

Supporting Information

Catalytic Conjugate Addition of Electron-Rich Heteroarenes to β,β - Disubstituted Enones

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General Experimental Details

All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. All glassware for moisture sensitive reactions was dried at 140 °C in an oven. Dichloromethane, ether, and tetrahydrofuran were dried with a solvent purification system by passing through a one-meter column of activated alumina. Anhydrous acetonitrile and methanol were purchased from Sigma-Aldrich and used as received. Flash column chromatography was performed on SiliFlash® P60 silica gel (40-63µm, 60Å) or using a Teledyne Isco Combiflash® Rf system with RediSep Gold™ columns using hexanes/ethyl acetate or hexanes/diethyl ether. Reaction products were visualized on TLC under UV light or by staining with KMnO₄ or cerium molybdate.

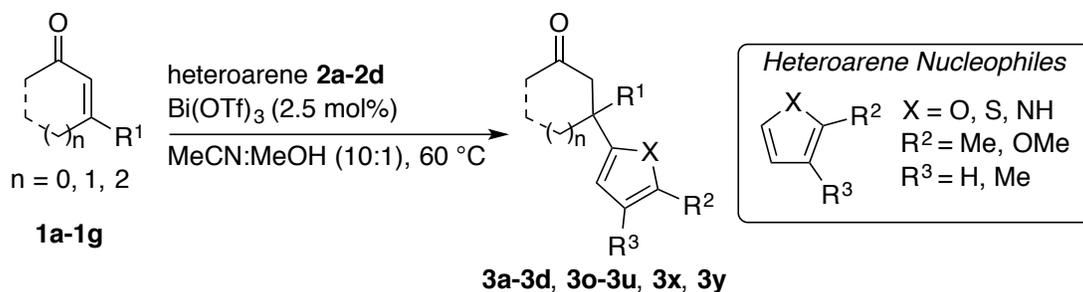
HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemical shifts are reported in ppm relative to a residual solvent peak (CDCl₃ = 7.26 ppm for ¹H and 77.16 ppm). Coupling constants are reported in hertz.

Materials

3-Methylcyclohex-2-en-1-one **1a**, 3-methylcyclopent-2-en-1-one **1d**, 4-methylpent-3-en-2-one **1f**, 3,5,5-trimethylcyclohex-2-en-1-one **1g**, 2-methylfuran **2b**, and 2-methoxythiophene **2c** were purchased from TCI and used without further purification. 2,3-Dimethylfuran **2a**, 2-methyl-1*H*-pyrrole **2d**, 1*H*-indole **2e**, 5-methoxy-1*H*-indole **2f**, *N*-methylindole **2i**, and 5-cyano-1*H*-indole **2h** were purchased from AK Scientific and used without further purification. 4-

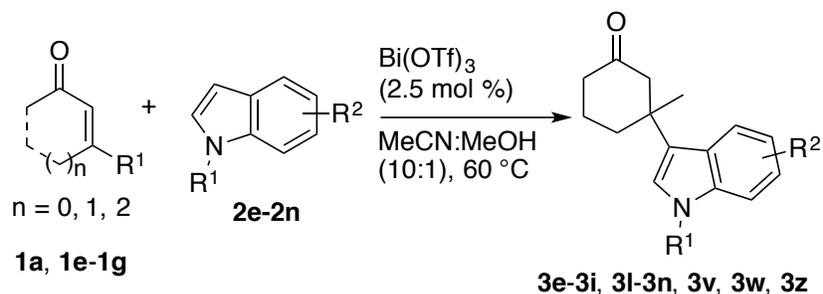
Methyl-1*H*-indole **2k**, 5-methyl-1*H*-indole **2l**, and 6-methyl-1*H*-indole **2m** were purchased from Combi-Blocks and used without further purification. 2-Methyl-1*H*-indole **2j** and 7-methyl-1*H*-indole **2n** were purchased from Sigma-Aldrich and used without any further purification. 5-Bromo-1*H*-indole **2g** was purchased from Frontier Scientific and used without further purification. Bismuth(III) trifluoromethanesulfonate was purchased from Strem Chemicals. 3-Ethyl-2-cyclohex-2-en-1-one **1b** was synthesized according to literature procedure.¹ 3-Benzyl-2-cyclohex-2-en-1-one **1c** was synthesized according to literature procedure.² 3-Methyl-2-cyclohept-2-en-1-one **1b** was synthesized according to literature procedure.³

General Procedure A: Acid-Catalyzed Conjugate Additions of Heteroarenes 2a-2d to Enones 1a-1g



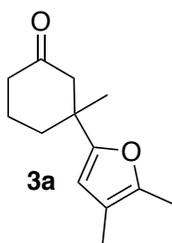
To a 1 dram vial was added Bi(OTf)₃ (4.2 mg, 0.0063 mmol, 0.025 equiv), heteroarene **2a**, **2b**, **2c** or **2d** (0.25 mmol, 1.00 equiv), enone **1a**, **1b**, **1c**, **1d**, **1e**, or **1f** (0.75 mmol, 3.00 equiv), and acetonitrile/methanol (10:1) solution (0.5 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 1-3 h. The mixture was cooled and concentrated under reduced pressure. The crude reaction mixture was dissolved in CDCl₃ (0.6 mL) and CH₂Br₂ (8.9 μL, 0.25 mmol) was added as an internal standard. NMR yields were determined by ¹H NMR spectroscopy of the crude reaction mixture. The crude reaction mixture was purified by flash column chromatography on silica gel (hexane:EtOAc) or (hexane:ether) to yield the desired ketones **3a-d**, **3o-3u**, **3x**, and **3y**.

General Procedure B: Acid-Catalyzed Conjugate Additions of Heteroarenes 2e-2n to Enones 1a and 1e-1g



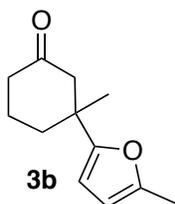
To a 1 dram vial was added the appropriate Bi(OTf)_3 (4.2 mg, 0.0063 mmol, 0.025 equiv), the appropriate indole **2e-2n** (0.250 mmol, 1.00 equiv), enone **1a** (1.25 mmol, 5.00 equiv), and an acetonitrile/methanol (10:1) solution (0.5 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 1-3 h. The mixture was cooled and concentrated under reduced pressure. The crude reaction mixture was dissolved in CDCl_3 (0.6 mL) and CH_2Br_2 (8.9 μL , 0.25 mmol) was added as an internal standard. NMR yields were determined by ^1H NMR spectroscopy of the crude reaction mixture. The crude reaction mixture was purified by flash column chromatography on silica gel (hexane:EtOAc) or (hexane:ether) to yield the desired ketones **3e-3i**, **3l-3n**, **3v**, **3w**, and **3z**.

Characterization Data for Ketones 3a-3i and 3l-3z

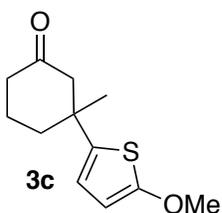


3-(4,5-dimethylfuran-2-yl)-3-methylcyclohexan-1-one (3a): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (84 μL , 0.75 mmol) and 2,3-dimethylfuran **2a** (26 μL , 0.25 mmol). The crude product was purified by flash column chromatography (80:20 hexanes:ether) to yield **3a** (46.2 mg, 0.220 mmol, 88%) as a colorless oil. ^1H NMR (600 MHz, CDCl_3): δ 5.80 (s, 1H), 2.74 (d, $J = 14.4$ Hz, 1H), 2.36-2.26 (m, 3H), 2.24-2.20 (m, 1H), 2.18 (s, 3H), 1.90-1.86 (m, 4H), 1.76-1.62 (m, 2H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 210.9, 156.5, 145.9,

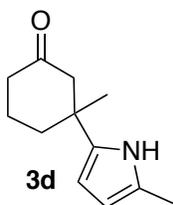
114.0, 108.3, 51.9, 40.7, 40.3, 35.9, 27.3, 22.1, 11.2, 9.8. HRMS (ESI) calcd. for $C_{13}H_{19}O_2^+$ $[M+H]^+$ 207.1380, found 207.1381.



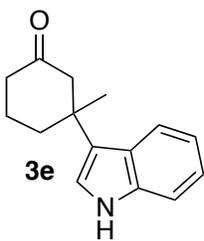
3-(5-methylfuran-2-yl)-3-methylcyclohexan-1-one (3b): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (84 μ L, 0.75 mmol) and 2-methylfuran **2b** (23 μ L, 0.25 mmol). The crude product was purified by flash column chromatography (80:20 hexanes:ether) to yield **3b** (43.9 mg, 0.228 mmol, 91%) as a colorless oil. 1H NMR (600 MHz, $CDCl_3$): δ 5.86 (d, $J = 2.4$ Hz, 1H), 5.81 (d, $J = 2.4$ Hz, 1H), 2.71 (d, $J = 14.4$ Hz, 1H), 2.36-2.16 (m, 4H), 2.24 (s, 3H), 1.90-1.81 (m, 1H), 1.76-1.58 (m, 2H), 1.30 (s, 3H). (100 MHz, $CDCl_3$): δ 210.9, 158.0, 150.9, 105.8, 105.7, 52.0, 40.8, 40.6, 36.0, 27.3, 22.2, 13.6. HRMS (ESI) calcd. for $C_{12}H_{17}O_2^+$ $[M+H]^+$ 193.1223, found 193.1228.



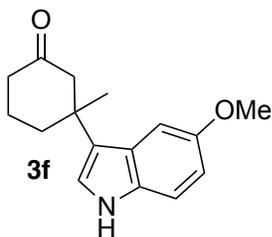
3-(5-methoxythiophen-2-yl)-3-methylcyclohexan-1-one (3c): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (84 μ L, 0.75 mmol) and 2-methoxythiophene **2c** (25 μ L, 0.25 mmol). The crude product was purified by flash column chromatography (80:20 hexanes:ether) to yield **3c** (39.3 mg, 0.175 mmol, 70%) as a orange oil. 1H NMR (600 MHz, $CDCl_3$): δ 6.38 (d, $J = 3.6$ Hz, 1H), 5.93 (d, $J = 3.6$ Hz, 1H), 3.83 (s, 3H), 2.77 (d, $J = 14.4$ Hz, 1H), 2.39 (d, $J = 14.4$ Hz, 1H), 2.35-2.23 (m, 2H), 2.07-1.99 (m, 1H), 1.92-1.84 (m, 2H), 1.81-1.73 (m, 1H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.6, 164.7, 139.0, 120.6, 102.6, 60.2, 53.6, 42.2, 40.7, 39.5, 31.2, 22.1. HRMS (ESI) calcd. for $C_{12}H_{17}O_2S^+$ $[M+H]^+$ 225.0955, found 225.0952



3-(5-methyl-1H-pyrrol-2-yl)-3-methylcyclohexan-1-one (3d): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (84 μL , 0.75 mmol) and 2-methyl-1H-pyrrole **2c** (22 μL , 0.25 mmol). The crude product was purified by flash column chromatography (80:20 hexanes:ether) to yield **3d** (33.6 mg, 0.174 mmol, 70%) as a white solid. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.64 (br, s, 1H), 5.79 (m, 1H), 5.75 (m, 1H), 2.74 (ddd, $J = 14.4, 1.6, 1.6$ Hz, 1H), 2.36 (d, $J = 14.4$ Hz, 1H), 2.33-2.26 (m, 2H), 2.23 (s, 3H), 2.08-1.98 (m, 1H), 1.92-1.80 (m, 2H), 1.75-1.63 (m, 1H), 1.32 (s, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 211.4, 136.4, 126.9, 105.8, 105.0, 53.1, 40.9, 39.7, 38.0, 29.5, 22.4, 13.2. HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{18}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 192.1394, found 192.1390.



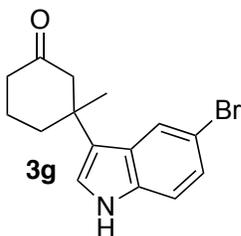
3-(1H-indol-3-yl)-3-methylcyclohexan-1-one (3e): Prepared according to General Procedure B from 3-methylcyclohex-2-en-1-one **1a** (140 μL , 1.25 mmol) and 1H-indole **2e** (29.3 mg, 0.250 mmol). The crude product was purified with a CombiFlash system (12 g column, 95:5 to 85:15 hexane:EtOAc) to yield **3e** (48.1 mg, 0.210 mmol, 84%) as a white solid. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.03 (br, s, 1H), 7.76 (d $J = 7.8$ Hz, 1H), 7.37 (d $J = 7.8$ Hz, 1H), 7.19 (dd, $J = 8.4, 7.8$ Hz, 1H), 7.10 (dd, $J = 8.4, 7.8$ Hz, 1H), 6.96 (d, $J = 2.4$ Hz, 1H), 2.91 (d, $J = 14.4$ Hz, 1H), 2.62-2.55 (m, 2H), 2.48 (d, $J = 14.4$ Hz, 1H), 2.36-2.24 (m, 2H), 1.96-1.79 (m, 3H), 1.53 (s, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 212.8, 137.4, 125.1, 122.2, 122.0, 121.9, 120.9, 119.1, 111.7, 54.4, 41.1, 40.2, 36.7, 29.4, 22.5. HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{18}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 228.1394, found 228.1390.



3-(5-methoxy-1*H*-indol-3-yl)-3-methylcyclohexan-1-one (3f):

Prepared according to General Procedure B from 3-methylcyclohex-2-en-1-one **1a** (140 μ L, 1.25 mmol) and 5-methoxy-1*H*-indole **2f** (37.0 mg, 0.250 mmol). The crude product was purified by flash column chromatography (70:30 hexanes:ether) to yield **3f** (37.2 mg, 0.145 mmol, 58%) as a white solid.

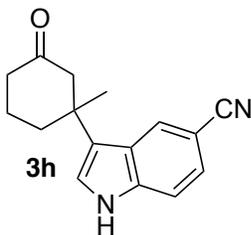
$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.89 (br, s, 1H), 7.26 (d, $J = 9.0$ Hz, 1H), 7.19 (d, $J = 2.4$ Hz, 1H), 6.94 (d, $J = 2.4$ Hz, 1H), 6.87 (dd, $J = 9.0, 2.4$ Hz, 1H) 3.87 (s, 3H), 2.89 (d, $J = 14.4$ Hz, 1H), 2.60-2.53 (m, 1H), 2.47 (d, $J = 14.4$ Hz, 1H), 2.36-2.24 (m, 2H), 1.96-1.79 (m, 2H), 1.59-1.41 (m, 4H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 212.7, 153.4, 132.7, 125.5, 123.1, 121.6, 112.2, 111.5, 103.8, 56.2, 54.4, 41.1, 40.1, 36.5, 29.1, 22.4. HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{20}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 258.1500, found 258.1493.



3-(5-bromo-1*H*-indol-3-yl)-3-methylcyclohexan-1-one (3g): Prepared

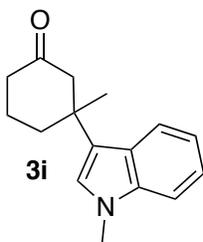
according to General Procedure B from 3-methylcyclohex-2-en-1-one **1a** (140 μ L, 1.25 mmol) and 5-bromo-1*H*-indole **2g** (49.0 mg, 0.250 mmol). The crude product was purified using a CombiFlash system (12 g column, 95:5 to 85:15 hexane:EtOAc) to yield **3g** (41.1 mg, 0.134 mmol, 54%) as a white solid. ^1H

NMR (600 MHz, CDCl_3): δ 8.39 (br, s, 1H), 7.88 (s, 1H), 7.29-7.25 (m, 2H), 6.98 (d, $J = 2.4$ Hz, 1H), 2.89 (d, $J = 14.4$ Hz, 1H), 2.56-2.52 (m, 1H), 2.50 (d, $J = 14.4$ Hz, 1H), 2.33-2.27 (m, 2H), 1.94-1.84 (m, 2H), 1.51 (s, 3H), 1.49-1.42 (m, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 212.7, 136.0, 126.8, 124.8, 123.5, 123.3, 121.6, 113.1, 112.4, 54.4, 41.1, 40.2, 36.7, 29.5, 22.4. HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{17}\text{BrNO}^+$ $[\text{M}+\text{H}]^+$ 306.0488, found 306.0492.



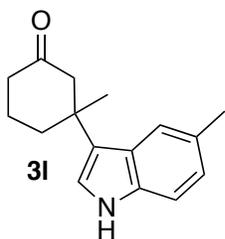
3-(1-methyl-3-oxocyclohexyl)-1H-indole-5-carbonitrile (3h): Prepared according to General Procedure B from 3-methylcyclohex-2-en-1-one **1a** (140 μ L, 1.25 mmol) and 5-cyano-1H-indole **2h** (49.0 mg, 0.250 mmol).

The crude product was purified by flash column chromatography (70:30 hexanes:ether) to yield **3h** (29.0 mg, 0.115 mmol, 46%) as a white solid. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.42 (br, s, 1H), 8.11 (m, 1H), 7.43-7.42 (m, 2H), 7.10 (d, $J = 2.4$, 1H), 2.89 (d, $J = 14.4$, 1H), 2.54-2.49 (m, 2H), 2.33-2.30 (m, 2H), 2.00-1.82 (m, 2H), 1.51 (s, 3H), 1.48-1.34 (m, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): 212.0, 139.0, 126.5, 125.0 (2C), 124.5, 123.0, 120.9, 112.5, 102.6, 54.3, 41.1, 40.3, 37.0, 29.8, 22.5. HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}^+$ $[\text{M}+\text{H}]^+$ 253.1335, found 253.1335.



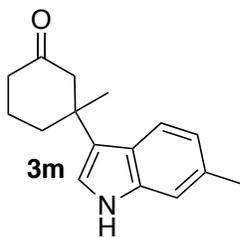
3-methyl-3-(1-methylindol-3-yl)cyclohexan-1-one (3i): Prepared according to General Procedure B from 3-methylcyclohex-2-en-1-one **1a** (140 μ L, 1.25 mmol) and 1-methylindole **2i** (31 μ L, 0.250 mmol). The crude product was purified by flash column chromatography (80:20 hexanes:ether) to yield **3i**

(42.5 mg, 0.176 mmol, 70%) as a orange oil. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.75 (d, $J = 7.8$ Hz, 1H), 7.30 (d, $J = 7.8$ Hz, 1H), 7.22 (ddd, $J = 7.8, 7.2, 1.2$ Hz, 1H), 7.09 (ddd, $J = 7.8, 7.2, 1.2$ Hz, 1H), 6.80 (s, 1H), 3.73 (s, 3H), 2.90 (ddd, $J = 14.4, 1.8, 1.8$ Hz, 1H), 2.62-2.55 (m, 1H), 2.47 (d, $J = 14.4$ Hz, 1H), 2.36-2.24 (m, 2H), 1.94-1.76 (m, 2H), 1.59-1.41 (m, 4H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 212.5, 138.0, 126.9, 125.5, 121.5, 121.0, 120.5, 118.6, 109.7, 54.5, 41.1, 40.1, 36.9, 32.8, 29.6, 22.5. HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{20}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 242.1539, found 242.1544.



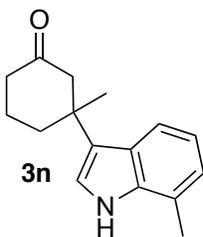
3-methyl-3-(5-methyl-1*H*-indol-3-yl)cyclohexan-1-one (3l): Prepared according to General Procedure B from 3-methylcyclohex-2-en-1-one **1a** (140 μ L, 1.25 mmol) and 5-methyl-1*H*-indole **2l** (33.5 mg, 0.250 mmol).

The crude product was purified using a CombiFlash system (12 g column, 95:5 to 85:15 hexane:EtOAc) to yield **3l** (35.0 mg, 0.145 mmol, 58%) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.91 (br, s, 1H), 7.53 (s, 1H), 7.26 (d, $J = 8.4$ Hz, 1H), 7.02 (dd, $J = 8.4, 0.6$ Hz, 1H), 6.92 (d, $J = 2.4$ Hz, 1H), 2.89 (ddd, $J = 14.4, 1.8, 1.8$ Hz, 1H), 2.62-2.52 (m, 1H), 2.51-2.42 (m, 4H), 2.36-2.22 (m, 2H), 1.95-1.79 (m, 2H), 1.55-1.45 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 212.7, 137.8, 131.9, 122.9, 121.9, 121.6, 120.9, 120.5, 111.6, 54.4, 41.1, 40.2, 36.8, 29.4, 22.5, 21.7. HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{20}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 242.1539, found 242.1545.



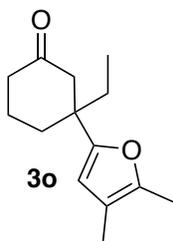
3-methyl-3-(6-methyl-1*H*-indol-3-yl)cyclohexan-1-one (3m): Prepared according to General Procedure B from 3-methylcyclohex-2-en-1-one **1a** (140 μ L, 1.25 mmol) and 6-methyl-1*H*-indole **2m** (33.5 mg, 0.250 mmol).

The crude product was purified using a CombiFlash system (12 g column, 95:5 to 85:15 hexane:EtOAc) to yield **3m** (45.7 mg, 0.189 mmol, 76%) as a white solid. ^1H NMR (600 MHz, CDCl_3): δ 7.89 (br, s, 1H), 7.63 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.16 (s, 1H), 6.94 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.88 (m, 1H), 2.90 (d, $J = 14.4$ Hz, 1H), 2.61-2.53 (m, 1H), 2.50-2.43 (m, 4H), 2.38-2.23 (m, 2H), 1.93-1.78 (m, 2H), 1.55-1.45 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 212.7, 137.8, 131.9, 122.9, 121.9, 121.6, 120.9, 120.5, 111.6, 54.4, 41.1, 40.2, 36.8, 29.4, 22.5, 21.7. HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{20}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 242.1539, found 242.1540.



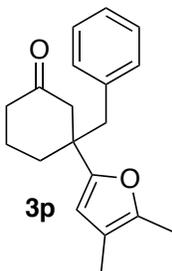
3-methyl-3-(7-methyl-1H-indol-3-yl)cyclohexan-1-one (3n): Prepared according to General Procedure B from 3-methylcyclohex-2-en-1-one **1a** (140 μ L, 1.25 mmol) and 7-methyl-1H-indole **2n** (33.5 mg, 0.250 mmol).

The crude product was purified using a CombiFlash system (12 g column, 95:5 to 85:15 hexane:EtOAc) to yield **3n** (45.7 mg, 0.189 mmol, 76%) as a white solid. ^1H NMR (600 MHz, CDCl_3): δ 8.06 (br, s, 1H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.08-6.94 (m, 3H), 2.92 (d, $J = 14.4$ Hz, 1H), 2.63-2.56 (m, 1H), 2.51-2.45 (m, 4H), 2.34-2.25 (m, 2H), 1.94-1.78 (m, 2H), 1.55-1.45 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 212.8, 136.9, 124.6, 122.6, 122.5, 121.9, 120.8, 119.4, 118.68, 54.5, 41.2, 40.2, 36.7, 29.4, 22.5, 16.8. HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{20}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 242.1539, found 242.1544.



3-(4,5-dimethylfuran-2-yl)-3-ethylcyclohexan-1-one (3o): Prepared according to General Procedure A from 3-ethylcyclohex-2-en-1-one **1b** (99 μ L, 0.75 mmol) and 2,3-dimethylfuran **2a** (26 μ L, 0.25 mmol). The crude product was purified with CombiFlash system (12 g column, 100:0 to 90:10 hexane:EtOAc)

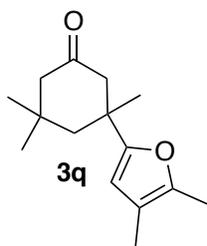
to yield **3o** (35.2 mg, 0.163 mmol, 65%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 5.76 (s, 1H), 2.67 (dd, $J = 14.4$ Hz, 1H), 2.32-2.21 (m, 3H), 2.17-2.12 (m, 4H), 1.85-1.78 (m, 4H), 1.77-1.68 (m, 2H), 1.58-1.50 (m, 2H), 0.70 (dt, $J = 7.8, 2.8$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 211.2, 154.3, 146.1, 114.0, 110.8, 49.4, 44.3, 41.1, 34.4, 33.7, 22.00, 11.4, 10.0, 8.4. HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{21}\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 221.1539, found 221.1537.



3-benzyl-3-(4,5-dimethylfuran-2-yl)cyclohexan-1-one (3p): Prepared

according to General Procedure A from 3-benzylcyclohex-2-en-1-one **1c** (129 μL , 0.75 mmol) and 2,3-dimethylfuran **2a** (26 μL , 0.25 mmol). The crude product was purified by flash column chromatography (80:20 hexanes:EtOAc)

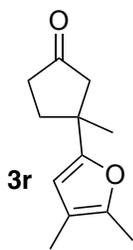
to yield **3p** (37.4 mg, 0.134 mmol, 53%) as a colorless oil. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.23-7.15 (m, 3H), 6.81 (d, $J = 6.5$ Hz, 2H), 5.62 (s, 1H), 3.02 (d, $J = 13.2$ Hz, 1H), 2.85 (d, $J = 13.2$ Hz, 1H), 2.45 (d, $J = 14.2$ Hz, 1H), 2.33-2.23 (m, 3H), 2.20 (s, 3H), 2.22 (m, 1H), 1.89-1.81 (m, 4H), 1.75 (m, 1H), 1.55-1.43 (m, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 211.0, 153.4, 146.1, 137.0, 130.4, 127.9, 126.5, 114.3, 111.9, 49.0, 47.8, 45.0, 40.9, 34.3, 21.9, 11.4, 10.0. HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{23}\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 283.1693, found 283.1697



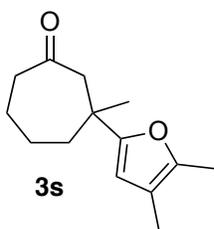
3-(4,5-dimethylfuran-2-yl)-3,5,5-trimethylcyclohexan-1-one (3q):

Prepared according to General Procedure A from 3,5,5-trimethylcyclohex-2-en-1-one **1g** (112 μL , 0.75 mmol) and 2,3-dimethylfuran **2a** (26 μL , 0.25 mmol). The crude product was purified with a CombiFlash system (12 g

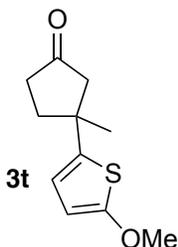
column, 95:5 to 85:15 hexane:EtOAc) to yield **3q** (34.9 mg, 0.149 mmol, 60% yield) as a white solid. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 5.77 (s, 1H), 2.72 (d, $J = 14.4$ Hz, 1H), 2.29-2.25 (m, 2H), 2.17-2.09 (m, 5H), 1.84 (s, 3H), 1.84 (d, $J = 14.4$ Hz, 1H), 1.30 (s, 3H), 1.02 (s, 3H), 0.51 (s, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 211.0, 156.4, 145.3, 114.5, 108.5, 54.4, 50.7, 48.6, 39.7, 35.7, 33.5, 31.7, 26.6, 11.4, 10.0. HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{23}\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 235.1693, found 235.1699.



3-(4,5-dimethylfuran-2-yl)-3-methylcyclopentan-1-one (3r): Prepared according to General Procedure A from 3-methylcyclopent-2-en-1-one **1d** (76 μL , 0.75 mmol) and 2,3-dimethylfuran **2a** (26 μL , 0.25 mmol). The crude product was purified by flash column chromatography (80:20 hexanes:EtOAc) to yield **3r** (36.2 mg, 0.188 mmol, 75%) as a yellow oil. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 5.80 (s, 1H), 2.65 (d, $J = 18.0$ Hz, 1H), 2.39-2.28 (m, 3H), 2.20 (d, $J = 18.0$ Hz, 1H), 2.15 (s, 3H), 1.97-1.90 (m, 1H), 1.88 (s, 3H), 1.41 (s, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 218.7, 157.0, 146.3, 114.2, 107.3, 51.4, 40.7, 37.1, 35.3, 25.9, 11.4, 10.0. HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 193.1223, found 193.1227.

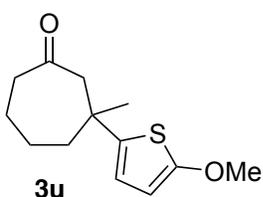


3-(4,5-dimethylfuran-2-yl)-3-methylcycloheptan-1-one (3s): Prepared according to General Procedure A from 3-methylcyclohept-2-en-1-one **1e** (99 μL , 0.75 mmol) and 2,3-dimethylfuran **2a** (26 μL , 0.25 mmol). The crude product was purified by flash column chromatography (80:20 hexanes:ether) to yield **3s** (43.7 mg, 0.198 mmol, 79%) as a colorless oil. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 5.75 (s, 1H), 2.98 (d, $J = 13.8$ Hz, 1H), 2.62 (d, $J = 13.8$ Hz, 1H), 2.42 (dd, $J = 6.0, 6.0$ Hz, 2H), 2.22-2.17 (m, 1H), 2.14 (s, 3H), 1.87 (s, 3H), 1.79-1.67 (m, 5H), 1.22 (s, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 213.4, 158.2, 145.7, 114.1, 107.0, 54.1, 44.3, 42.2, 37.6, 28.0, 25.6, 24.1, 11.4, 10.0. HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{21}\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 221.1536, found 221.1539.



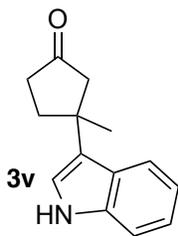
3-(5-methoxythiophen-2-yl)-3-methylcyclopentan-1-one (3t): Prepared according to General Procedure A from 3-methylcyclopent-2-en-1-one **1d** (76 μL , 0.75 mmol) and 2-methoxythiophene **2c** (25 μL , 0.25 mmol). The crude

product was purified with a CombiFlash system (12 g column, 95:5 to 90:10 hexane:EtOAc) to yield **3t** (29.7 mg, 0.141 mmol, 56%) as a yellow oil. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 6.41 (d, $J = 3.6$ Hz, 1H), 5.97 (d, $J = 3.6$ Hz, 1H), 3.85 (s, 3H), 2.64 (d, $J = 18.0$ Hz, 1H), 2.40-2.24 (m, 4H), 2.14-2.04 (m, 1H), 1.47 (s, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 218.17, 164.9, 139.2, 119.9, 103.0, 60.5, 53.7, 42.7, 38.3, 37.3, 29.2. HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{15}\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]^+$ 211.0787, found 211.0785.



3-(5-methoxythiophen-2-yl)-3-methylcycloheptan-1-one (3u):

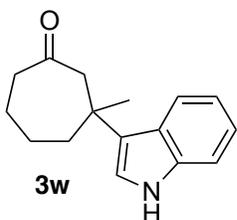
Prepared according to General Procedure A from 3-methylcyclohept-2-en-1-one **1e** (99 μL , 0.75 mmol) and 2-methoxythiophene **2c** (25 μL , 0.25 mmol). The crude product was purified by flash column chromatography (80:20 hexane:EtOAc) to yield **3u** (32.8 mg, 0.138 mmol, 55%) as a yellow oil. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 6.40 (d, $J = 3.6$ Hz, 1H), 5.95 (d, $J = 3.6$ Hz, 1H), 3.84 (s, 3H), 3.07 (d, $J = 13.7$ Hz, 1H), 2.69 (d, $J = 13.7$ Hz, 1H), 2.47-2.35 (m, 2H), 2.16-2.07 (m, 1H), 1.92-1.65 (m, 5H), 1.30 (s, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 213.0, 164.4, 140.4, 119.5, 102.7, 60.2, 56.2, 45.3, 44.2, 39.3, 31.4, 25.7, 20.9. HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{19}\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]^+$ 239.1100, found 239.1106.



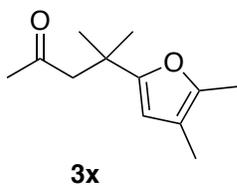
3-(1H-indol-yl)-3-methylcyclopentan-1-one (3v): Prepared according to General Procedure B from 3-methylcyclopent-2-en-1-one **1d** (127 μL , 1.25 mmol) and indole **2e** (29.3 mg, 0.250 mmol). The crude product was purified with a CombiFlash system (12 g column, 95:5 to 85:15 hexane:EtOAc) to yield

3v (19.8 mg, 0.093 mmol, 37%) as a colorless oil. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.01 (br, s,

1H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.39 (ddd, $J = 7.8, 1.2, 1.2$ Hz, 1H), 7.23 (ddd, $J = 7.8, 7.2, 1.2$ Hz, 1H), 7.13 (ddd, $J = 7.8, 7.2, 1.2$ Hz, 1H), 6.94 (d, $J = 2.4$ Hz, 1H) 2.82 (d, $J = 17.4$ Hz, 1H), 2.61-2.57 (m, 1H), 2.47 (d = $J = 17.4$ Hz, 1H), 2.40-2.36 (m, 1H), 2.33-2.27 (m, 1H), 2.24-2.19 (m, 1H), 1.62 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 219.7, 137.5, 125.6, 122.9, 122.2, 120.6, 120.2, 119.4, 111.7, 52.9, 40.0, 37.0, 35.8, 27.9. HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{16}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 214.1226, found 214.1226.

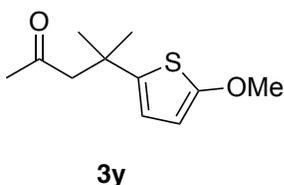


3-(1H-indol-3-yl)-3-methylcycloheptan-1-one (3w): Prepared according to General Procedure B from 3-methylcyclohept-2-en-1-one **1e** (99 μL , 1.25 mmol) and indole **2e** (29.3 mg, 0.250 mmol). The crude product was purified with a CombiFlash system (12 g column, 95:5 to 85:15 hexane:EtOAc) to yield **3w** (27.6 mg, 0.115 mmol, 46%) as a white solid. ^1H NMR (600 MHz, CDCl_3): δ 8.05 (br, s, 1H), 7.81 (d, $J = 7.8$ Hz, 1H), 7.37 (d, $J = 7.8$ Hz, 1H), 7.19 (dd, $J = 7.8, 7.2$ Hz, 1H), 7.11 (dd, $J = 7.8, 7.2$ Hz, 1H), 6.97 (s, 1H), 3.31 (d, $J = 13.8$ Hz, 1H), 2.83 (d, $J = 13.8$ Hz, 1H), 2.61-2.57 (m, 1H), 2.50-2.41 (m, 2H), 2.00-1.95 (m, 1H), 1.83-1.74 (m, 4H), 1.43 (s, 3H) ^{13}C NMR (100 MHz, CDCl_3): δ 214.7, 137.2, 125.4, 124.3, 121.9, 121.1, 120.4, 119.3, 111.6, 56.3, 44.4, 43.2, 37.2, 29.1, 25.8, 24.3. HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{20}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 242.1539, found 242.1546.



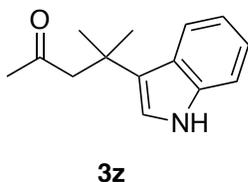
4-(4,5-dimethylfuran-2-yl)-4-methylpentan-2-one (3x): Prepared according to General Procedure A from 4-methylpent-3-en-2-one **1f** (84 μL , 0.75 mmol) and 2,3-dimethylfuran **2a** (26 μL , 0.25 mmol). The crude product was purified by flash column chromatography (80:20 hexanes:ether) to yield **3x** (36.9 mg, 0.189

mmol, 76%) as a colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.75 (s, 1H), 2.66 (s, 2H), 2.16 (s, 3H), 1.88 (s, 3H), 1.85 (s, 3H), 1.31 (s, 6H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 208.7, 158.2, 145.6, 114.3, 106.9, 54.6, 35.1, 31.4, 27.2, 11.4, 10.1. HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{19}\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 195.1380, found 195.1385.



4-(5-methoxythiophen-2-yl)-4-methylpentan-2-one (3y): Prepared according to General Procedure A from 4-methylpent-3-en-2-one **1f** (84 μL , 0.75 mmol) and 2-methoxythiophene **2c** (25 μL , 0.25 mmol).

The crude product was purified by flash column chromatography (80:20 hexanes:ether) to yield **3y** (34.9 mg, 0.164 mmol, 66%) as a yellow oil. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.40 (d, $J = 4.0$ Hz, 1H), 5.96 (d, $J = 4.0$ Hz, 1H), 3.84 (s, 3H), 2.65 (s, 2H), 1.92 (s, 3H), 1.41 (s, 6H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): 208.1, 164.3, 140.2, 119.6, 102.7, 60.2, 57.5, 36.9, 32.0, 29.7. HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{17}\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]^+$ 213.0944, found 213.0946.

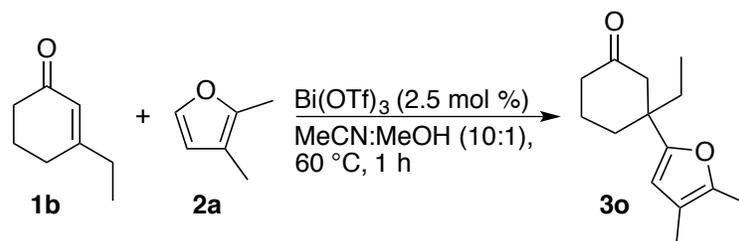


4-(1H-indol-3-yl)-4-methylpentan-2-one (3z): Prepared according to General Procedure B from 4-methylpent-3-en-2-one **1f** (140 μL , 1.25 mmol) and indole **2e** (29.3 mg, 0.250 mmol). The crude product was

purified with CombiFlash system (12 g column, 95:5 to 85:15 hexane:EtOAc) to yield **3z** (42.4 mg, 0.198 mmol, 79%) as a colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.99 (br, s, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.38 (ddd, $J = 8.0, 0.8, 0.8$ Hz, 1H), 7.20 (ddd, $J = 8.0, 7.2, 1.2$ Hz, 1H), 7.13 (ddd, $J = 8.0, 7.2, 1.2$ Hz, 1H), 6.95 (d, $J = 2.4$ Hz, 1H), 2.96 (s, 2H), 1.73 (s, 3H), 1.55 (s, 6H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 209.4, 137.3, 125.6, 123.8, 121.8, 120.9, 120.6, 119.3,

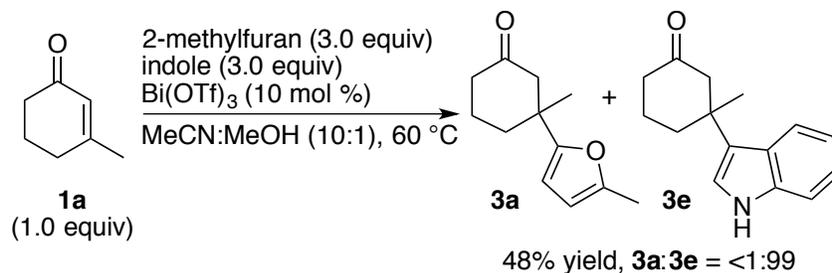
111.7, 55.2, 34.6, 31.9, 29.0. HRMS (ESI) calcd. for $C_{14}H_{18}O_2^+$ $[M+H]^+$ 215.1310, found 215.1314.

Experimental Procedure for 1.0 mmol Scale Conjugate Addition to Produce Enone **3o**



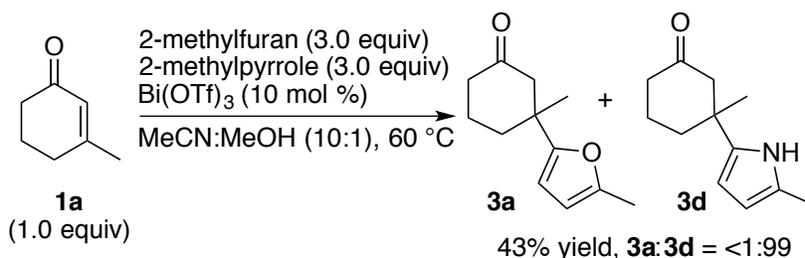
To a 1 dram vial was added $Bi(OTf)_3$ (16.8 mg, 0.025 mmol, 0.025 equiv), 2,3-dimethylfuran **2a** (104 μ L, 1.00 mmol), 3-ethylcyclohex-2-en-1-one **1b** (297 μ L, 3.00 mmol) and acetonitrile/methanol (10:1) solution (2.0 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 1 h. The crude product was purified with CombiFlash system (12 g column, 100:0 to 90:10 hexane:EtOAc) to yield **3o** (128 mg, 0.58 mmol, 58%) as a colorless oil.

Experimental Procedures for Competition Experiments between 2-Methylfuran, 2-Methylpyrrole, and Indole

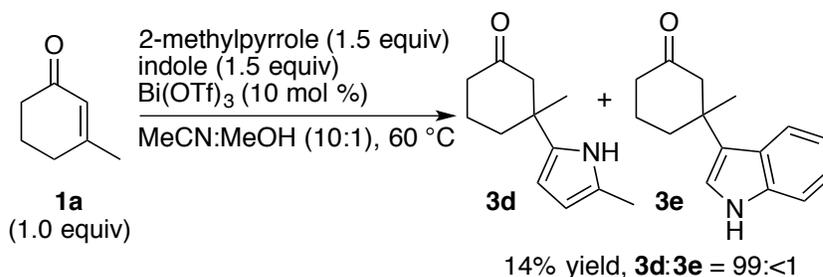


To a 1 dram vial was added $Bi(OTf)_3$ (16.8 mg, 0.0252 mmol, 0.100 equiv), 2-methylfuran (69 μ L, 0.75 mmol, 3.0 equiv), indole (87.9 mg, 0.750 mmol, 3.00 equiv), 3-methyl-2-cyclohexenone (28 μ L, 0.25 mmol, 1.00 equiv), and acetonitrile and methanol (10:1) solution (0.5 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 1 h. The mixture was cooled and

concentrated under reduced pressure. The crude reaction mixture was dissolved in CDCl_3 (0.6 mL) and CH_2Br_2 (8.9 μL , 0.25 mmol) was added as an internal standard. Yields were determined by ^1H NMR spectroscopy of the crude reaction mixture.



To a 1 dram vial was added $\text{Bi}(\text{OTf})_3$ (16.8 mg, 0.0252 mmol, 0.100 equiv), 2-methyl furan (69 μL , 0.75 mmol, 3.0 equiv), 2-methylpyrrole (75 μL , 0.75 mmol, 3.0 equiv), 3-methyl-2-cyclohexenone (28 μL , 0.25 mmol, 1.0 equiv), and an acetonitrile/methanol (10:1) solution (0.5 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60°C and allowed to stir at this temperature for 1 h. The mixture was cooled and concentrated under reduced pressure. The crude reaction mixture was dissolved in CDCl_3 (0.6 mL) and CH_2Br_2 (8.9 μL , 0.25 mmol) was added as an internal standard. Yields were determined by ^1H NMR spectroscopy of the crude reaction mixture.

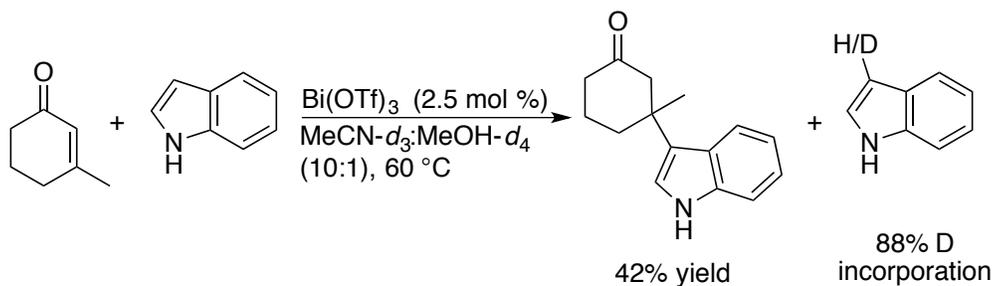


To a 1 dram vial was added $\text{Bi}(\text{OTf})_3$ (16.8 mg, 0.025 mmol, 0.100 equiv), 2-methylpyrrole (38 μL , 0.38 mmol, 1.50 equiv), indole (44.0 mg, 0.38 mmol, 1.50 equiv), 3-methyl-2-cyclohexenone (28 μL , 0.25 mmol, 1.00 equiv), and acetonitrile and methanol (10:1) solution

(0.5 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 1 h. The mixture was cooled and concentrated under reduced pressure. The crude reaction mixture was dissolved in CDCl₃ (0.6 mL) and CH₂Br₂ (8.9 μL, 0.13 mmol) was added as an internal standard. NMR yields were determined by ¹H NMR spectroscopy of the crude reaction mixture.

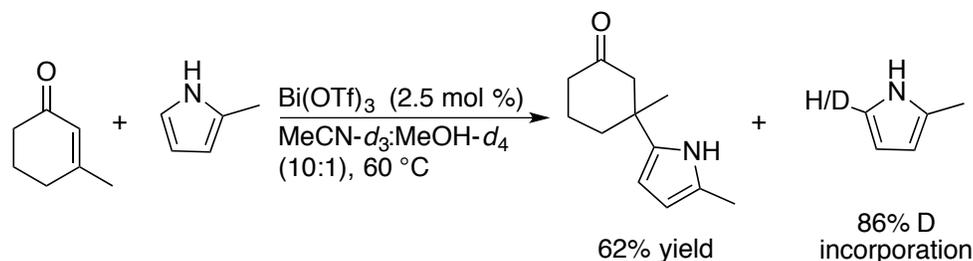
Catalyst Inhibition by Indole and Pyrrole

Conjugate addition reactions run in acetonitrile-*d*₃ and methanol-*d*₄ will generate TfOD, and the incorporation of deuterium at the C₃-position of indole (88%) and C₅-position of 2-methylpyrrole (86%) suggest that both indole and pyrrole interact with the acid catalyst. These results suggest that both pyrrole and indole nucleophiles can inhibit the acid catalyst and offers a plausible explanation for the lower reaction efficiency observed for the conjugate addition reactions of pyrrole and indole nucleophiles.



To a 1 dram vial was added Bi(OTf)₃ (0.84 mg, 0.006 mmol, 0.100 equiv), indole (7.0 mg, 0.06 mmol, 1.00 equiv), 3-methyl-2-cyclohexenone (34 μL, 0.30 mmol, 1.00 equiv), and acetonitrile-*d*₃ and methanol-*d*₄ (10:1) solution (0.1 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 2 h. The mixture was cooled and internal standard CH₂Br₂ (2.1 μL, 0.03 mmol) was added as an

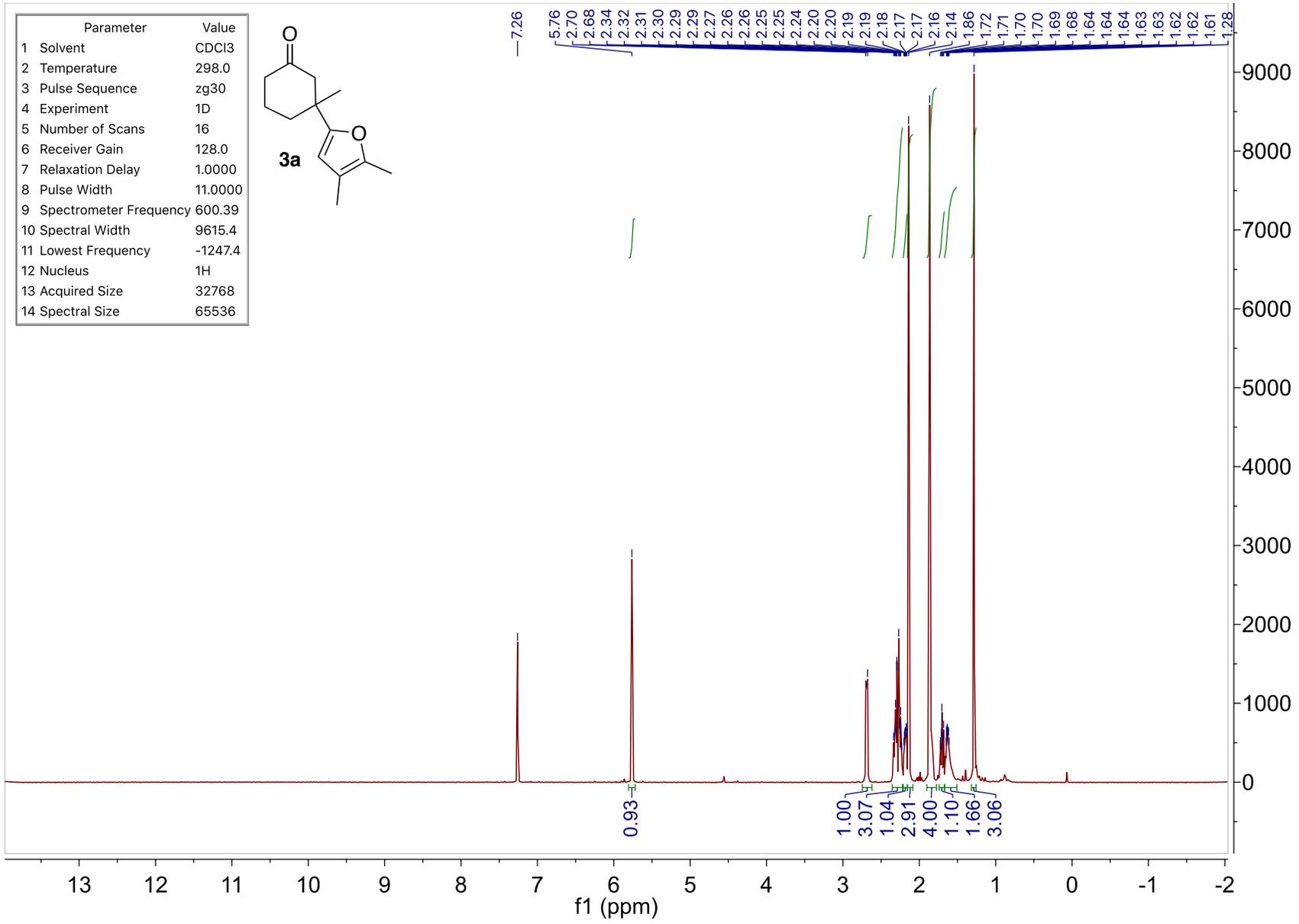
internal standard. NMR yields and deuterium incorporation were determined by ^1H NMR spectroscopy of the crude reaction mixture.

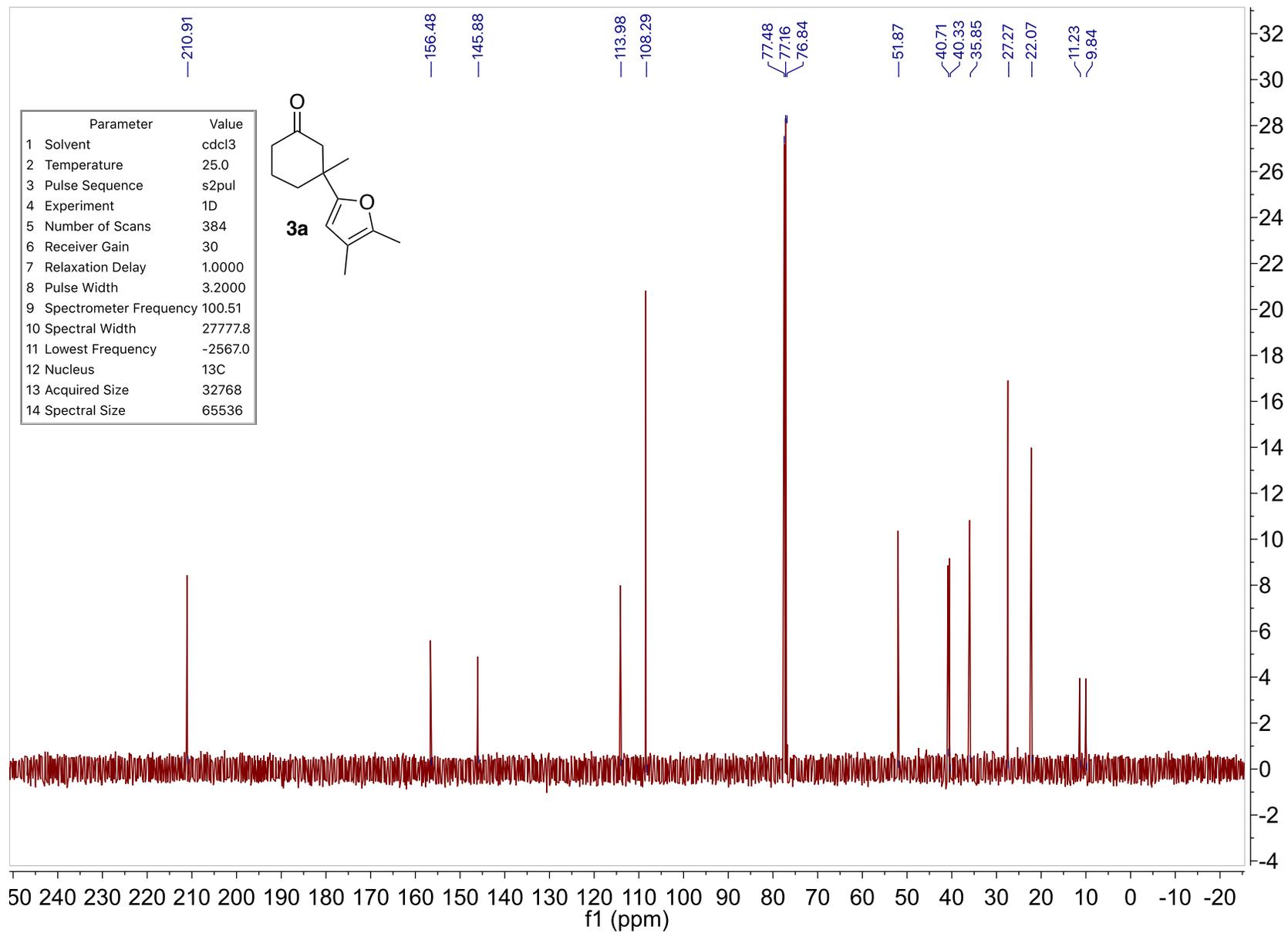


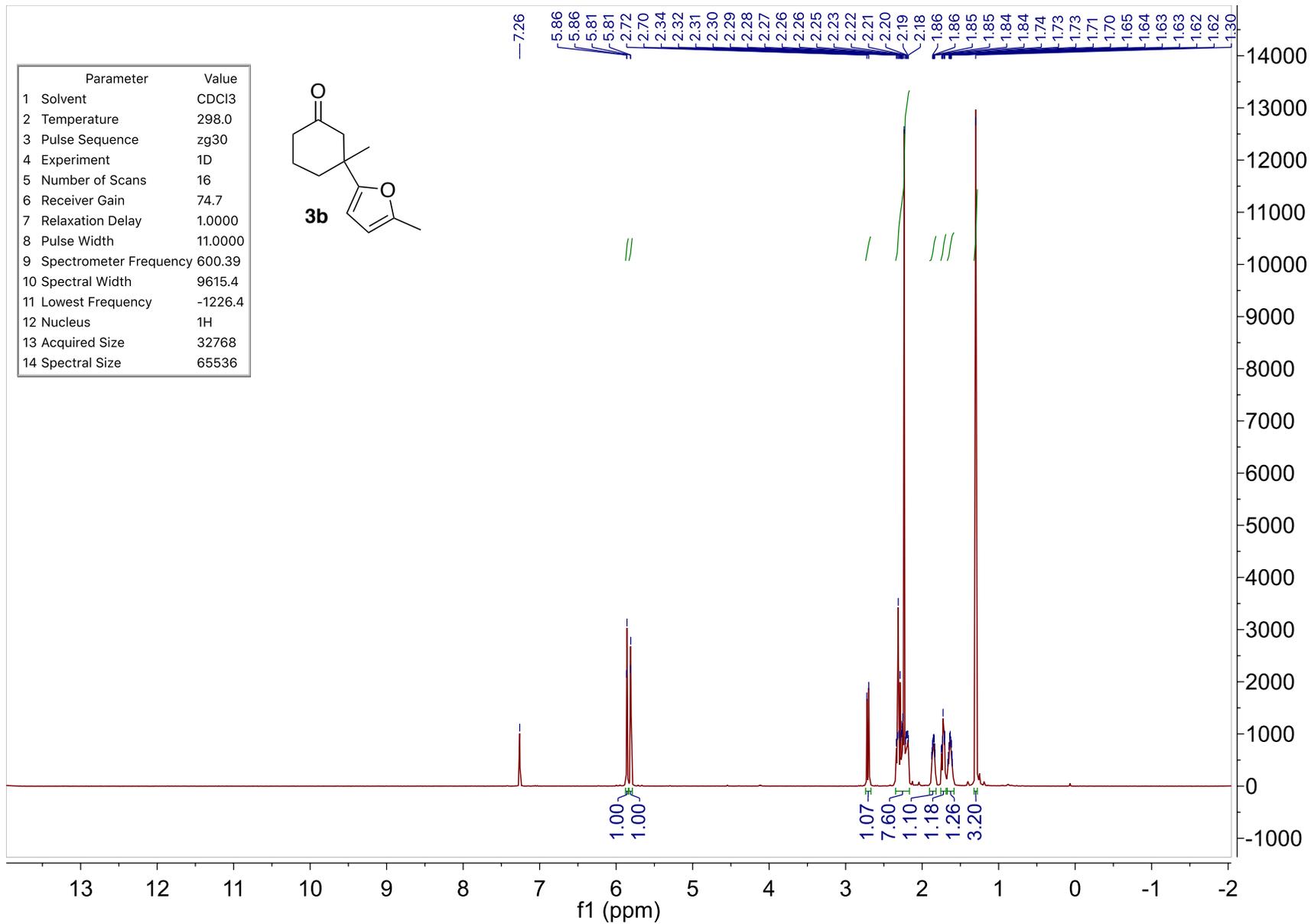
To a 1 dram vial was added $\text{Bi}(\text{OTf})_3$ (0.84 mg, 0.006 mmol, 0.100 equiv), pyrrole (6 μL , 0.06 mmol, 1.00 equiv), 3-methyl-2-cyclohexenone (34 μL , 0.30 mmol, 1.00 equiv), and acetonitrile- d_3 and methanol- d_4 (10:1) solution (0.1 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to $60\text{ }^\circ\text{C}$ and allowed to stir at this temperature for 2 h. The mixture was cooled and internal standard CH_2Br_2 (2.1 μL , 0.03 mmol) was added as an internal standard. NMR yields and deuterium incorporation were determined by ^1H NMR spectroscopy of the crude reaction mixture.

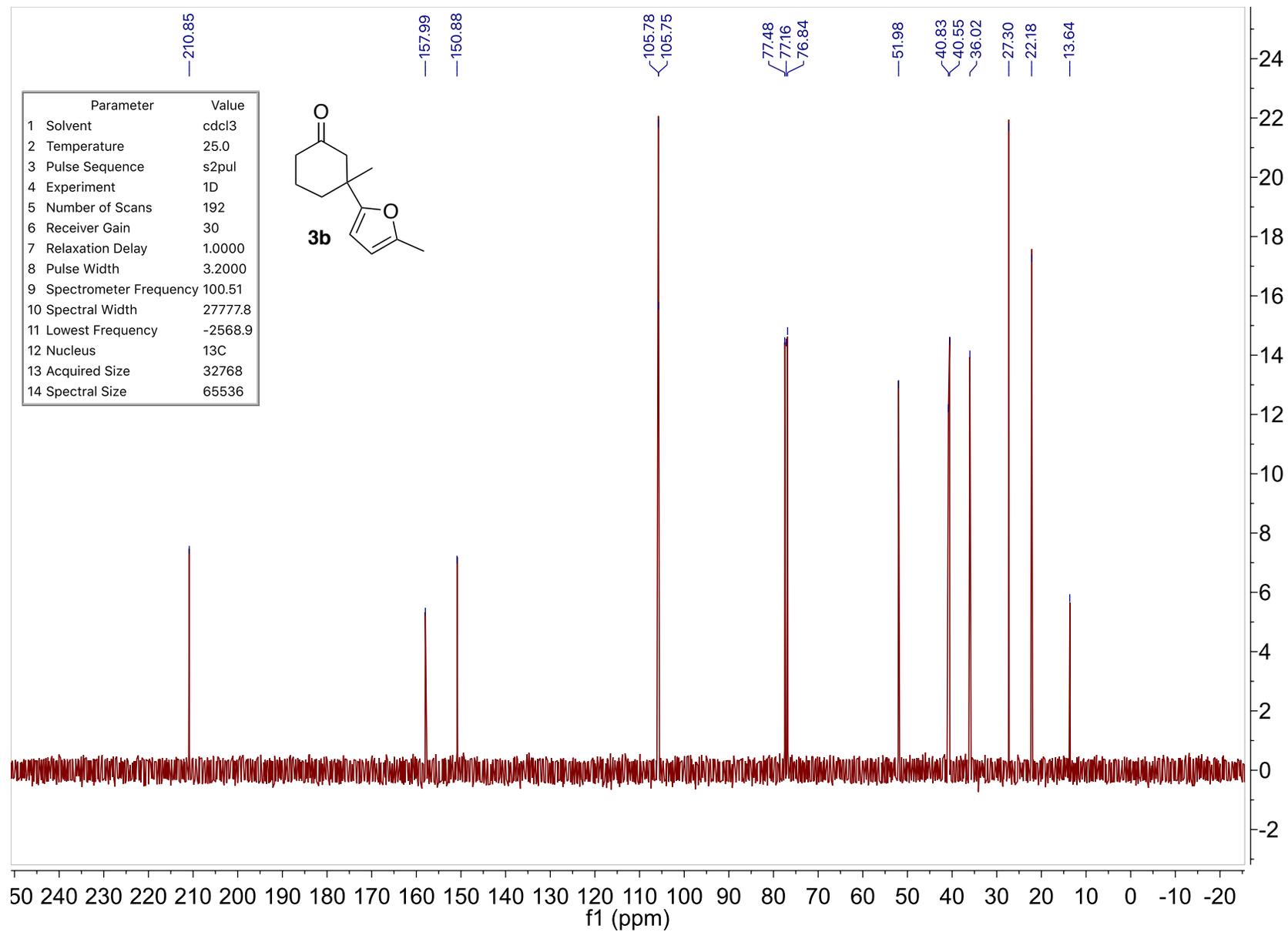
References

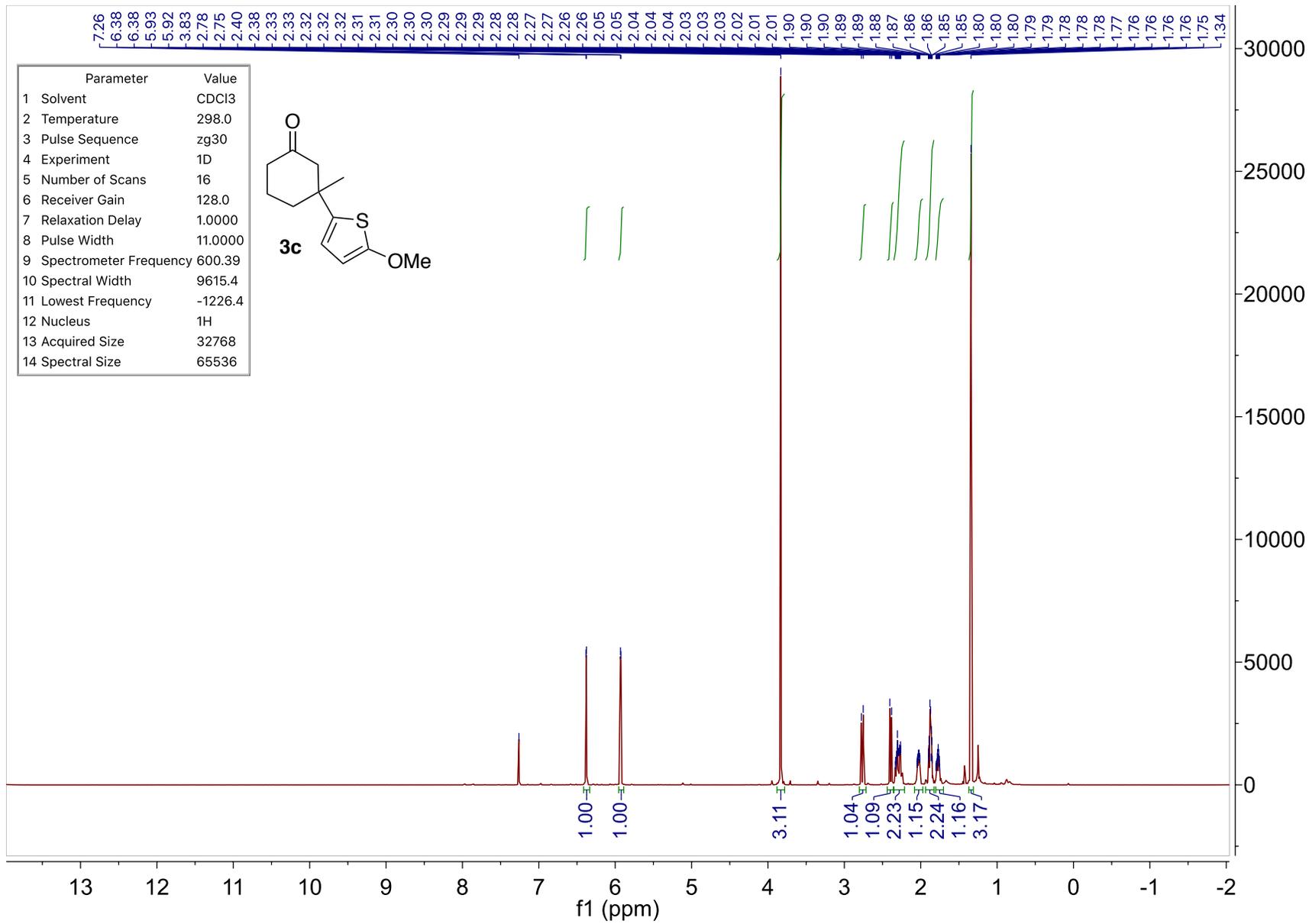
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- (2) Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Fares, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B., *J. Am. Chem. Soc.* **2013**, *135* (17), 6677-6693.
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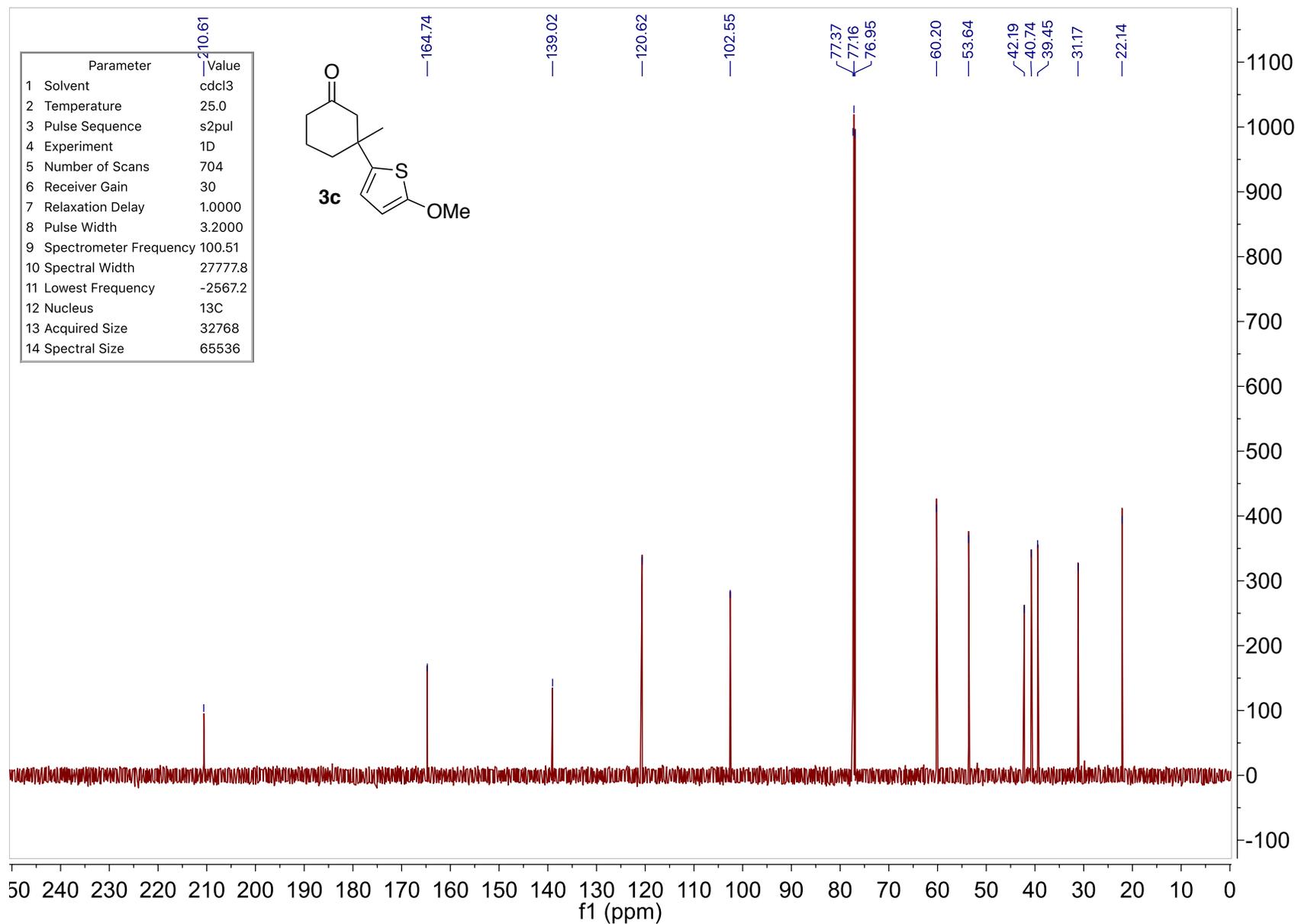


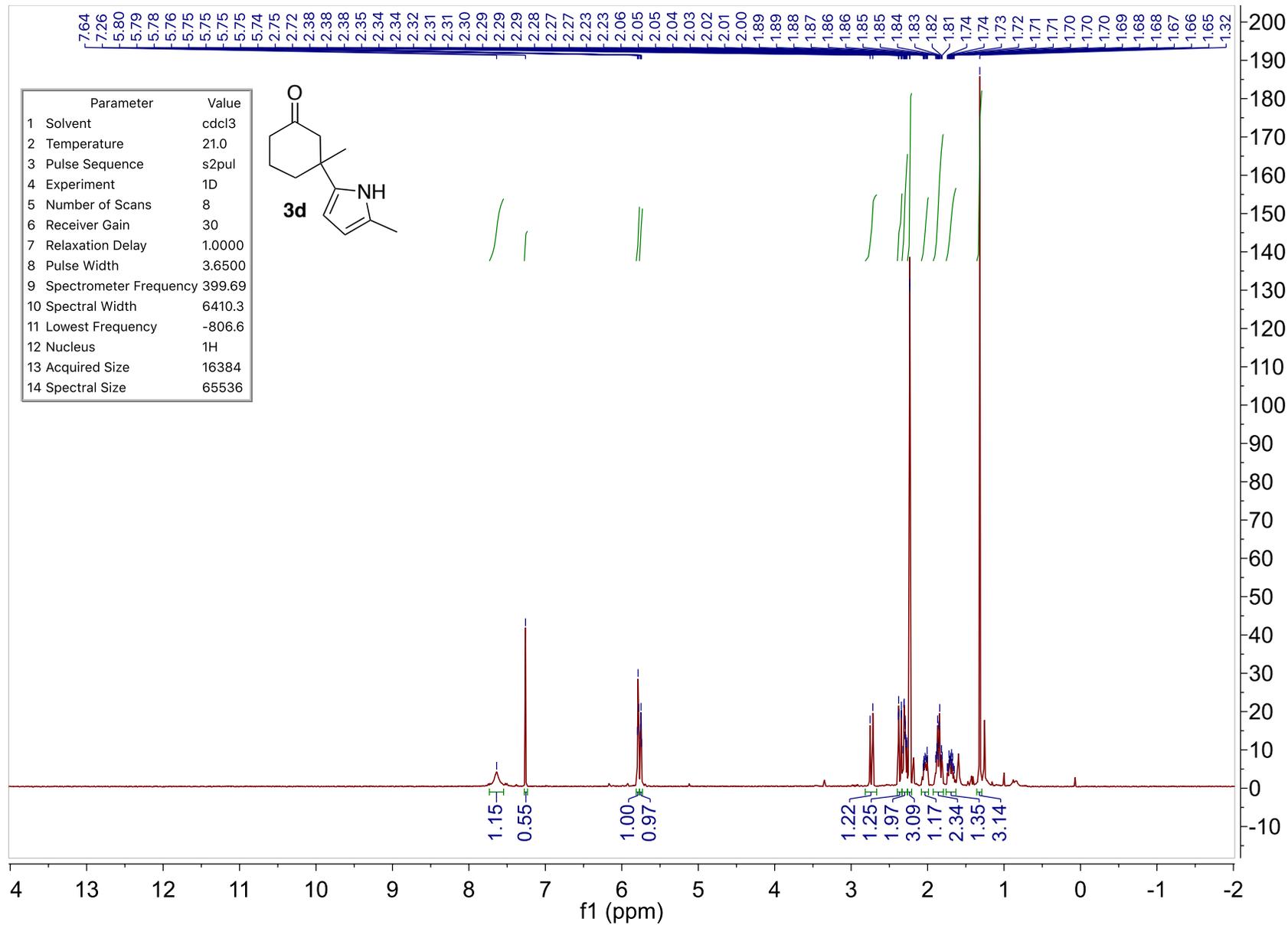


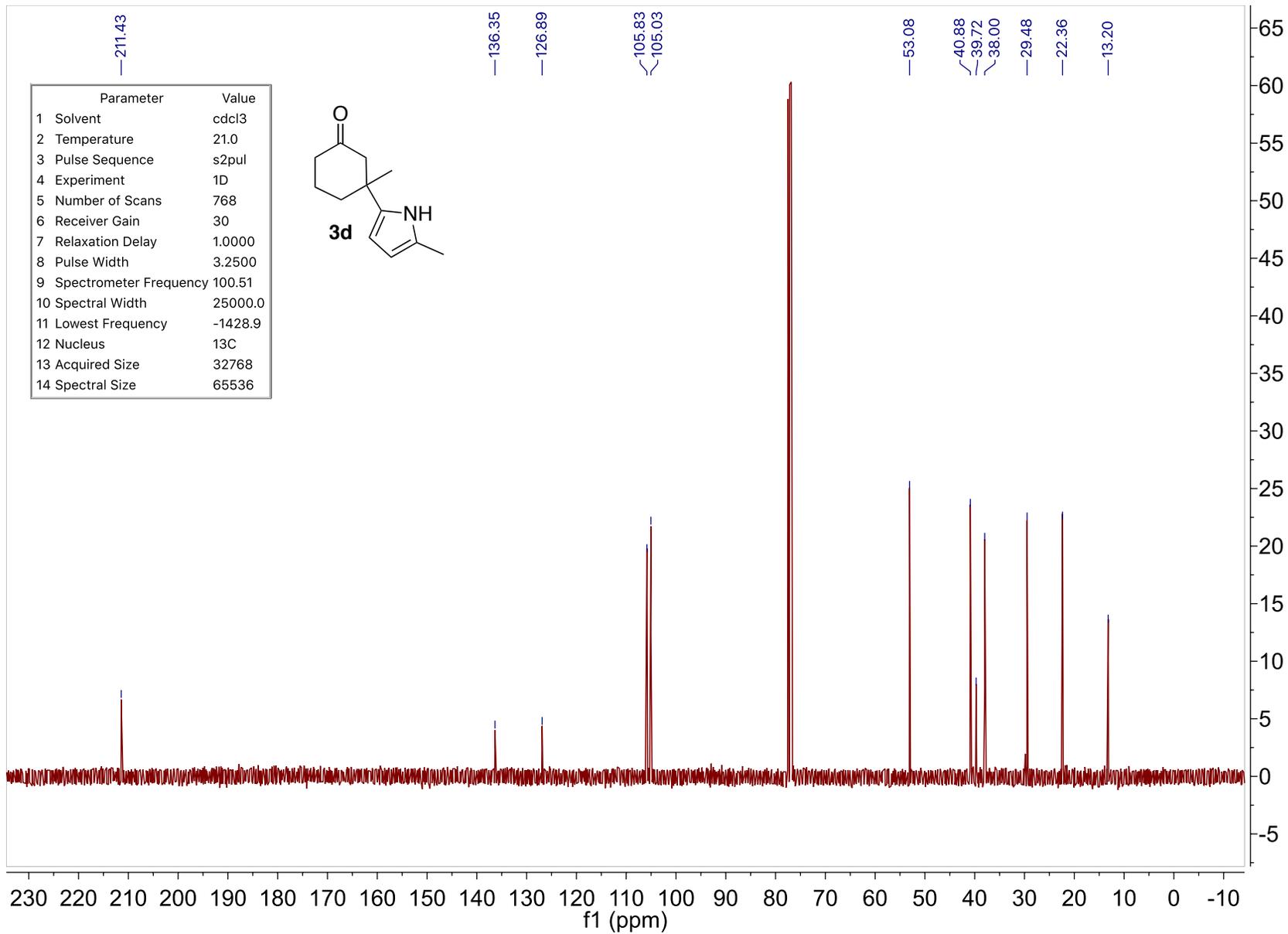


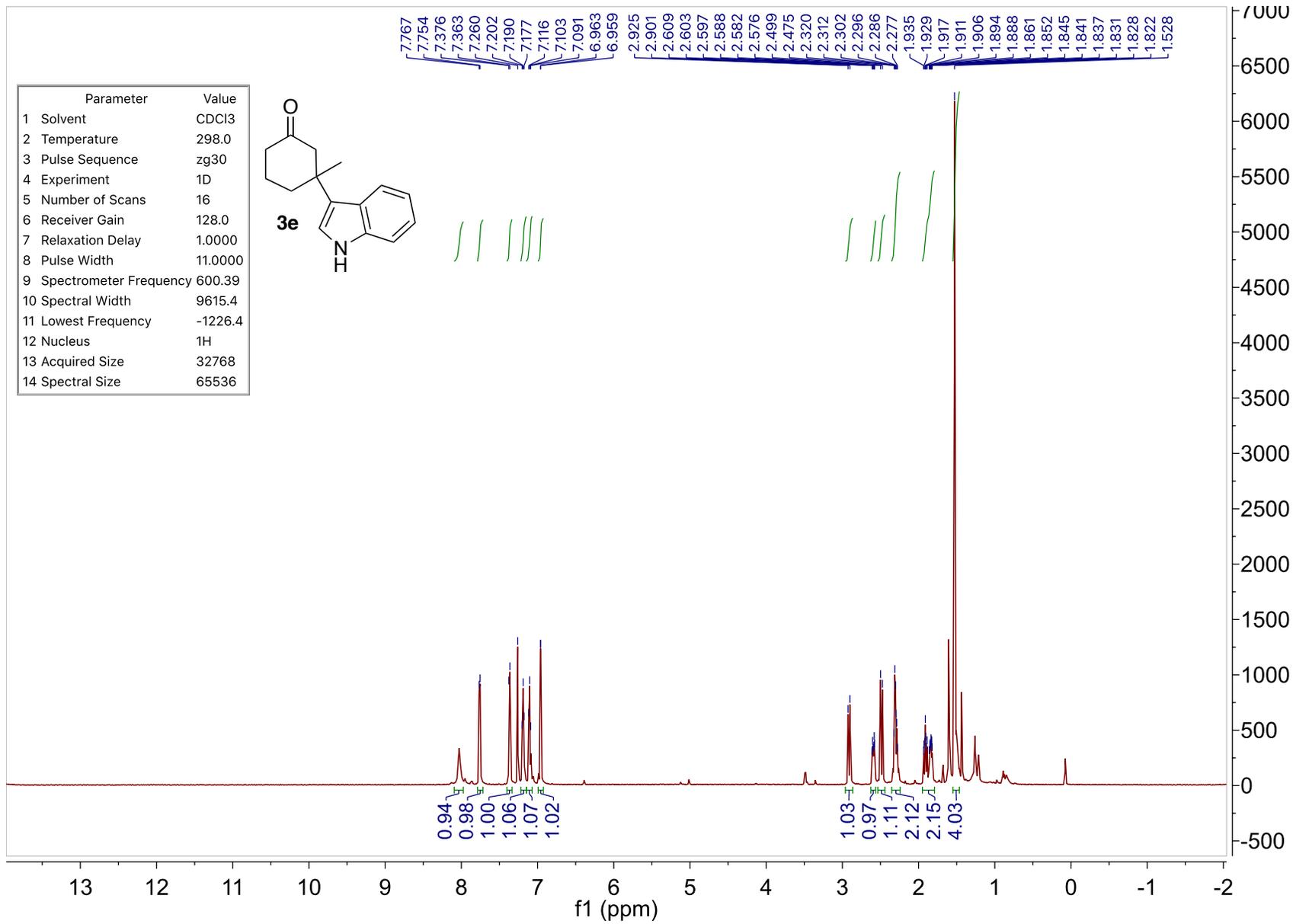


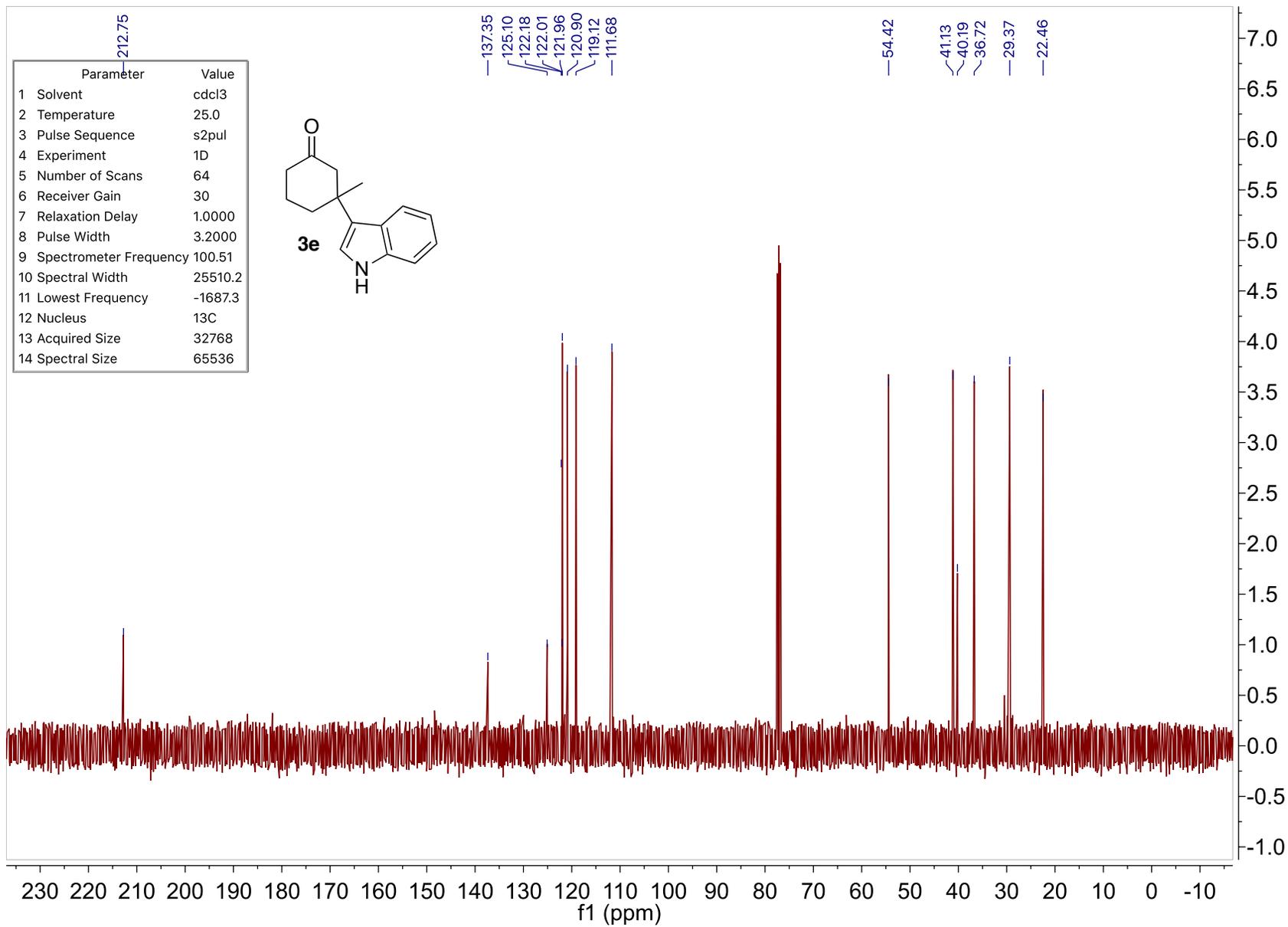


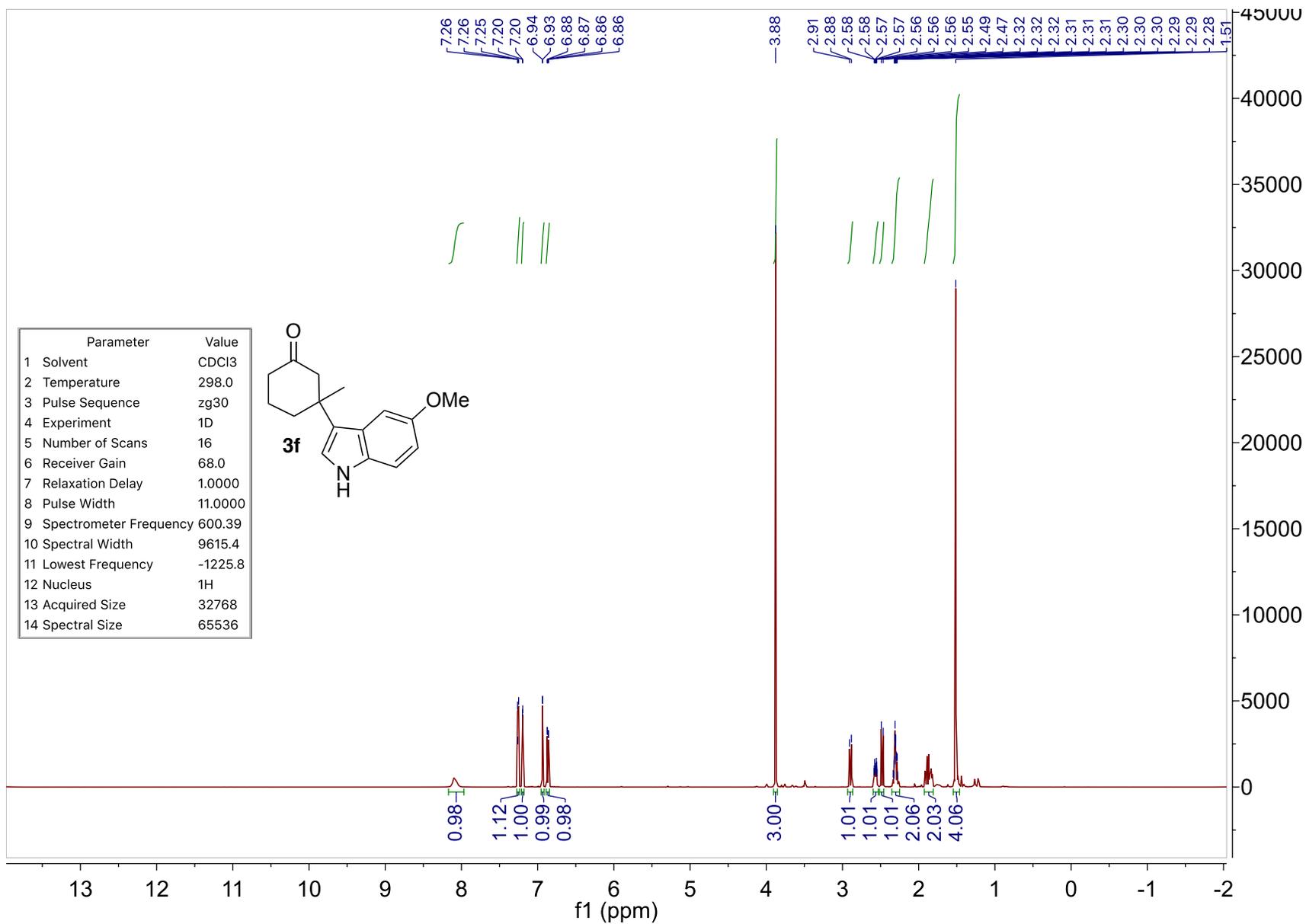


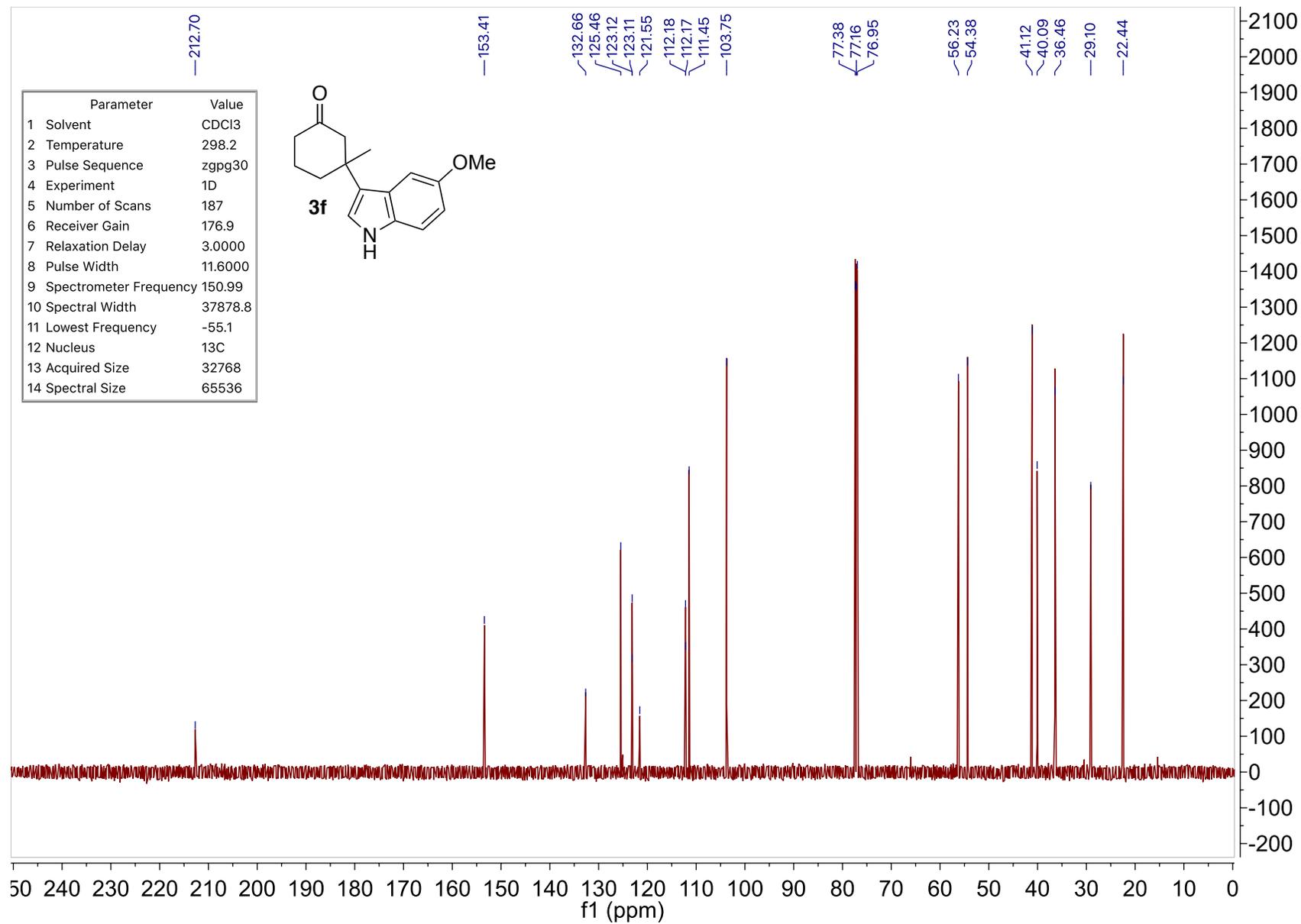


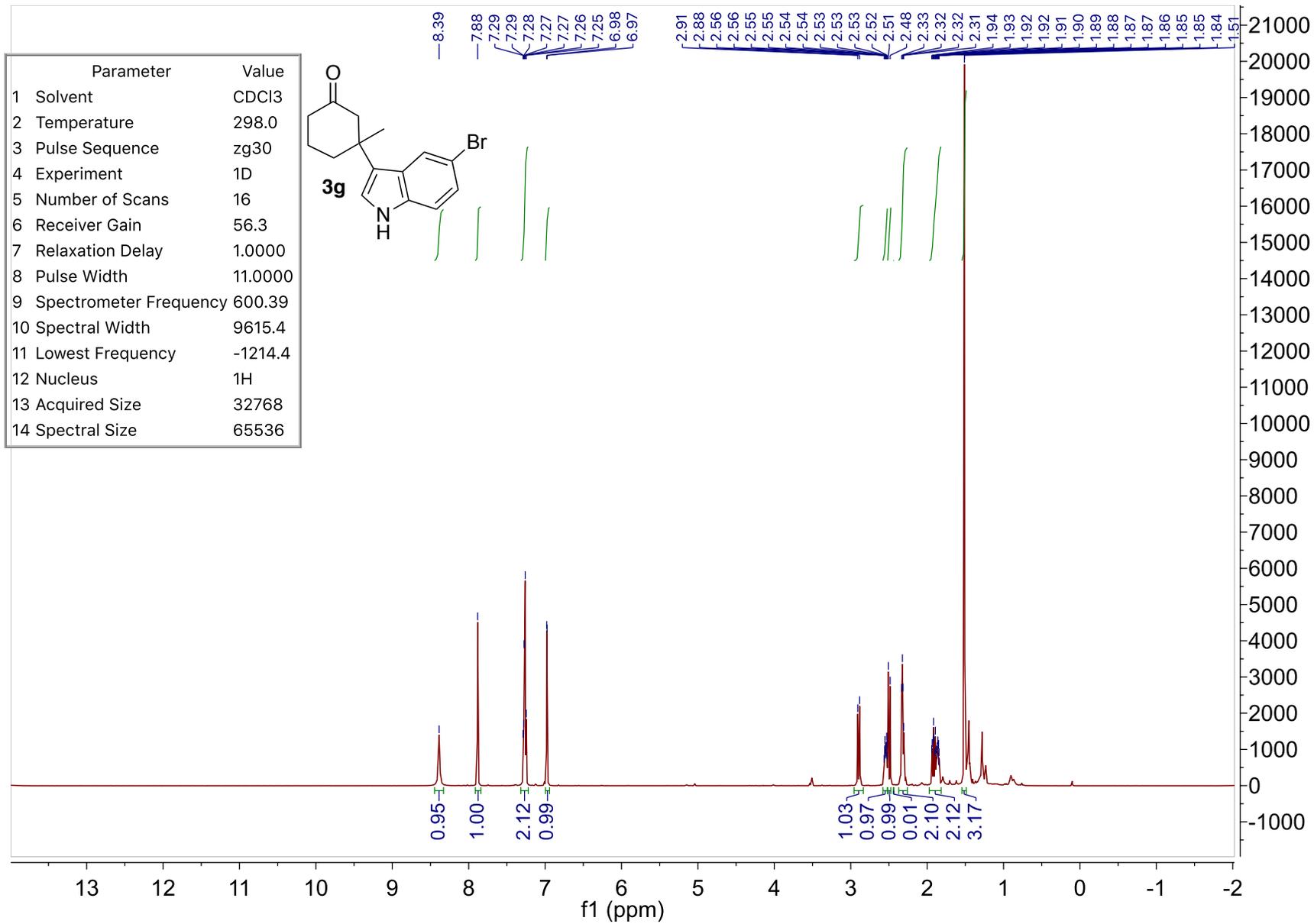


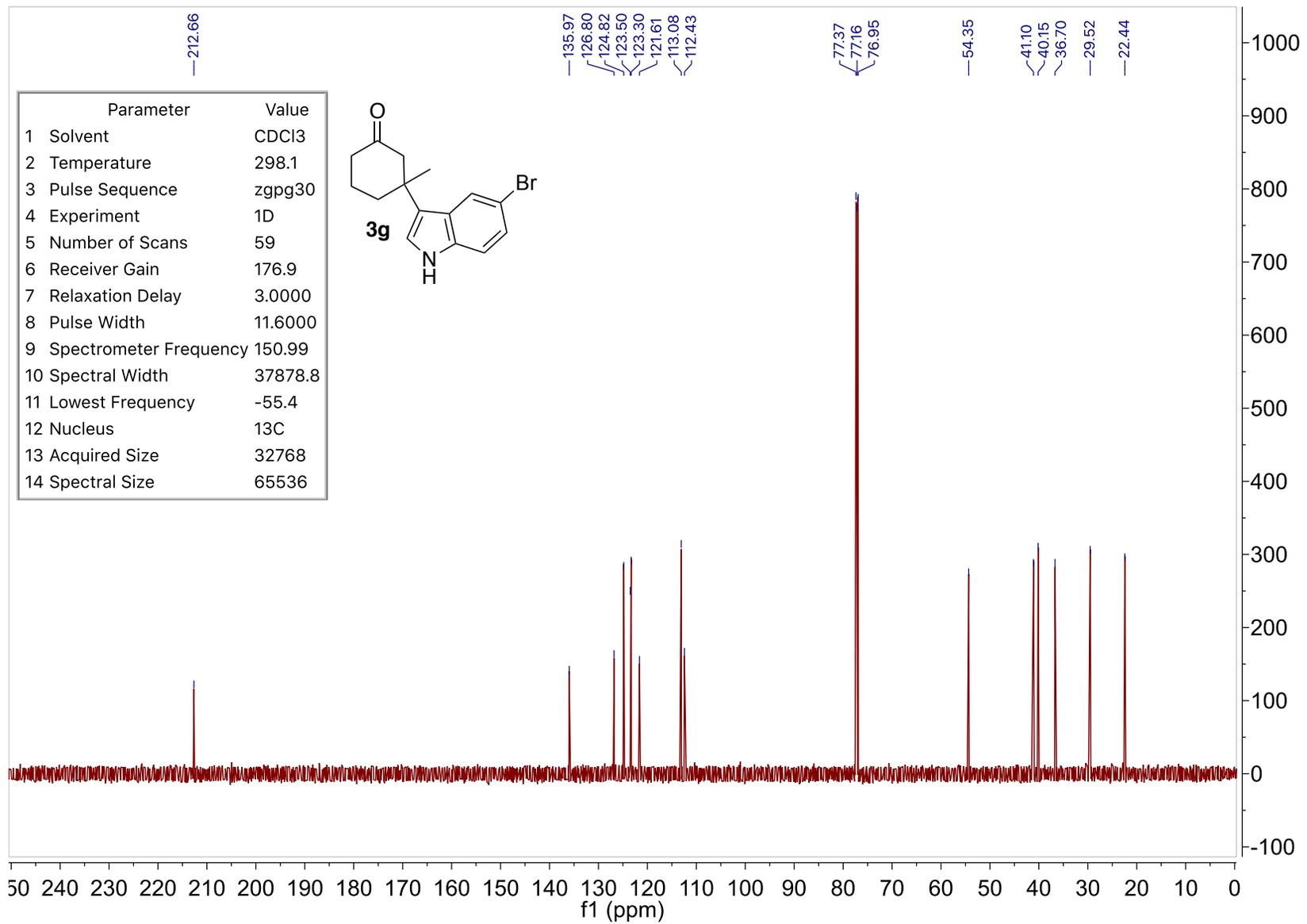


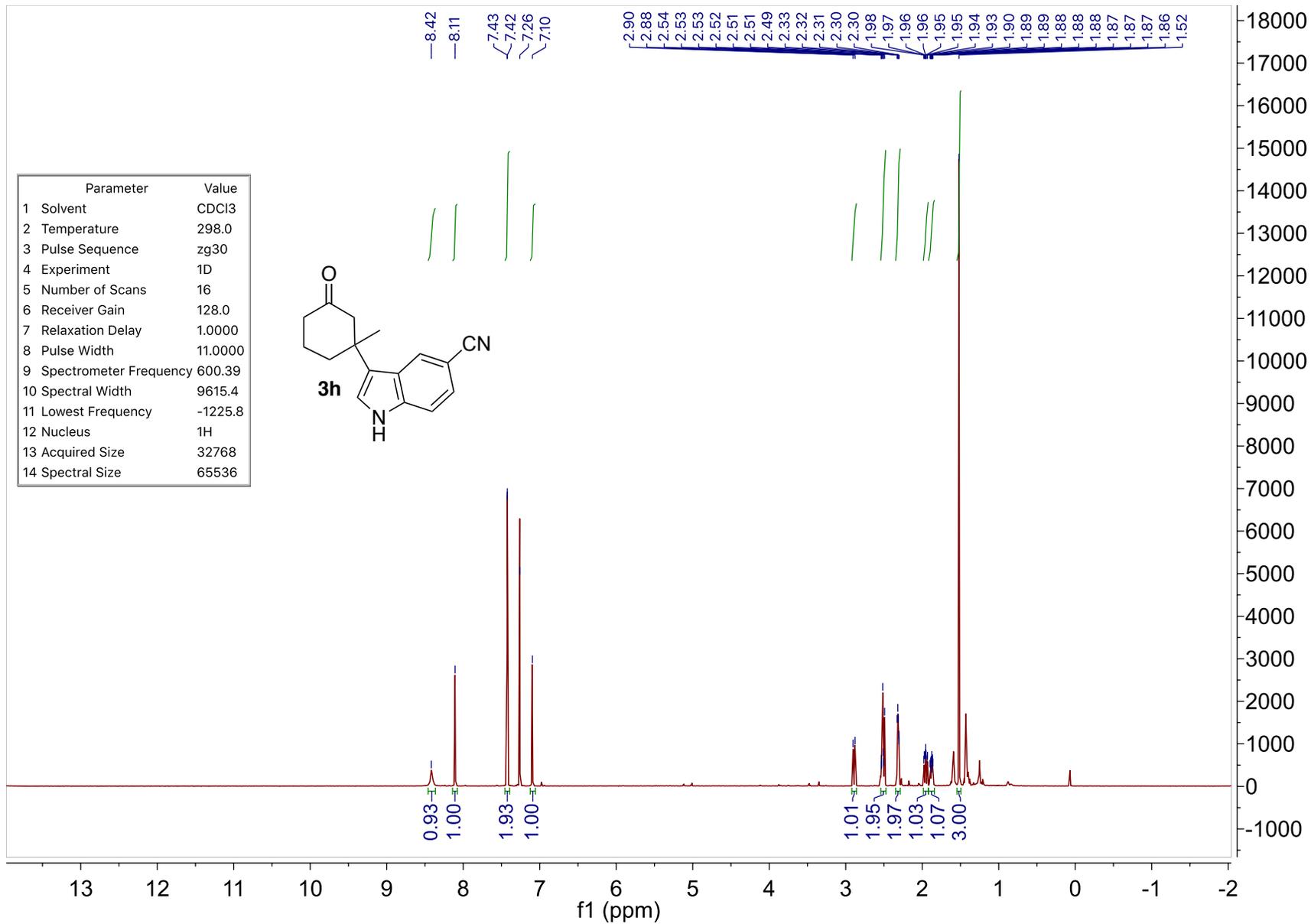


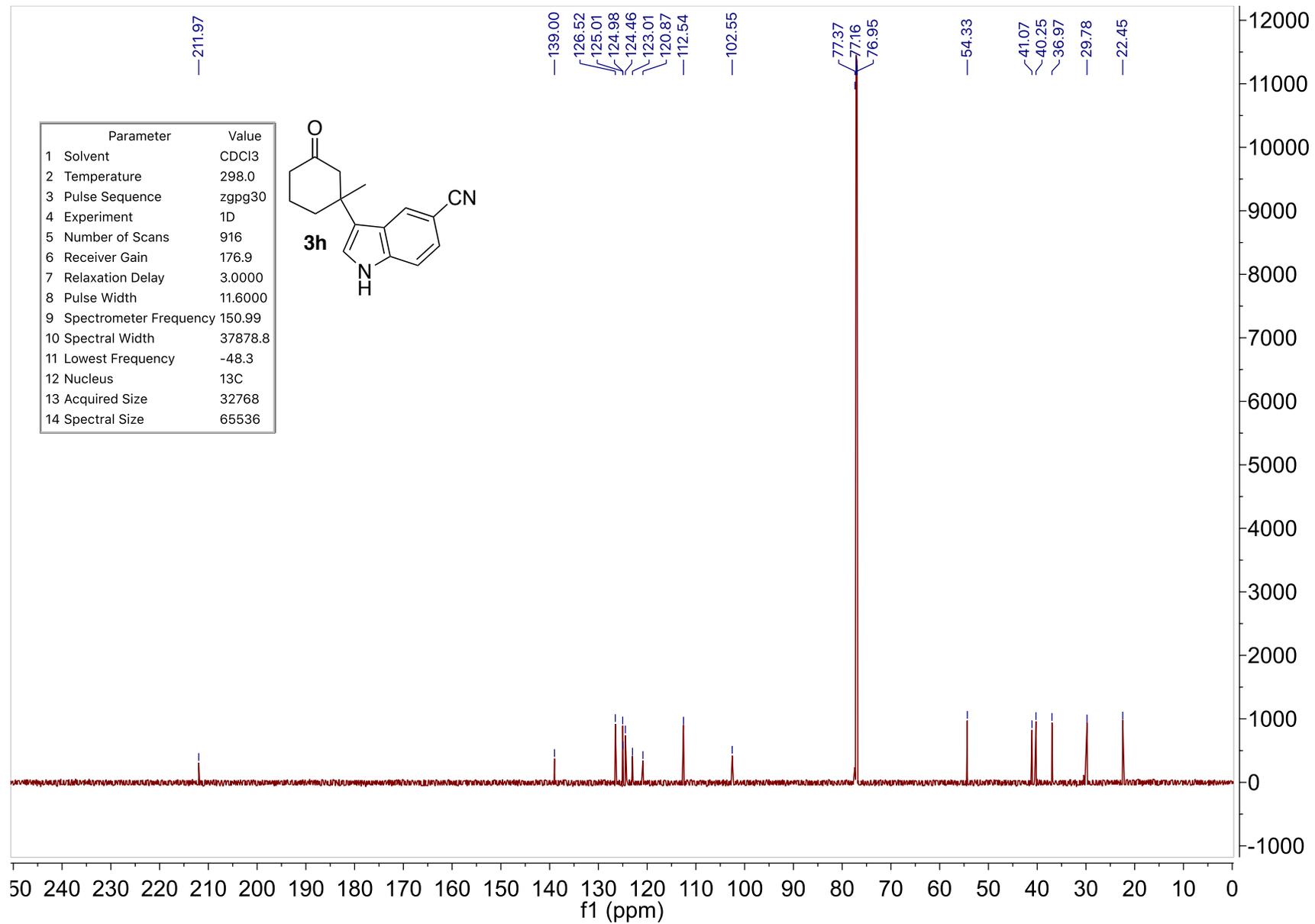


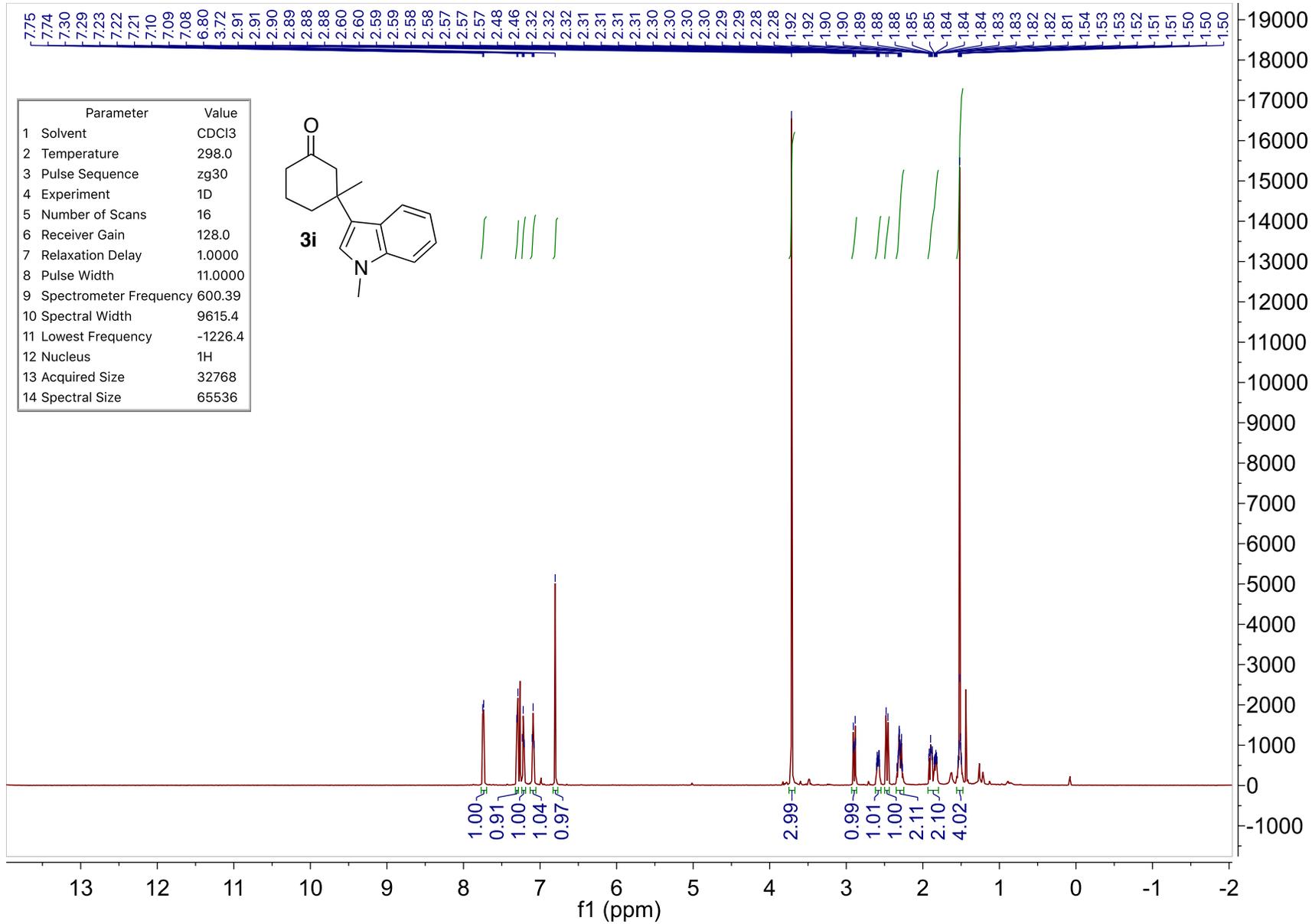


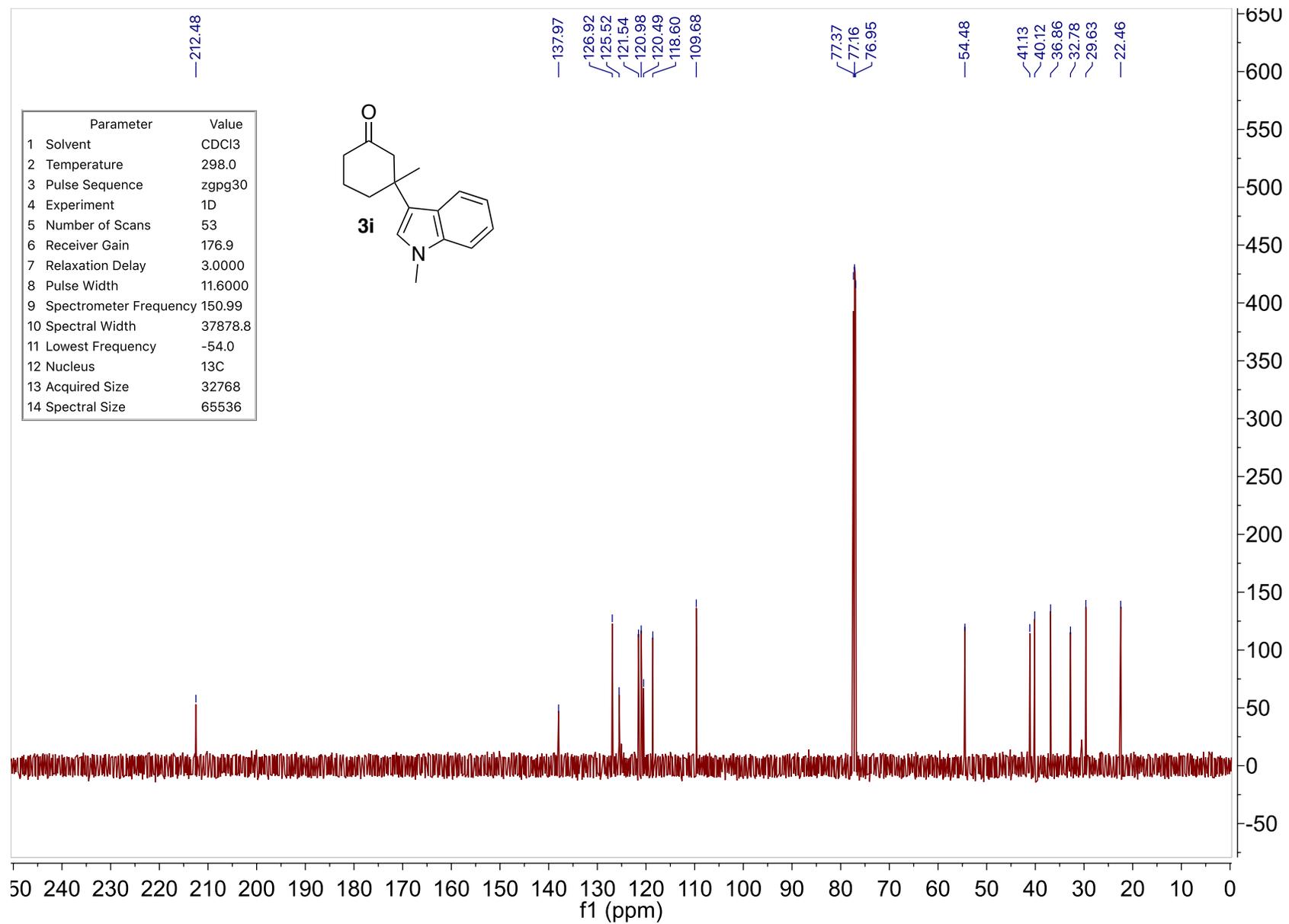


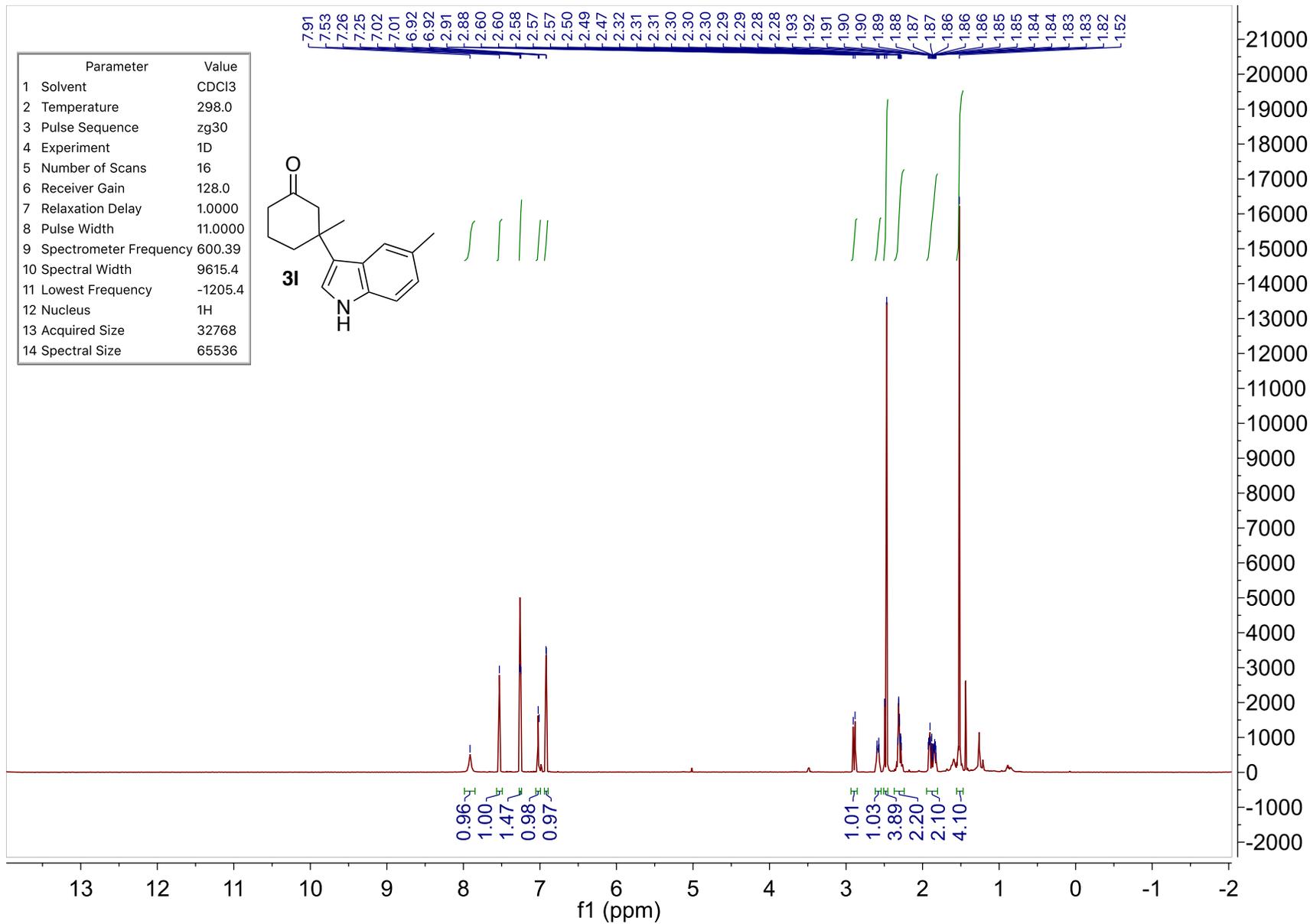


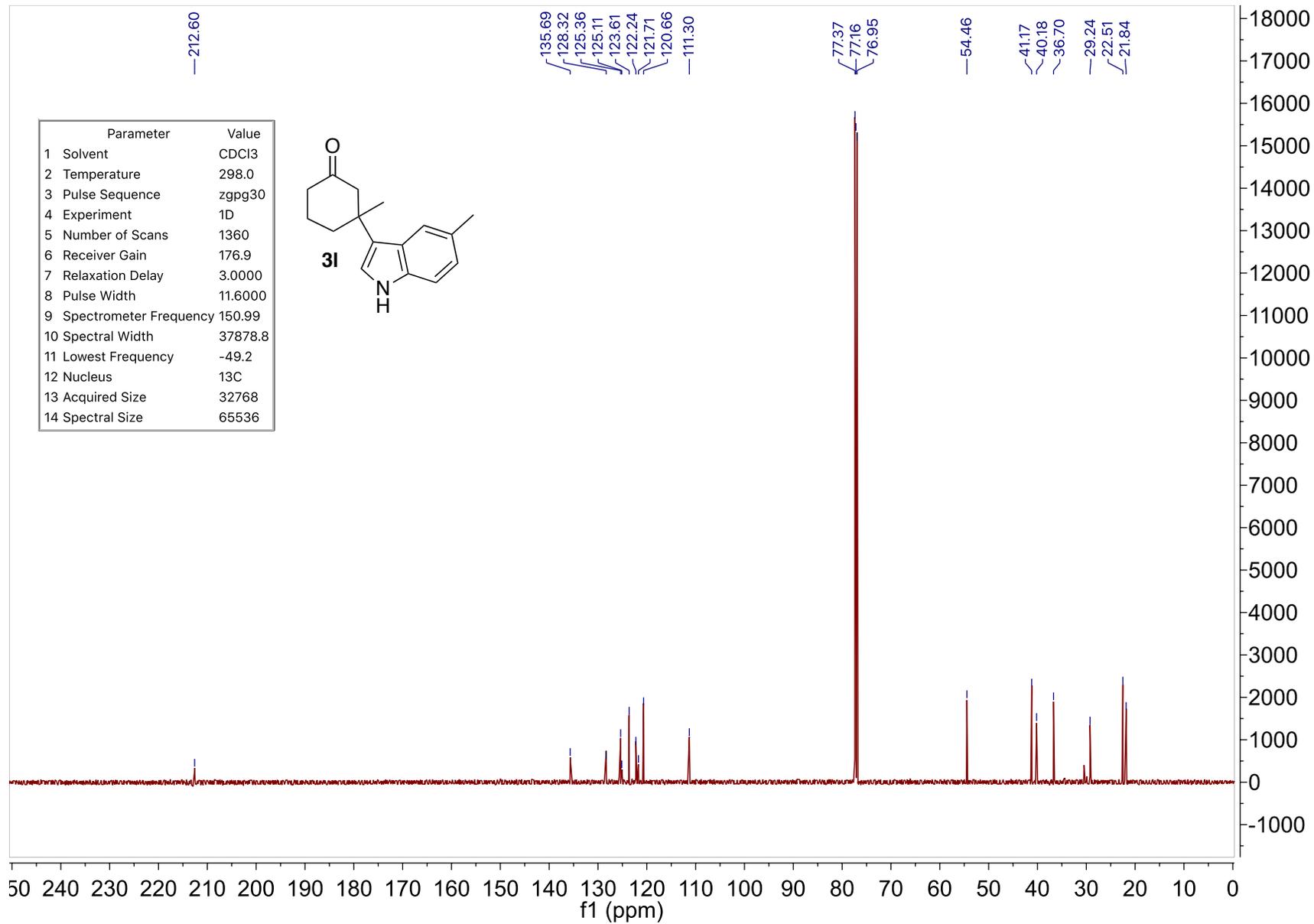


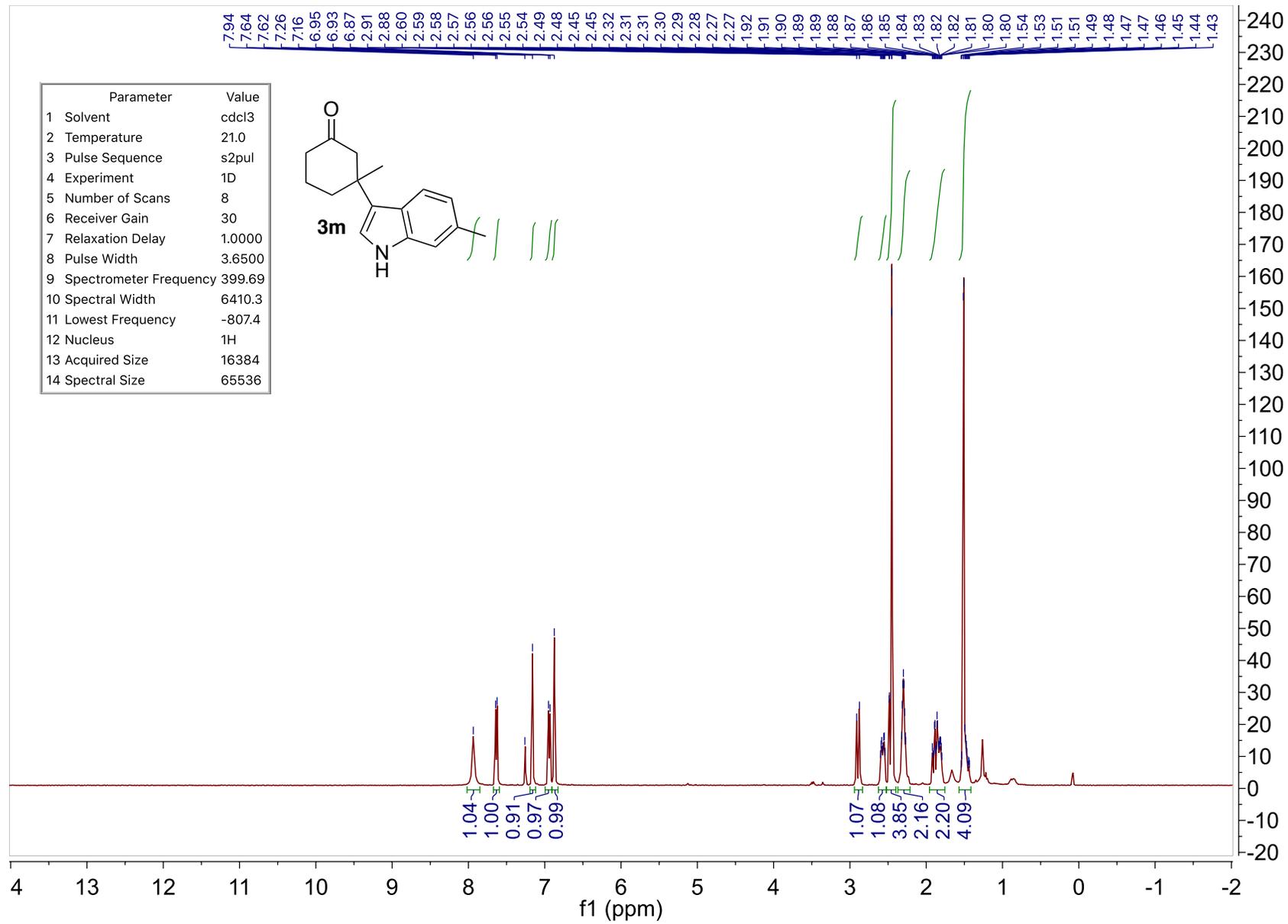


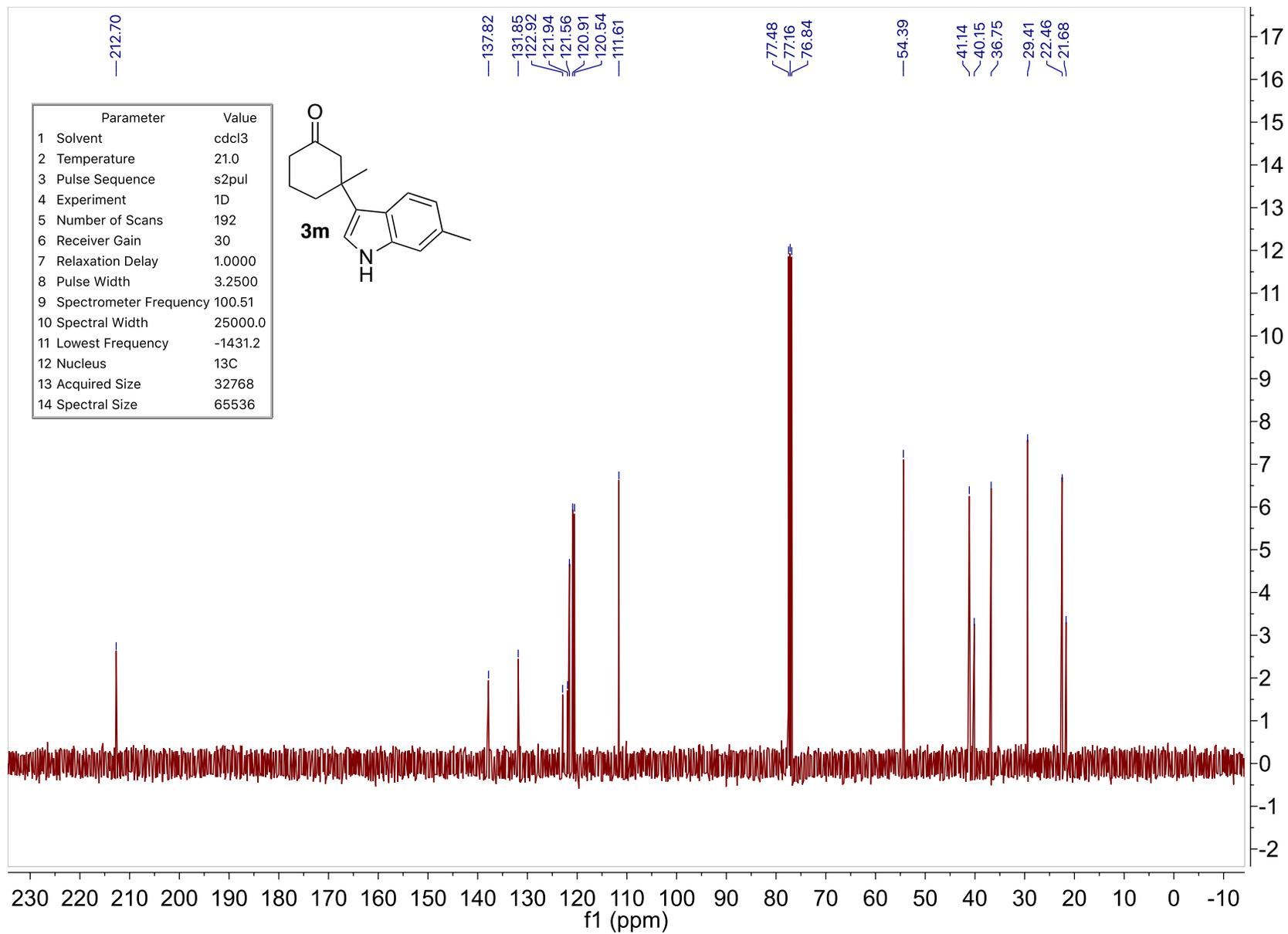


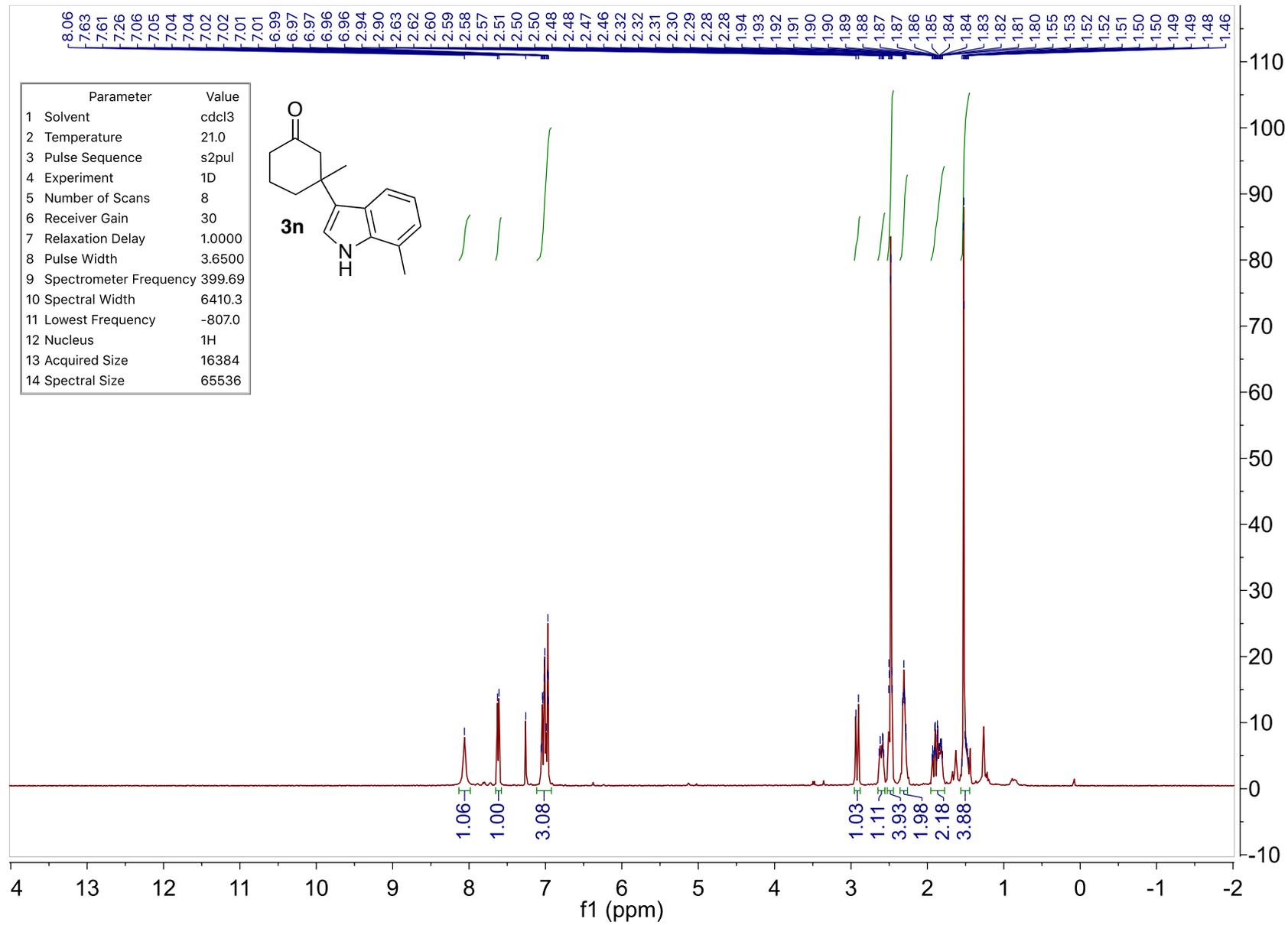


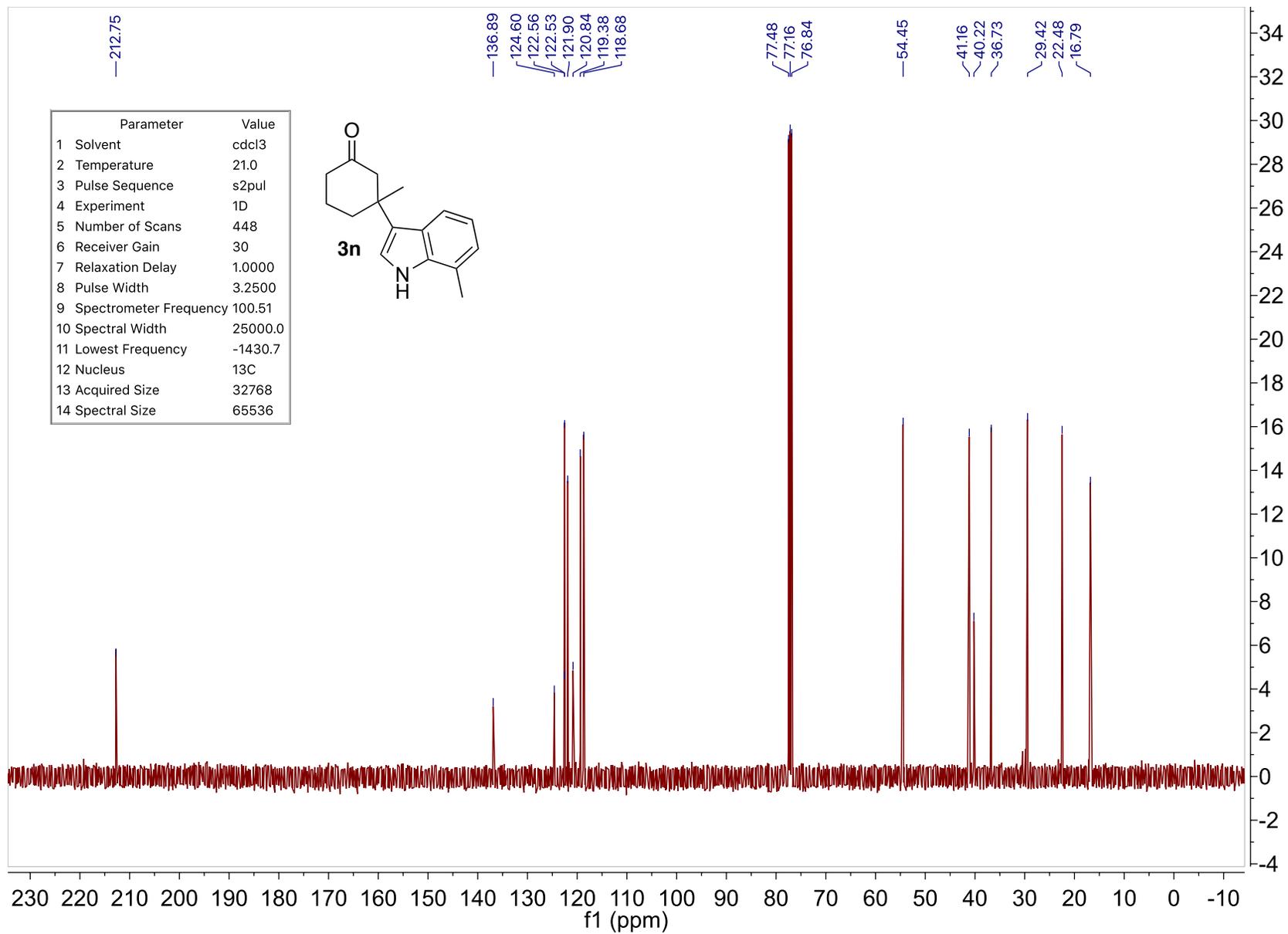












Parameter	Value
1 Solvent	cdcl3
2 Temperature	21.0
3 Pulse Sequence	s2pul
4 Experiment	1D
5 Number of Scans	8
6 Receiver Gain	30
7 Relaxation Delay	1.0000
8 Pulse Width	3.6500
9 Spectrometer Frequency	399.69
10 Spectral Width	6410.3
11 Lowest Frequency	-804.6
12 Nucleus	1H
13 Acquired Size	16384
14 Spectral Size	65536

