.53 (ddd,  $J = 4.9, 1.9, 0.9$  Hz, 1H), 7.58 (br s,

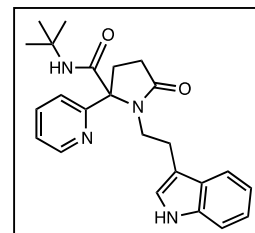


1H), 7.58 (td,  $J = 7.8, 1.9$  Hz, 3H), 7.30 (dt,  $J = 8.1, 1.1$  Hz, 1H), 7.18 (ddd,  $J = 7.6, 4.8, 1.1$  Hz, 1H), 7.08 (d,  $J = 8.6$  Hz, 2H), 6.72 (d,  $J = 8.6$  Hz, 2H), 4.40 (d,  $J = 15.1$  Hz, 1H), 4.00 (d,  $J = 15.1$  Hz, 1H), 3.74 (s, 3H), 2.61-2.52 (m, 4H), 1.20 (s, 9H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 177.9, 170.4, 159.3, 159.1, 148.5, 136.8, 130.4, 129.9, 123.7, 122.8, 114.0, 75.0, 55.4, 51.4, 46.0, 34.8, 29.8, 28.4.  $\text{IR } \nu$  ( $\text{cm}^{-1}$ ): 3400, 3330, 3211, 2965, 2933,

1669, 1511, 1455, 1432, 1243, 1174, 1152, 1112, 1031, 836, 749, 669, 514. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>22</sub>H<sub>28</sub>N<sub>3</sub>O<sub>3</sub>: [M+1] 382.2131, found 382.2128.

**1-(2-(1*H*-indol-3-yl)ethyl)-*N*-(*tert*-butyl)-5-oxo-2-(pyridin-2-yl)pyrrolidine-2-**

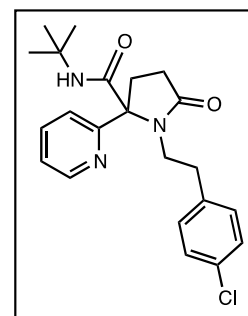
**carboxamide (15c).** Using the general procedure, this compound was obtained as a white solid in 61% yield (1.0 mmol scale) after purification by flash column chromatography (10% hexanes-EtOAc), *R<sub>f</sub>* 0.12 (10% hexanes-EtOAc), mp: 165-167 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ (ppm): 8.61 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 8.52 (br s, 1H), 8.14 (br s, 1H), 7.67 (td, *J* = 7.8, 1.9 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.30 (ddt, *J* = 8.0, 7.1, 1.0 Hz, 2H), 7.28-7.23 (m, 1H), 7.14 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.04 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.00 (d, *J* = 2.3 Hz, 1H), 3.62 (ddd, *J* = 14.3, 11.5, 5.4 Hz, 1H), 3.29-3.19 (m, 2H), 3.09-3.00 (m, 1H), 2.65-2.56 (m, 2H), 2.50-2.38 (m, 2H), 1.42 (s, 9H).



**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ (ppm): 177.1, 170.2, 160.5, 148.7, 137.7, 136.4, 127.6, 122.9, 122.4, 122.1, 122.0, 119.3, 119.2, 113.8, 111.2, 75.1, 51.5, 45.4, 34.8, 29.9, 28.8, 23.7. **IR** ν (cm<sup>-1</sup>): 3317, 3000, 2966, 1678, 1654, 1580, 1527, 1456, 1433, 1398, 1360, 1229, 1159, 1103, 1013, 997, 746, 728, 674. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>24</sub>H<sub>29</sub>N<sub>4</sub>O<sub>2</sub>: [M+1] 405.2291, found 405.2282.

***N*-(*tert*-butyl)-1-(4-chlorophenethyl)-5-oxo-2-(pyridin-2-yl)pyrrolidine-2-carboxamide**

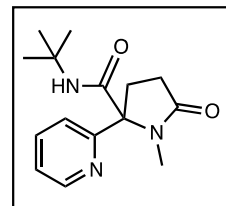
**(15d).** Using the general procedure, this compound was obtained as a pale yellow solid in 63% yield (1.0 mmol scale) after purification by flash column chromatography (60% EtOAc-hexanes), *R<sub>f</sub>* 0.12 (60% EtOAc-hexanes), mp: 98-100 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ (ppm): 8.61 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 8.51 (br s, 1H), 7.71 (td, *J* = 7.8, 1.9 Hz, 1H), 7.28 (ddd, *J* = 8.1, 5.0, 1.3 Hz, 1H), 7.24 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H),



3.51 (ddd, *J* = 14.4, 11.9, 5.3 Hz, 1H), 3.14-2.99 (m, 2H), 2.94-2.84 (m, 1H), 2.62-2.51 (m, 2H), 2.43-2.30 (m, 2H), 1.41 (s, 9H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ (ppm): 176.8, 169.8, 160.5, 148.8, 138.3, 137.8, 132.1, 130.3, 128.6, 123.0, 122.0, 75.0, 51.5, 46.2, 34.7, 33.4, 29.7, 28.8. **IR** ν (cm<sup>-1</sup>): 3366, 3053, 2972, 1684, 1656, 1587, 1512, 1491, 1434, 1389, 1365, 1224, 1154, 1090, 1016, 849, 808, 755, 594, 515. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for C<sub>22</sub>H<sub>27</sub>ClN<sub>3</sub>O<sub>2</sub>: [M+1] 400.1792, found 400.1793.

***N*-(*tert*-butyl)-1-methyl-5-oxo-2-(pyridin-2-yl)pyrrolidine-2-carboxamide (15e).** Using

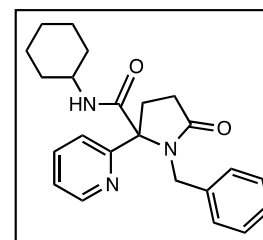
the general procedure, this compound was obtained as a pale yellow solid 75% yield (1.0 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.17 (EtOAc), mp: 91-93 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.89 (br s, 1H), 8.60 (ddd,  $J = 4.9, 1.9, 1.0$  Hz, 1H), 7.75 (td,  $J = 7.8, 1.9$  Hz, 1H), 7.31-7.21 (m, 2H), 2.84 (s,



3H), 2.56-2.46 (m, 2H), 2.40-2.29 (m, 1H), 2.25-2.15 (m, 1H), 1.38 (s, 9H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 176.9, 169.1, 160.5, 148.7, 138.0, 122.8, 121.3, 74.1, 51.4, 34.8, 29.5, 29.0, 28.7. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3312, 2965, 1681, 1662, 1587, 1526, 1471, 1456, 1433, 1410, 1382, 1279, 1229, 1117, 834, 780, 750, 655, 570. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for  $\text{C}_{15}\text{H}_{22}\text{N}_3\text{O}_2$ :  $[\text{M}+1]$  276.1712, found 276.1712.

**1-benzyl-*N*-cyclohexyl-5-oxo-2-(pyridin-2-yl)pyrrolidine-2-carboxamide (15f).** Using

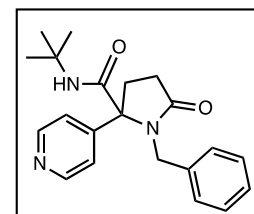
the general procedure, this compound was obtained as a white solid in 72% yield (1.0 mmol scale) after purification by flash column chromatography (80% EtOAc-hexanes),  $R_f$  0.20 (80% EtOAc-hexanes), mp: 118-120 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.54-8.51 (m, 1H), 7.57 (br s, 1H), 7.54 (td,  $J = 7.8, 1.9$  Hz, 1H), 7.26 (d,  $J = 8.0$  Hz, 1H), 7.20-7.15 (m, 4H), 7.12 (dd,  $J = 7.2, 2.5$  Hz, 2H), 4.43 (d,  $J = 15.3$



Hz, 1H), 4.14 (d,  $J = 15.2$  Hz, 1H), 3.77-3.62 (m, 1H), 2.66-2.54 (m, 4H), 1.76-1.70 (m, 2H), 1.64-1.54 (m, 3H), 1.36-1.25 (m, 2H), 1.15-1.06 (m, 1H), 0.98-0.81 (m, 2H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 177.7, 170.2, 158.8, 148.5, 137.6, 136.7, 128.9, 128.7, 128.5, 127.3, 123.4, 122.8, 74.7, 48.4, 46.5, 34.4, 32.5, 32.3, 29.6, 25.5, 24.8, 24.7. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3303, 2935, 2855, 1963, 1675, 1668, 1530, 1431, 1397, 1316, 1275, 1152, 1162, 760, 742, 700, 670, 641, 493. **HRMS (FAB<sup>+</sup>, M<sup>+</sup>)** calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_3\text{O}_2$ :  $[\text{M}+1]$  378.2182, found 378.2188.

**1-benzyl-*N*-(*tert*-butyl)-5-oxo-2-(pyridin-4-yl)pyrrolidine-2-carboxamide (15g).** Using

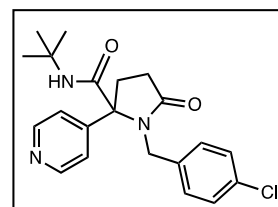
the general procedure, this compound was obtained as a pale yellow solid in 57% yield (1.0 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.15 (50% EtOAc-hexanes), mp: 137-139 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.69-8.60 (m, 2H), 7.33-7.30 (m, 2H), 7.29-7.26 (m, 3H), 7.19-7.16 (m, 2H),



5.49 (br s, 1H), 4.80 (d,  $J = 15.3$  Hz, 1H), 3.73 (d,  $J = 15.3$  Hz, 1H), 2.88-2.81 (m, 1H), 2.68-2.53 (m, 2H), 2.52-2.41 (m, 1H), 1.03 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 176.9, 169.2, 150.0, 148.7, 137.3, 129.3, 128.7, 128.3, 123.3, 74.3, 52.0, 46.1, 35.6, 29.3, 28.1. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3407, 3377, 2969, 2932, 1639, 1682, 1592, 1511, 1453, 1392, 1361, 1275, 1215, 1170, 815, 710, 517. HRMS ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_2$ :  $[\text{M}+1]$  352.2025, found 352.2030.

***N*-(*tert*-butyl)-1-(4-chlorobenzyl)-5-oxo-2-(pyridin-4-yl)pyrrolidine-2-carboxamide**

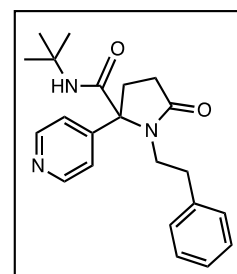
**(15h)**. Using the general procedure, this compound was obtained as a white solid in 50% yield (1.0 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.10 (EtOAc), mp: 120-122 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.64-8.54 (m, 2H), 7.24-7.20 (m, 4H), 7.09-7.04 (m, 2H), 5.40 (br s, 1H), 4.64 (d,  $J =$



15.4 Hz, 1H), 3.87 (d,  $J = 15.3$  Hz, 1H), 2.83 (ddd,  $J = 12.9, 8.8, 5.3$  Hz, 1H), 2.65-2.50 (m, 2H), 2.49-2.37 (m, 1H), 1.10 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 176.7, 169.1, 150.5, 148.1, 135.8, 134.0, 129.9, 129.2, 122.9, 74.1, 52.2, 45.5, 35.1, 29.2, 28.2. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3330, 2971, 1681, 1593, 1536, 1513, 1409, 1392, 1218, 1154, 1087, 819, 803, 522. HRMS ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{21}\text{H}_{25}\text{ClN}_3\text{O}_2$ :  $[\text{M}+1]$  386.1635, found 386.1630.

***N*-(*tert*-butyl)-5-oxo-1-phenethyl-2-(pyridin-4-yl)pyrrolidine-2-carboxamide** **(15i)**.

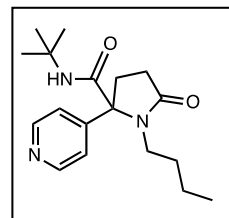
Using the general procedure, this compound was obtained as a white solid in 40% yield (1.0 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.10 (EtOAc), mp: 170-172 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.67 (dd,  $J = 4.7, 1.7$  Hz, 2H), 7.29-7.17 (m, 5H), 7.05-7.01 (m, 2H), 5.57 (br s, 1H), 3.43-3.27 (m, 2H), 2.92-2.77 (m, 2H), 2.64-2.32 (m, 4H), 1.40 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,



$\text{CDCl}_3$ )  $\delta$  (ppm): 175.7, 169.5, 150.6, 148.9, 138.4, 128.8, 128.7, 126.7, 122.6, 74.0, 52.6, 45.2, 34.4, 33.8, 29.5, 28.8. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3334, 2972, 1686, 1654, 1597, 1517, 1454, 1442, 1391, 1359, 1222, 1208, 1149, 838, 813, 755, 705, 621, 493. HRMS ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{22}\text{H}_{28}\text{N}_3\text{O}_2$ :  $[\text{M}+1]$  366.2182, found 366.2182.

***N*-(*tert*-butyl)-1-butyl-5-oxo-2-(pyridin-4-yl)pyrrolidine-2-carboxamide (15j).** Using

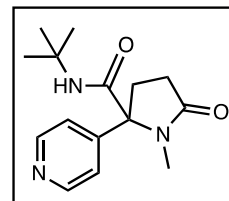
the general procedure, this compound was obtained as a pale yellow oil in 49% yield (1.0 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.10 (EtOAc).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.67 (s, 2H), 7.26-7.22 (m, 2H), 5.54 (br s, 1H), 3.29 (ddd,  $J = 13.6, 10.9, 5.6$  Hz, 1H), 2.97 (ddd,  $J = 13.6, 10.9, 5.2$  Hz,



1H), 2.92-2.83 (m, 1H), 2.50 (ddd,  $J = 16.7, 9.3, 6.3$  Hz, 1H), 2.43-2.33 (m, 1H), 2.26 (ddd,  $J = 12.9, 9.1, 6.3$  Hz, 1H), 1.49-1.32 (m, 2H), 1.39 (s, 9H), 1.28-1.12 (m, 2H), 0.81 (t,  $J = 7.3$  Hz, 3H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 175.8, 169.4, 150.5, 149.2, 122.5, 74.2, 52.5, 43.4, 34.0, 30.4, 29.4, 28.7, 20.6, 13.7. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3321, 2961, 2932, 2873, 1670, 1595, 1525, 1454, 1393, 1364, 1275, 1218, 1131, 1072, 816, 671, 510. **HRMS** ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{18}\text{H}_{28}\text{N}_3\text{O}_2$ :  $[\text{M}+1]$  318.2182, found 318.2183.

***N*-(*tert*-butyl)-1-methyl-5-oxo-2-(pyridin-4-yl)pyrrolidine-2-carboxamide (15k).** Using

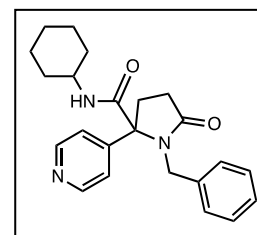
the general procedure, this compound was obtained as a white solid in 74% yield (1.0 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.10 (EtOAc), mp: 72-74 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.72-8.62 (m, 2H), 7.33-7.18 (m, 2H), 5.53 (br s, 1H), 2.84 (ddd,  $J = 13.3, 9.0, 6.5$  Hz, 1H), 2.77 (s, 3H),



2.62-2.51 (m, 1H), 2.45 (ddd,  $J = 17.2, 9.2, 6.4$  Hz, 1H), 2.25 (ddd,  $J = 13.0, 9.3, 6.8$  Hz, 1H), 1.39 (s, 9H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 176.0, 168.9, 150.4, 148.7, 122.2, 73.5, 52.5, 34.2, 29.5, 28.8, 28.3. **IR**  $\nu$  ( $\text{cm}^{-1}$ ): 3334, 3305, 3279, 2971, 2917, 1685, 1662, 1596, 1537, 1380, 1360, 1278, 1266, 1220, 1121, 1071, 832, 816, 664, 616, 504. **HRMS** ( $\text{FAB}^+$ ,  $\text{M}^+$ ) calcd for  $\text{C}_{15}\text{H}_{22}\text{N}_3\text{O}_2$ :  $[\text{M}+1]$  276.1712, found 276.1716.

**1-benzyl-*N*-cyclohexyl-5-oxo-2-(pyridin-4-yl)pyrrolidine-2-carboxamide (15l).** Using

the general procedure, this compound was obtained as a white solid in 68% yield (1.0 mmol scale) after purification by flash column chromatography (EtOAc),  $R_f$  0.10 (EtOAc), mp: 78-80 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.63 (d,  $J = 6.1$  Hz, 2H), 7.32-7.21 (m, 5H), 7.18-7.09 (m, 2H), 5.55 (br s, 1H), 4.80 (d,  $J = 15.2$  Hz, 1H),



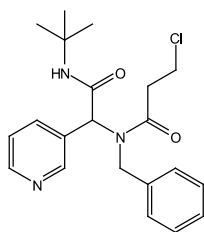
3.73 (d,  $J = 15.2$  Hz, 1H), 3.61-3.52 (m, 1H), 2.89 (ddd,  $J = 12.9, 8.4, 4.5$  Hz, 1H), 2.66-2.53 (m, 2H), 2.52-2.40 (m, 1H), 1.61-1.52 (m, 5H), 1.31-1.15 (m, 2H), 0.97 (dddd,  $J =$



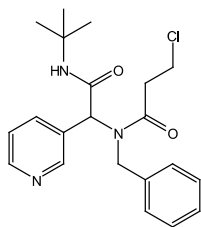
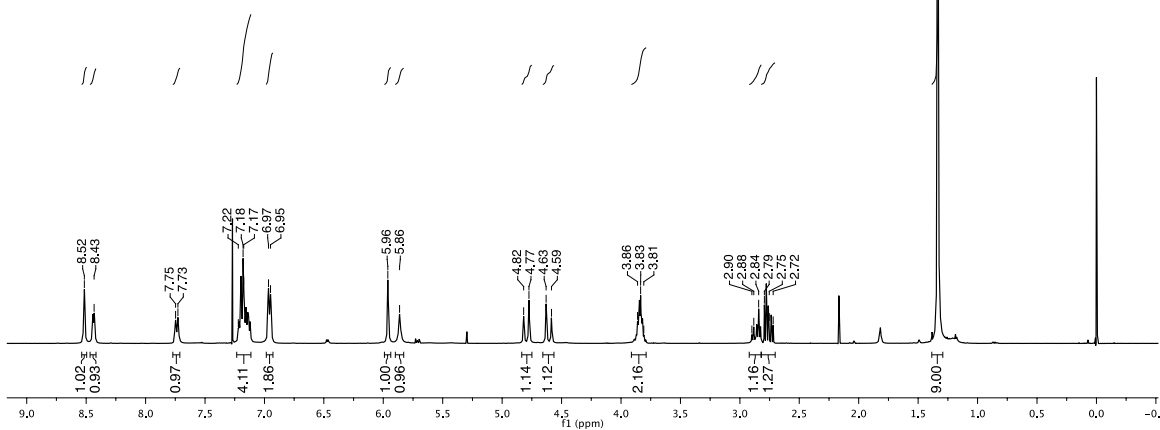
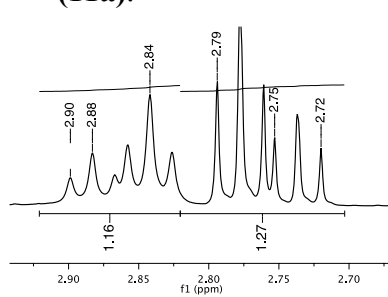
18.8, 15.7, 10.5, 4.2 Hz, 1H), 0.73-0.59 (m, 1H), 0.58-0.43 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 176.8, 169.2, 150.5, 147.9, 137.3, 129.3, 128.6, 128.2, 123.0, 74.2, 49.0, 45.9, 35.5, 32.4, 32.3, 29.3, 25.4, 24.9, 24.9. IR  $\nu$  ( $\text{cm}^{-1}$ ): 3349, 3320, 3034, 2926, 2852, 1958, 1737, 1698, 1670, 1647, 1595, 1526, 1496, 1445, 1388, 1359, 1239, 1165, 1062, 993, 819, 705, 623, 512. HRMS (FAB $^+$ , M $^+$ ) calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_3\text{O}_2$ : [M+1] 378.2182, found 378.2188.

# UGI ADDUCTS SPECTRA

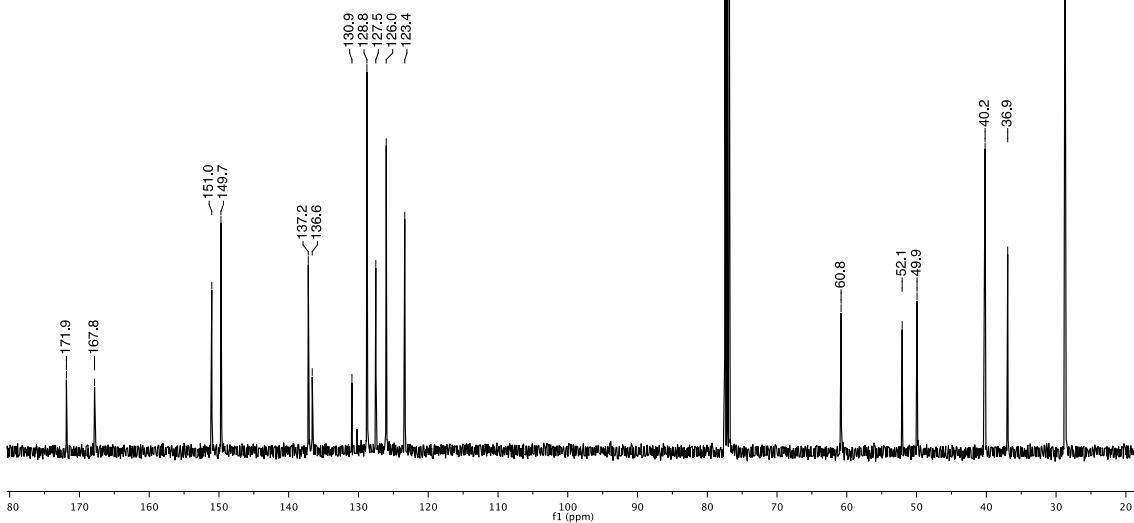
## *N*-benzyl-*N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloropropanamide (11a).



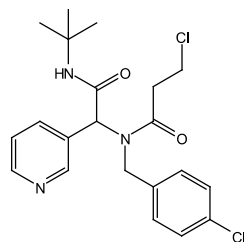
400 MHz, Chloroform-*d*



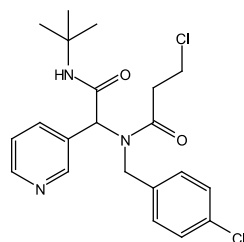
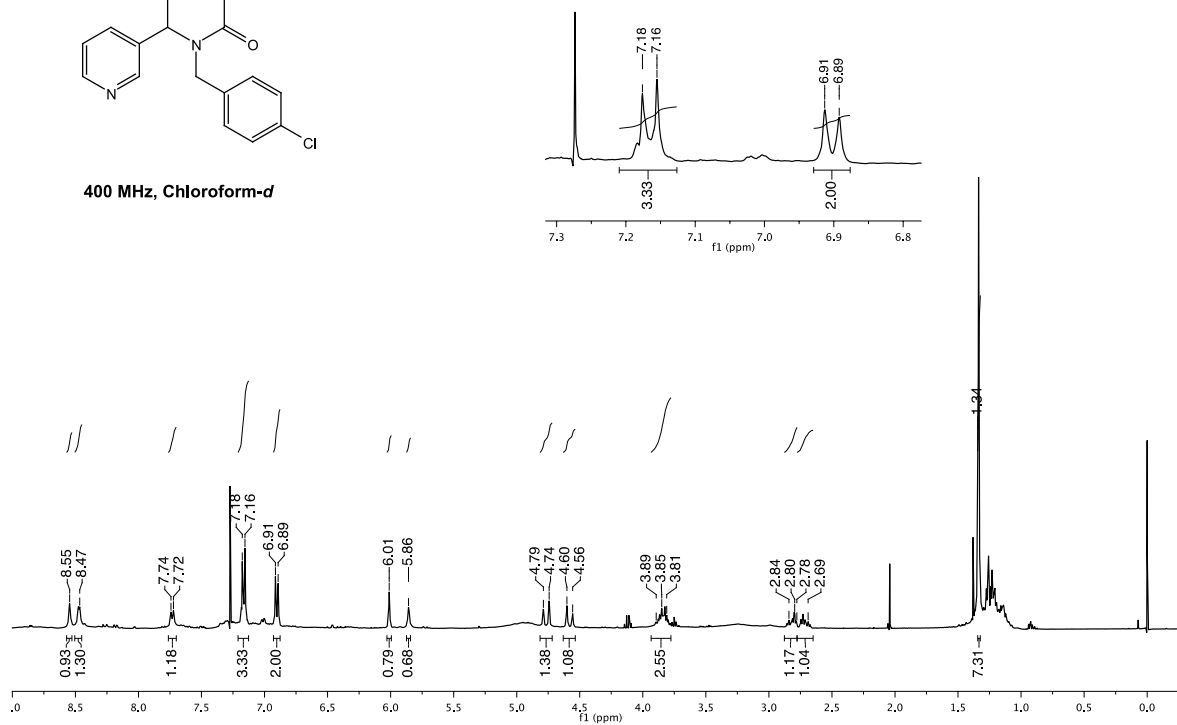
100 MHz, Chloroform-*d*



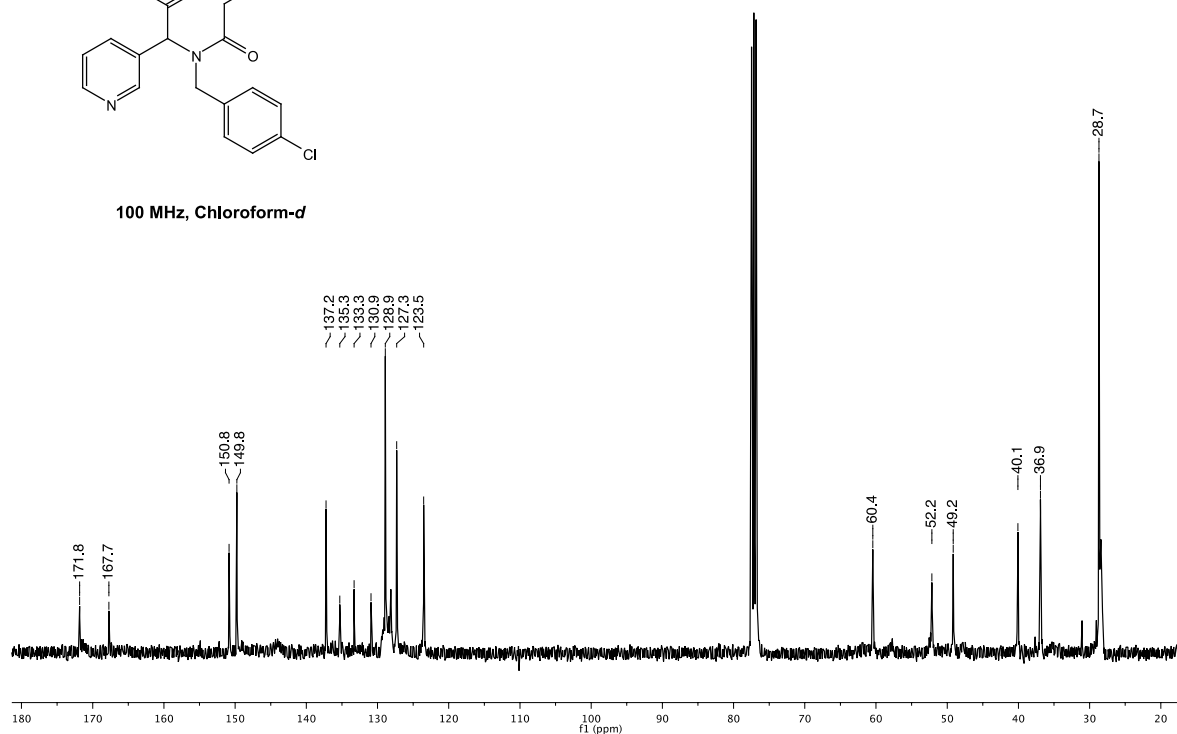
***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-(4-chlorobenzyl)propanamide (11b).**



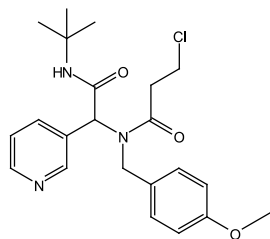
400 MHz, Chloroform-*d*



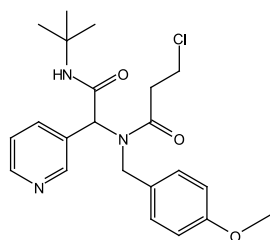
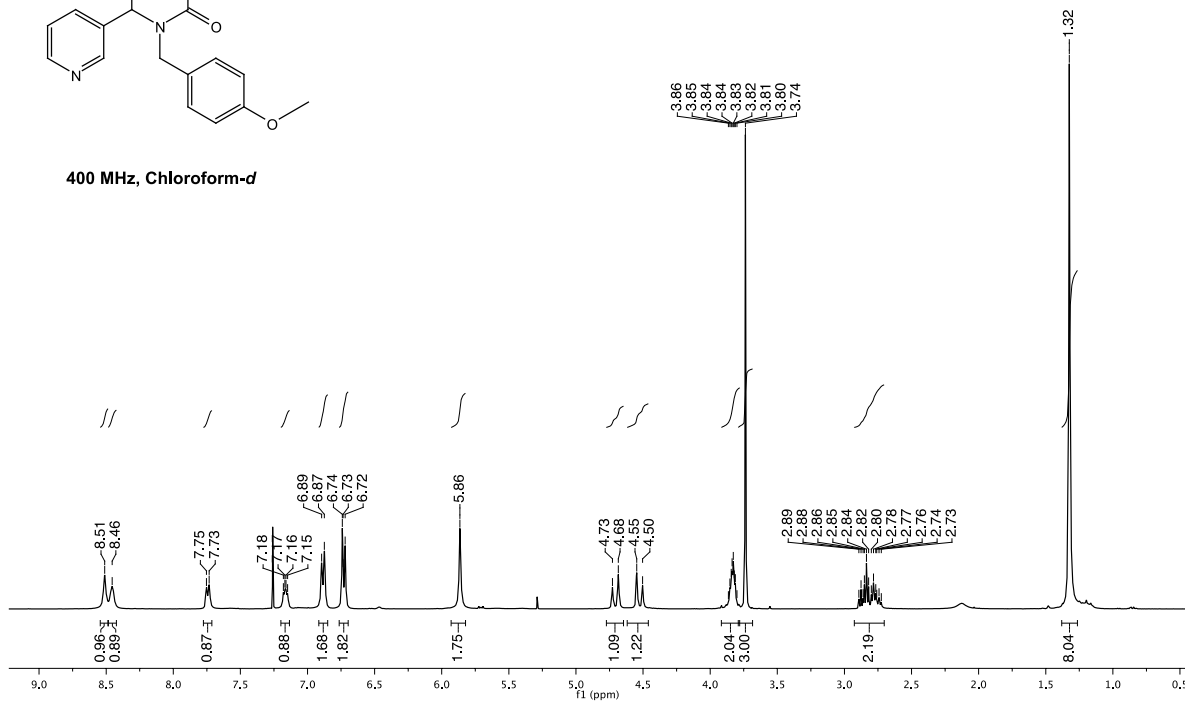
100 MHz, Chloroform-*d*



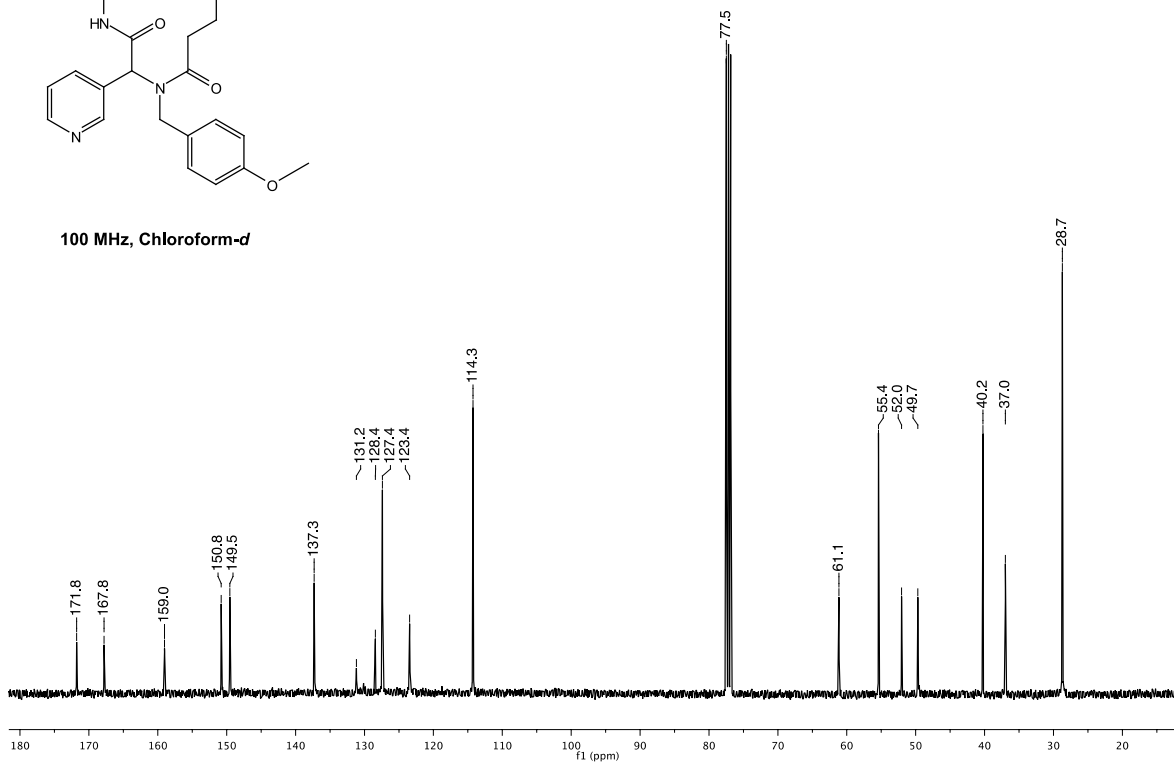
***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-(4-methoxybenzyl)propanamide (11c).**



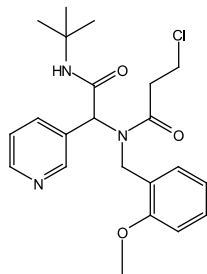
400 MHz, Chloroform-*d*



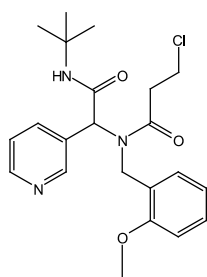
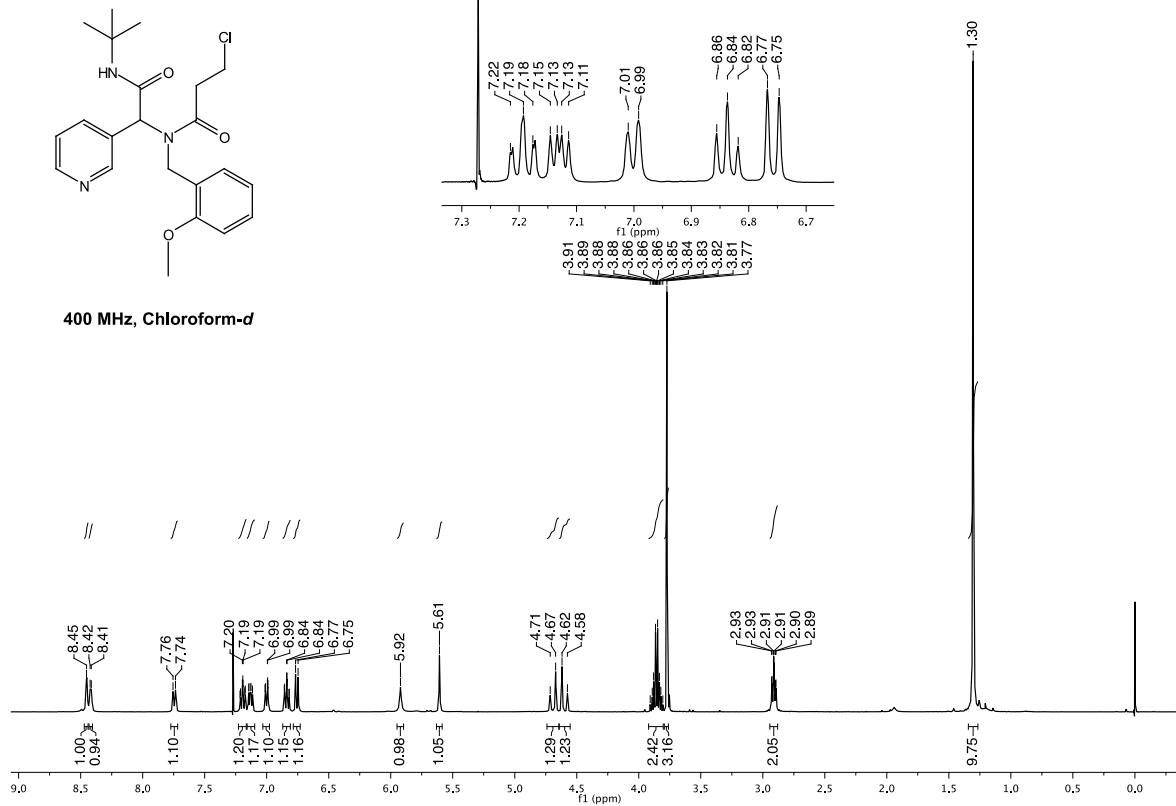
100 MHz, Chloroform-*d*



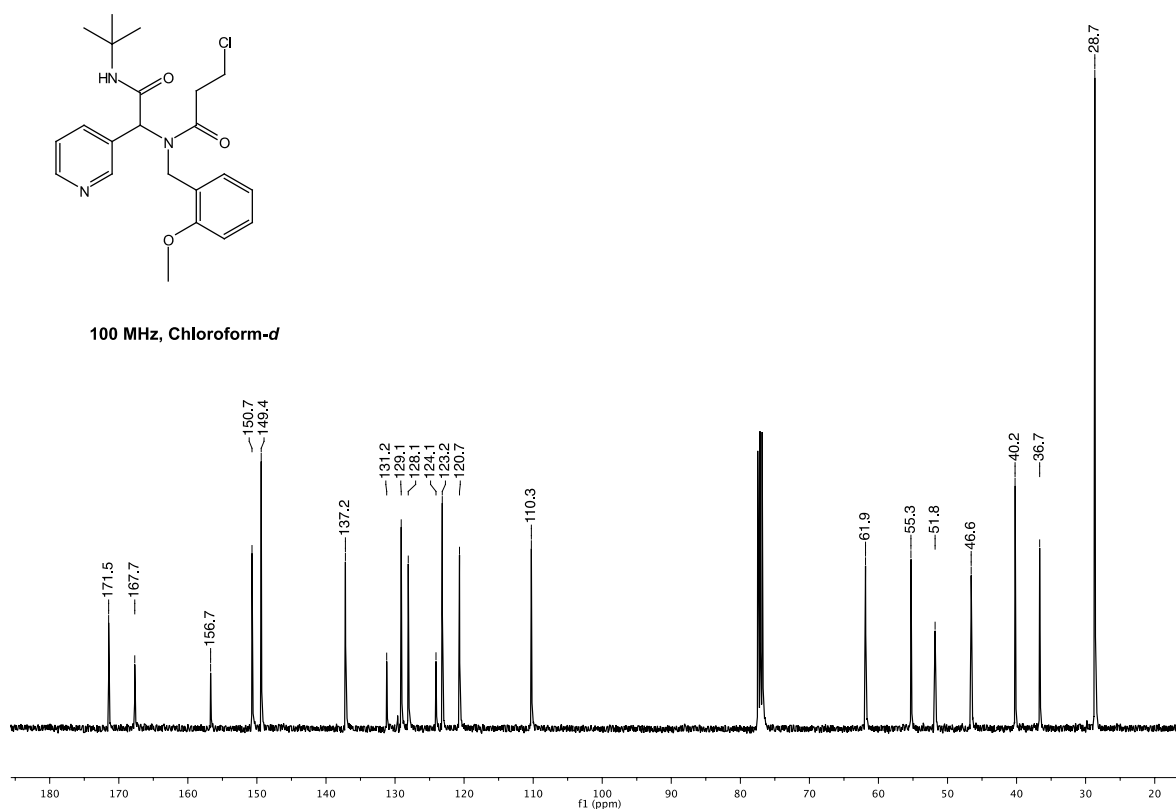
***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-(2-methoxybenzyl)propanamide (11d).**



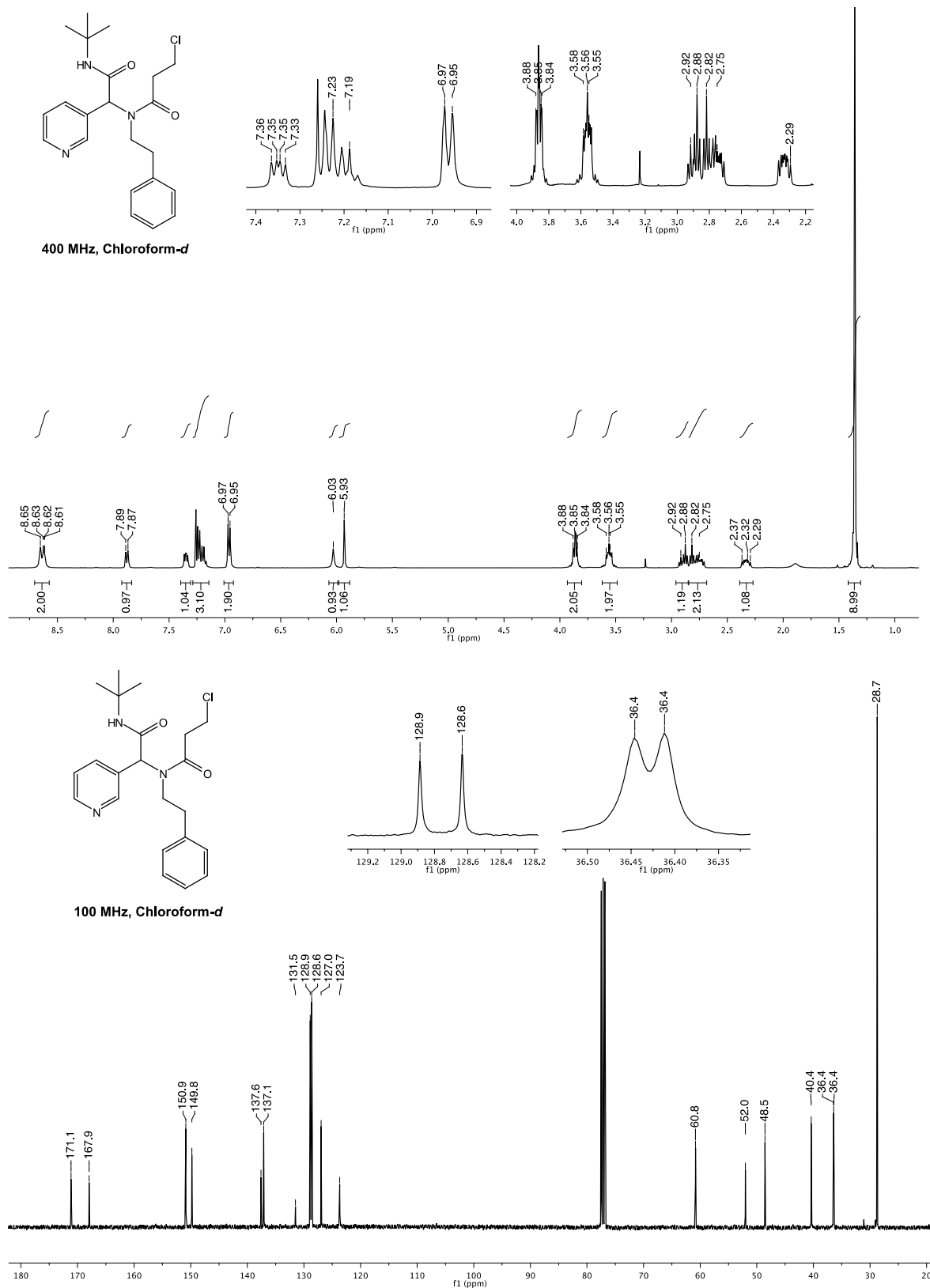
400 MHz, Chloroform-*d*



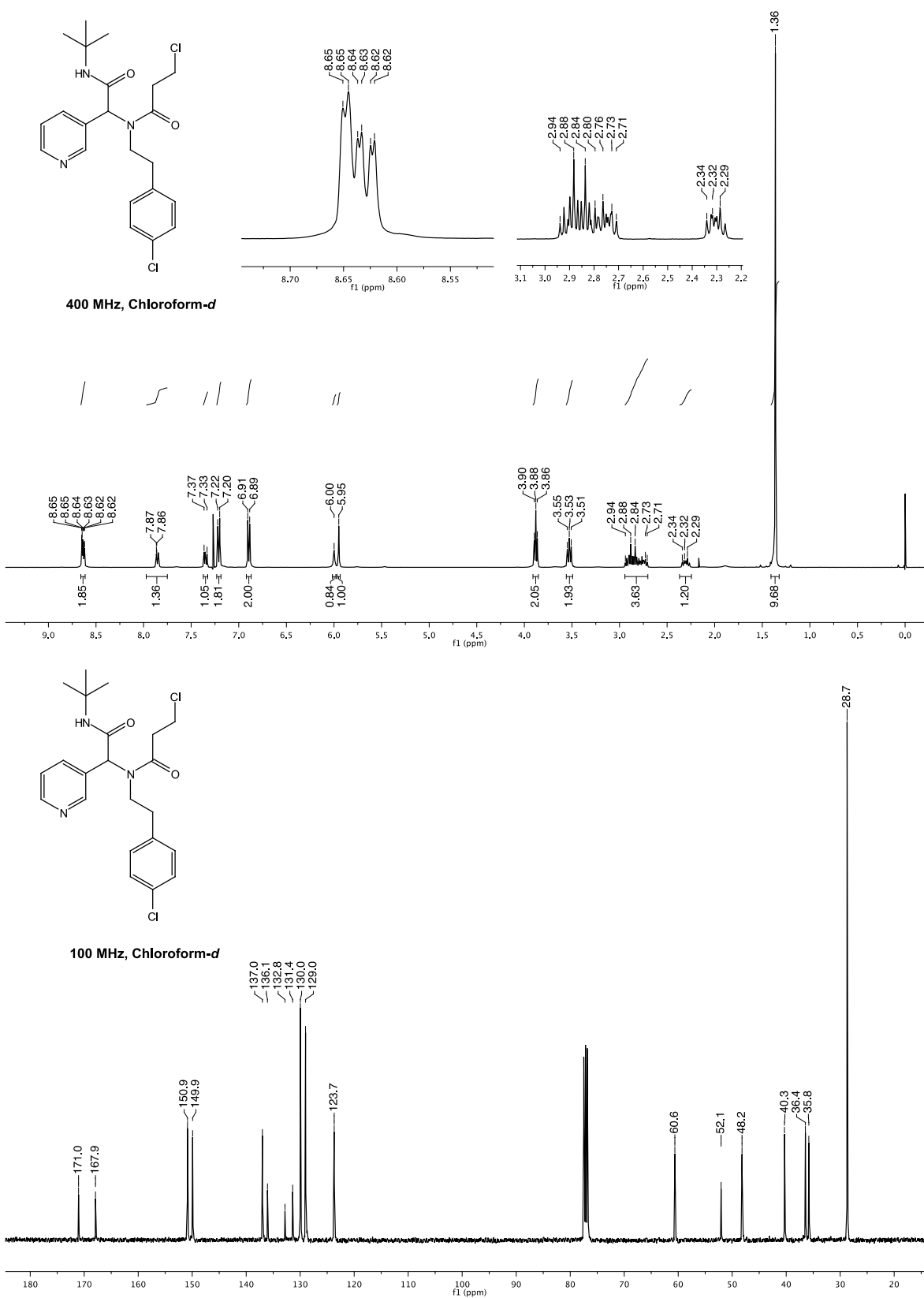
100 MHz, Chloroform-*d*



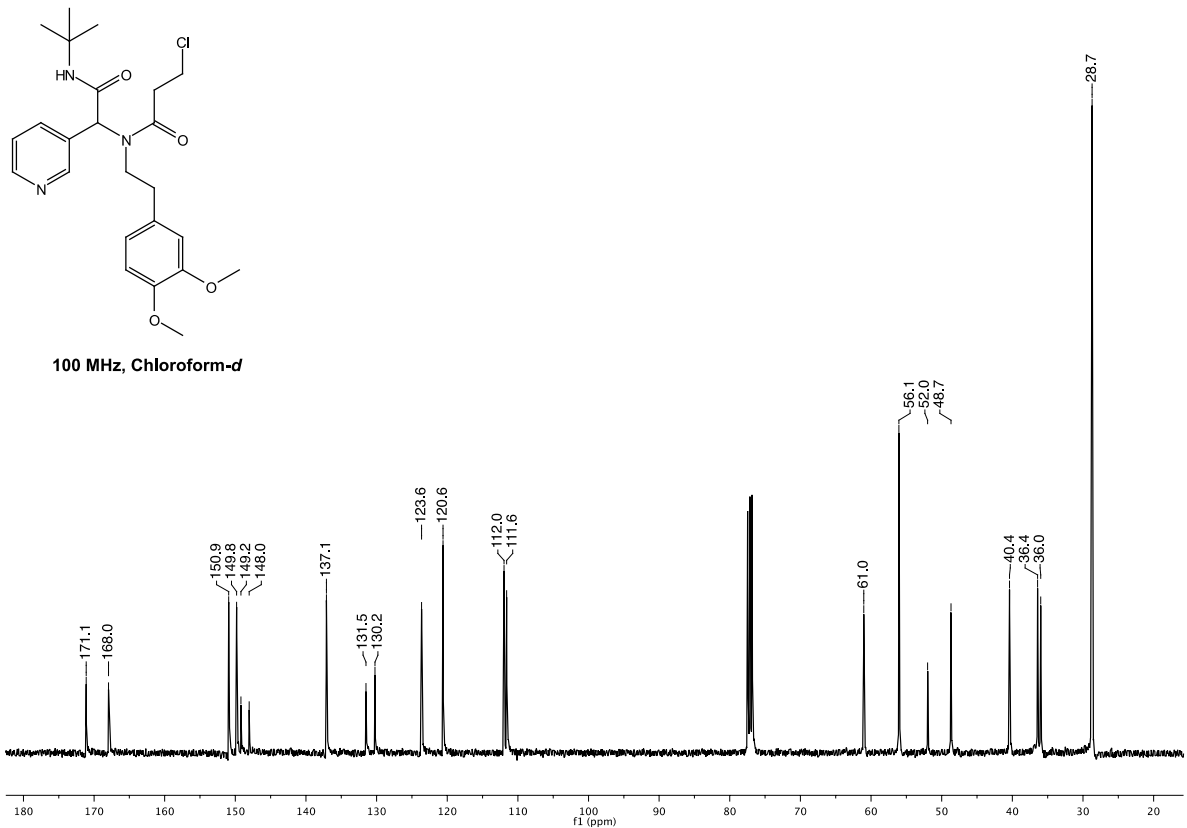
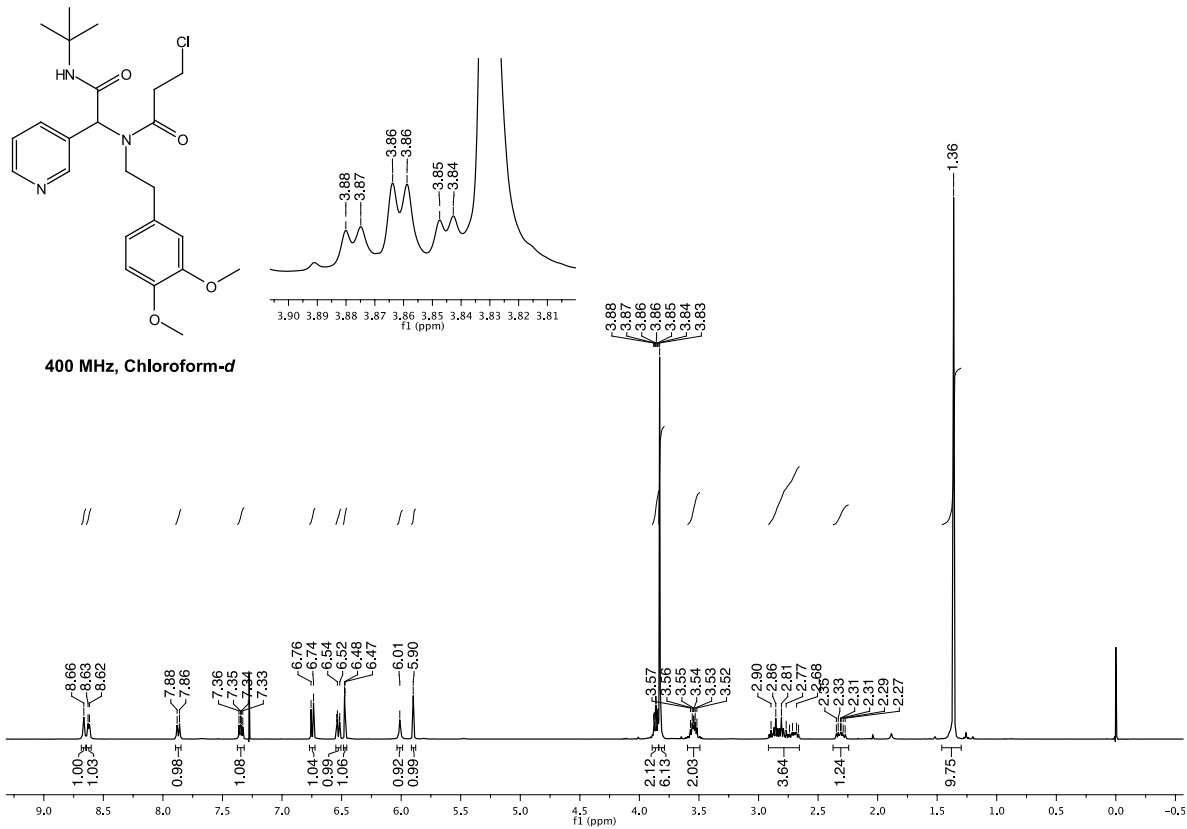
***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-phenethylpropanamide (11e)**



***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-(4-chlorophenethyl)propanamide (11f).**

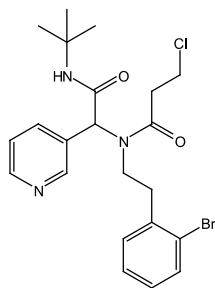


***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-(3,4-dimethoxyphenethyl)propanamide (11g).**

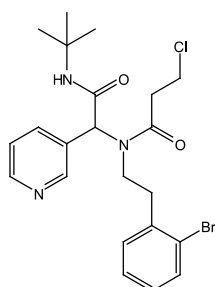
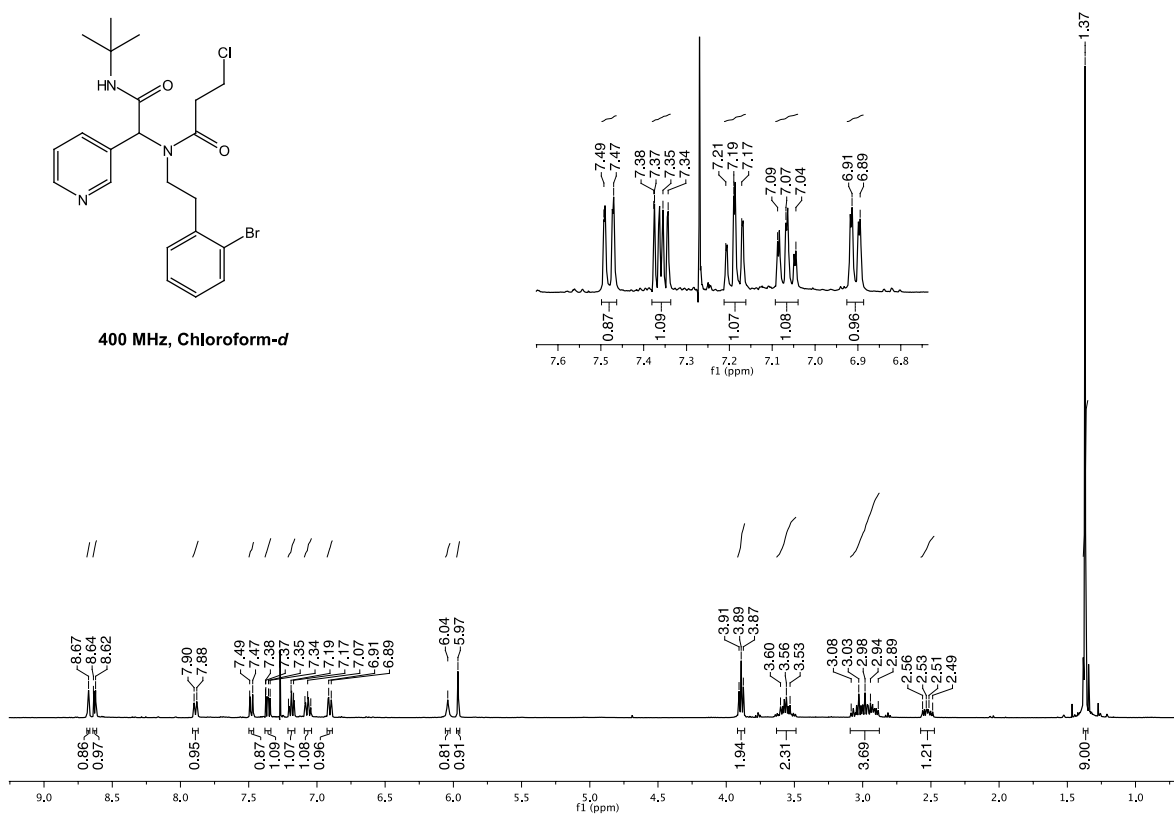




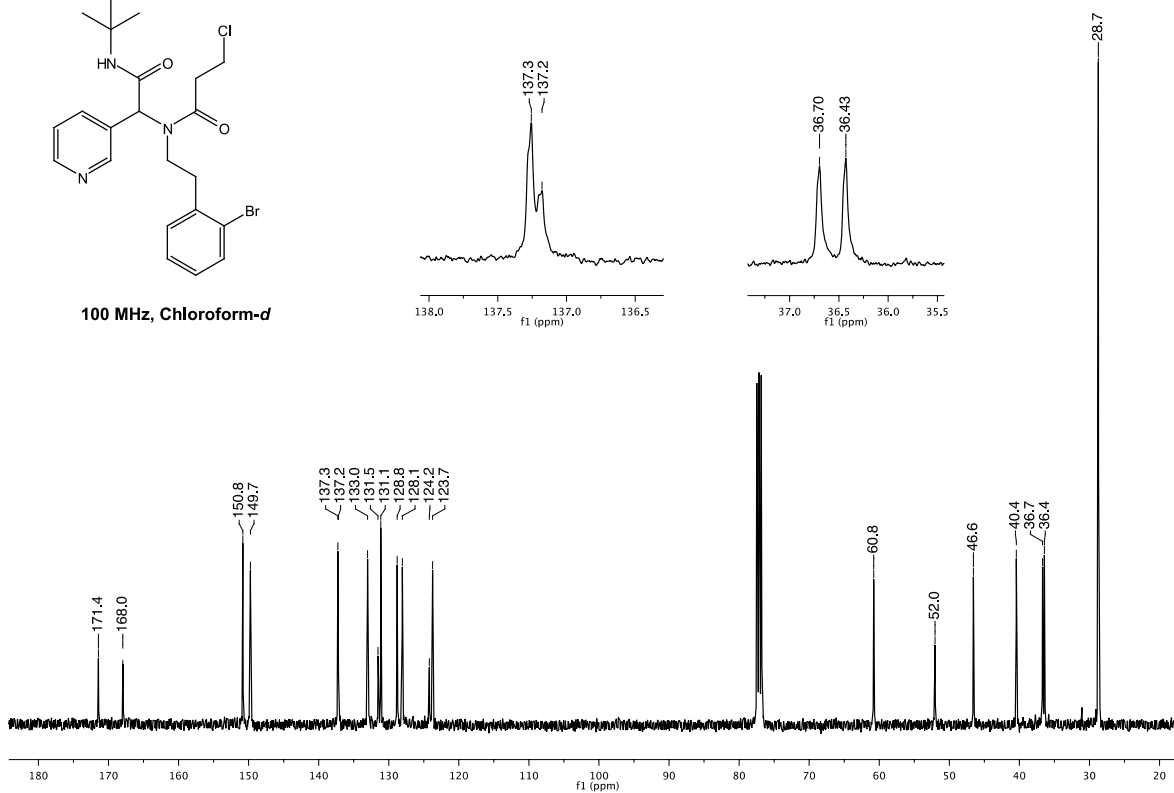
***N*-(2-bromophenethyl)-*N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloropropanamide (11h)**



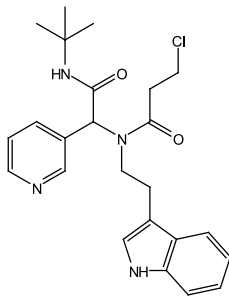
400 MHz, Chloroform-*d*



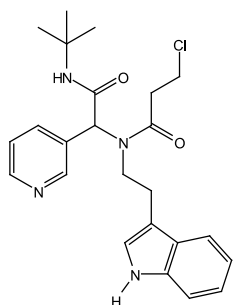
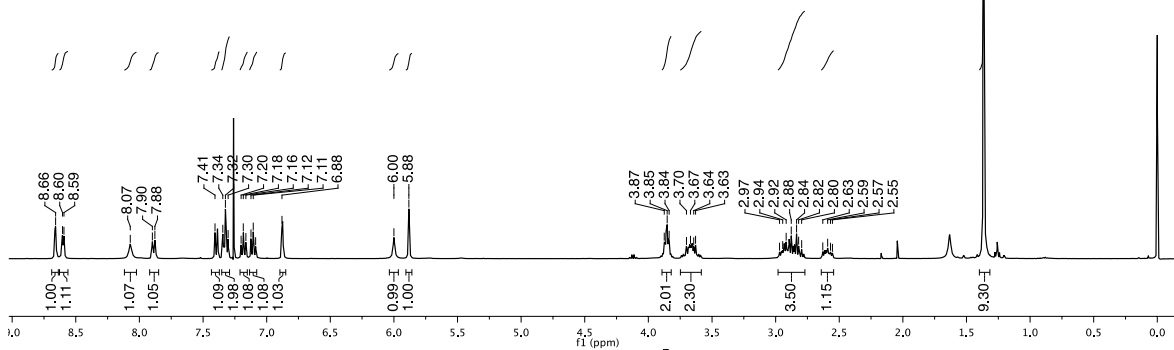
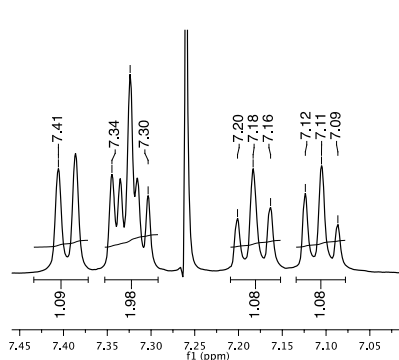
100 MHz, Chloroform-*d*



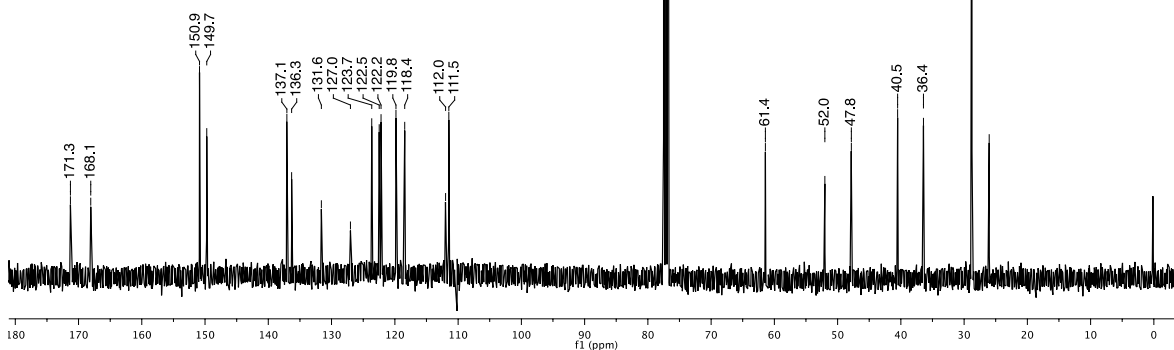
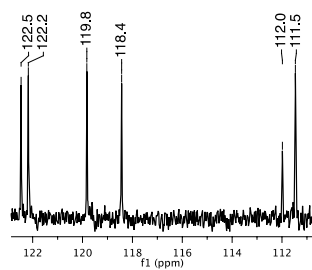
***N*-2-(1*H*-indol-3-yl)ethyl)-*N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloropropanamide (11i)**



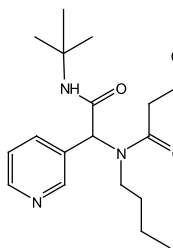
400 MHz, Chloroform-*d*



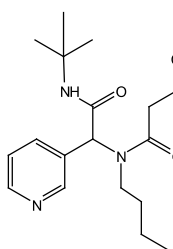
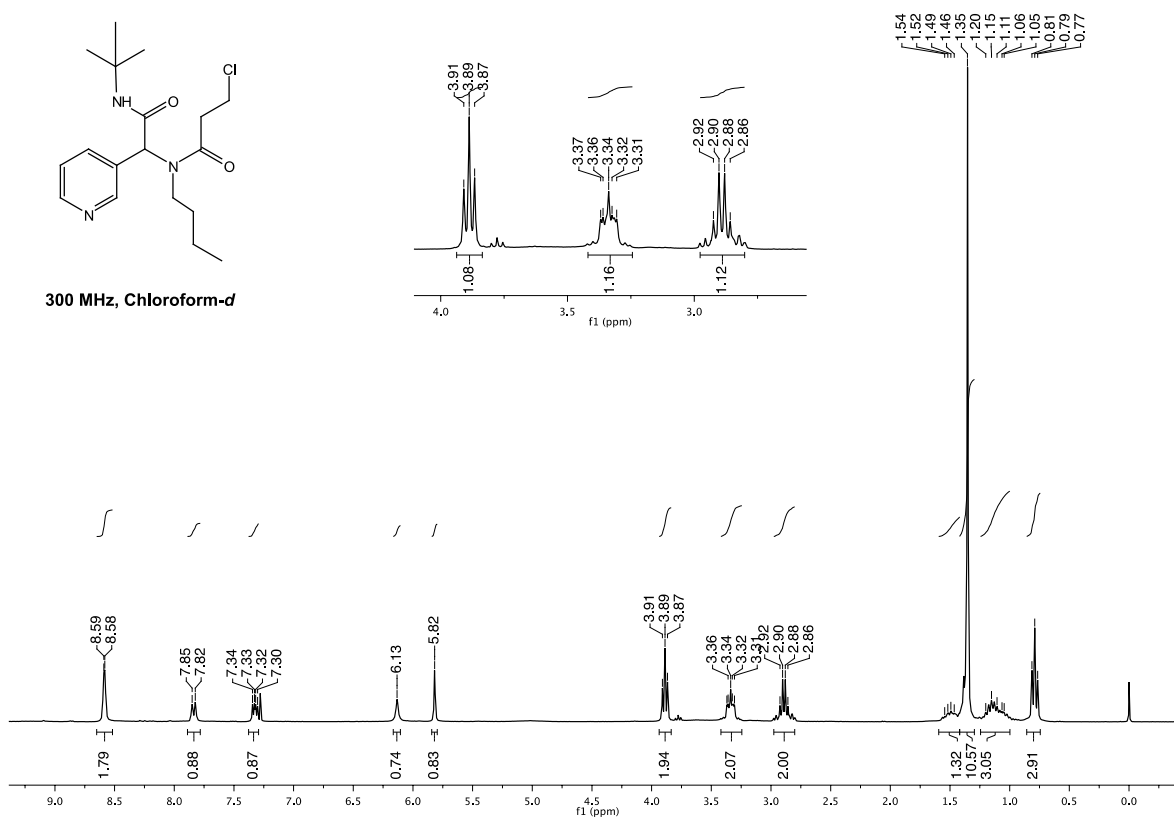
100 MHz, Chloroform-*d*



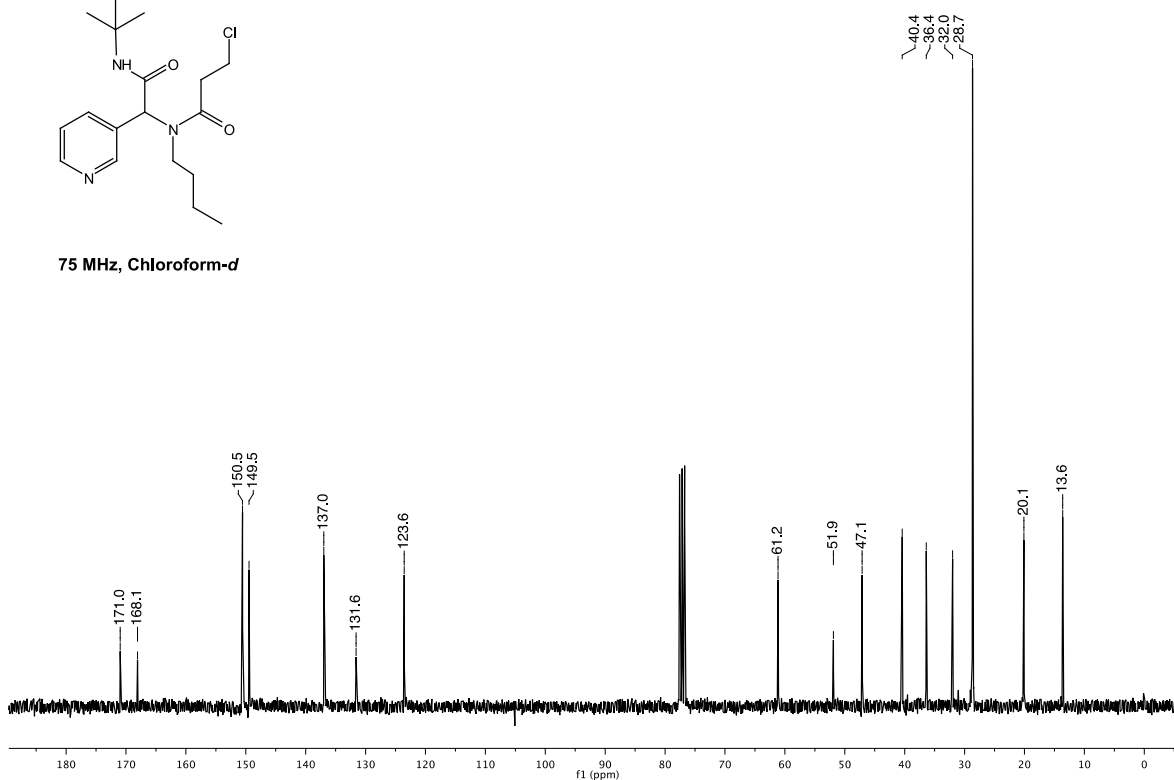
***N*-butyl-*N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloropropanamide (11j)**



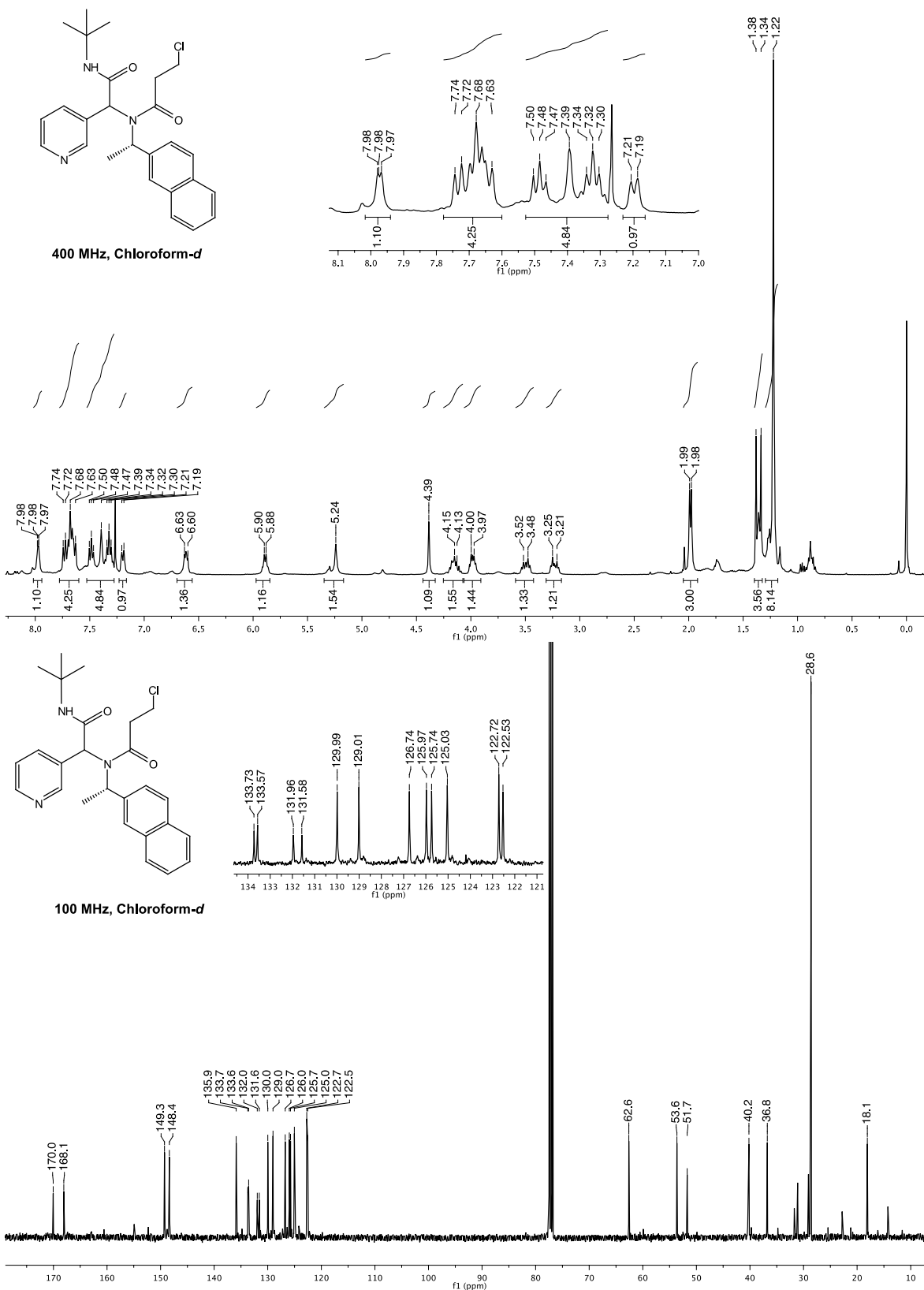
300 MHz, Chloroform-*d*



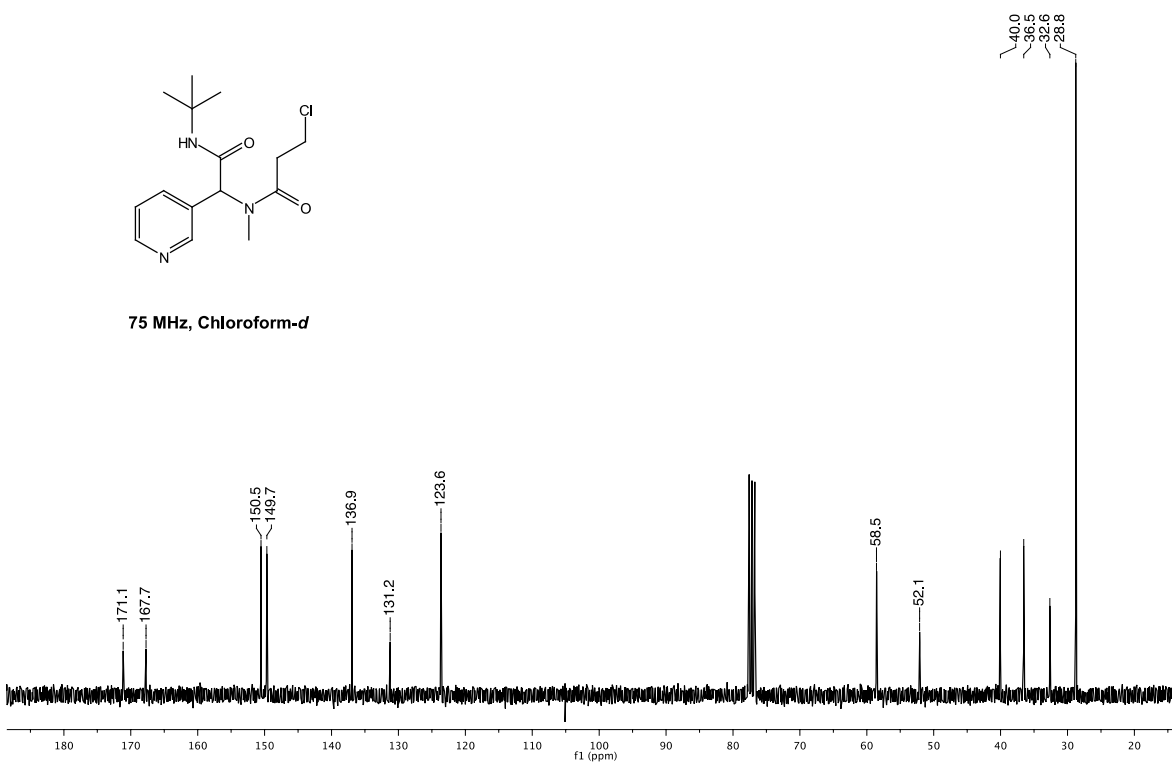
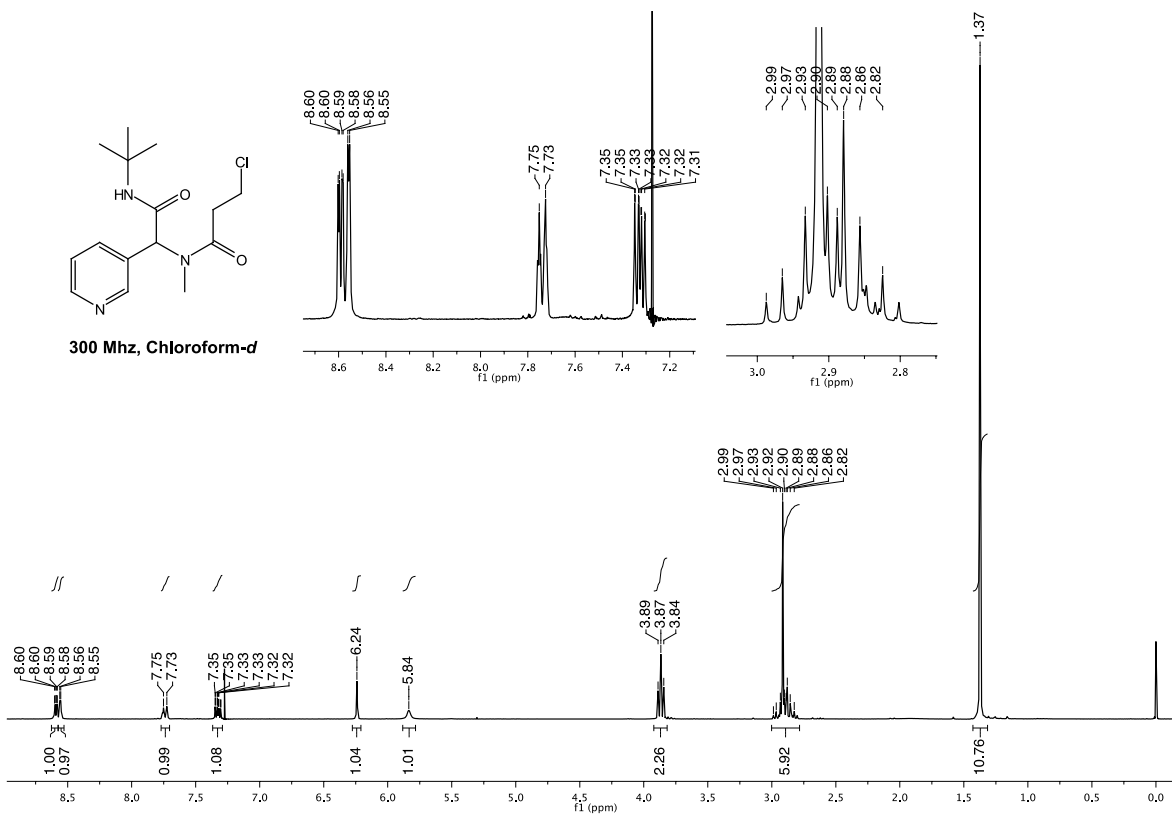
75 MHz, Chloroform-*d*



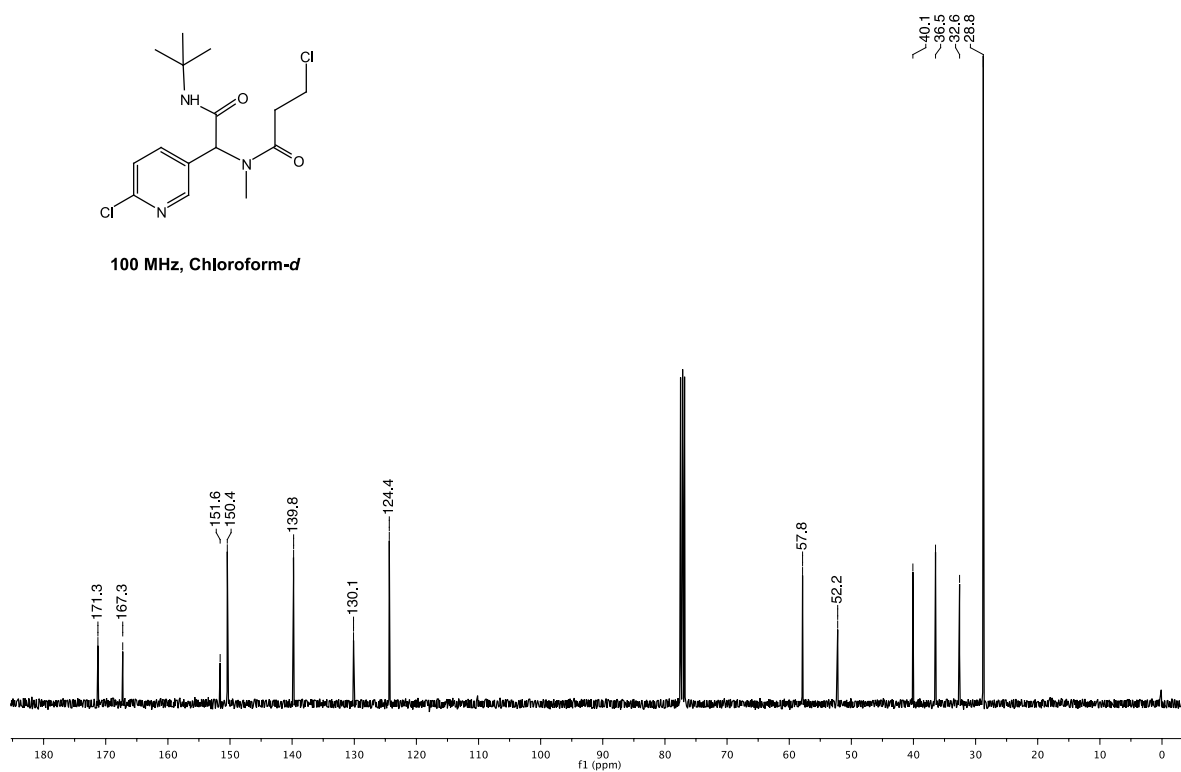
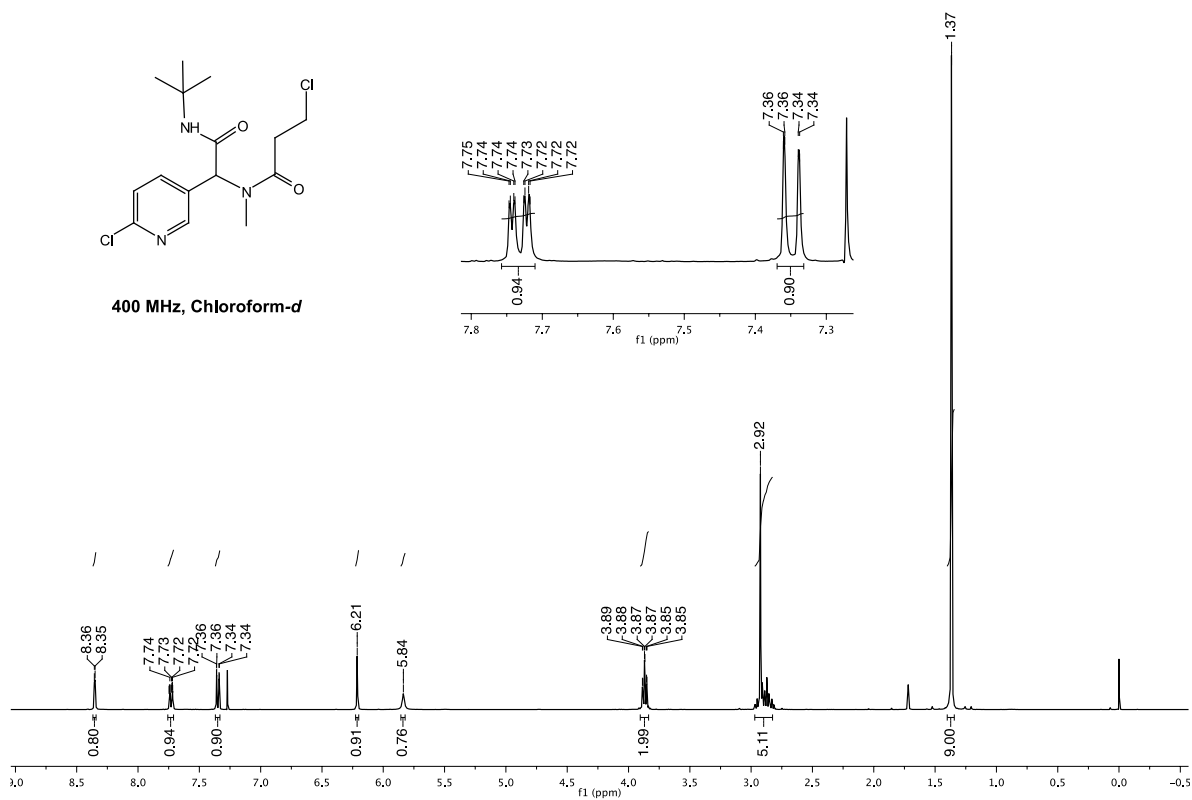
***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-((*S*)-1-(naphthalen-2-yl)ethyl)propanamide (11k)**



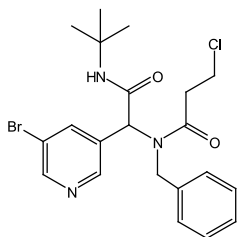
***N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloro-*N*-methylpropanamide (11)**



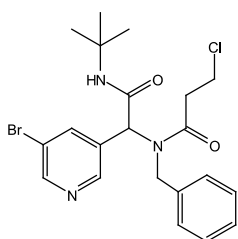
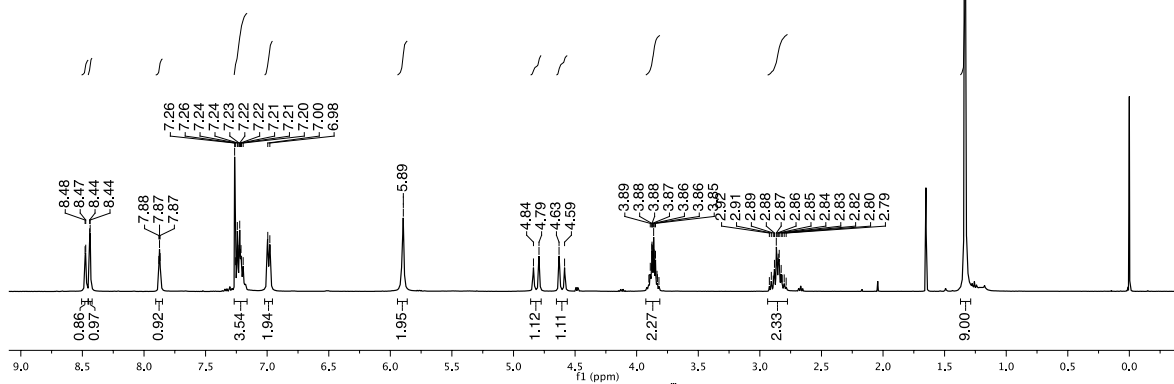
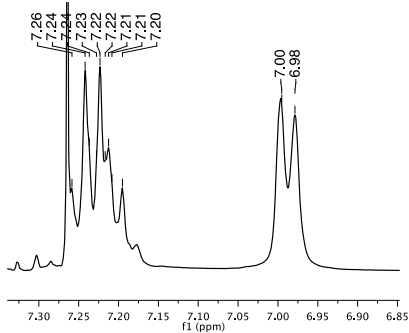
***N*-2-(*tert*-butylamino)-1-(6-chloropyridin-3-yl)-2-oxoethyl)-3-chloro-*N*-methylpropanamide (11m)**



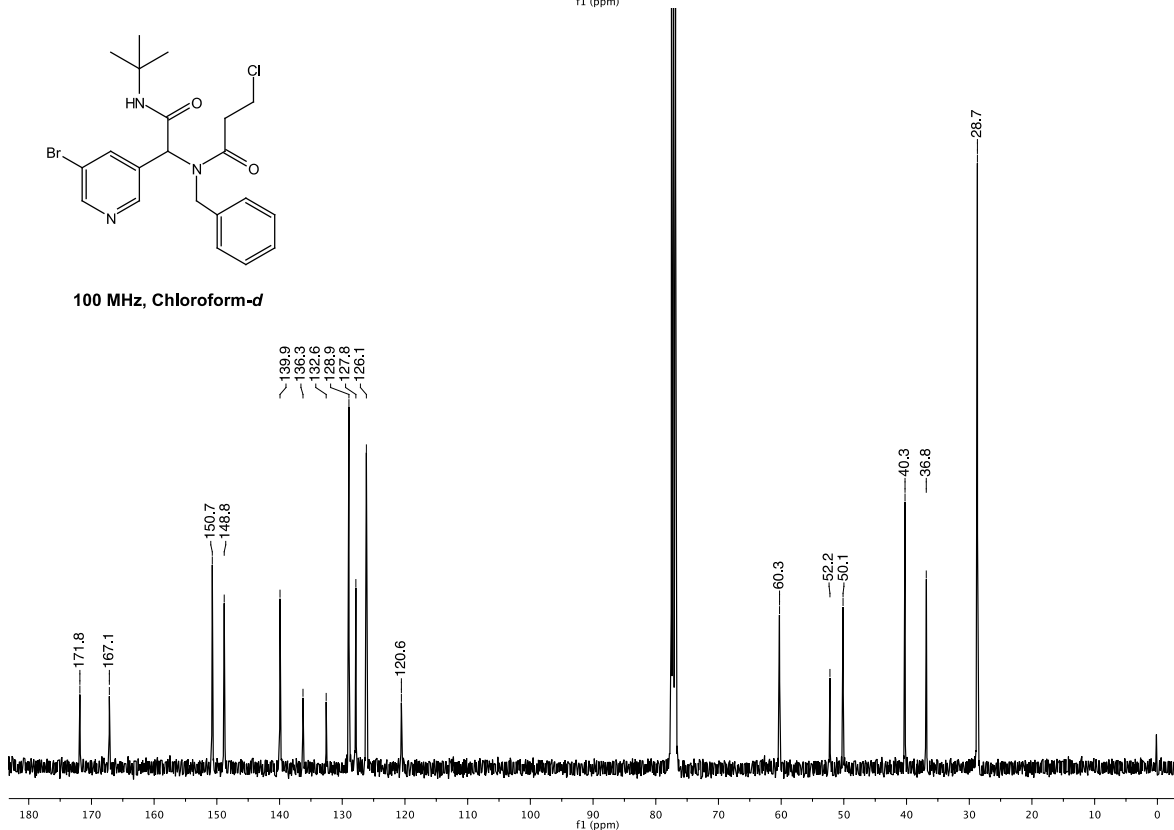
***N*3-benzyl-*N*-(1-(5-bromopyridin-3-yl)-2-(*tert*-butylamino)-2-oxoethyl)-3-chloropropanamide (11n)**



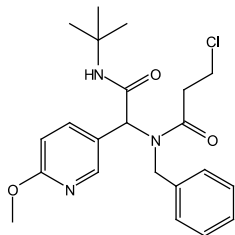
400 MHz, Chloroform-*d*



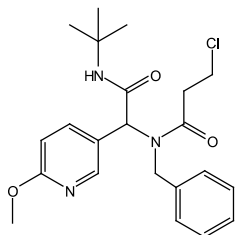
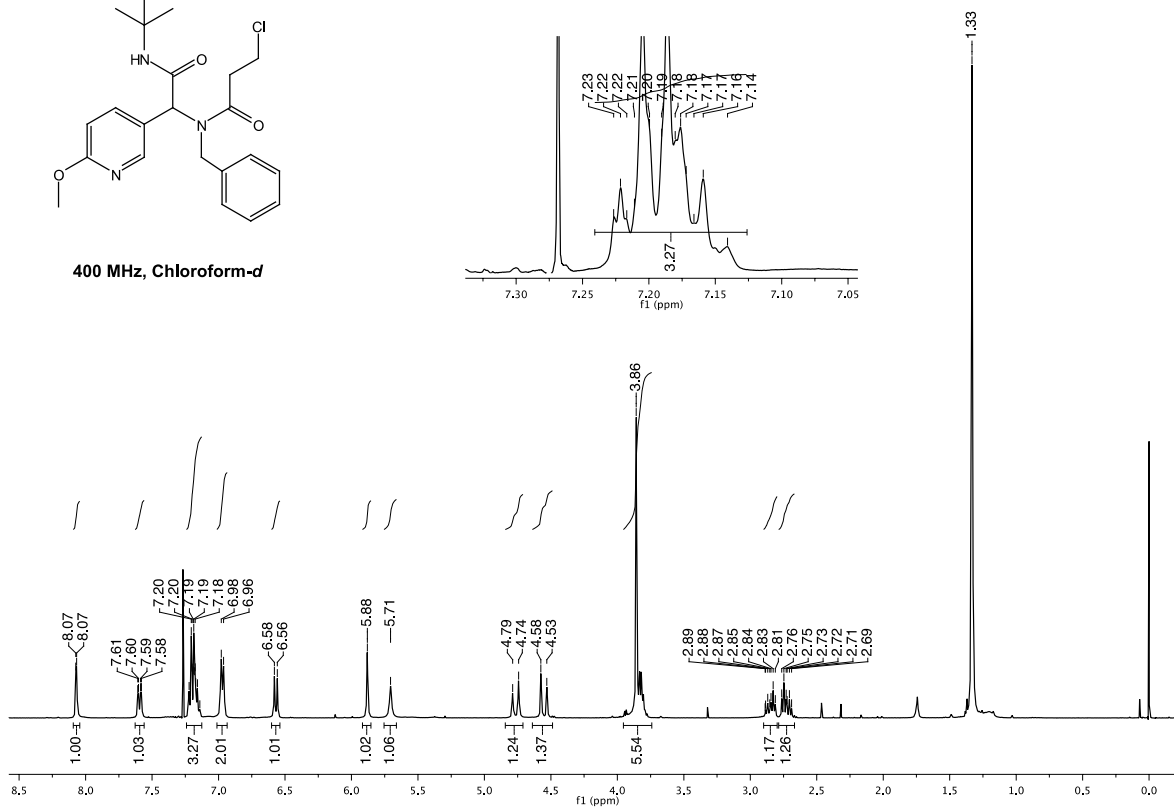
100 MHz, Chloroform-*d*



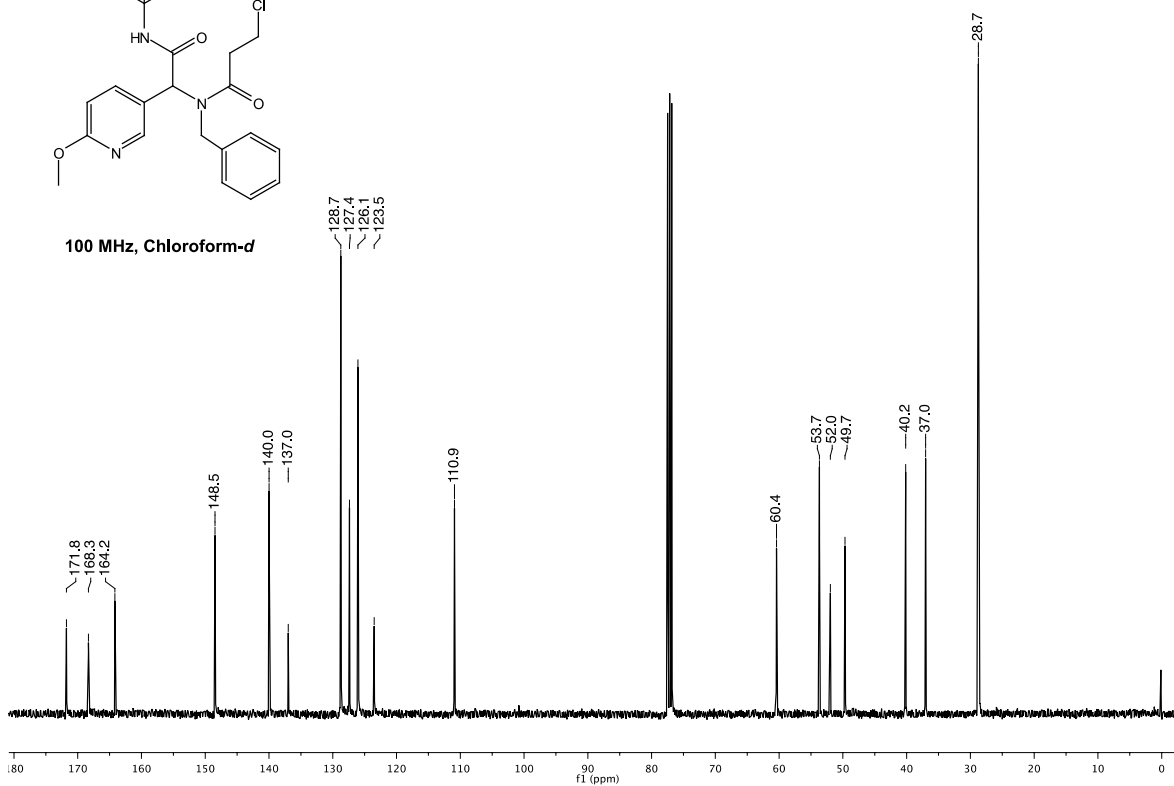
***N*-benzyl-*N*-(2-(*tert*-butylamino)-1-(6-methoxypyridin-3-yl)-2-oxoethyl)-3-chloropropanamide (11o)**



400 MHz, Chloroform-*d*

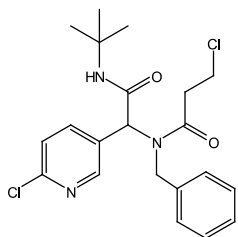


100 MHz, Chloroform-*d*

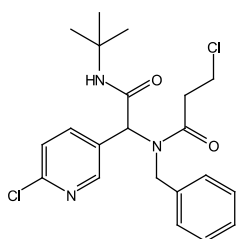
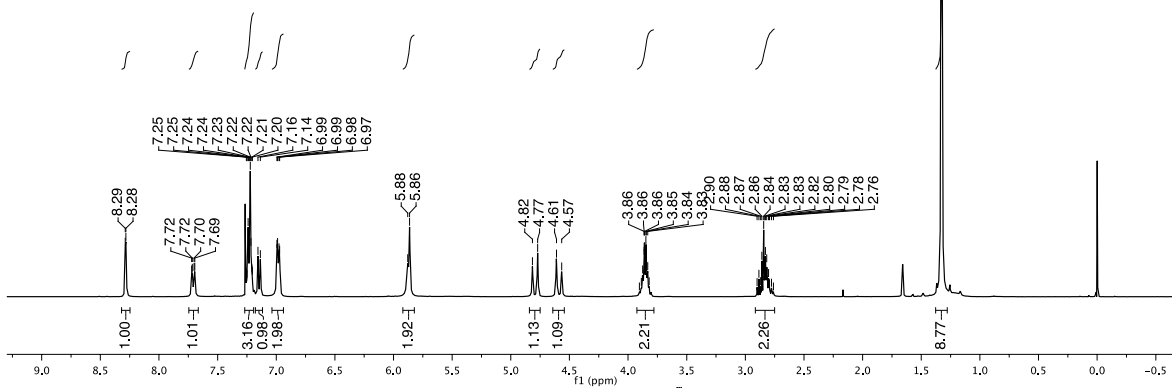
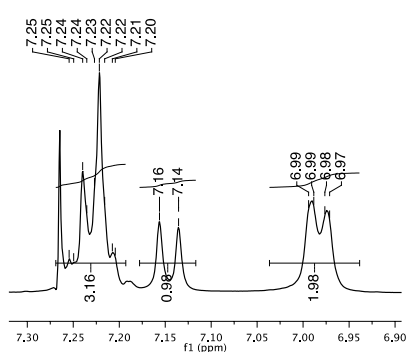




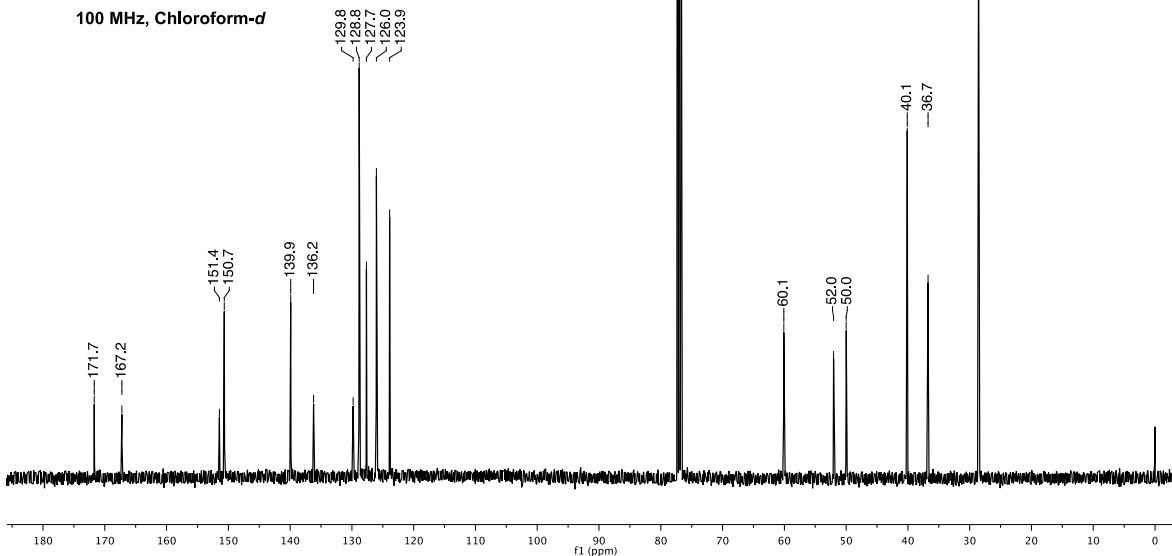
***N*-benzyl-*N*-(2-(*tert*-butylamino)-1-(6-chloropyridin-3-yl)-2-oxoethyl)-3-chloro  
propanamide (11p)**



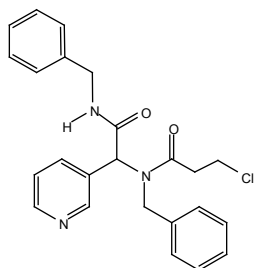
400 MHz, Chloroform-*d*



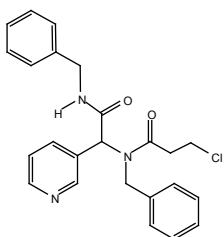
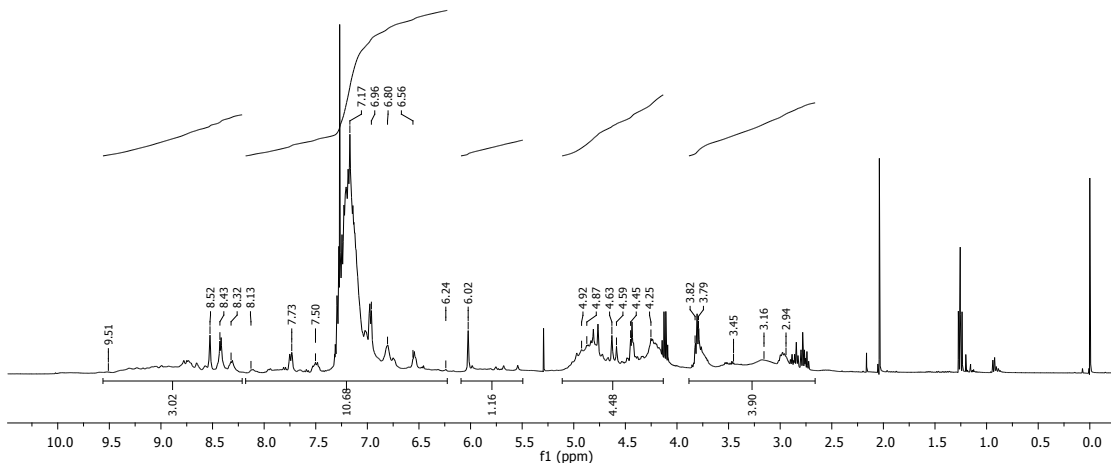
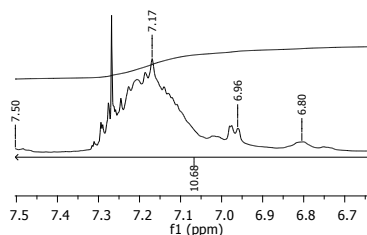
100 MHz, Chloroform-*d*



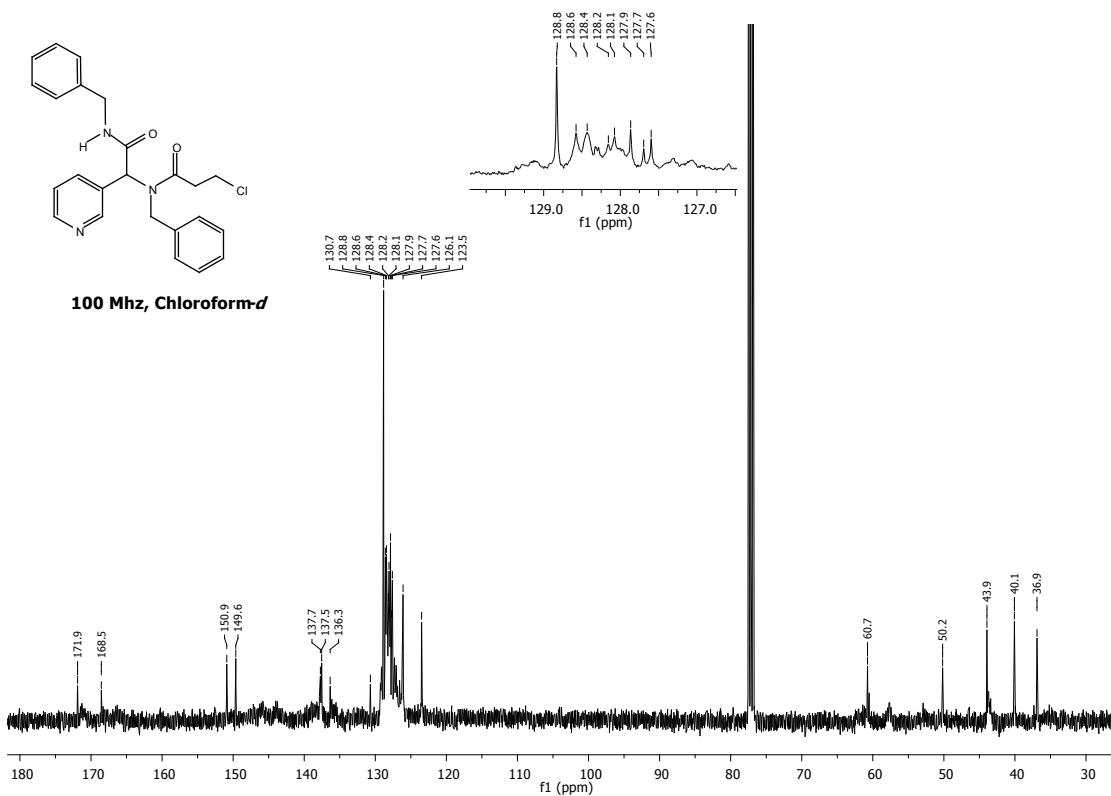
***N*-benzyl-*N*-(2-(benzylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-3-chloropropanamide (11q)**



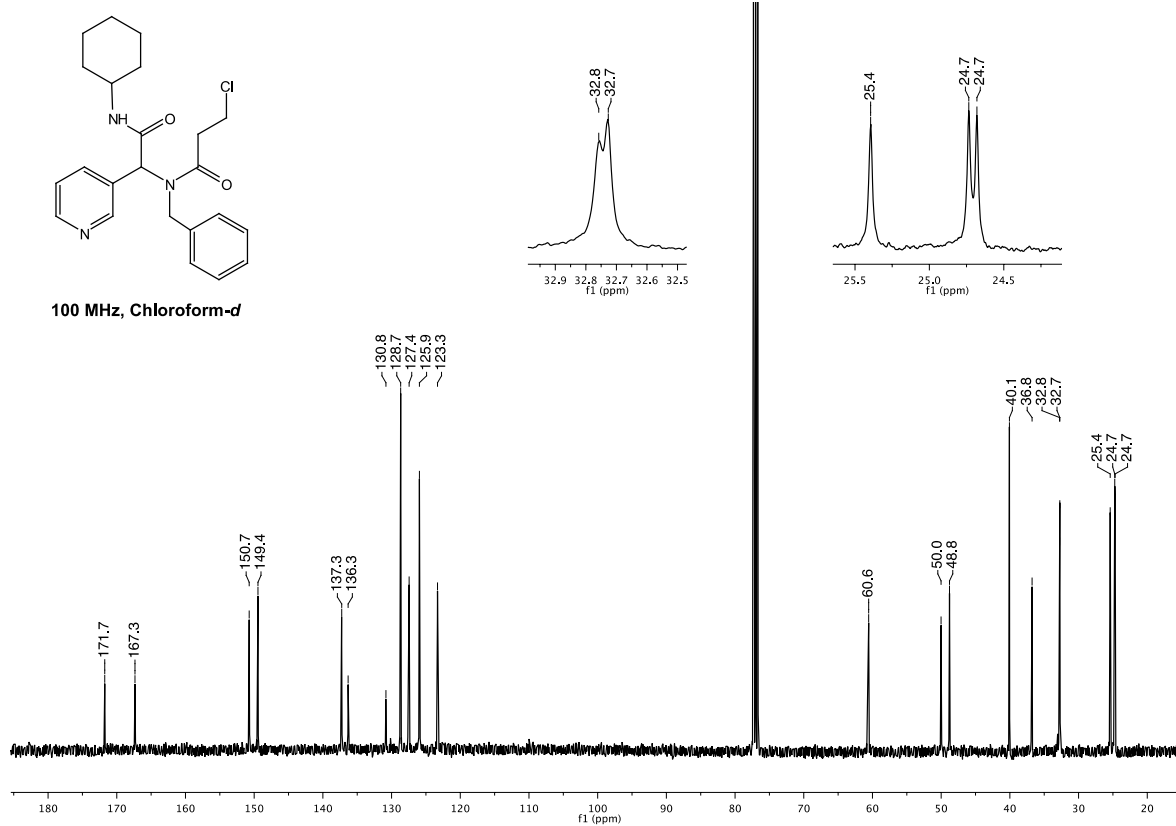
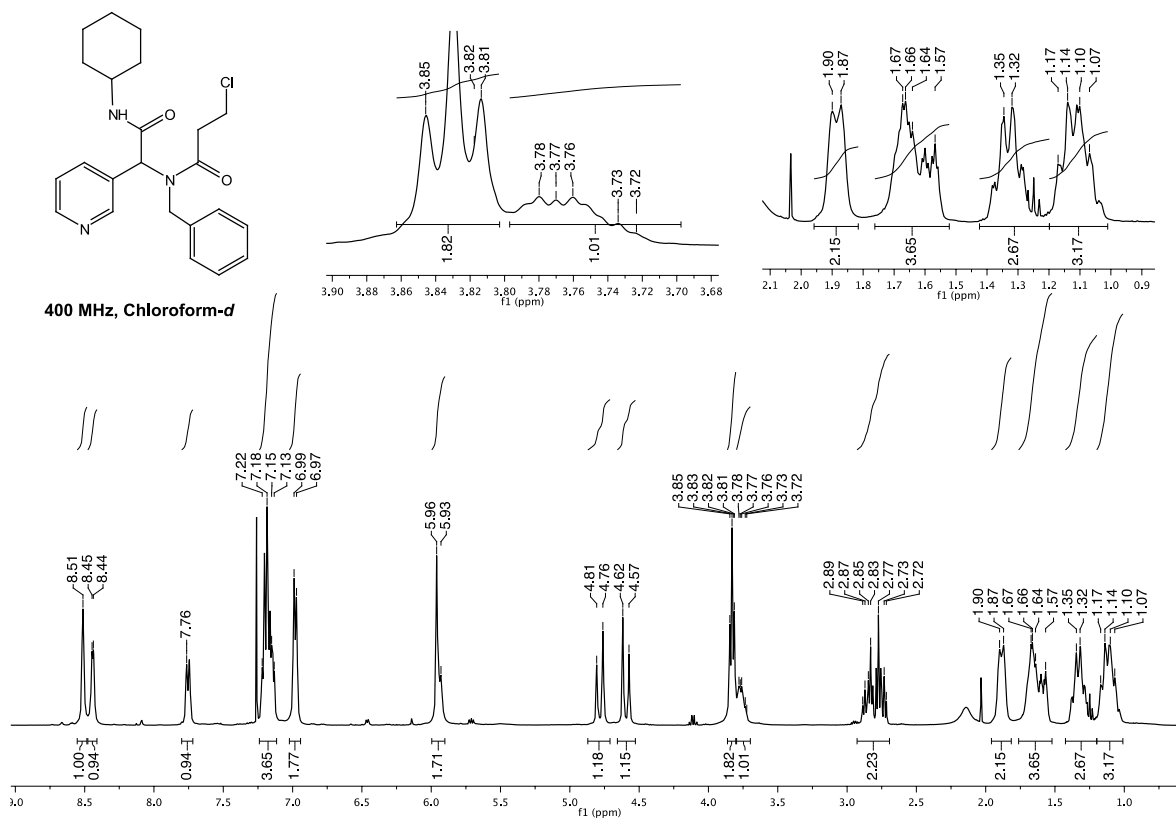
**400 MHz, Chloroform-*d***



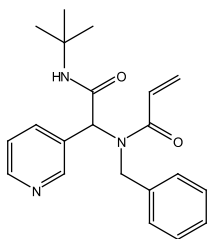
**100 Mhz, Chloroform-*d***



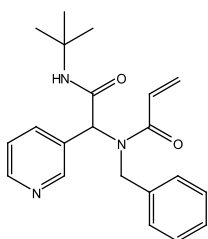
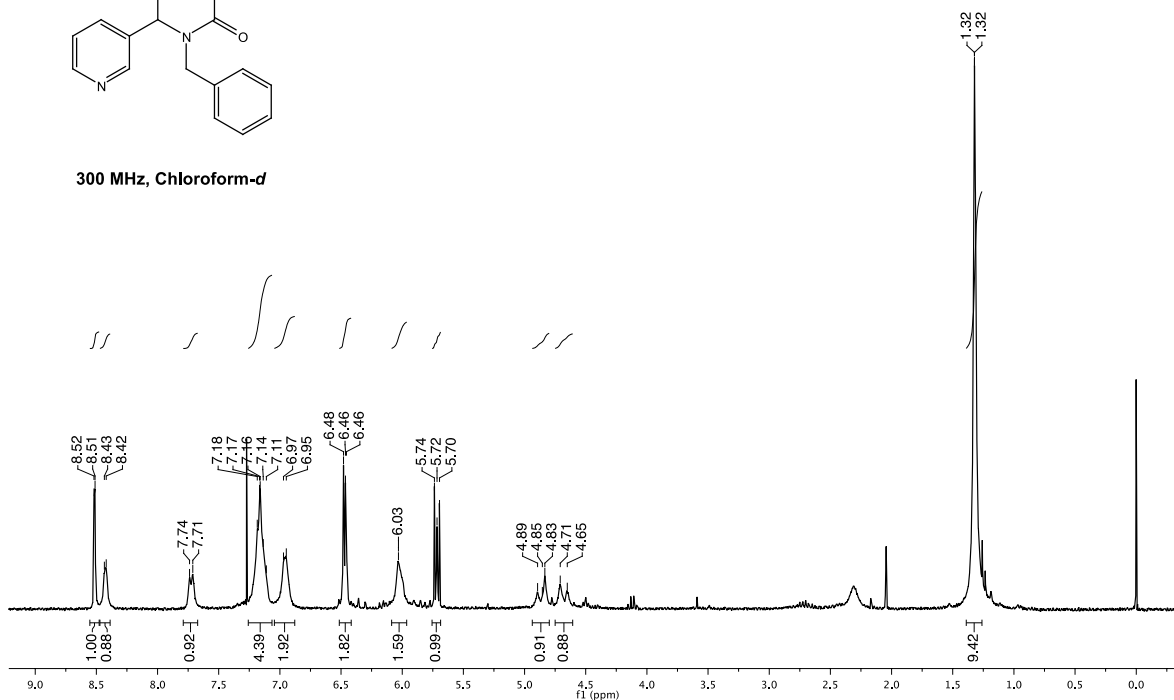
***N*-benzyl-3-chloro-*N*-(2-(cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl)propanamide (11r)**



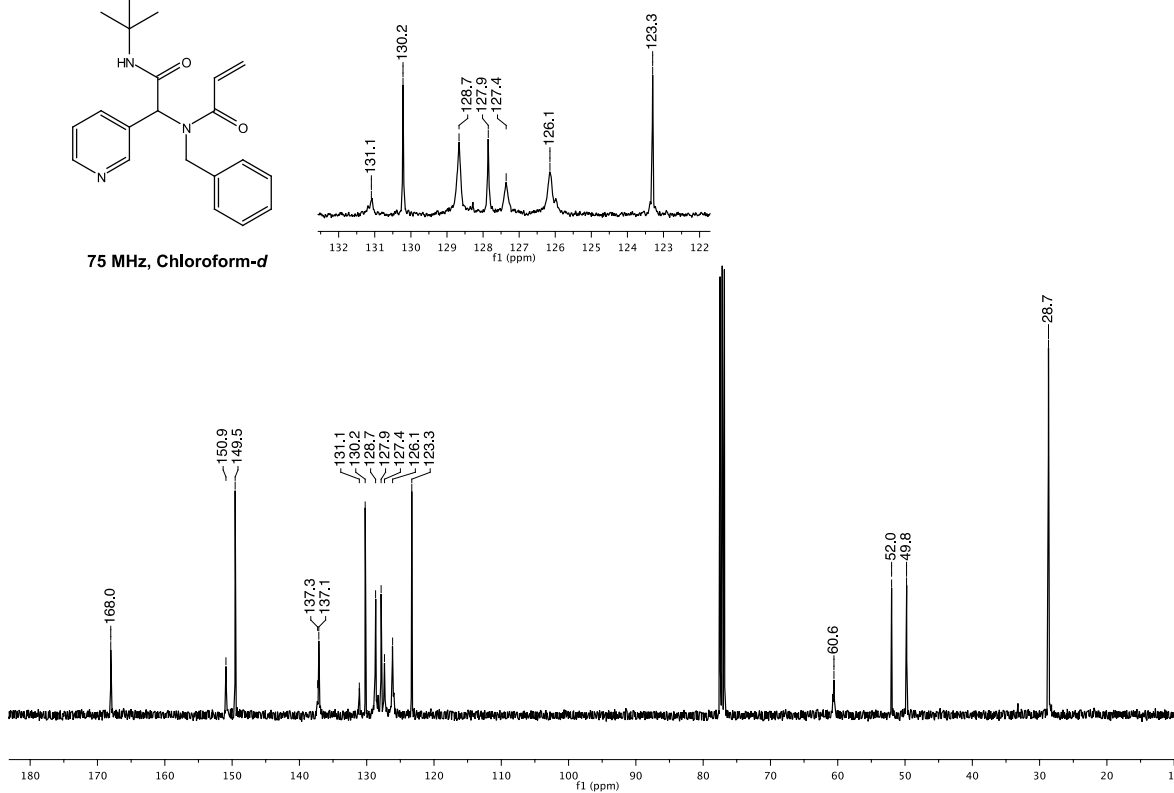
# *N*-benzyl-*N*-(2-(*tert*-butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)acrylamide (13)



300 MHz, Chloroform-*d*

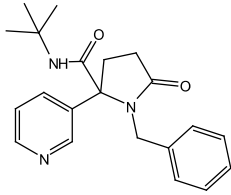


75 MHz, Chloroform-*d*

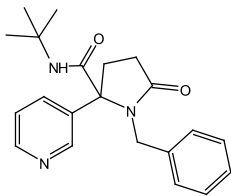
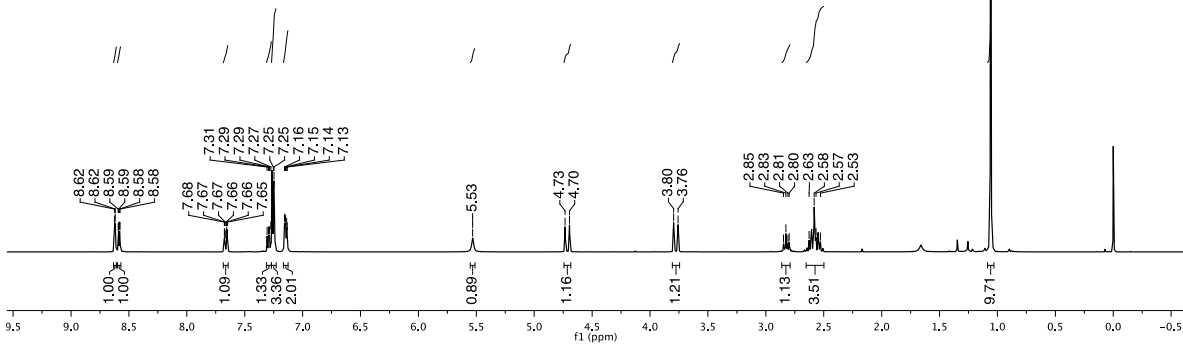
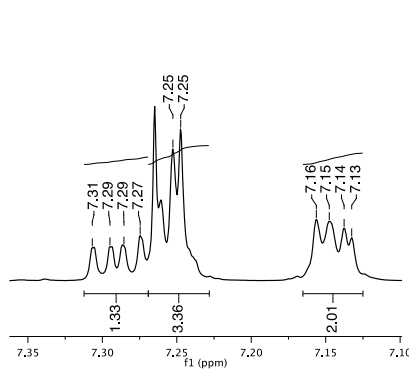


# COTININE ANALOGS SPECTRA

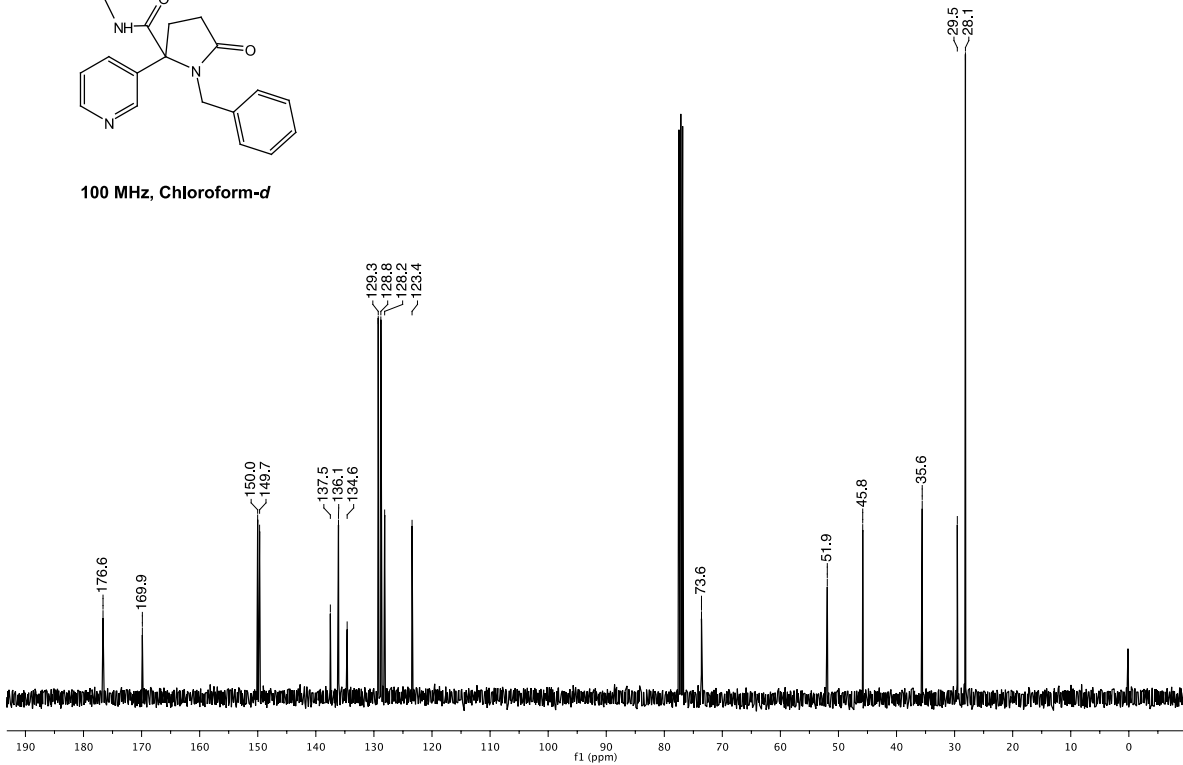
## 1-benzyl-N-(tert-butyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12a)



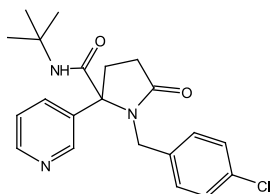
400 MHz, Chloroform-d



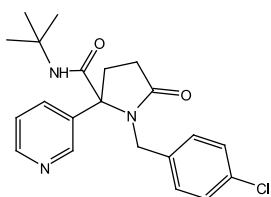
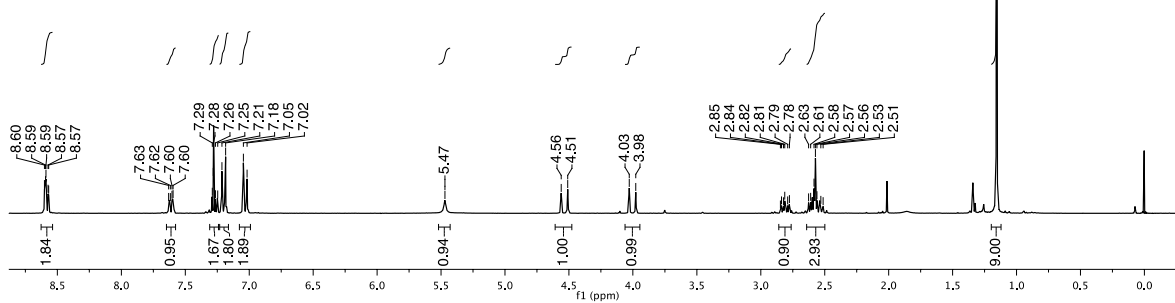
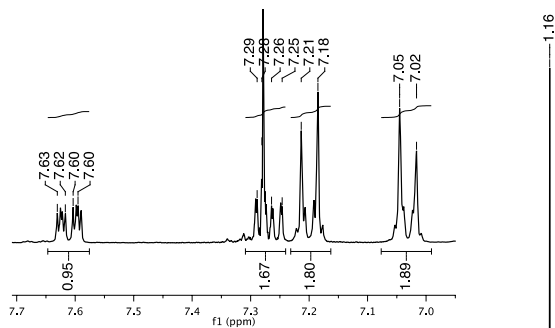
100 MHz, Chloroform-d



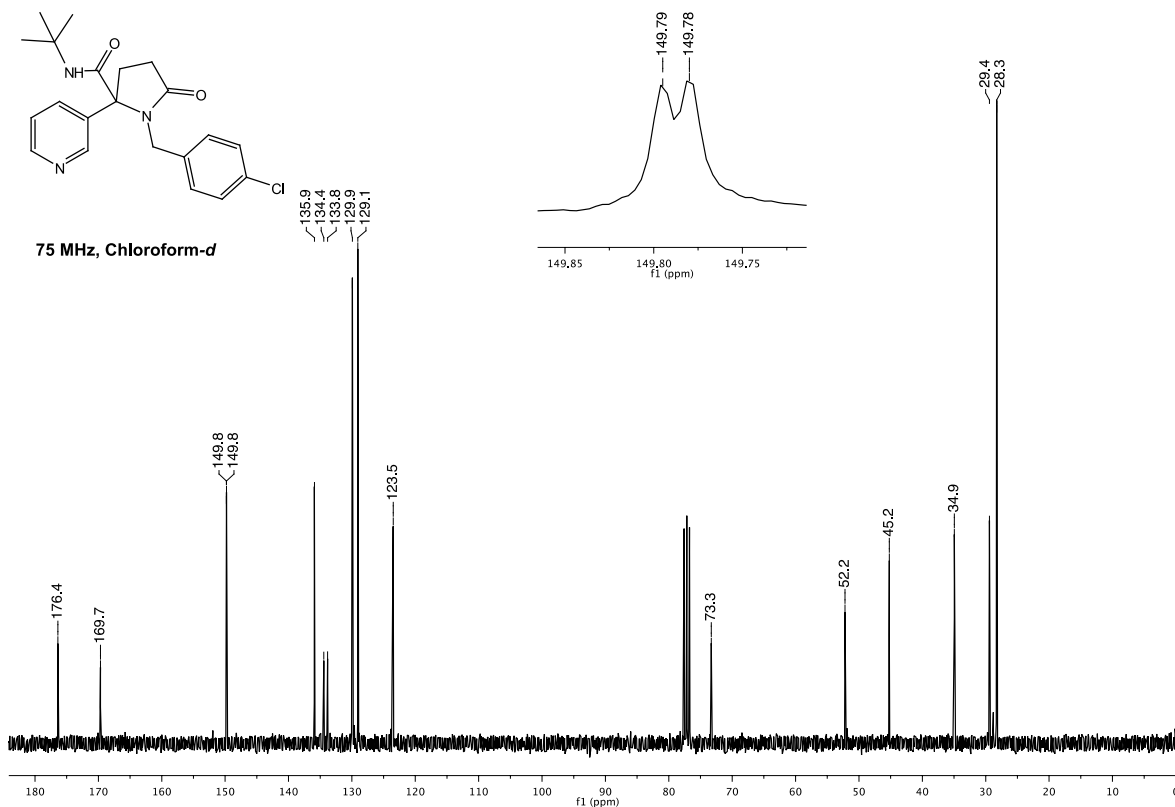
***N*-(*tert*-butyl)-1-(4-chlorobenzyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12b)**



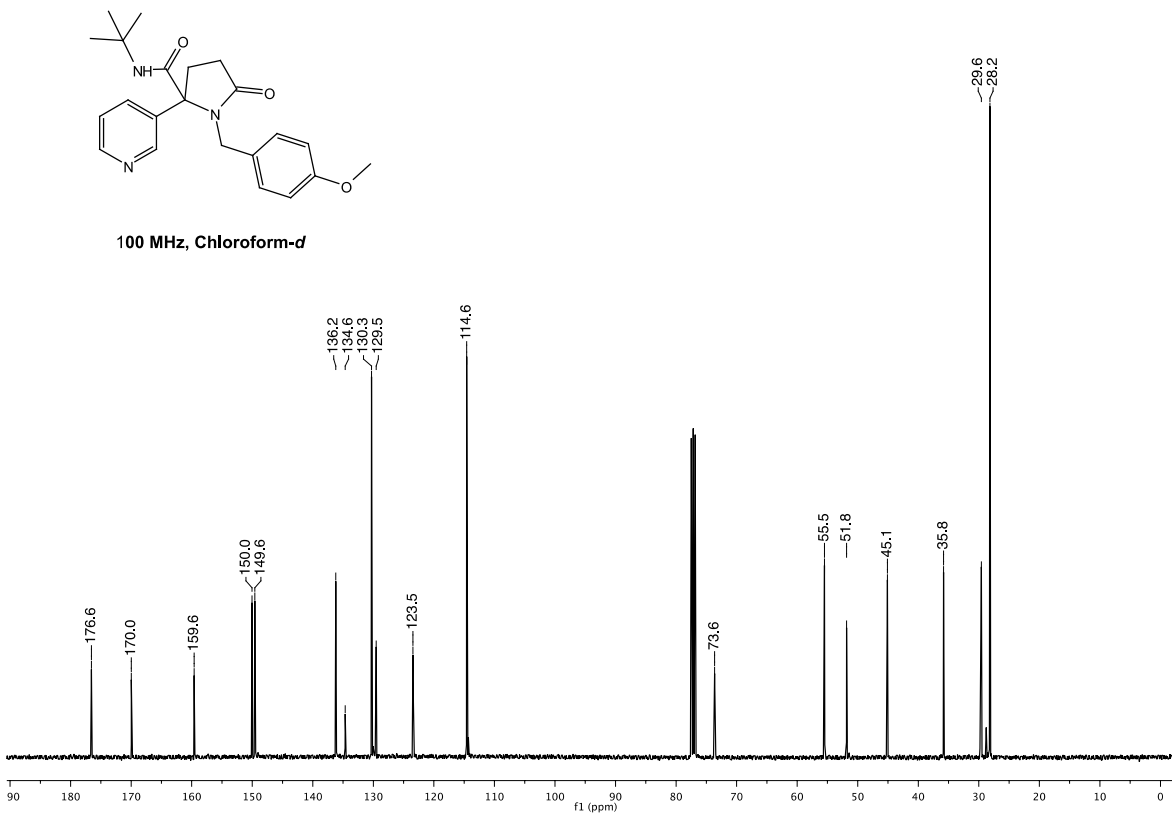
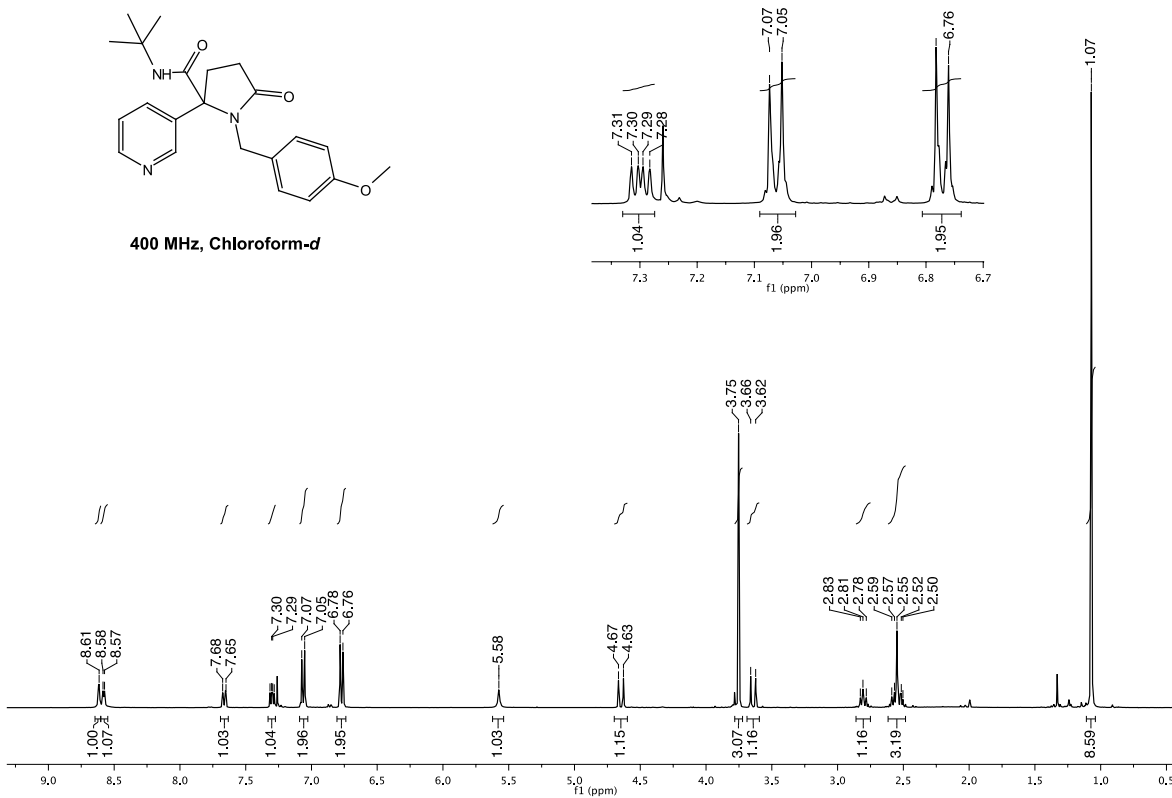
300 MHz, Chloroform-*d*



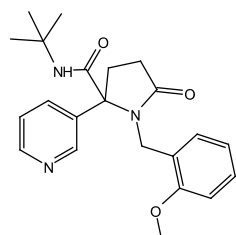
75 MHz, Chloroform-*d*



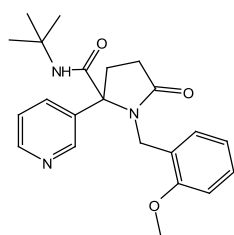
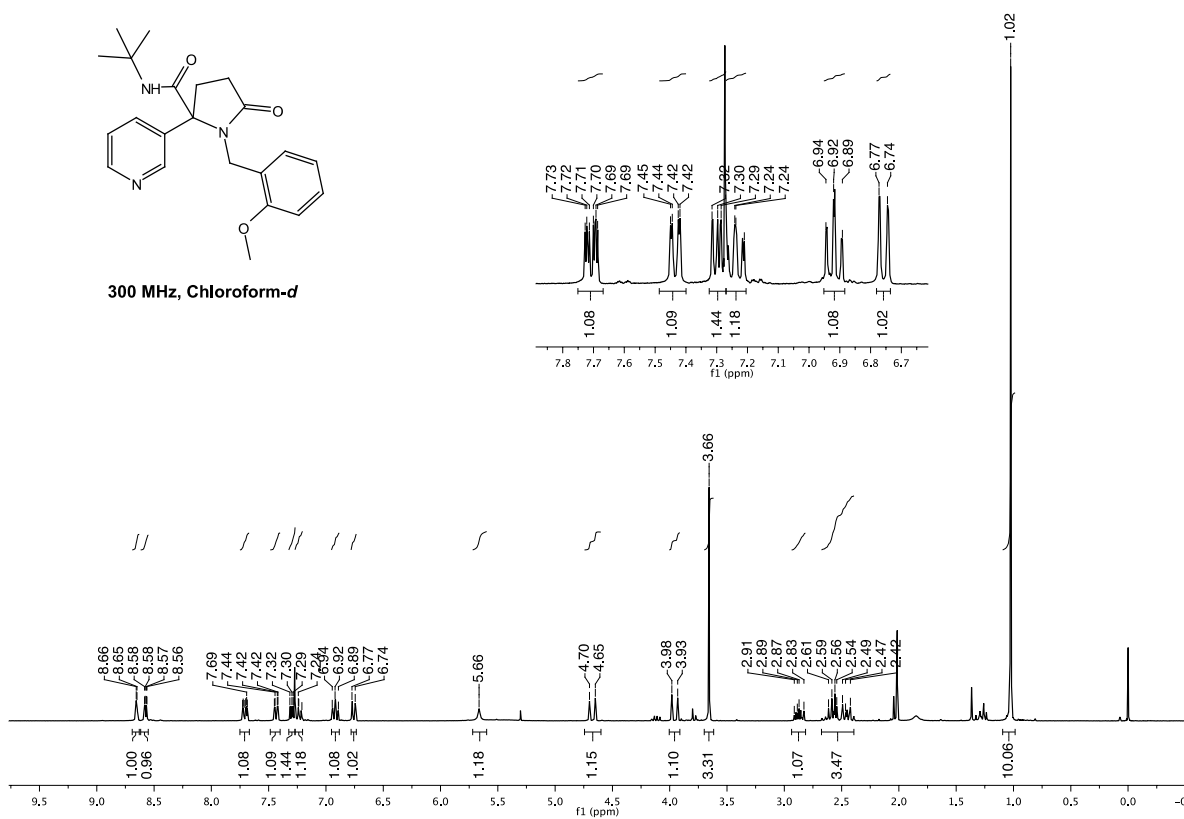
***N*-(*tert*-butyl)-1-(4-methoxybenzyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12c)**



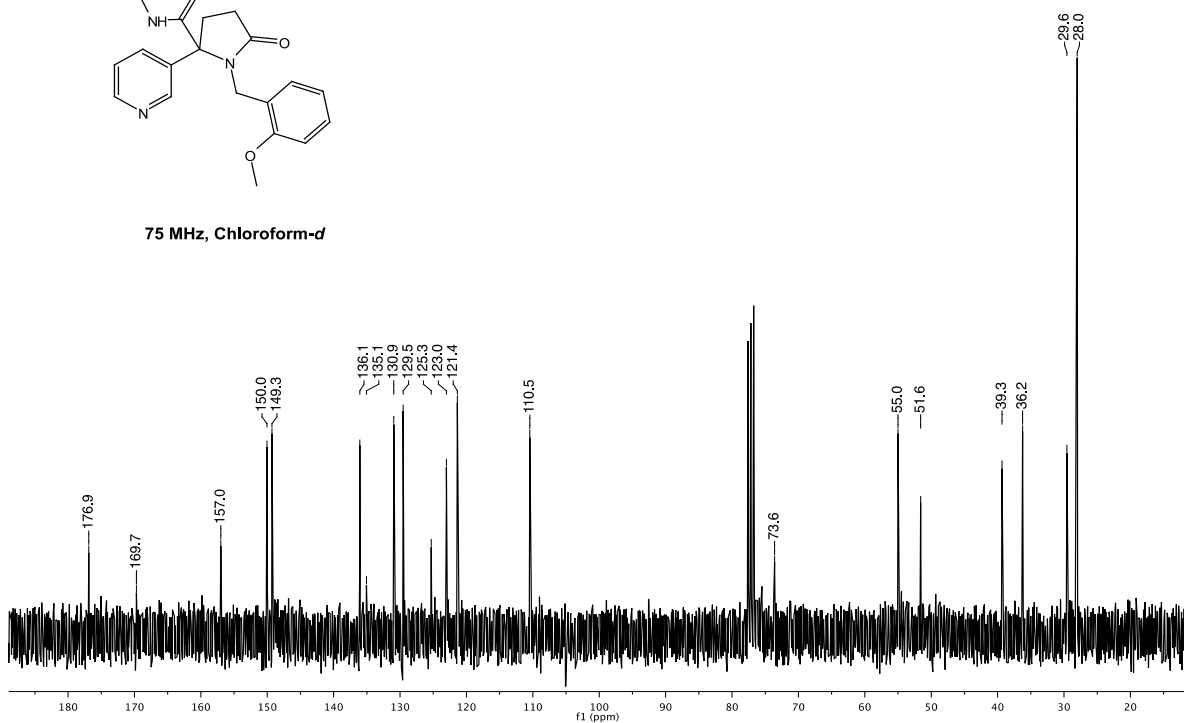
***N*-(*tert*-butyl)-1-(2-methoxybenzyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12d)**



300 MHz, Chloroform-*d*

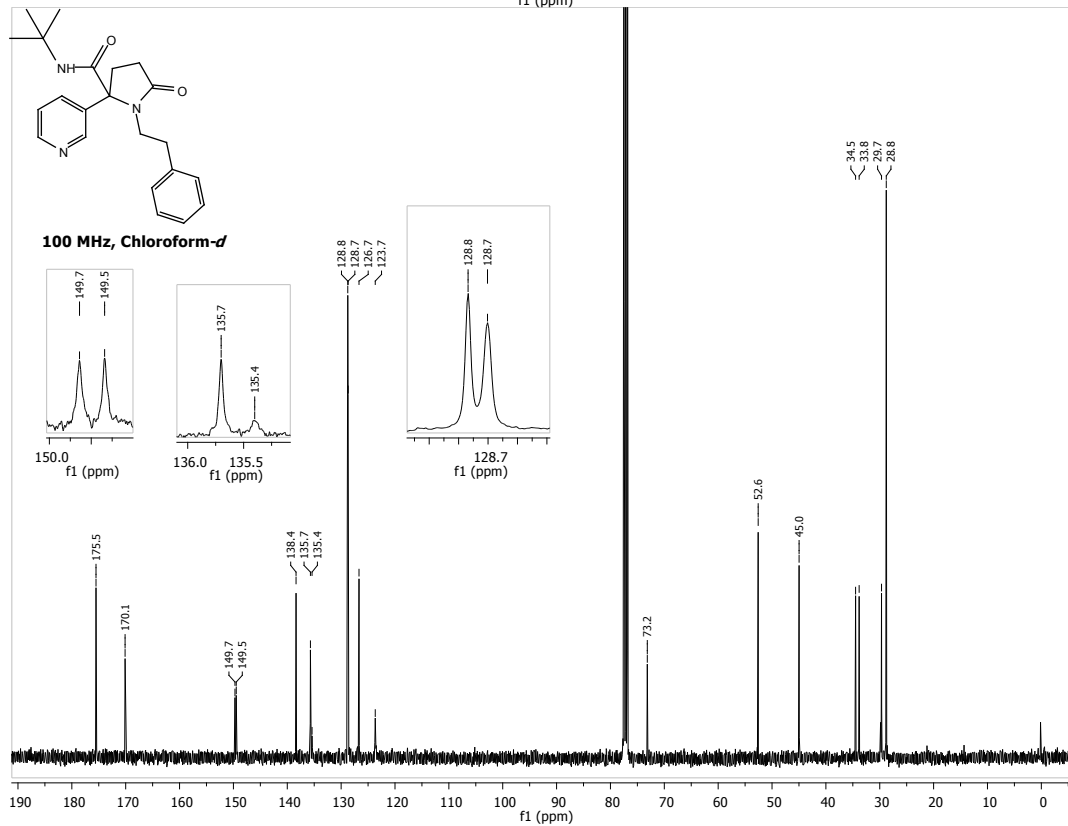
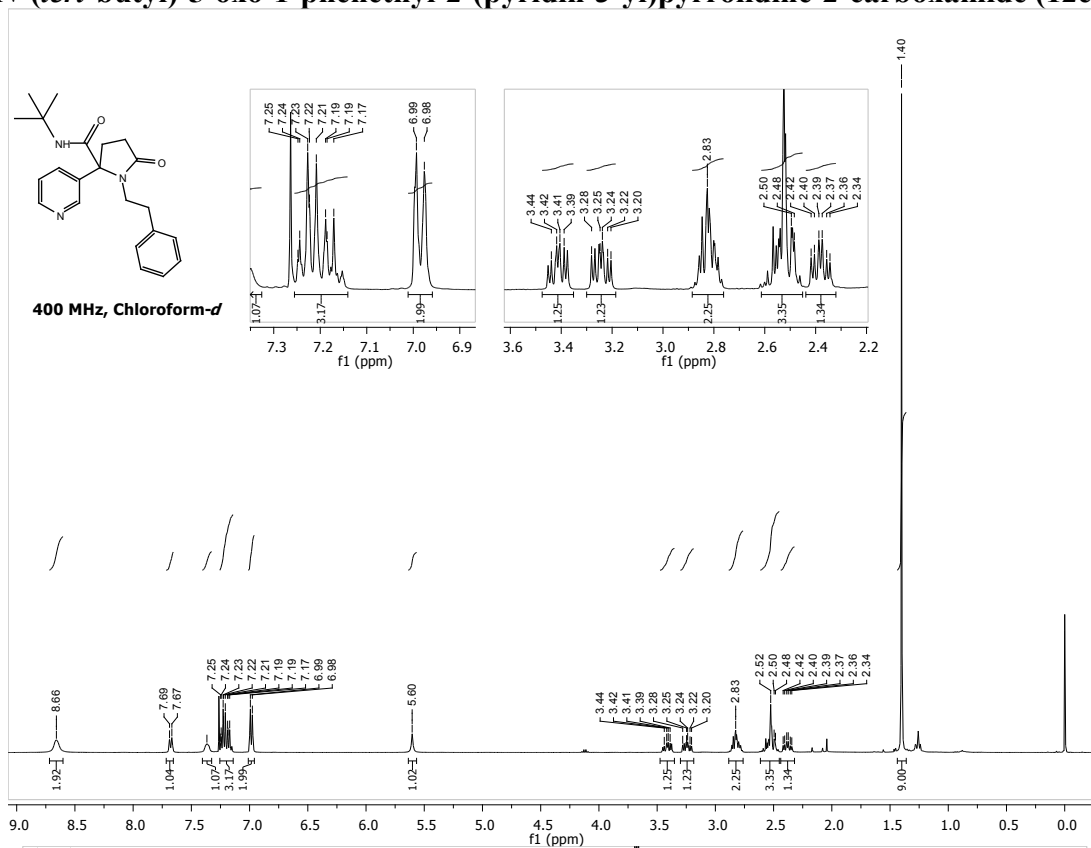


75 MHz, Chloroform-*d*

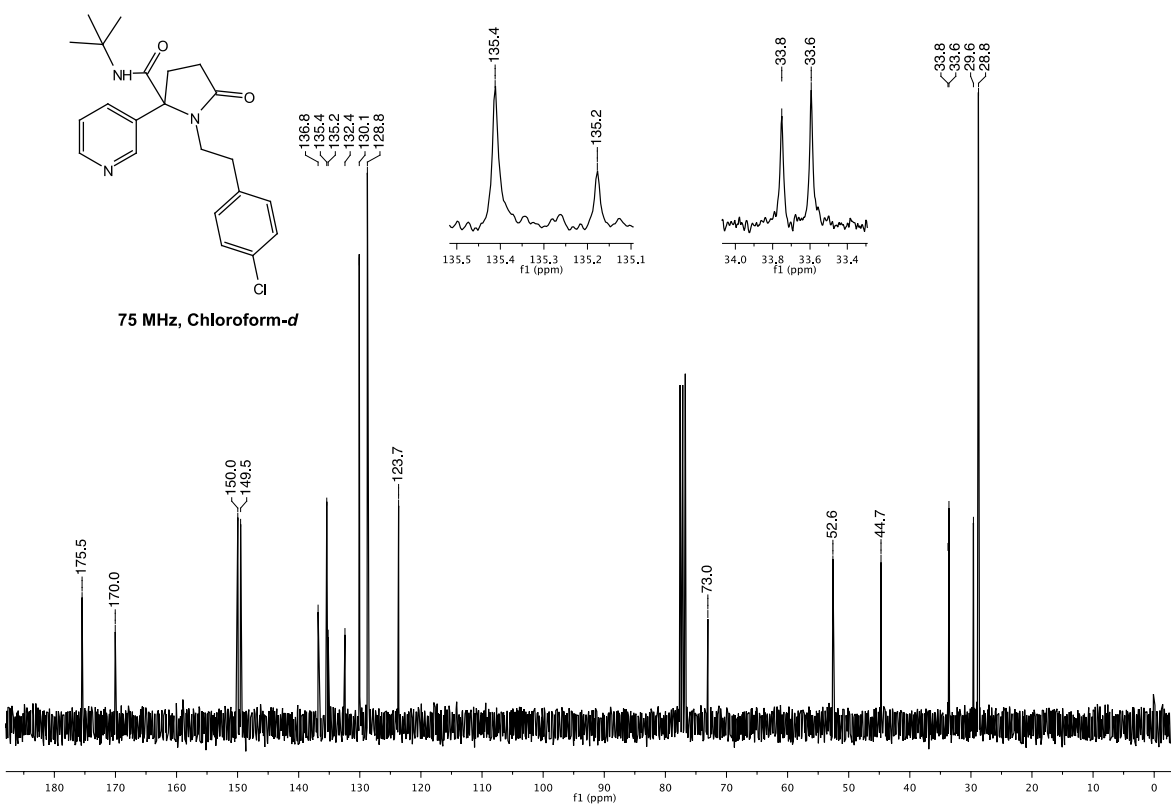
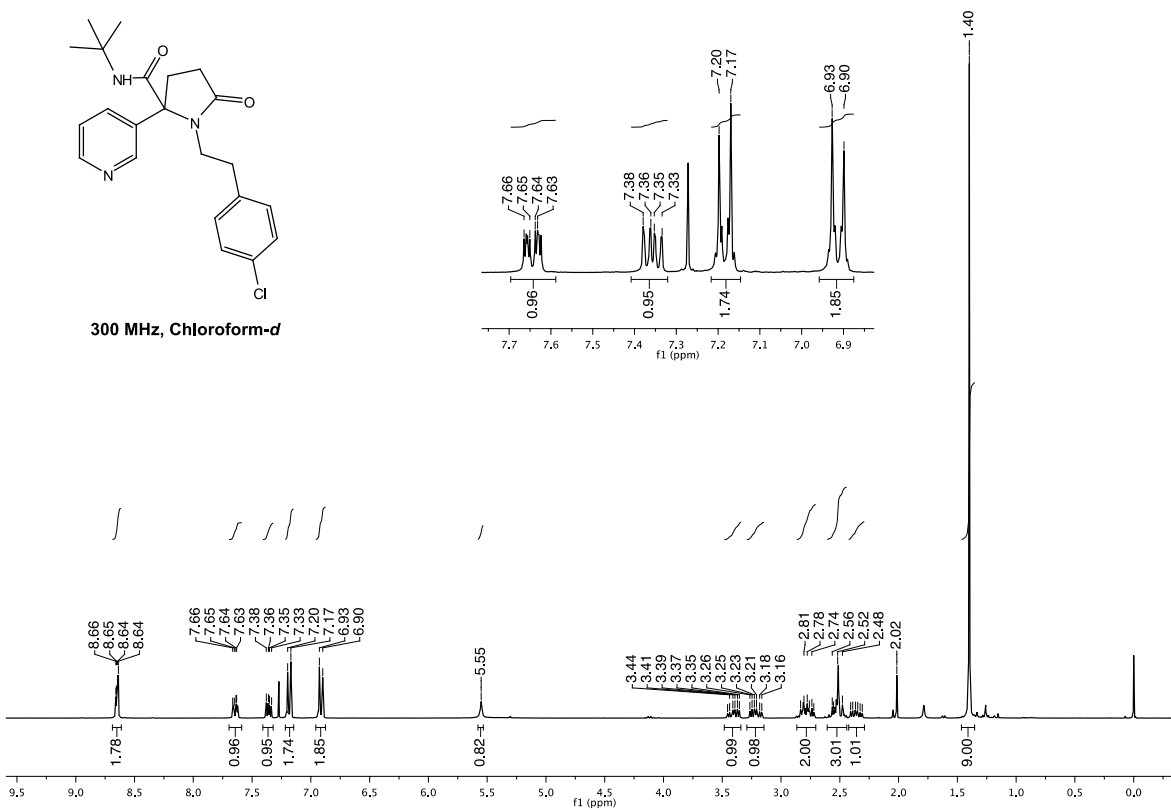




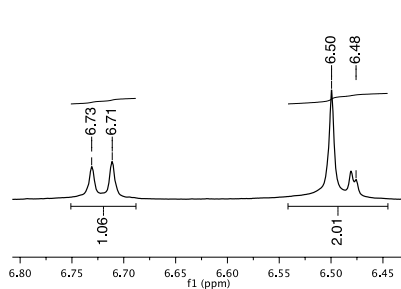
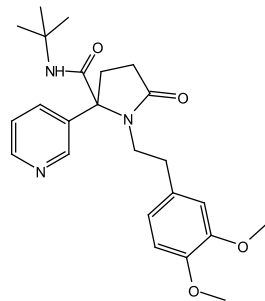
***N*-(*tert*-butyl)-5-oxo-1-phenethyl-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12e).**



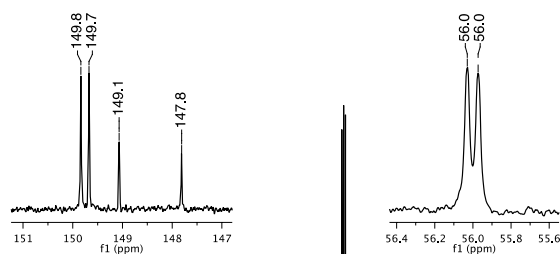
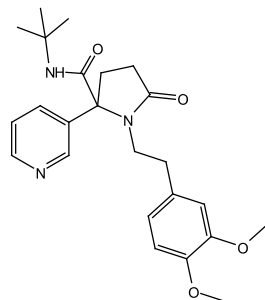
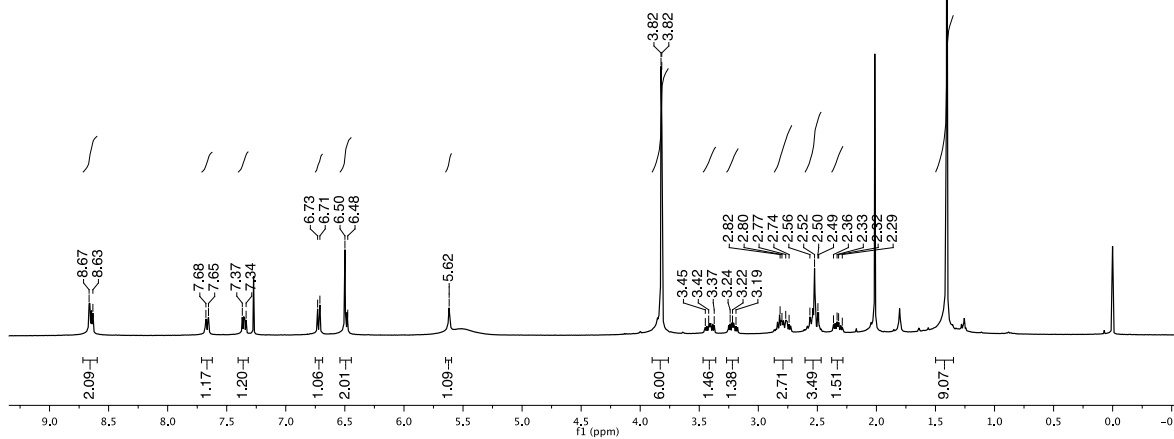
***N*-(*tert*-butyl)-1-(4-chlorophenethyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12f)**



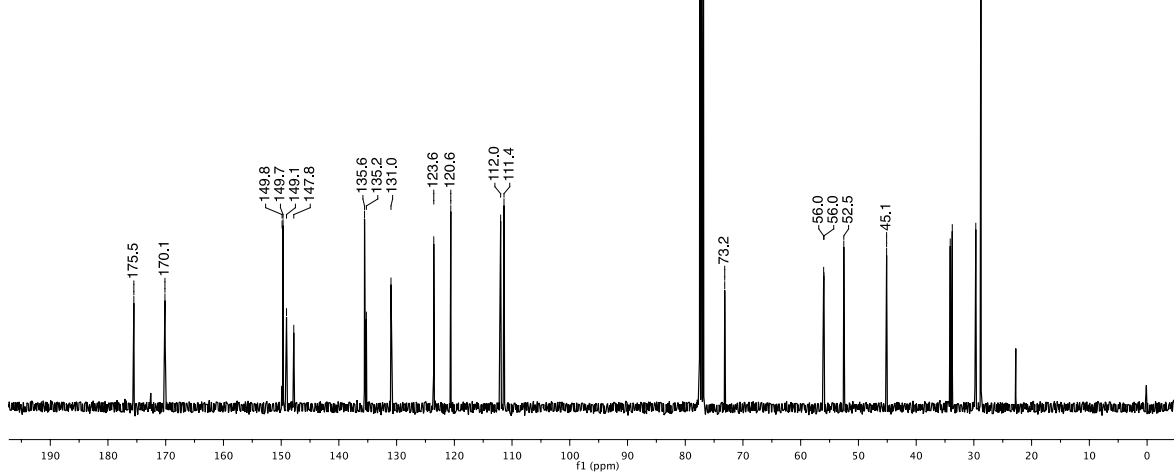
***N*-(*tert*-butyl)-1-(3,4-dimethoxyphenethyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12g)**



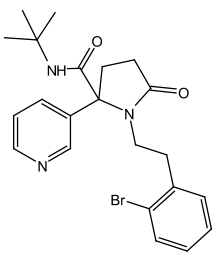
400 MHz, Chloroform-*d*



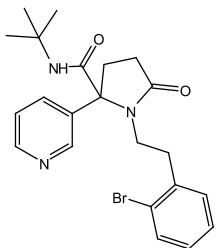
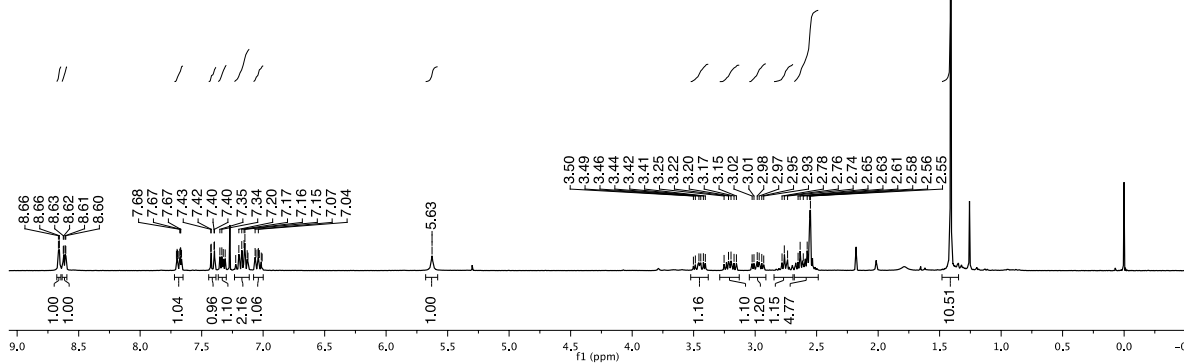
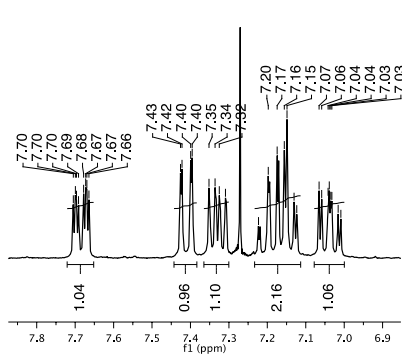
100 MHz, Chloroform-*d*



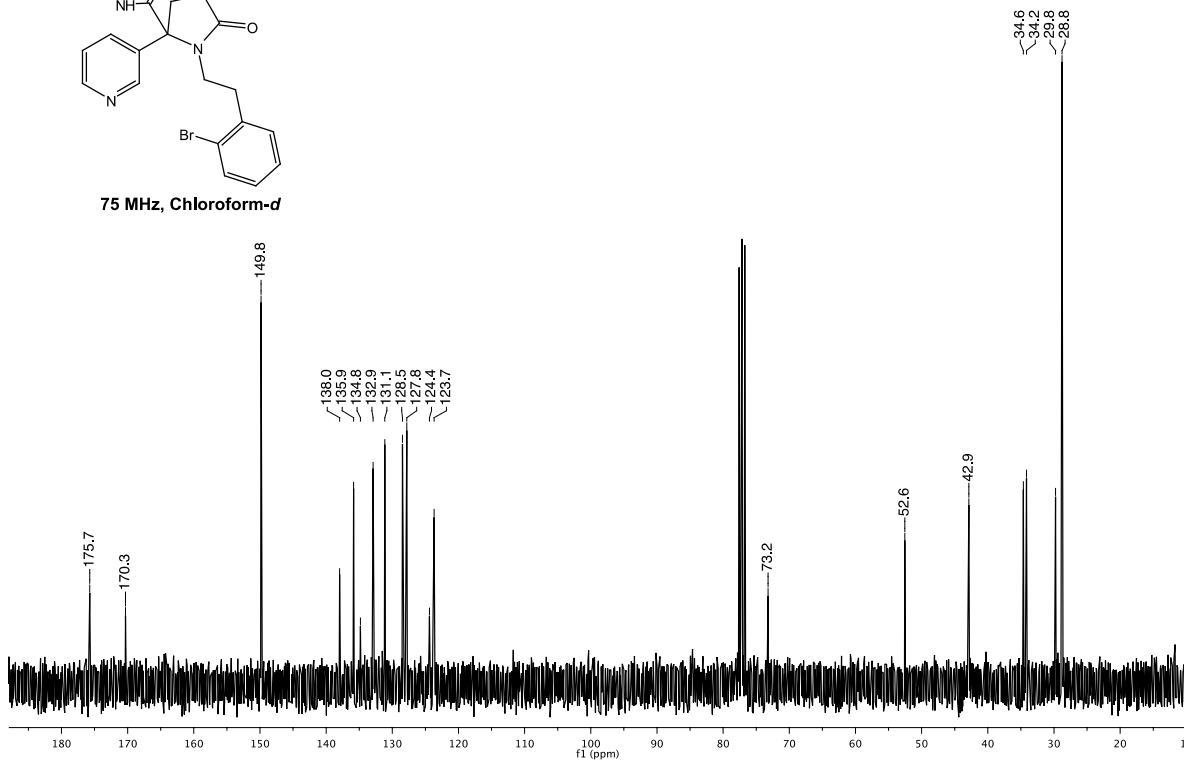
**1-(2-bromophenethyl)-N-(tert-butyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12h)**



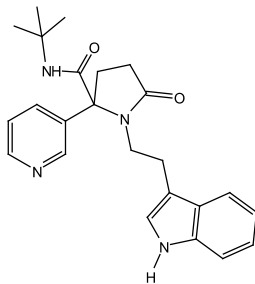
300 MHz, Chloroform-d



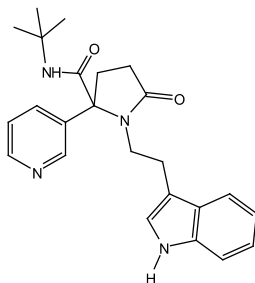
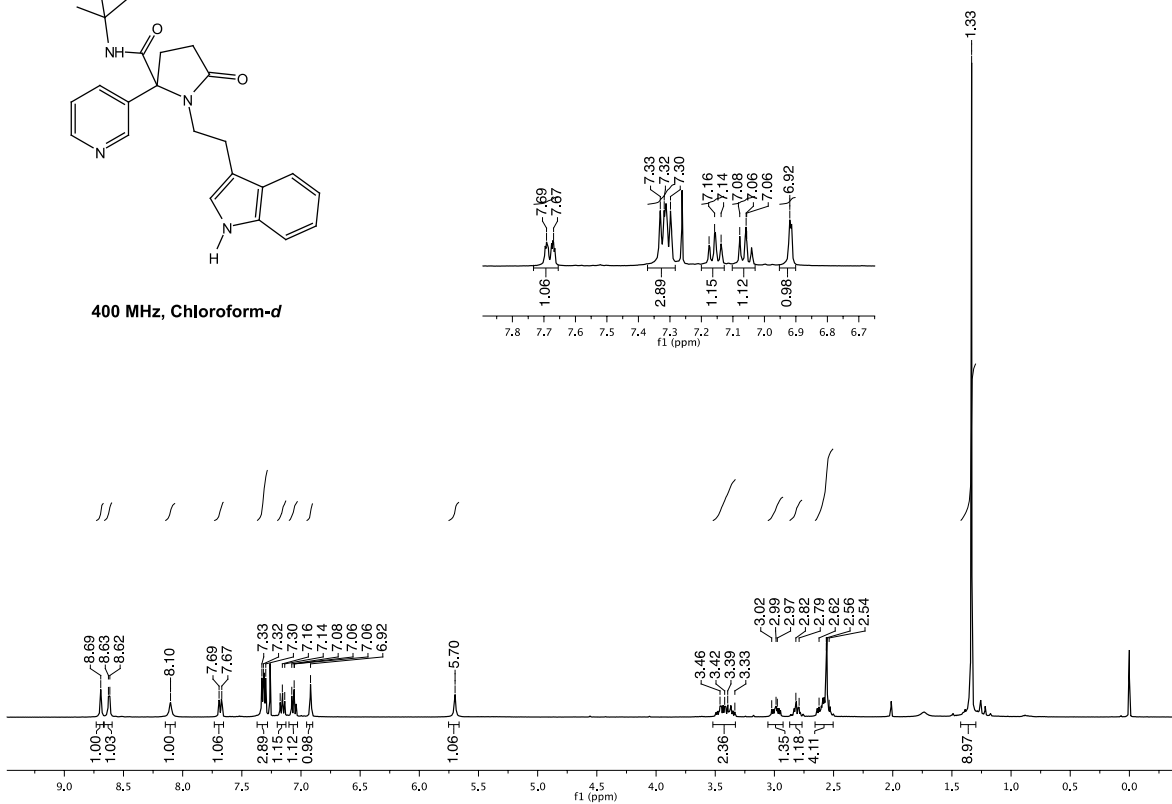
75 MHz, Chloroform-d



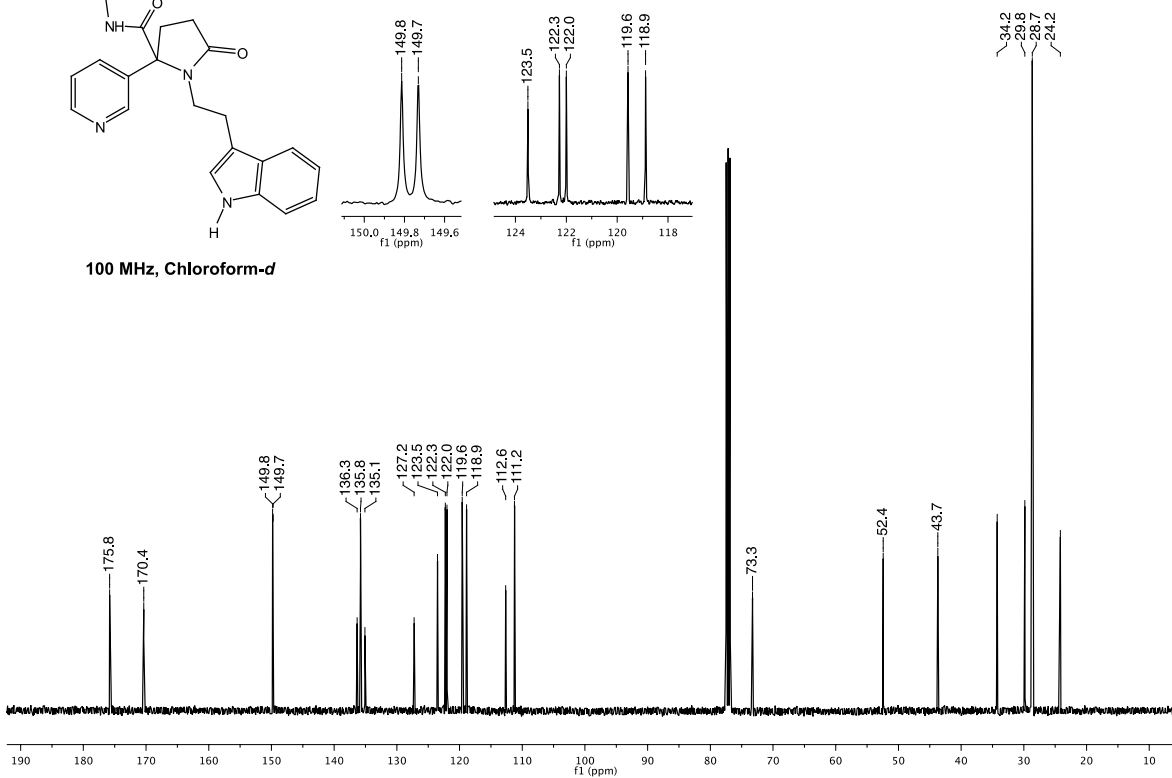
**1-(2-(1*H*-indol-3-yl)ethyl)-*N*-(*tert*-butyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12i)**



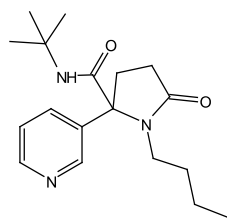
400 MHz, Chloroform-*d*



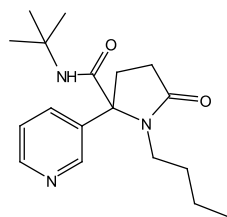
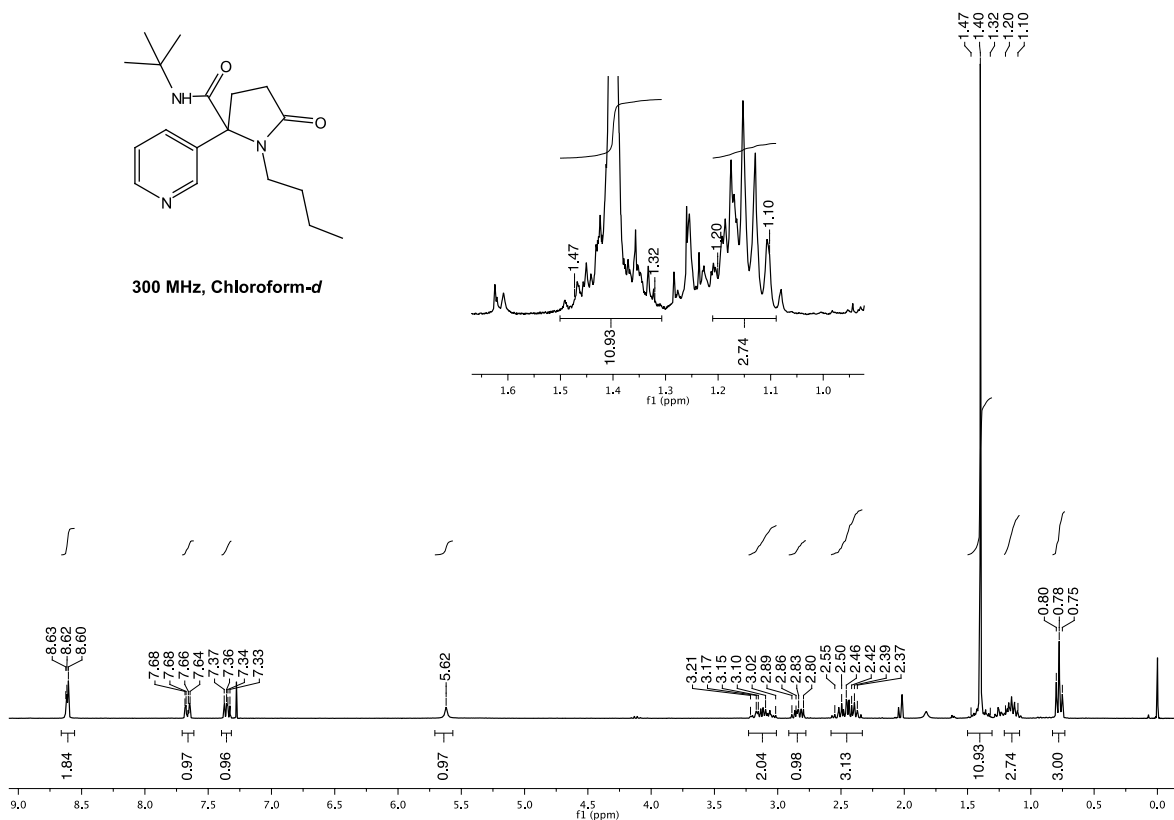
100 MHz, Chloroform-*d*



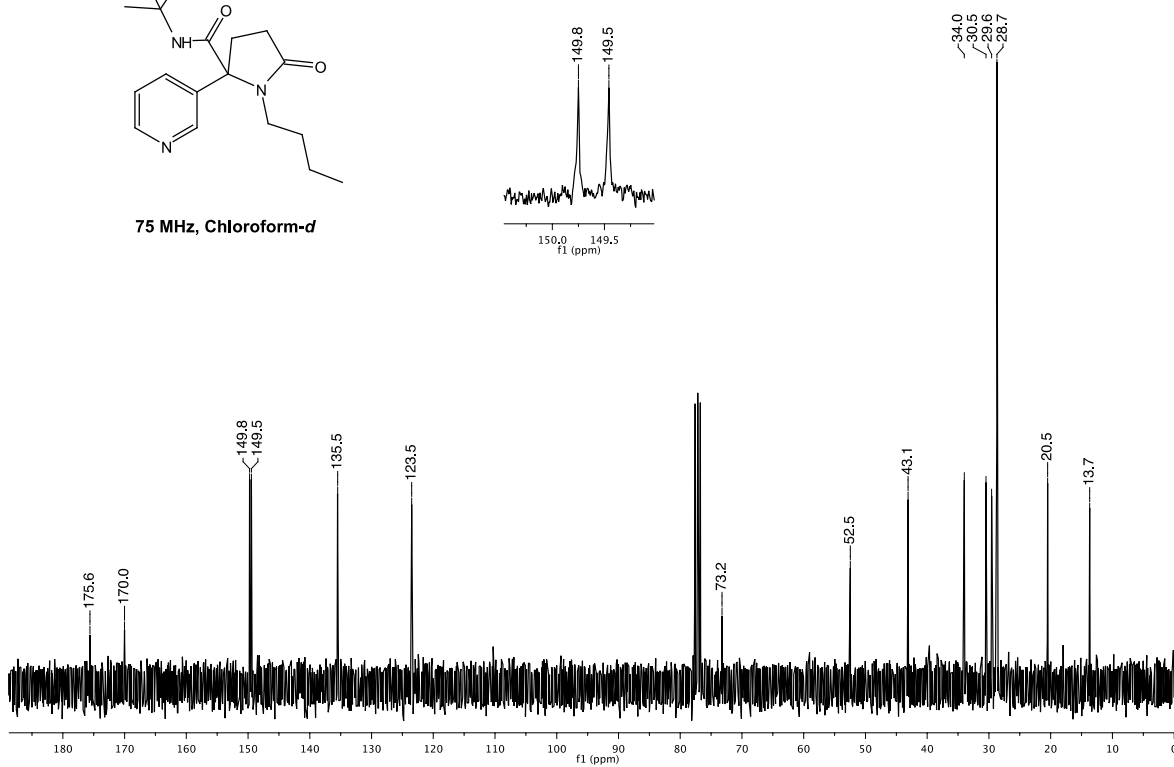
***N*-(*tert*-butyl)-1-butyl-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12j)**



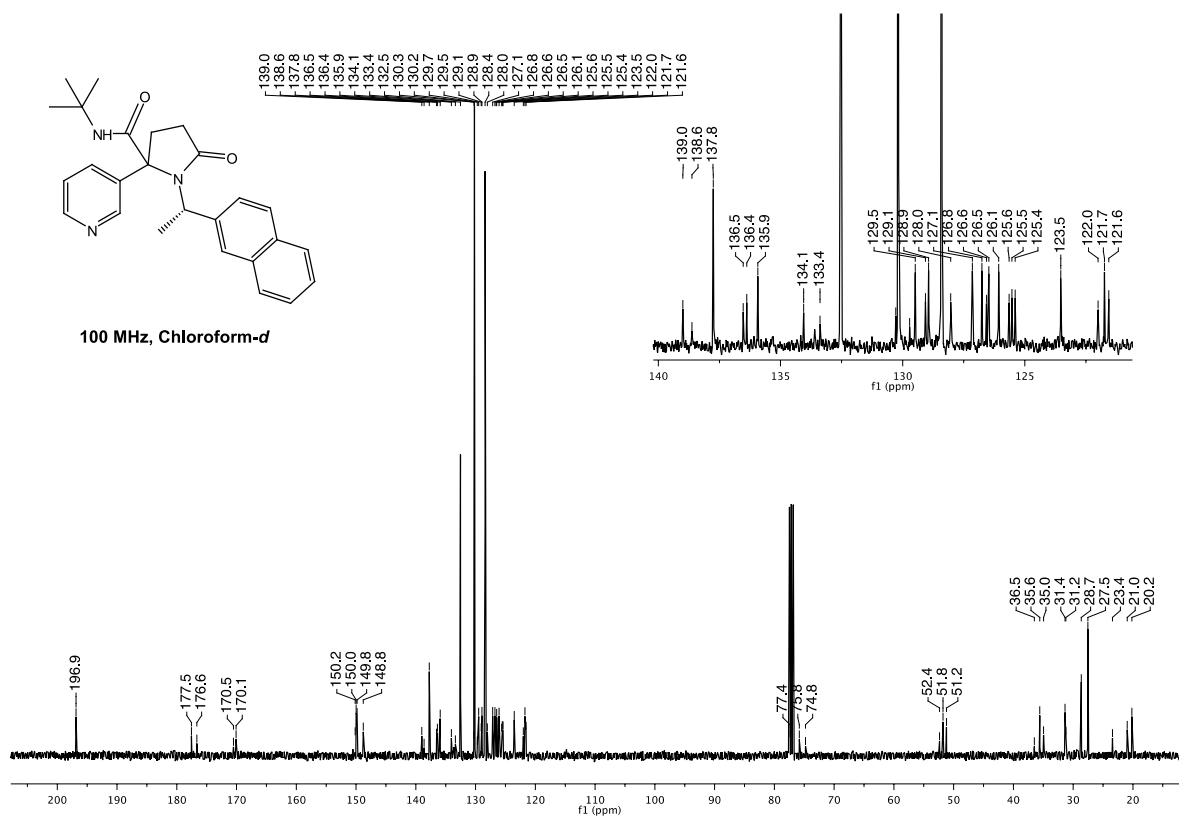
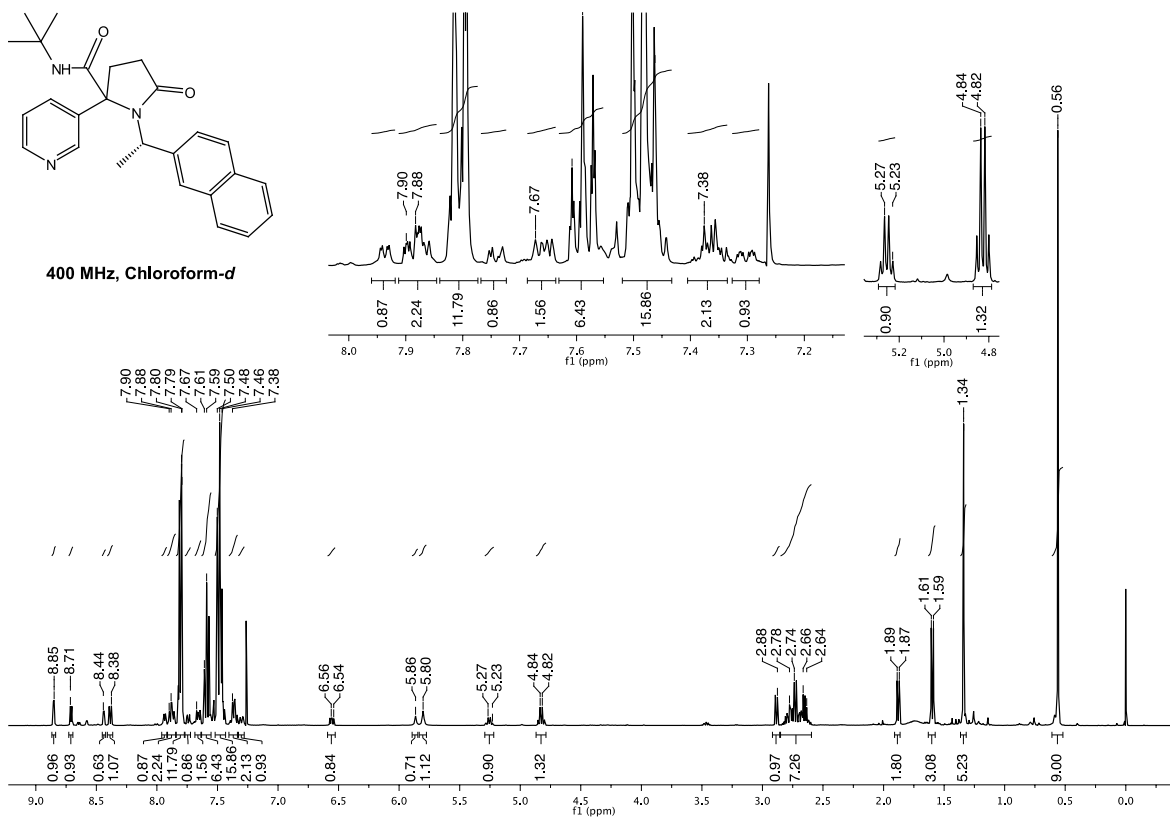
300 MHz, Chloroform-*d*



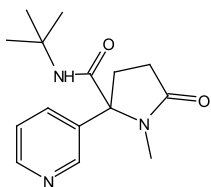
75 MHz, Chloroform-*d*



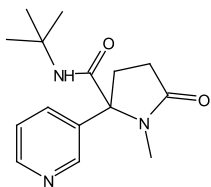
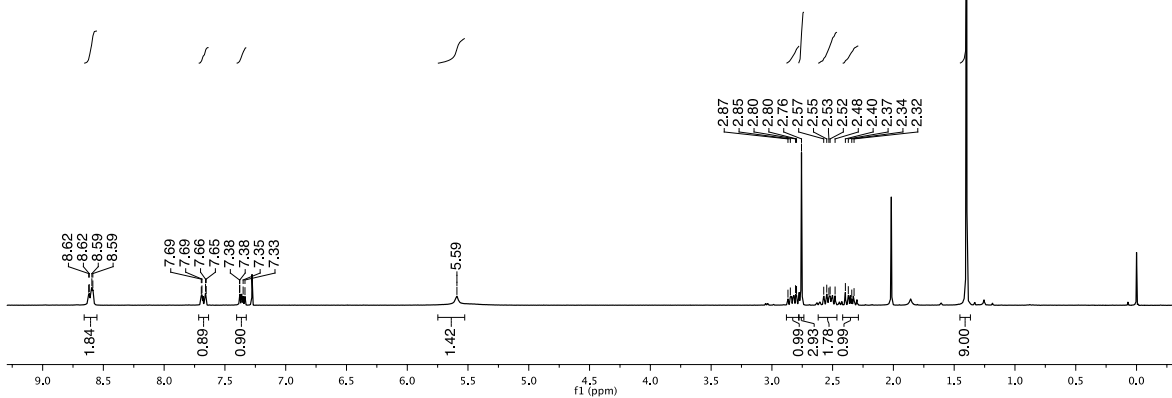
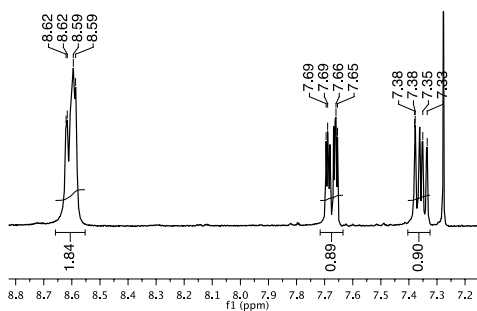
***N*-(*tert*-butyl)-1-((*S*)-1-(naphthalen-2-yl)ethyl)-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12k)**



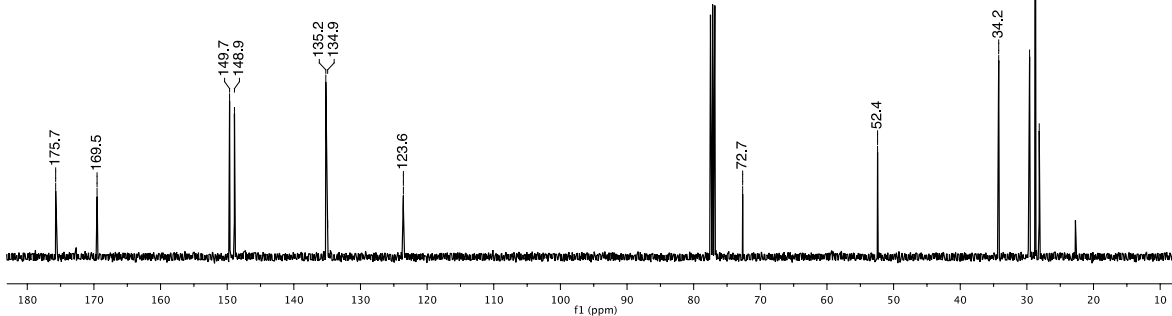
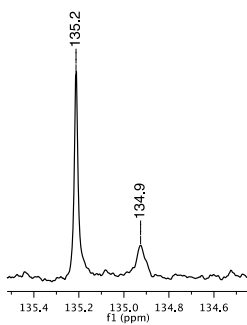
# *N*-(*tert*-butyl)-1-methyl-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12l)



400 MHz, Chloroform-*d*

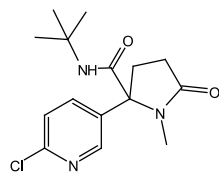


100 MHz, Chloroform-*d*

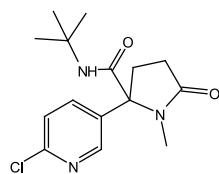
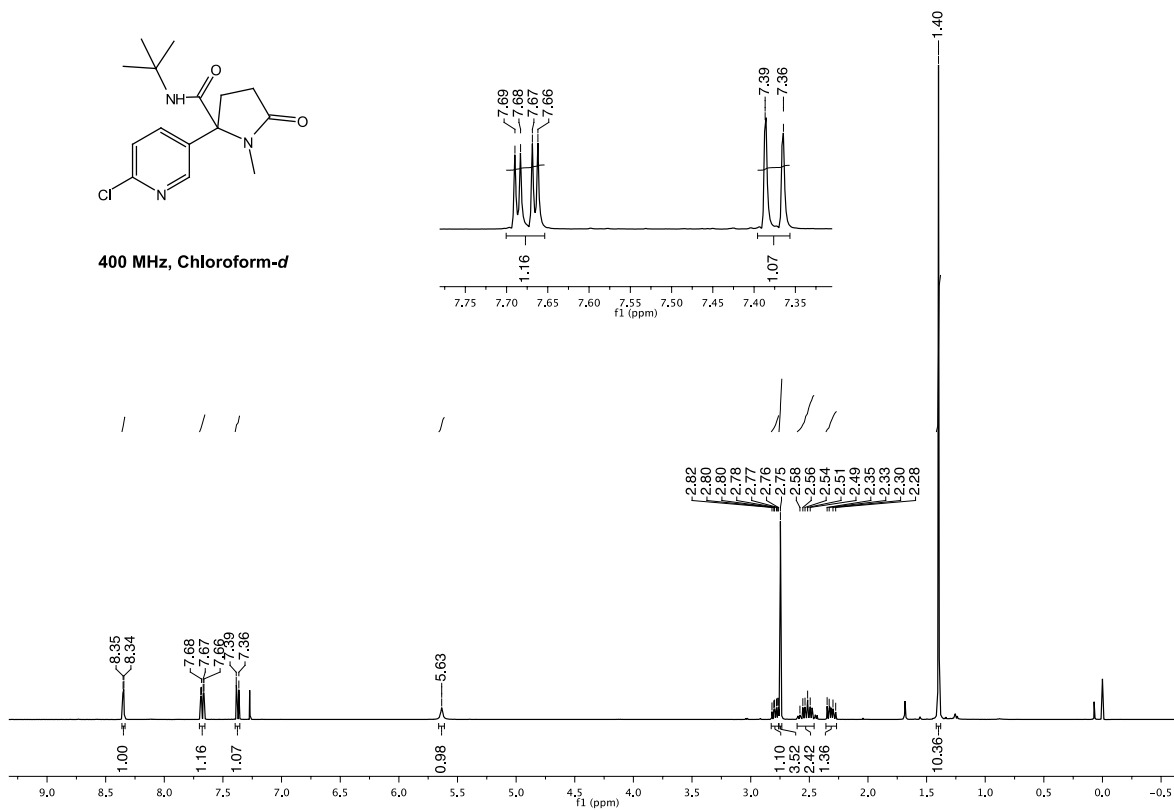




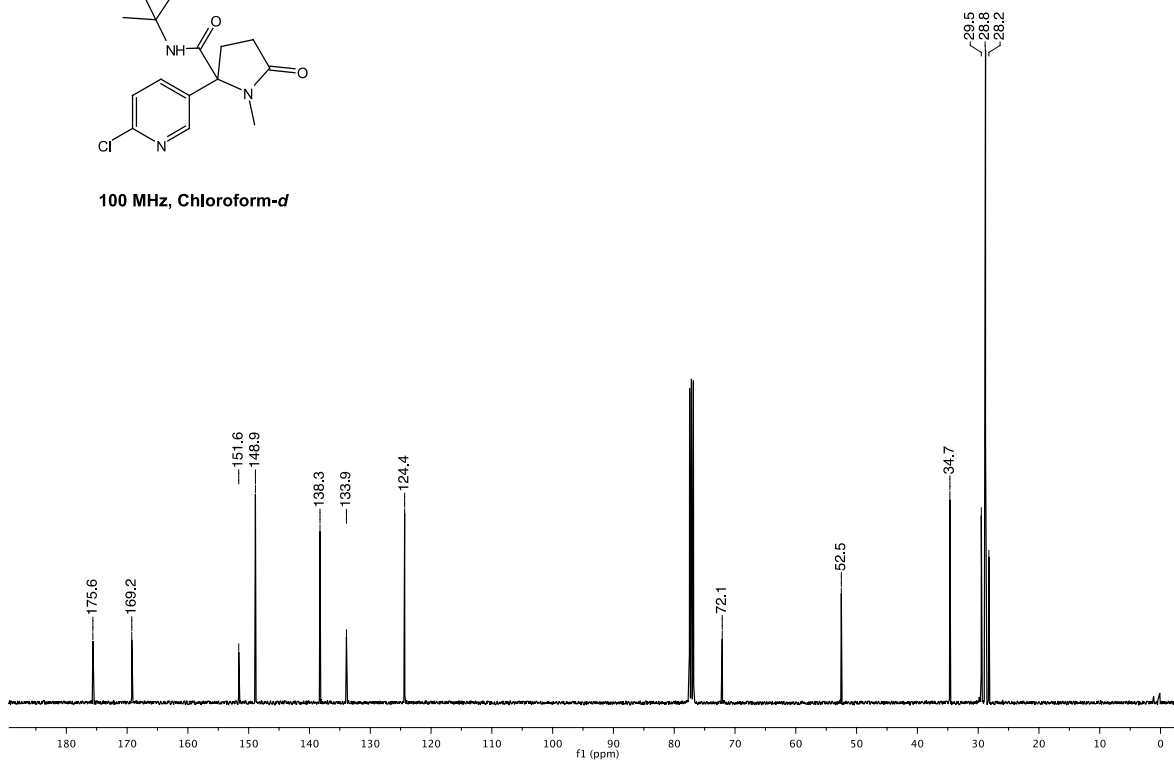
***N*-(*tert*-butyl)-2-(6-chloropyridin-3-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (12m)**



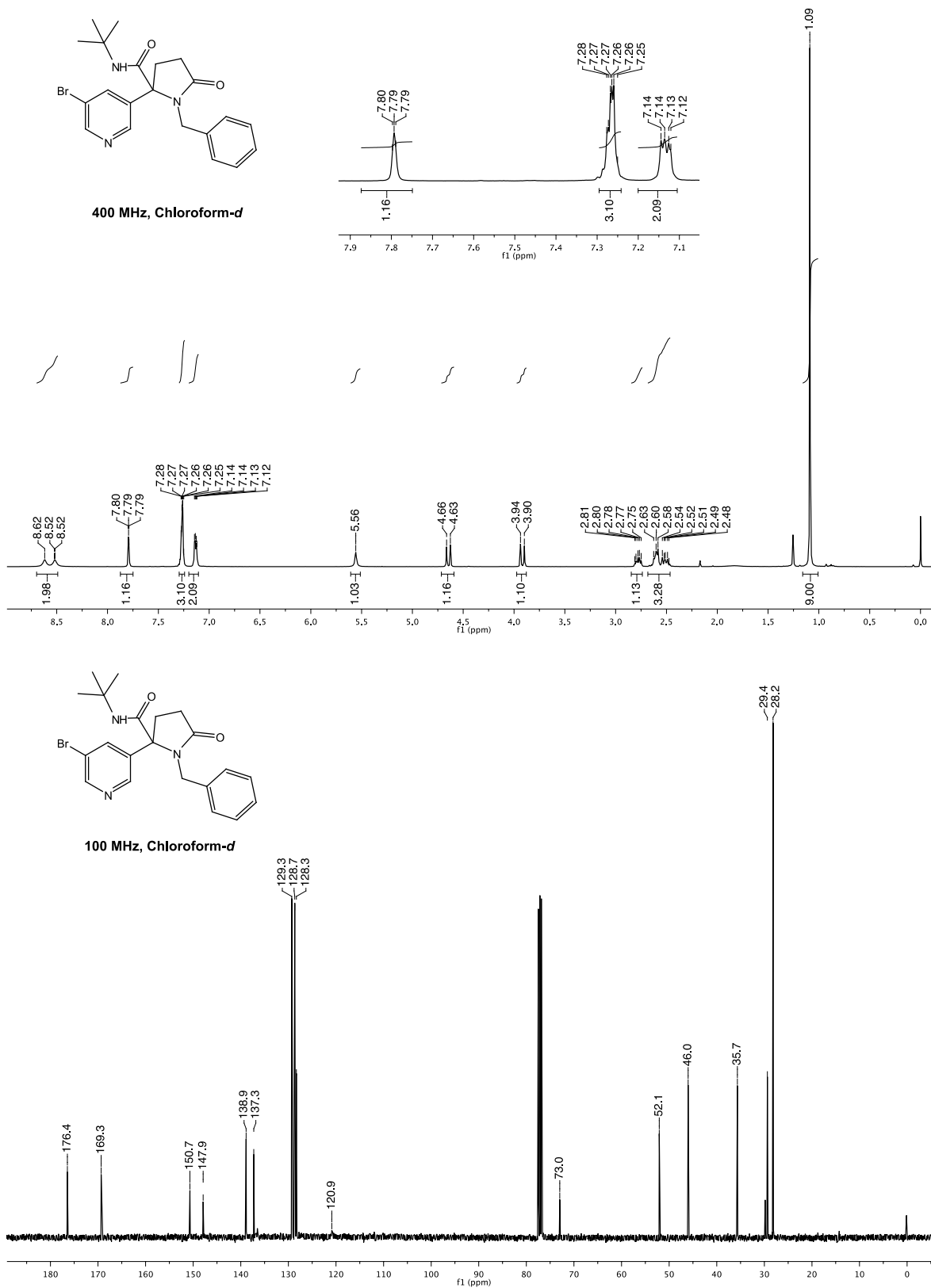
400 MHz, Chloroform-*d*



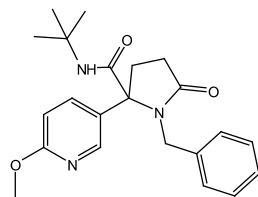
100 MHz, Chloroform-*d*



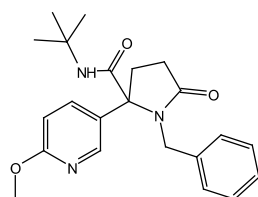
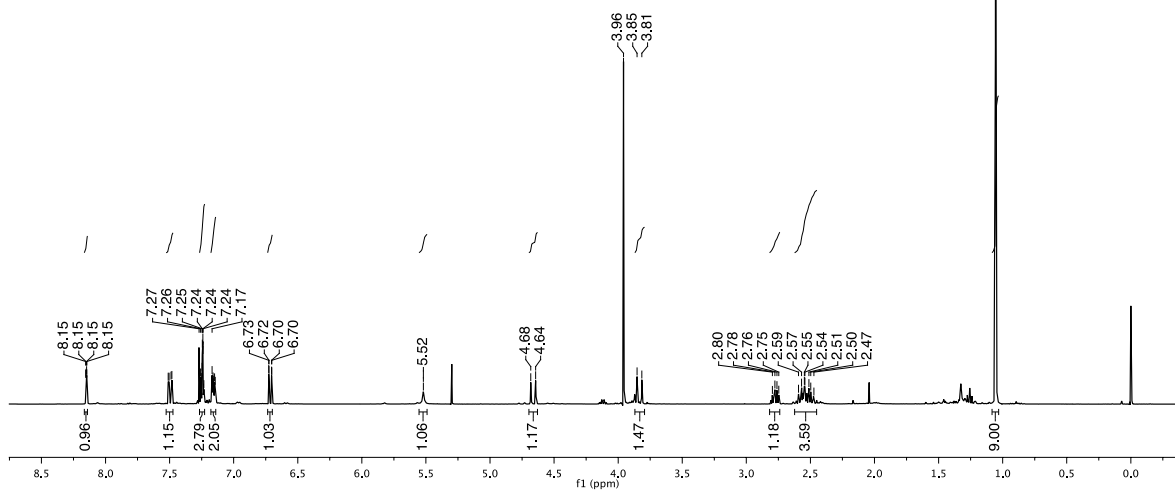
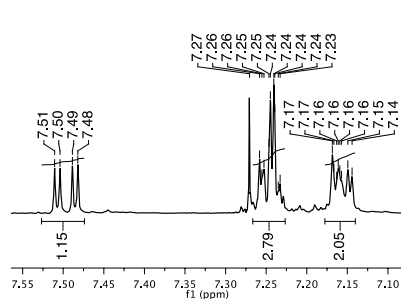
# 1-benzyl-2-(6-bromopyridin-3-yl)-N-(tert-butyl)-5-oxopyrrolidine-2-carboxamide (12n)



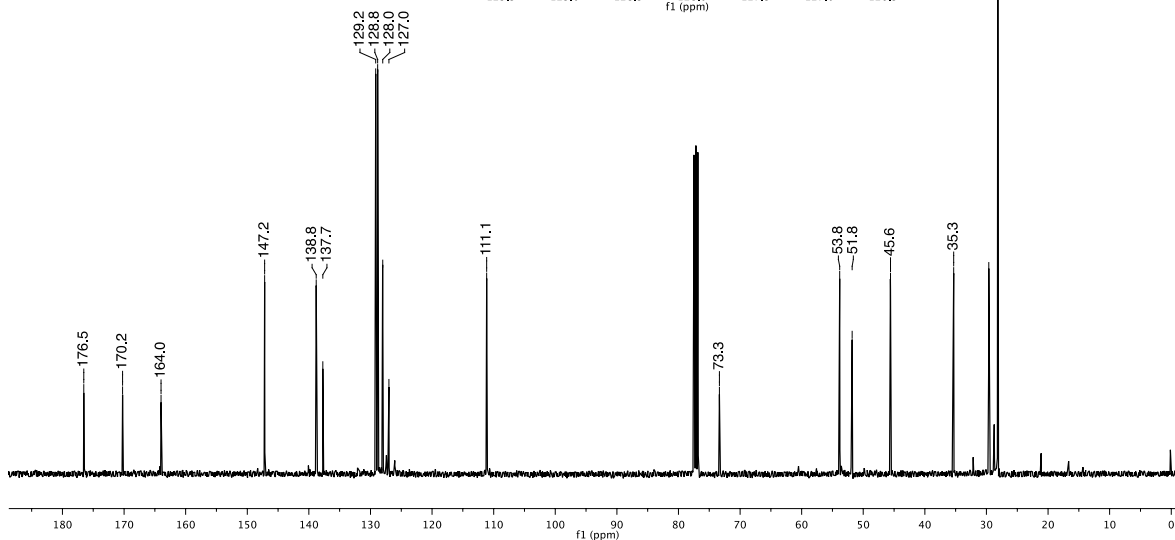
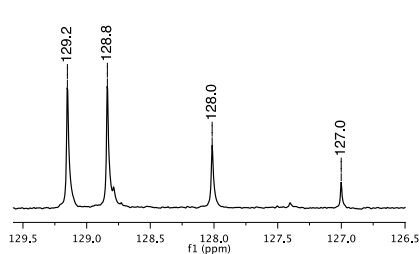
**1-benzyl-N-(tert-butyl)-2-(6-methoxypyridin-3-yl)-5-oxopyrrolidine-2-carboxamide (120)**



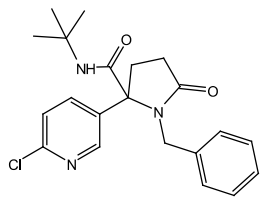
400 MHz, Chloroform-d



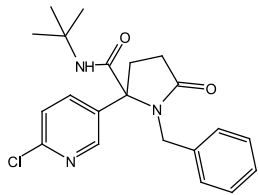
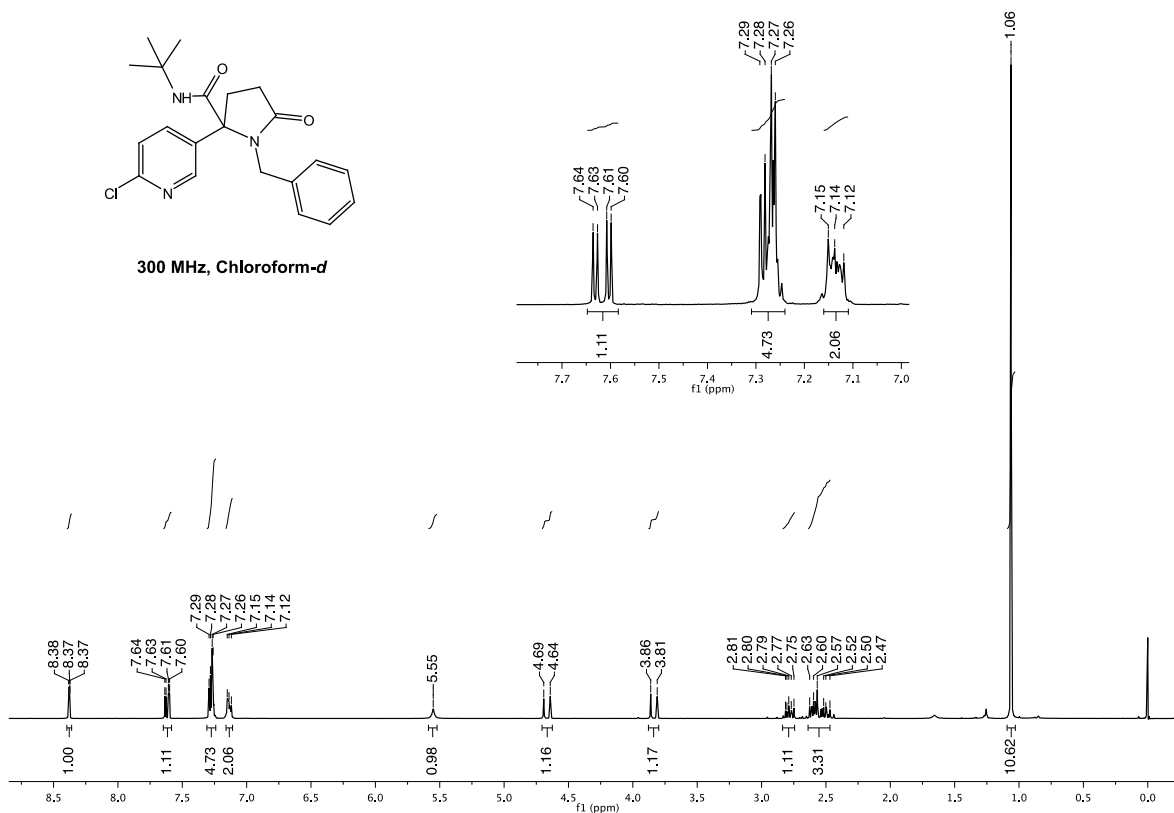
100 MHz, Chloroform-d



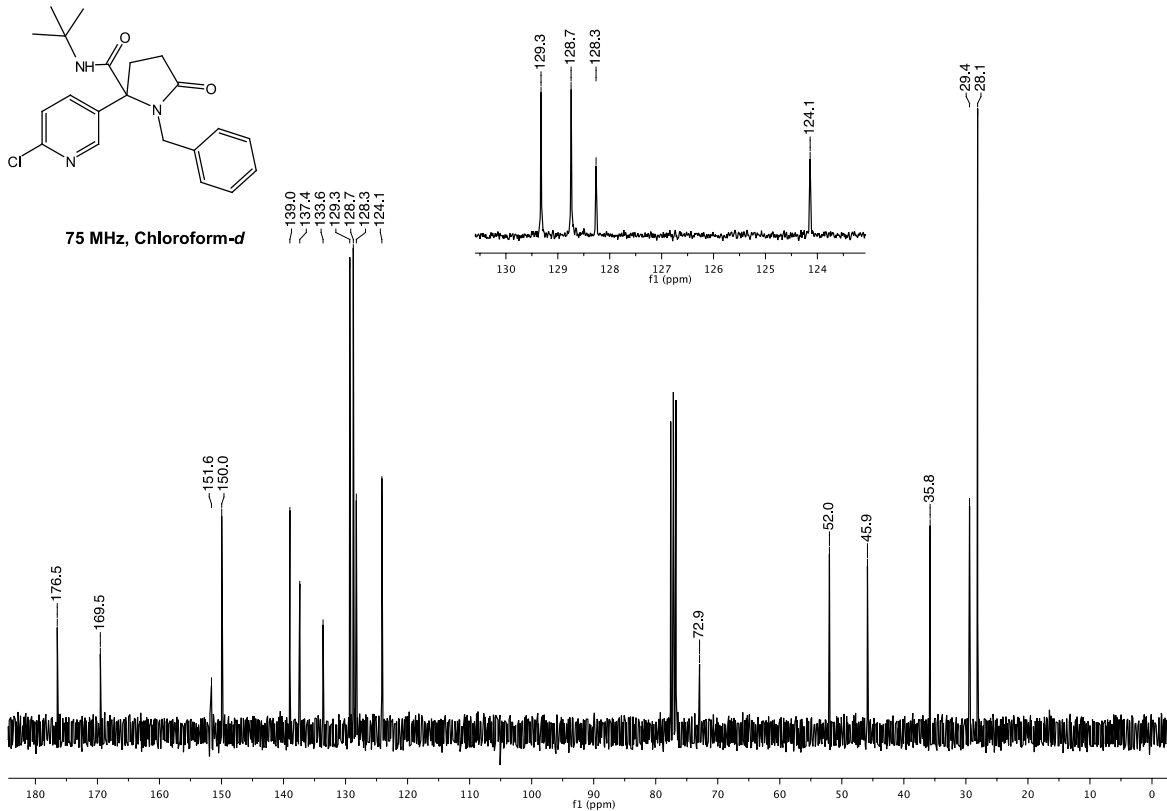
**1-benzyl-N-(tert-butyl)-2-(6-chloropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide (12p)**



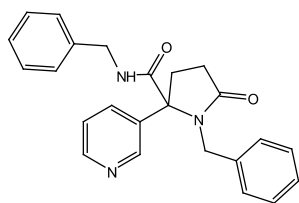
300 MHz, Chloroform-d



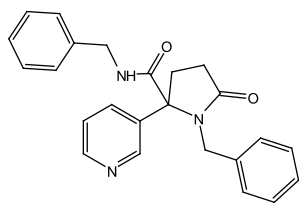
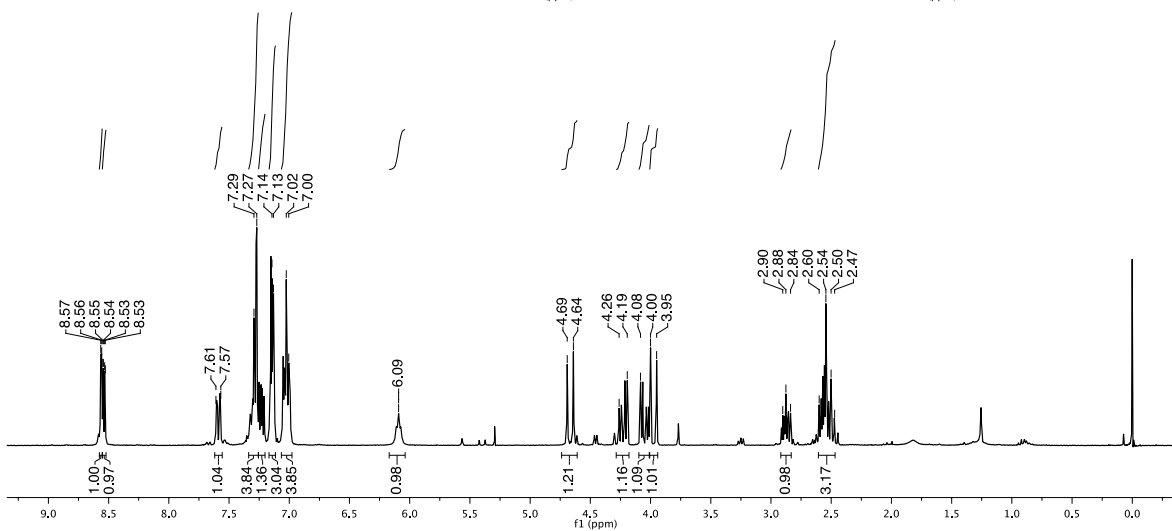
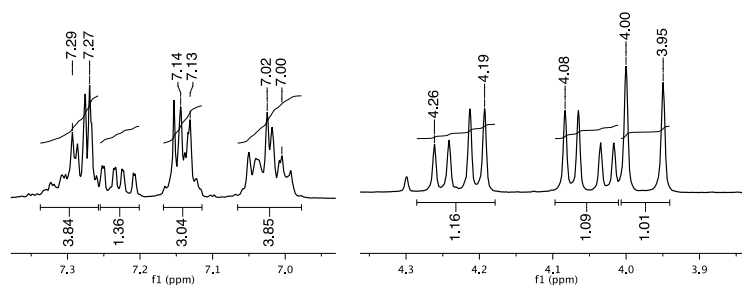
75 MHz, Chloroform-d



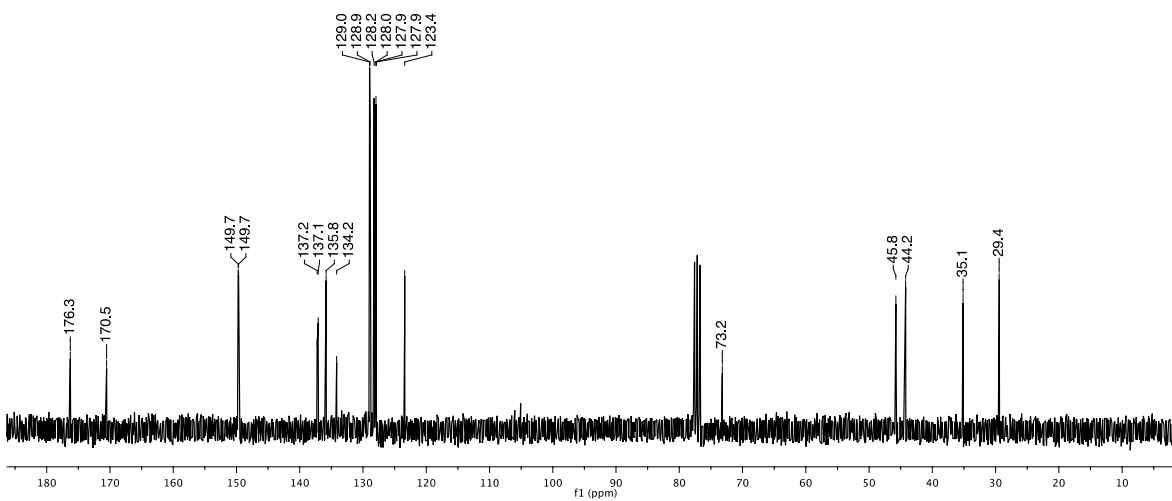
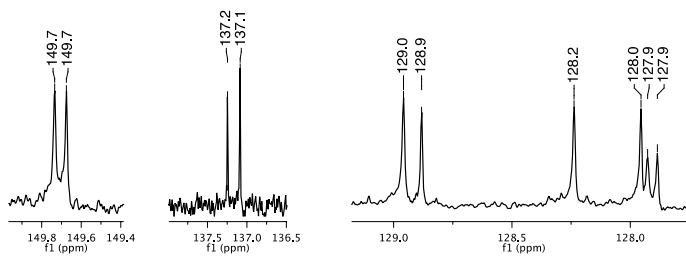
***N*,1-dibenzyl-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12q)**



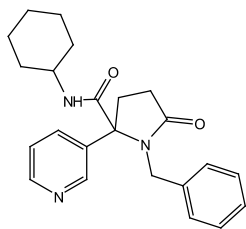
300 MHz, Chloroform-d



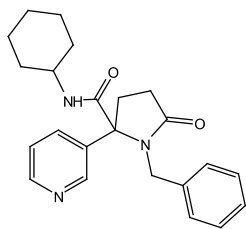
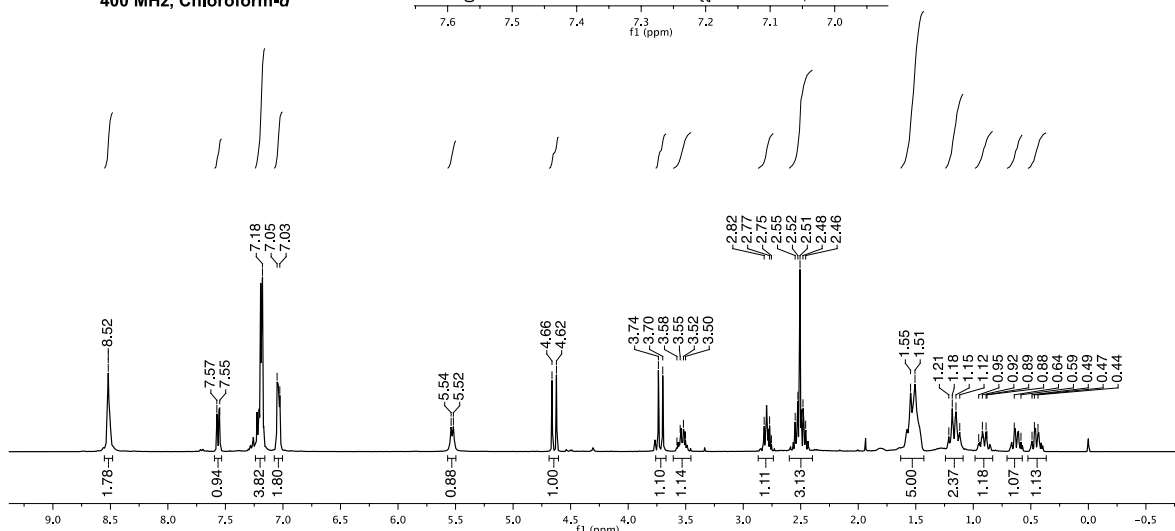
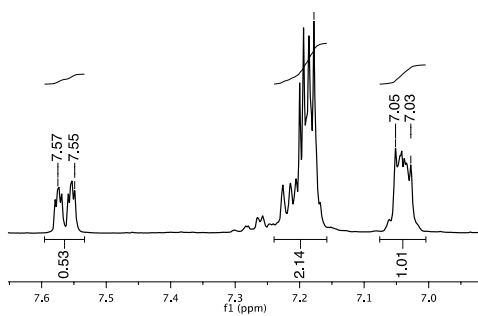
75 MHz, Chloroform-d



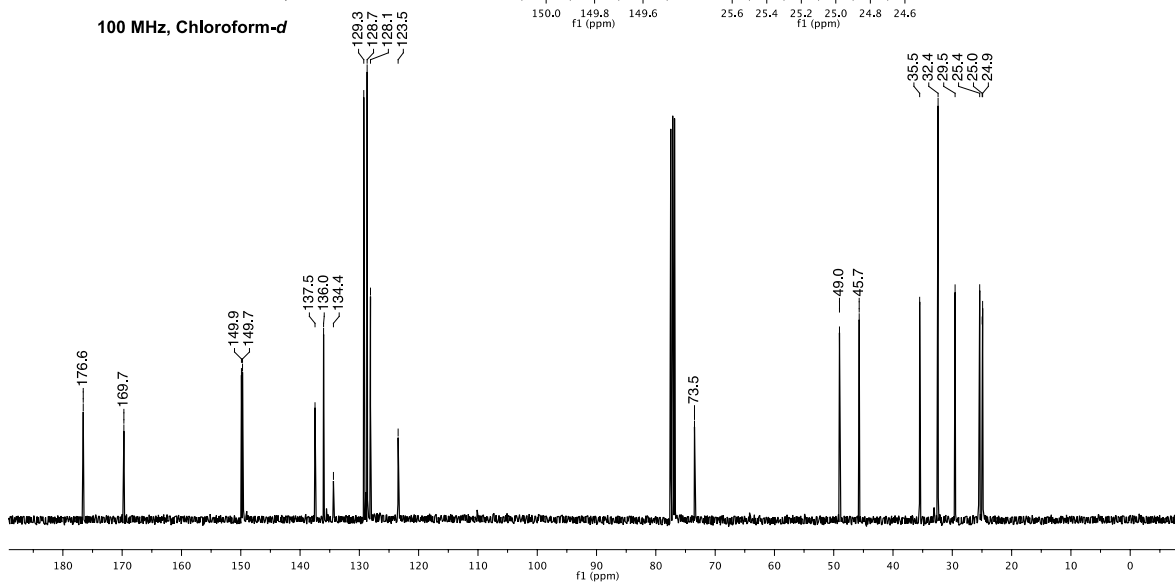
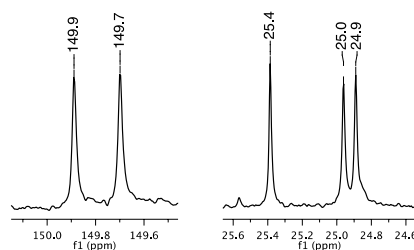
# 1-benzyl-N-cyclohexyl-5-oxo-2-(pyridin-3-yl)pyrrolidine-2-carboxamide (12r)



400 MHz, Chloroform-*d*

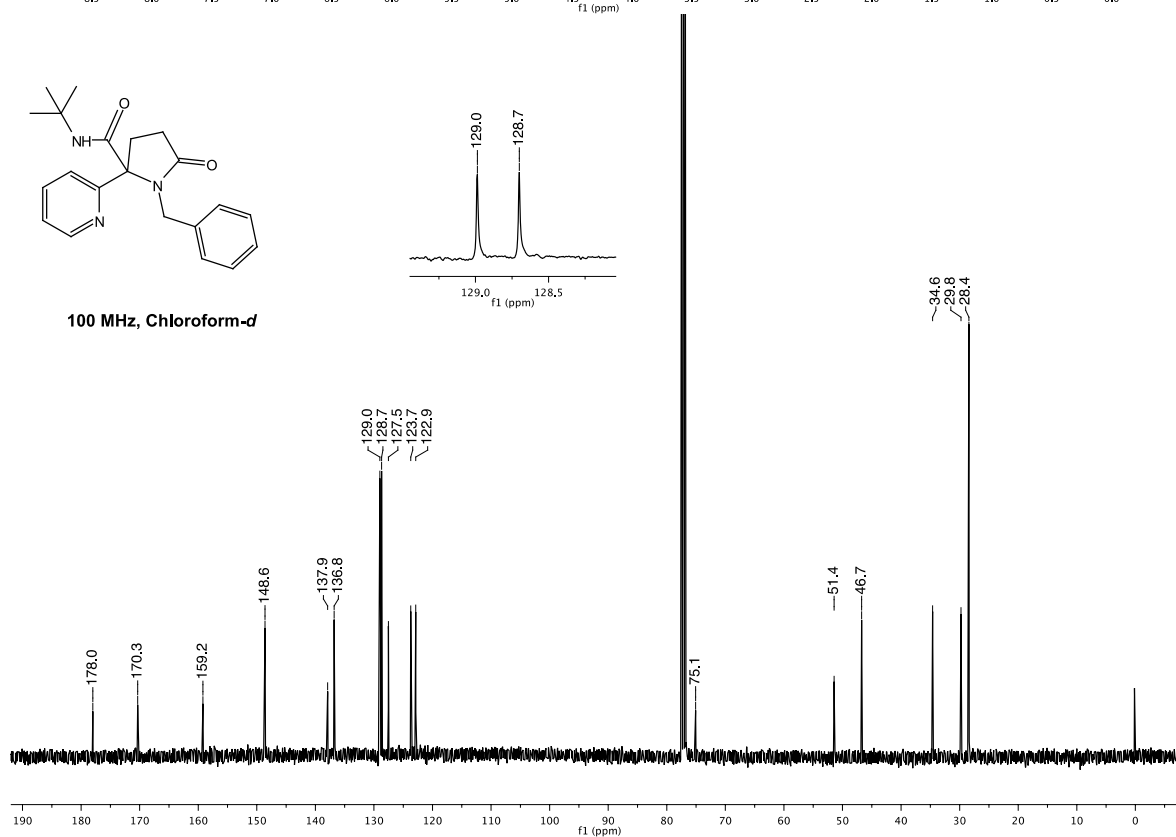
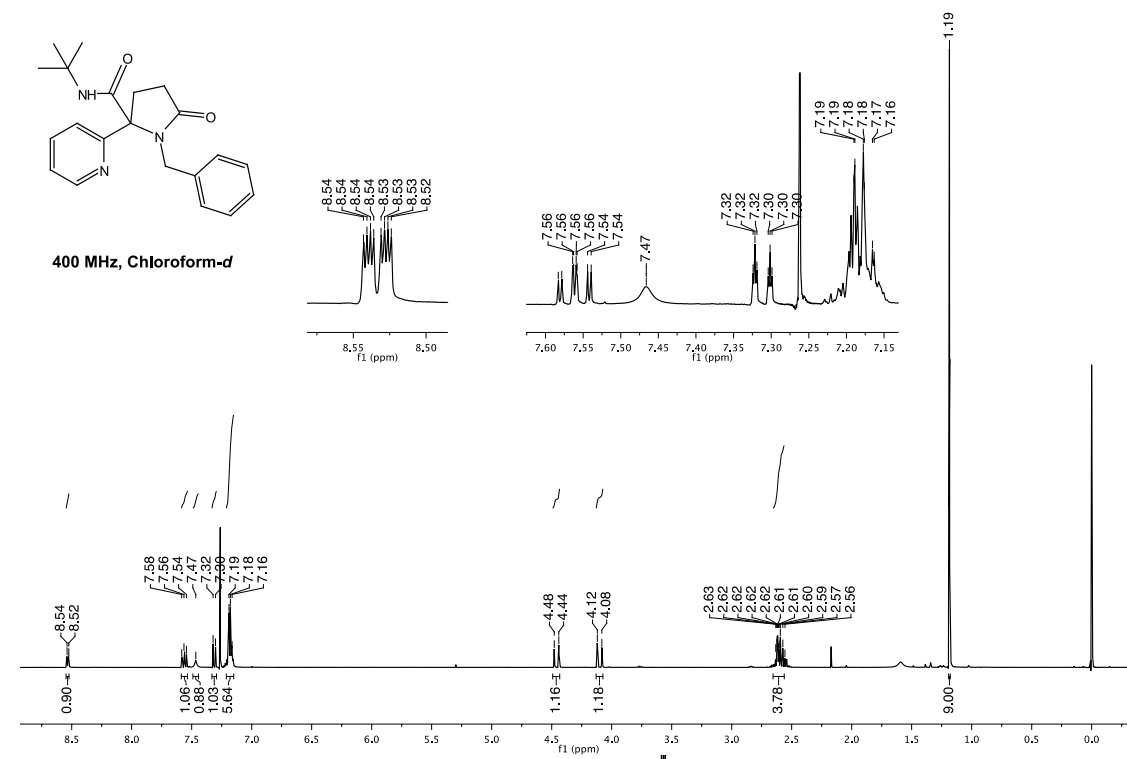


100 MHz, Chloroform-*d*

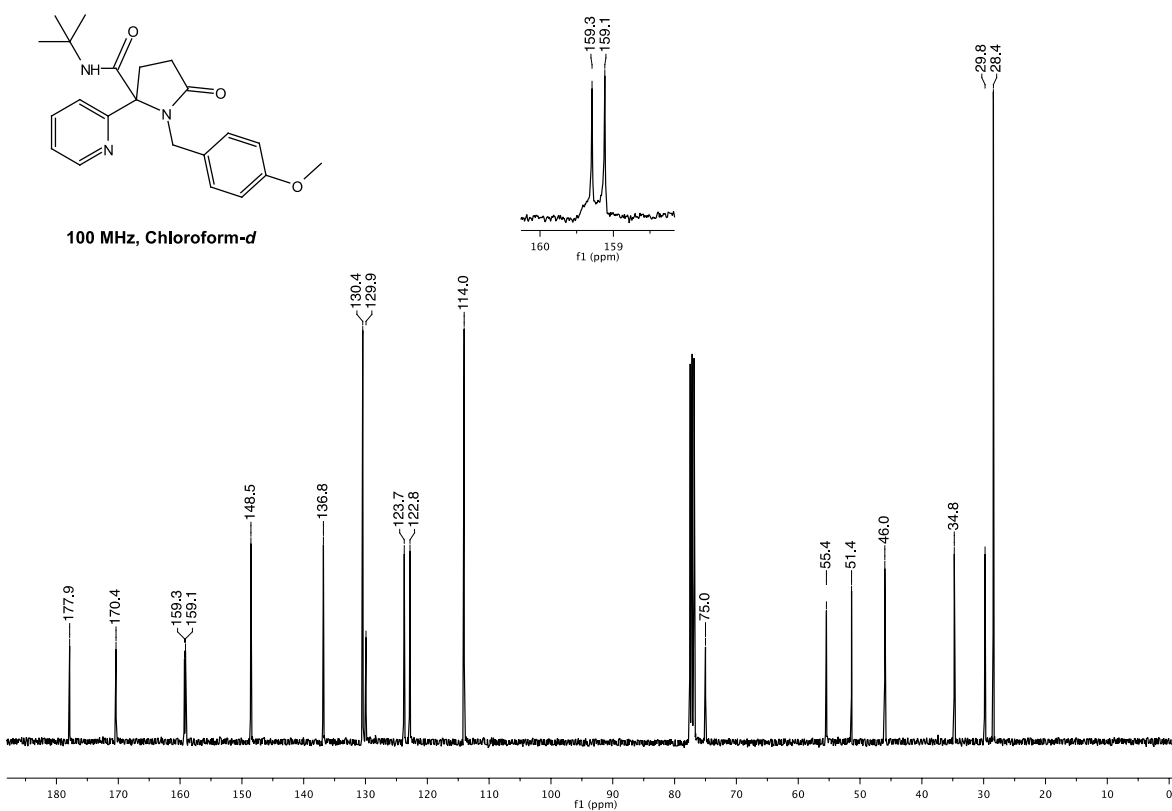
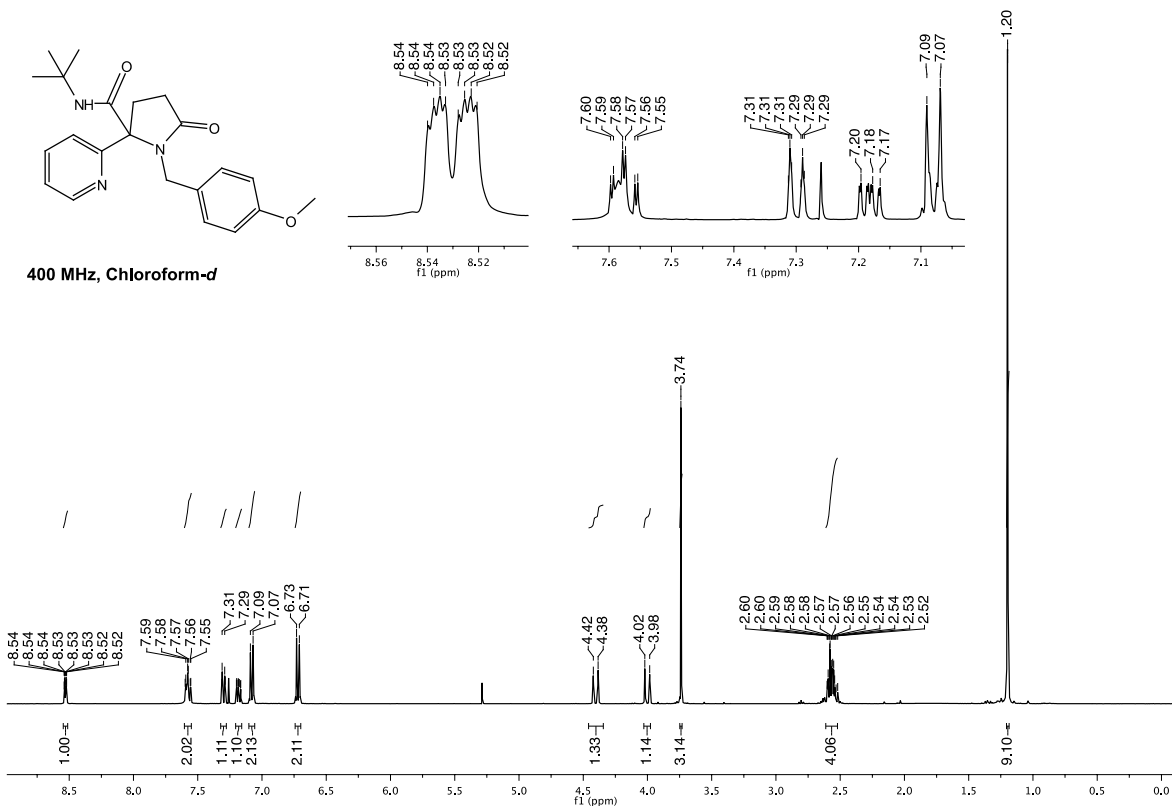


# ISO-COTININE ANALOGS SPECTRA

## 1-benzyl-N-(tert-butyl)-5-oxo-2-(pyridin-2-yl)pyrrolidine-2-carboxamide (15a)

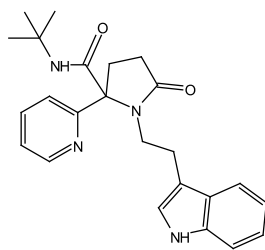


***N*-(*tert*-butyl)-1-(4-methoxybenzyl)-5-oxo-2-(pyridin-2-yl)pyrrolidine-2-carboxamide (15b)**

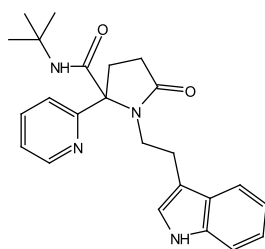
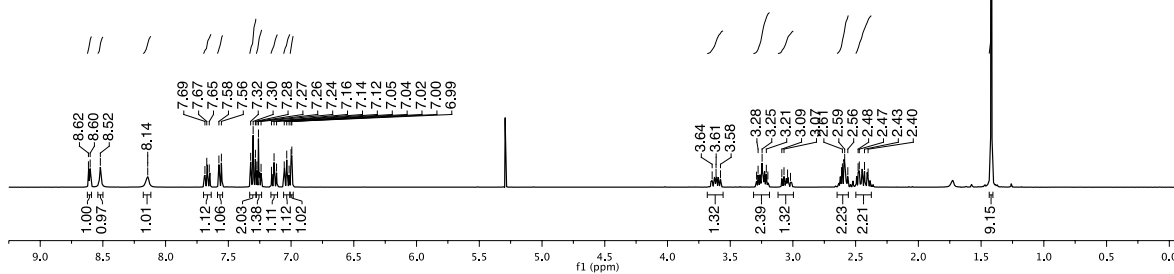
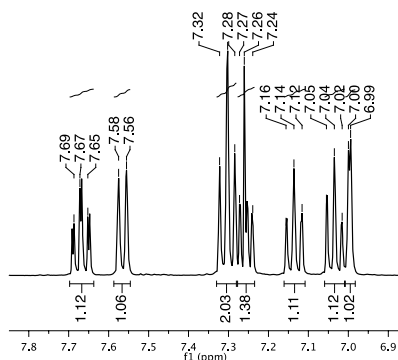




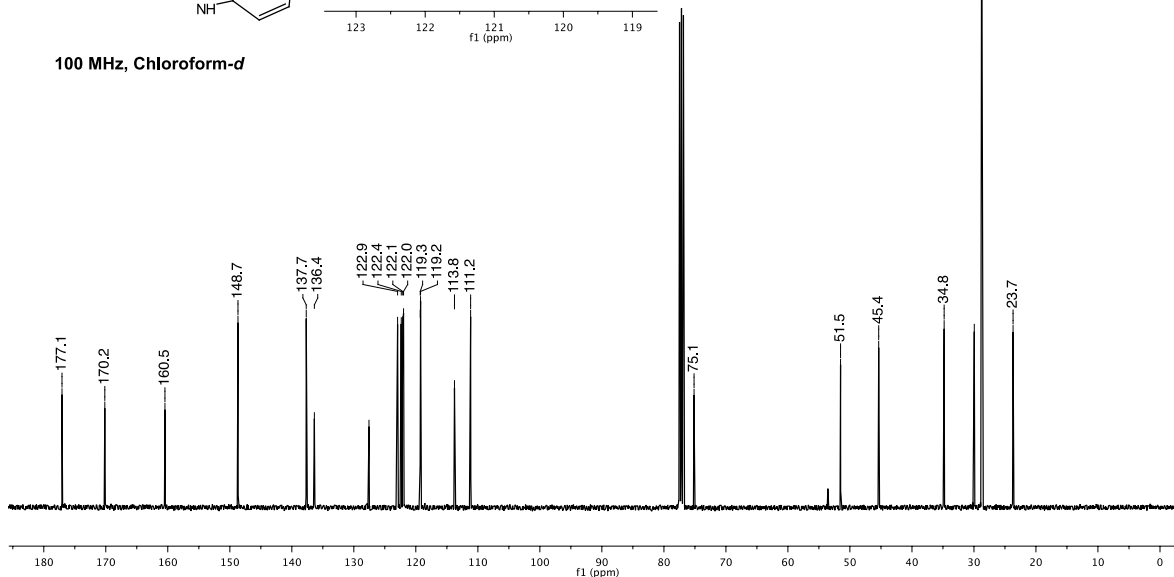
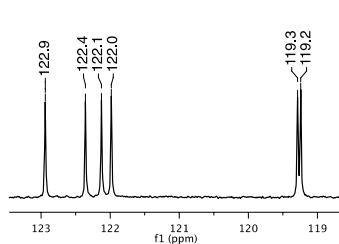
**1-(2-(1*H*-indol-3-yl)ethyl)-*N*-(*tert*-butyl)-5-oxo-2-(pyridin-2-yl)pyrrolidine-2-carboxamide (15c)**



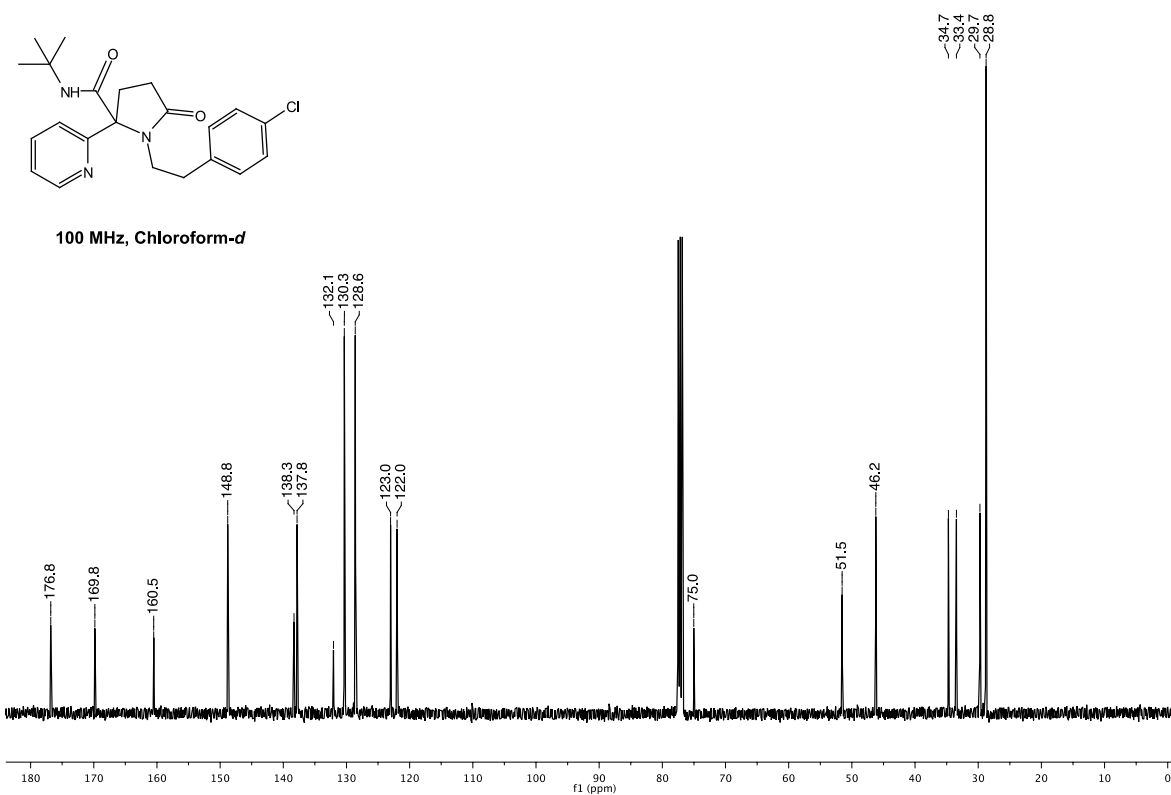
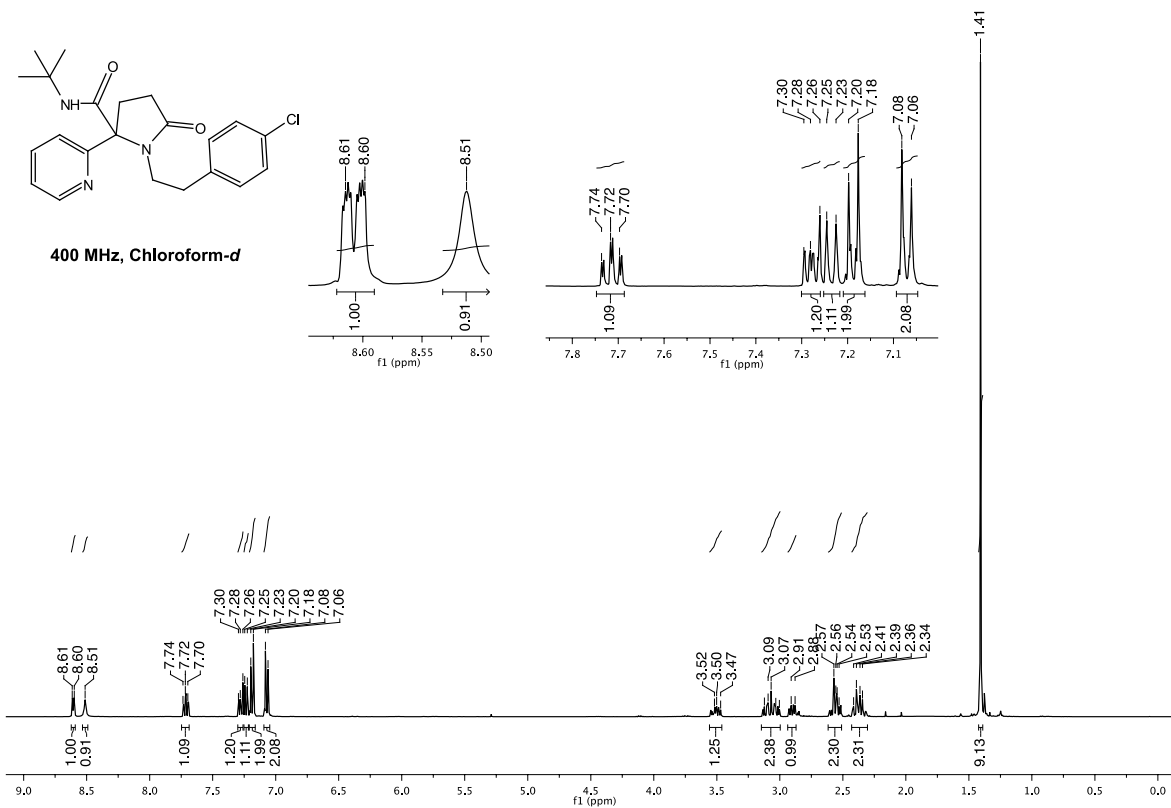
400 MHz, Chloroform-*d*



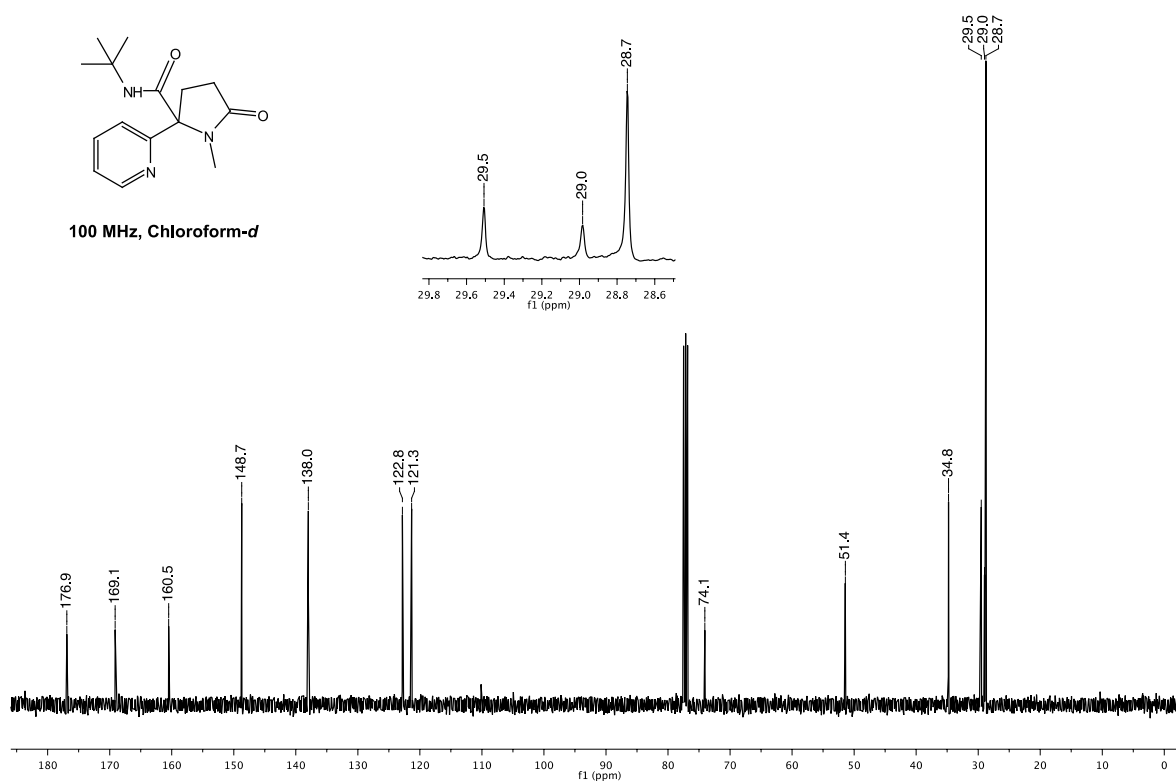
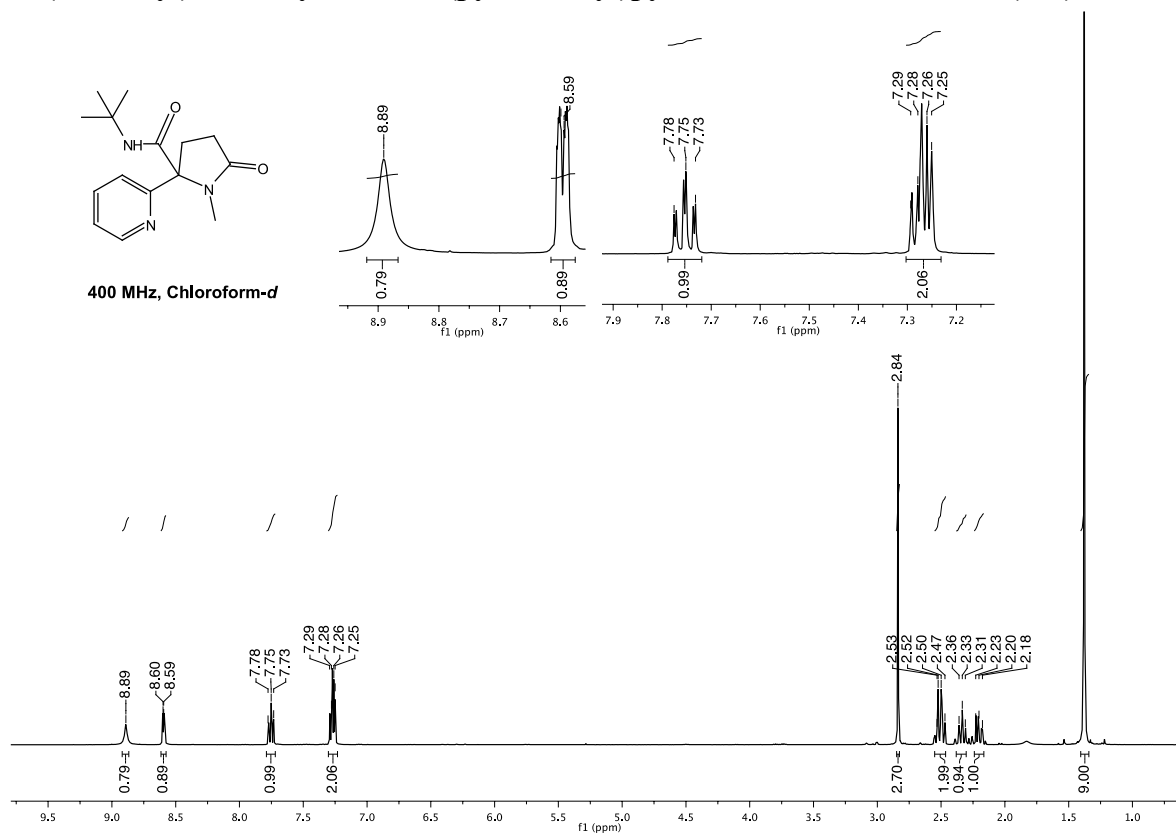
100 MHz, Chloroform-*d*



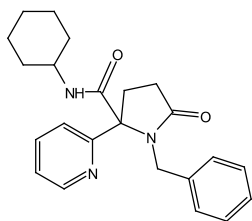
***N*-(*tert*-butyl)-1-(4-chlorophenethyl)-5-oxo-2-(pyridin-2-yl)pyrrolidine-2-carboxamide (15d)**



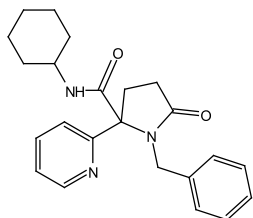
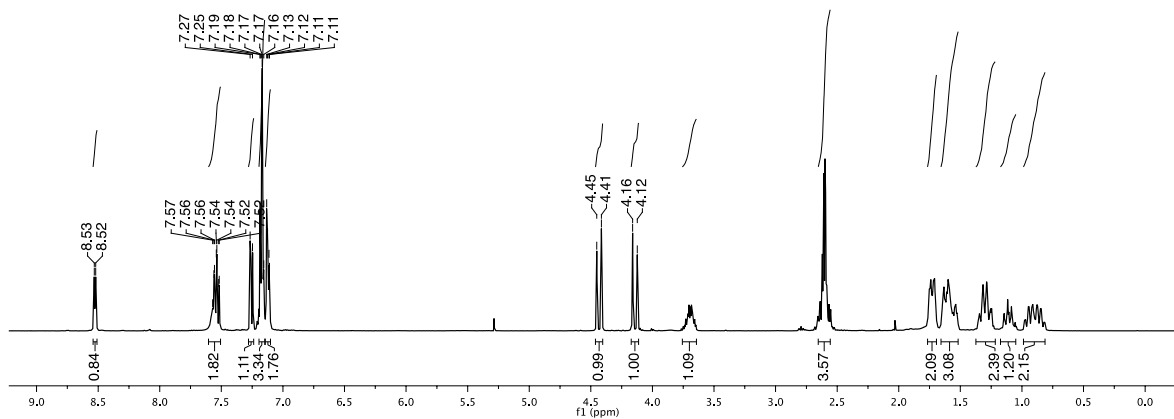
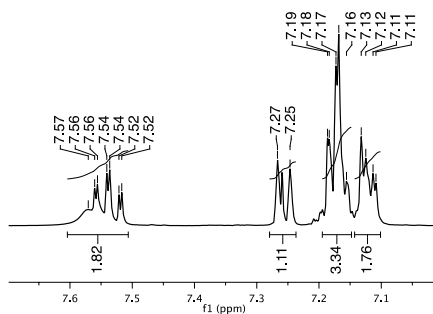
# *N*-(*tert*-butyl)-1-methyl-5-oxo-2-(pyridin-2-yl)pyrrolidine-2-carboxamide (15e)



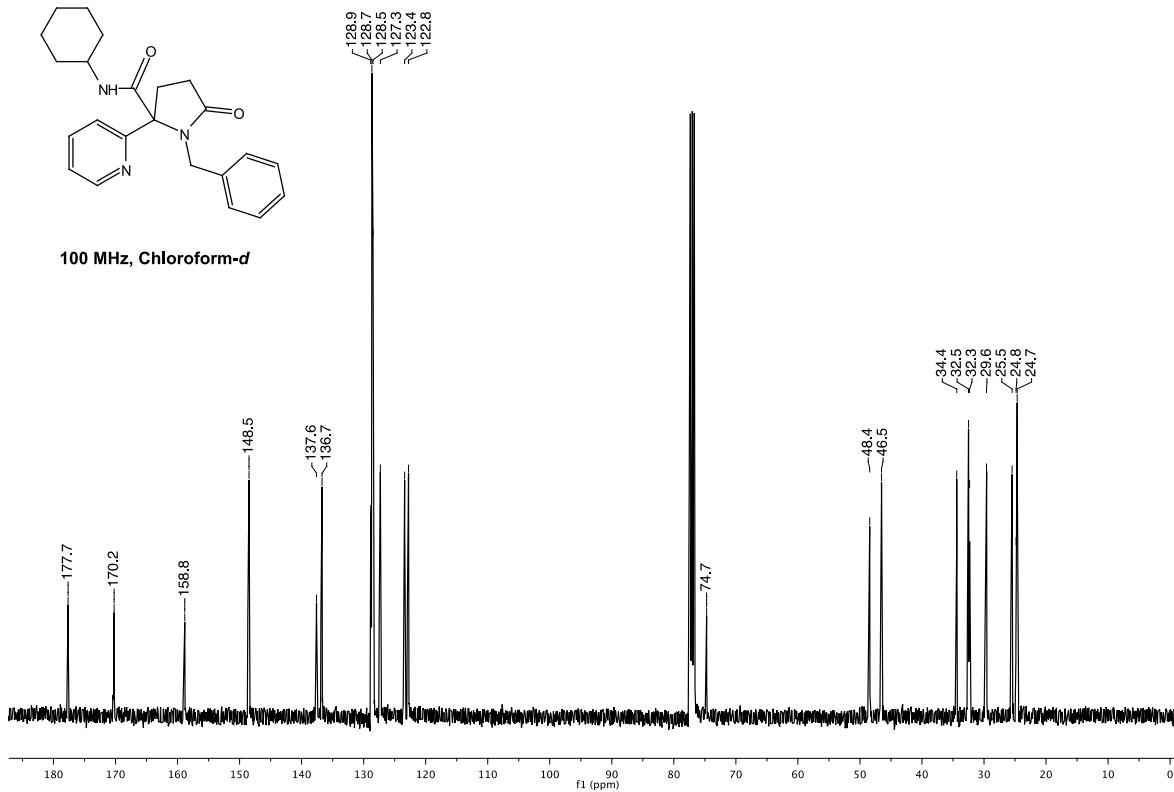
# 1-benzyl-N-cyclohexyl-5-oxo-2-(pyridin-2-yl)pyrrolidine-2-carboxamide (15f)



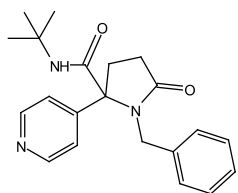
400 MHz, Chloroform-*d*



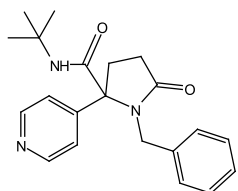
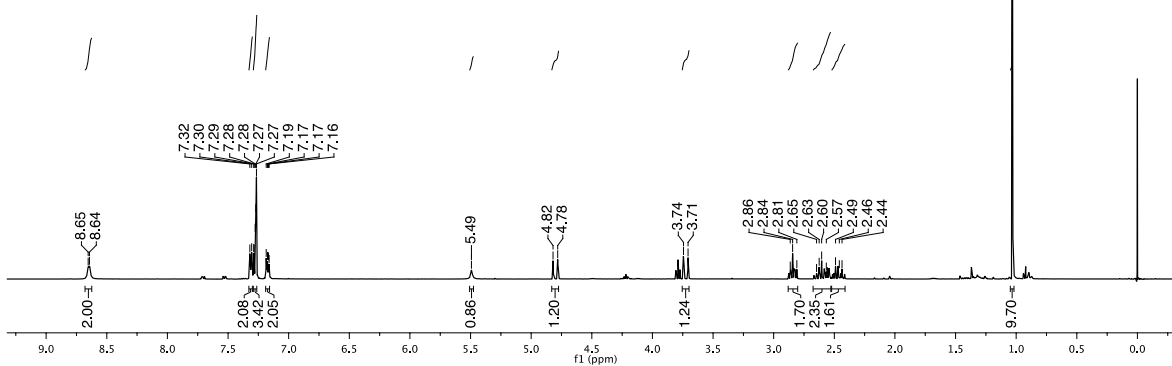
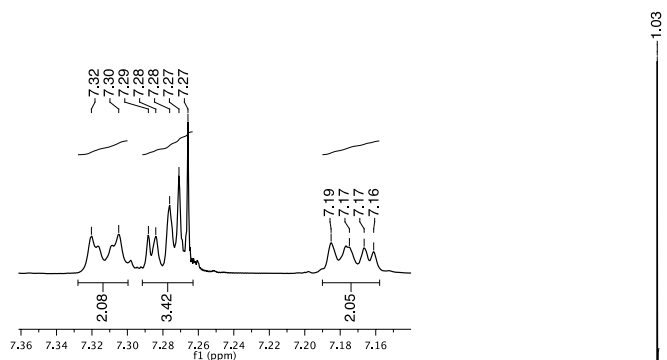
100 MHz, Chloroform-*d*



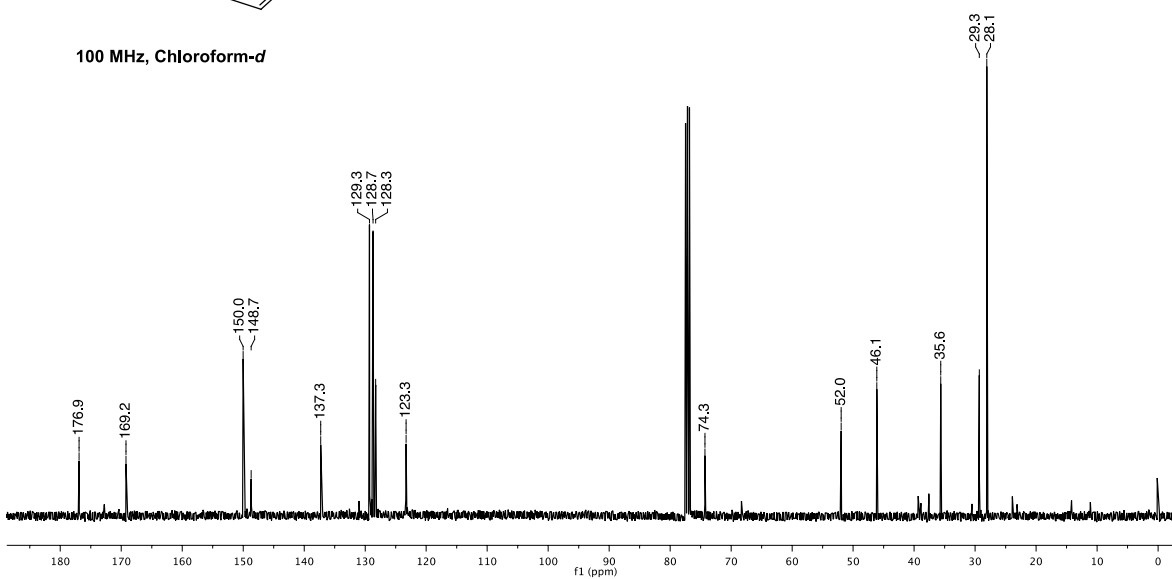
# 1-benzyl-N-(tert-butyl)-5-oxo-2-(pyridin-4-yl)pyrrolidine-2-carboxamide (15g)



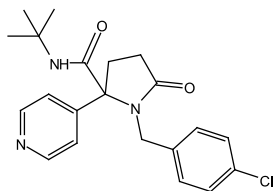
400 MHz, Chloroform-*d*



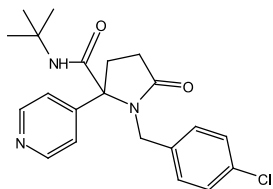
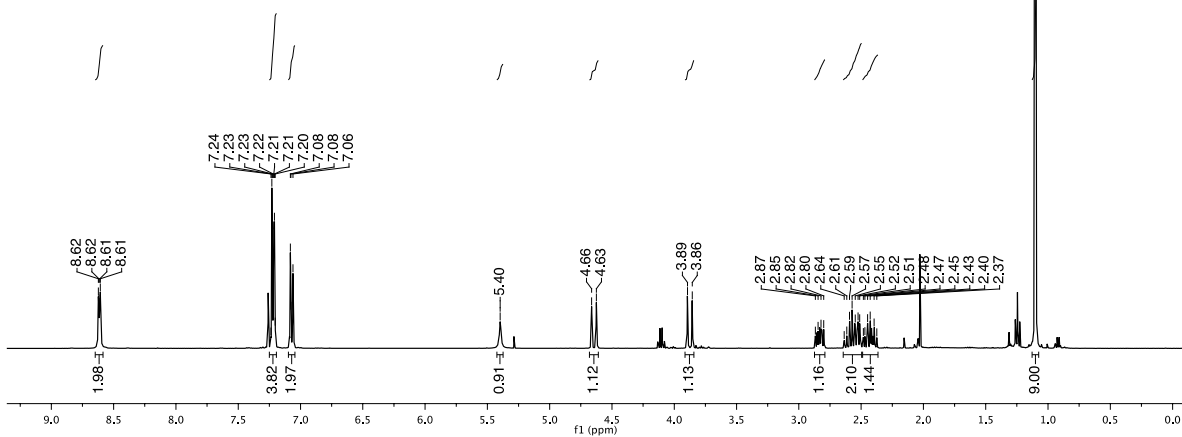
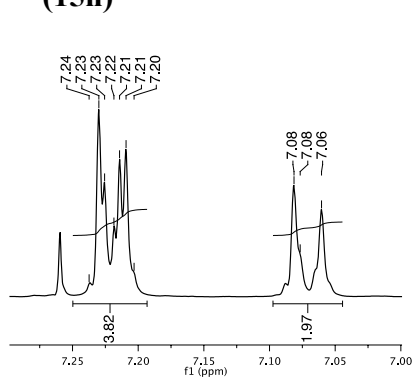
100 MHz, Chloroform-*d*



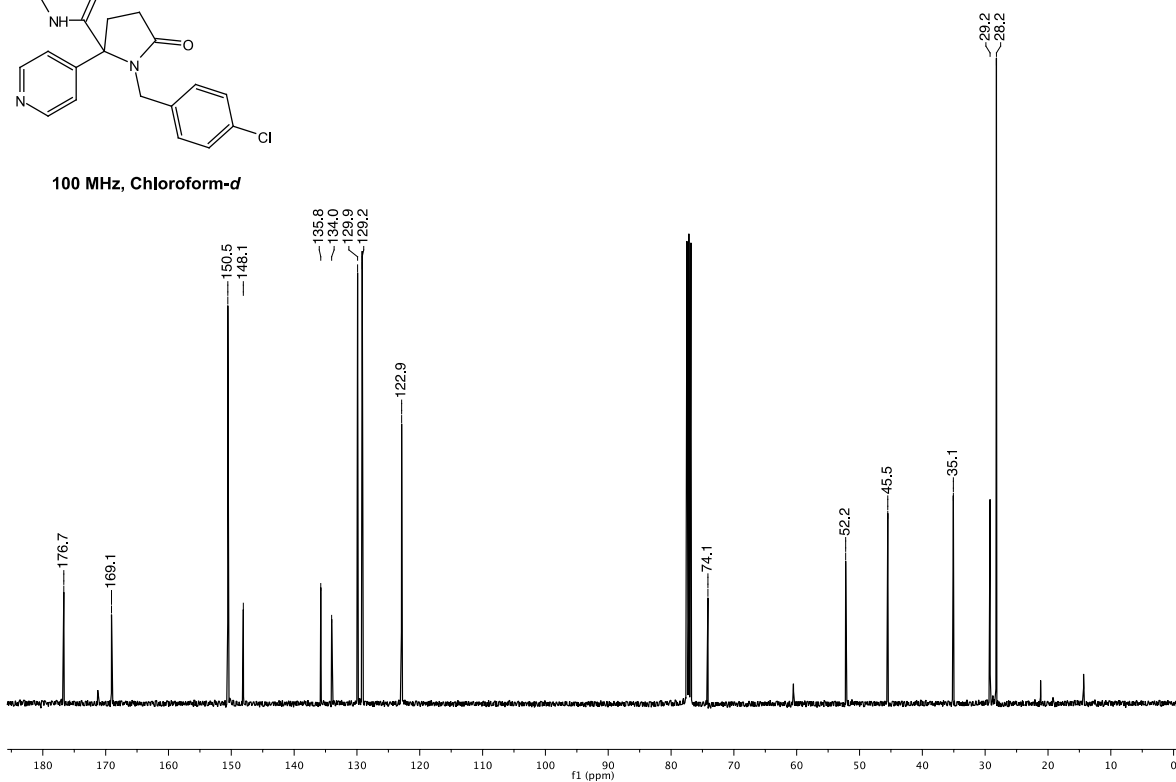
***N*-(*tert*-butyl)-1-(4-chlorobenzyl)-5-oxo-2-(pyridin-4-yl)pyrrolidine-2-carboxamide (15h)**



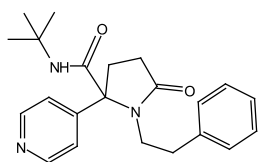
400 MHz, chloroform-*d*



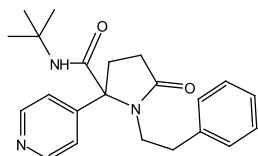
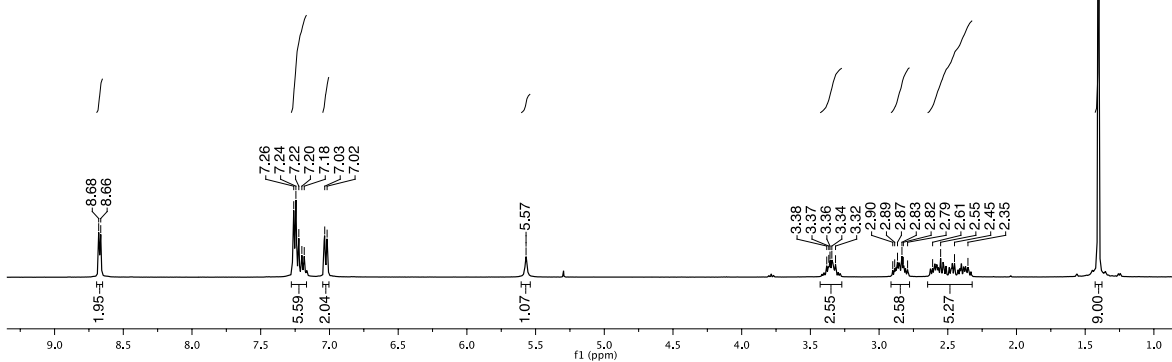
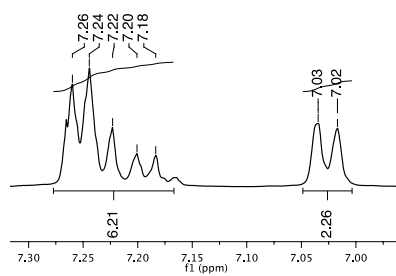
100 MHz, Chloroform-*d*



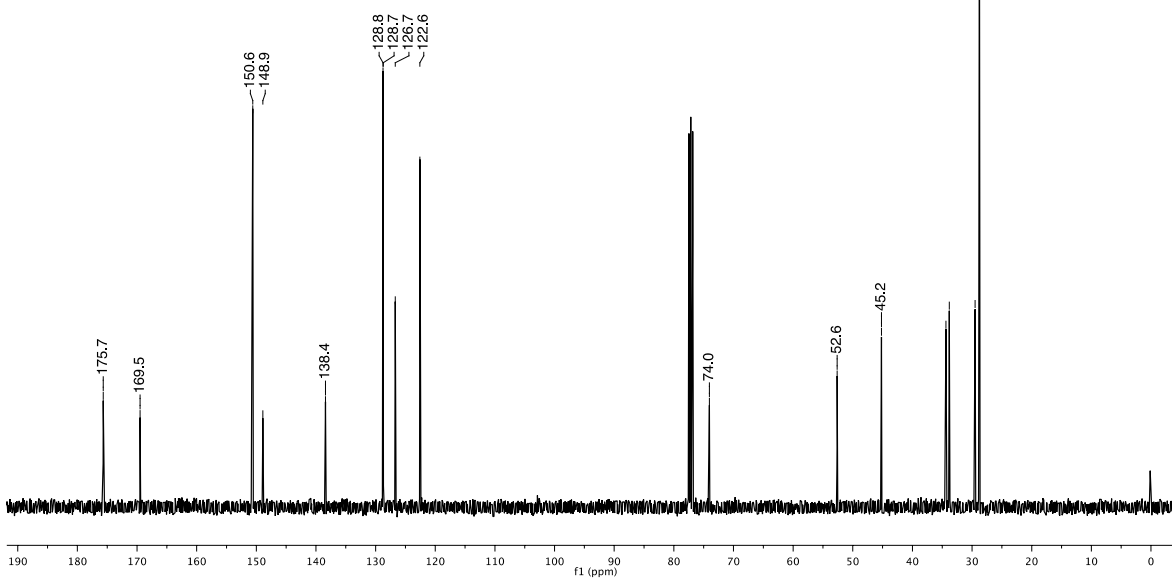
***N*-(*tert*-butyl)-5-oxo-1-phenethyl-2-(pyridin-4-yl)pyrrolidine-2-carboxamide (15i)**



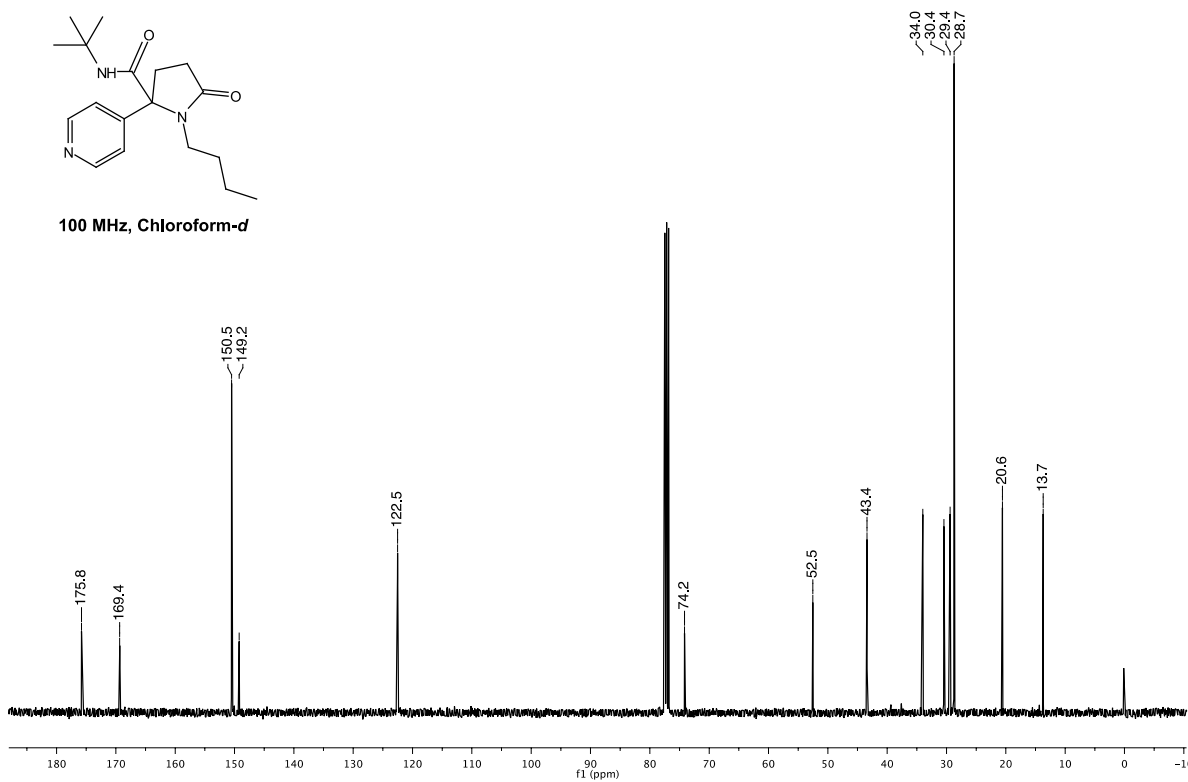
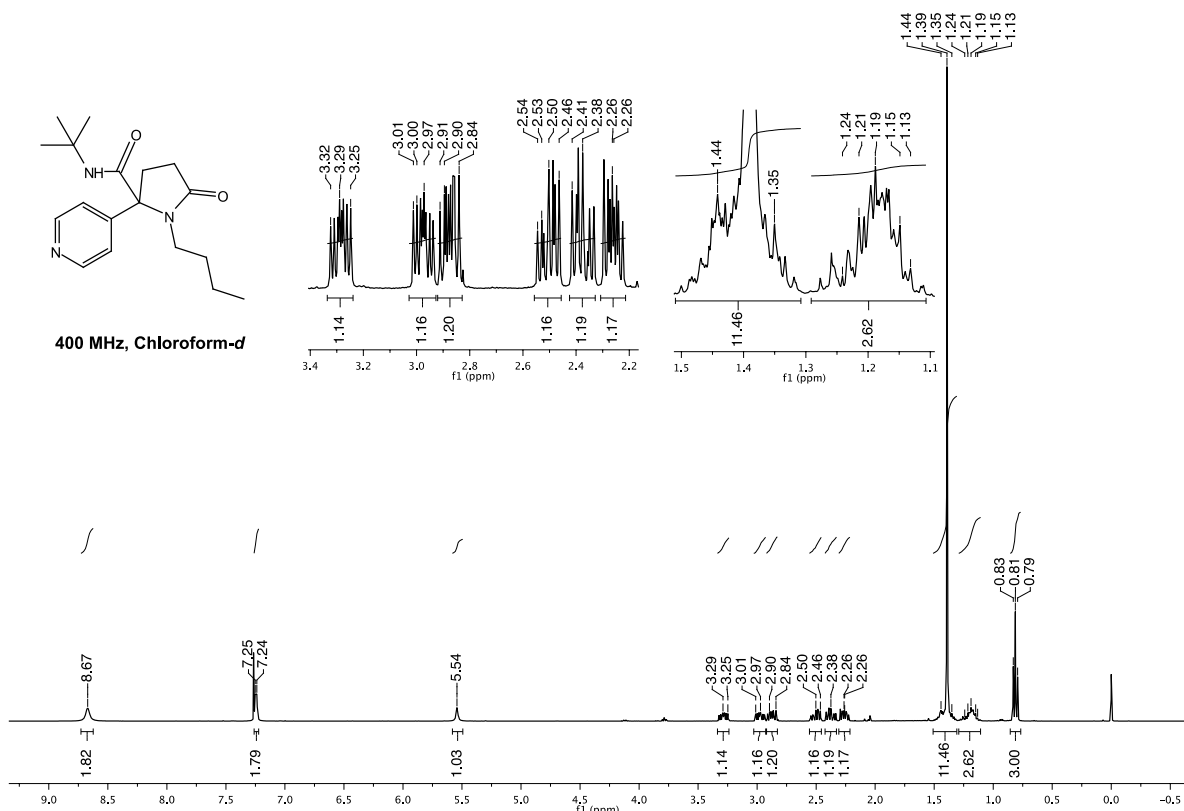
400 MHz, Chloroform-*d*



100 MHz, Chloroform-*d*

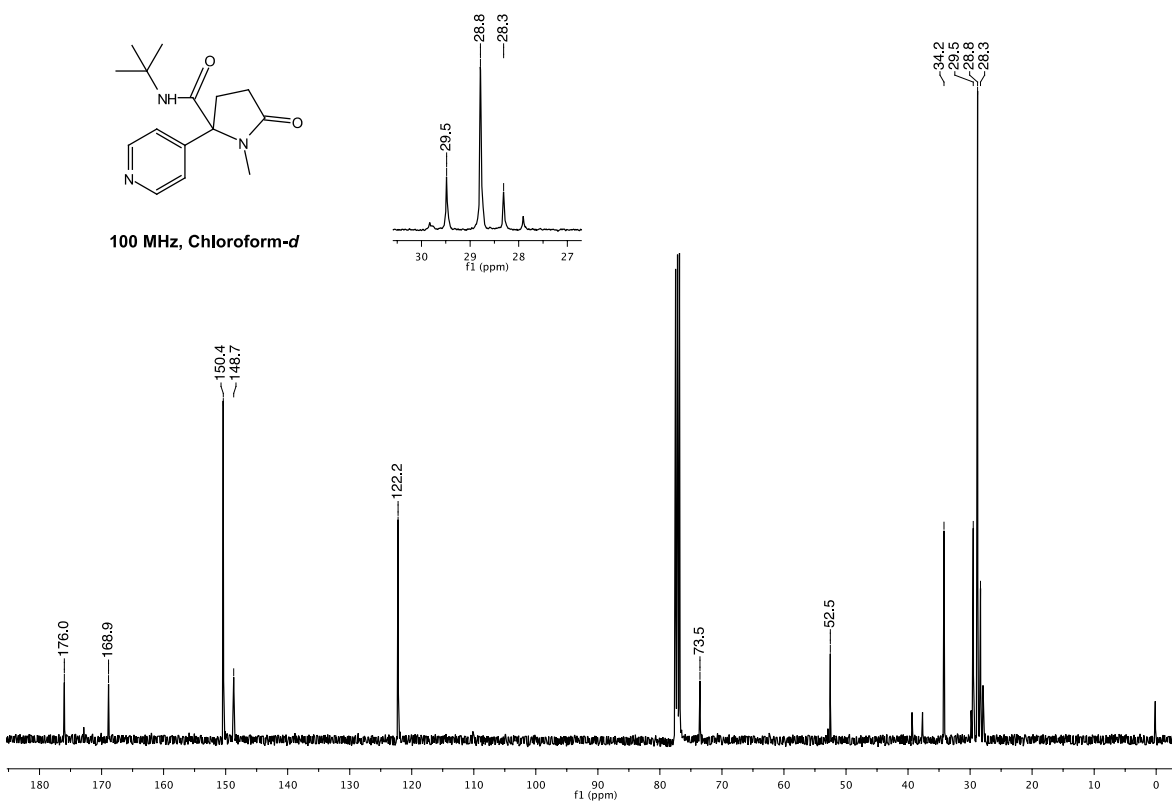
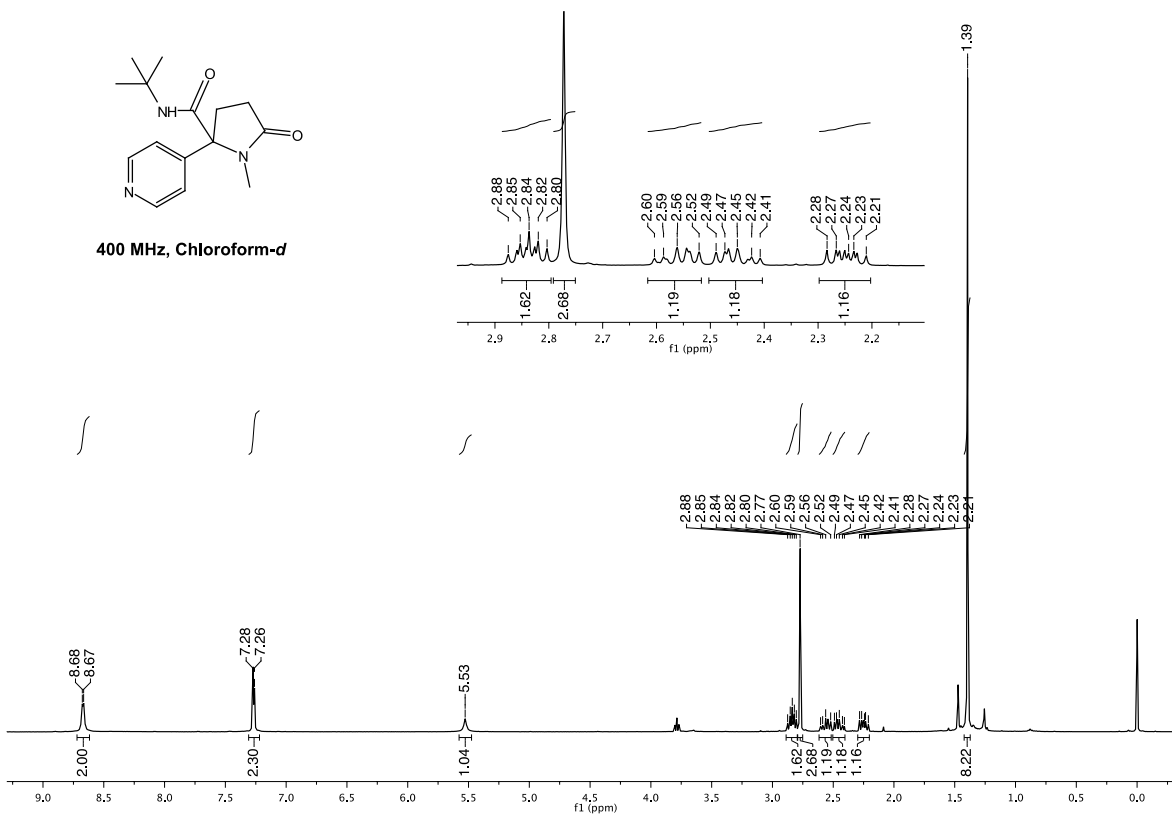


***N*-(*tert*-butyl)-1-butyl-5-oxo-2-(pyridin-4-yl)pyrrolidine-2-carboxamide (15j)**

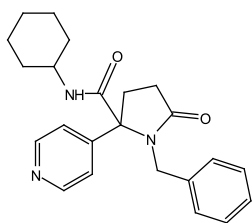




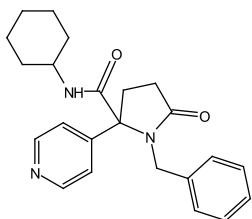
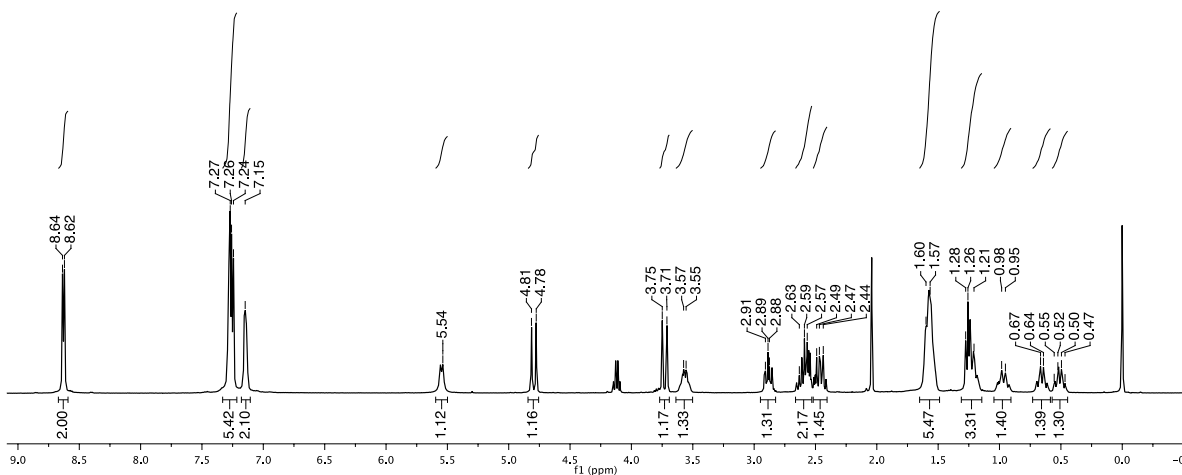
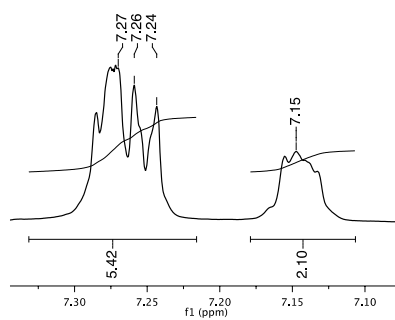
***N*-(*tert*-butyl)-1-methyl-5-oxo-2-(pyridin-4-yl)pyrrolidine-2-carboxamide (15k)**



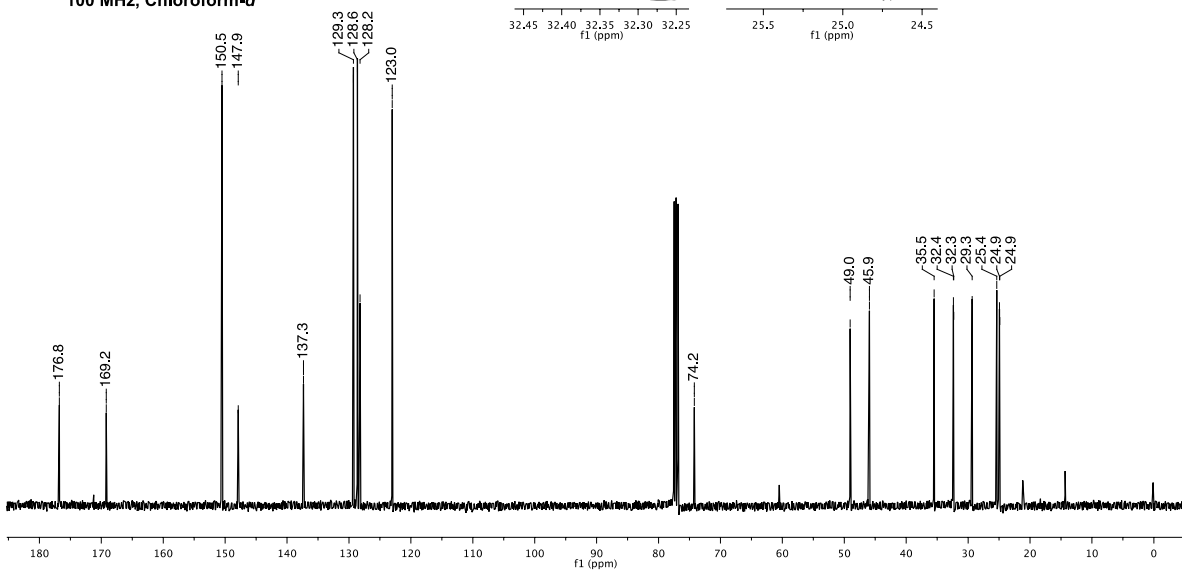
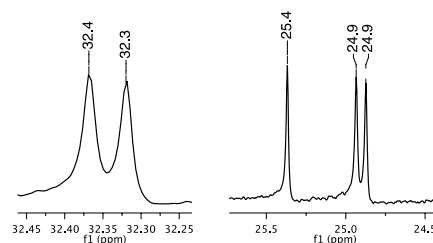
# 1-benzyl-N-cyclohexyl-5-oxo-2-(pyridin-4-yl)pyrrolidine-2-carboxamide (15l)



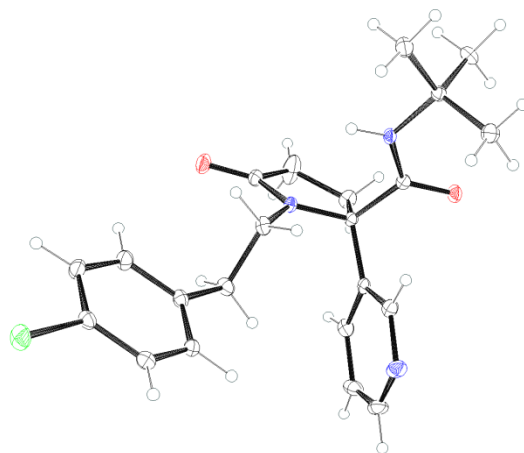
400 MHz, Chloroform-*d*



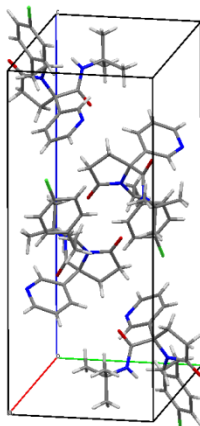
100 MHz, Chloroform-*d*



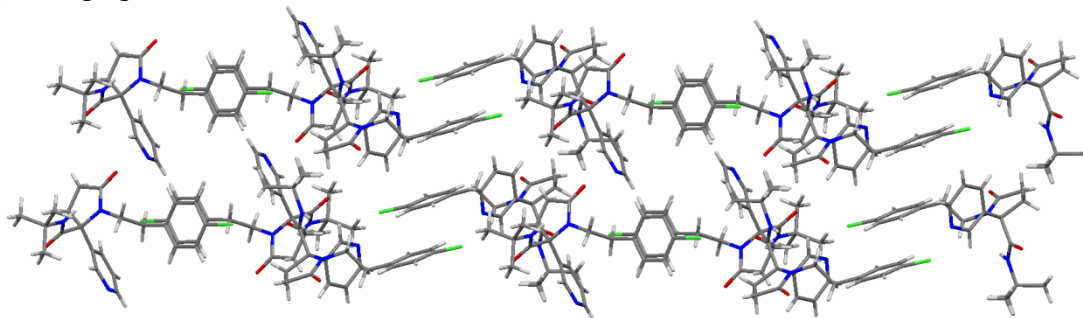
## X-Ray Crystallographic Data



**Figure 2.** Molecular structure for compound **12f**, thermal ellipsoids are drawn at 30 % probability for all atoms except than hydrogen.



**Figure 3.** Packing of compound **12f** with four molecules per unit cell, view along crystallographic *a* axis.



**Figure 4.** Crystal packing of compound **12f**, C-H... $\pi$  interactions between the chlorobenzene rings aligned the side chains in *head to tail* manner, the molecules are located one on the other being turned by almost 180° producing two orthogonal layers, view along crystallographic *b* axis.

**Table 4.** Crystallographic data of compound **12f**

<b>Compound</b>	<b>12f</b>
Chemical Formula	C <sub>22</sub> H <sub>26</sub> ClN <sub>3</sub> O <sub>2</sub>
Molecular Weight	399.91
Space Group	P 21/c
Crystal System	Monoclinic
T (K)	293
a (Å)	10.6870 (4)
b (Å)	9.1043 (3)
c (Å)	21.0968 (6)
α (°)	90.0
β (°)	98.623 (3)
γ (°)	90.0
Volume (Å <sup>3</sup> )	2029.47 (12)
Z	4
S	1.115
θ max	73.417
h, k, l, max	13, 11, 25
μ <sub>u</sub> (mm <sup>-1</sup> )	1.845
Nref	3967
Dx (g/cm <sup>-3</sup> )	1.309
R (reflections)	0.0409 (3277)
wR2 (reflections)	0.1276 (3967)