Temperature and Steric Hindrance-Regulated Selective Synthesis of Ketamine Derivatives and 2-Aryl-Cycloketone-1-Carboxamides via Nucleophilic Substitution and Favorskii Rearrangement

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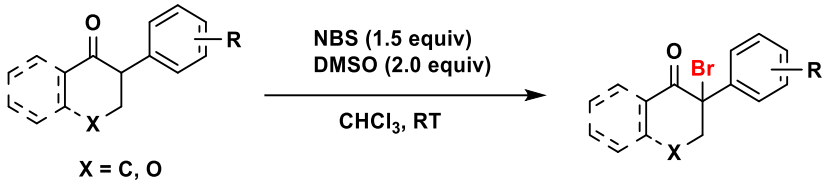
General Information

Chemicals and solvents were purchased from Energy Chemical (Shanghai, China) unless otherwise stated. All the commercial reagents and solvents were used as such without further purification. Analytical thin-layer chromatography (TLC) and silica gel were purchased from Qingdao Shuoyuan Silicone Technology Co., Ltd. Flash chromatography was used by Biotage Isolera One. Silica gel column was purchased from Changzhou Santai Technology Co., Ltd. All heating reactions were carried out using the metal bath. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV-300 spectrometer (300 MHz ^{1}H, 75 MHz ^{13}C) using $CDCl_3$, CD_3OD or DMSO-d6 solutions. Chemical shifts (δ) are expressed in ppm recorded using the residual solvent as the internal reference in all cases ($CDCl_3$: ^{1}H 7.26 ppm, ^{13}C 77.16 ppm; CD_3OD: ^{1}H 3.31 ppm, ^{13}C 49.00 ppm; DMSO-d_6: ^{1}H 2.50 ppm, ^{13}C 39.52 ppm). Signal splitting patterns are described as chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad), coupling constant in hertz (Hz), and integration. High-resolution mass spectrometry (HRMS) analysis was recorded on an LTQ Orbitrap Velos Prospectrometer. Density functional theory (DFT) calculations were conducted using the Gaussian09 software, employing the M062x/6-31g(d,p) level of theory for optimization, frequency analysis, and free energy calculations. The solvation effects were accounted for using the polarizable continuum model (PCM) [1] with tetrahydrofuran (THF) as the solvent. The free energies reported for each molecule correspond to their standard states (T = 298.15 K, P = 1 bar).

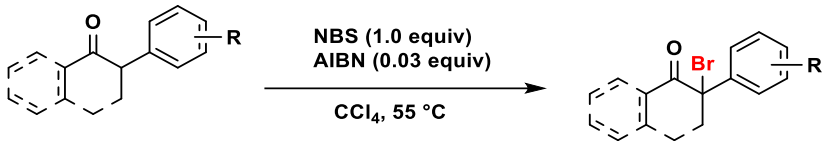
General synthesis procedure and characterization of substrates

Substrates **1a-1d** and **1f-1u** were synthesized according to Method I[2]. The procedures for the preparation of substrates **1e** and **1v** were followed with the literature (Method II)[3].**Method I**



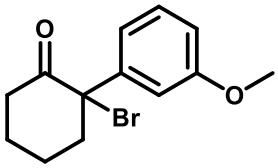
To a solution of 2-arylcycloket-1-ones (1 mmol, 1.0 equiv.) in $CHCl_3$ (4.0 mL), DMSO (2.0 mmol, 2.0 equiv.) and N-bromosuccinimide (1.5 mmol, 1.5 equiv.) were added successively at room temperature, and the mixture was stirred at room temperature until the consumption of starting material (monitored by TLC). Then the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ at room temperature, and the aqueous layer was extracted with dichloromethane (DCM) 2 times. The combined organic extracts were dried over anhydrous Na_2SO_4 and removed under a vacuum. The resulting crude product was purified by flash chromatography (petroleum ether/ethyl acetate) to afford the desired 2-bromo-2-aryl-cycloketones.

Method II



To a solution of 2-aryl-1-one (1.0 equiv.) in anhydrous CCl_4, N-bromosuccinimide (1.0 equiv.), and 2,2'-azabis[isobutyronitrile] (AIBN, 0.03 equiv.) were added at room temperature. The mixture was heated at 55 °C under an N_2 atmosphere until the consumption of NBS. After the reaction was cooled to room temperature, the precipitated succinimide was removed by filtration and CCl_4 was removed under reduced pressure. The resulting crude product was purified by flash chromatography (petroleum ether/ethyl acetate) to afford the desired 2-bromo-2-aryl-1-one.

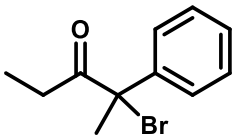
2-Bromo-2-(3-methoxyphenyl)cyclohexan-1-one (1e)[4].



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 96:4). Brown oil, 576 mg, 58% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.30 (t, *J* = 8.0 Hz, 1H), 7.02-6.91 (m, 2H), 6.85 (dd, *J* = 8.2, 2.0 Hz,

1H), 3.81 (s, 3H), 2.97 (ddt, *J* = 12.6, 6.8, 4.4 Hz, 2H), 2.67-2.40 (m, 2H), 2.03-1.74 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.9, 159.9, 140.8, 129.9, 119.6, 113.8, 113.7, 72.8, 55.5, 42.7, 39.0, 27.4, 23.5. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{13}H_{16}BrO_2$, 283.0328; found, 283.0323.

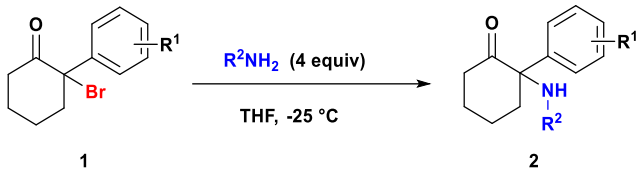
2-Bromo-2-phenylpentan-3-one (1v).



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 98:2). Colorless oil, 254 mg, 85% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.49-7.44 (m, 2H), 7.39-7.34 (m, 2H), 7.34-7.29 (m, 1H), 2.78 (dq, *J* = 17.3, 7.3 Hz, 1H), 2.35 (dq, *J* = 17.3, 7.3 Hz, 1H), 2.14 (s, 3H), 1.06 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 205.3, 140.3, 128.9, 128.4, 127.0, 71.1, 31.1, 31.0, 9.6. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{11}H_{14}BrO$, 241.0223; found, 241.0220.

General synthesis procedure and characterization of products

Synthesis of ketamine derivatives 2 by nucleophilic substitution.

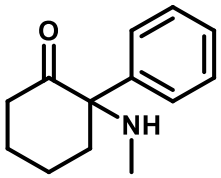


1 2

To a solution of 2-bromo-2-phenylcyclohexan-1-one (**1a**, 253.1 mg, 1.0 mmol) in THF (5.0 mL), methylamine (27 wt% in EtOH, 0.63 mL, 4.0 equiv.) was added dropwise at -25 °C under N_2 atmosphere. The reaction mixture was stirred at this temperature until TLC showed full conversion of **1a**, then the reaction was warmed to room temperature and quenched by saturated aqueous Na_2CO_3 (1.5 mL) and water (3.0 mL). The mixture was extracted with DCM (3 × 5 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and removed under a vacuum. The residue was dissolved in Et_2O (5.0 mL) and DCM (1.0 mL), 1 M HCl (5.0 mL), and H_2O (5.0 mL) were then added and stirred for 15 min. The aqueous layer was separated and washed with Et_2O (5.0 mL) and DCM (1.0 mL) 2 times. Then saturated aqueous Na_2CO_3 (3.0 mL) was added, and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and removed under a vacuum to afford 2-(methylamino)-2-phenylcyclohexan-1-one (**2a$_1$**, 163.5 mg, 80%) as a brown oil.

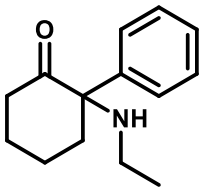
For the gram-scale nucleophilic substitution, to a solution of 2-bromo-2-phenylcyclohexan-1-one (**1a**, 1.80 g, 7.1 mmol) in THF (35.0 mL), methylamine (27 wt% in EtOH, 4.45 mL, 4.0 equiv.) was added dropwise at -25 °C under N_2 atmosphere. The reaction mixture was stirred at this temperature until TLC showed full conversion of **1a**, then the reaction was warmed to room temperature and quenched by saturated aqueous Na_2CO_3 (7.0 mL) and H_2O (30 mL). The mixture was extracted with DCM (3 × 30 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and removed under a vacuum. The residue was dissolved in Et_2O (17.0 mL) and DCM (3.0 mL), 1 M HCl (10 mL), and H_2O (20 mL) was then added and stirred for 15 min. The aqueous layer was separated and washed with Et_2O (16.0 mL) and DCM (3.0 mL) 2 times. Then saturated aqueous Na_2CO_3 (7.0 mL) was added, and the aqueous layer was extracted with DCM (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and removed under a vacuum to afford 2-(methylamino)-2-phenylcyclohexan-1-one (**2a$_1$**, 1.06 g, 73%) as a brown oil.

***2-(Methylamino)-2-phenylcyclohexan-1-one (2a$_1$)*[5].**



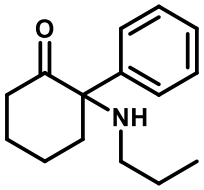
Brown oil, 163.5 mg, 80% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45-7.13 (m, 5H), 2.99-2.75 (m, 1H), 2.49-2.13 (m, 3H), 2.02 (s, 3H), 1.99-1.89 (m, 1H), 1.88-1.63 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.6, 138.9, 128.9, 127.6, 127.2, 69.9, 39.9, 35.5, 29.0, 27.9, 22.4. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{13}H_{18}NO$, 204.1383; found, 204.1379.

2-(Ethylamino)-2-phenylcyclohexan-1-one (2a$_2$).



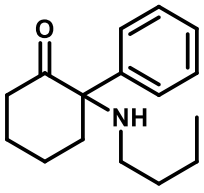
Brown oil, 160.0 mg, 74% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43-7.33 (m, 2H), 7.32-7.19 (m, 3H), 3.00-2.82 (m, 1H), 2.49-2.20 (m, 3H), 2.12 (s, 1H), 2.10-2.00 (m, 1H), 2.00-1.63 (m, 5H), 0.99 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.6, 139.4, 128.9, 127.5, 127.1, 69.8, 39.8, 36.6, 36.1, 27.8, 22.4, 15.7. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{20}NO$, 218.1539; found, 218.1534.

***2-Phenyl-2-(propylamino)cyclohexan-1-one (2a$_3$)*[6].**



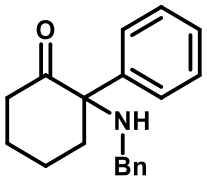
Yellow oil, 158.9 mg, 69% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.42-7.33 (m, 2H), 7.32-7.21 (m, 3H), 2.95-2.81 (m, 1H), 2.47-2.37 (m, 1H), 2.36-2.15 (m, 3H), 2.02-1.88 (m, 2H), 1.88-1.63 (m, 4H), 1.51-1.23 (m, 2H), 0.80 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.5, 139.5, 128.9, 127.5, 127.1, 69.6, 44.2, 39.8, 36.1, 27.7, 23.8, 22.4, 11.9. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO$, 232.1696; found, 232.1691.

***2-(Butylamino)-2-phenylcyclohexan-1-one (2a$_4$)*[6].**



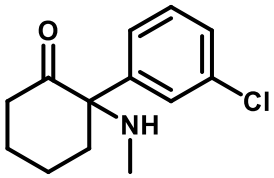
Yellow oil, 164.1 mg, 66% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43-7.32 (m, 2H), 7.31-7.16 (m, 3H), 2.88 (d, *J* = 10.5 Hz, 1H), 2.48-2.21 (m, 3H), 2.18 (s, 1H), 2.04-1.61 (m, 6H), 1.48-1.08 (m, 4H), 0.80 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.5, 139.5, 128.8, 127.4, 127.0, 69.7, 41.9, 39.8, 36.2, 32.8, 27.7, 22.4, 20.4, 14.0. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{16}H_{24}NO$, 246.1852; found, 246.1846.

2-(Benzylamino)-2-phenylcyclohexan-1-one (2a$_5$)[7]



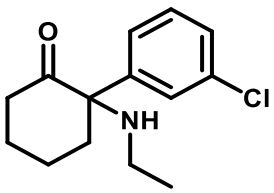
Light yellow oil, 147.0 mg, 53% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43-7.36 (m, 2H), 7.34-7.27 (m, 3H), 7.27-7.15 (m, 5H), 3.32 (dd, *J* = 85.9, 12.3 Hz, 2H), 2.93-2.82 (m, 1H), 2.60-2.39 (m, 2H), 2.39-2.30 (m, 1H), 2.02-1.88 (m, 2H), 1.88-1.69 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.4, 140.9, 139.5, 129.0, 128.4, 127.7, 127.3, 126.9, 70.1, 47.1, 40.0, 36.8, 27.8, 22.5. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{19}H_{22}NO$, 280.1696; found, 280.1692.

2-(3-Chlorophenyl)-2-(methylamino)cyclohexan-1-one (2c$_1$)



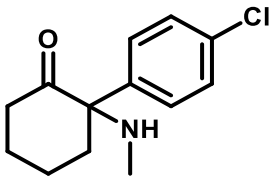
Yellow oil, 167.6 mg, 71% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36-7.23 (m, 3H), 7.11 (dt, *J* = 7.4, 1.6 Hz, 1H), 2.81 (ddd, *J* = 10.2, 5.3, 2.7 Hz, 1H), 2.50-2.40 (m, 1H), 2.37-2.27 (m, 1H), 2.25 (s, 1H), 2.04 (s, 3H), 2.02-1.92 (m, 1H), 1.91-1.67 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 210.8, 141.4, 135.0, 130.2, 127.8, 127.4, 125.5, 69.6, 39.9, 35.6, 29.0, 27.7, 22.3. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{13}H_{17}ClNO$, 238.0993; found, 238.0988.

2-(3-Chlorophenyl)-2-(ethylamino)cyclohexan-1-one (2c$_2$)



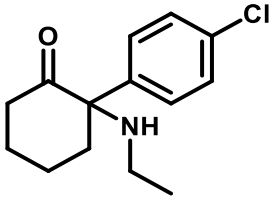
Yellow oil, 167.4 mg, 67% yield. **^{1}H NMR** (300 MHz, $CDCl_3$):δ 7.39-7.20 (m, 3H), 7.11 (d, *J* = 7.3 Hz, 1H), 2.92-2.70 (m, 1H), 2.54-2.39 (m, 1H), 2.38-2.21 (m, 2H), 2.14 (s, 1H), 2.11-1.94 (m, 2H), 1.93-1.60 (m, 4H), 1.02 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 210.7, 141.9, 134.9, 130.2, 127.8, 127.2, 125.4, 69.6, 39.8, 36.7, 36.3, 27.6, 22.3, 15.7. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{19}ClNO$, 252.1150; found, 252.1144.

2-(4-Chlorophenyl)-2-(methylamino)cyclohexan-1-one (2d$_1$).



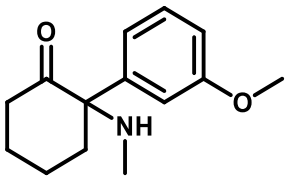
Yellow oil, 186.6 mg, 79% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.19 (dd, *J* = 49.4, 8.5 Hz, 4H), 2.78-2.63 (m, 1H), 2.41-2.30 (m, 1H), 2.28-2.13 (m, 2H), 1.95 (s, 3H), 1.92-1.83 (m, 1H), 1.82-1.51 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 210.9, 137.6, 133.3, 128.9, 128.6, 69.4, 39.7, 35.7, 28.8, 27.6, 22.2. HRMS (ESI^+) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}ClNO$, 238.0993; found, 238.0988.

2-(4-Chlorophenyl)-2-(ethylamino)cyclohexan-1-one (2d$_2$).



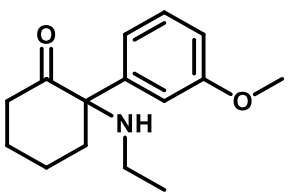
Yellow oil, 155.0 mg, 62% yield. **^{1}H NMR** (300 MHz, $CDCl_3$):δ 7.25 (dd, *J* = 47.7, 8.6 Hz, 4H), 2.88-2.68 (m, 1H), 2.49-2.36 (m, 1H), 2.35-2.19 (m, 2H), 2.15 (s, 1H), 2.10-1.88 (m, 2H), 1.88-1.54 (m, 4H), 0.99 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ211.0, 138.2, 133.4, 129.1, 128.6, 69.4, 39.7, 36.7, 36.4, 27.7, 22.3, 15.7. HRMS (ESI^+) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{19}ClNO$, 252.1150; found, 252.1144.

2-(3-Methoxyphenyl)-2-(methylamino)cyclohexan-1-one (2e$_1$).



Brown oil, 172.0 mg, 74% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.28 (t, *J* = 7.9 Hz, 1H), 6.79 (ddd, *J* = 7.7, 4.8, 2.1 Hz, 3H), 3.79 (s, 3H), 2.91-2.76 (m, 1H), 2.44-2.18 (m, 3H), 2.02 (s, 3H), 1.99-1.88 (m, 1H), 1.72 (tdd, *J* = 16.3, 12.3, 8.3 Hz, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.5, 160.1, 140.5, 129.9, 119.6, 113.3, 112.4, 69.8, 55.4, 39.9, 35.4, 29.0, 27.8, 22.4. HRMS (ESI^+) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1489; found, 234.1483.

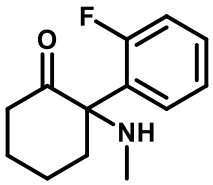
2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexan-1-one (2e$_2$)[8].



Brown oil, 152.9 mg, 62% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.27 (t, *J* = 7.9 Hz, 1H), 6.84-6.75 (m, 3H), 3.79

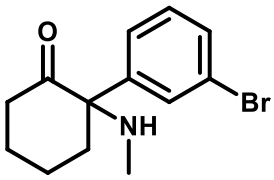
(s, 3H), 2.92-2.78 (m, 1H), 2.43-2.21 (m, 3H), 2.12 (s, 1H), 2.09-1.99 (m, 1H), 1.94 (ddd, *J* = 11.4, 6.5, 3.6 Hz, 1H), 1.87-1.59 (m, 4H), 0.98 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.3, 160.1, 141.1, 129.9, 119.4, 113.2, 112.3, 69.7, 55.3, 39.8, 36.6, 36.0, 27.7, 22.5, 15.8. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_2$, 248.1645; found, 248.1638.

2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one (2f)[9].



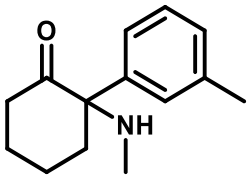
Yellow oil, 95.4 mg, 43% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43 (td, *J* = 7.7, 1.7 Hz, 1H), 7.37-7.27 (m, 1H), 7.21 (td, *J* = 7.5, 1.3 Hz, 1H), 7.06 (ddd, *J* = 11.5, 8.1, 1.2 Hz, 1H), 2.84-2.71 (m, 1H), 2.56-2.39 (m, 2H), 2.36 (s, 1H), 2.12 (s, 3H), 2.07-1.91 (m, 1H), 1.90-1.60 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 210.2, 161.2 (d, *J* = 247.1 Hz), 129.6 (d, *J* = 8.8 Hz), 128.9 (d, *J* = 4.7 Hz), 127.1 (d, *J* = 12.5 Hz), 124.3 (d, *J* = 3.2 Hz), 116.4 (d, *J* = 23.1 Hz), 68.40 (d, *J* = 2.3 Hz), 39.5, 38.3, 29.3, 28.6, 22.1. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{13}H_{17}FNO$, 222.1289; found, 222.1286.

2-(3-Bromophenyl)-2-(methylamino)cyclohexan-1-one (2g).



Brown oil, 208.8 mg, 74% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44-7.36 (m, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.17-7.11 (m, 1H), 2.83-2.71 (m, 1H), 2.49-2.38 (m, 1H), 2.36-2.22 (m, 1H), 2.15 (s, 1H), 2.03 (s, 3H), 2.00-1.92 (m, 1H), 1.89-1.64 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 210.8, 141.7, 130.8, 130.5, 130.3, 126.0, 123.2, 69.7, 39.9, 35.7, 29.0, 27.7, 22.3. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{13}H_{17}BrNO$, 282.0488; found, 282.0483.

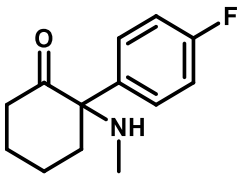
2-(Methylamino)-2-(m-tolyl)cyclohexan-1-one (2h).



Brown oil, 172.2 mg, 79% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25 (t, *J* = 7.6 Hz, 1H), 7.12-6.98 (m, 3H), 2.93-2.79 (m, 1H), 2.43-2.30 (m, 2H), 2.34 (s, 3H), 2.24 (s, 1H), 2.02 (s, 3H), 1.98-1.88 (m, 1H), 1.87-1.65 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.8, 138.9, 138.7, 128.7, 128.4, 127.8, 124.3, 69.9, 40.0, 35.4, 29.1, 27.9, 22.4, 21.7.

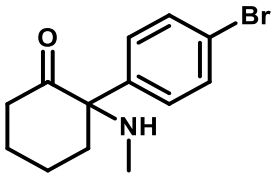
HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{14}H_{20}NO$, 218.1539; found, 218.1535.

2-(4-Fluorophenyl)-2-(methylamino)cyclohexan-1-one (2i).



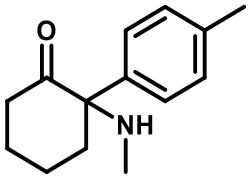
Brown oil, 180.6 mg, 82% yield. **^{1}H NMR** (300 MHz, CD_3OD): δ 7.57-7.48 (m, 2H), 7.35 (t, *J* = 8.6 Hz, 2H), 3.24 (dd, *J* = 13.6, 2.3 Hz, 1H), 2.57-2.39 (m, 2H), 2.34 (s, 3H), 2.15-1.96 (m, 3H), 1.88-1.72 (m, 2H). **^{13}C NMR** (75 MHz, CD_3OD): δ 207.0, 165.2 (d, *J* = 250.6 Hz), 132.1 (d, *J* = 8.8 Hz), 127.1 (d, *J* = 3.5 Hz), 118.2 (d, *J* = 22.2 Hz), 72.5, 40.0, 33.0, 28.5, 27.1, 22.7. HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{13}H_{17}FNO$, 222.1289; found, 222.1284.

2-(4-Bromophenyl)-2-(methylamino)cyclohexan-1-one (2j).



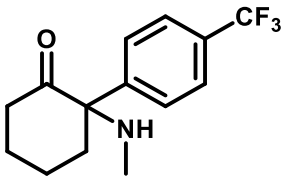
Light yellow oil, 198.2 mg, 70% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.52-7.44 (m, 2H), 7.13-7.06 (m, 2H), 2.83-2.71 (m, 1H), 2.47-2.37 (m, 1H), 2.27 (ddd, *J* = 14.0, 9.1, 4.7 Hz, 1H), 2.16 (s, 1H), 2.01 (s, 3H), 1.94 (ddd, *J* = 12.1, 5.6, 2.8 Hz, 1H), 1.87-1.61 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.0, 138.2, 132.0, 129.1, 121.7, 69.5, 39.8, 35.8, 29.0, 27.7, 22.3. HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{13}H_{17}BrNO$, 282.0488; found, 282.0483.

2-(Methylamino)-2-(p-tolyl)cyclohexan-1-one (2k).



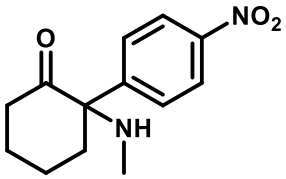
Brown oil, 175.0 mg, 81% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.14 (dd, *J* = 22.3, 8.2 Hz, 4H), 2.94-2.76 (m, 1H), 2.42-2.30 (m, 2H), 2.33 (s, 3H), 2.17 (s, 1H), 2.01 (s, 3H), 1.98-1.87 (m, 1H), 1.85-1.60 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.9, 137.3, 135.9, 129.6, 127.2, 69.7, 39.9, 35.5, 29.0, 27.9, 22.4, 21.1. HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{14}H_{20}NO$, 218.1539; found, 218.1534.

2-(Methylamino)-2-(4-(trifluoromethyl)phenyl) cyclohexan-1-one (2l).



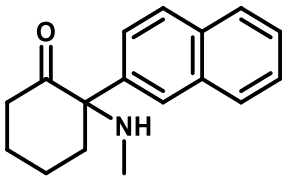
Yellow oil, 200.8 mg, 74% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.47 (dd, *J* = 76.0, 8.1 Hz, 4H), 2.86-2.69 (m, 1H), 2.53-2.36 (m, 1H), 2.32-2.21 (m, 1H), 2.19 (s, 1H), 2.01 (d, *J* = 2.2 Hz, 3H), 1.97-1.55 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 210.7, 143.4, 129.7 (q, *J* = 32.4 Hz), 127.7, 125.8 (dd, *J* = 7.0, 3.3 Hz), 124.1 (q, *J* = 272.0 Hz), 69.7, 39.8, 36.0, 28.9, 27.6, 22.1. HRMS (ESI^+) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}F_3NO$, 272.1257; found, 272.1250.

2-(Methylamino)-2-(4-nitrophenyl)cyclohexan-1-one (2m).



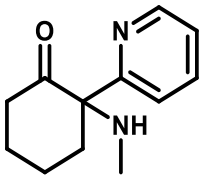
Red brown oil, 151.9 mg, 61% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 233.3, 8.9 Hz, 4H), 2.77-2.62 (m, 1H), 2.59-2.44 (m, 1H), 2.34-2.15 (m, 2H), 2.05 (s, 3H), 2.01-1.76 (m, 4H), 1.75-1.59 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 210.0, 147.3, 147.1, 128.3, 123.9, 69.7, 39.8, 36.8, 29.1, 27.4, 22.0. HRMS (ESI^+) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}N_2O_3$, 249.1234; found, 249.1228.

2-(Methylamino)-2-(naphthalen-2-yl)cyclohexan-1-one (2n).



Brown oil, 210.8 mg, 83% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.88-7.79 (m, 3H), 7.73 (d, *J* = 1.5 Hz, 1H), 7.54-7.44 (m, 2H), 7.29 (dd, *J* = 8.6, 1.9 Hz, 1H), 3.09-2.97 (m, 1H), 2.50-2.22 (m, 3H), 2.04 (s, 3H), 2.00-1.65 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.7, 136.3, 133.3, 132.7, 128.9, 128.2, 127.7, 126.5, 126.4, 126.4, 124.9, 70.1, 40.0, 35.7, 29.0, 28.0, 22.5. HRMS (ESI^+) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}NO$, 254.1539; found, 254.1533.

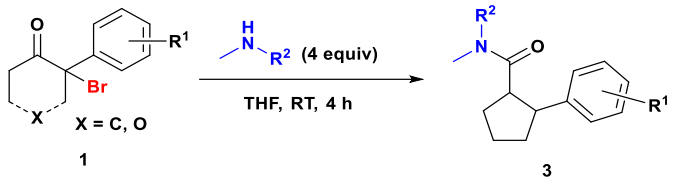
2-(Methylamino)-2-(pyridin-2-yl)cyclohexan-1-one (2o).



Yellow oil, 83.4 mg, 41% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.58 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.70 (td, *J* = 7.8, 1.8

Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.18 (ddd, J = 7.4, 4.8, 0.9 Hz, 1H), 2.94-2.82 (m, 1H), 2.53-2.43 (m, 1H), 2.41-2.26 (m, 2H), 2.07 (s, 3H), 2.00-1.91 (m, 1H), 1.87-1.60 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.2, 159.9, 149.5, 136.8, 122.4, 122.0, 72.0, 40.6, 35.9, 29.5, 27.9, 22.4. HRMS (ESI$^+$) m/z $[M + H]^+$ calcd for $C_{12}H_{17}N_2O$, 205.1335; found, 205.1331.

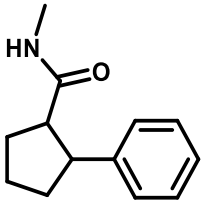
Synthesis of 2-aryl-cycloketone-1-carboxamides 3 by Favorskii-rearrangement.



To a solution of 2-bromo-2-phenylcyclohexan-1-one (**1a**, 253.1 mg, 1.0 mmol) in THF (3.0 mL), dimethylamine (2 M in THF, 2.0 mL, 4.0 equiv.) was added dropwise at room temperature under N_2 atmosphere. The reaction mixture was stirred at this temperature until TLC showed full conversion of **1a**, then saturated aqueous Na_2CO_3 (1.5 mL) and water (3.0 mL) were added. The mixture was extracted with DCM (3 × 5 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and removed under a vacuum. The resulting crude product was purified by flash chromatography (petroleum ether/ethyl acetate 83:17) to afford *N*,*N*-dimethyl-2-phenylcyclopentane-1-carboxamide (**3a$_4$**, 167.1 mg, 77%) as a colorless oil.

For the gram-scale Favorskii-rearrangement, to a solution of 2-bromo-2-phenylcyclohexan-1-one (**1a**, 2.20 g, 8.7 mmol) in THF (26.0 mL), dimethylamine (2 M in THF, 17.4 mL, 4.0 equiv.) was added dropwise at room temperature under N_2 atmosphere. The reaction mixture was stirred at this temperature until TLC showed full conversion of **1a**, then saturated aqueous Na_2CO_3 (9 mL) and water (25.0 mL) were added. The mixture was extracted with DCM (3 × 40 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and removed under a vacuum. The resulting crude product was purified by flash chromatography (petroleum ether/ethyl acetate 82:18) to afford *N*,*N*-dimethyl-2-phenylcyclopentane-1-carboxamide (**3a$_4$**, 1.27 g, 67%) as a colorless oil.

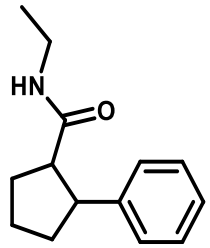
***N*-methyl-2-phenylcyclopentane-1-carboxamide (3a$_1$)**.



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 81:19). White solid, 75.4 mg, 37% yield at reflux. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36-7.16 (m, 5H), 5.19 (s, 1H), 3.33-3.18 (m, 1H), 2.68 (d, J =

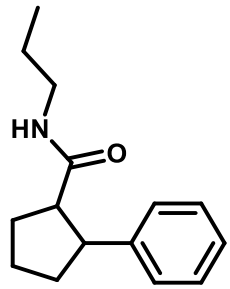
4.9 Hz, 3H), 2.50 (dd, *J* = 18.2, 8.7 Hz, 1H), 2.23-1.95 (m, 3H), 1.92-1.73 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.6, 144.4, 128.7, 127.3, 126.5, 55.0, 50.6, 35.3, 30.5, 26.4, 25.3. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{13}H_{18}NO$, 204.1383; found, 204.1381.

N-ethyl-2-phenylcyclopentane-1-carboxamide (3a$_2$).



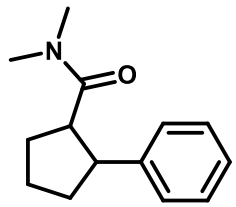
The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 82:18). Yellow oil, 90.0 mg, 41% yield at reflux. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36-7.14 (m, 5H), 5.07 (s, 1H), 3.30-3.02 (m, 3H), 2.45 (dd, *J* = 18.2, 8.7 Hz, 1H), 2.21-1.94 (m, 3H), 1.92-1.70 (m, 3H), 0.95 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.7, 144.3, 128.7, 127.4, 126.6, 55.2, 50.8, 35.2, 34.3, 30.2, 25.2, 14.9. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{20}NO$, 218.1539; found, 218.1535.

2-Phenyl-N-propylcyclopentane-1-carboxamide (3a$_3$).



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 84:16). Yellow oil, 147.2 mg, 64% yield at reflux. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35-7.10 (m, 5H), 5.24 (s, 1H), 3.32-3.08 (m, 2H), 3.00 (tt, *J* = 9.3, 4.6 Hz, 1H), 2.49 (dd, *J* = 18.3, 8.7 Hz, 1H), 2.23-1.94 (m, 3H), 1.93-1.70 (m, 3H), 1.40-1.24 (m, 2H), 0.73 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.7, 144.2, 128.7, 127.3, 126.5, 55.1, 50.7, 41.1, 35.2, 30.2, 25.1, 22.8, 11.3. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO$, 232.1696; found, 232.1692.

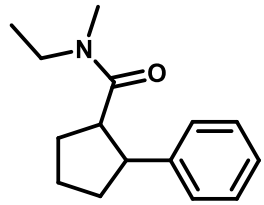
N,N-dimethyl-2-phenylcyclopentane-1-carboxamide (3a$_4$).



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 82:18). Colorless oil, 167.1 mg, 77% yield.**^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.34-7.21 (m, 4H), 7.21-7.13 (m, 1H), 3.55-3.42 (m, 1H), 3.07-2.95

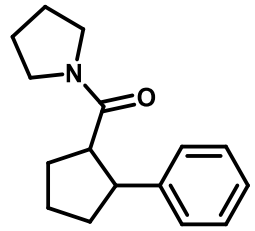
(m, 1H), 2.88 (s, 3H), 2.74 (s, 3H), 2.24-2.13 (m, 1H), 2.13-2.01 (m, 1H), 1.99-1.73 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.3, 144.7, 128.5, 127.4, 126.3, 49.9, 49.9, 37.2, 35.8, 34.7, 31.0, 25.5. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{20}NO$, 218.1539; found, 218.1536.

N-ethyl-N-methyl-2-phenylcyclopentane-1-carboxamide (3a$_5$). cis- and trans- as a mixture (trans- :cis- 1.05 : 1 by NMR)



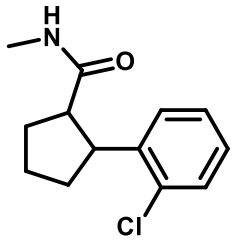
The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 87:13). Light Yellow oil, 147.1 mg, 64% yield. The configuration of **3a$_5$** was assigned based on the known configuration of the similar compound methyl 2-phenylcyclopentane-1-carboxylate.[10] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.30-7.21 (m, 8.8H), 7.20-7.14 (m, 2.0H), 3.56-3.36 (m, 3.2H), 3.29 (dq, *J* = 14.1, 7.1 Hz, 1.2H), 3.19-3.03 (m, 2.4H), 2.97 (dd, *J* = 17.0, 9.0 Hz, 2.3H), 2.85 (s, 3.2H, *trans*), 2.67 (s, 3.0H, *cis*), 2.23-2.15 (m, 2.2H), 2.09-2.00 (m, 2.3H), 1.98-1.77 (m, 8.7H), 1.01 (t, *J* = 7.1 Hz, 3.2H, *cis*), 0.88 (t, *J* = 7.2 Hz, 3.5H, *trans*). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.0, 174.7, 144.6, 144.5, 128.5, 128.5, 127.4, 127.3, 126.3, 50.1, 50.0, 49.8, 44.3, 42.7, 34.6, 34.5, 34.5, 33.2, 31.6, 30.8, 25.4, 25.4, 13.9, 12.3. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO$, 232.1696; found, 232.1693.

(2-Phenylcyclopentyl)(pyrrolidin-1-yl)methanone (3a$_6$).



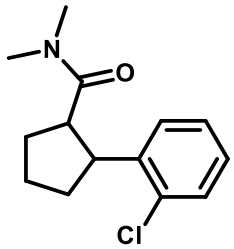
The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 80:20). Light pink oil, 179.8 mg, 74% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.33-7.26 (m, 4H), 7.25-7.16 (m, 1H), 3.54-3.34 (m, 3H), 3.32-3.21 (m, 1H), 2.94-2.81 (m, 2H), 2.26-2.14 (m, 1H), 2.12-1.98 (m, 2H), 1.97-1.83 (m, 3H), 1.83-1.61 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.9, 144.6, 128.5, 127.4, 126.3, 52.2, 50.2, 46.4, 45.9, 34.5, 30.7, 26.0, 25.4, 24.4. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{16}H_{22}NO$, 244.1696; found, 244.1691.

2-(2-Chlorophenyl)-N-methylcyclopentane-1-carboxamide (3b$_1$).



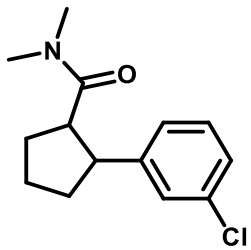
The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 70:30). White solid, 162.5 mg, 68% yield**. ^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37-7.25 (m, 2H), 7.21 (t, *J* = 7.0 Hz, 1H), 7.12 (td, *J* = 7.7, 1.6 Hz, 1H), 5.70 (s, 1H), 3.78 (q, *J* = 9.1 Hz, 1H), 2.80-2.71 (m, 1H), 2.68 (d, *J* = 4.8 Hz, 3H), 2.31-2.16 (m, 1H), 2.06 (dd, *J* = 15.0, 7.3 Hz, 2H), 1.96-1.80 (m, 2H), 1.68 (ddd, *J* = 17.3, 12.3, 8.5 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.3, 141.7, 134.2, 129.8, 127.8, 127.5, 127.2, 52.8, 46.4, 34.3, 30.7, 26.4, 25.2. HRMS (ESI^+) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}ClNO$, 238.0993; found, 238.0988.

2-(2-Chlorophenyl)-N,N-dimethylcyclopentane-1-carboxamide (3b₂).



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 80:20). Colorless oil, 203.4 mg, 81% yield. **^{1}H NMR** (300 MHz, CD_3OD): δ 7.38 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.24 (t, *J* = 7.1 Hz, 1H), 7.13 (td, *J* = 7.7, 1.5 Hz, 1H), 3.83 (dd, *J* = 17.6, 9.4 Hz, 1H), 3.36 (dd, *J* = 16.7, 8.2 Hz, 1H), 2.83 (s, 6H), 2.14 (dtd, *J* = 15.0, 11.7, 5.5 Hz, 2H), 1.96-1.79 (m, 3H), 1.79-1.65 (m, 1H). **^{13}C NMR** (75 MHz, CD_3OD): δ 177.3, 142.8, 135.1, 130.7, 129.1, 128.7, 128.4, 48.8, 47.8, 37.6, 36.2, 35.1, 31.6, 26.3. HRMS (ESI^+) *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{18}ClNNaO$, 274.0969; found,274.0961.

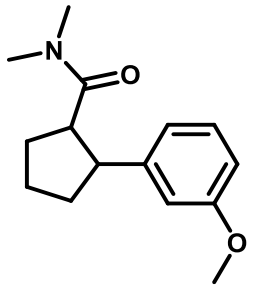
2-(3-Chlorophenyl)-N,N-dimethylcyclopentane-1-carboxamide (3c).



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 84:16). Colorless oil, 169.9 mg, 68% yield**. ^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.24-7.20 (m, 1H), 7.20-7.09 (m, 3H), 3.56-3.44 (m, 1H), 2.97 (dd, *J* = 16.7, 8.9 Hz, 1H), 2.89 (s, 3H), 2.81 (s, 3H), 2.23-2.11 (m, 1H), 2.10-1.99 (m, 1H), 1.93-1.70 (m, 4H). **^{113}C NMR** (75 MHz, $CDCl_3$): δ 174.8, 146.9, 134.3, 129.8, 127.4, 126.5, 125.9, 49.8, 49.3, 37.2, 35.9, 34.6, 30.9, 25.3. HRMS

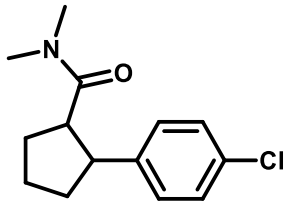
(ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{14}H_{19}ClNO$, 252.1150; found, 252.1145.

2-(3-Methoxyphenyl)-N,N-dimethylcyclopentane-1-carboxamide (3d).



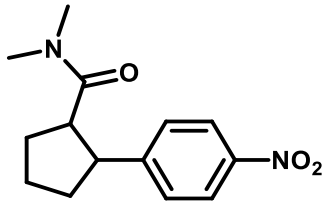
The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 84:16). Colorless oil, 174.3 mg, 71% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.18 (t, *J* = 7.9 Hz, 1H), 6.87-6.76 (m, 2H), 6.72 (dd, *J* = 8.1, 2.1 Hz, 1H), 3.78 (s, 3H), 3.45 (dd, *J* = 17.3, 9.3 Hz, 1H), 3.01 (dd, *J* = 16.6, 9.0 Hz, 1H), 2.88 (s, 3H), 2.76 (s, 3H), 2.23-2.11 (m, 1H), 2.04 (ddd, *J* = 9.0, 7.7, 4.1 Hz, 1H), 1.95-1.75 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.3, 159.7, 146.5, 129.5, 119.8, 113.2, 111.4, 55.3, 50.0, 49.7, 37.2, 35.8, 34.8, 31.0, 25.5. HRMS (ESI+) m/z [M + H]+ calcd for $C_{15}H_{22}NO_2$, 248.1645; found, 248.1639.

2-(4-Chlorophenyl)-N,N-dimethylcyclopentane-1-carboxamide (3e).



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 84:16). Colorless oil, 169.9 mg, 68% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25-7.14 (m, 4H), 3.54-3.42 (m, 1H), 2.99-2.89 (m, 1H), 2.88 (s, 3H), 2.79 (s, 3H), 2.11 (tdd, *J* = 11.7, 10.7, 4.5 Hz, 2H), 1.93-1.69 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.9, 143.1, 131.9, 128.8, 128.6, 50.0, 49.1, 37.2, 35.8, 34.5, 30.9, 25.3. HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{14}H_{19}ClNO$, 252.1150; found, 252.1145.

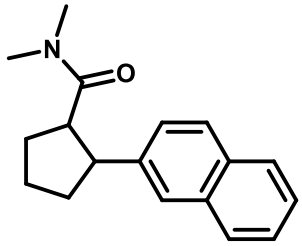
N,N-dimethyl-2-(4-nitrophenyl)cyclopentane-1-carboxamide (3f).



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 78:22). Red brown oil, 202.5 mg, 77% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.76 (dd, *J* = 212.7, 8.7 Hz, 4H), 3.75-3.62 (m, 1H), 2.98 (dd, *J* = 17.3, 9.3 Hz, 1H), 2.89 (s, 3H), 2.86 (s, 3H), 2.17 (tdd, *J* = 13.6, 10.7, 6.4 Hz, 2H), 1.96-1.73 (m, 4H). **^{13}C NMR** (75

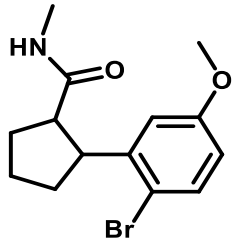
MHz, $CDCl_3$): δ 174.2, 152.7, 146.6, 128.3, 123.8, 50.1, 49.1, 37.2, 35.8, 34.3, 30.9, 25.2. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_3$, 263.1390; found, 263.1386.

N,N-dimethyl-2-(naphthalen-2-yl)cyclopentane-1-carboxamide (3g).



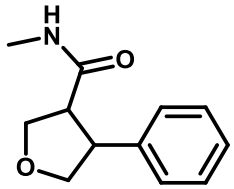
The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 85:15). Colorless oil, 157.9 mg, 59% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.82-7.73 (m, 3H), 7.69 (s, 1H), 7.48-7.37 (m, 3H), 3.66 (dd, *J* = 17.2, 9.2 Hz, 1H), 3.13 (dd, *J* = 16.5, 8.9 Hz, 1H), 2.87 (s, 3H), 2.72 (s, 3H), 2.25 (dd, *J* = 13.2, 6.7 Hz, 1H), 2.17-2.06 (m, 1H), 2.05-1.88 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.3, 142.1, 133.6, 132.4, 128.2, 127.8, 127.6, 126.0, 126.0, 125.8, 125.4, 50.1, 49.9, 37.2, 35.8, 34.8, 31.1, 25.6. HRMS (ESI^+) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{21}NNaO$, 290.1515; found, 290.1507.

2-(2-Bromo-5-methoxyphenyl)-N-methylcyclopentane-1-carboxamide (3h).



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 79:21). White solid, 148.7 mg, 48% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 3.0 Hz, 1H), 6.63 (dd, *J* = 8.8, 3.0 Hz, 1H), 5.29 (s, 1H), 3.78 (s, 3H), 3.68 (dd, *J* = 17.4, 9.0 Hz, 1H), 2.71 (d, *J* = 4.8 Hz, 3H), 2.65 (dd, *J* = 17.3, 8.6 Hz, 1H), 2.31-2.17 (m, 1H), 2.14-1.99 (m, 2H), 1.95-1.78 (m, 2H), 1.65 (ddd, *J* = 17.2, 12.5, 8.4 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.0, 159.3, 144.7, 133.7, 115.5, 114.1, 113.0, 55.6, 53.4, 49.1, 34.8, 30.4, 26.6, 25.3. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{19}BrNO_2$, 312.0594; found, 312.0589.

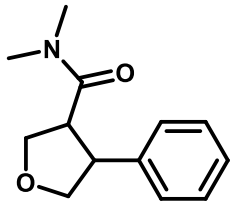
N-methyl-4-phenyltetrahydrofuran-3-carboxamide (3i$_1$).



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 80:20). Light yellow oil, 80.9

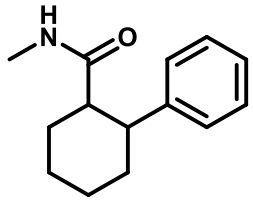
mg, 39% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.30-7.21 (m, 2H), 7.21-7.13 (m, 3H), 5.61 (s, 1H), 4.16 (dt, *J* = 11.3, 8.3 Hz, 2H), 4.00 (t, *J* = 8.2 Hz, 1H), 3.82-3.73 (m, 1H), 3.57 (q, *J* = 7.8 Hz, 1H), 2.86 (q, *J* = 7.9 Hz, 1H), 2.66 (d, *J* = 4.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.6, 141.2, 129.0, 127.5, 127.2, 75.5, 71.7, 55.0, 50.1, 26.5. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{12}H_{16}NO_2$, 206.1176; found, 206.1172.

N,N-dimethyl-4-phenyltetrahydrofuran-3-carboxamide (3i$_2$).



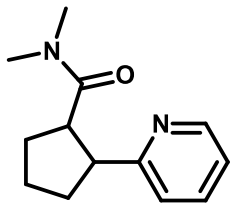
The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 83:17). Light yellow oil, 127.9 mg, 58% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37-7.20 (m, 5H), 4.28 (td, *J* = 8.1, 5.3 Hz, 2H), 4.01 (t, *J* = 8.1 Hz, 1H), 3.93 (dd, *J* = 8.4, 7.0 Hz, 1H), 3.82 (dd, *J* = 14.5, 7.2 Hz, 1H), 3.40 (q, *J* = 7.7 Hz, 1H), 2.94 (s, 3H), 2.82 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.0, 142.0, 128.9, 127.5, 127.0, 75.4, 71.7, 50.9, 49.8, 37.3, 35.9. HRMS (ESI^+) *m/z* $[M + Na]^+$ calcd for $C_{13}H_{17}NNaO_2$, 242.1151; found, 242.1146.

N-methyl-2-phenylcyclohexane-1-carboxamide (3j).



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 78:22). Light yellow oil, 138.3 mg, 64% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.31-7.22 (m, 2H), 7.22-7.12 (m, 3H), 4.97 (s, 1H), 2.78 (td, *J* = 11.5, 3.4 Hz, 1H), 2.45 (d, *J* = 4.9 Hz, 3H), 2.15 (td, *J* = 11.3, 3.5 Hz, 1H), 1.96-1.79 (m, 4H), 1.79-1.65 (m, 1H), 1.63-1.23 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.5, 145.2, 128.6, 127.3, 126.5, 53.2, 46.8, 33.7, 30.1, 26.2, 26.0, 25.6. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{20}NO$, 218.1539; found, 218.1536.

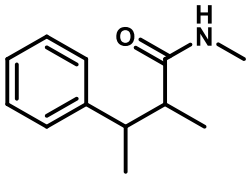
N,N-dimethyl-2-(pyridin-2-yl)cyclopentane-1-carboxamide (3k), cis- and trans- as a mixture (cis- :trans- 1.2 : 1 by NMR).



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 83:17). yellow solid, 137.6 mg, 63% yield. The configuration of **3k** was assigned based on the known configuration of the similar compound

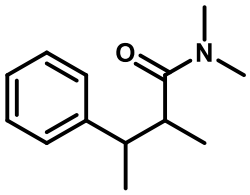
methyl 2-phenylcyclopentane-1-carboxylate.[10] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.47 (dd, *J* = 23.4, 4.2 Hz, 2.2H), 7.61-7.47 (m, 2.2H), 7.19 (dd, *J* = 7.8, 4.7 Hz, 2.2H), 7.07 (dddd, *J* = 7.5, 4.7, 2.5, 1.0 Hz, 2.2H), 3.71-3.36 (m, 4.7H), 2.85 (s, 6.0H, *trans*), 2.61 (d, *J* = 36.9 Hz, 7.4H, *cis*), 2.29 -1.99 (m, 8.3H), 1.98-1.54 (m, 7.7H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.3, 174.0, 163.4, 162.4, 149.4, 148.4, 136.4, 136.1, 123.8, 122.0, 121.6, 121.5, 51.9, 51.4, 47.8, 45.4, 37.3, 37.2, 35.7, 35.3, 34.2, 32.2, 30.9, 29.7, 25.4, 25.3. HRMS (ESI^+) *m/z* $[M + Na]^+$ calcd for $C_{13}H_{18}N_2NaO$, 241.1311; found, 241.1305.

N,2-dimethyl-3-phenylbutanamide (3v$_1$), syn- and anti- as a mixture (syn- :anti- = 1 : 5.1 by NMR).



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 85:15). Light yellow oil, 124.9 mg, 65% yield. The configuration of **3v$_1$** was assigned based on the known configuration of the similar compound methyl 2-methyl-3-phenylbutanoate.[11] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36-7.22 (m, 13.5H), 7.22-7.12 (m, 17.5H), 5.75 (s, 1H, *syn*), 5.08 (s, 4.9H, *anti*), 3.07-2.89 (m, 6.2H), 2.83 (d, *J* = 4.8 Hz, 3H, *syn*), 2.51 (d, *J* = 4.9 Hz, 15.3H, *anti*), 2.36-2.18 (m, 6.9H), 1.36-1.24 (m, 23.6H), 1.24-1.13 (m, 18.1H), 0.93 (d, *J* = 6.8 Hz, 3H, *syn*). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.7, 176.2, 145.8, 145.0, 128.5, 128.4, 127.7, 127.3, 126.5, 126.4, 49.5, 48.9, 43.6, 42.9, 26.3, 26.1, 20.6, 18.0, 17.0, 15.2. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{12}H_{18}NO$, 192.1383; found, 192.1379.

N,N,2-trimethyl-3-phenylbutanamide (3v$_2$), syn- and anti- as a mixture (syn- :anti- = 1.1 : 1 by NMR).

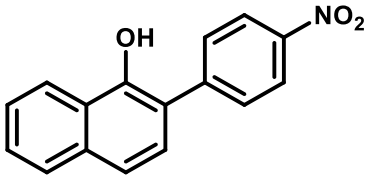


The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 86:14). Light yellow oil, 144.9 mg, 71% yield. The configuration of **3v$_2$** was assigned based on the known configuration of the similar compound methyl 2-methyl-3-phenylbutanoate.[11] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35-7.11 (m, 10.5H), 3.09 (s, 3.2H, *syn*), 3.07-2.95 (m, 5.4H), 2.87 (tt, *J* = 13.2, 6.6 Hz, 2.3H), 2.67 (d, *J* = 19.1 Hz, 6.0H, *anti*), 1.31 (d, *J* = 7.0 Hz, 3.4H, *syn*), 1.19 (dd, *J* = 6.7, 4.7 Hz, 6.5H, *anti*), 0.86 (d, *J* = 6.7 Hz, 3.5H, *syn*). **^{13}C NMR** (75 MHz, $CDCl_3$): δ176.3, 176.0, 146.0, 145.4, 128.5, 128.2, 127.8, 127.3, 126.4, 126.3, 43.9, 43.0, 42.6, 42.4, 37.6, 37.2, 35.9, 35.5, 20.7, 17.9, 16.9, 15.5. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd for $C_{13}H_{20}NO$, 206.1539; found, 206.1534.

3.3 The synthesis of 4 and 5.

To a solution of 2-bromo-2-(4-nitrophenyl)-3,4-dihydronaphthalen-1(2*H*)-one (**1t**, 1.0 mmol) in THF (5.0 mL), methylamine (27 wt% in EtOH, 0.63 mL, 4.0 equiv.) was added at room temperature under N_2 atmosphere. The reaction mixture was stirred at this temperature until TLC showed full conversion of **1t** (18 h), and then 7 mL water was added. The mixture was extracted with DCM (3 × 6 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and removed under a vacuum. The resulting crude product was purified by flash chromatography (petroleum ether/ethyl acetate) to afford 2-(4-nitrophenyl)naphthalen-1-ol (**4**, 137.2 mg, 52%) as a brown solid.

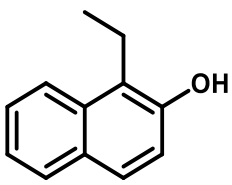
2-(4-nitrophenyl)naphthalen-1-ol (4)



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 86:14). Brown solid, 137.2 mg, 52% yield. **^{1}H NMR** (300 MHz, DMSO): δ 9.77 (s, 1H), 8.39-8.26 (m, 3H), 7.98-7.86 (m, 3H), 7.61-7.45 (m, 4H). **^{13}C NMR** (75 MHz, DMSO): δ 149.9, 146.2, 145.9, 134.4, 130.8, 127.8, 127.8, 126.9, 125.8, 125.7, 123.4, 122.7, 121.1, 120.3. HRMS (ESI$^+$) *m/z* $[M + H]^+$ calcd for $C_{16}H_{12}NO_3$ $[M + H]^+$, 266.0812; found, 266.0805.

To a solution of 1-bromo-1-ethylnaphthalen-2(1H)-one (**1u**, 1.0 mmol) in THF (5.0 mL), methylamine (27 wt% in EtOH, 0.63 mL, 4.0 equiv.) was added at -25 °C under N_2 atmosphere. The reaction mixture was stirred at this temperature until TLC showed full conversion of **1u** (approximately 4 h), then the reaction was warmed to room temperature and saturated aqueous $NaHCO_3$ (3.0 mL) was added. The mixture was extracted with DCM (3 × 6 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and removed under a vacuum. The resulting crude product was purified by flash chromatography (petroleum ether/ethyl acetate) to afford 1-ethylnaphthalen-2-ol[12] (**5**, 85.0 mg, 48%) as a yellow solid.

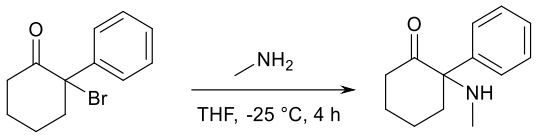
1-ethylnaphthalen-2-ol (5)[13]



The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 86:14). Yellow solid, 85.0 mg, 48% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 8.8

Hz, 1H), 7.54-7.46 (m, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 4.96 (s, 1H), 3.08 (q, J = 7.6 Hz, 2H), 1.30 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 150.1, 133.0, 129.6, 128.8, 127.7, 126.5, 123.2, 123.0, 121.8, 117.8, 18.4, 14.3. HRMS (ESI^+) m/z $[M - H]^-$ calcd for $C_{12}H_{11}O$, 171.0815; found, 171.0804.

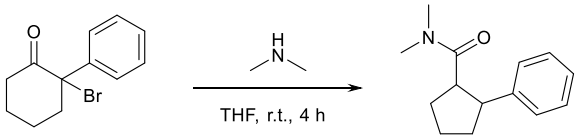
Table S1. Equivalent screening for $MeNH_2$ using substrate **1a**.



1a **2a$_1$**

Entry	1	2	3
Equiv. of amines	2.0	3.0	4.0
Yield of **2a$_1$** / %	62	75	80

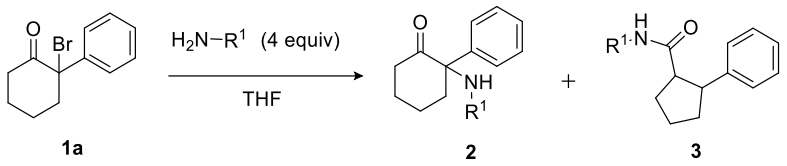
Table S2. Equivalent screening for Me_2NH using substrate **1a**.



1a **3a$_4$**

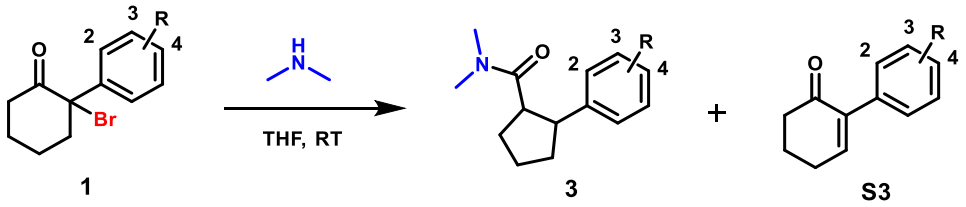
Entry	4	5	6
Equiv. of amines	2.0	3.0	4.0
Yield of **3a$_4$** / %	64	67	77

Table S3. Unsuccessful entries.



R^1	n	*T* / °C	Result
Me	0	-25	Resulting in a complex mixture
H	1	-25	No reaction (stirred for 12 h)
		r.t.	Resulting in a complex mixture
Ph	1	r.t.	No reaction (stirred for 24 h)
		reflux	Resulting in a complex mixture
HC≡CCH$_2$	1	r.t.	Resulting in a complex mixture

Table S4. The yield of Favorskii rearrangement products **3** and dehydrobromination products **S3** under optimized Favorskii rearrangement conditions.



R	Yield **3**	Yield **S3**
H	**3a**$_4$, 77%	**S3a**$_4$, 7%
2-Cl	**3b**$_2$, 81%	**S3b**$_2$, 4%
3-Cl	**3c**, 68%	**S3c**, 11%
4-Cl	**3e**, 68%	**S3d**, 10%
4-NO$_2$	**3f**, 77%	**S3f**, 6%
3-naphthalene	**3g**, 59%	**S3g**, 8%

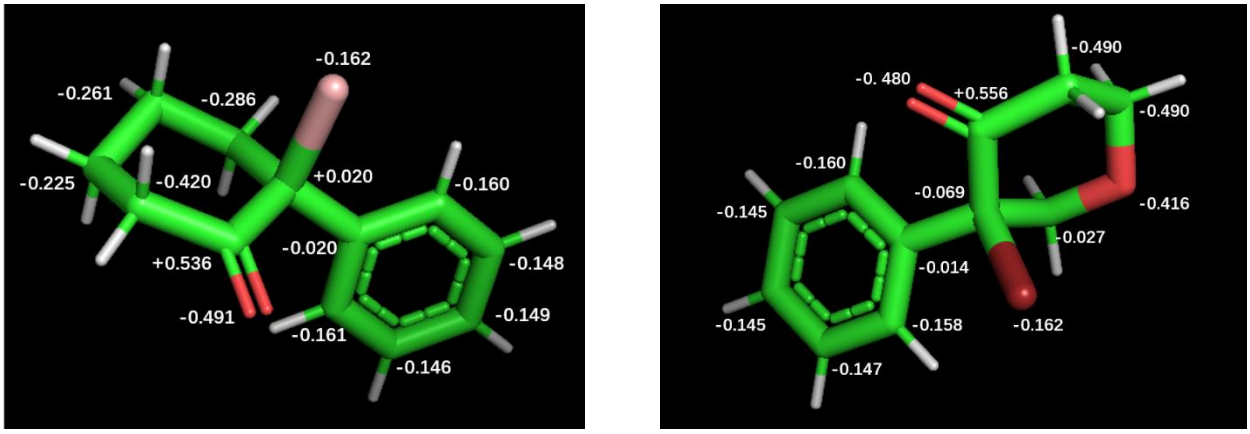


Figure S1. The calculated Mulliken charge of heavy atoms in **1a** (left) and **1q** (right)

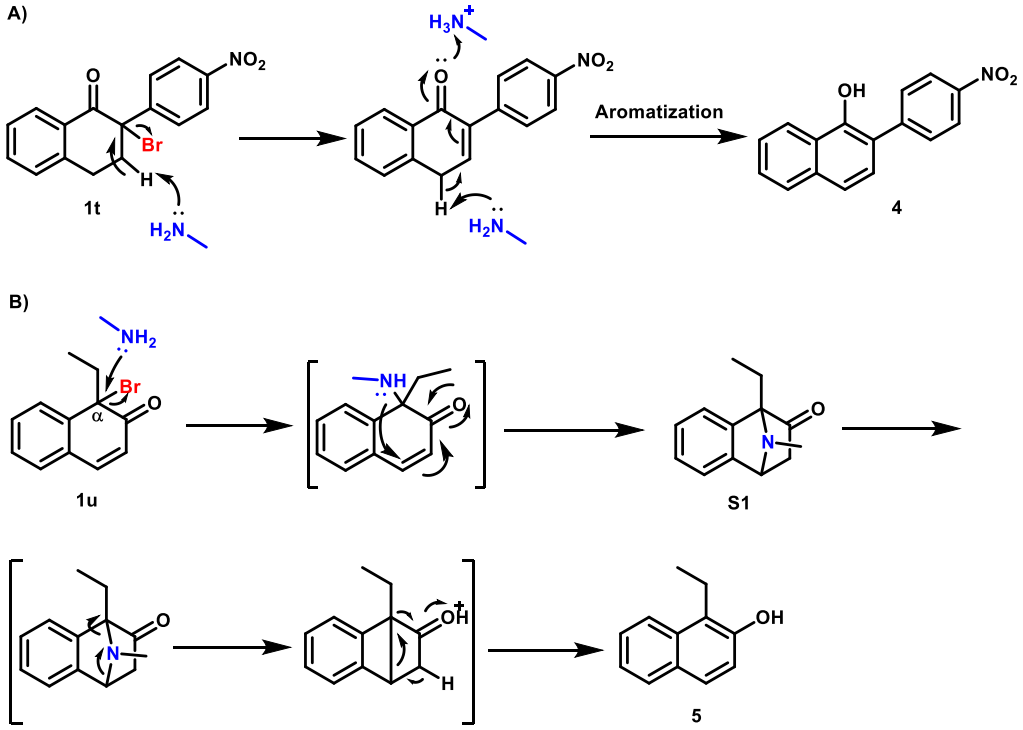


Figure S2. The proposed mechanism for the aromatization step of **1t** and **1u**.

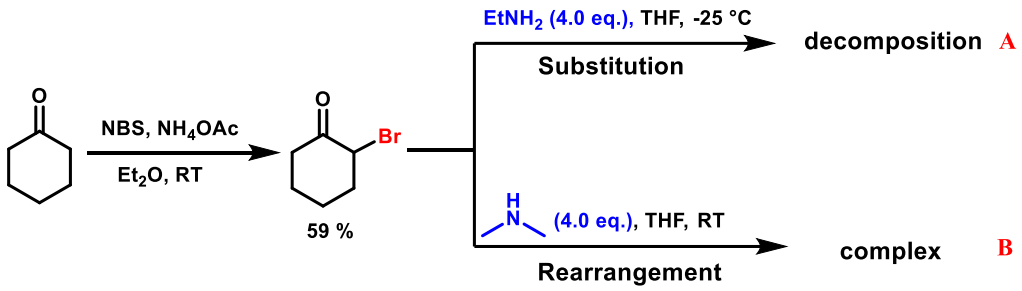
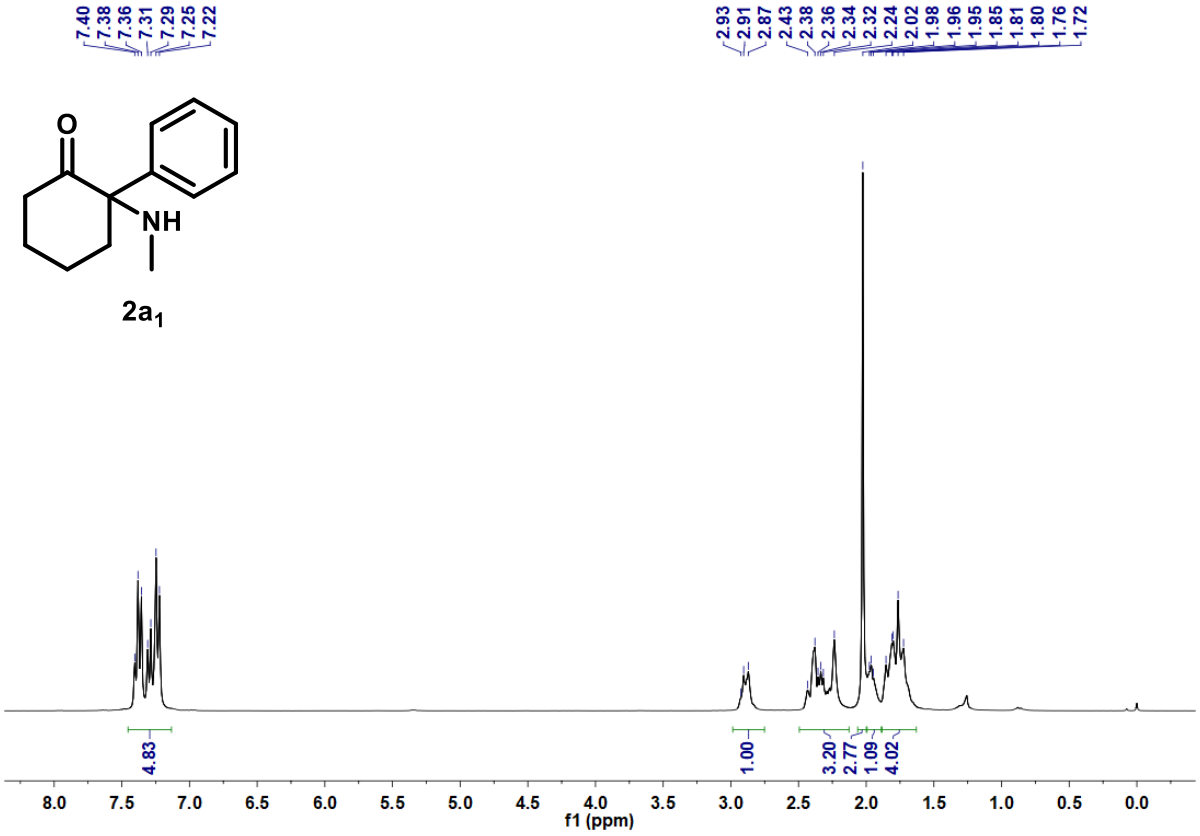
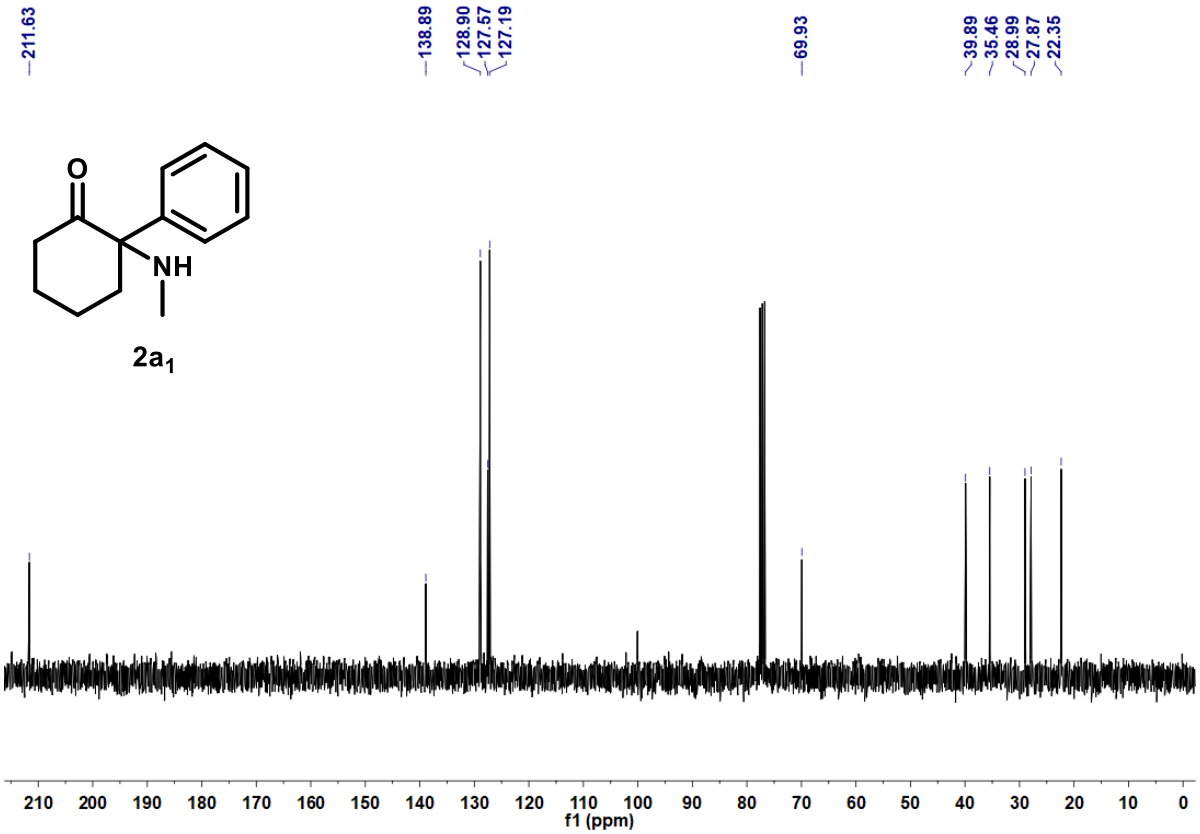
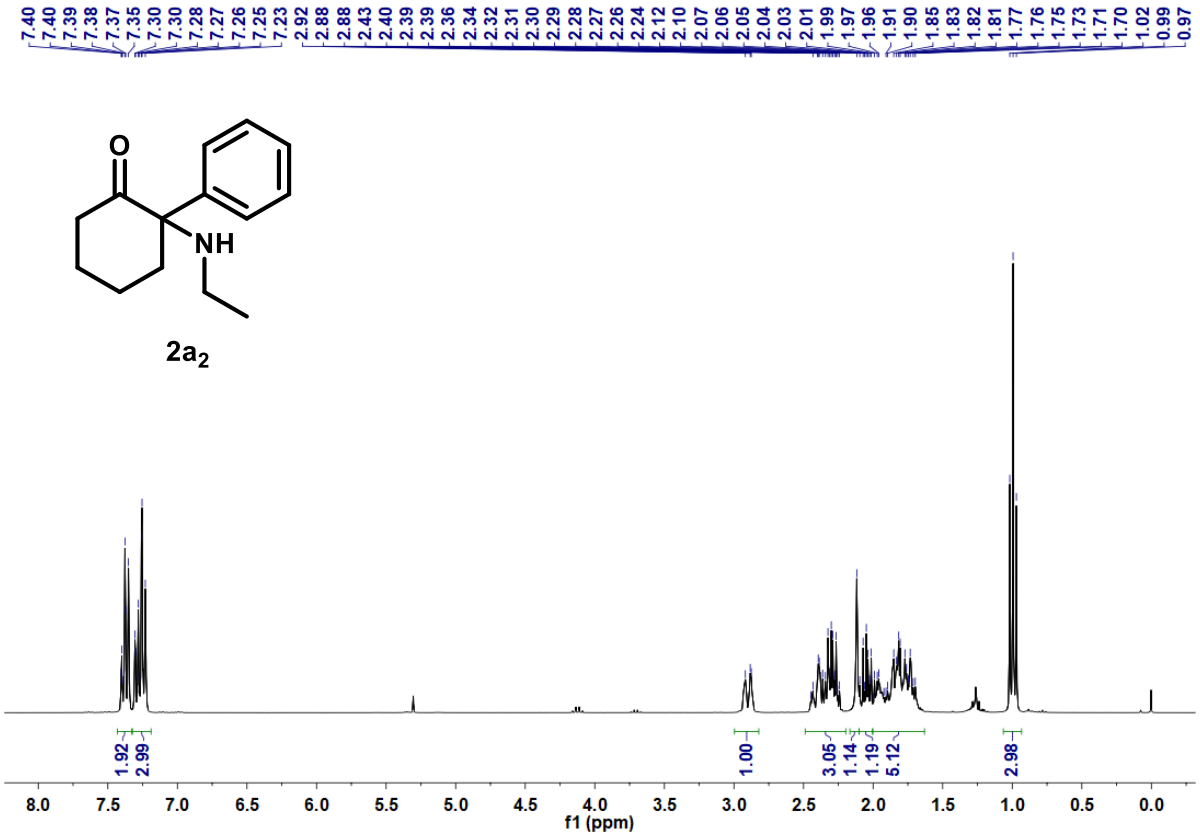


Figure S3. The reaction of 2-bromocyclohexanone with methyl or dimethylamine.

^{1}H NMR and ^{13}C NMR spectra of synthesized compounds



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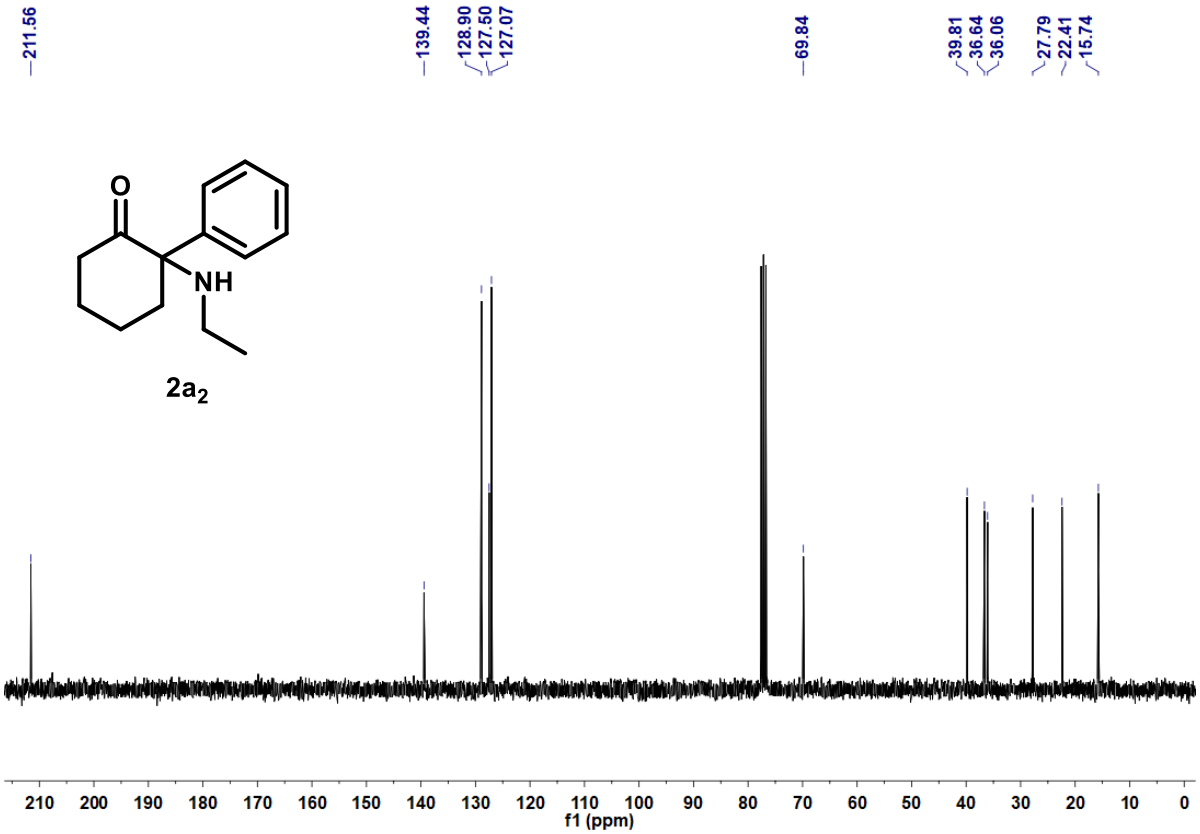
2.92 2.88 2.88 2.43 2.40 2.39 2.39 2.36 2.34 2.32 2.31 2.30 2.29 2.28 2.27 2.26 2.24 2.12 2.10 2.07 2.06 2.05 2.04 2.03 2.01 1.99 1.97 1.96 1.91 1.90 1.85 1.83 1.82 1.81 1.77 1.76 1.75 1.73 1.71 1.70 1.02 0.99 0.97
O
NH
2a2
1.92
2.99
1.00
3.05
1.14
1.19
5.12
2.98
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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127.07
69.84
39.81
36.64
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15.74
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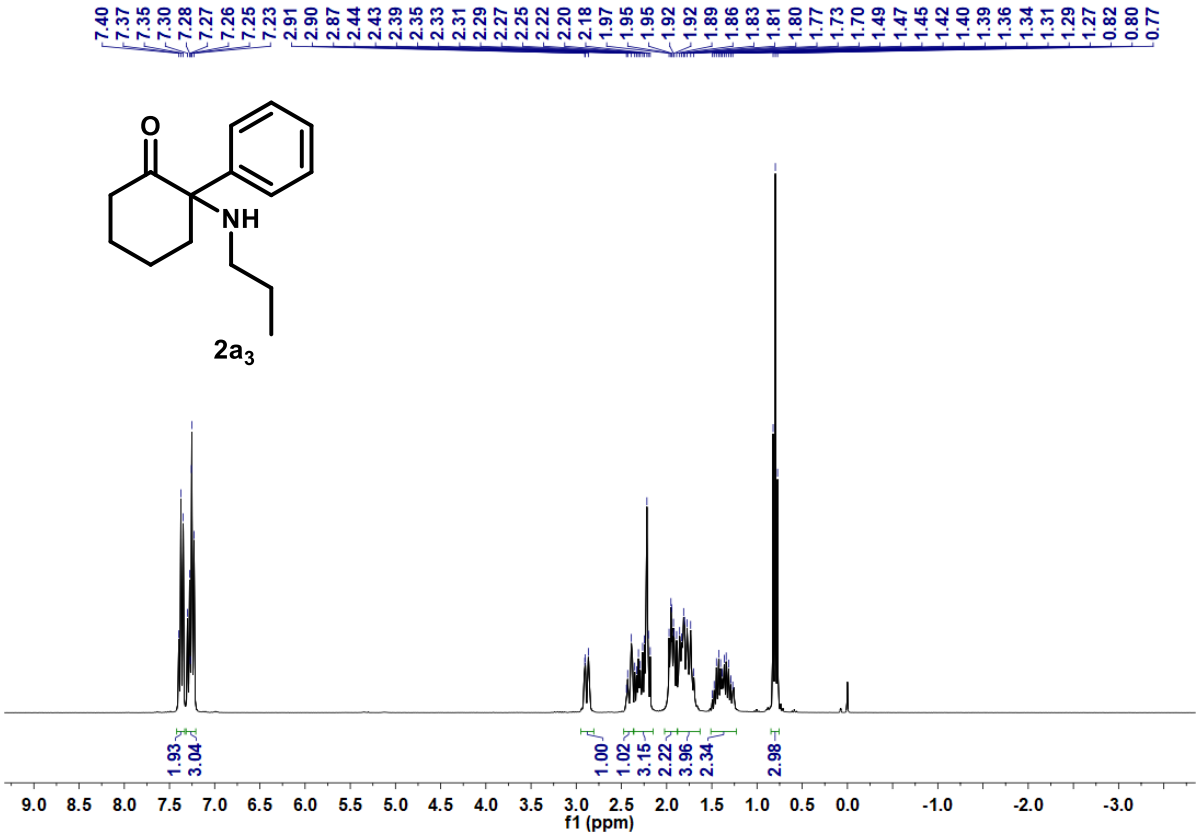
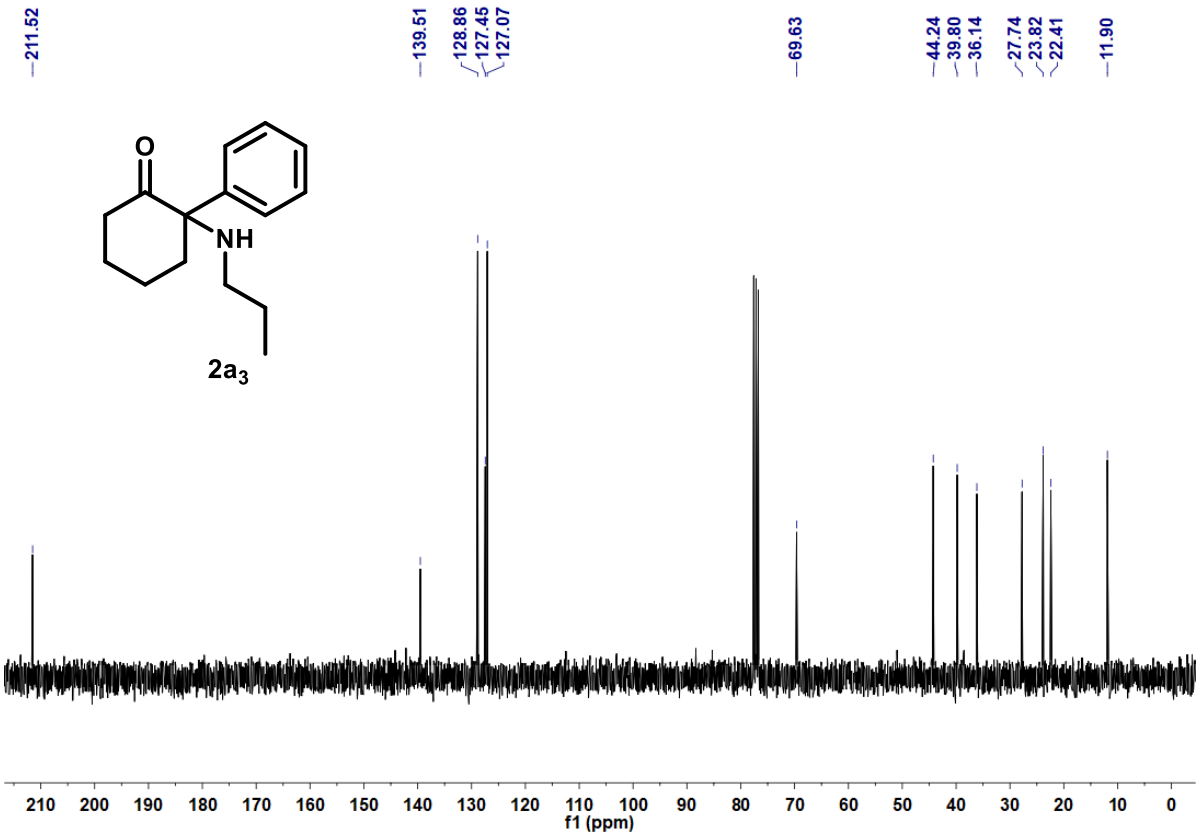
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.40 7.37 7.35 7.30 7.28 7.27 7.26 7.25 7.23 2.91 2.90 2.87 2.44 2.43 2.39 2.35 2.33 2.31 2.29 2.27 2.25 2.22 2.20 2.18 1.97 1.95 1.95 1.92 1.92 1.89 1.86 1.83 1.81 1.80 1.77 1.73 1.70 1.49 1.47 1.45 1.42 1.40 1.39 1.36 1.34 1.31 1.29 1.27 0.82 0.80 0.77
O
NH
2a3
1.93 3.04 1.00 1.02 3.15 2.22 3.96 2.34 2.98
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -1.0 -2.0 -3.0
f1 (ppm)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O
NH
2a3
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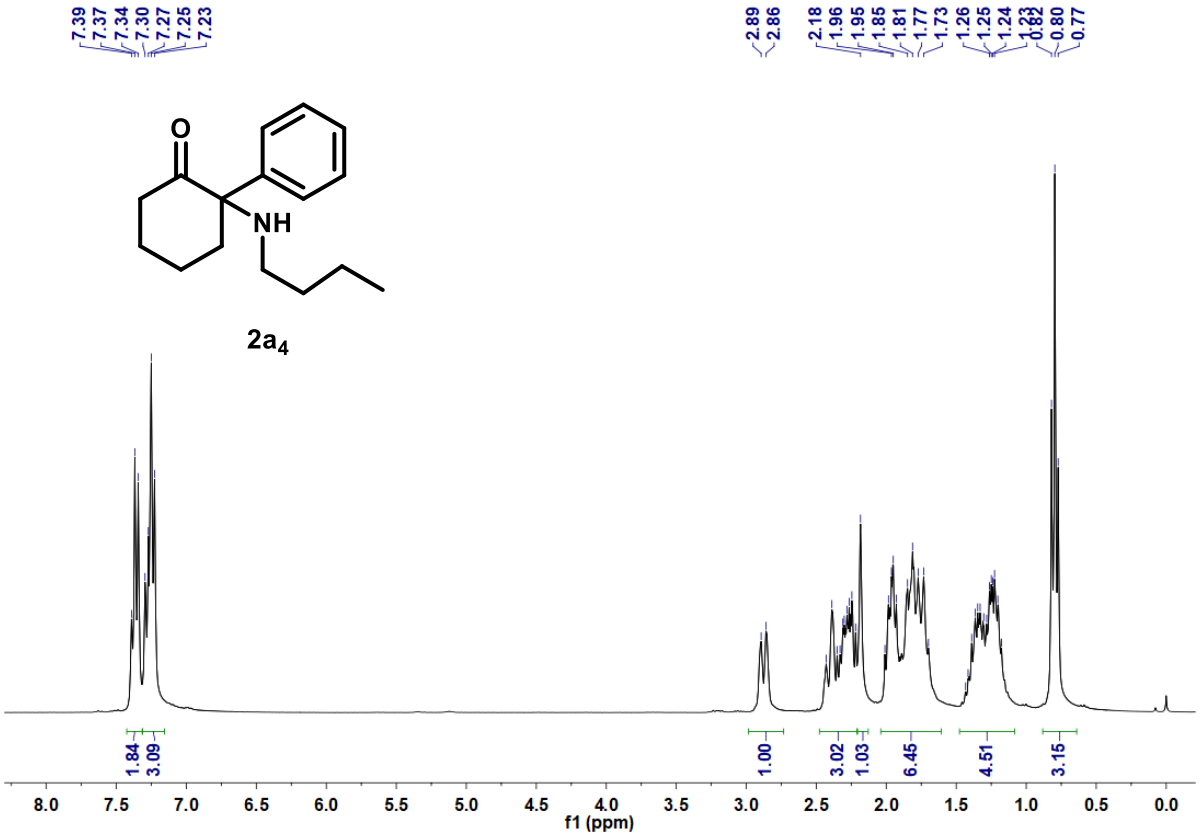
f1 (ppm)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7.25
7.23
2.89
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2.18
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1.95
1.85
1.81
1.77
1.73
1.26
1.25
1.24
0.82
0.80
0.77
O
NH
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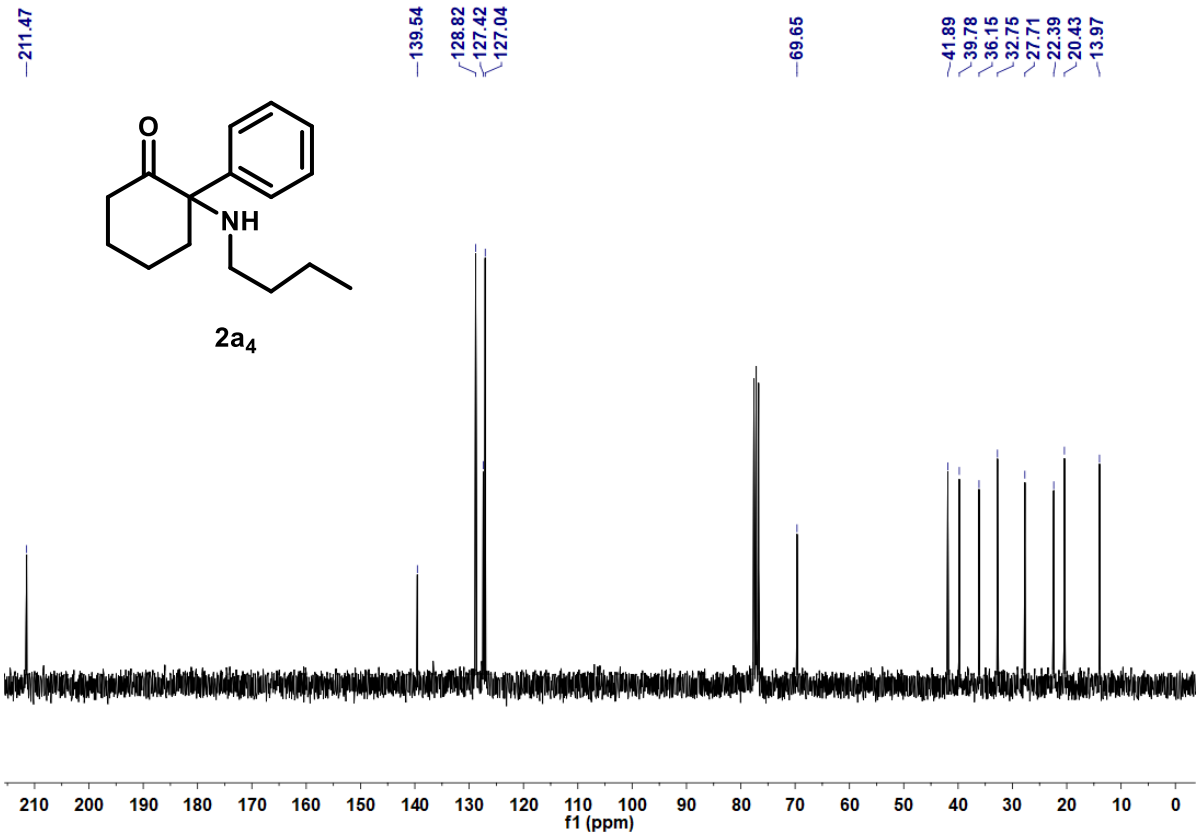
1.00
3.02
1.03
6.45
4.51
3.15
f1 (ppm)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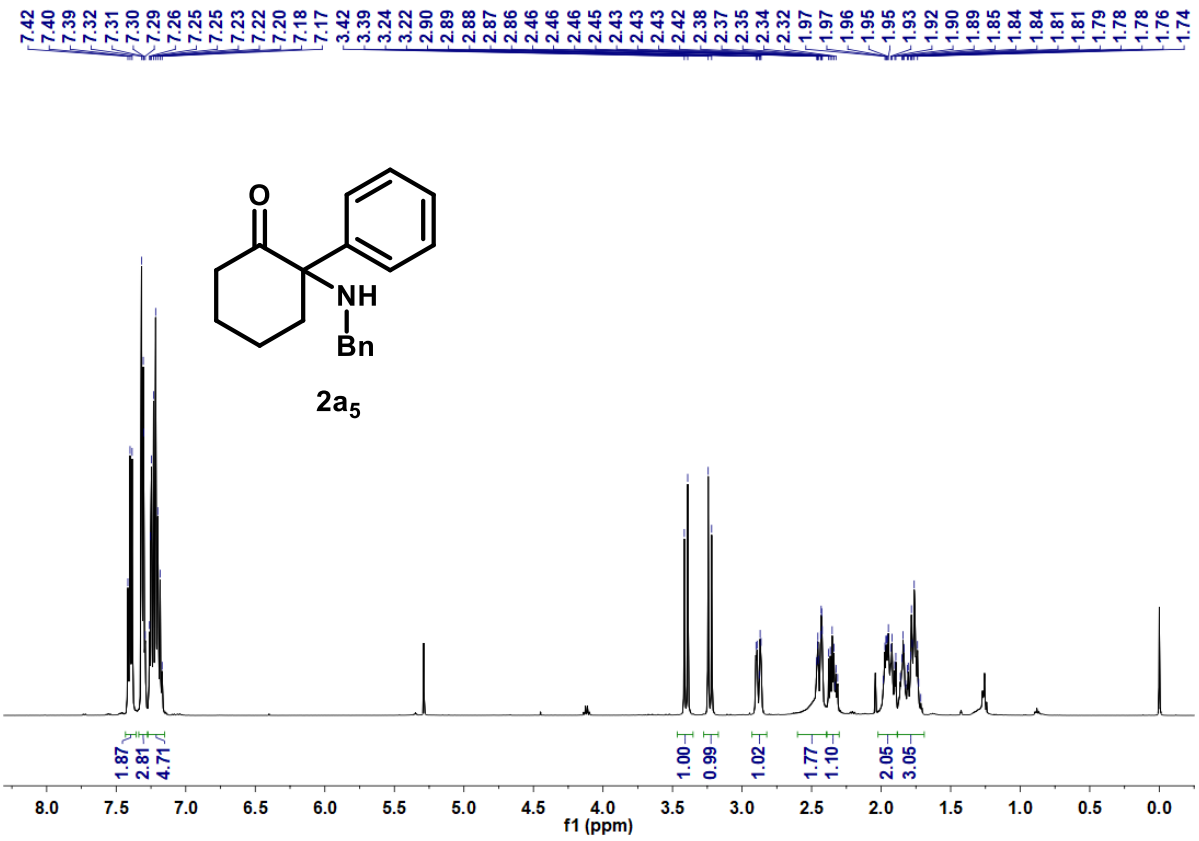
2a4
f1 (ppm)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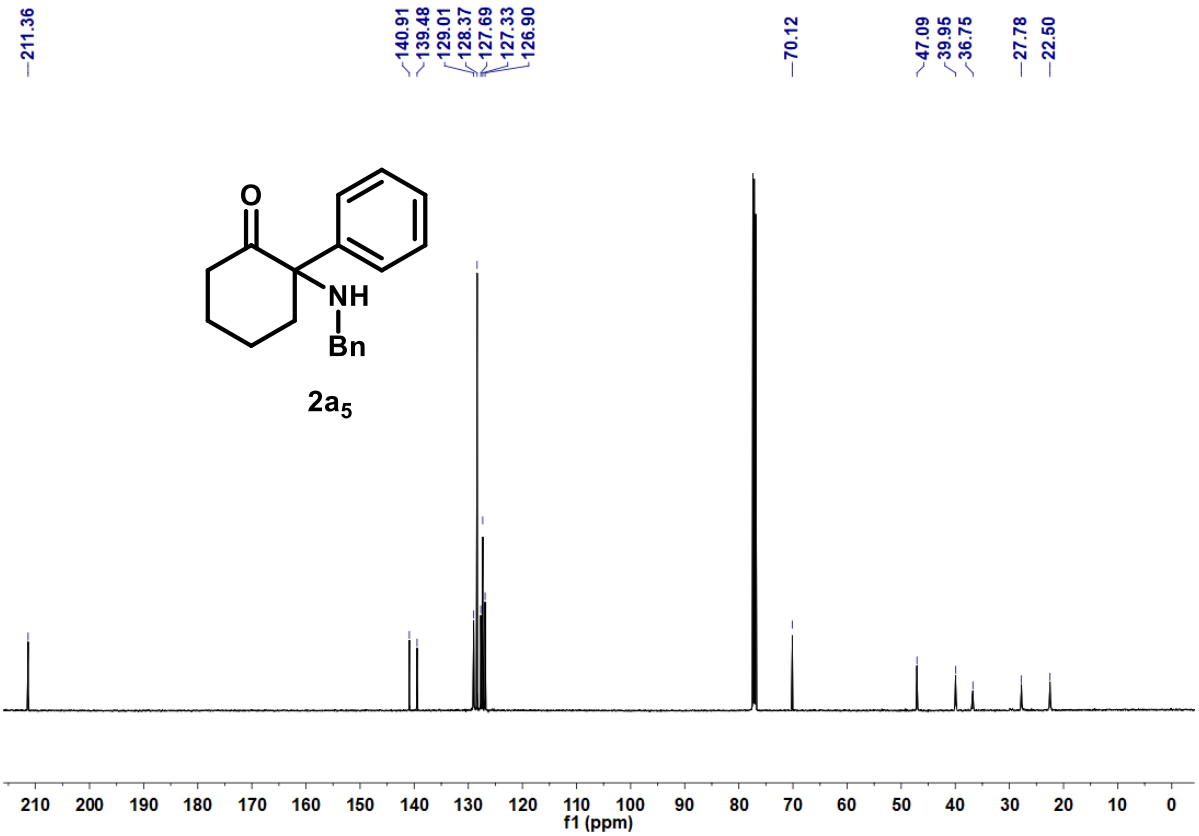
3.42 3.39 3.24 3.22 2.90 2.89 2.88 2.87 2.86 2.46 2.46 2.46 2.45 2.43 2.43 2.43 2.42 2.38 2.37 2.35 2.34 2.32 1.97 1.97 1.96 1.95 1.95 1.93 1.92 1.90 1.89 1.85 1.84 1.84 1.81 1.81 1.79 1.78 1.78 1.76 1.74
O
NH
Bn
2a5
1.87 2.81 4.71 1.00 0.99 1.02 1.77 1.10 2.05 3.05
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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47.09 39.95 36.75
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NH
Bn
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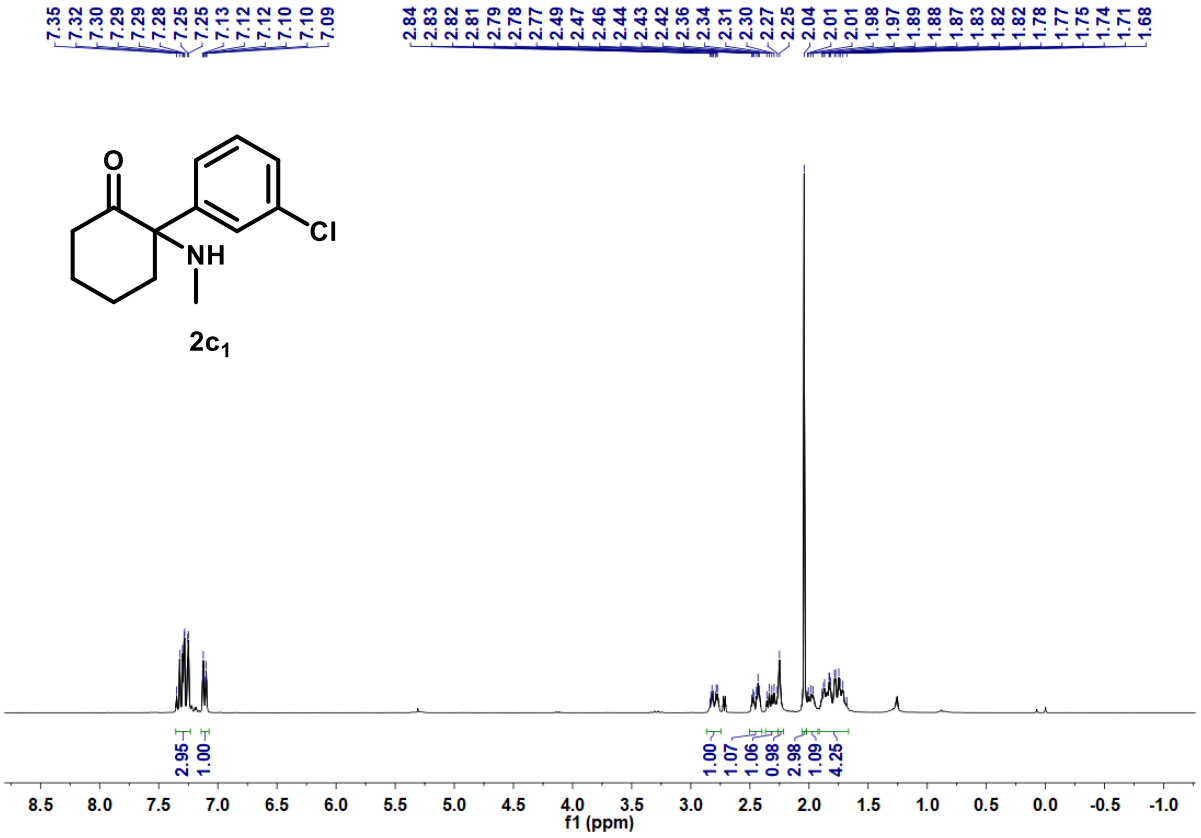
f1 (ppm)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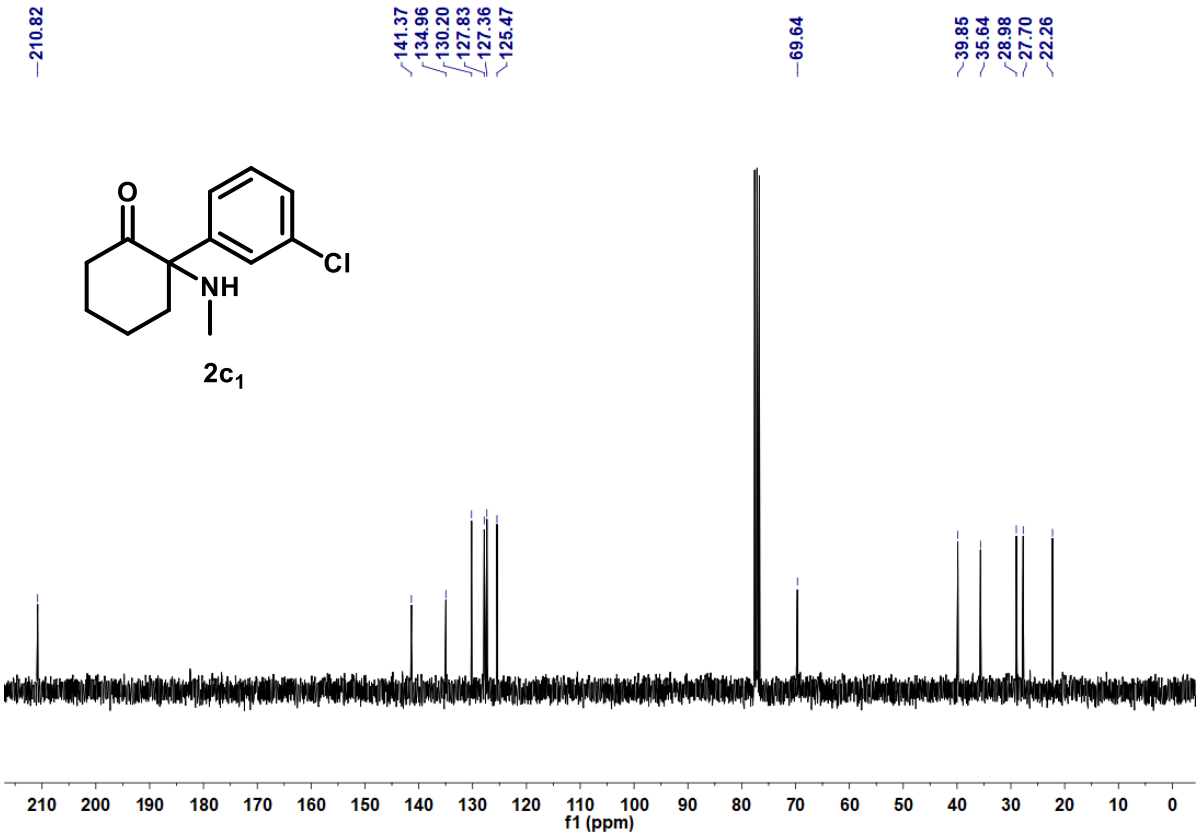
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Cl
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180
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50
40
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20
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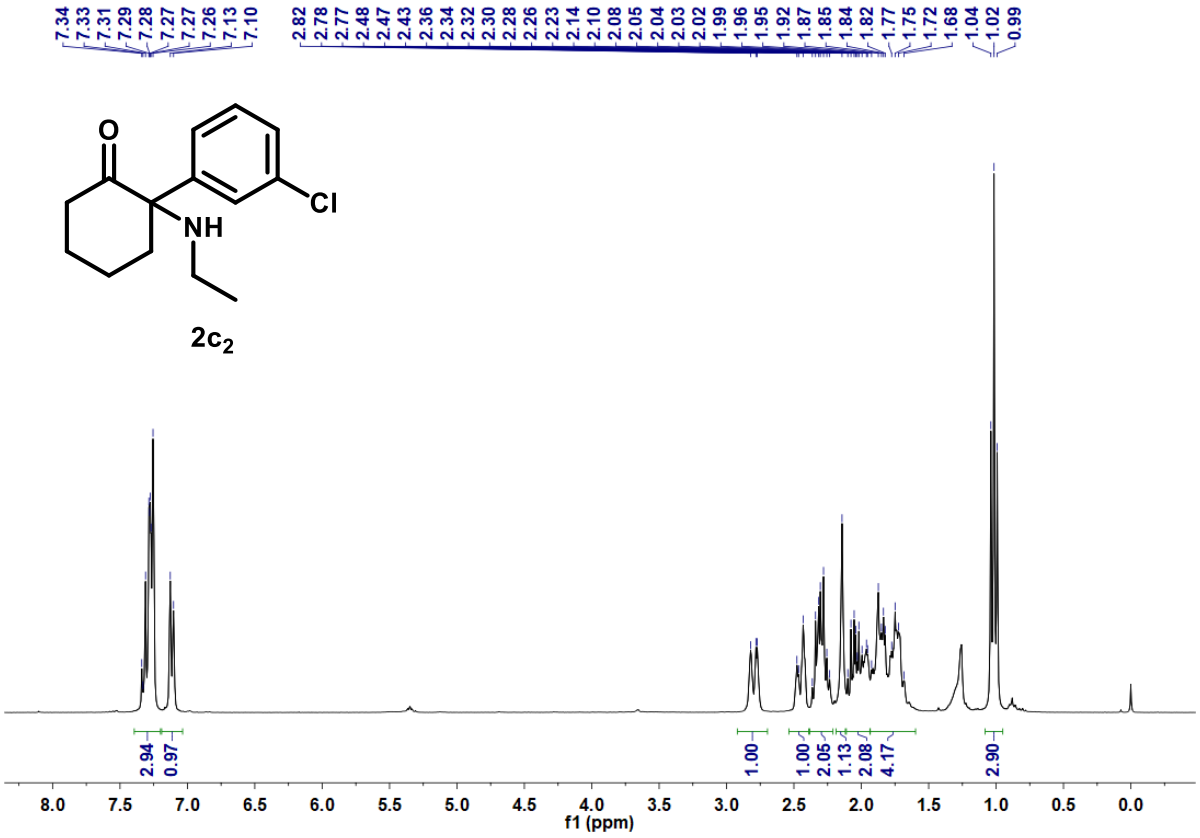
f1 (ppm)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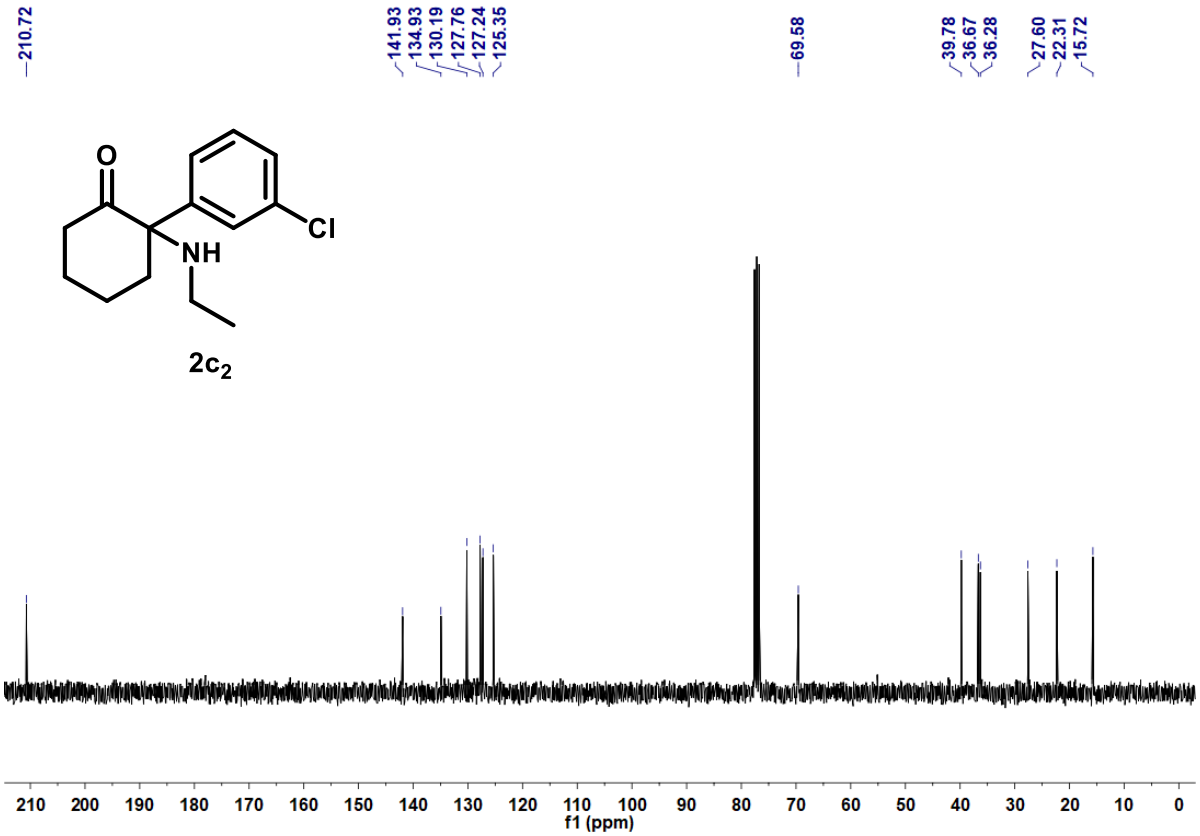
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Cl
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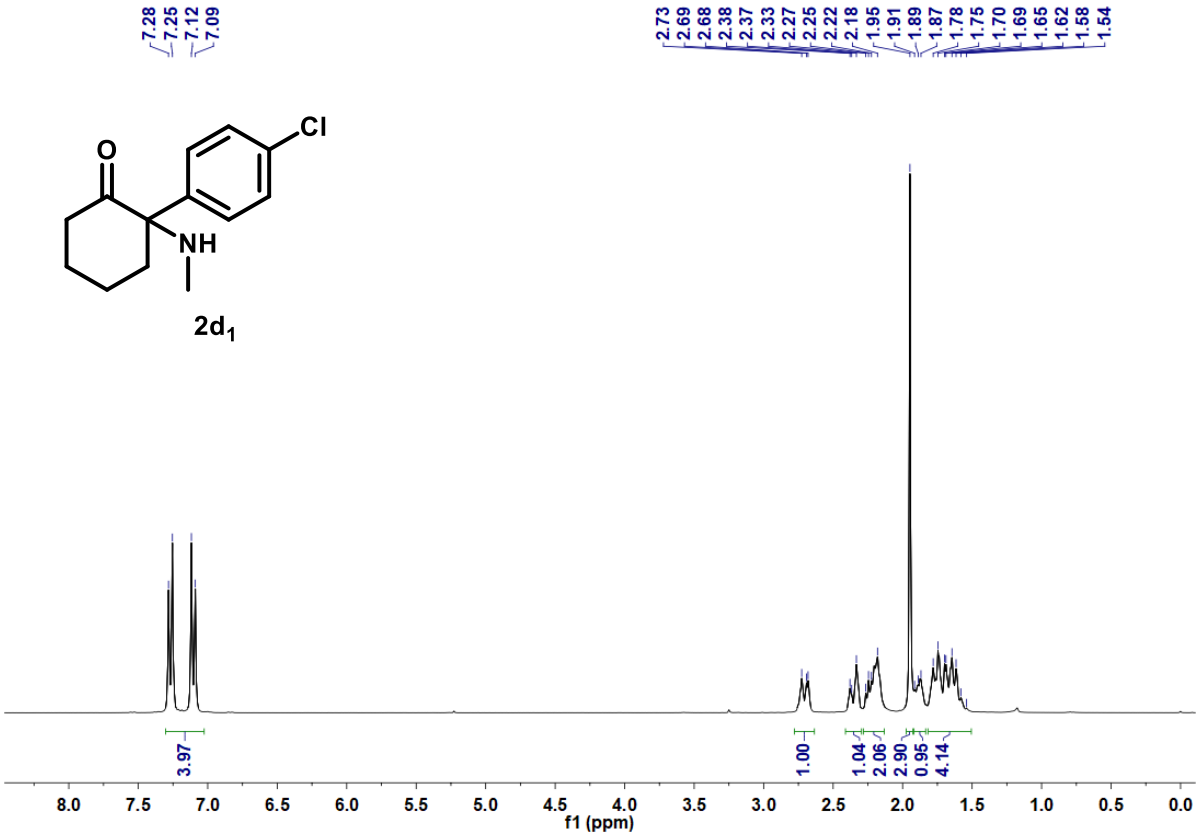
f1 (ppm)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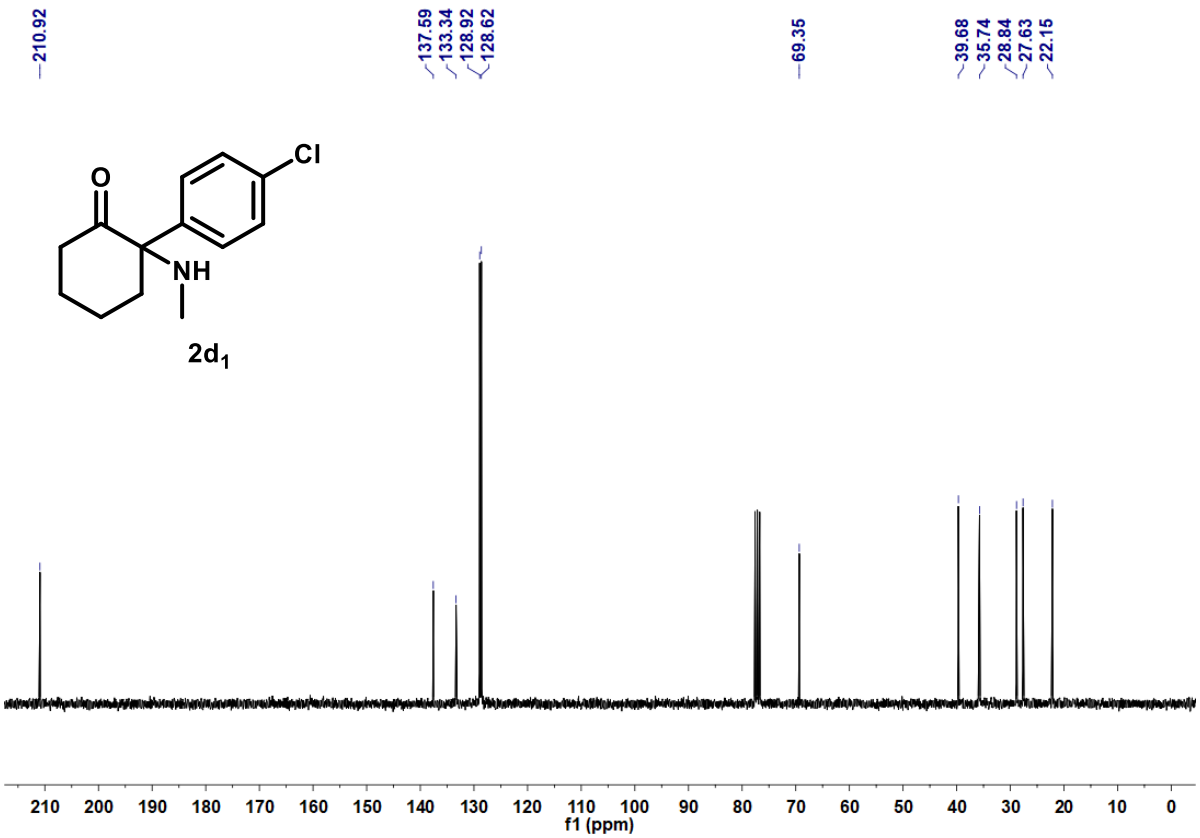
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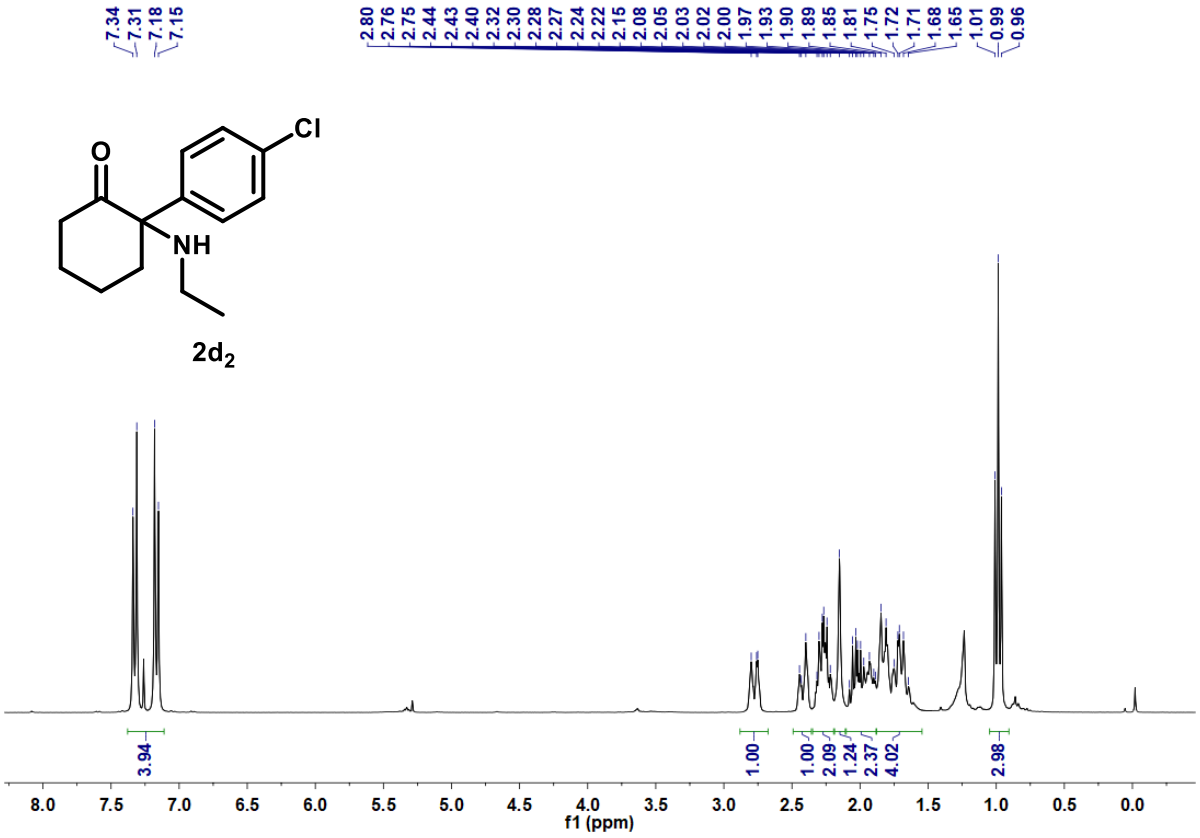
NH
2d1
f1 (ppm)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2.15
2.08
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2.02
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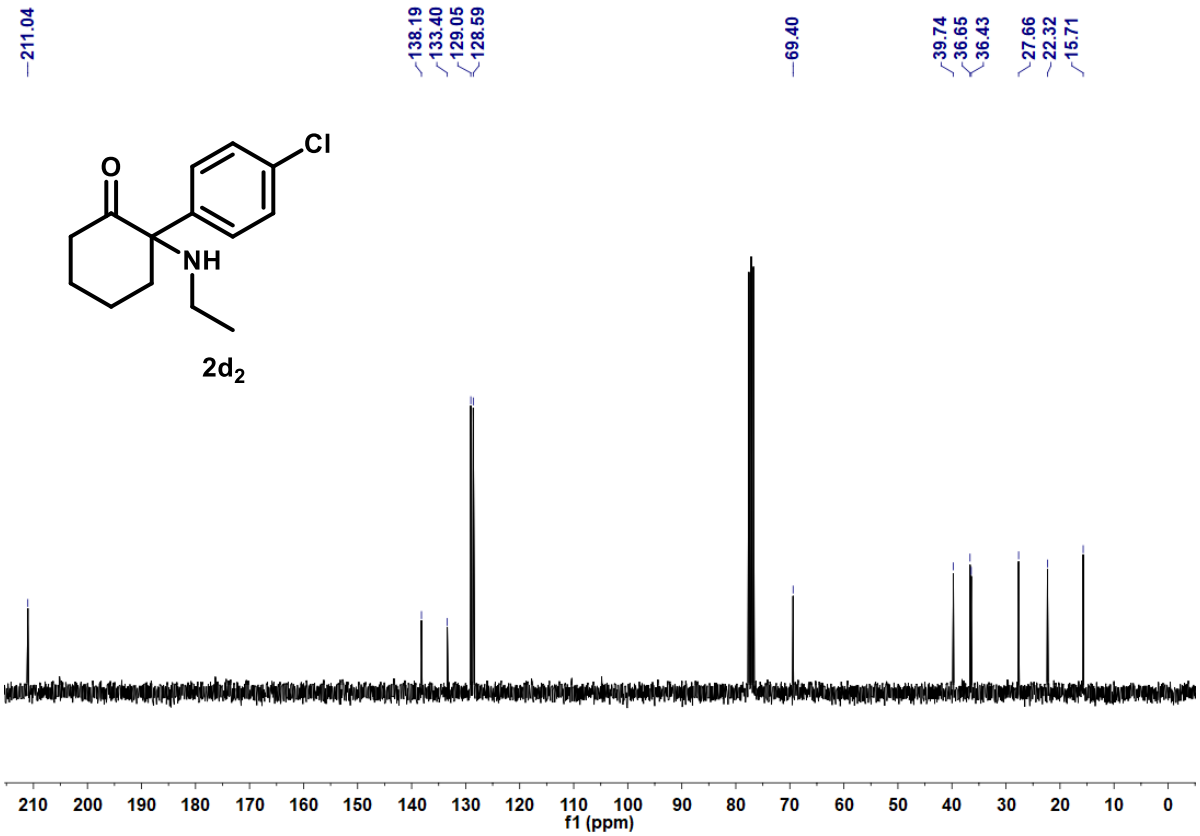
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Cl
NH
2d2
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200
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180
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90
80
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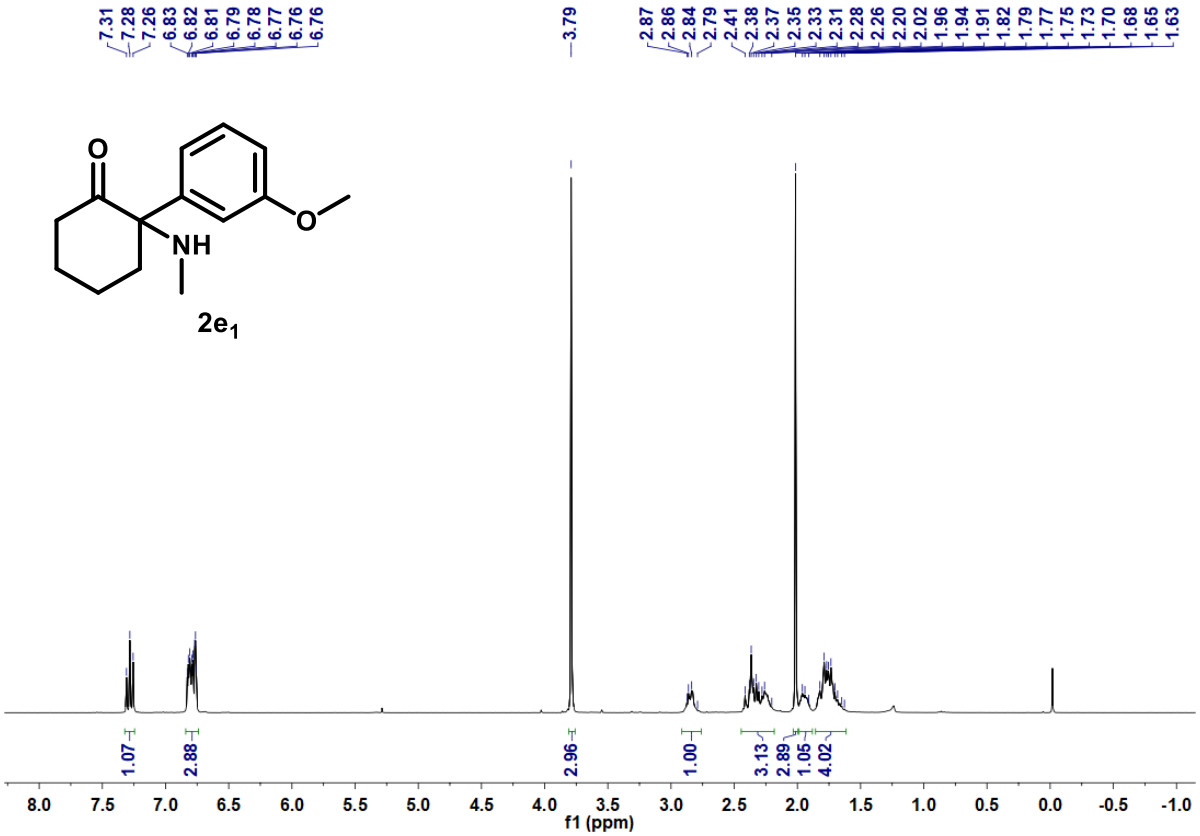
50
40
30
20
10
0
f1 (ppm)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2.79
2.41
2.38
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2.33
2.31
2.28
2.26
2.20
2.02
1.96
1.94
1.91
1.82
1.79
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1.75
1.73
1.70
1.68
1.65
1.63
O
NH
O
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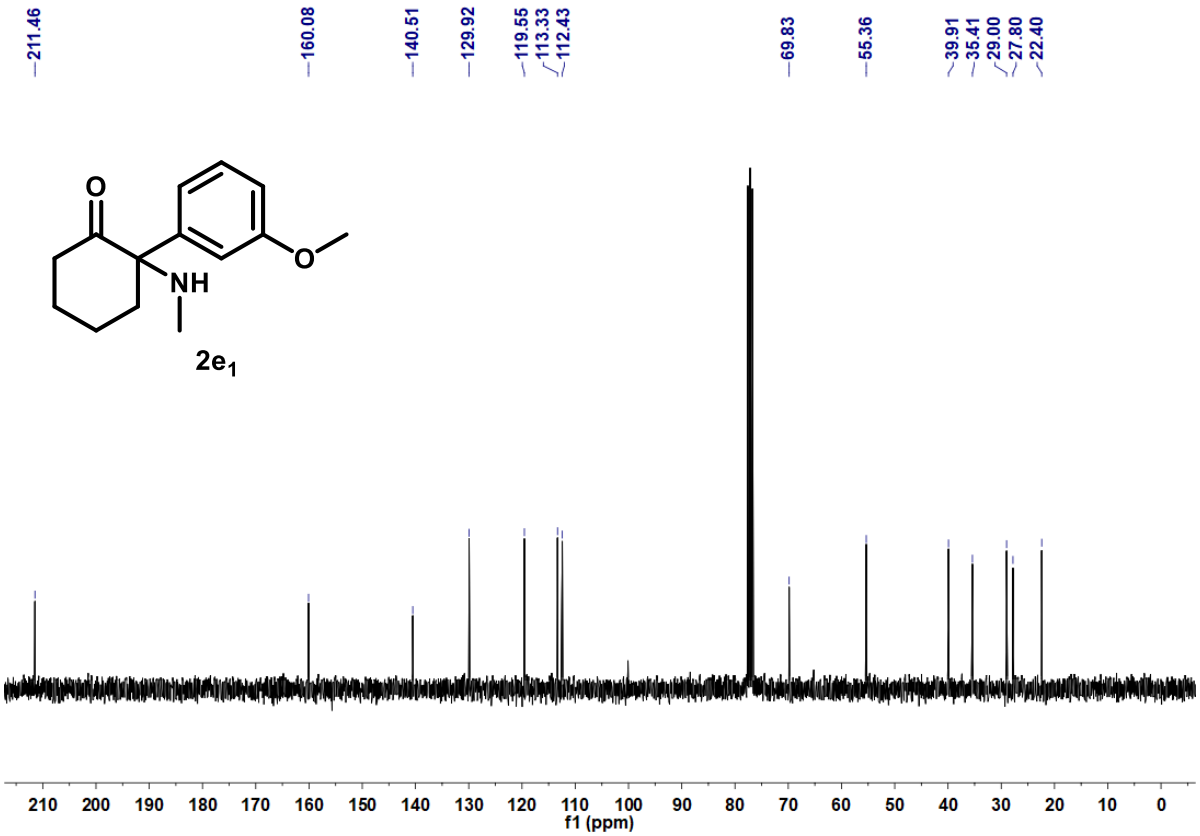
f1 (ppm)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O
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200
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180
170
160
150
140
130
120
110
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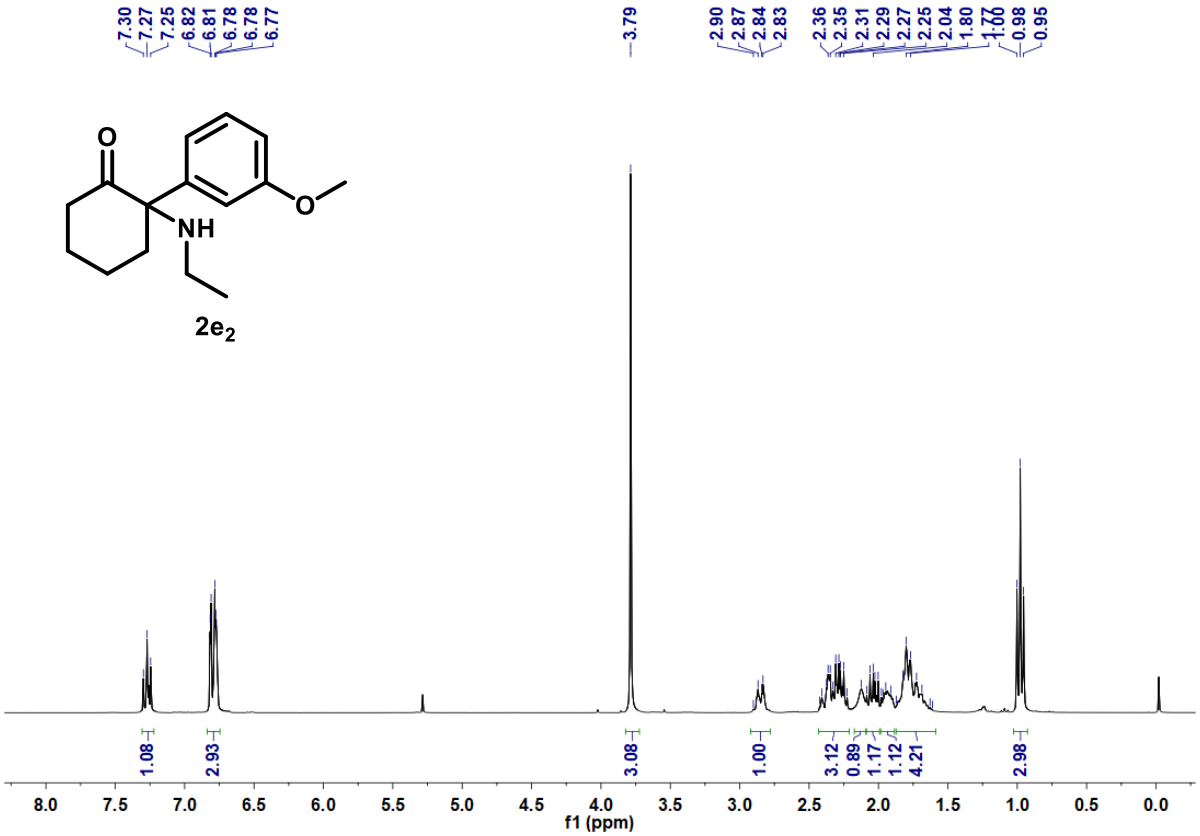
f1 (ppm)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2.90
2.87
2.84
2.83
2.36
2.35
2.31
2.29
2.27
2.25
2.04
1.80
1.00
0.98
0.95
O
NH
O
2e2
1.08
2.93
3.08
1.00
3.12
0.89
1.17
1.12
4.21
2.98
8.0
7.5
7.0
6.5
6.0
5.5
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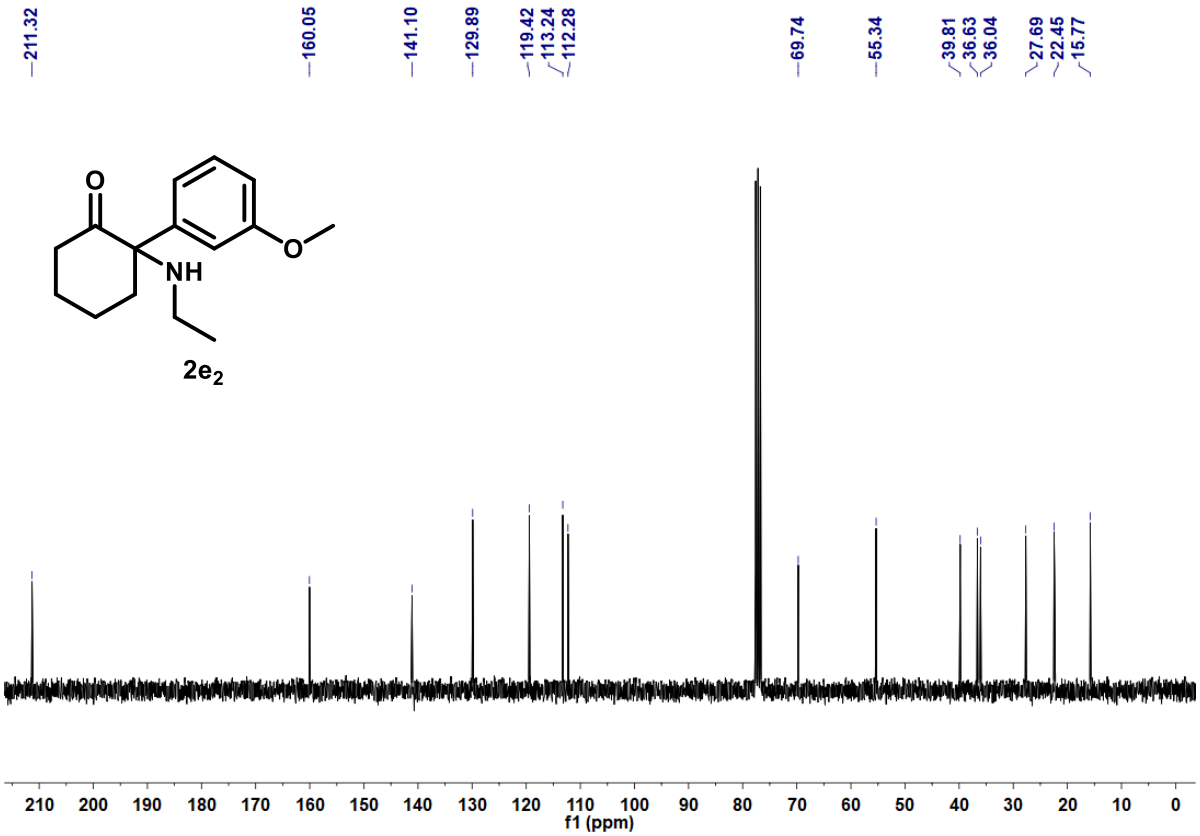
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69.74
55.34
39.81
36.63
36.04
27.69
22.45
15.77
O
NH
O
2e2
210
200
190
180
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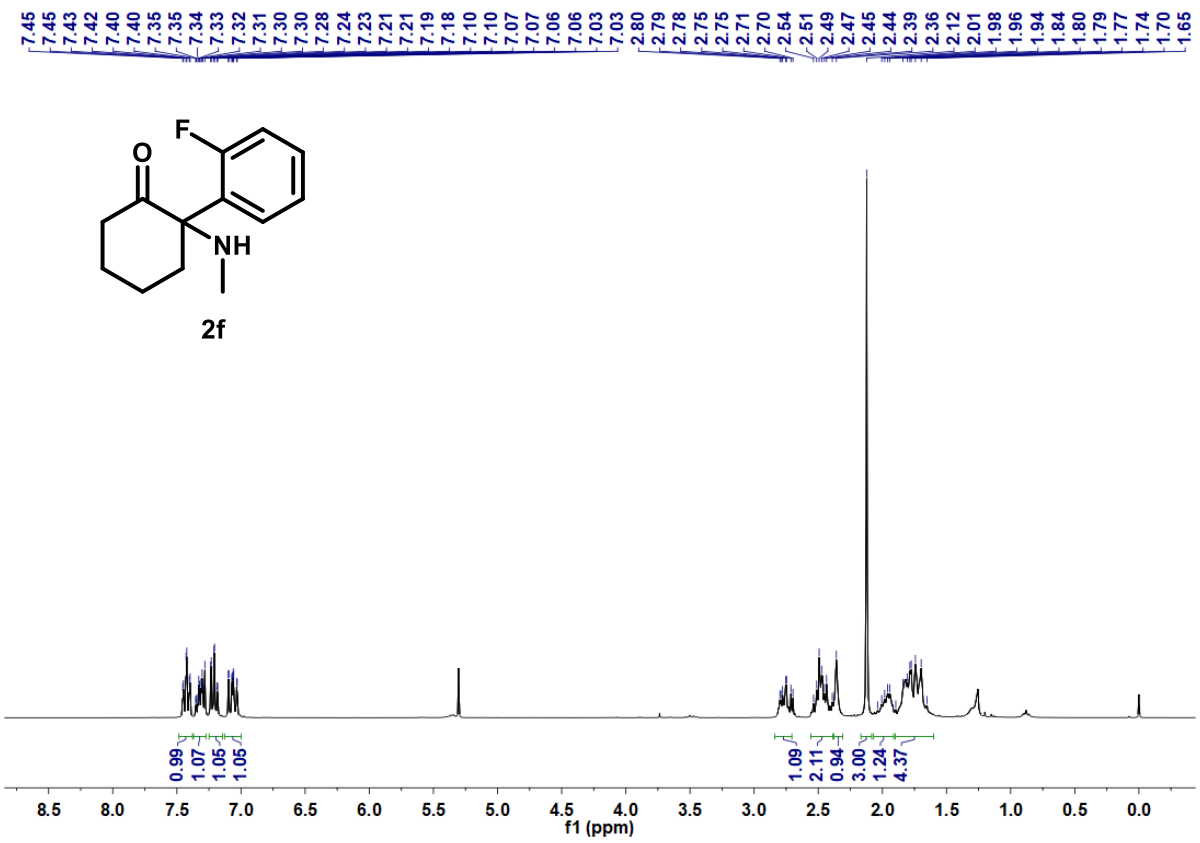
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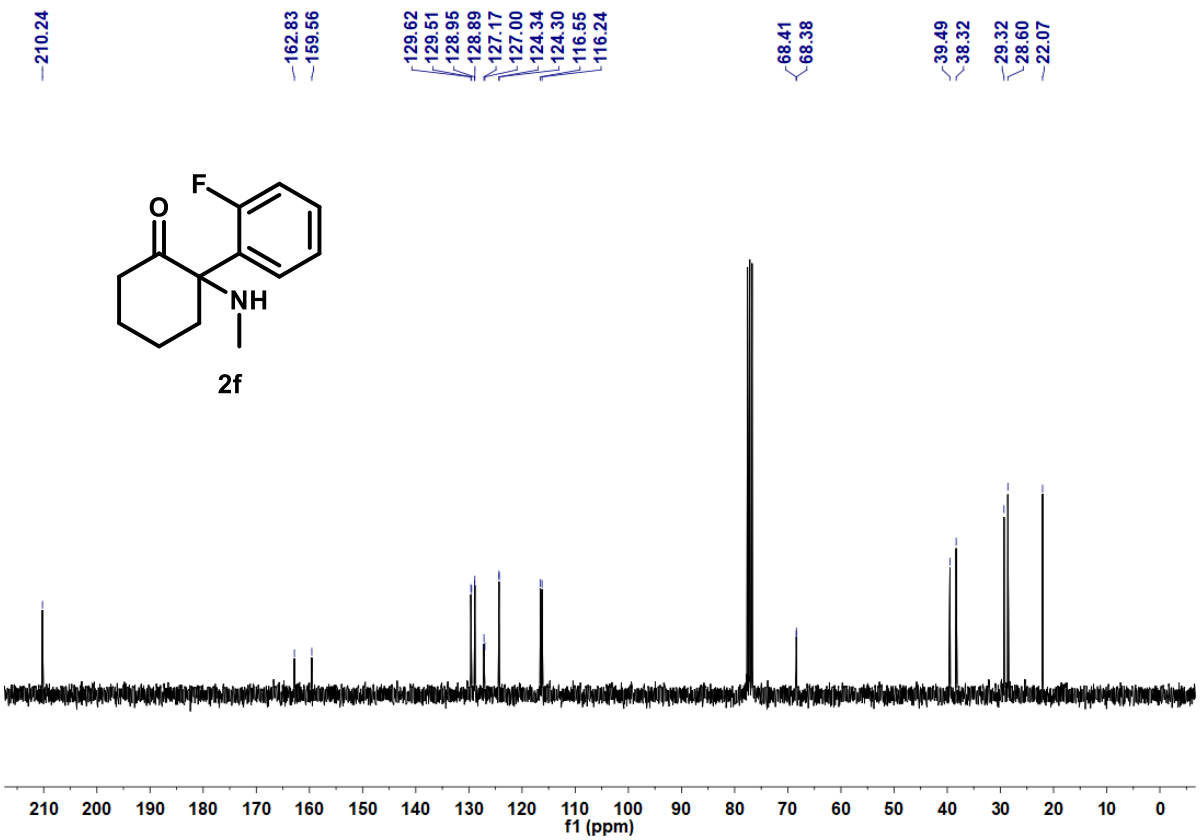
2.80 2.79 2.78 2.75 2.75 2.71 2.70 2.54 2.51 2.49 2.47 2.45 2.44 2.39 2.36 2.12 2.01 1.98 1.96 1.94 1.84 1.80 1.79 1.77 1.74 1.70 1.65
F
O
NH
2f
0.99 1.07 1.05 1.05 1.09 2.11 0.94 3.00 1.24 4.37
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


210.24
162.83 159.56
129.62 129.51 128.95 128.89 127.17 127.00 124.34 124.30 116.55 116.24
68.41 68.38
39.49 38.32
29.32 28.60 22.07
F
O
NH
2f
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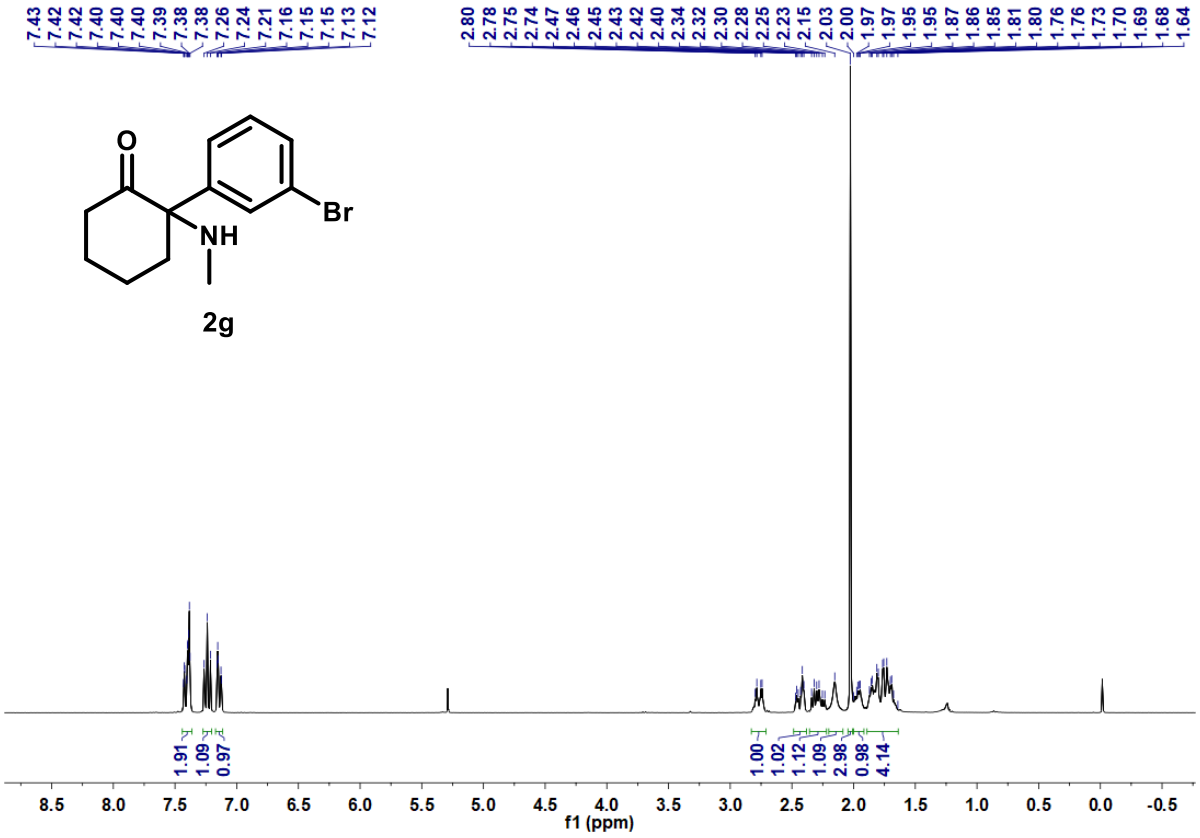
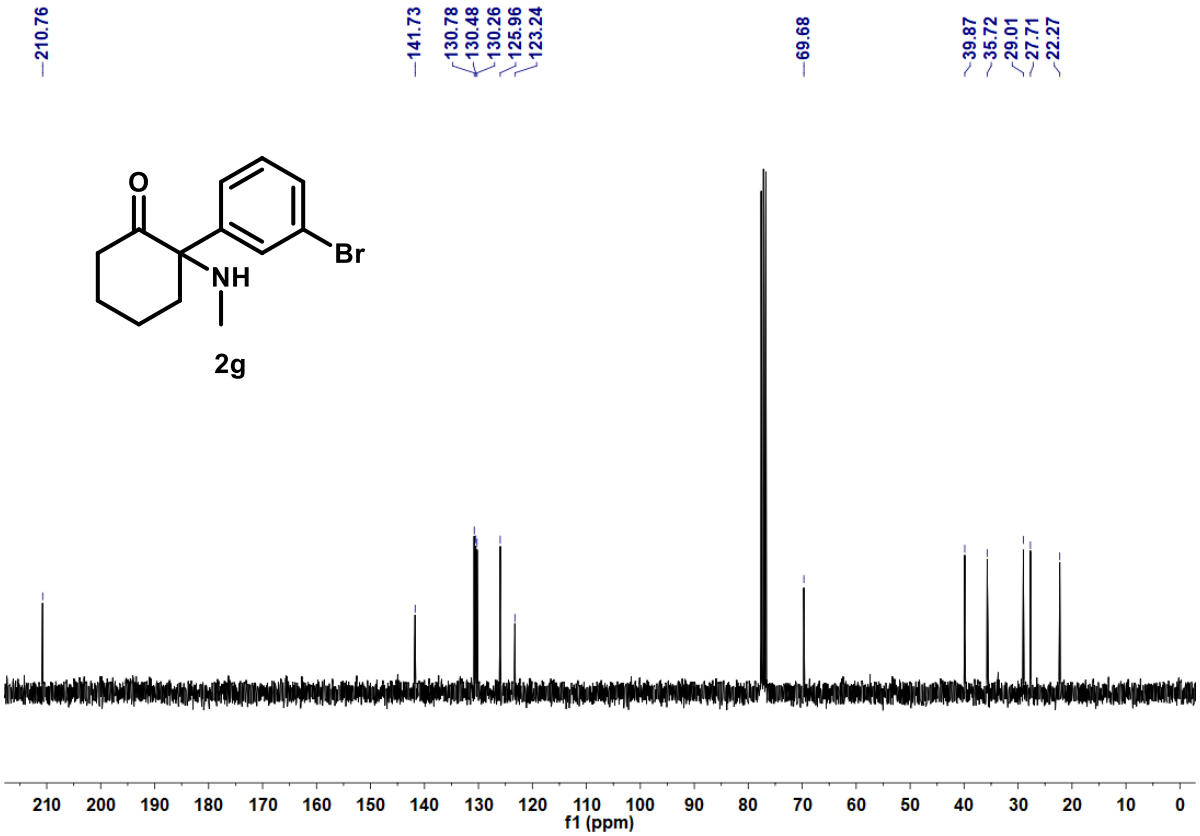
f1 (ppm)


7.43 7.42 7.42 7.40 7.40 7.40 7.39 7.38 7.38 7.26 7.24 7.21 7.16 7.15 7.15 7.13 7.12
2.80 2.78 2.75 2.74 2.47 2.46 2.45 2.43 2.42 2.40 2.34 2.32 2.30 2.28 2.25 2.23 2.15 2.03 2.00 1.97 1.97 1.95 1.95 1.87 1.86 1.85 1.81 1.80 1.76 1.76 1.73 1.70 1.69 1.68 1.64
O
NH
Br
2g
1.91 1.09 0.97
1.00 1.02 1.12 1.09 2.98 0.98 4.14
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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130.78
130.48
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123.24
69.68
39.87
35.72
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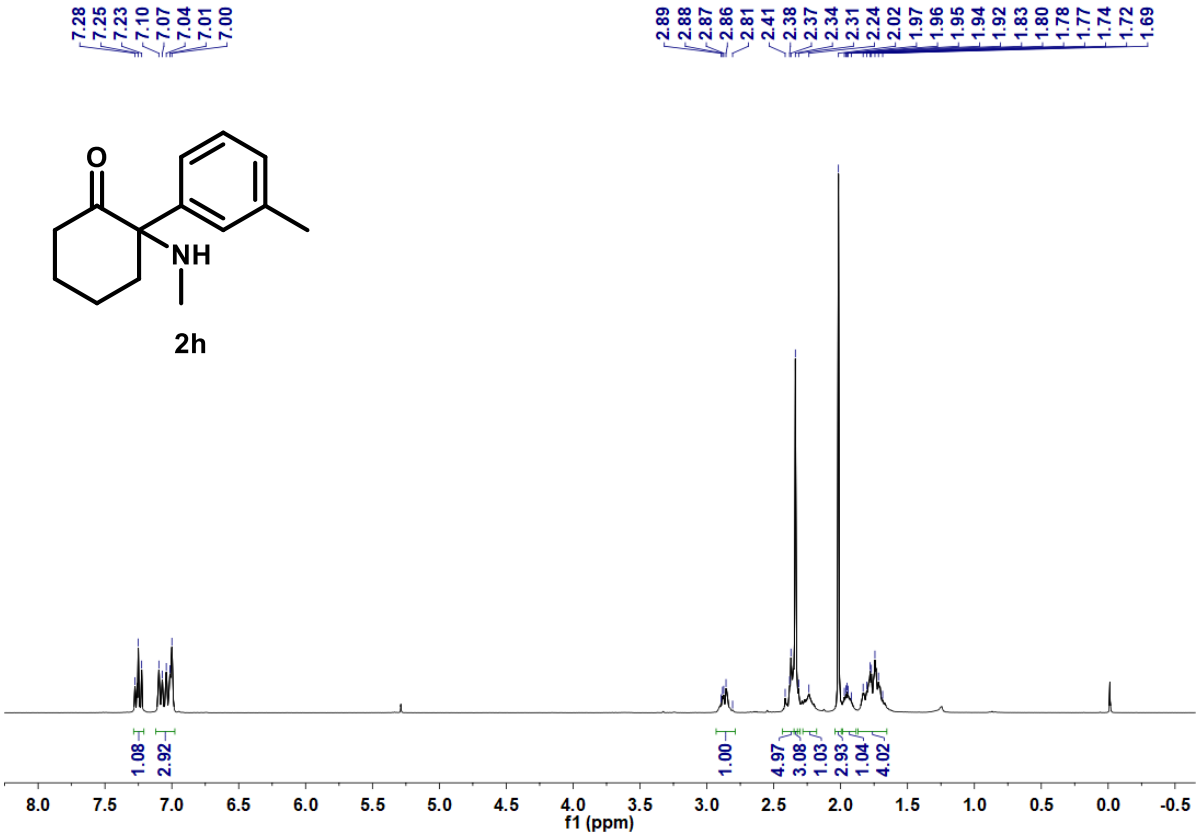
27.71
22.27
O
NH
Br
2g
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.10
7.07
7.04
7.01
7.00
2.89
2.88
2.87
2.86
2.81
2.41
2.38
2.37
2.34
2.31
2.24
2.02
1.97
1.96
1.95
1.94
1.92
1.83
1.80
1.78
1.77
1.74
1.72
1.69
O
NH
2h
1.08
2.92
1.00
4.97
3.08
1.03
2.93
1.04
4.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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0.5
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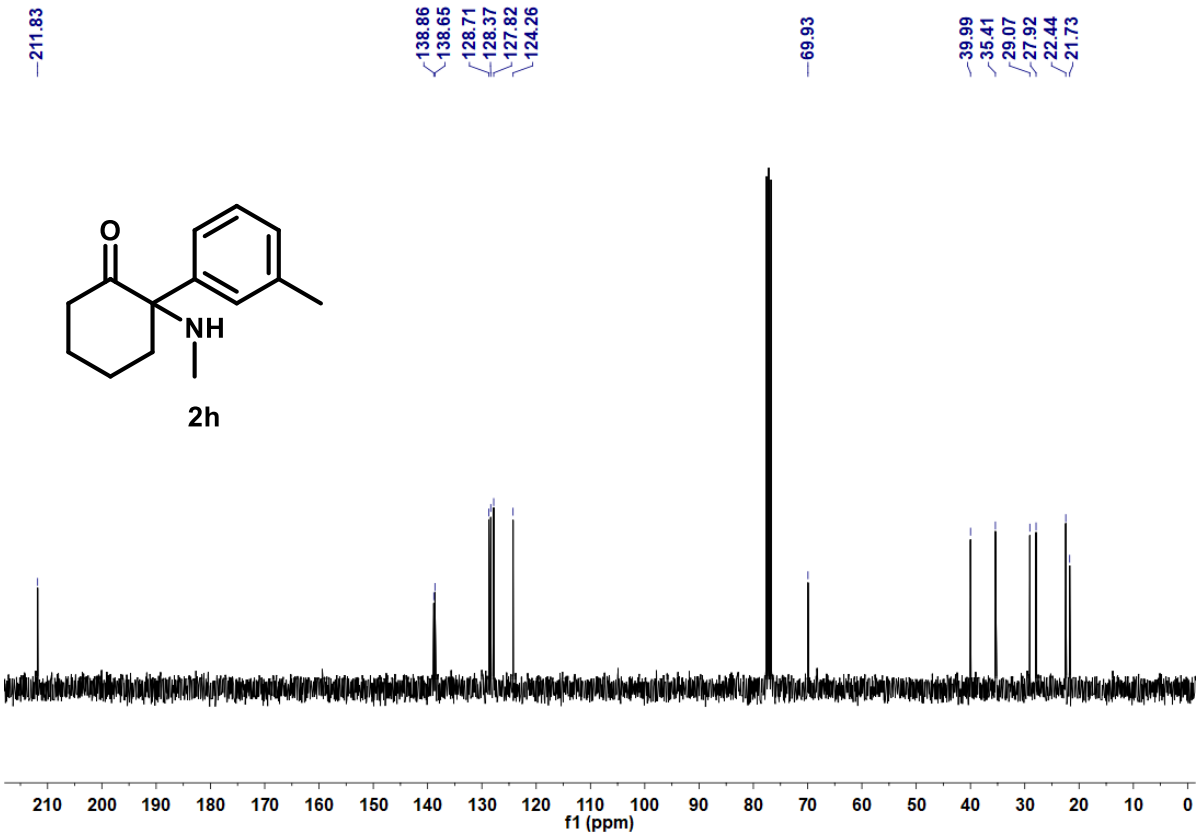
-0.5
f1 (ppm)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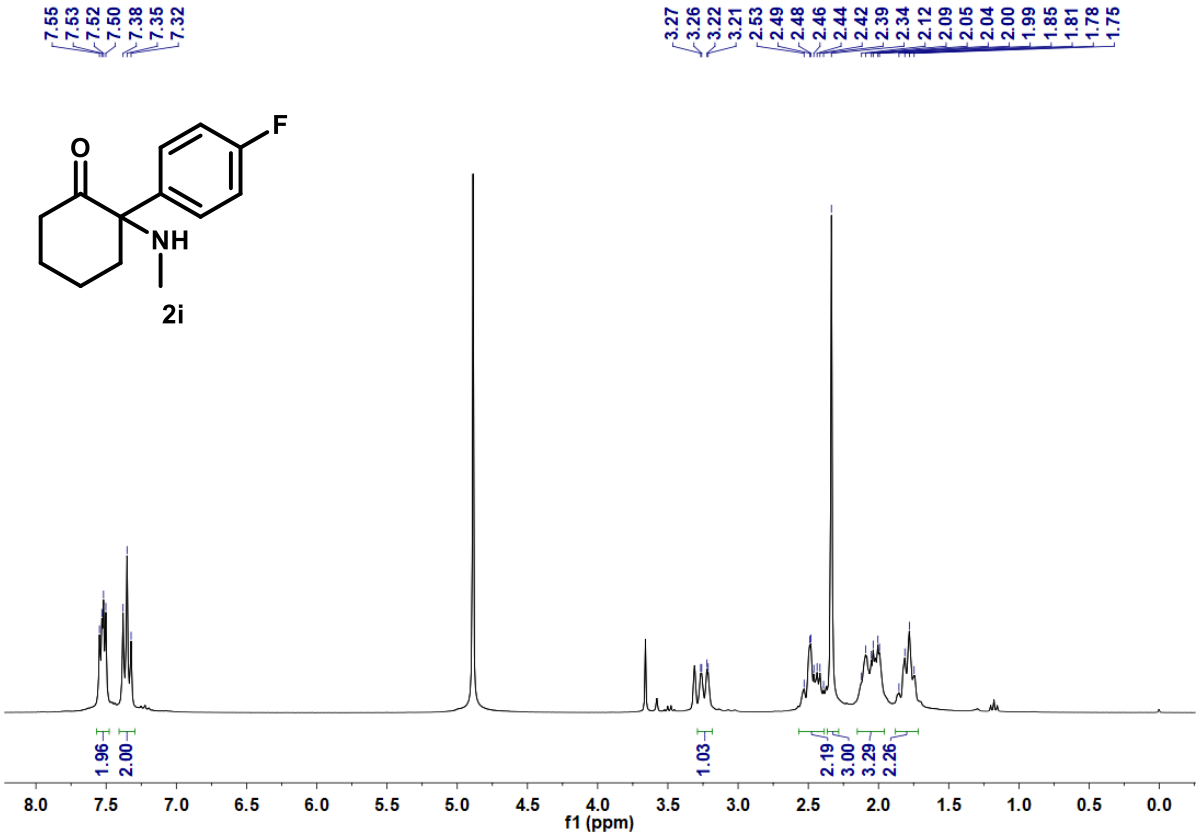
138.86
138.65
128.71
128.37
127.82
124.26
69.93
39.99
35.41
29.07
27.92
22.44
21.73
O
NH
2h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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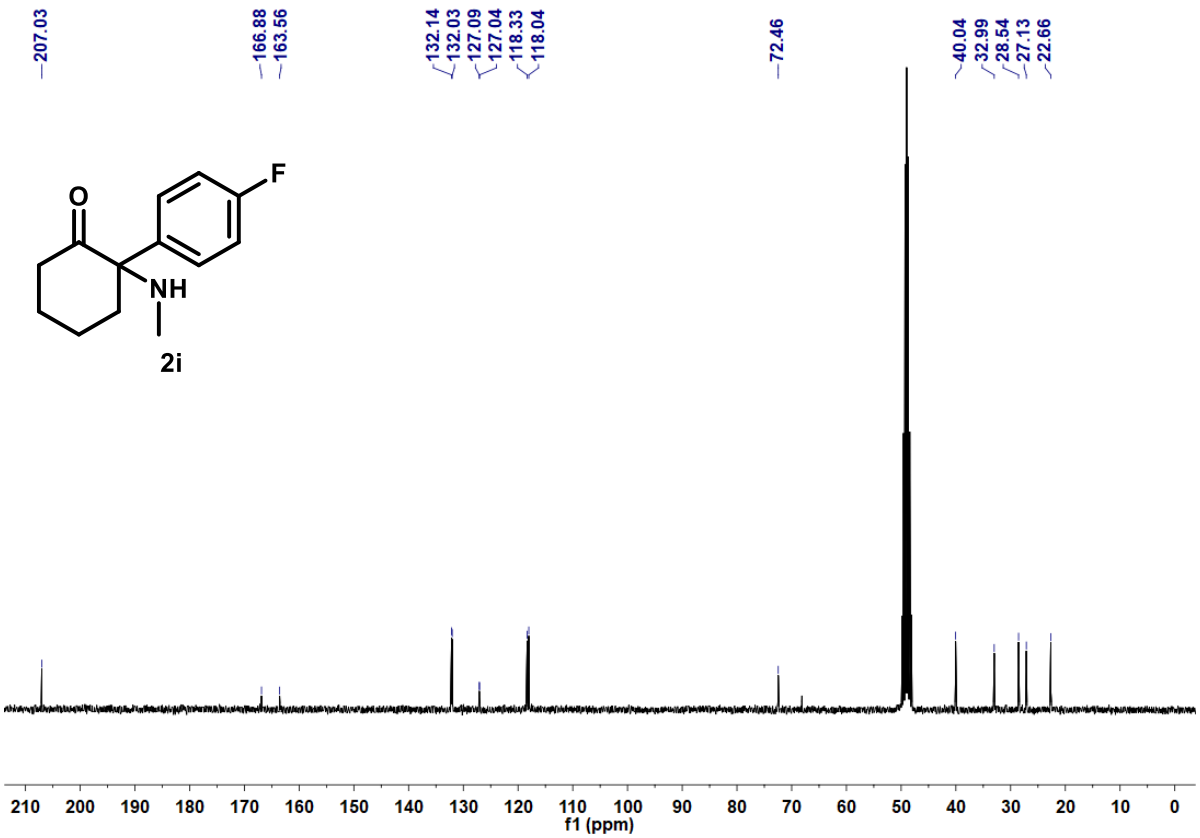
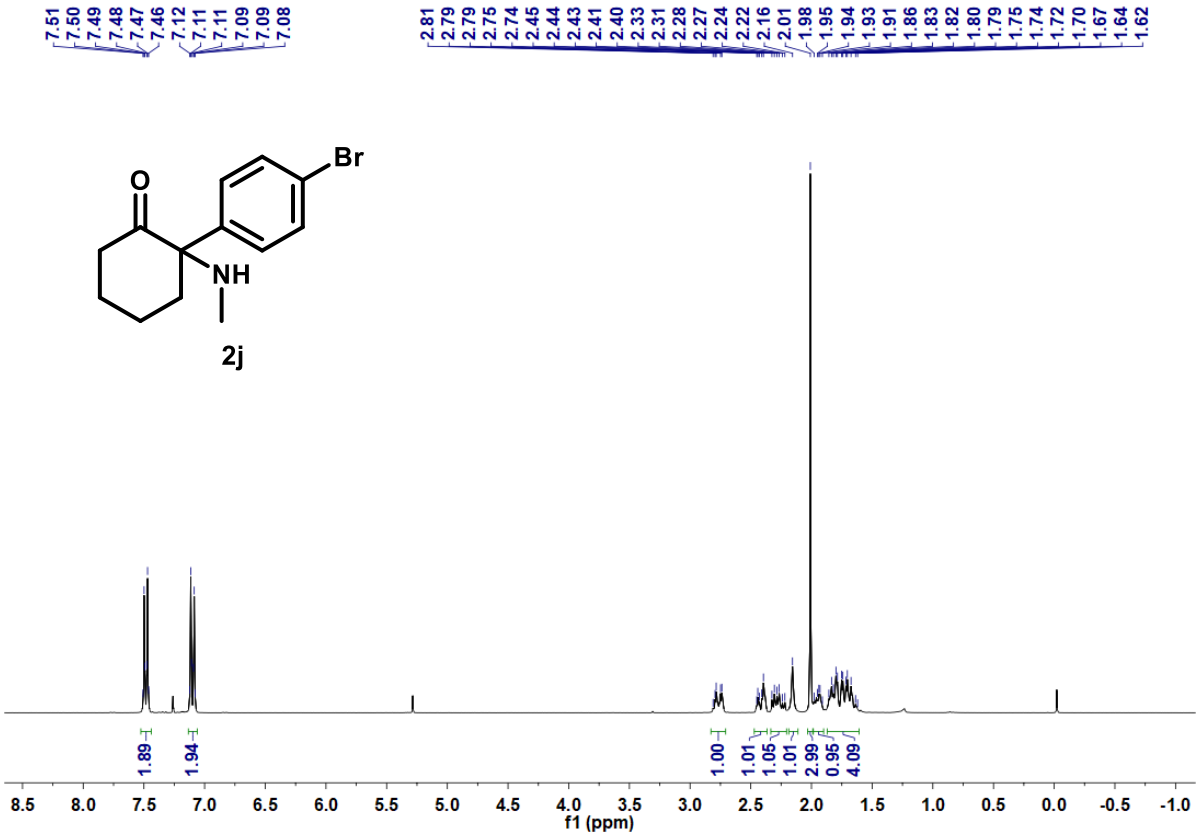
7.53
7.52
7.50
7.38
7.35
7.32
3.27
3.26
3.22
3.21
2.53
2.49
2.48
2.46
2.44
2.42
2.39
2.34
2.12
2.09
2.05
2.04
2.00
1.99
1.85
1.81
1.78
1.75
F
O
NH
2i
1.96
2.00
1.03
2.19
3.00
3.29
2.26
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


207.03
166.88
163.56
132.14
132.03
127.09
127.04
118.33
118.04
72.46
40.04
32.99
28.54
27.13
22.66
F
O
NH
2i
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.46
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7.11
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7.09
7.09
7.08
2.81
2.79
2.79
2.75
2.74
2.45
2.44
2.43
2.41
2.40
2.33
2.31
2.28
2.27
2.24
2.22
2.16
2.01
1.98
1.95
1.94
1.93
1.91
1.86
1.83
1.82
1.80
1.79
1.75
1.74
1.72
1.70
1.67
1.64
1.62
O
Br
NH
2j
1.89
1.94
1.00
1.01
1.05
1.01
2.99
0.95
4.09
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.5
2.0
1.5
1.0
0.5
0.0
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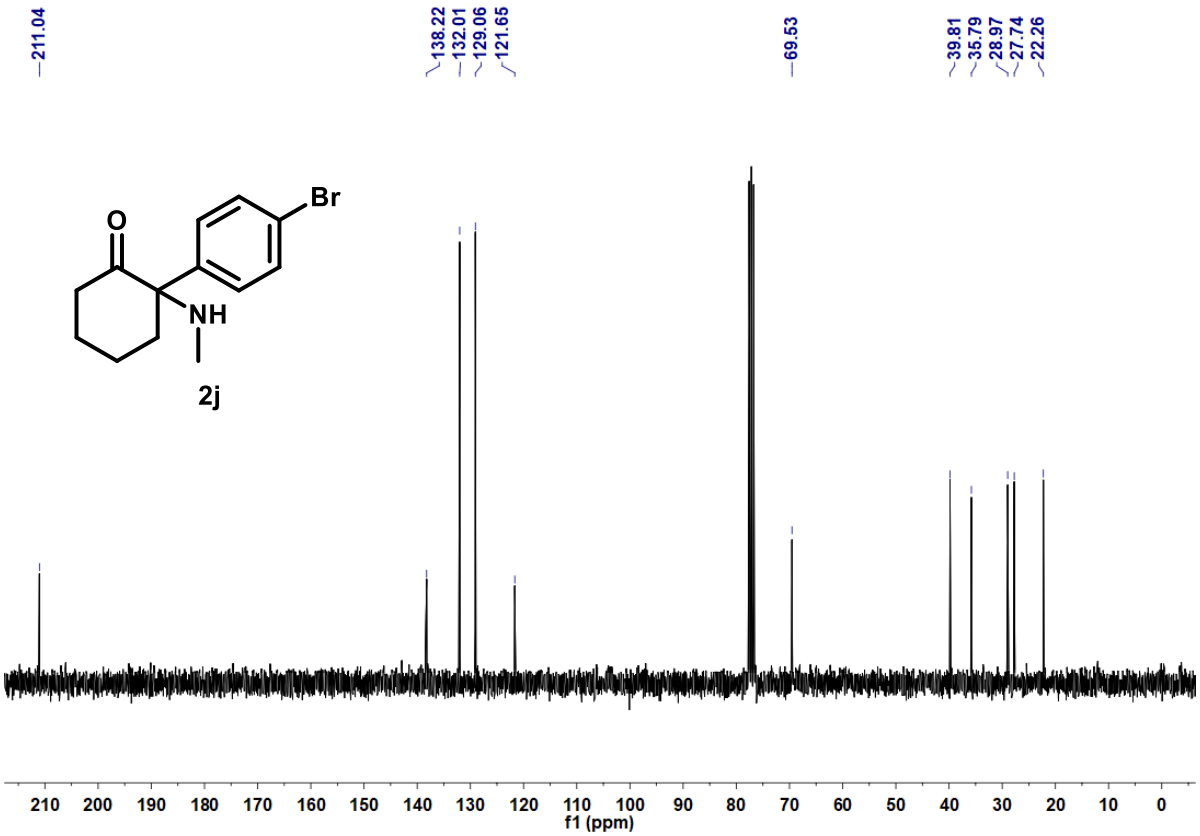
-1.0
f1 (ppm)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35.79
28.97
27.74
22.26
O
Br
NH
2j
210
200
190
180
170
160
150
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130
120
110
100
90
80
70
60
50
40
30
20
10
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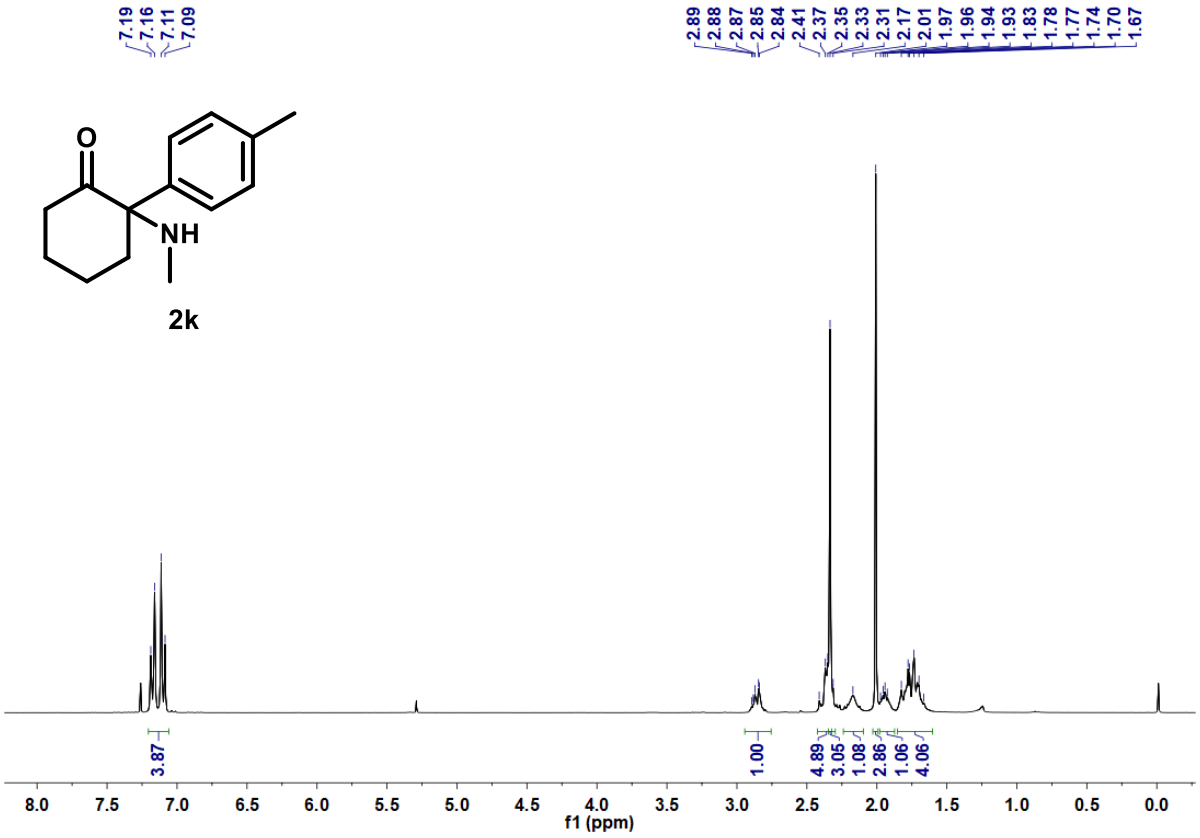
f1 (ppm)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2.85
2.84
2.41
2.37
2.35
2.33
2.31
2.17
2.01
1.97
1.96
1.94
1.93
1.83
1.78
1.77
1.74
1.70
1.67
O
NH
2k
3.87
1.00
4.89
3.05
1.08
2.86
1.06
4.06
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
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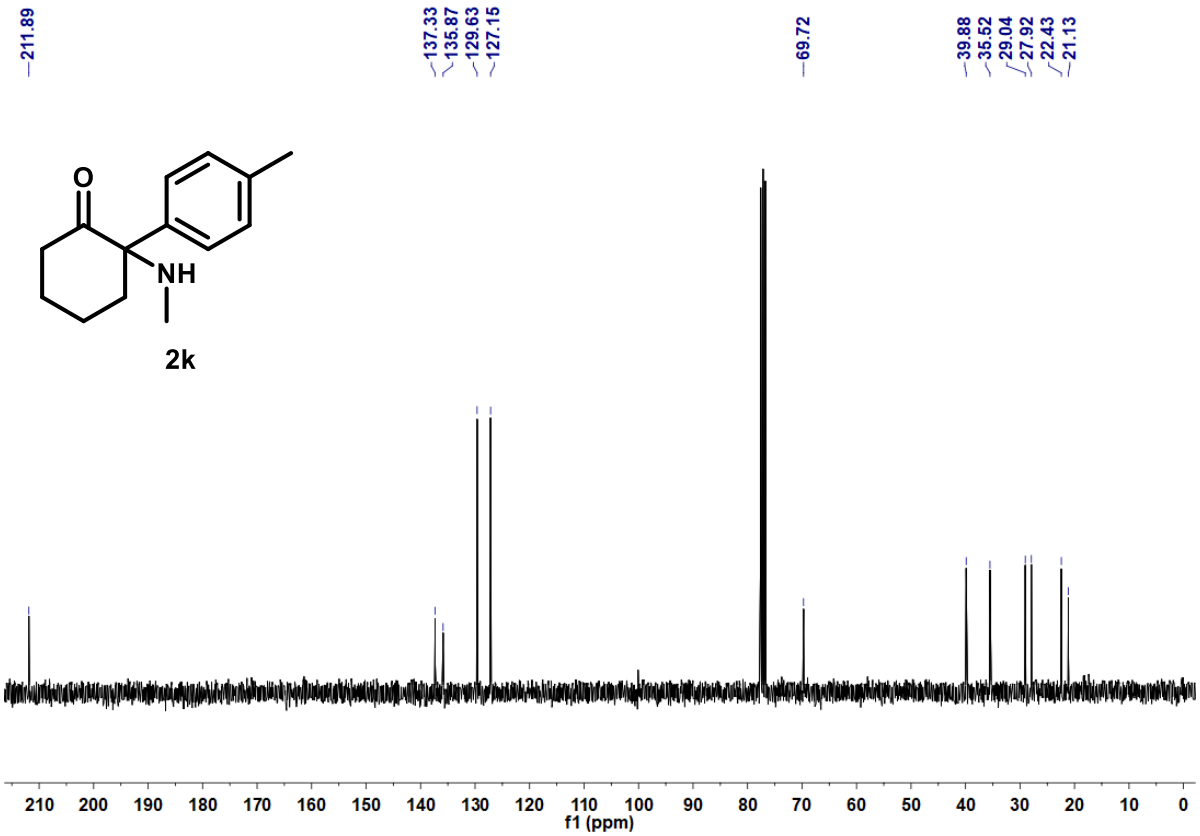
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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35.52
29.04
27.92
22.43
21.13
O
NH
2k
210
200
190
180
170
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150
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130
120
110
100
90
80
70
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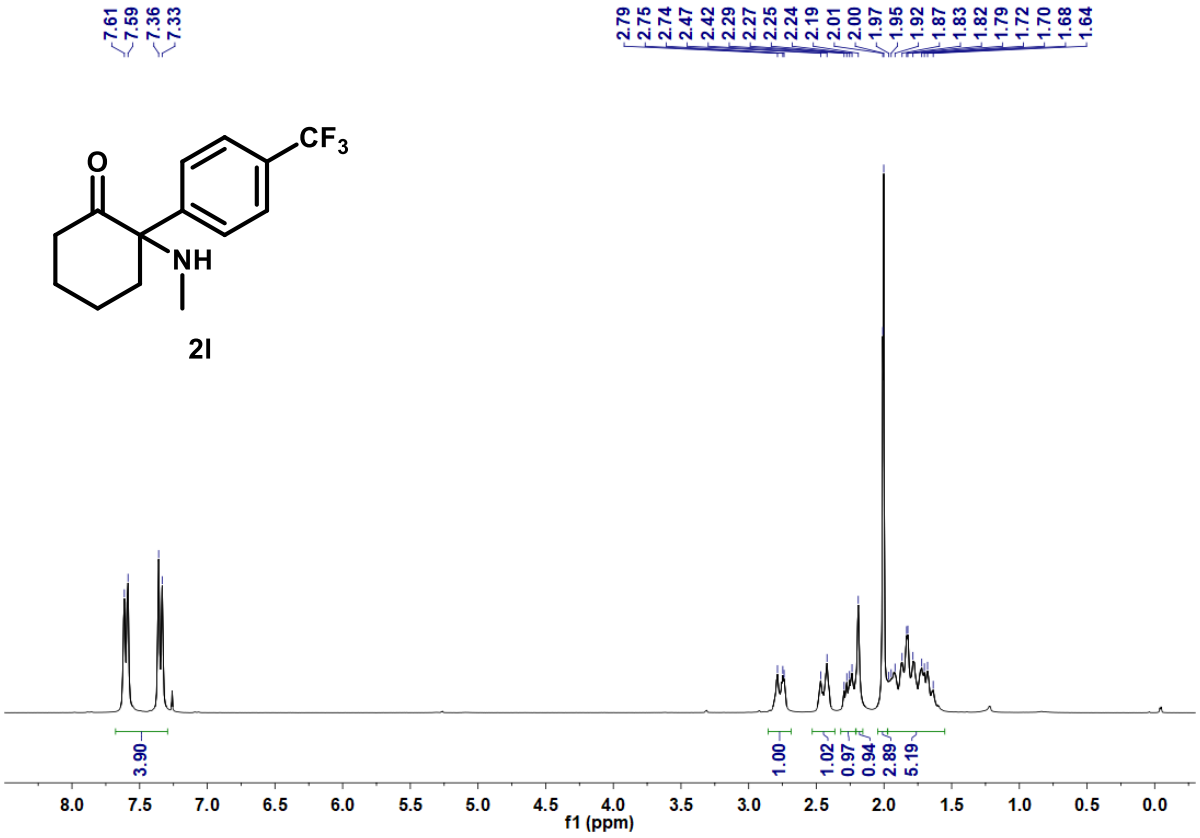
50
40
30
20
10
0
f1 (ppm)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2.25
2.24
2.19
2.01
2.00
1.97
1.95
1.92
1.87
1.83
1.82
1.79
1.72
1.70
1.68
1.64
O
CF3
NH
2l
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1.02
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0.94
2.89
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7.5
7.0
6.5
6.0
5.5
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4.5
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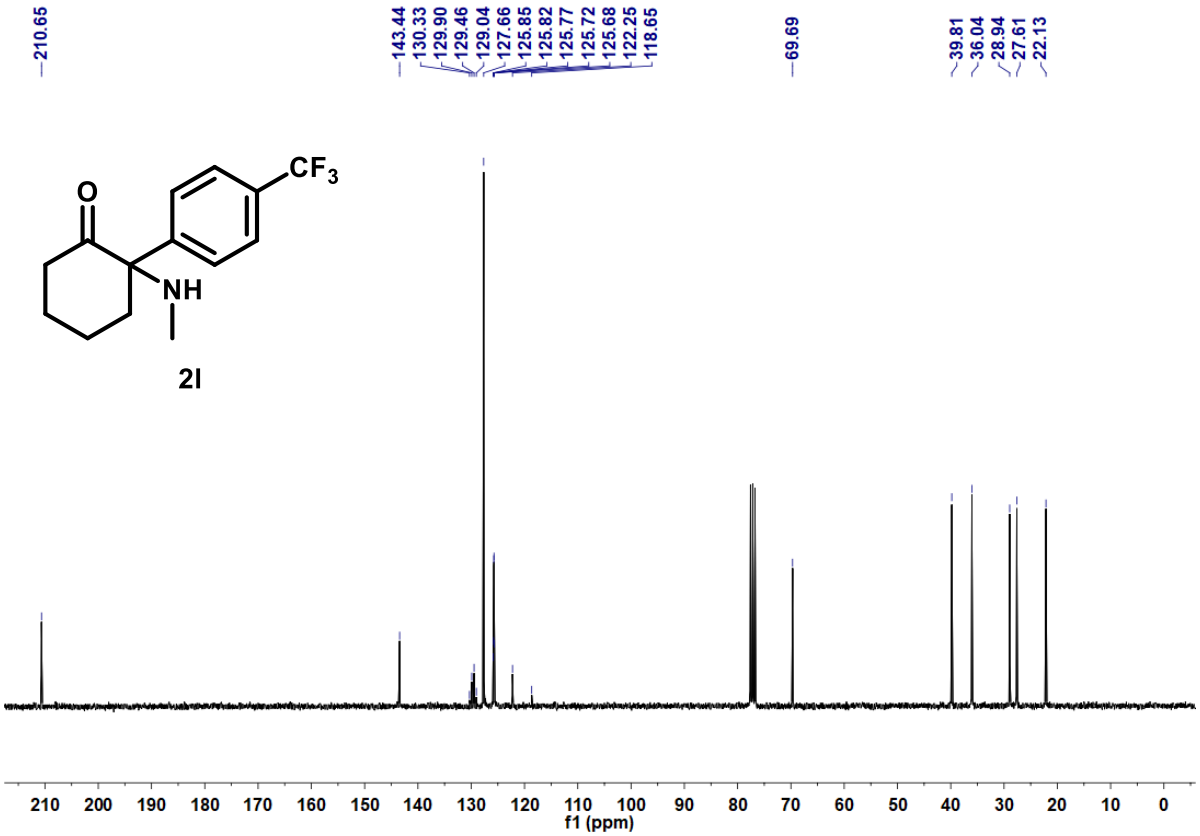
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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125.72
125.68
122.25
118.65
69.69
39.81
36.04
28.94
27.61
22.13
O
CF3
NH
2l
210
200
190
180
170
160
150
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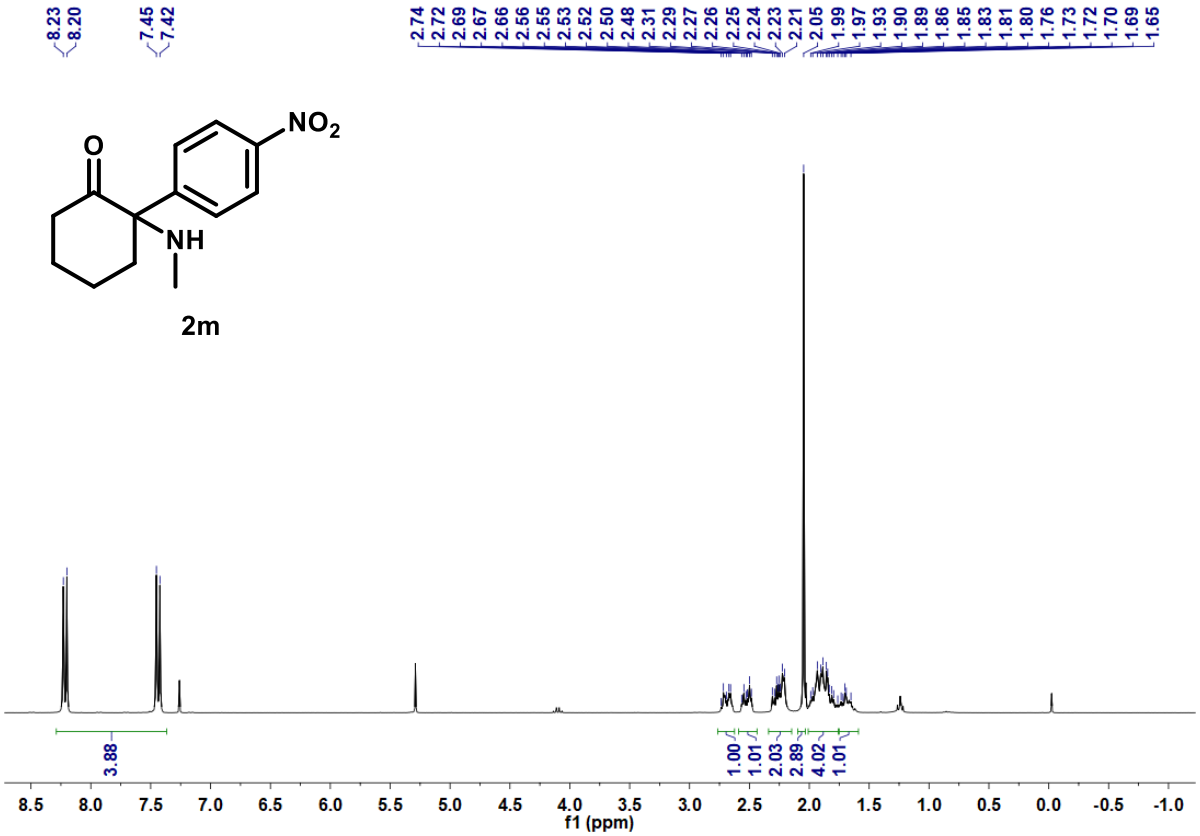
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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2.67
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2.53
2.52
2.50
2.48
2.31
2.29
2.27
2.26
2.25
2.24
2.23
2.21
2.05
1.99
1.97
1.93
1.90
1.89
1.86
1.85
1.83
1.81
1.80
1.76
1.73
1.72
1.70
1.69
1.65
O
NO2
NH
2m
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1.00
1.01
2.03
2.89
4.02
1.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.5
2.0
1.5
1.0
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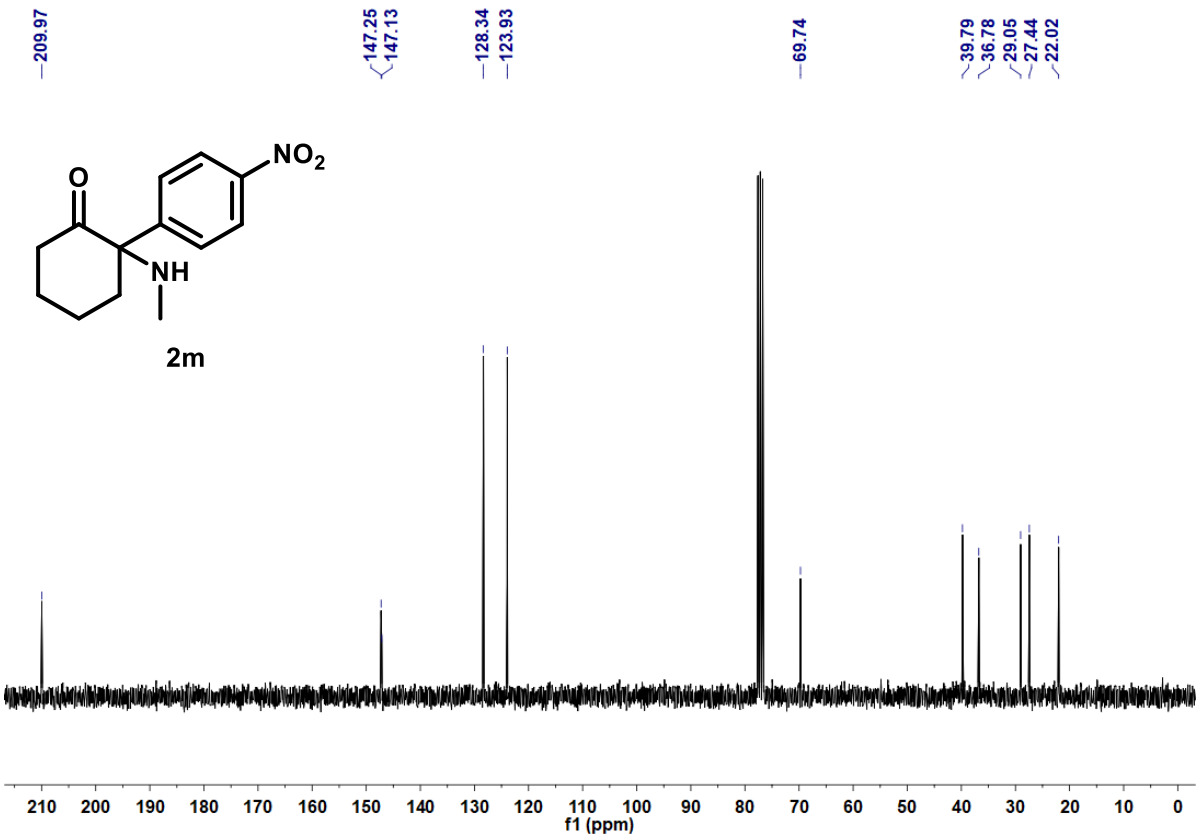
0.0
-0.5
-1.0
f1 (ppm)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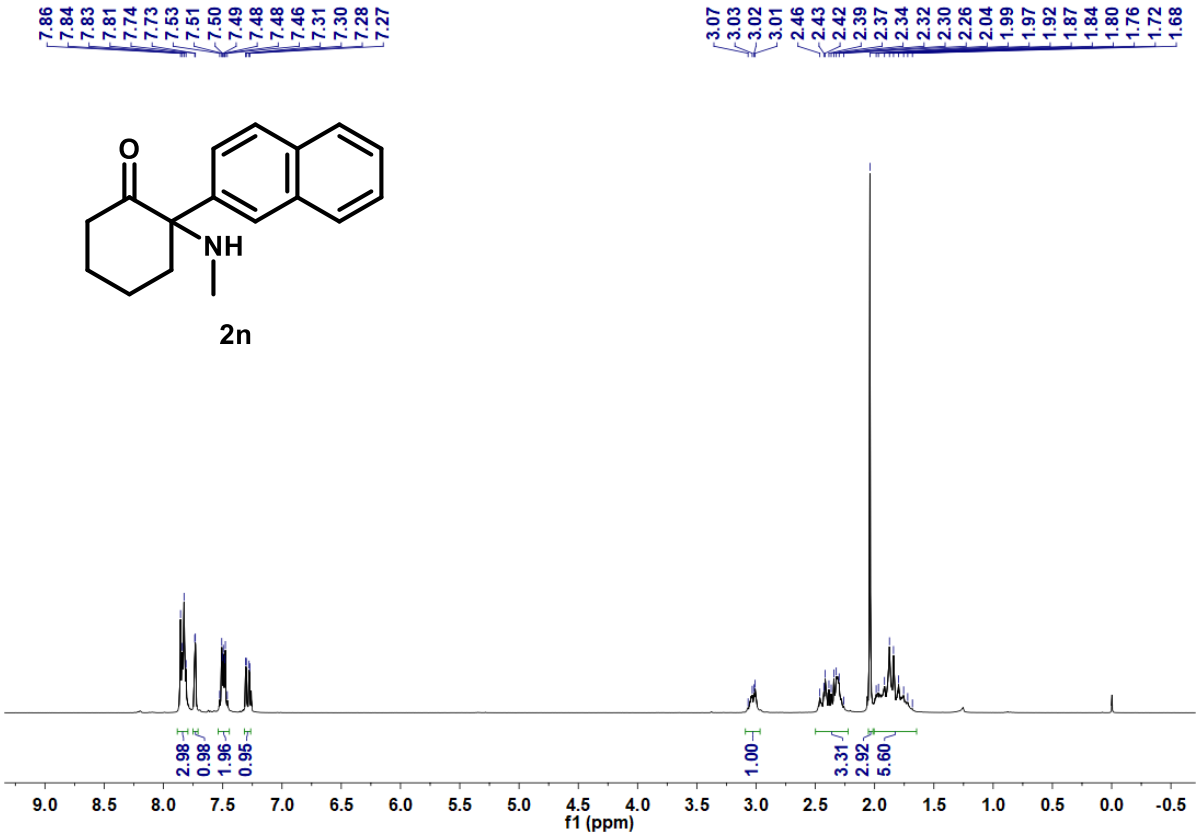
147.13
128.34
123.93
69.74
39.79
36.78
29.05
27.44
22.02
O
NO2
NH
2m
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.48
7.46
7.31
7.30
7.28
7.27
3.07
3.03
3.02
3.01
2.46
2.43
2.42
2.39
2.37
2.34
2.32
2.30
2.26
2.04
1.99
1.97
1.92
1.87
1.84
1.80
1.76
1.72
1.68
O
NH
2n
2.98
0.98
1.96
0.95
1.00
3.31
2.92
5.60
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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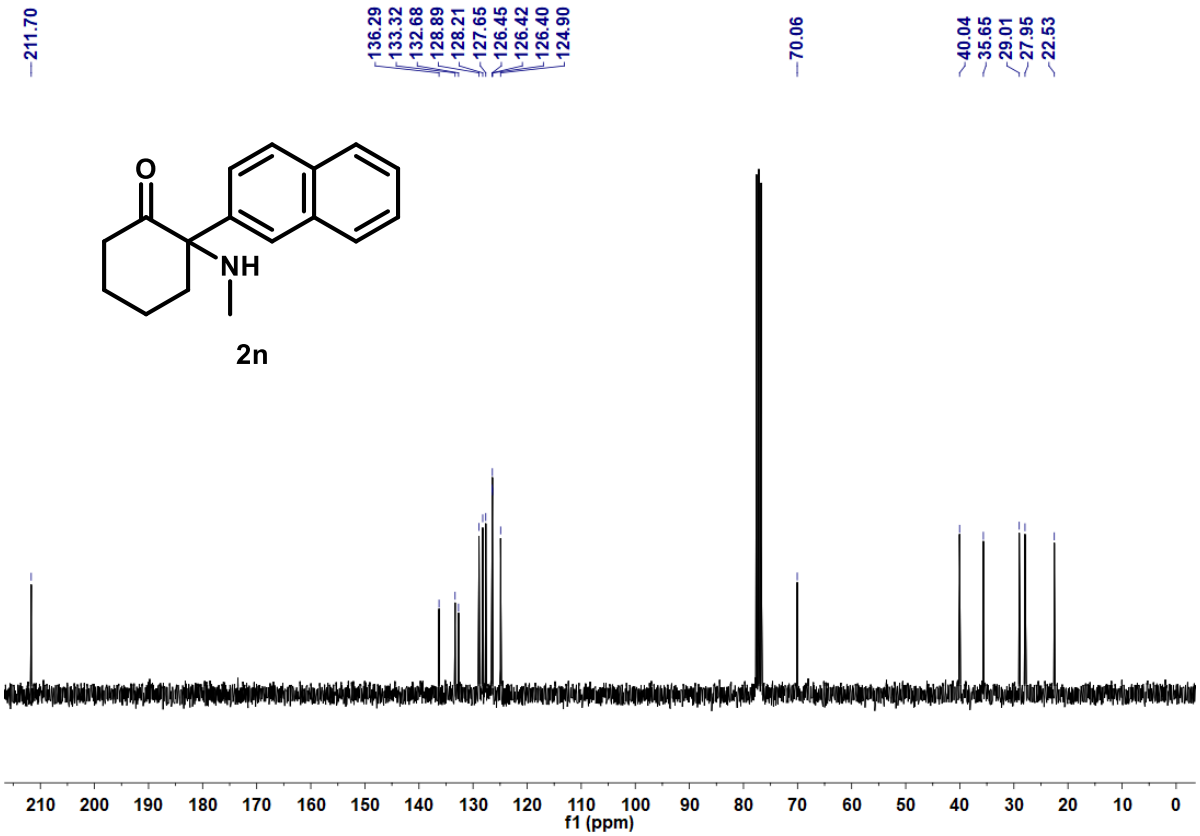
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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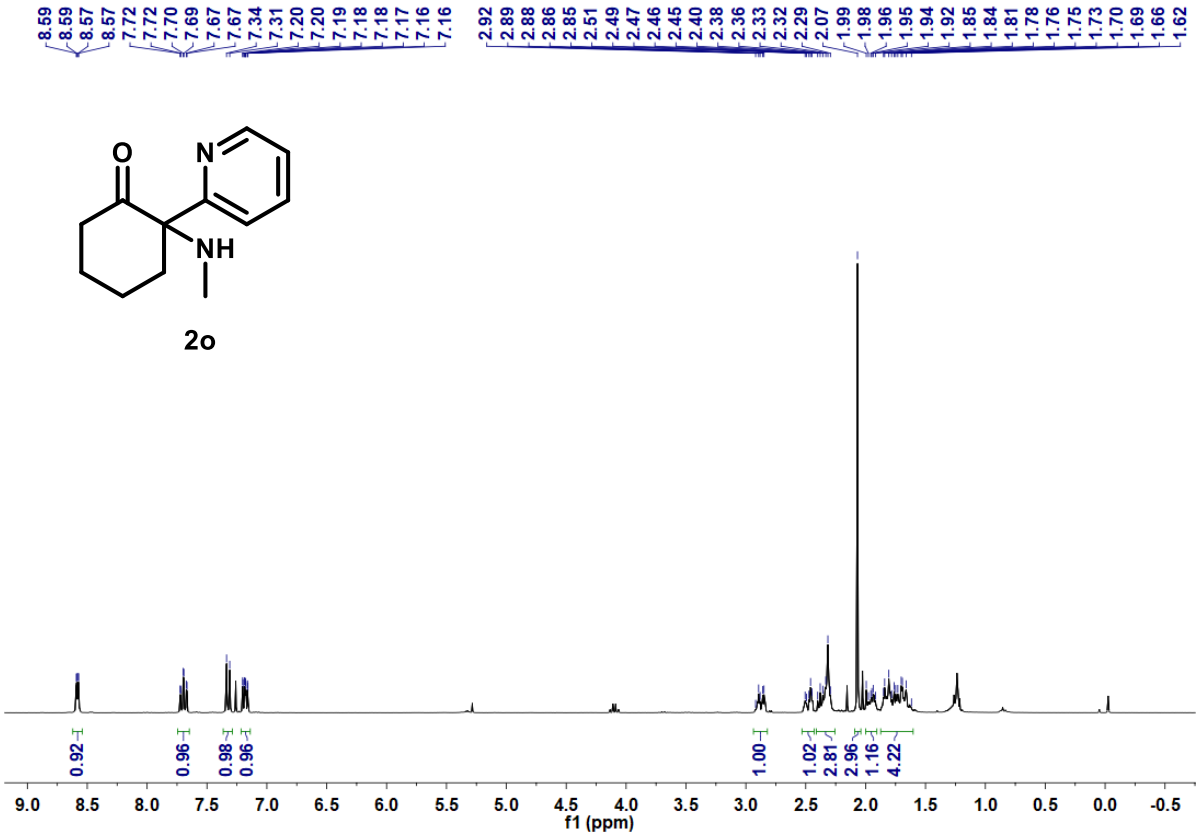
124.90
70.06
40.04
35.65
29.01
27.95
22.53
O
NH
2n
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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8.57
8.57
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7.72
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7.20
7.19
7.18
7.18
7.17
7.16
7.16
2.92
2.89
2.88
2.86
2.85
2.51
2.49
2.47
2.46
2.45
2.40
2.38
2.36
2.33
2.32
2.29
2.07
1.99
1.98
1.96
1.95
1.94
1.92
1.85
1.84
1.81
1.78
1.76
1.75
1.73
1.70
1.69
1.66
1.62
O
N
NH
2o
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0.96
0.98
0.96
1.00
1.02
2.81
2.96
1.16
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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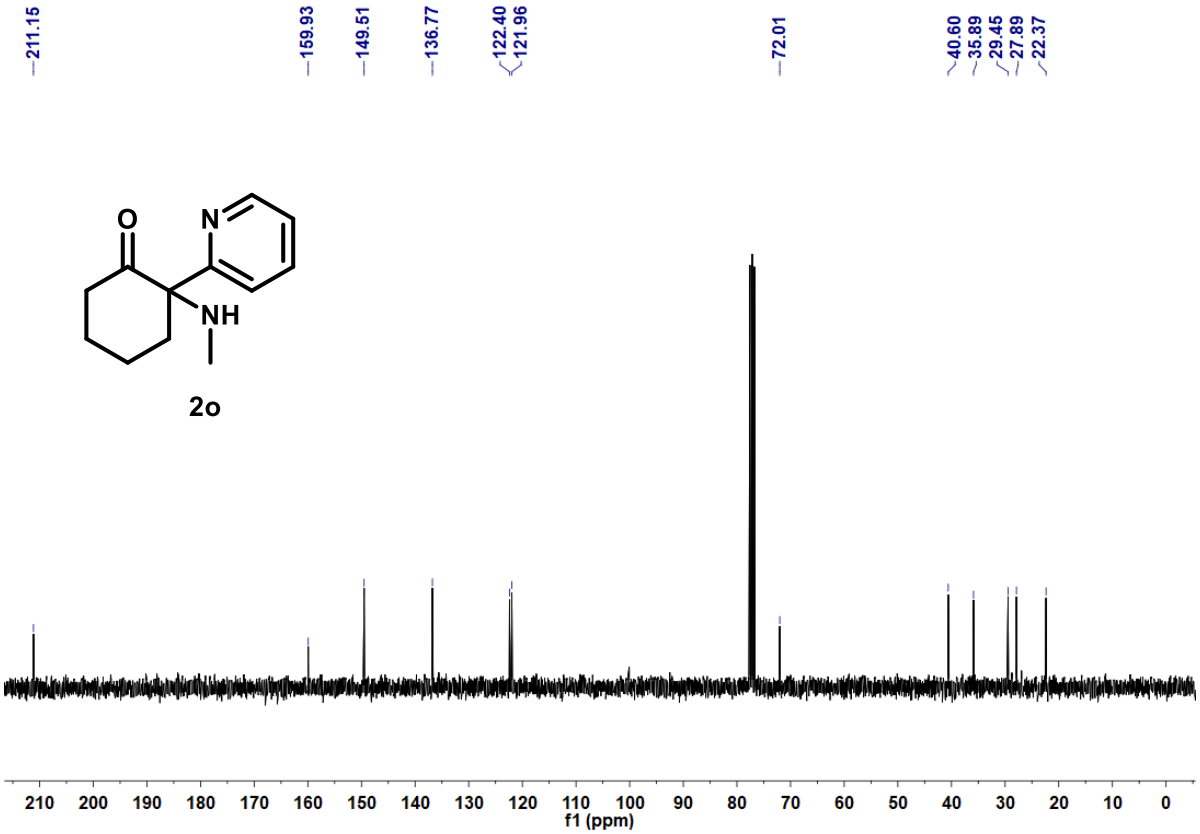
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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121.96
72.01
40.60
35.89
29.45
27.89
22.37
O
N
NH
2o
210
200
190
180
170
160
150
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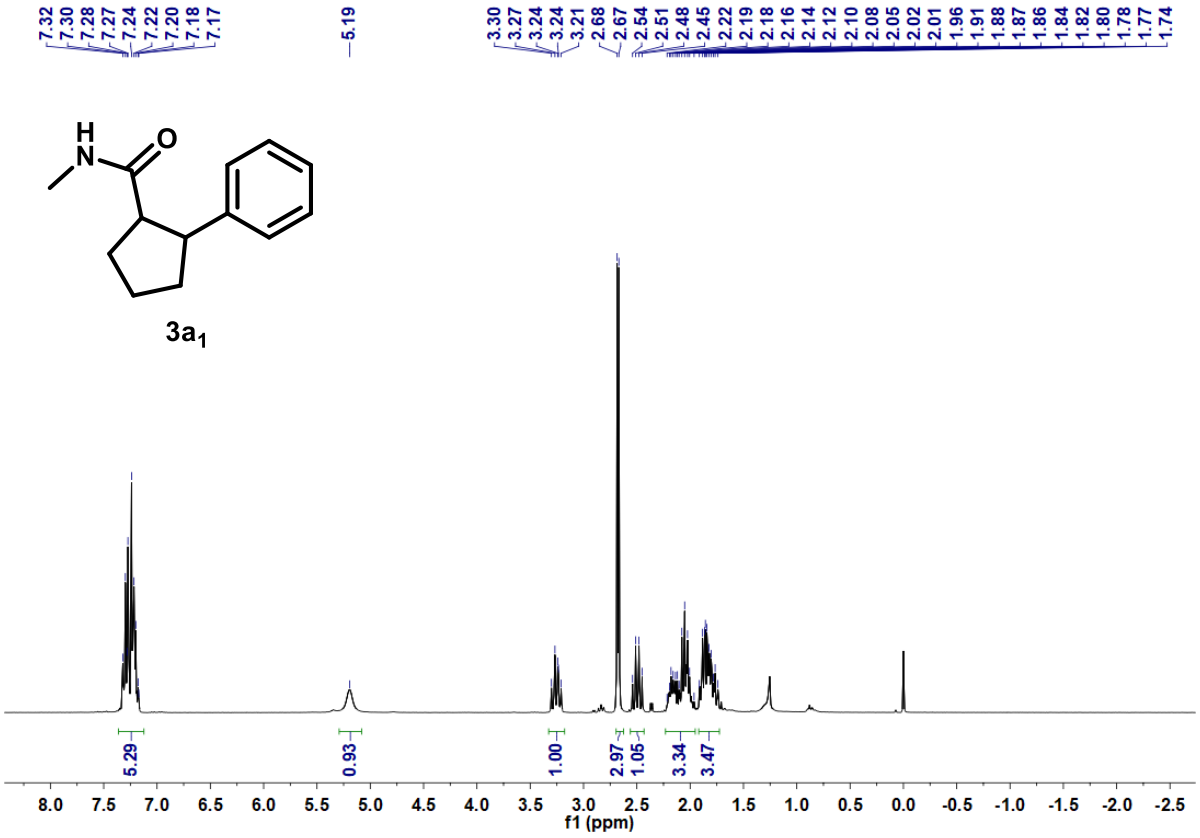
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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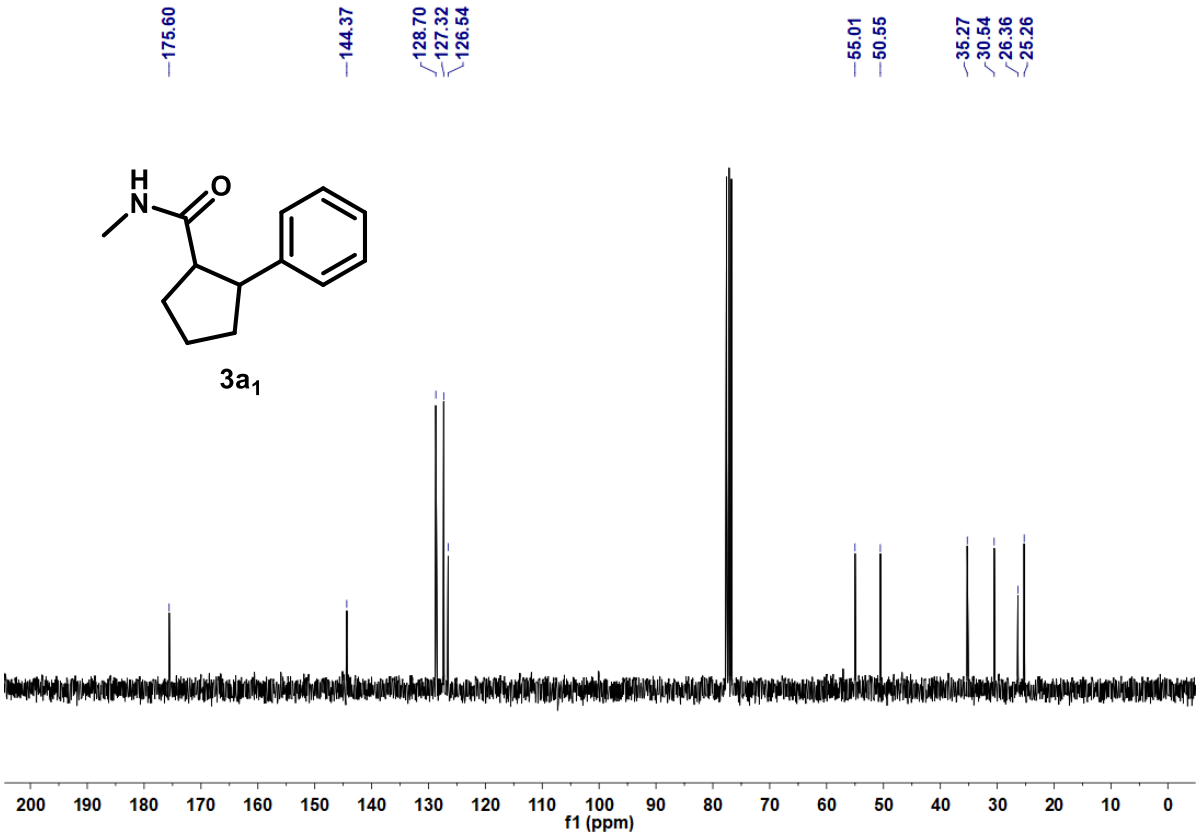
7.28
7.27
7.24
7.22
7.20
7.18
7.17
5.19
3.30
3.27
3.24
3.24
3.21
2.68
2.67
2.54
2.51
2.48
2.45
2.22
2.19
2.18
2.16
2.14
2.12
2.10
2.08
2.05
2.02
2.01
1.96
1.91
1.88
1.87
1.86
1.84
1.82
1.80
1.78
1.77
1.74
H
N
O
3a1
5.29
0.93
1.00
2.97
1.05
3.34
3.47
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0 -2.5
f1 (ppm)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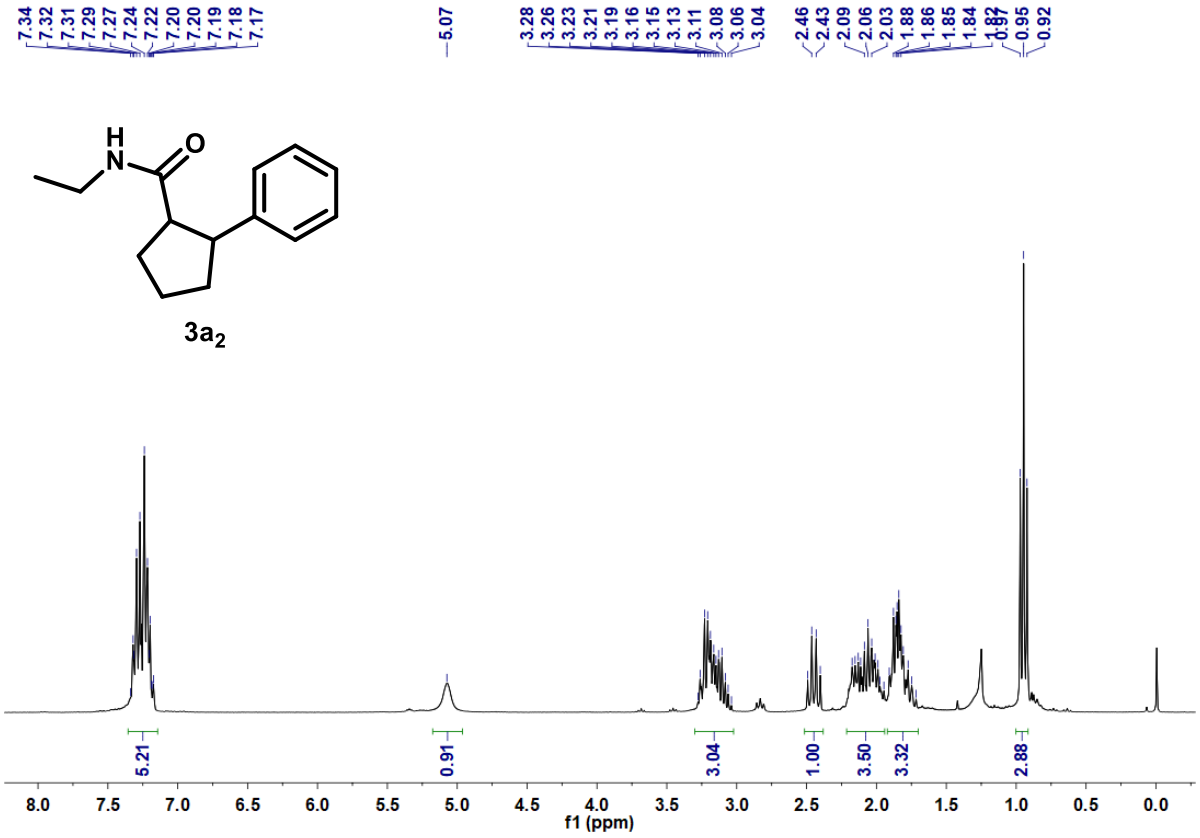
128.70
127.32
126.54
55.01
50.55
35.27
30.54
26.36
25.26
H
N
O
3a1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.31
7.29
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7.22
7.20
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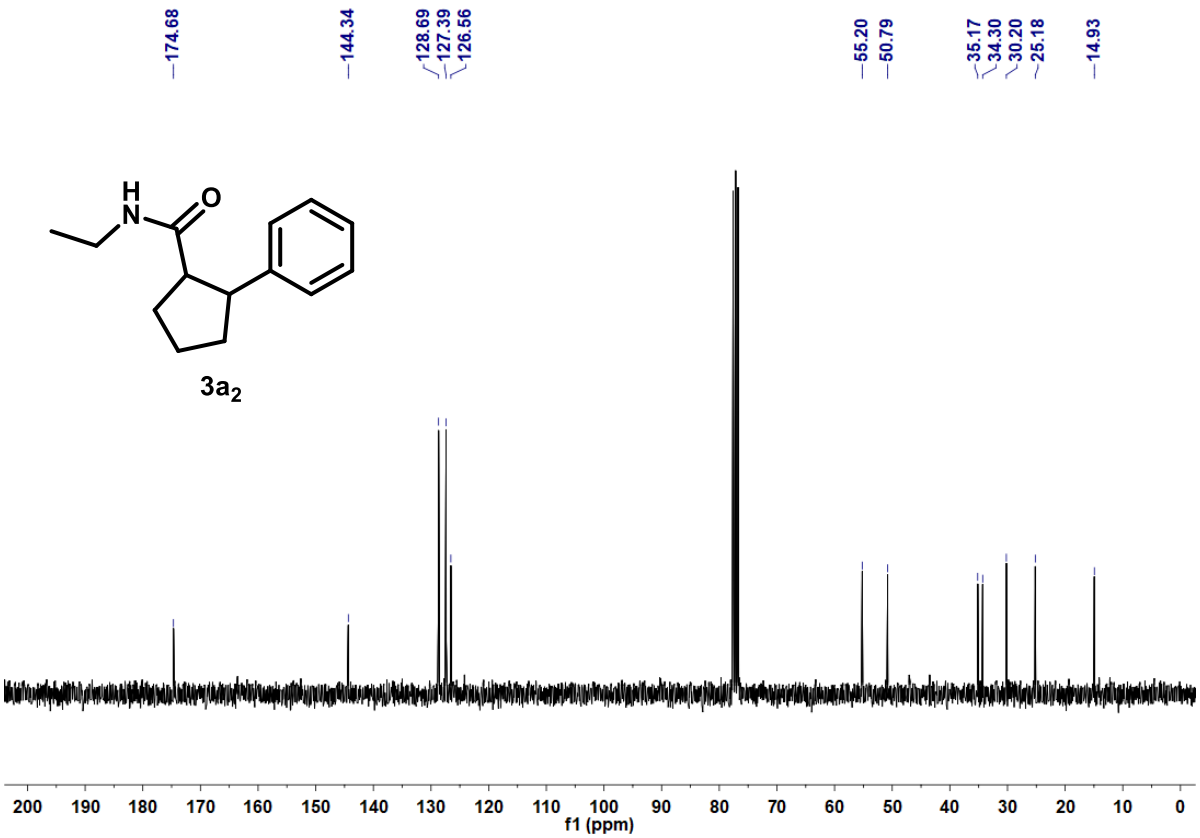
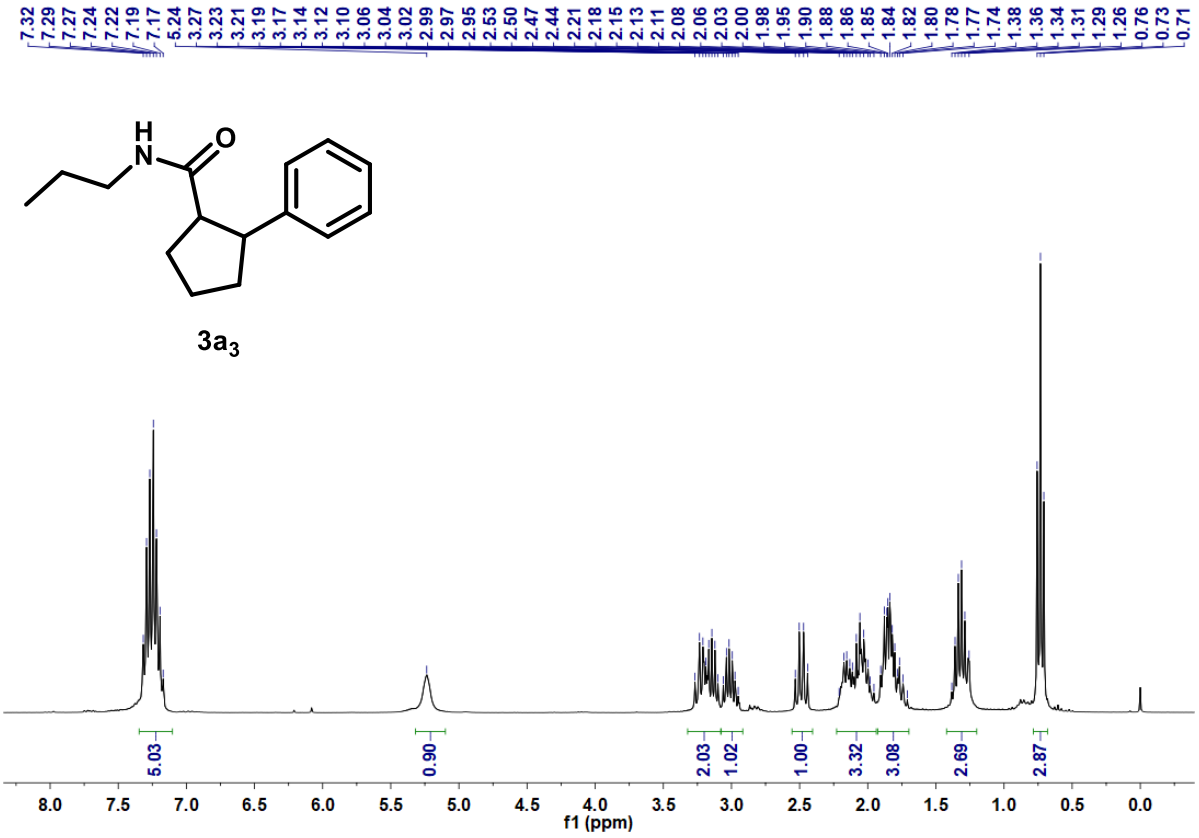
7.19
7.18
7.17
5.07
3.28
3.26
3.23
3.21
3.19
3.16
3.15
3.13
3.11
3.08
3.06
3.04
2.46
2.43
2.09
2.06
2.03
1.88
1.86
1.85
1.84
0.95
0.92
H
N
O
5.21
0.91
3.04
1.00
3.50
3.32
2.88
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

$3a_2$


174.68
144.34
128.69
127.39
126.56
55.20
50.79
35.17
34.30
30.20
25.18
14.93
H
N
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

$3a_2$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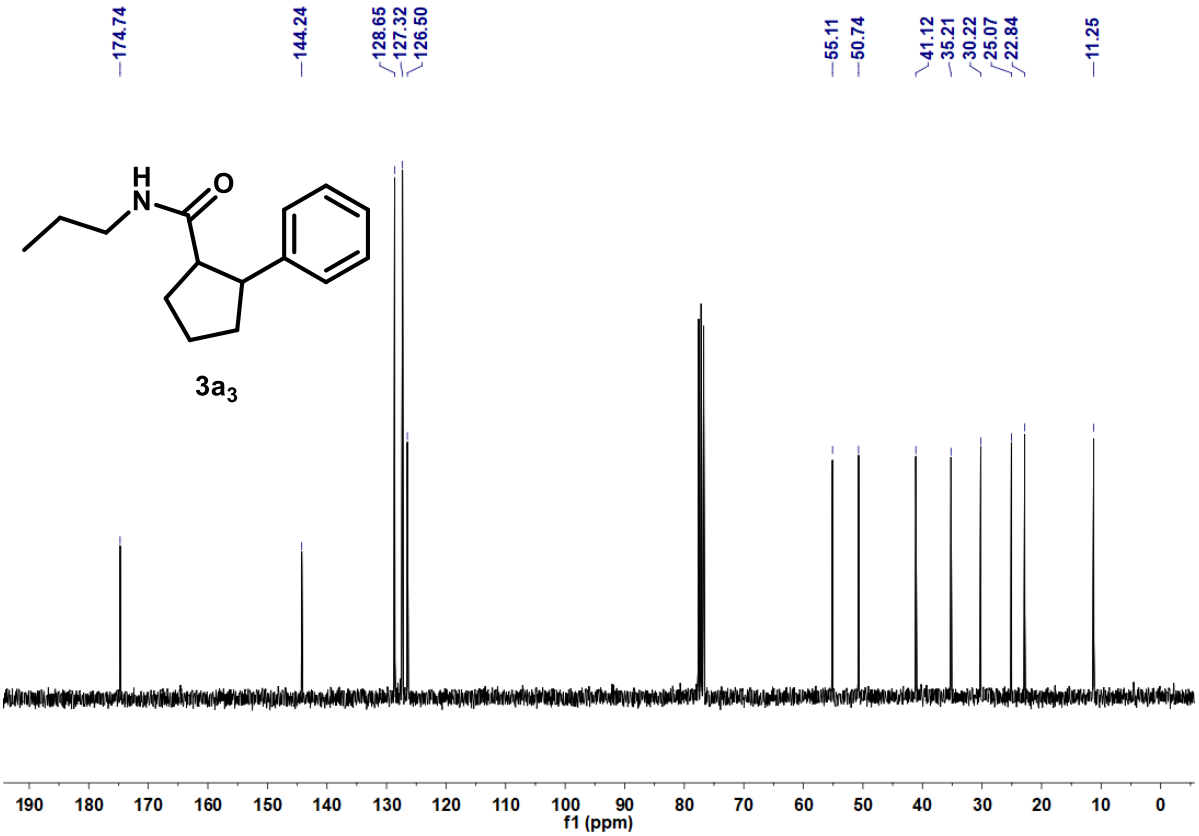
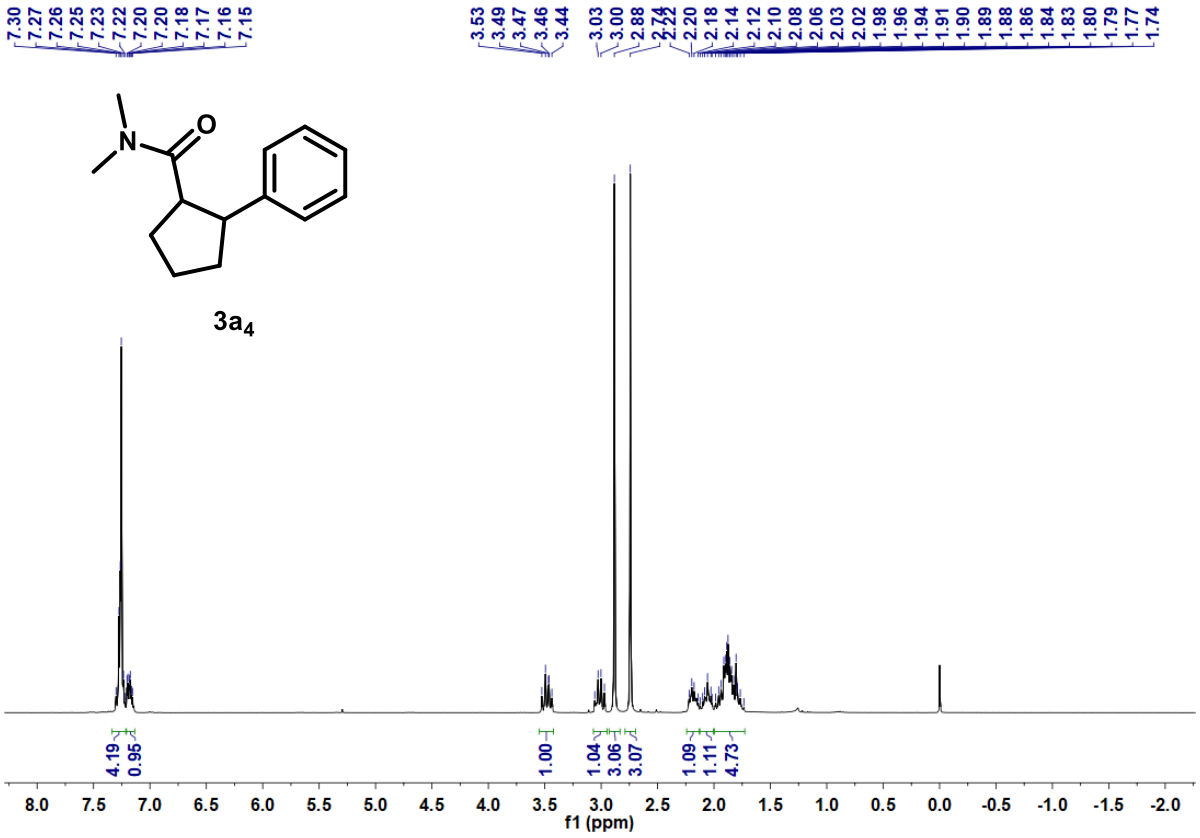
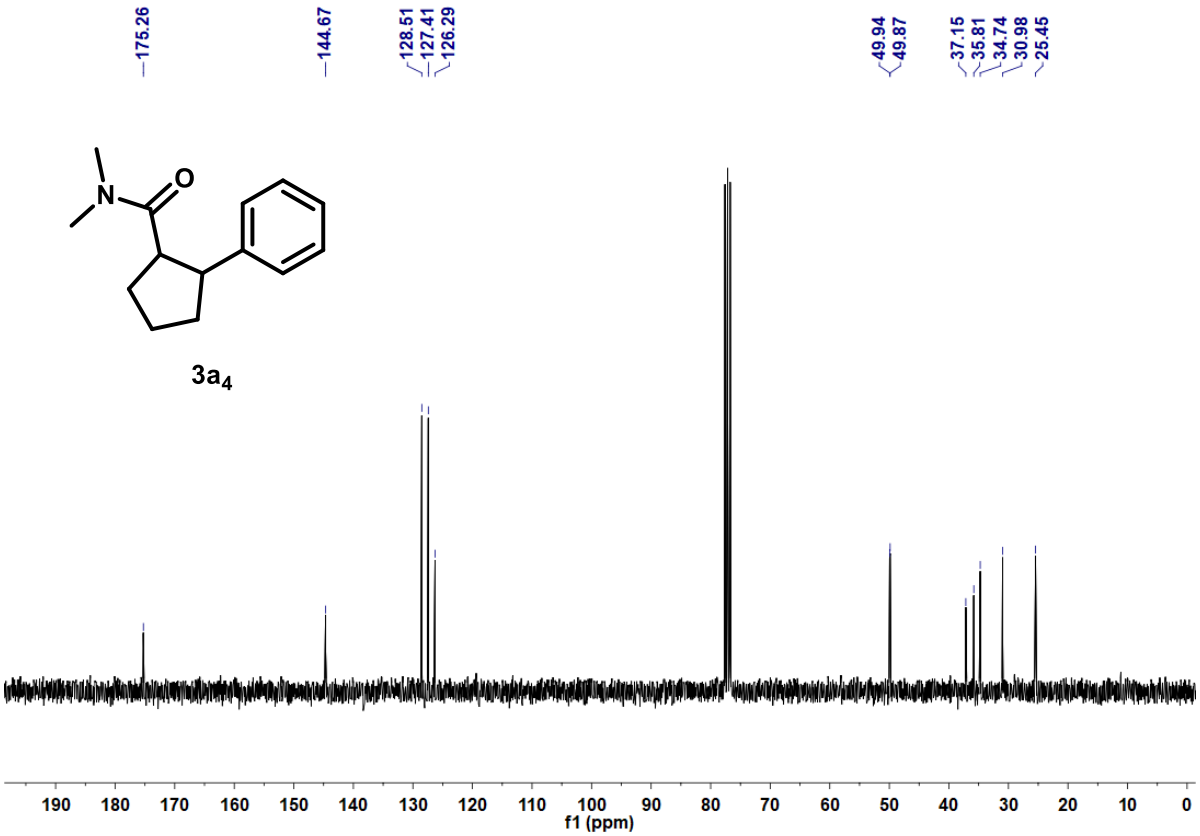
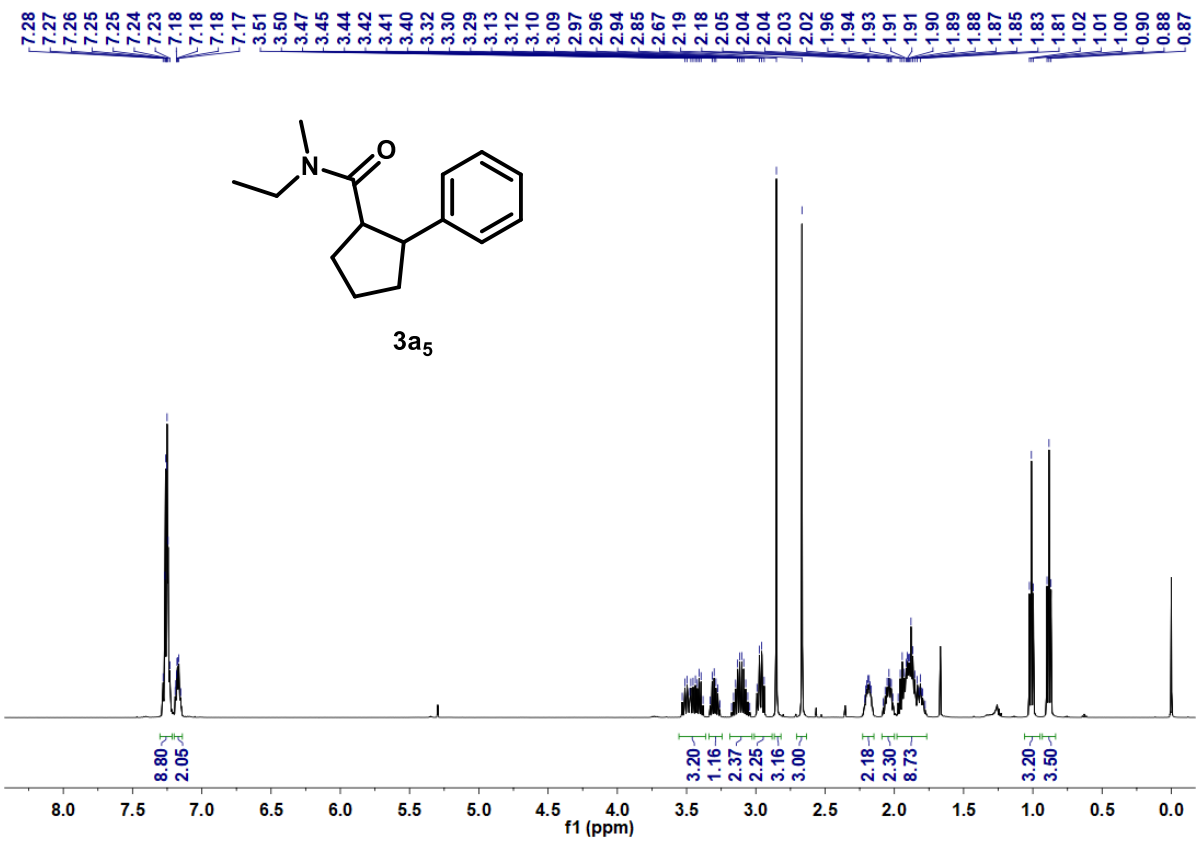
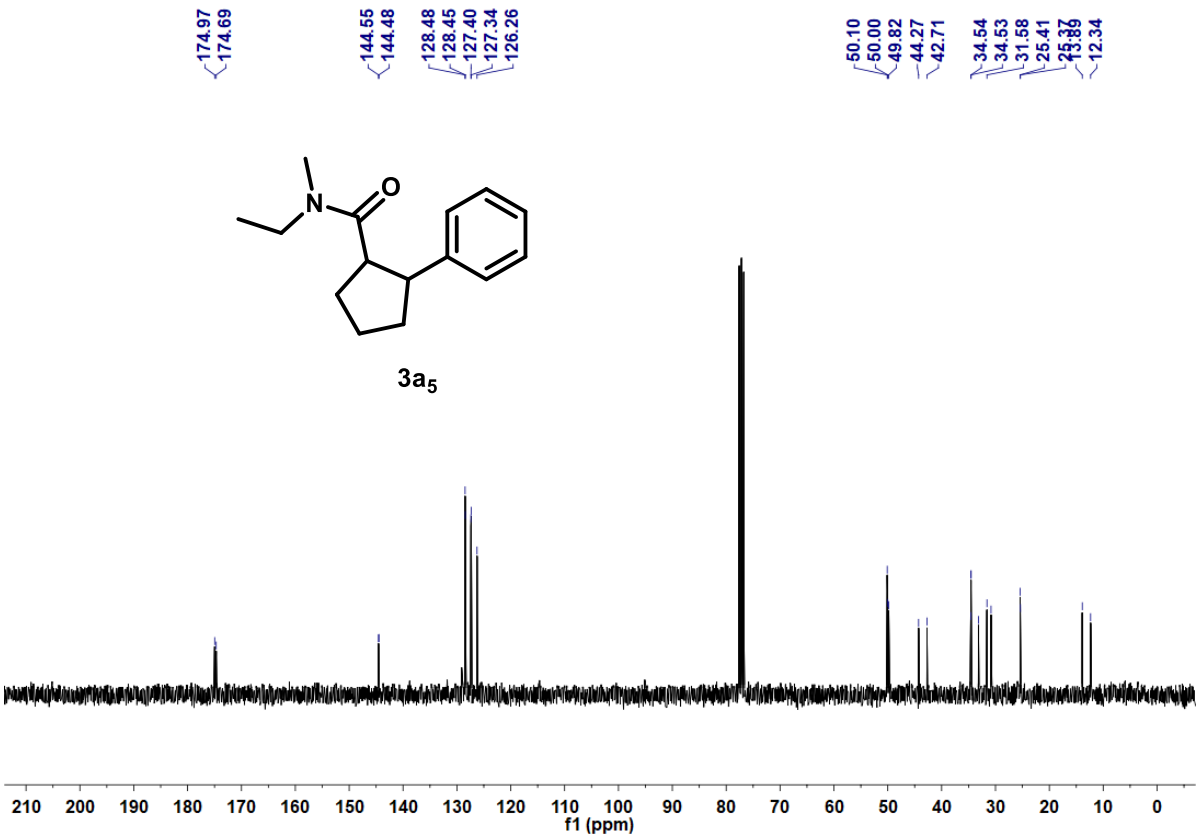
H
N
O
3a3
5.03 0.90 2.03 1.02 1.00 3.32 3.08 2.69 2.87
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

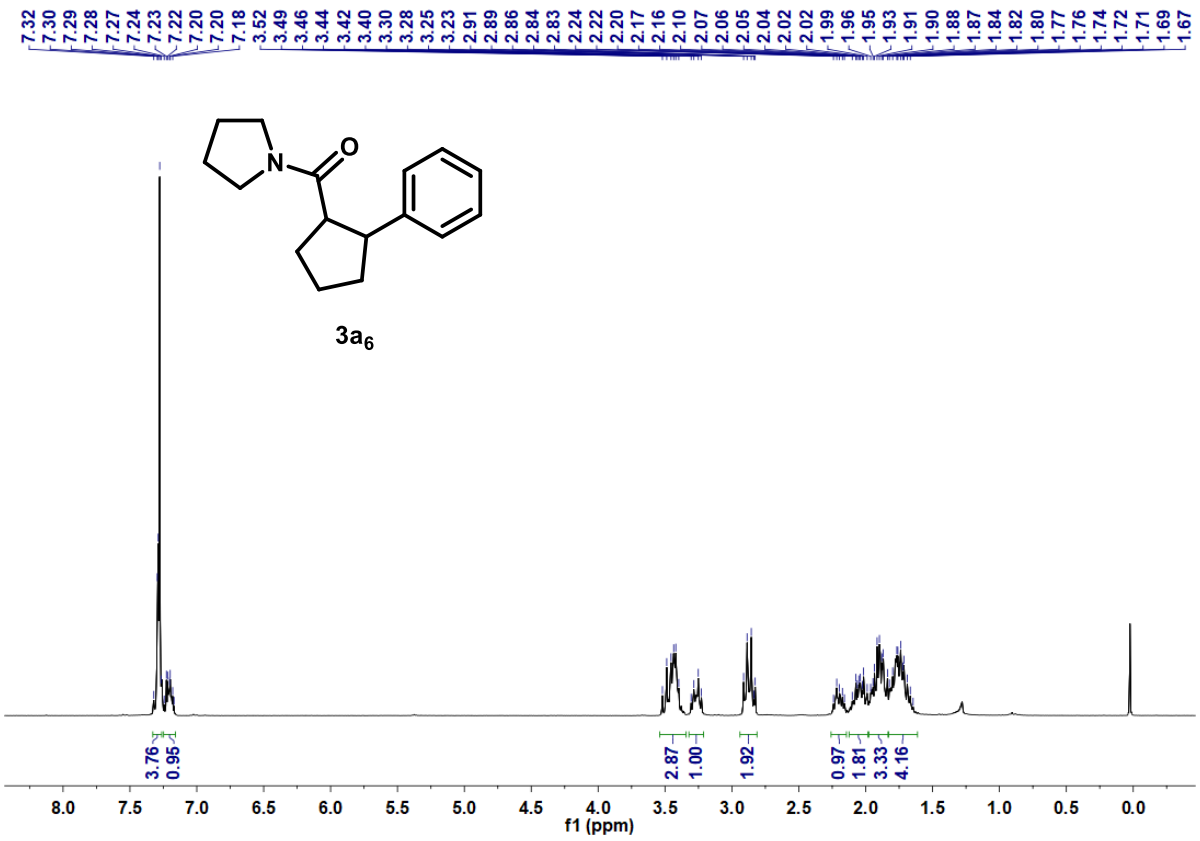

174.74 144.24 128.65 127.32 126.50 55.11 50.74 41.12 35.21 30.22 25.07 22.84 11.25
H
N
O
3a3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

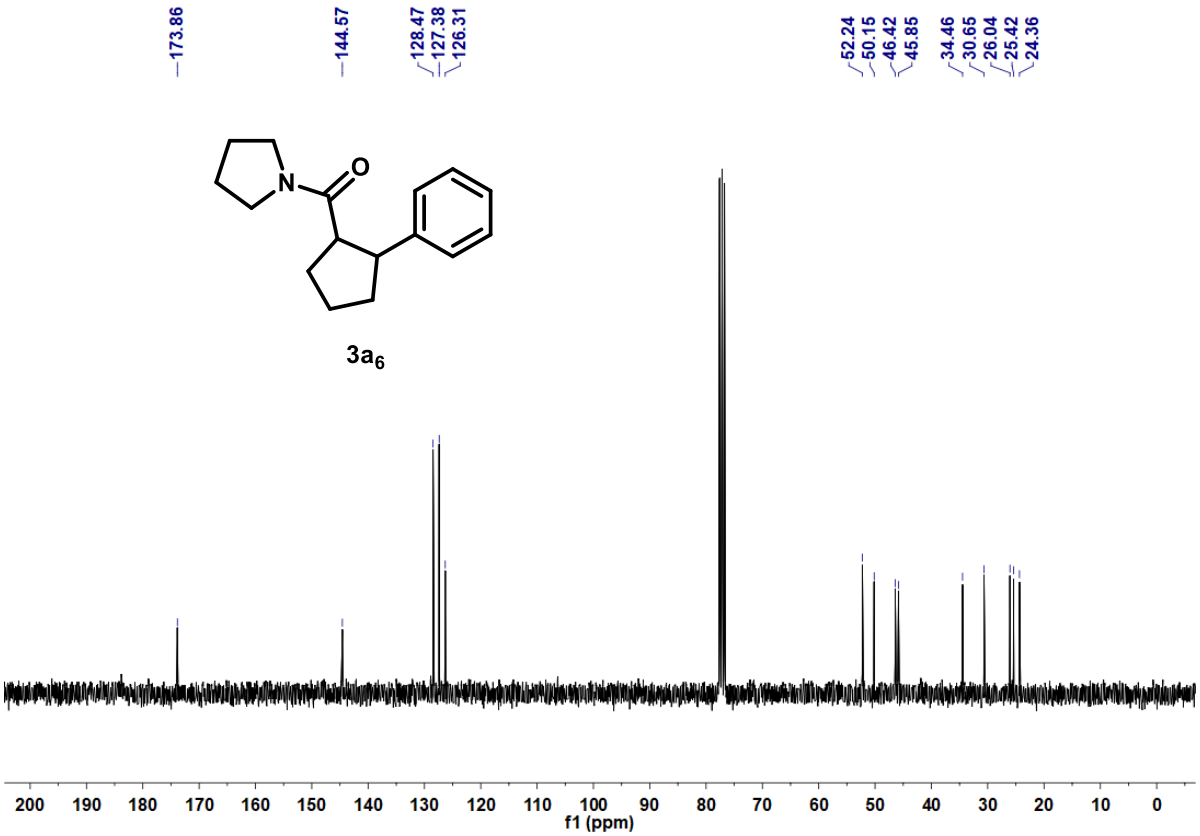

7.30
7.27
7.26
7.25
7.23
7.22
7.20
7.20
7.18
7.17
7.16
7.15
3.53
3.49
3.47
3.46
3.44
3.03
3.00
2.88
2.74
2.22
2.20
2.18
2.14
2.12
2.10
2.08
2.06
2.03
2.02
1.98
1.96
1.94
1.91
1.90
1.89
1.88
1.86
1.84
1.83
1.80
1.79
1.77
1.74
N
O
3a4
4.19
0.95
1.00
1.04
3.06
3.07
1.09
1.11
4.73
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
f1 (ppm)


175.26
144.67
128.51
127.41
126.29
49.94
49.87
37.15
35.81
34.74
30.98
25.45
N
O
3a4
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.28 7.27 7.26 7.25 7.25 7.24 7.23 7.18 7.18 7.18 7.17
3.51 3.50 3.47 3.45 3.44 3.42 3.41 3.40 3.32 3.30 3.29 3.13 3.12 3.10 3.09 2.97 2.96 2.94 2.85 2.67 2.19 2.18 2.05 2.04 2.04 2.03 2.02 1.96 1.94 1.93 1.91 1.91 1.90 1.89 1.88 1.87 1.85 1.83 1.81 1.02 1.01 1.00 0.90 0.88 0.87
N
O
3a5
8.80 2.05 3.20 1.16 2.37 2.25 3.16 3.00 2.18 2.30 8.73 3.20 3.60
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


174.97 174.69 144.55 144.48 128.48 128.45 127.40 127.34 126.26
50.10 50.00 49.82 44.27 42.71 34.54 34.53 31.58 25.41 12.34
N
O
3a5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.32 7.30 7.29 7.28 7.27 7.24 7.23 7.22 7.20 7.20 7.18
3.52 3.49 3.46 3.44 3.42 3.40 3.30 3.28 3.25 3.23 2.91 2.89 2.86 2.84 2.83 2.24 2.22 2.20 2.17 2.16 2.10 2.07 2.06 2.05 2.04 2.02 2.02 1.99 1.96 1.95 1.93 1.91 1.90 1.88 1.87 1.84 1.82 1.80 1.77 1.76 1.74 1.72 1.71 1.69 1.67
O
N
3a6
3.76
0.95
2.87
1.00
1.92
0.97
1.81
3.33
4.16
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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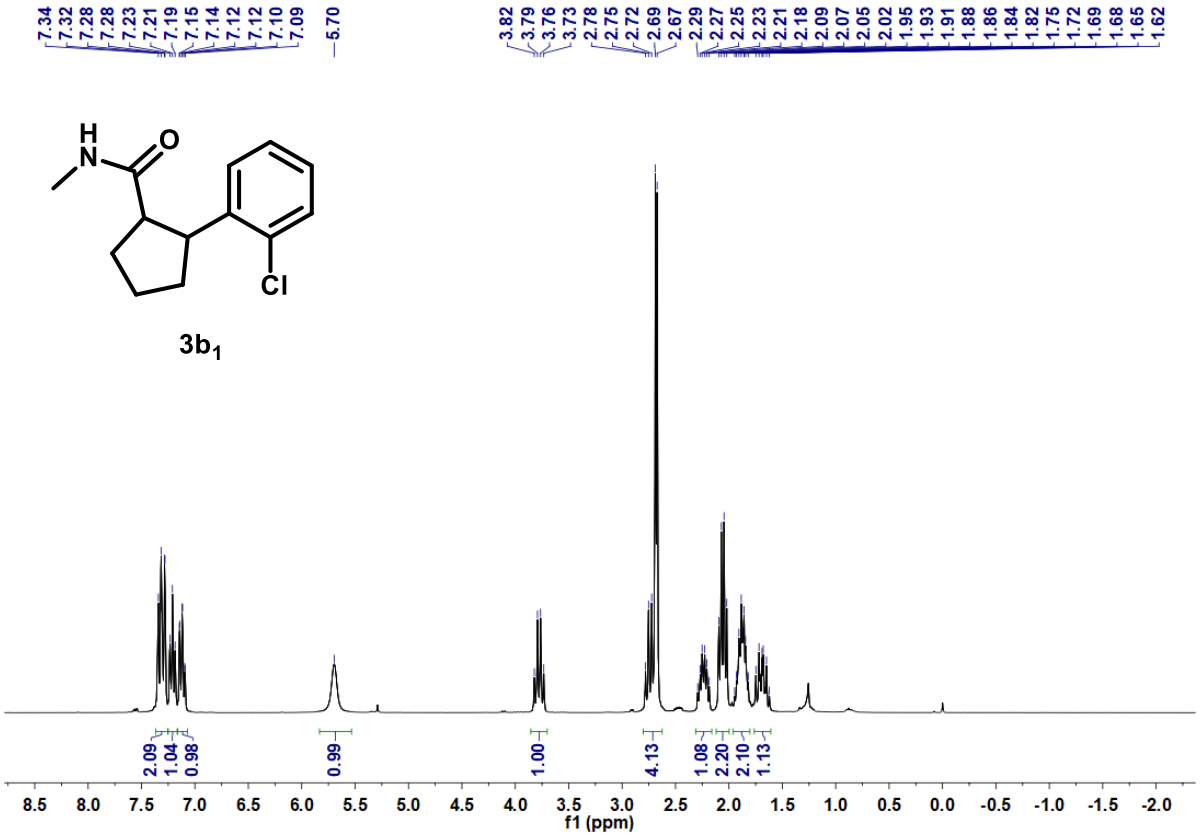
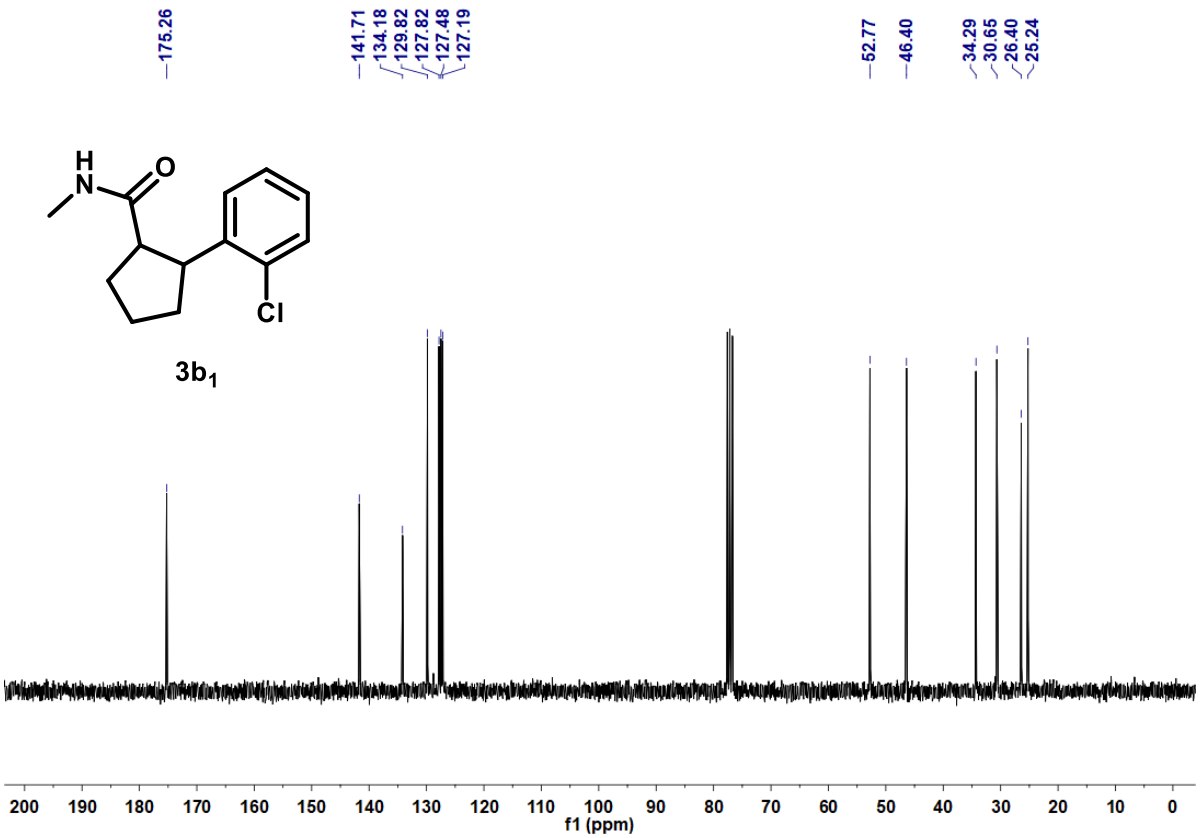
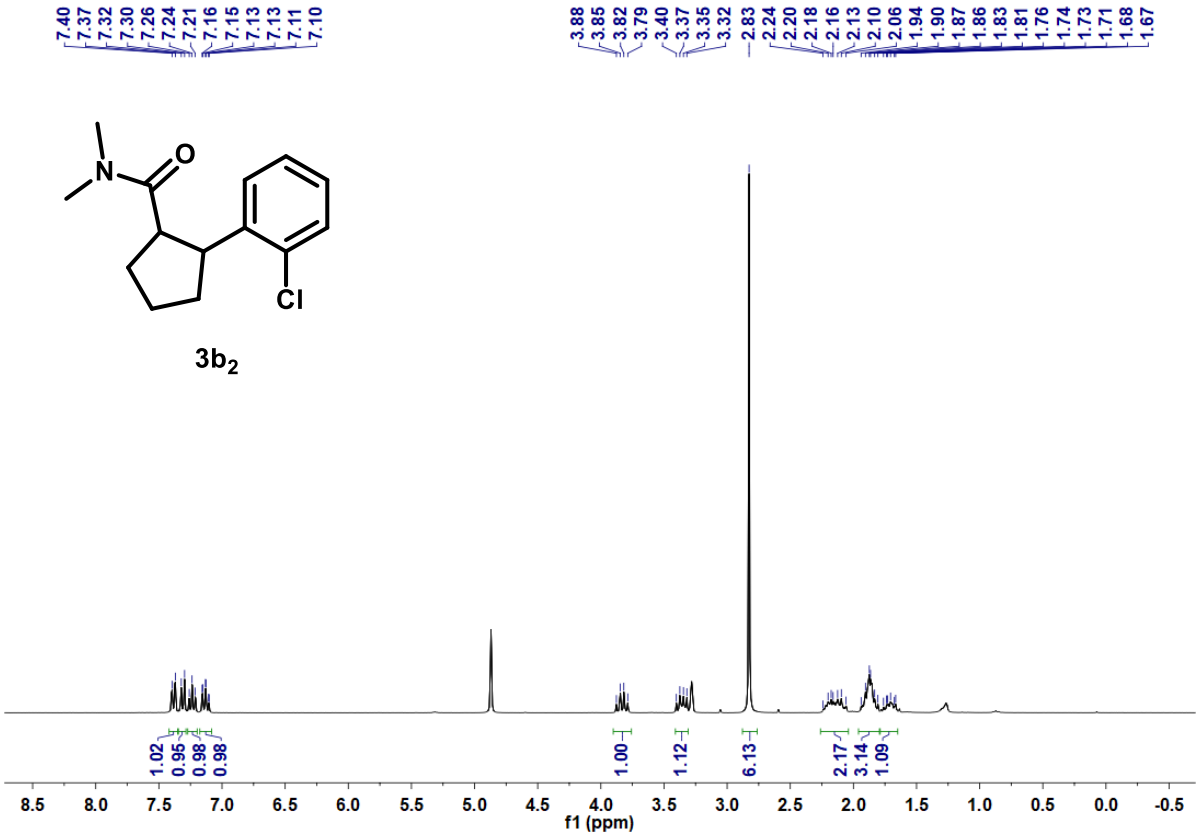
144.57
128.47
127.38
126.31
52.24
50.15
46.42
45.85
34.46
30.65
26.04
25.42
24.36
O
N
3a6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.34
7.32
7.28
7.28
7.23
7.21
7.19
7.15
7.14
7.12
7.12
7.10
7.09
5.70
3.82
3.79
3.76
3.73
2.78
2.75
2.72
2.69
2.67
2.29
2.27
2.25
2.23
2.21
2.18
2.09
2.07
2.05
2.02
1.95
1.93
1.91
1.88
1.86
1.84
1.82
1.75
1.72
1.69
1.68
1.65
1.62
H
N
O
Cl
2.09
1.04
0.98
0.99
1.00
4.13
1.08
2.20
2.10
1.13
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0
f1 (ppm)

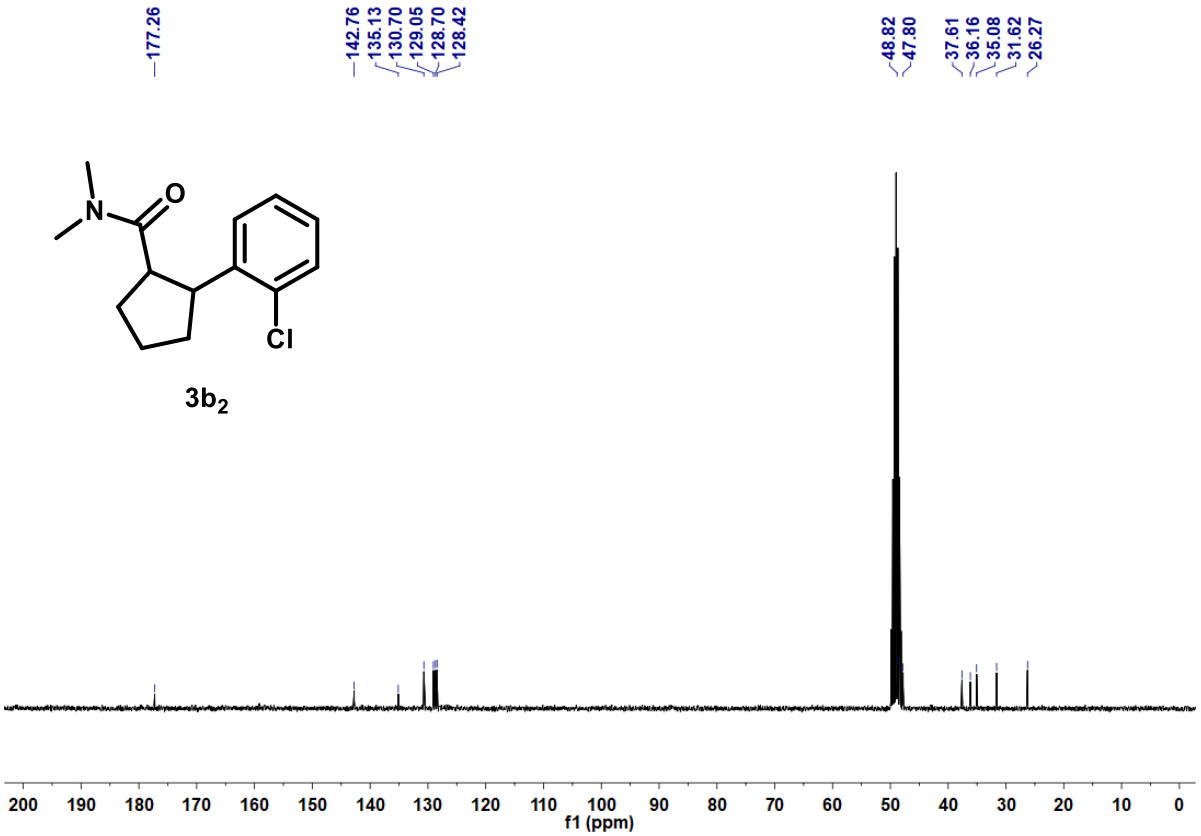
$3b_1$


175.26
141.71
134.18
129.82
127.82
127.48
127.19
52.77
46.40
34.29
30.65
26.40
25.24
H
N
O
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

$3b_1$


7.40
7.37
7.32
7.30
7.26
7.24
7.21
7.16
7.15
7.13
7.13
7.11
7.10
3.88
3.85
3.82
3.79
3.40
3.37
3.35
3.32
2.83
2.24
2.20
2.18
2.16
2.13
2.10
2.06
1.94
1.90
1.87
1.86
1.83
1.81
1.76
1.74
1.73
1.71
1.68
1.67
N
O
Cl
1.02
0.95
0.98
0.98
1.00
1.12
6.13
2.17
3.14
1.09
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

$3b_2$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142.76
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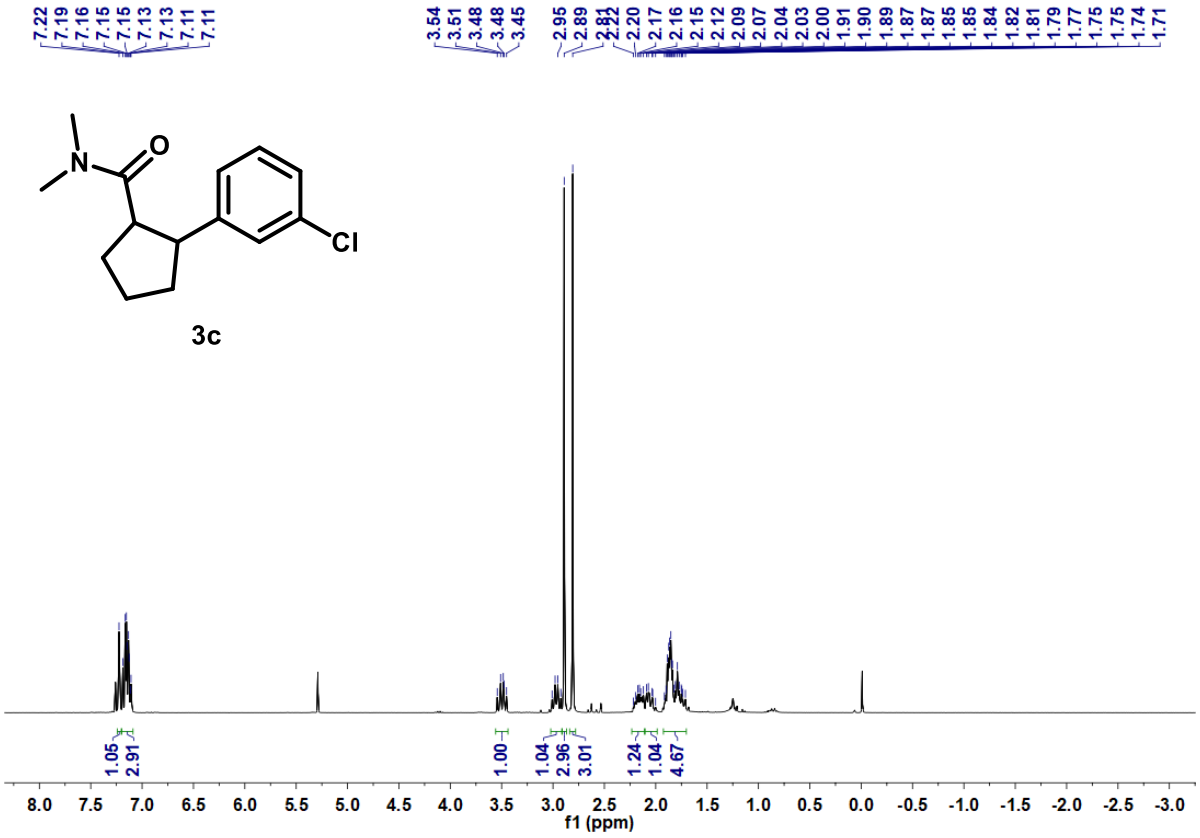
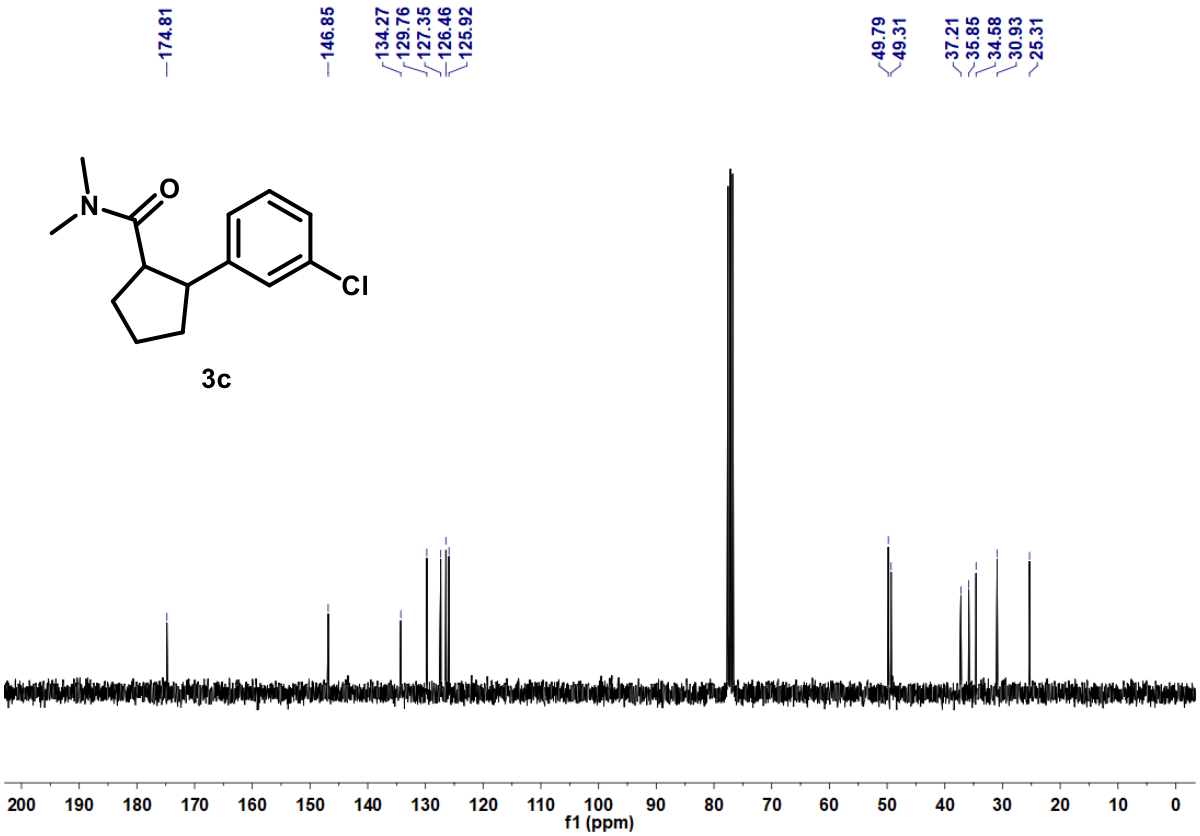
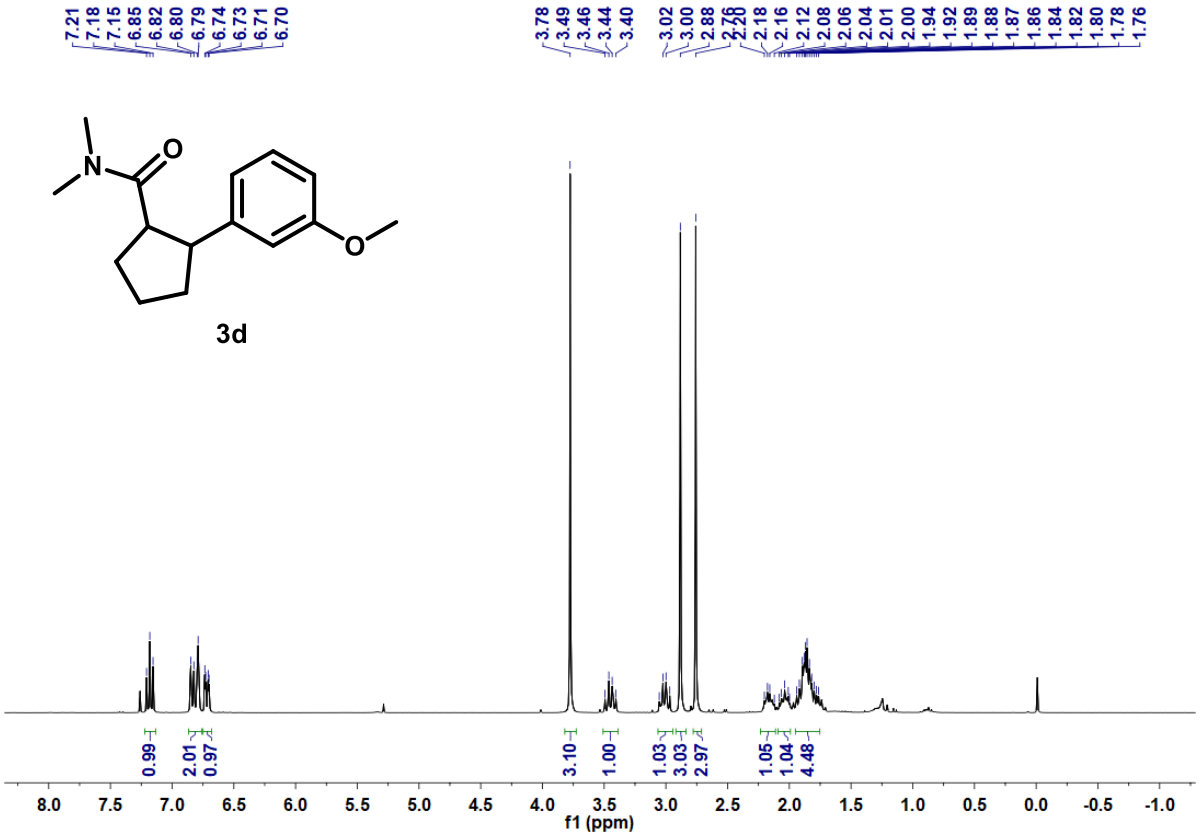
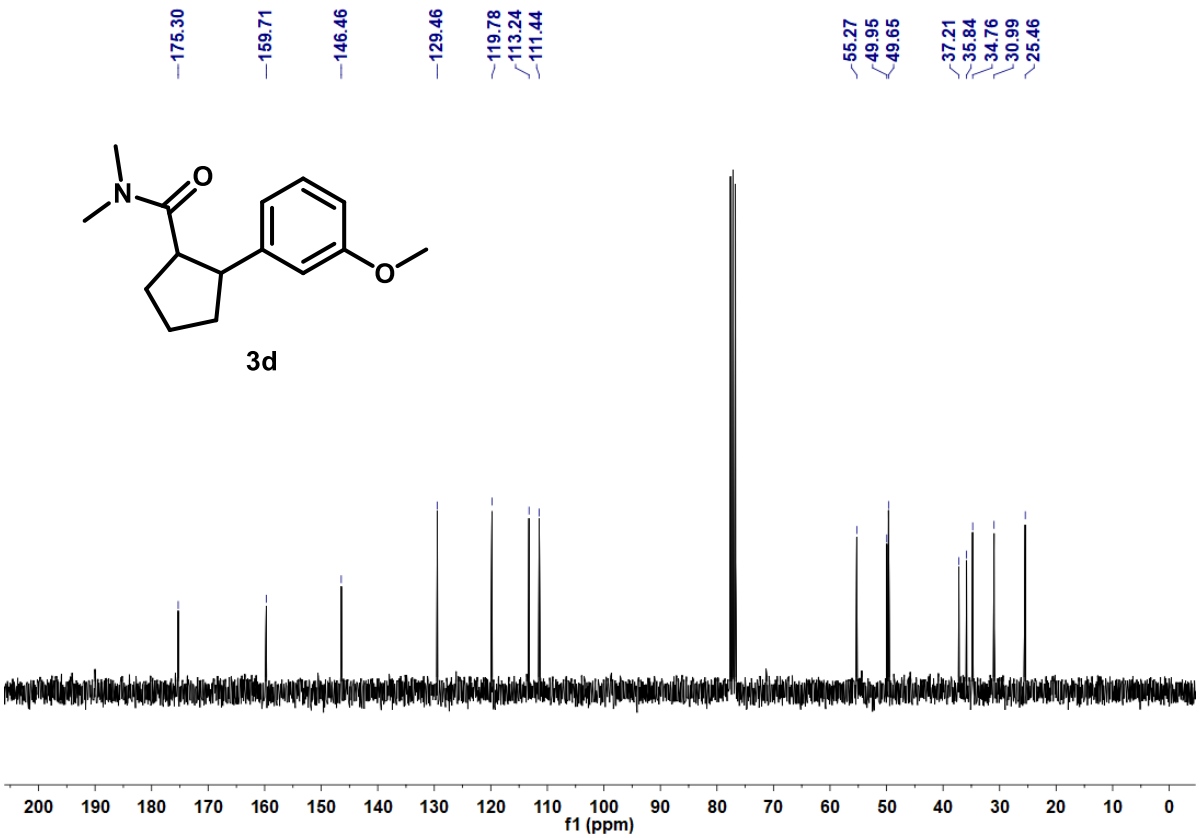
130.70
129.05
128.70
128.42
48.82
47.80
37.61
36.16
35.08
31.62
26.27
N
O
Cl
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

$3b_2$


7.22
7.19
7.16
7.15
7.15
7.13
7.13
7.11
7.11
3.54
3.51
3.48
3.48
3.45
2.95
2.89
2.81
2.20
2.17
2.16
2.15
2.12
2.09
2.07
2.04
2.03
2.00
1.91
1.90
1.89
1.87
1.87
1.85
1.85
1.84
1.82
1.81
1.79
1.77
1.75
1.75
1.74
1.71
N
O
Cl
3c
1.05
2.91
1.00
1.04
2.96
3.01
1.24
1.04
4.67
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0 -2.5 -3.0
f1 (ppm)


174.81
146.85
134.27
129.76
127.35
126.46
125.92
49.79
49.31
37.21
35.85
34.58
30.93
25.31
N
O
Cl
3c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.21
7.18
7.15
6.85
6.82
6.80
6.79
6.74
6.73
6.71
6.70
3.78
3.49
3.46
3.44
3.40
3.02
3.00
2.88
2.76
2.20
2.18
2.16
2.12
2.08
2.06
2.04
2.01
2.00
1.94
1.92
1.89
1.88
1.87
1.86
1.84
1.82
1.80
1.78
1.76
N
O
O
3d
0.99
2.01
0.97
3.10
1.00
1.03
3.03
2.97
1.05
1.04
4.48
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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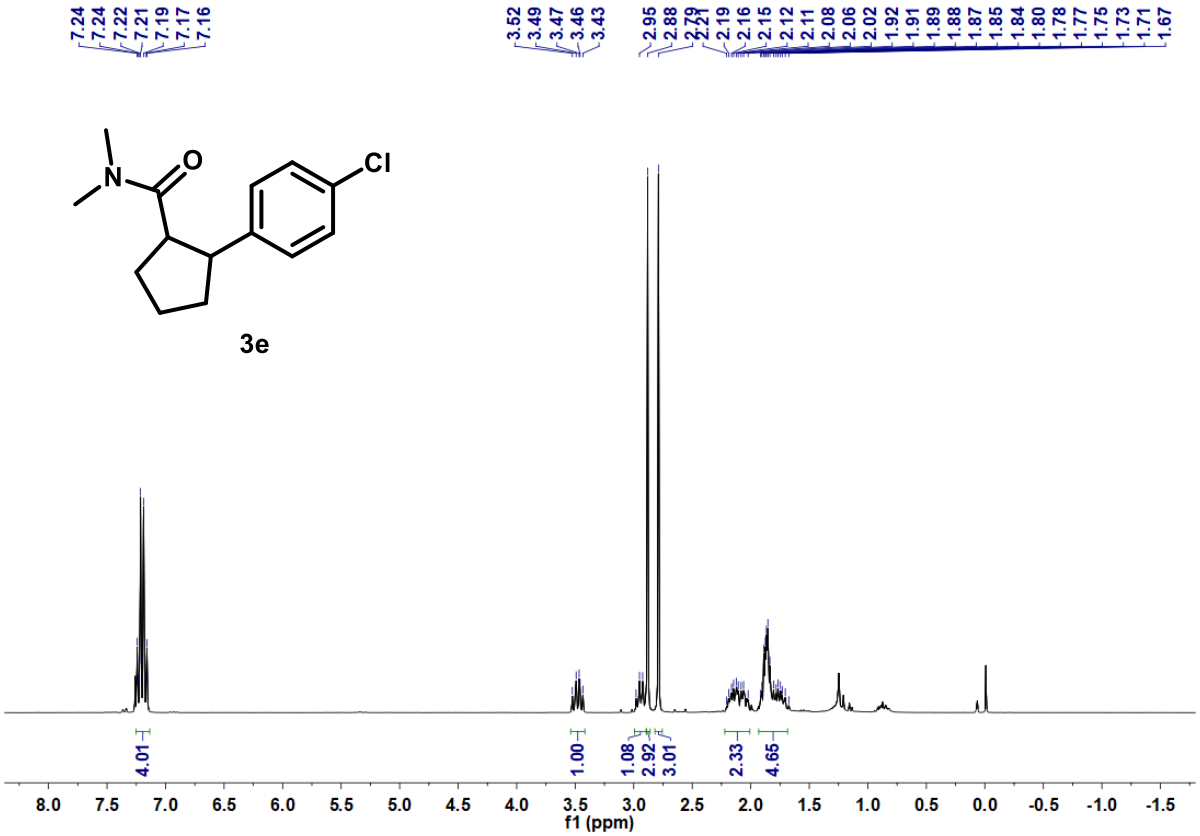
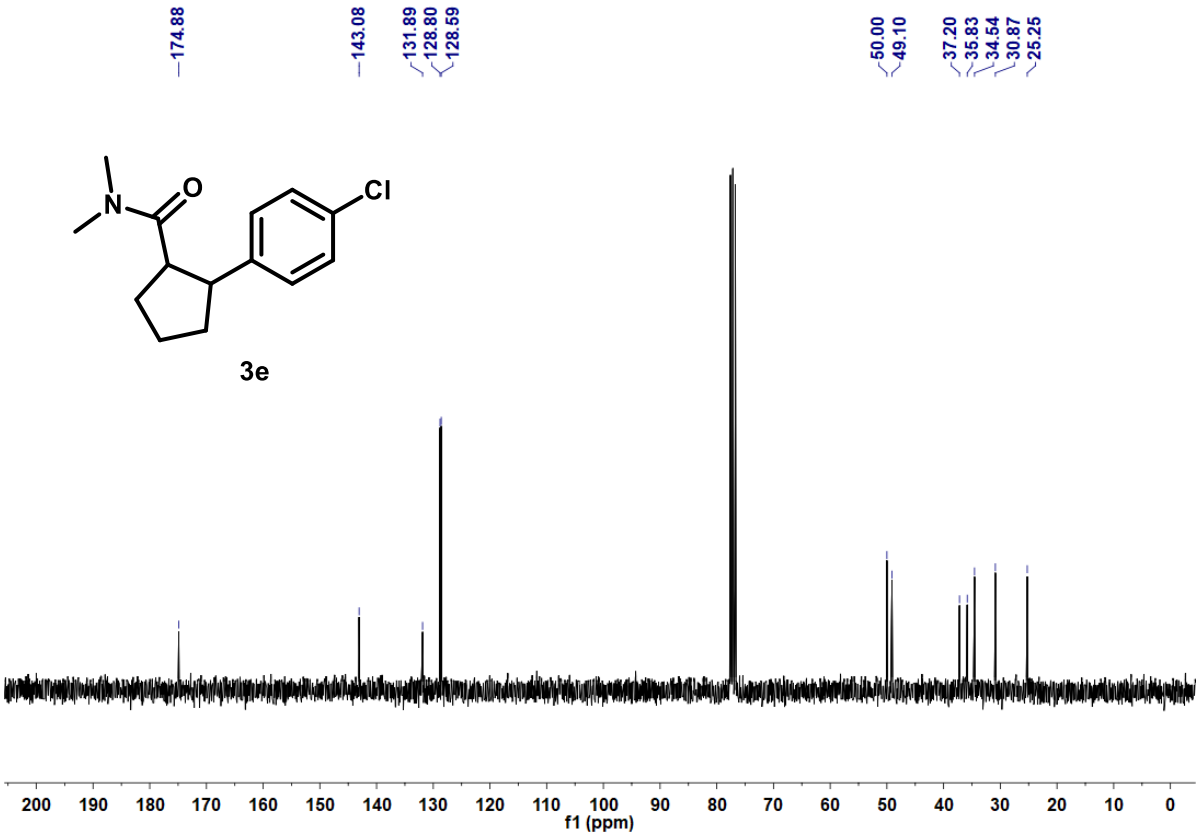
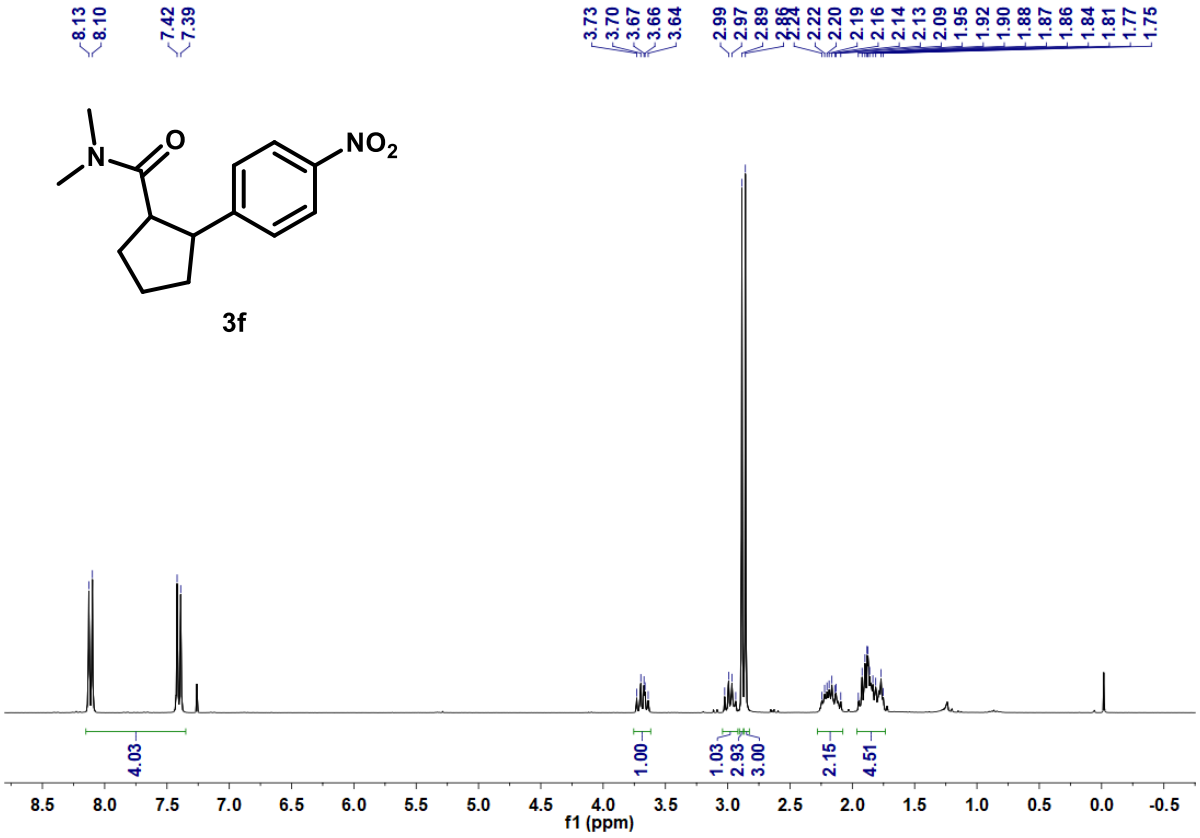
146.46
129.46
119.78
113.24
111.44
55.27
49.95
49.65
37.21
35.84
34.76
30.99
25.46
N
O
O
3d
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.24
7.24
7.22
7.21
7.19
7.17
7.16
3.52
3.49
3.47
3.46
3.43
2.95
2.88
2.79
2.21
2.19
2.16
2.15
2.12
2.11
2.08
2.06
2.02
1.92
1.91
1.89
1.88
1.87
1.85
1.84
1.80
1.78
1.77
1.75
1.73
1.71
1.67
O
N
Cl
3e
4.01
1.00
1.08
2.92
3.01
2.33
4.65
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
f1 (ppm)


174.88
143.08
131.89
128.80
128.59
50.00
49.10
37.20
35.83
34.54
30.87
25.25
O
N
Cl
3e
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.13
8.10
7.42
7.39
3.73
3.70
3.67
3.66
3.64
2.99
2.97
2.89
2.22
2.20
2.19
2.16
2.14
2.13
2.09
1.95
1.92
1.90
1.88
1.87
1.86
1.84
1.81
1.77
1.75
O
N
NO2
3f
4.03
1.00
1.03
2.93
3.00
2.15
4.51
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
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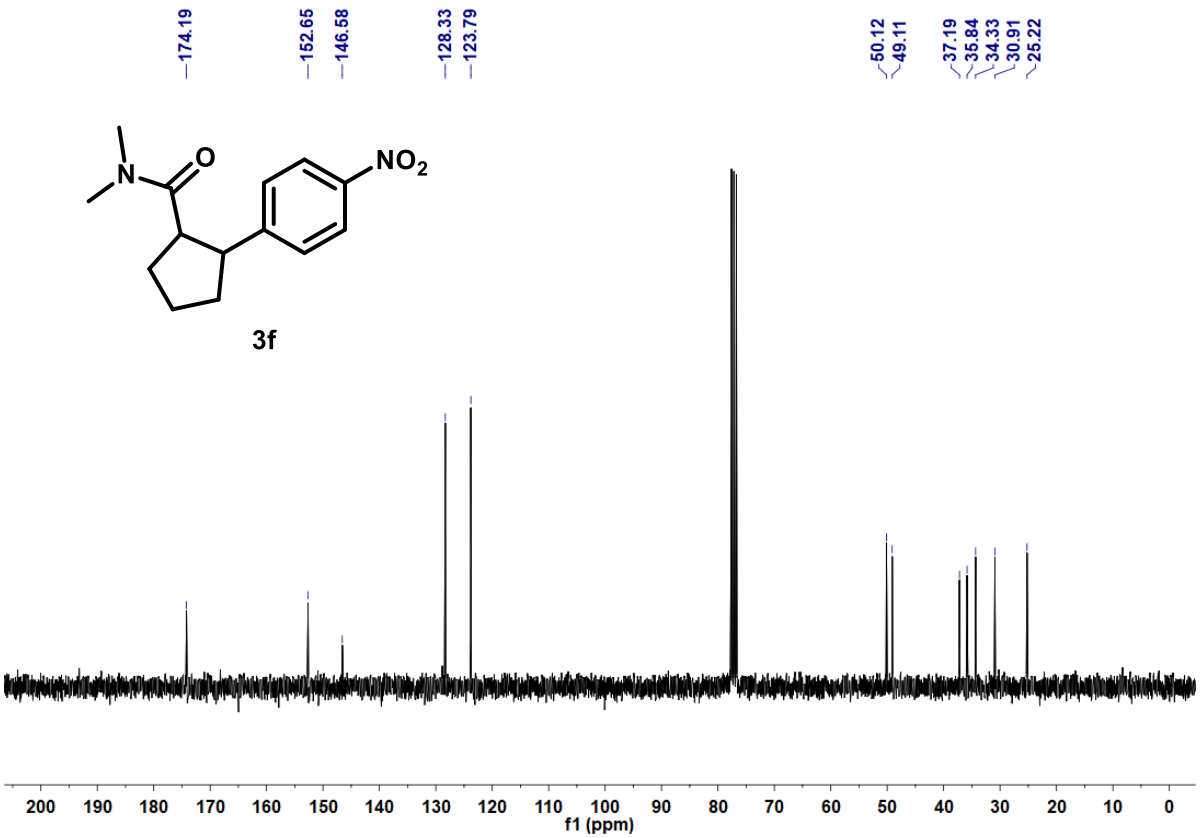
-0.5
f1 (ppm)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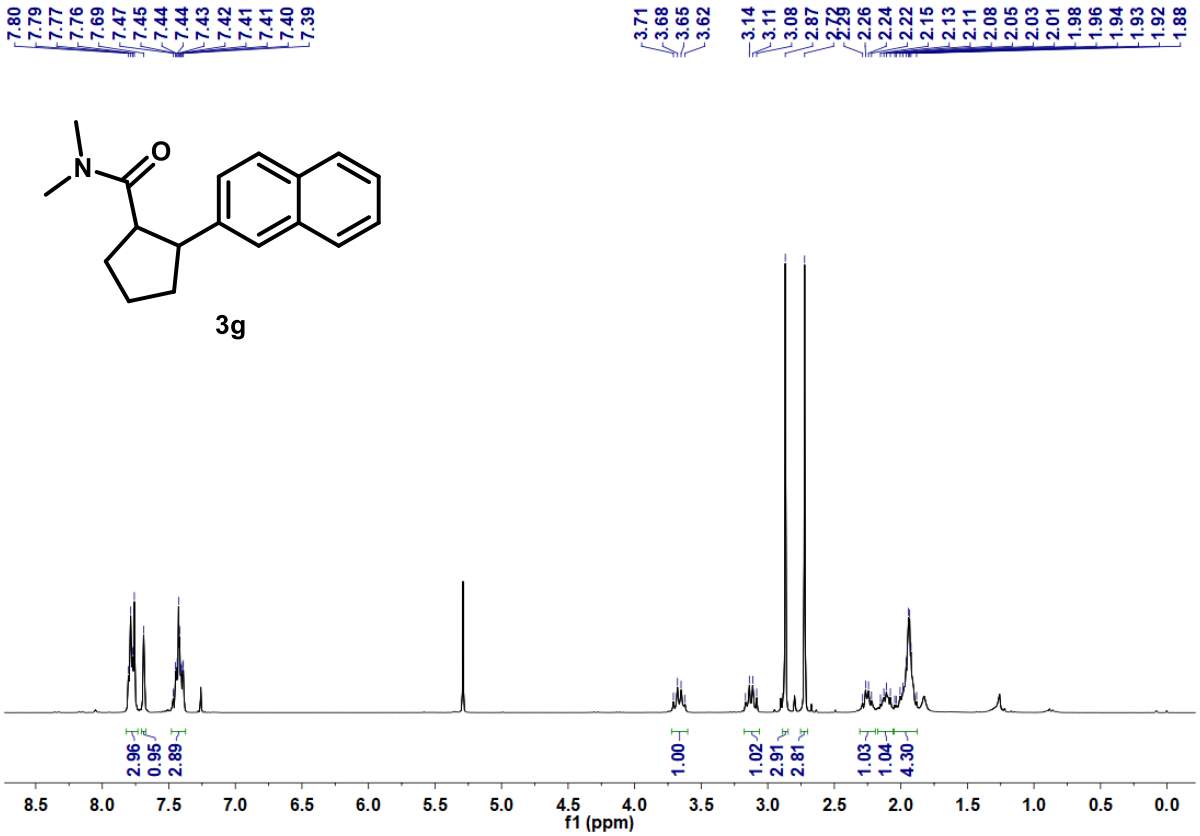
123.79
50.12
49.11
37.19
35.84
34.33
30.91
25.22
O
N
NO2
3f
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.41
7.40
7.39
3.71
3.68
3.65
3.62
3.14
3.11
3.08
2.87
2.26
2.24
2.22
2.15
2.13
2.11
2.08
2.05
2.03
2.01
1.98
1.96
1.94
1.93
1.92
1.88
N
O
3g
2.96
0.95
2.89
1.00
1.02
2.91
2.81
1.03
1.04
4.30
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
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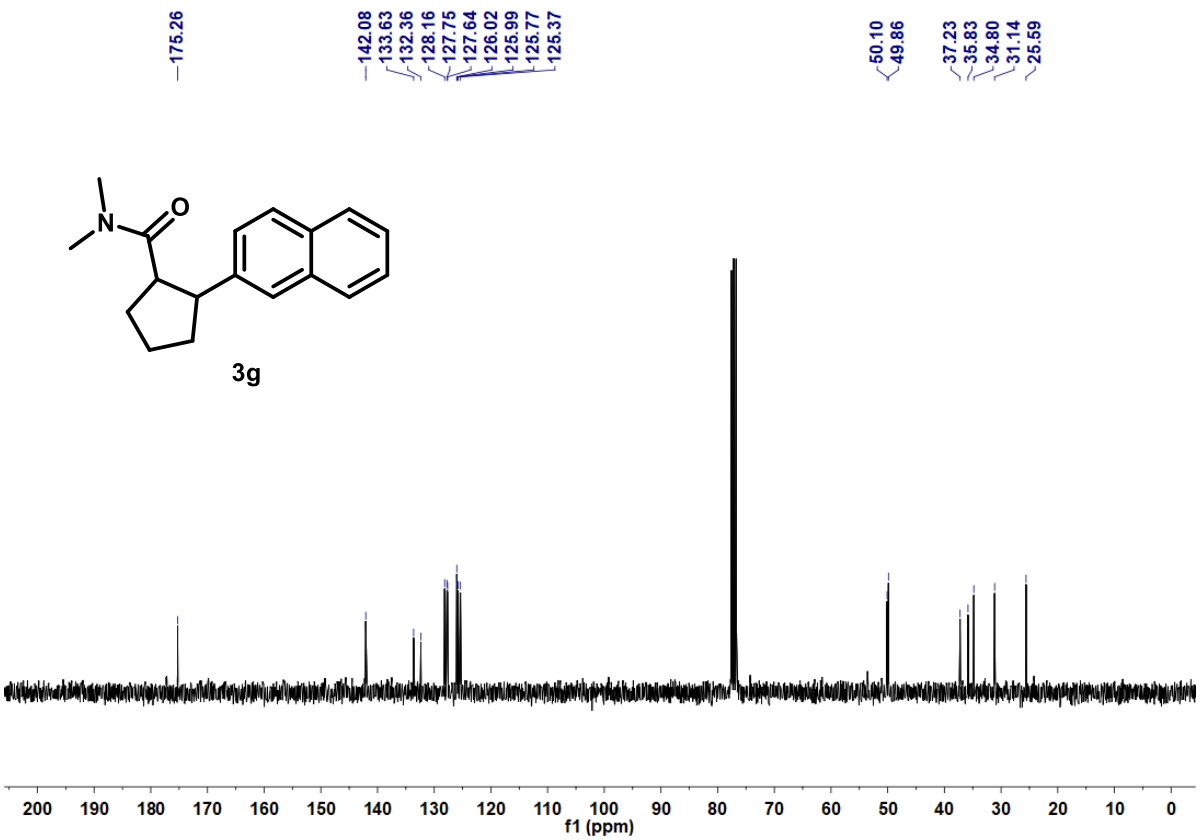
0.0
f1 (ppm)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125.37
50.10
49.86
37.23
35.83
34.80
31.14
25.59
N
O
3g
200
190
180
170
160
150
140
130
120
110
100
90
80
70
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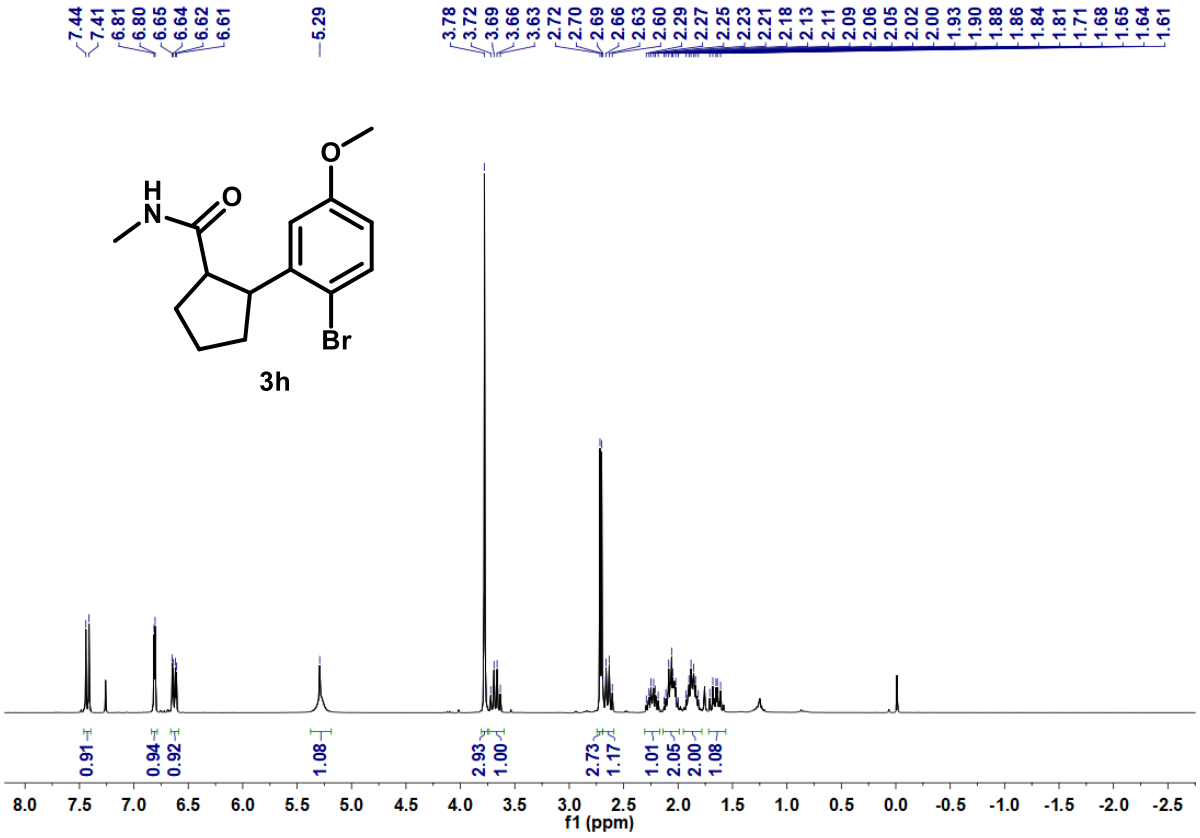
50
40
30
20
10
0
f1 (ppm)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6.61
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3.72
3.69
3.66
3.63
2.72
2.70
2.69
2.66
2.63
2.60
2.29
2.27
2.25
2.23
2.21
2.18
2.13
2.11
2.09
2.06
2.05
2.02
2.00
1.93
1.90
1.88
1.86
1.84
1.81
1.71
1.68
1.65
1.64
1.61
O
H
N
O
Br
3h
0.91
0.94
0.92
1.08
2.93
1.00
2.73
1.17
1.01
2.05
2.00
1.08
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0 -2.5
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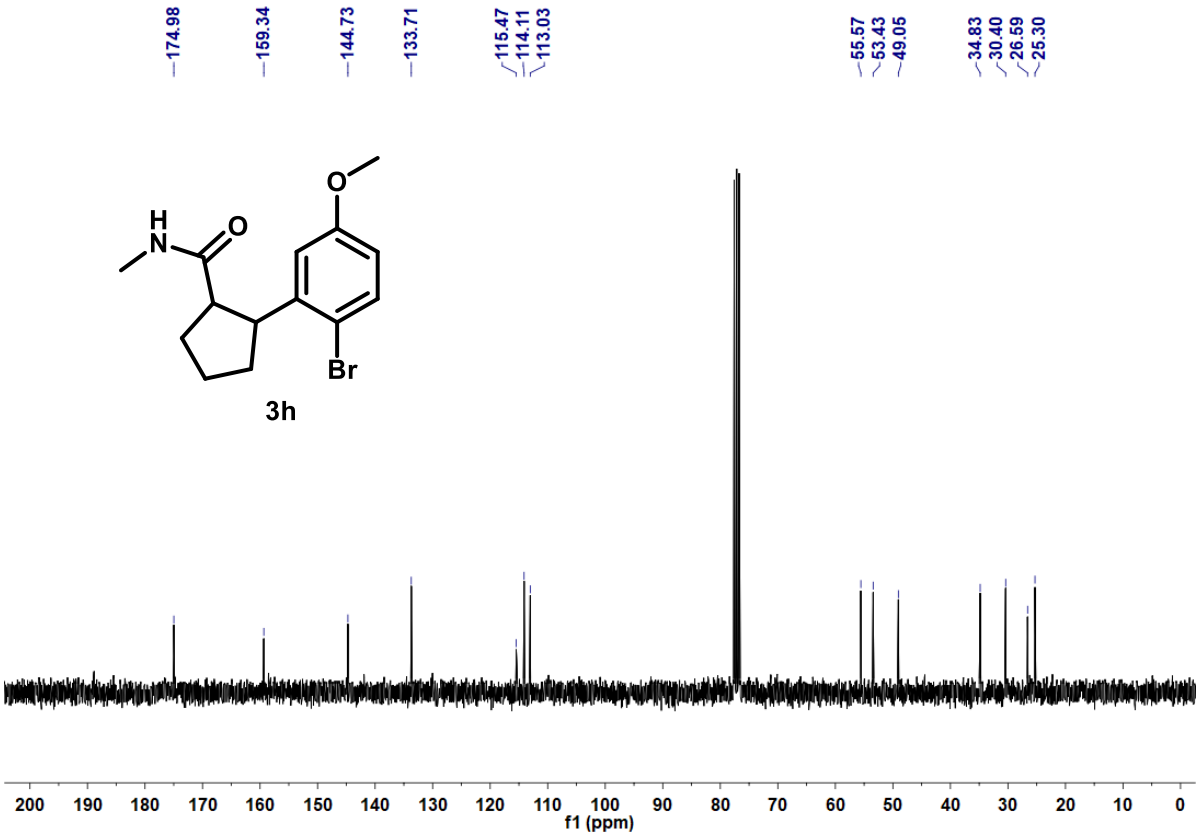
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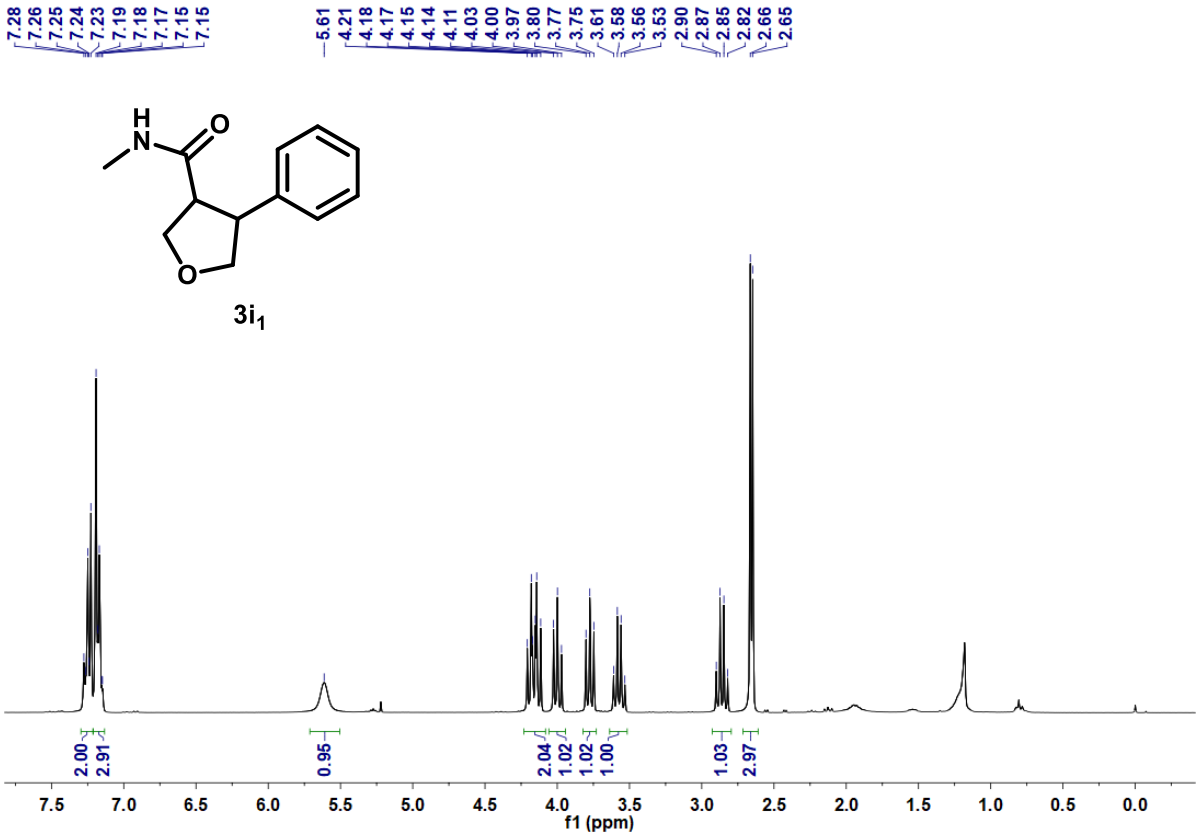
114.11
113.03
55.57
53.43
49.05
34.83
30.40
26.59
25.30
O
H
N
O
Br
3h
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.15
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4.18
4.17
4.15
4.14
4.11
4.03
4.00
3.97
3.80
3.77
3.75
3.61
3.58
3.56
3.53
2.90
2.87
2.85
2.82
2.66
2.65
H
N
O
O
3i1
2.00
2.91
0.95
2.04
1.02
1.02
1.00
1.03
2.97
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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1.0
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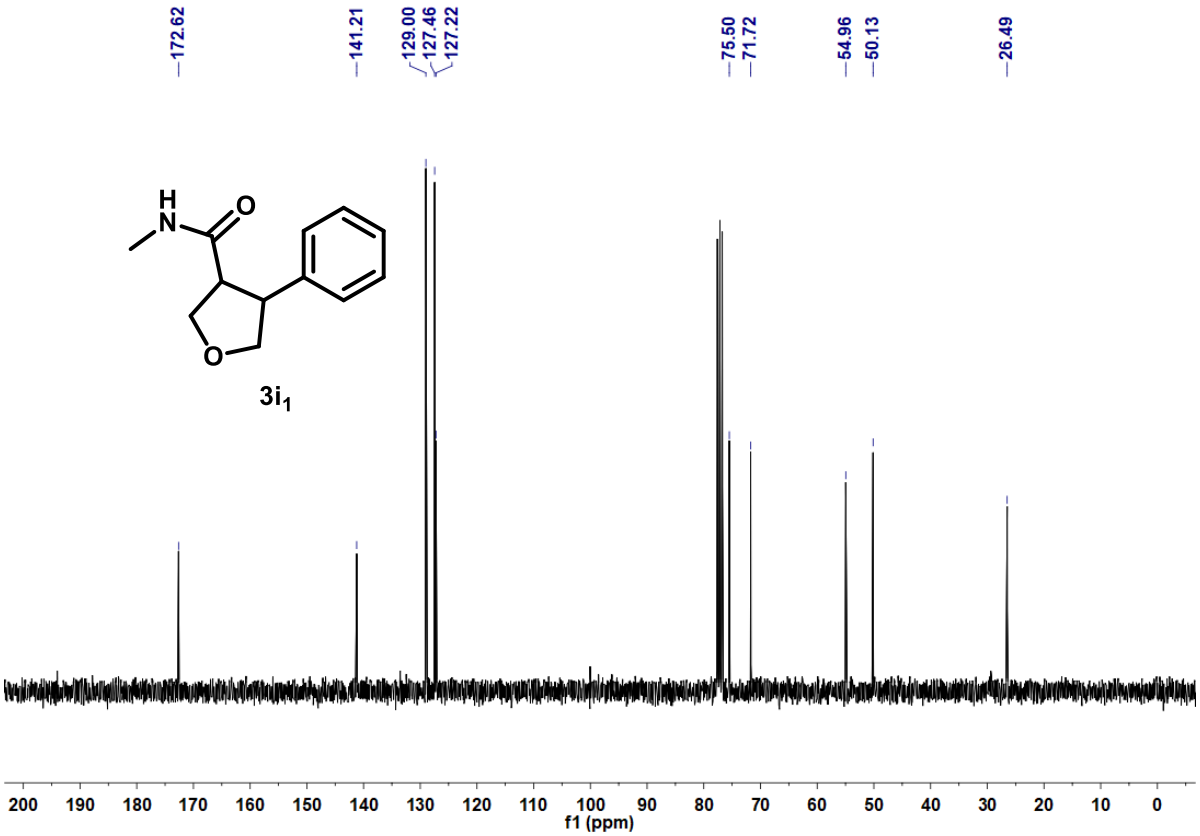
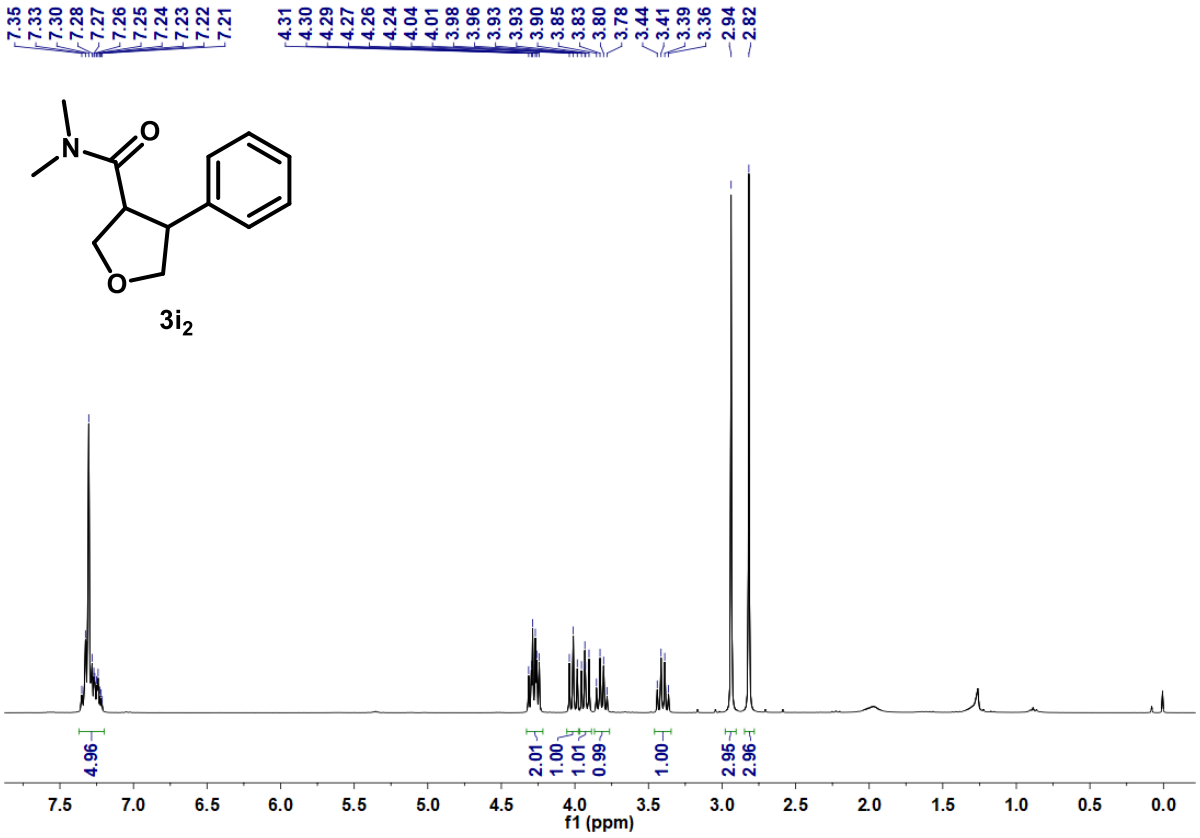
0.0
f1 (ppm)


172.62
141.21
129.00
127.46
127.22
75.50
71.72
54.96
50.13
26.49
H
N
O
O
3i1
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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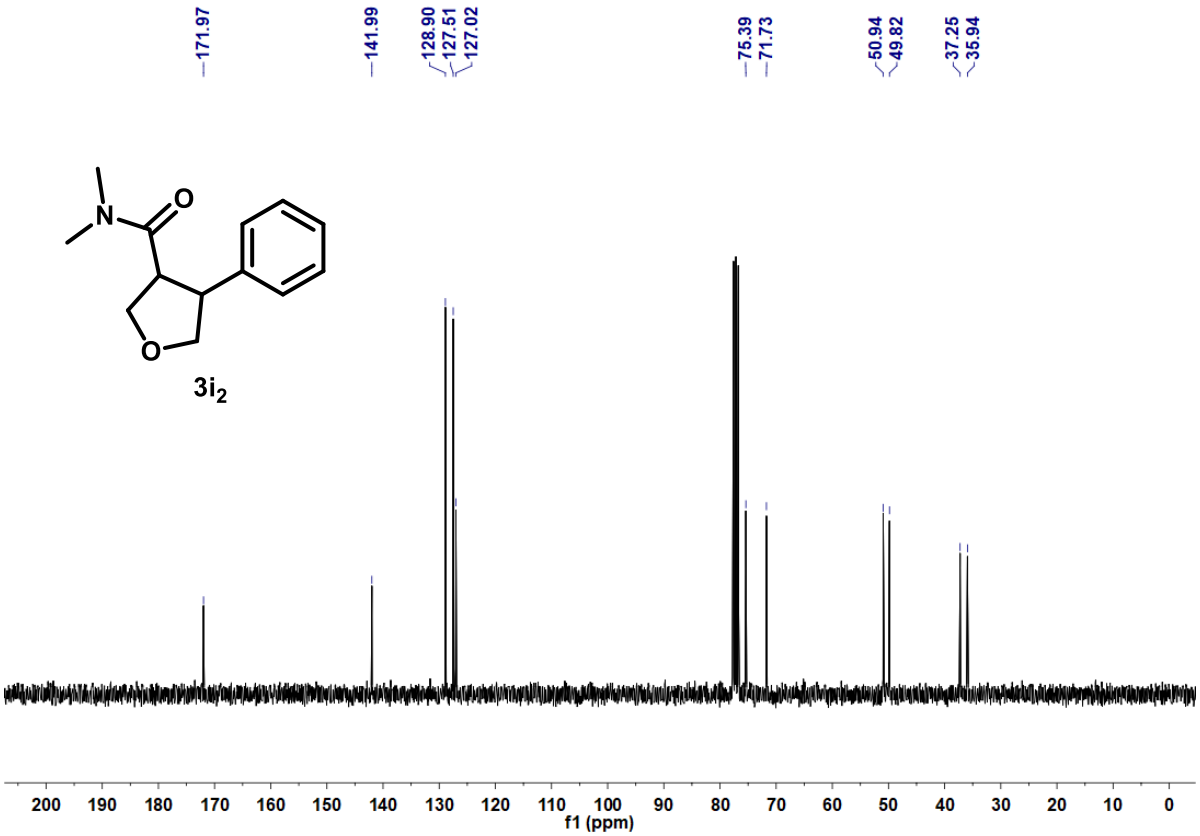
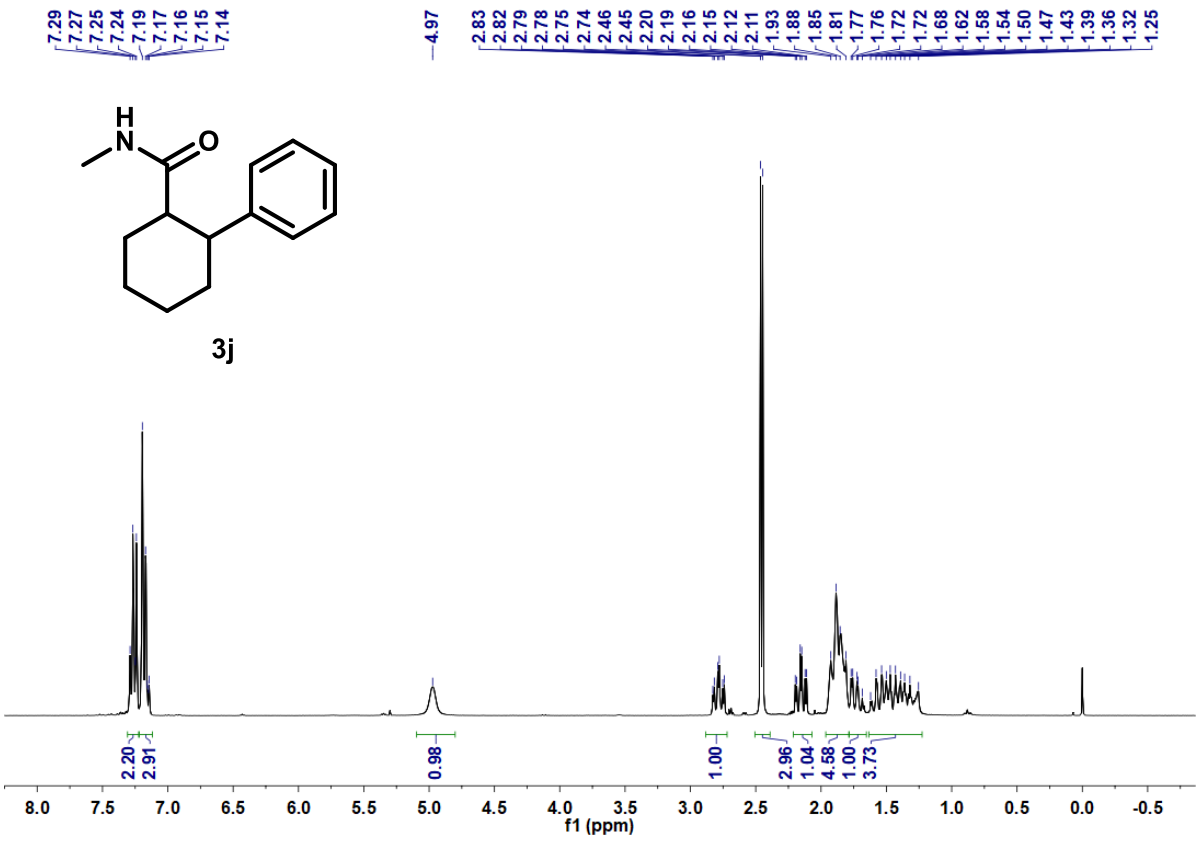
7.25
7.24
7.23
7.22
7.21
4.31
4.30
4.29
4.27
4.26
4.24
4.04
4.01
3.98
3.96
3.93
3.93
3.90
3.85
3.83
3.80
3.78
3.44
3.41
3.39
3.36
2.94
2.82
O
N
O
4.96
2.01
1.00
1.01
0.99
1.00
2.95
2.96
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

$3i_2$


171.97
141.99
128.90
127.51
127.02
75.39
71.73
50.94
49.82
37.25
35.94
O
N
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

$3i_2$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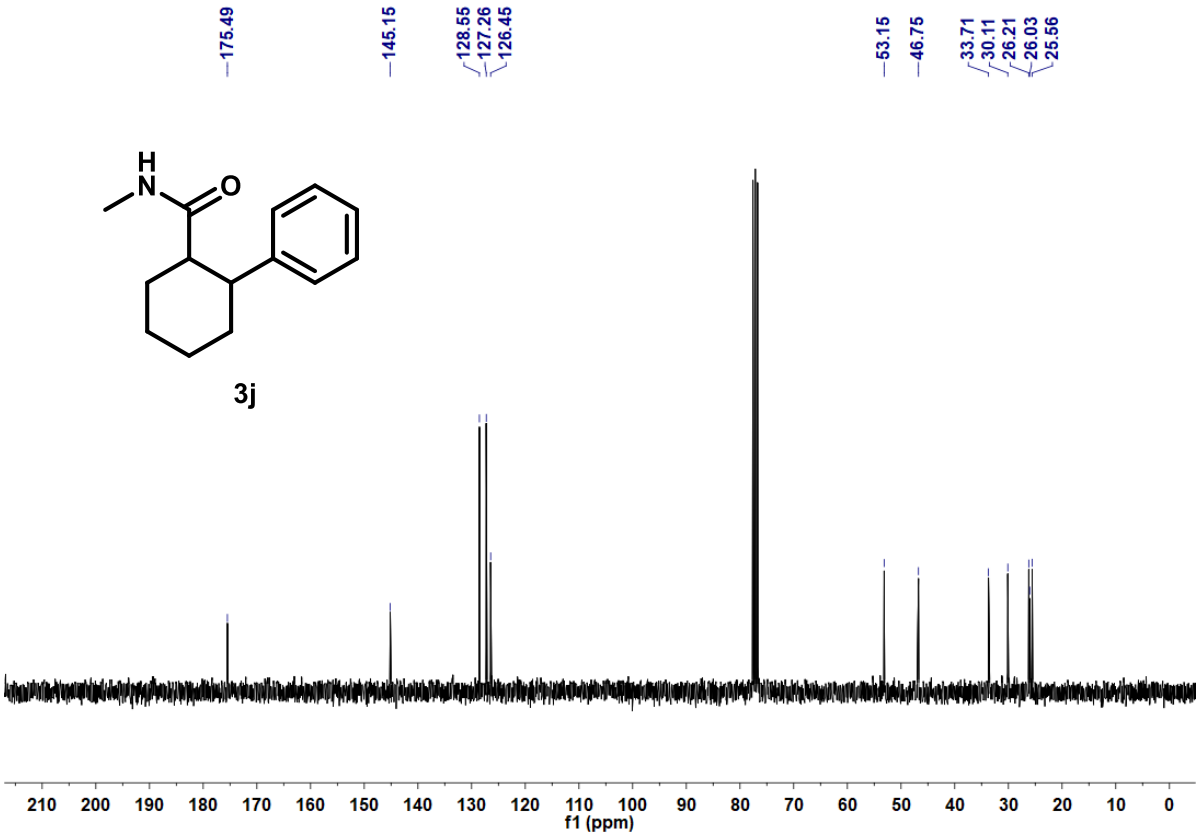
7.27
7.25
7.24
7.19
7.17
7.16
7.15
7.14
4.97
2.83
2.82
2.79
2.78
2.75
2.74
2.46
2.45
2.20
2.19
2.16
2.15
2.12
2.11
1.93
1.88
1.85
1.81
1.77
1.76
1.72
1.72
1.68
1.62
1.58
1.54
1.50
1.47
1.43
1.39
1.36
1.32
1.25
H
N
O
3j
2.20
2.91
0.98
1.00
2.96
1.04
4.58
1.00
3.73
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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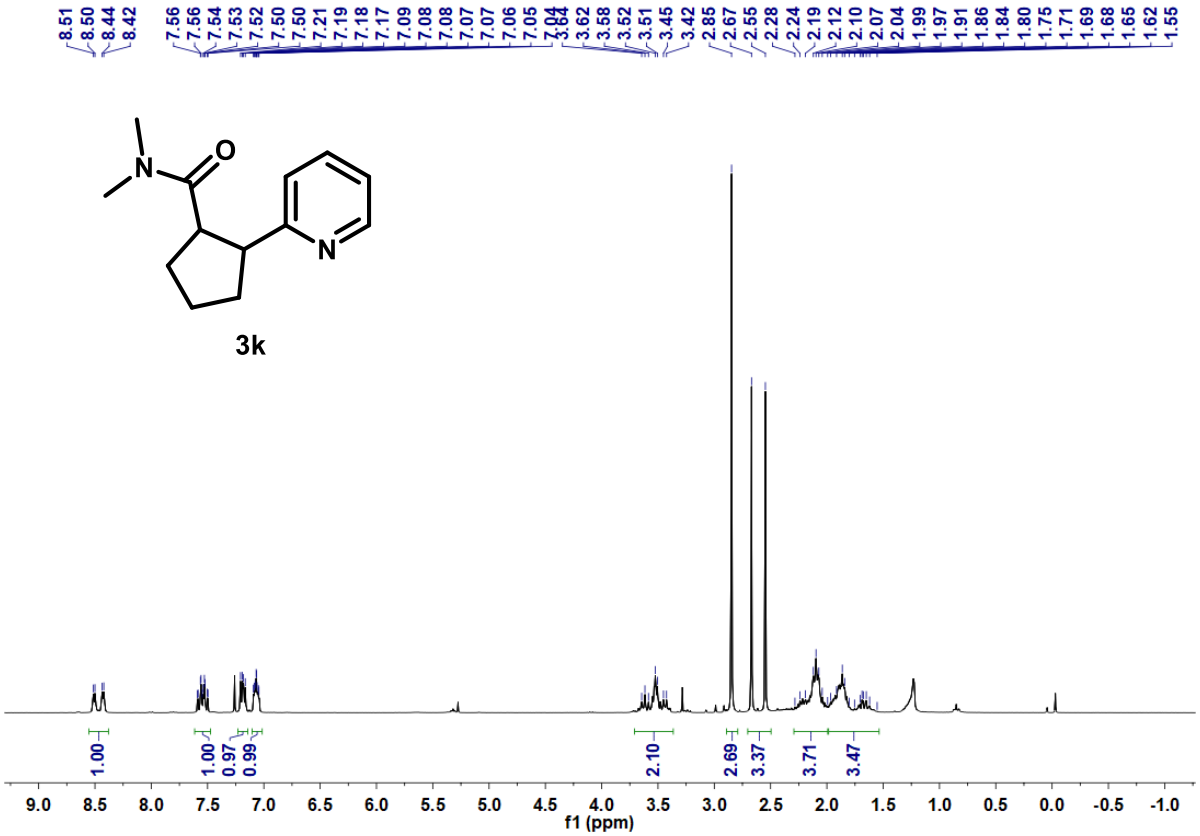
145.15
128.55
127.26
126.45
53.15
46.75
33.71
30.11
26.21
26.03
25.56
H
N
O
3j
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.53
7.52
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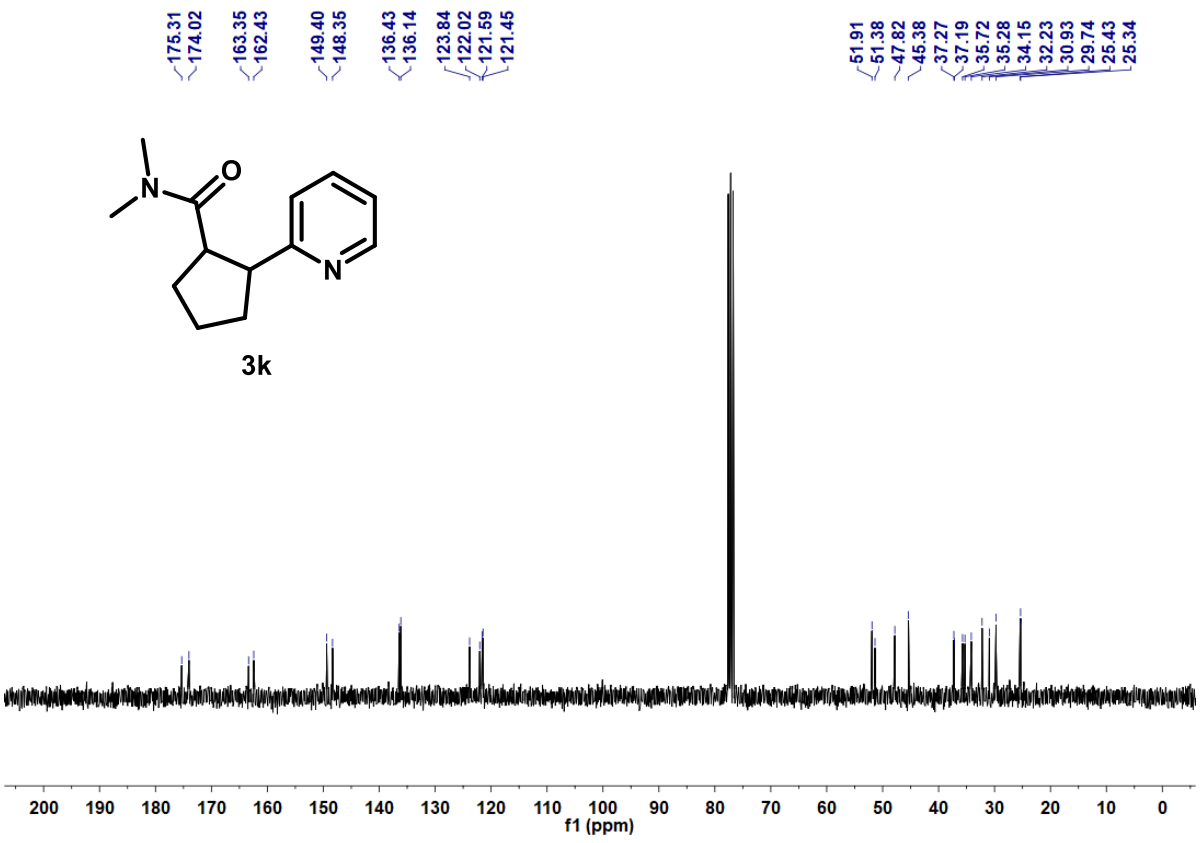
7.21
7.19
7.18
7.17
7.09
7.08
7.08
7.07
7.07
7.06
7.05
7.04
3.62
3.58
3.52
3.51
3.45
3.42
2.85
2.67
2.55
2.28
2.24
2.19
2.12
2.10
2.07
2.04
1.99
1.97
1.91
1.86
1.84
1.80
1.75
1.71
1.69
1.68
1.65
1.62
1.55
O
N
N
3k
1.00
1.00
0.97
0.99
2.10
2.69
3.37
3.71
3.47
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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122.02
121.59
121.45
51.91
51.38
47.82
45.38
37.27
37.19
35.72
35.28
34.15
32.23
30.93
29.74
25.43
25.34
O
N
N
3k
200
190
180
170
160
150
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130
120
110
100
90
80
70
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50
40
30
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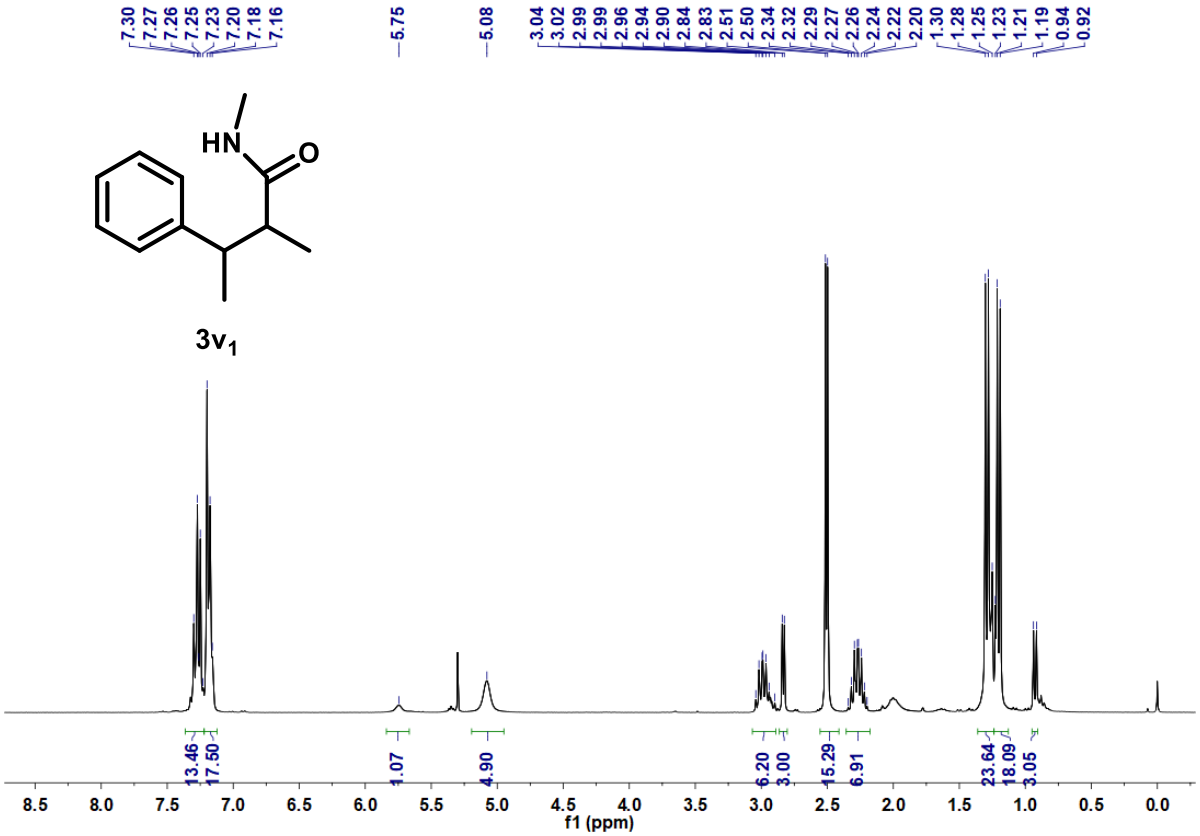
10
0
f1 (ppm)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7.16
5.75
5.08
3.04
3.02
2.99
2.96
2.94
2.90
2.84
2.83
2.51
2.50
2.34
2.32
2.29
2.27
2.26
2.24
2.22
2.20
1.30
1.28
1.25
1.23
1.21
1.19
0.94
0.92
HN
O
3v1
13.46
17.50
1.07
4.90
6.20
3.00
15.29
6.91
23.64
18.09
3.05
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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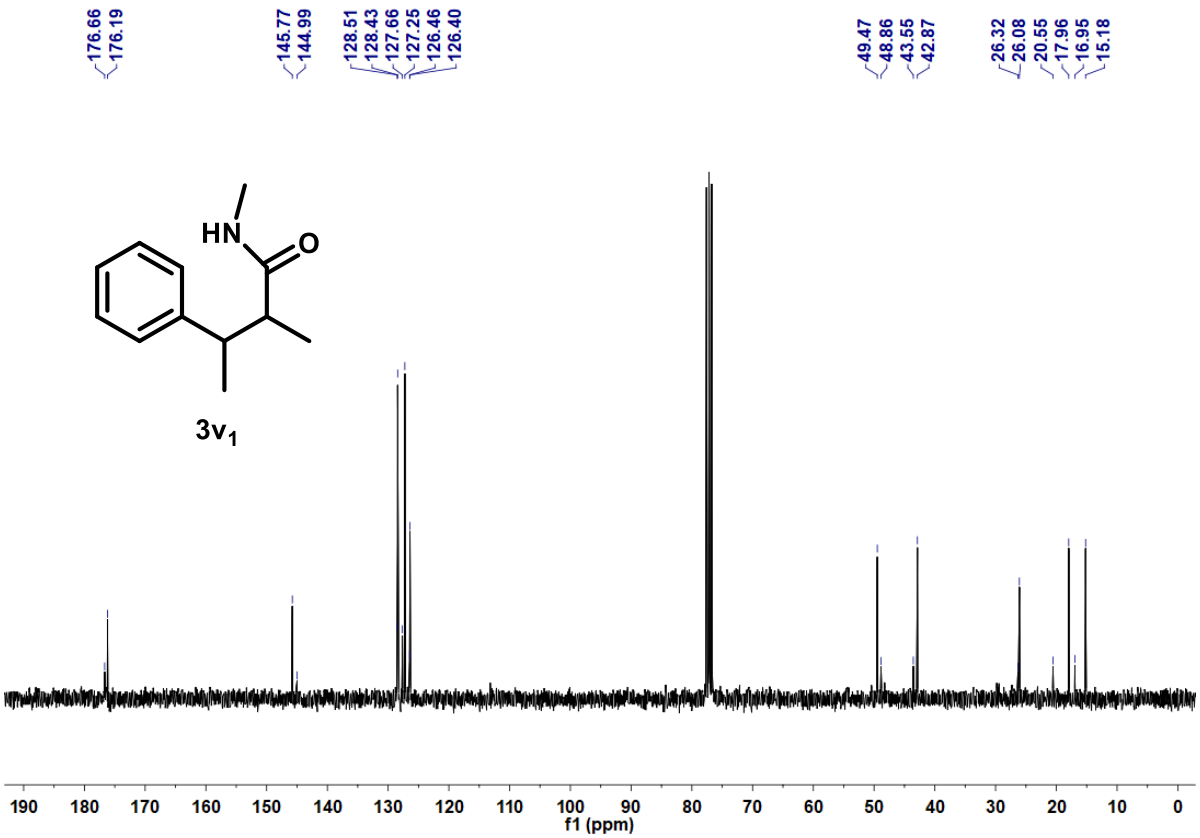
0.0
f1 (ppm)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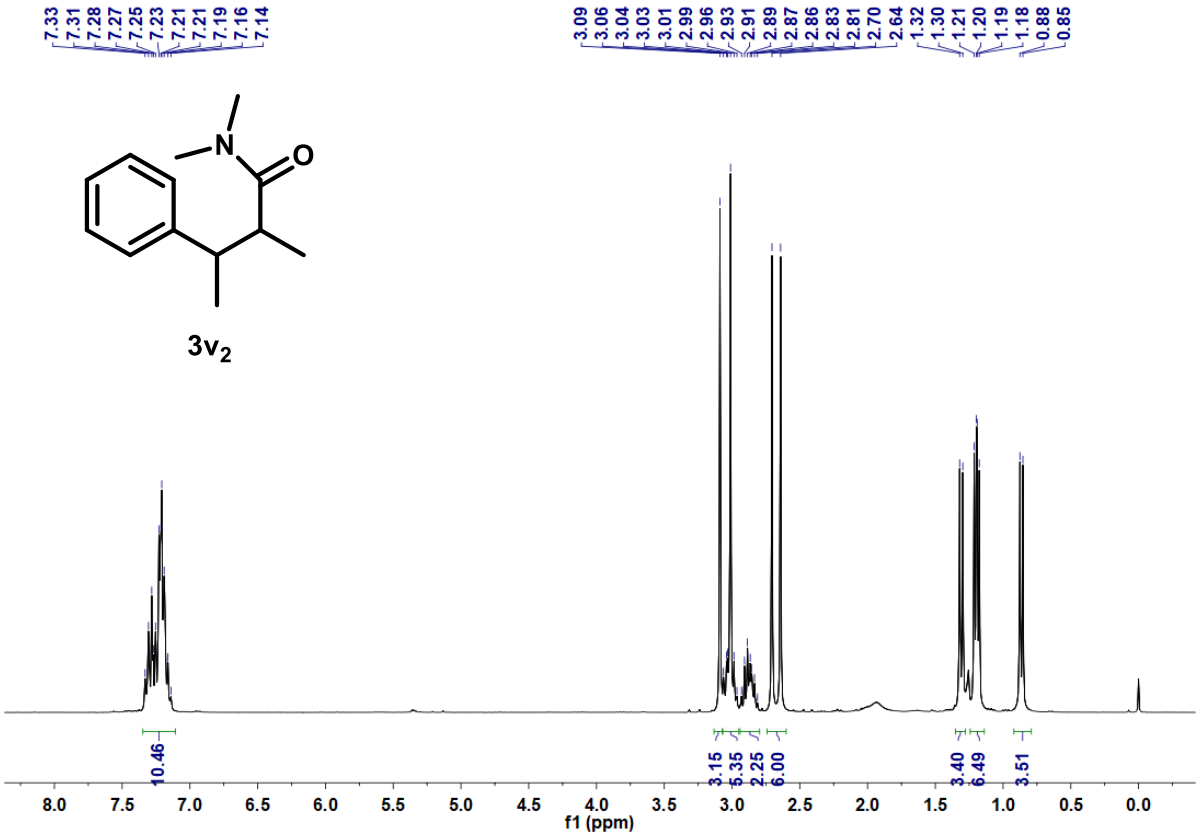
128.51
128.43
127.66
127.25
126.46
126.40
49.47
48.86
43.55
42.87
26.32
26.08
20.55
17.96
16.95
15.18
HN
O
3v1
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.31
7.28
7.27
7.25
7.23
7.21
7.21
7.19
7.16
7.14
3.09
3.06
3.04
3.03
3.01
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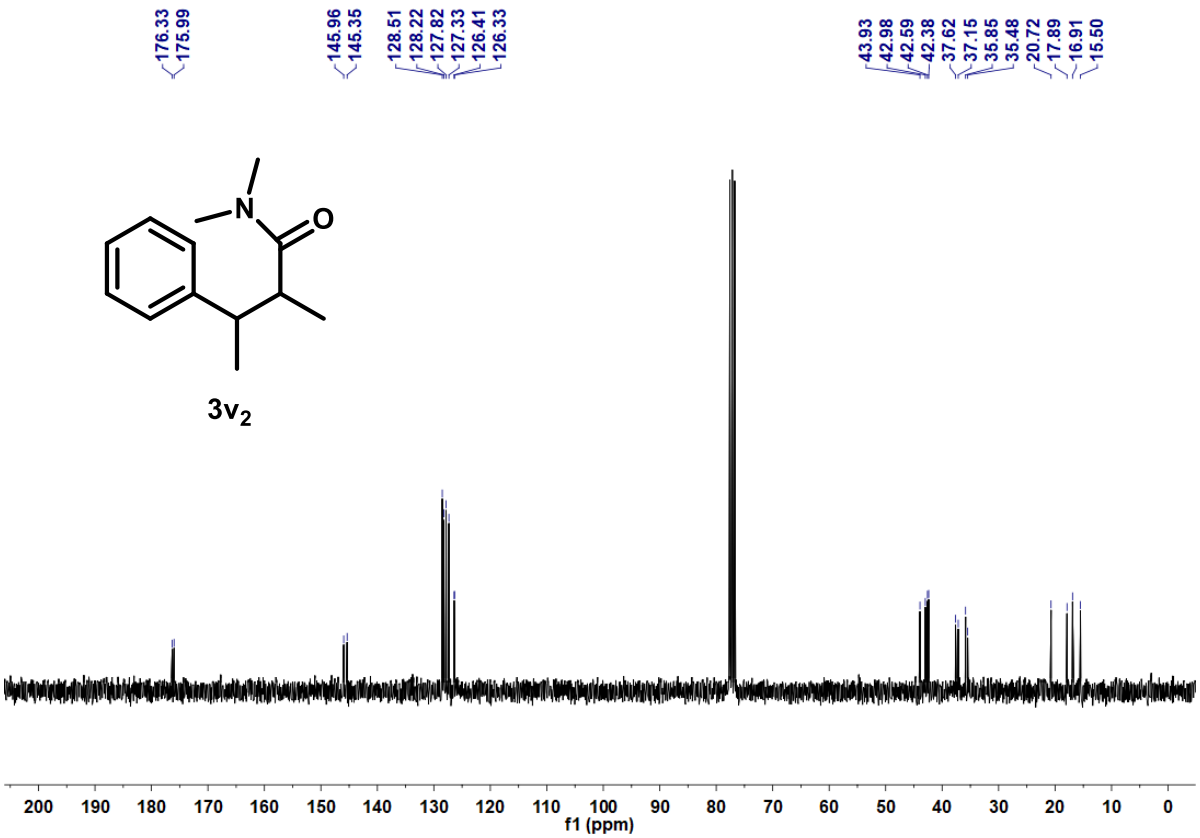
2.96
2.93
2.91
2.89
2.87
2.86
2.83
2.81
2.70
2.64
1.32
1.30
1.21
1.20
1.19
1.18
0.88
0.85
N
O
10.46
3.15
5.35
2.25
6.00
3.40
6.49
3.51
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

$3v_2$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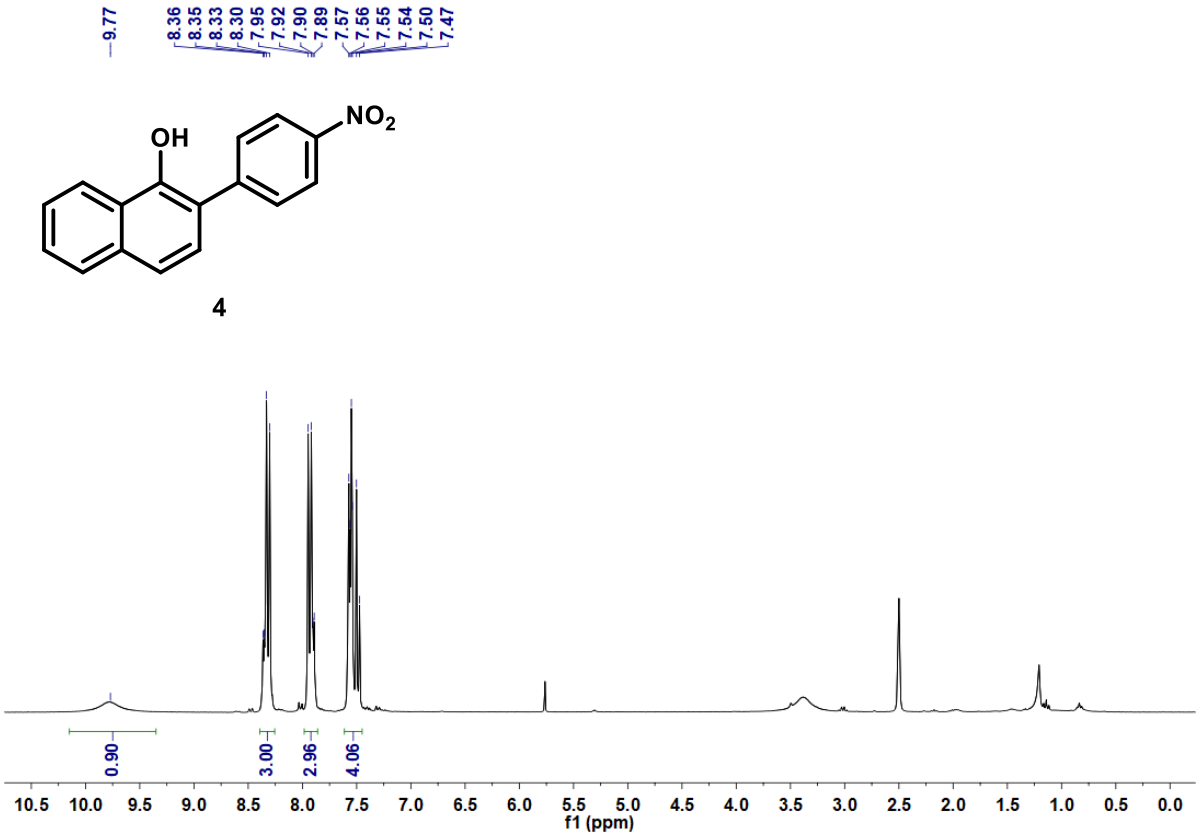
175.99
145.96
145.35
128.51
128.22
127.82
127.33
126.41
126.33
43.93
42.98
42.59
42.38
37.62
37.15
35.85
35.48
20.72
17.89
16.91
15.50
N
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

$3v_2$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8.33
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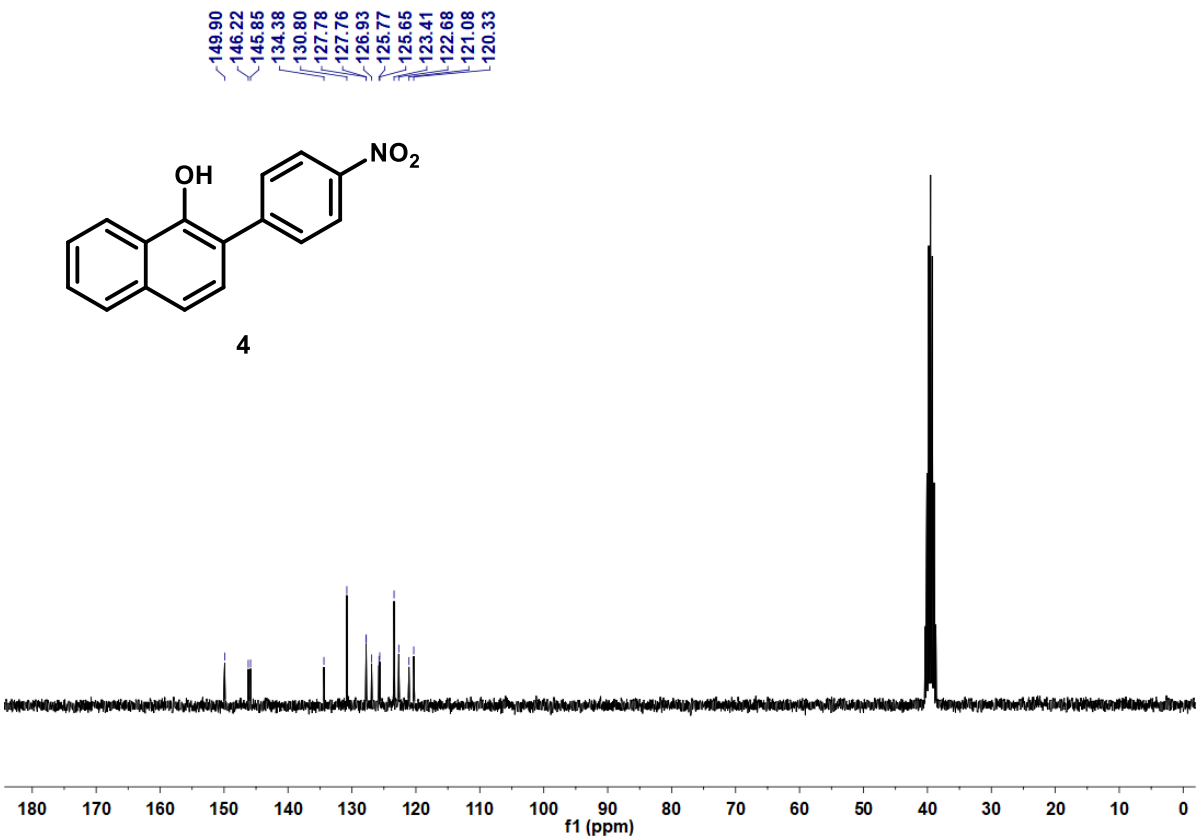
7.95
7.92
7.90
7.89
7.57
7.56
7.55
7.54
7.50
7.47
OH
NO2
4
0.90
3.00
2.96
4.06
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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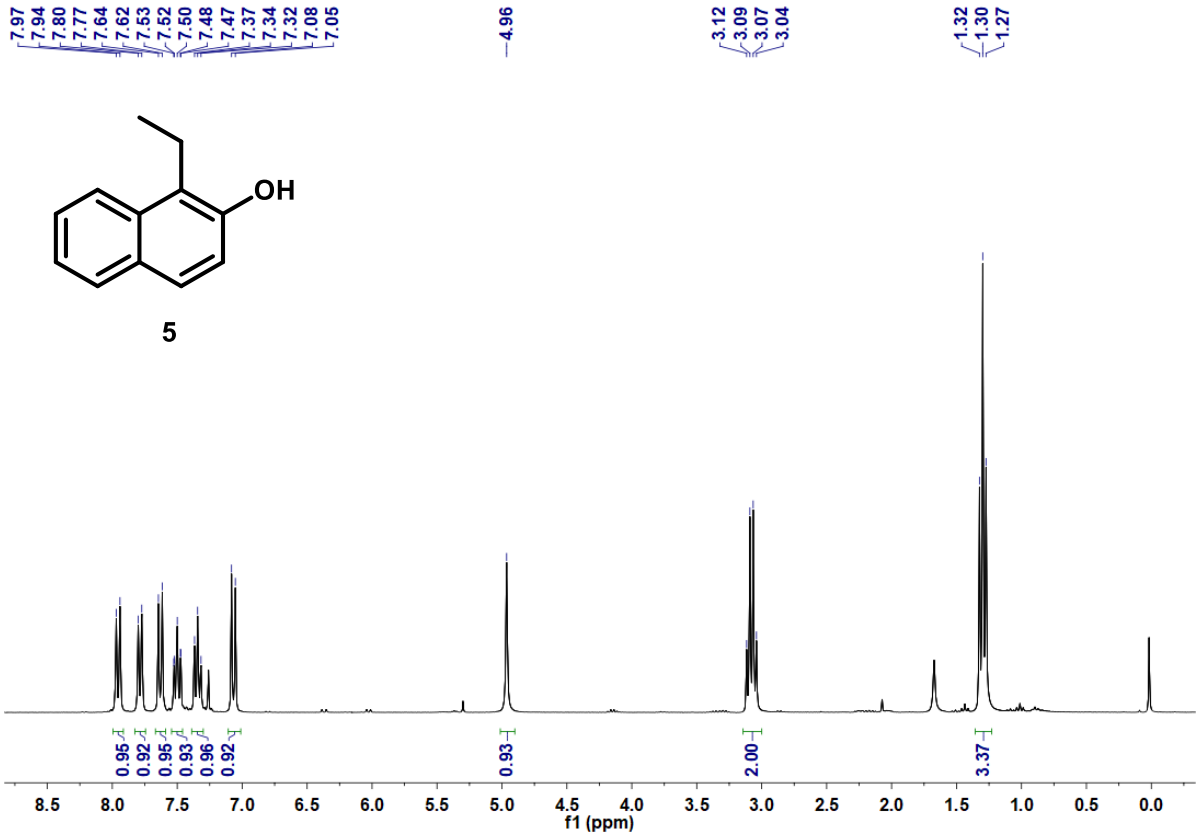
146.22
145.85
134.38
130.80
127.78
127.76
126.93
125.77
125.65
123.41
122.68
121.08
120.33
OH
NO2
4
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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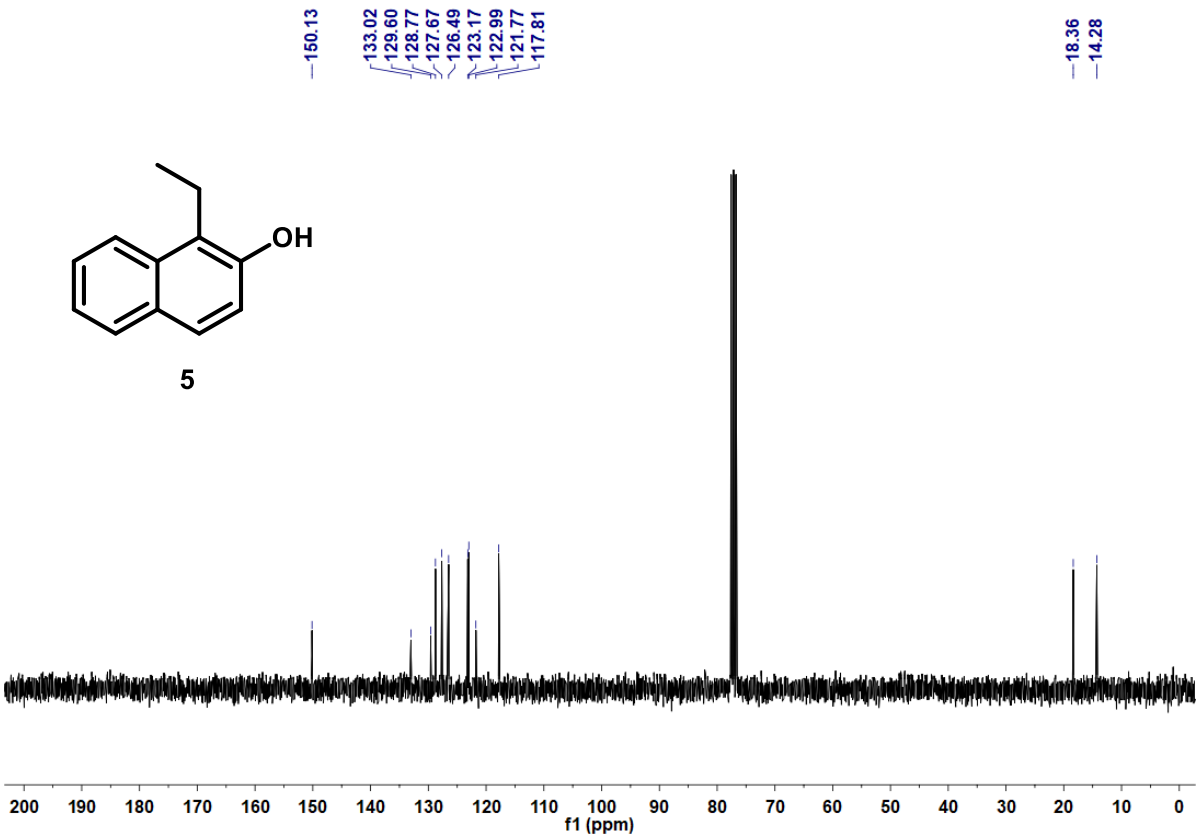
7.94
7.80
7.77
7.64
7.62
7.53
7.52
7.50
7.48
7.47
7.37
7.34
7.32
7.08
7.05
4.96
3.12
3.09
3.07
3.04
1.32
1.30
1.27
OH
5
0.95
0.92
0.95
0.93
0.96
0.92
0.93
2.00
3.37
f1 (ppm)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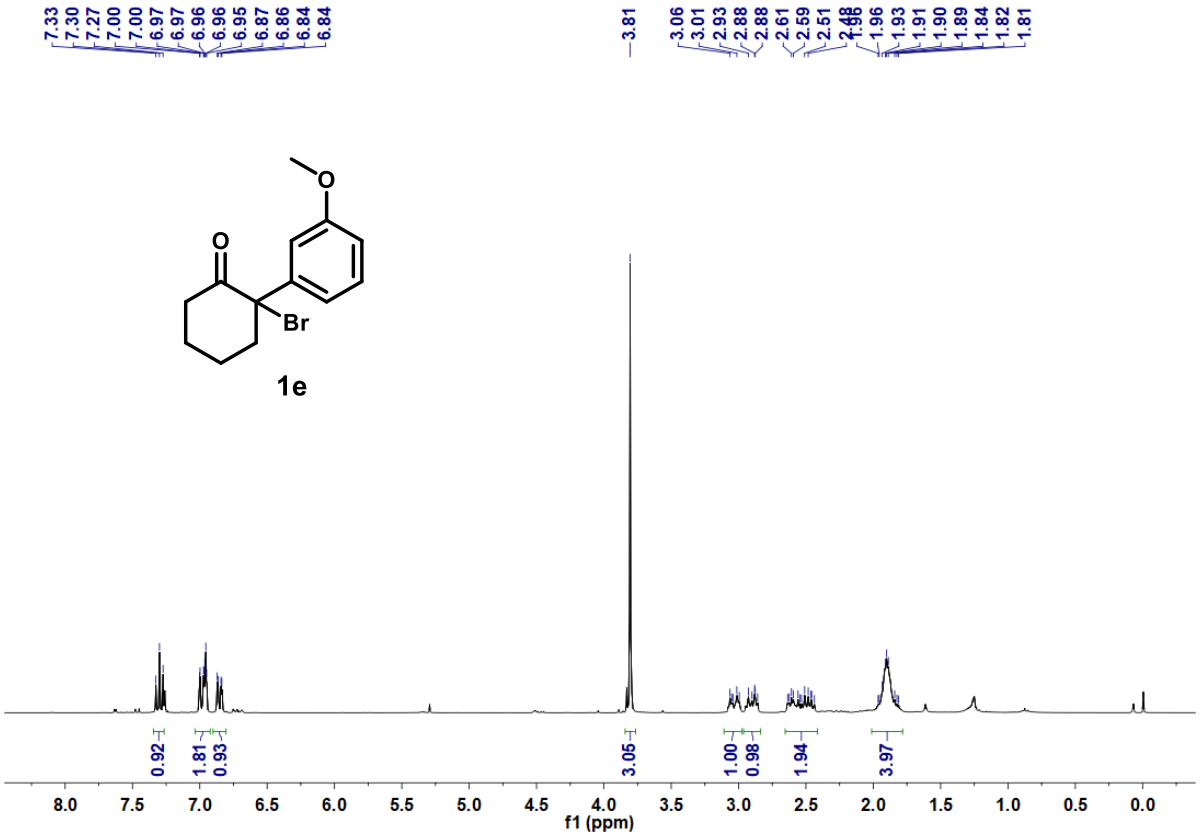
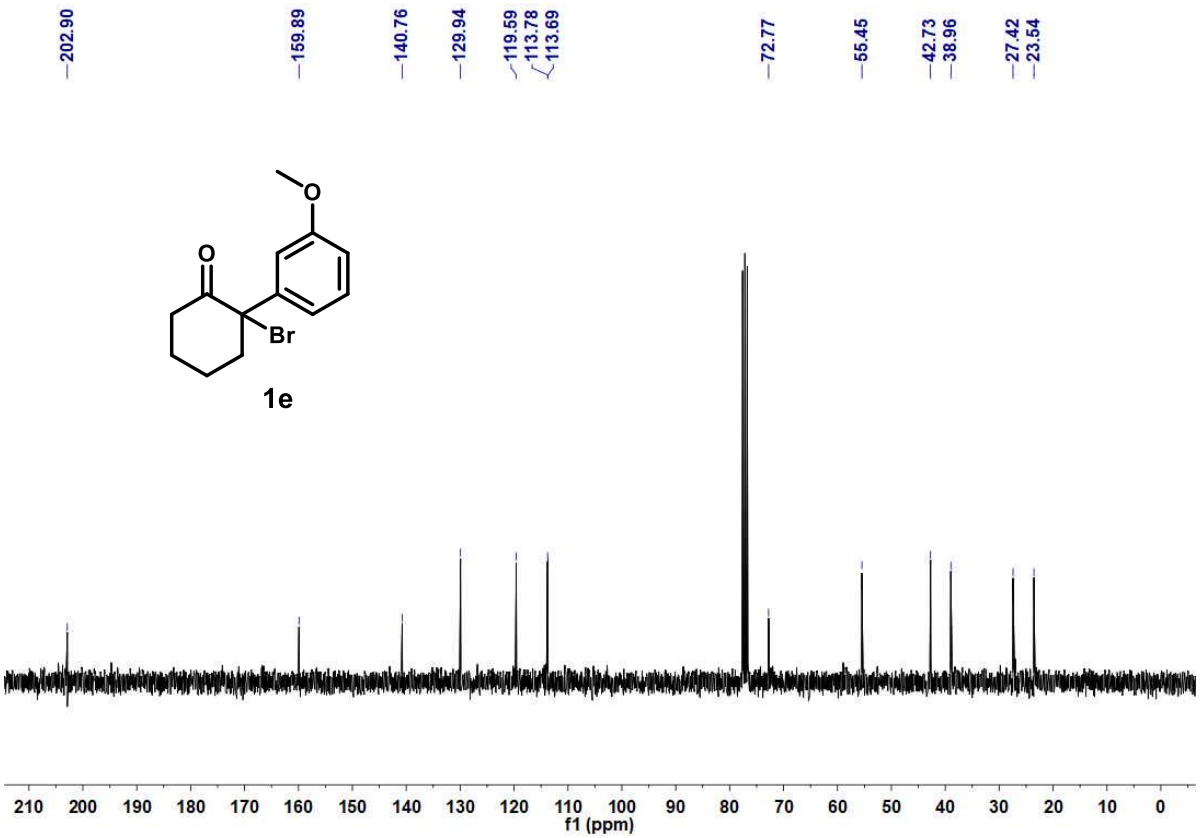
133.02
129.60
128.77
127.67
126.49
123.17
122.99
121.77
117.81
18.36
14.28
OH
5
f1 (ppm)


7.33
7.30
7.27
7.00
7.00
6.97
6.97
6.96
6.96
6.95
6.87
6.86
6.84
6.84
3.81
3.06
3.01
2.93
2.88
2.88
2.61
2.59
2.51
1.96
1.93
1.91
1.90
1.89
1.84
1.82
1.81
O
O
Br
1e
0.92
1.81
0.93
3.05
1.00
0.98
1.94
3.97
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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72.77
55.45
42.73
38.96
27.42
23.54
O
O
Br
1e
210
200
190
180
170
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150
140
130
120
110
100
90
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70
60
50
40
30
20
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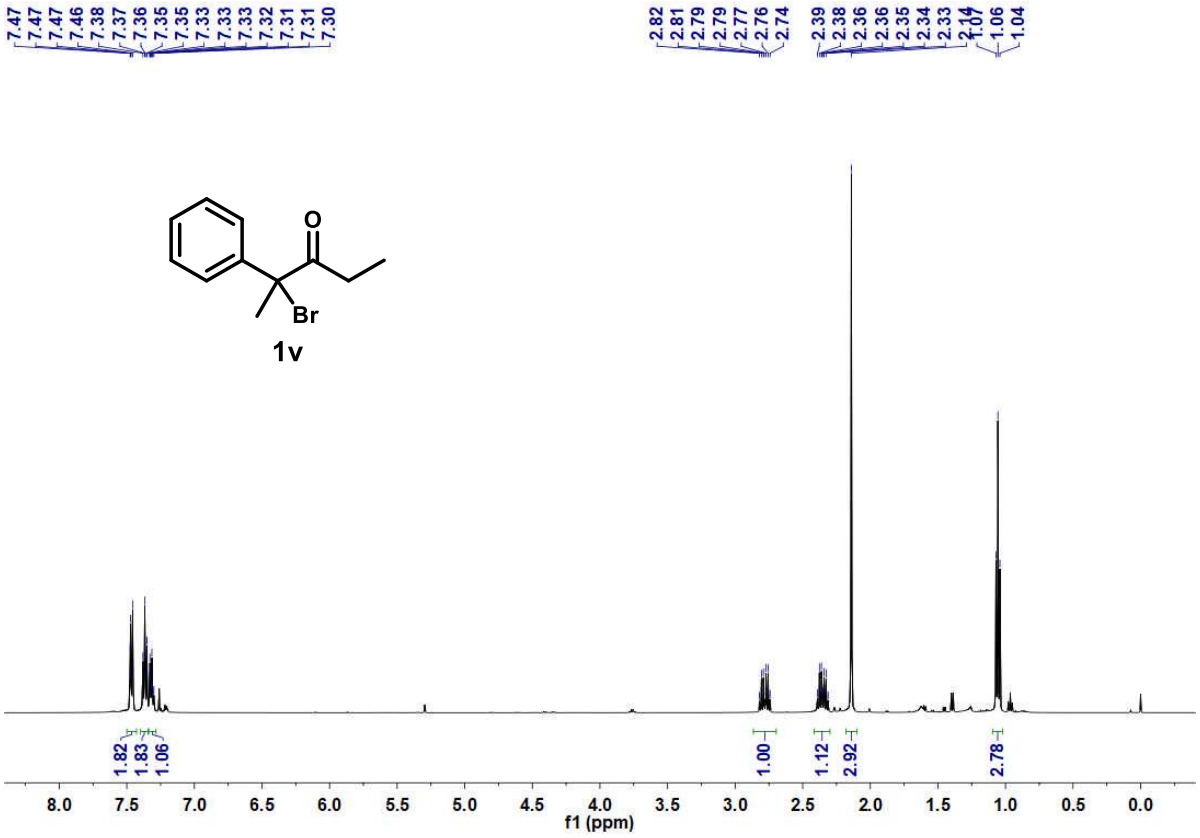
0
f1 (ppm)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7.47
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7.37
7.36
7.35
7.35
7.33
7.33
7.32
7.31
7.31
7.30
2.82
2.81
2.79
2.79
2.77
2.76
2.74
2.39
2.38
2.36
2.36
2.35
2.34
2.33
2.14
2.07
1.06
1.04
O
Br
1v
1.82
1.83
1.06
1.00
1.12
2.92
2.78
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
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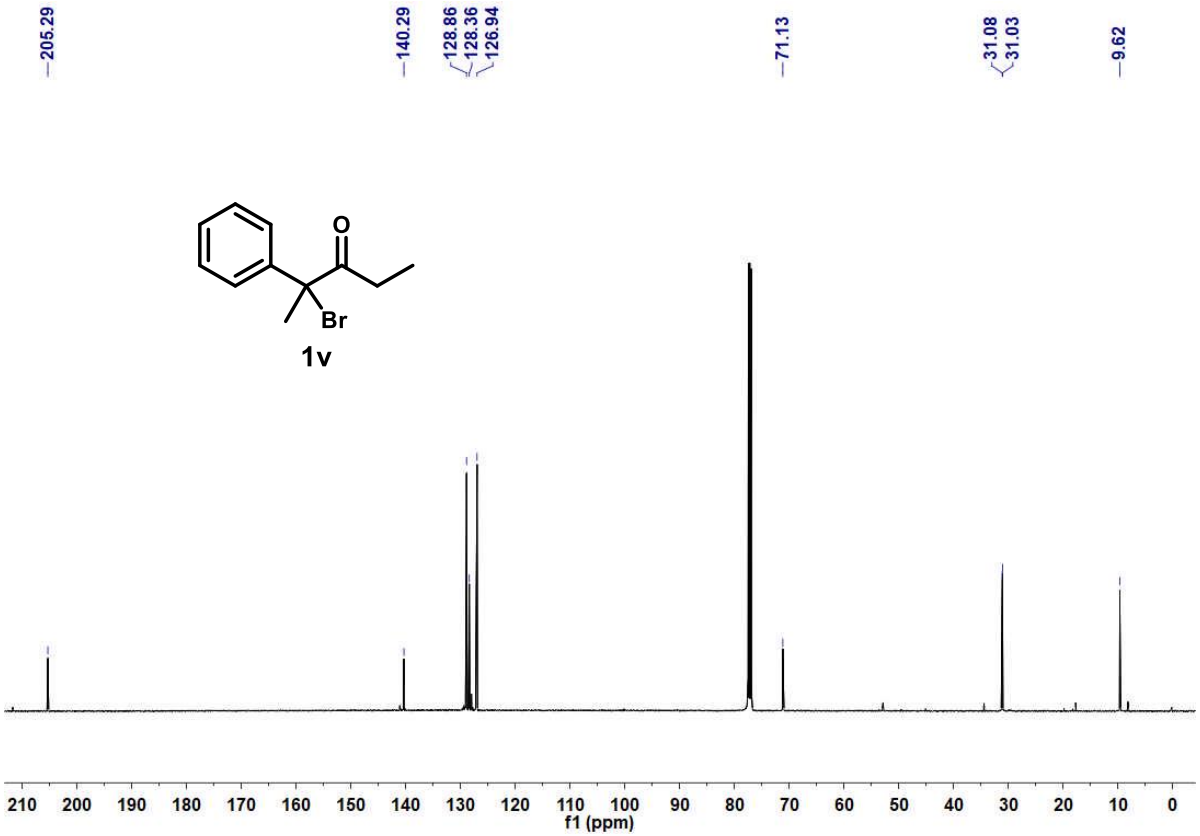
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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128.86
128.36
126.94
71.13
31.08
31.03
9.62
O
Br
1v
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

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