

Supporting Information

Chemo- and Stereoselective Transition Metal-Free Amination of Amides with Azides

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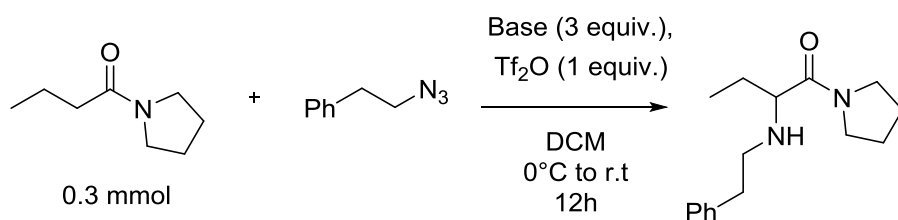
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General information

All glassware was oven dried at 100 °C before use. All solvents were distilled from appropriate drying agents prior to use. All reagents were used as received from commercial suppliers unless otherwise stated. Triflic anhydride was freshly distilled over P₂O₅ before use. Neat infra-red spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Wavenumbers ($\tilde{\nu} = 1/\lambda$) are reported in cm⁻¹. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionization (ESI) All ¹H-NMR and ¹³C-NMR experiments were recorded using Bruker AV-400, spectrometers at 300 K. Chemical shifts (δ) are quoted in ppm and coupling constants (J) are quoted in Hz. The 7.27 ppm resonance of residual CHCl₃ for proton spectra and 77.16 ppm resonance for carbon spectra were used as internal references. ¹H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q) or combinations thereof, splitting patterns that could not be interpreted were designated as multiplet (m). Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with kieselgel F254 with 0.2 mm thickness. Visualization was achieved by a combination of ultraviolet light (254 nm) and acidic potassium permanganate. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.).

Optimization tables

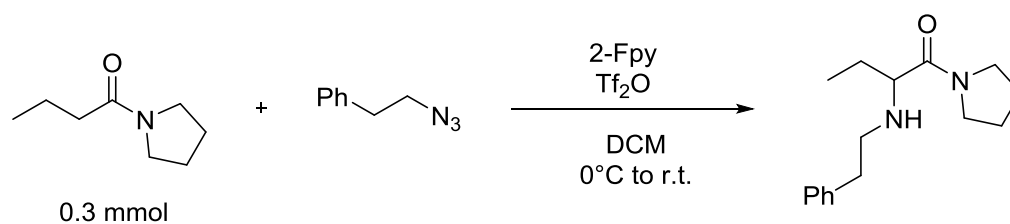
Table 1. Base screening



Entry	Reaction time	Temperature	Eq. azide	Base	Work up	Note	NMR yield
1	12h	0°C to r.t.	2	2-l-py	Na ₂ S ₂ O ₃	-	56%
2	12h	0°C to r.t.	1	2-l-py	Na ₂ S ₂ O ₃ - NaCl	-	33%
3	12h	0°C to r.t.	1	2-l-py	Na ₂ S ₂ O ₃ - NaCl	Molecular sieves	-
4	12h	0°C to r.t.	2	2-F-py	NaOH-NaCl	-	65%

5	12h	0°C to r.t.	1	Py	Na ₂ S ₂ O ₃ -NaCl	Molecular sieves	-
6	12h	0°C to r.t.	2	2-OMe-Py	NaOH-NaCl	-	30%
7	12h	0°C to r.t.	2	2-F-py	NaOH-NaCl	-	56% (prev. 65%)
8	12h	0°C to r.t.	2	Collidine	NaOH-NaCl	Different product formed	-
9	2h	0°C to r.t.	2	2-F-py	NaOH-NaCl	-	60%
10	2h	0°C to 40°C	2	2-F-py	NaOH-NaCl	-	59%

Table 2. Equivalents and work-up screening



Entry	Reaction time	Temperature	Eq. azide	Eq. base	Eq. Tf2O	Work up	Note	NMR yield
1	2h	0°C to r.t.	2	3	2	H ₂ O 30' Then NaHCO ₃	-	65%
2	2h	0°C to r.t.	2	3	1	NaHCO₃ overnight	-	74%
3	2h	0°C to r.t.	2	3	2	NaHCO ₃ overnight	-	73%
4	2h	0°C to r.t.	2	3	1.5	NaHCO ₃ overnight	-	70%
5	2h	0°C to r.t.	2	2	1	NaHCO ₃ overnight	-	80%

6	2h	0°C to r.t.	2	4	1.5	NaHCO ₃	-	75%
						overnight		
7	15+5 min	0°C to 120°C (μ W)	2	3	1	NaHCO ₃	-	15%
						overnight		
8	2h	0°C to r.t.	2	2	2	NaHCO ₃	-	80%
						overnight		
9	2h	0°C to r.t.	2	1.5	1	NaHCO ₃	-	80%
						overnight		
10	2h	0°C to r.t.	2	2	1	NaHCO₃	-	75%
						1h		
11	2h	0°C to r.t.	2	1.5	1	NaHCO ₃	-	33%* **
						1h		
12	2h	0°C to r.t.	2	1.5	1	NaOH	-	48%* **
						1h		
13	2h	0°C to r.t.	2	1	1	NaHCO ₃	-	60%*
						1h		
14	2h	0°C to r.t.	2	2	2	NaHCO ₃	-	79%
						1h		
15	2h	0°C to r.t.	1.5	2	1	NaHCO ₃	-	78%
						overnight		
16	2h	0°C to r.t.	3	2	1	NaHCO ₃	-	79%
						overnight		
17	30 min	0°C to r.t.	2	2	1	NaHCO ₃	-	85%
						1h		
18	2h	0°C to r.t.	2	2	1	NaHCO ₃	CH₃CN	
						1h		
19	2h	0°C to r.t.	2	2	1	NaHCO ₃	CHCl ₃	84%
						1h		

*Probable low quality of Tf2O

**Low conversion (starting material)

General procedure for the synthesis of the starting materials

Amides synthesis

Amides **1a**, **1b**, **1c**, **1e**, **1f**, **1m**, **1w** and **4** were synthesized from the corresponding chloride or acid according to the procedure reported by Peng et al.¹ Spectroscopic data are in accordance to the ones reported there. For the other amides, the synthetic procedure and the characterizations are reported below.

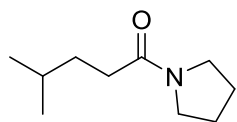
General procedure A:

To a solution of Et₃N (3 eq.) and amine (1.5 eq.) in DCM (0.2 M) at 0°C was slowly added the corresponding acyl chloride (1 eq.) and the reaction was allowed to warm to r.t. overnight. The reaction was quenched by addition of NH₄Cl, extracted with DCM, dried over Na₂SO₄ and evaporated. The crude product was purified by column chromatography (0 to 20% DMA2/DCM) to afford the pure amide.

General procedure B:

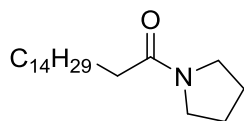
To a solution of Et₃N (2.4 eq.), amine (1.2 eq.) and carboxylic acid (1 eq.) in DMF (0.2 M) was added HATU (1.2 eq.) and the reaction was stirred at r.t. overnight. The reaction was quenched with NaOH 1M, extracted with DCM, dried over Na₂SO₄ and evaporated. The crude product was purified by column chromatography (0 to 20% DMA/DCM) to afford the pure amide.

4-Methyl-1-(pyrrolidin-1-yl)pentan-1-one (**1d**)



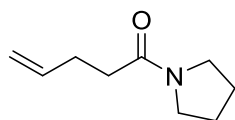
Synthesized from the corresponding chloride according to the procedure reported by Peng et al.¹ Quantitative yield. ¹H (400 MHz, CDCl₃) δ = 3.38 (dt, *J* = 19.4, 6.9 Hz, 2H), 2.21-2.18 (m, 2H), 1.90 (p, *J* = 6.8 Hz, 1H), 1.79 (p, *J* = 6.8 Hz, 1H), 1.55-1.47 (m, 3H), 0.85 (d, *J* = 6.4 Hz, 1H) ppm. ¹³C (100 MHz, CDCl₃) δ = 172.0, 46.6, 45.6, 33.8, 32.9, 27.9, 26.2, 24.4, 22.4 ppm. HRMS (ESI) *m/z* calculated for [M+Na]⁺ 192.1359, found 192.1356. ATR-FTIR (cm⁻¹): 2952, 2869, 1630, 1425, 1385, 1341, 1319.

1-(Pyrrolidin-1-yl)hexadecan-1-one (**1g**)



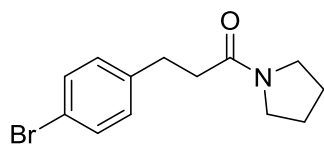
Synthesized from the corresponding chloride according to the procedure reported by Peng et al.¹ Quantitative yield. Spectroscopic data according to the literature.³

1-(Pyrrolidin-1-yl)pent-4-en-1-one (**1h**)



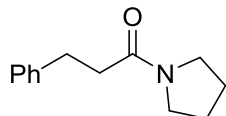
Quantitative yield. Synthesized from the corresponding chloride according to the procedure reported by Peng et al.¹ Spectroscopic data are in accordance to the literature.⁴

3-(4-Bromophenyl)-1-(pyrrolidin-1-yl)propan-1-one (1i)



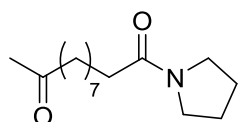
Synthesized from the corresponding acid according to the procedure reported by Peng et al.¹ 43% yield. Spectroscopic data are according to the literature.⁵

3-Phenyl-1-(pyrrolidin-1-yl)propan-1-one (1j)



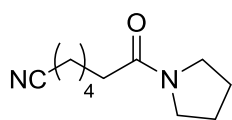
Synthesized from the corresponding chloride according to the procedure reported by Peng et al.¹ Quantitative yield. Spectroscopic data according to the literature.⁶

1-(Pyrrolidin-1-yl)undecane-1,10-dione (1k)



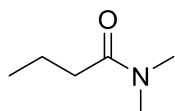
To a solution of amide (1 equiv.) and Pd(OAc)₂ (0.1 equiv.) in DMSO/water (0.33 M, 10/1, v/v) in a Schlenk under oxygen atmosphere was added TFA (1 equiv.) and the reaction was heated to 70°C overnight. The reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over Na₂SO₄ and evaporated. Column chromatography (0 to 20% DMA/DCM) afforded the pure amide (27%) as well as 73% recovered starting material. ¹H (400 MHz, CDCl₃) δ = 3.38 (dt, J = 21.9 Hz, 6.8 Hz, 4H), 2.35 (t, J = 7.4 Hz, 2H), 2.20 (t, J = 7.7 Hz, 2H), 2.07 (s, 3H), 1.92-1.74 (m, 4H), 1.59-1.48 (m, 4H), 1.27-1.20 (m, 8H) ppm. ¹³C (100 MHz, CDCl₃) δ = 209.4, 172.1, 46.7, 45.7, 43.8, 34.8, 29.8, 29.4, 29.2, 29.1, 26.1, 24.8, 24.4, 23.8 ppm. HRMS (ESI) m/z calculated for [M+Na]⁺ 276.1939, found 276.1928. ATR-FTIR (cm⁻¹): 2926, 2854, 1712, 1635, 1430, 1359, 1253, 1226, 914, 859, 721.

7-Oxo-7-(pyrrolidin-1-yl)heptanenitrile (1l)



To a solution of NaCN (1.4 eq.) in DMSO (1.5 M) was added 6-chloro-1-(pyrrolidin-1-yl)hexan-1-one (1 equiv., synthesized according to the procedure reported from Peng et al.¹) and the reaction was heated to 120°C for 15 minutes. After cooling the reaction mixture was evaporated. Column chromatography (0 to 20% DMA/DCM) afforded the pure amide (80%). ¹H (400 MHz, CDCl₃) δ = 3.43 (dt, J = 24.8 Hz, 6.9 Hz, 4H), 2.36 (t, J = 7.1 Hz, 2H), 2.27 (t, J = 7.3 Hz, 2H), 1.99-1.81 (m, 4H), 1.73-1.66 (m, 4H), 1.55-1.47 (m, 2H) ppm. ¹³C (100 MHz, CDCl₃) δ = 170.9, 119.6, 46.4, 45.5, 34.1, 28.3, 26.0, 25.2, 24.3, 23.8, 16.9 ppm. HRMS (ESI) m/z calculated for [M+Na]⁺ C₁₁H₁₈N₂ONa: 217.1317, found 217.1309. ATR-FTIR (cm⁻¹): 2939, 2869, 1629, 1429, 1341, 1254, 1227, 915, 858, 729.

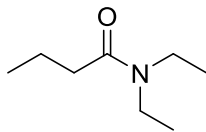
N,N-dimethylbutyramide (1n)



Prepared according to the general procedure A with a 98% yield. ¹H (400 MHz, CDCl₃) δ = 2.97 (s, 3H), 2.91 (s, 3H), 2.59 (t, J = 7.4 Hz, 2H), 1.63 (app sext, J = 7.4 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H) ppm. ¹³C (100 MHz, CDCl₃) δ = 173.1, 37.3, 35.4, 18.7, 14.1

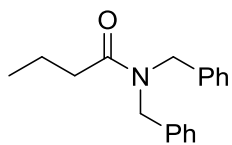
ppm. **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 138.0889, found 138.0889. **ATR-FTIR** (cm^{-1}): 2962, 2876, 1640, 1499, 1462, 1399, 1346, 1263, 1016, 801.

N,N-diethylbutyramide (**1o**)



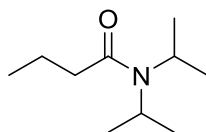
Prepared according to the general procedure A with a quantitative yield. **^1H** (400 MHz, CDCl_3) δ = 3.37 (q, J = 7.1 Hz, 2H), 3.30 (q, J = 7.1 Hz, 2H), 2.27 (t, J = 7.4 Hz, 2H), 1.72-1.63 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H) ppm. **^{13}C** (100 MHz, CDCl_3) δ = 172.3, 42.1, 40.1, 35.2, 19.0, 14.5, 14.1, 13.3 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ 144.1383, found 144.1383. **ATR-FTIR** (cm^{-1}): 2958, 2926, 2855, 1637, 1487, 1459, 1437, 1363, 1256, 1025, 860, 776, 723, 692, 542.

N,N-dibenzylbutyramide (**1p**)



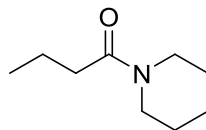
Prepared according to the general procedure A with a quantitative yield. **^1H** (400 MHz, CDCl_3) δ = 7.38-7.16 (m, 10H), 4.62 (s, 2H), 4.46 (s, 2H), 2.42 (t, J = 7.5 Hz, 2H), 1.79-1.74 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H) ppm. **^{13}C** (100 MHz, CDCl_3) δ = 173.7, 137.7, 136.8, 129.1, 128.7, 128.4, 127.7, 127.5, 126.5, 50.0, 48.2, 35.3, 19.0, 14.1 ppm. **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 290.1521, found 290.1515. **ATR-FTIR** (cm^{-1}): 3062, 3029, 2962, 2929, 2873, 1641, 1450, 1359, 1266, 1076, 909, 822, 729, 697.

N,N-diisopropylbutyramide (**1q**)



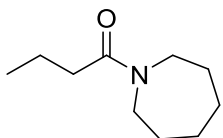
Prepared using procedure A with a 53% yield. **^1H** (400 MHz, CDCl_3) δ = 3.92-3.86 (m, 1H), 3.46-3.37 (m, 1H), 2.20-2.16 (m, 2H), 1.61-1.52 (m, 2H), 1.29 (d, J = 6.7 Hz, 6H), 1.12 (d, J = 6.7 Hz, 6H), 0.88 (t, J = 7.4 Hz, 3H) ppm. **^{13}C** (100 MHz, CDCl_3) δ = 172.0, 48.3, 45.6, 37.5, 21.2, 20.9, 19.0, 14.1 ppm. **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 194.1515, found 194.1513. **ATR-FTIR** (cm^{-1}): 3000, 2963, 2932, 2874, 1634, 1439, 1370, 1214, 1135, 1044, 884, 801.

1-(Piperidin-1-yl)butan-1-one (**1r**)



Prepared using procedure A with a quantitative yield. **^1H** (400 MHz, CDCl_3) δ = 3.54 (t, J = 5.5 Hz, 2H), 3.39 (t, J = 5.5 Hz, 2H), 2.31-2.27 (m, 2H), 1.70-1.60 (m, 4H), 1.57-1.49 (m, 4H), 0.96 (t, J = 7.4 Hz, 3H) ppm. **^{13}C** (100 MHz, CDCl_3) δ = 171.4, 46.8, 42.7, 35.5, 26.7, 25.8, 24.8, 19.0, 14.2 ppm. **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 178.1202, found 178.1201. **ATR-FTIR** (cm^{-1}): 2933, 2854, 1632, 1434, 1351, 1252, 1139, 1091, 953, 907, 852, 807, 730.

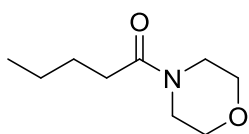
1-(Azepan-1-yl)butan-1-one (**1s**)



Prepared using procedure A with a quantitative yield. **^1H** (400 MHz, CDCl_3) δ = 3.50 (t, J = 6.0 Hz, 2H), 3.41 (t, J = 6.0 Hz, 2H), 2.27 (t, J = 7.5 Hz, 2H), 1.71-1.63 (m, 6H), 1.55-1.53 (m, 4H), 0.94 (t, J = 7.4 Hz, 3H) ppm. **^{13}C** (100 MHz, CDCl_3) δ

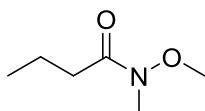
=172.7, 48.0, 46.0, 35.4, 29.4, 27.7, 27.2, 27.0, 18.9, 14.2 ppm. **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 192.1364, found 192.1358. **ATR-FTIR** (cm^{-1}): 2925, 2855, 1632, 1422, 1374, 1279, 1193, 1018, 903, 813, 753.

1-Morpholinopentan-1-one (1t)



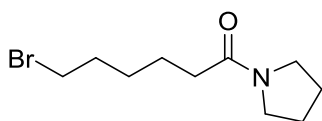
Synthesized from the corresponding chloride according to the procedure reported by Peng et al.¹ 34% yield. Spectroscopic data according to the literature.⁷

N-methoxy-N-methylbutyramide (1u)



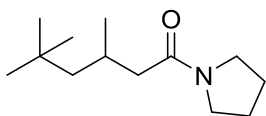
Prepared using procedure A with a 80% yield. **¹H** (400 MHz, CDCl₃) δ = 3.66 (s, 3H), 3.16 (s, 3H), 2.38 (t, J = 7.4Hz, 2H), 1.69-1.60 (m, 2H), 0.95 (t, J = 7.4Hz, 3H) ppm. **¹³C** (100 MHz, CDCl₃) δ = 174.7, 61.3, 33.9, 32.3, 18.2, 14.0 ppm. **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 154.0838, found 154.0838. **ATR-FTIR** (cm^{-1}): 2960, 2928, 2874, 2856, 1715, 1667, 1597, 1459, 1376, 1257, 1191, 1024, 860, 776, 692.

6-Bromo-1-(pyrrolidin-1-yl)hexan-1-one (1w)



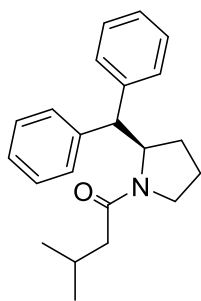
Synthesized from the corresponding chloride according to the procedure reported by Peng et al.¹ 34% yield. Spectroscopic data according to the literature.⁸

3,5,5-trimethyl-1-(pyrrolidin-1-yl)hexan-1-one (1x)



Prepared using procedure A with a quantitative yield. **¹H** (400 MHz, CDCl₃): δ = 3.45-3.37 (m, 4H), 2.24-2.04 (m, 3H), 1.95-1.79 (m, 4H), 1.28-1.06 (m, 2H), 0.96 (d, J = 6.3Hz, 3H), 0.88 (s, 9H) ppm. **¹³C** (100 MHz, CDCl₃) δ = 171.3, 51.1, 46.8, 45.6, 44.5, 31.2, 30.1, 26.8, 26.3, 24.5, 23.0 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ 212.2009, found 212.2007. **ATR-FTIR** (cm^{-1}): 2951, 2869, 1633, 1422, 1364, 1342, 1250, 1225, 1168, 924, 730.

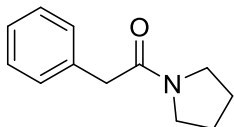
(R)-1-(2-benzhydrylpyrrolidin-1-yl)-3-methylbutan-1-one (1y)



Synthesized from the corresponding chloride according to the procedure reported by Peng et al.¹ 78% yield. NMR analysis shows the presence of 2 rotamers in ratio 7:3. **¹H** NMR signals are reported only for the major. **¹H** NMR (400 MHz, CDCl₃) δ = 7.35-7.12 (m, 10H), 5.11-5.07 (m, 1H), 4.58 (d, J = 5.9 Hz, 1H), 3.38-3.31 (m, 1H), 3.17-3.11 (m, 1H), 2.13-1.92 (m, 5H), 0.90 (dd, J = 11.8, 6.2 Hz, 6H) ppm. **¹³C** NMR (100 MHz, CDCl₃) δ = 171.5, 142.4, 142.4, 129.7, 129.2, 129.2, 129.0, 128.8, 128.6, 128.3, 128.1, 127.1, 127.0, 126.7, 126.2, 61.9, 59.6, 54.4, 52.4, 47.1, 44.9, 44.3, 42.5, 30.4, 27.7, 25.4, 25.4, 23.8, 22.9, 22.9, 22.8, 22.6, 21.5 ppm. **HRMS** (ESI) m/z calculated for $[M+Na]^+$

=344.1990, found 344.1981. **ATR-FTIR (cm⁻¹):** 2955, 2924, 2869, 2854, 1636, 1494, 1450, 1415, 1382, 1341, 732, 701.

2-Phenyl-1-(pyrrolidin-1-yl)ethan-1-one (1z)



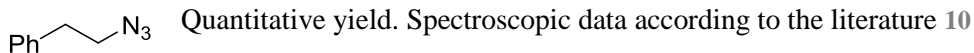
Synthesized from the corresponding chloride according to the procedure reported by Peng et al.¹ Quantitative yield. Spectroscopic data according to the literature.⁹

Azides synthesis

General Procedure for the synthesis of 2a-g

A solution of bromide (1 eq.) and NaN₃ (1.5 eq.) in DMF (0.2M) was heated at 80°C overnight. The reaction mixture was cooled, diluted with EtOAc, washed with H₂O and brine, dried over Na₂SO₄ and concentrated under vacuum, to afford the corresponding azide which was used without further purification.

(2-Azidoethyl)benzene (2a)



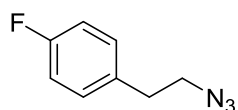
(Azidomethyl)benzene (2b)



1-Azidoheptane (2c)

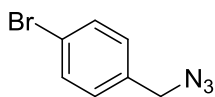


1-(2-Azidoethyl)-4-fluorobenzene (2d)



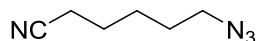
Quantitative yield. Spectroscopic data according to the literature.¹³

1-(Azidomethyl)-4-bromobenzene (2e)



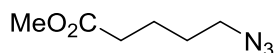
Quantitative yield. Spectroscopic data according to the literature.¹⁴

6-Azidohexanenitrile (2f)



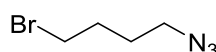
Quantitative yield. Spectroscopic data according to the literature.¹⁵

Methyl 5-azidopentanoate (2g)



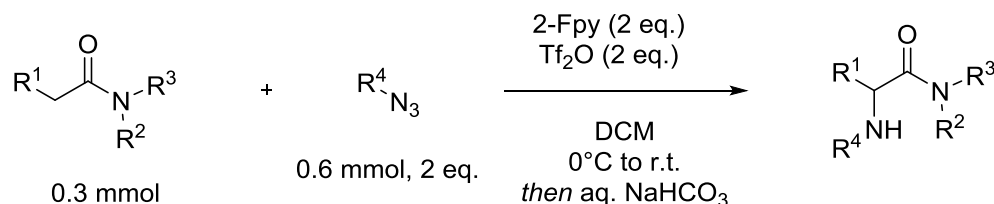
Quantitative yield. Spectroscopic data according to the literature.¹⁶

1-Azido-4-bromobutane (2h)



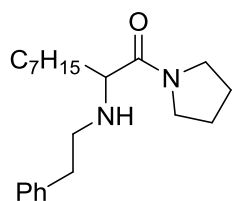
37% yield. Procedure and characterization according to the literature.¹⁷

General procedure for α -amination of amides



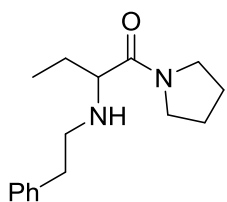
To a mixture of amide (0.3 mmol) and 2-fluoropyridine (0.6 mmol, 2 equiv., 58.3 mg, 51.6 μ l) in DCM (1 mL) triflic anhydride was added dropwise (0.6 mmol, 2 equiv., 84 mg, 51 μ L.) at 0 °C under Ar. The mixture was stirred for 15 minutes at this temperature. Then a solution of azide (0.6 mmol, 2 equiv.) in 0.5 mL of DCM was added and the mixture was brought to room temperature. N₂ release was observed after addition of the azide. After 30 min, 2 mL of a saturated solution of NaHCO₃ were added and the mixture was further stirred for 1h. The biphasic mixture was then diluted with DCM and washed with a 20 mL of NaHCO₃. The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure. Purification through column chromatography DCM/DMA (0 to 60% DMA) afforded the products.

2-(Phenethylamino)-1-(pyrrolidin-1-yl)nonan-1-one (3aa)



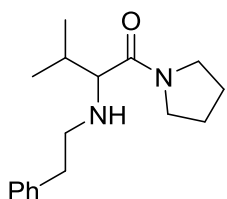
¹H NMR (400 MHz, CDCl₃) δ = 7.29-7.25 (m, 2H), 7.21-7.16 (m, 3H), 3.54-3.38 (m, 4H), 3.31 (t, *J* = 6.6 Hz, 1H), 2.87-2.78 (m, 2H), 2.75-2.70 (m, 1H), 2.65-2.60 (m, 1H), 1.97-1.90 (m, 2H), 1.87-1.80 (m, 2H), 1.56-1.51 (m, 2H), 1.40-1.26 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 173.8, 140.4, 128.9, 128.5, 126.2, 60.3, 50.2, 46.3, 45.8, 37.2, 33.9, 32.0, 29.9, 29.3, 26.3, 26.2, 24.3, 22.8, 14.2. HRMS (ESI) *m/z* calculated for [M+H⁺] = 331.2744, found 331.2738. ATR-FTIR (cm⁻¹): 3491, 2927, 2855, 1640, 1376, 1338, 750, 700.

2-(Phenethylamino)-1-(pyrrolidin-1-yl)butan-1-one (3ba)



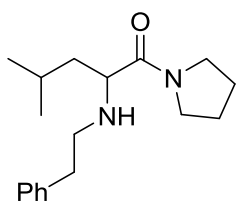
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.30-7.26 (m, 2H), 7.22-7.19 (m, 3H), 3.57-3.39 (m, 4H), 3.31 (t, J = 6.5 Hz, 1H), 2.89-2.80 (m, 2H), 2.78-2.73 (m, 1H), 2.29-2.65 (m, 1H), 1.93 (dd, J = 12.9, 6.5 Hz, 2H), 1.85 (dd, J = 12.9, 6.4 Hz, 2H), 1.62 (dt, J = 14.8, 7.3 Hz, 2H), 0.94 (t, J = 7.5 Hz, 3H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ = 172.2, 140.1, 128.9, 128.5, 126.3, 61.5, 50.1, 46.4, 45.9, 37.0, 26.6, 26.3, 24.3, 10.5 ppm. HRMS (ESI) m/z calculated for $[\text{M}+\text{H}^+]$ = 261.1961, found 261.1967. ATR-FTIR (cm^{-1}): 3502, 3297, 3026, 2875, 1633, 1428, 1340, 1226, 1150, 1031, 751, 700.

3-methyl-2-(phenethylamino)-1-(pyrrolidin-1-yl)butan-1-one (3ca)



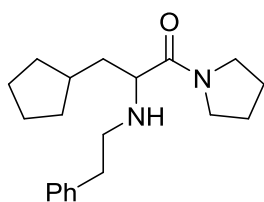
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.29-7.25 (m, 2H), 7.22-7.16 (m, 3H), 3.58-3.40 (m, 4H), 3.04 (d, J = 6.7 Hz, 1H), 2.87-2.76 (m, 2H), 2.73-2.68 (m, 1H), 2.60-2.56 (m, 1H), 1.96-1.89 (m, 2H), 1.87-1.76 (m, 4H), 0.98 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ = 173.8, 140.6, 128.9, 128.4, 126.1, 66.0, 50.5, 46.5, 45.7, 37.3, 31.7, 26.3, 24.3, 19.9, 18.8 ppm. HRMS (ESI) m/z calculated for $[\text{M}+\text{H}^+]$ = 255.2118, found 255.2121. ATR-FTIR (cm^{-1}): 3514, 3287, 3002, 2969, 2870, 2506, 2365, 1634, 1465, 1426, 1262, 1084, 750, 698.

4-Methyl-2-(phenethylamino)-1-(pyrrolidin-1-yl)pentan-1-one (3da)



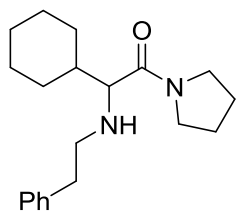
^1H (400 MHz, CDCl_3): δ = 7.30-7.19 (m, 5H), 3.56-3.34 (m, 5H), 2.91-2.61 (m, 4H), 1.97-1.82 (m, 6H), 1.48-1.29 (m, 2H), 0.95-0.92 (m, 6H) ppm. ^{13}C (100 MHz, CDCl_3): δ = 174.1, 140.4, 128.8, 128.4, 126.0, 58.6, 50.1, 46.1, 45.8, 43.0, 37.2, 26.2, 24.8, 24.2, 23.5, 22.3 ppm. HRMS (ESI) m/z calculated for $[\text{M}+\text{H}]^+$ = 289.2274, found 289.2275. ATR-FTIR (cm^{-1}): 3299, 3061, 3026, 2951, 2867, 1737, 1633, 1494, 1383, 1226, 1114, 1031, 915, 814, 748.

3-Cyclopentyl-2-(phenethylamino)-1-(pyrrolidin-1-yl)propan-1-one (3ea)



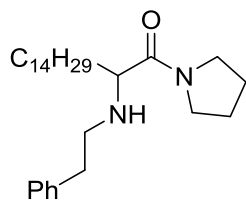
^1H (400 MHz, CDCl_3): δ = 7.21-7.10 (m, 5H), 3.47-3.25 (m, 5H), 2.79-2.54 (m, 4H), 2.20-2.14 (bs, 1H), 1.88-1.82 (m, 3H), 1.80-1.66 (m, 4H), 1.54-1.41 (m, 6H), 1.08-0.97 (m, 2H) ppm. ^{13}C (100 MHz, CDCl_3): δ = 173.8, 140.2, 128.8, 128.4, 126.1, 59.7, 50.0, 46.2, 45.8, 40.2, 37.0, 36.8, 33.3, 32.8, 36.2, 25.2, 24.2 ppm. HRMS (ESI) m/z calculated for $[\text{M}+\text{H}]^+$ = 315.2431, found 315.2432. ATR-FTIR (cm^{-1}): 3459, 3060, 3026, 2944, 2866, 1632, 1493, 1421, 1339, 1254, 1189, 1125, 1031, 984, 842, 748.

2-cyclohexyl-2-(phenethylamino)-1-(pyrrolidin-1-yl)ethan-1-one (3fa)



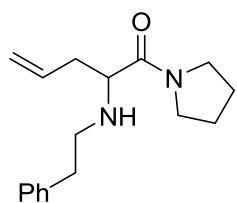
¹H NMR (400 MHz, CDCl₃) δ = 7.29-7.25 (m, 3H), 7.21-7.18 (m, 2H), 3.57-3.39 (m, 4H), 3.09 (d, J = 7.0 Hz, 1H), 2.84-2.79 (m, 2H), 2.75-2.69 (m, 1H), 2.59-2.54 (m, 1H), 2.00 (d, J = 12.8 Hz, 1H), 1.95-1.89 (m, 2H), 1.87-1.84 (m, 2H), 1.75-1.64 (m, 3H), 1.58-1.47 (m, 2H), 1.26-1.09 (m, 4H), 1.02-0.94 (m, 1H) ppm. **¹³C NMR (100 MHz, CDCl₃)** δ = 173.7, 140.6, 128.9, 128.4, 126.1, 65.6, 50.5, 46.6, 45.7, 41.8, 37.3, 30.2, 29.7, 26.6, 26.5, 26.4, 26.3, 24.3. **HRMS (ESI)** m/z calculated for $[M+H]^+$ = 315.2431, found 315.2421. **ATR-FTIR (cm⁻¹):** 3485, 2922, 2851, 1632, 1448, 1423, 750, 699.

2-(Phenethylamino)-1-(pyrrolidin-1-yl)hexadecan-1-one (3ga)



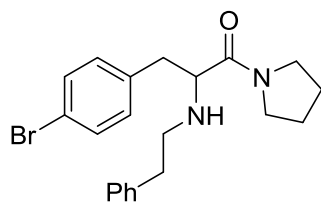
¹H (400 MHz, CDCl₃): δ = 7.14-7.05 (m, 5H), 3.38-3.18 (m, 5H), 2.72-2.49 (m, 4H), 1.82-1.69 (m, 4H), 1.43-1.39 (m, 2H), 1.29-1.11 (m, 24H), 0.77-0.74 (m, 3H) ppm. **¹³C (100 MHz, CDCl₃):** δ = 173.6, 140.2, 128.8, 128.4, 126.1, 60.2, 50.0, 46.3, 45.8, 37.1, 33.8, 32.0, 29.8, 29.7, 29.6, 29.4, 26.2, 26.0, 24.2, 22.8, 14.2 ppm. **HRMS (ESI)** m/z calculated for $[M+H]^+$ = 429.3839, found 429.3842. **ATR-FTIR (cm⁻¹):** 3462, 3027, 2921, 2851, 1638, 1453, 1422, 1339, 1252, 1190, 1118, 1032, 913, 839, 748.

2-(Phenethylamino)-1-(pyrrolidin-1-yl)pent-4-en-1-one (3ha)



¹H NMR (400 MHz, CDCl₃) δ = 7.28-7.26 (m, 2H), 7.21-7.17 (m, 3H), 5.79 (ddt, J = 17.2, 10.1, 7.2 Hz, 1H), 5.07 (ddd, J = 13.6, 11.1, 1.2 Hz, 2H), 3.52-3.50 (m, 1H), 3.47-3.39 (m, 4H), , 2.85-2.79 (m, 2H), 2.77-2.72 (m, 1H), 2.67-2.62 (m, 1H), 2.35-2.32 (m, 2H), 1.93-1.89 (m, 2H), 1.85-1.82 (m, 2H) ppm. **¹³C NMR (100 MHz, CDCl₃)** δ = 172.8, 140.2, 134.4, 128.9, 128.5, 126.2, 117.7, 60.0, 49.9, 46.4, 45.8, 38.0, 37.1, 26.2, 24.3 ppm. **HRMS (ESI)** m/z calculated for $[M+H]^+$ = 273.1961, found 273.1962. **ATR-FTIR (cm⁻¹):** 3470, 3304, 3062, 3025, 2971, 2930, 2873, 1631, 1493, 1425, 1338, 1118, 913, 748.

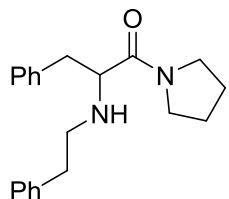
3-(4-Bromophenyl)-2-(phenethylamino)-1-(pyrrolidin-1-yl)propan-1-one (3ia)



¹H NMR (400 MHz, CDCl₃) δ = 7.37 (d, J =8.4 Hz, 2H), 7.29-7.26 (m, 2H), 7.21-7.17 (m, 3H), 7.06 (d, J =8.4, 2H), 3.49 (dd, J =9.1, 5.7 Hz, 1H), 3.46-3.41 (m, 1H), 3.20-3.14 (m, 1H), 2.91-2.70 (m, 5H), 2.67-2.56 (m, 2H), 1.96 (bs, 1H), 1.77-1.52 (m, 4H). ppm. **¹³C NMR (100 MHz, CDCl₃)** δ = 172.4,

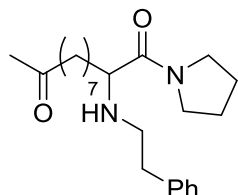
140.1, 137.1, 131.4, 131.2, 128.9, 128.5, 126.3, 120.5, 62.1, 49.8, 46.1, 45.7, 39.9, 37.1, 26.0, 24.1 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ =401.1223, found 401.1225. **ATR-FTIR** (cm^{-1}): 3460, 3300, 2931, 2877, 1634, 1487, 1433, 1339, 1256, 1012, 839, 804.

2-(Phenethylamino)-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (3ja)



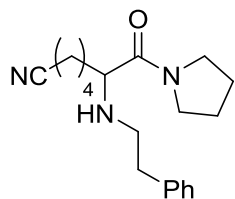
^1H NMR (400 MHz, CDCl_3) δ = 7.29-7.18 (m, 10H), 3.53 (dd, $J=9.7, 5.3$ Hz, 1H), 3.44-3.38 (m, 1H), 3.34-3.28 (m, 1H), 3.10 (dt, $J = 10.0, 6.8$ Hz, 1H), 2.98 (dd, $J = 12.8, 5.3$ Hz, 1H) 2.86-2.64 (m, 5H), 2.44-2.39 (m, 1H), 1.92 (bs, 1H), 1.71-1.53 (m, 3H), 1.46-1.39 (m, 1H) ppm. **^{13}C NMR (100 MHz, CDCl_3)** δ = 172.7, 140.2, 138.0, 129.5, 128.9, 128.5, 128.4, 126.7, 126.3, 62.4, 49.8, 46.0, 45.6, 40.8, 37.2, 25.9, 24.1 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ =323.2118, found 323.2120. **ATR-FTIR** (cm^{-1}): 3453, 3060, 3026, 2928, 2874, 1632, 1494, 1448, 1339, 749, 701, 574.

2-(Phenethylamino)-1-(pyrrolidin-1-yl)undecane-1,10-dione (3ka)



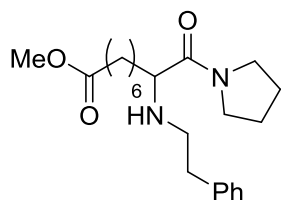
^1H (400 MHz, CDCl_3) δ = 7.21-7.11 (m, 5H), 3.45-3.23 (m, 5H), 2.78-2.54 (m, 4H), 2.33 (t, $J = 7.4$ Hz, 2H), 2.15-2.10 (bs, 1H), 2.05 (s, 3H), 1.88-1.75 (m, 4H), 1.47-1.46 (m, 2H), 1.24-1.17 (m, 8H). **^{13}C (100 MHz, CDCl_3)** δ = 209.3, 173.5, 140.2, 128.8, 128.4, 126.1, 60.2, 50.0, 46.2, 45.8, 43.8, 37.0, 33.6, 29.9, 29.6, 29.3, 26.2, 25.9, 24.2, 23.8 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ 373.2850, found 373.2849. **ATR-FTIR** (cm^{-1}): 3444, 3026, 2926, 2853, 1711, 1629, 1423, 1359, 1261, 1159, 1031, 914, 841, 749.

7-Oxo-6-(phenethylamino)-7-(pyrrolidin-1-yl)heptanenitrile (3la)



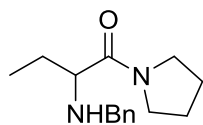
^1H (400 MHz, CDCl_3) δ = 7.30-7.20 (m, 5H), 3.55-3.30 (m, 5H), 2.87-2.62 (m, 4H), 2.33 (t, $J = 6.7$ Hz, 2H), 2.15-2.10 (bs, 1H), 1.97-1.84 (m, 4H), 1.70-1.46 (m, 6H) ppm. **^{13}C (100 MHz, CDCl_3)** δ = 173.1, 140.1, 128.8, 128.4, 126.1, 119.6, 59.9, 49.9, 46.3, 45.8, 37.0, 32.6, 26.2, 25.5, 25.2, 24.1, 17.1 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ 314.2227, found 314.2227. **ATR-FTIR** (cm^{-1}): 3300, 3026, 2933, 2870, 2244, 1623, 1426, 1339, 1225, 1152, 1031, 914, 841, 700.

Methyl 9-oxo-8-(phenethylamino)-9-(pyrrolidin-1-yl)nonanoate (3ma)



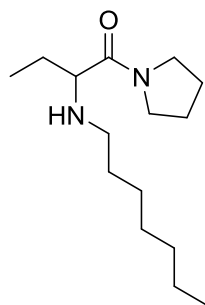
^1H NMR (400 MHz, CDCl_3) δ = 7.22-7.18 (m, 2H), 7.14-7.10 (m, 3H), 3.59 (s, 3H), 3.47-3.29 (m, 4H), 3.24 (t, $J = 6.5$ Hz, 1H), 2.76-2.71 (m, 2H), 2.68-2.64 (m, 1H), 2.58-2.54 (m, 1H), 2.22 (t, $J = 7.5$ Hz, 2H), 1.88-1.83 (m, 2H), 1.81-1.76 (m, 3H), 1.53-1.45 (m, 4H), 1.23-1.19 (m, 6H) ppm. **^{13}C NMR (100 MHz, CDCl_3)** δ = 174.4, 173.6, 140.2, 128.9, 128.5, 126.2, 60.2, 51.6, 50.2, 46.3, 45.9, 37.1, 34.2, 33.7, 29.5, 29.1, 26.3, 25.9, 25.0, 24.3 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ =375.2642, found 375.2636. **ATR-FTIR** (cm^{-1}): 3458, 2928, 2856, 1736, 1636, 1558, 1525, 1436, 1340, 1255, 1196, 1028, 914, 842, 701.

2-(Benzylamino)-1-(pyrrolidin-1-yl)butan-1-one (3bb)



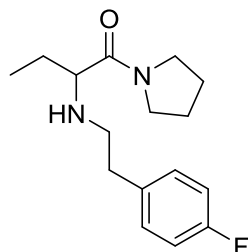
^1H (400 MHz, CDCl_3) δ = 7.37-7.22 (m, 5H), 3.85-3.44 (m, 4H), 3.34-3.21 (m, 3H), 2.27-2.21 (bs, 1H), 1.94-1.81 (m, 4H), 1.67-1.55 (m, 2H), 0.97 (t, J = 7.4Hz, 3H) ppm. ^{13}C (100 MHz, CDCl_3) δ = 173.4, 140.2, 128.2, 126.8, 60.0, 52.0, 46.0, 45.5, 26.6, 26.0, 24.1, 10.5 ppm. HRMS (ESI) calculated m/z for $[\text{M}+\text{H}]^+$ $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}$: 247.1805, found 247.1803. ATR-FTIR (cm^{-1}): 3488, 3301, 3026, 2931, 1635, 1494, 1454, 1396, 1333, 1260, 1121, 1084, 911, 858, 788, 730.

2-(Heptylamino)-1-(pyrrolidin-1-yl)butan-1-one (3bc)



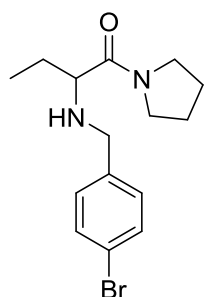
^1H (400 MHz, CDCl_3) δ = 3.56-3.40 (m, 4H), 3.27 (t, J = 6.5Hz, 1H), 2.54-2.36 (m, 2H), 2.24-2.19 (bs, 1H), 1.97-1.83 (m, 4H), 1.66-1.56 (m, 2H), 1.48-1.41 (m, 2H), 1.30-1.22 (m, 8H), 0.92 (t, J = 7.4Hz, 3H), 0.85 (t, J = 6.8Hz, 3H) ppm. ^{13}C (100 MHz, CDCl_3) δ = 173.6, 61.4, 48.6, 46.4, 45.8, 31.9, 30.4, 29.3, 27.4, 26.7, 26.3, 24.3, 22.7, 14.2, 10.5 ppm. HRMS (ESI) m/z calculated for $[\text{M}+\text{H}]^+$ 255.2431, found 255.2430. ATR-FTIR (cm^{-1}): 3300, 2956, 2925, 2872, 2856, 1625, 1427, 1378, 1224, 1154, 1089, 988, 915, 834, 726.

2-((4-Fluorophenethyl)amino)-1-(pyrrolidin-1-yl)butan-1-one (3bd)



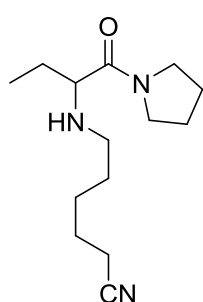
^1H (400 MHz, CDCl_3) δ = 7.16-7.12 (m, 2H), 6.95-6.91 (m, 2H), 3.50-3.38 (m, 4H), 3.25 (t, J = 6.5Hz, 1H), 2.81-2.57 (m, 4H), 2.06-2.03 (bs, 1H), 1.94-1.81 (m, 4H), 1.62-1.53 (m, 2H), 0.92 (t, J = 7.4Hz, 3H) ppm. ^{13}C (100 MHz, CDCl_3) δ = 173.4, 161.5 (d, J = 243.7Hz), 135.8 (d, J = 3.2Hz), 130.2 (d, J = 8.0Hz), 115.1 (d, J = 21.1Hz), 61.5, 50.0, 46.3, 45.8, 36.2, 26.6, 26.2, 24.2, 10.5 ppm. HRMS (ESI) m/z calculated for $[\text{M}+\text{H}]^+$ = 279.1867, found 279.1863. ATR-FTIR (cm^{-1}): 3298, 2964, 2933, 2875, 1623, 1509, 1427, 1340, 1257, 1191, 1097, 985, 825, 786.

2-((4-Bromobenzyl)amino)-1-(pyrrolidin-1-yl)butan-1-one (3be)



^1H (400 MHz, CDCl_3) δ = 7.41-7.39 (m, 2H), 7.21 (d, J = 8.5Hz, 2H), 3.76-3.13 (m, 6H), 2.17-2.15 (bs, 1H), 1.91-1.80 (m, 4H), 1.59-1.51 (m, 2H), 0.94 (t, J = 7.4Hz, 3H) ppm. ^{13}C (100 MHz, CDCl_3) δ = 173.5, 139.5, 131.4, 130.0, 120.7, 60.3, 51.5, 46.2, 45.7, 26.8, 26.2, 24.2, 10.6 ppm. HRMS (ESI) m/z calculated for $[\text{M}+\text{H}]^+$ = 325.0910, found 325.0905. ATR-FTIR (cm^{-1}): 3301, 2965, 2872, 1628, 1484, 1424, 1340, 1253, 1189, 1069, 914, 836, 749, 637.

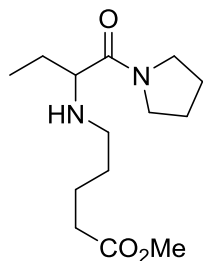
6-((1-Oxo-1-(pyrrolidin-1-yl)butan-2-yl)amino)hexanenitrile (3bf)



^1H (400 MHz, CDCl_3) δ = 3.57-3.41 (m, 4H), 3.23 (t, J = 6.5Hz, 1H), 2.58-2.52 (m, 1H), 2.41-2.31 (m, 3H), 1.99-1.81 (m, 5H), 1.68-1.46 (m, 8H), 0.94 (t, J = 7.4Hz, 3H) ppm. ^{13}C (100 MHz, CDCl_3) δ = 173.6, 119.8, 61.5, 48.1, 46.4, 45.8, 29.7, 26.8, 26.5,

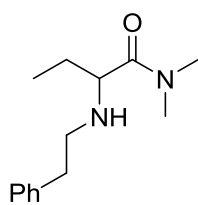
26.3, 25.4, 24.3, 17.2, 10.6 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ = 252.2070, found 252.2072. **ATR-FTIR** (cm^{-1}): 3433, 2933, 2872, 1619, 1426, 1378, 1339, 1226, 1124, 1032, 987, 835, 788, 685.

Methyl 5-((1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)amino)pentanoate (**3bg**)



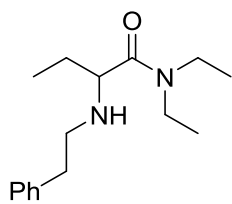
^1H (400 MHz, CDCl_3) δ = 3.64 (s, 3H), 3.56-3.41 (m, 4H), 3.24 (t, J = 6.5Hz, 1H), 2.58-2.35 (m, 2H), 2.30 (t, J = 7.5Hz, 2H), 2.01-1.84 (m, 5H), 1.67-1.45 (m, 6H), 0.93 (t, J = 7.4Hz, 3H). **^{13}C** (100 MHz, CDCl_3) δ = 174.2, 173.6, 61.4, 51.6, 48.0, 46.4, 45.8, 34.0, 29.9, 26.7, 26.3, 24.3, 22.8, 10.5. **HRMS** (ESI) m/z calculated for $[M+H]^+$ = 271.2016, found 271.2015. **ATR-FTIR** (cm^{-1}): 3456, 2952, 2874, 1734, 1625, 1523, 1432, 1340, 1224, 1166, 1031, 916, 837, 751.

N,N-dimethyl-2-(phenethylamino)butanamide (**3na**)



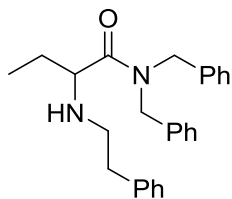
^1H (400 MHz, CDCl_3) δ = 7.33-7.20 (m, 5H), 3.50 (t, J = 6.4Hz, 1H), 3.03 (s, 3H), 3.01 (s, 3H), 2.88-2.64 (m, 4H), 2.17-2.11 (bs, 1H), 1.69-1.55 (m, 2H), 0.97 (t, J = 7.4Hz, 3H) ppm. **^{13}C** (100 MHz, CDCl_3) δ = 174.7, 140.1, 128.6, 128.2, 126.0, 59.1, 50.0, 36.9, 36.7, 35.6, 26.6, 10.2 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ = 235.1805, found 235.1803. **ATR-FTIR** (cm^{-1}): 3488, 3301, 3026, 2931, 1635, 1494, 1454, 1333, 1260, 1121, 1030, 911, 858, 730, 699.

N,N-diethyl-2-(phenethylamino)butanamide (**3oa**)



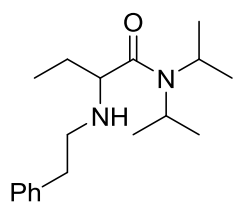
^1H (400 MHz, CDCl_3) δ = 7.33-7.22 (m, 5H), 3.65-3.56 (m, 1H), 3.47-3.38 (m, 2H), 3.32-3.23 (m, 2H), 2.90-2.66 (m, 4H), 2.58-2.48 (bs, 1H), 1.68-1.57 (m, 2H), 1.22 (t, J = 7.1Hz, 3H), 1.17 (t, J = 7.1Hz, 3H), 0.99 (t, J = 7.4Hz, 3H) ppm. **^{13}C** (100 MHz, CDCl_3): δ = 113.8, 140.0, 128.6, 128.2, 125.9, 59.0, 49.7, 41.2, 40.3, 36.8, 27.1, 14.8, 13.0, 10.3 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ = 263.2118, found 263.2117. **ATR-FTIR** (cm^{-1}): 3456, 3301, 3061, 3026, 2967, 2932, 2873, 1632, 1453, 1428, 1378, 1219, 1127, 1030, 923, 845, 729.

N,N-dibenzyl-2-(phenethylamino)butanamide (**3pa**)



^1H (400 MHz, CDCl_3) δ = 7.37-7.18 (m, 15H), 5.09 (d, J = 14.6Hz, 1H), 4.64-4.23 (m, 3H), 3.49-3.46 (m, 1H), 2.96-2.89 (m, 1H), 2.84-2.70 (m, 2H), 2.64-2.58 (m, 1H), 2.01-1.98 (bs, 1H), 1.74-1.56 (m, 4H), 0.98 (t, J = 7.4Hz, 3H) ppm. **^{13}C** (100 MHz, CDCl_3) δ = 175.7, 140.2, 137.5, 136.7, 129.0, 128.8, 128.7, 128.4, 127.8, 127.5, 126.6, 126.1, 59.7, 49.8, 49.4, 48.6, 37.0, 27.1, 10.6 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ 387.2431, found 387.2431. **ATR-FTIR** (cm^{-1}): 3285, 3085, 2960, 2931, 2873, 1641, 1548, 1460, 1324, 1223, 1105, 982, 892, 734.

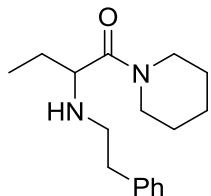
N,N-diisopropyl-2-(phenethylamino)butanamide (**3qa**)



^1H (400 MHz, CDCl_3) δ = 7.29-7.18 (m, 5H), 4.05 (sept, J = 6.6Hz, 1H), 3.52-3.43 (m, 1H), 3.39 (t, J = 6.2Hz, 1H), 2.88-2.62 (m, 4H), 2.39 (s, 1H), 1.66-1.50 (m, 2H), 1.43 (app t, J = 7.0Hz, 6H), 1.23 (d, J = 6.6Hz, 3H), 1.19 (d, J = 6.6Hz, 3H),

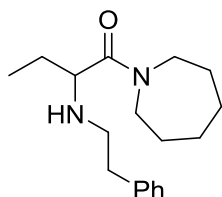
0.95 (t, $J = 7.4\text{Hz}$, 3H) ppm. ^{13}C (100 MHz, CDCl_3) $\delta = 173.6, 140.3, 128.8, 128.4, 126.1, 60.2, 50.1, 47.9, 46.2, 37.1, 27.1, 21.4, 20.9, 20.7, 10.3$ ppm. HRMS (ESI) m/z calculated for $[\text{M}+\text{H}]^+ = 291.2431$, found 291.2429. ATR-FTIR (cm^{-1}): 3460, 3300, 3062, 3001, 2965, 2932, 2874, 1630, 1437, 1324, 1210, 1122, 1039, 835, 749.

2-(Phenethylamino)-1-(piperidin-1-yl)butan-1-one (3ra)



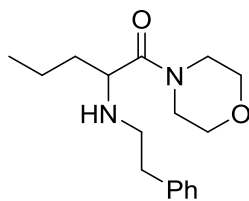
^1H (400 MHz, CDCl_3) $\delta = 7.33-7.20$ (m, 5H), 3.68-3.58 (m, 2H), 3.51-3.42 (m, 3H), 2.91-2.64 (m, 4H), 2.33-2.23 (bs, 1H), 1.71-1.55 (m, 8H), 0.97 (t, $J = 7.4\text{Hz}$, 3H) ppm. ^{13}C (100 MHz, CDCl_3) $\delta = 172.7, 140.1, 128.6, 128.2, 125.9, 58.9, 50.0, 46.2, 43.1, 36.9, 26.8, 26.7, 25.8, 24.5, 10.2$ ppm. HRMS (ESI) m/z calculated for $[\text{M}+\text{H}]^+ = 275.2118$, found 275.2115. ATR-FTIR (cm^{-1}): 3470, 3304, 3060, 3025, 2932, 2853, 1630, 1493, 1432, 1368, 1223, 1123, 1011, 952, 852, 748.

1-(Azepan-1-yl)-2-(phenethylamino)butan-1-one (3sa)



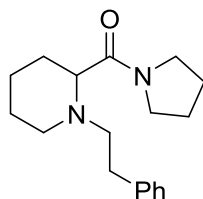
^1H (400 MHz, CDCl_3) $\delta = 7.27-7.23$ (m, 5H), 3.78-3.71 (m, 1H), 3.57-3.51 (m, 1H), 3.43-3.31 (m, 3H), 2.86-2.61 (m, 4H), 2.11-2.07 (bs, 1H), 1.77-1.52 (m, 10H), 0.96 (t, $J = 7.4\text{Hz}$, 3H) ppm. ^{13}C (100 MHz, CDCl_3) $\delta = 174.6, 140.3, 128.8, 128.4, 126.1, 59.4, 50.1, 47.5, 46.4, 37.1, 29.6, 27.8, 27.2, 27.1, 26.8, 10.6$ ppm. HRMS (ESI) m/z calculated for $[\text{M}+\text{H}]^+ = 289.2274$, found 289.2275. ATR-FTIR (cm^{-1}): 3299, 3061, 3026, 2952, 2854, 1629, 1555, 1424, 1372, 1268, 1144, 1030, 972, 847, 729.

1-Morpholino-2-(phenethylamino)pentan-1-one (3ta)



^1H (400 MHz, CDCl_3) $\delta = 7.34-7.24$ (m, 5H), 3.70-3.66 (m, 3H), 2.89-2.65 (m, 4H), 1.94-1.91 (bs, 1H), 1.59-1.37 (m, 4H), 0.96 (t, $J = 7.3\text{Hz}$, 3H) ppm. ^{13}C (100 MHz, CDCl_3) $\delta = 173.7, 140.3, 128.8, 128.5, 126.2, 67.2, 66.9, 57.9, 50.0, 45.8, 42.5, 37.2, 36.0, 19.2, 14.2$ ppm. HRMS (ESI) m/z calculated for $[\text{M}+\text{H}]^+ = 291.2067$, found 291.2069. ATR-FTIR (cm^{-1}): 3514, 3309, 3026, 2957, 2926, 2855, 1637, 1494, 1300, 1231, 1115, 1033, 910, 843, 700.

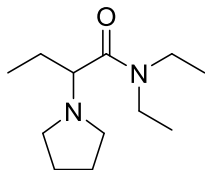
(1-Phenethylpiperidin-2-yl)(pyrrolidin-1-yl)methanone (3wa)



To a mixture of amide 1w (0.3 mmol) and 2-fluoropyridine (0.6 mmol, 2 equiv., 58.3 mg, 51.6 μL) in DCM (1 mL) triflic anhydride was added dropwise (0.6 mmol, 2 equiv., 84 mg, 51 μL .) at 0 $^\circ\text{C}$ under Ar. The mixture was stirred for 15 minutes at this temperature. Then a solution of azide 2a (0.6 mmol, 2 equiv) in 0.5 mL of DCM was added and the mixture was brought to room temperature. After 2 h, 2 mL of a saturated solution of NaHCO_3 were added and the mixture was further stirred for 30 minutes. The biphasic mixture was then diluted with DCM and washed with a 20mL of NaHCO_3 . The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure. Purification through column chromatography DCM/DMA (0 to 60% DMA) afforded the tertiary amine in 58% yield. ^1H (400 MHz, CDCl_3) $\delta = 7.28-7.17$ (m, 5H), 3.49-3.45 (m, 4H), 3.38-3.34 (m, 1H), 3.19-3.16 (m, 1H), 2.87-2.82 (m, 3H), 2.53-2.50 (m, 1H), 2.27-2.23 (m, 1H), 1.90-1.69 (m, 9H), 1.37-1.29 (m, 1H) ppm. ^{13}C (100 MHz, CDCl_3) $\delta = 173.8, 140.6, 128.9, 128.3, 126.0, 66.3, 50.5, 46.4, 45.7, 45.6, 37.2,$

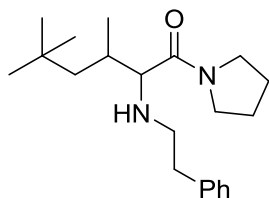
32.8, 31.0, 29.9, 26.3, 24.2, 20.5 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ 331.2744, found 331.2738. **ATR-FTIR** (cm^{-1}): 3307, 3026, 2949, 2867, 1632, 1453, 1364, 1250, 1189, 1054, 915, 869, 746.

N,N-diethyl-2-(pyrrolidin-1-yl)butanamide (**3oh**)



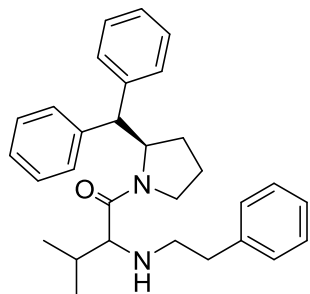
To a mixture of amide **1o** (0.3 mmol) and 2-fluoropyridine (0.6 mmol, 2 equiv., 58.3 mg, 51.6 μL) in DCM (1 mL) triflic anhydride was added dropwise (0.6 mmol, 2 equiv., 84 mg, 51 μL .) at 0 °C under Ar. The mixture was stirred for 15 minutes at this temperature. Then a solution of azide **2h** (0.6 mmol, 2 equiv) in 0.5 mL of DCM was added and the mixture was brought to room temperature. After 1 h, 2 mL of a saturated solution of NaHCO_3 were added and the mixture was further stirred for 2h. The biphasic mixture was then diluted with DCM and washed with a 20 mL of NaHCO_3 . The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure. Purification through column chromatography DCM/DMA (0 to 60% DMA) afforded the tertiary amine in 86% yield. **^1H (400 MHz, CDCl_3)** δ = 3.48-3.31 (m, 5H), 2.74-2.53 (m, 4H), 1.86-1.65 (m, 6H), 1.11 (dt, J = 22.6Hz, 7.1Hz, 6H), 0.86 (t, J = 7.5Hz, 3H) ppm. **^{13}C (100 MHz, CDCl_3)** δ = 171.4, 64.4, 50.4, 41.6, 40.4, 23.4, 14.7, 13.1, 10.9 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ = 213.1961, found 213.1959. **ATR-FTIR** (cm^{-1}): 3494, 2966, 2933, 2874, 2802, 1631, 1459, 1431, 1379, 1267, 1129, 1032, 933, 889, 785.

3,5,5-Trimethyl-2-(phenethylamino)-1-(pyrrolidin-1-yl)hexan-1-one (**3xa**)



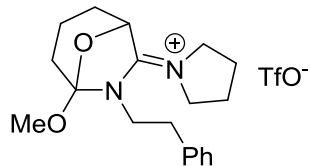
^1H (400 MHz, CDCl_3) δ = 7.30-7.19 (m, 5H), 3.56-3.41 (m, 4H), 3.13 (d, J = 4.7Hz, 1H *syn*), 3.00 (d, J = 6.6Hz, 1H *anti*), 2.88-2.70 (m, 3H), 2.60-2.54 (m, 1H), 2.00-1.83 (m, 5H), 1.75-1.71 (m, 2H), 1.02-0.87 (m, 13H) ppm. **^{13}C (100 MHz, CDCl_3)** δ = 173.8, 140.6, 128.9, 128.3, 126.0, 66.3, 50.5, 46.4, 45.7, 45.6, 37.2, 32.8, 31.0, 29.9, 26.3, 24.2, 20.5. **HRMS** (ESI) m/z calculated for $[M+H]^+$ 331.2744, found 331.2738. **ATR-FTIR** (cm^{-1}): 3307, 3026, 2949, 2867, 1632, 1453, 1420, 1338, 1227, 1189, 1015, 915, 840, 746.

1-((*R*)-2-Benzhydrylpyrrolidin-1-yl)-3-methyl-2-(phenethylamino)butan-1-one (**3ya**)



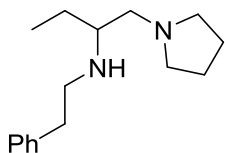
Purification of the crude product by flash chromatography gave 89 mg (68%) of the product as a white solid with a d.r. of 15:1. The major diastereoisomer was purified through preparative HPLC (column Waters, X select CSH perp C18, 5 μm , 30x150mm, Acetonitrile/ 1mM NH_4HCO_3 solution in water from 70% to 95%, flow 20 mL/min). NMR analysis shows the presence of 2 rotamers (ratio 4:1). ^1H NMR signals are reported only for the major. **^1H NMR (400 MHz, CDCl_3)** δ = 7.31-7.12 (m, 15H), 5.25-5.21 (m, 1H), 4.37 (d, J = 7 Hz, 1H), 3.42-3.36 (m, 1H), 3.21 (dt, J = 8.8, 4.0 Hz, 1H), 3.05 (d, J = 4.2 Hz, 1H), 2.81-2.77 (m, 2H), 2.71-2.66 (m, 1H), 2.55-2.50 (m, 1H), 1.92-1.87 (m, 2H), 1.80-1.65 (m, 4H), 0.87 (d, J = 6.8 Hz, 3H), 0.69 (d, J = 6.8 Hz, 3H). **^{13}C NMR (100 MHz, CDCl_3)** δ = 174.0, 142.4, 142.4, 140.7, 129.3, 129.1, 129.0, 128.9, 128.8, 128.5, 128.4, 128.2, 126.7, 126.4, 126.1, 65.1, 59.9, 53.6, 51.02, 46.4, 37.4, 31.1, 27.8, 23.9, 20.4, 17.1 ppm. **HRMS** (ESI) m/z calculated for $[M+H]^+$ = 441.2900, found 441.2889. **ATR-FTIR** (cm^{-1}): 3311, 3060, 3027, 2956, 2924, 2853, 1634, 1494, 1452, 1409, 1339, 1260, 749, 700.

1-(5-Methoxy-6-phenethyl-8-oxa-6-azabicyclo[3.2.1]octan-7-ylidene)pyrrolidin-1-ium trifluoromethanesulfonate 5



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.34 (t, $J=7.4$ Hz, 2H), 7.28 (d, $J=7.4$ Hz, 1H), 7.20 (d, $J=7.1$ Hz, 2H), 5.23 (s, 1H), 4.16-4.12 (m, 1H), 4.10, 4.06 (m, 1H), 3.93-3.89 (m, 1H), 3.82-3.78 (m, 2H), 3.72-3.64 (m, 2H), 3.51 (s, 3H), 3.13-3.04 (m, 2H), 2.24-2.16 (m, 2H), 2.15-2.09 (m, 2H), 1.98-1.90 (m, 5H), 1.82-1.78 (m, 1H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ = 162.3, 136.3, 129.2, 128.6, 127.6, 117.6, 78.3, 52.9, 51.5, 50.1, 44.3, 36.8, 30.00, 25.7, 24.2, 22.2, 17.6. **HRMS** (ESI) m/z calculated for $[\text{M}-\text{CF}_3\text{O}_3\text{S}^-]$ = 315.2067, found 315.2063. **ATR-FTIR** (cm^{-1}): 2957, 2925, 2853, 1732, 1673, 1635, 1455, 1338, 1262, 1151, 1000, 933, 897, 702.

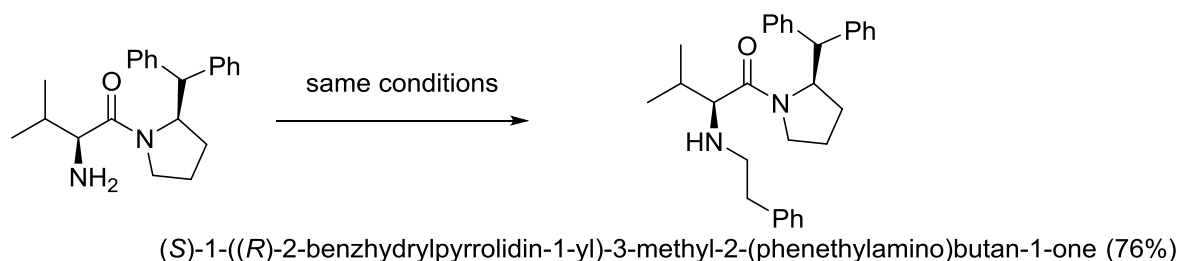
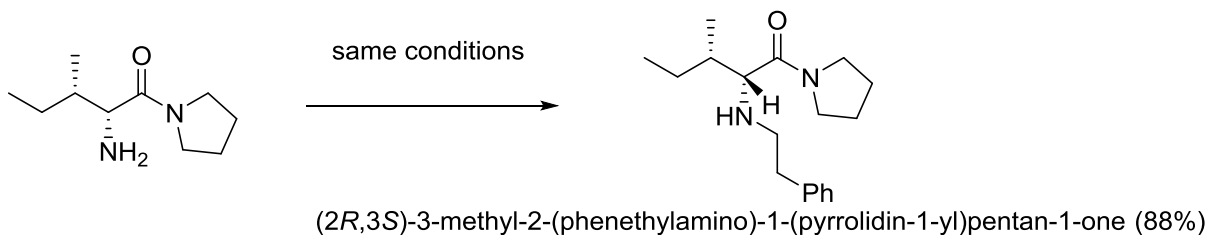
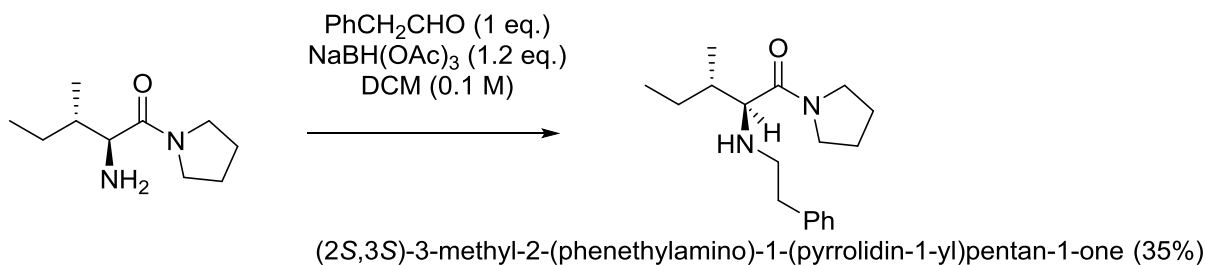
N-phenethyl-1-(pyrrolidin-1-yl)butan-2-amine 7



To a mixture of amide 1b (0.3 mmol) and 2-fluoropyridine (0.6 mmol, 2 equiv., 58.3 mg, 51.6 μL) in DCM (1 mL) was dropwise added triflic anhydride (0.6 mmol, 2 equiv., 84 mg, 51 μL) at 0 $^\circ\text{C}$ under Ar. The mixture was stirred for 15 minutes at this temperature. Then a solution of azide 2a (0.6 mmol, 2 equiv., 88 mg) in 0.5 mL of DCM was added and the mixture was brought to room temperature. After 30 min, NaBH_4 (1.2, 4 equiv., 45.4 mg) was added in 3 portions over 30 minutes under Ar at -78°C . The mixture was then allowed to warm to r.t. and was further stirred for 2h. The mixture was then quenched with NH_4Cl , then diluted with DCM and washed with a 20mL of NaHCO_3 . The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure. Purification through column chromatography DCM/DMA (0 to 60% DMA) afforded the amine in 9 mg, 12% yield. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.31-7.28 (m, 2H), 7.25-7.19 (m, 3H), 3.51 (bs, 1H), 3.12-3.06 (m, 1H), 2.88-2.74 (m, 3H), 2.61-2.40 (m, 5H), 2.32-2.30 (m, 1H), 1.72-1.56 (m, 5H), 1.39 (dt, $J = 14.1, 7.1$ Hz, 1H), 0.89 (t, $J = 7.6$ Hz, 3H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ = 139.9, 128.9, 128.6, 126.4, 62.7, 59.2, 58.1, 54.2, 49.1, 36.2, 25.1, 23.6, 10.1 ppm. **HRMS** (ESI) m/z calculated for $[\text{M}+\text{H}^+]$ = 247.2169, found 247.2169. **ATR-FTIR** (cm^{-1}): 3300, 3061, 3027, 2961, 2929, 2875, 2793, 1494, 1455, 1381, 1277, 1154, 1085, 905, 884, 749.

Determination of the relative configuration of compounds 3xa and 3ya

The identity of major diastereoisomers for compounds **3xa** and **3ya** was determined by synthesizing the similar α -amino amides from isoleucine, allo-isoleucine and (R)-valine.



The substrates were prepared from the corresponding α -amino acids using known procedure.¹⁸ The α -amino amides were then converted to secondary amines by reductive amination of 2-phenyl acetaldehyde using the following procedure:

The amine and phenylacetaldehyde (1 equiv.) were dissolved in DCM (0.1 M) at r.t. and NaBH(OAc)₃ (1.2 equiv.) was added. The reaction was stirred for 5 hours prior to quenching with water, extraction with EtOAc drying over Na₂SO₄ and concentration. The product was purified by column chromatography (20-50% EtOAc/heptane) to afford the pure secondary amide.

(2*S*,3*S*)-3-methyl-2-(phenethylamino)-1-(pyrrolidin-1-yl)pentan-1-one:

¹H (400 MHz, CDCl₃) δ = 7.27-7.18 (m, 5H), 3.57-3.41 (m, 4H), 3.11 (d, J = 7.3Hz, 1H), 2.83-2.56 (m, 4H), 1.94-1.72 (m, 6H), 1.59-1.55 (m, 1H), 1.19-1.12 (m, 1H), 0.90-0.86 (m, 6H) ppm.

(2*R*,3*S*)-3-methyl-2-(phenethylamino)-1-(pyrrolidin-1-yl)pentan-1-one:

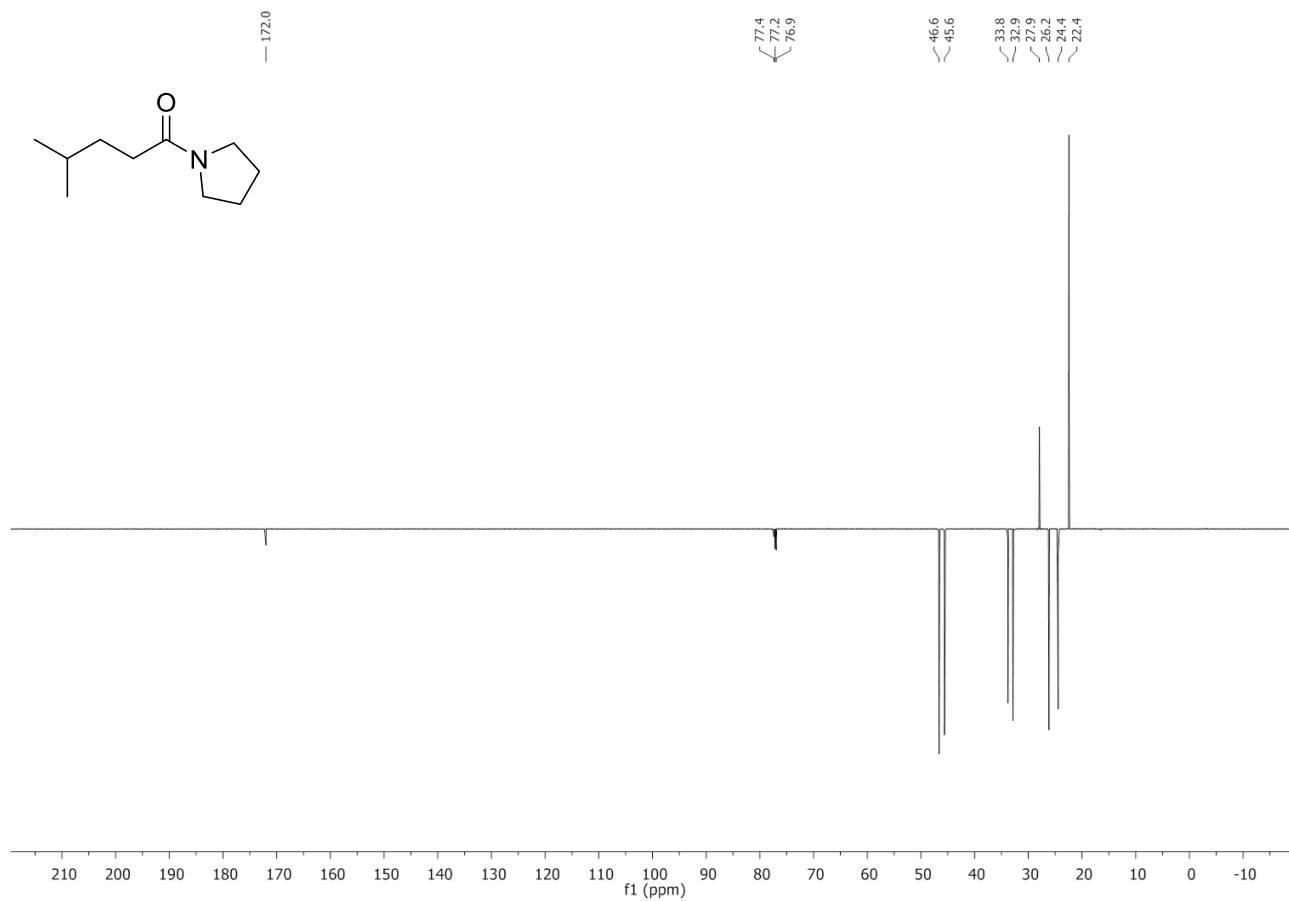
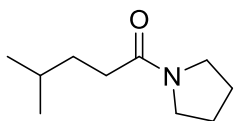
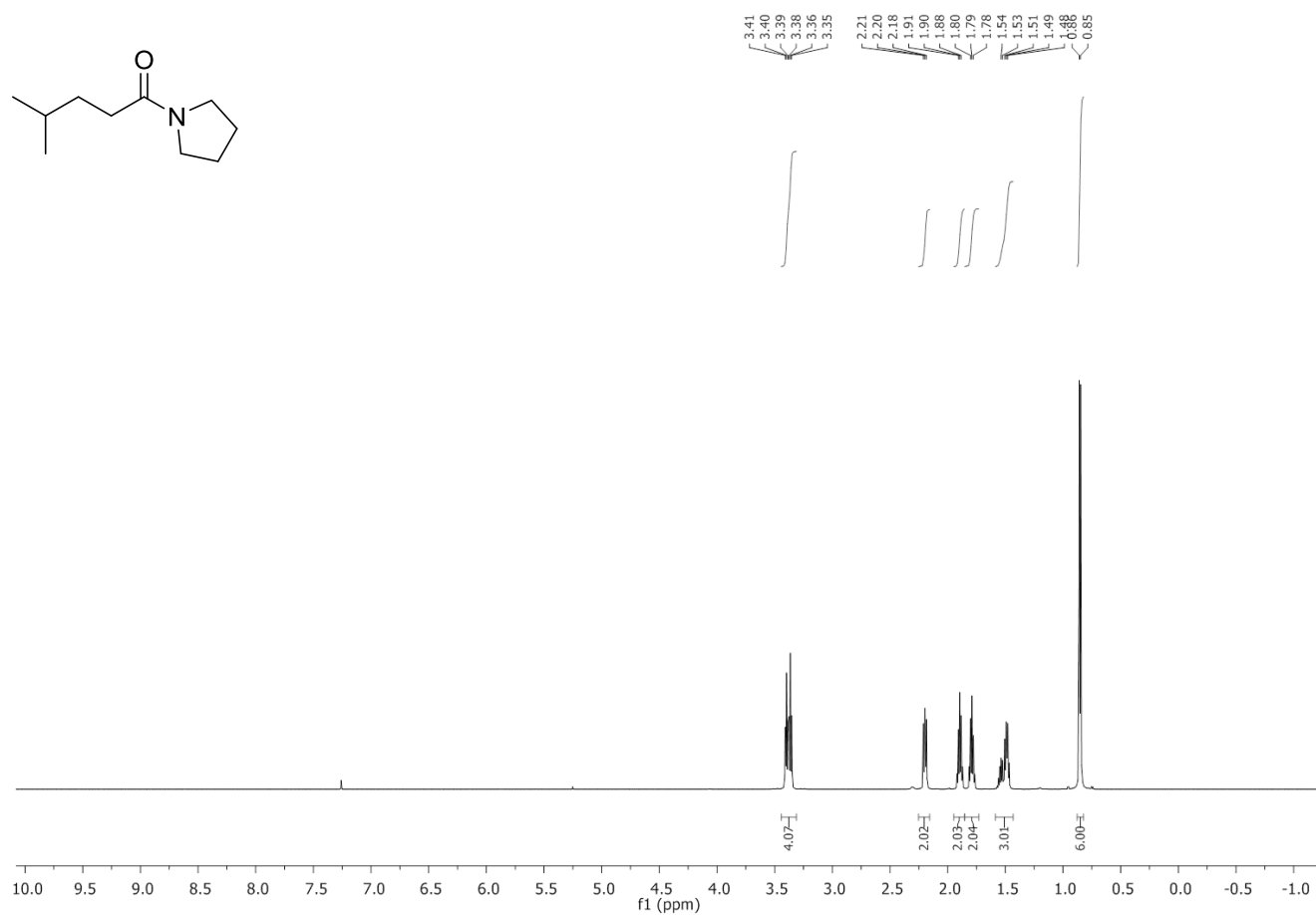
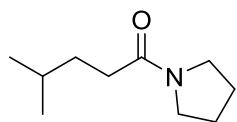
¹H (400 MHz, CDCl₃) δ = 7.30-7.19 (m, 5H), 3.58-3.39 (m, 4H), 3.30-3.26 (bs, 1H), 3.22 (d, J = 5Hz, 1H), 2.87-2.59 (m, 4H), 1.97-1.81 (m, 4H), 1.58-1.48 (m, 2H), 1.27-1.20 (m, 1H), 0.94-0.92 (m, 6H) ppm.

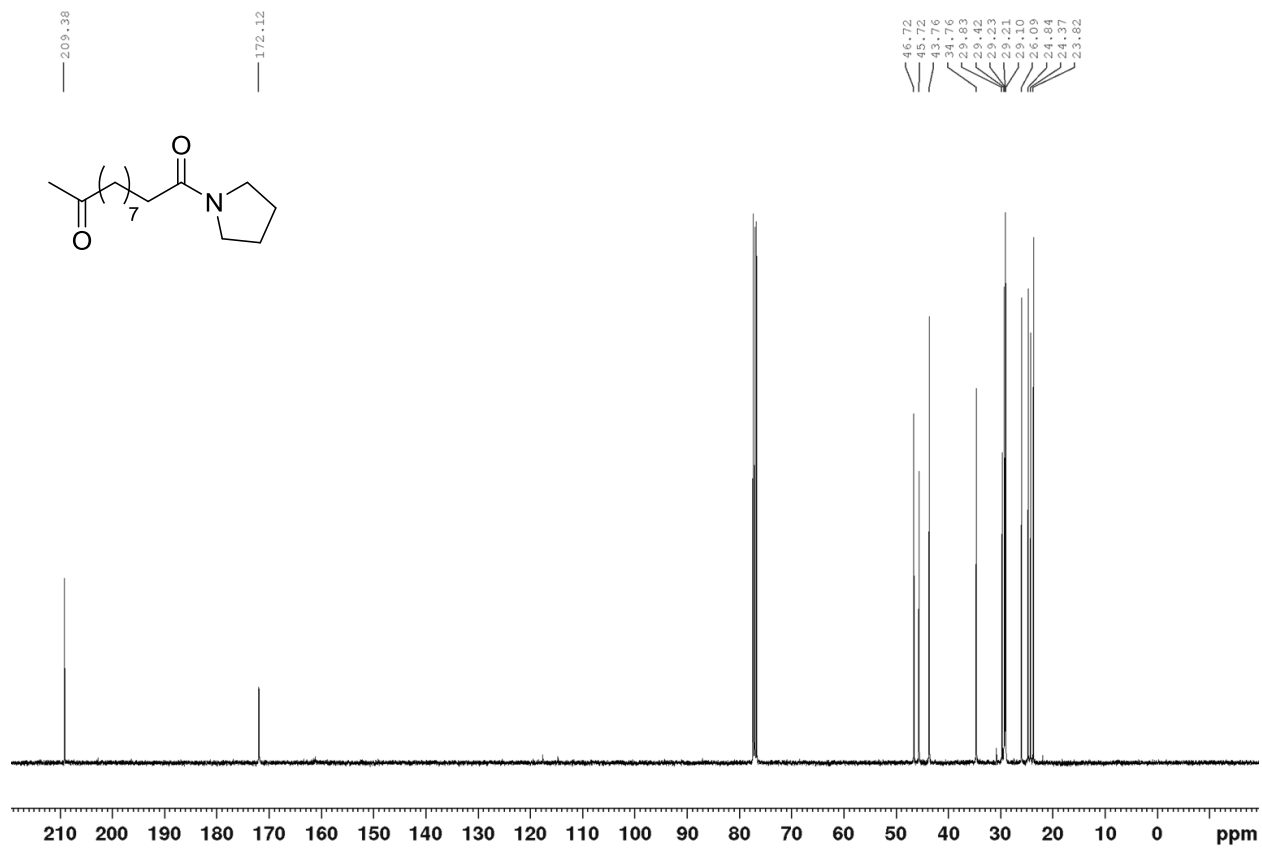
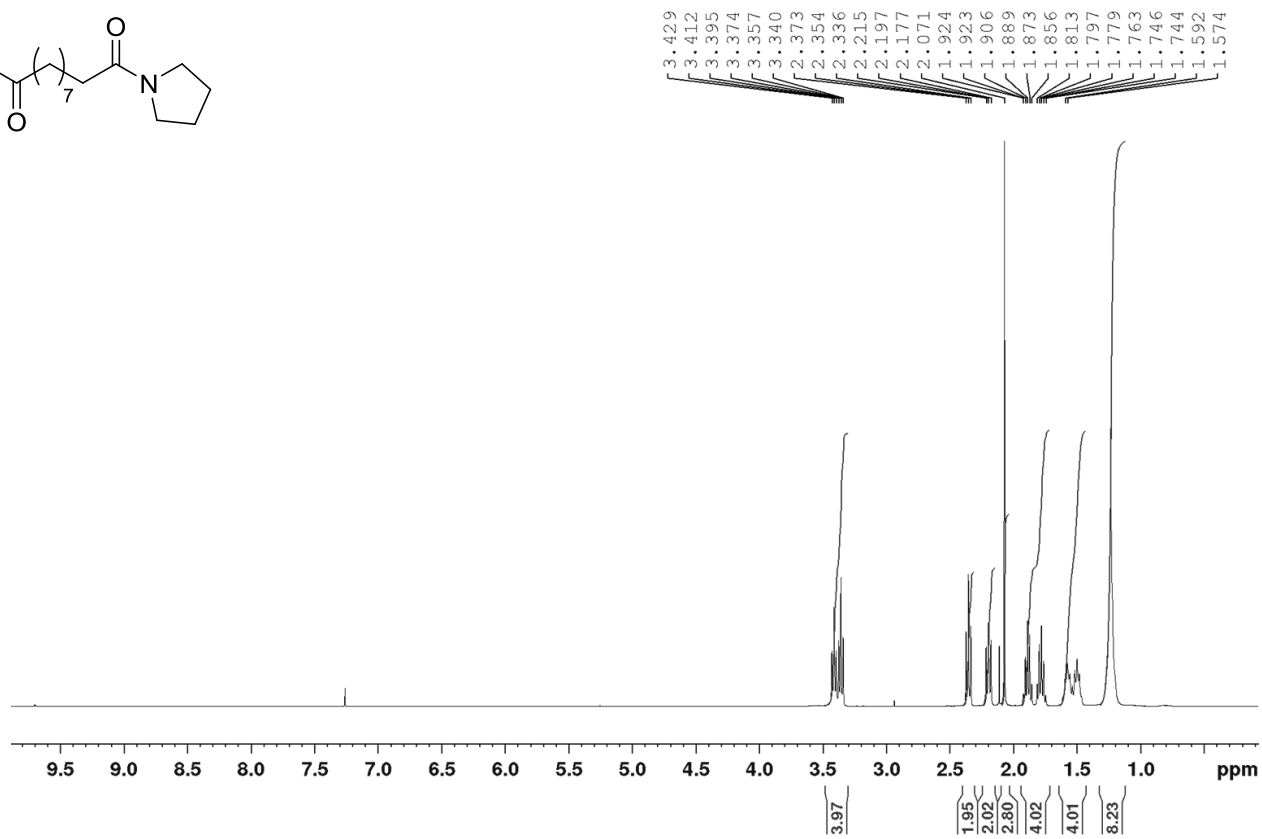
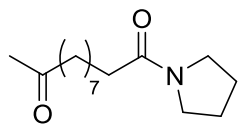
(*S*)-1-((*R*)-2-benzhydrylpyrrolidin-1-yl)-3-methyl-2-(phenethylamino)butan-1-one:

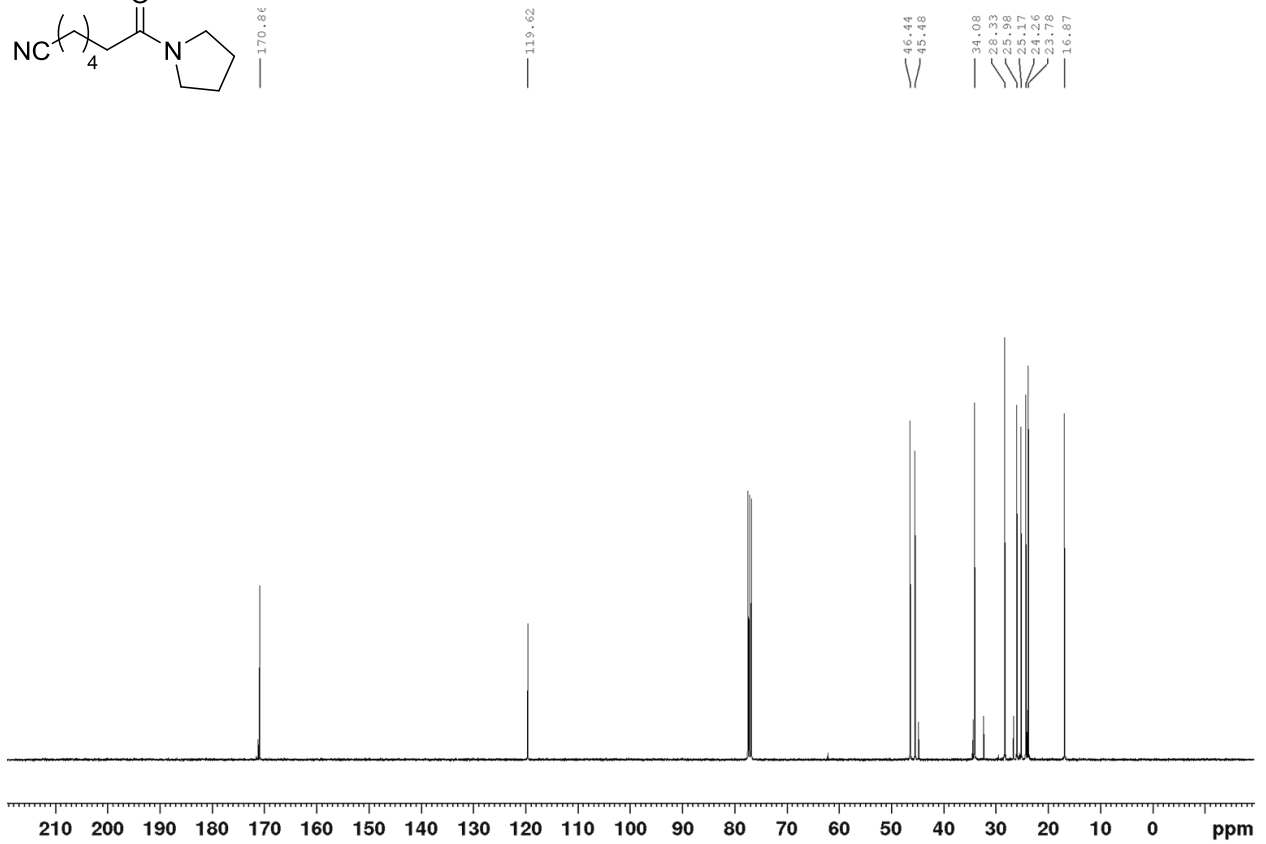
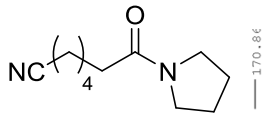
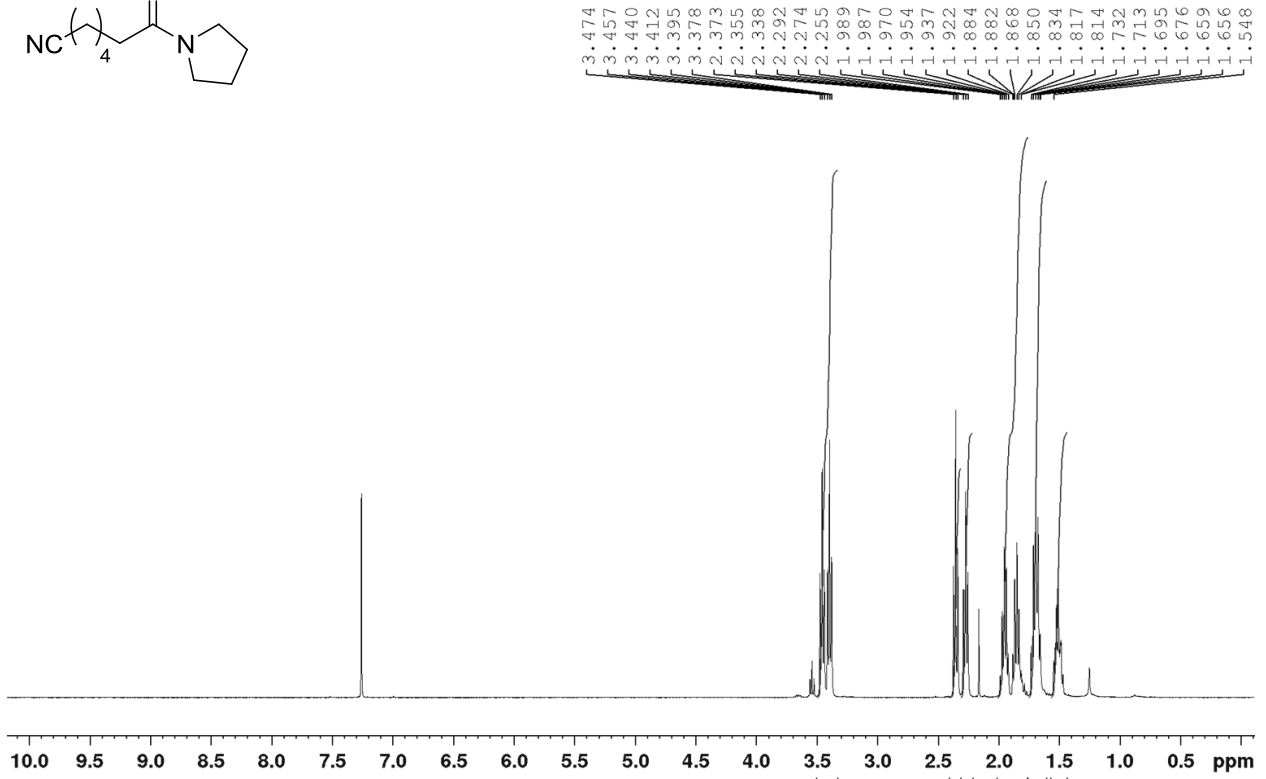
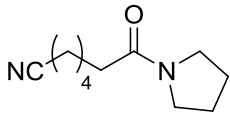
¹H (400 MHz, CDCl₃) δ = 7.15-7.00 (m, 15H), 5.08-5.04 (m, 1H), 4.9 (d, J = , 1H), 3.39-3.33 (m, 1H), 3.12-3.06 (m, 1H), 2.92 (d, J = , 1H), 2.70-2.56 (m, 3H), 2.36-2.31 (m, 1H), 1.91-1.60 (m, 5H), 1.30-1.24 (m, 1H), 0.88-0.84 (m, 6H) ppm.

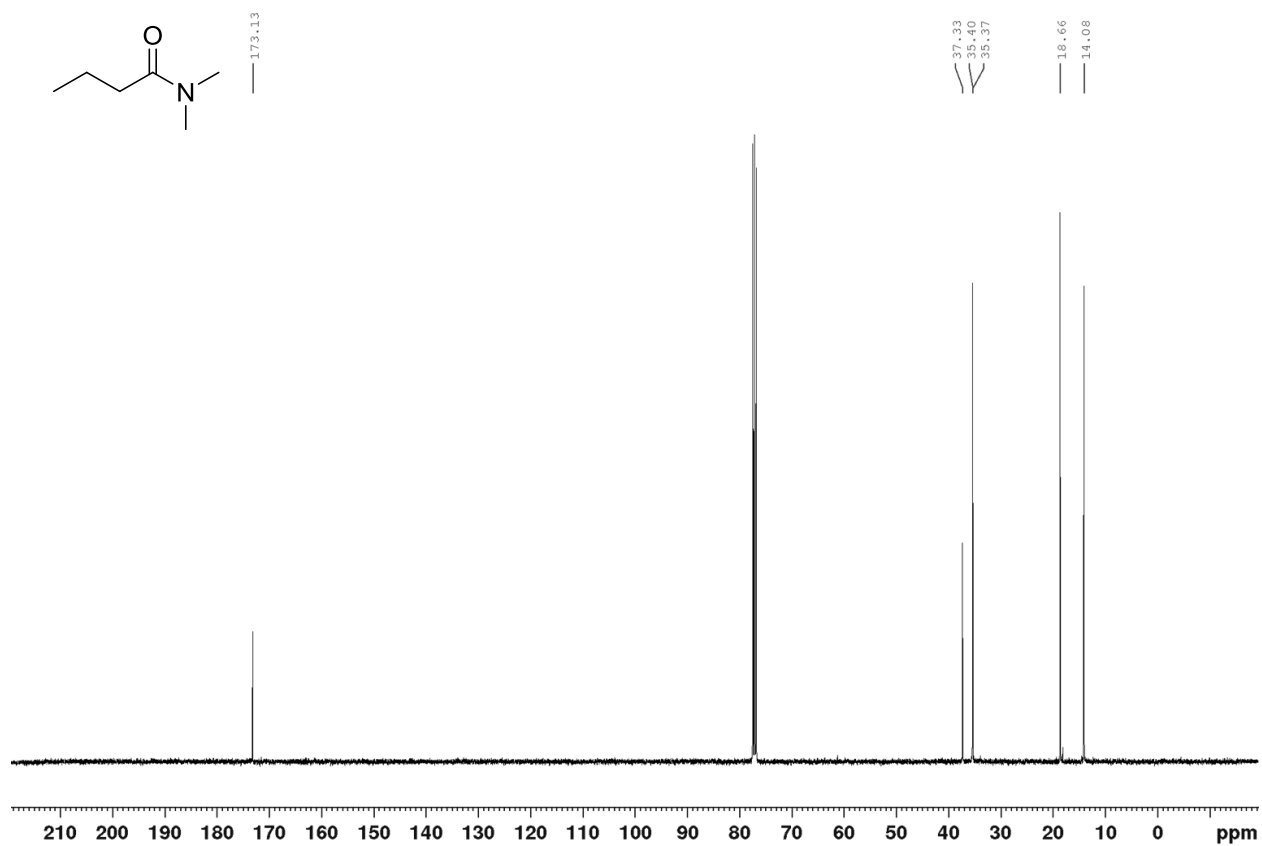
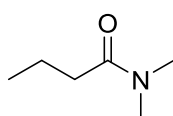
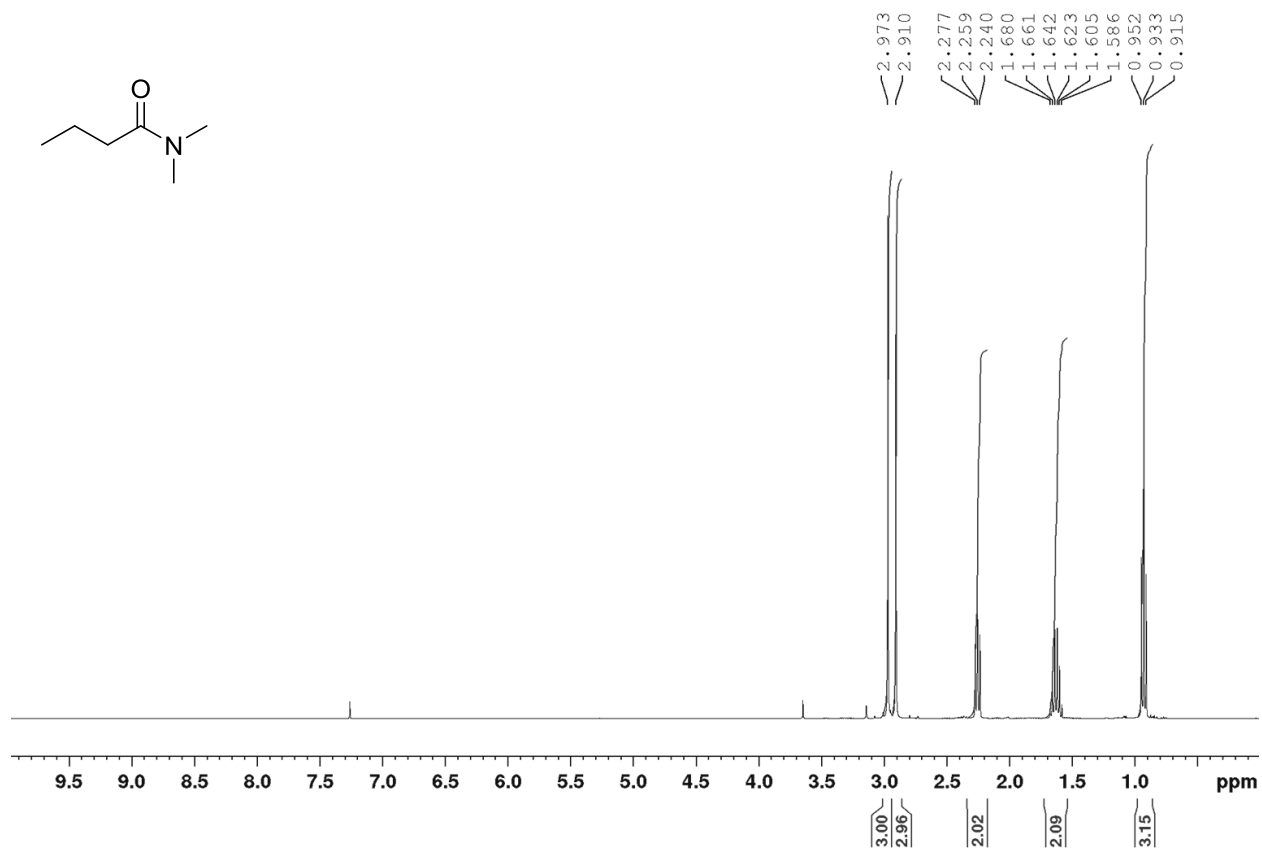
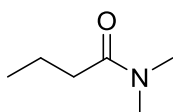
The relative configuration of **3xa** was determined by comparing the relative chemical shifts and coupling constants of the α -proton in (2S,3S)- and (2R,3S)-3-methyl-2-(phenethylamino)-1-(pyrrolidin-1-yl)pentan-1-one with the two diastereoisomers obtained in **3xa**. The chemical shift and coupling constant of the major diastereoisomer matches with the *anti* configuration (δ 3.00, d, $J = 6.6\text{Hz}$). The relative configuration of **3ya** was determined by comparing the product prepared from L-valine with the crude of **3ya**, and observing that it matches with the minor diastereoisomer. Therefore, the major product is the (*R,R*) isomer.

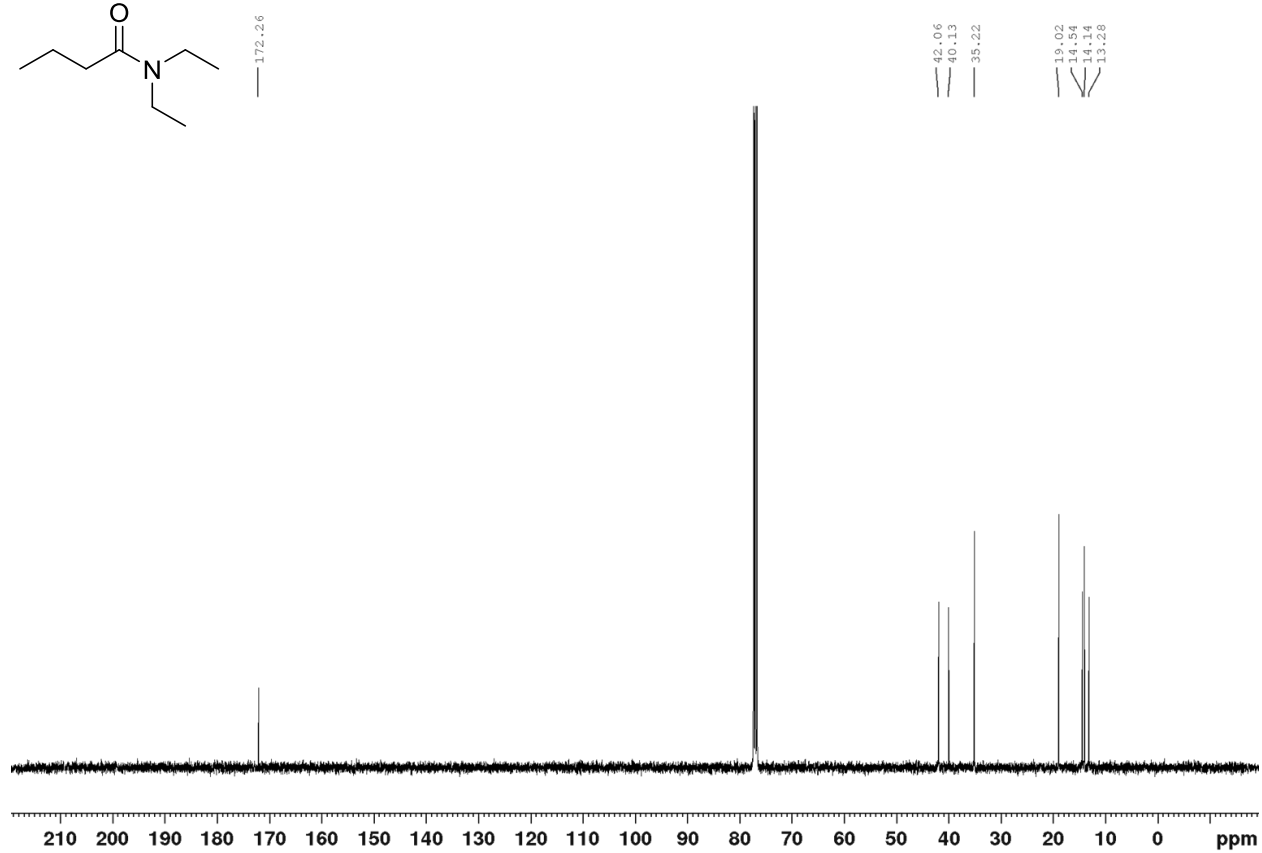
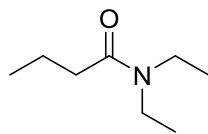
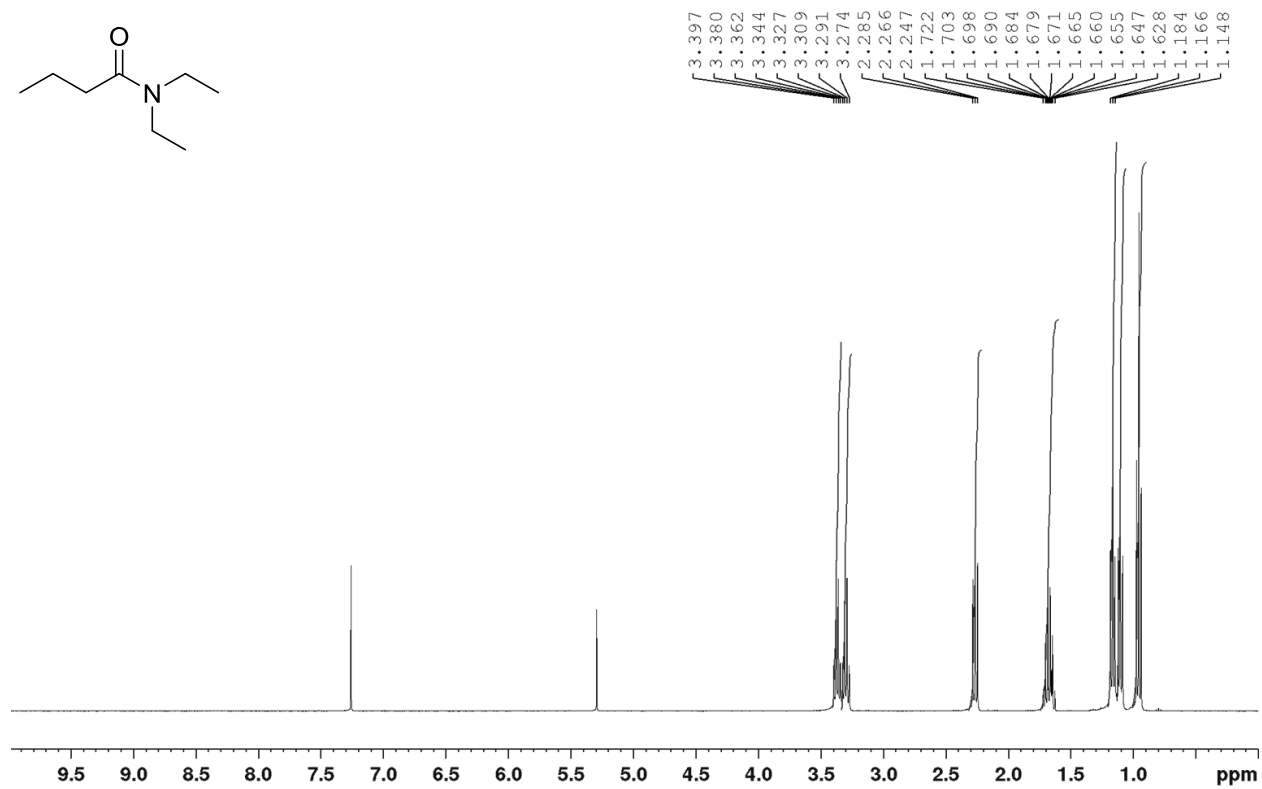
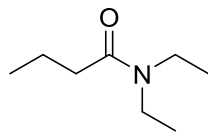
Spectra

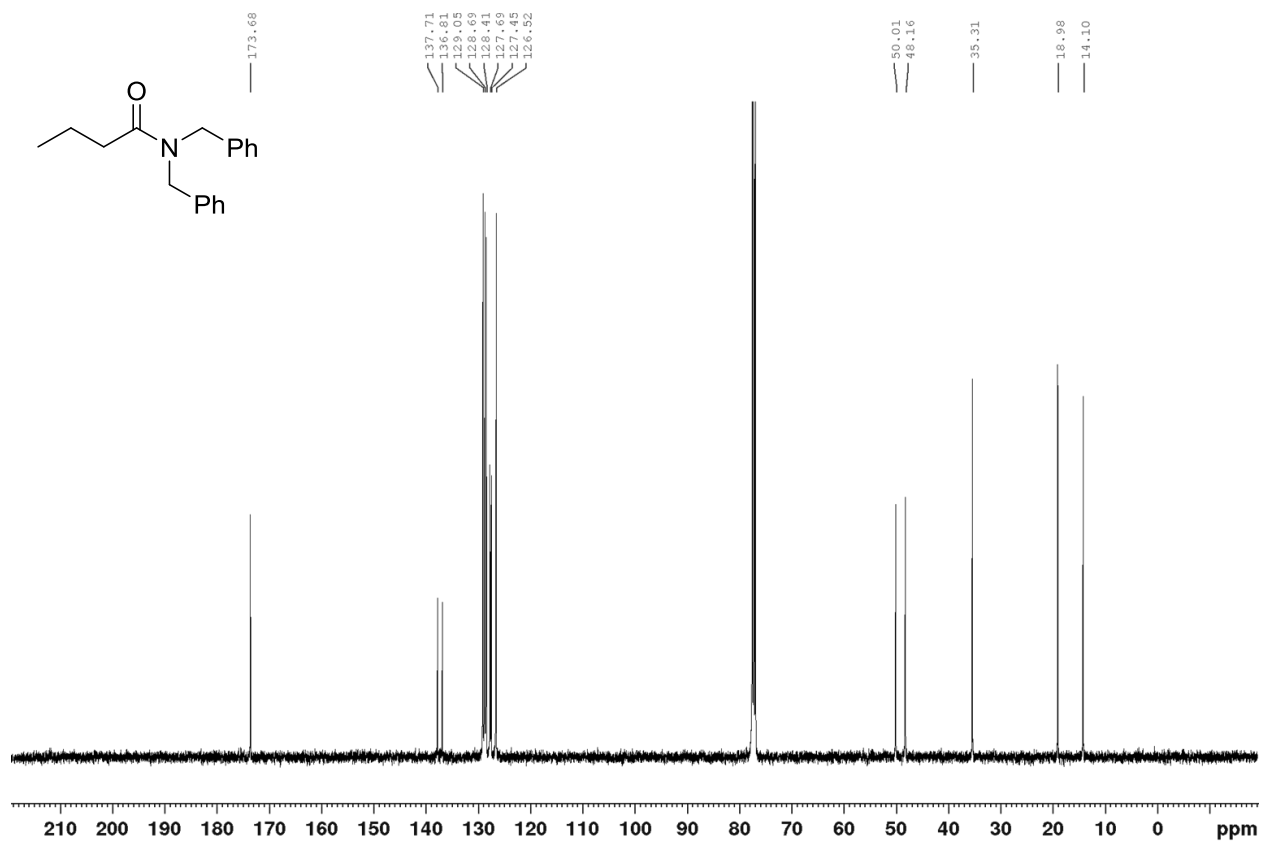
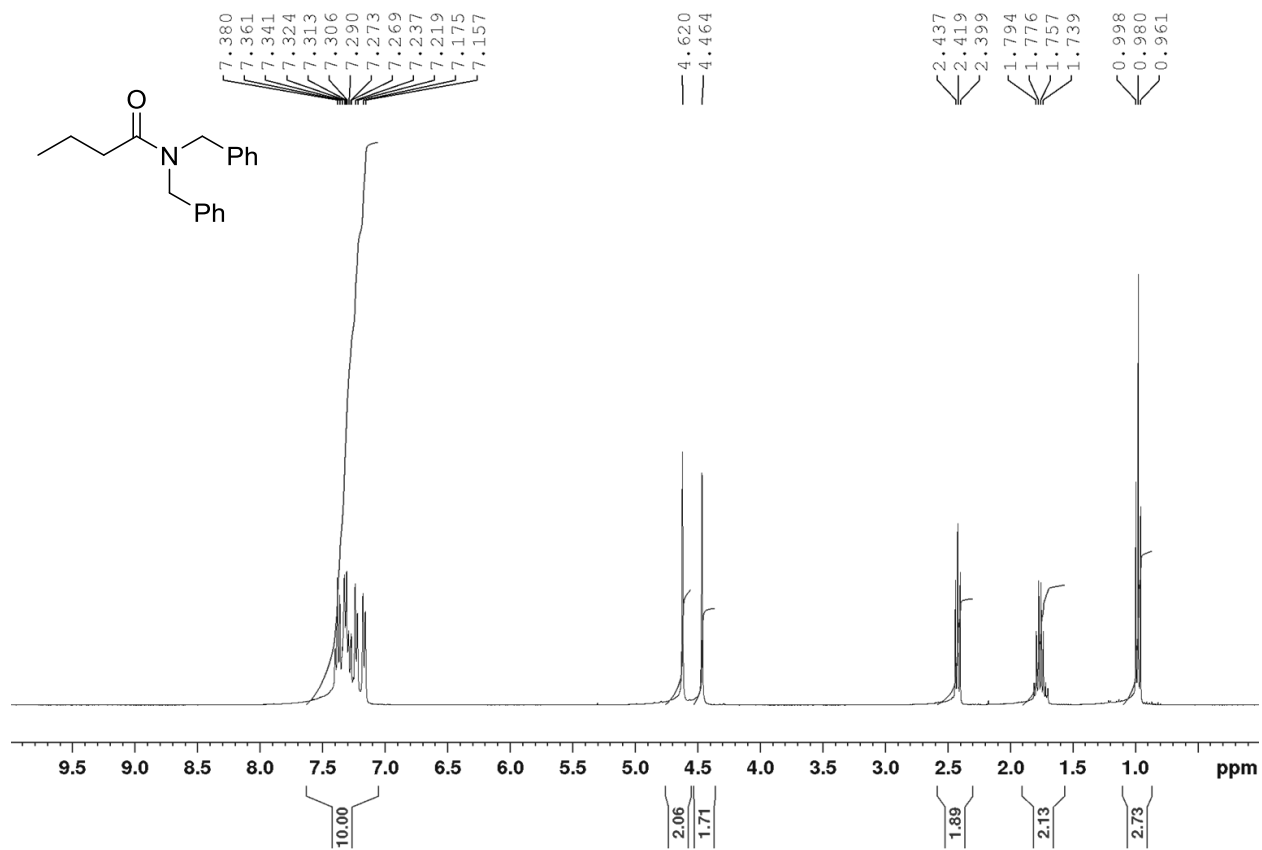


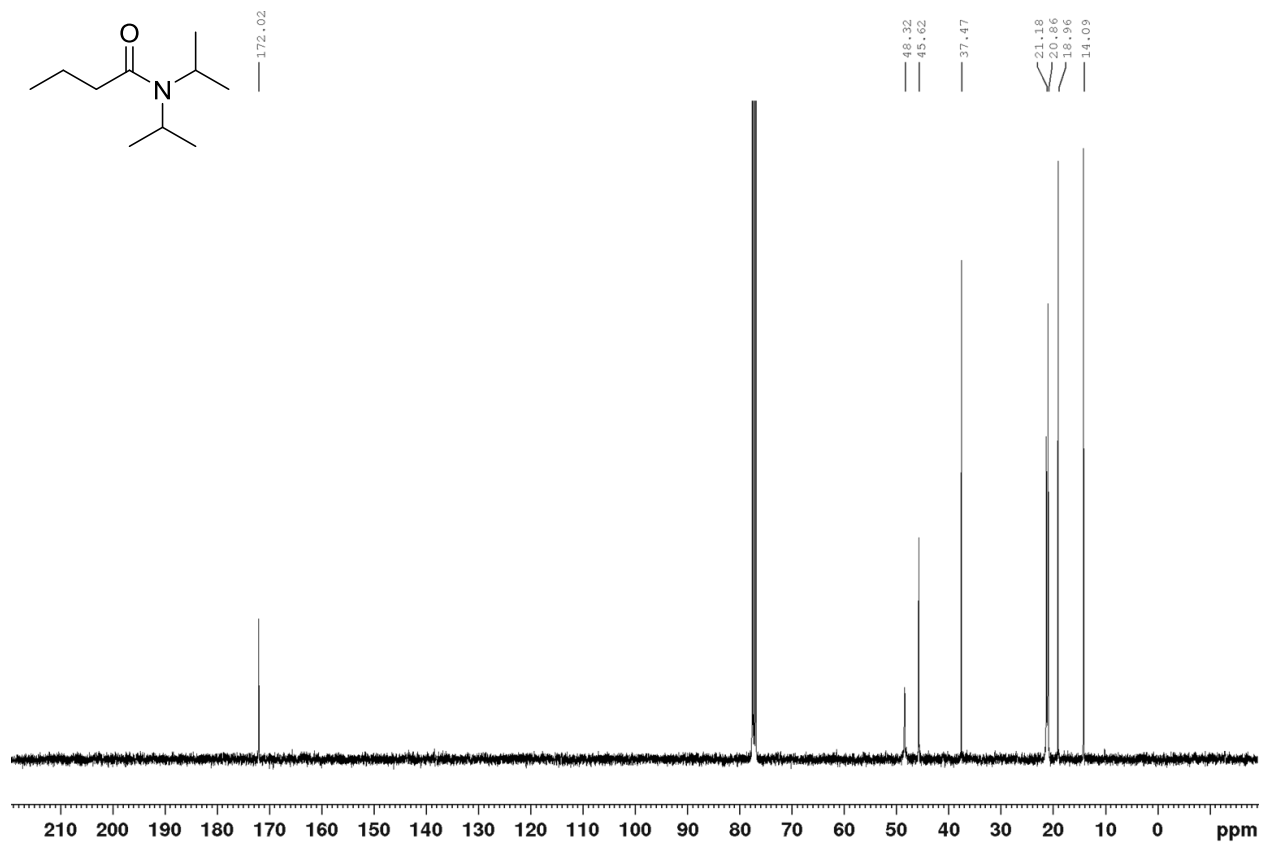
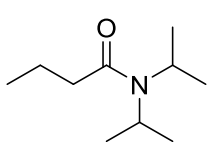
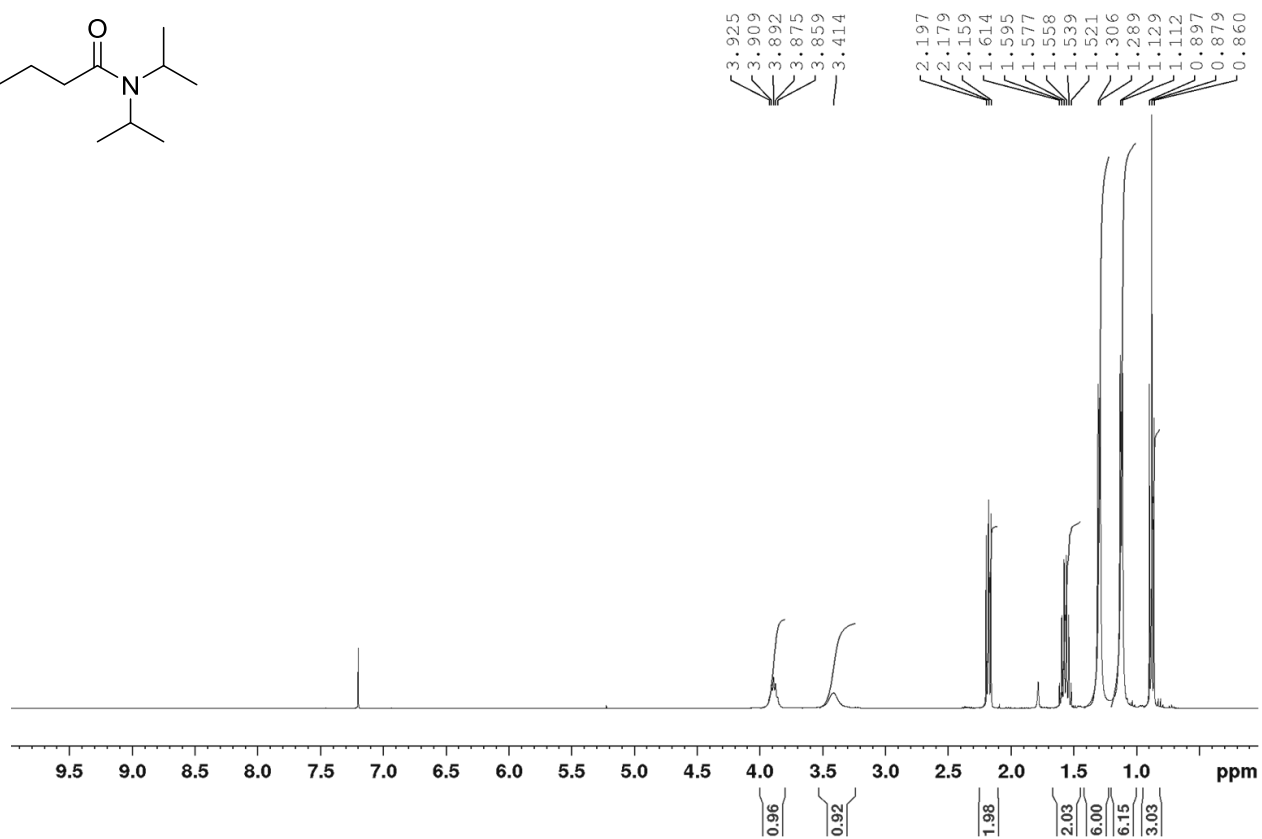
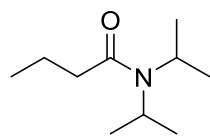


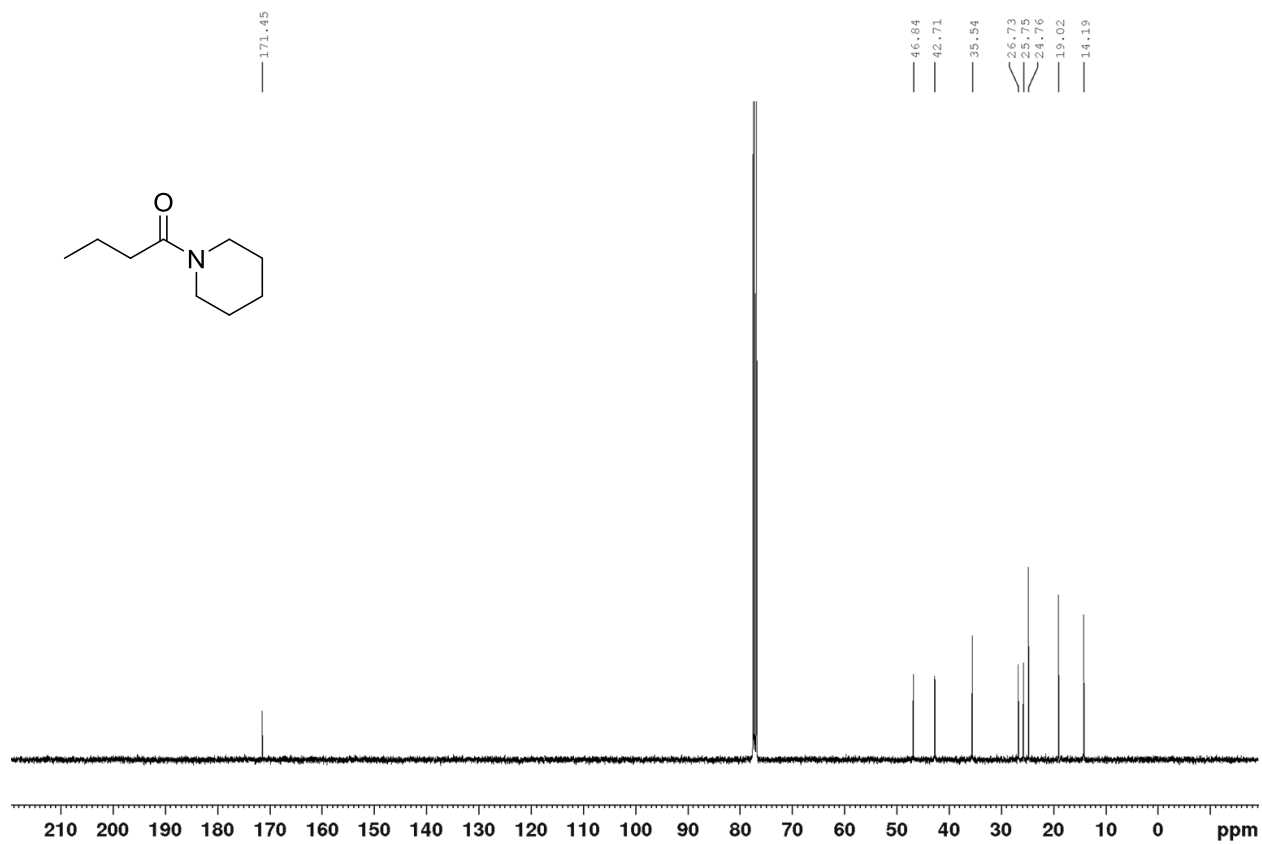
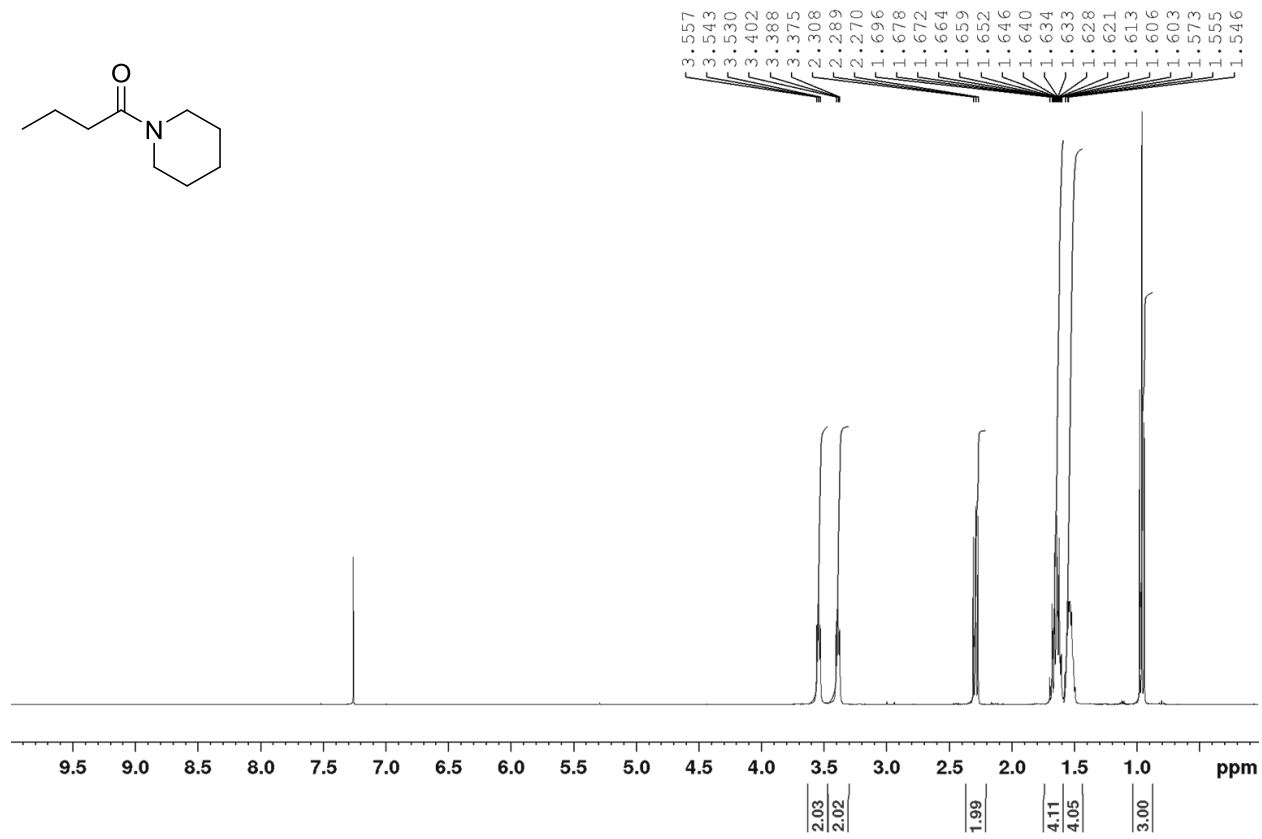


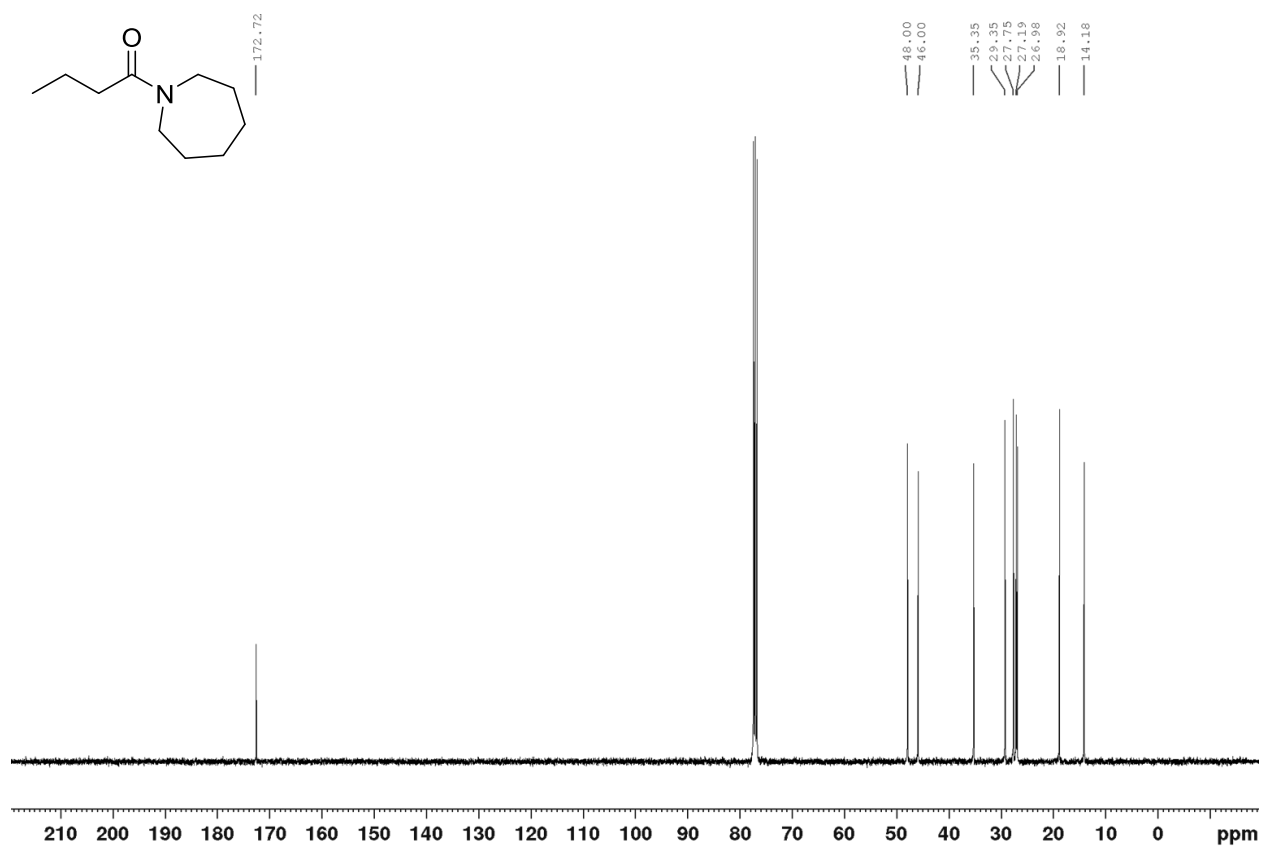
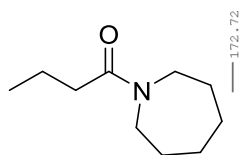
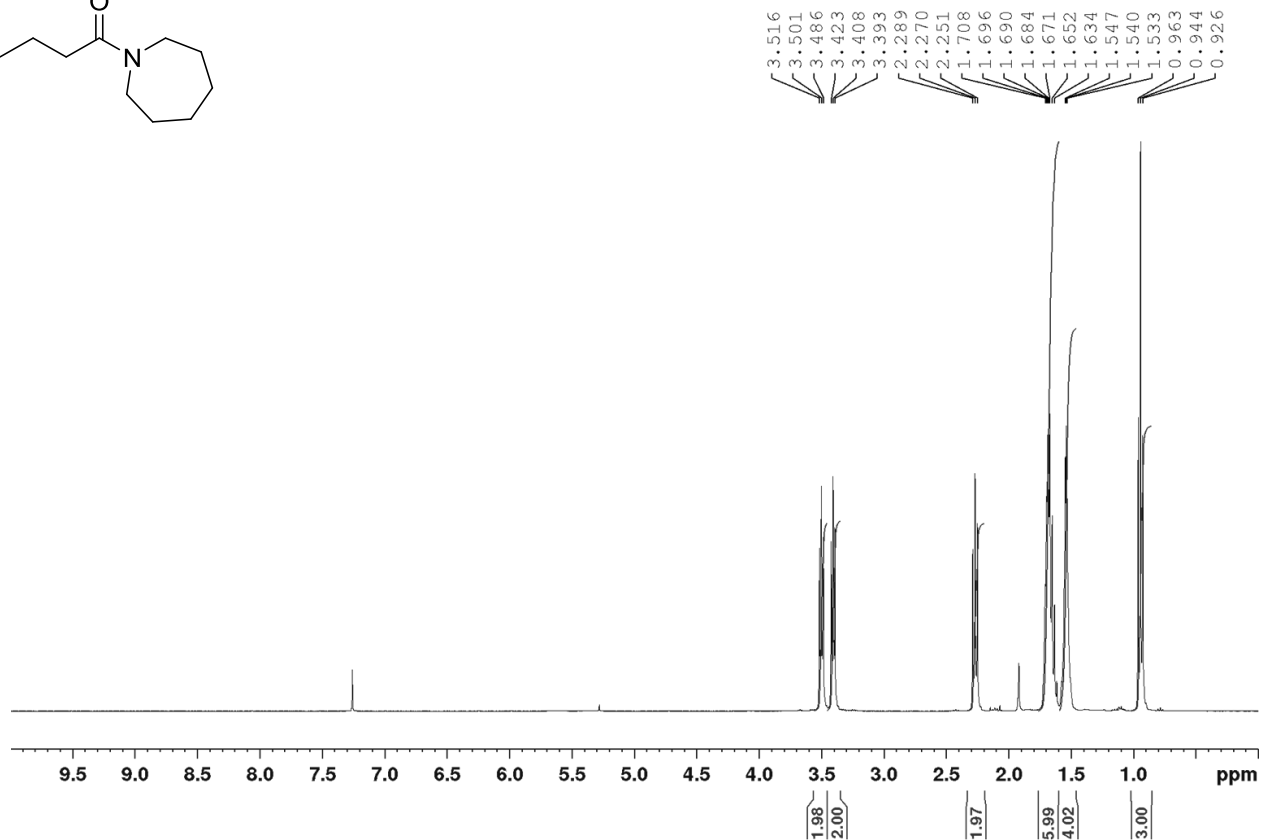
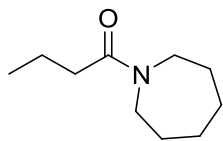


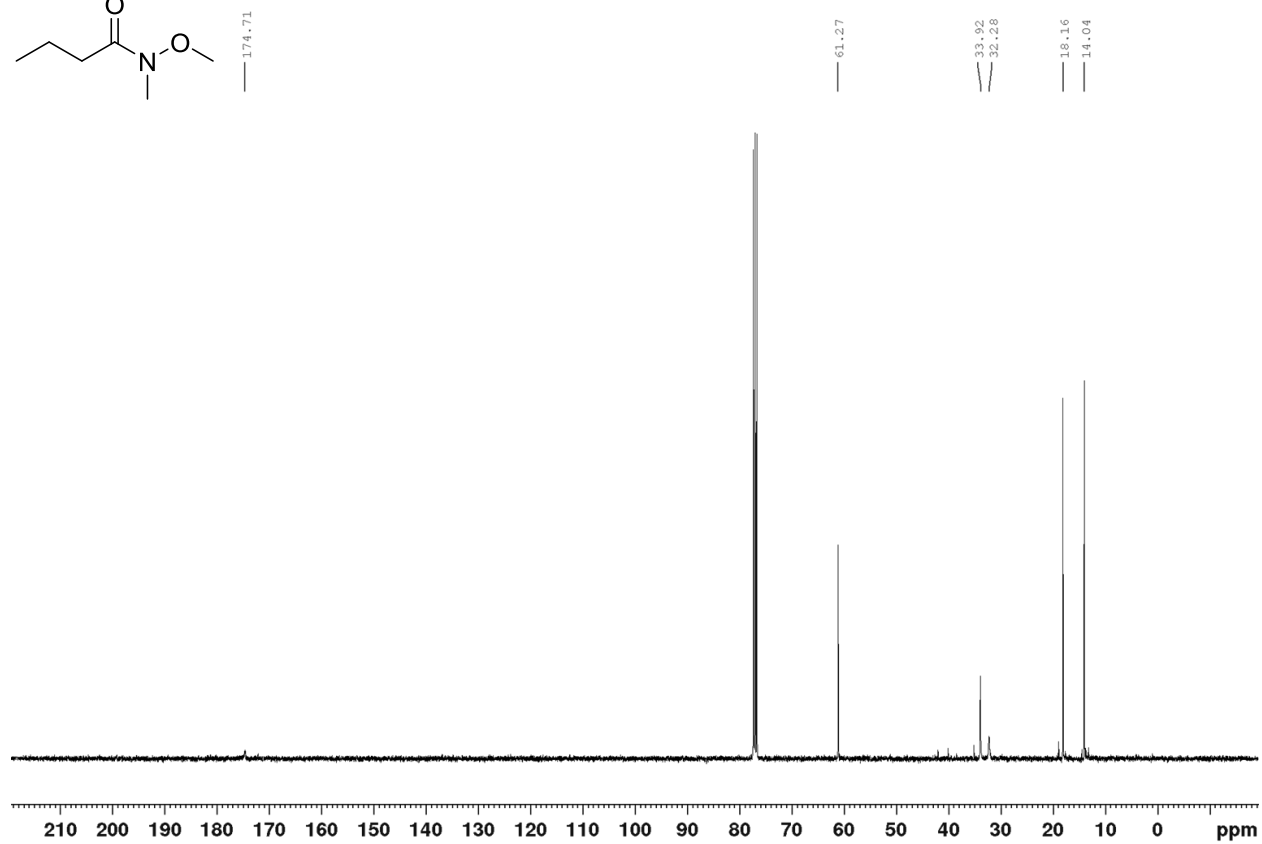
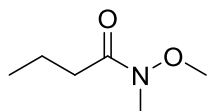
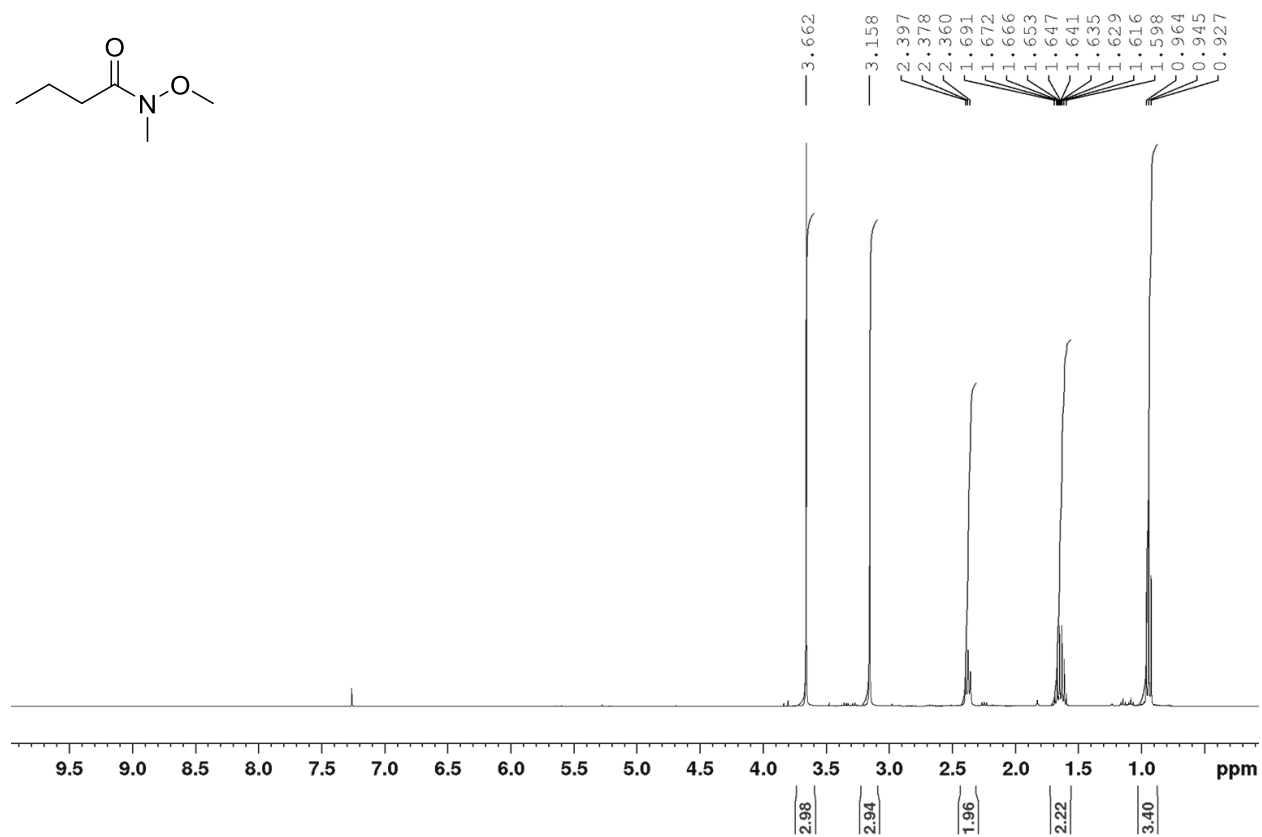
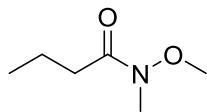


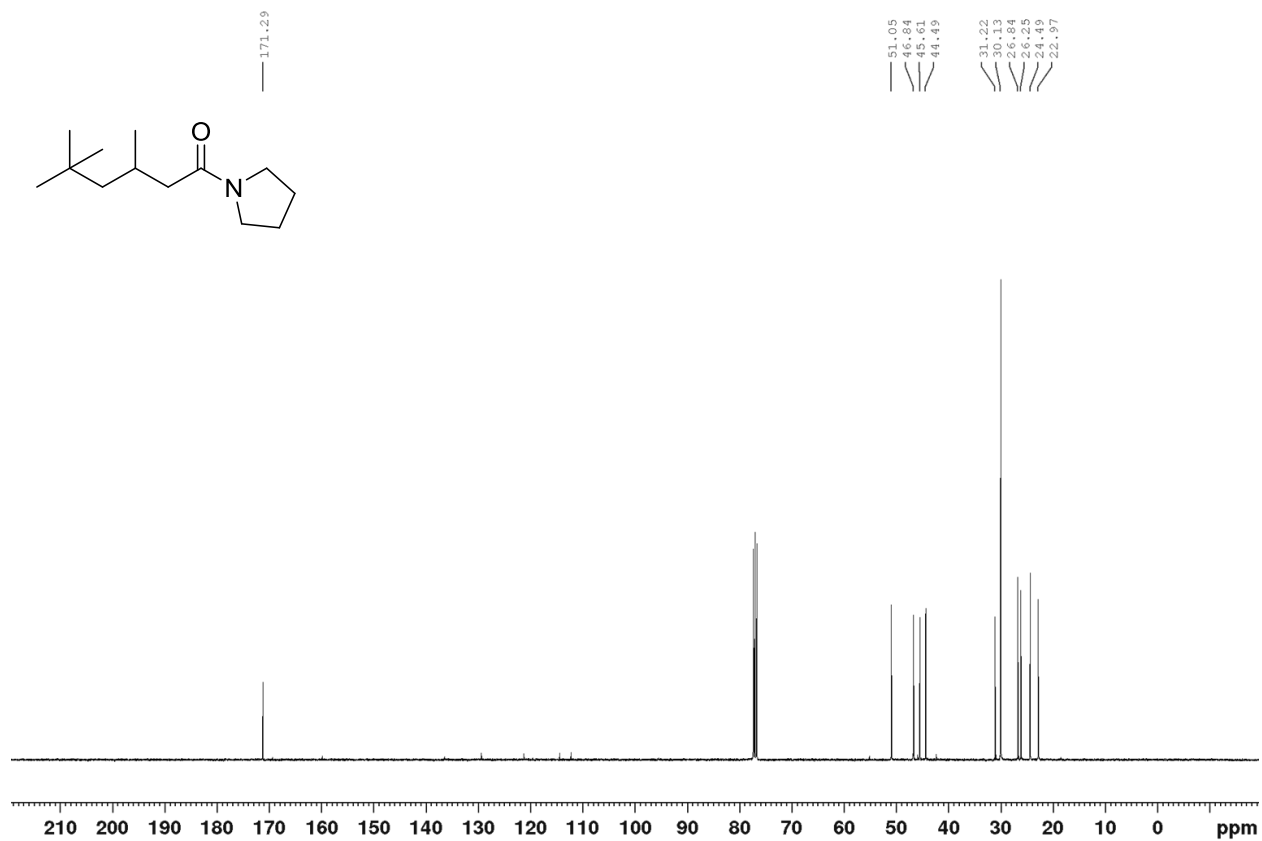
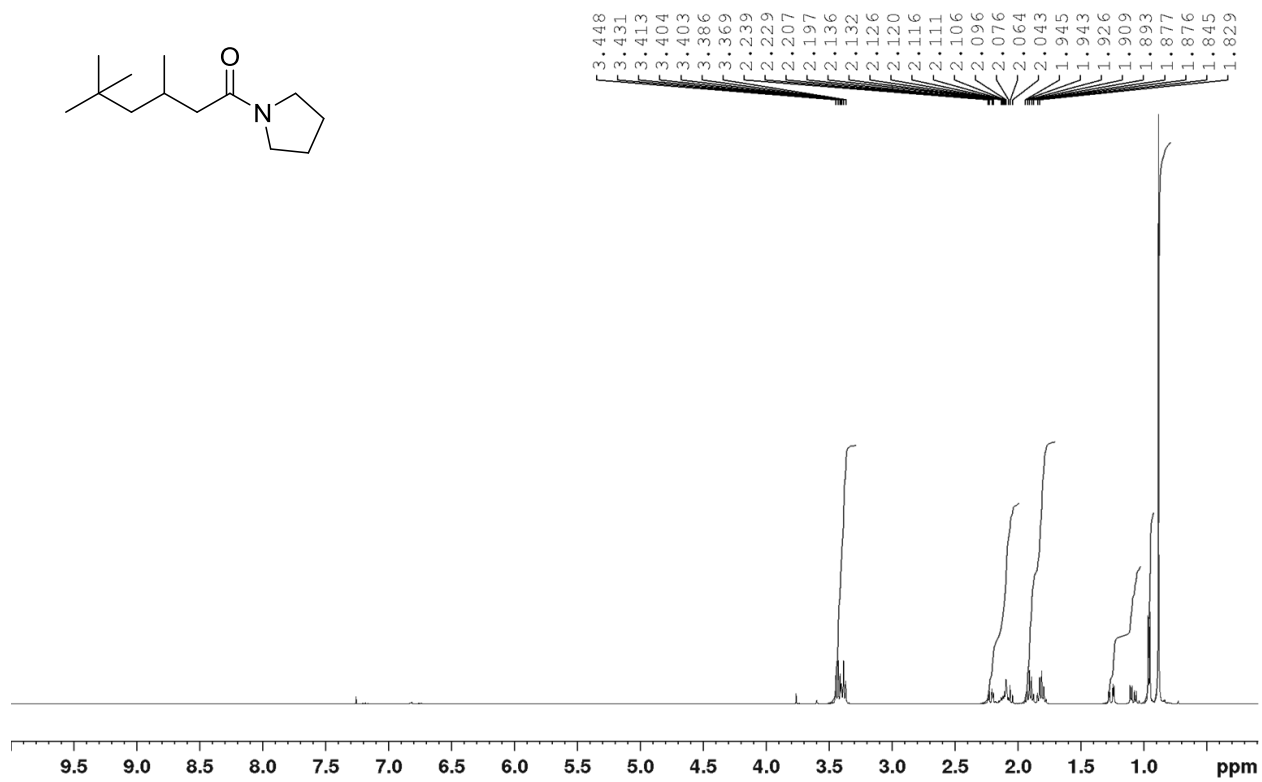


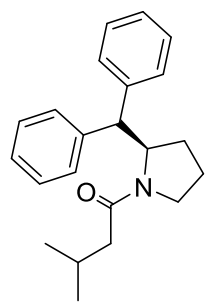
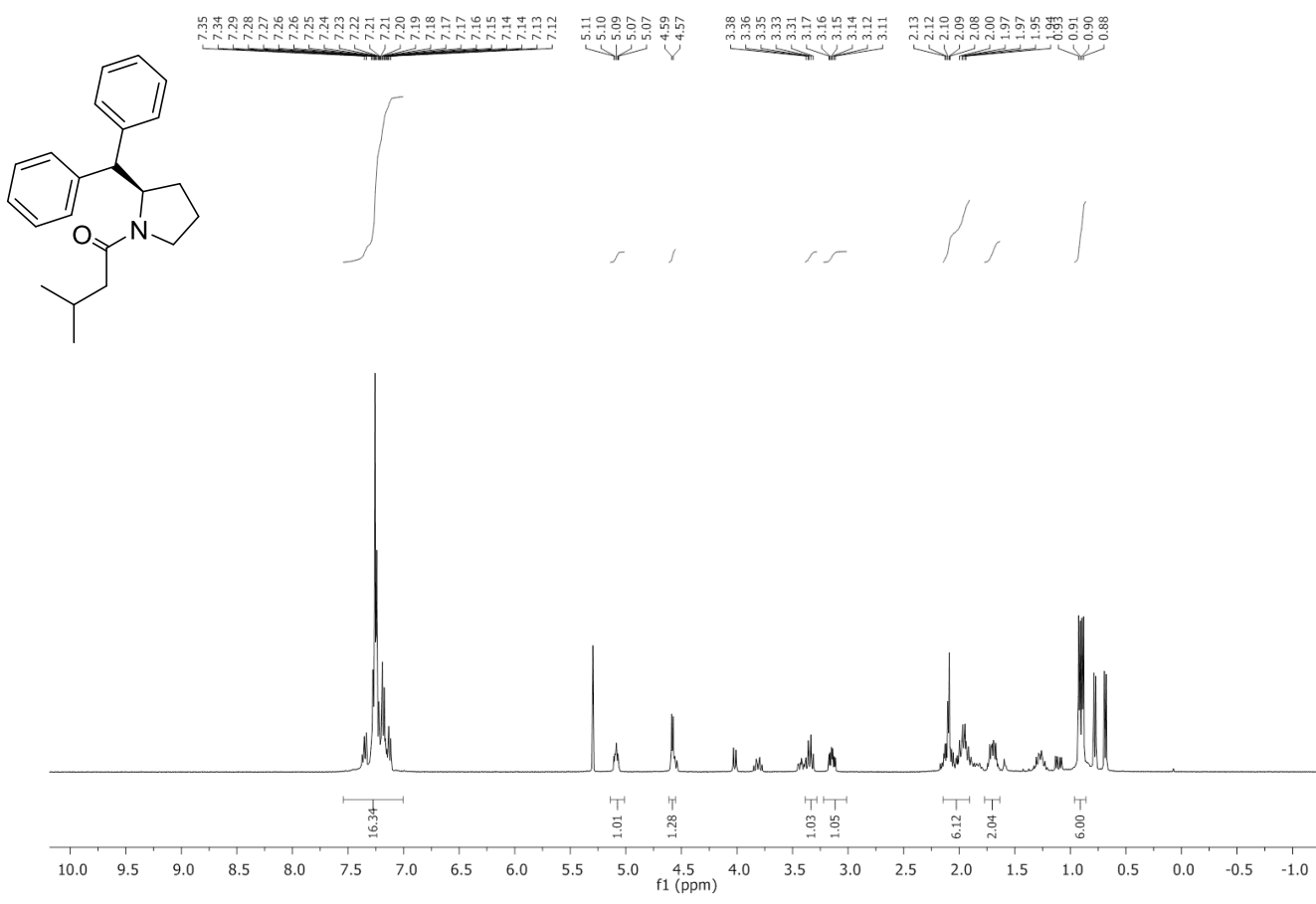


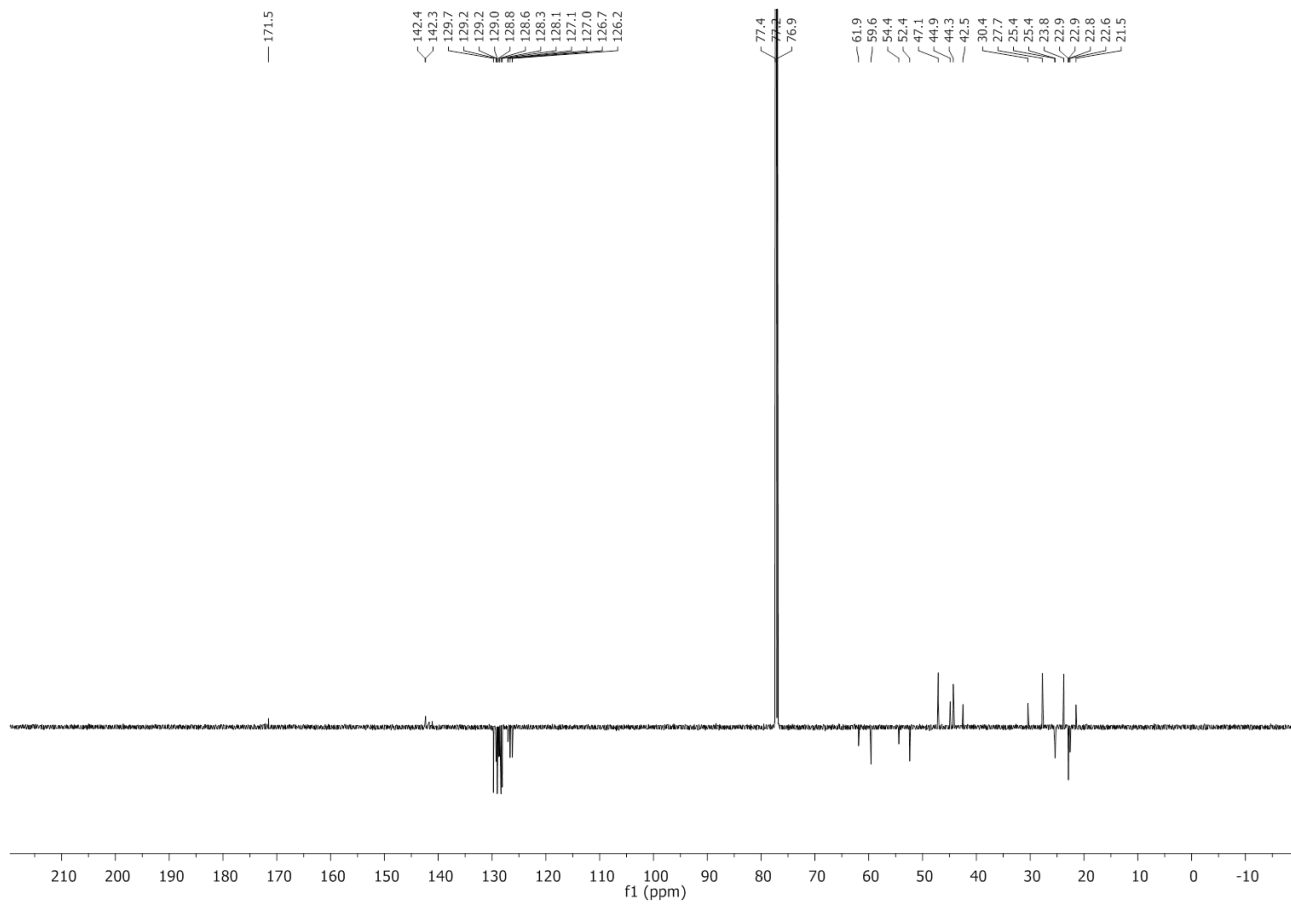


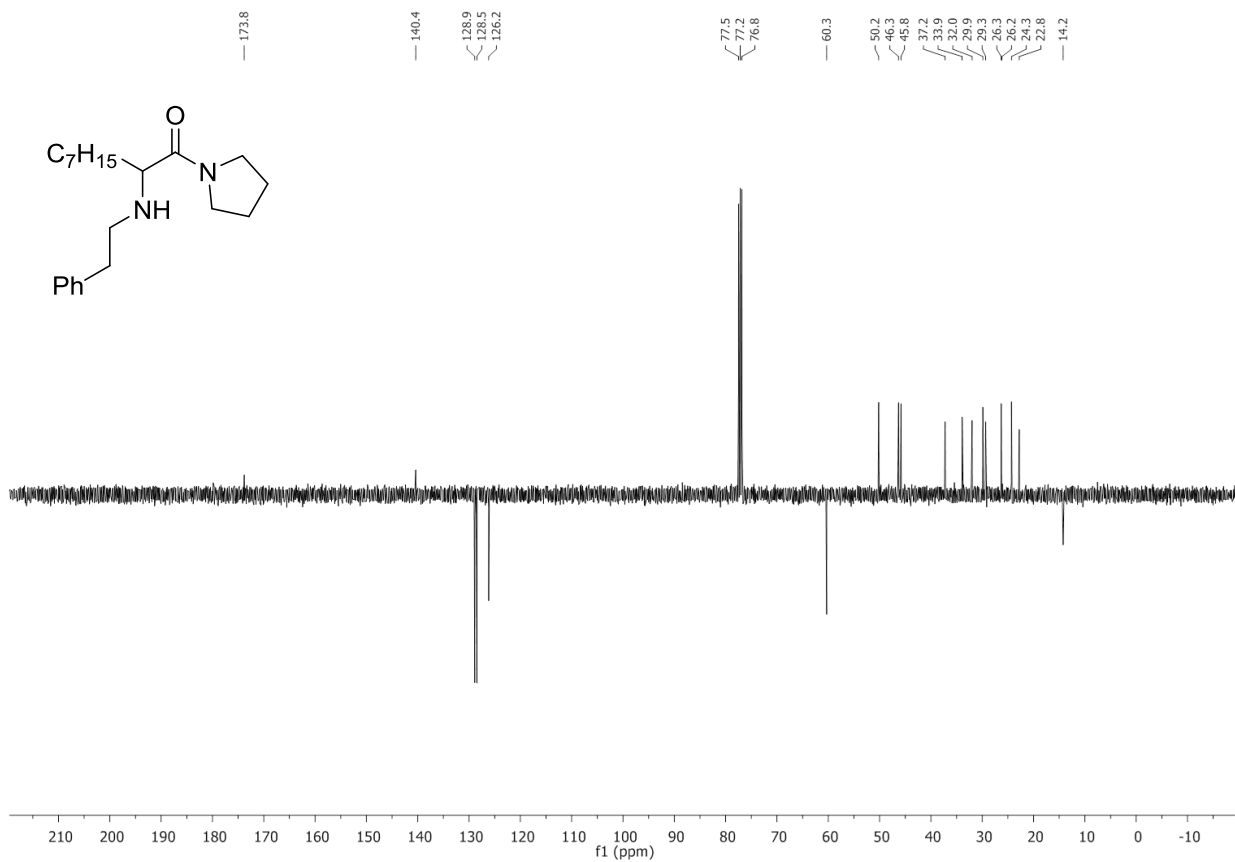
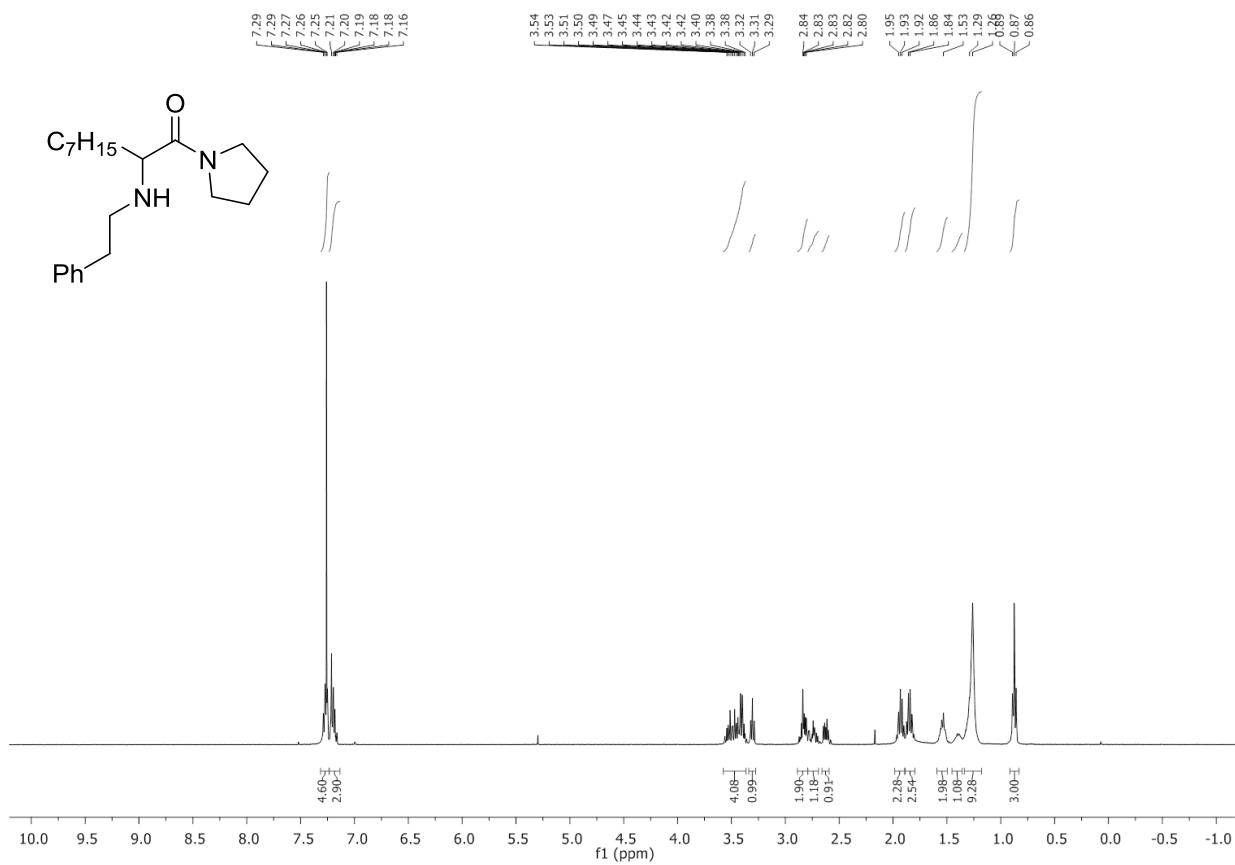


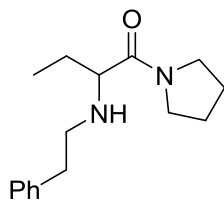
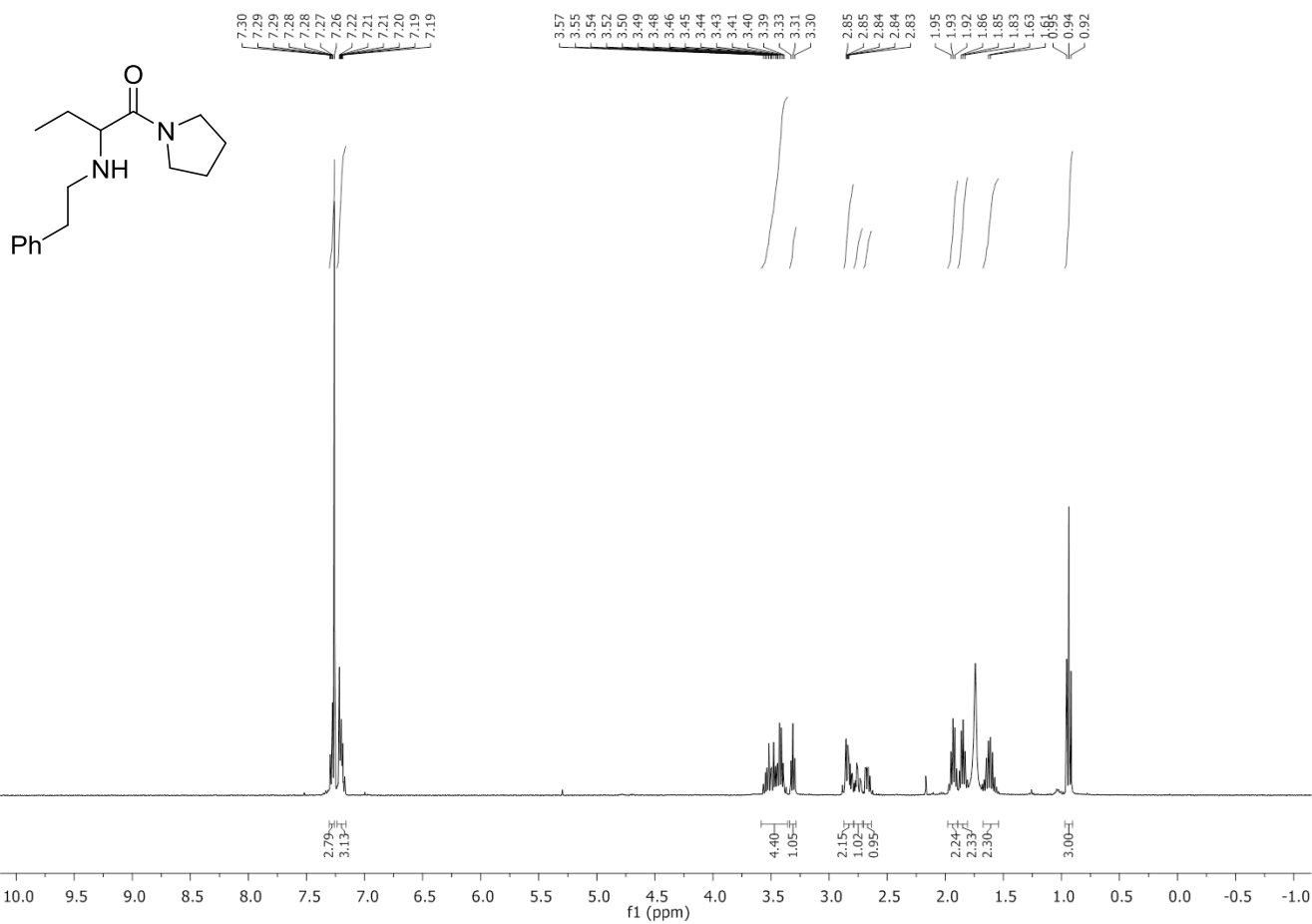


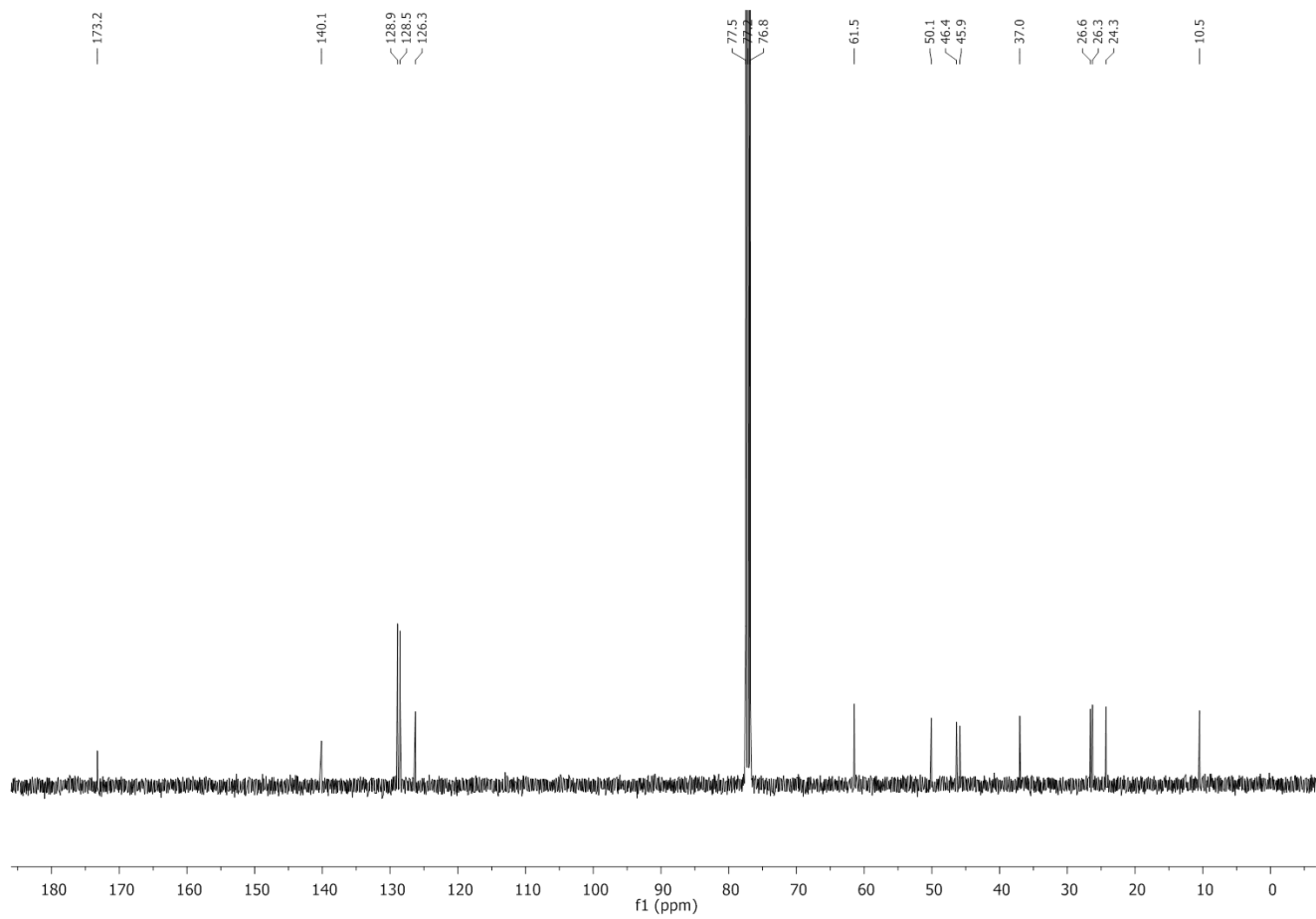


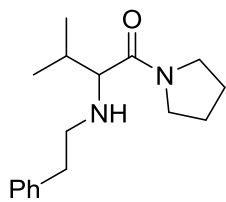
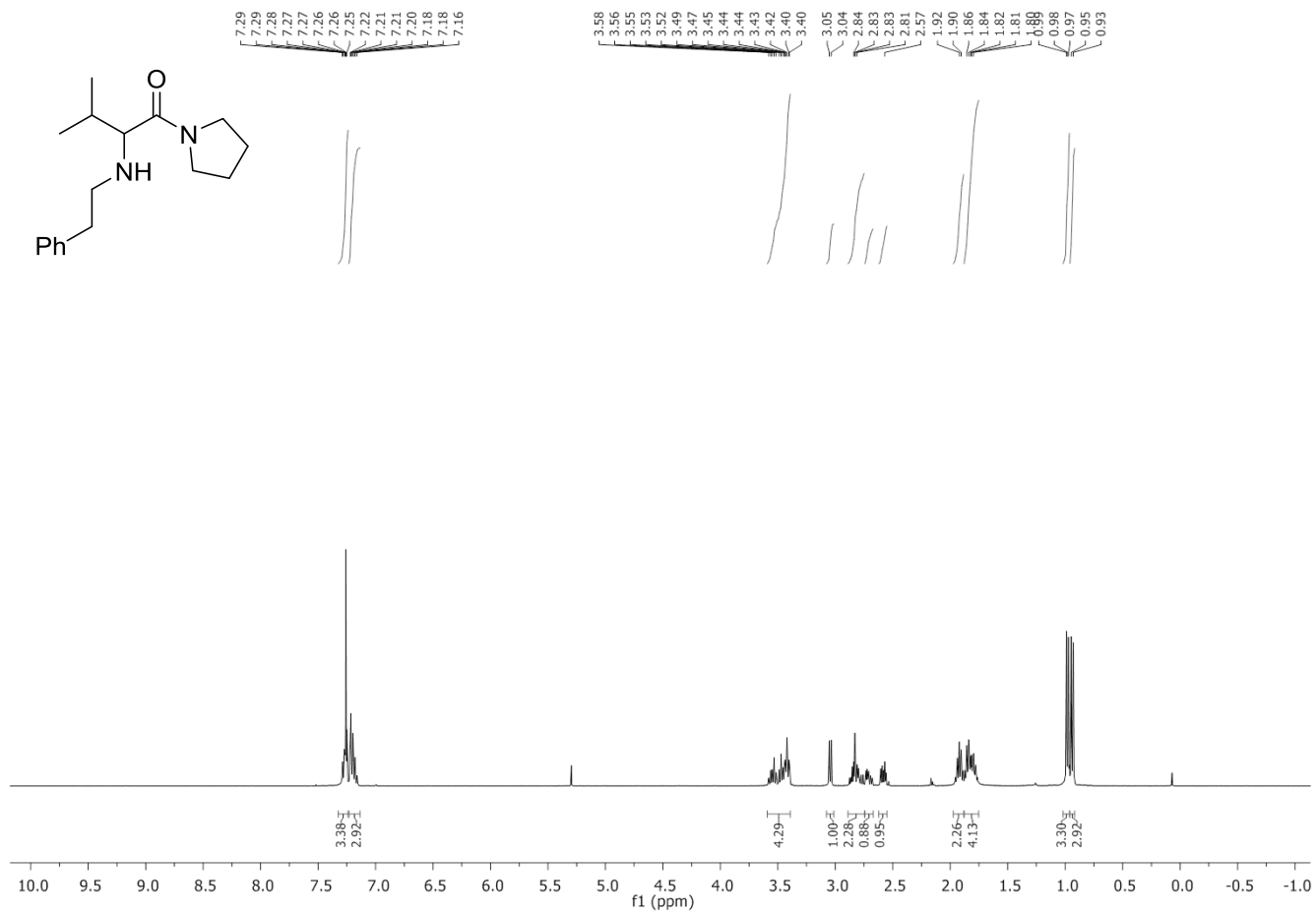
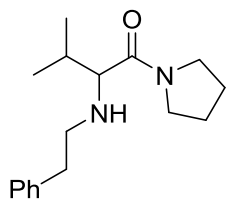


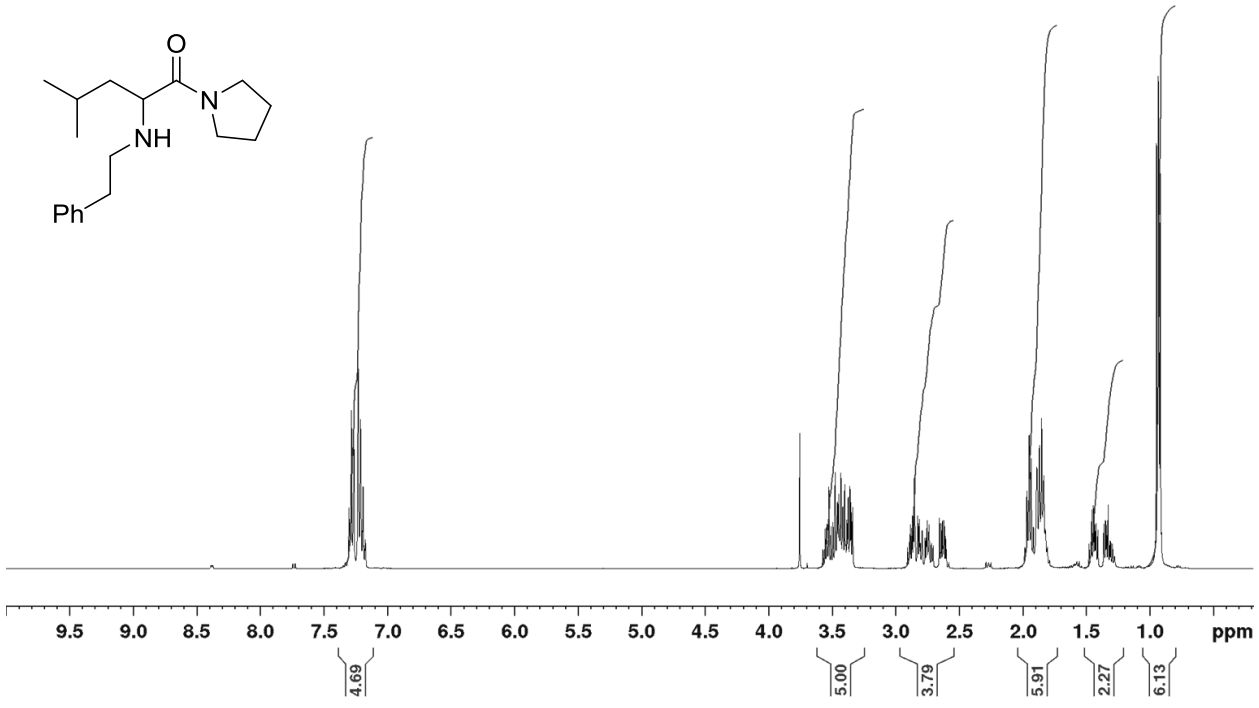
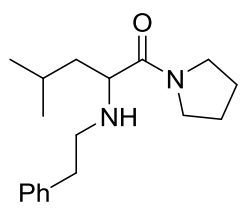
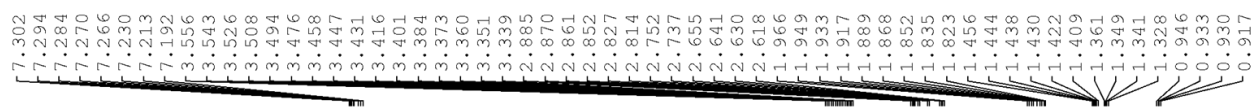
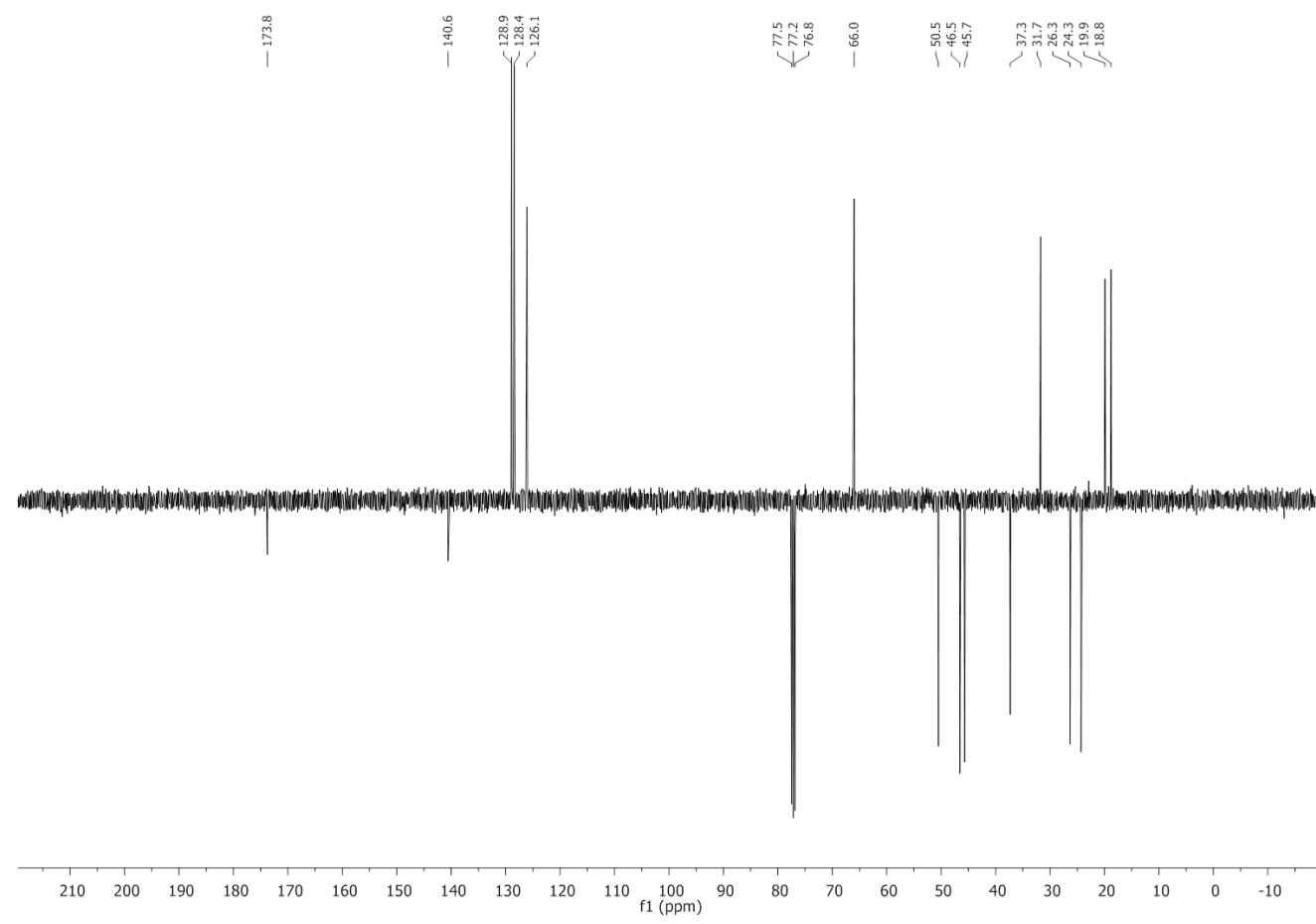


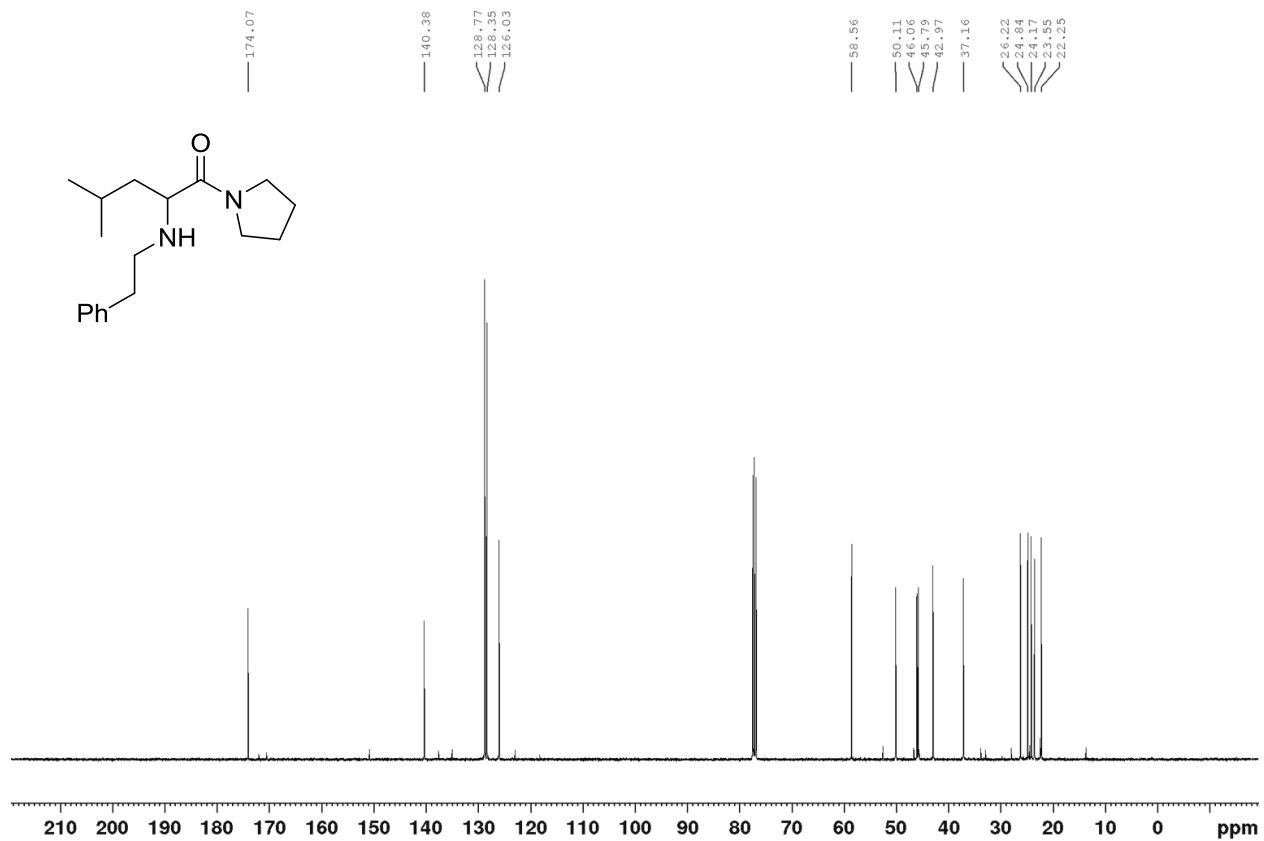


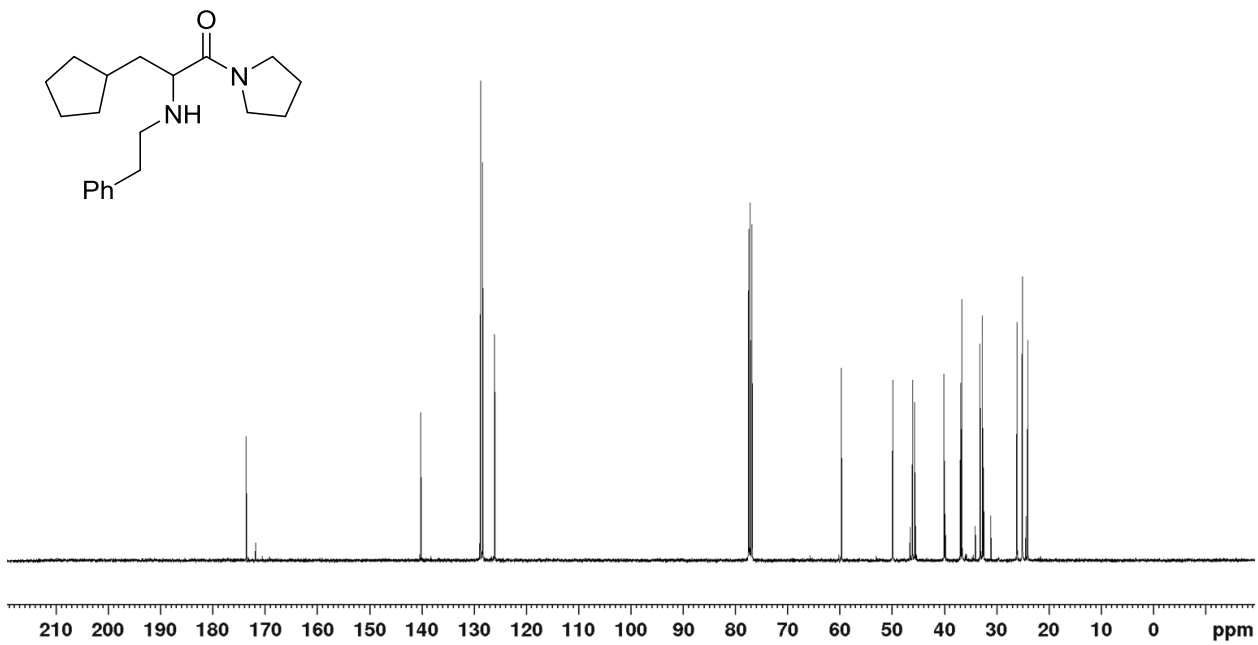
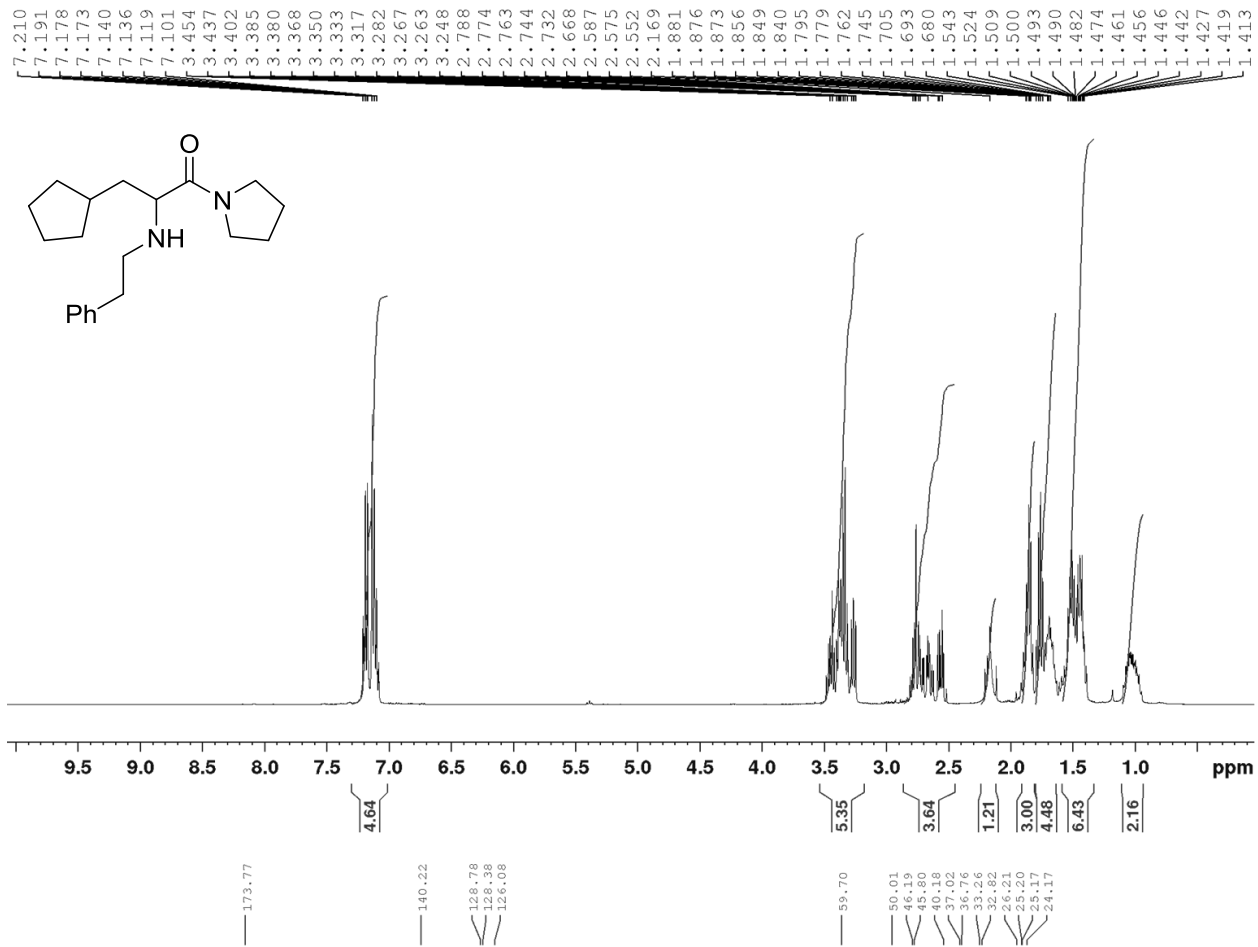


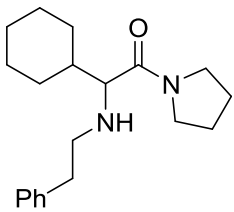
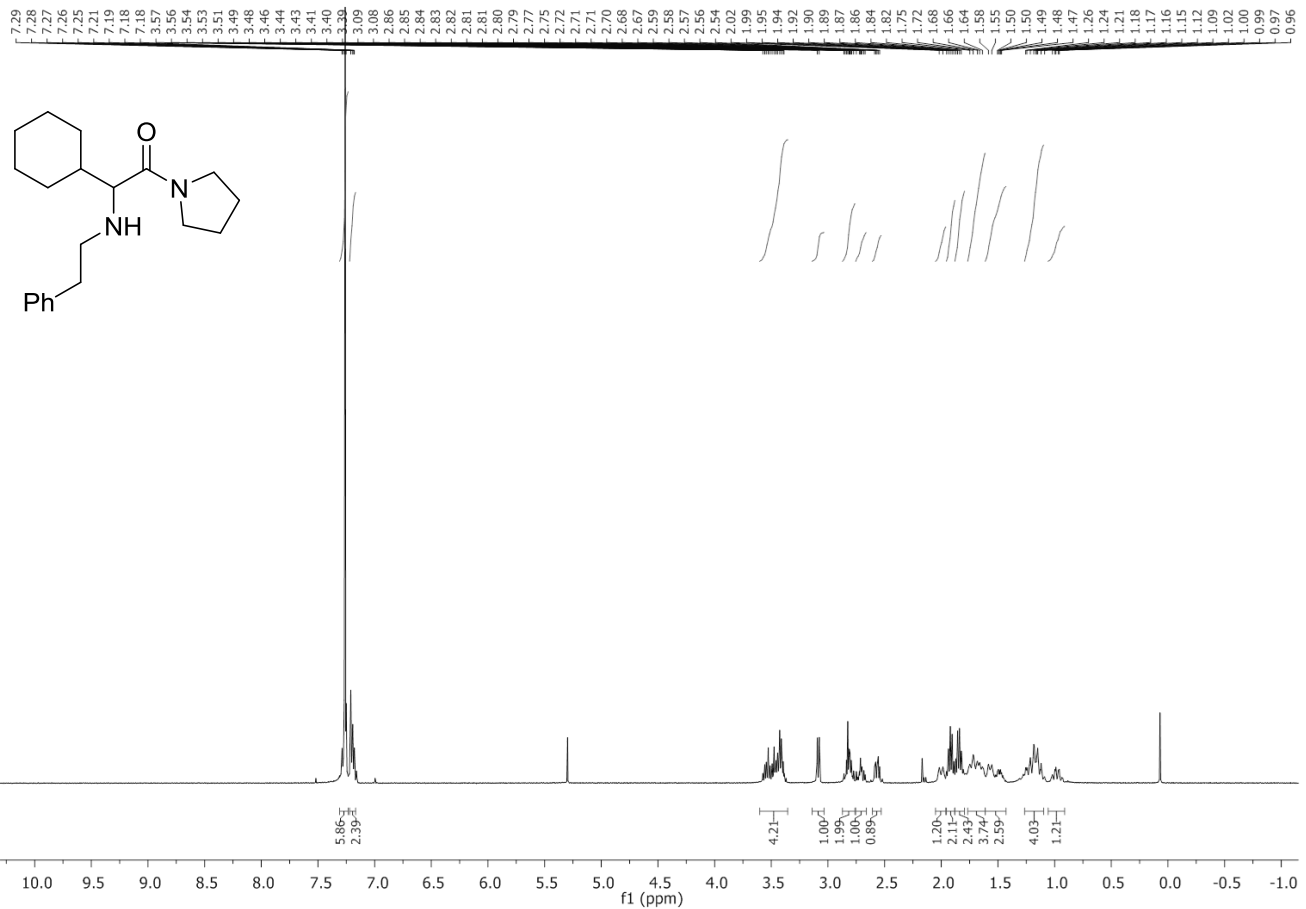


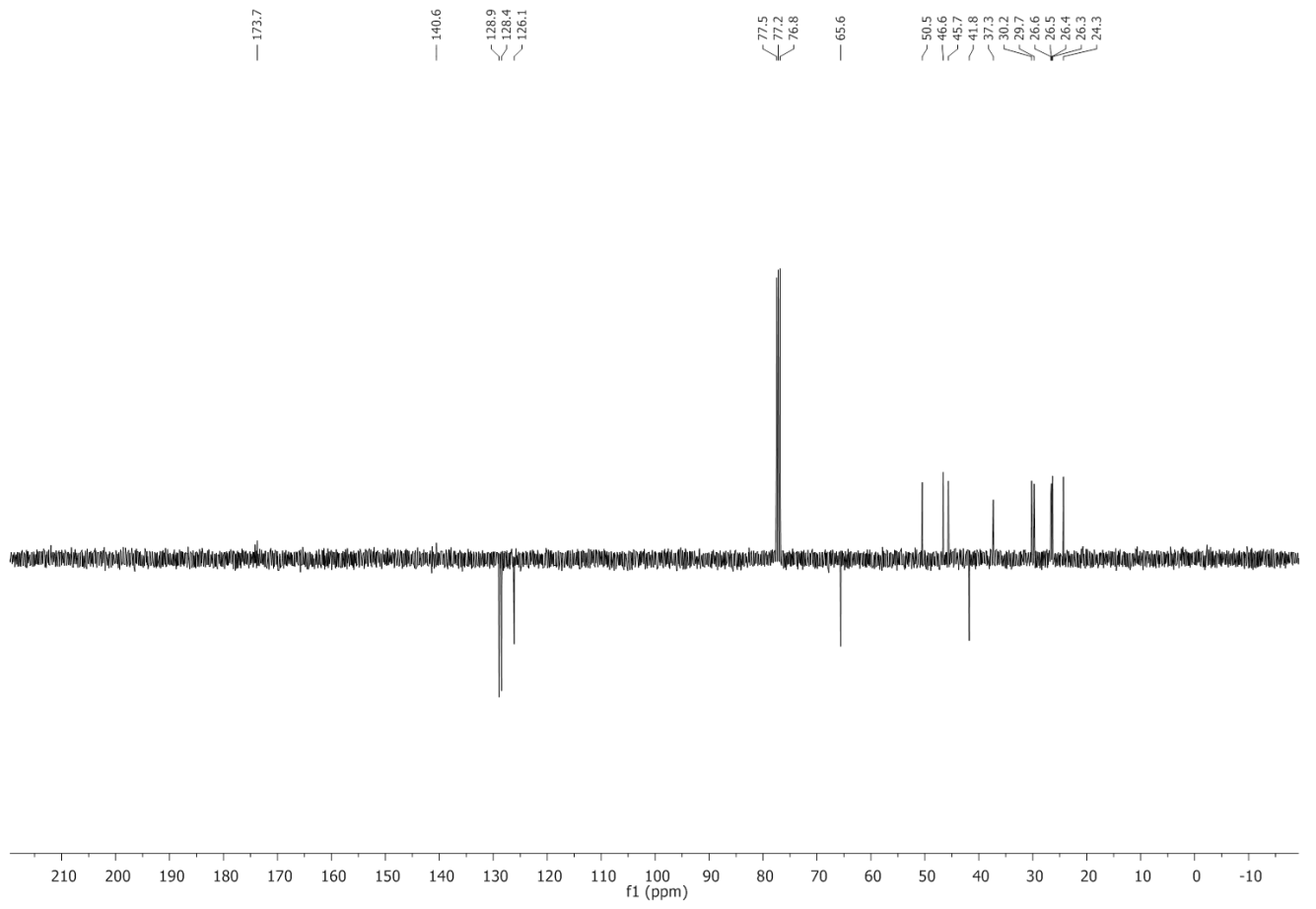


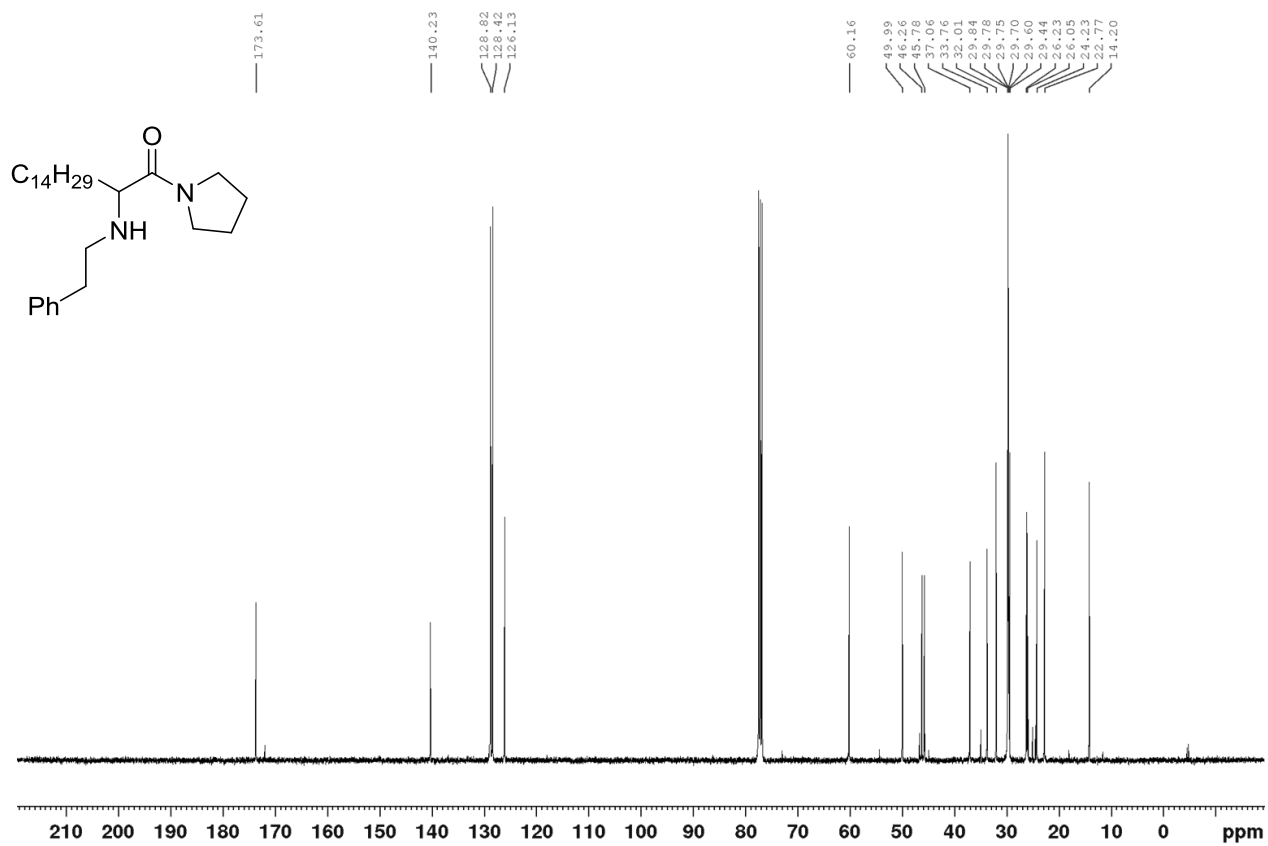
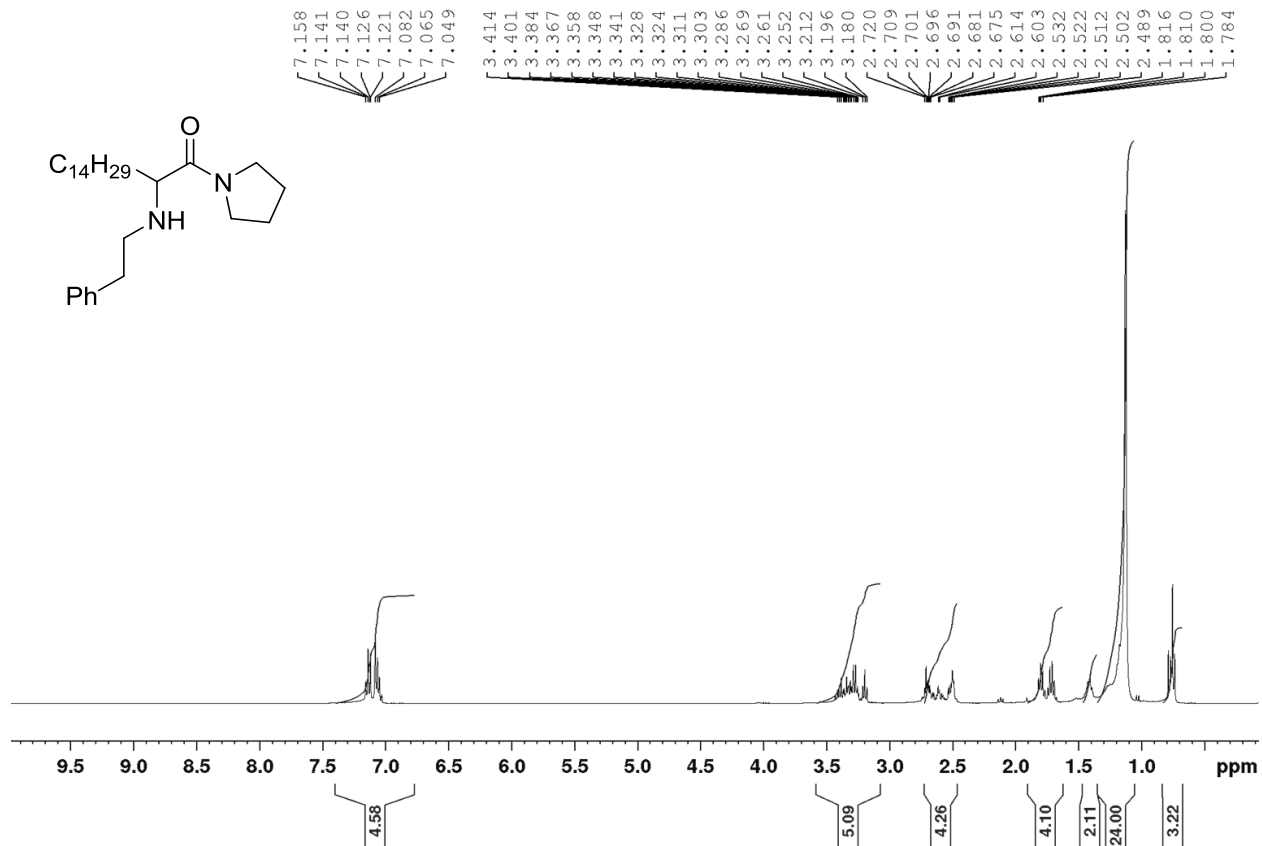


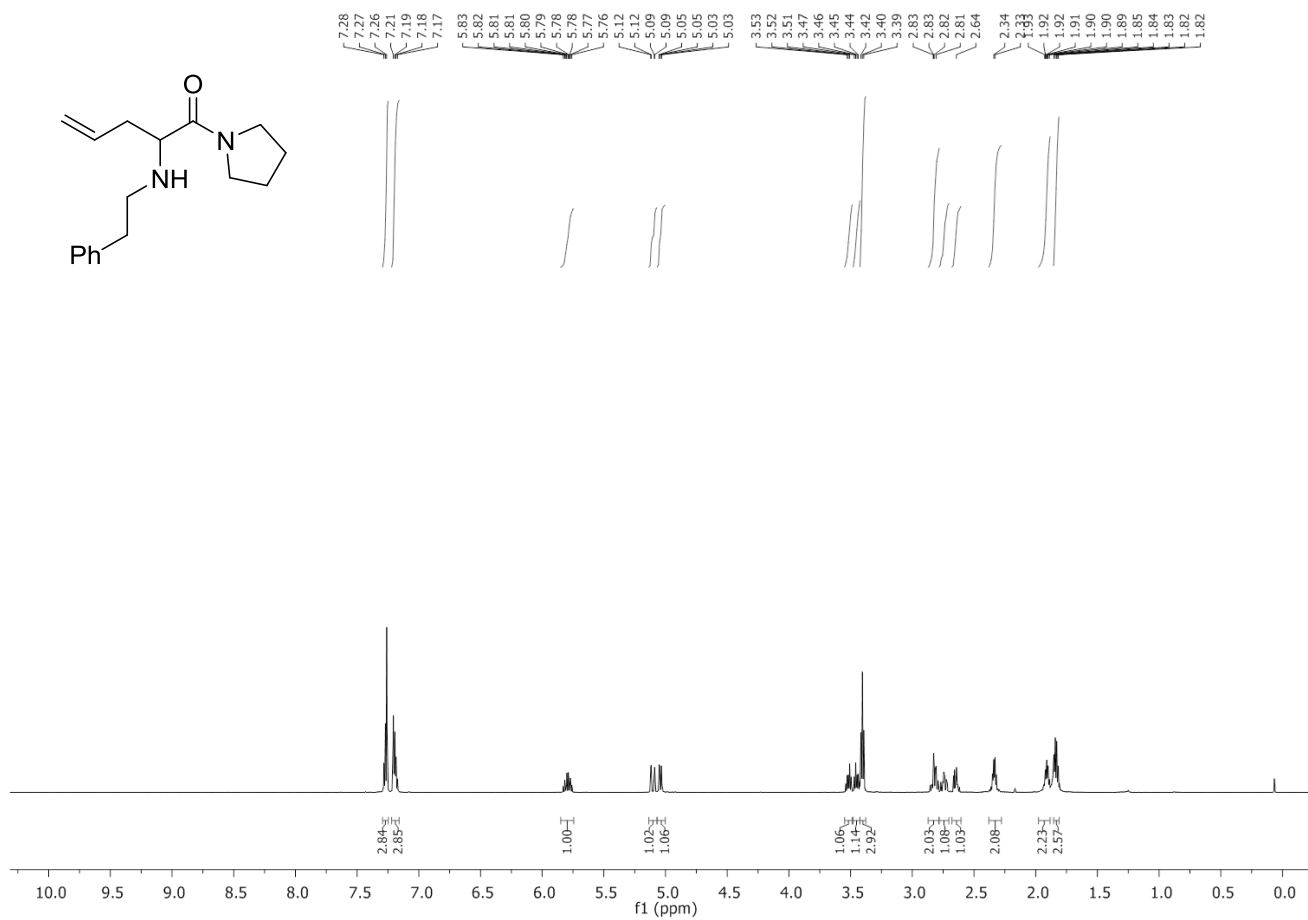
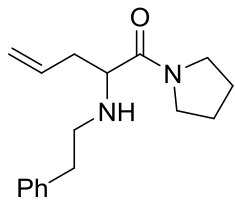


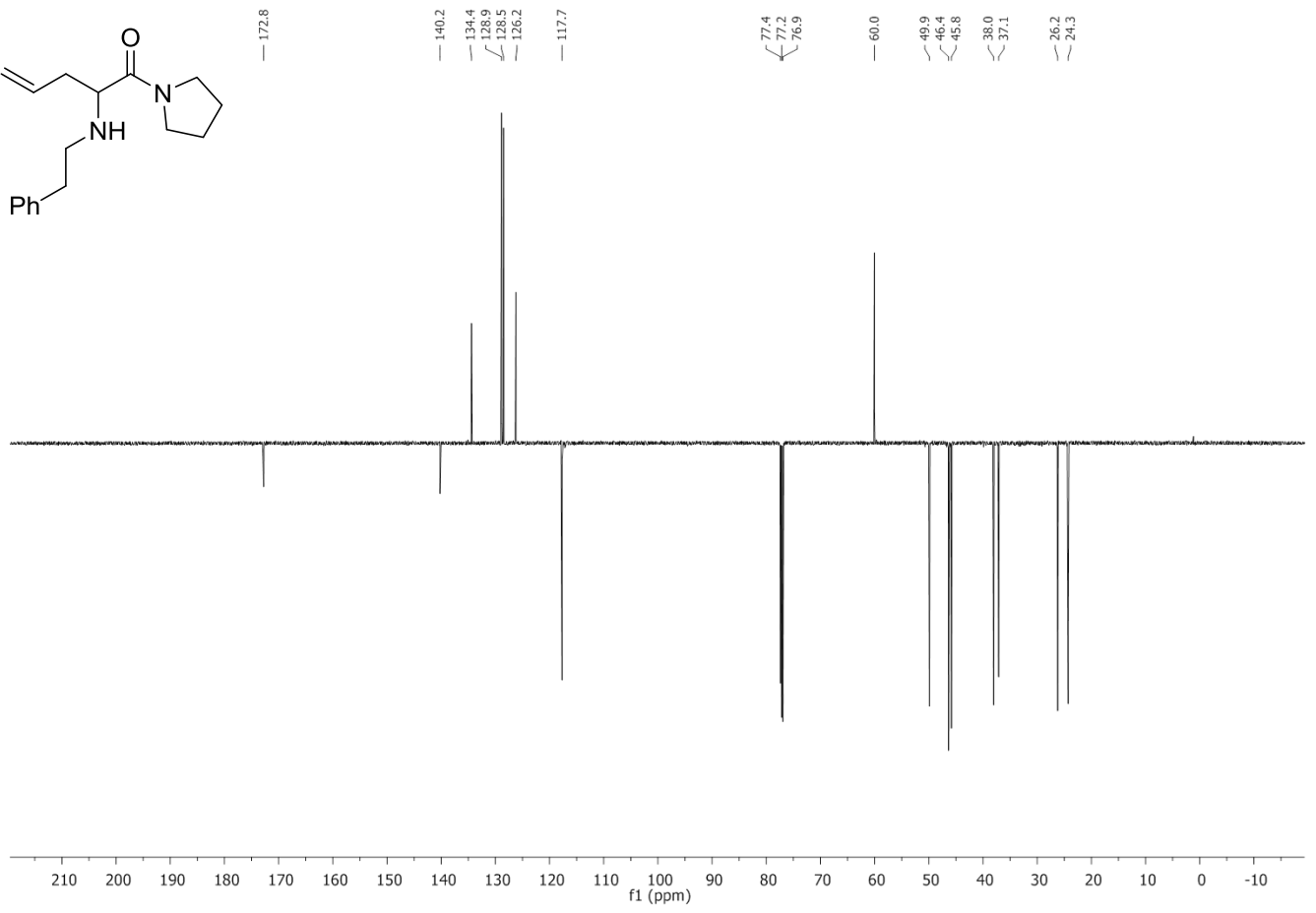
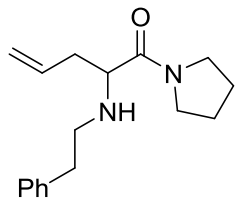


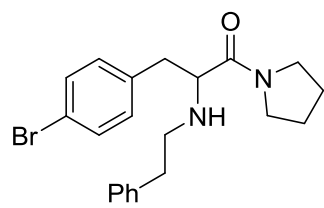
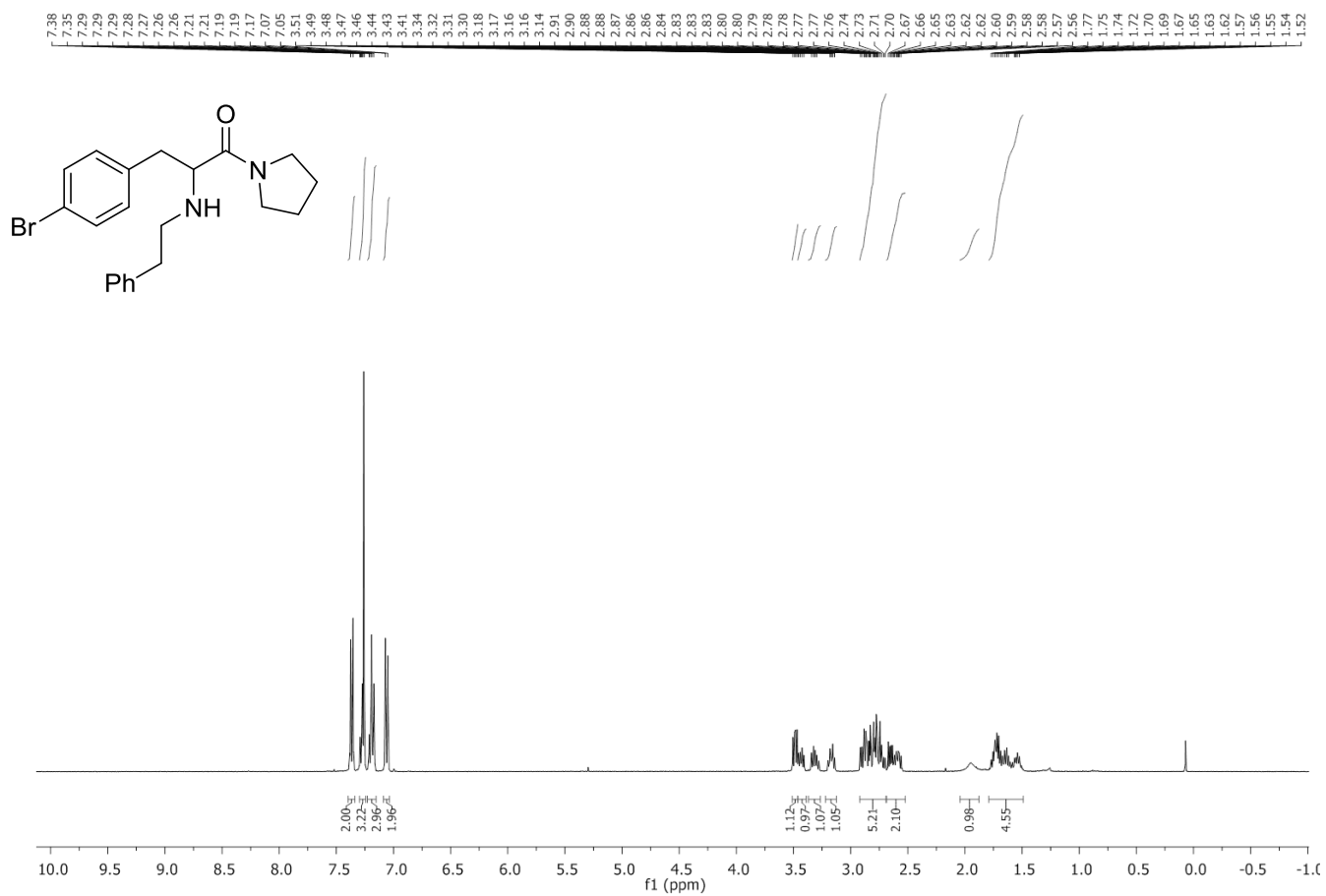


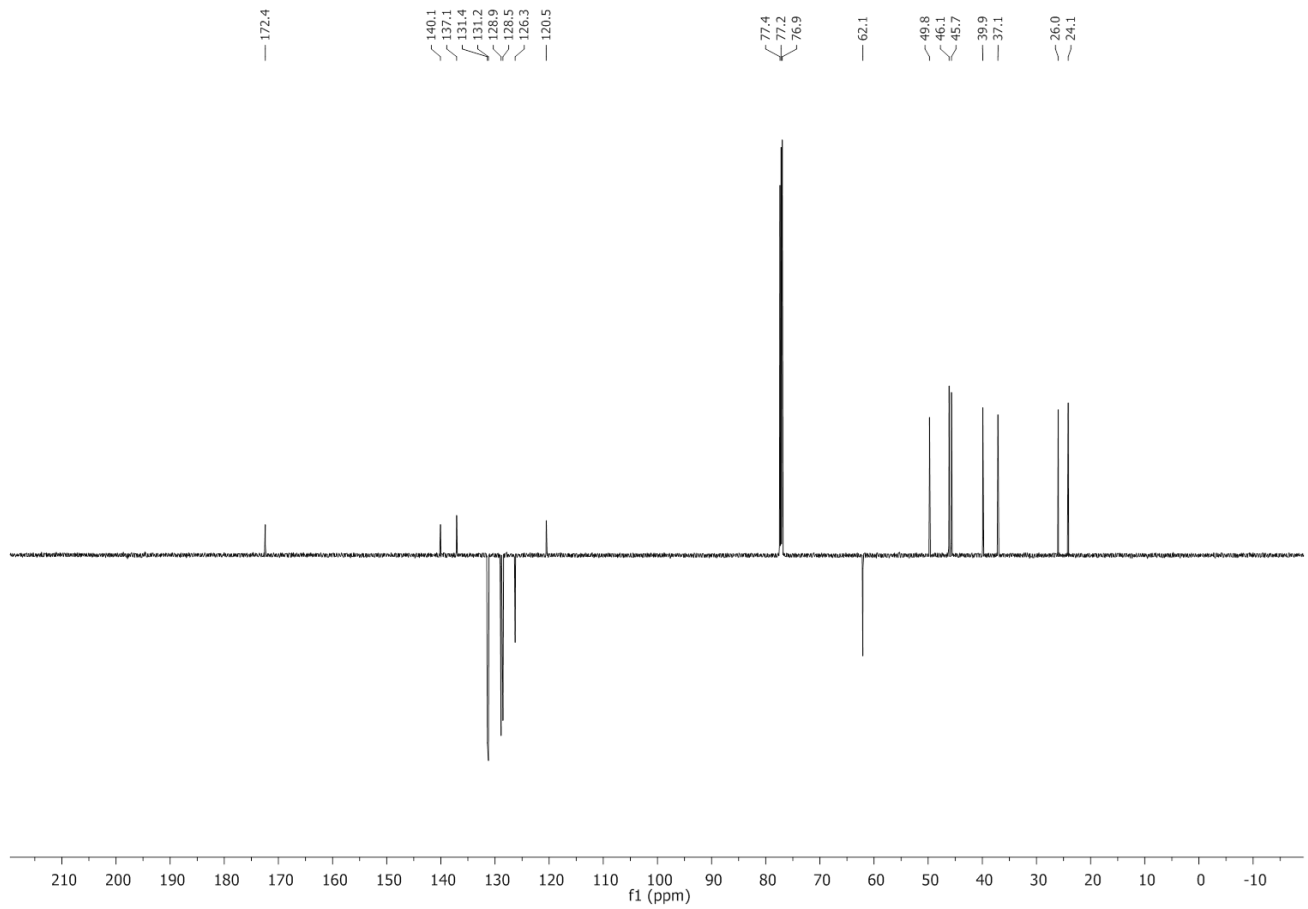


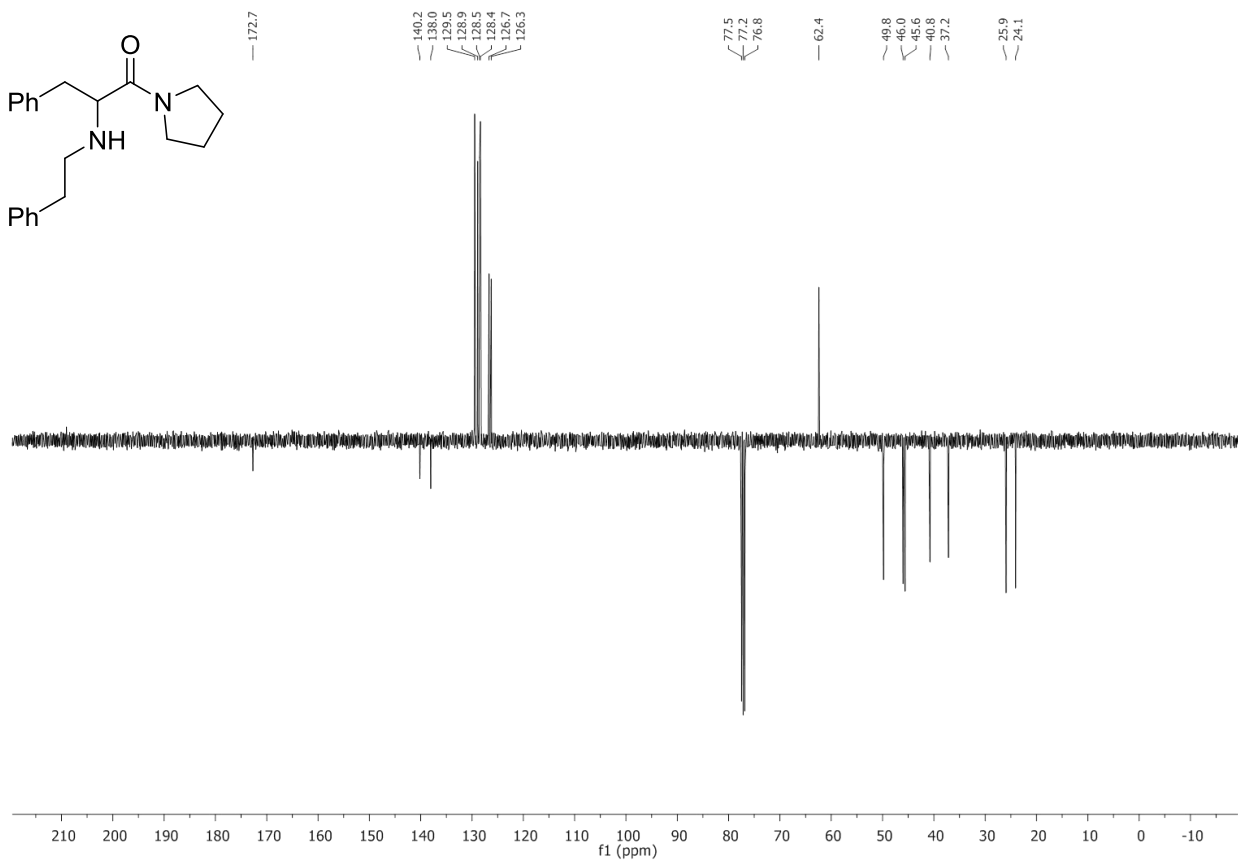
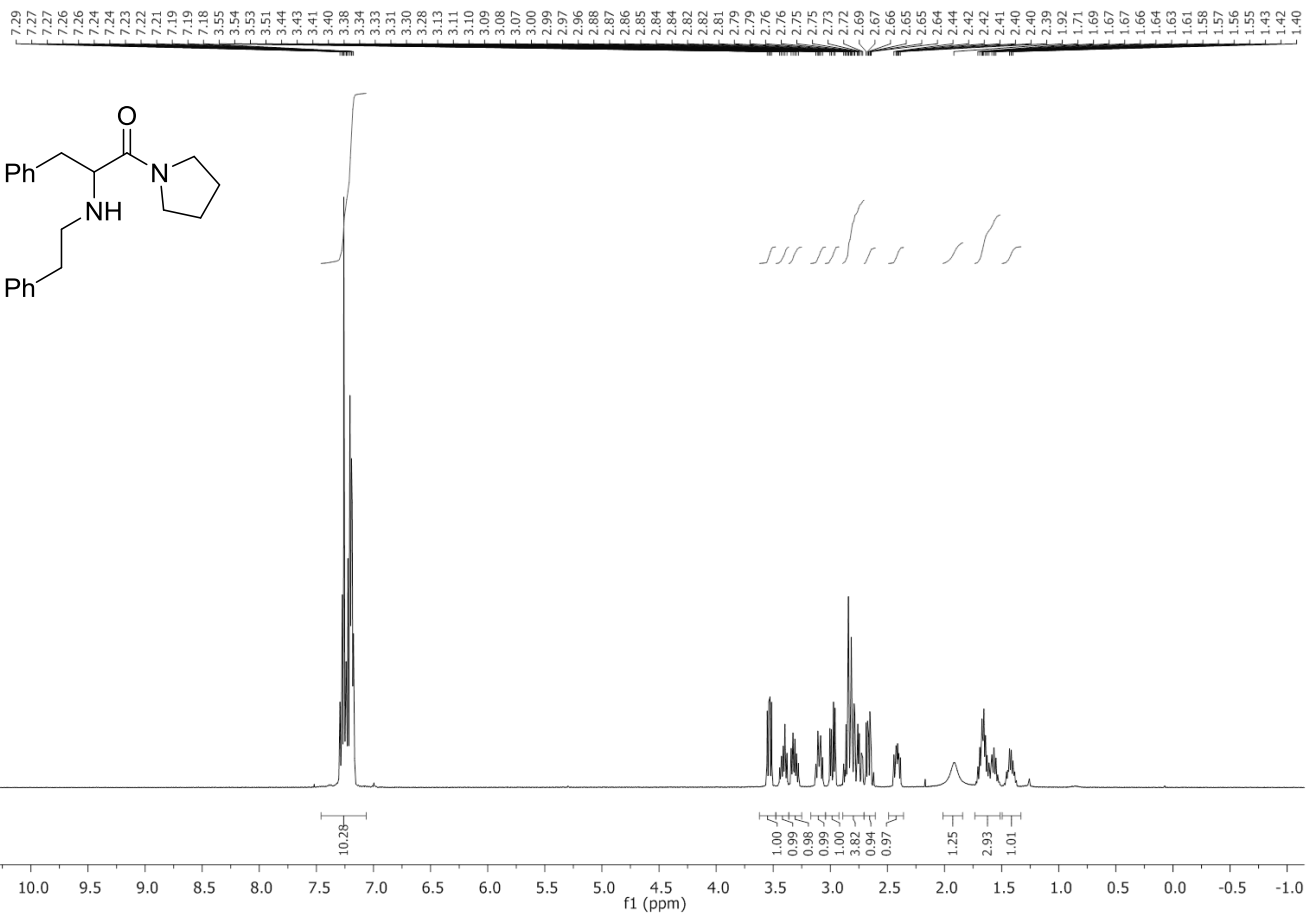


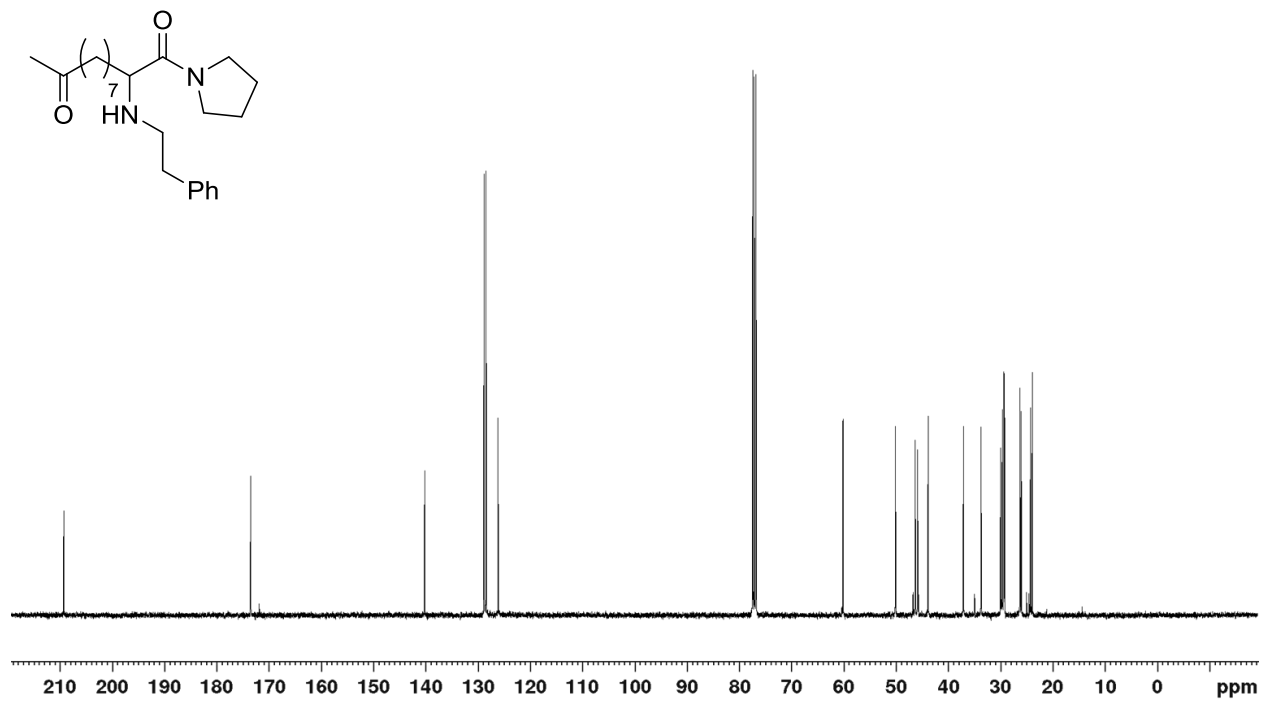
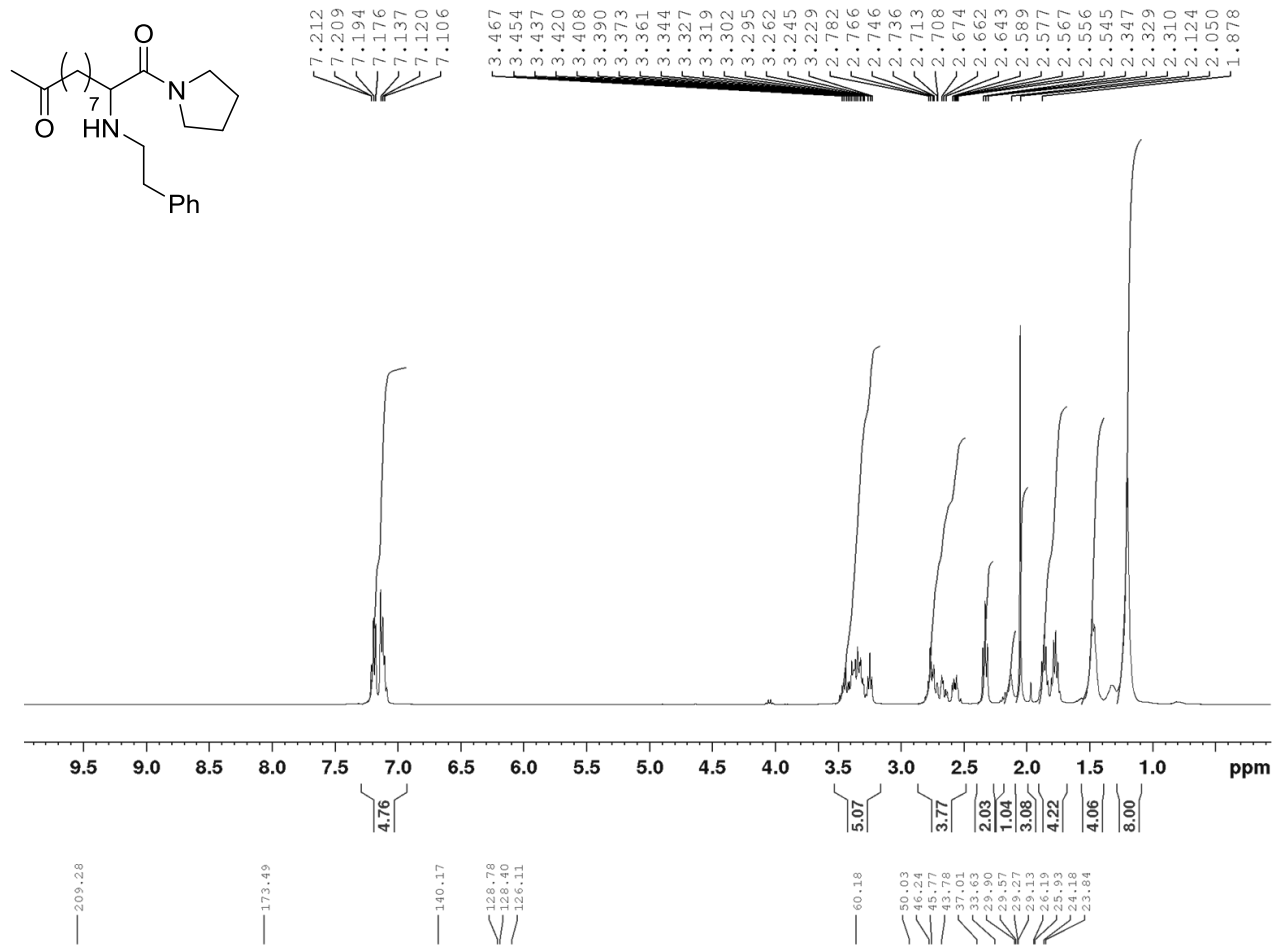


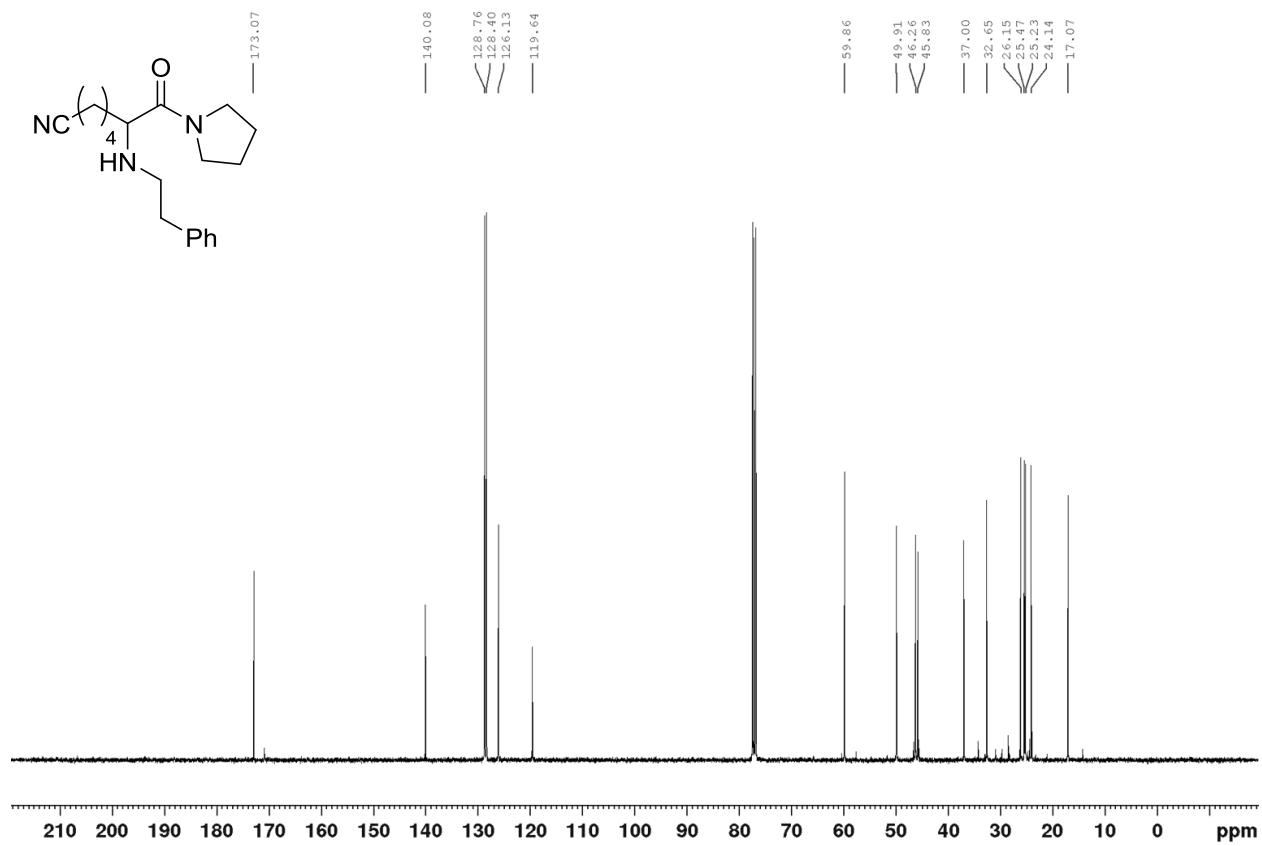
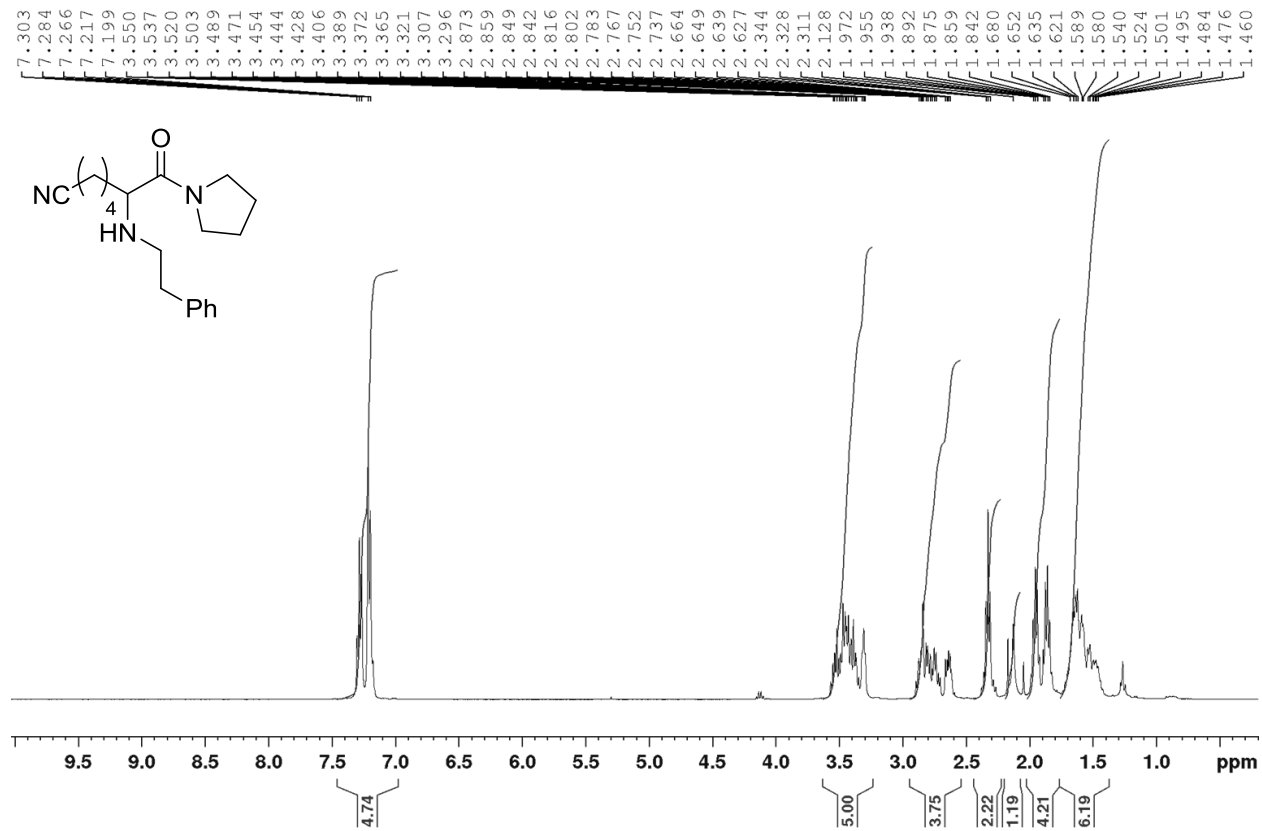


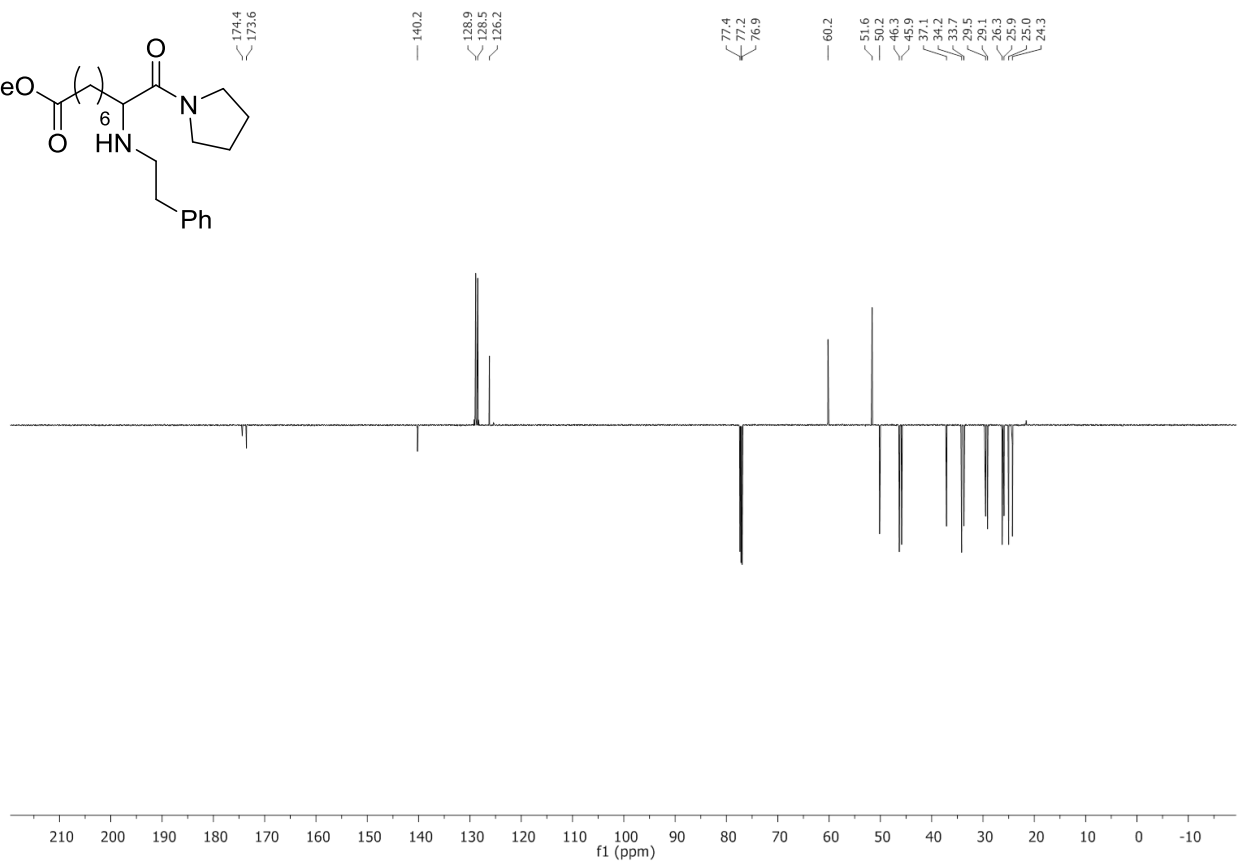
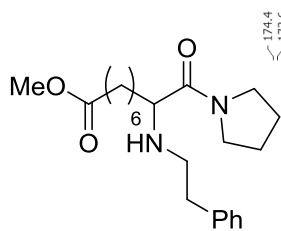
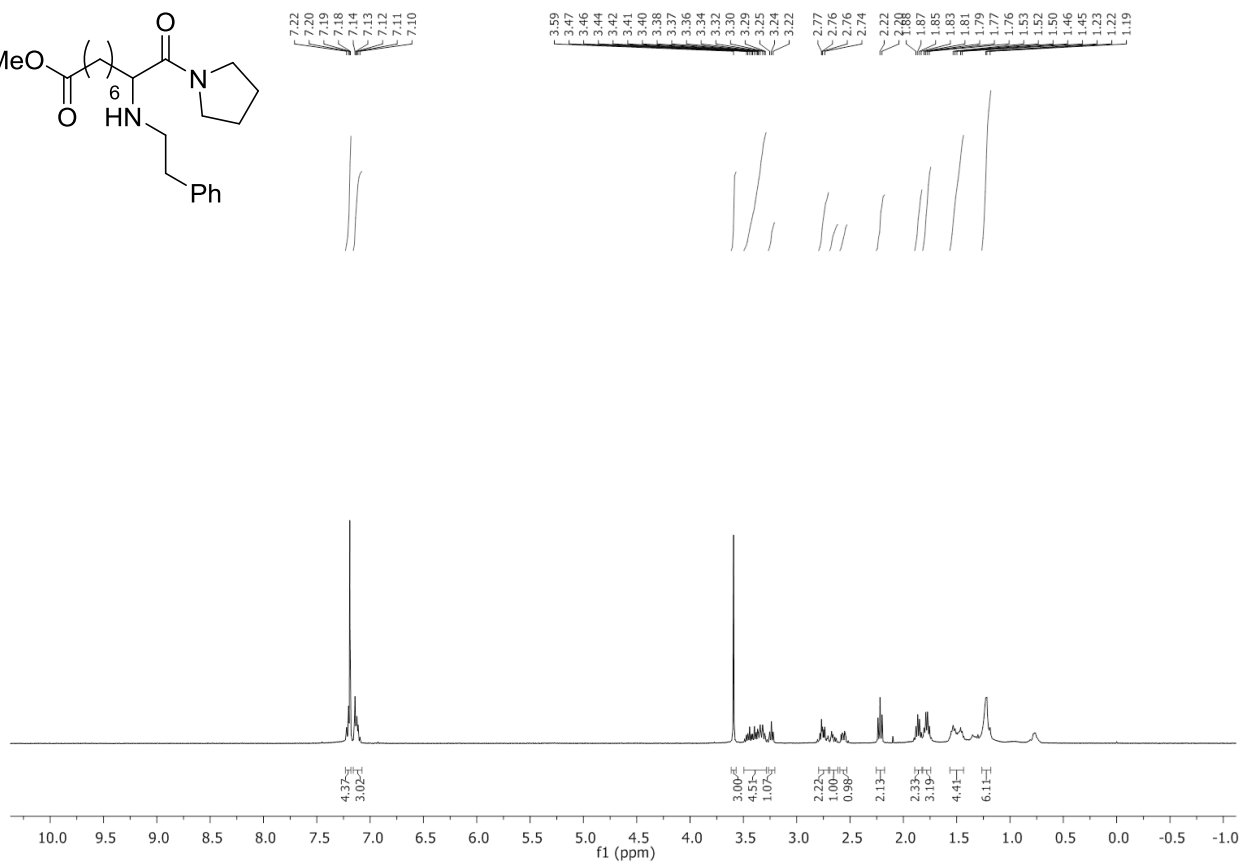
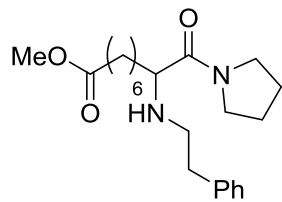


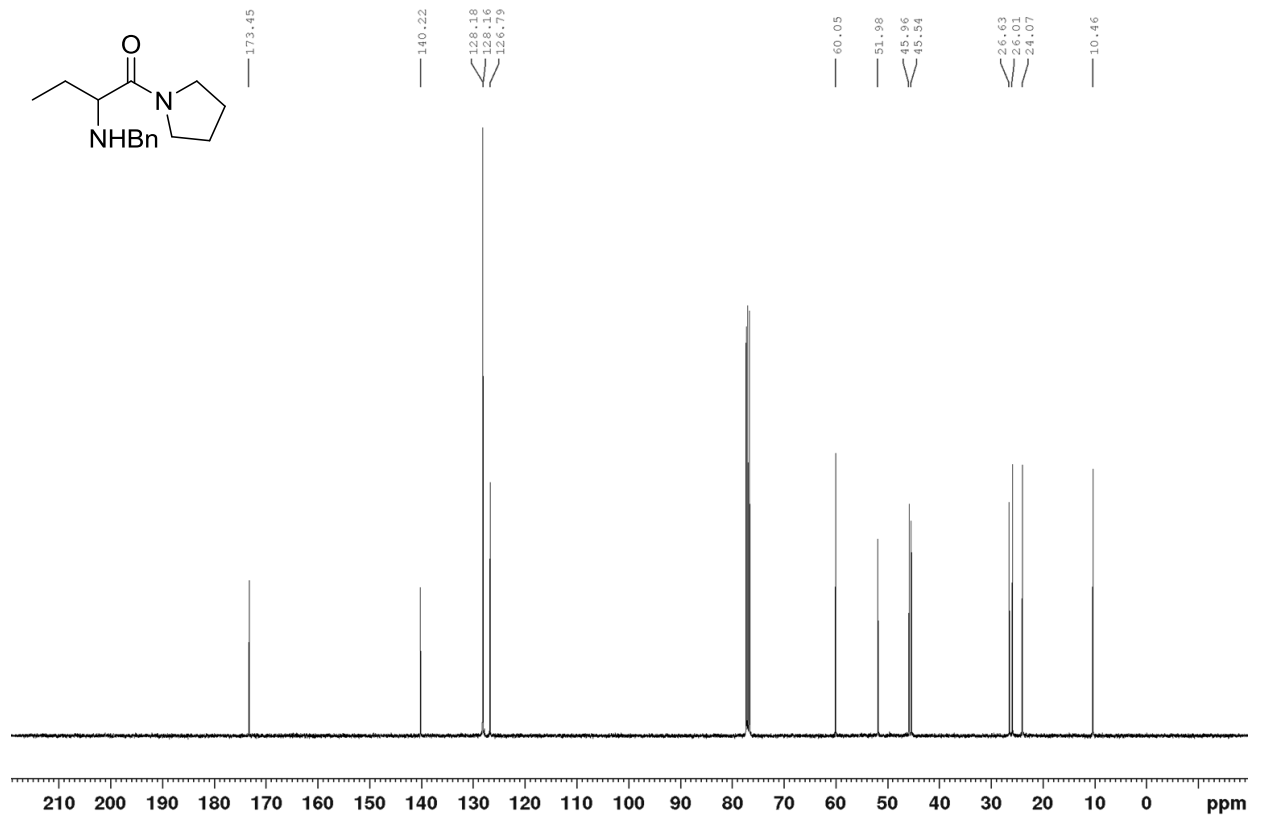
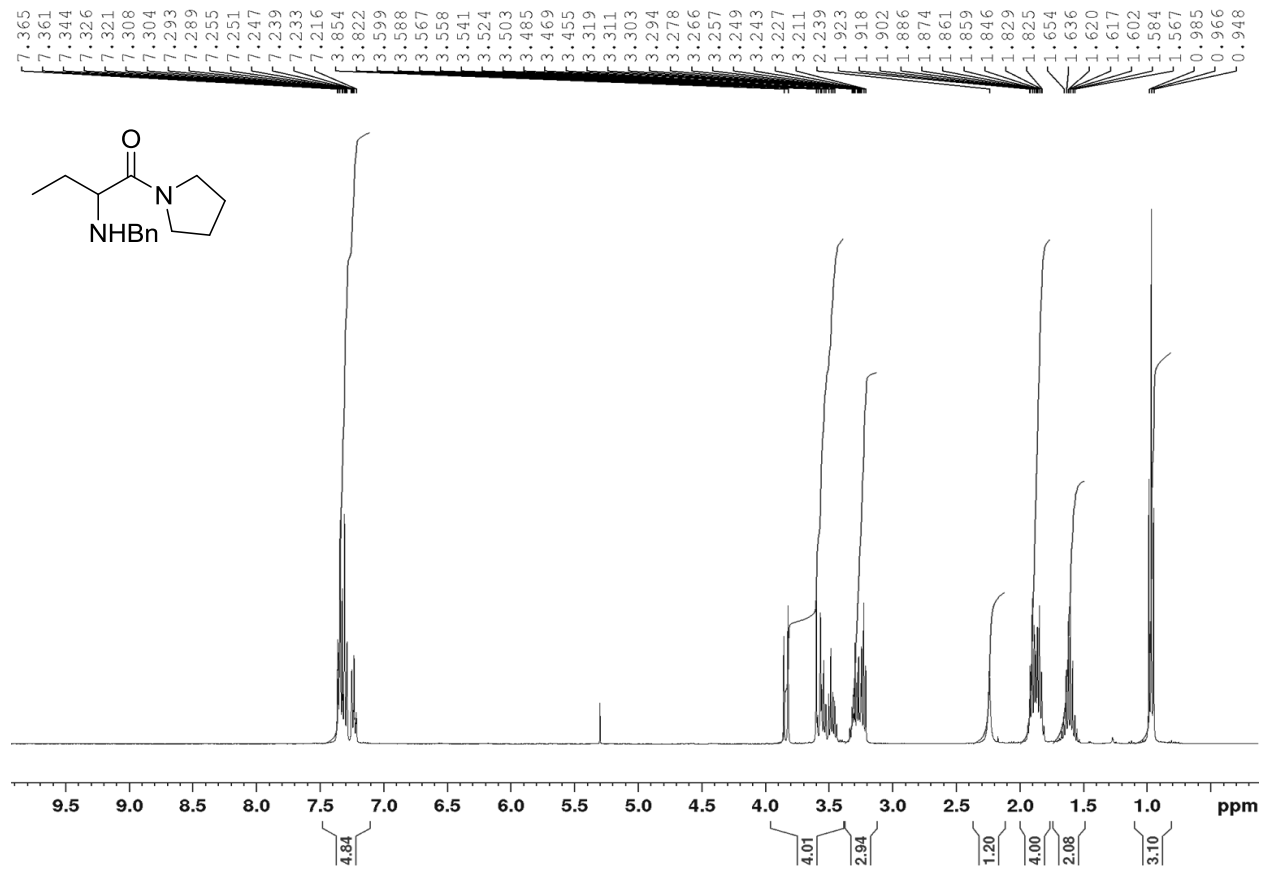


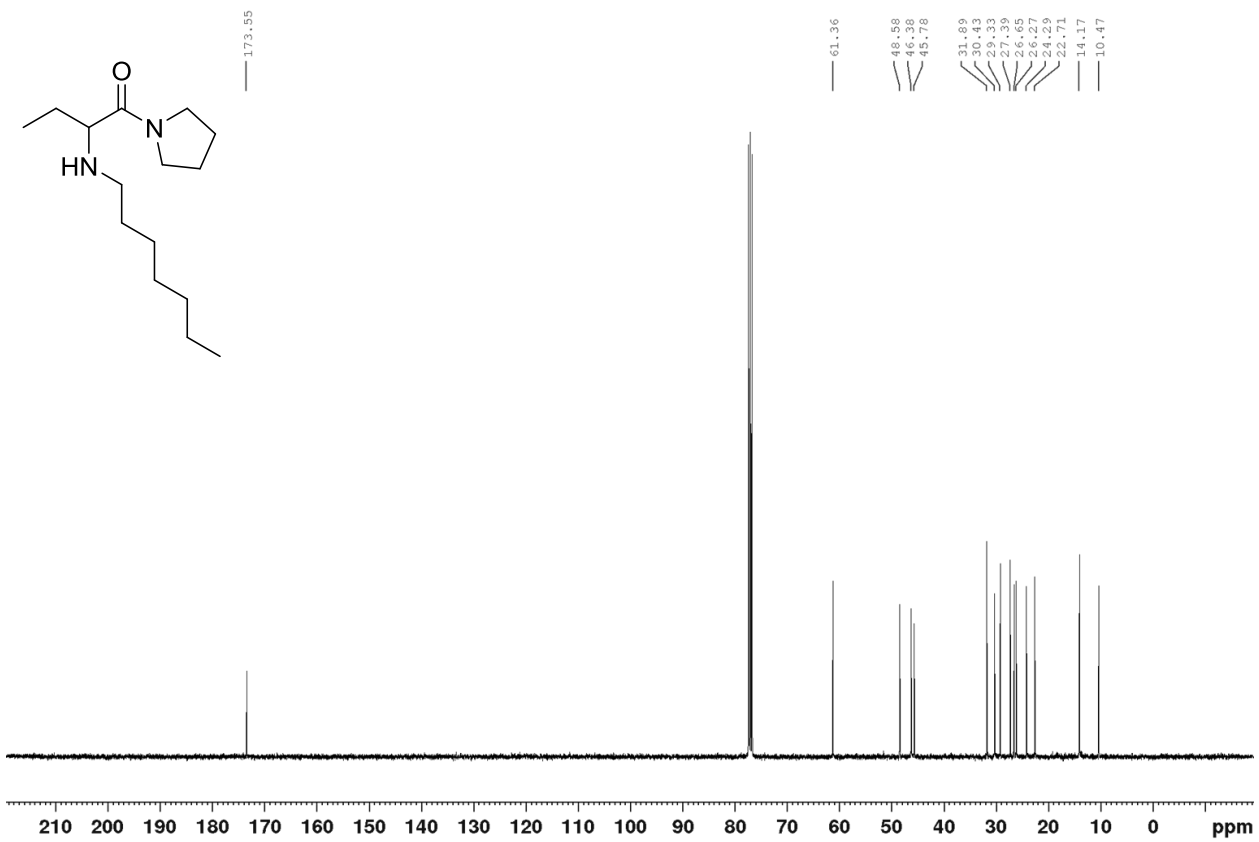
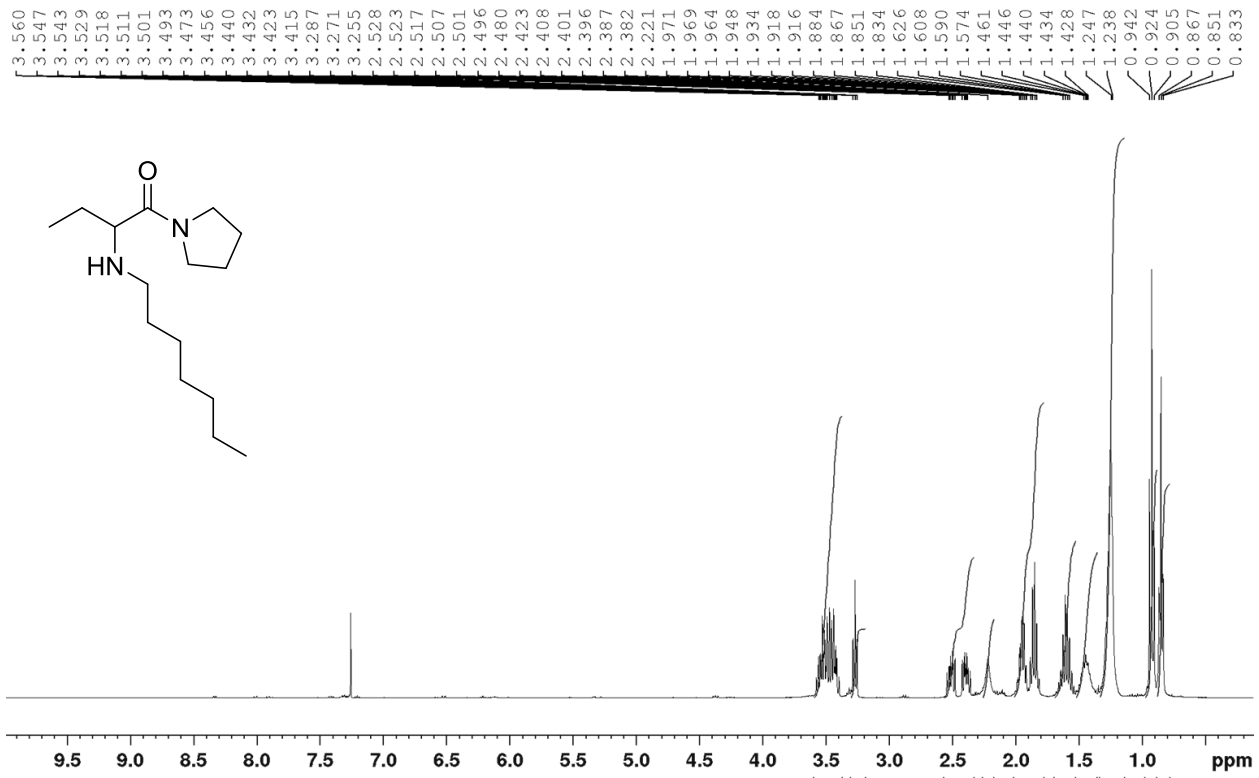


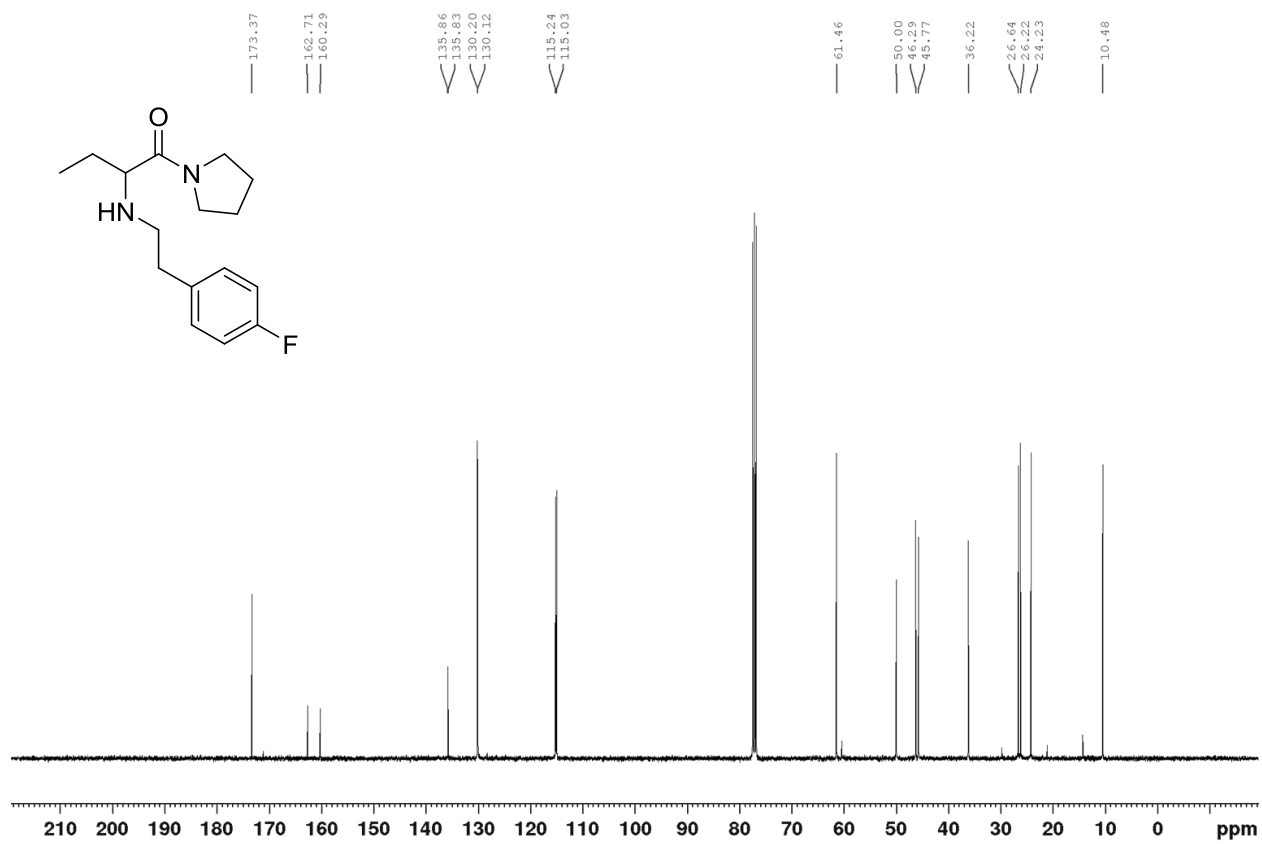
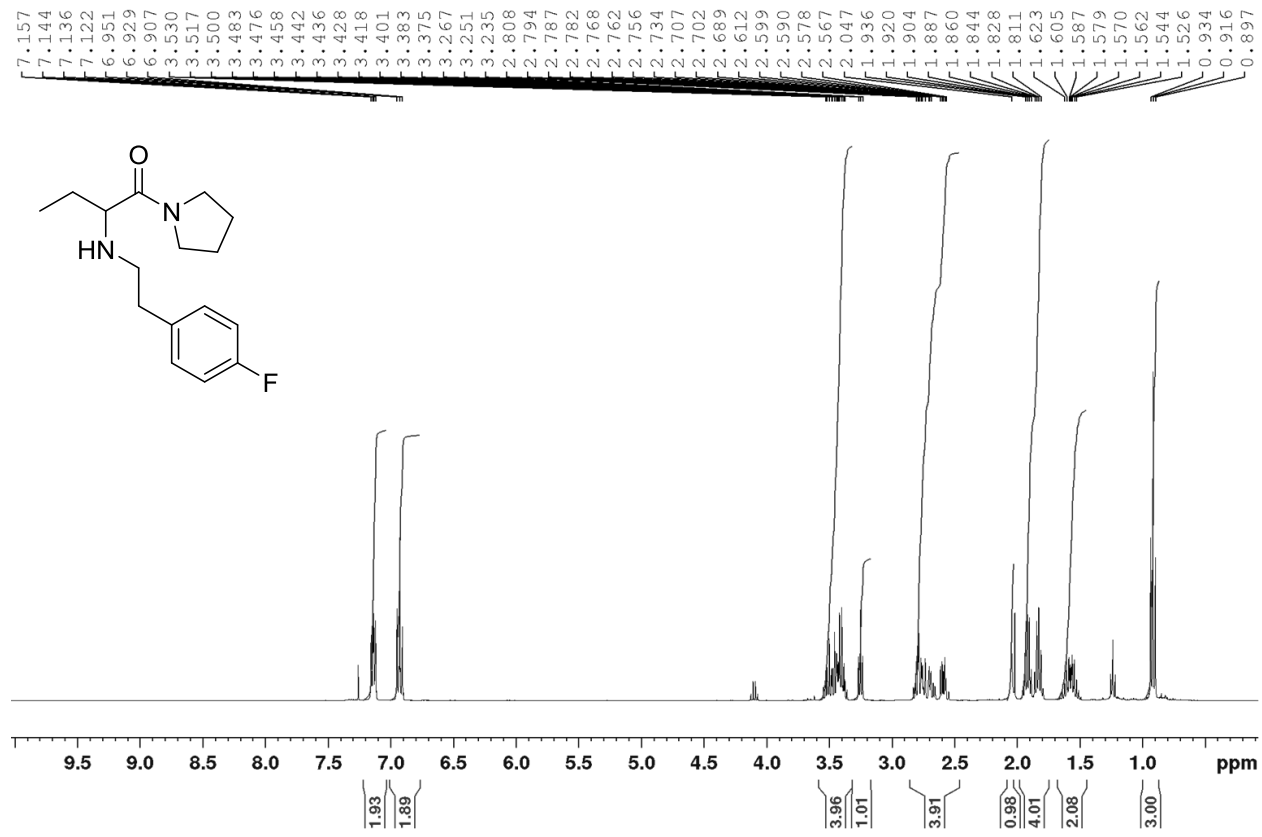


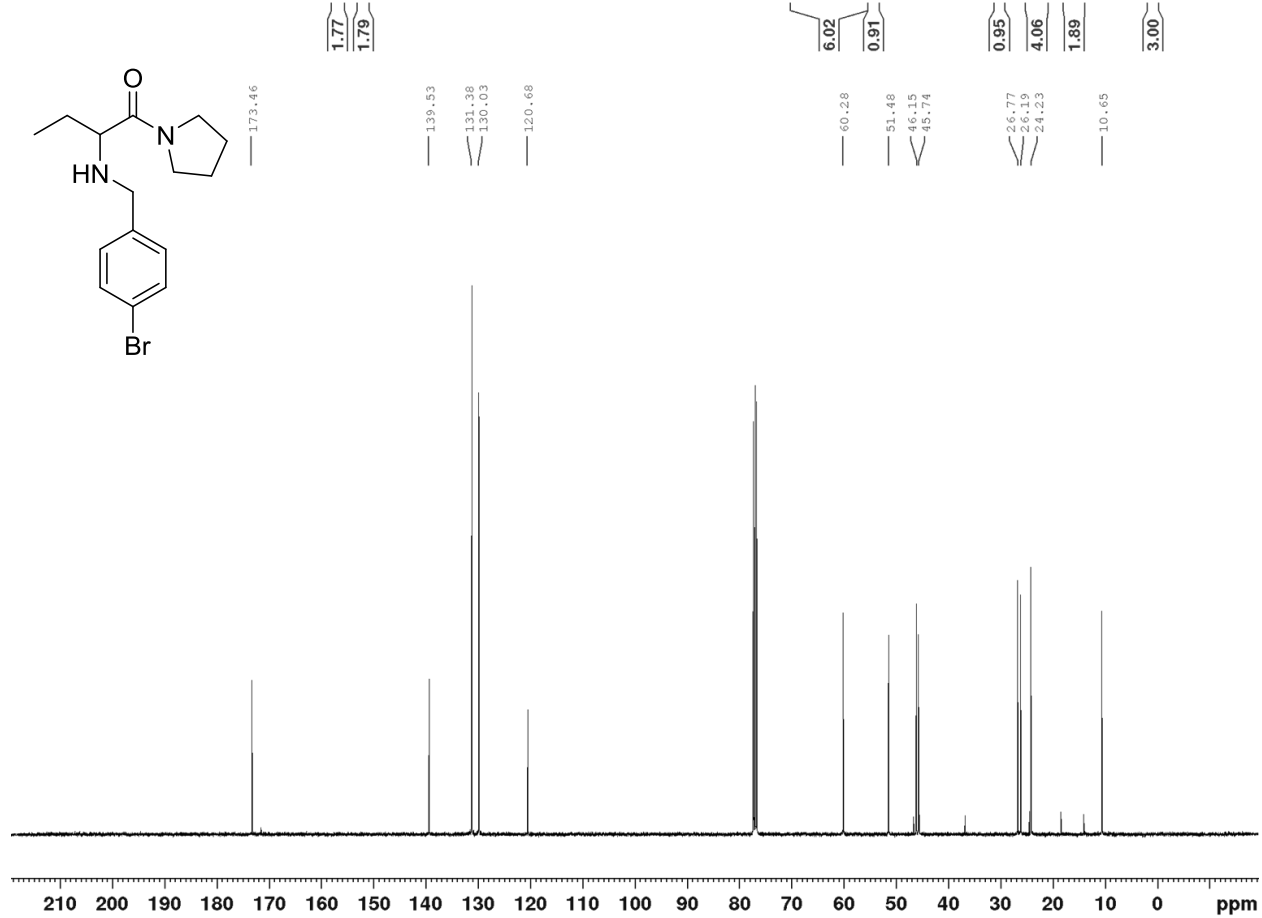
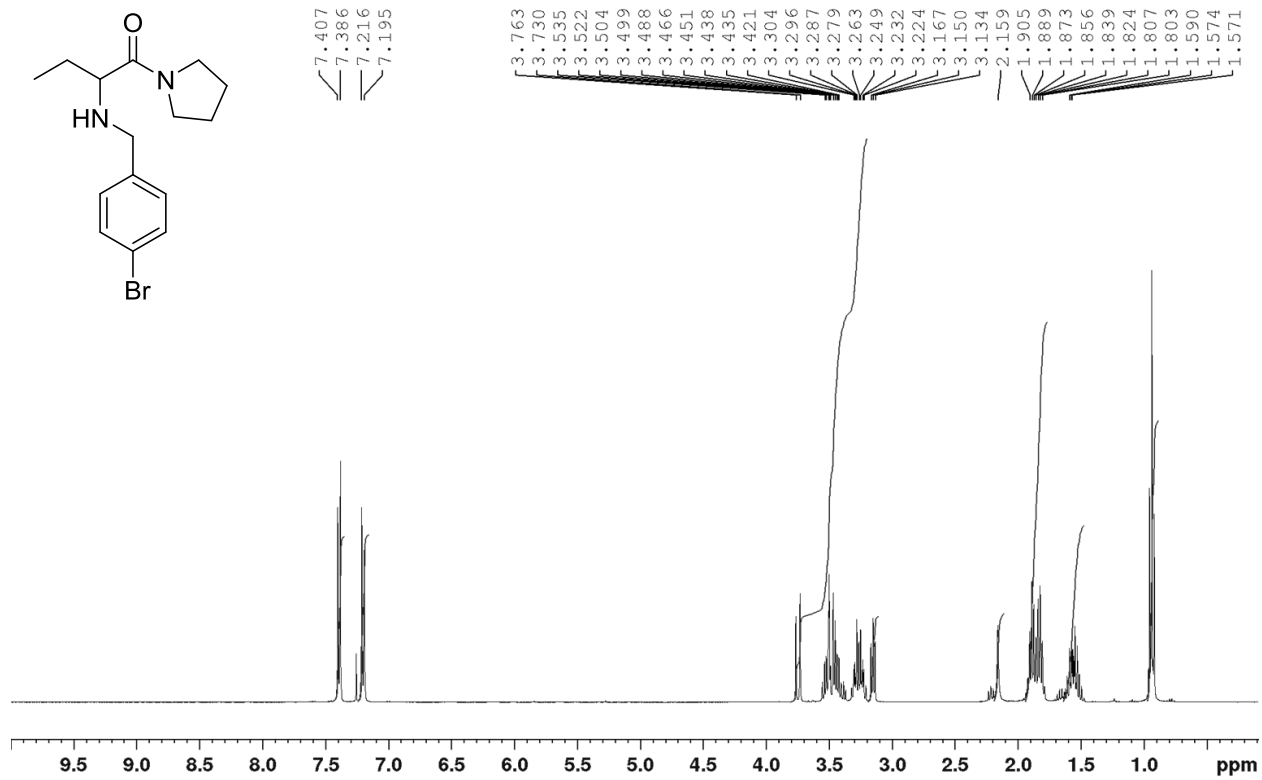


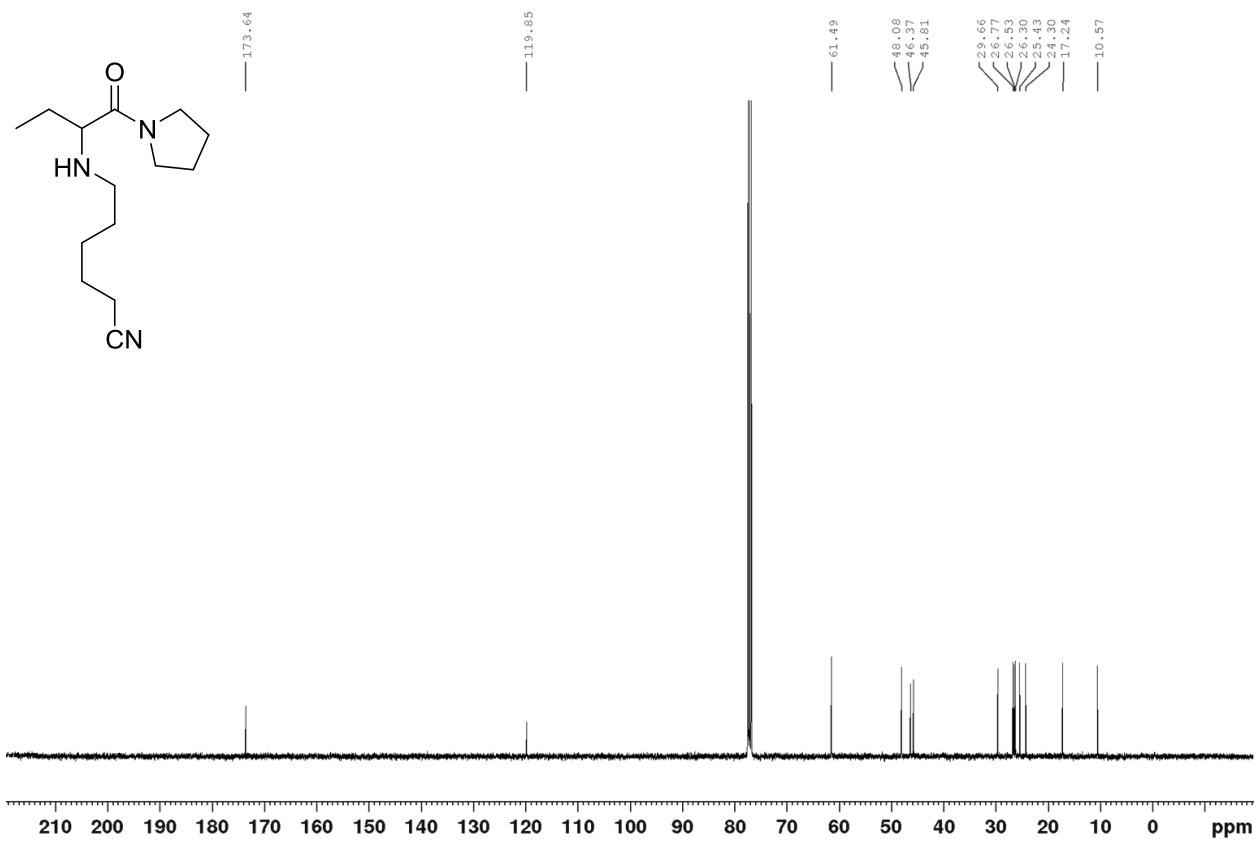
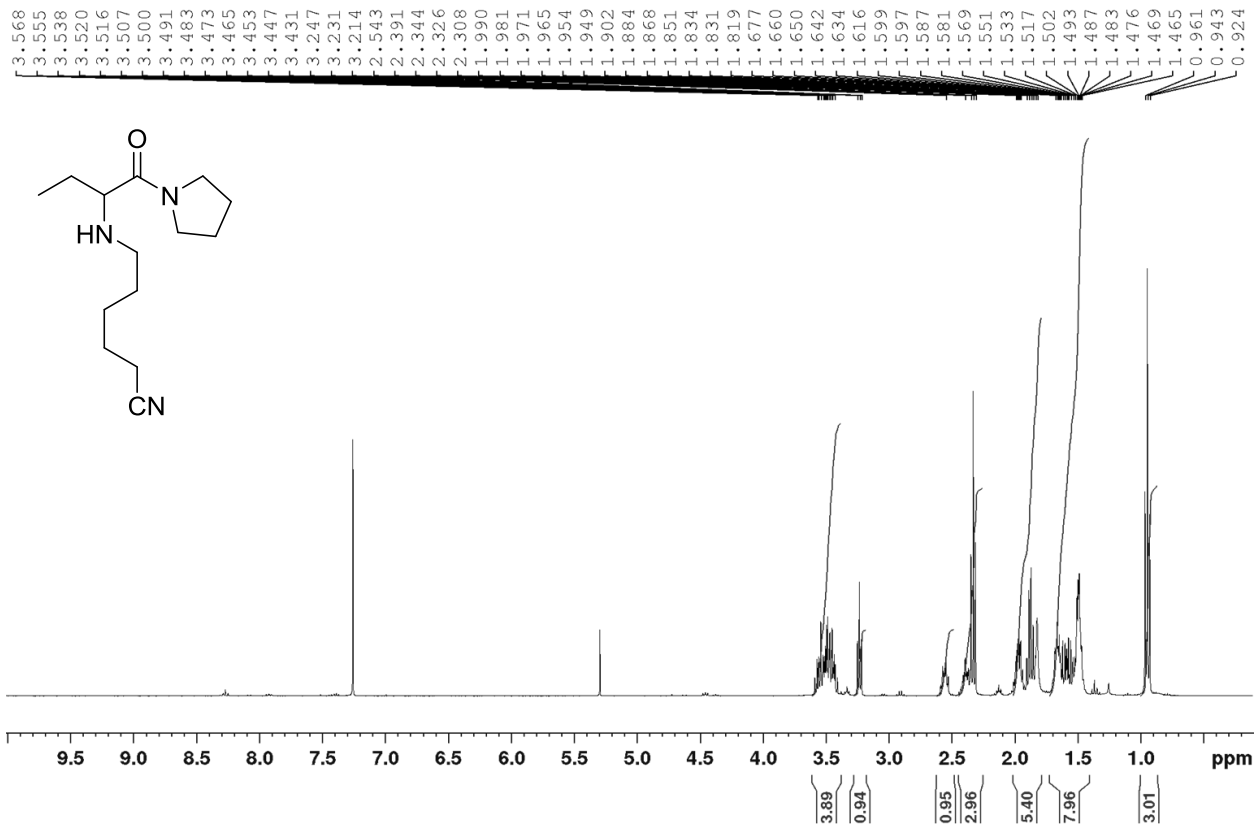


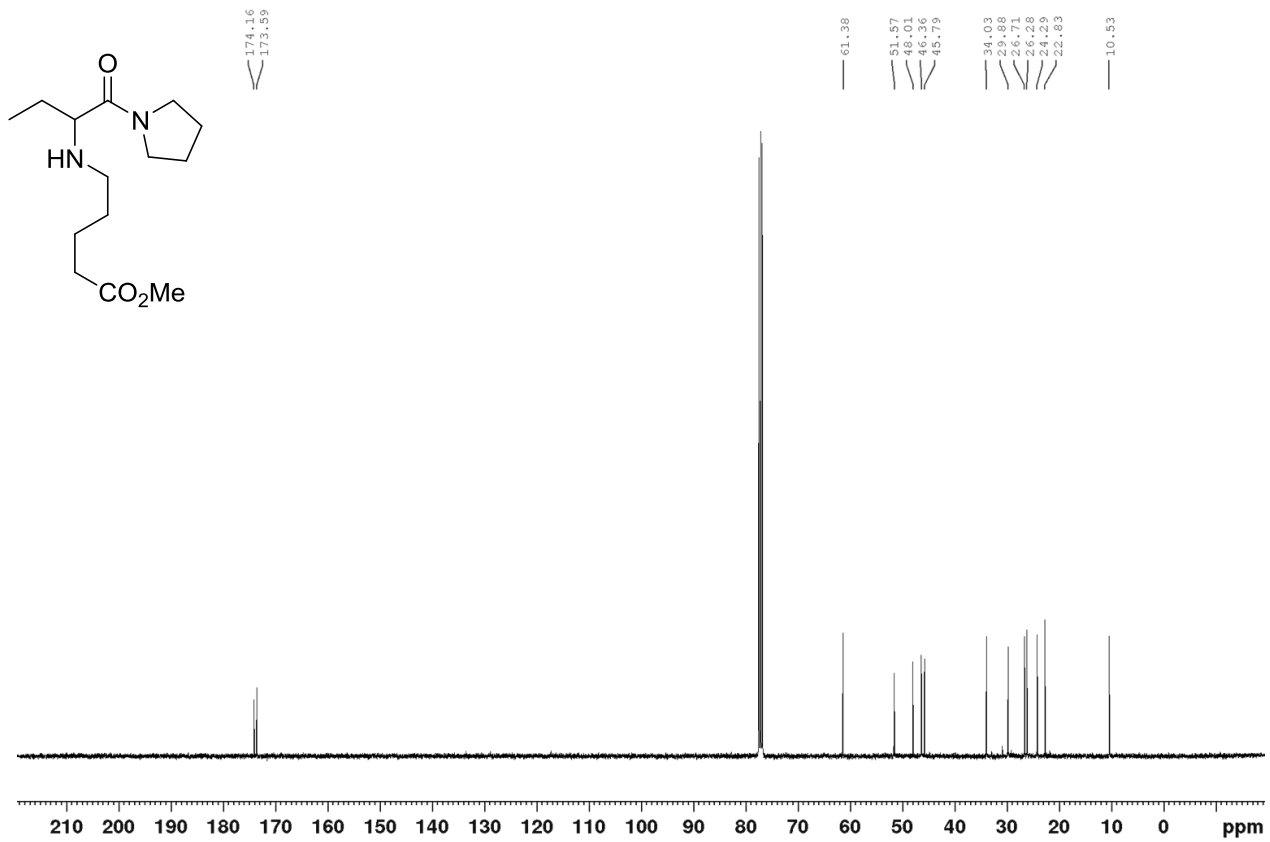
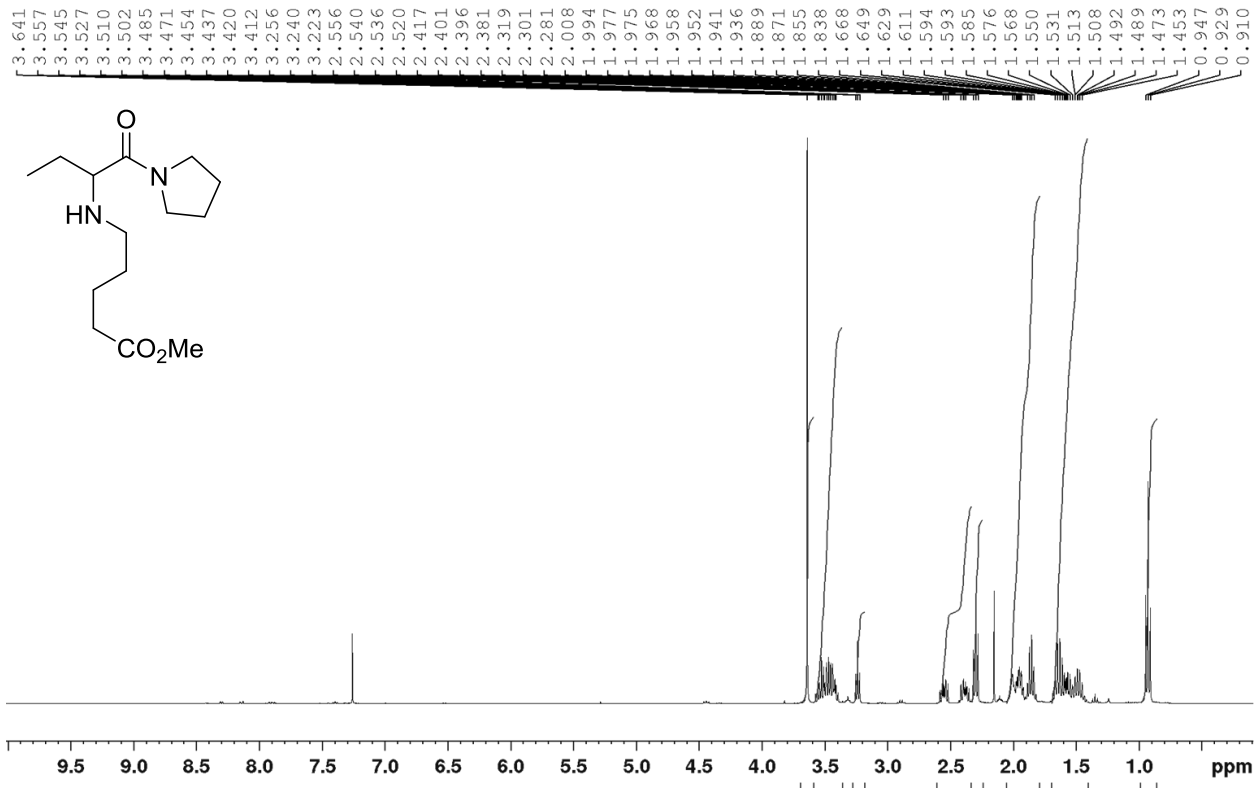


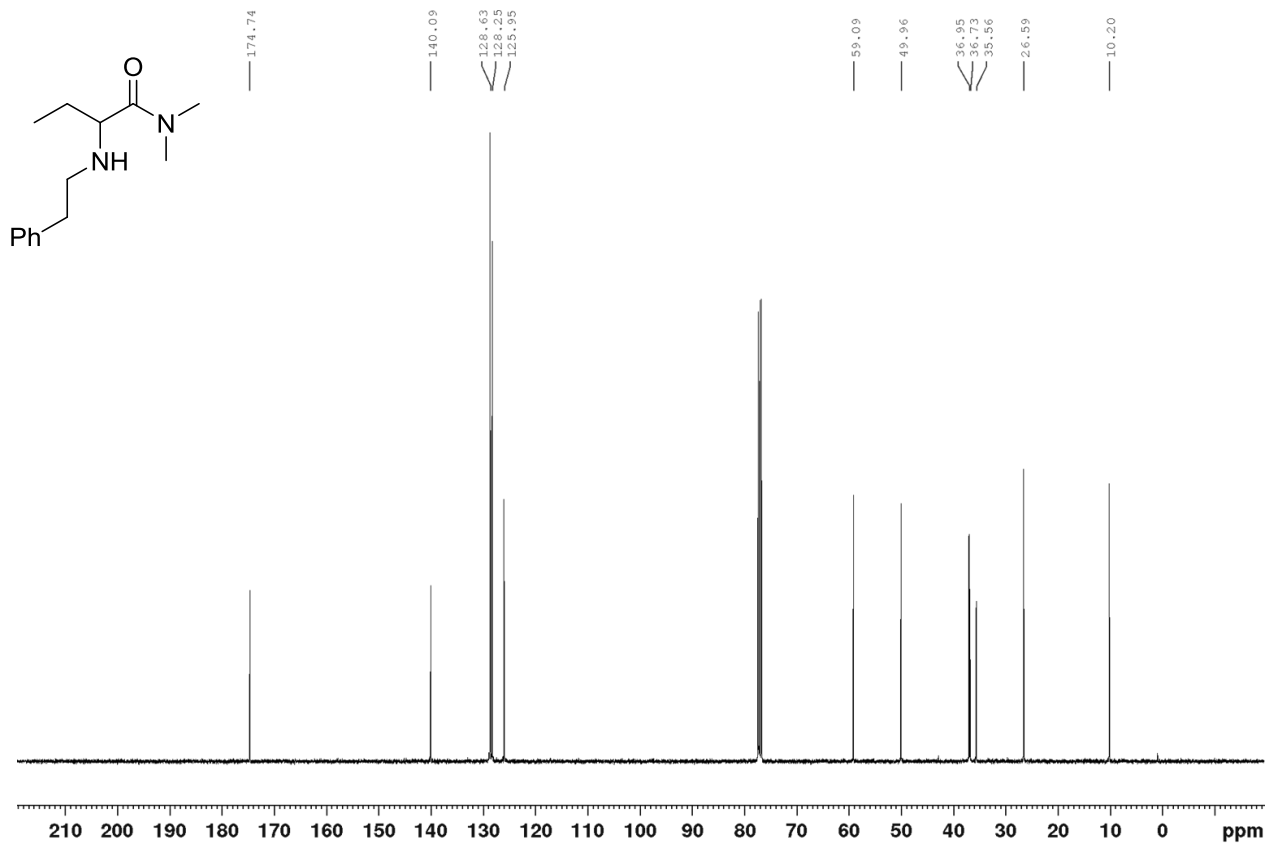
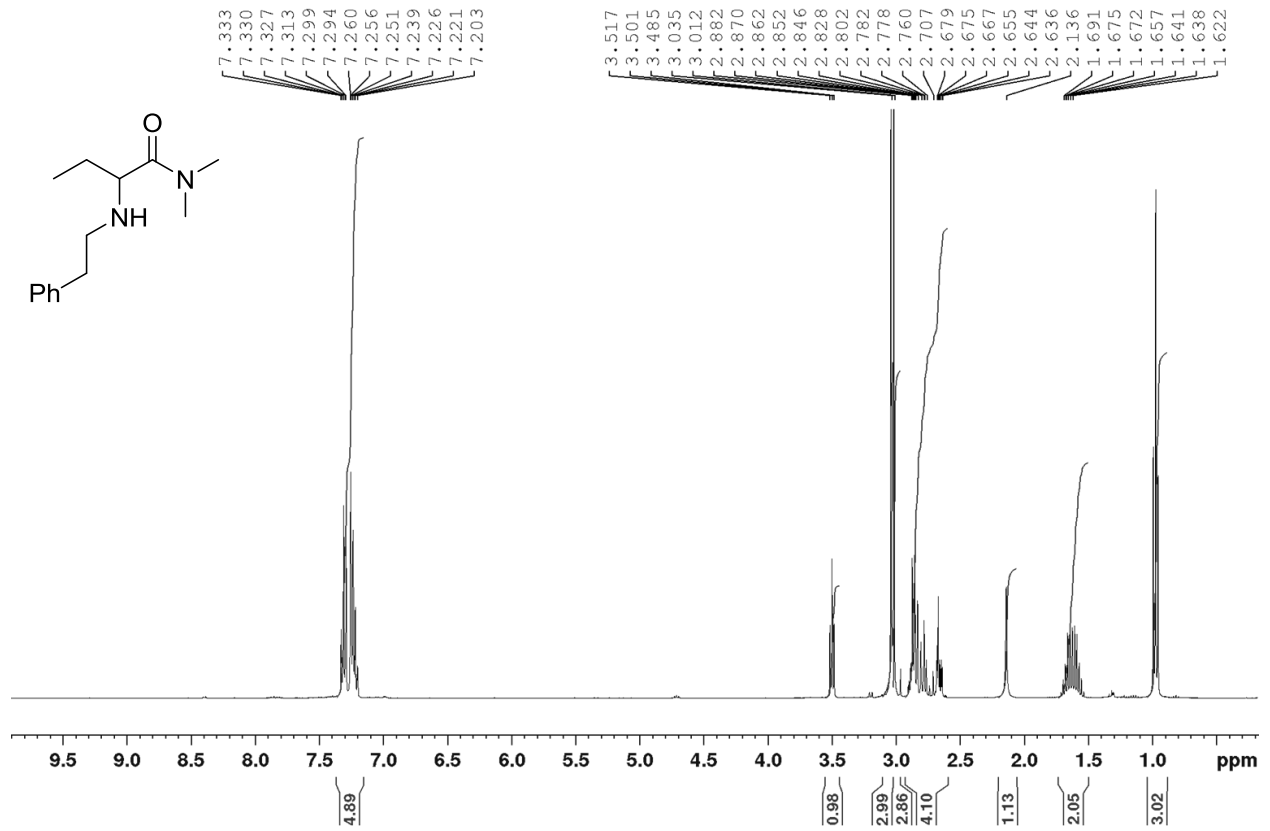


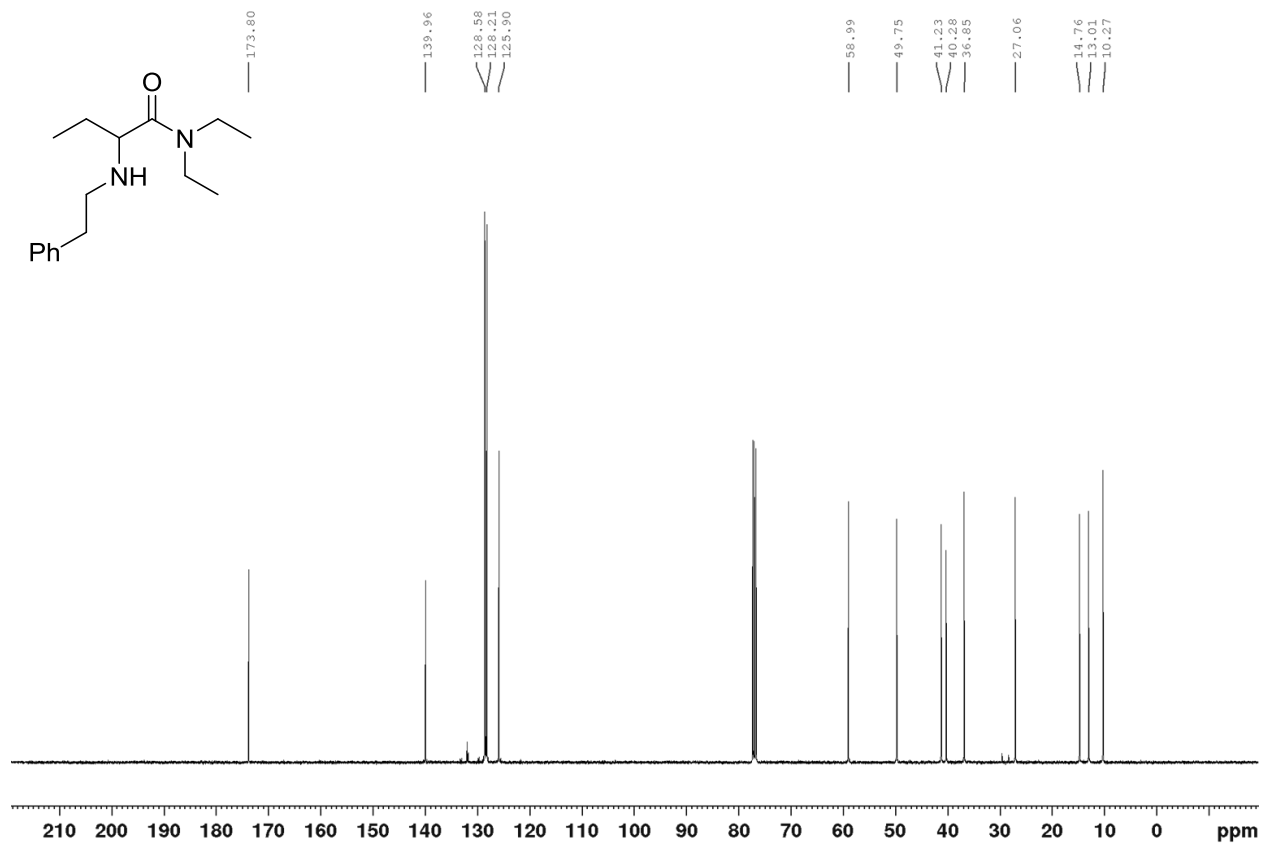
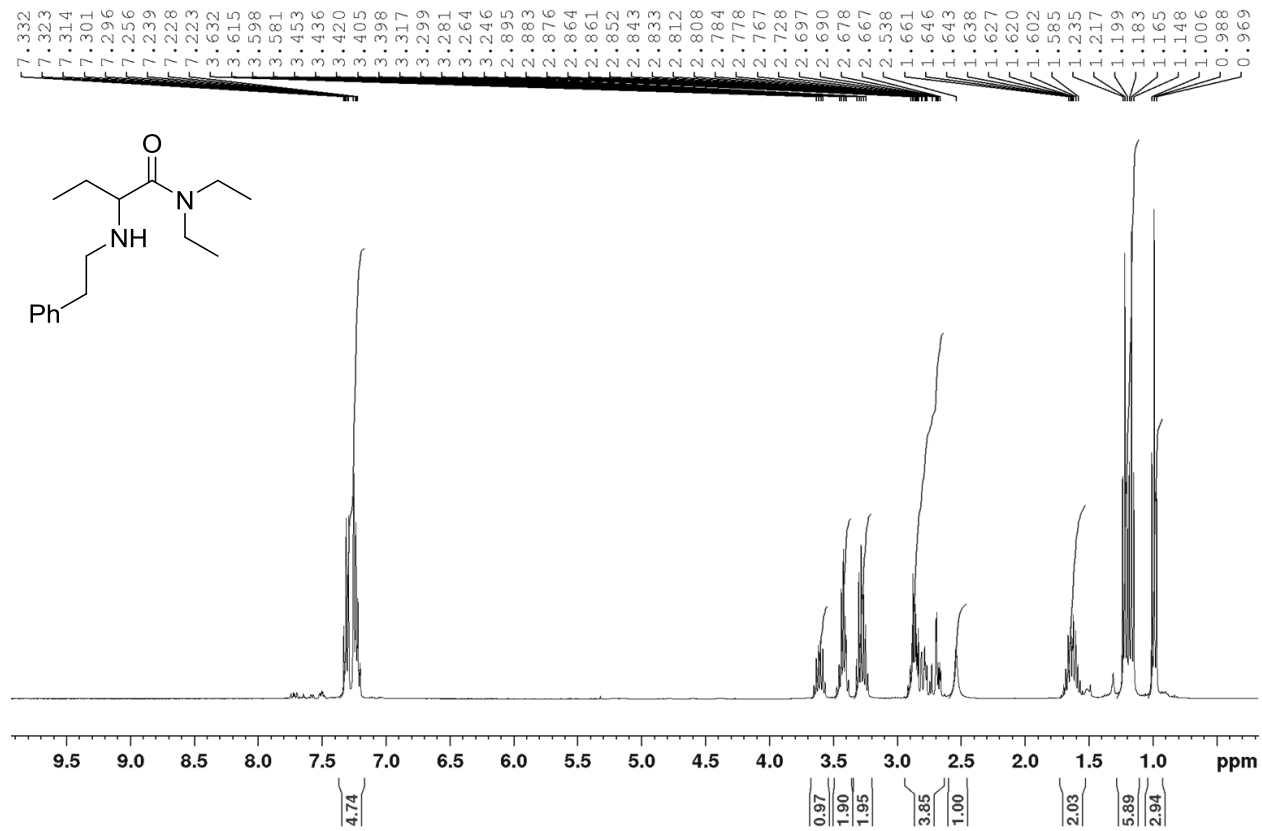


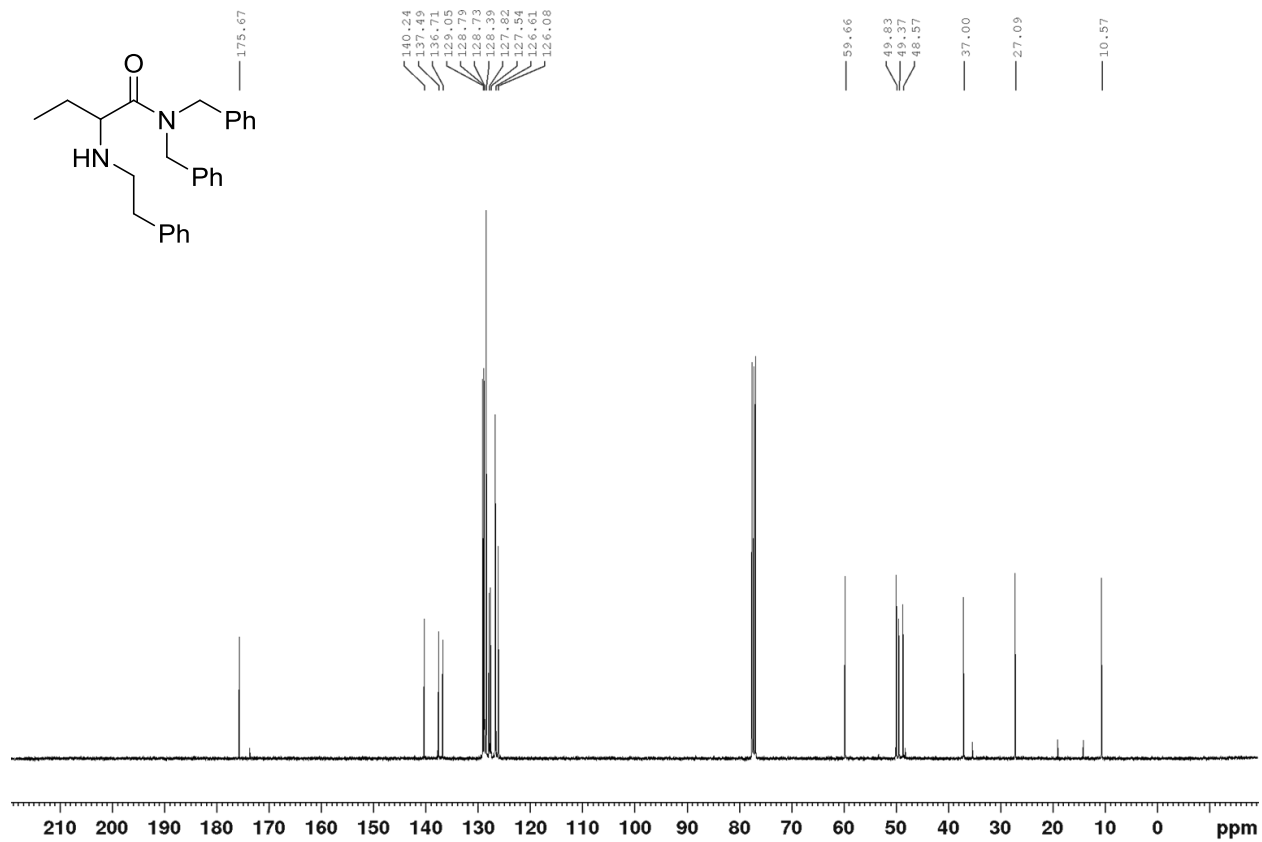
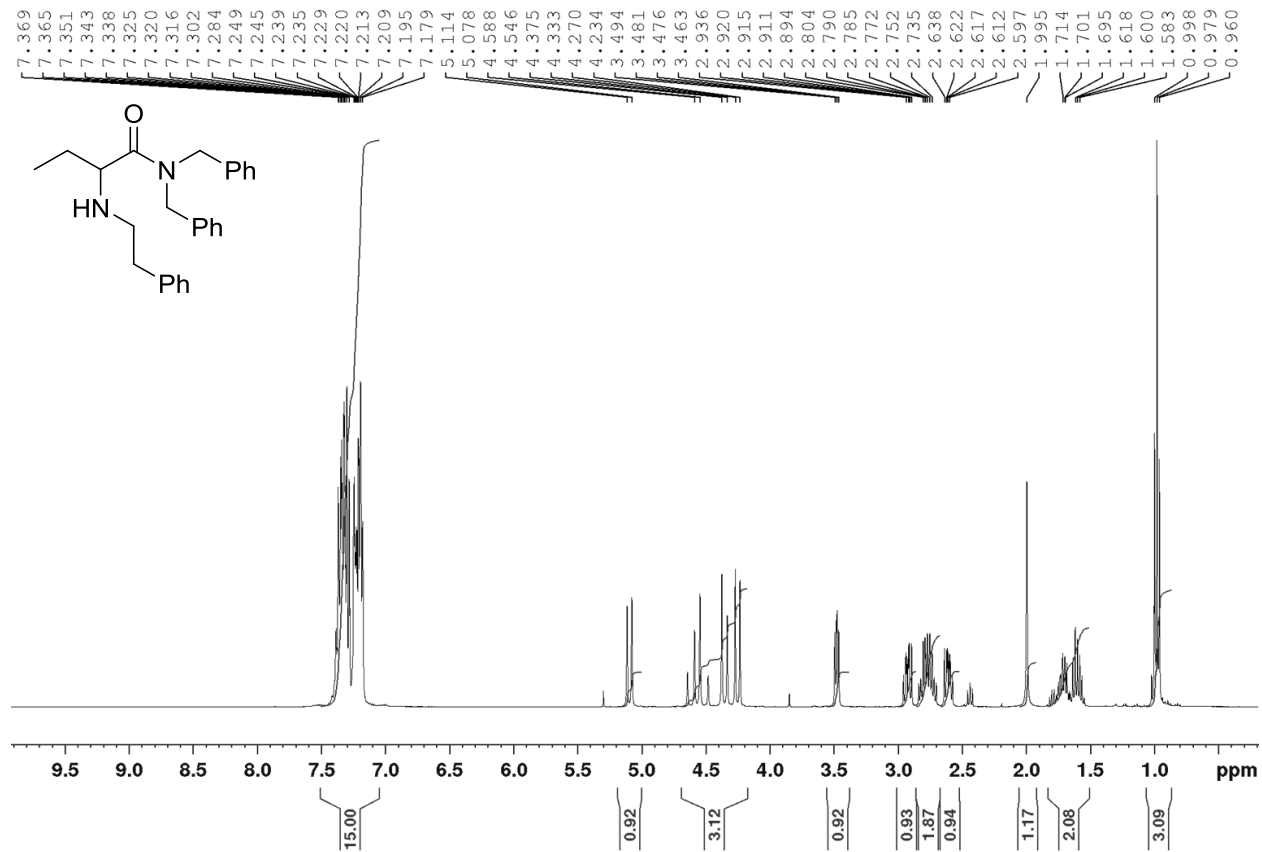


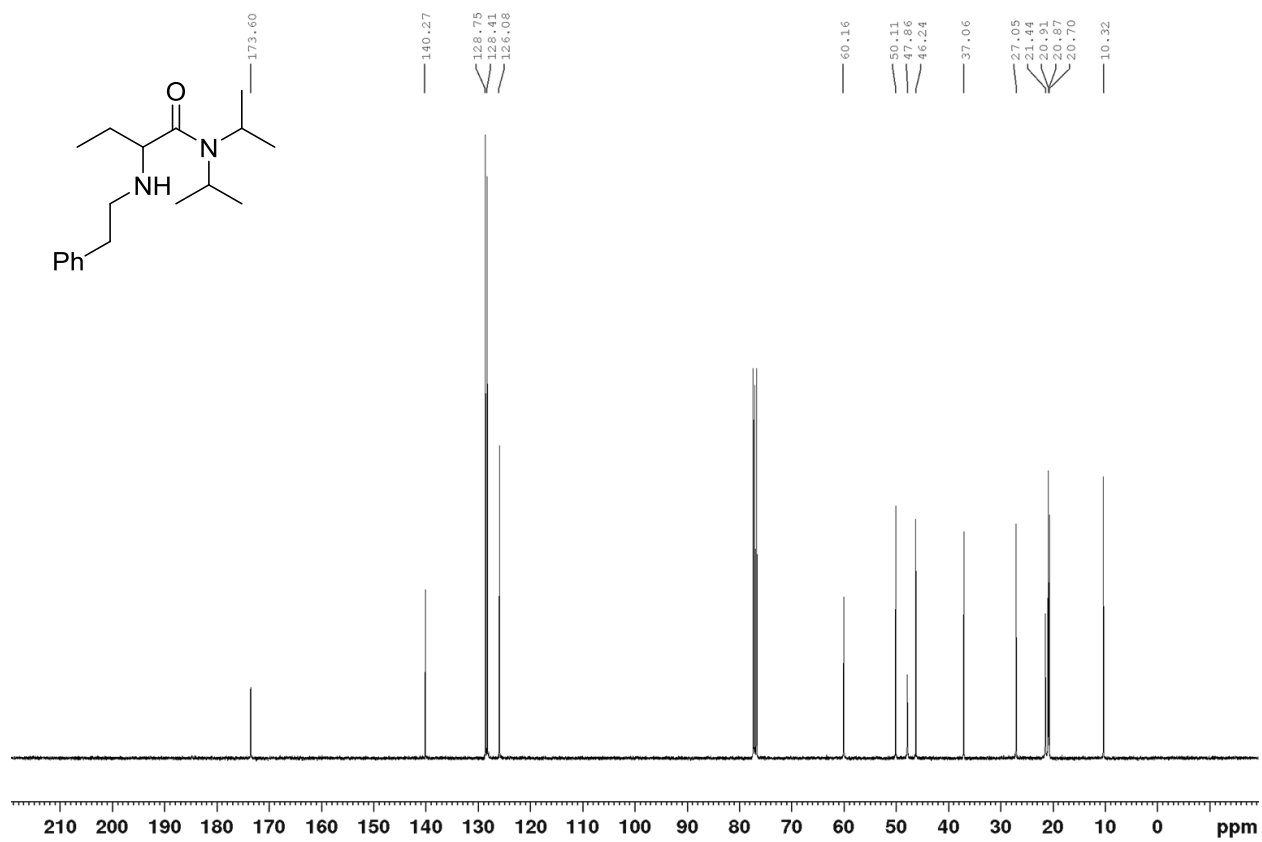
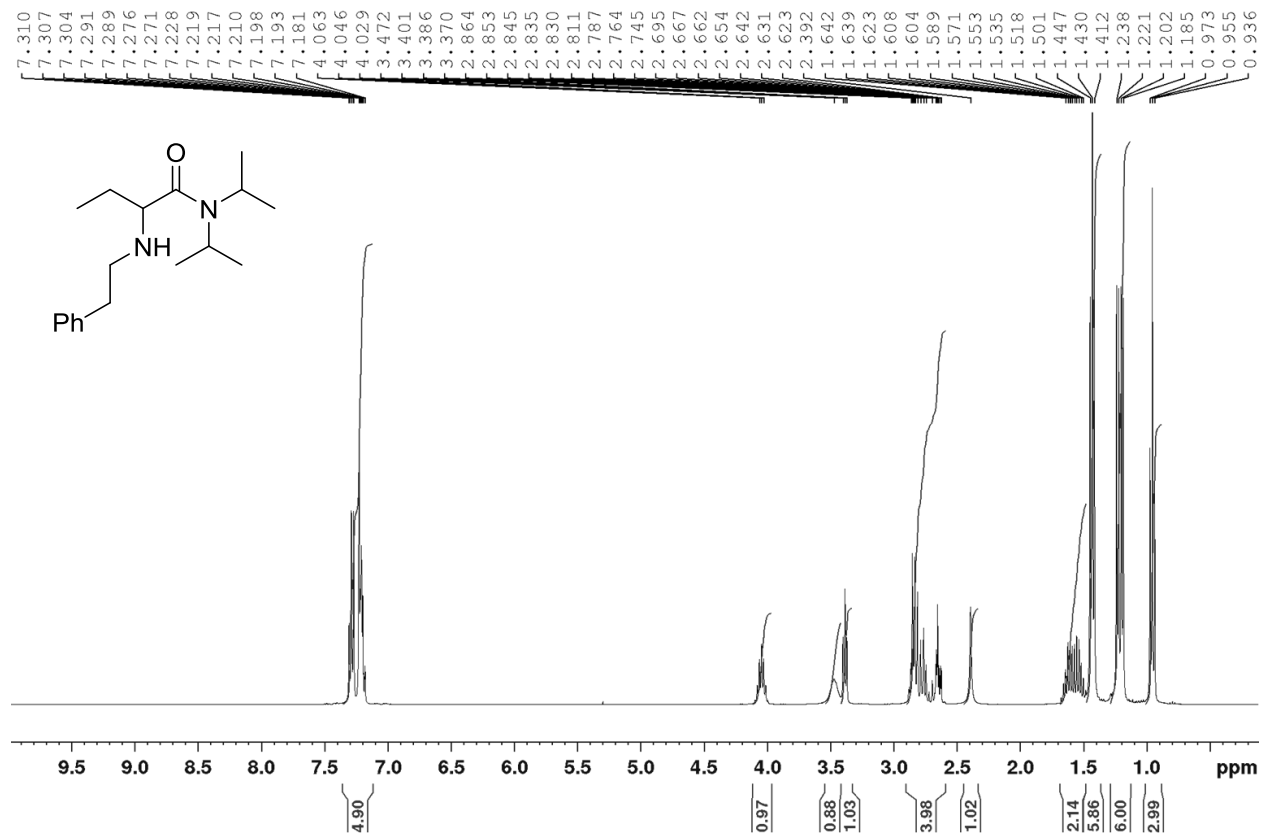


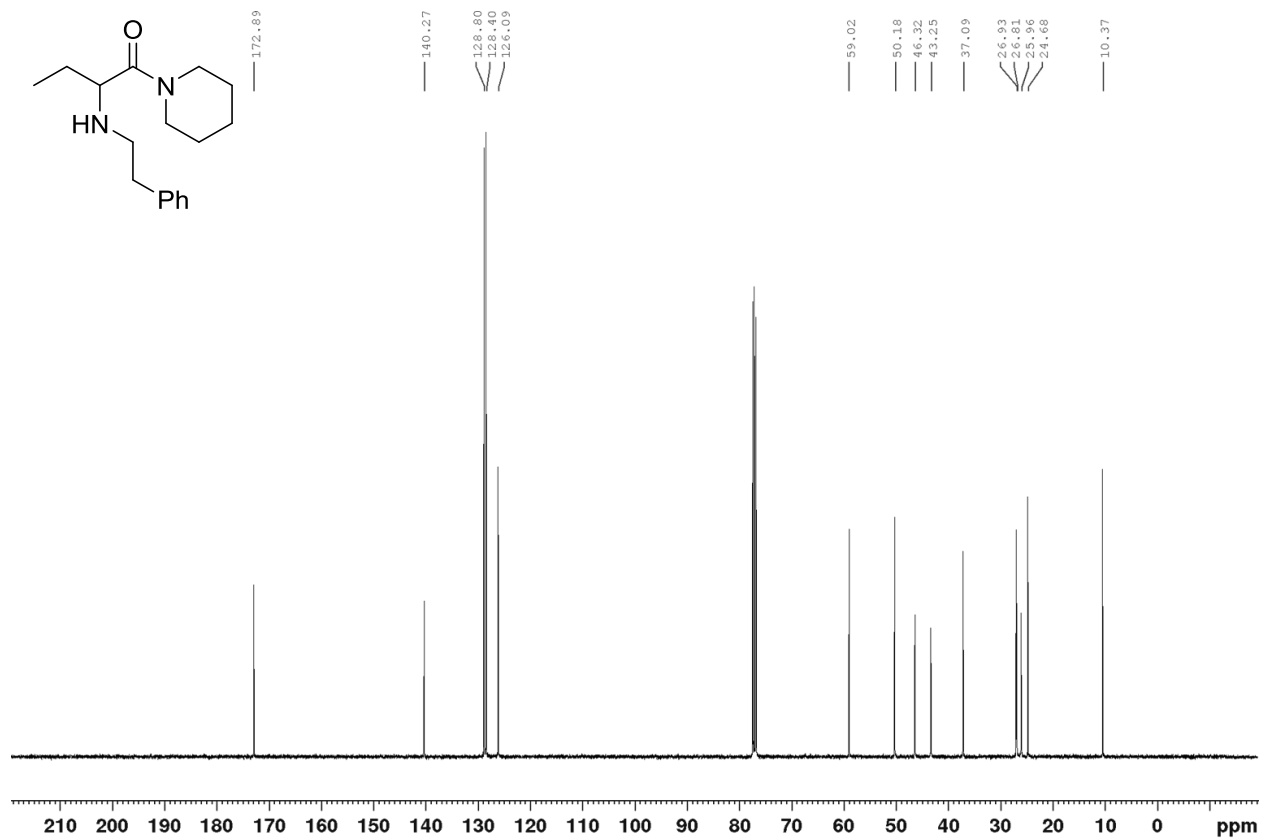
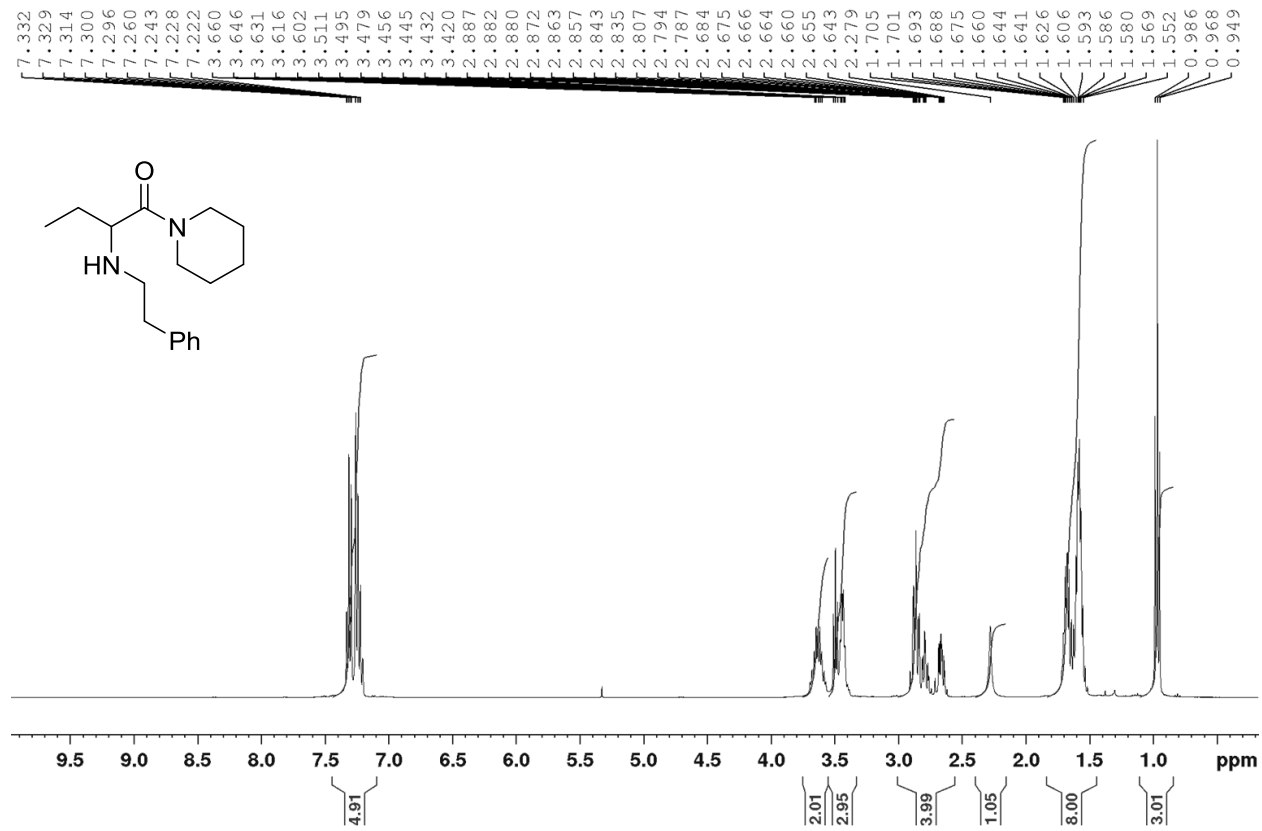


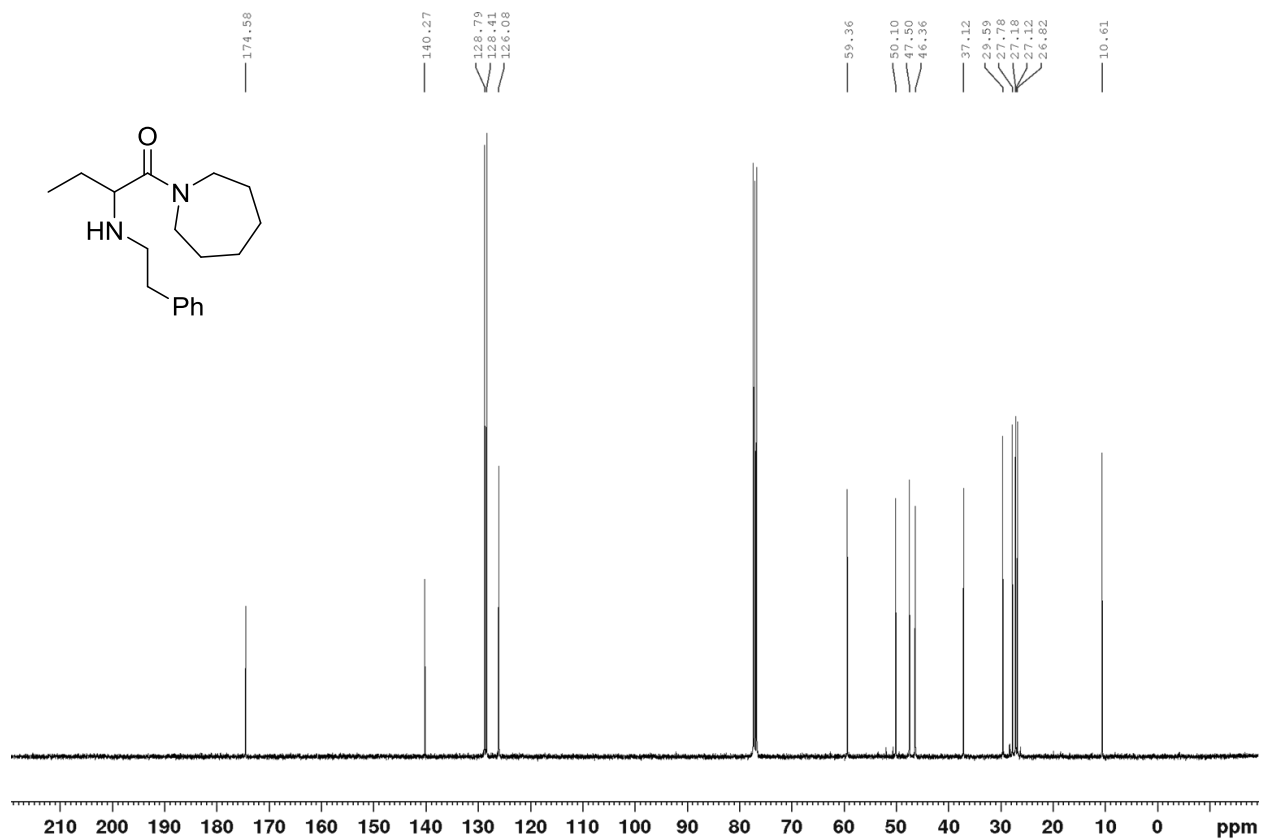
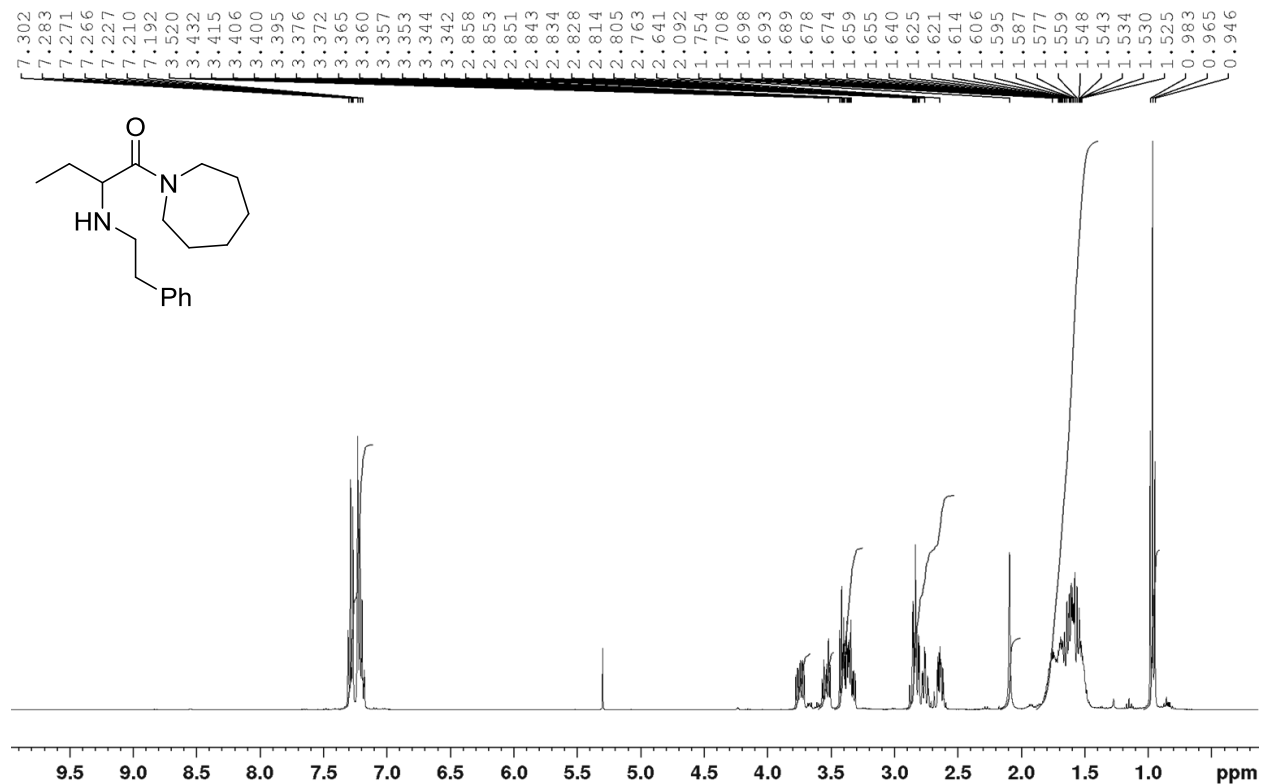


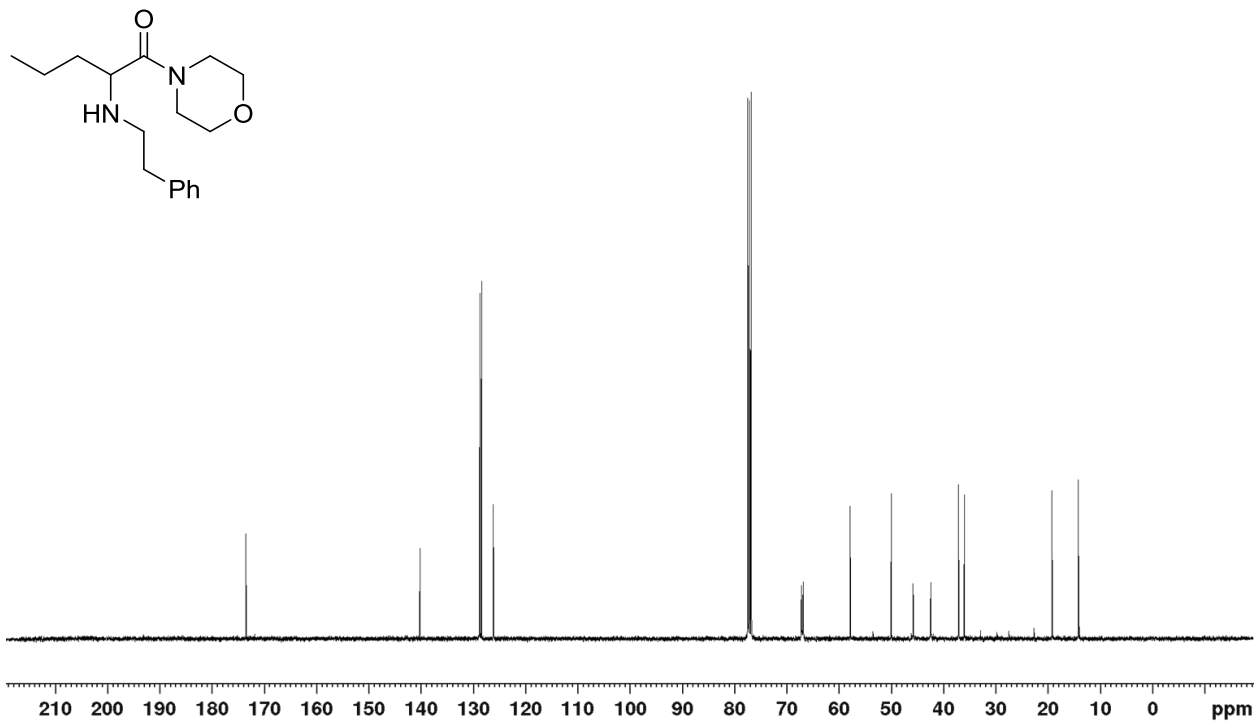
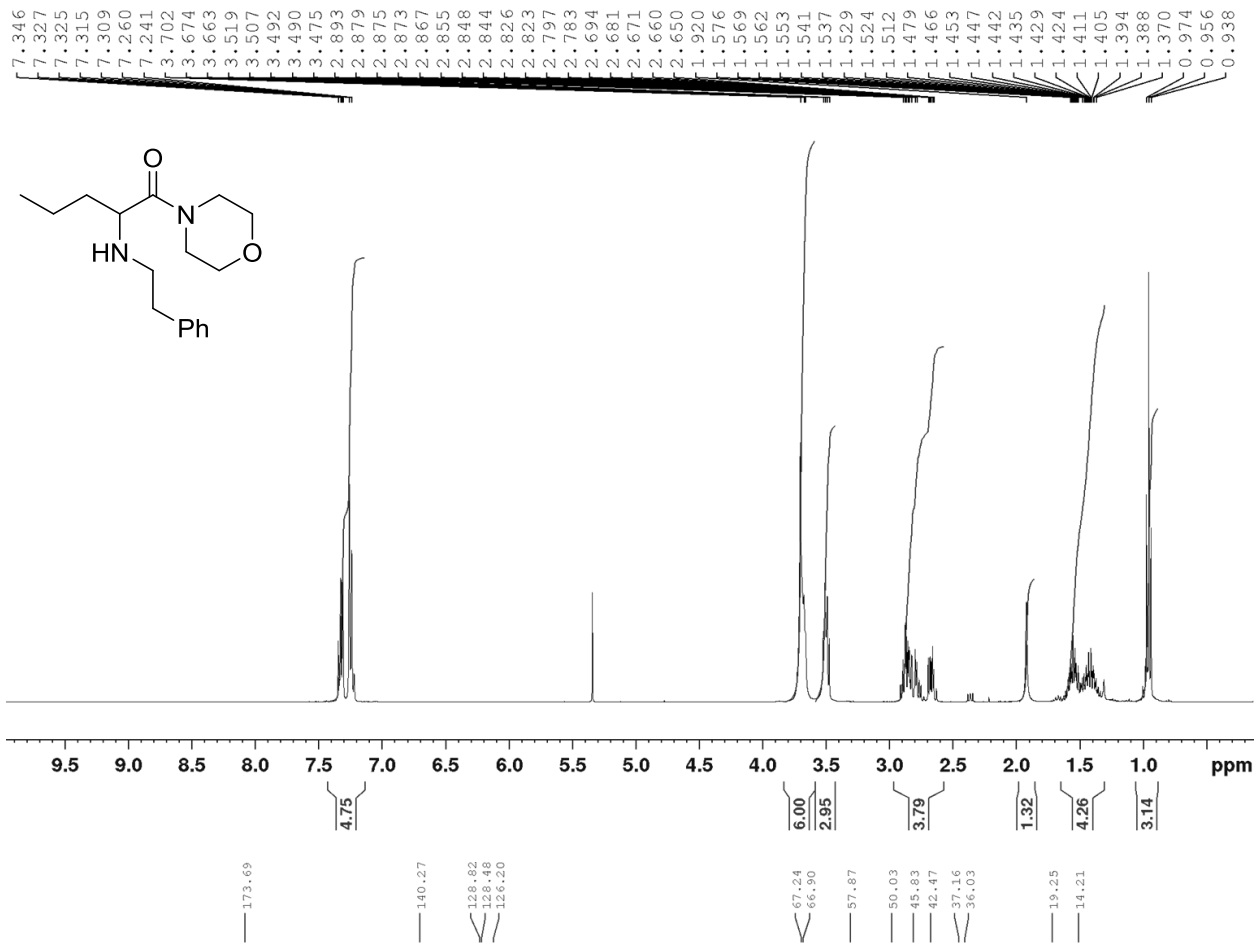


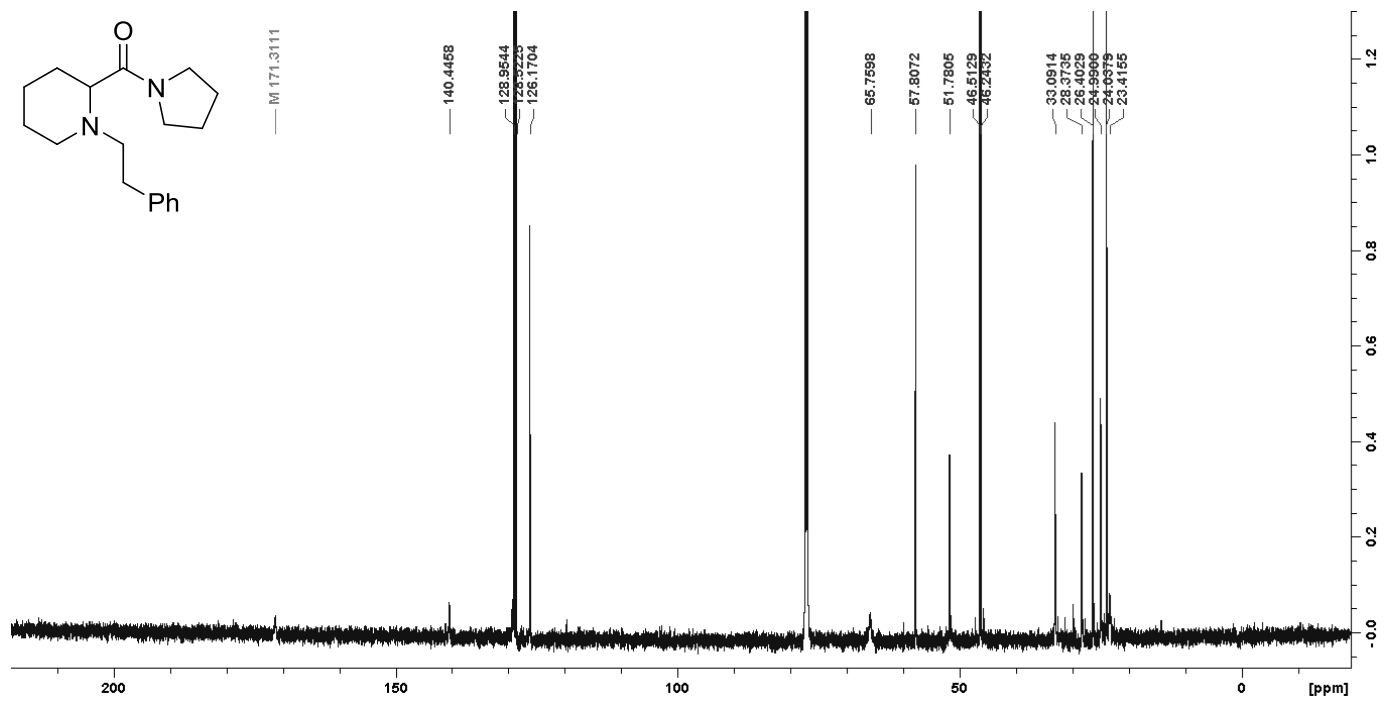
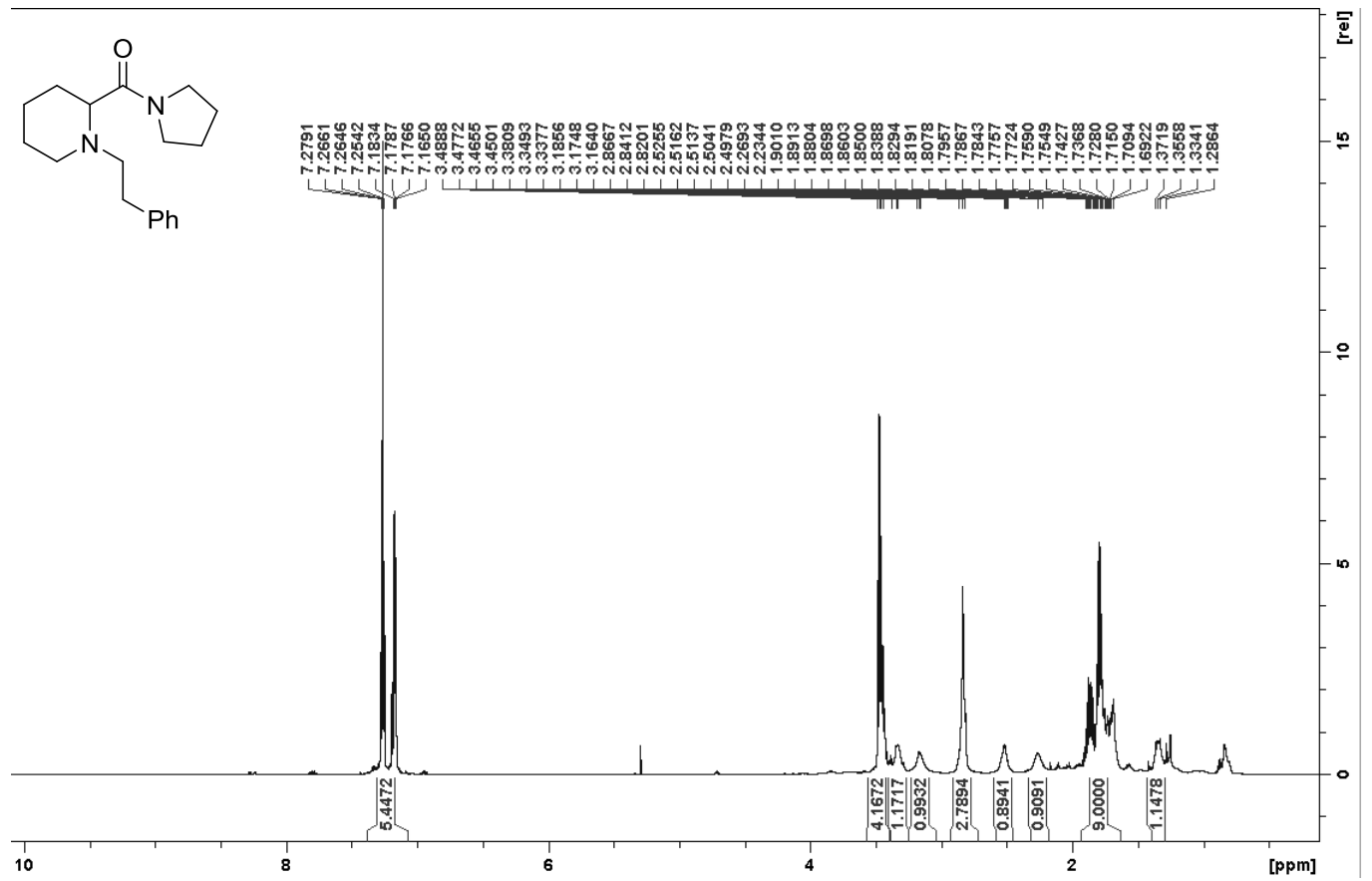


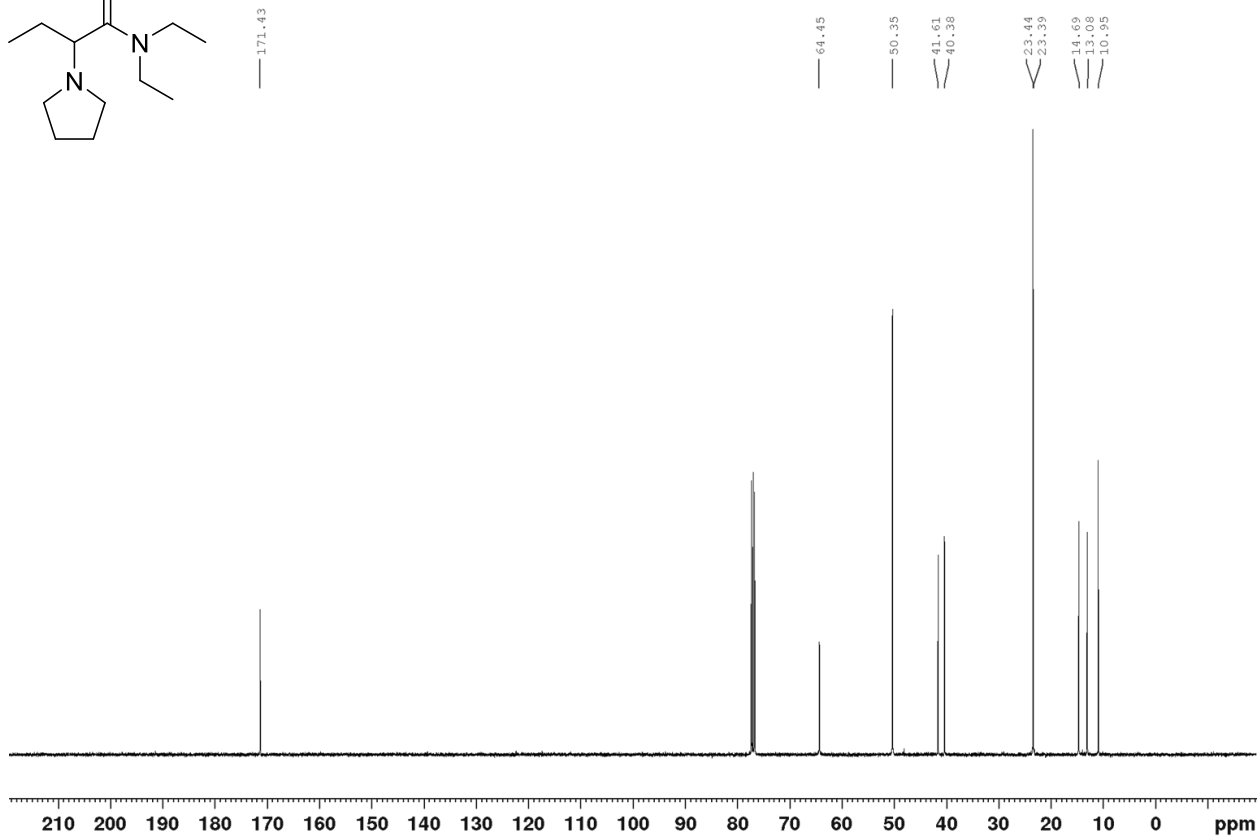
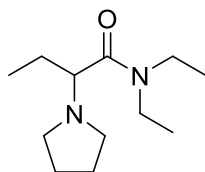
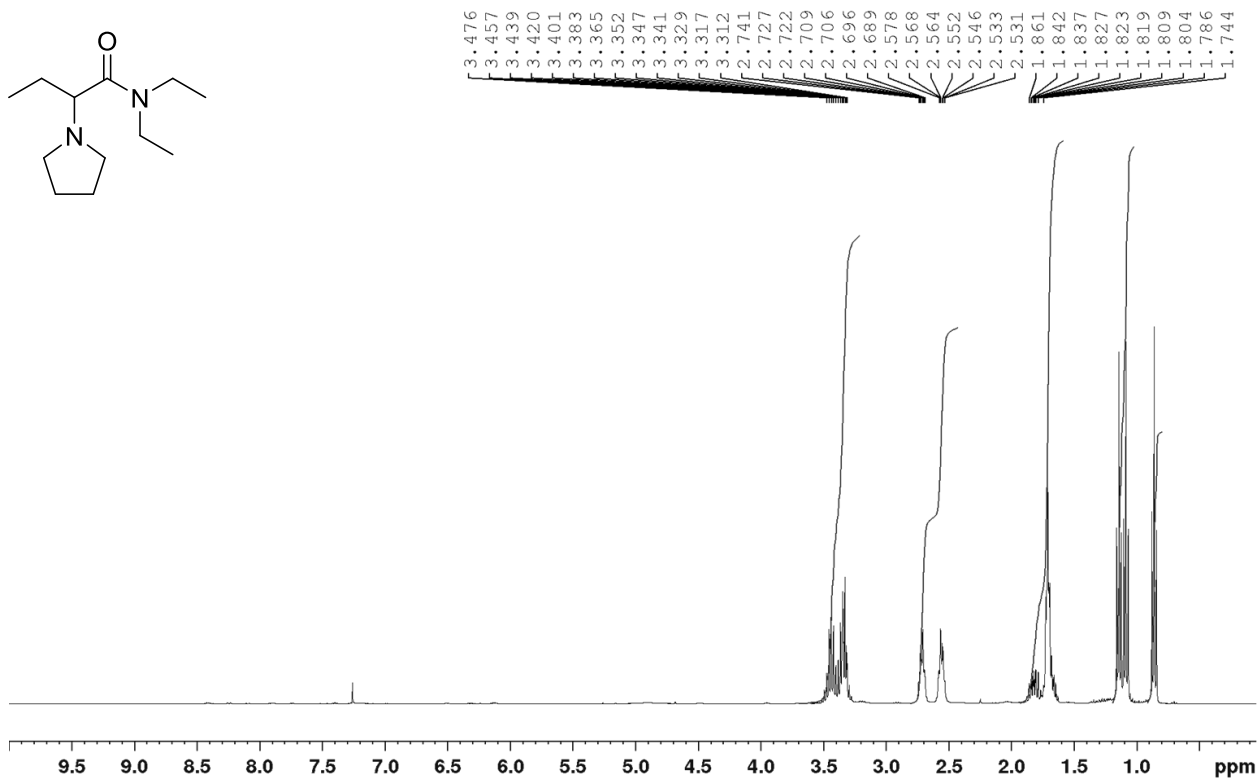
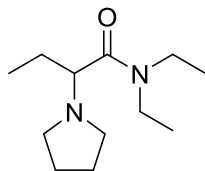


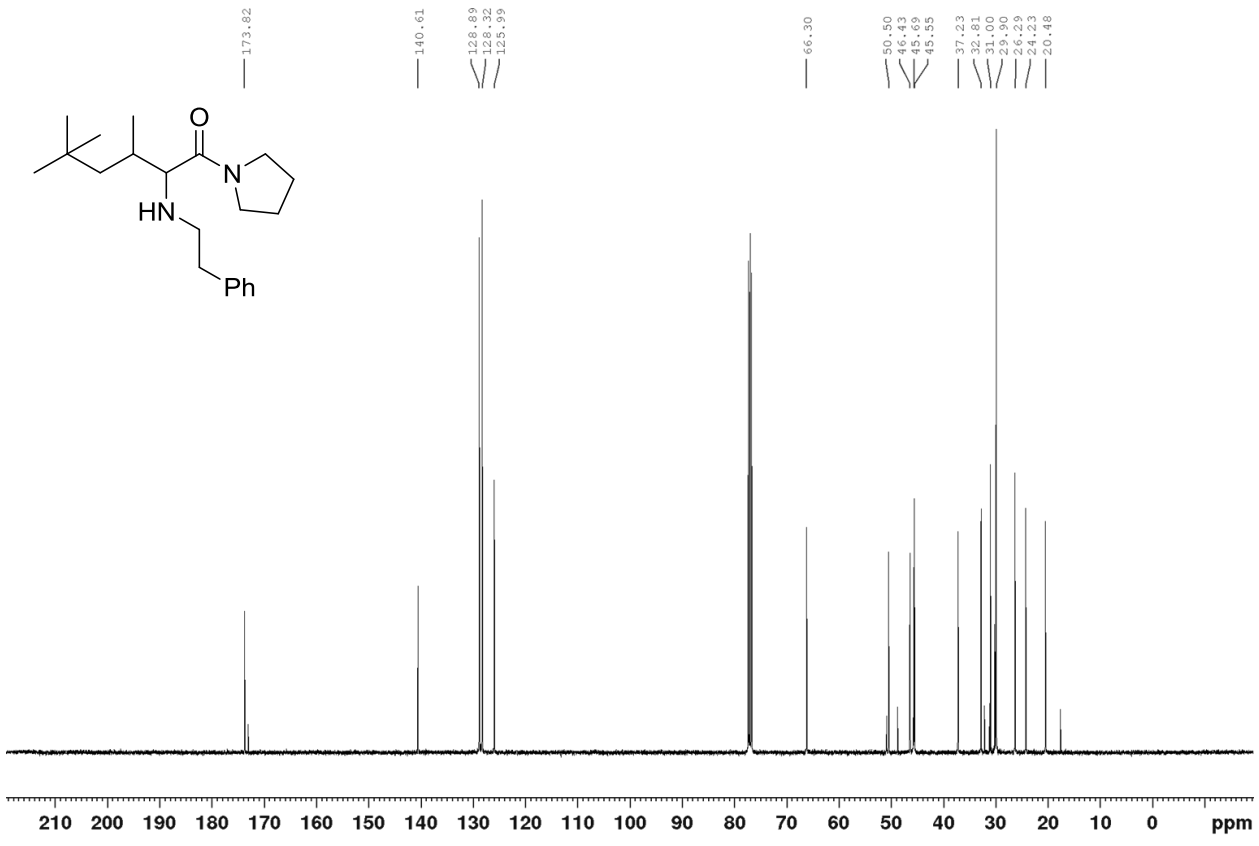
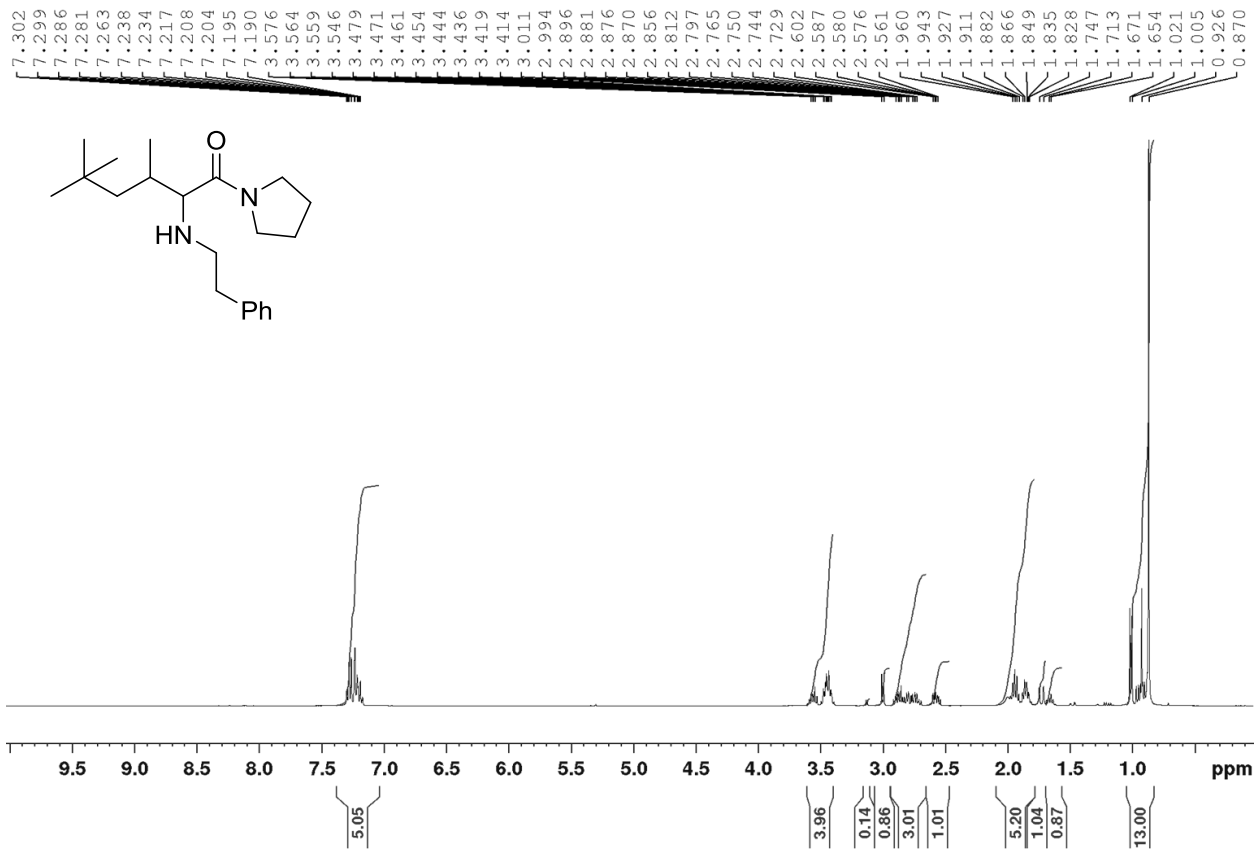




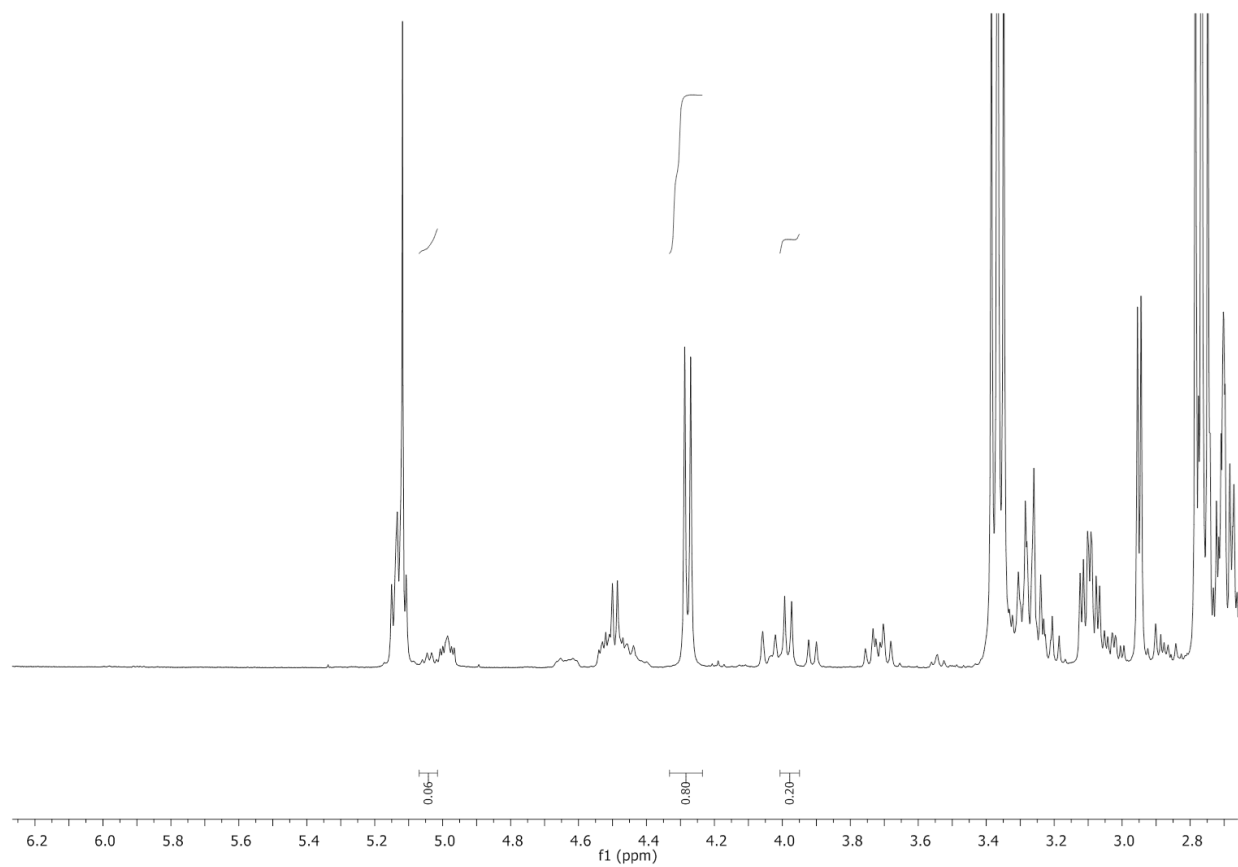




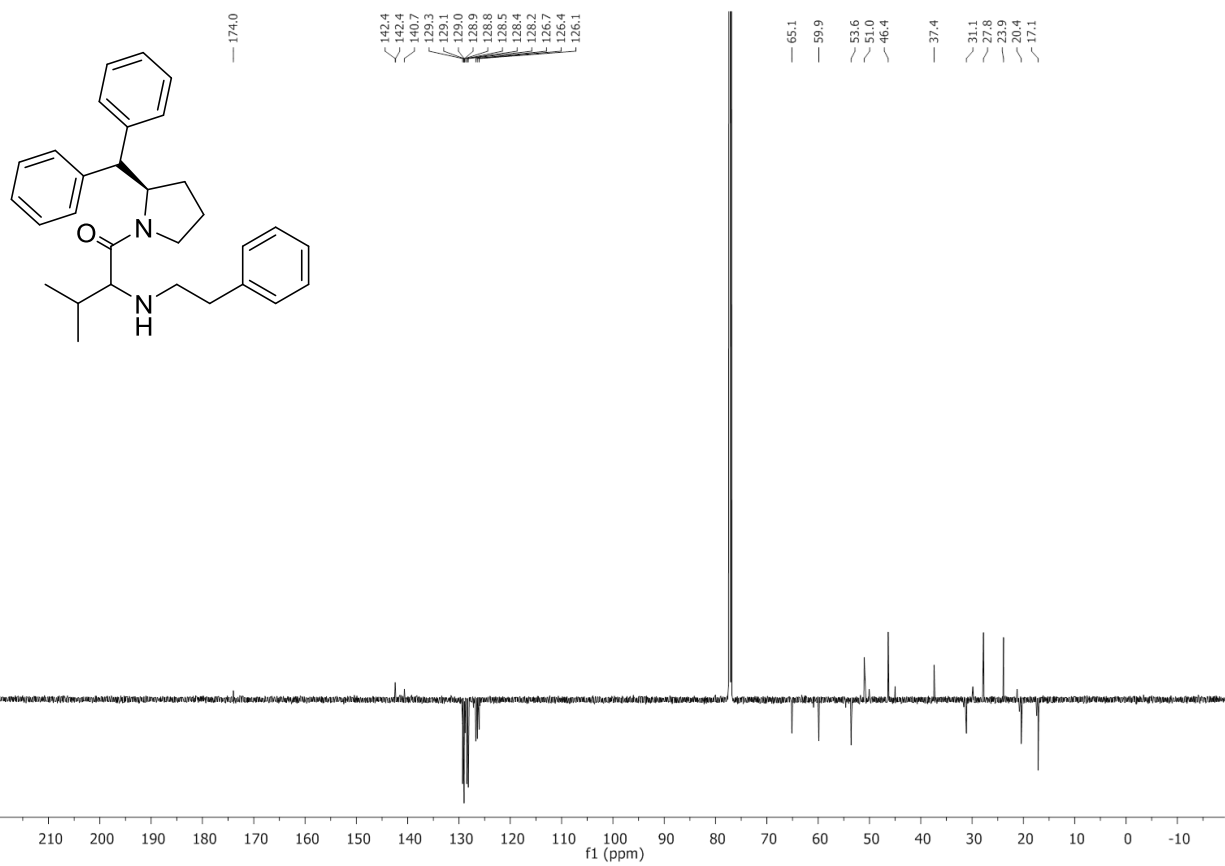
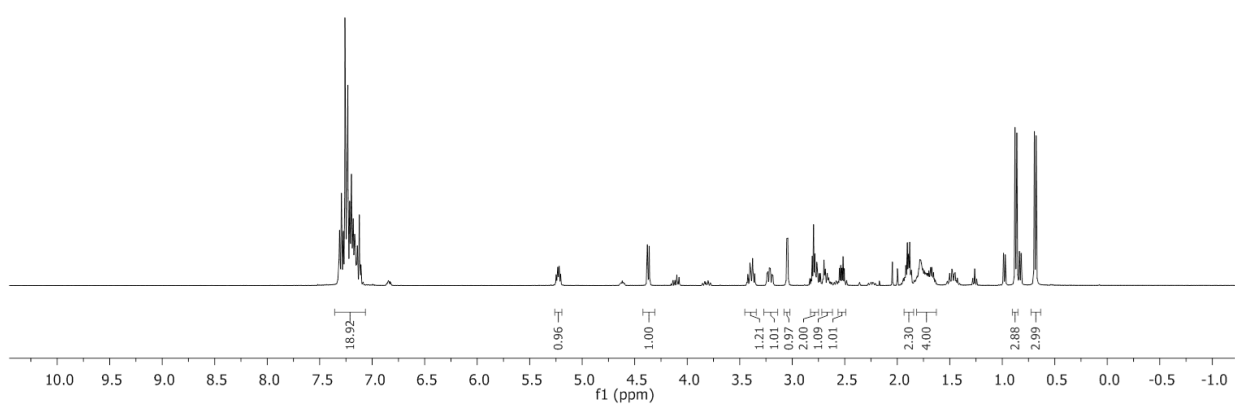
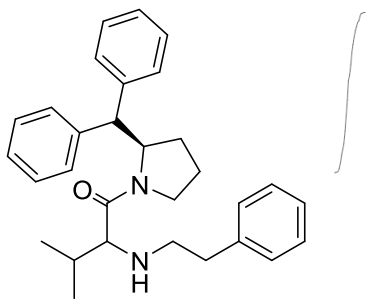


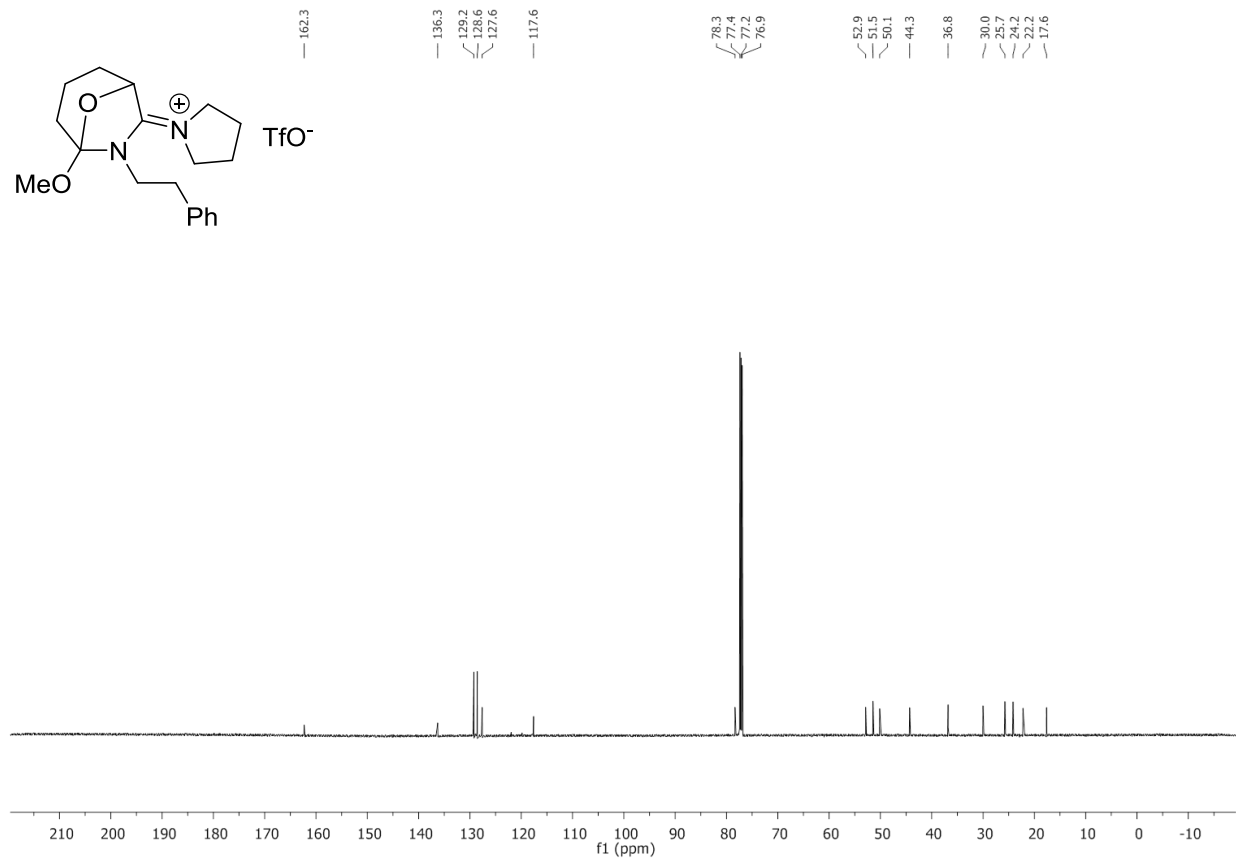
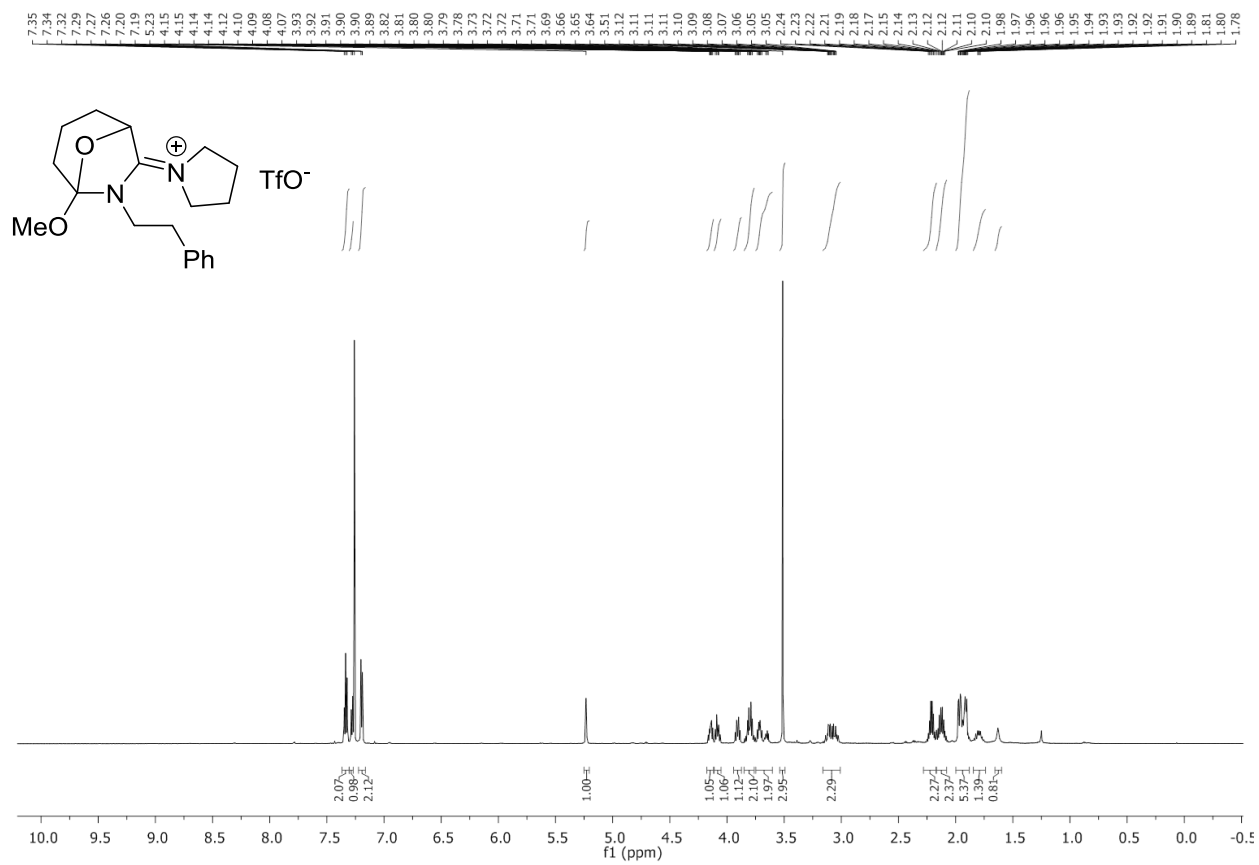


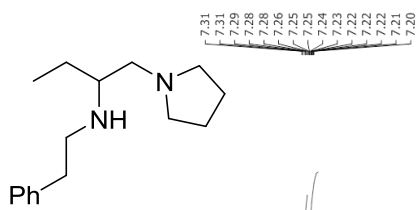
Determination of the d.r.



7.31 7.29 7.28 7.27 7.26 7.24 7.23 7.21 7.20 7.18 7.17 7.16 7.14 7.12 7.11 7.09 7.08 7.07 7.06 7.05 7.04 7.03 7.02 7.01 7.00 6.99 6.98 6.97 6.96 6.95 6.94 6.93 6.92 6.91 6.90 6.89 6.88 6.87 6.86 6.85 6.84 6.83 6.82 6.81 6.80 6.79 6.78 6.77 6.76 6.75 6.74 6.73 6.72 6.71 6.70 6.69 6.68 6.67 6.66 6.65 6.64 6.63 6.62 6.61 6.60 6.59 6.58 6.57 6.56 6.55 6.54 6.53 6.52 6.51 6.50 6.49 6.48 6.47 6.46 6.45 6.44 6.43 6.42 6.41 6.40 6.39 6.38 6.37 6.36 6.35 6.34 6.33 6.32 6.31 6.30 6.29 6.28 6.27 6.26 6.25 6.24 6.23 6.22 6.21 6.20 6.19 6.18 6.17 6.16 6.15 6.14 6.13 6.12 6.11 6.10 6.09 6.08 6.07 6.06 6.05 6.04 6.03 6.02 6.01 6.00 5.99 5.98 5.97 5.96 5.95 5.94 5.93 5.92 5.91 5.90 5.89 5.88 5.87 5.86 5.85 5.84 5.83 5.82 5.81 5.80 5.79 5.78 5.77 5.76 5.75 5.74 5.73 5.72 5.71 5.70 5.69 5.68 5.67 5.66 5.65 5.64 5.63 5.62 5.61 5.60 5.59 5.58 5.57 5.56 5.55 5.54 5.53 5.52 5.51 5.50 5.49 5.48 5.47 5.46 5.45 5.44 5.43 5.42 5.41 5.40 5.39 5.38 5.37 5.36 5.35 5.34 5.33 5.32 5.31 5.30 5.29 5.28 5.27 5.26 5.25 5.24 5.23 5.22 5.21 5.20 5.19 5.18 5.17 5.16 5.15 5.14 5.13 5.12 5.11 5.10 5.09 5.08 5.07 5.06 5.05 5.04 5.03 5.02 5.01 5.00 4.99 4.98 4.97 4.96 4.95 4.94 4.93 4.92 4.91 4.90 4.89 4.88 4.87 4.86 4.85 4.84 4.83 4.82 4.81 4.80 4.79 4.78 4.77 4.76 4.75 4.74 4.73 4.72 4.71 4.70 4.69 4.68 4.67 4.66 4.65 4.64 4.63 4.62 4.61 4.60 4.59 4.58 4.57 4.56 4.55 4.54 4.53 4.52 4.51 4.50 4.49 4.48 4.47 4.46 4.45 4.44 4.43 4.42 4.41 4.40 4.39 4.38 4.37 4.36 4.35 4.34 4.33 4.32 4.31 4.30 4.29 4.28 4.27 4.26 4.25 4.24 4.23 4.22 4.21 4.20 4.19 4.18 4.17 4.16 4.15 4.14 4.13 4.12 4.11 4.10 4.09 4.08 4.07 4.06 4.05 4.04 4.03 4.02 4.01 4.00 3.99 3.98 3.97 3.96 3.95 3.94 3.93 3.92 3.91 3.90 3.89 3.88 3.87 3.86 3.85 3.84 3.83 3.82 3.81 3.80 3.79 3.78 3.77 3.76 3.75 3.74 3.73 3.72 3.71 3.70 3.69 3.68 3.67 3.66 3.65 3.64 3.63 3.62 3.61 3.60 3.59 3.58 3.57 3.56 3.55 3.54 3.53 3.52 3.51 3.50 3.49 3.48 3.47 3.46 3.45 3.44 3.43 3.42 3.41 3.40 3.39 3.38 3.37 3.36 3.35 3.34 3.33 3.32 3.31 3.30 3.29 3.28 3.27 3.26 3.25 3.24 3.23 3.22 3.21 3.20 3.19 3.18 3.17 3.16 3.15 3.14 3.13 3.12 3.11 3.10 3.09 3.08 3.07 3.06 3.05 3.04 3.03 3.02 3.01 3.00 2.99 2.98 2.97 2.96 2.95 2.94 2.93 2.92 2.91 2.90 2.89 2.88 2.87 2.86 2.85 2.84 2.83 2.82 2.81 2.80 2.79 2.78 2.77 2.76 2.75 2.74 2.73 2.72 2.71 2.70 2.69 2.68 2.67 2.66 2.65 2.64 2.63 2.62 2.61 2.60 2.59 2.58 2.57 2.56 2.55 2.54 2.53 2.52 2.51 2.50 2.49 2.48 2.47 2.46 2.45 2.44 2.43 2.42 2.41 2.40 2.39 2.38 2.37 2.36 2.35 2.34 2.33 2.32 2.31 2.30 2.29 2.28 2.27 2.26 2.25 2.24 2.23 2.22 2.21 2.20 2.19 2.18 2.17 2.16 2.15 2.14 2.13 2.12 2.11 2.10 2.09 2.08 2.07 2.06 2.05 2.04 2.03 2.02 2.01 2.00 1.99 1.98 1.97 1.96 1.95 1.94 1.93 1.92 1.91 1.90 1.89 1.88 1.87 1.86 1.85 1.84 1.83 1.82 1.81 1.80 1.79 1.78 1.77 1.76 1.75 1.74 1.73 1.72 1.71 1.70 1.69 1.68 1.67 1.66 1.65 1.64 1.63 1.62 1.61 1.60 1.59 1.58 1.57 1.56 1.55 1.54 1.53 1.52 1.51 1.50 1.49 1.48 1.47 1.46 1.45 1.44 1.43 1.42 1.41 1.40 1.39 1.38 1.37 1.36 1.35 1.34 1.33 1.32 1.31 1.30 1.29 1.28 1.27 1.26 1.25 1.24 1.23 1.22 1.21 1.20 1.19 1.18 1.17 1.16 1.15 1.14 1.13 1.12 1.11 1.10 1.09 1.08 1.07 1.06 1.05 1.04 1.03 1.02 1.01 1.00 0.99 0.98 0.97 0.96 0.95 0.94 0.93 0.92 0.91 0.90 0.89 0.88 0.87 0.86 0.85 0.84 0.83 0.82 0.81 0.80 0.79 0.78 0.77 0.76 0.75 0.74 0.73 0.72 0.71 0.70 0.69 0.68 0.67 0.66 0.65 0.64 0.63 0.62 0.61 0.60 0.59 0.58 0.57 0.56 0.55 0.54 0.53 0.52 0.51 0.50 0.49 0.48 0.47 0.46 0.45 0.44 0.43 0.42 0.41 0.40 0.39 0.38 0.37 0.36 0.35 0.34 0.33 0.32 0.31 0.30 0.29 0.28 0.27 0.26 0.25 0.24 0.23 0.22 0.21 0.20 0.19 0.18 0.17 0.16 0.15 0.14 0.13 0.12 0.11 0.10 0.09 0.08 0.07 0.06 0.05 0.04 0.03 0.02 0.01 0.00 -0.01 -0.02 -0.03 -0.04 -0.05 -0.06 -0.07 -0.08 -0.09 -0.10

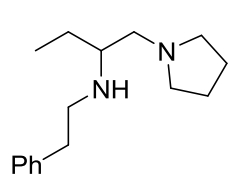
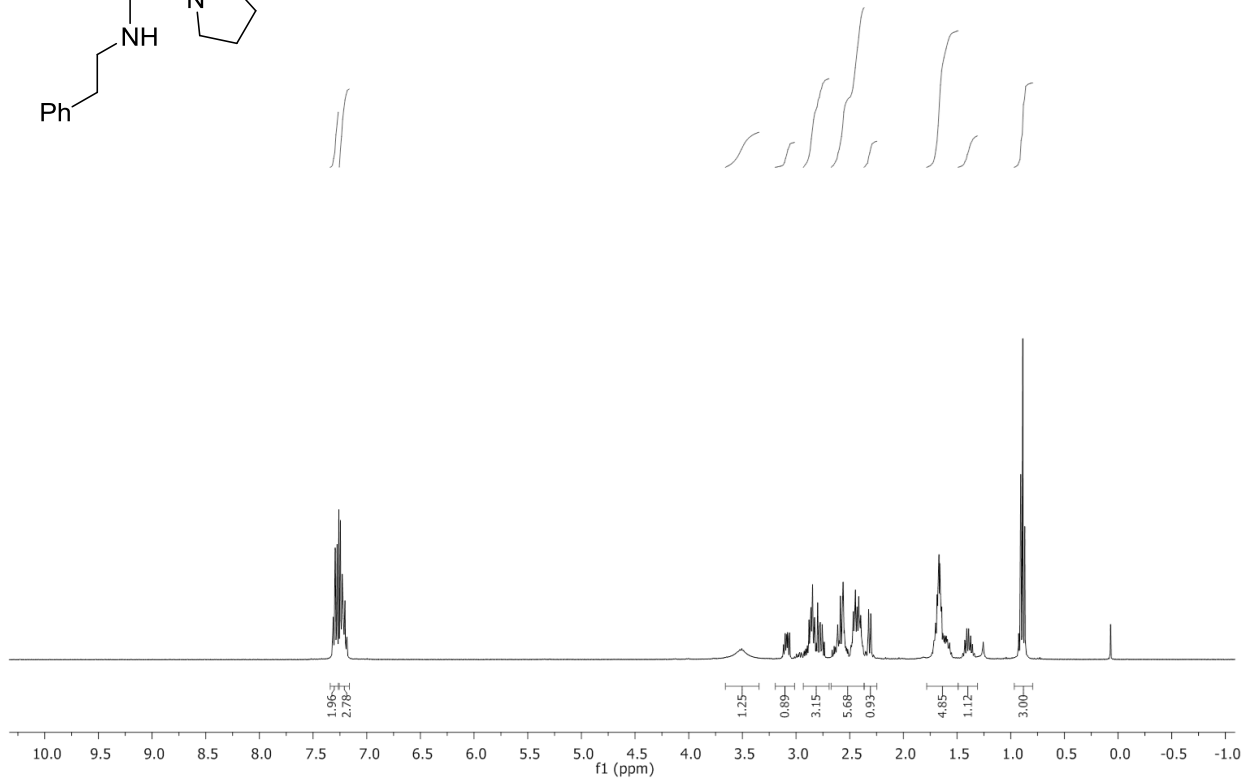






7.31
7.31
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7.28
7.28
7.26
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7.23
7.22
7.21
7.20

3.51
2.86
2.85
2.80
2.77
2.56
2.45
2.43
2.42
2.32
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0.87



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128.6
126.4

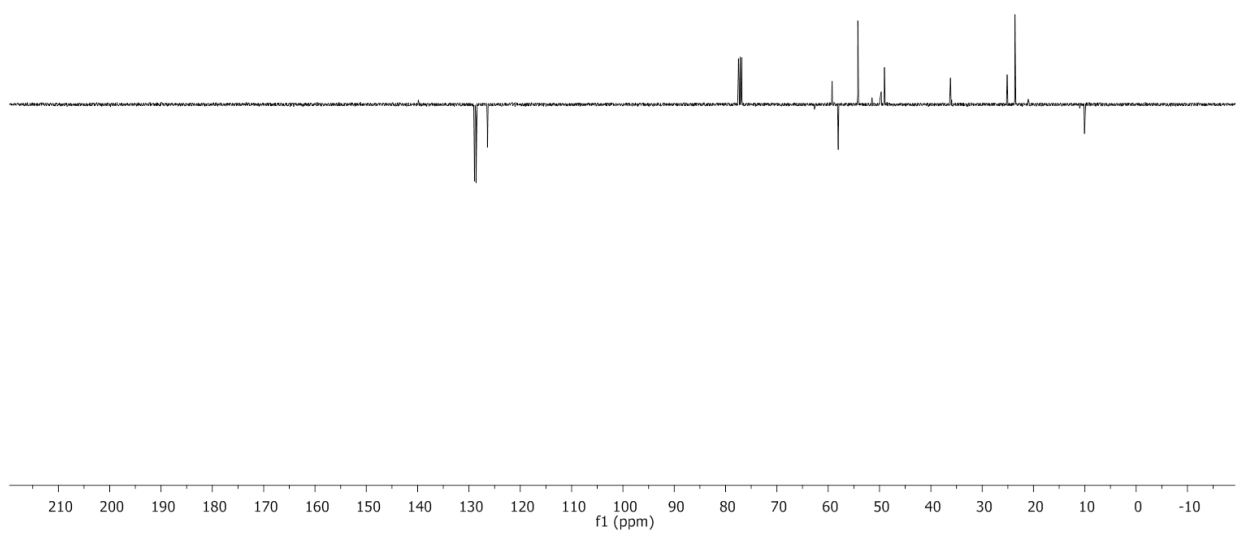
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77.2
76.8

59.2
58.1
54.2
49.1

36.2

25.1
23.6

10.1



Computations

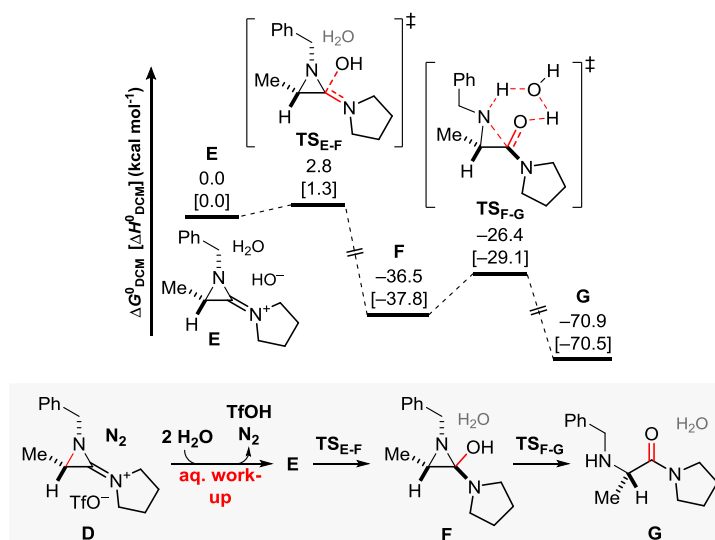
Computational Details

All DFT (density functional theory) calculations were carried out with the Gaussian09 program package.¹⁹ Geometry optimizations were performed using the M06-2X functional and the polarized double- ζ basis set 6-31+G*.²⁰ Geometry optimizations were carried out without any constraints. Ground state minima and transition states were confirmed by frequency calculations, yielding no and one imaginary frequency, respectively. The connectivity of the transition state structures was verified by intrinsic reaction coordinate calculations.²¹ The electronic energies obtained, E , were converted to relative free energies G^0 and enthalpies H^0 at 273.15 K and 1 atm by using zero point energy and thermal energy corrections obtained in the frequency calculation. Single-point energies were computed at the SMD(DCM)²² M06-2X/def2-QZVP²³ level of theory using the geometries optimized at the M06-2X/6-31+G* level. The free energy and enthalpy values discussed in the manuscript were derived from the electronic energy values obtained at the SMD(DCM) M06-2X/def2QZVP//M06-2X/6-31+G* level, E_{DCM} , according to the following equation: $G_{\text{DCM}}^0(H_{\text{DCM}}^0) = E_{\text{DCM}} + G^0(H^0) - E$. All energies are reported in hartrees/particle, unless noticed otherwise. Computed structures and molecular orbitals were visualized using the Chemcraft software.²⁴

Hydrolytic Liberation of Amide G

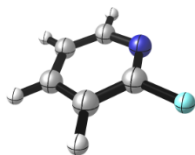
We have investigated the hydrolytic liberation of amide **G** from amidinium **D** computationally. As shown in Scheme 1-SI, the aziridine moiety in **E** was found to undergo a facile two-step hydrolytic opening. Accordingly, addition of water ($\text{TS}_{\text{E-F}}$), followed by water-mediated proton-transfer ($\text{TS}_{\text{F-G}}$) ultimately leads to amide **G** in a highly exergonic fashion ($\text{E} \rightarrow \text{G}$: $\Delta G_{\text{DCM}}^0 = -70.9 \text{ kcal mol}^{-1}$).

Scheme 1-SI. DFT computed pathway for the hydrolysis of amidinium **D** and **E**, respectively. DFT energies were derived at the SMD(DCM) Mo6-2X/def2-QZVP//Mo6-2X/6-31+G* level of theory. Free energies ΔG_{DCM}^0 and enthalpies ΔH_{DCM}^0 are given with respect to **E**.



Optimized Geometries

2-F-Pyridine



$$E_{\text{DCM}} = -347.566385$$

$$E = -347.401019$$

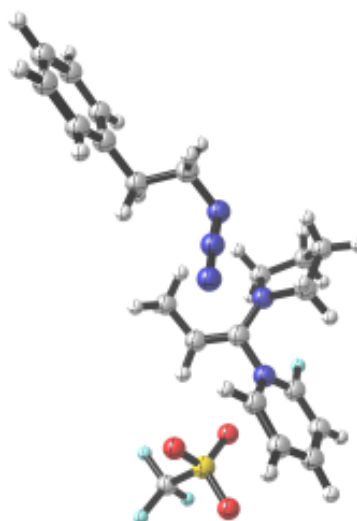
$$H^0 = -347.313285$$

$$G^0 = -347.347871$$

Cartesian coordinates:

C	-1.141837000	1.184352000	0.000037000
C	-1.799196000	-0.047658000	-0.000015000
C	-1.028374000	-1.204203000	-0.000109000
N	0.311389000	-1.197967000	0.000093000
C	0.890297000	-0.024232000	0.000081000
C	0.245715000	1.210568000	-0.000081000
H	-1.704616000	2.113047000	0.000257000
H	-2.881754000	-0.110469000	-0.000088000
H	-1.494990000	-2.185866000	0.000083000
F	2.231153000	-0.030272000	-0.000038000
H	0.821632000	2.128550000	-0.000026000

A`



$$E_{\text{DCM}} = -2112.371117$$

$$E = -2111.450164$$

$$H^0 = -2110.953487$$

$$G^0 = -2111.061200$$

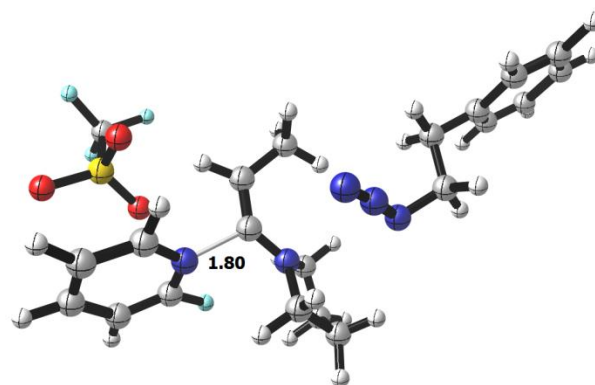
Cartesian coordinates:

C	0.380258000	-0.422272000	-0.446186000
H	1.213279000	-1.088901000	-0.225141000
C	0.530233000	0.878372000	-0.173460000
N	-0.297409000	1.930517000	-0.505628000
C	-0.385028000	3.148404000	0.299705000
H	0.606851000	3.601512000	0.468925000
H	-0.828514000	2.945100000	1.281970000
C	-0.694658000	2.169732000	-1.902842000
H	-1.666282000	1.701003000	-2.107267000
C	-0.802318000	3.693475000	-1.985411000
H	-1.503717000	4.023320000	-2.755946000
C	-1.239707000	4.074709000	-0.566861000

H	-1.075940000	5.129050000	-0.330116000
H	-2.298749000	3.838455000	-0.422007000
H	0.051708000	1.745708000	-2.582948000
H	0.180873000	4.126310000	-2.203578000
C	-0.860304000	-0.991297000	-1.059921000
H	-0.676573000	-1.309980000	-2.093127000
H	-1.173687000	-1.880615000	-0.501879000
H	-1.680177000	-0.267784000	-1.064137000
C	4.087539000	1.837149000	1.880781000
C	3.149771000	0.980691000	2.460616000
C	1.985872000	0.702884000	1.781012000
N	1.747662000	1.252310000	0.564425000
C	2.663429000	2.057231000	0.006917000
C	3.835365000	2.407661000	0.641276000
H	5.030419000	2.029345000	2.380958000
H	3.343937000	0.483453000	3.402346000
H	1.216546000	0.027747000	2.135091000
F	2.376056000	2.494872000	-1.200039000
H	4.545471000	3.036354000	0.119038000
C	-7.973127000	-2.198653000	1.278143000
C	-6.656625000	-1.752626000	1.187752000
C	-6.153014000	-1.249621000	-0.015750000
C	-6.997144000	-1.199504000	-1.128504000
C	-8.314875000	-1.645054000	-1.043130000
C	-8.806180000	-2.145852000	0.161368000
H	-8.347084000	-2.592474000	2.218796000
H	-6.007361000	-1.802315000	2.060041000
H	-6.615220000	-0.815939000	-2.072625000
H	-8.955781000	-1.607134000	-1.919223000
H	-9.831369000	-2.497646000	0.228548000
C	-4.741679000	-0.721290000	-0.093141000

H	-4.343920000	-0.824599000	-1.109004000
H	-4.087971000	-1.300789000	0.572158000
C	-4.691174000	0.756953000	0.309491000
H	-5.271932000	1.362260000	-0.388778000
H	-5.118585000	0.894802000	1.311610000
N	-3.316018000	1.305140000	0.257942000
N	-1.827265000	0.455297000	1.884411000
N	-2.574537000	0.834230000	1.123563000
O	5.228190000	-0.913841000	1.130617000
S	4.129014000	-1.309270000	0.243974000
O	2.971881000	-1.932030000	0.912617000
O	3.749835000	-0.303058000	-0.767224000
C	4.831416000	-2.682007000	-0.771718000
F	5.243817000	-3.685195000	0.005440000
F	5.872184000	-2.256033000	-1.491354000
F	3.909609000	-3.159582000	-1.615065000

TS_{A'-B}



$$E_{\text{DCM}} = -2112.351944$$

$$E = -2111.430581$$

$$H^0 = -2110.936057$$

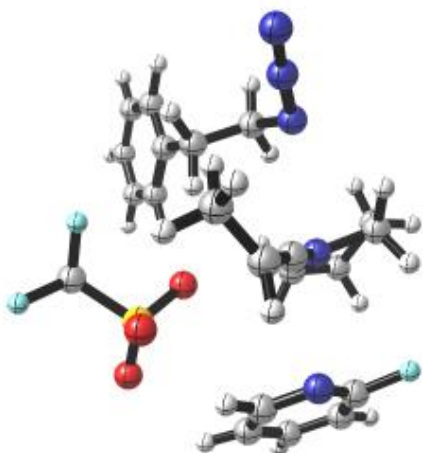
$$G^0 = -2111.043700$$

Negative frequency: -196.74 cm^{-1}

Cartesian coordinates:

C	-0.432179000	-0.401813000	-0.327445000
H	-1.351541000	-0.931981000	-0.579250000
C	-0.460877000	0.908686000	-0.141797000
N	0.332806000	1.851417000	0.362182000
C	0.490359000	3.167901000	-0.265676000
H	-0.498989000	3.630352000	-0.406606000
H	0.964413000	3.078773000	-1.248353000
C	0.682683000	1.882985000	1.799962000
H	1.627714000	1.345314000	1.943964000
C	0.840739000	3.375470000	2.094571000
H	1.540001000	3.563445000	2.912999000
C	1.321484000	3.946898000	0.754274000
H	1.171179000	5.025856000	0.667987000
H	2.382679000	3.724429000	0.607405000
H	-0.103393000	1.398814000	2.384921000
H	-0.129200000	3.807658000	2.363685000
C	0.825240000	-1.198348000	-0.138423000
H	0.648928000	-1.977705000	0.610415000
H	1.098191000	-1.700157000	-1.073158000
H	1.660498000	-0.576117000	0.195435000
C	-4.733627000	2.094185000	-1.071315000
C	-3.960804000	1.428851000	-2.024777000
C	-2.639837000	1.150994000	-1.733912000
N	-2.100905000	1.520923000	-0.560695000
C	-2.844314000	2.137884000	0.342986000
C	-4.167339000	2.478667000	0.135714000
H	-5.785961000	2.279439000	-1.257854000
H	-4.390471000	1.071289000	-2.952211000

H	-1.988189000	0.591968000	-2.396450000
F	-2.242161000	2.421699000	1.491696000
H	-4.724744000	2.959678000	0.929891000
C	8.246374000	-1.925815000	-1.055148000
C	6.920083000	-1.512774000	-1.166534000
C	6.172682000	-1.198764000	-0.027885000
C	6.780454000	-1.305866000	1.226274000
C	8.106203000	-1.718358000	1.342576000
C	8.842822000	-2.028632000	0.200499000
H	8.812257000	-2.172642000	-1.948744000
H	6.456629000	-1.439061000	-2.148629000
H	6.206426000	-1.069727000	2.120268000
H	8.561795000	-1.803577000	2.324894000
H	9.874953000	-2.354560000	0.288772000
C	4.756274000	-0.691986000	-0.148596000
H	4.171961000	-0.971223000	0.735630000
H	4.264402000	-1.141777000	-1.021144000
C	4.741307000	0.834579000	-0.285270000
H	5.205733000	1.296412000	0.587940000
H	5.308901000	1.145456000	-1.172222000
N	3.367796000	1.384108000	-0.332677000
N	2.096885000	0.887303000	-2.261329000
N	2.750973000	1.098475000	-1.362312000
O	-5.498462000	-1.003844000	-0.710882000
S	-4.166502000	-1.371619000	-0.226211000
O	-3.193384000	-1.744180000	-1.271820000
O	-3.602308000	-0.485529000	0.809475000
C	-4.429227000	-2.954863000	0.688280000
F	-4.949492000	-3.891317000	-0.107782000
F	-5.258493000	-2.777369000	1.719799000
F	-3.266611000	-3.417556000	1.166208000

B

$$E_{\text{DCM}} = -2112.353386$$

$$E = -2111.440532$$

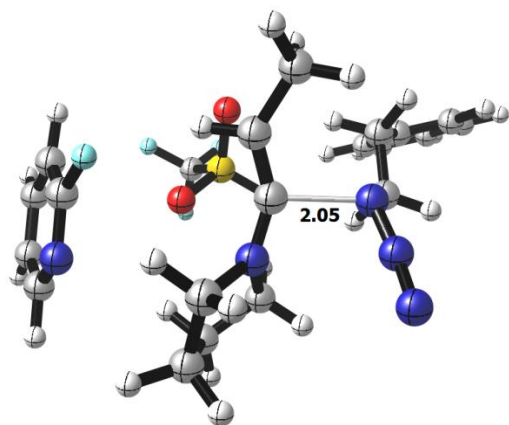
$$H^0 = -2110.945047$$

$$G^0 = -2111.053556$$

Cartesian coordinates:

C	-1.274127000	-0.517771000	2.330677000
H	-2.163691000	0.024941000	2.652938000
C	-1.389396000	-1.106571000	1.182775000
N	-1.535638000	-1.696919000	0.087936000
C	-2.039850000	-3.101552000	-0.012501000
H	-3.118609000	-3.064226000	0.164422000
H	-1.538442000	-3.700229000	0.747237000
C	-1.279529000	-1.110006000	-1.267656000
H	-0.197491000	-1.001839000	-1.381015000
C	-1.881929000	-2.153377000	-2.205505000
H	-1.386498000	-2.144911000	-3.178965000
C	-1.706841000	-3.477581000	-1.451429000
H	-2.361546000	-4.269395000	-1.821789000
H	-0.671290000	-3.829622000	-1.515056000
H	-1.716911000	-0.111727000	-1.312682000

H	-2.947227000	-1.950741000	-2.361217000
C	-0.031739000	-0.480128000	3.176242000
H	0.239591000	0.569805000	3.313329000
H	-0.234119000	-0.933929000	4.151130000
H	0.795833000	-1.003856000	2.697709000
C	-4.186580000	1.657543000	-1.982989000
C	-3.481620000	2.268658000	-0.946570000
C	-3.340273000	1.577107000	0.252514000
N	-3.826201000	0.338294000	0.446838000
C	-4.467009000	-0.204003000	-0.558222000
C	-4.705467000	0.379667000	-1.795960000
H	-4.323517000	2.164285000	-2.933666000
H	-3.016247000	3.241710000	-1.054523000
H	-2.795688000	2.016987000	1.084504000
F	-4.896632000	-1.471379000	-0.361523000
H	-5.259115000	-0.153247000	-2.560829000
C	5.370017000	-0.918179000	-1.967205000
C	4.555292000	-1.339150000	-0.919321000
C	3.280212000	-0.790668000	-0.741467000
C	2.834712000	0.192590000	-1.628544000
C	3.651874000	0.617827000	-2.676078000
C	4.917209000	0.061696000	-2.851160000
H	6.360199000	-1.348121000	-2.089529000
H	4.920870000	-2.091677000	-0.221905000
H	1.858310000	0.647244000	-1.471736000
H	3.300162000	1.396121000	-3.347471000
H	5.553850000	0.396569000	-3.665056000
C	2.381086000	-1.280094000	0.369608000
H	1.528147000	-0.598302000	0.479494000
H	2.927364000	-1.288161000	1.323794000
C	1.880229000	-2.693201000	0.060577000

TS_{B-C}

$$E_{\text{DCM}} = -2112.335634$$

$$E = -2111.428689$$

$$H^0 = -2110.934801$$

$$G^0 = -2111.041977$$

Negative frequency: -199.82 cm^{-1}

Cartesian coordinates:

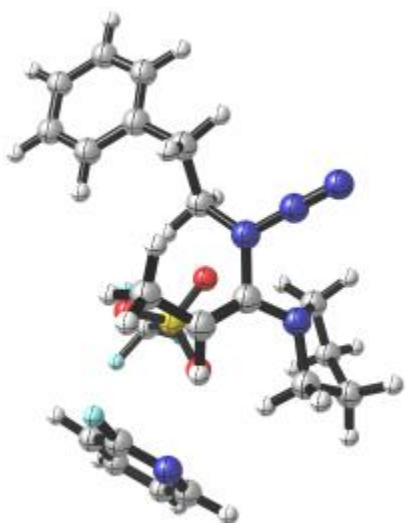
C	0.136913000	1.430930000	1.876379000
H	0.976033000	0.743651000	2.006328000
C	0.155190000	1.955959000	0.673897000
N	0.836807000	2.294385000	-0.357825000
C	0.625970000	1.765020000	-1.726685000
H	-0.013931000	2.470219000	-2.275328000
H	0.151382000	0.784783000	-1.669234000
C	2.089745000	3.103481000	-0.266763000
H	2.743985000	2.616601000	0.459582000
C	2.666772000	3.027540000	-1.682933000
H	3.758091000	2.984584000	-1.649004000
C	2.046200000	1.753854000	-2.276772000
H	2.064876000	1.741142000	-3.369244000
H	2.552204000	0.862242000	-1.894296000

H	1.852061000	4.118476000	0.060765000
H	2.367112000	3.904758000	-2.267286000
C	-0.824681000	1.575381000	3.006114000
H	-0.282896000	1.907685000	3.897950000
H	-1.617360000	2.289629000	2.783238000
H	-1.256226000	0.593816000	3.229479000
C	-6.689359000	-0.476036000	-0.075390000
C	-5.642981000	0.289313000	0.435081000
C	-4.317974000	-0.142228000	0.318302000
C	-4.052214000	-1.356402000	-0.321881000
C	-5.099080000	-2.122791000	-0.832119000
C	-6.417587000	-1.686580000	-0.711455000
H	-7.714279000	-0.131068000	0.029260000
H	-5.857933000	1.229513000	0.941080000
H	-3.021623000	-1.688669000	-0.419884000
H	-4.881646000	-3.067105000	-1.323214000
H	-7.230725000	-2.288647000	-1.107130000
C	-3.189933000	0.714254000	0.847964000
H	-2.351128000	0.086044000	1.167483000
H	-3.538150000	1.300353000	1.706703000
C	-2.711425000	1.663467000	-0.244641000
H	-2.204526000	1.092256000	-1.030716000
H	-3.554230000	2.218823000	-0.671536000
N	-1.739988000	2.656746000	0.327928000
N	-1.320214000	4.647551000	-0.869084000
N	-1.596595000	3.693875000	-0.332704000
O	-0.893182000	-0.947414000	-0.814399000
S	0.166747000	-1.360792000	0.125246000
O	1.448208000	-0.662474000	-0.078325000
O	-0.264041000	-1.493259000	1.521451000
C	0.543258000	-3.093511000	-0.390193000
F	0.961452000	-3.133273000	-1.658054000
F	-0.538697000	-3.866376000	-0.282261000

F	1.507140000	-3.612301000	0.379679000
C	4.601384000	-2.116689000	0.392871000
C	5.099639000	-1.504644000	-0.761564000
C	4.972075000	-0.129694000	-0.885291000
N	4.390671000	0.644034000	0.046048000
C	3.934693000	0.027913000	1.104559000
C	4.001912000	-1.335851000	1.366241000
H	4.664702000	-3.192844000	0.521192000
H	5.568745000	-2.083440000	-1.549545000
H	5.343165000	0.389504000	-1.766213000
F	3.332350000	0.817345000	2.017719000
H	3.560395000	-1.745257000	2.267196000

C	0.401905000	1.363043000	1.701255000
H	1.463892000	1.182033000	1.846484000
C	0.076606000	2.080197000	0.622527000
N	0.856921000	2.862147000	-0.205178000
C	0.702822000	2.808089000	-1.687737000
H	0.196175000	3.723814000	-2.025351000
H	0.135053000	1.926849000	-1.993409000
C	2.284885000	2.949292000	0.151011000
H	2.686989000	1.947438000	0.350938000
C	2.920676000	3.511136000	-1.115250000
H	3.996554000	3.321420000	-1.149599000
C	2.141791000	2.770058000	-2.206716000
H	2.235800000	3.222975000	-3.197292000
H	2.472613000	1.727718000	-2.255025000
H	2.408891000	3.571624000	1.043581000
H	2.755267000	4.593329000	-1.184420000
C	-0.534356000	0.746597000	2.692713000
H	-0.129489000	0.857690000	3.702595000
H	-1.527975000	1.204856000	2.676840000
H	-0.624507000	-0.328096000	2.492390000
C	-6.490939000	-1.104212000	-0.289413000
C	-5.716728000	0.041809000	-0.113328000
C	-4.480889000	-0.028588000	0.531238000
C	-4.023795000	-1.267890000	0.992314000
C	-4.793238000	-2.413579000	0.813220000
C	-6.029968000	-2.334349000	0.173192000
H	-7.451710000	-1.033874000	-0.791097000
H	-6.079794000	0.999935000	-0.478915000
H	-3.056810000	-1.344598000	1.486446000
H	-4.422968000	-3.369666000	1.170387000
H	-6.628766000	-3.229345000	0.032350000
C	-3.631226000	1.209250000	0.724153000
H	-3.468365000	1.395375000	1.792348000

C



$$E_{\text{DCM}} = -2112.349986$$

$$E = -2111.438570$$

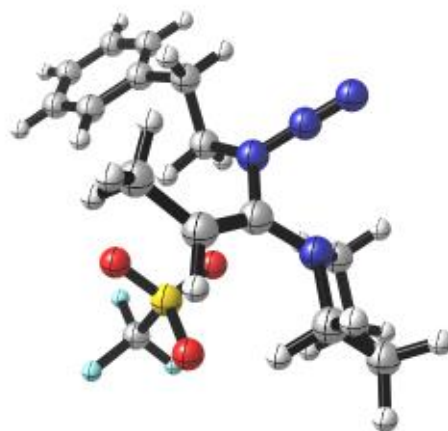
$$H^0 = -2110.942448$$

$$G^0 = -2111.045767$$

Cartesian coordinates:

H	-4.162220000	2.079691000	0.316728000
C	-2.292469000	1.018700000	0.022840000
H	-1.726493000	0.157353000	0.386204000
H	-2.387158000	0.900315000	-1.059468000
N	-1.358604000	2.172440000	0.273938000
N	-2.102996000	4.335041000	-0.394095000
N	-1.765223000	3.318478000	-0.076059000
O	-0.310021000	-0.121188000	-1.666742000
S	0.636873000	-0.894453000	-0.839682000
O	1.977105000	-0.308685000	-0.730357000
O	0.055156000	-1.410634000	0.410301000
C	0.899685000	-2.417113000	-1.854242000
F	1.458916000	-2.113357000	-3.028011000
F	-0.258355000	-3.037522000	-2.091126000
F	1.707379000	-3.278823000	-1.222752000
C	3.982793000	-2.494603000	0.661576000
C	4.811490000	-1.411244000	0.363768000
C	4.584793000	-0.210137000	1.019201000
N	3.622538000	-0.041606000	1.938362000
C	2.873181000	-1.084745000	2.190096000
C	2.974934000	-2.339001000	1.600024000
H	4.108094000	-3.445139000	0.152305000
H	5.600917000	-1.492321000	-0.375280000
H	5.193418000	0.665797000	0.806369000
F	1.917866000	-0.898955000	3.121476000
H	2.272290000	-3.123730000	1.853476000

C



$$E_{\text{DCM}} = -1764.778911$$

$$E = -1764.022714$$

$$H^0 = -1763.616310$$

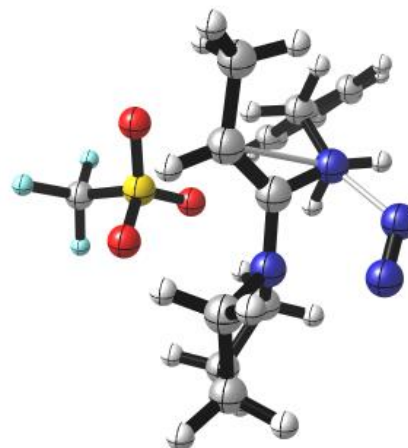
$$G^0 = -1763.704088$$

Cartesian coordinates:

C	-1.182729000	-1.207946000	2.059655000
H	-2.057324000	-0.718370000	2.476094000
C	-1.309660000	-1.671085000	0.811598000
N	-2.431515000	-1.885351000	0.039063000
C	-2.443271000	-1.585020000	-1.419729000
H	-2.472919000	-2.532270000	-1.977443000
H	-1.572074000	-0.994756000	-1.708525000
C	-3.722359000	-1.506566000	0.646293000
H	-3.635907000	-0.520043000	1.118095000
C	-4.660463000	-1.406662000	-0.553069000
H	-5.532032000	-0.785843000	-0.332258000
C	-3.740366000	-0.802579000	-1.618039000
H	-4.127934000	-0.892319000	-2.636289000
H	-3.550900000	0.252920000	-1.394516000
H	-4.016108000	-2.251286000	1.393963000
H	-5.008461000	-2.400856000	-0.859304000
C	0.059550000	-1.210016000	2.895433000

H	-0.179762000	-1.481882000	3.928091000
H	0.808711000	-1.920647000	2.533608000
H	0.496328000	-0.203967000	2.904633000
C	5.701362000	-0.404549000	-1.074648000
C	4.637606000	-1.294153000	-0.929029000
C	3.583519000	-1.004204000	-0.061119000
C	3.602305000	0.197353000	0.655785000
C	4.661782000	1.088093000	0.507178000
C	5.714781000	0.788688000	-0.356481000
H	6.515551000	-0.643476000	-1.752620000
H	4.629558000	-2.223030000	-1.495395000
H	2.782235000	0.454932000	1.323630000
H	4.658460000	2.020491000	1.063408000
H	6.538633000	1.486471000	-0.472916000
C	2.430080000	-1.971896000	0.109414000
H	2.423215000	-2.374796000	1.129980000
H	2.563771000	-2.818542000	-0.576727000
C	1.117211000	-1.251427000	-0.163809000
H	0.956055000	-0.385869000	0.484046000
H	1.019321000	-0.899644000	-1.194812000
N	-0.075032000	-2.120316000	0.139169000
N	-0.244430000	-4.191288000	-1.027991000
N	-0.155935000	-3.221037000	-0.481848000
O	-0.727604000	0.835227000	-1.004880000
S	-0.987141000	1.605210000	0.228452000
O	-2.357287000	1.495733000	0.739285000
O	0.088956000	1.491781000	1.229157000
C	-0.867663000	3.359345000	-0.336847000
F	-1.774503000	3.608796000	-1.285563000
F	0.342988000	3.613253000	-0.840562000
F	-1.081642000	4.198973000	0.678040000

TS_{C-D}



$$E_{\text{DCM}} = -1764.763736$$

$$E = -1764.019777$$

$$H^0 = -1763.615803$$

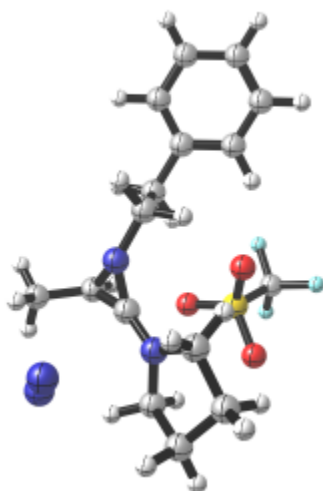
$$G^0 = -1763.700204$$

Negative frequency: -518.40 cm^{-1}

Cartesian coordinates:

C	-1.446148000	-1.176675000	1.958540000
H	-2.305873000	-0.509539000	1.928812000
C	-1.069095000	-1.746522000	0.778546000
N	-1.888730000	-1.852350000	-0.333728000
C	-1.495859000	-1.349666000	-1.692061000
H	-0.995494000	-2.158389000	-2.234473000
H	-0.818442000	-0.501044000	-1.572293000
C	-3.353434000	-1.752199000	-0.170632000
H	-3.584857000	-0.775283000	0.271150000
C	-3.860495000	-1.815122000	-1.605547000
H	-4.876561000	-1.424314000	-1.691461000
C	-2.825450000	-0.962663000	-2.346099000
H	-2.811071000	-1.146211000	-3.422813000
H	-3.015505000	0.098203000	-2.164647000

H	-3.696952000	-2.561491000	0.478143000	F	-1.975384000	4.015255000	0.769323000
H	-3.850465000	-2.850383000	-1.965060000				
C	-0.681145000	-1.238459000	3.224734000				
H	-1.374584000	-1.321715000	4.068074000				
H	0.041455000	-2.055787000	3.229635000				
H	-0.153167000	-0.282262000	3.340278000				
C	5.663446000	-0.754910000	-0.316970000				
C	4.509442000	-1.162395000	0.349202000				
C	3.319448000	-0.439433000	0.222978000				
C	3.297858000	0.700350000	-0.587229000				
C	4.452585000	1.108616000	-1.253213000				
C	5.636121000	0.383934000	-1.121166000				
H	6.583785000	-1.321212000	-0.203937000				
H	4.534458000	-2.047207000	0.983543000				
H	2.370560000	1.259945000	-0.685956000				
H	4.427435000	1.999616000	-1.874202000				
H	6.535011000	0.706485000	-1.638988000				
C	2.062012000	-0.908401000	0.917252000				
H	1.404682000	-0.059574000	1.132419000				
H	2.307621000	-1.409243000	1.860962000				
C	1.323965000	-1.909348000	0.017152000				
H	1.064265000	-1.442993000	-0.939376000				
H	1.965181000	-2.776574000	-0.167584000				
N	0.147395000	-2.416685000	0.744504000				
N	-1.296443000	-3.848663000	-0.553586000				
N	-0.280268000	-3.829078000	-0.029178000				
O	0.078797000	1.149745000	-0.591357000				
S	-0.960532000	1.625719000	0.340409000				
O	-2.314529000	1.132293000	0.025958000				
O	-0.592709000	1.544355000	1.759654000				
C	-1.061512000	3.435663000	-0.009414000				
F	-1.402510000	3.641463000	-1.283727000				
F	0.115721000	4.021851000	0.211588000				

D

$$E_{\text{DCM}} = -1764.892479$$

$$E = -1764.145103$$

$$H^0 = -1763.738525$$

$$G^0 = -1763.830854$$

Cartesian coordinates:

C	-1.238610000	-1.648556000	1.743777000
H	-0.679635000	-0.916387000	2.328517000
C	-1.692170000	-1.119607000	0.451920000
N	-2.472279000	-0.387253000	-0.264632000
C	-2.345092000	-0.233122000	-1.734233000
H	-2.592646000	-1.196528000	-2.197785000
H	-1.320375000	0.053634000	-1.979939000
C	-3.579575000	0.416976000	0.299523000
H	-3.149312000	1.324637000	0.732127000
C	-4.419904000	0.723533000	-0.938941000
H	-5.008929000	1.633599000	-0.807386000
C	-3.372899000	0.855813000	-2.055331000
H	-3.799807000	0.724258000	-3.052137000
H	-2.885760000	1.831660000	-1.994857000

H	-4.097299000	-0.164731000	1.066516000
H	-5.106582000	-0.105597000	-1.147616000
C	-1.923634000	-2.766011000	2.487017000
H	-2.661632000	-2.357231000	3.183957000
H	-2.427583000	-3.445101000	1.794793000
H	-1.190165000	-3.335043000	3.066190000
C	5.191904000	-2.611891000	-0.345750000
C	3.958848000	-2.582484000	0.305221000
C	3.072294000	-1.522247000	0.102965000
C	3.434490000	-0.489387000	-0.768929000
C	4.665712000	-0.517811000	-1.419083000
C	5.547688000	-1.578188000	-1.209671000
H	5.875263000	-3.438873000	-0.173640000
H	3.686713000	-3.388204000	0.984956000
H	2.740205000	0.333053000	-0.928626000
H	4.939025000	0.293823000	-2.087424000
H	6.509175000	-1.596970000	-1.714959000
C	1.718104000	-1.493897000	0.771276000
H	1.460991000	-0.474513000	1.076684000
H	1.723734000	-2.130356000	1.665488000
C	0.656128000	-1.999394000	-0.205902000
H	0.639167000	-1.371596000	-1.099165000
H	0.853524000	-3.037973000	-0.487038000
N	-0.685235000	-1.944714000	0.393533000
N	-4.421781000	-2.733498000	-0.127969000
N	-4.272491000	-3.182321000	-1.119943000
O	0.446493000	0.970718000	-0.849759000
S	-0.195296000	1.825884000	0.167221000
O	-1.358901000	2.581201000	-0.307986000
O	-0.377370000	1.157688000	1.469232000
C	1.088745000	3.103527000	0.519050000
F	1.361428000	3.812954000	-0.576959000
F	2.216730000	2.513418000	0.927934000

F 0.680199000 3.938562000 1.473419000

E



$E_{\text{DCM}} = -845.966734$

$E = -845.544605$

$H^0 = -845.148015$

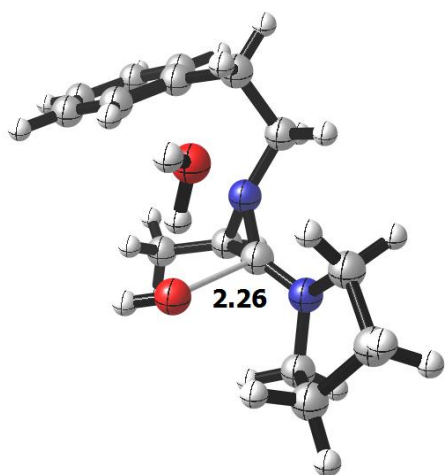
$G^0 = -845.219835$

Cartesian coordinates:

C 0.032075000 0.426565000 1.782906000
H 0.053949000 0.196425000 2.854316000
C 1.181076000 -0.100837000 1.008169000
N 2.448163000 -0.146925000 0.749820000
C 3.031287000 -1.182016000 -0.142072000
H 2.370144000 -1.245827000 -1.019842000
H 3.075673000 -2.136675000 0.391931000
C 3.326497000 1.028886000 0.902289000
H 3.885594000 0.943894000 1.841924000
C 4.233363000 0.903417000 -0.319924000
H 5.178281000 1.437878000 -0.191460000
C 4.417434000 -0.612971000 -0.467306000
H 4.738092000 -0.902427000 -1.470842000
H 5.164038000 -0.978673000 0.247834000

H 2.711677000 1.929462000 0.885556000
H 3.688438000 1.307512000 -1.178193000
C -0.773996000 1.631095000 1.380710000
H -0.487820000 2.481594000 2.009020000
H -0.568358000 1.871463000 0.336421000
H -1.842062000 1.431654000 1.523803000
C -4.466163000 0.088254000 0.605338000
C -3.553435000 -0.957527000 0.475659000
C -2.496434000 -0.874958000 -0.437229000
C -2.363270000 0.275516000 -1.220317000
C -3.283945000 1.316774000 -1.101090000
C -4.334446000 1.228402000 -0.188585000
H -5.284628000 0.009536000 1.315987000
H -3.669999000 -1.853946000 1.084133000
H -1.508001000 0.338232000 -1.893156000
H -3.174566000 2.206382000 -1.716215000
H -5.049304000 2.041412000 -0.095451000
C -1.479197000 -1.982162000 -0.567550000
H -0.855014000 -1.800647000 -1.448713000
H -1.974101000 -2.958631000 -0.648817000
C -0.537871000 -2.043694000 0.638075000
H -1.069467000 -2.331838000 1.553535000
H 0.268577000 -2.760290000 0.455562000
N 0.080810000 -0.757227000 0.906923000
O 1.251863000 1.709106000 -1.049455000
H 0.894692000 2.401913000 -1.620726000
O 0.761984000 -0.504277000 -2.004081000
H 1.024943000 0.745559000 -1.543915000
H 1.017782000 -0.552005000 -2.936039000

TS_{E-F}



$$E_{\text{DCM}} = -845.965462$$

$$E = -845.544965$$

$$H^0 = -845.147622$$

$$G^0 = -845.217025$$

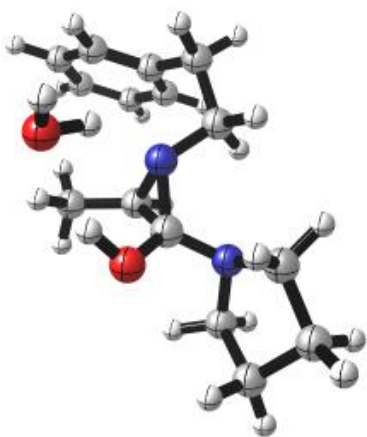
Negative frequency: -280.62 cm^{-1}

Cartesian coordinates:

C	0.054162000	-1.081737000	-1.237639000
H	0.057867000	-1.109958000	-2.334795000
C	1.212089000	-0.374125000	-0.663122000
N	2.484303000	-0.092605000	-0.829280000
C	3.019116000	1.167584000	-0.251567000
H	2.425189000	1.419931000	0.634131000
H	2.945342000	1.973541000	-0.988326000
C	3.474606000	-1.183589000	-0.746007000
H	3.973174000	-1.290769000	-1.716787000
C	4.430398000	-0.695587000	0.340135000
H	5.415703000	-1.164781000	0.271478000
C	4.471238000	0.818219000	0.098322000
H	4.817036000	1.380213000	0.969187000
H	5.132919000	1.053987000	-0.743699000

H	2.957649000	-2.104973000	-0.473657000
H	3.969737000	-0.914498000	1.308057000
C	-0.739594000	-2.160212000	-0.555679000
H	-0.334181000	-3.144362000	-0.813083000
H	-0.694936000	-2.017861000	0.523951000
H	-1.786028000	-2.111361000	-0.876468000
C	-4.536666000	-0.219626000	-0.784859000
C	-3.588799000	0.792995000	-0.929659000
C	-2.598657000	0.988317000	0.038308000
C	-2.567670000	0.147243000	1.155221000
C	-3.520650000	-0.859083000	1.307052000
C	-4.506199000	-1.046664000	0.338157000
H	-5.304037000	-0.356333000	-1.541923000
H	-3.624006000	1.445123000	-1.801338000
H	-1.773764000	0.288055000	1.887454000
H	-3.490342000	-1.502988000	2.182093000
H	-5.249308000	-1.830018000	0.458111000
C	-1.536480000	2.047063000	-0.124980000
H	-1.088954000	2.270140000	0.846967000
H	-1.962811000	2.966381000	-0.544838000
C	-0.408107000	1.577185000	-1.049096000
H	-0.752785000	1.499449000	-2.090250000
H	0.432952000	2.276143000	-1.007636000
N	0.071576000	0.265685000	-0.650297000
O	1.551928000	-1.110093000	1.450203000
H	1.042323000	-1.840732000	1.827221000
O	0.599334000	1.171321000	2.044594000
H	0.950940000	0.206517000	1.876694000
H	0.886347000	1.399875000	2.938612000

F



$$E_{\text{DCM}} = -846.031289$$

$$E = -845.618279$$

$$H^0 = -845.217361$$

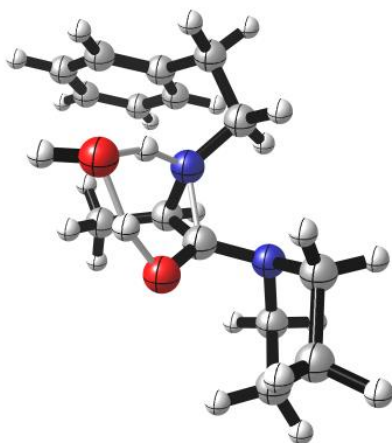
$$G^0 = -845.287063$$

Cartesian coordinates:

C	-0.049800000	-0.028899000	0.887810000
H	0.112022000	1.041794000	1.025422000
C	-1.353997000	-0.371738000	0.267615000
N	-2.272631000	0.683352000	0.035380000
C	-3.210555000	0.431187000	-1.082739000
H	-3.200520000	-0.633785000	-1.344758000
H	-2.918856000	1.012517000	-1.964323000
C	-3.059306000	1.042880000	1.236655000
H	-3.040641000	2.132864000	1.369877000
C	-4.481406000	0.564525000	0.944270000
H	-5.239051000	1.083950000	1.538412000
C	-4.594069000	0.840094000	-0.557152000
H	-5.401632000	0.287782000	-1.045433000
H	-4.763898000	1.909965000	-0.728731000
H	-2.620765000	0.581613000	2.126158000
H	-4.554292000	-0.511520000	1.136518000
C	0.678461000	-0.922667000	1.855268000

H	0.314646000	-0.741093000	2.872458000
H	0.527129000	-1.979537000	1.619650000
H	1.752648000	-0.712723000	1.827442000
C	3.724046000	1.756430000	0.777572000
C	2.808943000	1.702100000	-0.270599000
C	2.576744000	0.506691000	-0.960160000
C	3.287267000	-0.632631000	-0.576376000
C	4.214424000	-0.581813000	0.465124000
C	4.433372000	0.612275000	1.147466000
H	3.890308000	2.693353000	1.302013000
H	2.263920000	2.599923000	-0.558138000
H	3.106225000	-1.573868000	-1.091141000
H	4.757357000	-1.479347000	0.747747000
H	5.151027000	0.654626000	1.961710000
C	1.549900000	0.444668000	-2.066720000
H	1.647412000	-0.509951000	-2.597129000
H	1.732461000	1.241270000	-2.799007000
C	0.113749000	0.578720000	-1.549557000
H	-0.069125000	1.586337000	-1.149664000
H	-0.587243000	0.423336000	-2.378013000
N	-0.141478000	-0.436305000	-0.532283000
O	-1.980955000	-1.591643000	0.523070000
H	-1.372411000	-2.331528000	0.323420000
O	0.146269000	-3.188097000	-0.494604000
H	0.291653000	-2.243209000	-0.744282000
H	-0.028758000	-3.675111000	-1.310479000

TS_{F-G}



$$E_{\text{DCM}} = -846.010442$$

$$E = -845.593624$$

$$H^0 = -845.199665$$

$$G^0 = -845.267180$$

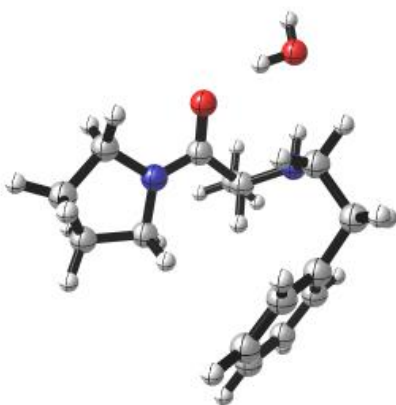
Negative frequency: -1054.22 cm^{-1}

Cartesian coordinates:

C	-0.115851000	-0.485995000	-0.756773000
H	0.085246000	-1.498978000	-0.410196000
C	-1.417423000	0.100984000	-0.321055000
N	-2.252637000	-0.744003000	0.469787000
C	-3.288187000	0.018947000	1.190441000
H	-2.900632000	1.003350000	1.466179000
H	-3.524300000	-0.531946000	2.108364000
C	-3.015697000	-1.699541000	-0.347894000
H	-3.311222000	-2.532625000	0.302249000
C	-4.255476000	-0.937956000	-0.849642000
H	-5.103085000	-1.608299000	-1.021307000
C	-4.526945000	0.100552000	0.263330000
H	-4.620318000	1.101295000	-0.162486000
H	-5.442792000	-0.125053000	0.818466000
H	-2.386696000	-2.100652000	-1.148524000

H	-4.022776000	-0.427867000	-1.787768000
C	0.568726000	-0.074535000	-2.028710000
H	0.290948000	-0.768305000	-2.828393000
H	0.254229000	0.928745000	-2.326996000
H	1.656470000	-0.098492000	-1.906296000
C	3.808114000	-1.726565000	-0.199407000
C	2.928324000	-1.323178000	0.801873000
C	2.657351000	0.033158000	1.014558000
C	3.291318000	0.976330000	0.202897000
C	4.183773000	0.578543000	-0.793391000
C	4.441391000	-0.774500000	-1.000126000
H	4.006726000	-2.783832000	-0.351379000
H	2.446928000	-2.071686000	1.429618000
H	3.081355000	2.033346000	0.352268000
H	4.671430000	1.327372000	-1.411209000
H	5.131709000	-1.088273000	-1.777704000
C	1.664124000	0.466238000	2.068646000
H	1.692604000	1.556953000	2.169418000
H	1.930125000	0.043693000	3.045462000
C	0.232006000	0.037262000	1.732339000
H	0.104670000	-1.047596000	1.792261000
H	-0.478198000	0.491348000	2.431011000
N	-0.109631000	0.473930000	0.378593000
O	-1.973997000	1.124680000	-0.984824000
H	-1.320164000	2.067888000	-0.810412000
O	-0.379429000	2.809004000	-0.365372000
H	0.072714000	1.565924000	0.098551000
H	0.115021000	3.246252000	-1.070783000

G



$$E_{\text{DCM}} = -846.085161$$

$$E = -845.668754$$

$$H^0 = -845.266024$$

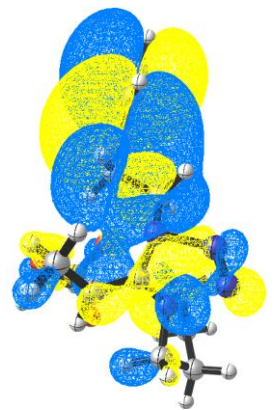
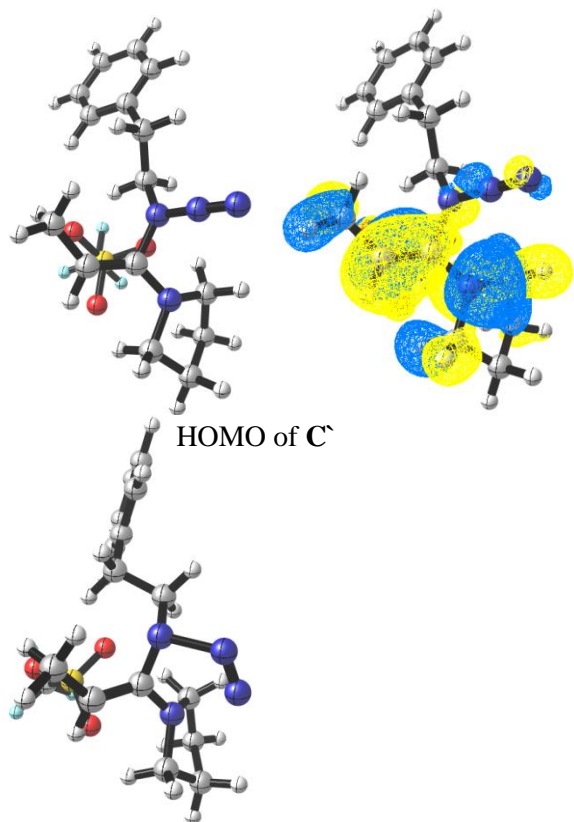
$$G^0 = -845.338590$$

Cartesian coordinates:

C	0.427407000	0.869714000	0.920932000
H	-0.381899000	0.135739000	0.855604000
C	1.643416000	0.321865000	0.154255000
N	1.753364000	-1.016615000	0.042816000
C	2.880045000	-1.616757000	-0.679125000
H	3.790788000	-1.552783000	-0.069799000
H	3.059064000	-1.067565000	-1.606408000
C	0.813007000	-2.024059000	0.555396000
H	-0.117573000	-2.011104000	-0.026346000
C	1.578355000	-3.336527000	0.361776000
H	0.907359000	-4.192483000	0.254723000
C	2.428667000	-3.063385000	-0.883544000
H	3.269034000	-3.753412000	-0.991600000
H	1.808024000	-3.136233000	-1.784231000

H	0.562927000	-1.838289000	1.603880000
H	2.229477000	-3.518269000	1.224782000
C	0.823087000	1.048228000	2.387954000
H	1.195005000	0.115254000	2.824485000
H	1.614517000	1.801846000	2.470047000
H	-0.045327000	1.388246000	2.958526000
C	-2.771690000	-1.749882000	-0.867500000
C	-2.379980000	-0.522470000	-1.400559000
C	-2.470791000	0.652570000	-0.646015000
C	-2.972429000	0.569489000	0.657287000
C	-3.357144000	-0.656311000	1.198466000
C	-3.256681000	-1.821724000	0.438078000
H	-2.704108000	-2.650060000	-1.473305000
H	-1.998790000	-0.471717000	-2.419178000
H	-3.036391000	1.475493000	1.255140000
H	-3.740196000	-0.701911000	2.214403000
H	-3.565402000	-2.776005000	0.855700000
C	-1.965382000	1.960700000	-1.198903000
H	-2.468171000	2.794832000	-0.697991000
H	-2.194708000	2.025705000	-2.270213000
C	-0.448724000	2.129542000	-1.009449000
H	0.078045000	1.343975000	-1.577715000
H	-0.138135000	3.085989000	-1.442185000
N	-0.065285000	2.127754000	0.400097000
O	2.507482000	1.068256000	-0.321708000
H	2.482493000	2.870832000	-0.394335000
O	2.249695000	3.820975000	-0.319930000
H	0.614196000	2.867365000	0.567531000
H	3.078843000	4.306785000	-0.233100000

Selected Molecular Orbitals



HOMO of TS_{C-D}

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